Ontario Health
Cancer Care Ontario

Guideline 4-1 Version 2

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

Neoadjuvant and adjuvant 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 2024 deferred the review of Guideline 4-1 Version 2. 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 4-1 Version 2 is comprised of 5 sections. You can access the summary and full report here:
https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/2311

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2. Hirte H, Poon R, Yao X, May T, Ethier JL, Petz L, Speakman J, Elit L. Neoadjuvant and Adjuvant Systemic Therapy for Newly Diagnosed Stage II-IV Epithelial Ovary, Fallopian Tube, or Primary Peritoneal Carcinoma: A Practice Guideline. Curr Oncol. 2022 Jan 8;29(1):231-242.

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Neoadjuvant and adjuvant 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.

Strength of Recommendations for This Guideline

Strength	Definition
Recommendation to use the intervention	The guideline Working Group* believes the benefits of the neoadjuvant or adjuvant 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 neoadjuvant or adjuvant therapy in the target patients 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 neoadjuvant or adjuvant therapy in the target patients are balanced and does not recommend a specific action.
Weak recommendation *not* to use the intervention	The guideline Working Group* believes the benefits and harms of the neoadjuvant or adjuvant therapy in the target patients are closely balanced or are more uncertain but still adequate to support the recommended action.
Recommendation *not* to use the intervention	The guideline Working Group* believes the harms of the neoadjuvant or adjuvant therapy in the target patients 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, two guideline methodologists, and two patient representatives.

GUIDELINE OBJECTIVES

To provide guidance for the use of neoadjuvant and adjuvant systemic therapy in women with newly diagnosed stage II, III, or IV epithelial ovary, fallopian tube, or primary peritoneal carcinoma (EOC).

TARGET POPULATION

Women with newly diagnosed stage II, III, or IV EOC.

INTENDED USERS

Gynecologic oncologists, medical oncologists, and other clinicians who are involved in the treatment of the target population in the province of Ontario.

RECOMMENDATIONS

Neoadjuvant chemotherapy

Recommendation 1 (Strength: Weak recommendation to use the intervention)
For women with stage III or IV EOC who may have a high-risk profile for primary cytoreductive surgery as determined by a gynecologic oncologist, neoadjuvant chemotherapy with three to four cycles of intravenous three-weekly paclitaxel (175 mg/m^2 over 3 hours) and carboplatin (area under the curve [AUC]=5/6), then interval cytoreductive surgery, followed in turn by three to four cycles of intravenous three-weekly paclitaxel (175 mg/m^2 over 3 hours) and carboplatin (AUC=5/6) can be recommended as an option.
Qualifying Statement for Recommendation 1
• High risk is defined as significant disease-related symptoms (e.g., moderate to severe pleural effusion, cachexia with poor oral intake, hypoalbuminemia and other poor nutritional status), low likelihood of achieving optimal cytoreduction (residual ≤1 cm, but ideally to no visible disease), or poor prognostic factors (e.g., poor performance status [PS] according to Eastern Cooperative Oncology Group, PS >2). The criteria were based on expert consensus from the Working Group and Expert Panel. • ***Added in 2024:*** For patients with newly diagnosed, primary stage III epithelial ovarian, fallopian tube, or primary peritoneal carcinoma, HIPEC should be considered for those with at least stable disease following neoadjuvant chemotherapy at the time of interval CRS if complete or optimal cytoreduction is achieved. (Recommendation 1a from Guideline 17-12 Indications for cytoreductive surgery with hyperthermic intraperitoneal chemotherapy)

Adjuvant therapy

Recommendation 2 (Strength: Recommendation to use the intervention)
For women with stage II, III, or IV EOC and potentially resectable disease as determined by a gynecologic oncologist, primary cytoreductive surgery, followed by six to eight cycles of intravenous three-weekly paclitaxel (175 mg/m^2 over 3 hours) and carboplatin (AUC=5/6) is recommended.
Qualifying Statements for Recommendation 2
• For those who are unable to tolerate paclitaxel, an alternate regimen consisting of docetaxel (75 mg/m^2) may be offered with carboplatin (AUC=5). • Adjuvant chemotherapy with six cycles of dose-dense weekly paclitaxel (80 mg/m^2) in combination with three-weekly carboplatin (AUC=6) administered intravenously can be considered for women with stage II, III, or IV EOC of Japanese descent.

Recommendation 3 (Strength: Recommendation *not* to use the intervention)
The addition of a third chemotherapy agent to standard paclitaxel and carboplatin is not recommended for use as adjuvant therapy in women with stage II, III, or IV EOC.

Recommendation 4 (Strength: Recommendation *not* to use the intervention)
The addition of valspodar or interferon gamma 1b to standard paclitaxel and carboplatin is not recommended for use as adjuvant therapy in women with stage III or IV EOC.

The incorporation of bevacizumab concurrent with paclitaxel and carboplatin is not recommended for use as adjuvant therapy unless bevacizumab is continued as maintenance therapy in women with stage III or IV EOC.
Qualifying Statement for Recommendation 4
• Concurrent use of intravenous three-weekly bevacizumab (7.5 mg/kg) with paclitaxel and carboplatin for six cycles and continued for up to 12 cycles or until progression as maintenance therapy can be recommended for women with newly diagnosed high-risk stage III (residual disease >1 cm or inoperable), or stage IV EOC. Refer to **Guideline 4-18** for details.

Recommendation 5 (Strength: Weak recommendation to use the intervention)
Intravenous paclitaxel (135 mg/m^2 over 24 hours) plus intraperitoneal cisplatin (100 mg/m^2) and paclitaxel (60 mg/m^2) can be considered for stage III optimally debulked women (≤1 cm residual disease) who did not receive neoadjuvant chemotherapy. Intraperitoneal administration of chemotherapy with bevacizumab should not be considered as an option for stage II to IV optimally debulked women (≤1 cm residual disease).

Neoadjuvant and adjuvant 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 the use of neoadjuvant and adjuvant systemic therapy in women with newly diagnosed stage II, III, or IV epithelial ovary, fallopian tube, or primary peritoneal carcinoma (EOC).

TARGET POPULATION

Women with newly diagnosed stage II, III, or IV EOC.

INTENDED USERS

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

RECOMMENDATIONS, KEY EVIDENCE, AND JUSTIFICATION

Note: 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 can be updated as soon as possible.

Neoadjuvant chemotherapy

Recommendation 1 (Strength: Weak recommendation to use the intervention)
For women with stage III or IV EOC who may have a high-risk profile for primary cytoreductive surgery as determined by a gynecologic oncologist, neoadjuvant chemotherapy with three to four cycles of intravenous (i.v.) three-weekly paclitaxel (175 mg/m^2 over 3 hours) and carboplatin (area under the curve [AUC]=5/6), then interval cytoreductive surgery, followed in turn by three to four cycles of i.v. three-weekly paclitaxel (175 mg/m^2 over 3 hours) and carboplatin (AUC=5/6) can be recommended as an option.
Qualifying Statement for Recommendation 1
• High risk is defined as significant disease related symptoms (e.g., moderate to severe pleural effusion, cachexia with poor oral intake, hypoalbuminemia and other poor nutritional status), low likelihood of achieving optimal cytoreduction (residual ≤1 cm, but ideally to no visible disease), or poor prognostic factors (e.g., poor performance status [PS] according to Eastern Cooperative Oncology Group, PS >2). The criteria were based on expert consensus from the Working Group and Expert Panel. • ***Added in 2024:*** For patients with newly diagnosed, primary stage III epithelial ovarian, fallopian tube, or primary peritoneal carcinoma, HIPEC should be considered for those with at least stable disease following neoadjuvant chemotherapy at the time of interval CRS if complete or optimal cytoreduction is achieved. (Recommendation 1a from Guideline 17-12 Indications for cytoreductive surgery with hyperthermic intraperitoneal chemotherapy)
Key Evidence for Recommendation 1

Three trials (EORTC 55971, CHORUS, and JCOG 0602) used a non-inferiority design [1-5] and one used a superiority design (SCORPION) [6,7] to compare upfront primary debulking surgery (followed by at least six cycles of carboplatin or cisplatin plus paclitaxel) to neoadjuvant chemotherapy (three to four cycles before and three to four cycles after interval debulking surgery). The aggregate quality of the evidence was judged to be moderate, based on the GRADE approach [8] (details in **Section 4**).

- In two (EORTC 55971 and CHORUS) [1,3] of the three non-inferiority trials, overall survival (OS) for neoadjuvant chemotherapy was demonstrated to be non-inferior to that of primary surgery while the third trial (JCOG 0602) [4] was unable to confirm the non-inferiority of neoadjuvant chemotherapy. Postoperative deaths within 28 days after surgery were less common in women who received neoadjuvant chemotherapy (p=0.0439) [1]. Grade 3 or 4 nausea (p=0.0057) and vomiting (p=0.0057) also occurred less frequently in women who received neoadjuvant chemotherapy [3]. Conversely, neoadjuvant chemotherapy was associated with more grade 3 or 4 leukopenia (p=0.0086) [5]. In the CHORUS trial [3], women who received neoadjuvant chemotherapy had slightly higher quality of life (QoL) scores at six months after treatment (p=0.0438) than those who received primary surgery.
- In the SCORPION trial, neoadjuvant chemotherapy failed to show superiority over primary surgery with respect to progression-free survival (PFS) (14.0 months versus 15.0 months; hazard ratio [HR], 1.05; 95% confidence interval [CI], 0.77 to 1.44, p=0.73) and toxicity profile [6]. However, QoL scores for emotional functioning (p=0.02), cognitive functioning (p=0.008), nausea and vomiting (p=0.047), dyspnea (p=0.013), insomnia (p=0.024), and hair loss (p=0.013) were shown to be more favourable in women who received neoadjuvant chemotherapy [7].
- Pooled analysis of individual patient data with long-term follow up from EORTC 55971 and CHORUS showed that women with stage IV disease had significantly better OS (24.3 months versus 21.2 months; HR, 0.76; 95% CI, 0.58 to 1.00, p=0.048) and PFS (10.6 months versus 9.7 months; HR, 0.77; 95% CI, 0.59 to 1.00, p=0.049) with neoadjuvant chemotherapy compared with primary surgery [9].

Justification for Recommendation 1

- Neoadjuvant chemotherapy is associated with lower postoperative mortality and a general trend toward fewer adverse events and higher QoL scores then primary cytoreductive surgery followed by adjuvant therapy.
- Despite the two earlier trials (EORTC 55971 and CHORUS) showing OS was non-inferior to that of primary cytoreductive surgery, the more recent trial (JCOG 0602) was unable to corroborate the non-inferiority of neoadjuvant chemotherapy. Additionally, the SCORPION trial failed to show superiority with respect to PFS for neoadjuvant chemotherapy. Thus, the Working Group members consider this a weak recommendation.
- The JCOG 0602 [4] trial administered up to eight cycles of paclitaxel and carboplatin in their study arms; however, there is no direct evidence comparing six cycles to more than six cycles of chemotherapy. Despite six cycles of paclitaxel and carboplatin (three before and three after interval debulking surgery) being by and large the standard, the Working Group members will defer to the end users to make their own decision based on individual clinical situation.
- The Working Group members (including two patient representatives) consider the criteria used to determine a high-risk profile both acceptable and feasible in Ontario.

Adjuvant therapy

Recommendation 2 (Strength: Recommendation to use the intervention)

For women with stage II, III, or IV EOC and potentially resectable disease as determined by a gynecologic oncologist, primary cytoreductive surgery, followed by six to eight cycles of i.v. three-weekly paclitaxel (175 mg/m^2 over 3 hours) and carboplatin (AUC=5/6) is recommended.

Qualifying Statements for Recommendation 2

- For those who are unable to tolerate paclitaxel, an alternate regimen consisting of docetaxel (75 mg/m^2) may be offered with carboplatin (AUC=5).
- Adjuvant chemotherapy with six cycles of dose-dense weekly paclitaxel (80 mg/m^2) in combination with three-weekly carboplatin (AUC=6) administered intravenously can be considered for women with stage II, III, or IV EOC of Japanese descent.

Key Evidence for Recommendation 2

Six trials [10-15] compared the efficacy of various platinum-based doublet regimens against standard paclitaxel and carboplatin, while four trials [16-22] compared a dose-dense weekly regimen against a standard three-weekly schedule. The aggregate quality of the evidence was judged to be moderate, based on the GRADE approach [8] (details in **Section 4**).

- In the HeCOG trial [10], paclitaxel plus alternating carboplatin and cisplatin did not significantly improve survival compared with paclitaxel plus carboplatin alone. Grade 3 or 4 nausea and vomiting (p=0.0135) occurred significantly more with paclitaxel plus alternating carboplatin and cisplatin.
- In the MITO-2 trial [11], carboplatin plus pegylated liposomal doxorubicin did not provide significant survival advantage over carboplatin plus paclitaxel and led to more grade 3 or 4 anemia (p=0.0003) and thrombocytopenia (p<0.01) but less neurotoxicity (p=0.0035).
- The SCOTROC 1 trial [12] did not demonstrate a survival advantage for carboplatin plus docetaxel over carboplatin plus paclitaxel. Treatment with carboplatin plus docetaxel was associated with more grade 3 or 4 neutropenia (p<0.01) but the women reported significantly better improvements in symptom scores.
- Paclitaxel plus nedaplatin achieved comparable survival outcomes as paclitaxel plus carboplatin (median follow-up of 47.6 months). The incidence of grade 3 or 4 leukopenia (p=0.0261) was significantly higher in the paclitaxel plus carboplatin regimen. Subgroup analysis showed that stage III to IV women experienced a significantly prolonged PFS (p=0.02) with paclitaxel plus nedaplatin [13].
- In the OV16 trial [14], four cycles of cisplatin plus topotecan followed by four cycles of carboplatin plus paclitaxel was significantly more toxic than eight cycles of carboplatin plus paclitaxel in terms of grade 3 or 4 neutropenia (p<0.01) and thrombocytopenia (p<0.01) and all-grade nausea (p=0.0096) and vomiting (p<0.01), but without improved survival. On the other hand, carboplatin plus paclitaxel was associated with substantially more all-grade neurosensory effects (p=0.0004).
- In a multi-arm trial (GOG 0182-ICON5) [15], two different sequential doublets (carboplatin plus topotecan or gemcitabine followed by carboplatin plus paclitaxel) were evaluated against the standard regimen of carboplatin plus paclitaxel. Both sequential doublets provided no improvements in either PFS or OS.
- In the GOG 0262 trial [16], weekly paclitaxel significantly prolonged PFS (14.2 months versus 10.3 months; HR, 0.62; 95% CI, 0.40 to 0.95, p=0.03). However, women who elected to receive bevacizumab with weekly paclitaxel (84% of women who underwent randomization) did not see a significant improvement in PFS.
- The JGOG 3016 trial [17], which recruited women in Japan, demonstrated that weekly paclitaxel significantly prolonged PFS (28.2 months versus 17.5 months; HR, 0.76; 95% CI, 0.62 to 0.91, p=0.0037) and OS (100.5 months versus 62.2 months; HR, 0.79; 95% CI, 0.63 to 0.99, p=0.039). In particular, women with serous tumours (OS, 100.5 months versus

61.2 months; HR, 0.76; 95% CI, 0.59 to 0.97, p=0.0252; PFS, 28.7 months versus 17.5 months; HR, 0.70; 95% CI, 0.57 to 0.86, p=0.0007), stage III disease with residual >1 cm or stage IV disease (OS, 50.9 months versus 35.0 months; HR, 0.75; 95% CI, 0.58 to 0.98, p=0.0323; PFS, 17.6 months versus 12.1 months; HR, 0.70; 95% CI, 0.56 to 0.89, p=0.0028) benefited considerably with weekly paclitaxel.

- Results from the ICON8 trial [18], which enrolled a predominantly European population, failed to show a significant improvement in PFS with weekly paclitaxel.
- Weekly paclitaxel was associated with higher frequency of grade 3 or 4 anemia [16,18,19]. ICON8 [18] also found higher rates of grade 3 or 4 neutropenia (p<0.01), leukopenia (p<0.01) and thrombocytopenia (p=0.0007) with weekly paclitaxel. For QoL assessment, women who received weekly paclitaxel generally reported lower scores in the Functional Assessment of Cancer Therapy – Taxane subscale (FACT-T) and Functional Assessment of Cancer Therapy - Ovarian Cancer Trial Outcome Index (FACT-O TOI) subscales but overall global QoL scores between the two treatment schedules did not differ significantly [16,20,21].
- Neither the ICON8 [18] nor MITO-7 [22] trials detected a significant improvement in survival for weekly carboplatin plus paclitaxel. Higher rates of grade 3 or 4 neutropenia (p<0.01) and leukopenia (p<0.01) were observed in women who received weekly carboplatin plus paclitaxel in the ICON8 trial [18], while weekly carboplatin plus paclitaxel was associated with less grade 3 or 4 neutropenia (p=0.0216) and leukopenia (p=0.0306) in the MITO-7 trial [22]. In addition, weekly carboplatin plus paclitaxel led to fewer incidences of thrombocytopenia (p<0.01) [22], vomiting (p=0.0238) [18], and neuropathy (p=0.0015) [22]. Patient-reported QoL scores for the FACT-O, FACT-O TOI, FACT/Gynecologic Oncology Group – Neurotoxicity (GOG-Ntx) and Ntx subscales tend to favour the weekly carboplatin plus paclitaxel regimen [21,22].

Justification for Recommendation 2

- The three-weekly regimen consisting of paclitaxel and carboplatin remains the standard of care. For those women who do not tolerate paclitaxel, the Working Group members consider docetaxel as an alternative owing to similar efficacy in terms of PFS while reducing the likelihood of neurotoxicity and improving the level of treatment-related QoL. Docetaxel is also less likely to induce hypersensitivity reactions.
- Although weekly paclitaxel can improve PFS and OS according to JGOG 3016, 36.2% of women discontinued this regimen prematurely due to toxic effects compared with 21.6% in the conventional regimen group. Since the trial enrolled only women living in Japan, there may exist pharmacogenomics differences between the Japanese and non-Japanese populations, which limits the generalizability of these results to the Ontario context. Considering the uncertainty of the evidence and the negative results from ICON8, the Working Group members could not make a recommendation for a dose-dense weekly regimen over a standard three-weekly schedule for the general population.
- In the GOG 0262 trial, the small subset of women (16% in each treatment group) who opted not to receive bevacizumab with weekly paclitaxel saw an improvement in PFS. However, OS was not analyzed while adverse events and QoL scores were not reported separately from those who received bevacizumab. Thus, there is no evidence for the Working Group to support adding bevacizumab into adjuvant therapy.
- Both the OV16 [14] and GOG 0182-ICON5 [15] trials administered up to eight cycles of paclitaxel and carboplatin in their study arms; however, there is no direct evidence comparing six cycles to more than six cycles of adjuvant chemotherapy. Despite six cycles of paclitaxel and carboplatin being by and large the standard, the Working Group members will defer to the end users to make their own decision based on individual clinical situation.

Recommendation 3 (Strength: Recommendation *not* to use the intervention)
The addition of a third chemotherapy agent to standard paclitaxel and carboplatin is not recommended for use as adjuvant therapy in women with stage II, III, or IV EOC.
Key Evidence for Recommendation 3
The efficacy of adding a third chemotherapy agent to a standard paclitaxel and carboplatin regimen was examined in six trials [15,23-27]. The aggregate quality of the evidence was judged to be moderate to high, based on the GRADE approach [8] (details in **Section 4**). • In the GOG 0182-ICON5 trial [15], a triplet combination with carboplatin, paclitaxel, and methoxypolyethylene glycosylated liposomal doxorubicin provided no survival advantage over carboplatin plus paclitaxel alone. • In the HeCOG trial [23], the addition of doxorubicin to cisplatin plus paclitaxel did not increase PFS (18.1 months versus 13.3 months, p=0.07) or OS (44.3 months versus 38.0 months, p=0.53). There were no differences in grade 3 or 4 adverse effects between the two treatment groups, with the exception of neurotoxicity, which was higher in the carboplatin plus paclitaxel regimen (p=0.0293). • In the AGO-OVAR 5 [24] and NSGO-EORTC GCG-NCIC CTG [25] trials, the addition of epirubicin to carboplatin plus paclitaxel did not improve survival and induced significantly more toxicity. Moreover, women who received epirubicin reported significantly worse global QoL scores at the end of treatment (p=0.001) and had significantly smaller improvement from baseline to mean global QoL scores (p=0.0112) [24]. • In both the GOG 0182-ICON5 [15] and AGO-OVAR 9 [26] trials, the addition of gemcitabine to carboplatin plus paclitaxel did not offer any survival benefits. In fact, women who received gemcitabine had a significantly reduced PFS (17.8 months versus 19.3 months; HR, 1.18; 95% CI, 1.06 to 1.32, p=0.0044) and experienced considerably more hematologic toxicities. Global QoL scores were also significantly worse with gemcitabine after three cycles (p=0.0218), but no significant differences were observed after completion of treatment [26]. • The addition of topotecan to a standard carboplatin plus paclitaxel regimen did not result in any advantage in survival at five years and was associated with higher rates of grade 3 or 4 anemia (p=0.0343) and neutropenia (p=0.0016) [27].
Justification for Recommendation 3
• The incorporation of a third chemotherapy drug to paclitaxel and carboplatin has not been shown to improve OS and PFS. Given the absence of a survival benefit along with increased toxicity, the Working Group members recommend not to use platinum-based triplet chemotherapy in women with stage II, III, or IV EOC.

Recommendation 4 (Strength: Recommendation *not* to use the intervention)
The addition of valspodar or interferon gamma 1b to standard paclitaxel and carboplatin is not recommended for use as adjuvant therapy in women with stage III or IV EOC. The incorporation of bevacizumab concurrent with paclitaxel and carboplatin is not recommended for use as adjuvant therapy unless bevacizumab is continued as maintenance therapy in women with stage III or IV EOC.
Qualifying Statement for Recommendation 4
• Concurrent use of i.v. three-weekly bevacizumab (7.5 mg/kg) with paclitaxel and carboplatin for six cycles and continued for up to 12 cycles or until progression as maintenance therapy can be recommended for women with newly diagnosed high-risk

stage III (residual disease >1 cm or inoperable), or stage IV EOC. Refer to **Guideline 4-18** for details.

Key Evidence for Recommendation 4

The efficacy of adding a targeted [28,30-32] or immunotherapy [29] agent to a standard paclitaxel and carboplatin regimen was examined in three trials. The aggregate quality of the evidence was judged to be moderate, based on the GRADE approach [8] (details in **Section 4**).

- The addition of valspodar to carboplatin plus paclitaxel did not improve survival and was significantly more toxic in terms of grade 3 or 4 anemia (p=0.0001), leukopenia (p<0.01), thrombocytopenia (p=0.0103), nausea (p=0.0042), vomiting (p=0.0271), and central and peripheral nervous system effects (p<0.01) [28].
- The addition of interferon gamma 1b (IFN-γ 1b) to standard carboplatin plus paclitaxel regimen was associated with a survival disadvantage and higher rates of grade 3 or 4 neutropenia (p=0.0152) and leukopenia (p=0.0003). The trial was terminated early at second interim analysis which revealed significantly shorter OS (37.4 months versus not estimable; HR, 1.45, 95% CI, 1.15 to 1.83, p=0.0014) for women receiving IFN-γ 1b [29].
- In the GOG 0218 trial [30-32], the addition of bevacizumab to carboplatin plus paclitaxel, followed by 16 cycles of placebo, was associated with a marked increase in grade 3 or 4 neutropenia (p=0.0465) and significantly lower FACT-O TOI scores (p<0.001) during therapy, but without any added benefit in survival.

Justification for Recommendation 4

- The incorporation of valspodar or bevacizumab (without continued treatment as maintenance) to paclitaxel and carboplatin resulted in increased toxicity and no improvement in survival. Hence, the Working Group members do not recommend either agent as adjuvant therapy for women with stage III or IV EOC. However, high-risk women, such as those with sub-optimally debulked stage III disease (residual disease >1 cm), inoperable stage III, or stage IV disease, appeared to benefit the most with the incorporation of bevacizumab concurrent with chemotherapy and continued as maintenance (refer to **Guideline 4-18** for details).
- Treatment with IFN-γ 1b in combination with paclitaxel and carboplatin causes significant harm and the Working Group members do not recommend this regimen as an immunotherapeutic option for women with stage III or IV EOC.

Recommendation 5 (Strength: Weak recommendation to use the intervention)

i.v. paclitaxel (135 mg/m^2 over 24 hours) plus intraperitoneal (i.p.) cisplatin (100 mg/m^2) and paclitaxel (60 mg/m^2) can be considered for stage III optimally debulked women (≤1 cm residual disease) who did not receive neoadjuvant chemotherapy.

i.p. administration of chemotherapy with bevacizumab should not be considered as an option for stage II to IV optimally debulked women (≤1 cm residual disease).

Key Evidence for Recommendation 5

Two trials (GOG 172 and GOG 252) [33-36] compared i.p. chemotherapy versus conventional i.v. chemotherapy. The quality of the evidence was judged to be moderate for both trials, based on the GRADE approach [8] (details in **Section 4**).

- In the GOG 172 trial [33], six cycles of standard i.v. cisplatin plus i.v. paclitaxel was being compared to an intensive regimen of i.v. paclitaxel over a 24-hour period followed by i.p. cisplatin and i.p. paclitaxel for six cycles. Significant improvements in both OS (65.6 months versus 49.7 months; HR, 0.75; 95% CI, 0.58 to 0.97, p=0.03) and PFS (23.8 months versus 18.3 months; HR, 0.80; 95% CI, 0.64 to 1.00, p=0.05) were observed with i.p. chemotherapy.

However, the decreased risk of death associated with i.p. chemotherapy was at the expense of more grade 3 or 4 leukopenia (p=0.0093), thrombocytopenia (p=0.0022) and neuropathy (p=0.0015) as well as worse QoL scores (for physical well-being, p<0.001; functional well-being, p<0.001; ovarian cancer symptoms, p<0.001; abdominal discomfort, p<0.001; and neurotoxicity, p=0.001) before cycle 4 and three to six weeks after treatment [34]. Moreover, the prognostic relevance of BRCA1 expression was examined in a post-hoc analysis. The authors reported that women with aberrant, but not normal BRCA1 expression had increased OS (84.1 months versus 47.7 months, p=0.0002) when treated with i.p. chemotherapy [35].

- The GOG 252 trial [36] compared dose-dense weekly i.v. paclitaxel with i.v. carboplatin (AUC=6) every three weeks (i.v. carboplatin) to two different i.p. chemotherapy regimens consisting of dose-dense weekly i.v. paclitaxel with i.p. carboplatin (AUC=6) every three weeks (i.p. carboplatin) and i.v. paclitaxel over three hours, followed by lowered-dose i.p. cisplatin plus i.p. paclitaxel every three weeks (i.p. cisplatin). Additionally, all women received i.v. bevacizumab every three weeks. Neither i.p. regimen significantly improved survival over the i.v. regimen. While the toxicity profile of i.p. carboplatin was similar to that of i.v. carboplatin, surprisingly, i.p. cisplatin was significantly less toxic in terms of grade 3 or 4 anemia (p=0.0008), neutropenia (p=0.0092), and thrombocytopenia (p<0.01) but not nausea and vomiting (p=0.0005). The patient-reported QoL scores across all subscales during treatment generally favoured the i.v. regimen over the two i.p. regimens.

Justification for Recommendation 5

- Given the results of the GOG 172 trial, the Working Group members determined that the substantial increase in OS and PFS conferred by i.v. paclitaxel plus i.p. cisplatin and paclitaxel outweigh the associated adverse events and lower patient-reported QoL scores.
- In the GOG 252 trial, both regimens consisting of i.p. chemotherapy plus bevacizumab offered no survival benefit and some harms in terms of toxicity and QoL. Thus, the Working Group members would not consider this as an acceptable treatment option.

RELATED GUIDELINES

- 4-18 *Consolidation or maintenance systemic therapy for newly diagnosed stage II, III, or IV epithelial ovary, fallopian tube, or primary peritoneal carcinoma.*
- 17-12 *Indications for hyperthermic intraperitoneal chemotherapy with cytoreductive surgery.*

Note: In 4-18 *Consolidation or maintenance systemic therapy for newly diagnosed stage II, III, or IV epithelial ovary, fallopian tube, or primary peritoneal carcinoma*, two weak recommendations were made for the concurrent use of bevacizumab or veliparib with adjuvant therapy for six cycles and continued use as maintenance therapy based on the available evidence. To date, the evidence is not consistent for bevacizumab to be considered as adjuvant therapy and as an option for maintenance treatments. Please refer to 4-18 for guidance on maintenance therapy. Future research is required to confirm whether bevacizumab or veliparib should be taken with adjuvant therapy.

FURTHER RESEARCH

Future high-quality randomized controlled trials (RCTs) are required to explore novel agents with or without chemotherapy as neoadjuvant and adjuvant treatments. Other RCTs that investigate the role of i.p. therapy and dose-dense weekly regimen in the neoadjuvant setting are also needed as well as the potential benefit of i.p. therapy after neoadjuvant chemotherapy. These studies could also provide treatment guidance for different histological types or molecular subsets in the target population.

GUIDELINE LIMITATIONS

The cost-effectiveness analysis is beyond the scope of the PEBC guideline. The Working Group will defer resource considerations to other decision makers.

Neoadjuvant and adjuvant 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 1), 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 1, 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 [37,38]. 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 [39] 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 at least one 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 "Ovarian Cancer": National Institute for Health and Care Excellence Evidence Search, Canadian Medical Association Journal Infobase, Scottish Intercollegiate Guidelines Network, American Society of Clinical Oncology, National Health and Medical Research Council – Australia Clinical Practice Guidelines Portal, and Cancer Council Australia – Cancer Guidelines Wiki. No guidelines were considered suitable for endorsement or adaptation.

GUIDELINE REVIEW AND APPROVAL

Internal Review

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

External Review

Feedback on the approved draft guideline is obtained from content experts and the target users through two processes. Through the Targeted Peer Review, several individuals with content expertise are identified by the GDG and asked to review and provide feedback on the guideline document. Through Professional Consultation, relevant care providers and other potential users of the guideline are contacted and asked to provide feedback on the guideline recommendations through a brief online survey.

DISSEMINATION AND IMPLEMENTATION

The guideline will be published on the OH (CCO) website and may 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), and the Guidelines International Network (GIN) Library.

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- Sara Miller for copy editing.

Neoadjuvant and adjuvant 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 the fifth leading cause of cancer death among women, accounting for 4.9% of all female cancer deaths in Canada. In Ontario, 1300 women (15.4 cases per 100,000) are expected to be diagnosed with ovarian cancer in 2020, of which 710 women (7.9 cases per 100,000) would die from the disease [40]. As nearly 75% of cases are diagnosed with advanced stage disease (International Federation of Gynecology and Obstetrics [FIGO] IIIC or IV) at presentation [41], ovarian cancer has the lowest survival rates of all the major gynecological cancers, with five-year and 10-year survival rates of 45% and 36%, respectively [42].

Currently, primary cytoreductive surgery followed by a combination of taxane and platinum-based chemotherapy is considered as the mainstay of first-line treatment for advanced epithelial ovarian cancer [43]. While the aim of surgery is to achieve optimal debulking of all macroscopic visible disease, many women will present with bulky residual tumour after surgery. An alternative approach to primary cytoreductive surgery is neoadjuvant chemotherapy with delayed surgery. However, evidence demonstrating increased rate of optimal debulking and reduction of surgery-related complications with this strategy remains controversial [44,45]. Selection of women for neoadjuvant chemotherapy or upfront debulking surgery is thus still up for debate. Furthermore, various administration schedules of chemotherapy have included i.p. delivery and dose-dense regimens. Given that the peritoneal cavity serves as the principal site of spread and relapse in most cases of advanced stage disease, i.p. therapy would enable the direct delivery of higher drug concentrations to the tumour while minimizing exposure to normal tissues such as the bone marrow. To date, i.p. therapy has not been widely adopted by clinicians due to higher cost and toxicity, and the unfamiliarity of catheter-placement techniques [33]. Additionally, there is a lack of guidance on the identification of women who may not tolerate or benefit from i.p. therapy.

Accordingly, the purpose of this systematic review is to develop an evidentiary base to inform recommendations as part of a clinical practice guideline on first-line systemic therapy options for newly diagnosed stage II, III or IV EOC. International prospective register of systematic reviews (PROSPERO) registration: CRD42017077773.

RESEARCH QUESTIONS

What is the most effective regimen to administer systemic therapy for women with newly diagnosed stage II, III, or IV EOC?

- What is the optimal regimen (dose/schedule/frequency) for women who will receive neoadjuvant therapy before interval cytoreduction?
- What is the optimal regimen (dose/schedule/frequency) for women who will receive adjuvant therapy after primary cytoreduction?
- What is the optimal regimen (dose/schedule/frequency) and most effective mode of administration (i.v. versus i.p.) for optimally debulked women (<1 cm residual disease) who will receive adjuvant therapy?

- Do women with *BRCA* mutation receiving neoadjuvant or adjuvant therapy have different optimal regimen (dose/schedule/frequency) and outcomes compared with women without *BRCA* mutation?
- Do women with different histological subtypes (low-grade serous, endometrioid, clear cell, mucinous, undifferentiated/unclassifiable), location subtypes, residues after cytoreduction, or stages receiving neoadjuvant or adjuvant therapy have different optimal regimen (dose/schedule/frequency) and outcomes?

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 for systematic reviews from January 2003 to October 3, 2019 was carried out using the electronic databases MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and PROSPERO. See Appendix 2 for the search strategies.

Search for Primary Literature

Literature Search Strategy

The primary literature was searched using the electronic databases MEDLINE, EMBASE, and Cochrane Library from January 2003 to October 3, 2019. Details of the literature search can be found in Appendix 2. In addition, conference proceedings of the American Society of Clinical Oncology, Society of Gynecologic Oncology, European Society Gynecologic Oncology, and European Society for Medical Oncology were searched from 2017 to 2019 for relevant abstracts. Full publications of included abstracts were searched up to October 2020 via PubMed. Reference lists from related systematic reviews and primary literature were scanned for potentially useful studies.

Study Selection Criteria and Process

Inclusion Criteria

1. Published as a full-text article or as a conference abstract.
2. Phase III RCT with a minimum sample size of 30 in each trial arm.
3. Included adult women with newly diagnosed stage II, III, or IV EOC.
4. Included chemotherapy, targeted therapy, immunotherapy, or hormonal therapy in the neoadjuvant or adjuvant setting.
5. Reported on at least one of the following outcomes: OS, PFS, incidence of grade ≥3 adverse events, and patient-reported outcomes.

Exclusion Criteria

1. Published in a language other than English.
2. Studies that recruited >20% recurrent (including relapsed, drug-sensitive, drug-resistant, drug-persistent, and drug refractory), inoperable, or stage I patients but did not have a subgroup analysis for patients with newly diagnosed stage II to IV disease.
3. Studies that investigated the role of hyperthermic intraperitoneal chemotherapy with cytoreductive surgery. This therapy has been reviewed in a separate guidance document (see **Related Guidelines)**.

A review of the titles and abstracts was conducted by one reviewer. For studies that warranted full-text review, two reviewers evaluated each study in collaboration, of which a consensus for final inclusion was reached after discussing with other Working Group members.

Data Extraction and Assessment of Risk of Bias

All included primary studies underwent data extraction by one reviewer. For each study, the principal author, publication year, country of origin, number of patients, age, treatment regimen, FIGO stage, tumour histology, residual disease, toxicity, survival, and patient-reported outcomes were recorded. For recommendation development, the critical outcomes are OS and PFS while the important ones are adverse events and patient-reported outcomes. Furthermore, only the following adverse events associated with systemic therapy were considered: treatment-related death, anemia, neutropenia/leukopenia, thrombocytopenia, nausea, vomiting, and neuropathy. All extracted data and information were audited by an independent auditor for accuracy and completeness. The Cochrane Collaboration's tool for randomized studies was used to assess risk of bias for each critical and important outcome [46].

Synthesizing the Evidence

Statistical analyses were performed with STATA version 15.1 [47] using the prtesti command for two-sample test of proportions. A p-value <0.05 was considered significantly different between two proportions. Due to clinical heterogeneity among the studies, a meta-analysis was deemed inappropriate. Instead, results from each study were presented individually in a descriptive fashion. An HR <1.0 indicates a lower probability of an event for the experimental intervention and a HR >1.0 indicates a lower probability of an event for the control intervention.

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 using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach [8].

RESULTS

Search for Systematic Reviews

The search for existing systematic reviews identified a number of publications that were considered relevant to the research questions. However, none of these systematic reviews included all the options for systemic therapy and therefore were not used as part of the evidence base.

Search for Primary Literature

Literature Search Results

A search for primary literature yielded a total of 10,890 unique citations, of which 10,663 were excluded after a review of titles and abstracts. Two hundred twenty-seven were considered as candidates, but upon full-text review, 180 did not meet the inclusion criteria. The remaining 47 full-text publications were included in this systematic review. For one trial (GOG 0218), which had three publications [30-32], data were abstracted for the control therapy versus the bevacizumab-concurrent therapy comparison only. In total, 33 trials from 47 full-text publications [1-7,9-36,48-58] formed the evidentiary basis for the guideline recommendations. See Appendix 3 for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram. Details of the study characteristics are presented in

Table 4-1. Survival outcomes are presented in Table 4-2. Adverse events and patient-reported outcomes are presented in Table 4-3. See Appendix 5 for subgroup analysis results.

Risk of Bias Assessment

The 33 trials were assessed according to the six domains of Cochrane Collaboration's Risk of Bias [46] (Appendix 6). All trials were judged to have low concerns regarding attrition bias and reporting bias. For the domain relating to selection bias, there was insufficient information about the sequence generation process to permit a judgement on risk in four trials [10,12,25,27]. Similarly, 18 trials [1,2,10,12,14-16,23-29,33-35,48,52-55] did not include further description of the method used for allocation concealment. Unclear risk of bias may be a consequence of incomplete reporting; however, it is uncertain whether this would have a notable effect on the results or conclusion of the trials. For the domains relating to performance bias and detection bias, a large majority of the trials [1-7,11,13-23,25-29,33-36,51,53-58] were designed as open label studies and therefore the blinding of participants, researchers, and outcome assessment was not intended. Overall, the risk of bias was judged to be moderate for all four trials [1-7] comparing neoadjuvant chemotherapy to primary surgery, for all four dose intensification trials [54-57], for all five trials [16-22,58] comparing a dose-dense weekly regimen to a standard three-weekly schedule, for both trials [33-36] comparing intraperitoneal chemotherapy to conventional intravenous chemotherapy, for both targeted therapy trials [28,30-32], and for the one immunotherapy trial [29]. With respect to the trials comparing different adjuvant chemotherapy regimens, the overall risk of bias was judged as high for two trials [25,27], moderate for 10 trials [10-15,23,26,49-51,53], and low for three trials [24,48,52]. According to the GRADE criteria [8], the overall results across the neoadjuvant trials are direct and there is no suspicion of relevant publication bias. Similarly, assessment for indirectness and publication bias was low across all the adjuvant trials. However, there are problems with precision due to the lack of blinding as well as inconsistency where several trials comparing various chemotherapy treatment schedules and routes of administration reported discordant treatment effects. Taken as a whole, the aggregate quality of the evidence was rated as low to moderate.

Table 4-1. Trials Selected for Inclusion

Study, year (trial)	Country	No. of pts	Med age	Treatment regimen	FIGO stage (%)	Histology (%)	Residual disease (%)
Neoadjuvant chemotherapy							
Vergote, 2010 [1]; Greimel, 2013 [2] (EORTC 55971)	Belgium, Canada, UK, Netherlands, Norway, Spain, Italy	334	63	3 cycles before and at least 3 cycles after interval debulking surgery of paclitaxel (175 mg/m^2) i.v. + carboplatin (AUC=6) i.v., or cisplatin (75 mg/m^2) i.v. or carboplatin (AUC≥5) i.v., administered every 3 weeks	IIIC: 75.7 IV: 24.3	Serous: 58.1 Mucinous: 3.3 Clear-cell: 1.2 Endometrioid: 1.5 Undifferentiated: 26.9 Other/unkn: 9.0	0cm: 51.2 0.1-1cm: 29.5 1.1-2cm: 5.8 >2cm: 11.9 Unkn: 1.6
		336	62	Primary debulking surgery followed by at least 6 cycles of paclitaxel (175 mg/m^2) i.v. + carboplatin (AUC=6) i.v., or cisplatin (75 mg/m^2) i.v., or carboplatin (AUC≥5) i.v., administered every 3 weeks. Interval debulking surgery was permitted if stable disease or a response was documented without optimal cytoreduction.	IIIC: 76.5 IV: 22.9	Serous: 65.5 Mucinous: 2.4 Clear-cell: 1.8 Endometrioid: 3.3 Undifferentiated: 20.5 Other/unkn: 6.5	0cm: 19.4 0.1-1cm: 22.2 1.1-2cm: 11.7 >2cm: 41.3 Unkn: 5.4
Kehoe, 2015 [3] (CHORUS)	UK, New Zealand	274	65	3 cycles before and 3 cycles after interval debulking surgery of paclitaxel (175 mg/m^2) i.v. + carboplatin (AUC=5/6) i.v., or carboplatin (AUC=5/6) i.v., administered every 3 weeks	III: 75.2 IV: 24.8	n=219 Serous: 84.5 Mucinous: 1.8 Clear-cell: 5.9 Endometrioid: 2.3 Other/unkn: 5.5	n=219 0cm: 36.1 ≤1cm: 31.1 >1cm: 24.7 Unkn: 8.1
		276	66	Primary debulking surgery followed by 6 cycles of paclitaxel (175 mg/m^2) i.v. + carboplatin (AUC=5/6) i.v., or carboplatin (AUC=5/6) i.v., administered every 3 weeks. Interval debulking surgery after three cycles of chemotherapy was permitted for residual tumours >1cm	III: 74.6 IV: 25.4	n=255 Serous: 85.9 Mucinous: 0.8 Clear-cell: 1.6 Endometrioid: 4.3 Other/unkn: 7.4	n=255 0cm: 15.3 ≤1cm: 22.4 >1cm: 53.7 Unkn: 8.6

Study, year (trial)	Country	No. of pts	Med age	Treatment regimen	FIGO stage (%)	Histology (%)	Residual disease (%)
Onda, 2020 [4]; Onda , 2016 [5] (JCOG 0602)	Japan	152	60.5	4 cycles before and 4 cycles after interval debulking surgery of paclitaxel (175 mg/m^2) i.v. + carboplatin (AUC=6) i.v., administered every 3 weeks	III: 69.1 IV: 30.9	n=130 Serous: 78.5 Mucinous: 1.5 Clear-cell: 3.1 Endometrioid: 3.1 Other: 13.8	n=130 0cm: 63.8 <1cm: 18.5 ≥1cm: 17.7
		149	59	Primary debulking surgery followed by 8 cycles of paclitaxel (175 mg/m^2) i.v. + carboplatin (AUC=6) i.v., administered every 3 weeks. Interval debulking surgery after the forth cycle of chemotherapy was permitted for residual tumours >1cm	III: 67.1 IV: 32.9	n=147 Serous: 78.2 Mucinous: 1.4 Clear-cell: 8.2 Endometrioid: 4.1 Other: 8.1	n=147 0cm: 30.6 <1cm: 32.0 ≥1cm: 37.4
Fagotti, 2020 [6]; Fagotti, 2016 [7] (SCORPION)	Italy	87	56.2 *	3 cycles before and 3 cycles after interval debulking surgery of paclitaxel (175 mg/m^2) i.v. + carboplatin (AUC=5) i.v. ± bevacizumab i.v., administered every 3 weeks	IIIC: 90.8 IV: 9.2	Serous: 100	n=74 0cm: 77.0 0.1-1cm: 21.6 >1cm: 1.4
		84	54.8 *	Primary debulking surgery followed by 6 cycles of paclitaxel (175 mg/m^2) i.v. + carboplatin (AUC=5) i.v. ± bevacizumab i.v., administered every 3 weeks. A secondary cytoreductive effort was not allowed in women left with gross residual tumour.	IIIC: 84.5 IV: 15.5	Serous: 97.6 Clear-cell: 1.2 Other: 1.2	0cm: 47.6 0.1-1cm: 45.2 >1cm: 7.2
Adjuvant chemotherapy ***Platinum-based doublet*** *Cisplatin versus carboplatin*							
Ozols, 2003 [48] (GOG 158)	US	392	NR	6 cycles of paclitaxel (175 mg/m^2) i.v. over 3 hours + carboplatin	III: 100.0	Serous: 74.0 Mucinous: 2.3 Clear-cell: 5.4	0cm/micro: 34.9 ≤1cm: 65.1

Study, year (trial)	Country	No. of pts	Med age	Treatment regimen	FIGO stage (%)	Histology (%)	Residual disease (%)
				(AUC=7.5) i.v., administered every 3 weeks		Endometrioid: 8.9 Other: 9.4	
		400		6 cycles of paclitaxel (135 mg/m^2) i.v. over 24 hours + cisplatin (75 mg/m^2) i.v. at 1 mg/min, administered every 3 weeks	III: 100.0	Serous: 70.3 Mucinous: 2.5 Clear-cell: 2.5 Endometrioid: 11.2 Other: 13.5	0cm/micro: 36.0 ≤1cm: 64.0
Greimel, 2006 [49]; du Bois, 2003 [50] (AGO-OVAR 3)	Germany	397	56.7 *	6 cycles of paclitaxel (185 mg/m^2) i.v. over 3 hours + carboplatin (AUC=6) i.v. over 30-60 minutes, administered every 3 weeks	IIB-C: 9.3 IIIA-C: 72.6 IV: 18.1	Serous/papillary: 70.8 Other: 29.2	≤1cm: 59.5 >1cm: 40.5
		386	57.7 *	6 cycles of paclitaxel (185 mg/m^2) i.v. over 3 hours + cisplatin (75 mg/m^2) i.v. over 30 minutes, administered every 3 weeks	IIB-C: 7.5 IIIA-C: 76.4 IV: 16.1	Serous/papillary: 69.9 Other: 30.1	≤1cm: 65.9 >1cm: 34.1
Cisplatin and carboplatin							
Dittrich, 2003 [51]	Austria	124	56	6 cycles of carboplatin (300 mg/m^2) i.v. + cisplatin (100 mg/m^2) i.v. on day 2, administered every 4 weeks	IC: 8.9 II: 12.1 III: 66.9 IV: 12.1	Serous: 71.8 Mucinous: 4.0 Clear-cell: 4.0 Endometrioid: 8.9 Other: 11.3	0cm: 37.1 <2cm: 26.6 2-5cm: 11.3 >5cm: 25.0
		123	55	6 cycles of cyclophosphamide (600 mg/m^2) i.v. over 1 hour + cisplatin (100 mg/m^2) i.v. on day 2, administered every 4 weeks	IC: 9.0 II: 8.9 III: 69.9 IV: 12.2	Serous: 78.1 Mucinous: 4.1 Clear-cell: 1.6 Endometrioid: 7.3 Other: 8.9	0cm: 33.3 <2cm: 27.7 2-5cm: 13.8 >5cm: 25.2
Aravantinos, 2005 [10] (HeCOG)	Greece	126	63	6 cycles of paclitaxel (175 mg/m^2) i.v. over 3 hours + carboplatin (AUC=7) i.v. over 1 hour on cycles 1, 3 and 5 + cisplatin (75 mg/m^2) i.v. over 2 hours on cycles 2, 4 and 6, administered every 3 weeks	IIC: 10.3 III: 73.0 IV: 16.7	Serous: 70.6 Mucinous: 7.2 Clear-cell: 3.2 Endometroid: 8.7 Undifferentiated: 2.4 Other/unkn: 7.9	No: 23.0 Yes: 77.0

Study, year (trial)	Country	No. of pts	Med age	Treatment regimen	FIGO stage (%)	Histology (%)	Residual disease (%)
		121	61	6 cycles of paclitaxel (175 mg/m^2) i.v. over 3 hours + carboplatin (AUC=7) i.v. over 1 hour, administered every 3 weeks	IIC: 7.4 III: 73.6 IV: 19.0	Serous: 67.0 Mucinous: 7.4 Clear-cell: 3.3 Endometroid: 6.6 Undifferentiated: 7.4 Other/unkn: 8.3	No: 20.7 Yes: 79.3
Anthracyclines							
Pignata, 2011 [11] (MITO-2)	Italy	410	57	6 cycles of carboplatin (AUC=5) i.v. over 30 minutes + pegylated liposomal doxorubicin (30 mg/m^2) i.v. over 1 hour, administered every 3 weeks	IC: 9.0 II: 9.5 III: 60.5 IV: 21.0	Serous: 66.1 Mucinous: 3.2 Clear-cell: 2.9 Endometrioid: 11.7 Undifferentiated: 7.1 Other/unkn: 9.0	0cm: 36.6 ≤1cm: 19.2 >1cm: 27.1 No debulking: 17.1
		410	57	6 cycles of paclitaxel (175 mg/m^2) i.v. over 3 hours + carboplatin (AUC=5) i.v. over 30 minutes, administered every 3 weeks	IC: 9.0 II: 9.7 III: 59.8 IV: 21.5	Serous: 63.2 Mucinous: 2.9 Clear-cell: 3.6 Endometrioid: 12.2 Undifferentiated: 7.6 Other/unkn: 10.5	0cm: 36.1 ≤1cm: 17.1 >1cm: 28.3 No debulking: 18.5
Taxanes							
Mouratidou, 2007 [52]	Greece	60	57	6 cycles of paclitaxel (175 mg/m^2) i.v. over 3 hours + cisplatin (75 mg/m^2) i.v. at rate of 1 mg/min, administered every 3 weeks	IIB-C: 23.3 III:30.0 IV: 46.7	Serous: 61.6 Mucinous: 10.0 Clear-cell: 3.4 Endometrioid: 18.4 Other: 6.6	NR
		60	59	6 cycles of cyclophosphamide (700 mg/m^2) i.v. + cisplatin (75 mg/m^2) i.v. at rate of 1 mg/min, administered every 3 weeks	IIB-C: 25.0 III: 28.3 IV: 46.7	Serous: 65.0 Mucinous: 8.4 Clear-cell: 1.6 Endometrioid: 16.6 Other: 8.4	
Vasey, 2004 [12]	UK, Greece, Switzerland, Finland,	539	59	6 cycles of docetaxel (75 mg/m^2) i.v. over 1 hour + carboplatin	IC-II: 19.0 III-IV: 81.0	Serous/papillary: 44.0 Mucinous: 4.0 Clear-cell: 5.0	0cm/micro: 33.0 ≤2cm: 30.0

Study, year (trial)	Country	No. of pts	Med age	Treatment regimen	FIGO stage (%)	Histology (%)	Residual disease (%)
(SCOTROC 1)	Poland, Austria, US, Australia, New Zealand			(AUC=5) i.v. over 1 hour, administered every 3 weeks		Endometrioid: 12.0 Other/unkn: 35.0	>2cm: 37.0
		538	59	6 cycles of paclitaxel (175 mg/m^2) i.v. over 3 hours + carboplatin (AUC=5) i.v. over 1 hour, administered every 3 weeks	IC-II: 20.0 III-IV: 80.0	Serous/papillary: 44.0 Mucinous: 2.0 Clear-cell: 4.0 Endometrioid: 10.0 Other/unkn: 40.0	0cm/micro: 33.0 ≤2cm: 30.0 >2cm: 37.0
Second-generation platinum							
Li, 2018 [13]	China	92	50.8 *	6 cycles of paclitaxel (175 mg/m^2) i.v. for at least 3 hours + nedaplatin (80 mg/m^2) i.v. over 2 hours, administered every 3 weeks	II: 30.8 III: 57.1 IV: 12.1	Serous: 62.6 Mucinous: 7.7 Clear-cell: 7.7 Endometrioid: 7.7 Other: 14.3	NR
		90	50.8 *	6 cycles of paclitaxel (175 mg/m^2) i.v. for at least 3 hours + carboplatin (AUC=5) i.v. over 2 hours, administered every 3 weeks	II: 21.1 III: 74.5 IV: 4.4	Serous: 65.2 Mucinous: 4.5 Clear-cell: 3.4 Endometrioid: 12.3 Other: 14.6	
Sequential doublet							
Hoskins, 2010 [14]; Brotto, 2016 [53] (OV16)	Canada, Belgium, Portugal, Austria, Italy, Spain, UK	409	57	4 cycles of cisplatin (50 mg/m^2) i.v. over 1 hour + topotecan (0.75 mg/m^2) i.v. over 30 minutes on days 1-5, followed by 4 cycles of paclitaxel (175 mg/m^2) i.v. over 3 hours + carboplatin (AUC=5) i.v. over 30 minutes, administered every 3 weeks	IIA-C: 9.1 IIIA-C: 67.2 IV: 23.7	Serous: 64.8 Mucinous: 2.2 Clear-cell: 5.9 Endometrioid: 6.8 Other/unkn: 20.3	0cm/micro: 22.0 <1cm: 24.9 ≥1cm: 33.0 No debulking/ Unkn: 20.1
		410	57	8 cycles of paclitaxel (175 mg/m^2) i.v. over 3 hours + carboplatin (AUC=5) i.v. over 30 minutes, administered every 3 weeks	IIA-C: 8.1 IIIA-C: 64.6 IV: 27.3	Serous: 68.3 Mucinous: 2.4 Clear-cell: 4.9 Endometrioid: 5.4 Other/unkn: 19.0	0cm/micro: 22.4 <1cm: 20.3 ≥1cm: 36.3 No debulking/ Unkn: 21.0

Study, year (trial)	Country	No. of pts	Med age	Treatment regimen	FIGO stage (%)	Histology (%)	Residual disease (%)
Platinum-based triplet *Anthracyclines*							
Aravantinos, 2008 [23] (HeCOG)	Greece	228	59	6 cycles of doxorubicin (40 mg/m^2) i.v. bolus + paclitaxel (175 mg/m^2) i.v. over 3 hours + cisplatin (75 mg/m^2) i.v., administered every 3 weeks	IIC: 7.0 III: 71.1 IV: 21.9	Serous: 65.8 Mucinous: 5.3 Clear-cell: 2.6 Endometrioid: 7.0 Other: 19.3	<2cm: 39.5 ≥2cm: 60.5
		223	60	6 cycles of paclitaxel (175 mg/m^2) i.v. over 3 hours + carboplatin (AUC=7) i.v., administered every 3 weeks	IIC: 8.5 III: 67.7 IV: 23.8	Serous: 69.5 Mucinous: 5.4 Clear-cell: 1.3 Endometrioid: 13.0 Other: 10.8	<2cm: 43.0 ≥2cm: 57.0
du Bois, 2006 [24] (AGO-OVAR 5)	Germany, France	647	60	6 cycles of paclitaxel (175 mg/m^2) i.v. over 3 hours + carboplatin (AUC=5) i.v. over 30-60 minutes + epirubicin (60 mg/m^2) i.v. over 30 minutes, administered every 3 weeks	IB: 0.0 IIB-C: 9.6 IIIA-C: 73.7 IV: 16.2 Unkn: 0.5	Serous/papillary: 73.6 Mucinous: 5.7 Endometrioid: 8.5 Other/unkn: 12.2	≤1cm: 59.5 >1cm: 28.7 Unkn: 11.8
		635	58	6 cycles of paclitaxel (175 mg/m^2) i.v. over 3 hours + carboplatin (AUC=5) i.v. over 30-60 minutes, administered every 3 weeks	IB: 0.1 IIB-C: 9.0 IIIA-C: 72.1 IV: 18.3 Unkn: 0.5	Serous/papillary: 72.6 Mucinous: 4.1 Endometrioid: 8.8 Other/unkn: 14.5	≤1cm: 61.1 >1cm: 27.1 Unkn: 11.8
Lindemann, 2012 [25] (NSGO-EORTC GCG-NCIC CTG)	France, Netherlands, Portugal, Italy, Spain, Norway, Denmark, Belgium, Canada, Sweden, UK, Croatia	445	57	6 to 9 cycles of epirubicin (75 mg/m^2) i.v. + paclitaxel (175 mg/m^2) i.v. over 3 hours + carboplatin (AUC=5) i.v. over 1 hour, administered every 3 weeks	IIB-C: 11.9 IIIA-C: 70.8 IV: 17.3	Serous: 68.1 Mucinous: 3.8 Clear-cell: 4.0 Endometrioid: 11.9 Undifferentiated: 1.8 Other/unkn: 10.4	<1cm: 39.8 ≥1cm: 60.2
		442	58	6 to 9 cycles of paclitaxel (175 mg/m^2) i.v. over 3 hours + carboplatin (AUC=5) i.v. over 1 hour, administered every 3 weeks	IIB-C: 12.2 IIIA-C: 73.5 IV: 14.3	Serous: 65.4 Mucinous: 3.6 Clear-cell: 4.3 Endometrioid: 12.0	<1cm: 41.9 ≥1cm: 58.1

Study, year (trial)	Country	No. of pts	Med age	Treatment regimen	FIGO stage (%)	Histology (%)	Residual disease (%)
						Undifferentiated: 3.2 Other/unkn: 11.5	
Gemcitabine							
du Bois, 2010 [26] (AGO-OVAR 9)	Germany, Denmark, France, Norway, Sweden, Serbia	860	59	6 cycles of paclitaxel (175 mg/m^2) i.v. over 3 hours + carboplatin (AUC=5) i.v. over 30-60 minutes + gemcitabine (800 mg/m^2) i.v. over 30-60 minutes on days 1 and 8, administered every 3 weeks	IA-C: 8.2 IIA-C: 10.1 IIIA-C: 65.3 IV: 16.3 Unkn: 0.1	Serous/papillary: 75.1 Mucinous/clear-cell: 4.7 Other: 20.2	≤1cm: 63.0 >1cm: 28.0 Unkn: 9.0
		882	60	6 cycles of paclitaxel (175 mg/m^2) i.v. over 3 hours + carboplatin (AUC=5) i.v. over 30-60 minutes, administered every 3 weeks	IA-C: 8.6 IIA-C: 9.4 IIIA-C: 65.8 IV: 16.2 Unkn: 0.0	Serous/papillary: 73.7 Mucinous/clear-cell: 4.5 Other: 21.8	≤1cm: 64.5 >1cm: 26.5 Unkn: 9.0
Topotecan							
Bolis, 2010 [27]	Italy	156	58.7 *	6 cycles of topotecan (1.0 mg/m^2) i.v. over 30 minutes on days 1-3 + paclitaxel (175 mg/m^2) i.v. over 3 hours on day 3 + carboplatin (AUC=5) i.v. over 30 minutes on day 3, administered every 3 weeks	III: 78.9 IV: 20.5 Unkn: 0.6	Serous: 75.0 Mucinous: 0.0 Clear-cell: 5.1 Endometrioid: 1.9 Undifferentiated: 12.2 Other/unkn: 5.8	≥1 to ≤2cm: 12.2 >2 to ≤5cm: 14.1 >5 to ≤10cm: 7.1 >10cm: 3.2 Unkn: 58.3 No debulking: 5.1
		170	57.4 *	6 cycles of paclitaxel (175 mg/m^2) i.v. over 3 hours + carboplatin (AUC=5) i.v. over 30 minutes, administered every 3 weeks	III: 75.9 IV: 24.1 Unkn: 0.0	Serous: 68.2 Mucinous: 2.4 Clear-cell: 6.5 Endometrioid: 9.4 Undifferentiated: 7.6 Other/unkn: 5.9	≥1 to ≤2cm: 11.8 >2 to ≤5cm: 14.1 >5 to ≤10cm: 8.2 >10cm: 3.5 Unkn: 60.0

Study, year (trial)	Country	No. of pts	Med age	Treatment regimen	FIGO stage (%)	Histology (%)	Residual disease (%)
							No debulking: 2.4
Platinum-based doublet/triplet							
Bookman, 2009 [15] (GOG 0182-ICON5)	US, UK, Italy, Australia,	861	58.5	4 cycles of topotecan (1.25 mg/m^2) i.v. on days 1-3 + carboplatin (AUC=5) i.v. on day 3, followed by 4 cycles of paclitaxel (175 mg/m^2) i.v. over 3 hours + carboplatin (AUC=6) i.v., administered every 3 weeks	III: 86.4 IV: 13.6	NR	NR
		861	59.3	4 cycles of gemcitabine (1.0 mg/m^2) i.v. on days 1 and 8 + carboplatin (AUC=6) i.v. on day 8, followed by 4 cycles of paclitaxel (175 mg/m^2) i.v. over 3 hours + carboplatin (AUC=6) i.v., administered every 3 weeks	III: 83.7 IV: 16.3		
		862	59.5	8 cycles of paclitaxel (175 mg/m^2) i.v. over 3 hours + carboplatin (AUC=5) i.v., administered every 3 weeks + alternating cycles of methoxypolyethylene glycosylated liposomal doxorubicin (30 mg/m^2) i.v., administered every 6 weeks	III: 86.2 IV: 13.8		
		864	59.1	8 cycles of gemcitabine (800 mg/m^2) i.v. over 30 minutes on days 1 and 8 + paclitaxel (175 mg/m^2) i.v. over 3 hours + carboplatin (AUC=5) i.v., administered every 3 weeks	III: 86.7 IV: 13.3		
		864	57.7	8 cycles of paclitaxel (175 mg/m^2) i.v. over 3 hours + carboplatin (AUC=6) i.v., administered every 3 weeks	III: 83.8 IV: 16.2		
Dose intensification							

Study, year (trial)	Country	No. of pts	Med age	Treatment regimen	FIGO stage (%)	Histology (%)	Residual disease (%)
Ray-Coquard, 2007 [54] (GINECO)	France	79	59	6 cycles of cyclophosphamide (1800 mg/m^2) i.v. over 30 minutes + epirubicin (50 mg/m^2) i.v. bolus + cisplatin (75 mg/m^2) i.v. over 30 minutes + filgrastim (5 µg/kg) per day s.c. on days 2-11, administered every 3 weeks	IIIA-C: 81.0 IV: 19.0	Serous: 67.1 Endometrioid: 7.6 Other: 25.3	Micro: 10.1 <2cm: 31.7 ≥2cm: 58.2
		85	60	6 cycles of cyclophosphamide (500 mg/m^2) i.v. over 30 minutes + epirubicin (50 mg/m^2) i.v. bolus + cisplatin (75 mg/m^2) i.v. over 30 minutes, administered every 3 weeks	IIIA-C: 77.6 IV: 22.4	Serous: 69.4 Endometrioid: 11.8 Other: 18.8	Micro: 14.1 <2cm: 30.6 ≥2cm: 55.3
Mobus, 2007 [55] (HIDOC-EIS)	Germany, Italy, UK, Austria, Switzerland, Spain, Slovakia, Belgium, Czech Republic	78	48.8 *	2 cycles of paclitaxel (200-250 mg/m^2) i.v. + cyclophosphamide (3 g/m^2) i.v. induction therapy with PBSC harvest after the first and/or second cycle, administered every 2 weeks, followed by 3 cycles of paclitaxel (200-250 mg/m^2) i.v. over 3-24 hours + carboplatin (AUC=20) i.v. on day 2 + melphalan (140 mg/m^2) i.v. over 20 minutes on day 2 in the third cycle, administered every 3 weeks	IIB: 5.1 IIIA-C: 79.5 IV: 15.4	Serous: 62.8 Mucinous: 3.8 Clear-cell: 0.0 Endometrioid: 10.3 Other/unkn: 23.1	0cm: 38.5 1 to <2cm: 48.7 ≥2cm: 11.5 unkn: 1.3
		71	49.1 *	6 cycles of paclitaxel (175 mg/m^2) i.v. over 3 hours + carboplatin (AUC=5) i.v. over 3 hours ± epirubicin (60 mg/m^2) i.v. or 4 cycles of topotecan (1.25 mg/m^2) i.v. on days 1-5, administered every 3 weeks	IIB: 2.8 IIIA-C: 81.7 IV: 15.5	Serous: 69.0 Mucinous: 0.0 Clear-cell: 1.4 Endometrioid: 14.1 Other/unkn: 15.5	0cm: 32.4 1 to <2cm: 54.9 ≥2cm: 11.3 unkn: 1.4

Study, year (trial)	Country	No. of pts	Med age	Treatment regimen	FIGO stage (%)	Histology (%)	Residual disease (%)
Spriggs, 2007 [56]	US	140	60.2	6 cycles of paclitaxel (120 mg/m^2) i.v. over 96 hours + cisplatin (75 mg/m^2) i.v. on day 5, administered every 3 weeks	III: 17.1 IV: 82.9	Serous: 77.2 Mucinous: 0.0 Clear-cell: 4.3 Endometrioid: 6.4 Undifferentiated: 2.1 Other/unkn: 10.0	NR
		140	58.3	6 cycles of paclitaxel (135 mg/m^2) i.v. over 24 hours + cisplatin (75 mg/m^2) i.v. on day 5, administered every 3 weeks	III: 15.0 IV: 85.0	Serous: 73.6 Mucinous: 2.1 Clear-cell: 3.6 Endometrioid: 7.1 Undifferentiated: 4.3 Other/unkn: 9.3	
Banerjee, 2013 [57] (SCOTROC 4)	UK, Australia, New Zealand	483	67.9	6 cycles of carboplatin (AUC=6) in first cycle and dose escalations in cycles 2-6 based on nadir neutrophil and platelet counts, administered every 3 weeks	IC: 12.2 II: 8.1 III: 65.8 IV: 13.9	NR	0cm/micro: 32.9 <2cm: 19.3 >2cm: 47.8
		481	67.7	6 cycles of carboplatin (AUC=6) i.v., administered every 3 weeks	IC: 12.5 II: 8.1 III: 66.1 IV: 13.3		0cm/micro: 32.7 <2cm: 19.1 >2cm: 48.2
Weekly versus every 3 weeks *Single-agent*							
Fruscio, 2011 [58]	Italy	146	57	9 cycles of cisplatin (50 mg/m^2) i.v., administered every week	IIIA-C: 82.9 IV: 17.1	Serous: 63.0 Mucinous: 6.2 Clear-cell: 2.7 Endometrioid: 12.3 Undifferentiated: 6.9 Other/unkn: 8.9	<1cm: 21.2 >1cm: 69.9 Unkn: 8.9
		139	58	6 cycles of cisplatin (75 mg/m^2) i.v., administered every 3 weeks	IIIA-C: 84.2 IV: 15.8	Serous: 64.0 Mucinous: 5.0 Clear-cell: 2.9 Endometrioid: 7.2	<1cm: 26.6 >1cm: 65.5 Unkn: 7.9

Study, year (trial)	Country	No. of pts	Med age	Treatment regimen	FIGO stage (%)	Histology (%)	Residual disease (%)
						Undifferentiated: 14.4 Other/unkn: 6.5	
Platinum-based doublet							
Chan, 2016 [16] (GOG 0262)	US, Canada, South Korea	346	NR	6 cycles of paclitaxel (80 mg/m^2) i.v. over 1 hour, administered every week + carboplatin (AUC=6) i.v. ± bevacizumab (15 mg/kg) i.v. beginning on cycle 2, administered every 3 weeks	II: 2.3 III: 69.7 IV: 28.0	Serous: 87.3 Mucinous: 0.9 Clear-cell: 3.2 Endometrioid: 2.3 Other: 6.3	Micro: 24.3 ≤1cm: 63.0 Unkn: 12.7
		346		6 cycles of paclitaxel (175 mg/m^2) i.v. over 3 hours + carboplatin (AUC=6) i.v. ± bevacizumab (15 mg/kg) i.v. beginning on cycle 2, administered every 3 weeks	II: 2.9 III: 64.4 IV: 32.7	Serous: 89.3 Mucinous: 1.2 Clear-cell: 2.0 Endometrioid: 2.3 Other: 5.2	Micro: 23.7 ≤1cm: 63.6 Unkn: 12.7
Harano, 2014 [20]; Katsumata, 2013 [17]; Katsumata, 2009 [19] (JGOG 3016)	Japan	312	57	6 cycles of paclitaxel (80 mg/m^2) i.v. over 1 hour, administered every week + carboplatin (AUC=6) i.v. over 1 hour, administered every 3 weeks	II: 19.9 III: 64.7 IV: 15.4	Serous: 55.4 Mucinous: 7.4 Clear-cell: 9.9 Endometrioid: 12.2 Other: 15.1	≤1cm: 46.2 >1cm: 53.8
		319	57	6 cycles of paclitaxel (180 mg/m^2) i.v. over 3 hours + carboplatin (AUC=6) i.v. over 1 hour, administered every 3 weeks	II: 16.9 III: 67.4 IV: 15.7	Serous: 57.1 Mucinous: 3.4 Clear-cell: 11.6 Endometrioid: 12.2 Other: 15.7	≤1cm: 45.5 >1cm: 54.5
Clamp, 2019 [18]; Blagden, 2020 [21] (ICON8)	UK, Mexico, Australia, New Zealand, South Korea, Ireland	523	61	6 cycles of paclitaxel (80 mg/m^2) i.v. over 1 hour, administered every week + carboplatin (AUC=5/6) i.v. over 30-60 minutes, administered every 3 weeks	IC-IIA: 10.7 IIB-C: 9.0 IIIA-C: 61.4 IV: 18.9	Serous: 69.8 Clear-cell: 7.9 Endometrioid: 3.6 Other: 18.7	NR
		521	62	6 cycles of paclitaxel (80 mg/m^2) i.v. over 1 hour + carboplatin	IC-IIA: 10.0 IIB-C: 7.1 IIIA-C: 62.6	Serous: 72.8 Clear-cell: 6.5 Endometrioid: 4.2	

Study, year (trial)	Country	No. of pts	Med age	Treatment regimen	FIGO stage (%)	Histology (%)	Residual disease (%)
				(AUC=2) i.v. over 30-60 minutes, administered every week	IV: 20.3	Other: 16.5	
		522	63	6 cycles of paclitaxel (175 mg/m^2) i.v. over 3 hours + carboplatin (AUC=5/6) i.v. over 30-60 minutes, administered every 3 weeks	IC-IIA: 10.7 IIB-C: 9.0 IIIA-C: 60.6 IV: 19.7	Serous: 73.2 Clear-cell: 6.1 Endometrioid: 5.0 Other: 15.7	
Pignata, 2014 [22] (MITO-7)	Italy, France	406	60	6 cycles of paclitaxel (60 mg/m^2) i.v. over 1 hour + carboplatin (AUC=2) i.v. over 30 minutes, administered every week	IC: 7.6 II: 7.6 III: 57.7 IV: 27.1	Serous: 67.5 Mucinous: 2.0 Clear-cell: 4.7 Endometrioid: 12.0 Undifferentiated: 5.9 Other/unkn: 7.9	0cm: 41.1 ≤1cm: 11.8 >1cm: 22.7 No debulking: 24.4
		404	59	6 cycles of paclitaxel (175 mg/m^2) i.v. over 3 hours + carboplatin (AUC=6) i.v. over 30 minutes, administered every 3 weeks	IC: 6.2 II: 8.2 III: 63.1 IV: 22.5	Serous: 71.8 Mucinous: 1.7 Clear-cell: 6.2 Endometrioid: 7.9 Undifferentiated: 6.0 Other/unkn: 6.4	0cm: 41.1 ≤1cm: 11.9 >1cm: 22.5 No debulking: 24.5
i.p. versus i.v.							
Lesnock, 2013 [35]; Wenzel, 2007 [34]; Armstrong, 2006 [33] (GOG 172)	US	205	NR	6 cycles of paclitaxel (135 mg/m^2) i.v. over 24 hours + cisplatin (100 mg/m^2) i.p. on day 2 + paclitaxel (60 mg/m^2) i.p. on day 8, administered every 3 weeks	III: 100.0	Serous: 77.1 Clear-cell: 5.3 Endometrioid: 8.3 Other: 9.3	0cm/micro: 38.0 ≤1cm: 62.0
		210		6 cycles of paclitaxel (135 mg/m^2) i.v. over 24 hours + cisplatin (75 mg/m^2) i.v. on day 2, administered every 3 weeks	III: 100.0	Serous: 81.0 Clear-cell: 4.3 Endometrioid: 5.7 Other: 9.0	0cm/micro: 35.7 ≤1cm: 64.3
Walker, 2019 [36] (GOG 252)	US	518	58	6 cycles of paclitaxel (80 mg/m^2) i.v. over 1 hour, administered every week, followed by carboplatin (AUC=6) i.p. + bevacizumab (15	II: 10.8 III: 83.4 IV: 5.8	Serous: 82.4 Mucinous: 1.0 Clear-cell: 5.6 Endometrioid: 0.4 Other/unkn: 10.6	Micro: 57.3 ≤1cm: 36.5 >1cm: 6.2

Study, year (trial)	Country	No. of pts	Med age	Treatment regimen	FIGO stage (%)	Histology (%)	Residual disease (%)
				mg/kg) i.v. beginning on cycle 2, administered every 3 weeks			
		521		6 cycles of paclitaxel (135 mg/m^2) i.v. over 3 hours on day 1 + cisplatin (75 mg/m^2) i.p. on day 2 + paclitaxel (60 mg/m^2) i.p. on day 8, bevacizumab (15 mg/kg) i.v. beginning on cycle 2, administered every 3 weeks	II: 9.8 III: 82.9 IV: 7.3	Serous: 84.3 Mucinous: 0.9 Clear-cell: 5.0 Endometrioid: 0.8 Other/unkn: 9.0	Micro: 58.7 ≤1cm: 34.9 >1cm: 6.4
		521		6 cycles of paclitaxel (80 mg/m^2) i.v. over 1 hour, administered every week, followed by carboplatin (AUC=6) i.v. + bevacizumab (15 mg/kg) i.v. beginning on cycle 2, administered every 3 weeks	II: 10.8 III: 84.6 IV: 4.6	Serous: 83.2 Mucinous: 0.4 Clear-cell: 6.2 Endometrioid: 1.0 Other/unkn: 9.2	Micro: 57.0 ≤1cm: 34.9 >1cm: 8.1
Targeted therapy							
Tewari, 2019 [30]; Monk, 2013 [31]; Burger, 2011 [32] (GOG 0218)	US, Canada, South Korea, Japan	625	60	6 cycles of paclitaxel (175 mg/m^2) i.v. + carboplatin (AUC=6) i.v. + bevacizumab (15 mg/m^2) i.v. beginning on cycles 2-6, followed by maintenance placebo i.v. on cycle 7-22, administered every 3 weeks	III: 73.8 IV: 26.2	Serous: 83.1 Mucinous: 0.8 Clear-cell: 3.7 Endometrioid: 2.2 Other/unkn: 10.2	n=461 ≤1cm: 44.5 >1cm: 55.5
		625	60	6 cycles of paclitaxel (175 mg/m^2) i.v. + carboplatin (AUC=6) i.v. + placebo i.v. beginning on cycles 2-6, followed by maintenance placebo i.v. on cycle 7-22, administered every 3 weeks	III: 75.5 IV: 24.5	Serous: 86.5 Mucinous: 1.0 Clear-cell: 1.9 Endometrioid: 3.4 Other/unkn: 7.2	n=472 ≤1cm: 46.2 >1cm: 53.8
Lhomme, 2008 [28]	US, France, Italy, Russia, Norway	381	59	12 doses of valspodar (5 mg/kg) p.o. every 6 hours + 6 cycles of paclitaxel (80 mg/m^2) i.v. over 3 hours + carboplatin (AUC=6) i.v.	IIIA-C: 68.0 IV: 31.7 Unkn: 0.3	Serous: 61.7 Mucinous: 2.6 Clear-cell: 2.3 Endometrioid: 5.4 Other/unkn: 28.0	<5cm/unkn: 57.0 ≥5cm: 43.0

Study, year (trial)	Country	No. of pts	Med age	Treatment regimen	FIGO stage (%)	Histology (%)	Residual disease (%)
				over 30-60 minutes, administered every 3 weeks			
		381	59	6 cycles of paclitaxel (175 mg/m^2) i.v. + carboplatin (AUC=6) i.v. over 30-60 minutes, administered every 3 weeks	IIIA-C: 64.6 IV: 35.4 Unkn: 0.0	Serous: 60.7 Mucinous: 4.4 Clear-cell: 2.0 Endometrioid: 8.0 Other/unkn: 24.9	<5cm/unkn: 57.0 ≥5cm: 43.0
Immunotherapy							
Alberts, 2008 [29]	Europe, North and South America	426	56	6 cycles of paclitaxel (175 mg/m^2) i.v. over 3 hours + carboplatin (AUC=6) i.v., administered every 3 weeks with Interferon gamma 1b (100 µg) s.c., administered 3 times a week	III: 76.5 IV: 23.5	NR	NR
		421	56	6 cycles of paclitaxel (175 mg/m^2) i.v. over 3 hours + carboplatin (AUC=6) i.v., administered every 3 weeks	III: 76.7 IV: 23.3		

Abbreviations: AUC, area under the curve; FIGO, International Federation of Gynecology and Obstetrics staging system; i.p., intraperitoneal; i.v., intravenous; med, median; micro, microscopic; No., number; NR, not reported; PBCS, peripheral stem cell support; p.o., oral; pts, patients; s.c., subcutaneous; unkn, unknown
*Mean age

Neoadjuvant chemotherapy

Four trials compared upfront primary debulking surgery to neoadjuvant chemotherapy followed by interval debulking surgery. Chemotherapy consisted of carboplatin or cisplatin plus paclitaxel and was administered for at least six cycles after primary debulking surgery or three to four cycles before and three to four cycles after interval debulking surgery. Three of the trials (EORTC 55971, CHORUS, and JCOG 0602) used a non-inferiority design [1-5] while the other was a superiority trial (SCORPION) [6,7]. In two of the three inferiority trials (EORTC 55971 with a median follow-up of 4.7 years, and CHORUS with a median follow-up of 4.4 years) [1,3], OS for neoadjuvant chemotherapy was demonstrated to be non-inferior to that of primary surgery while the third trial (JCOG 0602 with a median follow-up period of 6 years) [4] was unable to confirm the non-inferiority of neoadjuvant chemotherapy. Postoperative deaths within 28 days after surgery were less common in women who received neoadjuvant chemotherapy (0.6% versus 2.6%, p=0.0439) [1]. Grade 3 or 4 nausea (0.5% versus 4.8%, p=0.0057) and vomiting (0.5% versus 4.8%, p=0.0057) also occurred less frequently in women who received neoadjuvant chemotherapy [3]. Conversely, neoadjuvant chemotherapy was associated with more grade 3 or 4 leukopenia (4.6% versus 0%, p=0.0086) [5]. In terms of QoL assessment, the EORTC 55971 trial [1,2] reported no significant differences in any of the functioning scales between the treatment arms. In the CHORUS trial [3], women who received neoadjuvant chemotherapy had slightly higher scores at six months after treatment (mean difference, -7.6; 95% CI, -13.3 to -1.9, p=0.0438) than those who received primary surgery. As for the SCORPION trial [6] with a median follow-up of 59 months, neoadjuvant chemotherapy failed to show superiority over primary surgery with respect to PFS (14.0 months versus 15.0 months; HR, 1.05; 95% CI, 0.77 to 1.44, p=0.73) and toxicity profile. However, QoL scores for emotional functioning (p=0.02), cognitive functioning (p=0.008), nausea and vomiting (p=0.047), dyspnea (p=0.013), insomnia (p=0.024), and hair loss (p=0.013) were shown to be more favourable in women who received neoadjuvant chemotherapy [7].

All four trials attempted to identify subgroups of women based on FIGO stage, volume of residual disease, and histological subtypes that would benefit more or less from one of the treatments. In none of the subgroups was there evidence of superiority of one of the treatments. However, pooled analysis of individual patient data with long-term follow-up from the EORTC 55971 (median follow-up of 7.6 years) and CHORUS (median follow-up of 5.9 years) trials showed that women with stage IV disease had significantly better OS (24.3 months versus 21.2 months; HR, 0.76; 95% CI, 0.58 to 1.00, p=0.048) and PFS (10.6 months versus 9.7 months; HR, 0.77; 95% CI, 0.59 to 1.00, p=0.049) with neoadjuvant chemotherapy compared with primary surgery [9].

Table 4-2. Survival Outcomes

Study, year (trial)	Intervention	OS			PFS		
		Med (months)	HR (95% CI)	p-value	Med (months)	HR (95% CI)	p-value
Neoadjuvant chemotherapy							
Vergote, 2010 [1] (EORTC 55971)	CBP or CIS ± PTX → IDS	30.0	0.98 (0.84 to 1.13)	0.01*	12.0	1.01 (0.89 to 1.15)	NS
	PDS → CBP or CIS ± PTX	29.0			12.0		
Kehoe, 2015 [3] (CHORUS)	CBP ± PTX → IDS	24.1	0.87 (0.72 to 1.05)	90% CI: 0.98**	12.0	0.91 (0.76 to 1.09)	NS
	PDS → CBP ± PTX	22.6			10.7		
Onda, 2020 [4] (JCOG 0602)	CBP+ PTX → IDS	44.3	1.05 (0.84 to 1.33)	90.8% CI: 0.24[γ]	16.4	0.96 (0.75 to 1.23)	NS
	PDS → CBP+ PTX	49.0			15.1		
Fagotti, 2020 [6] (SCORPION)	CBP+ PTX ± BEV → IDS	43.0	1.12 (0.76 to 1.65)	0.56	14.0	1.05 (0.77 to 1.44)	0.73
	PDS → CBP+ PTX ± BEV	41.0			15.0		
Adjuvant chemotherapy ***Platinum-based doublet*** *Cisplatin versus carboplatin*							
Ozols , 2003 [48] (GOG 158)	CBP + PTX	57.4	RR: 0.84 (0.70 to 1.02)	NS[μ]	20.7	RR: 0.88 (0.75 to 1.03)	NS[μ]
	CIS + PTX	48.7			19.4		
du Bois, 2003 [50] (AGO-OVAR 3)	CBP + PTX	43.3	1.05 (0.87 to 1.26)	NS	17.2	1.05 (0.89 to 1.23)	NS[μ]
	CIS + PTX	44.1			19.1		
Cisplatin and carboplatin							
Dittrich, 2003 [51]	CBP + CIS	43.0	RR: 1.05 (0.76 to 1.46)	0.75	23.1	RR: 1.03 (0.74 to 1.41)	0.88
	CYP + CIS	41.2			29.7		
Aravantinos, 2005 [10] (HeCOG)	CIS/CBP + PTX	38.6	NR	0.79	39.0	NR	0.95
	CBP + PTX	40.6			38.0		
Anthracyclines							

Study, year (trial)	Intervention	OS			PFS		
		Med (months)	HR (95% CI)	p-value	Med (months)	HR (95% CI)	p-value
Pignata, 2011 [11] (MITO-2)	CBP + PLD	61.6	0.89 (0.72 to 1.12)	0.32	19.0	0.95 (0.81 to 1.13)	0.58
	CBP + PTX	53.2			16.8		
Taxanes							
Mouratidou, 2007 [52]	CIS + PTX	24.0	NR	0.35	12.0	NR	0.215
	CYP + CIS	20.0			9.0		
Vasey et al, 2004 [12] (SCOTROC 1)	CBP + DTX	2yr: 64.2%	1.13 (0.92 to 1.39)	0.238	15.0	0.97 (0.83 to 1.13)	0.707
	CBP + PTX	2yr: 68.9%			14.8		
Second-generation platinum							
Li, 2018 [13]	NDP + PTX	5yr: 63.5%	NR	0.65	5yr: 50.2%	NR	0.09
	CBP + PTX	5yr: 61.5%			5yr: 36.2%		
Sequential doublet							
Hoskins, 2010 [14] (OV16)	CIS + TPT → CBP + PTX	42.3	NR	NS	14.6	1.10 (0.94 to 1.28)	0.25
	CBP + PTX	42.1			16.2		
Bookman, 2009 [15] (GOG 0182-ICON5)	CBP + TPT → CBP + PTX	40.2	1.05 (0.93 to 1.19)	0.447	15.4	1.07 (0.96 to 1.19)	0.239
	CBP + PTX	44.1			16.0		
	CBP + GEM → CBP + PTX	39.6	1.11 (0.98 to 1.26)	0.093	15.4	1.04 (0.93 to 1.15)	0.503
	CBP + PTX	44.1			16.0		
Platinum-based triplet *Anthracyclines*							
Bookman, 2009 [15] (GOG 0182-ICON5)	CBP + PTX + PLD	44.2	0.95 (0.84 to 1.09)	0.462	16.4	0.98 (0.88 to 1.10)	0.796
	CBP + PTX	44.1			16.0		
Aravantinos, 2008 [23] (HeCOG)	DOX + PTX + CIS	44.3	NR	0.53	18.1	NR	0.07
	CBP + PTX	38.0			13.3		
	EPI + CBP + PTX	45.8	0.93 (0.81 to 1.08)	0.3652	18.4	0.95 (0.83 to 1.07)	0.3342

Study, year (trial)	Intervention	OS			PFS		
		Med (months)	HR (95% CI)	p-value	Med (months)	HR (95% CI)	p-value
du Bois, 2006 [24] (AGO-OVAR 5)	CBP + PTX	41.0			17.9		
Lindemann, 2012 [25] (NSGO-EORTC GCG-NCIC CTG)	EPI + CBP + PTX	42.4	0.96 (0.80 to 1.10)	NS	16.4	0.99 (0.90 to 1.20)	NS
	CBP + PTX	40.2			16.0		
Gemcitabine							
Bookman, 2009 [15] (GOG 0182-ICON5)	CBP +PTX + GEM	44.1	1.01 (0.89 to 1.14)	0.923	16.3	1.03 (0.92 to 1.14)	0.61
	CBP + PTX	44.1			16.0		
du Bois, 2010 [26] (AGO-OVAR 9)	GEM + CBP + PTX	49.5	1.05 (0.91 to 1.20)	0.5106	17.8	1.18 (1.06 to 1.32)	0.0044
	CBP + PTX	51.5			19.3		
Topotecan							
Bolis, 2010 [27]	TPT + CBP + PTX	5yr: 32%	RR: 0.85 (0.56 to 1.29)	NS	NR	NR	NS
	CBP + PTX	5yr: 32%					
Dose intensification							
Ray-Coquard, 2007 [54] (GINECO)	CYP (1800 mg/m^2) + EPI + CIS + FIL	30.0	NR	0.6	14.8	NR	0.55
	CYP (500 mg/m^2) + EPI + CIS	32.5			15.9		
Mobus, 2007 [55] (HIDOC-EIS)	CYP + PTX → HD (CBP + PTX + MEP) w/ PBSC	54.4	1.17 (0.71 to 1.94)	0.54	29.6	0.84 (0.56 to 1.26)	0.40
	CBP + PTX ± EPI or TPT	62.8			20.5		

Study, year (trial)	Intervention	OS			PFS		
		Med (months)	HR (95% CI)	p-value	Med (months)	HR (95% CI)	p-value
Spriggs, 2007 [56]	CIS + 96-hr i.v. PTX	30.5	1.17 (0.90 to 1.52)	NS	12.6	1.00 (0.78 to 1.28)	NS
	CIS + 24-hr i.v. PTX	29.9			12.4		
Banerjee, 2013 [57] (SCOTROC 4)	IDE CBP	30.7	1.02 (0.85 to 1.23)	0.82	12.1	1.01 (0.88 to 1.18)	0.93
	FD CBP	34.1			12.1		
Weekly versus every 3 weeks							
Single-agent							
Fruscio, 2011 [58]	CIS q1w	35.0	0.97 (0.75 to 1.26)	0.97	17.2	1.08 (0.83 to 1.40)	0.57
	CIS q3w	32.0			18.1		
Platinum-based doublet							
Chan, 2016 [16] (GOG 0262)	(CBP ± BEV) q3w + PTX q1w	40.2	0.94 (0.72 to 1.23)	NS	14.7	0.89 (0.74 to 1.06)	0.18
	(CBP + PTX ± BEV) q3w	39.0			14.0		
	CBP q3w + PTX q1w	NR	NR	NR	14.2	0.62 (0.40 to 0.95)	0.03
	(CBP + PTX) q3w				10.3		
	(CBP + BEV) q3w + PTX q1w	NR	NR	NR	14.9	0.99 (0.83 to 1.20)	0.60
	(CBP + PTX + BEV) q3w				14.7		
Katsumata, 2013 [17] (JGOG 3016)	CBP q3w + PTX q1w	100.5	0.79 (0.63 to 0.99)	0.039	28.2	0.76 (0.62 to 0.91)	0.0037
	(CBP + PTX) q3w	62.2			17.5		
Clamp, 2019 [18] (ICON8)	CBP q3w + PTX q1w	24.9$^{\Delta}$	NR	NR	20.8	0.90 (0.77 to 1.05)	0.35
	(CBP + PTX) q3w	24.5$^{\Delta}$			17.7		
	(CBP + PTX) q1w	25.4$^{\Delta}$	NR	NR	21.0	0.93 (0.78 to 1.08)	0.51
	(CBP + PTX) q3w	24.5$^{\Delta}$			17.7		
	(CBP + PTX) q1w	2yr: 77.3%	1.20 (0.90 to 1.61)	0.22	18.3	0.96 (0.80 to 1.16)	0.66

Study, year (trial)	Intervention	OS			PFS		
		Med (months)	HR (95% CI)	p-value	Med (months)	HR (95% CI)	p-value
Pignata, 2014 [22] (MITO-7)	(CBP + PTX) q3w	2yr: 78.9%			17.3		
i.p. versus i.v.							
Armstrong, 2006 [33] (GOG 172)	i.v. PTX + i.p. (CIS + PTX)	65.6	0.75 (0.58 to 0.97)	0.03	23.8	0.80 (0.64 to 1.00)	0.05
	i.v. (CIS + PTX)	49.7			18.3		
Walker, 2019 [36] (GOG 252)	i.v. PTX q1w + (i.p. CBP + i.v. BEV) q3w	78.9	0.95 (0.80 to 1.13)	NS	27.4	0.93 (0.80 to 1.07)	NS
	i.v. PTX q1w + i.v. (CBP + BEV) q3w	75.5			24.9		
	i.v. (PTX + BEV) q3w + i.p. (PTX + CIS) q3w	72.9	1.05 (0.88 to 1.24)	NS	26.2	0.98 (0.85 to 1.13)	NS
	i.v. PTX q1w + i.v. (CBP + BEV) q3w	75.5			24.9		
Targeted therapy							
Tewari, 2019 [30]; Burger, 2011 [32] (GOG 0218)	CBP + PTX + BEV	40.8	1.06 (0.94 to 1.20)	0.34	11.2	0.91 (0.80 to 1.04)	0.16
	CBP + PTX + PBO	41.1			10.3		
Lhomme, 2008 [28]	VAP + CBP + PTX	32.0	0.99 (0.83 to 1.19)	0.94	13.2***	0.96 (0.8 to 1.15)	0.67
	CBP + PTX	28.9			13.5***		
Immunotherapy							
Alberts, 2008 [29]	IFN-γ-1b + CBP + PTX	37.4[β]	1.45 (1.15 to 1.83)	0.0014	13.4	NR	0.796
	CBP + PTX	NE[β]			13.6		

Abbreviations: ATC, anthracycline; BEV, bevacizumab; CBP, carboplatin; CI, confidence interval; CIS, cisplatin; CYP, cyclophosphamide; DOX, doxorubicin; DTX, docetaxel; EPI, epirubicin; FD, flat dosing; FIL, filgrastim; GEM, gemcitabine; HD, high-dose; HR, hazard ratio; hr, hour; IDE, intrapatient dose escalation; IDS, interval debulking surgery; IFN-γ-1b, interferon

gamma-1b; i.p., intraperitoneal; i.v., intravenous; med, median; MEP, melphalan; NDP, nedaplatin; NE, not estimable/not reached; NR, not reported; NS, not significant; OS, overall survival; PBO, placebo; PBSC, peripheral blood stem cell; PDS, primary debulking surgery; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin; PTX, paclitaxel; q1w, every week; q3w, every 3 weeks; RR, relative risk; TPT, topotecan; VAP, valspodar; yr, year

*A hazard ratio of less than 1.25 was considered to indicate noninferiority

**The upper bound of the one-sided 90% CI for the hazard ratio of less than 1.18 to indicate noninferiority

***Time to progression

[γ]A hazard ratio of 0.953 was the boundary to reject the null hypothesis that neoadjuvant chemotherapy is inferior to primary debulking surgery in the planned settings

[μ]To indicate noninferiority

[β]The trial was terminated early following a protocol-defined second interim analysis

[Δ]Restricted mean survival

Table 4-3. Adverse Events and Quality of Life

Study, year (trial)	Intervention	N	Grade ≥3 adverse events, n(%)							N	Quality of life	
			Treatment-related death	Anemia	Neutropenia/ Leukopenia	Thrombocytopenia	Nausea	Vomiting	Neuropathy		Questionnaire (time points)	Results
Neoadjuvant chemotherapy												
Vergote, 2010 [1]; Greimel, 2013 [2] (EORTC 55971)	CBP or CIS ± PTX → IDS	322	2(0.6)	NR	NR	NR	NR	NR	NR	201	EORTC QLQ-C30 and QLQ-OV28 (at baseline, at cycle 3 and 6, at 6- and 12-month follow-up)	NS
	PDS → CBP or CIS ± PTX	310	8(2.6) p=0.0439							203		
Kehoe, 2015 [3] (CHORUS)	CBP± PTX → IDS	209	1(0.5)	NR	NR	NR	1(0.5)	1(0.5)	NR	227	EORTC QLQ-C30 and QLQ-OV28 (at baseline, after cycles 3 and 6, and at 6 and 12 months after treatment)	Patients who received IDS had significantly higher global scores than those who received PDS at 6 months after end of treatment (mean difference, -7.6, 95% CI, -13.3 to -1.9, p=0.0438).
	PDS → CBP± PTX	252	0(0.0) p=0.2611				12(4.8) p=0.0057	12(4.8) p=0.0057		230		
Onda, 2016 [5] (JCOG 0602)	CBP+ PTX → IDS	130-152	1(0.7)	33(25.4)	6(4.6)	1(0.8)	NR	NR	NR	NR	NR	NR
	PDS → CBP+ PTX	147-149	2(1.3) p=0.6004	28(19.0) p=0.1994	0(0.0) p=0.0086	0(0.0) p=0.2773						
Fagotti, 2016 [7] (SCORPION)	CBP+ PTX ± BEV → IDS	52	0(0.0)	2(3.8)	8(15.3)	0(0.0)	1(1.9)	2(3.8)	2(3.8)	49	EORTC QLQ-C30 and QLQ-OV28 (at baseline, at cycle 4 or before interval debulking surgery, at cycle 6, and 6 months after last cycle)	Patients who received IDS had significantly better mean scores for emotional functioning (p=0.02), cognitive functioning (p=0.008), nausea and vomiting (p=0.047), dyspnea (p=0.013), insomnia (p=0.024), and hair loss (p=0.013) than those who received PDS during therapy or follow-up.
	PDS → CBP+ PTX ± BEV	51	3(5.9) p=0.0754	4(7.8) p=0.3845	9(17.6) p=0.7528	2(3.9) p=0.1504	2(3.9) p=0.5447	3(5.8) p=0.6346	2(3.9) p=0.979	46		
Adjuvant chemotherapy *Platinum-based doublet* *Cisplatin versus carboplatin*												
Ozols, 2003 [48] (GOG 158)	CBP+ PTX	392	NR	NR	230(58.7)	154(39.3)	NR	NR	27(6.9)	NR	NR	NR
	CIS + PTX	400			254(63.5) p=0.1659	20(5.0) p<0.01			31(7.8) p=0.6276			
Greimel, 2006 [49];	CBP+ PTX	371-389	NR	23(5.9)	137(36.9)/ 124(32.0)	50(12.9)	23(5.9)	11(2.8)	7**(1.8)/ 28£(7.2)	366	EORTC QLQ-C30 (at baseline,	Patients who received CBP and PTX had

Study, year (trial)	Intervention	N	Grade ≥3 adverse events, n(%)							N	Quality of life	
			Treatment-related death	Anemia	Neutropenia/ Leukopenia	Thrombocytopenia	Nausea	Vomiting	Neuropathy		Questionnaire (time points)	Results
du Bois, 2003 [50] (AGO-OVAR 3)	CIS + PTX	373-384		15(3.9) p=0.1990	82(22.0)/ 41(10.7) p<0.01/ p<0.01	4(1.0) p<0.01	55(14.3) p=0.0001	40(10.4) p<0.01	16**(4.2)/ 52[£](13.5) p=0.0504/ p=0.0040	357	after cycles 1, 3 and 6, and at every 6 months afterwards)	significantly higher global scores than those who received CIS and PTX after cycle 3 (mean difference, -3.67, 95% CI, -6.97 to -0.37) and at the end of treatment (mean difference, -13.28, 95% CI, -18.88 to -7.68). Patients randomly assigned to CBP and PTX also showed significantly better mean scores for physical functioning (p=0.012), role functioning (p=0.005), and cognitive functioning (p=0.024) as well as less nausea and vomiting (p<0.001), less appetite loss (p<0.001), and less fatigue (p=0.033) after end of treatment.
Cisplatin and carboplatin												
Dittrich, 2003 [51]	CBP+ CIS	113-124	0(0.0)	30(26.3)	55(48.7)	87(76.3)	41(35.7)		5(4.3)	NR	NR	NR
	CYP + CIS	117-123	0(0.0) NS	15(12.8) p=0.0096	40(34.2) p=0.0256	26(22.2) p<0.01	32(26.9) p=0.1464		2(1.7) p=0.2421			
Aravantinos, 2005 [10] (HeCOG)	CIS /CBP + PTX	119	1(0.8)	18(15.1)	43(36.1)/ 23(19.3)	16(13.4)	10(8.4)		7(5.9)	NR	NR	NR
	CBP+ PTX	127	4(3.1) p=0.1965	10(7.9) p=0.0756	34(26.8)/ 16(12.6) p=0.1160/ p=0.1504	13(10.2) p=0.4360	2(1.6) p=0.0135		3(2.4) p=0.1662			
Anthracyclines												
Pignata, 2011 [11] (MITO-2)	CBP+ PLD	396	2(0.5)	40(10.1)	171(43.2)/ 57(14.4)	63(15.9)	7(1.8)	10(2.5)	1(0.3)	311	EORTC QLQ-C30 (at baseline, after cycles 3 and 6)	NS
	CBP+ PTX	407	4(1.0) p=0.4127	15(3.7) p=0.0003	202(49.6)/ 77(18.9) p=0.0691/ p=0.0872	8(2.0) p<0.01	7(1.7) p=0.9139	7(1.7) p=0.4287	12(2.9) p=0.0035	309		
Taxanes												

Study, year (trial)	Intervention	N	Grade ≥3 adverse events, n(%)							N	Quality of life	
			Treatment-related death	Anemia	Neutropenia/ Leukopenia	Thrombocytopenia	Nausea	Vomiting	Neuropathy		Questionnaire (time points)	Results
Mouratidou, 2007 [52]	CIS + PTX	60	NR	NR	54(90.0)	4(6.7)	16(26.7)		13(21.7)	NR	NR	NR
	CYP + CIS	60			49(81.7) p=0.1921	3(5.0) p=0.6915	17(28.3) p=0.8444		2(3.3) p=0.0023			
Vasey, 2004 [12] (SCOTROC 1)	CBP+ DTX	537-539	2(0.4)	59(10.9)	507(94.1)	49(9.1)	9(1.7)	8(1.5)	1[μ](0.2)/2[£] (0.4)	974*; 538**	EORTC QLQ-C30, QLQ-OV28 (before each cycle, at 6 months after treatment, and every 4 months for up to 2 years afterwards) and NScore (at baseline, after cycles 3 and 6, at 6 months after treatment, and every 4 months for up to a year afterwards)	Patients who received CBP and DTX showed significantly better improvements in symptom scores (pain, gastro-intestinal, hair loss, weakness, aches and pains; p<0.001) than those who received CBP and PTX during therapy. NScore (p=0.005) and neurotoxicity (p<0.001) also increased significantly more in patients randomly assigned to CBP and PTX on long term follow-up.
	CBP+ PTX	532-533	1(0.2) p=0.5498	43(8.1) p=0.1181	448(84.1) p<0.01	53(9.9) p=0.6551	5(0.9) p=0.2486	13(2.4) p=0.2871	2[μ](0.4)/8[£] (1.5) p=0.5496/ p=0.0634			
Second-generation platinum												
Li, 2018 [13]	NDP + PTX	92	NR	8(8.7)	10(10.9)	5(5.4)	3(3.3)		0(0.0)	NR	NR	NR
	CBP+ PTX	90		10(11.1) p=0.5876	21(23.3) p=0.0261	9(10.0) p=0.2438	5(5.6) p=0.4512		0(0.0) NS			
Sequential doublet												
Hoskins, 2010 [14]; Brotto, 2016 [53] (OV16)	CIS + TPT → CBP+ PTX	406	2(0.5)	NR	344(84.7)	185(45.6)	341*(84.0)	233*(57.4)	301*[£] (74.1)	363	EORTC QLQ-C30 and QLQ-OV28 (at baseline, on day 1 of cycles 3, 5 and 7, at the end of last cycle, and at 3 and 6 months after treatment)	NS
	CBP+ PTX	409	2(0.5) p=1.0		234(57.2) p<0.01	37(9.0) p<0.01	314*(76.8) p=0.0094	167*(40.8) p<0.01	344*[£] (84.1) p=0.0004	354		
Bookman, 2009 [15] (GOG 0182-ICON5)	CBP+ TPT → CBP+ PTX	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	CBP+ GEM → CBP+ PTX											
	CBP+ PTX											
Platinum-based triplet												

Study, year (trial)	Intervention	N	Grade ≥3 adverse events, n(%)							N	Quality of life	
			Treatment-related death	Anemia	Neutropenia/ Leukopenia	Thrombocytopenia	Nausea	Vomiting	Neuropathy		Questionnaire (time points)	Results
Anthracyclines												
Bookman, 2009 [15] (GOG 0182-ICON5)	CBP+ PTX + PLD	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	CBP+ PTX											
Aravantinos, 2008 [23] (HeCOG)	DOX + PTX + CIS	204-213	4(1.9)	21(10.1)	70(33.8)/ 37(17.9)	10(4.8)	6(2.9)		0(0.0)	NR	NR	NR
	CBP+ PTX	216-220	1(0.5) p=0.1790	17(7.9) p=0.4288	92(42.6)/ 37(17.1) p=0.0627/ p=0.8286	14(6.5) p=0.4497	3(1.4) p=0.2863		5(2.3) p=0.0293			
du Bois, 2006 [24] (AGO-OVAR 5)	EPI + CBP+ PTX	563-624	NR	129(21.1)	428(76.0)/ 401(65.6)	110(18.0)	43(6.9)	40(6.4)	4[Δ](0.6)/ 25[£](4.0)	338	EORTC QLQ-C30 (after every other cycle, after last cycle, and every 3 months for up to a year afterwards)	Patients who received additional EPI had significantly worse global scores than those who received only CBP and PTX (mean difference, 6.4, 95% CI, 2.7 to 10.1, p=0.001) at the end of treatment.
	CBP+ PTX	553-614		34(5.6) p<0.01	309(55.9)/ 160(26.3) p<0.01/ p<0.01	25(4.1) p<0.01	20(3.3) p=0.0041	18(2.9) p=0.0036	9[Δ](1.5)/ 21[£](3.4) p=0.1206/ p=0.5767	318		
Lindemann, 2012 [25] (NSGO-EORTC GCG-NCIC CTG)	EPI + CBP+ PTX	439-441	NR	33(7.5)	11(2.5)	2(0.5)	49(11.1)	47(10.7)	18[µ](4.1)/ 12[£](2.7)	284	EORTC QLQ-C30 (at baseline, after cycles 3, 6 and 9, and at every 6 months up to a year afterwards)	Patients who received additional EPI had a significantly smaller improvement from baseline to the mean (p=0.0112) and maximal (p=0.0374) global scores of the rest of the time points than those who received CBP and PTX.
	CBP+ PTX	434-439		6(1.4) p<0.01	5(1.1) p=0.1185	0(0.0) p=0.1380	18(4.1) p=0.0001	17(3.9) p=0.0001	7[µ](1.6)/ 15[£](3.4) p=0.0266/ p=0.5471	282		
Gemcitabine												
Bookman, 2009 [15] (GOG 0182-ICON5)	CBP+PTX + GEM	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	CBP+ PTX											
du Bois, 2010 [26] (AGO-OVAR 9)	GEM + CBP+ PTX	840-848	NR	151(17.8)	686(81.5)/ 595(70.2)	304(35.8)	36(4.3)	31(3.7)	25[µ](3.0)/ 62[£](7.4)	519	EORTC QLQ-C30 and QLQ-OV28 (at baseline, after cycle 3, after last cycle,	Patients who received additional GEM had significantly lower global scores than those who received only CBP and PTX after the cycle 3
	CBP+ PTX	860-873		38(4.4) p<0.01	534(62.1)/ 245(28.1) p<0.01/ p<0.01	41(4.7) p<0.01	28(3.2) p=0.2314	26(3.0) p=0.4216	19[µ](2.2)/ 56[£](6.5) p=0.2988/ p=0.4648	526		

Study, year (trial)	Intervention	N	Grade ≥3 adverse events, n(%)							N	Quality of life	
			Treatment-related death	Anemia	Neutropenia/ Leukopenia	Thrombocytopenia	Nausea	Vomiting	Neuropathy		Questionnaire (time points)	Results
											and at 3 months after treatment)	(p=0.0218). However, no significant differences were observed after end of treatment.
Topotecan												
Bolis, 2010 [27]	TPT + CBP+ PTX	156	NR	10(6.4)	62(39.7)	NR	3(1.9)	4(2.6)	2(1.3)	NR	NR	NR
	CBP+ PTX	170		3(1.8) p=0.0343	40(23.5) p=0.0016		1(0.6) p=0.2859	1(0.6) p=0.1451	2(1.2) p=0.9352			
Dose intensification												
Ray-Coquard, 2007 [54] (GINECO)	CYP (1800 mg/m^2) + EPI + CIS + FIL	73	2(2.7)	31(42.5)	37(50.7)/ 40(54.8)	24(32.9)	24(32.9)		NR	NR	NR	NR
	CYP (500 mg/m^2) + EPI + CIS	82	1(1.2) p=0.4955	17(20.7) p=0.0034	53(64.6)/ 33(40.2) p=0.08/ p=0.0691	10(12.2) p=0.0019	25(30.5) p=0.7484					
Mobus, 2007 [55] (HIDOC-EIS)	CYP + PTX → HD (CBP+ PTX + MEP) w/ PBSC	78	1(1.3)	NR	NR	NR	NR	NR	NR	NR	NR	NR
	CBP+ PTX ± EPI or TPT	71	0(0.0) p=0.335									
Spriggs, 2007 [56]	CIS + 96-hr i.v. PTX	138	3(2.2)	25(18.1)	71(51.4)	8(5.8)	NR	NR	6(4.3)	NR	NR	NR
	CIS + 24-hr i.v. PTX	138	6(4.3) p=0.3252	9(6.5) p=0.0033	80(58.0) p=0.2707	11(8.0) p=0.4709			4(2.9) p=0.5325			
Banerjee, 2013 [57] (SCOTROC 4)	IDE CBP	479	1(0.2)	87(18.2)	192(40.1)	206(43.0)	14(2.9)	20(4.2)	NR	NR	EORTC QLQ-C30 and QLQ-OV28 (before each cycle, and at 6 months after randomization)	NS
	FD CBP	477	0(0.0) p=0.3285	47(9.9) p=0.0002	97(20.3) p<0.01	72(15.1) p<0.01	6(1.3) p=0.0846	7(1.5) p=0.0122				
Weekly versus every 3 weeks												
Single-agent												
Fruscio, 2011 [58]	CIS q1w	146	NR	11(7.5)	13(8.9)	3(2.1)	36(24.7)	NR	1[£](0.7)	NR	NR	NR
	CIS q3w	139		5(3.6) p=0.1523	4(2.9) p=0.0327	0(0.0) p=0.0858	26(18.7) p=0.2199		0[£](0.0) p=0.3231			
Platinum-based doublet												

Study, year (trial)	Intervention	N	Grade ≥3 adverse events, n(%)							N	Quality of life	
			Treatment-related death	Anemia	Neutropenia/ Leukopenia	Thrombocytopenia	Nausea	Vomiting	Neuropathy		Questionnaire (time points)	Results
Chan, 2016 [16] (GOG 0262)	(CBP ± BEV) q3w + PTX q1w	340	6(1.8)	124(36.5)	246(72.4)	67(19.7)	20(5.9)	19(5.6)	3[μ](0.9)/9[£] (2.6)	277	FACT-O TOI, FACT/GOG-NTX and FACT-GOG-AD (at baseline, before cycle 4, 3 weeks after cycle 6, 36 and 63 weeks after cycle 1)	Patients who received PTX q1w had significantly lower scores in FACT-O TOI than those who received PTX q3w (maximum decrease, 2.7; 97.5% CI: -5.44 to -0.02, p=0.024) after cycle 6, but this difference was not clinically significant.
	(CBP+ PTX ± BEV) q3w	343	8(2.3) p=0.6448	54(15.7) p<0.01	286(83.4) p=0.0005	54(15.7) p=0.1708	11(3.2) p=0.0903	15(4.4) p=0.4717	3[μ](0.9)/7[£] (2.0) p=1.0/ p=0.6009	283		
Harano, 2014 [20]; Katsumata, 2009 [19] (JGOG 3016)	CBP q3w + PTX q1w	312	NR	214(68.6)	286(91.7)	136(43.6)	32(10.3)	9(2.9)	15[μ](4.8)/ 21[£](6.7)	200	FACT-G, FACT-T and FACT-OV (at baseline, after cycle 3 and 6, and at 12 months after randomization)	Patients who received PTX q1w had significantly worse FACT-T scores (p=0.02) than those who received PTX q3w. However, overall QoL scores did not differ significantly between the two groups.
	(CBP+ PTX) q3w	314		137(43.6) p<0.01	276(87.9) p=0.1163	120(38.2) p=0.1694	36(11.5) p=0.63	11(3.5) p=0.6698	12[μ](3.8)/ 20[£](6.4) p=0.5374/ p=0.8794	204		
Clamp, 2019 [18]; Blagden, 2020 [21] (ICON8)	CBP q3w + PTX q1w	513	NR	65(12.7) p<0.01	181(35.3)/ 80(15.6) p<0.01/ p<0.01	48(9.4) p=0.0007	13(2.5) p=0.9193	18(3.5) p=0.8601	3[μ](0.6)/ 21[£](4.1) p=0.0804/ p=0.0824	1540	EORTC QLQ-C30 and QLQ-OV28 (at baseline, before each cycle, 6-weekly to 9 months, 3-monthly to 2 years, and 6-monthly up to 5 years)	Patients who received either of the q1w regimen had significantly worst peripheral neuropathy scores than those who received treatment q3w at 9 months (p<0.001). However, scores for global health, emotional function, social function, and fatigue did not differ between the groups at 9 months.
	(CBP+ PTX) q1w	510		24(4.7) p=0.8813	152(29.8)/ 71(13.9) p<0.01/ p<0.01	16(3.1) p=0.3917	5(1.0) p=0.0548	6(1.2) p=0.0238	1[μ](0.2)/ 8[£](1.6) p=0.3132/ p=0.4832			
	(CBP+ PTX) q3w	508		25(4.9)	76(15.0)/ 22(4.3)	21(4.1)	13(2.6)	17(3.3)	0[μ](0.0)/ 11[£](2.2)			
Pignata, 2014 [22] (MITO-7)	(CBP+ PTX) q1w	399	1(0.3)	25(6.3)	167(41.9)/ 55(13.8)	4(1.0)	6(1.5)	5(1.3)	0(0.0)	308	FACT-O, FACT-O TOI and FACT/GOG-NTX (at baseline, and every week for the first 9 weeks)	Patients who received the q1w regimen had significantly better FACT-O, FACT-O TOI and FACT/GOG-NTX scores than those who received treatment q3w (treatment-by-time interaction, p<0.0001).
	(CBP+ PTX) q3w	400	2(0.5) p=0.6543	32(8.0) p=0.3511	200(50.0)/ 78(19.5) p=0.0216/ p=0.0306	27(6.8) p<0.01	8(2.0) p=0.59	5(1.3) p=1.0	10(2.5) p=0.0015	301		

Study, year (trial)	Intervention	N	Grade ≥3 adverse events, n(%)							N	Quality of life	
			Treatment-related death	Anemia	Neutropenia/ Leukopenia	Thrombocytopenia	Nausea	Vomiting	Neuropathy		Questionnaire (time points)	Results
i.p. versus i.v.												
Wenzel, 2007 [34]; Armstrong, 2006 [33] (GOG 172)	i.v. PTX + i.p. (CIS + PTX)	201	5(1.9)	NR	152(75.6)	24(11.9)	NR	NR	39(19.4)	198	FACT-O TOI (at baseline, before cycle 4, 3 to 6 weeks and 12 months after treatment)	Patients who received i.p. treatment showed significantly worse physical well-being, functional well-being, and ovarian cancer symptoms than those who received i.v. treatment before cycle 4 (p<0.001) and 3 to 6 weeks after treatment (p=0.001). Patients randomly assigned to i.p. treatment also reported significantly worse abdominal discomfort scores before cycle 4 (p<0.001) and neurotoxicity scores 3 to 6 weeks (p=0.001) and 12 months (p=0.003) after treatment.
	i.v. (CIS + PTX) i.v. (PTX + CIS)	210	4(1.9) p=1.0		134(63.8) p=0.0093	8(3.8) p=0.0022			18(8.6) p=0.0015	201		
Walker, 2019 [36] (GOG 252)	i.v. PTX q1w + i.p. (CBP + i.v. BEV) q3w	510	7(1.4) p=0.7927	134(26.3) p=0.9135	347(68.0) p=0.1631	77(15.1) p=0.2801	24(4.7) p=0.7672		23[£](4.5) p=0.3835	1437	FACT-O TOI, FACT/GOG-NTX and FACT/GOG-AD (at baseline, before cycle 4, 7, 13 and 21, and 84 weeks after starting treatment)	Patients who received i.p. CIS had significantly lower FACT-O TOI scores than those who received i.v. CBP (p<0.001) and i.p. CBP (p=0.003) before cycle 4. Patients randomly assigned to i.p. CIS also reported significantly worse neurotoxicity symptoms than those who received i.v. (p<0.001) or i.p. (p=0.005) CBP before cycle 13. Patients who received i.p. CBP (p=0.006) and i.p. CIS (p=0.002) reported significantly more
	i.v. (PTX + BEV) q3w + i.p. (PTX + CIS) q3w	508	10(2.0) p=0.631	91(17.9) p=0.0008	327(64.4) p=0.0092	31(6.1) p<0.01	56(11.0) p=0.0005		28[£](5.5) p=0.8896			
	i.v. PTX q1w + i.v. (CBP + BEV) q3w	511	8(1.6)	136(26.6)	368(72.0)	90(17.6)	26(5.1)		29[£](5.7)			

Study, year (trial)	Intervention	N	Grade ≥3 adverse events, n(%)							N	Quality of life	
			Treatment-related death	Anemia	Neutropenia/ Leukopenia	Thrombocytopenia	Nausea	Vomiting	Neuropathy		Questionnaire (time points)	Results
												abdominal discomfort than those who received i.v. CBP before cycle 7.
Targeted therapy												
Tewari, 2019 [30]; Monk, 2013 [31]; Burger, 2011 [32] (GOG 0218)	CBP+ PTX + BEV	607	10(1.6)	NR	384(63.3)	NR	NR	NR	NR	554	FACT-O TOI (before cycles 1, 4, 7, 13, and 21, and at 6 months after treatment)	Patients who received BEV had significantly lower FACT-O TOI scores (p<0.001) than those who received PBO during therapy. However, no significant differences were found after completion of treatment.
	CBP+ PTX + PBO	601	6(1.0) p=0.3576		347(57.7) p=0.0465					566		
Lhomme, 2008 [28]	VAP + CBP+ PTX	360-372	NR	125(34.4)	324(90.0)/ 263(72.5)	93(25.6)	31(8.3)	25(6.7)	76[β](20.4)	NR	NR	NR
	CBP+ PTX	369-377		81(21.8) p=0.0001	324(87.8)/ 188(50.7) p=0.3447/ p<0.01	66(17.8) p=0.0103	13(3.4) p=0.0042	12(3.2) p=0.0271	8[β](2.1) p<0.01			
Immunotherapy												
Alberts, 2008 [29]	IFN-γ-1b + CBP+ PTX	423	NR	29(6.9)	175(41.4)/ 45(10.6)	32(7.6)	NR	NR	NR	NR	NR	NR
	CBP+ PTX	418		22(5.3) p=0.3325	139(33.3)/ 17(4.1) p=0.0152/ p=0.0003	30(7.2) p=0.8247						

Abbreviations: ATC, anthracycline; BEV, bevacizumab; CBP, carboplatin; CI, confidence interval; CIS, cisplatin; CYP, cyclophosphamide; DOX, doxorubicin; DTX, docetaxel; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORTC QLQ-OV28, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Ovarian Cancer Module; EPI, epirubicin; FACT/GOG-AD, Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Abdominal Discomfort; FACT/GOG-NTX, Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity; FACT-G, Functional Assessment of Cancer Therapy - General; FACT-T, Functional Assessment of Cancer Therapy – Taxane subscale; FACT-O TOI, Functional Assessment of Cancer Therapy - Ovarian Cancer Trial Outcome Index; FD, flat dosing; FIL, filgrastim; GEM, gemcitabine; HD, high-dose; hr, hour; IDE, intrapatient dose escalation; IDS, interval debulking surgery; IFN-γ-1b, interferon gamma-1b; i.p., intraperitoneal; i.v., intravenous; MEP, melphalan; n, sample size; NDP, nedaplatin; NR, not reported; NS, not significant; PBCS, peripheral stem cell support; PBO, placebo; PDS, primary debulking surgery; PLD, pegylated liposomal doxorubicin; PTX, paclitaxel; QoL, quality of life; q1w, every week; q3w, every 3 weeks; TPT, topotecan; VAP, valspodar

[β]Includes ataxia, paresthesia, dizziness, headache, and hypoesthesia

*All grades

**Central

[μ]Motor

[Δ]Cranial

[£]Sensory

* Data available for EORTC QLQ-C30 and QLQ-OV28

**Data available for NScore

Adjuvant chemotherapy

Platinum-based doublet

Cisplatin versus carboplatin

Two trials (GOG 158 and AGO-OVAR 3) [48,50] demonstrated that carboplatin plus paclitaxel is non-inferior to cisplatin plus paclitaxel with respect to PFS. In the AGO-OVAR 3 trial, women were followed for a mean period of 49.9 months in the carboplatin plus paclitaxel arm and 48.5 months in the cisplatin plus paclitaxel arm. Carboplatin plus paclitaxel was associated with a higher frequency of grade 3 or 4 neutropenia (36.9% versus 22.0%, p<0.01), leukopenia (32.0% versus 10.7%, p<0.01), and thrombocytopenia (12.9% versus 1.0%, p<0.01), but a lower frequency of nausea (5.9% versus 14.3%, p=0.0001), vomiting (2.8% versus 10.4%, p<0.01), and sensory neuropathy (7.2% versus 13.5%, p=0.004) than cisplatin plus paclitaxel. Women who received carboplatin plus paclitaxel reported significantly higher global QoL scores after three cycles (mean difference, -3.67; 95% CI, -6.97 to -0.37) and at the end of treatment (mean difference, -13.28; 95% CI, -18.88 to -7.68). Moreover, mean scores for physical functioning (p=0.012), role functioning (p=0.005), and cognitive functioning (p=0.024) were significantly better with carboplatin plus paclitaxel [49]. When the women were stratified based on FIGO stage and volume of residual disease, no significant differences in survival were noted between the treatment regimens [50].

Cisplatin and carboplatin

After a median follow-up of six years, the platinum dose-intensified regimen with carboplatin plus cisplatin did not offer significant survival benefit over cyclophosphamide plus cisplatin and was associated with higher rates of grade 3 or 4 of anemia (26.3% versus 12.8%, p=0.0096), leukopenia (48.7% versus 34.2%, p=0.0256), and thrombocytopenia (76.3% versus 22.2%, p<0.01) [51]. In the HeCOG trial [10], paclitaxel plus alternating carboplatin and cisplatin did not significantly improve survival compared with paclitaxel plus carboplatin alone after a median follow-up of 61 months. Grade 3 or 4 nausea and vomiting (8.4% versus 1.6%, p=0.0135) occurred significantly more often with paclitaxel plus alternating carboplatin and cisplatin.

Anthracyclines

In the MITO-2 trial [11] with a median follow-up of 40 months, carboplatin plus pegylated liposomal doxorubicin did not provide a significant survival advantage over carboplatin plus paclitaxel and led to more grade 3 or 4 anemia (10.1% versus 3.7%, p=0.0003) and thrombocytopenia (15.9% versus 2.0%, p<0.01) but less neurotoxicity (0.3% versus 2.9%, p=0.0035). There were no significant differences in global QoL scores after three and six cycles between the treatment regimens.

Taxanes

One earlier trial compared cisplatin plus paclitaxel to cisplatin plus cyclophosphamide [52]. OS and PFS were improved with cisplatin plus paclitaxel but did not reach statistical significance. Toxicity profiles were similar between the two treatment regimens except for neurological symptoms, which favoured cisplatin plus cyclophosphamide (21.7% versus 3.3%, p=0.0023). In the other trial, SCOTROC 1 [12] did not demonstrate a survival advantage for carboplatin plus docetaxel over carboplatin plus paclitaxel after a median follow-up of 23 months. Treatment with carboplatin plus docetaxel was associated with more grade 3 or 4 neutropenia (94.1% versus 84.1%, p<0.01) but the women reported significantly better improvements in symptom scores.

Second-generation platinum

Paclitaxel plus nedaplatin (median follow-up of 44.6 months) achieved comparable survival outcomes as paclitaxel plus carboplatin (median follow-up of 47.6 months). The incidence of grade 3 or 4 leukopenia (10.9% versus 23.3%, p=0.0261) was significantly higher in the paclitaxel plus carboplatin regimen. Subgroup analysis showed that stage III to IV women experienced a significantly prolonged PFS (p=0.02) with paclitaxel plus nedaplatin [13].

Sequential doublet

In the OV16 trial [14] with a median follow-up of 43 months, four cycles of cisplatin plus topotecan followed by four cycles of carboplatin plus paclitaxel was significantly more toxic than eight cycles of carboplatin plus paclitaxel in terms of grade 3 or 4 neutropenia (84.7% versus 57.2%, p<0.01) and thrombocytopenia (45.6% versus 9.0%, p<0.01) and all-grade nausea (84.0% versus 76.8%, p=0.0096) and vomiting (57.4% versus 40.8%, p<0.01), but without improved survival. On the other hand, carboplatin plus paclitaxel was associated with substantially more all grades neurosensory effects (84.1% versus 74.1%, p=0.0004). There was also no significant QoL advantage for cisplatin plus topotecan followed by carboplatin plus paclitaxel [53]. In a multi-arm trial (GOG 0182-ICON5) [15], two different sequential doublets (carboplatin plus topotecan or gemcitabine followed by carboplatin plus paclitaxel) were evaluated against the standard regimen of carboplatin plus paclitaxel. Both sequential doublets provided no improvements in either PFS or OS after a median follow-up of 3.7 years. Subgroup analysis based on the extent of residual disease failed to show any survival benefit for one of the regimens.

Platinum-based triplet

Anthracyclines

The efficacy of adding doxorubicin as a third drug was examined in two trials. In the GOG 0182-ICON5 trial [15], a triplet combination with carboplatin, paclitaxel, and methoxypolyethylene glycosylated liposomal doxorubicin provided no survival advantage over carboplatin plus paclitaxel alone. There was also no difference in treatment effect based on the extent of residual disease. In the HeCOG trial [23], the addition of doxorubicin to cisplatin plus paclitaxel did not increase PFS (18.1 months versus 13.3 months, p=0.07) or OS (44.3 months versus 38.0 months, p=0.53) after a median follow-up of 57.5 months. There were no differences in grade 3 or 4 adverse effects between the two regimens, with the exception of neurotoxicity, which was higher in the carboplatin plus paclitaxel regimen (2.3% versus 0.0%, p=0.0293). Similarly, in the AGO-OVAR 5 [24] (median follow-up of 54 months) and NSGO-EORTC GCG-NCIC CTG [25] (median follow-up of 61 months) trials, the addition of epirubicin to carboplatin plus paclitaxel did not improve survival and induced significantly more toxicity. Moreover, women who received epirubicin reported significantly worse global QoL scores at the end of treatment (mean difference, 6.4; 95% CI, 2.7 to 10.1, p=0.001) and had significantly smaller improvement from baseline to mean global QoL scores (p=0.0112). Subgroup analysis based on FIGO stage and volume of residual disease did not favour one regimen over the other [24].

Gemcitabine

In both the GOG 0182-ICON5 [15] and AGO-OVAR 9 [26] (median follow-up of 49 months) trials, the addition of gemcitabine to carboplatin plus paclitaxel did not offer any survival benefits. In fact, women who received gemcitabine had a significantly reduced PFS (17.8 months versus 19.3 months; HR, 1.18; 95% CI, 1.06 to 1.32, p=0.0044) and experienced considerably more hematologic toxicities. Global QoL scores were also significantly worse with

gemcitabine after three cycles (p=0.0218), but no significant differences were observed after completion of treatment [26].

Topotecan

The addition of topotecan to a standard carboplatin plus paclitaxel regimen did not result in any advantages in survival at five years and was associated with higher rates of grade 3 or 4 anemia (6.4% versus 1.8%, p=0.0343) and neutropenia (39.7% versus 23.5%, p=0.0016). Subgroup analysis based on histological subtypes and volume of residual disease did not yield any differences in treatment effect [27].

Dose intensification

In the GINECO trial [54], increasing cyclophosphamide dose intensity from 500 to 1800 mg/m^2 (with filgrastim support) in a regimen with cisplatin and epirubicin did not improve survival outcomes after a median follow-up of 84 months. Higher cyclophosphamide dose resulted in significantly more grade 3 or 4 anemia (42.5% versus 20.7%, p=0.0034) and thrombocytopenia (32.9% versus 12.2%, p=0.0019). In the HIDOC-EIS trial [55], cyclophosphamide plus paclitaxel followed by high-dose carboplatin plus paclitaxel (with peripheral blood stem cell support) provided no survival benefit over standard dose chemotherapy with carboplatin and paclitaxel after 38.1 months. In another trial, prolonging paclitaxel infusion from 24 to 96 hours in combination with cisplatin produced no advantages in survival and was associated with higher incidences of grade 3 or 4 anemia (18.1% versus 6.5%, p=0.0033) [56]. In the SCOTROC 4 trial [57] with a median follow-up of 26 months, intrapatient dose escalation of carboplatin failed to increase efficacy compared with flat dosing and produced a significantly worse toxicity profile. Patient-reported QoL scores were similar between the two treatment regimens.

Weekly versus every 3 weeks

Single-agent

In an earlier trial, a dose-dense weekly regimen of single-agent cisplatin was compared to a standard three-weekly schedule. After a median follow-up of 16.8 years, weekly cisplatin caused higher rates of grade 3 or 4 leukopenia (8.9% versus 2.9%, p=0.0327) without providing a significant survival advantage over three-weekly cisplatin [58].

Platinum-based doublet

Three trials compared dose-dense weekly paclitaxel in combination with three-weekly carboplatin to standard paclitaxel and carboplatin administered every three weeks. In two of the trials (GOG 0262 with a median follow-up of 28 months and JGOG 3016 with a median follow-up of 76.8 months) [16,17], weekly paclitaxel significantly prolonged PFS (GOG 0262, 14.2 months versus 10.3 months; HR, 0.62; 95% CI, 0.40 to 0.95, p=0.03; JGOG 3016, 28.2 months versus 17.5 months; HR, 0.76; 95% CI, 0.62 to 0.91, p=0.0037) with the latter trial also observing a significantly better OS (100.5 months versus 62.2 months; HR, 0.79; 95% CI, 0.63 to 0.99, p=0.039). In particular, women with serous tumours (OS, 100.5 months versus 61.2 months; HR, 0.76; 95% CI, 0.59 to 0.97, p=0.0252; PFS, 28.7 months versus 17.5 months; HR, 0.70, 95% CI, 0.57 to 0.86, p=0.0007), stage III disease with residual volume greater than 1 cm or stage IV disease (OS, 50.9 months versus 35.0 months; HR, 0.75; 95% CI, 0.58 to 0.98, p=0.0323; PFS, 17.6 months versus 12.1 months; HR, 0.70; 95% CI, 0.56 to 0.89, p=0.0028) benefited considerably with weekly paclitaxel. However, women with clear cell or mucinous tumours, stage II disease, residual volume less than or equal to 1 cm, and disease of the fallopian tubes did not see any significant benefits from weekly paclitaxel. In the other trial with a median follow-up of 36.8 months, results from ICON8 [18] failed to show a significant

improvement in PFS with weekly paclitaxel nor was there any significant treatment effect in subgroups based on FIGO stage and histological subtype. However, it is important to note that JGOG 3016 [17] was conducted in Japan while ICON8 [18] enrolled a predominantly European population. Furthermore, women in the GOG 0262 trial who elected to receive bevacizumab with weekly paclitaxel (84% of women who underwent randomization) did not see a significant improvement in PFS. Overall, weekly paclitaxel was associated with higher frequency of grade 3 or 4 anemia across all three trials [16,18,19]. ICON8 [18] also found higher rates of grade 3 or 4 neutropenia (35.3% versus 15.0%, p<0.01), leukopenia (15.6% versus 4.3%, p<0.01) and thrombocytopenia (9.4% versus 4.1%, p=0.0007) with weekly paclitaxel. For QoL assessment, women who received weekly paclitaxel generally reported lower scores in the FACT-T and FACT-O TOI subscales but overall global QoL scores between the two treatment schedules did not differ significantly [16,20,21].

Two trials (MITO-7 with a median follow-up of 22.3 months and ICON8) [18,22] compared carboplatin plus paclitaxel administered every week versus every three weeks. Neither of these trials detected a significant improvement in survival for weekly carboplatin plus paclitaxel. Interestingly, higher rates of grade 3 or 4 neutropenia (29.8% versus 15.0%, p<0.01) and leukopenia (13.9% versus 4.3%, p<0.01) were observed in women who received weekly carboplatin plus paclitaxel in the ICON8 trial [18], while the opposite is true in the MITO-7 trial [22] where weekly carboplatin plus paclitaxel was associated with less grade 3 or 4 neutropenia (41.9% versus 50.0%, p=0.0216) and leukopenia (13.8% versus 19.5%, p=0.0306). In addition, weekly carboplatin plus paclitaxel led to fewer incidences of thrombocytopenia (1.0% versus 6.0%, p<0.01) [22], vomiting (1.2% versus 3.3%, p=0.0238) [18] and neuropathy (0.0% versus 2.5%, p=0.0015) [22]. Patient-reported QoL scores for the FACT-O, FACT-O TOI, FACT/GOG-Ntx and Ntx subscales tend to favour the weekly carboplatin plus paclitaxel regimen [21.22]. In none of the subgroups based on FIGO stage, extent of residual disease, and histological subtype was there any evidence of superiority of one of the treatment schedules.

i.p. versus i.v.

Two trials compared i.p. chemotherapy versus conventional i.v. chemotherapy. In the GOG 172 trial [33], six cycles of standard i.v. cisplatin plus i.v. paclitaxel (median follow-up of 48.2 months) was compared to an intensive regimen of i.v. paclitaxel over a 24-hour period followed by i.p. cisplatin and i.p. paclitaxel for six cycles (median follow-up of 52.6 months). Significant improvements in both OS (65.6 months versus 49.7 months; HR, 0.75; 95% CI, 0.58 to 0.97, p=0.03) and PFS (23.8 months versus 18.3 months; HR, 0.80; 95% CI, 0.64 to 1.00, p=0.05) were observed with i.p. chemotherapy. However, the decreased risk of death associated with i.p. chemotherapy was at the expense of more grade 3 or 4 leukopenia (75.6% versus 63.8%, p=0.0093), thrombocytopenia (11.9% versus 3.8%, p=0.0022), and neuropathy (19.4% versus 8.6%, p=0.0015) as well as worse QoL scores (for physical well-being, p<0.001; functional well-being, p<0.001; ovarian cancer symptoms, p<0.001; abdominal discomfort, p<0.001; and neurotoxicity, p=0.001) before cycle 4 and three to six weeks after treatment. Only symptoms of neurotoxicity (p=0.003) remained significantly worse in the long term (12 months after treatment) [34]. Moreover, the prognostic relevance of BRCA1 expression was examined in a post-hoc analysis of the GOG 172 trial [35]. The authors reported that women with aberrant, but not normal BRCA1 expression had increased OS (84.1 months versus 47.7 months, p=0.0002) when treated with i.p. chemotherapy after a median follow-up of 86 months. In the other trial, GOG 252 [36] compared dose-dense weekly i.v. paclitaxel with i.v. carboplatin (AUC=6) every three weeks (i.v. carboplatin) to two different i.p. chemotherapy regimens consisting of dose-dense weekly i.v. paclitaxel with i.p. carboplatin (AUC=6) every three weeks (i.p. carboplatin) and i.v. paclitaxel over three hours, followed by lowered-dose i.p. cisplatin plus i.p. paclitaxel every three weeks (i.p. cisplatin). Additionally, all women

received i.v. bevacizumab every three weeks. Neither i.p. regimen significantly improved survival over the i.v. regimen after a median follow-up of 84.8 months. While the toxicity profile of i.p. carboplatin was similar to that of i.v. carboplatin, surprisingly, i.p. cisplatin was significantly less toxic in terms of grade 3 or 4 anemia (17.9% versus 26.6%, p=0.0008), neutropenia (64.4% versus 72.0%, p=0.0092), and thrombocytopenia (6.1% versus 17.6%, p<0.01) but not nausea and vomiting (11.0% versus 5.1%, p=0.0005). The patient-reported QoL scores across all subscales during treatment generally favoured the i.v. regimen over the two i.p. regimens. When stratified by FIGO stage and volume of residual disease, none of the subgroups of women benefited more or less from any of the treatment regimen.

Targeted therapy

Results from an earlier trial (median follow-up of 736 days) showed that the addition of valspodar to carboplatin plus paclitaxel did not improve survival and was significantly more toxic in terms of grade 3 or 4 anemia (34.4% versus 21.8%, p=0.0001), leukopenia (72.5% versus 50.7%, p<0.01), thrombocytopenia (25.6% versus 17.8%, p=0.0103), nausea (8.3% versus 3.4%, p=0.0042), vomiting (6.7% versus 3.2%, p=0.0271), and central and peripheral nervous system effects (20.4% versus 2.1%, p<0.01) [28]. In the GOG 0218 trial [30-32], the addition of bevacizumab to carboplatin plus paclitaxel, followed by 16 cycles of placebo, was associated with a marked increase in grade 3 or 4 neutropenia (63.3% versus 57.7%, p=0.0465), but without any added benefit in survival after a median follow-up of 102.9 months. Women who received bevacizumab had significantly lower FACT-O TOI scores (p<0.001) during therapy but this QoL difference did not persist after completion of treatment. No treatment effect was observed based on *BRCA* mutation, histological subtype or FIGO stage.

Immunotherapy

The addition of IFN-γ 1b to standard carboplatin plus paclitaxel regimen was associated with a survival disadvantage and higher rates of grade 3 or 4 neutropenia (41.4% versus 33.3%, p=0.0152) and leukopenia (10.6% versus 4.1%, p=0.0003). The trial was terminated early at second interim analysis, which revealed significantly shorter OS (37.4 months versus not estimable; HR, 1.45; 95% CI, 1.15 to 1.83, p=0.0014) for women receiving IFN-γ 1b [29].

Ongoing, Unpublished, or Incomplete Studies

The National Library of Medicine (https://clinicaltrials.gov/) was searched on October 21, 2019 for potential trials meeting the selection criteria for this systematic review. There were eight ongoing trials that would be eligible for inclusion in the update of this guideline in the future.

Study of Upfront Surgery Versus Neoadjuvant Chemotherapy Followed by Interval Debulking Surgery for Patients With Stage IIIC and IV Ovarian Cancer	
Protocol ID:	NCT02859038
Study type:	Phase III RCT
Estimated enrollment:	456 participants
Last updated:	October 18, 2019
Estimated study completion date:	December 2022
Sponsor:	Shanghai Gynecologic Oncology Group
Status:	Recruiting

Multi-center, Randomized Controlled, Phase III Trials to Evaluate the Safety and Effectiveness After Reduction of Cycles of Neoadjuvant Chemotherapy for Advanced Epithelial Ovarian, Fallopian and Primary Peritoneal Cancer	
Protocol ID:	NCT03693248
Study type:	Phase III RCT
Estimated enrollment:	298 participants
Last updated:	December 10, 2019
Estimated study completion date:	December 31, 2023
Sponsor:	Seoul National University Hospital
Status:	Recruiting

Trial on Radical Upfront Surgery in Advanced Ovarian Cancer	
Protocol ID:	NCT02828618
Study type:	RCT
Estimated enrollment:	797 participants
Last updated:	August 16, 2019
Estimated study completion date:	April 2023
Sponsor:	AGO Study Group
Status:	Active, not recruiting

A Randomized Phase II/III Trial of Intravenous (IV) Paclitaxel Weekly Plus IV Carboplatin Once Every 3 Weeks Versus IV Paclitaxel Weekly Plus Intraperitoneal (IP) Carboplatin Once Every 3 Weeks in Women With Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Cancer	
Protocol ID:	NCT01506856
Study type:	Phase II/III RCT
Estimated enrollment:	654 participants
Last updated:	February 15, 2019
Estimated study completion date:	May 2020
Sponsor:	Gynecologic Oncology Trial & Investigation Consortium
Status:	Active, not recruiting

Addition of Decitabine to Carboplatin-Paclitaxel in First-Line Treatment of Advanced Ovarian Cancer: A Phase 2-3, Open-label, Randomised Controlled Trial	
Protocol ID:	NCT02159820
Study type:	Phase II/III RCT
Estimated enrollment:	500 participants
Last updated:	June 10, 2014
Estimated study completion date:	June 2024
Sponsor:	Chinese PLA General Hospital
Status:	Recruiting

A Phase 3 Placebo-Controlled Study of Carboplatin/Paclitaxel With or Without Concurrent and Continuation Maintenance Veliparib (PARP Inhibitor) in Subjects With Previously Untreated Stages III or IV High-Grade Serous Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer	
Protocol ID:	NCT02470585
Study type:	Phase III RCT
Estimated enrollment:	1140 participants
Last updated:	September 24, 2019
Estimated study completion date:	December 8, 2026
Sponsor:	AbbVie
Status:	Active, not recruiting

A Phase III, Multicenter, Randomized, Study of Atezolizumab Versus Placebo Administered in Combination With Paclitaxel, Carboplatin, and Bevacizumab to Patients With Newly-Diagnosed Stage III or Stage IV Ovarian, Fallopian Tube, or Primary Peritoneal Cancer	
Protocol ID:	NCT03038100
Study type:	Phase III RCT
Estimated enrollment:	1300 participants
Last updated:	January 9, 2020
Estimated study completion date:	December 1, 2021
Sponsor:	Hoffmann-La Roche
Status:	Active, not recruiting

A Phase III Trial of Carboplatin and Paclitaxel Plus Placebo Versus Carboplatin Paclitaxel Plus Concurrent and Extended Bevacizumab in Chinese Women With Newly Diagnosed, Previously Untreated, Stage III or Stage IV Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer	
Protocol ID:	NCT03635489
Study type:	Phase III RCT
Estimated enrollment:	100 participants
Last updated:	January 10, 2020
Estimated study completion date:	May 6, 2021
Sponsor:	Hoffmann-La Roche
Status:	Active, not recruiting

DISCUSSION

Newly diagnosed EOC most commonly presents with disease that is already at an advanced stage. Once diagnosed, the goals of treatment are to prevent or delay the recurrence of disease. This involves applying the available surgical and systemic therapy modalities in an optimal fashion. Factors that need to be considered when applying these treatment modalities

include patient variables (PS, co-morbidities, underlying genetic factors), the biology of the tumour and disease-related factors influencing ability to optimally debulk (with the goal of no visible residual disease on completion of surgery), theoretical considerations of early versus later debulking [59], the optimal sequencing of surgery and chemotherapy, the optimal dose, schedule and route of chemotherapy, the optimal combination of agents and duration of treatment, and the role of other targeted and biologic agents.

Historically, primary debulking surgery followed by adjuvant chemotherapy has been the standard of treatment for advanced EOC [43]. Several subsequent studies have since challenged the value of this approach by advocating for the use of neoadjuvant chemotherapy. Two earlier trials (EORTC 55971 and CHORUS) [1,3] showed that OS was non-inferior for neoadjuvant chemotherapy. Long-term follow-up data from both of these trials confirmed better survival with neoadjuvant chemotherapy, particularly in women with stage IV disease [9]. However, a more recent trial (JCOG 0602) [4] was unable to corroborate the non-inferiority of neoadjuvant chemotherapy. Additionally, The SCORPION trial [6] which used a superiority design, failed to show superiority with respect to PFS for neoadjuvant chemotherapy. Nonetheless, neoadjuvant chemotherapy was associated with lower postoperative mortality and a general trend towards fewer adverse events and higher QoL scores [1,3,7]. Given these considerations, as well as taking into account the theoretical benefit of reducing tumour bulk early on and thereby reducing the risk of emergence of drug resistant clones, the recommendation was to perform primary debulking surgery wherever possible (ideally in women who are deemed clinically fit and with potentially resectable disease), but to defer surgery in those women with high risk profiles that would contraindicate upfront cytoreductive surgery. Thus, all newly diagnosed stage II, III, or IV EOC should be assessed by a gynecologic oncologist to determine eligibility for surgical resection.

In the post-surgical adjuvant setting, six to eight cycles of three-weekly paclitaxel (175 mg/m^2) and carboplatin (AUC=5/6) is recommended after primary cytoreductive surgery. For those who are unable to tolerate paclitaxel, due to hypersensitivity reactions or peripheral neuropathy, an alternate regimen consisting of docetaxel (75 mg/m^2) may be offered with carboplatin (AUC=5) (SCOTROC 1) [12]. The docetaxel regimen resulted in numerically less neurotoxicity but greater hematologic toxicity. Dose-dense scheduling to improve efficacy has also been explored in a number of trials. Adjuvant chemotherapy with six cycles of dose-dense weekly paclitaxel (80 mg/m^2) in combination with three-weekly carboplatin (AUC=6) (JGOG 3016) [17] can be considered for women with stage II, III, or IV EOC of Japanese descent. This study enrolled only women living in Japan, and these results were not confirmed in the ICON-8 trial [18] in a mainly European population. It is possible that there are pharmacogenomic differences between the Japanese and non-Japanese populations, which limits the generalizability of these results to the Ontario context. Thus, this regimen could not be recommended outside the Japanese population.

The evidence for the incorporation of a third chemotherapy drug to paclitaxel and carboplatin (pegylated liposomal doxorubicin [GOG 0182-ICON5], doxorubicin [HeCOG], epirubicin [AGO-OVAR 5 and NSGO-EORTC GCG-NCIC CTG], gemcitabine [GOG-182-ICON5 and AGO-OVAR 9], and topotecan) [15,23-27] has not been shown to improve OS or PFS. Given the absence of a survival benefit along with increased toxicity associated with the addition of a third agent, it is not recommended to use platinum-based triplet chemotherapy in women with stage II, III, or IV EOC. In terms of targeted or immunotherapy agents, the addition of valspodar to carboplatin and paclitaxel chemotherapy resulted in increased toxicity and no improvement in survival [28]. Likewise, the addition of bevacizumab to carboplatin and paclitaxel (GOG 0218) [30-32] was associated with increased neutropenia, and did not show an OS benefit. In spite of this finding, high-risk women, defined as those with sub-optimally debulked (residual disease >1 cm) stage III disease, inoperable stage III, or stage IV disease, appeared to see a benefit in

survival with the incorporation of bevacizumab concurrent with chemotherapy and continued as maintenance [60-62]. A similar case could be made for advocating for the concurrent use of veliparib with adjuvant therapy and continued as maintenance in stage III or IV EOC with homologous-recombination deficiency [63]. Finally, the addition of IFN-γ 1b to standard carboplatin plus paclitaxel regimen was associated with a survival disadvantage and greater hematologic toxicity [29].

The role of intraperitoneal administration of chemotherapy has been less clear and has not been universally embraced as standard of care. GOG 172 [33,34] reported a significant improvement in OS and PFS with i.p. cisplatin and paclitaxel but at the expense of greater hematologic and neurologic toxicities and reduced QoL scores. The survival benefit was most marked in those women whose tumours had reduced BRCA1 expression [35]. Conversely, both regimens consisting of i.p. chemotherapy (i.p. cisplatin and i.p. carboplatin) plus bevacizumab in the GOG 252 trial [36] offered no survival benefit and some harms in terms of toxicity and QoL. This then raised the question as to why GOG 252 failed to confirm the superiority of i.p. chemotherapy as demonstrated in GOG 172. This may have been due to a number of differences in how GOG 252 was carried out compared to GOG 172, including 1) using the standard comparator arm of carboplatin and paclitaxel, which has been demonstrated to be superior to cisplatin and paclitaxel; 2) suboptimal protocol compliance and cross-over; 3) a lower dose of i.p. cisplatin (75 mg/m^2 compared to 100 mg/m^2); 4) paclitaxel infused over three hours rather than 24 hours in the i.p. cisplatin arm; and 5) the addition of bevacizumab to all arms. The Japanese iPocc trial (JGOG 3019), which is comparing the efficacy and safety of i.p. and i.v. carboplatin chemotherapy in combination with weekly i.v. administration of paclitaxel, has completed accrual and the results of this trial are expected to be available later in the year. This study is expected to either confirm or refute the results of the GOG 252 trial. Until these results are available, it was felt that the substantial increase in OS and PFS conferred by i.v. paclitaxel (135 mg/m^2) plus i.p. cisplatin (100 mg/m^2) and paclitaxel (60 mg/m^2) in the GOG 172 trial outweighed the associated adverse events and lower patient-reported QoL scores, especially in women with tumours having reduced BRCA1 expression. Accordingly, this regimen can be considered as a treatment option for stage III optimally debulked women (≤1 cm residual disease) who did not receive neoadjuvant chemotherapy. The ability to deliver i.p. chemotherapy will be influenced by consideration of this option at the time of primary debulking surgery (i.e., placement of the i.p. port at the time of surgery) and the experience and support at individual centres to be able to deliver this therapy. i.p. administration of chemotherapy with bevacizumab should not be considered as an option for stage II to IV optimally debulked women (≤1 cm residual disease).

While this systematic review included only RCTs as the evidentiary basis for guideline recommendations, it is not without limitations. Most notably, the generalizability of findings from some of the studies may be restricted. The JGOG 3016 trial [17] is a prime example in that it represented a very distinct subset of the general population. Another example of this potential for bias is the selection of women into the study that may already have a poorer prognosis. This could partially explain the large differences in median OS reported in the EORTC 55971 [1] and CHORUS [3] trials and those from the JCOG 0602 [4] and SCORPION [6] trials. Lastly, whether the surgeries performed in the studies are equivalent to those conducted in high-volume, specialized centres may impact survival outcomes. This is particularly important as it relates to i.p. therapy where the need for institutional infrastructure and expertise is considerable and must be available.

CONCLUSIONS

Women with newly diagnosed EOC should be evaluated by a gynecologic oncologist to determine eligibility for resection, and where ever possible be offered primary debulking

surgery. In those women with high-risk profiles, interval debulking after neoadjuvant chemotherapy should be considered. The standard of care consisting of i.v. carboplatin and paclitaxel is recommended. In women with pre-existing neuropathy, or those who develop this during treatment, and women with hypersensitivity reactions to paclitaxel, replacing the taxane with docetaxel should be an option. Currently, there is no evidence to support adding a third agent to the standard carboplatin and paclitaxel regimen and the results of the iPocc study will clarify the role of i.p. chemotherapy in this patient population.

Neoadjuvant and adjuvant 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 GDG Expert Panel and the PEBC Report Approval Panel (RAP) (Appendix 1). The results of these evaluations and the Working Group's responses are described below.

Expert Panel Review and Approval

Of the eight members of the GDG Expert Panel, seven members voted and one abstained, for a total of 87.5% response in August 2020. Of those who voted, seven approved the document (100%). The main comments from the GDG 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. The international recommendation for achieving optimal cytoreduction is no residual disease.	This remains controversial as optimal is still considered ≤1 cm; however, we have also added "ideally to no visible disease" to the qualifying statement for recommendation 1.
2. Please define poor performance status according to Eastern Cooperative Oncology Group.	We have added a definition to the qualifying statement for recommendation 1.
3. If the alternative to paclitaxel and carboplatin is offered, need to add the dose adjustment for carboplatin with docetaxel as per SCOTROC 1 trial [12].	We have added the dose adjustment for carboplatin to the qualifying statement for recommendation 2.
4. Should there be an additional statement somewhere about the role of additional maintenance treatments (bevacizumab, poly ADP ribose polymerase [PARP]) for certain subgroups?	Maintenance therapies are specifically addressed in a separate guidance document (4-18: Consolidation or maintenance systemic therapy for newly diagnosed stage II, III, or IV epithelial ovary, fallopian tube, or primary peritoneal carcinoma). Please see related guidelines.
5. Modify to Japanese heritage or descent or ethnicity, not from Japan.	We have modified the qualifying statement for recommendation 2 to "Japanese descent".
6. Really need to specify bevacizumab has no benefit with adjuvant chemotherapy if not continued but benefit when started with adjuvant chemotherapy and continued as maintenance for high-risk. Important to highlight as bevacizumab needs to be started with adjuvant chemotherapy and not only maintenance or last cycle of chemotherapy.	We have modified the wording of recommendation 4 to provide more clarity. We also added a qualifying statement to support the use of bevacizumab as adjuvant therapy concurrent with paclitaxel and carboplatin and continued as maintenance therapy in high-risk disease women.
7. Would suggest changing to "can be considered" as opposed to "is recommended" since debate around intraperitoneal chemotherapy persists as	We have modified recommendation 5 to "can be considered".

well as the negative results from GOG 252 [36].	
8. I think we should address HIPEC option better. There is strong evidence from the Willemien J. van Driel study [64] for OS benefit of 12 months in stage III disease patients that had neoadjuvant chemotherapy and had HIPEC at the time of interval cytoreductive surgery versus patients who had only interval cytoreductive surgery without HIPEC. I think we should add this to the treatment options for this group of patients.	This is beyond the scope for this review. HIPEC has been reviewed in a separate guidance document (17-12: Indications for hyperthermic intraperitoneal chemotherapy with cytoreductive surgery). Please see related guidelines.

RAP Review and Approval

Three RAP members, including the Scientific Director of PEBC, reviewed and approved this document in August 2020. The main comments from the RAP and the Working Group's responses are summarized in Table 5-2. Comments that are similar to those from GDG Expert Panel members in Table 5-1 are not listed again here to avoid duplication.

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

Comments	Responses
1. I find the qualifying statement for recommendation 1 a bit vague. Maybe consider adding one or two examples of the most common significant symptoms.	We have added a few examples of the most common significant disease-related symptoms to the qualifying statement for recommendation 1.
2. I am not clear as to why the use of neoadjuvant chemotherapy is a weak recommendation in comparison to a regular recommendation for adjuvant therapy. It appears the studies were fairly rigorous, the data strong, and there seems not to be a detrimental effect of neoadjuvant chemotherapy on surgical outcomes.	We have added a point to the justification for recommendation 1 to explain the rationale for a weak recommendation.

EXTERNAL REVIEW

Targeted Peer Review

Six targeted peer reviewers from Ontario, British Columbia and Quebec who are considered to be clinical and/or methodological experts on the topic were identified by the Working Group. Three agreed to be the reviewers (Appendix 1). Three responses were received. Results of the feedback survey are summarized in Table 5-3. The main comments from targeted peer reviewers and the Working Group's responses are summarized in Table 5-4.

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

	Reviewer Ratings (N=3)				
Question	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the guideline development methods.	0	0	0	2	1
2. Rate the guideline presentation.	0	0	1	1	1

3. Rate the guideline recommendations.	0	0	1	1	1
4. Rate the completeness of reporting.	0	0	1	1	1
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?	0	0	1	2	0
6. Rate the overall quality of the guideline report.	0	0	0	2	1
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
7. I would make use of this guideline in my professional decisions.	0	0	1	1	1
8. I would recommend this guideline for use in practice.	0	0	0	2	1
9. What are the barriers or enablers to the implementation of this guideline report?	None were stated by the reviewers				

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

Comments	Responses
1. The Working Group is very small so personal bias will affect the strength of recommendations, specifically relevant to the neoadjuvant chemotherapy question where there is bias of surgeons towards upfront surgery. This small size of the Working Group is my major problem with the paper as inevitably it will lead to this being more personal opinion than a true reflection of what the majority of those who practice in this area believe.	In addition to the Working Group (which included one medical oncologist, three gynecologic oncologists, two guideline methodologists, and two patient representatives), an expert panel comprised of a diverse group of seven clinicians (Table 5-1 and Table A1-2) as well as a three-person panel with methodology expertise (Table 5-2 and Table A1-3) reviewed and approved the recommendations.
2. Caelyx can replace Carbo-Taxol with equivalent efficacy.	In the MITO-2 trial [11] with a median follow-up of 40 months, carboplatin plus pegylated liposomal doxorubicin did not provide a significant survival advantage over carboplatin plus paclitaxel and led to more grade 3 or 4 anemia (10.1% versus 3.7%, p=0.0003) and thrombocytopenia (15.9% versus 2.0%, p<0.01) but less neurotoxicity (0.3% versus 2.9%, p=0.0035).
3. According to GOG 172, paclitaxel is given as 135 mg/m^2 over 24 hours with cisplatin. On the other hand, paclitaxel is given as 175 mg/m^2 over 3 hours with carboplatin.	We have added information regarding infusion duration to recommendation 1, 2 and 5.
4. There is a potential role for maintenance paclitaxel comparing 12 cycles to 3 cycles of paclitaxel after first-line chemotherapy. The recent application of PARP (SOLO-1) can not be ignored in first line strategy as within 8-12 weeks of completion of chemotherapy. The concept of maintenance/switch maintenance was not elaborated but is part of the continuum.	Maintenance therapies are specifically addressed in a separate guidance document (4-18: Consolidation or maintenance systemic therapy for newly diagnosed stage II, III, or IV epithelial ovary, fallopian tube, or primary peritoneal carcinoma). Please see qualifying statement for recommendation 4 and related guidelines.
5. The evaluation by a gynecologic oncologist for surgical eligibility (primary surgery	The criteria used to identify women who are not suitable for primary cytoreductive surgery were

versus interval cytoreduction) should be substantiated by reference.	based on expert consensus from the Working Group and Expert Panel.
6. Discussion on HIPEC, perhaps incorporate the conclusion from other guidelines.	This is beyond the scope for this review. HIPEC has been reviewed in a separate guidance document (17-12: Indications for hyperthermic intraperitoneal chemotherapy with cytoreductive surgery). Please see related guidelines.
7. Discussion on histological heterogeneity with regards to choice of treatment.	Subgroup analysis based on histological subtypes did not favour one regimen over the other (Appendix 5). Further research is required to provide treatment guidance for different histological types or molecular subsets in the target population.
8. Discussion on BRCA-HRD status as part of the decision-making assessment of the whole therapeutic strategy.	Only one post-hoc analysis examined the prognostic relevance of BRCA1 expression [35]. As briefly mentioned in the discussion, women with aberrant BRCA1 expression had increased OS when treated with i.p. chemotherapy. Further research is required to investigate BRCA-HRD status as part of treatment decision making in the target population.
9. How to justify recommending up to eight cycles of carboplatin and paclitaxel with the literature.	Despite the majority of the trials administering six cycles of carboplatin and paclitaxel, there were four trials (JCOG 0602 [4], OV16 [14], GOG 0182-ICON5 [15], and NSGO-EORTC GCG-NIC CTG[25]) that included up to eight cycles in their study arms. Therefore, six cycles is the standard but one could use up to eight and be within the parameters of prior trials.

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 with an interest in ovarian cancer in the PEBC database were contacted by email to inform them of the survey. One hundred ten professionals were contacted, all of which practice in Ontario. Sixteen (14.5%) responses were received. Eight stated that they did not have interest in this area or were unavailable to review this guideline at the time, and one stated they were now retired. The results of the feedback survey from seven people are summarized in Table 5-5. The main comments from the consultation and the Working Group's responses are summarized in Table 5-6.

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

	N=7 (6.4%)				
General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.	0	0	0	4	3
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.	0	0	0	3	4
3. I would recommend this guideline for use in practice.	0	0	0	3	4

4. What are the barriers or enablers to the implementation of this guideline report?	Barriers: • Knowledge of disease process and patient population • Access to resources and chemotherapy units, may limit the various treatment options. • Access to other supportive services (i.e., intensive care unit/emergency room) • Skilled practitioners Enablers: • Treatment options outlined use current and widely used chemotherapy regimens with consistent standards of oncology expertise at the medical evaluation and treatment delivery levels across regional cancer programs in Ontario.

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

Comments	Responses
1. Most gynecologic oncologists feel that optimal debulking is preferable to neoadjuvant chemotherapy. It is an issue of feasibility, surgeon skills, and decision making. These are hard to enunciate in a written document. Some surgeons are very aggressive, some not at all, and most in between.	This is certainly a valid point.

CONCLUSION

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

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Appendix 1: Affiliations and Conflict of Interest Declarations

Table A1-1: Members of the Working Group

Name	Affiliation	Declarations of interest
Hal Hirte Medical Oncologist	Division of Medical Oncology, Juravinski Cancer Centre, McMaster University, Hamilton, Ontario, Canada	Astra Zeneca and Merck advisory board member; participated in SOLO-1 and ICON7 trials.
Raymond Poon Health Research Methodologist	Program in Evidence-Based Care, Ontario Health (Cancer Care Ontario), Department of Oncology, McMaster University, Hamilton, Ontario, Canada	None declared
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
Taymaa May Gynecologic Oncologist	Department of Obstetrics and Gynecology, Princess Margaret Hospital, University of Toronto, Toronto, Ontario, Canada	None declared
Josee-Lyne Ethier Medical Oncologist	Division of Cancer Care and Epidemiology, Cancer Research Institute, Cancer Centre of Southeastern Ontario, Department of Oncology and Medicine, 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); local principal investigator for LIGHT trial (Astra Zeneca), MK-7339 and MK-7902 trials (Merck)
Lauri Petz Patient	Patient representative	None declared
Jane Speakman Patient	Patient representative	None declared
Laurie Elit Gynecologic Oncologist	Department of Obstetrics and Gynecology, McMaster University, Hamilton, Ontario, Canada	Co-investigator of clinical utility of BRCA testing— Grant from Astra Zeneca (2017-2019); Astra Zeneca advisory board member (2018-2019)

Table A1-2: Members of the Ovarian Cancer Guideline Development Group

Name	Affiliation	Declarations of interest

Limor Helpman Gynecologic Oncologist	Department of Obstetrics and Gynecology, Juravinski Cancer Centre, McMaster University, Hamilton, Ontario, Canada	Principal investigator for SOLO1, SOLO2, SOLO3, LIGHT (Astra Zeneca—Olaparib), and PRIMA (Tesaro—Niraparib)
Liat Hogen Gynecologic Oncologist	Department of Obstetrics and Gynecology, Princess Margaret Hospital, University of Toronto, Toronto, Ontario, Canada	None declared
Stephanie Lheureux Medical Oncologist	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; principal investigator for different 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 Medical Oncologist	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; site-principal investigator for 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 Medical Oncologist	Division of Medical Oncology, Western University, London, Ontario, Canada	Received honoraria from Astra Zeneca for speaking (Advisory Board); local principal investigator for Astra Zeneca, Merck, Tesaro, and Clovis
Allison Ball Gynecologic Oncologist	Department of Obstetrics and Gynecology, Royal Victoria Regional Health Centre, University of Toronto, Toronto, Ontario, Canada	Received honorarium from Astra Zeneca for speaking; principal investigator for the OVC.2 trial
Lilian Gien Gynecologic Oncologist	Department of Obstetrics and Gynecology, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada	None declared
Sarah E. Ferguson Gynecologic Oncologist	Department of Obstetrics and Gynecology, Princess Margaret Hospital, University of Toronto, Toronto, Ontario, Canada	None declared

Table A1-3: Members of the Report Approval Panel

Name	Affiliation	Declarations of interest
Jonathan Sussman Radiation Oncologist	Department of Oncology, Juravinski Cancer Centre, Hamilton, Ontario, Canada	None declared
William (Bill) Evans Professor Emeritus	Department of Oncology, McMaster University, Hamilton, Ontario, Canada	None declared
Sebastien Hotte Medical Oncologist	Department of Oncology, Juravinski Cancer Centre, Hamilton, Ontario, Canada	None declared

Table A1-4: Targeted Peer Reviewers

Name	Affiliation	Declarations of interest
Paul Hoskins Medical Oncologist	British Columbia Cancer Agency, Department of Medicine, University of British Columbia, Vancouver, British Columbia, Canada	Received $5000 in travel grant from AstraZeneca; principal investigator for GOT/FIRST and GOT/PRIMA (Niraparib); president of Gynecologic Oncology Canada (2014-2016);

		received pharma grants for meetings
Aalok Kumar Medical Oncologist	British Columbia Cancer Agency, Department of Medicine, University of British Columbia, Vancouver, British Columbia, Canada	Received $500 or more to act in a consulting capacity for GSK and AstraZeneca; received grants from AstraZeneca; principal investigator for PRIMA and ATHENA
Diane Provencher Gynecologic Oncologist	Head of Oncological Gynaecology Service, CHUM, Department of Obstetrics and Gynecology, Université de Montréal, Montreal, Quebec, Canada	None declared

Appendix 2: Literature Search Strategy

The search was conducted in Embase, Medline, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Health Technology Assessment on October 3, 2019.

Section A: Disease	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$)).mp.
	6	or/1-5
Section B: Intervention	7	drug therap$.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$)).mp.
	9	exp Immunotherapy/ or immunotherap$.mp.
	10	chemotherap$.mp.
	11	(adriamycin or carboplatin$ 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).mp.
	12	MEK$ inhibitor$.mp.
	13	(PD-325901 or Selumetinib or AZD6244 or PD184352 or PD-184352 or CI-1040 or PD035901 or TAK-733 or TAK733).mp.
	14	(binimetinib or MEK162 or MEK-162 or ARRY-162 or ARRY-438162).mp.

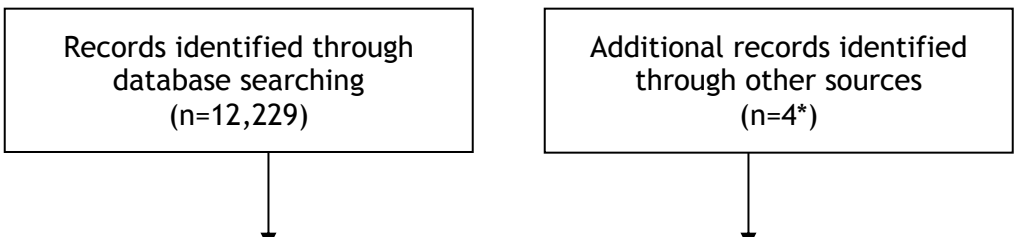
	15	(trametinib or GSK1120212 or GSK-1120212 or mekinist).mp.
	16	(cobimetinib or cotellic or XL518 or GDC-0973 or XL-518).mp.
	17	exp "Poly(ADP-ribose) Polymerase Inhibitors"/
	18	exp "Poly(ADP-ribose) Polymerase Inhibitors"/ or PARP$.mp.
	19	(olaparib or AZD 2281 or AZD2281 or Lynparza or AZD221).mp.
	20	(veliparib or ABT888 or talazoparib or BMN673 or nintedanib or iniparib or oregovomab or abagovomab or CA-125 or MUC 16 or pazopanib or niraparib or MK4827 or MK-4827).mp.
	21	(rucaparib or PF-01367338 or AG014699 or AG-014699).mp.
	22	(rapamune or rapamycin or sirolimus or I2190A or I-2190A or AY 22989 or AY 22-989).mp.
	23	(cediranib or recentin or AZD2171 or AZD-2171).mp.
	24	Antibodies, Monoclonal, Humanized/ or (bevacizumab or avastin).mp.
	25	mTOR inhibitor$.mp.
	26	(temsirolimus or CCI 779 or CCI-779 or Torisel).mp.
	27	(everolimus or afinitor or certican or RAD001 or (RAD adj1 "001") or (SDZ adj1 RAD) or SDZ-RAD).mp.
	28	(deforolimus or ridaforolimus or MK8669 or MK-8669 or AP23573 or AP-23573).mp.
	29	BRAF inhibitor$.mp.
	30	PLX8394.mp.
	31	(vemurafenib or RG7204 or RG-7204 or R05185426 or PLX4032 or PLX-4032 or zelboraf).mp.
	32	(dabrafenib or tafinlar or GSK2118436 or GSK-2118436).mp.
	33	(tumo?r-infiltrating lymphocyte$ therap$ or TIL$ therap$).mp.
	34	exp Cytokines/ad, ae, de, re, tu, to [Administration & Dosage, Adverse Effects, Drug Effects, Radiation Effects, Therapeutic Use, Toxicity]

	35	(interleukin-2 or IL-2 or interferon or IFN-alfa or immune checkpoint inhibitor$).mp.
	36	(thalidomide or sedoval or thalomid or revlimid or lenalidomide or CC5013 or CC-5013 or IMiD$).mp.
	37	(S-3APG or pomalidomide or pomalyst or imnovid or CC-4047 or CC4047).mp.
	38	bacille calmette-guerin.mp.
	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).mp.
	40	(Fulvestrant or faslodex or ZM 182780 or ZM-182780 or ICI182780 or ICI-182780 or ICI182,780 or ICI-182,780).mp.
	41	(letrozole or femara or CGS-20267 or CGS20267).mp.
	42	(anastrozole or arimidex or ICI D1033 or ICID1033 or ZD-1033 or ZD1033).mp.
	43	(examestane or aromasin or FCE-24304 or FCE24304).mp.
	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).mp.
	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 docetaxol or taxotere or RP-56976 or trabectedin or ecteinascidin or yondelis or ET-743 or NSC 684766).mp.
	47	or/7-46
Section C(1): Study design – randomized controlled trials	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$).mp.
	50	48 or 49
Section C(2): Study design – systematic reviews	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
Section D: Exclusion strategy	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
Combining Sections A, B, C, and D	66	(6 and 50) or (6 and 47 and 61)
	67	66 not 65
Limiting the final search by date and language	68	limit 67 to English language [Limit not valid in CDSR; records were retained]
	69	limit 68 to yr="2003 -Current"

Appendix 3: PRISMA Flow Diagram



Full-text articles excluded, with reasons
(n=180)
Not outcome of interest = 39
Mixed population = 44
Phase II = 17
Not comparison of interest = 46
Not intervention of interest = 32
Study protocol = 2

*Full publication of the ICON8 trial [18] was retrieved on December 5, 2019 via pubmed. In addition, the final primary endpoint analysis of JCOG 0602 [4] and SCORPION [6], as well as the final quality of life results of ICON8 [21] were retrieved via pubmed on October 15, 2020.

Appendix 4: Guideline Document History

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES and KEY CHANGES
	Search Dates	Data		
EBS 4-1-2	1980 to 2004	Full Report	Peer review publication. Web publication.	Archived
EBS 4-21	1988 to 2006	Full Report	Peer review publication. Web publication.	Archived
4-1 Version 2	2003 to 2019	Full Report	Updated web publication.	This updated version will cover EBS 4-1-2 and EBS 4-21

Appendix 5: Survival Outcomes for Subgroup Analysis

Study, year (trial)	Intervention	OS			PFS		
		Med (months)	HR (95% CI)	p-value	Med (months)	HR (95% CI)	p-value
Neoadjuvant chemotherapy							
FIGO stage							
Vergote, 2018 [9] (EORTC 55971 and CHORUS)	**Stage IIIC**						
	CBP or CIS ± PTX → IDS	30.8	1.04 (0.90 to 1.21)	0.569	12.2	1.06 (0.92 to 1.22)	0.429
	PDS → CBP or CIS ± PTX	28.4			11.7		
	Stage IV						
	CBP or CIS ± PTX → IDS	24.3	0.76 (0.58 to 1.00)	0.048	10.6	0.77 (0.59 to 1.00)	0.049
	PDS → CBP or CIS ± PTX	21.2			9.7		
Vergote, 2010 [1] (EORTC 55971)	**Stage III**						
	CBP or CIS ± PTX → IDS	30.6	1.07 (0.88 to 1.31)	0.4993	NR	NR	NR
	PDS → CBP or CIS ± PTX	30.4					
	Stage IV						
	CBP or CIS ± PTX → IDS	25.3	NR	NS	NR	NR	NR
	PDS → CBP or CIS ± PTX	25.3					
Kehoe, 2015 [3] (CHORUS)	**Stage III**						
	CBP ± PTX → IDS	NR	0.86 (0.69 to 1.06)	NS	NR	NR	NR
	PDS → CBP ± PTX						
	Stage IV						
	CBP ± PTX → IDS	NR	0.91 (0.63 to 1.30)	NS	NR	NR	NR
	PDS → CBP ± PTX						
	Stage III						

Study, year (trial)	Intervention	OS			PFS		
		Med (months)	HR (95% CI)	p-value	Med (months)	HR (95% CI)	p-value
Onda, 2020 [4] (JCOG 0602)	CBP+ PTX → IDS	44.2	1.04 (0.76 to 1.43)	NS	NR	NR	NR
	PDS → CBP+ PTX	49.3					
	Stage IV						
	CBP+ PTX → IDS	46.0	1.15 (0.73 to 1.81)	NS	NR	NR	NR
	PDS → CBP+ PTX	45.7					
Residual disease							
Vergote, 2010 [1] (EORTC 55971)	**No residual**						
	CBP or CIS ± PTX → IDS	38.2	1.11 (0.82 to 1.51)	0.5616	NR	NR	NR
	PDS → CBP or CIS ± PTX	45.0					
	1 to 10mm						
	CBP or CIS ± PTX → IDS	27.0	NR	NS	NR	NR	NR
	PDS → CBP or CIS ± PTX	32.3					
	>10mm						
	CBP or CIS ± PTX → IDS	25.5	NR	NS	NR	NR	NR
	PDS → CBP or CIS ± PTX	25.7					
Kehoe, 2015 [3] (CHORUS)	**No residual**						
	CBP ± PTX → IDS	47.3	NR	NS	NR	NR	NR
	PDS → CBP ± PTX	46.9					
	>0cm to ≤1cm						
	CBP ± PTX → IDS	23.2	NR	NS	NR	NR	NR
	PDS → CBP ± PTX	36.8					
	>1cm						
	CBP ± PTX → IDS	14.7	NR	NS	NR	NR	NR

Study, year (trial)	Intervention	OS			PFS		
		Med (months)	HR (95% CI)	p-value	Med (months)	HR (95% CI)	p-value
	PDS → CBP ± PTX CBP + PTX + PBO	15.5					
Onda, 2020 [4] (JCOG 0602)	**No residual**						
	CBP+ PTX → IDS	67.0	NR	NR	NR	NR	NR
	PDS → CBP+ PTX	NE					
	<1cm						
	CBP+ PTX → IDS	34.0	NR	NR	NR	NR	NR
	PDS → CBP+ PTX	54.9					
	≥1cm						
	CBP+ PTX → IDS	32.0	NR	NR	NR	NR	NR
	PDS → CBP+ PTX	43.0					
Fagotti, 2020 [6] (SCORPION)	**No residual**						
	CBP+ PTX ± BEV → IDS	NR	1.10 (0.61 to 1.97)	0.74	NR	1.01 (0.66 to 1.55)	0.96
	PDS → CBP+ PTX ± BEV						
Histological subtypes							
Onda, 2020 [4] (JCOG 0602)	**Clear-cell or mucinous**						
	CBP+ PTX → IDS	25.6	1.95 (0.71 to 5.34)	NS	NR	NR	NR
	PDS → CBP+ PTX	43.5					
	Other subtypes						
	CBP+ PTX → IDS	48.7	1.00 (0.76 to 1.32)	NS	NR	NR	NR
	PDS → CBP+ PTX	49.0					
Adjuvant chemotherapy ***BRCA mutation*** *i.p. versus i.v.*							
Lesnock, 2013 [35] (Post hoc analysis of GOG-172)	**Normal BRCA1**						
	i.v. PTX + i.p. (CIS + PTX)	58.1	NR	0.818	20.1	NR	NR
	i.v. (CIS + PTX)	50.4			17.7		
	Aberrant BRCA1						

Study, year (trial)	Intervention	OS			PFS		
		Med (months)	HR (95% CI)	p-value	Med (months)	HR (95% CI)	p-value
	i.v. PTX + i.p. (CIS + PTX)	84.1	NR	0.0002	34.7	NR	NR
	i.v. (CIS + PTX)	47.7			18.7		
Targeted therapy							
Tewari, 2019 [30] (GOG 0218)	**No mutation**						
	CBP + PTX + BEV	NR	0.97 (NR)	NS	NR	NR	NR
	CBP + PTX + PBO						
	BRCA 1/2						
	CBP + PTX + BEV	NR	1.37 (NR)	NS	NR	NR	NR
	CBP + PTX + PBO						
Histological subtypes *Platinum-based triplet*							
Bolis, 2010 [27]	**Serous tumours**						
	TPT + CBP + PTX	4yr: 56%	NR	NS	NR	NR	NR
	CBP + PTX	4yr: 50%					
	Non-serous tumours						
	TPT + CBP + PTX	4yr: 38%	NR	NS	NR	NR	NR
	CBP + PTX	4yr: 61%					
Weekly versus every 3 weeks							
Katsumata, 2013 [17] (JGOG 3016)	**Serous/endometrioid adenocarcinoma or other subtypes**						
	CBP q3w + PTX q1w	100.5	0.76 (0.59 to 0.97)	0.0252	28.7	0.70 (0.57 to 0.86)	0.0007
	(CBP + PTX) q3w	61.2			17.5		
	Clear-cell carcinoma or mucinous adenocarcinomas						
	CBP q3w + PTX q1w	NE	0.92 (0.53 to 1.61)	0.7757	18.7	1.06 (0.63 to 1.76)	0.8365
	(CBP + PTX) q3w	62.2			16.7		
Clamp, 2019 [18] (ICON8)	**Serous tumours**						
	CBP q3w + PTX q1w	NR	NR	NR	NR	0.92 (0.75 to 1.12)	NS
	(CBP + PTX) q3w						
	(CBP + PTX) q1w	NR	NR	NR	NR	0.93 (0.76 to 1.13)	NS

Study, year (trial)	Intervention	OS			PFS		
		Med (months)	HR (95% CI)	p-value	Med (months)	HR (95% CI)	p-value
	(CBP + PTX) q3w						
	Non-serous tumours						
	CBP q3w + PTX q1w	NR	NR	NR	NR	0.90 (0.63 to 1.28)	NS
	(CBP + PTX) q3w						
	(CBP + PTX) q1w	NR	NR	NR	NR	0.95 (0.65 to 1.38)	NS
	(CBP + PTX) q3w						
Targeted therapy							
Tewari, 2019 [30]; Burger, 2011 [32] (GOG 0218)	**Serous tumours**						
	CBP + PTX + BEV	NR	1.06 (NR)	NS	NR	0.91 (NR)	NS
	CBP + PTX + PBO						
	Non-serous tumours						
	CBP + PTX + BEV	NR	1.08 (NR)	NS	NR	0.89 (NR)	NS
	CBP + PTX + PBO						
FIGO stage							
Platinum-based doublet							
du Bois, 2003 [50] (AGO-OVAR 3)	**Stage IIB-III and residual ≤1cm**						
	CBP + PTX	59.4	0.92 (0.70 to 1.22)	NS	26.0	0.91 (0.72 to 1.25)	NS
	CIS + PTX	55.4			24.2		
	Stage IV or residual >1cm						
	CBP + PTX	31.4	1.08 (0.85 to 1.38)	NS	13.4	1.14 (0.91 to 1.43)	NS
	CIS + PTX	30.7			14.3		
Li, 2018 [13]	**Stage II**						
	NDP + PTX	NR	NR	0.84	NR	NR	0.06
	CBP + PTX						
	Stage III-IV						
	NDP + PTX	NR	NR	0.53	NR	NR	0.02
	CBP + PTX						
Platinum-based triplet							
du Bois, 2006 [24] (AGO-OVAR 5)	**Stage IIB-III and residual ≤1cm**						
	EPI + CBP + PTX	59.8	0.91 (0.73 to 1.12)	0.3683	27.1	0.91 (0.76 to 1.09)	0.2955
	CBP + PTX	57.0			23.7		

Study, year (trial)	Intervention	OS			PFS		
		Med (months)	HR (95% CI)	p-value	Med (months)	HR (95% CI)	p-value
	Stage IV or residual >1cm						
	EPI + CBP + PTX	28.7	0.96 (0.79 to 1.17)	0.6906	13.5	0.97 (0.81 to 1.17)	0.7560
	CBP + PTX	28.1			12.8		
du Bois, 2010 [26] (AGO-OVAR 9)	**Stage I-IIA**						
	GEM + CBP + PTX	NE	3.28 (0.89 to 12.11)	0.0592	NE	1.06 (0.54 to 2.07)	0.8724
	CBP + PTX						
	Stage IIB-IIIC and residual or Stage IV						
	GEM + CBP + PTX	45.8	1.03 (0.90 to 1.18)	0.6653	15.9	1.18 (1.05 to 1.32)	0.0042
	CBP + PTX	48.9			17.1		
Weekly versus every 3 weeks							
Katsumata, 2013 [17] (JGOG 3016)	**Stage II**						
	CBP q3w + PTX q1w	NE	0.83 (0.32 to 2.20)	0.7150	NE	0.91 (0.44 to 1.88)	0.8063
	(CBP + PTX) q3w						
	Stage III						
	CBP q3w + PTX q1w	83.3	0.77 (0.59 to 1.01)	0.0586	25.3	0.72 (0.58 to 0.90)	0.0041
	(CBP + PTX) q3w	56.3			16.8		
	Stage IV						
	CBP q3w + PTX q1w	35.8	0.93 (0.59 to 1.47)	0.7554	15.5	0.81 (0.53 to 1.23)	0.3161
	(CBP + PTX) q3w	32.7			11.5		
	Stage III and residual ≤1cm						
	CBP q3w + PTX q1w	NE	0.85 (0.52 to 1.38)	0.5086	45.5	0.75 (0.52 to 1.09)	0.1292
	(CBP + PTX) q3w				30.3		
	Stage III and residual >1cm or Stage IV						
	CBP q3w + PTX q1w	50.9	0.75 (0.58 to 0.98)	0.0323	17.6	0.70 (0.56 to 0.89)	0.0028
	(CBP + PTX) q3w	35.0			12.1		
	Stage I or II						

Study, year (trial)	Intervention	OS			PFS		
		Med (months)	HR (95% CI)	p-value	Med (months)	HR (95% CI)	p-value
Clamp, 2019 [18] (ICON8)	CBP q3w + PTX q1w	NR	NR	NR	NR	0.91 (0.49 to 1.69)	NS
	(CBP + PTX) q3w						
	(CBP + PTX) q1w	NR	NR	NR	NR	0.72 (0.36 to 1.41)	NS
	(CBP + PTX) q3w						
	Stage III						
	CBP q3w + PTX q1w	NR	NR	NR	NR	0.89 (0.72 to 1.10)	NS
	(CBP + PTX) q3w						
	(CBP + PTX) q1w	NR	NR	NR	NR	0.89 (0.72 to 1.10)	NS
	(CBP + PTX) q3w						
	Stage IV						
	CBP q3w + PTX q1w	NR	NR	NR	NR	0.93 (0.65 to 1.33)	NS
	(CBP + PTX) q3w						
	(CBP + PTX) q1w	NR	NR	NR	NR	1.08 (0.76 to 1.52)	NS
	(CBP + PTX) q3w						
Pignata, 2014 [22] (MITO-7)	**Stage IC to II**						
	(CBP + PTX) q1w	NR	NR	NR	NR	0.96 (0.42 to 2.17)	NS
	(CBP + PTX) q3w						
	Stage III-IV						
	(CBP + PTX) q1w	NR	NR	NR	NR	0.97 (0.80 to 1.17)	NS
	(CBP + PTX) q3w						
i.p. versus i.v.							
Walker, 2019 [36] (GOG 252)	**Stage II-III and no residual**						
	i.v. PTX q1w + (i.p. CBP + i.v. BEV) q3w	104.8	NR	NR	38.8	0.92 (0.75 to 1.13)	NS
	i.v. PTX q1w + i.v. (CBP + BEV) q3w	98.8			35.9		

Study, year (trial)	Intervention	OS			PFS		
		Med (months)	HR (95% CI)	p-value	Med (months)	HR (95% CI)	p-value
	i.v. (PTX + BEV) q3w + i.p. (PTX + CIS) q3w	NE	NR	NR	35.5	0.97 (0.79 to 1.19)	NS
	i.v. PTX q1w + i.v. (CBP + BEV) q3w	98.8			35.9		
	Stage II-III and residual ≤1cm						
	i.v. PTX q1w + (i.p. CBP + i.v. BEV) q3w	84.7	NR	NR	28.7	0.92 (0.79 to 1.07)	NS
	i.v. PTX q1w + i.v. (CBP + BEV) q3w	80.0			26.9		
	i.v. (PTX + BEV) q3w + i.p. (PTX + CIS) q3w	76.3	NR	NR	27.8	0.97 (0.83 to 1.13)	NS
	i.v. PTX q1w + i.v. (CBP + BEV) q3w	80.0			26.9		
	Stage III and residual ≤1cm						
	i.v. PTX q1w + (i.p. CBP + i.v. BEV) q3w	78.2	NR	NR	NR	NR	NR
	i.v. PTX q1w + i.v. (CBP + BEV) q3w	74.6					
	i.v. (PTX + BEV) q3w + i.p. (PTX + CIS) q3w	74.1	NR	NR	NR	NR	NR
	i.v. PTX q1w + i.v. (CBP + BEV) q3w	74.6					
	Stage III and residual >1cm or Stage IV						

Study, year (trial)	Intervention	OS			PFS		
		Med (months)	HR (95% CI)	p-value	Med (months)	HR (95% CI)	p-value
	i.v. PTX q1w + (i.p. CBP + i.v. BEV) q3w	50.5	NR	NR	16.7	NR	NR
	i.v. PTX q1w + i.v. (CBP + BEV) q3w	55.5			16.9		
	i.v. (PTX + BEV) q3w + i.p. (PTX + CIS) q3w	43.6	NR	NR	15.5	NR	NR
	i.v. PTX q1w + i.v. (CBP + BEV) q3w	55.5			16.9		
Targeted therapy							
Tewari, 2019 [30]; Burger, 2011 [32] (GOG 0218)	**Stage III**						
	CBP + PTX + BEV	42.9	1.08 (0.93 to 1.25)	NS	NR	residual ≤1cm: 0.78 (NR) residual >1cm: 0.98 (NR)	NS
	CBP + PTX + PBO	44.2					
	Stage IV						
	CBP + PTX + BEV	34.5	0.99 (0.78 to 1.26)	NS	NR	0.92 (NR)	NS
	CBP + PTX + PBO	32.6					
Residual disease *Platinum-based doublet*							
Bookman, 2009 [15] (GOG 0182-ICON5)	**Microscopic**						
	CBP + TPT → CBP + PTX	NR	0.92 (NR)	NS	NR	NR	NR
	CBP + PTX						
	CBP + GEM → CBP + PTX	NR	0.91 (NR)	NS	NR	NR	NR
	CBP + PTX						
	≤1cm						

Study, year (trial)	Intervention	OS			PFS		
		Med (months)	HR (95% CI)	p-value	Med (months)	HR (95% CI)	p-value
	CBP + TPT → CBP + PTX	NR	1.07 (NR)	NS	NR	NR	NR
	CBP + PTX						
	CBP + GEM → CBP + PTX	NR	1.10 (NR)	NS	NR	NR	NR
	CBP + PTX						
	>1cm						
	CBP + TPT → CBP + PTX	NR	1.09 (NR)	NS	NR	NR	NR
	CBP + PTX						
	CBP + GEM → CBP + PTX	NR	1.24 (NR)	NS	NR	NR	NR
	CBP + PTX						
Platinum-based triplet							
Bookman, 2009 [15] (GOG 0182-ICON5)	**Microscopic**						
	CBP + PTX + PLD	NR	0.86 (NR)	NS	NR	NR	NR
	CBP + PTX						
	CBP +PTX + GEM	NR	0.76 (NR)	NS	NR	NR	NR
	CBP + PTX						
	≤1cm						
	CBP + PTX + PLD	NR	0.93 (NR)	NS	NR	NR	NR
	CBP + PTX						
	CBP +PTX + GEM	NR	1.03 (NR)	NS	NR	NR	NR
	CBP + PTX						
	>1cm						
	CBP + PTX + PLD	NR	1.04 (NR)	NS	NR	NR	NR
	CBP + PTX						
	CBP +PTX + GEM	NR	1.11 (NR)	NS	NR	NR	NR
	CBP + PTX						
Bolis, 2010 [27]	**≥1cm to ≤2cm**						
	TPT + CBP + PTX	4yr: 66%	NR	NS	NR	NR	NR
	CBP + PTX	4yr: 48%					

Study, year (trial)	Intervention	OS			PFS		
		Med (months)	HR (95% CI)	p-value	Med (months)	HR (95% CI)	p-value
	>2cm						
	TPT + CBP + PTX	4yr: 57%	NR	NS	NR	NR	NR
	CBP + PTX	4yr: 57%					
Weekly versus every 3 weeks							
Katsumata, 2013 [17] (JGOG 3016)	**≤1cm**						
	CBP q3w + PTX q1w	NE	0.76 (0.49 to 1.19)	0.2343	NE	0.74 (0.53 to 1.04)	0.0838
	(CBP + PTX) q3w				60.9		
	>1cm						
	CBP q3w + PTX q1w	51.2	0.75 (0.57 to 0.97)	0.0267	17.6	0.71 (0.56 to 0.89)	0.0029
	(CBP + PTX) q3w	33.5			12.1		
Pignata, 2014 [22] (MITO-7)	**No residual**						
	(CBP + PTX) q1w	NR	NR	NR	NR	1.02 (0.70 to 1.49)	NS
	(CBP + PTX) q3w						
	≤1cm						
	(CBP + PTX) q1w	NR	NR	NR	NR	1.25 (0.74 to 2.10)	NS
	(CBP + PTX) q3w						
	>1cm						
	(CBP + PTX) q1w	NR	NR	NR	NR	0.72 (0.51 to 1.01)	NS
	(CBP + PTX) q3w						
Disease location *Weekly versus every 3 weeks*							
Katsumata, 2013 [17] (JGOG 3016)	**Ovarian**						
	CBP q3w + PTX q1w	100.5	0.77 (0.60 to 0.99)	0.0413	29.4	0.77 (0.62 to 0.94)	0.0119
	(CBP + PTX) q3w	69.5			18.5		
	Fallopian tube						
	CBP q3w + PTX q1w	NE	0.42 (0.09 to 1.95)	0.2677	NE	0.47 (0.15 to 1.47)	0.1855
	(CBP + PTX) q3w				53.4		
	Primary peritoneal						

Study, year (trial)	Intervention	OS			PFS		
		Med (months)	HR (95% CI)	p-value	Med (months)	HR (95% CI)	p-value
	CBP q3w + PTX q1w	42.4	0.64 (0.37 to 1.09)	0.1099	17.7	0.37 (0.22 to 0.64)	0.0005
	(CBP + PTX) q3w	37.2			11.8		

Abbreviations: BEV, bevacizumab; BRCA, breast cancer gene; CBP, carboplatin; CI, confidence interval; CIS, cisplatin; DOX, doxorubicin; EPI, epirubicin; GEM, gemcitabine; HR, hazard ratio; IDE, intrapatient dose escalation; IDS, interval debulking surgery; i.p., intraperitoneal; i.v., intravenous; med, median; NDP, nedaplatin; NE, not estimable/not reached; NR, not reported; NS, not significant; OS, overall survival; PBO, placebo; PDS, primary debulking surgery; PFS, progression-free survival; PTX, paclitaxel; q1w, every week; q3w, every 3 weeks; TPT, topotecan; yr, year

Appendix 6: Cochrane's Risk of Bias

Study, year (trial)	SELECTION BIAS		PERFORMANCE BIAS	DETECTION BIAS	ATTRITION BIAS	REPORTING BIAS	RISK OF BIAS
	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Overall
Neoadjuvant chemotherapy							
Vergote, 2010 [1]; Greimel, 2013 [2] (EORTC 55971)	L	U	H	H: PFS, AE, QoL; L: OS	L	L	M
Kehoe, 2015 [3] (CHORUS)	L	L	H	H: PFS, AE, QoL; L: OS	L	L	M
Onda, 2020 [4]; Onda, 2016 [5] (JCOG 0602)	L	L	H	H: PFS, AE; L: OS	L	L	M
Fagotti, 2020 [6], Fagotti, 2016 [7] (SCORPION)	L	L	H	H: PFS, AE, QoL; L: OS	L	L	M
Adjuvant chemotherapy ***Platinum-based doublet*** *Cisplatin versus carboplatin*							
Ozols, 2003 [48] (GOG 158)	L	U	U	U: PFS, AE; L: OS	L	L	L
Greimel, 2006 [49]; du Bois, 2003 [50] (AGO-OVAR 3)	L	L	U	U: PFS, AE, QoL; L: OS	L	L	M
Cisplatin and carboplatin							
Dittrich, 2003 [51]	L	L	H	H: PFS, AE; L: OS	L	L	M
Aravantinos, 2005 [10] (HeCOG)	U	U	U	U: PFS, AE; L: OS	L	L	M
Anthracyclines							
Pignata, 2011 [11] (MITO-2)	L	L	H	H: PFS, AE, QoL; L: OS	L	L	M
Taxanes							
Mouratidou, 2007 [52]	L	U	U	U: PFS, AE; L: OS	L	L	L
Vasey, 2004 [12] (SCOTROC 1)	U	U	U	U: PFS, AE, QoL; L: OS	L	L	M
Second-generation platinum							
Li, 2018 [13]	L	L	H	H: PFS, AE; L: OS	L	L	M
Sequential doublet							
Hoskins, 2010 [14]; Brotto, 2016 [53] (OV16)	L	U	H	H: PFS, AE, QoL; L: OS	L	L	M
Platinum-based triplet *Anthracyclines*							
Aravantinos, 2008 [23] (HeCOG)	L	U	H	H: PFS, AE; L: OS	L	L	M

Study, year (trial)	SELECTION BIAS		PERFORMANCE BIAS	DETECTION BIAS	ATTRITION BIAS	REPORTING BIAS	RISK OF BIAS
	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Overall
du Bois, 2006 [24] (AGO-OVAR 5)	L	U	U	U: PFS, AE, QoL; L: OS	L	L	L
Lindemann, 2012 [25] (NSGO-EORTC GCG-NIC CTG)	U	U	H	H: PFS, AE, QoL; L: OS	L	L	H
Gemcitabine							
du Bois, 2010 [26] (AGO-OVAR 9)	L	U	H	H: PFS, AE, QoL; L: OS	L	L	M
Topotecan							
Bolis, 2010 [27]	U	U	H	H: PFS, AE; L: OS	L	L	H
Platinum-based doublet/triplet							
Bookman, 2009 [15] (GOG 0182-ICON5)	L	U	H	H: PFS; L: OS	L	L	M
Dose intensification							
Ray-Coquard, 2007 [54] (GINECO)	L	U	H	H: PFS, AE; L: OS	L	L	M
Mobus, 2007 [55] (HIDOC-EIS)	L	U	H	H: PFS, AE; L: OS	L	L	M
Spriggs, 2007 [56]	L	L	H	H: PFS, AE; L: OS	L	L	M
Banerjee, 2013 [57] (SCOTROC 4)	L	L	H	H: PFS, AE, QoL; L: OS	L	L	M
Weekly versus every 3 weeks *Single-agent*							
Fruscio, 2011 [58]	L	L	H	H: PFS, AE; L: OS	L	L	M
Platinum-based doublet							
Chan, 2016 [16] (GOG 0262)	L	U	H	H: PFS, AE, QoL; L: OS	L	L	M
Harano, 2014 [20]; Katsumata, 2013 [17]; Katsumata, 2009 [19] (JGOG 3016)	L	L	H	H: PFS, AE, QoL; L: OS	L	L	M
Clamp, 2019 [18]; Blagden, 2020 [21] (ICON8)	L	L	H	H: PFS, AE, QoL; L: OS	L	L	M
Pignata, 2014 [22] (MITO-7)	L	L	H	H: PFS, AE, QoL; L: OS	L	L	M
i.p versus i.v.							
Lesnock, 2013 [35]; Wenzel,	L	U	H	H: PFS, AE, QoL; L: OS	L	L	M

Study, year (trial)	SELECTION BIAS		PERFORMANCE BIAS	DETECTION BIAS	ATTRITION BIAS	REPORTING BIAS	RISK OF BIAS
	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Overall
2007 [34]; Armstrong, 2006 [33] (GOG 172)							
Walker, 2019 [36] (GOG 252)	L	L	H	H: PFS, AE, QoL; L: OS	L	L	M
Targeted therapy							
Tewari, 2019 [30]; Monk, 2013 [31]; Burger, 2011 [32] (GOG 0218)	L	L	L	L: OS, PFS, AE, QoL	L	L	M
Lhomme, 2008 [28]	L	U	H	H: PFS, AE; L: OS	L	L	M
Immunotherapy							
Alberts, 2008 [29]	L	U	H	H: PFS, AE; L: OS	L	L	M

L=Low Risk M=Moderate Risk H=High Risk U=Unclear Risk

Abbreviations: AE, adverse events; OS, overall survival; PFS, progression-free survival; QoL, quality of life