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Review Article

Major clinical advances in gynecologic cancer in 2025: from de-escalation strategies to precision therapies beyond *BRCA*

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ABSTRACT

The landscape of gynecologic cancer management has continued to evolve substantially in 2025, driven by major clinical advances spanning surgical, radiation, and systemic therapies. Recent progress in precision oncology has expanded therapeutic options beyond the *BRCA* era. Immune checkpoint inhibitors have become integral components of treatment for selected gynecologic malignancies characterized by distinct molecular and histopathologic features, while novel biomarker-driven approaches continue to refine patient selection. In addition, antibody–drug conjugates, which combine tumor-targeted antibodies with cytotoxic payloads, have emerged as a promising therapeutic class, demonstrating encouraging antitumor activity across multiple disease settings. In an effort to overcome the limitations of novel single-agent therapies, clinical research has increasingly focused on combination strategies based on mechanistic rationale. In parallel, advances in surgical and radiation techniques have emphasized functional preservation and improvements in quality of life while maintaining oncologic outcomes. In this review, we summarize the most noteworthy research advances reported in 2025 and discuss their potential implications for future directions in the treatment of gynecologic cancers.

Keywords: Gynecologic Neoplasms; Precision Medicine; Immunotherapy; Immunoconjugates; Cytoreduction Surgical Procedures; Radiotherapy

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INTRODUCTION

The year 2024 marked a period of significant progress in *BRCA*- or homologous recombination deficiency (HRD)-driven poly (ADP-ribose) polymerase (PARP) inhibitor strategies in ovarian cancer and immunotherapy combinations in cervical and endometrial cancers [1-4]. Moving into 2025, research priorities have continued to evolve. In ovarian cancer, emerging trials have increasingly focused on therapeutic strategies for patients without *BRCA* mutations, addressing the unmet need in this large patient population. Meanwhile, in cervical and endometrial cancers, de-escalation strategies have gained prominence, supported by studies such as The Gynecologic Oncology Group (GOG)-278 and GOG-263 in cervical cancer and molecularly guided treatment approaches in endometrial cancer. In this review, we summarize the most noteworthy research advances reported throughout 2025 and discuss their potential implications in the treatment of gynecologic cancer.

OVARIAN CANCER

1. Primary debulking surgery vs. neoadjuvant chemotherapy in advanced ovarian cancer

Previous pivotal trials, including EORTC 55971, CHORUS, JCOG0602, and SCORPION, demonstrated that neoadjuvant chemotherapy followed by interval debulking surgery (NACT-IDS) was noninferior to primary debulking surgery (PDS) in terms of survival, while being associated with reduced perioperative morbidity [5-8]. However, these studies were limited by relatively low complete gross resection (R0) rates in the PDS arms and by the absence of standardized, externally validated surgical quality metrics.

To address these limitations, the TRUST trial (Trial of Radical Upfront Surgical Therapy in advanced ovarian cancer), a phase III, international, randomized study, was designed to determine whether PDS performed in high-volume centers under strict surgical quality standards provides superior survival outcomes compared with NACT-IDS in patients with advanced-stage ovarian cancer deemed resectable [9]. Patients with stage IIIB–IVB epithelial ovarian, fallopian tube, or primary peritoneal cancer were randomly assigned in a 1:1 ratio to undergo either PDS or NACT-IDS. Of the 796 patients, 73.8% were diagnosed with stage III disease. Complete resection rates were higher than those reported in previous trials, reaching 70% in the PDS group and 85% in the NACT-IDS group.

The TRUST study represents the first phase III study to demonstrate a progression-free survival (PFS) advantage with PDS over NACT-IDS in this disease setting, achieved without deterioration in quality of life (QoL), despite the absence of a significant overall survival (OS) benefit. PDS resulted in a modest but significant prolongation of PFS compared with NACT-IDS (median=22.1 vs. 19.7 months; hazard ratio (HR)=0.80; p=0.018). The magnitude of PFS benefit was greatest among patients with International Federation of Gynecology and Obstetrics (FIGO) stage III disease and in those achieving complete gross resection across all stages, with HRs of 0.73 and 0.69, respectively. The rate of major postoperative complications following PDS was acceptable, and overall QoL scores assessed using the EORTC QLQ-C30 did not differ significantly between the 2 groups at any time point.

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2. ICIs in the frontline treatment of advanced ovarian cancer

In advanced ovarian cancer, standard treatment includes cytoreductive surgery followed by platinum-based chemotherapy, with PARP inhibitor maintenance conferring significant survival benefit in *BRCA*-mutated or HRD tumors. In contrast, ovarian cancer is generally regarded as an immunologically "cold" tumor, and clinical activity of programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibitors as monotherapy has been limited [10]. Bevacizumab and PARP inhibitors are associated with modulation of the tumor microenvironment, providing a biological rationale for enhancing antitumor immune responses. PARP inhibitors increase neoantigen load and tumor mutation burden, which may drive a response to ICIs [11]. Moreover, ICIs may suppress PARP inhibitor–mediated PD-L1 upregulation, thereby potentially reducing the development of resistance to PARP inhibition [12]. Combinations of PARP inhibitors and ICIs have been explored in a variety of solid tumors, including ovarian, breast, prostate, and gastric cancers. On the basis of this background, DUO-O, KEYLYNK-001, and FIRST trials were designed to evaluate whether the integration of immune checkpoint inhibition into frontline chemotherapy and maintenance strategies could achieve meaningful clinical benefit in advanced ovarian cancer (**Table 1**).

The DUO-O study, a phase III, double-blind trial was performed in non-t*BRCA*-mutated ovarian cancer group. DUO-O added the anti-PD-L1 antibody durvalumab to platinum-based chemotherapy combined with bevacizumab, followed by maintenance therapy with durvalumab, bevacizumab, and olaparib. It demonstrated a significant PFS benefit primarily

Table 1. List of the major clinical research in ovarian cancer in 2025

Name	Design	No.	Inclusion criteria	Intervention	Control	Primary endpoint	Main results
First-line treatment, cytoreductive surgery							
TRUST	Phase III, randomized, open-label	688	· FIGO stage IIIB/C, IVA/B · Considered resectable · Fit enough to tolerate radical surgery	PDS	NACT+IDS	OS	· mPFS=22.1 vs. 19.7 mo; HR=0.80 (0.66–0.96); p=0.018 · mOS=54.3 vs. 48.3 mo; HR=0.89 (0.74–1.08); p=0.24 · Complete resection rate: 61.7% vs. 72% · Any major postoperative complications: 18% vs. 12% · 30-day postoperative mortality: 0.9% vs. 0.6%
First-line treatment, combination of immune checkpoint inhibitor and PARP inhibitor							
FIRST/ENGOT-OV44 trial	Phase III, randomized, double-blind	1,138	· FIGO stage III: inoperable, planned NAC or macroscopic residual disease after PDS · FIGO stage IIIC : complete resection during PDS if ≥5 cm extrapelvic disease · FIGO stage IV: high-grade nonmucinous epithelial histology	Arm 2: CP ± BEV + PBO, maintenance niraparib + PBO ± BEV Arm 3: CP ± BEV + dostarlimab, maintenance niraparib + dostarlimab ± BEV	CP ± BEV + PBO, maintenance PBO + PBO ± BEV (terminated)	PFS in arm 2 and 3	· mPFS=20.6 vs. 19.2 mo; HR=0.85 (0.73–0.99); p=0.035 · mOS=44.4 vs. 45.4 mo; HR=1.01 (0.86–1.19); p=0.906 · Grade ≥3 TEAE=81.8% vs. 85.6%
KEYLINK-001	Phase III, randomized, double-blind	1,367	· FIGO stage III–IV · BRCA1/2-nonmutated	Arm 1: CP ± BEV + pembrolizumab, maintenance olaparib + pembrolizumab ± BEV Arm 2: CP ± BEV + pembrolizumab, maintenance PBO + pembrolizumab ± BEV	CP ± BEV + PBO, maintenance PBO + PBO ± BEV	PFS in CPS ≥10, PFS in ITT	· Arm 1 vs. control, CPS ≥10 subgroup: mPFS=23.7 vs. 15.2 mo; HR=0.63 (0.49–0.80); p<0.0001 · ITT population: mPFS=22.1 vs. 14.6 mo; HR=0.68 (0.58–0.81); p<0.0001 · Grade ≥3 TRAE=65.7% vs. 51.1%

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Table 1. (Continued) List of the major clinical research in ovarian cancer in 2025

Name	Design	No.	Inclusion criteria	Intervention	Control	Primary endpoint	Main results
Platinum-resistant recurrence							
KEYNOTE-B96	Phase III, randomized, double-blind	643	· Platinum resistant disease · 1–2 prior systemic regimens	Weekly paclitaxel ± bevacizumab + pembrolizumab	Weekly paclitaxel ± bevacizumab + PBO	PFS	· mPFS=8.3 vs. 6.4 mo; HR=0.70 (0.58–0.84); p<0.0001 · mOS=17.7 vs. 14.0 mo; HR=0.81 (0.68–0.97); p=0.0114 · Grade ≥3 TRAE=67.5% vs. 55.3%
ROSELLA	Phase III, randomized, open-label	381	· Platinum resistant disease · 1–3 prior systemic regimens · Prior bevacizumab required	Relacorilant + nab-paclitaxel	Nab-paclitaxel	PFS per BICR, OS	· mPFS=6.54 vs. 5.52 mo; HR=0.70 (0.54–0.91); p=0.0076 · mOS=15.97 vs. 11.50 mo; HR=0.69 (0.52–0.92); p=0.0121 · ORR=36.9% vs. 30.1% · Grade ≥3 TEAEs=74.5% vs. 59.5%
MIRASOL	Phase III, randomized, open-label	453	· Platinum resistant disease · High-grade serous type · 1–3 prior systemic regimens · High FRα expression	Mirvetuximab soravtansine	Investigator's choice chemotherapy	PFS by INV	· mPFS=5.59 vs. 3.98 mo; HR=0.63 (0.513–0.785) · mOS=16.85 vs. 13.34 mo; HR=0.68 (0.534–0.840) · ORR=41.9% vs. 15.9%; OR=3.75 (2.400–5.852) · Grade ≥3 TRAE=44% vs. 55%
REFRαME-01-dose optimization	Phase II/III, randomized, open-label	57	· Platinum resistant disease · 1–3 prior systemic regimens · FRα expression ≥25%	Luveltamab tazevibulin	None	Safety, ORR, PK	· ORR=32% for 5.2 mg/kg, 13.8% for 4.3 mg/kg · DCR=96% for 5.2 mg/kg, 69% for 4.3 mg/kg · Grade ≥3 TEAE=78.6% for 5.2 mg/kg, 65.5% for 4.3 mg/kg
REJOICE-ovarian01	Phase II/III, randomized, open-label	107	· Platinum resistant disease · High-grade serous or endometrioid type · 1–3 prior systemic regimens	Raludotatug deruxtecan	None	ORR per BICR	· ORR per BICR=50.5% · DCR=77.6%

BEV, bevacizumab; BICR, blind independent committee reviewer; CP, carboplatin plus paclitaxel; CPS, combined positive score; DCR, disease control rate; FIGO, International Federation of Gynecology and Obstetrics; FRα, folate-receptor alpha; HR, hazard ratio; INV, investigator; ITT, intention-to-treat; mOS, median overall survival; mPFS, median progression-free survival; NAC, neoadjuvant chemotherapy; NACT + IDS, neoadjuvant chemotherapy followed by interval debulking surgery; OR, odds ratio; ORR, objective response rate; OS, overall survival; PARP, poly (ADP-ribose) polymerase; PBO, placebo; PDS, primary debulking surgery; PFS, progression-free survival; PK, pharmacokinetics; TEAE, treatment emergent adverse events; TRAE, treatment-related adverse events.

within this HRD group, highlighting the importance of biomarker-driven patient selection [13]. The phase III ENGOT-ov43/GOG-3036/KEYLYNK-001 study also showed a significant clinical improvement in PFS in patients who received platinum-based chemotherapy plus pembrolizumab followed by pembrolizumab plus olaparib maintenance therapy compared with chemotherapy alone (median PFS=22.1 vs. 14.6 months; HR=0.68; 95% confidence interval (CI)=0.58–0.81; p<0.0001) [14]. However, these 2 studies did not include an active control arm incorporating PARP inhibitors, which limits comparisons with the current standard of care.

Unlike prior studies, the FIRST/ENGOT-ov44 trial, a phase III, double-blind trial investigated the anti-PD-1 antibody dostarlimab in combination with chemotherapy and incorporated an active control group consisting of a PARP inhibitor maintenance arm, which represents a key strength of the study design [15]. The FIRST trial showed that the greatest benefit was achieved with combined immunotherapy and PARP inhibitor maintenance, particularly in HRD-positive and *BRCA*-mutated populations.

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3. Platinum-resistant recurrence: the role of ICIs

In patients with platinum-resistant ovarian cancer, weekly paclitaxel plus bevacizumab demonstrated the greatest survival benefit among evaluated regimens in the phase III AURELIA trial [16]. Meanwhile, ICIs have shown synergistic effects with both cytotoxic chemotherapy and vascular endothelial growth factor inhibitors [17,18]. The ENGOT-ov65/KEYNOTE-B96 study is a phase III, double-blind trial comparing pembrolizumab vs. placebo in combination with weekly paclitaxel and/or bevacizumab in patients with platinum-resistant ovarian cancer [19]. A total of 643 patients were assigned 1:1 ratio. In the intention-to-treat population, adding pembrolizumab to weekly paclitaxel and/or bevacizumab improved both PFS (median PFS=8.3 vs. 6.4 months; HR=0.70; 95% CI=0.58–0.84; p<0.0001) and OS (median OS=18.2 vs. 14.0 months; HR=0.76; 95% CI=0.61–0.94; p=0.0053), compared to the placebo group. This study is noteworthy as it is the first to demonstrate an improvement in OS with the addition of an ICI within this platinum-resistant disease setting.

4. Platinum-resistant recurrence: glucocorticoid receptor antagonists

Activation of the glucocorticoid receptor in ovarian cancer is associated with tumor progression, chemoresistance, and immune evasion through transcriptional reprogramming and modulation of cell survival pathways [20]. The phase III ROSELLA (GOG-3073/ENGOT-ov72) study introduced a new targeted selective glucocorticoid receptor, relacorilant, and nab-paclitaxel combination aimed at overcoming the intrinsic limitations of standard chemotherapy in platinum-resistant setting [21]. A total of 381 patients were allocated in a 1:1 ratio to receive relacorilant plus weekly nab-paclitaxel or weekly nab-paclitaxel alone. The dual primary endpoints were PFS by blind independent committee reviewer (BICR) and OS. Patients treated with relacorilant plus nab-paclitaxel demonstrated a statistically significant improvement in PFS (median PFS=6.54 vs. 5.52 months; HR=0.70; 95% CI=0.54–0.91; p=0.0076) and a clinically meaningful improvement in OS (median OS=15.97 vs. 11.50 months; HR=0.69; 95% CI=0.52–0.92; p=0.0121). Notably, this represents one of the phase III trials to demonstrate an OS benefit in the platinum-resistant setting. Importantly, this strategy enhances the efficacy of chemotherapy without replacing chemotherapy-based treatment.

5. Platinum-resistant recurrence: antibody–drug conjugates (ADCs)

Current approaches to the treatment of platinum-resistant ovarian cancer emphasize the development of novel therapeutic targets and the establishment of biomarker-directed strategies to enable personalized treatment [22]. Mirvetuximab soravtansine (MIRV), the first ADC developed and clinically evaluated in ovarian cancer, presented the final OS results from the phase III MIRASOL (GOG-3045/ENGOT-ov55) trial at SGO 2025 [23]. The MIRASOL trial enrolled patients with high folate receptor alpha (FRα)-expressing platinum-resistant high-grade serous ovarian cancer in a 1:1 ratio to receive MIRV or investigator's choice chemotherapy (ICC). With a median follow-up period of 30.5 months, survival benefit in PFS of MIRV over ICC maintained, with a HR of 0.63 (95% CI=0.513–0.785). Median OS for MIRV and ICC were 16.85 (95% CI=14.36–19.78) vs. 13.34 (95% CI=11.37–15.15) months (HR=0.68; 95% CI=0.534–0.840; p=0.0004).

REFRaME-01 (GOG-3086/ ENGOT-ov79/APGOT-ov9) is an ongoing phase II/III trial evaluating luveltamab tazevibulin, (FRα)-targeting ADC with a tubulin inhibitor payload. Its results from the phase II dose-optimization part were presented at SGO 2025 [24]. Patients with platinum-resistant ovarian cancer and a FRα tumor proportion score ≥25% were included. In the cohort receiving 5.2 mg/kg plus granulocyte-colony stimulating factor for

the first 2 cycles followed by 4.3 mg/kg for the remaining cycles, the objective response rate (ORR) was 32% and the disease control rate (DCR) was 96%.

Raludotatug deruxtecan targets cell-surface antigen CDH6 which is highly expressed in ovarian cancer cells. In the phase II dose-optimization part of the REJOICE-Ovarian01 study, an ORR of 50.5% by BICR and a DCR of 77.8% were reported [25].

UTERINE CORPUS CANCER

1. Molecularly guided adjuvant de-escalation in early-stage endometrial cancer

In early-stage endometrial cancer with high-intermediate risk, adjuvant vaginal brachytherapy has been the standard of care based on the PORTEC-2 trial [22], with treatment decisions traditionally guided by clinicopathologic factors such as age, histologic grade, depth of myometrial invasion, and lymphovascular space invasion (LVSI). The integration of the Cancer Genome Atlas–based molecular classification has enabled more refined risk stratification, as supported by combined analyses of the PORTEC-1 and PORTEC-2 trials [23].

The phase III PORTEC-4a trial evaluated a molecular profile–guided adjuvant strategy designed to de-escalate radiotherapy (RT) in favorable molecular subgroups, such as DNA polymerase Pol E (*POLE)*-mutated tumors, while intensifying treatment for unfavorable profiles, including those characterized by p53 abnormalities [21]. Based on these findings, the study reported that individualized molecular integrated profiling allowed 46% of patients with a favorable profile to safely avoid unnecessary brachytherapy without compromising oncologic outcomes (**Table 2**).

Although the PORTEC-4a trial represents an important advance by introducing molecularly guided adjuvant treatment for early-stage endometrial cancer, several limitations warrant consideration. Notably, surgical lymph node assessment was omitted in approximately 75% of patients, raising the possibility of occult nodal disease and understaging [24]. In addition, since trial initiation in 2016, major pivotal studies such as PORTEC-3, GOG-249, and GOG-258 and updates to FIGO staging and treatment guidelines have reshaped adjuvant treatment, resulting in discrepancies between the study design and current standards of care [25,26]. For example, in patients with unfavorable molecular profiles, those assigned to the control arm of PORTEC-4a received brachytherapy alone in accordance with the recommendations at the time of study design. However, current guidelines recommend external beam RT with concurrent chemotherapy for this patient population. Meanwhile, as evidence continues to accumulate regarding the favorable therapeutic efficacy of ICIs in mismatch repair deficient (MMRd) disease, it remains uncertain whether adjuvant ICIs would provide additional benefit over brachytherapy in patients with early-stage, high-intermediate–risk endometrial cancer [26]. This question warrants further investigation in future randomized clinical trials.

2. First-line treatment: ICI monotherapy

Immunotherapy has become an integral component of systemic treatment for endometrial cancer. ICI–based regimens, particularly in combination with anti-angiogenic agents, are now established in the second-line setting, and recent pivotal trials have demonstrated significant benefit when immunotherapy is added to first-line platinum-based chemotherapy, especially in patients with MMRd tumors [27-35]. Ongoing phase III trials, including

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Table 2. List of the major clinical research in corpus cancer in 2025

Name	Design	No.	Inclusion criteria	Intervention	Primary endpoint	Main results
Postoperative adjuvant radiotherapy						
PORTEC-4a	Phase III, randomized, open-label, noninferior	564	· Endometrioid endometrial cancer with high-intermediate risk features (ESMO-ESGO-ESTRO consensus 2016) · Surgically resected with curative intent	Molecular integrated risk profile-based adjuvant treatment vs. standard brachytherapy	Vaginal recurrence as the first event	· 5-yr vaginal recurrence rates=4.5% vs. 1.6%; HR=2.71 (0.79–9.34); non-inferiority p=0.005 · 5-yr OS rate=88.0% vs. 90.9%; HR=1.24 (0.72–2.13) · Patients with a favorable risk profile: 5-yr vaginal recurrence rates=4.1% vs. 0.9%; HR=3.97 (0.48–32.95)
First-line treatment: immune checkpoint inhibitor monotherapy						
NIVEC trial	Phase II, single-arm	15	· Stage I–III surgically resectable disease · MSI-H or MMRd · No prior immune checkpoint inhibitor	Nivolumab	CR rate	· Clinical CR rate=80% · Grade ≥3 TEAE=13.3%
Advanced/recurrent endometrial cancer after first-line platinum-based chemotherapy						
RAINFOL-01	Phase II, single-arm	64	· Metastatic or unresectable disease · Prior platinum chemotherapy and PD-(L)1 therapy · Measurable disease	Rinatabart sesutecan	Safety	· ORR=50.0% for 100 mg/m^2; 44.1% for 120 mg/m^2 · DCR=100% for 100 mg/m^2; 82.4% for 120 mg/m^2 · Grade ≥3 TEAE=77.3% for 100 mg/m^2; 83.3% for 120 mg/m^2
P-sam	Phase I/II, single-arm	51	· Advanced/recurrent disease · Progressed on prior platinum-based first-line therapy · Positive B7-H4 by tumor immunohistochemistry · Measurable disease	Puxitatug samrotecan	Safety	· mPFS=7.0 mo for 2.0 mg/kg, 6.9 mo for 2.4 mg/kg · ORR=23.5% for 2.0 mg/kg, 42.1% for 2.4 mg/kg · DCR=82.4% for 2.0 mg/kg, 84.2% for 2.4 mg/kg · Grade ≥3 TEAE=42.3% for 2.0 mg/kg, 36.0% for 2.4 mg/kg
KL264-01	Phase I/II, single-arm	128	· Metastatic or unresectable disease · Progressed after ≥1 prior platinum-based therapy · Prior anti PD-(L)1 therapy if MSI-H or MMRd tumor · Measurable disease	Sacituzumab tirumotecan	ORR	· mPFS=5.6 mo for 4 mg/kg, 7.3 mo for 5 mg/kg · ORR=29.8% for 4 mg/kg, 34.1% for 5 mg/kg · DCR=82.4% for 4 mg/kg, 84.2% for 5 mg/kg · Grade ≥3 TEAE=46.4% for 4 mg/kg, 77.3% for 5 mg/kg
STUDY 102 (E7386)	Phase II, single-arm	30	· Advanced/recurrent disease · Progressed on prior platinum-based chemotherapy and anti-PD-(L)1 therapy · ≤3 prior lines of systemc therapy	E7386 + lenvatinib	Safety	· mPFS=5.5 mo for overall, 10.8 mo for lenvatinib-naïve · ORR=36.7% for overall, 57.1% for lenvatinib-naïve · DCR=70.0% for overall, 71.4% for lenvatinib-naïve · Grade ≥3 TEAE=63.3%
Letrozole, abemaciclib and metformin	Phase II, single-arm	25	· Recurrent disease · ER-positive · Measurable disease · No prior CDK4/6 inhibitor and no current metformin use	Abemaciclib + metformin + letrozole	ORR, PFS6	· mPFS=19.4 mo · ORR=32% · PFS6=69.8% · Grade ≥3 TRAEs=52%

CDK4/6, cyclin-dependent kinase 4/6; CR, complete response; DCR, disease control rate; ER, estrogen receptor; ESMO-ESGO-ESTRO, European Society for Medical Oncology-European Society of Gynaecological Oncology-European Society for Therapeutic Radiology and Oncology; HR, hazard ratio; MMRd, mismatch repair deficiency; mPFS, median progression-free survival; MSI-H, microsatellite instability-high; OS, overall survival; ORR, objective response rate; PD-(L)1, programmed cell death protein 1 and programmed death-ligand 1; PFS6, 6-months progression-free survival rate; TEAE, treatment emergent adverse events; TRAE, treatment-related adverse events.

RAINBO and PETREC, are expected to further refine molecularly guided, personalized treatment strategies in endometrial cancer [27,28].

The DOMENICA trial (NCT05201547), which compares first-line dostarlimab with carboplatin and paclitaxel in patients with advanced or recurrent MMRd endometrial cancer,

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completed accrual of 264 patients in mid-2025 and is currently in the follow-up phase. By directly comparing immunotherapy monotherapy with standard chemotherapy, this study explores a de-escalation paradigm, questioning the necessity of upfront cytotoxic treatment in MMRd population.

Previous KEYNOTE-158 has demonstrated clinically meaningful antitumor activity of pembrolizumab monotherapy in patients with recurrent or advanced MMRd endometrial cancer. KEYNOTE-C93/GOG-3064/ENGOT-en15 (NCT05173987), is evaluating first-line pembrolizumab vs. platinum based chemotherapy in this population; if this trial shows positive results, it could substantially support a chemotherapy-free approach in the first-line setting.

The NIVEC trial provided preliminary insights into the potential clinical efficacy of first-line induction ICI monotherapy prior to standard surgery in MMRd endometrial cancer [29]. This phase II single-arm study enrolled patients with surgically resectable stage I–IIIC2 MMRd endometrial cancer. Nivolumab (a PD-1 inhibitor) was administered intravenously at a dose of 480 mg every 4 weeks for a total of 6 cycles. The primary endpoint was the rate of pathological or clinical complete response (CR). In the first-stage analysis of 15 patients reported at SGO 2025, the clinical CR rate was 80%, and no recurrences were observed during the follow-up period. Seven patients who achieved a clinical CR are being followed without undergoing hysterectomy. The study is currently proceeding to stage II with the enrollment of an additional 15 patients.

3. Second-line treatment: ADCs

For patients with recurrent endometrial cancer who failed standard platinum-based chemotherapy, trastuzumab deruxtecan is currently the most actively used ADC, and it received Food and Drug Administration approval in 2024 for the treatment of unresectable or metastatic human epidermal growth factor receptor 2-positive solid tumors based on the results of the DESTINY-PanTumor02 trial [30].

Rinatabart sesutecan (Rina-S) targets FRα and carries a topoisomerase I inhibitor as its cytotoxic payload. Results from the dose-expansion cohort B2 of the RAINFOL-01 study have been reported in patients with advanced or recurrent endometrial cancer [31]. In the cohort receiving Rina-S at 100 mg/m^2, the ORR was 50.0% and the DCR was 100%. In the 120 mg/m^2 cohort, the ORR and DCR were 44.1% and 82.4%, respectively. Confirmed radiologic responses were observed irrespective of FRα expression levels.

Puxitatug samrotecan (P-Sam) is a topoisomerase I inhibitor–based ADC targeting B7-H4. In the phase I/IIa BLUESTAR trial, P-Sam demonstrated encouraging antitumor activity in patients with B7-H4–positive endometrial cancer who had progressed after platinum-based chemotherapy and immunotherapy, with an ORR of 42.1% and a DCR of 84.2%. A phase III BLUESTAR-Endometrial01 trial is currently evaluating P-Sam monotherapy vs. physician's choice chemotherapy in this biomarker-selected population [32].

Sacituzumab tirumotecan (Sac-TMT) is an ADC comprising a tumor-associated calcium signal transducer 2 (TROP2)-directed monoclonal antibody and the cytotoxic payload KL610023, a topoisomerase I inhibitor. In the endometrial cancer cohort of the phase I/II MK-2870-001/KL264-01 study [33], the confirmed ORR and DCR were 29.8% and 82.4%, respectively, in the 4 mg/kg group, and 34.1% and 84.2%, respectively, in the 5 mg/kg group.

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The observed antitumor activity indicates that TROP2-targeted ADCs may represent a promising therapeutic strategy for patients with endometrial cancer.

4. Second-line treatment: combination approaches with targeted agents

A recent phase II study evaluated the addition of metformin, a modulator of the phosphatidylinositol 3-kinase (PI3K) signaling pathway, to abemaciclib plus letrozole in estrogen receptor–positive recurrent or metastatic endometrial cancer [34]. This approach builds on prior evidence that dysregulation of the receptor tyrosine kinase/renin-angiotensin system/β-catenin and PI3K pathways—present in the majority of estrogen receptor–positive endometrial cancers—converges on cyclin-dependent kinase 4/6-mediated cell-cycle activation [35,36]. While abemaciclib plus letrozole has shown modest efficacy, the addition of metformin was associated with numerically improved outcomes, particularly in molecularly selected tumors with no specific molecular profile without *RB1* or *CCNE1* alterations.

CERVICAL CANCER

1. Early-stage cervical cancer: de-escalation strategy of surgery

In early-stage cervical cancer, radical hysterectomy with pelvic lymphadenectomy (PLA) remains standard practice but carries a substantial burden of lymphatic and neurologic morbidity. The PHENIX trial is a noninferiority phase III trial that compared sentinel lymph node biopsy (SLNB) with PLA in patients with stage IA1 disease with LVSI, IA2–IIA1 disease, tumor size ≤3 cm, and no suspected lymph node or distant metastasis on preoperative imaging who were undergoing radical hysterectomy [37]. The primary endpoint was 3-year disease-free survival (DFS), and secondary endpoints included retroperitoneal lymph node recurrence, cancer-specific survival, and adverse events. The SLNB group demonstrated a 3-year DFS rate of 96.9%, which was noninferior to the 94.6% observed in the PLA group (HR=0.61; 95% CI=0.33–1.14). The 3-year cancer-specific survival rate was 99.2% in the SLNB group and 97.8% in the PLA group (HR=0.37; 95% CI=0.15–0.95). The SLNB group showed significantly lower complication rates than the PLA group, with fewer intraoperative complications (1.1% vs. 3.5%), and a lower overall incidence of adverse events, including lymphocyst formation, lymphedema, and pain (57.8% vs. 71.3%). In selected patients with early-stage cervical cancer, SLNB provides noninferior DFS with reduced morbidity compared with PLA, supporting its use as a safe de-escalation strategy.

GOG-278 was a prospective, observational cohort study designed to evaluate the safety, feasibility, and functional and quality-of-life outcomes of conservative (non-radical) surgical management in patients with early-stage cervical cancer [38,39]. Eligible patients with FIGO 2009 stage IA1 disease with LVSI or stage IA2–IB1 tumors ≤2 cm underwent simple hysterectomy or fertility-sparing cone biopsy with PLA. Among 224 enrolled patients, postoperative sexual, bladder, and bowel dysfunction were transient and generally resolved by 6 months in both groups. Among patients in the cone biopsy group, 31 expressed a desire for pregnancy, resulting in 16 pregnancies, including 4 spontaneous abortions, 3 preterm deliveries, and 9 full-term deliveries. After a median follow-up of 37 months (range, 0.2–93 months), 3 patients in the cone biopsy group experienced recurrence (3-year recurrence-free survival [RFS], 94.8%) and subsequently underwent hysterectomy, whereas no recurrences were observed in the simple hysterectomy group. Taken together, the PHENIX and GOG-278 studies provide complementary evidence: PHENIX establishes oncologic noninferiority through direct DFS comparison, whereas GOG-278 offers

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prospective insights into functional and quality-of-life outcomes in the absence of a control group (**Table 3**).

Table 3. List of the major clinical research in cervical cancer in 2025

Name	Design	No.	Inclusion criteria	Intervention	Primary endpoint	Main results
Early-stage cervical cancer						
PHENIX	Phase III, randomized, open-label, noninferior	838	· FIGO stage (2009) IA1 (LVSI+), IA2, IB1 and IIA1 · Tumor diameter ≤3 cm · No suspected LN on imaging · No distant metastasis · Negative for intraoperative frozen-section of sentinel LN	RH vs. RH and PLND	3-yr DFS	· 3-yr DFS rate=96.9% vs. 94.6%; HR=0.61 (0.33–1.14) · 3-yr CSS rate=99.2% vs. 97.8%; HR=0.37 (0.15–0.95) · Operative time=190 vs. 222 min; p<0.001 · Mean blood loss=134 vs. 161 mL; p=0.002 · Mean time of hospital stay=6.3 vs. 6.6 days; p=0.02 · Intraoperative complication rate=1.1 vs. 3.5%; p=0.02 · Any adverse events=57.8% vs. 71.3%; p<0.001
GOG-278	Prospective, observational	224	· FIGO stage (2009) IA1 (LVSI+), IA2, IB1 (≤2 cm) · Depth of invasion ≤10 mm · Negative margins on final cone biopsy	Arm 1: conization and PLND Arm 2: simple hysterectomy and PLND	Physical function, QOL	· Bladder and bowel function slightly decreased at 4–6 wk postoperatively but returned to baseline by 6 mo · Sexual function declined at 4–6 wk but improved to nearly baseline levels by 24 mo · QOL increased and cancer worry decreased · 12 patients reported a diagnosis of lymphedema
GOG-263	Phase III, randomized, open-label	340	· FIGO stage (2009) IB–IIA · ≥2 of intermediate risk factors after RH and PLND	CCRT with weekly cisplatin vs. RT alone	3-yr RFS	· 3-yr RFS rate=88.5% vs. 85.4%; HR=0.698 (0.408–1.192); p=0.09 · 3-yr OS rate=97.2% vs. 90.3%; HR=0.586 (0.286–1.99); p=0.07 · Grade ≥3 adverse events=42.9% vs. 15.3%; p<0.01
Locally advanced cervical cancer						
EMBRACE II	Prospective, observational	1,482	· FIGO stage (2009) IB–IVA · Planned to receive definitive chemoradiotherapy with curative intent	CCRT with advanced EBRT techniques (IMRT and VMAT), followed by MR-IGABT	Local/ nodal/ systemic control, OS, QOL, morbidity	· 3-yr PFS rate=78%; 5-yr PFS rate=73% · 3-yr OS rate=87%; 5-yr OS rate=82% · 3-yr local, pelvic, and para-aortic control rates=93%, 89%, and 88%, respectively · Late life-threatening gastrointestinal, genitourinary, and vaginal morbidity (grade ≥4), 1%
Metastatic/recurrent cervical cancer						
KL264-01	Phase I/II, single-arm	58	· Metastatic or unresectable disease · Progressed after ≥1 prior platinum-based therapy	Sacituzumab tirumotecan	ORR	· mPFS=6.1 mo · ORR=28% · Grade ≥3 TEAE=48%
DURVAC	Phase II, single-arm	30	· Recurrent or metastatic disease · Progressed after ≥1 prior platinum-based therapy · HPV 16/18-positive · Measurable disease	BVAC-C + durvalumab	PFS6	· PFS6=52% (36–74) · mPFS=8.7 mo · ORR=38% (CR=17%) · DCR=62% · mDOR=20 mo

CCRT, concurrent chemoradiotherapy; CSS, cancer-specific survival; DCR, disease control rate; DFS, disease-free survival; EBRT, external beam radiation therapy; FIGO, International Federation of Gynecology and Obstetrics; GOG, The Gynecologic Oncology Group; HPV, human papillomavirus; HR, hazard ratio; IMRT, intensity modulated radiation therapy; LN, lymph node; LVSI, lymphovascular space invasion; mDOR, median duration of response; mPFS, median progression-free survival; MR-IGABT, magnetic resonance imaging-based image-guided adaptive brachytherapy; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PLND, pelvic lymph node dissection; QOL, quality of life; RFS, recurrent-free survival; RH, radical hysterectomy; RT, radiotherapy; TEAE, treatment emergent adverse events; VMAT, volumetric modulated arc therapy.

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2. Optimizing RT strategies in cervical cancer

Based on GOG-109 [40], concurrent chemoradiotherapy (CCRT) is the standard for high-risk cervical cancer after radical hysterectomy, whereas patients with intermediate-risk disease defined by the Sedlis criteria typically managed with adjuvant RT alone [41], given the lack of evidence for a survival benefit from adding chemotherapy.

To adress this gap in evidence, a phase III open-label NRG Oncology/GOG-0263/KGOG 1008 trial was conducted [42]. The study was designed to compare adjuvant RT alone with CCRT in this intermediate-risk population, with RFS as the primary endpoint and OS and treatment-related toxicity as secondary endpoints. The results demonstrated no significant differences in RFS or OS between the RT alone and CCRT groups, whereas both acute and late toxicities were significantly increased in patients receiving CCRT (CCRT vs. RT, 3-year RFS=88.5% vs. 85.4%; p=0.09; 3-year OS=97.2% vs. 90.3%; p=0.07; grade ≥3 adverse events, 42.9% vs. 15.3%; p<0.01). Subgroup analyses demonstrated different outcomes according to RT techniques (conformal external beam radiation treatment [EBRT] vs. intensity modulated radiation treatment [IMRT]), indicating the need for further study to clarify these findings. Accordingly, adjuvant RT alone appears sufficient following radical hysterectomy among intermediate-risk population, suggesting therapeutic de-escalation and avoidance of unnecessary treatment intensity.

Historically, brachytherapy for cervical cancer was performed based on 2-dimensional orthogonal radiographs, with dose prescription critically dependent on point A as defined by the Manchester system [43]. Since the mid-2000s, image-guided adaptive brachytherapy (IGABT) has enabled precise dose escalation to cervical tumors while sparing normal tissues and has become the standard for definitive RT [44]. Its clinical benefit was established by the EMBRACE I and RetroEMBRACE studies, which demonstrated excellent local control and favorable survival outcomes [45,46].

The EMBRACE II study was designed to incorporate several key advances, including the use of EBRT techniques such as IMRT and volumetric modulated arc therapy, along with refined IGABT protocols featuring more stringent dose constraints for organs at risk. The primary objective of EMBRACE II was to prospectively benchmark the oncologic outcomes achieved in prior studies while further reducing treatment-related morbidity [47].

EMBRACE II is an international, prospective observational study of definitive chemoradiotherapy in patients with FIGO stage IB–IVA cervical cancer. Among 1,482 patients from 49 institutions with a median follow-up of 39 months, 3-year local, pelvic, and para-aortic control rates were 93%, 89%, and 88%, respectively, with 3- and 5-year OS rates of 87% and 82% [48]. In summary, the EMBRACE II protocol prospectively reproduced the excellent disease control and survival outcomes observed in EMBRACE I.

3. Emerging targeted and immunotherapeutic strategies

For the treatment of patients who have progressed after platinum-based chemotherapy, several phase II studies evaluating novel agents have been reported. Sac-TMT is an ADC targeting TROP2, which has been reported to be overexpressed in 88.7% of cervical cancers [49]. In the cervical cancer cohort of the phase I/II MK-2870-001/KL264-01 study, an analysis of 58 patients demonstrated an ORR of 28%, a median PFS of 6.1 months, and grade ≥3 treatment-emergent adverse events in 48% of patients [50]. Another therapeutic approach is the combination of BVAC-C, a therapeutic vaccine for cervical cancer, with durvalumab

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[51]. In patients with human papillomavirus 16- or 18-positive recurrent or metastatic cervical cancer receiving second-line or later therapy, treatment with BVAC-C plus durvalumab demonstrated an ORR of 38%, a 6-month PFS rate of 52%, a median PFS of 8.7 months, and a median duration of response of 20 months. Higher response rates were observed in patients with PD-L1–negative tumors, squamous cell carcinoma, and a treatment-free interval of ≥6 months.

CONCLUSION

In 2025, gynecologic oncology entered a new era characterized by biologically driven de-escalation and precision therapy. Across ovarian, endometrial, and cervical cancers, treatment paradigms have shifted beyond histology and *BRCA* status toward biomarker-guided strategies that optimize efficacy while minimizing morbidity. Advances in immunotherapy, ADCs, and molecular risk stratification have reshaped treatment approaches.

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