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Review Article

Major clinical research advances in gynecologic cancer in 2021

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ABSTRACT

In the 2021 series, we not only summarized the major clinical research advances in gynecologic oncology but also added discussions to every part, based on communications at the conference. A review of cervical cancer included adjuvant treatments such as radiation and chemoradiation (concurrent or sequential) after radical hysterectomy in early cervical cancer, and immune checkpoint inhibitors in advanced, recurrent, and metastatic disease. Ovarian cancer research included studies of secondary cytoreductive surgery in platinum-sensitive recurrent ovarian cancer, and various trials of immune checkpoint inhibitors with or without vascular endothelial growth factor inhibitors and conventional chemotherapy. The rechallenge of poly (ADP-ribose) polymerase inhibitor maintenance in heavily pretreated ovarian cancer were also addressed. For uterine corpus cancer, dostarlimab (anti-programmed cell death protein 1 antibody) alone, or a tyrosine kinase inhibitor in combination with pembrolizumab for advanced, metastatic, or recurrent endometrial cancer were reviewed. The survival differences between the intensive and minimalist follow-up protocols were also described. In this review, we compared salpingectomy with delayed oophorectomy and salpingo-oophorectomy in terms of quality of life in BRCA 1 and 2 pathogenic variant carriers.

Keywords: Immunotherapy; Molecular Targeted Therapy; Poly(ADP-Ribose) Polymerase; Adjuvant Chemotherapy; Adjuvant Radiotherapy; Cytoreduction Surgical Procedures; Prevention

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, “Major Clinical Advances in Gynecologic Cancer” was held at Daeyang AI Center at Sejong University on December 11, 2021 (**Table S1**).

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

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In this review, we summarized and discussed the major clinical research on gynecologic cancer in 2021 (**Table 1**).

CERVICAL CANCER

The major cervical cancer research findings reported in 2021 can be summarized in the following five categories:

1) The STARS trial investigated the role of adjuvant therapy after radical hysterectomy [1].
2) The OUTBACK trial examined outback chemotherapy after concurrent chemoradiation therapy (CCRT) in locally advanced cervical cancer [2].
3) The KN826 [3] & EMPOWER trials [4] explored the role of immunotherapy in first- and second-line chemotherapy.
4) The innovaTV 204 [5] study aimed to find a new target agent with a higher response rate in advanced, metastatic, and recurrent cervical cancer.
5) The CONCERV trial prospectively evaluated the feasibility of conservative surgery in early-stage, low-risk cervical cancer [6].

1. STARS trial

The STARS trial was a phase III randomized controlled trial that compared the effects of adjuvant radiation therapy (RT), CCRT, and sequential chemoradiation therapy (SCRT) in the International Federation of Gynaecology and Obstetrics (FIGO) stage IB–IIB patients with one or more risk factors for recurrence after radical hysterectomy [1]. The histological types included squamous cell carcinoma, adenocarcinoma, and adenosquamous carcinoma.

Table 1. Topic list of the major clinical researches in gynecologic cancer in 2021

Category	Content	Reference
I. Cervical cancer		
STARS	Adjuvant therapy after radical hysterectomy	[1]
OUTBACK	Outback chemotherapy after concurrent chemoradiation in locally advanced cervical cancer	[2]
KN826	Addition of pembrolizumab as first-line treatment in persistent, recurrent, and metastatic cervical cancer	[3]
EMPOWER	Cemiplimab as ≥2nd line treatment in recurrent, metastatic cervical cancer	[4]
InnovaTV 204	A new target agent with a higher response rate in advanced, metastatic, and recurrent cervical cancer	[5]
ConCerv	Feasibility of conservative surgery in early-stage, low-risk cervical cancer	[6]
II. Ovarian cancer		
DESKTOP III	Secondary cytoreductive surgery in patients with platinum sensitive recurrent ovarian cancer	[11]
IMagyn050	Adding atezolizumab to a chemotherapy plus bevacizumab in newly diagnosed stage III–IV ovarian cancer	[14]
JAVELIN Ovarian 100	Chemotherapy ± avelumab followed by avelumab maintenance vs. chemotherapy alone in previously untreated ovarian cancer	[15]
EFFORT	Adavosertib (WEE1 inhibitor) alone and in combination with olaparib in PARP inhibitor-resistant ovarian cancer	[20]
CAPRI	Combination of olaparib and ceralsertib (ATR inhibitor) in PARP inhibitor-resistant ovarian cancer	[21,22]
OReO/ENGOT Ov-38	PARPi maintenance rechallenge in heavily pretreated ovarian cancer	[23]
III. Uterine corpus cancer		
TOTEM	OS comparison between intensive vs. minimalist follow-up regimen in endometrial cancer	[29]
GARNET	Dostarlimab in patients with advanced solid tumors including MMRd/MSI-H endometrial cancer and MMRp endometrial cancer	[43]
KN775	Lenvatinib plus pembrolizumab vs treatment of physician's choice in patients with advanced, metastatic, or recurrent endometrial cancer	[37]
IV. Prevention of gynecologic cancer		
UKCTOCS	Effectiveness of early detection of ovarian cancer through longitudinal CA 125 and second line transvaginal ultrasonogram	[51]
TUBA	Comparing salpingectomy with delayed oophorectomy and salpingo-oohporectomy in terms of quality of life in BRCA 1 and 2 pathogenic variant carriers	[52]

ATR, ataxia-telangiectasia and Rad3-related; DESKTOP, Descriptive Evaluation of preoperative Selection KriTeria for Operability; MMRd, mismatch repair-deficient; MMRp, mismatch repair-proficient; MSI-H, microsatellite instability-high; OS, overall survival; PARPi, poly (ADP-ribose) polymerase inhibitor.

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The risk factors included lymph node metastasis, positive parametrium, positive margins, lymphovascular space involvement, and deep stromal invasion. It was possible to participate in the study if the patient had one or more risk factors. In this study. a total of 1,048 patients were enrolled and randomized into the RT, CCRT, and SCRT groups, in a ratio of 1:1:1. The primary endpoint was disease-free survival (DFS). In the intention-to-treat and per-protocol populations, the SCRT group had significantly better DFS than the RT group. Moreover, the overall survival (OS) of the SCRT group was significantly better than that of the RT group. However, there were no significant differences in DFS and OS between the CCRT and RT groups. There were also no significant differences in DFS and OS between the SCRT and CCRT groups. Therefore, the authors concluded that SCRT had a greater survival benefit than RT for post-radical hysterectomy and high-risk cervical cancer.

Efforts to find appropriate adjuvant therapy in intermediate- and high-risk groups after radical hysterectomy for early-stage cervical cancer have been ongoing for a long time. Regarding adjuvant therapy in the high-risk group, CCRT with 5-fluorouracil+cisplatin showed a significant improvement in survival compared to RT in the Intergroup trial 0107/GOG 109/SWOG-8797 study in the early 2000s [7]. The survival benefit of CCRT was reconfirmed in a population-based cohort study using the National Cancer Database [8]. In recent years, CCRT has become the standard adjuvant therapy for high-risk patients undergoing radical hysterectomy. The NOGGO-AGO intergroup study compared CCRT with cisplatin and SCRT composed of 4 cycles of paclitaxel + carboplatin followed by RT [9]. In that study, there was no difference in the survival rate between the CCRT and SCRT groups. However, CCRT and SCRT show different toxicity profiles. To date, SCRT has not yet been able to replace CCRT. In the STARS trial, SCRT reduced the risk of recurrence by 48% and 35% compared with RT and CCRT, respectively. Adverse events in the SCRT group were not different from those in the CCRT group, and gastrointestinal adverse events were fewer in the SCRT group than in the CCRT group [1]. One of the possible mechanisms for better survival in SCRT compared with RT or CCRT is the short interval between surgery and adjuvant treatment. Another mechanism suggested that paclitaxel + cisplatin is a better regimen for decreasing distant failure because weekly cisplatin is a radiosensitizer and has no advantage for distant control. Of note, the STARS trial had several limitations. First, the study design was problematic. The primary endpoint was not that CCRT and SCRT were compared, but that CCRT or SCRT would have a survival benefit compared to RT. Second, stratification according to risks was not performed when patients were randomized to three groups (RT, CCRT, and SCRT). Third, approximately 20% of patients received neoadjuvant chemotherapy. Fourth, the completion rate of treatment was 62% in the CCRT group, which was much lower than the 73% in the SCRT group. Owing to these problems, the authors also commented that SCRT may be a good treatment strategy and suggested that chemotherapy should be performed first, followed by RT, especially in a resource-limited country where the waiting time for RT is long because of a lack of RT resources. Further studies comparing the roles of CCRT and SCRT are necessary because the intermediate- and high-risk groups are mixed in the STARS trial. The NRG 0724 study comparing CCRT with cisplatin and CCRT with cisplatin followed by four cycles of paclitaxel + carboplatin, as adjuvant therapy for high-risk groups, and the GOG 263/KGOG 1008 study comparing adjuvant RT and CCRT with cisplatin in the intermediate-risk group are both still ongoing. Appropriate adjuvant therapy after radical hysterectomy will have to wait for the results of these studies.

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2. OUTBACK trial

The OUTBACK trial was a phase III randomized controlled trial evaluating the role of outback chemotherapy after CCRT in locally advanced cervical cancer patients with FIGO stage IB1 with lymph node metastasis, IB2, II, IIIB, and IVA, by randomizing them into a group receiving CCRT only and additional adjuvant therapy after CCRT [2]. Patients with nodal metastasis in the L3-L4 para-aortic area were excluded from the study. The histological types included squamous cell carcinoma, adenocarcinoma, and adenosquamous carcinoma. Additional chemotherapy (ACT) was 4 cycles of paclitaxel (155 mg/m^2) and carboplatin (AUC 5) every 3 weeks. A total of 926 patients were randomized 1:1 to receive CCRT and ACT. The primary endpoint was OS, and there were no significant intergroup differences between the two groups.

The primary concern with CCRT, the standard treatment for locally advanced cervical cancer, is the possibility of distant failure. Therefore, adjuvant systemic chemotherapy (outback chemotherapy) has been considered a solution to reduce distant failure after CCRT. In a randomized controlled trial published in 2011, CCRT with gemcitabine + cisplatin followed by gemcitabine + cisplatin showed a significantly improved survival rate compared to CCRT with gemcitabine + cisplatin [10]. Grade 3 and 4 toxicities were significantly higher in the ACT group. In contrast, outback chemotherapy did not improve patient survival in the OUTBACK trial. OUTBACK trials have several limitations. First, the rate of failure to implement adjuvant chemotherapy is high. For example, 22% of the patients did not start adjuvant chemotherapy, and 38% did not complete adjuvant chemotherapy. Moreover, since only four cycles of adjuvant chemotherapy are used, low-dose intensity is also a potential concern. One strategy to reduce distant failure after CCRT in the future is the use of immunotherapy during and after CCRT. A study comparing CCRT and CCRT + durvalumab (CALLA trial) has completed patient registration, and a study comparing CCRT and CCRT + pembrolizumab (KEYNOTE-A18/ENGO-cx11) is currently ongoing.

3. KeyNote-826 trial

Following the positive results of the GOG-240 trial, showing a significant improvement in survival by adding bevacizumab to first-line chemotherapy for persistent, recurrent, and metastatic cervical cancer, platinum-based chemotherapy plus bevacizumab has become standard care. Although the response rate of immune checkpoint inhibitors in persistent, recurrent, and metastatic cervical cancer has been reported in several studies, there have been no phase III studies showing improved survival following treatment.
The KeyNote-826 study is the first phase III study to show that when immune checkpoint inhibitors are added to standard care for persistent, recurrent, and metastatic cervical cancer, a significant improvement in survival is found. The results of this study will likely lead to a significant change in the treatment of cervical cancer. The KeyNote-826 trial was a phase III randomized controlled trial showing an additional improvement in survival rate by adding immunotherapy to standard care [3]. A total of 617 patients with persistent, recurrent, and metastatic cervical cancer were randomized to receive paclitaxel + cisplatin/carboplatin ± bevacizumab, or paclitaxel + cisplatin/carboplatin ± bevacizumab + pembrolizumab (up to 35 cycles). DFS and OS were significantly improved in the pembrolizumab group in the all-comers population. The safety profile was manageable by adding pembrolizumab.

4. EMPOWER trial

In the treatment of cervical cancer, the activity of immune checkpoint inhibitors as a second-line, or higher, chemotherapy has been introduced through several studies, but there has not been a phase III study showing the superiority of immune checkpoint inhibitors compared

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to cytotoxic chemotherapy corresponding to the current standard of care. The EMPOWER trial is the first phase III study to show the superiority of immune checkpoint inhibitors over second-line treatment in the treatment of recurrent, metastatic cervical cancer. The results of this study will likely lead to a paradigm shift in the treatment of cervical cancer. The EMPOWER trial is a phase III randomized controlled trial that showed the efficacy of immunotherapy in recurrent, metastatic cervical cancer resistant to platinum-based chemotherapy previously performed for persistent, metastatic, and recurrent cervical cancer [4]. The histological types included squamous cell carcinoma, adenocarcinoma, and adenosquamous carcinoma. A total of 608 patients were randomized 1:1 to either cemiplimab or physician-choice chemotherapy. Chemotherapy included pemetrexed, gemcitabine, topotecan, and irinotecan. The primary endpoint was OS. Compared to chemotherapy, cemiplimab demonstrated significant improvement in OS in all populations, including squamous cell and adenocarcinoma populations.

5. InnovaTV 204 trial

Tisotumab vedotin (TV) is another drug that has recently shown promising activities in the treatment of cervical cancer. TV is an antibody-drug conjugate that targets tissue factors. This was evaluated in the Innova TV 204 phase II trial [5]. Patients included in the study had recurrent or extrapelvic metastatic cervical cancer and had received two or fewer at least two prior systemic chemotherapy regimens for recurrent or metastatic disease. Patients had progressive disease during or after doublet chemotherapy (paclitaxel plus either platinum or topotecan) with bevacizumab, if eligible. The histological types included squamous cell carcinoma, adenocarcinoma, and adenosquamous carcinoma. A total of 101 patients were evaluated, with an objective response rate (ORR) of 24%. The complete response, partial response, and stable disease rates were 7%, 17%, and 49%, respectively. Most tumor responses were rapid, with a median response of 1.4 months. The median duration of response (DOR) was 8.3 months (95% confidence interval [CI]=4.2-not reached) and the median progression-free survival (PFS) was 4.2 months (95% CI=3.0–4.4 months). Furthermore, TV had a manageable safety profile.

6. ConCerv trial

The ConCerv trial evaluated the feasibility of conservative surgery in women with early-stage, low-risk cervical cancer [6]. This study included women with FIGO 2009 stage IA2-IB1 cervical cancer ≤2 cm, without lymphovascular space invasion, a depth of invasion ≤10 mm, and a negative conization margin. Conservative surgery was conization followed by lymph node assessment for women wishing to preserve fertility, and simple hysterectomy with lymph node assessment for women who did not want to preserve fertility. A total of 100 patients were included in this study. The surgery types were conization followed by lymph node dissection in 44 women, simple hysterectomy with lymph node evaluation in 40 women, and inadvertent simple hysterectomy followed by lymph node dissection in 16 women. Three patients experienced recurrence within 2 years following surgery, and the cumulative incidence of recurrence was 3.5%.

OVARIAN CANCER

1. Secondary cytoreductive surgery (SCS) in recurrent ovarian cancer

The role of SCS in patients with platinum-sensitive recurrent ovarian cancer is controversial. The findings of three multicenter, randomized, phase III trials (DESKTOP III [NCT01611766],

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Table 2. Comparison of three trials for secondary cytoreductive surgery in patients with platinum-sensitive recurrent ovarian cancer

Variables	DESKTOP III	GOG 213	SOC-1
Total	407	485	357
Age (yr)	60.5	57	54.1
Serous histology	80.6%	86%	84.9%
Progression-free interval (mo)	19.9	19.7	16.1
Complete gross resection	74.2%	67%	77%
Platinum-based chemotherapy	89%	100%	97%
2nd line bevacizumab	23.1%	84%	1%
2nd line PARP inhibitor maintenance	11%	0%	4.9%

PARP, poly (ADP-ribose) polymerase; DESKTOP, Descriptive Evaluation of preoperative Selection KriTeria for Operability; GOG, Gynecologic Oncology Group; SOC, Surgery or chemotherapy in recurrent Ovarian Cancer.

GOG-213 [NCT00565851], and SOC-1 [NCT01611766]) have been published [11-13]. All three trials were distinct in terms of the patient cohort, eligibility criteria for surgery, and center selection (**Table 2**).

We noted inconsistent results from the three studies (DESKTOP III and SOC-1 trials vs. GOG-213 trial). One explanation may be related to the difference in bevacizumab usage. In the GOG 213 trial, 84% of patients received bevacizumab. In contrast, in the DESKTOP III and SOC-1 trials, only 23% and 1% of patients received bevacizumab, respectively. Another explanation may be the different processes used in each trial for selecting patients and centers.

The final analysis from DESKTOP III was published in the New England Journal of Medicine in 2021 [12]. The primary endpoint analysis of the DESKTOP III trial reported a median OS of 53.7 months with surgery and 46.0 months without surgery (p=0.02).

DESKTOP III is the first surgical study to demonstrate a meaningful survival benefit among patients with ovarian cancer, with an acceptable incidence of complications and without a detrimental effect on the quality of life, based on the Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) score.

The authors emphasized that all patients with a first relapse after a platinum-free interval of at least 6 months should be assessed to determine if surgery is an option, and that the AGO score should be incorporated into the evaluation.

2. Unsatisfactory results from front-line chemo-immunotherapy

Two randomized phase III studies failed to show the benefit of adding immune checkpoint inhibitors to chemotherapy as first-line therapy and for maintenance in patients with newly diagnosed ovarian cancer [14,15].

In IMagyn 050, adding atezolizumab to a chemotherapy plus bevacizumab backbone did not improve PFS compared with chemotherapy plus bevacizumab alone in either the intention-to-treat or programmed death-ligand 1 (PD-L1) positive (immune cells [IC>1%) populations. Exploratory PFS analyses in the PD-L1 IC ≥5% subgroup showed a trend toward atezolizumab (PFS: hazard ratio [HR]=0.64, 95% CI=0.43–0.96).

The JAVELIN Ovarian 100 study did not meet either of its two primary objectives of improving PFS with two avelumab regimens with chemotherapy versus chemotherapy alone. PD-L1 status did not predict the benefit of avelumab treatment, either as maintenance therapy

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or in combination with chemotherapy. These findings did not concur with results from the JAVELIN Ovarian 200 study. In these two studies, the addition of PD-L1 inhibitors was unsatisfactory. Current attention is focused on doublet or triplet combination trials, including the DUO-O [16], FIRST/ENGOT-ov44 [17], KEYLINK-001/ENGOT-ov43 [18], and ATHENA [19] studies, which investigated immune checkpoint inhibitors with PARP inhibitors and/or bevacizumab in the first-line setting.

3. Overcoming PARP inhibitor resistance

As more patients receive PARP inhibitors as maintenance therapy as part of first- or second-line treatment, resistance to platinum agents and PARP inhibitors is inevitable. The EFFORT [20] and CAPRI [21,22] studies use targeting agents involved in DNA damage responses (DDR). OReO (NCT03106987) evaluated PARP inhibitor retreatment in PARP inhibitor responders [23]. Various DDR inhibitors have been developed for anticancer therapy. PARP, ataxia-telangiectasia, Rad3-related (ATR), and WEE1 are the key components of different DDR pathways. PARP inhibitors are the best-studied class of DDR inhibitors. ATR inhibitors and WEE1 inhibitors are currently being investigated in clinical trials, especially in PARPi-resistant settings. In this review, the results of two phase II studies (EFFORT: WEE1 inhibitor, CAPRI: ATR inhibitor) and one phase III study (olaparib rechallenge with maintenance Olaparib [OReO]) were reviewed.

EFFORT showed that adavosertib (WEE1 inhibitor) alone and in combination with olaparib demonstrated efficacy in patients with PARP inhibitor-resistant ovarian cancer irrespective of BRCA status (ORR 29% from adavosertib+olaparib, ORR 23% from adavosertib alone) [20]. CAPRI evaluated the combination of a PARP inhibitor (olaparib) and ATR inhibitor (ceralasertib) in patients who were on a PARP inhibitor and experienced disease progression [22]. They showed that olaparib and ceralasertib were well-tolerated (no grade 4/5 toxicities) and showed clinical activity (ORR 46%) in platinum-sensitive patients who had progression with prior PARP inhibitors. However, there was no objective response in 12 platinum-resistant patients [21].

OReO/ENGOT Ov-38 is a randomized, double-blind trial, and the first phase III study to evaluate PARPi maintenance rechallenge. Patients enrolled in the BRCA1/2 mutated (BRCAm) (≥18 months [m] first-line [1 L] or ≥12 m 2 L + prior PARPi exposure [PPE]) and non-BRCAm (≥12 m 1 L or 6 m 2 L + PPE) cohorts were randomized (2:1; stratified by prior bevacizumab [yes vs. no] and prior lines of PBC [≤3 vs. ≥4]) to olaparib (O) tablets (300 mg bid [or 250 if 300 not previously tolerated]) or placebo (P) until progression. The primary endpoint was investigator-assessed PFS using Response Evaluation Criteria in Solid Tumours (RECIST) v1.1. OReO showed that, in a heavily pretreated ovarian cancer population, rechallenge with maintenance olaparib following response to platinum-based chemotherapy provided a statistically significant improvement in PFS compared with placebo, regardless of the BRCAm cohort (HR=0.57, 95% CI=0.37–0.87; nonBRCAm cohort: HR=0.43, 95% CI=0.26–0.71).

Future studies must investigate the following questions: 1) Who will benefit from PARP inhibitor retreatment? 2) Is the current "cut-off" of the previous PARP inhibitor duration the most appropriate? 3) Can we expect the same responses between women with progression prior to PARP inhibitors and those who progress after completion of the PARP inhibitor? 4) Are there several different effects if the PARP inhibitor is changed, for example, olaparib to olaparib/niraparib to olaparib?

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UTERINE CORPUS CANCER

The incidence and mortality of endometrial cancer have been increasing [24-26]. The mortality rate is projected to rise by 19% between 2014 and 2035, and to 9 deaths per 100,000 females by 2035 [27]. The majority of endometrial cancers are diagnosed in the early stages and have a favorable prognosis. Survivorship has been highlighted and many gynecologic oncologists have enquired about the optimal follow-up protocol for patients with endometrial cancer. Routine cytology is not conducted as part of pelvic examination during follow-up [28] and the role of ultrasound, tumor markers, or computed tomography (CT) scans has also been questioned. To date, evidence for the ideal follow-up intervals is lacking. The TOTEM study compared the OS of an intensive (INT) vs. minimalist (MIN) 5-year follow-up regimen for endometrial cancer [29].

Endometrial cancer with unfavorable biomarkers, such as p53 abnormality [30], HER2 overexpression [31] or recurrent endometrial cancer, are the main reasons for the increased mortality among patients with endometrial cancer. Additionally, the search for effective new treatment has been met with limited success [32,33]. Significant improvement in recurrence-free survival among patients with high-risk endometrial tumors with p53 abnormality is achieved by adding chemotherapy during and after adjuvant radiation [34], regardless of the histologic type. The NRG Oncology GY-026 study investigated the treatment of HER2 positive endometrial cancer by adding trastuzumab to paclitaxel and carboplatin and found that it increased OS [32]. The GY-026 study is an international three-arm, phase III study of women with primary stage I–IV, HER2-positive endometrial cancer. The study examined the role of mono (trastuzumab) or dual inhibition of HER2 (trastuzumab/pertuzumab) in addition to cytotoxic chemotherapy.

In addition to p53 abnormality and HER2 overexpression, patients with mismatch repair deficiency (dMMR) or microsatellite instability-high (MSI-H), DNA polymerase epsilon (POLE) mutation, and nonspecific molecular profile (NSMP) are also considered distinct subgroups of endometrial cancer [35]. In contrast to other solid tumors, endometrial cancer is believed to be an ideal target for immunotherapy because of the unique immune landscape of the tumors, including a higher tumor mutation burden. Moreover, dMMR or MSI-H are surrogate markers for high tumor mutations, and are considered a predictive marker for immunotherapy. Consequently, several clinical trials have focused on dMMR or MSI-H tumors treated with immune checkpoint inhibitors in solid tumors, including endometrial cancer [36]. Recently, the GARNET and KEYNOTE 775 [37] trials have shown promising results in patients with recurrent endometrial cancer and also dMMR or MSI-H.

1. TOTEM

In endometrial cancer, only a few randomized controlled trials have been conducted to assess the role of a reduced number of scheduled visits. The contribution of routine serum, cytological, or imaging follow-up in improving OS or quality of life has not been observed. The TOTEM study is a multicenter randomized controlled clinical trial involving two follow-up regimens with different test intensities for endometrial cancer [29]. Patients with surgically treated endometrial cancer and who were in complete clinical remission as confirmed by imaging and FIGO stages I-IV were included. The patients were stratified by centers and low- or high-risk of recurrence, and then randomized to INT or MIN hospital-based follow-up regimens. In total, 1847 patients were included in the final analysis between 2008 and 2018.

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Regarding follow-up protocols for the low-risk group defined as FIGO stage 1A and low-grade, one of the biggest differences between the MIN and INT arms was the lack of routine Pap smear and CT scans in the MIN arm. Routine CT scans were obtained in the 12th and 24th months after randomization during the 5-year follow-up in INT arm. The MIN arm was followed up every 6 months for 5 years. The INT arm was followed up every 4 months for the first 2 years, and every 6 months for the latter 3 years. For the high-risk group defined as FIGO stage IA with grade 3 or IB or above, no routine Pap smear, ultrasound, or tumor markers were planned in the MIN arm. However, routine CT scans in the 12th and 24th month after randomization were identical between the two arms. In all patients, unscheduled examinations were arranged if there were abnormal test results or clinical suspicion.

Overall compliance with the scheduled follow-up visits was 75.3% (INT 74.7% vs. MIN 75.9%). On the contrary, the mean number of recorded exams (laboratory or imaging) was significantly higher in the INT than in the MIN arms (9.7% vs. 2.9%, p<0.0001). After a median follow-up of 66 months, the 5-year OS rate was 91.3%, 90.6% in the INT arm and 91.9% in the MIN arm, respectively (HR=1.12, 95% CI=0.85–1.48, p=0.429). According to recurrence risk, the 5-year OS rate was 94.1% (INT) and 96.8% (MIN) (HR=1.48, 95% CI=0.92–2.37, p=0.104) in the low-risk group, and 85.3% (INT) and 84.7% (MIN) (HR=0.96, 95% CI=0.68–1.36, p=0.814) in the high-risk group. Health-related quality of life (HRQoL) data were available only for a subgroup of patients (50% at baseline) and did not differ between the arms. As a result, the INT follow-up protocol did not improve OS, even in high-risk patients, nor did it influence HRQoL. Based on these results, the authors suggested that the frequent routine use of imaging and laboratory examinations in these patients should be discouraged.

These findings may be applicable in patients with a low risk of recurrence. However, concerns remain for the high-risk patients. In the TOTEM study, patients with aggressive histology and/or advanced disease accounted for approximately 10% of the entire cohort, which appears to be too underpowered to draw any conclusions. Other limitations include the lack of molecular classification and incomplete data on lymphovascular space invasion and HRQoL. Of note, 80.4% of relapses in the low-risk group were diagnosed with clinical examination combined with other examinations, and 53.2% of relapses were identified with clinical examination and CT scan. This means that imaging and laboratory examinations still play a role in detecting recurrence, but should not be used for routine testing. There are three ongoing clinical trials (ENDCAT [38], ENSURE [39,40], and OPAL [41]) that are determining the optimal follow-up protocol for endometrial cancer. However, only patients with stage I or low/intermediate risk are eligible, which means that uncertainty for optimal follow-up in high-risk endometrial cancer may continue unless a new clinical trial for high-risk patients is developed.

2. GARNET

Dostarlimab is an anti-programmed cell death protein 1 (PD-1) antibody, and GARNET is a phase I single-arm study of dostarlimab monotherapy in expanded cohorts of multiple tumor types [42]. The endometrial cancer cohort (A1, A2) included patients with recurrent/advanced dMMR/MSI-H (A1) or MMR-proficient (pMMR)/microsatellite instability-stable (MSS) (A2) endometrial cancer who had ≤2 prior lines of treatment for recurrent or advanced disease, and progression after platinum doublet therapy. Patients received 500 mg Q3W of dostarlimab for the first four cycles, followed by 1,000 mg Q6W, until disease progression or discontinuation. The primary endpoints were ORR and DOR using RECIST. irRECIST was the secondary endpoint.

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In the interim analysis [43], 129 and 161 patients were enrolled in A1 and A2, respectively. pMMR/MSS patients had more aggressive histology (type II, 77.6% vs. 34.3%) and were more heavily pretreated (2 or above prior lines of chemotherapy, 53.8% vs. 36.1%) than dMMR/MSI-H patients. Radiation history was similar between the two groups. Based on RECIST, the ORRs in the dMMR/MSI-H and pMMR/MSS cohorts were 43.5% and 14.1%, respectively. Disease control rates in the dMMR/MSI-H and pMMR/MSS groups were 55.6% and 34.6%, respectively. The median DOR was not reached in either arm at the time of the analysis. The irORR was 44.8% in patients with dMMR/MSI-H and 14.4% in patients with pMMR/MSS. Overall, the efficacy results based on irRECIST were similar to those of RECIST. Most treatment-emergent adverse events were grade 1–2 (75.5%), with 5.5% discontinuation. The manageable toxicity profiles have been reported previously. In August 2021, the FDA approved dostarlimab for adult patients with dMMR recurrent or advanced solid tumors, including endometrial cancer.

Currently, dostarlimab is being evaluated in a phase III clinical trial (RUBY) in combination with standard chemotherapy in patients with recurrent or primary advanced endometrial cancer [44]. Another PD-1 inhibitor, pembrolizumab, is also being studied in a different phase III clinical trial (NRG GY-018) [45]. The NRG GY-018 study aimed to determine the efficacy of pembrolizumab in combination with paclitaxel and carboplatin in patients with advanced disease stages (measurable stage III or IVA, stage IVB, and recurrent endometrial cancer stratified by MMR status). A clinical trial with a PD-L1 inhibitor is also ongoing. The AtTEnd/ENGOT-en7 is a multicenter phase III double-blind randomized controlled trial of atezolizumab in combination with paclitaxel and carboplatin in women with advanced/recurrent endometrial cancer [46,47].

3. Keynote 775

The Keynote 775 study is a multicenter, open-label, randomized, phase III trial that compared the efficacy and safety of lenvatinib plus pembrolizumab versus treatment of physician's choice in patients with advanced, metastatic, or recurrent endometrial cancer after one prior platinum-based chemotherapy [37]. Patients were randomized to receive lenvatinib 20 mg orally QD plus pembrolizumab 200 mg IV Q3W or treatment of the physician's choice (doxorubicin, 60 mg/m^2 IV Q3W or paclitaxel, 80 mg/m^2 IV Q 3wk on/1wk off). Randomization was stratified by MMR status, and patients with pMMR tumors were further stratified by ECOG performance status, geographic region, and history of pelvic radiation. The primary endpoints were PFS and OS.

In total, 827 patients (697 with pMMR and 130 with dMMR) were randomly assigned to receive either lenvatinib plus pembrolizumab (411 patients) or chemotherapy (416 patients). The median PFS was longer in patients with lenvatinib plus pembrolizumab than with chemotherapy (pMMR population: 6.6 vs. 3.8 months, HR=0.60, 95% CI=0.50–0.72, p<0.001; dMMR population: 10.7 vs. 3.7 months, HR=0.36, 95% CI=0.23–0.57, p<0.001; overall: 7.2 vs. 3.8 months, HR=0.56, 95% CI=0.47–0.66, p<0.001). The median OS was better with lenvatinib plus pembrolizumab than with chemotherapy (pMMR population: 17.4 vs. 12.0 months, HR=0.68, 95% CI=0.56–0.84, p<0.001; dMMR population: not reached vs. 8.6 months, HR=0.37, 95% CI=0.11–0.62, p<0.001; overall: 18.3 vs. 11.4 months, HR=0.62, 95% CI=0.51–0.75, p<0.001). Adverse events of grade 3 or higher occurred in 88.9% of the patients who received lenvatinib plus pembrolizumab, and 72.7% of those who received chemotherapy.

This is the first clinical trial showing that a combination of immune checkpoint inhibitors and tyrosine kinase inhibitors led to superior survival rate compared to chemotherapy

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among patients with recurrent endometrial cancer with prior platinum-based chemotherapy, regardless of MMR status. The benefit appeared to be more prominent in patients with dMMR. In the dMMR subgroup in the Keynote 775 study, 40% of ORR with lenvatinib plus pembrolizumab was observed, which was significantly higher than the 12.3% observed in the chemotherapy group. KEYNOTE 146 [48] is a baseline study for KEYNOTE 775. It is a multinational, open-label, single-arm study of lenvatinib plus pembrolizumab in patients with selected solid tumors, including endometrial cancer. Among 118 patients with endometrial cancer in this study, 11 showed dMMR with a 63.6% ORR at the 24th week. Although this was a very promising result, further verification is warranted because of the study's small sample size. The clinically meaningful activity of lenvatinib plus pembrolizumab was confirmed in the KEYNOTE 775 study. The safety profile of dMMR patients was generally consistent with that of the full study population. Treatment-related adverse events of grade 3 or above were relatively high at 95.3%. Dose reduction, interruption, and discontinuation were observed in 64.1%, 71.9%, and 43.8% of dMMR patients, respectively. Hypothyroidism and hypertension were the most common symptoms observed. The combination of lenvatinib plus pembrolizumab was approved by the FDA only for patients with pMMR or MSS in July 2021. Currently, the combination of lenvatinib and pembrolizumab is being evaluated as a frontline treatment in patients with endometrial cancer. ENGOT-en9/LEAP-001 is a phase III study investigating first-line lenvatinib plus pembrolizumab versus chemotherapy in newly diagnosed patients with stage III, IV, or recurrent endometrial cancer [49,50].

In summary, the strong activity of dostarlimab, an anti PD-1 antibody, was observed in the GARNET study regardless of previous lines of therapy for patients with dMMR endometrial cancer. In the KEYNOTE 775 study, superior OS and PFS with lenvatinib plus pembrolizumab over chemotherapy were observed across all patient subgroups, including MMR status. Multiple studies on immune checkpoint inhibitors in the presence or absence of multiple kinases are ongoing, which may change the standard of treatment for endometrial cancer in the future.

PREVENTION OF GYNECOLOGIC CANCER

The major research results related to the prevention of gynecological cancer reported in 2021 can be summarized into two categories as follows:

1) Long-term follow-up results of the UKCTOCS study that evaluated the effectiveness of early ovarian cancer detection [51].
2) A TUBA trial compared salpingectomy with delayed oophorectomy and salpingo-oophorectomy in terms of quality of life in BRCA 1 and 2 pathogenic variant carriers [52].

1. UKCTOCS trial

The UKCTOCS trial was a randomized controlled trial to determine whether ovarian cancer population screening can reduce deaths due to ovarian cancer [51]. In this trial, 202,638 women from the general population were randomly assigned to two annual screening groups and a no screening group. One of the annual screening modalities was multimodal screening which consisted of longitudinal CA 125 and second-line transvaginal ultrasonography. The other was ultrasound screening. In the initial report of this trial in 2015, multimodal screening was associated with an increased number of patients diagnosed with stage I-II ovarian cancer, but neither of the two screening methods reduced the risk of ovarian cancer. In 2021, the long-term mortality effects of ovarian cancer screening in the UKCTOCS showed a reduction in stage III or IV disease incidence in the multimodal screening group. However,

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this reduction did not translate into a reduction in ovarian cancer mortality. Based on this study, general population screening for ovarian cancer is not recommended.

2. TUBA trial

Prophylactic bilateral salpingo-oophorectomy in BRCA 1 and 2 pathogenic mutation carriers has been shown to reduce the risk of ovarian cancer by 96%. Risk-reducing bilateral salpingo-oophorectomy (RRSO) is recommended for patients in their late 30s who are BRCA 1 pathogenic carriers, and patients in their early 40s who are BRCA 2 pathogenic carriers. However, in this case, early menopause is problematic and may lead to a decrease in the quality of life. Recently, based on the theory that high-grade serous carcinoma, the most common type of epithelial ovarian cancer, is of tubal origin, a preventive strategy of first performing only salpingectomy and later performing oophorectomy in BRCA 1 and 2 pathogenic carriers was proposed. Whether this strategy sufficiently reduces the risk of ovarian cancer has not yet been investigated in prospective trials. The TUBA trial was a prospective non-randomized trial that compared the menopause-related quality of life of risk-reducing salpingectomy with delayed oophorectomy and RRSO in BRCA 1 and 2 pathogenic carriers [52]. This study included 577 BRCA 1 and 2 pathogenic carriers. Of these, 394 underwent risk-reducing salpingectomy, and 154 had RRSO. The menopause-related quality of life was improved in patients who underwent risk-reducing salpingectomy compared to those who underwent RRSO regardless of hormone replacement therapy. Additional follow-up studies are required to determine the oncologic safety of risk-reducing salpingectomies.

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SUPPLEMENTARY MATERIAL

Table S1

Asian Society of Gynecologic Oncology (ASGO) Review Course 2021: major clinical advances in gynecologic cancer

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REFERENCES

1. Huang H, Feng YL, Wan T, Zhang YN, Cao XP, Huang YW, et al. Effectiveness of sequential chemoradiation vs concurrent chemoradiation or radiation alone in adjuvant treatment after hysterectomy for cervical cancer: the STARS phase 3 randomized clinical trial. JAMA Oncol 2021;7:361-9.
PUBMED | CROSSREF
2. Luke JJ, Rutkowski P, Queirolo P, Del Vecchio M, Mackiewicz J, Chiarion Sileni V, et al. Pembrolizumab versus placebo after complete resection of high-risk stage II melanoma: efficacy and safety results from the KEYNOTE-716 double-blind phase III trial. Ann Oncol 2021;32:S1314-5.
CROSSREF
3. 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
4. Tewari KS, Monk BJ, Vergote I, Miller Ade Melo AC, Kim HS, et al. EMPOWER-Cervical 1/GOG-3016/ENGOT-cx9: results of phase 3 trial of cemiplimab vs investigator's choice (IC) chemotherapy (chemo) in recurrent/metastatic (R/M) cervical carcinoma. Ann Oncol 2021;32:940-1.
CROSSREF
5. 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
6. Schmeler KM, Pareja R, Lopez Blanco A, Humberto Fregnani J, Lopes A, Perrotta M, et al. ConCerv: a prospective trial of conservative surgery for low-risk early-stage cervical cancer. Int J Gynecol Cancer 2021;31:1317-25.
PUBMED | CROSSREF
7. Peters WA 3rd, Liu PY, Barrett RJ 2nd, Stock RJ, Monk BJ, Berek JS, et al. Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. J Clin Oncol 2000;18:1606-13.
PUBMED | CROSSREF
8. Trifiletti DM, Swisher-McClure S, Showalter TN, Hegarty SE, Grover S. Postoperative chemoradiation therapy in high-risk cervical cancer: re-evaluating the findings of Gynecologic Oncology Group Study 109 in a large, population-based cohort. Int J Radiat Oncol Biol Phys 2015;93:1032-44.
PUBMED | CROSSREF
9. Sehouli J, Runnebaum IB, Fotopoulou C, Blohmer U, Belau A, Leber H, et al. A randomized phase III adjuvant study in high-risk cervical cancer: simultaneous radiochemotherapy with cisplatin (S-RC) versus systemic paclitaxel and carboplatin followed by percutaneous radiation (PC-R): a NOGGO-AGO Intergroup Study. Ann Oncol 2012;23:2259-64.
PUBMED | CROSSREF
10. Dueñas-González A, Zarbá JJ, Patel F, Alcedo JC, Beslija S, Casanova L, et al. Phase III, open-label, randomized study comparing concurrent gemcitabine plus cisplatin and radiation followed by adjuvant gemcitabine and cisplatin versus concurrent cisplatin and radiation in patients with stage IIB to IVA carcinoma of the cervix. J Clin Oncol 2011;29:1678-85.
PUBMED | CROSSREF
11. Coleman RL, Spirtos NM, Enserro D, Herzog TJ, Sabbatini P, Armstrong DK, et al. Secondary surgical cytoreduction for recurrent ovarian cancer. N Engl J Med 2019;381:1929-39.
PUBMED | CROSSREF
12. Harter P, Sehouli J, Vergote I, Ferron G, Reuss A, Meier W, et al. Randomized trial of cytoreductive surgery for relapsed ovarian cancer. N Engl J Med 2021;385:2123-31.
PUBMED | CROSSREF

13. Shi T, Zhu J, Feng Y, Tu D, Zhang Y, Zhang P, et al. Secondary cytoreduction followed by chemotherapy versus chemotherapy alone in platinum-sensitive relapsed ovarian cancer (SOC-1): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol 2021;22:439-49.
PUBMED | CROSSREF

14. Moore KN, Bookman M, Sehouli J, Miller A, Anderson C, Scambia G, et al. Atezolizumab, bevacizumab, and chemotherapy for newly diagnosed stage III or IV ovarian cancer: placebo-controlled randomized phase III trial (IMagyn050/GOG 3015/ENGOT-OV39). J Clin Oncol 2021;39:1842-55.
PUBMED | CROSSREF

15. Monk BJ, Colombo N, Oza AM, Fujiwara K, Birrer MJ, Randall L, et al. Chemotherapy with or without avelumab followed by avelumab maintenance versus chemotherapy alone in patients with previously untreated epithelial ovarian cancer (JAVELIN Ovarian 100): an open-label, randomised, phase 3 trial. Lancet Oncol 2021;22:1275-89.
PUBMED | CROSSREF

16. Harter P, Bidziński M, Colombo N, Floquet A, Pérez MJ, Kim JW, et al. DUO-O: A randomized phase III trial of durvalumab (durva) in combination with chemotherapy and bevacizumab (bev), followed by maintenance durva, bev and olaparib (olap), in newly diagnosed advanced ovarian cancer patients. J Clin Oncol 2019;37:TPS5598.
CROSSREF

17. Hardy-Bessard AC, Moore KN, Mirza MR, Asselain B, Redondo A, Pfisterer J, et al. ENGOT-OV44/FIRST study: A randomized, double-blind, adaptive, phase III study of platinum-based therapy with dostarlimab (TSR-042) + niraparib versus standard-of-care (SOC) platinum-based therapy as first-line treatment of stage 3/4 non-mucinous epithelial ovarian cancer (OC). J Clin Oncol 2019;37:TPS5600.
CROSSREF

18. Vergote I, Sehouli J, Salutari V, Zola P, Madry R, Wenham RM, et al. ENGOT-OV43/KEYLYNK-001: a phase III, randomized, double-blind, active- and placebo-controlled study of pembrolizumab plus chemotherapy with olaparib maintenance for first-line treatment of BRCA-nonmutated advanced epithelial ovarian cancer. J Clin Oncol 2019;37:TPS5603.
CROSSREF

19. Monk BJ, Coleman RL, Fujiwara K, Wilson MK, Oza AM, Oaknin A, et al. ATHENA (GOG-3020/ENGOT-ov45): a randomized, phase III trial to evaluate rucaparib as monotherapy (ATHENA-MONO) and rucaparib in combination with nivolumab (ATHENA-COMBO) as maintenance treatment following frontline platinum-based chemotherapy in ovarian cancer. Int J Gynecol Cancer 2021;31:1589-94.
PUBMED | CROSSREF

20. Westin SN, Coleman RL, Fellman BM, Yuan Y, Sood AK, Soliman PT, et al. EFFORT: EFficacy Of adavosertib in parp ResisTance: a randomized two-arm non-comparative phase II study of adavosertib with or without olaparib in women with PARP-resistant ovarian cancer. J Clin Oncol 2021;39:5505.
CROSSREF

21. Shah PD, Wethington SL, Pagan C, Latif N, Tanyi J, Martin LP, et al. Combination ATR and PARP Inhibitor (CAPRI): a phase 2 study of ceralasertib plus olaparib in patients with recurrent, platinum-resistant epithelial ovarian cancer. Gynecol Oncol 2021;163:246-53.
PUBMED | CROSSREF

22. Wethington SL, Shah PD, Martin LP, Tanyi JL, Latif NA, Morgan MA, et al. Combination of PARP and ATR inhibitors (olaparib and ceralasertib) shows clinical activity in acquired PARP inhibitor-resistant recurrent ovarian cancer. J Clin Oncol 2021;39:5516.
CROSSREF

23. Cortés J, Kim SB, Chung WP, Im SA, Park YH, Hegg R, et al. Trastuzumab deruxtecan (T-DXd) vs trastuzumab emtansine (T-DM1) in patients (Pts) with HER2+ metastatic breast cancer (mBC): results of the randomized phase III DESTINY-Breast03 study. Ann Oncol 2021;32:S1287-8.
CROSSREF

24. Lortet-Tieulent J, Ferlay J, Bray F, Jemal A. International patterns and trends in endometrial cancer incidence, 1978–2013. J Natl Cancer Inst 2018;110:354-61.
PUBMED | CROSSREF

25. National Cancer Institute. Cancer stat facts: uterine cancer [Internet]. Bethesda, MD: National Cancer Institute; 2021 [cited 2022 Jan 30]. Available from: https://seer.cancer.gov/statfacts/html/corp.html.

26. Cancer Research UK. Uterine cancer mortality statistics [Internet]. Oxford: Cancer Research UK; 2021 [cited 2022 Jan 30]. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/uterine-cancer/mortality#heading-Three.

27. Smittenaar CR, Petersen KA, Stewart K, Moitt N. Cancer incidence and mortality projections in the UK until 2035. Br J Cancer 2016;115:1147-55.
PUBMED | CROSSREF

28. Novetsky AP, Kuroki LM, Massad LS, Hagemann AR, Thaker PH, Powell MA, et al. The utility and management of vaginal cytology after treatment for endometrial cancer. Obstet Gynecol 2013;121:129-35.
PUBMED | CROSSREF
29. Zola P, Ciccone G, Pivano E, Fuso L, Peirano E, Cuonzo DD, et al. Intensive versus minimalist follow-up in patients treated for endometrial cancer: a multicentric randomized controlled trial (The TOTEM study—NCT00916708). J Clin Oncol 2021;39:5506.
CROSSREF
30. Garg K, Leitao MM Jr, Wynveen CA, Sica GL, Shia J, Shi W, et al. p53 overexpression in morphologically ambiguous endometrial carcinomas correlates with adverse clinical outcomes. Mod Pathol 2010;23:80-92.
PUBMED | CROSSREF
31. Diver EJ, Foster R, Rueda BR, Growdon WB. The therapeutic challenge of targeting HER2 in endometrial cancer. Oncologist 2015;20:1058-68.
PUBMED | CROSSREF
32. Fader AN, Roque DM, Siegel E, Buza N, Hui P, Abdelghany O, et al. Randomized phase II trial of carboplatin-paclitaxel compared with carboplatin-paclitaxel-trastuzumab in advanced (stage III–IV) or recurrent uterine serous carcinomas that overexpress Her2/Neu (NCT01367002): updated overall survival analysis. Clin Cancer Res 2020;26:3928-35.
PUBMED | CROSSREF
33. Ferriss JS, Erickson BK, Shih IM, Fader AN. Uterine serous carcinoma: key advances and novel treatment approaches. Int J Gynecol Cancer 2021;31:1165-74.
PUBMED | CROSSREF
34. León-Castillo A, de Boer SM, Powell ME, Mileshkin LR, Mackay HJ, Leary A, et al. Molecular classification of the PORTEC-3 trial for high-risk endometrial cancer: impact on prognosis and benefit from adjuvant therapy. J Clin Oncol 2020;38:3388-97.
PUBMED | CROSSREF
35. Kandoth C, Schultz N, Cherniack AD, Akbani R, Liu Y, Shen H, et al. Integrated genomic characterization of endometrial carcinoma. Nature 2013;497:67-73.
PUBMED | CROSSREF
36. Petrelli F, Ghidini M, Ghidini A, Tomasello G. Outcomes following immune checkpoint inhibitor treatment of patients with microsatellite instability-high cancers: a systematic review and meta-analysis. JAMA Oncol 2020;6:1068-71.
PUBMED | CROSSREF
37. Makker V, Colombo N, Casado Herráez A, Santin AD, Colomba E, Miller DS, et al. Lenvatinib plus pembrolizumab for advanced endometrial cancer. N Engl J Med 2022;386:437-48.
PUBMED | CROSSREF
38. Beaver K, Williamson S, Sutton C, Hollingworth W, Gardner A, Allton B, et al. Comparing hospital and telephone follow-up for patients treated for stage-I endometrial cancer (ENDCAT trial): a randomised, multicentre, non-inferiority trial. BJOG 2017;124:150-60.
PUBMED | CROSSREF
39. Ezendam NP, de Rooij BH, Kruitwagen RF, Creutzberg CL, van Loon I, Boll D, et al. ENdometrial cancer SURvivors' follow-up carE (ENSURE): less is more? Evaluating patient satisfaction and cost-effectiveness of a reduced follow-up schedule: study protocol of a randomized controlled trial. Trials 2018;19:227.
PUBMED | CROSSREF
40. U.S. National Library of Medicine. ENdometrial Cancer SURvivors' Follow-up carE (ENSURE): less is more? (ENSURE) [Internet]. Bethesda, MD: National Institutes of Health; 2019 [cited 2022 Jan 30]. Available from: https://clinicaltrials.gov/ct2/show/NCT02413606.
41. U.S. National Library of Medicine. Follow-up of endometrial cancer patients (OPAL) [Internet]. Bethesda, MD: National Institutes of Health; 2017 [cited 2022 Jan 30]. Available from: https://clinicaltrials.gov/ct2/show/NCT01853865.
42. U.S. National Library of Medicine. Study of TSR-042, an anti-programmed cell death-1 receptor (PD-1) monoclonal antibody, in participants with advanced solid tumors (GARNET) [Internet]. Bethesda, MD: National Institutes of Health; 2022 [cited 2022 Jan 30]. Available from: https://clinicaltrials.gov/ct2/show/NCT02715284.
43. Oaknin A, Gilbert L, Tinker AV, Brown J, Mathews C, Press J, et al. Safety and antitumor activity of dostarlimab in patients with advanced or recurrent DNA mismatch repair deficient/microsatellite instability-high (dMMR/MSI-H) or proficient/stable (MMRp/MSS) endometrial cancer: interim results from GARNET-a phase I, single-arm study. J Immunother Cancer 2022;10:10.
PUBMED | CROSSREF
44. U.S. National Library of Medicine. 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 Institutes of Health; 2021 [cited 2022 Jan 30]. Available from: https://clinicaltrials.gov/ct2/show/NCT03981796.

45. U.S. National Library of Medicine. Testing the addition of the immunotherapy drug pembrolizumab to the usual chemotherapy treatment (paclitaxel and carboplatin) in stage III-IV or recurrent endometrial cancer [Internet]. Bethesda, MD: National Institutes of Health; 2022 [cited 2022 Jan 30]. Available from: https://clinicaltrials.gov/ct2/show/NCT03914612.
46. U.S. National Library of Medicine. Atezolizumab trial in endometrial cancer - AtTEnd (AtTEnd) [Internet]. Bethesda, MD: National Institutes of Health; 2022 [cited 2022 Jan 30]. Available from: https://clinicaltrials.gov/ct2/show/NCT03603184.
47. Colombo N, Barretina-Ginesta MP, Beale PJ, Harano K, Hudson E, Marmé F, et al. AtTEnd/ENGOT-en7: a multicenter phase III double-blind randomized controlled trial of atezolizumab in combination with paclitaxel and carboplatin in women with advanced/recurrent endometrial cancer. J Clin Oncol 2019;37:37. CROSSREF
48. Makker V, Taylor MH, Aghajanian C, Oaknin A, Mier J, Cohn AL, et al. Lenvatinib plus pembrolizumab in patients with advanced endometrial cancer. J Clin Oncol 2020;38:2981-92. PUBMED | CROSSREF
49. Marth C, Vulsteke C, Pérez MJ, Makker V, Braicu EI, McNeish IA, et al. ENGOT-en9/LEAP-001: a phase III study of first-line pembrolizumab plus lenvatinib versus chemotherapy in advanced or recurrent endometrial cancer. J Clin Oncol 2020;38:38. CROSSREF
50. U.S. National Library of Medicine. Pembrolizumab (MK-3475) plus lenvatinib (E7080/MK-7902) versus chemotherapy for endometrial carcinoma (ENGOT-en9 / MK-7902-001) (LEAP-001) [Internet]. Bethesda, MD: National Institutes of Health; 2021 [cited 2022 Jan 30]. Available from: https://clinicaltrials.gov/ct2/show/NCT03884101.
51. Menon U, Gentry-Maharaj A, Burnell M, Singh N, Ryan A, Karpinskyj C, et al. Ovarian cancer population screening and mortality after long-term follow-up in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial. Lancet 2021;397:2182-93. PUBMED | CROSSREF
52. Steenbeek MP, Harmsen MG, Hoogerbrugge N, de Jong MA, Maas AH, Prins JB, et al. Association of salpingectomy with delayed oophorectomy versus salpingo-oophorectomy with quality of life in BRCA1/2 pathogenic variant carriers: a nonrandomized controlled trial. JAMA Oncol 2021;7:1203-12. PUBMED | CROSSREF