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DiscovHER PAN-206: Phase 2 Tumour-Agnostic Study of Zanidatamab in Patients With Previously Treated Human Epidermal Growth Factor Receptor 2–Overexpressing Solid Tumours

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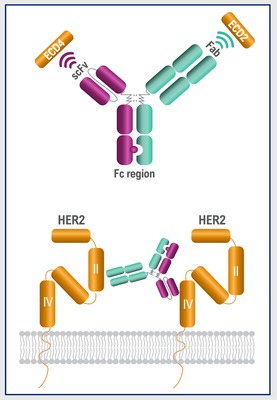
Background

- Human epidermal growth factor receptor 2 (HER2) overexpression and/or amplification is observed across many solid tumour types,[1] making tissue-agnostic evaluation of HER2-targeted therapy a valuable strategy for assessing potential clinical benefit in HER2-expressing cancers that are too rare to study individually[2-4]
- While trastuzumab deruxtecan (T-DXd) has a tissue-agnostic indication for previously treated patients with advanced HER2-positive (immunohistochemistry [IHC] 3+) solid tumours, its use may be limited by a safety profile that includes a risk for interstitial lung disease[2,5,6]
- There is an ongoing need for new, effective, and well-tolerated therapies that target HER2-expressing solid tumours

Zanidatamab Structure and Targeted Binding



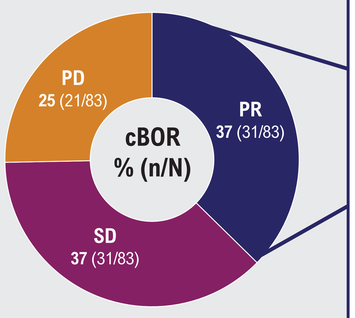
ECD, extracellular domain; Fab, fragment antigen-binding; Fc, fragment crystallisable; HER2, human epidermal growth factor receptor 2; scFv, single chain variable fragment.

- Zanidatamab is a dual HER2-targeted bispecific antibody that binds to 2 distinct sites on HER2, promoting HER2 receptor crosslinking and driving multiple antitumour mechanisms of action, including[7]:
  - Facilitation of HER2 internalisation and subsequent degradation
  - Reduction of HER2 cell surface expression and inhibition of HER2 signalling pathways
  - Activation of immune-mediated effects (complement-dependent cytotoxicity as well as antibody-dependent cellular cytotoxicity and phagocytosis)
- Zanidatamab received US Food and Drug Administration accelerated approval for previously treated, unresectable, or metastatic HER2-positive (IHC 3+) biliary tract cancer (BTC) and conditional authorisations in the EU and China based on the phase 2 HERIZON-BTC-01 trial (confirmed objective response rate [cORR], 52%)[8-11]

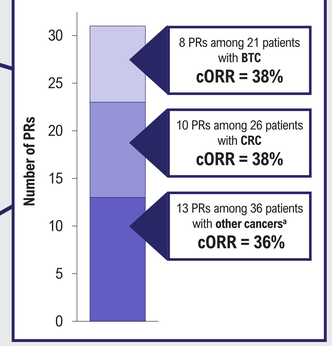
Tissue-Agnostic Activity of Zanidatamab

- In a first-in-human phase 1 study of heavily pretreated patients with HER2-expressing (IHC 3+, 2+ or 1+) or *HER2*-amplified (fluorescence in situ hybridization-positive) solid tumours, zanidatamab demonstrated promising antitumour activity and manageable safety across multiple tumour types, including BTC (cORR, 38%), colorectal cancer (cORR, 38%), and a mixed group of other cancers (cORR, 36%)[12]
  - The similar efficacy across tumour types supports a tissue-agnostic approach for the ongoing clinical development of zanidatamab

FIH Phase 1 Study



Overall cORR = 37% (31/83)

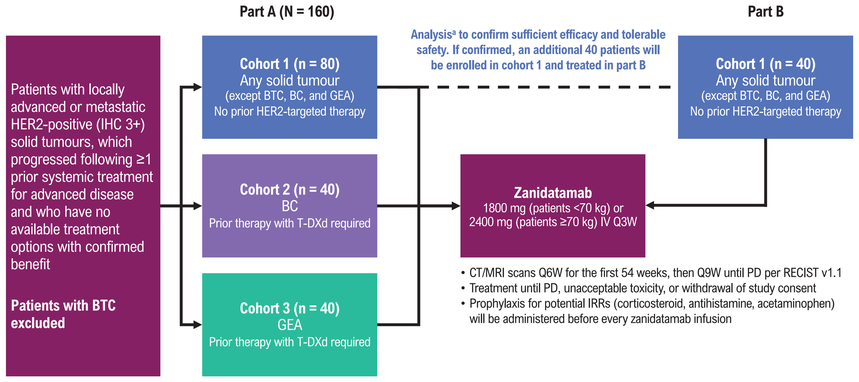


Data from Meric-Bernstam F, et al. *Lancet Oncol*. 2022;23(12):1558-70.

[a]Other cancer types: ampullary, bladder, duodenum, endometrial, fallopian tube, hepatocellular carcinoma, lacrimal gland, non-small cell lung, ovarian, pancreatic, parotid gland, salivary gland, small bowel, vulval, and cancer of unknown origin.

BTC, biliary tract cancer; cBOR, confirmed best overall response; cORR, confirmed objective response rate; CRC, colorectal cancer; FIH, first-in-human; PD, progressive disease; PR, partial response; SD, stable disease.

DiscovHER PAN-206 Study Design



[a]Two interim analyses will be performed in this study. The first and second interim analyses will take place approximately 3 months after 25 and 50 patients have been treated in cohort 1, respectively. During these analyses, the study may continue enrolling patients.
BC, breast cancer; BTC, biliary tract cancer; CT, computed tomography; GEA, gastro-oesophageal adenocarcinoma; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; IRR, infusion-related reaction; IV, intravenously; MRI, magnetic resonance imaging; PD, progressive disease; Q3W, every 3 weeks; Q6W, every 6 weeks; Q9W, every 9 weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1; T-DXd, trastuzumab deruxtecan.

- DiscovHER PAN-206 (NCT06695845) is an ongoing, open-label, single-arm, multicentre, phase 2 study evaluating the efficacy and safety of zanidatamab in patients with previously treated HER2-positive (IHC 3+) locally advanced, unresectable, or metastatic solid tumours (except BTC)

Select DiscovHER PAN-206 Study Endpoints

Primary Endpoint

- cORR per RECIST v1.1 as assessed by ICR
  - The proportion of patients with a best overall response of CR or PR

Select Secondary Endpoints

- cORR per RECIST v1.1 as assessed by the investigator
- Duration of response per RECIST v1.1 as assessed by ICR and by the investigator
- Time to response as assessed by ICR and by the investigator
- Disease control rate as assessed by ICR and by the investigator
- Progression-free survival as assessed by ICR and by the investigator
- Overall survival
- Safety and tolerability as assessed by the frequency of TEAEs, SAEs, dose reductions, and treatment discontinuations as well as patient-reported impact of treatment toxicity

cORR, confirmed objective response rate; CR, complete response; ICR, independent central review; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

- Responses will be evaluated by cohort and tumour type
- Time-to-event measurements will be summarised using Kaplan-Meier estimates

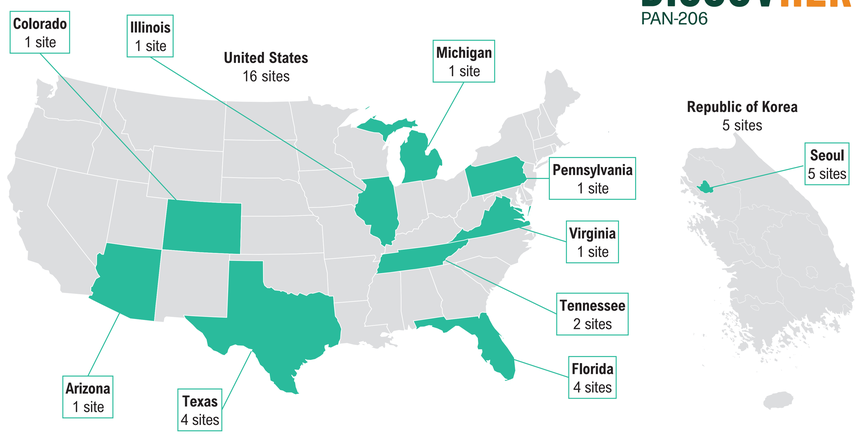
Key Eligibility Criteria for DiscovHER PAN-206

✓ Inclusion Criteria	✗ Exclusion Criteria
• Aged ≥18 years at the time of signing the informed consent	• Cohort 1: prior HER2-targeted therapy
• Locally advanced, unresectable, or metastatic solid tumours (except BTC, defined as gallbladder cancer or cholangiocarcinoma) that progressed following ≥1 prior systemic treatment for metastatic or advanced disease and have no available treatment options with confirmed benefit	• Prior treatment with zanidatamab
• Cohorts 2 (BC) and 3 (GEA): prior therapy with T-DXd is required	• Prior treatment with systemic antineoplastic therapy, including hormonal therapies for BC, or any investigational therapy within 4 weeks or 5 half-lives (whichever is longer) before cycle 1 day 1, except in the case of antibody-based anticancer therapy, which requires ≥4 weeks of washout
• HER2 IHC 3+ status, determined by a designated central laboratory	• Known or suspected leptomeningeal disease and/or untreated brain metastasis
• Adequate tumour sample to submit for central HER2 testing	• Uncontrolled or significant cardiovascular disease
• Presence of ≥1 measurable lesion as assessed by ICR based on RECIST v1.1	• Ongoing toxicity related to prior cancer therapy
• ECOG PS of 0 or 1	• History of life-threatening hypersensitivity to monoclonal antibodies or to recombinant proteins or excipients in the drug formulation of zanidatamab
• Life expectancy ≥3 months per the investigator's opinion	• CRC with known *KRAS*/*NRAS* and *BRAF* mutations
	• NSCLC with known *ALK* and *EGFR* mutations and *ROS1* fusion

ALK, anaplastic lymphoma kinase; BC, breast cancer; *BRAF*, v-raf murine sarcoma viral oncogene homolog B; BTC, biliary tract cancer; CRC, colorectal cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; *EGFR*, epidermal growth factor receptor; GEA, gastro-oesophageal adenocarcinoma; HER2, human epidermal growth factor receptor 2; ICR, independent central review; IHC, immunohistochemistry; *KRAS*, KRAS proto-oncogene, GTPase; *NRAS*, NRAS proto-oncogene, GTPase; NSCLC, non-small cell lung cancer; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1; *ROS1*, ROS proto-oncogene 1; T-DXd, trastuzumab deruxtecan.

DiscovHER PAN-206 Study Status

Pan Tumor Cancer Study
DISCOVHER
PAN-206



- This trial is actively enrolling patients at multiple sites in the US and the Republic of Korea, with plans to potentially expand recruitment to additional countries across Europe

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Support and Acknowledgements: This trial is funded by Jazz Pharmaceuticals. Under the direction of the authors, Marita Chakhtoura, MS, PhD, of Red Nucleus (Yardley, PA, USA), provided medical writing and editorial support, which was funded by Jazz Pharmaceuticals, in accordance with Good Publication Practice (GPP 2022) guidelines (https://www.ismpp.org/gpp-2022). Jazz Pharmaceuticals also reviewed and edited the poster for scientific accuracy. The authors would like to thank all of the study investigators, study staff, nursing team, and patients for their participation in this research.
Disclosures: Vivek Subbiah has served in a consulting or advisory role for AbbVie, Bayer HealthCare Pharmaceuticals, Illumina, Incyte Corporation, Jazz Pharmaceuticals, LabCorp, Regeneron Pharmaceuticals, Relay Therapeutics, and Roche; has received support for other professional activities from Aadi Biosciences, Clinical Care Communications, Illumina, Jazz Pharmaceuticals, Med Learning Group, Medscape, and Phenon Therapeutics; received grants/contracts from AbbVie, AgenSys, Alfa-Sigma, Altulin, Amgen, Bayer HealthCare Pharmaceuticals, Berghealth, Blueprint Medicines, Boston Biomedical, Boston Pharmaceuticals, Celgene Corporation, Dragonfly Therapeutics, Exelixis, FUJIFILM Medical Systems USA, Genentech USA, GlaxoSmithKline, Idera Pharma, Incyte Corporation, Inhibrx, LOXO Oncology, MedImmune, Multivir, Nanocarrier, the National Cancer Institute; the National Comprehensive Cancer Network, Novartis Pharma, OncLive, Oncusp, PERS, Pfizer, PharmaMar, Relay Therapeutics, Roche, and Takeda Oncology; and has received travel accommodations and expenses from the American Society of Clinical Oncology, the European Society of Medical Oncology, Helsinn Healthcare SA, and Incyte Corporation outside the submitted work.

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Poster presented at the 2025 ESMO Congress; 17–21 October 2025; Berlin, Germany and Online