Valemetostat Plus Pembrolizumab in 1L NSCLC Without Actionable Genomic Alterations Expressing PD-L1 With TPS ≥ 50%

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SUMMARY

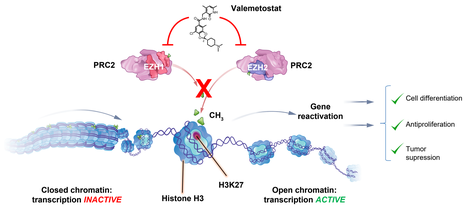
- DS3201-330 (jRCT2031240572; NCT06644768) is a multicenter, randomized, open-label, phase 1b/2 study evaluating the safety and efficacy of valemetostat tosylate (valemetostat) in combination with pembrolizumab in patients with advanced or metastatic first-line (1L) non-small-cell lung cancer (NSCLC) without actionable genomic alterations (AGAs) and with programmed death ligand 1 (PD-L1) tumor proportion score (TPS) ≥ 50%
- Phase 1 enrollment began October 30, 2024 and is ongoing
- An estimated 137 patients are to be enrolled at approximately 60 sites
  - Phase 1 sites are currently in Argentina, Brazil, China, Japan, and the USA; additional countries are to be added for phase 2

If you have a patient who could be eligible to participate, please contact Daiichi Sankyo for clinical trial information at dsclinicaltrial_jp@daiichisankyo.com or CTRinfo_us@daiichisankyo.com

Background

- Lung cancer is the leading cause of cancer-related mortality worldwide, with NSCLC accounting for ~80%–85% of all lung cancer cases[1–4]
- Immune surveillance limits tumor growth; the presence of tumor-infiltrating CD8+ cytotoxic T cells and a high CD8+ effector T cell/FoxP3+ regulatory T cell ratio in cancer tissues are associated with a favorable prognosis[5]
- Programmed death-1 (PD-1) is expressed by activated T cells to downregulate immune responses by interacting with PD-L1; blocking this interaction in vitro restores cytotoxic T cell activity in the tumor microenvironment (TME) improving antitumor responses[5–7]
- Pembrolizumab is an anti-PD-1 antibody approved for the 1L treatment of patients with metastatic or stage III NSCLC expressing PD-L1 (TPS ≥ 50%) who are not eligible for surgical resection or definitive chemoradiation[8]
- Despite the efficacy of single-agent pembrolizumab, a significant proportion of patients in the 1L setting develop resistance due to decreased tumor immunogenicity and an immunosuppressive TME, highlighting the need for additional agents that increase the activity of anti-PD-1/PD-L1 therapy to improve patient outcomes
- In previous in vitro and in vivo studies, using NSCLC cell lines and mouse models respectively, inhibition of enhancer of zeste homolog (EZH)2 improved tumor immunogenicity by increasing infiltration of CD8+ and CD4+ T cells and upregulating the expression of major histocompatibility (MHC) class genes[9]; inhibition of EZH2 with valemetostat may improve the efficacy of anti-PD-1/PD-L1 therapy by enhancing tumor immunogenicity
- Valemetostat is a potent and selective oral dual inhibitor of EZH2 and EZH1, that has demonstrated clinical efficacy and favorable tolerability in multiple hematologic malignancies, and is approved in Japan for the treatment of adult T-cell leukemia/lymphoma and peripheral T-cell lymphoma[10–15]
  - Aberrant expression of EZH2 or EZH1 has been observed in various cancers, including NSCLC, and increases trimethylation of histone H3 at lysine 27 (H3K27me3) leading to transcriptional repression of genes involved in tumor suppression, stem cell maintenance, and cell differentiation[15–17]
  - Inhibition of EZH2 and EZH1 with valemetostat suppresses H3K27me3, reactivating the expression of silenced genes (**Figure 1**)[10]

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.

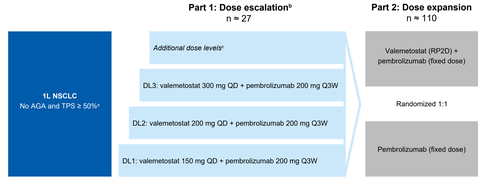
- Here, we present the study objectives, eligibility criteria, and endpoints for a phase 1b/2 trial assessing valemetostat and pembrolizumab for 1L NSCLC with PD-L1 TPS ≥ 50% and no AGAs

Methods

Study design

- DS3201-330 is a global, multicenter, randomized, open-label, phase 1b/2 trial evaluating the safety and efficacy of valemetostat with fixed-dose pembrolizumab in patients with advanced or metastatic 1L 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%, who have not received prior systemic therapy for advanced or metastatic NSCLC
- The trial is composed of a dose escalation part (phase 1b) to assess the safety of the combination and establish the recommended phase 2 dose (RP2D) of valemetostat, followed by a dose expansion part (phase 2) comparing the efficacy of valemetostat plus pembrolizumab versus pembrolizumab alone (**Figure 2**)
  - Phase 1b: patients will be enrolled in cohorts of 3–6 patients and receive oral valemetostat at escalating doses of 150–300 mg once daily together with pembrolizumab intravenously (IV) at a fixed 200 mg dose every 3 weeks (Q3W)
  - Phase 2: patients will be randomized (1:1) to receive either valemetostat at the RP2D plus pembrolizumab (200 mg IV Q3W) or pembrolizumab alone

Figure 2. Study design



[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 alteration; DL, dose level; NSCLC, non-small-cell lung cancer; PD-L1, programmed death ligand 1; QD, once daily; Q3W, every 3 weeks; RP2D, recommended phase 2 dose; TPS, tumor proportion score.

- Target enrollment is ~27 patients in phase 1b and ~110 patients in phase 2
  - Key eligibility criteria are shown in **Table 1**

Table 1. Key eligibility criteria

Key inclusion criteria

- Age ≥ 18 years[a]
- 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 or 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
- CT- or MRI-measurable disease based on local imaging assessment using RECIST v1.1
- PD-L1 TPS ≥ 50% (determined by local testing using 22C3 pharmDx PD-L1 IHC assay or central testing)
- Eastern Cooperative Oncology Group performance status score of 0–1
- Adequate organ and bone marrow function

Key exclusion criteria

- 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
- Active, known, or suspected autoimmune disease requiring treatment, and/or diagnosis of immunodeficiency and receiving systemic steroid therapy or other form of immunosuppressive treatment
- Uncontrolled or significant cardiovascular disease
- Spinal cord compression or clinically active CNS metastases
- History of interstitial lung disease/pneumonitis or radiation pneumonitis
- Concomitant use of moderate or strong CYP3A inducers

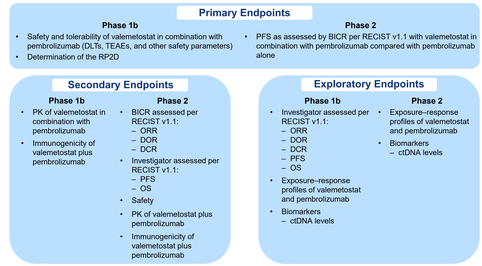
[a]Or the minimum legal adult age, whichever is greater.
AGA, actionable genomic alteration; *ALK*, anaplastic lymphoma kinase; *BRAF*, proto-oncogene B-raf; CNS, central nervous system; CT, computed tomography; CYP3A, cytochrome P450 3A; *EGFR*, epidermal growth factor receptor; EZH, enhancer of zeste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

- Treatment will continue until disease progression, unacceptable toxicity, consent withdrawal, or other reasons outlined in the protocol
  - Tumor assessment will occur every 9 weeks during the first year of treatment, and every 12 weeks thereafter, and a 30-day follow-up visit after the last treatment dose or before starting new anticancer treatment, whichever occurs first
  - Long-term safety follow-up visits will occur every 3 months for at least 3 years, from first dose of study drug

Objectives and endpoints

- Phase 1b will assess the safety of valemetostat combined with pembrolizumab, and determine the RP2D of valemetostat
  - The RP2D will be determined considering the overall assessment of phase 1b data, including safety, efficacy, and available pharmacokinetic and biomarker data
  - Preliminary clinical activity will also be assessed
- Phase 2 will compare the efficacy of valemetostat (at the RP2D established in phase 1b) in combination with pembrolizumab with pembrolizumab alone
- **Figure 3** presents the primary, secondary, and exploratory endpoints of the trial

Figure 3. Study endpoints



BICR, blinded independent central review; ctDNA, circulating tumor DNA; DCR, disease control rate; DLT, dose-limiting toxicity; DOR, duration of response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended phase 2 dose; TEAE, treatment-emergent adverse event.

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ACKNOWLEDGMENTS

- This study is sponsored by Daiichi Sankyo, Inc., in collaboration with Merck Sharp & Dohme, LLC, Rahway, NJ, USA
- All authors contributed to and approved the presentation
- Editorial support was provided by Karolina Lech and James Matthews of Excerpta Medica, funded by Daiichi Sankyo, Inc., and in accordance with Good Publication Practice guidelines

Presented at the Annual Meeting of the Japanese Society of Medical Oncology (JSMO); March 6–8, 2025; Kobe, Japan