Phase 1b Study of Valemetostat in Combination With Datopotamab Deruxtecan (Dato-DXd) in Advanced Non-squamous Non-small-cell Lung Cancer (NSCLC): Initial Safety Results

2023P

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SUMMARY

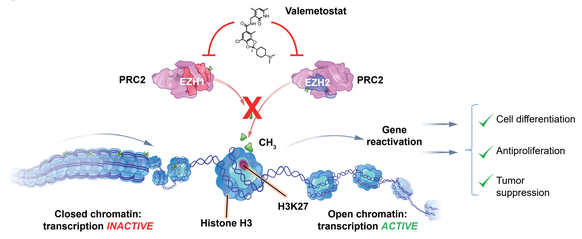
- Valemetostat tosylate (valemetostat) is an oral, selective, dual inhibitor of enhancer of zeste homolog (EZH)2 and EZH1 that has demonstrated clinical activity and a favorable safety profile in multiple hematologic malignancies[1–4]
  - Its mechanism of action suggests a potential to sensitize cancer cells to DNA-damaging agents (DDAs), such as 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 non-squamous (ns) non-small-cell lung cancer (NSCLC)[8,9]
- Here, we describe the preliminary safety and tolerability results of valemetostat + Dato-DXd in advanced nsNSCLC in an ongoing phase 1b trial (NCT06244485)
- There were no new safety findings; the overall safety profile was generally similar to that of valemetostat or Dato-DXd monotherapy

BACKGROUND

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[10,11]
  - Valemetostat has been shown to maximally suppress H3K27me3, thus upregulating silenced genes (**Figure 1**)[5]
  - Valemetostat has demonstrated clinical efficacy and favorable tolerability in multiple hematologic malignancies[1–4]
- EZH2 controls gene expression, including those 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[6,7,12,13]
- Valemetostat prevents H3K27me3, altering gene expression patterns that may upregulate *SLFN11* and enhance cancer-cell sensitivity to DDAs, including ADCs

Figure 1. Mechanism of action of valemetostat

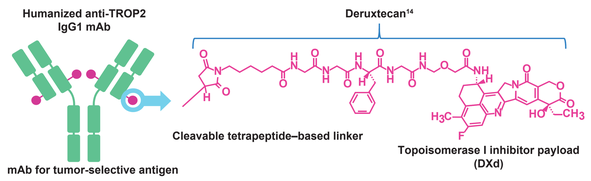


CH_3, trimethyl group; EZH, enhancer of zeste homolog; H3K27, histone H3 at lysine 27; PRC2, polycomb repressive complex 2.

Dato-DXd

- Dato-DXd is an ADC composed of a humanized anti-TROP2 monoclonal antibody, a plasma-stable tetrapeptide-based cleavable linker, and a DXd payload (**Figure 2**)[8,14,15]
- 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[9]
  - Among patients with nsNSCLC, Dato-DXd reduced the risk of disease progression or death by 37% compared with docetaxel (hazard ratio, 0.63; 95% confidence interval, 0.51–0.79; as assessed by blinded independent central review)
    - Within the nsNSCLC subgroup, median PFS was longer with Dato-DXd than with docetaxel (5.5 months vs 3.6 months, respectively)
- In 2025, Dato-DXd 6.0 mg/kg received accelerated approval in the US for the treatment of adult patients with locally advanced or metastatic epidermal growth factor receptor (*EGFR*)-mutated NSCLC who have received prior EGFR-directed therapy and platinum-based chemotherapy[16]

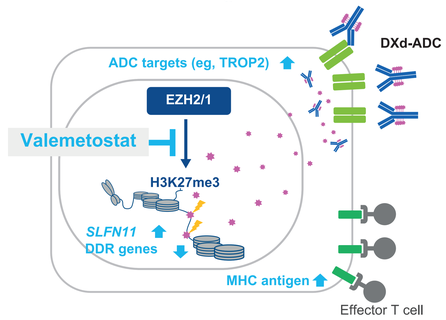
Figure 2. Structure of Dato-DXd



Dato-DXd, datopotamab deruxtecan; IgG1, immunoglobulin G1; mAb, monoclonal antibody; TROP2, trophoblast cell-surface antigen 2.

- Preclinical studies have demonstrated synergistic effects of combining valemetostat with DXd ADCs in various solid tumors (**Figure 3**)[17]
- Here, we report for the first time preliminary safety and tolerability data of valemetostat at escalating dose levels in combination with fixed-dose Dato-DXd in patients with nsNSCLC

Figure 3. Rationale for combining valemetostat with DXd ADCs



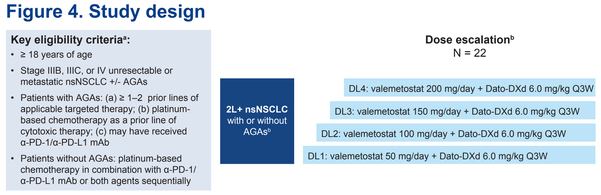
ADC, antibody–drug conjugate; DDR, DNA damage response; DXd, deruxtecan; EZH2/1, enhancer of zeste homolog 2/1; H3K27me3, trimethylation of histone H3 at lysine 27; MHC, major histocompatibility complex; *SLFN11*, Schlafen 11; TROP2, trophoblast cell-surface antigen 2.

METHODS

Study design

- DS3201-324 (NCT06244485) is a multicenter, open-label, phase 1b "Master Protocol" trial assessing the safety and tolerability of valemetostat in combination with DXd ADCs as second-line or later therapy for patients with solid tumors
  - This sub-protocol enrolled patients with advanced metastatic nsNSCLC
- In this dose-escalation study, patients received valemetostat at 50–200 mg orally (PO) once daily (QD) under fasting conditions and Dato-DXd 6.0 mg/kg intravenously (IV) every 3 weeks (Q3W) in 28-day cycles (**Figure 4**)
- The primary endpoints are safety and tolerability of valemetostat in combination with Dato-DXd in nsNSCLC

Figure 4. Study design



[a]Eligibility was not based on the presence/absence of an AGA or TROP2 expression. [b]This is based on a Bayesian Optimal Interval design. 2L+, second line or later; α-PD-1, anti programmed death protein 1; α-PD-L1, programmed death ligand 1; AGA, actionable genomic alteration; Dato-DXd, datopotamab deruxtecan; DL, dose level; mAb, monoclonal antibody; ns, non-squamous; NSCLC, non-small-cell lung cancer; Q3W, every 3 weeks; TROP2, trophoblast cell-surface antigen 2.

RESULTS

Patient enrollment, disposition, and demographics

- At data cutoff (March 6, 2025), 22 patients had been enrolled and received valemetostat 50 mg (n = 3), 100 mg (n = 6), 150 mg (n = 6), or 200 mg (n = 7) + Dato-DXd
- Baseline demographics and disease characteristics are presented in **Table 1**
  - The median age was 65 years, and 59% (n = 13) of patients were female
- Median treatment duration at data cutoff was 3.7 months, and 11 (50%) patients remained on treatment
  - Reasons for discontinuation were disease progression (n = 6); treatment-emergent adverse events (TEAEs) including decreased appetite, respiratory failure, stomatitis, fatigue (n = 1 each; total n = 4); and death due to progressive disease (n = 1)

Table 1. Baseline demographics and disease characteristics

Characteristic	Valemetostat dose + Dato-DXd 6.0 mg/kg				Total (N = 22)
	50 mg/day (n = 3)	100 mg/day (n = 6)	150 mg/day (n = 6)	200 mg/day (n = 7)	
Age, median (range), years	62	61	59	64	65 (39–77)
Sex, n (%)					
Male	1 (33)	5 (83)	1 (17)	2 (29)	9 (41)
Female	2 (67)	1 (17)	5 (83)	5 (71)	13 (59)
Country of enrollment, n (%)					
US	3 (100)	1 (17)	1 (17)	5 (71)	10 (45)
Japan	0	5 (83)	5 (83)	2 (29)	12 (55)
Smoking status, n (%)					
Never	0	2 (33)	3 (50)	2 (29)	7 (32)
Former	3 (100)	4 (67)	2 (33)	5 (71)	14 (64)
Current	0	0	1 (17)	0	1 (4)
ECOG PS score, n (%)					
0	0	3 (50)	3 (50)	0	6 (27)
1	3 (100)	3 (50)	3 (50)	7 (100)	16 (73)
Histology, n (%)					
Adenocarcinoma	3 (100)	6 (100)	6 (100)	7 (100)	22 (100)
History of brain metastasis, n (%)					
Yes	1 (33)	2 (33)	1 (17)	2 (29)	6 (27)
No	2 (67)	4 (67)	5 (83)	5 (71)	16 (73)
Prior lines of therapy, n (%)					
1	0	0	2 (33)	1 (14)	3 (14)
2	2 (67)	1 (17)	2 (33)	4 (57)	9 (41)
3	0	4 (67)	1 (17)	1 (14)	6 (27)
≥ 4	1 (33)	1 (17)	1 (17)	1 (14)	4 (18)
Prior anticancer therapies, n (%)					
Platinum-based chemotherapy	3 (100)	6 (100)	6 (100)	7 (100)	22 (100)
Other chemotherapy	3 (100)	6 (100)	6 (100)	7 (100)	22 (100)
Anti-PD-1/anti-PD-L1 immunotherapy	3 (100)	4 (67)	3 (50)	6 (86)	16 (73)
Targeted therapy for indicated AGAs	1 (33)	5 (83)	4 (67)	3 (43)	13 (59)
Other cancer therapy	3 (100)	5 (83)	1 (17)	2 (29)	11 (50)

AGA, actionable genomic alteration; Dato-DXd, datopotamab deruxtecan; ECOG PS, Eastern Cooperative Oncology Group performance status; PD-1, programmed death protein 1; PD-L1, programmed death ligand 1.

Safety and tolerability

- No dose-limiting toxicities were observed across dose levels, and no valemetostat maximum tolerated dose has been identified up to 200 mg
- Twenty (91%) patients experienced ≥ 1 TEAE
- The most common TEAEs (any grade) were stomatitis (59%), decreased appetite (41%), and alopecia (36%) (**Table 2**)

Table 2. TEAEs (all grades) in ≥ 10% of all patients

Preferred term, n (%)	Valemetostat dose + Dato-DXd 6.0 mg/kg				Total (N = 22)
	50 mg/day (n = 3)	100 mg/day (n = 6)	150 mg/day (n = 6)	200 mg/day (n = 7)	
Stomatitis	1 (33)	4 (67)	5 (83)	3 (43)	13 (59)
Decreased appetite	1 (33)	2 (33)	3 (50)	3 (43)	9 (41)
Alopecia	1 (33)	3 (50)	3 (50)	1 (14)	8 (36)
Nausea	2 (67)	2 (33)	2 (33)	1 (14)	7 (32)
Constipation	0	3 (50)	3 (50)	0	6 (27)
Anemia	0	1 (17)	2 (33)	3 (43)	6 (27)
Dysgeusia	0	2 (33)	1 (17)	2 (29)	5 (23)
Fatigue	0	1 (17)	2 (33)	2 (29)	5 (23)
Decreased lymphocyte count	1 (33)	0	0	3 (43)	4 (18)
Malaise	0	2 (33)	1 (17)	0	3 (14)
Decreased platelet count	0	0	2 (33)	1 (14)	3 (14)

Dato-DXd, datopotamab deruxtecan; TEAE, treatment-emergent adverse event.

- Grade ≥ 3 TEAEs occurred in 11 patients (50%), most commonly decreased lymphocyte count (18%), decreased appetite (14%), and fatigue (9%) (**Table 3**)

Table 3. Grade ≥ 3 TEAEs

Preferred term, n (%)	Valemetostat dose + Dato-DXd 6.0 mg/kg				Total (N = 22)
	50 mg/day (n = 3)	100 mg/day (n = 6)	150 mg/day (n = 6)	200 mg/day (n = 7)	
Decreased lymphocyte count	1 (33)	0	0	3 (43)	4 (18)
Decreased appetite	0	1 (17)	2 (33)	0	3 (14)
Fatigue	0	0	1 (17)	1 (14)	2 (9)
Anemia	0	0	0	1 (14)	1 (5)
Dizziness	0	0	0	1 (14)	1 (5)
Respiratory failure	0	0	0	1 (14)	1 (5)
Nausea	0	0	1 (17)	0	1 (5)
Stomatitis	0	0	1 (17)	0	1 (5)
Pneumonia	0	0	1 (17)	0	1 (5)
Pneumocystis jirovecii pneumonia	0	1 (17)	0	0	1 (5)
Disease progression	0	1 (17)	0	0	1 (5)
Chronic cardiac failure	1 (33)	0	0	0	1 (5)

Dato-DXd, datopotamab deruxtecan; TEAE, treatment-emergent adverse event.

- Serious adverse events were reported in 7 patients (32%) (**Table 4**); stomatitis and respiratory failure were assessed as related to study treatment

Table 4. SAEs

Preferred term	n	NCI CTCAE grade	Valemetostat dose (+ Dato-DXd 6.0 mg/kg)
Cardiac failure chronic	1	3	50 mg/day
Pneumocystis jirovecii pneumonia	1	3	100 mg/day
Disease progression	1	5	100 mg/day
Pneumonia	1	3	150 mg/day
Stomatitis	1	3	150 mg/day
Dizziness	1	3	200 mg/day
Respiratory failure	1	4, 5[a]	200 mg/day

[a]Grade 4 and Grade 5 both occurred in the same patient; Grade 5 respiratory failure was adjudicated as interstitial lung disease related to Dato-DXd. Dato-DXd, datopotamab deruxtecan; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; SAE, serious adverse event.

- All adverse events of special interest were Grade 1 or 2, except for 1 patient with Grade 3 stomatitis, which resulted in treatment discontinuation (valemetostat 150 mg QD + Dato-DXd 6.0 mg/kg Q3W) (**Table 5**)

Table 5. AESIs, any grade

	Valemetostat dose + Dato-DXd 6.0 mg/kg				Total (N = 22)
	50 mg/day (n = 3)	100 mg/day (n = 6)	150 mg/day (n = 6)	200 mg/day (n = 7)	
Patients with any AESI, n (%)	1 (33)	4 (67)	5 (83)	3 (43)	13 (59)
Ocular surface events, n (%)					
Punctate keratitis	0	0	0	1 (14)	1 (5)
Blepharitis	0	0	1 (17)	0	1 (5)
Lacrimation increased	0	0	1 (17)	0	1 (5)
Conjuctivitis	0	2 (33)	0	0	2 (9)
Oral mucositis/stomatitis, n (%)					
Stomatitis	1 (33)	4 (67)	5 (83)	3 (43)	13 (59)
Oral pain	0	0	1 (17)	0	1 (5)

AESI, adverse event of special interest; Dato-DXd, datopotamab deruxtecan.

CONCLUSIONS

- Valemetostat + Dato-DXd demonstrated manageable safety and tolerability in patients with advanced nsNSCLC
- There were no new safety findings, and the overall safety profile was generally similar to that of monotherapy valemetostat or Dato-DXd
- Valemetostat 200 mg PO QD + Dato-DXd 6.0 mg/kg IV Q3W will be further investigated in a dose-expansion phase of this trial
- Enrollment is currently ongoing in the US, Japan, and China

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ACKNOWLEDGMENTS

- This study is sponsored by Daiichi Sankyo
- In July 2020, Daiichi Sankyo and AstraZeneca entered a global collaboration to jointly develop and commercialize Dato-DXd, except in Japan where Daiichi Sankyo maintains exclusive rights
- All authors contributed to and approved the presentation
- Writing and editorial support were provided by Naomi Blommaert, MSc, of Excerpta Medica, funded by Daiichi Sankyo, in accordance with Good Publication Practice guidelines

DISCLOSURES

Leadership: NEXT Oncology Virginia; **Consulting or advisory roles:** Amgen, ArriVent Biopharma, AstraZeneca/MedImmune, Black Diamond Therapeutics, Bristol-Myers Squibb, CRISPR Therapeutics, Daiichi Sankyo/AstraZeneca, Gritstone Bio, Gritstone Oncology, GSK, Incyte, Janssen R&D, Jazz Pharmaceuticals, Lilly, Merck, Mersana, Mirati Therapeutics, Novartis, Regeneron, Revolution Medicines, Sanofi, Synthekine, Takeda, Blueprint Medicines; **Honoraria:** AbbVie, Amgen, Astellas Pharma, AstraZeneca/MedImmune, Bayer, Bristol-Myers Squibb, CytomX Therapeutics, Janssen Oncology, Merck, Novartis, Prelude Therapeutics, Takeda; **Research funding:** ADCT, Alkermes, Amgen, Astellas Pharma, AstraZeneca, Astex Pharmaceuticals, AbbVie, Black Diamond Therapeutics, Blueprint Medicines, Boehringer Ingelheim, Bristol-Myers Squibb, BluPrint Oncology, CytomX Therapeutics, Daiichi Sankyo, Gritstone, Ignyta, Incyte, Janssen Oncology, LAM Therapeutics, Lilly, Loxo, Macrogenics, Medikine, MedImmune, Mersana, Nalo Therapeutics, Novartis, Plexxikon, Prelude Therapeutics, Regeneron, Revolution Medicines, Roche, Rubius, Scorpion Therapeutics, Synthekine

Presented at the European Society for Medical Oncology (ESMO) Congress; October 17–21, 2025; Berlin, Germany.

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