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Consensus on drivers of maintenance treatment choice and patterns of care in advanced ovarian cancer

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► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/ijgc-2024-005497).

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Received 20 March 2024
Accepted 13 September 2024

To cite: Perez-Fidalgo A, Schmalfeldt B, George A, *et al*. *Int J Gynecol Cancer* Published Online First: [please include Day Month Year]. doi:10.1136/ijgc-2024-005497

ABSTRACT

Objectives Maintenance therapies, including poly (ADP-ribose) polymerase (PARP) inhibitors and/or bevacizumab, have substantially improved the prognosis of patients with advanced ovarian cancer. Owing to the variability in treatment strategies across Europe, a Delphi study was conducted among European experts to understand the heterogeneity of clinical practice and identify key factors driving maintenance treatment decisions for advanced ovarian cancer.

Methods A pragmatic literature review was conducted to identify key questions regarding maintenance treatment strategies in patients with advanced ovarian cancer. Utilizing a Delphi methodology, consensus was assessed among a panel of 16 experts using a questionnaire based on results of the pragmatic literature review.

Results Panelists agreed that *BRCA* mutation and homologous recombination status should be assessed in parallel at diagnosis, and that first-line platinum chemotherapy may be initiated concurrently. There was a consensus that alternative homologous recombination deficiency tests are acceptable provided they are clinically validated. Panelists agreed that Response Evaluation Criteria in Solid Tumors (RECIST) and CA-125 elimination rate constant K (KELIM) scores can help assess tumor chemosensitivity and guide treatment-related decisions. Panelists defined high-risk disease as International Federation of Gynecology and Obstetrics (FIGO) stage IV disease or stage III with residual disease after initial/interval cytoreduction. Risk of disease progression was a key determinant of choice between PARP inhibitor, bevacizumab, or both in combination, as maintenance therapy in advanced ovarian cancer.

Conclusions Key drivers for selecting advanced ovarian cancer maintenance treatments include tumor mutational status as a key biomarker and clinician perception of the risk for early disease progression.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Advanced ovarian cancer is a disease for which there are multiple therapeutic options currently available, with heterogeneity in treatment guidelines across Europe.

WHAT THIS STUDY ADDS

⇒ Our study used the Delphi methodology to assess European views on factors that influence advanced ovarian cancer maintenance therapeutic choices. Key drivers for maintenance treatment decision-making included the identification of tumor mutational status using validated testing at diagnosis, and the identification of patients who are at high risk of disease progression.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The consensus opinions on drivers include mutational status, phenotypic characteristics, and perceptions for the risk of early disease progression. The consensus provides additional insight and discussion among clinicians treating advanced ovarian cancer that will ultimately benefit patient outcomes.

INTRODUCTION

Annually, about 320 000 cases of epithelial ovarian cancer are diagnosed globally, with 64% mortality and approximately 75% of patients presenting with advanced disease at diagnosis.[1 2] Patients with newly diagnosed advanced ovarian cancer receive primary debulking surgery followed by chemotherapy with platinum and paclitaxel, or neoadjuvant chemotherapy with interval debulking surgery in the case of favorable response to chemotherapy.[2] In both scenarios, subsequent maintenance therapy should be considered. The addition of bevacizumab to chemotherapy, followed by maintenance with bevacizumab showed improved progression-free survival versus placebo in stage III–IV ovarian cancer in the GOG-218 and ICON-7 randomized clinical trials. However, post hoc analyses suggested an overall survival benefit with bevacizumab only in patients with a poor prognosis due to poor chemosensitivity (CA-125 elimination rate constant K (KELIM) assessment), and high risk of disease progression.[3–6]

The approval of poly (ADP-ribose) polymerase (PARP) inhibitors provided new maintenance

treatments for patients across the *BRCA* mutation and homologous recombination deficiency spectrum.[7] SOLO1, PRIMA, PRIME, and ATHENA-MONO trials assessed the efficacy of maintenance PARP inhibitor versus placebo in patients with high-grade serous or endometrioid ovarian cancer (with/without *BRCA 1/2* mutations) treated with platinum-based chemotherapy; different improvements in progression-free survival and overall survival rates according to patient biomarkers were recorded.[8–11] The PRIMA trial reported an efficacy gradient in patients treated with maintenance niraparib versus placebo, based on homologous recombination deficiency status (*BRCA* mutated>*BRCA* wild-type, homologous recombination-deficient>*BRCA* wild-type, homologous recombination-proficient tumors).[10] Similar results were seen in PRIME and ATHENA-MONO. In PAOLA-1, greater differences in progression-free survival were recorded in patients with homologous recombination-deficient tumors (with/without *BRCA* mutations), treated with maintenance bevacizumab and olaparib compared with bevacizumab and placebo.[8]

Maintenance therapy decisions for patients with advanced ovarian cancer are variable across Europe, owing to inconsistencies in guidelines (including disease stage and extent of surgical debulking, and tumor mutational status) and differences in national reimbursement policies.[12 13] Consequently, patients with similar clinical characteristics may be prescribed different treatments. With variable maintenance therapy selection, understanding key treatment drivers in the first-line setting is important. This study assessed views of European experts using the Delphi technique.[14]

METHODS

Study objectives

The primary objective was to understand the heterogeneity of clinical practice and identify drivers of maintenance treatment decisions for advanced ovarian cancer. The secondary objective was to identify factors that influence initial therapy choices for advanced ovarian cancer. Using published guidelines, Delphi methodology assessed consensus among experts questioned on advanced ovarian cancer diagnosis and the patient treatment journey (Figures 1 and 2).[15]

Design and process for the pragmatic literature review

A pragmatic literature review identified published evidence that elucidated treatment drivers for advanced ovarian cancer, providing the basis for developing Delphi survey questions. Articles published until February 2022 were identified from EMBASE searches (Online supplemental table 1). Randomized controlled trials, systematic reviews, observational and prospective studies relating to advanced ovarian cancer, first-line maintenance therapy, and initial therapy were identified.

The search also identified articles describing treatment choices and factors influencing treatment eligibility (ie, mutational drivers and disease stage, initial response to prior chemotherapy, KELIM score, and patient demographics). A scientific committee comprising three medical experts reviewed the results of the literature review. Subsequently, the Delphi survey was developed and approved.

The composition of the Delphi panel

Experts (n=16) were recruited from the following countries: Austria, Belgium, Denmark, France, Germany, Ireland, Italy, Norway,

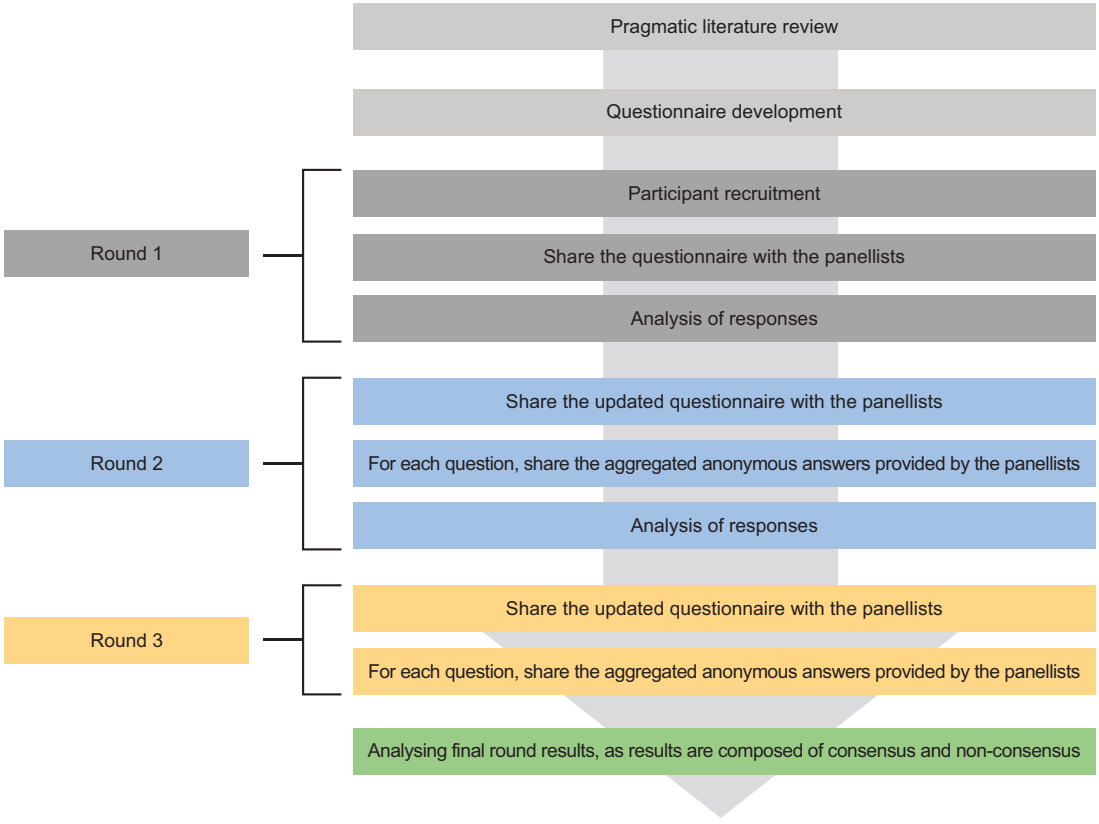

Figure 1 Study workflow.

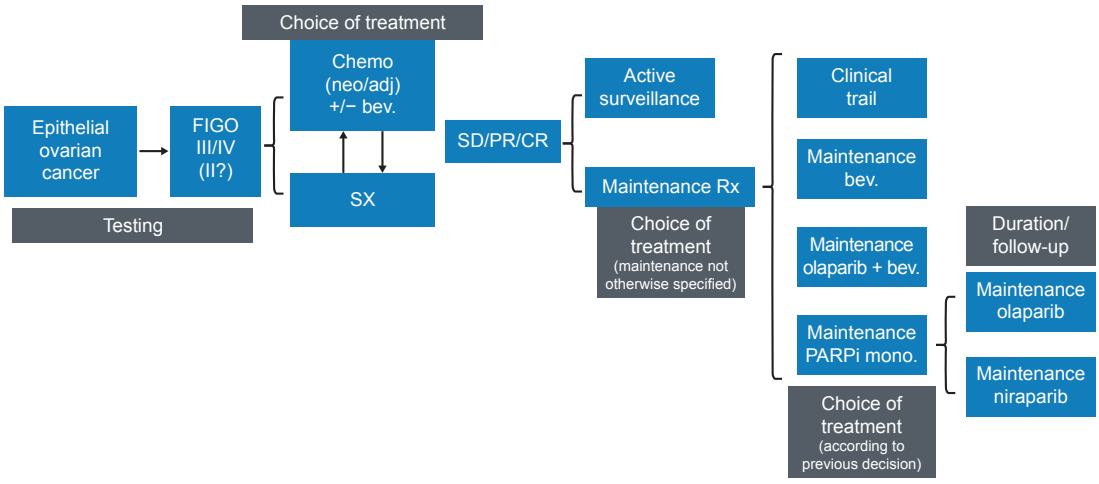

Figure 2 Patients with advanced ovarian cancer: treatment journeys. adj, adjuvant; CR, complete response; FIGO, International Federation of Gynecology and Obstetrics; mono., monotherapy; neo, neoadjuvant; PARP, poly (ADP-ribose) polymerase; PR, partial response; Rx, treatment; SD, stable disease; SX standard treatment.

Portugal, Spain, Sweden, Switzerland, and the United Kingdom. The number of recruited experts was within a recommended range of Delphi panelists previously recorded in the literature.[16] Panelists were selected because they are gynecologic or medical oncologists involved in developing European or country-specific advanced ovarian cancer management guidelines. A blinded design ensured anonymity of responses.

Operational design and process

Questionnaires were developed based on the literature review results (Figure 2), and experts rated their level of agreement to several statements across 25 items comprising 117 sub-questions. Participants added comments to cover all relevant drivers of treatment choice (Online supplemental table 2). Agreement or disagreement was assessed using a nine-point Likert scale (one–three, disagree; four–six, agree; seven–nine, fully agree), dichotomous options (yes or no), and multiple-choice questions describing the frequency of responses and common components.

Each round was divided into seven sections, (Online supplemental tables 2 and 3). Rounds one, two, and three comprised 25, 21, and 20 questions, respectively; questions without consensus were collected and questionnaires were updated for the following round. For dichotomous questions, consensus was declared when ≥80% of participants voted 'yes' (agreement) or did not vote 'yes' (disagreement)[17]; statements that achieved agreement were included in the last round of questioning. Categories 'agree' and 'fully agree' were combined to compute the percentage for each item. The proportion of respondents who achieved consensus or no consensus (agreement or disagreement) are presented.

Ethical approval

No ethical approval was required. Oral consent was provided at the recruitment stage, prior to initiating questionnaires.

RESULTS

Questionnaires focused on the following topics: molecular testing, first-line treatment choice, maintenance treatment choice following primary chemotherapy, and duration of follow-up (Online supplemental tables 2 and 3). Consensus was found based on percentage agreement/disagreement for 59 and 18 statements, respectively, while 40 statements achieved no consensus.

When questioned on the timing of *BRCA*/homologous recombination deficiency testing and for which subtypes, consensus was achieved for collecting core biopsies in patients receiving neoadjuvant chemotherapy treatment, and immediate testing for *BRCA* mutations and homologous recombination deficiency status on tissue sample availability. As shown in Table 1, consensus was achieved on the following: (1) parallel germline *BRCA* and homologous recombination deficiency tests upfront before treatment; histological advanced ovarian cancer diagnosis prior to homologous recombination deficiency testing; (2) lack of interchangeability of homologous recombination deficiency testing by homologous recombination repair mutation panel testing; (3) initiation of primary chemotherapy as soon as possible before mutation test results are received.

Consensus was achieved to use validated tests, provided validation was carried out in a randomized controlled trial tumor/data set; experts discouraged the use of non-validated tests (even if commercially available) (Table 1). The predictive value of methylation status and use of somatic homologous recombination deficiency testing for all ovarian cancer histologies did not reach consensus (Table 1); however, all experts agreed on the use of somatic tumor testing for mismatch repair in patients with clear cell, endometrioid, or mucinous carcinomas. For characteristics that defined patients with high-risk disease, consensus was reached on the following: FIGO stage III with residual disease after initial/interval cytoreduction; FIGO stage IV; poor chemotherapy response to neoadjuvant chemotherapy; and poor tumor primary chemosensitivity measured by KELIM scores (Table 2).

Consensus was reached for assessing chemotherapy response after neoadjuvant chemotherapy to help define subsequent advanced ovarian cancer maintenance systemic treatment decisions. There was consensus that high-grade carcinomas with no previous bowel obstruction/sub-occlusion/resection should not be systematically treated with bevacizumab (Table 2). Furthermore,

Table 1 Considerations for advanced ovarian cancer mutation testing in a clinical setting

Question	Variables	Agreement (%)	Disagreement (%)
Statements that achieved consensus			
Regarding molecular biomarker testing for advanced ovarian cancer patients, how do you agree or disagree with the following statements?	Testing for *BRCA* mutation/homologous recombination deficiency status should be performed as soon as a tissue sample is available	**100.0**	0.0
	Additional core biopsies should be collected for patients receiving neoadjuvant treatment to enable immediate biomarker testing	**94.0**	6.0
	It is acceptable to start first-line systemic therapy before ordering tests for *BRCA*/homologous recombination deficiency	**94.0**	6.0
	Both tests (*BRCA* mutation and homologous recombination deficiency) should be ordered at the same time upfront	**87.0**	13.0
	A histological diagnosis of high-grade ovarian cancer is needed before tumor testing for homologous recombination deficiency	**81.0**	19.0
Regarding appropriate HR tests for advanced ovarian cancer patients, how do you agree or disagree with the following statements?	It is also acceptable for the use of other academic homologous recombination deficiency tests provided a previous validation at least in a randomized clinical trial cohort	**100.0**	0.0
	Any commercially available tests, regardless as to whether they have been validated in clinical trials, can be used for guiding treatment decisions	13.0	**87.0**
	Homologous recombination deficiency testing should not be replaced by homologous recombination mutation panel testing	**94.0**	6.0
	A separate test for somatic *BRCA* is not required, as this can be collected in the homologous recombination test	**87.5**	12.5
Statements that did not achieve consensus			
Regarding molecular biomarker testing for advanced ovarian cancer patients, how do you agree or disagree with the following statements?	When possible, methylation status should be performed	50.0	50.0
	Patients with all histological subtypes of ovarian cancer, including mucinous ovarian cancer that shows a good response to platinum-based chemotherapy, should be offered somatic tumor testing for homologous recombination deficiency	25.0	**75.0**
Regarding sequence of biomarkers testing for advanced ovarian cancer patients, how do you agree or disagree with the following statement?	Homologous recombination deficiency should only be offered in high-grade serous or endometrioid ovarian cancer subtypes	37.0	**63.0**

Bold values indicate the achieved (≥80% agreement or disagreement) or nearest-to-consensus across each statement.

consensus was achieved that, in patients with early good response (cycle 1–3) reached with primary chemotherapy (Response Evaluation Criteria in Solid Tumors (RECIST) or KELIM score), bevacizumab should be discontinued after terminating chemotherapy to allow maintenance PARP inhibitor monotherapy, especially in those with low-risk and homologous recombination deficiency-negative disease. However, if bevacizumab has been initiated, it should be continued regardless of chemotherapy response. A quarter of panelists agreed that patients with high-risk disease should receive bevacizumab regardless of *BRCA* mutations and homologous recombination deficiency status (Table 2). However, 75% agreed that a poor chemosensitivity after 1–3 cycles of initial chemotherapy should indicate bevacizumab addition, almost reaching consensus.

When panelists were questioned about the use of PARP inhibitors, consensus was reached on the following: (1) requirement for *BRCA*/homologous recombination deficiency testing results to guide maintenance PARP inhibitor/bevacizumab therapy after primary chemotherapy; (2) consideration of response according to RECIST in addition to homologous recombination deficiency/*BRCA* status when finalizing maintenance treatment approach without adding other biomarkers; (3) continuing bevacizumab (if started) as maintenance treatment with addition of PARP inhibitor maintenance in patients with *BRCA* mutations or homologous recombination deficient (with *BRCA* wild-type/unknown) tumors; and (4) initiating PARP inhibitor monotherapy in patients not treated with first-line bevacizumab (Table 3). Half of panelists agreed that treatment decisions for bevacizumab should be made earlier than for PARP inhibitor (Table 3). Similarly, 69% agreed that biomarkers, such as KELIM, should be considered when finalizing maintenance treatment. For patients with homologous recombination unknown and *BRCA* wild-type/unknown status receiving first-line bevacizumab plus primary chemotherapy, 56% of panelists agreed that bevacizumab should remain as maintenance monotherapy.

Panelists were asked whether continuing maintenance treatment in isolated localized recurrence is recommended and how radiological progression can define progressive disease. There was consensus to treat isolated recurrent disease with local therapy before interrupting maintenance treatment. Consensus was not achieved for the definition of progressive disease, as 75% of panelists agreed this is radiological

Table 2 Considerations for high-risk disease and advanced ovarian cancer first-line treatment

Question	Variables	Agreement (%)	Disagreement (%)
Statements that achieved consensus			
What characteristics are you considering when defining a patient of high-risk in your practice?	Chemotherapy response should be assessed after neoadjuvant chemotherapy to define further systemic treatment decisions	**81.0**	19.0
Regarding adding bevacizumab to first-line platinum-based regimen in patients with **high-grade serous or high-grade endometrioid carcinomas with no previous bowel obstruction/sub-occlusion or extensive bowel resection**, how do you agree or disagree with the following statements?	Patients with homologous recombination deficiency tumors do not need to automatically receive bevacizumab first line	**82.0**	18.0
	Patients with *BRCA* mutation and/or homologous recombination deficiency tumors should receive bevacizumab first line, regardless of being 'high-risk'	12.0	**88.0**
	Patients with *BRCA* wild-type/unknown and/or homologous recombination proficient/homologous recombination unknown tumors should receive bevacizumab upfront, regardless of being 'high-risk'	18.7	**81.3**
	If an early good response (cycle 1–3) is achieved in platinum-based chemotherapy with bevacizumab, it is accepted that bevacizumab can be discontinued after terminating the chemotherapy, so that PARP inhibitor could be used as monotherapy maintenance treatment	18.7	**81.3**
What characteristics are you considering when defining a patient of high-risk in your practice?	High-risk advanced ovarian cancer is defined as FIGO III with residual disease after initial/interval cytoreduction or FIGO IV	**87.5**	12.5
	Worse chemotherapy response after neoadjuvant chemotherapy may be considered a high-risk characteristic	**81.3**	18.7
	Tumor primary chemosensitivity measured by worse KELIM scores may indicate a high-risk characteristic	**81.3**	18.7
Regarding adding bevacizumab to first-line platinum-based regimen in patients with **high-grade serous or high-grade endometrioid carcinomas and previous bowel obstruction/sub-occlusion or extensive bowel resection**, how do you agree or disagree with the following statements?	If an early good response (cycle 1–3) is achieved in platinum-based chemotherapy (ie, RECIST or KELIM score), it is accepted that bevacizumab is not added to chemotherapy, so that PARP inhibitor could be	**87.5**	12.5
	Patients with high-risk disease should receive bevacizumab upfront, regardless of *BRCA*/homologous recombination deficiency status	12.5	**87.5**
Statements that did not achieve consensus			
Regarding adding bevacizumab to first-line platinum-based regimen in patients with **high-grade serous or high-grade endometrioid carcinomas with no previous bowel obstruction/sub-occlusion or extensive bowel resection**, how do you agree or disagree with the following statements?	Patients with high-risk disease should receive bevacizumab upfront, regardless of *BRCA*/homologous recombination deficiency status	25.0	**75.0**
Regarding adding bevacizumab to first-line platinum-based regimen in patients with **high-grade serous or high-grade endometrioid carcinomas and previous bowel obstruction/sub-occlusion or extensive bowel resection**, how do you agree or disagree with the following statements?	Patients with *BRCA* wild-type/unknown and/or homologous recombination proficient/homologous recombination unknown tumors should receive bevacizumab upfront, regardless of being 'high-risk'	25.0	**75.0**
	Poor chemosensitivity after 1–3 cycles of initial chemotherapy (eg, determined by RECIST or KELIM score) should be an indication for adding bevacizumab	**75.0**	25.0

Bold values indicate the achieved (≥80% agreement or disagreement) or nearest-to-consensus across each statement. Furthermore the bold statements help indicate the differences among the patient characteristics.
FIGO, International Federation of Gynecology and Obstetrics; KELIM, CA-125 elimination rate constant K; PARP, poly(ADP-ribose) polymerase; RECIST, Response Evaluation Criteria in Solid Tumors.

Table 3 Considerations for advanced ovarian cancer maintenance therapy

Question	Variables	Agreement (%)	Disagreement (%)
Statements that achieved consensus			
The decision to use maintenance PARP inhibitor or bevacizumab (or both) should be made at the same time shortly after starting platinum-based chemotherapy	The decision to include bevacizumab and/or PARP inhibitor in the patient's first-line treatment should be made at the same time during receipt of platinum-based chemotherapy	19.0	**81.0**
	Homologous recombination deficiency/*BRCA* results are needed before a final decision on the use of maintenance treatment can be made	**88.0**	12.0
For *BRCA* mutation patients, who are already receiving bevacizumab (as part of the first-line regimen), you would recommend:	Keep bevacizumab and add PARP inhibitor as maintenance regimen	**88.0**	12.0
For homologous recombination deficiency (with *BRCA* wild-type/unknown) patients, who are already receiving bevacizumab (as part of the first-line regimen), you would recommend:	Keep bevacizumab and add PARP inhibitor as maintenance regimen	**94.0**	6.0
For *BRCA* mutation patients, not receiving bevacizumab (as part of the first-line regimen), you would recommend:	Add PARP inhibitor as maintenance regimen	**88.0**	12.0
The decision to use maintenance PARP inhibitor or bevacizumab (or both) should be made at the same time shortly after starting platinum-based chemotherapy	Response according to RECIST should be considered in addition to homologous recombination deficiency/*BRCA* when making a final decision on maintenance treatment with no need to add other biomarkers	**93.8**	6.2
For homologous recombination deficiency (with *BRCA* wild type/unknown) patients, not receiving bevacizumab (as part of first line), you would recommend:	Add PARP inhibitor as a maintenance regimen	**81.3**	18.7
Statements that did not achieve consensus			
The decision to use maintenance PARP inhibitor or bevacizumab (or both) should be made at the same time shortly after starting platinum-based chemotherapy	The decision to add bevacizumab has to be made earlier than PARP inhibitor in the treatment pathway	50.0	50.0
	Additional clinical biomarkers, such as KELIM, should be considered in addition to homologous recombination deficiency/*BRCA* when making a final decision on maintenance treatment	**69.0**	31.0
For homologous recombination unknown (with *BRCA* wild-type/unknown) patients, who are already receiving bevacizumab (as part of the first-line regimen), you would recommend:	Keep bevacizumab alone as maintenance therapy	**56.0**	44.0

Bold values indicate the achieved (≥80% agreement or disagreement) or nearest-to-consensus across each statement.
KELIM, CA-125 elimination rate constant K; PARP, poly(ADP-ribose) polymerase.

progression according to RECIST, with/without worsening (or appearance) of clinical symptoms; 25% agreed this definition only includes worsening of clinical symptoms.

Lastly, when questioned on the relevant supportive measures in patients receiving maintenance therapy, there was consensus on the importance of nutritional and psychological care during treatment. Panelists agreed that nutritional teams must follow up with patients during early treatment stages, and psychological support to caregivers should be offered by specialized teams (81.3% and 87.5%, respectively). However, 63% of panelists agreed that surgical teams should not follow up with patients, even in early maintenance therapy stages.

DISCUSSION

Summary of main results

Overall, panelists agreed that the key drivers for advanced ovarian cancer maintenance therapy treatment decisions are mutational status, phenotypic characteristics, and perceived risks for early disease progression.

Results in the context of published literature

The complexities of first-line advanced ovarian cancer treatment decision-making, differences in national regulations for drug access, and availability of predictive biomarkers have led to treatment variability across Europe. This Delphi analysis focused on biomarker strategy, and factors for treatment decision-making and maintenance therapy, that are relevant to clinicians.

The feasibility of parallel *BRCA*/homologous recombination deficiency testing was dependent on the availability of tissue samples.

Supported by the inclusion criteria of the PAOLA-1/ENGOT-ov25 and PRIMA/ENGOT-OV26/GOG-301 phase III randomized trials assessing maintenance therapy with PARP inhibitor, the European Society for Medical Oncology recommended that homologous recombination deficiency testing should be offered for high-grade disease only[8 18 19]; this is aligned with the consensus for homologous recombination deficiency testing achieved in this study. Nevertheless, panelists recommended the initiation of first-line platinum-containing chemotherapy prior to availability of test results, as studies have identified that delays between cytoreduction surgery and chemotherapy may elicit worse outcomes.[8 20]

Turnaround time for homologous recombination deficiency testing is an issue that may have influenced the consensus for the concurrent use of *BRCA*/homologous recombination deficiency testing before any maintenance treatment decisions; this approach is in line with a previously published European consensus.[21] Given the importance of *BRCA*/homologous recombination deficiency testing, panelists recommended the need for a multidisciplinary team to support timely homologous recombination deficiency testing and highlighted the importance of clinically validated tests. Panelists agreed that homologous recombination mutation panels should not replace validated homologous recombination deficiency assays that assess genomic instability.

Panelists reached consensus about somatic tumor testing for mismatch repair for clear cell, endometrioid, or mucinous carcinomas, as patients with advanced ovarian cancer are mismatch repair deficient, and the identification of Lynch syndrome-associated ovarian carcinomas is crucial for familial and genetic counseling.[22 23] However, determining DNA methylation status in patients with *BRCA* mutations was considered exploratory, and did not achieve consensus.

Selecting optimal maintenance treatment following first-line platinum chemotherapy is not a straightforward decision between bevacizumab and/or PARP inhibitor, or no maintenance therapy. Historically bevacizumab was shown to be active in patients with bulky disease. In a predefined subgroup analysis of the ICON-7 trial, in patients with a poor disease prognosis, a significant difference in overall survival was recorded between chemotherapy alone and bevacizumab plus chemotherapy (34.5 months, 95% CI 32.0 to 37.0 vs 39.3 months, 95% CI 37.0 to 41.7, respectively).[20] Similarly, in the GOG-0218 trial assessing patients with FIGO stage IV disease, chemotherapy plus concurrent and maintenance bevacizumab resulted in greater overall survival compared with chemotherapy alone.[22] In line with these two phase III trial results, panelists defined high-risk advanced ovarian cancer as FIGO stage III (with residual disease after initial/interval cytoreduction) or IV disease; therefore, residual disease after surgery may be an important adverse risk factor.[24]

KELIM scores, described as an early indicator of the chemotherapy efficacy, is based on the CA-125 longitudinal kinetics observed during the first 100 treatment days with platinum-containing chemotherapy.[25] Retrospective analyses of the GOG-0218 and ICON-7 trials identified a survival benefit in participants treated with bevacizumab who had high-risk advanced ovarian cancer and poorly chemosensitive disease defined by an unfavorable KELIM score (<1.0).[6 26] Our Delphi analysis identified consensus for the suitability of KELIM to indicate chemosensitivity and predict poor survival. The development of PARP inhibitors and their significant efficacy have made the treatment decision process more complex. Guidelines recommend single-agent PARP inhibitor, or in combination with bevacizumab, for patients with *BRCA* and/or homologous recombination deficiency status whose disease is responsive to first-line platinum-based chemotherapy.[8 18 27]

Platinum sensitivity and *BRCA*/homologous recombination deficiency status are indeed predictive factors for PARP inhibitor sensitivity. In line with clinical trials evaluating PARP inhibitor maintenance, panelists recommended that no evidence of disease or a complete/partial response on completion of first-line platinum-based chemotherapy is required for the initiation of PARP inhibitor maintenance. The PRIMA, PRIME, and ATHENA trials assessed PARP inhibitor maintenance after primary chemotherapy and recorded a benefit irrespective of *BRCA*/homologous recombination deficiency status; therefore, PARP inhibitor monotherapy is a treatment option for patients not requiring or receiving bevacizumab. For patients with *BRCA* wild-type/unknown and homologous recombination deficient tumors already treated with bevacizumab and chemotherapy, there was consensus for the continuation of bevacizumab.[10] In patients with high-risk disease with *BRCA*/homologous recombination deficiency status, panelists agreed that bevacizumab should not automatically be added to first-line platinum-containing chemotherapy. Chemotherapy response might be relevant for maintenance treatment decision-making. However, the impact of chemosensitivity on the efficacy of olaparib with bevacizumab could not be assessed in the PAOLA-1 trial.

Defining disease progression during maintenance treatment is fundamental, owing to the high risk of relapse of advanced ovarian cancer.[2] Although consensus was not achieved, a large proportion of panelists defined this as radiological progression associated with or without the worsening of clinical symptoms. Retrospective analysis of oligometastatic progressive advanced ovarian cancer during maintenance PARP inhibitor therapy has shown encouraging progression-free survival after local treatment without withdrawing PARP inhibitor therapy.[28 29] Based on these results, panelists achieved consensus on the use of local therapy to treat isolated recurrent disease, without disrupting maintenance treatment.

Strengths and weaknesses

The main strength of this study is the Delphi methodology approach, which helps with understanding treatment decision-making in different European countries. While our methodology may be affected by the number of participants, Delphi studies are driven by the expertise of panelists. Therefore, the consensuses recorded here are valuable, as they are based on the opinions of highly specialized oncologists or gynecologists who have strong expertise in ovarian cancer across Western Europe. Although we utilized a representative panel from across Western Europe, the expert consensus recorded does not include perspectives of oncologists from Eastern Europe. Lastly, the use of one literature search database rather than multiple sources in our methodology may have reduced the extent of our search coverage. However, the search results supported questionnaire development and facilitated expert panel discussions, justifying the sole use of EMBASE as suitable for this purpose.

Implications for practice and future research

Consensus was achieved for first-line bevacizumab treatment in patients with no previous bowel obstruction/sub-occlusion/resection, owing to the increased risk of bevacizumab-related bowel complications, including bleeding and perforation.[30] Our results suggest cautious use of anti-angiogenic drugs in patients who have had prior bowel surgery. International real-world studies have shown heterogeneity in the use of advanced ovarian cancer maintenance therapies.[31–35] Variability of clinical trial design (inclusion/exclusion criteria, control arms, and treatment schedules), toxicity profiles, biomarker testing, patient and physician preferences, and regulation of healthcare reimbursement may contribute to this.[13]

CONCLUSION

Recorded consensus from panelists' responses to the questionnaires suggest that parallel *BRCA*/homologous recombination deficiency testing at diagnosis in patients with advanced ovarian cancer is an important requirement for first-line and maintenance treatment decisions, regardless of the histological subtype. PARP inhibitor maintenance should be used in patients with *BRCA* mutations and/or who are homologous recombination deficiency. However, there was a lower propensity to use such treatments in the all-comer population. Bevacizumab maintenance is considered preferentially in patients with high-risk disease exhibiting *BRCA* wild-type/unknown and/or homologous recombination deficiency status unknown tumors. In addition, consensus supported the use of clinical biomarkers, including indicators of chemotherapy response, to support decisions about PARP inhibitor/bevacizumab use. Conversely, no consensus was reached on some aspects of management that will continue to rely on clinical judgment.

Further evidence may inform updates to future consensus. Ongoing trials, such as NIRVANA and AGO-OVAR 28/ENGOT-ov57, aim to show the benefit of PARP inhibitor monotherapy versus bevacizumab plus PARP inhibitor in patients with advanced ovarian cancer.[36 37] Moreover, the SALVOVAR trial is investigating the heterogeneity of *BRCA*/homologous recombination deficiency assays and the benefit of chemotherapy dose intensification in patients who are poorly chemosensitive with high-risk diseases. Future research is required on maintenance therapy in patients with FIGO stage II disease, with histologies other than high-grade serous, and with stable disease following first-line chemotherapy.

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Acknowledgements We acknowledge Xin Yan Li, Nichola Roebuck, and Bruno D'Almeida of GSK, for providing expertise and time during this study. Medical writing support, including assisting authors with the development of the initial draft and incorporation of comments, was provided by Hussain Merchant, MSc, and editorial support, including figure preparation, formatting, proofreading and submission was provided by Ian Norton, PhD, and Melissa Ward, BA, all of Scion (a division of Prime, London, UK), according to Good Publication Practice guidelines (link). The study was funded by GSK, London, UK. The sponsor was involved in the study design and collection, analysis, and interpretation of data, as well as data checking of information provided in the manuscript. However, ultimate responsibility for opinions, conclusions and data interpretation lies with the authors.

Contributors All authors were involved in the study investigation as well as the writing, reviewing and editing of the manuscript. BS, APF, and BY were involved in the development of study design, screening of literature, development of questionnaire for Delphi consensus, collection, analysis and interpretation of data. APF is the guarantor of this study.

Funding Funding for this study was provided by GSK.

Competing interests BY has had consulting positions for MSD, AstraZeneca, GSK-TESARO, Bayer, Roche-Genentech, ECS Progastrin, Novartis, LEK, Amgen, Clovis Oncology, Merck Serono, BMS, Seagen, Myriad, Menarini, Gilead, and Eisai. APF has had advisory roles for AstraZeneca, GSK-Tesaro, Clovis, PharmaMar, Abilify Pharma, and Eisai; has been a speaker for AstraZeneca, GSK-Tesaro, Clovis, PharmaMar, Karyopharm and Seagen; and has received research grants to their institution from GSK, PharmaMar, AstraZeneca, and Novartis. BS has received grants/research support from AstraZeneca, Roche, MSD, and GSK; honoraria or consultation fees from AstraZeneca, Roche, MSD, GSK, and Eisai; and has participated in company-sponsored speakers bureaus for AstraZeneca, Roche, MSD, GSK, and Eisai. AG has received honoraria from AstraZeneca, GSK, Merck, Roche, and Clovis; and has been a speaker for AstraZeneca, GSK, Merck, and Clovis. CG has received grants from AstraZeneca, MSD, Novartis, GSK, BerGen Bio, Merdannex, Roche, and Verastem; and has received honoraria from AstraZeneca, MSD, GSK, Clovis, Verastrem, Takeda, Eisai, Cor2Ed, and Peer Voice. SP has received honoraria from AstraZeneca, MSD, GSK, Roche, Clovis, Immunogen and AbbVie; and research/funding from AstraZeneca, Roche, MSD, and GSK. DL has had consulting or advisory roles for AstraZeneca, Corcept, Clovis Oncology, Daiichi Sankyo, Genmab, GSK, Immunogen, MSD, Novartis, Oncoinvest, Novocure, Seagen, Sutro; has received research funding to their institution from AstraZeneca, Clovis Oncology, Pharma & Genmab, GSK, Immunogen, Incyte, MSD, Novartis, Pharmamar, Roche, Seagen, alkermes and Corcept; has received travel accommodation/expenses from AstraZeneca, GSK and MSD. MPBG has had advisory roles for AstraZeneca, MSD, GSK, Clovis, PharmaMar, and Eisai; has been a speaker for AstraZeneca, MSD, GSK, Clovis, and PharmaMar; and has received travel accommodation and expenses from AstraZeneca, MSD, GSK, and PharmaMar. IR has had advisory roles for Roche, AstraZeneca, GSK, and Clovis; has received grants/research support from Roche, AstraZeneca, and GSK; has received honoraria from PharmaMar, Roche, AstraZeneca, GSK, MSD, Eisai, and Seagen; and has been a sponsored speaker for PharmaMar, Roche, AstraZeneca, GSK, and MSD. CGr has received funding from AstraZeneca, Meda Pharma, and Roche Diagnostics; honoraria or consultation fees from AstraZeneca, Celgene, Clovis, Eisai, GSK, MSD, PharmaMar, Roche, and Vifor Pharma; and has participated in company-sponsored speakers bureaus for Amgen, AstraZeneca, Eisai, GSK, MSD, PharmaMar, and Roche. TVG has consulted/advised for

AstraZeneca, BioNTech, Eisai, GSK, ImmunoGen, Incyte, Karyopharm, MSD/Merck, OncXerna Therapeutics, Seagen, Tubulis, Zentalis; travel, accommodations, and/or expenses paid by AstraZeneca, ImmunoGen, MSD/Merck, PharmaMar; research funding from Amgen, AstraZeneca, and Roche; all payments are institutional. MR has received grants/research support from Neye Foundation, Novo Nordisk Foundation, and AstraZeneca; and has received honoraria or consultation fees from Laegeforeningen/Danish Medical Association, AstraZeneca, and GSK. DCC has received honoraria from Amgen, AZD, GSK, Janssen, Pfizer, and MSD Oncology; has had consulting or advisory roles with Seagen, Genmab, MSD Oncology, and GSK; and has received research funding from Roche and Pfizer. JF has received honoraria from AstraZeneca and GSK. LB has received funding from AstraZeneca, Helse Vest, and the University of Bergen; has been a sponsored speaker for GSK and MSD. AL has received funding from Sanofi, Roche, GSK, BMS, AstraZeneca, Ose Immuno, Lovance, Agenus, Arcagy Gineco, Ability Pharma, Apmonia, Blueprint Medicines Corporation, MSD, Clovis, Merck Serono, Onko+, Zentalis, Kephren, and Medscape. TdIMR has received grants/research support from Seagen, MSD, and Pfizer; honoraria or consultation fees from AstraZeneca, Pfizer, MSD, GSK, Gilead, Clovis Oncology, and Esai; and has participated in company-sponsored speakers bureaus for AstraZeneca, GSK, and MSD. PH has received honoraria from Amgen, AstraZeneca, GSK, Roche, Sotio, Stryker, Zai Lab, MSD, Clovis, Eisai, Mersana, and Exscientia; has participated in advisory boards for AstraZeneca, Roche, GSK, Clovis, Immunogen, MSD, Miltenyi, Novartis, and Eisai; and has received research funding to their institution from AstraZeneca, Roche, GSK, Genmab, DFG, European Union, DKH, Immunogen, Seagen, Clovis, and Novartis. CK has received honoraria or consultation fees from GSK, AstraZeneca, Novartis, PharmaMar, Genomic Health, Roche, Eli Lilly, Merck MSD, Pfizer, and Daiichi Sankyo; has participated in company-sponsored speakers bureaus for GSK, AstraZeneca, Novartis, and Roche; and has received travel support from GSK, AstraZeneca, and Roche. JS-B has received honoraria or consultation fees from AstraZeneca, GSK, and MSD; and has received grants/research support from AstraZeneca, Novartis, Pfizer, and Roche.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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