A Phase Ib Study to Evaluate HMBD-001 in Combination with Docetaxel with or without Cetuximab in Participants with Advanced Squamous Non-Small Cell Lung Cancers, and HMBD-001 in Combination with Cetuximab in Participants with Advanced Squamous Cell Cancers

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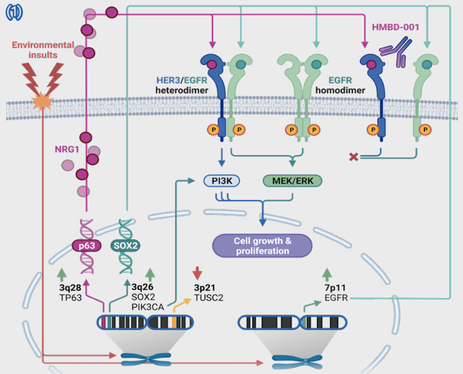
Background

Disease[1]

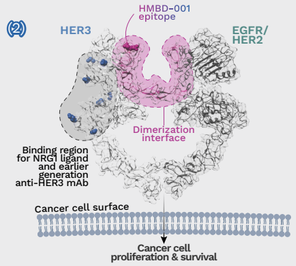
- **Squamous cell carcinomas (SCCs)** originate from epithelial tissues and have a common etiology
- **Environmental insults** lead to genetic aberrations, such as the amplification of Chr 3q and the loss of Chr 3p, which are early markers of oncogenesis in SCCs
  - ***Amplification of Chr 3q:*** Increases transcriptional activity of TP63, SOX2, and PIK3CA, promoting the expression of HER3 ligand (NRG1), EGFR ligand, and enhancing activation of the PI3K pathway, respectively
  - ***Loss of Chr 3p:*** Leads to the deletion of several putative tumor suppressor proteins, including TUSC2 (an inhibitor of EGFR)
- Additionally, **Chr 7p**, which encodes EGFR, is frequently amplified in SCCs
- In SCCs, **EGFR is frequently overexpressed**. However, monotherapy targeting EGFR may induce a **compensatory upregulation of HER3/pHER3**, subsequently activating the PI3K pathway and leading to therapeutic resistance
- Therefore, **dual inhibition of EGFR and HER3** signaling pathways may provide a more efficacious treatment strategy for SCCs

A unifying hypothesis of etiology and tumorigenesis in squamous cell carcinomas and role of anti-HER3 therapeutics[1]



HMBD-001

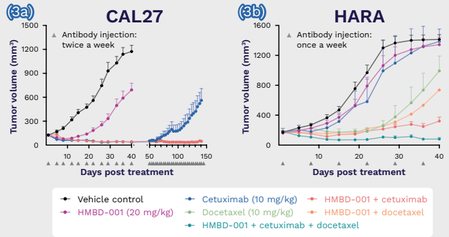
- **HMBD-001** is a differentiated and potentially best-in-class HER3-targeting antibody with a novel mechanism of action
  - HMBD-001 binds to a unique epitope on the domain II dimerization interface of HER3, **effectively blocking EGFR/HER2-HER3 heterodimerization** and potently inhibiting PI3K signaling, irrespective of ligand binding to the receptor



- HMBD-001 is also being investigated in two other clinical trials: One in the UK for patients with metastatic castration-resistant prostate cancer (mCRPC) (NCT05057013), and another in Australia for patients with HER3 signaling aberrations (NCT05919537)

Efficacy Across Tumor Models[1,2]

- Combining HMBD-001 with cetuximab shows potent and sustained anti-tumor activity in squamous models, with the addition of docetaxel further enhancing this effect



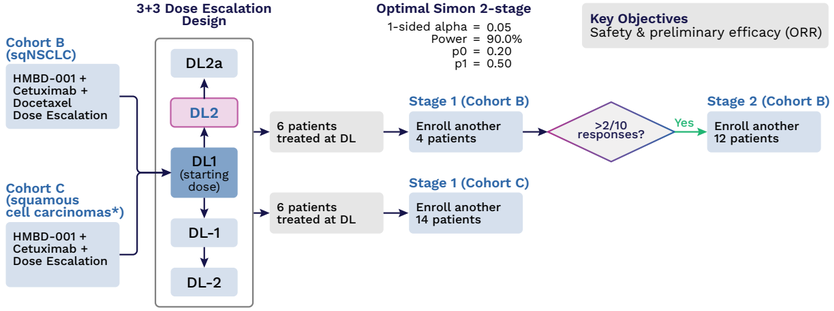
In vivo efficacy studies of HNSCC (CAL27, 3a) and sqNSCLC (HARA, 3b) squamous models treated with HMBD-001, cetuximab, docetaxel, and their combinations.

Phase Ia Safety and Efficacy

- In the Phase I dose escalation study (NCT05057013), HMBD-001 was found to be safe and well-tolerated as a monotherapy at doses up to 3,000 mg QW[3]
- Among 23 heavily pre-treated evaluable patients, the disease control rate (DCR) was 47.8%
- One patient with pancreatic ductal adenocarcinoma (PDAC) harboring an NRG1 gene fusion achieved a partial response (PR) after two cycles of HMBD-001 monotherapy. This response was durable, with the best overall tumor shrinkage reaching 61.3% after 8 cycles

Methods

Trial Design



*sqNSCLC, HNSCC, esophageal SCC, cutaneous SCC, cervical SCC

Cohort B uses an Optimal Simon 2-stage design with initial 3+3 safety lead-in to evaluate safety and efficacy of HMBD-001 with docetaxel and cetuximab in sqNSCLC

Cohort C is a pilot, signal-seeking cohort to gather preliminary safety and efficacy data on HMBD-001 and cetuximab without chemotherapy in various squamous cell carcinomas

Cohort A (HMBD-001 + docetaxel in sqNSCLC) is closed for patient enrollment

Objectives

	Cohort B (Advanced or metastatic sqNSCLC)	Cohort C (Advanced or metastatic SCCs)	Cohort A
Primary	• Safety and tolerability of HMBD-001 in combination with cetuximab and chemotherapy • Preliminary anti-tumor activity (ORR)	• Safety and tolerability of HMBD-001 in combination with cetuximab	Closed to Recruitment
Secondary	• Preliminary anti-tumor activity (DOR, DCR, PFS, OS and 1-year OS rate)	• Preliminary anti-tumor activity (ORR, DOR, DCR, PFS, OS and 1-year OS rate)	
	• Pharmacokinetic profile of HMBD-001 • Immunogenicity of HMBD-001		
Exploratory	• Pharmacodynamic effects of HMBD-001 and their correlation with benefit or resistance • Genomic analysis of HMBD-001 and correlation with benefit and resistance		

Eligibility Criteria

- At least 18 years old, or the age of majority according to local laws if the age of majority is above 18 years
- **Cohort B:** Advanced or metastatic sqNSCLC with disease progression after at least one platinum-based therapy and prior anti-PD1 or anti-PDL1 treatment. No more than two prior lines of systemic therapy for advanced disease. Prior anti-PD(L)1 treatment is not required for participants in countries where this is not standard of care
- **Cohort C:** Advanced or metastatic sqNSCLC, HNSCC, ESCC, CSCC or cervical SCC with at least one prior line of systemic therapy, and no more than three lines of prior treatment in the metastatic setting
- No prior treatment with HMBD-001, docetaxel, cetuximab, or any other EGFR or HER3 targeting agents
  - Prior treatment with docetaxel is allowed for Cohort C
- At least a lesion measurable by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1
- Eastern Cooperative Oncology Group (ECOG) performance status 0-1
- Minimum life expectancy of 3 months
- Clinically or radiologically stable brain metastases, if any, for at least 28 days prior to the first dose of study drug
- Adequate baseline organ and hematologic functions

Study Sites

Singapore
1. National Cancer Centre Singapore
2. Tan Tock Seng Hospital

Australia
3. Linear Clinical Research, WA
4. Southern Oncology Clinical Research Unit, SA
5. Cabrini Hospital, VIC
6. Peninsula & South Eastern Haematology & Oncology Group, VIC
7. Genesis Care St Leonards, NSW
8. ICON Cancer Centre, QLD

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- This study is conducted in collaboration with Merck KGaA, under a clinical trial collaboration and supply agreement for cetuximab

Clinical Trial Page

Clinical trial number: NCT05910827

A Phase 1b Study to Evaluate HMBD-001 in Combination with Docetaxel with or without Cetuximab in Participants with Advanced Squamous Non-Small Cell Lung Cancers, and HMBD-001 in Combination with Cetuximab, in Participants with Advanced Squamous Cell Cancers

clinicaltrials.gov/study/NCT05910827

References

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2. Thakkar et al., Combining anti-HER3 antibody, HMBD-001, with EGFR inhibition and chemotherapy may improve treatment outcomes in squamous NSCLC, WCLC 2023, Poster #P1.12-05.
3. De Bono et al., A CRUK Phase I/IIA, First in Human Dose-Escalation and Expansion Trial of HMBD-001 (An Anti-HER3 Antibody) in Patients with Advanced HER3 Positive Solid Tumors, ESMO 2023, Poster #FPN:687P