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Meeting Report

Meeting report from the 2020 Annual (virtual) Meeting of the American Society of Clinical Oncology

1. Introduction

The 2020 56th annual meeting of the American Society of Clinical Oncology (ASCO) was held virtually for the first time due to the COVID-19 pandemic. Though you may not have missed the $10 muffins, we missed the opportunity to network with our colleagues. Fortunately, this year's scientific content was second to none. The meeting was led by ASCO president Howard Burris III, medical oncologist at Sarah Cannon Research Institute and Tennessee Oncology and the theme of the meeting was "Unite and Conquer; Accelerating Progress Together". Dr. Burris recognized the impact of the pandemic and importance of continuing to provide high-level care to cancer patients, who are particularly vulnerable to COVID 19. He addressed the goal to reduce the global burden of cancer through drug development, clinical trials, and the use of technology to overcome barriers and improve care delivery and research. One major effort is to mandate that insurance carriers, including Medicare, cover the routine costs associated with clinical trial participation. This initiative would greatly enhance access and enrollment to trials for all patients and accelerate progress in cancer care.

The meeting also presented many promising advances in gynecologic oncology. The focus was multifaceted and included targeted therapies, PARP inhibitors, immunotherapy, and surgery with developments in multiple disease sites. Below we present some of the highlights from this year's meeting.

2. Ovarian cancer

2.1. The revival of secondary cytoreductive surgery

This year, two prospective trials evaluating secondary cytoreductive surgery (SCS) were presented; Table 1 provides an overview of both trials. Du Bois and colleagues, after validation of their selection criteria and demonstrating a benefit in progression free survival (PFS), reported the final results of the phase 3, randomized DESKTOP III trial (#6000) evaluating the impact of SCS in recurrent ovarian cancer [1]. The investigators reported an overall survival (OS) benefit in the surgery arm with a median survival of 53.7 months compared to 46.2 months in those who did not undergo surgery. The true benefit was seen in women who underwent complete resection at the time of surgery (60.7 months versus 46.2 months). It is important to note that patients who were not able to undergo complete resection had a worse outcome (median survival 28.8 months) when compared to the no surgery arm. In a separate randomized phase 3 study from China, SOC 1/SGOG-OV2 (#6001), SCS was also evaluated. In this study, there were designated selection criteria based on the iModel score in conjunction with PET-CT scan imaging to determine complete resection [2]. Zang and colleagues reported that SCS was associated with a benefit in PFS of 17.4 versus 11.9 months, though OS outcomes are still maturing. Similarly to DESKTOP III, those with residual disease did worse than chemotherapy alone. Therefore, though these results differed from GOG 213 which reported no difference in OS outcomes with SCS, both groups concluded that SCS is of benefit when performed in carefully selected patients, and that SCS should be done at centers of excellence/experience in which the opportunity to resect disease completely is optimal.

Lastly, another study of SCS presented was a randomized phase 2 trial of SCS with or without carboplatin hyperthermic intraperitoneal chemotherapy (HIPEC) in women with recurrent platinum sensitive ovarian cancer (#6016) [3]. The study randomized 98 patients and reported 0% perioperative mortality and comparable outcomes to those undergoing SCS only. Though preliminary, PFS and OS rates were not significantly different and did not demonstrate that HIPEC was superior to SCS alone.

2.2. Further insight into the activity of PARP inhibitors (PARPi) and PARPi combinations

This year, SOLO2 (#6002), a randomized Phase 3 trial of olaparib maintenance therapy in women with relapsed platinum-sensitive BRCA-mutated ovarian cancer following response to platinum-based therapy, became the first report of mature OS data from a Phase 3 setting [4]. The study enrolled 295 patients and previously reported a 13.6 month improvement in the primary endpoint of PFS in 2017. In this final analysis of SOLO2, a median improvement in OS of 12.9 months was observed (38.8 versus 51.7 months), with a hazard ratio of 0.74 (95% CI 0.54–1.00; $p = 0.0537$). While this finding was just shy of the threshold for statistical significance, the magnitude of the observed OS benefit was striking. Additionally, it is important to note that this final analysis included patients who received subsequent PARPi therapy, including 38% of patients in the control arm and 10% of those in the olaparib arm. When adjusted for subsequent PARPi in the placebo group, the observed improvement in median OS was 16.3 months (35.4 versus 51.7 months), with a hazard ratio of 0.56 (95% CI 0.35–0.97). These results support the use of maintenance PARPi in patients with BRCA-mutated platinum sensitive recurrent ovarian cancer who are PARPi naïve.

The primary analysis of NRG-GY004, a Phase 3 trial comparing the combination of cediranib and olaparib or olaparib monotherapy to platinum-based chemotherapy in relapsed platinum-sensitive ovarian cancer was also presented (#6003) [5]. This study asked whether a non-platinum alternative could improve PFS over platinum-based chemotherapy in platinum-sensitive ovarian cancer. The combination cediranib and olaparib did not meet the primary endpoint of improving PFS compared to chemotherapy, with a median PFS of 10.4 months for the combination and 10.3 months for chemotherapy (hazard ratio 0.856, 95% CI 0.663–1.105, $p = 0.077$), although the observed activity was comparable for both PFS and objective response rates. Due to a hierarchical statistical design, the activity of olaparib monotherapy was not formally compared to chemotherapy, but a median PFS of

Table 1
Comparison of the phase 3 trials in secondary cytoreductive surgery.

	Du Bois	Zang
Eligibility criteria	• Platinum free interval ≥ 6 months • ECOG 0 • No residual disease after primary surgery • Ascites ≤ 500 mL	iModel factors • Platinum free interval ≥ 6 months • ECOG score • Residual disease after primary surgery • Ascites • CA-125 value
Complete resection	75%	76.7%
Mortality (60 day)	0%	0%

8.2 months was observed. Side effects with the combination of cediranib and olaparib were significant; while hematologic adverse events were higher with chemotherapy, rates of non-hematologic adverse events were higher with cediranib/olaparib, and the discontinuation rate due to adverse events was 21%. Pre-specified subgroup analyses were notable for the high response rates and significant activity seen with both olaparib monotherapy and cediranib/olaparib combination in patients with a germline BRCA mutation. Further investigation of the cediranib/olaparib combination is ongoing in NRG-GY005 and ICON9, and these studies will give us additional insight into the activity of this combination in these settings.

Two Phase 2 trials reported this ASCO also provided additional insight into PARPi activity as monotherapy or in combination. NSGO-AVANOVA2 (#6012) was a randomized Phase 2 study compared combination niraparib and bevacizumab to niraparib monotherapy in relapsed platinum-sensitive ovarian cancer [6]. In an updated analysis, there was continued improvement in PFS, with a hazard ratio of 0.34 (95% CI 0.21–0.54, $p < 0.0001$). With 52% event maturity, the hazard ratio for OS was non-significant at 0.75 (95% CI 0.44–1.28, $p = 0.30$). While these results support increased activity of anti-angiogenic/PARP inhibitor combinations over PARPi alone, the activity of this combination in comparison to standard of care platinum therapy has not been established. The LIGHT study (#6013) further characterized the activity of olaparib as primary therapy for relapsed PARPi naïve platinum-sensitive ovarian cancer [7]. As expected, activity in BRCA-mutated tumors (germline or somatic) was highest, with response rates of 64 to 69% and median PFS of 10.8 to 11.0 months, while activity in BRCA-wild type HR deficient tumors (as assessed by the Myriad MyChoice assay) was more modest (response rate of 29%, median PFS 7.2 months), and activity in BRCA-wild type HR proficient tumors was lowest (response rate of 10%, median PFS 5.4 months).

Two additional studies provided insight on the dosing of niraparib and raised questions about how best to follow patients on PARP inhibitor maintenance. Weight and platelet-based dosing of niraparib was incorporated into the PRIMA study after enrollment was approximately two-thirds complete. Mirza and colleagues (#6050) reported no impact on efficacy of this individualized starting dose, with a hazard ratio for PFS with maintenance niraparib of 0.59 (95% CI 0.46–0.76) in patients enrolled to PRIMA who received the fixed starting dose of 300 mg daily regardless of weight or platelets, and a hazard ratio of 0.69 (95% CI 0.48–0.98) for those patients who received the individualized starting dose [8]. The interaction test p-value for efficacy based upon starting dose was 0.30. Finally, a study by Tjokrowidjaja and colleagues (#6014) utilizing data from the SOLO2 trial intriguingly suggested that nearly half of patients experiencing RECIST progression on trial did not meet GCIG CA125 progression criteria [9]. Some of these patients still experienced a rising CA125; however, approximately one quarter of patients had a stable or falling CA125. This observation raises the question of whether patients on PARPi maintenance should have regular imaging as opposed to relying on CA-125 surveillance alone. However, the study did not report how many patients had symptoms, and it is possible that some patients without rising CA125 would have been identified due to symptomatic recurrence.

2.3. Antibody-drug conjugates and immunotherapy

Activity from the combination of the folate-receptor alpha-targeting antibody-drug conjugate mirvetuximab soravtansine in combination with bevacizumab in tumors demonstrating medium or high FRα membrane staining was reported (#6004) [10]. Overall, an objective response rate of 47% was observed, with a response rate of 64% in patients with high FRα expression. Response rates were high regardless of platinum status, with a response rate of 59% in platinum-resistant patients and 69% in platinum-sensitive cases. As reported at last year's European Society of Medical Oncology (ESMO) meeting, FORWARD1, the randomized Phase 3 trial of mirvetuximab soravtansine failed to meet its primary endpoint of improved activity compared to chemotherapy in platinum-resistant ovarian cancer; however, the selectivity of the assay used to determine FRα expression may also have contributed to this outcome. Results from the upcoming Phase 3 study MIRASOL of mirvetuximab soravtansine in true high FRα expressers will be of high interest in the further development of this interesting agent.

Final results from the KEYNOTE100 study of pembrolizumab monotherapy in relapsed ovarian cancer were also reported (#6005) [11]. Overall activity across the cohort remained low, with an overall response rate of 8.5%. However, there was a trend towards increased activity in patients with high PD-L1 expression (defined as a CPS score ≥ 10), with response rate ranging from 11.6 to 18.2% in these patients. These findings again highlight the limited activity of PD1/PD-L1-directed therapy in ovarian cancer and the need for biomarkers to identify the small percentage of patients who may derive benefit from these agents.

3. Uterine cancer

A single arm Phase 2 trial reported on the activity of the Wee1 inhibitor adavosertib in uterine serous carcinomas (#6009) [12]. A response rate of 29.4% was observed in this small trial of 34 evaluable patients and the clinical benefit rate (responses and stable disease for at least 6 months) was 50%. While the authors hypothesized that a combination of a *TP53* mutation together with oncogenically-driven replication stress and additional cell cycle dysregulation could make these cells particular sensitive to the effects of Wee1 inhibition, no clear correlation was identified between single gene alterations and clinical outcomes in their sample set. Adavosertib is associated with some toxicities, and over 50% of patients required at least one dose reduction, although dose discontinuations due to adverse events were infrequent. Given the limited options for uterine serous cancers, targeting Wee1 may represent a novel therapeutic alternative in this challenging disease, although validation of these study results is needed.

Lheureux and colleagues reported results from a trial comparing the combination of nivolumab and cabozantinib to nivolumab monotherapy in recurrent endometrial cancer (#6010) [13]. The combination of nivolumab and bevacizumab had increased activity, with a median PFS of 5.3 months (compared to 1.9 months), and a response rate of 25% (compared to 16.7%). In an exploratory cohort of patients who had received prior immune checkpoint therapy or who had carcinosarcomas, 5 of 21 patients who had received prior immunotherapy had a response, while 1 of 9 carcinosarcoma patients did. These results further support the development of anti-angiogenic tyrosine-kinase inhibitors together with immune checkpoint blockade in endometrial cancer.

4. Cervix cancer

An analysis of disease free and disease specific survival in patients with early stage cervical cancer who underwent sentinel lymph node biopsy versus bilateral pelvic lymphadenectomy was reported from two prospective trials (SENTICOL I and II) (#6006) [14]. The study used blue dye and radioactive tracer and was done predominantly via minimally invasive route (study conducted prior to the Laparoscopic Approach to Cervical Cancer (LACC) trial results). The results demonstrated that there were no significant differences between the two groups and that sentinel lymph nodes can be performed in this setting; however, this was a low risk group as only ~12% of the study population required adjuvant therapy, and we anxiously await the evaluation of sentinel lymph node biopsy in patients with high risk cervical cancer.

A phase 3 study evaluating the role of adjuvant therapy after radical hysterectomy in cervical cancer (STARS trial) was also presented (#6007) [15]. Huang and colleagues randomized over 1000 patients with intermediate or high risk factors following surgery to radiation therapy, chemoradiation (with cisplatin weekly), or radiation therapy with sequential chemoradiation (2 cycles of cisplatin and paclitaxel before and after radiation). The primary outcome, disease free survival at 3 years, was highest in the sequential chemoradiation arm (90% versus 85% in chemoradiation arm and 82% in radiation arm). This difference was most significant in those with high-risk features and associated with a decreased risk of death. Ongoing trials though the RTOG and GOG evaluating the role of systemic chemotherapy after chemoradiation (±surgery) will help determine if this is truly practice changing, but the data are promising.

In an ancillary data analysis of GOG 49, 92, and 141 of early stage cervical cancer patients, Levinson et al. re-evaluated the Sedlis criteria of intermediate risk factors (#6019) [16]. They noted that recurrence in squamous cell carcinoma was associated independently with lymphovascular space invasion, depth of invasion, and tumor size; however, for adenocarcinoma, only tumor size >4 cm was associated with recurrence. This presentation suggests that recurrence rates may be influenced by different factors in squamous cell and adenocarcinoma of the cervix.

The novel combination of camrelizumab (PD1 inhibitor) plus apatinib (tyrosine kinase inhibitor targeting VEFGR2) was studied in a phase II open label trial of 45 women with advanced cervical cancer after prior systemic chemotherapy (#6021) [17]. The authors noted two complete responses and 23 partial responses for an objective response rate of 59.6%. Though PDL1 expression resulted in a longer PFS, responses were noted in both populations. The regimen was associated with tolerable toxicities and demonstrates promising anti-tumor activity in a typically poor prognostic group.

5. Rare tumors

The first prospective trial of immunotherapy in gestational trophoblastic neoplasia, TROPHIMMUNE, was presented (#6008) [18]. In this study, 15 patients received avelumab after demonstrating resistance to monotherapy. Fifty percent of patients achieved monotherapy, including 5 patients who would have received polychemotherapy after failing both single agent regimens. The five patients who were resistant to avelumab were able to achieve a complete response after receiving chemotherapy. Toxicities were mild and one patient successfully delivered an infant following treatment.

Blanc and colleagues presented a study of high dose chemotherapy and autologous stem cell rescue (HDC-aSCR) in patients with ovarian small cell carcinoma, hypercalcemic type (#6023) [19]. This intense regimen included surgery followed by chemotherapy (cisplatin, doxorubicin, etoposide, and cyclophosphamide) and if a complete response was noted, patients received HDC-aSCR with or without pelvic radiation. They noted a median overall survival of 36.4 months and a 2-year event free survival of 40%. If pelvic radiation were administered, a 57% recurrence free survival was noted. This study provides additional

Table 2
Trials in progress.

Name (n)	Brief study overview	Eligibility	Primary endpoint
Cervix cancer trials			
JGOG 1082 (290 patients)	Phase III Concurrent chemoradiation versus systemic chemotherapy with platinum/taxane	Stage Ib–IIb with positive parametria or pelvic lymph nodes	OS
innovaTV 205/ENGOT-cx8/GOG-3024 (170 patients)	Phase Ib/II: Tisotumab vedotin ± bevacizumab, pembrolizumab, or carboplatin	Recurrent/meta-static cervical cancer	ORR
ENGOT-cx11/KEYNOTE-A18 (980 patients)	Phase III: Chemoradiation ± pembrolizumab	Locally advanced cervical cancer	PFS
Endometrial cancer (EC) trials			
SIENDO/ENGOT-EN5 (192 patients)	Phase 3: Maintenance selinexor versus placebo after combination chemotherapy	Recurrent or advanced EC	PFS
ENGOT-en9/LEAP-001 (not reported)	Phase 3: Pembrolizumab plus lenvatinib versus chemotherapy in first-line treatment of advanced or recurrent endometrial cancer	Advanced/recurrent EC	PFS
DUO-E/GOG-3041/ENGOT-EN10 (~700 patients)	Phase 2: Carboplatin, paclitaxel ± durvalumab followed by placebo versus durvalumab versus durvalumab + olaparib maintenance	Advanced or recurrent (chemo naïve) EC	PFS
ENGOT-EN6/NSGO-RUBY (470 patients)	Phase 3: Carboplatin and paclitaxel ± dostarlimab	Advanced or first recurrent EC	PFS
GINECO-UTOLA (147 patients)	Phase 2: Olaparib maintenance	Platinum sensitive (primary or recurrent) EC	PFS
Ovary cancer (EOC) trials			
DUETTE (192 patients)	Phase 2: Olaparib versus olaparib and ceralasertib versus placebo maintenance after recurrent platinum chemotherapy	Platinum sensitive recurrent EOC after prior PARPi maintenance therapy (BRCAm and wt)	PFS
ENGOT-OV44/FIRST study (not reported)	Phase 3: Platinum based therapy ± dostarlimab followed by niraparib ± dostarlimab maintenance	Primary stage III–IV EOC	PFS
OVIHIPEC-2	Primary cytoreductive surgery with or without HIPEC	Stage III EOC	OS
MIRASOL (GOG-3045/ENGOT OV-55) (430 patients)	Phase 3: Miravetuxmab soravtansine vs MD choice chemotherapy	Platinum resistant high grade EOC with high folate alpha expression	PFS
NOGGO Ov-42/MAMOC (190 patients)	Phase 3: Rucaparib vs placebo maintenance after chemotherapy and bevacizumab	Advanced EOC, BRCAwt	PFS

insights into the management of a rare but aggressive histology with improvements in outcome.

6. Conclusions

This year's virtual ASCO meeting provided continued progress and outcomes in areas such as PARPi and, secondary cytoreductive surgery in ovarian cancer, and evaluation of novel agents (e.g. adavosertib, camrelizumab, and mirvetuximab) or approaches (HDC-aSCR) across all gynecologic malignancies. Table 2 lists selected trials in progress presented at the meeting. These and other ongoing trials are likely to accelerate progress at faster paces than seen before. Even though we couldn't be together for the meeting, the theme of "unite and conquer" resonates strongly.

Declaration of competing interest

Ritu Salani has no relevant conflict of interest related to the manuscript. Joyce F. Liu reports advisory board participation for AstraZeneca, Clovis, Genentech, Merck, Regeneron, and Tesaro/GSK, outside the submitted work; and funding to her institution for study conduct as PI on trials from 2X Oncology, Aravive, Arch Oncology, AstraZeneca, Bristol-Myers Squibb, Clovis Oncology, CytomX Therapeutics, GlaxoSmithKline, Regeneron, Surface Oncology, Tesaro, and Vigeo Therapeutics, outside the submitted work.

Both authors were involved in the conception, design, review and editing of the manuscript.

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