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 IIIB–IV ovarian cancer (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

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<th>Results</th>
<th>AEs</th>
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<tr>
<td>Surgical interventions</td>
<td>Harter P</td>
<td>LION (NCT00772218) - Randomized prospective; primary ovarian cancer, FIGO III–IV</td>
<td>Surgical intervention</td>
<td>1°: OS</td>
<td>Median OS: LNE 65.5 mo vs. No-LNE 69.2 mo (HR=1.06; 95% CI=0.83–1.34; p=0.60)</td>
<td>LNE a/w longer surgery time, increased blood loss, increased transfusion rates, increased re-laparotomy rates, infections, and mortality within 60 days of surgery. 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.</td>
</tr>
<tr>
<td></td>
<td>Du Bois A</td>
<td>AGO DESKTOP II/ENGOT ov20 (NCT01667377) - Randomized phase III interim analysis; platinum-sensitive recurrent ovarian cancer after 1st-line treatment week/+AGO score</td>
<td>Platinum-based cytotoxic therapy; surgical intervention</td>
<td>2°: PFS, QOL</td>
<td>OS: data still maturing</td>
<td></td>
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<tr>
<td></td>
<td>de Boer SM</td>
<td>PORTEC-3 (NCT00411388) - Randomized phase III; high risk endometrial cancer</td>
<td>Platinum-based cytotoxic therapy+RT</td>
<td>2°: OS, FFS</td>
<td>5-yr OS: 62% for CT vs. 77% for RT (HR=0.79; 95% CI=0.57–1.12; p=0.183)</td>
<td></td>
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<tr>
<td>Anti-angiogenics</td>
<td>Ledermann JA</td>
<td>ICON6 (NCT00352194) - Double-blind, placebo-controlled phase III — OS results; platinum-sensitive recurrent ovarian cancer after 1st-line treatment</td>
<td>Cediranib</td>
<td>1°: OS</td>
<td>OS: 19.9 mo in placebo and 27.3 mo in maintenance (HR=0.85; 95% CI=0.66–1.10; p=0.210)</td>
<td>Diarrhea, neutropenia, hypertension, and voice changes were more common with CT+cediranib, and diarrhea, hypothyroidism, and voice changes were more common during maintenance cediranib.</td>
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<tr>
<td></td>
<td>Lheureux S</td>
<td>ENMD-2076 Aurora A kinase/tyrosine kinase inhibitor (NCT0194510) - Phase II; recurrent clear cell ovarian cancer</td>
<td>ENMD-2076</td>
<td>1°: ORR, 6-mo PFS</td>
<td>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=0.034); in PTEN no change in PFS</td>
<td>Most common AEs were hypertension, nausea, and diarrhea.</td>
</tr>
<tr>
<td></td>
<td>Dhani NC</td>
<td>Cabozantinib Multi-target kinase inhibitor (NCT01935934) - Single-arm phase II; recurrent/metastatic endometrial cancer</td>
<td>Cabozantinib</td>
<td>1°: RR, 12-wk PFS</td>
<td>Median PFS: 4.8 mo (95% CI=4.4–6.4) with estimated 6-mo PFS of 43% (95% CI=27%–59%)</td>
<td>Most common toxicities were fatigue, nausea, diarrhea, and hand-foot syndrome. Most frequent grade 3/4 toxicity was hypertension.</td>
</tr>
<tr>
<td>PARPi</td>
<td>Friedlander M</td>
<td>SOLO-2 (NCT0174353) - HRQOL analysis for patients in phase III SOLO-2 trial; platinum-sensitive recurrent BRCACA ovarian cancer after 2nd-line treatment with CR or PR</td>
<td>Olaparib</td>
<td>1°: FACT-O TOI</td>
<td>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)</td>
<td>Nausea, fatigue, vomiting, diarrhea, and abdominal pain. Heme AEs of anemia, neutropenia, and thrombocytopenia.</td>
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<td></td>
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<td></td>
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<td>2°: duration of QOL by TWIST and QAPFS</td>
<td>TWIST: 15.5 mo with olaparib vs. 7.2 mo with placebo (95% CI=−2.9–8.6; p=0.001)</td>
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<tr>
<td></td>
<td>Ledermann JA</td>
<td>SOLO-2 (NCT0174353) - Randomized phase III — AEs; platinum-sensitive recurrent BRCACA ovarian cancer after 2nd-line treatment with CR or PR</td>
<td>Olaparib</td>
<td>1°: AEs</td>
<td>AEs of fatigue/asthenia, vomiting, and nausea</td>
<td>Most common AEs with olaparib were grade 1/2 and included: nausea, fatigue/asthenia, anemia, and vomiting. Anemia was the most common grade ≥3.</td>
</tr>
<tr>
<td></td>
<td>Wolford JE</td>
<td>Kauffmen et al.</td>
<td>Cost effective analysis; recurrent ovarian cancer</td>
<td>Niraparib, Rucaparib, Olaparib</td>
<td>1°: cost-effectiveness (cost vs. PFS)</td>
<td>Cost-effectiveness: platinum ($1,672/PFS mo), non-platinum ($6,668/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)</td>
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(continued to the next page)
Table 1. Summary of ASCO 2017 gynecologic oncology trials (Continued)

<table>
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<tr>
<td>Inhibitor therapy</td>
<td>Varga A</td>
<td>Abstract 5513</td>
<td>Pembrolizumab</td>
<td>Anti-PD-1 immunotherapy</td>
<td>1°: safety and tolerability; 2°: confirmed ORR</td>
<td>ORR: 11.5% (95% CI=2.4%–30.2%)</td>
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<tr>
<td></td>
<td></td>
<td>(NCT02054804)</td>
<td>Nonrandomized, multi-cohort phase Ib trial — 15.5-mo follow-up; platinum resistant ovarian cancer</td>
<td>Pembrolizumab</td>
<td>Anti-PD-1 immunotherapy</td>
<td>1°: safety and tolerability; 2°: confirmed ORR</td>
</tr>
<tr>
<td></td>
<td>Hollebecque A</td>
<td>Abstract 5504</td>
<td>Nivolumab</td>
<td>Anti-PD-1 immunotherapy</td>
<td>1°: ORR, safety</td>
<td>ORR at 31 wk: 21% and disease control rate (ORR+stable disease) 71%</td>
</tr>
<tr>
<td></td>
<td>(NCT02488759) - Single-arm, multi-cohort; phase I/Ib; recurrent/metastatic HPV-associated cancers</td>
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<tr>
<td></td>
<td>Schellens JH</td>
<td>Abstract 5514</td>
<td>Pembrolizumab</td>
<td>Anti-PD-1 immunotherapy</td>
<td>1°: ORR; 2°: DDR, safety/efficacy</td>
<td>ORR: 17% (95% CI=8%–31%)</td>
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<tr>
<td></td>
<td>(NCT02660034) - Phase Ib trial — 15.5-mo follow-up; platinum resistant ovarian cancer</td>
<td>Pembrolizumab</td>
<td>Anti-PD-1 immunotherapy</td>
<td>1°: ORR; 2°: DDR, safety/efficacy</td>
<td>ORR: 17% (95% CI=8%–31%)</td>
<td>Most common AEs was arthralgia, nausea, pruritis, rash, and diarrhea.</td>
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<tr>
<td></td>
<td></td>
<td>(NCT02488759) - Single-arm, multi-cohort phase II; preliminary results; advanced cervical squamous cell cancer with progression or intolerance to standard therapy</td>
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<tr>
<td>Anti-hormone therapy</td>
<td>Knipprath- Mézărescu AM</td>
<td>Abstract 5515</td>
<td>Letrozole</td>
<td>Aromatase inhibitor</td>
<td>1°: PFS</td>
<td>PFS at 12 m: 65% without and 84% with letrozole</td>
</tr>
<tr>
<td></td>
<td>(NCT02628067) - Single-arm, multi-cohort phase II; preliminary results; advanced cervical squamous cell cancer with progression or intolerance to standard therapy</td>
<td>Letrozole</td>
<td>Aromatase inhibitor</td>
<td>1°: PFS</td>
<td>PFS at 12 m: 65% without and 84% with letrozole</td>
<td>Not reported.</td>
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</tbody>
</table>
Inclusion criteria
- Platinum sensitive ovarian cancer
- 1st relapse
- Positive AGO score
- ECOG PS 0
- <500 mL ascites
- h/o complete CRS

Systematic PPALND

No LAD

2nd cytoreductive surgery with goal of complete resection

Platinum-based CT after surgery

No surgery

Immediate platinum-based CT

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 relaparotomy), 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].


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
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.

Inclusion criteria
- High risk endometrial cancer
- Stage I grade 3 wks/deep invasion or+LVSI
- Stage II–III
- Stage I–III serous or clear cell
- WHO PS 0–2
- Complete macroscopic resection

Pathology review

Pelvic RT 48.6 Gy

Pelvic RT 48.6 Gy+CT:
cisplatin 50 mg/m²×2

Four 21-day cycles CT:
carboplatin AUC 5
paclitaxel 175 mg/m²

5 weeks  2 weeks  12 weeks
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.
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].
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 (BRCAmut) 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...
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 NOV A 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 NOV A studies presented at ASCO highlighted analyses of efficacy of niraparib maintenance monotherapy with 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...
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 $\text{ARID1A}$ and $\text{PTEN}$ expression (Fig. 9). In this study loss of $\text{ARID1A}$ expression (a known negative prognostic factor in clear cell ovarian cancer), correlated with significantly improved PFS at 6 months (33% with $\text{ARID1A}$ 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.
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.

REFERENCES


