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Valemetostat and T-DXd for HER2-Low, Previously Treated, Unresectable or Metastatic Breast Cancer

Yoichi Naito,[1] Sara M. Tolaney,[2] Senthil Damodaran,[3] Funda Meric-Bernstam,[3] Shanu Modi,[4] Avani Mohapatra,[5] Yuka Iko,[6] Siwen He,[5] Keiko Nakajima,[5] Naoto T. Ueno[7]

[1]National Cancer Center East, Chiba, Japan; [2]Dana-Farber Cancer Institute, Boston, MA, US; [3]MD Anderson Cancer Center, Houston, TX, US; [4]Memorial Sloan Kettering Cancer Center, New York, NY, US; [5]Daiichi Sankyo Inc., Basking Ridge, NJ, US; [6]Daiichi Sankyo Co. Ltd., Tokyo, Japan; [7]University of Hawai'i Cancer Center, Honolulu, HI, US

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Presenting Author Conflict OF Interest Self－Declaration Form

Presenting Author Name Yoichi Naito

	Applicability	If applicable, company name, etc..
(1) Position as an officer or advisor	No	
(2) Ownership of stock	No	
(3) Royalties or licensing fees	No	
(4) Honoraria, etc.	Yes	AstraZeneca, Eisai, Ono, Guardant, Takeda, Eli Lilly, Novartis, Pfizer, Chugai, PDR pharma, Nihon Kayaku, Taiho, Bristol, Bayer, Daiichi Sankyo, MSD, Gilead
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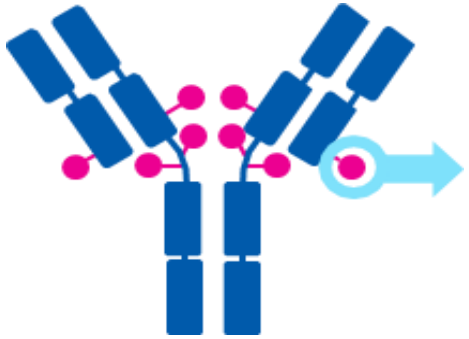
(10) Endowed course	No	
(11) Other remuneration	No	

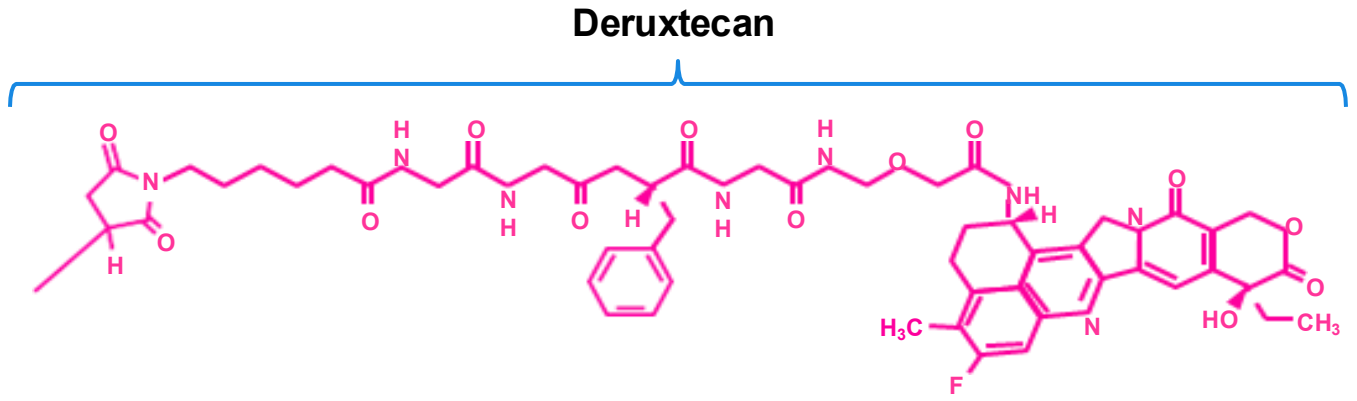
Background

- **Trastuzumab deruxtecan** (T-DXd) is an antibody-drug conjugate (ADC) composed of 3 parts: [1–3]
  - A humanized anti-human epidermal growth factor receptor 2 (HER2) immunoglobulin G1 (IgG1) monoclonal antibody (mAb) with the same amino acid sequence as trastuzumab
  - A topoisomerase I inhibitor payload (an exatecan derivative, DXd)
  - A tetrapeptide-based cleavable linker that covalently bonds the other 2 components
- The released DXd payload enters the cell nucleus and inhibits topoisomerase I, which can induce DNA damage and tumor cell apoptosis [1,2]

Humanized anti-HER2 IgG1 mAB



Deruxtecan



Cleavable tetrapeptide-based linker

Topoisomerase I inhibitor payload (DXd)

CH_3, trimethyl group

1. Nakada T, et al. *Chem Pharm Bull (Tokyo)* 2019;67:173–185. 2. Ogitani Y, et al. *Clin Cancer Res* 2016;22:5097–5108. 3. Ogitani Y, et al. *Cancer Sci* 2016;107:1039–1046.

Background

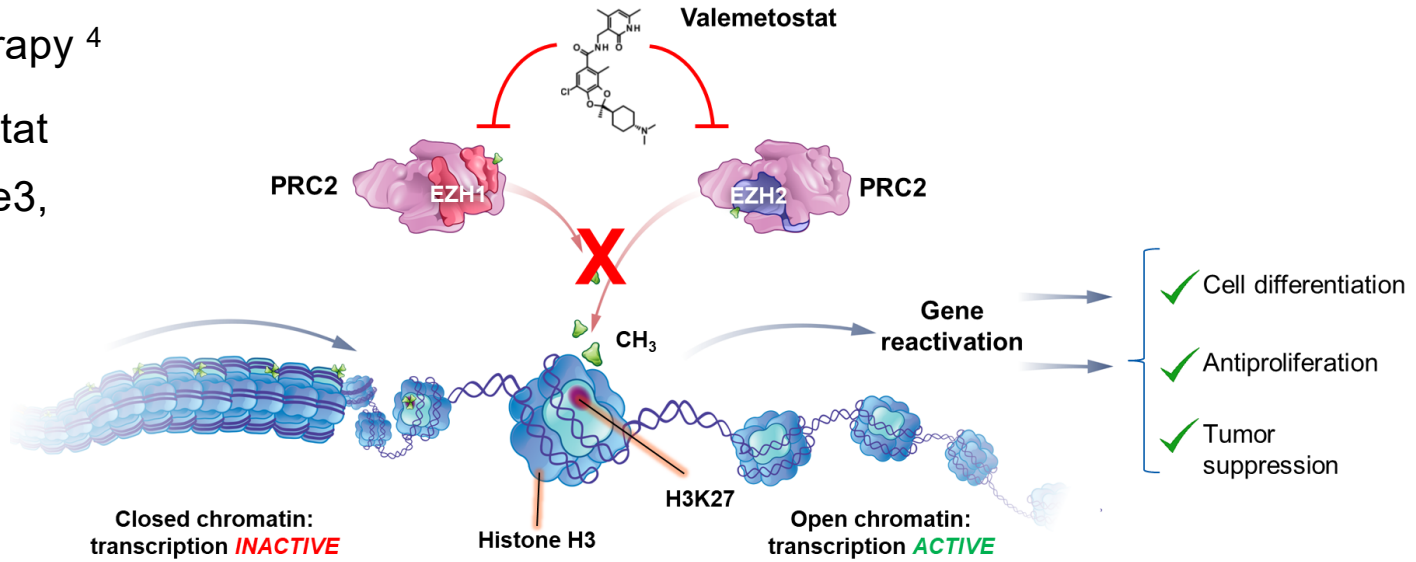
- **Trastuzumab deruxtecan** (T-DXd) is approved in more than 55 countries, including the US and EU, for patients with HER2-low breast cancer (BC) previously treated with chemotherapy in the metastatic setting or with disease recurrence within 6 months of completing adjuvant chemotherapy [1,2]
- Regulatory approvals of T-DXd for treatment of HER2-low advanced BC were based primarily on outcomes from the randomized, phase 3 DESTINY-Breast04 trial (NCT03734029), in which T-DXd (5.4 mg/kg every 3 weeks) significantly prolonged progression-free survival (PFS) and overall survival (OS) vs. physician's choice of chemotherapy [3]

[a] Physicians' choice: capecitabine, eribulin, gemcitabine, paclitaxel, or nab-paclitaxel.

1. AstraZeneca Press Release, 21 February 2022. 2. ENHERTU® (fam-trastuzumab deruxtecan-nxki) [prescribing information]. 3. Modi S, et al. *N Engl J Med* 2022;387:9–20.

Background

- **Valemetostat tosylate** (valemetostat) is a novel, potent, and selective dual inhibitor of enhancer of zeste homolog (EZH)2 and EZH1 [1]
  - EZH2 and EZH1 catalyze trimethylation of histone H3 at lysine 27 (H3K27me3), leading to transcriptional repression; global H3K27me3 accumulation has been noted in various solid tumors and hematologic malignancies [2,3]
  - EZH2-mediated protein phosphatase 2A inactivation has been shown to confer resistance to HER2-targeted therapy [4]
  - Dual inhibition of EZH2 and EZH1 with valemetostat has been shown to maximally suppress H3K27me3, thus upregulating genes silenced by H3K27me3 [1]
  - To date, valemetostat has demonstrated clinical efficacy and favorable tolerability in multiple hematologic malignancies (approved in Japan for patients with R/R PTCL and ATLL) [5–8]



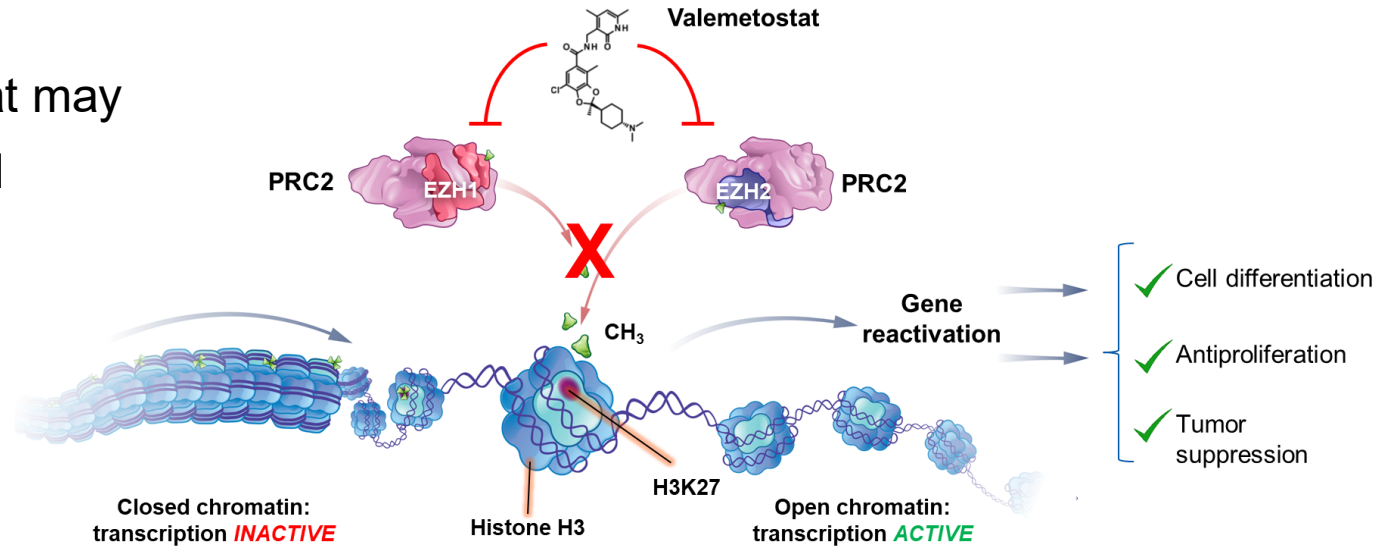
H3K27, histone H3 at lysine 27; PRC2, polycomb repressive complex 2.

ATLL, adult T-cell leukemia lymphoma; R/R PTCL, relapsed/refractory peripheral T-cell lymphoma.

1. Yamagishi M, et al. *Cell Rep* 2019;29:2321–2337.e7 2. Herviou L, et al. *Oncotarget* 2016;7:2284–2296. 3. Nakagawa M, et al. *Cancer Sci* 2018;109:2342–2348. 4. Bao Y, et al. *Nat Commun* 2020;11:5878. 5. Izutsu K, et al. *Blood* 2023;141:1159–1168. 6. Izutsu K, et al. *Blood* 2023;142 (Suppl):1731. 7. Zinzani PL, et al. *Lancet Oncol* 2024;25:1602–1613. 8. Maruyama D, et al. *Lancet Oncol* 2025;25:1589–1601.

Background

- **EZH2 controls gene expression,** including the expression of genes involved in the DNA damage response such as DNA/RNA helicase Schlafen 11 (*SLFN11*) [1]
  - *SLFN11* expression levels indicate sensitivity to DNA-damaging agents (DDAs) in various solid tumors; in response to DNA damage, *SLFN11* binds to chromatin, blocking replication and inducing apoptosis [1,2]
  - Downregulation of *SLFN11* has been observed in chemotherapy-resistant tumor cells due to the presence of H3K27me3 at the *SLFN11* gene locus [1–4]
  - Inhibition of EZH2 and EZH1 by valemetostat may upregulate *SLFN11* and enhance cancer cell sensitivity to DDAs, including ADCs



H3K27, histone H3 at lysine 27; PRC2, polycomb repressive complex 2.

ADCs, antibody-drug conjugates.

1. Gardner EE, et al. *Cancer Cell* 2017;31:286–299. 2. Murai J, et al. *Mol Cell* 2018;69:371–384.e6. 3. Shee K, et al. *PLoS One* 2019;14:e0224267. 4. Zoppoli G, et al. *Proc Natl Acad Sci U S A* 2012;109:15030–15035.

Background

Valemetostat + DXd ADCs in solid tumors:

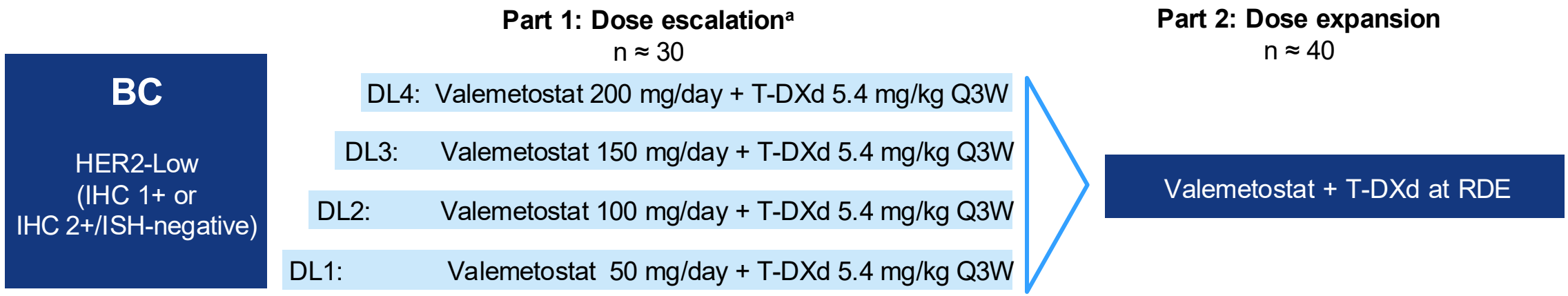
- Preclinical studies demonstrate synergistic effects of combining valemetostat with DXd ADCs in various solid tumors (data on file)
- DS3201-324 (NCT06244485) is a global, multicenter, open-label, phase 1b 'Master Protocol' trial assessing the safety, tolerability, and efficacy of valemetostat in combination with ADCs as second-line or later therapy for patients with advanced solid tumors, currently including three sub-protocols:
  - Unresectable or metastatic HER2-low BC: valemetostat + T-DXd
  - Advanced or metastatic HER2-positive gastric cancer or gastroesophageal junction adenocarcinoma: valemetostat + T-DXd
  - Advanced or metastatic non-squamous non-small-cell lung carcinoma: valemetostat + datopotamab deruxtecan
- Here, we present the study objectives, eligibility criteria, and endpoints for the HER2-low BC sub-protocol of the DS3201-324 Master Protocol trial

ADCs, antibody-drug conjugates; BC, breast cancer; DXd, deruxtecan; HER2, human epidermal growth factor receptor 2; T-DXd, trastuzumab deruxtecan.

Study design

HER2-low BC sub-protocol of the DS3201-324 Master Protocol trial

- Each sub-protocol (cohort) comprises a dose-escalation phase (Part 1) followed by a dose-expansion phase (Part 2)
  - In Part 1 of the BC cohort, patients will receive valemetostat orally at escalating doses of 50–200 mg/day and T-DXd intravenously at a fixed dose of 5.4 mg/kg every 3 weeks (Q3W)
  - In Part 2, patients will receive valemetostat and T-DXd at the recommended dose for expansion (RDE), based on the results of Part 1
  - Target enrollment in each cohort is approximately 70 patients, with 30 in Part 1 and 40 in Part 2



[a] Dose escalation is based on a Bayesian Optimal Interval design. Intermediate dose levels may be explored.
DL, dose level; IHC, immunohistochemistry; ISH, in situ hybridization.

Key eligibility criteria

Inclusion criteria

- Age ≥ 18 years[a]
- Pathologically documented BC that is unresectable or metastatic, and has progressed on and would no longer benefit from endocrine therapy in patients who are hormone receptor-positive
- ≥ 1 measurable lesion based on investigator imaging assessment (CT or MRI scans) using RECIST v1.1
- Previously treated with 1–2 prior lines of chemotherapy disease in the recurrent or metastatic setting[b]
- History of low HER2 expression (IHC 2+/ISH-negative or IHC 1+/[ISH-negative/untested])
- ECOG PS score of 0–1
- Adequate organ and bone marrow function

Exclusion criteria

- Prior treatment with an EZH inhibitor
- Prior ADC treatment consisting of an exatecan derivative that is a topoisomerase I inhibitor
- Prior anti-HER2 therapy in the metastatic setting
- Uncontrolled or significant cardiovascular disease
- Spinal cord compression or clinically active CNS metastases
- Concomitant use of moderate or strong CYP3A inducers

[a]Or the minimum legal adult age, whichever is greater. [b]Recurrence ≤ 6 months of (neo)adjuvant chemotherapy counts as 1 line of chemotherapy. Monotherapy with mammalian target of rapamycin inhibitors, poly adenosine diphosphate-ribose polymerase inhibitors, programmed death-1 inhibitors, programmed death ligand 1 inhibitors, histone deacetylase inhibitors, or cyclin-dependent kinase 4/6 inhibitors and endocrine therapies does not count as prior lines of chemotherapy.

ADC, Antibody-drug conjugate; BC, breast cancer; CNS, central nervous system; CT, computed tomography; CYP3A, cytochrome P450 3A; ECOG PS, Eastern Cooperative Oncology Group performance status; EZH, enhancer of zeste homolog; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; MRI, magnetic resonance imaging; RECIST, Response Evaluation Criteria in Solid Tumors.

Study procedures

- Treatment with valemetostat + T-DXd in the HER2-low BC sub-protocol of the DS3201-324 Master Protocol trial will continue until disease progression or unacceptable adverse events
- During treatment, tumor assessment will occur every 6 weeks during the first year and every 12 weeks thereafter
- After treatment, patients are to be followed every 3 months for at least 3 years (from first dose of study drug) for survival outcomes
- A planned interim futility analysis will be performed when 20 patients are enrolled in Part 2 and have ≥ 6 months of follow-up from the first dose of study drug
- Part 1 will assess the safety, tolerability, and recommended dose for expansion (RDE) of valemetostat combined with T-DXd
- The RDE will be decided based on considerations of the statistical model, maximum tolerated dose, safety, efficacy, pharmacokinetics (PK), and biomarker data
- Preliminary clinical activity will also be assessed
- Part 2 will further assess the efficacy and safety of the combination at the RDE established in Part 1

BC, breast cancer; DXd, deruxtecan; HER2, human epidermal growth factor receptor 2; T-DXd, trastuzumab deruxtecan.

Study endpoints

Endpoint	Description
Primary	
• Safety & tolerability (Part 1 and 2)	• Incidence of DLTs (Part 1 only) and TEAEs (NCI-CTCAE v5.0)
• ORR (Part 2)	• Proportion of patients achieving CR or PR (RECIST v1.1 criteria)
Secondary	
• OS	• Time from first dose to death
• PFS	• Time from first dose to disease progression or death
• DOR	• Time from first response (CR/PR) to tumor progression or death
• ORR (Part 1)	• Proportion of patients achieving CR or PR (RECIST v1.1 criteria)
• Safety and tolerability (Part 2)	• Incidence of TEAEs (all-grade, grade 3/4, serious, leading to discontinuation)
• PK	• Plasma/serum concentrations of valemetostat & ADC-associated moieties
Exploratory	
• Exposure-response PK	• Relationship between drug exposure and efficacy/ safety endpoints
• ADC immunogenicity	• Antidrug antibody prevalence (pre-existing and treatment-emergent)
• Valemetostat pharmacodynamics	• H3K27me3 inhibition on-study
• Tumor imaging (G-score)	• Tumor growth on radiographic assessments
• Valemetostat + ADC biomarkers	• *SLFN11* protein expression, RNA gene expression, immune profiling, HER2 expression; associations with clinical response[a]

[a]HER2 protein expression will be tested in a central laboratory by the PATHWAY anti-HER2 (4B5) IHC and/or HER2 ISH assay on tumor biopsy samples collected before, during, and after study treatments, to understand its association with clinical response.

ADC, antibody-drug conjugate; CR, complete response; DLTs, dose-limiting toxicities; DOR, duration of response; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; ORR, overall response rate; OS, overall survival; PFS, progression-free response; PK, pharmacokinetics; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; TEAEs, treatment-emergent adverse events.

Conclusions

- Valemetostat has demonstrated clinical activity and a favorable safety profile in multiple hematologic malignancies [1–4]
  - Its mechanism of action suggests that it may sensitize cancer cells to the DNA-damaging effects of ADCs such as T-DXd by modulating gene expression, including upregulation of *SLFN11* [5–7]
- T-DXd is a HER2-directed ADC that has shown superior efficacy to standard chemotherapy in patients with previously treated, HER2-low advanced BC [8]
- The phase 1b DS3201-324 Master Protocol signal-seeking study will establish whether adding valemetostat to T-DXd can further improve the efficacy of T-DXd in patients with previously treated, advanced, HER2-low BC, while retaining an overall favorable safety profile
- Enrollment is ongoing in the US, Japan, and China
- If you have a patient that may be eligible to participate in the DS3201-324 (NCT06244485) Master Protocol trial, please contact Daiichi Sankyo for clinical trial information at DS3201-324SiteCommunications@dsi.com

ADC, antibody-drug conjugate; BC, breast cancer; HER2, human epidermal growth factor receptor 2; T-DXd, trastuzumab deruxtecan.

1. Izutsu K, et al. *Blood* 2023;141:1159–1168. 2. Izutsu K, et al. *Blood* 2023;142:1731. 3. Zinzani PL, et al. *Lancet Oncol* 2024;25:1602–1613. 4. Maruyama D, et al. *Lancet Oncol* 2025;25:1589–1601.
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