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

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1
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3 **recommendations on clinical research in ovarian cancer**
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6

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16 6th Gynecologic Cancer InterGroup (GCIIG)
17 Ovarian Cancer Consensus Conference on Clinical Research^z
18
19
20

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88 **Summary (116/ max 150 words)**

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

99
100 **Word count (4499 /max 4500 words)**

101
102 **Introduction**

103 The Gynecologic Cancer InterGroup (GCIG) consists of thirty-three clinical research groups that span the globe
104 (Supplement page 2) and has organised an ovarian cancer consensus conference on clinical research approximately
105 every five years.¹ The planning of the sixth GCIG ovarian cancer consensus conference (OCCC6) was initiated in
106 May 2017, with the intent to meet in Leuven, Belgium, 9th-11th October 2020. Due to the COVID-19 pandemic,
107 OCCC6 was first postponed and later held virtually 15th-21st October 2021.^{2,3}

108
109 **Consensus process**

110 The OCCC6 Scientific Committee identified twenty key topics, organised within four topic groups together with
111 tabulation of unmet needs for future clinical research. Each GCIG member group appointed two delegates. Draft
112 consensus statements were prepared, together with designation of presenters and discussants for each statement.
113 Primary references for the development of consensus statements were identified through the roster of clinical trials
114 represented by each GCIG Member Group responsible for conducting academic clinical research in ovarian cancer,
115 supplemented by non-GCIG trials selected by topic group discussants. All references were disclosed during the
116 consensus conference and reviewed by all participants, with active moderation by topic group co-chairs. Searches
117 on PubMed using terms “ovarian”, “cancer”, “neoplasms”, and “studies” from January 1st 2015, until October 1
118 2021 were utilized to ensure consideration of all relevant studies published after the last consensus conference in
119 2015. Only papers published in English were reviewed. The final reference list was generated on the basis of
120 originality and relevance to the consensus guidelines.

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

129
130 **Consensus statements**

131 **First-line treatment**

132 First-line treatment statements are summarised in table 1. Epithelial tumours of ovarian, fallopian, and peritoneal
133 origin were grouped together as epithelial ovarian cancer (EOC) for the purposes of this meeting. Initial tumour
134 stage, selection of patients for neoadjuvant chemotherapy (NACT), and presence of any visible residual disease
135 following cytoreductive surgery are key prognostic factors for women with advanced EOC.⁴ Primary cytoreductive
136 surgery (PCS) remains the preferred option when there is a reasonable likelihood of achieving complete
137 cytoreduction after evaluation by an expert gynaecological oncological team, and NACT should be used for poor
138 surgical candidates or for whom complete cytoreduction seems unlikely.⁵ The decision between PCS or NACT must
139 be based on patient’s performance status and extent of disease determined by imaging and/or surgical assessment. In
140 addition, the OCCC6 incorporates histology as a decision factor, favouring PCS for patients with less chemo-
141 sensitive histological types even if complete cytoreduction is questionable.

142 Statement 2 on stratification factors applies for first-line trials using PCS or NACT. Chemotherapy remains the
143 second pillar for treatment of EOC, consisting of 6 cycles of 3 weekly paclitaxel and carboplatin with or without

144 bevacizumab.⁶⁻⁸ Weekly paclitaxel-weekly carboplatin (MITO-7/ENGOT-ov10), or weekly paclitaxel and 3-weekly
145 carboplatin in Japanese patients with high grade serous ovarian cancer (HGSOC) are acceptable alternatives.^{9,10} The
146 statement 5 on IP therapy and HIPEC was much debated with an approval rate of only 30 out of 33 GCIG groups (2
147 groups opposing and 1 abstaining). It should be underscored that this statement is not about standard of care but
148 accepting IP therapy and HIPEC as reference treatment arm within clinical trials.

149 The incorporation of maintenance therapy with PARPi after first line chemotherapy in high grade serous or
150 endometrioid types,¹¹⁻¹³ should be considered as part of the reference arm, at least for patients with BRCAm tumour
151 (germline or somatic) or BRCAwt/HR-deficient disease, either alone or combined with bevacizumab. The optimal
152 maintenance therapy for patients with BRCAwt/HR-proficient tumours, if any, remains unknown. Incorporation of
153 maintenance as part of the reference arm should not change the primary endpoints, which remain PFS and
154 OS (although not necessary as dual endpoints). Safety and patient-reported outcomes (PROs) should be included as
155 secondary endpoints. . PFS2 (defined as the time from randomisation to the second objective disease progression or
156 death) should be considered as well due to the potential impact of PARPi on the efficacy of subsequent therapies.

157 Utilisation of appropriate stratification factors is key for optimal interpretation of clinical trials. In addition to classical
158 prognostic factors such as FIGO stage, timing of surgery, residual disease after surgery, performance status, and
159 histology, predictive biomarkers tested with validated assays need to be incorporated. The most relevant example is
160 *BRCA1/2* mutation or HR-deficiency testing.

161 There is a need for clinical research in patients with high-risk stage I¹⁴ or II EOC. These trials, through international
162 cooperation, may address specific questions for this patient population.

163
164 Recurrent ovarian cancer.

165 Recurrent ovarian cancer statement are summarised in table 2. Building on findings from OCCC5 in 2015,¹⁵ OCCC6
166 recommended that platinum free interval should be replaced by a treatment free interval (TFI) specific to certain
167 therapies, such as platinum (TFIp), PARPi (TFI_{PARPi}), as well as other specific clinical and molecular factors.

168 Agents targeting DNA damage response (DDR) are best suited for *TP53* aberrant tumours whereas agents targeting
169 angiogenesis may be suitable for all histologies. Predictive biomarkers for PARPi and other agents targeting DDR
170 could be important for eligibility and/or stratification. The exposure and/or response to prior therapies is also
171 increasingly important for clinical trial design and interpretation. For example, in an exploratory analysis of SOLO-
172 2/ENGOT-ov21, among patients who recurred and were re-treated with platinum therapy, the median PFS was 7
173 months after prior maintenance with olaparib compared to 14.3 months after placebo, suggesting that prior PARPi
174 exposure might compromise subsequent response to platinum.¹⁶ Most importantly, the TFIp remains a key prognostic
175 factor, but should not be used in isolation of these other important clinical and molecular features. Although no good
176 data exist on a cut-off TFIp interval we agreed that it was reasonable to treat patients with relapse within e.g. 12
177 weeks might be selected for a next line of therapy without platinum.

178 The standard of care for patients with recurrent EOC for whom platinum is an option has been a platinum-containing
179 regimen (carboplatin + pegylated liposomal doxorubicin preferred). When considering which chemotherapy backbone
180 to use, there are three options with differences in schedule, toxicity profile, and to a modest degree, efficacy (- Table
181 S1 – supplement page 5).¹⁷⁻²⁰

182 Level 1 evidence supports repeat use of maintenance bevacizumab in the recurrent setting.²¹ Although level 1
183 evidence also exists for repeat use of PARPi in the recurrent maintenance setting, the magnitude of benefit appears
184 small and such repeat use should not be considered the reference arm until the group of patients who derive benefit is
185 better elucidated.²² At a minimum, stratification for prior PARPi and/or prior bevacizumab should be considered in
186 clinical trials where platinum is an option for treatment.

187 In studies evaluating patients with disease recurrence considered inappropriate for platinum and who are naïve to
188 bevacizumab, bevacizumab in combination with cytotoxic chemotherapy should be the control arm or, if mixed
189 population (bevacizumab pretreated or not) are enrolled, bevacizumab should be a stratification factor. Possible
190 monotherapy cytotoxic options are outlined in Table S2 (supplement page 5).²³⁻²⁷

191 Biomarker directed trial eligibility should consider broader inclusion of patients irrespective of TFIp. Successful
192 application of this concept has already been demonstrated in both ARIEL 4 and FORWARD II (Supplement page
193 6).^{28,29}

194 Based on three randomised trials, secondary cytoreduction should be considered in trials where platinum is an option,
195 using a validated score (Supplement page 6).³⁰⁻³²

196
197 Statements on non-high grade serous ovarian cancer (non-HGSOC).

198 Statements on non-high grade serous ovarian cancer (non-HGSOC) are summarised in table 3. High grade
199 endometrioid ovarian cancer with aberrant p53 expression has sufficient molecular³³ and phenotypic³⁴ similarity to
200 HGSOC to be included in the same studies. Ovarian carcinosarcomas are monoclonal in origin and driven by
201 molecular changes found in EOC.³⁵ Therefore if the epithelial component has aberrant p53 expression these

202 malignancies can be included in HGSOV studies (with stratification). Little information is to be gained from studies
203 that do not stratify according to histological type, especially with clear cell, low grade serous or mucinous ovarian
204 cancer, unless the study is molecularly based.

205
206 In histologically defined settings (non-high grade serous/endometrioid ovarian cancer), eligibility should rely on
207 centralized pathology review using predefined morphological criteria (e.g. World Health Organisation classification³⁶)
208 and immunohistochemical biomarkers (see Supplement page 7).³⁶⁻³⁸

209 In malignant ovarian germ cell tumours (MOGCT), studies minimising long term treatment-related toxicity are
210 important. Active surveillance is only a suitable reference arm when patients have undergone complete surgical
211 staging and have blood tumour markers (e.g. alpha-fetoprotein for endodermal sinus tumours) compatible with stage
212 I disease. There is no level one evidence to guide prioritisation of potential reference arms for studies of recurrent
213 MOGCT.

214 In sex cord stromal ovarian tumours (SCST), the ALIENOR/ENGOT-ov7 study (which compared weekly paclitaxel
215 to weekly paclitaxel plus concomitant and maintenance bevacizumab) demonstrated that randomised trials can be
216 completed with international collaboration.³⁹ As surgery and/or radiotherapy can be of clinical benefit in recurrent
217 SCST, these patients could also be included in clinical trials with the presence or absence of measurable tumour before
218 randomisation incorporated as a stratification factor. In SCST patients who are not candidates for chemotherapy,
219 endocrine therapy such as aromatase inhibitors represent a potential control arm despite their low response rate.⁴⁰
220 International collaboration has facilitated completion of randomised trials in low grade serous^{41,42} and clear cell⁴³
221 ovarian cancer. In rare tumour types, parallel clinical trials using harmonised protocols can be run with upfront
222 agreement for combined final analysis. In very rare tumour types comparison of single arm studies with historical
223 controls or real-world data is required. Construction of reliable contemporary real-world data sets to facilitate this
224 comparison is needed.

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

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

230
231
232 Statements on critical elements in future clinical trials.

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

238 Primary endpoints in Phase 1 trials include safety, and/or pharmacokinetics/pharmacodynamic data. In phase 2
239 trials, overall response rate is the primary endpoint for single-arm studies and may be used in randomised trials.
240 However, in randomised phase II trials including a combination of agents, PFS can be the primary endpoint as ORR
241 is not expected to be different. Disease control rate should not be used as a primary endpoint as there is no clear
242 definition of the duration of stable disease needed to qualify for disease control. In addition, the incorporation of
243 stable disease within a small non-randomized trial increases the risk of interpretation bias due to clinical
244 heterogeneity. If used as an exploratory endpoint, duration of stabilization must be pre-defined, with a
245 recommended duration of at least 6 months. In phase 3 trials, PFS assessed by investigator and OS are the preferred
246 primary endpoints (although not necessary as dual endpoints). If also a BICR analysis was performed, this analysis
247 should be reported as well. A sample-based or full Blinded Independent Central Review (BICR) may be a secondary
248 endpoint (Supplement page 8). The use of multiple primary analytical endpoints requires adjustment for multiplicity.

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

254 The incorporation of PROs allows better reporting of toxicity (e.g. the NCI PRO-CTCAE scoring system) and health-
255 related quality of life (HrQL).⁴⁹ PROs should be incorporated in clinical trials following appropriate guidelines (e.g.
256 SPIRIT-PRO⁵⁰ and CONSORT-PRO⁵¹) and be included in statistical analysis plans. When PFS is a primary endpoint,
257 consideration could be given including PROs as an additional endpoint, and the trial be powered accordingly. PRO

258 and HrQL measures should continue past disease progression and until initiation of the next intervention, with
259 inclusion of strategies to avoid missing data.

260

261 **Unmet needs**

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

263 1. Understanding of ovarian cancer biology.

264 The biology underpinning many key clinical observations remains uncertain, including mechanisms of intrinsic and
265 acquired resistance to platinum, taxanes, PARP inhibitors, immune checkpoint inhibitors and anti-angiogenic agents.

266 The critical need is for predictive biomarkers that are confirmed in a statistical treatment-by-biomarker outcome
267 interaction test. Prognostic biomarkers, associated with outcome independent of treatment, cannot *a priori* be applied
268 as therapeutic targets or predictive biomarkers. Identifying patients who may develop clinically-significant toxicities
269 is also critical. Simple, reliable and affordable biomarkers that can be prospectively evaluated and validated in clinical
270 trials are an urgent unmet need, and it is imperative that clinical trials incorporate prospective biosample collection to
271 support translational research. These samples must be made available to researchers worldwide.

272 2. Clinical trial design.

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

278 3. Patient inclusion and engagement.

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

282

283 **Conclusion**

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

289

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303 **Authors' Contributions**

304
305 I. Vergote: literature search, figures, study design, data analysis, data interpretation, writing and approval of final
306 manuscript. The authors (D. Lorusso, C. Gourley, I. McNeish, B. Votan, S. Mahner, I. Ray-Coquard, J.S. Berek, D.
307 Tan, N. Colombo, R. Zang, N. Concin, D. O'Donnell, C.S. Herrington and A. Poveda) were involved in the planning,
308 preparation, literature research, presentation during the meeting and active participation in the scientific discussions
309 and the formal consensus process, writing, final review, editing and approval of the manuscript. A. Gonzalez-Martin:
310 has participated as: Member of the Scientific Committee, Chair of Topic I Group, Proposer of first draft of statements,
311 Discussant during the Consensus Conference meeting, Presenter of the statements, Contributor to the manuscript with
312 a summary of Group. M. Raza Mirza: planning of this conference, as chair of a subgroup, leading discussions on
313 unmet needs, methodology, preparing of questions, leading all related virtual meetings and leading the subgroup
314 conference part. Finally in writing and reviewing the manuscript. A. du Bois: planning, preparation, literature research,

315 presentation during the meeting and participation in the scientific discussions and the formal consensus process,
316 writing the manuscript, final review and editing. A.Okamoto, K. Moore, F. Kridelka: writing, literature search, data
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319 and interpretation, review and editing. A. Rauh-Hain: data interpretation, Data discussion, writing, review & editing.
320 C. Marth: participation on the consensus process (presentation and discussion), writing of the manuscript. K. Fujiwara:
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323 methodology, project administration, supervision, visualization, writing, review & editing. G.C.E. Stuart: contribution
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325 conference. Shared responsibility for funding acquisition, project administration and supervision. For the manuscript
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327 Vergote and co-chaired by M.A. Bookman.

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Table 1 First line treatment

<p>Statement 1</p>	<p>Selection of patients for neoadjuvant chemotherapy (NACT) or primary cytoreductive surgery (PCS) (Approval 32/33 groups, 1 opposed)</p> <p>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.</p> <ol style="list-style-type: none"> 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. <ul style="list-style-type: none"> - 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.
<p>Statement 2</p>	<p>Stratification factors (SF) (Approval 33/33 groups)</p> <p>First line trials should include validated prognostic stratification factors and predictive factors according to the protocol design and the intervention explored.</p> <ol style="list-style-type: none"> 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.
<p>Statement 3</p>	<p>Acceptable reference arms for systemic treatment? (Approval 33/33 groups)</p> <ol style="list-style-type: none"> 1. Backbone systemic therapy is based on the carboplatin-paclitaxel combination <ul style="list-style-type: none"> - 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. <ul style="list-style-type: none"> o Dose dense weekly IV Paclitaxel 80 mg/m² 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/m² can be an acceptable option. 2. Maintenance therapy should be considered in the reference arm for HGSOC/HGEOC <ul style="list-style-type: none"> - 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.
<p>Statement 4.</p>	<p>Challenges of maintenance therapy (Approval 33/33 groups)</p> <ol style="list-style-type: none"> 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).
<p>Statement 5</p>	<p>Intraperitoneal chemotherapy and hyperthermic intraperitoneal chemotherapy (HIPEC) (Approval 30/33 groups, 2 opposed*, 1 abstain)</p> <ol style="list-style-type: none"> 1. Any form of IP therapy or HIPEC cannot be regarded as a reference treatment arm within clinical trials
<p>Statement 6</p>	<p>Future trials for high-risk Stage I or Stage II disease (Approval 33/33 groups)</p> <p>High-risk stage I and II studies are needed, using international cooperation.</p> <ol style="list-style-type: none"> 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.
<p>*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</p>	

Table 2. Statements on recurrent ovarian cancer

<p>Statement 7</p>	<p>Categorisation by clinical and molecular factors (Approval 33/33 groups)</p> <p>1. Eligibility should be categorised and/or stratified according to:</p> <ul style="list-style-type: none"> - Histology: high grade serous and high grade endometrioid (with aberrant p53 IHC) vs. others - <i>BRCA1/2</i> 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 <p>2. Eligibility based only on the interval from last platinum treatment is discouraged.</p>
<p>Statement 8</p>	<p>Platinum-based regimens as reference arm (Approval 32/33 groups, 1 opposed*)</p> <p>1. Platinum-containing regimens should be the reference arm in patient populations where response to platinum is expected. These include patients with:</p> <ul style="list-style-type: none"> - 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 <p>2. Appropriate reference arms include:</p> <ul style="list-style-type: none"> - Platinum-based combination regimens (carboplatin + pegylated liposomal doxorubicin preferred) - PARP inhibitor therapy can be an appropriate alternative reference arm in patients with <i>BRCAm 1/2</i> who have received >2 prior platinum lines and who are PARPi naïve. <p>3. Maintenance options in the reference arm should be based on study design and prior exposure</p> <ul style="list-style-type: none"> - 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. <p>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.</p>
<p>Statement 9</p>	<p>Non-platinum regimens as reference arm (Approval 31/33 groups, 2 opposed*)</p> <p>1. Reference arms should contain non-platinum-based regimens when response to platinum is not expected:</p> <ul style="list-style-type: none"> - 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 <p>2. Potential reference arms may include:</p> <ul style="list-style-type: none"> - 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. <p>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.</p> <p>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.</p>
<p>Statement 10</p>	<p>Biomarker directed trials may allow a broader population based on clinical and molecular factors (Approval 33/33 groups)</p> <p>The reference arm of biomarker-driven trials may include both platinum and non-platinum regimens according to patient clinical characteristics, with appropriate stratification.</p>
<p>Statement 11</p>	<p>Secondary cytoreductive surgery (Approval 32/33 groups, 1 abstain*)</p> <p>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.</p> <p>2. Secondary cytoreduction should be considered in all patients with recurrent disease fulfilling criteria predictive of successful complete resection</p> <p>3. Secondary cytoreduction as a component of protocol-directed management (post-randomisation) would only be permitted if included within the trial design.</p> <ul style="list-style-type: none"> - 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)
<p>*See Supplement page 4</p>	

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

<p>Statement 12</p>	<p>Comparator systemic therapy for randomised studies with epithelial non-HGSOC (Approval 33/33 groups)</p> <ol style="list-style-type: none"> 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.
<p>Statement 13</p>	<p>Systemic treatment reference arms for studies of patients with adult malignant ovarian germ cell tumours (Approval 33/33 groups)</p> <ol style="list-style-type: none"> 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.
<p>Statement 14</p>	<p>Systemic treatment reference arms for studies of patients with sex cord stromal ovarian tumours (Approval 33/33 groups)</p> <ol style="list-style-type: none"> 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.
<p>Statement 15</p>	<p>Optimal trial design in rare or molecularly defined ovarian subgroups (Approval 33/33 groups)</p> <ol style="list-style-type: none"> 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.
<p>Statement 16</p>	<p>Inclusion of subgroups of patients to address frailty, ethnic diversity or comorbidity profile (Approval 33/33 groups)</p> <ol style="list-style-type: none"> 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)

<p>Statement 17</p>	<p>Imaging (Approval 33/33 groups)</p> <p>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.</p> <ol style="list-style-type: none"> 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.
<p>Statement 18</p>	<p>Primary endpoints (Approval 33/33 groups)</p> <ol style="list-style-type: none"> 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.
<p>Statement 19</p>	<p>New trial designs can expedite progress in clinical trials for ovarian cancer (Approval 32/33 groups, 1 abstain***)</p> <ol style="list-style-type: none"> 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.
<p>Statement 20</p>	<p>Patient reported outcomes (PROs) and quality of life measures (Approval 33/33 groups)</p> <ol style="list-style-type: none"> 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.
<p>* RECIST 1.1¹⁴ ** not necessary as dual endpoints ***See Supplement page 4</p>	

