A HER3 antibody that uniquely blocks the HER3 heterodimerization interface effectively inhibits tumor growth in pre-clinical models with potentially oncogenic HER3 mutations

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ABSTRACT NUMBER
5796

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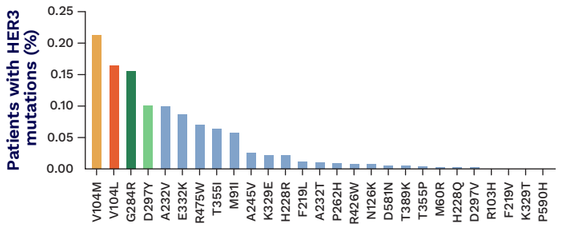
Background & rationale

- HER3 activation, via NRG1 ligand-dependent and -independent heterodimerization with HER2 or EGFR, has been associated with tumor progression and acquired resistance to therapies in multiple indications[1]
- HER3 mutations, identified in approximately 1.5% of all cancers[2], may drive oncogenic signaling, via enhanced receptor heterodimerization[3], leading to rapid tumor growth[4]
- Targeted therapy aimed at inhibiting aberrant signaling driven by HER3 mutations could offer significant clinical advantages for cancer patients harboring these mutations. However, there are currently no approved targeted therapies
- HMBD-001, a clinical-stage anti-HER3 antibody, designed to uniquely block the HER3 dimerization interface, potently inhibits HER3 heterodimerization and downstream signaling[5] and may offer a targeted treatment option for HER3 mutations

Real-world NGS data analysis identifies the extracellular domain (ECD) mutations V104M/L, G284R, and D297Y as the most prevalent HER3 mutations

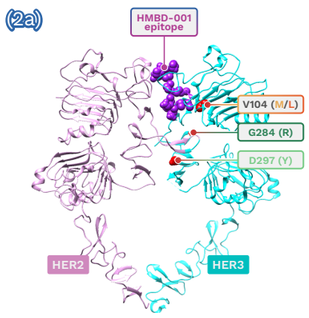
(1)



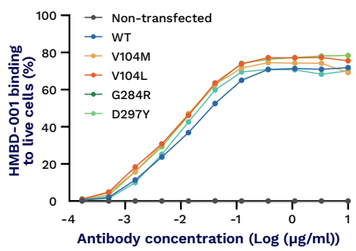
Percentage of lineage-agnostic cancer patients harboring each HER3 mutation as indicated, obtained from Caris's database. Note: HER3 mutations included in this analysis consist of mutations annotated by Caris as pathogenic/likely pathogenic and additional selected mutations annotated as Variant of Uncertain Significance (VUS) in Caris database

The four most prevalent HER3 mutations are located within the HER3 dimerization interface, suggesting a potential impact on heterodimerization, and do not overlap with the HMBD-001 binding epitope

(2a)



(2b)

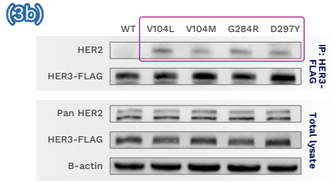


Structure of (2a) HER2-HER3 dimer. HER2 and HER3 are shown in pink and cyan respectively. Positions of the mutated residues on HER3 are represented as red balls, while HMBD-001 epitope is represented as purple balls. (2b) Binding of HMBD-001 to HER3 WT, V104L/M, G284R and D297Y mutant receptors expressed on HEK293T cells.

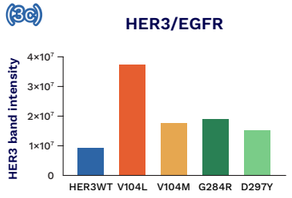
Mutant HER3 receptors, V104M/L, G284R, and D297Y, show increased heterodimerization with both HER2 and EGFR compared to wild type HER3

(3a)

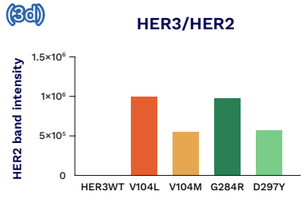
(3b)



(3c)



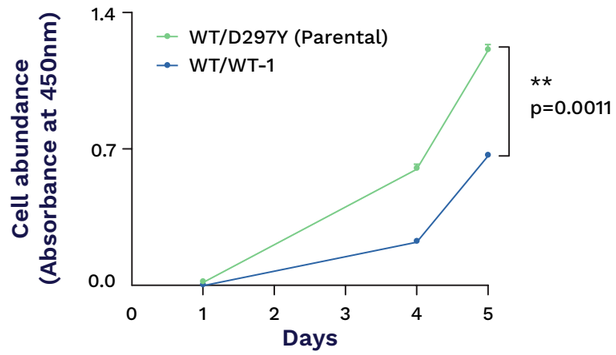
(3d)



Levels of HER3 wild type and the four selected mutant receptors dimerization with (3a) EGFR and (3b) HER2 as shown by co-immunoprecipitation in CAL27 cells with stable overexpression of HER3 wild type, V104L/M, G284R or D297Y mutant receptors in the absence of NRG1 ligand. Band intensities of (3c) HER3 and (3d) HER2 that were immunoprecipitated together with EGFR and HER3 respectively.
WT: wild type; IP: immunoprecipitation.

Conversion of an endogenous D297Y HER3 mutation, to wild type via CRISPR editing significantly reduces the growth of KYSE-150, a HER3 mutant cell line

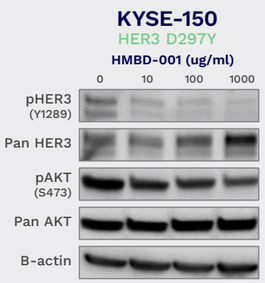
(4)



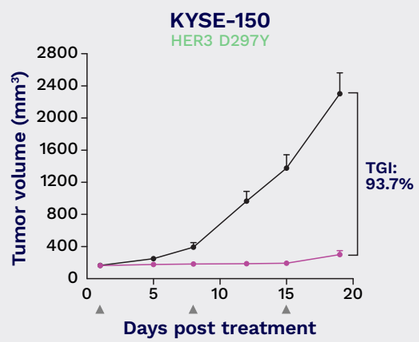
Proliferation of KYSE-150 parental (WT/D297Y) cells as compared to that of CRISPR edited homozygous WT (WT/WT-1) cells in the absence of NRG1 ligand. WT: wild type.

HMBD-001 blocks downstream signaling and significantly inhibits tumor growth in preclinical models harboring HER3 mutations

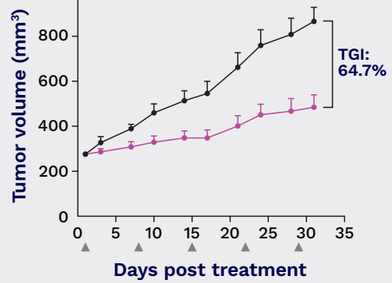
(5a)



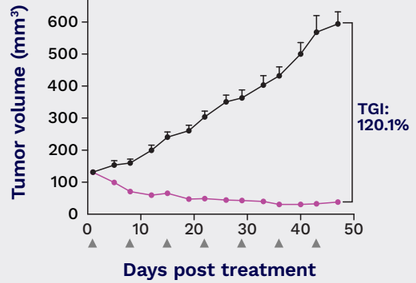
(5b)



(5c)



(5d)



(5a) Phosphorylation levels of HER3 and AKT in KYSE-150 cells upon 24 h treatment with increasing doses of HMBD-001 as indicated. In vivo efficacy studies of (5b) KYSE-150, (5c) CTG-2446, and (5d) TGBC18TKB HER3 mutant cancer xenograft models treated with HMBD-001.

Vehicle
HMBD-001: 20 mg/kg
Antibody injection: Once a week

Conclusion

- HER3 mutations are potential biomarkers for identifying patients who may respond to HMBD-001
- Real-world NGS data identifies V104M, V104L, G284R, and D297Y as the most prevalent HER3 mutations across cancers
- Structural analysis and FACS binding on HER3 mutation cell lines confirm that HER3 mutations do not alter HMBD-001 binding or its ability to block downstream signaling
- HER3 mutations (V104M, V104L, G284R, and D297Y) lead to increased heterodimer formation with EGFR and HER2, which in turn increase signaling and growth of HER3 mutant expressing cells
- In multiple cell- and patient-derived xenograft models with HER3 mutations, HMBD-001 monotherapy achieves significant tumor growth inhibition
- Phase 1b monotherapy clinical trial of HMBD-001 is currently recruiting patients with aberrant HER3 signaling (NCT05919537)

Learn more

HMBD-001 is currently in clinical trials in the UK (NCT05057013), and in Australia evaluating patients with squamous non-small cell lung cancer (NCT05910827) and patients with genetic aberrations in HER3 signaling (NCT05919537).

hummingbirdbioscience.com/hmbd-001

References

[1]Haikala HM, *et al*. Clin Cancer Res. (2021). 27(13):3528-3539.
[2]Caris RWE data (2022).
[3]Jaiswal BS, *et al*. Cancer Cell. (2013);23(5):603-617.
[4]Mishra, Rosalin *et al*. Oncology Rev. (2018). 12(1):355.
[5]Thakkar D, *et al*. Mol Cancer Ther. (2020). 19(2):490-501.