**Rare Tumors**

Moderators: Jubilee Brown, MD, and Michael Frumovitz, MD

May 5, 5:30 p.m. CST

**MILO/ENGOT-ov11: Phase-3 Study of Binimetinib versus Physician's Choice Chemotherapy in Recurrent or Persistent Low-grade Serous Carcinomas of the Ovary, Fallopian Tube, or Primary Peritoneum**

R.N. Grisham. *Memorial Sloan Kettering Cancer Center, New York, NY, USA*

**Objective:** Low-grade serous ovarian carcinomas (LGSOC) have historically low chemotherapy responses. Alterations affecting the MAPK pathway, most commonly KRAS/BRAF, are present in 30%–60% of LGSOC. A phase II study of the MEK inhibitor selumetinib showed promising response rate of 15% in LGSOC, and binimetinib, a potent MEK1/2 inhibitor, has demonstrated activity across multiple cancers.

**Method:** MILO (MEK-inhibitor in low-grade serous ovarian cancer)/ENGOT-ov11 was an open-label, 2:1-randomized study of binimetinib (45-mg BID) versus PCC in LGSOC. Eligible patients had recurrent or persistent measurable LGSOC following ≥1 prior platinum-based chemotherapy, ≤3 prior chemotherapy lines, and no prior MEK or BRAF inhibitor. The primary endpoint was progression-free survival (PFS) by blinded central review; additional assessments were overall survival (OS), overall response rate (ORR), duration of response (DOR), clinical-benefit rate, biomarkers, and safety.

**Results:** A total of 303 patients were randomized (201 binimetinib, 102 PCC). Median PFS was 9.1 months (95% CI 7.3–11.3) for binimetinib and 10.6 months (95% CI 9.2–14.5) for PCC (HR = 1.21, 95% CI 0.79–1.86, closed early for futility). Secondary efficacy endpoints were similar in the 2 groups: ORR = 16% (complete/partial responses, CR/PRs, 32) versus 13% (CR/PRs =13), median DOR 8.1 months (range 0.3–12.0+ months) versus 6.7 months (0.3–9.7+ months), and median OS 25.3 versus 20.8 months for binimetinib and PCC, respectively. Safety results were consistent with known safety profile of binimetinib; most common grade ≥3 events were blood CK increased (20%) and hypertension (20%). Post-hoc analysis suggests a possible association between KRAS mutation and response to binimetinib.

**Conclusion:** Although MILO did not meet its primary endpoint, binimetinib showed activity in LGSOC across the efficacy endpoints evaluated. Chemotherapy responses were higher than predicted. Further evaluation is warranted.

---

**A Randomized Phase II/III Study to Assess the Efficacy of Trametinib in Patients with Recurrent or Progressive Low-Grade Serous Ovarian or Peritoneal Cancer**

D.M. Gershenson. *The University of Texas MD Anderson Cancer Center, Houston, TX, USA*

**Objective:** Low-grade serous carcinoma of the ovary/peritoneum (LGSOC) is a rare subtype, accounting for 5%–10% of all serous cancers and is characterized by alterations in the MAPK pathway, relative chemoresistance, and prolonged overall survival (OS) compared to high-grade serous carcinoma. NRG Oncology in the United States and the National Cancer Research Network (NCRN) in the United Kingdom collaborated on a phase II–III trial to assess the efficacy of a MEK inhibitor trametinib (TRAM) compared to physician's choice standard of care (SOC) in recurrent LGSOC.

**Method**: Patients were randomized 1:1 to receive either TRAM 2 mg daily or 1 of 5 SOC options (weekly paclitaxel, PLD, topotecan, letrozole, or tamoxifen) until disease progression. Patients who progressed on SOC were allowed to cross over to TRAM. The primary objective tested the progression-free survival (PFS) superiority of TRAM versus SOC. Secondary objectives included toxicity, quality of life (QOL), and objective response rate (ORR) by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Exploratory objectives were OS and PFS and ORR after crossover. PFS and OS curves were estimated using the Kaplan-Meier method and compared by a 1-sided, $\alpha = 0.025$ log rank test.

**Results:** A total of 260 patients (48.1% had >3 prior lines of therapy) were enrolled between February 2014 and April 2018. Median follow-up was 31.4 months. PFS was significantly improved for TRAM compared to SOC (median 13.0 vs 7.2 months, HR = 0.48, 95% CI 0.36–0.64, $P < 0.0001$). ORR was 26.2% for TRAM versus 6.2% for SOC (OR = 5.4, 95% CI 2.39–12.21, $P < 0.0001$). Response duration for TRAM was significantly better than that for SOC (median 13.63 months, 95% CI 8.08–18.76, vs 5.88 months, 95% CI 2.76–12.19). Preliminary analysis of QOL patient-reported outcomes shows no significant therapy effects. Main grade >3 adverse events in TRAM versus SOC were hematologic toxicity (13.4% vs 9.4%), gastrointestinal toxicity

(27.6% vs 29%), skin toxicity (15% vs 3.9%), and vascular toxicity (18.9% vs 8.6%). Median OS for TRAM versus SOC was 37.0 months (95% CI 30.3–NE) versus 29.2 months (95% CI 23.5–51.6) (HR = 0.75, 95% CI 0.51–1.11). For 88 patients who crossed over to TRAM, median PFS was 10.8 months (95% CI 7.3–12.0), and ORR was 15% (95% CI 0.07–0.22).

**Conclusion:** Compared to physician's choice SOC, TRAM was associated with significantly improved PFS and ORR in women with recurrent LGSOC.

---

**Phase II study of enzalutamide in androgen receptor positive (AR+) recurrent high-grade and low-grade serous ovarian cancer**

R.N. Grisham[a,b], D.D. Giri[a], A. McDonnell[a], A. Iasonos[a], Q. Zhou[a], K. Li[a], J. Girshman[a], R.E. O'Cearbhaill[c], D. Zamarin[a,b] and C. Aghajanian[a,b]. *[a]Memorial Sloan Kettering Cancer Center, New York, NY, USA, [b]Weill Cornell Medical College, New York, NY, USA, [c]Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY, USA*

**Objective:** This was a single-institution, phase II, Simon 2-stage with safety lead-in study of the oral androgen-receptor (AR+) antagonist, enzalutamide, in patients with recurrent AR+ ovarian cancer with measurable disease and 1–3 prior lines of chemotherapy. The primary objective was to determine the proportion of patients surviving progression free for 6 months (PFS6) and overall response rate by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria, with 7/58 responses or PFS6 of 13 being considered a positive study.

**Method:** Following consent, archival tissue was screened for AR+ by immunohistochemistry with ≥5% considered positive. Enrolled patients were treated with enzalutamide 160 mg po daily until progression of disease or treatment discontinuation. A cycle was 28 days. Adverse events were graded by Common Terminology Criteria for Adverse Events (CTCAE) V 4.0.

**Results:** Between November 2013 and July 2018, 160 patients were screened, and 59 patients (45 high-grade serous [HGS], 14 low-grade serous [LGS]) consented to treatment on the study (1 patient was replaced; efficacy cohort = 58, safety cohort = 59). There were 1 confirmed and 1 unconfirmed partial responses (PR); PFS6 was 22% (90% CI 15.1%–100%) with PFS6 for those with HGS 19.8% (90% CI 12.7%–100%) and for LGS 38.5% (21.7%–100%). Median PFS was 3.5 months. There were no toxicities >grade 3 related to the study drug. Related grade 3 toxicities occurred in 6 patients (1 fatigue, 2 rash, 1 hypertension, 1 anemia, and 1 transaminase elevation).

**Conclusion**: The study met its primary endpoint, with 13 patients (22%) remaining progression free at 6 months. However, the response rate was low. Enzalutamide was well tolerated and may offer a well-tolerated treatment option in select patients.

---

**Phase II study of pembrolizumab for high-grade neuroendocrine tumors of the cervix and vulva**

M. Frumovitz, S.N. Westin, T. Yap, J.A. Rodon, D.D. Karp, A. Abonofal, A.A. Jazaeri and A. Naing. *The University of Texas MD Anderson Cancer Center, Houston, TX, USA*

**Objective:** The aim of this study was to investigate the efficacy and safety of pembrolizumab in women with metastatic high-grade neuroendocrine tumors of the lower genital tract.

**Method:** This was a prespecified cohort of an open-label, investigator-initiated phase II basket trial of pembrolizumab in patients with rare tumors. Patients must have failed prior treatment in the past 6 months before study enrollment. Patients were enrolled from August 2016 to October 2018. The primary endpoint was nonprogression rate (NPR) at 27 weeks. Subjects were evaluated every 9 weeks (3 cycles) with radiographic imaging to assess response to treatment.

**Results:** Seven patients (6 cervix, 1 vulva) were included in this cohort. No patients met the primary endpoint of nonprogression at 27 weeks. At first radiologic assessment, 1 patient had stable disease while 6 patients had progression. The single patient with stable disease at 9 weeks went on to have disease progression at 14 weeks. The median progression-free survival was 2.1 months (range 0.8–3.3 months). Severe treatment-related adverse events (≥grade 3) were seen in 2 of 7 patients (29%). One patient had asymptomatic elevation of serum alkaline phosphatase, while the other had asymptomatic elevation of serum alanine aminotransferase.

**Conclusion:** Pembrolizumab alone showed minimal activity in women with high-grade neuroendocrine tumors of the lower genital tract. Treatment was well tolerated in the majority of study participants with low rate of severe adverse events.

**Phase II study of durvalumab alone or in combination with ADXS11-001 (AXAL) in recurrent/persistent or metastatic cervical cancer**

B. Slomovitz[a], W.H. Bradley[b], S. Ghamande[c], D.M. O'Malley[d], M. Huang[e], H.S. Chon[f], S. Vangala[g], S. Sheeri[g], A.A. Gutierrez[g] and K.N. Moore[h]. [a]*Sylvester Comprehensive Cancer Center, University of Miami Health Center, Miami, FL, USA,* [b]*Froedtert and the Medical College of Wisconsin, Milwaukee, WI, USA,* [c]*Georgia Regents University, Augusta, GA, USA,* [d]*The Ohio State University, Columbus, OH, USA,* [e]*University of Miami, Sylvester Comprehensive Cancer Center, Miami, FL, USA,* [f]*H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL, USA,* [g]*Advaxis, Inc., Princeton, NJ, USA,* [h]*The University of Oklahoma Stephenson Cancer Center, Oklahoma City, OK, USA*

**Objective**: Our goal was to evaluate the safety, tolerability, and efficacy of PD-L1 immune checkpoint blockade (durvalumab) alone or in combination with a tumor-selective vaccination (ADXS11-001) in patients with persistent-recurrent or metastatic cervical cancer (PRmCC) and metastatic HPV+ SCCHN in part A (dose escalation) or with PRmCC in part B (dose-expansion). Part B results are reported here.

**Method**: This was an open-label, randomized trial comparing durvalumab versus durvalumab + ADXS11-001 in patients with PRmCC. ADXS11-001, an attenuated *Listeria monocytogenes,* expresses HPV E7 protein, to induce HPV-specific cytotoxic T cells to infiltrate the tumor. ADXS11-001 ($1 \times 10^9$ CFU) was dosed IV q4 weeks. Durvalumab (10 mg/kg) was dosed IV q2 weeks. The primary objectives were objective response rate (ORR), progression-free survival (PFS) according to RECIST v. 1.1, and safety by NCI CTCAE v 4.03.

**Results**: A total of 54 PRmCC patients were enrolled and randomized 1:1 to each arm. Twenty (74.1%) and 22 (81.5%) were evaluable for tumor response in the durvalumab and durvalumab + ADXS11-001 arms, respectively. Fewer patients had received 4 or more prior regimens for recurrent/metastatic disease or palliation in the durvalumab arm compared to the durvalumab + ADXS11-001 arm (3.7% vs 25.9%). The confirmed ORR was similar for both groups with 2 partial responses in durvalumab (10 %) and 1 partial response and 1 complete response in durvalumab + ADXS11-001 (9%). Median PFS was numerically higher in durvalumab than in durvalumab + ADXS11-001: durvalumab was 5.0 months (95% CI 1.9–6.9) and durvalumab + ADXS11-001 was 2.1 months (95% CI 1.7–3.8). The incidence of grade ≥3 treatment-related adverse events was lower in subjects in the durvalumab arm (2 [7.4%] of 27 subjects) than in the durvalumab + ADXS11-001 arm (7 [25.9%] of 27). The most common grade ≥3 treatment-related adverse events in the durvalumab arm included thrombocytopenia, thyroiditis, diabetic ketoacidosis, and type I diabetes mellitus (1.3% each); in the durvalumab + ADXS11-001 arm they included anemia (14.8%), hypotension (11.1%), and acute respiratory failure, fatigue, nausea, vomiting, and pain (1.3% each). One grade 5 event (acute respiratory failure) occurred in the durvalumab + ADXS11-001 arm and was deemed possibly related to either or both agents.

**Conclusion**: The combination of durvalumab + ADXS11-001 appears to be safe and tolerable but requires close monitoring. The ORR was similar across arms, and the PFS in the durvalumab arm was numerically higher than that observed with durvalumab + ADXS11-001. Two objective responses were previously reported in subjects in part A, dose escalation of the study (ADXS11-001 at $1 \times 10^9$ CFU + MEDI 3 mg/kg, $n = 4$), including a complete response. The evaluation of *Lm*-constructs in combination with an anti-PD-1/-L1 antibody or other agents is ongoing.

---

**A randomized phase II study of chemoradiation and pembrolizumab for locally advanced cervical cancer: Presentation of safety data**

L.R. Duska[a,b], J.M. Scalici[c], G.R. Petroni[a] and T.N. Showalter[a]. [a]*University of Virginia, Charlottesville, VA, USA,* [b]*University of Virginia School of Medicine, Charlottesville, VA, USA,* [c]*Mitchell Cancer Institute, University of South Alabama, Mobile, AL, USA*

**Objective:** There is a strong rationale for using immune checkpoint inhibitors (ICI) in locally advanced cervical cancer (LACC), particularly in combination with SOC chemoRT (CRT). The question of sequential versus concurrent use has not been addressed prospectively. Moreover, the safety of combining ICI with pelvic CRT has not been established. The current study was designed in part to evaluate the safety of the combination.

**Method:** This is a randomized, phase II, open-label multicenter study. Patients ≥18 years with LACC, stages IB-IVA (FIGO 2009) were randomized 1:1 to pembrolizumab (pembro) after CRT (arm 1) or pembro during CRT (arm 2). CRT therapy was identical for both arms with standard weekly cisplatin dosing. Pembro 200 mg was administered as a 30-minute infusion Q3 weeks for 3 doses: beginning week 9 (arm 1) after CRT or week 1 during CRT (arm 2). All patients receiving any protocol

treatment were evaluated for safety. Safety assessments included incidence and severity of adverse events and occurrence of dose-limiting toxicities (DLTs) as defined per protocol. Blood and tumor were collected at defined time points for translational study.

**Results:** As of August 2019, 60 (of planned 88) patients have begun treatment; 52 completed and have complete adverse event data (24 arm 1; 28 arm 2). Overall there were 22 G3 and 11 G4 treatment-related adverse events: most common was lymphopenia (8 arm 1; 12 arm 2). Adverse events of special interest are presented in **Table 1**. Two patients had grade 3 diarrhea, 1 in each arm. Two patients experienced 3 DLTs (both arm 2): grade 3 diarrhea (1), grade 3 nausea (1), grade 3 vomiting (1). Most patients completed 6 cisplatin treatments (100% arm 1 vs 82% arm 2); 83% in both arms completed 3 infusions of pembro. All but 2 patients completed radiation (2 patients in arm 2 withdrew from protocol), 79% and 75% in <8 weeks in arms 1 and 2, respectively.

**Conclusion**: With complete safety data for 52 patients, we have demonstrated the safety and feasibility of the combination of ICI and pelvic CRT. Based upon these data, no major differences in total number of adverse events of special interest are evident by arm. The safety stopping bounds were not crossed, and the study is continuing with accrual. At study completion, we will address the scientific question of which treatment regimen is the most biologically promising.

**Table 1.** Adverse events of clinical interest; possibly, probably or definitely related to pembrolizumab

| | | Arms | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | N=24 Arm 1 (Pembro after CRT) | | | | | N=28 Arm 2 (Pembro during CRT) | | | | | N=52 ----- Total | | | | |
| Category | AE | G1 | G2 | G3 | G4 | G5 | G1 | G2 | G3 | G4 | G5 | G1 | G2 | G3 | G4 | G5 |
| GASTROINTESTINAL | ABDOMINAL DISTENSION | | | | | | 1 | | | | | 1 | | | | |
| | ABDOMINAL PAIN | 3 | | | | | 2 | | | | | 5 | | | | |
| | BLOATING | 1 | | | | | | | | | | 1 | | | | |
| | COLITIS | | | | | | | 1 | | | | | 1 | | | |
| | COLONIC STENOSIS | | | | | | | | | 1 | | | | | 1 | |
| | CONSTIPATION | 2 | | | | | 2 | 1 | | | | 4 | 1 | | | |
| | DIARRHEA | 12 | 3 | 1 | | | 15 | 3 | 1 | | | 27 | 6 | 2 | | |
| | DRY MOUTH | | 1 | | | | 1 | | | | | 1 | 1 | | | |
| | DYSPEPSIA | | | | | | 1 | | | | | 1 | | | | |
| | GASTROESOPHAGEAL REFLUX DISEASE | | | | | | 1 | | | | | 1 | | | | |
| | MUCOSITIS ORAL | 3 | 1 | | | | | | | | | 3 | 1 | | | |
| | NAUSEA | 9 | 10 | 1 | | | 7 | 8 | 2 | | | 16 | 18 | 3 | | |
| | PROCTITIS | | | | | | 2 | | | | | 2 | | | | |
| | RECTAL PAIN | | | | | | 2 | | | | | 2 | | | | |
| | STOMACH PAIN | | | | | | 1 | | | | | 1 | | | | |
| | VOMITING | 4 | 6 | 1 | | | 3 | 3 | 1 | | | 7 | 9 | 2 | | |
| REPRODUCTIVE/BREAST | DYSPAREUNIA | 1 | | | | | | | | | | 1 | | | | |
| | OTHER | | 1 | | | | | | | | | | 1 | | | |
| | PELVIC PAIN | 1 | 2 | | | | | | | | | 1 | 2 | | | |
| | PERINEAL PAIN | 1 | | | | | | | | | | 1 | | | | |
| | VAGINAL DISCHARGE | 2 | 2 | | | | | | | | | 2 | 2 | | | |
| | VAGINAL HEMORRHAGE | 1 | | | | | | | | | | 1 | | | | |
| | VAGINAL PAIN | | 1 | | | | | | | | | | 1 | | | |
| | VAGINAL PERFORATION | | | | | | | | 1 | | | | | 1 | | |
| RESPIRATORY/THORACIC/MEDIASTINAL | OTHER | 1 | | | | | | | | | | 1 | | | | |
| | SORE THROAT | 1 | | | | | | | | | | 1 | | | | |

| | | Arms | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | N=24<br>Arm 1<br>(Pembro after CRT) | | | | | N=28<br>Arm 2<br>(Pembro during CRT) | | | | | N=52<br>-----<br>Total | | | | |
| Category | AE | G1 | G2 | G3 | G4 | G5 | G1 | G2 | G3 | G4 | G5 | G1 | G2 | G3 | G4 | G5 |
| SKIN/SUBCUTANEOUS TISSUE | ALOPECIA | 1 | | | | | 1 | | | | | 2 | | | | |
| | HYPERHIDROSIS | 1 | | | | | | 1 | | | | 1 | 1 | | | |
| | OTHER | 2 | | | | | 1 | | | | | 3 | | | | |
| | PRURITUS | 1 | | | | | 2 | | | | | 3 | | | | |
| | RASH ACNEIFORM | | | | | | 1 | | | | | 1 | | | | |
| | RASH MACULO-PAPULAR | | | | | | 2 | | | | | 2 | | | | |
| *OVERALL MAXIMUM – Highest grade* | **** | 8 | 13 | 2 | | | 9 | 10 | 3 | 1 | | 17 | 23 | 5 | 1 | |