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Medical Oncologists for  
Cancer Patients

# HERTHENA-PanTumor01: Expansion of a Global Phase 2 Trial of HER3-DXd in Patients With Advanced/Metastatic Solid Tumors

Izuma Nakayama,<sup>1</sup> Takahiro Kogawa,<sup>2</sup> Tomohiro Nishina,<sup>3</sup> Thomas Powles,<sup>4</sup> Jin Won Kim,<sup>5</sup> Yen-Yang Chen,<sup>6</sup> Francois Ghiringhelli,<sup>7</sup> Thorsten Goetze,<sup>8</sup> Mariette Labots,<sup>9</sup> Valentina Gambardella,<sup>10</sup> Oliver Bechter,<sup>11</sup> Christos Fountzilas,<sup>12</sup> Dani R. Castillo,<sup>13</sup> Meredith McKean,<sup>14</sup> Funda Meric-Bernstam,<sup>15</sup> James W. Smithy,<sup>16</sup> Jérôme Fayette,<sup>17</sup> Fan Jin,<sup>18</sup> Y. K. Chang,<sup>19</sup> Kendall Sullivan,<sup>19</sup> Sue Yueh,<sup>19</sup> Andrea Sporchia,<sup>19</sup> Ragini Kudchadkar,<sup>19</sup> **Hidetoshi Hayashi**<sup>20</sup>

## Hidetoshi Hayashi

<sup>1</sup>Department of Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan; <sup>2</sup>Early Clinical Development Division, The Cancer Institute Hospital of JFCR, Tokyo, Japan; <sup>3</sup>Gastrointestinal Medical Oncology, National Hospital Organization Shikoku Cancer Center, Ehime, Japan; <sup>4</sup>Oncology Department, Barts Cancer Institute, Queen Mary University of London, London, UK; <sup>5</sup>Seoul National University Bundang Hospital, Seongnam, South Korea; <sup>6</sup>Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan; <sup>7</sup>Centre Georges-François Leclerc, Dijon, France; <sup>8</sup>Frankfurt Institute of Clinical Cancer Research, University Cancer Center Frankfurt-Marburg, Frankfurt, Germany; <sup>9</sup>Cancer Center Amsterdam, Amsterdam UMC location, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands; <sup>10</sup>INCLIVA Health Research Institute, Valencia, Spain; <sup>11</sup>Department of General Medical Oncology, University Hospitals Leuven, Leuven, Belgium; <sup>12</sup>Department of Medicine, Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA; <sup>13</sup>Medical Oncology, City of Hope Comprehensive Cancer Center, Duarte, CA, USA; <sup>14</sup>Drug Development Unit, Sarah Cannon Research Institute, Nashville, TN, USA; <sup>15</sup>Investigational Cancer Therapeutics Department, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; <sup>16</sup>Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA; <sup>17</sup>Medicine Department, Centre Léon Bérard, Lyon, France; <sup>18</sup>Merck & Co., Inc., North Wales, PA, USA; <sup>19</sup>Daiichi Sankyo, Inc, Basking Ridge, NJ, USA; <sup>20</sup>Medical Oncology, Kindai University Hospital, Osaka, Japan



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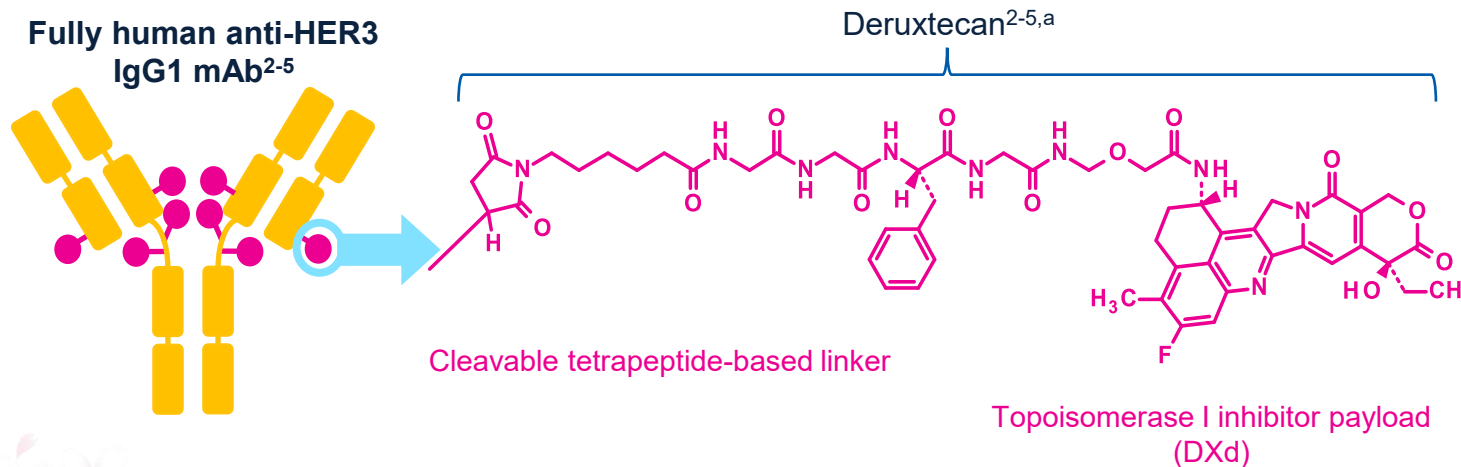


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# Background

- Increased expression of human epidermal growth factor receptor 3 (HER3), a key member of the HER/EGFR family of receptor tyrosine kinases, is recognized as a **driver of poor clinical outcomes across multiple types of solid tumors**<sup>1</sup>
- **HER3-DXd is an antibody-drug conjugate** composed of a human anti-HER3 monoclonal antibody linked to a topoisomerase I inhibitor payload via a stable tetrapeptide-based, tumor-selective, cleavable linker<sup>2-4</sup>



## The 7 Key Attributes of HER3-DXd

- The mAb directs the DXd ADC to the tumor cell**
1. High drug-to-antibody ratio of  $\approx 8^{4,5,b}$
- The linker binds the mAb to the payload**
2. Plasma-stable linker-payload<sup>2-5,b</sup>
  3. Tumor-selective cleavable linker<sup>2-6,b</sup>
- The payload induces cell death when delivered to the tumor**
4. Topoisomerase I inhibitor<sup>2-5,b</sup>
  5. High potency<sup>2-5,b</sup>
  6. Short systemic half-life<sup>2,3,b,c</sup>
  7. Bystander antitumor effect<sup>4,7,b</sup>

ADC, antibody-drug conjugate; DXd, topoisomerase I inhibitor payload (an exatecan derivative); EGFR, epidermal growth factor receptor; HER, human epidermal growth factor receptor; IgG, immunoglobulin G; mAb, monoclonal antibody.

<sup>a</sup> The clinical relevance of these features is under investigation. <sup>b</sup> Refers to the linker and payload. <sup>c</sup> Based on animal data.

1. Inaki K, et al. *PLoS One*. 2022;17(9):e0274140.
2. Nakada T, et al. *Chem Pharm Bull (Tokyo)*. 2019;67(3):173-185.
3. Ogitani Y, et al. *Clin Cancer Res*. 2016;22(20):5097-5108.
4. Koganemaru S, et al. *Mol Cancer Ther*. 2019;18(11):2043-2050.
5. Hashimoto Y, et al. *Clin Cancer Res*. 2019;25(23):7151-7161.
6. Haratani K, et al. *J Clin Invest*. 2020;130(1):374-388.
7. Ogitani Y, et al. *Cancer Sci*. 2016;107(7):1039-1046.

# Background (cont)



**HER3-DXd has demonstrated clinically meaningful activity and a manageable safety profile** in a number of cancer types, including NSCLC and early and metastatic breast cancer, across a range of HER3 expression levels<sup>1-4</sup>



Preclinical models, including those of melanoma and gastric cancer, have demonstrated antitumor activity of HER3-DXd<sup>5,6</sup>



HERTHENA-PanTumor01 is a global, multicohort, open-label, single-arm, phase 2 trial evaluating the efficacy and safety of HER3-DXd in previously treated patients with advanced solid tumors<sup>7,8</sup>



Ten solid tumor-specific cohorts have previously been described (n≈400 patients)<sup>7,8</sup>; here we describe 3 additional expansion cohorts (n≈340 patients):

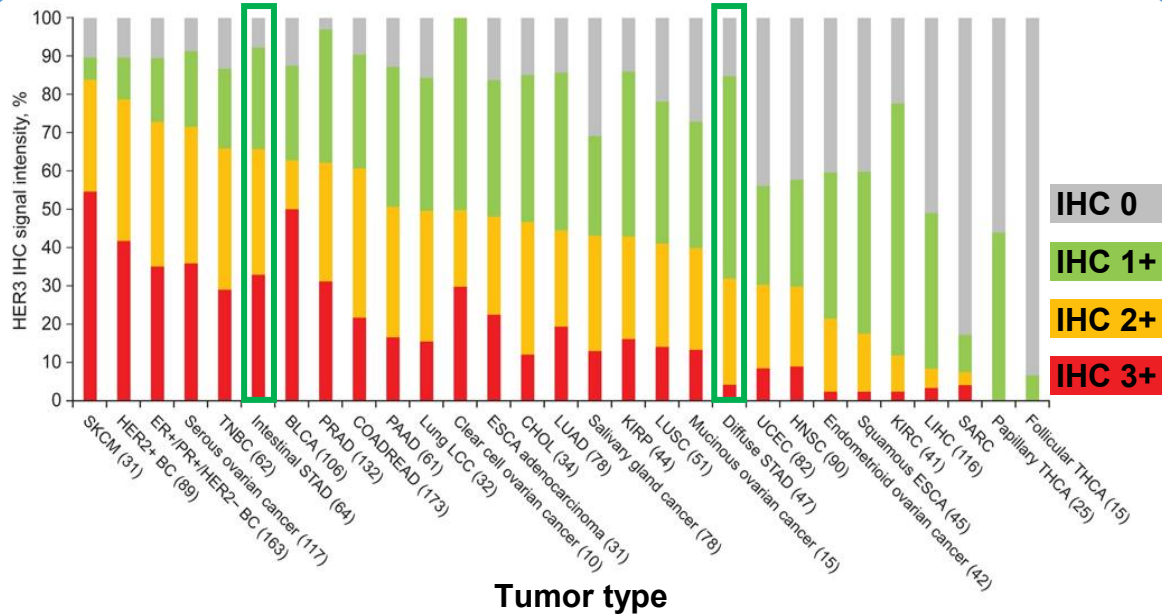
- 2L gastric cancer<sup>a</sup>
- HR+/HER2- breast cancer
- Non-AGA NSCLC<sup>b</sup>

2L, second line; 5-FU, 5-fluorouracil; AGA, actionable genomic alteration; HER, human epidermal growth factor receptor; HR, hormone receptor; NSCLC, non-small cell lung cancer; PBC, platinum-based chemotherapy; PD-1, programmed cell death 1 protein.

<sup>a</sup> The expansion 2L gastric cancer cohort varies from the prior gastric cancer cohort in the accepted prior therapies for inclusion. The prior gastric cancer cohort included patients with ≥2 prior therapies, including PBC ± anti-PD-1 therapy, whereas the expansion 2L gastric cancer cohort included only patients with 1 prior therapy comprising 5-FU chemotherapy ± anti-PD-1 therapy. <sup>b</sup> Documented absence of an actionable driver mutation.

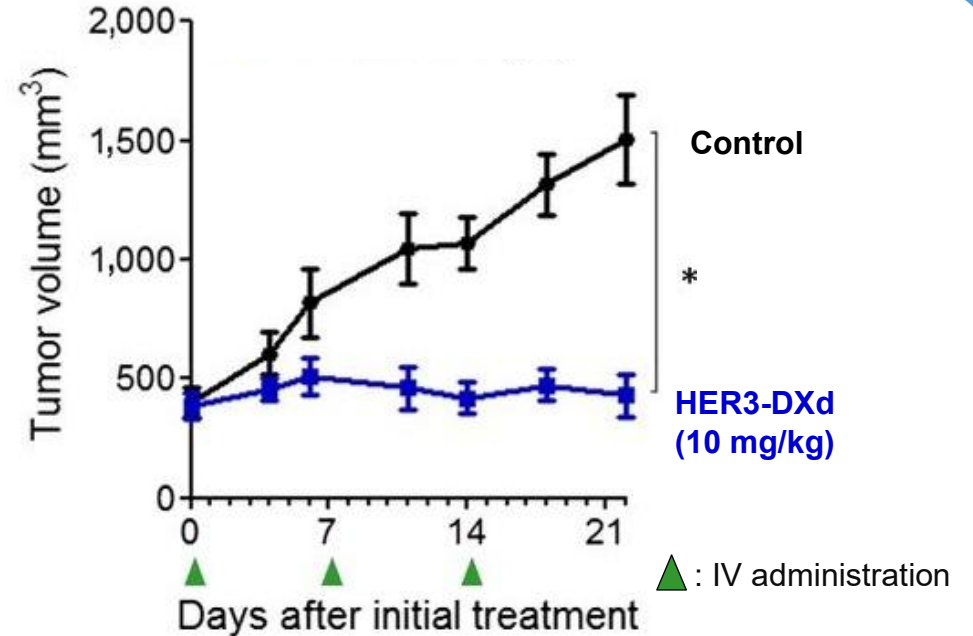
1. Yu HA, et al. *J Clin Oncol*. 2023;41(35):5363-5375. 2. Krop IE, et al. *J Clin Oncol*. 2023;41(36):5550-5560. 3. Pistilli B, et al. *Nat Med*. 2025;31(10):3492-3503. 4. Brasó-Maristany F. *Nat Commun*. 2024;15(1):5826. 5. Hashimoto Y, et al. *Clin Cancer Res*. 2019;25(23):7151-7161. 6. Haratani K, et al. *J Clin Invest*. 2020;130(1):374-388. 7. Bhatia AK, et al. *J Clin Oncol*. 2024;42(16 suppl). Abstract TPS3164. 8. Powles T, et al. ESMO 2024. Poster 690TIP.

# Background: HER3-DXd in Gastric Cancer



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HER3 protein expression was observed in tumor samples from patients with GEJ cancer (STAD; green outlines)<sup>1</sup>



Hashimoto Y, et al. Clin Cancer Res. 2019; 25 (23): 7159. Copyright © 2019, American Association for Cancer Research

Tumor shrinkage was observed following HER3-DXd administration in a PDX murine model of gastric cancer<sup>2</sup>



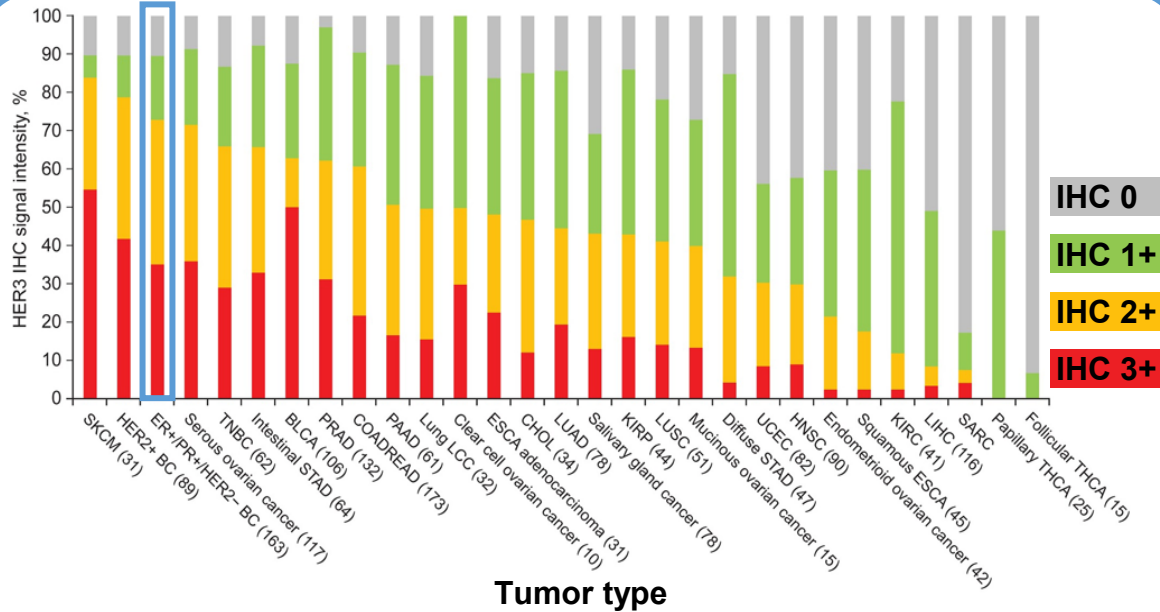
**HERTHENA-PanTumor01 will evaluate the efficacy and safety of HER3-DXd in patients with gastric cancer who have received only 1 prior therapy, consisting of 5-FU chemotherapy ± anti-PD-1 therapy<sup>a</sup>**

2L, second line; 5-FU, 5-fluorouracil; BC, breast cancer; BLCA, bladder cancer; CHOL, cholangiocarcinoma; COADREAD, colon adenocarcinoma and rectal adenocarcinoma; ER, estrogen receptor; ESCA, esophageal carcinoma; GEJ, gastroesophageal junction; HER, human epidermal growth factor receptor; HNSC, head and neck squamous cell; IHC, immunohistochemistry; IV, intravenous; KIRC, kidney renal clear cell carcinoma; KIRP, kidney renal papillary cell carcinoma; LCC, large cell carcinoma; LIHC, liver hepatocellular carcinoma; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; PAAD, pancreatic adenocarcinoma; PD-1, programmed cell death 1 protein; PDX, patient-derived xenograft; PR, progesterone receptor; PRAD, prostate adenocarcinoma; SARC, sarcoma; SKCM, skin cutaneous melanoma; STAD, stomach adenocarcinoma; THCA, thyroid cancer; TNBC, triple-negative breast cancer; UCEC, uterine corpus endometrial carcinoma.

<sup>a</sup> Statistically significant difference compared with the control ( $P < .01$ ), analyzed using a Student *t* test. <sup>a</sup> The prior gastric cancer cohort included patients with  $\geq 2$  prior therapies, including PBC ± anti-PD-1 therapy, whereas the expansion 2L gastric cancer cohort included only patients with 1 prior therapy comprising 5-FU chemotherapy ± anti-PD-1 therapy.

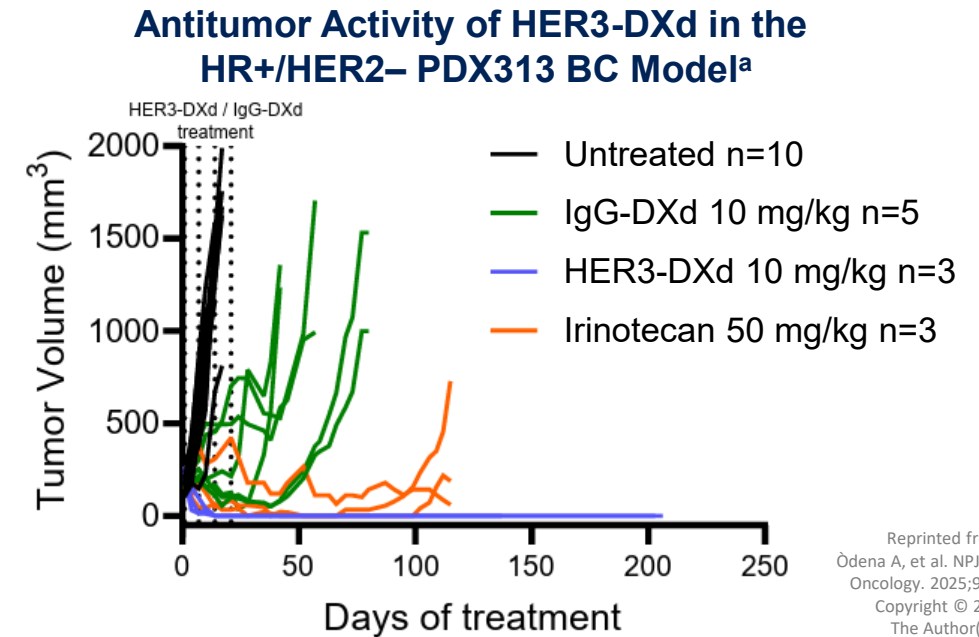
1. Inaki K, et al. PLoS One. 2022;17(9):e0274140. 2. Hashimoto Y, et al. Clin Cancer Res. 2019;25(23):7151-7161.

# Background: HER3-DXd in Breast Cancer



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HER3 protein expression was also observed in tumor samples from patients with HR+/HER2- BC (blue outline)<sup>1</sup>



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- HER3-DXd showed antitumor activity in multiple xenograft models of BC<sup>2</sup>
- Activity was seen across baseline HER3 levels,<sup>3</sup> in both the presence and absence of HER2 expression<sup>4</sup>

## HER3 is expressed in BC, and HER3-DXd demonstrated antitumor activity in preclinical models

BC, breast cancer; BLCA, bladder cancer; CHOL, cholangiocarcinoma; COADREAD, colon adenocarcinoma and rectal adenocarcinoma; ER, estrogen receptor; ESCA, esophageal carcinoma; HER, human epidermal growth factor receptor; HR, hormone receptor; HNSC, head and neck squamous cell; HNSCC, head and neck squamous cell carcinoma; IHC, immunohistochemistry; KIRC, kidney renal clear cell carcinoma; KIRP, kidney renal papillary cell carcinoma; LCC, large cell carcinoma; LIHC, liver hepatocellular carcinoma; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; PAAD, pancreatic adenocarcinoma; PDX, patient-derived xenograft; PR, progesterone receptor; PRAD, prostate adenocarcinoma; SARC, sarcoma; SKCM, skin cutaneous melanoma; THCA, thyroid cancer; TNBC, triple-negative breast cancer; UCEC, uterine corpus endometrial carcinoma.

<sup>a</sup> The PDX313 xenograft model is a HR+/HER2- model, with HER3 IHC membrane positivity <25%. Similar antitumor activity was observed in a number of PDX models with ≥75% HER3 IHC membrane positivity.

1. Inaki K, et al. *PLOS One*. 2022;17(9):e0274140. 2. Hashimoto Y, et al. *Clin Cancer Res*. 2019;25(23):7151-7161. 3. Ödena A, et al. *NPJ Prec Oncol*. 2025;9(1):393. 4. Koyama K, et al. *Cancer Res*. 2020;80(16 suppl). Abstract 5201.

# Background: HER3-DXd in Breast Cancer (cont)

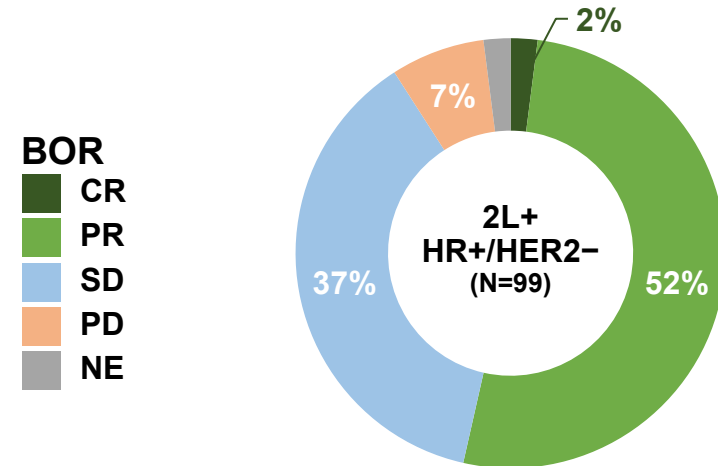
The 5.6-mg/kg Q3W regimen of HER3-DXd has consistently demonstrated a **manageable and tolerable safety profile**<sup>1-6</sup>

ICARUS-Breast01: **Clinical activity was observed** in HR+/HER2- mBC following progression on CDK4/6 inhibitors, **across baseline HER3 expression levels**<sup>1</sup>

- cORR of 53.5% (90% CI, 44.8%-62.1%)
- mPFS of 9.2 months (95% CI, 8.0-12.8 months)
- Positive trend seen between HER3-enriched populations and PFS

Clinical activity was also observed in other trials of HER3-DXd in mBC (U31402-A-J101<sup>a</sup> and BRE-354<sup>b</sup>) as well as early-stage BC (SOLTI VALENTINE and SOLTI TOT-HER3)<sup>2-6</sup>

## Efficacy Data From the Phase 1 ICARUS-Breast01 Trial of HER3-DXd in mBC<sup>1</sup>



mPFS (95% CI), months: **9.2 (8.0-12.8)**



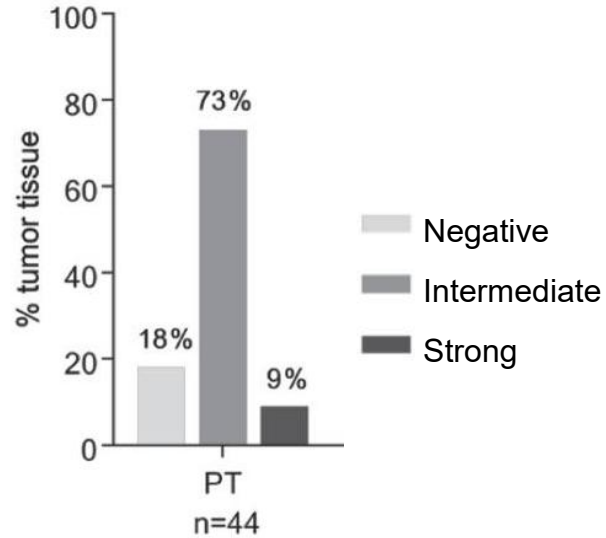
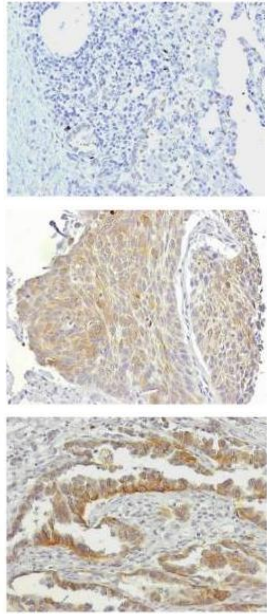
**In HERTHENA-PanTumor01, a larger, global mBC patient population will expand on these findings and help to identify subpopulations of responders to HER3-DXd**

2L+, second line and later; BC, breast cancer; BOR, best overall response; CDK4/6, cyclin-dependent kinase 4/6; cORR, confirmed objective response rate; CR, complete response; HER, human epidermal growth factor receptor; HR, hormone receptor; mBC, metastatic breast cancer; mPFS, median progression-free survival; NE, not evaluable; PD, progressive disease; PR, partial response; Q3W, every 3 weeks; SD, stable disease; TNBC, triple-negative breast cancer.

<sup>a</sup> The U31402-A-J101 study is a phase 1/2 trial in patients with HER3+ mBC. <sup>b</sup> The BRE-354 study is a phase 2 trial in patients with TNBC, HR+/HER2-, or HER2+ mBC.

1. Pistilli B, et al. *Nat Med*. 2025;31:3492-3503. 2. Krop IE, et al. *J Clin Oncol*. 2023;41(36):5550-5560. 3. Hamilton EP, et al. *J Clin Oncol*. 2023;41(16 suppl). Abstract 1004. 4. Oliveira M, et al. SABCS 2024. Abstract LB1-06. 5. Villacampa G, et al. ESMO BC 2025. Poster 195P. 6. Oliveira M, et al. ESMO BC 2023. Abstract 124O.

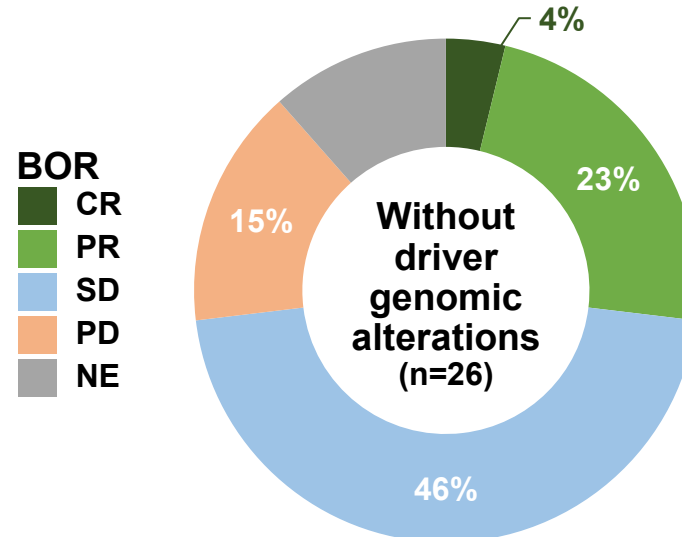
# Background: HER3-DXd in Lung Cancer



Reprinted from Scharpenseel H, et al. *Scientific Reports*. 2019;9(1):7406. Creative Commons Attribution 4.0 International License (<https://creativecommons.org/licenses/by/4.0/>). Representative HER3 staining of negative (top), intermediate (middle), and strong (bottom) expression is shown.

HER3 is commonly expressed in NSCLC tissue<sup>1</sup>

## Efficacy Data From Patients With NSCLC Without Driver Genomic Alterations From Cohort 2 of the U31402-A-U102 Trial<sup>2</sup>



mPFS (95% CI), months: 4.2 (2.5-10.8)  
mOS (95% CI), months: 15.2 (5.5-NE)

Promising **efficacy results** were observed in patients with no **AGAs** in the **phase I U102 trial** (cORR, 26.9% [95% CI, 11.6%-47.8%])

Responses were durable (mDOR, 4.2 months) and the safety profile was manageable, consistent with previous reports

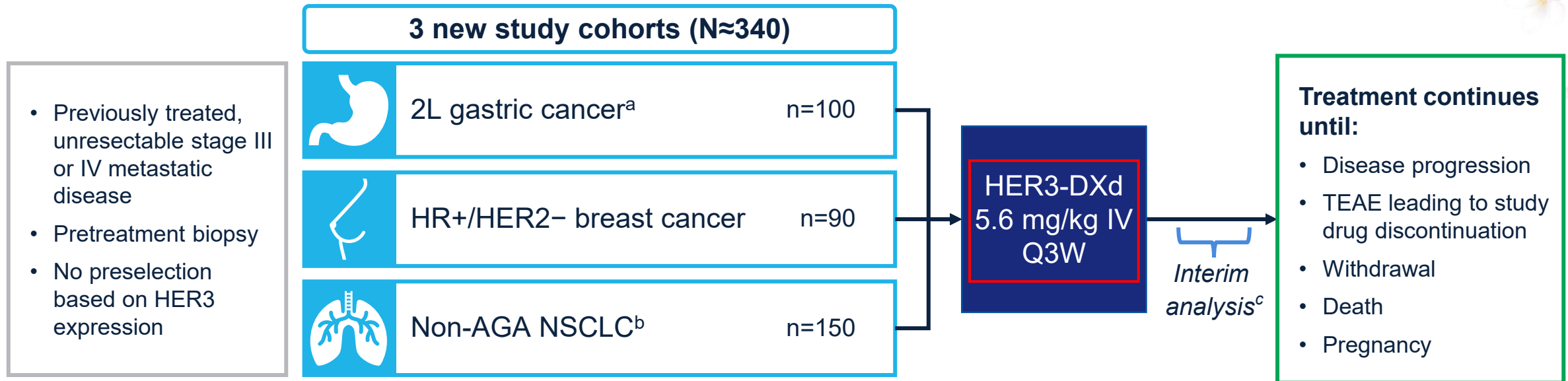


**HERTHENA-PanTumor01 will evaluate HER3-DXd in patients with NSCLC without AGAs**

AGA, actionable genomic alteration; BOR, best overall response; cORR, confirmed objective response rate; CR, complete response; HER3, human epidermal growth factor receptor 3; mDOR, median duration of response; mOS, median overall survival; mPFS, median progression-free survival; NE, not evaluable; NSCLC, non-small cell lung cancer; PD, progressive disease; PR, partial response; SD, stable disease.

1. Scharpenseel H, et al. *Sci Rep*. 2019;9:7406. 2. Steuer CE, et al. *J Clin Oncol*. 2025;43(25):2816-2826.

# HERTHENA-PanTumor01 (NCT06172478): Study Design



- Tumor assessments will occur Q6W ( $\pm 7$  days) for the first 48 weeks, then Q12W ( $\pm 14$  days) thereafter

2L, second line; 5-FU, 5-fluorouracil; AGA, actionable genomic alteration; HER, human epidermal growth factor receptor; HR, hormone receptor; IV, intravenous; NSCLC, non-small cell lung cancer; PBC, platinum-based chemotherapy; PD-1, programmed cell death 1 protein; Q3W, every 3 weeks; Q6W, every 6 weeks; Q12W, every 12 weeks; TEAE, treatment-emergent adverse event.




<sup>a</sup> The expansion 2L gastric cancer cohort varies from the prior gastric cancer cohort in the accepted prior therapies for inclusion. The prior gastric cancer cohort included patients with  $\geq 2$  prior therapies, including PBC  $\pm$  anti-PD-1 therapy, whereas the expansion 2L gastric cancer cohort included only patients with 1 prior therapy comprising 5-FU chemotherapy  $\pm$  anti-PD-1 therapy. <sup>b</sup> Documented absence of an actionable driver mutation.

<sup>c</sup> For the 2L gastric and NSCLC cohorts, a nonbinding interim futility analysis will be performed when  $\approx 30$  patients have had  $\geq 12$  weeks of follow-up from study drug administration. An interim analysis is not planned for the breast cancer cohort, as the ICARUS-Breast01 study has already demonstrated preliminary proof of concept.<sup>1</sup>

1. Pistilli B, et al. *Nat Med*. 2025;31(10):3492-3503.

# Key Eligibility Criteria

## Inclusion criteria

<b>All cohorts</b>	<ul style="list-style-type: none"> <li>Age ≥18 years</li> <li>Locally advanced unresectable or metastatic disease (not curable by surgery or radiation)</li> <li>≥1 measurable lesion<sup>a</sup> (per RECIST version 1.1)</li> </ul>	<ul style="list-style-type: none"> <li><b>Pretreatment tumor tissue sample</b> containing ≥100 viable tumor cells<sup>b</sup></li> <li>ECOG PS of 0 or 1</li> <li>Adequate bone marrow reserve and organ function</li> </ul>
 <b>2L gastric cancer</b>	<ul style="list-style-type: none"> <li><b>HER2-negative</b> tumor tissue (IHC 0/1+ or IHC 2+/ISH negative)<sup>c,d</sup></li> </ul>	<ul style="list-style-type: none"> <li>Disease progression following <b>only 1 prior line of systemic therapy<sup>e</sup></b> including 5-FU-based chemotherapy ± anti-PD-(L)1 therapy</li> </ul>
 <b>Breast cancer</b>	<ul style="list-style-type: none"> <li>Pathologically documented <b>HER2-negative</b> (IHC 0/1+ or IHC 2+/ISH negative) and <b>HR-positive expression<sup>c</sup></b></li> </ul>	<ul style="list-style-type: none"> <li><b>Only 1 prior line of chemotherapy</b></li> <li>Tumor progression on or after CDK4/6i + endocrine therapy</li> </ul>
 <b>NSCLC</b>	<ul style="list-style-type: none"> <li><b>Advanced nonsquamous NSCLC with the absence of AGAs</b></li> </ul>	<ul style="list-style-type: none"> <li>Relapse or disease progression following <b>only 1 prior PBC ± anti-PD-(L)1</b> for metastatic disease</li> </ul>

## Exclusion criteria

<b>All cohorts</b>	<ul style="list-style-type: none"> <li>HER2+ (IHC 3+ or IHC 2+/ISH positive) gastric cancer,<sup>c</sup> nasopharyngeal cancer, or mucosal or uveal melanoma</li> <li>History of ILD/pneumonitis that required corticosteroids or current or suspected ILD/pneumonitis</li> <li>Clinically severe respiratory compromise resulting from intercurrent pulmonary illnesses</li> </ul>	<ul style="list-style-type: none"> <li>Clinically active spinal cord compression or brain metastases or any history or current evidence of LMD<sup>f</sup></li> <li><b>Prior treatment with an anti-HER3 antibody</b> and/or ADC that consists of a <b>topoisomerase I inhibitor</b></li> <li><b>Prior treatment with a topoisomerase I inhibitor</b> in the advanced or metastatic setting</li> </ul>
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2L, second line; 5-FU, 5-fluorouracil; ADC, antibody-drug conjugate; AGA, actionable genomic alteration; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; HER, human epidermal growth factor receptor; HR, hormone receptor; IHC, immunohistochemistry; ILD, interstitial lung disease; ISH, in situ hybridization; LMD, leptomeningeal disease; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer; PBC, platinum-based chemotherapy; PD-(L)1, programmed cell death 1 (ligand 1); RECIST, Response Evaluation Criteria in Solid Tumors.

<sup>a</sup> On CT or MRI by investigator assessment. <sup>b</sup> From a biopsy taken since progression or a pretreatment biopsy from ≥1 lesion not previously irradiated. <sup>c</sup> As classified by American Society of Clinical Oncology–College of American Pathologists guidelines. <sup>d</sup> As determined prior to enrollment by assessment in a local laboratory that is Clinical Laboratory Improvement Amendments certified (US sites) or accredited based on specific country regulations. <sup>e</sup> For patients whose tumors are claudin (CLDN) 18.2 positive, treatment with 5-FU-based chemotherapy with CLDN18.2-directed therapy in the first-line setting is allowed. <sup>f</sup> Defined as being symptomatic or untreated or requiring therapy with corticosteroids or anticonvulsants.

# Study Endpoints

## Primary endpoints

- ORR as assessed by investigator per RECIST 1.1

## Secondary endpoints

- Safety and tolerability
- CBR,<sup>a</sup> DOR, DCR, TTR, and PFS as assessed by investigator per RECIST 1.1
- OS
- PK
- **Correlation between HER3 protein expression by IHC and efficacy**

## Exploratory endpoints

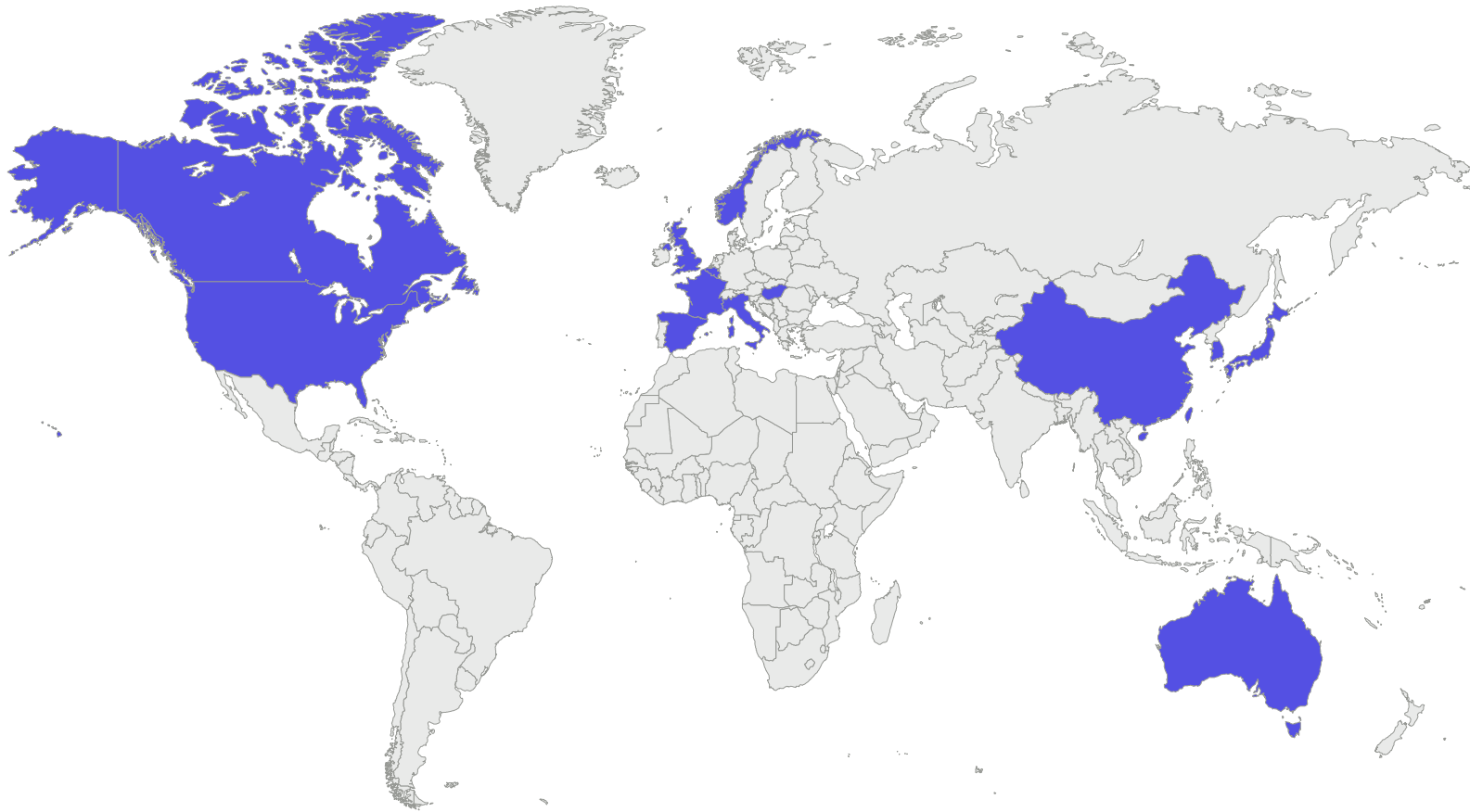
- Immunogenicity
- ORR by BICR per RECIST 1.1
- Correlation between potential biomarkers
- Relationship between pharmacokinetics and exposure response
- NSCLC cohort: intracranial response (ORR, DOR, DCR) by BICR per CNS RECIST

BICR, blinded independent central review; CBR, clinical benefit rate; CNS, central nervous system; DCR, disease control rate; DOR, duration of response; HER3, human epidermal growth factor receptor 3; IHC, immunohistochemistry; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; RECIST, Response Evaluation Criteria in Solid Tumors; TTR, time to response.

<sup>a</sup> Defined as the proportion of patients with a best overall response of confirmed complete response, confirmed partial response, or stable disease lasting  $\geq 183$  days.

# Enrollment Status

- Across the whole HERTHENA-PanTumor01 study, a total of  $\approx 740$  patients are planned to be enrolled in sites spanning North America, Europe, East Asia, and Australasia



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- Funding for this study was provided by Daiichi Sankyo Company, Limited, and Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA
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