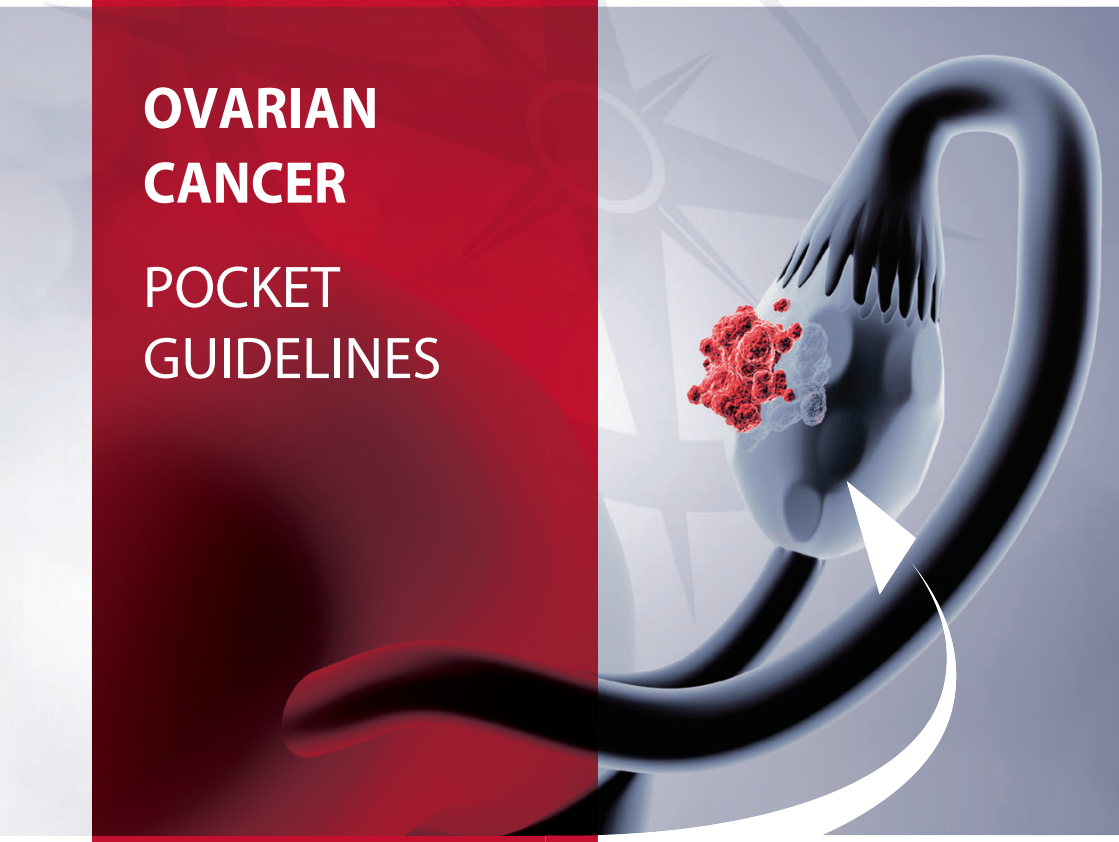
ESGO Guidelines
and Quality Indicators

OVARIAN CANCER

POCKET GUIDELINES



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ESGO
European Society of Gynaecological Oncology

POCKET GUIDELINES

Based on

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

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The development of guidelines 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, another CC took place on 15-16 June 2022 in Valencia, Spain. Pathology expertise was added by including ESP. Following the ESMO Standard Operating Procedures (SOPs) for CC, the aim was to discuss new or contentious topics and develop recommendations to improve and harmonise the management of patients with ovarian cancer.

The need for a CC was identified by the ESGO and ESMO Guidelines Committees. A. Fagotti (ESGO), J. Ledermann (ESMO) and X. 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 United States of America to four working groups (WGs) based on their expertise, ensuring good representation across the three societies. An ESMO scientific advisor and a methodologist (ESGO) were also included in the CC panel. Two WG Chairs for each WG were nominated by the CC Chairs as follows:

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-Martín).

Literature search was conducted by the ESGO methodologist using the Medline® database to ensure that the recommendations were evidence-based. Prior the CC, the WGs discussed published data and clinical experience and drafted recommendations. Organisation of the pre-consensus process and onsite conference was managed by the ESMO Guidelines staff.

During the CC, the four WGs further discussed and agreed on the draft recommendations in parallel sessions. These were presented to the entire panel before voting, where they were discussed and modified as required. Forty individuals were eligible to vote on recommendations (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. The ESGO methodologist and the ESMO scientific advisor did not participate in the voting of recommendations. Voting was anonymous. Members could abstain from voting if they perceived that they had insufficient expertise or a conflict of interest.

For recommendations 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, Developmentand Evaluation (GRADE) methodology, described in the ESMO SOPs. The aim was to provide further insight into the division of opinions to illustrate the extent to which consensus was/was not likely.

An adapted version of the 'Infectious Diseases Society of America-United States Public Health Service Grading System' was used to define the level of evidence and grade of recommendation for each recommendation proposed, based on the data available up to the time of the CC:

LEVELS OF EVIDENCE

I Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well conducted, randomised trials without heterogeneity

II Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity

III Prospective cohort studies

IV Retrospective cohort studies or case-control studies

V Studies without control group, case reports, expert opinions

GRADES OF RECOMMENDATIONS

A Strong evidence for efficacy with a substantial clinical benefit, strongly recommended

B Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended

C Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs…), optional

D Moderate evidence against efficacy or for adverse outcome, generally not recommended

E Strong evidence against efficacy or for adverse outcome, never recommended

These ESGO-ESMO-ESP CC recommendations are intended for use by all health professionals involved in the management of patients with ovarian cancer across all allied disciplines. They do not include any economic analysis of the strategies. Any clinician seeking to apply or consult these CC recommendations is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment.

ESGO would like to thank all the participants of the ESGO-ESMO-ESP CC for their constant availability, work, and for making possible the development of these CC recommendations on ovarian cancer (see below).

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Pathology and molecular biology

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

A	An adequate surgical specimen or image-guided biopsy of treatment-naive tumour is the preferred sample for diagnosis and molecular testing.
B	In all cases, the sample should contain a sufficient number of tumour cells (preferably ≥30%). A cell block from peritoneal or pleural effusions may be used for molecular analysis.
A	*BRCA*-mut (germline and/or somatic) testing is recommended at diagnosis for patients with high-grade non-mucinous tubo-ovarian carcinoma regardless of stage.
B	Routine tumour testing for non-*BRCA* homologous recombination gene mutations is not required; however, it should be encouraged in the research setting.
A	Genomic instability tests are recommended in patients with *BRCA* wild-type (wt) high-grade non-mucinous International Federation of Gynecology and Obstetrics stage III-IV tubo-ovarian carcinoma at diagnosis as this provides useful predictive information for first-line maintenance therapy decisions.
B A	A genomic instability test that has been clinically validated in large cohorts or, preferably, phase III trials should be used.
A	There are no validated predictive markers of primary resistance to platinum or poly (ADP-ribose) polymerase inhibitors (PARPis) at diagnosis and none can be recommended at present.
E	General population screening for tubo-ovarian carcinoma cannot be recommended because screening does not reduce cancer deaths.
D	CA-125 with or without HE4 should not be used alone to differentiate between benign, borderline and malignant ovarian tumours.

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

A	Routine monitoring of CA-125 after completion of first-line chemotherapy is an option that should be discussed with the patient.
B	The CA-125 ELIMination rate constant K 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.

A Routine monitoring for circulating tumour DNA (ctDNA) and circulating tumour cells is not recommended but should be encouraged within the context of research projects.

C 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.

B Chemotherapy response score at interval cytoreductive surgery on an omental (preferred) or adnexal specimen provides prognostic information and is recommended.

C Testing for a reversion mutation in tumour samples at relapse can be considered in *BRCA*-mutated tumours.

3. How should low-grade serous carcinoma (LGSC) and high-grade serous carcinoma (HGSC) be diagnosed?

A 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.

A The distinction between LGSC and HGSC is based on a combination of morphology and p53 immunohistochemistry (IHC); in diagnostically challenging cases, referral for a specialist opinion and/or molecular testing is recommended.

A 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.

A In designating the primary site of extrauterine HGSC, the recommendations of the International Collaboration on Cancer Reporting should be followed.

A Staining for Wilms tumour protein (WT-1) is recommended when the primary origin of HGSC (adnexal versus uterine) is unclear.

A Results of p53 IHC should be reported as 'wt or normal' or 'mutation-type or aberrant' rather than positive or negative.

A As a minimum, paired box 8, oestrogen receptor, WT-1 and p53 IHC should be carried out on diagnostic biopsies with a morphological suspicion of LGSC or HGSC.

C Testing for *HER2* status in mucinous carcinoma can be considered to identify patients who may benefit from *HER2*-targeted strategies.

C Testing for *KRAS* and *BRAF* mutational status in LGSC can be considered to identify patients who may benefit from targeted strategies.

4. What is the role of molecular classification in ovarian endometrioid carcinoma (EC) and clear-cell carcinoma (CCC)?

B A TCGA-based molecular classification as used for endometrial carcinomas can be considered to stratify ovarian EC.

D Molecular markers are not recommended for prognostication in ovarian CCC.

A DNA mismatch repair IHC and/or microsatellite instability testing is recommended in ovarian EC and CCC.

Early-stage disease and pelvic mass in pregnancy

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

A It is recommended to evaluate all patients with suspicious adnexal masses during pregnancy at a specialist referral centre.

A Ultrasound by an expert is the recommended first-line imaging procedure when an adnexal mass is diagnosed during pregnancy.

A Magnetic resonance imaging (MRI) is recommended as a second stage test for the characterisation of indeterminate ovarian masses.

E The routine use of beta-human chorionic gonadotropin and alpha-fetoprotein is not recommended during pregnancy.

A A proactive surgical approach depending upon gestational age is recommended in cases of high risk for malignancy during pregnancy.

A Where needed, platinum-based chemotherapy at the same dosage as in non-pregnant women is recommended as standard chemotherapy after the first trimester of pregnancy.

B Paclitaxel can also be administered to pregnant women.

A Pregnant patients who receive chemotherapy for ovarian carcinoma need follow-up in high-risk obstetric units.

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

A The option of fertility-sparing surgery should be discussed in young patients with early-stage ovarian carcinoma.

A Women with ovarian carcinoma who want to preserve their fertility need to be managed in an oncofertility clinic.

A Subjective assessment of the adnexal mass by an ultrasound 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.

A 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.

A Minimally invasive surgery avoiding tumour rupture is an acceptable approach for women who wish to preserve their fertility.

E It is not recommended to biopsy the unaffected ovary unless there is suspicion of involvement.

A In patients who wish to retain their fertility, cryopreservation of gametes rather than ovarian tissue is recommended.

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

A 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.

A Patients with stage I-II high-grade EC should be offered adjuvant platinum-based chemotherapy.

C Adjuvant chemotherapy may be omitted for adequately staged IA or IB CCC.

C Adjuvant chemotherapy may be considered for stage IC1 CCC.

A Adjuvant chemotherapy is recommended for stages IC2, IC3 and II CCC.

A Patients with high-risk stage I-II mucinous ovarian carcinoma should be offered adjuvant platinum-based chemotherapy.

8. How should ovarian serous borderline tumours with peritoneal implants be managed?

A Since the pathological analysis of implants is complex, it is recommended that the histological review of specimens is carried out by an expert pathologist.

A It is recommended to manage women with stage II-III ovarian serous borderline tumours at a specialist centre.

A It is recommended to keep the distinction between invasive and non-invasive implants for subsequent management.

A It is recommended to surgically resect peritoneal and omental disease to differentiate invasive from non-invasive implants.

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

A It is recommended to completely remove all peritoneal implants combined with peritoneal staging as a standard treatment procedure.

A Removal of enlarged or suspicious lymph nodes is recommended without routine systematic lymphadenectomy.

C Adjuvant chemotherapy could be considered for stage II LGSC.

C Endocrine treatment following chemotherapy could be considered for stage II LGSC.

10. How should incidental serous tubal intraepithelial carcinoma (STIC) or microscopic HGSC be managed?

B It is recommended that microscopic HGSC be managed as HGSC.

A Sectioning and Extensively Examining the FIMbriated end (SEE-FIM) is recommended in risk-reducing bilateral salpingo-oophorectomy.

A SEE-FIM is recommended when there is doubt regarding the origin of the carcinoma (endometrial, tubal, ovarian, peritoneal).

B It is suggested that the pathologist examines microscopically the whole fimbriae in benign conditions.

A In STIC, staging of the peritoneum is recommended.

B — In STIC, it is recommended that (re)-staging is carried out, preferably by a minimally invasive procedure.

A — In STIC, hysterectomy should be considered, particularly in patients with a germline *BRCA1* mutation (g*BRCA1*-mut).

B — In STIC, if the uterus is preserved, endometrial sampling in patients with a g*BRCA1*-mut is recommended.

E — In STIC, lymphadenectomy is not recommended.

D — Adjuvant chemotherapy is not recommended in surgically staged STIC.

A — In cases of STIC, testing for g*BRCA1/2*-muts and other high-penetrance hereditary genes is mandatory.

Advanced stage (including older/frail patients)

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

A — The selection of patients for primary cytoreductive surgery or neoadjuvant chemotherapy (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.

A — Primary cytoreductive surgery is the preferred option and should be offered if a complete resection seems achievable.

B — Primary cytoreductive surgery is the preferred option in patients with LGSC if residual disease <1 cm can be achieved.

A — NACT with interval cytoreductive surgery 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.

A — 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.

B — Candidates for surgery based on a multidisciplinary team (MDT) report should proceed to a laparotomy with the intent of complete cytoreduction.

A

C

Contrast-enhanced computed tomography, MRI and positron emission tomography-computed tomography with a structured radiology report are considered as options for the initial evaluation of patients with advanced ovarian carcinoma.
Ultrasound by an expert sonographer may be used to assess tumour extent and resectability in the pelvis and abdominal cavity

A

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.

B

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.

C

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.

C

Currently, there are no specific validated biomarkers that are predictive of the success of surgical resection.

E

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.

A

Enlarged or suspicious lymph nodes should be removed to achieve complete resection.

C

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.

B

Resection of isolated parenchymal liver metastases should be considered to achieve a complete cytoreduction.

12. What is the role of hyperthermic intraperitoneal chemotherapy (HIPEC) in newly diagnosed tubo-ovarian carcinoma?

No consensus on the role of HIPEC and interval cytoreductive surgery 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?

B	Molecular characteristics of tumour, patients and disease-related factors should be considered in the decision-making process for maintenance options.
A	The use of bevacizumab in combination with chemotherapy and as maintenance is recommended independently from any biomarker.
A	Bevacizumab should be administered in combination with platinum-paclitaxel chemotherapy and as maintenance for a maximum of 15 months.
A	Carcinosarcoma should be treated as HGSC.
A B	LGSC should be treated with paclitaxel-carboplatin chemotherapy with or without bevacizumab. Chemotherapy followed by maintenance with endocrine therapy is an option in stage III and IV tumours.
A	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 chemotherapy with or without bevacizumab should receive PARPis with or without bevacizumab.
B C	Patients with HGSC/high-grade EC without a *BRCA*-mut and who are GIS--negative (with a validated test) may receive platinum-based chemotherapy in combination with bevacizumab followed by bevacizumab maintenance or platinum-based chemotherapy followed by niraparib or rucaparib if in CR/PR/NED. No maintenance treatment might be an option.
B	Patients with HGSC/high grade EC without a *BRCA*-mut and GIS unknown could receive platinum-based chemotherapy in combination with bevacizumab followed by bevacizumab maintenance or platinum-based chemotherapy followed by niraparib or rucaparib if in CR/PR/NED.
A	When used as maintenance in patients in CR/PR/NED to platinum-based chemotherapy, olaparib (alone or in combination with bevacizumab) and rucaparib are recommended for 2 years, and niraparib is recommended for 3 years.

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

D	Patients should not be excluded from diagnostic procedures, clinical trials and specific treatments for tubo-ovarian carcinoma based only on chronological age.
A	Vulnerability should be assessed in patients 70 years or any age with at least two comorbidities, if possible, with the support of a geriatric specialist. This assessment should focus on patient functions (activities of daily living/instrumental activities of daily living), nutrition, psychological well-being, comorbidities and concomitant medications and should not delay the start of therapy.
B	Whenever possible, considering vulnerability, complexity of surgery and patient motivation, primary complete surgery is recommended.
B	NACT can be considered as an alternative in patients with vulnerability and extensive disease.
A	The surgery should be carried out in expert centres involving scheduled surgery, prehabilitation, intensive post-operative management, enhanced recovery and home care.
A	The standard chemotherapy regimen is paclitaxel-carboplatin every 3 weeks. 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.
A	When indicated, PARPis and/or bevacizumab should be offered to older patients carefully monitoring toxicity and concomitant medications.

Recurrent disease

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

A	Patients with tubo-ovarian carcinoma in first relapse >6 months since the end of first-line platinum-based chemotherapy should be assessed for secondary cytoreductive surgery in a gynaecological oncology centre experienced in surgery for ovarian cancer.
A	Prospectively validated algorithms should be used as a guide to identify optimal candidates for secondary cytoreductive surgery with complete tumour resection.
D	NACT before cytoreductive surgery at relapse cannot be recommended outside of clinical trials.
D	HIPEC is not recommended in cytoreductive surgery for relapsed disease.
B	Cytoreductive surgery could be offered to patients with subsequent relapses in whom complete resection appears feasible.
B A	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. These patients should be managed within an MDT.
B	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.
B	For oligometastatic recurrence, several treatment modalities such as surgery, infield radiotherapy and thermal ablation should be considered within an MDT.
B	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 performance status, type of maintenance treatments and patient preferences, regardless of their *BRCA* status.
C	After local ablative/surgical tumour management, continuation of maintenance treatment with the same regimen could be considered.

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

A B	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. Bevacizumab may still be considered depending on patient's symptoms and response to chemotherapy.
A	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 chemotherapy followed by maintenance should be prioritised for patients in need of rapid symptom control.
A	For patients eligible for platinum and no prior PARPis but prior bevacizumab, platinum-based chemotherapy followed by PARPi maintenance is preferred as long as CR/PR/NED is achieved, regardless of their *BRCA* and HRD status.
A	For patients eligible for platinum and prior PARPis but no prior bevacizumab, a platinum-based combination with bevacizumab followed by maintenance should be recommended. The preferred chemotherapy partner for bevacizumab in the recurrent setting is carboplatin-pegylated liposomal doxorubicin (PLD).
B	For patients eligible for platinum and prior use of bevacizumab and PARPis, a platinum-based chemotherapy should still be recommended and rechallenge options of maintenance agents could be considered.
A	Monitoring of safety should be carried out according to drug-specific recommendations, with special focus on late safety issues.
C	Routine oncological follow-up is recommended including imaging and/or CA-125 according to local practice and after discussion with the patient.
A	In the recurrent setting, the duration of PARPis as maintenance should be until progressive disease or unacceptable toxicity.
A	Bevacizumab rechallenge in combination with platinum should be considered in patients already pre-treated with bevacizumab in the first line.
A	The preferred chemotherapy partner for bevacizumab (rechallenge) in the recurrent setting is carboplatin-PLD.
B	Patients in response to platinum-based chemotherapy 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.

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

A	For patients progressing on platinum-based therapy or after a short treatment-free interval 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.
A	Patients should be included in clinical trials, when possible, as there is a significant need for improved treatment options in this setting.
A	For patients who have not received prior bevacizumab, the addition of this agent to weekly paclitaxel, PLD or topotecan should be considered. The combination of weekly paclitaxel and bevacizumab is the preferred option based on trial subset analysis.
C	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.
A	Patients with LGSC relapse should be considered for treatment with trametinib after platinum failure or for endocrine therapy.
A	Supportive care alone should be considered when expected benefit of chemotherapy is limited.
A	Systematic assessment of QoL and symptoms during treatment is recommended to start early supportive care and prevent or improve symptoms, QoL and survival.

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

C	QoL and symptom assessment via validated tools could be considered as part of the routine follow-up in all patients with ovarian carcinoma.
A	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.

NOTES

Access full ESGO Guidelines: www.esgo.org/explore/guidelines

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