Abstract TPS8660

SigVie-003: phase 3 trial in progress of frontline sigvotatug vedotin plus pembrolizumab vs pembrolizumab alone in non-small cell lung cancer (NSCLC) with PD-L1 TPS ≥50%

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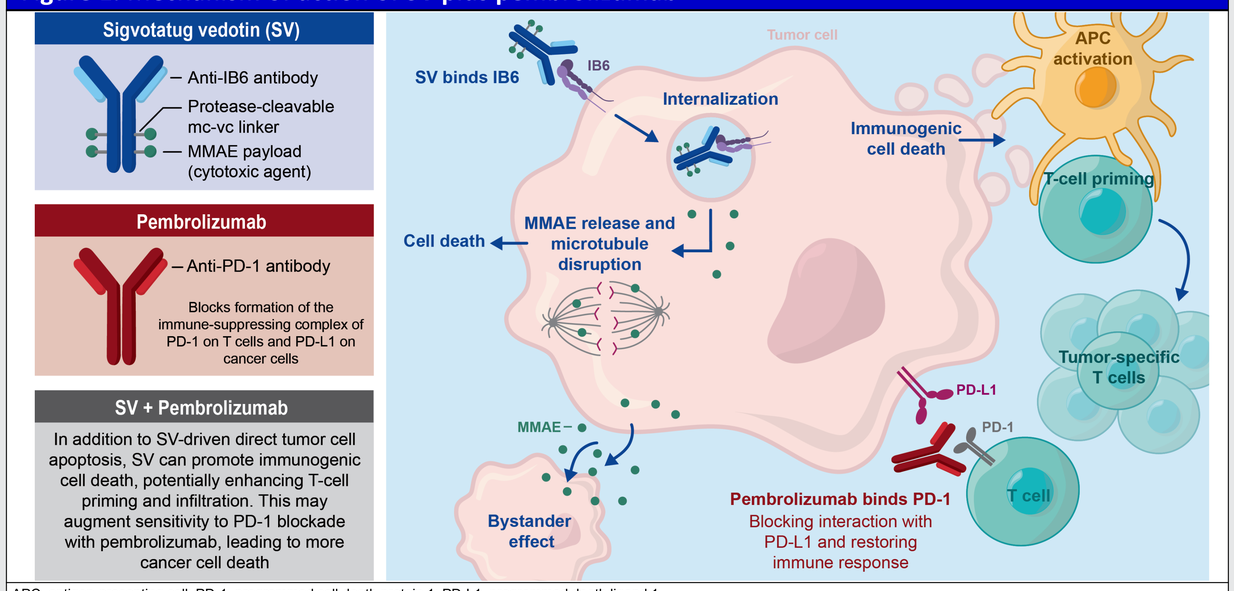
Background

- Integrin beta-6 (IB6) is a tumor-associated membrane protein linked to poor outcomes in solid tumors, including NSCLC, where it is expressed in >90% of cases[1-7]
- Sigvotatug vedotin (SV) is a novel, IB6-directed, antibody-drug conjugate that consists of a humanized monoclonal antibody specific to IB6 linked via a protease-cleavable linker to monomethyl auristatin E (MMAE)[1]
- SV has shown manageable safety and encouraging antitumor activity as monotherapy in advanced NSCLC in the phase 1 SGNB6A-001 study,[7] and is currently being evaluated as a monotherapy in the phase 3 SigVie-002 study[8]
- In addition to the cytotoxic effects of MMAE, preclinical studies demonstrated the ability of SV to induce immunogenic cell death and enhance antitumor activity when combined with pembrolizumab, a PD-1 inhibitor (**Figure 1**)[9,10]
- Therefore, SV plus pembrolizumab is also being evaluated in the SGNB6A-001 study; results of the combination demonstrated promising antitumor activity (objective response rate [ORR], 86% in subgroup with PD-L1 TPS ≥50%) with a manageable safety profile in advanced NSCLC[11]
- Based on these results, the phase 3 SigVie-003 study (NCT06758401) is evaluating SV plus pembrolizumab as a first-line therapy in NSCLC with PD-L1 TPS ≥50%[12]

Figure 1. Mechanism of action of SV plus pembrolizumab[a]



APC, antigen-presenting cell; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1.
[a]SV is an investigational agent.

Trial design

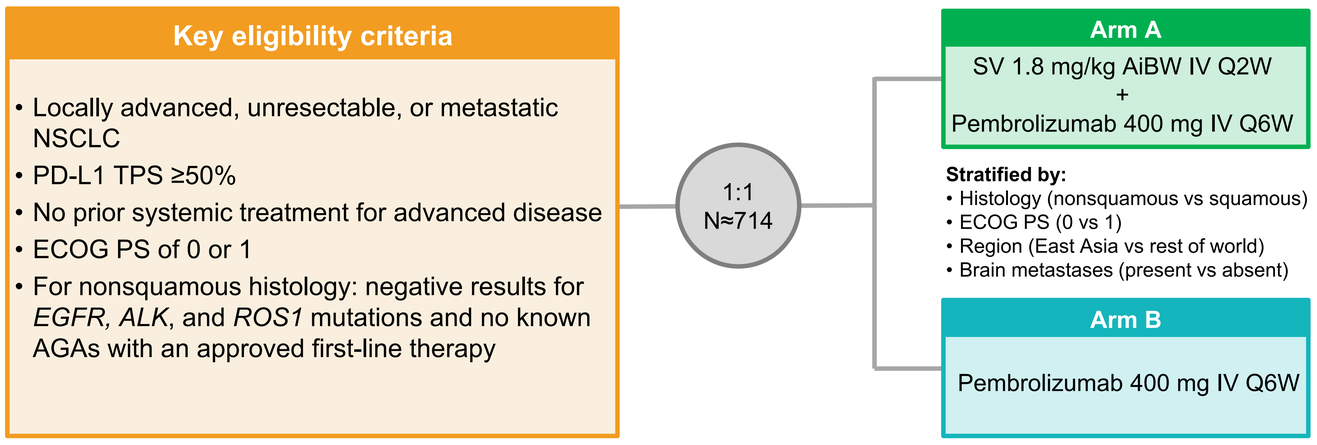
- SigVie-003 is an open-label, randomized, controlled study evaluating the efficacy of SV plus pembrolizumab vs pembrolizumab monotherapy as first-line treatment in adults with locally advanced, unresectable, or metastatic NSCLC with high PD-L1 expression (TPS ≥50%) (**Figure 2**)
- Patients with nonsquamous histology must have negative documentation for *EGFR, ALK,* and *ROS1* mutations and have no known actionable genomic alterations (AGAs) with approved first-line treatments per local standard of care (**Table 1**)
- Approximately 714 patients will be randomized at a 1:1 ratio to receive either SV 1.8 mg/kg AiBW (adjusted ideal body weight) intravenously on days 1, 15, and 29 (Q2W) plus pembrolizumab 400 mg intravenously on day 1 of a 42-day cycle (Q6W) or pembrolizumab 400 mg monotherapy Q6W
- Dual primary endpoints are overall survival (OS) and progression-free survival (PFS) by blinded independent central review (BICR) per RECIST v1.1
- Enrollment is active and began on July 23, 2025 (**Figure 3**)

Table 1. Key patient inclusion and exclusion criteria

Key inclusion criteria
• Age ≥18 years or minimum age of consent in accordance with local regulations
• Pathologically confirmed stage IIIB or IIIC, not eligible for surgical resection or definitive chemoradiation, or metastatic stage IV NSCLC[a]
• Patients with nonsquamous histology must have documented negative test results for *EGFR*, *ALK*, and *ROS1* AGAs and no other known AGAs[b] with approved frontline therapies per local standard of care
• PD-L1 TPS of ≥50% as determined by local testing with retrospective confirmation to be done centrally using a PD-L1 IHC assay[c]
• Measurable disease per RECIST 1.1
• ECOG PS of 0 or 1
• Adequate baseline hematologic, hepatic, and renal function
• Patients must have provided informed consent and be willing and able to adhere to the protocol
Key exclusion criteria
• History of the following conditions:
• Another malignancy ≤3 years before first dose of study treatment
• Certain respiratory conditions, including noninfectious or drug-induced ILD or pneumonitis or any grade ≥3 pulmonary disease unrelated to the underlying malignancy
• Grade ≥2 peripheral neuropathy
• Uncontrolled diabetes mellitus
• Autoimmune disease that has required systemic treatment within last 2 years
• Active CNS lesions, including untreated or symptomatic brain metastases and leptomeningeal metastasis[d]
• Prior or current therapies:
• Systemic therapy, including anti-PD-(L)1 therapy, for locally advanced, unresectable, or metastatic NSCLC except for:
• (Neo)adjuvant anti-PD-(L)1 if recurrence or progression occurred ≥9 months after the last dose
• Other (neo)adjuvant or definitive therapy if recurrence or progression occurred ≥6 months after the last dose
• Prior radiotherapy to the lung ≤6 months before first dose of study treatment
• If not otherwise prohibited, chemotherapy, biologics, and/or other immunotherapy ≤4 weeks prior to first dose of study treatment (2 weeks for palliative radiotherapy)
• Investigational agent (drug or vaccine) ≤30 days or ≤5 half-lives (whichever is longer) before first dose of study treatment
• Any prior therapy with an immune-oncology agent directed toward a stimulatory or co-inhibitory T-cell receptor
• Any prohibited concomitant therapy within 21 days of the first dose of study intervention
• Prior treatment with an MMAE-derived or IB6-targeting agent

AJCC, American Join Committee on Cancer; AGA, actionable genomic alteration; CNS; central nervous system; IHC, immunohistochemistry; ILD; interstitial lung disease; UICC, Union for International Cancer Control.
[a]Per AJCC version 8.0 and UICC staging system 8th edition. [b]Including but not limited to AGAs in *NTRK, BRAF, RET*, and *MET*. [c]Patients must either have an acceptable tumor sample available from ≤6 months or be willing to undergo a biopsy procedure. [d]Definitively treated brain metastases are allowed if stable ≥14 days after definitive treatment completion at the time of study entry and have not required steroids for symptom management for ≥7 days prior to study treatment initiation; clinically inactive brain lesions with a diameter <0.5 cm are allowed.

Figure 2. SigVie-003 study design



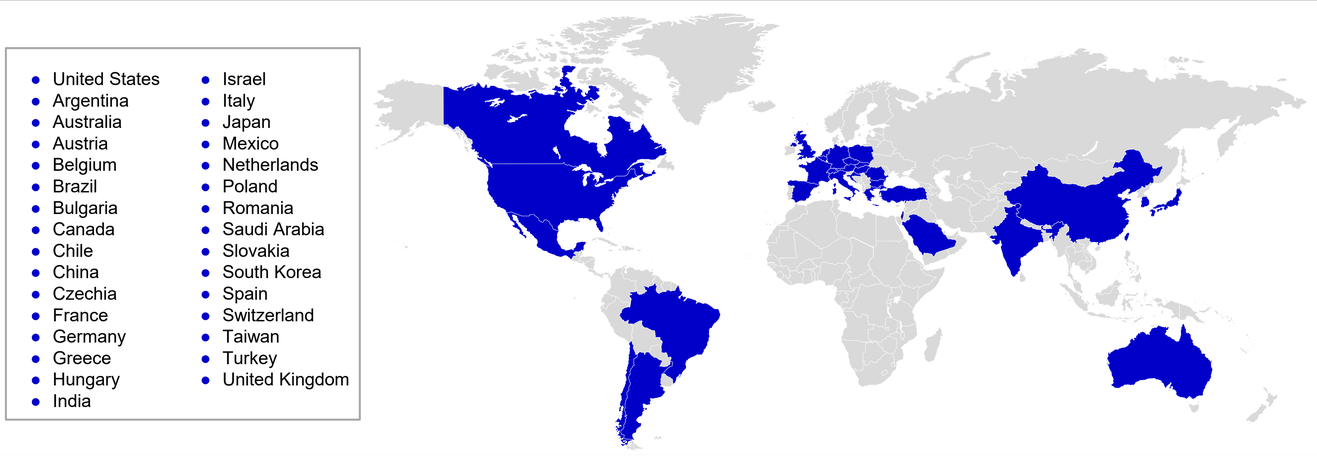
Endpoints

Primary
- Overall survival (OS)
- Progression-free survival (PFS) by BICR[a]

Secondary
- Confirmed ORR and DOR by BICR[a]
- Confirmed ORR, DOR, and PFS by investigator[a]
- Safety and tolerability
- PK and immunogenicity (incidence of ADAs) of SV when combined with pembrolizumab

ADA, antidrug antibody; AiBW, adjusted ideal body weight; ALK, anaplastic lymphoma kinase; BICR, blinded independent central review; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; IV, intravenous; NSCLC, non–small cell lung cancer; ORR, objective response rate; PK, pharmacokinetics; Q2W, Days 1, 15, and 29 of a 42-day cycle; Q6W, Day 1 of a 42-day cycle; RECIST, Response Evaluation Criteria in Solid Tumors; ROS1, ROS proto-oncogene 1; TPS, tumor proportion score.
[a]Per RECIST v1.1

Figure 3. Enrollment sites[a]



[a]Please refer to ClinicalTrials.gov (NCT06758401) for the most current information on participating sites.

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Funding: This study is sponsored by Pfizer

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Acknowledgments: The authors thank the participating patients and their families, investigators, sub-investigators, research nurses, study coordinators, and operations staff for their support of this important trial. Editorial and medical writing support was provided by Caitlin Cash, PhD, of Nucleus Global, and was funded by Pfizer. This presentation is based on the SigVie-003 clinical trial protocol manuscript (Frontline sigvotatug vedotin plus pembrolizumab vs pembrolizumab for non-small cell lung cancer with PD-L1 tumor proportion score ≥50%: phase III study design, Reck M, et al., *Future Oncol*, Dec 13, 2025, Taylor & Francis, reprinted by permission of the publisher Informa UK Limited trading as Taylor & Francis Ltd)