HBM4003 Phase I Dose-Escalation Study

Summary of Phase I Data Readout

September 2021

HBM HOLDINGS-B

02142.HK

www.harbourbiomed.com

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Executive Summary

- **Unmet medical needs：** current anti-CTLA-4 monotherapy and combination therapies are still limited by safety profile
- **HBM4003：** a next generation anti-CTLA-4 fully human heavy-chain-only antibody with enhanced ADCC for Treg depletion
  - Endorsed by global leading experts in IO therapy aiming to transform the global IO landscape with breakthrough innovation
- **Phase 1 trial: the preliminary data demonstrated favorable safety and efficacy**
  - Well tolerated
  - Preliminary efficacy data are encouraging
- **It represents significant clinical needs with potential to be backbone of next gen IO therapy**
- **Next step：** global development kicked off aiming to unlock potential of broad tumor setting

Agenda

01 Company Overview

02 HBM4003 Phase I Data Readout

03 HBM4003 Outlook

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Harbour Biomed
Leading the Next Wave of Antibody Therapeutics in Immunology and Oncology

Differentiated Innovative Portfolio

Robust Product Portfolio

2 near-term commercialization assets

7 ongoing clinical trials

8 significant preclinical assets

Unique Market Position

first-in-class, T cell engager, bispecific antibodies

Harbour Biomed
Leading the Next Wave of Antibody Therapeutics in Immunology and Oncology

Highly Effective and Disruptive Engine

Leading Discovery Platforms

3 fully human antibody platforms

1 single B cell technology

World Class Research Team

105+ discovery scientists, **60+** PhD

3 global research centers

10+ in-house late-stage preclinical/clinical products within **4** years

Global Collaboration

45+ global partners license-out

abbvie · Dana-Farber Cancer Institute · Lilly · Mount Sinai · VIR · BioMap 百图生科

Manufacturing Commercialization

8500 m^2 pilot factory in Suzhou
Fast building core commercial team

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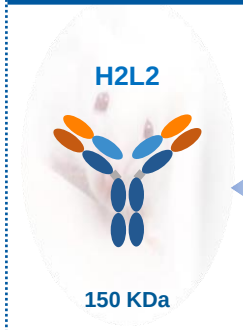
Integrated Platforms Enable Sustainable Invention of Novel Molecules

Harbour Antibody Platforms Combined with Single B Cell Cloning Offers A Complete and Advanced Technology Solution for Consistently Discovering Next-Gen Fully Human Antibody Therapeutics

H2L2 —Full IgG Antibody Discovery Platform



HBM1007

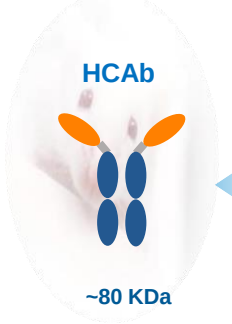
A allosteric fully human antibody against CD73 for the treatment of solid tumors

HBM7015

A bifunctional fusion protein for the treatment of solid tumors

Robust and highly efficient, global IP and clinically validated

HCAb —Next-Generation Heavy-Chain-Only Antibody Discovery Platform



HBICE™

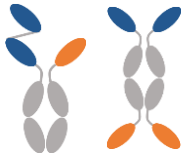
A Unique, HCAb-Based Platform For Immune Cell Engagers

HBM4003

A next generation anti-CTLA4 antibody

Unique fully human HCAb, versatile for broad applications

HBICE™ — HCAb-Based Platform for Immune Cell Engagers



HBM7020

A BCMAxCD3 bispecific antibody

HBM7008

A B7H4×4-1BB bispecific antibody

Self-developed, unique geometric flexibility, promising bispecific biology

Antibody generation with Single B Cell cloning method in 3-5 months*

Animal Immunization	SBC	SC Sequence	Recombinant Antibody	Lead Characterization
1-2 months	1 -2 weeks	(1-2 weeks)	(4-5 weeks)	1-2 weeks

** Traditional hybridoma method need 7-9 months with an additional 3-6 months of humanization*

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Agenda

01 Company Overview

02 **HBM4003 Phase I Data Readout**

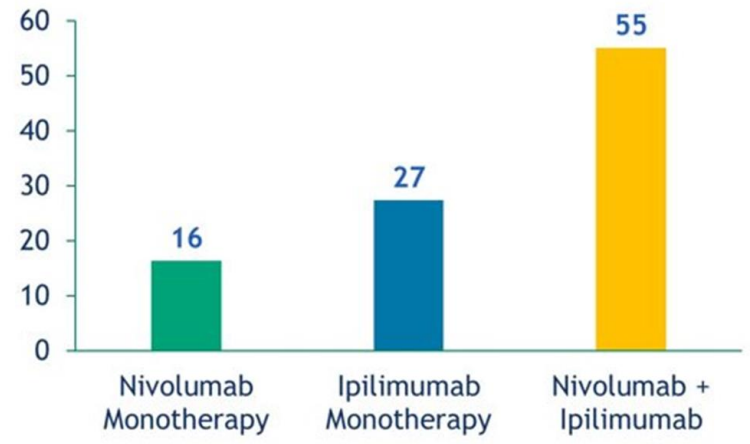
Section 1: Target Selection & Molecule Overview

03 HBM4003 Outlook

Current Anti-CTLA-4 Monotherapy and Combination Therapies are Still Limited by Safety Profile

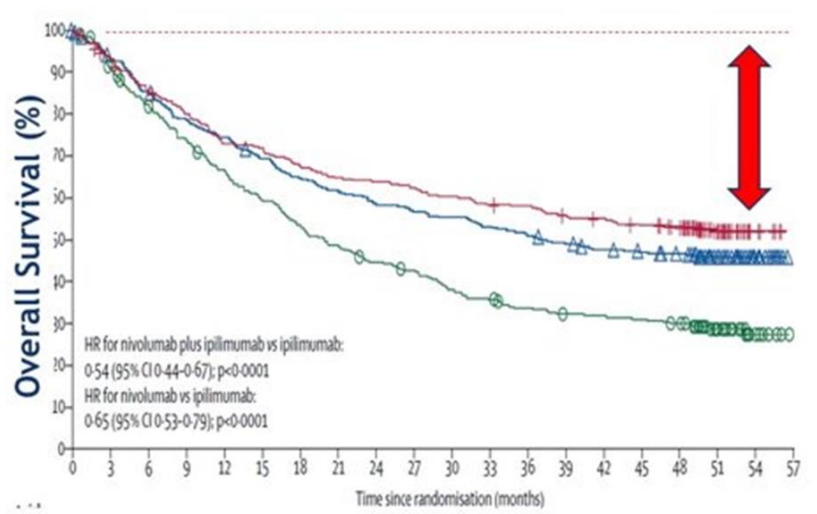
Toxicity limits the potential of PD-1/CTLA-4 combo

Grade 3/4 TRAE (%)



Hodi S et al, Lancet Oncology 2018; Larkin J et al, NEJM 2015

Increasing the therapeutic ceiling is the next step



James Larkin, Long-term data from the CheckMate 067 study, ESMO 2019

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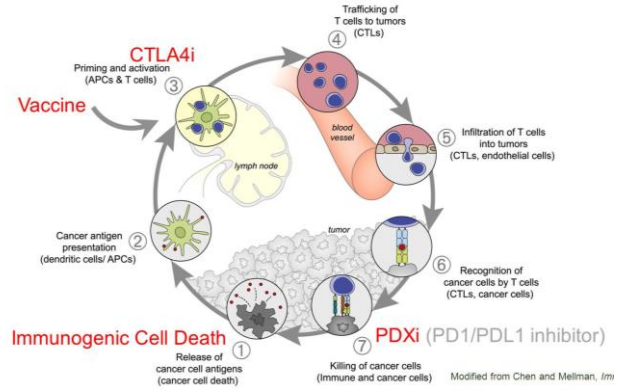
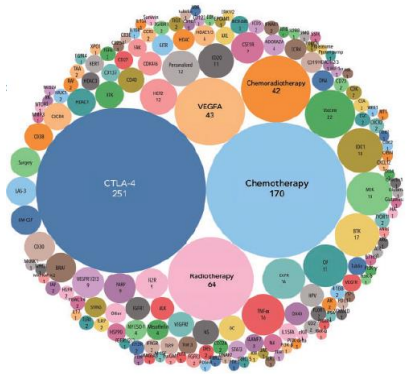
HBM4003: Target Selection & Molecule Design Was Recommended & Endorsed by Global SAB Members & Thought Leaders to Achieve Breakthrough of IO Therapy

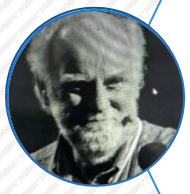
PD-1(L1) and CTLA-4 are the only 3 proven IO targets



CTLA-4 is the most preferred combo choice



HBM4003 is endorsed by global leading experts in IO therapy aiming to transform the global IO landscape with breakthrough innovation



Dr. Frank Grosveld

Fellow of Royal Society and Member of Royal Netherlands Academy of Arts and Sciences

Professor and former Head of Department of Cell Biology & Department of Clinical Genetics at Erasmus University Medical Center

Dr. Robert Kamen

Venture Partner at Third Rock Ventures

Former President & Unit Head of Abbott Bioresearch Centre

Dr. Jon Wigginton

Chief Medical Officer, Cullinan Oncology; Advisos of MPM Capital

Former Therapeutic Area Head of Immuno-Oncology, Early Clinical Research at BMS

Former President of the Society for Immunotherapy of Cancer

Dr. Shivaani Kummar

Director, Phase 1 Clinical Research Program, Division of Oncology Stanford School of Medicine

Professor of Medicine & Radiology at Stanford University Medical Centre

Specialty Sarcoma

Dr. John M Kirkwood

Distinguished Service Professor Medicine, University of Pittsburg

Usher Professor of Medicine, Dermatology, Clinical and Translational Science at The University of Pittsburg School of Medicine

Specialty Global Melanoma and Skin Cancer

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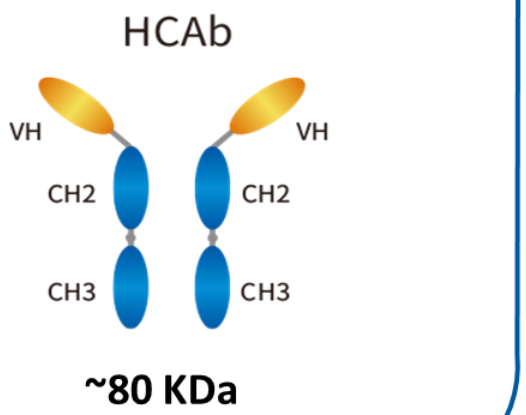
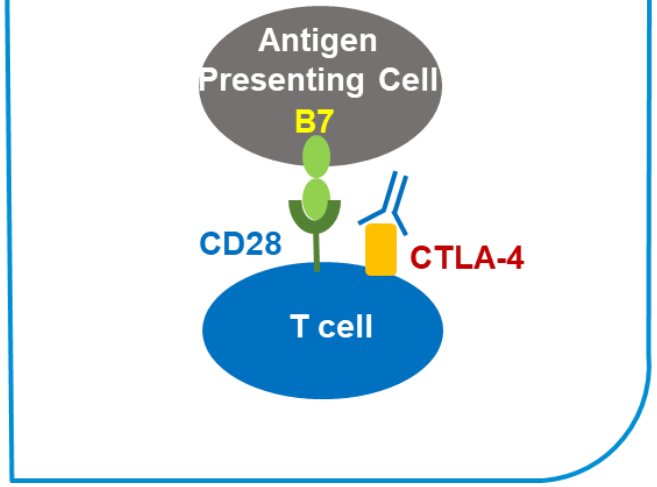
HBM4003-A Next Generation Anti-CTLA-4 Fully Human Heavy-Chain-Only Antibody with Enhanced ADCC for Treg Depletion

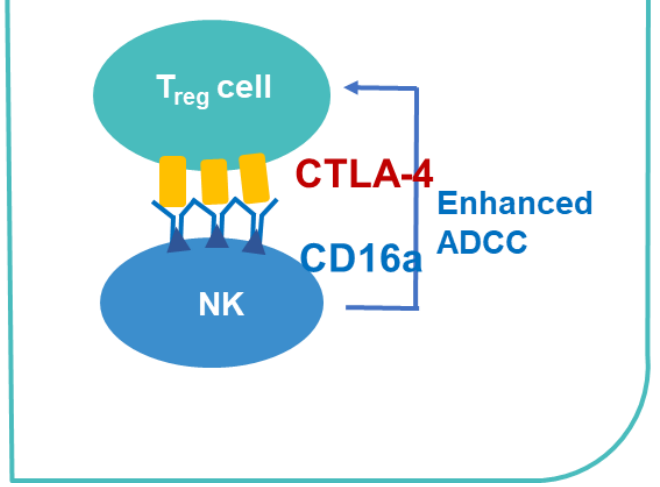
Platform



MoA 1– Checkpoint Inhibit



MoA 2–T_{reg} Depletion

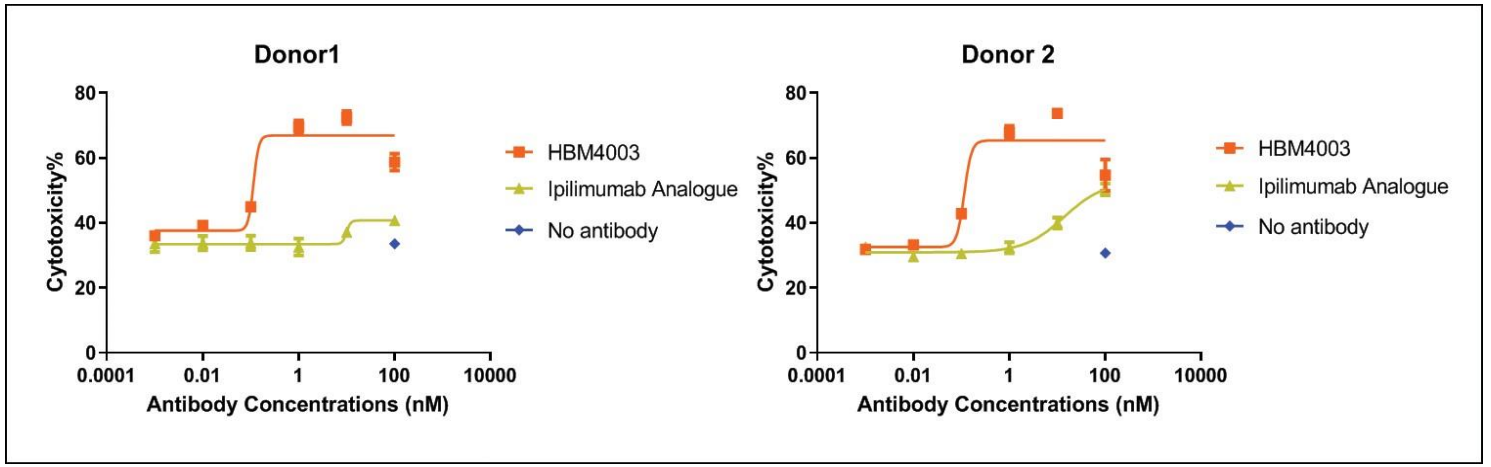


- The HCAb molecules have only 2 heavy chains linked by disulfide bonds. Each heavy chain consists of 1 heavy chain variable region and 2 heavy chain constant regions (CH2 and CH3) without the CH1 region
- The potential features of HCAb include unique binding epitopes, high affinity, and high tissue/tumor penetration
- HBM4003 demonstrated near dose-proportional pharmacokinetics (PK), extended pharmacodynamic (PD) effect, and low immunogenicity

HBM4003 Preclinical Data: Superior Treg Depletion Activity (100x More Potent Than Ipilimumab Analogue)

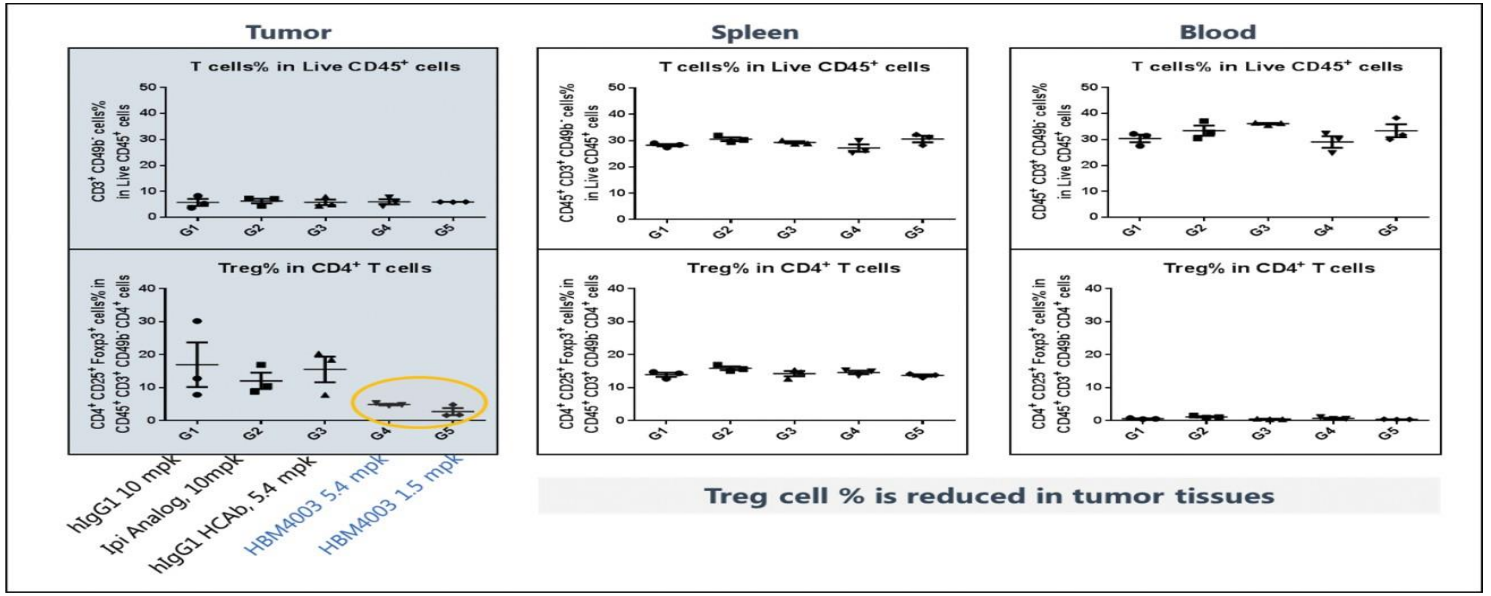
Superior Treg depletion activity in comparison to ipilimumab analogue as measured in vitro via ADCC killing assay

Treg Depletion by HBM4003 in Primary Human PBMCs in
in vitro ADCC Assay



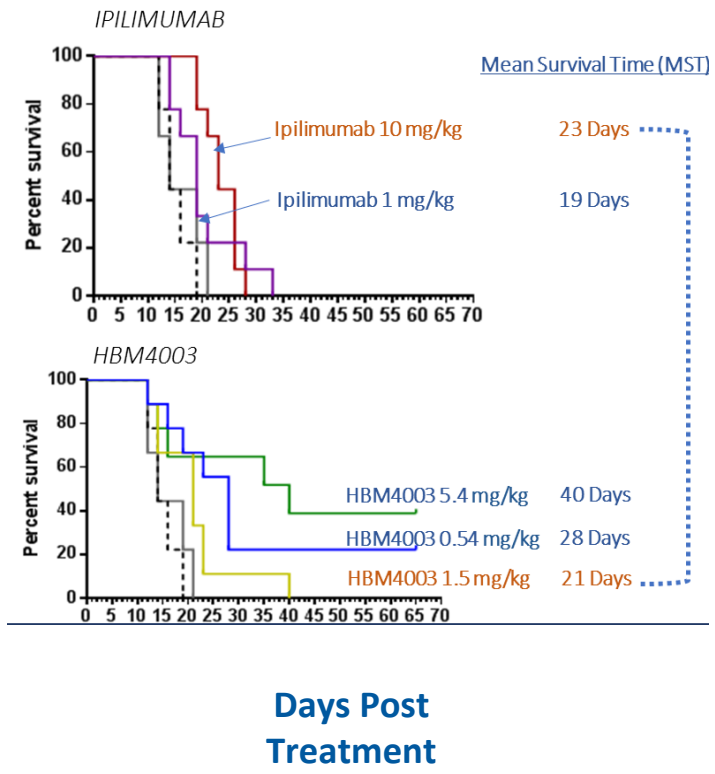
Led to Substantial Depletion of TIL Tregs in MC38 Bearing hCTLA-4 KI Mice

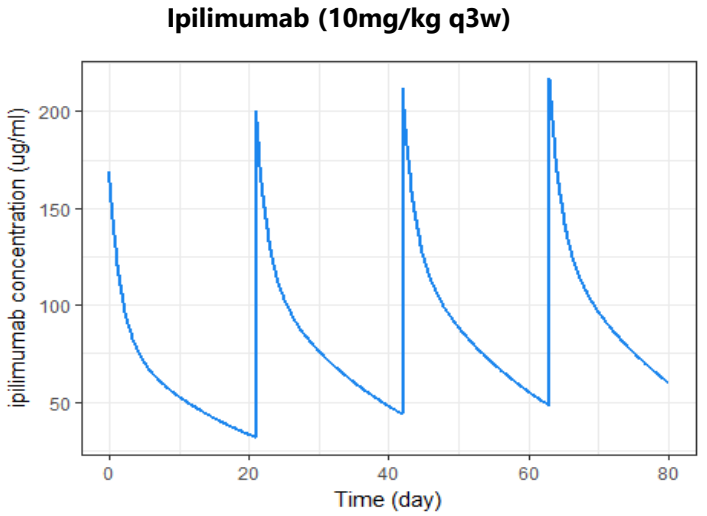
In Vivo T_{reg} (%) in Tumor, Spleen, and Blood in MC38-Bearing hCTLA-4 KI Mice (3 mice per group)
Samples were collected 24hrs post 2nd dosing and analyzed by FACS

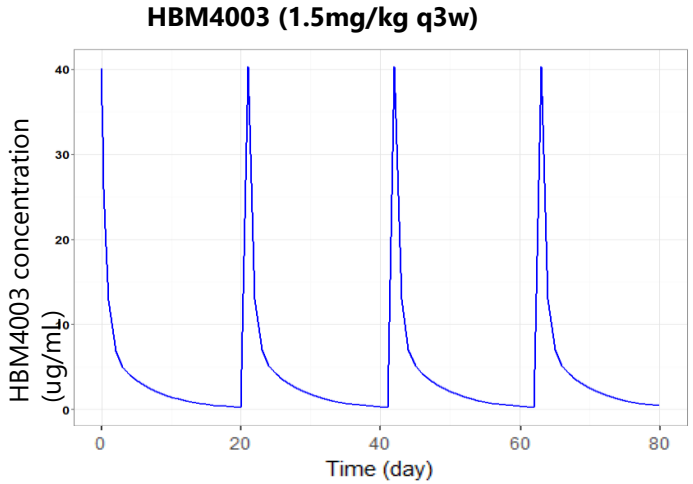


HBM4003 Preclinical Data: Comparable Mean Survival Time At 1/6 Of Dose Compared to Ipilimumab, and Predicted Human Exposure Is Much Lower (~1/35 of AUC)

Survival Prolongation (Mean Survival Time)







Simulated PK exposure at steady state		
$AUC_{(0\text{-}tau)}$ µg*day/ml	Cmax µg/ml	Cmin µg/ml
1942.7	744.9	576.3

$AUC_{(0\text{-}tau)}$ µg*day/ml	Cmax µg/ml	Cmin µg/ml
54.27	40.26	2.50

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01 Company Overview

02 **HBM4003 Phase I Data Readout**

Section 2: Phase 1 study Design & Patient Features

03 HBM4003 Outlook

HBM4003 Mono Therapy: Study4003.1 Overall Design Outline

Includes Two Parts and the Abstract of Part 1 Has Been Submitted to ESMO 2021

Part1:
Dose escalation in previously treated (including anti-PD-1 therapy) advanced solid tumors

Primary endpoint:
- Proportion of patients with DLT

0.6 mg/kg Q3W

0.45 mg/kg Q3W

0.3 mg/kg QW

HBM4003 IV QW or Q3W

Part2:
Dose expansion

- **Primary endpoint:**
  - ORR
- **Secondary endpoints:**
  - DOR, DCR, DDC, maximum tumor shrinkage

Melanoma、HCC、RCC…

HBM4003 IV Q3W

Data cutoff 12 April 2021

ClinicalTrials.gov identifier: NCT04135261

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Key Patient Features and Demographics

- 20 patients with advanced solid tumors, at 4 Australian sites
- Heavily pre-treated population
  - 13 out of 20 patients (65%) having received 2 or more prior regimens
  - 8 out of 20 patients (40%) were treated previously with immune checkpoint inhibitor
  - The average age of subjects is 62.5 (SD= 11.5)

	0.3mg/kg QW (N=7)	0.45mg/kg Q3W (N=7)	0.6mg/kg Q3W (N=6)	Total (N=20)
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)

Tumor Type	Safety Assessment (n)	Post-Treatment Data for Anti-tumor Assessment (n)
Endometrial Carcinoma	1	1
PRCC	1	1
ccRCC	4	3
Prostate Cancer	2	2
HCC	1	1
Penile Cancer	1	
Testicular cancer	1	
Esophagus Cancer	2	1
Colorectal Cancer	1	1
Breast Cancer	2	2
Bladder Cancer	1	1
HNSCC	1	1
NSCLC	1	
Mesothelial Cancer	1	1
TOTAL	20	15

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Agenda

01 Company Overview

02 **HBM4003 Phase I Data Readout**

Section 3: Safety Data Readout

03 HBM4003 Outlook

HBM 4003 Were Well Tolerated

- **No toxicity was reported related to lung, kidney, heart or endocrine system**
- **No treatment-related serious adverse event (TRSAE) was reported at 0.45 mg/kg Q3W**
- **No TRAE was > Grade 3**
  - Grade 3 TRAEs included diarrhea, and 1 case of abnormal liver function test who has HCC. All were manageable and reversible
- **The most common TRAE of any grade was diarrhea/enterocolitis**
  - The most common irAEs were diarrhea/enterocolitis and skin rash
- **Maximum tolerated dose (MTD) was not achieved**
  - No DLT was observed in any Q3W dose level
  - 1 DLT was reported at 0.3mg/kg QW due to Grade 3 diarrhea which was well managed with the SOC
- **0.45 mg/kg Q3W was recommended as the phase II dose (RP2D) for dose expansion**

Differentiated Safety Profile Were Indicated From Preliminary Data

- More severe baseline conditions - more prior treatments(including PD-1), higher ECOG, broad range of solid tumors mixed with cold tumors vs > 1 line melanoma
- irAE & G3 TRAE focused on diarrhea vs broad involvement with vital organs

	HBM4003 0.45mg/kg Q3W, n(%)	Ipilimumab 3mg/kg Q3W, n(%)	Ipilimumab 3mg/kg Q3W, n(%)
Total No. patients	7	111(pooled)	137/131(AE)
Tumor types	Solid tumors	melanoma	melanoma
Prior treatment lines	≥2: 5(71.4) Prior PD-(L)1 Therapy: 3(42.9)	Prior systemic anti-cancer therapy(>1):100(90.1) Prior IO Therapy: 61(55.0)	Prior systemic anti-cancer therapy(>1):137(100)
ECOG	0: 3(42.9) 1: 4(57.1)	-	0: 72(52.6) 1: 64(46.7) 2: 1(0.7)
TRAE	4 (57.1)	88(79.3)	105(80.2)
irAE	**Total: 2 (28.6)** Enterocolitis 1(14.3) Hepatic 1(14.3)	**Total: 68(61.3)**	**Total: 80(61.1)** Dermatologic 57(43.5) Diarrhea 36(27.5) Colitis 10(7.6) Endocrine 10(7.6) Hepatic 5(3.8) Other 6(4.6)
G ≥3 irAE	**Total: 1(14.3)** Hepatic 1(14.3)	**G≥3 TRAE** 16(14.4) Diarrhea 3(2.7) Colitis 3(2.7)	**Total: 19(14.5)** Diarrhea 6(4.6) Colitis 7 (5.3) Dermatologic 2(1.5) Endocrine 5(3.8) Other 3(2.3)

TEAE: treatment emergent adverse event; TRAE: treatment related adverse event; irAE: immune related adverse event; TRSAE: treatment related severe adverse event; FIH: first in human; DLT: dose limiting toxicity; RP2D: recommended phase 2 dose. Ipilimumab data are from 14Dec2017, EMA/6592/2018, Committee for Medicinal Products for Human Use (CHMP) ; Hodi FS, et al. N Engl J Med. 2010.

Agenda

01 Company Overview

02 **HBM4003 Phase I Data Readout**

Section 4: Efficacy & PD Marker Data

03 HBM4003 Outlook

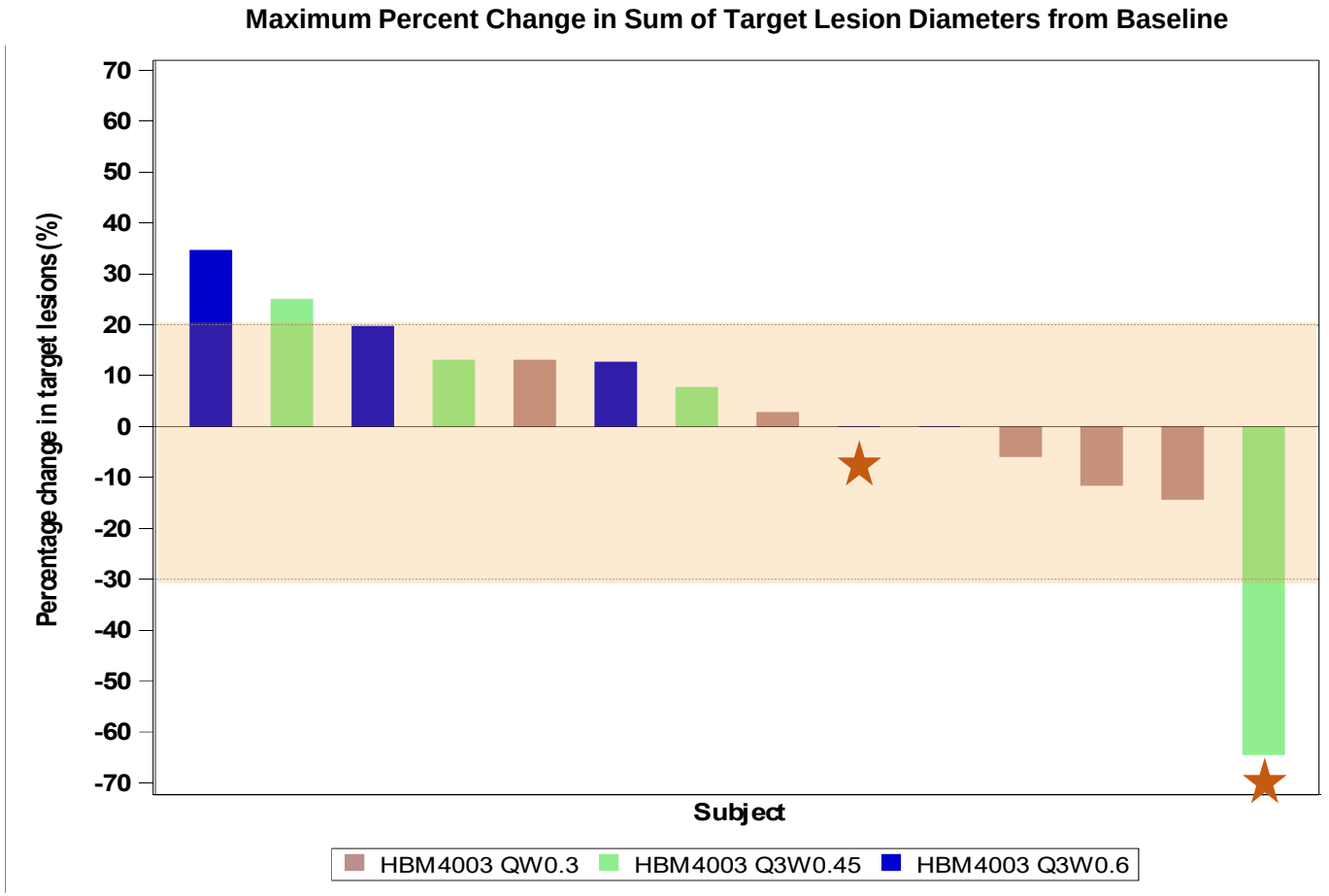
Preliminary Efficacy Data Are Encouraging For HBM 4003 In This Monotherapy Dose Escalation Study

- **2 clinical responders**
  - 1 patient with HCC who was pre-treated with Sorafenib, Lenvatinib and anti-PD-1 had confirmed partial response (PR)
  - 1 patient with CRPC had PSA response for > 26 weeks with SD in RECIST assessment
- **9 patients had stable disease (SD 60%)**
  - 15 patients had at least 1 post-treatment tumor assessment
  - tumor shrinkage were reported with 3 patients

- Efficacy is assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.
- An independent imaging reading group was hired to review CT scan and RECIST assessment for responders

Encouraging Preliminary Efficacy Have Been Observed with HBM 4003 Monotherapy

- FIH with Dose Escalation, Heavily Pre-treated(including PD-1) , Broad Range of Solid Tumors



	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

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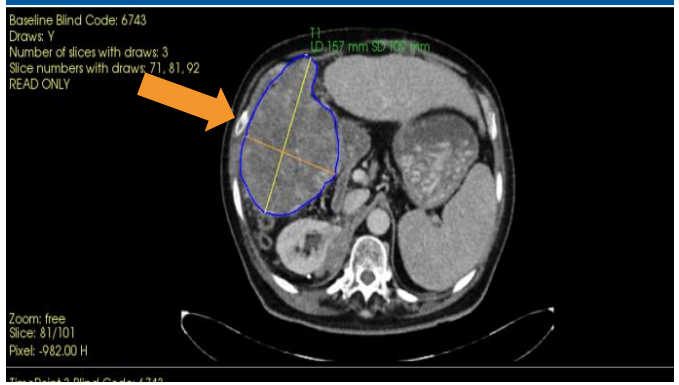
HCC Patient: Confirmed PR in Target Lesion

- **Patient background**
  - 64-year-old man, Asian, HBV infected
  - Prior treatments: sorafenib, lenvatinib and anti-PD-1
  - HBM 4003, 0.45 mg/kg Q3W
- **Strong & durable efficacy observed**
  - **Tumor reduction reached 64.4%** for target lesions and non-target lesions were no longer detectable 16 weeks after the last dose

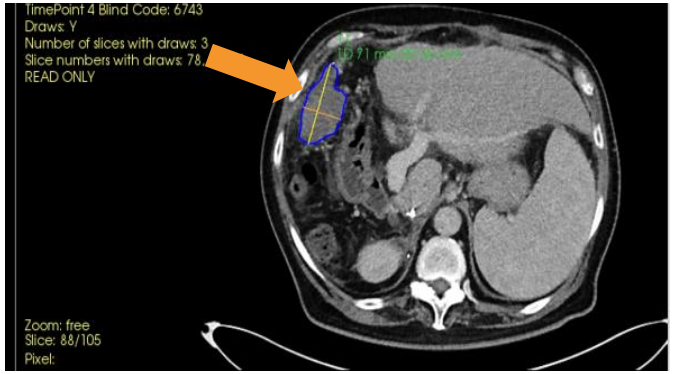
	Location	Baseline	6 W	12 W	16 W	24 W
Non target Lesions	Lung , LN, Left Liver	NA	Non PD/Non CR			Not detectable
Target lesions (mm)	Right Superior Liver, Right Kidney	225	175	115	105	80
	Change from baseline	N/A	22.2%	48.9%	53.3%	64.4% PR
AFP u/L		170	5	5	9	7
Overall response		NA	SD	PR	PR	PR

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

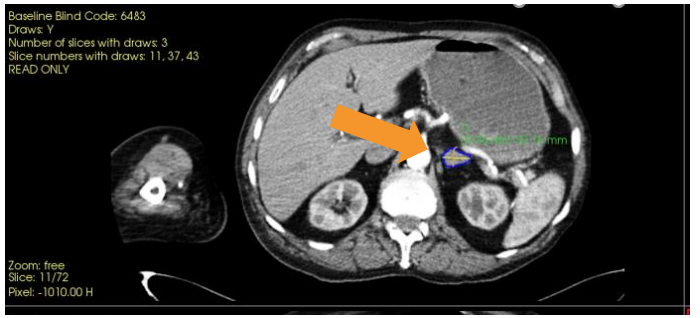
- **Patient profile**
  - 80-year-old man, HBM 4003 0.6 mg/kg Q3W
  - Prior treatments: docetaxel, cabazitaxel and bicalutamide
- **PSA response**
  - more than 50% reduction in PSA level from baseline at 6 week
- **Extended clinical benefits**
  - The PSA response still remained at week 45 from first dose, 26 weeks after the last dose
  - The SD of adrenal and axillary lymph node by RECIST 1.1 continued until week 45

Treatment cessation

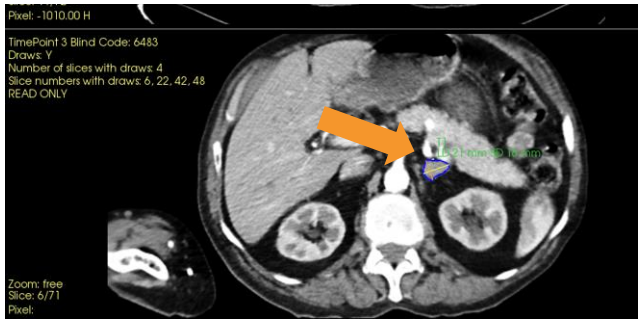
	May 2020	Jun 2020	July 2020	Apr 2021	Assessment
	Baseline	6 W	12 W	45 W	
PSA (ng/ml)	240	92	89	58	PSA response
Sum of Diameter (mm)	70	71	63	ND	SD
% Change Baseline	NA	1	-10	NA	NA

Target Lesion

Baseline



16 Week



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

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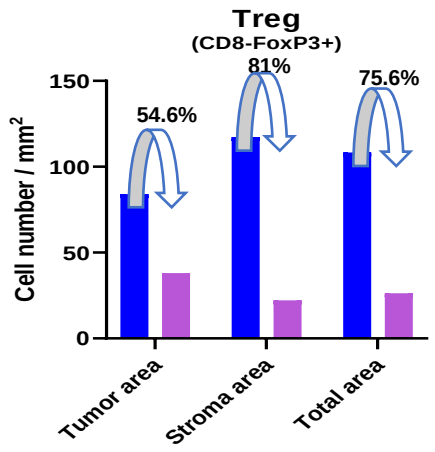
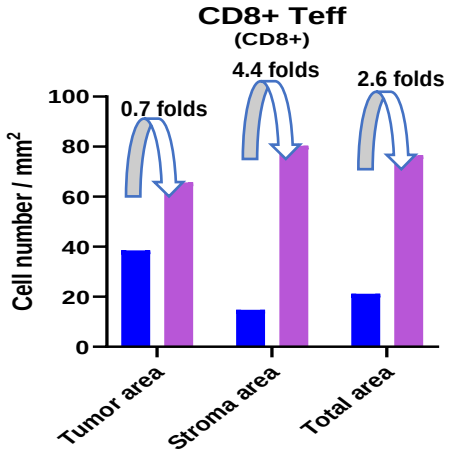
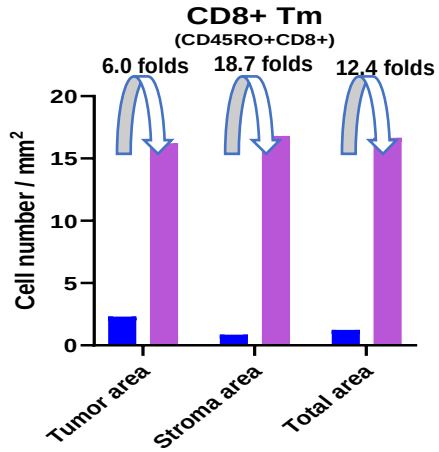
PD Marker: Selective Intratumor Treg Depletion Validated by Paired Biopsy Data

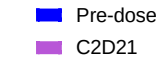
- HBM4003 Selectively Depleted Intratumor Treg and Increased CD8+Teff and CD8+Tm Cells

Tumor Biopsy



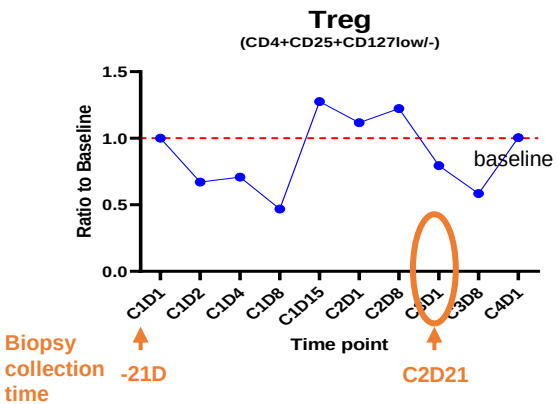


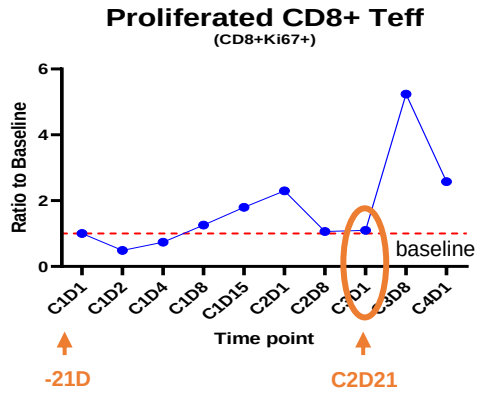




- Subject 89301, 48y, Male, Chromophobe RCC, HBM4003 0.45mg/kg Q3W
- 6w tumor assessment: SD

Peripheral Blood





Consistent with preclinical data

- Treg depletion is selective and sustained in tumor microenvironment comparing to peripheral blood
- Increase of CD8+ Teff cells is observed in tumor microenvironment and peripheral blood

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Conclusion--The Preliminary Data from This Phase 1 Trial Demonstrate Encouraging Activity across a Range of Tumors with Improved Tolerability for HBM 4003 Vs Ipilimumab

- **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 novel MOA of strong Treg depletion has been validated by both pre-clinical and clinical biopsy data**

- **HBM 4003 is well tolerated**
  - The most common TRAE of any grade was diarrhea/enterocolitis
  - No toxicity was reported related to lung, kidney, heart or endocrine system
  - No TRAE was > Grade 3
  - Maximum tolerated dose (MTD) was not achieved

- **Preliminary efficacy data is encouraging for HBM 4003 monotherapy**
  - 9(out of 15) patients achieved SD
  - 1 patient pre-treated by all SOCs (including PD-1) was confirmed as PR, 1 patient had PSA response with SD by RECIST

- **0.45 mg/kg Q3W was recommended as the phase II dose (RP2D) for dose expansion**

Agenda

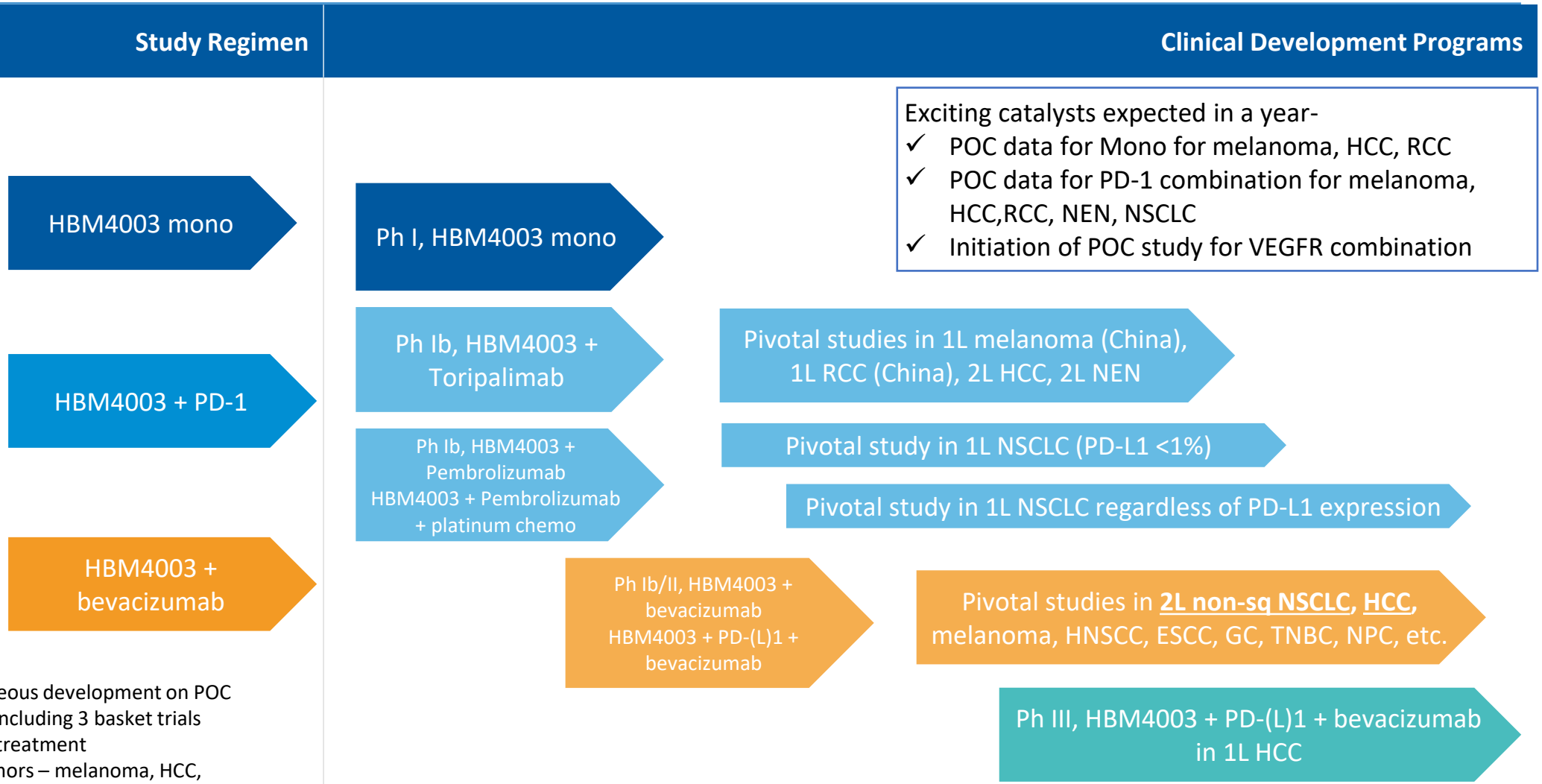
01 Company Overview

02 HBM4003 Phase I Data Readout

03 **HBM4003 Outlook**

HARBOUR26 BIOMED

Global Development Kicked Off for HBM4003 Aiming to Unlock Potential of Broad Tumor Setting With Multiple Exciting Catalysts In 2022



1. Global, simultaneous development on POC
2. 5 trials ongoing including 3 basket trials
3. Mono & combo treatment
4. Various solid tumors – melanoma, HCC, NET/NEC, RCC, NSCLC (HNSCC, ESCC,TNBC…)

Abbreviations: ESCC: esophageal squamous cell carcinoma; GC: gastric cancer; HCC: hepatocellular carcinoma; HNSCC: head and neck squamous cell carcinoma
NEN: neuroendocrine neoplasms; NPC: nasopharyngeal carcinoma; NSCLC: non-small-cell lung carcinoma; TNBC: triple-negative breast cancer

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HBM 4003's Development Receives Continuous Strong Support from Global Investigators & Advisor Board Members

Shivaani Kummar

Director, Phase 1 Clinical Research Program, Division of Oncology Stanford School of Medicine

Professor of Medicine & Radiology at Stanford University Medical Centre

Specialty Sarcoma

John M Kirkwood

Distinguished Service Professor Medicine, University of Pittsburg

Usher Professor of Medicine, Dermatology, Clinical and Translational Science at The University of Pittsburg School of Medicine

Specialty Global Melanoma and Skin Cancer

Paul de Souza

Professor, St George Private Hospital, Kogarah, NSW, Australia

Ren Zhenggang

Director of Department of Hepatic Medical Oncology, Zhongshan Hospital, Fudan University,

Shukui Qin

Deputy Dean of General Hospital os Eastern Theater Command; Secretary-general of Chinese Society of Clinical Oncology (CSCO)

Hao Jihui

Deputy Dean of Tianjin Medical University Cancer Institute & Hospital

Jin Li

Vice President of Federation Asian Alliance Clinical Oncology (FACO),
Board Chairman of Chinese Society of Clinical Oncology (CSCO)

Ye Dingwei

Deputy Dean of Fudan University Shanghai Cancer Center, Director of Department of Urology Surgery.

Shen Lin

Deputy Dean of Peking University Cancer Hospital, Director of Department of Gastrointestinal Oncology

HBM4003 Represents Significant Clinical Needs with Potential to be Backbone of Next Gen IO Therapy

CTLA4 a clinically validated I/O target

Novel design, heavy chain Ab and Treg depletion

Significant improvement of efficacy and safety profile to achieve therapy breakthrough with Monotherapy

Enhanced combination therapy with broad applications and extended benefits

- **Significant Improvement of Clinical Outcomes**
- **Unlock Potential of Immuno-Oncology Therapy**

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THANK YOU

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