

SAFFRON-103: a phase 1b study of the safety and efficacy of sitravatinib combined with tislelizumab in patients with locally advanced or metastatic non-small cell lung cancer

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ABSTRACT

Background Some patients with locally advanced/metastatic non-small cell lung cancer (NSCLC) respond poorly to anti-programmed cell death protein 1 (PD-1)/anti-programmed death-ligand 1 (PD-L1) treatments.

Combination with other agents may improve the outcomes. This open-label, multicenter, phase 1b trial investigated the combination of sitravatinib, a spectrum-selective tyrosine kinase inhibitor, plus anti-PD-1 antibody tislelizumab.

Methods Patients with locally advanced/metastatic NSCLC were enrolled (Cohorts A, B, F, H, and I; N=22–24 per cohort). Cohorts A and F included patients previously treated with systemic therapy, with anti-PD-(L)1-resistant/refractory non-squamous (cohort A) or squamous (cohort F) disease. Cohort B included patients previously treated with systemic therapy, with anti-PD-(L)1-naïve non-squamous disease. Cohorts H and I included patients without prior systemic therapy for metastatic disease, no prior anti-PD-(L)1/immunotherapy, with PD-L1-positive non-squamous (cohort H) or squamous (cohort I) histology. Patients received sitravatinib 120 mg orally one time per day plus tislelizumab 200 mg intravenously every 3 weeks, until study withdrawal, disease progression, unacceptable toxicity, or death. The primary endpoint was safety/tolerability among all treated patients (N=122). Secondary endpoints included investigator-assessed tumor responses and progression-free survival (PFS).

Results Median follow-up was 10.9 months (range: 0.4–30.6). Treatment-related adverse events (TRAEs) occurred in 98.4% of the patients, with ≥Grade 3 TRAEs in 51.6%. TRAEs led to discontinuation of either drug in 23.0% of the patients. Overall response rate was 8.7% (n/N: 2/23; 95% CI: 1.1% to 28.0%), 18.2% (4/22; 95% CI: 5.2% to 40.3%), 23.8% (5/21; 95% CI: 8.2% to 47.2%), 57.1% (12/21; 95% CI: 34.0% to 78.2%), and 30.4% (7/23; 95% CI: 13.2% to 52.9%) in cohorts A, F, B, H, and I, respectively. Median duration of response was not reached in cohort A and ranged from 6.9 to 17.9 months across other cohorts. Disease control was achieved in 78.3–90.9% of the patients. Median PFS ranged from 4.2 (cohort A) to 11.1 months (cohort H).

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Anti-programmed cell death protein 1 (PD-1) or anti-programmed death-ligand 1 (PD-L1) therapy has clinical benefit in locally advanced/metastatic non-small cell lung cancer (NSCLC), but some patients have poor responses or develop resistance. Preliminary clinical data from studies in selected NSCLC populations suggest that combining multi-targeted tyrosine kinase inhibitors (TKIs) with PD-(L)1 inhibitors may improve responses and warrants further investigation.

WHAT THIS STUDY ADDS

⇒ This trial is the first study of combination therapy with the multi-TKI sitravatinib, which targets TAM (TYRO3, AXL, MER) and split kinase family receptors, plus the anti-PD-1 monoclonal antibody tislelizumab in patients with locally advanced/metastatic NSCLC. Results indicated no unexpected safety signals, with objective tumor responses observed across a broad range of NSCLC treatment settings, including in patients naïve to or previously treated with systemic treatment, naïve to anti-PD-(L)1 treatment or with resistant/refractory disease, and with either non-squamous or squamous histology.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Study results support continued investigation of sitravatinib plus tislelizumab in phase 3 studies in selected patient with NSCLC populations.

Conclusions In patients with locally advanced/metastatic NSCLC, sitravatinib plus tislelizumab was tolerable for most patients, with no new safety signals and overall safety profiles consistent with known profiles of these agents. Objective responses were observed in all cohorts, including in patients naïve to systemic and anti-PD-(L)1 treatments, or with anti-PD-(L)1 resistant/

refractory disease. Results support further investigation in selected NSCLC populations.

Trial registration number NCT03666143.

BACKGROUND

As monotherapy, first-line use of anti-programmed cell death protein 1 (PD-1) and anti-programmed death-ligand 1 (PD-L1) antibodies in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) has been reported to prolong progression-free survival (PFS) and overall survival (OS) compared with chemotherapy, with the greatest benefits typically seen in tumors with elevated levels of PD-L1 expression (tumor proportion score $\geq 50\%$).^{1,2} A meta-analysis of metastatic NSCLC trials estimated 1-year PFS rates for first-line PD-1 blockade of 40.3% among patients with NSCLC with PD-L1 $\geq 50\%$, 35.0% in those with PD-L1 of 1–49%, and 19.9% in patients with PD-L1 $< 1\%$.³ Similarly, this analysis estimated 2-year OS rates in patients receiving first-line PD-1 blockade of 47.5%, 34.9%, and 16.7% in the respective PD-L1 subgroups.³ These data highlight the need for alternative regimens for patients who may achieve only limited clinical benefit from first-line anti-PD-(L)1 monotherapy.

In later lines of therapy, anti-PD-(L)1 therapies have been shown to prolong OS versus docetaxel, although the benefits for long-term PFS are less clear, and objective response rates (ORRs) are typically limited.^{4–7} In addition, many patients with NSCLC treated with PD-(L)1 inhibitor therapy (at first-line or later stages) have cancers that are refractory to treatment, or that develop resistance and progress following an initial response,⁷ highlighting the need for effective treatment options in subsequent lines.

A key investigational strategy for improving treatment outcomes is the combination of anti-PD-(L)1 therapies with other agents that have immunomodulatory and anti-tumor properties.^{8,9} A broad spectrum of such combinations is currently under exploration in NSCLC,^{8,9} including the combination of sitravatinib with anti-PD-(L)1 therapy.

Sitratavinib (MGCD516) is an orally available, spectrum-selective tyrosine kinase inhibitor (TKI) targeting TAM family receptors (TYRO3, AXL, MER) and split kinase family receptors (including vascular endothelial growth factor receptor 2 (VEGFR-2), KIT, and the platelet-derived growth factor receptor family).¹⁰ TAM receptor tyrosine kinases are expressed on antigen-presenting cells, such as macrophages, and are involved in immune system homeostasis, particularly in the regulation of phagocytotic clearance of dying cells and suppression of inflammation.¹¹ TAM receptor signaling has been implicated in tumor metastasis, and receptor overexpression has been reported in various cancers, including lung cancer.¹¹ Targeting TAM family receptors affects macrophage polarization, favoring an immunostimulatory macrophage phenotype (M1) over an immunosuppressive phenotype (M2), thereby promoting an antitumor immune microenvironment.¹⁰ Meanwhile, targeting

VEGFR and KIT reduces the number of regulatory T cells and monocytic myeloid-derived suppressor cells (MDSCs), thereby further relieving immunosuppression^{12,13} and creating an immune microenvironment that favors the antitumor activity of PD-(L)1 inhibition.^{10,13}

Preclinical studies demonstrate that sitravatinib reduces the number of MDSCs and increases the ratio of M1/M2-polarized macrophages, promoting the expansion of antitumor cytotoxic T cells, which may help overcome resistance to immune checkpoint inhibitors and augment antitumor immune responses.¹⁰ In vivo, sitravatinib has been shown to have potent antitumor activity in mice and enhance the efficacy of PD-1 inhibition.¹⁰ The present phase 1b study was therefore conducted to characterize the safety, tolerability, and preliminary antitumor activity of sitravatinib in combination with the anti-PD-1 monoclonal antibody tislelizumab.

Tislelizumab has high binding affinity for PD-1, with different binding epitopes and more complete blockade of PD-L1 binding to PD-1 compared with nivolumab and pembrolizumab.¹⁴ In addition, tislelizumab was specifically engineered to minimize Fc γ receptor binding on macrophages.¹⁵ Phase 3 trials in patients with locally advanced or metastatic NSCLC have shown that tislelizumab monotherapy as second-line or third-line therapy improved OS, PFS, and ORR compared with docetaxel,¹⁶ while combining tislelizumab with chemotherapy as first-line therapy improved ORR and PFS versus chemotherapy alone.^{17,18}

In the present trial, the combination of sitravatinib and tislelizumab was assessed in patients with a variety of advanced solid tumors. The NSCLC cohorts encompassed patients with non-squamous and squamous histology, varying levels of tumor cell (TC) PD-L1 expression, and those naïve to or previously treated with systemic therapy. Discrete cohorts were included for patients who had resistant/refractory disease on or after prior anti-PD-(L)1 therapy, enabling assessment of the ability of sitravatinib plus tislelizumab treatment to overcome such resistance.

METHODS

Study design and patient population

An open-label, multicenter, single-arm, non-randomized phase 1b clinical trial was conducted in Australia and China, where 16 sites enrolled patients with NSCLC.

The study enrolled nine cohorts of patients with various advanced solid tumors, including five cohorts of patients with NSCLC (figure 1; online supplemental table 1). All patients in the NSCLC cohorts were required to be aged ≥ 18 years, with histologically or cytologically confirmed disease, at least one measurable lesion (as defined by Response Evaluation Criteria in Solid Tumors [RECIST] V.1.1), with the selected target lesion(s) not previously treated with local therapy, or with progression following local therapy, with an Eastern Cooperative Oncology Group performance status ≤ 1 , and no documented epidermal growth factor receptor mutation (wild-type

Tislelizumab 200 mg IV Q3W + sitravatinib 120 mg PO QD

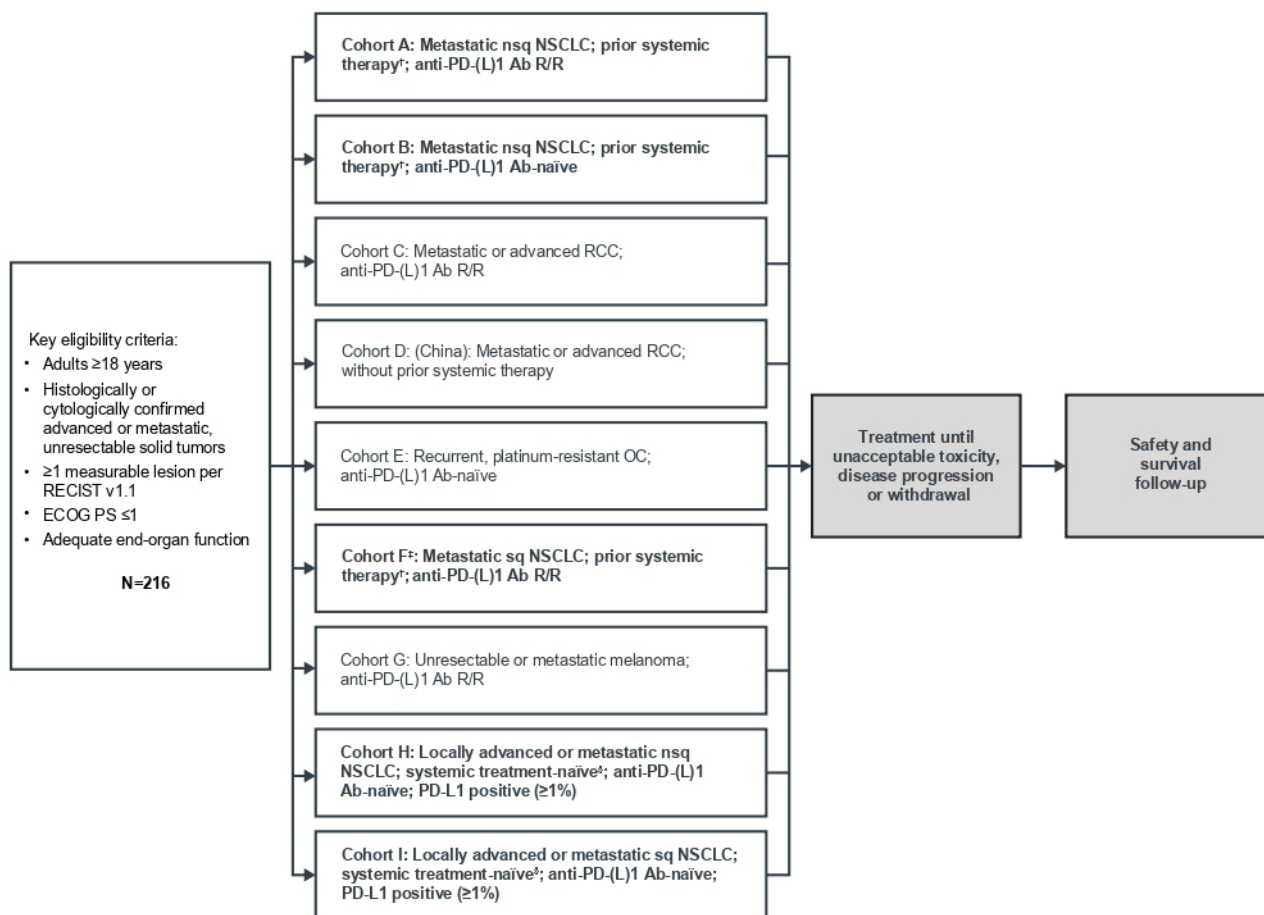


Figure 1 Study design of SAFFRON-103: an open-label, multicenter, non-randomized, Phase 1b trial.* *This manuscript is focused on the five cohorts of patients with locally advanced or metastatic NSCLC, as indicated in bold font (cohorts A, B, F, H, and I, respectively). As summarized in online supplemental table 1, additional inclusion criteria for each of these NSCLC cohorts included: wild-type *EGFR* status, without documented *ALK* rearrangement, *ROS1* rearrangement, or *BRAF* mutations for cohorts A, B and H; no documented *EGFR* mutation, *BRAF* mutation, *ALK* rearrangement, or *ROS1* rearrangement for cohorts F and I. For patients in cohorts A and B with unknown *EGFR* mutation status, as well as patients in cohorts H and I, archival/fresh biopsy tumor tissues (formalin-fixed paraffin-embedded (FFPE) blocks with tumor tissues or unstained FFPE slides) were required during the screening period. If no archival tissue(s) could be provided, a fresh biopsy was mandatory. Documented test results were defined as those identified by local or central tissue-based testing. Full inclusion and exclusion criteria are provided in the online supplemental file, [†]For cohorts A and F: disease progression on or after 1–3 lines of systemic therapy, including anti-PD-(L)1 therapy as the most recent treatment for metastatic NSCLC; for cohort B: disease progression on or after 1–2 lines of systemic therapy, without prior exposure to an anti-PD-(L)1 therapy, [‡]The protocol was amended for cohort F from anti-PD-1/PD-L1 antibody treated or naïve metastatic, squamous NSCLC, to include anti-PD-1/PD-L1 antibody treated metastatic, squamous NSCLC, [§]No prior treatment with systemic therapy in the metastatic setting. Ab, antibody; ALK, anaplastic lymphoma kinase; BRAF, B-Raf proto-oncogene, serine/threonine kinase; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; IV, intravenous; non-sq, non-squamous; NSCLC, non-small cell lung cancer; PD-1; programmed cell death protein 1; PD-L1, programmed death-ligand 1; PO, orally; QD, every day; Q3W, every 3 weeks; R/R, resistant/refractory; RCC, renal cell carcinoma; RECIST, Response Evaluation Criteria in Solid Tumors; ROS1, proto-oncogene tyrosine-protein kinase ROS1; sq, squamous.

status was required for non-squamous cohorts), anaplastic lymphoma kinase/proto-oncogene tyrosine-protein kinase ROS1 rearrangement, or B-Raf proto-oncogene, serine/threonine kinase mutations.

Additional cohort-specific inclusion criteria are summarized in figure 1 and in online supplemental file, which include full inclusion and exclusion criteria.

Interventions

All patients were allocated to receive sitravatinib 120 mg orally one time per day plus tislelizumab 200 mg intravenously every 3 weeks, until study withdrawal, disease progression, unacceptable toxicity, or death. In the event of significant toxicities, the dose of sitravatinib could be reduced to 80 mg or 60 mg one time per day,

with re-escalation not recommended but permitted on a case-by-case basis. Dose reductions were not permitted for tislelizumab. For both drugs, treatment could temporarily be suspended if required for suspected drug-related toxicities (for up to 28 days for sitravatinib and up to 12 weeks for tislelizumab). Treatment beyond investigator-assessed disease progression was permitted in cases of suspected pseudoprogression, with the patient's consent.

Endpoints and assessments

The primary endpoint was the characterization of safety and tolerability, assessed throughout the study by monitoring adverse events (AEs) and serious AEs, relevant physical examination, ECGs, and laboratory assessments as needed. Treatment-emergent adverse events (TEAEs) were defined as those with an onset date (or a worsening in severity from baseline) on, or after, the first dose of study drug and up to 30 days following study drug discontinuation or initiation of new anticancer therapy, whichever occurred first, or up to 90 days after the last dose of tislelizumab for potential immune-mediated AEs (imAEs) (regardless of whether a new anticancer therapy is initiated). AEs were graded based on National Cancer Institute Common Terminology Criteria for Adverse Events V.5.0 and coded using Medical Dictionary for Regulatory Activities (MedDRA) V.24.0. Assessment of the incidence of potential imAEs was based on sponsor identification using a predefined list of MedDRA preferred terms derived from the known potential imAEs of tislelizumab and other anti-PD-1 antibodies.

Evaluation of antitumor activity was a secondary endpoint and included investigator-assessed evaluation per RECIST V.1.1 of ORR, disease control rate (DCR), PFS, and duration of response (DoR). Tumor assessments were performed using CT scans (preferred) or MRI of the chest, abdomen, and pelvis, as well as any other known or suspected sites of disease. Imaging was performed approximately every 6 weeks during the first year of the study, and approximately every 9 weeks thereafter.

Exploratory endpoints included OS and exploration of the potential predictive role of PD-L1 expression with regard to antitumor activity. PD-L1 assessment was conducted by the VENTANA SP263 immunohistochemistry assay by a central laboratory using archival or fresh biopsy tumor tissue. PD-L1 expression was determined by the percentage of TCs with any membrane staining above background. Subgroup analysis of PD-L1 TC expression used cut-offs of 1% (for cohorts A, B, and F) or 50% (for cohorts H and I). A full list of all study endpoints is provided in the online supplemental file.

Statistical analyses

The study planned to enroll 220–240 patients overall, including approximately 20 patients in each of the NSCLC cohorts. The sample size was not driven by statistical considerations.

Safety analyses were performed in the safety analysis set, encompassing all patients who received ≥ 1 dose of

either study drug, with results summarized using descriptive statistics. PFS and OS analyses used the safety analysis set (where applicable, patients without post-baseline tumor assessment for PFS were censored at day 1). Tumor response analyses used the efficacy evaluable analysis set, which included all dosed patients with measurable disease at baseline per RECIST V.1.1 and who had ≥ 1 evaluable post-baseline tumor assessment, unless treatment was discontinued due to disease progression or death before tumor assessment.

ORR and DCR were determined and are reported with Clopper-Pearson two-sided 95% CIs. Median PFS, DoR, and OS were estimated using Kaplan-Meier methodology, with 95% CIs estimated using the Brookmeyer and Crowley method.

RESULTS

Patients and treatment

In total, 220 patients with NSCLC were screened and 122 were enrolled in the study between January 3, 2019, and February 10, 2021 (online supplemental figure 1). Of these 122 patients (the total NSCLC population), 115 were included in the five cohorts, with each cohort including 22–24 patients (the safety analysis set for these five cohorts) (table 1; online supplemental figure 1).

The remaining seven patients had previously treated squamous NSCLC and were included in the total NSCLC study population for safety analyses, but excluded from the five cohorts. These patients were enrolled prior to a protocol amendment that limited cohort F to those with resistant/refractory disease after anti-PD-(L)1 inhibitor therapy, and were either PD-(L)1 inhibitor naïve ($n=6$) or had not received anti-PD-(L)1 therapy as the most recent treatment ($n=1$). In addition, one patient with PD-L1 $<1\%$ was enrolled in cohort H in violation of the protocol-mandated PD-L1-positive status for this cohort; this case was classified as a protocol deviation (data were included in the safety and efficacy analyses but excluded from the PD-L1 subgroup analyses).

As of the data cut-off (November 8, 2021), among the total NSCLC population, 86.1% of the patients had discontinued treatment, 2.5% continued to receive tislelizumab monotherapy, 11.5% continued to receive the combination, and no patients were receiving sitravatinib monotherapy (online supplemental figure 1). The median study follow-up was 10.9 months (range: 0.4–30.6) and varied between cohorts, from a median of 9.1 months in cohort A to 12.1 months in cohort B (online supplemental figure 1).

Patient demographics and baseline characteristics were generally balanced across cohorts, with the exception of characteristics dictated by cohort-specific eligibility criteria (table 1). Among all patients, the median age was 61.0 years (range: 25–79 years), most patients were male (79.5%), Asian (87.7%), and had metastatic disease at study entry (94.3%) (table 1). In the anti-PD-(L)1 therapy resistant/refractory cohorts (A and F), the majority of

Table 1 Patient demographics and baseline characteristics (safety analysis set)

	Previously treated with systemic therapy*			No prior systemic therapy for metastatic disease		Total NSCLC population (N=122)
	Anti-PD-(L)1 R/R		Anti-PD-(L)1 naïve	Anti-PD-(L)1 naïve		
	Non-sq NSCLC (cohort A; n=24)	Sq NSCLC (cohort F; n=23)	Non-sq NSCLC (cohort B; n=22)	PD-L1+, non-sq NSCLC (cohort H; n=22)	PD-L1+, sq NSCLC (cohort I; n=24)	
Median age, years (range)	60.0 (43–78)	62.0 (25–79)	60.0 (46–74)	60.5 (41–78)	65.0 (56–71)	61.0 (25–79)
<65 years, n (%)	16 (66.7)	15 (65.2)	15 (68.2)	15 (68.2)	11 (45.8)	77 (63.1)
≥65 years, n (%)	8 (33.3)	8 (34.8)	7 (31.8)	7 (31.8)	13 (54.2)	45 (36.9)
Sex, n (%)						
Male	16 (66.7)	20 (87.0)	18 (81.8)	15 (68.2)	22 (91.7)	97 (79.5)
Female	8 (33.3)	3 (13.0)	4 (18.2)	7 (31.8)	2 (8.3)	25 (20.5)
Race, n (%)						
Asian	18 (75.0)	18 (78.3)	20 (90.9)	21 (95.5)	24 (100.0)	107 (87.7)
White	6 (25.0)	5 (21.7)	2 (9.1)	1 (4.5)	0 (0)	15 (12.3)
ECOG performance status, n (%)						
0	6 (25.0)	7 (30.4)	4 (18.2)	4 (18.2)	5 (20.8)	26 (21.3)
1	18 (75.0)	16 (69.6)	18 (81.8)	18 (81.8)	19 (79.2)	96 (78.7)
Tobacco use, n (%)						
Never	6 (25.0)	1 (4.3)	4 (18.2)	11 (50.0)	3 (12.5)	26 (21.3)
Current	3 (12.5)	1 (4.3)	5 (22.7)	1 (4.5)	5 (20.8)	15 (12.3)
Former	15 (62.5)	21 (91.3)	13 (59.1)	10 (45.5)	16 (66.7)	81 (66.4)
Metastatic disease, [†] n (%)	24 (100.0)	22 (95.7)	22 (100.0)	19 (86.4)	21 (87.5)	115 (94.3)
Most common location of metastasis, [‡] n (%)						
Lymph nodes	17 (70.8)	19 (82.6)	15 (68.2)	18 (81.8)	18 (75.0)	94 (77.0)
Lung	20 (83.3)	18 (78.3)	18 (81.8)	13 (59.1)	11 (45.8)	85 (69.7)
Bone	9 (37.5)	3 (13.0)	6 (27.3)	7 (31.8)	9 (37.5)	34 (27.9)
Prior anticancer drug therapy, n (%)	24 (100.0)	23 (100.0)	22 (100.0)	1 (4.5) [§]	4 (16.7)	81 (66.4)
Prior anti-PD-(L)1 therapy as last therapy, n (%)	24 (100.0)	23 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	47 (58.0)
Number of prior regimens, n (%) ^l						
1	9 (37.5)	4 (17.4)	19 (86.4)	1 (100.0)	3 (75.0)	39 (48.1)
2	13 (54.2)	17 (73.9)	3 (13.6)	0 (0.0)	1 (25.0)	35 (43.2)
3	2 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (6.2)
4	0 (0.0)	2 (8.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.5)

*For cohorts A and F: disease progression on or after 1–3 lines of systemic therapy, including anti-PD-(L)1 therapy as the most recent treatment for metastatic NSCLC; for cohort B: disease progression on or after 1–2 lines of systemic therapy, without prior exposure to an anti-PD-(L)1 therapy; full eligibility criteria are provided in the online supplemental file, [†]At study entry, [‡]Data presented are for the three most common sites of metastasis in the total NSCLC population, [§]Patient received cytotoxic chemotherapy in the adjuvant setting, ^{||}One patient received adjuvant therapy and three patients received locally advanced therapy, ^lPercentage is based on patients with prior anticancer drug therapy.

ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; R/R, resistant/refractory; sq, squamous.

patients had received ≥2 lines of prior systemic therapy (cohort A: 54.2%; cohort F: 78.3%), including an anti-PD-(L)1 regimen, which included tislelizumab in 41.7% of the patients in cohort A and 26.1% in cohort F.

All 122 enrolled patients received ≥1 dose of sitravatinib plus tislelizumab and were included in the safety analysis set (online supplemental figure 1). The median duration of sitravatinib exposure was 18.1 weeks (range: 0.7–105.3

weeks), with a mean relative dose intensity of 79.8% (SD: 19.7) (online supplemental table 2). The median duration of tislelizumab exposure was 21.4 weeks (range: 3.0–126.1 weeks), with a mean relative dose intensity of tislelizumab of 93.4% (SD: 11.7), and a median of seven cycles received (range: 1–39 cycles) (online supplemental table 2).

Safety and tolerability

Among the total NSCLC population (safety analysis set), TEAEs were reported in all patients, and are summarized in online supplemental table 3. Treatment-related TEAEs (treatment-related adverse events [TRAEs]) of any grade were reported in 98.4% of the patients, and TRAEs of Grade 3 or higher were reported in 51.6% of the patients (online supplemental table 4). The most commonly reported TRAEs were increased aspartate aminotransferase (AST) in 45.9% of the patients, increased alanine aminotransferase (ALT) in 43.4%, diarrhea in 41.0%, and palmar-plantar erythrodysesthesia (PPE) syndrome in 34.4%; few patients experienced \geq Grade 3 TRAEs of these types (increased AST: 0.8% of the patients; increased ALT: 2.5%; diarrhea: 1.6%; PPE syndrome: 4.9%) (table 2). The most common \geq Grade 3 TRAE was hypertension in 14.8% of the patients (table 2). Overall, the incidence and nature of TRAEs appeared generally consistent between individual study cohorts (table 2 and online supplemental table 4).

TRAEs leading to discontinuation of either drug occurred in 23.0% of the patients (online supplemental table 4), with immune-mediated lung disease and diarrhea each reported in three patients (2.5%), hemoptysis, cardiac failure, and PPE syndrome each reported in two patients (1.6%), and all other causes (including increased AST and increased ALT) reported in a single patient only. TRAEs related to sitravatinib led to sitravatinib discontinuation in 17.2% of the patients, with hemoptysis, immune-mediated lung disease, and diarrhea each reported in two patients (1.6%), and all other causes in single patients only. TRAEs related to tislelizumab led to tislelizumab discontinuation in 9.0% of the patients, with the only cause reported in more than one patient being immune-mediated lung disease (in three patients [2.5%]). Dose modification of sitravatinib (including dose reduction and/or interruption) owing to TRAEs occurred in 71.3% of the patients (online supplemental table 4), most commonly due to PPE syndrome in 17.2% of the patients. Increased AST and ALT led to sitravatinib dose modification in 7.4% and 8.2% of the patients, respectively. For tislelizumab, dose modification (including dose delay [drug withheld beyond the visit window] or interruption of the infusion) owing to TRAEs occurred in 41.8% of the patients, most commonly due to ALT increase, diarrhea, and hepatic function abnormal, each occurring in 4.1% of the patients. Increased AST led to tislelizumab dose modification in 3.3% of the patients.

Serious TRAEs were reported in 36.1% of the patients, with diarrhea and hepatic function abnormal the most

common events (4.1%). TRAEs leading to death were reported in five patients (4.1%) and included: two cases of 'death' (no further reason provided) and one of multiple organ dysfunction syndrome related to both study drugs (the primary cause of death was disease progression); one case of ischemic stroke related to sitravatinib only; and one case of cardiac failure with respiratory failure related to tislelizumab only.

Potential imAEs with tislelizumab (as per the predefined list of preferred terms derived from the known potential imAEs of tislelizumab and other anti-PD-1 antibodies, and regardless of whether these events were considered by investigators to be treatment-related) were reported in 54.9% of the patients in the total NSCLC population (table 3). The most common categories of potential imAEs were immune-mediated hypothyroidism (34.4%), immune-mediated pneumonitis (20.5%), and immune-mediated hepatitis (10.7%) (table 3). Of the 25 patients who experienced immune-mediated pneumonitis (by category), eight patients (32.0%) experienced \geq Grade 3 events, including pneumonia in seven patients and immune-mediated lung disease in one patient. Though two patients (8.0%) had Grade 5 pneumonia imAEs, both were considered as infectious pneumonia that was not related to treatment. Among patients with immune-mediated pneumonitis (by category), seven patients (28.0%) discontinued treatment due to such events, including cases of pneumonia (two patients), immune-mediated lung disease (three patients), interstitial lung disease (one patient), and pneumonitis (one patient). The most frequent individual types of potential imAEs were hypothyroidism (30.3%), pneumonia (12.3%), and hyperglycemia (9.0%) (online supplemental table 5).

Antitumor activity: tumor responses

Across the five cohorts, 110 patients were included in the efficacy evaluable analysis set. Confirmed objective responses were observed in all five NSCLC cohorts (table 4). ORR appeared highest in the cohorts with PD-L1-positive NSCLC who had not received prior systemic therapy (including PD-L1 inhibitors), with ORRs of 57.1% (95% CI: 34.0% to 78.2%) in those with non-squamous histology (cohort H) and 30.4% (95% CI: 13.2% to 52.9%) in those with squamous histology (cohort I). Among the cohorts of patients who had previously been treated with systemic therapy, in those who were anti-PD-(L)1 naïve and had non-squamous histology (cohort B), ORR was 23.8% (95% CI: 8.2% to 47.2%), while in patients with anti-PD-(L)1 resistant/refractory disease, ORR was 8.7% (95% CI: 1.1% to 28.0%) in patients with non-squamous histology (cohort A) and 18.2% (95% CI: 5.2% to 40.3%) in those with squamous histology (cohort F).

Across all cohorts, all responses were partial, with no complete responses identified (table 4 and figure 2). Disease control was achieved in the majority of patients (78.3–90.9% of the patients per cohort), and few patients experienced progressive disease as their best overall

Table 2 TRAE incidence reported in ≥10% of the patients (safety analysis set)

Patients, n (%)	Previously treated with systemic therapy*						No prior systemic therapy for metastatic disease					
	Anti-PD-(L)1 R/R			Anti-PD-(L)1 naïve			Anti-PD-(L)1 naïve			Total NSCLC population (N=122)		
	Non-sq NSCLC (cohort A; n=24)		Sq NSCLC (cohort F; n=23)	Non-sq NSCLC (cohort B; n=22)		Non-sq NSCLC (cohort H; n=22)	PD-L1+, sq NSCLC (cohort I; n=24)		PD-L1+, sq NSCLC (cohort I; n=24)		Total NSCLC population (N=122)	
	Grade	Any	≥3	Grade	Any	≥3	Grade	Any	≥3	Grade	Any	≥3
AST increased†	6 (25.0)	0 (0.0)	7 (30.4)	0 (0.0)	15 (68.2)	1 (4.5)	14 (63.6)	0 (0.0)	13 (54.2)	0 (0.0)	56 (45.9)	1 (0.8)
ALT increased‡	6 (25.0)	0 (0.0)	9 (39.1)	0 (0.0)	12 (54.5)	2 (9.1)	12 (54.5)	1 (4.5)	12 (50.0)	0 (0.0)	53 (43.4)	3 (2.5)
Diarrhea	9 (37.5)	1 (4.2)	9 (39.1)	0 (0.0)	8 (36.4)	0 (0.0)	10 (45.5)	0 (0.0)	10 (41.7)	0 (0.0)	50 (41.0)	2 (1.6)
PPE syndrome§	7 (29.2)	1 (4.2)	9 (39.1)	1 (4.3)	10 (45.5)	1 (4.5)	9 (40.9)	2 (9.1)	7 (29.2)	1 (4.2)	42 (34.4)	6 (4.9)
Hypertension	8 (33.3)	4 (16.7)	8 (34.8)	4 (17.4)	5 (22.7)	2 (9.1)	5 (22.7)	3 (13.6)	7 (29.2)	4 (16.7)	36 (29.5)	18 (14.8)
Hypothyroidism	2 (8.3)	0 (0.0)	9 (39.1)	0 (0.0)	6 (27.3)	0 (0.0)	10 (45.5)	0 (0.0)	8 (33.3)	0 (0.0)	35 (28.7)	0 (0.0)
Decreased appetite	6 (25.0)	0 (0.0)	6 (26.1)	0 (0.0)	7 (31.8)	0 (0.0)	3 (13.6)	0 (0.0)	7 (29.2)	0 (0.0)	31 (25.4)	0 (0.0)
Weight decreased	6 (25.0)	1 (4.2)	3 (13.0)	0 (0.0)	7 (31.8)	0 (0.0)	2 (9.1)	1 (4.5)	8 (33.3)	1 (4.2)	29 (23.8)	4 (3.3)
Blood creatine kinase increased	2 (8.3)	0 (0.0)	3 (13.0)	0 (0.0)	4 (18.2)	0 (0.0)	7 (31.8)	0 (0.0)	8 (33.3)	0 (0.0)	25 (20.5)	0 (0.0)
Blood lactate dehydrogenase increased	4 (16.7)	0 (0.0)	3 (13.0)	0 (0.0)	1 (4.5)	0 (0.0)	4 (18.2)	0 (0.0)	8 (33.3)	0 (0.0)	22 (18.0)	0 (0.0)
Proteinuria	5 (20.8)	0 (0.0)	4 (17.4)	1 (4.3)	6 (27.3)	1 (4.5)	7 (31.8)	0 (0.0)	0 (0.0)	0 (0.0)	22 (18.0)	2 (1.6)
Blood thyroid stimulating hormone increased	6 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (18.2)	0 (0.0)	4 (18.2)	0 (0.0)	5 (20.8)	0 (0.0)	21 (17.2)	0 (0.0)
Rash	3 (12.5)	0 (0.0)	5 (21.7)	0 (0.0)	5 (22.7)	0 (0.0)	2 (9.1)	0 (0.0)	5 (20.8)	0 (0.0)	21 (17.2)	0 (0.0)
Platelet count decreased	6 (25.0)	1 (4.2)	1 (4.3)	0 (0.0)	3 (13.6)	1 (4.5)	5 (22.7)	1 (4.5)	4 (16.7)	0 (0.0)	20 (16.4)	3 (2.5)
Nausea	8 (33.3)	0 (0.0)	4 (17.4)	0 (0.0)	1 (4.5)	0 (0.0)	1 (4.5)	0 (0.0)	3 (12.5)	1 (4.2)	19 (15.6)	1 (0.8)
Blood creatine kinase MB increased	3 (12.5)	0 (0.0)	5 (21.7)	0 (0.0)	3 (13.6)	0 (0.0)	3 (13.6)	0 (0.0)	3 (12.5)	0 (0.0)	17 (13.9)	0 (0.0)
Vomiting	5 (20.8)	0 (0.0)	2 (8.7)	0 (0.0)	2 (9.1)	0 (0.0)	2 (9.1)	0 (0.0)	3 (12.5)	0 (0.0)	15 (12.3)	0 (0.0)
Blood pressure increased	1 (4.2)	1 (4.2)	2 (8.7)	0 (0.0)	6 (27.3)	2 (9.1)	1 (4.5)	0 (0.0)	2 (8.3)	0 (0.0)	13 (10.7)	3 (2.5)

Adverse events were graded based on NCI CTCAE V5.0 and coded using MedDRA V24.0.

*For cohorts A and F: disease progression on or after 1–3 lines of systemic therapy, including anti-PD-(L)1 therapy as the most recent treatment for metastatic NSCLC; for cohort B: disease progression on or after 1–2 lines of systemic therapy, without prior exposure to an anti-PD-(L)1 therapy; full eligibility criteria are provided in the online supplemental file.

†Data reported are for the incidence of TRAEs by preferred term reported in ≥10% of the total NSCLC study population

‡Among the total NSCLC population, AST increased and ALT increased TRAEs led to treatment discontinuation in one patient each (both of these TRAEs were in the same patient, and both tislelizumab and sitravatinib were discontinued). AST increased and ALT increased TRAEs led to sitravatinib dose modification in 7.4% and 8.2% of the patients, respectively, and led to tislelizumab dose delay in 3.3% and 4.1% of the patients, respectively.

§Among the total NSCLC population, PPE syndrome TRAEs led to sitravatinib treatment discontinuation in 1 (0.8%) patient and sitravatinib dose modification in 21 (17.2%) patients.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; MB, myocardial band; MedDRA, Medical Dictionary for Regulatory Activities; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; non-sq, non-squamous; NSCLC, non-small cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; PPE, palmar-plantar erythrodysesthesia; R/R, resistant/refractory; sq, squamous; TRAE, treatment-related adverse event.

Table 3 Potential immune-mediated AEs (safety analysis set)

	Previously treated with systemic therapy*			No prior systemic therapy for metastatic disease		Total NSCLC population (N=122)
	Anti-PD-(L)1 R/R		Anti-PD-(L)1 naïve	Anti-PD-(L)1 naïve		
	Non-sq NSCLC (cohort A; n=24)	Sq NSCLC (cohort F; n=23)	Non-sq NSCLC (cohort B; n=22)	PD-L1+, non-sq NSCLC (cohort H; n=22)	PD-L1+, sq NSCLC (cohort I; n=24)	
Patients with ≥1 potential immune-mediated AEs of any Grade, n (%)	11 (45.8)	10 (43.5)	10 (45.5)	14 (63.6)	17 (70.8)	67 (54.9)
Immune-mediated AE by category, † n (%)						
Immune-mediated hypothyroidism	2 (8.3)	9 (39.1)	9 (40.9)	10 (45.5)	11 (45.8)	42 (34.4)
Immune-mediated pneumonitis	5 (20.8)	1 (4.3)	5 (22.7)	5 (22.7)	5 (20.8)	25 (20.5)
Immune-mediated hepatitis	2 (8.3)	2 (8.7)	3 (13.6)	4 (18.2)	2 (8.3)	13 (10.7)
Immune-mediated type 1 diabetes mellitus	1 (4.2)	0 (0.0)	0 (0.0)	3 (13.6)	6 (25.0)	11 (9.0)
Immune-mediated hyperthyroidism	2 (8.3)	0 (0.0)	2 (9.1)	0 (0.0)	2 (8.3)	7 (5.7)
Immune-mediated colitis	1 (4.2)	1 (4.3)	0 (0.0)	2 (9.1)	1 (4.2)	6 (4.9)
Immune-mediated myocarditis	0 (0.0)	0 (0.0)	1 (4.5)	0 (0.0)	0 (0.0)	1 (0.8)
Immune-mediated myositis/rhabdomyolysis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.2)	1 (0.8)
Immune-mediated pancreatitis	0 (0.0)	0 (0.0)	1 (4.5)	0 (0.0)	0 (0.0)	1 (0.8)
Immune-mediated thyroiditis	0 (0.0)	0 (0.0)	1 (4.5)	0 (0.0)	0 (0.0)	1 (0.8)

Data presented are for potential immune-mediated AEs identified by sponsor. Identification of potential AEs was based on a list of MedDRA preferred terms, derived from the from following sources: (i) immune-mediated AEs reported for other approved PD-(L)1 inhibitors; (ii) immune-mediated AEs reported in the published literature for PD-(L)1 inhibitors. Most sources of publications are late-phase clinical trial results.

*For cohorts A and F: disease progression on or after 1–3 lines of systemic therapy, including anti-PD-(L)1 therapy as the most recent treatment for metastatic NSCLC; for cohort B: disease progression on or after 1–2 lines of systemic therapy, without prior exposure to an anti-PD-(L)1 therapy; full eligibility criteria are provided in the online supplemental file,

†Patients with multiple events for a given MedDRA preferred term within a category or with AEs relating to multiple preferred terms within a category were counted once within each category. For the incidence of immune-mediated AEs by preferred term, please see online supplemental table 4.

AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; non-sq, non-squamous; NSCLC, non-small cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; R/R, resistant/refractory; sq, squamous.

response (4.5–14.3% of the patients per cohort). Among responders, median DoR ranged from 6.9 months (95% CI: 3.5 to 7.6) in cohort F to 17.9 months (95% CI: 2.9 to 17.9) in cohort B, and was not reached in cohort A (95% CI: 3.1 to not evaluable [NE]).

ORR by subgroup based on PD-L1 expression level is shown in online supplemental table 6. Higher PD-L1 expression was associated with a trend towards increased ORR in patients with non-squamous NSCLC who had not received prior systemic therapy (cohort H): ORR was 44.4% (95% CI: 13.7% to 78.8%) in the PD-L1 1–49% subgroup and 63.6% (95% CI: 30.8% to 89.1%) in the PD-L1 ≥50% subgroup. No clear association was found between ORR and PD-L1 expression in other cohorts.

Antitumor activity: PFS

Among patients with PD-L1-positive NSCLC who had not received prior systemic therapy, median PFS was 11.1 months (95% CI: 5.5 to NE) in patients with non-squamous histology (cohort H) and 5.4 months (95% CI: 2.8 to 8.6) in those with squamous histology (cohort I)

(figure 3A). Among the cohorts of patients who had previously been treated with systemic therapy, in those who were anti-PD-(L)1 naïve and had non-squamous histology (cohort B), median PFS was 7.0 months (95% CI: 2.7 to 11.2), while in patients with anti-PD-(L)1 resistant/refractory disease, median PFS was 4.2 months (95% CI: 2.7 to 5.8) in patients with non-squamous histology (cohort A) and 5.3 months (95% CI: 4.1 to 7.1) in those with squamous histology (cohort F). The 95% CI for median PFS overlapped for all five cohorts.

Analysis of median PFS by PD-L1 expression subgroups is shown in online supplemental table 6. Higher PD-L1 expression was associated with longer PFS in patients with non-squamous NSCLC who had not received prior systemic therapy (cohort H): PFS was 7.2 months (95% CI: 1.3 to 11.1) in the PD-L1 1–49% subgroup and 11.8 months (95% CI: 5.5 to NE) in the PD-L1 ≥50% subgroup. No clear association was found between median PFS and PD-L1 expression in other cohorts.

Table 4 Analysis of confirmed disease response per RECIST V.1.1 (efficacy evaluable analysis set)

	Previously treated with systemic therapy*			No prior systemic therapy for metastatic disease	
	Anti-PD-(L)1 R/R		Anti-PD-(L)1 naïve	Anti-PD-(L)1 naïve	
	Non-sq NSCLC (cohort A; n=23)	Sq NSCLC (cohort F; n=22)	Non-sq NSCLC (cohort B; n=21)	PD-L1+, non-sq NSCLC (cohort H; n=21)	PD-L1+, sq NSCLC (cohort I; n=23)
ORR, % (95% CI)	8.7 (1.1 to 28.0)	18.2 (5.2 to 40.3)	23.8 (8.2 to 47.2)	57.1 (34.0 to 78.2)	30.4 (13.2 to 52.9)
Best overall response, n (%)					
CR	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
PR	2 (8.7)	4 (18.2)	5 (23.8)	12 (57.1)	7 (30.4)
SD	16 (69.6)	16 (72.7)	13 (61.9)	6 (28.6)	11 (47.8)
PD	2 (8.7)	1 (4.5)	3 (14.3)	2 (9.5)	3 (13.0)
NE	3 (13.0)	1 (4.5)	0 (0.0)	1 (4.8)	2 (8.7)
DCR, % (95% CI)	78.3 (56.3 to 92.5)	90.9 (70.8 to 98.9)	85.7 (63.7 to 97.0)	85.7 (63.7 to 97.0)	78.3 (56.3 to 92.5)
Median DoR, months (95% CI)	NR (3.1 to NE)	6.9 (3.5 to 7.6)	17.9 (2.9 to 17.9)	9.7 (5.6 to NE)	8.1 (7.0 to NE)

*For cohorts A and F: disease progression on or after 1–3 lines of systemic therapy, including anti-PD-(L)1 therapy as the most recent treatment for metastatic NSCLC; for cohort B: disease progression on or after 1–2 lines of systemic therapy, without prior exposure to an anti-PD-(L)1 therapy; full eligibility criteria are provided in the online supplemental file. ORR was defined as the proportion of patients with CR or PR. DCR was defined as the proportion with CR, PR, or SD. CIs for ORR and DCR are Clopper-Pearson two-sided 95% CIs. DoR was defined as the time interval between the date of the earliest qualifying response and the date of PD or death, whichever occurred first. Median DoR was estimated using the Kaplan-Meier method, with 95% CI estimated using the Brookmeyer and Crowley method. CR, complete response; DCR, disease control rate; DoR, duration of response; NE, not evaluable; non-sq, non-squamous; NR, not reached; NSCLC, non-small cell lung cancer; ORR, objective response rate; PD, progressive disease; PD-L1, programmed cell death protein 1; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; R/R, resistant/refractory; SD, stable disease; sq, squamous.

Antitumor activity: OS

Among patients with PD-L1-positive NSCLC who had not received prior systemic therapy, median OS was 17.4 months (95% CI: 11.8 to NE) in patients with non-squamous NSCLC (cohort H) and not reached (95% CI: 6.7 to NE) in those with squamous NSCLC (cohort I) (figure 3B). Among the cohorts of patients who had previously been treated with systemic therapy, in those who were anti-PD-(L)1 naïve and had non-squamous histology (cohort B), median OS was 15.3 months (95% CI: 11.4 to NE), while in patients with anti-PD-(L)1 resistant/refractory disease, median OS was 10.1 months (95% CI: 5.9 to 17.8) in patients with non-squamous histology (cohort A) and 10.5 months (95% CI: 4.9 to NE) in those with squamous histology (cohort F).

DISCUSSION

This open-label, multicenter, phase 1b study was designed to evaluate the safety, tolerability, and preliminary antitumor activity of sitravatinib and tislelizumab in solid tumors. We report findings from the five locally advanced/metastatic NSCLC cohorts: patients previously treated with systemic therapy for metastatic disease with anti-PD-(L)1 resistant/refractory non-squamous NSCLC (cohort A), anti-PD-(L)1-naïve non-squamous NSCLC (cohort B), or anti-PD-(L)1 resistant/refractory, squamous NSCLC

(cohort F); and patients without prior systemic therapy for metastatic disease, with PD-L1-positive non-squamous NSCLC (cohort H), or PD-L1-positive squamous NSCLC (cohort I). No new or unexpected safety signals were identified with the combination of sitravatinib and tislelizumab across the five NSCLC cohorts. Furthermore, objective responses were observed in all cohorts.

Although approximately half of the patients (51.6%) in the SAFFRON-103 NSCLC cohorts experienced a \geq Grade 3 TRAE, less than one-quarter of patients (23.0%) discontinued treatment due to a TRAE, indicating that the combination was tolerable for most patients. Most Grade 1/2 TRAEs and more than half of the \geq Grade 3 TRAEs were manageable with treatment interruption, dose modification, or active supportive treatment. The most common TRAEs included elevated liver enzymes and diarrhea, and the most common \geq Grade 3 TRAEs were hypertension and PPE syndrome. PPE syndrome has previously been reported with multitargeted TKIs;¹⁹ few cases in the present study were \geq Grade 3 events, and only one led to sitravatinib discontinuation. Similarly, although almost half of the patients experienced increased AST and ALT TRAEs, most were Grade 1/2 and \geq Grade 3 events were rare. Only one patient discontinued from treatment due to increased ALT or AST. Hepatic toxicities and diarrhea are commonly associated with both agents due to different

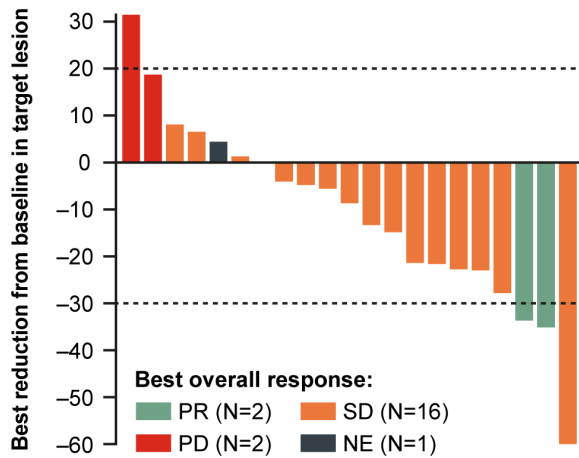
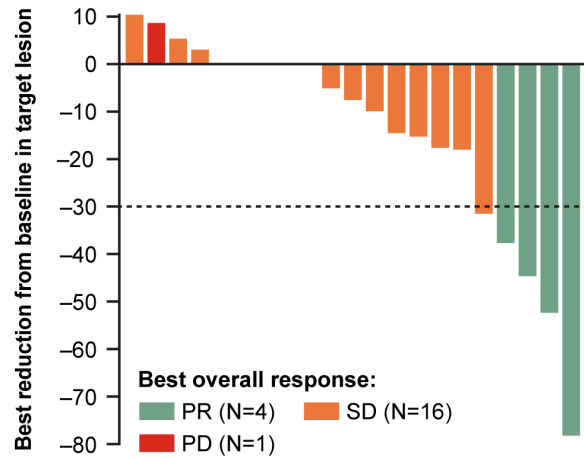
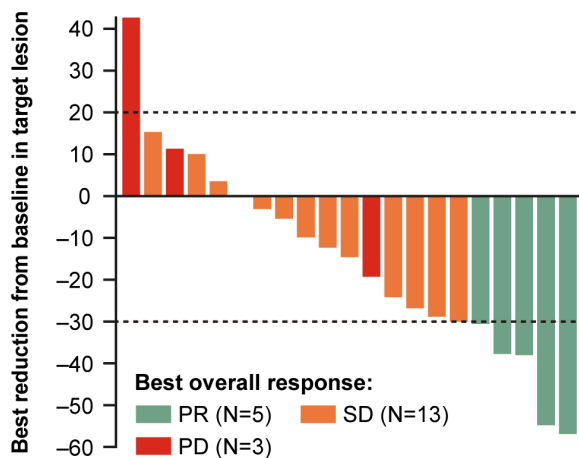
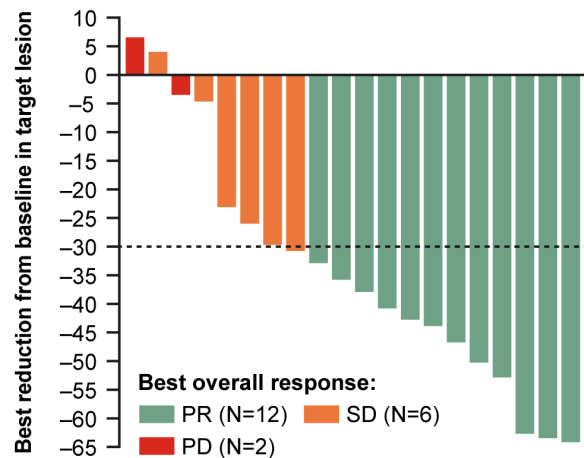
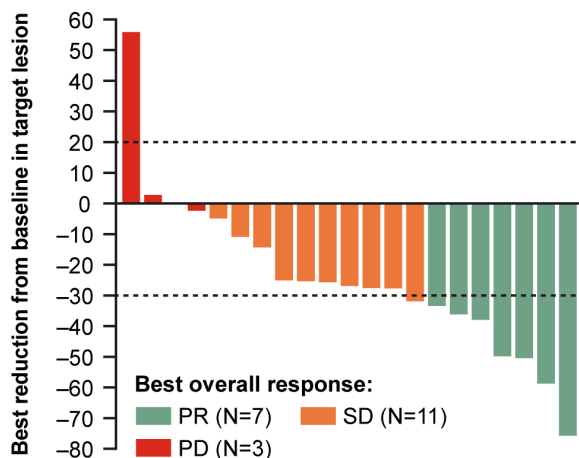
A. Cohort A: Anti-PD-(L)1 R/R, non-sq NSCLC[†]B. Cohort F: Anti-PD-(L)1 R/R, sq NSCLC[†]C. Cohort B: Anti-PD-(L)1 naïve, non-sq NSCLC[†]D. Cohort H: PD-L1+, non-sq NSCLC[‡]E. Cohort I: PD-L1+, sq NSCLC[‡]

Figure 2 Best percentage change in target lesion from baseline by confirmed best overall response (efficacy evaluable analysis set*). *Patients without baseline or post-baseline target lesion measurements are not presented on the plots (cohort A: n=2; cohort F: n=1; cohort H: n=1; cohort I: n=2), [†]Previously treated with systemic therapy (for cohorts A and F: disease progression on or after 1–3 lines of systemic therapy, including anti-PD-(L)1 therapy as the most recent treatment for metastatic NSCLC; for cohort B: disease progression on or after 1–2 lines of systemic therapy, without prior exposure to an anti-PD-(L)1 therapy; full eligibility criteria are provided in the online supplemental file), [‡]No prior systemic therapy for metastatic disease. NE, not estimable; non-sq, non-squamous; NSCLC, non-small cell lung cancer; PD, progressive disease; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PR, partial response; R/R, resistant/refractory; SD, stable disease; sq, squamous.

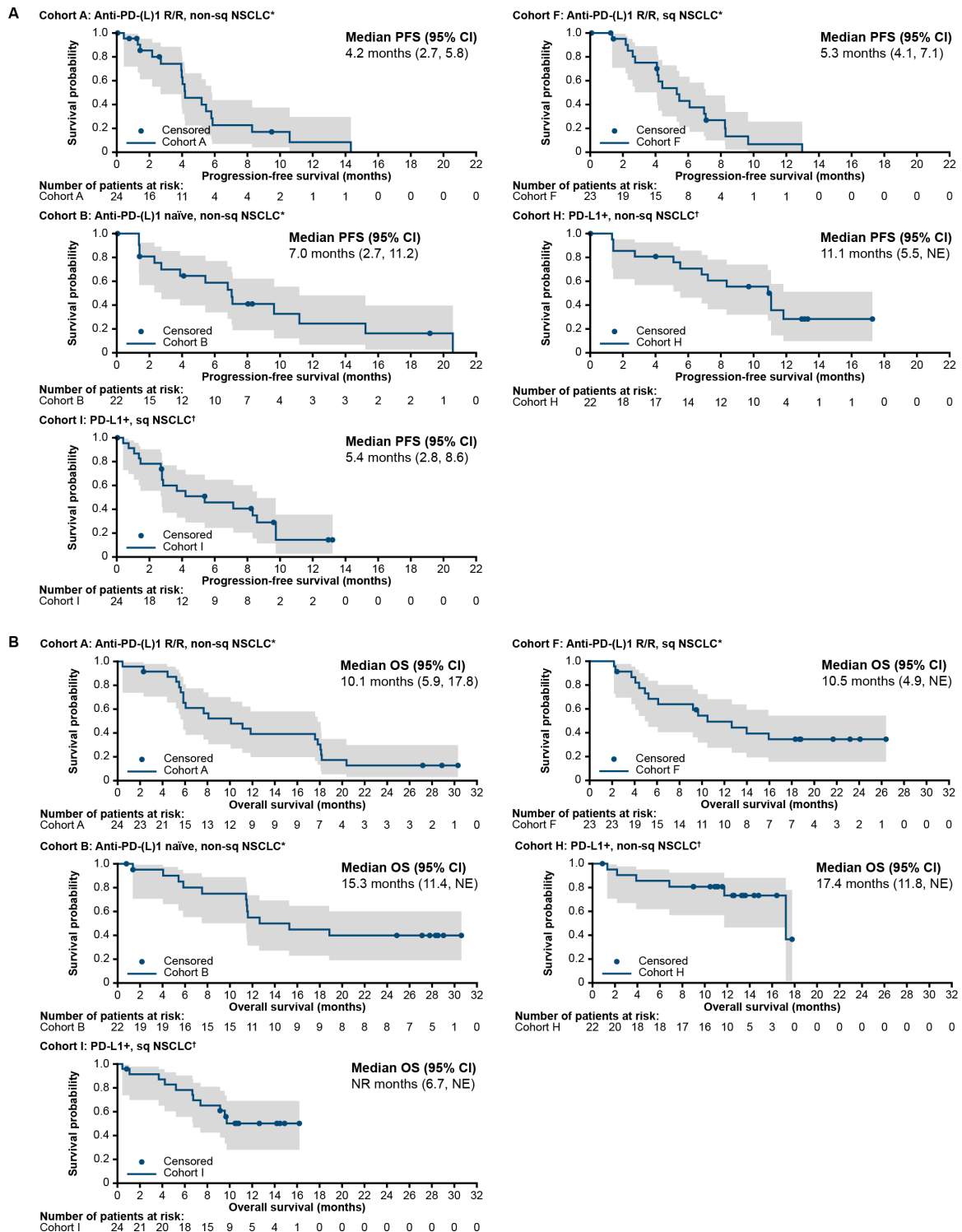


Figure 3 Progression-free survival (A) and overall survival (B) (safety analysis set). *Previously treated with systemic therapy. (for cohorts A and F: disease progression on or after 1–3 lines of systemic therapy, including anti-PD-(L)1 therapy as the most recent treatment for metastatic NSCLC; for cohort B: disease progression on or after 1–2 lines of systemic therapy, without prior exposure to an anti-PD-(L)1 therapy; full eligibility criteria are provided in the online supplemental file), †No prior systemic therapy for metastatic disease. PFS was defined as the time from the date of first dose of study drugs to the date of the first documentation of progressive disease or death, whichever occurred first. Figures present Kaplan-Meier plots of PFS, with the shaded area representing the 95% CI. Median PFS was estimated using the Kaplan-Meier method, with 95% CI estimated using the Brookmeyer and Crowley method. Figures present Kaplan-Meier plots of OS, with the shaded area representing the 95% CI. Median OS was estimated using the Kaplan-Meier method, with 95% CI estimated using the Brookmeyer and Crowley method. NE, not evaluable; non-sq, non-squamous; NSCLC, non-small cell lung cancer; NR, not reached; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; R/R, resistant/refractory; sq, squamous.

toxicity mechanisms, and therefore the incidences of these AEs with combined therapy in the present study may reflect the compound effect of these discrete mechanisms.^{19–21} With regard to the incidence of hypertension, sitravatinib targets VEGFR2, and hypertension is a common and dose-dependent AE of VEGF inhibitors.²² However, prior evidence suggests that AEs associated with multitargeted TKIs can be controlled by prophylactic measures, such as use of antihypertensive and frequent emollients.²³ Reassuringly, sitravatinib-related hypertension did not lead to sitravatinib treatment discontinuation in any patients in the present study.

The safety profile of sitravatinib plus tislelizumab observed here in patients with NSCLC was consistent with that observed in other cancer types.^{24–26} The safety profile of the combination treatment was also in line with that known for anti-PD-(L)1 and multitargeted TKI monotherapies.^{19–21 27} For example, in a phase 1/1b study of sitravatinib monotherapy in patients with heavily pretreated advanced solid tumors, sitravatinib demonstrated a manageable safety profile, with hypertension the most commonly reported \geq Grade 3 TRAE (in 20.7% of the patients), consistent with the present study.²⁷ The safety profile of sitravatinib plus tislelizumab in our study is also consistent with that reported in the phase 2 MRTX-500 trial of sitravatinib plus nivolumab in patients with non-squamous NSCLC who progressed on or after checkpoint inhibitor therapy, in which 66% of the patients experienced Grade 3–4 TRAEs, with hypertension again being the most common (in 22% of the patients).²⁸

Potential imAEs were identified from all reported TEAEs using a group of predefined MedDRA preferred terms, derived from the known imAEs of tislelizumab and other anti-PD-1 agents. This approach provided a comprehensive assessment of potential imAE incidence, but also had limitations as it did not consider the nature of the imAE or the relationship between the drug and event as assessed by investigators. Significant deviation might be expected for immune-mediated pneumonitis—the most common imAE category reported in this study—and more specifically pneumonia, because etiologically infective lung inflammation is commonly observed in patients with advanced NSCLC, regardless of the given treatment. Additionally, the incidence of potential imAEs was confounded by the use of combination treatment, as some toxicities might be attributed to both sitravatinib and tislelizumab, such as diarrhea and elevated liver enzymes.

Objective responses were observed across all five NSCLC cohorts, with an ORR range of 8.7%–57.1%. The trends in median PFS and median OS across the cohorts were largely consistent with those observed for ORR. The greatest ORR was observed among patients with PD-L1-positive treatment-naïve NSCLC, the highest being in those with non-squamous histology (cohort H, 57.1%), followed by those with squamous NSCLC (cohort I, 30.4%). These treatment-naïve patients with either type of histology were also the only cohorts included

in this analysis that required PD-L1-positive disease for enrollment, and this outcome is in line with previous data showing higher efficacy of PD-(L)1 blockade among patients with increasing levels of PD-L1 positivity.^{1–3} Indeed, anti-PD-(L)1 monotherapy is now a standard first-line treatment option for patients with advanced NSCLC with high PD-L1 expression.²⁹ In particular, the effect of the sitravatinib and tislelizumab combination in the PD-L1-positive treatment-naïve non-squamous NSCLC cohort was encouraging in the context of data for anti-PD-1 monotherapy in similar settings. In KEYNOTE-042, a phase 3 study evaluating pembrolizumab monotherapy as first-line treatment in patients with locally advanced or metastatic squamous and non-squamous NSCLC, the ORR with pembrolizumab monotherapy was 27.3% in patients with PD-L1 tumor proportion score \geq 1%.³⁰ There is no reported ORR specifically for patients with non-squamous histology and squamous histology in this study. The higher ORR in the present study in cohort H, though of small sample size, indicates that sitravatinib in combination with tislelizumab might bring additional benefit to this group of patients. Although addition of sitravatinib to tislelizumab may have superior clinical efficacy when compared with that of anti-PD-L1 monotherapy, the combination requires further evaluation in this population in a larger, randomized trial.

There remains an unmet therapeutic need for patients with advanced NSCLC with anti-PD-(L)1 resistant/refractory disease, especially for those who have also already received platinum-based chemotherapy.^{7 29 31} The available treatments include docetaxel, pemetrexed, or erlotinib,²⁹ which have historically been shown to have limited survival benefit after first-line platinum-based chemotherapy and are associated with toxicities.^{31–35} In the cohorts of patients in the present study who had received prior systemic therapy and had resistant/refractory disease following an anti-PD-(L)1 antibody as their most recent therapy, the response rate with sitravatinib plus tislelizumab was moderate in those patients with non-squamous histology (cohort A, ORR of 8.7%), and promising for those patients with squamous histology (cohort F, ORR of 18.2%). In context, there is very limited clinical data available on the effects of re-treatment with an anti-PD-(L)1 monoclonal antibody after failure of immune checkpoint inhibitor therapy, with most of the relevant studies being retrospective with a limited sample size; the majority of these analyses reported an ORR of 0% to 8.3% (except one study which reported an ORR of 27%), with median OS ranging from 5.8 to 7.5 months.^{36–41}

Previously, there has been a lack of evidence for combination therapy with multitargeted TKIs and anti-PD-(L)1 agents in patients with squamous anti-PD-(L)1 resistant/refractory NSCLC. Among such patients in cohort F in the present study, ORR and DCR were 18.2% and 90.9%, respectively, with a median PFS of 5.3 months. Although the sample size was small, to our knowledge, these data represent the first report of the antitumor activity of an anti-PD-1 inhibitor plus a multitargeted TKI in patients

with anti-PD-(L)1 resistant/refractory squamous NSCLC. These preliminary findings from cohort F indicate that treatment with sitravatinib and tislelizumab may overcome anti-PD-(L)1 treatment resistance for squamous NSCLC, potentially through the immunomodulatory effects of sitravatinib, which has been observed in animal models and in patients. In murine tumors, treatment with sitravatinib led to significantly decreased tumor-associated immunosuppressive myeloid cells such as MDSC cells and M2 macrophages, and increased the number of effective CD4⁺ T cells and exhausted CD8⁺ T cells characterized by PD-1 and cytotoxic T-lymphocytes-associated protein 4 expression.¹⁰ In addition, sitravatinib demonstrated potent antitumor activity alone and enhanced the efficacy of PD-1 blockade when combined with PD-1 blockade in anti-PD-(L)1 refractory murine tumor models.¹⁰ Immunomodulatory effects of sitravatinib, leading to a less immunosuppressive tumor microenvironment, have previously been reported in clinical studies in patients with oral cavity cancer, when used in combination with an anti-PD-1 antibody (nivolumab).⁴²

With regard to the cohort of patients with non-squamous anti-PD-(L)1 resistant/refractory disease (cohort A), although a response was observed in only 2 of 23 patients (ie, 8.7%), the DCR was 78.3%, and median PFS and median OS were 4.2 months and 10.1 months, respectively. Several other studies have explored responses to anti-PD-(L)1 and multitargeted TKI combination therapy in patients with non-squamous NSCLC. In the phase 2 MRTX-500 trial, the combination of sitravatinib plus the anti-PD-1 therapy nivolumab resulted in an ORR of 18% in patients with non-squamous NSCLC with disease progression on or after anti-PD-(L)1 therapy (with or without platinum-doublet chemotherapy).²⁸ However, this analysis of the MRTX-500 trial only included a subgroup of patients who had experienced clinical benefit with the prior anti-PD-(L)1 therapy, and then progressed²⁸ (ie, resistant disease per the definition used in the present trial), and thus excluded patients who had no initial response to anti-PD-(L)1 therapy (ie, refractory disease). In contrast, cohort A of the present study included patients with non-squamous disease that was resistant or refractory to prior anti-PD-(L)1 therapy. Consequently, given the differences in patient population, it is not possible to compare response rates in the present study with those in the MRTX-500 trial. In another study in non-squamous metastatic NSCLC (COSMIC-021), treatment with the combination of the multitargeted TKI cabozantinib and the anti-PD-L1 agent atezolizumab resulted in an ORR of 19% among the cohort of 81 patients who had disease progression following a prior immune checkpoint inhibitor and ≤ 2 prior lines of systemic therapy.⁴³ While the ORR in this cohort of COSMIC-021 compared favorably with that in cohort A of the present study (8.7%), the proportion of patients with progressive disease was higher (16.0% vs 8.7%), while DCR (80% vs 78%), median PFS (4.5 vs 4.2 months), and median OS (13.8 vs 10.1 months) were

similar. Although the ORR with sitravatinib plus tislelizumab in the present study was moderate in this difficult-to-treat patient population with advanced non-squamous NSCLC resistant or refractory to anti-PD-(L)1 therapy, we believe further evaluation in a larger sample size study is warranted given the DCR, PFS, and OS results.

Regarding the potential predictive role of various thresholds of PD-L1 expression, TC PD-L1 expression $\geq 50\%$ was associated with a trend towards increased ORR and median PFS in patients with anti-PD-L1-naïve, PD-L1-positive, non-squamous NSCLC who had not previously received systemic therapy (cohort H). However, no clear association was found between the assessed PD-L1 expression thresholds and outcomes in the other cohorts. While prior studies have reported that patients with NSCLC with high PD-L1 expression benefit the most from anti-PD-(L)1 monotherapy,^{1–3} our results suggest the potential for sitravatinib and tislelizumab combination therapy to provide higher ORRs across various thresholds of PD-L1 expression. However, these results should be interpreted cautiously as the sample sizes were small within each PD-L1 expression subgroup, and further study is required.

The results of the present study add to the clinical evidence supporting the rationale for combining anti-PD-(L)1 and multitargeted TKI therapies and corroborate the need for continued investigation of such combinations in phase 3 trials. An ongoing phase 3 trial is assessing sitravatinib plus tislelizumab compared with docetaxel monotherapy in patients with locally advanced or metastatic NSCLC with disease progression after platinum-based chemotherapy and anti-PD-(L)1 antibody treatment (ClinicalTrials.gov NCT04921358).⁴⁴ Further ongoing phase 3 studies in patients with advanced/metastatic NSCLC with disease progression on/after platinum-based chemotherapy and anti-PD-(L)1 antibody treatment are evaluating other combinations of multikinase inhibitors combined with anti-PD-(L)1 therapies, including cabozantinib plus atezolizumab (in the CONTACT-01 trial; ClinicalTrials.gov NCT04471428),⁴⁵ lenvatinib plus pembrolizumab (in the LEAP-008 trial; NCT03976375),⁴⁵ and famitinib plus camrelizumab (ClinicalTrials.gov NCT05106335).⁴⁶

The strength of this phase 1b study can be attributed to the inclusion of a broad spectrum of NSCLC cohorts. However, there were several limitations, including the inherent nature of its open-label, single-arm study design, the low number of patients per arm, and a lack of geographical/racial diversity in the enrolled patient population.

CONCLUSION

In this phase 1b study in patients with non-squamous or squamous locally advanced or metastatic NSCLC who were either previously treated or treatment-naïve, sitravatinib plus tislelizumab was tolerable for most patients, and the overall safety profile was consistent with the known profiles of these agents, with no new safety signals

observed. Objective responses were observed across NSCLC cohorts, including in patients who were naïve to systemic treatment and naïve to anti-PD-(L)1 treatment, and in those with anti-PD-(L)1 resistant/refractory disease. These results support further investigation of sitravatinib plus tislelizumab in selected patient with NSCLC populations.

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Ethics approval The protocol and amendments were approved by the Institutional Review Board/Independent Ethics Committee for each study site. The study was conducted in conformance with the International Conference on Harmonization E6

guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, and all applicable local laws and regulations. All patients were required to provide written informed consent prior to participation in the study.

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Data availability statement On request, and subject to certain criteria, conditions, and exceptions, BeiGene, will provide access to individual de-identified participant data from BeiGene-sponsored global interventional clinical studies conducted for medicines (1) for indications that have been approved or (2) in programs that have been terminated. BeiGene will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data requests may be submitted to DataDisclosure@beigene.com.

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