A Phase 1b, Multicenter, Open-Label Study of Valemetostat in Combination With DXd Antibody–Drug Conjugates (ADCs), Trastuzumab Deruxtecan (T-DXd) or Datopotamab Deruxtecan (Dato-DXd), in Patients With Solid Tumors

Jacob Sands,[1] Sara M. Tolaney,[1] Naoto T. Ueno,[2] Alexander Spira,[3] Noboru Yamamoto,[4] Yelena Janjigian,[5] Yoichi Naito,[6] Senthil Damodaran,[7] Funda Meric-Bernstam,[7] Shanu Modi,[5] Peter Enzinger,[1] Avani Mohapatra,[8] Yuka Iko,[9] Siwen He,[8] Keiko Nakajima,[8] Kohei Shitara[6]

[1]Dana-Farber Cancer Institute, Boston, MA, US; [2]University of Hawai'i Cancer Center, Honolulu, HI, US; [3]Virginia Cancer Specialists, Fairfax, VA, US; [4]National Cancer Center Hospital, Tokyo, Japan; [5]Memorial Sloan Kettering Cancer Center, New York, NY, US; [6]National Cancer Center East, Chiba, Japan; [7]MD Anderson Cancer Center, Houston, TX, US; [8]Daiichi Sankyo Inc., Basking Ridge, NJ, US; [9]Daiichi Sankyo Ltd., Tokyo, Japan

SUMMARY

- Valemetostat is an oral inhibitor of EZH2/1 that has demonstrated clinical activity and an acceptable safety profile in multiple hematologic malignancies[1–3]
- T-DXd and Dato-DXd are topoisomerase-I inhibitor ADCs that have shown superior efficacy to standard chemotherapy in several cancer types[7–10]
- This signal-seeking study will establish if valemetostat used in combination with T-DXd or Dato-DXd can further improve the efficacy of these ADCs in solid tumors while retaining an overall acceptable safety profile
- Enrollment is currently ongoing at sites in the US and Japan
- The Master Protocol design allows for inclusion of additional sub-protocols
- **If you have a patient that could benefit from participation in this trial, please contact Daiichi Sankyo for clinical trial information at DS3201-324SiteCommunications@dsi.com**

BACKGROUND

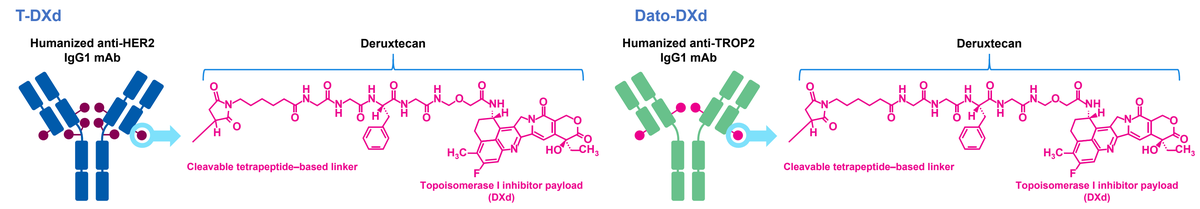
DXd ADCs

- T-DXd is a human epidermal growth factor receptor 2 (HER2)-directed ADC composed of a humanized anti-HER2 antibody, a topoisomerase I inhibitor payload (DXd), and an enzymatically cleavable tetrapeptide-based linker (**Figure 1**)[1–4]
  - T-DXd is approved in the US as the first HER2-directed therapy for previously treated patients with metastatic HER2+ solid tumors, including gastric cancer (GC) and gastroesophageal junction (GEJ) adenocarcinoma[4]
  - Worldwide regulatory approvals of T-DXd for treatment of previously treated HER2+ GC/GEJ were based primarily on outcomes from the phase 2 DESTINY-Gastric01[5] (NCT03329690) trial, in which T-DXd (6.4 mg/kg every 3 weeks [Q3W]) significantly improved the response rate and overall survival (OS) vs. chemotherapy, and the single-arm DESTINY-Gastric02[6] (NCT04014075) trial
- Dato-DXd is a novel trophoblast cell-surface antigen 2 (TROP2)-directed ADC composed of a humanized anti-TROP2 immunoglobulin G1 (IgG1) monoclonal antibody with a plasma-stable cleavable linker that delivers a DXd directly into tumor cells (**Figure 1**)[7–8]
  - In the phase 3 TROPION-Lung01 trial (NCT04656652), Dato-DXd significantly improved progression-free survival (PFS) compared with standard chemotherapy in patients with previously treated, locally advanced or metastatic non-small-cell lung cancer (NSCLC)[7]
  - In patients with nonsquamous NSCLC, Dato-DXd reduced the risk of disease progression or death by 25% compared to docetaxel (hazard ratio [HR], 0.63; 95% confidence interval [CI], 0.51–0.78; p = 0.004) as assessed by blinded independent central review; median PFS was 5.6 months in patients treated with Dato-DXd vs. 3.7 months with docetaxel
  - In February 2024, a biologics license application for Dato-DXd was accepted in the US for the treatment of adult patients with locally advanced or metastatic nonsquamous NSCLC who have received prior systemic therapy[8]

Figure 1. Structures of T-DXd and Dato-DXd

T-DXd and Dato-DXd are ADCs composed of 3 parts:

1. A humanized anti-HER2 (T-DXd) / anti-TROP2 (Dato-DXd) IgG1 mAb with the same amino acid sequence as trastuzumab
2. A topoisomerase I inhibitor payload (an exatecan derivative, DXd)
3. A tetrapeptide-based cleavable linker that covalently bonds the other 2 components

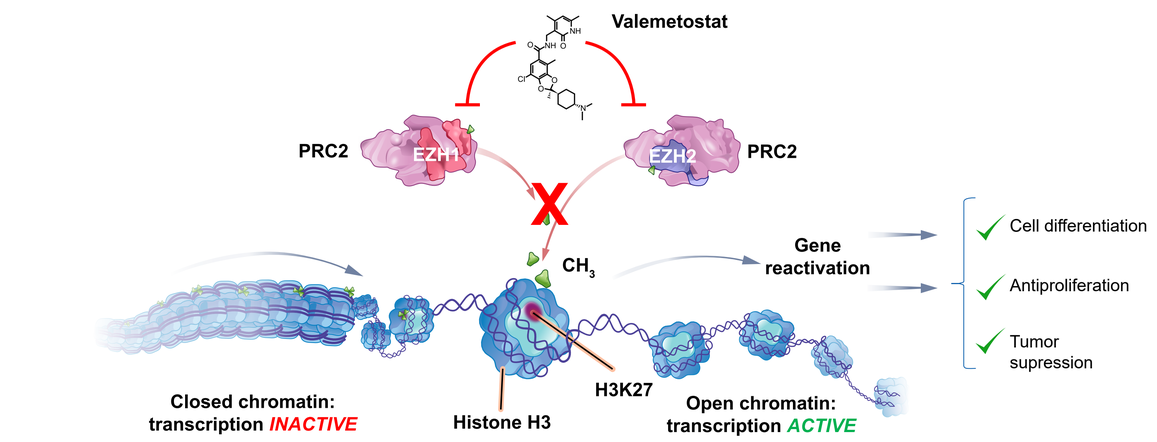


mAb, monoclonal antibody.

Valemetostat

- Enhancer of zeste homolog (EZH)2 controls gene expression, including the expression of genes involved in DNA damage response such as DNA/RNA helicase Schlafen 11 (*SLFN11*)[9]
  - *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[9,10]
  - Downregulation of SLFN11 has been observed in chemotherapy-resistant tumor cells due to trimethylation of histone H3 at lysine 27 (H3K27me3) at the *SLFN11* gene locus[9–12]
  - EZH2 and EZH1 catalyze H3K27me3, leading to transcriptional repression; global H3K27me3 accumulation has been noted in various solid tumors and hematologic malignancies[13,14]
- Valemetostat tosylate (valemetostat) is a novel, potent, and selective dual inhibitor of EZH2 and EZH1 that has demonstrated clinical efficacy and favorable tolerability in multiple hematologic malignancies[15–18]
  - Dual inhibition of EZH2 and EZH1 with valemetostat has shown to maximally suppress H3K27me3, thus upregulating genes silenced by H3K27me3 (**Figure 2**)[19]
  - Inhibition of EZH2 and EZH1 by valemetostat may upregulate *SLFN11* and enhance cancer cell sensitivity to DDAs, including ADCs

Figure 2. Mechanism of action of valemetostat



CH_3, trimethyl group; EZH, enhancer of zeste homolog; H3K27, histone H3 at lysine 27; PRC2, polycomb repressive complex 2.

Valemetostat + ADCs in solid tumors

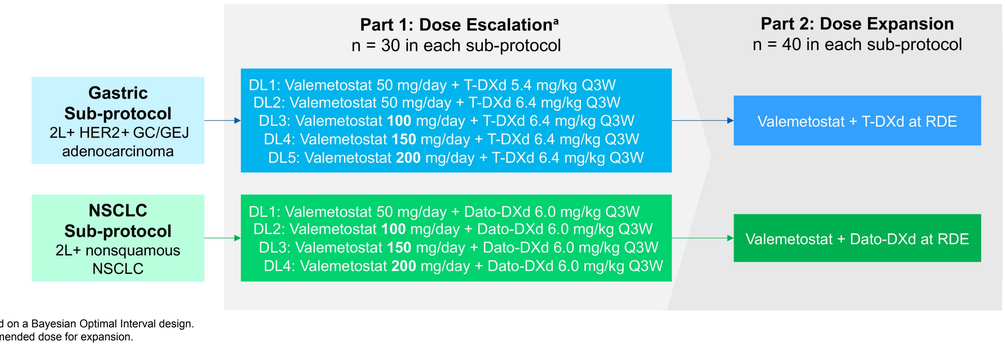
- Preclinical studies have shown the synergistic effects of valemetostat in combination with DXd ADCs in various solid tumors *(data on file)*
- DS3201-324 (NCT06244485) is an open-label, phase 1b "Master Protocol" trial assessing the safety, tolerability, and efficacy of valemetostat in combination with T-DXd or Dato-DXd in patients with second-line or later (2L+) advanced solid tumors
- We present study design, eligibility criteria, objectives and endpoints for two sub-protocols enrolling patients with GC/GEJ adenocarcinoma (T-DXd combination) and nonsquamous NSCLC (Dato-DXd combination)

METHODS

Study design

- This global, phase 1b Master Protocol trial includes independent sub-protocols defined by disease type and treatment combination, each including a preliminary dose-escalation part (Part 1) followed by a dose expansion part (Part 2) (**Figure 3**)
  - The **gastric** sub-protocol assesses valemetostat + T-DXd in patients with 2L+ advanced or metastatic HER2+ GC/GEJ adenocarcinoma
  - The **NSCLC** sub-protocol assesses valemetostat + Dato-DXd in patients with 2L+ locally advanced, unresectable, or metastatic nonsquamous NSCLC
- Key trial eligibility criteria include ≥ 1 measurable lesion (per Response Evaluation Criteria in Solid Tumors [RECIST] v1.1), Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0–1, and adequate organ function (**Table 1**)
- Target enrollment is approximately 70 patients per sub-protocol, including 30 patients in the dose-escalation part and 40 patients in the dose-expansion phase

Figure 3. Study design



[a]This is based on a Bayesian Optimal Interval design.
RDE, recommended dose for expansion.

Table 1. Key eligibility criteria

Inclusion criteria	Exclusion criteria
All sub-protocols	
• Age ≥ 18 years[a] • ≥ 1 measurable lesion based on investigator imaging assessment (CT or MRI scans) using RECIST v1.1 • ECOG PS score of 0–1 • Adequate organ and bone marrow function	• Prior treatment with an EZH inhibitor • Uncontrolled or significant cardiovascular disease • Spinal cord compression or clinically active CNS metastases • Use of moderate or CYP3A inducers • Clinically severe pulmonary compromise • Systemic treatment with corticosteroids (>10 mg daily prednisone equivalents) • Clinically severe pulmonary compromise resulting from intercurrent pulmonary illnesses
Gastric sub-protocol	
• Pathologically documented GC or GEJ adenocarcinoma that is unresectable or metastatic and has progressed on trastuzumab or an approved trastuzumab biosimilar-containing regimen[b] • Locally confirmed HER2+ (IHC3+ or IHC2+/ISH+)	• Prior ADC consisting of an exatecan derivative that is a topoisomerase I inhibitor • Clinically significant gastrointestinal disorders[c] • Pleural effusion, ascites, or pericardial effusion that requires drainage, peritoneal shunt, or cell-free and concentrated ascites reinfusion therapy
NSCLC sub-protocol	
• Pathologically documented stage IIIb, IIIc, or IV nonsquamous NSCLC, with or without AGAs[d] • NSCLC is unresectable or metastatic • Patients with AGA: (a) at least 1 or 2 prior lines of applicable targeted therapy; (b) platinum-based chemotherapy as a prior line of cytotoxic therapy; (c) may have received α-PD-1/α-PD-L1 mAb • Patients without AGA: platinum-based chemotherapy in combination with α-PD-1/α-PD-L1 mAb or both agents sequentially	• Prior use of a chemotherapeutic agent, including an ADC, targeting topoisomerase I or TROP2

[a]Or the minimum legal adult age, whichever is greater; [b]Prior neoadjuvant or adjuvant therapy with a trastuzumab-containing regimen can be counted as a line of therapy if the patient progressed on or within 6 months of completing neoadjuvant or adjuvant therapy; [c]Includes hepatic disorders, bleeding, inflammation, occlusion, ileus, Grade > 1 diarrhea, jaundice, intestinal paralysis, malabsorption syndrome, ulcerative colitis, inflammatory bowel disease, or partial bowel obstruction; [d]AGAs include *EGFR, ALK, ROS1, NTRK, BRAF* V600E, *MET* exon 14 skipping, *RET*, or *KRAS* G12C mutations.
AGA, actionable genomic alteration; ALK, anaplastic lymphoma kinase; BRAF, B-rapidly accelerated fibrosarcoma; CNS, central nervous system; CT, computed tomography; CYP3A, cytochrome P450 3A; EGFR, epidermal growth factor receptor; EZH, enhancer of zeste homolog; GC, gastric cancer; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; KRAS, Kirsten rat sarcoma; mAb, monoclonal antibody; MRI, magnetic resonance imaging; MET, proto-oncogene; NTRK, neurotrophic tyrosine receptor kinase; PD-1, programmed death-1; PD-L1, programmed death ligand 1; RECIST, Response Evaluation Criteria in Solid Tumors; RET, rearranged during transfection; ROS1, proto-oncogene tyrosine-protein kinase.

Objectives and endpoints

- The dose-escalation (Part 1) will assess the safety, tolerability, recommended dose for expansion (RDE) of valemetostat and T-DXd (gastric cohort), or the RDE of valemetostat with Dato-DXd (NSCLC cohort) for expansion, and preliminary clinical activity of each combination
  - The RDE(s) will be decided based on considerations of the statistical model, maximum tolerated dose, safety, efficacy, pharmacokinetics (PK), and biomarker data
- The primary endpoint in Part 1 is safety and tolerability and in Part 2 is the overall response rate (ORR); secondary endpoints for both protocols include duration of response (DOR), PFS, OS, and PK (**Table 2**)
- The dose-expansion (Part 2) will further assess the efficacy and safety of each combination at the RDE established in Part 1

Table 2. Trial endpoints

Endpoint	Description
Primary	
• Safety & tolerability (Part 1)	Incidence of DLTs and TEAEs (NCI-CTCAE v5.0)
• ORR (Part 2)	Proportion of patients achieving CR or PR (RECIST v1.1 criteria)
Secondary	
• OS	Time from enrollment to death
• PFS	Time from enrollment 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

CR, complete response; DLTs, dose-limiting toxicity; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; ORR, overall response rate; PR, partial response; TEAEs, treatment-emergent adverse events.

REFERENCES

1. Nakada T, et al. *Chem Pharm Bull (Tokyo)* 2019;67:173–85.
2. Ogitani Y, et al. *Clin Cancer Res* 2016;22:5097–108.
3. Ogitani Y, et al. *Cancer Sci* 2016;107:1039–46.
4. Enhertu approved in the US as first tumour-agnostic HER2-directed therapy for previously treated patients with metastatic HER2-positive solid tumours. [Press Release]. AstraZeneca, April 6, 2024.
5. Shitara K, et al. *N Engl J Med* 2020;382:2419–30.
6. Van Cutsem E, et al. *Lancet Oncol* 2023;24:744–56.
7. Ahn MJ, et al. *Ann Oncol* 2023;34:S1305–06.
8. Datopotamab deruxtecan Biologics License Application accepted in the US for patients with previously treated advanced nonsquamous non-small cell lung cancer. [Press release]. AstraZeneca, Feb 19, 2024.
9. Gardner EE, et al. *Cancer Cell* 2017;31:286–99.
10. Murai J, et al. *Mol Cell* 2018;69:371–84.
11. Zoppoli G, et al. *Proc Natl Acad Sci U S A* 2012;109:15030–35.
12. Shee K, et al. *PLoS One* 2019;14:e0224267.
13. Herviou L, et al. *Oncotarget* 2016;7:2284–96.
14. Nakagawa M, Kitabayashi I. *Cancer Sci* 2018;109:2342–48.
15. Izutsu K, et al. *Blood* 2023;141:1159–68.
16. Izutsu K, et al. *Blood* 2023;142:1731.
17. Horwitz SM, et al. *Blood* 2023;142:302.
18. Jacobsen E, et al. *Blood* 2023;142:303.
19. Yamagishi M, et al. *Cell Rep* 2019;29:2321–37.

ACKNOWLEDGEMENTS

- This study is sponsored by Daiichi Sankyo Inc.
- All authors contributed to and approved the poster
- Writing and editorial support were provided by Naomi Blommaert and Brian Kaiser of Excerpta Medica, funded by Daiichi Sankyo Inc., in accordance with Good Publication Practice guidelines
- Daiichi Sankyo and AstraZeneca entered into a global collaboration to jointly develop and commercialize ENHERTU and DS-1062, except in Japan where Daiichi Sankyo maintains exclusive rights

Presented at the American Society of Clinical Oncology (ASCO) 60th Annual Meeting; May 31 – June 4, 2024; Chicago, ILL, US