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## Fifth Ovarian Cancer Consensus Conference of the Gynecologic Cancer InterGroup: first-line interventions

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## Review article

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

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## **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.

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

**Key message:** Surgery remains a key component of first line therapy of ovarian cancer. Three-weekly carboplatin and paclitaxel is the control arm of choice, although other regimens shown to be superior or non-inferior in at least one randomised trial are options. Overall survival is the preferred primary endpoint. Progression-free survival supported by supplementary outcome data, is acceptable in the absence of a demonstrable overall survival benefit.

## **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.

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

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

Since the 4th OCCC, two large randomised trials incorporating bevacizumab have been published. In GOG 218, 1873 women with Stage III-IV EOC were randomly assigned to one of 3 regimens: carboplatin AUC 6, paclitaxel 175 mg/m<sup>2</sup> and intravenous placebo starting with cycle



2 every 3 weeks for 6 cycles followed by placebo maintenance every 3 weeks for 16 additional cycles; carboplatin, paclitaxel and bevacizumab 15 mg/kg followed by placebo maintenance; and finally carboplatin, paclitaxel and bevacizumab followed by maintenance bevacizumab 15 mg/kg. PFS was significantly prolonged when bevacizumab was used concurrently and after chemotherapy compared to chemotherapy alone (median 14.1 vs. 10.3 months, HR 0.72, 95% CI 0.625-0.824). There was no difference in PFS with the addition of concurrent bevacizumab to standard chemotherapy and no improvement in OS for any of the groups (median 39.3 vs. 38.7 vs. 39.7 months, HR 0.92, 95% CI 0.72-1.12) [18, 19]. The ICON7 trial randomly assigned 1528 patients with high-risk early stage or advanced stage ovarian cancer to carboplatin AUC 5-6 and paclitaxel 175 mg/m<sup>2</sup> every 3 weeks with or without bevacizumab 7.5 mg/kg. Bevacizumab was initiated with chemotherapy and continued for 12 additional maintenance cycles after chemotherapy. The addition of bevacizumab resulted in a significantly prolonged PFS (median 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 months, HR 0.99, 95% CI 0.85-1.14). In a pre-planned analysis, the addition of bevacizumab resulted in a significantly better PFS (median 18.1 v. 10.5 months, HR 0.73, 95% CI 0.60-0.93) and OS (median 36.6 v. 28.8 months, HR 0.64, 95% CI 0.48-0.85) in women at 'high risk of progression' (Stage III disease with >1.0 cm residual disease following PDS, inoperable patients with Stage III, and Stage IV disease) [17, 20]. The results reported in the primary publications have led the European Medicines Agency (EMA) to adopt first-line bevacizumab in many European countries, but opinions vary regarding dose and duration of bevacizumab, as well as the subgroup of patients (III-IV, or 'high risk of progression') most likely to benefit.

The delegates noted these variations, and there was no consensus regarding the incorporation of bevacizumab in first line therapy trials.

The importance of assessing the role of intraperitoneal therapy remains; the survival advantage of intraperitoneal cisplatin and paclitaxel observed in GOG 172 persists with longer follow up [21] and there are several ongoing clinical trials evaluating intraperitoneal therapy using cisplatin, carboplatin and paclitaxel in varying doses, schedules and modes of administration. Support for IP chemotherapy is largely based on the results of GOG 172 where 429 patients with Stage III EOC with no more than 1 cm of residual disease following PDS were

randomised to receive IV paclitaxel 135 mg/m<sup>2</sup> followed by either IV cisplatin 75 mg/m<sup>2</sup> or IP cisplatin 100 mg/m<sup>2</sup> and IP paclitaxel 60 mg/m<sup>2</sup>. The median PFS and OS were significantly 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, p=0.03 respectively) [21, 22]. A recent meta-analysis of 8 randomised controlled trials following PDS showed that patients receiving IP chemotherapy were less likely to die from their disease (HR 0.79, 95% CI 0.70-0.90) and their disease free interval (DFI) was significantly prolonged (HR 0.79, 95% CI 0.69-0.90) [23].

Two trials have been completed and one is still recruiting. In the GOG 252 trial, patients with ≤1 cm residual disease were randomly assigned to IV weekly paclitaxel, IV carboplatin and bevacizumab every 3 weeks for 6 cycles followed by 15 cycles of bevacizumab versus weekly IV paclitaxel, IP carboplatin every 3 weeks and bevacizumab as in arm 1 versus a modified version of the GOG 172 IP arm (IP cisplatin and IV and IP paclitaxel) and bevacizumab as in arm 1. Results of this trial presented after the 5th OCCC showed median PFS times of between 26.8 to 28.7 months for patients with optimally debulked Stage II-III disease with no regimen showing an advantage over others [24]. In the second GCIg study OV21/PETROC, three cycles of IP therapy was compared with IV therapy after interval debulking surgery. The trial started as a 3-arm 'pick the winner' with IP cisplatin or carboplatin and D1, 8 paclitaxel given IV and IP on D8 compared with the same schedule of carboplatin and paclitaxel given IV. At an interim assessment by the IDMC, the IP cisplatin arm was dropped with a recommendation to continue a two-arm trial comparing IV and IP carboplatin with IV and IV/IP paclitaxel. Due to funding problems, the trial completed recruitment as a randomised phase II study with an amended primary endpoint of 9-month progressive disease rate (PDR). The results presented after the 5th OCCC demonstrated a 9-month PDR of 24.5% in the IP carboplatin and IP/IV paclitaxel arm compared to 42.2% in the IV carboplatin and IV paclitaxel arm in the Intention to Treat analysis (p=0.03). The JGOG 3019 iPocc trial (NCT01506856) is still recruiting and compares IV carboplatin and IP carboplatin in combination with IV paclitaxel every 3 weeks [24]. There was agreement that IP could be included as a stratified control arm for first-line trials. In conclusion IP therapy, weekly paclitaxel or a three-weekly schedule of carboplatin and paclitaxel with bevacizumab could be included as a control arm of a controlled clinical trial, as these strategies

have been compared to standard three-weekly carboplatin and paclitaxel, but stratification should be performed if more than one control arm therapy is included.

Two additional groups of patients were identified that require special research initiatives. There is lack of data from prospective clinical trials for frail and elderly patients who have consistently been shown to have a poor outcome [25]. In addition, many frail patients are excluded from current trials due to a poor Performance Status. In fact two separate analyses of the Surveillance, Epidemiology, and End Results (SEER) database have shown lower than average chemotherapy utilisation among elderly patients, especially in the presence of multiple comorbidities [26, 27]. In order to determine the safest and most effective regimen, it was agreed that clinical trials examining this question should incorporate a validated pre-treatment Comprehensive Geriatric Assessment (CGA) or one of its validated modifications such as the Cancer and Ageing Research Group (CARG) Geriatric Assessment and Toxicity Score or GINECO Geriatric Vulnerability Score (GVS) [28, 29]. The GOG 273 is a first-line study that has recently completed enrolment of patients >70 years old. Patients were randomly assigned to: single agent IV carboplatin AUC 5 every 3 weeks, IV carboplatin AUC 5 and paclitaxel 135 mg/m<sup>2</sup> every 3 weeks or IV carboplatin AUC 5 every 3 weeks with paclitaxel 60 mg/m<sup>2</sup> weekly. The primary objective of the trial was to explore the association between the Geriatric Assessment Score (GAS) derived from the predictive model for chemotherapy toxicity for elderly adults with cancer on chemotherapy and tolerance to chemotherapy [30]. In addition, the GINECO-led GCIG EWOC-1 trial (Elderly patients With Ovarian Cancer) (NCT02001272) is enrolling women over 70 years with a GVS >3, randomly assigned to carboplatin and paclitaxel every 3 weeks, carboplatin alone every 3 weeks or weekly carboplatin and paclitaxel. The primary endpoint is treatment success defined as the ability to deliver 6 courses of chemotherapy without premature termination for progression, death or unacceptable toxicity [31]. Thus, there was broad support for clinical trials aimed to define the optimal control arm for frail and elderly patients using validated CGA tools and patient reported outcomes (PRO) in addition to survival.

Uncertainty remains about the place of adjuvant chemotherapy for early (Stage I and II) EOC. The optimal control arm for the subset of patients receiving chemotherapy has yet to be clearly defined [32]. The choice of adjuvant therapy and its duration remain to be determined.

The updated 10-year follow-up data of the EORTC-ACTION trial and ICON 1 confirmed the improved OS and recurrence free survival (RFS) favouring platinum-based chemotherapy [33]. Questions about whether single agent carboplatin or platinum and taxane combination chemotherapy should be used, and how many cycles of treatment should be given remain [32].

### **B3: What should be the endpoints for first-line trials? (Table 4)**

Overall survival remains the gold standard for demonstrating benefit in first-line trials. OS is unambiguous, not subject to interpretation bias and also represents a concrete direct benefit to the patient [34]. However, PFS has been accepted by the EMA for first-line studies with bevacizumab without demonstrating any overall survival benefit [18]. The multiplicity of subsequent therapies, and in particular unintended cross-over to the experimental drug can lead to a blunting of the OS advantage afforded by the initial therapy, thereby confounding its therapeutic benefit [1]. In addition, the long post progression survival afforded to many patients with recurrent EOC requires long follow-up and large sample size that make clinical trials examining OS after first-line therapies impractical [35]. The inclusion of short-term supportive factors such as Patient Reported Outcomes Quality of Life (PROQOL) assessments have been proposed to add further weight to a benefit in PFS. As in the 4th OCCC, PFS, defined as the time from randomization to documented disease progression or death and measured with validated assessment tools, was considered a valid primary endpoint and surrogate for OS. PFS has been shown to correlate with OS in some but not all tumour models such as in colorectal and non-small cell lung cancer [36, 37]. Nevertheless, PFS is unaffected by the effect of treatment crossover or subsequent salvage therapy, which make it an attractive endpoint in the first line setting. Documenting progression is however inherently prone to error and bias that are contingent on the interval between and accuracy/validity of the tumour assessments [38]. Similarly imbalances in the censoring between the control and intervention groups could lead to informative censoring and lead to over/underestimation of the treatment effect [39]. There was broad consensus among the 29 cooperative groups that every effort should be deployed to minimize bias such as using validated tumour assessment tools, applying consistent assessment schedules across treatment groups that take into account the projected difference

in median PFS and methods to reduce the problem of informative censoring [40]. However, the magnitude of a statistically significant gain in PFS, and in particular the clinical importance of the difference needs to be taken into account. Similarly, differences in PFS should take toxicity and risk associated with specific interventions into consideration. An illustrative example would be the addition of erlotinib to gemcitabine in advanced pancreatic cancer which resulted in a statistically significant but small 2-week gain in survival at the price of additional toxicity and risk [41]. To address these issues, the consensus conference acknowledged the importance of aiming for a clinically relevant benefit in PFS that clearly exceeds risk as well as measuring relevant PRO, side effects and the pharmaco-economics associated with the proposed intervention. Improvements in meaningful PRO and health related quality of life (QOL) measures are especially relevant when the incremental gains in survival are small as they can make the case for or argue against a particular intervention [42]. The interpretation of PRO is challenging, as they are by definition subjective and difficult to generalize between patient populations. Methods to assess PRO differ substantially between trials and many trials reporting such outcomes do not uniformly define what constituted their endpoints, the duration of response or methods to confirm it [43]. It is therefore important to include validated tools to assess prospectively relevant and tailored QOL measures, particularly in trials of maintenance therapy. For example GOG 178, which randomised patients to 3 or 12 cycles of IV paclitaxel every 28 days after platinum and taxane therapy demonstrated a significant prolongation of in PFS in the 12-cycle arm (HR 2.31, 95% CI 1.08-4.94) at the price of more neurotoxicity and with no significant OS benefit [44]. Another secondary endpoint under investigation is the time to first or second subsequent therapy (TFST or TSST), defined as the time from randomization at first-line until the institution of the next or third-line therapy. In recurrent ovarian cancer, TSST may provide a clinically meaningful endpoint for patients, demonstrating a continuing benefit of an experimental treatment beyond progression, adding weight to the PFS benefit. It is easier to measure than PFS2, the time from primary to subsequent progression [45]. TSST should be explored in first-line therapy trials. Finally, even when PFS is chosen as the primary endpoint, the consensus conference participants all agreed on the importance of measuring OS as a secondary endpoint.

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.

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## References

1. Thigpen T, du Bois A, McAlpine J et al. First-Line Therapy in Ovarian Cancer Trials. *International Journal of Gynecological Cancer* 2011; 21(4):756–762.
2. du Bois A, Rochon J, Pfisterer J, Hoskins WJ. Variations in institutional infrastructure, physician specialization and experience, and outcome in ovarian cancer: A systematic review. *Gynecol. Oncol.* 2009; 112(2):422–436.
3. Vergote I, Tropé CG, Amant F et al. Neoadjuvant Chemotherapy or Primary Surgery in Stage IIIC or IV Ovarian Cancer. *N Engl J Med* 2010; 363(10):943–953.
4. Kehoe S, Hook J, Nankivell M et al. Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): an open-label, randomised, controlled, non-inferiority trial. *The Lancet* 2015; 386(9990):249–257.
5. Elattar A, Bryant A, Winter-Roach BA et al. *Optimal primary surgical treatment for advanced epithelial ovarian cancer*, Chichester, UK: John Wiley & Sons, Ltd, 1996. doi:10.1002/14651858.CD007565.pub2.
6. du Bois A, Reuss A, Pujade-Lauraine E et al. Role of surgical outcome as prognostic factor in advanced epithelial ovarian cancer: a combined exploratory analysis of 3 prospectively randomized phase 3 multicenter trials: by the Arbeitsgemeinschaft Gynaekologische

- Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR) and the Groupe d'Investigateurs Nationaux Pour les Etudes des Cancers de l'Ovaire (GINECO). *Cancer* 2009; 115(6):1234–1244.
7. Rodriguez N, Rauh-Hain JA, Shoni M et al. Changes in serum CA-125 can predict optimal cytoreduction to no gross residual disease in patients with advanced stage ovarian cancer treated with neoadjuvant chemotherapy. *Gynecol. Oncol.* 2012; 125(2):362–366.
  8. Chi DS, Ramirez PT, Teitcher JB et al. Prospective Study of the Correlation Between Postoperative Computed Tomography Scan and Primary Surgeon Assessment in Patients With Advanced Ovarian, Tubal, and Peritoneal Carcinoma Reported to Have Undergone Primary Surgical Cytoreduction to Residual Disease 1 cm or Less. *Journal of Clinical Oncology* 2007; 25(31):4946–4951.
  9. Préfontaine M, Gelfand AT, Donovan JT, Powell JL. Reproducibility of Tumor Measurements in Ovarian Cancer: A Study of Interobserver Variability. *Gynecol. Oncol.* 1994; 55(1):87–90.
  10. Nick AM, Coleman RL, Ramirez PT, Sood AK. A framework for a personalized surgical approach to ovarian cancer. *Nat Rev Clin Oncol* 2015; 12(4):239–245.
  11. Böhm S, Faruqi A, Said I et al. Chemotherapy Response Score: Development and Validation of a System to Quantify Histopathologic Response to Neoadjuvant Chemotherapy in Tubo-Ovarian High-Grade Serous Carcinoma. *Journal of Clinical Oncology* 2015; 33(22):2457–2463.
  12. Stuart GCE, Kitchener H, Bacon M et al. 2010 Gynecologic Cancer InterGroup (GCIg) consensus statement on clinical trials in ovarian cancer: report from the Fourth Ovarian Cancer Consensus Conference. 2011; 21(4):750–755.
  13. Katsumata N, Yasuda M, Takahashi F et al. Dose-dense paclitaxel once a week in combination with carboplatin every 3 weeks for advanced ovarian cancer: a phase 3, open-label, randomised controlled trial. *The Lancet* 2009; 374(9698):1331–1338.
  14. Katsumata N, Yasuda M, Isonishi S et al. Long-term results of dose-dense paclitaxel and carboplatin versus conventional paclitaxel and carboplatin for treatment of advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer (JGOG 3016): a randomised, controlled, open-label trial. *The Lancet Oncology* 2013; 14(10):1020–1026.
  15. Pignata S, Scambia G, Katsaros D et al. Carboplatin plus paclitaxel once a week versus every 3 weeks in patients with advanced ovarian cancer (MITO-7): a randomised, multicentre, open-label, phase 3 trial. *The Lancet Oncology* 2014; 15(4):396–405.
  16. Chan JK, Brady MF, Penson RT et al. Weekly vs. Every-3-Week Paclitaxel and Carboplatin for Ovarian Cancer. *N Engl J Med* 2016; 374(8):738–748.



17. Perren TJ, Swart AM, Pfisterer J et al. A Phase 3 Trial of Bevacizumab in Ovarian Cancer. *N Engl J Med* 2011; 365(26):2484–2496.
18. Burger RA, Brady MF, Bookman MA et al. Incorporation of Bevacizumab in the Primary Treatment of Ovarian Cancer. *N Engl J Med* 2011; 365(26):2473–2483.
19. Cohn DE, Kim KH, Resnick KE et al. At What Cost Does a Potential Survival Advantage of Bevacizumab Make Sense for the Primary Treatment of Ovarian Cancer? A Cost-Effectiveness Analysis. *Journal of Clinical Oncology* 2011; 29(10):1247–1251.
20. Oza AM, Cook AD, Pfisterer J et al. Standard chemotherapy with or without bevacizumab for women with newly diagnosed ovarian cancer (ICON7): overall survival results of a phase 3 randomised trial. *The Lancet Oncology* 2015; 16(8):928–936.
21. Tewari D, Java JJ, Salani R et al. Long-Term Survival Advantage and Prognostic Factors Associated With Intraperitoneal Chemotherapy Treatment in Advanced Ovarian Cancer: A Gynecologic Oncology Group Study. *Journal of Clinical Oncology* 2015; 33(13):1460–1466.
22. Armstrong DK, Bundy B, Wenzel L et al. Intraperitoneal Cisplatin and Paclitaxel in Ovarian Cancer. *N Engl J Med* 2006; 354(1):34–43.
23. Jaaback K, Johnson N, Lawrie TA. *Intraperitoneal chemotherapy for the initial management of primary epithelial ovarian cancer*, Chichester, UK: John Wiley & Sons, Ltd, 1996. doi:10.1002/14651858.CD005340.pub3.
24. Fujiwara K. Three ongoing intraperitoneal chemotherapy trials in ovarian cancer. *J Gynecol Oncol* 2012; 23(2):75–77.
25. Hershman D, Jacobson JS, McBride R et al. Effectiveness of platinum-based chemotherapy among elderly patients with advanced ovarian cancer. *Gynecol. Oncol.* 2004; 94(2):540–549.
26. Sundararajan V, Hershman D, Grann VR et al. Variations in the use of chemotherapy for elderly patients with advanced ovarian cancer: a population-based study. *J Clin Oncol* 2002; 20(1):173–178.
27. Fairfield KM, Murray K, Lucas FL et al. Completion of Adjuvant Chemotherapy and Use of Health Services for Older Women With Epithelial Ovarian Cancer. *Journal of Clinical Oncology* 2011; 29(29):3921–3926.
28. Hurria A, Togawa K, Mohile SG et al. Predicting Chemotherapy Toxicity in Older Adults With Cancer: A Prospective Multicenter Study. *Journal of Clinical Oncology* 2011; 29(25):3457–3465.
29. Falandry C, Weber B, Savoye A-M et al. Development of a geriatric vulnerability score in

- elderly patients with advanced ovarian cancer treated with first-line carboplatin: a GINECO prospective trial. *Annals of Oncology* 2013; 24(11):2808–2813.
30. Tew WP, Muss HB, Kimmick GG et al. Breast and ovarian cancer in the older woman. *J Clin Oncol* 2014; 32(24):2553–2561.
  31. *Chemotherapy: First-Line Strategy*. Springer International Publishing, 2016:49–61.
  32. Adams G, Zekri J, Wong H et al. Platinum-based adjuvant chemotherapy for early-stage epithelial ovarian cancer: single or combination chemotherapy? *BJOG: An International Journal of Obstetrics & Gynaecology* 2010; 117(12):1459–1467.
  33. Collinson F, Qian W, Fossati R et al. Optimal treatment of early-stage ovarian cancer. *Annals of Oncology: official journal of the European Society for Medical Oncology / ESMO* 2014; 25(6):1165–1171.
  34. Wilson MK, Karakasis K, Oza AM. Outcomes and endpoints in trials of cancer treatment: the past, present, and future. *The Lancet Oncology* 2015; 16(1):e32–e42.
  35. Broglio KR, Berry DA. Detecting an overall survival benefit that is derived from progression-free survival. *J Natl Cancer Inst* 2009; 101(23):1642–1649.
  36. Buyse M, Burzykowski T, Carroll K et al. Progression-Free Survival Is a Surrogate for Survival in Advanced Colorectal Cancer. *Journal of Clinical Oncology* 2007; 25(33):5218–5224.
  37. Foster NR, Qi Y, Shi Q et al. Tumor response and progression-free survival as potential surrogate endpoints for overall survival in extensive stage small-cell lung cancer. *Cancer* 2010; 117(6):1262–1271.
  38. Zhuang SH, Xiu L, Elsayed YA. Overall Survival: A Gold Standard in Search of a Surrogate. *The Cancer Journal* 2009; 15(5):395–400.
  39. Ranganathan P, Pramesh CS. Censoring in survival analysis: Potential for bias. *Perspect Clin Res* 2012; 3(1):40.
  40. Shih W. Problems in dealing with missing data and informative censoring in clinical trials. *Current controlled trials in cardiovascular medicine* 2002; 3(1):4.
  41. Moore MJ, Goldstein D, Hamm J et al. Erlotinib Plus Gemcitabine Compared With Gemcitabine Alone in Patients With Advanced Pancreatic Cancer: A Phase III Trial of the National Cancer Institute of Canada Clinical Trials Group. *Journal of Clinical Oncology* 2007; 25(15):1960–1966.
  42. Gourgou-Bourgade S, Bascoul-Mollevis C, Desseigne F et al. Impact of FOLFIRINOX Compared With Gemcitabine on Quality of Life in Patients With Metastatic Pancreatic

Cancer: Results From the PRODIGE 4/ACCORD 11 Randomized Trial. *Journal of Clinical Oncology* 2013; 31(1):23–29.

43. Joly F, Vardy J, Pintilie M, Tannock IF. Quality of life and/or symptom control in randomized clinical trials for patients with advanced cancer. *Annals of Oncology* 2007; 18(12):1935–1942.
44. Markman M, Liu PY, Wilczynski S et al. Phase III Randomized Trial of 12 Versus 3 Months of Maintenance Paclitaxel in Patients With Advanced Ovarian Cancer After Complete Response to Platinum and Paclitaxel-Based Chemotherapy: A Southwest Oncology Group and Gynecologic Oncology Group Trial. *Journal of Clinical Oncology* 2003; 21(13):2460–2465.
45. Ledermann J, Harter P, Gourley C et al. Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by BRCA status in a randomised phase 2 trial. *The Lancet Oncology* 2014; 15(8):852–861.
46. Rastogi P, Anderson SJ, Bear HD et al. Preoperative Chemotherapy: Updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27. *Journal of Clinical Oncology* 2008; 26(5):778–785.
47. Cortazar P, Zhang L, Untch M et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. *The Lancet* 2014; 384(9938):164–172.

**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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**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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**Table 3. B.2. What different control arms could be considered for trials of first-line therapy?**

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1. Intravenous 3-weekly carboplatin and paclitaxel remain the standard chemotherapy drugs for first-line therapy in advanced stage ovarian cancer.
  2. Acceptable additions or variations in dose, schedule, and route of delivery should be supported by at least one clinical trial demonstrating non-inferiority or superiority to a taxane/platinum. So far the following alternatives have been identified:
    - Weekly intravenous paclitaxel is an acceptable alternative to three weekly intravenous paclitaxel in combination with 3-weekly intravenous carboplatin.
    - The addition of bevacizumab to the control arm after primary surgery is acceptable.
    - Intraperitoneal therapy after primary surgery with less than 1 cm residual disease is acceptable as a control arm, both platinum and paclitaxel should be included using a validated schedule.
  3. If more than one of the above regimens are included in the control arm of the same study then they should be stratified for.
  4. Trials are needed to define the control arm for elderly and frail patients, defined on the basis of comprehensive geriatric assessment.
  5. If chemotherapy is to be used in early stage disease platinum based chemotherapy 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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**Online Appendix:**

The Gynecologic Cancer InterGroup (GCIg) 5th Ovarian Cancer Consensus Conference (OCCC) was held in Tokyo, Japan from 7-9 November 2015. It provided international consensus on 15 important questions in 4 topic areas, which were generated in accordance with the mission statement “International Consensus for Designing Better Clinical Trials” in order to design and to pursue future clinical trials and research in ovarian cancer. The methodology for obtaining consensus was well established previously, and the 5th OCCC followed the same procedure. All twenty-nine clinical trial groups of GCIg participated in the 5th OCCC. Draft consensus statements were discussed in topic groups as well as in a plenary forum. The final statements were then presented to all 29 member groups for voting in order to document the level of consensus. Full consensus was obtained for 11 of the 15 statements with 28/29 groups agreeing to 3 statements, and 27/29 groups agreeing to 1 statement. The high acceptance rate of the statements among trial groups reflects the fact that we share common questions and equal values.