In vivo efficacy of the antibody-drug conjugate (ADC) PB-vcMMAE-5 in an ovarian cancer patient-derived xenograft (PDX) model expressing truncated core 2 O-glycans

Kwong Y. Tsang[1], Massimo Fantini[1], Anjum Zaki[1], Sharon A Mavroukakis[1], Christina M. Annunziata[2], Philip M. Arlen[1]

[1]Precision Biologics, Inc., Bethesda, MD, 20814; [2]American Cancer Society, Glen Allen, VA, 23058

Introduction:

Aberrant O-glycosylation, particularly the expression of truncated core 2 O-glycans, is strongly associated with ovarian cancer progression, metastasis, and poor prognosis, highlighting the need for novel targeted therapies. We developed a novel antibody-drug conjugate (ADC), PB-vcMMAE-5, composed of the monoclonal antibody PB-223 conjugated to monomethyl auristatin E (MMAE) via an mc-vc-PABc linker. PB-vcMMAE-5 possesses a drug-to-antibody ratio of 3.92, demonstrates high plasma stability, and has shown potent anti-ovarian cancer activity with favorable tolerability in preclinical studies. This study evaluated the anti-tumor efficacy and safety of PB-vcMMAE-5 in an ovarian cancer patient-derived xenograft (PDX) model.

Experimental Design:

PB-223 binding to the ovarian PDX tissue was confirmed by immunohistochemistry (IHC), demonstrating an H-score of 180. In vivo efficacy studies were conducted in BALB/c nude mice bearing subcutaneous ovarian cancer PDX tumors Mice (n = 6/group) received weekly intravenous treatments for five weeks with PBS control, MMAE alone, PB-223 alone, or PB-vcMMAE-5 at 3 mg/kg or 9 mg/kg. Tumor volumes were measured throughout the study, and tumor growth inhibition (TGI) percentages were calculated. Hematology, clinical chemistry, mouse body weight and viable tumor cell content were also evaluated to assess safety and tolerability.

Results:

Baseline tumor volumes were approximately 151 mm^3 across all groups. By day 39 following treatment initiation, the mean tumor volume in the PBS control group was 1369.34 ± 118.98 mm^3. Treatment with MMAE alone reduced the mean tumor volume to 385.8 ± 57.52 mm^3. PB-vcMMAE-5 treatment resulted in mean tumor volumes of 203.08 ± 69.09 mm^3 at 3 mg/kg and 0.00 ± 0.00 mm^3 at 9 mg/kg. In contrast, treatment with PB-223 alone yielded a mean tumor volume of 1511.97 ± 195.21 mm^3. The corresponding tumor growth inhibition (TGI) values were 80.76% for MMAE alone, 95.78% for PB-vcMMAE-5 at 3 mg/kg, 200.00% for PB-vcMMAE-5 at 9 mg/kg, and -11.75% for PB-223 alone. Complete and sustained tumor regression was observed in the 9 mg/kg PB-vcMMAE-5 treatment group. No significant adverse pathological

findings or abnormalities in hematology and clinical chemistry parameters or body weight were observed at efficacious doses.

Conclusion:

PB-vcMMAE-5 demonstrated potent and durable anti-tumor activity in an ovarian cancer PDX model, with complete and sustained tumor regression achieved at 9 mg/kg and an excellent safety profile. These findings support the further development of PB-vcMMAE-5 as a promising therapeutic candidate for ovarian cancers expressing truncated core 2 O-glycans.