ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

ORIGINAL ARTICLE

First-in-human phase 1 study of the anti-TIGIT antibody vibostolimab as monotherapy or with pembrolizumab for advanced solid tumors, including non-small-cell lung cancer☆

J. Niu[1*], C. Maurice-Dror[2], D. H. Lee[3], D.-W. Kim[4], A. Nagrial[5,6], M. Voskoboynik[7], H. C. Chung[8], K. Mileham[9], U. Vaishampayan[10], D. Rasco[11], T. Golan[12], T. M. Bauer[13], A. Jimeno[14], V. Chung[15], E. Chartash[16], M. Lala[17], Q. Chen[18], J. A. Healy[16] & M.-J. Ahn[19]

[1]Medical Oncology, Banner MD Anderson Cancer Center, Gilbert, USA; [2]Medical Oncology Division, Rambam Health Care Campus, Haifa, Israel; [3]Department of Oncology, Asan Medical Center, Seoul; [4]Department of Internal Medicine, Seoul National University College of Medicine and Seoul National University Hospital, Seoul, South Korea; [5]Medical Oncology, Blacktown Hospital, Blacktown; [6]Medical Oncology, University of Sydney, Sydney; [7]Alfred Health and Monash University, Melbourne, Australia; [8]Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea; [9]Levine Cancer Institute, Atrium Health, Charlotte; [10]Oncology/Internal Medicine, Karmanos Cancer Center, Detroit; [11]START Center for Cancer Care, San Antonio, USA; [12]The Oncology Institute, Sheba Medical Center at Tel-Hashomer, Tel Aviv University, Tel Aviv, Israel; [13]Drug Development, Sarah Cannon Research Institute/Tennessee Oncology, PLLC, Nashville; [14]Medicine, University of Colorado, Anschutz Cancer Pavilion, Aurora; [15]Medical Oncology, City of Hope National Medical Center, Duarte; [16]Oncology Early Development, Merck & Co., Inc., Kenilworth, NJ; [17]OED-QP2IO, Merck & Co., Inc., Kenilworth, NJ; [18]BARDS, Merck & Co., Inc., Kenilworth, NJ, USA; [19]Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea

Available online 18 November 2021

Background: In this first-in-human phase 1 study (NCT02964013; MK-7684-001), we investigated the safety and efficacy of the anti-TIGIT (T cell immunoglobulin and ITIM domain) antibody vibostolimab as monotherapy or in combination with pembrolizumab.

Patients and methods: Part A enrolled patients with advanced solid tumors, and part B enrolled patients with non-small-cell lung cancer (NSCLC). Patients received vibostolimab 2.1-700 mg alone or with pembrolizumab 200 mg in part A and vibostolimab 200 mg alone or with pembrolizumab 200 mg in part B. Primary endpoints were safety and tolerability. Secondary endpoints included pharmacokinetics and objective response rate (ORR) per RECIST v1.1.

Results: Part A enrolled 76 patients (monotherapy, 34; combination therapy, 42). No dose-limiting toxicities were reported. Across doses, 56% of patients receiving monotherapy and 62% receiving combination therapy had treatment-related adverse events (TRAEs); grade 3-4 TRAEs occurred in 9% and 17% of patients, respectively. The most common TRAEs were fatigue (15%) and pruritus (15%) with monotherapy and pruritus (17%) and rash (14%) with combination therapy. Confirmed ORR was 0% with monotherapy and 7% with combination therapy. In part B, 39 patients had anti-PD-1 (programmed cell death protein 1)/PD-L1 (programmed death-ligand 1)-naive NSCLC (all received combination therapy), and 67 had anti-PD-1/PD-L1-refractory NSCLC (monotherapy, 34; combination therapy, 33). In patients with anti-PD-1/PD-L1-naive NSCLC: 85% had TRAEs—the most common were pruritus (38%) and hypoalbuminemia (31%); confirmed ORR was 26%, with responses occurring in both PD-L1-positive and PD-L1-negative tumors. In patients with anti-PD-1/PD-L1-refractory NSCLC: 56% receiving monotherapy and 70% receiving combination therapy had TRAEs—the most common were rash and fatigue (21% each) with monotherapy and pruritus (36%) and fatigue (24%) with combination therapy; confirmed ORR was 3% with monotherapy and 3% with combination therapy.

Conclusions: Vibostolimab plus pembrolizumab was well tolerated and demonstrated antitumor activity in patients with advanced solid tumors, including patients with advanced NSCLC.

Key words: vibostolimab, MK-7684, pembrolizumab, advanced solid tumors, immune checkpoint inhibitor, non-small-cell lung cancer

*Correspondence to: Dr Jiaxin Niu, Co-Director, Lung Cancer Program, Associate Director, Head & Neck Cancer Program, Banner MD Anderson Cancer Center, 2946 East Banner Gateway Drive, Gilbert, AZ 85234, USA. Tel: +1-480-256-3644; Fax: +1-480-256-5097

E-mail: jiaxin.niu@bannerhealth.com (J. Niu).

☆Note. Previous presentation: The data in this manuscript were included, in part, in an oral presentation at the annual Society for Immunotherapy of Cancer (SITC) congress held 7-11 November 2018, and in two posters presented at the European Society for Medical Oncology (ESMO) Virtual Congress held 19-21 September 2020.

INTRODUCTION

Despite great advancement in past decades, lung cancer remains the leading cause of cancer deaths worldwide.[1] In patients with advanced non-small-cell lung cancer (NSCLC) eligible for targeted therapies, 5-year survival rates vary widely from 15% to 50%.[2] Immunotherapy has revolutionized lung cancer treatment, and checkpoint inhibition with programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) blockade has been widely used as monotherapy or in combination with chemotherapy in the first-line setting in patients with advanced NSCLC.[3-8] An overall survival (OS) benefit has been demonstrated with first-line pembrolizumab, an anti-PD-1 antibody, with median OS up to 30 months in the KEYNOTE-024 study and 22 months in the KEYNOTE-189 study.[3,9] Unfortunately, long-term follow-up data from KEYNOTE-024 and KEYNOTE-189 showed that most patients did not respond initially or acquired resistance to immunotherapy over time, with merely 22.8% and 11.8%, respectively, of patients remaining progression free at 3 years.[10,11]

T-cell immunoglobulin and ITIM domain (TIGIT) is an immunomodulatory receptor that functions as an inhibitory immune checkpoint in innate and adaptive immunity. TIGIT forms part of a complex regulatory network that consists of positive (CD226) and negative (TIGIT) immunomodulatory receptors on T cells and their ligands, CD155 and CD112, expressed on tumor cells and antigen-presenting cells.[12] CD226 is widely expressed on most immune cells, whereas TIGIT is highly expressed on memory T cells, T-regulatory (T_{reg}) cells, natural killer (NK) cells, and NK T cells.[13,14] In cancer, TIGIT is co-expressed with PD-1 on tumor antigen-specific $CD8^+$ T cells and $CD8^+$ tumor-infiltrating lymphocytes (TILs) in mice and humans.[15] On ligand binding, TIGIT exerts direct inhibition of NK-cell cytotoxicity and T-cell activity and competitive attenuation of the $CD155^+$-mediated CD226 activation.[13,16] In preclinical models, TIGIT blockade has demonstrated modest antitumor activity as monotherapy and enhanced effects when combined with a PD-1/PD-L1 inhibitor.[17] Combining anti-TIGIT with anti-PD-1 immunotherapy can increase proliferation, cytokine production, and degranulation of tumor antigen-specific $CD8^+$ T cells and $CD8^+$ TILs in patients with advanced solid tumors.[15] The phase 2 CITYSCAPE study demonstrated improved antitumor activity in the first-line setting with anti-PD-1/PD-L1 and anti-TIGIT combination therapy, compared with anti-PD-1/PD-L1 monotherapy, and exhibited a tolerable safety profile.[18] These data support the hypothesis that combination therapy with anti-PD-1/PD-L1 and anti-TIGIT blockade may improve efficacy compared with anti-PD-1/PD-L1 monotherapy and that within-class combination strategies have the potential to address an unmet clinical need in patients with NSCLC.

Vibostolimab (MK-7684) is a humanized immunoglobulin G1 monoclonal antibody that binds to TIGIT and blocks its interaction with its ligands, CD112 and CD155. In this first-in-human phase 1 study of patients with advanced solid tumors (NCT02964013), we evaluated the safety and tolerability, efficacy, and pharmacokinetic (PK) profiles of escalating doses of vibostolimab monotherapy or of vibostolimab plus the PD-1 inhibitor pembrolizumab. We also report outcomes in patients with NSCLC who were naive to, or whose disease progressed on, previous anti-PD-1/PD-L1 therapy.

METHODS

Study design

This first-in-human, multicenter, open-label, phase 1 study evaluated vibostolimab as monotherapy or combined with pembrolizumab. The study comprised two parts: part A was a dose-escalation and dose-confirmation phase, and part B was an expansion phase in specific tumor types or populations. In part A, eligible patients had histologically or cytologically confirmed metastatic solid tumors for which there were no available therapies expected to convey clinical benefit. In part B, eligible patients had advanced or metastatic NSCLC classified as PD-1/PD-L1-inhibitor treatment refractory [patients received $\geq$2 doses of anti-PD-1/PD-L1 therapy as per local guidelines and had documented progressive disease (PD) as per RECIST v1.1 $<$24 weeks after the last dose of anti-PD-1/PD-L1 therapy] or as PD-1/PD-L1-inhibitor treatment naive (patients had been previously untreated or had PD despite having previously received platinum-containing chemotherapy but not anti-PD-1/PD-L1 therapy). All patients with *EGFR* (epidermal growth factor receptor) or *ALK* (anaplastic large-cell lymphoma kinase) mutant tumors should have received an approved targeted therapy before this study to be considered eligible. All patients had measurable disease as per RECIST v1.1, Eastern Cooperative Oncology Group performance status (ECOG PS) $\leq$1, and archival tumor tissue sample or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated. Patients were enrolled regardless of PD-L1 status.

Patients enrolled in part A received escalating doses of vibostolimab monotherapy (arm 1) or vibostolimab with pembrolizumab 200 mg every 3 weeks (Q3W; arm 2); patients who discontinued vibostolimab monotherapy because of PD were eligible to cross over to receive combination therapy. Using a modified toxicity probability interval design, six predetermined vibostolimab dose levels were explored—2.1 mg, 7 mg, 21 mg, 70 mg, 210 mg, and 700 mg—administered every 3 weeks (Q3W). During dose-escalation, $\geq$3 patients were required to receive each dose, and $\leq$6 were enrolled in the same cycle at each new dose. Dose-escalation and dose-confirmation ended after 14 patients were treated at any of the selected doses. Patients enrolled in part B received vibostolimab 200 mg Q3W as monotherapy or with pembrolizumab 200 mg Q3W. All patients were allocated by nonrandom assignment and received all study treatment intravenously for $\leq$35 cycles or until PD, unacceptable toxicity, or patient or investigator decision.

The study was conducted in accordance with International Conference on Harmonization guidelines for Good Clinical Practice and with the principles of the Declaration

of Helsinki. The protocol was approved by the institutional review boards/independent ethics committees of all participating institutions. All patients provided written informed consent before participating.

Outcomes and assessments

The primary endpoints were safety and tolerability. PK profiles for monotherapy and combination therapy with pembrolizumab and objective response rate (ORR) based on investigator review per RECIST v1.1 were secondary endpoints; duration of response (DOR), progression-free survival (PFS) based on investigator review as per RECIST v1.1, and OS were exploratory endpoints. Additional details are provided in the Supplemental Methods, available at https://doi.org/10.1016/j.annonc.2021.11.002.

Safety and tolerability were assessed by review of adverse events (AEs), serious AEs (SAEs), laboratory tests, vital signs, electrocardiogram measurements, and physical examinations. AEs and SAEs were monitored throughout treatment and for 30 and 90 days, respectively, after the last dose of study treatment; severity was graded according to the Common Terminology Criteria for Adverse Events version 4.0.

Tumor imaging [e.g. computed tomography (CT), magnetic resonance imaging, positron emission tomography] was carried out at baseline and Q9W after the first dose until confirmed PD, initiation of new anticancer therapy, withdrawal of consent, loss to follow-up, death, or end of study. PD-L1 expression by immunohistochemistry (IHC) was assessed on archival (<5 years old) or fresh tumor tissue using PD-L1 IHC 22C3 pharmDx (Agilent Technologies, Carpinteria, CA).

Vibostolimab serum concentrations were measured across the 3-week dosing interval over multiple dosing cycles for all dose levels evaluated to provide a robust characterization of the PK profiles for both monotherapy and combination therapy with pembrolizumab. Specifically, intensive PK samples were drawn at predose, at the end of infusion, and postdose at 2 hours and on days 2, 3, 5, 8, 15, and 21 (predose of the next dosing cycle) in dosing cycles 1 to 4 to capture the PK profile after the first dose, as well as accumulation after multiple dosing to steady state. Predose PK samples were also drawn at cycles 6 and 9, and every 4 cycles thereafter for assessment of longer-term PK.

Statistical analysis

Safety was assessed in the all-patients-as-treated (APaT) population of patients who received ≥1 dose of study treatment. The dose-limiting toxicity (DLT) population included patients in the APaT population who were observed for safety for 21 days after the first dose of assigned treatment or experienced a DLT <21 days after the first dose of assigned treatment; data for patients who experienced PD with monotherapy and crossed over to receive combination therapy were not included.

The PK analysis was assessed in the per-protocol population, which comprised patients who sufficiently complied with the protocol to ensure that the data they generated would be likely to exhibit the effects of treatment according to the underlying scientific model.

Efficacy was assessed in the full analysis population, which comprised all patients with measurable disease at baseline who received ≥1 dose of study treatment. For ORR, point estimates and 95% confidence intervals (CIs) were analyzed separately for patients in the monotherapy and combination therapy groups. Response in the anti-PD-1/PD-L1-naive population was evaluated by PD-L1 expression and stratified by tumor proportion score (TPS; <1% or ≥1%). DOR, PFS, and OS were estimated using the Kaplan-Meier method. The clinical data cut-off was 4 August 2020. The PK data cut-off was 12 October 2020.

RESULTS

Part A

Seventy-six patients with advanced solid tumors enrolled in part A (vibostolimab monotherapy, 34; vibostolimab plus pembrolizumab, 42) (Supplementary Figure S1A, available at https://doi.org/10.1016/j.annonc.2021.11.002; Supplemental Results, available at https://doi.org/10.1016/j.annonc.2021.11.002). Median age was 64 years (range, 24-82), 57% of patients were men, 53% had ECOG PS 1, and 88% had previously received ≥1 line of treatment in the advanced setting (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2021.11.002). Median duration of follow-up (time from first dose to death or data cut-off) was 34 months [interquartile range (IQR), 6-43]. Most patients discontinued study treatment because of PD, regardless of treatment group (Supplementary Figure S1A, available at https://doi.org/10.1016/j.annonc.2021.11.002). After experiencing PD, 15 patients crossed over from the monotherapy group to the combination group.

In the monotherapy group, median days on therapy was 43 (range, 1-312) and median number of vibostolimab doses was 3 (range, 1-15). In the combination group, median days on therapy was 48 (range, 1-486) and median number of doses was 3 (range, 1-21). In the crossover group, median days on therapy was 43 (range, 1-400) and median number of doses was 3 (range, 1-15). No DLTs were observed.

In the monotherapy group, 33 patients (97%) experienced AEs; the most common were anemia (35%) and fatigue (32%) (Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2021.11.002). Treatment-related adverse events (TRAEs) were reported in 19 patients (56%); the most common were fatigue (15%) and pruritus (15%) (Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2021.11.002). Grade 3-4 TRAEs were reported in three patients (9%); the most common were maculopapular rash, anemia, and diarrhea (one patient each). Immune-mediated AEs (imAEs) and infusion reactions were reported in five patients (15%): infusion reactions ($n = 3$); adrenal insufficiency ($n = 1$); and severe skin reactions ($n = 1$).

In the combination group, 40 patients (95%) experienced AEs; the most common were nausea (21%) and rash (21%).

TRAEs were reported in 26 patients (62%); the most common were pruritus (17%) and rash (14%). Grade 3-4 TRAEs occurred in seven patients (17%); the most common were maculopapular rash, adrenal insufficiency, and increased alanine aminotransferase ($n = 1$ each). imAEs and infusion reactions were reported in nine patients (21%); the most common were adrenal insufficiency, colitis, hyperthyroidism, and infusion reaction ($n = 2$ each).

SAEs for both treatment groups are reported in Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2021.11.002.

In the monotherapy group, no patients achieved confirmed objective response for an ORR of 0%; one additional patient with PD-1-refractory NSCLC achieved unconfirmed partial response (PR) (Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2021.11.002). Confirmed disease control rate (DCR), defined as the sum of confirmed response, PR, and stable disease (SD), was achieved in 11 of 34 patients (32%) (Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2021.11.002). In the combination group, three patients achieved confirmed objective response for an ORR of 7% (all PRs; tumor types: PD-1-refractory NSCLC, gastric cancer, or adenocarcinoma of unknown origin); seven additional patients achieved unconfirmed PRs for unconfirmed ORR of 20% (tumor types: PD-1-naive bladder cancer, PD-1-naive NSCLC, pancreatic cancer, gastric cancer, urothelial cancer, or adenocarcinoma of unknown origin) (Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2021.11.002). Confirmed DCR was achieved in 17 of 42 patients (40%) (Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2021.11.002). Median DOR was 8 months (range, 6-13) for the responders in the combination therapy group. One patient who crossed over achieved a confirmed PR. Among assessable patients, five patients in the monotherapy group, 13 patients in the combination group, and three patients in the crossover group experienced reduced target lesion size (Supplementary Figure S2, available at https://doi.org/10.1016/j.annonc.2021.11.002). Most new lesions were generally identified within the first 10 weeks after treatment initiation (Supplementary Figure S3, available at https://doi.org/10.1016/j.annonc.2021.11.002). All PRs were evident at the first tumor assessment at week 9 (Supplementary Figure S4, available at https://doi.org/10.1016/j.annonc.2021.11.002).

Part B

A total of 106 patients with NSCLC were enrolled in part B: 39 patients were classified as anti-PD-1/PD-L1 naive and received combination therapy; 34 patients were classified

Table 1. Baseline characteristics in part B

Characteristic	Anti-PD-1/PD-L1-naive NSCLC	Anti-PD-1/PD-L1-refractory NSCLC	
	vibostolimab + pembrolizumab $n = 39$	vibostolimab monotherapy $n = 34$	vibostolimab + pembrolizumab $n = 33$
Age, median, years (range)	62 (47-80)	64 (36-78)	66 (42-84)
Male	27 (69)	18 (53)	19 (58)
ECOG PS			
0	7 (18)	13 (38)	12 (36)
1	32 (82)	21 (62)	21 (64)
Previous therapy			
Maintenance	1 (3)	0	0
Adjuvant	3 (8)	0	2 (6)
1	11 (28)	8 (24)	5 (15)
2	8 (21)	11 (32)	14 (42)
3	3 (8)	8 (24)	7 (21)
4	3 (8)	3 (9)	0
≥5	4 (10)	4 (12)	5 (15)
Missing	6 (15)	0	0
Previous anti-PD-1/PD-L1 therapy[a]			
Atezolizumab	—	5 (15)	4 (12)
Atezolizumab, durvalumab	—	1 (3)	0
Atezolizumab, nivolumab	—	0	2 (6)
Durvalumab	—	3 (9)	3 (9)
Nivolumab	—	11 (32)	15 (45)
Nivolumab, pembrolizumab	—	1 (3)	2 (6)
Pembrolizumab	—	12 (35)	7 (21)
Unknown	—	1 (3)	0
PD-L1 status			
TPS <1%	12 (31)	8 (24)	17 (52)
TPS ≥1%	11 (28)	12 (35)	6 (18)
Unknown	16 (41)	14 (41)	10 (30)

Data are presented as *n* (%) unless indicated otherwise. Percentages may not total 100 because of rounding.
ECOG PS, Eastern Cooperative Oncology Group performance status; NSCLC, non-small-cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; TPS, tumor proportion score.
[a] Previous immunotherapy includes patients who received monotherapy or combination therapy; patients might have received >1 line of anti-PD-1/PD-L1 therapy and might have been captured in >1 category.

Table 2. Adverse event summary in part B

n (%)	Anti-PD-1/PD-L1-naive NSCLC	Anti-PD-1/PD-L1-refractory NSCLC	
	vibostolimab + pembrolizumab *n* = 39	vibostolimab monotherapy *n* = 34	vibostolimab + pembrolizumab *n* = 33
AE	38 (97)	34 (100)	32 (97)
Grade 3-5	19 (49)	17 (50)	17 (52)
Serious	13 (33)	12 (35)	11 (33)
Led to discontinuation	3 (8)	2 (6)	3 (9)
Led to death	3 (8)[a]	1 (3)[b]	3 (9)[c]
Most common any-grade AEs (≥10% in either group)			
Pyrexia	14 (36)	3 (9)	3 (9)
Hypoalbuminemia	13 (33)	2 (6)	0
Fatigue	8 (21)	10 (29)	12 (36)
Headache	8 (21)	4 (12)	3 (9)
Rash	8 (21)	8 (24)	7 (21)
Constipation	6 (15)	6 (18)	4 (12)
Decreased appetite	6 (15)	12 (35)	7 (21)
Pneumonia	6 (15)	6 (18)	2 (6)
Dyspnea	5 (13)	6 (18)	4 (12)
Myalgia	5 (13)	2 (6)	1 (3)
Arthralgia	4 (10)	6 (18)	4 (12)
Chills	4 (10)	3 (9)	2 (6)
Hypokalemia	4 (10)	2 (6)	0
Nausea	4 (10)	5 (15)	9 (27)
Cough	3 (8)	5 (15)	3 (9)
Dizziness	3 (8)	4 (12)	4 (12)
Abdominal pain	2 (5)	3 (9)	4 (12)
Musculoskeletal chest pain	0	1 (3)	4 (12)
Musculoskeletal pain	0	0	4 (12)
Most common grade 3-5 AEs (≥5% in either group)			
Pneumonia	4 (10)	4 (12)	2 (6)
Decreased lymphocyte count	3 (8)	0	1 (3)
Hypotension	2 (5)	0	0
Anemia	1 (3)	2 (6)	2 (6)
Hypertension	1 (3)	0	2 (6)
Hyponatremia	1 (3)	0	2 (6)
Back pain	0	0	2 (6)
Cancer pain	0	0	2 (6)
Constipation	0	2 (6)	0
Treatment-related AE[d]	33 (85)	19 (56)	23 (70)
Grade 3-5	6 (15)	5 (15)	5 (15)
Serious	4 (10)	2 (6)	1 (3)
Led to discontinuation	1 (3)	1 (3)	1 (3)
Led to death	0	0	1 (3)[e]
Most common any-grade treatment-related AEs (≥10% in either group)			
Pruritus	15 (38)	3 (9)	12 (36)
Hypoalbuminemia	12 (31)	1 (3)	0
Pyrexia	8 (21)	2 (6)	1 (3)
Decreased lymphocyte count	7 (18)	0	0
Rash	6 (15)	7 (21)	7 (21)
Fatigue	5 (13)	7 (21)	8 (24)
Arthralgia	2 (5)	4 (12)	0
Decreased appetite	2 (5)	3 (9)	4 (12)
Nausea	1 (3)	4 (12)	2 (6)
Most common grade 3-5 treatment-related AEs (≥0% in either group)			
Decreased lymphocyte count	3 (8)	0	0
Hypotension	1 (3)	0	0
Rash	1 (3)	1 (3)	0
Increased lipase	0	1 (3)	1 (3)
Dyspnea	0	0	1 (3)
Erosive duodenitis	1 (3)	0	0
Gastroesophageal reflux disease	1 (3)	0	0
Hyponatremia	1 (3)	0	0
Back pain	0	0	1 (3)
Colitis	0	1 (3)	0
Depression	0	0	1 (3)
Fatigue	0	0	1 (3)
Hyperlipasemia	0	1 (3)	0
Hypertension	0	0	2 (6)
Macular rash	0	1 (3)	0

Continued

Table 2. Continued

n (%)	Anti-PD-1/PD-L1-naive NSCLC	Anti-PD-1/PD-L1-refractory NSCLC	
	vibostolimab + pembrolizumab *n* = 39	vibostolimab monotherapy *n* = 34	vibostolimab + pembrolizumab *n* = 33
Musculoskeletal pain	0	0	1 (3)
Pneumonitis	0	0	1 (3)

AE, adverse event; NSCLC, non-small-cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.
[a] One patient experienced grade 5 congestive cardiac failure during follow-up, one patient experienced grade 5 pneumonia during follow-up, and one patient experienced grade 5 pneumonia aspiration during follow-up.
[b] Patient experienced grade 5 general physical health deterioration during follow-up.
[c] One patient experienced grade 5 pneumonia during follow-up, one patient experienced (treatment-related) grade 5 pneumonia during treatment cycle 1, and one patient experienced grade 5 pneumocystis jirovecii pneumonia during follow-up.
[d] Determined by the investigator to be related to the study drug.
[e] One patient experienced treatment-related grade 5 pneumonia during treatment cycle 1.

as anti-PD-1/PD-L1 refractory and received monotherapy; and 33 were classified as anti-PD-1/PD-L1 refractory and received combination therapy (Supplementary Figure S1B, available at https://doi.org/10.1016/j.annonc.2021.11.002). In the anti-PD-1/PD-L1-naive population, median age was 62 years (range, 47-80), 69% of patients were men, 82% had ECOG PS 1, and 74% had previously received ≥1 therapy in the advanced setting (Table 1). In the anti-PD-1/PD-L1-refractory population, median age was 65 years (range, 36-84), 55% of patients were men, 63% had ECOG PS 1, and 97% had previously received ≥1 therapy in the advanced setting; the most common previous anti-PD-1/PD-L1 therapies were nivolumab (39%) and pembrolizumab (28%) (Table 1). Median duration of follow-up (time from first dose to death or data cut-off) was 24 months (IQR, 21-28). Most patients discontinued study treatment because of PD, regardless of population or treatment group (Supplementary Figure S1B, available at https://doi.org/10.1016/j.annonc.2021.11.002).

In the anti-PD-1/PD-L1-naive population, median days on therapy was 84 (range, 1-729); median number of doses was five (range, 1-35) for vibostolimab and for pembrolizumab. In the anti-PD-1/PD-L1-refractory population, median days on therapy was 50 (range, 1-707); median number of doses was three (range, 1-35) for vibostolimab and for pembrolizumab.

In the anti-PD-1/PD-L1-naive population, 38 patients (97%) experienced AEs; the most common were pyrexia (36%) and hypoalbuminemia (33%) (Table 2). TRAEs were reported in 33 patients (85%); the most common were pruritus (38%) and hypoalbuminemia (31%) (Table 2). No patients who received monotherapy and six patients (15%) who received combination therapy experienced grade 3-4 TRAEs; the most common with combination therapy were decreased lymphocyte count (*n* = 3), hypotension (*n* = 1), and rash (*n* = 1). imAEs and infusion reactions were reported in 10 patients (26%); the most common were infusion reactions (*n* = 4), hypophysitis (*n* = 2), hypothyroidism

Table 3. Response summary based on investigator assessment per RECIST v1.1 in part B

n (%)	Anti-PD-1/PD-L1-naive NSCLC			Anti-PD-1/PD-L1-refractory NSCLC	
	vibostolimab + pembrolizumab *n* = 39	Patients with available PD-L1 data		vibostolimab monotherapy *n* = 34	vibostolimab + pembrolizumab *n* = 33
		TPS ≥1% *n* = 12	TPS <1% *n* = 11		
With confirmation					
ORR (CR + PR)	10 (26)	4 (33)	3 (27)	1 (3)	1 (3)
CR	1 (3)	1 (8)	0	0	0
PR	9 (23)	3 (25)	3 (27)	1 (3)	1 (3)
SD	10 (26)	6 (50)	2 (18)	10 (29)	14 (42)
DCR (CR + PR + SD)	20 (51)	10 (83)	5 (45)	11 (32)	15 (45)
PD	14 (36)	1 (8)	5 (45)	18 (53)	15 (45)
Not available[a]	5 (13)	1 (8)	1 (9)	5 (15)	3 (9)
Median DOR, months (range)[b]	NR (4.1 to 21.1+)	12.4 (4.1 to 16.4)	NR (18.6+ to 21.1+)	8.5 (8.5 to 8.5)	NR (10.2+ to 10.2+)
Without confirmation					
ORR (CR + PR)	11 (28)	5 (42)	3 (27)	2 (6)	1 (3)
CR	1 (3)	1 (8)	0	0	0
PR	10 (26)	4 (33)	3 (27)	2 (6)	1 (3)
SD	10 (26)	6 (50)	2 (18)	9 (26)	14 (42)
DCR (CR + PR + SD)	21 (54)	11 (92)	5 (45)	11 (32)	15 (45)
PD	14 (36)	1 (8)	5 (45)	18 (53)	15 (45)
Not available[a]	4 (10)	0	1 (9)	5 (15)	3 (9)

CR, complete response; DCR, disease control rate; DOR, duration of response; NR, not reached; NSCLC, non-small-cell lung cancer; ORR, objective response rate; PD, progressive disease; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PR, partial response; SD, stable disease; TPS, tumor proportion score.
[a] Includes patients with insufficient data for assessment of response per RECIST v1.1 or those without postbaseline assessment as of the data cut-off date.
[b] '+' indicates that no progressive disease was present at the time of the last disease assessment.

($n = 2$), and pneumonitis ($n = 2$). The safety profile for the anti-PD-1/PD-L1-refractory population was generally similar (Table 2; Supplementary Table S5, available at https://doi.org/10.1016/j.annonc.2021.11.002).

In the anti-PD-1/PD-L1-naive population, 10 patients achieved confirmed objective responses [ORR, 26%; complete response (CR), 1; PR, 9]; another patient achieved an unconfirmed PR (Table 3). Confirmed DCR was achieved in 20 of 39 patients (51%) (Table 3). Median DOR was not reached (NR; range, 4.1-21.1+ months). When evaluating response by PD-L1 status, 4 of 12 patients with PD-L1 TPS ≥1% achieved confirmed objective responses (ORR, 33%; CR, 1; PR, 3), and 3 of 11 patients with PD-L1 TPS <1% achieved confirmed objective responses (ORR, 27%; all PRs); DCR was 83% and 45%, respectively, and median DOR was 12.4 months (range, 4.1-16.4 months) and NR (range, 18.6+ to 21.1+ months), respectively. Among assessable patients, 19 experienced reduced target lesion size (Figure 1A). New lesions were identified within the first 40 weeks after treatment initiation (Figure 2A). All responses were evident at the first tumor assessment at week 9 (Figure 3A).

In the anti-PD-1/PD-L1-refractory population, two patients achieved confirmed PRs (monotherapy ORR, 3%; combination therapy ORR, 3%); another patient receiving monotherapy achieved an unconfirmed PR (Table 3). Confirmed DCR was achieved in 11 patients (32%) and 17 patients (40%) in the monotherapy group and combination therapy group, respectively. DOR was 8.5 months in the responder receiving monotherapy and is still ongoing past 10 months in the responder receiving combination therapy. Among assessable patients, six receiving monotherapy and eight receiving combination therapy experienced reduced target lesion size (Figure 1B and C). New lesions were identified by week 25 after treatment initiation (Figure 2B and C). All responses were evident by week 12 (Figure 3B and C).

Given the small sample size of overall patients with PD-L1 TPS >50% ($n = 3$), formal analysis of efficacy in this patient subset was not conducted. One of those three patients, however, experienced an objective response.

In the anti-PD-1/PD-L1-naive population, median PFS was 5 months (95% CI 2-8 months); the 6-month PFS rate was

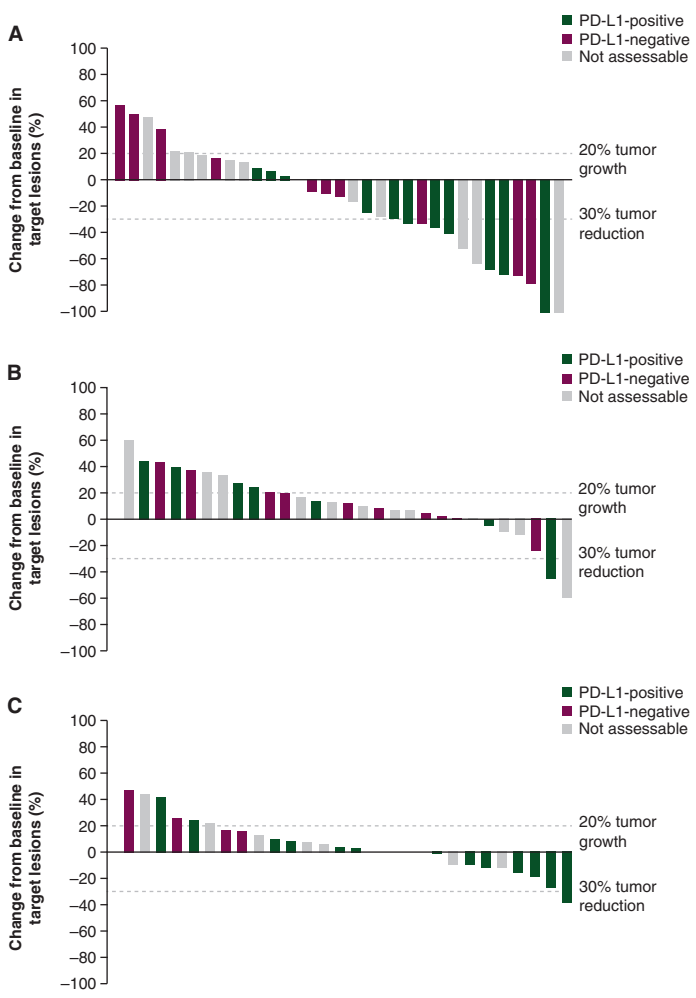

Figure 1. Best percentage change from baseline in target lesion size based on investigator assessment as per RECIST v1.1 in part B.
(A) Vibostolimab plus pembrolizumab in anti-PD-1/PD-L1-naive NSCLC. (B) Vibostolimab monotherapy in anti-PD-1/PD-L1-refractory NSCLC. (C) Vibostolimab plus pembrolizumab in anti-PD-1/PD-L1-refractory NSCLC. Includes all patients with ≥1 measurable postbaseline target lesion measurement.
NSCLC, non-small-cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

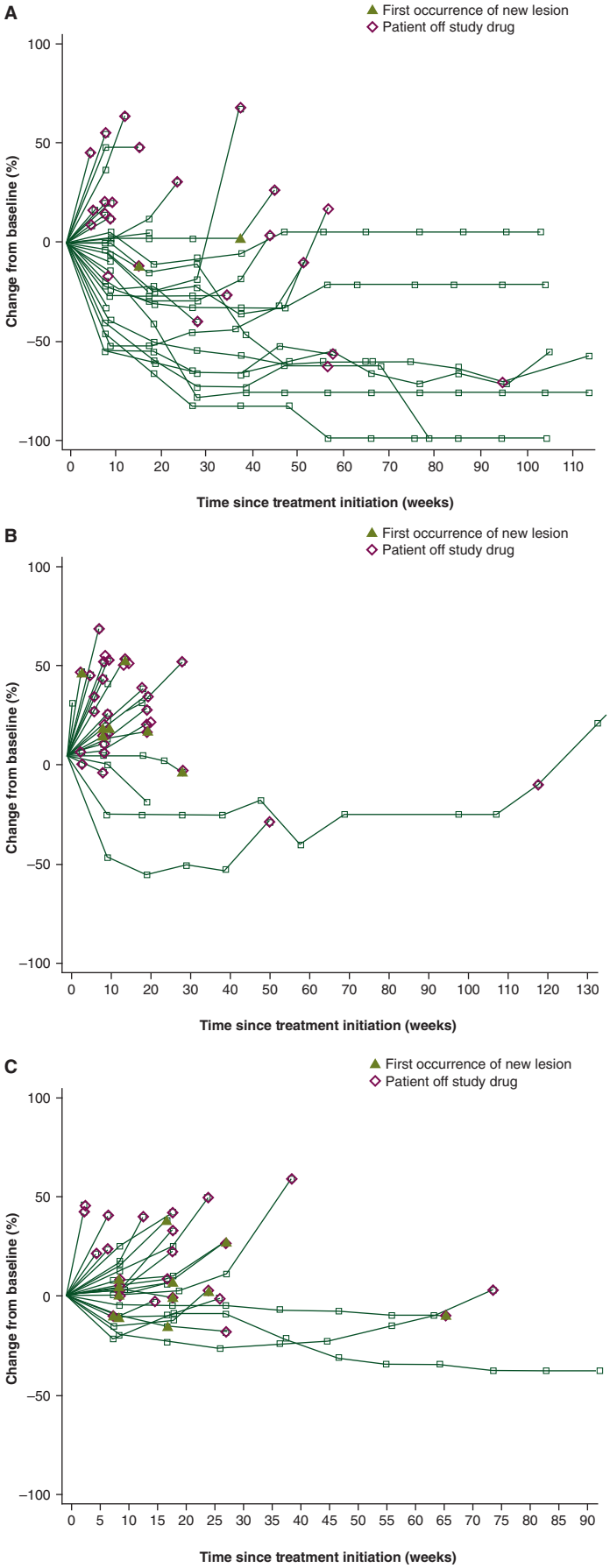

Figure 2. **Longitudinal percentage change in target lesion from baseline based on investigator assessment as per RECIST v1.1 in part B.**

47%. Based on evaluation by PD-L1 status (TPS ≥1% versus <1%), median PFS was 9 months (95% CI 3-13 months) versus 3 months (95% CI 2-NR months); 6-month PFS rates were 83% and 36%, respectively. In the anti-PD-1/PD-L1-refractory population (monotherapy and combination therapy), median PFS was 2 months (95% CI 2-3 months) and 2 months (95% CI 2-4 months); 6-month PFS rates were 10% and 25%, respectively.

In the anti-PD-1/PD-L1-naive population, median OS was 11 months (95% CI 8-22 months); the 6-month OS rate was 76%. When evaluating by PD-L1 status (TPS ≥1% versus <1%), median OS was 14 months (95% CI 6-NR months) versus NR (95% CI 6-NR months); 6-month OS rates were 92% and 82%, respectively. In the anti-PD-1/PD-L1-refractory population (monotherapy and combination therapy), median OS was 11 months (95% CI 8-19 months) and 13 months (95% CI 8-18 months); 6-month OS rates were 69% and 75%, respectively.

PK and dose selection

Available PK data from patients with advanced solid tumors from part A and part B of the study treated with escalating doses of vibostolimab from 2.1 mg to 700 mg Q3W, when given as monotherapy or in combination with 200 mg Q3W pembrolizumab, showed that serum vibostolimab exposures increased in a dose-dependent manner (Supplemental Results, available at https://doi.org/10.1016/j.annonc.2021.11.002).

DISCUSSION

In this first-in-human phase 1 study, vibostolimab as monotherapy or in combination with pembrolizumab was well tolerated and had a manageable safety profile across all doses tested and all patient populations evaluated. In part A, dose-escalation and dose-confirmation proceeded to completion without any DLTs, and no treatment-related deaths were reported. Promising antitumor activity in both the monotherapy and the combination therapy groups was observed among this heavily pretreated patient population. In part B, which enrolled patients with NSCLC, efficacy evaluations demonstrated promising antitumor activity with vibostolimab plus pembrolizumab in the anti-PD-1/PD-L1-naive population and in patient subpopulations with either PD-L1 TPS ≥1% or PD-L1 TPS <1%. Antitumor activity with vibostolimab monotherapy or vibostolimab plus pembrolizumab was modest in the anti-PD-1/PD-L1-refractory population.

TIGIT and PD-1 are often co-expressed on tumor antigen-specific $CD8^+$ T cells and $CD8^+$ TILs, and combination blockade with anti-PD-1/PD-L1 and anti-TIGIT antibodies has demonstrated enhanced proliferation and function of such cytotoxic T cells when compared with monotherapy with each agent.[15,19] Although cross-trial comparisons should be interpreted with caution, despite up to 50% of the cohort having previously received >2 lines of chemotherapy, results in the current study in the anti-PD-1/PD-L1-naive population with PD-L1 TPS ≥1% NSCLC demonstrated improved antitumor activity with an ORR of 33% compared with that previously reported in the phase 2 KEYNOTE-010 study in patients with advanced PD-L1-positive (TPS ≥1%) NSCLC who received second-line pembrolizumab monotherapy (2 mg/kg) as follows: ORR, 18%; median PFS, 4 months; and median OS, 10 months.[20]

Studies investigating the safe and effective use of anti-PD-1/PD-L1 and anti-TIGIT combination therapy in patients with solid tumors are limited. One such study is the phase 2 CITYSCAPE study ($N = 135$) comparing the first-line anti-TIGIT antibody tiragolumab combined with the anti-PD-L1 antibody atezolizumab versus atezolizumab monotherapy in patients who did not previously receive systemic treatment for locally advanced unresectable or metastatic PD-L1-positive (TPS ≥1%) NSCLC.[18] In the CITYSCAPE study, combination therapy improved ORR (37.3% versus 20.6%) and median PFS (5.6 versus 3.9 months) compared with atezolizumab monotherapy. The safety profile was tolerable, with 80.6% of patients reporting a TRAE with tiragolumab plus atezolizumab versus 72.0% with atezolizumab.[18] In an exploratory analysis from the CITYSCAPE study, improved clinical benefits with combination therapy were seen in the subset of patients with PD-L1 expression ≥50%: ORR was 66%, there was a 70% reduction in the risk for PD (95% CI 0.15-0.61) versus placebo, and median PFS was unassessable with tiragolumab plus atezolizumab versus 4 months with atezolizumab monotherapy. Data from the current study and from CITYSCAPE provide further evidence of the enhanced antitumor effects of anti-TIGIT and anti-PD-1/PD-L1 antibody blockade that may be acting through the synergistic mechanisms of action of augmented NK-cell activation of $CD8^+$ TILs, although data from randomized phase 3 studies are still needed. Unfortunately, the current understanding of disease mechanisms has not yet yielded definitive biomarkers. Enhanced clinical benefits seen in the current study, however, and in the KEYNOTE-010 as well as CITYSCAPE in patient subgroups with PD-L1 expression status ≥1% provide support for the possible use of PD-L1 as a surrogate biomarker for patients with anti-PD-1/PD-L1-naive NSCLC as we continue to search for a mechanistic biomarker for anti-TIGIT therapy.

The findings presented from this phase 1 study are limited by the modest sample sizes and limited PD-L1 sample availability. Thus, the analyses in this study are underpowered for statistical validation, and results should be interpreted with caution. Furthermore, the evaluation of a

(A) Vibostolimab plus pembrolizumab in anti-PD-1/PD-L1-naive NSCLC. (B) Vibostolimab monotherapy in anti-PD-1/PD-L1-refractory NSCLC. (C) Vibostolimab plus pembrolizumab in anti-PD-1/PD-L1-refractory NSCLC. Includes all patients with ≥1 postbaseline target lesion measurement.
NSCLC, non-small-cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

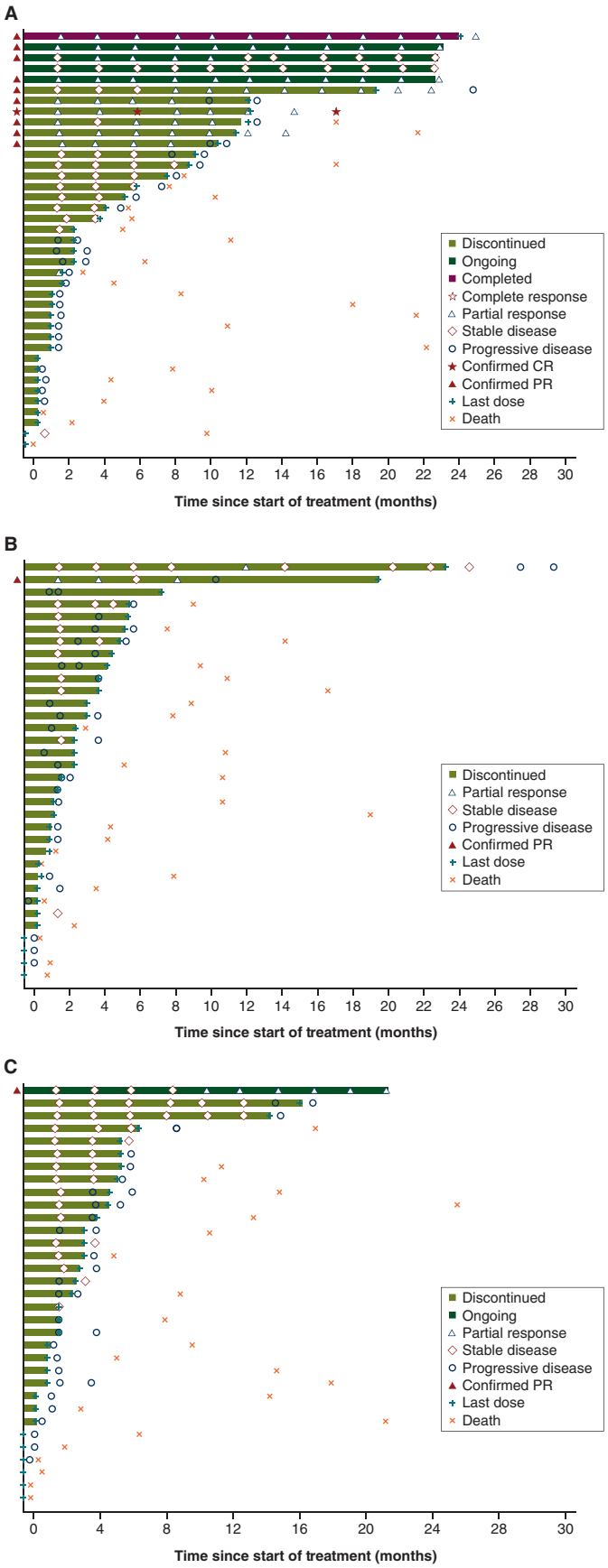

Figure 3. Treatment exposure and response duration based on investigator assessment as per RECIST v1.1 in part B.
(A) Vibostolimab plus pembrolizumab in anti-PD-1/PD-L1-naive NSCLC. (B) Vibostolimab monotherapy in anti-PD-1/PD-L1-refractory NSCLC. (C) Vibostolimab plus pembrolizumab in anti-PD-1/PD-L1-refractory NSCLC. Line length represents the time to the last dose of study treatment.
CR, complete response; NSCLC, non-small-cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PR, partial response.

small population of patients with PD-1/PD-L1-inhibitor-refractory disease was exploratory and did not provide insight into whether resistance was primary or acquired.

Taken together, our data provide promising antitumor activity in patients with advanced solid tumors and in PD-1/PD-L1-inhibitor-naive patients with advanced solid tumors treated with vibostolimab plus pembrolizumab, and they support further investigation of the treatment combination. Further evaluation of the efficacy of vibostolimab monotherapy and vibostolimab combination therapy at 200 mg Q3W—the recommended phase 2 dose are ongoing (NCT04738487, NCT04165070, NCT04725188) in patients with select advanced solid tumors and NSCLC.

ACKNOWLEDGEMENTS

The authors thank the study patients and their families and caregivers, the primary investigators and site personnel for participating in the study, and Kapil Mayawala of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA for his assistance interpreting the pharmacokinetic and dose selection data. Medical writing and/or editorial assistance was provided by Dominic Singson, MD, and Holly C. Cappelli, PhD, CMPP, of ApotheCom (Yardley, PA, USA). This assistance was funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

FUNDING

This work was supported by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA (no grant number).

ROLE OF THE FUNDING SOURCE

The funder participated in study design, data analysis and interpretation, and manuscript writing and maintained the study database. All authors had full access to the data and had final responsibility for the decision to submit the manuscript for publication.

DISCLOSURE

JN reports personal fees from AstraZeneca, Blueprint Medicines, Boehringer Ingelheim, Exelixis, Immvira, Johnson & Johnson, Merck, Mirati Therapeutics, and Takeda, outside the submitted work. CM-D reports personal fees from Bristol Myers Squibb, Biomica, MSD, and Pfizer, outside the submitted work. DHL reports personal fees from AbbVie, AstraZeneca, BC Pharma, Blueprint Medicine, Boehringer Ingelheim, Bristol Myers Squibb, ChongKunDang, CJ Healthcare, Eli Lilly, Genexine, Janssen, Menarini, Merck, MSD, Mundipharma, Novartis, Ono, Pfizer, Roche, Samyang Biopharm, ST Cube, and Takeda; and nonfinancial support from Blueprint Medicine and Takeda, outside the submitted work. D-WK reports a grant from Merck to his institution for the work under consideration; grants from Alpha Biopharma, Amgen, AstraZeneca, Boehringer Ingelheim, Bridge BioTherapeutics, ChongKeunDang, Daiichi-Sankyo, GSK, Hanmi, Janssen, Merus, Mirati, Novartis, ONO, Pfizer, Roche, Takeda, TP Therapeutics, Xcovery, and Yuhan, outside the submitted work; and personal fees from Amgen and Daiichi-Sankyo, outside the submitted work. MV reports personal fees from AstraZeneca outside the submitted work. HCC reports grants to his institution from Amgen, Bristol Myers Squibb-ONO, GSK, Incyte, Lilly, MSD, Merck-Serono, Neigene, Taiho, and Zymework, outside the submitted work; and personal fees from Amgen, Bristol Myers Squibb, Celltrion, Gloria, Lilly, Merck-Serono, MSD, Taiho, and Zymework, outside the submitted work. KM has participated in advisory boards for AstraZeneca, Bayer, Bristol Myers Squibb, and Takeda and speakers' bureaus for Merck, outside the submitted work. UV reports grants and personal fees from Merck for the work under consideration; grants from Astellas and Bristol Myers Squibb, outside the submitted work; and personal fees from AAA, Alkermes, Astellas, Bayer, Bristol Myers Squibb, Exelixis, and Pfizer, outside the submitted work. DR reports research funding from Merck for the work under consideration and research funding from Arcus and Compugen, outside the submitted work. TG reports research funding to his institution from AstraZeneca and MSD; has received honoraria from MSD and Rafael Pharmaceuticals; served as consultant or advisor to AbbVie, AstraZeneca, Bayer, MSD, and Teva; and received travel expenses from AstraZeneca and MSD, outside the submitted work. TMB reports a grant from Merck for the work under consideration and grants to his institution from AbbVie, Aileron Therapeutics, Amgen, ARMO Biosciences, Astellas Pharma, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Calithera Biosciences, Clovis Oncology, Daiichi Sankyo, Deciphera, Five Prime Therapeutics, Foundation Medicine, Genentech, GlaxoSmithKline, Ignyta, Immunocore, Immunogen, Incyte, Jacobio, Janssen, Karyopharm Therapeutics, Kolltan Pharmaceuticals, Leap Therapeutics, Lilly, Loxo, MabVax, Medpacto, Merck, Merrimack, Millennium, Mirati Therapeutics, MedImmune, Moderna Therapeutics, Novartis, Onyx, Peleton, Pfizer, Phosplatin Therapeutics, Principa Biopharma, Roche, Sanofi, Stemline Therapeutics, Takeda, and Top Alliance BioScience, outside the submitted work; personal fees from AstraZeneca, Bayer, Blueprint Medicines, Bristol Myers Squibb, Exelixis, Foundation Medicine, Guardant Health, Lilly, Loxo, and Pfizer, outside the submitted work; nonfinancial support from Bayer, Bristol Myers Squibb, Foundation Medicine, Guardant Health, Ignyta, Lilly, Loxo, and Moderna Therapeutics, outside the submitted work; and payments to institution for consulting from Ignyta, Leap Therapeutics, Moderna Therapeutics, and Pfizer, outside the submitted work. AJ reports research funding to institution from Debiopharm, Iovance, Khar, Merck, Moderna, Pfizer, and SQZ, outside the submitted work. VC reports a grant from Merck outside of the submitted work and personal fees from AstraZeneca, Coherus, Ipsen, and Pfizer, outside the submitted work. M-JA reports personal fees from Alpha Pharmaceutical, AstraZeneca, Bristol Myers Squibb, Lilly, Merck, MSD, Takeda, and Yuhan, outside the submitted work. EC and JAH are employees of Merck Sharp

& Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. All other authors have declared no conflicts of interest.

DATA SHARING

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA (MSD) is obligated to protect the rights and privacy of trial patients. To fulfill the company's obligation, MSD has a procedure in place for evaluating and fulfilling requests for sharing company clinical trial data with qualified external scientific researchers. As outlined on the MSD data sharing website (available at: http://engagezone.msd.com/ds_documentation.php), a detailed research proposal that includes the background and rationale, objectives of the research, a scientific hypothesis, statistical analysis plan, and publication plan must be submitted through EngageZone along with the curricula vitae of all researchers, including the biostatistician. Completed applications will be promptly assessed for feasibility. If the request is considered to be feasible, a committee of MSD subject matter experts will assess the scientific validity of the request and the qualifications of the requestors. If the proposal is approved, the researcher must enter into a standard data-sharing agreement with MSD before anonymized data is provided; this is in line with data privacy legislation. There are circumstances that may prevent MSD from sharing the requested data, including country or region-specific regulations such as the European Union General Data Privacy Regulation. If the request is declined, it will be communicated to the investigator. MSD data-sharing metrics can be accessed at https://www.merck.com/clinical-trials/pdf/MicrositeDataSharingMetrics_20190711.pdf.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71(3):209-249.
2. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology. Non-small cell lung cancer. Version 4. 2021. Plymouth Meeting, PA: National Comprehensive Cancer Network; 2021.
3. Reck M, Rodriguez-Abreu D, Robinson AG, et al. Updated analysis of KEYNOTE-024: pembrolizumab versus platinum-based chemotherapy for advanced non-small-cell lung cancer with PD-L1 tumor proportion score of 50% or greater. *J Clin Oncol*. 2019;37(7):537-546.
4. Mok TSK, Wu Y-L, Kudaba I, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. *Lancet*. 2019;393(10183):1819-1830.
5. Gandhi L, Rodriguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med*. 2018;378(22):2078-2092.
6. Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. *N Engl J Med*. 2018;379(21):2040-2051.
7. Herbst RS, Giaccone G, de Marinis F, et al. Atezolizumab for first-line treatment of PD-L1-selected patients with NSCLC. *N Engl J Med*. 2020;383(14):1328-1339.
8. Socinski MA, Jotte RM, Cappuzzo F, et al. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. *N Engl J Med*. 2018;378(24):2288-2301.
9. Gadgeel S, Rodríguez-Abreu D, Speranza G, et al. Updated analysis from KEYNOTE-189: pembrolizumab or placebo plus pemetrexed and platinum for previously untreated metastatic nonsquamous non-small-cell lung cancer. *J Clin Oncol*. 2020;38(14):1505-1517.
10. IASLC WCLC Virtual: KEYNOTE-189 confirms continued benefit of adding pembrolizumab to chemotherapy in metastatic non-small cell lung cancer. News release. Published February 9, 2021. Available at https://www.practiceupdate.com/content/iaslc-wclcnbspvirtual-keynote-189-confirms-continued-benefit-of-adding-pembrolizumab-to-chemotherapy-in-metastatic-non-small-cell-lung-cancer/113387. Accessed August 3, 2021.
11. Reck M, Rodriguez-Abreu D, Robinson AG, et al. Five-year outcomes with pembrolizumab versus chemotherapy for metastatic non-small-cell lung cancer with PD-L1 tumor proportion score $\geq$ 50. *J Clin Oncol*. 2021;39(21):2339-2349.
12. Levin SD, Taft DW, Brandt CS, et al. Vstm3 is a member of the CD28 family and an important modulator of T-cell function. *Eur J Immunol*. 2011;41(4):902-915.
13. Stanietsky N, Rovis TL, Glasner A, et al. Mouse TIGIT inhibits NK-cell cytotoxicity upon interaction with PVR. *Eur J Immunol*. 2013;43(8):2138-2150.
14. Dardalhon V, Schubart AS, Reddy J, et al. CD226 is specifically expressed on the surface of Th1 cells and regulates their expansion and effector functions. *J Immunol*. 2005;175(3):1558-1565.
15. Chauvin J-M, Pagliano O, Fourcade J, et al. TIGIT and PD-1 impair tumor antigen-specific CD8$^+$ T cells in melanoma patients. *J Clin Invest*. 2015;125(5):2046-2058.
16. Chauvin J-M, Zarour HM. TIGIT in cancer immunotherapy. *J Immunother Cancer*. 2020;8(2):e000957.
17. He DX, Nie C, Zheng L, et al. Abstract 5614: combination of anti-TIGIT and anti-PD-1 antibodies enhance antitumor response in a PD-1/TIGIT double HuGEMM™ model engrafted with mouse syngeneic tumors. *Cancer Res*. 2020;80(suppl 16):5614.
18. Rodriguez-Abreu D, Johnson ML, Hussein MA, et al. Primary analysis of a randomized, double-blind, phase II study of the anti-TIGIT antibody tiragolumab (tira) plus atezolizumab (atezo) versus placebo plus atezo as first-line (1L) treatment in patients with PD-L1-selected NSCLC (CITYSCAPE). *J Clin Oncol*. 2020;38(suppl 15):Abstract 9503.
19. Johnston RJ, Comps-Agrar L, Hackney J, et al. The immunoreceptor TIGIT regulates antitumor and antiviral CD8(+) T cell effector function. *Cancer Cell*. 2014;26(6):923-937.
20. Herbst RS, Baas P, Kim D-W, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet*. 2016;387(10027):1540-1550.