JAMA Oncology | Review | WOMEN'S HEALTH

Rethinking Treatment Intensification in Poorly Chemosensitive Ovarian Cancer
A Review

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IMPORTANCE Despite the integration of bevacizumab and poly(ADP-ribose) polymerase inhibitors into first-line treatment of advanced high-grade serous ovarian cancer, survival remains poor for the substantial subset of patients whose tumors respond insufficiently to platinum-based chemotherapy and who, therefore, frequently do not achieve complete cytoreductive surgery (the 2 red flags population). This Review examines the rationale, current evidence, and emerging strategies for systemic treatment intensification—or chemosensitization—aimed at improving tumor response before initiating maintenance therapy.

OBSERVATIONS Achieving minimal residual disease before maintenance depends on 2 key determinants: surgical completeness and intrinsic tumor chemosensitivity. Pragmatic indicators of chemosensitivity—KELIM (modeled cancer antigen 125 elimination rate constant K), pathological chemotherapy response score, and radiologic response—are now cited in European Society for Medical Oncology–European Society of Gynaecological Oncology and American Society of Clinical Oncology guidelines, while *BRCA*/homologous recombination deficiency status may not reliably predict neoadjuvant carboplatin-paclitaxel response. Across post hoc analyses of phase 3 trials (ICON-7, GOG-0218, ICON-8, ICON-8B, VELIA, and IMagyn050), patients with poorly chemosensitive disease may have derived greater benefit from intensification strategies. Weekly dose-dense paclitaxel was associated with improved survival in the 2 red flags subgroup of ICON-8. Bevacizumab, added either to standard postoperative chemotherapy or to neoadjuvant dose-dense chemotherapy, showed signals of greater benefit on both progression-free and overall survival in high-risk and poorly chemosensitive subsets. In contrast, poly(ADP-ribose) polymerase inhibitor and immune checkpoint inhibitor combinations showed meaningful activity only in selected subgroups, supporting further evaluation of innovative DNA repair–targeting agents and immunotherapeutic approaches in these populations.

CONCLUSIONS AND RELEVANCE Early identification of poorly chemosensitive advanced high-grade serous ovarian cancer enables a response-adapted first-line strategy in which treatment intensification is selectively offered to patients most likely to benefit—an approach now being prospectively evaluated in the phase 3 SALVOVAR and phase 1/2 RegeNovar trials. This framework provides a clinically actionable platform to test novel therapies aimed at increasing complete interval cytoreduction rates and improving survival in a population with otherwise limited options.

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Ovarian cancer remains the fifth leading cause of cancer-related death among women worldwide despite recent therapeutic progress.[1] The past decade has changed first-line management of advanced high-grade serous ovarian cancer (HGSOC) through 3 converging strategies: (1) chemotherapy dose intensification, evaluated in the JGOG-3016, GOG-0262, and ICON-8 trials[2-4]; (2) the addition of bevacizumab to first-line chemotherapy, evaluated in the ICON-7, GOG-0218, and ICON-8B trials[5-7]; and (3) poly(ADP-ribose) polymerase inhibitor (PARPi) maintenance, established in *BRCA*-mutated disease through SOLO-1 and subsequently extended to broader populations in the PRIMA, PRIME, ATHENA-MONO, FLAMES, and PAOLA-1 trials.[8-13]

These advances have improved long-term outcomes most clearly in the 20% to 25% of patients with *BRCA*-mutated tumors and, to a lesser degree, in the 20% to 25% with *BRCA* wild-type (*BRCA*wt) tumors exhibiting homologous recombination deficiency (HRD positive). However, outcomes remain poor for the substantial subgroup of patients whose tumors are insufficiently responsive to standard platinum-based chemotherapy and who, as a result, frequently fail to achieve complete interval cytoreductive surgery (ICS). In this population, bevacizumab maintenance confers only modest benefit, and eligibility for PARPi maintenance is restricted to patients who achieve at least a partial response to chemotherapy.[11-13]

In this context, one strategy warranting further investigation is to intervene earlier in the course of chemotherapy to enhance tumor response and minimize residual disease before transitioning to maintenance therapy. By amplifying the effect of systemic therapy during the initial treatment phase—through treatment intensification or chemosensitization—this approach has the potential to improve outcomes and prolong survival.

This Review summarizes the rationale and clinical evidence for this response-adapted approach. We examine how to identify patients with poorly chemosensitive HGSOC by integrating surgical outcome and tumor biology, the clinical evidence for available intensification strategies, and the future directions being tested in dedicated prospective trials. The search strategy and review methodology are described in the eAppendix in the Supplement.

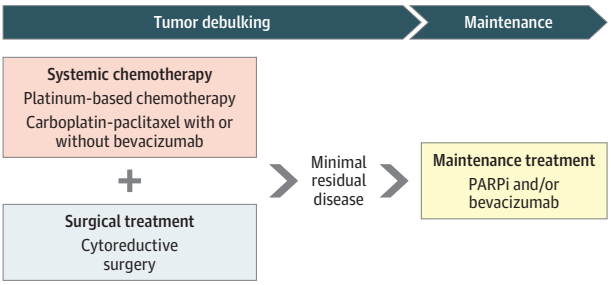
Identifying Patients With Poorly Chemosensitive HGSOC

Surgical and Biological Determinants of Minimal Residual Disease and Impact on Subsequent Maintenance Treatment Efficacy

About 75% of ovarian cancers are diagnosed at FIGO (International Federation of Gynecology and Obstetrics) stage III or IV.[1] Standard first-line management combines an initial debulking phase—comprising cytoreductive surgery and 6 to 8 cycles of platinum-paclitaxel chemotherapy, with or without bevacizumab—aimed at minimizing residual disease, before the maintenance phase (**Figure 1**).

When complete primary cytoreductive surgery (PCS) is feasible with acceptable morbidity, it is performed up front and followed by adjuvant postoperative chemotherapy.[14,15] When complete resection is unlikely on the basis of imaging, laparoscopy, tumor burden, or patient condition, neoadjuvant chemotherapy (NACT) is given to enable ICS.[14] In the TRUST phase 3 trial, PCS did not improve overall survival (OS) over NACT followed by ICS in the intent-to-treat population, though progression-free survival (PFS) and a potential OS benefit were observed in the subset of patients with stage III disease achieving complete resection.[16] The proportion of patients receiving NACT has steadily increased worldwide and now exceeds 50% in many countries.[17,18]

Figure 1. Flowchart of the Standard Medical and Surgical Treatment in High-Grade Serous Ovarian Carcinoma to Obtain a Minimum Residual Disease Before Starting Maintenance Treatment



PARPi indicates poly(ADP-ribose) polymerase inhibitor.

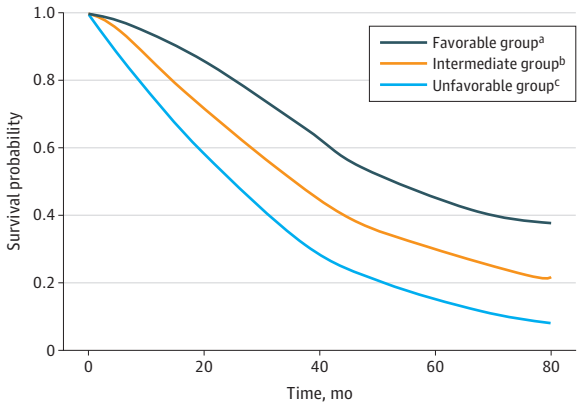
Three subsequent maintenance options follow first-line therapy: (1) bevacizumab alone for 12 to 15 months; (2) PARPi monotherapy with olaparib, niraparib, or rucaparib for 24 to 36 months (with olaparib restricted to *BRCA*-mutated tumors); or (3) olaparib combined with bevacizumab for patients with *BRCA*-mutated or HRD-positive disease.[15,19] Two clinical and biological features have been prospectively shown to modulate the maintenance treatment benefit. First, the disease-risk category influences bevacizumab benefit. Patients with stage III disease undergoing complete PCS are typically classified as low risk, whereas patients with residual disease after surgery, those treated with NACT followed by ICS, and those with stage IV disease are considered high risk.[19] Bevacizumab provides its largest benefit in patients with bulky or high-risk disease.[5,6,19,20]

Second, *BRCA* mutation and HRD status are the strongest predictors of PARPi efficacy, with the greatest benefit observed in *BRCA*-mutated tumors and a smaller but consistent benefit in *BRCA*wt HRD-positive disease.[15] In contrast to bevacizumab, the benefit from PARPi efficacy seems greatest in patients with deep responses to platinum-based chemotherapy or complete cytoreduction.[11,20,21] In the PAOLA-1 trial, the largest OS benefit from olaparib added to bevacizumab maintenance was observed in patients with HRD-positive tumors who underwent complete PCS,[20] and PARPi trials more broadly required at least a partial response to platinum-based chemotherapy for eligibility.

These observations have generated interest in pragmatic indicators of chemosensitivity as predictors of maintenance benefit. The modeled cancer antigen 125 (CA-125) elimination rate constant K (KELIM), derived from the longitudinal kinetics of CA-125 during NACT or adjuvant chemotherapy, quantifies the magnitude of tumor response to chemotherapy and is now cited in the 2024 European Society for Medical Oncology–European Society of Gynaecological Oncology and 2025 American Society of Clinical Oncology clinical guidelines.[14,22] In the VELIA trial, veliparib maintenance benefit was greater in patients with favorable KELIM of 1.0 or higher in both *BRCA*-mutated tumors (hazard ratio [HR], 0.28; 95% CI, 0.13-0.61) and *BRCA*wt HRD-positive tumors (HR, 0.62; 95% CI, 0.32-1.20) than in patients with

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Figure 2. Conceptual Line Graph of the Complementary Prognostic Values of Surgical Completeness and Chemotherapy Efficacy for Survival



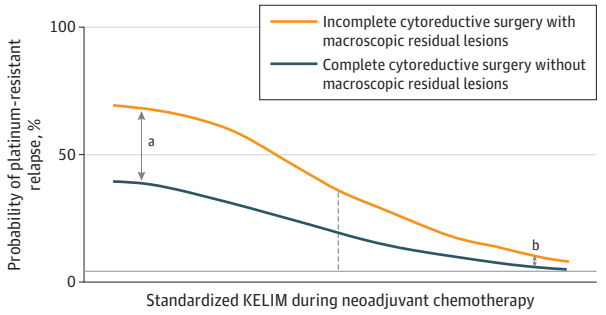
Curves are illustrative, not fitted survival data. Chemotherapy efficacy is assessed by modeled cancer antigen 125 elimination rate constant K (KELIM) score.

[a]Optimal/complete cytoreductive surgery and favorable KELIM of 1.0 or higher.

[b]Suboptimal/incomplete cytoreductive surgery and favorable KELIM of 1.0 or higher, or optimal/complete cytoreductive surgery and unfavorable KELIM of lower than 1.0.

[c]Suboptimal/incomplete cytoreductive surgery and unfavorable KELIM of lower than 1.0.

Figure 3. Conceptual Line Graph of the Interaction Between Standardized KELIM During Neoadjuvant Chemotherapy and Completeness of Interval Cytoreductive Surgery in Relation to Risk of Subsequent Platinum-Resistant Relapse



Percentages are illustrative, not fitted data. The dashed line indicates modeled cancer antigen 125 elimination rate constant K (KELIM) of approximately 1.0; values to the left of the dashed line indicate low/unfavorable KELIM, while values to the right indicate high/favorable KELIM.

[a]Large difference at low KELIM.

[b]Small difference at low KELIM.

unfavorable KELIM less than 1.0 (corresponding HRs, 0.79 [95% CI, 0.38-1.65] and 1.12 [95% CI, 0.63-2.00]).[23]

The pathological Chemotherapy Response Score (CRS; scored as CRS1 [no or minimal response], CRS2 [partial response], and CRS3 [complete or near-complete response]) similarly quantifies histological tumor regression in ICS specimens after NACT and may predict PARPi maintenance benefit. In a retrospective analysis, median PFS with PARPi maintenance was 61 months in patients with CRS3, 20 months with CRS2, and 14 months with CRS1, irrespective of *BRCA* or HRD status.[24-26] CRS is also cited in current international guidelines, although its clinical use is limited to the NACT setting and constrained by interobserver variability, as well as by the absence of a clear prognostic distinction between CRS1 and CRS2.[14]

Combining Surgical Outcome and Chemosensitivity: The 2-Flag Framework

Pooled retrospective analyses from CHIVA, AGO-OVAR7, AGO-OVAR9, ICON-7, ICON-8, and the Gynecologic Cancer Intergroup meta-analysis consistently show that chemotherapy response and completeness of cytoreduction are independent prognostic determinants of PFS and OS.[27-29] Combined assessment of KELIM (chemotherapy response magnitude) and surgical outcome (completeness of cytoreduction), each classified as favorable (green flag) or unfavorable (red flag), defines 3 prognostic groups (**Figure 2**): patients with favorable KELIM and complete cytoreduction (2 green flags) have the best outcomes, patients with 1 favorable and 1 unfavorable factor (1 green and 1 red flag) have intermediate prognosis, and patients with unfavorable KELIM and incomplete surgery (2 red flags) have the poorest outcomes.[27-31]

In addition, a retrospective analysis of CHIVA, subsequently validated in an independent dataset, showed that the prognostic impact of complete cytoreduction was greatest in patients with unfavorable KELIM.[30,32] In this subgroup, complete ICS markedly reduced the relative risk of platinum-resistant relapse—to a greater extent than in patients with favorable KELIM—suggesting that surgery may compensate for the limited debulking effect of chemotherapy in those with poor response (**Figure 3**).

Surgical outcome and chemosensitivity have different determinants and require different interventions. Surgical outcomes depend on team expertise, patient selection, and the institutional ability to achieve complete macroscopic resection, with European Society of Gynaecological Oncology guidelines recommending a minimum institutional volume of 20 cases per year.[33] Chemotherapy response, in contrast, primarily reflects intrinsic tumor biology.[31] Improving chemotherapy efficacy in poorly chemosensitive tumors offers a complementary route to minimize residual disease, facilitate complete ICS in the neoadjuvant setting, and improve survival.

Pragmatic and Emerging Tools to Assess Chemosensitivity

Treatment intensification increases toxic effects, so reliable early indicators of poor chemosensitivity are needed to guide patient selection. Most evidence has accumulated in the neoadjuvant setting, in which tumor response can be monitored during NACT.

Several studies have evaluated whether *BRCA* mutation and HRD status predict response to NACT, given their established role in predicting PARPi sensitivity.[34] In 3 independent international datasets (British, French, and Italian), these biomarkers did not reliably predict NACT efficacy or the likelihood of complete ICS. Pathological CRS3 rates were similar between *BRCA*-mutated and *BRCA*wt tumors (31% vs 34% in the British dataset; 14% vs 15% in the French dataset; and 38% vs 35% in the Italian dataset) and between HRD-positive and HRD-negative tumors (16% vs 23% in the French dataset and 39% vs 32% in the Italian dataset).[35,36] Possible explanations include attenuation of the HRD effect by paclitaxel or biological heterogeneity within *BRCA* or HRD-positive tumors. Across all 3 datasets, the most consistent predictor of NACT efficacy was the modeled KELIM score.[35,36]

Radiological response by Response Evaluation Criteria in Solid Tumors 1.1 on standard computed tomography (CT) scan has shown

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Table. Retrospective Studies of Large Randomized Trials Suggesting Benefit From Chemotherapy Intensification in the First-Line Setting of High-Grade Serous Ovarian Cancer, Categorized by Level of Evidence

Treatment intensification approach	Trial and assessed treatments	Population tested	Median PFS, mo	PFS HR (95% CI)	Median OS, mo	OS HR (95% CI)	Level of evidence[a]
Chemotherapy intensification with or without bevacizumab	ICON-8 Group 1: carboplatin AUC 5-6 on day 1 + paclitaxel, 175 mg/m^2, on day 1 every 3 wk × 6 cycles Group 2: carboplatin AUC 5-6 on day 1 + paclitaxel, 80 mg/m^2, on days 1, 8, and 15 every 3 wk × 6 cycles Group 3: carboplatin AUC 2 on days 1, 8, and 15 + paclitaxel, 80 mg/m^2, on days 1, 8, and 15 every 3 wk × 6 cycles	Overall population[4]	Group 1: 23.9 Group 2: 25.3 Group 3: 24.8	Group 1: reference Group 2: 0.92 (0.78-1.09) Group 3: 0.94 (0.80-1.10)	Group 1: 47.4 Group 2: 54.8 Group 3: 53.4	Group 1: reference Group 2: 0.87 (0.73-1.05) Group 3: 0.91 (0.76-1.09)	I
		Poorly chemosensitive disease (KELIM <1.0) and incomplete PCS[27]	Group 1: 7.7 Group 2: 13.1 Group 3: 18.7	Group 1: reference Group 2: 0.67 (0.44-1.02) Group 3: 0.50 (0.31-0.79)	Group 1: 29.6 Group 2: 34.0 Group 3: 48.0	Group 1: reference Group 2: 0.81 (0.52-1.28) Group 3: 0.58 (0.35-0.95)	III
		Poorly chemosensitive disease (KELIM <1.0) and incomplete ICS[27]	Group 1: 5.6 Group 2: 8.7 Group 3: 9.2	Group 1: reference Group 2: 0.53 (0.37-0.76) Group 3: 0.63 (0.45-0.88)	Group 1: 20.3 Group 2: 31.4 Group 3: 21.7	Group 1: reference Group 2: 0.57 (0.39-0.82) Group 3: 0.72 (0.51-1.01)	III
	ICON-8B Arm B1: carboplatin AUC 5 on day 1 + paclitaxel, 175 mg/m^2, on day 1 every 3 wk + bevacizumab, 7.5 mg/kg × 6 cycles, then bevacizumab × 18 cycles Arm B2 (closed early): carboplatin AUC 5 on day 1 + paclitaxel, 80 mg/m^2, on days 1, 8, and 15 every 3 wk × 6 cycles Arm B3: carboplatin AUC 5 on day 1 + paclitaxel, 80 mg/m^2, on days 1, 8, and 15 every 3 wk + bevacizumab, 7.5 mg/kg × 6 cycles, then bevacizumab × 18 cycles	Overall population[7]	Arm B1: 16.7 Arm B3: 22.2	Arm B1: reference Arm B3: 0.75 (0.62-0.90)	Arm B1: 39.6 Arm B3: 49.8	Arm B1: reference Arm B3: 0.79 (0.65-0.95)	I
	ICON-8 and ICON-8B (indirect weighted comparison) Arm B0: carboplatin AUC 5-6 + paclitaxel, 175 mg/m^2, every 3 wk × 6 cycles (reference) Arm B1: carboplatin AUC 5 + paclitaxel, 175 mg/m^2, every 3 wk + bevacizumab × 6 cycles, then bevacizumab × 18 cycles Arm B2: carboplatin AUC 5-6 + paclitaxel, 80 mg/m^2, on days 1, 8, and 15 every 3 wk × 6 cycles Arm B3: carboplatin AUC 5 + paclitaxel, 80 mg/m^2, on days 1, 8, and 15 every 3 wk + bevacizumab × 6 cycles, then bevacizumab × 18 cycles	NACT setting with poorly chemosensitive disease (KELIM <1.0)[46,47]	Arm B0: 7.9 Arm B1: 11.0 Arm B2: 9.4 Arm B3: 15.4	Arm B0: reference Arm B1: 0.70 (0.49-1.00) Arm B2: 0.90 (0.63-1.28) Arm B3: 0.62 (0.43-0.87)	Arm B0: 25.8 Arm B1: 28.7 Arm B2: 29.4 Arm B3: 36.7	Arm B0: reference Arm B1: 0.72 (0.52-1.00) Arm B2: 0.78 (0.57-1.07) Arm B3: 0.62 (0.45-0.86)	III
		Poorly chemosensitive disease (KELIM <1.0) and incomplete ICS[46,47]	Arm B0: 5.6 Arm B1: 10.2 Arm B2: 8.6 Arm B3: 15.3	Arm B0: reference Arm B1: 0.52 (0.32-0.84) Arm B2: 0.62 (0.40-0.99) Arm B3: 0.44 (0.29-0.68)	Arm B0: 46.6 Arm B1: 43.9 Arm B2: 45.4 Arm B3: 32.0	Arm B0: reference Arm B1: 0.76 (0.50-1.18) Arm B2: 0.61 (0.41-0.91) Arm B3: 0.65 (0.42-1.00)	III
Bevacizumab addition to standard chemotherapy	ICON-7 Arm 1: carboplatin AUC 5-6 + paclitaxel, 175 mg/m^2, every 3 wk × 6 cycles Arm 2: carboplatin AUC 5-6 + paclitaxel, 175 mg/m^2 × 6 cycles + bevacizumab, 7.5 mg/kg × 17-18 cycles every 3 wk	Overall population[48]	Arm 1: 17.5 Arm 2: 19.9	Arm 1: reference Arm 2: 0.93 (0.81-1.05)	Arm 1: 58.6 Arm 2: 58.0	Arm 1: reference Arm 2: 0.99 (0.85-1.14)	I
		High risk: suboptimal PCS for stage III disease[5]	Arm 1: 10.5 Arm 2: 16.0	Arm 1: reference Arm 2: 0.73 (0.61-0.88)	Arm 1: 30.2 Arm 2: 39.7	Arm 1: reference Arm 2: 0.78 (0.63-0.97)	II
		Poorly chemosensitive disease (KELIM <1.0) and high-risk disease[49]	Arm 1: 5.7 Arm 2: 9.5	Arm 1: reference Arm 2: 0.56 (0.52-0.59)	Arm 1: 20.6 Arm 2: 29.7	Arm 1: reference Arm 2: 0.78 (0.58-1.04)	III
	GOG-0218 Arm 1: carboplatin AUC 6 + paclitaxel, 175 mg/m^2, every 3 wk × 6 cycles Arm 2: carboplatin AUC 6 + paclitaxel, 175 mg/m^2 + concurrent bevacizumab, 15 mg/kg, cycles 2-6 every 3 wk Arm 3: carboplatin AUC 6 + paclitaxel, 175 mg/m^2 + concurrent and maintenance bevacizumab, 15 mg/kg, cycles 2-22 every 3 wk	Overall population[6]	Arm 1: 10.3 Arm 2: 11.2 Arm 3: 14.1	Arm 1: reference Arm 2: 0.91 (0.79-1.04) Arm 3: 0.71 (0.62-0.84)	Arm 1: 41.1 Arm 2: 40.8 Arm 3: 43.4	Arm 1: reference Arm 2: 1.06 (0.94-1.20) Arm 3: 0.96 (0.85-1.09)	I
		High-risk: suboptimal PCS for stage III disease[6]	Arm 1: 12.0 Arm 2: 12.7 Arm 3: 18.0	Arm 1: reference Arm 2: 0.84 (0.71-0.99) Arm 3: 0.64 (0.55-0.76)	Arm 1: 37.8 Arm 2: 34.9 Arm 3: 42.8	Arm 1: reference Arm 2: 1.09 (NA) Arm 3: 0.90 (NA)	II
		Poorly chemosensitive disease (KELIM <1.0) and high-risk disease[50]	Arm 1: 6.1 Arm 3: 9.8	Arm 1: reference Arm 3: 0.64 (0.53-0.78)	Arm 1: 31.8 Arm 3: 36.3	Arm 1: reference Arm 3: 0.79 (0.65-0.97)	III

(continued)

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Table. Retrospective Studies of Large Randomized Trials Suggesting Benefit From Chemotherapy Intensification in the First-Line Setting of High-Grade Serous Ovarian Cancer, Categorized by Level of Evidence (continued)

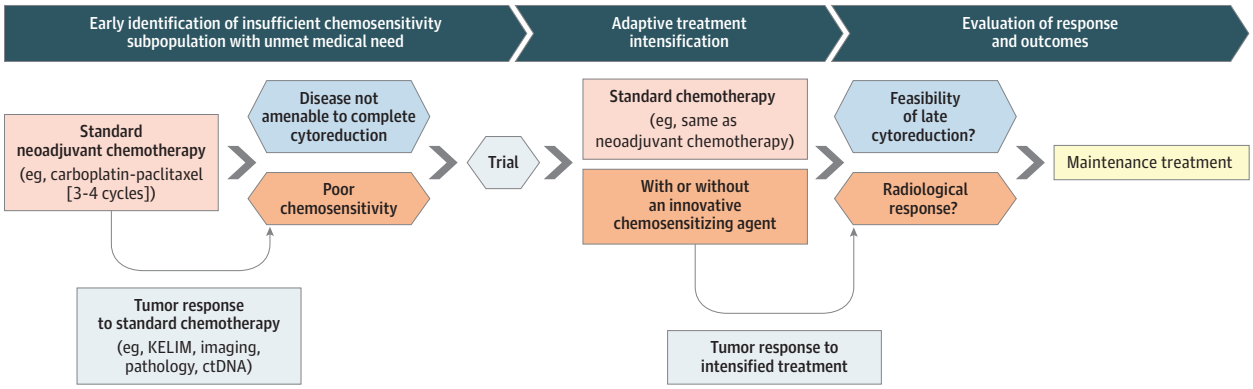
Treatment intensification approach	Trial and assessed treatments	Population tested	Median PFS, mo	PFS HR (95% CI)	Median OS, mo	OS HR (95% CI)	Level of evidence[a]
Veliparib addition	VELIA Arm 1: carboplatin AUC 6 on day 1 + paclitaxel, 175 mg/m^2, on day 1 or paclitaxel, 80 mg/m^2, on days 1, 8, and 15 every 3 wk × 6 cycles Arm 2: carboplatin AUC 6 on day 1 + paclitaxel (as above) every 3 wk + veliparib, 150 mg, twice daily × 6 cycles Arm 3: carboplatin AUC 6 on day 1 + paclitaxel (as above) every 3 wk + veliparib, 150 mg, twice daily × 6 cycles, then veliparib, 400 mg, twice daily × 30 cycles	Overall population[51]	Arm 1: 17.3 Arm 2: 15.2 Arm 3: 23.5	Arm 1: reference Arm 2: 1.07 (0.90-1.29) Arm 3: 0.68 (0.56-0.83)	Arm 1: 57.8 Arm 2: 58.0 Arm 3: 59.2	Arm 1: reference Arm 2: 1.03 (0.86-1.24) Arm 3: 0.95 (0.78-1.14)	I
		HRD negative[51]	Arm 1: 11.5 Arm 2: NA Arm 3: 15.0	Arm 1: reference Arm 2: NA Arm 3: 0.81 (0.60-1.09)	NA	Arm 1: reference Arm 2: NA Arm 3: 1.14 (0.83-1.49)	II
		Poorly chemosensitive disease (KELIM <1.0) and HRD-negative disease operated with PCS[23]	Arm 1: 6.7 Arm 2: 10.2 Arm 3: 14.8	Arm 1: reference Arm 2: 0.79 (0.49-1.30) Arm 3: 0.52 (0.30-0.92)	NA	NA	III
Immunotherapy addition	IMagyn050 Arm 1: carboplatin AUC 6 + paclitaxel, 175 mg/m^2, every 3 wk × 6 cycles + bevacizumab, 15 mg/kg, on cycles 2-22 Arm 2: carboplatin AUC 6 + paclitaxel, 175 mg/m^2, every 3 wk × 6 cycles + bevacizumab, 15 mg/kg, on cycles 2-22 + atezolizumab, 1200 mg, on day 1 of cycles 1-22	Overall population[52]	Arm 1: 18.4 Arm 2: 19.5	Arm 1: reference Arm 2: 0.92 (0.79-1.07)	Arm 1: 49.2 Arm 2: NA	Arm 1: reference Arm 2: 0.92 (0.78-1.09)	I
		Poorly chemosensitive disease (KELIM <1.0) and suboptimal PCS[53]	Arm 1: 11.3 Arm 2: 14.3	Arm 1: reference Arm 2: 0.75 (0.59-0.95)	NA	NA	III
	NeoPembrov, phase 2 Arm 1:carboplatin AUC 5-6 + paclitaxel, 175 mg/m^2, every 3 wk × 5-6 cycles, maintenance up to 2 y Arm 2: carboplatin AUC 5-6 + paclitaxel, 175 mg/m^2, every 3 wk + pembrolizumab, 200 mg, every 3 wk × 5-6 cycles, maintenance up to 2 y	Overall population[54]	Arm 1: 20.8 Arm 2: 19.4	NA	Arm 1: 35.3 mo Arm 2: 49.8 mo	NA	I
		D8B/FOXP3 ratio (>1.5)[55]	Arm 1: 20 Arm 2: 38	Arm 1: reference Arm 2: 0.42 (0.18-0.98)	Arm 1: 35 Arm 2: NA	Arm 1: reference Arm 2: 0.33 (0.11-0.90)	III
		High CD8B/ENTPD1 expression ratio[55]	Arm 1: 19 Arm 2: 33	Arm 1: reference Arm 2: 0.53 (0.24-1.20)	Arm 1: 34 Arm 2: NA	Arm 1: reference Arm 2: 0.36 (0.13-0.97)	III

Abbreviations: AUC, area under the curve; HR, hazard ratio; HRD, homologous recombination deficiency; ICS, interval cytoreductive surgery; KELIM, modeled cancer antigen 125 elimination rate constant K; NA, not available; NACT, neoadjuvant chemotherapy; OS, overall survival; PCS, primary cytoreductive surgery; PFS, progression-free survival.

[a] For levels of evidence, I indicates randomized prospective primary end point analysis of the trial overall population; II, prespecified subgroup/biomarker analysis within a randomized trial; and III, exploratory analysis: indirect cross-trial weighted comparison or hypothesis-generating biomarker subgroup analysis.

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Figure 4. Flowchart Showing Conceptual Framework for Clinical Trials Evaluating the Added Value of Innovative Chemosensitizing Agents in Patients With Ovarian Cancer Selected for Poor Response to Standard Neoadjuvant Chemotherapy and Considered Suitable for Treatment Intensification Assessment



ctDNA indicates circulating tumor DNA; KELIM, modeled cancer antigen 125 elimination rate constant K.

inconsistent association with NACT efficacy, reflecting the limited sensitivity of CT scans for peritoneal disease and, particularly, for microinfiltrative carcinomatosis.[37,38] Imaging performance is improving with newer modalities. Whole-body diffusion-weighted magnetic resonance imaging outperforms CT scan for predicting disease resectability, with sensitivity above 90% and specificity of 98%.[14] Expert abdominal or transvaginal ultrasonography shows high specificity (98%) and accuracy (about 90%) for nonresectability, though interpretation is operator dependent.[14] Fluorodeoxyglucose positron emission tomography/CT and fluorodeoxyglucose positron emission tomography/magnetic resonance imaging demonstrate strong performance in assessing response to NACT; in one study, an early reduction in fluorodeoxyglucose uptake was associated with a higher rate of CRS3 (52.9% vs 8.7%; $P = .003$).[39] Artificial-intelligence radiomics models further improve prediction of treatment response, with one integrated radiogenomic model achieving an area under the curve of 0.78 vs 0.47 for standard clinical models.[40]

Circulating tumor DNA kinetics have emerged as a promising marker, though available data remain limited.[41,42] In a post hoc analysis of the CHIVA phase 2 trial, a decline in circulating free DNA between baseline and cycle 2 of NACT was associated with improved PFS and OS and predicted complete resection at ICS (odds ratio, 3.94; 95% CI, 1.45-10.70; $P = .007$).[43]

Several additional candidate biomarkers have been proposed, including serum markers (lactate dehydrogenase, growth differentiation factor 15, and human epididymis protein 4), genomic and expression markers (*CCNE1*, *ABCB1*, *ERBB2*, BMP9), regulatory pathways (Aurora A, FOXD3, and HOTAIR), proteomic signatures, ex vivo 3-dimensional microtumor testing, and multiple microRNAs linked to platinum or taxane resistance.[14,44,45] Heterogeneity of findings and the absence of large prospective validation currently limit clinical implementation. In current practice, the modeled KELIM score and pathological CRS are the most clinically mature pragmatic indicators of chemosensitivity, although none has been prospectively validated.

Therapeutic Strategies for Intensification

To our knowledge, no validated chemosensitization strategy currently exists for poorly responsive HGSOC in the first-line setting. However, multiple post hoc analyses of phase 3 trials converge on a consistent signal: intensification provides greater benefit in patients selected for poor chemosensitivity, even when the overall trial result was neutral or modest (**Table**[48]).

Increasing Chemotherapy Dose Intensity

The Japanese JGOG-3016 phase 3 trial showed that a weekly dose-dense regimen of carboplatin area under the curve of 6 with paclitaxel, 80 mg/m^2, on days 1, 8, and 15 every 3 weeks improved PFS and OS over standard every-3-weeks carboplatin area under the curve of 6 with paclitaxel, 180 mg/m^2.[2] This benefit was not reproduced in broader international populations. Indeed, ICON-8, conducted predominantly in European populations, compared standard chemotherapy given every 3 weeks with 2 weekly dose-dense regimens and found no PFS or OS benefit overall.[4] However, a post hoc analysis demonstrated that the 2 red flags subgroup, defined by unfavorable KELIM (<1.0) and disease not amenable to complete resection, derived a 40% to 50% PFS and OS benefit from intensification, regardless of surgery timing (Table).[27]

Bevacizumab as a Potential Chemosensitizing Agent

In platinum-resistant recurrent disease, the AURELIA trial established that bevacizumab added to weekly paclitaxel improved PFS over chemotherapy alone, supporting a chemosensitizing interaction between bevacizumab and weekly paclitaxel.[56] In the first-line setting, interpretation is more complex because bevacizumab is given both with chemotherapy and as maintenance.

In the postoperative adjuvant setting following PCS, GOG-0218 and ICON-7 demonstrated improved outcomes when bevacizumab was added to standard carboplatin-paclitaxel given every 3 weeks, with the largest benefit in high-risk disease.[5,6,19] In ICON-7, bevacizumab increased the radiological response rate by approximately 20% in patients with measurable disease (67% vs 48%). Post hoc analyses incorporating KELIM showed greater OS benefit in patients with unfavorable KELIM than in those with favorable KELIM, in both ICON-7 (HR, 0.78 vs 0.93) and GOG-0218 (PFS HR, 0.64 [95% CI, 0.53-0.78] vs 0.88 [95% CI, 0.68-1.13]; OS HR, 0.79 [95% CI, 0.65-0.97] vs 1.05 [95% CI, 0.79-

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1.39]) (Table).[49,50] These data are consistent with an additive or chemosensitizing effect of bevacizumab when combined with standard postoperative adjuvant chemotherapy in poorly chemosensitive tumors.

Phase 2 trials provide convergent evidence in the neoadjuvant setting. ANTHALYA modestly increased complete ICS rates (59% vs 51%) when bevacizumab was added to standard NACT, while GEICO-1205 improved operability (89% vs 67%; $P = .03$) and increased the $CD8^+/CD4^+FOXP3^+$ tumor-infiltrating lymphocyte ratio without changing overall response.[57,58]

The interaction between bevacizumab and intensified chemotherapy is more nuanced and may vary by treatment setting. In GOG-0262, conducted predominantly in the postoperative adjuvant setting after PCS, the PFS benefit of weekly dose-dense paclitaxel over standard chemotherapy given every 3 weeks disappeared when bevacizumab was added.[3] One interpretation is that bevacizumab, or its maintenance effect, offset the modest benefit of adjuvant chemotherapy intensification. In contrast, ICON-8B, conducted predominantly in the NACT setting, showed that bevacizumab combined with weekly dose-dense chemotherapy improved CRS3 rate (32% vs 21%), PFS (HR, 0.75; 95% CI, 0.62-0.90), and OS (HR, 0.79; 95% CI, 0.65-0.95) compared with bevacizumab plus standard chemotherapy given every 3 weeks.[7] An emerging hypothesis is that bevacizumab preferentially enhances dose-dense chemotherapy in the neoadjuvant setting when disease is in place rather than in the postoperative adjuvant setting.

To explore this hypothesis, indirect weighted survival analyses compared the neoadjuvant arms of ICON-8 and ICON-8B.[46,47] In patients with unfavorable KELIM, adding bevacizumab to standard carboplatin-paclitaxel every 3 weeks was associated with improved outcomes (PFS HR, 0.70 [95% CI, 0.49-1.00]; OS HR, 0.72 [95% CI, 0.52-1.00]), particularly when complete ICS had not been achieved. In contrast, in patients with favorable KELIM, the same combination suggested a deleterious effect emerging after 2 years (PFS HR, 1.23; 95% CI, 0.89-1.70), most pronounced after complete ICS (HR, 1.39; 95% CI, 0.92-2.10), suggesting a time-dependent effect modulated by residual disease. When bevacizumab was combined with weekly dose-dense paclitaxel, outcomes were improved in patients with unfavorable KELIM (PFS HR, 0.62 [95% CI, 0.43-0.87]; OS HR, 0.62 [95% CI, 0.45-0.86]), consistent over time regardless of ICS completeness, and were neutral in those with favorable KELIM. These data support a sustained synergistic effect of bevacizumab with weekly dose-dense neoadjuvant paclitaxel in patients with unfavorable KELIM.[46,47]

Taken together, in the postoperative adjuvant setting following PCS, bevacizumab combined with standard carboplatin-paclitaxel every 3 weeks improves survival, with the largest benefit in high-risk and poorly chemosensitive disease. In the neoadjuvant setting, bevacizumab combined with weekly dose-dense paclitaxel-carboplatin improves tumor response and survival, again most clearly in poorly chemosensitive disease.

PARP Inhibitors as Chemosensitizing Agents

PARPi are now used predominantly as maintenance therapy, but several trials have explored their role as chemosensitizing agents. Veliparib was originally developed for this purpose, because its weaker PARP-DNA trapping confers lower myelotoxic effects than PARPi, permitting concurrent administration with chemotherapy, a strategy reflected in the 3-arm VELIA design comprising a control arm, a concurrent-only arm, and a concurrent-plus-maintenance arm.[51] The mechanistic rationale rests on catalytic PARP inhibition impairing base-excision repair and thereby potentiating platinum-induced DNA damage, an effect distinct from the synthetic lethality and trapping that drive PARPi maintenance benefit. VELIA showed clear PFS benefit only in *BRCA*-mutated tumors, with modest improvements in *BRCA*wt HRD-positive and HRD-negative subgroups, and the development of veliparib in this indication was discontinued. Several secondary analyses, however, supported a moderate chemosensitizing potential. In the concurrent-only arm compared with control, patients had higher radiographic objective response rate (79% vs 74%) and greater 50% CA-125 response after 3 NACT cycles (31% vs 23%), with a numerical PFS improvement particularly among patients with HRD-negative disease and unfavorable KELIM (median PFS, 10.2 vs 6.7 months; HR, 0.79; 95% CI, 0.49-1.30) (Table).[23] These findings may be consistent with a potential chemosensitizing or additive effect of veliparib during chemotherapy, even in the absence of a clear maintenance benefit.

Other PARPi-chemotherapy combinations, including olaparib in the NUVOLA trial and pamiparib in a single-arm study, have been limited by additive hematological toxic effects.[59,60] This has constrained further development.

Immune Checkpoint Inhibitors as Chemosensitizing Agents

Phase 3 trials of anti–programed cell death 1 protein/programed cell death 1 ligand 1 antibodies combined with first-line chemotherapy, including JAVELIN Ovarian 100, IMagyn050, DUO-O, ATHENA-COMBO, KEYLYNK-001, and FIRST, have not produced clinically meaningful improvements in PFS or OS. Subgroup analyses by programed cell death 1 ligand 1 expression, tumor mutational burden, or *BRCA*/HRD status have not identified a clearly responsive population.[52,61-65] These results align with the immunologically cold biology of most HGSOC tumors, where low mutational burden, sparse T-cell infiltration, and an immunosuppressive microenvironment limit immune checkpoint inhibitor (ICI) efficacy.[54,66]

However, exploratory analyses suggest possible chemosensitizing effects in selected subsets. In KEYLYNK-001, post hoc analysis suggested benefit from pembrolizumab added to chemotherapy in patients with incomplete cytoreduction and HRD-negative tumors who did not receive bevacizumab (median PFS, 11.9 vs 10.1 months; HR, 0.69; 95% CI, 0.53-0.90; median OS, 44.5 vs 37.3 months; HR, 0.89; 95% CI, 0.63-1.05). These findings are limited by the nonrandomized use of bevacizumab and the exploratory nature of the analyses.[65] In IMagyn050, a post hoc analysis suggested a possible PFS benefit from atezolizumab in the 2 red flags subgroup, defined by unfavorable KELIM and suboptimal cytoreduction.[53]

Several phase 2 trials have evaluated the addition of ICIs to NACT to increase complete ICS rates. NeoPembrOV did not improve complete ICS overall (67% vs 57%) but suggested benefit in tumors with favorable tumor-infiltrating lymphocyte profiles in exploratory analyses.[54,55] KGOG3046/TRU-D reported a 74% complete ICS rate and 17% pathological complete response with durvalumab and tremelimumab added to chemotherapy. In INEOV, higher intraepithelial $CD8^+$ T-cell infiltration was associated with greater pathological response.[67] Together, these data suggest that ICIs may benefit selected subsets with bulky, poorly chemosensitive, or immunogenic tumors, but no validated selection biomarker has yet emerged.

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Discussion and Perspectives

This Review addresses an unmet medical need that deserves greater attention in the ongoing development of first-line strategies for HGSOC. Achieving minimal residual disease before maintenance therapy depends on 2 determinants: surgical completeness and intrinsic tumor chemosensitivity. Surgical outcome reflects expertise, patient selection, and early disease recognition,[33] while chemosensitivity reflects tumor biology and is increasingly assessable using pragmatic indicators such as KELIM, pathological CRS, and radiological response, all of which are now cited in international guidelines.[31] Patients with both unfavorable indicators, the 2 red flags subgroup, face the poorest prognosis and represent an important unmet medical need.

Across the trials reviewed, a consistent signal supports response-adapted intensification. Weekly dose-dense paclitaxel benefited the 2 red flags subgroup of ICON-8.[27] Bevacizumab added to standard adjuvant or to neoadjuvant dose-dense chemotherapy improved PFS and OS preferentially in residual and poorly chemosensitive disease.[46,49,50] Exploratory analyses of veliparib, atezolizumab, and pembrolizumab indicated activity in selected subsets defined by HRD-negative status, unfavorable KELIM, or immune phenotype.[23,53,65]

Two caveats temper these findings. First, all signals are derived from post hoc or exploratory analyses and require prospective validation in trials specifically designed to test response-adapted intensification. Second, distinguishing chemosensitization during chemotherapy from maintenance benefit after chemotherapy is methodologically challenging, particularly for bevacizumab, which is given in both phases.

Beyond the strategies already evaluated in phase 3 trials, several emerging approaches are being developed with innovative drugs. Cell-cycle checkpoint inhibitors targeting ATR, WEE1, ATM, or CDK2; PI3K and epidermal growth factor receptor inhibitors; and antibody-drug conjugates targeting FOLR1, TROP2, CDH6, NaPi2b, TA-MUC1, CLDN6, HER2, B7-H3, or B7-H4, among others, represent rational chemosensitizing or replacement strategies in chemoresistant disease.[68,69] However, concurrent administration with conventional chemotherapy is currently constrained by overlapping toxic effects, which has favored development of these agents as maintenance in patients with poor-prognosis features such as HRD-negative status or theranostic biomarkers including HER2 expression. Next-generation immunotherapies, including bispecific T-cell engagers, therapeutic vaccines, chimeric antigen receptor T cells, and tumor-infiltrating lymphocyte–based adoptive cell therapy, may provide mechanistic alternatives where conventional ICIs have proven insufficient.[70,71] Another intensification non-systemic approach is hyperthermic intraperitoneal chemotherapy following ICS, which appears to be particularly beneficial for patients with poor chemosensitivity, including those with unfavorable KELIM or *BRCA*wt disease.[72-74]

Regarding future trial design, the data presented herein support a response-adapted strategy in which intensification is reserved for patients least likely to benefit from standard therapy. Offering systemic treatment intensification to all patients with newly diagnosed ovarian cancer—irrespective of their initial response to therapy—would not be appropriate, as tumor responses to chemotherapy are heterogeneous, *BRCA* and HRD status correlate only weakly with response to NACT, and intensification increases cumulative toxic effects. These considerations argue against a one-size-fits-all approach and support individualized strategies guided by early assessment of chemosensitivity. Moreover, a selective, response-adapted approach is ethically justified in a high-risk population in whom poor outcomes are otherwise expected if treatment is not adapted before the maintenance phase.

This conceptual framework—in which innovative intensification strategies are specifically evaluated in patients with a poor response to standard NACT, to determine whether they translate into improved outcomes (**Figure 4**)—is now being implemented prospectively. The international phase 3 SALVOVAR trial evaluates a switch to weekly dose-dense chemotherapy in patients with poor chemosensitivity (KELIM <1.0) and unresectable disease after 3 to 4 cycles of NACT, defining the 2 red flags scenario.[75] The trial will determine whether intensification improves late resectability and OS, and may provide prospective validation of KELIM as a marker of chemosensitivity in this setting.[76] The RegeNovar phase1/2 trial evaluates the addition of ubamatamab, a bispecific antibody targeting MUC16 and CD3, to carboplatin-paclitaxel-bevacizumab in patients with a poor response after 3 to 4 cycles of NACT and disease not amenable to complete ICS.[77,78] Response-adapted intensification has precedents in other solid tumors: in poor-prognosis nonseminomatous germ cell tumors, unfavorable serum tumor marker decline after 1 BEP (bleomycin-etoposide-cisplatin) cycle triggers a switch to paclitaxel-BEP-oxaliplatin (GETUG-13)[79]; in *ERBB2*-positive breast cancer, residual invasive disease after NACT triggers adjuvant T-DM1 (KATHERINE).[80] Achieving minimal residual disease through optimized initial therapy—both surgical and systemic—remains a central therapeutic objective before maintenance and represents a promising path to improved long-term survival in poorly chemosensitive HGSOC.

ARTICLE INFORMATION

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