HERTHENA-PanTumor01: A Global, Multicohort, Phase 2 Trial of HER3-DXd in Relapsed/Refractory Metastatic Solid Tumors

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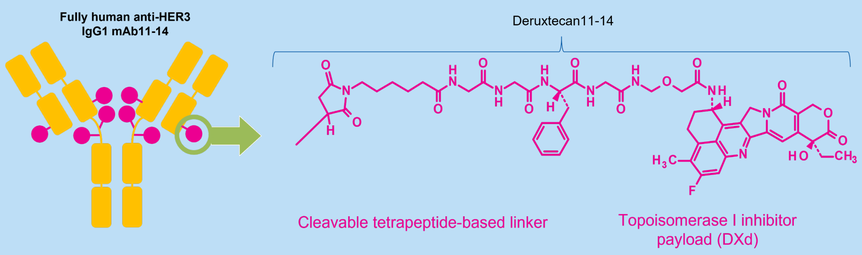
BACKGROUND

- HER3 is widely expressed in multiple solid tumors, including melanoma, gastric cancer, and head and neck cancer[1-10]
  - High HER3 expression is associated with shorter survival in patients with these cancers[2-10]
  - HER3 is highly expressed in patient-derived xenografts and human tumor specimens from HPV+ HNSCCs[10]
- Patritumab deruxtecan (HER3-DXd) is an investigational, HER3-directed ADC composed of a human IgG1 monoclonal antibody to HER3 (patritumab) covalently linked to a topoisomerase I inhibitor payload (an exatecan derivative) via a stable tetrapeptide-based cleavable linker[11-16] (**Figure 1**)
- In patients with previously treated metastatic *EGFR*-mutated NSCLC, HER3-DXd demonstrated a manageable safety profile and clinically meaningful and durable responses across a range of HER3 expression levels and mechanisms of resistance to EGFR TKI therapy[17]
  - HER3 membrane expression is increased after EGFR TKI treatment in patients with *EGFR*-mutated NSCLC[18]
- In heavily pretreated metastatic breast cancer, HER3-DXd demonstrated a manageable safety profile and durable efficacy across breast cancer subtypes and in patients with HER3-high and HER3-low tumor membrane expression[19]
- In preclinical studies, HER3-DXd demonstrated antitumor activity in models of other tumor types, including melanoma and gastric cancer[11,15]
- HERTHENA-PanTumor01 (NCT06172478) is a global, multicohort, open-label, phase 2 trial evaluating the efficacy and safety of HER3-DXd in previously treated patients with relapsed/refractory metastatic cutaneous melanoma, HER2-negative gastric cancer, or head and neck squamous cell carcinoma

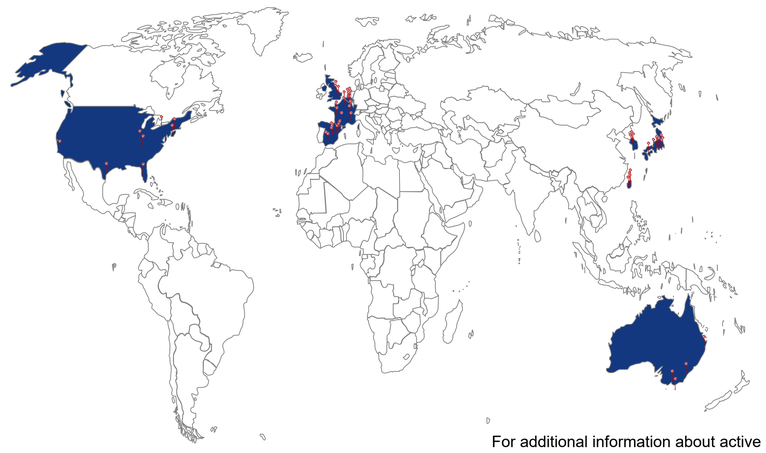
Figure 1. HER3-DXd Structure and Attributes



Payload mechanism of action: topoisomerase I inhibitor[11-14,a]
High potency of payload[11-14,a]
High drug-to-antibody ratio ≈8[11,12,a]
Payload with short systemic half-life[12,13,a,b]
Stable linker-payload[12-14,a]
Tumor-selective cleavable linker[11-15,a]
Bystander antitumor effect[12,16,a]

[a] The clinical relevance of these features is under investigation.
[b] Based on animal data.

ENROLLMENT



Enrollment sites span Asia, Australia, Europe, and the United States

Enrollment start: 26 February 2024
Estimated study completion: 30 April 2026
First patients received first dose: 25 March 2024

Location	Active sites, n
Australia	4
Belgium	4
France	8
Japan	7
Republic of Korea	4
Spain	8
Taiwan	4
United Kingdom	3
United States	8

For additional information about active study sites, please scan the QR code at the top of the poster.

METHODS

- The objective of this study is to evaluate the efficacy of HER3-DXd monotherapy in locally advanced or metastatic solid tumors previously treated with standard treatments
- Approximately 120 patients (40 patients per cohort) will be enrolled in this study (**Figure 2**)
- Study endpoints and key eligibility criteria are summarized in **Tables 1** and **2**
  - A pretreatment biopsy (or tissue collected from a biopsy since progression while on or after the previous treatment) is required for study entry
- Tumor assessments are performed at baseline and every 6 weeks (±7 days) in the first 48 weeks after cycle 1 day 1 and then every 12 weeks (±7 days) thereafter (**Figure 2**)
  - Blood samples are collected for biomarkers and pharmacokinetics
  - Healthcare resource utilization is recorded on every postbaseline visit. Optional HEOR qualitative interviews are done at baseline and at the end of cycle 4 (±7 days) or at treatment discontinuation
- All patients will be assessed by contrast-enhanced MRI[a] at baseline for any evidence of brain lesions
  - All patients with melanoma and those with gastric cancer or HNSCC with evidence of brain metastases at baseline will undergo brain imaging every 6 weeks (±7 days) for the first 48 weeks, then every 12 weeks (±14 days) until radiographic disease progression per RECIST version 1.1
  - For patients with gastric cancer or HNSCC with no evidence of brain lesions at baseline, no postbaseline imaging will be required

[a] Computed tomography with contrast is allowed if MRI is contraindicated.

STUDY DESIGN

Figure 2. HERTHENA-PanTumor01 Study Design

Common eligibility criteria
- Unresectable stage III or IV disease
- Pretreatment biopsy[a]
- No preselection based on HER3 expression; HER3 expression to be evaluated retrospectively

Melanoma (N≈40)
- Cutaneous melanoma[b]
- *BRAF* wild type or mutant
- Previously treated with ≥1 anti–PD-1 or anti–PD-L1 antibody[c]

HNSCC (N≈40)
- Primary tumor site must be in the oral cavity, oropharynx, hypopharynx, or larynx
- HPV positive or negative
- Previously treated with ≥1 and <3 lines of therapy, including PBC ± anti–PD-1 or anti–PD-L1 antibody[d]

Gastric or GEJ carcinoma (N≈40)
- HER2-negative GC/GEJC
- Previously treated with ≥2 prior lines of PBC ± anti–PD-1 antibody

HER3-DXd 5.6 mg/kg IV Q3W

Interim analysis

Treatment continues until:
- Disease progression
- TEAE leading to study drug discontinuation
- Withdrawal
- Death

Assessments
- Tumor assessments are done at baseline, every 6 weeks in the first 48 weeks after C1D1, and then every 12 weeks thereafter
- Scheduled CNS contrast-enhanced MRI[e] is done only in the melanoma cohort
  - All patients with melanoma undergo imaging at baseline, every 6 weeks in the first 48 weeks after C1D1, and then every 12 weeks thereafter
- For patients with gastric carcinoma and HNSCC, only those with evidence of inactive brain metastases at baseline have ongoing brain imaging

[a] HER3 expression is not required for inclusion. The pretreatment tumor tissue requirement may be waived if medically infeasible after discussion and agreement with the study sponsor. [b] Includes patients with acral and non-acral melanoma. [c] Other ICIs, such as anti-CTLA4 and anti-LAG3 therapies, are acceptable. If a patient has *BRAF*m melanoma, their disease must have progressed on a BRAF/MEK inhibitor as well. [d] Sequential or in combination. [e] Computed tomography with contrast is allowed if MRI is contraindicated.

STUDY ENDPOINTS

Table 1. Primary, Secondary, and Exploratory Endpoints

Primary endpoint

Objective response rate[a]

Secondary endpoints

- Safety
- Duration of response[a]
- Disease control rate[a]
- Clinical benefit rate[a]
- Time to response[a]
- Progression-free survival[a]
- Overall survival
- Pharmacokinetics
- Correlation between HER3 protein expression by IHC and efficacy

Exploratory endpoints

- Immunogenicity
- Objective response rate[b]
- Correlation between potential biomarkers (genomic alterations, gene expression, and gene signature) and efficacy
- Relationship between pharmacokinetics and exposure-response
- Healthcare resource utilization
- Intracranial efficacy of HER3-DXd in the melanoma cohort[c]

[a] By investigator per RECIST 1.1. [b] By BICR per RECIST 1.1. [c] Per CNS RECIST.

ELIGIBILITY CRITERIA

Table 2. Key Eligibility Criteria

Inclusion criteria

All patients
- Age ≥18 years (or local age of consent)
- Locally advanced unresectable or metastatic disease not curable by surgery or radiation
- ≥1 measurable lesion on CT or MRI by investigator assessment per RECIST 1.1
- Pretreatment tumor tissue sample from a biopsy taken since progression or pretreatment biopsy from ≥1 lesion not previously irradiated[a]
- ECOG PS of 0 or 1
- Adequate bone marrow reserve and organ function within 14 days prior to C1D1

Cutaneous melanoma[b]
- Histologically or cytologically confirmed melanoma[b]
- Disease progression on or after ≥1 prior line of anti–PD-1 or anti–PD-L1 therapy[c]
- *BRAF* wild type or mutant; if a patient has *BRAF*m melanoma, their disease must have progressed on a BRAF/MEK inhibitor as well

Head and neck squamous cell carcinomas
- HNSCCs that are HPV positive or negative
- Primary tumor site that arose from the oral cavity, oropharynx, hypopharynx, or larynx
- Disease progression after treatment with ≥1 and <3 lines of therapy, including PBC ± anti–PD-1 or anti–PD-L1 therapy

Gastric or GEJ carcinoma
- Confirmed HER2-negative (IHC 0/1+ or IHC 2+/ISH-negative) gastric or GEJ adenocarcinoma as classified by ASCO-CAP guidelines and determined by local assessment prior to enrollment
- Disease progression after treatment with ≥2 prior lines of therapy including PBC ± anti–PD-1 therapy

Exclusion criteria

- HER2+ gastric cancer as classified by ASCO-CAP guidelines and determined by local assessment prior to enrollment
- Nasopharyngeal cancer, nasal cavity cancer, paranasal sinus cancer, or cancer from unknown locations
- Mucosal or uveal melanoma
- History of (non-infectious) ILD/pneumonitis, current ILD/pneumonitis, or suspected ILD/pneumonitis based on imaging during screening
- Clinically severe respiratory compromise resulting from intercurrent pulmonary illnesses
- Evidence of clinically active spinal cord compression or brain metastases or any history or current evidence of leptomeningeal disease, defined as being symptomatic or untreated or requiring therapy with corticosteroids or anticonvulsants
- Prior treatment with an anti-HER3 antibody and/or ADC that consists of an exatecan derivative that is a topoisomerase I inhibitor (eg, trastuzumab deruxtecan)

[a] HER3 expression is not required for inclusion. The pretreatment tumor tissue requirement may be waived if medically infeasible after discussion and agreement with the study sponsor. [b] Includes patients with acral melanoma. [c] Previous use of other ICIs (ie, anti-CTLA4, anti-LAG-3) is acceptable. Prior anti-PD-(L)1 therapy in the adjuvant setting is allowed if there is recurrence within 12 weeks of the last dose.

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ABBREVIATIONS

ADC, antibody-drug conjugate; ASCO-CAP, American Society of Clinical Oncology–College of American Pathologists; BICR, blinded independent central review; BRAF, B-Raf proto-oncogene or its protein product; C, cycle; CNS, central nervous system; CT, computed tomography; CTLA4, cytotoxic T-lymphocyte associated protein 4; D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; GC, gastric carcinoma; GEJ, gastroesophageal junction; HEOR, health economics and outcomes research; HER3, human epidermal growth factor receptor 3; HNSCC, head and neck squamous cell carcinoma; HPV, human papillomavirus; ICI, immune checkpoint inhibitor; Ig, immunoglobulin; IHC, immunohistochemistry; ILD, interstitial lung disease; ISH, in situ hybridization; IV, intravenous; LAG3, lymphocyte activation gene 3 protein; m, mutant; mAb, monoclonal antibody; MEK, mitogen-activated protein kinase kinase; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer; ORR, objective response rate; PBC, platinum-based chemotherapy; PD-1, programmed cell death 1 protein; PD-L1, programmed cell death 1 ligand 1; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; TEAE, treatment-emergent adverse event; TKI, tyrosine kinase inhibitor.

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