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SPECIAL ARTICLE

Newly diagnosed and relapsed epithelial ovarian cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up☆

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Available online 17 August 2023

Key words: epithelial ovarian cancer, guideline, diagnosis, surgery, treatment, follow-up

INCIDENCE AND EPIDEMIOLOGY

Epithelial ovarian cancer (EOC) represents a heterogeneous spectrum of disease entities at a clinical, pathological and molecular level. Ovarian cancer is the second most lethal gynaecological malignancy worldwide behind cervical cancer and the first in developed countries, with ∼200 000 women dying globally in 2020.[1] A study of epidemiological trends from 1990 to 2019 showed that highly developed regions had the highest burden and mortality.[2]

Infertility or nulliparity, estrogen hormone treatment and obesity have been reported as risk factors for EOC and could account for the rising incidence of the disease in developed countries.[3] Oral contraceptive use, especially over longer periods, and breastfeeding can reduce incidence.[4] A recent large study revealed significant heterogeneity of associations for 14 EOC risk factors across histological subtypes.[3] Higher parity, younger age at menopause and tubal ligation were most strongly associated with reduced risk in endometrioid carcinomas (ECs) and clear-cell carcinomas (CCCs), while endometriosis was associated with an increased risk in both EOC subtypes.[3] Serous and poorly differentiated carcinomas had modest associations with parity and menopausal hormonal therapy use and stronger associations with a family history of ovarian cancer.[3] Deleterious germline *BRCA1/2* mutations (g*BRCA1/2*-muts) are associated with a 16%-65% increased risk of EOC, predominantly of high-grade serous histology.[5] Women with mutations in mismatch repair genes (Lynch syndrome) have a 10%-12% lifetime risk of developing EOC, which tends to be of either EC or CCC subtype.[6]

DIAGNOSIS, PATHOLOGY AND MOLECULAR BIOLOGY

Diagnostic work-up

There is currently no reliable screening method for ovarian cancer. Most women are diagnosed based on symptoms, with the majority presenting at an advanced stage. Recognised symptoms include abdominal/pelvic pain, constipation, diarrhoea, urinary frequency, vaginal bleeding, abdominal distension and fatigue. In advanced disease, ascites and abdominal masses lead to bloating, nausea, anorexia, dyspepsia and early satiety. Extension of disease into the pleural cavities can produce effusions and respiratory symptoms.

The standard work-up for patients suspected of having EOC should include detailed history and clinical examination with relevant laboratory and imaging tests (Table 1). Measurement of serum cancer antigen 125 (CA-125) aids diagnosis and is elevated in ∼85% of patients with advanced disease. CA-125 is less useful in early-stage disease, as it is

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☆Note: Approved by the ESMO Guidelines Committee: April 2002, last update July 2023. This publication supersedes the previously published version—*Ann Oncol.* 2013;24(suppl 6):vi24-vi32.

Table 1. Diagnosis of EOC
Work-up if EOC is suspected
• Detailed history and clinical examination • Serum CA-125 • Serum CEA and CA 19-9, in the case of MC, and endoscopy, if either or both are elevated • Transabdominal and transvaginal US by expert examiner • CT of thorax, abdomen and pelvis • Pathological examination of adequate tumour sample from diagnostic biopsy or surgical specimen • Cytological assessment of pleural effusion if present

CA 19-9, carbohydrate antigen 19-9; CA-125, cancer antigen 125; CEA, carcinoembryonic antigen; CT, computed tomography; EOC, epithelial ovarian cancer; MC, mucinous carcinoma; US, ultrasound.

only elevated in ∼50% of International Federation of Gynecology and Obstetrics (FIGO) stage I cases. Elevated CA-125 is not specific to ovarian cancer and may be elevated in non-gynaecological malignancies and benign conditions (e.g. endometriosis and ovarian cysts).[7]

Measuring serum carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 levels in addition to CA-125 may help distinguish primary mucinous ovarian tumours from a gastrointestinal metastasis. In this scenario, endoscopies should be considered, especially if the CA-125/CEA ratio is $\leq$25/1.[8]

Initial imaging should comprise pelvic ultrasound (US; transabdominal and/or transvaginal) and computed tomography (CT) of the thorax, abdomen and pelvis to complete clinical staging and aid surgical planning. US-based diagnostic models [International Ovarian Tumor Analysis (IOTA) Simple Rules risk model or IOTA Assessment of Different NEoplasias in the adneXa (ADNEX) model] are preferable to CA-125, the human epididymis protein 4 (HE4) or the Risk of Ovarian Malignancy Algorithm, as they are superior in distinguishing between benign and malignant ovarian tumours and performed better than the Risk of Malignancy Index in a randomised controlled trial (RCT).[8]

A definitive diagnosis of ovarian cancer requires pathological examination by an expert pathologist of tumour samples from either a diagnostic biopsy or, preferably, a surgical specimen. An adequate amount of tissue, particularly if neoadjuvant chemotherapy (ChT) is planned, allows genetic tumour testing for therapeutic stratification. If a complete pathological response is achieved, sufficient viable tumour tissue may be unavailable for genetic testing following interval cytoreductive surgery (ICS). Cytological assessment of ascites (in early-stage disease) and of pleural fluid (if present and safely assessable) is required to complete staging.

Pathology and molecular biology

EOC represents the majority (∼90%) of ovarian malignancies. The 2020 World Health Organization (WHO) classification based on histopathology, immunohistochemistry (IHC) and molecular analysis recognises at least five distinct subtypes of malignant EOC: high-grade serous carcinoma (HGSC; 70% of cases), EC (10%), CCC (6%-10%), low-grade serous carcinoma (LGSC; 5%) and mucinous carcinoma (MC; 3%-4%), along with other rare entities including mesonephric-like carcinoma, mixed-cell tumour, malignant Brenner tumour, carcinosarcoma and undifferentiated carcinoma.[9] Each subtype represents a distinct disease entity with a different site of origin, pathogenesis, clinical features and prognosis. The complexity of subclassification and its effect on personalised treatment choice underline the importance of histological tumour typing by an expert gynaecological pathologist. Details of the molecular features of HGSC, EC, CCC, LGSC and MC are provided in the Supplementary Material Section 1, available at https://doi.org/10.1016/j.annonc.2023.07.011. IHC staining patterns and molecular features of the different subtypes are summarised in Table 2. Certain genomic or molecular alterations, such as *BRCA1/2*-mut or homologous recombination deficiency (HRD), are helpful in predicting the magnitude of benefit of targeted therapy with poly (ADP-ribose) polymerase inhibitors (PARPis) in high-grade tumours.[10]

Recommendations

- If EOC is suspected, diagnostic work-up should include serum CA-125 measurement, pelvic US by an expert examiner and CT scan of the thorax, abdomen and pelvis [III, A].
- Pathological diagnosis should be made according to the 2020 WHO classification by an expert gynaecological pathologist [IV, A].
- All patients with high-grade ovarian cancer should be tested for germline and/or somatic *BRCA1/2*-muts at diagnosis [I, A].
- Testing for HRD is recommended in advanced high-grade cancers [I, A].

STAGING AND RISK ASSESSMENT

All patients with ovarian cancer should be surgically staged according to the revised 2014 FIGO staging system for EOC (Table 3).[11] The histotype and primary site (i.e. ovary, fallopian tube or peritoneum) of the tumour should be established and recorded as part of routine staging for treatment planning.

There is a strong prognostic link between the degree of postoperative residual disease and patient survival.[12] Preoperative imaging can help predict the likelihood of suboptimal cytoreductive surgery.[13] Extension of tumour from the omentum to the spleen or liver surface (stage IIIC) should be differentiated from isolated liver or spleen parenchymal metastases (stage IVB). CT and positron emission tomography (PET)—CT imaging have been shown to underestimate bowel or mesenteric involvement compared with surgical exploration.[14] Diffusion-weighted magnetic resonance imaging may have better sensitivity than CT for detecting involvement of surgically critical tumour sites including mesenteric root infiltration, small bowel and colon carcinomatosis.[15]

When the disease appears suitable for cytoreduction as assessed by imaging, and there are no surgical or medical

Table 2. Pathology and molecular biology of EOC subtypes

		HGSC	EC	CCC	LGSC	MC
IHC staining	p53	Abnormal	Abnormal/normal	Normal	Normal	Normal
	p16	+	−	−		
	WT-1	+	−	−	+	−
	ER	+/−	+	−	+	−
	PAX8	+	+		+	−
	Vimentin		+			
	HNF1β			+		
	CDX2					+
Molecular alterations (decreasing prevalence from top to bottom)		*TP53* *BRCA1/2* HRD	*CTNNB1* *ARID1A* *PTEN* *KRAS* *TP53* (high-grade EC) MSI/dMMR	*ARID1A* *PI3KCA* *PTEN* MSI/dMMR	*KRAS* *BRAF* *RAF*	*CDKN2A* *KRAS* *HER2*

CCC, clear-cell carcinoma; CDX2, homeobox protein CDX-2; dMMR, mismatch repair deficiency; EC, endometrioid carcinoma; EOC, epithelial ovarian cancer; ER, estrogen receptor; HGSC, high-grade serous carcinoma; HNF1β, hepatocyte nuclear factor-1β; HRD, homologous recombination deficiency; IHC, immunohistochemistry; LGSC, low-grade serous carcinoma; MC, mucinous carcinoma; MSI, microsatellite instability; PAX8, paired box gene 8; WT-1, Wilms tumour 1.

contraindications, surgical staging (through midline laparotomy or initial laparoscopy) should be carried out to explore the extent of the disease in the abdominoperitoneal cavity and assess the likelihood of achieving optimal cytoreduction (no gross visible residual disease or complete resection).

Recommendations

- The revised 2014 FIGO staging system for EOC should be used [I, A].

MANAGEMENT OF EARLY EOC (FIGO STAGE I-II)

Figure 1 provides a treatment algorithm for the management of FIGO stage I-II EOC. Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2023.07.011, provides a summary of the benefit of adjuvant systemic therapy for FIGO stage I-II EOC.

Surgery

The aim of surgery for early EOC is complete resection of the tumour and to undertake adequate staging, including:

Table 3. FIGO staging system for EOC[11]

Stage I: Tumour confined to ovaries or fallopian tube(s)	
IA	Tumour limited to one ovary (capsule intact) or fallopian tube, without tumour on ovarian or fallopian tube surface and without malignant cells in the ascites or peritoneal washings
IB	Tumour limited to both ovaries (capsules intact) or fallopian tubes, without tumour on ovarian or fallopian tube surface and without malignant cells in the ascites or peritoneal washings
IC	Tumour limited to one or both ovaries or fallopian tubes, with any of the following:
IC1	Surgical spill
IC2	Capsule ruptured before surgery or tumour on ovarian or fallopian tube surface
IC3	Malignant cells in the ascites or peritoneal washings
Stage II: Tumour involves one or both ovaries or fallopian tubes with pelvic extension (below pelvic brim) or primary peritoneal cancer	
IIA	Extension and/or implants on uterus and/or fallopian tubes and/or ovaries
IIB	Extension to other pelvic intraperitoneal tissues
Stage III: Tumour involves one or both ovaries or fallopian tubes or primary peritoneal cancer, with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes	
IIIA1	Positive retroperitoneal lymph nodes only (cytologically or histologically proven):
IIIA1(i)	Metastasis $\leq$10 mm in greatest dimension
IIIA1(ii)	Metastasis $>$10 mm in greatest dimension
IIIA2	Microscopic extra-pelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes
IIIB	Macroscopic peritoneal metastasis beyond the pelvis $\leq$2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes
IIIC	Macroscopic peritoneal metastasis beyond the pelvis $>$2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes (includes extension of tumour to capsule of liver and spleen without parenchymal involvement of either organ)
Stage IV: Distant metastasis excluding peritoneal metastases	
IVA	Pleural effusion with positive cytology
IVB	Parenchymal metastases and metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)

EOC, epithelial ovarian cancer; FIGO, International Federation of Gynecology and Obstetrics.
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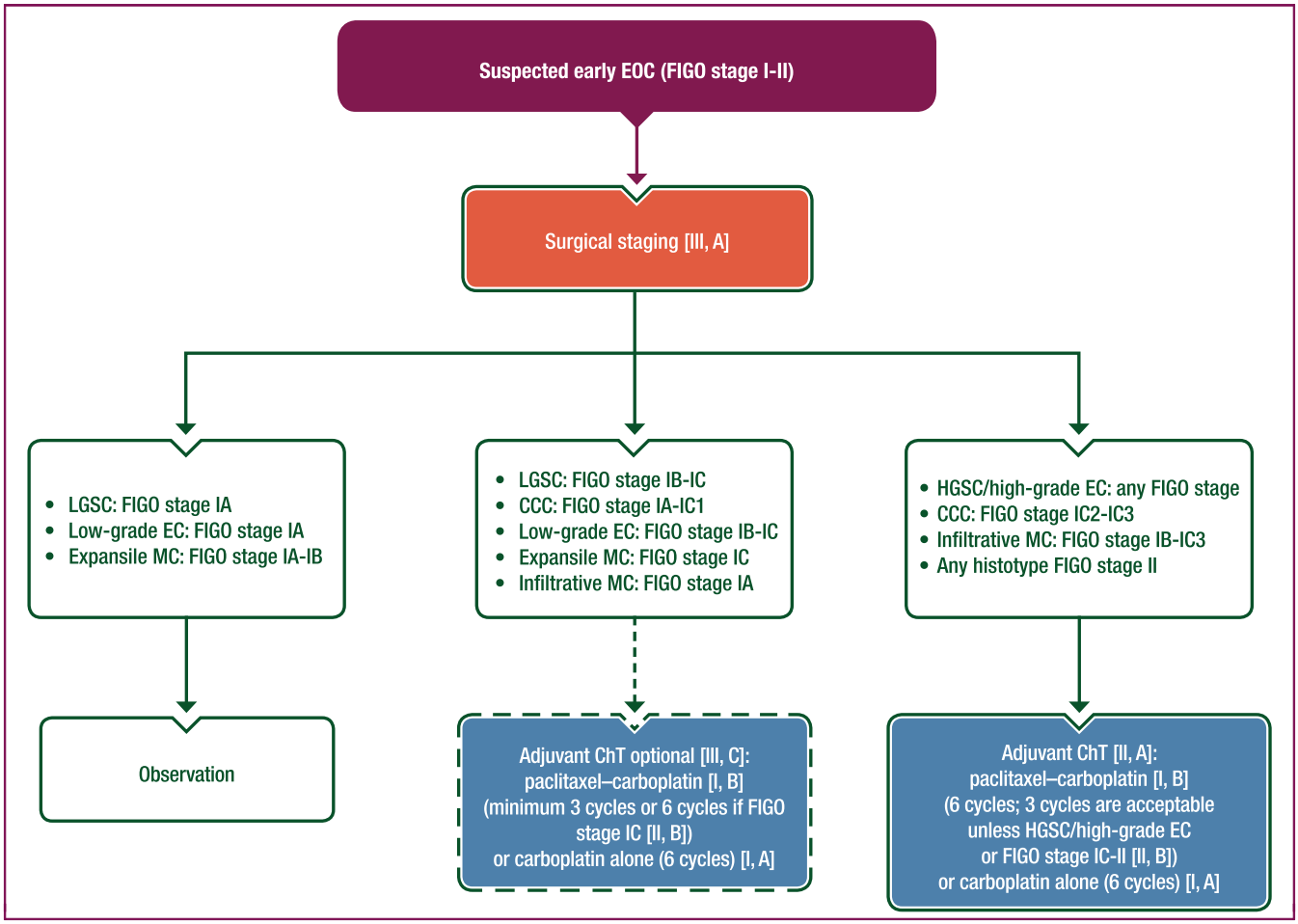

Figure 1. Management of early EOC (FIGO stage I-II).
See Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2023.07.011, for a summary of the benefit of adjuvant systemic therapy for early EOC (FIGO I-II stage).
Purple: general categories or stratification; red: surgery; blue: systemic anticancer therapy; white: other aspects of management; dashed lines: optional therapy.
CCC, clear-cell carcinoma; ChT, chemotherapy; EC, endometrioid carcinoma; EOC, epithelial ovarian cancer; FIGO, International Federation of Gynecology and Obstetrics; HGSC, high-grade serous carcinoma; LGSC, low-grade serous carcinoma; MC, mucinous carcinoma.

- Midline laparotomy
- Inspection and palpation of the whole abdominal cavity
- Peritoneal washing with cytological examination
- Biopsies from all visible lesions and all abdominal fields
- Bilateral salpingo-oophorectomy
- Hysterectomy
- Omentectomy
- Appendicectomy in MC
- Systematic pelvic and para-aortic lymphadenectomy

Whether a laparoscopic approach is a safe alternative to midline laparotomy is being debated, but as prospective trials are lacking and the risk of capsule rupture increases,[16] midline laparotomy remains the standard procedure. Surgical staging will provide prognostic information and define whether ChT is needed.

The availability of an intra-operative frozen section to identify a malignant epithelial cancer may allow the appropriate surgical staging to be done without the need for a second operative procedure. Depending on the histological grade and subtype, $\leq$60% of patients with apparent early EOC will be upstaged after comprehensive surgical staging, which can impact progression-free survival (PFS) and overall survival (OS).[17,18]

Systematic pelvic and para-aortic lymphadenectomy for staging purposes is recommended for high-grade histologies. The rate of lymph node metastases in patients with low-grade EC or expansile MC is $<$1%.[19] Therefore, lymphadenectomy could be omitted in patients with these subtypes and with radiologically and clinically negative nodes. Further information on the role of lymphadenectomy in stage I EOC is provided in the Supplementary Material Section 2, available at https://doi.org/10.1016/j.annonc.2023.07.011.

Fertility-sparing surgery can be considered in young patients, but always after full discussion with the patient about potential risks. Patients with any stage IA histotype or stage IC1-2 with unilateral ovarian involvement and favourable histology (i.e. low-grade tumours) would be amenable to contralateral ovary and uterus preservation, in combination with the other recommended surgical staging procedures.[20]

Systemic therapy

Adjuvant platinum-based ChT significantly prolongs OS and PFS in patients with early-stage EOC, as demonstrated in the joint analysis of ACTION and ICON1 trials and a

Cochrane systematic review.[21-23] An updated analysis showed the benefit of adjuvant ChT largely depended on histological subtype (see Figure 1 and Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2023.07.011).[22] A large Surveillance, Epidemiology and End Results series of stage I EC demonstrated no improvement in grade 1-2 EC.[24] In CCC, retrospective studies of an Asian population did not identify any benefit with adjuvant ChT for early-stage disease (stage IA-IC1).[25] In stage I MC, adjuvant ChT may be avoided for either expansile subtype or grade 1 infiltrative based on the excellent prognosis.[26]

The standard adjuvant ChT consists of six cycles of platinum-based ChT. A Gynecologic Oncology Group (GOG) trial comparing three versus six cycles of adjuvant paclitaxel—carboplatin did not identify a significant reduction in recurrence risk with longer treatment, but additional toxicity occurred.[27] Only serous carcinoma seems to benefit from longer adjuvant therapy compared with non-serous tumours.[28] The optimal ChT regimen (platinum alone or a platinum-based combination) is not completely resolved.[22]

Recommendations

- Surgical staging is recommended in presumed early-stage ovarian cancer for classification and recommendation of optimal systemic therapy [III, A].
- Adjuvant ChT in early-stage ovarian cancer is generally recommended for FIGO stage I-IIB (see exceptions below) [II, A], either paclitaxel—carboplatin [I, B] or carboplatin (six cycles) alone [I, A].
- For patients receiving paclitaxel—carboplatin, a minimum of three cycles are recommended except for HGSC/high-grade EC or any stage IC-II regardless of histotype, for which six cycles are suggested [II, B].
- The benefit of adjuvant ChT is uncertain and can be considered as optional [III, C] for:
  - o LGSC stage IB-IC
  - o CCC stage IA-IC1
  - o Low-grade EC stage IB-IC
  - o Expansile MC stage IC
  - o Infiltrative MC stage IA
- Adjuvant ChT is not recommended in completely staged patients with LGSC stage IA, low-grade EC stage IA or expansile MC stage IA-IB [II, E].

MANAGEMENT OF ADVANCED EOC (FIGO STAGE III-IV)

Surgery

In advanced EOC, surgery aims to achieve a complete or optimal cytoreduction, defined as total macroscopic tumour clearance with no residual visible disease, since this has been shown to significantly increase OS and PFS.[12] This needs maximal surgical effort and may require intestinal resection, diaphragmatic and peritoneal stripping, splenectomy and removal of bulky para-aortic lymph nodes and, in some cases, extra-abdominal disease.[29] An increasing body of evidence suggests that surgical expertise and specialist training result in improvements in the rate of complete cytoreduction. Thus, patients with advanced disease are advised to undergo surgery in specialised centres with adequate infrastructure and trained teams.[30] Patients with macroscopic complete resection and clinically negative nodes do not benefit from systematic lymphadenectomy, which unnecessarily increases the rate of post-operative complications and mortality.[31]

The timing of surgical cytoreduction in relation to ChT is still debated. The gold standard in patients with stage III-IV disease is primary cytoreductive surgery (PCS), if physically able to undergo surgery and complete resection seems achievable, followed by systemic treatment (Figure 2). PCS is also recommended in patients with less chemosensitive subtypes (e.g. MC or LGSC), even if uncertainty about achieving complete resection exists and a small residual tumour (<1 cm) is likely to remain.[32]

Prospective trials have shown that three cycles of platinum-based neoadjuvant ChT (NACT) followed by ICS and completion of ChT was not inferior to PCS followed by ChT in patients with advanced bulky stage IIIC or IV disease, for whom complete resection at primary surgery is unlikely or extensive surgery is not tolerable due to frailty or other significant comorbidities.[33,34] In all neoadjuvant trials, however, the PFS and OS were lower than in primary surgery trials. Due to the limitations of randomised NACT trials, it is not yet determined whether NACT and ICS could be an option for patients for whom complete resection at primary surgery seems feasible. This is being addressed in the TRUST/ENGOT-OV33/Arbeitsgemeinschaft Gynäkologische Onkologie (AGO)-OVAR OP.7 trial (NCT02828618).

Systemic therapy

Systemic ChT after surgery is recommended for all advanced ovarian cancer, and consideration should be given to the inclusion of antiangiogenic and maintenance therapies (Figure 2).

ChT. Standard ChT consists of six cycles of paclitaxel (175 mg/m^2)—carboplatin [area under the curve (AUC) 5-6] intravenously (i.v.) every 3 weeks.[35] Prolonging ChT for more than six cycles or adding a third drug does not result in a better outcome.[36] For patients with contraindications to paclitaxel (i.e. allergy, neuropathy or intolerance), combining carboplatin with docetaxel or pegylated liposomal doxorubicin (PLD) can be considered as an alternative.[37,38]

The improved PFS and OS seen in the Japanese dose-dense ChT trial[39] using weekly paclitaxel was not confirmed in a further three randomised trials (GOG-262,[40] ICON8[41] and MITO-7[42]). Outcomes were similar and ICON8 did not show differences in quality of life (QoL).[43] An improved QoL, however, was seen in MITO-7 using weekly carboplatin (AUC 2) and a lower weekly paclitaxel dose (60 mg/m^2), making this regimen a potential alternative for more frail patients.

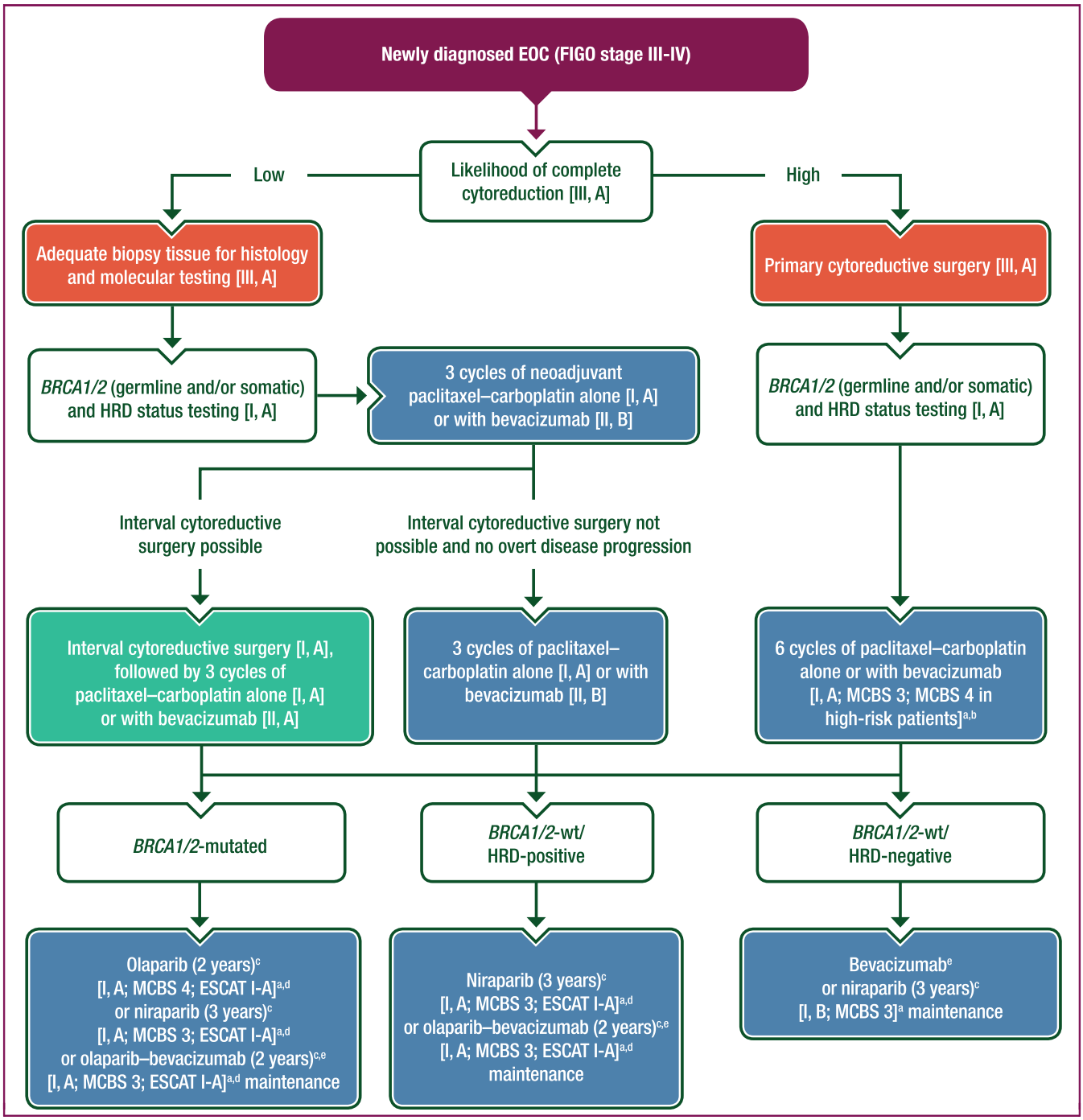

Figure 2. Management of advanced EOC (FIGO stage III-IV).

Purple: general categories or stratification; red: surgery; blue: systemic anticancer therapy; turquoise: combination of treatments or other systemic treatments; white: other aspects of management.

AUC, area under the curve; ChT, chemotherapy; EMA, European Medicines Agency; EOC, epithelial ovarian cancer; ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; FDA, Food and Drug Administration; FIGO, International Federation of Gynecology and Obstetrics; HRD, homologous recombination deficiency; MCBS, ESMO-Magnitude of Clinical Benefit Scale; PARPi, poly (ADP-ribose) polymerase inhibitor; wt, wild type.

[a]ESMO-MCBS v1.1[104] was used to calculate scores for new therapies/indications approved by the EMA or FDA. The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms).

[b]Weekly ChT with paclitaxel (60 mg/m^2)—carboplatin (AUC 2) can be an alternative in frail patients [I, B].

[c]Only when patients have complete or partial response to platinum or no evidence of disease. For patients without response to platinum, a PARPi is not indicated; these patients can be managed with bevacizumab maintenance if appropriate (mainly stable disease), or with second-line therapy if they have progressive disease (see Figure 3).

[d]ESCAT scores apply to alterations from genomic-driven analyses only. These scores have been defined by the guideline authors, assisted if needed by the ESMO Translational Research and Precision Medicine Working Group.[103] See Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2023.07.011, for more information on ESCAT scores.

[e]Option for patients for whom bevacizumab was added to paclitaxel—carboplatin.

A meta-analysis of five randomised trials[44] using post-operative intraperitoneal (i.p.) ChT reported a benefit in PFS and OS compared with i.v. ChT regimens in patients with a small volume (<1 cm) or no residual disease after surgery. Nevertheless, the negative results of the GOG-252 trial (a large randomised phase III trial comparing two i.p. platinum-based regimens, i.p. carboplatin AUC 6 or i.p. cisplatin 75 mg/m^2, with i.v. administration combined with bevacizumab),[45] together with the greater toxicity and complexity of i.p. administration, have led to the decline of this strategy as a standard of care.

Hyperthermic i.p. perioperative ChT (HIPEC) in first line has been explored in OVHIPEC, a randomised phase III trial comparing NACT followed by ICS with or without HIPEC.[46] The trial showed significantly longer PFS and OS without increased toxicity with HIPEC. Nevertheless, an imbalance of prognostic factors such as tumour histotype, the lack of stratification based on well-recognised prognostic factors such as tumour *BRCA1/2*-mut and HRD status and the limited sample size made it very difficult to extrapolate these results. In another randomised trial, HIPEC did not show survival superiority over standard treatment.[47] Given these concerns, HIPEC continues to be an area of research and should not be considered as standard therapy.

Antiangiogenic therapy in the first line. Bevacizumab is a monoclonal antibody targeting vascular endothelial growth factor (VEGF). Two large RCTs, GOG-218[48] and ICON7,[49] showed that the addition of bevacizumab to paclitaxel—carboplatin first-line therapy followed by bevacizumab as maintenance resulted in a statistically significant increase in PFS versus ChT alone, but without an OS benefit. A *post hoc* subgroup analysis suggested a greater benefit in PFS and OS in the clinical 'high-risk' population (defined as patients with stage III and macroscopic residual tumour >1 cm or stage IV).[50] In ICON7 the dose of bevacizumab was 7.5 mg/kg and the duration of treatment was shorter (12 months). Although this lower dose is used by some, the licensed dose of bevacizumab is 15 mg/kg given for 15 months in combination with first-line paclitaxel—carboplatin ChT to patients with stage IIIB-IV (FIGO 1988 classification) ovarian cancer, regardless of histology. In the ENGOT-OV15 study, a longer duration of bevacizumab administration (30 versus 15 months) did not improve PFS.[51]

Bevacizumab in combination with NACT has been explored in two small randomised trials, ANTHALYA and GEICO 1205/NOVA.[52,53] Although no increase in grade 3-4 toxicities compared with ChT alone was reported, the potential benefit of two to three doses of bevacizumab before ICS is debatable due to its lack of impact on complete resection rate and PFS.

HRD and PARPis. Up to 50% of HGSCs are detected as HRD-positive with current tests. Included in these are 15%-20% of g*BRCA1/2*-mut cases. Somatic *BRCA1/2*-muts, epigenetic silencing via hypermethylation of the *BRCA1* promoter and deficiency in other proteins and pathways involved in the homologous recombination repair of DNA double-strand breaks contribute to the remainder of positive tests.[54] HRD positivity with or without *BRCA1/2*-mut is a well-established predictive factor of the magnitude of response to PARPis. The incorporation of PARPis as maintenance after first-line ChT has led to a new era in the first-line management of advanced HGSC/high-grade EC with unprecedented benefit in patients with *BRCA1/2*-mutated or *BRCA1/2*-wild type (wt)/HRD-positive tumours. Supplementary Material Section 3, available at https://doi.org/10.1016/j.annonc.2023.07.011, provides detailed information on the SOLO1,[55] PAOLA-1/ENGOT-OV25[56] and PRIMA/ENGOT-OV26/GOG-3012[57] trials, which led to the approval of olaparib in *BRCA1/2*-mutated tumours, olaparib—bevacizumab in HRD-positive tumours and niraparib regardless of biomarker status of the tumour, respectively. The results of the ATHENA-MONO/GOG-3020/ENGOT-OV45[58] and VELIA[59] trials with rucaparib and veliparib, respectively, are also described.

A descriptive OS analysis of SOLO1 at 7-year follow-up[60] and the final OS analysis of PAOLA-1[61] have shown a benefit in OS for olaparib in patients with *BRCA1/2*-mutated tumours and olaparib—bevacizumab in patients with HRD-positive tumours regardless of *BRCA1/2*-mut status (see Supplementary Material Section 3, available at https://doi.org/10.1016/j.annonc.2023.07.011).

Non-high-grade serous advanced ovarian cancer. Paclitaxel—carboplatin is the standard systemic ChT used in LGSC, CCC and MC. Multiple retrospective studies, however, showed lower response rates in these histotypes compared with HGSC.[62-64] Bevacizumab has shown activity in all histotypes including those less chemoresponsive, e.g. LGSC or CCC.[49] The majority of LGSCs have high expression of estrogen receptor (ER) and progesterone receptor (PgR); retrospective studies suggest a possible therapeutic value of hormone therapy in the maintenance of newly diagnosed advanced LGSC.[65] This intervention is currently under evaluation in a prospective RCT (NCT04095364).

Recommendations

- Patients with advanced EOC should be evaluated for PCS by a specialised team, with the aim of achieving complete cytoreduction (absence of all visible residual disease) [III, A].
- When complete cytoreductive surgery is feasible, PCS is recommended [III, A]; otherwise, obtaining adequate biopsy tissue for histology and molecular testing is recommended [III, A].
- When complete cytoreductive surgery is not feasible, NACT for three cycles followed by ICS and three cycles of paclitaxel—carboplatin are recommended [I, A].
- Bevacizumab in the neoadjuvant setting, before ICS, can be considered [II, B].
- When ICS is not possible, and in the absence of overt disease progression, three additional cycles of paclitaxel—carboplatin alone [I, A] or with bevacizumab [II, B] are recommended.
- Systemic therapy decisions should be informed by *BRCA1/2*-mut (germline and/or somatic) and HRD status testing carried out at primary diagnosis [I, A].

- Paclitaxel (175 mg/m^2)—carboplatin (AUC 5-6) every 3 weeks for six cycles is the standard first-line ChT in advanced ovarian cancer [I, A].
- The schedule of weekly ChT with paclitaxel (60 mg/m^2)—carboplatin (AUC 2) can be considered as an alternative in frail patients [I, B].
- Bevacizumab improves PFS in patients with stage III-IV ovarian cancer and should be considered in addition to paclitaxel—carboplatin [I, A; European Society for Medical Oncology-Magnitude of Clinical Benefit Scale (ESMO-MCBS) v1.1 score: 3; MCBS v1.1 score: 4 in high-risk patients].
- Given the controversy about i.p. ChT [I, E] and HIPEC [II, D], they are not considered a standard of care in first-line treatment.
- Maintenance treatment with PARPis, with or without bevacizumab, is recommended for patients with *BRCA1/2*-mutated or *BRCA1/2*-wt/HRD-positive tumours with no evidence of disease at the end of ChT or a complete or partial response to platinum—paclitaxel first-line ChT [I, A].
  - For *BRCA1/2*-mutated: olaparib for 2 years [ESMO-MCBS v1.1 score: 4; ESMO Scale for Clinical Actionability of molecular Targets (ESCAT) score: I-A], niraparib for 3 years [ESMO-MCBS v1.1 score: 3; ESCAT score: I-A] or olaparib—bevacizumab for 2 years [ESMO-MCBS v1.1 score: 3; ESCAT score: I-A].
  - For *BRCA1/2*-wt/HRD-positive: niraparib for 3 years [ESMO-MCBS v1.1 score: 3; ESCAT score: I-A] or olaparib—bevacizumab for 2 years [ESMO-MCBS v1.1 score: 3; ESCAT score: I-A).
- Maintenance treatment with either bevacizumab [I, A] or niraparib for 3 years [I, B; ESMO-MCBS v1.1 score: 3] can be recommended for HRD-negative tumours, with the latter following complete or partial response to platinum—paclitaxel first-line ChT. The choice of treatment should be based on disease and clinical characteristics of the patient.
- Maintenance with anti-estrogen therapy after first-line platinum-based ChT can be considered in LGSC [IV, B].

MANAGEMENT OF RECURRENT EOC

Patient assessment

Up to 70% of patients with stage III-IV high-grade ovarian cancer will relapse within 3 years. Relapse rates for early-stage ovarian cancer are much lower.

Several factors need to be assessed when selecting a treatment for patients with recurrent disease (Figure 3).

Systemic therapy of recurrent disease is based on platinum-containing or non-platinum-containing regimens. There are currently no molecular biomarkers to predict efficacy of platinum rechallenge. The definition of platinum sensitivity based on a 6-month cut-off of treatment-free interval from last platinum (TFIp) was challenged during the Fifth Gynecological Cancer InterGroup (GCIG) Ovarian Cancer Consensus Conference and later discontinued in clinical practice following the 2018 ESMO—European Society of Gynaecological Oncology (ESGO) Consensus Conference, as many factors may influence TFIp (e.g. the frequency of follow-up and interval of diagnostic tests) and the response to platinum (i.e. histotype or *BRCA1/2*-mut status).[32,66] Not all patients with TFIp >6 months respond to platinum (objective response rate 47.2%-66%),[32] and conversely, platinum-based combinations have demonstrated activity in patients with TFIp <6 months.[67]

Surgery for relapse

The role of surgery for patients with a first relapse >6 months after the end of platinum-based ChT in the first line was addressed by one non-randomised trial and three prospective randomised trials.[68-71]

The DESKTOP series defined the AGO score to identify patients for whom complete resection is feasible. In patients with a positive AGO score—defined as having complete resection at primary surgery (alternatively FIGO stage I-II), good performance status (Eastern Cooperative Oncology Group 0) and absence of ascites (<500 ml)—the likelihood of achieving a complete resection is 76%.[68] Subsequently, DESKTOP III demonstrated a benefit in OS and PFS for patients with positive AGO scores randomised into secondary cytoreductive surgery followed by platinum-based ChT versus ChT alone.[69]

The SOC-1 trial had a similar design, but patients were selected according to the iModel. This trial was also positive for PFS, but OS data are still immature.[70]

The GOG-0213 trial did not show a superiority with respect to surgery.[71] Although many explanations have been proposed, the most convincing is the absence of objective selection criteria for surgery.

Systemic therapy when platinum is an option

Patients should be considered for platinum-based therapy at relapse if platinum is not contraindicated and there is a reasonable likelihood that the patient may benefit from platinum rechallenge (no progression during platinum-based therapy or shortly thereafter) (Figure 3).

ChT options. A meta-analysis of randomised trials comparing carboplatin-based doublet ChT with carboplatin monotherapy demonstrated a benefit in PFS and OS.[72] Current partners for combination therapy with carboplatin include paclitaxel, gemcitabine or PLD,[73-75] and the selection should be based on safety profile and patient preference. Based on safety profile, the combination of carboplatin—PLD is considered the preferred option.[75] If combination therapy is contraindicated, carboplatin monotherapy remains an option. Treatment is usually recommended for four to six cycles.

Platinum hypersensitivity reactions (HSRs) affect ~5% of the general cancer population. Several outpatient-based platinum 'desensitisation' protocols exist for gynaecological oncology patients with HSRs that permit the successful re-introduction of platinum-based therapy (carboplatin or cisplatin) after patients have experienced HSRs.[76]

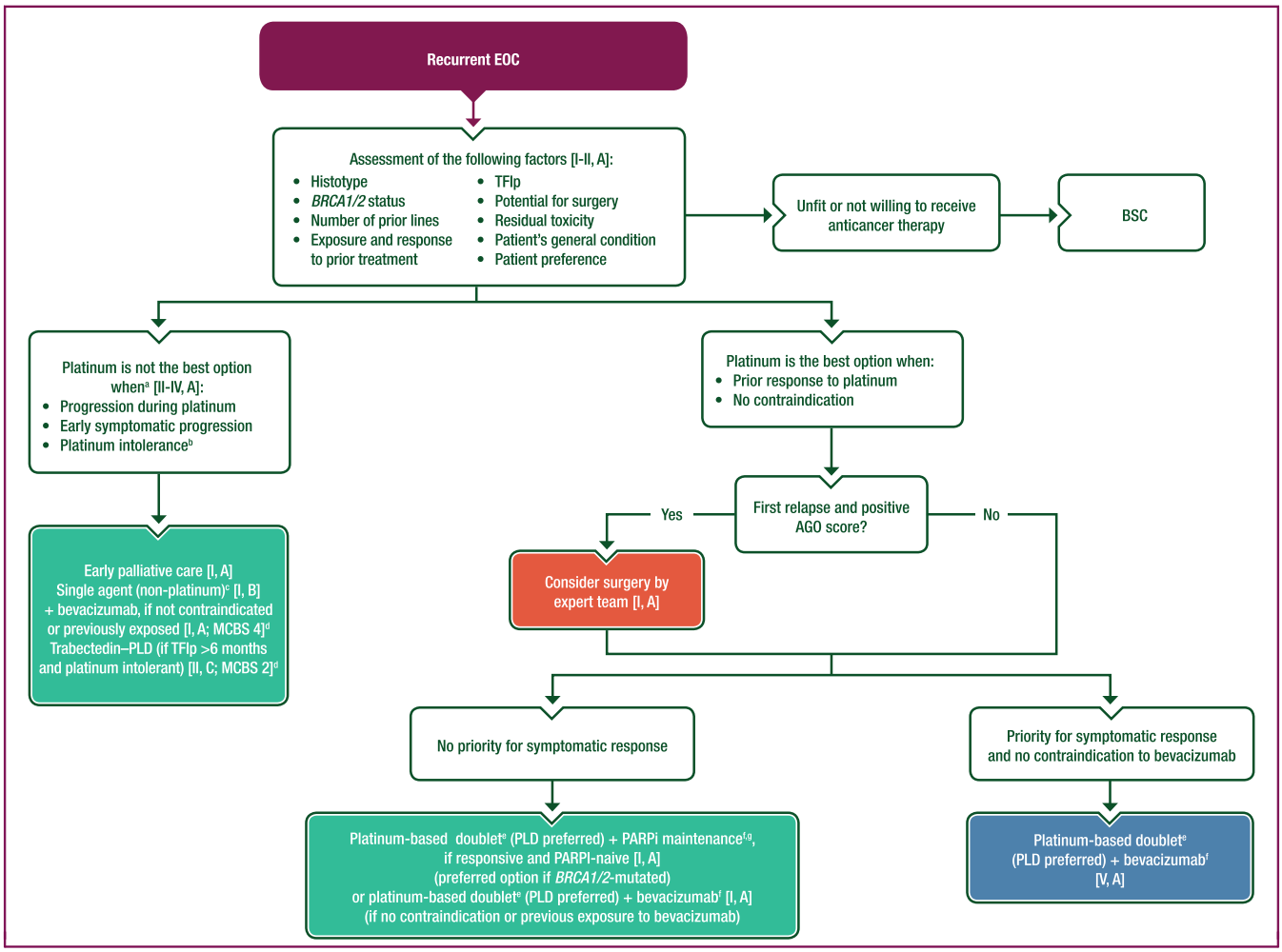

Figure 3. Management of recurrent EOC.
Purple: general categories or stratification; red: surgery; blue: systemic anticancer therapy; turquoise: combination of treatments or other systemic treatments; white: other aspects of management.
AGO, Arbeitsgemeinschaft Gynaekologische Onkologie; BSC, best supportive care; EMA, European Medicines Agency; EOC, epithelial ovarian cancer; FDA, Food and Drug Administration; MCBS, ESMO-Magnitude of Clinical Benefit Scale; mut, muation; PARPi, poly (ADP-ribose) polymerase inhibitor; PLD, pegylated liposomal doxorubicin; TFIp, treatment-free interval from last platinum.
[a]Patient choice and quality-of-life issues may also suggest that platinum is not the best option.
[b]In patients with platinum intolerance who have relapsed >6 months from previous platinum, the combination of trabectedin and PLD may be recommended [II, C; ESMO-MCBS v1.1 score: 2 for patients with platinum-sensitive disease; EMA approved, not FDA approved].
[c]Weekly paclitaxel, PLD, topotecan or gemcitabine.
[d]ESMO-MCBS v1.1[104] was used to calculate scores for new therapies/indications approved by the EMA or FDA. The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms).
[e]Paclitaxel, PLD or gemcitabine (carboplatin—gemcitabine—bevacizumab: ESMO-MCBS v1.1 score: 3).[d]
[f]Until disease progression or next line of treatment is started [I, A].
[g]Olaparib for *BRCA1/2*-mutated: ESMO-MCBS v1.1 score: 2;[d] niraparib regardless of *BRCA1/2*-mut status: ESMO-MCBS v1.1 score: 3;[d] rucaparib regardless of *BRCA1/2*-mut status: ESMO-MCBS v1.1 score: 3.[d]

In the absence of contraindications to platinum, there is no role for a non-platinum-based combination at first relapse, as was demonstrated by the lack of improvement in OS in the randomised phase III INOVATYON trial, which compared trabectedin—PLD with carboplatin—PLD in a subgroup of patients with a TFIp of 6-12 months.[77]

Antiangiogenic therapy. Bevacizumab is approved in combination with platinum-based combination therapy and then as maintenance therapy in patients with a TFIp >6 months. Bevacizumab with platinum combinations (either paclitaxel or gemcitabine followed by bevacizumab maintenance) leads to a significant benefit in objective response rate and PFS.[71,78] OS was similar in both arms, partially explained by the high rate of crossover to bevacizumab in subsequent lines of therapy.[78] PLD—carboplatin—bevacizumab has demonstrated a statistically significant PFS and OS advantage compared with carboplatin—gemcitabine—bevacizumab, making the former combination the preferred option if a carboplatin-based doublet with bevacizumab is selected.[79]

A rechallenge of bevacizumab combined with a carboplatin-based doublet is associated with a significant improvement in median PFS compared with ChT alone in patients previously treated with bevacizumab and having relapsed with TFIp >6 months.[80] Bevacizumab rechallenge has not been licensed in Europe, however, and is, therefore, not widely available.

In phase III trials, bevacizumab was administered until progression or unacceptable toxicity occurred. Treatment should be maintained until clinical or radiological progression and should not be discontinued based solely on rising CA-125.

Further information is provided in the Supplementary Material Section 4, available at https://doi.org/10.1016/j.annonc.2023.07.011.

PARPis. Three PARPis (olaparib, niraparib and rucaparib) are approved for maintenance therapy of patients with high-grade tubo-ovarian carcinoma that achieve a response to platinum rechallenge, irrespective of *BRCA1/2*-mut or HRD status. Details of the outcome from four randomised trials (Study 19, SOLO2, NOVA and ARIEL3) are given in the Supplementary Material Section 4, available at https://doi.org/10.1016/j.annonc.2023.07.011.

The recommended length of PARPi treatment remains unclear. In NOVA and ARIEL3 treatment was stopped at progression, but in Study 19 and SOLO2 patients were allowed to continue olaparib beyond progression, if it was considered beneficial. From a clinical perspective, treatment beyond disease progression may have particular value in slow-growing tumours or in the context of oligometastatic disease (e.g. single site of progression). All trials have shown that there is a small group of 'super-responder' patients (∼10%) without progression after 5 years on treatment with PARPis.

Recently, data on OS after maintenance therapy raised concern about a possible detrimental effect of PARPis, particularly for non-g*BRCA1/2*-mut carriers. The OS analyses, however, were secondary and underpowered endpoints. Long-term OS data from the NOVA trial and interim survival analysis of the NORA study have not categorically confirmed the initial concern.[81,82] Intermediate endpoints such as PFS2 (time to second subsequent therapy) or death suggest a continuing benefit from PARPis beyond progression. Nevertheless, an exploratory analysis in SOLO2 suggested that g*BRCA1/2*-mut carriers who received olaparib had a poorer response to platinum-based therapy on subsequent relapse,[83] raising the hypothesis that PARPis may encourage platinum resistance. The licence for use of PARPis has not been changed by the European Medicines Agency (EMA), but has been withdrawn by the Food and Drug Administration (FDA) for niraparib and rucaparib (but not olaparib) in non-g*BRCA1/2*-mut carriers. It is advisable, therefore, to have a discussion with patients without a *BRCA1/2*-mut about the benefits and risks of PARPis.

There is currently no approval for pre-treatment with a PARPi. One trial, OREO/ENGOT-OV38, showed a positive short-lived benefit for some patients retreated with olaparib.[84]

Toxicity of PARPis is generally manageable through dose individualisation (for niraparib), dose reductions and dose interruptions. The rate of acute myeloid leukaemia and myelodysplastic syndromes is higher among g*BRCA1/2*-mutated patients and in the recurrent setting compared with first line. This can probably be explained by an accumulative exposure to platinum.[85]

Several factors need to be taken into consideration for the selection of PARPis or anti-VEGF therapies in relapse including histotype, *BRCA1/2*-mut status, prior therapies (PARPi and/or bevacizumab), expected response to platinum ChT, presence of symptoms (specifically ascites), persistent toxicities from prior therapies, no contraindication to bevacizumab and patient preference. Generally, for symptomatic patients requiring a rapid treatment response, the combination of carboplatin with bevacizumab would be recommended (Figure 3).

Further information is provided in the Supplementary Material Section 4, available at https://doi.org/10.1016/j.annonc.2023.07.011.

Systemic therapy when platinum is not an option

For some patients with recurrent ovarian cancer, platinum rechallenge may not be considered clinically appropriate. For these patients, alternative systemic treatments are available. Patients with good performance status should be prioritised for novel therapies within clinical trials. Integrating early palliative care is particularly crucial.

Non-platinum ChT options. Single-agent non-platinum ChT regimens include weekly paclitaxel, topotecan, gemcitabine, PLD and oral metronomic cyclophosphamide. These have shown modest activity in patients with relapsed ovarian cancer for whom platinum is not an option, with 10%-15% objective response rate and median OS of 10-12 months.[86-90] With regard to selecting a particular regimen, there are no robust randomised data to support one agent over another, and not all are licensed for this indication. The choice should be guided by patient preference and toxicity profile. The optimal duration of treatment is unclear; in clinical trials, ChT with non-platinum agents was planned until tumour progression or unacceptable toxicity.

Trabectedin—PLD is approved in Europe for patients relapsing >6 months after last platinum.[91] This combination is an option when such patients are ineligible for further platinum.

Data with antibody-drug conjugates have shown encouraging results (see Supplementary Material Section 4, available at https://doi.org/10.1016/j.annonc.2023.07.011).

Antiangiogenic therapy. The addition of bevacizumab to second- or third-line non-platinum ChT (paclitaxel, PLD or topotecan) in the AURELIA trial demonstrated an improvement in median PFS, tumour response rate and QoL scores compared with ChT alone.[92] Notably, this trial excluded all patients at increased risk of intestinal fistulae (progression during first-line platinum, history of bowel obstruction or serosal invasion), and <10% of patients had been previously exposed to bevacizumab.

Systemic therapy for non-high-grade subtypes

Less common histological subtypes such as CCC, carcinosarcoma or LGSC are known to be less responsive to ChT including platinum.[93] For these patients, once platinum is no longer an option, participation in clinical trials is strongly

recommended.[94] For LGSC, one randomised phase III trial demonstrated significantly improved PFS and response rate for the mitogen-activated protein kinase kinase (MEK) inhibitor trametinib compared with standard of care (single-agent ChT or hormonal therapy at the choice of the investigator).[95] Another phase III trial with binimetinib, however, did not have a positive result.[96] These slowly proliferating tumours frequently express ER and/or PgR, and although objective tumour responses are low, hormonal therapies can be used to control tumour growth (e.g. aromatase inhibitors, tamoxifen or luteinising hormone-releasing hormone agonists).

Recommendations

- The following should be assessed when selecting treatment for patients with recurrent disease [I-III, A]:
  - o Histotype
  - o *BRCA1/2*-mut status
  - o Number of prior lines of treatment
  - o Exposure and response to prior treatment
  - o TFIp
  - o Possibility of achieving a complete secondary surgical cytoreduction
  - o Residual ChT toxicity
  - o The patient's general condition and preferences
- Patients with first relapse of ovarian cancer after >6 months of last platinum administration should be evaluated by a gynaecological oncology centre experienced in surgery for ovarian cancer to identify potential candidates for surgical cytoreduction [I, A].
- Patients who have previously responded to platinum without early symptomatic relapse should be treated with either a platinum-based doublet (PLD, gemcitabine or paclitaxel) with bevacizumab [I, A; carboplatin—gemcitabine—bevacizumab ESMO-MCBS v1.1 score: 3] or a platinum-based doublet followed by maintenance with PARPi therapy if a response is achieved and the patient has not been previously exposed to PARPis [I, A; olaparib for *BRCA1/2*-mutated: ESMO-MCBS v1.1 score: 2; niraparib regardless of *BRCA1/2*-mut status: ESMO-MCBS v1.1 score: 3; rucaparib regardless of *BRCA1/2*-mut status: ESMO-MCBS v1.1 score: 3].
- For patients requiring rapid response, the combination of a platinum-based doublet (PLD, gemcitabine or paclitaxel) with bevacizumab is preferred [V, A; carboplatin—gemcitabine—bevacizumab ESMO-MCBS v1.1 score: 3].
- Bevacizumab should be continued until disease progression (symptomatic) or the next line of treatment is started, as continuation of bevacizumab beyond progression has not been evaluated in the recurrent setting [I, A].
- PARPis should be continued until disease progression or the next line of treatment is started [I, A], as the benefit of continuing treatment beyond progression has not been demonstrated conclusively to date [III, B].
- Platinum rechallenge following treatment with a non-platinum regimen (monotherapy or combination) could be considered if the tumour did not progress during prior platinum therapy [III, B].
- Patients with relapsed EOC for whom platinum is not an option should be defined by [II-IV, A]:
  - o Proven resistance (progression during platinum)
  - o Expected resistance (early symptomatic progression post-platinum, response to rechallenge unlikely)
  - o Platinum intolerance
  - o Patient choice
  - o QoL issues
- For patients not candidates to receive platinum, integrating palliative care early in the treatment pathway is strongly recommended [I, A].
- Single-agent non-platinum options that can be recommended include weekly paclitaxel, PLD, topotecan and gemcitabine [I, B].
- In patients with platinum intolerance who have relapsed >6 months from previous platinum, trabectedin—PLD may be recommended [II, C; ESMO-MCBS v1.1 score: 2 for patients with platinum-sensitive disease; EMA approved, not FDA approved].
- Bevacizumab should be recommended in combination with weekly paclitaxel, PLD or topotecan in patients without contraindications to bevacizumab and not previously exposed to bevacizumab [I, A; ESMO-MCBS v1.1 score: 4].
- Hormonal therapy is recommended for relapsed LGSC [II, A].
- For patients with recurrent LGSC, treatment with the MEK inhibitor trametinib should be considered after prior platinum-based ChT and hormone therapy (not EMA approved) [I, A].

FOLLOW-UP, LONG-TERM IMPLICATIONS AND SURVIVORSHIP

Surveillance

Although a cure is unlikely after relapse, effective therapies exist for the treatment of patients with recurrent ovarian cancer. Therefore, surveillance in these patients is indicated with a combination of thorough symptom review and physical examination. Studies have noted that 26%-50% of recurrences are in the pelvis[97] suggesting a role for pelvic examination in the follow-up of ovarian cancer. Disease recurrence, however, may be located outside of the pelvis, e.g. in lymph nodes, liver, lungs or peritoneal carcinomatosis and may not be detectable by pelvic examination. CT scans have been noted to have a sensitivity of 79% and specificity of 84% for detecting relapse in a large pooled meta-analysis.[98] CT scans are indicated if symptoms suggest recurrent disease or if the CA-125 is rising.[98]

CA-125 has been evaluated in the surveillance of ovarian cancer and has been noted to be elevated 2-5 months before radiographic detection of cancer. In a large prospective phase III Medical Research Council UK OV05/EORTC 55955 trial, there was no difference in OS when ChT was initiated based solely on rising CA-125 levels versus

when disease recurrence had become clinically evident.[99] The benefit of surveillance with CA-125 in the current era—when more sensitive radiological detection methods such as PET–CT and complete secondary cytoreduction and targeted therapy have been shown to improve outcomes—has yet to be defined.

BRCA1/2-mut carriers and survival

Although surveillance is generally undertaken for 5 years after the most recent remission, longer follow-up may be considered in *BRCA1/2*-mut carriers, given their improved long-term survival and need for breast cancer surveillance. In a pooled analysis of 1213 EOC cases with pathogenic g*BRCA1*-mut ($n = 909$) or g*BRCA2*-mut ($n = 304$) and of 2666 non-carriers, an improved 5-year OS was noted among *BRCA1/2*-mut carriers with ovarian cancer.[100] A more recent report of 15-year survival data in *BRCA1/2*-mut carriers suggests that the survival benefit appears to be within the first 5 years and decreases over time.[101]

Recommendations

- Surveillance of ovarian cancer patients can include CA-125 determination, physical examination and CT scan evaluation [IV, B].
- *BRCA1/2*-mut carriers can be considered for follow-up beyond 5 years [III, B].
- Long-term *BRCA1/2*-mut survivors should be referred to high-risk breast cancer clinics for follow-up [I, A].[102]

METHODOLOGY

This Clinical Practice Guideline (CPG) was developed in accordance with the ESMO standard operating procedures for CPG development (https://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology). The relevant literature has been selected by the expert authors. A table of ESCAT scores is included in Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2023.07.011. ESCAT scores have been defined by the authors, assisted if needed by the ESMO Translational Research and Precision Medicine Working Group.[103] A table of ESMO-MCBS scores is included in Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2023.07.011. ESMO-MCBS v1.1[104] was used to calculate scores for new therapies/indications approved by the EMA or FDA (https://www.esmo.org/Guidelines/ESMO-MCBS). The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee. The FDA/EMA or other regulatory body approval status of new therapies/indications is reported at the time of writing this CPG. Levels of evidence and grades of recommendation have been applied using the system shown in Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2023.07.011.[105] Statements without grading were considered justified standard clinical practice by the authors. For future updates to this CPG, including eUpdates and Living Guidelines, please see the ESMO Guidelines website: https://www.esmo.org/guidelines/guidelines-by-topic/gynaecological-cancers/newly-diagnosed-and-relapsed-epithelial-ovarian-cancer.

ACKNOWLEDGEMENTS

Manuscript editing support was provided by Ioanna Ntai, Catherine Evans, Claire Bramley and Jennifer Lamarre (ESMO Guidelines staff); this support was funded by ESMO. Nathan Cherny, Chair of the ESMO-MCBS Working Group, and Urania Dafni, Giota Zygoura, Georgia Dimopoulou and Tereza Dellaporta of Frontier Science Foundation Hellas provided review and validation of the ESMO-MCBS scores. Nicola Latino (ESMO Scientific Affairs staff) provided coordination and support of the ESMO-MCBS scoring and Angela Corstorphine of Kstorfin Medical Communications Ltd provided medical writing and editing support in the preparation of the ESMO-MCBS table; this support was funded by ESMO. Dr Svetlana Jezdic (ESMO Medical Affairs staff) provided coordination and support of the ESCAT scoring.

FUNDING

No external funding has been received for the preparation of this guideline. Production costs have been covered by ESMO from central funds.

DISCLOSURE

AGM reports personal fees for advisory board membership from Alkermes, Amgen, AstraZeneca, Clovis Oncology, Eisai, Genmab, GSK, HederaDx, Illumina, ImmunoGen, MacroGenics, Mersana, MSD, Novartis, Oncoinvent, PharmaMar, Regeneron, Roche, SOTIO, Sutro Biopharma and Tubulis; personal fees as an invited speaker from AstraZeneca, Clovis Oncology, GSK, MSD, Novocure, Roche, Takeda and Zai Lab; institutional funding as coordinating principal investigator (PI) from Aravive, GSK, Novartis and Roche; and a non-remunerated role as Steering Committee Member for MSD. PH reports personal fees for advisory board membership from AstraZeneca, Clovis Oncology, GSK, ImmunoGen, Mersana, Miltenyi, MSD, Novartis and Roche; personal fees as an invited speaker from Amgen, Eisai, Stryker and Zai Lab; personal fees for lectures from AstraZeneca, GSK, MSD and Roche; personal fees as an Independent Data Monitoring Committee (IDMC) member from SOTIO; institutional funding as Trial Chair from AstraZeneca, GSK, ImmunoGen and Roche; institutional funding as local PI from Genmab; institutional funding from Clovis Oncology and Seagen; and a non-remunerated role as PI from AstraZeneca. AL reports personal fees for advisory board membership from Zentalis Pharmaceuticals; personal fees as an invited speaker from GSK and Medscape; personal fees for consultancy from GLG; personal fees for a writing engagement from Onko+; fees paid to her institute for advisory board membership from Ability Pharma, Apmonia, AstraZeneca, Blueprint, Clovis Oncology, GSK, Merck Serono and MSD; fees paid to her institute as an invited speaker from AstraZeneca, Clovis Oncology and Kephren Publishing; fees paid to her institute for consultancy from Orion and

Owkin; fees paid to her institute for steering committee membership from MSD; institutional funding as a PI in clinical trials from Agenus, AstraZeneca, Bristol Myers Squibb (BMS), GSK, Iovance; MSD and Roche; institutional funding as a Chief Investigator in clinical trials from AstraZeneca and OSE Immunotherapeutics; institutional research grants as a PI in translational research from ARCAGY-GINECO, AstraZeneca and Sanofi; a non-remunerated role as an IDMC member for Clovis Oncology, as an IDMC Chair for Pfizer (proprietary information) and as a member of the GCIG; and non-remunerated academic research projects for LXRepair and Owkin. DL reports personal fees for advisory board membership from AstraZeneca, Clovis Oncology, Corcept, Genmab, GSK, ImmunoGen, MSD, Oncoinvest, PharmaMar, Seagen and Sutro Biopharma; personal fees as an invited speaker from AstraZeneca, Clovis Oncology, Genmab, GSK, ImmunoGen, MSD, PharmaMar and Seagen; personal fees for consultancy from AstraZeneca, Clovis Oncology, Genmab, GSK, ImmunoGen, MSD, Novartis, PharmaMar and Seagen; travel grants from AstraZeneca, Clovis Oncology and GSK; institutional funding as coordinating PI from Clovis Oncology, Genmab and MSD; institutional funding for a clinical trial/contracted research from AstraZeneca, Clovis Oncology, Genmab, GSK, ImmunoGen, Incyte, MSD, Novartis, Roche and Seagen; institutional funding for founding an academic trial from Clovis Oncology, GSK, MSD and PharmaMar; a non-remunerated role as a PI in clinical trials for AstraZeneca, Clovis Oncology, Genmab, GSK, ImmunoGen, Incyte, MSD, Novartis, PharmaMar, Roche and Seagen; and a non-remunerated role as a member of the Board of Directors of GCIG. REM reports personal fees for advisory board membership from AstraZeneca, GSK and Merck; personal fees as an invited speaker from AstraZeneca, Clovis Oncology and GSK; and personal fees for expert testimony from Ellipses and Shionogi. BP reports personal fees for advisory board membership from AstraZeneca, Clovis Oncology, Eisai, GSK, GOG Foundation, Lilly, Merck, Mersana, Seattle Genetics, Sutro and Tesaro; personal fees for consulting from Arquer Diagnostics, Atossa, Bioascend, Deciphera, Elevar, Imab, Onclive, Onconova Therapeutics, PeerView, Toray and WebMD; institutional funding as local PI from Acrivon, AstraZeneca, Celgene, Celsion, Clovis Oncology, Eisai, GSK, ImmunoGen, Incyte, Karyopharm, Merck, Mersana, Roche Genentech, Seattle Genetics, Sutro, Takeda, Tesaro, Toray and VBL Therapeutics; membership of the GOG Partners group at the GOG Foundation; and membership of the Board of Directors of the Society of Gynecologic Oncology (SGO). IRC reports personal fees for advisory board membership from Adaptimmune, Agenus, Amgen, AstraZeneca, BMS, Clovis Oncology, Daiichi Sankyo, Deciphera, EQRX, Eisai, GSK, MacroGenics, Merck Sereno, Mersana, Novartis, Oxnea, Roche and Sutro Biopharma; fees paid to her institute for advisory board membership from MSD; fees paid to her institute for translational research from BMS; a non-remunerated role as President of GINECO; and a non-remunerated role as PI for PAOLA-1. DSPT reports personal fees for advisory board membership from AstraZeneca, Bayer, Boehringer Ingelheim, Eisai, Genmab, GSK, MSD and Roche; personal fees as an invited speaker from AstraZeneca, Eisai, GSK, Merck Serono, MSD, Roche and Takeda; ownership of stocks/shares of Asian Microbiome Library (AMiLi); institutional research grants from AstraZeneca, Bayer, Karyopharm Therapeutics and Roche; institutional funding as coordinating PI from AstraZeneca and Bergen Bio; institutional funding as local PI from Bayer, Byondis B.V. and Zeria Pharmaceutical Co Ltd; a previous non-renumerated role as Chair of the Asia-Pacific Gynecologic Oncology Trials Group (APGOT); a previous non-renumerated role as the Society President of the Gynecologic Cancer Group Singapore; non-renumerated membership of the Board of Directors of the GCIG; and product samples from AstraZeneca, Cyclacel Pharmaceuticals, Eisai and MSD (non-financial interest). EB declares no conflicts of interest. AO reports personal fees for advisory board membership from Agenus, AstraZeneca, Clovis Oncology, Corcept Therapeutics, Deciphera Pharmaceuticals, Eisai, Exelisis, EMD Serono, F. Hoffmann-La Roche, Genmab, GSK, ImmunoGen, Itheos, Merck Sharps & Dohme de España, SA, Mersana Therapeutics, Novocure, OncXerna Therapeutics, Inc., PharmaMar, Regeneron, Sattucklabs, Seagen and Sutro Biopharma; personal fees for travel/accommodation from AstraZeneca, PharmaMar and Roche; institutional funding from Abbvie Deutschland, Advaxis Inc., Aeterna Zentaris, Amgen, Aprea Therapeutics AB, BMS, Clovis Oncology Inc, Eisai Co, Ltd, F. Hoffmann-La Roche Ltd, ImmunoGen Inc, Merck, Sharp & Dohme de España SA, Millennium Pharmaceuticals Inc, PharmaMar SA, Regeneron Pharmaceuticals and Tesaro Inc.; non-remunerated roles at ESMO (member, Officer, Co-Chair of the ESMO Gynaecological Cancers Congress 2023-2025, Chair of the Gynaecological Track ESMO 2019, Scientific Track Member Gynaecological Cancers ESMO 2018, ESMO 2020, ESMO 2022, member of the Gynaecological Cancers Faculty and Subject Editor for the Gynaecological CPGs); a non-remunerated role at GCIG (member and Cervix Cancer Chair on behalf of GEICO); and membership of ASCO, GOG and SEOM. JAL reports personal fees for advisory board membership for Artios Pharma, AstraZeneca, BMS, Clovis Oncology, Eisai, Ellipses, GSK, Immagene, ImmunoGen, Merck/MSD, Miltenyi, Novocure, Nuvation and VBL Therapeutics; personal fees as an invited speaker from AstraZeneca, Clovis Oncology, GSK and Neopharm; personal fees as an IDMC member from Mersana and Sutro Bio; a remunerated leadership role as an Associate Editor of Therapeutic Advances in Medical Oncology (Sage Publishing); institutional research grants from AstraZeneca and MSD/Merck; non-remunerated roles at ESMO (Officer and Subject Editor for the Gynaecological CPGs); and a non-remunerated leadership role as Vice-President of ESGO (2019-2021).

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