Phase 2 Study of Sacituzumab Govitecan, Domvanalimab, and Zimberelimab in Metastatic Non–Small Cell Lung Cancer: VELOCITY-Lung Substudy-01

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VELOCITY-Lung SS01

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Conclusions

- In Substudy-01 of VELOCITY-Lung, the combination of first-line SG + dom + zim showed promising activity in patients with mNSCLC and across PD-L1 subgroups (PD-L1 TPS <1% or ≥1%)
  - Investigator-confirmed ORRs were numerically higher in the subgroups with PD-L1 TPS ≥1% vs <1%
- The combination of SG + dom + zim was consistent with the known safety profiles of each drug as a single agent, and no new safety concerns were identified

Plain Language Summary

- Advanced NSCLC (lung cancer that has spread throughout the body) is hard to treat. Many patients with NSCLC are first treated with medicines containing platinum as well as with immunotherapy, but this does not always shrink the tumors
- NSCLC can start from different types of cells or tissues in the lungs, squamous and nonsquamous, and these can react differently to cancer treatments
- Recently, researchers showed that a drug called sacituzumab govitecan could shrink lung cancer tumors
- We report the first results of the VELOCITY-Lung Substudy-01, which tested sacituzumab govitecan, domvanalimab, and zimberelimab in people with advanced NSCLC
- The combination of these three drugs could shrink NSCLC tumors or stop them from growing in many patients, regardless of tumor tissue type
- Most patients could take this drug combination, and although some had serious problems, we did not see any unexpected side effects

Introduction

- Although recent improvements in clinical outcomes have been achieved with checkpoint inhibitors (alone or in combination with chemotherapy), there is a significant unmet need to increase tumor responses, prolong survival, and for less toxic treatments in metastatic non–small cell lung cancer (mNSCLC) lacking actionable genomic alterations[1-3]
- Sacituzumab govitecan (SG) is a Trop-2–directed antibody-drug conjugate; based on results from the phase 2 EVOKE-02 trial (NCT05186974),[4] SG is under investigation in combination with pembrolizumab in the randomized phase 3 EVOKE-03 trial (NCT05609968) as a first-line therapy for mNSCLC in patients with programmed cell death-ligand 1 (PD-L1) expression ≥50%
- Combination of domvanalimab (dom), an Fc-silent anti–T-cell immunoglobulin and ITIM domain (TIGIT) antibody, and zimberelimab (zim), an anti–programmed cell death protein 1 (PD-1) antibody, has shown promising antitumor activity possibly enhanced by the dual blockade of TIGIT and PD-1, and manageable toxicity in the first-line setting[5]
- The randomized, phase 3 STAR-121 trial (NCT05502237) of dom and zim in combination with chemotherapy versus pembrolizumab with chemotherapy as first-line treatment for mNSCLC with no actionable genomic alterations is also ongoing
- Substudy-01 of the open-label, phase 2 VELOCITY-Lung trial (NCT05633667) is evaluating efficacy and safety of novel treatment combinations in patients with mNSCLC who have not received prior systemic treatment for metastatic disease
  - Here, we report results for patients randomized to the SG + dom + zim treatment group

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Methods

- Adult patients with untreated stage IV NSCLC, no actionable genomic alterations, Eastern Cooperative Oncology Group performance status ≤1, and any PD-L1 expression were randomized to available treatment groups
  - Randomization was stratified by baseline PD-L1 expression, assessed by Ventana PD-L1 (SP263) assay (≥50% vs <50% tumor staining), and histology (squamous vs nonsquamous)
- This substudy reports data from the preliminary stage, which will be followed by an expansion stage that is contingent on the preliminary stage efficacy and safety outcomes
- Patients received SG (10 mg/kg on days 1 and 8) + dom (1200 mg on day 1) + zim (360 mg on day 1) intravenously, in 21-day cycles
- The primary end point was objective response rate (ORR)
  - Progression-free survival (PFS), duration of response (DOR), and safety were secondary end points

Results

- 25 patients were enrolled in the preliminary stage of the SG + dom + zim treatment group
- As of 28 February 2025, the study is ongoing in 11 patients (44%), 4 (16%) of which are continuing treatment
  - 11 patients (44%) discontinued the study due to death following disease progression and 3 (12%) withdrew consent
  - The median survival follow-up was 14.2 months
- Demographics and baseline characteristics are summarized in **Table 1**

Table 1. Demographics and Baseline Characteristics

Characteristic[a]	SG + dom + zim (N = 25)
Median age, years (range)	66 (42–78)
<65	9 (36)
≥65	16 (64)
Male	17 (68)
Race	
Asian	18 (72)
Black	1 (4)
White (not Hispanic or Latino)	6 (24)
Baseline ECOG PS	
0	5 (20)
1	20 (80)
Tobacco use	
Former	16 (64)
Current	6 (24)
Never	3 (12)
Disease stage at screening	
Stage IVA	11 (44)
Stage IVB	14 (56)
Histology	
Nonsquamous	17 (68)
Squamous	8 (32)
PD-L1 status	
<1%	13 (52)
1%-49%	11 (44)
≥50%	1 (4)
Prior anticancer therapies in (neo)adjuvant setting	
0	22 (88)
1	2 (8)
2	1 (4)
Prior radiotherapy	6 (24)

[a]Data indicate n (%), unless otherwise specified.
dom, domvanalimab; ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed cell death-ligand 1; SG, sacituzumab govitecan; zim, zimberelimab.

- Overall, ORR was 44%, with responses in both histologies (**Table 2**)
  - The median DOR (90% CI) was 7.0 (3.5–13.9) months

Table 2. BOR and Response Rates

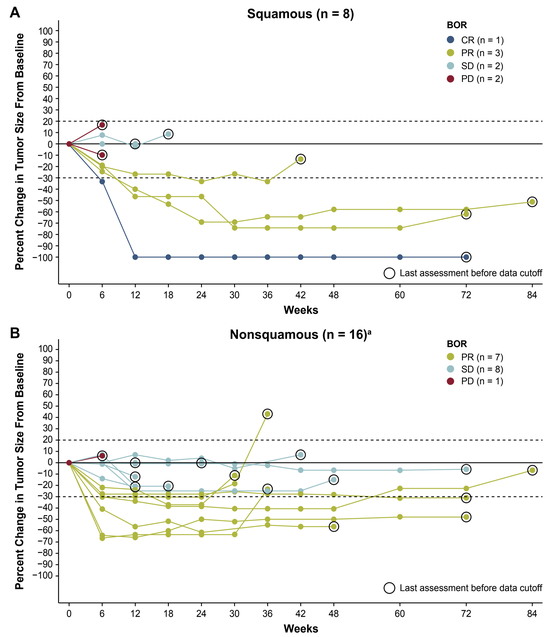
	Overall (N = 25)	Histology		PD-L1 Expression	
		Squamous (n = 8)	Nonsquamous (n = 17)	TPS <1% (n = 13)	TPS ≥1% (n = 12)
BOR, n (%)[a]					
CR	1 (4)	1 (13)	0	0	1 (8)
PR	10 (40)	3 (38)	7 (41)	5 (38)	5 (42)
SD	10 (40)	2 (25)	8 (47)	7 (54)	3 (25)
PD	3 (12)	2 (25)	1 (6)	1 (8)	2 (17)
ORR, n (%)[b]	11 (44)	4 (50)	7 (41)	5 (38)	6 (50)
90% CI[c]	27–62	19–81	21–64	17–65	25–76
DCR, n (%)[d]	21 (84)	6 (75)	15 (88)	12 (92)	9 (75)
90% CI[c]	67–94	40–95	67–98	68–100	47–93

Responses were confirmed ≥4 weeks after the first detection of response, by the investigator per RECIST v1.1.
[a]One patient (nonsquamous and TPS ≥1% subgroups) was not assessed.
[b]ORR was defined as the proportion of patients with CR or PR as BOR.
[c]Two-sided CI based on the Clopper-Pearson exact method.
[d]DCR was defined as the proportion of patients with CR, PR, or SD ≥6 weeks as BOR.
BOR, best overall response; CR, complete response; DCR, disease control rate; ORR, objective response rate; PD, progressive disease; PD-L1, programmed cell death-ligand 1; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors, version 1.1; SD, stable disease; TPS, tumor proportion score.

Results (continued)

- After 18 weeks, most patients with complete or partial response as best overall response had tumor reduction of ≥30% from baseline (**Figure 1**)

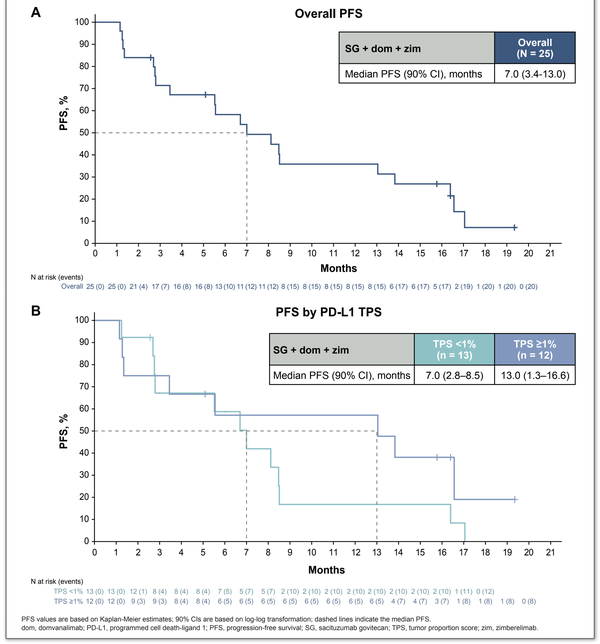
Figure 1. Tumor Response by BOR and Histology



[a]One patient with nonsquamous mNSCLC died before the first assessment.
BOR, best overall response; CR, complete response; mNSCLC, metastatic non–small cell lung cancer; PD, progressive disease; PR, partial response; SD, stable disease.

- Overall, median PFS was 7.0 months with a 6-month PFS rate of 58% (**Figure 2A**)
- Median PFS was 13.0 months among patients with TPS ≥1% and 7.0 months in those with TPS <1% (**Figure 2B**)
- Median PFS was 5.6 months in patients with squamous and 7.0 months in those with nonsquamous NSCLC

Figure 2. PFS Overall and by PD-L1 TPS



PFS values are based on Kaplan-Meier estimates; 90% CIs are based on log-log transformation; dashed lines indicate the median PFS.
dom, domvanalimab; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival; SG, sacituzumab govitecan; TPS, tumor proportion score; zim, zimberelimab.

- All patients had ≥1 any-grade treatment-emergent adverse events (TEAEs) (**Table 3**)
  - Grade 3–4 TEAEs occurred in 19 patients (76%)
- 2 patients (8%) had TEAEs leading to death (cardiogenic shock [n = 1] and septic shock [n = 1]); none were considered related to study drugs

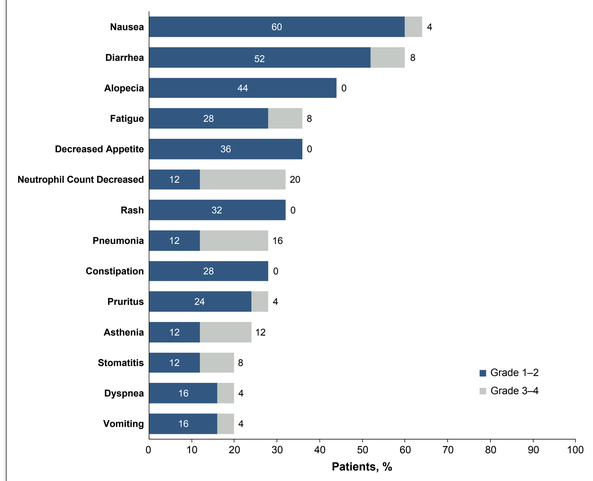
Table 3. Safety Summary

TEAEs, n (%)	SG + dom + zim (N = 25)
Any grade	25 (100)
Related to any study drug	24 (96)
Grade 3–4	19 (76)
Related to any study drug	17 (68)
Serious	11 (44)
Related to any study drug	5 (20)
Leading to dose reduction of any study drug	14 (56)
Leading to discontinuation of ≥1 study drug[a]	7 (28)
Leading to discontinuation of all ongoing study drugs[b]	2 (8)
Leading to death	2 (8)
Related to any study drug	0

Analysis was conducted in the safety analysis set, defined as all patients who received ≥1 dose of any study drug, based on the treatment received.
[a]Reasons for discontinuation of study drugs were asthenia, decreased neutrophil count, increased alanine aminotransferase, IRR, septic shock, stomatitis, streptococcal pneumonia (1 each).
[b]Ongoing study drug was defined as a study drug that was planned to be administered and was not discontinued or completed before the TEAE start date.
dom, domvanalimab; IRR, infusion-related reaction; SG, sacituzumab govitecan; TEAE, treatment-emergent adverse event; zim, zimberelimab.

- Nausea, diarrhea, and alopecia were the most frequent TEAEs of any grade (**Figure 3**)
  - The most frequent grade 3-4 TEAEs included decreased neutrophil count and pneumonia

Figure 3. TEAEs Reported in ≥20% of Patients



TEAE, treatment-emergent adverse event.

- Immune-related AEs and IRRs of any grade occurred in 8 patients (32%), including 2 (8%) who had grade 3–4 events (**Table 4**)
  - 5 patients (20%) had immune-related AEs and IRRs considered related to treatment, and 1 patient (4%) had grade 3-4 treatment-related maculopapular rash

Table 4. Summary of Immune-Related AEs and IRRs

TEAEs, n (%)[a]	SG + dom + zim (N = 25)
Any grade	8 (32)
Related to any study drug	5 (20)
Hypothyroidism	2 (8)
Pneumonitis	2 (8)
Enterocolitis	1 (4)
Maculopapular rash[b]	1 (4)
IRR	1 (4)
Grade 3–4	2 (8)
Related to any study drug	1 (4)
Maculopapular rash[b]	1 (4)
Leading to interruption of any study drug	1 (4)

[a]Immune-related AEs and IRRs. [b]Immune-related AEs included grade ≥3 AEs for specific preferred terms under Skin and subcutaneous tissue disorders and all grades of AEs for other preferred terms in custom PD-1 immune-related AE search list.
AE, adverse event; dom, domvanalimab; IRR, infusion-related reaction; PD-1, programmed cell death protein 1; SG, sacituzumab govitecan; TEAE, treatment-emergent adverse event; zim, zimberelimab.