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Meeting Report

Highlights from the gynecologic oncology track at the 2017 Annual Meeting of the American Society of Clinical Oncology

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INTRODUCTION

The American Society of Clinical Oncology (ASCO) 2017 Annual Meeting was held again at the McCormick Convention Center in Chicago, IL, USA. Over 37,500 international physicians, nurses, researchers, and exhibitors descended on the Windy City from June 2nd, 2017 through June 6th, 2017. This year's ASCO presidential theme, "Making a Difference in Cancer Care with You," embodied the principle of taking care of those with cancer by promoting teamwork among oncologic professionals to facilitate cancer advancements [1]. This review highlights the notable gynecologic oncology clinical research presented at the 2017 ASCO Annual Meeting.

For the 2017 ASCO, the gynecologic oncology track ran the full gamut of the meeting, with an oral abstract plenary session emphasizing practice changing clinical trials (**Table 1**), a poster session with over 100 posters from which 12 were selected for discussion, education sessions focused on survivorship and immunotherapy, and a final plenary that emblazoned the cancer genome. Each session underscored the new novel approaches and therapies involved in caring for women struggling with gynecologic malignancies.

1. Surgical trials: lymphadenectomy in ovarian neoplasms (LION) and Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) DESKTOP III/ENGOT ov20 trial

Surgical trials have been historically difficult to execute because of the inherent complexity of standardizing surgical procedures. Differences in technique and expertise between one surgeon to the next, as well as for the difficulty with blinding within a surgical trial continue to represent the most troublesome hurdles in trial design. The above notwithstanding, two successful surgical trials where presented this year, with findings that could change the surgical management of patients with advanced/recurrent ovarian cancer. The first trial was the lymphadenectomy (LAD) in ovarian cancer, or the LION trial. This trial was a randomized, prospective study of utilizing a systemic LAD vs. no LAD in those newly diagnosed with International Federation of Gynecology and Obstetrics (FIGO) stage IIB–IV ovarian cancer with clinically and radiologic negative lymph nodes (LNs) (**Fig. 1**). To overcome the surgeon expertise and technique variance, centers had to qualify in surgical skills prior to participation in the trial. Importantly, patients underwent randomization after complete surgical cytoreduction had been achieved, with optimal debulking defined as a complete macroscopic resection. This trial showed no improvement in overall survival (OS) (69 months with no LAD vs. 65 months with LAD; hazard ratio [HR]=1.06; 95% confidence interval [CI]=0.83–1.34;

Table 1. Summary of ASCO 2017 gynecologic oncology trials

Factor	First author	Trial and eligibility	Agent	Endpoints	Results	AEs
Surgical interventions	Harter P Abstract 5500	LION (NCT00712218) - Randomized prospective; primary ovarian cancer, FIGO IIB–IV	Surgical intervention	1°: OS 2°: PFS, QOL	Median OS: LNE 65.5 mo vs. No-LNE 69.2 mo (HR=1.06; 95% CI=0.83–1.34; p=0.650) Median PFS: 25.5 mo in both arms (HR=1.11; 95% CI=0.92–1.34)	LNE a/w longer surgery time, increased blood loss, increased transfusion rates, increased re-laparotomy rates, infections, and mortality within 60 days of surgery.
	Du Bois A Abstract 5501	AGO DESKTOP III/ENGOT ov20 (NCT01166737) - Randomized phase III interim analysis; platinum-sensitive recurrent ovarian cancer after 1st-line treatment week/+AGO score	Platinum-based cytotoxic therapy; surgical intervention	1°: OS 2°: PFS, TFST	OS: data still maturing Median PFS: 14 mo without and 19.6 mo with surgery (HR=0.66; 95% CI=0.52–0.83; p<0.001); with complete resection, the median PFS is 21.2 mo (HR=0.56 vs. no-surgery arm; p<0.001) TFST: 21 mo without vs. 13.9 mo with surgery (HR=0.61; 95% CI=0.48–0.77; p<0.001)	No excess mortality within the surgical arm and among the grade 3/4 AEs that occurred within 60 days, only leukopenia/neutropenia was more frequent in the no-surgery arm.
CT/RT	de Boer SM Abstract 5502	PORTEC-3 (NCT00411138) - Randomized phase III; high risk endometrial cancer	Platinum-based cytotoxic therapy+RT	1°: OS, FFS	5-yr OS: 82% for CTRT vs. 77% for RT (HR=0.79; 95% CI=0.57–1.12; p=0.183) 5-yr FFS: 76% for CTRT vs. 69% for RT (HR=0.77; 95% CI=0.58–1.03; p=0.078) Patients with stage III disease: 5-yr FFS: 69% for CTRT vs. 58% for RT (95% CI=0.45–0.97; p=0.032) 5-yr OS: 79% for CTRT vs. 70% for RT (HR=0.69; 95% CI=0.44–1.09; p=0.114)	Most common grade 3 or >AEs between both groups are hematological, gastrointestinal, or related to pain. The only significant difference between the 2 groups was with sensory/motor neuropathy that was seen more frequently in the chemo-radiaton group (grade 2).
	Matei D Abstract 5505	GOG 258 (NCT00942357) - Randomized phase III; stage III–IVA (<2 cm residual disease) or stage I–II serous or clear cell endometrial cancer	Platinum-based cytotoxic therap+RT	1°: RFS 2°: OS, toxicities, QOL	RFS: vaginal recurrence 3% for CTRT vs. 7% for CT (HR=0.36; 95% CI=0.16–0.82), pelvic and para-aortic recurrences 10% for CTRT vs. 21% for CT (HR=0.43; 95% CI=0.28–0.66); distant recurrences more common with 28% for CTRT vs. 21% for CT (HR=1.36; 95% CI=1.00–1.86) OS: data still maturing; but 5-yr OS estimated 70% CTRT and 73% CT	Common greater than grade 3 events were myelosupression (40% vs. 52%), gastrointestinal (13% vs. 4%), metabolic (15% vs. 19%), neurological (7% vs. 6%), and infectious (4% vs. 5%).
Anti-angiogenics	Ledermann JA Abstract 5506	ICON6 (NCT00532194) - Double-blind, placebo-controlled phase III — OS results; platinum-sensitive recurrent ovarian cancer after 1st-line treatment	Cedirinib VEGFRi	1°: OS 2°: PFS	OS: 19.9 mo in placebo and 27.3 mo in maintenance (HR=0.85; 95% CI=0.66–1.10; p=0.210) Median PFS: 8.7 mo in placebo and 11.0 mo in maintenance (HR=0.56; 95% CI-=0.44–0.70; p<0.001)	Diarrhea, neutropenia, hypertension, and voice changes were more common with CT+cediranib, and diarrhea, hypothyroidism, and voice changes were more common during maintenance cedirinib.
	Lheureux S Abstract 5522	Princess Margaret phase II consortium (NCT01914510) - Phase II; recurrent clear cell ovarian cancer	ENMD-2076 Aurora A kinase/ tyrosine kinase inhibitor	1°: ORR, 6-mo PFS	Median PFS: 3.7 mo (95% CI=3.4–4.4); in *ARID1A* loss was 4.1 mo (95% CI=3.5–10.3) vs. *ARID1A* positive 3.6 mo (95% CI=1.7–3.9) (p=0.024); in *PTEN* no change in PFS	Most common AEs were hypertension, nausea, and diarrhea.
	Dhani NC Abstract 5524	Princess Margaret, Chicago, and California phase II consortia; PHL86 (NCT01935934) - Single-arm phase II; recurrent/metastatic endometrial cancer	Cabozantinib Multi-target kinase inhibitor	1°: RR, 12-wk PFS 2°: OS; baseline molecular status of archival tumor	Median PFS: 4.8 mo (95% CI=4.4–6.4) with estimated 6-mo PFS of 43% (95% CI=27%–59%) Mutational analysis: *KRAS* with *PTEN* or *PIK3CA* mutations in 9 serous/endometrioid patients, 8/9 met 12-wk PFS endpoint, with a median PFS 5.9 mo (95% CI=4.1–15.4)	Most common toxicities were fatigue, nausea, diarrhea, and hand-foot syndrome. Most frequent grade 3/4 toxicity was hypertension.
PARPi	Friedlander M Abstract 5507	SOLO-2 (NCT01874353) - HRQOL analysis for patients in phase III SOLO-2 trial; platinum-sensitive recurrent BRCA+ovarian cancer after 2nd-line treatment with CR or PR	Olaparib PARPi	1°: FACT-O TOI 2°: duration of QOL by TWiST and QAPFS	FACT-O TOI: no detrimental effect on QOL for maintenance therapy with olaparib vs. placebo (–2.90 vs. –2.87; 95% CI=–2.19–2.13; p=0.980) TWiST: 13.5 mo with olaparib vs. 7.2 mo with placebo (95% CI=2.9–8.6; p<0.001) QAPFS: mean 14.0 mo with olaparib vs. 7.3 mo with placebo (95% CI=5.0–8.5; p<0.001)	Nausea, fatigue, vomiting, diarrhea, and abdominal pain. Heme AEs of anemia, neutropenia, and thrombocytopenia.
	Ledermann JA Abstract 5518	SOLO-2(NCT01874353) - Randomized phase III — AEs; platinum-sensitive recurrent BRCA +ovarian cancer after 2nd-line treatment with CR or PR	OlaparibPARPi	1°: AEs 2°: safety and tolerability	AEs of fatigue/asthenia, vomiting, and nausea improved as treatment continued, though could last for several months Most AEs were manageable by supportive treatment, dose interruptions (olaparib, 45%; placebo, 18%) and dose reductions (olaparib, 25%; placebo, 3%)	Most common AEs with olaparib were grade 1–2 and included; nausea, fatigue/asthenia, anemia, and vomiting. Anemia was the most common grade ≥3.
	Wolford JE Abstract 5516	Kauffmen et al, Study 10 & ARIEL2, NOVA Cost effective analysis; recurrent ovarian cancer	Niraparib, Rucaparib, Olaparib PARPi	1°: cost-effectiveness (cost vs. PFS) 2°: ICERs	Cost-effectiveness: platinums ($1,672/PFS mo), non-platinums ($6,688/mo), bevacizumab ($12,482/mo), olaparib ($16,469/mo), rucaparib ($16,781/mo), and niraparib ($18,157/mo with mutation and $18,253/mo without mutation)	AEs were factored into the model within the heme complication and non-heme complications nodes of the Markov Model.

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Table 1. Summary of ASCO 2017 gynecologic oncology trials (Continued)

Factor	First author	Trial and eligibility	Agent	Endpoints	Results	AEs
	Mirza MR Abstract 5517	NOVA (NCT0184724) - Randomized, controlled, double-blind, phase III — PR analysis; platinum-sensitive recurrent ovarian cancer with PR- ≥2 prior lines	Niraparib PARPi	1°: PFS 2°: OS, PFS2, CT-free interval, HRQOL	49% of patients in the *BRCA*mut and non-*BRCA*mut cohorts entered NOVA with a PR following the most recent platinum PFS events: *BRCA*mut 45% niraparib vs. 72% placebo patients non-*BRCA*mut; 56% niraparib and 80% placebo patients in the cohorts	Most common AEs were thrombocytopenia, anemia, neutropenia, leukopenia, palpitations, nausea, constipation, vomiting, abdominal pain/distention, mucositis/stomatitis, diarrhea, dyspepsia, dry mouth, fatigue, and decreased appetite.
	Del Campo JM Abstract 5560	NOVA (NCT0184724) - Randomized, controlled, double-blind, phase III — platinum resistant analysis; platinum-sensitive recurrent ovarian cancer with PR — ≥2 prior lines	Niraparib PARPi	1°: PFS (randomization-death or progressive disease) → estimated probability of disease progression after 6 mo	Platinum-reistant rates (in placebo arm): *BRCA*mut: 42% non-*BRCA*mut: 53% combined: 49%	Most common AEs were thrombocytopenia, anemia, neutropenia, leukopenia, palpitations, nausea, constipation, vomiting, abdominal pain/distention, mucositis/stomatitis, diarrhea, dyspepsia, dry mouth, fatigue, and decreased appetite.
	Matulonis UA Abstract 5534	NOVA (NCT0184724) - Randomized, controlled, double-blind, phase III — long-term benefit; platinum-sensitive recurrent ovarian cancer with PR — ≥2 prior lines	Niraparib PARPi	1°: PFS 2°: impact on subsequent therapy (PFS2-PFS1)	Estimated probability PFS at 24 mo: *BRCA*mut: 0.42 (95% CI=0.30–0.55) for niraparib vs. 0.16 (0.07–0.28) for placebo non-*BRCA*mut 0.27 (0.19–0.35) for niraparib vs. 0.12 (0.06–0.21) for placebo PFS2-PFS1: similar in the 2 treatment groups	Most common AEs were thrombocytopenia, anemia, neutropenia, leukopenia, palpitations, nausea, constipation, vomiting, abdominal pain/distention, mucositis/stomatitis, diarrhea, dyspepsia, dry mouth, fatigue, and decreased appetite.
	Friedlander M Abstract 3013	The Safety, Pharmacokinetics and Antitumor Activity of the BGB-A317 in Combination With the BGB-290 in Subjects With Advanced Solid Tumors (NCT02660034) - Phase 1/1b; advanced solid tumors (ovarian, breast, prostate, gastric, bladder, pancreatic, and small cell lung cancers)	BGB-A317 Anti-PD-1 immunotherapy BGB-290 PARPi	1°: MTD, RP2D 2°: preliminary anti-tumor activity, pharmokinectics profile	MTD: BGB-A317 200 mg IV q 3 wk + BGB-290 40 mg PO BID 38 patients were treated → decreased tumor burder in 16, PR in 7 (ovary, uterine, pancreatic) and 1 CR (ovary)	Most common AEs was fatigue; Immune-related AEs reported were hypophysitis and autoimmune hepatitis.
Immuno-therapy	Varga A Abstract 5513	KEYNOTE-028 (NCT02054806) - Nonrandomized, multi-cohort phase Ib trial — 15.5-mo follow-up; platinum resisteant ovarian cancer; PD-L1 positivity	Pembrolizumab Anti-PD-1 immunotherapy	1°: safety and tolerability 2°: confirmed ORR	ORR: 11.5% (95% CI=2.4%–30.2%) Tumor reduction: 6/26 (23.1%) of patients Median PFS: 1.9 mo (95% CI=1.8–3.2) OS: 13.1 mo (95% CI=6.7–17.5)	Most common were arthralgia, nausea, pruritus, rash, and diarrhea.
	Hollebecque A Abstract 5504	CheckMate 358 (NCT02488759) - Single-arm, multi-cohort; phase I/II; recurrent/metastatic HPV-associated cancers	Nivolumab Anti-PD-1 immunotherapy	1°: ORR, safety 2°: DOR, PFS, OS	ORR at 31 wk: 21% and disease control rate (ORR+stable disease) 71% Median PFS: 5.5 mo (95% CI=3.5–not reached) OS: data still maturing, but median OS at 6 mo was 87%	Immune-mediated reactions: enterocolitis, hepatitis, dermatitis (including toxic epidermal necrolysis), neuropathy, and endocrinopathy.
	Schellens JH Abstract 5514	KEYNOTE-158 (NCT02628067) - Single-arm, multi-cohort phase II — preliminary results; advanced cervical squamous cell cancer with progression or intolerance to standard therapy	Pembrolizumab Anti-PD-1 immunotherapy	1°: ORR 2°: DOR, safety/efficacy	ORR: 17% (95% CI=8%–31%) ORR at ≥27 wk: 27% (95% CI=8%–55%)	Most common were arthralgia, nausea, pruritus, rash, and diarrhea.
Anti-hormone	Knipprath-Mészáros AM Abstract 5515	Aromatase inhibitor maintenance therapy in high grade advanced ovarian cancer to delay first recurrence Non-randomized, controlled trial; primary ovarian cancer; (FIGO III–IV), ER+, after adjuvant CT	Letrozole Aromatase inhibitor	1°: PFS	PFS at 12 mo: 65% without and 84% with letrozol PFS at 24 mo: 46% without and 74% with letrozol (p=0.020)	Not reported.

a/w, associated with ; AE, adverse event; AGO, Arbeitsgemeinschaft Gynäkologische Onkologie; ASCO, American Society of Clinical Oncology; CI, confidence interval; CR, complete response; CT, chemotherapy; CTRT, chemotherapy and radiation therapy; DOR, duration of response; ER, estrogen receptor; FACT-O TOI, Functional Assessment of Cancer Therapy-Ovarian Trial Outcome Index; FFS, failure-free survival; FIGO, International Federation of Gynecology and Obstetrics; GOG, Gynecologic Oncology Group; HPV, human papillomavirus; HR, hazard ratio; HRQOL, health-related quality of life; HRD, human resources division; ICER, incremental cost-effectiveness ratio; LION, lymphadenectomy in ovarian neoplasms; LN, lymph node; LNE, lymphadenectomy; MTD, maximum-tolerated dose; ORR, overall response rate; OS, overall survival; PARPi, poly (adenosine diphosphate [ADP]-ribose) polymerase inhibitor; PD-L1, programmed death-ligand 1; PD-1, programmed death-1; PFS, progression-free survival; PORTEC, Postoperative Radiation Therapy in Endometrial Carcinoma; PR, partial response; QAPFS, quality-adjusted progression-free survival; QOL, quality of life; RFS, recurrence-free survival; RP2D, recommended phase II dose; RR, response rate; RT, radiation therapy; SOLO, studies of olaparib in ovarian cancer; TFST, time to start of first subsequent therapy; TWiST, time without symptoms of disease or toxicity of treatment; VEGFRi, vascular endothelial growth factor receptor inhibitor.

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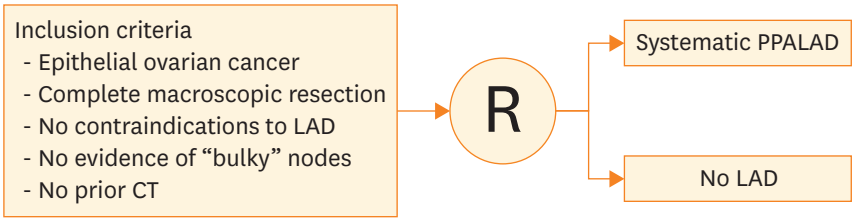

Fig. 1. LION trial design schema.
LAD, lymphadenectomy; LION, lymphadenectomy in ovarian neoplasms; PPALND, pelvic and para-aortic lymphadenectomy; R, randomize.

p=0.650) or progression-free survival (PFS) (26 months in both arms; HR=1.11; 95% CI=0.92–1.34; p=0.300) in the LAD group, even when micro-metastases were discovered. Furthermore, in the patients that had received a LAD, they demonstrated higher rates of perioperative and postoperative complications (e.g., infections, lymphocysts, and increased rate of re-laparotomy), and postoperative mortality, thus indicating that standard LAD in those with no clinical or radiographic evidence of lymphadenopathy is unwarranted [2].

The second gynecologic surgical trial was the AGO DESKTOP III/ENGOT ov20 study. This was an interim analysis of the randomized, phase III trial comparing 2nd-line chemotherapy (CT) vs. secondary cytoreductive surgery followed by CT in those patients with platinum-sensitive, recurrent ovarian cancer (**Fig. 2**). To be eligible for the study, patients had to have a positive AGO-score, including an Eastern Cooperative Oncology Group (ECOG) performance score of 0, complete cytoreduction at the time of their initial surgery, and <500 mL of ascites at recurrence, all previously shown in retrospective studies to be positive predictors of surgical resectability for secondary cytoreductive surgery. CT was chosen based on institutional preference. OS data is still maturing, but median PFS and time to start of first subsequent therapy (TSFT) was significantly improved in those that had received secondary cytoreductive surgery (PFS: 14 months without vs. 20 months with surgery; HR=0.66; 95% CI=0.52–0.83; p<0.001 and TSFT: 21 months without vs. 14 months with surgery; HR=0.61, 95% CI=0.48–0.77; p<0.001), even in those patients where complete cytoreduction was not achieved. Additionally, there was no substantial differences in grade 3 or above adverse events (AEs) between the 2 groups, except for myelosuppression which was more common in the CT group [3].

2. Postoperative radiation therapy [RT] for endometrial cancer: Postoperative Radiation Therapy in Endometrial Carcinoma (PORTEC)-3 and Gynecologic Oncology Group (GOG) 258

Though its widely known that surgery is the primary treatment modality for endometrial cancer, the addition of adjuvant therapy for those with intermediate or greater recurrence

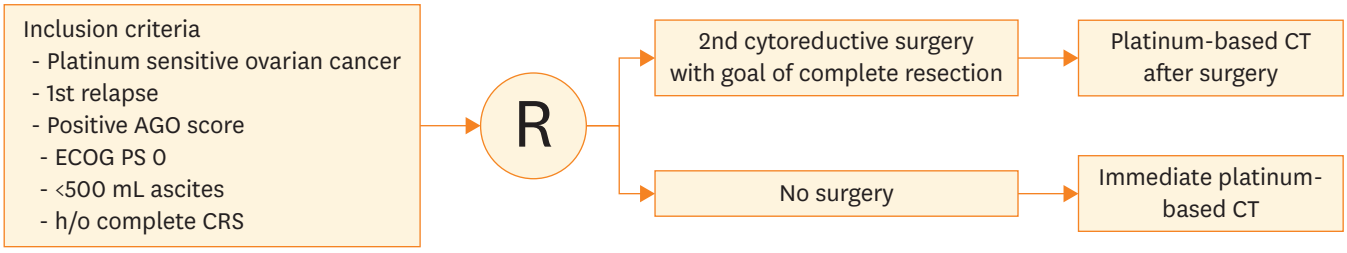

Fig. 2. AGO DESKTOP III/ENGOT ov20 design schema.
AGO, Arbeitsgemeinschaft Gynäkologische Onkologie; CRS, cytoreductive surgery; CT, chemotherapy; ECOG, Eastern Cooperative Oncology Group; h/o, history of; PS, performance score.

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risk still varies from institution to institution as there has been a lack of standardization for adjuvant treatment guidelines.

Two trials presented at ASCO this year, PORTEC-3 and GOG 258 explored the role of chemoradiation therapy (CRT), RT alone, or CT alone, in the adjuvant space. While the previously reported PORTEC-2 study emphasized the benefit of utilizing vaginal brachytherapy to decrease vaginal recurrences in those patients with high-intermediate risk endometrial cancer, PORTEC-3 specifically was designed to compare adjuvant CT administration concurrently with and subsequent to RT vs. RT alone in the high-risk endometrial cancer patients (**Fig. 3**). With the final endpoints of 5-year OS and failure-free survival (FFS), the long awaited final data reported at the ASCO 2017 revealed that adjuvant CT did not significantly improve the 5-year OS (82% CTRT vs. 77% RT; HR=0.79; 95% CI=0.57–1.12; p=0.183) or FFS (76% CTRT vs. 69% RT; HR=0.77; 95% CI=0.58–1.03; p=0.078), except in those with stage III endometrial cancer where there was shown to be an 11% improvement in FFS in those who received adjuvant CT vs. RT alone. Furthermore, this trial also contained an extensive quality of life analysis, that correlated the more severe toxicities experienced by those who received adjuvant CT with lower quality of life during and 6 months after the treatment period [4].

As a superiority trial, GOG 258 examined the difference between CRT and CT alone in patients with stage III–IVA endometrial cancer optimally debulked, which they defined as less than 2 cm of residual disease (**Fig. 4**). The trial results demonstrated that although the addition of radiation did reduce the local vaginal recurrence rates (3% CTRT vs. 7% CTRT; HR=0.36; 95% CI=0.16–0.82), distal recurrences were more common (28% CTRT vs. 21% CT; HR=1.36; 95% CI=1.00–1.86) and therefore was no overall improvement in recurrence-free survival (RFS: HR=0.9; 95% CI=0.74–1.10). In addition, although the acute toxicities were similar between the CRT and CT alone groups, there was a slight increase in toxicity for the chemoradiation group (e.g., myelosuppression, gastrointestinal, metabolic, and neurologic toxicities), calling into question the addition of radiation as adjuvant radiation [5]. Consequently then, although these studies presented at ASCO are distinct, PORTEC-3 and GOG 258 both indicate that there may be no role for CRT in those patients with endometrial cancer that are at an advanced stage and at high risk for recurrence.

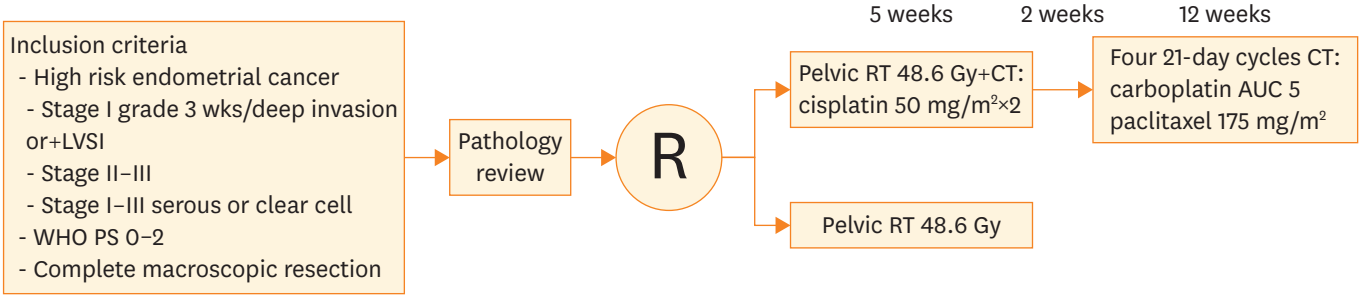

Fig. 3. PORTEC-3 design schema.
Radiotherapy given in 1.8 Gy daily fractions.
Cisplatin (Platinol®; Bristol-Myers Squibb Company, Princeton, NJ, USA), paclitaxel (Taxol®; Bristol-Myers Squibb Company).
CT, chemotherapy; LVSI, lymphovascular space invasion; PORTEC, Postoperative Radiation Therapy in Endometrial Carcinoma; PS, performance score; R, randomize; RT, radiation therapy; WHO, World Health Organization.

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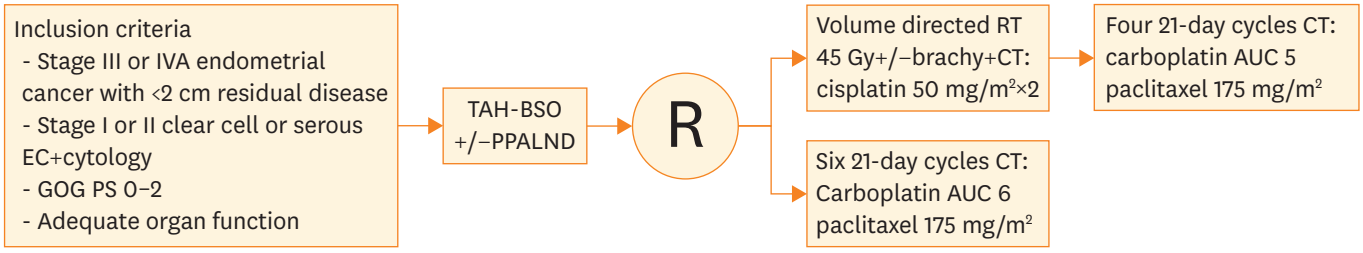

Fig. 4. GOG 258 design schema.
CT, chemotherapy; EC, endometrial cancer; GOG, Gynecologic Oncology Group; PPALND, pelvic and para-aortic lymphadenectomy; PS, performance score; R, randomize; RT, radiation therapy; TAH-BSO, total abdominal hysterectomy with bilateral salpingo-oophorectomy.

3. Breaking the immune tolerance of cervical cancer: CheckMate-358 and KEYNOTE-158

Recurrent and advanced human papillomavirus (HPV)-associated cancers, especially cervical cancer, have overall dismal PFS and response rates to standard systemic chemotherapy doublets. Some progress has been made with the survival advantage (i.e., 3.7 months) conferred through integration of antiangiogenesis therapy using the anti-vascular endothelial growth factor (VEGF) molecule, bevacizumab. Using a bevacizumab-based triplet regimen, response rates in the first-line setting for treatment of recurrent or metastatic disease approach 50%. No effective therapies have been identified for second-line treatment with responses of available chemotherapy ranging from 0% up to 10%. Thus, prognosis remains poor and is certainly not aided through the ability of HPV to escape host immune-mediated identification and eradication. It is believed that this tenacious virility is captured by the capacity of HPV to induce increased expression of programmed death-ligand 1 (PD-L1), evidenced by the upregulated expression of PD-L1 in cervical cancer. This has prompted immunotherapy trials in cervical cancer in order to find agents that can break this immune tolerance.

As a phase I/II, single-arm, multi-cohort trial, CheckMate-358 enrolled patients with recurrent or metastatic HPV-associated cancers that had received no more than 2 prior lines of systemic therapy (**Fig. 5**). All patients received nivolumab (Opdivo®; Bristol-Myers Squibb Company) monotherapy, a programmed death-1 (PD-1) inhibitor, until progression or toxicity. HPV and PD-L1 status was not assessed prior to enrollment. HPV and PD-L1 status was not assessed prior to enrollment. The primary endpoint was overall response rate (ORR) and secondary endpoints included duration of response (DOR), PFS, and OS. Of the 24 patients enrolled with cervical, vaginal and vulvar patients, only the cervical cancer patients demonstrated a response (n=19 cervix patients; 1 complete response [CR] and 4 partial response [PR] for a 26% ORR; 95% CI=9.1–51.2), and those responses proved to be durable

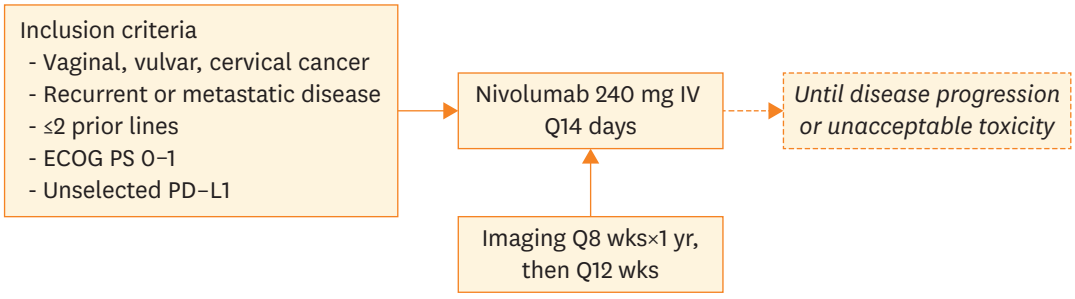

Fig. 5. CHECKMATE-358 design schema.
Nivolumab (Opdivo®; Bristol-Myers-Squibb Company).
ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed death-ligand 1; PS, performance score; Q, every.

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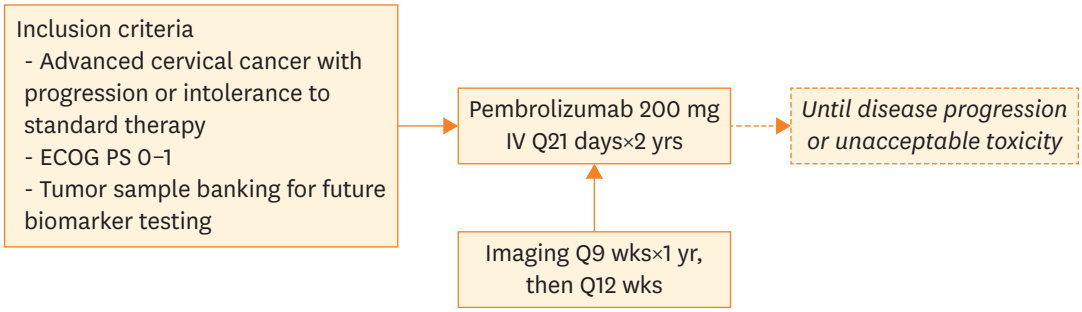

Fig. 6. KEYNOTE-158 design schema.
ECOG, Eastern Cooperative Oncology Group; PS, performance score; Q, every.

for at least 6 months. The disease control rate seems to be comparable irrespective of PD-L1 expression, however, because of the small sample size it is difficult to determine the actual significance. Additionally, nivolumab was very well tolerated with minimal toxicity [6].

Similarly, KEYNOTE-158 preliminary results were also based on a single-arm, multi-cohort phase II trial investigating anti-PD-1 immunotherapy for the treatment of cervical cancer (**Fig. 6**). Enrollment included those patients with advanced cervical squamous cell cancer with noted progression or intolerance to standard therapy. In KEYNOTE-158 patients received pembrolizumab monotherapy for 2 years or until progression or toxicity. As a phase II trial, this study investigated the safety and efficacy of the PD-1 inhibitor, as well as the anti-tumor activity as ORR and DOR. PD-L1 status was not assessed at time of enrollment but was retrospectively reviewed. Notably the ORR seemed to strengthen with an increase in follow-up as those initially enrolled had an ORR of 17% (95% CI=8%–31%) and at greater than 27 weeks the ORR increased to 27% (95% CI=8%–55%) [7]. It is unclear whether initial responses had been masked by pseudoprogression. Results from these 2 trials have prompted the development of at least 2 large phase III randomized trials using anti-PD-1/PD-L1 molecules for recurrent/metastatic cervical cancer in the first-line and/or second-line setting.

4. Spotlight on the OAK study of non-small cell lung cancer

While not a gynecologic cancer trial, the OAK study presented at ASCO, was a phase III trial investigating atezolizumab (Tecentriq™ 1,200 mg IV Q3 weeks; Genentech, Inc., South San Francisco, CA, USA), a PD-L1 inhibitor, vs. docetaxel (Taxotere® 75 mg/m2 IV Q3 weeks; Aventis Pharmaceuticals Inc., Bridgewater, NJ, USA) for the treatment of advanced non-small cell lung cancer in patients who had previously been treated with two or more lines of chemotherapy. The importance of this trial is that it is the largest phase III randomized trial of checkpoint inhibition to report and the study design was unique in that provided clinical benefit was apparent, patients on the atezolizumab arm were allowed to continue on atezolizumab beyond progression by RECIST criteria. Fifty-one percent of the patients (n=162) randomized to the atezolizumab arm who progressed by RECIST v1.1 (n=332), continued atezolizumab post-progression. For the entire study, the primary analysis of OS at the time of progression by RECIST favored atezolizumab (8.6 vs. 6.4 months; HR=0.73; 95% CI=0.62–0.87). However, when focusing on the basket of patients that continued with atezolizumab post-progression, the median OS was 12.7 months (95% CI=9.3–14.9). This phenomenon of post-progression prolongation of survival suggests that cancer immunotherapy may alter tumor biology so that the survival benefit conferred by checkpoint inhibition may be masked by traditional RECIST endpoints such as PFS and response rate [8].

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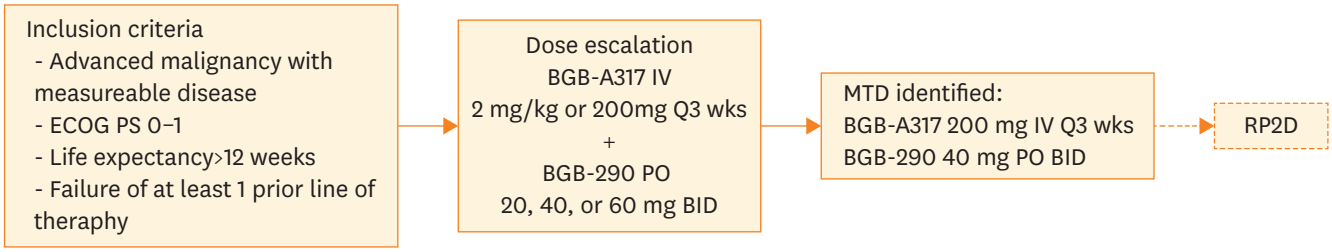

Fig. 7. Anti-PD-1 monoclonal antibody BGB-A317+PARPi BGB-290 in advanced solid tumors design schema.
BID, twice a day; ECOG, Eastern Cooperative Oncology Group; MTD, maximum tolerated dose; PD-1, programmed death-1; PO, per os; PS, performance score; Q, every; RP2D, recommended phase II dose.

5. Novel combinations: poly (adenosine diphosphate [ADP]-ribose) polymerase inhibitor (PARPi)+immunotherapy

As the field moves forward, novel combinations and translational science will continue to be important. Friedlander et al. [9], explored the hypothesis of combining synthetic lethality with checkpoint inhibition in a study that evaluated not only gynecologic cancers, but also advanced solid tumors of the breast, prostate, stomach, bladder, pancreas and small-cell lung cancer. The hypothesis invokes the upregulation of tumor-specific antigens, ultimately increasing the tumors susceptibility to immune-mediated detection and clearance.

The study was a phase I/Ib, dose escalation and dose expansion trial, that combined the anti-PD-1 monoclonal antibody, BGB-A317, with a PARPi, BGB-290 (**Fig. 7**). As a phase I trial, the primary endpoints were to determine the maximum tolerated dose (MTD) and the recommended phase II dose (RP2D). Secondary endpoints included exhibiting the preliminary anti-tumor activity, as well as the pharmacokinetics of the drug combination. With a total of 38 patients on trial at the time the data was presented at ASCO, a MTD was determined and 16 patients had demonstrated a tumor response by evidence of observed decrease in tumor burden, as well as PR in 5 patients and CR in 1 patients with specifically with ovarian cancer, indicating not only the clinical feasibility of the combination, but the exciting promise that these novel combinations hold based on our understanding of their symbiotic pharmacokinetics, prompting further clinical development of this combination, as well as other novel combinations [9]. The RP2D for BGB-290 is 60 mg BID, but has yet to be determined for the combination.

6. Other studies of interest: PARPi, anti-angiogenic, and anti-hormonal therapies

Other notable trials presented at the 2017 ASCO Annual Meeting were studies containing PARPi, anti-angiogenics, and an anti-hormonal agent. The PARPi studies included 2 studies focused on the studies of olaparib (Lynparza™; Patheon Pharmaceuticals, Inc., Cincinnati, OH, USA) in ovarian cancer (SOLO)-2 trial, 3 trials that focused on the NOVA trial and a cost-effectiveness study that focused on the 3 Food and Drug Administration (FDA) approved PARPi. The SOLO-2 trial was a randomized, double-blind, multi-center, phase II trial investigating olaparib as a maintenance monotherapy vs. placebo in patients with platinum-sensitive, *BRCA* mutation positive (*BRCA*mut) ovarian cancer. The significantly increased PFS of this study that showed a 70% reduction in progression/death with olaparib was presented at the 2017 Society of Gynecologic Oncology (SGO) Meeting in National Harbor, MD, USA [10]. At this year's ASCO Annual Meeting, the SOLO-2 data presented was concentrated on the secondary findings, AEs and health-related quality of life (HRQOL). AE data presented, found that for the most part the AEs reported for those patients on the olaparib maintenance therapy

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were grade 1–2, improved over time while on continued treatment, and were largely managed easily with dose reductions, interruptions or supportive care [11]. The HRQOL analysis of SOLO-2, utilized the Functional Assessment of Cancer Therapy-Ovarian Trial Outcome Index (FACT-O TOI) to measure quality of life, incorporating functional and physical well-being assessed at multiple time points during treatment. Results from this study indicated that there were no significant negative effects of the maintenance olaparib on quality of life, and combining the quality of life (QOL) data with the PFS data to create a quality-adjusted PFS (QAPFS), showed a significantly improved QAPFS of 14% for olaparib vs. the 7% for placebo [12]. The NOVA trial (originally reported at the 2016 Annual Congress of the European Society of Medical Oncology with secondary endpoints presented at the 2017 SGO Annual Meeting), was a randomized, double blind phase III trial comparing niraparib (Zejula™; TESARO, Inc., Waltham, MA, USA) maintenance monotherapy vs. placebo, which showed a significant increase in PFS despite *BRCA* mutation status [13]. The 3 additional NOVA studies presented at ASCO highlighted analyses of efficacy of niraparib maintenance monotherapy on partial response, development of platinum resistance and the long-term benefit and its effect on subsequent therapies. These studies found that those with a partial response as well as those with acquired platinum-resistance also enjoyed the PFS benefits observed in the overall study population [14,15]. In addition, maintenance therapy with niraparib was not accompanied by a negative impact on subsequent therapies at progression [16]. Finally, a cost-effective analysis was presented that evaluated the three FDA-approved PARPi, olaparib, niraparib, and rucaparib (Rubraca®; Clovis Oncology, Inc., Boulder, CO, USA) as they were approved, in comparison to the chemotherapeutic agents utilized for the treatment of recurrent ovarian cancer (**Fig. 8**, Markov chain). With costs prior to progression of $159,748 for olaparib, $186,269 for rucaparib, and $529,821 for niraparib maintenance for those with a mutation the costs are 8.5, 10 and 28 times the cost of platinum therapies concluding that the high monthly cost of the PARPi(s) ($17,700 for niraparib, $16,488 for rucaparib, and $16,178 for olaparib) were not balanced by the costs of the IV agents, even when factoring in costs of infusion and associated toxicities, more commonly found with the chemotherapeutic therapies [17].

There were 3 important trials presented investigating anti-angiogenic therapies. The data from ICON-6, a phase III, 3-arm double blind trial examining cediranib (AZD2171 20 mg PO every day [QD]; AstraZeneca Pharmaceuticals, Wilmington, DE, USA) with CT and as a maintenance vs. placebo with CT in platinum-sensitive recurrent ovarian cancer, was originally reported in 2016 [18]. The data showed a significant increase in PFS at the time of the publication and possibly a gain in OS. Unfortunately, the ICON-6 study team reported

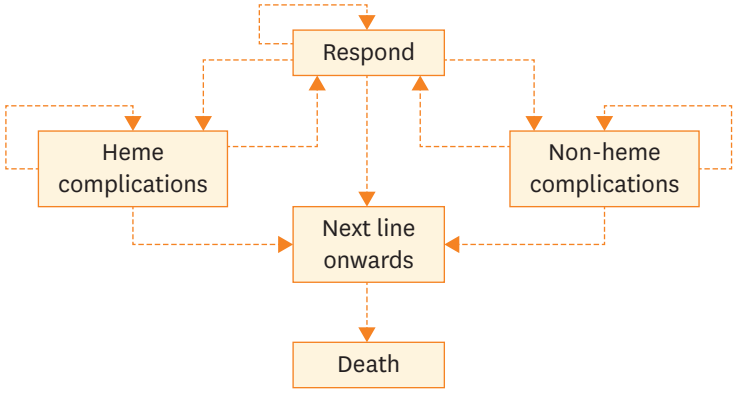

Fig. 8. Cost effective analysis of FDA approved PARPi(s): the Markov model.
FDA, Food and Drug Administration; PARPi, poly (adenosine diphosphate [ADP]-ribose) polymerase inhibitor.

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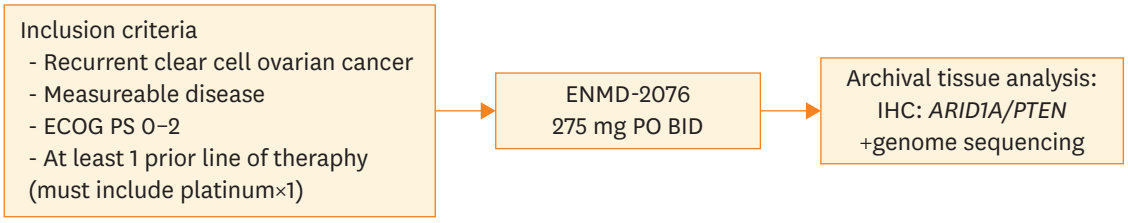

Fig. 9. Princess Margaret phase II consortium: ENMD-2076 in setting of *ARID1A* and *PTEN* expression design schema.
BID, twice a day; ECOG, Eastern Cooperative Oncology Group; IHC, immunohistochemistry; PO, per os; PS, performance score.

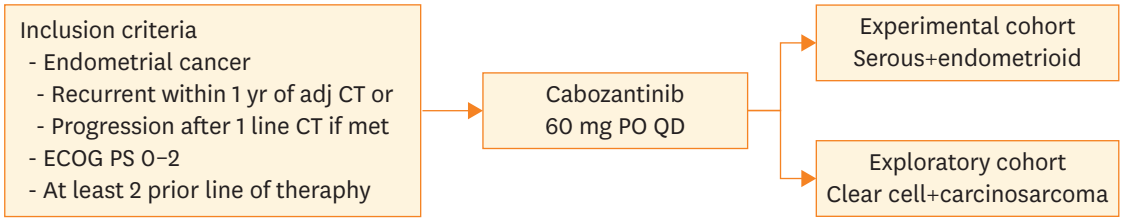

Fig. 10. Princess Margaret, Chicago, and California phase II consortia: PHL86 design schema.
Cabozantinib (Cometriq™; Exelixis, Inc., South San Francisco, CA, USA).
CT, chemotherapy; ECOG, Eastern Cooperative Oncology Group; PO, per os; PS, performance score; QD, every day.

at ASCO 2017 that at final analysis there was no significant improvement in OS (20 months for CT+placebo vs. 27 months for CT+cediranib; HR=0.85; 95% CI=0.66–1.10; p=0.210) that could be attributed to the incorporation of cediranib into the treatment plan [19]. A second trial examining anti-angiogenic therapy utilized tyrosine kinase inhibitor, ENMD-2076. This phase II trial was notable for its specificity for recurrent clear cell ovarian cancer in those who had received a prior platinum in the setting of *ARID1A* and *PTEN* expression (**Fig. 9**). In this study loss of *ARID1A* expression (a known negative prognostic factor in clear cell ovarian cancer), correlated with significantly improved PFS at 6 months (33% with *ARID1A* loss vs. 20%; HR not reported) among women receiving ENMD-2076 [20]. The last anti-angiogenic trial we will discuss was a trial that explored the application of anti-angiogenic therapy for recurrent, metastatic endometrial cancer. This trial was a multi-center, phase II trial utilizing the multi-targeted kinase inhibitor, cabozantinib, in patients who recurred within one year of receiving adjuvant treatment (**Fig. 10**). Durable responses ranging from 3 to 12 months were observed in patients with endometrioid histology as well as among those with serous cancers. These findings are noteworthy given that there is an absence of acceptable second-line therapies for patients with advanced/recurrent endometrial cancers [21].

Additionally, there was a trial considering an anti-hormonal agent to be used as a maintenance therapy in newly diagnosed grade 3, FIGO stage III/IV ovarian cancer with proven estrogen receptor (ER) positivity. A single institution, prospective trial, patients with ER positive advanced ovarian cancer were given aromatase inhibitor, letrozole, as a maintenance therapy with the primary endpoint of PFS (**Fig. 11**). The PFS reported was significantly increased for those receiving the aromatase inhibitor maintenance therapy at 12 months (65% vs. 84%) and 24 months (46% vs. 74%) (p=0.020; HR not reported) [22]. Although letrozole has recently shown promise as a maintenance therapy for low grade ovarian cancer by a trial performed by Gershenson et al. [23], this is the first study investigating its use within advanced, high grade ovarian tumors. These findings merit further analysis of utilizing anti-hormonal agents as maintenance therapy in low grade, as well as high grade ovarian cancer.

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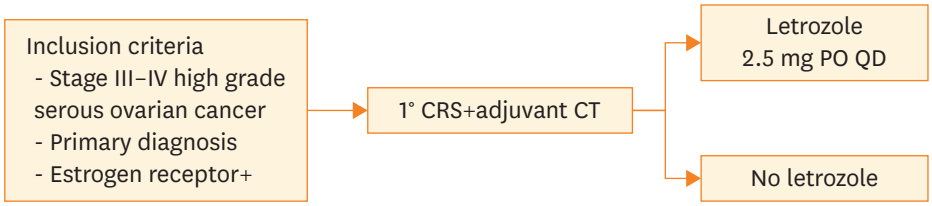

Fig. 11. Aromatase inhibitor maintenance therapy design schema.
Letrozole (Femara®; Novartis Pharma AG, Basel, Switzerland).
CRS, cytoreductive surgery; CT, chemotherapy; PO, per os; QD, every day.

CONCLUSION

In the previous decade, the therapeutic landscape in ovarian cancer was dominated by debate on the definition of and the survival advantage afforded through optimal cytoreduction, the efficacy and tolerability of intravenous-intraperitoneal chemotherapy, the reproducibility of the Japanese dose-dense paclitaxel data, and candidacy for neoadjuvant chemotherapy. As seen at this latest ASCO Annual Meeting, the paradigm has shifted with scientific inquiry focused on novel approaches using targeted therapy, including checkpoint blockade, synthetic lethality, and antivascular therapies such as VEGF inhibition. As new molecules are identified, they also are likely to be combined into novel therapeutic regimens to undergo further clinical evaluation. The immediate future in gynecologic cancer research is likely to place emphasis on such novel combinations, including PARP-1 and checkpoint dual inhibition. Further along, we are likely to harness the therapeutic potential of cancer stem cell identification and targeting [24], gene editing (e.g., CRISPR/Cas 9), and ultimately, gene therapy. Of course, the role of translational science in our field is implicit.

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