

A Phase I trial of Nab-Paclitaxel/Bevacizumab (AB160) Nano-Immunoconjugate Therapy for Metastatic Gynecological Malignancies: MC1371 (NCT02020707)

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Objectives: AB160 is a 160 nm nano-immunoconjugate consisting of nab-paclitaxel (NP) nanoparticles non-covalently coated with bevacizumab (BEV) for targeted delivery into tissues expressing high levels of vascular-endothelial growth factor (VEGF). Both taxanes (GOG-0129C, GOG-0126R, GOG-0127V) and BEV (GOG-0229E, AURELIA, GOG-0227C) have demonstrated clinical activity in heavily treated metastatic endometrial cancer (EC), ovarian cancer (OC), and cervical cancer (CC), respectively. We sought to test the safety, pharmacokinetics, and preliminary efficacy of AB160 in patients with gynecologic cancers.

Methods: A 3+3 phase I trial was conducted in patients with EC, platinum-resistant OC, and CC who had prior systemic treatment for metastatic disease to determine the maximum tolerated dose (MTD) of AB160 administered intravenously on days 1, 8 and 15 of a 28-day cycle. The starting dose level (DL1) was NP at 125 mg/m² with BEV at 50 mg/m². There were 2 higher dose levels: DL2 (NP at 150 mg/m² with BEV at 60 mg/m²) and DL3 (NP at 175 mg/m² with BEV at 70 mg/m²). Dose limiting toxicities (DLT) included grade (G) 4 neutropenia or anemia, PLT <25,000, serum creatinine ≥2 times baseline, G2-4 neurologic toxicity or G3-4 non-hematologic toxicities. Disease evaluations were conducted after every 2 treatment cycles using RECIST criteria. Patients were treated until progression of disease (PD) or intolerability. Samples were collected for pharmacokinetic (PK) studies. Having established the recommended phase II dose (RP2D), the safety profile and anti-tumor activity of the RP2D of AB-complex was further examined in patients with previously treated EC and patients with previously treated OC.

Results: Nine women were enrolled (5 with EC and 4 with OC) onto the dose escalation cohort; 3 to each dose level, as no DLTs were observed. All 9 patients have discontinued treatment. Reasons for discontinuation included PD (5 pts), adverse reactions (3 pts.), and patient choice (1 pt.). The median number of cycles administered was 5 (2-14). The most common severe (G3/4) toxicities include neutropenia (44.4%) and leukopenia (22.2%). There

have been 5 partial responses ([PR] 55.5%): 1 on DL1 and 2 each on DL2 and DL3. Two patients are alive without PD, 3 alive with PD, and 4 dead following PD. Median time to PD was 1.1 years and 18-month overall survival rate was 77.8%. Pharmacokinetic analyses demonstrated that AB160 allowed 50% higher paclitaxel dosing and that paclitaxel was cleared in a manner commonly observed with therapeutic antibodies.

Based on these findings, 6 EC and 6 OC patients were enrolled and treated at DL2. One OC patient lacks treatment data having just enrolled. Of the remaining 11 patients, treatment had been discontinued by all 6 EC patients and 1 OC patient. Reasons included: PD (EC: 4; OC: 1), and adverse events (EC: 2). The median number of treatment cycles was 4 (range: 1-11) for the EC cohort and unreached for the OC cohort. The most common severe (G3/4) toxicities included leukopenia (EC: 83.3%; OC: 20%), neutropenia (EC: 50%; OC: 40%), lymphopenia (EC: 33.3%), anemia (EC: 33.3%; OC: 20%), hyponatremia (EC: 16.7%; OC: 40%) and fatigue (EC: 33.3%). There were 2 PR in the EC cohort and 1 in the OC cohort. All 6 EC patients have had PD, with median PFS being 5.3 months.

Conclusions: AB160 therapy is safe and demonstrates promising clinical activity in patients with previously treated metastatic gynecologic malignancies. Pharmacokinetic studies suggest that AB160 functions as an antibody-drug conjugate.

Multiple choice or true/false question:

What is the mechanism of action of AB160?

- A. Angiogenesis inhibitor
- B. Immune checkpoint inhibitor
- C. Nano-immunoconjugate (antibody-drug conjugate)**
- D. Tyrosine kinase inhibitor

What is the most common Grade 3+ adverse event related to AB160 in patients with gynecologic cancers?

- A. Colitis
- B. Fatigue
- C. Hematologic AEs (neutropenia, leukopenia, anemia)**

D. Peripheral neuropathy

Approximately what percentage of patients treated on the Phase I dose escalation portion of MC1371 were alive 18 months after study enrollment?

- A. 25%
- B. 50%
- C. 75%**
- D. 100%

Learning Objective:

1. Summarize the safety, pharmacokinetics and efficacy of AB160 (nab-paclitaxel/bevacizumab nano-immunoconjugate) in patients with previously treated endometrial and ovarian cancers.