Sitravatinib + tislelizumab in patients with metastatic non-small cell lung cancer

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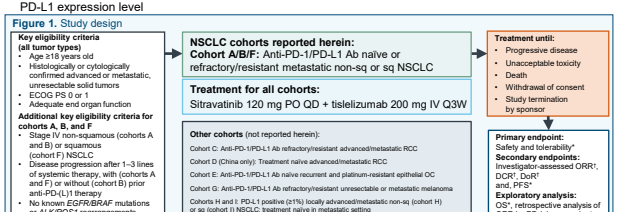
Introduction

- Patients with advanced non-small cell lung cancer (NSCLC) often develop progressive disease, but treatment options are limited for patients heavily pretreated with anti-programmed death protein/ligand-1 (PD-[L]1) antibodies and/or chemotherapy[1–3]
- Sitravatinib is an oral spectrum-selective tyrosine kinase inhibitor targeting TAM (TYRO3, AXL, MER) and split tyrosine-kinase domain-containing receptors (VEGFR2, KIT)[4]
  - Preclinical studies demonstrate that sitravatinib reduces the number of myeloid-derived suppressor cells and regulatory T cells and increases the ratio of M1/M2 polarized macrophages, which may help overcome resistance to immune checkpoint inhibitors and augment antitumor immune responses[4]
- Tislelizumab is an anti-PD-1 antibody with high affinity and binding specificity for PD-1 that has been engineered to minimize binding to FcγR on macrophages to abrogate antibody-dependent phagocytosis, a potential mechanism of resistance[5,6]
- Combining a PD-1 inhibitor and an agent with immune modulatory and antitumor properties may enhance antitumor activity beyond that provided by either agent alone[4,7]
- A Phase 1b study assessed the safety, tolerability, and antitumor activity of sitravatinib + tislelizumab in various solid tumors
  - We report results from metastatic NSCLC cohorts including both anti-PD-(L)1-naïve patients and those with tumors refractory/resistant (R/R) to anti-PD-(L)1 therapy

Methods

- An open-label, multicenter, non-randomized, multi-cohort, Phase 1b trial was conducted (NCT03666143)
- Study design and endpoints are summarized in **Figure 1**
- Cohorts reported herein (A, B, and F) included patients with squamous or non-squamous metastatic NSCLC treated with 1–3 prior lines of systemic therapy, with or without an anti-PD-(L)1 inhibitor, enrolled regardless of PD-L1 expression level

Figure 1. Study design



Safety, tolerability, PFS, and OS were assessed using the safety analysis set (all patients receiving ≥1 dose of study drug); †Tumor responses were assessed using the efficacy evaluable analysis set (all dosed patients who had measurable disease at baseline per RECIST v1.1 and who had ≥1 evaluable post-baseline tumor assessment unless treatment was discontinued due to disease progression or death before tumor assessment)

Ab, antibody; ALK, anaplastic lymphoma kinase; BRAF, v-raf murine sarcoma viral oncogene homolog B1; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; IV, intravenously; NSCLC, non-small cell lung cancer; Nsq, non-squamous; OC, ovarian cancer; ORR, objective response rate; OS, overall survival; PD-1, programmed cell protein-1; PD-L1, programmed death ligand-1; PFS, progression-free survival; PO, orally; QD, once-daily; Q3W, once every three weeks; RCC, renal cell carcinoma; RECIST, Response Evaluation Criteria in Solid Tumors; ROS1, c-ros oncogene 1; Sq, squamous

Results

Patients

- From December 2018–June 2020, 75 patients were enrolled, including:
  - 46 patients with non-squamous NSCLC and 29 patients with squamous NSCLC;
  - 28 anti-PD-(L)1-naïve patients and 47 with disease R/R to PD-(L)1 therapy
- Median follow-up at the time of data cut-off (October 13, 2020) was 10.1 months (range: 0.4 to 18.8)
- 10 patients (13.3%) remained on treatment
- Baseline characteristics are summarized in **Table 1**

Table 1. Demographics and baseline characteristics

		Total (N=75)
Age, years	Median (range)	60.0 (25–79)
Sex, n (%)	Male	59 (78.7)
	Female	16 (21.3)
Race, n (%)	Asian	62 (82.7)
	White	13 (17.3)
ECOG PS, n (%)	0	17 (22.7)
	1	58 (77.3)
Prior lines of anticancer therapy, n (%)	1	35 (46.7)
	≥2	40 (53.3)
Duration of last therapy, months	Median (range)	4.5 (0.7–24.9)

ECOG PS, Eastern Cooperative Oncology Group performance status

Conclusions

- Sitravatinib + tislelizumab had a manageable safety and tolerability profile, which is consistent with what has previously been reported in patients with non-squamous or squamous metastatic NSCLC who were either pretreated or naïve to anti-PD-(L)1 treatment
- The combination demonstrated preliminary antitumor activity, both in patients who were naïve to anti-PD-(L)1 treatment and in those with anti-PD(L)1 R/R disease, with an overall ORR of 16.9%, DCR of 84.5% and PFS of 5.5 months
- These results support the further investigation of sitravatinib + tislelizumab in metastatic NSCLC patient populations

Safety

- Median duration of exposure was 17.9 weeks (range: 1.3 to 78.1) for sitravatinib and 18.1 weeks (range: 3.0 to 78.1) for tislelizumab
- Mean relative dose intensity was 79.7% (SD: 20.3) for sitravatinib and 93.7% (SD: 11.8) for tislelizumab
- All patients had a treatment-emergent adverse event (TEAE) and treatment-related adverse event (TRAE) (**Table 2**)
  - Hypertension was the most commonly reported Grade ≥3 TEAE and TRAE
  - No cases of hypertension led to treatment discontinuation
- 73.3% of patients experienced dose modification (including dose reduction and/or interruption) of sitravatinib due to TEAEs
- TRAEs leading to death were reported in three patients, including one case each of ischemic stroke (considered related to sitravatinib), cardiac failure with pneumonia and respiratory failure (considered related to tislelizumab), and unspecified death (considered related to both drugs)

Table 2. Summary of TEAE and TRAE incidence (safety analysis set)

Patients, n (%)	All patients (N=75)	
	TEAEs	TRAEs
Any AE	75 (100.0)	75 (100.0)
Grade ≥3 AE	55 (73.3)	38 (50.7)
Serious AE	41 (54.7)	26 (34.7)
Grade ≥3 serious AE	34 (45.3)	14 (18.7)
AE leading to death	10 (13.3)	3 (4)
AE leading to sitravatinib discontinuation	15 (20.0)	13 (17.3)
AE leading to tislelizumab discontinuation	10 (13.3)	9 (12.0)
AE leading to sitravatinib dose modification*	55 (73.3)	54 (72.0)
AE leading to tislelizumab dose modification†	30 (40.0)	28 (37.3)
Grade ≥3 AEs reported in ≥5% of patients‡		
Hypertension	12 (16.0)	11 (14.7)
Death	4 (5.3)	1 (1.3)
Stomatitis	5 (6.7)	5 (6.7)
Pneumonia	4 (5.3)	2 (2.7)

**AE leading to sitravatinib dose modification includes dose reduction and/or interruption; †AE leading to tislelizumab dose modification includes dose delay and/or interruption; ‡Incidences reported by preferred term for any TEAE or TRAE reported in ≥5% of patients. All AEs are treatment-emergent and graded based on National Cancer Institute–Common Terminology Criteria for Adverse Events (version 5.0)*

AE, adverse event; TEAE, treatment-emergent AE; TRAE, treatment-related AE

Efficacy: Tumor response

- In the overall population, confirmed objective response rate (ORR) was 16.9% (**Table 3**)
  - ORR was numerically higher in patients naïve to anti-PD-(L)1 therapy (22.2%) compared with patients with anti-PD-(L)1 R/R disease (13.6%)
  - Median duration of response was 7.0 months, which did not differ between patients naïve to anti-PD-(L)1 therapy and patients with anti-PD-(L)1 R/R disease
- Confirmed partial response and stable disease were reported in 12 (16.9%) and 48 (67.6%) patients, respectively, in the overall patient population. Few patients (n=8 [11.3%]) had progressive disease (**Table 3** and **Figure 2**)
- Disease control was achieved in >80% of patients in both anti-PD-(L)1 pretreated and naïve groups (**Table 3**)

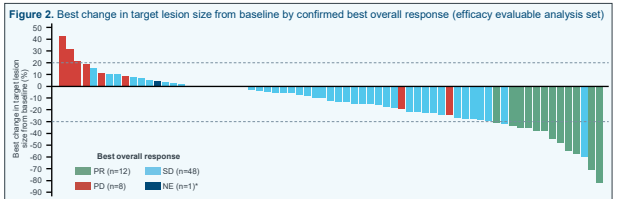
Table 3. Analysis of confirmed disease response per RECIST v1.1 (efficacy evaluable analysis set)

	Total (N=71)
ORR, % (95% CI)	16.9 (9.1, 27.7)
Best overall response, n (%)	
Complete response	0 (0.0)
Partial response	12 (16.9)
Stable disease	48 (67.6)
Progressive disease	8 (11.3)
NE	3 (4.2)*
DCR*, % (95% CI)	84.5 (74.0, 92.0)
Median DoR, months (95% CI)	7.0 (2.9, NE)

**Includes two patients who died early with no post-baseline tumor assessment and one patient with an NE tumor response; †DCR = complete response + partial response + stable disease*

CI, confidence interval; DCR, disease control rate; DoR, duration of response; NE, non-evaluable; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumors

Figure 2. Best change in target lesion size from baseline by confirmed best overall response (efficacy evaluable analysis set)



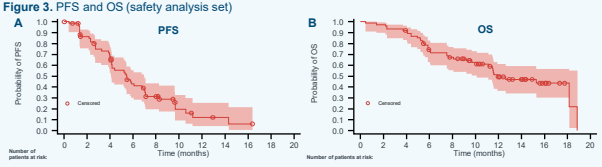
**Two patients with no post-baseline tumor assessment due to early death were not included in this figure;Tumor responses assessed by investigators per RECIST v1.1*

NE, non-evaluable; PD, disease progression; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease

Efficacy: Survival

- In the overall population, median progression-free survival (PFS) was 5.5 months (95% CI: 4.1, 7.0) (**Figure 3A**)
  - Median PFS was numerically longer in patients naïve to anti-PD-(L)1 therapy (7.0 months [95% CI: 2.7, 11.2]) compared with those with anti-PD-(L)1 R/R disease (5.2 months [95% CI: 4.1, 5.9])
- Median overall survival (OS) was 11.9 months (95% CI: 10.1, 18.8) in the overall population (**Figure 3B**), 15.3 months (95% CI: 11.5, 18.8) in anti-PD-(L)1-naïve patients, and 10.1 months (95% CI: 6.1, 18.1) in those with anti-PD-(L)1 R/R disease
  - OS data are not mature (median follow-up duration: 14.1 months)

Figure 3. PFS and OS (safety analysis set)

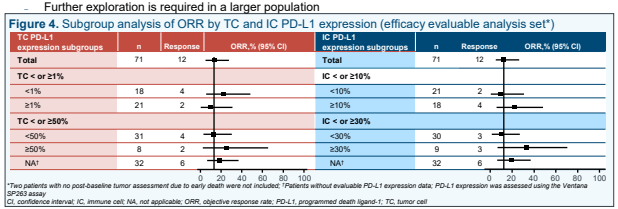


NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival

Efficacy: Tumor response by PD-L1 expression

- Defined cut-offs for PD-L1 tumor cell (TC) or immune cell (IC) expression were used to investigate whether there was an association between PD-L1 expression and tumor response (**Figure 4**)
  - A trend for higher ORR was observed in patents with higher PD-L1 IC expression
  - No association was observed between ORR and PD-L1 TC
  - Further exploration is required in a larger population

Figure 4. Subgroup analysis of ORR by TC and IC PD-L1 expression (efficacy evaluable analysis set*)



**Two patients with no post-baseline tumor assessment due to early death were not included; †Patients without evaluable PD-L1 expression data; PD-L1 expression was assessed using the Ventana SP263 assay*

CI, confidence interval; IC, immune cell; NA, not applicable; ORR, objective response rate; PD-L1, programmed death ligand-1; TC, tumor cell

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