



## 5th Ovarian Cancer Consensus Conference of the Gynecologic Cancer InterGroup: First Line Interventions

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	<p>cancer clinical trials should be a) patients undergoing primary debulking surgery (PDS) and b) patients receiving neo-adjuvant chemotherapy (NACT). The amount of residual disease following surgery should further stratify patients into those with absent gross residual disease and others. (2) Control arms for chemotherapy: for advanced stage ovarian cancer the standard is intravenous 3-weekly carboplatin and paclitaxel. Acceptable alternatives, which should be stratified variables in trials when more than one regimen is offered, include weekly paclitaxel plus 3-weekly carboplatin, the addition of bevacizumab to 3-weekly carboplatin and paclitaxel, and intraperitoneal therapy. (3) Trial Endpoints: overall survival (OS) is the preferred primary endpoint for first line clinical trials with or without a maintenance component. Progression-free survival (PFS) is an alternative primary endpoint, but if PFS is chosen OS must be measured as a secondary endpoint and PFS must be supported by additional endpoints, including predefined patient reported outcomes (PROs) and time to first (TFST) or second subsequent therapy (TSST). For neoadjuvant therapy, additional 'window of opportunity' endpoints should be included.</p>

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## Review article

### 5th Ovarian Cancer Consensus Conference of the Gynecologic Cancer InterGroup: First Line Interventions

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Key words: ovarian cancer, first-line chemotherapy, clinical trials

**Abstract**

The consensus statements regarding first line therapies in women with ovarian cancer, reached at the 5th Ovarian Cancer Consensus Conference (OCCC) held in Tokyo, Japan, in November 2015 are reported. Three topics were reviewed and the following statements are recommended: (1) Surgery: the subgroups that should be considered in first line ovarian cancer clinical trials should be a) patients undergoing primary debulking surgery (PDS) and b) patients receiving neo-adjuvant chemotherapy (NACT). The amount of residual disease following surgery should further stratify patients into those with absent gross residual disease and others. (2) Control arms for chemotherapy: for advanced stage ovarian cancer the standard is intravenous 3-weekly carboplatin and paclitaxel. Acceptable alternatives, which should be stratified variables in trials when more than one regimen is offered, include weekly paclitaxel plus 3-weekly carboplatin, the addition of bevacizumab to 3-weekly carboplatin and paclitaxel, and intraperitoneal therapy. (3) Trial Endpoints: overall survival (OS) is the preferred primary endpoint for first line clinical trials with or without a maintenance component. Progression-free survival (PFS) is an alternative primary endpoint, but if PFS is chosen OS must be measured as a secondary endpoint and PFS must be supported by additional endpoints, including predefined patient reported outcomes (PROs) and time to first (TFST) or second subsequent therapy (TSST). For neoadjuvant therapy, additional 'window of opportunity' endpoints should be included.

## Introduction

At the 5th Ovarian Cancer Consensus Conference (OCCC) of the Gynecologic Cancer InterGroup (GCIg) held in Tokyo, Japan, in November 2015, representatives of 29 cooperative research groups studying gynaecologic cancers gathered to establish international consensus on issues critical to the conduct of randomized trials. Group B, one of the 4 discussion groups, addressed three questions related to first line therapies in newly diagnosed ovarian cancer patients.

### **B1: What defines the clinical subgroups for comparator studies?**

#### **Primary debulking surgery (PDS) or neo-adjuvant (primary) chemotherapy (Table 1)**

There was unanimous consensus regarding the importance of surgery for patients with newly diagnosed ovarian cancer [1]. The importance of involving a qualified gynaecological oncologist in the evaluation of a newly diagnosed patient with epithelial ovarian cancer (EOC) for primary debulking surgery (PDS) or neoadjuvant (primary) chemotherapy (NACT) was universally supported. It was endorsed by a systematic review of the literature which showed that in countries with well-established sub-specialty training the choice of a gynaecological oncologist is paramount in the treatment of ovarian cancer [2]. In patients with advanced FIGO stage disease (International Federation of Gynecology and Obstetrics), they are best qualified to determine whether the patient is suitable for PDS or primary chemotherapy. The use of primary chemotherapy is increasing partly because it has become clear that a complete resection of tumour confers a better prognosis. Furthermore, two trials in patients with potentially resectable disease have shown that the survival of women undergoing primary chemotherapy is not worse than those who have PDS. In the EORTC 55971 trial 670 patients with FIGO Stage IIIC-IV EOC were randomized to undergo PDS followed by chemotherapy or NACT followed by interval debulking surgery (IDS). Compared to PDS, NACT resulted in a higher rate of optimal cytoreduction defined as <10 mm of residual disease and no difference in progression free survival (PFS) or overall survival (OS) [3]. In the CHORUS trial, 550 patients with FIGO Stage III-IV EOC were randomised to PDS or NACT. Patients undergoing NACT had comparable three-year and median OS as well as comparable PFS and the NACT was deemed non-inferior [4]. Nevertheless, the rate of patients who achieved complete resection was very low.

## Residual disease and outcome (Table 2)

The amount of residual disease at the time of surgery is the key determinant of patient outcome with survival being best in patients with no gross residual disease at the end of surgery. In a large meta-analysis of 11 retrospective studies that included 4735 patients with advanced stage EOC, OS and PFS were significantly prolonged in patients with total gross resection, i.e. microscopic residual disease. In a Cochrane meta-analysis comparing patients with  $\leq 1$  cm residual disease vs.  $>1$  cm residual disease, the survival advantage for lower volume residual disease patients remained significant but was attenuated [5]. Similarly, in a review of three prospective randomised trials examining platinum and taxane-based chemotherapy regimens, investigators from the AGO and GINECO showed a similar association between PFS, OS and the amount of residual disease. There was prognostic dichotomization of patients into a group with no residual disease who had a better PFS and OS compared to those with 0-10 mm, or  $>10$  mm residual disease [6]. For those patients undergoing NACT, response to treatment should be assessed following 3 cycles of chemotherapy using sequential serum CA-125 levels and imaging [7]. After evaluation by a gynaecologic oncologist and radiologist, two clinical subgroups emerge; those who are candidates for IDS and those who are not suitable for surgery. Similarly, two prognostic subgroups emerge following IDS; those with no gross residual disease and patients with gross residual disease.

The extent of residual disease should be clearly documented by the operating gynaecological surgeon. However, it is recognised that there are limitations to the accurate recording of residual disease, in both the measurement of lesions and quantification of tumour residuum. Nevertheless, surgical documentation should stratify between grossly tumour free,  $\leq 1$  cm and  $\geq 1$  cm.

The extent of residual disease is dependent on the surgeon's will, experience, skill and infrastructure of the institution. A surgeon's interpretation of the radicality of the operation varies, and it is helpful to record the time the patient spent in the operating room [8, 9].

Patients undergoing NACT should be considered for 'window-of-opportunity' studies that offer access to tumour biopsies at diagnosis followed by second tumour biopsies at IDS.

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Such studies can provide valuable information on the impact of novel agents and combination therapies on the treatment response and molecular profile of tumours [10]. Objective scoring of response using a tiered Chemotherapy Response Score (CRS) in the momentum following NACT in patients with high grade serous cancer may be the first step towards developing a refined system to evaluate response objectively in this group of patients [11]. These data should be validated in further trials.

**B2: What different control arms could be considered for trials of first-line therapy? (Table 3)**

The regimen of 6 cycles of intravenous (IV) paclitaxel (175 mg/m<sup>2</sup>) and carboplatin (AUC 5-6) administered every 3 weeks recommended at the 4th OCCC remains a standard treatment for clinical trials [12]. In addition, the consensus statement concluded that dose-dense weekly paclitaxel plus 3-weekly carboplatin or intraperitoneal (IP) chemotherapy, as given in Gynecologic Oncology Group (GOG) study 172, were acceptable control arms. Although these regimens differed from three-weekly carboplatin and paclitaxel in dose, schedule and route of delivery they were included as options for a control arm on the basis that at least one clinical trial that showed superiority to the standard intravenous taxane/platinum combination [1].

The key alternative regimens arose from the Japanese GOG (JGOG) study 3016 in which 631 women with Stage II-IV EOC were randomly assigned to treatment with IV carboplatin AUC 6 and paclitaxel 175 mg/m<sup>2</sup> every three weeks or to cycles of carboplatin AUC 6 every three weeks with weekly paclitaxel 80 mg/m<sup>2</sup> for up to nine cycles. Since the 4th OCCC there has been an updated analysis demonstrating a sustained significant improvement in PFS for patients receiving dose-dense therapy compared with conventional treatment (median 28.2 vs. 17.5 months, hazard ratio (HR) 0.76, 95% CI 0.62-0.91) and OS (median 100.5 vs. 62.2 months, HR 0.79, 95% CI 0.63-0.99) [13, 14].

However, a benefit in PFS was not seen in two other trials with weekly paclitaxel. Neither trial directly compared the weekly schedule of paclitaxel in JGOG 3016. MITO-7 included 810 patients with Stage IC-IV EOC were randomly assigned to receive either IV paclitaxel 175 mg/m<sup>2</sup> and carboplatin AUC 6 every 3 weeks for 6 cycles or IV paclitaxel 60 mg/m<sup>2</sup> and carboplatin AUC 2, both weekly for 18 weeks. The median PFS in the dose-dense

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3 weekly therapy arm was 18.3 months compared with 17.3 months with standard treatment (HR  
4 0.96, 95% CI 0.80-1.16) and there was no significant difference in the probability of survival at  
5 24 months (77.3% vs. 78.9%, HR 1.20, 95% CI 0.90-1.61) [15]. In GOG 262, 792 patients with  
6 Stage II-IV EOC were randomly assigned to paclitaxel 175 mg/m<sup>2</sup> and carboplatin AUC 6 every 3  
7 weeks or weekly paclitaxel 80 mg/m<sup>2</sup> with carboplatin AUC 6 every 3 weeks. The choice of  
8 bevacizumab 15 mg/kg every 3 weeks was optional for patients in both arms and was a  
9 stratification factor prior to randomization. There was no difference in PFS among patients  
10 assigned to the dose-dense compared with the conventionally dosed chemotherapy group  
11 (median 14.8 vs. 14.3 months, HR 0.97, 95% CI 0.79-1.18). However, there was a difference in  
12 median PFS within the group of 16% of patients who did not receive bevacizumab. In the dose-  
13 dense group, the median PFS was 14.2 months compared with 10.3 months in those receiving  
14 conventionally dosed three-weekly chemotherapy (HR 0.62, 95% CI 0.30-0.95). No difference in  
15 PFS was detected in those patients receiving bevacizumab [16]. A further two-part trial  
16 evaluating dose-dense intravenous weekly chemotherapy and then the incorporation of  
17 bevacizumab, ICON 8 (NCT01654146), is still in progress. In ICON 8A, patients with high-risk  
18 early stage (FIGO 1C) or advanced stage EOC were randomised to carboplatin and paclitaxel  
19 every 3 weeks, carboplatin every 3 weeks and weekly paclitaxel, or carboplatin and paclitaxel  
20 weekly. The trial allows patients to enter after primary debulking surgery or with neoadjuvant  
21 chemotherapy and planned delayed (interval) surgery. The trial is in follow up having recruited  
22 1560 patients. The second part, ICON 8B, is ongoing and includes patients with >1 cm residual  
23 disease, Stage IV, or those in whom NACT is planned. The standard arm is three weekly  
24 carboplatin and paclitaxel with bevacizumab 7.5 mg/kg, as used in ICON7, and the two  
25 experimental arms are carboplatin 3-weekly with weekly paclitaxel or the same regimen with  
26 bevacizumab [17]. Whilst doubt remains about the value of weekly paclitaxel, there was  
27 consensus that this schedule could be incorporated as a stratified control arm of first-line trials  
28 based on the positive results of one phase III trial.

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30 Since the 4th OCCC, two large randomised trials incorporating bevacizumab have been  
31 published. In GOG 218, 1873 women with Stage III-IV EOC were randomly assigned to one of 3  
32 regimens: carboplatin AUC 6, paclitaxel 175 mg/m<sup>2</sup> and intravenous placebo starting with cycle  
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3 2 every 3 weeks for 6 cycles followed by placebo maintenance every 3 weeks for 16 additional  
4 cycles; carboplatin, paclitaxel and bevacizumab 15 mg/kg followed by placebo maintenance;  
5 and finally carboplatin, paclitaxel and bevacizumab followed by maintenance bevacizumab 15  
6 mg/kg. PFS was significantly prolonged when bevacizumab was used concurrently and after  
7 chemotherapy compared to chemotherapy alone (median 14.1 vs. 10.3 months, HR 0.72, 95%  
8 CI 0.625-0.824). There was no difference in PFS with the addition of concurrent bevacizumab to  
9 standard chemotherapy and no improvement in OS for any of the groups (median 39.3 vs. 38.7  
10 vs. 39.7 months, HR 0.92, 95% CI 0.72-1.12) [18, 19]. The ICON7 trial randomly assigned 1528  
11 patients with high-risk early stage or advanced stage ovarian cancer to carboplatin AUC 5-6 and  
12 paclitaxel 175 mg/m<sup>2</sup> every 3 weeks with or without bevacizumab 7.5 mg/kg. Bevacizumab was  
13 initiated with chemotherapy and continued for 12 additional maintenance cycles after  
14 chemotherapy. The addition of bevacizumab resulted in a significantly prolonged PFS (median  
15 19.8 vs. 17.4 months, HR 0.87, 95% CI 0.77-0.99) but no difference in OS (median 58.6 v. 58.0  
16 months, HR 0.99, 95% CI 0.85-1.14). In a pre-planned analysis, the addition of bevacizumab  
17 resulted in a significantly better PFS (median 18.1 v. 10.5 months, HR 0.73, 95% CI 0.60-0.93)  
18 and OS (median 36.6 v. 28.8 months, HR 0.64, 95% CI 0.48-0.85) in women at 'high risk of  
19 progression' (Stage III disease with >1.0 cm residual disease following PDS, inoperable patients  
20 with Stage III, and Stage IV disease) [17, 20]. The results reported in the primary publications  
21 have led the European Medicines Agency (EMA) to adopt first-line bevacizumab in many  
22 European countries, but opinions vary regarding dose and duration of bevacizumab, as well as  
23 the subgroup of patients (III-IV, or 'high risk of progression') most likely to benefit.  
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43 The delegates noted these variations, and there was no consensus regarding the  
44 incorporation of bevacizumab in first line therapy trials.  
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46 The importance of assessing the role of intraperitoneal therapy remains; the survival  
47 advantage of intraperitoneal cisplatin and paclitaxel observed in GOG 172 persists with longer  
48 follow up [21] and there are several ongoing clinical trials evaluating intraperitoneal therapy  
49 using cisplatin, carboplatin and paclitaxel in varying doses, schedules and modes of  
50 administration. Support for IP chemotherapy is largely based on the results of GOG 172 where  
51 429 patients with Stage III EOC with no more than 1 cm of residual disease following PDS were  
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3 randomised to receive IV paclitaxel 135 mg/m<sup>2</sup> followed by either IV cisplatin 75 mg/m<sup>2</sup> or IP  
4 cisplatin 100 mg/m<sup>2</sup> and IP paclitaxel 60 mg/m<sup>2</sup>. The median PFS and OS were significantly  
5 longer in the IP group vs. the IV group (23.8 vs. 18.3 months, p=0.05 and 65.6 vs. 49.7 months,  
6 p=0.03 respectively) [21, 22]. A recent meta-analysis of 8 randomised controlled trials following  
7 PDS showed that patients receiving IP chemotherapy were less likely to die from their disease  
8 (HR 0.79, 95% CI 0.70-0.90) and their disease free interval (DFI) was significantly prolonged (HR  
9 0.79, 95% CI 0.69-0.90) [23].

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17 Two trials have been completed and one is still recruiting. In the GOG 252 trial, patients  
18 with ≤1 cm residual disease were randomly assigned to IV weekly paclitaxel, IV carboplatin and  
19 bevacizumab every 3 weeks for 6 cycles followed by 15 cycles of bevacizumab versus weekly IV  
20 paclitaxel, IP carboplatin every 3 weeks and bevacizumab as in arm 1 versus a modified version  
21 of the GOG 172 IP arm (IP cisplatin and IV and IP paclitaxel) and bevacizumab as in arm 1.  
22 Results of this trial presented after the 5th OCCC showed median PFS times of between 26.8 to  
23 28.7 months for patients with optimally debulked Stage II-III disease with no regimen showing  
24 an advantage over others [24]. In the second GCG study OV21/PETROC, three cycles of IP  
25 therapy was compared with IV therapy after interval debulking surgery. The trial started as a 3-  
26 arm 'pick the winner' with IP cisplatin or carboplatin and D1, 8 paclitaxel given IV and IP on D8  
27 compared with the same schedule of carboplatin and paclitaxel given IV. At an interim  
28 assessment by the IDMC, the IP cisplatin arm was dropped with a recommendation to continue  
29 a two-arm trial comparing IV and IP carboplatin with IV and IV/IP paclitaxel. Due to funding  
30 problems, the trial completed recruitment as a randomised phase II study with an amended  
31 primary endpoint of 9-month progressive disease rate (PDR). The results presented after the  
32 5th OCCC demonstrated a 9-month PDR of 24.5% in the IP carboplatin and IP/IV paclitaxel arm  
33 compared to 42.2% in the IV carboplatin and IV paclitaxel arm in the Intention to Treat analysis  
34 (p=0.03). The JGOG 3019 iPocc trial (NCT01506856) is still recruiting and compares IV  
35 carboplatin and IP carboplatin in combination with IV paclitaxel every 3 weeks [24]. There was  
36 agreement that IP could be included as a stratified control arm for first-line trials. In conclusion  
37 IP therapy, weekly paclitaxel or a three-weekly schedule of carboplatin and paclitaxel with  
38 bevacizumab could be included as a control arm of a controlled clinical trial, as these strategies  
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3 have been compared to standard three-weekly carboplatin and paclitaxel, but stratification  
4 should be performed if more than one control arm therapy is included.  
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7 Two additional groups of patients were identified that require special research  
8 initiatives. There is lack of data from prospective clinical trials for frail and elderly patients who  
9 have consistently been shown to have a poor outcome [25]. In addition, many frail patients are  
10 excluded from current trials due to a poor Performance Status. In fact two separate analyses of  
11 the Surveillance, Epidemiology, and End Results (SEER) database have shown lower than  
12 average chemotherapy utilisation among elderly patients, especially in the presence of multiple  
13 comorbidities [26, 27]. In order to determine the safest and most effective regimen, it was  
14 agreed that clinical trials examining this question should incorporate a validated pre-treatment  
15 Comprehensive Geriatric Assessment (CGA) or one of its validated modifications such as the  
16 Cancer and Ageing Research Group (CARG) Geriatric Assessment and Toxicity Score or GINECO  
17 Geriatric Vulnerability Score (GVS) [28, 29]. The GOG 273 is a first-line study that has recently  
18 completed enrolment of patients >70 years old. Patients were randomly assigned to: single  
19 agent IV carboplatin AUC 5 every 3 weeks, IV carboplatin AUC 5 and paclitaxel 135 mg/m<sup>2</sup> every  
20 3 weeks or IV carboplatin AUC 5 every 3 weeks with paclitaxel 60 mg/m<sup>2</sup> weekly. The primary  
21 objective of the trial was to explore the association between the Geriatric Assessment Score  
22 (GAS) derived from the predictive model for chemotherapy toxicity for elderly adults with  
23 cancer on chemotherapy and tolerance to chemotherapy [30]. In addition, the GINECO-led  
24 GCIG EWOC-1 trial (Elderly patients With Ovarian Cancer) (NCT02001272) is enrolling women  
25 over 70 years with a GVS >3, randomly assigned to carboplatin and paclitaxel every 3 weeks,  
26 carboplatin alone every 3 weeks or weekly carboplatin and paclitaxel. The primary endpoint is  
27 treatment success defined as the ability to deliver 6 courses of chemotherapy without  
28 premature termination for progression, death or unacceptable toxicity [31]. Thus, there was  
29 broad support for clinical trials aimed to define the optimal control arm for frail and elderly  
30 patients using validated CGA tools and patient reported outcomes (PRO) in addition to survival.  
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52 Uncertainty remains about the place of adjuvant chemotherapy for early (Stage I and II)  
53 EOC. The optimal control arm for the subset of patients receiving chemotherapy has yet to be  
54 clearly defined [32]. The choice of adjuvant therapy and its duration remain to be determined.  
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3 The updated 10-year follow-up data of the EORTC-ACTION trial and ICON 1 confirmed the  
4 improved OS and recurrence free survival (RFS) favouring platinum-based chemotherapy [33].  
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6 Questions about whether single agent carboplatin or platinum and taxane combination  
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8 chemotherapy should be used, and how many cycles of treatment should be given remain [32].  
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### 11 12 **B3: What should be the endpoints for first-line trials? (Table 4)**

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14 Overall survival remains the gold standard for demonstrating benefit in first-line trials.  
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16 OS is unambiguous, not subject to interpretation bias and also represents a concrete direct  
17 benefit to the patient [34]. However, PFS has been accepted by the EMA for first-line studies  
18 with bevacizumab without demonstrating any overall survival benefit [18]. The multiplicity of  
19 subsequent therapies, and in particular unintended cross-over to the experimental drug can  
20 lead to a blunting of the OS advantage afforded by the initial therapy, thereby confounding its  
21 therapeutic benefit [1]. In addition, the long post progression survival afforded to many  
22 patients with recurrent EOC requires long follow-up and large sample size that make clinical  
23 trials examining OS after first-line therapies impractical [35]. The inclusion of short-term  
24 supportive factors such as Patient Reported Outcomes Quality of Life (PROQOL) assessments  
25 have been proposed to add further weight to a benefit in PFS. As in the 4th OCCO, PFS, defined  
26 as the time from randomization to documented disease progression or death and measured  
27 with validated assessment tools, was considered a valid primary endpoint and surrogate for OS.  
28 PFS has been shown to correlate with OS in some but not all tumour models such as in  
29 colorectal and non-small cell lung cancer [36, 37]. Nevertheless, PFS is unaffected by the effect  
30 of treatment crossover or subsequent salvage therapy, which make it an attractive endpoint in  
31 the first line setting. Documenting progression is however inherently prone to error and bias  
32 that are contingent on the interval between and accuracy/validity of the tumour assessments  
33 [38]. Similarly imbalances in the censoring between the control and intervention groups could  
34 lead to informative censoring and lead to over/underestimation of the treatment effect [39].  
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36 There was broad consensus among the 29 cooperative groups that every effort should be  
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38 deployed to minimize bias such as using validated tumour assessment tools, applying consistent  
39 assessment schedules across treatment groups that take into account the projected difference  
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3 in median PFS and methods to reduce the problem of informative censoring [40]. However, the  
4 magnitude of a statistically significant gain in PFS, and in particular the clinical importance of  
5 the difference needs to be taken into account. Similarly, differences in PFS should take toxicity  
6 and risk associated with specific interventions into consideration. An illustrative example would  
7 be the addition of erlotinib to gemcitabine in advanced pancreatic cancer which resulted in a  
8 statistically significant but small 2-week gain in survival at the price of additional toxicity and  
9 risk [41]. To address these issues, the consensus conference acknowledged the importance of  
10 aiming for a clinically relevant benefit in PFS that clearly exceeds risk as well as measuring  
11 relevant PRO, side effects and the pharmaco-economics associated with the proposed  
12 intervention. Improvements in meaningful PRO and health related quality of life (QOL)  
13 measures are especially relevant when the incremental gains in survival are small as they can  
14 make the case for or argue against a particular intervention [42]. The interpretation of PRO is  
15 challenging, as they are by definition subjective and difficult to generalize between patient  
16 populations. Methods to assess PRO differ substantially between trials and many trials  
17 reporting such outcomes do not uniformly define what constituted their endpoints, the  
18 duration of response or methods to confirm it [43]. It is therefore important to include  
19 validated tools to assess prospectively relevant and tailored QOL measures, particularly in trials  
20 of maintenance therapy. For example GOG 178, which randomised patients to 3 or 12 cycles of  
21 IV paclitaxel every 28 days after platinum and taxane therapy demonstrated a significant  
22 prolongation of in PFS in the 12-cycle arm (HR 2.31, 95% CI 1.08-4.94) at the price of more  
23 neurotoxicity and with no significant OS benefit [44]. Another secondary endpoint under  
24 investigation is the time to first or second subsequent therapy (TFST or TSST), defined as the  
25 time from randomization at first-line until the institution of the next or third-line therapy. In  
26 recurrent ovarian cancer, TSST may provide a clinically meaningful endpoint for patients,  
27 demonstrating a continuing benefit of an experimental treatment beyond progression, adding  
28 weight to the PFS benefit. It is easier to measure than PFS2, the time from primary to  
29 subsequent progression [45]. TSST should be explored in first-line therapy trials. Finally, even  
30 when PFS is chosen as the primary endpoint, the consensus conference participants all agreed  
31 on the importance of measuring OS as a secondary endpoint.  
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The advent of neoadjuvant chemotherapy in the first-line setting for EOC presents a unique set of opportunities to establish novel trial endpoints. NACT provides a real-time evaluation of the tumour response that may help in quickly deciding which treatments are ineffective. The response to NACT can also serve as a prognostic indicator along with more traditional indicators such as stage, grade and residual disease [46]. Pathologic complete response (pCR) rates in the setting of NACT for breast cancer have been shown to be significantly related to OS, leading the authors to conclude that agents or interventions that improve pCR are likely to improve long-term outcomes [47] and leading the FDA to use this endpoint for accelerated drug approval. However, so far, data on the impact of pCR after neoadjuvant chemotherapy on OS in patients with advanced ovarian cancer are lacking. In contrast to breast cancer, surgery in the intraperitoneal and retroperitoneal compartments for ovarian cancer is more complex, making pathologic evaluation of pCR very challenging. Several alternative meaningful endpoints for NACT trials in EOC have been proposed including total gross resection rates, treatment response scores and molecularly defined response scores [11].

### Future directions

The extent of residual disease remains a key prognostic factor and further trials limited to 'expert' surgical centres will determine whether the outcome of the timing of surgery is affected by the quality of surgery. Until the full results of ongoing trials with weekly paclitaxel, intraperitoneal therapy and the integration of bevacizumab become available, these therapeutic approaches need to be incorporated as a stratification variable in first-line trials. Clinical trials addressing the poor survival of elderly or frail patients are urgently needed as the survival of this group of women consistently lags behind other groups. The increasing use of neoadjuvant (primary) chemotherapy provides opportunities for short-term trials to evaluate novel treatments prior to surgery; translational endpoints in these 'window of opportunity' studies need to be better defined and validated. Whilst the importance of OS as a primary endpoint is recognised, there are practical reasons to use PFS but the methodology of PFS as a primary endpoint needs to be robust and supported by supplementary validated measurements in first-line studies such as PROQOL and PFS2, or its surrogate TSST.

## Acknowledgements

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**Table 1. B.1 What defines the clinical subgroups that should be used for comparator studies?**

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1. After initial diagnosis of advanced disease patients should be assessed for primary debulking surgery by a qualified gynaecologic oncology surgeon or primary chemotherapy, forming 2 separate major clinical subgroups.
  2. The goal with primary surgery is macroscopic complete resection.
    - After primary surgery 3 clinical subgroups emerge, no macroscopic residual,  $\leq 1$  cm or  $>1$  cm macroscopic residual disease. The extent of residual disease must be clearly documented by the surgeon.
  3. After primary chemotherapy 2 clinical subgroups emerge, those who are candidates for interval debulking surgery and those who are not suitable for surgery.
    - After interval debulking surgery 2 clinical subgroups emerge, no macroscopic residual, macroscopic residual disease. The extent of residual disease must be clearly documented by the surgeon.
    - Patients not suitable for interval debulking surgery include patients progressing on therapy and those medically unfit for surgery.
  4. Patients receiving neoadjuvant chemotherapy should be considered for novel combination therapy trials, particularly window of opportunity studies.
  5. [Unmet need] Specific trials should be performed to account for age-related/morbidity related factors.
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Review

**Table 2. B.1 (Cont.) Subgroups identified**

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1. Primary debulking surgery (PDS) with no macroscopic residual
  2. PDS with macroscopic residual  $\leq 1$  cm
  3. PDS with macroscopic residual  $>1$  cm
  4. Neoadjuvant chemotherapy, interval debulking surgery (NACT/IDS) with no macroscopic residual
  5. NACT/IDS with macroscopic residual
  6. NACT with insufficient response or progression
  7. NACT unfit for surgery
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6 **Table 3. B.2. What different control arms could be considered for trials of first-line**  
7 **therapy?**  
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- 9 1. Intravenous 3-weekly carboplatin and paclitaxel remain the standard chemotherapy  
10 drugs for first-line therapy in advanced stage ovarian cancer.  
11  
12 2. Acceptable additions or variations in dose, schedule, and route of delivery should be  
13 supported by at least one clinical trial demonstrating non-inferiority or superiority to a  
14 taxane/platinum. So far the following alternatives have been identified:  
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16     • Weekly intravenous paclitaxel is an acceptable alternative to three weekly  
17 intravenous paclitaxel in combination with 3-weekly intravenous carboplatin.  
18  
19     • The addition of bevacizumab to the control arm after primary surgery is  
20 acceptable.  
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22     • Intraperitoneal therapy after primary surgery with less than 1 cm residual disease  
23 is acceptable as a control arm, both platinum and paclitaxel should be included  
24 using a validated schedule.  
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26 3. If more than one of the above regimens are included in the control arm of the same  
27 study then they should be stratified for.  
28  
29 4. Trials are needed to define the control arm for elderly and frail patients, defined on the  
30 basis of comprehensive geriatric assessment.  
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32 5. If chemotherapy is to be used in early stage disease platinum based chemotherapy  
33 should be the control arm.  
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**Table 4. B.3 What should be the endpoints for first-line trials?**

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1. Overall survival (OS) is the ideal primary end point for 1st line trials, with or without a maintenance component, but is difficult to demonstrate in ovarian cancer because of long post progression survival and crossover.
  2. Progression-free survival (PFS) measured with validated assessment tools is a valid primary endpoint.
  3. If PFS is utilized as primary endpoint:
    - The projected magnitude of benefit should be clinically relevant and clearly exceed risk.
    - Methods should be employed to reduce bias and informative censoring.
    - Pre-specified assessment schedules applied consistently across treatment groups at intervals shorter than projected progression-free intervals.
    - OS must be measured as a secondary endpoint.
    - PFS should be supported by additional endpoints such as, time to first or second subsequent treatment, relevant patient reported outcomes (PRO), severity of adverse effects and pharmaco-economic evaluation.
  4. PRO should include prospective quality of life (QoL) assessment using validated tools; assessment methods should be tailored to the design of the trial, with specific methodologies developed to measure QoL in maintenance trials.
  5. Specific additional endpoints should be defined for neoadjuvant 'window of opportunity' studies. Examples include PFS, total gross resection rate, treatment response score, and molecularly defined endpoints.
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