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Major clinical research advances in gynecologic cancer in 2020

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ABSTRACT

In 2020 series, we summarized the major clinical research advances in gynecologic oncology with providing representative figures of the most influential study for 1 of each 3 gynecologic cancers: cervix, ovary, and uterine corpus. Review for cervical cancer covered targeted agents and immune checkpoint inhibitors, adjuvant radiation therapy or concurrent/sequential chemoradiation therapy after radical hysterectomy in early cervical cancer, radical surgery in early cervical cancer; and prevention and screening. Ovarian cancer research included studies of various combinations of poly (ADP-ribose) polymerase inhibitors with chemotherapy, immune checkpoint inhibitors, and/or vascular endothelial growth factor inhibitors according to the clinical setting. For uterine corpus cancer, molecular classification upon which the decision of adjuvant treatments might be based, World Health Organization recommendation of 2-tier grading system (low grade vs. high grade), sentinel lymph node assessment and ovarian preservation in clinically early-stage endometrial cancer were reviewed. Molecular targeted agents including immune checkpoint inhibitors which showed promising anti-tumor activities in advanced/recurrent endometrial cancer were also included in this review.

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

INTRODUCTION

The major advances in clinical research for cervical cancer during 2020 can be summarized into 4 parts: 1) targeted agents and immune checkpoint inhibitors; 2) adjuvant radiation therapy (RT) or concurrent chemoradiation therapy (CCRT) after radical hysterectomy in early cervical cancer; 3) radical surgery in early cervical cancer; and 4) prevention and screening for cervical cancer.

In ovarian cancer, poly (ADP-ribose) polymerase inhibitors (PARPi) have continued to dominate the landscape of practice-changing randomized clinical trials after 4 phase III trials.
Major advances in gynecologic cancer

Table 1. Summary of clinical trials for ovarian cancer

| Category                        | Phase III                     | Phase II                              | Ongoing                |
|---------------------------------|-------------------------------|---------------------------------------|------------------------|
| First-line and maintenance      | JAVELIN100 (CTx+avelumab)      | DUO-O (CTx+bev+ola+durvalumab)        |                        |
|                                 | IMagynO-50 (CTx+bev+atezolimumab) | FIRST (CTx+nira+dostarlimab+bev)     |                        |
|                                 |                               | KEYLINK-001 (CTx+ola+pembrolizumab+bev) |                        |
| First-line maintenance          | PAOLA-1 ancillary (ola+bev)   | OVARIO (nira+bev)                     | ATHENA (rucaparib+nivolumab) |
| Neoadjuvant therapy             |                               |                                       |                        |
| Platinum-sensitive recurrence   | NRG-GY004 (ola+cediranib)     | MEDIOLA (ola+durvalumab+bev)          | ICON9 (ola+cediranib)  |
|                                 | SOLO3 (ola)*                   |                                       |                        |
| Platinum-resistant recurrence   | SOLO2 ancillary (ola)         | NCT02595892 (berzosertib+gemcitabine) | NRG-GY005 (ola+cediranib) |
| PARPi-resistance                |                               | EVOLVE (ola+cediranib)                |                        |

CTx, chemotherapy; Bev, bevacizumab; nira, niraparib; ola, olaparib; PARPi, poly (ADP-ribose) polymerase inhibitors.

*Positive results.

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

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In this review, for the first time, we picked one of the most influential studies from ovary and uterine corpus cancer, for representative figures.

UTERINE CERVIX

1. Targeted agents and immune checkpoint inhibitors

Phase I/II studies evaluating several types of anti-PD-1, anti-PD-L1, and anti-CTLA-4 monoclonal antibodies in recurrent and/or metastatic cervical cancer have been reported. Results of evaluating the immune checkpoint inhibitor alone or in combination with a cytotoxic agent or other targeted agents or dual immune checkpoint inhibitors have been reported.

Preliminary results of balstilimab (anti-PD-1) alone and balstilimab/zalifrelimab (anti-CTLA-4) combination therapy in recurrent and metastatic cervical cancer have been reported in ESMO annual meeting [5]. The authors presented data from 2 phase II trials, of single-agent balstilimab (NCT03104699) and in combination with zalifrelimab (NCT03495882) evaluating PARPi in the front-line setting have been published (SOLO-1, PRIMA, VELIA, and PAOLA-1) [1-4]. Major clinical researches on combination of PARPi with chemotherapy (CTx), immune checkpoint inhibitors, and/or vascular endothelial growth factor (VEGF) inhibitors were reviewed according to the clinical setting (Table 1).

In endometrial cancer, there have been remarkable research advances which will apply in practice in the near future. Molecular classification was incorporated into one of histologic subtypes of endometrial cancer and gynecologic oncologists should choose the adjuvant treatments based on not only the conventional clinicopathological factors but also this information. In addition to this molecular classification, 2 tier grading system (low grade vs. high grade) of endometrioid adenocarcinoma of endometrium was recommended by the World Health Organization (WHO). In terms of surgical management of endometrial cancer, sentinel lymph node assessment was found to be feasible in clinical stage I endometrial cancer even with high grade and ovarian preservation seems to be safe particularly in clinically early-stage endometrial cancer. In advanced/recurrent endometrial cancer, molecular target agents including immune checkpoint inhibitors showed promising anti-tumor activities in various clinical situations for which Food and Drug Administration (FDA) has approved for its use. Lastly, increased physical activity in endometrial cancer patients was found to be associated with increased survivals in a cohort study.

In this review, for the first time, we picked one of the most influential studies from ovary and uterine corpus cancer, for representative figures.

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in recurrent and metastatic cervical cancer [5]. This was the largest study using immune checkpoint inhibitors in cervical cancer [5]. The objective response rates (ORRs) were 14% and 22% for balstilimab alone and balstilimab/zalifrelimab combination therapy, respectively [5]. Response rates were higher for patients with PD-L1 expression and squamous cell carcinoma [5]. However, responses were also seen in adenocarcinoma patients without PD-L1 expression [5]. Considering that pembrolizumab was approved by FDA for fast tract approval with an ORR of 14% in patients with PD-L1 expression, these results are considered a significant efficacy.

Results of phase I/II trial using tisotumab vedotin in previously treated recurrent or metastatic cervical cancer was reported [6]. Tisotumab vedotin is an antibody-drug conjugate directed to tissue factor. About 51% of patients previously received 2 or more lines of treatment, and 67% of patients received prior bevacizumab + doublet CTx [6]. The ORR was 24% and complete remission was observed in 7% of patients with a manageable safety profile [6].

2. Adjuvant radiation or CCRT after radical hysterectomy in early cervical cancer

The results of a phase III randomized controlled trial comparing standard 4-field pelvic RT with pelvic intensity modulated RT (IMRT) in patients with cervical cancer requiring postoperative RT were reported [7]. The primary endpoint of this study was acute gastrointestinal toxicity reported by patients using a validated patient-reported outcome instrument. Patient-reported adverse events were lower after IMRT compared to standard RT. However, physician-reported adverse events did not differ between the 2 treatment groups. This study showed that clinicians underreported symptomatic gastrointestinal adverse events compared with patients in this disease setting. Thus, the authors concluded that patient-reported symptomatic adverse events are more important to access [7].

A phase III trial comparing sequential chemoradiation vs. radiation alone or concurrent chemoradiation in adjuvant treatment after radical hysterectomy for stage IB1–IIA2 cervical cancer (STARS study, NCT00806117) has been reported in ASCO annual meeting [8,9]. In the intention-to-treat population, sequential chemoradiation was associated with a higher 3-year disease-free survival than radiation alone (90% vs. 82%; hazard ratio [HR]=0.52; 95% confidence interval [CI]=0.35–0.76) and concurrent chemoradiation (90% vs. 85%; HR=0.65; 95% CI=0.44–0.96). Sequential chemoradiation was also associated with a higher 5-year overall survival (OS) than radiation alone (92% vs. 88%; HR=0.58; 95% CI=0.35–0.95). However, there were no differences in disease-free and overall survival between concurrent chemoradiation or radiation alone.

3. Radical surgery in early cervical cancer

After the publication of the LACC trial results, the quality-of-life outcome of the LACC trial was reported separately [10]. In this study, postoperative quality of life was similar between open and minimally invasive radical hysterectomy groups [10]. In addition, a retrospective study and a meta-analysis which comparing open vs. minimally invasive radical hysterectomy were published. The outcomes were similar with those of LACC trial [11,12].

One of the reasons for the poor oncologic outcome of the minimally invasive radical hysterectomy group in the LACC trial was the failure to complete the learning curve for minimally invasive radical hysterectomy. An observational cohort study was reported to show
the effect of the completion of a learning curve on postoperative survival outcomes in robotic radical hysterectomy [13]. In this study, the learning phase of robotic radical hysterectomy in early-stage cervical cancer was at least 61 procedures, with higher survival rates in the women treated thereafter. Another reason for the poor oncologic outcome in the minimally invasive radical hysterectomy group in the LACC trial was the absence of a maneuver to prevent intraperitoneal seeding and tumor injury caused by uterine manipulation. A European, multicenter, retrospective, observational cohort study (SUCCOR study) investigated the association between protective surgical maneuver and the risk of relapse after minimally invasive radical hysterectomy [14]. In this study, avoiding the uterine manipulator and using maneuvers to avoid tumor spread at the time of colpotomy in minimally invasive surgery was associated with similar outcomes to open surgery [14].

An international, multicenter, retrospective cohort study evaluating whether the performance of radical hysterectomy improves oncological outcome in patients with intraoperative detection of lymph node involvement compared to CCRT (ABRAX study) was reported [15]. There were no differences in disease-free and overall survival between abandoned vs. completed radical hysterectomy followed by definitive CCRT in patients with intraoperative detection of lymph node positivity [15].

**4. Prevention and screening for cervical cancer**
While many studies have shown that human papillomavirus (HPV) vaccines reduce the risk of cervical intraepithelial neoplasia, few studies have shown whether it reduces the risk of invasive cervical cancer. Research has been reported that HPV vaccination reduces the incidence of cervical cancer at the population level [16]. In this study, the incidence rate ratio of the vaccinated population was 0.37 (95% CI=0.21–0.57) compared with the unvaccinated population after adjusting for all covariates. The incidence rate ratio was 0.12 (95% CI=0.00–0.34) for women vaccinated before the age of 17 years and 0.47 (95% CI=0.27–0.75) for women vaccinated between 17 to 30 years [16].

**OVARY**

**1. First-line therapy and maintenance**
The phase III JAVELIN Ovarian 100 trial [17] evaluated avelumab (PD-L1 inhibitor) in combination with and/or following CTx vs. CTx alone in patients with newly diagnosed stage III–IV epithelial ovarian cancer. HR for progression-free survival (PFS) in avelumab arms vs. CTx alone group were 1.43 (95% CI=1.051–1.946) for CTx → avelumab (n=332) and 1.14 (95% CI=0.832–1.565) for CTx+avelumab → avelumab (n=331). Median PFS was 16.8 months (95% CI=13.5–NE) for CTx → avelumab, 18.1 months (95% CI=14.8–NE) for CTx+ avelumab → avelumab, and NE (95% CI=18.2–NE) for control group (n=335). In both avelumab arms, PFS was not improved vs. control, prespecified futility boundaries were crossed, and the trial was stopped.

The phase III IMagyn050/GOG 3015/ENGOT-Ov39 trial assessed the bevacizumab-containing therapy with or without atezolizumab (PD-L1 inhibitor) for newly diagnosed stage III-IV ovarian cancer [18]. Eligible patients were randomized 1:1 to atezolizumab 1,200 mg or placebo cycles 1–22, with paclitaxel 175 mg/m² + carboplatin AUC6 cycles 1–6 + bevacizumab 15 mg/kg cycles 2–22 with 3 weeks interval. There was no statistically significant PFS improvement in either, the intention to treat population (median 18.4 months with placebo
vs. 19.5 months with atezolizumab; HR=0.92; 95% CI=0.79–1.07) or the PD-L1+ population
(median 18.5 vs. 20.8 months; HR=0.80; 95% CI=0.65–0.99).

As in these 2 studies, the results of the addition PD-L1 inhibitors are disappointing, several
trials including DOU-O [19], FIRST/ENGOT-Ov44 [20], KEYLYNK-001/ENGOT-Ov43 [21]
investigated that first-line therapy of CTx in combination with immune checkpoint inhibitors,
PARPi and/or bevacizumab and maintenance treatment in newly diagnosed advanced ovarian
cancer patients are ongoing.

2. First-line maintenance
The phase II OVARIO trial [22] evaluated the maintenance therapy of niraparib with
bevacizumab in advanced ovarian cancer following first-line platinum-based CTx with
bevacizumab. All patients (n=105) underwent tissue testing for homologous recombination
deficiency (HRD). Bevacizumab was injected 15 mg/kg every 3 weeks up to 15 months,
and niraparib, 300 or 200 mg once daily was started within 12 weeks of completing first-
line treatment and continued for 3 years or until progression. Preliminary data suggest
that niraparib maintenance in combination with bevacizumab is efficacious in the overall
population and across all biomarker subgroups (75% of patients remained progression free
at 12-months analysis), consistent with the continuum of clinical benefit observed with
niraparib single maintenance therapy in the PRIMA trial [2].

The phase III PAOLA-1/ENGOT-ov25 trial evaluated the addition of maintenance olaparib to
bevacizumab in women with advanced ovarian cancer who were in response after first-line
platinum-based CTx with bevacizumab [4]. Results of sub-group analysis were presented
at IGCS 2020 [23]. The median PFS increased from 14.7 months with bevacizumab alone to
20.3 months with the combination maintenance of olaparib plus bevacizumab (HR=0.60;
95% CI=0.49–0.74) in higher-risk patients (International Federation of Gynaecology and
Obstetrics [FIGO] stage III with residual tumor at upfront surgery or neoadjuvant CTx, or
FIGO stage IV; n=266) and from 22.9 months to 39.3 months (HR=0.46; 95% CI=0.30–0.72)
in lower-risk group (FIGO stage III with complete resection at upfront surgery; n=121). The
effect of olaparib plus bevacizumab provided the greatest PFS benefit over placebo plus
bevacizumab in higher- and lower-risk patients who were HRD positive or who had a tumor
BRCA mutation.

In patients newly diagnosed with advanced OC, the 5-year follow up data from the SOLO
1 trial [24] demonstrated continued benefit derived from 2 years of maintenance olaparib
in patients with BRCA mutation: 48.3% of those who received olaparib (n=260) remained
progression free at 5 years, compared with 20.5% of patients who received placebo (n=131).
The median PFS was 56.0 months in olaparib maintenance group and 13.8 months in placebo
(HR=0.33; 95% CI=0.25–0.43). Almost half of patients in complete response (CR) after first-
line CTx remained free from relapse 5 years later.

3. Platinum-sensitive recurrence
A phase III NRG-GY004 study compared olaparib monotherapy or the combination of
cediranib (VEGF inhibitor) and olaparib to standard platinum-based CTx in platinum
sensitive recurrent ovarian cancer [25]. The HR for PFS was 0.856 (95% CI=0.66–1.11;
p=0.077) between cediranib plus olaparib (n=189) and standard of care (SOC) (n=187) and
1.20 (95% CI=0.93–1.54) between olaparib (n=189) and SOC, with median PFS of 10.3, 8.2,
and 10.4 months for SOC, olaparib, and cediranib plus olaparib, respectively. Response rates
were 71.3% (SOC), 52.4% (olaparib), and 69.4% (cediranib plus olaparib). Patients receiving cediranib plus olaparib (vs. SOC) had more frequent ≥ grade 3 adverse events including gastrointestinal (30.1% vs. 8.4%), hypertension (31.7% vs. 1.8%), and fatigue (17.5% vs. 1.8%). Cediranib plus olaparib demonstrated similar activity to SOC in recurrent platinum sensitive ovarian cancer, however, did not meet the primary endpoint of improved PFS.

The phase II MEDIOLA study \[26\] evaluated combining of olaparib plus durvalumab (doublet cohort, n=32) and olaparib, durvalumab plus bevacizumab (triplet cohort, n=31) in patients with non-germline \textit{BRCA}-mutated platinum sensitive relapsed ovarian cancer. The triplet combination therapy showed promising efficacy for women with germline \textit{BRCA} wild type platinum sensitive recurrent ovarian cancer, with 77.4% (90% CI=61.7–88.9) disease control rate at 24 weeks (vs. 28.1% [90% CI=15.5–43.9] in doublet cohort) and median PFS of 14.7 months (95% CI=10.0–18.1) compared with 5.5 months (95% CI=3.6–7.5) in doublet cohort. The most common grade ≥3 adverse events in doublet cohort were anemia (22%), lipase increased (6%) and anemia (13%), hypertension (13%), fatigue (6%) in triplet cohort. The combination of olaparib, durvalumab and bevacizumab showed promising efficacy as treatment in the absence of CTx for women with germline \textit{BRCA} wild type platinum-sensitive relapsed advanced ovarian cancer.

A phase III SOLO3 trial evaluated the efficacy of olaparib vs. non-platinum CTx (pegylated liposomal doxorubicin, paclitaxel, gemcitabine, or topotecan) in patients with germline \textit{BRCA}-mutated platinum-sensitive relapsed ovarian cancer who had received at least 2 prior lines of platinum-based CTx \[27\]. The primary end point was ORR assessed by blinded independent central review. ORR and PFS were significantly higher with olaparib (n=151) than with non-platinum CTx (n=72) (72.2% vs. 51.4%; odds ratio [OR]=2.53; 95% CI=1.40–4.58; p=0.002 and 13.4 vs. 9.2 months; HR=0.62; 95% CI=0.43–0.91; p=0.013, respectively). According to these results, “CTx -free” treatment with olaparib is a reasonable option for women with a \textit{BRCA} mutation and platinum-sensitive relapsed ovarian cancer.

### 4. Platinum-resistant recurrence

A phase II trial has shown significantly prolonged PFS with the addition of the ATR kinase inhibitor ‘berzosertib’ to gemcitabine in women with recurrent platinum-resistant high-grade serous ovarian cancer \[28\]. Eighty-eight patients were assessed for eligibility, of whom 70 were randomly assigned to treatment with gemcitabine alone (36 patients) or gemcitabine plus berzosertib (34 patients). Gemcitabine (1,000 mg/m²) was injected on day 1 and day 8, or gemcitabine plus berzosertib (210 mg/m²) was intravenously injected on day 2 and day 9 of a 21-day cycle until disease progression or intolerable toxicity. Median PFS was 22.9 weeks (90% CI=17.9–72.0) in the berzosertib/gemcitabine group vs. 14.7 weeks (90% CI=0.7–36.7) in the gemcitabine group (HR=0.57; 90% CI=0.33–0.98; p=0.044). Median PFS was 27.7 vs. 9.0 weeks (HR=0.29; p=0.0087) among patients with a platinum-free interval of <3 months. The benefit of the combination was greatest in patients with a platinum-free interval of <3 months. The most common treatment-related grade ≥3 adverse events were decreased neutrophil count (39% in the gemcitabine group vs. 47% in the combination group) and decreased platelet count (6% vs. 24%). This study shows a benefit of adding berzosertib to gemcitabine in platinum-resistant high-grade serous ovarian cancer.

### 5. PARPi-resistance

The phase II EVOLVE trial investigated combining cediranib with olaparib for ovarian cancer after progression on a PARPi \[29\]. Women with high-grade serous ovarian cancer were...
enrolled into 1 of 3 cohorts: platinum sensitive after PARPi; platinum resistant after PARPi; or progression on standard CTx after progression on PARPi. Among 34 heavily pretreated patients, objective responses were observed in 0 of 11 (0%) platinum-sensitive patients, 2 of 10 (20%) platinum-resistant patients, and 1 of 13 (8%) in the progressed patients. Sixteen-week PFS rates were 55%, 50%, and 39%, respectively. The most common grade ≥3 adverse events were diarrhea (12%) and anemia (9%). Acquired genomic alterations at PARPi progression were reversion mutations in BRCA1, BRCA2, or RAD51B (19%); CCNE1 amplification (16%); and ABCB1 upregulation (15%). The activity of cediranib–olaparib varied according to the PARPi resistance mechanism.

The SOLO2/ENGOT Ov-21 ancillary study [30] demonstrated the efficacy of subsequent CTx for patients with BRCA mutated platinum-sensitive recurrent epithelial ovarian cancer progressing on olaparib or placebo. A post-hoc analysis of time to second progression (TTSP) calculated from the date of progression after olaparib maintenance to next progression or death as a surrogate of first post-olaparib treatment PFS. TTSP was longer in the placebo (n=69) compared to the olaparib (n=78) arm: 11.1 vs. 7.0 months (HR=1.93; 95% CI=1.35–2.76). TTSP was 14.3 vs. 7.0 months with platinum-based CTx and 8.3 vs. 5.5 months with non-platinum CTx in the placebo and olaparib arm respectively. In this SOLO2 post-hoc comparison, some degree of resistance to standard subsequent CTx is noted in the olaparib arm. The best post-olaparib management should be studied in prospective manner.

6. Secondary cytoreductive surgery (2nd CRS) in platinum-sensitive recurrent ovarian cancer

Two randomized phase III trials in platinum-sensitive recurrent ovarian cancer affirmed the role of 2nd CRS. The AGO DESKTOP III/ENGOT-Ov20 trial [31] enrolled 407 patients with platinum-sensitive recurrent ovarian cancer and a positive AGO score as defined by an Eastern Cooperative Oncology Group status of 0, an ascites volume of ≤500 mL and complete resection (R0) at initial CRS who were then randomized to receive either second-line CTx or 2nd CRS followed by CTx. 2nd CRS led to a significant improvement in OS (53.7 months with surgery and 46.2 months without surgery; HR=0.76; 95% CI=0.59–0.97; p=0.03) exclusively among those patients in whom performed R0 2nd CRS (Fig. 1). For subgroup analysis of this study, patients were divided into 3 subgroups: 1) control arm, 2) surgical arm without R0, and 3) surgical arm with R0 [32]. Time to first subsequent therapy (TFST) in the surgical arm was significantly longer compared to the non-surgical arm (21.3 vs. 16.0 months; p<0.001). TFST in group 1 vs. 2 vs. 3 was 16.0 vs. 16.1 vs. 26.3 months, respectively (HR=0.53; 95% CI=0.42–0.68; p<0.001). TFST is prolonged substantially by R0.

The SOC1/SGOG-Ov2 trial [33] used the iMODEL score [34] combined with PET-CT to select patients predicted to undergo R0 surgery, and demonstrated that 2nd CRS followed by CTx improved PFS relative to the PFS after CTx alone (17.4 vs. 11.9 months; HR=0.58; 95% CI=0.45–0.74; p<0.001).

These results are deviated from those of an earlier randomized phase 3 trial, GOG-213 [35], which did not find that 2nd CRS followed by CTx improved OS relative to OS after CTx alone (HR=1.29; 95% CI=0.97–1.72; p=0.08). Together these trials suggest that clinical benefit from 2nd CRS is dependent on achievement of R0 and that the effect may be alleviated by systemic therapy such as bevacizumab (84% use in GOG-213); they also demonstrate the value of implementing careful patient-selection tools, such as the AGO score (DESKTOP III) and iMODEL (SOC1/SGOG-Ov2) (Table 2).
Table 2. Comparison of GOG-213, AGO DESKTOP-III, and SOC-1/SOGG-Ov2 trials

| Variable                        | GOG-213 [35] | AGO DESKTOP-III [31] | SOC-1/SOGG-Ov2 [33] |
|--------------------------------|-------------|---------------------|---------------------|
| Age (yr)                        | 57          | 61                  | 54                  |
| Study design                    | Phase 3 randomized | Phase 3 randomized | Phase 3 randomized |
| Enrolled patients (period)      | 485 (2007–2017) | 407 (2010–2014)     | 357 (2012–2019)     |
| Selection criteria              | TF1 >6 mo   | TF1 >6 mo, AGO score | TF1 >6 mo, iMODEL + PET-CT |
| Median PFI (mo)                 | 19.7        | 19.9                | 16.1                |
| Cross-over to surgery (control violation) | 2%    | 4%                  | 6%                  |
| Complete resection at 2nd CRS   | 67%         | 75%                 | 77%                 |
| Mortality                       | 0.4% (30-day) | 0.5% (90-day)      | 0% (60-day)         |
| Subsequent surgery in control arm after relapse | NA      | 11%                 | 37%                 |
| 2nd line bevacizumab/PARPi use  | 84%/NA      | 23%/<5%             | 1%/10%              |
| Median PFS, surgery vs. no surgery (mo) | 18.9 vs. 16.2 (HR=0.82; 95% CI=0.66–1.01) | 18.4 vs. 14.0 (HR=0.66; 95% CI=0.54–0.82; p=0.001) | 17.4 vs. 11.9 (HR=0.58; 95% CI=0.45–0.74; p=0.001) |
| Median OS, surgery vs. no surgery (mo) | 50.6 vs. 64.7 (HR=1.29; 95% CI=0.97–1.72; p=0.08) | 53.7 vs. 46.2 (HR=0.76; 95% CI=0.59–0.97; p=0.03) | Data maturing |

AGO, Arbeitsgemeinschaft Gynäkologische Onkologie; CI, confidence interval; HR, hazard ratio; NA, non-available; OS, overall survival; PARPi, poly(ADP-ribose) polymerase inhibitors; PET-CT, positron emission tomography-computed tomography; PFI, progression-free interval; PFS, progression-free survival; 2nd CRS, secondary cytoreductive surgery; TF1, treatment-free interval.

*AGO score (Eastern Cooperative Oncology Group performance status 0, ascites ≤500 mL, and complete resection at initial surgery); †iMODEL [34].
1. New molecular classification and binary grading

Endometrial cancer usually shows better prognosis compared to other gynecologic malignancies mainly due to its early presentation to clinic [36]. Nevertheless, recurrence rate significantly increases in advanced disease or early disease with high-risk features for recurrence. To reduce the rate of recurrence, various adjuvant treatments have been tested and validated through clinical trials. However, one of limitations in providing these adjuvant therapies, risk stratification to select adjuvant therapy was solely based on pathological findings including grade, lympho-vascular invasion, and cervical stromal invasions, etc. which may be affected by interobserver variabilities [37]. More on that, there is no universal consensus on which pathological definition is optimized for stratifying risk factors for recurrence in endometrial cancer, although low, intermediate, intermediate high, and high-risk groups are generally introduced to use in practice [36].

The Cancer Genome Atlas introduced the molecular classification in endometrial cancer which demonstrated the prominent prognostic role [38]. Four molecular subgroups including p53-abnormal (p53abn), POLE-ultramutated (POLEmut), mismatch repair-deficient (MMRd), and no specific molecular profile (NSMP) showed distinct prognostic differences providing a significant impact on the treatment of endometrial cancer. Afterwards it has validated through clinical studies that the integration of the molecular classification with conventional clinicopathological findings has improved prognostic accuracy in non-selected cohort or patients with intermediate risk factors [39,40] but not in exclusively high-risk patients. Adjuvant chemoradiotherapy vs. radiotherapy alone in women with high-risk endometrial cancer (PORTEC-3) is a randomized clinical trial investigating the benefit of combined adjuvant CCRT vs. pelvic RT alone for women with high-risk endometrial cancer [41] and it showed a significant benefit in survivals with CCRT over RT alone. Using tissue samples of PORTEC-3, León-Castillo et al. [42] recently reported the prognostic relevance of the molecular classification and sought to find the molecular subgroup which benefit from adjuvant CCRT in this high-risk cohort (Fig. 2).

From the view of prognostic value of the molecular classification, patients with p53abn had worst prognosis in contrast to the best survival outcomes of patients with POLEmut, otherwise, patients with MMRd or NSMP showed intermediate clinical outcomes. In terms of predictive role of these molecules, patients with p53abn had the highest benefit from CCRT with an absolute benefit of over 20% for 5-year survivals. Patients with POLEmut or MMRd showed no benefit and a trend toward benefit from CCRT was observed in patients with NSMP partly due to small number of patients which deemed to be not fully powered to detect differences. The PORTEC-4a trial comparing standard adjuvant brachytherapy in women with intermediate-risk endometrial cancer with individualized adjuvant treatment on the basis of the patients’ integrated molecular profile is ongoing [43] and CTNNB1mut may become an additional molecular subgroup in NSMP patients according to the results. Although, there is still lack of evidence about the robust or cost-effective methods of detecting mutations of POLE or CTNNB1, there seems to be no doubt to use the molecular classification in practice.

Young endometrial cancer patients who have clinically early stage and strongly desire to preserve fertility, hormonal treatment is known to be a feasible option, however, it was unknown whether the molecular classification provide any role of predicting response to hormonal treatment and Chung et al. [44] recently found better response rate in patients with
NSMP compared with MMRd Among 57 patients with clinically stage I and low grade, patients with MMRd had a significantly lower CR/partial response rate than those with NSMP patients in terms of the best overall response (44.4% vs. 82.2%, p=0.018) and CR rate at 6 months (11.1% vs. 53.3%, p=0.010). Based on the results, mismatch repair (MMR) status could be used as a predictive biomarker for selecting patients who could benefit from hormone therapy. And, in the hormonal treatment indications of early endometrial cancer, there was still lack of evidence about whether hormonal treatment can be a safe option for endometrial cancer patients with moderately differentiated tumor grade. A Gynecologic Cancer Inter-Group study observed that CR was achieved in 43.4%, 56.5% and 65.2% of the patients after 6, 9, and 12 months from the initiation of progestin, respectively, achieving 73.9% of an overall CR rate. Although the sample size is very small (23 patients and all were grade 2) the CR rates seem to be identical with the results from previous studies in patients with grade 1. Considering WHO is recommending 2 tier-grading system (grade 1 and 2 as low vs. grade 3 as high), broadened indication for hormonal treatment in endometrial cancer can be discussed with patients who strongly desire for fertility preservation. And, as described above, proactive molecular tests especially for MMR in endometrial biopsy sample may provide the more accurate prognosis enabling early stratification and risk assignment to direct care.

2. Ovarian preservation and sentinel lymph node mapping for early endometrial cancer

During surgical staging, bilateral salpingo-ophorectomy (BSO) and lymph node assessment are routinely recommended for patients with endometrial cancer. However, with low

Fig. 2. Role of integration of molecular profiling in high-risk EC. Molecular analysis can increase prognostic accuracy in patients with high-risk EC and patients with p53abn had the highest benefit from adjuvant chemoradiation compared with adjuvant radiation alone. However, no benefit of adding chemotherapy on adjuvant radiation was observed in patients with POLEmut or MMRd suggesting its predictive role of expecting response to adjuvant chemotherapy. CI, confidence interval; CTRT, combined adjuvant chemotherapy and radiotherapy; EC, endometrial cancer; HR, hazard ratio; LVSI, lymph-vascular space invasion; MMRd, mismatch repair-deficient; NSMP, no specific molecular profile; p53abn, p53-abnormal; POLEmut, POLE-ultramutated; RFS, recurrence-free survival; RT, radiotherapy.
incidence of ovarian metastasis in clinically early disease, it has been suggested to preserve ovary for selected patients with endometrial cancer amid ongoing debate [46-49]. Shin et al. analyzed the data of 539 patients who were diagnosed with early-stage endometrial cancer and found BSO did not affect survivals of patients (non-BSO; 5-year survival rate 98.6% vs. BSO; 5-year survival rate 93.0%, \( p=0.089 \)) which is supporting the safety of ovarian preservation in young patients with early-stage endometrial cancer. However, ovarian preservation should not be recommended for patients with family history involving ovarian cancer risk (e.g. BRCA mutation, Lynch syndrome, etc.).

Like less radical surgical approach of ovarian preservation for early-stage disease, sentinel lymph node biopsy (SLNB) has also been proposed as a less invasive strategy for nodal assessment for early disease [50,51] and showed acceptable results through 3 important clinical trials [52-54]. In these trials, sensitivity per patients was reported from 84% to 100% and negative predictive value per patient was between 97% and 99.6%. However, its role in patients with high grade tumors remains unclear since the proportion of patients with grade 3 showed 13%, 28%, and 49%, respectively. Cusimano et al. [55] performed a prospective multicenter cohort study comparing SLNB and lymphadenectomy for clinical stage I endometrial cancer with grade 2 endometrioid or high-grade using indocyanine green. Among 156 patients enrolled, 126 (80.7%) patients had grade 3 and SLNB had a sensitivity of 96% and a negative predictive value of 99% for the detection of nodal metastasis demonstrating similar diagnostic accuracy and prognostic ability as lymphadenectomy in patients with high-grade endometrial cancer who are at greatest risk for nodal metastasis [55].

3. Targeted agents in advanced or recurrent endometrial cancer

Uterine serous carcinoma is highly aggressive among endometrial cancer subtypes. 20%-25% of uterine serous carcinoma shows Her2/Neu amplification [56-58], a receptor tyrosine kinase and the target of the mAb trastuzumab. Fader et al. [59] reported updated survival analysis of randomized phase II trial comparing carboplatin paclitaxel and carboplatin paclitaxel with trastuzumab in advanced or recurrent uterine serous carcinomas that overexpress Her2/Neu. Sixty-one patients were randomized. And OS was significantly higher in the trastuzumab group compared with the control group, with medians of 29.6 months vs. 24.4 months (HR=0.58; 90% CI=0.34–0.99; \( p=0.046 \)). More on that, the benefit was most significant in those with CTx-naïve advanced disease, with survival median not reached in the trastuzumab group vs. 24.4 months in the control group (HR=0.49; 90% CI=0.25–0.97; \( p=0.041 \)) with similar toxicities.

Palbociclib is an oral selective inhibitor of the CDKs 4 and 6. In estrogen receptor (ER) positive breast cancer, palbociclib combined with letrozole resulted in significantly longer progression free survival than that with letrozole alone [60]. Since ER positive endometrial cancer is also hormone dependent tumor like ER positive breast cancer, combination of palbociclib and letrozole was expected to increase survivals when compared with letrozole alone. Mirza et al. [61] performed a randomized double-blind placebo-controlled phase II trial of palbociclib combined with letrozole in patients with ER positive advanced/recurrent endometrial cancer and, of 77 enrolled patients, it was reported that letrozole plus palbociclib significantly improved progression free survival compared with letrozole alone: median 8.3 vs. 3.0 months, respectively; HR=0.56 (95% CI=0.32–0.98; \( p=0.041 \)). Grade 3/4 adverse events were significantly higher with letrozole plus palbociclib (anemia 8% vs. 3%; neutropenia 42% vs. 0%) however, patient-reported outcomes were identical [61].
Endometrial cancer has been considered as an ideal target for immunotherapy based on its unique immunological landscape. For example, prevalence of expression of PD-1/PD-L1 is highest (40%–80% in endometrioid, 10%–68% in serous, and 23%–69% in clear) among gynecologic malignancies and high tumor mutational burden results in highly immunogenic tumor with tumor specific neoantigens [38,62,63]. The KEYNOTE-158 study is a multicohort, single-arm, open-label, phase 2 study assessing pembrolizumab (anti-PD-1 antibody) monotherapy in patients with recurrent non colorectal cancers with MMRd/MSI-H [64]. During median follow up of 13.4 months, 233 enrolled patients showed ORR was 34.3% (95% CI=28.3–40.8). Endometrial cancer was most common (49/233, 21.0%) with ORR of 57.1% (95% CI=42.2–71.2), which was the best response rate among 27 tumor types in this study. Dostarlimab, another type of anti-PD-1 antibody, showed similar promising results in recurrent or advanced MMRd endometrial cancer [65]. Among 104 women with median follow-up of 11.2 months, ORR was 42.3% (95% CI=30.6–54.6) and 9 patients (12.7%) showed a CR, and 21 patients (29.6%) showed partial response which were durable (median duration of response was not reached). Nivolumab also showed promising anti-tumor activity as ORR of 36% in 13 MMRd endometrial cancer patients [66].

For patients with MMR-proficient/microsatellite-stable (MSS) endometrial cancer, immune checkpoint inhibitor combination with multiple kinase inhibitors showed promising antitumor activity. Lenvatinib, a multiple kinase inhibitor against the VEGF receptor (VEGFR1, VEGFR2, and VEGFR3), was tested as a combination with pembrolizumab in a phase Ib/II study of previously treated endometrial carcinoma [67]. Among enrolled 108 patients with a median follow-up of 18.7 months, 94 patients (87.0%, 94/108) had MSS tumor and ORR at 24 weeks was 36.2% (26.5% to 46.7%). Higher ORR was observed in MSI-high tumors at 63.6% (30.8% to 89.1%), however, small number of patients is limitation (11 patients with MSI-high tumors). Of note, PD-L1 status did not correlate with ORR in this trial. Severe drug induced adverse effects occurred in 83/124 (66.9%) patients. A phase Ib/II study with lenvatinib plus pembrolizumab was performed in selected advanced solid tumors including 23 patients with endometrial cancer [68]. The overall response rate at 24 weeks and overall ORR for endometrial cancer were both 52% (12/23; 95% CI=30.6–73.2) and median duration of response has not reached at the time of analysis. MMR status is unknown in this trial, however, PD-L1 status also did not affect the rate of response.

Cabozantinib, a small molecule inhibitor of the tyrosine kinases c-Met and VEGFR2, and also inhibits AXL and RET, combination with nivolumab demonstrated improved oncological outcomes compared to nivolumab alone in heavily pre-treated women with recurrent endometrial cancer in a randomized phase II study [69]. Among enrolled 76 evaluable patients, only 2 patients were MSI-high. ORR and stable disease were higher in combination arm (25% vs. 16.7% and 44.4% vs. 11.1%, respectively) which were translated into significant clinical benefit favoring combination arm (p<0.001). PARP inhibitor, talazoparib, with avelumab also exhibited active antitumor activity in MSS recurrent/persistent endometrial cancer. In 35 patients enrolled, progression free survival at 6 months was 25.8% (95% CI=12.4–41.4) and median progression free survival was 3.65 months (95% CI=2.4–5.4 months) [70]. There are many ongoing trials investigating the efficacy of immunotherapy in combination with other multiple kinase inhibitors or PARPi which will remain to be seen.

4. Physical activity and survivals

It was suggested that active physical activity is associated with improved survival after an endometrial cancer diagnosis in a prospective cohort study by Friedenreich et al [71].
425 women with endometrial cancer were followed up for a median of 14.5 years and the interviewer-administered Lifetime Total Physical Activity Questionnaire recorded pre- and post-diagnosis physical activity. Among occupational, household, and recreational physical activities, higher post-diagnosis recreational physical activity was strongly associated with both improved disease-free survival (HR=0.33; 95% CI=0.17–0.64; p=0.001) and OS (HR=0.33; 95% CI=0.15–0.75; p=0.007). The strongest associations with survival were experienced by women who maintained high levels of recreational physical activity throughout their pre-diagnosis lifetime and into their endometrial cancer survivorship. Based on this study, clinicians should recommend physical activity to patients with newly diagnosed endometrial cancer and survivors to improve quality of life and possibly even survival.

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