Highlights from the 2017 Society of Gynecologic Oncology (SGO) annual meeting on women's cancer

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SUMMARY

From 12-15th March, the Society of Gynecological Oncology hosted its 48th annual meeting. The meeting continues to be one of the key educational and scientific events for physicians treating and caring for women with gynaecologic cancer. This summary will discuss some of the key studies presented during the meeting, with a focus on medical oncology. For a complete overview of abstracts presented in National Harbor we refer to the Society of Gynecological Oncology website: www.sgo.org.

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OLAPARIB MAINTENANCE DELAYS DISEASE PROGRESSION IN PLATINUM-SENSITIVE RELAPSED OVARIAN CANCER PATIENTS

In a previously reported phase II study (Study 19), the PARP inhibitor olaparib provided a significant progression-free survival (PFS) improvement over placebo in patients with platinum-sensitive, relapsed, high-grade serous ovarian cancer.[1] This benefit was most pronounced in patients harbouring a *BRCA1/2* mutation. The SOLO2/ENGOT-Ov21 study was set up to validate these findings in the *BRCA1/2* mutant population in a phase III setting. In total, 295 patients were randomised (2:1) to maintenance olaparib (300 mg bid; tablet) or placebo.[2] The primary endpoint of the trial was investigator-assessed PFS, while key secondary objectives included time to first subsequent therapy or death (TFST), time to second progression (PFS2) and overall survival (OS). Eligible patients had *BRCA1/2* mutation-positive platinum-sensitive relapsed ovarian cancer and previously received two lines of platinum-based therapy, with at least a partial response (PR) to the last platinum therapy.

The median age of patients in the study was 56 years and approximately 60% of patients received two prior treatment lines (approximately 15% four lines or more). In both arms, 40% of patients had a platinum-free interval of six to twelve months and about 47% experienced a complete response (CR) on the last platinum therapy. With a median follow up of 22 months, maintenance therapy with olaparib resulted in a 70% reduction in the risk of progression or death compared to placebo. The median PFS was 19.1 months on olaparib versus 5.5 months with placebo (HR[95%CI]: 0.30[0.22-0.41]; p<0.0001) (*Figure 1*). This benefit in PFS was even more pronounced in a second PFS analysis with blinded independent review, where a median PFS of 30.2 months was seen with olaparib as compared to 5.5 months with placebo (HR[95%CI]: 0.25[0.18-0.35]; p<0.0001). Also the secondary endpoints of the study were superior with olaparib maintenance. The median TFST was 27.9 months with olaparib versus 7.1 months with placebo

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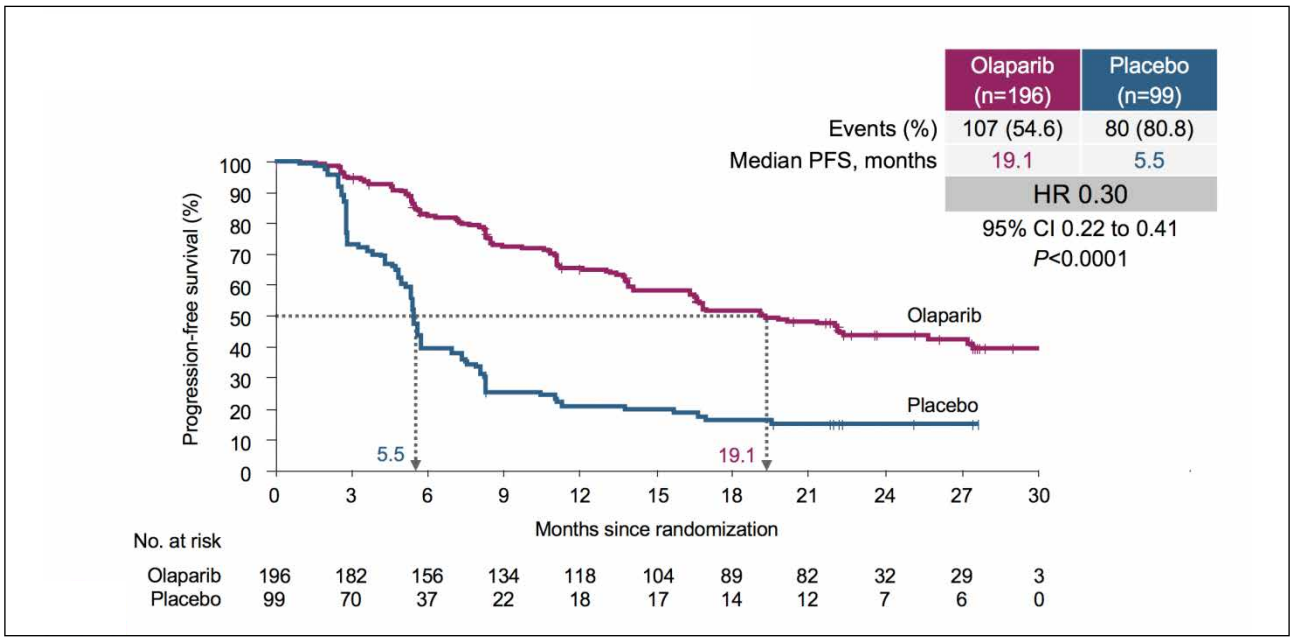

FIGURE 1. Investigator assessed progression-free survival in the phase III SOLO-2 study.[2]

(HR[95%CI]: 0.28[0.21-0.38]; p<0.0001), the median PFS2 was not reached with olaparib versus 18.4 months with placebo (HR[95%CI]: 0.50[0.34-0.72]; p=0.0002). Finally, the time to second subsequent therapy (TSST) was significantly delayed with olaparib (median not reached versus 18.2 months; HR[95%CI]: 0.37[0.26-0.53]; p<0.0001). The OS data were not yet mature.[2]

In the olaparib arm, toxicity was mostly low grade. The incidence of grade 3 or higher adverse events (AEs) was 36.9% with olaparib versus 18.2% with placebo. AEs led to treatment discontinuation in 10.8% of patients under olaparib as compared to 2% in the placebo arm. The most common AEs with olaparib were nausea (75.9%; grade ≥3: 2.6%]), fatigue (37.9%, grade ≥3: 1.0%), vomiting (37.4%, grade ≥3: 2.6%), diarrhoea (32.8%, grade ≥3: 1.0%), neutropenia (11.8%, grade ≥3: 2.6%) and thrombocytopenia (8.2%, grade ≥3: 0%]). All grade anaemia was seen in 43.6% of olaparib treated patients, with grade 3 or higher severity in 19.5%. Patient-reported outcomes showed no detriment for olaparib in average change from baseline in the Trial Outcome Index score.[2]

In summary, SOLO2 demonstrated a statistically significant PFS improvement in patients receiving olaparib, by investigator assessment and by independent review. The PFS benefit was supported by a significant delay in TFST, PFS2 and TSST in the olaparib group. Except for anaemia, toxicity associated with olaparib maintenance was mostly low grade. As such, SOLO2 is the first phase III trial to show that olaparib maintenance treatment provides a significant clinical benefit to patients with platinum-sensitive, relapsed ovarian cancer and a *BRCA1/2* mutation.

NO SURVIVAL BENEFIT WITH MAINTENANCE CHEMOTHERAPY IN WOMEN WITH OVARIAN CANCER AFTER DEBULKING SURGERY AND ADJUVANT PLATINUM-BASED CHEMOTHERAPY

The GOG 212 trial addressed a common problem in the management of ovarian cancer. Upfront surgery and chemotherapy leads to a clinical complete response (CCR) for many patients, but a substantial proportion of patients who achieve a CCR eventually have recurrent disease, which often proves fatal. A total of 1,157 women who attained CCR with surgery and a first-line platinum-taxane combination chemotherapy were randomised to surveillance, conventional paclitaxel (135 mg/m^2), or a novel paclitaxel conjugate CT-2103.[3]

The study provided a suggestion of a trend towards a worse survival in patients randomised to conventional paclitaxel, which was associated with a hazard ratio of 1.104 versus the surveillance group. This difference did not reach statistical significance (97.5%CI: 0.884-1.38). The five month difference in the CT-2103 arm also did not reach statistical significance versus the surveillance arm (HR[97.5%Ci]: 0.979[0.781-1.23]). Both paclitaxel arms had significantly better PFS versus surveillance, which was associated with a

median PFS of 13.4 months. Patients randomised to CT-2103 had a median PFS of 16.3 months (HR[95%-CI]: 0.847[0.721-0.995]) and those receiving conventional paclitaxel had a median PFS of 18.9 months (HR[95%CI]: 0.783[0.666-0.921]).[3]

Grade 3/4 AEs occurred in 50.7% of patients treated with CT-2103, 39.3% of the paclitaxel group, and in 12.5% of the surveillance group. Grade 3/4 neurotoxicity, occurred in 12.4% of the CT-2103 arm and 7.2% of the paclitaxel arm as compared to 1.9% of the surveillance group. Grade 2 alopecia occurred in 24.5% of the CT-2103 group, 44.9% of the paclitaxel group, and 13.9% of the surveillance group. Patient-reported quality-of-life data suggested no difference, at best, and possibly a small decrement in the paclitaxel groups at various time points.[3]

As such, maintenance chemotherapy failed to improve survival rates for women in complete remission from ovarian cancer after debulking surgery and adjuvant platinum-based chemotherapy.

CHEMO-IMMUNOTHERAPY WITH MOTOLIMOD AND PEGYLATED DOXORUBICIN DOES NOT IMPROVE OUTCOMES IN RECURRENT OR PERSISTENT OVARIAN CANCER

A phase II, randomised, placebo-controlled trial was conducted in women with recurrent epithelial ovarian carcinoma to evaluate the efficacy and safety of motolimod (a Toll-like receptor 8 [TLR8] agonist that stimulates robust innate immune responses) combined with pegylated liposomal doxorubicin (PLD) (a chemotherapeutic that induces immunogenic cell death).[4] Women with ovarian, fallopian tube, or primary peritoneal carcinoma were randomised 1:1 to receive PLD in combination with blinded motolimod or placebo. The addition of motolimod to PLD did not significantly improve OS (p=0.923, HR: 1.22) or PFS (p=0.943, HR: 1.21). The combination was well tolerated, with no synergistic or unexpected serious toxicity. In prespecified subgroup analyses, motolimod-treated patients who experienced injection site reactions (ISR) had a lower risk of death compared to those who did not experience ISR. In addition, pretreatment in vitro responses of immune biomarkers to TLR8 stimulation predicted OS outcomes in patients receiving motolimod on study. Immune score (tumour infiltrating lymphocytes), TLR8 single-nucleotide polymorphisms, and mutational status in *BRCA* and other DNA repair genes did not correlate with OS or PFS.[4]

CONFIRMED EFFICACY FOR RUCAPARIB IN PLATINUM-SENSITIVE OVARIAN CANCER

In ARIEL2 Part 1, rucaparib demonstrated activity in patients with relapsed, platinum-sensitive high-grade ovarian carcinoma with a germline or somatic *BRCA* mutation (g*BRCA*^{mut} or s*BRCA*^{mut}).[5] ARIEL2 Part 2 includes patients who received three to four prior lines of chemotherapy. In an analysis presented at SGO 2017, updated data from ARIEL2 Parts 1 and 2 were pooled to evaluate the objective response rate (ORR) and safety of rucaparib in patients with relapsed, platinum-sensitive high-grade ovarian carcinoma with a g*BRCA*^{mut} or s*BRCA*^{mut}.[6]

In total, 58 patients from ARIEL2 part 1 (N=41) or part 2 (N=17) were eligible for this analysis. All participants received rucaparib 600 mg orally twice daily continuously in 28-day cycles until disease progression or unacceptable toxicity. Results showed that 69.0% of the 58 included patients achieved an objective response with a median duration of response of 9.2 months. The study further demonstrated that 61.5%, 90.0%, 75.0% and 60.0% of women with a progression-free interval of six to nine months (N=26), nine to twelve months (N=10), twelve to eighteen months (N=12), and greater than eighteen months (N=10) achieved an objective response, respectively. The most frequently reported treatment-emergent AEs were nausea, asthenia, vomiting, and anaemia. Investigators observed no treatment-related deaths.[6]

A second abstract devoted to ARIEL2 demonstrated that *BRCA1* and *RAD51C* promoter hypermethylation confers sensitivity to rucaparib. Promoter hypermethylation is a mechanism of gene downregulation, and *BRCA1* and *RAD51C* promoter methylation was previously shown to be associated with decreased gene expression in ovarian cancers. The ARIEL2 analysis reported at the SGO meeting included 165 participants with evaluable tumour samples. The results showed that 12.7% of tumours had *BRCA1* promoter methylation and 2.4% had *RAD51C* promoter methylation, and the promoter methylation was mutually exclusive of *BRCA1* mutation and other homologous recombination genes (p=0.015). All four tumours with methylated *RAD51C* promoter and sixteen of twenty evaluable specimens with methylated *BRCA*1 promoter had high loss of LOH (80% association overall).[7]

Response data showed investigator-assessed responses to rucaparib in eleven of twenty-one (52.4%) of the *BRCA*-methylated cases, three of four (75%) *RAD51C*-methylated cases, and 29% of *BRCA* wild type/

LOH-high cases. The median duration of response was 6.1 months for *BRCA1* methylated cases and 9.5 months for *RAD51C* methylated cases. Additionally, two patients with *CDK12*-mutated tumours had prolonged responses to rucaparib. *CDK12* is involved in regulation of RNA splicing, and its loss leads to downregulation of many DNA repair genes and possibly homologous repair deficiency.[7]

As such, this analysis revealed that *BRCA1* and *RAD51C* methylation in ovarian carcinomas is associated with high loss of heterozygosity and sensitivity to rucaparib.

POSITIVE RESULTS WITH LISTERIA-BASED HUMAN PAPILLOMAVIRUS IMMUNOTHERAPY AXALIMOGENE FILOLISBAC IN SECOND- AND THIRD-LINE METASTATIC CERVICAL CANCER

Axalimogene filolisbac (AXAL) immunotherapy consists of live attenuated *Listeria monocytogenes*, bioengineered to secret HPV-16 E7 protein, fused with a truncated fragment of the hemolysin listeriolysin O. The immunotherapeutic agent targets HPV-transformed cells, induces antitumor T-cell immunity, and breaks immune tolerance in the tumour microenvironment. In an earlier phase II trial, AXAL plus or minus cisplatin, led to a twelve month survival of 32% in patients with previously treated cervical cancer. During SGO 2017 results were presented with AXAL in the phase II GOG/NRG 0265 trial, involving patients with recurrent, metastatic cervical cancer. GOG/NRG 0265 enrolled 63 patients in two stages. All patients had received at least one prior line of systemic therapy for recurrent/persistent metastatic cervical cancer, beyond primary curative treatment.[8]

The first stage of the trial included 27 patients. If AXAL led to a 15% absolute improvement in the benchmark one year survival of 20% (later refined to 24.5%), the trial would proceed to the second stage. After that goal was met, investigators enrolled an additional 36 patients. The co-primary endpoints were twelve month OS and safety/tolerability of AXAL. Investigators reported data on 50 evaluable patients, who had a median age of 46 (range, 29-70). A majority of the patients (26/50) received two or more prior lines of therapy, 28 had exposure to bevacizumab, and 43 had received pelvic radiation therapy. The patients had a median OS of 6.2 months, and 19 of 50 remained alive for twelve months, resulting in a twelve month survival of 38%. This represents a 52% improvement versus the logistic model-predicted milestone survival rate of 24.5% and is the highest twelve month survival rate to date in this patient population. The results also compare favourably with those of a previous trial of bevacizumab where a 30% one-year survival rate was seen. One patient achieved a complete response with AXAL and fifteen had stable disease. HPV genotyping for 41 patients showed that 35 tested positive for the virus, including 33 evaluable patients, sixteen who tested positive for HPV-16 and seventeen positive for HPV-18. The HPV-16 positive subgroup had a twelve month survival of 44% and median OS of 17.8 months for those patients alive at twelve months. The HPV-18 positive subgroup had a twelve month OS of 41% and median OS of 15.7 months among those alive at twelve months.[8]

The next step in clinical evaluation of AXAL will be a phase III trial as adjuvant monotherapy to prevent recurrence in patients with high-risk cervical cancer treated with chemo-radiation.

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