Valemetostat and Trastuzumab Deruxtecan (T-DXd) in Patients With Human Epidermal Growth Factor Receptor 2 (HER2)-Low, Previously Treated, Unresectable or Metastatic Breast Cancer

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SUMMARY

- 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 antibody–drug conjugates (ADCs), such as T-DXd, by modulating gene expression, including upregulation of Schlafen 11 *(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 breast cancer (BC)[8]
- This phase 1b signal-seeking study will establish whether adding valemetostat to T-DXd can further improve the efficacy of this ADC in patients with previously treated, advanced, HER2-low BC, while retaining an overall favorable safety profile
- Enrollment is ongoing in the US and Japan
- **If you have a patient that could be eligible to participate, please contact Daiichi Sankyo for clinical trial information at DS3201-324SiteCommunications@dsi.com**

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BACKGROUND

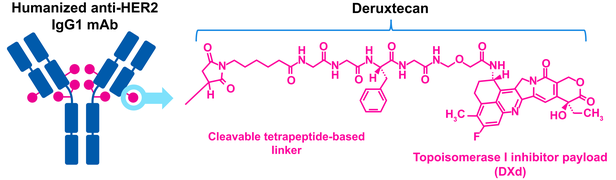
T-DXd

- T-DXd is an ADC composed of a humanized anti-HER2 monoclonal antibody (mAb) linked to a topoisomerase I inhibitor payload (DXd) via an enzymatically cleavable tetrapeptide-based linker (**Figure 1**)[9–11]
- The released DXd payload enters the cell nucleus and inhibits topoisomerase I, which can induce DNA damage and tumor cell apoptosis[9–10]
- T-DXd is approved in more than 55 countries, including the US, for patients with HER2-low BC previously treated with chemotherapy in the metastatic setting or with disease recurrence within 6 months of completing adjuvant chemotherapy[12,13]

Figure 1. Structure of T-DXd

T-DXd is an ADC composed of 3 parts:

- A humanized anti-HER2 immunoglobulin G1 (IgG1) 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



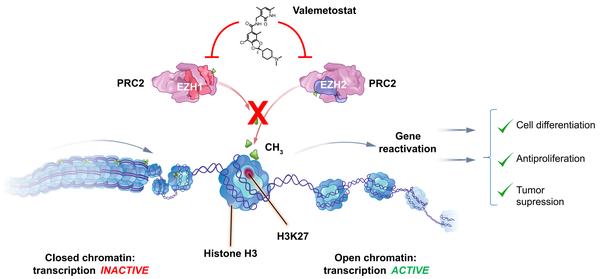
CH_3, trimethyl group.

- Regulatory approvals of T-DXd for treatment of HER2-low advanced BC were based primarily on outcomes from the randomized, phase 3 DESTINY-Breast04[8] (NCT03734029) trial, in which T-DXd (5.4 mg/kg every 3 weeks [Q3W]) significantly prolonged progression-free survival (PFS) and overall survival (OS) vs. physician's choice of chemotherapy

Valemetostat

- Valemetostat tosylate (valemetostat) is a novel, potent, and selective dual inhibitor of enhancer of zeste homolog (EZH)2 and EZH1[5]
  - 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[14,15]
  - EZH2-mediated protein phosphatase 2A inactivation has been shown to confer resistance to HER2-targeted therapy[16]
  - Dual inhibition of EZH2 and EZH1 with valemetostat has been shown to maximally suppress H3K27me3, thus upregulating genes silenced by H3K27me3 (**Figure 2**)[5]
  - Till date, valemetostat has demonstrated clinical efficacy and favorable tolerability in multiple hematologic malignancies (approved in Japan for patients with R/R PTCL and ATLL)[1–4]

Figure 2. Mechanism of action of valemetostat



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

- EZH2 controls gene expression, including the expression of genes involved in the DNA damage response such as DNA/RNA helicase *SLFN11*[6]
  - *SLFN11* expression levels indicate sensitivity to DNA-damaging agents (DDAs) in various solid tumors; in response to DNA damage, *SLFN11* binds to chromatin, causing a replication block and inducing apoptosis[6,7]
  - Downregulation of *SLFN11* has been observed in chemotherapy-resistant tumor cells due to the presence of H3K27me3 at the *SLFN11* gene locus[6,7,17,18]
- Inhibition of EZH2 and EZH1 by valemetostat may upregulate *SLFN11* and enhance cancer cell sensitivity to DDAs, including ADCs

Valemetostat + DXd ADCs in solid tumors

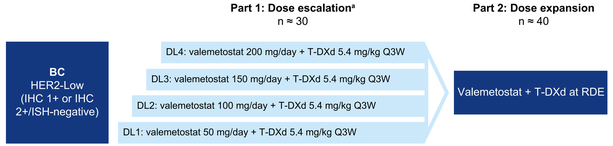
- Preclinical studies demonstrate synergistic effects of combining valemetostat with DXd ADCs in various solid tumors (data on file)
- DS3201-324 (NCT06244485) is a global, multicenter, open-label, phase 1b "Master Protocol" trial assessing the safety, tolerability, and efficacy of valemetostat in combination 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 nonsquamous 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

CLINICAL TRIAL DESIGN

Study design

- Each sub-protocol (cohort) comprises of a dose-escalation part (Part 1) followed by a dose-expansion part (Part 2) (**Figure 3**)
  - 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 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

Figure 3. Study design



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

- Target enrollment in each cohort is approximately 70 patients, with 30 in Part 1 and 40 in Part 2
  - Key eligibility criteria are shown in **Table 1**
- Treatment 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 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

Table 1. Key eligibility criteria

Inclusion criteria	Exclusion 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 in the recurrent or metastatic setting[b] • Has a 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	• 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, therapy counts as 1 line of chemotherapy. Monotherapy of 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 do not count as prior lines of chemotherapy.
CNS, central nervous system; CT, computed tomography; CYP3A, cytochrome P450 3A; ECOG PS, Eastern Cooperative Oncology Group performance status; MRI, magnetic resonance imaging; RECIST, Response Evaluation Criteria in Solid Tumors.

Objectives and endpoints

- Part 1 will assess the safety, tolerability, and 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
- The primary endpoint is safety and tolerability in Part 1, and a co-primary endpoint of safety and overall response rate ([ORR]; per RECIST v1.1 criteria) in Part 2 (**Table 2**)
- Secondary endpoints include ORR (Part 1 only), duration of response (DOR), PFS, OS, and PK

Table 2. 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 & 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.
CR, complete response; DLTs, dose-limiting toxicities; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PR, partial response; TEAEs, treatment-emergent adverse events.

REFERENCES

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*. Published online October 29, 2024.
4. Maruyama D, et al. *Lancet Oncol*. Published online October 29, 2024.
5. Yamagishi M, et al. *Cell Rep* 2019;29:2321–2337.
6. Gardner EE, et al. *Cancer Cell* 2017;31:286–299.
7. Murai J, et al. *Mol Cell* 2018;69:371–384.
8. Modi S, et al. *N Engl J Med* 2022; 387:9–20.
9. Nakada T, et al. *Chem Pharm Bull* (Tokyo) 2019;67:173–185.
10. Ogitani Y, et al. *Clin Cancer Res* 2016;22:5097–5108.
11. Ogitani Y, et al. *Cancer Sci* 2016;107:1039–1046.
12. AstraZeneca. Enhertu significantly improved both progression-free and overall survival in DESTINY-Breast04 trial in patients with HER2-low metastatic breast cancer. https://www.astrazeneca.com/media-centre/press-releases/2022/enhertu-improves-pfs-and-os-in-her2-low-bc.html#modal-historic-confirmation. Accessed September 24, 2024.
13. ENHERTU® (fam-trastuzumab deruxtecan-nxki) [prescribing information]. Basking Ridge, NJ: Daiichi Sankyo, Inc.; April 2024.
14. Hervieu L, et al. *Oncotarget* 2016;7:2284–2296.
15. Nakagawa M, Kitabayashi I. *Cancer Sci* 2018;109:2342–2348.
16. Bao Y, et al. *Nature Comm* 2020;11:5878.
17. Shee K, et al. *PLoS One* 2019;14:e0224267.
18. Zoppoli G, et al. *Proc Natl Acad Sci U S A* 2012;109:15030–15035.

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