Safety of Valemetostat Plus Pembrolizumab in Advanced or Metastatic 1L NSCLC Without Actionable Genomic Alterations Expressing PD-L1 With TPS ≥ 50%: Interim Results from the Phase 1b Trial

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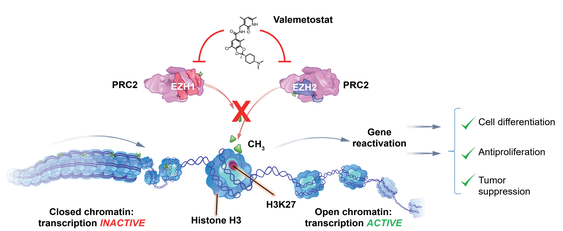
SUMMARY

- Pembrolizumab is a programmed death (PD)-1 receptor monoclonal antibody (mAb) approved as monotherapy or combined with chemotherapy for the treatment of advanced or metastatic non-small-cell lung cancer (NSCLC)[1]
- Valemetostat is an oral, dual inhibitor of enhancer of zeste homolog (EZH)2/EZH1 that has shown favorable tolerability and efficacy in hematologic malignancies[2,3] and preliminary safety in solid tumors[4]
- Inhibition of EZH2/EZH1 with valemetostat could augment the immunotherapeutic effects of pembrolizumab
- Here, we report preliminary safety and dose-escalation results from a phase 1b study of valemetostat + pembrolizumab as first-line (1L) treatment for patients with advanced or metastatic NSCLC without actionable genomic alterations (AGAs) and expressing programmed death-ligand 1 (PD-L1) with a tumor proportion score (TPS) ≥ 50%
- The combination of valemetostat at doses of 150–300 mg/day plus pembrolizumab 200 mg every three weeks (Q3W) was well tolerated, with a safety profile similar to that for each individual agent

INTRODUCTION

- Pembrolizumab is a mAb that binds to the PD-1 receptor, inhibiting its interaction with PD-ligands L1/L2, and is approved as monotherapy or in combination with chemotherapy for advanced or metastatic NSCLC[1]
- While pembrolizumab monotherapy demonstrates clinical activity in this population,[5,6] a substantial proportion of patients remain unresponsive due, in part, to low tumor immunogenicity and an immunosuppressive tumor microenvironment (TME)[7,8]
- Many tumors escape immune surveillance through increased expression of negative regulators of the immune response, including immune checkpoint regulators such as PD-1/PD-L1 and CTLA-4, and overexpression of EZH2[9–11]
- EZH2 plays a pivotal role in the TME by interacting with multiple cell types, governing the activation, differentiation, and polarization of immune cells, while also regulating tumor cell proliferation, immune escape, and invasion[11]
- Treatment combinations are needed to augment the efficacy of anti-PD-1/PD-L1 therapy by overcoming low immunogenicity and TME immunosuppression
- Valemetostat is an oral, dual inhibitor of EZH2 and EZH1 that suppresses trimethylation of histone H3 at lysine 27, reactivating the expression of silenced genes (**Figure 1**)[2,3,12–15]
  - It has been approved in Japan for treatment of relapsed or refractory peripheral T-cell lymphoma and adult T-cell leukemia/lymphoma[5–8,12,13]

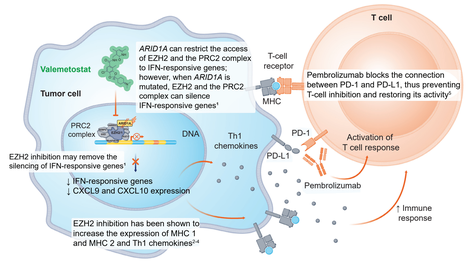
Figure 1. Mechanism of action of valemetostat



CH3, trimethyl group; EZH, enhancer of zeste homolog; H3K27, histone H3 at lysine 27; PRC2, polycomb repressive complex 2.

- In preclinical studies in NSCLC cell lines and murine models, EZH2 inhibition increases cluster of differentiation (CD)8$^+$/CD4$^+$ T-cell infiltration of the tumor microenvironment and upregulates major histocompatibility complex class I genes, indicating valemetostat's potential to enhance immunotherapy efficacy[2,3,14,16–18]
- Inhibition of EZH2 and EZH1 with valemetostat may reactivate the expression of silenced genes, and may therefore, potentiate the efficacy of anti-PD-1/PD-L1 therapy by restoring tumor immunogenicity via epigenetic modulation and activate the antitumor response[16–18] (**Figure 2**)
- Valemetostat could create a favorable TME for immune therapy and prime tumor status to enhance the antitumor response of immunotherapy when combined with pembrolizumab[16–20]
- Here, we report preliminary safety results of valemetostat + pembrolizumab from a phase 1b study (DS3201-330) in advanced or metastatic 1L NSCLC without AGAs and expressing PD-L1 with TPS score ≥ 50%

Figure 2. The proposed mechanism of action of valemetostat plus pembrolizumab



AEBP2, adipocyte enhancer-binding protein 2; ARID1A, AT-rich interaction domain 1A; CXCL, chemokine (C-X-C motif) ligand; EED, embryonic ectoderm development; EZH, enhancer of zeste homolog; IFN, interferon; JARID2, jumonji and AT-rich interaction domain containing 2; MHC, major histocompatibility complex; PCL, polycomb-like proteins; PD-1, programmed death-1; PD-L1, programmed death ligand 1; PRC2, polycomb repressive complex 2; RbAP46/48, retinoblastoma-binding protein 46/48 also known as RBBP7; SUZ12, suppressor of zeste 12 protein homolog; Th1, Type 1 T helper.

METHODS

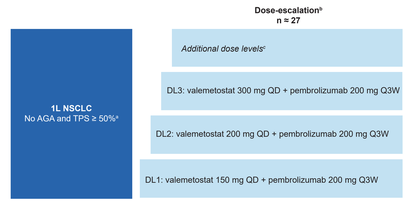
- DS3201-330 is a global, multicenter, open-label, randomized, phase 1b trial (NCT06644768) evaluating valemetostat with pembrolizumab in patients ≥ 18 of age with previously untreated advanced or metastatic NSCLC
- Patients had NSCLC without AGAs (genes with approved therapies, such as *EGFR, ALK, ROS1, NTRK, BRAF, RET, MET*, or other actionable oncogenic drivers) and with PD-L1 TPS ≥ 50%
  - Key eligibility criteria are presented in **Table 1**
- In the dose-escalation part (phase 1b), patients received oral valemetostat at escalating doses of 150–300 mg once daily, in combination with intravenous pembrolizumab 200 mg Q3W (**Figure 3**)
- The primary endpoints of the phase 1b were safety, tolerability, and determination of the recommended phase 2 dose (RP2D)

Table 1. Key eligibility criteria

Inclusion criteria	Exclusion criteria
Histologically documented NSCLC meeting the following criteria: • Stage IIIB or IIIC disease ineligible for resection or chemoradiation, or Stage IV disease at time of enrollment/ randomization • No prior systemic therapy for advanced or metastatic disease • Negative test results for *EGFR, ALK,* and *ROS1* AGAs • No known AGAs in *NTRK, BRAF, RET, MET*, or other actionable oncogenic drivers with locally approved therapies	Prior treatment with any EZH inhibitors and/or any anti-PD-1, anti-PD-L1, or anti-PD-L2 agents or agents directed against other stimulatory or co-inhibitory T-cell receptors
CT- or MRI-measurable disease based on local imaging assessment using RECIST v1.1	Active, known, or suspected autoimmune disease requiring treatment, and/or diagnosis of immunodeficiency and receiving systemic steroid therapy or other form of immunosuppressive treatment
PD-L1 TPS ≥ 50% (by local testing with 22C3 pharmDx PD-L1 IHC assay or central testing)	Uncontrolled or significant cardiovascular disease
Eastern Cooperative Oncology Group performance status score of 0/1	Spinal cord compression or clinically active CNS metastases
Adequate organ and bone marrow function	History of interstitial lung disease/pneumonitis or radiation pneumonitis
	Concomitant use of moderate or strong CYP3A inhibitors or inducers and/or P-gp inhibitor

AGA, actionable genomic alteration; ALK, anaplastic lymphoma kinase; BRAF, proto-oncogene B-raf; CNS, central nervous system; CT, computed tomography; CYP3A, cytochrome P450 3A; EGFR, epidermal growth factor receptor; EZH, enhancer of zeste homolog; IHC, immunohistochemistry; MET, mesenchymal epithelial transition; MRI, magnetic resonance imaging; NSCLC, non-small-cell lung cancer; NTRK, neurotrophic tyrosine receptor kinase; PD-1, programmed death-1; PD-L1/2, programmed death ligand 1/2; P-gp, P-glycoprotein; RECIST, Response Evaluation Criteria in Solid Tumors; RET, rearranged during transfection; ROS1, ROS proto-oncogene 1 gene; TPS, tumor proportion score.

Figure 3. Phase 1b dose-escalation



[a]Local testing using 22C3 pharmDx PD-L1 immunohistochemistry assay or central testing. [b]This is based on a Bayesian Optimal Interval design. [c]Additional dose levels may be considered based on review of available safety, tolerability, pharmacokinetic data, and exposure–response for safety and efficacy
1L, first-line; AGA, actionable genomic alterations; DL, dose level; NSCLC, non-small-cell lung cancer; PD-L1, programmed death ligand 1; Q3W, once every three weeks; QD, once daily; TPS, tumor proportion score.

RESULTS

Patient enrollment, disposition, and demographics

- At interim data cutoff (February 2, 2026), 24 patients had been enrolled in phase 1b and treated with valemetostat 150 mg (n = 5; 21%), 200 mg (n = 9; 37%), or 300 mg (n = 10; 42%) + pembrolizumab 200 mg
- A total of 14 patients (58%) remained on treatment, and 10 patients (42%) discontinued:
  - 3/5 patients (60%) in the valemetostat 150-mg group, due to progressive disease (PD) (n = 2) and physician decision (n = 1)
  - 2/9 patients (22%) in the valemetostat 200-mg group, due to PD (n = 2)
  - 5/10 patients (50%) in the valemetostat 300-mg group, due to death caused by PD-related cardiopulmonary arrest, adverse events (n = 1 each), and PD (n = 3)
- Median (range) treatment duration at data cutoff was 3.0 months (0.3–8.0) in the overall population, 3.8 months (1.9–6.1) for valemetostat 150 mg, 2.8 (0.9–8.0) months for valemetostat 200 mg, and 2.8 months (0.3–6.2) for valemetostat 300 mg
- Baseline demographics and disease characteristics are presented in **Table 2**
  - The median age was 70.0 years; 79% (n = 19) of patients were male, 63% (n = 15) had adenocarcinoma histology, and 17% (n = 4) had a history of brain metastasis

Table 2. Baseline demographics and disease characteristics

Characteristic	Valemetostat dose			Total
	150 mg (n = 5)	200 mg (n = 9)	300 mg (n = 10)	N = 24
Age, years, median (range)[a]	70.0 (58–83)	71.0 (49–84)	69.0 (57–80)	70.0 (49–84)
Sex, n (%)				
Male	4 (80)	6 (67)	9 (90)	19 (79)
Female	1 (20)	3 (33)	1 (10)	5 (21)
Race, n (%)				
White	2 (40)	5 (56)	3 (30)	10 (42)
Asian	3 (60)	4 (44)	7 (70)	14 (58)
Region of enrollment, n (%)				
North America	2 (40)	2 (22)	0	4 (17)
Asia	3 (60)	4 (44)	7 (70)	14 (58)
Rest of the world	0	3 (33)	3 (30)	6 (25)
Smoking status, n (%)				
Never	1 (20)	0	1 (10)	2 (8)
Former	2 (40)	8 (89)	8 (80)	18 (75)
Current	2 (40)	1 (11)	1 (10)	4 (17)
ECOG PS score, n (%)				
0	0	5 (56)	2 (20)	7 (29)
1	5 (100)	4 (44)	8 (80)	17 (71)
Histology, n (%)				
Adenocarcinoma	3 (60)	7 (78)	5 (50)	15 (63)
Squamous	2 (40)	2 (22)	5 (50)	9 (38)
Tumor stage at study entry, n (%)				
III	0	0	2 (20)	2 (8)
IV	5 (100)	9 (100)	8 (80)	22 (92)
Brain metastasis at study entry, n (%)				
Yes	0	1 (11)	1 (10)	2 (8)
No	5 (100)	8 (89)	9 (90)	22 (92)
History of brain metastases, n (%)				
Yes	1 (20)	2 (22)	1 (10)	4 (17)
No	4 (80)	7 (78)	9 (90)	20 (83)
History of other metastases, n (%)				
Yes	3 (60)	7 (78)	7 (70)	17 (71)
No	2 (40)	2 (22)	3 (30)	7 (29)

Baseline value is defined as the last non-missing value taken before the first dose of study treatment.
[a]Age is calculated as the number of completed years between date of birth and date of informed consent. ECOG PS, Eastern Cooperative Oncology Group performance status.

Safety and tolerability

- All patients enrolled (N = 24) received the study drug and were included in the safety assessment
- Overall, 23 patients (96%) experienced ≥ 1 treatment-emergent adverse event (TEAE) of any grade, most commonly anemia (42%; 10/24), rash, and decreased appetite (21%; 5/24, each) (**Table 3**)
- Grade ≥ 3 TEAEs were reported in 8 patients (33%), most commonly cancer pain (8%; 2/24), which was the only Grade ≥ 3 TEAE that occurred in > 1 patient
- Serious adverse events (SAEs) were reported in 7 patients (29%) (**Table 4**)
- No adverse events of special interest or dose-limiting toxicities were observed across dose levels
- There were no TEAEs associated with study drug discontinuation

Table 3. TEAEs (all grades) occurring in ≥ 10% of all patients

Preferred term, n (%)	Valemetostat dose + pembrolizumab 200 mg IV			Total
	150 mg (n = 5)	200 mg (n = 9)	300 mg (n = 10)	N = 24
Anemia	3 (60)	4 (44)	3 (30)	10 (42)
Rash	1 (20)	1 (11)	3 (30)	5 (21)
Dysgeusia	1 (20)	3 (33)	1 (10)	5 (21)
Decreased appetite	1 (20)	2 (22)	2 (20)	5 (21)
Alopecia	1 (20)	2 (22)	1 (10)	4 (17)
Hypertriglyceridemia	1 (20)	2 (22)	0	3 (13)
Nausea	1 (20)	0	2 (20)	3 (13)
Blood alkaline phosphatase increased	0	0	3 (30)	3 (13)
Platelet count decreased	0	2 (22)	1 (10)	3 (13)
Alanine aminotransferase increased	0	2 (22)	1 (10)	3 (13)
Hypothyroidism	1 (20)	2 (22)	0	3 (13)
Diarrhea	0	2 (22)	1 (10)	3 (13)

IV, intravenous(ly); TEAE, treatment-emergent adverse event.

Table 4. All treatment-emergent SAEs

Preferred term, n (%)	n	NCI CTCAE grade	Valemetostat dose + pembrolizumab 200 mg IV
Syncope	1	3	150 mg
Decreased appetite*	1	3	200 mg
Pneumocystis jirovecii Pneumonia*	1	2	200 mg
Atrial fibrillation**	1	3	200 mg
Weight decreased**	1	2	200 mg
Cancer pain**	1	3	200 mg
Respiratory tract infection	1	3	200 mg
Respiratory failure****	1	5	300 mg
Pleural effusion (dose not changed)****	1	3	300 mg
Skin necrosis*****	1	3	300 mg
Pleural effusion (dose delay)****	1	3	300 mg
Dysphea	1	3	300 mg
Infectious pleural effusion	1	3/5***	300 mg

[x]XRT induced calcaneal met.
*Occurred in the same patient
**Occurred in the same patient
***Occurred in the same patient
****Occurred in the same patient
CTCAE, Common Terminology Criteria for Adverse Events; IV, intravenous(ly); met, metastasis; NCI, National Cancer Institute; SAE, serious adverse event; XRT, radiation therapy.

CONCLUSIONS

- The combination of valemetostat at doses of 150–300 mg/day plus pembrolizumab demonstrated manageable safety and tolerability in patients with advanced or metastatic 1L NSCLC expressing PD-L1 with TPS ≥ 50% and no AGAs
- No new safety findings were identified, and the overall safety profile was generally comparable to that of the individual agents

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DISCLOSURES

- S. W. G.: Daiichi Sankyo – advisory role

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