Safety and efficacy of sitravatinib plus tislelizumab in patients with PD-L1-positive, locally advanced or metastatic, nonsquamous 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 nonsquamous NSCLC.

The combination demonstrated promising antitumor activity (ORR, 57.1%; median PFS, 11.1 months; median OS, 17.4 months).

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, nonsquamous 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 nonsquamous 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%, nonsquamous NSCLC.

METHODS

- This was an open-label, nonrandomized, phase 1b study
- The primary endpoint was safety and tolerability (**Figure 1**)
- Between November 7, 2019, and December 23, 2020, 22 patients were enrolled. All patients were included in the safety analysis set, and 21 patients in the efficacy-evaluable analysis set

Figure 1. Study design

Key eligibility criteria:
- Adults ≥18 years
- Locally advanced or metastatic nonsquamous 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]

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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, tested at a central laboratory).

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 60.5 years (range: 41-78), and 68.2% of patients were male (**Table 1**)
- Median study follow-up was 11.8 months (range: 0.9-17.9)
- As of the data cutoff (November 8, 2021), all patients experienced at least one treatment-emergent adverse event (TEAE), with a ≥grade 3 TEAE occurring in 59.1% of patients (**Table 2**)
- Treatment-related adverse events (TRAEs) of any grade and ≥grade 3 were reported in 95.5% and 50.0% of patients, respectively; serious TRAEs were observed in 36.4% (**Table 2**)
- The most commonly reported ≥grade 3 TEAE and ≥grade 3 TRAE were hypokalemia (18.2%) and hypertension (13.6%), respectively
- 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 57.1% (95% CI: 34.0, 78.2) with all 12 patients achieving partial response (**Figure 2**)
- Disease control rate was 85.7% (95% CI: 63.7, 97.0)

Table 1. Patient baseline characteristics (safety analysis set)

	N=22
Median age, years (range)	60.5 (41-78)
Male sex, n (%)	15 (68.2)
Race, n (%)	
Asian/White	21 (95.5)/1 (4.5)
ECOG performance status, n (%)	
0/1	4 (18.2)/18 (81.8)
Tobacco use, n (%)	
Never/Current/Former	11 (50.0)/1 (4.5)/10 (45.5)
Disease stage, n (%)	
Metastatic	19 (86.4)
Prior anticancer drug therapy, n (%)[a]	1 (4.5)

[a]One patient received adjuvant therapy.

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

Table 2. Summary of AEs (safety analysis set)

	N=22	
Patients, n (%)	**TEAEs**	**TRAEs**
Any AE	22 (100.0)	21 (95.5)
≥Grade 3	13 (59.1)	11 (50.0)
Serious AE	10 (45.5)	8 (36.4)
≥Grade 3	8 (36.4)	4 (18.2)
AE leading to death	2 (9.1)[a]	2 (9.1)
AE leading to sitravatinib discontinuation	2 (9.1)[b]	2 (9.1)
AE leading to tislelizumab discontinuation	1 (4.5)[c]	1 (4.5)
AE leading to sitravatinib dose modification[d]	16 (72.7)	16 (72.7)
AE leading to tislelizumab dose modification[e]	13 (59.1)	12 (54.5)

[a]Unexplained death (n=1) and multiple organ dysfunction syndrome (n=1); [b]Death (n=1) and pneumonitis related to sitravatinib and tislelizumab (n=1); [c]Death (n=1); [d]AE leading to sitravatinib dose modification included dose reduction and/or interruption; [e]AE leading to tislelizumab dose modification included dose delay.

Abbreviations: AE, adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

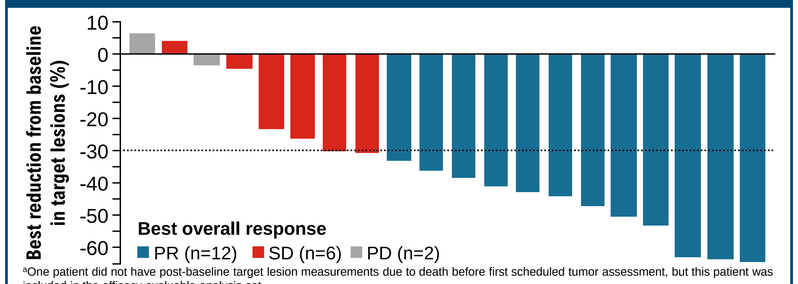
Table 3. TEAEs with ≥30% frequency (safety analysis set)

Patients, n (%)	N=22
Patients with ≥1 TEAE	22 (100.0)
Aspartate aminotransferase increased	14 (63.6)
Alanine aminotransferase increased	12 (54.5)
Diarrhea	11 (50.0)
Hypothyroidism	10 (45.5)
Hypoalbuminemia	9 (40.9)
Palmar-plantar erythrodysesthesia syndrome	9 (40.9)
Blood creatine phosphokinase increased	7 (31.8)
Hypokalemia	7 (31.8)
Proteinuria	7 (31.8)

Abbreviation: TEAE, treatment-emergent adverse event.

- Higher PD-L1 staining in tumor cells correlated with a trend for increased ORR and median progression-free survival (PFS) (**Table 4**); the median overall survival (OS) in the higher PD-L1 expression level subgroup was not reached
- Median PFS was 11.1 months (95% CI: 5.5, not estimable [NE]) and median OS was 17.4 months (95% CI: 11.8, NE) (**Figure 3**)

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



[a]One patient did not have post-baseline target lesion measurements due to death before first scheduled tumor assessment, but this patient was included in the efficacy evaluable analysis set.

Abbreviations: BOR, best overall response; PD, progressive disease; PR; partial response; SD, stable disease.

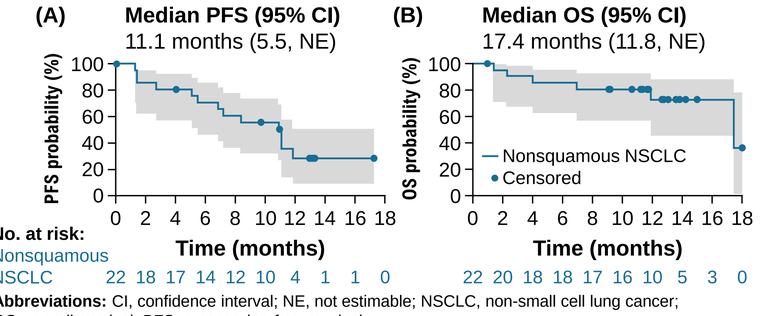
Table 4. Efficacy analysis by PD-L1 subgroup

	Efficacy-evaluable analysis set (N=21[a])		Safety analysis set (N=22[a])		
	n	**ORR (95% CI)**	**n**	**mPFS (95% CI)**	**mOS (95% CI)**
PD-L1 TC 1-49%	9	44.4 (13.7, 78.8)	10	7.2 (1.3, 11.1)	17.4 (1.3, 17.4)
PD-L1 TC ≥50%	11	63.6 (30.8, 89.1)	11	11.8 (5.5, NE)	NR (11.8, NE)

[a]One patient had <1% PD-L1 TC expression level and did not meet the inclusion criteria for this cohort. This patient was included in both the safety and efficacy evaluable analysis sets but was excluded from the PD-L1 subgroup analysis.

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; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival.

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Disclosures

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