Gynecologic Cancer InterGroup consensus recommendations on clinical research in ovarian cancer

Ignace Vergote, MD[a], Antonio Gonzalez-Martin, MD[b], Domenica Lorusso, MD[c], Charlie Gourley MD[d], Mansoor Raza Mirza, MD[e], Jean-Emmanuel Kurtz, MD[f], Aikou Okamoto, MD[g], Kathleen Moore MD[h], Frédéric Kridelka, MD[i], Iain McNeish, PhD[j] , Alexander Reuss, MSc[k], Bénédicte Votan, MSc[l] , Andreas du Bois, [m]Sven Mahner, MD[n], Isabelle Ray-Coquard[o] MD, Elise C. Kohn MD[p], Jonathan S. Berek, MD[q], David SP Tan, MD[r], Nicoletta Colombo, MD[s], Rongyu Zang, MD[t], Nicole Concin, MD[u], Dearbhaile O'Donnell, MD[v], Alejandro Rauh-Hain, MD[w], C Simon Herrington, [d], Christian Marth, MD[x], Andres Poveda, MD[y], Keiichi Fujiwara, MD[z] , Gavin C.E. Stuart, MD[ab], Amit M Oza MD[cd], Michael A Bookman, MD[ef]
On behalf of the participants of the
6th Gynecologic Cancer InterGroup (GCIG)
Ovarian Cancer Consensus Conference on Clinical Research[z]

[a] Belgium and Luxemburg Gynaecological Oncology Group (BGOG) and Chair of the consensus meeting and University Hospitals Leuven, Belgium
[b] Grupo Español de Cáncer de Ovario (GEICO) and Clinica Universidad de Navarra, Madrid and and Program for Solid Tumors at Madrid and Center for Applied Medical Research (CIMA), Pamplona, Spain;
[c] Multicenter Italian Trials in Ovarian cancer and gynecologic malignancies (MITO) and Fondazione Policlinico Gemelli IRCCS, Rome, Italy
[d] Scottish Gynaecological Cancer Trials Group (SGCTG) and Cancer Research UK Edinburgh Centre, Institute of Genetics and Cancer, University of Edinburgh, Edinburgh, UK
[e] Nordic Society of Gynecologic oncology – Clinical Trial Unit (NSGO-CTU) and Rigshospitalet, Copenhagen, Denmark
[f] Groupe d'Investigateurs National des Etudes des Cancers Ovariens et du sein (GINECO) and Strasbourg Cancer Institute – ICANS-Europe; Strasbourg, France
[g] Japanese Gynecologic Oncology Group (JGOG) and The Jikei University School of Medicine, Tokyo, Japan
[h] Gynecologic Oncology Group-Foundation (GOG-F) and OU Health Stephenson Cancer Center, US
[i] BGOG and CHU Liège, Liège, Belgium
[j] National Cancer Research Institute (NCRI) and Department of Surgery and Cancer, Imperial College London, UK
[k] Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) Study Group and Coordinating Center for Clinical Trials, Philipps University, Marburg, Germany[l] Association de Recherche Cancers Gynécologiques (ARCAGY) – GINECO, Paris, France
[m] Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) Study Group and Kliniken Essen Mitte (KEM), Essen, Germany
[n] Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) Study Group and University Hospital, LMU Munich, Munich, Germany
[o] Groupe d'Investigateurs National des Etudes des Cancers Ovariens et du sein (GINECO) and Centre Leon Berard & University Claude Bernard Lyon I, Lyon, France;
[p] National Cancer Institute, National Institutes of Health, USA

[q]Women's Cancer Research Network-Cooperative Gynecologic Oncology Investigators (WCRN-COGI) and Stanford Cancer Institute, Stanford, CA, USA
[r] Asia Pacific Gynecologic Oncology Trials Group (APGOT) and Gynecologic Cancer Group Singapore (GCGS) and National University Cancer Institute, National University Health System, Singapore; Loo Lin School of Medicine and Cancer Science Institute, National University of Singapore, Singapore
s Mario Negri Gynecologic Oncology (MaNGO) and European Institute of Oncology IRCCS Milan, and University of Milan-Bicocca, Milan, Italy
[t] Shanghai Gynecologic Oncology Group (SGOG) and Zhongshan Hospital, Fudan University, Shanghai, China
[u] Arbeitsgemeinschaft Gynäkologische Onkologie-Austria (AGO-A) and Medical University Innsbruck, Austria and and Kliniken Essen Mitte (KEM), Essen, Germany
[v] Cancer Trials Ireland (CTI) and St. James's Hospital, Dublin, Ireland
[w] Global Gynecologic Oncology Consortium (G-GOC) and The University of Texas MD Anderson Cancer Center, Houston, TX, USA
[x] Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) Study Group and Medical University Innsbruck, Austria
[y] GEICO and Past-Chair Gynecologic Cancer InterGroup (GCIG) and Hospital Quironsalud, Valencia, Spain
[z] Gynecologic Cancer Clinical Trials and Investigation Consortium (GOTIC) and Past-Chair GCIG and Saitama Medical University International Medical Center, Saitama, Japan
[ab] Canadian Cancer Trials Group (CCTG) and University of British Columbia, Vancouver, Canada
[cd] Princess Margaret Hospital Consortium (PMHC) and Chair GCIG and Princess Margaret Cancer Centre, University of Toronto, Toronto, Ontario, Canada
[ef] GOG-Foundation and Co-Chair of the consensus meeting and San Francisco Medical Center, CA, US

[z] See list of participants in Supplemental file page 9-11 (to be included as authors in Pubmed).

Correspondance:
Prof Em Ignace Vergote
BGOG
University Hospitals Leuven
Herestraat 49
3000 Leuven
Belgium – European Union
Ignace.vergote@uzleuven.be
+32 16345128

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.

Acknowledgments

The authors wish to thank Katherine Bennett and Jennifer O'Donnell of the GCIG (Kingston, Ontario, Canada), and Sherill Osborne of The Emmes Company, LLC (Rockville, Maryland, USA) for their technical and administrative support, and Nancy Trolin, Heidi Camps and Hanne Geleyns of the University Hospitals Leuven (Leuven, Belgium, European Union) for their administrative support. For the audiovisual support we wish to thank Wim Zwarts, Kit Serverius, Erik van Eycken, Jens Maes, and Marc Krottje of Diverze (Bonheiden, Belgium, European Union).

This work was supported by unrestricted grants from AstraZeneca (Cambridge, UK), Chugai Pharmaceutical (Tokyo, Japan), Clovis Oncology (Boulder, Colorado, USA), , GlaxoSmithKline (Brentford, UK), Immunogen (Waltham, Massachusetts, USA), Karyopharm (Newton, Massachuchetts, USA), Merck Sharp & Dohme Corp. (Kenilworth, New Jersey, USA), Novocure (Jersey), Hoffmann-La Roche Ltd (Basel, Switzerland), PharmaMar (Madrid, Spain, European Union), Seagen (Zug, Switzerland), Takeda (Osaka, Japan), and Zeria Pharmaceutical Co. Ltd (Tokyo, Japan), The agenda, presentations, manuscript and statements were entirely developed without involvement of these funding sources.

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, presentation during the meeting and participation in the scientific discussions and the formal consensus process, writing the manuscript, final review and editing. A.Okamoto, K. Moore, F. Kridelka: writing, literature search, data interpretation, review and editing. J-E Kurtz: investigation, writing original draft, review and editing. A. Reuss: conceptualization, investigation, methodology and writing, review & editing. E. Kohn: literature search, data analysis and interpretation, review and editing. A. Rauh-Hain: data interpretation, Data discussion, writing, review & editing. C. Marth: participation on the consensus process (presentation and discussion), writing of the manuscript. K. Fujiwara: conceptualisation, methodology, project administration, funding acquisition. A. Oza: design, participation in consensus meeting, discussion of findings, manuscript review, editing. M.A. Bookman: conceptualization, methodology, project administration, supervision, visualization, writing, review & editing. G.C.E. Stuart: contribution to the manuscript in many aligned with the Credit taxonomy, responsible for the methodology of the consensus conference. Shared responsibility for funding acquisition, project administration and supervision. For the manuscript itself, responsible for part of the writing as a reviewer and editor. The consensus meeting was chaired by I. Vergote and co-chaired by M.A. Bookman.

Conflict of Interest Statements

I. Vergote: grants: Corporate Sponsored Research Amgen (2019-2020) and Roche (2019-2020): payment to my institution; Contracted Research Oncoinvent AS (2019-2020) and Genmab (2019): payment to my institution. Consulting fees with payment to my institution: Amgen (Europe) GmbH (2019), AstraZeneca (2019-2020), Clovis Oncology inc. (2019), Carrick Therapeutics (2019), Deciphera Pharmaceuticals (2020), Elevar Therapeutics (2020), F. Hoffmann-La Roche Ltd (2019-2020), Genmab (2019-2020), GSK (2019-2020), Immunogen Inc. (2019-2020), Mersana (2020), Millennium Pharmaceuticals (2019), MSD (2019-2020), Novocure (2020), Octimet Oncology (2019), Oncoinvent AS (2019-2020), Sotio a.s. (2019-2020), Verastem Oncology (2020), Zentalis (2020). Consulting fees with payment to me: Deciphera Pharmaceuticals (2021), Jazzpharma (2021-2022), Oncoinvent AS (2021-2022). Honoraria: Agenus (2021), Aksebio (2021), AstraZeneca (2021-2022), Bristol Myers Squibb (2021), Deciphera Pharmaceuticals (2021), Eisai (2021), F. Hoffmann-La Roche Ltd (2021), Genmab (2021), GSK (2021), Immunogen Inc. (2021-2022), Jazzpharma (2021-2022), Karyopharm (2021), MSD (2021-2022), Novocure (2021-2022), Novartis (2021), Oncoinvent AS (2021-2022), Seagen (2021), Sotio a.s. (2021-2022). Participation on a Data Safety Monitoring Board or Advisory Board: Agenus (2021), AstraZeneca (2021-2022), Bristol Myers Squibb (2021), Deciphera Pharmaceuticals (2021), Eisai (2021), F. Hoffmann-La Roche Ltd (2021), Genmab (2021), GSK (2021), Immunogen Inc. (2021-2022), MSD (2021-2022), Novocure (2021-2022), Novartis (2021), , Seagen (2021), Sotio a.s. (2021-2022). Travel Support from Amgen, MSD, Tesaro, AstraZeneca and Roche.

A. Gonzalez-Martin: grants: Tesaro/GSK and Roche (funding for IST trial); Consulting fees from Alkermes, Amgen, AstraZeneca, Clovis Oncology, Genmab, GSK, ImmunoGen, Merck Sharp & Dohme, Novartis, Oncoinvent, Pfizer/Merck, PharmaMar, Roche, Sotio, Sutro; Honoraria from AstraZeneca, PharmaMar, Roche, GSK, Clovis; Meeting/travel support from AstraZeneca, Pharmamar Roche, TESARO: A GSK Company; Participation on a Data Safety Monitoring Board or Advisory Board for Alkermes, Amgen, AstraZeneca, Clovis Oncology, Genmab, GSK, ImmunoGen, Merck Sharp & Dohme, Novartis, Oncoinvent, Pfizer/Merck, PharmaMar, Roche, Sotio, Sutro; Leaderships: GEICO (Grupo Español de Investigación en Cancer de Ovario) Chair ENGOT Chair (2018-2020).

D. Lorusso: grants for GSK, MSD, CLOVIS ONCOLOGY; Consulting fees For Pharmamar, Merck Serono; honoraria from GSK, Clovis Oncology, Astra Zeneca, MSD; Payment for expert testimony from Clovis Oncology; Meeting- travel support from GSK, Roche, Pharmamar; Participation on a Data Safety Monitoring Board or Advisory Board from Novartis, Seagen, MSD, Astra Zeneca, Immunogen, Genmab, Amgen, Clovis Oncology, GSK, Merck Serono; Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid: Chair of Gynecological Cancer Accademy, Bord of Director of Gynecological cancer Intergroup.

C. Gourley: grants: Grants for clinical and translational research paid to my Institution: AstraZeneca and Novartis; Grants for clinical research paid to my institution: GlaxoSmithKline, Tesaro, Clovis, MSD, BergenBio, Aprea, Nucana; Grant for preclinical research paid to my institution: Medannexin. Consulting fees paid to me: AstraZeneca, MSD, GlaxoSmithKline, Tesaro. Honoraria for lectures/presentations: AstraZeneca, MSD, GlaxoSmithKline, Tesaro, Clovis, Roche, Nucana, Chugai, Takeda, Cor2Ed (preparing educational material). Advisory Board attendance: AstraZeneca, MSD, GlaxoSmithKline, Tesaro, Roche, Nucana, Chugai. Leadership: Committee Member of Scottish Medicines Consortium.

M. Raza Mirza: Research grants from Astra Zeneca, Ultimovacs,Apexigen and GSK. Honoraria as invited speaker from Astra Zeneca and GSK. Advisory Boards for Astra Zeneca, GSK, Karyopharm, Nuvation Bio, Roche, Zailab, Merck, Biocad, Boehringer Ingelheim. Member of Board of Directors from Karyopharm and Sera Prognostics. Stocks/Shares: Karyopharm and Sera Prognostics. Study Chair (institutional) from Deciphara and Mersana.

J-E Kurtz: honoraria: Clovis; Meeting/travel support: AstraZeneca, GlaxoSmithKline;Participation on a Data Safety Monitoring Board or Advisory Board for AstraZeneca and GlaxoSmithKline.

A. Okamoto: grants to my institution: Kaken Pharmaceutical Co.,Ltd.,Chugai Pharmaceutical Co., Ltd.,Tsumura & Co.,Daiichi Sankyo Co., Ltd.,Shinnihonseiyaku Co., Ltd.Mochida Pharmaceutical Co., Ltd.,CMIC Holdings Co., Ltd.,ASKA Pharmaceutical Co., Ltd.,Takeda Pharmaceutical Company Ltd.,Pfizer Japan Inc.,AstraZeneca K.K.,Terumo Corporation,MSD K.K.,Fuji Pharma Co., Ltd.,Kissei Pharmaceutical Co., Ltd.,Meiji Holdings Co., Ltd.,Taiho Pharmaceutical Co., Ltd.,Nippon Shinyaku Co., Ltd.,Linical Co., Ltd.,Gyne Mom Co.Ltd.Honoraria to individuals: Takeda Pharmaceutical Company Ltd.,AstraZeneca K.K.,Zeria Pharmaceutical Co., Ltd.,MSD K.K., Chugai Pharmaceutical Co Ltd., Kaken Pharmaceutical Co.,Ltd.,Eisai Co., Ltd.

K. Moore: consulting fees from Aravive, Astra Zeneca, Alkemeres, Blueprint pharma, Elevar, Eisai/Serono, GSK/Tesaro, Genentech/Roche, Immunogen, IMab, Lilly, Mereo, Merck, Mersana, Myriad, OncXerna, Onconova, Tarveda, VBL Therapeutics. Honoraria from Astra Zeneca, PER, OncLive, Research to Practice, Medscape. Participation on a Data Safety Monitoring Board or Advisory Board : Incyte, SQZ. Leadership: GOG Partners Associate Dir, NRG Ov com chair.

F. Kridelka: consulting fees: AstraZeneca, Pharmamar, Roche, Lilly, Merck. Honoraria: AstraZeneca, Pharmamar, Roche, Lilly, Merck. Participation on a Data Safety Monitoring Board or Advisory Board: AstraZeneca, Pharmamar. Leadership: BGOG Steering Committee Member.

I. McNeish: personal Honoraria from GSK and AstraZeneca and Advisory Boards (personal) for Clovis Oncology, Astra Zeneca, GSK/Tesaro. IDMC-personal from Transgene.

A. Reuss: no conflicts.

B. Votan: no conflicts.

A. du Bois: honararia from Astra Zeneca, Zodiac, GSK/Tesaro, Clovis, AMGEN, MSD; Participation on a Data Safety Monitoring Board or Advisory Board for Astra Zeneca, Roche, GSK/Tesaro, Clovis, AMGEN, GenMab, MSD; Leaderships: AGO Study Group and ENGOT.

S. Mahner: grants all institutional: AbbVie, AstraZeneca, Clovis, Eisai, GlaxoSmithKline, Medac, MSD, Novartis, Olympus, PharmaMar,Pfizer, Roche, Sensor Kinesis, Teva, and Tesaro. Consulting fees institutional: AbbVie, AstraZeneca, Clovis, Eisai, GlaxoSmithKline, Medac, MSD, Novartis, Olympus, PharmaMar, Pfizer, Roche, Sensor Kinesis, Teva, and Tesaro. Honoraria (institutional): AbbVie, AstraZeneca, Clovis, Eisai, GlaxoSmithKline, Medac, MSD, Novartis, Olympus, PharmaMar, Pfizer, Roche, Sensor Kinesis, Teva, and Tesaro. mEETING/travel support: AbbVie, AstraZeneca, Clovis, Eisai, GlaxoSmithKline, Medac, MSD, Novartis, Olympus, PharmaMar, Pfizer, Roche, Sensor Kinesis, Teva, and Tesaro.

I. Ray-Coquard: honoraria from Amgen, AstraZeneca, BMS, Clovis Oncology, Genmab, GSK, ImmunoGen, Merck Sharp & Dohme, Novartis, Pfizer/Merck-Sereno, Deciphera, Mersana, Agenus, PharmaMar, Roche; Leadership: President of the GINECO Group; Meeting and travel support from Roche, Astra Zeneca, GSK, Clovis, MSD.

E. Kohn: no conflicts.

J.S. Berek: research Grants from Immunogen and Tesaro; Participation on a Data Safety Monitoring Board or Advisory Board: MK-7339-001 ENGOT-ov43 Safety DMC MK-3475 B96 DMC; OncoQuest Pharm board.

D. Tan: grants or contracts (institution): National Medical Research Council Singapore, Karyopharm therapeutics, Pangestu Family Foundation Gynaecological Cancer Research Fund, BMS, Astra Zeneca, Roche, Bayer; Consulting fees: Astra Zeneca, Bayer, Eisai, Merck Serono, GSK, Genentech/Roche, MSD, Genmab. Honoraria: Astra Zeneca, GSK, Roche, Eisai, MSD, Merck Serono. Leadership: GCGS president, APGOT Chair. Stock or stock options: AMILI (Asian Microbiome Library).

N. Colombo: present Manuscript: provision of study materials (payment to me); Consulting fees from Roche; PharmaMar; AstraZeneca; Clovis Oncology; MSD; GlaxoSmithKline; Tesaro; Pfizer; BIOCAD; Immunogen; Mersana; Eisai; Oncxerna (all payment to me); honoraria from AstraZeneca, Tesaro, Novartis, Clovis, MSD, GlaxoSmithKline, Eisai (all payment to me).

R. Zang: no conflicts.

N. Concin: consulting fees: Seagen, Akesobio, Ensai, GSK, AstraZeneca, Mersana, Seattle Genetics, eTheRNA immunotherapies NY; Honoraria: GSK, Mersana, MSD, Medscape Oncology, AstraZeneca, TouchIME; Meeting and travel support: Roche, Genmab, Amgen; Participation on a Data Safety Monitoring Board or Advisory Board: Seagen, Akesobio, Ensai, GSK, AstraZeneca, Mersana, Seattle Genetics, eTheRNA immunotherapies NV. Leaderships: President ESGO, Co-Chair ENGOT Early Drug Development Network.

D. O'Donnell: no conflicts.

A. Rauh-Hain: support for the present manuscript and Grants from National Institutes of Health/National Cancer Institute: K08 CA234333.

C.S. Herrington: no conflicts.

C. Marth: consulting fees from Roche, Novartis, Amgen, MSD, AstraZeneca, Pfizer, Pharmamar, Curelean, Vertex, Tesaro, GSK, Seagen; Honoraria from Roche, Novartis, Amgen, MSD, Pharmamar, Astra Zeneca, Tesaro, GSK, Seagen; Meeting/travel support from Roche and Astra Zeneca; Participation Data Safety Monitoring Board or Advisory Board for Roche, Novartis, Amgen, MSD, Astra Zeneca, Pfizer, Pharmamar, Cerulean, Vertex, Tesaro, GSK, Seagen.

A. Poveda: participation on Advisory Board: AstraZeneca and GSK (personal payment).

K. Fujiwara: participation on a Data Safety Monitoring Board or Advisory Board: MERCK: ENGOT-en11/MK-3475-B21/GOG-3053. Leaderships: GenomeBC.

G.C.E. Stuart: participation on a Data Safety Monitoring Board or Advisory Board: MERCK- ENGOT-en11/MK-3475-B21/GOG-3053. Leadership: GenomeBC.

A. Oza: Leaderships: chair GCIG – Unpaid; CEO Ozmosis Research - Unpaid.

M.A. Bookman: participation on a Data Safety Monitoring Board or Advisory Board: Aravive (protocol Steering Comittee, fees to institution), Immunogen and Genentech-Roche (DSMB and Advisory Board, fees to institution), Merck and Sharp & Dohme (Advisory Board, fees to institution).

Ethics Committee approval

Not applicable.

References

1 Bookman MA, Okamoto A, Stuart G, et al. Harmonising clinical trials within the Gynecologic Cancer InterGroup: consensus and unmet needs from the Fifth Ovarian Cancer Consensus Conference. *Ann Oncol.* 2017; **28(suppl_8):**viii30–35.

2 du Bois A, Quinn M, Thigpen T, et al. Gynecologic Cancer Intergroup; AGO-OVAR; ANZGOG; EORTC; GEICO; GINECO; GOG; JGOG; MRC/NCRI; NCIC-CTG; NCI-US; NSGO; RTOG; SGCTG; IGCS; Organizational team of the two prior International OCCC. 2004 consensus statements on the management of ovarian cancer: final document of the 3rd International Gynecologic Cancer Intergroup Ovarian Cancer Consensus Conference (GCIG OCCC 2004). *Ann Oncol* 2005;**16 Suppl 8**:viii7–12.

3 Stuart GC, Kitchener H, Bacon M, et al. Gynecologic Cancer InterGroup (GCIG) consensus statement on clinical trials in ovarian cancer: report from the Fourth Ovarian Cancer Consensus Conference. *Int J Gynecol Cancer* 2011; **21**:750–5.

4 du Bois A, Reuss A, Pujade-Lauraine E, Harter P, Ray-Coquard I, Pfisterer J. Role of surgical outcome as prognostic factor in advanced epithelial ovarian cancer: a combined exploratory analysis of 3 prospectively randomized phase 3 multicenter trials: by the Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR) and the Groupe d'Investigateurs Nationaux Pour les Etudes des Cancers de l'Ovaire (GINECO). *Cancer*. 2009;**115:**1234–44. doi: 10.1002/cncr.24149.

5 du Bois A, Rochon J, Pfisterer J, Hoskins WJ. Variations in institutional infrastructure, physician specialization and experience, and outcome in ovarian cancer: a systematic review. *Gynecol Oncol*. 2009; **112**:422–36. doi: 10.1016/j.ygyno.2008.09.036.

6 Bookman M. Optimal primary therapy of ovarian cancer. *Ann Oncol*. 2016; **27(Suppl 1)**:i58-i62. doi: 10.1093/annonc/mdw088.

7 Burger RA, Brady MF, Bookman MA,et al. Gynecologic Oncology Group. Incorporation of bevacizumab in the primary treatment of ovarian cancer. *N Engl J Med*. 2011; **29;365**:2473–83. doi: 0.1056/NEJMoa1104390.

8 Perren TJ, Swart AM, Pfisterer J, et al. ICON7 Investigators. A phase 3 trial of bevacizumab in ovarian cancer. **N Engl J Med**. 2011;**365**:2484–96. doi: 10.1056/NEJMoa1103799.

9 Pignata S, Scambia G, Katsaros D, et al. Multicentre Italian Trials in Ovarian cancer (MITO-7); Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens et du sein (GINECO); Mario Negri Gynecologic Oncology (MaNGO); European Network of Gynaecological Oncological Trial Groups (ENGOT-OV10); Gynecologic Cancer InterGroup (GCIG) Investigators. Carboplatin plus paclitaxel once a week versus every 3 weeks in patients with advanced ovarian cancer (MITO-7): a randomised, multicentre, open-label, phase 3 trial. *Lancet Oncol*. 2014; **15**:396–405. doi: 10.1016/S1470-2045(14)70049-X.

10 Katsumata N, Yasuda M, Isonishi S, et al. Japanese Gynecologic Oncology Group. Long-term results of dose-dense paclitaxel and carboplatin versus conventional paclitaxel and carboplatin for treatment of advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer (JGOG 3016): a randomised, controlled, open-label trial. *Lancet Oncol*. 2013;**14**:1020-6. doi: 10.1016/S1470-2045(13)70363-2.

11 Moore K, Colombo N, Scambia G, et al. Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. *N Engl J Med*. 2018; **27**:2495–505. doi: 10.1056/NEJMoa1810858.

12 Ray-Coquard I, Pautier P, Pignata S, et al. PAOLA-1 Investigators. Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer. *N Engl J Med*. 2019; **19**:2416–28. doi: 10.1056/NEJMoa1911361.

13 González-Martín A, Pothuri B, Vergote I, et al; PRIMA/ENGOT-OV26/GOG-3012 Investigators. Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. *N Engl J Med*. 2019; **19**:2391–402. doi: 10.1056/NEJMoa1910962.

14. Colombo N, Sessa C, du Bois A, et al. ESMO-ESGO consensus conference recommendations on ovarian cancer: pathology and molecular biology, early and advanced stages, borderline tumours and recurrent disease. *Ann Oncology* 2019; **30**:672–705

15 Wilson MK, Pujade-Lauraine E, Aoki D, et al, participants of the Fifth Ovarian Cancer Consensus Conference. Fifth Ovarian Cancer Consensus Conference of the Gynecologic Cancer InterGroup: recurrent disease. *Ann Oncol*. 2017;**28**:727-732.

16 J. Frenel, J. Kim, D. Berton-Rigaud, R. et al. Efficacy of subsequent chemotherapy for patients with BRCA1/2 mutated platinum-sensitive recurrent epithelial ovarian cancer (EOC) progressing on olaparib vs placebo: The SOLO2/ENGOT Ov-21 trial. *Ann Oncol*. 2020; **31(suppl 4):** S551–89.

17 Aghajanian C, Blank SV, Goff BA, et al. OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. *J Clin Oncol*. 2012;**30**:2039–45.

18 Aghajanian C, Goff B, Nycum LR, Wang YV, Husain A, Blank SV. Final overall survival and safety analysis of OCEANS, a phase 3 trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent ovarian cancer. *Gynecol Oncol*. 2015;**139**:10–6.

19 Coleman RL, Brady MF, Herzog TJ, et al. Bevacizumab and paclitaxel-carboplatin chemotherapy and secondary cytoreduction in recurrent, platinum-sensitive ovarian cancer (NRG Oncology/Gynecologic Oncology Group study GOG-0213): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol*. 2017;**18**:779–91.

20 Pfisterer J, Shannon CM, Baumann K, et al. AGO-OVAR 2.21/ENGOT-ov18 Investigators. Bevacizumab and platinum-based combinations for recurrent ovarian cancer: a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2020;**21**:699–709.

21. Pignata S, Lorusso D, Joly F,et al. MITO16b/MANGO–OV2/ENGOT–ov17 Investigators. Carboplatin-based doublet plus bevacizumab beyond progression versus carboplatin-based doublet alone in patients with platinum-sensitive ovarian cancer: a randomised, phase 3 trial. *Lancet Oncol*. 2021;**22**:267–76.

22 E. Pujade-Lauraine, F. Selle, G. Scambia, et al. Maintenance olaparib rechallenge in patients (pts) with ovarian carcinoma (OC) previously treated with a PARP inhibitor (PARPi): Phase IIIb OReO/ENGOT-ov38 trial. *Ann Oncol*. 2021; **32 (suppl_5)**: S1283–346._

23 Pujade-Lauraine E, Fujiwara K, Ledermann JA, et al.Avelumab alone or in combination with chemotherapy versus chemotherapy alone in platinum-resistant or platinum-refractory ovarian cancer (JAVELIN Ovarian 200): an open-label, three-arm, randomised, phase 3 study. *Lancet Oncol*. 2021;**22**:1034–46.

24 Moore KN, Oza AM, Colombo N, et al. Phase III, randomized trial of mirvetuximab soravtansine versus chemotherapy in patients with platinum-resistant ovarian cancer: primary analysis of FORWARD I. *Ann Oncol.* 2021;**32**:757–65.

25 Gaillard S, Oaknin A, Ray-Coquard I, et al. Lurbinectedin versus pegylated liposomal doxorubicin or topotecan in patients with platinum-resistant ovarian cancer: A multicenter, randomized, controlled, open-label phase 3 study (CORAIL). *Gynecol Oncol*. 2021;**163**:237–45.

26 K. Omatsu, J. Hamanishi, N. Katsumata, et al. Nivolumab versus gemcitabine or pegylated liposomal doxorubicin for patients with platinum-resistant (advanced or recurrent) ovarian cancer: Open-label, randomized trial in Japan (NINJA trial). *Ann Oncol* 2020; **31 (suppl_4):** S551–89.

27 Pujade-Lauraine E, Hilpert F, Weber B, et al. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: The AURELIA open-label randomized phase III trial. *J Clin Oncol*. 2014;**32**:1302–8.

28 Oza AM, Lisyanskaya AS, Fedenko AA, et al. Subgroup analysis of rucaparib versus chemotherapy as treatment for BRCA-mutated, advanced, relapsed ovarian carcinoma: Effect of platinum sensitivity in the randomized, phase 3 study ARIEL4. *J Clin Oncol* 2021;**39**,15 suppl: 5517.

29 O'Malley DM, Oaknin A, Matulonis UA,et al. Mirvetuximab soravtansine, a folate receptor alpha (FRα)-targeting antibody-drug conjugate (ADC), in combination with bevacizumab in patients (pts) with platinum-agnostic ovarian cancer: Final analysis. *J Clin Oncol* 2021; **39** (suppl 15; abstr 5504).

30 Harter P, Sehouli J, Vergote I, for the DESKTOP III investigators. Randomized trial of cytoreductive surgery for relapsed ovarian cancer. *N Engl J Med* 2021;**385**:2123–31.

31 Coleman RL, Spirtos NM, Enserro D, et al. Secondary Surgical Cytoreduction for Recurrent Ovarian Cancer. *N Engl J Med*. 2019;**381**:1929–39.

32 Shi T, Zhu J, Feng Y,et al. Secondary cytoreduction followed by chemotherapy versus chemotherapy alone in platinum-sensitive relapsed ovarian cancer (SOC-1): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol.* 2021;**22**:439–49.

33 Hollis RL, Thomson JP, Stanley B et al. Molecular stratification of endometrioid ovarian carcinoma predicts clinical outcome. *Nat Commun*. 2020;**11**:4995. doi: 10.1038/s41467-020-18819-5.

34 Hollis RL, Stanley B, Thomson JP, et al. Integrated molecular characterisation of endometrioid ovarian carcinoma identifies opportunities for stratification. *NPJ Precis Oncol* 2021;**5:**47. doi: 10.1038/s41698-021-00187-y.

35 Zhao S, Bellone S, Lopez S, et al. Mutational landscape of uterine and ovarian carcinosarcomas implicates histone genes in epithelial–mesenchymal transition. *Proc Natl Acad Sci*. 2016;**113**:12238–43.

36 Cheung AN, Ellenson LH, Gilks CB, et al (eds). Tumours of the ovary. In: WHO Classification of Female Genital Tumours, IARC, Lyon, 2020, pp. 32-167.

37 Köbel M, Bak J, Bertelsen BI, et al. Ovarian carcinoma histotype determination is highly reproducible, and is improved through the use of immunohistochemistry. *Histopathology* 2014; **64**: 1004–13.

38 Rambau PF, McIntyre JB, Taylor J, et al. Morphologic reproducibility, genotyping, and immunohistochemical profiling do not support a category of seromucinous carcinoma of the ovary. *Am J Surg Pathol* 2017; **41**:685–95.

39 Ray-Coquard I, Harter P, Lorusso D, et al. Effect of Weekly Paclitaxel With or Without Bevacizumab on Progression-Free Rate Among Patients With Relapsed Ovarian Sex Cord-Stromal Tumors: The ALIENOR/ENGOT-ov7 Randomized Clinical Trial. *JAMA Oncol*. 2020;**6**:1923–30.
40 Banerjee SN, Tang M, O'Connell RL, et al. A phase 2 study of anastrozole in patients with oestrogen receptor and/progesterone receptor positive recurrent/metastatic granulosa cell tumours/sex-cord stromal tumours of the ovary: The PARAGON/ANZGOG 0903 trial. *Gynecol Oncol.* 2021;**163**:72-78.
41 Monk BJ, Grisham RN, Banerjee S, et al. MILO/ENGOT-ov11: Binimetinib Versus Physician's Choice Chemotherapy in Recurrent or Persistent Low-Grade Serous Carcinomas of the Ovary, Fallopian Tube, or Primary Peritoneum. *J Clin Oncol*. 2020;**38**:3753–62.
42 Gershenson DM, Miller A, Brady WE, et al. Trametinib versus standard of care in patients with recurrent low-grade serous ovarian cancer (GOG 281/LOGS): an international, randomised, open-label, multicentre, phase 2/3 trial. *Lancet*. 2022;**39**:541–53-
43 Sugiyama T, Okamoto A, Enomoto T, et al. Randomized Phase III Trial of Irinotecan Plus Cisplatin Compared With Paclitaxel Plus Carboplatin As First-Line Chemotherapy for Ovarian Clear Cell Carcinoma: JGOG3017/GCIG Trial. *J Clin Oncol*. 2016;**34**:2881–7.
44 Kurtz JE, Kaminsky MC, Floquet A, et al. Ovarian cancer in elderly patients: carboplatin and pegylated liposomal doxorubicin versus carboplatin and paclitaxel in late relapse: a Gynecologic Cancer Intergroup (GCIG) CALYPSO sub-study. *Ann Oncol*. 2011;**22**:2417–23.
45. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; **45**: 228-47.
46 Dodd LE, Korn EL, Freidlin B, et al. Blinded Independent Central Review of Progression-Free Survival in Phase III Clinical Trials: Important Design Element or Unnecessary Expense? *J Clin Oncol.* 2008;**26**:3791–6.
47 Shi Q, and Sargent DJ. Key Statistical Concepts in Cancer Research Clinical Advances in Hematology & Oncology Volume 13, Issue 3 March 2015.
48 Rahman R , Fell J, Ventz S, et al. Deviation from the Proportional Hazards Assumption in Randomized Phase 3 Clinical Trials in Oncology: Prevalence, Associated Factors, and Implications. *Clin Cancer Res* 2019;**25**:6339–45.
49 Basch E, Reeve BB, Mitchell SA, et al. Development of the National Cancer Institute's patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE). *J Natl Cancer Inst*. 2014;**106** doi:10.1093/jnci/dju244.
50 Calvert M, Kyte D, Mercieca-Bebber R, et al. Guidelines for Inclusion of Patient-Reported Outcomes in Clinical Trial Protocols: The SPIRIT-PRO Extension. *JAMA*. 2018;**319**:483–94.
51 Calvert M, Blazeby J, Altman DG, Revicki DA, Moher D, Brundage MD; CONSORT PRO Group. Reporting of patient-reported outcomes in randomized trials: the CONSORT PRO extension. *JAMA*. 2013;**309**:814–22.