Valemetostat and Trastuzumab Deruxtecan (T-DXd) in Previously Treated, Advanced, or Metastatic Human Epidermal Growth Factor Receptor 2 (HER2)-Positive Gastric or Gastro-Esophageal Junction (GEJ) Adenocarcinoma

Kohei Shitara,[1] Peter Enzinger,[2] Avani Mohapatra,[3] Yelena Janjigian[4]

[1]National Cancer Center East, Chiba, Japan; [2]Dana-Farber Cancer Institute, Boston, MA, US; [3]Daiichi Sankyo Inc., Basking Ridge, NJ, US; [4]Memorial Sloan Kettering Cancer Center, New York, NY, US

SUMMARY

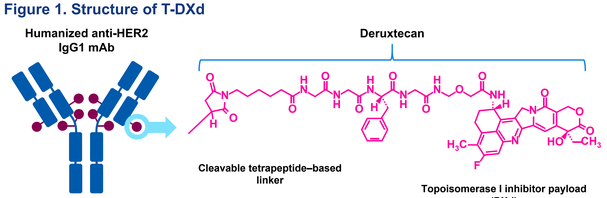
- Valemetostat is an oral inhibitor of enhancer of zeste homolog (EZH)2/1 that has demonstrated clinical activity and an acceptable safety profile in multiple hematologic malignancies[1–4]; its mechanism of action suggests it may sensitize cancer cells to the DNA-damaging effects of antibody–drug conjugates (ADCs) such as T-DXd[5–7]
- T-DXd is a HER2-directed ADC that has shown superior efficacy to standard chemotherapy in patients with previously treated, advanced HER2+ gastric cancer (GC)/GEJ adenocarcinoma[8,9]
- This 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+ GC/GEJ adenocarcinomas, while retaining an overall favorable safety profile
- Enrollment is ongoing across sites in the US and Japan
- **If you have a patient that could potentially be eligible for participation in this trial, please contact Daiichi Sankyo for clinical trial information at DS3201-324SiteCommunications@dsi.com**

BACKGROUND

T-DXd

- T-DXd is an ADC composed of a humanized anti-HER2 antibody, a topoisomerase I inhibitor payload (DXd), and an enzymatically cleavable tetrapeptide-based linker (**Figure 1**)[10–12]
  - T-DXd is approved in the US for previously treated patients with metastatic HER2+ solid tumors, including adult patients with locally advanced or metastatic HER2+ (immunohistochemistry [IHC] 3+ or IHC 2+/in situ hybridization [ISH]+) GC/GEJ adenocarcinoma who have received a prior trastuzumab-based regimen[13]
  - In the phase 2 DESTINY-Gastric01[8] (NCT03329690) trial, T-DXd significantly improved the response rate and overall survival (OS) vs physician's choice of chemotherapy

Figure 1. Structure of T-DXd

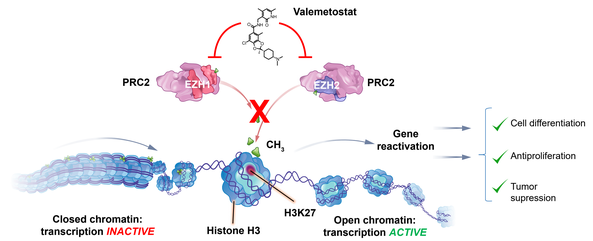


Ig, immunoglobulin; mAb, monoclonal antibody.

Valemetostat

- Valemetostat tosylate (valemetostat) is a novel, potent, and selective dual inhibitor of EZH2 and EZH1[5]
  - EZH2 and EZH1 catalyze trimethylation of histone H3 at lysine 27 (H3K27me3), leading to transcriptional repression[14,15]
  - Inhibition of EZH2 and EZH1 with valemetostat has been shown to maximally suppress H3K27me3, thus upregulating silenced genes (**Figure 2**)[5]
  - Valemetostat has demonstrated clinical efficacy and favorable tolerability in multiple hematologic malignancies[1–4]

Figure 2. Mechanism of action of valemetostat



CH_3, trimethyl group; H3K27, Histone 3 (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 Schlafen 11 (*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[6,7,16,17]
- Inhibition of EZH2 and EZH1 by valemetostat may upregulate *SLFN11* and enhance cancer cell sensitivity to DDAs, including ADCs
- DS3201-324 (NCT06244485) is an open-label, phase 1b "Master Protocol" trial assessing the safety, tolerability, and efficacy of valemetostat in combination with DXd ADCs as second-line or later therapy for patients with advanced tumors, including the following sub-protocols:
  - **Advanced or metastatic HER2+ GC or GEJ adenocarcinoma sub-protocol:** valemetostat + T-DXd
  - **Advanced or metastatic nonsquamous non-small cell lung carcinoma sub-protocol:** valemetostat + datopotamab deruxtecan (Dato-DXd)
- Here, we present the study design for the GC/GEJ sub-protocol of the DS3201-324 Master Protocol trial

METHODS

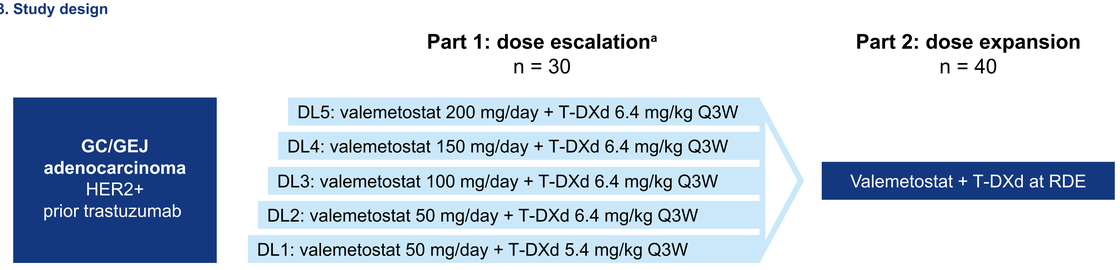
Study design

- This global, phase 1b trial consists of a dose-escalation part (Part 1) followed by a dose-expansion part (Part 2) (**Figure 3**)
  - In Part 1, patients will receive valemetostat orally at doses of 50–200 mg/day and T-DXd intravenously Q3W at doses of either 5.4 or 6.4 mg/kg; intermediate dose levels may be explored
  - In Part 2, patients will receive valemetostat and T-DXd at the RDE, based on the results of Part 1
- Target enrollment is approximately 70 patients, with 30 in Part 1 and 40 in Part 2
  - Key patient 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 will be followed every 3 months for at least 3 years (from first dose of study drug) for survival outcomes
- An interim futility analysis will be performed when 20 patients are enrolled at the RDE and have ≥ 6 months of follow-up from the first dose of study drug

Objectives and endpoints

- Part 1 will assess the safety, tolerability, and RDE of valemetostat combined with T-DXd
  - The RDE will be determined 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 endpoints are safety and tolerability in Part 1 and overall response rate (ORR) in Part 2 (**Table 2**)
- Secondary endpoints include duration of response (DOR), progression-free survival (PFS), OS, and PK

Figure 3. Study design



[a]This is based on a Bayesian Optimal Interval design. DL, dose level; RDE, recommended dose for expansion; Q3W, every 3 weeks.

Table 1. GC/GEJ sub-protocol: key eligibility criteria

Inclusion criteria
• Age ≥ 18 years[a]
• Pathologically documented GC or GEJ adenocarcinoma that is unresectable or metastatic and has progressed on trastuzumab or an approved trastuzumab biosimilar-containing regimen[b]
• ≥ 1 measurable lesion based on investigator imaging assessment (CT or MRI scans) using RECIST v1.1
• Locally confirmed HER2+ (IHC3+ or IHC2+/ISH+)
• ECOG PS score of 0–1
• Adequate organ and bone marrow function
Exclusion criteria
• Prior treatment with an EZH inhibitor
• Prior ADC consisting of an exatecan derivative that is a topoisomerase I inhibitor
• Uncontrolled or significant cardiovascular disease
• Clinically significant gastrointestinal disorder[c]
• Spinal cord compression or clinically active CNS metastases
• Pleural effusion, ascites, or pericardial effusion that requires drainage, peritoneal shunt, or cell-free and concentrated ascites reinfusion therapy
• Use of moderate or strong CYP3A inducers

[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.
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.

Table 2. 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
Exploratory	
• Exposure-response PK	Relationship between drug exposure and efficacy/safety endpoints
• ADC immunogenicity	Anti-drug antibody prevalence (pre-existing and treatment-emergent)
• Valemetostat PD	H3K27me3 inhibition on-study
• Tumor imaging (G-score)	Describe tumor growth on radiographic assessments
• Valemetostat + ADC biomarkers	SLFN11 protein expression, RNA gene expression, immune profiling, HER2 expression; associations with clinical response

CR, complete response; DLT, dose-limiting toxicity; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PD, pharmacodynamics; PR, partial response; TEAE, treatment-emergent adverse event.

REFERENCES

1. Izutsu K, et al. *Blood* 2023;141:1159–68.
2. Izutsu K, et al. *Blood* 2023;142:1731.
3. Horwitz SM, et al. *Blood* 2023;142:302.
4. Jacobsen E, et al. *Blood* 2023;142:303.
5. Yamagishi M, et al. *Cell Rep* 2019;29:2321–37.
6. Gardner EE, et al. *Cancer Cell* 2017;31:286–99.
7. Murai J, et al. *Mol Cell* 2018;69:371–84.
8. Shitara K, et al. *N Engl J Med* 2020;382:2419–30.
9. Van Cutsem E, et al. *Lancet Oncol* 2023;24:744–56.
10. Nakada T, et al. *Chem Pharm Bull* (Tokyo) 2019;67:173–85.
11. Ogitani Y, et al. *Clin Cancer Res* 2016;22:5097–108.
12. Ogitani Y, et al. *Cancer Sci* 2016;107:1039–46.
13. AstraZeneca [press release 2024]. ENHERTU® approved in the US as first tumour-agnostic HER2-directed therapy for previously treated patients with metastatic HER2-positive solid tumors. Available from: chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://www.daiichisankyo.com/files/news/pressrelease/pdf/202404/20240405_E.pdf. Accessed April 6, 2024.
14. Hervieu L, et al. *Oncotarget* 2016;7:2284–96.
15. Nakagawa M, Kitabayashi I. *Cancer Sci* 2018;109:2342–8.
16. Zoppoli G, et al. *Proc Natl Acad Sci U S A* 2012;109:15030–5.
17. Shee K, et al. *PLoS One* 2019;14:e0224267.

ACKNOWLEDGMENTS

- This study is sponsored by Daiichi Sankyo Inc. In March 2019, AstraZeneca entered into a global development and commercialization collaboration agreement with Daiichi Sankyo for trastuzumab deruxtecan (T-DXd; DS-8201)
- 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, in accordance with Good Publication Practice guidelines
- Daiichi Sankyo and AstraZeneca entered into a global collaboration to jointly develop and commercialize T-DXd; DS-8201, except in Japan where Daiichi Sankyo maintains exclusive rights

DISCLOSURES

Dr. Shitara, consulting: ALX Oncology, Amgen, Astellas Pharma, AstraZeneca, Bayer, Bristol-Myers Squibb, Daiichi Sankyo, Guardant Health, MSD, Novartis, Ono Pharmaceutical, Takeda, Zymeworks; honoraria: Astellas Pharma, AstraZeneca, Bristol-Myers Squibb, Janssen, Lilly, Ono Pharmaceutical; research funding: Amgen, Astellas Pharma, Chugai Pharma, Daiichi Sankyo, Eisai, MSD, Ono Pharmaceutical, PRA Health Sciences, Taiho Pharmaceutical.

Presented at the European Society for Medical Oncology Gastrointestinal Cancers (ESMO-GI) 2024 Congress; June 26–29, 2024; Munich, Germany