Safety and efficacy of sitravatinib plus tislelizumab in patients with PD-L1-positive, locally advanced or metastatic, squamous non-small cell lung cancer; SAFFRON-103

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Conclusions

Sitravatinib plus tislelizumab had a manageable safety and tolerability profile in patients with PD-L1 ≥1%, locally advanced or metastatic squamous NSCLC.

The combination demonstrated promising antitumor activity (ORR, 30.4%; median PFS, 5.4 months; median OS, not reached).

A phase 3 study investigating this combination therapy in advanced NSCLC is currently recruiting (NCT04921358).

BACKGROUND

Patients with programmed death-ligand 1-expressing (PD-L1 ≥1%), locally advanced or metastatic, squamous non-small cell lung cancer (NSCLC) have a poor prognosis and despite the availability of anti-programmed cell death protein 1 (PD-1)-based treatments, there remains a need for further treatment options.[1]

Sitravatinib, a selective tyrosine kinase inhibitor, may help to reduce the number of myeloid-derived suppressor cells and regulatory T cells, promotes the expansion of antitumor cytotoxic T cells, and increases the ratio of M1/M2-polarized macrophages.[2-4]

Tislelizumab, an anti-PD-1 antibody engineered to minimize binding to FcγR on macrophages, has shown clinical activity in patients with advanced solid tumors, including squamous NSCLC.[5,6]

This phase 1b study assessed safety, tolerability, and antitumor activity of sitravatinib and tislelizumab in advanced solid tumors (NCT03666143). We report results from patients with PD-L1 ≥1%, squamous NSCLC.

METHODS

- This was an open-label, nonrandomized, phase 1b study
- The primary endpoint was safety and tolerability (**Figure 1**)
- Between May 12, 2020 and February 10, 2021, 24 patients were enrolled. All patients were included in the safety analysis set, and 23 patients in the efficacy-evaluable analysis set

Figure 1. Study design

Key eligibility criteria:
- Adults ≥18 years
- Locally advanced or metastatic squamous NSCLC
- Wild-type *EGFR* status without *ALK/ROS1* rearrangements or *BRAF* mutations
- ≥1 measurable lesion per RECIST v1.1
- ECOG PS ≤1
- No prior systemic treatment in the metastatic setting
- No exposure to immunotherapy
- PD-L1 expression ≥1%[a]

↓

Sitravatinib 120 mg PO QD (free-base formulation) + tislelizumab 200 mg IV Q3W

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Treatment until unacceptable toxicity, disease progression, withdrawal, or death

Safety and survival follow-up

Primary endpoint:
- Safety and tolerability

Secondary endpoints:
- ORR, DoR, DCR, PFS (all per RECIST v1.1); plasma concentrations and the derived PK parameters of sitravatinib

Exploratory endpoints:
- OS; serum concentrations of tislelizumab and anti-tislelizumab antibodies; changes of potential pharmacodynamic biomarkers in response to sitravatinib plus tislelizumab

[a]PD-L1 staining on ≥1% of tumor cells (VENTANA SP263 immunohistochemistry assay).

Abbreviations: *ALK*, anaplastic lymphoma kinase; *BRAF*, B-Raf; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; *EGFR*, epidermal growth factor receptor; IV, intravenous; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PK, pharmacokinetic; PO, oral; Q3W, every 3 weeks; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; *ROS1*, proto-oncogene tyrosine-protein kinase ROS.

RESULTS

Safety

- The median age was 65.0 years (range: 56-71), and 91.7% of patients were male (**Table 1**)
- Median study follow-up was 9.4 months (range: 0.4-16.2)
- As of the data cutoff (November 8, 2021), treatment-emergent adverse events (TEAEs) of any grade and grade ≥3 were reported in 100% and 66.7% of patients, respectively; serious TEAEs were observed in 50.0% (**Table 2**)
- Treatment-related adverse events (TRAEs) of any grade and grade ≥3 were reported in 95.8% and 58.3% of patients, respectively; serious TRAEs were observed in 37.5% (**Table 2**)
- The most commonly reported ≥grade 3 TEAE and TRAE was hypertension (16.7%)
- Ten patients experienced TEAEs leading to sitravatinib discontinuation (including death, hemoptysis, immune-mediated lung disease, pneumonia, and cardiac failure); five patients experienced TEAEs leading to tislelizumab discontinuation (including death, pneumonia, immune-related lung disease, and malaise)
- The most common TEAEs occurring in ≥30% of patients are listed in **Table 3**

Efficacy

- In the efficacy-evaluable population, confirmed objective response rate (ORR) was 30.4% (95% CI: 13.2, 52.9) with all seven patients achieving partial response (**Figure 2**)
- Disease control rate was 78.3% (95% CI: 56.3, 92.5)

Table 1. Patient baseline characteristics (safety analysis set)

	N=24
Median age, years (range)	65.0 (56-71)
Male sex, n (%)	22 (91.7)
Race, n (%)	
Asian	24 (100.0)
ECOG performance status, n (%)	
0/1	5 (20.8)/19 (79.2)
Tobacco use, n (%)	
Never/Current/Former	3 (12.5)/5 (20.8)/16 (66.7)
Disease stage, n (%)	
Metastatic	21 (87.5)
Prior anticancer drug therapy, n (%)[a]	4 (16.7)

[a]One patient received adjuvant therapy and three patients received locally advanced therapy.
Abbreviation: ECOG, Eastern Cooperative Oncology Group.

Table 2. Summary of AEs (safety analysis set)

	N=24	
Patients, n (%)	**TEAEs**	**TRAEs**
Any AE	24 (100.0)	23 (95.8)
≥Grade 3	16 (66.7)	14 (58.3)
Serious AE	12 (50.0)	9 (37.5)
≥Grade 3	7 (29.2)	4 (16.7)
AE leading to death	2 (8.3)[a]	0 (0)
AE leading to sitravatinib discontinuation	10 (41.7)	8 (33.3)
AE leading to tislelizumab discontinuation	5 (20.8)	3 (12.5)
AE leading to sitravatinib dose modification[b]	16 (66.7)	15 (62.5)
AE leading to tislelizumab dose modification[c]	11 (45.8)	11 (45.8)

[a]Death (n=1) and pneumonia (n=1); [b]AE leading to sitravatinib dose modification included dose reduction and/or interruption; [c]AE leading to tislelizumab dose modification included dose delay and/or interruption.
Abbreviations: AE, adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

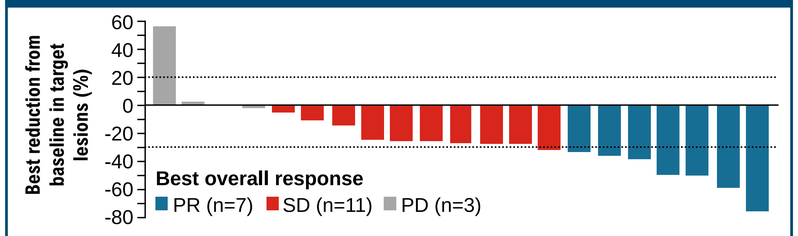
Table 3. TEAEs with ≥30% frequency (safety analysis set)

Patients, n (%)	N=24
Patients with ≥1 TEAE	24 (100.0)
Aspartate aminotransferase increased	14 (58.3)
Alanine aminotransferase increased	12 (50.0)
Hypoalbuminemia	11 (45.8)
Diarrhea	10 (41.7)
Weight decreased	10 (41.7)
Anemia	9 (37.5)
Blood creatine phosphokinase increased	8 (33.3)
Blood lactate dehydrogenase increased	8 (33.3)
Constipation	8 (33.3)
Hyponatremia	8 (33.3)
Hypothyroidism	8 (33.3)

Abbreviation: TEAE, treatment-emergent adverse event.

- There were no obvious trends between tumor cell PD-L1 expression and ORR, progression-free survival (PFS) or overall survival (OS) (**Table 4**)
- Median PFS was 5.4 months (95% CI: 2.8, 8.6), and median OS was not reached (95% CI: 6.7, not estimable) (**Figure 3**)

Figure 2. Best percentage change in target lesion from baseline by confirmed BOR per investigator (efficacy-evaluable analysis set[a])



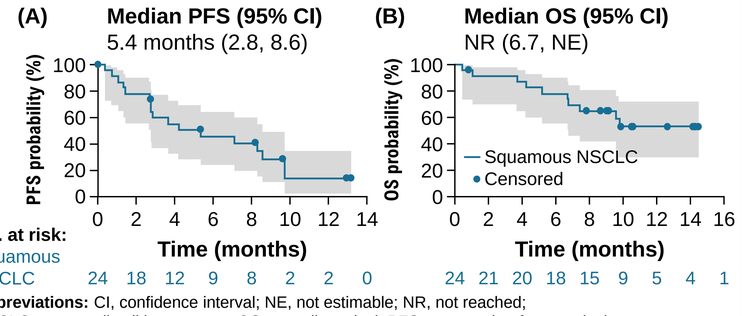
[a]Two patients did not have baseline or post-baseline target lesion measurements.
Abbreviations: BOR, best overall response; PD, progressive disease; PR; partial response; SD, stable disease.

Table 4. Efficacy analysis by PD-L1 subgroup

	Efficacy-evaluable analysis set (N=23)		Safety analysis set (N=24)		
	n	**ORR (95% CI)**	**n**	**mPFS (95% CI)**	**mOS (95% CI)**
PD-L1 TC 1-49%	12	33.3 (9.9, 65.1)	13	5.4 (1.5, 9.7)	9.72 (7.4, NE)
PD-L1 TC ≥50%	11	27.3 (6.0, 61.0)	11	4.2 (0.7, NE)	NR (1.1, NE)

Abbreviations: CI, confidence interval; mOS, median overall survival; mPFS, median progression-free survival; NE, not estimable; NR, not reached; ORR, objective response rate; PD-L1, programmed death-ligand 1; TC, tumor cell.

Figure 3. (A) Progression-free survival and (B) Overall survival (safety analysis set)



Abbreviations: CI, confidence interval; NE, not estimable; NR, not reached; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival.

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Disclosures

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