Valemetostat Plus Trastuzumab Deruxtecan (T-DXd) or Datopotamab Deruxtecan (Dato-DXd) in Patients With Solid Tumors

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SUMMARY

- Valemetostat tosylate (valemetostat), an oral inhibitor of enhancer of zeste homolog (EZH)2 and EZH1, has demonstrated clinical activity and a favorable safety profile in multiple hematologic malignancies[1–3]
  - Its mechanism of action suggests that it may sensitize cancer cells to DNA-damaging agents (DDAs), such as topoisomerase I inhibitor payload (DXd)-based antibody–drug conjugates (ADCs), by modulating gene expression, including upregulation of *Schlafen 11 (SLFN11)*[4–6]
- Trastuzumab deruxtecan (T-DXd) is a human epidermal growth factor receptor 2 (HER2)-directed ADC that has shown superior efficacy to standard chemotherapy in previously treated patients with advanced solid tumors, including HER2-low breast cancer (BC)[7] and HER2+ gastric cancer (GC)/gastroesophageal junction (GEJ) adenocarcinoma[8,9]
- Datopotamab deruxtecan (Dato-DXd) is a trophoblast cell-surface antigen 2 (TROP2)-directed ADC that has shown promising activity in patients with previously treated advanced nonsquamous non-small-cell lung cancer (NSCLC)[10,11]
- The phase 1b signal-seeking study, DS3201-324 (NCT06244485), will establish whether adding valemetostat to T-DXd or Dato-DXd can further improve the efficacy of the ADC in patients with previously treated advanced solid tumors, including HER2-low BC, HER2+ GC/GEJ, and nonsquamous NSCLC, while retaining an overall favorable safety profile
- Enrollment is ongoing in the USA and Japan

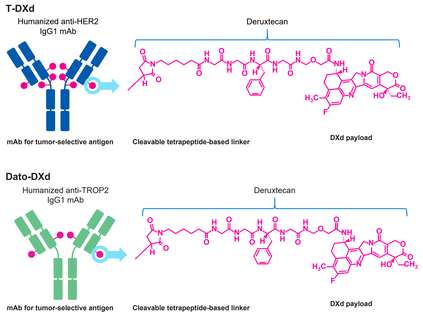
If you have a patient who could be eligible to participate, please contact DS3201-324SiteCommunications@dsi.com for clinical trial information

Background

DXd ADCs

- T-DXd is a HER2-directed ADC composed of a humanized anti-HER2 monoclonal antibody (mAb), a cleavable tetrapeptide-based linker, and a DXd payload (**Figure 1**)[12–14]
  - T-DXd is approved in the USA, for previously treated patients with HER2+ solid tumors, including those with HER2-low BC in the metastatic setting or with disease recurrence within 6 months of completing adjuvant chemotherapy,[15,16] and those with locally advanced or metastatic HER2+ GC/GEJ adenocarcinoma who have received a prior trastuzumab-based regimen[17]
  - Regulatory approvals of T-DXd for treatment of HER2-low advanced BC were based primarily on outcomes from the randomized, phase 3 DESTINY-Breast04[7] (NCT03734029) trial, in which T-DXd significantly prolonged progression-free survival (PFS) and overall survival (OS) versus physician's choice of chemotherapy
  - In the phase 2 DESTINY-Gastric01 (NCT03329690) trial, T-DXd significantly improved the response rate and OS versus physician's choice of chemotherapy[8]
- Dato-DXd is a TROP2-directed ADC composed of a humanized anti-TROP2 mAb, a plasma-stable tetrapeptide-based cleavable linker, and a DXd payload (**Figure 1**)[10]
  - In a randomized, phase 3 trial (TROPION-Lung01; NCT04656652), Dato-DXd significantly prolonged PFS compared with standard chemotherapy in patients with previously treated, locally advanced or metastatic NSCLC with or without actionable genomic alterations[11]
  - Within the nonsquamous population, median PFS was longer with Dato-DXd than with docetaxel (5.6 months vs 3.7 months, respectively)
  - In January 2025, a biologics license application for Dato-DXd was accepted in the USA for the treatment of adults with locally advanced or metastatic epidermal growth factor receptor-mutated (*EGFR*-mutated) NSCLC who have received prior systemic therapies, including an EGFR-directed therapy[18]

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

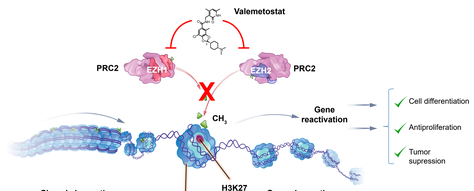


Dato-DXd, datopotamab deruxtecan; HER2, human epidermal growth factor receptor 2; IgG, immunoglobulin G; mAb, monoclonal antibody; T-DXd, trastuzumab deruxtecan; TROP2, trophoblast cell-surface antigen 2.

Valemetostat

- Valemetostat is a novel, potent, and selective dual inhibitor of EZH2 and EZH1[1–4]
  - 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[19,20]
  - EZH2-mediated protein phosphatase 2A inactivation has been shown to confer resistance to HER2-targeted therapy[21]
  - Dual inhibition of EZH2 and EZH1 with valemetostat has been shown to maximally suppress H3K27me3, thus upregulating genes silenced by H3K27me3 (**Figure 2**)[4]
  - 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)[1–3]

Figure 2. Mechanism of action of valemetostat



CH_3, methyl group; EZH, enhancer of zeste homolog; 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, including the DNA/RNA helicase *SLFN11*[5]
  - *SLFN11* expression levels indicate sensitivity to DDAs in various solid tumors; in response to DNA damage, *SLFN11* binds to chromatin, causing a replication block and inducing apoptosis[5,6]
  - Downregulation of *SLFN11* has been observed in chemotherapy-resistant tumor cells due to the presence of H3K27me3 at the *SLFN11* gene locus[5,6,22,23]
- Inhibition of EZH2 and EZH1 by valemetostat may upregulate *SLFN11* and enhance cancer cell sensitivity to DDAs, including DXd-based ADCs

Valemetostat + DXd ADCs in solid tumors

- Preclinical studies in various solid tumor models demonstrate that the effect of DXd ADCs is enhanced when combined with valemetostat (data on file)
- DS3201-324 (NCT06244485) is a 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, including 3 sub-protocols:
  - Unresectable or metastatic HER2-low BC: valemetostat + T-DXd
  - Advanced or metastatic HER2+ GC/GEJ adenocarcinoma: valemetostat + T-DXd
  - Advanced or metastatic nonsquamous NSCLC: valemetostat + Dato-DXd
- Here, we present the study design, patient eligibility criteria, and study objectives and endpoints for all 3 sub-protocols of the DS3201-324 Master Protocol trial

Methods

Study design

- Each sub-protocol (cohort) comprises a dose-escalation part (Part 1) followed by a dose-expansion part (Part 2) (**Figure 3**)
  - In Part 1, patients in each protocol will receive valemetostat orally at escalating doses of 50–200 mg/day plus either: T-DXd in BC and GC/GEJ cohorts intravenously at a dose of 5.4 mg/kg or 6.4 mg/kg every 3 weeks (Q3W); or Dato-DXd in the nonsquamous NSCLC cohort at 6.0 mg/kg intravenously Q3W
  - In Part 2, patients will receive valemetostat plus T-DXd or valemetostat plus Dato-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.
AGA, actionable genomic alteration; BC, breast cancer; Dato-DXd, datopotamab deruxtecan; DL, dose level; GC, gastric cancer; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; NSCLC, non-small-cell lung cancer; Q3W, every 3 weeks; RDE, recommended dose for expansion; T-DXd, trastuzumab deruxtecan.

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

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 v 1.1 • 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 • Concomitant use of moderate or strong CYP3A inducers
BC sub-protocol	
• Pathologically documented BC that is unresectable or metastatic, and has progressed on and would no longer benefit from endocrine therapy in hormone receptor-positive patients • Previously treated with 1–2 prior lines of chemotherapy in the recurrent or metastatic setting[b] • Has a history of HER2-low expression (IHC 2+/ISH− or IHC 1+/ISH−/untested])	• Prior ADC treatment consisting of an exatecan derivative that is a topoisomerase I inhibitor • Prior anti-HER2 therapy in the metastatic setting
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[c] • Locally confirmed HER2+ (IHC3+ or IHC2+/ISH+)	• Prior ADC consisting of an exatecan derivative that is a topoisomerase I inhibitor • Clinically significant gastrointestinal disorders[d] • Pleural effusion, ascites, or pericardial effusion that requires drainage, peritoneal shunt, or cell-free and concentrated ascites reinfusion therapy
NSCLC sub-protocol[e]	
• Pathologically documented stage IIIb, IIIc, or IV nonsquamous NSCLC, with or without AGAs[f] • NSCLC is unresectable or metastatic • Patients with an 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 an AGA: platinum-based chemotherapy in combination with α-PD-1/α-PD-L1 mAb or both agents sequentially	• Squamous histology • Mixed small-cell lung cancer and NSCLC histology • Activating *HER2* mutations (single nucleotide variant exon 20 insertion) • 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]Recurrence ≤ 6 months after (neo)adjuvant chemotherapy, therapy counts as 1 line of chemotherapy. Monotherapy of mammalian target of rapamycin inhibitors, poly adenosine diphosphate-ribose polymerase inhibitors, PD1 inhibitors, PD-L1 inhibitors, histone deacetylase inhibitors, or cyclin-dependent kinase 4/6 inhibitors and endocrine therapies do not count as prior lines of chemotherapy. [c]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. [d]Includes hepatic disorders, bleeding, inflammation, occlusion, ileus, Grade > 1 diarrhea, jaundice, intestinal paralysis, malabsorption syndrome, ulcerative colitis, inflammatory bowel disease, or partial bowel obstruction. [e]Eligibility is not based on the presence/absence of an AGA or TROP2 expression. [f]AGAs include *EGFR, ALK, ROS1, NTRK, BRAF V600E, MET* exon 14 skipping, *RET*, or *KRAS* G12C mutations.
ADC, antibody–drug conjugate; AGA, actionable genomic alteration; ALK, anaplastic lymphoma kinase; BC, breast cancer; BRAF, B-rapidly accelerated fibrosarcoma; CNS, central nervous system; CT, computed tomography; CYP3A, cytochrome P450 3A; ECOG PS, Eastern Cooperative Oncology Group performance status; 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; MET, proto-oncogene; MRI, magnetic resonance imaging; NTRK, neurotrophic tyrosine receptor kinase; NSCLC, non-small-cell lung cancer; PD1, programmed death-1; PD-L1, programmed death ligand 1; RECIST, Response Evaluation Criteria in Solid Tumors; RET, rearranged during transfection; ROS, proto-oncogene 1, receptor tyrosine kinase; TROP2, trophoblast cell-surface antigen 2.

- 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 ≥ 3 years (from first dose of study drug) for survival outcomes
- An 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

Objectives and endpoints

- Part 1 will assess the safety, tolerability, and RDE of valemetostat combined with T-DXd (BC and GC/GEJ cohorts) or with Dato-DXd (NSCLC cohort)
  - 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 for all cohorts, and an additional co-primary endpoint of safety and overall response rate ([ORR]; per Response Evaluation Criteria in Solid Tumors v1.1 criteria) in Part 2 for the BC cohort (**Table 2**)
- Secondary endpoints include ORR (Part 1 only), duration of response, PFS, OS, and PK

Table 2. Study endpoints

Endpoint	Description
Primary	
• Safety & tolerability (Part 1 for GC/GEJ adenocarcinoma and NSCLC cohorts, Part 1 and 2 for BC cohort) • ORR (Part 2)	• Incidence of DLTs and TEAEs (NCI-CTCAE v5.0) • Proportion of patients achieving CR or PR (RECIST v1.1 criteria)
Secondary	
• OS • PFS • DOR • ORR (Part 1) • Safety & tolerability (Part 2) • PK	• Time from enrollment to death • Time from enrollment to disease progression or death • Time from first response (CR/PR) to tumor progression or death • Proportion of patients achieving CR or PR (RECIST v1.1 criteria) • Incidence of TEAEs (all-grade, Grade 3/4, serious, leading to discontinuation) • Plasma/serum concentrations of valemetostat & ADC-associated moieties
Exploratory	
• Exposure-response PK • ADC immunogenicity • Valemetostat pharmacodynamics • Tumor imaging (G-score) • Valemetostat + ADC biomarkers	• Relationship between drug exposure and efficacy/safety endpoints • Antidrug–antibody prevalence (pre-existing and treatment-emergent) • H3K27me3 inhibition on-study • Describe tumor growth on radiographic assessments • SLFN11 protein expression, RNA gene expression, immune profiling, HER2 expression, TROP2 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; BC, breast cancer; CR, complete response; DLTs, dose-limiting toxicities; DOR, duration of response; GC, gastric cancer; GEJ, gastroesophageal junction; H3K27me3, trimethylation of histone H3 at lysine 27; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NSCLC, non-small-cell lung cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SLFN11, Schlafen 11; TEAEs, treatment-emergent adverse events; TROP2, trophoblast cell-surface antigen 2.

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