493TiP - A CRUK phase I/IIA, first in human dose-escalation and expansion trial of HMBD-001 (an anti-HER-3 antibody) in patients with advanced HER3 positive solid tumours.

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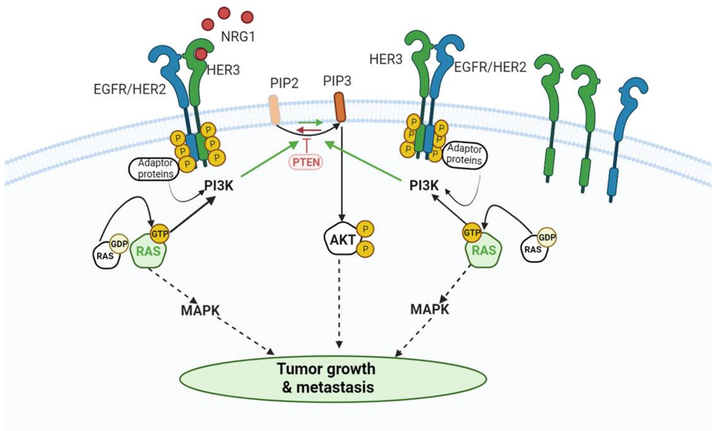
Background

- Human epidermal growth factor receptor (HER)3 is a member of the HER family of transmembrane proteins
- HER3 lacks kinase activity and must be transactivated by dimerisation with a kinase-active partner for signal transduction
- In ligand-dependent activation, NRG1 stabilises HER3 in open conformation. However, ligand-independent heterodimerisation can also occur (Figure 1)
- Overexpression of HER3 observed in multiple tumour types (HNSCC, NSCLC, breast, gastric, colorectal, prostate, ovarian, melanoma) and associated with poor clinical outcome
- HER3 activation has thus been implicated in acquired resistance to EGFR/ HER2 therapies and endocrine therapy in advanced prostate cancer, with paracrine generation of NRG1 by stromal cells including myeloid cells and fibroblasts

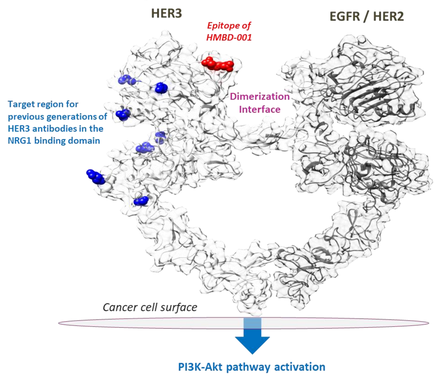
Figure 1: Key mechanisms of HER3 activation and downstream signalling



HMBD-001

- IgG1 humanised monoclonal antibody specifically targeting HER3 with a novel mechanism of action
- Binds a unique epitope on the domain II dimerisation interface of HER3 (Figure 2) in both the 'open' and 'closed' conformation
- Pharmacologically active whether HER3 activation is driven in a ligand-dependent manner by NRG1 binding or in a ligand-independent manner (commonly by overexpression of HER2 or EGFR)
- Potently inhibits the phosphorylation of HER3 and downstream signalling through the PI3K/AKT/mTOR and MAPK pathways, and tumour cell proliferation

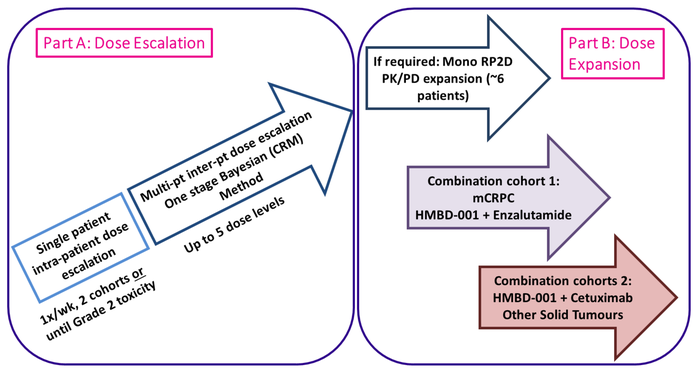
Figure 2: HMBD-001 binding to HER3



Trial Design

- First in human (FIH), open label, multi-centre, dose escalation and expansion trial will assess the safety, PK, pharmacodynamic and preliminary anti-tumour activity of HMBD-001, as a monotherapy and in combination, in subjects with HER3 expressing advanced solid tumours.
- Comprised of an initial dose-escalation phase (Part A) in advanced solid tumours resistant/refractory to conventional treatment known to overexpress HER3 or with NRG1 fusions, followed by a combination agent(s) dose escalation and dose expansion (Part B) in metastatic castration-resistant prostate cancer and other solid tumours (NCT05057013) (Figure 3)

Figure 3: Trial Design Schema



Part A of the trial consists of an initial intra-patient dose escalation stage (Figure 4), followed by an inter-patient dose escalation stage utilising a one-stage Bayesian continuous reassessment method design (see Table 1 for details of cohorts 1&2 (intra-patient) and 3-5 (inter-patient)).

Figure 4: HMBD-001 Monotherapy Dose Escalation Design Schema

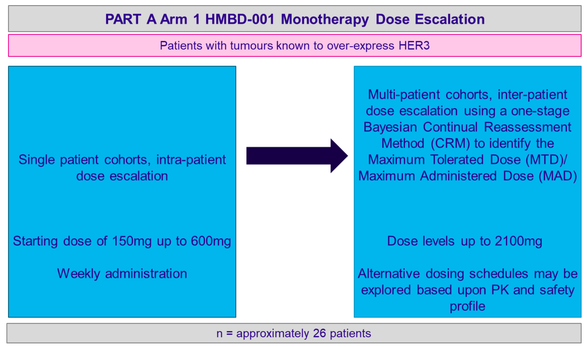


Table 1: Dosing regimens for dose escalation cohorts 1-5

Cohort	Week 1 (Day 1)	Week 2 (Day 8)	Week 3 (Day15)	Week 4 (Day 22)
Intra-Patient Dose Escalation				
1 (n=1)	150mg	150mg	300mg	300mg
2 (n=1)	300mg	300mg	600mg	600mg
3 (n=3)	600mg	600mg	600mg	600mg
4 (n=3)	1200mg	1200mg	1200mg	1200mg
5 (n=3)	1800mg	1800mg	1800mg	1800mg

Primary Objectives:

Part A Dose Escalation
- To assess the safety and tolerability profile of HMBD-001.
- To propose a recommended dose and schedule for Phase II evaluation (RP2D) of HMBD-001.

Part B Combination Dose Escalation and Dose Expansion Phase
- To propose a recommended dose and schedule for Phase II evaluation of HMBD-001 (RP2D) in combination with other anti-cancer therapies.
- To evaluate preliminary evidence of antitumour activity of HMBD-001 in the chosen expansion tumour types by determining the Overall Response Rate (ORR).

Trial Progress

- The trial began enrolling in October 2021 and is ongoing in the UK.
- Cohort 1 – 4 have been completed and cohort 5 is currently active.
- Archival tumour tissue will be retrospectively analysed, and pre- and on-treatment tumour biopsies may be collected.
- Potential predictive and pharmacodynamic biomarkers including pHER3, pERK, p70S6K, Ki67 and cleaved caspase 3 will be evaluated alongside circulating tumour biomarkers

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