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Bevacizumab in first-line postoperative treatment of advanced ovarian cancer: from high-risk stratification to precision decision-making

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Bevacizumab is an important component of first-line therapy for advanced epithelial ovarian cancer; however, the precise identification of patients who will benefit and how to optimize its use in the era of poly (ADP-ribose) polymerase inhibitors (PARPi) remains a core challenge in clinical practice. This review systematically revisits the pivotal phase III trials GOG-0218 and ICON7, together with their inherent limitations, with a particular focus on the role of KELIM score as a dynamic marker of chemotherapy sensitivity in predicting bevacizumab efficacy. Based on the interaction test from GOG-0218, the available evidence suggests that BRCA/homologous recombination deficiency (HRD) status does not alter the single-agent activity of bevacizumab; however, these genetic markers remain crucial for guiding PARPi or combination regimens. A key clinical dilemma arises when patients with a BRCA mutation have already received bevacizumab during first-line chemotherapy: should bevacizumab be continued or discontinued during the maintenance phase? This review presents a preference analysis and individualized decision-making factors based on available indirect evidence and current guidelines. Finally, a clinical decision pathway that integrates KELIM assessment with HRD testing is proposed to provide an evidence-based reference framework for the rational use of bevacizumab in first-line advanced ovarian cancer.

KEYWORDS
advanced ovarian cancer, bevacizumab, BRCA, first-line treatment, HRD, KELIM SCORE, PARP inhibitor

1 Introduction

High-grade serous carcinoma (HGS) is the most common histological type of ovarian cancer. Despite advances in cytoreductive surgery and platinum-based chemotherapy, approximately 70% of patients relapse within 2 years of initial treatment, and the 5-year overall survival (OS) rate remains below 50% (Bowtell et al., 2015; Balkwill et al., 2026). In recent years, the introduction of poly (ADP-ribose) polymerase inhibitors (PARPi) inhibitors has substantially improved the prognosis of patients with BRCA mutations or homologous recombination deficiencies (HRD). Nevertheless, nearly half of the patients, particularly those with homologous recombination-proficient (HRP) disease, do not benefit from PARPi maintenance therapy (González-Martín et al., 2023). Consequently, carboplatin

plus paclitaxel, with or without the anti-angiogenic agent bevacizumab, remains the backbone of the first-line therapy for these patients.

Bevacizumab is a humanized monoclonal antibody targeting vascular endothelial growth factor (VEGF). The large phase III trials GOG-0218 and ICON7 demonstrated that adding bevacizumab to standard chemotherapy followed by continuous maintenance significantly prolongs progression-free survival (PFS) in high-risk patients, and an OS benefit was observed in a pre-specified high-risk subgroup of ICON7 (stage IV or stage III with residual disease >1 cm after primary debulking surgery) (Burger et al., 2011; Oza et al., 2015). However, the "high-risk" classification is a relatively crude clinical parameter, and a substantial proportion of patients who receive bevacizumab derive no clear benefit. With the advent of precision medicine, there is an urgent need for more accurate selection of patients who will truly benefit from bevacizumab.

Moreover, the emergence of PARPi fundamentally reshaped the maintenance treatment landscape. The role of bevacizumab has shifted from "single-agent maintenance" to a "combination partner" for PARPi, as shown in the PAOLA-1 trial, which established the value of olaparib plus bevacizumab in HRD-positive populations (Ray-Coquard et al., 2023; Lorusso et al., 2024). Nevertheless, for patients with a BRCA mutation who have already received bevacizumab during first-line chemotherapy, the optimal maintenance strategy—whether to continue bevacizumab together with a PARPi or to switch to PARPi monotherapy—lacks direct high-level evidence and represents a difficult clinical decision.

This review aimed to systematically synthesize the evidence on bevacizumab use in first-line advanced ovarian cancer, objectively evaluate the potential roles of the KELIM score and BRCA/HRD status in treatment decisions, and propose a clinical thinking framework based on the best available evidence. It is important to emphasize that the framework described herein relies mainly on indirect evidence and *post hoc* analyses. Prospective validation is lacking for some clinical situations, and clinical judgement must always be individualized.

1.1 Literature search strategy

This is a narrative review. A comprehensive literature search was performed in PubMed/MEDLINE and Embase from database inception to 30 June 2026 (last search date). The search strategy combined the following terms using Boolean operators: ("bevacizumab" OR "Avastin") AND ("ovarian cancer" OR "ovarian neoplasm" OR "ovarian carcinoma") AND ("KELIM" OR "CA-125 kinetics" OR "BRCA" OR "homologous recombination deficiency" OR "HRD" OR "PARP inhibitor" OR "biomarker"). Reference lists of key articles and relevant clinical practice guidelines were manually searched. Studies were considered eligible if they reported on bevacizumab use in first-line advanced ovarian cancer, biomarker analyses relevant to bevacizumab efficacy, or clinical practice guidelines from major oncology societies. Only English-language publications were included. Conference abstracts, editorials, and case reports were excluded. No formal systematic review protocol was registered, and the synthesis is narrative rather than quantitative.

2 Pivotal phase III trials: foundations and limitations

2.1 Overview of GOG-0218 and ICON7

GOG-0218 enrolled 1 873 patients with stage III–IV epithelial ovarian cancer who were randomly assigned to one of three arms: chemotherapy plus placebo, chemotherapy plus concurrent bevacizumab (15 mg/kg every 3 weeks) plus placebo maintenance, or chemotherapy plus concurrent bevacizumab followed by bevacizumab maintenance (total 15 months). The median PFS in the bevacizumab maintenance arm was extended from 10.3 months to 14.1 months (hazard ratio [HR] 0.71, 95% confidence interval [CI] 0.63–0.81), whereas OS was not significantly different (Burger et al., 2011).

The ICON7 included 1 528 patients who were randomized to receive chemotherapy with or without bevacizumab (7.5 mg/kg every 3 weeks) concurrently, after which the bevacizumab group continued maintenance for 12 months. In the overall population, PFS improved (HR 0.81, 95% CI 0.70–0.94), but OS did not. However, in a pre-specified high-risk subgroup (stage IV or stage III with residual disease >1 cm; 30% of the overall population), bevacizumab significantly prolonged median OS (39.7 months vs. 30.2 months; HR 0.78, 95% CI 0.63–0.97) (Oza et al., 2015).

2.2 Differences in high-risk definitions and evidence limitations

Subgroup analyses of both trials indicated that the OS benefit of bevacizumab was confined to specific high-risk patient subsets, but the two studies differed importantly in how "high-risk" was defined (detailed in Table 1):

- The ICON7 defined the high-risk subgroup (*post hoc* exploratory analysis) as patients with stage IV disease, stage III disease with postoperative residual disease >1 cm, or inoperable/unresected stage III disease. In this subgroup, the OS HR was 0.78 (95% CI 0.63–0.97) (Oza et al., 2015).
- GOG-0218 required that stage III patients have "any gross residual disease" at the time of study entry. A *post hoc* analysis indicated a more pronounced OS benefit for stage IV patients (HR 0.72, 95% CI 0.53–0.97), whereas the benefit for stage III patients with any gross residual disease did not reach statistical significance (Burger et al., 2011; Tewari et al., 2019).

The stricter cut-off used in ICON7 (>1 cm) compared with GOG-0218 (any gross residual disease) may partly explain the differing magnitude of the OS benefit seen in the high-risk subgroups. Importantly, both definitions stem from *post hoc* exploratory analyses and were not prespecified stratification factors in the original trial designs, which is a significant limitation in the level of evidence they provide.

Declaration of evidence limitations: The "high-risk" definitions used in GOG-0218 and ICON7 originate from *post hoc* exploratory subgroup analyses rather than from pre-specified primary analysis plans. Therefore, the OS benefit conclusions derived from these analyses carry a relatively low grade of evidence. Subsequent KELIM validation studies built upon this foundation by assessing tumor

TABLE 1 Comparison of bevacizumab regimens and high-risk definitions in GOG-0218 and ICON7.

Item	GOG-0218	ICON7
Study phase	Phase III randomised controlled trial	Phase III randomised controlled trial
Population	Newly diagnosed stage III-IV epithelial ovarian cancer	Newly diagnosed stage IIb-IV epithelial ovarian cancer (including high-risk early stage)
Bevacizumab dose	15 mg/kg every 3 weeks	7.5 mg/kg every 3 weeks
Treatment duration	Concurrent (up to 6 cycles) + maintenance (total 15 months)	Concurrent (up to 6 cycles) + maintenance (total 12 months)
Control arm	Chemotherapy alone	Chemotherapy alone
Overall PFS benefit	Median PFS 10.3 → 14.1 months, HR 0.71 (0.63–0.81)	Median PFS 17.3 → 19.0 months, HR 0.81 (0.70–0.94)
Overall OS benefit	None (median OS 41.1 vs. 43.4 vs. 40.8 months)	None
High-risk definition (exploratory)	Stage III with any gross residual disease + stage IV (by entry criteria)	Stage IV; stage III with residual >1 cm; inoperable stage III
OS benefit in high-risk subgroup	Stage IV: HR 0.72 (0.53–0.97); stage III with residual not significant	HR 0.78 (0.63–0.97)
Evidence limitation	High-risk from entry criteria; OS benefit from *post hoc* analysis	Subgroup pre-specified but still exploratory

Abbreviations: HR, hazard ratio; CI, confidence interval; PFS, progression-free survival; OS, overall survival.
High-risk definitions in both trials are derived from *post hoc* exploratory analyses; therefore, the associated OS, benefits represent a lower level of evidence compared to pre-specified primary endpoints.

-intrinsic chemosensitivity have provided a more predictive dynamic marker for the precise use of bevacizumab.

3 Core predictive biomarkers for bevacizumab efficacy

3.1 KELIM score: a dynamic measure of chemosensitivity

Definition and calculation: The KELIM score quantifies tumor -intrinsic sensitivity to chemotherapy by modelling the rate of decline in CA-125 during the first 100 days of first-line treatment. The KELIM score was first described and validated in the CALYPSO trial (You et al., 2013). The calculation can be performed using an online tool (available at http://www.biomarker-kinetics.org/). A low KELIM score (<1.0) indicates a chemotherapy-"indolent" tumor, whereas a high score (≥1.0) indicates a chemotherapy-sensitive tumour (You et al., 2022; Ambrosino et al., 2026).

Evidence for predicting bevacizumab benefit: A validation study based on the GOG-0218 dataset (2022) demonstrated that, among patients with high-risk disease, only those with a KELIM score <1.0 experienced a clear OS benefit from bevacizumab (median OS 35.1 vs. 29.1 months; HR 0.79, 95% CI 0.65–0.97). In contrast, patients with a KELIM score ≥1.0 showed no difference in OS, regardless of whether they received bevacizumab (HR 1.11) (You et al., 2022). Similar findings were observed in *post hoc* analyses of ICON7 (Ambrosino et al., 2026). Additional real-world studies have confirmed the independent prognostic value of the KELIM score in patients receiving contemporary treatment modalities (Lv et al., 2025).

Clinical implications: The KELIM score is an easily accessible dynamic marker that can serve as a supplementary tool for selecting patients who are most likely to benefit from bevacizumab. For patients with a KELIM score ≥1.0, the available evidence from *post hoc* analyses suggests no clear benefit from bevacizumab. However, the predictive value of KELIM has not been prospectively validated, and these findings should be interpreted with caution pending confirmatory studies. The KELIM cutoff of 1.0 has been applied consistently across multiple independent cohorts, including CALYPSO, ICON7, GOG-0218, the ESME cohort (n = 743), and the CHIVA trial. However, these are predominantly retrospective or *post hoc* analyses. Prospective validation with pre-specified thresholds, standardized KELIM calculation methods, and diverse patient populations is needed before KELIM can be adopted as a routine treatment-selection tool.

3.2 BRCA/HRD status: no evidence of predictive value for single-agent bevacizumab

3.2.1 Interaction test from GOG-0218

A pre-planned biomarker analysis of GOG-0218 sequenced homologous recombination repair (HRR) genes (including BRCA1/2 and other HRR genes) in 1,195 patients and tested whether gene status modified the effect of bevacizumab. In this analysis, no significant interaction was detected between BRCA/HRR status and bevacizumab treatment effect on PFS (interaction HR 1.33, 95% CI 0.95–1.85, p = 0.10) (Norquist et al., 2018). Likewise, the final OS analysis identified no biomarker (including BRCA/HRD) that could predict bevacizumab activity (Burger et al., 2011; Tewari et al., 2019). However, interaction tests are inherently underpowered, and the absence of a statistically significant interaction does not exclude

TABLE 2 Predictive value of biomarkers for bevacizumab efficacy: evidence and current clinical utility.

Biomarker	Study design	Assay/cut off	Prespecified vs. exploratory	Interaction statistic	Effect estimate (95% CI)	Validation status	Clinical utility
KELIM	Post-hoc (GOG-0218/ ICON7)	CA-125 kinetics; cut off 1.0	Post-hoc	Not applicable	OS HR 0.79 (0.65–0.97) for KELIM<1.0	Prognostic validated; predictive not prospectively validated	Potential selection tool (hypothesis-generating)
HRR gene mutations (including BRCA1/2)	Pre-planned biomarker analysis (GOG-0218)	HRR gene panel (16 genes)	Pre-planned	p = 0.10 (interaction HR 1.33, 95% CI 0.95–1.85)	No significant interaction	Not predictive	Guides PARPi, not bevacizumab
Immune molecular subtype (TCGA)	Exploratory (ICON7)	Gene expression (DASL)	Exploratory	Not reported	Immunoreactive: PFS HR 0.67 (0.42–1.05), P = 0.08; proliferative: PFS HR 0.55 (0.34–0.90), P = 0.016	Not prospectively validated	Exploratory – not for clinical use
c-MET/VEGFR-2 high co-expression	Exploratory (ICON7)	Immunofluorescence	Exploratory	Not reported	OS HR 2.00 (1.08–3.72)	Not validated	Not for clinical use
Tumour-infiltrating leucocytes	Exploratory (MITO16A)	Immune infiltration	Exploratory	Not reported	Shorter PFS	Not validated	Not for clinical use

Abbreviations: HR, hazard ratio; CI, confidence interval; OS, overall survival; PFS, progression-free survival; PARPi, poly (ADP-ribose) polymerase inhibitor; HRD, homologous recombination deficiency; TILs, tumour-infiltrating leucocytes.
A KELIM, score <1.0 indicates chemotherapy-indolent tumours, whereas ≥1.0 indicates chemosensitive tumours. The predictive value of KELIM, for bevacizumab benefit has been validated in prospective cohorts, whereas all other biomarkers listed remain exploratory and require independent validation. HRD, and ViRP, were excluded due to lack of sufficient published data with peer-reviewed full-text evidence.

the possibility of a clinically meaningful subgroup effect. These findings should therefore be interpreted as "no evidence of predictive interaction," rather than "evidence of no predictive interaction".

3.2.2 Translational analysis of ICON7

The ICON7 translational study classified tumors as HRD-type or non-HRD -type and found no clear interaction between the HRD status and bevacizumab efficacy (Kommoss et al., 2017). The "rebound effect" after bevacizumab discontinuation was observed in both HRD and non-HRD tumors, further supporting the notion that the mechanism of bevacizumab activity is not directly linked to HRD status.

3.2.3 Clinical implication

Based on the available evidence, the BRCA/HRD status should not be used as a criterion for selecting patients for bevacizumab monotherapy. The value of these genetic markers lies in guiding PARPi or combination regimens; for example, BRCA-mutated patients may be considered for PARPi monotherapy maintenance, while HRD-positive (non-BRCA -mutated) patients may be considered for the bevacizumab + PARPi combination (see Section 4.1). A summary of the predictive biomarkers is presented in Table 2.

3.3 Relationship between BRCA mutation and KELIM score and their independent value

BRCA mutation is a well-established favorable prognostic marker that largely reflects high sensitivity to platinum-based chemotherapy. A French study that enrolled 743 patients with advanced high-grade serous ovarian cancer reported that the median standardized KELIM score was significantly higher in BRCA-mutated patients than in wild-type patients (1.16 vs. 1.06; p = 0.001) (You et al., 2013). A similar trend was observed in Asian cohorts (Liu et al., 2025).

Subgroup	Median PFS
BRCA wild-type/KELIM <1.0	12.0 months
BRCA mutated/KELIM <1.0	16.0 months
BRCA wild-type/KELIM ≥1.0	18.8 months
BRCA mutated/KELIM ≥1.0	28.8 months

Importantly, this association is a group-level trend and should not be extrapolated simplistically to individual patients. The same French study clearly illustrated prognostic differences among the four subgroups.

These data indicate three points: (i) the proportion of KELIM ≥1.0 is indeed higher among BRCA-mutated patients; (ii) a subset of BRCA-mutated patients still has a KELIM score <1.0 and their prognosis is significantly worse than that of BRCA-mutated patients with KELIM ≥1.0, implying that even in the presence of a BRCA mutation some tumors show intrinsic chemotherapeutic "indolence"; and (iii) the KELIM score can further refine prognosis within both BRCA-mutated and BRCA wild-type populations.

Clarifying statement: The above analysis is intended to illustrate the group-level association and individual variability between BRCA status and KELIM score; it is not meant to suggest that BRCA status should determine bevacizumab use. In contrast, the core message of this review is that regardless of BRCA status, the decision to use bevacizumab should be guided by the KELIM score. Patients with a KELIM score <1.0 (whether they carry a BRCA mutation) constitute the potential benefit population for bevacizumab, whereas patients with a KELIM score ≥1.0 (again regardless of BRCA status) are not routinely recommended for bevacizumab. The value of BRCA/HRD status is in guiding PARP inhibitors or combination strategies, and not in selecting bevacizumab therapy.

4 The evolving role of bevacizumab in the PARP inhibitor era

4.1 Evidence from the PAOLA-1 trial

PAOLA-1 was a phase III randomized controlled trial that enrolled 806 patients with newly diagnosed advanced ovarian cancer (stage III–IV) who achieved a complete or partial response after first-line platinum-based chemotherapy plus bevacizumab. Patients were randomized (2:1) to receive maintenance olaparib + bevacizumab or placebo + bevacizumab (Ray-Coquard et al., 2019; 2023).

The primary endpoint was PFS. Among patients with HRD-positive tumours (approximately 48% of the intention-to-treat population), the median PFS was 37.2 months in the olaparib + bevacizumab group vs. 17.7 months in the placebo + bevacizumab group (HR 0.33, 95% CI 0.25–0.45). The 5-year PFS rates were 46.1% and 19.2%, respectively. OS analysis showed that the addition of olaparib to bevacizumab reduced the risk of death by 38% in the HRD-positive subgroup (HR 0.62, 95% CI 0.45–0.85), with 5-year OS rates of 65.5% and 48.4%, respectively (Ray-Coquard et al., 2023; Lorusso et al., 2024).

In the HRD-negative subgroup, no clinically meaningful difference in PFS or OS was observed between the combination and bevacizumab monotherapy arms (OS HR 1.19, 95% CI 0.88–1.63). Further stratified analyses indicated that the PFS and OS benefits of the combination therapy were primarily limited to HRD-positive patients.

Taken together, the evidence supports the following:

- For patients with HRD-positive, non-BRCA -mutated tumors, the PAOLA-1 study demonstrated that olaparib + bevacizumab maintenance therapy provides superior PFS and OS compared with bevacizumab alone, and this combination has become a standard-of-care maintenance option for this population.
- For patients with a BRCA mutation, the SOLO-1 trial showed that maintenance olaparib monotherapy yields a 7-year OS rate of 67.0% (Moore et al., 2018; DiSilvestro et al., 2023). There is currently no high-level evidence directly comparing a PARP inhibitor + bevacizumab combination with a PARP inhibitor alone in the BRCA-mutated population; therefore, the relative merits of the two strategies remain to be clarified.
- For HRD-negative patients, the combination of olaparib + bevacizumab has not demonstrated benefit.

4.2 A difficult clinical dilemma: discontinuation or continuation of bevacizumab in BRCA-mutated patients who received bevacizumab during first-line chemotherapy

4.2.1 Clinical scenario

In real-world practice, some patients with advanced ovarian cancer receive bevacizumab during first-line chemotherapy because of high-risk features (e.g., stage IV, bulky residual disease, or KELIM <1.0), and a BRCA1/2 pathogenic mutation was subsequently discovered. At the point of maintenance therapy, the treating physician faces a choice between two strategies: (A) continuing bevacizumab and adding a PARP inhibitor or (B) discontinuation of bevacizumab and maintenance with a PARP inhibitor alone. No phase III randomized controlled trial has directly compared these two strategies.

4.2.2 Available indirect evidence

Evidence tending to favour bevacizumab discontinuation (strategy B):

- SOLO-1 trial: Olaparib monotherapy maintenance was highly effective in BRCA-mutated patients, and the vast majority of enrolled patients did not receive bevacizumab during first-line chemotherapy (DiSilvestro et al., 2023).
- FZOCUS-1 trial: This phase III study directly compared a PARP inhibitor (fuzuloparib) alone vs. a PARP inhibitor plus an anti-angiogenic agent (apatinib) in the maintenance phase. Among patients with BRCA mutation/HRD-positive tumors, the addition of the anti-angiogenic agent did not provide additional PFS benefit (combination vs. monotherapy HR approximately 0.57 vs. 0.58) (Wu et al., 2026). However, the study used apatinib (not bevacizumab) and patients had not received anti-angiogenic therapy during the preceding chemotherapy phase; therefore, the generalizability of these findings to the current clinical scenario requires caution.
- Retrospective studies: Bevacizumab monotherapy maintenance did not show any oncological benefit in patients with BRCA-mutations (Duska et al., 2025).

TABLE 3 Factors favouring PARPi monotherapy versus combination (PARPi + bevacizumab) as maintenance in BRCA-mutated patients who received bevacizumab during first-line chemotherapy.

Consideration	Favouring PARPi monotherapy (discontinue bevacizumab)	Favouring combination (PARPi + bevacizumab)
Very high-risk features (stage IV, bulky residual, KELIM<1.0)	Absent	Present
Response to initial therapy	Complete remission (CR)	Partial remission (PR)
Tolerability of bevacizumab	Grade ≥2 adverse events (hypertension, proteinuria, thrombosis)	Well tolerated, no grade ≥2 toxicity
Economic/accessibility	Cost-sensitive or not reimbursed	Favourable financial situation or reimbursement
Patient preference	Prefers avoiding multidrug toxicity and burden	Accepts more intensive strategy

No head-to-head phase III RCT, evidence is available. This table is based on indirect evidence from SOLO-1 (DiSilvestro et al., 2023), FZOCUS-1 (Wu et al., 2026), PAOLA-1 (Ray-Coquard et al., 2019; 2023), and NCCN, guideline expert opinion (NCCN, 2026). For patients without very high-risk features, those who achieved CR, or those with poor tolerability to bevacizumab, switching to PARPi, monotherapy may be considered a reasonable option.

- Toxicity and cost considerations: Combination therapy increases the incidence of adverse events such as hypertension and proteinuria as well as healthcare costs (Ray-Coquard et al., 2023).

Evidence tending to favour continuation of bevacizumab (strategy A):

- PAOLA-1 trial: The combination of olaparib and bevacizumab was superior to bevacizumab alone in HRD-positive patients, including those with a BRCA mutation (Ray-Coquard et al., 2023; Lorusso et al., 2024). However, the control arm in that study was bevacizumab alone, not a PARP inhibitor alone; therefore, it does not directly answer whether the combination is superior to PARP inhibitor monotherapy.

4.2.3 Position of the NCCN guidelines (version 4.2026)

The latest NCCN guidelines state the following: "After first-line therapy with bevacizumab, data are limited on maintenance therapy with a single-agent PARPi for patients with a germline or somatic BRCA1/2 P/LP variants. However, based on the magnitude of the benefit of PARPi maintenance therapy for other subgroups, single-agent PARPi can be considered." This statement indicates that, despite limited direct evidence, single-agent PARP inhibitor maintenance can be considered for patients with a BRCA mutation who have received bevacizumab during first-line treatment, thereby providing authoritative support for the "switch to PARPi monotherapy" strategy.

4.2.4 Preference analysis and individualised decision-making factors

Based on the NCCN framework and the most recent evidence, several factors may help in individualized decision-making. The results are summarized in Table 3.

4.2.5 Declaration of evidence gaps

It must be emphasized that the preference analysis presented above is based largely on indirect evidence and expert consensus. Specifically, no prospective randomized data directly compare PARPi monotherapy with PARPi + bevacizumab in BRCA-mutated patients who received bevacizumab during first-line chemotherapy. The FZOCUS-1 trial provides the closest indirect comparison, but its use of apatinib and the absence of anti-angiogenic exposure during the chemotherapy phase limit its direct extrapolation. Well-designed head-to-head studies are eagerly required.

4.3 Interpretation of different study designs

Understanding the differences in study designs is essential for correct interpretation of the evidence:

- GOG-0218/ICON7 employed a "concurrent chemotherapy + maintenance monotherapy" design, addressing the question of whether bevacizumab should be used.
- FZOCUS-1 used a "pure maintenance" design (no anti-angiogenic agent during chemotherapy), addressing the question of whether an anti-angiogenic agent should be added when a PARP inhibitor is already being used for maintenance.
- Conclusions from one design cannot be directly extrapolated to a different clinical context.

Cross-trial extrapolation in this review is based on the following considerations: (1) all five trials (GOG-0218, ICON7, PAOLA-1, SOLO-1, and FZOCUS-1) enrolled patients with newly diagnosed advanced high-grade ovarian cancer; (2) the intervention (bevacizumab) and the biomarkers (KELIM, BRCA, HRD) were assessed in comparable clinical contexts; and (3) the direction of findings is consistent across trials. However, important differences exist in eligibility criteria, bevacizumab dose and duration, HRD assay definitions, and primary endpoints. These differences limit the strength of cross-trial inferences, and the proposed decision

framework should be viewed as an integrative synthesis rather than a direct comparison across trials.

5 Other exploratory biomarkers

Beyond the KELIM score and BRCA/HRD status, translational analyses of ICON7 and GOG-0218 identified several other molecular markers that might correlate with bevacizumab efficacy. These exploratory biomarkers are included for completeness and to illustrate the breadth of ongoing research, not to suggest clinical utility. All of these markers remain at the exploratory stage; none have been prospectively validated, and none have demonstrated sufficient evidence for routine clinical decision-making (see also Table 2 for a summary). Their inclusion should not be interpreted as endorsement of their use in practice.

5.1 TCGA molecular subtypes

Using DASL gene-expression profiling on FFPE tumor tissue from 359 evaluable patients in the ICON7, Kommoss et al. explored the association between TCGA molecular subtypes and bevacizumab benefit. The two subtypes with the poorest prognosis, proliferative and mesenchymal, appear to derive relatively greater benefits from bevacizumab. For the proliferative subtype, the median PFS was extended by 10.1 months (HR 0.55, 95% CI 0.34–0.90; p = 0.016). For the mesenchymal subtype, the gain was 8.2 months (HR 0.78, 95% CI 0.44–1.40, p = 0.41). In contrast, the immunoreactive and differentiated subtypes showed only limited benefit (Kommoss et al., 2017). The clinical accessibility of TCGA subtyping is limited and the findings await prospective validation.

5.2 Immune molecular subtype

In the ICON7 translational study, 34% of tumours were classified as the immunoreactive molecular subtype, characterised by upregulation of immune-related genes and downregulation of angiogenesis-related genes. In this subgroup, the addition of bevacizumab conferred only a modest and non-significant improvement in PFS (median improvement 3.8 months; HR 0.67, 95% CI 0.42–1.05, P = 0.08) and no significant OS benefit (HR 0.76, 95% CI 0.33–1.76, P = 0.52) (Kommoss et al., 2017). These findings suggest that patients with immunoreactive tumours may derive limited benefit from bevacizumab; however, this observation is exploratory and requires prospective validation.

5.3 High co-expression of c-MET and VEGFR-2

Preclinical studies have indicated that c-MET/VEGFR-2 heterocomplexes can antagonize VEGF inhibition through the activation of the c-MET signalling pathway. A quantitative immunofluorescence study on tissue microarrays from 178 ICON7 patients showed that high co-expression of c-MET and VEGFR-2 was an independent predictor of worse OS among bevacizumab-treated patients (median OS 39.3 months vs. > 60 months; HR 2.00, 95% CI 1.08–3.72) (Morgan et al., 2022). This finding was present in only approximately 19% of patients, and the sample size was limited; therefore, independent validation is needed.

5.4 Tie2 dynamic changes

Circulating angiogenic-protein network analysis from ICON7 identified Tie2 (angiopoietin-1 receptor) as a possible "vascular progression marker" in bevacizumab-treated ovarian cancer patients. Dynamic changes in plasma Tie2 concentration predicted disease progression, and a combination of Tie2 and CA-125 achieved a predictive accuracy of 74.1% for disease progression, which was substantially higher than of −125 alone (47.3%). This finding requires prospective validation (Zhou et al., 2016).

5.5 Tumour-infiltrating leucocytes

Results from the phase IV MITO16A/MaNGO OV-2 trial indicated that the level of immune infiltration may be associated with shorter PFS in bevacizumab-treated patients, suggesting that the immune context might influence the effectiveness of anti-angiogenic therapy (Pivetta et al., 2025).

6 Clinical decision pathway: an evidence-based thinking framework

The following pathway integrates the evidence summarized above and is proposed as a reference framework for clinical workflow, not as a rigid standard (a visual flow chart is provided in Figure 1). Therefore, individual patient characteristics, drug availability, and patient preferences should always be considered.

Step 1 – Diagnosis.

- Confirm the diagnosis of advanced (stage III–IV) high-grade serous or endometrioid ovarian carcinoma.

Step 2 – High-risk assessment.

- Assess whether the patient meets ICON7 high-risk criteria (stage IV, postoperative residual disease >1 cm, or inoperable/unresected stage III).
- If No: The benefit of bevacizumab has not been demonstrated; proceed with standard carboplatin-paclitaxel chemotherapy, then determine maintenance based on HRD status.
- If Yes: Proceed to Step 3.

Step 3 – KELIM-guided bevacizumab use.

- Calculate the KELIM score from CA-125 kinetics during the first 100 days of chemotherapy.
- If KELIM ≥1.0: The benefit of bevacizumab has not been demonstrated; use standard chemotherapy, then determine maintenance based on HRD status.
- If KELIM <1.0: Add bevacizumab (7.5 or 15 mg/kg every 3 weeks) concurrently with chemotherapy and continue as maintenance for a total of approximately 15 months. Then proceed to Step 4.

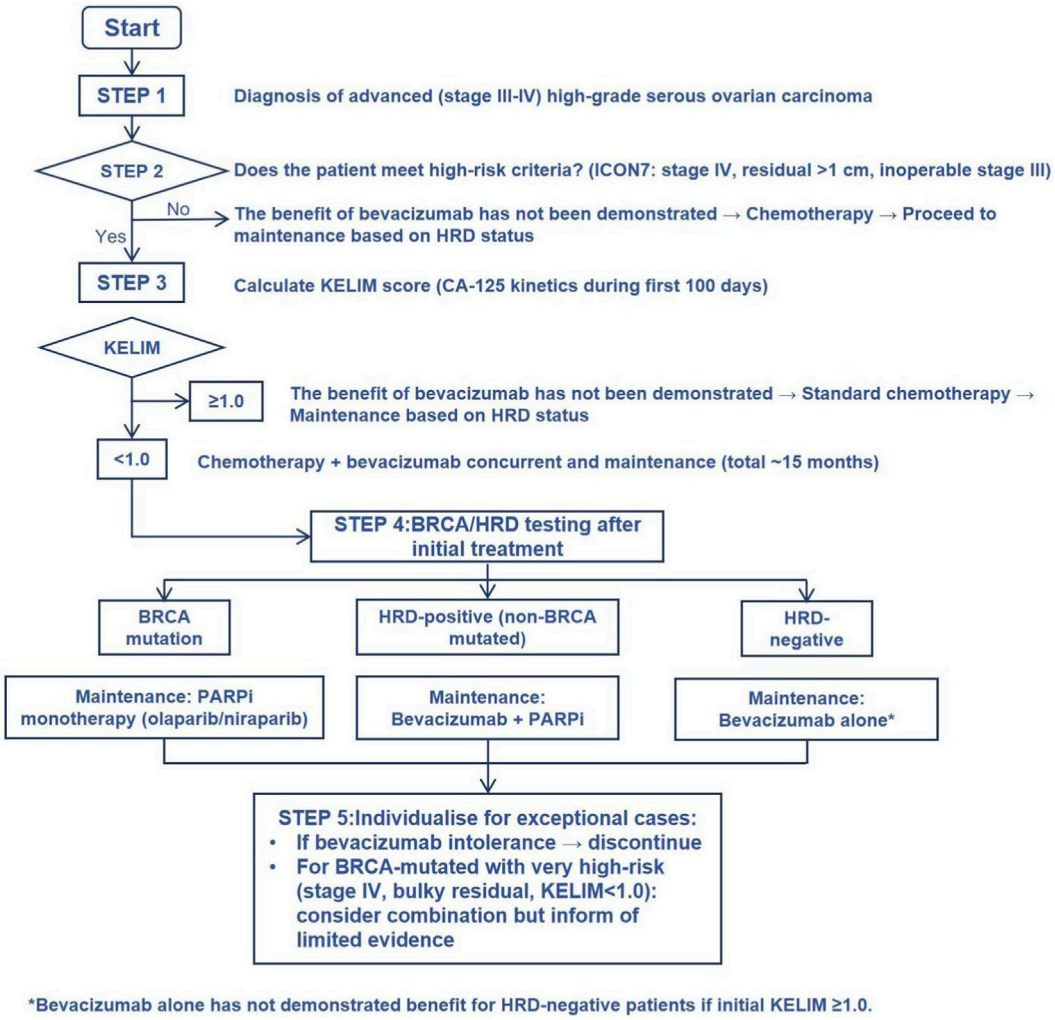


FIGURE 1
Clinical decision pathway for bevacizumab use in first-line advanced ovarian cancer. Legend: Flow diagram summarizing the evidence-based clinical decision framework for the use of bevacizumab in first-line postoperative treatment of advanced (stage III–IV) high-grade serous ovarian carcinoma. The pathway integrates initial risk assessment (ICON7 high-risk criteria), KELIM score calculation (chemotherapy-induced CA-125 kinetics during the first 100 days), and post-treatment BRCA/HRD testing to guide maintenance therapy. Individual patient characteristics, drug tolerability, and patient preferences should be considered in each step. Evidence levels: Level A: Supported by prospective randomized controlled trial evidence. Level B: Supported by pre-specified subgroup or *post hoc* analyses of randomized trials. Level C: Supported by indirect evidence and expert consensus. Level D: Exploratory only; not for clinical decision-making. Symbols: Rectangles represent clinical actions or treatment decisions. Diamonds represent binary decision points (yes/no or comparison). Arrows indicate the direction of the clinical workflow. The asterisk (*) indicates a note: *Not recommended for HRD-negative patients if initial KELIM ≥1.0. Detailed description of the pathway: Step 1: Diagnosis of advanced (stage III–IV) high-grade serous ovarian carcinoma. Step 2: Assess whether the patient meets the - high-risk criteria according to ICON7 (stage IV, postoperative residual disease >1 cm, or inoperable stage III). If No: The benefit of bevacizumab has not been demonstrated, proceed with standard carboplatin-paclitaxel chemotherapy, then determine maintenance based on HRD status.*(Evidence level: B)* If Yes: Proceed to Step 3. Step 3: The KELIM score was calculated from the CA-125 kinetics during the first 100 days of chemotherapy. If KELIM ≥1.0:The benefit of bevacizumab has not been demonstrated, and standard chemotherapy is followed by maintenance based on HRD status.*(Evidence level: B)* If KELIM <1.0:Add bevacizumab (7.5 or 15 mg/kg every 3 weeks) concurrently with chemotherapy and continue as maintenance for a total duration of approximately 15 months. Then proceed to Step 4.*(Evidence level: B)* Step 4: Perform BRCA/HRD testing after initial treatment. BRCA mutation → Maintenance: PARP inhibitor monotherapy (olaparib or niraparib).*(Evidence level: A)* HRD-positive (non-BRCA mutated) → Maintenance: Bevacizumab + PARP inhibitor (olaparib + bevacizumab).*(Evidence level: B)* HRD-negative → Maintenance: Bevacizumab alone (only if initial KELIM <1.0) or observation. *(Evidence level: B for KELIM < 1.0; Level C for observation)* (Note: Bevacizumab alone has not demonstrated benefit for HRD-negative patients if initial KELIM ≥1.0.) Step 5: Individualise for exceptional cases: If bevacizumab intolerance (grade ≥2 adverse events) occurs, discontinue bevacizumab.*(Evidence level: C)* For BRCA-mutated patients with very high-risk features (stage IV, bulky residual disease, KELIM <1.0), a bevacizumab + PARP inhibitor combination may be considered, but the patient must be informed of limited evidence.*(Evidence level: C) Note:* This pathway is based on current evidence (GOG-0218, ICON7, PAOLA-1, SOLO-1, FZOCUS-1, and KELIM validation studies) and expert guidelines (NCCN 2026). It is intended as a reference framework and is not a mandatory treatment standard.

Step 4 – BRCA/HRD testing and maintenance decision.

- Perform BRCA/HRD testing after initial treatment.
- BRCA mutation: Maintenance with PARP inhibitor monotherapy (olaparib or niraparib).
- HRD-positive (non-BRCA-mutated): Maintenance with bevacizumab + PARP inhibitor (olaparib + bevacizumab).
- HRD-negative: Maintenance with bevacizumab alone (only if initial KELIM <1.0) or observation. (Note: Bevacizumab alone has not demonstrated benefit for HRD-negative patients if initial KELIM ≥1.0).

Step 5 – Individualisation for exceptional cases.

- If bevacizumab intolerance (grade ≥2 adverse events) occurs, discontinue bevacizumab.
- For a BRCA-mutated patient with very high-risk features (stage IV, bulky residual disease, KELIM <1.0) who tolerates bevacizumab well, a bevacizumab + PARPi combination may be considered, but the patient must be informed of the limited evidence.
- Note: This pathway is based on current evidence (GOG-0218, ICON7, PAOLA-1, SOLO-1, FZOCUS-1, and KELIM validation studies) and expert guidelines (NCCN 2026). It is intended as a reference framework and is not a mandatory treatment standard.

7 Unresolved issues and future directions

- External validation of the KELIM score: The predictive value of the KELIM score requires further validation in different chemotherapy settings (e.g., carboplatin + liposomal doxorubicin), across diverse populations, and in real-world data (Wang et al., 2025).
- Rebound effect after bevacizumab discontinuation: Some studies suggest that disease progression may accelerate after bevacizumab is stopped; therefore, the optimal duration of therapy and monitoring strategies after discontinuation need to be explored (Duska et al., 2025).
- Liquid biopsy and radiomics: Approaches such as cfDNA fragmentation profiling and radiomics models have shown potential for predicting bevacizumab efficacy, and merit prospective investigation (Lamia et al., 2026).
- Immune subtype and other molecular markers: Prospective trials are needed to assess whether the immune subtype and other exploratory markers can effectively identify patients in whom bevacizumab should be avoided (Kommoss et al., 2017; Pivetta et al., 2025).
- Head-to-head trials: There is an urgent need for a direct randomized comparison of "PARP inhibitor monotherapy" vs. "PARP inhibitor + bevacizumab" in BRCA-mutated patients who have already received bevacizumab during first-line chemotherapy.

8 Conclusion and key summary points

- The most appropriate candidates for bevacizumab appear to be high-risk patients with a KELIM score <1.0. For patients with KELIM ≥1.0, even if they meet the high-risk criteria, the available evidence suggests no clear benefit and benefit has not been demonstrated in this subgroup.
- Existing evidence (GOG-0218 interaction test) does not indicate that BRCA/HRD status predicts the efficacy of single-agent bevacizumab; therefore, BRCA/HRD status should not be used as a basis for selecting bevacizumab.
- The value of BRCA/HRD status lies in guiding PARP inhibitor or combination treatment: patients with a BRCA mutation may be considered for PARP inhibitor monotherapy, whereas patients with HRD-positive, non-BRCA -mutated disease may be considered for bevacizumab + PARP inhibitor combination maintenance.
- For patients with a BRCA mutation who received bevacizumab during first-line chemotherapy, available indirect evidence suggests a preference for discontinuing bevacizumab and switching to PARP inhibitor monotherapy during maintenance. A combination strategy may be considered as an alternative in selected cases (HRD-positive, very high-risk features, and good tolerability), but patients must be fully informed of the current lack of direct comparative evidence.
- The decision framework presented here is intended as an evidence-based thinking aid, not a mandatory treatment standard. In clinical practice, decisions should be made after careful consideration of individual patient characteristics, drug availability, and patient preferences in the context of shared decision-making.

9 Critical View

This review focuses on the precise application of bevacizumab as a first-line postoperative treatment for advanced ovarian cancer. It distinguishes itself from existing literature in three main respects.

First, it emphasizes the central role of KELIM score in selecting patients who are likely to derive the greatest benefit from bevacizumab. Current guidelines and most reviews still rely primarily on the crude clinical-pathological "high-risk" criteria (stage IV and residual disease) for bevacizumab use. However, the *post hoc* analyses of GOG-0218/ICON7 have clearly shown that patients with a KELIM score ≥1.0 obtain no OS benefit from bevacizumab even when they meet high-risk criteria, whereas those with a KELIM score <1.0 are the true beneficiaries. This review systematically compiled the validation evidence for the KELIM score and placed it at the beginning of the decision pathway.

Second, it clarifies that the BRCA/HRD status does not alter the efficacy of single-agent bevacizumab. In clinical practice, it is not uncommon to see patients being excluded from bevacizumab simply because they carry a BRCA mutation or, conversely, to see a mistaken assumption that patients with a BRCA mutation "naturally do not need" bevacizumab. Based on the negative interaction test from GOG-0218, this review explicitly stated that these genetic markers should not be used to select bevacizumab. Furthermore, analysis of the relationship between BRCA mutations and the KELIM score shows that genetic status cannot substitute for a dynamic assessment of tumor chemosensitivity.

Third, it directly confronts the evidence gap concerning maintenance strategies for patients with BRCA-mutations who received bevacizumab during first-line chemotherapy. This dilemma has not been adequately addressed in the current

guidelines. This review provides a structured preference-analysis framework based on indirect evidence and NCCN guidelines, offering practical considerations (HRD status, very high-risk features, tolerability, etc.) for clinicians facing this challenging situation.

The limitations of this review include the fact that the core tool (KELIM score) and decision framework rely largely on retrospective analyses and *post hoc* explorations, lacking prospective validation. The external validity of some indirect evidence (such as the FZOCUS-1 trial) is limited, and for many exploratory biomarkers (immune subtype, c-MET/VEGFR-2, etc.), the current data are insufficient to support their clinical use; as emphasized in Section 5, these markers remain hypothesis-generating and should not be used for clinical decision-making until prospectively validated.

Contribution to the field: This review provides a structured, evidence-based reference framework for the precise use of bevacizumab in first-line - treatment of advanced ovarian cancer. This clarifies the lack of predictive value of BRCA/HRD status for single-agent bevacizumab, thus helping avoid a common clinical misconception. It also clearly identifies the current evidence gaps (in particular, the lack of head-to-head studies on discontinuation strategies) and proposes concrete directions for future research.

Scope and depth: This review focuses on the use of bevacizumab in the first-line postoperative setting for advanced (stages III–IV) high-grade serous ovarian cancer. Other histological types, neoadjuvant settings, and recurrent-disease settings were not covered. In terms of depth, core evidence on the KELIM score, BRCA/HRD, PAOLA-1, SOLO-1, GOG-0218, and ICON7 is presented in detail with critical appraisal, whereas exploratory biomarkers are summarized more concisely as a reference.

Author contributions

LZ: Writing – review and editing, Writing – original draft. LS: Funding acquisition, Supervision, Conceptualization, Writing – review and editing, Data curation, Writing – original draft, Visualization.

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Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

Ambrosino, F. A., Pisano, C., Napoli, M. D., Ventriglia, J., Tambaro, R., Rossetti, S., et al. (2026). KELIM score: a marker of chemosensitivity in ovarian cancer. *Cancer Treat. Rev.* 143, 103071. doi: 10.1016/j.ctrv.2025.103071

Balkwill, F. R., Laumont, C. M., and Burdett, N. (2026). Rethinking ovarian cancer III: the past decade and future directions. *Nat. Rev. Cancer*. 26 (6), 452–471. doi: 10.1038/s41568-026-00916-0

Bowtell, D. D., Böhm, S., Ahmed, A. A., Aspuria, P. J., Bast, R. C., Beral, V., et al. (2015). Rethinking ovarian cancer II: reducing mortality from high-grade serous ovarian cancer. *Nat. Rev. Cancer* 15 (11), 668–679. doi: 10.1038/nrc4019

Burger, R. A., Brady, M. F., Bookman, M. A., Fleming, G. F., Monk, B. J., Huang, H., et al. (2011). Incorporation of bevacizumab in the primary treatment of ovarian cancer. *N. Engl. J. Med.* 365 (26), 2473–2483. doi: 10.1056/NEJMoa1104390

DiSilvestro, P., Banerjee, S., and Colombo, N. (2023). Overall survival with maintenance olaparib at a 7-Year Follow-Up in patients with newly diagnosed advanced ovarian cancer and a BRCA mutation: the SOLO1/GOG 3004 trial. *J. Clin. Oncol.* 41 (3), 609–617. doi: 10.1200/JCO.22.01549

Duska, L. R., Lim, J., Calderón Boyle, T. A., Guinter, M., Halloran, S., Hartman, J., et al. (2025). The BEV1L study: do real-world outcomes associated with the addition of bevacizumab to first-line chemotherapy in patients with ovarian cancer reinforce clinical trial findings. *Cancer* 131 (10), e35821. doi: 10.1002/cncr.35821

González-Martín, A., Harter, P., Leary, A., Lorusso, D., Miller, R. E., Pothuri, B., et al. (2023). Newly diagnosed and relapsed epithelial ovarian cancer: ESMO clinical practice guideline for diagnosis, treatment and follow-up. *Ann. Oncol.* 34 (10), 833–848. doi: 10.1016/j.annonc.2023.07.011

Kommoss, S., Winterhoff, B., Oberg, A. L., Konecny, G. E., Wang, C., Riska, S. M., et al. (2017). Bevacizumab may differentially improve ovarian cancer outcome in patients with proliferative and mesenchymal molecular subtypes. *Clin. Cancer Res.* 23 (14), 3794–3801. doi: 10.1158/1078-0432.CCR-16-2196

Lamia, M. R., Perri, E., Baldassarre, G., Pignata, S., D'Alessio, C., Limongello, D., et al. (2026). Bevacizumab in ovarian cancer: clinical data and predictive and prognostic biomarkers. *Clin. Transl. Med.* 16 (1), e70591. doi: 10.1002/ctm2.70591

Liu, Y., Yuan, L., Lin, Z., Huixian, M., Huangyang, M., and Cheng, W. (2025). The serum LDH level and KELIM scores are potential predictors of a benefit from bevacizumab first-line therapy for patients with advanced ovarian cancer. *Clin. Transl. Oncol.* 27 (1), 340–350. doi: 10.1007/s12094-024-03569-3

Lorusso, D., Mouret-Reynier, M. A., Harter, P., Cropet, C., Caballero, C., Wolfrum-Ristau, P., et al. (2024). Updated progression-free survival and final overall survival with maintenance olaparib plus bevacizumab according to clinical risk in patients with newly diagnosed advanced ovarian cancer in the phase III PAOLA-1/ENGOT-ov25 trial. *Int. J. Gynecol. Cancer* 34 (4), 550–558. doi: 10.1136/ijgc-2023-004995

Lv, J., Xu, Y., Zeng, C., Huang, F., and Tao, S. (2025). Predictive value of the KELIM index for progression-free survival in ovarian cancer under current treatment modalities. *Int. J. Womens Health* 17, 2291–2297. doi: 10.2147/IJWH.S533323

Moore, K., Colombo, N., Scambia, G., Kim, B. G., Oaknin, A., Friedlander, M., et al. (2018). Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. *N. Engl. J. Med.* 379 (26), 2495–2505. doi: 10.1056/NEJMoa1810858

Morgan, R. D., Ferreras, C., Peset, I., Avizienyte, E., Renehan, A. G., Edmondson, R. J., et al. (2022). c-MET/VEGFR-2 co-localisation impacts on survival following bevacizumab therapy in epithelial ovarian cancer: an exploratory biomarker study of the phase 3 ICON7 trial. *BMC Med.* 20 (1), 59. doi: 10.1186/s12916-022-02270-y

Norquist, B. M., Brady, M. F., Harrell, M. I., Walsh, T., Lee, M. K., Gulsuner, S., et al. (2018). Mutations in homologous recombination genes and outcomes in ovarian carcinoma patients in GOG 218: an NRG oncology/gynecologic oncology group study. *Clin. Cancer Res.* 24 (4), 777–783. doi: 10.1158/1078-0432.CCR-17-1327

Oza, A. M., Cook, A. D., Pfisterer, J., Embleton, A., Ledermann, J. A., Pujade-Lauraine, E., et al. (2015). Standard chemotherapy with or without bevacizumab for women with newly diagnosed ovarian cancer (ICON7): overall survival results of a phase 3 randomised trial. *Lancet Oncol.* 16 (8), 928–936. doi: 10.1016/s1470-2045(15)00086-8

Pivetta, E., Canzonieri, V., Bagnoli, M., Chiodini, P., Spina, A., Arenare, L., et al. (2025). Tumour-infiltrating leucocytes as prognostic biomarkers of bevacizumab-treated ovarian cancer patients results from the phase IV MITO16A/MaNGO OV-2 clinical trial. *NPJ Precis. Oncol.* 9 (1), 355. doi: 10.1038/s41698-025-01146-7

Ray-Coquard, I., Pautier, P., Pignata, S., Pérol, D., González-Martín, A., Berger, R., et al. (2019). Olaparib plus bevacizumab as first-line maintenance in ovarian cancer. *N. Engl. J. Med.* 381 (25), 2416–2428. doi: 10.1056/NEJMoa1911361

Ray-Coquard, I., Leary, A., Pignata, S., Cropet, C., González-Martín, A., Marth, C., et al. (2023). Olaparib plus bevacizumab first-line maintenance in ovarian cancer: final overall survival results from the PAOLA-1/ENGOT-ov25 trial. *Ann. Oncol.* 34 (8), 681–692. doi: 10.1016/j.annonc.2023.05.005

Tewari, K. S., Burger, R. A., Enserro, D., Norquist, B. M., Swisher, E. M., Brady, M. F., et al. (2019). Final overall survival of a randomized trial of bevacizumab for primary treatment of ovarian cancer. *J. Clin. Oncol.* 37 (26), 2317–2328. doi: 10.1200/JCO.19.01009

Wang, Y., Yu, Y., Yuan, H., Wang, L., Bian, P., Yang, Y., et al. (2025). Predictive value of the KELIM in neoadjuvant treatment for patients with advanced ovarian cancer. *Front. Oncol.* 15, 1677070. doi: 10.3389/fonc.2025.1677070

Wu, L., Wang, J., Li, Q., Wang, D., Zhang, C., Tang, J., et al. (2026). Fuzuloparib with or without apatinib as maintenance therapy in newly diagnosed, advanced ovarian cancer (FZOCUS-1): a multicenter, randomized, double-blind, placebo-controlled phase 3 trial. *CA Cancer J. Clin.* 76 (1), e70042. doi: 10.3322/caac.70042

You, B., Colomban, O., Heywood, M., Lee, C., Davy, M., Reed, N., et al. (2013). The strong prognostic value of KELIM, a model-based parameter from CA 125 kinetics in ovarian cancer: data from CALYPSO trial (a GINECO-GCIG study). *Gynecol. Oncol.* 130 (2), 289–294. doi: 10.1016/j.ygyno.2013.05.013

You, B., Purdy, C., Copeland, L. J., Swisher, E. M., Bookman, M. A., Fleming, G., et al. (2022). Identification of patients with ovarian cancer experiencing the highest benefit from bevacizumab in the first-line setting on the basis of their tumor-intrinsic chemosensitivity (KELIM): the GOG-0218 validation study. *J. Clin. Oncol.* 40 (34), 3965–3974. doi: 10.1200/JCO.22.01207

Zhou, C., Clamp, A., Backen, A., Berzuini, C., Renehan, A., Banks, R. E., et al. (2016). Systematic analysis of circulating soluble angiogenesis-associated proteins in ICON7 identifies Tie2 as a biomarker of vascular progression on bevacizumab. *Br. J. Cancer* 115 (2), 228–235. doi: 10.1038/bjc.2016.194