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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

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Supplement

Content

Supplement 1. GCIG Member Groups participating in OCCC6

AGO (Arbeitsgemeinschaft Gynäkologische Onkologie, Wiesbaden, Germany), AGO-AUST (Arbeitsgemeinschaft Gynäkologische Onkologie Austria, Innsbruck, Austria), AGOG (Asian Gynecologic Oncology Group, Taoyuan, Taiwan), ANZGOG (Australia and New Zealand Gynecological Oncology Group, Sydney, Australia), BGOG (Belgium and Luxembourg Gynaecological Oncology Group, Leuven, Belgium), BRASGYN (Brazilian Society for Gynecological Cancer Research, Soa Paolo, Brazil), CCTG (Canadian Cancer Trials Group, Kingston, Canada), CEEGOG (Central and Eastern European Gynecologic Oncology Group, Prague, Czech), CTI (Cancer Trials Ireland, Dublin, Ireland), DGOG (Dutch Gynecologic Oncology Group, Leiden, The Netherlands), EORTC-GCG (European Organization for Research and Treatment of Cancer-Gynaecological Cancer Group, Brussels, Belgium), G-GOC (Global Gynecologic Oncology Consortium, Houston, USA), GCGS (Gynecologic Cancer Group Singapore, Singapore), GEICO (Grupo Español de Cáncer de Ovario, Madrid, Spain), GICOM (Grupo de Investigación en Cáncer de Ovario y Tumores Ginecológicos de México, Mexico City, Mexico), GINECO (Groupe d'Investigateurs National des Etudes des Cancers Ovariens et du sein, Paris, France), GOG-F (Gynecologic Oncology Group Foundation, Philadelphia, USA), GOTIC (Gynecologic Oncology Trial and Investigation Consortium, Saitama, Japan), ISGO (Israeli Society of Gynecologic Oncology, Holon, Israel), JGOG (Japanese Gynecologic Oncology Group, Tokyo, Japan), KGOG (Korean Gynecologic Oncology Group, Seoul, Korea), KolGOTrg (Kolkata Gynecological Oncology Trials & Translational Research Group, Kolkata, India), MaNGO (Mario Negri Gynecologic Oncology Group, Milan, Italy), MITO (Multicenter Italian Trials in Ovarian Cancer, Naples, Italy), NCI-US (National Cancer Institute – USA, Bethesda, USA), NCRI (National Cancer Research Institute, London, UK), NOGGO (Nord-Ostdeutsche Gesellschaft Fur Gynäkologische Onkologie, Berlin, Germany), NSGO-CTU (Nordic Society of Gynaecological Oncology-Clinical Trial Unit, Copenhagen, Denmark), PMHC (Princess Margaret Hospital Consortium, Toronto, Canada), SAKK (Swiss Group for Clinical Cancer Research, Bern, Switzerland), SGCTG (Scottish Gynaecological Cancer Trials Group, Glasgow, UK), SGOG (Shanghai Gynecologic Oncology Group, Shanghai, China), Women's Cancer Research Network-Cooperative Gynecologic Oncology Investigators (WCRN-COGI).

Supplement 2. Methodology

GCIG has adopted written standard operating practices for consensus meetings (see manuscript Ref 2 (du Bois A,et al). Core representation on the Scientific Committee should be reflective of the GCIG Member Groups and geographic regions, and included the current OCCC Chair and co-Chair (2); current and past Chair of the GCIG Ovarian Cancer Committee (2); current and past Chair of GCIG (2); current (or past) Chairs of the Translational Research, Harmonization (Stats), Harmonization (Ops), and Symptom Benefit Committees (4); Representation from GCIG Operations (2); ISGyP (Pathology) GCIG Liaison (1), total of 13 core members, as endorsed by the GCIG Executive Committee and GCIG Member Groups.

Responsibilities of the Scientific Committee included convening of advanced planning discussions at least 2 years prior to the OCCC, formulation of draft key questions to guide the development of consensus statements, allocation of key questions among the four Topic Groups, and nomination of chairs and co-chairs for each Topic Group.

Once the four topic group chairs and co-chairs were identified (8), as well as a coordinator for unmet needs (1), these individuals were included in regular meetings of the Scientific Committee, with approximately 20 members (allowing for some overlapping roles). The Scientific Committee then approved the allocation of GCIG representatives (2 per GCIG Group) and supplemental domain experts across the four Topic Groups.

According to the SOP of the GCIG on the consensus meetings the participants were chosen as follows:
- Each GCIG member group designated two expert representatives to be invited with attention to providing adequate coverage of sub-specialties (including surgery, medical oncology, translational science, pathology, radiation oncology, etc).
- Existing Members of the Scientific Committee were not required to be included within the 2 person quota for each GCIG Member Group.
- The GCIG member groups specified the expertise of each delegate in order that they may be accurately assigned to Topic Groups (by the Scientific Committee).
- At least one of the member group's representatives should have been involved in GCIG Ovarian Cancer trials **and/or** authored/co-authored a publication/presentation of a GCIG Initiative **and/or** Ovarian Cancer trial since the prior OCCC.
- Groups were also encouraged to consider nominating at least one younger investigator to support mentorship and leadership transition.
- The 2 representatives were advised to discuss the preliminary questions and statements prior to the meeting within their group.
- Each GCIG member group had to appoint one of the 2 representatives as voting member.

Supplement 3. Reasons for voting disagreements

Statement 5.

- 2 groups were opposed and 1 abstained because they state that level 1 evidence exists for intraperitoneal chemotherapy/hyperthermic intraperitoneal chemotherapy (HIPEC)

Statement 8.

- 1 group preferred removing 12 weeks and leaving unspecified

Statement 9

- 1 group preferred removing 12 weeks and leaving unspecified

Statement 11

- 1 group abstained because at the time of OCCC6 the DESKTOP III/ENGOT-ov20 study was not yet published (currently published, see reference 29)

Statement 12

- 1 group reminds that the trametinib study was positive for PFS and underpowered but trended for OS and is considered practice changing. It is recognized that trametinib is not available for LGSOC in all jurisdictions (Gershenson D.M., Miller A., Brady W. A randomized phase II/III study to assess the efficacy of trametinib in patients with recurrent or progressive low-grade serous ovarian or peritoneal ancer. *Ann.Oncol*. 2019;**30 (suppl_5 page 7):**v851–v934).

Supplement 4. Recurrent disease

Treatment decisions for the management of advanced ovarian cancer in the front line impact the treatment strategy at the time of recurrence and necessarily will change the design of clinical trials in this setting. In terms of clinical trial design in the recurrent setting, key factors on which agreement is required includes 1) accurate categorization of patient populations based on clinical and molecular factors. These categories or criteria will define eligibility for trials and are far more complex than just the time interval from last platinum as has been stated for decades. Based on these categories, 2) agreement on appropriate control arms for specific categories is the next priority. When in clinical trials a platinum containing control arm or when non platinum options are acceptable, is outlined here. The secondary cytoreduction either as a part of clinical trials or as an accepted part of the treatment paradigm for women with recurrent disease meeting validated criteria for secondary cytoreduction is included. Finally, the welcome development of biomarker directed agents necessitates new clinical trial design that define eligibility based on the biomarker without consideration for the TFIp.

Supplemental Table S1. Chemotherapy backbone when platinum is an option.[17–20]

Study	Randomization	N	Median PFS (mo)	HR, p-value	Median OS (mo)	HR, p-value
OCEANS	C/gem + placebo	242	8.4	HR = 0.484 p<0.0001	32.9	HR = 0.952 p = 0.6479
	C/gem + bev until progression	242	12.4		33.6	
GOG-0213	C/P	337	10.4	HR = 0.628 p<0.0001	37.3	HR = 0.829 p = 0.056
	C/P + bev until progression	377	13.8		42.2	HR = 0.823* p = 0.0447*
AGO OVAR 2.21	C/Gem + bev until progression	294	11.7	HR = 0.807 P=0.0128	27.8	HR 0.81 P=0.032
	C/PLD + bev until progression	277	13.3		31.9	

Supplemental Table S2. Possible monotherapy cytotoxic options when platinum is not an option.[22–26]

Study	Study Population	Chemotherapy Arm	Overall Response Rate (ORR)	Median Progression Free Survival
JAVELIN Ovarian 200 (n=190)	≤3 priors, 75% PROC and 25% Platinum refractory (28% prior BEV)	Pegylated liposomal doxorubicin (PLD)	4%	3.5 months
FORWARD I Re-read (n=61)	PROC 1-3 priors high FRα (33% prior BEV)	Paclitaxel or PLD or Topotecan	6%	3.2 months
CORAIL (n=199)	PROC ≤ 3 priors (46% prior BEV)	PLD or Topotecan	12%	3.6 months
NINJA (n=159)	PROC 77% > 2 prior	Gemcitabine or PLD	13%	3.8 months
AURELIA (n=182)	PROC ≤ 2 priors; 25% Platinum refractory (8% prior BEV)	Paclitaxel or PLD or Topotecan	13%	3.4 months

PROC: platinum resistant ovarian cancer

ARIEL 4 was the randomized phase 3 trial of rucaparib in BRCA associated recurrent ovarian cancer irrespective of TFIp with appropriate control arms based on TFIp.[27] FORWARD II was a study of the antibody drug conjugate (ADC) mirvetuximab plus bevacizumab in folate receptor α high tumours irrespective of TFIp.[28] With developing biomarkers such as cyclin e amplification, replication stress and other immunohistochemical markers for use of ADCs, clinical trial designs need to evolve to allow participation irrespective of TFIp.

Three randomised studies evaluated the role of secondary debulking surgery in patients with "platinum sensitive" ovarian cancer recurrence. DESKTOP III/ENGOT-ov20 selected patients based on a validated algorithm of excellent performance status, complete surgical resection at the time of first cytoreduction and ascites < 500 mL^3 and demonstrated a statistically significant improvement in overall survival (OS) (HR 0.75; 95% CI 0.58-.96; p=0.02) with the biggest impact among those patients where resection to no gross residual was achieved at surgery.[29] GOG-213 did not find an OS improvement with secondary surgery although this trial presented notable differences with the previous one, mainly based on the inclusion of bevacizumb in combination with chemotherapy as well as the lack of validated patient selection.[30] One consistent finding between the studies was the inferior outcomes of patients randomized to surgery with incomplete resection as compared to those with no surgery. The SGOG-SOC-1 demonstrated a significant increase in 2-year PFS and median PFS for patients receiving secondary surgery, selected according to the iModel criteria.[31]

Supplement 5. Statements on specific subgroups

Table S3 - Diagnostic Biomarkers in epithelial ovarian cancer (typical profiles[35,36])*

- Ovarian Carcinomas
  - High grade serous carcinoma – WT1 positive, ER/PR positive, p53 aberrant, PAX 8 positive
  - Low grade serous carcinoma – WT1 positive, ER/PR positive, p53 wild type, PAX8 positive
  - Endometrioid carcinoma – WT1 negative, ER/PR positive, p53 wild type (minority aberrant, particularly high grade tumours), PAX8 positive
    - Includes endometrioid carcinomas with mucinous differentiation previously termed seromucinous carcinoma[36,37]
  - Clear cell carcinoma – WT1 negative, p53 wild type (minority aberrant), ER/PR negative, napsin A positive, HNF1β positive, PAX8 positive
  - Mucinous carcinoma (intestinal type) – WT1 negative, ER/PR negative, p53 wild type or aberrant, PAX8 negative
- Sex cord stromal tumours – Adult granulosa cell tumour – *FOXL2* C134W mutation
- Small cell carcinoma of the ovary, hypercalcaemic type – *SMARCA4* mutation/BRG1 loss

*Note that there are exceptions to these profiles. Specific diagnostic criteria should be developed as part of individual trial protocols.

Supplement 6. Statement 18 – Primary endpoints

When overall or objective response rate (ORR) is considered, it is defined as the sum of RECIST-determined complete plus partial responses.[45] RECIST responses (table 4) are defined as confirmed responses and incorporates criteria for clinical progression. During the conference, there was consensus that disease control rate is neither a defined nor validated primary endpoint. In phase 3 and (and in randomised phase 2 trials) progression-free survival (PFS) or overall survival (OS), but not CA-125, are the primary endpoints; furthermore, investigating multiple primary endpoints requires adjusting methods such as alpha splitting or hierarchical testing. 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. Indeed, assessment of efficacy of the addition of a new agent(s) (e.g., combination regimens) requires a randomised design. However, randomization is sometimes not feasible, particularly in the setting of very rare tumours, where historical controls can be used. An important consensus was reached regarding the optional nature of blinded independent committee review for PFS. However, both a sample-based or full BICR could be included as a secondary endpoint, although if performed, results of both analyses (investigator and BICR) should be reported.

157 **Supplement 7. Participants of OCCC6 (to be mentioned in Pubmed)**
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