

Developmental Therapeutics in Gynecologic Cancer

Moderators: Kunle Odunsi, MD, and Debra Richardson, MD

May 28, 4:00 p.m. CST

A phase I/II study of chemo-immunotherapy with durvalumab (durva) and pegylated liposomal doxorubicin (PLD) in platinum-resistant recurrent ovarian cancer (PROC): Genomic sequencing and updated efficacy results

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Objective: The objectives of this study, where durvalumab (durva, an anti-PD-L1 antibody) is added to pegylated liposomal doxorubicin (PLD), standard therapy for platinum-resistant ovarian cancer (PROC), are to evaluate the efficacy and safety of the combination and to identify genomic characteristics associated with response and progression-free survival (PFS).

Method: This is a phase I/II, multicenter, single-arm, open-label study (NCT02431559). PLD is reported to have a 6-month PFS (PFS6) of 25%. The null hypothesis of $PFS6 \leq 25\%$ was tested against the alternative hypothesis at 0.05 level using 90% 2-sided CI; the primary endpoint, PFS6, was reported at ESMO 2018. Exom sequencing was done on PBMCs and tumor samples at baseline. Updated efficacy and DNA sequencing results are provided.

Results: In phase II, 40 patients (median age 65 years [32–83] years) each received at least 1 dose of the study drug (PLD 40 mg/m² + durva 1,500 mg every 4 weeks IV). PFS6 by RECIST1.1 was 47.7% (per protocol $n = 36$, 90% CI 33.1–60.9) and 42.9% (ITT $n = 40$, 90% CI 27–57.8). Response rate (ORR) was 22.5% (90% CI 10.8–38.5, 4 CR, 5 PR); median PFS was 5.5 (0.3 to 28.8+) months; and median overall survival was 17.6 (1.7 to 32.5+) months. Treatment-related adverse events \geq grade 3 in ≥ 2 patients were palmar-plantar erythrodysesthesia syndrome/rash (27.5%), stomatitis (10%), lymph count decrease (10%), lipase increase (5%), and anemia (5%). Exom sequencing data are available for 28 of 40 patients. No patient had *BRCA1/BRCA2* mutation; 3 patients had hypermutated non-MSI phenotypes. Analysis of copy numbers found multiple potential mechanisms for resistance to the PLD + durva combo. Deletions of *LRP1B* were previously shown to drive resistance to PLD. We also found that PFS ($P = 0.0016$) for patients on PLD + durva negatively correlated with *LRP1B* deletions. Patients with *MYC* amplifications had a lower response ($P = 0.0005$) and shorter PFS ($P = 0.006$, HR = 2.889) on the PLD + durva combination. In the TCGA ovarian cancer dataset, *MYC* amplification is linked to overexpression of *IDO1*, *CXCL17*, *CXCL11*, suggesting a unique immune suppressive microenvironment driven by *MYC* amplifications. Additional analyses including *BRCA* mutation are ongoing and will be presented.

Conclusion: The PLD + durva combination has a tolerable safety profile and promising efficacy. The study met its primary endpoint with improvement in PFS6. We confirm the negative impact of *LRP1B* deletions on PLD-based therapies. *MYC* amplification may be central in driving resistance to the combination and has not been previously linked to PLD efficacy.

Pembrolizumab window study: Illuminating the immunologic landscape in gynecologic cancers

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Objective: A “window of opportunity” study in newly diagnosed ovarian (OV) and endometrial (EM) carcinoma patients was conducted to assess changes in PD-L1 expression and immune cell recruitment in response to pembrolizumab, a PD-1 inhibitor.

Method: Patients with newly diagnosed OV or EM cancer were eligible. Participants underwent biopsy pre-pembrolizumab therapy (200 mg IV once) followed by repeat tumor acquisition >7 days later. Subsequent treatment was per standard of care (SOC), and after completion, participants were allowed optional pembrolizumab maintenance therapy every 3 weeks for 12 months. Primary objectives were to determine (1) feasibility and safety of pembrolizumab prior to SOC therapy (frequency

and grade of immune-related events) and (2) changes in PD-L1 expression (by immunohistochemistry with monoclonal antibody clone 22C3 on FFPE specimens;| Qualtek, PA) scored using a quantitative modified proportion score (MPS) and qualitative assessment of immune presence at the stromal interface (SI). Exploratory objectives included assessment of cytokines (CXCL10, IFNg, IL10, IL12p70, IL-1b, IL-2ra, IL-6, TNFa) in EDTA plasma samples at baseline and during treatment. Descriptive statistics are provided.

Results: Fifteen patients enrolled and received pembrolizumab. Primary sites included OV 13, EM 2. One patient experienced fever as an immune-related toxicity after a single dose with no impact on SOC. Eleven patients had adequate pre- and post-treatment tissue samples for paired PD-L1 MPS and 9 for SI assessment. Baseline and post-treatment PD-L1 MPS ranged from 0 to 95 (median 1) and 0 to 85 (median 6), respectively. SI was negative at baseline in 6 of 9 assessable cases. PD-L1 MPS score increased in 7 cases. SI switched from negative to positive in 3 cases. Combining both parameters, 8 of 10 assessable tumor specimens demonstrated either an increase in PD-L1 MPS or a switch from negative to positive SI. Five patients had pre- and post-treatment plasma samples. CXCL10, IFNg, IL10, IL-2ra, and TNFa levels all increased after pembrolizumab in responding patients (CR/PR), but decreased in the 1 patient who progressed on-treatment.

Conclusions: A single dose of pembrolizumab prior to SOC increased PD-L1 MPS and/or SI immune cells, suggesting potential for local tumor immunologic recruitment. In addition, increases in systemic inflammation after 1 dose of pembrolizumab were noted, but increases in cytokine production were limited to the responding patients.

Intraperitoneal or subcutaneously administered IL-15 superagonist (N-803) increases NK cell cytotoxicity in ovarian cancer

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Objective: Our goal was to determine the effect of an IL-15 superagonist (N-803) on the immune microenvironment in the peritoneal cavity and peripheral blood when administered weekly as maintenance therapy in a phase II clinical trial.

Method: Patients who received at least 3 cycles of intraperitoneal (IP) chemotherapy first line are randomized to IP versus subcutaneous (SC) administration of N-803 weekly for 4 weeks for cycle 1 followed by SC dosing weekly for 4 weeks every other month for 4 cycles as maintenance therapy. Peripheral blood mononuclear cells (PBMCs) and IP washings are collected at baseline and prior to delivery of each cycle of N-803. Ki67 levels by flow cytometry were examined for CD4+, CD8+, and CD4+Foxp3+. Cytotoxicity assays were performed against ovarian cancer cell lines. CyTOF (Fluidigm, mass cytometry) was performed to comprehensively evaluate immune evolution and checkpoint marker expression during weekly time points.

Results: To date there have been no grade 4 or 5 adverse events. The most frequent adverse events are injection site reaction (Gr 1), chills (Gr 2), and flu-like symptoms (Gr 3). Flow cytometric data of PBMCs from 6 patients to date indicate that N-803 treatment induces maximal proliferation (Ki-67) on peripheral blood NK cells by day 8 post-treatment and cytotoxicity by day 15, but activity wanes at later time points; CD8+ T cells follow a similar pattern (**Figure 1A**). NK cell cytotoxicity against ovarian cancer cell lines was maximal at day 15 following N-803. Cytof analysis of IP washings correlate with peripheral blood findings in that Ki67 is maximal at day 8 post-treatment for NK, CD8+, and CD4+ cells. NKG2D, an activating receptor for NK cytotoxicity, is maximal on peritoneal NK and CD8+ T cells at day 15. The decrease in proliferation at day 8 correlates with an increase and retention of PD-1 expression in both the NK and CD8+ T cell population (**Figure 1B**).

Conclusion: N-803 (IL-15) improves NK cell activation and ovarian cancer target killing initially. However, NK cell activation and killing are countered by inhibitory signaling provided by the PD-1/PD-L1 axis. These findings suggest checkpoint blockade, in combination with IL-15, may result in significant increase in patient-derived NK cell function against ovarian cancer.

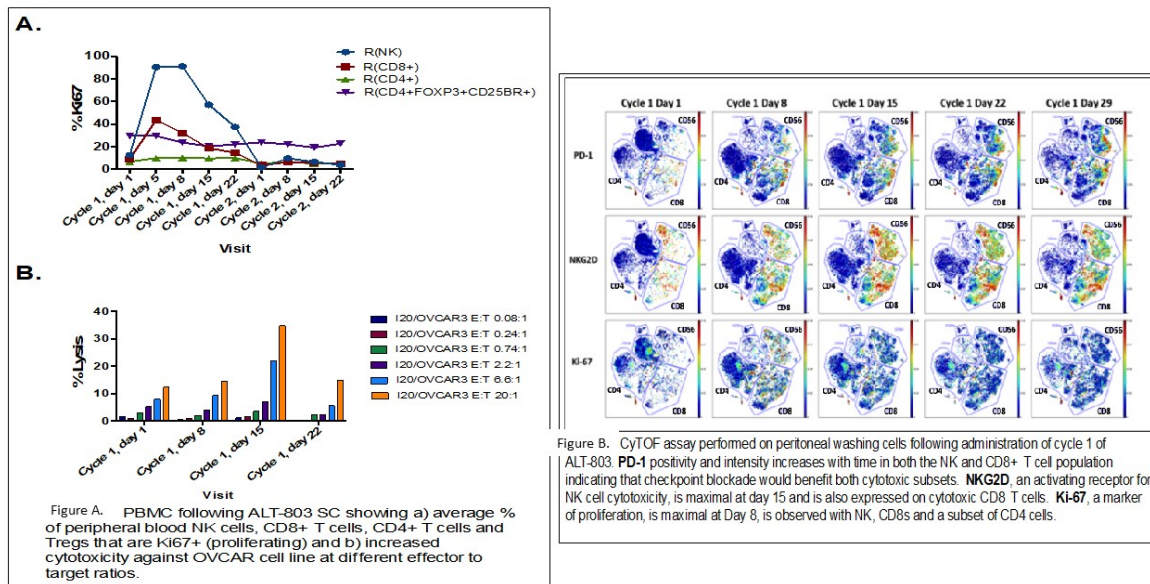


Fig. 1.

A phase I clinical trial of autologous chimeric antigen receptor (CAR) T cells genetically engineered to secrete IL-12 and to target the MUC16ecto antigen in patients (pts) with MUC16ecto+ recurrent high-grade serous ovarian cancer (HGSOC)

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Objective: Chimeric antigen receptor (CAR) T cell therapy has shown efficacy in leukemia. MUC16^{ecto} is a tumor-associated antigen that is highly expressed in certain solid tumors, including high-grade serous ovarian cancer. We conducted a first-in human phase I dose escalating trial testing the safety of autologous 4H11-28z/fIL-12/EFGR^t CAR T cells in patients with recurrent MUC16^{ecto}+ HGSOC (NCT02498912). We incorporated regional intraperitoneal (IP) and intravenous (IV) delivery of the cells.

Method: 4H11-28z/fIL-12/EFGR^t CAR T cells were genetically modified to target MUC16^{ecto} antigen and to secrete IL-12. Given the concern for potential systemic toxicity, the vector included a gene for truncated epidermal growth factor receptor (EGFR). Patients with recurrent measurable MUC16^{ecto}+ (confirmed by immunohistochemistry) HGSOC with 2–7 prior cytotoxics were eligible. Fifty percent of planned CAR T cell dose was given IV, and if tolerated, the remaining 50% IP 1–2 days later. The primary endpoint was safety using Common Terminology Criteria for Adverse Events (CTCAE) criteria. Secondary endpoints included response by Response Evaluation Criteria in Solid Tumors (RECIST)/irRECIST criteria. Standard dose escalation proceeded based on dose-limiting toxicity (DLT) assessment at 4 dose levels (3×10^5 to highest treated dose of 1×10^7 CAR T cells/kg). An additional cohort was treated at dose level 3 (3×10^6 CAR T cells/kg) following pretreatment with cyclophosphamide/fludarabine. Correlative studies included serial measurement of cytokine levels and CAR T cell persistence in blood and ascites.

Results: Eighteen heavily pretreated patients with MUC16^{ecto}+ HGSOC received CAR T cells. Intense monitoring for on-target, off-tumor toxicity by clinical (including cornea) and radiological examination found no significant toxicity in the cohorts of patients treated with CAR T cells alone. As expected, cytokine release syndrome was observed at all doses. No DLT occurred in cohorts I–IV. Best response seen was stable disease. In the cohort with lymphodepleting chemotherapy (cohort V) 2/3 patients experienced DLT (hemophagocytic lymphohistiocytosis/macrophage activation-like syndrome). No further patients were treated with that combination. **Figure 1** shows CAR T cells persistence in peripheral blood (1–12 weeks).

Conclusion: IV and IP IL-12 secreting MUC16^{ecto}-targeted CAR T cells were safely administered in the absence of chemotherapy. Toxicity was observed when the CAR T cells were given post-lymphodepleting chemotherapy. Dose escalation of CAR T cells will continue to dose level 5 (3×10^7 CAR T cells/kg). Based on our preclinical data, we aim to enhance persistence of the CAR T cells by administering them combination with anti-PD-1 therapy.

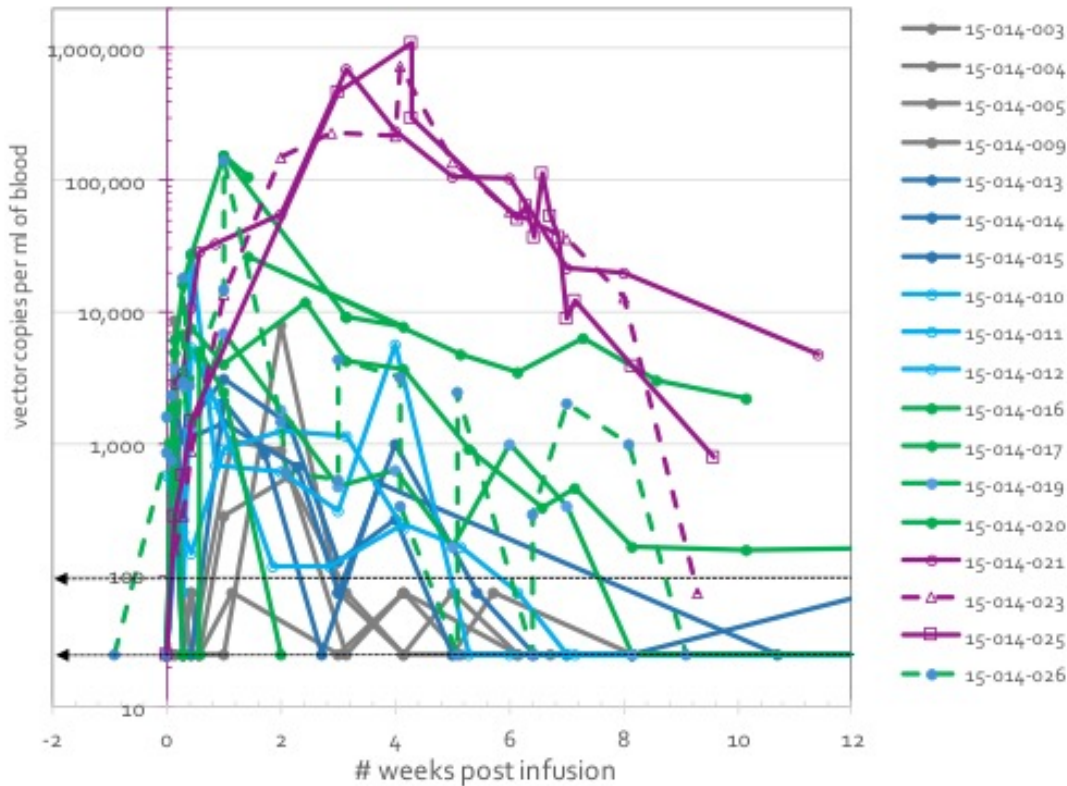


Fig. 1.

A phase 1 study of XMT-1536 in patients with solid tumors likely to express NaPi2b: A summary of dose escalation
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Objective: XMT-1536 is a first-in-class antibody-drug conjugate NaPi2B (SLC34A2), a transmembrane sodium-phosphate transporter that is expressed in ovarian carcinoma, non-small cell lung cancer (NSCLC), and other tumors. The purpose of this study was to determine the maximum tolerated dose (MTD) and/or the RP2D dose, and to evaluate the safety, tolerability, and preliminary efficacy of XMT-1536.

Method: Patients were enrolled in escalating dose cohorts of 3 mg/m² to 43 mg/m² (dose levels 1 to 7A, at q3w or q4w) and assessed for safety, pharmacokinetics, and response (via Response Evaluation Criteria in Solid Tumors v1.1). A safety review committee reviewed each cohort prior to escalation to the next higher dose level.

Results: To date, 59 patients have been enrolled (Table 1) including 37 patients with ovarian cancer and 11 patients with NSCLC. Most common treatment-related adverse events have been grade 1 and 2 transient AST elevations and fatigue. Three patients have experienced dose-limiting toxicity (DLT): grade 3 AST increased at dose level 6 (40 mg/m² q3w) and dose level 5A (30 mg/m² q4w) and treatment discontinuation following grade 2 AST increased and grade 1 ALT increased at dose level 6A (36 mg/m² q4w). There were no DLTs reported in the highest cohort completed (dose level 7A, 43 mg/m² q4w, n = 7). Thirty-two adverse events have been reported, of which 4 were determined to be possibly or probably related to XMT-1536 (congestive cardiac failure, 2 pyrexia, and vomiting).

Conclusion: XMT-1536 has been well tolerated with no DLTs reported in the highest dose level completed (dose level, 43 mg/m² q4w). Confirmed responses and prolonged stable disease have been observed. Dose expansion in high-grade serous ovarian carcinoma and NSCLC, adenocarcinoma subtype, is currently enrolling (NCT03319628). In addition, the safety review committee has recommended escalating to dose level 8A (52 mg/m² q4w), and enrollment in this cohort has been initiated. Complete safety data, confirmed response data, and biomarker expression for represented dose levels will be provided at the SGO 2020 meeting.

Table 1. Study MER-XMT-1536-1.

Dose Level	Dose (mg/m ²)	n (female/male)	Tumor Type (n)	DLTs (n)
1	3.0 (q3w)	1 (1/0)	Ovarian (n = 1)	---
2	6.0 (q3w)	1 (1/0)	Ovarian (n = 1)	---
3	12.0 (q3w)	7 (4/3)	Ovarian (n = 1) NSCLC (n = 2) Endometrial (n = 3) Papillary renal (n = 1)	---
4	20.0 (q3w)	6 (6/0)	Ovarian (n = 3) NSCLC (n = 1) Endometrial (n = 1) Salivary duct (n = 1)	---
5	30.0 (q3w)	4 (3/1)	Ovarian (n = 3) NSCLC (n = 1)	---
6	40.0 (q3w)	1 (1/0)	Ovarian (n = 1)	Grade 3 AST (n = 1)
4A	20.0 (q4w)	9 (8/1)	Ovarian (n = 8) Papillary renal (n = 1)	---
5A	30.0 (q4w)	15 (15/0)	Ovarian (n = 9) NSCLC (n = 2) Endometrial (n = 4)	Grade AST (n = 1)
6A	36.0 (q4w)	8 (7/1)	Ovarian (n = 7) NSCLC (n = 1)	Treatment discontinuation following grade 2 AST, grade 1 ALT (n = 1)
7A	43.0 (q4w)	7 (2/5)*	Ovarian (n = 3) NSCLC (n = 4)	---

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; DLT = dose-limiting toxicity; NSCLC = non-small cell lung cancer; q3w = every 3 weeks dosing; q4w = every 4 weeks dosing.

*One patient was not evaluable due to clinical disease progression not related to this study.

Demcizumab combined with paclitaxel for platinum-resistant ovarian, primary peritoneal, and fallopian tube cancer (EOC): The SIERRA multi-institutional open-label phase Ib trial

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Objective: Our goal is to evaluate the safety of demcizumab (DLL4 targeted IgG2 humanized monoclonal antibody; potent inhibitor of the Notch pathway) in combination with weekly paclitaxel in platinum-resistant EOC; to estimate the maximum tolerated dose (MTD) or maximum administered dose (MAD); and to determine the recommended phase two dose. Objective response rate (ORR) was a secondary objective.

Method: We conducted a 3+3 dose-escalation trial in patients with recurrent, platinum-resistant EOC with RECIST v. 1.1 measurable disease and four or fewer prior chemotherapy regimens. Two dosing cohorts (2.5 mg/kg and 5 mg/kg) were initially targeted; however, an intermediate dose level (3.5 mg/kg) was prescribed if the 5 mg/kg dose was not tolerable. Demcizumab was administered intravenously on days 1 and 15 and paclitaxel (80 mg/m² IV) weekly on days 1, 8, and 15 for each of three 28-day cycles: the three-cycle doublet could be repeated once if safe. Thereafter, paclitaxel was administered until unacceptable toxicity or disease progression was reached.

Results: Nineteen patients were enrolled (3 at each dose level). No dose-limiting toxicity (DLT) was observed; however, an intermediate dose level (3.5 mg/kg) was enrolled ($n = 3$) and expanded ($n = 10$) based on emerging safety data from other studies in the demcizumab program. The most common adverse events of any grade were diarrhea (68%), fatigue (58%), peripheral edema (53%), and nausea (53%). Grade ≥ 3 adverse events included hypertension (26%), abdominal pain, anemia, neutropenia, and urosepsis (11% each). Demcizumab-related adverse events of any grade were fatigue (42%), hypertension (37%), diarrhea (32%), and headache (32%). Pulmonary hypertension, grade 2 ($n = 2$) and grade 1 ($n = 1$), was observed. No DLTs were recorded, and the MTD was not reached. ORR was 21% (95% CI 6–45%); clinical benefit rate (CBR) was 42% (95% CI 20–66%). Two of five patients with prior bevacizumab treatment had an objective response, and two others had confirmed stable disease (≥ 12 weeks). See **Figure 1**.

Conclusion: Demcizumab in combination with paclitaxel has a manageable toxicity profile and showed activity in patients with heavily pretreated platinum-resistant ovarian cancer. Ongoing investigation is evaluating the next-generation bispecific VEGF/DLL4 antibody, navicixizumab, in combination with paclitaxel.

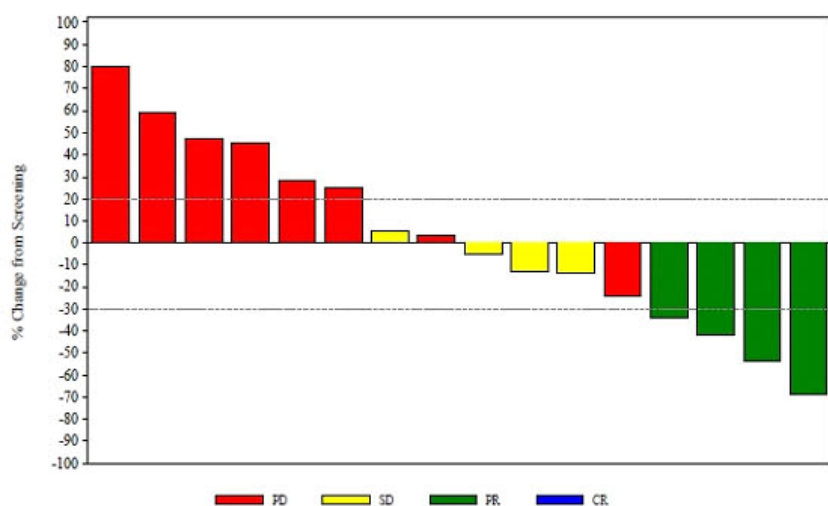


Fig. 1. Waterfall plot of the maximum percent decrease in tumor size by best overall response. PD: progressive disease; SD stable disease; PR: partial response; CR: complete response.

A phase Ib study of navicixizumab and weekly paclitaxel in heavily pretreated platinum resistant ovarian, primary peritoneal or fallopian tube cancer

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Objective: Anti-VEGF and anti-DLL4 have both demonstrated single-agent activity in ovarian cancer. Navicixizumab is an anti-DLL4/VEGF IgG2 bispecific monoclonal antibody that had a response rate of 25% (3/12) in heavily pretreated ovarian cancer patients in an earlier single-agent phase 1a trial. This is an ongoing phase 1b study designed to assess the safety and efficacy of

paclitaxel and navicixizumab in platinum-resistant ovarian cancer patients who received at least 3 prior therapies and/or bevacizumab.

Method: Paclitaxel 80 mg/m² was given on days 1, 8, and 15, and navicixizumab was given on days 1 and 15 of every 28-day cycle. This study was designed as a dose escalation trial assessing navicixizumab doses of 3 or 4 mg/kg followed by an expansion cohort. The expansion cohort was undertaken with 3 mg/kg of navicixizumab as higher doses did not show increased activity, but did result in more pronounced chronic toxicity in the phase 1a study. A standardized treatment algorithm for hypertension is being employed.

Results: Forty-four patients were treated; 5 are still ongoing. The median number of prior therapies was 4 (range 2–12). All 44 patients had received prior paclitaxel; 68% had received bevacizumab; and 41% had received a PARP inhibitor. One patient (2%) had a RECIST 1.1 complete response; 18 patients (41%) had a partial response; 15 (34%) had stable disease; 7 (16%) had progressive disease; and 3 (7%) were NE. The clinical benefit rate was 77%. Twenty-four of 36 (75%) patients with an elevated CA-125 had a GCIg-defined response. The median duration of response was 5.7 months, and the median time to progression was 7.3 months. The related adverse effects (all grades) that occurred in >15% of the patients were hypertension (68%), fatigue (48%), headache (27%), neutropenia (21%), pulmonary hypertension (18%), and diarrhea (16%). Other related adverse events of significance were infusion reaction (9%), grade 4 thrombocytopenia (2%), and grade 4 gastrointestinal perforation (2%). Antidrug antibody was detected in 4 of 25 patients who have been evaluated and had at least 1 follow-up ADA sample; drug exposure was affected in 3 patients.

Conclusion: These interim efficacy data in heavily pretreated platinum-resistant ovarian cancer patients are encouraging. The safety profile appears to be manageable with hypertension being the most common adverse event related to navicixizumab. Final data will be presented.

A randomized phase II evaluation of weekly gemcitabine plus pazopanib versus weekly gemcitabine alone in the treatment of persistent or recurrent epithelial ovarian, fallopian tube or primary peritoneal carcinoma

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Objective: Angiogenesis inhibition is a valuable strategy for ovarian cancer (EOC). Pazopanib is a potent small molecular inhibitor of VEGF-1, -2, -3, PDGFR, c-kit, and has activity as a single agent in ovarian cancer. We designed a trial to assess the benefit of adding pazopanib to gemcitabine in patients with recurrent EOC.

Method: An open-label, randomized, multisite, phase 2 trial was conducted (NCT01610206) including patients with platinum-resistant or sensitive disease, 3 or fewer prior lines of chemotherapy, and measurable/evaluable disease. Patients were randomly assigned to weekly gemcitabine 1,000 mg/m² on days 1 and 8 of a 21-day cycle, with or without pazopanib 800 mg QD, stratified by platinum sensitivity and number of prior lines (1 vs 2 or 3). The primary endpoint was progression-free survival (PFS).

Results: A total of 148 patients were enrolled 2012–2017. Median age was 63 years (30–82 years); 60% were platinum-resistant; and surveillance was 13 months (0.4–54 months). Median PFS was 5.3 (95% CI 4.2–5.8) versus 2.9 months (95% CI 2.1–4.1) in the gemcitabine arm. The PFS effect was most pronounced in the platinum-resistant group (5.32 vs 2.33 months Tarone-Ware, $P < 0.001$). There was no difference in overall survival (OS). Overall recurrence rate (PR 20% vs 11%, $\chi^2 P = 0.02$) and DCR (80% vs 60%, $\chi^2 P < 0.001$) were higher in the combination. High-grade adverse events in the combination arm included grade 3 or lower: hypertension (15%), neutropenia (35%), and thrombocytopenia (12%).

Conclusions: The addition of pazopanib to gemcitabine enhanced anti-tumor activity; those with platinum-resistant disease derived the most benefit from combination therapy, even in the setting of receiving prior bevacizumab.

Apatinib plus camrelizumab in patients with advanced cervical cancer: A multicentre, open-label, single-arm, phase II trial

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Objective: Apatinib is a selective inhibitor of vascular endothelial growth factor receptor-2 (VEGFR2). We aimed to assess the efficacy and safety of apatinib plus camrelizumab, a fully humanized anti-PD-1 monoclonal antibody, in patients with advanced cervical cancer.

Method: In this open-label, single-arm, phase 2 study done at 4 centers in China, eligible patients were aged 18 years or older, had an Eastern Cooperative Oncology Group performance status of 0 or 1, progressed after at least 1 line of systemic chemotherapy for metastatic, recurrent, or persistent cervical cancer, and had measurable disease. Patients received oral apatinib 250 mg once daily and intravenous camrelizumab 200 mg every 2 weeks. Treatment continued until disease progression, unacceptable toxicity, and withdrawal of consent. The primary endpoint was the objective response rate (ORR) assessed by the Response Evaluation Criteria in Solid Tumor (RECIST, version 1.1). An optimal Simon 2-stage design was employed to test the null hypothesis of a 17% ORR versus 35% alternative (1-sided alpha 0.10, 80% power), if more than 3 responses out of the first 16 patients were observed, then the study will continue to enroll a total of 44 patients.

Results: Between January 21, 2019, and August 1, 2019, 45 patients were enrolled and received at least 1 dose of camrelizumab (safety population). The median age was 51 years (range 33–67 years). Median previous treatment lines was 2 (range 1–4). In the first stage, 8 responses were noted among 16 patients, which met the first-stage criteria; then the study continued to stage 2. As of October 25, 2019, the median follow-up was 6.7 months (range 1.7–9.23). Twenty-five (57.1%) of 42 patients who had at least 1 post-baseline tumor assessment (efficacy evaluable set) achieved an objective response, including 1 (2.2%) complete response and 24 (53.3%) partial response. The disease control rate was 88.1% (37/42). The median duration of response has not yet been reached. Thirty-one (68.9%) patients had grade ≥ 3 treatment-related adverse events (TRAEs). Grade ≥ 3 TRAEs occurring in $\geq 5\%$ of patients were hypertension (22.2%), fatigue (15.6%), anemia (13.3%), and thrombocytopenia (6.7%). See **Figure 1**.

Conclusion: Apatinib plus camrelizumab showed promising antitumor activity and tolerable toxicities in patients with advanced cervical cancer.

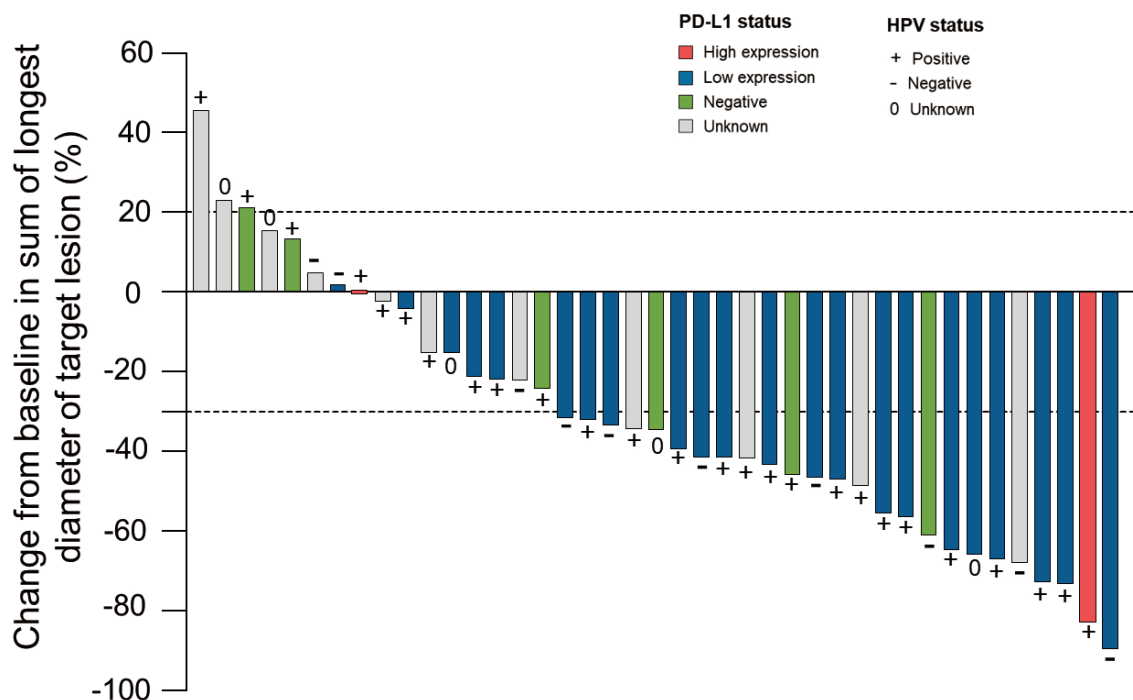


Fig. 1.