Gynaecological Cancers 1

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

*Ignace Vergote, Antonio Gonzalez-Martin, Domenica Lorusso, Charlie Gourley, Mansoor Raza Mirza, Jean-Emmanuel Kurtz, Aikou Okamoto, Kathleen Moore, Frédéric Kridelka, Iain McNeish, Alexander Reuss, Bénédicte Votan, Andreas du Bois, Sven Mahner, Isabelle Ray-Coquard, Elise C Kohn, Jonathan S Berek, David S P Tan, Nicoletta Colombo, Rongyu Zang, Nicole Concin, Dearbhaile O'Donnell, Alejandro Rauh-Hain, C Simon Herrington, Christian Marth, Andres Poveda, Keiichi Fujiwara, Gavin C E Stuart, Amit M Oza, Michael A Bookman, on behalf of the participants of the 6th Gynecologic Cancer InterGroup (GCIG) Ovarian Cancer Consensus Conference on Clinical Research**

The Gynecologic Cancer InterGroup (GCIG) sixth Ovarian Cancer Conference on Clinical Research was held virtually in October, 2021, following published consensus guidelines. The goal of the consensus meeting was to achieve harmonisation on the design elements of upcoming trials in ovarian cancer, 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 four topic groups on clinical research in ovarian cancer including first line treatment, recurrent disease, disease subgroups, and future trials. Unanimous consensus was obtained for 14 of 20 statements, with greater than 90% concordance in the remaining six statements. The high acceptance rate following active deliberation among 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 the harmonisation of international clinical research in ovarian cancer.

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This is the first paper in a **Series** of two papers on Gynaecological Cancers

*Members listed in the appendix (pp 9–11)

Belgium and Luxembourg Gynaecological Oncology Group (BGOG), Leuven, Belgium (Prof I Vergote MD, F Kridelka MD); **University Hospitals Leuven, Leuven, Belgium** (Prof I Vergote); **Grupo Español de Cáncer de Ovario (GEICO), Madrid, Spain** (A Gonzalez-Martin MD, A Poveda MD); **Clinica Universidad de Navarra, Madrid, Spain** (A Gonzalez-Martin); **Program for Solid Tumors at Madrid, and Center for Applied Medical Research (CIMA), Universidad de Navarra, Pamplona, Spain** (A Gonzalez-Martin); **Multicenter Italian Trials in Ovarian Cancer and Gynecologic Malignancies (MITO), Naples, Italy** (D Lorusso MD); **Fondazione Policlinico Gemelli IRCCS, Rome, Italy** (D Lorusso); **Scottish Gynaecological Cancer Trials Group (SGCTG), Cancer Research UK, Edinburgh, UK** (C Gourley MD, C S Herrington MD); **Institute of Genetics and Cancer, University of Edinburgh, Edinburgh, UK** (C Gourley, C S Herrington); **Nordic Society of Gynecologic Oncology Clinical Trial Unit (NSGO-CTU), Copenhagen, Denmark** (M R Mirza MD); **Rigshospitalet, Copenhagen, Denmark** (M R Mirza); **Groupe d'Investigateurs National des Etudes des Cancers Ovariens et du Sein (GINECO), Paris, France** (J-E Kurtz MD, I Ray-Coquard MD); **Centre Leon Berard and University Claude Bernard Lyon I, Lyon, France** (I Ray-Coquard); **Strasbourg**

Introduction

The Gynecologic Cancer InterGroup (GCIG) consists of 33 clinical research groups worldwide (appendix p 2) and has organised an ovarian cancer consensus conference on clinical research approximately every 5 years.[1] The planning of the sixth GCIG ovarian cancer consensus conference (OCCC6) was initiated in May, 2017, with the intent to meet on Oct 9–11, 2020, in Leuven, Belgium. Due to the COVID-19 pandemic, OCCC6 was first postponed and later held virtually on Oct 15–21, 2021.[2,3]

Consensus process

The OCCC6 scientific committee identified 20 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.

To maximise participation across time zones, lectures were prerecorded and available before and during the meeting. Adaptive technology was used to record live discussions and provide extended commentary after each session. All statements were presented three times with the opportunity for sequential revisions to be made between each session. Each of the 33 groups had a single vote and all voted electronically on the 20 statements within the first 24 h 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. Further details on the methods are in the appendix (p 3).

Consensus statements

First-line treatment

Consensus statements on first-line treatment are summarised in panel 1. Epithelial tumours of ovarian, fallopian, and peritoneal origin were grouped together as epithelial ovarian cancer for the purposes of this meeting. Initial tumour stage, selection of patients for neoadjuvant chemotherapy, and the presence of any visible residual disease following cytoreductive surgery are key prognostic factors for women with advanced epithelial ovarian cancer.[4] Primary cytoreductive surgery remains the preferred option if complete cytoreduction is achievable after evaluation by an expert from the gynaecological oncology team, whereas neoadjuvant chemotherapy should be used for patients for whom surgery is not suitable or when complete cytoreduction is unlikely.[5] The decision about whether to perform primary cytoreductive surgery or administer neoadjuvant chemotherapy must be based on patient performance status and the extent of disease as determined by imaging or surgical assessment (or both). In addition, the OCCC6 incorporates histology as a decision factor, favouring primary cytoreductive surgery for patients with histological types that have low chemosensitivity, even if complete cytoreduction is questionable.

Statement 2 on stratification factors applies for first-line trials using primary cytoreductive surgery or neoadjuvant chemotherapy. Chemotherapy remains the second pillar for treatment of epithelial ovarian cancer, consisting of six cycles of paclitaxel and carboplatin with or without bevacizumab every 3 weeks.[6–8] Weekly paclitaxel with weekly carboplatin[9] or weekly paclitaxel and carboplatin every 3 weeks in Japanese patients (both native and living

Cancer Institute, Strasbourg, France (J-E Kurtz)**; Japanese Gynecologic Oncology Group (JGOG), Tokyo, Japan** (A Okamoto MD)**; The Jikei University School of Medicine, Tokyo, Japan** (A Okamoto)**; Gynecologic Oncology Group-Foundation (GOG-F), Philadelphia, PA, USA** (K Moore MD, M A Bookman MD)**; OU Health Stephenson Cancer Center, Oklahoma City, OH, USA** (K Moore)**; Centre Hospitalier Universitaire de Liège, Liège, Belgium** (F Kridelka)**; National Cancer Research Institute (NCRI), London, UK** (I McNeish PhD)**; Department of Surgery and Cancer, Imperial College London, London, UK** (I McNeish)**; Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) Study Group, Munich, Germany** (A Reuss MSc, A du Bois MD, S Mahner MD)**; AGO -Austria, Innsbruck, Austria** (N Concin MD, C Marth MD)**; Coordinating Center for Clinical Trials, Philipps University, Marburg, Germany** (A Reuss)**; Association de Recherche Cancers Gynécologiques (ARCAGY)–GINECO, Paris, France** (B Votan MSc)**; Kliniken Essen Mitte (KEM), Essen, Germany** (A du Bois, N Concin)**; University Hospital, Ludwig Maximilians University, Munich, Germany** (S Mahner MD)**; National Cancer Institute, National Institutes of Health, Bethesda, MD, USA** (E C Kohn MD)**; Women's Cancer Research Network-Cooperative Gynecologic Oncology Investigators (WCRN-COGI), Fresno, CA,** (J S Berek MD)**; Stanford Cancer Institute, Stanford, CA, USA** (J S Berek)**; Asia Pacific Gynecologic Oncology Trials Group (APGOT), Seoul, South Korea,** (D S P Tan MD)**; Gynecologic Cancer Group Singapore (GCGS), Singapore** (D S P Tan)**; Cancer Science Institute, National University of Singapore, Singapore** (D S P Tan)**; Mario Negri Gynecologic Oncology (MaNGO), Milan, Italy** (N Colombo MD)**; European Institute of Oncology, Milan, Italy** (N Colombo)**; University of Milano-Bicocca, Milan, Italy** (N Colombo)**; Shanghai Gynecologic Oncology Group (SGOG), Shanghai, China**

abroad) with high-grade serous ovarian cancer,[10] are acceptable alternatives. Statement 5 on intraperitoneal therapy and hyperthermic intraperitoneal chemotherapy (HIPEC) was much debated with an approval rate of only 30 out of 33 GCIG groups (two groups opposing and one abstaining). It should be highlighted that this statement is not about standard of care, but about accepting intraperitoneal therapy and HIPEC as reference treatment groups within clinical trials.

The incorporation of maintenance therapy with poly (ADP-ribose) polymerase (PARP) inhibitors after first-line chemotherapy in high-grade serous or endometrioid types[11–13] should be considered as part of the reference group, at least for patients with tumours harbouring *BRCA1* or *BRCA2* mutations (germline or somatic) or those with wild-type *BRCA* genes but homologous recombination deficiency, either alone or combined with bevacizumab. The optimal maintenance therapy

Panel 1: First-line treatment

Statement 1

Selection of patients for neoadjuvant chemotherapy or primary cytoreductive surgery (PCS) (32 of 33 groups approved, one opposed)

PCS after assessment in an expert gynecological oncology unit is preferred. Neoadjuvant chemotherapy followed by interval cytoreductive surgery (ICS) is a valid alternative only if PCS is not feasible.

1 PCS or three to four cycles of neoadjuvant chemotherapy followed by ICS are valid options after evaluation of the complexity of surgery, the likelihood of complete cytoreduction, 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 a poor response to platinum-based therapy, even if complete resection is questionable (eg, low-grade serous or mucinous carcinoma)
   - Neoadjuvant chemotherapy 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 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 (33 of 33 groups approved)

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* neoadjuvant chemotherapy), outcome of surgery (no residual *vs* any residual tumour), histological type (high-grade serous ovarian cancer or high-grade endometrioid ovarian cancer *vs* other non-high-grade serous or endometrioid ovarian cancers), or patient status should be included as stratification factors depending on the trial hypothesis
2 Predictive biomarkers, such as *BRCA* status and homologous recombination status (tested by a validated assay), should be included as stratification factors, especially in trials with PARP inhibitors
3 New biomarkers measured by a validated assay should be prospectively evaluated in first-line trials and properly powered for this endpoint

Statement 3

Acceptable reference groups for systemic treatment (33 of 33 groups approved)

1 Backbone systemic therapy is based on the carboplatin–paclitaxel combination
   - Six cycles of intravenous carboplatin (target AUC 5–6 mg/mL per min) every 3 weeks and paclitaxel 175 mg/m² remains the reference group for first-line chemotherapy in advanced ovarian cancer; the addition of bevacizumab is acceptable
   - Dose dense intravenous paclitaxel 80 mg/m² weekly with carboplatin every 3 weeks is an alternative reference group to intravenous carboplatin–paclitaxel every 3 weeks only in populations for whom level 1 evidence of a benefit exists
   - Weekly carboplatin AUC 2 combined with paclitaxel 60 mg/m² can be an acceptable option
2 Maintenance therapy should be considered in the reference group for high-grade serous or high-grade endometrioid ovarian cancer
   - Patients with *BRCA*-mutated tumours (either germline or somatic) or *BRCA* wild-type and homologous-recombination-deficient tumours should receive a PARP inhibitor as maintenance, with or without bevacizumab
   - The role of maintenance therapy for patients with homologous-recombination-proficient tumours is not completely defined; these patients may receive PARP inhibitors or bevacizumab as maintenance, and even observation alone might be appropriate depending on the trial design

Statement 4

Challenges of maintenance therapy (33 of 33 groups approved)

1 Progression-free survival and overall survival should remain the primary endpoints
2 PARP inhibitors might affect the effectiveness of subsequent treatments in the recurrence setting, therefore post-treatment progression data* and PFS2† should also be considered as key secondary endpoints

(Continues on next page)

(Panel 1 continued from previous page)

3 Maintenance treatment trials should have validated patient-reported outcomes and safety assessments, such as PRO-CTCAE and quality-adjusted endpoints (Q-TWiST or quality-adjusted progression-free survival)

Statement 5

Intraperitoneal chemotherapy and HIPEC (30 of 33 groups approved, two opposed‡, one abstained)

1 Any form of intraperitoneal therapy or HIPEC cannot be regarded as a reference treatment within clinical trials

Statement 6

Future trials for high-risk stage I or stage II disease (33 of 33 groups approved)

Studies in high-risk stage I and II disease are needed, with 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 should remain as the reference group

AUC=area under the concentration versus time curve. PARP=poly (ADP-ribose) polymerase. PRO-CTCAE=Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events. FIGO=International Federation of Gynecology and Obstetrics. HIPEC=hyperthermic intraperitoneal chemotherapy. Q-TWiST=Quality Adjusted Time Without Symptoms and Toxicity. *Post-treatment progression data: type and timing of subsequent therapy. †PFS2 is the time from randomisation to the second objective disease progression or death. ‡See appendix (p 4).

for patients with wild-type *BRCA* and homologous-recombination-proficient tumours, if any, remains unknown. Incorporation of maintenance as part of the reference group should not change the primary endpoints, which remain progression-free survival and overall survival, although not necessarily as dual endpoints. Safety and patient-reported outcomes (PROs) should be included as secondary endpoints. Progression-free survival 2 (known as PFS2), defined as the time from randomisation to the second objective disease progression or death, should also be considered due to the potential effect of PARP inhibitors on the efficacy of subsequent therapies.

The utilisation of appropriate stratification factors is key for optimal interpretation of clinical trials. In addition to classical prognostic factors (such as the International Federation of Gynecology and Obstetrics 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 to test for *BRCA1* and *BRCA2* mutations and homologous recombination deficiency.

There is a need for clinical research in patients with high-risk stage I[14] or II epithelial ovarian cancer. These trials, through international cooperation, might address specific questions for this patient population.

Recurrent ovarian cancer

Recurrent ovarian cancer statements are summarised in panel 2. Building on findings from OCCC5 in 2015,[15] OCCC6 recommended that the platinum-free interval should be replaced by a treatment-free interval (TFI) specific to particular therapies, such as platinum, PARP inhibitors, and other specific clinical and molecular factors.

Agents targeting DNA damage response are best suited for *TP53*-aberrant tumours, whereas agents targeting angiogenesis might be suitable for all histological types. Predictive biomarkers for PARP inhibitors and other agents targeting DNA damage response could be important for eligibility or stratification. The exposure or response to previous therapies is also increasingly important for clinical trial design and interpretation. For example, in an exploratory analysis of the SOLO-2/ENGOT-ov21 trial, among patients who had disease recurrence and were re-treated with platinum therapy, median progression-free survival was 7 months after previous maintenance with olaparib compared with 14·3 months after placebo, suggesting that previous PARP inhibitor exposure might compromise subsequent response to platinum.[16] Most importantly, the TFI after platinum therapy 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 cutoff TFI after platinum, we agreed that it was reasonable for patients who had relapsed within 12 weeks of their last platinum dose to be selected for a next line of therapy that excludes platinum.

The standard of care for patients with recurrent epithelial ovarian cancer for whom platinum therapy is an option has been a platinum-containing regimen (carboplatin plus pegylated liposomal doxorubicin preferably). When considering which chemotherapy backbone to use, there are three options with differences in schedule, toxicity profile, and to a modest degree efficacy (appendix p 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 PARP inhibitors in the recurrent maintenance setting, the advantages appear small and such repeated use should not be considered in the reference group until the benefits to patients are better elucidated.[22] At a minimum, stratification for previous PARP inhibitor use and/or with previous bevacizumab use should be considered in clinical trials in which platinum therapy is an option for treatment.

(R Zang MD); **Zhongshan Hospital, Fudan University, Shanghai, China** (R Zang); **Medical University of Innsbruck, Innsbruck, Austria** (N Concin, C Marth); **Cancer Trials Ireland (CTI), Dublin, Ireland** (D O'Donnell MD); **St James's Hospital, Dublin, Ireland** (D O'Donnell); **Global Gynecologic Oncology Consortium (G-GOC), Houston, TX, USA** (A Rauh-Hain MD); **MD Anderson Cancer Center, The University of Texas, Houston, TX, USA** (A Rauh-Hain); **Hospital Quironsalud, Valencia, Spain** (A Poveda); **Gynecologic Cancer Clinical Trials and Investigation Consortium (GOTIC), North Kanto, Japan** (K Fujiwara MD); **Saitama Medical University International Medical Center, Saitama, Japan** (K Fujiwara); **Canadian Cancer Trials Group (CCTG), Kingston, ON, Canada** (G C E Stuart MD); **University of British Columbia, Vancouver, BC, Canada** (G C E Stuart); **Princess Margaret Hospital Consortium (PMHC), Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada** (A M Oza MD); **San Francisco Medical Center, San Francisco, CA, USA** (M A Bookman)

Correspondence to:
Prof Ignace Vergote, BGOG, University Hospitals Leuven, 3000 Leuven, Belgium
ignace.vergote@uzleuven.be

See **Online** for appendix

Panel 2: **Statements on recurrent ovarian cancer**

Statement 7

Categorisation by clinical and molecular factors (33 of 33 groups approved)

1 Eligibility should be categorised or stratified according to:
   - Histology: high-grade serous and high-grade endometrioid (with aberrant p53 immunohistochemistry) versus others
   - *BRCA1* and *BRCA2* mutation status
   - Number of previous lines of treatment
   - Exposure and response to previous treatments
   - Treatment-free interval from last platinum treatment
   - 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 the reference group (32 of 33 groups approved, one opposed)*

1 Platinum-containing regimens should be the reference group in patient populations in which response to platinum is expected; these populations include patients with:
   - Tumours without progression during platinum therapy or shortly following the last platinum dose (eg, within 12 weeks) and
   - Have responded to the most recent platinum therapy, or the patient had no prior platinum therapy, or no residual tumour at the start of platinum therapy
2 Appropriate reference groups include:
   - Platinum-based combination regimens (carboplatin plus pegylated liposomal doxorubicin preferred)
   - PARP inhibitors can be an appropriate alternative reference group in patients with mutated *BRCA1* or *BRCA2* who have received more than two previous platinum lines, and who are PARP inhibitor naive
3 Maintenance options in the reference group should be based on study design and previous exposure, and include:
   - PARP inhibitors in patients who have responded to platinum-based therapy
   - Bevacizumab in combination with chemotherapy and as maintenance, including in patients who have previously received a PARP inhibitor or bevacizumab
4 Previous exposure to PARP inhibitors or bevacizumab should be included as stratification factors; information on duration of exposure and timing of progression (during *vs* after treatment) should be considered as inclusion or stratification factors

Statement 9

Non-platinum regimens as the reference group (31 of 33 groups approved, two opposed)*

1 Reference groups should contain non-platinum-based regimens when response to platinum therapy is not expected:
   - Tumours that have progressed on platinum therapy or shortly following last platinum dose (eg, within 12 weeks) or
   - Tumours that have not responded to previous platinum therapy
2 Potential reference groups could include:
   - Single agent chemotherapy such as pegylated liposomal doxorubicin, weekly paclitaxel, gemcitabine, or topotecan
   - Incorporation of bevacizumab for patients receiving pegylated liposomal doxorubicin, weekly paclitaxel, or topotecan
3 Supportive care (without anticancer therapy) can be included as an option in patients who have received more than four treatment lines or for whom there are no standard-of-care options
4 Patients with primary platinum refractory tumours (ie, those who have progressed on, or within 12 weeks of, first platinum treatment) constitute a specific patient cohort and should be enrolled in dedicated trials or stratified if they are enrolled in trials for patients not suitable for platinum re-treatment

Statement 10

Biomarker-directed trials to allow a broader population based on clinical and molecular factors (33 of 33 groups approved)

The reference group 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 (32 of 33 groups approved, one abstained)*

1 Secondary cytoreduction is permitted before clinical trial enrolment and should be included as a stratification factor before randomisation, along with extent of residual disease
3 Secondary cytoreduction should be considered in all patients with recurrent disease who meet criteria predictive of successful complete resection
3 Secondary cytoreduction as a component of protocol-directed management (after 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 (eg, AGO score)

AGO=Arbeitsgemeinschaft Gynäkologische Onkologie. *See appendix (p 4).

In studies evaluating patients with disease recurrence but who are not suitable for platinum therapy and who are naive to bevacizumab treatment, bevacizumab in combination with cytotoxic chemotherapy should be the control group or, if a mixed population (bevacizumab pretreated or not) are enrolled, bevacizumab should be a stratification factor. Possible monotherapy cytotoxic options are outlined in the appendix (p 5).[23–27]

Biomarker-directed trials should consider a broader inclusion of patients irrespective of TFI after platinum. Successful application of this concept has already been shown in both the ARIEL 4 and FORWARD II studies (appendix p 6).[28,29] On the basis of three randomised trials, secondary cytoreduction should be considered in trials in which platinum therapy is an option, using a validated score (appendix p 6).[30–32]

Non-high-grade serous ovarian cancer

Statements on non-high-grade serous ovarian cancer are summarised in panel 3. High-grade endometrioid ovarian cancer with aberrant p53 expression has sufficient molecular[33] and phenotypic[34] similarity to high-grade serous ovarian cancer to be included in the same studies. Ovarian carcinosarcomas are monoclonal in origin and driven by molecular changes found in epithelial ovarian cancer.[35] Therefore, if the epithelial

Panel 3: **Statements on non-high-grade serous ovarian cancer**

Statement 12

Comparator systemic therapy for randomised studies with epithelial non-high-grade serous ovarian cancer (33 of 33 groups approved)

1. Platinum-based chemotherapy is a reasonable reference group for epithelial stage I and II non-high-grade serous ovarian cancer
2. Carboplatin and paclitaxel with or without bevacizumab is the recommended first-line reference group for randomised clinical trials of stage III or IV non-high-grade serous ovarian cancer
3. Ovarian cancer studies should be performed within a histologically defined setting following a specialist gynaecological pathology review according to predefined diagnostic criteria
4. High-grade endometrioid ovarian cancers (and carcinosarcomas) with aberrant p53 immunohistochemistry should be considered for inclusion in studies with high-grade serous ovarian cancer and with appropriate stratification
5. No single consensus reference group exists for relapse; suitable physician's choice options include chemotherapy or endocrine therapy (or both) according to the setting and type under investigation

Statement 13

Systemic treatment reference groups for studies of patients with adult malignant ovarian germ cell tumours (33 of 33 groups approved)

1. First-line reference group options in germ cell studies include surgery and active surveillance (stage I), surgery and chemotherapy (high-risk stage I, stage II–IV) or chemotherapy alone (stage IV). In patients suitable for chemotherapy, bleomycin, etoposide, and cisplatin should be the control group within clinical trials
2. Careful treatment de-escalation is an important future research objective

Statement 14

Systemic treatment reference groups for studies of patients with sex cord stromal ovarian tumours (33 of 33 groups approved)

1. First-line reference group options in sex cord stromal tumour studies include surveillance (stage I or completely resected advanced disease) or systemic therapy for stage II–IV (bleomycin, etoposide, and cisplatin, or carboplatin and paclitaxel)
2. Reference arm options for relapsed sex cord stromal tumour include: bleomycin, etoposide, and cisplatin (if chemotherapy naive), carboplatin and paclitaxel, weekly paclitaxel, and aromatase inhibitors depending on previous systemic treatment exposure

Statement 15

Optimal trial design in rare or molecularly defined ovarian subgroups (33 of 33 groups approved)

1. In subgroups in which incidence allows, international multicentre trials with randomisation against reference therapy should be performed
2. In very rare subgroups, randomised trials might not be feasible; innovative designs (eg, platform studies) could be considered with a deductive 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 (33 of 33 groups approved)

1. Under-representation of patients recruited into clinical trials in terms of frailty and co-morbidities adversely affects the generalisability of findings; when 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. Patients with ovarian cancer should be included in the assessment, validation, and development of vulnerability scoring tools such as the geriatric vulnerability score
3. Equitable access for all ethnic and socioeconomic groups within clinical trials is crucial; multinational collaborative efforts to include diverse ethnic groups in clinical trials would facilitate the investigation of pharmacogenomics and pharmacokinetic factors

component has aberrant p53 expression then these malignancies can be included in high-grade serous ovarian cancer studies (with stratification). Little information is 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 has a molecular focus.

In histologically defined settings (non-high-grade serous or endometrioid ovarian cancer), eligibility should rely on a centralised pathology review using predefined morphological criteria (eg, the WHO classification[36]) and immunohistochemical biomarkers (appendix p 7).[36–38]

In malignant ovarian germ cell tumours, studies minimising long-term treatment-related toxicity are important. Active surveillance is only a suitable reference group when patients have undergone complete surgical staging and have blood tumour markers (eg, alpha-fetoprotein for endodermal sinus tumours) compatible with stage I disease. There is no level 1 evidence that can guide the prioritisation of potential reference groups for studies of recurrent malignant ovarian germ cell tumours.

In sex cord stromal ovarian tumours, the ALIENOR/ENGOT-ov7 study, which compared weekly paclitaxel to weekly paclitaxel plus concomitant and maintenance bevacizumab, showed that randomised trials can be completed with international collaboration.[39] As surgery or radiotherapy can be of clinical benefit in recurrent sex cord stromal ovarian tumours, these patients could also be included in clinical trials, with the presence or absence of measurable tumours before randomisation incorporated as a stratification factor. In patients with sex cord stromal ovarian tumours who are not candidates for chemotherapy, endocrine therapy, such as aromatase inhibitors, represents a potential control group despite their low response rate associated with aromatase inhibitors.[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 and contemporary real-world datasets to facilitate this comparison is needed. If feasible, clinical trials should include frail patients. Expansion cohorts or subgroup analysis of frail patients should be considered to better understand toxicity and pharmacokinetic ranges in these 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.

Crucial elements in future clinical trials

Statements on crucial elements in future clinical trials are summarised in panel 4. There is no standardised method for analysing PET data or other functional diagnostic modalities in ovarian cancer, especially following the introduction of targeted therapy and immunotherapy in clinical trials. New modalities should be added as exploratory endpoints. Intervals between scanning should not differ between study groups, as this could introduce bias.

Primary endpoints in phase 1 trials include safety, pharmacokinetics, and pharmacodynamic data. In phase 2 trials, overall response rate is the primary endpoint for single-arm studies and can be used in randomised trials. However, in randomised phase 2 trials that include a combination of agents, progression-free survival can be the primary endpoint as the overall response rate 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-randomised trial increases the risk of interpretation bias due to clinical heterogeneity. If used as an exploratory endpoint, the duration of stabilisation must be predefined, with a recommended duration of at least 6 months. In phase 3 trials, progression-free survival assessed by an investigator and overall survival are the preferred primary endpoints (although they do not necessarily have to be dual endpoints). If a blinded independent central review (BICR) analysis is to be performed, this analysis should be reported as well. A sample-based or full BICR can be a secondary endpoint (appendix p 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 (eg, progression-free survival and overall survival in biomarker positive and intention-to-treat populations). 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 for better reporting of toxicity (eg, the US National Cancer Institute's PRO version of the Common Terminology Criteria for Adverse Events) and health-related quality of life.[49] PROs should be incorporated in clinical trials following appropriate guidelines (eg, the PRO extensions of the Standard Protocol Items: Recommendations for Interventional Trials[50] and Consolidated Standards of Reporting Trials[51]) and should be included in statistical analysis plans. When progression-free survival is a primary endpoint, consideration could be given to PROs as an additional endpoint, and the trial be powered accordingly. PRO and health-related quality-of-life measures should continue

Panel 4: Statements on crucial elements in future trial design

Statement 17

Imaging (33 of 33 groups approved)

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 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 patient; 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 be harmonised across all arms and independent of cycle lengths, which might 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 (33 of 33 groups approved)

1 Phase 1 expansion (phase 1b) trials can be used to extend safety analyses or to evaluate pharmacokinetic and 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 is defined as the sum of complete and partial responses as determined by RECIST (version 1.1)[14]; RECIST-determined responses are defined as confirmed responses, and RECIST incorporates criteria for clinical progression
4 Disease control rate, the sum of complete plus partial responses plus stable disease, is neither a defined nor validated primary endpoint
5 Progression-free survival and overall survival are the primary endpoints* for phase 3 trials and can be used in randomised phase 2 trials
6 Progression-free survival should be assessed by the 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 a 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 (eg, immune-related RECIST), 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 new agents (eg, combination regimens) requires a randomised design
11 Due to changes in staging of ovarian cancer and changes in the definition and 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, for which randomised designs are not feasible

Statement 19

New trial designs can expedite progress in clinical trials for ovarian cancer (32 of 33 groups approved, one abstained)

1 Novel trial designs across diseases, cohorts, molecular selectors, and drugs may be used to evaluate preliminary pharmacodynamic and clinical activity; they must incorporate accepted validated primary endpoints and the results need to be substantiated 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 of optimised outcomes (eg, hierarchical testing, group sequential designs)
4 Analysis of treatment outcomes across subgroups or stratification factors should be prespecified and adequately powered in the protocol

Statement 20

Patient reported outcomes (PROs) and quality-of-life measures (33 of 33 groups approved)

1 Incorporation of self-reported toxicity assessment (eg, PRO-CTCAE) should be considered
2 Predefined 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 PROs should continue past disease progression and continue until initiation of next intervention
3 If progression-free survival 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 (eg, ISOQOL, CONSORT-PRO)
5 All clinical trials that include PROs should incorporate strategies to avoid and address missing data

CONSORT-PRO=Consolidated Standards of Reporting Trials–Patient-Reported Outcomes extension. ISOQOL=International Society for Quality-of-Life Research. RECIST=Response Evaluation Criteria in Solid Tumours. PRO-CTCAE=Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events. *Do not have to be dual endpoints.

Search strategy and selection criteria

Primary references for the development of consensus statements were identified from the roster of clinical trials represented by each Gynecologic Cancer InterGroup (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. PubMed searches were conducted using the terms "ovarian", "cancer", "neoplasms", and "studies" for articles published from Jan 1, 2015, to Oct 1, 2021, to ensure consideration of all relevant studies published after the previous 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.

past disease progression and until initiation of the next intervention, with the inclusion of strategies to avoid missing data.

Unmet needs

The four topic groups identified three broad areas of substantial unmet need: the understanding of ovarian cancer biology, clinical trial design, and patient inclusion and engagement.

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. There is a crucial need for predictive biomarkers that are substantiated in a statistical treatment-by-biomarker outcome interaction test. Prognostic biomarkers, associated with outcome independent of treatment, cannot be applied a priori as therapeutic targets or predictive biomarkers. Identifying patients who might develop clinically significant toxicities is also crucial. 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.

Clinical trial design

Reliable and objective methods to assess frailty are urgently needed, and international cooperation and innovative methodologies are required for trials in rare patient populations. Extended follow-up will allow for 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.

Patient inclusion and engagement

Greater patient engagement is needed in trial design and development, as is the inclusion of patients in low-income and middle-income countries and patients across all spectrums of diversity. Patient engagement will also be essential before future OCCCs 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. Although 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 summarised within these consensus statements will help to improve clinical trial design to address the unmet needs for women with ovarian cancer.

Contributors

IV was responsible for the literature search, figures, study design, data analysis, data interpretation, writing, and approval of final manuscript. DL, CG, IM, BV, SM, IR-C, JSB, DSPT, NCol, RZ, NCon, DO'D, CSH, and AP were involved in the planning, preparation, literature research, writing, final review, editing, and approval of the manuscript, presented during the meeting, and actively participated in the scientific discussions and the formal consensus process. AG-M was a member of the scientific committee and chair of a subgroup (first-line treatments), proposed the first draft of statements, was a discussant during the consensus conference meeting, presented the statements, and contributed to the manuscript with a summary from the subgroup. MRM was involved in the planning of the conference, was chair of a subgroup, led discussions on unmet needs, was involved in the methodology, prepared questions, led all related virtual meetings, and led the subgroup conference part. With regard to writing and reviewing the manuscript, AdB was involved in the planning, preparation, literature research, presentation during the meeting and participation in the scientific discussions, formal consensus process, writing the manuscript, final review, and editing. AO, KM, FK, J-EK, AR, ECK, AR-H, CM, and MAB contributed to the literature search, writing, review, and editing. AO, KM FK, EK, and AR-H interpreted the data. J-EK and AR were involved in the investigations. AR, KF, and MAB were responsible for conceptualisation and methodology. AR-H was responsible for the discussion of the data. CM participated in the consensus process. KF was responsible for project administration and funding acquisition. AMO contributed to the design, participated in the consensus meeting, and discussed the findings. MAB was involved in project administration, supervision, and visualisation. GCES applied CRediT taxonomy (contributor roles taxonomy) to the manuscript and was responsible for the methodology of the consensus conference, shared responsibility for funding acquisition, project administration, and supervision, and was responsible for part of the writing of the manuscript as a reviewer and editor. The consensus meeting was chaired by IV and co-chaired by MAB.

Declaration of interests

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