Gynecologic Cancer InterGroup consensus recommendations on clinical research in ovarian cancer

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Summary (116/ max 150 words)

The Gynecologic Cancer InterGroup (GCIG) sixth Ovarian Cancer Conference on Clinical Research (OCCC6) was held virtually in October 2021 following published consensus guidelines. The goal of the consensus meeting was to achieve harmonization on design elements of upcoming trials, to select important questions for future study and to identify unmet needs. All 33 GCIG member groups participated in the development, refinement, and adoption of 20 statements within 4 topic groups on clinical research including first line treatment, recurrent disease, disease subgroups and future trials. Unanimous consensus was obtained for 14 of 20 statements, with >90% concordance in the remaining 6 statements. The high acceptance rate following active deliberation amongst the GCIG groups confirmed that a consensus process could be applied in a virtual setting. Together with detailed categorisation of unmet needs, these consensus statements will promote harmonisation of international clinical research in ovarian cancer.

Word count (4499 /max 4500 words)

Introduction
The Gynecologic Cancer InterGroup (GCIG) consists of thirty-three clinical research groups that span the globe (Supplement page 2) and has organised an ovarian cancer consensus conference on clinical research approximately every five years. The planning of the sixth GCIG ovarian cancer consensus conference (OCCC6) was initiated in May 2017, with the intent to meet in Leuven, Belgium, 9th-11th October 2020. Due to the COVID-19 pandemic, OCCC6 was first postponed and later held virtually 15th-21st October 2021.1,2

Consensus process
The OCCC6 Scientific Committee identified twenty key topics, organised within four topic groups together with tabulation of unmet needs for future clinical research. Each GCIG member group appointed two delegates. Draft consensus statements were prepared, together with designation of presenters and discussants for each statement. Primary references for the development of consensus statements were identified through the roster of clinical trials represented by each GCIG Member Group responsible for conducting academic clinical research in ovarian cancer, supplemented by non-GCIG trials selected by topic group discussants. All references were disclosed during the consensus conference and reviewed by all participants, with active moderation by topic group co-chairs. Searches on PubMed using terms “ovarian”, “cancer”, “neoplasms”, and “studies” from January 1st 2015, until October 1 2021 were utilized to ensure consideration of all relevant studies published after the last consensus conference in 2015. Only papers published in English were reviewed. The final reference list was generated on the basis of originality and relevance to the consensus guidelines.

To maximise participation across time zones, lectures were pre-recorded and available before and during the meeting. Adaptive technology was utilised for recording of live discussions and extended commentary after each session. All statements were presented three times with opportunity for sequential revision between each session. Each of the thirty-three groups had one vote and all voted electronically on the twenty statements within the first twenty-four hours following the final session. The consensus statements, voting records, unmet needs, and commentary are presented according to each topic group. Areas of unmet needs for future research were collected and prioritised during the meeting, but without formal consensus voting. For further details on the methodology we refer to the supplement page 3.

Consensus statements
First-line treatment
First-line treatment statements are summarised in table 1. Epithelial tumours of ovarian, fallopian, and peritoneal origin were grouped together as epithelial ovarian cancer (EOC) for the purposes of this meeting. Initial tumour stage, selection of patients for neoadjuvant chemotherapy (NACT), and presence of any visible residual disease following cytoreductive surgery are key prognostic factors for women with advanced EOC. Primary cytoreductive surgery (PCS) remains the preferred option when there is a reasonable likelihood of achieving complete cytoreduction after evaluation by an expert gynaecological oncological team, and NACT should be used for poor surgical candidates or for whom complete cytoreduction seems unlikely. The decision between PCS or NACT must be based on patient’s performance status and extent of disease determined by imaging and/or surgical assessment. In addition, the OCCC6 incorporates histology as a decision factor, favouring PCS for patients with less chemo-sensitive histological types even if complete cytoreduction is questionable.
Statement 2 on stratification factors applies for first-line trials using PCS or NACT. Chemotherapy remains the second pillar for treatment of EOC, consisting of 6 cycles of 3 weekly paclitaxel and carboplatin with or without bevacizumab. Weekly paclitaxel-weekly carboplatin (MITO-7/ENGOT-ov10), or weekly paclitaxel and 3-weekly carboplatin in Japanese patients with high-grade serous ovarian cancer (HGSOC) are acceptable alternatives. The statement 5 on IP therapy and HIPEC was much debated with an approval rate of only 30 out of 33 GCIG groups (2 groups opposing and 1 abstaining). It should be underscored that this statement is not about standard of care but accepting IP therapy and HIPEC as reference treatment arm within clinical trials.

The incorporation of maintenance therapy with PARPi after first line chemotherapy in high grade serous or endometrioid types should be considered as part of the reference arm, at least for patients with BRCAm tumour (germline or somatic) or BRCAwt/HR-deficient disease, either alone or combined with bevacizumab. The optimal maintenance therapy for patients with BRCAwt/HR-proficient tumours, if any, remains unknown. Incorporation of maintenance as part of the reference arm should not change the primary endpoints, which remain PFS and OS (although not necessary as dual endpoints). Safety and patient-reported outcomes (PROs) should be included as secondary endpoints. PFS2 (defined as the time from randomisation to the second objective disease progression or death) should be considered as well due to the potential impact of PARPi on the efficacy of subsequent therapies.

Utilisation of appropriate stratification factors is key for optimal interpretation of clinical trials. In addition to classical prognostic factors such as FIGO stage, timing of surgery, residual disease after surgery, performance status, and histology, predictive biomarkers tested with validated assays need to be incorporated. The most relevant example is BRCA1/2 mutation or HR-deficiency testing. There is a need for clinical research in patients with high-risk stage I or II EOC. These trials, through international cooperation, may address specific questions for this patient population.

Recurrent ovarian cancer.

Recurrent ovarian cancer statement are summarised in table 2. Building on findings from OCCC5 in 2015, OCCC6 recommended that platinum free interval should be replaced by a treatment free interval (TFIp) specific to certain therapies, such as platinum (TFIp), PARPi (TFIp\textsubscript{PARPi}), as well as other specific clinical and molecular factors. Agents targeting DNA damage response (DDR) are best suited for TP53 aberrant tumours whereas agents targeting angiogenesis may be suitable for all histologies. Predictive biomarkers for PARPi and other agents targeting DDR could be important for eligibility and/or stratification. The exposure and/or response to prior therapies is also increasingly important for clinical trial design and interpretation. For example, in an exploratory analysis of SOLO-2/ENGOT-ov21, among patients who recurred and were re-treated with platinum therapy, the median PFS was 7 months after prior maintenance with olaparib compared to 14.3 months after placebo, suggesting that prior PARPi exposure might compromise subsequent response to platinum. Most importantly, the TFIp remains a key prognostic factor, but should not be used in isolation of these other important clinical and molecular features. Although no good data exist on a cut-off TFIp interval we agreed that it was reasonable to treat patients with relapse within e.g. 12 weeks might be selected for a next line of therapy without platinum.

The standard of care for patients with recurrent EOC for whom platinum is an option has been a platinum-containing regimen (carboplatin + pegylated liposomal doxorubicin preferred). When considering which chemotherapy backbone to use, there are three options with differences in schedule, toxicity profile, and to a modest degree, efficacy (Table S1 – supplement page 5). Level 1 evidence supports repeat use of maintenance bevacizumab in the recurrent setting. Although level 1 evidence also exists for repeat use of PARPi in the recurrent maintenance setting, the magnitude of benefit appears small and such repeat use should not be considered the reference arm until the group of patients who derive benefit is better elucidated. At a minimum, stratification for prior PARPi and/or prior bevacizumab should be considered in clinical trials where platinum is an option for treatment.

In studies evaluating patients with disease recurrence considered inappropriate for platinum and who are naïve to bevacizumab, bevacizumab in combination with cytotoxic chemotherapy should be the control arm or, if mixed population (bevacizumab pretreated or not) are enrolled, bevacizumab should be a stratification factor. Possible monotherapy cytotoxic options are outlined in Table S2 (supplement page 5). Biomarker directed trial eligibility should consider broader inclusion of patients irrespective of TFIp. Successful application of this concept has already been demonstrated in both ARIEL 4 and FORWARD II (Supplement page 6).

Based on three randomised trials, secondary cytoreduction should be considered in trials where platinum is an option, using a validated score (Supplement page 6).

Statements on non-high grade serous ovarian cancer (non-HGSOC).
Statements on non-high grade serous ovarian cancer (non-HGSOc) are summarised in table 3. High grade endometrioid ovarian cancer with aberrant p53 expression has sufficient molecular\textsuperscript{33} and phenotypic\textsuperscript{34} similarity to HGSOc to be included in the same studies. Ovarian carcinomas are monoclonal in origin and driven by molecular changes found in EOC.\textsuperscript{35} Therefore if the epithelial component has aberrant p53 expression these malignancies can be included in HGSOc studies (with stratification). Little information is to be gained from studies that do not stratify according to histological type, especially with clear cell, low grade serous or mucinous ovarian cancer, unless the study is molecularly based.

In histologically defined settings (non-high grade serous/endometrioid ovarian cancer), eligibility should rely on centralized pathology review using predefined morphological criteria (e.g. World Health Organisation classification\textsuperscript{36}) and immunohistochemical biomarkers (see Supplement page 7).\textsuperscript{36-38} In malignant ovarian germ cell tumours (MOGCT), studies minimising long term treatment-related toxicity are important. Active surveillance is only a suitable reference arm when patients have undergone complete surgical staging and have blood tumour markers (e.g. alpha-fetoprotein for endodermal sinus tumours) compatible with stage I disease. There is no level one evidence to guide prioritisation of potential reference arms for studies of recurrent MOGCT.

In sex cord stromal ovarian tumours (SCST), the ALIENOR/ENGOT-ov7 study (which compared weekly paclitaxel to weekly paclitaxel plus concomitant and maintenance bevacizumab) demonstrated that randomised trials can be completed with international collaboration.\textsuperscript{39} As surgery and/or radiotherapy can be of clinical benefit in recurrent SCST, these patients could also be included in clinical trials with the presence or absence of measurable tumour before randomisation incorporated as a stratification factor. In SCST patients who are not candidates for chemotherapy, endocrine therapy such as aromatase inhibitors represent a potential control arm despite their low response rate.\textsuperscript{40}

International collaboration has facilitated completion of randomised trials in low grade serous\textsuperscript{41,42} and clear cell\textsuperscript{43} ovarian cancer. In rare tumour types, parallel clinical trials using harmonised protocols can be run with upfront agreement for combined final analysis. In very rare tumour types comparison of single arm studies with historical controls or real-world data is required. Construction of reliable contemporary real-world data sets to facilitate this comparison is needed.

If feasible, clinical trials should include frail patients. Expansion cohorts or subgroup analysis of frailer patients should be considered to better understand toxicity and pharmacokinetic ranges in frail patients.\textsuperscript{44}

Global efforts are urgently required to encourage equity of trial access across socioeconomic and ethnic patient groups in all stages of drug development to maximise the generalisability of findings regarding toxicity, tolerability and efficacy.

**Statements on critical elements in future clinical trials.**

Statesments on critical elements in future clinical trials are summarized in table 4. There is no standardised method for analysing positron emission tomography (PET) data or other functional diagnostic modalities in ovarian cancer, especially following introduction of targeted therapy and immunotherapy in clinical trials. New modalities should be added as exploratory endpoints. Intervals between scanning should not be different between study arms, as this may introduce bias.

Primary endpoints in Phase I trials include safety, and/or pharmacokinetics/pharmacodynamic data. In phase 2 trials, overall response rate is the primary endpoint for single-arm studies and may be used in randomised trials. However, in randomised phase II trials including a combination of agents, PFS can be the primary endpoint as ORR is not expected to be different. Disease control rate should not be used as a primary endpoint as there is no clear definition of the duration of stable disease needed to qualify for disease control. In addition, the incorporation of stable disease within a small non-randomized trial increases the risk of interpretation bias due to clinical heterogeneity. If used as an exploratory endpoint, duration of stabilization must be pre-defined, with a recommended duration of at least 6 months. In phase 3 trials, PFS assessed by investigator and OS are the preferred primary endpoints (although not necessary as dual endpoints). If also a BICR analysis was performed, this analysis should be reported as well. A sample-based or full Blinded Independent Central Review (BICR) may be a secondary endpoint (Supplement page 8). The use of multiple primary analytical endpoints requires adjustment for multiplicity.

Identification of predictive biomarkers and analysis of treatment effects in biologically defined subpopulations are essential. Trial populations must be stratified accordingly, and efficacy of the treatment should be reported in all subgroups. In confirmatory clinical trials, multiple endpoints need to be assessed (e.g. PFS and OS in biomarker
positive and ITT population). Thus, novel statistical designs such as hierarchical testing are needed. Secondary endpoints also require adjustment for multiplicity and sample size should be adjusted accordingly.\textsuperscript{46-48}

The incorporation of PROs allows better reporting of toxicity (e.g. the NCI PRO-CTCAE scoring system) and health-related quality of life (HrQL).\textsuperscript{46} PROs should be incorporated in clinical trials following appropriate guidelines (e.g. SPIRIT-PRO\textsuperscript{50} and CONSORT-PRO\textsuperscript{51}) and be included in statistical analysis plans. When PFS is a primary endpoint, consideration could be given including PROs as an additional endpoint, and the trial be powered accordingly. PRO and HrQL measures should continue past disease progression and until initiation of the next intervention, with inclusion of strategies to avoid missing data.

### Unmet needs

The four topic groups identified three broad areas of significant unmet need.

1. Understanding of ovarian cancer biology.

   The biology underpinning many key clinical observations remains uncertain, including mechanisms of intrinsic and acquired resistance to platinum, taxanes, PARP inhibitors, immune checkpoint inhibitors and anti-angiogenic agents. The critical need is for predictive biomarkers that are confirmed in a statistical treatment-by-biomarker outcome interaction test. Prognostic biomarkers, associated with outcome independent of treatment, cannot \textit{a priori} be applied as therapeutic targets or predictive biomarkers. Identifying patients who may develop clinically-significant toxicities is also critical. Simple, reliable and affordable biomarkers that can be prospectively evaluated and validated in clinical trials are an urgent unmet need, and it is imperative that clinical trials incorporate prospective biosample collection to support translational research. These samples must be made available to researchers worldwide.

2. Clinical trial design.

   Reliable objective methods to assess frailty are urgently needed, whilst international co-operation and innovative methodologies are required for trials in rare patient populations. Extended follow-up will allow assessment of long-term toxicities and identification of exceptional responders. Trials must embrace technology, including remote patient assessment and digital imaging and pathology evaluation. Access to individual patient data is essential for meta-analyses.

3. Patient inclusion and engagement.

   Greater patient engagement is needed in trial design and development, as is inclusion of patients in low/middle income countries and patients across all spectrums of diversity. Patient engagement will also be essential prior to future OCCC to identify key priorities.

### Conclusion

Improved molecular characterisation of ovarian cancer types and the continued emergence of diverse treatment modalities, has complicated the design, analysis, and interpretation of clinical trials. While many studies benefit from international collaboration, harmonisation is necessary to achieve key study objectives that can be generalised across multiple study populations. Attention to the research guidelines encapsulated within these consensus statements will help improve clinical trial design to address the unmet needs for women with ovarian cancer.

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### Authors’ Contributions


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References


