Harbour BioMed: Advancing Global Biotherapeutics Innovation

Dr. Jingsong Wang

Founder, Chairman and CEO
Harbour BioMed
Harbour BioMed Rapidly Progressing Toward a Global Leading Biopharmaceutical Company

A Global Biotherapeutics Company Focusing on Breakthrough Medicines

• Established in 2016
• Transformed into a clinical stage company in 2017

Therapeutic Focus:
• Immunology
• Immuno-Oncology

USA  Netherlands  China


• 3 INDs in 2018
• Tanfanercept entered Ph2 in 2018
• HBM4003 entered Ph1 in 2019

• Successfully listed in HKEX
• Batoclimab entered Ph2 for first wave indications

• Batoclimab & Tanfanercept entered Ph3
• HBM4003 in multiple Ph1/2 globally
• 2 new assets apply for INDs globally
Leading Next Gen Biotherapeutics Innovation to Address Unmet Medical Needs in Global Market

Next Gen Therapeutics

4 products in clinical stage, two near-term commercialization (HBM9161, HBM9036)

6 highly differentiated products with INDs by 2022

Industry Leading Platforms

Worldwide patent protection

45+ industry and academic partners

9 innovative therapeutics entered clinical trial

Global Innovation Ecosystem

Industry Leading Discovery Platforms

Differentiated Portfolio
Build a Highly Differentiated Portfolio Leveraging Industry Leading Fully Human Technology Platforms

- Worldwide patent protection
- Validated by 45+ industry and academic partners
- 9 projects in clinical stage
- >200 internal and external projects leveraging HBM platforms

Advantages of HBM Fully Human Antibody Platforms

**Fully human classical antibody H2L2**
1. Efficient and reliable (no need for humanization, high affinity)
2. Excellent druggability (immunity in mice, evolution by natural selection)
3. Great safety (low immunogenicity)

**Fully human heavy chain antibody HCAb**
1. Scarcity (the only fully human transgenic mice heavy chain antibody platform in the world)
2. Flexibility (widely used)
3. Good penetrability (small size, easy to penetrate tumor and tissue)

**Fully human bispecific antibody HBICE**
1. Unique and proven bispecific antibody mechanism
Internationally Renowned Scientific Advisory Board

FRANK GROSVELD
PhD
- Co-founder and CSO of Harbour Antibodies, inventor of Harbour Mice®
- Professor and former Head of the Department of Cell Biology and the Department of Clinical Genetics at the Erasmus University Medical Center
- Fellow of the Royal Society and a member of the Royal Netherlands Academy of Arts and Sciences

ROBERT KAMEN
PhD
- Venture Partner at Third Rock Ventures
- Co-founder and former chairman of BioAssets
- Former director of Neon Therapeutics and Harbour Antibodies
- Former president and unit head of Abbott Bioresearch Centre, Former SVP at Genetics Institute, Inc.
- Ph.D. in biochemistry and molecular biology from Harvard University

KENNETH MURPHY
MD, PhD
- Member of the National Academy of Sciences
- Eugene Opie First Centennial Professor of Pathology & Immunology, Washington University School of Medicine in St. Louis
- Ph.D. in pharmacology and M.D. from Hopkins University School of Medicine

JON WIGGINTON
MD
- Chief Medical Officer, Cullinan Oncology; Advisos of MPM Capital
- Former Chief Medical Officer and SVP of Clinical Development at MacroGenics, Inc.
- Former Therapeutic Area Head of Immunology, Early Clinical Research at BMS
- Former President of the Society for Immunotherapy of Cancer

ROBERT KRAMER
PhD
- CSO of Portage Biotech Inc.
- Former VP and Head of Discovery for Oncology Therapeutics at Janssen Research & Development, LLC
- Former VP Drug Discovery and Research for Bristol-Myers Squibb (BMS)
- Ph.D. in pharmacology from the University of Vermont

PETER MOESTA
PhD
- Former executive roles at Bristol-Myers Squibb
- Oversaw the development, production and worldwide launch of important medicines, such as Humira, Yervoy and Opdivo

ZHIGANG TIAN
MD, PhD
- Academician of the Chinese Academy of Engineering
- Professor of the University of Science and Technology of China
- Council member of International Union of Immunological Societies
- Council member of Federation of Immunological Societies of Asia-Oceania
## Robust Pipeline Combining Advanced Clinical Programs and Next-Gen Biotherapeutics Addressing Highly Unmet Needs

<table>
<thead>
<tr>
<th>Project</th>
<th>Target</th>
<th>Indication</th>
<th>Commercial Rights</th>
<th>Status</th>
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<tr>
<td><strong>Immunology</strong></td>
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<tr>
<td>Batoclimab HBM9161</td>
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<td>MG</td>
<td>Greater China</td>
<td>Ph 2 ongoing, Ph 3 ongoing</td>
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<td>NMOSD</td>
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<td>PH 2 ongoing</td>
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<td>ITP</td>
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<td>IND approval by NMPA, IND application accepted by NMPA</td>
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<td></td>
<td>Ph 2/3 ongoing</td>
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<td></td>
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<td>CIDP</td>
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<td>Ph 1b/2 ongoing</td>
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<tr>
<td></td>
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<td>PV</td>
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<td>Breakthrough Therapy Designation, Ph 3 ongoing</td>
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<tr>
<td><strong>Immunology</strong></td>
<td>Tanfamorecept HBM9036</td>
<td>TNFα</td>
<td>Dry Eye Disease</td>
<td>Greater China</td>
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<td></td>
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<td>Ph 3 ongoing</td>
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<tr>
<td>HBM9022</td>
<td>SARS-COV-2</td>
<td>COVID-19</td>
<td>Global License to AbbVie</td>
<td>Ph 1b/2 ongoing, Combo with PD-1 Ph 1 ongoing</td>
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<tr>
<td>HBM9378</td>
<td>TSLP</td>
<td>Asthma</td>
<td>Global</td>
<td>Ph 2/3 ongoing</td>
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<tr>
<td><strong>Immunology</strong></td>
<td>HBM4003</td>
<td>CTLA-4</td>
<td>Global</td>
<td>Combo with PD-1 Ph 1 ongoing</td>
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<td>Solid Tumors a</td>
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<td>Solid Tumors b</td>
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<td></td>
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<td>Solid Tumors c</td>
<td></td>
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<tr>
<td><strong>Immunology-Oncology</strong></td>
<td>HBM7008</td>
<td>B7H4×4-1BB</td>
<td>Solid Tumors</td>
<td>Ph 1b/2 ongoing</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Global</td>
<td>Combo with PD-1 Ph 1 ongoing</td>
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<tr>
<td>HBM1022</td>
<td>CCR8</td>
<td>Solid Tumors</td>
<td>Global</td>
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<tr>
<td>HBM1020</td>
<td>B7H7</td>
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<td>HBM7020</td>
<td>BCMA×CD3</td>
<td>Multiple Myeloma</td>
<td>Ex-Greater China1</td>
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<tr>
<td>HBM1007</td>
<td>CD73</td>
<td>Solid Tumors</td>
<td>Global</td>
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</tbody>
</table>

1. Greater China rights out-licensed to Hualan Genetics
   a. Melanoma, HCC, RCC and Other Advanced Solid Tumors
   b. Melanoma, HCC, NEN and Other Advanced Solid Tumors
   c. NSCLC and Other Advanced Solid Tumors

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**Breakthrough Therapy Designation**

**IND**

**Phase I**

**Phase II**

**Phase III**

**BLA**

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**Program from Harbour**

**Discovery**

**Pre-Clinical**

**In-license Program**

**Registralional Clinical Trial**

**Partner**

**Harbour Discovery Platforms**

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**HBM**

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5
Building World-class CMC & Manufacturing Capacity & Enhanced Commercial Strategy

CMC & GMP Manufacturing Capability

CMC Process Development
- In-house CMC
  - Cell line / Cell culture / Purification / Formulation / Analytical development
- 15-20 projects
  - IND/BLA filling / CDMO Management / Process development, Process characterization, Process validation
Pilot Plant, Ready by 2022

Commercialization Strategy

Stage 1: Focus on Immunology
Stage 2: Oncology 2025 -

- HEOR Study
- Launch Readiness
- Pricing Study
- Policy Landscaping
- Stakeholder Engagement

Commercial Launch Readiness in Full Swing
Rapid Progress for Key Assets Towards Bringing Innovative Therapeutics to Patients Around the World

2021

- 4 clinical products with 2 in Ph 3 and 1 in global Ph 1/2
- 6 highly differentiated preclinical products with 2 entering IND application

2022

- 3 BLAs
  - 3 products in registrational trials globally
  - Multiple next gen therapeutics entering INDs

2023 & Beyond

- 2 commercial products and serials of product launches
- 3 products in registrational trials globally
- Multiple next gen therapeutics in global clinical trials
Harbour BioMed Advancing Global Biotherapeutics Innovation

**Next Gen Therapeutics**
- Biology-driven
- Unmet medical needs driven
- Industry leading technologies to provide sustainable innovation engine
- Highly differentiated portfolio with FIC/BIC next gen therapeutics

**Advancing Global Biotherapeutics Innovation**
- Global Innovation Centers
- Collaboration with leading global biopharmaceutical companies and top-notch academies to advance next gen therapeutics
- Development and commercialization of HBM products globally
- Global Innovation
THANK YOU

HBM HOLDINGS-B
02142.HK
www.harbourbiomed.com
Unleash Powerful Technology for HBM’s Sustained Innovation

Dr. Yiping Rong
Head of Research, Harbour BioMed

HBM HOLDINGS-B
02142.HK
www.harbourbiomed.com
Drive Transformational Innovation with Three Pillars in HBM R&D

Transformational innovation in drug R&D

Global Talents

Internal sites, partners, SAB network

Disease Science

Antibody Technology

Dana-Farber Cancer Institute
Mount Sinai
Erasmus MC
Universiteit Utrecht
HBM’s Antibody Discovery Platform is the Engine of Portfolio Innovation
Cutting Edge Fully Human Antibody Platforms Enable Sustained Invention of Novel Molecules

<table>
<thead>
<tr>
<th>H2L2 – Full IgG Antibody Discovery Platform</th>
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</thead>
<tbody>
<tr>
<td><strong>H2L2</strong></td>
</tr>
<tr>
<td>150 KDa</td>
</tr>
<tr>
<td><strong>HBM1020</strong></td>
</tr>
<tr>
<td>A fully human antibody against B7 family target for the treatment of solid tumors</td>
</tr>
<tr>
<td><strong>HBM9378</strong></td>
</tr>
<tr>
<td>A fully human antibody against TSLP for severe asthma</td>
</tr>
</tbody>
</table>

**Robust and highly efficient, global IP and clinically validated**

<table>
<thead>
<tr>
<th>HCAb – Next-Generation Heavy-Chain-Only Antibody</th>
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<tbody>
<tr>
<td><strong>HCAb</strong></td>
</tr>
<tr>
<td>~80 KDa</td>
</tr>
<tr>
<td><strong>HBM4003</strong></td>
</tr>
<tr>
<td>A next generation anti-CTLA4 antibody</td>
</tr>
</tbody>
</table>

**Unique fully human HCAb, versatile for broad applications**

<table>
<thead>
<tr>
<th>HBICE® – HCAb-Based Bispecific Platform for Immune Cell Engagers</th>
</tr>
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<tbody>
<tr>
<td><strong>HBICE</strong></td>
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<tr>
<td><strong>HBM7020</strong></td>
</tr>
<tr>
<td>A BCMAxCD3 bispecific antibody</td>
</tr>
<tr>
<td><strong>HBM7008</strong></td>
</tr>
<tr>
<td>A B7H4×4-1BB bispecific antibody</td>
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</tbody>
</table>

**Self-developed, unique geometric flexibility, promising bispecific biology**

<table>
<thead>
<tr>
<th>Platform + 1 Ph1 + 1 Ph2</th>
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<tbody>
<tr>
<td><strong>$ 178 M</strong></td>
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<tr>
<td>Platform only</td>
</tr>
<tr>
<td><strong>$1.1 B</strong></td>
</tr>
<tr>
<td>Platform + 1 Ph2</td>
</tr>
<tr>
<td><strong>$ 4.8 B</strong></td>
</tr>
<tr>
<td>Nanobody + 1 BLA + 1 Ph2</td>
</tr>
<tr>
<td><strong>$ 2.5 B</strong></td>
</tr>
<tr>
<td>Platform + 1 Ph1</td>
</tr>
<tr>
<td><strong>$ 1.6 B</strong></td>
</tr>
<tr>
<td>3 BsAb slots based on Biclonics platform</td>
</tr>
<tr>
<td><strong>$ 3.2 B</strong></td>
</tr>
<tr>
<td>3 BsAb ADC slots based on Duobody platform</td>
</tr>
</tbody>
</table>

1

$2.5 B
Integrated Technology Platforms Ensure Efficient Discovering Next-Gen Fully Human Antibody Therapeutics

**Antibody generation with Single B Cell cloning method (Beacon) in ~4 months**

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

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

**Transgenic fully human antibody mice**
- No need for humanization, affinity maturation
- H2L2 and HCAb with knock-out or inducible immunization techniques

**Single B cell cloning (Beacon System)**
- Accelerated antibody discovery process and increased productivity
- Deep mining of rare clones

Display and antibody engineering to support bispecific molecule design
Advancing HBM Core Technologies for Next-Gen Therapeutics Beyond Harbour Mice

**Delivery Technology**
- mRNA technology for immunogen or drug delivery to tackle difficult targets

**Protein Engineering**
- Combine human antibody platforms and protein engineering to generate multifunctional molecules

**Conjugation Technology**
- Novel conjugation technology for bringing new modalities against solid tumors

**Artificial Intelligence**
- Artificial Intelligence for accelerating drug discovery and translation research
Advancing HBM Core Technologies for Next-Gen Therapeutics

Using mRNA Technology to Tackle Challenging Targets for Ab Generation

**Good immunogen is key to generate GPCR antibodies**

<table>
<thead>
<tr>
<th>Immunogen</th>
<th>issues</th>
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<tbody>
<tr>
<td>Proteins</td>
<td>Generally not available</td>
</tr>
<tr>
<td>Cells</td>
<td>Low target expression, raise non-specific immune response</td>
</tr>
<tr>
<td>DNA</td>
<td>Low immune response</td>
</tr>
<tr>
<td>mRNA</td>
<td>Technical difficulty ?</td>
</tr>
</tbody>
</table>

**7TM GPCR**

**Tailored and efficient mRNA-lipid nanoparticles (LNP)**

CCR8-mRNA-LNP had homogeneous size distribution and > 80% encapsulation efficiency

**Identified candidate with cross-reactivity to cyno CCR8**

binding to human CCR8

EC50 = 0.93 nM

binding to cyno CCR8

EC50 = 1.20 nM
Advancing HBM Core Technologies for Next-Gen Therapeutics

HBM Proprietary Fully Human HCAb Site-Specific ADC is the New Class ADC Platform

Smaller size (~ 85 KDa) ✓ better tissue penetration
Access special epitope ✓ better target internalization
Site-specific conjugation ✓ High homogeneous product
Fully human antibody sequences ✓ No additional tags
✓ No non-natural amino acids
✓ No changes on glycosylation patterns
Simple conjugation ✓ Good manufacturability
Flexibility ✓ Expand to other modalities e.g. bsAb

Homogeneous Product

Improved Internalization

Enhanced Cytotoxicity

- MS TIC of HCAb-ADC
- >90% DAR=2
- pHrodo_iFL, NCI-H929
- MFI
- Time (h)
- cell viability %
- Ab conc. (nM)
HBM Innovative R&D Strategy is Powered by Unique Technology Platform
Current IO Therapy – Only 20-30% Patients Respond to PD1/PDL1 Therapies

- **Huge PD1/PD-L1 market**
- A large number of indications: lung cancer, liver cancer, gastric cancer, esophageal cancer, melanoma, lymphoma, urothelial cancer, breast cancer, nasopharyngeal cancer, colorectal cancer, cervical cancer, etc.
- 70-80% of patients are resistant or have no response for PD1/PD-L1 -- huge market potential

### Expected PD1/L1 Market Size in 2025 (unit: USD Mil)

- 50,000

### Most Patients Are Resistant or Not Responded to PD1/PDL1 Treatment

- 30% PD1/PD-L1 responders
- 70% PD1/PD-L1 non-responders

Data source: Frost & Sullivan, Southwest Securities

Note: Compiled data of PD1/PDL1 development and marketed drugs
HBM Provides Innovative Solutions for Next-Gen Immuno-Oncology Therapy

The Major Causes of Current IO Limitation

1. No enough immune cells in tumor microenvironment (TME)
2. Suppressive immune cells in TME (Tregs, MDSC, CAF etc.)
3. Complementary immune evasion pathways besides PD1/PD-L1

HBM Next-Gen IO Therapy Strategy

1. Increase T/NK cell infiltration/proliferation via immune cell engager (HBICE, SBC, Fc engineering)
2. Depletion of regulatory T cells (eADCC, Afucosylation, HCAb)
3. Innovative targets and pathways of the B7 family (H2L2, HBICE, mRNA/DNA immunization, ADC)

Scientific Strategy is Warranted by Cutting-edge Technologies

Goal: Breakthrough Efficacy with Improved Safety Profile
### Solution 1:
**Immune Cell Engager (HBICE®) is One of the Exciting Solutions to Turn Cold Tumor to Hot Tumor**

<table>
<thead>
<tr>
<th>HBICE®</th>
<th>Target validation</th>
<th>Lead generation</th>
<th>candidate selection</th>
<th>Pre-clinical</th>
<th>IND</th>
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<tbody>
<tr>
<td>HBM7020</td>
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<tr>
<td></td>
<td>Multiple myeloma</td>
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<td>HBM7008</td>
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<tr>
<td></td>
<td>Ovary cancer, TNBC, Lung cancers</td>
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<td></td>
<td>Multiple solid tumors</td>
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<tr>
<td></td>
<td>Gastric cancer, pancreatic cancer</td>
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</table>
HBICE® Expands Immune Cell Engagers Beyond CD3 TCE

**Tumor-associated Antigens For Specific Targeting**
- A panel of TAA antibodies on various of tumors

**Agonistic Modules For Immune Cell Activation**
- A panel of immune cell (T, NK, DC, Mϕ) activation or co-stimulatory engagers

**Immune Cell Engager**
- Deliver tumor-killing effects unachievable by combination therapies only in TME

**Asymmetric ‘2+1’ HBICE (A-HBICE)**
- CD3 mediated cytotoxic T engaging and directly kill tumor cells with CRS

**‘2+2’ symmetric HBICE (S-HBICE)**
- 4-1BB mediated tumor dependent T cell activation including memory T without CRS
HBM is at the Forefront of New Generation of T-Cell Engager Bispecific Antibodies

**FcyR engaging**
- Rat IgG2b
- Mouse IgG2a
- Catumaxumab

**FcyR-silenced**
- Blinatumomab
  - Short half life
  - Extended half-life

**Optimized aCD3, 2+1 format**
- RG7802
  - Optimized aCD3

**Trispecific or 2nd signal bispecific combination**
- 4-1BB/CD28/4-1BB
- Optimized CD3
- TAA
HBM7008: First-in-Class Bispecific Antibody from the HBICE® Platform

Highlights:

1) MoA: Crosslinking dependent 4-1BB activation is stringently mediated by B7H4 binding
2) Molecule: Based on HBICE® platform to optimize the geometry for 4-1BB clustering, T/Tumor cell dual binding
3) Druggability: Fully human sequences from Harbour mice undergone natural in-vivo selection. Symmetrical format with excellent biophysical properties
4) Indications: Mutual exclusively expressed with PD-L1, potential for PD1/PD-L1 therapy refractory patients, particularly in multiple gynecological cancers
HBICE® Platform Provides the Best Geometry Design for the MoA of HBM7008

Format Engineering

4-1BB Binding

B7H4 Binding

T Activation

Linker/Sequence Engineering
Encouraging monkey DRF and Tox data also suggest its excellent PK and safety profile

HBM7008: First-in-Class Bispecific Antibody from the HBICE® Platform

B7H4 dependent 4-1BB activation and T cell stimulation

HBM7008 completely leads tumor regression in B7H4 positive syngeneic model

CT26-hB7H4 tumor growth curve

- Isotype control, 1 mg/kg
- HBM7008, 1 mg/kg
Two main mechanisms of immune tolerance: T cell receptor-mediated immune exhaustion; Regulatory T cell-mediated immune surveillance

<table>
<thead>
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<th>IND</th>
<th>Ph1</th>
<th>Ph2</th>
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<tbody>
<tr>
<td>HBM4003 (CTLA4)</td>
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## Unique Treg Depletion Mechanism to Develop Next-Gen Antibody Therapeutics

### HBM1022 (CCR8)

<table>
<thead>
<tr>
<th>Highlights</th>
<th>Details</th>
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<tbody>
<tr>
<td>• Potently antagonizes CCL1-CCR8 signaling and depletes CCR8-expressing cells</td>
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<tr>
<td>• First reported functional antibody that cross-reacts with human &amp; cyno</td>
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<tr>
<td>• The only CCR8 antibody shown anti-tumor efficacy in animal models instead of using surrogate antibody</td>
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**Indication**
Solid Tumors

**Development Stage**
IND in 2022

### HBM4003 (CTLA-4)

<table>
<thead>
<tr>
<th>Highlights</th>
<th>Details</th>
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<tbody>
<tr>
<td>• Enhanced ADCC strategy to deplete CTLA4+ Treg cells in tumor</td>
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<tr>
<td>• The world’s first fully human heavy chain antibody to enter the clinical study</td>
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<tr>
<td>• Developing monotherapy and combo clinical research</td>
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</table>

**Indication**
Solid Tumors

**Development Stage**
Monotherapy Ph1b/2
Combo therapy Ph1

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**Diagram**

1. High CCR8 expressing Tread molt for antibody mediated depletion via ADCC
2. CCR8 blockade inhibit ligand CCL1 induced chemotaxis of Treg

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**Image**

[Image of diagram showing Treg depletion mechanisms]
HBM1022: CCR8 is a Novel Target Expressed on Tumor Infiltrated Treg Cells

HBM1022 Highlights:
1. Potent tumor resident T_{reg} depletion activity
2. Potent inhibition of CCL1-induced signaling pathway / in vivo anti-tumor efficacy
3. Comparable human/cyno binding affinity
4. Significant potential for breast cancer, colon cancer, and multiple solid tumors and hematological malignancies

Mechanism of Action

1. High CCR8 expressing Tregs allow for antibody mediated depletion via ADCC
2. CCR8 blockade inhibit ligand CCL1 induced chemotaxis of Treg into TME

Breast cancer, Analysis of over 70 individual patients
Immunity 2016, 45:1122–1134
HBM1022: A Unique CCR8 Antibody Shows Treg Cell Depletion and Anti-Tumor Efficacy in Pre-clinical Models

**High On-cell Affinity to Human/Cyno CCR8**

(Human/Cyno CCR8 On-cell affinity KD (pM))

- **Human CCR8**: 21.3
- **Cyno CCR8**: ECD, ECL1, ECL2, ECL3

**Mono and Combo Efficacy in Syngeneic Knock-in Mouse Model**

HBM1022 preclinical study was presented on the 16th PEGS Boston Summit in August 2020
The most important tumor immunomodulatory family, Targets of current immuno-oncology drugs are all from this family.

**Solution 3:**
Focus on Novel Immune Escape Pathway *Develop First-in-Class Targets in B7 Family*

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<th>Lead generation</th>
<th>Candidate Selection</th>
<th>Pre-clinical</th>
<th>IND</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBM7008 (B7H4x4-1BB)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBM1020 (B7H7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undisclosed</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
**HBM1020: First-in-Class Fully Human mAb Against a Novel B7 Family Target**

**Highlights:**

1) First-in-class target potentially serves as an alternative immune escape pathway
2) Potent receptor blocking, T cell activation activity and excellent in vivo efficacy in humanized tumor models
3) Huge potential to treat PD-L1 negative or anti-PD1/PD-L1 refractory cancer patients

**Diagram:**
- **T cell**
  - TCR
  - MHC I
  - PD1

- **Tumor cell**
  - B7
  - PD-L1

- **HBM1020**

- **H2L2**

IND in 2022
HBM1020: First-in-Class Antibody Shows Promising Anti-Tumor Preclinical Efficacy in Multiple Cancer Types

Lead Antibody Shows Strong T Cell Activation

T cell activation test

- IFN-γ (pg/ml)
  - HBM1020
  - TAB
  - IgG1

Dose Levels:
- 10nM
- 2nM
- 0.4nM
- 0.08nM
- 0.016nM
- 0.0032nM

Lead Antibody Shows Strong Tumor Growth Inhibition

Breast Cancer Human PBMC Mouse Model

- PBS, i.p., BiW x 3 weeks
- Ab1, 5mg/kg, i.p., BiW x 3 weeks
- Ab1, 10mg/kg, i.p., BiW x 3 weeks
- Ab1, 20mg/kg, i.v., BiW x 3 weeks
- Keytruda, 10mg/kg, i.p., BiW x 3 weeks

Tumor volume (mm³±SEM)

Treatment time (days)
<table>
<thead>
<tr>
<th>Technology</th>
<th>Disease</th>
<th>Mechanism</th>
<th>Target</th>
<th>Drugability</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICE: Immune cell engager</td>
<td>Treg: Regulatory T modulation/depletion</td>
<td>IEP: Novel immune escape pathway</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**HBM Continuously Drives Innovative Portfolio and Leads the Next-Gen Therapeutics**

- **Preclinical**
  - Treg
  - ICE
  - IEP

- **Ph1**
  - Treg
  - ICE
  - IEP

- **Ph2**
  - Treg
  - ICE
  - IEP

- **Ph3**
  - Treg
  - ICE
  - IEP
THANK YOU

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Breakthrough IO Therapy for Unmet Medical Needs
Treg Depletion – A Novel Mechanism Unlocking Therapeutic Potential

Prof. Shun Lu
Director of Clinical Medicine Department
Shanghai Chest Hospital

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DISCLOSURE

• Received research support from AstraZeneca, Hutchison, BMS, Heng Rui, Beigene and Roche, Hansoh, Lilly Suzhou Pharmaceutical Co.Ltd
• Received speaker fees from Astra Zeneca, Roche, Hansoh, Hengrui Therapeutics
• An advisor and consultant of Astra Zeneca, Pfizer, BoehringerIngelheim, Hutchison MediPharma, ZaiLab, GenomiCare, Yuhan Corporation, Menarini, InventisBio Co. Ltd., and Roche.
Cancer Is A Major Public Health Problem and the Second Leading Cause of Death Worldwide

Number of new cases in 2020, both sexes, all ages

- Breast: 2,261,419 (11.7%)
- Lung: 2,206,771 (11.4%)
- Colorectum: 1,931,590 (10.0%)
- Prostate: 1,414,259 (7.3%)
- Stomach: 1,089,103 (5.6%)
- Oesophagus: 604,100 (3.1%)
- Cervix uteri: 604,127 (3.1%)
- Liver: 905,677 (4.7%)
- Other cancers: 8,275,743 (42.9%)

Total: 19,292,789 cases

Number of deaths in 2020, both sexes, all ages

- Lung: 1,796,144 (18.0%)
- Colorectum: 935,173 (9.4%)
- Liver: 830,180 (8.3%)
- Stomach: 768,793 (7.7%)
- Prostate: 375,304 (3.8%)
- Pancreas: 466,003 (4.7%)
- Other cancers: 3,557,464 (35.7%)
- Oesophagus: 544,076 (5.5%)
- Breast: 684,996 (6.9%)

Total: 9,958,133 deaths

- Lung cancer is the most frequent cause of cancer-related deaths worldwide.
- Much progress has been made in research, cancer screening, and personalized therapy (precision medicine) in recent years. However, most patients with advanced cancer will ultimately progress which remains a great unmet medical need.

Cancer Immunotherapy – 2013 Science “Breakthrough of the Year” and 2014 Special Nature Edition
Cancer Immunotherapy – 2013 Science “Breakthrough of the Year” and 2014 Special Nature Edition

THE NOBEL PRIZE IN PHYSIOLOGY OR MEDICINE 2018

James P. Allison • Tasuku Honjo
“for their discovery of cancer therapy by inhibition of negative immune regulation”

THE NOBEL ASSEMBLY AT KAROLINSKA INSTITUTET
Immune Combination Regimens Are in Full Swing, And the Exploration of New Combinations and New Targets Is the Key to Overcome IO Resistance

- 3-fold increase in number of combination trials in 2020 compared to 2017
- Added 129 targets from 124 target groups

- Chemotherapy, CTLA-4 and VEGF/R are most common partners in combination with anti-PD-(L)1

---

The Combination of CTLA-4 Antibody and PD-1 Antibody Has Synergistic Effect – Traditional View

<table>
<thead>
<tr>
<th>Anti-CTLA-4</th>
<th>Anti-PD-1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Main organs acted in:</strong></td>
<td><strong>Main organs acted in:</strong></td>
</tr>
<tr>
<td>• Lymph nodes, spleen and tumor tissue</td>
<td>• Tumor tissue</td>
</tr>
<tr>
<td><strong>The main phase of being affected:</strong></td>
<td><strong>The main phase of being affected:</strong></td>
</tr>
<tr>
<td>• The priming phase of T cells activation</td>
<td>• The effector phase of activated T cells</td>
</tr>
<tr>
<td><strong>Main mechanism:</strong></td>
<td><strong>Main mechanism:</strong></td>
</tr>
<tr>
<td>• Block the interaction between CTLA-4 and its ligand CD80/86, and relieve the inhibition of CTLA-4 on T cell activation</td>
<td>• Block the interaction between PD-1 and its ligand PD-L1, and relieve the inhibition of PD-1 on activated T cells</td>
</tr>
<tr>
<td>• Kills and inhibits Treg cells</td>
<td></td>
</tr>
</tbody>
</table>

Antoni Ribas, NEJM epub June 2012
Anti-CTLA-4 Treatment Improves anti-PD-1 Responses and Durability in Multiple Tumor Types

### Anti-CTLA-4 Enhances anti-PD-1 Durability

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Median PFS (Months)</th>
<th>Median OS (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD-1</td>
<td>+Ipi</td>
<td>PD-1</td>
</tr>
<tr>
<td>1L Melanoma</td>
<td>Checkmate-067</td>
<td>6.9</td>
</tr>
<tr>
<td>NSCLC (PD-L1 ≥1%)</td>
<td>Checkmate-227</td>
<td>4.2</td>
</tr>
<tr>
<td>Metastatic Sarcoma</td>
<td>Alliance A091401</td>
<td>1.7</td>
</tr>
</tbody>
</table>


Note: Reflects clinical data from various Nivolumab (PD-1) and Nivolumab + Ipilimumab (PD-1 + CTLA-4) trials; NR denotes median not reached.

(1) Objective Response Rate: 2L+ CRC, Urothelial Carcinoma, NSCLC, Esophagogastric, 3L+ SCLC; Overall Response Rate: 1L Melanoma, Metastatic Sarcoma, HCC; Disease Control Rate: Mesothelioma.

### Combination Has Demonstrated Stronger Anti-tumor Response

### 2-3x Improvement in Certain Tumors
High rates of somatic mutations and high proportion of patients with immune-inflamed contexture in NSCLC contribute to increased sensitivity to immunotherapy.
Immunotherapy has Comprehensively Changed the Treatment Landscape for Advanced Lung Cancer, but There Are Still Many Unknowns to be Explored

Radiotherapy
- Radiotherapy + IO
  - PACIFIC
  - KN799

Targeted therapies
- Combination with targeted therapies, e.g. VEGF, EGFRTKI
  - IMPOWER-150
  - ORIENT-31

Immunotherapy
- Ipilimumab + nivolumab
- Tremelimumab + durvalumab
- Enhanced T-cell stimulation (vaccine) Novel agents (i.e. ea.ant - NK-R, immune checkpoint inhibitor)
  - CheckMate 227
  - MYSTIC
  - KEYNOTE 598

Chemotherapy
Use the immunomodulatory effects of chemotherapy
- KEYNOTE-021G
- KEYNOTE-189
- KEYNOTE-407
- IMPOWER-131
- IMPOWER-132
- CHKLMATE 227
## Immunotherapy for Metastatic NSCLC: Monotherapy? Combinations? What Is the Future?

### KEYNOTE-024
- COVER driver gene negative population
- Significantly improved ORR compared with IO monotherapy
- However, it has encountered a therapeutic bottleneck

### IMPOWER-110
- From IO monotherapy to combination therapies

### KEYNOTE-042

#### IO mono
- Only cover PD-L1-positive population
- ORR needs to be improved

#### Combo chemotherapy
- Cover driver gene negative population
- Significantly improved ORR compared with IO monotherapy
- However, it has encountered a therapeutic bottleneck

#### Combo radiotherapy

#### Combo anti-angiogenesis

#### IO combinations

### What is the future?
- Further explore the mechanisms of tumor development and drug resistance, screen effective biomarkers, and more precise treatment
- Explore new combination treatment strategies and find more effective therapeutic targets

---

At present, the approved indications of pembrolizumab for lung cancer in mainland China are: ① PD-L1 TPS ≥ 1% for first-line treatment of EGFR, ALK-negative locally advanced or metastatic NSCLC; ② combo pemetrexed/platinum for first-line treatment of EGFR, ALK-negative metastatic non-squamous NSCLC; ③ combo carboplatin and paclitaxel for first-line treatment of metastatic NSCLC patients. Nivolumab has been indicated for second-line treatment of advanced NSCLC in mainland China. Atezolizumab in Combination with Carboplatin and Etoposide for the First-Line Treatment of Extended Staged Small Cell Lung Cancer. Durvalumab in Mainland China for the treatment of Stage III unresectable NSCLC that has not progressed after concurrent chemoradiotherapy.
Paradigm 2021 – First Line Treatments for NSCLCL without Actionable Driver Mutations

**Advanced NSCLC without actionable driver mutations**

**PD-(L)1 ≥50%**
- PD-(L)1 + chemo
- PD-1 + CTLA-4
- PD-1 + CTLA-4 + chemo

**PD-(L)1 1-49%**
- PD-(L)1 + chemo
- PD-1 + CTLA-4
- PD-1 + CTLA-4 + chemo

**PD-(L)1 <1%**
- PD-(L)1 + chemo
- PD-1 + CTLA-4
- PD-1 + CTLA-4 + chemo

**Anti-PD-1 monotherapy:**
- Pembrolizumab, Atezolizumab, Cemiplimab

**ICI + chemo:**
- Pembrolizumab + carboplatin + pemetrexed (nsq)
- Atezolizumab + carboplatin + paclitaxel + bevacizumab (nsq)
- Atezolizumab + carboplatin + nab-paclitaxel (nsq)
- Pembrolizumab + carboplatin + paclitaxel or nab-paclitaxel (sq)
- Nivolumab + ipilimumab + 2 cycles of chemotherapy (nsq/sq)

**ICI combination:**
- Nivolumab + ipilimumab
The Efficacy of anti-PD-(L)1 Monotherapies as First Line Treatment for NSCLC

<table>
<thead>
<tr>
<th>Study name</th>
<th>KEYNOTE-024¹</th>
<th>CheckMate-026²</th>
<th>KEYNOTE-042³</th>
<th>IMPOWER 110⁴</th>
<th>MYSTIC⁵</th>
<th>PEARL⁶</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study drug</td>
<td>Pembrolizumab</td>
<td>Nivolumab</td>
<td>Pembrolizumab</td>
<td>Atezolizumab</td>
<td>Durvalumab</td>
<td>Durvalumab</td>
</tr>
<tr>
<td>Target population</td>
<td>PD-L1 ≥ 50% advanced NSCLC</td>
<td>PD-L1 ≥ 1% advanced NSCLC</td>
<td>PD-L1 ≥ 1% advanced NSCLC</td>
<td>PD-L1-selected advanced NSCLC</td>
<td>Advanced NSCLC</td>
<td>Advanced NSCLC</td>
</tr>
<tr>
<td>Patients enrolled</td>
<td>305</td>
<td>423</td>
<td>1247</td>
<td>262</td>
<td>572</td>
<td>1118</td>
</tr>
<tr>
<td>Main results</td>
<td>PFS: 10.3 vs 6.0m 2-yOS: 51.7% vs 34.2%</td>
<td>PFS (PD-L1 ≥ 5%): 4.2 vs 5.9 m, study failed to meet primary endpoint</td>
<td>OS: 16.4 vs 12.1m 2yOS: 39% vs 28%</td>
<td>OS: 20.0 vs 13.7m 2yOS: 45% vs 30%</td>
<td>TC3/IC3: 20.2 vs 13.1m 1-yOS: 60.9% vs 50.6%</td>
<td>OS (TC ≥ 25%): 16.3 vs 12.9m Study fails to meet primary endpoint</td>
</tr>
<tr>
<td>HR (95% CI) P value</td>
<td>0.5 (0.37-0.68) P = 0.001</td>
<td>1.15 (0.91 – 1.45) P = 0.2511</td>
<td>0.82 (0.71-0.93) P = 0.0018</td>
<td>0.65 (0.45-0.94) P = 0.0003</td>
<td>0.59 (0.4-0.89) P = 0.0106</td>
<td>0.76 (0.56-1.02) P = 0.036</td>
</tr>
</tbody>
</table>

1. Martin Reck et al. 2019 WCLC  
3. Tony S K Mok, et al. 2019  
4. Spigel et al. IMpower110 Interim OS Analysis. 2019 ESMO  
5. 2018 ESMO-ASIA.  
# The Efficacy of anti-PD-(L)1 + Chemotherapy as First Line Treatment for NSCLC

<table>
<thead>
<tr>
<th>Key Parameter</th>
<th>Pembro + Pemetrexed + Platinum (KN-189)</th>
<th>Pembro + Carbo + Abraxane or Paclitaxel (KN-407)</th>
<th>Nivo + Ipi (CM-227 Part 1)</th>
<th>Nivo + Ipi + 2 cycles Platinum + Paclitaxel (sq) or Pemetrexed (non-sq) (CM-9LA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Non-sq NSCLC Whole population N = 616</td>
<td>Sq NSCLC Whole population N = 559</td>
<td>Sq + non-sq NSCLC Whole population N = 1166</td>
<td>Sq + non-sq NSCLC Whole population N = 719</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>OS, PFS, intragroup crossover allowed</td>
<td>OS, PFS, intragroup crossover allowed</td>
<td>PFS in high TMB, OS in PD-L1 ≥ 1% Intragroup crossover not allowed</td>
<td>OS, intragroup crossover not allowed</td>
</tr>
<tr>
<td>ORR</td>
<td>48.3% pembro + chemotherapy Vs. 19.9% chemotherapy</td>
<td>62.6% pembro + chemotherapy Vs. 38.4% chemotherapy</td>
<td>33.1% nivo-mpi Vs. 27.8% chemotherapy</td>
<td>38% nivo-mpi-chemotherapy Vs. 25% chemotherapy</td>
</tr>
<tr>
<td>PFS</td>
<td>9.0 mos pembro + chemotherapy Vs. 4.9 mos chemotherapy (HR = 0.49)</td>
<td>8.0 mos pembro + chemotherapy Vs. 5.1 mos chemotherapy (HR = 0.57)</td>
<td>5.1 mos nivo-mpi Vs. 5.5 mos chemotherapy (HR = 0.79)</td>
<td>6.7 mos nivo-mpi-chemotherapy Vs. 5.0 mos chemotherapy</td>
</tr>
<tr>
<td>OS</td>
<td>22.0 mos pembro + chemotherapy Vs. 10.6 mos chemotherapy (HR = 0.56)</td>
<td>17.1 mos pembro + chemotherapy Vs. 11.6 mos chemotherapy (HR = 0.71)</td>
<td>17.1 mos nivo-mpi Vs. 13.9 mos chemotherapy (HR = 0.73)</td>
<td>15.6 mos nivo-mpi-chemotherapy Vs. 10.9 mos chemotherapy (HR = 0.66) (HR = 0.69 at IA)</td>
</tr>
<tr>
<td>Survival rate</td>
<td>70.0% vs. 48.1% 12-month OS 45.7% vs. 27.3% 24-month OS</td>
<td>73% vs. 50% 12-month OS</td>
<td>64% vs. 54% 12-month OS 40% vs. 30% 24-month OS</td>
<td>63% vs. 47% 12-month OS</td>
</tr>
<tr>
<td>Duration of Response</td>
<td>12.4 mos pembro + chemotherapy Vs. 7.1 mos chemotherapy</td>
<td>8.8 mos pembro + chemotherapy Vs. 4.9 mos chemotherapy</td>
<td>19.6 mos nivo-mpi Vs. 5.8 mos chemotherapy</td>
<td>11.3 mos nivo-mpi-chemotherapy Vs. 5.6 mos chemotherapy</td>
</tr>
<tr>
<td>Grade 3-4 (5) (Treatment related) AEs</td>
<td>72.1% pembro + chemotherapy Vs. 66.8% chemotherapy (Entire Population, All Causes)</td>
<td>74% pembro + chemotherapy Vs. 70% chemotherapy (Entire Population, All Causes)</td>
<td>32.8% nivo-mpi Vs. 36.0% chemotherapy (Treatment-related)</td>
<td>47% nivo-mpi-chemotherapy Vs. 38% chemotherapy (Treatment-related)</td>
</tr>
<tr>
<td>Discontinuation Rate</td>
<td>33.6% pembro + chemotherapy Vs. 16.3% chemotherapy (Entire Population, All Causes)</td>
<td>27% pembro + chemotherapy Vs. 13% chemotherapy (Entire Population, All Causes)</td>
<td>18.1% nivo-mpi Vs. 9.1% chemo (Treatment-related)</td>
<td>19% nivo-mpi-chemotherapy vs. 7% chemotherapy (Treatment-related)</td>
</tr>
</tbody>
</table>

The Efficacy of PD-1 + Chemotherapy Is limited in PD-L1 Negative Patients, While Addition of First Generation CTLA-4 Antibody Only Brings Moderate Excess Benefit

Keynote-189 study: Pembrolizumab + chemotherapy for non-sq NSCLC, PFS in PD-L1 <1% subgroup

CheckMate 227 study: Nivo + ipi, Nivo + chemotherapy and chemotherapy for NSCLC, PFS in PD-L1 <1% subgroup

- The benefit of PFS by PD-1 + chemotherapy in subgroup of PD-L1 <1% was limited and not as high as subgroup of PD-L1 >1%.
- Combination of first generation anti-CTLA-4 antibody with anti-PD-1 only brings moderate excess benefit over PD-1 + chemotherapy in this population.
- There remains high unmet medical needs for NSCLC patients in the immunotherapy era, especially in patients who have negative PD-L1 expression.

Treg Is the Main Suppressor of Anti-Tumor Immunity and Is Associated with Poor Prognosis

Treg suppress anti-tumor immunity via various mechanisms

High infiltration of Tregs in tumors is associated with a poor prognosis in various types of cancers


TILs: HBV Tumor-infiltrating leukocytes
NILs: Non-tumor-infiltrating leukocytes
PBMCs: Peripheral blood mononuclear cells

Tregs suppress anti-tumor immunity via various mechanisms:
- Dominant consumption of IL-2
- Inhibitory cytokines
- Induction of Apoptosis
- ATP-Adenosine metabolism
- ATP release from apoptotic Treg
- Promote IDO expression on APC
- Inhibition via DC
- Treg reinvigoration by Immune checkpoint blockade

Immune checkpoint molecules mediated immunosuppression and Treg activation

NSCLC
HBV-related HCC

Overall survival

Relapse-free survival

CD4+ Treg count

TREG

CD4+FOXP3+ Lo

CD4+FOXP3+ Hi

TILs
NILs
PBMCs

No. at risk
Survival (years)

p=0.006

HR=0.48
High Infiltration of Tregs in Tumors and Regional Lymph Nodes but not in Peripheral Blood Is Associated with A Significant Poor Prognosis in NSCLC

Regional lymph nodes

Resected tumor

Peripheral blood

Resected tumor

FIGURE 4. Kaplan-Meier recurrence-free survival curve according to Foxp3 expression, log-rank $p = 0.004$. 

Ratio of PD-1 Positivity (%) in CD8+ T cells to PD-1 Positivity (%) in eTreg Cells Predicts Responses to PD-1 Blockade Therapies

Group R (PD-1 positivity in CD8+TILs ≥40% and PD-1 expression ratio of CD8+ T cells to eTreg cells in TILs ≥1) had significant better PFS compared with other patients.
Around 10% of patients treated with anti-PD-1 had hyperprogression and dismal prognosis

- Hyperprogressive disease (HPD) was defined as disease progression at the first evaluation with ΔTGR exceeding 50%.
- Among 406 advanced NSCLC patients treated with PD-(L)1 inhibitors, 56 (13.8%) were classified as having HPD.
- Patients experiencing HPD within the first 6 weeks of PD-(L)1 inhibitor treatment had significantly lower OS compared with patients with progressive disease (median OS, 3.4 months [95%CI, 2.8-7.5 months] vs 6.2 months [95%CI, 5.3-7.9 months]; hazard ratio, 2.18 [95%CI, 1.29-3.69]; P = .003).
- Among 59 eligible patients treated with chemotherapy, 3 (5.1%) were classified as having HPD.
PD-1+ Tregs Amplified by PD-1 Blockade Promote Hyperprogression of Cancer

Depletion of Treg may help to treat and prevent hyperprogression during an-PD-1 treatment

- (Left) Comparison of GC tissue samples before and after anti–PD-1 therapy revealed that the treatment markedly increased tumor-infiltrating proliferative (Ki67+) eTreg cells in HPD patients.
- (Up) in mice, antibody-mediated blockade of PD-1 in Treg cells increased their proliferation and suppression of antitumor immune responses.
Anti-tumor Activity Is Mainly Achieved by Intratumoral Treg Depletion, While CTLA-4 Blockade Might Cause IrAEs and even Treg Hyper-proliferation

IrAE is caused by inhibiting the conversion of autoreactive T cells into Tregs, while cancer immunotherapeutic effect is achieved by intratumoral Treg depletion.

CTLA-4 blockade disrupts the CTLA-4 dependent feedback loop and causes the CD28-mediated expansion of tumor-associated Treg cells.

_Marangoni et al._ Cell 2021, 184, 3998–4015.
Anti-Tumor Activity of CTLA-4 Antibody Is Dependent on Intratumoral Treg Depletion, While Not Necessarily Dependent on CTLA-4 Blockade

Depletion of intratumoral Tregs is associated with efficacy in both animal models and patients treated with anti-CTLA-4 antibody

- In mouse model, Anti-FcR mAb administration abrogated the therapeutic effect of Ipilimumab.

- In mouse model, anti-CTLA-4 mAb HL12 and HL32 that lost blocking activities remain effective in local Treg depletion and tumor rejection.

- Patients who responded to ipilimumab had decreased intratumoral Tregs post treatment.

Romano et al, PNAS. 2015 May 12;112(19):6140-5.
CTLA-4 Blockade Enhances Proliferation of Tregs and Limits the Anti-Tumor Activity

• In mouse model, blockade of CTLA-4 enhances intratumoral Treg proliferation, while simultaneously blockade of IL-2 could inhibit this effect.

• Treg level in peripheral blood increased at Week 6 following treatment with ipilimumab.

• Higher Treg level was found in the tumor of patients treated with ipilimumab compared to untreated patients.

Summary: Develop Treg Targeted Treatment to Expand the Therapeutic Potential of IO

- Treg is the main suppressor of anti-tumor immunity, high infiltration of Tregs in tumors is associated with poor prognosis

- Hyperprogression and dismal prognosis associated with anti-PD-1 treatment, might be caused by amplification of PD-1+ Tregs in tumor

- Anti-tumor activity of CTLA-4 antibody is mainly dependent on intratumoral Treg depletion

Next generation anti-CTLA-4 antibody with enhanced Treg depletion might overcome the resistance to immunotherapy and expand the therapeutic potential

The image was modified from: Smyth et al. Immunology & Cell Biology. 2014: 92(60):473-474.
THANK YOU

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HBM4003 Leading the Way of Next Gen IO therapy
Clinical Validation of Treg Depletion Mechanism

Dr. Xiaoxiang Chen
Chief Development Officer, Harbour BioMed

HBM HOLDINGS-B
02142.HK
www.harbourbiomed.com
HBM4003: Next Generation Anti-CTLA-4 With Encouraging Efficacy and Safety Profile

HBM4003 is a next generation anti-CTLA-4 fully human Heavy-Chain-Only Antibody (HCAb) with enhanced ADCC for $T_{reg}$ depletion and unique PK resulting reduced drug exposure.

HBM4003 demonstrated potent tumor growth inhibition and prolonged survival in mouse tumor models and a favorable safety profile compared to Ipilimumab.

Preliminary clinical data from mono dose escalation trial validated MOA and PK/PD profile and demonstrated encouraging efficacy and tolerability. The 1st clinical abstract has been presented at annual ESMO Congress in September 2021.

Ph2 trials have been kicked off globally for both mono and combo therapy, covering various solid tumors including melanoma, HCC, RCC, NEN and NSCLC.
HBM4003: Leading Development of Next Gen Anti-CTLA-4 Therapeutics with Novel MoA to Improve Efficacy and Safety

Source: Company websites, filings and other publicly available information.
Unique Design With Dual Mechanism of Action – Checkpoint Inhibition and Treg Depletion

- **HBM4003 dual mechanism of action** inhibits negative signaling from the interaction of CTLA-4 and the co-stimulatory molecule B7, and depletes immune suppressive regulatory T cells ($T_{reg}$) through enhanced ADCC.
- HBM4003 demonstrated near dose-proportional pharmacokinetics (PK), extended pharmacodynamic (PD) effect, and low immunogenicity.
Preclinical Evidence – Superior TIL T\textsubscript{reg} Depletion Activity

100x More Potent Than Ipilimumab Analogue

**Superior T\textsubscript{reg} Depletion Activity in Comparison to Ipilimumab Analogue as Measured in Vitro via ADCC Killing Assay**

- T\textsubscript{reg} depletion by HBM4003 in primary human PBMCs in in vitro ADCC assay

**Led to Substantial Depletion of TIL T\textsubscript{regs} in MC38 Bearing hCTLA-4 KI Mice**

- In vivo T\textsubscript{reg} (%) in tumor, spleen, and blood in MC38-bearing hCTLA-4 KI mice (3 mice per group)
- Samples were collected 24hrs post 2\textsuperscript{nd} dosing and analyzed by FACS
Translation Medicine Evidence – Selective Intratumor T<sub>reg</sub> Depletion and CD8+ Stimulation

**Tumor Biopsy**

- **Treg (CD8+FoxP3+)**: 54.6%, 81%, 75.6%
- **CD8+ Teff (CD8+)**: 0.7 folds, 4.4 folds, 2.6 folds
- **CD8+ Tm (CD45RO+CD8+)**: 6.0 folds, 18.7 folds, 12.4 folds

**Peripheral Blood**

- **Treg (CD4+CD8+CD127low/-)**: baseline
- **Proliferated CD8+ Teff (CD8+Ki67+)**: baseline

**Validation of Preclinical Data**

- Subject 89301, 48y, Male, Chromophobe RCC, HBM4003 0.45mg/kg Q3W
- 6w tumor assessment: SD
Dual Mechanism Makes HBM4003 More Efficient with Optimized Therapeutic Profile

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)

Ipilimumab (10mg/kg q3w)

- AUC (0-tau) \( \mu g \cdot day/ml \): 1942.7
- Cmax \( \mu g/ml \): 744.9
- Cmin \( \mu g/ml \): 576.3

Simulated PK Exposure at Steady State

HBM4003 (1.5mg/kg q3w)

- AUC (0-tau) \( \mu g \cdot day/ml \): 54.27
- Cmax \( \mu g/ml \): 40.26
- Cmin \( \mu g/ml \): 2.50

Days Post Treatment
Global Development Roadmap for HBM4003 Aiming to Unlock Potential of Broad Tumor Setting

<table>
<thead>
<tr>
<th>Year</th>
<th>2019</th>
<th>2020</th>
<th>2021</th>
<th>2022</th>
<th>2023</th>
<th>2024</th>
<th>2025</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**HBM4003 mono**

- **4003.1 (Phase 1a)**
  - Mono dose escalation, solid tumors
  - Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4

**HBM4003 combo with anti-PD1**

- **4003.1 (Phase 1b/2)**
  - Melanoma, HCC, RCC

- **4003.2 (Phase 1b/2)**
  - Dose escalation, + PD-1, Solid tumors

- **4003.2 Phase 2**
  - (Melanoma)

- **4003.3 (Phase 1b/2)**
  - Dose escalation, + PD-1, Solid tumors

- **4003.3 Phase 1b**
  - (NET/NEC)

- **4003.5 Phase 2**
  - (HCC)

- **4003.6 Phase 1b**
  - (NET/NEC)

**Phase 2/3 Recruitment**

- Phase 3, Mono, solid tumors
- Phase 3, combo PD-1 in Melanoma
- Phase 3, combo PD-1 in 2L HCC
- Phase 3, combo PD-1 and anti-VEGF in 1L HCC
- Phase 2 pivotal, combo PD-1 in NET/NEC
- Phase 3, combo with PD-1 and chemo in NSCLC

**Phase 1 Recruitment**

- Phase 1 recruitment
- Phase 1b/2 recruitment
- Phase 2/3 recruitment

1. Global, simultaneous development on POC
2. 5 ongoing trials including 2 basket trials
3. Mono & combo treatment
4. Various solid tumors – melanoma, HCC, NSCLC, NET/NEC, etc.

---

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Mono Therapy: Study 4003.1 Overall Design Outline
Includes Two Parts: Part 1 Abstract Read Out at 2021 ESMO Congress

Part 1
Dose Escalation in Previously Treated (Including Anti-PD-1 Therapy) Advanced Solid Tumors

- Primary endpoint:
  - Proportional of patients with DLT

  - 0.6mg/kg Q3W
  - 0.45mg/kg Q3W
  - 0.3mg/kg QW

HBM4003 IV QW or Q3W

Part 2
Dose Expansion

- Primary endpoint:
  - ORR

- Secondary endpoints:
  - DOR, DCR, DDC, maximum tumor shrinkage

Melanoma, HCC, RCC...

HBM4003 IV Q3W

Note: ClinicalTrials.gov identifier: NCT04135261. Data cutoff 12 April 2021.
4003.1 – Key Patient Features and Demographics
Heavily Pre-treated including PD-1, Diversified Cancer Types Mixed with Rare, Cold Tumors

- 20 patients with advanced solid tumors (no melanoma patients), 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)
- None of the patients studied had melanoma

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Safety Assessment (n)</th>
<th>Post-Treatment Data for Anti-tumor Assessment (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrial Carcinoma</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>PRCC</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>ccRCC</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Prostate Cancer</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>HCC</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Penile Cancer</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Testicular Cancer</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Esophagus Cancer</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Colorectal Cancer</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Bladder Cancer</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>HNSCC</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>NSCLC</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Mesothelial Cancer</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>20</strong></td>
<td><strong>15</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age, mean (SD)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0.3mg/kg QW (N=7)</td>
<td>67.6 (8.3)</td>
<td>62.3 (10.2)</td>
</tr>
<tr>
<td>0.45mg/kg Q3W (N=7)</td>
<td>56.8 (15.0)</td>
<td>62.5 (11.5)</td>
</tr>
<tr>
<td>0.6mg/kg Q3W (N=6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (N=20)</strong></td>
<td>62.5 (11.5)</td>
<td><strong>Total (N=20)</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ECOG PS, n(%)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>3 (42.9)</td>
<td>3 (50.0)</td>
</tr>
<tr>
<td></td>
<td>3 (42.9)</td>
<td>9 (45.0)</td>
</tr>
<tr>
<td>1</td>
<td>4 (57.1)</td>
<td>3 (50.0)</td>
</tr>
<tr>
<td></td>
<td>11 (55.0)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N of Previous Treatment Lines, n(%)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2 (28.6)</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>2 (28.6)</td>
<td>2 (28.6)</td>
</tr>
<tr>
<td>2 or more</td>
<td>3 (42.8)</td>
<td>5 (71.4)</td>
</tr>
<tr>
<td></td>
<td>5 (83.3)</td>
<td>13 (65.0)</td>
</tr>
<tr>
<td>Previous PD-1/PD-L1 Therapies, n(%)</td>
<td>2 (28.6)</td>
<td>3 (42.9)</td>
</tr>
<tr>
<td></td>
<td>3 (50.0)</td>
<td>8 (40.0)</td>
</tr>
</tbody>
</table>
No toxicity was reported related to lung, kidney, heart or endocrine system.

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, manageable & reversible with SOC.

Maximum tolerated dose (MTD) was not achieved
- No dose limiting toxicity (DLT) was observed in any Q3W dose level.

No treatment-related serious adverse event (TRSAE) was reported at 0.45mg/kg Q3W.

**4003.1 – HBM4003 Was Well Tolerated**

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>0.3mg/kg QW (N=7)</th>
<th>0.45mg/kg Q3W (N=7)</th>
<th>0.6mg/kg Q3W (N=6)</th>
<th>Total (N=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3</td>
<td>Any Grade</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Any irAE</td>
<td>4 (57.1)</td>
<td>1 (14.3)</td>
<td>2 (28.6)</td>
<td>1 (14.3)</td>
</tr>
<tr>
<td>Enterocolitis</td>
<td>2 (28.6)</td>
<td>0 (0.0)</td>
<td>1 (14.3)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (14.3)</td>
<td>1 (14.3)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Rash</td>
<td>3 (42.9)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Abnormal hepatic function(1)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (14.3)</td>
<td>1 (14.3)</td>
</tr>
<tr>
<td>Immune-mediated hepatitis</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

Source: Publicly available posters HBM4003 data presented at ESMO 2021 Congress.

Note: Enterocolitis includes colitis and immune-mediated enterocolitis; rash includes rash and rash maculo-popular.

(1) As measured by elevated blood bilirubin and transaminases levels, and abnormal liver function test scores.

Recommended Phase 2 (RP2D) Dose: 0.45mg/kg Q3W
Even with limited number of patients, encouraging HBM4003 safety profile especially given the extent of pre-treatment in patients

- More severe baseline conditions: more prior treatments (including PD-(L)1), higher ECOG, broad range of solid tumors mixed with cold tumors vs ≥ 2 line melanoma for Ipilimumab
- irAE & TRAE focused on diarrhea vs broad involvement with vital organs

<table>
<thead>
<tr>
<th>HBM4003 Overall, n(%)</th>
<th>HBM4003 0.45mg/kg Q3W, n(%)</th>
<th>Ipilimumab 3mg/kg Q3W, n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total No. Patients</strong></td>
<td>20 (pooled)</td>
<td>7</td>
</tr>
<tr>
<td><strong>Tumor Types</strong></td>
<td>Solid tumors</td>
<td>Solid tumors</td>
</tr>
<tr>
<td><strong>Prior Treatment Lines</strong></td>
<td>≥2: 13 (65.0)</td>
<td>≥2: 5 (71.4)</td>
</tr>
<tr>
<td></td>
<td>Prior PD-(L)1 Therapy: 8 (40.0)</td>
<td>Prior PD-(L)1 Therapy: 3 (42.9)</td>
</tr>
<tr>
<td><strong>ECOG</strong></td>
<td>0: 9 (45.0)</td>
<td>0: 3 (42.9)</td>
</tr>
<tr>
<td></td>
<td>1: 11 (55.0)</td>
<td>1: 4 (57.1)</td>
</tr>
<tr>
<td></td>
<td>2: 1 (0.7)</td>
<td>2: 1 (0.7)</td>
</tr>
<tr>
<td><strong>TRAE</strong></td>
<td>20 (76.9)</td>
<td>4 (57.1)</td>
</tr>
<tr>
<td><strong>irAE</strong></td>
<td>Total: 11 (55.0)</td>
<td>Total: 2 (28.6)</td>
</tr>
<tr>
<td></td>
<td>Enterocolitis: 6 (30.0)</td>
<td>Enterocolitis: 1 (14.3)</td>
</tr>
<tr>
<td></td>
<td>Diarrhea: 4 (20.0)</td>
<td>Abnormal hepatic function(1): 1 (5.0)</td>
</tr>
<tr>
<td></td>
<td>Rash: 3 (15.0)</td>
<td>Immune-mediated hepatitis: 1 (5.0)</td>
</tr>
<tr>
<td></td>
<td>Abnormal hepatic function(1): 1 (5.0)</td>
<td>Abnormal hepatic function(1): 1 (14.3)</td>
</tr>
<tr>
<td></td>
<td>Total: 1 (25.0) (No irAEs &gt; G3)</td>
<td>Total: 1 (14.3) (No irAE &gt; G3)</td>
</tr>
<tr>
<td></td>
<td>Enterocolitis: 1 (5.0)</td>
<td>Abnormal hepatic function(1): 1 (14.3)</td>
</tr>
<tr>
<td></td>
<td>Diarrhea: 4 (20.0)</td>
<td>Abnormal hepatic function(1): 1 (5.0)</td>
</tr>
</tbody>
</table>

(1) As measured by elevated blood bilirubin and transaminases levels, and abnormal liver function test scores.
4003.1 – Encouraging Preliminary Efficacy Been Observed with HBM4003 Monotherapy

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

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>0.3mg/kg QW (n=7)</th>
<th>0.45mg/kg Q3W (n=7)</th>
<th>0.6mg/kg Q3W (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>PR</td>
<td>0 (0.0)</td>
<td>1 (14.3)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>SD</td>
<td>5 (71.4)</td>
<td>0 (0.0)</td>
<td>4 (66.7)</td>
</tr>
<tr>
<td>PD</td>
<td>1 (14.3)</td>
<td>3 (42.9)</td>
<td>1 (16.7)</td>
</tr>
</tbody>
</table>

Tumor Shrinkage Reported for 3 SD Patients (0.3mg/kg QW)

Note: FIH = first in human; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; Breast cancer (BC), colorectal cancer (CRC), clear cell renal cell carcinoma (RCC), esophageal cancer (EC), mesothelial cancer (MC), prostate cancer (PC), bladder cancer (BLC), papillary renal cell carcinoma (PRCC), head and neck squamous cell carcinoma (HNSCC), hepatocellular carcinoma (HCC).
4003.1 – Preliminary Monotherapy Efficacy Data Show Potential in Multiple Solid Tumors
Effect Could Be Attributed to HBM4003’s Dual MOA vs. Ipilimumab Which Showed Efficacy Primarily in Melanoma

HBM4003 Monotherapy

- **2 Clinical Responses**
  - 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 > 71 weeks with SD in RECIST assessment
- **Study did not include melanoma patients**
- **9 patients had stable disease (SD 60%)**
  - 15 patients had at least 1 post-treatment tumor assessment
  - Tumor shrinkage was reported in 3 patients

Ipilimumab Monotherapy

- **Most Clinical Responses in solid tumors are in melanoma**
- All clinical responses in solid tumors were dosed at 3 or 10mg/kg
- With >1000 patients, 4 clinical responses were reported across all solid tumors outside of melanoma

Note: 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.
4003.1 – HCC Patient pre-treated with PD-1 mAb: Confirmed PR in Target Lesion

Patient profile
- 64-year-old man, Asian, HBV infected
- Prior treatments: sorafenib, lenvatinib and anti-PD-1
- HBM4003, 0.45 mg/kg Q3W

Strong and durable efficacy observed
- Tumor reduction reached 64.4% at week 22 and continued to remain as 64.4% at week 40 for target lesions, response of non-target lesions was CR at week 22

<table>
<thead>
<tr>
<th>Location</th>
<th>Baseline</th>
<th>6 W</th>
<th>11 W</th>
<th>16 W</th>
<th>22W</th>
<th>28 W</th>
<th>34W</th>
<th>40 w</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target Lesions (mm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right Superior Liver, Right Kidney</td>
<td>225</td>
<td>175</td>
<td>115</td>
<td>105</td>
<td>80</td>
<td>80</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>Change From Baseline</td>
<td>N/A</td>
<td>22.2%</td>
<td>48.9%</td>
<td>53.3%</td>
<td>64.4%</td>
<td>64.4%</td>
<td>64.4%</td>
<td>64.4%</td>
</tr>
<tr>
<td>AFP u/L</td>
<td>170</td>
<td>5</td>
<td>5</td>
<td>9</td>
<td>6</td>
<td>7</td>
<td>10</td>
<td>ND</td>
</tr>
<tr>
<td>Overall Response</td>
<td>NA</td>
<td>SD</td>
<td>PR</td>
<td>PR</td>
<td>PR</td>
<td>PR</td>
<td>PR</td>
<td>PR</td>
</tr>
</tbody>
</table>

Note: HCC = hepatocellular carcinoma; PR = partial response. The target lesion was measured at the longest diameter.
## 4003.1 – CRPC Patient: Durable SD by RECIST 1.1 associated with PSA Response

### Patient profile
- 80-year-old man, HBM4003 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 continues until week 71
- The SD of adrenal and axillary lymph node by RECIST 1.1 also last until week 35, no CT scan has been done since then but the patient stay well without any anti-tumor treatment

<table>
<thead>
<tr>
<th>May 2020</th>
<th>Jun 2020</th>
<th>July 2020</th>
<th>Dec 2020</th>
<th>Jan 2021</th>
<th>Apr 2021</th>
<th>Sep 2021</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>5 W</td>
<td>10 W</td>
<td>30w</td>
<td>35W</td>
<td>45 W</td>
<td>71 W</td>
</tr>
<tr>
<td>PSA (ng/ml)</td>
<td>240</td>
<td>92 PSA response</td>
<td>89 PSA response</td>
<td>89 PSA response</td>
<td>74 PSA response</td>
<td>58 PSA response</td>
</tr>
<tr>
<td>Sum of Diameter of TLS(mm)</td>
<td>45</td>
<td>45</td>
<td>45</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Overall Response</td>
<td>NA</td>
<td>SD</td>
<td>SD</td>
<td>-</td>
<td>SD</td>
<td>-</td>
</tr>
</tbody>
</table>

Note: CRPC = castration-resistant prostate cancer; SD: stable disease; PSA: prostate-specific antigen; TLs: Target lesions

★Treatment Cessation
Conclusions: Preliminary Data Demonstrate Encouraging Activity across a Broad Range of Tumors with Improved Tolerability for HBM4003 vs Ipilimumab

HBM4003 is the next generation anti-CTLA-4 fully human HCAb with enhanced ADCC for \( T_{\text{reg}} \) depletion and the first HCAb under clinical development

### Novel MOA

- Selective intratumor Treg depletion been validated by both pre-clinical and clinical evidence

### 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

### Encouraging Efficacy

- 9 (out of 15) patients achieved SD with heavily pre-treated tumors
- 2 clinical response- 1 patient pre-treated by all SOCs (including PD-1) was confirmed as PR, 1 patient had PSA response with SD by RECIST
HBM4003 Outlook
The First Full Evidence Chain to Demonstrate Next Gen Treg MoA Therapeutics
THANK YOU

HBM HOLDINGS-B
02142.HK
www.harbourbiomed.com
Batoclimab: A Breakthrough Therapy for Autoimmune Diseases

Prof. Chongbo Zhao
Professor of Neurology
Huashan Hospital of Fudan University
• About 4.5% of the population has autoimmune diseases

• > 80 autoimmune diseases

• > 30 of these neuroimmunological disorders

• The nervous system can be secondarily affected due to a variety of autoimmune diseases (SLE, Sicca syndrome, etc.)
Neuroimmunology Evolution

Neuroscience and Immunology

Nervous System
- Developmental process
- Homeostasis
- Injury response

Immune System
- Developmental process
- Homeostasis
- Injury response
CNS: Not An Immunoprivilaged Site Anymore
Common Features of Neuroimmune Disorders

Gene susceptibility

- Susceptibility Gene
  - Loss of autoimmunity regulation
  - Lymphocytes that respond to autoantigens

Environmental stimulation

- Infection tissue damage inflammation
- Tissue antigen presenting cell activation
- Autoreactive lymphocytes enter tissues
- Autoreactive T/B Lymphocyte Activation
- Tissue damage: Development of autoimmune diseases

Intrinsic factors
- Gene susceptibility
  - HLA polymorphisms
  - SNPs enriched in major immune pathways
  - Genetic susceptibility of the X chromosome ? Female ↑

Extrinsic/Predisposing Factors
- Pathogen infection
  - EBV, CMV, C. jejuni, etc
- Gut bacteria
  - GDP-L-fucose synthase
- Tumor
  - Ectopic antigen
- Vitamin D

Molecular mimicry
Epitope spreading
## Neuro Immune Disease – Central Inflammatory Demyelination

<table>
<thead>
<tr>
<th>Disease/Target Antigen</th>
<th>Pathogenic autoantibody</th>
<th>Hallmark autoantibody</th>
<th>Clinical characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>MS</td>
<td>None</td>
<td>None</td>
<td>Relapsing-remitting; neurological signs and symptoms</td>
</tr>
<tr>
<td>NMOSD</td>
<td>AQP4</td>
<td>AQP4</td>
<td>Optic neuritis; transverse myelitis; area postrema syndrome</td>
</tr>
<tr>
<td>ADEM</td>
<td>~40% MOG</td>
<td>MOG</td>
<td>Acute encephalopathy; neurological symptoms and signs; optic neuritis; myelitis</td>
</tr>
<tr>
<td>MOG-AD</td>
<td>MOG</td>
<td>MOG</td>
<td>Recurrent optic neuritis; papilledema; myelitis; cranial nerve involvement</td>
</tr>
<tr>
<td>GFAP</td>
<td>GFAP</td>
<td>GFAP</td>
<td>Subacute and chronic meningitis; encephalitis; myelitis; papilledema</td>
</tr>
</tbody>
</table>

Front Neurol. 2021 Apr 14;12:664664.
### Pathogenic Antibody

<table>
<thead>
<tr>
<th>Pathogenic Antibody</th>
<th>Clinical Main Phenotype</th>
<th>Tumor Correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>NMDAR IgG1</td>
<td>Pan-encephalitis; autonomic dysfunction; extrapyramidal symptoms</td>
<td>~60%, ovarian teratoma</td>
</tr>
<tr>
<td>LGI1 IgG1, IgG4</td>
<td>Limbic encephalitis; dysmyotonia of face, shoulder and arm; hyponatremia</td>
<td>5 – 10%, thymoma</td>
</tr>
<tr>
<td>AMPAR</td>
<td><strong>Limbic</strong> encephalitis</td>
<td>&gt; 50%, cell lung cancer, thymoma, breast cancer</td>
</tr>
<tr>
<td>GABABR</td>
<td>Limbic encephalitis; cerebellar ataxia</td>
<td>&gt; 50%, small cell lung cancer</td>
</tr>
<tr>
<td>GABAAR</td>
<td>Intractable epilepsy</td>
<td>~30%, thymoma</td>
</tr>
<tr>
<td>GlyR</td>
<td>PERM; brain stem encephalitis</td>
<td></td>
</tr>
<tr>
<td>CASPR2 IgG1, IgG4</td>
<td>Limbic encephalitis; Autonomic dysfunction; Neuromyotonia; Insomnia</td>
<td>20%, thymoma</td>
</tr>
<tr>
<td>MGIuR1</td>
<td>Cerebellar ataxia; ageusia</td>
<td>~10%, Hodgkin lymphoma</td>
</tr>
<tr>
<td>MGIuR5</td>
<td>Encephalitis; epilepsy</td>
<td>&lt; 10%, lymphoma</td>
</tr>
<tr>
<td>IgLON5 IgG4</td>
<td>Sleep disorder; extrapyramidal symptoms</td>
<td></td>
</tr>
<tr>
<td>DPPX IgG1, IgG4</td>
<td>Diarrhea; encephalitis; epilepsy; PERM; cerebellar ataxia</td>
<td>&lt; 10%, lymphoma</td>
</tr>
</tbody>
</table>

Front Neurol. 2021 Apr 14;12:664664.
# Neuro Immune Disease – Peripheral Neuropathy

<table>
<thead>
<tr>
<th>Disease</th>
<th>Target antigen</th>
<th>Autoantibody</th>
<th>Clinical characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDP</td>
<td>Unknown</td>
<td>None</td>
<td>Acute peripheral neuropathy</td>
</tr>
<tr>
<td>AMAN</td>
<td>GM1, GD1a</td>
<td>GM1, GD1a</td>
<td>Motor axonal neuropathy</td>
</tr>
<tr>
<td>AMSAN</td>
<td>GalNAcGD1a, GM1, GD1a</td>
<td>GalNAcGD1a, GM1, GD1a</td>
<td>Sensorimotor axonal neuropathy</td>
</tr>
<tr>
<td>Miller-Fisher</td>
<td>GQ1b, GT1a</td>
<td>GQ1b, GT1a</td>
<td>Ophthalmoplegia; Ataxia; Loss of tendon reflexes</td>
</tr>
<tr>
<td>CIDP</td>
<td>Mostly unknown</td>
<td>Unknown</td>
<td>Chronic sensorimotor neuropathy</td>
</tr>
<tr>
<td></td>
<td>NF155</td>
<td>NF155</td>
<td>Tremor; deep sensory ataxia</td>
</tr>
<tr>
<td></td>
<td>NF186/140</td>
<td>NF186/140</td>
<td>Progressive disease course</td>
</tr>
<tr>
<td>CNTN1</td>
<td>CNTN1</td>
<td>Deep sensory ataxia; glomerulonephritis</td>
<td></td>
</tr>
<tr>
<td>Caspr1</td>
<td>Caspr1</td>
<td>Severe sensorimotor neuropathy; pain</td>
<td></td>
</tr>
<tr>
<td>MMN</td>
<td>GM1</td>
<td>GM1</td>
<td>Chronic progressive asymmetric motor neuropathy; motor block</td>
</tr>
<tr>
<td>MAG-PN</td>
<td>MAG</td>
<td>MAG</td>
<td>Deep sensory ataxia; distal muscle weakness</td>
</tr>
<tr>
<td>CANOMAD</td>
<td>GD3, GD1b, GT1b, GQ1b</td>
<td>IgM, cold agglutinin</td>
<td>Deep sensory ataxia; ophthalmoplegia</td>
</tr>
</tbody>
</table>
# Neuro Immune Disease – Neuromuscular Junction Disease

<table>
<thead>
<tr>
<th>Disease</th>
<th>Target antigen</th>
<th>Autoantibody</th>
<th>Clinical Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>MG</td>
<td>AChR</td>
<td>AChR IgG1, IgG3</td>
<td>Fluctuating skeletal muscle weakness</td>
</tr>
<tr>
<td>MuSK</td>
<td>MuSK</td>
<td>MuSK IgG4</td>
<td></td>
</tr>
<tr>
<td>LRP4</td>
<td>LRP4</td>
<td>LRP4 IgG1, IgG2</td>
<td></td>
</tr>
<tr>
<td>LEMS</td>
<td>Presynaptic membrane VGCC</td>
<td>VGCC</td>
<td>Fluctuating skeletal muscle weakness; lower limb &gt; &gt; upper limb; autonomic dysfunction; tendon reflex facilitation phenomenon</td>
</tr>
</tbody>
</table>

**Diagram:**
- APC (Adaptive) Cells
- Naive CD4 T cells
- Chronic inflammation
- TGF-β, IL-6, IL-21
- Th17
- IL-17, etc.
- Inflammatory cytokines
- BAFF, APRIL
- Anti-AChR antibody
- Synaptic vesicle
- ACh
- VGCC
- LRP4
- MUSK
- DOK7

*Front Neurol. 2021 Apr 14;12:664664.*
Clinical Practice and Unmet Medical Needs in Neuroimmune Diseases

First Generation:
Steroid/IVIg/PLEX/Immunosuppressant chemicals

Second Generation:
Immunosuppressant biologics
Anti-CD20 mAb

Next Generation:
FcRn antagonist
A more effective and differentiated treatment for autoimmune diseases
Batoclimab: A Breakthrough Therapy for IgG Mediated Autoimmune Diseases with a Portfolio-in-a-product Approach

Competitive Advantages

**Strong Efficacy**
- Strong & dose-dependent IgG reduction
- Clinical POC established across indications

**Safety**
- Full human IgG with low immunogenicity risk
- Less likely to lead to inflammation with reduced effector function
- Well tolerated, majority of AEs are mild and/or moderate

**Convenient Treatment**
- Fixed-dose subcutaneous injection
- Possible for patient self-administration
- Improved patient compliance

**Batoclimab**

![Diagram showing the mechanism of action of Batoclimab]
Batoclimab – Ph1 Study Results* (PD: Serum IgG reduction)

Significant Reduces Serum IgG Following SC or IV, Results was Published on AAO 2019

- Mean maximum IgG reduction of 78.4% from baseline at weekly SC dose of 680mg (4 doses), suggests HBM9161 is potential to be best in class product

- An average reduction in total IgG of 47% was observed following single SC dose of 765 mg

- Total IgG reduction increased with increasing doses, with a nadir at approximately 8-10 days after a single dose

* Data cut off Dec 14, 2018
Getting Specific: Targeting Fc Receptor in Myasthenia Gravis

Nature Reviews Immunology

Published: 17 August 2007

FcRn: the neonatal Fc receptor

Nature Reviews Neurology

Published: 25 March 2011

Antibody responses

FcRn – not just a modulator

Yvonne Bordon

NEUROMUSCULAR DISEASE

Getting specific: targeting Fc receptors in myasthenia gravis

Jan D. Lüemann
Myasthenia Gravis (MG) – a Prototypical Autoantibody Mediated Disease
Significant Unmet Medical Needs for Myasthenia Gravis

- **Limited efficacy with available treatments - huge unmet medical needs**
  - ~200,000 people in China affected
  - 85% MG patients progress to generalized MG
  - 20% MG patients may experience a life-threatening crisis

**First-line steroids treatment:** serious adverse reactions to long-term use
- Osteonecrosis of the femoral head
- Gastric ulcer
- Full moon face
- Cataract

**Immunosuppressants:** such as azathioprine, limited efficacy and slow onset

**IVIg/PLEX:**
- Expensive;
- limited accessory

Batoclimab is granted by NMPA "Breakthrough Therapy Designation" for MG

Poor Quality of Life of MG Patients Under Current Treatment

A snapshot of Chinese MG patients Quality of Life in a 2018 survey

34% exacerbation

47% comorbidity

41 years old

Patients experienced exacerbation within 6 months, living in fear.

47.4% patients suffer from at least one comorbid condition.

Average age of surveyed patients are 41.1 years old, the prime time of life.

Batoclimab Phase 2 Study for the Treatment of gMG: Study Design

**Key I/E criteria:**
- MGFA grade II-IVa
- MG-ADL≥6
- AChR-Ab or MUSK-Ab positive

**Target population:**
Patients on stable treatment who fail to achieve full control of MG

**Efficacy endpoints:**
- MG-ADL, QMG score improvement compared with baseline
- Primary time point: Day 43

**Safety endpoint:**
- Safety and tolerability

**Clinical pharmacological endpoints:**
- Change of anti-AChR IgG, total IgG and IgG subtypes compared with baseline
- Batoclimab PK
- Biomarkers (gene expression, serum inflammatory markers)

❖ Two interim data reviews are pre-specified when ~15 and all subjects completed efficacy endpoint assessment at the primary time point (Day 43), respectively.
❖ Because a few subjects are still in the open-label or follow-up period, this data release only includes data in the double-blind treatment period (up to Day 43).
❖ Unblinded team has been set up to review and evaluate unblinded data, including albumin, ALP, IA package.
Rapid and Robust IgG Reduction
Available Evidence Suggests that Reduced Levels of Pathogenic IgG in Patients with MG are Associated with Clinical Benefit
Batoclimab gMG Ph2 Study
- Fast, Substantial, and Persistent Clinical Improvements

**MG-ADL**
- Change from Baseline in MG-ADL ± SE
- Drug administration

**QMG**
- Change from Baseline in QMG ± SE
Durable Clinical Improvements vs Placebo

Durable Response

Proportion of subjects in the double-blind period who had improved MG-ADL score at different thresholds of 2 points or more and continued for at least 4 weeks from baseline.

Proportion of subjects in the double-blind period who had improved QMG score at different thresholds of 3 points or more and continued for at least 4 weeks from baseline.
Batoclimab: Exciting Results of Ph2 Study

- Fast, strong and sustained benefit; clinically meaningful and statistically significant
- Strong correlation between IgG level reduction and disease improvement; validating focus on IgG-mediated disorders
- International leading position and profound influence in the autoimmune neurological disorders area
- China's independent development: led by Chinese MG experts, focuses on Chinese clinical and Chinese MG patients, fully developed by China, earlier than the same class molecule development 2-3 years
- The first breakthrough therapy designated by CDE in the neuroimmune diseases area
Batoclimab: Global Publication
### Highlights of HARMONI Study – Ph3

HARMONI MRCT Ongoing: 29 sites, 144 subjects

<table>
<thead>
<tr>
<th>Event</th>
<th>Timeline</th>
</tr>
</thead>
<tbody>
<tr>
<td>First SIV</td>
<td>14th Sep 2021</td>
</tr>
<tr>
<td>First patient Screening</td>
<td>15th Sep 2021</td>
</tr>
<tr>
<td>First patient randomization</td>
<td>25th Sep 2021</td>
</tr>
<tr>
<td>Interim analysis</td>
<td>July 2022</td>
</tr>
<tr>
<td>Last patient randomization</td>
<td>Aug 2022</td>
</tr>
<tr>
<td>LPLV</td>
<td>May 2023</td>
</tr>
<tr>
<td>Date base lock</td>
<td>Jul 2023</td>
</tr>
</tbody>
</table>
Baticlimab Position in Autoimmune Disease Therapy

Autoimmune disease

- Great complicated clinical manifestations
- Huge unmet medical needs due to limited treatment options and severe side effects

Next generation of promising therapy, targeting the root cause shared across various autoimmune diseases

Provides the first clinical study evidence of anti-FcRn therapy in Chinese patients

Compelling overall efficacy and safety profile
THANK YOU

HBM HOLDINGS-B
02142.HK
www.harbourbiomed.com