Poster #: 888

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

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Introduction

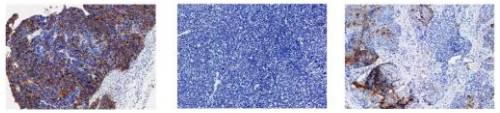
Aberrant O-glycosylation, particularly the expression of truncated core 2 O-glycans, is strongly associated with ovarian cancer progression, metastasis, and poor prognosis, underscoring the need for targeted therapies. We developed a novel antibody-drug conjugate (ADC), PB-vcMMAE-5 (U159-18095-vcMMAE) comprising the monoclonal antibody, PB-223 (U159-18095) conjugated to monomethyl auristatin E (MMAE) via an mc-vc-PABc linker. PB-vcMMAE-5 has a drug-to-antibody ratio of 3.92, demonstrates high plasma stability, and has exhibited potent anti-ovarian cancer activity with favorable tolerability in preclinical studies. This study evaluated the antitumor 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 (LD1-0032-200655) 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 received weekly intravenous treatments for five weeks with PBS control (Group I, n=6), PB-vcMMAE-5 at 3 mg/kg (Group 2, n=3), PB-vcMMAE-5 at 9 mg/kg (Group 3, n=3), PB-vcMMAE-5 at 3 mg/kg (Group 4, n=3), PB-vcMMAE-5 at 9 mg/kg (Group 5, n=3), MMAE alone (Group 6, n=6), or unconjugated PB-223 (group 7, n=6). Tumor volumes were measured throughout the study, and tumor growth inhibition (TGI) was calculated. Hematological parameters, clinical chemistry, body weight and viable tumor cell content were also evaluated to assess safety and tolerability of the treatments.

Results

Figure 1. IHC staining with ovarian-cancer PDX using PB-223 (100x)



LD1-0032-200655 (H score:180) | LD2-0032-200775 H score:0 | LD1-0032-362879 H score:100

H-Score = [1 x (% cell 1+) + 2 x (% cell 2+) + 3 x (% cell 3+)]

(1)H-Score <=9, - ; (2) 10 <= H-Score <=9, + ;
(3) 100 <= H-Score <=199, ++; (4) 200 <=H-Score<=300, +++.

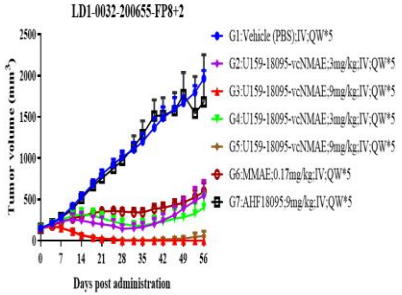


Figure 2. Tumor growth curves of each treatment group in LD1-0032-200655 subcutaneous ovarian cancer PDX mouse model (n=3/6)

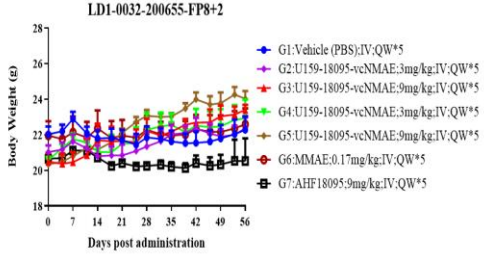


Figure 3. Body weight changes of test articles in the LD1-0032-200655 human-derived ovarian cancer BALB/c-nude mouse xenograft

Table1. Summary of efficacy endpoints of the test articles in LD1-0032-200655 ovarian cancer PDX model

Groupp	Treatment	Tumor volume (Day 0)	Tumor volume (Day 39)	TGI (%) (Day 39)	*P* value vs Group 1 (Day 39)a
1	PBS	151.21 ± 8.65	1,369.34 ± 118.98	-----.	----
2	U159-18095-vcMMAE (3 mg/kg)	151.64 ± 6.11	203.08 ± 69.09	95.78	****
3	U159-18095-vcMMAE (9 mg/kg)	151.38 ± 5.90	0.00 ± 0.00	200.00	****
4	U159-18095-vcMMAE (3 mg/kg)	151.37 ± 13.22	210.43 ± 89.47	95.15	****
5	U159-18095-vcMMAE (9 mg/kg)	151.97 ± 12.22	10.67 ± 10.67	192.93	****
6	MMAE	151.45 ± 7.73	385.80 ± 57.52	80.76	****
7	AHF18095	151.70 ± 5.45	1,511.97 ± 195.21	-11.75	NS

a: *p* was calculated .based on tumor volume. Analysis was performed with one-way ANOVA. **** *p<0.0001*

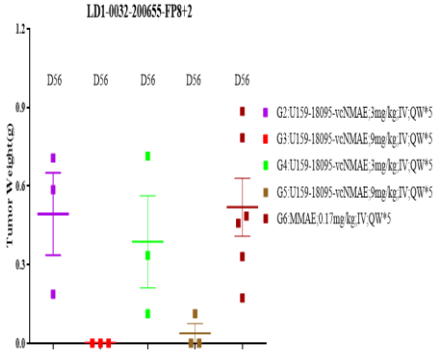


Figure 4. The tumor weight of the test articles in the LD1-0032-200655 human-derived ovarian cancer BALB/c-nude mouse PDX model

Conclusions

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. The treatment was well tolerated, with hematological and clinical chemistry analyses showing no evidence of treatment-related life-threatening systemic toxicity. These findings support the further development of PB-vcMMAE-5 as a promising therapeutic candidate for ovarian cancers expressing truncated core 2 O-glycans.