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Review Article

Major clinical research advances in gynecologic cancer in 2022: highlight on late-line PARP inhibitor withdrawal in ovarian cancer, the impact of ARIEL-4, and SOLO-3

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ABSTRACT

In the 2022 series, we summarized the major clinical research advances in gynecologic oncology based on communications at the conference of Asian Society of Gynecologic Oncology Review Course. The review consisted of 1) Ovarian cancer: long-term follow-up data, new poly (ADP-ribose) polymerase (PARP) inhibitors, overall survival (OS) issues with PARP inhibitor monotherapy, hyperthermic intraperitoneal chemotherapy, immunotherapy, and antibody-drug conjugate; 2) Cervical cancer: surgery in early stage disease, therapy for locally advanced stage and advanced, metastatic, or recurrent setting; and 3) Corpus cancer: follow-up regimen, immune checkpoint inhibitor, WEE1 inhibitor, selective inhibitor of nuclear export. A special note was made on the withdrawal of PARP inhibitor from the market for heavily pretreated ovarian cancer patients based on the final OS results of ARIEL-4 and SOLO-3 due to concerns of increased risk of death.

Keywords: Overall Survival; Immunotherapy; Molecular Targeted Therapy; Poly(ADP-Ribose) Polymerase Inhibitor; Hyperthermic Intraperitoneal Chemotherapy

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Synopsis
In 2022, three large pharmaceutical companies voluntarily withdrew poly (ADP-ribose) polymerase (PARP) inhibitors for heavily pretreated ovarian cancer patients, based on the updated results from ARIEL4 (Rubraca®; Clovis), SOLO3 (Lynparza®; AstraZeneca), and QUADRA (Zejula®; GSK). Following the immediate sanction of the Food and Drug Administration, academic societies announced relevant recommendations: PARP inhibitor monotherapy should not be routinely offered to patients for the treatment of platinum-sensitive recurrent ovarian cancer or to patients with either *BRCA1/2* wild-type or platinum-resistant recurrent ovarian cancer. Notwithstanding, a careful interpretation of study results other than the primary endpoints that did not have sufficient statistical power in the confirmatory study is needed. PARP inhibitor monotherapy in select populations should be individualized, considering that evidence on the use of PARP inhibitors in this setting is evolving and data are continuing to emerge.

INTRODUCTION

Long-term overall survival (OS) data from several prospective clinical trials of ovarian and uterine cervical cancers were reported in 2022. Although OS was set as a secondary endpoint, not a primary endpoint, in almost all clinical trials, and therefore, the OS results need to be interpreted carefully, their clinical impact seems substantial. Based on the results of ARIEL-4 and SOLO-3, poly (ADP-ribose) polymerase (PARP) inhibitors for heavily pretreated ovarian cancer patients have been withdrawn by drug companies due to concerns of increased risk of death. Based on the Asian Society of Gynecologic Oncology (ASGO) review course 2022 (**Table 1**, **Fig. S1**) [1-27], this review summarizes the outstanding study results in gynecologic cancer in 2022 and provides future perspectives.

OVARIAN CANCER

1. PARP inhibitors in newly diagnosed advanced ovarian cancer

SOLO1/GOG-3004 7-year follow-up data

The incorporation of PARP inhibitors has revolutionized ovarian cancer management and become the standard of care.

SOLO1/GOG-3004 is a landmark phase III randomized controlled trial (RCT) and its updated results were reported in 2022 [1]. This trial randomly assigned patients with newly diagnosed advanced ovarian cancer and *BRCA1* and/or *BRCA2* mutations in clinical response to platinum-based chemotherapy to olaparib maintenance therapy (n=260) or placebo (n=131) for up to 2 years [28]. A significant improvement in investigator-assessed progression-free survival (PFS) with olaparib maintenance therapy has been reported as the primary endpoint [28,29], followed by other additional endpoints [30,31].

At the time, 7 years after the last patient was randomly assigned, 149 of 391 patients had died (data maturity 38.1%). Although not statistically significant by the prespecified criteria, there was a clinically meaningful improvement in OS with olaparib maintenance therapy vs. placebo (median, not reached vs. 75.2 months; hazard ratio [HR]=0.55; 95% confidence interval [CI]=0.40–0.76; p=0.0004) (p<0.0001 required to declare statistical significance)

Table 1. Topic list of the major clinical researches in gynecologic cancer in 2022

Category	Study
1. Ovarian cancer	
Long-term follow-up data	· SOLO1 [1]: OS with maintenance olaparib at a 7-year follow-up in patients with newly diagnosed advanced ovarian cancer and a BRCA mutation
	· PAOLA-1 [2]: Final OS results from the phase III PAOLA-1/ENGOT-ov25 trial evaluating maintenance olaparib plus bevacizumab in patients with newly diagnosed advanced ovarian cancer
New PARP inhibitor	· ATHENA-MONO [3]: A randomized, phase III trial to evaluate rucaparib monotherapy as maintenance treatment in patients with newly diagnosed ovarian cancer
	· OVARIO [4]: Phase II trial of combination niraparib plus bevacizumab maintenance therapy in advanced ovarian cancer following first-line platinum-based chemotherapy with bevacizumab
	· FZOCUS-2 [5]: Fuzuloparib maintenance therapy in patients with platinum-sensitive, recurrent ovarian carcinoma: a multicenter, randomized, double-blind, placebo-controlled, phase III trial
	· MEDIOLA [6]: Phase II study of olaparib plus durvalumab and bevacizumab: initial results in patients with non-germline BRCA-mutated platinum sensitive relapsed ovarian cancer
OS issue with PARP inhibitor monotherapy	· ARIEL3 [7]: OS results from ARIEL3: a phase 3 randomized, double-blind study of rucaparib vs. placebo following response to platinum-based chemotherapy for recurrent ovarian carcinoma
	· ARIEL4 [8]: Rucaparib versus standard-of-care chemotherapy in patients with relapsed ovarian cancer and a deleterious BRCA1 or BRCA2 mutation: an international, open-label, randomised, phase 3 trial
	· SOLO3 [9]: Final OS results from SOLO3: Phase III trial assessing olaparib monotherapy versus non-platinum chemotherapy in heavily pretreated patients with germline BRCA1 - and/or BRCA2-mutated platinum-sensitive relapsed ovarian cancer
HIPEC	· Lim et al. [10]: Survival after HIPEC and primary or interval cytoreductive surgery in ovarian cancer: a randomized clinical trial
	· KGOG3042 [11]: Comparative effectiveness of HIPEC following interval cytoreductive surgery in patients with advanced-stage ovarian cancer undergoing NAC: multicenter, prospective, cohort study
Immunotherapy	· KGOG3046/TRU-D [12]: A phase II study of durvalumab and tremelimumab with front-line NAC in patients with advanced-stage ovarian cancer
	· ARTISTRY-1 [13]: Nemvaleukin alfa monotherapy and in combination with pembrolizumab in patients with advanced solid tumors
Antibody drug conjugate	· SORAYA (mirvetuximab soravtansine) [14]: Efficacy and safety of mirvetuximab soravtansine in patients with platinum-resistant ovarian cancer with high folate receptor alpha expression
2. Cervical cancer	
Surgery in early stage	· SENTIX [15]: Pathological assessment of sentinel lymph node in early-stage cervical cancer
Locally advanced stage	· CALLA [16]: Durvalumab, in combination with and following chemoradiotherapy, in locally advanced cervical cancer: results from the phase 3 international, randomized, double-blind, placebo-controlled calla trial
	· LUFT [17]: Randomized phase III trial of maintenance chemotherapy with tegafur-uracil versus observation following concurrent chemoradiotherapy for locally advanced cervical cancer
Advanced, metastatic or recurrent setting	· KEYNOTE-826 [18]: Pembrolizumab + chemotherapy in patients with persistent, recurrent, or metastatic cervical cancer: Subgroup analysis of KEYNOTE-826
	· Innova TV/GOG 3024 [19]: Addition of a new cohort with first-line tisotumab vedotin + pembrolizumab + carboplatin ± bevacizumab in recurrent/metastatic cervical cancer
	· EMPOWER [20]: Survival with cemiplimab in recurrent cervical cancer
	· CheckMate-358 [21]: Safety and efficacy of nivolumab ± ipilimumab in patients with recurrent/metastatic cervical cancer in checkmate 358
	· GX188E [22]: Efficacy and safety of GX-188E, a therapeutic DNA vaccine, combined with pembrolizumab in HPV 16-and/or 18-positive advanced cervical cancer (phase II)
3. Corpus cancer	
Follow-up regimen	· TOTEM [23]: Effectiveness of intensive versus minimalist follow-up regimen on survival in patients with endometrial cancer: a randomized, pragmatic, parallel group, multicenter trial
Immune checkpoint inhibitor	· KEYNOTE-158 [24]: Pembrolizumab in patients with microsatellite instability-high advanced endometrial cancer
	· GARNET [25]: Dostarlimab in advanced/recurrent mismatch repair deficient/microsatellite instability–high or proficient/stable endometrial cancer
	· KEYNOTE-775 [69]: Lenvatinib plus pembrolizumab for advanced endometrial cancer
WEE1 inhibitor	· ADAGIO [26]: A phase IIb international study of the WEE1 inhibitor adavosertib in women with recurrent or persistent uterine serous carcinoma
Selective inhibitor of nuclear export	· SIENDO [27]: Randomized phase III study of maintenance selinexor versus placebo in endometrial cancer: impact of subgroup analysis and molecular classification

HIPEC, hyperthermic intraperitoneal chemotherapy; HPV, human papillomavirus; NAC, neoadjuvant chemotherapy; OS, overall survival; PARP, poly (ADP-ribose) polymerase.

[1]. Notably, this analysis was unadjusted for subsequent therapy, and 44.3% of patients in the placebo group received PARP inhibitors as a subsequent line of therapy. Furthermore, with a median follow-up of 88 months, SOLO1/GOG-3004 represents the longest follow-up for any PARP inhibitor in newly diagnosed advanced ovarian cancer.

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The olaparib group also showed improved time to first subsequent therapy (TFST) (median, 64.0 vs. 15.1 months; HR=0.37; 95% CI=0.28–0.48) and time to second subsequent therapy (TSST) (median, 93.2 vs. 40.7 months; HR=0.50; 95% CI=0.37–0.67), compared with the placebo group.

After a 7-year follow-up, the safety profile of olaparib maintenance therapy was consistent with previous reports [28,29]. The incidences of myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) remain low (1.5% vs. 0.8%), and new primary malignancies remain balanced (5.4% vs. 6.2%) between the olaparib and placebo groups [1].

The updated results of SOLO1/GOG-3004 support the use of olaparib maintenance therapy in patients with newly diagnosed advanced *BRCA1/2*-mutated ovarian cancer. A final OS analysis will be conducted once the data maturity reaches 60%, as planned [28].

PAOLA-1/ENGOT-ov25 final OS results

The OS results of a phase III RCT, PAOLA-1/ENGOT-ov25, were reported by the European Society for Medical Oncology (ESMO) Congress 2022 [2]. In this trial, 806 patients with newly diagnosed advanced high-grade ovarian cancer who responded to first-line platinum-based chemotherapy plus bevacizumab were randomly assigned to receive olaparib maintenance therapy (n=537) or a placebo (n=269) for up to 2 years [32]. All patients received bevacizumab every three weeks for up to 15 months, including when administered with chemotherapy. Previously, the primary endpoint PFS has been reported, and the addition of olaparib maintenance therapy significantly improved investigator-assessed PFS, especially in patients with homologous recombination deficiency (HRD)-positive tumors, including those without *BRCA1/2* mutation [32].

Median follow-up was 61.7 and 61.9 months in the olaparib and placebo groups, respectively (data maturity 55.3%). Overall, the 2 groups showed similar OS (median, 56.5 vs. 51.6 months; 5-year OS rate, 47.3% vs. 41.5%; HR=0.92; 95% CI=0.76–1.12; p=0.4118) [2]. Notably, 45.7% of patients in the placebo group and 19.6% of patients in the olaparib group received PARP inhibitors during any subsequent treatment.

Subsequent preplanned exploratory analysis revealed that the addition of olaparib maintenance therapy significantly prolonged OS in patients with HRD-positive tumors (median, 75.2 vs. 57.3 months; HR=0.62; 95% CI=0.45–0.85) and *BRCA1/2*-mutated tumors (median, 75.2 vs. 66.9 months; HR=0.60; 95% CI=0.39–0.93). However, no benefit was observed in patients with HRD-positive tumors, excluding *BRCA1/2*-mutated tumors (HR=0.71; 95% CI=0.45–1.13) and HRD-negative tumors (HR=1.19; 95% CI=0.88–1.63) [2].

The safety profile of olaparib plus bevacizumab maintenance therapy was consistent with that in a previous report [32]. The incidence of MDS/AML remained low between the olaparib and placebo groups (1.6% vs. 2.2%); the same was true for the incidence of new primary malignancies (4.1% vs. 2.9%) [2].

The updated results of PAOLA-1/ENGOT-ov25 support the use of olaparib plus bevacizumab maintenance therapy in patients with newly diagnosed advanced HRD-positive ovarian cancer.

ATHENA-MONO/GOG-3020/ENGOT-ov45

ATHENA/GOG-3020/ENGOT-ov45 is a phase III RCT consisting of 2 separate and fully

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independently powered comparisons evaluating rucaparib monotherapy (ATHENA-MONO) and rucaparib plus nivolumab (ATHENA-COMBO) as maintenance treatment for patients with newly diagnosed advanced high-grade ovarian cancer who responded to first-line platinum-based chemotherapy [3].

In ATHENA-MONO, 538 patients were randomly assigned to receive either rucaparib monotherapy (n=427) or placebo (n=111) for up to 2 years. At the time of randomization, the patients were stratified according to the timing of surgery, residual disease after chemotherapy, and HRD classification. HRD was identified in 234 patients. The primary endpoint, investigator-assessed PFS, and safety results from ATHENA-MONO were reported in 2022 [3].

Rucaparib maintenance monotherapy significantly improved PFS compared with placebo in the intention-to-treat (ITT) population (median, 20.2 vs. 9.2 months; HR=0.52; 95% CI=0.40–0.68); HRD-positive population (median, 28.7 vs. 11.3 months; HR=0.47; 95% CI=0.31–0.72); and HRD-negative population (median, 12.1 vs. 9.1 months; HR=0.65; 95% CI=0.45–0.95). The most common grade ≥3 treatment-emergent adverse events (TEAEs) were anemia (28.7% vs. 0% in the rucaparib and placebo groups, respectively) and neutropenia (14.6% vs. 0.9%). MDS/AML was reported in 2 patients in the rucaparib group (1 with MDS during treatment and 1 with AML during long-term follow-up) and in no patients in the placebo group [3].

At the ESMO Congress 2022, the research team reported results from subgroup analyses according to International Federation of Gynaecology and Obstetrics (FIGO) stage (III or IV), timing of surgery (primary surgery or interval debulking), and residual disease after chemotherapy (no residual disease or residual disease) [33]. As a result, rucaparib maintenance therapy, rather than placebo, improved investigator-assessed PFS across all subgroups.

ATHENA-MONO demonstrated that first-line rucaparib maintenance therapy is effective, with a significant benefit in patients with advanced ovarian cancer with or without high-risk factors for progression at baseline, irrespective of HRD [3,33].

OVARIO

The efficacy and safety of OVARIO in a single-arm phase II study was published in 2022 [4]. A total of 10 patients with newly diagnosed advanced ovarian cancer who had an attempt at optimal debulking surgery and responded to first-line platinum-based chemotherapy with bevacizumab were enrolled and received maintenance therapy with niraparib for up to 3 years plus bevacizumab for up to 15 months, including when administered with chemotherapy. While *BRCA1/2*-mutated tumors were identified in 29 (27.6%) patients, HRD-positive, HRD-negative, and HRD-undetermined tumors were identified in 49 (46.7%), 38 (36.2%), and 18 (17.1%) patients, respectively.

Overall, the PFS rate at 18 months, which was the primary endpoint, was 62% (95% CI=52%–71%). In the HRD-positive, HRD-negative, and HRD-undetermined groups, the 18-month PFS rates were 76% (95% CI=61–87), 47% (95% CI=31–64), and 56% (95% CI=31–79), respectively. After a median follow-up 28.7 months, the median PFS in the overall population was 19.6 months. The median PFS in the HRD-positive and HRD-negative groups was 28.3, and 14.2 months, respectively. The most common grade ≥3 treatment-related adverse events (TRAEs) were thrombocytopenia (39.0%), anemia (34.3%), and hypertension (25.7%). MDS and AML each occurred in one patient after 25 and 32 cycles, respectively [4].

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First-line maintenance therapy with niraparib plus bevacizumab showed promising PFS with an acceptable safety profile consistent with the known safety profiles of each drug as monotherapy. Similar to OVARIO, an ongoing phase II RCT, NIRVANA-1/GINECO-ov129b/ENGOT-ov63 (NCT05183984) [34], and a phase III RCT, AGO-OVAR 28/ENGOT-ov57 (NCT05009082) [35], are investigating the efficacy and safety of niraparib plus bevacizumab maintenance therapy vs. niraparib maintenance therapy in newly diagnosed advanced high-grade ovarian cancer. However, NIRVANA-1 enrolled patients with FIGO stage III and no residual disease after upfront surgery, AGO-OVAR 28 enrolled patients with FIGO stage III–IV, and patients who were scheduled for neoadjuvant chemotherapy (NAC) and interval debulking surgery (IDS) were also allowed. The primary endpoint of both trials is PFS.

2. PARP inhibitors in platinum-sensitive recurrent ovarian cancer

FZOCUS-2

FZOCUS-2 is a phase III RCT assessing the efficacy and safety of fuzuloparib vs. placebo as a maintenance therapy after response to second- or later-line platinum-based chemotherapy in patients with high-grade platinum-sensitive recurrent ovarian cancer [5].

A total of 252 patients were enrolled and randomly assigned to either fuzuloparib maintenance therapy (n=167) or placebo (n=85). At the time of randomization, patients were stratified according to *BRCA 1/2* mutation status, platinum-free interval after penultimate platinum-based chemotherapy, and best response to the most recent platinum-based chemotherapy. Co-primary endpoints, PFS assessed by a blinded independent review committee in the overall population and in patients with germline *BRCA1/2* mutations, were reported in 2022 [5].

After a median follow-up of 8.5 months, fuzuloparib maintenance therapy showed significantly better blinded independent central review (BICR)-assessed PFS compared with placebo in the overall population (median, 12.9 vs. 5.5 months; HR=0.25; 95% CI=0.17–0.36). Fuzuloparib maintenance therapy also resulted in improved BICR-assessed PFS in patients with germline *BRCA1/2* mutations (median, HR=0.14; 95% CI=0.07–0.28) and in those without germline *BRCA1/2* mutations (HR=0.46; 95% CI=0.29–0.74). The most common grade ≥3 TEAEs reported in the fuzuloparib group were anemia (25.1%), thrombocytopenia (16.8%), and neutropenia (12.6%). No MDS/AML were reported [5].

FZOCUS-2 demonstrated that fuzuloparib maintenance therapy is effective with significant PFS improvement in patients with platinum-sensitive recurrent ovarian cancer, regardless of germline *BRCA1/2* mutation status, with a manageable safety profile [5]. Currently, fuzuloparib is available only in China. Nevertheless, the use of fuzuloparib in ovarian cancer is expected to increase further, as clinical trials of fuzuloparib have shown promising results with acceptable toxicities [36].

MEDIOLA final OS results

A Phase II MEDIOLA study evaluated the efficacy and safety of doublet olaparib in combination with durvalumab (an anti-programmed death-ligand 1 [PD-L1] monoclonal antibody) and triplet, olaparib, durvalumab, and bevacizumab therapy in patients with non-germline *BRCA1/2*-mutated, platinum-sensitive recurrent ovarian cancer. Both doublet and triplet treatments were well tolerated with acceptable safety profiles. Previously, median PFS of doublet and triplet cohorts were reported as 5.5 and 14.7 months, respectively [6].

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In 2022, the final OS results of MEDIOLA were presented at the ESMO Congress 2022 [37]. In total, 32 and 31 patients received doublet and triplet therapy, respectively. After a median follow-up of 23.2 and 31.9 months in the doublet and triplet cohorts, respectively, the median OS was 26.1 and 31.9 months, respectively. For the doublet and triplet cohorts, the 12-month OS rates were 77.6% and 96.8%, respectively, and the 24-month OS rates were 50.8% and 64.5%, respectively. The disease control rate (DCR) at 56 weeks was 9.4% for the doublet cohort and 38.7% for the triplet cohort.

Olaparib plus durvalumab and bevacizumab demonstrated encouraging response rates and survival outcomes compared to olaparib plus durvalumab in patients with non-germline *BRCA1/2*-mutated, platinum-sensitive recurrent ovarian cancer. Further investigation of triplet treatments as a non-chemotherapy treatment for this population is warranted. Meanwhile, the results of OPEB-01, a single-arm phase II study investigating the efficacy and safety of triplet maintenance therapy (olaparib, pembrolizumab, and bevacizumab) in patients with *BRCA* wild-type, platinum-sensitive recurrent ovarian cancer who respond to platinum-based chemotherapy, will be published soon and are expected to add scientific evidence on the triplet strategy [38].

ARIEL3 final OS results

The OS results of a phase III RCT, ARIEL3, were reported at the International Gynecologic Cancer Society 2022 Annual Global Meeting [39]. In this trial, 564 patients with high-grade, platinum-sensitive recurrent ovarian cancer who responded to second-line or later platinum-based chemotherapy were randomly assigned to receive either rucaparib maintenance therapy (n=375) or placebo (n=189) [7]. At the time of randomization, patients were stratified by homologous recombination repair gene mutation status, progression-free interval after penultimate platinum-based chemotherapy, and best response to the most recent platinum-based chemotherapy.

Previously, the primary endpoint, PFS, has been reported: rucaparib maintenance therapy significantly improved investigator-assessed PFS, especially in patients with germline or somatic *BRCA1/2* mutations, and in patients with HRD-positive tumors, defined as *BRCA1/2* mutated or *BRCA1/2* wild-type and high loss of heterozygosity (LOH). Across all primary analysis groups, rucaparib significantly improved PFS in patients with platinum-sensitive recurrent ovarian cancer who had achieved a response to platinum-based chemotherapy [7].

After a median follow-up of 77.0 months, 410 of 564 patients died (data maturity, 72.7%). In the overall population, no difference in OS was observed between the rucaparib and placebo groups (median, 36.0 vs. 43.2 months; HR=0.995; 95% CI=0.809–1.223). Notably, 45.8% of the patients in the placebo group received subsequent PARP inhibitor therapy. OS benefit from rucaparib was not observed both in *BRCA1/2*-mutant cohort (median, 45.9 vs. 47.8 months; HR=0.832; 95% CI=0.581–1.192) and in HRD cohort (median, 36.0 vs. 43.2 months; HR=0.995; 95% CI=0.809–1.223), which was also true in *BRCA1/2* wild-type/LOH-low and *BRCA1/2* wild-type/LOH-unknown cohorts. Nevertheless, PFS2, time from randomization to progression on subsequent therapy, was significantly longer with rucaparib than placebo in overall population (median, 20.6 vs. 16.3 months; HR=0.703; 95% CI=0.579–0.854), in *BRCA1/2* mutant cohort (median, 26.1 vs. 18.4 months; HR=0.672; 95% CI=0.480–0.941), and in HRD cohort (median, 24.7 vs. 18.4 months; HR=0.719; 95% CI=0.558–0.923) [39]. This safety was consistent with previous reports [7,40]. The incidence of MDS/AML was similar between the rucaparib and placebo groups (3.8% vs. 3.2%, p=0.72).

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Although no OS benefit was observed, the PFS benefit of rucaparib was maintained through the subsequent line of therapy. Therefore, rucaparib maintenance therapy may be offered to patients with platinum-sensitive recurrent ovarian cancer who have not already received PARP inhibitors and have responded to platinum-based chemotherapy regardless of *BRCA1/2* mutation status.

3. PARP inhibitor monotherapy in recurrent ovarian cancer

ARIEL4 final OS results

The OS results of a phase III RCT, ARIEL4, were reported at the ESMO Congress 2022 [41]. In this trial, 349 patients with germline or somatic *BRCA1/2*-mutated, high-grade, recurrent ovarian cancer who had received ≥2 prior lines of chemotherapy, including ≥1 platinum-based regimen, were randomly assigned to receive rucaparib monotherapy (n=233) or chemotherapy according to institutional guidelines (n=116) [8].

Rucaparib monotherapy provided statistically significant improvement in investigator-assessed PFS (primary endpoint), compared with chemotherapy in the efficacy population (median, 7.4 vs. 5.7 months; HR=0.64; 95% CI=0.49–0.84; p=0.0010) and in the ITT population (median, 7.4 vs. 5.7; HR=0.67; 95% CI=0.52–0.86; p=0.0017). Most treatment-emergent adverse events were grade 1 or 2 [8].

Analysis for OS (secondary endpoint) at 70% data maturity revealed that rucaparib did not improve OS in the ITT population (median, 19.4 vs. 25.4 months; HR=1.313; 95% CI=0.999–1.725; p=0.0507). OS favored chemotherapy over rucaparib. However, among patients with platinum-sensitive disease, the OS was similar between the rucaparib and chemotherapy groups (median, 29.4 vs. 27.6; HR=1.071; 95% CI=0.709–1.618). In contrast, among patients with platinum-resistant disease, the rucaparib group showed significantly worse OS than the chemotherapy group (median, 14.2 vs. 22.2 months; HR=1.511; 95% CI=1.053–2.170). OS was confounded by the high rate of crossover;69% of patients in the control group crossed over to receive rucaparib. Rucaparib safety was consistent with that reported previously [8,42].

SOLO3 final OS results

The OS results of a phase III RCT, SOLO3, were reported at the Society of Gynecologic Oncology 2022 Annual Meeting on Women's Cancer [9]. In this trial, 266 patients with germline *BRCA1/2*-mutated, high-grade, platinum-sensitive recurrent ovarian cancer who had received ≥2 prior lines of platinum-based chemotherapy were randomly assigned to either olaparib monotherapy (n=178) or single-agent non-platinum chemotherapy (n=88) [43]. Olaparib monotherapy provided clinically relevant and statistically significant improvements in objective response rate (ORR; primary endpoint) and PFS (secondary endpoint) compared with single-agent non-platinum chemotherapy [43].

Analysis for OS (secondary endpoint) at approximately 60% data maturity revealed that no difference in OS between the olaparib and control groups (median, 34.9 vs. 32.9 months; HR=1.07; 95% CI=0.76–1.49; p=0.714). PFS2 was not different between the two groups (median, 23.6 vs. 19.6 months; HR=0.80; 95% CI=0.56–1.15; p=0.229). Notably, 11% of patients in the olaparib group and 25% of patients in the control group withdrew from the study before death, and 62.5% of patients in the control group received PARP inhibitors in any subsequent line of therapy [9].

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In post hoc subgroup analysis limited to patients who had received 2 prior lines of chemotherapy, the olaparib group showed significantly better PFS than the control group (median, 16.4 vs. 9.0 months; HR=0.46; 95% CI=0.29–0.75). OS favored the olaparib group over the control group; however, the difference was not statistically significant (median, 37.9 vs. 28.8 months; HR=0.83; 95% CI=0.51–1.38). Conversely, in post hoc subgroup analysis limited to those who had received ≥3 prior lines of chemotherapy, PFS favored the olaparib group over the control group; however, the difference was not statistically significant (median, 9.4 vs. 9.2 months; HR=0.85; 95% CI=0.55–1.45). However, OS was inferior in the olaparib group compared to the control group; however, the difference was not statistically significant (median, 29.9 vs. 39.4 months; HR=1.33; 95% CI=0.84–2.18) [9].

Impact of ARIEL4 and SOLO3 results

Based on the updated results from ARIEL4, which suggest a potential detrimental effect of third-line rucaparib monotherapy in ovarian cancer, Clovis Oncology has voluntarily withdrawn Rubraca® for the treatment of patients with *BRCA1/2*-mutated ovarian cancer after ≥2 prior lines of chemotherapy in June 2022 [44].

Based on the updated results from SOLO3, which suggest a potential detrimental effect of fourth-line olaparib monotherapy in ovarian cancer, in August 2022, AstraZeneca asked to voluntarily withdraw Lynparza®'s accelerated approval for the treatment of patients with germline *BRCA1/2*-mutated advanced ovarian cancer who have been treated with ≥3 prior lines of chemotherapy [45].

In September 2022, GSK also voluntarily withdrew Zejula®'s indication for the treatment of patients with HRD-positive advanced ovarian cancer who have been treated with ≥3 prior lines of chemotherapy [46]. The approval of Zejula® for this indication was based on the QUADRA study, a single-arm phase II study [47]; however, a confirmative phase III RCT has not yet been conducted.

All these voluntary withdrawals of monotherapy with three different PARP inhibitors were quickly sanctioned by the Food and Drug Administration (FDA). Accordingly, American Society of Clinical Oncology (ASCO) rapidly updated a guideline on PARP inhibitor therapy for the management of ovarian cancer, which was published in 2020. They now recommend that PARP inhibitor monotherapy should not be routinely offered to patients for the treatment of platinum-sensitive recurrent ovarian cancer and to patients with either *BRCA1/2* wild-type or platinum-resistant recurrent ovarian cancer. However, at the same time, they also mentioned that evidence on the use of PARP inhibitors in this setting is evolving and data continue to emerge, so that any decision to proceed with PARP inhibitor monotherapy in select populations (*BRCA1/2* mutations, no prior PARP inhibitor use, platinum-sensitive, advanced lines of treatment) should be based on individualized patient and provider assessments of risks, benefits, and preferences (**Fig. 1**) [41].

Hyperthermic intraperitoneal chemotherapy (HIPEC)

Since the findings of the first randomized trial (Interval Debulking Surgery +/− Hyperthermic Intraperitoneal Chemotherapy in Stage III Ovarian Cancer [OVHIPEC]) were published [48], 2 additional trials reported the clinical benefit of HIPEC after interval cytoreductive surgery in patients with advanced ovarian cancer.

Lim et al. conducted a randomized phase III trial of HIPEC after primary or interval maximal cytoreductive surgery in patients with stage III or IV primary ovarian cancer [10]. The primary

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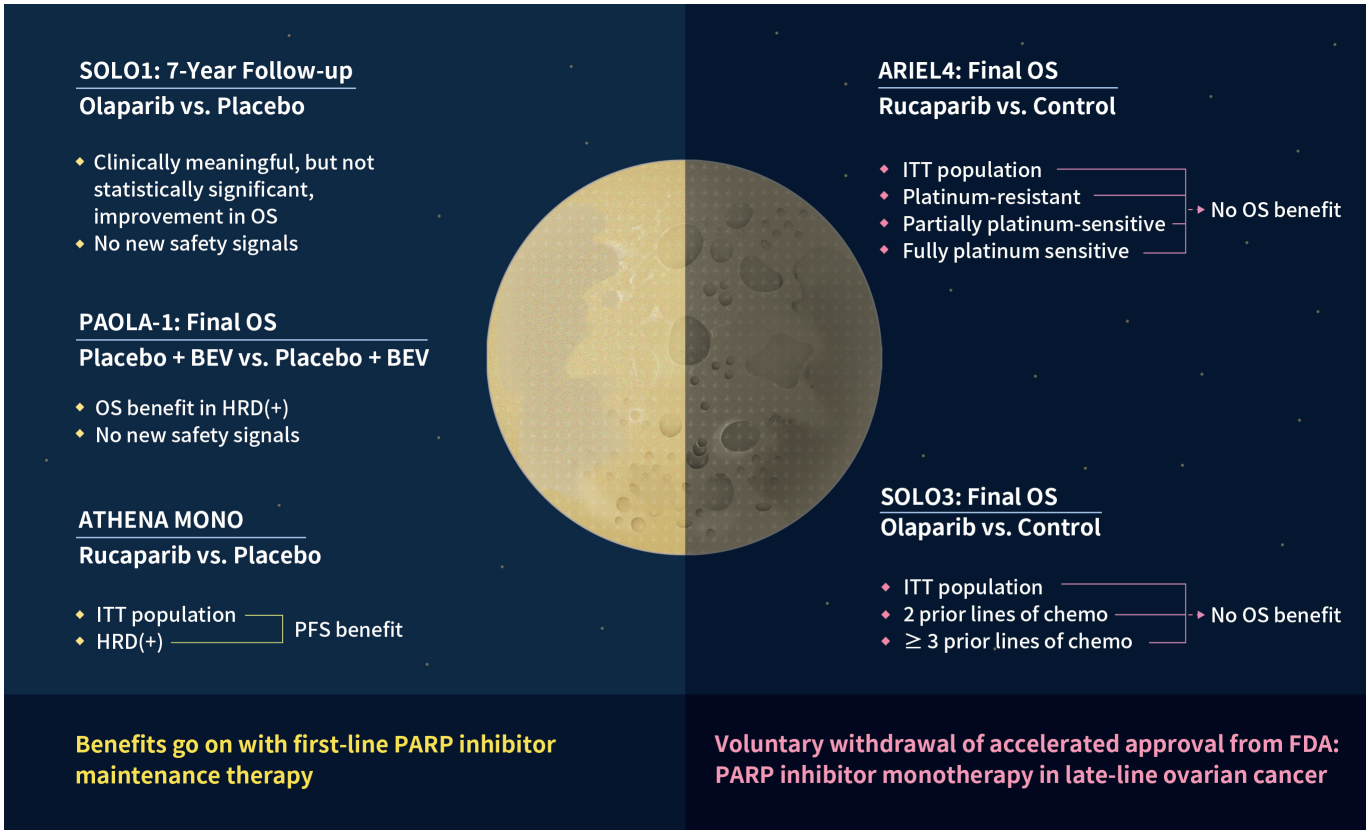

Fig. 1. Light and shade of PARP inhibitor in the treatment of ovarian cancer.
FDA, Food and Drug Administration; HRD, homologous recombination deficiency; ITT, intention-to-treat; OS, overall survival; PARP, poly (ADP-ribose) polymerase.

endpoint was PFS. Of 184 enrolled patients, the addition of HIPEC to cytoreductive surgery did not improve PFS in patients with advanced epithelial ovarian cancer (EOC) (median PFS, 18.8 months in the control group vs. 19.8 months in the HIPEC group, p=0.43). Although, in the subgroup of interval cytoreductive surgery after NAC, HIPEC provided an improvement of both PFS (15.4 months in the control group vs. 17.4 months in the HIPEC group; HR=0.60; 95% CI=0.37–0.99; p=0.04) and OS (48.2 months in the control group vs. 61.8 months in the HIPEC group; HR=0.53; 95% CI=0.29–0.96; p=0.04)]. The health-related quality of life (HRQOL) outcomes of the trial were reported separately [49]. In this study, HIPEC with cytoreductive surgery showed no statistically significant difference in HRQOL outcomes.

A multicenter, non–randomized prospective cohort study comparing the effectiveness of HIPEC following interval cytoreductive surgery in patients with advanced ovarian cancer (KGOG 3042, NCT03448354) was reported at the IGCS annual meeting [11]. In the ITT population, HIPEC was associated with improved PFS (14.2 months in the control group vs. 22.9 months in the HIPEC group; HR=0.61; 95% CI=0.43–0.87; p=0.005) and OS (53.0 months in the control group vs. not–reached in the HIPEC group; HR=0.31; 95% CI=0.14–0.67; p=0.002) in patients with stage III and IV EOC without serious adverse events.

The outcomes of both trials were similar to those of the OVHIPEC trial, supporting the clinical benefit of HIPEC after interval cytoreductive surgery after NAC for advanced ovarian cancer with regard to decreased recurrence and mortality rates. Future studies must investigate the following issues: 1) the benefit of HIPEC in patients with stage IV disease, 2)

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the efficacy of HIPEC according to residual disease and BRCA/HRD status, and 3) the impact of maintenance therapy (Bevacizumab, PARP inhibitor) after HIPEC.

Immunotherapy

KGOG 3046/TRU-D is a single-arm phase II study of the combination of dual immune checkpoint inhibition with front-line NAC in patients with advanced-stage EOC [50]. Patients with clinical stage IIIC-IV EOC were offered three cycles of durvalumab and tremelimumab with chemotherapy for NAC followed by IDS. After surgery, 3 cycles of durvalumab and adjuvant chemotherapy followed by durvalumab maintenance therapy (total 12 cycles) were administered. The primary endpoint was 12 months' PFS rate. The interim analysis showed the clinical activity and manageable toxicity profile for the addition of durvalumab and tremelimumab; 45 patients were evaluated, with an ORR of 87% [12]. Complete response (CR), partial response (PR), and stable disease (SD) rates were 7%, 80%, and 13%, respectively. In an exploratory analysis to identify immune biomarkers and investigate immune dynamic changes during neoadjuvant chemoimmunotherapy (NACI), a significant number of exhausted CD39+CD8 tumor-infiltrating lymphocytes (TILs) decreased after NAC, while T-cell inflamed gene expression profile scores increased, indicating tumor microenvironment conversion to an inflamed phenotype. They suggested CCR8+ regulatory T (Treg) cells as a predictive biomarker for NACI and dynamic changes in PD1+CCR8+ Treg cells as prognostic factors; however, further validation is necessary [51].

ARTISTRY-1 is a phase I/II trial evaluating the novel engineered cytokine, nemvaleukin alfa, in combination with pembrolizumab in patients with advanced solid tumors, including platinum-resistant ovarian cancer. Recent data from a cohort with heavily pretreated platinum-resistant ovarian cancer were reported at the Society of Gynecologic Oncology annual meeting [52]. The combination of emvaleukin and pembrolizumab showed an ORR of 28.6% and a DCR of 71.4%, including 2 durable CRs in 14 evaluable patients. The safety profile in patients with platinum-resistant ovarian cancer was consistent with that in the overall safety population. The US FDA granted fast-track designation to nemvaleukin + pembrolizumab for the treatment of platinum-resistant ovarian cancer [13]. The phase III ARTISTRY-7 trial in patients with platinum-resistant ovarian cancer will further evaluate nemvaleukin + pembrolizumab; the trial is ongoing and recruiting (NCT05092360) [53].

Antibody-drug conjugate

Mirvetuximab soravtansine (MIRV) is a first-in-class antibody-drug conjugate comprising a folate receptor alpha (FRα)-binding antibody, a cleavable linker, and maytansinoid DM4, a potent tubulin-targeting agent. SORAYA was an international, single-arm, phase III study evaluating MIRV in patients with FRα-high platinum-resistant high-grade serous epithelial ovarian, primary peritoneal, or fallopian tube cancers [14]. The primary endpoint was ORR confirmed by the investigator. MIRV demonstrated clinically meaningful antitumor activity in patients with FRα-high platinum-resistant ovarian cancer with an ORR of 32.4%, including 5 CRs. Consistent antitumor activity was observed, regardless of the prior number of therapies or prior PARP inhibitor. The safety profile of MIRV in SORAYA was consistent with that observed in previous studies. Most adverse events were low-grade, reversible ocular and gastrointestinal events, which were manageable with supportive care. These results support that the FDA should grant accelerated approval to MIRV for patients with FRα-high platinum-resistant high-grade serous epithelial ovarian, primary peritoneal, or fallopian tube cancers who have received one to 3 prior systemic treatment regimens [54]. An ongoing confirmatory phase III randomized controlled trial (MIRASOL – NCT04209855) is comparing the efficacy

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and safety of MIRV vs. the investigator's choice of chemotherapy in these patients [55]. In addition, the clinical benefits of MIRV monotherapy are being assessed in patients with platinum-sensitive ovarian cancer (PICCOLO – NCT05041257) [56].

CERVICAL CANCER

The results of a major cervical cancer study reported in 2022 can be summarized into 3 categories: 1) Surgery trials for early-stage cervical cancer; 2) Clinical trials evaluating add-back chemotherapy or maintenance therapy after concurrent chemoradiation therapy (CCRT) for locally advanced cervical cancer; and 3) Clinical trials evaluating new chemotherapeutic agents for advanced, metastatic, and recurrent cervical cancers.

1. Early-stage cervical cancer

SENTIX trial

Sentinel lymph node biopsy (SLNB) is a method for detecting lymph node metastases in gynecological cancers. SLNB can help in staging by accurately identifying lymph node metastasis while minimizing surgical morbidity compared with conventional lymph node dissection. In addition, SLNB can improve the detection range of lymph node metastasis by improving the detection of small-volume lymph node metastasis, including small macrometastasis (MAC), micrometastasis (MIC), and isolated tumor cells through pathologic ultrastaging compared to conventional lymph node dissection. SLNB is regarded as a reasonable alternative surgical procedure to assess lymph node status in earlystage cervical cancer. However, there are no precise guidelines for standardized pathological ultrastaging. The SENTIX trial was a prospective observational trial evaluating SLNB without pelvic lymph node dissection in 647 patients with early-stage cervical cancer, including stage IA1 with lymphovascular space invasion to stage IB2 (2 cm or smaller disease for fertility-sparing treatment) without suspicious lymph nodes on imaging study before surgery [15]. Frozen section evaluation of sentinel lymph nodes (SLNs) and pathologic ultrastaging were mandatory. All detected SLN were examined by one section (standard assessment corresponding to the examination of non-SLN) and consequently processed by ultrastaging (paraffin blocks sectioned at 150 μm intervals; 2 sections from each level, stained with hematoxylin and eosin and immunohistochemically) until there is no remaining tissue (**Fig. 2**) [57].

Of the 82 cases (12.7%) with positive SLN, standard assessment detected only 46 patients (56.1%) with pN1 (83.7% MAC; 25.6% MIC). An additional 35 cases were detected by ultrastaging: 20 cases (24.4%) at level 1, 9 cases (11.0%) at levels 2–4, and 6 cases (7.3%) at level 5 or higher. The number of patients diagnosed with pN1 was directly related to the intensity of SLN pathological assessment. Pathological ultrastaging of the SLN protocol should consist of at least 4 levels. The strength of the SENTIX study was that it revealed the importance of the SLN ultrastaging protocol in cervical cancer.

The sufficient number of slide cuttings to evaluate the SLN in gross processing and pathological ultrastaging of lymph nodes is still debatable. In addition, there is no consensus regarding the thickness of the slices and the distance between slices. In the SENTIX trial, the results showed that pathologic ultrastaging of the SLN protocol should consist of at least 4 levels. However, because the gross processing of the SLN is varies according to the pathologic ultrastaging protocol and the direction of cutting and interval between cutting is varies depending on the pathologic ultrastaging protocol, it is difficult to apply this result

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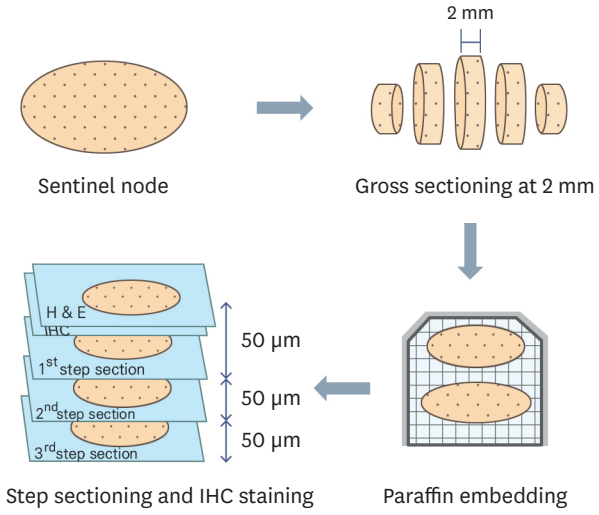

Fig. 2. Sentinel lymph node ultrastaging protocol in the SENTIX trial protocol. Modified from Holloway et al. [57] with permission.
H&E, hematoxylin and eosin; IHC, immunohistochemically

to all pathologic ultrastaging protocols. It may be reasonable to consider that the higher the number of slide cuttings, the higher the sensitivity of pathologic ultrastaging. However, the cost of pathologic ultrastaging would increase accordingly, and its application in routine practice may be difficult. Importantly, the direct comparison between intensive pathologic ulatrastaging, in which cutting is done until no tissue remains, and pathologic ultrastaging, in which one or two slices are cut, is important. However, no randomized trial has been conducted on this to date. One retrospective study compared these 2 types of ultrastaging protocols [58]. There were no differences in the incidence of SLN metastasis between the 2 ultrastaging protocols [58]. Therefore, it is difficult to conclude that the intensive pathologic ultrastaging protocol is better than other protocols that include only one or two slices. Further evaluation is needed to confirm the standard pathological ultrastaging method.

LACC trial

After the LACC trial results were published [59], open radical hysterectomy is the standard treatment in early cervical cancer. However, there are still disagreements regarding whether the cervical cancer surgery method should be changed. The final analysis of the LACC trial was reported in 2022 with the OS results and subgroup analysis of the LACC trial after all patients had completed surveillance at 4.5 years [60]. A total of 631 patients (312 open and 319 minimally invasive radical hysterectomies) were evaluated in this study. The rates of disease-free survival (DFS) and OS at 4.5 years were reported for both surgical approaches. The primary outcome was DFS, which was superior in the open surgery arm for both the ITT and per-protocol (PP) populations. In the ITT population (n=631), the 4.5-year DFS rate was 96% in the open surgery arm and 85% in the minimally invasive surgery (MIS) arm. In the PP population (n=526), DFS rates were 97.3% and 86%, respectively. The HR for DFS in the ITT population was 3.91 (95% CI, 2.02-7.58; $P < 0.0001$). The MIS approach was also associated with significantly worse DFS and OS as well as a higher risk of local/regional recurrence in the ITT population. The HR for cumulative local/regional recurrence was 4.70 (95% CI, 1.95-11.37; $P = 0.001$). The HR for DFS was 3.99 (95% CI, 2.12-7.51; $P < .0001$), and the HR for OS was 2.71 (95% CI, 1.32-5.59; $P = 0.007$). The analysis revealed worse DFS with MIS for patients with tumors greater than 2 cm (HR, 4.25; 95% CI, 1.73-10.4; $P = 0.002$). The analysis also

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revealed worse DFS with MIS for patients without prior conization (HR, 5.85; 95% CI, 2.47-13.9; $P < 0.0001$) but no significant difference between the study arms for patients with prior conization (HR, 1.27; 95% CI, 0.39-4.17; $P = 0.69$). In addition, the rate of carcinomatosis at recurrence was higher with MIS than with open surgery (24% and 0%, respectively). A previously published study based on an interim analysis of survival rates (59.7% of patients followed for 4.5 years) of the LACC trial patients reported similar results. Another systematic review and meta-analysis showed that the MIS group had an increased risk of cervical cancer [61]. One of the reasons for the worse oncologic outcome in the MIS group in the LACC trial was the absence of a maneuver to protect intraperitoneal dissemination and tumor damage caused by the uterine manipulator. In the final report of the LACC trial, there was a comparison of survival outcomes between the loop electrosurgical excision procedure (LEEP) group and the non-LEEP group before radical hysterectomy, and there was no decrease in survival in patients who underwent LEEP before radical hysterectomy among MIS radical hysterectomy. This result also suggests the importance of using protective maneuvers in MIS radical hysterectomy. Another reason is that tumors are affected by carbon dioxide (CO2) exposure to the pneumoperitoneum. Exposure of tumors to circulating CO2 and peritoneal injury due to pneumoperitoneum pressure can cause peritoneal seeding. Further randomized surgical trials are needed to resolve the debate f the LACC trial, and protective maneuvers to prevent tumor spillage during MIS should be standardized.

2. Maintenance immunotherapy or oral chemotherapy after CCRT in locally advanced cervical cancer: CALLA trial, LUFT trial

CCRT is the standard treatment for locally advanced cervical cancer; however, CCRT may result in distant failure. Therefore, add-back chemotherapy has been suggested to reduce the risk of distant failure after CCRT. However, the OUTBCK trial failed to show the benefits of add-back chemotherapy after CCRT. The results of 2 phase III randomized controlled trials evaluating the benefits of maintenance immunotherapy or oral chemotherapy during and/or after CCRT have been reported.

CALLA trial

The CALLA trial was a phase III randomized controlled trial evaluating the role of immunotherapy during and after CCRT in locally advanced cervical cancer patients with node-positive stage IB2 to IIB disease or stage IIIA to IVA disease with any node status. The histological types included squamous cell carcinoma, adenocarcinoma, and adenosquamous carcinoma. A total of 770 patients with locally advanced cervical cancer were treated with CCRT and additional add-back chemotherapy after CCRT. Additional add-back chemotherapy included durvalumab (fixed dose of 1,500 mg) or placebo every 4 weeks for up to 24 cycles or until disease progression [16,62]. The 12-month PFS rate for the placebo plus CCRT group was 73.3%, compared with 76% in the durvalumab plus CCRT group. The 24-month PFS rate was 62.1% in the placebo plus CCRT group and 65.9% in the durvalumab plus CCRT group (HR=0.84; 95% CI=0.65–1.08; p=0.174). The primary endpoint was PFS, and there were no significant intergroup differences between the two groups. Median OS was not mature in the placebo and durvalumab groups at a median follow-up of 20.3 and 20.4 months, respectively (HR=0.78; 95% CI=0.55–1.10; p=0.156). The ORR was 80.5% in the placebo group, which included a CR rate of 40.3% and PR rate of 40.3%. In the durvalumab group, the ORR was 82.6%, CR was 42.9%, and PR was 39.7%. The localized and distant disease progression rates were not significantly different between the two groups. The CALLA trial indicated that durvalumab in combination with CCRT did not significantly improve the PFS of patients with locally advanced cervical cancer.

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LUFT trial

The LUFT trial evaluated the efficacy of maintenance chemotherapy using tegafur-uracil (UFT) after CCRT in locally advanced cervical cancer patients with FIGO (2008) stage Ib2–IVa cervical cancer, who have squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma [17]. Maintenance chemotherapy with oral UFT after surgery has been shown to prolong survival in patients with breast, lung, gastric, and colon cancers. A total of 351 patients with locally advanced cervical cancer were treated with CCRT and randomized to either the observation group or the UFT maintenance group. The 5-year PFS rate in the observation group was 61.3% (90% CI=54.8–67.1) compared with 62.0% (90% CI=55.4–67.8) in the UFT maintenance group. The HR of PFS for the UFT maintenance group and observation group was 0.92 (90% CI=0.69–1.22). The 5-year OS rates were 77.6% (90% CI=71.8–82.4) in the observation group and 76.1% (90% CI=70.1–81.1) in the UFT maintenance group (p=0.869). HR of OS was 1.04 (90% CI=0.73–1.47). Severe adverse events occurred significantly more frequently in the UFT group than in the observation group. The LUFT trial did not find improvement in PFS or OS compared with the CCRT alone group.

The primary concern with CCRT is the possibility of distant failure. One strategy for reducing distant failure after CCRT is the use of immunotherapy during and after CCRT. Based on the results of OUTBACK [63], CALLA, and LUFT trials, maintenance therapy for locally advanced cervical cancer must be strategized with other agents. Improvements over standard CCRT remain a challenge in locally advanced cervical cancer, and further research is required to optimize patient outcomes. A study comparing CCRT and CCRT plus pembrolizumab (KEYNOTE-A18/ENGO-cx11) is ongoing. A study comparing CCRT with CCRT plus triapine is also ongoing. The role of a four-agent regimen, including paclitaxel plus carboplatin plus pembrolizumab with or without bevacizumab, should be evaluated as additional chemotherapy after CCRT.

3. New active therapeutic agents in advanced, metastatic, and recurrent cervical cancer: KEYNOTE-826, GOG 3024/Innova TV 205, EMPOWER, Checkmate 358, and GX 188E trials

A subgroup analysis of the KEYNOT-826 trial was reported in 2022. The Empower trial showed superior efficacy of chemo-free immunotherapy in cervical cancer, and the final results of this trial were reported in 2022. The efficacy of dual immunotherapy was evaluated in the Checkmate 358 trial, and the combination of therapeutic vaccines and immunotherapy was evaluated in the GX 1883 trial. The GOG 3024/Innova TV 205 trial demonstrated the efficacy of antibody-drug conjugates in cervical cancer.

KEYNOTE-826

The KEYNOTE-826 trial was a phase III study that showed that when an immune checkpoint inhibitor (ICI) was added to standard care for persistent, recurrent, and metastatic cervical cancer [64]. A total of 617 patients were randomized to receive paclitaxel plus cisplatin (or carboplatin) with or without bevacizumab or pembrolizumab (up to 35 cycles) and paclitaxel plus cisplatin (or carboplatin) with or without bevacizumab. In 2021, the KEYNOTE-826 trial reported significant improvements in PFS and OS in an all-comers population. In 2022, a subgroup analysis including those defined by PD-L1 combined positive score (CPS), bevacizumab use, histology, and previous CCRT exposure was reported [18]. The baseline characteristics of the all-comer population did not differ significantly between the both arms. More than 50% of the patients had a CPS ≥10 in both groups. In 2022, the results of the KEYNOTE-826 subgroup analysis will be reported. In the subgroup analysis,

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the pembrolizumab group showed prolonged PFS and OS compared to the placebo group, irrespective of bevacizumab use, histology, platinum use, and prior CCRT. The benefits of pembrolizumab are generally consistent across broad selection of key patient subgroups. The results of KEYNOTE-826 are expected to significantly change the treatment of cervical cancer. Pembrolizumab plus chemotherapy, with or without bevacizumab, is a new standard of care for persistent, recurrent, and metastatic cervical cancer.

GOG 3024/Innova TV 205

Tisotumab vedotin (TV) is an antibody-drug conjugate that combines antibodies against tissue factors that interfere with microtubule assembly. The single-arm phase II trial, GOG 3023/Innova TV 204, showed an ORR of 24% (95% CI=15.9–33.3) when using TV in previously treated recurrent or metastatic cervical cancer [65]. Most tumor responses to TV were rapid, with a median time to response of 1.4 months. TV has shown an effective response in the treatment of recurrent or metastatic cervical cancer. This was evaluated in the GOG 3024/Innova TV 205 dose expansion phase II trial [19]. Dose expansion Arm E (TV plus pembrolizumab in previously untreated patients) enrolled 33 patients and long-term follow-up data from Arm D (TV plus carboplatin in previously untreated patients) and Arm F (TV plus pembrolizumab in previously treated patients). The ORR for Arm E was 41% (95% CI=23.7–59.4) and the median duration of response (DOR) was not reached. The median PFS was 5.3 months (95% CI=4.0–12.2). The ORR for Arm F was 38.2% (95% CI=22.2–56.4) and the median DOR was 14 months (95% CI=2.8–not reached). The median PFS was 5.6 months (95% CI=2.7–14.2). Most adverse events were grade 1 or grade 2, with a tolerable safety profile; however, there is a need for mitigation strategies for ocular toxicity. These data provide a rationale for the inclusion of TV in combination therapy to improve outcomes of first-line recurrent or metastatic cervical cancer.

EMPOWER

The effect of using ICI as second-line or higher chemotherapy for cervical cancer has been reported in several studies. The EMPOWER trial is the first phase III trial of ICI compared to platinum-based chemotherapy, which is the current standard of treatment. The EMPOWER trial is a phase III randomized controlled trial that showed the efficacy of immunotherapy in recurrent and metastatic cervical cancer resistant to platinum-based chemotherapy previously performed for persistent, metastatic, and recurrent cervical cancer. Interim OS analysis showed that cemiplimab significantly improved OS compared with the investigator's choice single-agent chemotherapy in persistent, metastatic, and recurrent cervical cancer (median follow-up, 18.2 months) [20]. In 2022, a final survival analysis after a 1-year follow-up period was reported. The median follow-up was 30.2 (18.0–50.2) months. Cemiplimab significantly improved OS compared to the investigators' choice, reducing the risk of death by 31%, 45%, and 34% in squamous cell carcinoma, adenocarcinoma including adenosquamous carcinoma, and the overall population, respectively. In the PD-L1 population, cemiplimab increased OS in patients with PD-L1 ≥1% and PD-L1 <1%, with 38% and 35% lower risk of death, respectively. In the long-term follow-up, cemiplimab significantly and clinically improved OS in patients with persistent, metastatic, and recurrent cervical cancer after first-line platinum-based chemotherapy.

Checkmate-358

In earlier studies, nivolumab demonstrated clinically meaningful antitumor activity as a single agent and in the N3I1 and N1I3 dosing schedules with ORRs of 26%, 27%, and 41%, respectively [66]. At ESMO 2022, the update involved a longer follow-up period of 30.4

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months from the phase I/II Checkmate-358 clinical trial [21]. Patients were treated with nivolumab monotherapy, two different dosing regimens for 24 months or less, or until disease progression: nivolumab 240 mg every 2 weeks (n=19); 3 mg/kg of nivolumab every 2 weeks plus 1 mg/kg of ipilimumab every 6 weeks (n=45; N3I1); or 1 mg/kg of nivolumab every 2 weeks plus 3 mg/kg of ipilimumab every 3 weeks for four cycles followed by 240 mg of nivolumab every 2 weeks (n=45; N1I3). Based on an early efficacy signal in the N1I3 arm, the trial protocol was amended to include an N1I3 expansion arm in which 44 patients received first-line chemotherapy and 23 patients received second-line chemotherapy. At a minimum follow-up of 24 months, the ORR was 26% (95% CI=9–51), 31% (95% CI=18–47), and 38% (95% CI=29–48) with nivolumab, N3I1, and N1I3, respectively. The median PFS was 5.1 months (95% CI=1.9–9.1), 3.8 months (95% CI=2.1–10.3), and 5.8 months (95% CI=3.8–9.3) with nivolumab, N3I1, and N1I3, respectively. The median OS was 21.6 months (95% CI=8.3–46.9), 15.2 months (95% CI=9.0–36.2), and 20.9 months (95% CI=14.4–32.8), respectively. The results showed durable responses in patients regardless of tumor PD-L1 status across all treatment arms. Regarding safety, no new signals were identified; however, the incidence of toxicity appeared to be higher with N1I3 than with N3I1 or nivolumab monotherapy. Checkmate-358 showed that nivolumab monotherapy or in combination with ipilimumab can provide clinically meaningful and durable responses in patients with recurrent metastatic cervical cancer, regardless of tumor PD-L1 expression.

GX-188E

GX-188E is a therapeutic DNA vaccine for non-resectable HPV 16 and/or HPV 18 positive cervical cancer. GX-188E induces HPV E6 and E7 specific T-cell responses. According to the KEYNOTE-158 trial, patients who were PD-L1 negative (CPS <1) did not respond to pembrolizumab treatment [67]. A phase II trial of GX-188E combined with pembrolizumab evaluated the effectiveness and safety of patients with PD-L1positive and PD-L1 negativity in advanced or recurrent cervical cancer [22]. A total of 65 patients who received intramuscular GX-188E (2 mg, specific time points) and intravenous pembrolizumab (200 mg every 3 weeks) for 24 months or until disease progression were enrolled. In the final efficacy analysis evaluating the efficacy-evaluable population (60 patients), the ORR of 31.7% and patients with a CPS <1 showed a response rate of 25.0%, while the patients with a CPS ≥1 showed a response rate of 36.1%. The OS was 17.2 months and the median DOR was 12.3 months. These data showed an impressive response rate, regardless of PD-L1 expression, in patients with advanced or recurrent cervical cancer. GX-188E plus pembrolizumab was safe and tolerable compared with KEYNOTE-158 (pembrolizumab monotherapy). This combination therapy could be a potential treatment for PD-L1 negative with advanced or recurrent cervical cancer.

CORPUS CANCER

1. TOTEM study

What is the optimal follow-up protocol for patients with endometrial cancer? The TOTEM study [23] was designed to answer this question. The TOTEM study was a randomized multicenter trial comparing intensive (INT) vs. minimalist (MIN) follow-up protocols in patients with endometrial cancer stages I–IV. The primary endpoint was OS, and the secondary endpoints were relapse-free survival, proportion of asymptomatic relapses, HRQOL, compliance, and costs. Patients were stratified by risk of relapse as low-risk (LoR; FIGO stage 1A with low grade) or high-risk (HiR; FIGO stage IA with high grade or ≥IB). For patients with LoR, the MIN group planned only 11 physical examinations without blood

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tests, vaginal cytology, or imaging studies, whereas the INT group had 13 visits, including yearly vaginal cytology and annual computed tomography (CT) scans (chest, abdomen, and pelvis) in the first 2 years. For HiR patients, the MIN group scheduled 13 visits and annual CT scans in the first 2 years, whereas the INT group had 14 visits with CA 125, ultrasound (twice per year for 3 years, then yearly), annual vaginal cytology, and CT scans. Additionally, unscheduled visits were allowed.

Over 10 years (November 2008 and July 2018), 1,871 patients were randomly assigned, and 1,847 patients (98.7%) were available for the final analysis, of which 60% were at low risk, with a median follow-up of 69 months. No difference in the 5-year OS was found between the MIN and INT groups (91.9% in the MIN group vs. 90.6% in the INT group; HR=1.13; 95% CI=0.86–1.50; p=0.380). In the subgroup analyses, there were no differences in age, type of treatment, risk of relapse, and level of adherence. No statistically significant differences were observed in the probability of relapse or asymptomatic relapse. The effectiveness of the MIN over the INT protocol remains unknown, particularly in advanced stage (stage III or IV with any grade) or aggressive histology (nonendometrioid with any stage), since the proportions of these subsets were only 4.6% and 8.2%, respectively. However, with the high level of evidence, there was no need to routinely add vaginal cytology, tumor markers, or imaging studies to the MIN protocols based on the level of relapse. These findings also support "choosing wisely," which is an initiative to avoid unnecessary Pap tests in endometrial cancer [68].

2. ICIs

The efficacy and safety of pembrolizumab in patients with previously treated advanced microsatellite instability-high or mismatch repair-deficient (MSI-H/dMMR) endometrial cancer have been reported. The KEYNOTE-158 study [24] was a non-randomized, open-label, multi-cohort, phase II trial in which patients with MSI-H/dMMR endometrial cancer were selected from cohort D (endometrial cancer regardless of MSI or MMR status) and cohort K (any advanced non-colorectal cancer with MSI-H/dMMR). Between February 1, 2016, and September 23, 2020, 90 patients with MSI-H/dMMR endometrial cancer were enrolled in cohorts D (11 patients) and K (79 patients). As of the data cutoff date (October 5, 2020), 18 of 90 patients treated with pembrolizumab (20%) had completed 35 cycles, and discontinuation occurred in 52 (58%) patients. The ORR was 48% (95% CI=37–60), and the median PFS was 13.1 (95% CI=4.3–34.4) months. The median DOR and OS were not reached. No new safety signals were found. Of the patients, 76% showed ≥1 TRAEs (grades 3–4, 12%) without fatal events. In this study population, pembrolizumab demonstrated active and durable antitumor activity with manageable toxicity. NRG-GY018 [69] is an ongoing phase III randomized, placebo-controlled study of pembrolizumab in addition to paclitaxel and carboplatin for chemo-naïve advanced or recurrent endometrial cancer, which is assessing the efficacy of pembrolizumab as first-line treatment.

GARNET [70] was a single-arm, open-label, phase I trial of dostarlimab in advanced solid tumors with two endometrial cancer cohorts (MSI-H/dMMR, cohort A1; microsatellite stable or mismatch repair-proficient [MSS/pMMR], cohort A2). The primary endpoints were ORR and DOR by BICR using the RECIST v1.1. A third interim analysis was reported at ASCO 2022 [25]. A total of 153 patients with MSI-H/dMMR and 161 patients with MSS/pMMR were enrolled. The ORRs were 45.5% (MSI-H/dMMR) and 15.4% (MSS/pMMR), respectively. The median DOR was not reached (MSI-H/dMMR) and 19.4 months (MSS/pMMR). The median OS was not reached (MSI-H/dMMR) and 16.9 months (MSS/pMMR). The majority of TRAEs were grade 1 or 2, and 27 patients (8.6%) discontinued treatment because of TRAE. No

morbidity related to dostarlimab was observed. Hypothyroidism (n=12, 8%) was the most common any-grade immune-related TRAE. Dostarlimab showed durable antitumor activity in endometrial cancer, regardless of the MSI/MMR status. MSI-H/dMMR was associated with a higher response rate and longer survival. Dostarlimab is now being tested in a phase III trial (ENGOT-EN6/NSGO-RUBY) [71] as a first-line treatment combined with paclitaxel and carboplatin in recurrent or advanced endometrial cancer.

Study 309–KEYNOTE-775 [26] was a confirmatory, randomized, open-label phase III trial comparing the oncological outcomes between pembrolizumab plus lenvatinib and physicians' choice of chemotherapy (doxorubicin or paclitaxel) in patients with endometrial cancer who had received one platinum-based chemotherapy. Patients were stratified according to MMR status, ECOG, and prior history of pelvic radiation. A total of 827 patients (697 patients, pMMR; 130 patients, dMMR) were randomly assigned to receive pembrolizumab plus lenvatinib (411 patients) or chemotherapy (416 patients). Pembrolizumab plus lenvatinib led to significantly longer PFS (pMMR population: 6.6 vs. 3.8 months; HR=0.60; 95% CI=0.50–0.72; p<0.001; overall: 7.2 vs. 3.8 months; HR=0.56; 95% CI=0.47–0.66; p<0.001) and OS (pMMR: 17.4 vs. 12.0 months; HR=0.68; 95% CI=0.56–0.84; p<0.001; overall: 18.3 vs. 11.4 months; HR=0.62; 95% CI=0.51–0.75; p<0.001) than chemotherapy, which was published in February 2022. At ESMO 2022 [72], there was an update of a subgroup analysis in patients with dMMR endometrial cancer (65 patients receiving pembrolizumab + lenvatinib; 65 receiving chemotherapy). Higher ORR (40.0% vs. 12.3%) and longer median DOR (not reached vs. 4.1 months) were observed in patients receiving pembrolizumab + lenvatinib with longer median PFS (10.7 vs. 3.7 months) and OS (not reached vs. 8.6 months) compared with that in patients receiving chemotherapy. As a first-line treatment, pembrolizumab + lenvatinib is being studied in a trial. ENGOT-en9/LEAP-001 [73] is a phase III, randomized, open-label study of pembrolizumab plus lenvatinib vs. chemotherapy for the first-line treatment of advanced or recurrent endometrial cancer.

There are several ongoing studies to find enhanced antitumor activity of ICIs in combination with other target agents, including PARP inhibitors and/or anti-VEGFs [74-76]; however, the efficacy remains to be seen.

3. WEE1 inhibitor

Serous carcinoma of the endometrium is a distinct histological and molecular subtype of endometrial cancer. p53 abnormality, one of the most significant findings in serous histology, suggests cell cycle dysregulation. Adavosertib is a potent and selective oral inhibitor of WEE1 kinase, a key regulator of G2/M and S phase cell cycle checkpoints. A single-arm, two-stage, phase II study [77] of adavosertib monotherapy in recurrent uterine serous carcinoma demonstrated active and durable anti-tumor activity. In a total of 34 evaluable patients, the ORR was 29.4% (95% CI=15.1–47.5) and the median PFS was 6.1 months, and the median DOR was 9.0 months. Common TRAE were diarrhea (76.5%), fatigue (64.7%), nausea (61.8%), and hematologic toxicity. An international phase IIB study [27] evaluating the efficacy of adavosertib monotherapy in patients with recurrent or persistent uterine serous carcinoma is ongoing.

4. Aromatase inhibitor in combination with CDK4/6 inhibitor

Estrogen receptor (ER)-positive endometrial cancer is considered an ideal target for anti-estrogen therapy. CDK4/6 is a critical mediator of resistance to hormonal therapy. A two-stage, phase II study [78] was performed to evaluate the antitumor activity of a combination

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of an aromatase inhibitor (letrozole) and a CDK4/6 inhibitor (abemaciclib) in recurrent ER-positive endometrial cancer. The primary endpoints were ORR by RECIST 1.1 and PFS rate at 6 months. As of December 3, 2021, treatment had been initiated in 30 patients: the ORR was 30% (95% CI=14.7–49.4), median PFS was 9.1 months, PFS at 6 months was 55.6% (95% CI=35.1–72), and the median DOR was 7.4 months. Frequent TRAEs ≥grade 3 were neutropenia (20%) and anemia (17%). Grade, prior hormonal treatment, MMR status, and progesterone receptor level were not predictive markers.

5. Selective inhibitor of nuclear export (SINE)

Selinexor is an oral SINE that induces the accumulation of tumor suppressor proteins in the cell nucleus by inhibiting nuclear export protein (XPO1). Hypothetically, this leads to an increased apoptotic activity in cancer cells. ENGOT-EN5/GOG-3055/SIENDO [79] was a randomized, double-blind, placebo-controlled phase III study evaluating weekly selinexor as maintenance therapy vs. placebo in patients with endometrial cancer after first- or second-line chemotherapy. The primary endpoint was PFS, and the secondary endpoints were OS, PFS by BICR, and patient-reported outcomes. A predefined exploratory endpoint was used based on the histological subtype and molecular classification. A total of 263 patients (174 patients, selinexor; 89 patients, placebo) with advanced/recurrent endometrial cancer after one line of taxane-platinum therapy with CR or PR were analyzed. The median PFS was 5.7 months in the selinexor group and 3.8 months in the placebo group (adjusted HR=0.70; p=0.024), which was a statistically significant improvement. Among patients with available molecular classification, subgroup analysis of patients with TP53wt showed a PFS of 13.7 months with selinexor vs. 3.7 months with placebo (HR=0.375; 95% CI=0.210–0.670; p=0.003). Patients with MSS/pMMR had a PFS of 6.9 months with selinexor vs. 5.4 months with placebo (HR=0.593; 95% CI=0.388–0.905, p=0.007). In terms of molecular classification, patients with no specific molecular profiles (NSMPs, TP53wt + MSS) showed a substantial difference in median PFS with selinexor vs. placebo: not reached and 3.71 months, respectively (HR=0.163; 95% CI=0.060–0.444; p<0.0001). Analyses of the other 3 molecular categories (POLEmut, MSI-H, and p53abn) did not reveal significant differences in PFS. A confirmatory trial focusing on patients with TP53wt or NSMP is warranted.

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SUPPLEMENTARY MATERIAL

Fig. S1

Asian Society of Gynecologic Oncology 2022 Review Course, Incheon Hyatt Hotel, December 10, 2022.

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