

**Abstracts Presented for the 48th Annual Meeting of the Society of Gynecologic Oncology  
March 12-15, 2017  
National Harbor, MD**

**Scientific Plenary VI: Late Breaking Abstracts**

**Tuesday, March 14, 2017**

Moderator: Don Dizon, MD, *Massachusetts General Hospital/Harvard University, Boston, MA, USA*

**1 - Late Breaking Abstract**

**A phase III trial of maintenance therapy in women with advanced ovarian/fallopian tube/peritoneal cancer after a complete clinical response to first-line therapy: An NRG oncology study**

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**Objective:** To compare overall survival (OS) of maintenance chemotherapy (P and PP) to surveillance (S) in women with advanced ovarian/fallopian tube/peritoneal (O/PC/FT) cancer who attained complete clinical response (CCR) following first-line platinum-taxane therapy.

**Method:** Women diagnosed with O/PC/FT cancer who attained CCR following first-line platinum-taxane-based chemotherapy were randomized 1:1:1 to surveillance or maintenance, P 135 mg/m<sup>2</sup> (3-hour infusion) q 28 days for 12 cycles or PP (15 min infusion) at the same dose and schedule. OS based on an intention-to-treat analysis was the primary efficacy endpoint. The study was designed to have 90% power to detect a 25% reduction in the hazard of death due to taxane treatment. Adverse events (AEs) were categorized and graded according to Common Terminology for Adverse Events version 3.0. Patient-reported outcomes (PROs) were assessed using the Functional Assessment of Cancer Therapy–Ovary Trial Outcome Index (FACT–TOI) and Gynecologic Oncology Group Neurotoxicity (FACT/GOG–Ntx) subscale.

**Results:** Between March 2005 and January 2014, 1,157 individuals were enrolled. AEs occurred more frequently among those treated with a taxane. Grade 2 or worse gastrointestinal (GI) AEs were more frequent among those treated with a taxane (PP 20.3%, P 27%, vs S 11%) and consisted primarily of nausea, vomiting, diarrhea, or constipation. Grade 2 or worse neurologic AEs occurred more often with taxane treatment (PP 46%, P 36%, vs S 14%). The Data Monitoring Committee recommended releasing results following the third scheduled interim analysis, which indicated that the relative death hazards passed the futility boundaries for both taxane regimens. Six hundred deaths had been reported, and the median duration of follow-up was 5.9 years. No deaths were attributed to the study treatment. Estimated median survivals were 54.8, 51.3, and 60.0 months for S, P, and PP, respectively. Compared to S, the relative hazard of death was 1.104 for P (97.5% CI 0.884–1.38) and 0.979 for PP (97.5% CI 0.781–1.23). While not a primary endpoint of this study, the median times to recurrence were S 13.4, P 18.9, and PP 16.3 months. Relative to S, the hazard of first progression or death (PFS) was 0.783 for P (95% CI 0.666–0.921) and 0.847 for PP (95% CI 0.721–0.995). Results from analyses of PROs will be presented.

**Conclusion:** Maintenance treatment with P or PP is associated with GI and neurological AEs, but neither study regimen provides an appreciable increase in the duration of overall survival.

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**2 - Late Breaking Abstract**

**Treatment with olaparib monotherapy in the maintenance setting significantly improves progression-free survival in patients with platinum-sensitive relapsed ovarian cancer: Results from the phase III SOLO2 study**

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**Objective:** SOLO2 (ENGOT Ov-21; NCT01874353) evaluated the efficacy and tolerability of the tablet formulation of olaparib (Lynparza), an oral PARP inhibitor (PARPi), in patients with platinum-sensitive relapsed ovarian cancer (PSROC). SOLO2 aimed to confirm findings from a positive phase II trial in all-comer patients with PSROC (Study 19; NCT00753545) in which those having a *BRCA1/2* mutation (*BRCAm*) derived the greatest progression-free survival (PFS) benefit from olaparib (400 mg bid; capsule).

**Method:** This randomized, double-blind, phase III study enrolled patients with PSROC and a *BRCAm* who were in response to their most recent platinum-based chemotherapy after  $\geq 2$  lines of treatment. Patients were randomized 2:1 to maintenance olaparib (300 mg bid; tablet) or placebo. The primary endpoint was investigator-assessed PFS (RECIST v1.1); a sensitivity analysis of PFS was performed by blinded independent central review (BICR).

**Results:** Of 295 patients randomized, 294 received study treatment (olaparib,  $n = 195$ ; placebo,  $n = 99$ ). Patient characteristics were well balanced between arms: partial remission at entry (olaparib 54% and placebo 53%); platinum-free interval  $>6-12$  months (40% and 40%);  $\geq 3$  prior lines of chemotherapy (43% and 37%). Olaparib achieved a highly statistically significant increase over placebo both in PFS, by investigator assessment and BICR, and in PFS2 (Table 1). Overall survival data are immature. In the olaparib arm, toxicity was mostly low grade (nausea, all grades, 75.9% [grade  $\geq 3$ , 2.6%]; fatigue, 37.9% [1.0%]; vomiting, 37.4% [2.6%]; diarrhea, 32.8% [1.0%]; neutropenia, 11.8% [2.6%]; and thrombocytopenia, 8.2% [0%]), except for anemia (all grades, 43.1%; grade  $\geq 3$ , 19.5%). Treatment discontinuation due to toxicity was 10.8%. Patient-reported outcomes showed no detriment for olaparib in average change from baseline in the Trial Outcome Index score.

**Conclusion:** Olaparib tablet maintenance treatment in SOLO2 led to a clinically meaningful, statistically significant PFS benefit in patients with PSROC and a *BRCAm*. Key endpoints of PFS by BICR and PFS2 substantiated the efficacy benefit. Maintenance treatment with the tablet formulation of olaparib was well tolerated, with a low incidence of discontinuation due to toxicity.

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### 3 – Late Breaking Abstract

#### A prospective phase II trial of the listeria-based human papillomavirus immunotherapy axalimogene filolisbac in second- and third-line metastatic cervical cancer: A NRG oncology group trial

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**Objective:** Recurrent metastatic cervical cancer (RMCC), largely due to infections with high-risk (HR) types of human papillomavirus (HPV), remains an area of high unmet need for patients progressing after  $\geq 1$  line of systemic chemotherapy (sCTx). This prospective, P2, 2-stage trial evaluated AXAL, a *Listeria monocytogenes* (Lm) immunotherapy agent (IO), as a monotherapy in second- and third-line RMCC patients. Coprimary objectives were to assess AXAL tolerability/safety and frequency of patients who survive for  $\geq 12$  months after therapy. Secondary objectives included objective response rate (ORR) and overall survival (OS). The association between presence/type of HR HPV and measures of clinical response was explored.

**Method:** AXAL is a live, attenuated Lm IO that targets human HPV-transformed cells with an HPV16-E7 fusion protein, stimulates antitumor T-cell immunity, and hinders tumor immune tolerance. Preclinical/clinical evidence shows that AXAL is active against multiple HR HPV types. Eligible patients ( $\geq 18$  years, measurable disease, GOG PS of 0/1) were given IV AXAL ( $1 \times 10^9$  CFU) on day 1 and every 28 days for 3 doses in stage 1 (S1) or until disease progression or 1 year in stage 2 (S1). A tissue sample for HPV genotyping was optional.

**Results:** S1 was completed; S2 was stopped early after a temporary clinical hold on AXAL and review of available data showed results consistent with S1. Of 54 patients enrolled, 50 were treated; the 12-month OS rate was 38%. There was 1 confirmed complete response, and 15 patients had a best OR of stable disease. Tissue samples ( $n = 39$ ) were analyzed; 35 were HPV+. Of these, 16 patients were HPV16 family, with 7 (44%) achieving 12-month OS; 17 patients were HPV18 family, with 7 (41%) achieving 12-month OS. All patients ( $n = 50$ ) had  $\geq 1$  adverse event (AE). Treatment-related AEs (TRAEs) occurred in 96% of patients; 53% had grade 1–2 TRAEs only; 39% had grade 3 TRAEs; and 4% had a possibly related grade 4 TRAE. The most common TRAEs,  $>30\%$ , were fatigue, chills, anemia, and nausea.

**Conclusion:** Historical 12-month OS rates in heavily pretreated patients with RMCC are  $<30\%$ . At 1 year 38% of patients were alive after treatment with AXAL, exceeding the extensive prospective historical data; this is a 52% improvement versus a predicted model-based 12-month OS of 25%. ORR and disease control were seen. Results in HPV16 RMCC patients are consistent with the mechanism of action of AXAL; similar activity was also seen in HPV18 patients.

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#### 4 – Late Breaking Abstract

##### **A phase II, randomized, double-blind, placebo-controlled study of chemo-immunotherapy combination using motolimod with pegylated liposomal doxorubicin in recurrent or persistent ovarian cancer: A Gynecologic Oncology Group partners study**

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**Objective:** A phase II, randomized, 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.

**Method:** Women with ovarian, fallopian tube, or primary peritoneal carcinoma were randomized 1:1 to receive PLD in combination with blinded motolimod or placebo. Randomization was stratified by platinum-free interval ( $\leq 6$  vs  $>6$ –12 months) and GOG performance status (0 vs 1). Treatment cycles were repeated every 28 days until disease progression.

**Results:** The addition of motolimod to PLD did not significantly improve overall survival (OS; log rank 1-sided  $P = 0.923$ , HR = 1.22) or progression-free survival (PFS; log rank 1-sided  $P = 0.943$ , HR = 1.21). The combination was well tolerated, with no synergistic or unexpected serious toxicity. Most patients experienced adverse events of fatigue, anemia, nausea, decreased white blood cells, and constipation. 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 (tumor infiltrating lymphocytes), TLR8 single-nucleotide polymorphisms, and mutational status in *BRCA* and other DNA repair genes did not correlate with OS or PFS.

**Conclusion:** The addition of motolimod to PLD did not improve clinical outcomes compared to placebo. However, subset analyses identified statistically significant differences in the OS of motolimod-treated patients on the basis of ISR and in vitro immune responses. Collectively, these data may provide important clues for identifying patients for treatment with immunomodulatory agents in novel combinations and/or delivery approaches.

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#### 5 – Late Breaking Abstract Session

##### **A multiinstitutional, prospective randomized open-blinded end-point trial for safety of oral apixaban versus subcutaneous enoxaparin for thromboprophylaxis in women with suspected gynecologic malignancy**

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**Objective:** Rates of venous thromboembolism (VTE) after surgery for gynecologic cancer are as high as 26% for deep venous thrombosis (DVT) and 9% for pulmonary embolism (PE). Thromboprophylaxis with 28-day therapy of subcutaneous (SQ) enoxaparin is recommended for these patients, but adherence is low and costs are high. We evaluated the safety of apixaban, an oral factor Xa inhibitor, compared to enoxaparin for postoperative thromboprophylaxis in women with suspected gynecologic cancer.

**Method:** This study was closed for safety accrual after a statistically determined, planned analysis was performed. The primary outcome was major bleeding events. Secondary outcomes included VTE events, compliance, quality of life, and satisfaction. Patients were randomized 1:1 to 28 days of 2.5 mg of apixaban or 40 mg of SQ enoxaparin therapy. Women ages 18–89 years with suspected gynecologic cancer undergoing surgery were eligible. Exclusions included history of VTE or bleeding disorder, concomitant use of SSRI, SNRIs, NSAIDs, or significant renal/liver disease.

**Results:** A total of 154 patients were recruited with 77 randomized to each study arm. Groups were similar for all demographic characteristics. No major bleeding or VTE events were recorded for the women who completed the safety study for either group, yielding a 95% CI of 0–3.9%. Other adverse events were similar between the arms and included hematoma, wound dehiscence/infection, dizziness, allergic reaction, arthralgia, bruising, rash, epistaxis, vaginal discharge/hemorrhage, and dyspnea. Arthralgia was the most common, occurring in 5% of women (7% vs 3%,  $P = 0.411$ ). No grade 4 or 5 adverse events (AEs) were reported. Four patients were evaluated for suspected VTE (3.3% vs 3.3%,  $P = 1.00$ ) during the treatment period; no VTE was found. No related AEs were reported after therapy was stopped. Participants in the apixaban arm had significantly less pain (OR = 0.01, 95% CI 0.0–0.1,  $P < .001$ ) and less difficulty with taking the medication (OR = 69.1, 95% CI 4.0–1181.0,  $P < .001$ ). Adherence was similar between arms (91% vs 86%,  $P = 0.210$ ). Change in physical QOL was also similar ( $P = 0.115$ ).

**Conclusion:** These data suggest apixaban is potentially safe for postoperative VTE prophylaxis with a similar risk profile as enoxaparin. Patient satisfaction was greater for women taking apixaban versus enoxaparin among women with gynecologic cancer. A noninferiority study is being developed to assess efficacy for VTE prevention.