Phase I Dose-Escalation Study of HBM4003, an anti-CTLA-4 Heavy Chain Only Monoclonal Antibody

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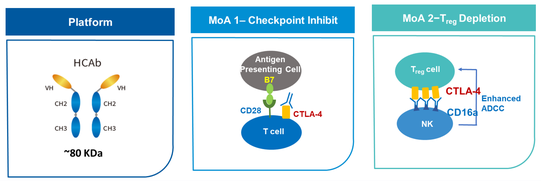
BACKGROUND

- Ipilimumab is the only marketed anti-CTLA-4 monoclonal antibody. Treatment with Ipilimumab is associated with occurrence of immune-related adverse events (irAEs) which can be life-threatening.
- HBM4003 is a fully human heavy chain only monoclonal antibody (HCAb) to CTLA-4, which was engineered to deplete Treg cells by enhanced antibody-dependent cellular cytotoxicity (ADCC) activity, in addition to its block of CTLA-4-B7 interaction.
- The HCAb molecules have only 2 heavy chains linked by disulfide bonds. Each heavy chain consists of 1 heavy chain variable region and 2 heavy chain constant regions (CH2 and CH3) without the CH1 region.
- The potential features of HCAb include unique binding epitopes, high affinity, and high tissue/tumor penetration.

Figure 1 HCAb Platform and HBM4003 Mechanism of Action



METHODS

Study Overview and Endpoints

- This is a first-in-human, Phase I study.
- In Part 1, an i3+3 design was used to guide the dose-escalation. Patients (Pts) were enrolled into 3 dose levels: 0.3mg/kg QW (28-day cycle), 0.45mg/kg Q3W (21-day cycle), and 0.6mg/kg Q3W (21-day cycle).
- The primary endpoint for Part 1 is the proportion of pts with dose-limiting toxicity (DLT).
- Data analysis for this presentation was based on a data cut-off of 12 April 2021.
- Part 2 is the dose expansion stage.

Key Inclusion Criteria

- Adult pts with histologically or cytologically confirmed advanced solid tumors that must have progressed after treatment with all relevant and clinically appropriate standard therapies, or for which no effective standard therapy is available, or the patient has a contraindication to standard therapy

Key Exclusion Criteria

- Previously received or is currently receiving CTLA-4 antibody or any CTLA-4 bispecific antibody
- Previous immune checkpoint inhibitors PD-1 or PD-L1 therapy within 8 weeks of first dose

RESULTS

Patient Disposition and Demographics

- As of 12 Apr 2021, 20 pts with advanced solid tumors have been treated at 4 Australian sites.
- Heavily pre-treated population, with 13 out of 20 pts (65%) having received 2 or more prior regimens (i.e. 3rd line+)
- 8 out of 20 pts (40%) were treated previously with immune checkpoint inhibitor.

Table 1 Patient Demographics

	0.3mg/kg QW (N=7)	0.45mg/kg Q3W (N=7)	0.6mg/kg Q3W (N=6)	Total (N=20)
Sex, n(%)				
Male	5 (71.4)	5 (71.4)	4 (66.7)	14 (70.0)
Female	2 (28.6)	2 (28.6)	2 (33.3)	6 (30.0)
Race, n(%)				
Asian	2 (28.6)	1 (14.3)	0 (0.0)	3 (15.0)
Non-Asian	5 (71.4)	6 (85.7)	6 (100.0)	17 (85.0)
Age, mean (SD)	67.6 (8.3)	62.3 (10.2)	56.8 (15.0)	62.5 (11.5)
ECOG PS, n(%)				
0	3 (42.9)	3 (42.9)	3 (50.0)	9 (45.0)
1	4 (57.1)	4 (57.1)	3 (50.0)	11 (55.0)
N of Previous Treatment Lines, n(%)				
0	2(28.6)	0	0	2 (10.0)
1	2(28.6)	2(28.6)	1(16.7)	5 (25.0)
2 or more	3(42.8)	5(71.4)	5(83.3)	13 (65.0)
Previous PD-1/PD-L1 Therapies, n(%)	2 (28.6)	3 (42.9)	3 (50.0)	8 (40.0)

Abbreviations: ECOG: Eastern Cooperative Oncology Group; PD-1:programmed cell death protein 1; PD-L1:programmed death-ligand 1; PS: performance status; SD: standard deviation

Safety and Tolerability

- A total of 15 (75%) pts reported treatment-related adverse events (TRAEs). The most common TRAE of all grades was diarrhea/enterocolitis (7/6 pts).
- Grade 3 TRAE included diarrhea (6 [30%] pts) and hepatic function abnormal (1 [5%] pt). All were manageable and reversible. No TRAE was >Grade 3.
- The most common irAEs were diarrhea/enterocolitis and skin rash. No toxicity was reported related to lung, kidney, heart or endocrine system.
- There was 1 DLT reported at 0.3mg/kg QW due to Grade 3 diarrhea. No DLT was observed in any Q3W dose level.
- Maximum tolerated dose (MTD) was not achieved.

* Diarrhea and enterocolitis was recorded at the different stage of the event based on diagnosis.

Table 2 Immune-Related Adverse Events

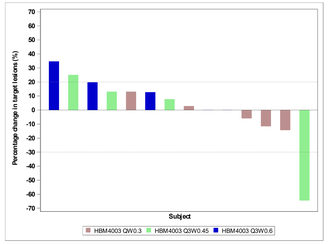
Preferred Term	0.3mg/kg QW (N=7)		0.45mg/kg Q3W (N=7)		0.6mg/kg Q3W (N=6)		Total (N=20)	
	Any Grade	Grade≥ 3	Any Grade	Grade≥ 3	Any Grade	Grade≥ 3	Any Grade	Grade≥ 3
Any irAE	4 (57.1)	1 (14.3)	2 (28.6)	1 (14.3)	5 (83.3)	3 (50.0)	11 (55.0)	5 (25.0)
Enterocolitis	2 (28.6)	0 (0.0)	1 (14.3)	0 (0.0)	3 (50.0)	0 (0.0)	6 (30.0)	1 (5.0)
Diarrhea	1 (14.3)	1 (14.3)	0 (0.0)	0 (0.0)	3 (50.0)	3 (50.0)	4 (20.0)	4 (20.0)
Rash	3 (42.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (15.0)	0 (0.0)
Hepatic function abnormal	0 (0.0)	0 (0.0)	1 (14.3)	1 (14.3)	0 (0.0)	0 (0.0)	1 (5.0)	1 (5.0)
Immune-mediated hepatitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	1 (5.0)	0 (0.0)

Note: Enterocolitis includes colitis and immune-mediated enterocolitis; rash includes rash and rash maculo-popular; hepatic function abnormal includes blood bilirubin increased, Liver function test increased and transaminases increased.

Efficacy

- Efficacy is assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.
- 15 patients had post-treatment tumor assessments
  - 1 pt had confirmed partial response (PR);
  - 9 pts had stable disease (SD) with tumor shrinkage in 3 pts.

Figure 2 Maximum Percent Change in Sum of Target Lesion Diameters from Baseline



	0.3mg/kg QW (N=7)	0.45mg/kg Q3W (N=7)	0.6mg/kg Q3W (N=6)
Best Overall Response, n (%)			
CR	0 (0.0)	0 (0.0)	0 (0.0)
PR	0 (0.0)	1 (14.3)	0 (0.0)
SD	5 (71.4)	0 (0.0)	4 (66.7)
PD	1 (14.3)	3 (42.9)	1 (16.7)

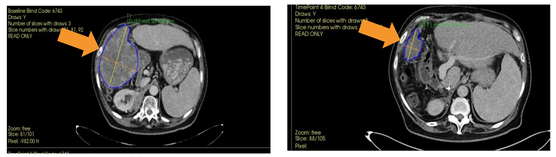
Abbreviations: CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease
Tumor types (from left to right): breast cancer; colorectal cancer; clear cell renal cell carcinoma; esophagus cancer; breast cancer; clear cell renal cell carcinoma; mesothelial cancer; prostate cancer; prostate cancer; bladder cancer; papillary renal cell carcinoma; head and neck squamous cell carcinoma; endometrial carcinoma; hepatocellular carcinoma

HCC Patient: Confirmed PR in Target Lesion (0.45mg/kg Q3W)

- 64-year-old man, Asian, HBV infected
- Prior treatments: sorafenib, lenvatinib and anti-PD-1
- Extended clinical benefit was observed after treatment discontinuation. Tumor reduction reached 64.4% for target lesions and non-target lesions were no longer detectable 16 weeks after the last dose.
- Extended pharmacodynamic effect: ~40% T_{reg} depletion (till Day 8 after dosing) & ~5-fold increase of T cell proliferation (till Day 21 after dosing) in blood

Target Lesion

Baseline | 16 Week



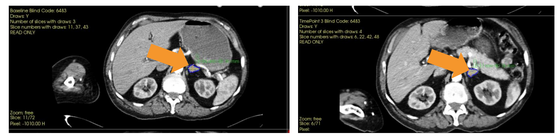
HCC: hepatocellular carcinoma; PR: partial response
Note: The target lesion was measured at the longest diameter.

CRPC Patient: SD by RECIST 1.1 with PSA Response (0.6mg/kg Q3W x 2, introduced on Named Pt basis at 0.3 mg/kg Q3W x 1 on PI's recommendation to control diarrhea)

- 80-year-old man
- Prior treatments: docetaxel, cabazitaxel and bicalutamide
- PSA response: more than 50% reduction in PSA level from baseline at 6 week
- Extended clinical benefit observed
  - The PSA response is continuing at week 45 from first dose, which is 26 weeks after the last dose.
  - The SD of adrenal and axillary lymph node by RECIST 1.1 was continuing at week 45
  - Non-PD/non-CR for bone lesions
- Extended pharmacodynamic effect: ~20% Treg depletion (till Day 15 after dosing) & ~15-fold increase of T cell proliferation (till Day 21 after dosing) in blood

Target Lesion

Baseline | 12 Week



CRPC: castration-resistant prostate cancer; SD: stable disease; PI: principal investigator; PSA: prostate-specific antigen

Pharmacokinetics

- AUC increased approximately proportional to dose
- The half-life of HBM4003 was about 2 to 5 days, and minimum accumulation was observed after multiple dosing, which is in line with pre-clinical findings.
- Only 1 patient tested anti-drug antibody (ADA) positive at one visit with a low titer of 2

Table 3 Summary of Pharmacokinetic Parameters after Single-Administration

	0.3mg/kg QW (N=7)	0.45mg/kg Q3W (N=7)	0.6mg/kg Q3W (N=5)
C_{max} (μg/mL)	6.10±1.15	10.5±2.41	10.0±3.78
T_{max} (h)	2.12(1.50,3.00)	1.73(1.52,3.02)	3.05(3.00,5.53)
C_{trough} (μg/mL)	0.425±0.113[a]	0.119±0.0929[b]	0.229±0.0268[c]
$AUC_{0\text{-last}}$ (μg*h/mL)	245±56.0	546±113[d]	754±47.5[e]

C_{max}: maximum concentration; T_{max}: time to reach the maximum concentration; C_{trough}: trough concentration (168 h post-dose for QW administration and 504 h post-dose for Q3W administration); $AUC_{0\text{-last}}$: area under the curve from time zero to time of the last quantifiable concentration
Note: Pharmacokinetic parameters are presented as mean ± SD. T_{max} is presented as median (minimum, maximum).
a: N=6, b: N=4, c: N=3, subjects were excluded from summary statistics because the sampling time were outside of the window.
d: N=5, e: N=2, subjects were excluded due to incomplete sample collection.

CONCLUSIONS/DISCUSSION

- HBM4003 is the next generation anti-CTLA-4 fully human HCAb with enhanced ADCC for Treg depletion and the first HCAb under clinical development
- The preliminary data from this Phase 1 trial demonstrate favorable safety and efficacy profile for HBM4003:
  - All TRAEs were manageable and reversible. The most common irAE was diarrhea/enterocolitis, and no toxicity reported related to lung, kidney, heart or endocrine system.
  - The initial anti-tumor efficacy of HBM4003 monotherapy was encouraging, especially with two responders who had been refractory to multiple therapies including the PD-1 therapy.
- The clinical data also confirm its unique PK profile and demonstrate minimal immunogenicity.
- The MTD was not achieved and 0.45 mg/kg Q3W was recommended as the phase II dose for dose expansion.

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CONFLICT OF INTEREST

P De Souza is on an EISAI Australian advisory board for renal cancer (2021) and was an advisor for BioSceptre Australia Pty Ltd. from 2018 to 2019. JJ, MDA, XC, XG, XT, RZ, and LL are employees at Harbour BioMed.

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