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Review Article

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Major clinical research advances in gynecologic cancer in 2019

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ABSTRACT

In 2019, 12 topics were selected as the major research advances in gynecologic oncology. Herein, we first opted to introduce the significant clinical activity of pembrolizumab in women with advanced cervical cancer based on the results of the phase 2 KEYNOTE-158 trial. Thereafter, we reviewed 5 topics, including systemic lymphadenectomy in the advanced stage with no gross residual tumor, secondary cytoreductive surgery in recurrent ovarian cancer according to the results of Gynecologic Oncology Group-213 trial, dose-dense weekly paclitaxel scheduling as first-line chemotherapy, the utility of intraperitoneal therapy in the advanced stage, and an update on poly(ADP-ribose) polymerase (PARP) inhibitors for the treatment of ovarian cancer. Additionally, we conducted a thorough review of emerging data from several clinical trials on PARP inhibitors according to drug, target population, and combined usage. For uterine corpus cancer, we reviewed adjuvant therapy for high-risk disease and chemotherapy in advanced/recurrent disease. For the field of radiation oncology, we discussed the utility of neoadjuvant chemotherapy added to chemoradiotherapy and the treatment of radiation-induced cystitis using hyperbaric oxygen. Finally, we discussed the use of individualized therapy with humanized monoclonal antibodies (trastuzumab emtansine and sacituzumab govitecan-hziy) and combination therapy (fulvestrant plus alpesilib, fulvestrant plus anastrozole, and ribociclib plus endocrine therapy) for women with advanced breast cancer.

Keywords: Immunotherapy; Poly(ADP-ribose) Polymerase Inhibitors; Adjuvant Therapy; Humanized Monoclonal Antibody; Combination Therapy

INTRODUCTION

Among the 12 topics presented herein regarding the major clinical research advances in 2019, we opted to specifically present an update on Poly(ADP-ribose) polymerase (PARP) inhibitors. Following the publication of the findings of the SOLO-1 trial (NCT01844986) in the *New*

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Author Contributions

Conceptualization: S.D.H., K.M., K.J.W., M.M.R.; Project administration: K.J.W.; Supervision: K.J.W.; Writing - original draft: K.M., S.D.H., L.K.H., E.K.Y., L.J.Y., L.Y.Y., H.F.H., M.M.R.; Writing - review & editing: K.M., S.D.H., L.K.H., E.K.Y., L.J.Y., L.Y.Y., H.F.H., M.M.R., K.J.W.

England Journal of Medicine [1], PARP inhibitors beyond olaparib were actively evaluated in women with ovarian cancer in different clinical settings. In the Platelet-Rich plasma Injection Management for Ankle OA (PRIMA) trial, patients with newly diagnosed advanced ovarian cancer that responded to platinum-based chemotherapy had significantly longer progression-free survival (PFS) with PARP inhibitors than those administered the placebo, regardless of homologous-recombination deficiency or proficiency [2]. As patients were enrolled despite their biomarker status or the time of surgery in the Veliparib With Carboplatin and Paclitaxel and as Continuation Maintenance Therapy in Subjects With Newly Diagnosed Stage III or IV, High-grade Serous, Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer (VELIA) trial (NCT02470585), the benefit of PARP inhibitors can be safely extended to all patients with newly diagnosed advanced ovarian cancer [3].

In this review, we summarized the remarkable findings of studies on PARP inhibitors. The 12 topics related to the major clinical research advances in gynecologic cancer in 2019 are presented in **Table 1**.

UTERINE CERVIX

1. Immunotherapy

The results of the KEYNOTE-158 basket trial were first reported at the 2018 American Society of Clinical Oncology (ASCO) Annual Meeting. These findings led to the approval of the single-agent, pembrolizumab, for the treatment of women with recurrent or metastatic cervical cancer expressing programmed death-ligand 1 (PD-L1; combined positive score [CPS] ≥1) by the U.S. Food and Drug Administration.

In 2019, pembrolizumab was found to display notable clinical activity in women with previously treated advanced cervical cancer in the phase 2 KEYNOTE-158 trial [4]. A total of 98 previously treated women with advanced cervical cancer received 200 mg pembrolizumab 3 times per week for 2 years or experienced disease progression or intolerable toxicity. Most patients (83.7%) had PD-L1-positive tumors based on a CPS value ≥1. The overall response rate of the study population was 12.2%, with a median follow-up of 10.2 months: 3 complete responses and 9 partial responses. All 12 women with objective responses had PD-L1-positive

Table 1. Twelve topics related to the major clinical research advances in gynecologic cancer in 2019

Site of cancer	Topic	Reference
Uterine cervix	Immunotherapy	[1]
Ovary	Systemic lymphadenectomy in advanced ovarian cancer	[2]
	Secondary cytoreductive surgery in recurrent ovarian cancer	[4]
	Dose-dense weekly paclitaxel scheduling	[9]
	Intraperitoneal therapy	[13]
	PARP inhibitor update	[18-26, 28-30]
Uterine corpus	Adjuvant therapy for high-risk endometrial cancer: GOG-258 and GOG-249	[35,36]
	Chemotherapy for high-risk endometrial cancer: JGOG-2043 and GOG-261	[38,39]
Radiation oncology	Inferiority of NAC plus CRT to CRT alone	[40]
	Treatment of radiation-induced cystitis with hyperbaric oxygen	[42]
Breast	Humanized monoclonal antibodies in breast cancer	[43,44]
	Combination therapy in breast cancer	[45,47,51]

CRT, chemoradiotherapy; GOG, Gynecologic Oncology Group; NAC, neoadjuvant chemotherapy; PARP, poly (ADP-ribose) polymerase.

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tumors. Women with PD-L1-positive tumors had a longer median overall survival (OS) than those with PD-L1-negative tumors (11 months vs. 9.4 months).

Adverse events of any grade were found in 65.3% of cases, and grade 3 or higher adverse events were found in 12.2% of participants. Approximately one-quarter of participants experienced immune-mediated adverse events: 2 hepatitis, 2 severe skin reactions, and 1 adrenal insufficiency.

OVARY

1. Systemic lymphadenectomy in advanced ovarian cancer

The lymph node is involved in as many as 80% of cases of women with ovarian cancer [5]. Although systematic lymphadenectomy is a feasible and safe procedure for advanced ovarian cancer, its therapeutic role remains controversial. Retrospective studies have suggested significant survival benefits of systematic lymphadenectomy in women with primary cytoreductive surgery for the advanced stage. However, in 2005, Panici et al. [6] suggested that systematic lymphadenectomy improves PFS but not OS in women with advanced ovarian carcinoma optimally debulked. They designed a randomized clinical trial to determine whether systematic aortic and pelvic lymphadenectomy (n=216) could improve PFS and OS compared to the resection of bulky nodes alone (n=211). The median PFS was 29.4 and 22.4 months (95% confidence interval [CI]=1.0–14.4 months, p=0.01) and the 5-year OS rates were 48.5% and 47% (hazard ratio [HR]=0.97, 95% CI=0.74–1.29, p=0.85) in the systematic lymphadenectomy and the control arms, respectively.

In 2019, Harter et al. [7] reported the results of the Lymphadenectomy in Ovarian Neoplasms (LION) trial in the *New England Journal of Medicine*. Based on their findings, systematic lymphadenectomy in patients with advanced ovarian cancer that lacked gross residual tumor and normal lymph nodes was not associated with improved PFS or OS relative to no lymphadenectomy. A total of 647 patients were assigned to either undergo (n=323) or not undergo (n=324) lymphadenectomy. Median PFS was 25.5 months in both groups (HR=1.11; 95% CI=0.92–1.34; p=0.29) while median OS was 69.2 months in women without lymphadenectomy and 65.5 months in women with lymphadenectomy (HR=1.06; 95% CI=0.83–1.34; p=0.65). Infections treated with antibiotics, lymph cysts, and repeat laparotomies for complications were more common in women with lymphadenectomy. The authors assumed that the removal of these tumor cells could further reduce residual tumor burden to an extent that would improve prognosis. However, lymphadenectomy did not provide a survival benefit, despite the presence of positive nodes in 55.7% of patients in the lymphadenectomy group.

2. Secondary cytoreductive surgery in recurrent ovarian cancer

Recurrence occurs in almost all women with advanced ovarian cancer. Similar to primary surgical cytoreduction, secondary cytoreductive surgery could be considered for patients with recurrent disease. According to current guidelines from the National Comprehensive Cancer Network, secondary cytoreductive surgery is one of the treatment options for women with platinum-sensitive ovarian cancer [8]. However, based on the results of the Gynecologic Oncology Group (GOG)-213 trial, a phase 3 randomized prospective trial published by Coleman et al. [9], no survival benefits were obtained from secondary cytoreductive surgery followed by chemotherapy compared to chemotherapy alone in women with platinum-

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sensitive recurrent ovarian cancer. The median OS was 50.6 months in women with surgery and 64.7 months in women without surgery (HR=1.29; 95% CI=0.97–1.72; p=0.08) while median PFS was 18.9 months in women with surgery and 16.2 months in women without surgery (HR=0.82; 95% CI=0.66–1.01). Further, secondary cytoreductive surgery was not found to have an OS benefit over chemotherapy alone.

The DESKTOP-III trial (NCT01166737) was designed in a similar manner to the GOG-213 trial to evaluate the efficacy of secondary cytoreductive surgery; however, some differences exist between the 2 trials (**Table 2**) [10]. The DESKTOP-III trial comprised patients with complete gross resection after primary debulking surgery alone. This trial achieved complete gross resection in 68% of its study population, a finding similar to that of the GOG-213 trial which had 67% [11]. Although 84% of the study population received bevacizumab in GOG-213, only up to 20% of patients in DESKTOP-III received bevacizumab. Presently, we are awaiting the final results of the DESKTOP-III trial.

3. Dose-dense weekly paclitaxel scheduling

In the phase 3 ICON8 trial conducted by Gynecologic Cancer Intergroup and recently published in the Lancet, the first-line weekly dose-dense chemotherapy did not improve PFS compared to the thrice-weekly chemotherapy in women with stage IC–IV epithelial ovarian cancer [12]. The 1,566 eligible women were randomly assigned to the following three arms:

1) carboplatin area under the curve (AUC) 5 or AUC 6 3-weekly + 175 mg/m^2 paclitaxel 3-weekly (group 1 [control arm], n=522)
2) carboplatin AUC 5 or AUC 6 3-weekly + 80 mg/m^2 paclitaxel weekly (group 2, n=523)
3) carboplatin AUC 2 weekly + and 80 mg/m^2 paclitaxel weekly (group 3, n=521)

There was no significant difference in PFS with either weekly regimen (median, 17.7 months; [interquartile range, 10.6-not reached] in group 1, 20.8 months [11.9–59.0] in group 2, 21.0 months [12.0–54.0] in group 3; p=0.350 for group 2 vs. 1; p=0.510 for group 3 vs. 1). Grades 3 or 4 toxic effects were frequent in women administered weekly treatment; however, most were uncomplicated.

Dose-dense weekly paclitaxel scheduling in epithelial ovarian cancer has already garnered remarkable attention in the past decade. The Japanese Gynecologic Oncology Group (JGOG)-3016 trial showed that dose-dense weekly paclitaxel-carboplatin improved survival outcomes in women with advanced epithelial ovarian cancer compared to the conventional thrice-weekly schedule [13]. A total of 637 Japanese women with newly diagnosed epithelial ovarian cancer were randomly assigned to receive 3 weekly doses of 180 mg/m^2 paclitaxel with carboplatin or weekly dose-dense 80 mg/m^2 paclitaxel with carboplatin thrice-weekly. Another randomized controlled trial, GOG-262, randomly assigned 692 women with stage

Table 2. Scheme of the DESKTOP-3 and GOG-213 trials

Variables	DESKTOP-3	GOG-213
Design	Randomized phase 3 trial	Randomized phase 3, 1:1 trial
Primary endpoint	Overall survival	Overall survival
Enrolled patients (study period)	408 women (2010–2015)	485 women (2007–2017)
Patient selection	Treatment-free interval >6 months, AGO score	Treatment-free interval >6 months
Race/ethnicity	2% East-Asian	49.5% East-Asian
Complete resection	72.5%	67%
Bevacizumab in 2nd-line	20%	84%
HR for death (surgery vs. no surgery)	Still blinded	1.29 (95% CI=0.97–1.72; p=0.08)

AGO, Arbeitsgemeinschaft Gynaekologische Onkologie; CI, confidence interval; HR, hazard ratio; GOG, Gynecologic Oncology Group.

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II–IV epithelial ovarian cancer to receive 3-weekly 175 mg/m^2 or weekly 80 mg/m^2 paclitaxel treatment with carboplatin [14]. Unlike the JGOG-3016, 84% of participants in GOG-262 received bevacizumab in addition to chemotherapy. No difference was observed in PFS between the 2 treatment groups; however, weekly paclitaxel improved PFS in the subgroup that did not receive bevacizumab.

In summary, weekly dose-dense paclitaxel chemotherapy cannot be generally recommended as a first-line regimen for women with epithelial ovarian cancer. However, it could be considered a first-line regimen option for Japanese women with ovarian cancer as potential ethnic differences might affect its pharmacological action.

4. Intraperitoneal (IP) therapy

Although reduced quality of life and increased toxicity are observed during IP treatment, intravenous (IV) paclitaxel with IP cisplatin and paclitaxel improved the PFS (23.8 vs. 18.3 months, p=0.05) and OS (65.6 vs. 49.7 months, p=0.03) of women with optimally debulked stage III ovarian cancer compared to IV paclitaxel-cisplatin in the GOG-172 trial [15]. However, data from the recently published GOG-252 trial in the *Journal of Clinical Oncology* showed conflicting results [16]. When combined with bevacizumab, neither IP carboplatin nor cisplatin improved the outcomes of women with advanced ovarian cancer compared to IV carboplatin. A total of 1,560 women were enrolled and randomly assigned to the following three arms:

1) IV paclitaxel 80 mg/m^2 weekly + IV carboplatin (IV carboplatin group [control arm], n=521)
2) IV paclitaxel 80 mg/m^2 weekly + IP carboplatin (IP carboplatin group, n=518)
3) IV paclitaxel 135 mg/m^2 3-weekly + IP cisplatin 75 mg/m^2 day 2+ IP paclitaxel 60 mg/m^2 day 8 (IP cisplatin group, n=521)

All enrolled women received bevacizumab 15 mg/kg IV 3-weekly in cycles 2–22. The median PFS was 24.9 months, 27.4 months (HR=0.925; 95% CI=0.802–1.07), and 26.2 months (HR=0.977; 95% CI=0.847–1.13) while median OS was 75.5 months, 78.9 months (HR=0.949; 95% CI=0.799–1.128), and 72.9 months (HR=1.05; 95% CI=0.799–1.128) in the IV carboplatin arm, IP carboplatin arm, and IP cisplatin arm, respectively. Grades 3 or 4 toxic effects were more common in the IP cisplatin arm; however, there was no increase in gastrointestinal perforations, fistulas, or necrosis in the IP cisplatin arm. The researchers suggested that IP therapy could remain an option for selected optimally debulked cases. Further, the regimen in the GOG-172 trial was recommended for use without bevacizumab.

5. Update on PARP inhibitors

First-line therapy

PARP inhibitors (niraparib, olaparib, and rucaparib) have been approved as maintenance therapy for patients with recurrent ovarian cancer who responded to platinum-based therapy and demonstrated efficacy according to their *BRCA* or homologous-recombination status (**Table 3**) [17-19]. Olaparib was approved as first-line maintenance therapy for the *BRCAmut* population based on promising results from the SOLO-1 trial [1].

Recently published first-line trials (Avastin and OLAparib in 1st Line [PAOLA-1], PRIMA, VELIA) [2,3,20] will completely change the management of ovarian cancer patients. Notably, however, major differences exist in trial designs, control arms, study populations (particularly sensitivity to prior platinum and residual disease), and timing of PARP inhibitor

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Table 3. Summary of clinical trials for PARP inhibitors

Variables	PARP inhibitor	PARP inhibitor+VEGF inhibitor	PARP inhibitor+ICI	PARP inhibitor+ICI+VEGF inhibitor
First-line maintenance	SOLO-1 (olaparib) PRIMA (niraparib)	PAOLA-1 (olaparib+bev)	ATHENA (rucaparib+nivolumab)† MITO-25 (rucaparib+bev)†	
First-line treatment & maintenance	VELIA (veliparib)			FIRST (niraparib+TSR042+bev)† DUO-O (olaparib+durvalumab+bev)† ENGOT-ov43 (olaparib+pembro±bev)†
Recurrence maintenance, platinum sensitive	SOLO-2 (olaparib) NOVA (niraparib) ARIEL3 (rucaparib)	ICON-9 (olaparib+cediranib)†		
Recurrence treatment, platinum sensitive	SOLO-3 (olaparib) QUADRA (niraparib)	AVANOVA-2 (niraparib+bev) NRG GY-004 (olaparib+cediranib)†	MEDIOLA (olaparib+durvalumab)*	MEDIOLA (olaparib+durvalumab+bev)†,‡
Recurrence treatment, platinum resistant		NRG GY-005 (olaparib+cediranib)†	TOPACIO (niraparib+pembrolizumab)	

bev, bevacizumab; ICI, immune checkpoint inhibitor; PARP, poly(ADP-ribose) polymerase; VEGF, vascular endothelial growth factor.
*Abstract only; †Ongoing study; ‡Expansion cohort.

initiation (concomitant with chemotherapy vs. maintenance only), ultimately rendering meaningful comparison impossible. The differences between the trials are evident when the control arms of the trials are compared, as they perform in a markedly different manner in different populations.

A study on the effects of niraparib as a first-line treatment was published in 2019 by González-Martín et al. [2]. These researchers presented the results of the randomized, double-blind phase 3 PRIMA trial, where benefits were observed with maintenance niraparib in patients with newly diagnosed ovarian cancer. Patients with high-risk ovarian cancer (International Federation of Gynaecology and Obstetrics [FIGO] III and IV), with response after frontline platinum therapy, were included despite their homologous-recombination deficiency (HRD) status. A total of 733 patients were randomized in a 2:1 ratio to receive niraparib or placebo for 36 months or until disease progression. In the overall population, a significantly longer PFS in the niraparib group (13.8 vs. 8.2 months, HR=0.62; p<0.001) and a higher gain in tumors with HRD, both *BRCA*-mutated and *BRCA* wild-type (21.9 months vs. 10.4 months, HR=0.43; p<0.001) were observed. OS at the 24-month analysis tended to increase OS in the niraparib group compared to the placebo group (84% vs 77%, HR=0.7; 95% CI=0.44–1.11).

Promising results from VELIA/GOG-3005, a randomized phase 3 trial with veliparib combined with first-line chemotherapy and maintenance therapy, were published by Coleman et al. [3]. The trial comprised patients with stage III and IV ovarian cancer, regardless of *BRCA* or HRD status. A total of 1,140 patients were randomized (1:1:1) to receive chemotherapy plus veliparib followed by either veliparib (veliparib throughout) or placebo maintenance or control with chemotherapy plus placebo followed by placebo maintenance. The regimen of carboplatin, paclitaxel, and veliparib (6 cycles) followed by 30 cycles of maintenance veliparib led to a significantly longer PFS in the intention-to-treat population. Median PFS in the intention-to-treat cohort was 23.5 vs. 17.3 months in the control group (HR=0.68; p<0.001). A higher benefit was observed in the BRCA mutation cohort (34.7 vs 22.0 months, HR=0.44; p<0.001) and the HRD cohort, including *BRCAmut* (31.9 vs. 20.5 months, HR=0.57; p<0.001). In the veliparib concomitant only group, no benefits were observed for the improved PFS. At the time of publication, data regarding OS were not mature. Regarding safety, most adverse advents were reported in the veliparib throughout group, which had higher incidence of thrombocytopenia, anemia, and nausea.

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Recurrent ovarian cancer

Del Campo et al. published data regarding the efficacy of niraparib maintenance therapy in patients with recurrent ovarian cancer based on the best response to the final platinum-based chemotherapy [21]. Data were evaluated based on the results from the ENGOT-OV16/NOVA trial [17], a double-blind, randomized study of 553 patients with recurrent, platinum-sensitive ovarian cancer. Patients from the niraparib group achieved clinical benefit, with a significantly longer PFS than those in the placebo group, regardless of complete response (CR) or partial response (PR) to their last platinum-based therapy in the *BRCA* mutation cohort (CR: HR=0.3; p<0.0001 and PR: HR=0.24; p<0.0001) and non-*BRCA* mutation cohort (CR: HR=0.58; p=0.0082 and PR: HR=0.35; p<0.0001). The status and reports of severe symptoms were low in all groups.

Matulonis et al. [22] reported time without symptoms and toxicity (TWiST) in patients from the same ENGOT-OV16/NOVA trial. TWiST was estimated to be the difference between the mean PFS and time with toxicity or symptoms (number of days with symptomatic grade ≥2 between randomization and progression). Compared to those administered placebo, patients administered niraparib experienced a benefit of 2.95 years without toxicity or symptoms in the *BRCA* mutation cohort and 1.34 years in the non-*BRCA* mutation cohort, ultimately depicting the potential of patients to experience a better quality of life.

The effect of age on the efficacy and safety of rucaparib maintenance treatment was previously investigated. Ledermann et al. analyzed data from three age-based subgroups from ARIEL3 where patients were randomized to receive either rucaparib or placebo [23]. Maintenance with rucaparib was demonstrated to improve PFS in all age subgroups compared to placebo; however, the highest benefit was observed in patients <65 years with median PFS of 11.1 vs 5.4 months in the control group (HR=0.33; 95% CI=0.25–0.43). Patients aged 65–74 and ≥75 had had a longer PFS of 3 and 3.7 months, respectively, than those in the control group. In addition, the safety profile was consistent across the subgroups.

Late-line therapy

The QUADRA trial evaluated the safety and efficacy of niraparib monotherapy as a late-line treatment for high-grade ovarian cancer [24]. In this open-label, single-arm phase 2 trial, patients were administered more than three previous chemotherapy regimens, regardless of their HRD status and platinum status (sensitive, resistant or refractory). Further, they received daily niraparib until disease progression. The primary endpoint was to evaluate the efficacy of niraparib on HRD-positive tumors that are sensitive to the final platinum-based therapy. A total of 463 patients were enrolled: 47 patients met the primary endpoint and 28% (13/47) achieved overall response (95% CI=15.6–42.6; p=0.00053). The median duration of response was 9.2 months, and 68% (37/47) of patients achieved disease control. The overall response rate was 10% (38 of 387 response-evaluable) and was highest in patients with *BRCA*-mutated and HRD-positive tumors. No new safety signals were identified.

Dose and tolerability

Previous analysis from the NOVA phase 3 trial revealed a platelet count <150,000/μL and body weight <77 kg as predictive factors for the poor tolerability of niraparib. Based on these findings, a reduction of the starting-dose to 200 mg was recommended for this group of patients [17]. Data from the PRIMA trial were presented at the Society of Gynecologic Oncology annual meeting 2019 [25]. The results of this trial prospectively confirmed that niraparib tolerability was improved when dosing was derived according to body weight (<77

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kg) and platelet count (150,000/μL). A post hoc analysis of the phase 2 QUADRA trial also showed that patients with either lower body weight or platelet count experienced more ≥3 grade toxicity. Further, efficacy was preserved in the group administered a reduced daily mean dose (≤200 mg) of niraparib [26].

Combination therapy with a PARP inhibitor and vascular endothelial growth factor inhibitor

The combination of a PARP inhibitor and an anti-angiogenic agent as maintenance therapy has demonstrated efficacy with improved PFS in patients with recurrent ovarian cancer [27,28]. The efficacy and safety of the more intensive first-line maintenance regimen of olaparib plus bevacizumab were investigated in the PAOLA-1/ENGOT-ov25 trial and published in December 2019 by Ray-Coquard et al [20]. This trial was a randomized, double-blind study of patients that were newly diagnosed with FIGO stage III and IV ovarian cancer that responded to platinum-based therapy plus bevacizumab irrespective of their BRCA mutation status. A total of 806 patients were randomized (2:1) to receive olaparib plus bevacizumab or placebo plus bevacizumab. Median PFS was 22.1 months in the olaparib group and 16.6 in the placebo group (HR=0.59; 95% CI 0.49–0.72; p<0.001). Further, the longest duration was observed in the *BRCA*-mutated and HRD-positive tumors. Grades 3–5 adverse events were reported by 57% of patients in the olaparib group and 51% in the placebo group. The most common events were hypertension and anemia.

Positive results were published by Mirza et al. [29] regarding niraparib and bevacizumab for the treatment of recurrent ovarian cancer. The NSGO-AVANOVA2/ENGOT-OV24 phase 2 superiority trial compared niraparib monotherapy to niraparib plus bevacizumab. A total of 97 patients with platinum-sensitive recurrent ovarian cancer, regardless of the number of previous lines of therapy and HRD status, were randomized in a 1:1 ratio. Combination treatment was found to significantly increase PFS compared to niraparib monotherapy, with a median PFS of 11.9 vs. 5.5 months (HR=0.35; p<0.001). Further, a significant benefit was observed despite the HRD status or a chemo-free interval greater or less than 12 months. The proportion of patients with objective response was higher with combination therapy (62%) than monotherapy (30%). More grade ≥3 events were registered in the combination group owing to more frequent hypertension.

Combination therapy with a PARP inhibitor and immunotherapy

Konstantinopoulos et al. [30] published the results from the ovarian cohort of the Niraparib in Combination With Pembrolizumab in Patients With Triple-negative Breast Cancer or Ovarian Cancer (TOPACIO; NCT02657889)/KEYNOTE-162 trial, a single-arm phase 1 and 2 trial with niraparib combined with pembrolizumab for patients with recurrent ovarian cancer, regardless of their *BRCA* status. A total of 62 patients were included in the study (9 in phase 1 and 53 in phase 2). Interestingly, 3 patients (5%) had confirmed CR, 8 patients (13%) had PR, and 28 patients (47%) had stable disease. Moreover, the objective response was consistent across the subgroups based on platinum sensitivity status, *BRCA* status, or HRD status. The median duration of response was not reached (range, 4.2 to ≥14.5 months) and no new safety signals were identified.

Combination therapy with a PARP inhibitor and a phosphoinositide 3-kinase (PI3K) inhibitor

To date, every trial that explored the combination of PARP inhibitors with targeted agents, such as cediranib and buparlisib, failed to demonstrate their clinical synergism in homologous-recombination repair (HRR)-proficient ovarian cancer. Konstantinopoulos et al. [31] were the first to present clinical evidence of synergism between PARP inhibitor and a

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targeted agent in *BRCA* wild-type, platinum-resistant ovarian cancer through a multicenter, open-label, phase 1b trial. Of the 28 patients with epithelial ovarian cancer, the overall response was 33% (95% CI 7-70) in patients with germline *BRCA* mutations and platinum-resistant or refractory disease. As the overall response rate was substantially higher than that expected from olaparib monotherapy (4%–5%) or alpelisib monotherapy (<5%) in this setting, clinical synergism was suggested. Plausible mechanisms of the clinical synergism include the use of a PI3K inhibitor to sensitize HRR-proficient ovarian cancers to PARP inhibitors, which suggest the potential use of PARP inhibitors beyond the HRR-deficient setting. The most common grade 3–4 adverse events were hyperglycemia (16%), nausea (9%), and increased alanine aminotransferase concentrations (9%).

UTERINE CORPUS

1. Adjuvant therapy in high-risk endometrial cancer

The preventive role of radiotherapy in locoregional recurrent endometrial cancer has been well established; however, external-beam radiotherapy (EBRT) does not significantly improve OS in women with early-stage or low-risk endometrial cancer [32,33]. Based on distant metastasis, chemotherapy is considered to be the standard of care; however, the role of radiotherapy remains controversial [34].

GOG-258: chemoradiation vs. chemotherapy alone in stage III–IVA endometrial cancer

Last year, the Randomized Trial of Radiation Therapy With or Without Chemotherapy for Endometrial Cancer (PORTEC-3; NCT00411138) trial demonstrated that adjuvant chemoradiotherapy improved the PFS in women with stage III endometrial cancer relative to radiotherapy alone [35]. Based on the data from the phase 3 GOG-258 trial, Matei et al. [36] demonstrated that chemoradiotherapy did not improve relapse-free survival (RFS) relative to chemotherapy alone in women with high-risk endometrial cancer [36]. A total of 736 eligible women with stage III–IV of any histologic type or stage I–II non-endometrioid type endometrial cancers, were randomly assigned (1:1) to receive adjuvant chemoradiotherapy or chemotherapy only after surgery. The chemoradiotherapy group received 50 mg/m^2 cisplatin on days 1 and 29 with EBRT followed by 175 mg/m^2 paclitaxel plus carboplatin at AUC 5 to 6 thrice-weekly for 4 cycles. The chemotherapy only group received 175 mg/m^2 paclitaxel plus carboplatin at AUC 5 to 6 thrice-weekly for 6 cycles. As a result, the 5-year RFS was 59% in women administered chemoradiotherapy and 58% in those administered chemotherapy alone (HR=0.90; 90% CI=0.74–1.10). Although the recurrence of vaginal (2% vs. 7%, HR=0.36, 95% CI=0.14–0.82) and lymph node (11% vs. 20%, HR=0.43; 95% CI=0.28–0.66) was less frequent in women administered chemoradiotherapy, distant recurrence (27% vs. 21%, HR =1.36; 95% CI=1.00–1.86) was more common in women treated with chemoradiotherapy. Grade 3 or 4 toxic effects occurred in 58% of the chemoradiotherapy group and 63% of the chemotherapy only group.

GOG-249: pelvic radiotherapy vs. brachytherapy plus chemotherapy in high-intermediate and high-risk early-stage endometrial cancer

In another GOG study, an open-label phase 3 trial, the potential to replace adjuvant pelvic radiotherapy with vaginal cuff brachytherapy with chemotherapy (VAB-C) was determined in women with high-risk early-stage (grade 2 or 3, positive LVSI, IB–II endometrioid, I–II serous or clear cell) endometrial cancer [37]. In this trial, VCB-C was not superior to pelvic radiotherapy based on the survival outcomes and toxicities. A total of 601 women were

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randomly assigned (1:1) to receive VAB-C or pelvic radiotherapy. Pelvic radiotherapy was performed with the standard 4-field techniques or intensity-modulated radiotherapy. The pelvic radiotherapy dose was 45–50.4 Gy over 5–6 weeks. Women with VCB-C concomitantly received brachytherapy and chemotherapy comprising of 175 mg/m^2 paclitaxel and carboplatin thrice-weekly. The 5-year RFS was 0.76 (95% CI=0.70–0.81) for radiotherapy and 0.76 (95% CI=0.70–0.81) for VCB-C (HR=0.92; 90% confidence limit=0.69–1.23). Further, the 5-year OS was 0.87 (95% CI=0.83–0.91) for radiotherapy and 0.85 (95% CI=0.81–0.90) for VCB-C (HR=1.04; 90% confidence limit=0.71 –1.52). Although the incidence of vaginal or distant recurrences did not differ, pelvic or para-aortic lymph node recurrences were less frequent in women with radiotherapy (HR=0.42; 95% CI=0.24–0.94). The researchers mentioned that pelvic radiotherapy is adequately managed in women with high-risk early-stage endometrial cancer.

2. Chemotherapy for high-risk endometrial cancer

JGOG-2043: doxorubicin plus cisplatin vs. docetaxel plus cisplatin vs. paclitaxel plus carboplatin

According to the results of GOG-122, doxorubicin-cisplatin can be recommended for use as the standard regimen for adjuvant chemotherapy in advanced and recurrent endometrial cancers [11]. Additionally, taxanes such as paclitaxel and docetaxel were reported to be effective [34,38]. In *JAMA Oncology*, Nomura et al. [39] demonstrated that women administered doxorubicin-cisplatin, docetaxel-cisplatin, or paclitaxel-carboplatin as adjuvant chemotherapy after surgery for endometrial cancer had similar oncologic outcomes. In this multicenter, open-label, phase 3 randomized clinical trial, 788 women with stage I–II endometrial cancer at high-risk or stage III–IVA were enrolled and randomly assigned (1:1:1) to receive 60 mg/m^2 doxorubicin plus 50 mg/m^2 cisplatin, 70 mg/m^2 docetaxel plus 60 mg/m^2 cisplatin, and 180 mg/m^2 paclitaxel plus carboplatin AUC 6, respectively. The 5-year PFS was 73.3%, 79.0%, and 73.9% in women administered doxorubicin-cisplatin, docetaxel-cisplatin, or paclitaxel-carboplatin, respectively (2-sided p=0.12). Further, the 5-year OS was 82.7%, 88.1%, and 86.1% in women administered doxorubicin-cisplatin, docetaxel-cisplatin, or paclitaxel-carboplatin, with no significant differences observed (2-sided p=0.37). Although the superiority of docetaxel-cisplatin and paclitaxel-carboplatin over doxorubicin-cisplatin was not demonstrated, the authors suggested that the 3 regimens are comparable in efficacy and tolerability.

GOG-261: paclitaxel plus carboplatin vs. paclitaxel plus ifosfamide

The results from the phase 3 NRG Oncology clinical trial, GOG-261, were reported at the 2019 ASCO Annual Meeting. Based on the results, paclitaxel-carboplatin was not inferior to paclitaxel-ifosfamide in the survival outcomes [40]. A total of 449 women with chemotherapy naïve stage I-IVB or recurrent uterine carcinosarcoma were enrolled and randomly assigned (1:1) to receive 175 mg/m^2 paclitaxel plus carboplatin AUC 5–6 or 135 mg/m^2 paclitaxel plus 1.6 g/m^2 ifosfamide on days 1–3. Median OS (37 vs. 29 months, HR=0.87; 90% CI=0.70–1.075; p<0.01 for non-inferiority [NI], p>0.1 for superiority [S]) was not inferior; however, PFS (16 vs. 12 months, HR=0.73; p<0.01 for NI, p<0.01 for S) was longer in women administered paclitaxel-carboplatin than those administered paclitaxel-ifosfamide. Most toxic events in women with paclitaxel-carboplatin were hematologic complications, and confusion and genitourinary hemorrhage were worse in women administered paclitaxel-ifosfamide.

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RADIATION ONCOLOGY

1. Inferiority of neoadjuvant chemotherapy (NAC) plus chemoradiotherapy (CRT) to CRT alone

A randomized phase II study conducted by da Costa et al. [41] and published online in the *Journal of Clinical Oncology* showed that combination therapy with gemcitabine and cisplatin followed by CRT did not improve the outcomes of patients with locally advanced cervical cancer compared to CRT alone. Of the 107 patients enrolled in the study, 55 and 52 were randomly assigned to the NAC arm and CRT-alone arm, respectively. Most patients were found to have squamous cell carcinoma (87.8%). Further, the primary end point was 3-year PFS while the secondary end points were response rate, 3-year locoregional control, 3-year OS, safety, and quality of life. After a median follow-up of 31.7 months, NAC was associated with an inferior PFS, with 3-year PFS rates of 40.9% vs. 60.4% in the CRT arm (HR=1.84; 95% CI=1.04–3.26; p=0.033). Additionally, NAC was associated with a lower OS (3-year OS rate, 60.7% vs. 86.8%, HR=2.79; 95% CI=1.29–6.01; p=0.006). After treatment completion, CR rates were 56.3% in the NAC arm and 80.3% in the CRT arm (p=0.008). Toxicities were similar in both arms, with the exception of hypomagnesemia and neuropathy, which were more common with NAC.

2. Treatment of radiation-induced cystitis using hyperbaric oxygen

Late radiation cystitis often occurs in 23% to 80% of patients while severe hematuria is reported to occur in 5% to 8% of patients with prostate, rectal, or gynecologic cancers [42]. Symptoms of late radiation cystitis include hematuria, increased urinary frequency and urgency, incontinence, and dysuria. Hyperbaric oxygen therapy (HBOT) was suggested to relieve the symptoms caused by radiotherapy; however, only little evidence regarding the use of HBOT is available as small sized randomized studies have failed to demonstrate its benefit.

The first study published online on September 16, ahead of print, in *Lancet Oncology* revealed that HBO can alleviate symptoms of late radiation cystitis in patients that underwent pelvic radiotherapy [43]. Oscarsson et al. [43] conducted a randomized, controlled phase II–III study with HBOT in patients with radiation-induced cystitis. Of the 223 patients screened between May 9, 2012, and Dec 20, 2017, 87 were enrolled and randomly assigned to receive either hyperbaric oxygen therapy (n=42) or standard care (n=45). The intent-to-treat population included 79 patients (41 in HBOT, 38 in standard care) with symptoms of late radiation cystitis. Most patients had prostate cancer (68%) followed by cervical cancer (23%). The median time from radiotherapy to inclusion in the study was over 4 years for both groups. The primary outcome was the urinary total score based on the Expanded Prostate Cancer Index Composite (EPIC) score. Significantly better improvements were observed with HBOT for the bother and incontinence EPIC scores and the bowel EPIC scores. The difference between the change in the group mean of the urinary total EPIC score at visit 4 was 10.1 points (95% CI=2.2–18.1; p=0.013, 17.8 points [standard deviation=18.4] in the HBOT group vs. 7.7 points [15.5] in the standard care group). Of the 41 patients in the HBOT group, 17 (41%) experienced transient grade 1–2 adverse events, related to sight and hearing, during the period of hyperbaric oxygen therapy. SF-36 scores had better improvements with HBOT than standard care, especially a significant improvement in general health (p=0.0006).

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BREAST

1. Humanized monoclonal antibodies in breast cancer

Trastuzumab emtansine for residual invasive human epidermal growth factor receptor 2 (HER2)-positive breast cancer

Drug treatments for HER2-positive breast cancer have enabled a remarkable success story, and trastuzumab emtansine (T-DM1), an antibody-drug conjugate, has demonstrated remarkable activity against metastatic breast cancer after progression with the use of trastuzumab. Neoadjuvant chemotherapy before definitive surgery is an established treatment approach for operable breast cancer. Further, patients with residual invasive disease at surgery following neoadjuvant therapy have a higher risk of disease recurrence or death than patients with a pathological CR.

A Study of Trastuzumab Emtansine Versus Trastuzumab as Adjuvant Therapy in Patients With HER2-Positive Breast Cancer Who Have Residual Tumor in the Breast or Axillary Lymph Nodes Following Preoperative Therapy (KATHERINE; NCT01772472) is a phase 3, open-label trial comprising of patients with HER2-positive early breast cancer with a residual invasive disease in the breast or axilla at surgery post-treatment with a neoadjuvant containing a taxane and trastuzumab [44]. Patients were randomly assigned to receive adjuvant T-DM1 or trastuzumab, which is the current standard of treatment, for 14 cycles. Among the 1,486 randomly assigned patients, invasive disease or death occurred in 91 patients in the T-DM1 group (12.2%) and 165 patients in the trastuzumab group (22.2%). Invasive disease-free survival was significantly higher in the T-DM1 group than the trastuzumab group (HR=0.50; 95% CI=0.39–0.64; p<0.001). The safety data were consistent with the known safety profile of T-DM1, with more adverse events being associated with T-DM1 than trastuzumab alone.

These results are clinically meaningful and could be used to establish a new standard of care for patients with residual disease after neoadjuvant therapy.

Sacituzumab govitecan-hziy in refractory metastatic triple-negative breast cancer

Sacituzumab govitecan-hziy is an antibody–drug conjugate against human trophoblast cell-surface antigen 2 (Trop-2), with SN-38, a cytotoxic warhead. Sacituzumab govitecan-hziy enables the delivery of high concentrations of SN-38 to tumors.

In a phase 1/2 single-group, multicenter trial involving 108 patients with triple-negative breast cancers and intravenously administered 10 mg/kg of sacituzumab govitecan-hziy on days 1 and 8 of each 21-day cycle, the response rate (3 CR and 33 PR) was 33.3% (95% CI=24.6–43.1) and the median duration of response was 7.7 months (95% CI=4.9–10.8) [45]. Four deaths occurred during treatment and 3 patients (2.8%) discontinued treatment due to adverse events. The grades 3 or 4 adverse events (in ≥10% of the patients) were anemia and neutropenia and 10 patients (9.3%) had febrile neutropenia.

As patients were heavily pretreated with a median of 3 previous therapies (range, 2 to 10), where standard chemotherapy is associated with low response rates (10% to 15%) and short PFS (2 to 3 months), the high response rate is remarkable and warrants further evaluation in future phase III trials.

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2. Combination therapy in breast cancer

Alpelisib for PIK3CA-mutated, hormone receptor–positive advanced breast cancer

More than 70% of breast cancer cases are hormone receptor (HR)–positive and HER2–negative, and approximately 40% of these patients have activating mutations in the PIK3CA gene, which results in the hyperactivation of the α isoform of PI3K. Alpelisib is an orally bioavailable, small-molecule, α-specific inhibitor of PI3K.

SOLAR-1 is a randomized, double-blind, placebo-controlled, phase 3 trial of fulvestrant plus alpesilib or placebo in patients with HR-positive, HER2-negative advanced breast cancer who had previously received endocrine therapy [46]. Patients were categorized into two cohorts according to their tumor-tissue PIK3CA mutation status (PIK3CA-mutated vs. not PIK3CA-mutated). The primary end point was PFS, as assessed by the investigator, in the cohort with PIK3CA-mutated cancer.

A total of 572 patients underwent randomization, including 341 patients with confirmed tumor-tissue PIK3CA mutations. In the cohort of patients with PIK3CA-mutated cancer, PFS at the median follow-up of 20 months was 11.0 months (95% CI=7.5–14.5) in the alpelisib–fulvestrant group and 5.7 months (95% CI=3.7–7.4) in the placebo-fulvestrant group (HR=0.65; 95% CI=0.50–0.85; p<0.001). In the cohort without PIK3CA-mutated cancer, the hazard ratio was 0.85 (95% CI=0.58–1.25). Further, the response rate was higher in the combination group in the PIK3CA-mutated cohort (26.6% vs. 12.8%). The most frequent grade 3 or 4 adverse events were hyperglycemia (36.6% in the alpelisib–fulvestrant group vs. 0.7% in the placebo–fulvestrant group), rash (9.9% vs. 0.3%), and diarrhea (6.7% vs. 0.3%).

The efficacy and safety profiles of alpelisib were found to be better than those of other PI3K inhibitors whose development was discontinued. Further, its clinical utility could be determined.

OS with fulvestrant plus anastrozole in metastatic breast cancer

In a previous report (S0226 study), the combination of anastrozole, an aromatase inhibitor, with fulvestrant, a selective estrogen-receptor down-regulator, was demonstrated to prolong PFS and marginally prolong OS relative to anastrozole alone [47]. The final results regarding OS was reported this year [48].

Of the 707 patients who had undergone randomization, 694 had data available for analysis. The combination therapy group had a median OS of 49.8 months relative to the 42.0 months observed in the anastrozole-alone group (HR for death=0.82; 95% CI=0.69–0.98; p=0.03). In a subgroup analysis, OS among women who did not previously receive tamoxifen was longer with the combination therapy than anastrozole alone (median, 52.2 and 40.3 months; HR=0.73; 95% CI=0.58–0.92); among women that had previously received tamoxifen, OS was similar between the 2 groups (median, 48.2 and 43.5 months; HR=0.97; 95% CI=0.74–1.27) (p=0.09 for interaction).

Conversely, other trials (FACT2 and SoFEA3) [49,50] revealed that the combination of an aromatase inhibitor and fulvestrant was not superior to the aromatase inhibitor alone. This could be observed in the patient population included in the S0226 study, where most patients did not have any prior exposure to endocrine therapy and might have been more sensitive to endocrine treatment.

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OS with ribociclib plus endocrine therapy in breast cancer

Although young age at the diagnosis of breast cancer has been associated with worse outcomes and less sensitivity to endocrine therapy, data on young premenopausal or perimenopausal women have been limited. In a previous report, ribociclib, a CDK4/6 inhibitor, combined with endocrine therapy (goserelin and letrozole or tamoxifen) was reported to improve PFS relative to endocrine therapy alone [51]. The updated OS, which was the key secondary endpoint, was reported this year [52].

The addition of ribociclib to endocrine therapy resulted in a significantly longer OS than treatment with endocrine therapy alone. In fact, the estimated OS at 42 months was 70.2% (95% CI=63.5–76.0) in the ribociclib group and 46.0% (95% CI=32.0–58.9) in the placebo group (HR=0.71; 95% CI=0.54–0.95; p=0.00973). The survival benefit observed in the subgroup containing 495 patients administered an aromatase inhibitor was consistent with that observed in the overall intention-to-treat population (HR for death=0.70; 95% CI=0.50–0.98).

These results validate the use of the CDK4/6 inhibitor combined with endocrine therapy as the first-line standard of care, even for premenopausal patients. The findings presented herein could also contribute to future trial designs for premenopausal or perimenopausal patients with breast cancer.

CONCLUSION

Today, more effort, time, and money are required before the safety and effectiveness of therapies can be investigated in clinical trials. Despite the need for more studies, many researchers are dedicated to improving the health of women worldwide. As a result, we anticipate the publication of pioneering research in the future.

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