152P - A Phase I Study of HBM4003, an anti-CTLA-4 Heavy Chain Only Monoclonal Antibody, in Combination with Toripalimab in Advanced Melanoma

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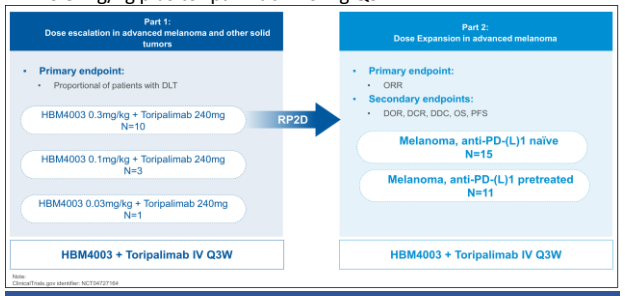
Background

- Porustobart (HBM4003) is a next generation anti-CTLA-4 fully human heavy chain only monoclonal antibody (HCAb) engineered to deplete Treg cells by enhanced antibody dependent cellular cytotoxicity (ADCC) activity.
- Toripalimab is a humanized immunoglobulin G4 monoclonal antibody against PD-1, which is approved for the treatment of melanoma in China.
- HBM4003 and toripalimab have complementary mechanisms to harness antitumor immune response.
- Here we reported updated results of a phase I study that evaluated HBM4003 plus toripalimab in advanced melanoma.

Design and Method

- This study includes two parts. In the dose-escalation part, patients with solid tumors received HBM4003 at 3 dose levels (0.03 mg/kg [n=1], 0.1 mg/kg [n=3], and 0.3 mg/kg [n=10]) plus toripalimab 240 mg every three weeks (Q3W). In the dose-expansion part, patients with advanced melanoma (n=26) received the recommended phase 2 dose (RP2D) of HBM4003 0.3 mg/kg plus toripalimab 240 mg Q3W.



Baseline Demographics

- As of 31 Aug 2022, a total of 40 patients had been dosed.
- A total of 36 patients were treated with RP2D in Part 1 (10 patients) and Part 2 (26 patients) including 34 patients with advanced melanoma. The 34 patients with melanoma were categorized as anti-PD-(L)1-naïve group (Cohort A, 17 patients) and anti-PD-(L)1 pretreated group (Cohort B, 17 patients).
- The demographics and baseline characteristics of patients in Cohort A and Cohort B were showed in Table1.

Table 1. Patient demographics and baseline characteristics

Demographics or characteristic	Cohort A (n=17)	Cohort B (n=17)
Sex, n(%)		
Male	10 (58.8)	6 (35.3)
Female	7 (41.2)	11 (64.7)
Age, mean (SD)	54.7 (14.3)	52.3 (12.9)
ECOG PS, n(%)		
0	6 (35.3)	8 (47.1)
1	11 (64.7)	9 (52.9)
No. of previous treatment lines, n(%)		
0	14 (82.4)	0 (0.0)
1	3 (17.6)	6 (35.3)
2 or more	0 (0.0)	11 (64.7)
Melanoma subtype, n(%)		
Cutaneous (non-acral)	3 (17.6)	2 (11.8)
Acral	5 (29.4)	3 (17.6)
Mucosal	6 (35.3)	10 (58.8)
Unknown	3 (17.6)	2 (11.8)
LDH, n(%)		
≤ ULN	14 (82.4)	8 (47.1)
> ULN	3 (17.6)	9 (52.9)

Efficacy

- For Cohort A, the ORR and DCR were 53.3% and 73.3% respectively in the 15 patients with post-treatment tumor assessment; For Cohort B, the ORR and DCR were 11.8% and 35.3% respectively (Table 2).

Table 2. Tumor assessment by RECIST 1.1 in Cohort A and Cohort B

Patients with post-treatment tumor assessment, n	Cohort A (n=15)	Cohort B (n=17)
ORR, (%)	53.3	11.8*
ORR, (95% CI)	26.6 - 78.7	1.5 - 36.4
DCR, (%)	73.3	35.3
DCR, (95% CI)	44.9 - 92.2	14.2 - 61.7
ORR in melanoma subtype, (%)		
Cutaneous (non-acral)	66.7 (2/3)	0.0 (0/2)
Acral	50.0 (2/4)	0.0 (0/3)
Mucosal	60.0 (3/5)	20.0 (2/10)
Unknown	33.3 (1/3)	0.0 (0/2)

Note: *includes 1 patient assessed as pseudoprogression

- Waterfall plots of Cohort A and Cohort B are shown in Figure 1 and Figure 2, respectively.
- The median time to objective response was 64.0 days in Cohort A and 85.0 days in Cohort B. PFS or OS data are not mature by the cut-off date.

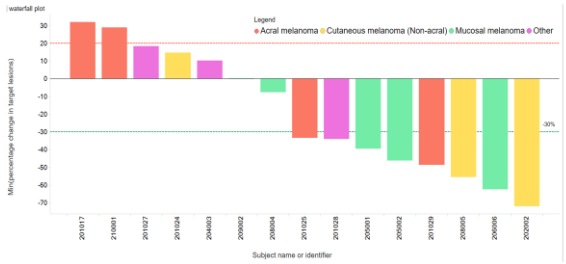


Figure 1. Waterfall plot of melanoma patients in anti-PD-(L)1-naïve group with post-treatment tumor assessment

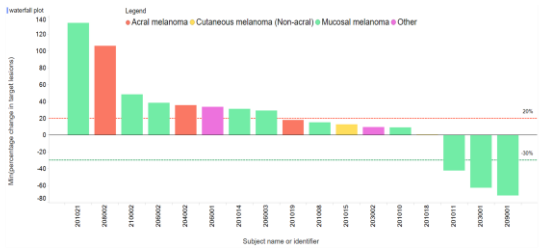


Figure 2. Waterfall plot of melanoma patients in anti-PD-(L)1 pretreated group with post-treatment tumor assessment

Safety

- Treatment-related adverse events (TRAEs) were reported in 87.5% (35/40) patients, and ≥Grade 3 TRAEs were reported in 20.0% (8/40) patients (Table 3).
- The most common (≥10%) TRAEs were showed in Table 4.

Table 3. Summary of Adverse Event in Different Dose Level

Preferred Term	HBM4003 0.03 mg/kg + Toripalimab 240 mg n (%)	HBM4003 0.1 mg/kg + Toripalimab 240 mg n (%)	HBM4003 0.3 mg/kg + Toripalimab 240 mg n (%)
Total pts No.	1 (100.0)	3 (100.0)	36 (100.0)*
TEAE	1 (100.0)	3 (100.0)	35 (97.2)
All TRAE	1 (100.0)	1 (33.3)	33 (91.7)
≥ G3 TRAE	1 (100.0)	0 (0.0)	7 (19.4)
All irAE	0 (0.0)	0 (0.0)	20 (55.6)
≥ G3 irAE	0 (0.0)	0 (0.0)	4 (11.1)
TRSAE	0 (0.0)	0 (0.0)	9 (25.0)
TRAE leading to discontinuation	0 (0.0)	0 (0.0)	4 (11.1)

Note: Pt: patients; MTD: maximum tolerated dose; TEAE: treatment emergent adverse event; TRAE: treatment related adverse event; TRSAE: treatment related severe adverse event.
*includes 2 non-melanoma patients

Table 4. The Most Common (≥10%) TRAEs by Preferred Term

Preferred Term	n (%)	Preferred Term	n (%)
Rash	12 (30.0)	Aspartate aminotransferase increased	6 (15.0)
Alanine aminotransferase increased	10 (25.0)	Fatigue	5 (12.5)
white blood cell count decreased	9 (22.5)	Gamma-glutamyltransferase increased	5 (12.5)
Anaemia	7 (17.5)	Lymphocyte count decreased	5 (12.5)
Pyrexia	7 (17.5)	Decreased appetite	4 (10.0)
Diarrhea	6 (15.0)	Hyperthyroidism	4 (10.0)
Hypothyroidism	6 (15.0)	Nausea	4 (10.0)

Pharmacokinetics

- Nearly dose-proportional PK exposure across dose levels
- Half-life is about ~4.6 days, limited drug accumulation in serum after multiple dosing
- Low to moderate inter-individual variability

PK Parameters*	0.03 mg/kg Q3W (N=1)	0.1 mg/kg Q3W (N=3)	0.3 mg/kg Q3W (N=36)
C_{max} (μg/mL)	0.571 (-)	1.16 (34.24)	5.20 (18.46)[a]
AUC_{0-inf} (μg*h/mL)	24.7 (-)	75.5 (42.94)	302 (25.40)[b]
$t_{1/2}$ (hr)	64.9 (-)	119 (27.51)	111 (38.70)[b]

*: Pharmacokinetic parameters are presented as Geometric Mean (CV%); C_{max}: maximum concentration; AUC_{0-inf}: area under the curve from time zero to time of the last quantifiable concentration; -: Not available.
a: n=31, b: n=30

Pharmacodynamics

- HBM4003 depleted blood Tregs temporarily and increased CD4+ T, CD8+ T cell proliferation subsequently (Figure 3).

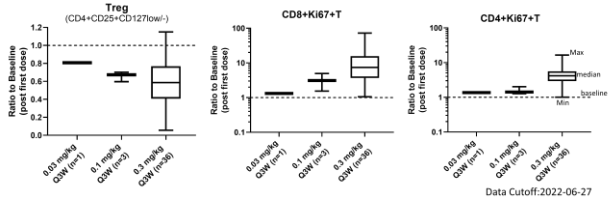


Figure 3. PBMCs from patients (before and after HBM4003 treatment) were analyzed by flow cytometry. The minimal Treg population in 1st cycle, maximal CD8+Ki67+ and CD4+Ki67+ population in first 4 cycles were compared to the baseline.

Conclusion

- HBM4003 0.3 mg/kg plus toripalimab 200mg Q3W showed promising anti-tumor activity and an acceptable safety profile in patients with advanced melanoma including highly difficult to treat acral and mucosal subtypes. Further investigation of this combination therapy is warranted in a randomized, phase 3 study.

Commercial Relationships Disclosure: Bixia Tang, Zhihong Chi, Yu Chen, Yu Jiang, Meiyu Fang, Quanli Gao, Gang Huang, Xiubao Ren, Yu Yao, Jing Chen, Xiaoshi Zhang, Rongqing Li, and Jun Guo do not have conflict of interests; Humphrey Gardner, Luyin Ding, Yuan Geng, Shuai Zhao, Yupeng Yang, Zailian Lu, and Yedong Wang are employees of Harbour BioMed.

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