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ORIGINAL RESEARCH

A phase Ib/II dose expansion study of subcutaneous sasanlimab in patients with locally advanced or metastatic non-small-cell lung cancer and urothelial carcinoma

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Background: Sasanlimab is an antibody to the programmed cell death protein 1 receptor. We report updated data of subcutaneous sasanlimab in non-small-cell lung cancer (NSCLC) and urothelial carcinoma dose expansion cohorts from a first-in-human phase Ib/II study.

Patients and methods: Patients were ≥18 years of age with NSCLC or urothelial carcinoma, and no prior immunotherapies, who progressed on or were intolerant to systemic therapy, or for whom systemic therapy was refused or unavailable. Patients received subcutaneous sasanlimab at 300 mg every 4 weeks (q4w). Primary objectives were to evaluate safety, tolerability, and clinical efficacy by objective response rate (ORR).

Results: Sixty-eight and 38 patients with NSCLC and urothelial carcinoma, respectively, received subcutaneous sasanlimab. Overall, sasanlimab was well tolerated; 13.2% of patients experienced grade ≥3 treatment-related adverse events. Confirmed ORR was 16.4% and 18.4% in the NSCLC and urothelial carcinoma cohorts, respectively. ORR was generally higher in patients with high programmed death-ligand 1 (PD-L1) expression (≥25%) and high tumor mutational burden (TMB; >75%). In the NSCLC and urothelial carcinoma cohorts, median progression-free survival (PFS) was 3.7 and 2.9 months, respectively; corresponding median overall survival (OS) was 14.7 and 10.9 months. Overall, longer median PFS and OS correlated with high PD-L1 expression and high TMB. Longer median PFS and OS were also associated with T-cell inflamed gene signature in the urothelial carcinoma cohort.

Conclusions: Subcutaneous sasanlimab at 300 mg q4w was well tolerated with promising clinical efficacy observed. Phase II and III clinical trials of sasanlimab are ongoing to validate clinical benefit. Subcutaneous sasanlimab may be a potential treatment option for patients with NSCLC or urothelial carcinoma.

Key words: non-small-cell lung cancer, PD-1, phase I, sasanlimab, urothelial carcinoma

INTRODUCTION

Binding of programmed death-ligand 1 and death-ligand 2 (PD-L1 and PD-L2) to the programmed cell death protein 1 (PD-1) receptor on T cells leads to inhibition of T-cell proliferation, cytokine production, and cytotoxic functions. In certain tumor types, PD-L1 and PD-L2 expression is up-regulated, and active T-cell immune surveillance of tumors is inhibited.[1-5] Several immunotherapies administered intravenously are available for a variety of tumor types that target elements of the PD-1 pathway. These include atezolizumab, avelumab, cemiplimab, durvalumab, nivolumab, and pembrolizumab.[1-6]

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Sasanlimab (PF-06801591) is a humanized, hinge region-stabilized immunoglobulin G4 monoclonal antibody that selectively binds to human PD-1. Sasanlimab blocks the interaction between PD-1 and PD-L1/-L2, thus releasing the PD-1 pathway-mediated inhibition of the immune response, and leads to an antitumor immune response.[7,8] Sasanlimab has been shown to induce T-cell proliferation and secretion of interferon-γ and other pro-inflammatory cytokines in human activated CD8+ T cells.[9] Sasanlimab has shown similar binding affinity to PD-1 compared with pembrolizumab and nivolumab.[7,8]

The purpose of this first-in-human phase I, open-label study was to evaluate the safety, tolerability, pharmacokinetics (PK), and antitumor activity of intravenous and subcutaneous sasanlimab. The trial comprised a dose escalation phase (part 1, with sasanlimab administered intravenously or subcutaneously to establish the maximum tolerated dose) in patients with locally advanced or metastatic solid tumors and a dose expansion phase (part 2, with sasanlimab administered subcutaneously) in patients with advanced or metastatic non-small-cell lung cancer (NSCLC) or urothelial carcinoma. Results from the dose escalation phase have been reported and the subcutaneous administration was well tolerated, with an acceptable PK profile, offering patients a potentially more convenient and expeditious route of administration.[10,11] Interim dose expansion data in patients with NSCLC or urothelial carcinoma have been reported.[12,13] Here, we report the safety, efficacy, and PK of subcutaneous sasanlimab as well as biomarker analyses in NSCLC and urothelial carcinoma dose expansion cohorts after completion of the study.

PATIENTS AND METHODS

Study design

The first-in-human, phase I, open-label, multicenter, multiple-dose study (NCT02573259) was completed at 45 centers in seven countries between 10 February 2016 and 19 November 2020. The trial included two parts: dose escalation (part 1) and dose expansion (part 2; Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2023.101589). Methods and results from part 1 in patients with locally advanced or metastatic solid tumors have been reported.[10] All patients in part 2 received subcutaneous sasanlimab 300 mg every 4 weeks (q4w). Part 2 included two cohorts: cohort 1 included patients with NSCLC, and cohort 2 included patients with urothelial carcinoma. The study was approved by institutional review boards and independent ethics committees at each center. The study was conducted in accordance with all local legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects, the International Conference on Harmonisation Good Clinical Practice Guidelines, and the Declaration of Helsinki. All patients provided written informed consent. Patients were not involved in the design and conduct of this research.

Patients

All patients were ≥18 years of age, with an Eastern Cooperative Oncology Group performance status of 0 or 1, and adequate liver, renal, and bone marrow function. Patients had one or more measurable lesion as defined by RECIST V.1.1 and had not received any prior anti-PD-1/PD-L1 therapies. Patients had either histological or cytological diagnosis of locally advanced or metastatic NSCLC or urothelial carcinoma, and had progressed on or were intolerant to systemic therapy, or standard-of-care systemic therapy was refused or unavailable.

Patients with NSCLC with no known anaplastic lymphoma kinase (ALK) or epidermal growth factor receptor (EGFR) mutations had not received more than one line of prior systemic therapy and had to have either: progressed on or after platinum-containing systemic therapy; been intolerant to standard-of-care systemic therapy; or refused standard-of-care systemic therapy. Patients with ALK- or EGFR-positive NSCLC had received prior systemic therapies, including at least one line of ALK- or EGFR-targeting drugs and chemotherapy limited to one line of a platinum-based regimen, and they had progressed on or after both types of therapies.

Patients with urothelial carcinoma had received no more than two lines of prior systemic therapy and either: progressed on or after platinum-containing systemic therapy; had been intolerant to platinum-containing systemic therapy; had disease recurrence within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy; were ineligible for platinum-containing systemic therapy; or refused standard-of-care systemic therapy.

Patients were excluded if they had: active brain or leptomeningeal metastases; active, known, or suspected autoimmune disease; a history of lung disease; a cardiac condition within 6 months, or other malignancy within 5 years before registration, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma *in situ* of the breast or the cervix, or low-grade prostate cancer on surveillance, or other concurrent malignancy with a low likelihood of becoming metastatic.

Endpoints

The primary endpoints were safety [adverse events (AEs) and laboratory abnormalities] and objective response based on RECIST V.1.1 or immune-related (ir) RECIST (irRECIST). The secondary endpoints were: time to progression (TTP); time to response (TTR); progression-free survival (PFS)/irPFS; duration of stable disease (DOSD)/irDOSD; duration of response (DOR)/irDOR; median time to death and proportion of patients alive at 6 months, 1 year, and 2 years; trough sasanlimab concentration for selected cycles; and the incidence of antidrug antibodies (ADAs) and neutralizing antibodies (NAbs) against sasanlimab. Correlation of baseline PD-L1 expression and tumor mutational burden (TMB) with antitumor activity was assessed as exploratory endpoints.

Statistical analyses

The sample size for patients with NSCLC was 70 patients. There was no hypothesis testing in part 2 of the study. An estimation approach was used to characterize the precision of response data. The estimation of objective response rate (ORR) using $n = 70$ is described as follows. Suppose that the ORR estimate is 19% in part 2 with $n = 70$, then the 80% and 90% confidence intervals (CIs) of the true ORR will be 13.4% to 25.2% and 12.2% to 27.3%, respectively. Note that an ORR of 19% was observed in a clinical trial for nivolumab in patients with previously treated NSCLC. Additionally, ∼30 patients with urothelial carcinoma were to be enrolled, based on clinical considerations of expanding the safety database.

The following analysis populations were included. The safety analysis population included all enrolled patients who received at least one dose of sasanlimab. The full analysis population included all enrolled patients. The modified intent-to-treat (mITT) population was defined as all randomized patients who received at least one dose of sasanlimab, had measurable disease baseline assessment and at least one post-baseline assessment or disease progression, global deterioration of health status, or death. The per-protocol analysis population included all enrolled patients who received at least one dose of sasanlimab and who did not have major treatment deviations during cycle 1. Two PK analysis populations were included: the PK concentration population, defined as all treated patients who had at least one post-dose concentration measurement, and the PK parameter analysis population, defined as all treated patients who had sufficient information to estimate at least one PK parameter of interest. The pharmacodynamic/biomarker analysis population included all enrolled patients with at least one pharmacodynamic/biomarker parameter evaluated at pre- and/or post-dose. The immunogenicity analysis population included patients who received at least one dose of sasanlimab and had at least one ADA or NAb sample collected.

Efficacy endpoints were defined as follows. ORR was defined as the proportion of patients with a confirmed complete response (CR) or partial response (PR). PFS was defined as time from treatment start date to date of first documentation of progression or death due to any cause. DOSD was defined as time from start of treatment until the criteria for progression were met. DOR was defined as time from first documentation of PR or CR to date of first documentation of objective progression or death. Disease control rate (DCR) was defined as the proportion of patients who achieved CR or PR, or stable disease. TTR was defined as time from study treatment date to first documentation of PR or CR. TTP was defined as time from start date to date of first documentation of objective progression. Time to death [i.e. overall survival (OS)] was time from treatment start date to date of death due to any cause. ORR was based on confirmed responses, and two-sided 95% CIs were calculated using the exact binomial method. Time-to-event data were analyzed using the Kaplan—Meier method.

Safety endpoints were summarized descriptively. All AEs and laboratory test abnormalities were graded by the investigator according to the National Cancer Institute Common Terminology Criteria for Adverse Events V.4.03, and coded using the Medical Dictionary for Regulatory Activities V.23.1. Blood samples for PK analyses were collected at regular intervals throughout the study and were assayed using a validated analytical method. PK parameters were summarized descriptively unless otherwise stated.

PD-L1 expression was assayed on pre-dose formalin-fixed paraffin-embedded (FFPE) tumor tissue by immunohistochemistry at HistoGeneX (Antwerp, Belgium) using the Ventana 263 antibody. Percentage of PD-L1-positive tumor cells from each sample was determined by a board-certified pathologist. The following expression cohorts were evaluated: $<$1%, 1% to $<$50%, and $\geq$50% PD-L1 for NSCLC; and $<$1%, 1% to $<$25%, and $\geq$25% PD-L1 for urothelial carcinoma.

RNA and DNA were isolated from pre-treatment FFPE tumor tissue and analyzed by whole transcript and whole exome sequencing, respectively, by Personalis (Menlo Park, CA). TMB was calculated from the whole exome sequencing data as the number of non-synonymous single-nucleotide variants per megabase. Clinical benefit (with OS and PFS endpoints) from the treatment was evaluated in low, intermediate, and high subgroups defined by TMB quartiles. These were defined as: low TMB $\leq$6.215, intermediate TMB $>$6.215 to $<$10.1625, and high TMB $\geq$10.1625 for NSCLC; and low TMB $\leq$6.59, intermediate TMB $>$6.59 to $<$8.78, and high TMB $\geq$8.78 for urothelial carcinoma. Kaplan—Meier curves for OS and PFS by TMB were generated using survfit and visualized using ggsurvplot R packages. *P* values were determined by the log-rank test comparing the subgroups.

For gene expression analyses, the clustering analysis was carried out using the T-cell inflamed gene set as described by Ayers et al.[14] Transcript-level gene expression was quantified using transcripts per million (TPM) values for each gene. TPM values were then log2 transformed for further analysis. Individual gene expression was then centered and scaled to evaluate relative gene expression among patients. Patients with NSCLC or urothelial carcinoma were clustered based on how they expressed the T-cell inflamed genes in an unsupervised way. This two-way hierarchical clustering showed two clusters of patients: cluster 1 with a higher level of gene expression and cluster 2 with a lower level of gene expression. Two-way unsupervised clustering was done on the centered and scaled gene expression for all patients and all 18 genes using hclust and presented in a heatmap using the pheatmap R package.

Statistical analyses of clinical data were conducted using SAS V.9.4 (Cary, NC). Biomarker data analyses used R V.3.6.3. Survival package V.3.2.13 was used for survival analysis, including generating survival statistics and Kaplan—Meier plots. hclust and pheatmap functions were used to generate the two-way clustering heatmaps. The data cut-off date for these analyses was 19 November 2020.

Table 1. Patient demographics and baseline characteristics

Characteristic	NSCLC (n = 68)	Urothelial carcinoma (n = 38)	Total (n = 106)
Age, mean (range), years	65.9 (38-85)	64.1 (34-88)	65.2 (34-88)
Sex, *n* (%)			
Male	53 (77.9)	25 (65.8)	78 (73.6)
Female	15 (22.1)	13 (34.2)	28 (26.4)
Race, *n* (%)			
White	50 (73.5)	30 (78.9)	80 (75.5)
Asian	18 (26.5)	8 (21.1)	26 (24.5)
ECOG PS, *n* (%)			
0	10 (14.7)	14 (36.8)	24 (22.6)
1	58 (85.3)	24 (63.2)	82 (77.4)
Histopathology, *n* (%)			
Squamous	29 (42.6)	0	29 (27.4)
Adenocarcinoma	39 (57.4)	0	39 (36.8)
Smoking history, *n* (%)			
Never smoked	16 (23.5)	22 (57.9)	38 (35.9)
Ex-smoker	36 (52.9)	11 (28.9)	47 (44.3)
Current smoker	16 (23.5)	5 (13.2)	21 (19.8)
Brain metastases, *n* (%)	3 (4.4)	0	3 (2.8)
Prior surgery, *n* (%)	18 (26.5)	8 (21.1)	26 (24.5)
Prior systemic therapy, *n* (%)	52 (76.5)	33 (86.8)	85 (80.2)
Number of prior regimens, median (range)	1.0 (1-4)	1.0 (1-3)	1.0 (1-4)
Number of prior regimens, *n* (%)			
1	46 (67.6)	23 (60.5)	69 (65.1)
2	4 (5.9)	8 (21.1)	12 (11.3)
3	1 (1.5)	2 (5.3)	3 (2.8)
>3	1 (1.5)	0	1 (0.9)
Types of prior therapy, *n* (%)			
Chemotherapy	52 (76.5)	33 (86.8)	85 (80.2)
Targeted therapy (approved or investigational)	8 (11.8)	0	8 (7.5)
Immunotherapy (OX-40 or CTLA-4)	0	1 (2.6)	1 (0.9)
Number of prior regimens with advanced/metastatic disease, *n* (%)			
1	39 (57.4)	16 (42.1)	55 (51.9)
2	3 (4.4)	7 (18.4)	10 (9.4)
3	1 (1.5)	2 (5.3)	3 (2.8)
>3	1 (1.5)	0	1 (0.9)
Types of prior therapy with advanced/metastatic disease, *n* (%)			
Chemotherapy	44 (64.7)	25 (65.8)	69 (65.1)
Targeted therapy	8 (11.8)	0	8 (7.5)
Immunotherapy (OX-40 or CTLA-4)	0	0	0
PD-L1 expression, *n* (%)			
<1%	28 (41.2)	17 (44.7)	45 (42.5)
≥1%	29 (42.6)	15 (39.5)	44 (41.5)
Not determined	11 (16.2)	6 (15.8)	17 (16.0)

Safety analysis population.
CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; ECOG PS, Eastern Cooperative Oncology Group performance status; NSCLC, non-small-cell lung cancer; PD-L1, programmed death-ligand 1.

RESULTS

Patients and treatment

In part 2 of the study, 68 patients with NSCLC and 38 patients with urothelial carcinoma were enrolled in two cohorts and received subcutaneous sasanlimab 300 mg q4w. Among patients with NSCLC and urothelial carcinoma, most were male (77.9% and 65.8%) and white (73.5% and 78.9%), respectively. Mean (range) age was 65.9 (38-85) years and 64.1 (34-88) years for patients with NSCLC and urothelial carcinoma, respectively. The median (range) number of prior regimens for patients with NSCLC and urothelial carcinoma was 1 (1-4) and 1 (1-3), respectively (Table 1). Overall, at the time of data cut-off, 96 of 106 patients discontinued treatment. Disease progression (39.6%) was the most common reason for treatment discontinuation. The median (range) treatment duration in the NSCLC and urothelial carcinoma cohorts was 133.0 (11-851) days and 117.0 (21-841) days, respectively. The median (range) duration of follow-up in the NSCLC and urothelial carcinoma cohorts was 7.2 (0.4-28.8) months and 8.7 (0.7-28.7) months, respectively.

Pooled safety

In a pooled safety analysis of the NSCLC and urothelial carcinoma cohorts (n = 106), 98 (92.5%) patients experienced at least one treatment-emergent AE (TEAE) (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2023.101589); 59 (55.7%) patients experienced at least one treatment-related AE (TRAE) (Table 2). The most commonly reported TRAEs experienced by at least 5% of patients included: hyperthyroidism in 11 (10.4%) patients; lipase increased and pruritus, each in 8 (7.5%) patients; and hypothyroidism, increased alanine aminotransferase, increased aspartate

Table 2. Treatment-related adverse events[a]

MedDRA PT, *n* (%)	NSCLC (*n* = 68)			Urothelial carcinoma (*n* = 38)			Total (*n* = 106)		
	Grade 3	Grade 4	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4	Any grade
Any AE	8 (11.8)	1 (1.5)	42 (61.8)	5 (13.2)	0	17 (44.7)	13 (12.3)	1 (0.9)	59 (55.7)
Hyperthyroidism	0	0	8 (11.8)	0	0	3 (7.9)	0	0	11 (10.4)
Lipase increased	1 (1.5)	1 (1.5)	5 (7.4)	1 (2.6)	0	3 (7.9)	2 (1.9)	1 (0.9)	8 (7.5)
Pruritus	0	0	5 (7.4)	0	0	3 (7.9)	0	0	8 (7.5)
ALT increased	0	0	4 (5.9)	0	0	2 (5.3)	0	0	6 (5.7)
Amylase increased	0	0	4 (5.9)	2 (5.3)	0	2 (5.3)	2 (1.9)	0	6 (5.7)
AST increased	0	0	4 (5.9)	0	0	2 (5.3)	0	0	6 (5.7)
Hypothyroidism	0	0	3 (4.4)	0	0	3 (7.9)	0	0	6 (5.7)
Rash	0	0	4 (5.9)	0	0	2 (5.3)	0	0	6 (5.7)
Anemia	0	0	5 (7.4)	0	0	0	0	0	5 (4.7)
Asthenia	1 (1.5)	0	3 (4.4)	0	0	2 (5.3)	1 (0.9)	0	5 (4.7)
Nausea	0	0	4 (5.9)	0	0	1 (2.6)	0	0	5 (4.7)
Pyrexia	0	0	5 (7.4)	0	0	0	0	0	5 (4.7)
Pneumonitis	0	0	4 (5.9)	0	0	0	0	0	4 (3.8)
Lacrimation increased	0	0	0	0	0	2 (5.3)	0	0	2 (1.9)
Transaminases increased	0	0	0	1 (2.6)	0	2 (5.3)	1 (0.9)	0	2 (1.9)

Safety analysis population.

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; MedDRA PT, Medical Dictionary for Regulatory Activities Preferred Term; NSCLC, non-small-cell lung cancer.

[a]Most common treatment-related AEs were those that occurred in ≥5% of any grade treatment-related AEs in either the NSCLC or urothelial carcinoma cohort, coded using MedDRA V.23.1 and graded according to CTCAE V.4.03. No grade 5 treatment-related AEs were reported. One additional grade 5 treatment-related AE of arrhythmia was reported 33 days after the last dose of sasanlimab. This was assessed as treatment-related by the investigator but was not considered a treatment-related AE by predefined on-treatment period and statistical analysis.

aminotransferase, increased amylase, and rash, each in 6 (5.7%) patients.

Forty-four (41.5%) patients experienced grade 3 or higher TEAEs; 14 (13.2%) patients experienced grade 3 or higher TRAEs. Grade 3 or higher TRAEs included: increased lipase in three (2.8%) patients; increased amylase and increased blood alkaline phosphatase, each in two (1.9%) patients; and arrhythmia, asthenia, fatigue, jaundice, increased blood potassium, decreased lymphocyte count, increased transaminase, decreased appetite, hypermagnesemia, ageusia, anosmia, cognitive disorder, and hypotension, each in one (1.5%) patient. One (0.9%) patient reported a grade 4 TRAE of increased lipase. There were no grade 5 TRAEs; however, one additional grade 5 TRAE of arrhythmia was reported 33 days after the last dose of sasanlimab. This was assessed as treatment-related by the investigator but was not considered a TRAE by predefined on-treatment period and statistical analysis. Few patients experienced treatment-related injection site bruising or induration, with injection site bruising and injection site induration reported only in the NSCLC cohort, each by one (1.5%) patient, both grade 1.

TRAEs leading to permanent treatment discontinuation were pneumonitis ($n = 1$, 1.5%; grade 2) in the NSCLC cohort, and arrhythmia and increased transaminases in the urothelial carcinoma cohort (each $n = 1$, 2.6%; both grade 3).

Efficacy in patients with NSCLC

In the NSCLC cohort ($n = 67$, mITT population), the confirmed ORR (95% CI) (Table 3) based on RECIST V.1.1 was 16.4% (8.5% to 27.5%); response outcomes based on irRECIST showed similar but slightly improved trends (Table 3). The median TTR (range) was 2.7 (1.4-12.0) months, and the median DOR (95% CI) was 21.8 [5.8-not estimable (NE)] months. Eleven patients achieved a PR and 27 patients had stable disease with a corresponding DCR (95% CI) of 56.7% (44.0% to 68.8%). The median DOSD (95% CI) was 6.5 (3.7-10.1) months. The median TTP (95% CI) was 3.7 (1.9-5.7) months.

Median PFS (95% CI) was 3.7 (1.9-5.5) months. Median irPFS (95% CI) was 5.5 (2.8-8.2) months. Median OS (95% CI) was 14.7 (7.1-NE) months.

The response rate was higher in patients with high PD-L1 expression [ORR (95% CI) 36.4% (10.9% to 69.2%) in PD-L1 ≥50% versus 14.3% (4.0% to 32.7%) in PD-L1 <1%] and high TMB (ORR 41.7% in high TMB versus 8.3% in low TMB) (Table 3; Figure 1). Change in tumor size over time by tumor type and PD-L1 status is shown in Supplementary Figure S2, available at https://doi.org/10.1016/j.esmoop.2023.101589.

Median PFS (95% CI) was longer in patients with PD-L1 ≥50% [14.9 (1.7-NE) months] versus <1% [3.7 (1.8-9.2) months] and ≥1% to <50% [3.6 (1.8-5.5) months] (Figure 2). Median PFS (95% CI) was 6.01 (2.60-NE) months, 3.88 (1.87-9.26) months, and 1.84 (1.81-NE) months for high, intermediate, and low TMB, respectively. Median PFS was longer in high TMB but not statistically significant (Supplementary Figure S3, available at https://doi.org/10.1016/j.esmoop.2023.101589).

Whole-transcriptome profiles were available for 51 patients with NSCLC. Transcriptome and gene expression profile (GEP) analysis of the T-cell inflamed gene set did not demonstrate any significant differences in PFS: median (95% CI) PFS was 5.42 (3.75-NE) months in the low GEP cluster and 1.87 (1.84-9.26) months in the high GEP cluster (Supplementary Figure S4, available at https://doi.org/10.1016/j.esmoop.2023.101589).

Table 3. Best overall response by PD-L1 expression and TMB

Tumor response, *n* (%)	RECIST V.1.1				irRECIST
	PD-L1 expression—NSCLC				
	Overall ($n = 67$)	PD-L1 <1% ($n = 28$)	PD-L1 ≥1% to <50% ($n = 17$)	PD-L1 ≥50% ($n = 11$)	Overall ($n = 67$)
ORR, % (95% CI)[a]	16.4 (8.5-27.5)	14.3 (4.0-32.7)	11.8 (1.5-36.4)	36.4 (10.9-69.2)	19.4 (10.8-30.9)
CR	0	0	0	0	0
PR	11 (16.4)	4 (14.3)	2 (11.8)	4 (36.4)	13 (19.4)
SD	27 (40.3)	11 (39.3)	8 (47.1)	4 (36.4)	31 (46.3)
PD	24 (35.8)	9 (32.1)	6 (35.3)	3 (27.3)	18 (26.9)
Not evaluable	5 (7.5)	4 (14.3)	1 (5.9)	0	5 (7.5)
PD-L1 expression—urothelial carcinoma					
	Overall ($n = 38$)	PD-L1 <1% ($n = 17$)	PD-L1 ≥1% to <25% ($n = 8$)	PD-L1 ≥25% ($n = 7$)	Overall ($n = 38$)
ORR, % (95% CI)[a]	18.4 (7.7-34.3)	11.8 (1.5-36.4)	50.0 (15.7-84.3)	14.3 (0.4-57.9)	21.1 (9.6-37.3)
CR	0	0	0	0	0
PR	7 (18.4)	2 (11.8)	4 (50.0)	1 (14.3)	8 (21.1)
SD	13 (34.2)	4 (23.5)	1 (12.5)	6 (85.7)	17 (44.7)
PD	15 (39.5)	11 (64.7)	1 (12.5)	0	10 (26.3)
Not evaluable	3 (7.9)	0	2 (25.0)	0	3 (7.9)
TMB—NSCLC					
	Low ($n = 12$)	Intermediate ($n = 24$)	High ($n = 12$)	Unknown ($n = 19$)	Total ($n = 67$)
ORR	1 (8.3)	5 (20.8)	5 (41.7)	0	11 (16.4)
CR	0	0	0	0	0
PR	1 (8.3)	5 (20.8)	5 (41.7)	0	11 (16.4)
SD	3 (25.0)	10 (41.7)	4 (33.3)	10 (52.6)	27 (40.3)
PD	6 (50.0)	8 (33.3)	3 (25.0)	7 (36.8)	24 (35.8)
Not evaluable	2 (16.7)	1 (4.2)	0	2 (10.5)	5 (7.5)
TMB—urothelial carcinoma					
	Low ($n = 9$)	Intermediate ($n = 16$)	High ($n = 9$)	Unknown ($n = 4$)	Total ($n = 38$)
ORR	1 (11.1)	3 (18.8)	2 (22.2)	1 (25.0)	7 (18.4)
CR	0	0	0	0	0
PR	1 (11.1)	3 (18.8)	2 (22.2)	1 (25.0)	7 (18.4)
SD	3 (33.3)	6 (37.5)	3 (33.3)	1 (25.0)	13 (34.2)
PD	4 (44.4)	5 (31.3)	4 (44.4)	2 (50.0)	15 (39.5)
Not evaluable	1 (11.1)	2 (12.5)	0	0	3 (7.9)

Modified intent-to-treat population.
CI, confidence interval; CR, complete response; ir, immune-related; NSCLC, non-small-cell lung cancer; ORR, objective response rate; PD, progressive disease; PD-L1, programmed death-ligand 1; PR, partial response; SD, stable disease; TMB, tumor mutational burden.
[a]Using exact method based on binomial distribution.

Median OS (95% CI) was longer in patients with PD-L1 ≥50% [NE (3.3-NE) months] and ≥1% to <50% [NE (6.9-NE) months] versus <1% [11.1 (6.2-16.4) months; Supplementary Figure S5, available at https://doi.org/10.1016/j.esmoop.2023.101589]. Median OS (95% CI) was also longer in patients with intermediate TMB [NE (11.14-NE) months] or high TMB [NE (16.00-NE) months] compared with those with low TMB [5.36 (3.25-NE) months; Supplementary Figure S5, available at https://doi.org/10.1016/j.esmoop.2023.101589]. However, no differences in OS between GEP subgroups were observed: median (95% CI) OS was NE (16.00-NE) months in the low GEP cluster and 14.70 (8.08-NE) months in the high GEP cluster (Supplementary Figure S6, available at https://doi.org/10.1016/j.esmoop.2023.101589).

Efficacy in patients with urothelial carcinoma

In the urothelial carcinoma cohort ($n = 38$, mITT), the confirmed ORR (95% CI) (Table 3) based on RECIST V.1.1 was 18.4% (7.7% to 34.3%); response outcomes based on irRECIST showed similar but slightly improved trends (Table 3). The median TTR (range) was 2.3 (1.4-5.5) months and the median DOR (95% CI) was 13.9 (3.8-NE) months. Seven patients achieved a PR and 13 patients had stable disease with a corresponding DCR (95% CI) of 52.6% (35.8% to 69.0%). The median DOSD (95% CI) was 8.5 (3.7-NE) months. The median TTP (95% CI) was 3.7 (1.9-8.5) months.

Median PFS (95% CI) was 2.9 (1.9-3.8) months. Median irPFS (95% CI) was 3.8 (2.0-14.5) months. Median OS (95% CI) was 10.9 (7.2-19.9) months.

The response rate was higher in patients with high PD-L1 expression [ORR (95% CI) 14.3% (0.4% to 57.9%) in PD-L1 ≥25% versus 11.8% (1.5% to 36.4%) in PD-L1 <1%] and high TMB (ORR 22.2% in high TMB versus 11.1% in low TMB) (Table 3; Figure 1). Change in tumor size over time by tumor type and PD-L1 status is shown in Supplementary Figure S2, available at https://doi.org/10.1016/j.esmoop.2023.101589.

Median PFS (95% CI) was longer in patients with PD-L1 1% to <25% [12.5 (1.9-NE) months] and ≥25% [8.5 (3.4-NE) months] versus <1% [1.9 (1.8-3.7) months] (Figure 2).

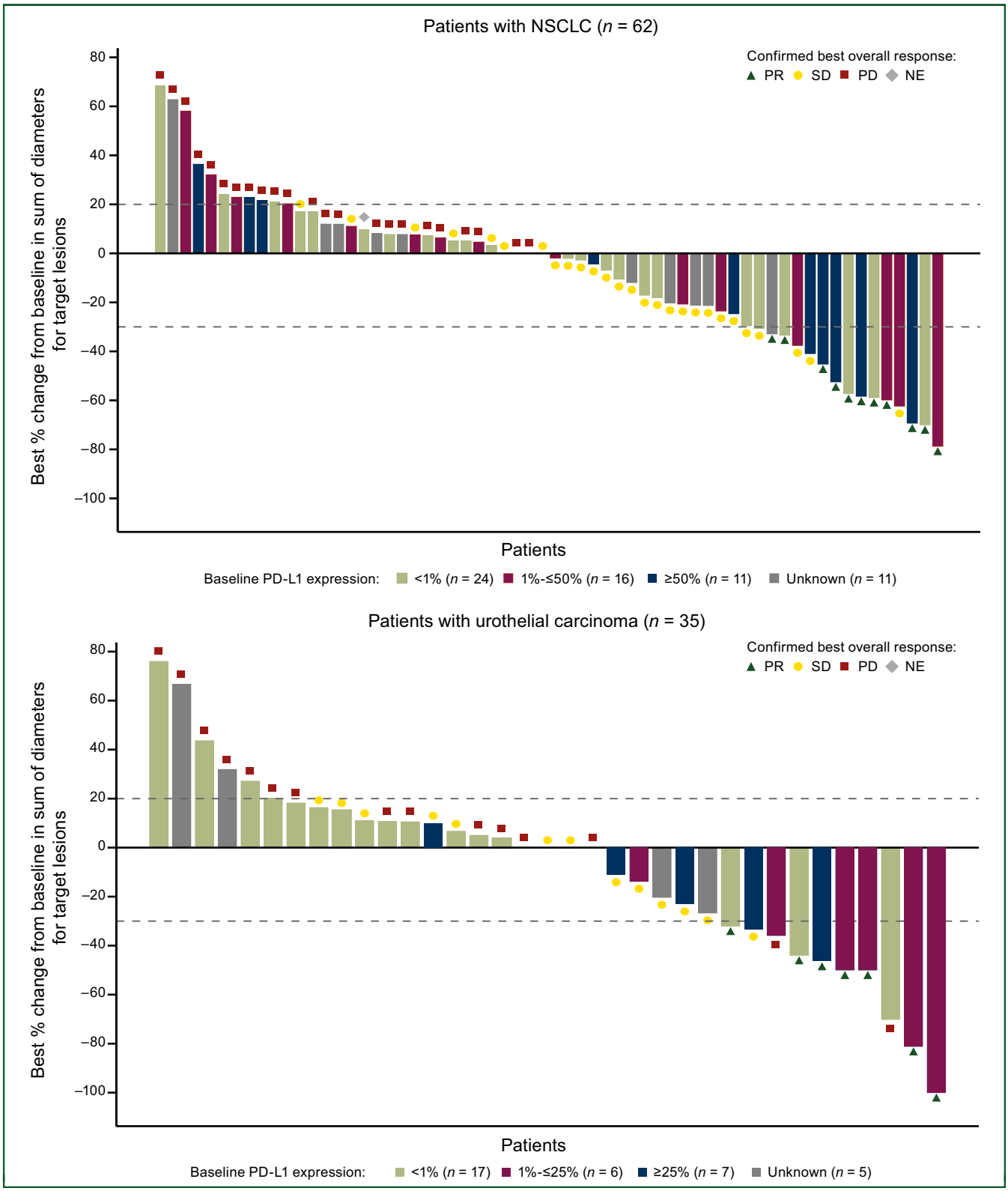

Figure 1. Waterfall plot of tumor size change by baseline PD-L1 status in patients with NSCLC and urothelial carcinoma. Modified intent-to-treat population. Based on investigator assessment as per RECIST V.1.1.

NE, not evaluable; NSCLC, non-small-cell lung cancer; PD, progressive disease; PD-L1, programmed death-ligand 1; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

No significant differences in PFS between TMB subgroups were observed: median PFS (95% CI) was 1.87 (1.84-NE), 3.55 (1.84-NE), and 2.50 (1.97-NE) months for low, intermediate, and high TMB, respectively (Supplementary Figure S3, available at https://doi.org/10.1016/j.esmoop.2023.101589).

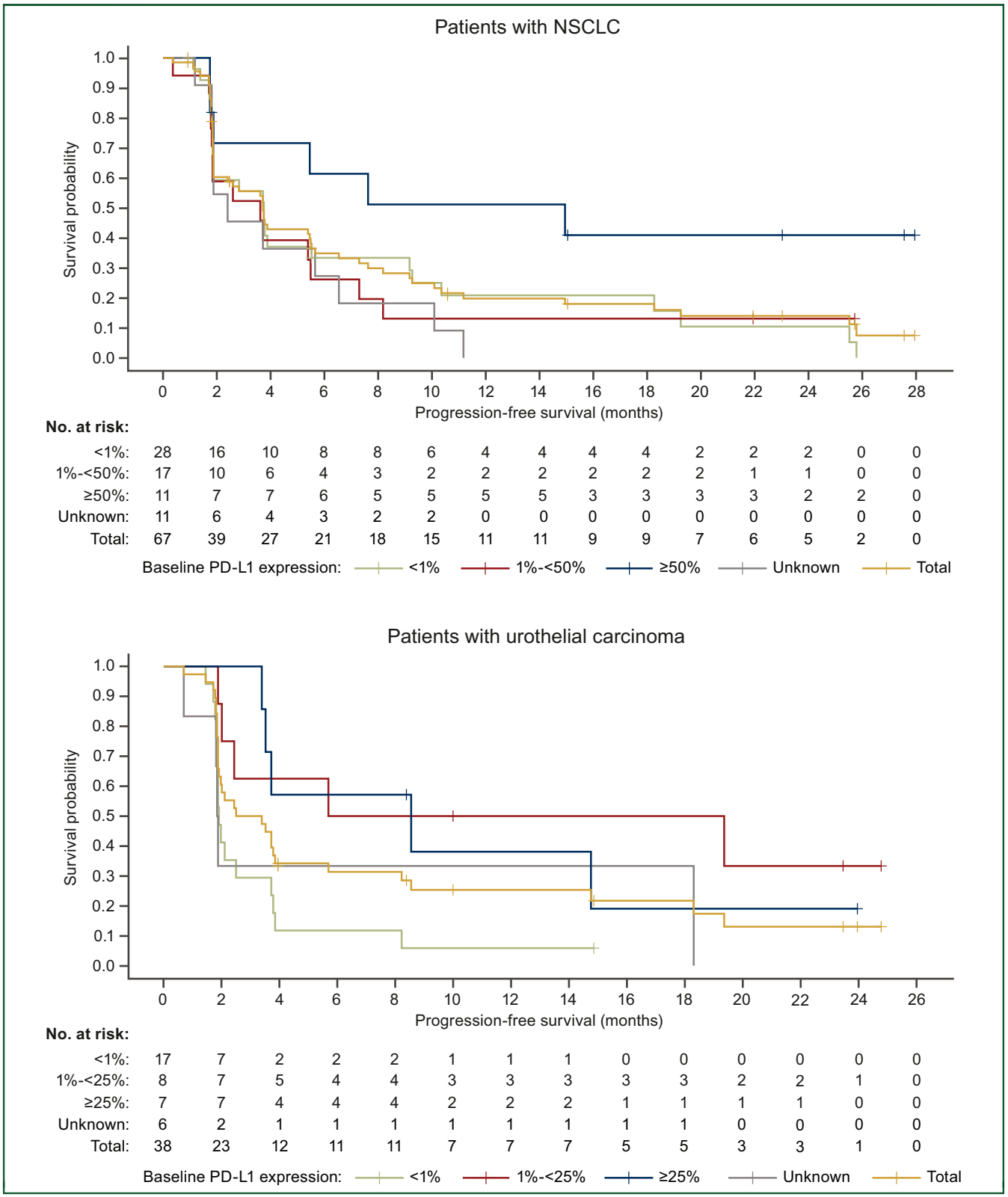

Figure 2. Kaplan–Meier plot of progression-free survival by baseline PD-L1 expression in patients with NSCLC and urothelial carcinoma. Modified intent-to-treat population. Based on investigator assessment as per RECIST V.1.1.

NSCLC, non-small-cell lung cancer; PD-L1, programmed death-ligand 1; RECIST, Response Evaluation Criteria in Solid Tumors.

Whole-transcriptome profiles were available for 32 patients with urothelial carcinoma. Median PFS (95% CI) was significantly longer in patients with a high GEP [5.68 (3.52-19.40) months] versus those with a low GEP [1.84 (1.81-NE) months] (Supplementary Figure S4, available at https://doi.org/10.1016/j.esmoop.2023.101589).

Median OS (95% CI) was longer in patients with PD-L1 1% to <25% [NE (2.0-NE) months] versus <1% [10.3 (4.3-16.7) months] and ≥25% [10.3 (3.4-NE) months] (Supplementary Figure S5, available at https://doi.org/10.1016/j.esmoop.2023.101589). No significant differences in OS between TMB subgroups were observed: median OS (95% CI) was 9.13 (3.52-NE), 10.87 (7.23-NE), and 19.91 (10.32-NE) months for low, intermediate, and high TMB, respectively (Supplementary Figure S5, available at https://doi.org/10.1016/j.esmoop.2023.101589). However, OS was significantly longer in patients with a high GEP compared with those with a low GEP: median (95% CI) OS was 5.78 (3.71-NE) months in the low GEP cluster and 18.30 (10.28-NE) months in the high GEP cluster (Supplementary Figure S6, available at https://doi.org/10.1016/j.esmoop.2023.101589).

Pharmacokinetics

Following subcutaneous administration of sasanlimab at 300 mg q4w in patients with NSCLC or urothelial carcinoma, trough values increased from the first dose on cycle 1 day 1 through cycle 4 day 1, and generally without further increase thereafter, suggesting achievement of steady state. Overall, trough and post-dose serum concentration (cycle 1 day 1) levels were generally similar between the two tumor types and consistent with part 1 of the study.[10]

Immunogenicity

For patients with NSCLC or urothelial carcinoma, 5/64 (7.8%) and 3/37 (8.1%) ADA-assessable patients were treatment-induced ADA positive, with a median onset at days 85 and 140, respectively. The presence of ADA was not associated with hypersensitivity. For the NSCLC and urothelial carcinoma cohorts, 3/64 (4.7%) and 1/37 (2.7%) NAb-assessable patients were NAb positive, respectively.

DISCUSSION

Subcutaneous administration of sasanlimab 300 mg q4w was well tolerated in patients with NSCLC or urothelial carcinoma, with most of the AEs being mild or moderate in severity, and very low rates of treatment-related injection site reactions. The observed safety profile of sasanlimab was consistent with part 1 of the study.[10] Across both cohorts, the most frequently reported TRAEs were hyperthyroidism (10.4%), increased lipase (7.5%), and pruritus (7.5%). The frequency and severity of TRAEs are in line with clinical expectations, and similar to those reported with other immune checkpoint inhibitors, such as pembrolizumab, nivolumab, atezolizumab, avelumab, and cemiplimab, in patients with NSCLC or urothelial carcinoma, though lower rates of rash, itching, and fatigue are observed with sasanlimab.[15-31] Following subcutaneous sasanlimab dosing, overall immunogenicity incidence was low. In addition, trough and post-dose serum concentration levels were generally similar between NSCLC and urothelial carcinoma cohorts, and consistent with part 1 of the study.[10]

Promising clinical efficacy of subcutaneous sasanlimab was observed in patients with advanced or metastatic NSCLC and urothelial carcinoma. In patients with NSCLC, the confirmed ORR was 16.4%, median OS was 14.7 months, and median PFS was 3.7 months. The observed clinical activity was aligned with other anti-PD-1 or anti-PD-L1 agents in patients with NSCLC: for example, nivolumab in the CheckMate trials;[25-28] pembrolizumab in the KEYNOTE trials;[29-31] cemiplimab in EMPOWER;[15] avelumab in JAVELIN;[16] and atezolizumab in OAK.[24] In patients with urothelial carcinoma, the confirmed ORR was 18.4%, median OS was 10.9 months, and median PFS was 2.9 months. These results remained in line with those reported for other immune checkpoint inhibitors in patients with urothelial carcinoma: for example, nivolumab in the CheckMate trials;[20,21] pembrolizumab in the KEYNOTE trials;[18,19] atezolizumab in the IMVigor trials;[22,23] and avelumab in JAVELIN.[17]

Gene signature and pathways associated with clinical benefits were identified in urothelial carcinoma, with considerable overlap seen with the large phase III JAVELIN Bladder 100 trial of avelumab, an approved immune checkpoint inhibitor.[32] Antitumor responses of sasanlimab were demonstrated in patients with NSCLC or urothelial carcinoma irrespective of baseline tumor PD-L1 level, but were generally greater in patients with higher tumor PD-L1 expression. This observation of higher response frequency in patients with higher PD-L1 expression is concurrent with reports investigating other immune checkpoint inhibitors in both NSCLC[15,24,30,31] and urothelial carcinoma[20,23,32] populations. Exploratory analyses based on TMB and GEP were mixed. Higher ORR (both NSCLC and urothelial carcinoma) and longer OS (NSCLC only) were reported in patients with intermediate or high TMB compared with those with low TMB. Both OS and PFS were longer in patients with urothelial carcinoma with a high GEP versus those with a low GEP. Improved clinical outcomes in patients with higher TMB have also been observed with nivolumab[26,28] and atezolizumab[23] in both NSCLC and urothelial carcinoma. Additionally, response to pembrolizumab[33] and nivolumab[34] in patients with urothelial carcinoma has also been shown to positively correlate with GEP score. However, further investigation is needed to fully understand the impact of TMB and GEP on response to immune checkpoint inhibitors, particularly in different tumor types.

Finally, subcutaneous administration is more convenient and a preferred administration method for patients.[10,35,36] Importantly, subcutaneous administration has a number of other advantages over intravenous administration for patients, health care providers, and payers, including improving patient experience, improving health-related quality of life, reducing medical costs, decreasing clinical time (including drug preparation), and increasing resource efficiency.[10,11]

Conclusion

In conclusion, subcutaneous administration of sasanlimab at 300 mg q4w was well tolerated, with a favorable benefit–risk profile. Further clinical trials of sasanlimab as

monotherapy and as part of a combination regimen (including with targeted therapies, Bacillus Calmette-Guérin, PF-07263689, and SEA-TGT) are ongoing to validate clinical benefits. Sasanlimab may be a potential treatment option for patients with NSCLC or urothelial carcinoma, with subcutaneous administration offering greater convenience.[11]

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DATA SHARING

Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

GLOSSARY

A glossary of the terms used is available in the Supplementary Materials available at https://doi.org/10.1016/j.esmoop.2023.101589.

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