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SPECIAL ARTICLE

ESGO—ESMO—ESP consensus conference recommendations on ovarian cancer: pathology and molecular biology and early, advanced and recurrent disease☆

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☆Note: These consensus statements were developed by ESMO, ESGO and ESP and are published in Annals of Oncology. The three scoieties nominated participants who attended the consensus conference and co-authored the final manuscript. Please see appendix for members of the ESGO-ESMO-ESP Ovarian Cancer Consensus Conference Working Group.

The European Society of Gynaecological Oncology, the European Society for Medical Oncology (ESMO) and the European Society of Pathology held a consensus conference (CC) on ovarian cancer on 15-16 June 2022 in Valencia, Spain. The CC panel included 44 experts in the management of ovarian cancer and pathology, an ESMO scientific advisor and a methodologist. The aim was to discuss new or contentious topics and develop recommendations to improve and harmonise the management of patients with ovarian cancer. Eighteen questions were identified for discussion under four main topics: (i) pathology and molecular biology, (ii) early-stage disease and pelvic mass in pregnancy, (iii) advanced stage (including older/frail patients) and (iv) recurrent disease. The panel was divided into four working groups (WGs) to each address questions relating to one of the four topics outlined above, based on their expertise. Relevant scientific literature was reviewed in advance. Recommendations were developed by the WGs and then presented to the entire panel for further discussion and amendment before voting. This manuscript focuses on the recommendation statements that reached a consensus, their voting results and a summary of evidence supporting each recommendation.

Key words: chemotherapy, maintenance treatment, molecular biology, ovarian cancer, pathology, surgery

INTRODUCTION

Ovarian cancer is the second-highest cause of death among all gynaecological cancers.[1] The estimated number of new cases in Europe in 2020 was 66 693 with 44 053 deaths.[2] More than two-thirds of patients are diagnosed at an advanced stage. Ovarian cancer diagnosed in young women raises concerns about their fertility. When diagnosed during pregnancy, maternal and fetal factors need to be considered.

More than 90% of malignant ovarian tumours are designated tubo-ovarian carcinoma (also referred to as epithelial ovarian cancer). The most common and most lethal tubo-ovarian carcinoma is high-grade serous carcinoma (HGSC).[3] Less frequent epithelial subtypes with distinct morphological and molecular characteristics include high-grade endometrioid carcinoma (EC), low-grade serous carcinoma (LGSC) and clear-cell carcinoma (CCC).

The development of guideline recommendations is one of the core activities of both the European Society of Gynaecological Oncology (ESGO) and the European Society for Medical Oncology (ESMO), as part of their mission to improve the quality of care for patients with cancer across Europe. The European Society of Pathology (ESP) promotes high-quality pathology diagnosis for all patients. Following the 2018 ESMO—ESGO consensus conference (CC) on ovarian cancer,[4] another CC took place on 15-16 June 2022 in Valencia, Spain, to discuss new or contentious topics. Pathology expertise was added by including ESP. The aim was to improve and harmonise the management of patients with ovarian cancer. Published evidence was evaluated incorporating clinical experience to arrive at consensus recommendations through an anonymous voting procedure.

This manuscript focuses on the recommendation statements that reached a consensus and their voting results. The summary of evidence supporting each recommendation is available in the Supplementary Material, available at https://doi.org/10.1016/j.annonc.2023.11.015. For topics not covered in this article, please refer to the 2018 ESMO—ESGO CC recommendations on ovarian cancer,[4] the ESMO Clinical Practice Guidelines (CPGs) for diagnosis, treatment and follow-up of patients with epithelial ovarian cancer[5] and non-epithelial ovarian cancer[6] and the ESGO/International Society of Ultrasound in Obstetrics and Gynecology (ISUOG)/International Ovarian Tumor Analysis (IOTA)/European Society for Gynaecological Endoscopy (ESGE) consensus statement on preoperative diagnosis of ovarian tumours.[7]

METHODOLOGY

The CC followed the ESMO Standard Operating Procedures (SOPs) for CCs, available here: https://www.esmo.org/guidelines/esmo-guidelines-methodology. Collection and review of author declarations of interest (DOIs) followed the ESMO DOI policy, available here: https://www.esmo.org/about-esmo/how-we-work/declaration-of-interest.

The need for a CC was identified by the ESGO and ESMO Guidelines Committees. Anna Fagotti (ESGO), Jonathan Ledermann (ESMO) and Xavier Matias-Guiu (ESP) were designated as CC Chairs. The CC Chairs defined four broad topics and assigned 41 additional experts from Europe with representation from Asia and the USA to four working groups (WGs) based on their expertise, ensuring good representation across the three societies. Two WG Chairs for each WG were nominated by the CC Chairs as follows (see Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2023.11.015, for all participants):

1. Pathology and molecular biology (Chairs: B. Davidson and A. Leary)
2. Early-stage disease and pelvic mass in pregnancy (Chairs: F. Amant and C. Gourley)
3. Advanced stage (including older/frail patients) (Chairs: N. Concin and D. Lorusso)
4. Recurrent disease (Chairs: C. Fotopoulou and A. González-Martin)

Literature searches were conducted by a methodologist (F. Planchamp) using the Medline® database to ensure that

the recommendations were evidence-based. The search terms for each WG topic are provided in Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2023.11.015. The reference list of each identified article was reviewed for other potentially relevant papers. WG members were allowed to consider other publications not identified in the literature search.

The WGs discussed published data and clinical experience and drafted recommendation statements. These were reviewed by the CC Chairs.

During the CC, 40 individuals were eligible to vote on recommendation statements (3 CC Chairs, 8 WG Chairs and 29 WG members). Four WG members were unable to attend/vote in person but participated in post-CC voting and authorship of the final manuscript. F. Planchamp and C. Sessa (ESMO scientific advisor) did not participate in the voting of consensus recommendations but authored the final manuscript.

In parallel sessions, the four WGs further discussed and agreed on the draft statements. These were presented to the entire panel before voting, where they were discussed and modified as required. An adapted version of the 'Infectious Diseases Society of America-United States Public Health Service Grading System'[8] was used to define the level of evidence (LoE) and grade of recommendation (GoR) for each recommendation proposed, based on the data available up to the time of the CC (i.e. as of 14 June 2022) (see Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2023.11.015).

Voting was anonymous. Members could abstain from voting if they perceived that they had insufficient expertise or a conflict of interest. Results of $\geq$75% agreement and $\leq$20% disagreement were considered a consensus. Results of $<$75% agreement or $>$20% disagreement were not considered a consensus.

Recommendation statements that reached a consensus are detailed in the manuscript. The statements that did not reach consensus are reported in the Supplementary Material, available at https://doi.org/10.1016/j.annonc.2023.11.015. For recommendation statements that did not reach consensus onsite after two rounds of voting, a post-CC exploration of disagreements was conducted using a modified Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology, described in the ESMO SOPs.[9,10] The aim was to provide further insight into the division of opinions to illustrate the extent to which consensus was/was not likely.

All LoEs and GoRs were reviewed post-CC by F. Planchamp to verify that they could be fully supported by available evidence. If an LoE could not be confirmed by existing evidence, an alternative LoE was proposed. Similarly, if any inconsistencies were found between the strength of evidence and the assigned GoR, an alternative GoR was proposed.

All authors were asked to vote again anonymously online on recommendation statements with updated LoEs and/or GoRs. The voting results for these revised statements were considered as final and are included in the manuscript. All participants approved the final manuscript.

RESULTS

Percentages might not add up to 100% due to rounding.

Pathology and molecular biology

See Supplementary Material Section 1, available at https://doi.org/10.1016/j.annonc.2023.11.015, for detailed supporting evidence for these recommendations.

1. Which molecular and genomic tests should be carried out at diagnosis as prognostic or predictive markers for high-grade tubo-ovarian carcinoma?

Adequate tissue or a cell block from a cytology specimen is needed for molecular testing, which can identify mutations and/or inform treatment decisions [e.g. poly (ADP-ribose) polymerase inhibitors (PARPis) when *BRCA1/2* pathogenic variant mutations (*BRCA1/2*-muts) are present]. Adequate DNA is required for *BRCA1/2* genetic testing. Germline *BRCA1/2* mutations (g*BRCA1/2*-muts), confirmed on testing normal cellular material, are present in 13%-15% of HGSCs and somatic *BRCA1/2*-muts in 5%-7% of tumours.[11] Genomic instability tests should be carried out in newly diagnosed high-grade non-mucinous tubo-ovarian carcinoma. These tests identify functional disturbance in homologous recombination repair of DNA damage that can be present due to *BRCA* mutations and other factors, such as mutations in homologous recombination repair genes.[12-14] Cancer antigen 125 (CA-125) and human epididymis protein 4 (HE4) are two serological markers used to assist in the diagnosis of tubo-ovarian carcinoma.[15]

Recommendation 1.1: An adequate surgical specimen or image-guided biopsy of treatment-naive tumour is the preferred sample for diagnosis and molecular testing [IV, A].

Consensus: 100% (41) yes, 0% (0) no, 0% (0) abstain (41 voters)

Recommendation 1.2: In all cases, the sample should contain a sufficient number of tumour cells (preferably $\geq$30%). A cell block from peritoneal or pleural effusions may be used for molecular analysis [IV, B].

Consensus: 97.6% (40) yes, 2.4% (1) no, 0% (0) abstain (41 voters)

Recommendation 1.3: *BRCA*-mut (germline and/or somatic) testing is recommended at diagnosis for patients with high-grade non-mucinous tubo-ovarian carcinoma regardless of stage [I, A].

Consensus: 98% (39) yes, 3% (1) no, 0% (0) abstain (40 voters)

Recommendation 1.4: Routine tumour testing for non-*BRCA* homologous recombination gene mutations is not required; however, it should be encouraged in the research setting [IV, B].

Consensus: 100% (40) yes, 0% (0) no, 0% (0) abstain (40 voters)

Recommendation 1.5: Genomic instability tests are recommended in patients with *BRCA* wild-type (wt) high-grade

non-mucinous[a] International Federation of Gynecology and Obstetrics (FIGO) stage III-IV tubo-ovarian carcinoma at diagnosis as this provides useful predictive information for first-line maintenance therapy decisions [I, A].

Consensus: 100% (40) yes, 0% (0) no, 0% (0) abstain (40 voters)

Recommendation 1.6: A genomic instability test that has been clinically validated in large cohorts [III, B] or, preferably, phase III trials should be used [I, A].

Consensus: 100% (40) yes, 0% (0) no, 0% (0) abstain (40 voters)

Recommendation 1.7: There are no validated predictive markers of primary resistance to platinum or PARPis at diagnosis and none can be recommended at present [IV, A].

Consensus: 100% (40) yes, 0% (0) no, 0% (0) abstain (40 voters)

Recommendation 1.8: General population screening for tubo-ovarian carcinoma cannot be recommended because screening does not reduce cancer deaths [I, E].

Consensus: 100% (40) yes, 0% (0) no, 0% (0) abstain (40 voters)

Recommendation 1.9: CA-125 with or without HE4 should not be used alone to differentiate between benign, borderline and malignant ovarian tumours [IV, D].

Consensus: 97.6% (40) yes, 0% (0) no, 2.4% (1) abstain (41 voters)

2. What is the role of circulating and tissue biomarkers during treatment and follow-up?

CA-125 is frequently used to monitor the response to chemotherapy (ChT), but there is less certainty about its use for follow-up. In the neoadjuvant setting, modelled CA-125 ELIMination rate constant K (KELIM) predicts the likelihood of complete interval cytoreductive surgery (ICS) and the risk of subsequent platinum-resistant relapse.[16-18] Histopathological examination of omental specimens is used to determine the ChT response score (CRS) and is a reproducible prognostic tool to assess the response to neoadjuvant ChT (NACT).[19-22] Reversion *BRCA*-muts in tumour or in circulating tumour DNA (ctDNA) are markers for resistance to PARPis.[23] Further investigation is needed to evaluate the utility of ctDNA outside of research.

Recommendation 2.1: Routine monitoring of CA-125 after completion of first-line ChT is an option that should be discussed with the patient [IV, A].

Consensus: 88% (35) yes, 8% (3) no, 5% (2) abstain (40 voters)

Recommendation 2.2: The CA-125 KELIM calculated using longitudinal CA-125 over the first 100 days of treatment provides prognostic information, and testing for this dynamic circulating marker can be considered [III, B].

Consensus: 78% (31) yes, 13% (5) no, 10% (4) abstain (40 voters)

Recommendation 2.3: Routine monitoring for ctDNA and circulating tumour cells is not recommended but should be encouraged within the context of research projects [IV, A].

Consensus: 100% (40) yes, 0% (0) no, 0% (0) abstain (40 voters)

Recommendation 2.4: Testing ctDNA for reversion mutations can be considered in patients with *BRCA*-mutated tubo-ovarian carcinoma treated with at least one line of platinum and eligible for PARPi treatment [III, C].

Consensus: 95% (38) yes, 0% (0) no, 5% (2) abstain (40 voters)

Recommendation 2.5: CRS at ICS on an omental (preferred) or adnexal specimen provides prognostic information and is recommended [III, B].

Consensus: 75% (30) yes, 20% (8) no, 5% (2) abstain (40 voters)

Recommendation 2.6: Testing for a reversion mutation in tumour samples at relapse can be considered in *BRCA*-mutated tumours [III, C].

Consensus: 93% (37) yes, 5% (2) no, 3% (1) abstain (40 voters)

3. How should LGSC and HGSC be diagnosed?

Most LGSCs arise in the ovary[24] and develop from benign serous tumours and serous borderline tumours (SBTs), while most HGSCs develop from serous tubal intraepithelial carcinoma (STIC) at the fimbrial end of the fallopian tube.

The distinction between LGSC and HGSC is based on a combination of morphology and p53 immunohistochemistry (IHC). Mutations in *KRAS* or *BRAF* are common in LGSC and *TP53* mutations are ubiquitous in HGSC.

Recommendation 3.1: LGSC and HGSC should be regarded as two distinct neoplasms with different morphology, underlying molecular events and behaviour and do not represent different grades of the same tumour type [IV, A].

Consensus: 100% (40) yes, 0% (0) no, 0% (0) abstain (40 voters)

Recommendation 3.2: The distinction between LGSC and HGSC is based on a combination of morphology and p53 IHC; in diagnostically challenging cases, referral for a specialist opinion and/or molecular testing is recommended [IV, A].

Consensus: 100% (40) yes, 0% (0) no, 0% (0) abstain (40 voters)

Recommendation 3.3: In cases with morphology suggestive of LGSC but aberrant p53 protein expression and/or *TP53* mutation, it is recommended that the tumour be classified as HGSC [IV, A].

Consensus: 93% (37) yes, 0% (0) no, 8% (3) abstain (40 voters)

Recommendation 3.4: In designating the primary site of extrauterine HGSC, the recommendations of the Interna-

[a](HGSC and EC)

tional Collaboration on Cancer Reporting should be followed [III, A].

Consensus: 100% (40) yes, 0% (0) no, 0% (0) abstain (40 voters)

Recommendation 3.5: Staining for Wilms tumour protein (WT-1) is recommended when the primary origin of HGSC (adnexal versus uterine) is unclear [IV, A].

Consensus: 100% (40) yes, 0% (0) no, 0% (0) abstain (40 voters)

Recommendation 3.6: Results of p53 IHC should be reported as 'wt or normal' or 'mutation-type or aberrant' rather than positive or negative [IV, A].

Consensus: 100% (40) yes, 0% (0) no, 0% (0) abstain (40 voters)

Recommendation 3.7: As a minimum, paired box 8, estrogen receptor, WT-1 and p53 IHC should be carried out on diagnostic biopsies with a morphological suspicion of LGSC or HGSC [IV, A].

Consensus: 100% (40) yes, 0% (0) no, 0% (0) abstain (40 voters)

Recommendation 3.8: Testing for *HER2* status in mucinous carcinoma can be considered to identify patients who may benefit from *HER2*-targeted strategies [IV, C].

Consensus: 95% (38) yes, 3% (1) no, 3% (1) abstain (40 voters)

Recommendation 3.9: Testing for *KRAS* and *BRAF* mutational status in LGSC can be considered to identify patients who may benefit from targeted strategies [IV, C].

Consensus: 95% (38) yes, 5% (2) no, 0% (0) abstain (40 voters)

4. What is the role of molecular classification in ovarian EC and CCC?

EC and CCC are endometriosis-associated neoplasms[25] and the endometriosis can be completely overgrown.

The Cancer Genome Atlas (TCGA)-based molecular classification used for endometrial carcinomas has been applied to ovarian EC, as it is prognostically useful. Data regarding the role of the TCGA classification in ovarian CCC are less robust. DNA mismatch repair (MMR) IHC and/or microsatellite instability (MSI) testing is recommended in all cases to help identify Lynch-syndrome-related ovarian EC and CCC.[26-28]

Recommendation 4.1: A TCGA-based molecular classification as used for endometrial carcinomas can be considered to stratify ovarian EC [IV, B].

Consensus: 95% (38) yes, 5% (2) no, 0% (0) abstain (40 voters)

Recommendation 4.2: Molecular markers are not recommended for prognostication in ovarian CCC [IV, D].

Consensus: 90.2% (37) yes, 0% (0) no, 9.8% (4) abstain (41 voters)

Recommendation 4.3: DNA MMR IHC and/or MSI testing is recommended in ovarian EC and CCC [II, A].

Consensus: 100% (40) yes, 0% (0) no, 0% (0) abstain (40 voters)

Early-stage disease and pelvic mass in pregnancy

See Supplementary Material Section 2, available at https://doi.org/10.1016/j.annonc.2023.11.015, for detailed supporting evidence for these recommendations.

5. How should an adnexal mass be managed in pregnant women?

Ultrasound (US) and magnetic resonance imaging (MRI) are first-line imaging modalities for detailed locoregional disease assessment (depending on availability of expertise). The role of serum tumour markers is still unclear.

Most functional cysts undergo spontaneous resolution before 16 weeks of gestation and expectant management is reasonable. Surgery can be carried out safely during pregnancy, preferably within 22 weeks of gestation.[29] If advanced-stage tubo-ovarian carcinoma is diagnosed during the first half of pregnancy, termination should be considered. In patients wishing to preserve their pregnancy, platinum-based ChT including paclitaxel can be considered.[29]

Prenatal exposure to maternal ChT does not impair organ function or child development.[30,31]

Recommendation 5.1: It is recommended to evaluate all patients with suspicious adnexal masses during pregnancy at a specialist referral centre [V, A].

Consensus: 95.1% (39) yes, 0% (0) no, 4.9% (2) abstain (41 voters)

Recommendation 5.2: US by an expert is the recommended first-line imaging procedure when an adnexal mass is diagnosed during pregnancy [III, A].

Consensus: 95.1% (39) yes, 2.4% (1) no, 2.4% (1) abstain (41 voters)

Recommendation 5.3: MRI is recommended as a second-stage test for the characterisation of indeterminate ovarian masses [IV, A].

Consensus: 92.7% (38) yes, 0% (0) no, 7.3% (3) abstain (41 voters)

Recommendation 5.4: The routine use of beta-human chorionic gonadotropin and alpha-fetoprotein is not recommended during pregnancy [IV, E].

Consensus: 100% (39) yes, 0% (0) no, 0% (0) abstain (39 voters)

Recommendation 5.5: A proactive surgical approach depending upon gestational age is recommended in cases of high risk for malignancy during pregnancy [IV, A].

Consensus: 92.7% (38) yes, 0% (0) no, 7.3% (3) abstain (41 voters)

Recommendation 5.6: Where needed, platinum-based ChT at the same dosage as in non-pregnant women is recommended as standard ChT after the first trimester of pregnancy [IV, A].

Consensus: 97% (38) yes, 0% (0) no, 3% (1) abstain (39 voters)

Recommendation 5.7: Paclitaxel can also be administered to pregnant women [IV, B].

Consensus: 95% (37) yes, 0% (0) no, 5% (2) abstain (39 voters)

Recommendation 5.8: Pregnant patients who receive ChT for ovarian carcinoma need follow-up in high-risk obstetric units [IV, A].

Consensus: 97.6% (40) yes, 0% (0) no, 2.4% (1) abstain (41 voters)

6. How should an adnexal mass be managed for women who want to retain their fertility?

Fertility-sparing surgery appears safe in patients with borderline tumours, non-epithelial tumours, low-grade stage IA (serous, endometrioid or mucinous expansile subtype) and selected IC1 stages.[32]

Oncofertility clinics are best positioned to provide a model of care for patients eligible for fertility preservation using a checklist for a high-quality fertility-preservation programme.[33]

Recommendation 6.1: The option of fertility-sparing surgery should be discussed in young patients with early-stage ovarian carcinoma [IV, A].

Consensus: 100% (39) yes, 0% (0) no, 0% (0) abstain (39 voters)

Recommendation 6.2: Women with ovarian carcinoma who want to preserve their fertility need to be managed in an oncofertility clinic [V, A].

Consensus: 97% (38) yes, 3% (1) no, 0% (0) abstain (39 voters)

Recommendation 6.3: Subjective assessment of the adnexal mass by a US expert is recommended. If not available, the IOTA Assessment of Different NEoplasias in the adneXa model (ADNEX) in combination with CA-125 is recommended to differentiate between benign, borderline, early- or advanced-stage ovarian carcinoma and secondary carcinomas in young women who want to preserve their fertility [III, A].

Consensus: 90% (35) yes, 8% (3) no, 3% (1) abstain (39 voters)

Recommendation 6.4: Unilateral salpingo-oophorectomy with surgical staging is recommended in young patients with a malignancy apparently confined to the ovary and who want to preserve their fertility [III, A].

Consensus: 95% (37) yes, 3% (1) no, 3% (1) abstain (39 voters)

Recommendation 6.5: Minimally invasive surgery avoiding tumour rupture is an acceptable approach for women who wish to preserve their fertility [IV, A].

Consensus: 95% (37) yes, 5% (2) no, 0% (0) abstain (39 voters)

Recommendation 6.6: It is not recommended to biopsy the unaffected ovary unless there is suspicion of involvement [V, E].

Consensus: 97% (38) yes, 0% (0) no, 3% (1) abstain (39 voters)

Recommendation 6.7: In patients who wish to retain their fertility, cryopreservation of gametes rather than ovarian tissue is recommended [V, A].

Consensus: 97% (38) yes, 0% (0) no, 3% (1) abstain (39 voters)

7. How should high-grade EC, CCC and high-risk mucinous stage I-II tubo-ovarian carcinomas be managed?

In these histological subtypes, the debate relates to lymph node resection. Data are retrospective; in general, the risk of lymph node metastases is 20% in stage I and 40% in stage II[34] but can vary according to grade and histology in different series ($\leq$17.4% for early-stage, high-grade EC, 7%-12% in early-stage CCC and $\leq$30% in infiltrative mucinous ovarian cancer).[35-37]

Randomised trials in patients with stage I-II tubo-ovarian carcinoma demonstrated that adjuvant platinum-based ChT prolonged survival, but did not prospectively evaluate histological subtypes.[38,39] High-grade EC has a similar prognosis to HGSC and is worse than low-grade EC. It is not clear whether there is any survival benefit for adjuvant ChT in stage IA or IB CCC.[40,41]

Recommendation 7.1: Complete surgical resection including total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, systematic pelvic and para-aortic lymph node dissection, peritoneal biopsies and cytological analysis should be the standard surgical procedure in stage I-II high-grade EC, CCC and high-risk mucinous ovarian carcinoma [IV, A].

Consensus: 97% (38) yes, 3% (1) no, 0% (0) abstain (39 voters)

Recommendation 7.2: Patients with stage I-II high-grade EC should be offered adjuvant platinum-based ChT [IV, A].

Consensus: 100% (39) yes, 0% (0) no, 0% (0) abstain (39 voters)

Recommendation 7.3: Adjuvant ChT may be omitted for adequately staged IA or IB CCC [IV, C].

Consensus: 90% (35) yes, 5% (2) no, 5% (2) abstain (39 voters)

Recommendation 7.4: Adjuvant ChT may be considered for stage IC1 CCC [IV, C].

Consensus: 92% (36) yes, 8% (3) no, 0% (0) abstain (39 voters)

Recommendation 7.5: Adjuvant ChT is recommended for stages IC2, IC3 and II CCC [IV, A].

Consensus: 100% (39) yes, 0% (0) no, 0% (0) abstain (39 voters)

Recommendation 7.6: Patients with high-risk stage I-II mucinous ovarian carcinoma should be offered adjuvant platinum-based ChT [IV, A].

Consensus: 97% (38) yes, 0% (0) no, 3% (1) abstain (39 voters)

8. How should ovarian SBTs with peritoneal implants be managed?

Ovarian SBT is defined as a non-invasive, low-grade, proliferative serous epithelial neoplasm.[42] In 14%-30% of SBTs, extraovarian peritoneal implants are present.[43-46] The 2020 World Health Organization classification distinguishes

between non-invasive and invasive implants. Invasive implants are defined as "in most cases the epithelial component predominates, especially with a micropapillary/cribriform pattern associated with retraction artefact, and there is destructive invasion of underlying structures or obliteration of normal omental architecture by invasive tumour".[42] The prognosis is worse in patients with invasive implants.[44,45]

Recommendation 8.1: Since the pathological analysis of implants is complex, it is recommended that the histological review of specimens is carried out by an expert pathologist [V, A].

Consensus: 100% (41) yes, 0% (0) no, 0% (0) abstain (41 voters)

Recommendation 8.2: It is recommended to manage women with stage II-III ovarian SBTs at a specialist centre [V, A].

Consensus: 95.1% (39) yes, 2.4% (1) no, 2.4% (1) abstain (41 voters)

Recommendation 8.3: It is recommended to keep the distinction between invasive and non-invasive implants for subsequent management [IV, A].

Consensus: 92% (36) yes, 5% (2) no, 3% (1) abstain (39 voters)

Recommendation 8.4: It is recommended to surgically resect peritoneal and omental disease to differentiate invasive from non-invasive implants [V, A].

Consensus: 100% (39) yes, 0% (0) no, 0% (0) abstain (39 voters)

9. How should early-stage LGSC with non-invasive peritoneal implants be managed?

Randomised data on ChT or hormone treatment are absent, but LGSC is far less chemosensitive than HGSC (although most reports are from the relapsed setting).[47-50]

In a meta-analysis of retrospective studies investigating apparent early-stage, low-grade tubo-ovarian carcinoma, the incidence of occult lymph node metastases was 2.9%.[51]

Recommendation 9.1: It is recommended to completely remove all peritoneal implants combined with peritoneal staging as a standard treatment procedure [IV, A].

Consensus: 100% (39) yes, 0% (0) no, 0% (0) abstain (39 voters)

Recommendation 9.2: Removal of enlarged or suspicious lymph nodes is recommended without routine systematic lymphadenectomy [IV, A].

Consensus: 85% (33) yes, 15% (6) no, 0% (0) abstain (39 voters)

Recommendation 9.3: Adjuvant ChT could be considered for stage II LGSC [IV, C].

Consensus: 92% (36) yes, 5% (2) no, 3% (1) abstain (39 voters)

Recommendation 9.4: Endocrine treatment following ChT could be considered for stage II LGSC [V, C].

Consensus: 90% (35) yes, 8% (3) no, 3% (1) abstain (39 voters)

10. How should incidental STIC or microscopic HGSC be managed?

The frequency of STIC detected in risk-reducing bilateral salpingo-oophorectomies (RRBSOs) in high-risk populations (patients with a *BRCA*-muts) is quite variable (0.4%-8.5%) but ~10-fold higher than in low-risk populations.[52-55] There is no precise definition for 'microinvasive' tubal HGSC, but STICs associated with 'microscopic' invasive HGSC may be the source of peritoneal HGSC and, therefore, should be managed as HGSC.[56]

The accurate sampling of the tuba by Sectioning and Extensively Examining the FIMbriated end (SEE-FIM) protocol—recommended both in women with a *BRCA*-mut and those with an unknown genetic predisposition—and the improved diagnostic criteria, including the use of p53 and ki-67 immunostainings, has identified occult lesions, which were previously missed in classical grossing procedures, as STIC.[57-59]

There is an increased risk of peritoneal carcinoma developing with follow-up after RRBSO if a STIC is present, which supports staging of the peritoneum.[60]

Recommendation 10.1: It is recommended that microscopic HGSC be managed as HGSC [V, B].

Consensus: 97% (38) yes, 3% (1) no, 0% (0) abstain (39 voters)

Recommendation 10.2: SEE-FIM is recommended in RRBSO [IV, A].

Consensus: 85.4% (35) yes, 0% (0) no, 14.6% (6) abstain (41 voters)

Recommendation 10.3: SEE-FIM is recommended when there is doubt regarding the origin of the carcinoma (endometrial, tubal, ovarian, peritoneal) [IV, A].

Consensus: 97% (38) yes, 0% (0) no, 3% (1) abstain (39 voters)

Recommendation 10.4: It is suggested that the pathologist examines microscopically the whole fimbriae in benign conditions [V, B].

Consensus: 87% (34) yes, 3% (1) no, 10% (4) abstain (39 voters)

Recommendation 10.5: In STIC, staging of the peritoneum is recommended [II, A].

Consensus: 97% (38) yes, 3% (1) no, 0% (0) abstain (39 voters)

Recommendation 10.6: In STIC, it is recommended that (re)-staging is carried out, preferably by a minimally invasive procedure [III, B].

Consensus: 92% (36) yes, 5% (2) no, 3% (1) abstain (39 voters)

Recommendation 10.7: In STIC, hysterectomy should be considered, particularly in patients with a g*BRCA1*-mut [IV, A].

Consensus: 82% (32) yes, 10% (4) no, 8% (3) abstain (39 voters)

Recommendation 10.8: In STIC, if the uterus is preserved, endometrial sampling in patients with a g*BRCA1*-mut is recommended [IV, B].

Consensus: 100% (39) yes, 0% (0) no, 0% (0) abstain (39 voters)

Recommendation 10.9: In STIC, lymphadenectomy is not recommended [V, E].

Consensus: 95% (37) yes, 0% (0) no, 5% (2) abstain (39 voters)

Recommendation 10.10: Adjuvant ChT is not recommended in surgically staged STIC [IV, D].

Consensus: 100% (39) yes, 0% (0) no, 0% (0) abstain (39 voters)

Recommendation 10.11: In cases of STIC, testing for g*BRCA1/2*-muts and other high-penetrance hereditary genes is mandatory [II, A].

Consensus: 100% (39) yes, 0% (0) no, 0% (0) abstain (39 voters)

Advanced stage (including older/frail patients)

See Supplementary Material Section 3, available at https://doi.org/10.1016/j.annonc.2023.11.015, for detailed supporting evidence for these recommendations.

11. How should patients with advanced tubo-ovarian carcinoma be selected for primary cytoreductive surgery?

Evaluation for surgery. The standard treatment for the initial management of advanced tubo-ovarian carcinoma is primary cytoreductive surgery (PCS) or, in those not considered suitable for upfront surgery, NACT followed by ICS. Randomised trials have shown, although with some limitations, that in advanced-stage tubo-ovarian carcinoma, NACT had similar long-term survival to PCS and improved perioperative outcomes.[61-64] The outcome of patients undergoing PCS in these trials, however, was unfavourable compared with other studies.

Structured computed tomography (CT) imaging reports or diffusion-weighted MRI have been used to predict tumour load, localisation and the feasibility of complete resection.[65-67] Positron emission tomography (PET)—CT seems as accurate as CT in detecting disease spread, with a possible small advantage in detecting lymph node and distant metastases. PET—CT, however, seems to be less reliable than diffusion-weighted MRI for the detection of intraperitoneal metastases.[68,69]

Centres complying with ESGO quality indicators for advanced ovarian cancer surgery and perioperative management ensure that patients receive the appropriate treatment for their disease.[70,71] PCS is the preferred approach if a complete resection seems achievable with acceptable morbidity. These criteria are different for patients with LGSC. NACT is less effective in LGSC than in HGSC and cytoreduction to <1 cm (or optimal) is preferable to no surgery; a residual tumour ≤ 1 cm showed a significant advantage in progression-free survival (PFS) and overall survival (OS).[72]

Role of lymphadenectomy. The therapeutic value has been debated for a long time, but recent evidence from a large phase III randomised trial failed to show therapeutic benefit of systematic lymphadenectomy for patients with complete gross resection of peritoneal disease and non-suspicious lymph nodes both on preoperative imaging and intraoperative clinical evaluation.[73] Additional data have also shown that a comprehensive lymphadenectomy is of no benefit in patients with advanced ovarian cancer with rare histological subtypes.[74] The presence of cardiophrenic lymph nodes in advanced ovarian cancer is a negative prognostic factor, but the impact of resection of these lymph nodes on survival remains unknown.[75,76]

Recommendation 11.1: The selection of patients for PCS or NACT must be carried out in an accredited ovarian cancer centre (according to the ESGO quality indicators for ovarian cancer surgery 2016/2020) in a multidisciplinary setting [IV, A].

Consensus: 100% (39) yes, 0% (0) no, 0% (0) abstain (39 voters)

Recommendation 11.2: PCS is the preferred option and should be offered if a complete resection seems achievable [I, A].

Consensus: 100% (39) yes, 0% (0) no, 0% (0) abstain (39 voters)

Recommendation 11.3: PCS is the preferred option in patients with LGSC if residual disease <1 cm can be achieved [IV, B].

Consensus: 100% (39) yes, 0% (0) no, 0% (0) abstain (39 voters)

Recommendation 11.4: NACT with ICS is a valid alternative for patients with a low likelihood of initial complete resection and with chemosensitive histological types or for those who are poor surgical candidates due to medical conditions [I, A].

Consensus: 92% (36) yes, 5% (2) no, 3% (1) abstain (39 voters)

Recommendation 11.5: Patients should be medically assessed for surgery, and this should be based on clearly defined criteria requiring a thorough evaluation by a specialist in gynaecological oncology. Medically unfit patients should additionally receive an internal medicine and/or anaesthesiology evaluation. Eastern Cooperative Oncology Group and American Society of Anesthesiology scores must be documented [IV, A].

Consensus: 100% (39) yes, 0% (0) no, 0% (0) abstain (39 voters)

Recommendation 11.6: Candidates for surgery based on a multidisciplinary team (MDT) report should proceed to a laparotomy with the intent of complete cytoreduction [III, B].

Consensus: 97% (34) yes, 0% (0) no, 3% (1) abstain (35 voters)

Recommendation 11.7: Contrast-enhanced CT, MRI and PET—CT with a structured radiology report are considered as options for the initial evaluation of patients with advanced ovarian carcinoma [III, A]. US by an expert sonographer may be used to assess tumour extent and resectability in the pelvis and abdominal cavity [III, C].

Consensus: 100% (35) yes, 0% (0) no, 0% (0) abstain (35 voters)

Recommendation 11.8: Patients must be counselled for cytoreductive surgery by providing an extensive discussion about the risk and benefits of the procedure specifically for that patient and outlining a comprehensive list of potential perioperative major and minor complications [IV, A].

Consensus: 95% (37) yes, 3% (1) no, 3% (1) abstain (39 voters)

Recommendation 11.9: Patients for whom there is concern for incomplete cytoreductive surgery based on a structured radiology report may undergo a laparoscopic evaluation by a gynaecological oncologist to assess the extent of intra-abdominal disease [III, B].

Consensus: 92% (36) yes, 5% (2) no, 3% (1) abstain (39 voters)

Recommendation 11.10: Scoring systems may play a role in guiding the evaluation and ultimately triage patients for primary management. There is currently no universally accepted scoring system that could be recommended [III, C].

Consensus: 90% (35) yes, 10% (4) no, 0% (0) abstain (39 voters)

Recommendation 11.11: Currently, there are no specific validated biomarkers that are predictive of the success of surgical resection [IV, C].

Consensus: 97% (38) yes, 3% (1) no, 0% (0) abstain (39 voters)

Recommendation 11.12: Systematic pelvic and para-aortic lymphadenectomy should not be carried out in patients with advanced disease who have undergone intra-abdominal macroscopically complete resection and have non-suspicious lymph nodes both on preoperative imaging and intraoperative clinical evaluation [I, E].

Consensus: 100% (39) yes, 0% (0) no, 0% (0) abstain (39 voters)

Recommendation 11.13: Enlarged or suspicious lymph nodes should be removed to achieve complete resection [IV, A].

Consensus: 100% (38) yes, 0% (0) no, 0% (0) abstain (38 voters)

Recommendation 11.14: The impact of resection of suspicious or enlarged extra-abdominal lymph nodes remains unclear but should be considered if complete macroscopic resection can be achieved intra-abdominally [IV, C].

Consensus: 95% (37) yes, 3% (1) no, 3% (1) abstain (39 voters)

Recommendation 11.15: Resection of isolated parenchymal liver metastases should be considered to achieve a complete cytoreduction [IV, B].

Consensus: 100% (39) yes, 0% (0) no, 0% (0) abstain (39 voters)

12. What is the role of hyperthermic intraperitoneal ChT in newly diagnosed tubo-ovarian carcinoma?

One prospective trial of hyperthermic intraperitoneal ChT (HIPEC) demonstrated an improvement in recurrence-free survival and OS for patients with FIGO stage III tubo-ovarian carcinoma who received HIPEC at ICS.[77] The results of this trial have led to considerable discussion.[77-80] No consensus on the role of HIPEC and ICS was reached, which reflects the current difference in opinion among the participants.

13. Which patients should receive bevacizumab, maintenance therapy with PARPis or the combination of PARPis with bevacizumab and for how long?

In two randomised clinical trials, a statistically significant increase in PFS was seen when bevacizumab was added to paclitaxel—carboplatin first-line therapy followed by bevacizumab maintenance compared with ChT alone.[81,82]

Bevacizumab has shown activity in all tubo-ovarian carcinoma histotypes, including LGSC, and can be considered as a maintenance option in less-chemosensitive tumours.[83] The majority of LGSCs present elevated estrogen and progesterone receptor expression, and retrospective studies suggest that hormone therapy could have therapeutic value in the maintenance setting of newly diagnosed advanced LGSC.[84]

Up to 50% of HGSC cases are associated with homologous recombination deficiency (HRD).[85] Trials have shown a significant prolongation of PFS, greatest among patients with a tumour *BRCA*-mut, followed by patients with *BRCA*-wt HRD-positive tumours.[86] The PFS results in *BRCA*-wt HRD-negative tumours are less conclusive with some trials reporting a benefit[12,87] (rucaparib is not licensed in first-line use) and others showing no improvement.[13]

Recommendation 13.1: Molecular characteristics of tumour, patients and disease-related factors should be considered in the decision-making process for maintenance options [II, B].

Consensus: 100% (36) yes, 0% (0) no, 0% (0) abstain (36 voters)

Recommendation 13.2: The use of bevacizumab in combination with ChT and as maintenance is recommended independently from any biomarker [I, A].

Consensus: 89% (33) yes, 8% (3) no, 3% (1) abstain (37 voters)

Recommendation 13.3: Bevacizumab should be administered in combination with platinum—paclitaxel ChT and as maintenance for a maximum of 15 months [I, A].

Consensus: 97% (33) yes, 0% (0) no, 3% (1) abstain (34 voters)

Recommendation 13.4: Carcinosarcoma should be treated as HGSC [IV, A].

Consensus: 100% (36) yes, 0% (0) no, 0% (0) abstain (36 voters)

Recommendation 13.5: LGSC should be treated with paclitaxel—carboplatin ChT with or without bevacizumab [II, A]. ChT followed by maintenance with endocrine therapy is an option in stage III and IV tumours [IV, B].

Consensus: 85.4% (35) yes, 12.2% (5) no, 2.4% (1) abstain (41 voters)

Recommendation 13.6: Patients with HGSC/high-grade EC and *BRCA*-muts or genomic instability score (GIS)-positive (with a validated test) in complete response (CR)/partial response (PR)/no evidence of disease (NED) after platinum-based ChT with or without bevacizumab should receive PARPis with or without bevacizumab [I, A].

Consensus: 100% (37) yes, 0% (0) no, 0% (0) abstain (37 voters)

Recommendation 13.7: Patients with HGSC/high-grade EC without a *BRCA*-mut and who are GIS-negative (with a validated test) may receive platinum-based ChT in combination with bevacizumab followed by bevacizumab maintenance or platinum-based ChT followed by niraparib or rucaparib if in CR/PR/NED [I, B]. No maintenance treatment might be an option [I, C].

Consensus: 97% (36) yes, 0% (0) no, 3% (1) abstain (37 voters)

Recommendation 13.8: Patients with HGSC/high-grade EC without a *BRCA*-mut and GIS unknown could receive platinum-based ChT in combination with bevacizumab followed by bevacizumab maintenance or platinum-based ChT followed by niraparib or rucaparib if in CR/PR/NED [I, B].

Consensus: 97% (35) yes, 0% (0) no, 3% (1) abstain (36 voters)

Recommendation 13.9: When used as maintenance in patients in CR/PR/NED to platinum-based ChT, olaparib (alone or in combination with bevacizumab) and rucaparib are recommended for 2 years, and niraparib is recommended for 3 years [I, A].

Consensus: 97% (34) yes, 0% (0) no, 3% (1) abstain (35 voters)

14. How should older/frail patients with tubo-ovarian carcinoma be investigated and treated?

Older patients are under-represented in clinical trials due to their poor performance status (PS) and comorbidities,[88] and their outcomes are poorer.[89] Geriatric assessment gathers information on functional, mental and nutritional status, emotional conditions and social support.[90] Vulnerability scores have been validated in clinical trials.[90,91]

Surgery, frequently carried out in an emergency context and in unspecialised centres, is often incomplete, with higher post-operative complications.[92] ChT may be underutilised.[93,94]

Recommendation 14.1: Patients should not be excluded from diagnostic procedures, clinical trials and specific treatments for tubo-ovarian carcinoma based only on chronological age [IV, D].

Consensus: 100% (35) yes, 0% (0) no, 0% (0) abstain (35 voters)

Recommendation 14.2: Vulnerability should be assessed in patients $\geq$70 years or any age with at least two comorbidities, if possible, with the support of a geriatric specialist [IV, A]. This assessment should focus on patient functions (activities of daily living/instrumental activities of daily living), nutrition, psychological well-being, comorbidities and concomitant medications [II, A] and should not delay the start of therapy [IV, A].

Consensus: 97% (35) yes, 0% (0) no, 3% (1) abstain (36 voters)

Recommendation 14.3: Whenever possible, considering vulnerability, complexity of surgery and patient motivation, primary complete surgery is recommended [III, B].

Consensus: 100% (36) yes, 0% (0) no, 0% (0) abstain (36 voters)

Recommendation 14.4: NACT can be considered as an alternative in patients with vulnerability and extensive disease [III, B].

Consensus: 97% (34) yes, 0% (0) no, 3% (1) abstain (35 voters)

Recommendation 14.5: The surgery should be carried out in expert centres involving scheduled surgery, pre-habilitation, intensive post-operative management, enhanced recovery and home care [IV, A].

Consensus: 97% (34) yes, 3% (1) no, 0% (0) abstain (35 voters)

Recommendation 14.6: The standard ChT regimen is paclitaxel—carboplatin every 3 weeks [I, A]. The continuous weekly paclitaxel 60 mg/m^2—carboplatin area under the curve (AUC) 2 schedule may provide better tolerability and quality of life (QoL) and can be considered as an alternative option [II, A].

Consensus: 92% (33) yes, 6% (2) no, 3% (1) abstain (36 voters)

Recommendation 14.7: When indicated, PARPis and/or bevacizumab should be offered to older patients carefully monitoring toxicity and concomitant medications [II, A].

Consensus: 97% (35) yes, 3% (1) no, 0% (0) abstain (36 voters)

Recurrent disease

See Supplementary Material Section 4, available at https://doi.org/10.1016/j.annonc.2023.11.015, for detailed supporting evidence for these recommendations.

15. What is the role of surgery in recurrent tubo-ovarian carcinoma?

The aims of surgery are either therapeutic cytoreduction or palliation. Two of three randomised trials of cytoreductive surgery at first relapse have shown an improvement in PFS, and one has shown an OS benefit in operated versus non-operated patients.[95-97]

No prospective randomised evidence exists regarding the evaluation of the benefit of cytoreductive surgery for subsequent relapses. Data are based on a multicentre retrospective series for tertiary and quaternary cytoreductive surgery.[98]

Palliative surgical intervention for bowel obstruction in peritoneally disseminated tubo-ovarian carcinoma is challenging. Surgical bypass or stoma formation and non-surgical therapies, such as bowel decompression,

endoscopic stent placements and percutaneous endoscopic gastrostomies, can be considered if conservative pharmacological management is not working. Surgical morbidity is high[99] and an MDT expert approach is crucial.

Oligometastatic disease (OMD) definitions vary according to tumour type and diagnostic method. The most frequent sites of OMD include lymph nodes, liver, spleen, lung, bone and brain.[100,101] The site of the disease is an important independent prognostic factor.[100] Surgery, infield radiotherapy (RT) and thermal ablation are all used for OMD.

Recommendation 15.1: Patients with tubo-ovarian carcinoma in first relapse >6 months since the end of first-line platinum-based ChT should be assessed for secondary cytoreductive surgery in a gynaecological oncology centre experienced in surgery for ovarian cancer [I, A].

Consensus: 100% (35) yes, 0% (0) no, 0% (0) abstain (35 voters)

Recommendation 15.2: Prospectively validated algorithms should be used as a guide to identify optimal candidates for secondary cytoreductive surgery with complete tumour resection [I, A].

Consensus: 100% (35) yes, 0% (0) no, 0% (0) abstain (35 voters)

Recommendation 15.3: NACT before cytoreductive surgery at relapse cannot be recommended outside of clinical trials [IV, D].

Consensus: 75.6% (31) yes, 9.8% (4) no, 14.6% (6) abstain (41 voters)

Recommendation 15.4: HIPEC is not recommended in cytoreductive surgery for relapsed disease [II, D].

Consensus: 97% (33) yes, 3% (1) no, 0% (0) abstain (34 voters)

Recommendation 15.5: Cytoreductive surgery could be offered to patients with subsequent relapses in whom complete resection appears feasible [III, B].

Consensus: 81% (29) yes, 8% (3) no, 11% (4) abstain (36 voters)

Recommendation 15.6: In selected patients, palliative surgery to relieve mechanical obstruction may be indicated after failure of conservative measures, either to remove the tumour obstructing the bowel or to carry out a diversion procedure such as a stoma [IV, B]. These patients should be managed within an MDT [IV, A].

Consensus: 97.6% (40) yes, 0% (0) no, 2.4% (1) abstain (41 voters)

Recommendation 15.7: Palliative surgery should be offered only after careful consideration in patients with unfavourable conditions, such as rapidly progressing disease without further systemic options, gastric outlet/upper gastrointestinal obstruction and multilevel sites of obstruction [IV, B].

Consensus: 92.7% (38) yes, 4.9% (2) no, 2.4% (1) abstain (41 voters)

Recommendation 15.8: For oligometastatic recurrence, several treatment modalities such as surgery, infield RT and thermal ablation should be considered within an MDT [IV, B].

Consensus: 97% (34) yes, 0% (0) no, 3% (1) abstain (35 voters)

Recommendation 15.9: The following factors should be considered to decide treatment modality for oligometastatic recurrence: site of recurrence, time to recurrence, number of lesions, treatment-related morbidity, patient PS, type of maintenance treatments and patient preferences, regardless of their *BRCA* status [IV, B].

Consensus: 100% (34) yes, 0% (0) no, 0% (0) abstain (34 voters)

Recommendation 15.10: After local ablative/surgical tumour management, continuation of maintenance treatment with the same regimen could be considered [IV, C].

Consensus: 94% (32) yes, 3% (1) no, 3% (1) abstain (34 voters)

16. What is the role of molecularly targeted therapy in recurrent disease?

The selection of molecularly targeted therapy with platinum-based therapy—currently bevacizumab or PARPis—is driven by biological factors, prior use of molecularly targeted therapy and regulatory approvals. Bevacizumab added to platinum-based ChT and continued as maintenance increases the tumour response rate and PFS without an OS benefit.

In randomised trials, PARPis significantly prolonged PFS in the recurrent setting, when given as maintenance after response to platinum until progression or unacceptable toxicity. This benefit was more pronounced in patients with a *BRCA*-mut but still relevant in patients with *BRCA*-wt tumours regardless of HRD status. Their use in recurrent disease is currently diminishing as they are now often used after first-line ChT (see Question 13). Second-line molecularly targeted therapy needs to take account of first-line treatment. Rechallenge with the same molecularly targeted drug is currently experimental and does not have regulatory approval. It is an area where more research is needed.

Patients on maintenance treatment should be monitored proactively to manage potential side-effects[102] and ensure a continued optimal clinical benefit.[103-106]

Recommendation 16.1: For patients with *BRCA*-mutated tumours, eligible for platinum and no prior PARPis and no prior bevacizumab use, a platinum-based combination followed by PARPis is recommended after CR/PR/NED [I, A]. Bevacizumab may still be considered depending on patient's symptoms and response to ChT [II, B].

Consensus: 94% (32) yes, 3% (1) no, 3% (1) abstain (34 voters)

Recommendation 16.2: For patients with *BRCA*-wt or unknown tumours eligible for platinum and no prior PARPis and no prior bevacizumab, maintenance therapy is recommended with PARPis (after CR/PR/NED) or bevacizumab. Bevacizumab added to ChT followed by maintenance should be prioritised for patients in need of rapid symptom control [I, A].

Consensus: 97% (34) yes, 0% (0) no, 3% (1) abstain (35 voters)

Recommendation 16.3: For patients eligible for platinum and no prior PARPis but prior bevacizumab, platinum-based ChT followed by PARPi maintenance is preferred as long as CR/PR/NED is achieved, regardless of their *BRCA* and HRD status [I, A].

Consensus: 97% (30) yes, 0% (0) no, 3% (1) abstain (31 voters)

Recommendation 16.4: For patients eligible for platinum and prior PARPis but no prior bevacizumab, a platinum-based combination with bevacizumab followed by maintenance should be recommended [I, A]. The preferred ChT partner for bevacizumab in the recurrent setting is carboplatin—pegylated liposomal doxorubicin (PLD) [I, A].

Consensus: 90% (27) yes, 3% (1) no, 7% (2) abstain (30 voters)

Recommendation 16.5: For patients eligible for platinum and prior use of bevacizumab and PARPis, a platinum-based ChT should still be recommended [I, B] and rechallenge options of maintenance agents could be considered (see recommendations 16.9, 16.11).

Consensus: 97% (29) yes, 0% (0) no, 3% (1) abstain (30 voters)

Recommendation 16.6: Monitoring of safety should be carried out according to drug-specific recommendations, with special focus on late safety issues [I, A].

Consensus: 100% (30) yes, 0% (0) no, 0% (0) abstain (30 voters)

Recommendation 16.7: Routine oncological follow-up is recommended including imaging and/or CA-125 according to local practice and after discussion with the patient [III, C].

Consensus: 97% (30) yes, 0% (0) no, 3% (1) abstain (31 voters)

Recommendation 16.8: In the recurrent setting, the duration of PARPis as maintenance should be until progressive disease or unacceptable toxicity [I, A].

Consensus: 100% (32) yes, 0% (0) no, 0% (0) abstain (32 voters)

Recommendation 16.9: Bevacizumab rechallenge in combination with platinum should be considered in patients already pre-treated with bevacizumab in the first line [I, A].

Consensus: 91% (29) yes, 6% (2) no, 3% (1) abstain (32 voters)

Recommendation 16.10: The preferred ChT partner for bevacizumab (rechallenge) in the recurrent setting is carboplatin—PLD [I, A].

Consensus: 97% (29) yes, 0% (0) no, 3% (1) abstain (30 voters)

Recommendation 16.11: Patients in response to platinum-based ChT after prior PARPi maintenance therapy may be considered for a PARPi-maintenance rechallenge given a duration of prior PARPi exposure of 18 months in the first line and 12 months in further lines or 12 months and 6 months for patients with a *BRCA*-mut or *BRCA*-wt status, respectively [II, B].

Consensus: 94% (29) yes, 0% (0) no, 6% (2) abstain (31 voters)

17. What is the role of non-platinum drugs and supportive care options?

Non-platinum drugs and supportive care options are mainly used in patients not eligible for platinum rechallenge due to progression on platinum-based therapy or after a short treatment-free interval (TFI). The prognosis of these patients is poor and the main treatment objectives are symptom palliation and maintenance of QoL. Non-platinum ChT is given alone or with bevacizumab.[107,108] In LGSC, endocrine therapy or trametinib is used.[50] The efficacy of available therapies is limited and patients should be offered participation in new clinical trials when possible.[109]

There are no validated predictive factors to identify patients who may benefit from palliative ChT. Low baseline global health status, poor physical function and the presence of abdominal/gastrointestinal symptoms are predictors of early discontinuation.

Recommendation 17.1: For patients progressing on platinum-based therapy or after a short TFI or for those who are intolerant of platinum and not eligible for platinum rechallenge, various management options should be considered, ranging from non-platinum single-agent systemic therapy to supportive care alone [I, A].

Consensus: 97% (30) yes, 0% (0) no, 3% (1) abstain (31 voters)

Recommendation 17.2: Patients should be included in clinical trials, when possible, as there is a significant need for improved treatment options in this setting [IV, A].

Consensus: 100% (41) yes, 0% (0) no, 0% (0) abstain (41 voters)

Recommendation 17.3: For patients who have not received prior bevacizumab, the addition of this agent to weekly paclitaxel, PLD or topotecan should be considered [I, A]. The combination of weekly paclitaxel and bevacizumab is the preferred option based on trial subset analysis [II, A].

Consensus: 87% (26) yes, 3% (1) no, 10% (3) abstain (30 voters)

Recommendation 17.4: The combination of trabectedin and PLD could be considered in those patients who are intolerant to platinum who have relapsed after 6 months from the last platinum dose [II, C].

Consensus: 77% (24) yes, 16% (5) no, 6% (2) abstain (31 voters)

Recommendation 17.5: Patients with LGSC relapse should be considered for treatment with trametinib after platinum failure [I, A] or for endocrine therapy [II, A].

Consensus: 97% (30) yes, 0% (0) no, 3% (1) abstain (31 voters)

Recommendation 17.6: Supportive care alone should be considered when expected benefit of ChT is limited [III, A].

Consensus: 100% (30) yes, 0% (0) no, 0% (0) abstain (30 voters)

Recommendation 17.7: Systematic assessment of QoL and symptoms during treatment is recommended to start early supportive care and prevent or improve symptoms, QoL and survival [III, A].

Consensus: 88% (28) yes, 9% (3) no, 3% (1) abstain (32 voters)

18. What is recommended regarding evaluation of QoL/ survivorship issues and follow-up after treatment?

Treatment and tumour-related symptoms are often underestimated and can be present during treatment and follow-up. Symptoms and QoL should be assessed as early as possible and patients should have access to early supportive care which may improve symptoms, QoL and survival. This includes psycho-oncology, social care, physiotherapy and patient support groups.

Oncological follow-up aims to detect recurrence and/or secondary cancers, monitor QoL, manage iatrogenic toxicity and provide holistic supportive care.

There is no standard protocol or frequency for follow-up. A reasonable approach involves patient assessment every 3-4 months for the first 2 years and every 6 months during years 3-5. Follow-up may be individualised according to prognostic factors and treatment modalities, e.g. maintenance therapy. Follow-up beyond 5 years should be discussed individually.[110,111]

Recommendation 18.1: QoL and symptom assessment via validated tools could be considered as part of the routine follow-up in all patients with ovarian carcinoma [IV, C].

Consensus: 96% (26) yes, 0% (0) no, 4% (1) abstain (27 voters)

Recommendation 18.2: Long-term follow-up is recommended for all patients with tubo-ovarian carcinoma by a physician experienced in the treatment and follow-up of patients with gynaecological cancer [III, A].

Consensus: 90% (27) yes, 10% (3) no, 0% (0) abstain (30 voters)

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