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

#690TiP

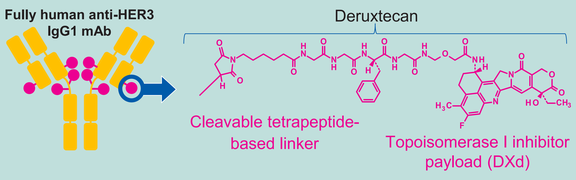
Thomas Powles,[1] Aarti Bhatia,[2] Barbara Burtness,[2] Takahiro Kogawa,[3] Tomohiro Nishina,[4] Izuma Nakayama,[5] Christos Fountzilas,[6] Dani R. Castillo,[7] Meredith McKean,[8] Funda Meric-Bernstam,[9] Nicoletta Colombo,[10] James W. Smithy,[11] Jerome Fayette,[12] Sunandana Chandra,[13] David W. Sternberg,[14] Kendall Sullivan,[14] Sue Yueh,[14] Graham Clinthorne,[14] Ragini Kudchadkar,[14] Hidetoshi Hayashi[15]

[1]Bart's Cancer Institute, Queen Mary University of London, London, UK; [2]Yale School of Medicine, Yale Cancer Center, New Haven, CT, USA; [3]The Cancer Institute Hospital of JFCR, Tokyo, Japan; [4]National Hospital Organization Shikoku Cancer Center, Ehime, Japan; [5]National Cancer Center Hospital East, Kashiwa, Japan; [6]Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA; [7]City of Hope Comprehensive Cancer Center, Duarte, CA, USA; [8]Sarah Cannon Research Institute, Nashville, TN, USA; [9]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [10]Università degli Studi di Milano-Bicocca; IEO – Istituto Europeo di Oncologia, Milan, Italy; [11]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [12]Centre Léon Bérard, Lyon, France; [13]Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Chicago, IL, USA; [14]Daiichi Sankyo, Inc, Basking Ridge, NJ, USA; [15]Kindai University Hospital, Osaka, Japan

BACKGROUND

- Patritumab deruxtecan (HER3-DXd) is an investigational, HER3-directed ADC composed of a fully human anti-HER3 IgG1 monoclonal antibody (patritumab) linked to a topoisomerase I inhibitor payload (an exatecan derivative) via a stable tetrapeptide-based cleavable linker (**Figure 1**)
- HER3-DXd has demonstrated clinically meaningful and durable efficacy in previously treated metastatic *EGFR*-mutated NSCLC and heavily pretreated advanced breast cancer across a range of baseline HER3 expression levels, with a manageable safety profile[1-3]
- HER3 expression is observed in many types of cancer, including melanoma, HNSCC, and gastric/GEJ, ovarian, cervical, endometrial, bladder, esophageal squamous cell, pancreatic, and prostate cancers (among others)[4-9]
- Expression of HER3 has been associated with poor clinical outcomes, including decreased survival, in patients with these tumor types[4-9]
- For patients with treatment-resistant solid tumors, better treatments are needed as second- and later-line therapies have demonstrated limited efficacy and durability[10-19]
- HERTHENA-PanTumor01 (NCT06172478) is an ongoing, global, multicohort, open-label, phase 2 trial assessing the efficacy and safety of HER3-DXd 5.6 mg/kg IV Q3W in relapsed/refractory melanoma, HNSCC, and gastric/GEJ, ovarian, cervical, endometrial, bladder, esophageal squamous cell, pancreatic, and prostate cancers

Figure 1. HER3-DXd Structure and Attributes



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

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

Copies of this poster obtained through this QR code and/or https://bit.ly/DS_ESMO24 are for personal use only and may not be reproduced without written permission of the authors.

Corresponding author: thomas.powles1@nhs.net

An interactive digital version of this poster, with an audio summary by Dr Thomas Powles, can be found through this QR Code.

METHODS

- The primary objective of the HERTHENA-PanTumor01 study is to evaluate the efficacy of HER3-DXd 5.6 mg/kg IV Q3W in patients with previously treated unresectable or metastatic solid tumors
- Approximately 40 patients will be enrolled into each of the 10 tumor-type cohorts (**Figure 2**)
  - Tumor types include melanoma, gastric/GEJ, head and neck, ovarian, cervical, endometrial, bladder, esophageal, pancreatic, and prostate
- Study endpoints and key eligibility criteria are summarized in **Tables 1** and **2**
  - A pretreatment biopsy from a lesion not previously irradiated (or tissue collected from a biopsy since progression while on or after the previous treatment) is required for study entry
- Tumor assessments will be performed at baseline and every 6 weeks in the first 48 weeks after cycle 1 day 1 and every 12 weeks thereafter
- All patients will be assessed by contrast-enhanced MRI at baseline for any evidence of brain lesions
  - All patients with melanoma and those with other tumor types with evidence of brain lesions 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 tumor types other than melanoma with no evidence of brain lesions at baseline, no postbaseline imaging will be required
- In the prostate cancer cohort, PSA response and symptomatic skeletal-related events will also be assessed
- Blood samples will be collected for biomarker and pharmacokinetic analyses
- Healthcare resource utilization data will be documented at every postbaseline visit. HEOR qualitative interviews are optional and done at baseline, the end of cycle 4, or treatment discontinuation

ENDPOINTS

Table 1. HERTHENA-PanTumor01 Endpoints

Primary Endpoints

- Confirmed objective response rate[a]
- Prostate cohort only: PSA50 response rate[b]

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
- Prostate cohort only
  - Radiographic progression-free survival[c]
  - PSA30 response rate[d]
  - Time to first subsequent anticancer therapy
  - Time to first symptomatic skeletal-related event

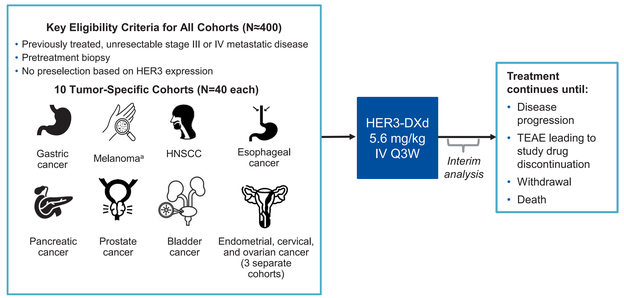
Exploratory Endpoints

- Immunogenicity
- Objective response rate[e]
- Correlation between potential biomarkers (genomic alterations, gene expression, and gene signature, and imaging) and efficacy
- Relationship between pharmacokinetics and exposure response
- Healthcare resource utilization
- Melanoma cohort only: intracranial response (ORR, DOR, DCR) by BICR per CNS-RECIST

[a] By investigator per RECIST 1.1. [b] Defined as the proportion of patients achieving a ≥50% decrease in PSA from baseline to the lowest postbaseline PSA result, confirmed by a consecutive PSA assessment ≥3 weeks later. [c] Per PCWG3 criteria. [d] Defined as the proportion of patients achieving a ≥30% decrease in PSA from baseline to the lowest postbaseline PSA result, confirmed by a consecutive PSA assessment ≥3 weeks later. [e] By BICR per RECIST 1.1 in select cohorts (at sponsor's discretion).

STUDY DESIGN

Figure 2. HERTHENA-PanTumor01 Study Design



[a] Cutaneous, including acral melanoma.

STUDY SITES

Enrollment Sites in Asia, Australia, Europe, and the United States

Enrollment start: 26 February 2024
Estimated study completion: 30 April 2026
First patients received first dose: 29 March 2024

Location	Sites, n
Australia	5
Belgium	5
France	8
Japan	9
Republic of Korea	6
Spain	9
Taiwan	5
United Kingdom	4
United States	10

For additional information about active study sites, please scan the QR code for the digital interactive poster at the bottom of this poster.

KEY 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[a]
- Pretreatment tumor tissue sample from a biopsy taken since progression or pretreatment biopsy from ≥1 lesion not previously irradiated[b]
- ECOG PS of 0 or 1
- Adequate bone marrow reserve and organ function within 14 days prior to C1D1

Cutaneous melanoma
- Histologically or cytologically confirmed cutaneous (acral or nonacral) melanoma
- Disease progression on or after ≥1 prior line of anti–PD-1 or anti–PD-L1 therapy[c]
- *BRAF* wild type or mutant; if patient has *BRAF*-mutant melanoma, they must have had disease progression on a BRAF/MEK inhibitor

Head and neck squamous cell carcinomas
- HNSCCs that are HPV positive or negative
- Primary tumor site must have arisen initially from the oral cavity, oropharynx, hypopharynx, or larynx
- Disease progression after 1 to 3 lines of systemic therapy, including ≥1 line of anti–PD-(L)1 therapy (alone or in combination) and PBC

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 prior to enrollment by local assessment
- Disease progression after ≥2 prior lines of systemic treatment that included PBC ± anti–PD-1 therapy

Ovarian carcinoma
- Pathologically documented high-grade serous epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer
- Documented disease progression ≥4 weeks after the last dose of PBC and <6 months after the last dose of PBC in the advanced or metastatic setting[d]

Cervical cancer
- Pathologically or cytologically documented recurrent or persistent squamous or adenosquamous carcinoma or adenocarcinoma of the uterine cervix
- Disease progression after ≥1 line of systemic therapy in the recurrent or metastatic setting. This may include prior anti–PD-(L)1 treatment and/or tissue factor–directed ADC (tisotumab vedotin) per regional standard of care

Endometrial cancer
- Pathologically or cytologically documented endometrial cancer, irrespective of MSI or mismatch repair status
- Documented disease progression after 1 to 3 prior lines of PBC-containing systemic treatment and an anti–PD(L)-1 therapy–containing regimen (in combination or sequentially)

Bladder cancer
- Unresectable or metastatic urothelial carcinoma of the bladder, renal pelvis, ureter, or urethra; small cell/neuroendocrine tumors are not allowed even if mixed histology
- Disease relapse or progression on 1 to 3 prior lines of systemic therapy, with ≥1 line of an anti–PD-(L)1 treatment with chemotherapy or enfortumab vedotin (sequentially or in combination)[e]

Esophageal carcinoma
- Pathologically or cytologically documented esophageal squamous cell carcinoma
- Must have documented disease progression after having received 2 prior lines of therapy, including previous PBC ± an anti–PD-1 therapy–containing regimen (in combination or sequentially)

Pancreatic carcinoma
- Pathologically or cytologically documented pancreatic adenocarcinoma
- Relapsed or had disease progression after having received 1 prior line of systemic therapy in the locally advanced/metastatic setting

Prostate cancer
- Castration-resistant adenocarcinoma of the prostate without neuroendocrine differentiation or small cell histology
- Surgically or medically castrated, with testosterone levels of <50 ng/dL
- Relapsed or had disease progression after having received treatment with ≥1 of the following novel hormonal agents: abiraterone, enzalutamide, apalutamide, or darolutamide and ≥1 cytotoxic chemotherapy regimen that included a taxane

Exclusion Criteria
- HER2+ gastric cancer as classified by ASCO-CAP guidelines and determined by local assessment prior to enrollment
- Nasopharyngeal cancer
- Mucosal or uveal melanoma
- History of ILD/pneumonitis that has required corticosteroids, current ILD, or suspected ILD based on imaging during screening
- Clinically severe respiratory compromise resulting from intercurrent pulmonary illnesses
- Use of chronic systemic corticosteroids >10 mg/day (prednisone or equivalent)
- 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)
- Previous treatment with irinotecan in the advanced or metastatic setting

[a] Patients with prostate cancer with bone-only disease may be eligible. [b] HER3 expression not required for inclusion. The pretreatment tumor tissue requirement may be waived (if medically infeasible) after discussion and agreement with the study sponsor. [c] Other ICIs, such as anti-CTLA4 and anti-LAG3 therapies, are acceptable. [d] Prior use of folate reductase alpha–targeting ADC is allowed. [e] Prior FGFR inhibitor treatment is allowed.

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, serine/threonine kinase; C1D1, cycle 1 day 1; CNS, central nervous system; CT, computed tomography; CTLA4, cytotoxic T-lymphocyte associated antigen 4; DCR, disease control rate; DOR, duration of response; DXd, topoisomerase I inhibitor payload (an exatecan derivative); ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; FGFR, fibroblast growth factor receptor; GEJ, gastroesophageal junction; HEOR, health economics and outcomes research; HER, human epidermal growth factor receptor; HNSCC, head and neck squamous cell carcinoma; HPV, human papillomavirus; ICI, immune checkpoint inhibitor; IgG1, immunoglobulin G1; IHC, immunohistochemistry; ILD, interstitial lung disease; ISH, in situ hybridization; IV, intravenous; LAG3, lymphocyte activation gene 3 protein; mAb, monoclonal antibody; MEK, mitogen-activated protein kinase kinase; MRI, magnetic resonance imaging; MSI, microsatellite instability; NSCLC, non-small cell lung cancer; ORR, objective response rate; PBC, platinum-based chemotherapy; PCWG3, Prostate Cancer Working Group 3; PD-1, programmed cell death 1 protein; PD-(L)1, programmed cell death 1 (ligand 1); PD-L1, programmed cell death 1 ligand 1; PSA, prostate-specific antigen; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; TEAE, treatment-emergent adverse event.

ACKNOWLEDGEMENTS

- We thank the patients, their families, and their caregivers for their participation
- We also thank the clinical investigators and study members for their contributions
- This study is sponsored by Daiichi Sankyo, Inc
- Medical writing support was provided by Erinn Gideons, PhD, CMPP (Nucleus Global, an Inizio company), and was funded by Daiichi Sankyo Company, Limited and Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. Editorial support was provided in accordance with Good Publication Practice guidelines (ismpp.org/gpp-2022)

DISCLOSURES

TP reports advisory board frees for AstraZeneca, Bristol Myers Squibb, Exelixis, Incyte, Ipsen, Merck, Novartis, Pfizer, Seattle Genetics, Merck Serono, Astellas, Johnson & Johnson, Eisai, Roche, and MSD; travel awards from Roche, Pfizer, MSD, AstraZeneca, Ipsen; sponsor from Mashup; honoraria from Gilead; institutional research grant awards from AstraZeneca, Roche, Bristol Myers Squibb, Exelixis, Ipsen, Merck, MSD, Seattle Genetics, Novartis, Pfizer, Merck Serono, Astellas, Johnson & Johnson, Eisai; institutional honoraria from Gilead.

REFERENCES

1. Yu HA, et al. *J Clin Oncol*. 2023;41(35):5363-5375.
2. Yu HA, et al. *Ann Oncol*. 2024;35(5):437-447.
3. Krop IE, et al. *J Clin Oncol*. 2023;41(36):5550-5560.
4. Inaki K, et al. *PLoS One*. 2022;17(9):e0274140.
5. Ocana A, et al. *J Natl Cancer Inst*. 2013;105(4):266-273.
6. Li Q, et al. *Oncotarget*. 2017;8(40):67140-67151.
7. Shteinman ER, et al. *Pathology*. 2023;55(5):629-636.
8. Kojima Y, et al. *Cancer Cell Int*. 2023;23(1):18.
9. Wang Y, et al. *Oncotarget*. 2015;6(40):42868-42878.
10. Safyan RA, et al. *Am Soc Clin Oncol Educ Book*. 2024;44(3):e438598.
11. Arance A, et al. *J Clin Oncol*. 2023;41(1):75-85.
12. Goldinger SM, et al. *Eur J Cancer*. 2022;162:22-33.
13. Shitara K, et al. *Lancet Oncol*. 2018;19(11):1437-1448.
14. Johnson DE, et al. *Nat Rev Dis Primers*. 2020;6(1):92.
15. Sambasivan S. *Cancer Treat Res Commun*. 2022;33:100629.
16. Ang DJM, Chan JJ. *J Gynecol Oncol*. 2024;35(2):e65.
17. Rubinstein M, et al. *Gynecol Oncol*. 2022;167(3):540-546.
18. Jones RJ, et al. *Br J Cancer*. 2024;130(6):897-907.
19. Gao T-T, et al. *BMC Cancer*. 2022;22(1):992.

Presented at: ESMO Congress 2024; 13-17 September 2024; Barcelona, Spain, and virtual. Poster 690TiP.