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Review Article

Gynecologic oncology in 2024: breakthrough trials and evolving treatment strategies for cervical, uterine corpus, and ovarian cancers

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ABSTRACT

This review summarized the results of clinical trials in 2024 that were believed to have a significant impact on clinical practice in the field of gynecologic oncology. The SHAPE trial, INTERLACE and KEYNOTE-A18 trials, and BEATcc and COMPASSION-16 trials were included in early-stage, locally advanced, and recurrent/metastatic cervical cancer, respectively. For uterine corpus cancer, updated survival data of the four trials (NRG-GY018, RUBY, AtTEnd, DUO-E) for endometrial cancer and the first survival data of LMS-04 trial for leiomyosarcoma were described. For ovarian cancer, the final overall survival results of PRIMA study were followed by DUO-O, ATHENA-combo, and FIRST-ENGOT-OV44 trial in different disease conditions. Finally, the results of DESTINY-PanTumor02, a basket trial of trastuzumab deruxtecan, were briefly addressed.

Keywords: Gynecologic Neoplasms; Immunotherapy; Molecular Targeted Therapy; Poly(ADP-Ribose) Polymerase Inhibitor; Immunoconjugates

INTRODUCTION

The review of 2024 not only summarizes the key findings of major studies published that year but also includes critical letters and scientific commentaries on each paper to provide a broader and more comprehensive understanding. Additionally, key points presented at major gynecologic oncology congresses have been incorporated, facilitating a clearer understanding of the evolution and trends in research over time.

Conflict of Interest
No potential conflict of interest relevant to this article was reported.

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CERVICAL CANCER

In 2024, several noteworthy studies in cervical cancer were presented (**Table 1**), including the SHAPE trial for early cervical cancer, the INTERLACE and KEYNOTE (KN)-A18 trials for locally advanced cervical cancer, and the BEATcc and COMPASSION-16 trials for recurrent and metastatic cervical cancer. Here, we aim to highlight the key findings from each of these clinical trials.

1. Early cervical cancer

The likelihood of parametrial invasion is less than 1% in International Federation of Gynaecology and Obstetrics (FIGO) 2009 stage IB1 cervical cancer have provided evidence supporting the feasibility of performing less radical hysterectomy [1]. The SHAPE trial is a phase III, non-inferiority study comparing extrafascial simple hysterectomy to radical hysterectomy in patients with 2009 FIGO stage IA2 or IB1 (<2 cm) cervical cancer [2]. The study evaluated the 3-year pelvic recurrence rate, which was 2.52% versus 2.17%, respectively (hazard ratio [HR]=1.01; 95% confidence interval [CI]=0.42–2.44), showing no statistically significant difference. Significantly, urinary incontinence within 4 weeks post-surgery was lower in the simple hysterectomy group (2.4% vs. 5.5%, p=0.048), highlighting the benefit of reduced urine voiding-related complications compared to radical hysterectomy. Consequently, for cervical cancers ≤2 cm with an invasion depth of <10 mm on pathology or less than 50% of cervical stromal tissue involvement on magnetic resonance imaging, extrafascial simple hysterectomy can be selectively performed, providing a strong evidence base for its adoption.

Researchers provided commentary on the SHAPE trial. Despite being conducted in patients with low-risk early cervical cancer, the SHAPE trial reported a higher-than-expected 2.7% (9 cases) of positive vaginal margins in the radical hysterectomy group, raising concerns about the reliability of surgical quality [3].

Following the publication of the SHAPE study, additional exploratory analyses were reported. The SHAPE study compared simple hysterectomy and radical hysterectomy through randomization but did not randomize patients based on surgical approaches, such as minimally invasive surgery (MIS) versus open surgery. Among those undergoing simple hysterectomy, 83% underwent MIS, while 17% underwent open surgery. The study reported no significant difference in the pelvic recurrence rates between the 2 groups (4.3% in the MIS group vs. 5.3% in the open surgery group). Consequently, it was concluded that, based on the criteria of the SHAPE study, there is no statistical evidence to suggest that the MIS approach is associated with poorer clinical outcomes [4].

Regarding these results, Ramirez [5] pointed out that the analysis was post-hoc rather than predefined, highlighting the need for further validation. He also noted the occurrence of peritoneal carcinomatosis in the MIS group.

2. Locally advanced cervical cancer

A meta-analysis reported improved overall survival (OS) in cervical cancer when the cycle length of neoadjuvant chemotherapy was ≤14 days and the cisplatin dose exceeded 25 mg/m^2 per week [6]. In line with this finding, a phase III INTERLACE study used a short course weekly carboplatin and paclitaxel regimen as induction chemotherapy. The trial compared weekly induction chemotherapy followed by cisplatin-based chemoradiotherapy (CRT)

Table 1. List of the major clinical research in cervical cancer in 2024

Study name	Design	No.	Inclusion criteria	Intervention	Control	Primary endpoint	PFS	OS
Early-stage cervical cancer								
SHAPE	Phase III, randomized, noninferior	700	• Stage IA2 or IB1 (<2 cm) • Invasion depth <10 mm or less than 50% of cervical stromal tissue • No evidence of lymph node metastasis	Extrafascial simple hysterectomy	Type II RH	3-yr pelvic recurrence	3-yr pelvic recurrence: 2.52% vs2.17%, HR=1.12; 95% CI=0.47–2.67	HR=1.09; 95% CI=0.38–3.14
RTOG 0724/ GOG-0724	Phase III, randomized, open-label	235	• Stage IA2, IB, IIA • Positive pelvic or para-aortic nodes or positive parametrium after surgery	CRT/VBT followed by TC for 4 cycles	CRT/VBT	DFS	4-yr DFS: 76.2% vs. 76.9%, HR=1.05; 95% CI=0.65–1.68	4-yr OS: 87.3% vs. 89.0%, HR=1.05; 95% CI=0.65–1.68
SENTIX	Prospective, observation	594	• Stage IA1 (LVSI) – IB1 • Squamous cell or adenocarcinoma usual type	Bilateral SLN detection followed by type B/C RH	Not available	2-yr DFS	2-yr DFS rate, 93.3%	2-yr OS rate, 97.9%; 3-yr OS rate, 96.9%
Locally advanced cervical cancer								
INTERLACE	Phase III, randomized, open-label	500	• Stage Ib1 (node+), IB2, II, IIIB, IVA • Squamous, adeno, adenosquamous carcinoma, no nodes above aortic bifurcation on imaging, no prior pelvic RT	Induction chemotherapy (weekly TC for 6 wk) followed by CRT	CRT	PFS (by investigator) OS	5-yr PFS rate: 72% vs. 64%, HR=0.65; 95% CI=0.46–0.91	5-yr OS rate: 80% vs. 72%, HR=0.60; 95% CI=0.40–0.91; p=0.015
KEYNOTE-A18	Phase III, randomized, double-blind	1,060	• Stage IB2–IIB (node+) or stage III–IVA cervical cancer	Pembrolizumab + CRT/VBT, followed by maintenance pembrolizumab	Placebo + CRT/VBT, followed by maintenance placebo	PFS (by investigator) OS	3-yr PFS rate: 69.3% vs. 56.9%, HR=0.68; 95% CI=0.56–0.84	3-yr OS rate: 82.6% vs. 74.8%, HR=0.67; 95% CI=0.50–0.90; p=0.0040
CC3	Phase III, randomized, open-label	286	• Stage IB3–IVA • Squamous type • Measurable disease	Nimotuzumab + CRT/VBT	CRT/VBT	3-yr PFS	1-yr PFS, 96.1% vs. 92.1%, HR=0.76; 95% CI=0.33–1.72; p=0.507	1-yr OS: 99.1% vs. 99.0%, HR=1.52; 95% CI=0.36–6.36; p=0.565
Metastatic/recurrent cervical cancer								
BEATcc	Phase III, randomized, open-label	410	• Metastatic, persistent or recurrent cervical cancer • No prior systemic therapy • Measurable disease	Atezolizumab + TC or TP + bevacizumab followed by maintenance bevacizumab and atezolizumab	TC or TP + bevacizumab followed by maintenance bevacizumab	PFS (by investigator) OS	Median PFS: 13.7 vs. 10.4 mo, HR=0.62; 95% CI=0.49–0.78; p<0.0001	Median OS: 32.1 vs. 22.8 mo, HR=0.68; 95% CI=0.52–0.88; p=0.0046
SKB264-II-06	Phase II, open-label, basket trial	40	• Recurrent or metastatic cervical cancer • Received 1 or 2 prior systemic regimens • Progressed on or after platinum-doublet chemotherapy	Sac-TMT + pembrolizumab every 6 wk	None	Safety ORR	6-mo PFS rate, 65.7% (45.8–79.7) and ORR, 57.9%	Not available
COMPASSION-16	Phase III, randomised, double-blind	445	• Metastatic, persistent or recurrent cervical cancer • No prior systemic therapy • Squamous, adeno, adenosquamous carcinoma	Cadonilimab + TC or TP +/– bevacizumab followed by maintenance cadonilimab and/or bevacizumab	Placebo + TC or TP +/– bevacizumab followed by maintenance placebo and/or bevacizumab	PFS (BICR) OS	Median PFS: 12.7 vs. 8.1 mo, HR=0.62; 95% CI=0.49–0.80; p<0.0001	Median OS: NR vs. 22.8 mo, HR=0.64; 95% CI=0.48–0.86; p=0.0011

BICR, blinded, independent, central review; CI, confidence interval; CRT, chemoradiotherapy; DFS, disease-free survival; HR, hazard ratio; LVSI, lymph-vascular space invasion; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RH, radical hysterectomy; RT, radiotherapy; Sac-TMT, sacituzumab tirumotecan; SLN, sentinel lymph node; TC, paclitaxel and carboplatin; TP, paclitaxel and cisplatin; VBT, vaginal brachytherapy.

versus cisplatin-based CRT alone in patients with 2008 FIGO stage IB1 (node-positive), IB2, II, IIIB, and IVA cervical cancer. The induction chemotherapy regimen consisted of paclitaxel (80 mg/m^2) and carboplatin (area under the curve [AUC] 2) administered

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weekly for 6 weeks. The primary endpoints demonstrated significant improvements in the induction chemotherapy arm: a 5-year progression-free survival (PFS) rate of 72% versus 64% (HR=0.65; 95% CI=0.46–0.91) and a 5-year OS rate of 80% versus 72% (HR=0.60; 95% CI=0.40–0.91; p=0.015). These results highlight the superiority of adding induction chemotherapy to the standard treatment approach.

The INTERLACE study included a higher proportion of young patients, resulting in a lower dropout rate compared to what is typically observed in real-world settings. Additionally, 59% of patients were treated with three-dimensional conformal radiotherapy, which is considered an old-fashioned treatment modality compared to current clinical guidelines. The study also included patients with less extensive nodal disease than those in the EMBRACE-1 trial and excluded patients with para-aortic nodal disease. For these reasons, concerns have been raised that applying neoadjuvant chemotherapy directly to clinical practice may be premature [7].

KN-A18 is a phase III randomized, double-blind trial conducted in 1,060 patients with 2014 FIGO stage IB2–IIB (node-positive) or stage III–IVA cervical cancer. The experimental arm consisted of pembrolizumab (200 mg every 3 weeks) combined with CRT and vaginal brachytherapy (VBT), followed by maintenance pembrolizumab (400 mg every 6 weeks for 15 cycles). This was compared to the control arm of CRT/VBT alone. Among the stratified factors, radiotherapy-related considerations included the use of intensity-modulated radiotherapy (IMRT) or volumetric-modulated arc therapy (VMAT) versus non-IMRT or non-VMAT techniques. In the first interim analysis, the PFS was reported as 0.70 (95% CI=0.55–0.89; p=0.002). The 2-year OS rate was 87% in the pembrolizumab-CRT group compared to 81% in the CRT group [8]. In the second interim analysis, the primary endpoint results showed a 3-year PFS rate of 69.3% in the experimental arm versus 56.9% in the control arm (HR=0.68; 95% CI=0.56–0.84; p<0.001) and a 3-year OS rate of 82.6% in the experimental arm versus 74.8% in the control arm (HR=0.67; 95% CI=0.50–0.90; p=0.004) [9]. In the KN-A18 study, pembrolizumab demonstrated a HR of 0.60 (95% CI=0.42–0.86) in the non-White population and 0.83 (95% CI=0.59–1.15) in the White population, making it difficult to draw definitive conclusions about ethnicity-related differences [10]. The strengths of this study include the rapid enrollment of a large global cohort of 1,060 patients, the use of high-quality conformal radiation, and the increased OS benefit observed in the second interim analysis (HR=0.67; compared to HR=0.73 in the first interim analysis), indicating the potential for further survival benefit with continued follow-up [11]. In conclusion, the KN-A18 study is the first phase III trial to achieve a statistically significant improvement in OS for locally advanced cervical cancer. Strategies to expand access to programmed cell death protein 1 (PD-1) inhibitor combination therapy, which may pose a financial burden in low-income countries, should also be considered. When comparing the CALLA trial, which utilized a programmed death-ligand 1 (PD-L1) inhibitor, certain factors emerge as potential contributors to the differing outcomes observed despite similar conditions. These include the presence of ethnic disparities, a relatively higher proportion of patients with stage IIIB disease, heterogeneity in PD-L1 expression levels, and the notion that an 18.5-month follow-up period may have been too short to fully assess the long-term effects of immunotherapy [12]. The U.S. Food and Drug Administration approved the label for use only in stage III–IVA patients in 2014 [13].

3. Metastatic and recurrent cervical cancer

The BEATcc study is a phase III, randomized, open-label trial conducted in patients with metastatic, persistent, or recurrent cervical cancer. In the experimental arm, patients received atezolizumab (1,200 mg) combined with bevacizumab (15 mg/kg), paclitaxel,

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and cisplatin or carboplatin every 3 weeks. In the control arm, patients were treated with bevacizumab, paclitaxel, and cisplatin or carboplatin every 3 weeks. The study demonstrated a median PFS of 13.7 versus 10.4 months (HR=0.62; 95% CI=0.49–0.78; p<0.0001) and a median OS of 32.1 versus 22.8 months (HR=0.68; 95% CI=0.52–0.88; p=0.0046) in the experimental and control arms, respectively [14]. While the KN-826 study utilized the PD-1 inhibitor, pembrolizumab, the BEATcc study employed a PD-L1 inhibitor, atezolizumab. Another distinguishing feature of the BEATcc study is that bevacizumab was given until disease progression, and PD-L1 status was not incorporated as a selection criterion [15].

The COMPASSION-16 study was a phase III trial conducted in patients with metastatic, persistent, or recurrent cervical cancer who had not received prior systemic therapy [16]. Cadonilimab is a bispecific antibody that activates T cells by blocking both PD-1 and cytotoxic T-lymphocyte associated protein 4 pathways. The trial compared cadonilimab (10 mg/kg) plus paclitaxel (175 mg/m^2) and cisplatin (50 mg/m^2) or carboplatin (AUC 4–5) with or without bevacizumab (15 mg/kg) every 3 weeks versus placebo plus the same regimen. The results showed a median PFS of 12.7 versus 8.1 months (HR=0.62; 95% CI=0.49–0.80; p<0.0001). Median OS was not reached in the cadonilimab arm versus 22.8 months in the placebo arm (HR=0.64; 95% CI=0.48–0.86; p=0.0011). Cadonilimab treatment showed greater survival benefits when bevacizumab was not used. Compared to cases where bevacizumab was used, the HRs were 0.46 versus 0.81 for PFS and 0.50 versus 0.84 for OS. The authors suggested that this finding supports the consideration of cadonilimab in patients who are unable to receive bevacizumab. In contrast to the low participation of Asian populations in studies such as GOG-240, KN-826, and BEATcc, this study included 445 Asian patients. Survival benefits were observed not only in the PD-L1 positive population but also in the PD-L1 negative group, which is presumed to be attributed to the bispecific binding capability of cadonilimab [17].

UTERINE CORPUS CANCER

1. Endometrial cancer

The Cancer Genome Atlas (TCGA) marked a shift from the traditional classification of endometrial cancer into types I and II to a modern framework based on molecular classification [18]. Four trials (NRG-GY018, RUBY, AtTEnd, and DUO-E) investigating the integration of immunotherapy as a first-line treatment for advanced or recurrent endometrial cancer reported their first interim analysis in 2023 and have continued to provide updates on survival data through 2024 [19]. The most notable effects of PD-1/PD-L1 inhibitors have been observed in deficient mismatch repair (dMMR) cases, establishing dMMR as an agnostic biomarker or a predictive marker for favorable outcomes.

While the 4 trials share similarities, there are notable differences worth highlighting (**Table 2**). Regarding patient inclusion, the NRG-GY018 trial excluded carcinosarcoma cases, whereas the RUBY and AtTEnd trials included them. For the primary endpoint, the RUBY and AtTEnd studies evaluated both PFS and OS, whereas the NRG-GY018 and DUO-E trials focused solely on PFS. In terms of survival statistical analysis, the NRG-GY018 trial independently analyzed PFS in dMMR and proficient mismatch repair (pMMR) subgroups. In contrast, the RUBY and AtTEnd trials employed a hierarchical approach, first analyzing the dMMR subgroup, followed by the entire study population, highlighting a key methodological difference. Additionally, the duration of immunotherapy varied: 2 years in NRG-GY018, 3 years in RUBY, and until progressive disease (PD) in AtTEnd and DUO-E [20,21].

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Table 2. Comparisons of four phase III randomized trials evaluating the efficacy of front-line immune checkpoint inhibitors in advanced or recurrent endometrial cancer

Trials	RUBY part 1	NRG-GY018	AtTEnd	DUO-E
Patients	494	816	551	718
Drug	Dostarlimab	Pembrolizumab	Atezolizumab	Durvalumab + olaparib
Treatment duration	About 3 yr	About 2 yr	Until progression	Until progression
Permitted treatment interval from previous chemotherapy	≥6 mo	≥12 mo	≥6 mo	≥12 mo
Carcinosarcoma	Included	Excluded	Included	Included
Primary outcomes	PFS, OS	PFS in dMMR and pMMR	PFS, OS	PFS
PFS in ITT population	mPFS: 11.8 vs. 7.9 mo HR=0.64; 95% CI=0.51–0.80; p<0.001	Not available	mPFS: 10.1 vs. 8.9 mo HR=0.74; 95% CI=0.61–0.91; p=0.0022	mPFS, 15.1 vs. 10.2 vs. 9.6 mo Durva + ola arm vs. control, HR=0.55; 95% CI=0.43–0.69; p<0.0001 Durva arm vs. control, HR=0.71; 95% CI=0.57–0.89; p=0.003
PFS in dMMR	mPFS: NR vs. 7.7 mo HR=0.28; 95% CI=0.16–0.50; p<0.001	mPFS: NR vs. 7.6 mo HR=0.30; 0.19–0.48; p<0.001	mPFS: NE vs. 6.9 mo HR=0.36; 95% CI=0.23–0.57; p=0.0005	mPFS: 31.8 vs. NR vs. 7.0 mo Durva + ola arm vs. control, HR=0.41; 95% CI=0.21–0.75 Durva arm vs. control, HR=0.42; 95% CI=0.22–0.80
PFS in pMMR	mPFS, 9.9 vs. 7.9 mo HR=0.76; 95% CI=0.59–0.98	mPFS, 13.1 vs. 8.7 mo HR=0.54; 95% CI=0.41–0.71; p<0.001	mPFS, 9.5 vs. 9.2 mo HR=0.92; 95% CI=0.73–1.16; p=0.38	mPFS, 15.0 vs. 9.9 vs. 9.7 mo Durva + ola arm vs. control, HR=0.57; 95% CI=0.44–0.73 Durva arm vs. control, HR=0.77; 95% CI=0.60–0.97
OS in ITT population	mOS, 44.6 vs. 28.2 mo HR=0.69; 95% CI=0.54–0.89; p=0.002	Not available	mOS, 38.7 vs. 30.2 mo HR=0.82; 95% CI=0.63–1.07; p=0.048	mOS, NR vs. NR vs. 25.9 mo Durva + ola arm vs. control, HR=0.59; 95% CI=0.42–0.83; p<0.003 Durva arm vs. control, HR=0.77; 95% CI=0.56–1.07; p=0.120
OS in dMMR	mOS, NR vs. 31.4 mo HR=0.32; 95% CI=0.17–0.63; p=0.0002	mOS, NR vs. NR HR=0.55; 95% CI=0.25–1.19; p=0.0617	mOS, NE vs. 25.7 mo HR=0.41; 95% CI=0.22–0.76; p=0.0026	Not available
OS in pMMR	mOS, 34.0 vs. 27.0 mo HR=0.79; 95% CI=0.60–1.04; p=0.0493	mOS, 28.0 vs. 27.4 mo HR=0.79; 95% CI=0.53–1.17; p=0.1157	mOS, 31.5 vs. 28.6 mo HR=1.00; 95% CI=0.74–1.35; p=0.54	Not available
Any grade ≥3 AE	72.2% vs. 60.2%	75.3% vs. 45.8%	66.9% vs. 63.8%	67.2% vs. 54.9% vs. 56.4%

AE, adverse event; CI, confidence interval; dMMR, deficient mismatch repair; HR, hazard ratio; ITT, intention-to-treat; mOS, median overall survival; mPFS, median progression-free survival; NE, not evaluable; NR, not reached; OS, overall survival; PFS, progression-free survival; pMMR, proficient mismatch repair.

From this point onward, the newly updated findings from 2024 will be introduced for each clinical trial. The NRG-GY018 study, presented in 2023, demonstrated that the addition of pembrolizumab to carboplatin and paclitaxel significantly improved PFS, achieving a HR of 0.3 in the dMMR group and 0.54 in the pMMR group, with statistical significance observed in both cohorts for the primary endpoint [22]. At the 2024 Society of Gynecologic Oncology (SGO) Annual Meeting, the analysis of the secondary endpoint, OS, demonstrated favorable benefits in both the dMMR and pMMR subgroups. Additionally, 75% of the whole population exhibited PD-L1 combined positive score ≥1, and pembrolizumab improved PFS in both dMMR and pMMR subgroups, irrespective of the PD-L1 status. In conclusion, the addition of pembrolizumab to chemotherapy in advanced or recurrent endometrial cancer demonstrated supportive outcomes as a first-line treatment, regardless of MMR status.

The RUBY study comprises 2 parts: Part 1 evaluates dostarlimab monotherapy as maintenance therapy, while Part 2 investigates the combination of dostarlimab and niraparib as maintenance therapy. The RUBY Part 1 study presented the second interim analysis of updated OS and PFS2 in 2024 SGO. In Part 1 of the study, the overall population demonstrated a statistically significant OS benefit with a HR of 0.69 over a 37.2-month

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follow-up period (previously reported HR 0.64 at 24 months in 2023). In Part 2 of the study, the primary endpoint was PFS evaluated in the overall population and the pMMR subgroup. The results showed a statistically significant PFS benefit in both the overall population and the pMMR group, with HR of 0.60 and 0.63, respectively.

The AtTEnd trial is a phase III study conducted in patients with newly diagnosed endometrial cancer with measurable disease, inoperable stage III–IV endometrial carcinoma or carcinosarcoma, or recurrent disease with no prior chemotherapy or PD ≥6 months after primary/adjuvant systemic therapy [23]. In the experimental group, patients received carboplatin, paclitaxel, and atezolizumab (for 6–8 cycles), followed by maintenance treatment with atezolizumab until PD. In the control group, patients received carboplatin, paclitaxel, and a placebo (for 6–8 cycles), followed by maintenance treatment with a placebo until PD. The primary endpoints were PFS assessed by investigators and OS.

In the dMMR subgroup, a comparison between the atezolizumab and placebo groups revealed survival outcomes of 'not estimated' versus 25.7 months, with a HR of 0.41 (95% CI=0.22–0.76; p=0.0026). Remarkably, 20% of the participants in the study were Asian. Differences in diet and gut microbiota have been proposed as potential factors influencing the effectiveness of immunotherapy in the pMMR subgroup. The lack of molecular classification analysis is an important limitation of this study.

A commentary on the AtTEnd study pointed out that the subgroup analysis of key factors, including histological subtype, MMR status, and the substantial representation of Asian patients, was not comprehensively conducted. Moreover, the 95% CI of 0.23–0.57 in the dMMR subgroup suggests some degree of uncertainty, raising concerns about the interpretation of the results [24]. It was further argued that treating Asians as a homogeneous group might be an oversimplification. Differences in dietary patterns, sodium intake, and vitamin consumption across Asian countries can lead to variations in the gut microbiome, reflecting the heterogeneity of the Asian region [16].

In response to these concerns, the authors of the AtTEnd trial provided the following statements: They clarified that race was not considered a confounding factor but was instead used as a stratification variable. The authors recommended interpreting the findings in the context of Asia versus non-Asia patients as hypothesis-generating. Crucially, the width of the confidence intervals suggested that the upper limit might hold clinical significance. Since participants from South Korea and Japan accounted for 90% of the Asian cohort, the authors considered this group relatively homogeneous [25].

The DUO-E trial utilized durvalumab, a PD-L1 inhibitor, and importantly incorporated olaparib, a poly(ADP-ribose) polymerase (PARP) inhibitor, in combination. In the dMMR subgroup, PFS was reported with HR of 0.42 for the durvalumab monotherapy group and 0.41 for the durvalumab and olaparib combination group, showing no additional effect from the PARP inhibitor. In contrast, in the pMMR subgroup, the durvalumab monotherapy group showed an HR of 0.77, while the durvalumab and olaparib combination group demonstrated an HR of 0.57. These findings suggest that further research is needed to explore the role of the PARP inhibitor in the pMMR group [26].

The four key studies previously discussed in advanced or recurrent endometrial cancer were conducted on patients with residual disease, meaning they were in a non-curative setting.

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In contrast, the KN-B21 study stands out by administering immune checkpoint inhibitors with curative intent to patients with high-risk endometrial cancer. The KN-B21 trial is a phase III, randomized, double-blind study evaluating the efficacy of pembrolizumab in combination with carboplatin and paclitaxel in patients with high-risk endometrial cancer and no residual macroscopic disease, including those with 2009 FIGO stage I–II non-endometrioid tumors with myometrial invasion or 2009 FIGO stage III/IVA disease [27]. The median disease-free survival (DFS) has not yet been reached, with events reported at 22%. In the overall population, the DFS HR was 1.02 (95% CI=0.79–1.32; p=0.570). In the subgroup analysis, the dMMR group demonstrated an HR of 0.31 (95% CI=0.14–0.69), while the pMMR group showed an HR of 1.20 (95% CI=0.91–1.57). The lack of difference in DFS in the intention-to-treat (ITT) population is in contrast with the results demonstrated in NRG-GY018 study. The authors hypothesized that in tumors like pMMR endometrial cancer which have low immunogenicity, higher levels of tumor antigens are required for immune checkpoint inhibitors including pembrolizumab to be more effective. In contrast, in dMMR patients, pembrolizumab may be effective even with a low tumor burden due to the highly immunogenic nature of the disease.

The chemotherapy-free combination of pembrolizumab and lenvatinib (an oral tyrosine kinase inhibitor) has demonstrated an improved survival, in terms of both PFS and OS, in the pMMR group compared to the physician's choice of chemotherapy (either weekly paclitaxel or doxorubicin) in the second-line treatment setting for endometrial cancer, as shown in the KEYNOTE-775 study [28]. However, in the first-line setting of pMMR/microsatellite stable endometrial cancer, the LEAP-001 study found that pembrolizumab plus lenvatinib did not show a PFS or OS benefit compared to carboplatin and paclitaxel (PFS: HR=0.91; 95% CI=0.76–1.09 and OS: HR=0.93; 95% CI=0.77–1.12) [29]. It did not demonstrate statistical significance satisfying the predefined criterion for non-inferiority.

New attempts to apply immune checkpoint inhibitors as neoadjuvant treatment have also garnered attention. The PAM study was a phase I trial conducted in patients with dMMR endometrial cancer of any stage or grade who were scheduled for primary surgery [30]. The study involved pembrolizumab 200 mg every 3 weeks for 2 cycles before surgical resection. The primary endpoints were the pathological response rate and adverse events (AEs) leading to delays in surgery. The overall response rate was 37.5% (with 0% complete response [CR] and 37.5% partial response [PR]). These results contrast with those observed in dMMR rectal cancer, where a 100% CR rate was achieved [31]. Additionally, 75.0% (6/8) of patients showed a decrease in the sum of the longest diameter of the tumor, and none of the evaluable patients showed PD. There were no grade ≥3 AEs observed.

2. Leiomyosarcoma

LMS-04 is a phase III study comparing doxorubicin 75 mg/m^2 plus trabectedin 1.1 mg/m^2 every 3 weeks (6 cycles) followed by maintenance trabectedin 1.1 mg/m^2 every 3 weeks (17 cycles) to doxorubicin 75 mg/m^2 every 3 weeks (6 cycles) in patients with metastatic or surgically unresectable uterine or soft tissue leiomyosarcoma, who have no prior systemic therapy and measurable disease [32]. Trabectedin is a marine-derived antitumor agent that acts on the DNA minor groove. The primary endpoint showed a median PFS of 12 months versus 6 months, with a HR of 0.37 (95% CI=0.26–0.53). The secondary endpoint demonstrated a median OS of 33 versus 24 months, with a HR of 0.65 (95% CI=0.44–0.95). Fifty-nine percent of patients treated with doxorubicin crossed over to trabectedin in subsequent treatment, and the combination therapy group showed longer PFS2 (26 vs. 13 months, HR=0.46; 95% CI=0.32–0.65).

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OVARIAN CANCER

1. First-line PARP inhibitor maintenance therapy

The primary efficacy analysis of the PRIMA study reported in 2019 showed that niraparib as first-line maintenance therapy significantly extended PFS in the homologous recombination deficiency (HRD) subgroup, with a median PFS of 21.9 versus 10.4 months (HR=0.43; 95% CI=0.31–0.59; p<0.001) [33]. At the time, the OS data were immature. Recently, the final OS results have been reported. After a median follow-up of 6.2 years, PFS benefit was maintained across overall, HRD, and homologous recombination proficient (HRP) population, but OS did not show a significant difference between the niraparib arm and the control arm (**Table 3**).

Several factors have been proposed to explain the observed disparity between PFS and OS. It has been suggested that survival in the control arm of the PRIMA study was better compared to other similar studies, leading to hypotheses that may explain this finding. It was suggested that the 48.4% crossover treatment in the control arm, along with the longer duration of PARP inhibitor maintenance (3 years) compared to other studies, may have contributed to the favorable outcomes observed in the control arm. Niraparib toxicity, which resulted in treatment discontinuation and dose interruptions, may have led to data censoring, potentially inflating PFS outcomes, while inadequate drug exposure could have adversely affected OS. Lastly, the potential for cross-resistance arising from subsequent platinum use following PARP inhibitor treatment was also highlighted [34,35].

Table 3. List of the major clinical research in ovarian cancer in 2024

Study name	Design	No.	Inclusion criteria	Intervention	Control	Primary endpoint	PFS	OS
First-line treatment, combination of immune checkpoint inhibitor and PARP inhibitor								
DUO-O	Phase III, randomized, double-blind	1,130	· Stage III–IV high-grade epithelial · No prior systemic therapy · Non-tBRCAm	TC + bevacizumab + durvalumab, followed by maintenance bevacizumab + durvalumab + olaparib	TC + bevacizumab + placebo, followed by maintenance bevacizumab + placebo + placebo	PFS by investigator	Median PFS: 25.1 vs. 19.3 mo, HR=0.61; 95% CI=0.51–0.73 HRD+ group, Median PFS: 45.1 vs. 23.3 mo, HR=0.46; 95% CI=0.33–0.65	HR=0.95; 95% CI=0.76–1.20; p=0.68 HRD+ group, HR=0.84; 95% CI=0.51–1.37
ATHENA combo	Phase III, randomized, double-blind	863	· Stage III–IV high-grade epithelial · Complete or partial response after first-line platinum-based chemotherapy	Maintenance rucaparib + nivolumab	Maintenance rucaparib + placebo	PFS by investigator	Median PFS: 15.0 vs. 20.2 mo, HR=1.29; 95% CI=1.08–1.53	Median OS: 49.4 vs. 58.0 mo, HR=1.13; 95% CI=0.93–1.38
First-line treatment, PARP inhibitor maintenance								
PRIMA	Phase III, randomized, double-blind	733	· Stage III with visible residual tumor after primary debulking surgery or inoperable stage III or IV · High-grade serous or endometrioid · Complete or partial response after first-line platinum-based chemotherapy	Maintenance niraparib	Maintenance placebo	PFS by BICR	5-yr PFS rate, 22% vs. 12%; HRD+ group, 35% vs. 16%; HRD– group, 8% vs. 7%	5-yr OS rate: 42% vs. 44%, HR=1.01; 95% CI=0.84–1.23; p=0.8834 HRD+ group: 55% vs. 56%, HR=0.95; 95% CI=0.70–1.29 HRD– group: 29% vs. 27%, HR=0.93; 95% CI=0.69–1.26
NeoPembrOV	Phase II, randomized, open label	91	· Stage IIIC/IV high-grade serous or endometrioid types · Upfront complete resection was unachievable · PCI score <30	TC + pembrolizumab, followed by maintenance pembrolizumab	TC	CRR at IDS	Median PFS, 19.4 vs. 20.8 mo; CRR, 74% vs. 70%; ORR, 72% vs. 60%	Median OS, 49.8 vs. 35.3 mo

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Table 3. (Continued) List of the major clinical research in ovarian cancer in 2024

Study name	Design	No.	Inclusion criteria	Intervention	Control	Primary endpoint	PFS	OS
Platinum-sensitive recurrence								
ANITA	Phase III, randomized, double-blind	417	• Recurrent high-grade serous, endometrioid or undifferentiated • TFI >6 mo • ≤2 prior lines of chemotherapy	Carboplatin doublet + atezolizumab followed by maintenance atezolizumab + niraparib	Carboplatin doublet + placebo followed by maintenance placebo + niraparib	PFS by investigator	Median PFS: 11.2 vs. 10.1 mo, HR=0.92; 95% CI=0.74–1.13; p=0.28	Not available
ATALANTE	Phase III, randomized, double-blind	614	• Recurrent epithelial non-mucinous • TFI >6 mo • 1 or 2 prior chemotherapy lines	Carboplatin-based chemotherapy + bevacizumab + atezolizumab followed by maintenance atezolizumab	Carboplatin-based chemotherapy + bevacizumab + placebo followed by maintenance placebo	PFS	Median PFS: 13.6 vs. 11.3 mo, HR=0.83; 95% CI=0.69–0.98; p=0.035	Median OS, 35.75 vs. 30.62 mo
Platinum-resistant recurrence								
NRG-GY005	Phase II/III, randomised, open-label, superiority	562	• Platinum-refractory or resistant high-grade serous/ endometrioid • Evaluable disease	ARM 1: cediranib + olaparib ARM 2: cediranib	Weekly paclitaxel, topotecan or PLD	PFS, OS	Median PFS, ARM 1 vs. ARM 3: 5.2 vs. 3.4 mo, HR=0.796; 95% CI=0.597–1.060; p=0.145	Median OS, ARM 1 vs. ARM 3: 12.8 vs. 13.6 mo, HR=1.027; 95% CI=0.771–1.368
AGO-OVAR 2.29/ENGOT-ov34	Phase III, randomized, double-blind	574	• Recurrent high-grade serous, endometrioid or undifferentiated • 1st or 2nd relapse: Treatment-free interval <6 mo, or 3rd relapse	Weekly paclitaxel or PLD + bevacizumab + atezolizumab	Weekly paclitaxel or PLD + bevacizumab + placebo	PFS, OS	Median PFS: 6.3 vs. 6.6 mo, HR=0.88; 95% CI=0.73–1.05; p=0.15	Median OS: 14.3 vs 13.0 mo, HR=0.83; 95% CI=0.68–1.01; p=0.06
Clear cell carcinoma								
LARA	Phase II, open-label, two-stage	27	• Recurrent clear cell carcinoma of ovary or endometrium • Relapse after at least 1 line of platinum-based chemotherapy • Measurable disease	Pembrolizumab + lenvatinib	None	ORR at 24 wk	PFS at 12 wk, 60% (38.4–76.1); PFS at 24 wk, 48% (27.8–65.6); ORR at 24 wk, 44.0% (24.4–65.1)	NA
BrUOG 354	Phase II, randomized, Two-arm, two-stage	44	• Recurrent extra-renal clear cell carcinoma • Relapse after at least 1 line of platinum-based chemotherapy • Measurable disease	Arm 1: Nivolumab, Arm 2: Nivolumab + ipilimumab	None	ORR	Median PFS: ARM, 1: 2.2 mo; ARM, 2: 5.6 mo ORR: Arm 1, 14.3%; Arm 2, 33%	Median OS: Arm 1, 17 mo; Arm 2, 24.6 mo
Surgery								
SOC-1	Phase II/III, randomised, open-label	357	• Platinum-sensitive recurrence • Had one previous platinum-based chemotherapy, TFI >6 mo • Resectable disease according to the iMODEL and PET/CT	Secondary cytoreduction	No surgery	OS, PFS	Median PFS: 18.0 vs. 11.9 mo, HR=0.55; 95% CI=0.44–0.69; p<0.0001	Median OS: 58.1 vs. 52.1 mo, HR=0.80; 95% CI=0.61–1.05; p=0.11
CARACO	Phase III, randomised, open-label	379	• Newly diagnosed stage III–IV • No pre-and intra-operative suspicious lymph nodes >2 cm • Feasible optimal primary surgery or if not feasible interval surgery after NAC (residual tumor <1 cm)	No retroperitoneal pelvic and paraaortic lymphadenectomy	Retroperitoneal pelvic and paraaortic lymphadenectomy	PFS	Median PFS: 14.8 vs. 18.5 mo, HR=0.98; 95% CI=0.78–1.22; p=0.86	Median OS: 48.9 vs. 58.0 mo, HR=0.96; 95% CI=0.75–1.22; p=0.72

BICR, blinded, independent, central review; CI, confidence interval; CRR, complete resection rate; HR, hazard ratio; HRD, homologous recombination deficiency; IDS, interval debulking surgery; NAC, neoadjuvant chemotherapy; ORR, objective response rate; OS, overall survival; PCI, peritoneal cancer index; PET/CT, positron emission tomography/computed tomography; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin; TC, paclitaxel and carboplatin; TFI, treatment-free interval.

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2. First-line combination of PARP inhibitors and immune checkpoint inhibitors

The DUO-O study is a phase III, randomized, double-blind trial conducted in patients with stage III–IV high-grade epithelial ovarian cancer. The experimental arm consisted of carboplatin, paclitaxel, and bevacizumab combined with durvalumab, followed by maintenance therapy with bevacizumab, durvalumab, and olaparib. Final PFS results were reported as follows: In the non-tBRCAm HRD group, the median PFS was 45.1 months in the experimental arm versus 23.3 months in the control arm (HR=0.46; 95% CI=0.33–0.65). In the non-tBRCAm group (ITT population), the median PFS was 25.1 months in the experimental arm versus 19.3 months in the control arm (HR=0.61; 95% CI=0.51–0.73). However, since the control arm did not include olaparib, the current standard of care, it is not possible to evaluate the magnitude of the synergistic effect between durvalumab and olaparib.

The ATHENA Combo trial, a phase III study presented at European Society for Medical Oncology 2024, evaluated patients with stage III–IV high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who achieved a complete or partial response following first-line platinum-based chemotherapy. In the experimental arm, patients received maintenance treatment with rucaparib 600 mg twice a day plus nivolumab 480 mg, while the control arm received maintenance rucaparib 600 mg twice a day plus placebo. PFS by investigator assessment was the primary endpoint. The results showed a median PFS of 15.0 versus 20.2 months (HR=1.29; 95% CI=1.08–1.53) and a median OS of 49.4 versus 58.0 months (HR=1.13; 95% CI=0.93–1.38) [36].

The FIRST-ENGOT-OV44 trial is a phase III, double-blind, randomized study investigating the addition of dostarlimab to platinum-based chemotherapy and niraparib maintenance, with or without bevacizumab, as a first-line treatment for stage III or IV non-mucinous epithelial ovarian cancer. Recently, it was announced that the study met its primary endpoint of PFS, and the results will be presented at an upcoming scientific meeting [37].

3. Platinum-sensitive recurrence

The ANITA phase III trial targeted patients with recurrent ovarian cancer who had a platinum-free interval of ≥6 months and had received no more than two prior lines of chemotherapy [38]. The study compared carboplatin doublet plus atezolizumab (6 cycles) followed by maintenance atezolizumab plus niraparib, versus carboplatin doublet plus placebo (6 cycles) followed by maintenance placebo plus niraparib. The median PFS was 11.2 months versus 10.1 months (HR=0.92; 95% CI=0.74–1.13; p=0.28). Subgroup analysis revealed no differences based on PD-L1 status or BRCA mutation status.

4. Platinum-resistant recurrence

The NRG-GY005 trial was a phase II/III study comparing cediranib plus olaparib, cediranib alone, and standard chemotherapy (weekly paclitaxel, topotecan, or pegylated liposomal doxorubicin) in patients with platinum-refractory or platinum-resistant ovarian cancer. When comparing the combination therapy with chemotherapy, the median PFS was 5.2 versus 3.4 months (HR=0.796; 95% CI=0.597–1.060; p=0.145), and the median OS was 12.8 versus 13.6 months (HR=1.027; 95% CI=0.771–1.368). This study is notable for comparing an oral non-chemotherapy regimen with intravenous chemotherapy. While it demonstrated clinical activity in terms of PFS, it did not establish superiority over chemotherapy.

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5. Secondary cytoreductive surgery

The role of secondary cytoreductive surgery (SCS) in platinum-sensitive recurrent ovarian cancer remains a subject of ongoing debate. The SOC-1 trial investigated SCS versus no surgery in patients with platinum-sensitive recurrent ovarian cancer, who had undergone one previous platinum-based chemotherapy and had a treatment-free interval (TFI) >6 months. The iMODEL score and PET imaging were utilized to determine surgery candidates, which may have resulted in the inclusion of a higher proportion of high-risk patients. In 2021, the median PFS was reported as 17.4 versus 11.9 months (HR=0.58; 95% CI=0.45–0.74; p<0.0001) [39]. Recently, the final OS results of the SOC-1 study have been reported [40]. The median PFS was 18.0 versus 11.9 months (HR=0.55; 95% CI=0.44–0.69). Although statistical significance was not achieved, OS in the ITT population was 58.1 versus 52.1 months (HR=0.80; 95% CI=0.61–1.05; p=0.11). In the no-surgery group, 35% of patients crossed over to surgery. A crossover-adjusted analysis of OS showed an adjusted HR of 0.76 (95% CI=0.58–0.99). In the prespecified subgroup analysis of OS, patients with 20 or fewer relapse sites demonstrated NE versus 69.5 months (HR=0.69; 95% CI=0.46–1.03). The results of SOC-1 add to the body of evidence from previous studies, including the Desktop III trial, which demonstrated an OS benefit from surgery, and the GOG-213 trial, which did not. This study provides additional support for decision-making regarding SCS in patients with recurrent ovarian cancer.

6. Immune checkpoint inhibitor in neoadjuvant setting

Despite the publication of studies such as EORTC 55971, CHORUS, and SCORPION, which investigated neoadjuvant chemotherapy followed by interval debulking surgery, there has been a persistent unmet need to enhance the efficacy of neoadjuvant chemotherapy. NeoPembrOV was a phase II, non-comparative, randomized study conducted in patients with stage IIIC/IV ovarian, primary peritoneal, or fallopian tube cancer for whom upfront complete resection was unachievable and who had a Peritoneal Cancer Index score <30 [41]. The experimental arm consisted of carboplatin, paclitaxel, and pembrolizumab, followed by maintenance pembrolizumab, while the control arm received carboplatin and paclitaxel alone. The primary endpoint was the complete resection rate (CRR) at interval debulking surgery. The CRR was 74% in the experimental arm versus 70% in the control arm. Median PFS was 19.4 months versus 20.8 months, and median OS was 49.8 versus 35.3 months. The limitations of this study include its small sample size and non-comparative statistical design. However, the introduction of pembrolizumab as part of neoadjuvant therapy is considered a feasible approach within the context of current treatment practices.

A BASKET TRIAL OF TRASTUZUMAB DERUXTECAN: DESTINY-PanTumor02

The DESTINY-PanTumor02 study is a phase II trial investigating trastuzumab deruxtecan (T-DXd) across seven tumor cohorts [42]. Human epidermal growth factor receptor 2 (HER2) immunohistochemistry (IHC) scoring was conducted following the current guidelines established by the American Society of Clinical Oncology and the College of American Pathologists for evaluating HER2 in gastric cancer. The inclusion criteria were HER2-expressing solid tumors (IHC 3+ or 2+), locally advanced or metastatic disease following ≥1 systemic treatment, or cases where no alternative treatments were available. Among the gynecologic malignancies, the study included endometrial, cervical, and ovarian cancers.

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T-DXd, a HER2-directed antibody-drug conjugate (ADC), was administered at a dose of 5.4 mg/kg every three weeks. The primary endpoint was the objective response rate (ORR) which was 57.5% for endometrial cancer, 50.0% for cervical cancer, and 45% for ovarian cancer. The most significant efficacy was observed in the IHC 3+ population, with ORRs of 84.6% in endometrial cancer, 75.0% in cervical cancer, and 63.6% in ovarian cancer. This study highlights the potential for tumor-agnostic therapy in HER2-expressing solid tumors. Approximately 10% of the study participants experienced interstitial lung disease (ILD) or pneumonitis, with grade 3 events occurring in 0.4%. No safety-related risk factors were identified.

The primary suspected cause of lung damage associated with T-DXd is its payload. Other factors, such as drug dosage and underlying lung conditions in patients, may also contribute. Since ILD can be life-threatening, management strategies should include dose modification, drug discontinuation, and steroid therapy as appropriate [43].

CONCLUSION

In early cervical cancer, less radical surgery has become a viable option. For cases of locally advanced and recurrent cervical cancer, the addition of immunotherapy has demonstrated a survival benefit. In endometrial cancer, data supporting the dMMR group as a strong candidate for immunotherapy have matured. It has been established that sufficient tumor neoantigens are crucial for the effectiveness of immunotherapy. Research on PARP inhibitors and ADCs is progressing in ovarian cancer.

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