Clinical research in ovarian cancer: consensus recommendations from the Gynecologic Cancer InterGroup

Gynecologic Cancer InterGroup consensus recommendations on clinical research in ovarian cancer

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On behalf of the participants of the
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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.[1] 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.[2,3]

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.[4] 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.[5] 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.[6–8] 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.[9,10] 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,[11–13] 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 [14] 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,[15] OCCC6 recommended that platinum free interval should be replaced by a treatment free interval (TFI) specific to certain therapies, such as platinum (TFIp), PARPi (TFI_{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.[16] 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 TPIp 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).[17–20]
Level 1 evidence supports repeat use of maintenance bevacizumab in the recurrent setting.[21] 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.[22] 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).[23–27]
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).[28,29]
Based on three randomised trials, secondary cytoreduction should be considered in trials where platinum is an option, using a validated score (Supplement page 6).[30–32]

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[33] and phenotypic[34] similarity to HGSOC to be included in the same studies. Ovarian carcinosarcomas are monoclonal in origin and driven by molecular changes found in EOC.[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[36]) and immunohistochemical biomarkers (see Supplement page 7).[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.[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.[40]
International collaboration has facilitated completion of randomised trials in low grade serous[41,42] and clear cell[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.[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.

Statements 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 1 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.[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).[49] PROs should be incorporated in clinical trials following appropriate guidelines (e.g. SPIRIT-PRO[50] and CONSORT-PRO[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 *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

I. Vergote: literature search, figures, study design, data analysis, data interpretation, writing and approval of final manuscript. The authors (D. Lorusso, C. Gourley, I. McNeish, B. Votan, S. Mahner, I. Ray-Coquard, J.S. Berek, D. Tan, N. Colombo, R. Zang, N. Concin, D. O'Donnell, C.S. Herrington and A. Poveda) were involved in the planning, preparation, literature research, presentation during the meeting and active participation in the scientific discussions and the formal consensus process, writing, final review, editing and approval of the manuscript. A. Gonzalez-Martin: has participated as: Member of the Scientific Committee, Chair of Topic I Group, Proposer of first draft of statements, Discussant during the Consensus Conference meeting, Presenter of the statements, Contributor to the manuscript with a summary of Group. M. Raza Mirza: planning of this conference, as chair of a subgroup, leading discussions on unmet needs, methodology, preparing of questions, leading all related virtual meetings and leading the subgroup conference part. Finally in writing and reviewing the manuscript. A. du Bois: planning, preparation, literature research,

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Table 1 First line treatment

Statement 1	**Selection of patients for neoadjuvant chemotherapy (NACT) or primary cytoreductive surgery (PCS)** *(Approval 32/33 groups, 1 opposed)*
	PCS after assessment in an expert Gynecological Oncology unit is preferred. NACT followed by interval cytoreductive surgery (ICS) is a valid alternative only if PCS is not feasible. 1. PCS or 3-4 cycles of NACT followed by ICS are valid options after evaluation of the complexity of surgery, the likelihood of complete cytoreduction (R0) and the histological type confirmed by biopsy. - PCS is preferred if a complete resection seems achievable or for patients with tumour histological types associated with limited response to platinum-based therapy, even if complete resection is questionable (e.g.low grade serous or mucinous carcinoma). - NACT with ICS is the preferred option in patients with chemosensitive histological types AND with a low likelihood of an initial complete resection OR who are poor surgical candidates. 2. Optimal assessment includes a combination of patient status, biological factors, and disease extent by imaging and/or surgical evaluation. 3. The extent of disease at the beginning and at the end of cytoreductive surgery should be thoroughly documented.
Statement 2	**Stratification factors (SF)** *(Approval 33/33 groups)*
	First line trials should include validated prognostic stratification factors and predictive factors according to the protocol design and the intervention explored. 1. Prognostic factors such as BRCA status, FIGO stage, timing of surgery (PCS vs NACT), outcome of surgery (no residual versus any residual tumour), histological type (high grade serous ovarian cancer (HGSOC)/high grade endometrioid ovarian cancer (HGEOC) vs others non-HGSOC/HGEOC), or patient status should be included as stratification factors depending on the trial hypothesis. 2. Predictive biomarkers should be included as stratification factors, such as BRCA status and homologous recombination (HR) status (tested by a validated assay) especially in trials with poly-ADP ribose polymerase inhibitors (PARPi). 3. New biomarkers measured by a validated assay should be prospectively evaluated in first line trials properly powered for this endpoint.
Statement 3	**Acceptable reference arms for systemic treatment?** *(Approval 33/33 groups)*
	1. Backbone systemic therapy is based on the carboplatin-paclitaxel combination - 6 cycles of IV 3-weekly carboplatin area under the curve (AUC) 5-6 and paclitaxel 175 mg/m2 remains the reference arm for first-line chemotherapy in advanced ovarian cancer. The addition of bevacizumab is acceptable. o Dose dense weekly IV Paclitaxel 80 mg/m^2 with 3-weekly carboplatin is an alternative reference arm to 3-weekly IV carboplatin/paclitaxel only in populations for whom level 1 evidence of a benefit exists. o Weekly carboplatin AUC 2/paclitaxel 60 mg/m^2 can be an acceptable option. 2. Maintenance therapy should be considered in the reference arm for HGSOC/HGEOC - Patients with BRCA mutated (BRCAm) tumours (either germline or somatic) or BRCA wild type (BRCAwt)/HR deficient (HRd) should receive a PARPi as maintenance, with or without bevacizumab. - The role of maintenance therapy for patients with HR-proficient tumours is not completely defined. These patients may receive PARPi or bevacizumab as maintenance, and even observation depending on the trial design.
Statement 4.	**Challenges of maintenance therapy** *(Approval 33/33 groups)*
	1. Progression-free survival (PFS) and overall survival (OS) should remain the primary endpoints. 2. PARPi may impact the effectiveness of subsequent treatments in the recurrence setting, therefore post-treatment progression data** and PFS2*** should also be considered key secondary endpoints. 3. Maintenance treatment trials should have validated patient reported outcomes (PROs) and safety assessments, such as proCTCAE and quality adjusted endpoints (Q-TWIST or quality adjusted PFS).
Statement 5	**Intraperitoneal chemotherapy and hyperthermic intraperitoneal chemotherapy (HIPEC)** *(Approval 30/33 groups, 2 opposed*, 1 abstain)*
	1. Any form of IP therapy or HIPEC cannot be regarded as a reference treatment arm within clinical trials
Statement 6	**Future trials for high-risk Stage I or Stage II disease** *(Approval 33/33 groups)*
	High-risk stage I and II studies are needed, using international cooperation. 1. Separate trials should address specific questions for patients with high-risk stage I or stage II epithelial ovarian cancer, defined by histological, clinical and biological factors. 2. Platinum-based chemotherapy remains the reference arm.
*See Supplement page 4 **post-treatment progression data: type and timing of subsequent therapy *** PFS2: time from randomisation to the second objective disease progression or death	

Table 2. Statements on recurrent ovarian cancer

Statement 7	**Categorisation by clinical and molecular factors** *(Approval 33/33 groups)*
	1. Eligibility should be categorised and/or stratified according to: - Histology: high grade serous and high grade endometrioid (with aberrant p53 IHC) vs. others - *BRCA1/2* mutation status - Number of prior lines of treatment - Exposure and response to prior treatments - Treatment-free interval from last platinum (TFIp) - Outcome of surgery for recurrent disease 2. Eligibility based only on the interval from last platinum treatment is discouraged.
Statement 8	**Platinum-based regimens as reference arm** *(Approval 32/33 groups, 1 opposed*)*
	1. Platinum-containing regimens should be the reference arm in patient populations where response to platinum is expected. These include patients with: - Tumours without progression during platinum or shortly following last platinum dose (e.g. within 12 weeks) - Tumours that have responded to the most recent platinum. - No prior platinum therapy - No residual tumour at the start of platinum therapy 2. Appropriate reference arms include: - Platinum-based combination regimens (carboplatin + pegylated liposomal doxorubicin preferred) - PARP inhibitor therapy can be an appropriate alternative reference arm in patients with *BRCAm 1/2* who have received >2 prior platinum lines and who are PARPi naïve. 3. Maintenance options in the reference arm should be based on study design and prior exposure - PARPi in those who have responded to platinum-based therapy. - Bevacizumab in combination with chemotherapy and as maintenance, including in those who have previously received a PARP inhibitor and/or bevacizumab. 4. Prior exposure to PARPi and/or bevacizumab should be included as stratification factors. Information on duration of exposure and timing of progression (during vs following) should be considered as inclusion or stratification factors.
Statement 9	**Non-platinum regimens as reference arm** *(Approval 31/33 groups, 2 opposed*)*
	1. Reference arms should contain non-platinum-based regimens when response to platinum is not expected: - Tumours that have progressed on platinum or early (e.g. within 12 weeks) following last platinum dose - Tumours not achieving a response to prior platinum 2. Potential reference arms may include: - Single agent chemotherapy, such as pegylated liposomal doxorubicin (PLD), weekly paclitaxel, gemcitabine, or topotecan - Incorporation of bevacizumab for those receiving PLD, weekly paclitaxel or topotecan. 3. Supportive care (without anti-cancer therapy) can be included as an option in patients who have received >4 treatment lines or where there are no standard of care options. 4. Patients with primary platinum refractory tumours (progressed on or within 12 weeks of first platinum treatment) constitute a specific patient cohort and should be enrolled in dedicated trials, or should be stratified if enrolled in trials for patients not suitable for platinum re-treatment.
Statement 10	**Biomarker directed trials may allow a broader population based on clinical and molecular factors** *(Approval 33/33 groups)*
	The reference arm of biomarker-driven trials may include both platinum and non-platinum regimens according to patient clinical characteristics, with appropriate stratification.
Statement 11	**Secondary cytoreductive surgery** *(Approval 32/33 groups, 1 abstain*)*
	1. Secondary cytoreduction is permitted prior to clinical trial enrolment and should be included as a stratification factor pre-randomisation, along with extent of residual disease. 2. Secondary cytoreduction should be considered in all patients with recurrent disease fulfilling criteria predictive of successful complete resection 3. Secondary cytoreduction as a component of protocol-directed management (post-randomisation) would only be permitted if included within the trial design. - When included as a component of protocol-directed therapy, secondary cytoreduction should be reserved for patients selected using a validated score (e.g. AGO score)
*See Supplement page 4	

Table 3 Statements on non-high grade serous ovarian cancer (non-HGSOC)

Statement 12	**Comparator systemic therapy for randomised studies with epithelial non-HGSOC** *(Approval 33/33 groups)*
	1. Platinum-based chemotherapy is a reasonable reference arm for epithelial stage I/II non-HGSOC 2. Carboplatin and paclitaxel with or without bevacizumab is the recommended first line reference arm for randomised clinical trials of stage III or IV non-HGSOC. 3. Ovarian cancer studies should be performed within a histologically defined setting following specialist gynaecological pathology review according to pre-defined diagnostic criteria. 4. High grade endometrioid ovarian cancers (and carcinosarcomas) with aberrant p53 immunohistochemistry should be considered for inclusion in studies with HGSOC with appropriate stratification. 5. In relapse there is not a single consensus reference arm. Suitable physician's choice options include chemotherapy and/or endocrine therapy according to the setting and type under investigation.
Statement 13	**Systemic treatment reference arms for studies of patients with adult malignant ovarian germ cell tumours** *(Approval 33/33 groups)*
	1. First line reference arm options in germ cell studies include surgery and active surveillance (stage I), surgery and chemotherapy (high risk stage I, stage II to IV) or chemotherapy alone (stage IV). In patients suitable for chemotherapy bleomycin, etoposide and cisplatin (BEP) should be the control arm within clinical trials. 2. Careful treatment de-escalation is an important future research objective.
Statement 14	**Systemic treatment reference arms for studies of patients with sex cord stromal ovarian tumours** *(Approval 33/33 groups)*
	1. First line reference arm options in sex cord stromal tumour (SCST) studies include surveillance (stage I or completely resected advanced disease) or systemic therapy for stage II to IV (BEP or carboplatin and paclitaxel). 2. Reference arm options for relapsed SCST include: BEP (if chemotherapy naïve), carboplatin and paclitaxel, weekly paclitaxel and aromatase inhibitors, depending on prior systemic treatment exposure.
Statement 15	**Optimal trial design in rare or molecularly defined ovarian subgroups** *(Approval 33/33 groups)*
	1. In subgroups where incidence allows, international multicentre trials with randomisation against reference therapy should be performed. 2. In very rare subgroups randomised trials may not be feasible. Innovative designs (e.g. platform studies) could be considered with an a priori definition of benefit. Signals of efficacy may therefore be sought in single arm trials.
Statement 16	**Inclusion of subgroups of patients to address frailty, ethnic diversity or comorbidity profile** *(Approval 33/33 groups)*
	1. Under-representation of patients recruited into clinical trials in terms of frailty and co-morbidities adversely affects the generalisability of findings. Where possible studies involving agents with defined acceptable toxicity should include broad inclusion criteria, with appropriate stratification for these factors. Alternatively, trials specifically recruiting or dedicated to frail patients should be considered. 2. Ovarian cancer patients should be included in the assessment, validation and development of vulnerability scoring tools such as the geriatric vulnerability score (GVS). 3. Equitable access for all ethnic and socioeconomic groups within clinical trials is critical. Multinational collaborative efforts to include diverse ethnic groups in clinical trials would facilitate the investigation of pharmacogenomics and pharmacokinetic factors.

Table 4 Statements on critical elements in future trial design (see comment)

Statement 17	**Imaging** (Approval 33/33 groups)
	Computed tomography (CT) with oral and intravenous contrast remains the primary endpoint modality and must be performed per protocol-designated intervals (or when triggered by clinical circumstances) in trials for ovarian cancer. 1. Magnetic resonance imaging (MRI) is an acceptable alternative, especially for patients who cannot tolerate iodinated intravenous contrast or oral contrast. 2. Imaging must include chest, abdomen, and pelvis. 3. The same modality as used in the baseline evaluation must be used throughout the assessment of a subject; exceptions can be made for allergy or intolerance to contrast media. 4. Timing of imaging should be appropriate to the aim of the study, the time to expected outcome, feasibility of execution, and harmonised across all arms, independent of cycle lengths, which may differ. Context specific baseline scans must be included for assessment. 5. Incorporation of secondary or developmental imaging and molecular biomarker endpoints may be evaluated and must be validated against CT. 6. New imaging approaches must fit the anticipated clinical value pertinent to the aims of the study for which they are developed and applied.
Statement 18	**Primary endpoints** (Approval 33/33 groups)
	1. Phase 1 expansion (phase 1b) trials can be used to extend safety analyses, and/or to evaluate pharmacokinetic and/or pharmacodynamic endpoints. 2. Response rate is the primary activity endpoint of a single arm phase 2 study, and it may be used in randomised phase 2 clinical trials. 3. Overall or objective response rate (ORR) is defined as the sum of RECIST*-determined complete plus partial responses. RECIST* responses are defined as confirmed responses and incorporates criteria for clinical progression. 4. Disease control rate (DCR), the sum of complete plus partial responses plus stable disease, is neither a defined nor validated primary endpoint. 5. PFS and OS are the primary endpoints** for phase 3 and can be used in randomised phase 2 trials. 6. PFS should be assessed by investigator when used as the primary endpoint, irrespective of the blinding or placebo control. A sample-based or full Blinded Independent Central Review (BICR) could be included as secondary endpoint. If the BICR analysis is performed, results of both analyses should be reported. 7. Use of multiple primary endpoints requires methods to adjust for multiplicity, such as alpha splitting or hierarchical testing. 8. Other response criteria, such as those developed for application to immunotherapy clinical trials (immune [I or ir]RECIST, etc), have not been validated in ovarian cancer trials and cannot be used as the primary endpoint. 9. Measurement of CA-125 response should not be used as a primary endpoint. 10. Assessment of efficacy of the addition of a new agent(s) (e.g., combination regimens) requires a randomised design. 11. Due to changes in staging of ovarian cancer and changes in the definition/diagnosis of different histological and molecular types, historical controls cannot be relied on and should only be used in the setting of very rare tumours, where randomised designs are not feasible.
Statement 19	**New trial designs can expedite progress in clinical trials for ovarian cancer** (Approval 32/33 groups, 1 abstain***)
	1. Novel trial designs across diseases, cohorts, molecular selectors, and/or drugs may be used to evaluate preliminary pharmacodynamic and/or clinical activity. They must incorporate accepted validated primary endpoints and the results need to be confirmed in appropriately designed randomised clinical trials. 2. Multi-arm trials can facilitate exploration of novel approaches while optimising operational efficiency. 3. Incorporation of novel statistical methods permit prospectively planned and powered analyses that allow for dissection for optimised outcomes (e.g., hierarchical testing, group sequential designs, etc). 4. Analysis of treatment outcomes across subgroups and/or stratification factors should be prespecified and adequately powered in the protocol.
Statement 20	**Patient reported outcomes (PROs) and quality of life measures** (Approval 33/33 groups)
	1. Incorporation of self-reported toxicity assessment, e.g., PRO-CTCAE (Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events) should be considered. 2. Pre-defined patient reported outcome (PRO) endpoints should be included in the statistical analysis plan in randomised trials, particularly when there is a difference in equipoise between arms, such as extended maintenance therapy or additional agents. If feasible, such PRO should continue past disease progression and continue until initiation of next intervention. 3. If PFS is the primary endpoint, consideration could be given to including PROs as an additional primary endpoint. 4. Inclusion and reporting of PRO endpoints in protocols should follow the published guidelines, i.e., ISOQOL (International Society for Quality of Life Research), CONSORT-PRO (CONsolidated Standards Of Reporting Trials-PRO). 5. All clinical trials that include PRO should incorporate strategies to avoid and address missing data.
* RECIST 1.1[14] ** not necessary as dual endpoints ***See Supplement page 4	