

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

Kalogera, E., Suman, V.J., Nevala, W.K., Finnes, H.D., Schimke, J.M., Strand, C.A., Glaser, G.E., Grudem, M.E., Jatoi, A., Klampe, C.M., Kumar, A., Langstraat, C.L., Wahner-Hendrickson, A.E., Weroha, S.J., Reid, J.M., Markovic, S.N., Block, M.S.

ABSTRACT

OBJECTIVE

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.

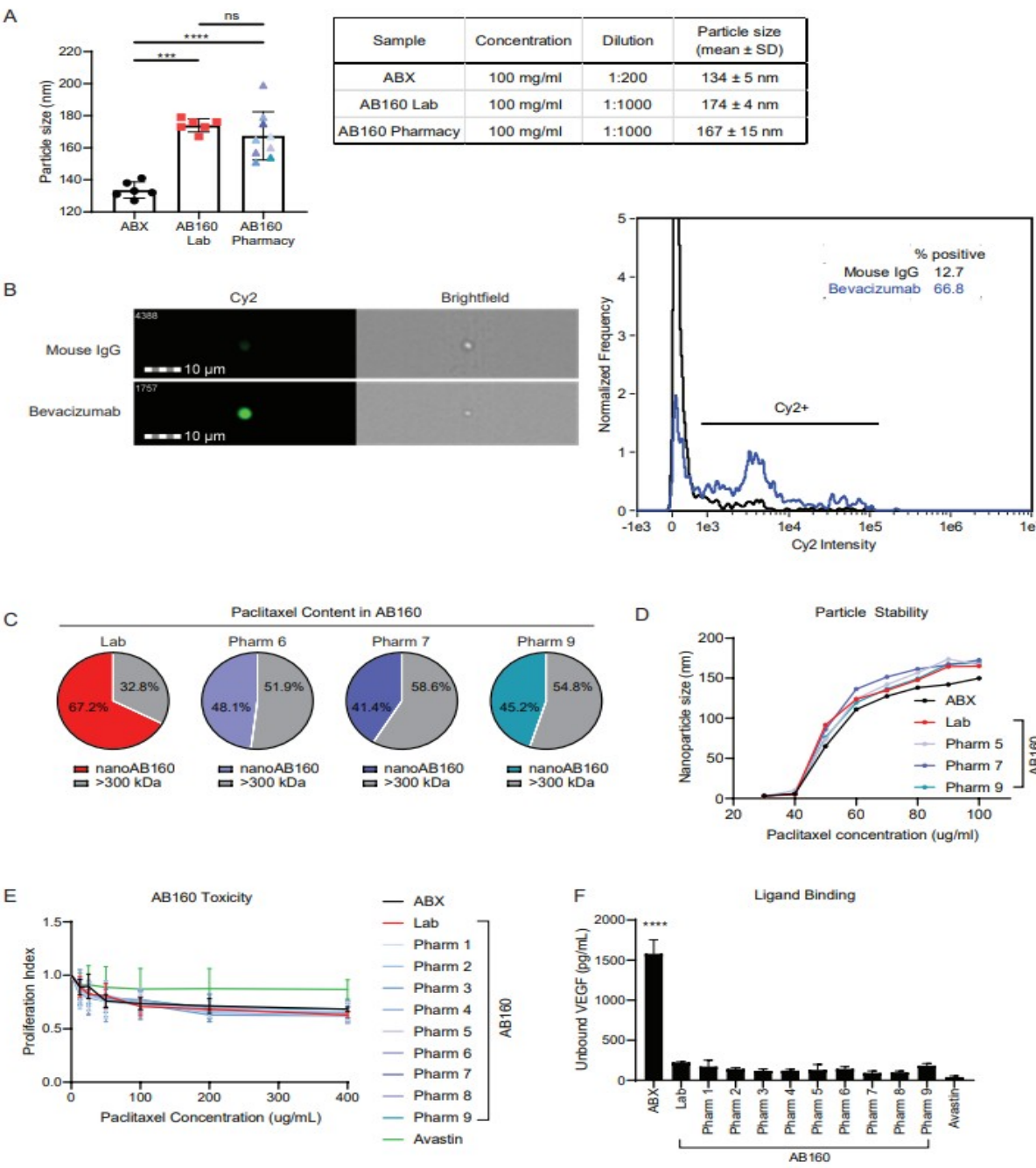
RESULTS

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.

FIGURE 1. PRECLINICAL DATA



Preclinical data: **A.** Particle size of clinical AB160 was compared to laboratory prepared AB160 and commercial ABX using nanoparticle tracking technology of Nanosight. Several samples were run for each sample type. **B.** Bevacizumab and antibody isotype control were conjugated to Cy2 and co-incubated with ABX. Amnis Image Stream was utilized for confocal images and determination of MFI and percentage of fluorescent particles for ABX labeled with either isotype control or bevacizumab. **C.** AB160 nanoparticles were separated by size exclusion filtration of 300kD. Paclitaxel content of each fraction was determined by HPLC. Pie charts show the distribution of paclitaxel in clinically and lab produced AB160. **D.** Multiple dilutions for lab and clinical AB160 and ABX were prepared. Particle size measurements were determined by dynamic light scattering (Nanostar) for each dilution and plotted by concentration and mean particle size. **E.** A375 cells were incubated overnight with lab and clinical AB160, ABX and bevacizumab only at concentrations for 6.25 to 400 mcg/mL of paclitaxel. Proliferation was measured by DNA replication using the thymidine derivative EdU. Proliferation index was determined by dividing each experimental sample by the total proliferation in untreated cells. **F.** Ligand binding was determined by ability of ABX, lab and clinical AB160, and bevacizumab to bind VEGF out of solution. Soluble VEGF was measured with human VEGF duoset antibodies from R and D Systems. Unbound levels of VEGF are shown.

CLINICAL TRIAL OBJECTIVES

Primary goals

- Dose escalation cohort: to determine the maximally tolerated dose (MTD) or recommended phase II dose (RP2D) of AB-complex among patients with gynecologic cancers.
- Endometrial cancer expansion cohort: to further assess the safety profile and anti-tumor activity of the RP2D of AB-complex for patients with previously treated endometrial cancer.
- Ovarian cancer expansion cohort: to further assess the safety profile and anti-tumor activity of the RP2D of AB-complex for patients with previously treated ovarian cancer.

Secondary goals

- To gather preliminary data on tumor response rate and progression free survival time of AB-complex among patients with gynecologic cancers

Correlative research goals (Dose escalation cohort only)

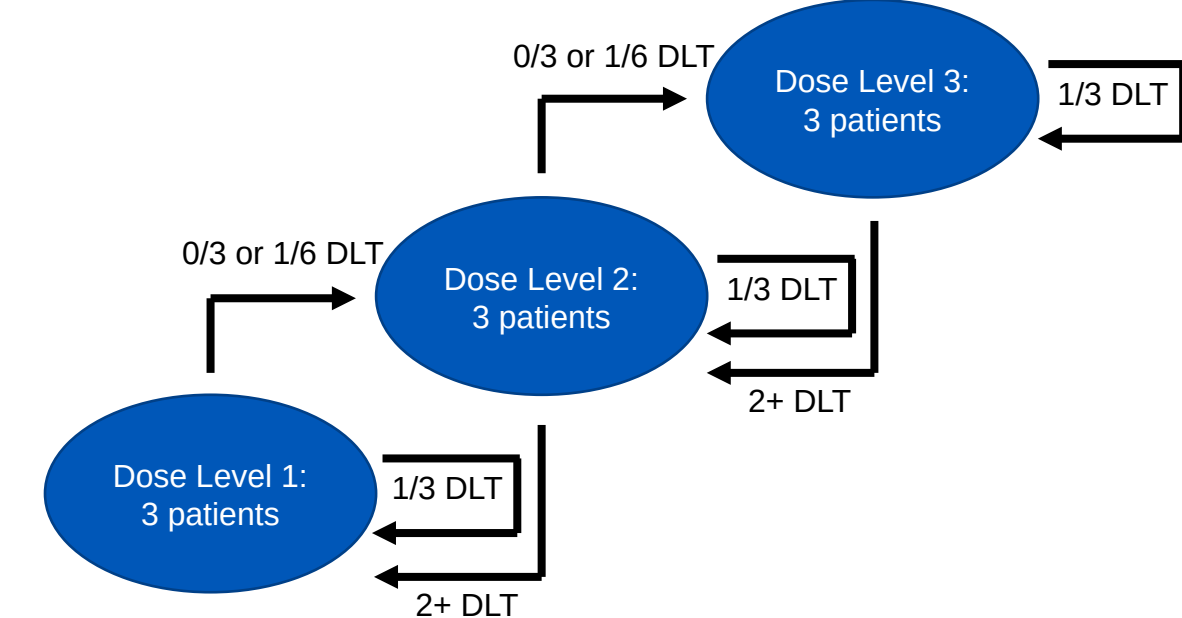
- To determine the pharmacokinetics of paclitaxel administered in the context of AB-complex

DOSE ESCALATION AND EXPANSION

FIGURE 2. STUDY DESIGN

Gynecologic Cancer Dose Escalation Cohort

- Recurrent endometrial cancer or platinum-resistant ovarian cancer
- Prior treatment with carboplatin and paclitaxel
- Measurable disease or CA 125-evaluable disease



Endometrial cancer Expansion Cohort

- 1-3 lines of prior cytotoxic or immune checkpoint inhibitor therapy
- Must have received carboplatin/paclitaxel AND an immune checkpoint inhibitor
- Measurable disease

Ovarian cancer Expansion Cohort

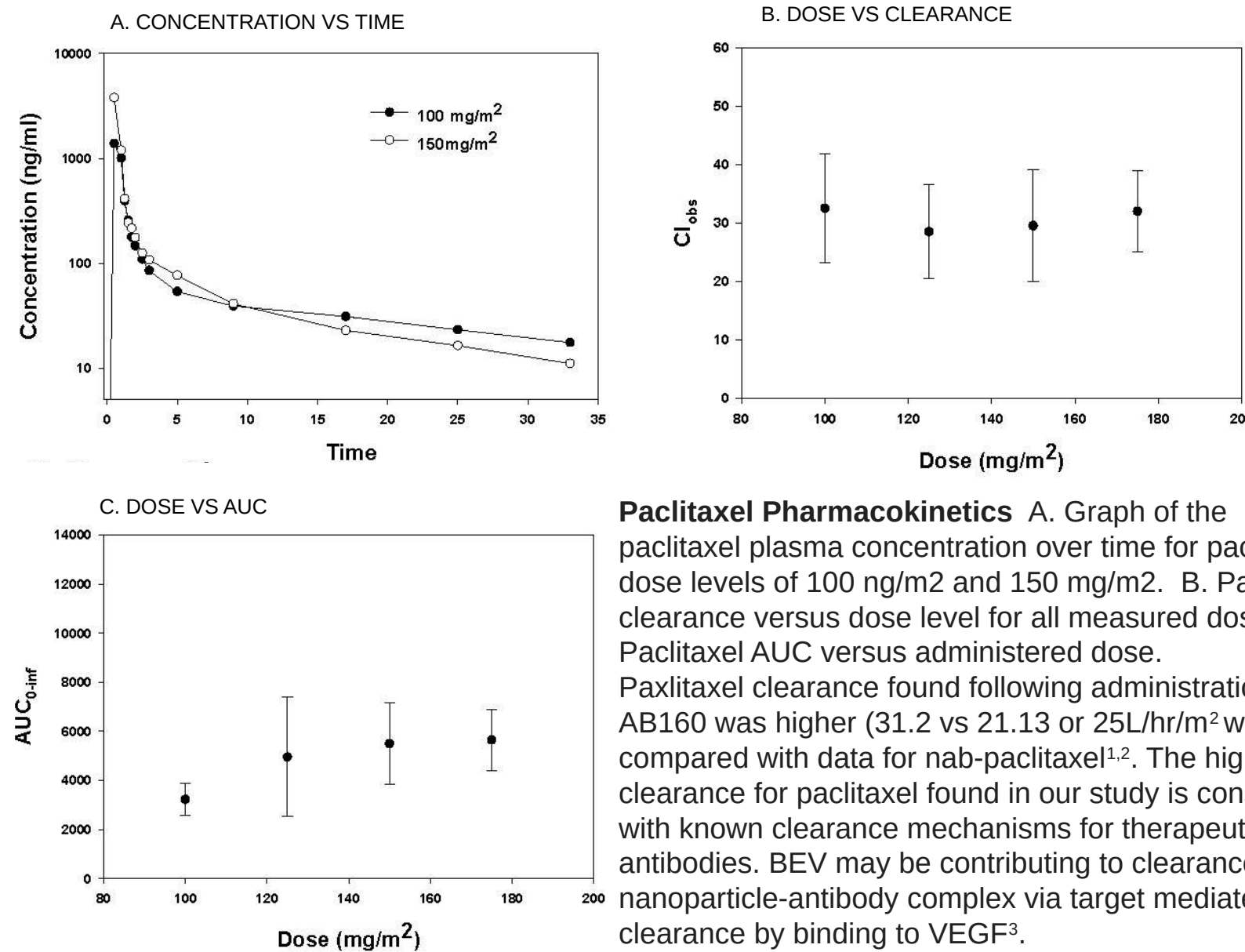
- 1-4 prior lines of cytotoxic therapy
- Must have received carboplatin/paclitaxel AND bevacizumab
- If 1-2 prior lines, must be platinum-resistant/refractory
- If 3-4 prior lines, may be platinum-sensitive or platinum-resistant/refractory
- Measurable disease or CA 125-evaluable disease

Dose Level	Dose (Abraxane)	Dose (Avastin)
1	125 mg/m ²	50 mg/m ²
2	150 mg/m ²	60 mg/m ²
3	175 mg/m ²	70 mg/m ²

TABLE 1. BASELINE PATIENT CHARACTERISTICS

	Dose escalation cohort (n=10)	Endometrial cancer dose expansion cohort (n=6)	Ovarian cancer dose expansion cohort (n=5)
Age: median (range)	61 (41-74)	67 (47-72)	70 (44-77)
Race			
White	4 (40%)	5 (83.3%)	5 (100%)
Asian	0	1 (16.7%)	0
Not reported	6 (60%)	0	0
Primary site – histology			
Endometrium – endometrioid	4 (40%)	2 (33.3%)	-
Endometrium – serous	0	3 (50%)	-
Endometrium – squamous cell	0	1 (16.7%)	-
Endometrium – carcinosarcoma	1 (10%)	0	-
Endometrium – mixed	1 (10%)	0	-
Ovarian/fallopian/peritoneal – serous	2 (20%)	-	4 (80%)
Ovarian/fallopian/peritoneal – carcinosarcoma	2 (20%)	-	1 (20%)
Prior cytotoxic and immunotherapy regimens			
Paclitaxel/carboplatin +/- bevacizumab	10 (100%)	6 (100%)	5 (100%)
Gemcitabine/carboplatin +/- bevacizumab	1 (10%)	1 (16.7%)	2 (40%)
Liposomal doxorubicin/carboplatin +/- bevacizumab	1 (10%)	1 (16.7%)	1 (20%)
Liposomal doxorubicin +/- bevacizumab	0	0	3 (60%)
Cisplatin/ifosfamide	2 (20%)	0	0
Pembrolizumab +/- lenvatinib	0	6 (100%)	0
Disease site(s)			
Peritoneum/retroperitoneum	7 (70%)	2 (33.3%)	2 (40%)
Lymph nodes	7 (70%)	5 (83.3%)	4 (80%)
Liver	2 (20%)	1 (16.7%)	2 (40%)
Lungs	2 (20%)	2 (33.3%)	3 (60%)
CA125 level			
Within normal limits	3 (30%)	1 (16.7%)	1 (20%)
Above normal limits	5 (50%)	5 (83.3%)	4 (80%)
Not reported	2 (20%)	0	0

FIGURE 3. PHARMACOKINETICS



Paclitaxel Pharmacokinetics: A. Graph of the paclitaxel plasma concentration over time for paclitaxel dose levels of 100 ng/m² and 150 mg/m². B. Paclitaxel clearance versus dose level for all measured doses. C. Paclitaxel AUC versus administered dose. Paclitaxel clearance found following administration of AB160 was higher (31.2 vs 21.13 or 25L/hr/m² when compared with data for nab-paclitaxel^{1,2}. The higher clearance for paclitaxel found in our study is consistent with known clearance mechanisms for therapeutic antibodies. BEV may be contributing to clearance of nanoparticle-antibody complex via target mediated clearance by binding to VEGF³.

TABLE 2. ADVERSE EVENTS REGARDLESS OF ATTRIBUTION

Toxicity	G2	G3	G4	G2	G3	G4	G2	G3	G4
Abdominal pain	10.0%	10.0%		16.7%			40.0%		
Anemia	70.0%	10.0%		50.0%	33.3%		60.0%	20.0%	
Anorexia	20.0%								
Arthralgia	20.0%			16.7%					
Aspartate aminotransferase increase				16.7%					
Aspiration		10.0%							
Constipation	10.0%								
Dehydration	10.0%			33.3%					
Diarrhea				16.7%					
Fatigue	80.0%	10.0%		50.0%	33.3%		20.0%	20.0%	
Gastroesophageal reflux disease							20.0%		
Heart failure							20.0%		
Hematuria				16.7%					
Hypertension	50.0%			33.3%			20.0%	40.0%	
Hypoalbuminemia				16.7%					
Hypocalcemia				16.7%					
Hypokalemia				16.7%					
Hyponatremia							40.0%		
Leukocytosis		10.0%							
Lymphocyte count decrease	30.0%	10.0%	10.0%	16.7%	33.3%		40.0%		
Maculo-papular rash	10.0%			16.7%			20.0%		
Malaise	10.0%								
Myalgia	30.0%								
Muscle weakness lower limb		10.0%		16.7%					
Nail loss							20.0%		
Nausea	40.0%			16.7%	16.7%		40.0%		
Neutrophil count decrease	30.0%	30.0%	20.0%	33.3%	16.7%	33.3%	40.0%	40.0%	
Oral mucositis							20.0%		
Peripheral motor neuropathy							20.0%		
Peripheral sensory neuropathy	40.0%			16.7%			40.0%		
Platelet count decrease				16.7%					
Pneumonitis	10.0%						20.0%		
Proteinuria	10.0%								
Pustular rash	10.0%								
Small intestinal obstruction							20.0%		
Thromboembolic event	10.0%	10.0%					20.0%		
Vomiting				16.7%			20.0%		
Weight gain	10.0%								
WBC decrease	60.0%	20.0%	10.0%	83.3%			20.0%	40.0%	20.0%

FIGURE 4. BEST OBJECTIVE RESPONSE: WATERFALL PLOT

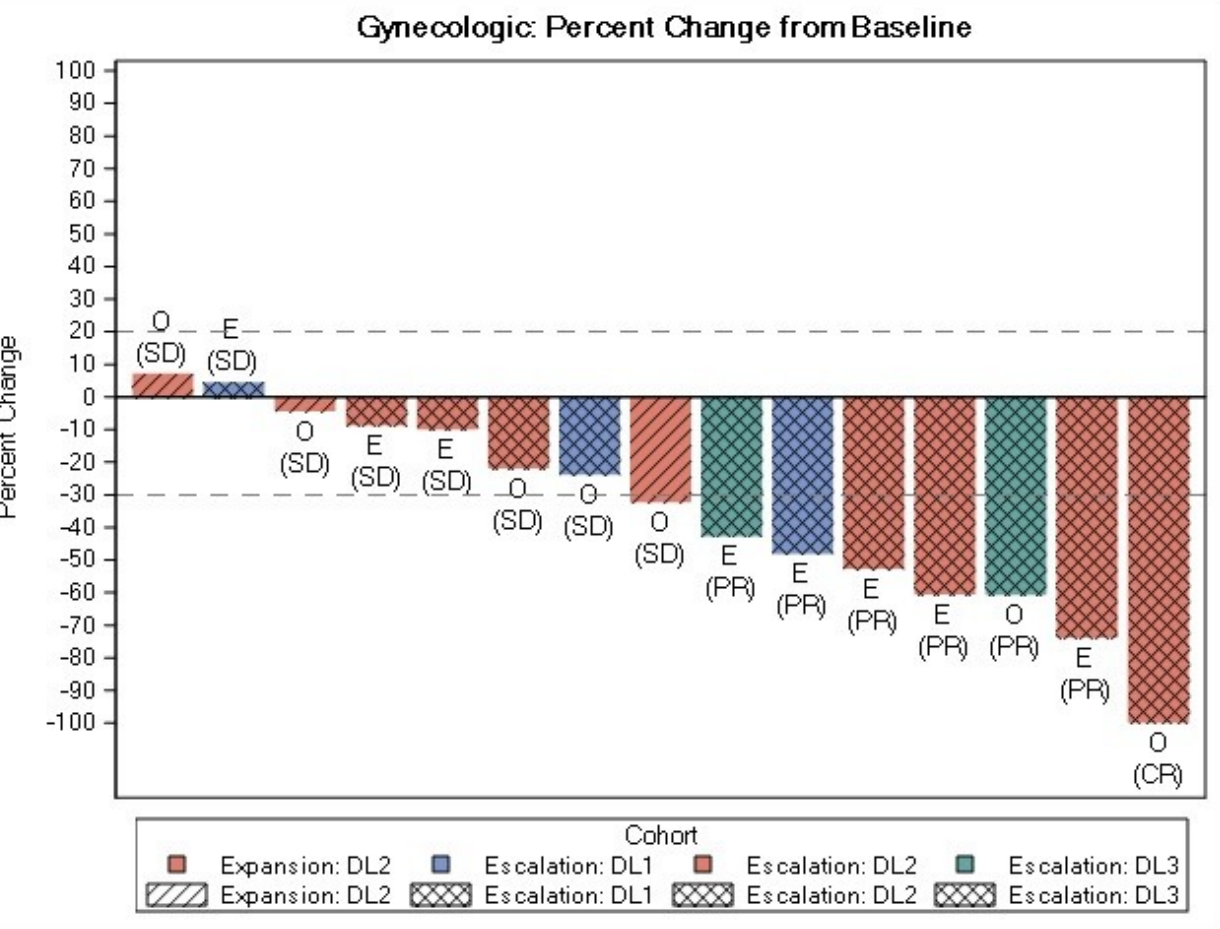
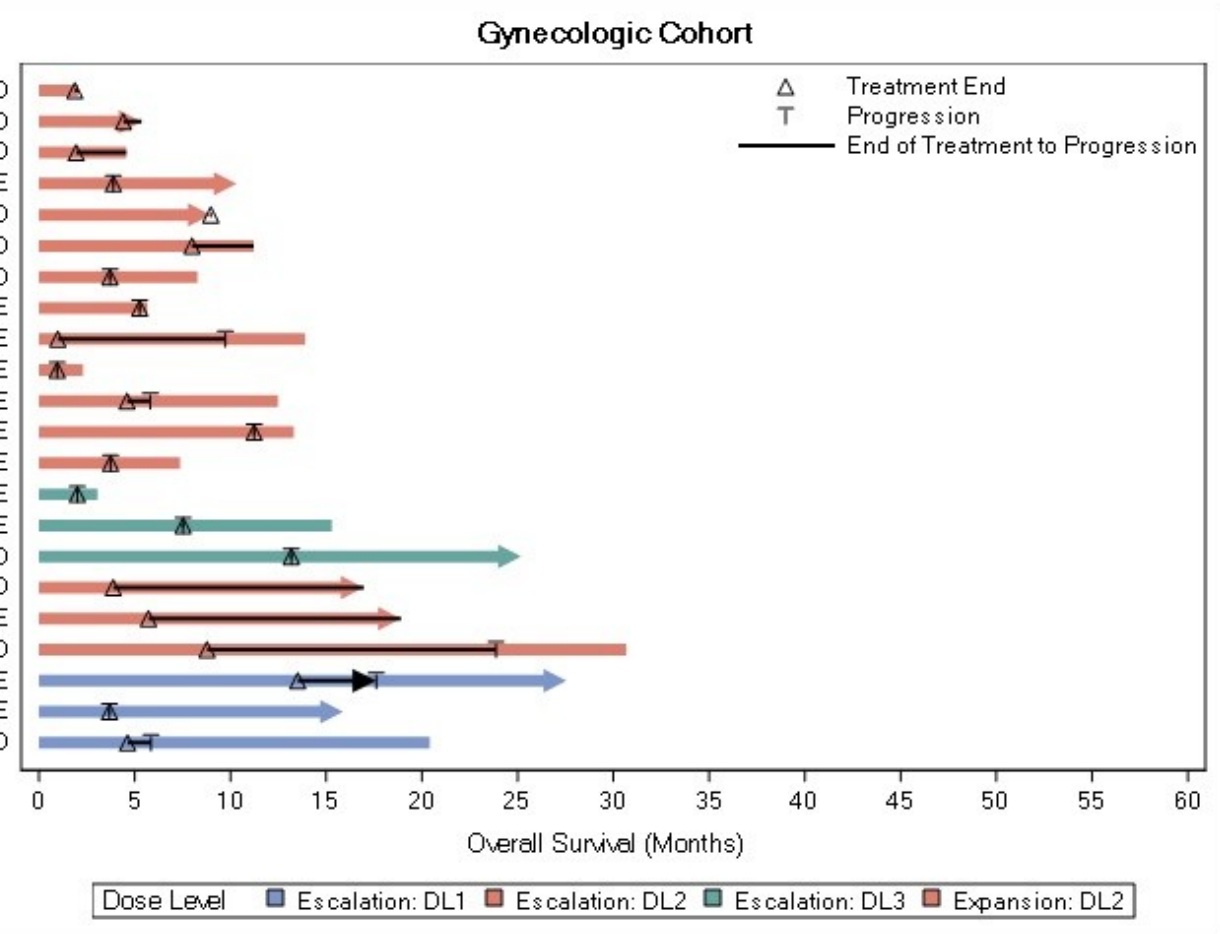


FIGURE 5. DURATION OF RESPONSE: SWIMMER PLOT



CONCLUSIONS

- AB160 nanoparticles have an acceptable safety profile in patients with recurrent/metastatic endometrial and ovarian cancer (recommended Phase II dose: 150 mg/m² NP, 60 mg/m² BEV)
- AB160 therapy results in promising clinical activity in patients with previously treated gynecologic cancers.
- Pharmacokinetic studies suggest that AB160 functions as an antibody-drug conjugate

ACKNOWLEDGEMENTS

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