Valemetostat and Datopotamab Deruxtecan in Previously Treated, Advanced, Unresectable, or Metastatic Nonsquamous NSCLC

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SUMMARY

- Valemetostat tosylate (valemetostat) is an oral inhibitor of enhancer of zeste homolog (EZH)2 and EZH1 that has demonstrated clinical activity and also a favorable safety profile in multiple hematologic malignancies[1–4]
  - Its mechanism of action suggests 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*)[5–7]
- 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)[8,9]
- This phase 1b signal-seeking study will assess whether adding valemetostat to Dato-DXd enhances the efficacy of this ADC in patients with previously treated, advanced, nonsquamous NSCLC, while preserving an overall manageable safety profile
- Enrollment is ongoing at 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**

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BACKGROUND

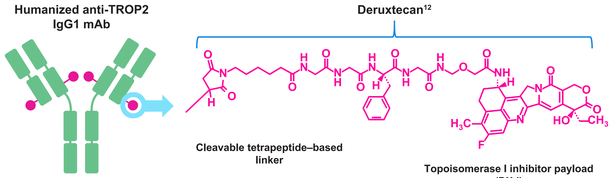
Dato-DXd

- Dato-DXd is a TROP2-directed ADC composed of a humanized anti-TROP2 immunoglobulin G1 (IgG1) antibody covalently linked to a potent DXd via a plasma-stable tetrapeptide-based cleavable linker (**Figure 1**)[8]
- In a randomized, phase 3 trial (TROPION-Lung01; NCT04656652), Dato-DXd significantly prolonged progression-free survival (PFS) compared with standard chemotherapy in patients with previously treated, locally advanced or metastatic NSCLC with or without actionable genomic alterations (AGAs)[9]
  - In patients with nonsquamous NSCLC, Dato-DXd reduced the risk of disease progression or death by 37% compared with docetaxel (hazard ratio [HR], 0.63; 95% confidence interval [CI], 0.51–0.78) as assessed by blinded independent central review
    - Within the nonsquamous population, median PFS was longer with Dato-DXd than with docetaxel (5.6 months vs 3.7 months, respectively)
- In February 2024, a biologics license application for Dato-DXd was accepted in the US for the treatment of adults with locally advanced or metastatic nonsquamous NSCLC who have received prior systemic therapy[10]

Figure 1. Structure of Dato-DXd

Dato-DXd is an ADC composed of 3 parts[8,11]:

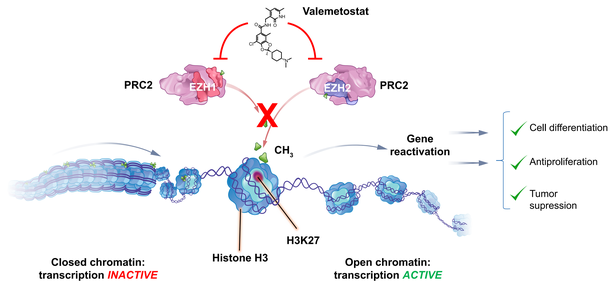
- A monoclonal antibody (mAb) for a tumor-selective antigen
- A tetrapeptide-based cleavable linker that covalently bonds the other 2 components
- A topoisomerase I inhibitor payload (an exatecan derivative, DXd)



Valemetostat

- 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; global H3K27me3 accumulation has been noted in various solid tumors and hematologic malignancies[13,14]
  - 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 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 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[6,7,15,16]
- Inhibition of EZH2 and EZH1 by valemetostat may upregulate *SLFN11* and enhance cancer cell sensitivity to DDAs, including ADCs

METHODS

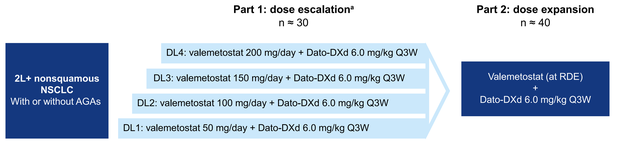
Valemetostat + DXd ADCs in solid tumors

- Preclinical studies demonstrate synergistic effects of combining valemetostat with DXd ADCs in various solid tumors *(data on file)*
- DS3201-324 (NCT06244485) is a multicenter, 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 (2L+) therapy for patients with advanced tumors, currently including 3 subprotocols:
  - **Advanced or metastatic nonsquamous NSCLC:** valemetostat + Dato-DXd
  - **Unresectable or metastatic human epidermal receptor (HER)2-low breast cancer:** valemetostat + trastuzumab deruxtecan (T-DXd)
  - **Advanced or metastatic HER2+ gastric or gastroesophageal junction adenocarcinoma:** valemetostat + T-DXd
- Here, we present the study design, eligibility criteria, objectives, and endpoints for the nonsquamous NSCLC subprotocol

Study design

- This phase 1b study 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 at escalating doses of 50–200 mg orally once daily under fasting conditions and Dato-DXd 6.0 mg/kg intravenously every 3 weeks (Q3W); intermediate dose levels may be explored
  - In Part 2, patients will receive valemetostat and 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.
DL, dose level.

- Target enrollment is approximately 70 patients per subprotocol, with 30 in Part 1 and 40 in Part 2
- Key eligibility criteria are shown in **Table 1**
  - Eligibility is not based on presence/absence of an AGA nor TROP2 expression

Table 1. Key eligibility criteria

Inclusion criteria	Exclusion criteria
• Age ≥ 18 years[a] • ≥ 1 measurable lesion based on investigator imaging assessment using RECIST v1.1 • ECOG PS score of 0–1 • Adequate organ function • Pathologically documented stage IIIB, IIIC, or IV nonsquamous NSCLC, with or without AGAs[b] that is unresectable or metastatic • Patients with AGAs[b]: (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 AGAs: platinum-based chemotherapy in combination with α-PD-L1/mAb or both agents sequentially	• Squamous histology • Mixed small-cell lung cancer and NSCLC histology • Activating *HER2* mutations (single nucleotide variant or exon 20 insertion) • Prior TROP2-targeted therapy or exposure to any agent, including ADCs, targeting topoisomerase I

[a]Or the minimum legal adult age, whichever is greater. [b]Patients with AGAs must have ≥ 1 documented AGA: *EGFR*, *ALK*, *ROS1*, *NTRK*, *BRAF* V600E, *MET* exon 14 skipping, *RET*, or *KRAS* G12C mutations. Patients without AGAs must have documented negative test results for *EGFR* and *ALK* genomic alterations, and have no known AGAs in *ROS1*, *NTRK*, *BRAF* V600E, *MET* exon 14 skipping, *RET*, or *KRAS* G12C mutations.
ALK, anaplastic lymphoma kinase; *BRAF*, v-raf murine sarcoma viral oncogene homolog B 1; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; *KRAS*, Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; MET, mesenchymal epithelial transition proto-oncogene, receptor tyrosine kinase; NTRK, neurotrophic tyrosine receptor kinase; α-PD-1, alpha programmed death-1; α-PD-L1, alpha programmed death-ligand 1; RECIST, Response Evaluation Criteria in Solid Tumors; RET, rearranged during transfection; ROS1, reactive oxygen species proto-oncogene 1, receptor tyrosine kinase.

- 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
- An interim futility analysis will be performed when 20 patients are enrolled at the RDE

Objectives and endpoints

- Part 1 will assess the safety, tolerability, and RDE of valemetostat combined with Dato-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 endpoints are safety and tolerability in Part 1 and overall response rate (ORR) in Part 2 (**Table 2**)
- Secondary endpoints include PFS, overall survival (OS), and PK

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	
• TROP2-response	Relationship between TROP2 expression level by IHC and clinical response
• Exposure-response PK	Relationship between drug exposure and efficacy/safety endpoints
• ADC immunogenicity	Antidrug 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; DLTs, dose-limiting toxicities; DOR, duration of response; IHC, immunohistochemistry; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PD, pharmacodynamics; PR, partial response; TEAEs, treatment-emergent adverse events.

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