

2010 Gynecologic Cancer InterGroup (GCIG) Consensus Statement on Clinical Trials in Ovarian Cancer *Report From the Fourth Ovarian Cancer Consensus Conference*

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and on behalf of the participants of the 4th Ovarian Cancer Consensus Conference (OCCC)

Abstract: 2010 Gynecologic Cancer InterGroup (GCIG) consensus statement on clinical trials in ovarian cancer. This report provides the outcomes from the Fourth Ovarian Cancer Consensus Conference.

Key Words: Ovarian cancer consensus conference, Gynecologic cancer intergroup

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Despite modest improvements in the outcome of women with a diagnosis of epithelial ovarian cancer over the past decades, this disease remains most commonly diagnosed in its advanced stages and associated with poor outcomes. Thus, new knowledge generated through the rigorous conduct of well-designed clinical trials is critical to improving outcomes for women with this diagnosis. Such trials, when conducted through the mechanism of an international cooperative of clinical trials groups such as the Gynecologic Cancer InterGroup (GCIG), have the added benefit of collective intellectual strength, rapid accrual and completion, and, potentially, a generalizability across multiple populations of women. The GCIG currently comprises a cooperative of 23 clinical trial groups.

Over the past 2 decades, there have been 3 Ovarian Cancer Consensus conferences (OCCCs) convened by the GCIG, each resulting in published consensus statements,^{1–3} the most recent of which is frequently cited in the literature, reflecting the international impact of the conclusions of the GCIG consensus process. At the third OCCC, the recom-

mendation was that the GCIG convene again in 4 to 5 years to review the latest evidence from high-quality clinical trials.

METHODOLOGY

In 2008, the General Assembly voted to plan that the fourth OCCC be held in Vancouver, Canada in 2010. The timing would allow for key data to have been presented by the spring of 2010. It was acknowledged that the rigor of the consensus process used in 2004⁴ be emulated in any subsequent consensus conferences and agreed that such a conference should engage the industry partners of the GCIG and address new, evolving issues.

In 2008, a scientific planning committee (SPC) was convened to develop the agenda and process of the fourth OCCC. The chairpersons were identified as the then chair of the GCIG (G.C.E.S.; NCIC CTG) and the chair-elect (H.K.; MRC/NCRI UK). Members, intended to reflect geographic and expertise diversity, included: operations manager (M.B.), past conference chair (A.d.B.; AGO Germany), and others (M.F.; ANZGOG), (J.L.; MRC/NCRI UK), (C.M.; AGO Austria), (T.T.; GOG US), and (E.T.; NCI US). The SPC identified 3 broad areas to be addressed and allowed for one inclusive heading to address new and evolving subject areas. The 3 broad areas included:

- A. First-line therapy (T.T., A.d.B.)
- B. Molecular agents and targeted therapy (J.L., C.M.)
- C. Recurrent Disease (M.F., E.T.)

For each of the 3 areas, 2 group chairs were identified to develop the questions to be addressed, arrange speakers

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for each topic, and lead the preparation of resulting manuscripts. The evolving areas, to be considered under a fourth heading, would include: patient-reported outcomes, survivorship, and inclusion of the elderly in clinical trials.

The fourth OCCC invited participation from each member group. Each member group was assigned a specified number of delegates based on prior accrual to GCIG trials. The group chairs were then asked to nominate individual delegates who would be attending on behalf of their group. Consideration across disciplines, geography, and expertise was requested. This process produced a total of 77 delegates. Each industry partner was invited to identify one representative to attend on their behalf. Furthermore, each industry sponsor of the consensus conference was invited to identify one observer-attendee representative. The past chairs of prior consensus conferences were also invited as was the inaugural chair of the GCIG (J.V.) and the editor of the *International Journal of Gynecologic Cancer* (U.B.).

CONSENSUS PROCESS

The process to generate a consensus statement, as previously described in the 3rd OCCC,⁴ was again followed in the fourth OCCC. After the SPC agreed on the 3 key subject areas, and the group chairs were identified for each area, questions were generated, which were then also agreed on by the SPC. This provided a set of 13 questions, for each of which a consensus statement would be developed. For each question, and with representation across groups sought, a presenter and a discussant were identified from among the list of delegates. The presenter was asked to prepare a presentation that summarized available evidence to inform a statement in response to the question. The discussant, who was asked to provide a critique of the presentation, added additional evidence as appropriate. Both of these presentations for all 13 questions were then circulated to all conference attendees for review and consideration.

At the time of the conference, the first day allowed for a plenary 10-minute oral presentation by each presenter and discussant in response to the question. On the second day, using breakout groups, a draft consensus statement was prepared. All 13 draft statements were then presented and reviewed in plenary format by the group Chairs and all attendees invited to comment. Returning to the breakout groups, each draft statement was refined based on the comments. These statements were returned to the plenary forum for review. Further refinement of the statements was then conducted by the group chairs. On the following day, each pair of group chairs presented the final draft statement to the plenary forum for any final corrections and/or changes. As each member group would only have one vote on each consensus statement, there was time allowed for each member group to convene and reach internal consensus. The final statements were then presented by the conference chairs to the plenary audience and a vote taken. The level of consensus of the 23 member groups is reflected in this vote.

RESULTS

Full consensus was obtained in 12 of the 13 statements. In 1 of the 13 statements, 21 of the 23 groups gave full consensus.

Consensus Statements

A1-1: What Are the Appropriate End Points for Different Trials: (Maintenance, Upfront Chemotherapy Trials Including Molecular Drugs)?

- Appropriate end points for clinical trials should reflect the achievement of clinical benefit, which is defined as improvement of one or more of the following subjective and objective endpoints:
 - toxicity
 - time without symptoms
 - patient reported outcomes (PRO)
 - progression-free survival (PFS)
 - overall survival (OS)
- In addition, cost-effectiveness should be evaluated when feasible.

A1-2: What Are the Appropriate End Points for Different Trials: (Maintenance, Upfront Chemotherapy Trials Including Molecular Drugs)?

- The recommended primary end points for future frontline/maintenance clinical trials in ovarian cancer are:
 - Phase 2 screening for activity
 - PFS, PFS at defined time point, or response
 - Phase 3
 - Early ovarian cancer—Recurrence-free survival (note: recurrence = recurrent disease + deaths from any cause).
 - Advanced ovarian cancer—Both PFS and OS are important end points to understand the full impact of any new treatment. Although overall survival is an important end point, PFS is most often the preferred primary end point for trials because of the confounding effect of the postrecurrence/progression therapy on OS. Each protocol should specify if PFS or OS is the preferred end point. Regardless of which is selected, the study should be designed and powered for both PFS and OS when feasible.
 - Maintenance trials—These criteria should be applied to trials that include maintenance therapy.

Level of Consensus: All of the 23 Member Groups

The consensus conference identified 3 key end points that are relevant for the design of all trials in this population of women. First is the need to ensure that appropriate clinical benefit is well defined. Although statistically, this may be considered in the context of OS and/or PFS, it is critically important to ensure that patient-reported outcomes including therapy-induced toxicity symptoms and period of time without any symptoms are included. Wherever possible, trials should be sufficiently powered to consider both OS and PFS. Second, there is a need to ensure that aspects of cost-effectiveness are incorporated as appropriate into the design of trials. Third, it was noted that the primary end points may vary depending on the study design (eg, phase 2/3, maintenance, etc).

A2: Are There Any Subgroups Defined by Tumor Biology Who Need Specific Treatment Options/Trials?

- Histopathology remains the criterion standard to classify epithelial ovarian cancer subgroups; however, there is emerging evidence to show different genetic and molecular profiles. Because there are different clinical behavior patterns for some of the histopathological subgroups, it is advised that separate trials are developed for the following subgroups:
 - Clear cell carcinoma
 - Mucinous carcinoma
 - Low-grade serous cancer
- When trials for the aforementioned subgroups are not available, patients within these subgroups should be entered into ongoing phase 3 studies.

Level of Consensus: All of the 23 Member Groups

That histopathology remains the “criterion standard” is a critical benchmark; however, the recommendation that separate trials be developed for clear cell, mucinous, and low-grade serous cancers recognizes that subtypes are correlated with distinct prognostic groupings. Furthermore, it was widely acknowledged that future molecular characterizations of ovarian cancers may supersede the current criterion standard.

A3: Is the 2004 GCIG Recommended Standard Comparator Arm Still Valid?

- The standard arm must contain a taxane and a platinum agent administered for 6 cycles. The recommended regimen is paclitaxel (175 mg/m²) and carboplatin (area under the curve, 5–6) intravenously administered every 3 weeks.
- 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.

Level of Consensus: All of the 23 Member Groups

The consensus of the conference, based on available evidence, was that the standard comparator arm has not changed markedly since 2004. This statement stands even after considering contemporary data from trials assessing dose intensification, addition of a third cytotoxic agent, and alternate delivery routes. It is recognized that new dose dense regimens may prove to have superior results in the future compared with a standard taxane/platinum regimen.

A4: What Is the Role of Modifying Dose, Schedule, and Delivery of Chemotherapy?

- Optimizing dose, schedule, and route of delivery of available agents is under ongoing study.
- Two specific approaches, namely, the alteration of dose/schedule and the use of intraperitoneal therapy, have been shown to be superior in at least one trial:

- Dose-dense weekly paclitaxel plus carboplatin every 3 weeks as given in JGOG 3016⁵
- Intraperitoneal chemotherapy as given in GOG 172⁶

Level of Consensus: All of the 23 Member Groups

The optimal regimen for the treatment of women with advanced ovarian cancer may change as new evidence from well-designed clinical trials becomes available. The 2 noted studies are viewed with optimism.^{5,6} Conference participants recognized the importance of timely accrual to well-designed large phase 3 trials to provide evidence to inform the optimal regimen. Through the GCIG, the diversity of the populations is provided, ensuring results are globally relevant.

A5: What Role Does Surgery Play Today?

- Surgical staging should be mandatory and should be performed by a gynecologic oncologist.
- The ultimate goal is cytoreduction to microscopic disease. There is evidence that reduction of macroscopic disease to ≤1 cm or less is associated with some benefit. The term “optimal” cytoreduction should be reserved for those with no macroscopic residual disease.
- Documentation must be provided as to the level of cytoreduction (at least microscopic vs macroscopic).
- Delayed primary surgery after neoadjuvant chemotherapy is an option for selected patients with stage IIIC or IV ovarian cancer as included in EORTC 55971⁷

Level of Consensus: 21 of the 23 Member Groups

Surgery remains an integral component of the successful treatment of women with advanced ovarian cancer. New evidence has affected the timing of this surgery and the extent of initial efforts to achieve optimal cytoreduction. This evidence needs be accommodated in the design of new trials in this population.

Minority statement

Neoadjuvant chemotherapy cannot be regarded as adequate routine therapy strategy of advanced ovarian cancer and should be limited to selected patients with very advanced International Federation of Gynecology and Obstetrics stage IIIC or IV disease and contraindications against upfront debulking surgery or tumor dissemination, implying no chance for complete resection.

The lack of consensus reflected a lack of confidence by the 2 groups in the evidence base for the last bullet point.

B1 Molecular Prognostic and Predictive Factors: What Should Be the Standards for Clinical Trials?

- Current prognostic and predictive markers are not adequately validated or useful.
- Histotype-specific biomarkers are useful for subtype classification and should be included in histotype-specific clinical trials. Central pathologic review should be encouraged for these trials.

- The design of clinical trials should include the collection of biological specimens to address important translational research questions.
- The collection of biological specimens at the time of relapse and subsequent progression should be encouraged to allow comparison with primary samples.

Level of Consensus: All of the 23 Member Groups

The conference addressed a number of molecular markers as surrogate outcomes and predictive factors; however, the consensus of the conference was that although most of these markers hold significant promise, there is no standard molecular profile that must be included in all trials. It was recommended that the collection of biological specimens be considered in each and every clinical trial at predetermined intervals. This recognizes that there are multiple issues to be addressed and harmonized in the collection of tissues in different jurisdictions and central analysis.

B-2 What Are the Promising Targets for Future Therapeutic Approaches?

- The most promising targets in clinical trials are those in angiogenesis and homologous recombination deficiency pathways.
- To select patients for trials investigating these targets, predictive biomarkers are required. Understanding mechanisms of resistance is a priority.
- Other promising targets currently being studied based on ovarian cancer biology include:
 - PI3-kinase and Ras/Raf pathways
 - folate receptor
 - immune targets/cytokines, notch/hedgehog, IGF merit further investigation.
- Targeted agents should be studied both as single agents and in combination based on appropriate preclinical data.

Level of Consensus: All of the 23 Member Groups

Future targets for novel therapeutic agents are diverse and multiple. Several issues were discussed to advance the identification of best targets. Phase 1 and innovative phase 2 trials are recommended to expedite the understanding of these agents and the optimal inclusion in active chemotherapeutic regimens. Tumor tissue collection for correlative biology studies is warranted in all trials. The sharing of new knowledge and data internationally is a critical aspect of being able to have sufficient evidence to guide future studies.

B-3 Do We Have Appropriate Methods for Evaluating Targeted Therapies?

- Currently, there is no other validated method, other than the standard methods, for evaluating targeted therapies.
- To evaluate targeted therapies, it is important to demonstrate an appropriate effect on the target in early-phase studies.
- Patient selection for clinical trials should be based on the known biology of target action and appropriately validated.

- Criteria other than response (RECIST) are relevant and assessment of patient-reported outcomes, quality of life, and measurement of the duration of stable disease may provide valuable information about efficacy.
- New trial designs such as randomized feasibility studies, or trials using a patient as their own control, should be used to evaluate novel agents.
- CA-125 and functional imaging should be validated for use with targeted agents.

Level of Consensus: All of the 23 Member Groups

This statement is critically important to consider in the development of trials, which include the use of novel therapeutics. Although there are no other validated methods of evaluation than standard parameters such as the RECIST criteria and CA-125, it is acknowledged that future trials must build upon new knowledge from preclinical studies on new targets. Functional imaging will become a much more significant component of these studies.

B-4 Which Targeted Therapies Could Be Regarded as Part of a Control Arm in Ovarian Cancer Clinical Trials?

- Bevacizumab could be incorporated in the control arm of a randomized trial, as a consequence of the results of 25 trials^{8,9} with bevacizumab, which met their primary end point.
- Future trials of targeted agents must include measures that better characterize meaningful outcomes for patients (eg, cost-effectiveness, clinical benefit, which includes toxicity and quality of life).

Level of Consensus: All of the 23 Member Groups

At the time of the consensus conference in June 2010, only the preliminary results of GOG 218 study⁸ had been made available, and it was recognized that the ICON 7 study⁹ preliminary results would become available in the very near future. As such, the B4 statement was reconsidered by the GCIg at the time of the fall 2010 meeting. This revised statement received full concurrence by member groups, reflected in the level of consensus (23 of 23). This statement acknowledges that bevacizumab is an effective agent in the first-line setting, but further study is necessary to identify optimal dose, schedule, and regimen.

C1: What Is the Role of Cytoreductive Surgery for Recurrent Ovarian Cancer?

- Surgery may be appropriate in selected patients.
- As yet, there is no level 1 evidence, which demonstrates a survival advantage associated with surgical cytoreduction for women with recurrent ovarian cancer.
- Randomized phase 3 trials evaluating the role of surgery in recurrent ovarian cancer are a priority.
- Cytoreductive surgery for women with recurrent ovarian cancer may be beneficial if it results in optimal cytoreduction as defined in A5.

Level of Consensus: All of the 23 Member Groups

The role that surgery contributes to the long-term survival of women with recurrent ovarian cancer is not well-supported with evidence. Clinical practice has been propagated by consideration of such issues as diagnosis, relief of symptoms, and inferential application of cytoreductive data in the first-line setting. There is an urgent need to consider new data from existing and future trials that address this issue. All patients with recurrent disease should be considered for inclusion in a clinical trial where appropriate.

C2: How to Define Distinct Patient Populations in Need of Specific Therapeutic Approaches?

- Distinct patient populations for clinical trial enrolment may be considered by interval from last platinum therapy.
- Each trial will need to specify how they define the date of progression (CA-125 alone, radiological, and symptomatic).
- The following subgroups should be considered:
 - Progression while receiving last line of platinum-based therapy or within 4 weeks of last platinum dose
 - Progression-free interval since last line of platinum of less than 6 months
 - Progression-free interval since last line of platinum of 6 to 12 months
 - Progression-free interval since last line of platinum of more than 12 months*
- The PFI is defined from the last date of platinum dose until PD.
- Document whether patient had maintenance/consolidation therapy—which agent and for how long.
- Document histological type, molecular markers (such as BRCA), and surgery for recurrent disease.

Level of Consensus: All of the 23 Member Groups

Recent literature has attempted to describe specific populations of patients with recurrent ovarian cancer to prescribe optimal treatment and define the rate of response. However, this has been inconsistent, and no one set of definitions has been universally accepted. To conduct effective clinical trials through the GCIG, it is necessary to have an agreed-upon statement to stratify patients appropriately. The consensus statement reached reflects a detailed consideration of all evidence and an active discussion. It is noted that the progression-free interval is defined as the time from the last date of platinum therapy.

C3: Should End Points for Trials With Recurrent Disease Vary From Those of First-line Trials?

- Phase 3 trials for patients with recurrent epithelial ovarian cancer (progression-free interval since last line of platinum

num of more than 6 months from the last day of platinum dose until PD) should be large enough to detect clinically meaningful differences in both PFS and OS. Trial design should consider scheduled interim analyses to monitor for futility.

- In phase 2 trials for recurrent disease standard end points such as response rate (RECIST or GCIG-defined CA-125 response) and PFS are appropriate. Additional end points may include symptom benefit and clinical benefit.
- The choice of the primary end point needs to be fully justified with appropriate power calculations.
- Symptom control/Quality of life (for early relapse) and OS (for late relapse) may be the preferred primary end points, although PFS should still be used in the assessment of new treatments.
- Future research should include the development and validation of primary and secondary end points such as clinical benefit, which includes health-related quality of life, patient-reported outcomes, time without symptoms or toxicity, and cost-effectiveness.
- Note:
 - Early relapse = progression-free interval since last line of platinum of less than 6 months from the last day of platinum dose until PD.
 - Late relapse = progression-free interval since last line of platinum of more than 6 months from the last day of platinum dose until PD.

Level of Consensus: All of the 23 Member Groups

This statement has not shifted substantially since the 2004 statements; however, the need to develop meaningful and reproducible quality of life and symptom control end points is once again emphasized. The separate manuscript from this conference on patient-reported outcomes is highly relevant to the conduct of clinical trials in the population of women with recurrent cancer.


C4: Is CA-125 Progression Alone Sufficient for Entry/Eligibility Into Clinical Trials?

- Asymptomatic patients who meet GCIG definition of CA125 progression (without radiological or clinical evidence of recurrence) could be eligible for specific clinical trials.
- There is evidence that treating patients with asymptomatic CA-125 increase does not improve OS.

Level of Consensus: All of the 23 Member Groups

The inclusion of CA-125 measurement alone as an entry criterion into appropriate clinical trials was quickly supported by the conference. Furthermore, there was a strong endorsement that there are no data to support routine treatment of women with only an elevated CA-125 in the recurrent setting, in prolonging survival. It remains important to identify the optimal type of trial to benefit this group of patients.

*For this group, a platinum-based combination therapy should be the control arm for randomized trials.



4th Ovarian Cancer Consensus Conference
June 25 – 27, 2010
Vancouver, British Columbia
Canada

EVOLVING ISSUES FROM THE 4th OCCC

ELDERLY

- Optimal surgery/adjuvant therapy/chemotherapy
- Specific geriatric assessments/prognostic analyses stratified by age
- Considerations for inclusion of women over 65 in clinical trials

PATIENT REPORTED OUTCOMES (PROs)

- Quality of life/impact on sexual function/treatment toxicity
- Economic assessment/cost effectiveness
- Consideration for use of PROs in clinical trials

SURVIVORSHIP

- Definition and scope
- Plans, future guidelines and intervention strategies
- Issues of timing, measurement and data collection

FIGURE 1. Evolving issues from the fourth OCCC.

Patients enrolled in such trials should have documentation of response by clinical, biochemical, and radiological means.

EVOLVING ISSUES

In the planning for this consensus conference, it became apparent that there are evolving issues that must be considered in the development of clinical trials in the population of women affected by ovarian cancer (Fig. 1). These issues reflect the importance of patients, family, and lay persons in contributing to these studies. Separate companion manuscripts from this conference provide a detailed report on each issue.

CONCLUSION

The fourth OCCC has contributed to a body of knowledge about the conduct of large phase 3 clinical trials in the population of women affected by ovarian cancer, using both the infrastructure of the GCI and the international collaboration to conduct such trials. Consensus conferences are important in this context for 2 reasons. First, when conducting clinical trials across national and cooperative group boundaries, it is imperative to have agreed-upon methodologies, end points, and metrics to produce results that are clinically relevant, comparable, and generalizable. This conference served to further advance the knowledge provided in earlier such conferences and to provide new parameters for trial design. Second, the importance of knowledge translation requires that such trials are conducted in a timely manner with results that directly impact on the outcome of women with ovarian cancer. In this context, consideration of patient-reported outcomes, inclusion of the elderly, and issues of survivorship were incorporated into this conference directly.

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