J Gynecol Oncol. 2024 Mar;35(2):e66
https://doi.org/10.3802/jgo.2024.35.e66
pISSN 2005-0380·eISSN 2005-0399

JOURNAL OF GYNECOLOGIC ONCOLOGY

Review Article

Major clinical research advances in gynecologic cancer in 2023: a tumultuous year for endometrial cancer

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Received: Jan 11, 2024
Revised: Jan 16, 2024
Accepted: Jan 16, 2024
Published online: Jan 25, 2024

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ABSTRACT

In the 2023 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) Endometrial cancer: immune checkpoint inhibitor, antibody drug conjugates (ADCs), selective inhibitor of nuclear export, CDK4/6 inhibitors WEE1 inhibitor, poly (ADP-ribose) polymerase (PARP) inhibitors. 2) Cervical cancer: surgery in low-risk early-stage cervical cancer, therapy for locally advanced stage and advanced, metastatic, or recurrent setting; and 3) Ovarian cancer: immunotherapy, triplet therapies using immune checkpoint inhibitors along with antiangiogenic agents and PARP inhibitors, and ADCs. In 2023, the field of endometrial cancer treatment witnessed a landmark year, marked by several practice-changing outcomes with immune checkpoint inhibitors and the reliable efficacy of PARP inhibitors and ADCs.

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

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

Author Contributions
Conceptualization: S.S.H., L.J.Y., L.Y.Y., P.J.Y., S.D.H.; Data curation: L.Y.J., K.S.I., H.G.H., Y.E.J., N.J.J., Y.G.W., S.J.H., K.N.K., K.T.H., K.T.W., C.Y.J., C.A., L.H., J.E., C.H.W., S.D.H.; Formal analysis: S.S.H., L.J.Y., L.Y.Y., P.J.Y., S.D.H.; Funding acquisition: S.D.H.; Investigation: S.S.H., L.J.Y., L.Y.Y., P.J.Y., S.D.H.; Methodology: S.S.H., L.J.Y., L.Y.Y., P.J.Y., S.D.H.; Project administration: S.S.H., L.J.Y., L.Y.Y., P.J.Y., S.D.H.; Resources: S.S.H., L.J.Y., L.Y.Y., P.J.Y., S.D.H.; Software: S.S.H., L.J.Y., L.Y.Y., P.J.Y., S.D.H.; Supervision: S.D.H.; Validation: S.S.H., L.J.Y., L.Y.Y., P.J.Y., S.D.H.; Visualization: S.S.H., L.J.Y., L.Y.Y., P.J.Y., S.D.H.; Writing - original draft: S.S.H., L.J.Y., L.Y.Y., P.J.Y., L.Y.J., K.S.I., H.G.H., Y.E.J., N.J.J., Y.G.W., S.J.H., K.N.K., K.T.H., K.T.W., C.Y.J., C.A., L.H., J.E., C.H.W., S.D.H.; Writing - review & editing: S.S.H., L.J.Y., L.Y.Y., P.J.Y., L.Y.J., K.S.I., H.G.H., Y.E.J., N.J.J., Y.G.W., S.J.H., K.N.K., K.T.H., K.T.W., C.Y.J., C.A., L.H., J.E., C.H.W., S.D.H.

INTRODUCTION

The *Journal of Gynecologic Oncology* review group has held a conference and compiled a list of major clinical studies on gynecologic cancer since 2020. With support from the Asian Society of Gynecologic Oncology (ASGO), a review course titled, "ASGO 2023 REVIEW COURSE" was held at Grand Hyatt Incheon on December 9, 2023 (**Fig. S1**). Based on the ASGO 2023 REVIEW COURSE (**Table 1**), this review summarizes the outstanding study results in gynecologic cancer in 2023 and provides future perspectives.

ENDOMETRIAL CANCER

The year 2023 was a landmark year in the field of endometrial cancer treatment. A new staging system for endometrial cancer has been introduced and several practice-changing outcomes with immune checkpoint inhibitors were presented at various international conferences and published [34]. Additionally, the use of poly (ADP-ribose) polymerase (PARP) inhibitors and antibody-drug conjugates (ADCs) demonstrated reliable outcomes, making it truly a pivotal year for endometrial cancer. Below, we will review each of these clinical trial results and their implications.

1. Anti-PD1 antibody: RUBY and NRG-GY018

The RUBY/ENGOT-EN6/GOG3031/NSGO consists of 2 parts of worldwide, randomized, double-blind, multi-center phase 3 study targeting individuals with newly diagnosed advanced or recurrent endometrial cancer with various histologic types including carcinosarcoma [35]. In part 1, the trial assesses the combination of dostarlimab with carboplatin-paclitaxel (PC), followed by dostarlimab, in comparison to PC with a placebo, followed by a placebo. Part 2 investigates the effects of dostarlimab combined with PC, subsequently followed by dostarlimab and niraparib, versus a placebo with PC and then a placebo.

The results of part 1 showed that treatment with dostarlimab combined with PC significantly enhanced the progression-free survival (PFS) at 24 months in individuals with primary advanced or recurrent endometrial cancer (hazard ratio [HR]=0.64; 95% confidence interval [CI]=0.51–0.80; p<0.001), revealing considerable advantages particularly in patients with deficient mismatch repair (dMMR)/high microsatellite instability (MSI-H) (HR=0.28; 95% CI=0.16–0.50; p<0.001) [1]. It is noteworthy that patients with *TP*53mut also demonstrated similarly significant results in favor of adding dostarlimab. Clinically meaningful results were also observed in the analysis of one of the co-primary endpoints, which was the overall survival (OS). In terms of safety profile, it was manageable and consistent with that of individual drugs. Recently, the results of part 2 were announced through media as positive, suggesting that niraparib could be a viable treatment option in combination of dostarlimab for endometrial cancer [36].

The NRG-GY018 is a randomized, blinded, placebo-controlled phase 3 trial evaluating pembrolizumab in combination with standard of care chemotherapy (PC) versus placebo plus standard of care chemotherapy alone for the treatment of advanced or recurrent endometrial cancer [2]. The primary outcome was PFS in the dMMR and proficient mismatch repair (pMMR) cohorts. Treatment with pembrolizumab combined with PC significantly enhanced the PFS at 12 months in dMMR (HR=0.30; 95% CI=0.19–0.48; p<0.001) and pMMR (HR, 0.54; 95% CI, 0.41 to 0.71; p<0.001), independently with expected adverse effects of

Table 1. Topic list of the major clinical researches in gynecologic cancer in 2023

Category	Study
1. Corpus cancer	
Anti-PD-1 antibody	• RUBY [1]: Dostarlimab plus chemotherapy for primary advanced or recurrent endometrial cancer
	• NRG-GY018 [2]: Pembrolizumab plus chemotherapy in advanced endometrial cancer
Anti-PD-L1 antibody	• DUO-E [3]: Durvalumab plus carboplatin/paclitaxel followed by maintenance durvalumab with or without olaparib as first-line treatment for advanced endometrial cancer
	• AtTEnd [4]: Atezolizumab in combination with carboplatin and paclitaxel in women with newly diagnosed advanced/recurrent endometrial carcinoma
	• MITO END-3 [5]: Avelumab, carboplatin, and paclitaxel in treating advanced or recurrent endometrial cancer
Antibody drug conjugate	• DESTINY-PanTumor02 [6]: Efficacy and safety of trastuzumab deruxtecan in patients with HER2-expressing solid tumors:
	• STATICE [7]: Trastuzumab deruxtecan for HER2-expressing advanced or recurrent uterine carcinosarcoma
Selective inhibitor of nuclear export	• SIENDO [8]: Oral selinexor as maintenance therapy after first-line chemotherapy for advanced or recurrent endometrial cancer
Aromatase and CDK4/6 inhibitors	• Letrozole and abemaciclib [9]: A phase 2 study of letrozole and abemaciclib in estrogen receptor-positive recurrent endometrial cancer
Wee1 inhibitor	• ADAGIO [10]: A phase 2 study of the WEE1 inhibitor adavosertib in recurrent uterine serous carcinoma
PARP inhibitor	• UTOLA [11]: Randomized phase 2 trial of olaparib as maintenance therapy in platinum-sensitive advanced endometrial carcinoma
2. Cervical cancer	
Low-risk early-stage cervical cancer	• SHAPE [12]: Randomized phase 3 trial comparing radical hysterectomy and pelvic node dissection vs simple hysterectomy and pelvic node dissection in patients with low-risk early-stage cervical cancer
Locally advanced stage	• KEYNOTE-A18 [13]: Pembrolizumab plus chemoradiotherapy for high-risk locally advanced cervical cancer: a randomized, double-blind, phase 3 study
	• INTERLACE [14]: Randomised phase 3 trial of induction chemotherapy followed by chemoradiation compared with chemoradiation alone in locally advanced cervical cancer
Primary metastatic or recurrent cervical cancers	• BEATcc [15]: Atezolizumab plus bevacizumab and chemotherapy for metastatic, persistent, or recurrent cervical cancer: a randomised, open-label, phase 3 trial
	• InnovaTV 301 [16]: Randomized, open-label, phase 3 study of tisotumab vedotin vs investigator's choice of chemotherapy in 2L or 3L recurrent or metastatic cervical cancer
	• AdvanTIG-202 [17]: Phase 2 randomized, multicenter, open-label study of tislelizumab with or without ociperlimab in patients with previously treated recurrent/metastatic cervical cancer
3. Ovarian cancer	
Immunotherapy	• ATALANTE/ENGOT-ov29 [18]: Atezolizumab combined with bevacizumab and platinum-based therapy for platinum-sensitive ovarian cancer: placebo-controlled randomized phase 3 trial
	• KGOG3046/TRU-D [19]: Phase 2 study of durvalumab and tremelimumab with front-line neoadjuvant chemotherapy in patients with advanced-stage ovarian cancer
	• VIRO-15 [20]: Clinical activity of olvimulogene nanivacirepvec-primed immunochemotherapy in heavily pretreated patients with platinum-resistant or platinum-refractory ovarian cancer: nonrandomized phase 2 study
	• ANITA [21]: Phase 3, randomized, double blinded trial of platinum-based chemotherapy with or without atezolizumab followed by niraparib maintenance with or without atezolizumab in patients with recurrent ovarian, tubal, or peritoneal cancer and platinum treatment free interval of more than 6 months
Triplet therapies	• MEDIOLA [22]: Phase 2 study of Olaparib plus durvalumab and bevacizumab: initial results in patients with non-germline *BRCA*-mutated platinum sensitive relapsed ovarian cancer
	• DUO-O [23]: Durvalumab with paclitaxel/carboplatin and bevacizumab, followed by maintenance durvalumab, bevacizumab, and olaparib in patients with newly diagnosed advanced ovarian cancer without a tumor *BRCA1/2* mutation: randomized, placebo-controlled phase 3 trial
	• OPEB-01 [24]: Triplet maintenance therapy of olaparib, pembrolizumab and bevacizumab in women with *BRCA* wild-type, platinum-sensitive recurrent ovarian cancer: single-arm phase 2 study
Antibody drug conjugate and others	• SORAYA [25]: Efficacy and safety of mirvetuximab soravtansine in patients with platinum-resistant ovarian cancer with high folate receptor alpha expression
	• MIRASOL [26]: Initial report of mirvetuximab soravtansine vs. investigator's choice of chemotherapy in platinum-resistant, advanced high-grade epithelial ovarian, primary peritoneal, or fallopian tube cancers with high folate receptor-alpha expression: phase 3 study
	• DESTINY-PanTumor02 [6]: Efficacy and safety of trastuzumab deruxtecan in patients with HER2-expressing solid tumors:
	• STRO-002 [27]: Luveltamab tazevibulin, an anti-folate receptor alpha (FRα) antibody drug conjugate, safety and efficacy in a broad distribution of FRα expression in patients with recurrent epithelial ovarian cancer: phase 1 dose expansion cohorts
	• UpRi [28]: Phase 1 expansion study of upifitamab rilsodotin, a NaPi2b-directed dolaflexin antibody drug conjugate in ovarian cancer
	• Relacorilant [29]: Relacorilant + Nab-paclitaxel in patients with recurrent, platinum-resistant ovarian cancer: A three-arm, randomized, controlled, open-label phase 2 study
	• BOUQUET [30]: Phase 2 biomarker-directed platform study: cobimetinib or atezolizumab + bevacizumab for persistent/recurrent rare epithelial ovarian cancer
	• HIPEC KGOG 3042 [31]: Hyperthermic intraperitoneal chemotherapy after interval cytoreductive surgery for patients with advanced-stage ovarian cancer who had received neoadjuvant chemotherapy
	• HIPEC-KOV-03R [32]: Ten-year treatment outcomes of consolidation hyperthermic intraperitoneal chemotherapy for ovarian cancer
	• PIPAC [33]: Pressurized intraperitoneal aerosol chemotherapy (PIPAC) with cisplatin and doxorubicin in patients with ovarian cancer: a systematic review

HER2, human epidermal growth factor receptor-2; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

https://doi.org/10.3802/jgo.2024.35.e66

pembrolizumab and combination of chemotherapy. The updated analyses were recently presented at the European Society for Medical Oncology (ESMO) 2023 conference showing equivalent PFS identified in dMMR cohort based on mechanism of MMR loss (methylation vs. no methylation) [37].

2. Anti-programmed death-ligand 1 (PD-L1) antibody: DUO-E, AtTEnd, and MITO END-3

The DUO-E/GOG-3041/ENGOT-EN10 study, a phase 3 international, double-blind, placebo-controlled trial, examined whether adding the durvalumab to the PC, followed by maintenance treatment with durvalumab alone or in combination with olaparib, improves treatment results in patients with newly diagnosed advanced or recurrent endometrial cancer [3]. The primary endpoints were to compare PFS in the durvalumab and durvalumab plus olaparib groups against the control group. Within the intent-to-treat population, a statistically significant improvement in PFS was observed with durvalumab (HR=0.71; 95% CI=0.57–0.89; p=0.003) and in the combination of durvalumab and olaparib (HR=0.55; 95% CI=0.43–0.69; p<0.001), when compared to the control group.

Predefined exploratory subgroup analyses revealed an improvement in PFS both in dMMR (durvalumab vs. control, HR=0.42; 95% CI=0.22–0.80 and durvalumab plus olaparib vs. control, HR=0.41; 95% CI=0.21–0.75) and pMMR subgroups (durvalumab vs. control, HR=0.77; 95% CI=0.60–0.97 and durvalumab plus olaparib vs. control, HR=0.57; 95% CI=0.44–0.73) suggesting that the efficacy of durvalumab appears to be most remarkable in the dMMR group, while the role of adding olaparib seems no additional benefit in this group. In contrast, in the pMMR group, the effect of durvalumab alone is relatively marginal, suggesting a more important role for olaparib in this population. Of note, PFS benefit was also found in PD-L1 positive (tumor area positivity [TAP], as threshold 1%) subgroups (durvalumab vs. control, HR=0.63; 95% CI=0.48–0.83 and durvalumab plus olaparib vs. control, HR=0.42; 95% CI=0.31–0.57).

AtTEnd is a global phase 3 clinical trial of atezolizumab in combination with PC in women with newly diagnosed advanced/recurrent endometrial carcinoma including carcinosarcoma [4]. Primary endpoints, using a hierarchical strategy, included PFS in the dMMR group, as well as PFS and OS across the entire population. In the dMMR population, the addition of atezolizumab showed a significantly improved PFS (HR=0.36; 95% CI=0.23–0.57; p<0.001). The superior PFS was also confirmed for all comers (HR=0.74; 95% CI=0.61–0.91; p=0.022) with expected and tolerable toxicities of atezolizumab. For all comers, it showed a trend towards improved OS.

One intriguing finding is that atezolizumab did not demonstrate effectiveness in patients from Asian regions. In the subgroup analysis for PFS, the HRs for Asian patients (20% of the overall study population) and non-Asian patients were found to be 1.17 (95% CI=0.71–1.94) and 0.66 (95% CI=0.52–0.82), respectively. This was similarly observed in the DUO-E study which was presented at the 2023 ASGO conference, where the subgroup analysis for PFS also showed HRs of 0.98 (durvalumab vs. control, 95% CI=0.65–1.49) and 0.59 (durvalumab vs. control, 95% CI=0.45–0.76) for Asian and non-Asian patients, respectively, with Asian patients comprising about 30% of the entire population. These results suggest that immune checkpoint inhibitors appear to be less effective for Asian population. However, this is based on subgroup analyses and cannot be considered conclusive. Further clinical trial results from Asian regions are necessary.

https://doi.org/10.3802/jgo.2024.35.e66

MITO END-3 is a randomized phase 2 trial comparing PC with carboplatin, paclitaxel, and avelumab in treating advanced (stage III-IV) or recurrent endometrial cancer, which showed results comparable to those observed in the DUO-E and AtTEnd trials [5].

3. ADC: DESTINY and STATICE

Trastuzumab deruxtecan is an ADC targeting human epidermal growth factor receptor-2 (HER2), composed of a humanized monoclonal antibody identical in amino acid sequence to trastuzumab, a cleavable linker that remains stable in plasma, and deruxtecan, an inhibitor of topoisomerase-I [38]. The DESTINY-PanTumor02 trial is an open-label phase 2 study assessing the effectiveness of trastuzumab deruxtecan in treating HER2-positive locally advanced or metastatic diseases following ≥1 systemic therapy or in the absence of other treatment options [6]. The main endpoint was the objective response rate (ORR) confirmed by the investigator. At primary analysis of 267 patients, 40 endometrial cancer patients (at eligibility, HER2 3+, 40%; HER2 2+ 60%) were enrolled. By cohort, ORRs by independent central review were 57.5% for endometrial (95% CI=40.9–73.0) demonstrating meaningful clinical benefit. STATICE trial is a phase 2, multicenter study investigating the efficacy and safety of trastuzumab deruxtecan in patients with recurrent uterine carcinosarcoma expressing HER2 [7]. The ORR by central review in the HER2-high and HER2-low groups were 54.5% (95% CI=32.2–75.6) and 70.0% (95% CI=34.8–93.3) showing potent anti-tumor activity. Toxicities of trastuzumab deruxtecan were manageable in both studies.

4. Selective inhibitor of nuclear export: SIENDO

Selinexor, an oral agent, inhibits the nuclear export protein exportin 1 (XPO1) and has shown effectiveness against solid tumors. SIENDO/ENGOT-EN5/GOG-3055 was a randomized multicenter phase 3 study evaluating the efficacy and safety for front-line maintenance therapy with selinexor (80 mg once weekly [QW]) following chemotherapy in patients with advanced or recurrent endometrial cancer [8]. Selinexor showed a 50% statistically significant improvement in median PFS compared to placebo (HR=0.70; p=0.049). In a pre-specified subgroup of patients with p53 wild type, the improvement in median PFS was statistically significant (HR=0.38; p<0.001). The drug was well-tolerated, with no new safety concerns emerging, and a 10.5% discontinuation rate due to adverse events. Selinexor is currently undergoing trials in endometrial cancer with p53 wild type. EC-042 (XPORT-EC-042; NCT05611931) is a global, phase 3, randomized, double-blind study evaluating Selinexor (60 mg QW) as a maintenance therapy following systemic therapy in patients with TP53 wild-type advanced or recurrent endometrial cancer [39].

5. Aromatase and CDK4/6 inhibitors

A phase 2, 2-stage study of letrozole (aromatase inhibitor) and abemaciclib (CDK4/6 inhibitor) in recurrent estrogen receptor (ER) positive endometrial cancer was conducted [9]. Primary end points were ORR and PFS rate at 6 months. The study reported an ORR of 30% (95% CI=14.7–49.4). PFS at 6 months was 55.6% (95% CI=35.1–72) with the median duration of response (DOR) of 7.4 months demonstrating encouraging and durable evidence of activity in recurrent ER positive endometrial cancer.

6. Wee1 inhibitor: ADAGIO

ADAGIO is a single-arm 2-stage phase 2 international study in women with recurrent or persistent uterine serous carcinoma to evaluate the efficacy of oral adavosertib [10]. The primary endpoint is the ORR and rate of PFS at 6 months. The ORR was 26.0% (all were partial responses) and the PFS rate at 6 months was 18.1%. While adavosertib demonstrated

https://doi.org/10.3802/jgo.2024.35.e66

effectiveness in tumor reduction, it raised safety issues. Treatment-related adverse events of grade 3 or higher were seen in 60.6% of patients, causing 14.7% to discontinue treatment. Over half of the patients needed dose reductions or pauses in the adavosertib treatment.

7. PARP inhibitor (UTOLA)

UTOLA is a placebo-controlled, multicenter, 2-arm, phase 2 trial comparing olaparib versus placebo in maintenance therapy after chemotherapy in patients with advanced or metastatic endometrial cancer who achieved disease control after 1st line platinum-based chemotherapy [11]. The primary endpoint was PFS. Median PFS in the intention-to-treat (ITT) population was 5.6 months (90% CI=3.8–7.4) and 4.0 months (95% CI=3.6–7.4) in olaparib and placebo arms respectively (HR=0.94; p=0.290). In the HRD tumors, which is 49.7% of entire population, median PFS was statistically higher with olaparib (5.4 months; 90% CI=3.6–9.6) vs placebo (3.6 months; 90% CI=1.8–4.9) with a HR of 0.59 (p=0.020) suggesting olaparib may prolong PFS in HRD-positive advanced or metastatic endometrial cancer.

CERVICAL CANCER

Major cervical cancer studies reported in 2023 can be divided into 3 categories; 1) A surgical trial for early-stage, low-risk cervical cancer (SHAPE); 2) Clinical trials evaluating immunotherapy with chemoradiation (KEYNOTE A-18) or induction chemotherapy followed by chemoradiation (INTERLACE) in locally advanced cervical cancer; 3) Clinical trials evaluating combination of immunotherapy, anti-angiogenic therapy, and chemotherapy (BEATcc), ADCs therapy (innovaTV 301), or new combinations of anti-TIGIT plus immunotherapy (AdvanTIG-202) in primary metastatic or recurrent cervical cancer.

1. Low-risk early-stage cervical cancer

Several retrospective studies have shown that approximately <1% of patients with low-risk, early-stage cervical cancer have parametrial involvement [40-44]. In addition, resection of parametrium, which causes injuries of the autonomic plexus can lead to bladder dysfunction, sexual dysfunction, and rectal dysmotility [45]. Therefore, simple hysterectomy with pelvic node assessment may be an option for this group of patients.

SHAPE trial

The SHAPE trial, a groundbreaking study presented by Plante et al. [12], at the 2023 American Society of Clinical Oncology (ASCO) Annual Meeting, has sparked a potential transformation in the treatment of low-risk, early-stage cervical cancer. This trial, which began in 2012 under the Canadian Cancer Trials Group, enrolled 700 patients to compare the outcomes of simple hysterectomy versus radical hysterectomy with pelvic node dissection in low-risk cervical cancer. The definition of low-risk cervical cancer in SHAPE trial is shown in **Table 2**. This was a non-inferiority trial. Primary endpoint was a pelvic relapse free survival initially but changed to pelvic recurrence rate at 3 years due to very low event rate. The 3-year pelvic recurrence rates were 3.1% and 2.9% for simple and radical hysterectomy groups, respectively. The results revealed that simple hysterectomy, a less invasive procedure, was not inferior to radical hysterectomy in terms of pelvic recurrence rates. With a mere 0.35% difference in recurrence rates at three years, simple hysterectomy not only challenges the necessity of the more aggressive radical hysterectomy for low-risk patients but also promises a safer approach with fewer surgery-related adverse events. This finding is particularly significant considering the similar rates of adjuvant therapy and OS between the 2 groups,

https://doi.org/10.3802/jgo.2024.35.e66

Table 2. The definition of low-risk cervical cancer in SHAPE trial

Definition
Squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma
Stage IA2 and IB1 by 2009 FIGO stage
Stomal invasion <10 mm on LEEP/cone specimen
Stroma invasion <50% on MRI
Maximal dimension of tumor ≤20 mm
Grade 1, 2, 3

FIGO, International Federation of Gynecology and Obstetrics; LEEP, loop electrosurgical excision procedure; MRI, magnetic resonance imaging.

indicating comparable post-operative and long-term outcomes. However, extrapelvic recurrence and cervical cancer related death was higher in simple hysterectomy group although it was not statistically significant. More patients in radical hysterectomy group underwent open surgery.

The trial's emphasis on patient safety and quality of life is reflected in its detailed analysis of surgical complications and outcomes. Patients undergoing simple hysterectomy experienced notably fewer complications, such as intraoperative bleeding, ureteral and bladder injuries, and postoperative infections. Moreover, the study highlighted the reduced incidence of acute and late urinary retention and incontinence in this group. Beyond the clinical benefits, the trial underscored improvements in patients' quality of life, including less pain, better global health status, and fewer symptoms related to body image, vaginal changes, and menopause. Sexual health also saw improvements, with patients reporting better outcomes in desire, arousal, lubrication, and overall satisfaction.

This shift towards less invasive surgical options, as evidenced by the SHAPE trial's findings, marks a significant evolution in the management of low-risk early-stage cervical cancer. It signifies a move towards treatment strategies that balance efficacy with patient well-being, prioritizing not just the survival but the overall life quality of patients. These insights pave the way for a new standard in gynecologic oncology, where the choice of surgical method can be tailored more precisely to the patient's individual risk profile and needs, potentially altering the traditional approach to surgical management in cervical cancer.

2. Immunotherapy with chemoradiation or induction chemotherapy followed by chemoradiation in locally advanced cervical cancer: KEYNOTE A-18 trial, INTERLACE trial

Concurrent chemoradiation is the standard treatment for locally advanced cervical cancer; however, a high rate of distant failure after chemoradiation is still an important problem. The phase 2 KEYNOTE-158 study showed 14.3% ORR in patients with ≥1 prior line of chemotherapy in PD-L1-positive metastatic or recurrent cervical cancer [46]. In the phase 3 KEYNOTE-826 study, the addition of pembrolizumab to platinum-based chemotherapy ± bevacizumab has shown clinically meaningful PFS and OS improvements in metastatic, persistent, or recurrent cervical cancer [47]. In addition, the phase 2 single arm Cx2 study have shown that induction chemotherapy followed by chemoradiation for locally advanced cervical cancer may be feasible with a complete or partial response rate of 70% [38]. Therefore, the efficacy and safety of pembrolizumab plus concurrent chemoradiation or induction chemotherapy followed by chemoradiation for locally advanced cervical cancer need further evaluation.

https://doi.org/10.3802/jgo.2024.35.e66

KEYNOTE-A18 trial

KEYNOTE-A18, also referred to as ENGOT-cx11/GOG-3047, is a phase 3 randomized, double-blind trial evaluating pembrolizumab in combination with external beam radiotherapy plus concurrent chemotherapy (cisplatin), followed by brachytherapy compared to placebo plus concurrent chemoradiotherapy for the treatment of newly diagnosed high-risk (stage IB2-IIB with lymph node-positive disease, and stage II-IVA with and without lymph node-positive disease) locally advanced cervical cancer [13]. The primary endpoints were PFS and OS. A total of 1,060 patients were enrolled and randomized in the study. Results from a preplanned interim analysis indicated that the combination of pembrolizumab with concurrent chemoradiotherapy led to a statistically significant and clinically meaningful improvement in PFS compared to concurrent chemoradiotherapy alone (HR=0.70; 95% CI=0.55–0.89; p=0.002). Although the OS data were not mature at the time of the interim analysis, a positive trend in favor of pembrolizumab plus concurrent chemoradiotherapy was observed (HR=0.73; 95% CI=0.49–1.07). The trial is ongoing, and further follow-up is required to assess OS. The safety profile of pembrolizumab in this trial was consistent with findings from previously reported studies, with no identification of new safety signals.

INTERLACE trial

The GCIG INTERLACE trial investigated whether induction chemotherapy before standard chemoradiation improves both PFS and OS [14]. Women with squamous, adeno- or adenosquamous carcinoma International Federation of Gynecology and Obstetrics (FIGO, 2008) stage IB1 with node positive, IB2, II, IIIB, IVA were eligible. Five hundred patients were recruited with a median age of 46 years. Induction chemotherapy preceding chemoradiotherapy demonstrated a 73% 5-year PFS rate and an 80% 5-year OS rate. In contrast, those undergoing chemoradiation alone exhibited lower rates of 64% for PFS (HR=0.65; 95% CI=0.46–0.91; p=0.013) and 72% for OS (HR=0.61; 95% CI=0.40–0.91; p=0.040). The median follow-up duration was 64 months. Grade ≥3 adverse events were reported in 59% of individuals receiving induction chemotherapy plus chemoradiotherapy, compared to 48% in those receiving chemoradiation alone.

3. Clinical trials evaluating combination of immunotherapy, anti-angiogenic therapy, and chemotherapy, ADCs therapy, or new combinations of anti-TIGIT plus immunotherapy in primary metastatic or recurrent cervical cancers: BEATcc trial, innovaTV 301 trial, AdvanTIG-202 trial

GOG 240 and KEYNOTE-826 trials showed improved survival with bevacizumab and pembrolizumab added to platinum-based chemotherapy for metastatic or recurrent cervical cancer [47,48]. Thus, the efficacy and safety of combination (immunotherapy, bevacizumab, and chemotherapy) therapy need to be evaluated for metastatic or recurrent cervical cancer. In the innovaTV 204 trial, tisotumab vedotin (TV) showed clinically meaningful and durable antitumor activity in women with previously treated metastatic or recurrent cervical cancer [49]. Therefore, the assessment of the efficacy and safety of TV when utilized in the second- or third-line for patients with metastatic or recurrent cervical cancer with disease progression on doublet chemotherapy may be meaningful. Human and murine tumor-infiltrating CD8+ T cells express high levels of TIGIT [50]. In addition, antibody co-blokcade of TIGIT and PD-L1 elicits tumor rejection in preclinical models [51]. Therefore, analyzing the safety and efficacy of anti-programmed cell death protein 1 (PD-1) ± anti-TIGIT in patients with previously treated metastatic or recurrent cervical cancer would be worthwhile.

https://doi.org/10.3802/jgo.2024.35.e66

BEATcc (ENGOT-Cx10/GEICO 68-C/JGOG1081/GOG-3030) trial

The BEATcc trial is a randomized phase 3 study assessing the efficacy of adding atezolizumab to bevacizumab and a platinum doublet as first-line chemotherapy for metastatic (stage IVB), persistent, or recurrent cervical cancer [15]. The histological types considered included squamous cell carcinoma, adenocarcinoma, and adenosquamous carcinoma. A total of 410 patients were randomly assigned in a 1:1 ratio to receive bevacizumab plus paclitaxel-cis/carboplatin with or without atezolizumab. The primary endpoints were investigator-assessed PFS and OS. Compared to standard chemotherapy, the addition of atezolizumab to standard chemotherapy (bevacizumab plus paclitaxel-cis/carboplatin) resulted in a 38% reduction in the risk of progression or recurrence (median PFS 13.7 vs. 10.4 months, HR=0.62; p<0.001) and a 32% reduction in the risk of death (median OS 32.1 vs. 22.8 months, HR=0.68; p=0.005), with no new adverse events reported. Furthermore, significant improvements were observed in all key secondary endpoints, including OS, DOR, time to treatment failure, and second PFS.

InnovaTV 301 (ENGOT-Cx12/GOG-3057) trial

TV is an ADC comprising a tissue factor-directed human monoclonal antibody covalently linked to the microtubule-disrupting agent monomethyl auristatin E (MMAE). The innovaTV 301 trial, a randomized, open-label, phase 3 study, aims to assess the superiority of TV over conventional chemotherapy in recurrent or metastatic cervical cancer [16]. Eligible patients, who had received fewer than three prior lines of chemotherapy, encompassed various histological types, including squamous cell carcinoma, adenocarcinoma, and adenosquamous carcinoma. A total of 502 patients were randomly assigned in a 1:1 ratio to receive either TV or investigator's choice chemotherapy, which included topotecan, vinorelbine, gemcitabine, irinotecan, or pemetrexed. TV demonstrated a statistically significant improvement in PFS (median 4.2 vs. 2.9 months, HR=0.67; p<0.001) and OS (median 11.5 vs. 9.5 months, HR=0.70; p=0.004). Patients in the TV arm experienced specific drug-related adverse events, such as ocular diseases, peripheral neuropathy, alopecia, and epistaxis. However, these events were manageable and tolerable, consistent with previous experience from the innovaTV 204 trial.

AdvanTIG-202 trial

The AdvanTIG-202 trial is an ongoing a phase 2 study using tislelizumab (TIS), an anti-PD-1 monoclonal antibody, with or without ociperlimab (OCI), an anti-TIGIT monoclonal antibody, to treat previously treated metastatic or recurrent cervical cancer [17]. In stage I, 40 patients were enrolled and randomized to each group. Then cohort 1 (TIS + OCI group) was expanded to a total of 98 patients in stage 2. Cohort 1 showed an ORR of 22.5% (95% CI=15.8–30.3) when using TIS with OCI. In the PD-L1 positive subgroup, assessed by the tumor area positivity algorithm, the ORR was 26.2% (95% CI=17.2–36.9). This result demonstrates a significant improvement in ORR compared to the historical control ORR of 14.3% with anti-PD-1 therapy [46]. In the updated analysis (data cut-off, June 1, 2023), the median DOR was 17.3 (95% CI=16.9–not estimable) months for cohort 1 and 16.9 (95% CI=16.9–not estimable) months for PD-L1 positive patients, indicating a durable response. Cohort 2 demonstrated an ORR of 32.5% with 5 complete responses and 8 partial responses, indicating the potential benefit of TIS monotherapy in patients with previously treated recurrent or metastatic cervical cancer. However, due to the small sample size of cohort 2 (n=40), interpretation was limited. In cohort 1, adverse events above grade 3 were observed in 18% of cases, mostly presenting as anemia and rash. These data suggest the promising antitumor activity and durable responses for both the overall population and PD-L1 positive subgroup when compared with historical data.

https://doi.org/10.3802/jgo.2024.35.e66

OVARIAN CANCER

Major ovarian cancer studies reported in 2023 can be divided into 3 categories; 1) Immunotherapy; 2) Triplet therapies using immune checkpoint inhibitors along with antiangiogenic agents and PARP inhibitors; 3) ADCs therapy and others (**Fig. 1**).

1. Immunotherapy

ATALANTE/ENGOT-ov29

ATALANTE/ENGOT-ov29 is the placebo-controlled randomized phase 3 study of atezolizumab combined with bevacizumab and platinum-based therapy for platinum-sensitive ovarian cancer [18]. Patients were randomly assigned 2:1 to atezolizumab (1,200 mg once every 3 weeks [Q3W] or equivalent) or placebo for up to 24 months, combined with bevacizumab and 6 cycles of chemotherapy doublet, stratified by platinum-free interval, PD-L1 status, and chemotherapy regimen. Coprimary end points were PFS in the intention-to-treat and PD-L1-positive populations.

Six hundred and fourteen patients were randomly assigned: 410 to atezolizumab and 204 to placebo. After 3 years' median follow-up, the PFS difference between atezolizumab and placebo did not reach statistical significance (median 13.5 vs 11.3 months, HR=0.83; 95% CI=0.69–0.99; p=0.041) or in PD-L1-positive (median 15.2 vs 13.1 months, HR=0.86; 95% CI=0.63–1.16; p=0.300) populations. The immature OS HR was 0.81 (median 35.5 vs 30.6 months with atezolizumab vs. placebo, 95% CI=0.65–1.01).

	VEGFi	PARPi	ICI	VEGFi ± ICI	VEGFi ± PARPi	PARPi ± ICI	VEGFi ± PARPi ± ICI	PARPi ± VEGFi ± ICI	± VEGFi ± PARPi + ICI	ADC
1L Tx	CT+Bev **GOG 218**		CT+Avelumab **JAVELIN 100**	CT+Bev+Atezo **IMagyn50**		CT+Avelumab +Talazo JAVELIN **PARP100**	CT+Bev+Durva +Ola **DUO-O**	CT+Dostarl+Nira w/wo bev **FIRST**	CT+Pembro+Ola w/wo bev **KEYLINK-001/ ENGOT-Ov43**	
	CT+Bev **ICON7**	CT+Veliparib **VELIA**	CT+Durva +Tremelimumab **TRU-D**							
1L M	CT+Bev **BOOST**	Olaparib **SOLO-1**			Bev±Ola **PAOLA-1**	Rucaparib +Nivolumab **ATHENA combo**				
		Niraparib **PRIMA**			Niraparib±Bev **NIRVANA**					
PSOC		Olaparib **SOLO-2**		CT+Bev±Atezo **ATALANTE**		CT+Niraparib +Atezolizumab **ANITA**	CT+Bev+Durva +Ola **OPEB-01**		Ola+Durva±Bev **MEDIOLA**	T-DXd **DESTINY PANTUMOR02**
		Niraparib **NOVA**								Mirvetuximab **SORAYA MIRASOL**
PROC			PLD+Avelumab **JAVELIN 200**	Cediranib+Ola **AGO OVAR 2.28**						UpRi **UPGRADE-A**
										Luvelta **STRO002**

POSITIVE NEGATIVE ONGOING

Fig. 1. Incorporation of PARPi, anti-angiogenic therapy, immunotherapy, and ADC in ovarian cancer.
ADC, antibody drug conjugate; Atezo, atezolizumab; Bev, bevacizumab; CT, chemotherapy; Dostarl, dostarlimab; Durva, durvalumab; PARPi, poly (ADP-ribose) polymerase inhibitors; ICI; immune checkpoint inhibitor; 1L Tx, First-line treatment; 1L M, First-line maintenance; Nira, niraparib; Ola, Olaparib; Pembro, pembrolizumab; PROC, platinum-resistant ovarian cancer; PSOC, platinum-sensitive ovarian cancer; Talazo, talazoparib; T-DXd, trastuzumab deruxtecan; UpRi, upifitamab rilsodotin; VEGFi, vascular endothelial growth factor inhibitor.

https://doi.org/10.3802/jgo.2024.35.e66

KGOG3046/TRU-D

KGOG3046/TRU-D is the phase 2 study of durvalumab and tremelimumab with front-line neoadjuvant chemotherapy (NAC) in patients with advanced-stage ovarian cancer [19]. Patients with stage IIIC-IVB ovarian cancer were offered three cycles of durvalumab (1,500 mg) and tremelimumab (75 mg) with NAC, followed by interval debulking surgery (IDS). After IDS, 3 cycles of durvalumab (1,120 mg) and adjuvant chemotherapy followed by durvalumab maintenance (1,120 mg [total 12 cycles]) were administered. The primary endpoint was 12-month PFS rate.

Twenty-three patients were enrolled. The median follow-up duration was 29.2 months (range 12.0–42.2). The 12-, 24-, and 30-month PFS rates were 63.6%, 45.0%, and 40.0%, respectively. All patients underwent IDS, with an R0 resection rate of 73.9%, and 17.4% achieved pathological complete response. Skin rashes were the most common treatment-related adverse events.

VIRO-15

VIRO-15 is the phase 2 study of clinical activity of olvimulogene nanivacirepvec (Olvi-Vec)-primed immunochemotherapy in heavily pretreated patients with platinum-resistant or platinum-refractory ovarian cancer [20]. Olvi-Vec was administered via a temporary intraperitoneal dialysis catheter as 2 consecutive daily doses (3×10^9 pfu/d) followed by platinum-doublet chemotherapy with or without bevacizumab. Primary outcomes were ORR and cancer antigen 125 (CA-125) assay, and PFS. Secondary outcomes included DOR, disease control rate (DCR), safety, and OS.

Twenty-seven patients with platinum-resistant (n=14) or platinum-refractory (n=13) ovarian cancer were enrolled. Median follow-up duration was 47.0 months (95% CI=35.9 months–not reached [NR]). Overall, ORR was 54% (95% CI=33%–74%), with a DOR of 7.6 months (95% CI=3.7–9.6 months). The DCR was 88% (21/24). The ORR by CA-125 was 85% (95% CI=65%–96%). Median PFS by RECIST 1.1 was 11.0 months (95% CI=6.7–13.0 months), and the PFS 6-month rate was 77%. Median PFS was 10.0 months (95% CI=6.4 months–NR) in the platinum-resistant group and 11.4 months (95% CI=4.3–13.2 months) in the platinum-refractory group. The median OS was 15.7 months (95% CI=12.3–23.8 months) in all patients, with a median OS of 18.5 months (95% CI=11.3–23.8 months) in the platinum-resistant group and 14.7 months (95% CI=10.8–33.6 months) in the platinum-refractory group.

ENGOT Ov41/GEICO 69-O/ANITA

ENGOT Ov41/GEICO 69-O/ANITA is the phase 3, randomized, double blinded trial of platinum based chemotherapy with or without atezolizumab followed by niraparib maintenance with or without atezolizumab in patients with recurrent ovarian, tubal, or peritoneal cancer and platinum treatment free interval of more than 6 months [21]. The patients were randomly assigned to Arm A (n=209, platinum-based chemotherapy plus a placebo of atezolizumab followed by maintenance niraparib plus a placebo of atezolizumab) or Arm B (n=208, platinum-based chemotherapy plus atezolizumab followed by maintenance niraparib plus atezolizumab). The primary endpoint was PFS.

The final results of ANITA were presented at the ESMO Congress 2023. At a median follow-up of 36 months, patients who received atezolizumab in addition to chemotherapy and maintenance experienced a median PFS of 11.2 months (95% CI=10.1–12.1) compared with 10.1 months (95% CI=9.2–11.2) among patients who were treated with placebo in place of

https://doi.org/10.3802/jgo.2024.35.e66

atezolizumab (HR=0.89; 95% CI=0.71–1.10; p=0.280). Moreover, no significant PFS benefit was observed with the addition of atezolizumab among patients with PD-L1-positive disease (HR=0.87; 95% CI=0.61–1.25), PD-L1-negative disease (HR=0.93; 95% CI=0.70–1.24), or those with PD-L1 non-informative status (HR=1.06; 95% CI=0.50–2.25).

2. Triplet therapies

Triplet therapy for ovarian cancer is based on the idea that using an immune checkpoint inhibitor along with an antiangiogenic agent and a PARP inhibitor may enhance the antitumor effect and overcome resistance to each agent. It is a question whether more is better in ovarian cancer, especially in non-*BRCA*-mutated groups. The consistent activity of triplet therapy was observed across three studies, MEDIOLA, DUO-O, and OPEB-01.

MEDIOLA in non-gBRCAm cohort

Phase 2 MEDIOLA (NCT02734004) evaluated the efficacy and safety of a chemotherapy-free triplet therapy of olaparib (O), durvalumab (D), and bevacizumab (B) (n=31) and a doublet therapy of O+D (n=32) in patients with non-germline *BRCA*-mutated (non-g*BRCA*m) platinum-sensitive relapsed ovarian cancer [52]. All patients had progressed after receiving 1–2 prior lines of platinum-based chemotherapy and received O (300 mg orally [po] twice a day [bid]) and D (1,500 mg intravenously [iv] every 4 weeks [Q4W]) with or without B (10 mg/kg iv every 2 weeks [Q2W]) until disease progression. Initial results were reported at ESMO Virtual Congress 2020. The median PFS for the triplet combination was 14.7 months, and the ORR was 87.1%. Both median PFS (5.5 months) and ORR (34.4%) were lower for the doublet therapy, suggesting promising activity for the triplet therapy.

Final OS results were reported at ESMO Congress 2022 [22]. Patients who received the triplet combination showed a longer median OS (31.9 vs. 26.1 months) and a higher 56-week DCR (38.7% vs. 9.4%), compared to those who received the doublet combination. In terms of safety, both combinations were consistent with what was expected for the single agents, without new safety signals in longer-term follow-up. Such promising results from MEDIOLA inflated researchers' expectations of the efficacy of the same triplet combination in newly diagnosed ovarian cancer.

DUO-O/ENGOT-ov46/AGO-OVAR23/GOG-302

Results of DUO-O/ENGOT-ov46/AGO-OVAR23/GOG-3025 (NCT03737643), a phase 3 randomized controlled trial (RCT), was reported in ASCO 2023 Annual Meeting [23]. In DUO-O, 1,130 patients with non-somatic *BRCA*-mutated (non-s*BRCA*m), newly diagnosed stage III-IV high-grade epithelial ovarian cancer were randomly assigned to Arm 1 (n=378; PC with B [15 mg/kg iv Q3W], followed by B maintenance), Arm 2 (n=374; PC with B+D [1,120 mg iv Q3W], followed by B+D maintenance), or Arm 3 (n=378; PC with B+D, followed by B+D+O [300 mg po bid] maintenance) with a 1:1:1 ratio. The primary endpoint was PFS in Arm 3 versus Arm 1, tested first in the non-t*BRCA*m HRD+ population and then in the ITT population.

Prespecified interim analysis revealed significantly better PFS in Arm 3 than Arm 1 in the non-t*BRCA*m HRD+ population (HR=0.49; 95% CI=0.34–0.69; p<0.001) and in the ITT population (HR=0.63; 95% CI=0.52–0.76; p<0.001). PFS improvement was also observed in the HRD negative subgroup (HR=0.68; 95% CI=0.54–0.86). In comparisons of Arm 2 versus Arm 1, no significant difference in PFS was observed in the ITT population. Safety was generally in line with the known profiles of each agent [23].

https://doi.org/10.3802/jgo.2024.35.e66

DUO-O was the first phase 3 RCT to meet its primary endpoint in ovarian cancer using an immune checkpoint inhibitor. However, the design of DUO-O does not clearly allow identification of the individual contributions of durvalumab and olaparib.

OPEB-01/APGOT-OV4

Efficacy of triplet therapy in non-*BRCA*m, platinum-sensitive recurrent ovarian cancer was also evaluated in OPEB-01/APGOT-OV4, a single-arm phase 2 study [24]. In this study, 44 patients with non-*BRCA*m, confirmed by both germline and somatic tests, who were immunotherapy naïve and had received two lines of platinum-based chemotherapy and showed complete response or partial response were enrolled and received triplet maintenance therapy with O (300 mg po bid), B (15 mg/kg iv Q3W), pembrolizumab (P) (200 mg iv Q3W).

During the median follow-up duration of 22.9 months, the 6-month PFS rate was observed as 88.6% (95% CI=75.4–96.2), meeting the pre-specified primary endpoint. The secondary endpoints were reported as follows: median PFS, 22.4 months; 12-month PFS rate, 84.0% (95% CI=69.3–92.0); and median OS, 28.6 months. The triplet maintenance therapy demonstrated tolerable toxicity with manageable side effects. In exploratory analysis, a favorable response was associated with HRD positivity (p=0.043) and PD-L1 combined positive score ≥1 (p<0.001) [24].

Triplet therapy showed efficacy with tolerable safety in patients with non-*BRCA*m, newly diagnosed advanced or platinum-sensitive recurrent ovarian cancer. Further studies investigating a specific patient group who might have benefit from the triplet therapy, as well as cost-effectiveness studies, are warranted.

3. ADC and others

SORAYA study

Mirvetuximab soravtansine (MIRV), one of the ADCs, targets folate receptor α (FRα). The SORAYA study evaluates the efficacy and safety of monotherapy with MIRV in patients with platinum-resistant ovarian cancer (PROC) with high FRα. FRα-high membrane staining was demonstrated by immunohistochemistry (IHC), and 105 patients were evaluated. The primary endpoint is the ORR confirmed by the investigator and the secondary endpoint is the DOR [25].

The ORR was confirmed by the investigator, including 5 cases of complete response and 29 cases of partial response, and the ORR was 32.4%, meeting the primary endpoint. The median DOR was 6.9 months. In patients with 1 to 2 prior therapy, the ORR by investigator was 35.3% (95% CI=22.4–49.9) and in patients with three priors was 30.2% (95% CI=18.3–44.3). The ORR by investigator was 38.0% (95% CI=24.7–52.8) in patients with prior PARP inhibitor exposure and 27.5% (95% CI=15.9–41.7) in those without.

MIRV has been proven to be clinically meaningful with high ORR and durable response in PROC patients with high expression of FRα. This means it could become a standard treatment option for cancer patients.

MIRASOL study

MIRASOL is a randomized phase 3 trial to determine the efficacy of MIRV versus standard chemotherapy in patients with PROC. Patients were randomly assigned 1:1 to receive MIRV at a dose of 6 mg/kg every 21 days and to receive standard chemotherapy of paclitaxel, pegylated

https://doi.org/10.3802/jgo.2024.35.e66

liposomal doxorubicin, or topotecan. The primary endpoint was PFS and secondary endpoints were ORR, OS, and patient-reported outcomes. Other endpoints included safety and tolerability [26].

In the study results, PFS increased by 35% to 5.62 months in the MIRV group and 3.98 months in the standard chemotherapy treatment group, showing statistically significant results. The secondary endpoint was met with a statistically significant ORR of 42% in the MIRV group and 16% in the standard chemotherapy group. OS in patients in the MIRV group increased by 33% compared to patients receiving standard chemotherapy.

In PROC, MIRV is the first treatment to demonstrate a survival benefit compared to standard chemotherapy and clinically meaningful improvements in PFS, ORR, and OS regardless of prior therapy or PARP inhibitor treatment.

DESTINY-PANTUMOUR 02 study

Trastuzumab deruxtecan (T-DXd) is a HER2-directed ADC approved for HER2-expressing breast and gastric cancer and HER2-mutant non-small cell lung cancer. The DESTINY-PanTumor 02 is a phase 2, open-label, multicenter study targeting advanced solid tumors that do not use T-DXd as a treatment. Patients with HER2 expression confirmed as 2+ or 3+ on immunochemical staining were enrolled. Patients received 5.4 m/kg of T-DXd Q3W, and the primary endpoint was ORR [6].

For ovarian cancer, the ORR was 45%, and according to HER2 expression, it was 36.8% in IHC 2+ patients and 63.6% in IHC 3+ patients. Median PFS for ovarian cancer was 5.9 months, 12.5 months for IHC 3+, and 4.1 months for IHC 2+. Median OS was 20 months, 13.2 months for IHC 3+ and 13.2 months for IHC 2+. The ORR according to HER2 in situ hybridization (ISH) and plasma HER2 amplification was higher in tumor ISH positive and plasma HER2 amplification positive.

T-DXd showed a therapeutic response according to IHC expression of HER2 in patients with endometrial, cervical, or ovarian cancer, and the response was greater in patients with IHC 3+ tumors. These data suggest that T-DXd is a potential treatment for patients with gynecologic HER2-expressing tumors whose disease has progressed on prior treatment.

STRO-002 study

Luveltamab tazevibulin (Luvelta) is a novel FRα-targeting ADC equipped with a stable cleavable linker and a 3-aminophenyl hemiasterlin warhead (DAR 4) that induces cytotoxicity and immunological cell death. The study enrolled 44 patients with advanced ovarian cancer who had PROC after 1 to 3 prior lines or platinum sensitive disease or after 2 to 3 prior lines of platinum chemotherapy. Patients were randomly assigned 1:1 to receive 4.3 mg/kg IV Q3W until disease progression or 5.2 mg/kg iv. The primary end point is ORR, and the secondary end points are safety, PFS, and DOR [27].

The ORR across all patient populations was 32%. Depending on the level of FRα expression, the ORR was 37.5% and the DCR was 81% in patients with FRα expression >25%, proving that it provides significant clinical benefit. The ORR for patients with tumor proportion score (TPS) ≤25% was 11.1% (n=9), and for patients with TPS >25%, the ORR was 37.5%. It has been shown that a starting dose of 5.2 mg/kg provides greater benefit to patients compared to 4.3 mg/kg. The population with >25% TPS had a median PFS of 6.1 months and median

https://doi.org/10.3802/jgo.2024.35.e66

DOR of 5.5 months, regardless of starting dose. The population with TPS ≤25% had a median PFS of 2.7 months and median DOR of 2.9 months, regardless of starting dose.

UpRi study

Upifitamab rilsodotin (UpRi) is an ADC targeting NaPi2b, a sodium-dependent phosphate transporter. Patients with PROC who had previously received up to 4 lines of treatment were included, and patients were treated with 36 or 43 mg/m^2, up to a maximum dose of up to 80 mg, Q4W for patients with a body surface area ≥1.8 m^2, administered intravenously. Primary objectives were to assess safety and evaluate efficacy, including ORR and DCR [28].

The clinical trial was paused due to a comprehensive safety issue regarding bleeding events in patients receiving UpRi.

Relacorilant

Relacorilant is an oral drug aimed at blocking cortisol's effects to enhance the effectiveness of chemotherapy in various cancers. In the randomized, controlled, open label, and phase 2 trial, patients received relacorilant with nab-paclitaxel either intermittently or continuously, or nab-paclitaxel alone to assess for its efficacy and safety platinum resistance/refractory ovarian cancer [29]. The result showed that intermittent administration of relacorilant with nab-paclitaxel improved PFS and DOR with significance and trend of improvement in OS was observed. Phase 3 trial is now underway based on theses results.

Bouquet trial

At the ESMO 2023 conference, the first result from ENGOT-GYN2/GOG-3051-BOUQUET phase 2 biomarker-directed platform study for patient with persistent rare epithelial ovarian cancer was presented [30]. The cobimetinib arm, focusing on patients with BRAF/KRAS/NRASand/or NF1 LOF alterations revealed a 33% completed ORR and an impressive 89% DCR at 6 months especially in low grade serous ovarian cancer and mesonephric like adenocarcinoma. Additionally, the atezolizumab plus bevacizumab arm (non-matched arm), while showing a modest 14% ORR, demonstrated a 75% 6-month PFS rate. These findings suggest further investigation whether the integration of adjunct metronomic cyclophosphamide enhances tumor cell death and immune response.

HIPEC KGOG 3042

KGOG 3042 is a study conducted from January 2015 to February 2019, of 123 patients with stages IIIC-IV ovarian cancer to determine the benefits of adding hyperthermic intraperitoneal chemotherapy (HIPEC) to IDS [31]. Patients were divided into 2 groups: 43 received HIPEC with IDS, and 80 underwent IDS alone. Those treated with HIPEC had a higher rate of complete resection and a longer PFS, without increasing severe postoperative complications. However, OS did not differ significantly between the two groups. These results suggest that HIPEC may enhance PFS when combined with IDS, meriting further investigation in the context of advanced ovarian cancer treatment.

HIPEC-KOV-03R

In this study, 87 patients with primary epithelial ovarian cancer who underwent second-look surgery with or without HIPEC were analyzed [32]. Results showed that HIPEC significantly improved 10-year PFS but did not have a marked impact on OS. Despite higher toxicity rates, these were manageable and did not affect further treatment, underscoring the need for more research on HIPEC's role in ovarian cancer.

https://doi.org/10.3802/jgo.2024.35.e66

Pressurized intraepithelial aerosol chemotherapy (PIPAC)

PIPAC has been studied in ovarian cancer through various phase of clinical trials demonstrating a novel approach for drug delivery. Early studies indicated histopathological tumor regression and improved survival rate in certain cohort. For instance, the application of PIPAC with doxorubicin and cisplatin showed a promising DCR in recurrent platinum resistance high grade ovarian cancer patients with reporting up to a 50% survival rate at 1 year and notable OS benefit [33]. However, further studies are warranted to find appropriate anti-cancer drug and dosage.

SUPPLEMENTARY MATERIAL

Fig. S1

Asian Society of Gynecologic Oncology 2023 REVIEW COURSE at Grand Hyatt Incheon on December 9, 2023.

REFERENCES

1. Mirza MR, Chase DM, Slomovitz BM, dePont Christensen R, Novák Z, Black D, et al. Dostarlimab for primary advanced or recurrent endometrial cancer. N Engl J Med 2023;388:2145-58. PUBMED | CROSSREF
2. Eskander RN, Sill MW, Beffa L, Moore RG, Hope JM, Musa FB, et al. Pembrolizumab plus chemotherapy in advanced endometrial cancer. N Engl J Med 2023;388:2159-70. PUBMED | CROSSREF
3. Westin SN, Moore K, Chon HS, Lee JY, Thomes Pepin J, Sundborg M, et al. Durvalumab plus carboplatin/paclitaxel followed by maintenance durvalumab with or without olaparib as first-line treatment for advanced endometrial cancer: the phase III DUO-E trial. J Clin Oncol 2024;42:283-99. PUBMED | CROSSREF
4. Colombo N, Harano K, Hudson E, Galli F, Antill Y, Choi CH, et al. LBA40 Phase III double-blind randomized placebo controlled trial of atezolizumab in combination with carboplatin and paclitaxel in women with advanced/recurrent endometrial carcinoma. Ann Oncol 2023;34:S1281-2. CROSSREF
5. Pignata S, Scambia G, Schettino C, Arenare L, Pisano C, Lombardi D, et al. Carboplatin and paclitaxel plus avelumab compared with carboplatin and paclitaxel in advanced or recurrent endometrial cancer (MITO END-3): a multicentre, open-label, randomised, controlled, phase 2 trial. Lancet Oncol 2023;24:286-96. PUBMED | CROSSREF
6. Meric-Bernstam F, Makker V, Oaknin A, Oh DY, Banerjee S, González-Martín A, et al. Efficacy and safety of trastuzumab deruxtecan in patients with HER2-expressing solid tumors: primary results from the DESTINY-PanTumor02 phase II trial. J Clin Oncol 2024;42:47-58. PUBMED | CROSSREF
7. Nishikawa T, Hasegawa K, Matsumoto K, Mori M, Hirashima Y, Takehara K, et al. Trastuzumab deruxtecan for human epidermal growth factor receptor 2-expressing advanced or recurrent uterine carcinosarcoma (NCCH1615): the STATICE trial. J Clin Oncol 2023;41:2789-99. PUBMED | CROSSREF
8. Vergote I, Pérez-Fidalgo JA, Hamilton EP, Valabrega G, Van Gorp T, Sehouli J, et al. Oral Selinexor as maintenance therapy after first-line chemotherapy for advanced or recurrent endometrial cancer. J Clin Oncol 2023;41:5400-10. PUBMED | CROSSREF
9. Konstantinopoulos PA, Lee EK, Xiong N, Krasner C, Campos S, Kolin DL, et al. A phase II, two-stage study of letrozole and abemaciclib in estrogen receptor-positive recurrent endometrial cancer. J Clin Oncol 2023;41:599-608. PUBMED | CROSSREF
10. Liu JF, Xiong N, Campos SM, Wright AA, Krasner C, Schumer S, et al. Phase II study of the WEE1 inhibitor adavosertib in recurrent uterine serous carcinoma. J Clin Oncol 2021;39:1531-9. PUBMED | CROSSREF
11. Joly F, Brachet PE, Lacourtoisie SA, Asselain B, Floquet A, Collard O, et al. Multicentre randomized phase II trial of olaparib as maintenance therapy in platinum-sensitive advanced endometrial carcinoma: the GINECO-UTOLA study. J Clin Oncol 2020;38:TPS6109. CROSSREF
12. Plante M, Kwon JS, Ferguson S, Samouëlian V, Ferron G, Maulard A, et al. An international randomized phase III trial comparing radical hysterectomy and pelvic node dissection (RH) vs simple hysterectomy and pelvic node dissection (SH) in patients with low-risk early-stage cervical cancer (LRESCC): a Gynecologic Cancer Intergroup study led by the Canadian Cancer Trials Group (CCTG CX.5-SHAPE). J Clin Oncol 2023;41:LBA5511. CROSSREF

13. Lorusso D, Xiang Y, Hasegawa K, Scambia G, Galves ML, Elias PR, et al. LBA38 Pembrolizumab plus chemoradiotherapy for high-risk locally advanced cervical cancer: a randomized, double-blind, phase III ENGOT-cx11/GOG-3047/KEYNOTE-A18 study. Ann Oncol 2023;34:S1279-80. CROSSREF
14. McCormack M, Gallardo Rincón D, Eminowicz G, Diez P, Farrelly L, Kent C, et al. LBA8 A randomised phase III trial of induction chemotherapy followed by chemoradiation compared with chemoradiation alone in locally advanced cervical cancer: the GCIG INTERLACE trial. Ann Oncol 2023;34:S1276. CROSSREF
15. Oaknin A, Gladieff L, Martinez-Garcia J, Villacampa G, Takekuma M, De Giorgi U, et al. Atezolizumab plus bevacizumab and chemotherapy for metastatic, persistent, or recurrent cervical cancer (BEATcc): a randomised, open-label, phase 3 trial. Lancet 2024;403:31-43. PUBMED | CROSSREF
16. Vergote IB, Gonzalez Martin A, Fujiwara K, Kalbacher E, Bagameri A, Ghamande S, et al. LBA9 innovaTV 301/ENGOT-cx12/GOG-3057: a global, randomized, open-label, phase III study of tisotumab vedotin vs investigator's choice of chemotherapy in 2L or 3L recurrent or metastatic cervical cancer. Ann Oncol 2023;34:S1276-7. CROSSREF
17. Lee JY, Wu L, Boonyapipat S, Kim HS, Lee JW, Wang L, et al. 744MO AdvanTIG-202: phase II randomized, multicenter, open-label study of tislelizumab (TIS) with or without ociperlimab (OCI) in patients (pts) with previously treated recurrent/metastatic (R/M) cervical cancer (CC). Ann Oncol 2023;34:S509-10. CROSSREF
18. Kurtz JE, Pujade-Lauraine E, Oaknin A, Belin L, Leitner K, Cibula D, et al. Atezolizumab combined with bevacizumab and platinum-based therapy for platinum-sensitive ovarian cancer: placebo-controlled randomized phase III ATALANTE/ENGOT-ov29 trial. J Clin Oncol 2023;41:4768-78. PUBMED | CROSSREF
19. Park J, Lee JB, Lim MC, Kim BG, Kim JW, Kim S, et al. Phase II study of durvalumab and tremelimumab with front-line neoadjuvant chemotherapy in patients with advanced-stage ovarian cancer: primary analysis in the original cohort of KGOG3046/TRU-D. J Immunother Cancer 2023;11:e007444. PUBMED | CROSSREF
20. Holloway RW, Mendivil AA, Kendrick JE, Abaid LN, Brown JV, LeBlanc J, et al. Clinical activity of olvimulogene nanivacirepvec-primed immunochemotherapy in heavily pretreated patients with platinum-resistant or platinum-refractory ovarian cancer: the nonrandomized phase 2 VIRO-15 clinical trial. JAMA Oncol 2023;9:903-8. PUBMED | CROSSREF
21. Gonzalez Martin A, Sanchez Lorenzo L, Colombo N, dePont Christensen R, Heitz F, Meirovitz M, et al. A phase III, randomized, double blinded trial of platinum based chemotherapy with or without atezolizumab followed by niraparib maintenance with or without atezolizumab in patients with recurrent ovarian, tubal, or peritoneal cancer and platinum treatment free interval of more than 6 months: ENGOT-Ov41/GEICO 69-O/ANITA trial. Int J Gynecol Cancer 2021;31:617-22. PUBMED | CROSSREF
22. Banerjee S, Imbimbo M, Roxburgh P, Kim JW, Kim MH, Plummer R, et al. 529MO Phase II study of olaparib plus durvalumab with or without bevacizumab (MEDIOLA): final analysis of overall survival in patients with non-germline *BRCA*-mutated platinum-sensitive relapsed ovarian cancer. Ann Oncol 2022;33:S788-9. CROSSREF
23. Harter P, Trillsch F, Okamoto A, Reuss A, Kim JW, Rubio-Pérez MJ, et al. Durvalumab with paclitaxel/carboplatin (PC) and bevacizumab (bev), followed by maintenance durvalumab, bev, and olaparib in patients (pts) with newly diagnosed advanced ovarian cancer (AOC) without a tumor *BRCA1/2* mutation (non-t*BRCA*m): Results from the randomized, placebo (pbo)-controlled phase III DUO-O trial. J Clin Oncol 2023;41:LBA5506. CROSSREF
24. Kim YN, Park B, Kim JW, Kim BG, Kim SW, Kim HS, et al. Triplet maintenance therapy of olaparib, pembrolizumab and bevacizumab in women with *BRCA* wild-type, platinum-sensitive recurrent ovarian cancer: the multicenter, single-arm phase II study OPEB-01/APGOT-OV4. Nat Commun 2023;14:5476. PUBMED | CROSSREF
25. Matulonis UA, Lorusso D, Oaknin A, Pignata S, Dean A, Denys H, et al. Efficacy and safety of mirvetuximab soravtansine in patients with platinum-resistant ovarian cancer with high folate receptor alpha expression: results from the SORAYA study. J Clin Oncol 2023;41:2436-45. PUBMED | CROSSREF
26. Moore KN, Angelergues A, Konecny GE, Banerjee SN, Pignata S, Colombo N, et al. Phase III MIRASOL (GOG 3045/ENGOT-ov55) study: Initial report of mirvetuximab soravtansine vs. investigator's choice of chemotherapy in platinum-resistant, advanced high-grade epithelial ovarian, primary peritoneal, or fallopian tube cancers with high folate receptor-alpha expression. J Clin Oncol 2023;41:LBA5507. CROSSREF
27. Oaknin A, Fariñas-Madrid L, García-Duran C, Martin LP, O'Malley DM, Schilder RJ, et al. Luveltamab tazevibulin (STRO-002), an anti-folate receptor alpha (FolRα) antibody drug conjugate (ADC), safety and efficacy in a broad distribution of FolRα expression in patients with recurrent epithelial ovarian cancer (OC): Update of STRO-002-GM1 phase 1 dose expansion cohort. J Clin Oncol 2023;41:5508. CROSSREF

28. Richardson D, Hamilton E, Barve M, Anderson C, Taylor S, Lakhani N, et al. Updated results from the phase 1 expansion study of upifitamab rilsodotin (UpRi; XMT-1536), a NaPi2b-directed dolaflexin antibody drug conjugate (ADC) in ovarian cancer (076). Gynecol Oncol 2022;166:S48. CROSSREF
29. Colombo N, Van Gorp T, Matulonis UA, Oaknin A, Grisham RN, Fleming GF, et al. Relacorilant + nab-paclitaxel in patients with recurrent, platinum-resistant ovarian cancer: a three-arm, randomized, controlled, open-label phase II study. J Clin Oncol 2023;41:4779-89. PUBMED | CROSSREF
30. Ray-Coquard IL, Pignata S, Lee JY, Coleman RL, Brown J, Kim JW, et al. 747MO First results from the ENGOT-GYN2/GOG-3051/BOUQUET phase II biomarker-directed platform study: Cobimetinib (cobi) or atezolizumab (atezo) + bevacizumab (bev) for persistent/recurrent rare epithelial ovarian cancer (eOC). Ann Oncol 2023;34:S511-2. CROSSREF
31. Lee JY, Lee YJ, Son JH, Kim S, Choi MC, Suh DH, et al. Hyperthermic intraperitoneal chemotherapy after interval cytoreductive surgery for patients with advanced-stage ovarian cancer who had received neoadjuvant chemotherapy. JAMA Surg 2023;158:1133-40. PUBMED | CROSSREF
32. Yoo JG, Kim JH, Park EY, Kim I, Lim MC, Lee SJ. Ten-year treatment outcomes of consolidation hyperthermic intraperitoneal chemotherapy for ovarian cancer (HIPEC-KOV-03R). J Gynecol Oncol 2023;34:e72. PUBMED | CROSSREF
33. Taliento C, Restaino S, Scutiero G, Arcieri M, Bernardi G, Martinello R, et al. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) with cisplatin and doxorubicin in patients with ovarian cancer: a systematic review. Eur J Surg Oncol 2023;49:107250. PUBMED | CROSSREF
34. Berek JS, Matias-Guiu X, Creutzberg C, Fotopoulou C, Gaffney D, Kehoe S, et al. FIGO staging of endometrial cancer: 2023. J Gynecol Oncol 2023;34:e85. PUBMED | CROSSREF
35. ClinicalTrials.gov. A study to evaluate dostarlimab plus carboplatin-paclitaxel versus placebo plus carboplatin-paclitaxel in participants with recurrent or primary advanced endometrial cancer (RUBY) [Internet]. Bethesda, MD: National Library of Medicine; 2023 [cited 2024 Jan 9]. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT03981796.
36. Rosa K. Dostarlimab plus chemo followed by dostarlimab/niraparib improves PFS in endometrial cancer [Internet]. Cranbury, NJ: MJH Life Sciences; 2023 [cited 2024 Jan 9]. Available from: https://www.onclive.com/view/dostarlimab-plus-chemo-followed-by-dostarlimab-niraparib-improves-pfs-in-endometrial-cancer.
37. Mileshkin L, Bochtler T, Pauli C, Durán-Pacheco G, Arslan C, Bigot F, et al. LBA16 Primary analysis of efficacy and safety in the CUPISCO trial: a randomised, global study of targeted therapy or cancer immunotherapy guided by comprehensive genomic profiling (CGP) vs platinum-based chemotherapy (CTX) in newly diagnosed, unfavourable cancer of unknown primary (CUP). Ann Oncol 2023;34:S1254-335. CROSSREF
38. Ogitani Y, Aida T, Hagihara K, Yamaguchi J, Ishii C, Harada N, et al. DS-8201a, A novel HER2-targeting ADC with a novel DNA topoisomerase I inhibitor, demonstrates a promising antitumor efficacy with differentiation from T-DM1. Clin Cancer Res 2016;22:5097-108. PUBMED | CROSSREF
39. Vergote I, Mirza MR, Coleman RL, Perez-Fidalgo JA, Monk BJ, Valabrega G, et al. ENGOT-EN20/GOG-3083/xport-EC-042: A phase 3, randomized, placebo-controlled, double-blind, multicenter trial of selinexor in maintenance therapy after systemic therapy for patients with P53 wild-type, advanced or recurrent endometrial carcinoma. J Clin Oncol 2023;41:TPS5627. CROSSREF
40. Kinney WK, Hodge DO, Egorshin EV, Ballard DJ, Podratz KC. Identification of a low-risk subset of patients with stage IB invasive squamous cancer of the cervix possibly suited to less radical surgical treatment. Gynecol Oncol 1995;57:3-6. PUBMED | CROSSREF
41. Covens A, Rosen B, Murphy J, Laframboise S, DePetrillo AD, Lickrish G, et al. How important is removal of the parametrium at surgery for carcinoma of the cervix? Gynecol Oncol 2002;84:145-9. PUBMED | CROSSREF
42. Stegeman M, Louwen M, van der Velden J, ten Kate FJ, den Bakker MA, Burger CW, et al. The incidence of parametrial tumor involvement in select patients with early cervix cancer is too low to justify parametrectomy. Gynecol Oncol 2007;105:475-80. PUBMED | CROSSREF
43. Wright JD, Grigsby PW, Brooks R, Powell MA, Gibb RK, Gao F, et al. Utility of parametrectomy for early stage cervical cancer treated with radical hysterectomy. Cancer 2007;110:1281-6. PUBMED | CROSSREF
44. Frumovitz M, Sun CC, Schmeler KM, Deavers MT, Dos Reis R, Levenback CF, et al. Parametrial involvement in radical hysterectomy specimens for women with early-stage cervical cancer. Obstet Gynecol 2009;114:93-9. PUBMED | CROSSREF
45. Landoni F, Maneo A, Zapardiel I, Zanagnolo V, Mangioni C. Class I versus class III radical hysterectomy in stage IB1-IIA cervical cancer. A prospective randomized study. Eur J Surg Oncol 2012;38:203-9. PUBMED | CROSSREF
46. Chung HC, Ros W, Delord JP, Perets R, Italiano A, Shapira-Frommer R, et al. Efficacy and safety of pembrolizumab in previously treated advanced cervical cancer: results from the phase II KEYNOTE-158 study. J Clin Oncol 2019;37:1470-8. PUBMED | CROSSREF

47. Colombo N, Dubot C, Lorusso D, Caceres MV, Hasegawa K, Shapira-Frommer R, et al. Pembrolizumab for persistent, recurrent, or metastatic cervical cancer. N Engl J Med 2021;385:1856-67. PUBMED | CROSSREF
48. Tewari KS, Sill MW, Long HJ 3rd, Penson RT, Huang H, Ramondetta LM, et al. Improved survival with bevacizumab in advanced cervical cancer. N Engl J Med 2014;370:734-43. PUBMED | CROSSREF
49. Coleman RL, Lorusso D, Gennigens C, González-Martín A, Randall L, Cibula D, et al. Efficacy and safety of tisotumab vedotin in previously treated recurrent or metastatic cervical cancer (innovaTV 204/GOG-3023/ENGOT-cx6): a multicentre, open-label, single-arm, phase 2 study. Lancet Oncol 2021;22:609-19. PUBMED | CROSSREF
50. Johnston RJ, Comps-Agrar L, Hackney J, Yu X, Huseni M, Yang Y, et al. The immunoreceptor TIGIT regulates antitumor and antiviral CD8$^+$ T cell effector function. Cancer Cell 2014;26:923-37. PUBMED | CROSSREF
51. Chu X, Tian W, Wang Z, Zhang J, Zhou R. Co-inhibition of TIGIT and PD-1/PD-L1 in cancer immunotherapy: mechanisms and clinical trials. Mol Cancer 2023;22:93. PUBMED | CROSSREF
52. Drew Y, Penson RT, O'Malley DM, Kim JW, Zimmermann S, Roxburgh P, et al. 814MO Phase II study of olaparib (O) plus durvalumab (D) and bevacizumab (B) (MEDIOLA): Initial results in patients (pts) with non-germline *BRCA*-mutated (non-g*BRCA*m) platinum sensitive relapsed (PSR) ovarian cancer (OC). Ann Oncol 2020;31:S615-6. CROSSREF