SAFFRON-301: SITRAVATINIB PLUS TISLELIZUMAB IN ADVANCED/METASTATIC NSCLC PROGRESSING ON/AFTER CHEMOTHERAPY AND ANTI–PD-(L)1

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Background

- Patients with advanced NSCLC who progress following chemotherapy and/or CPI-based immunotherapy targeting PD-1/PD-L1 have limited efficacious treatment options[1]
- Combining CPIs with agents that target molecular and cellular mechanisms of resistance to CPIs is a rational approach to overcoming resistance[2]
- RTK inhibitors can stimulate the immune system and cause synergistic effects that stimulate tumor shrinkage[3]
- Sitravatinib is an oral spectrum-selective TKI that targets TAM receptors (TYRO3/AXL/MERTK) and split-kinase domain containing receptors (VEGFR2/KIT) and can shift the immunosuppressive tumor microenvironment toward an immunostimulatory state[3-5]
- In the phase 1b SAFFRON-103 study, combination therapy with sitravatinib and the anti–PD-1 antibody, tislelizumab, had promising efficacy in patients with metastatic NSCLC who were refractory/resistant to anti–PD-(L)1[6]
- The phase 3 SAFFRON-301 study was performed to confirm the efficacy signal observed in SAFFRON-103

AXL, AXL receptor tyrosine kinase; CPI, checkpoint inhibitor; KIT, KIT proto-oncogene tyrosine kinase; MERTK, MER proto-oncogene tyrosine kinase; NSCLC, non-small cell lung cancer; PD-1; programmed cell death protein-1 ; PD-L1, programmed death-ligand 1; RTK, receptor tyrosine kinase; TKI, tyrosine kinase inhibitor; TRYO 3, TYRO3 protein tyrosine kinase; VEGFR2, vascular endothelial growth factor receptor-2.

1. Moliner L, et al. *ESMO Open.* 2023:8:1-3. 2. Horvath L, et al. *Mol Cancer.* 2020;19:1411. 3. Du W, et al. *JCI Insight.* 2018;3: e124184. doi:10.1172/jci.insight.124184. 4. Bauer T, et al. *Invest New Drugs.* 2022;40:990-1000. 5. Patwardhan PP, et al. *Oncotarget.* 2015*; 5*: 4093-4109. 6. Zhao J, et al. *J Immunother Cancer.* 2023;11:e006055. doi:10.1136/jitc-2022-006055.

SAFFRON-301 Study Design

- Open-label, randomized, multicenter phase 3 clinical study (NCT04921358)

Key eligibility criteria
- Histologically or cytologically confirmed unresectable locally advanced or metastatic NSCLC
- No known *EGFR*- or *BRAF*-sensitizing mutation, or *ALK* or *ROS1* rearrangement
- Previously treated, disease progression on or after platinum-based chemotherapy and anti–PD-L(1) Ab[a]

R
1:1
N=377[b]

SITRA + TIS (N=187)
SITRA 100 mg PO QD
TIS 200 mg IV Q3W

Chemotherapy (N=190)
Docetaxel 75 mg/m^2 IV Q3W

Treatment until disease progression, intolerable toxicity, death, or withdrawal of consent

Primary endpoints (alpha splitting)
- OS
- PFS (IRC by RECIST 1.1)

Secondary endpoints
- PFS (investigator)
- ORR
- DoR
- DCR
- Safety

Stratification factors
- Histological subtype (non-squamous/squamous)
- PD-L1 expression (<1% TC/≥1%)
- Race (Asian/non-Asian)

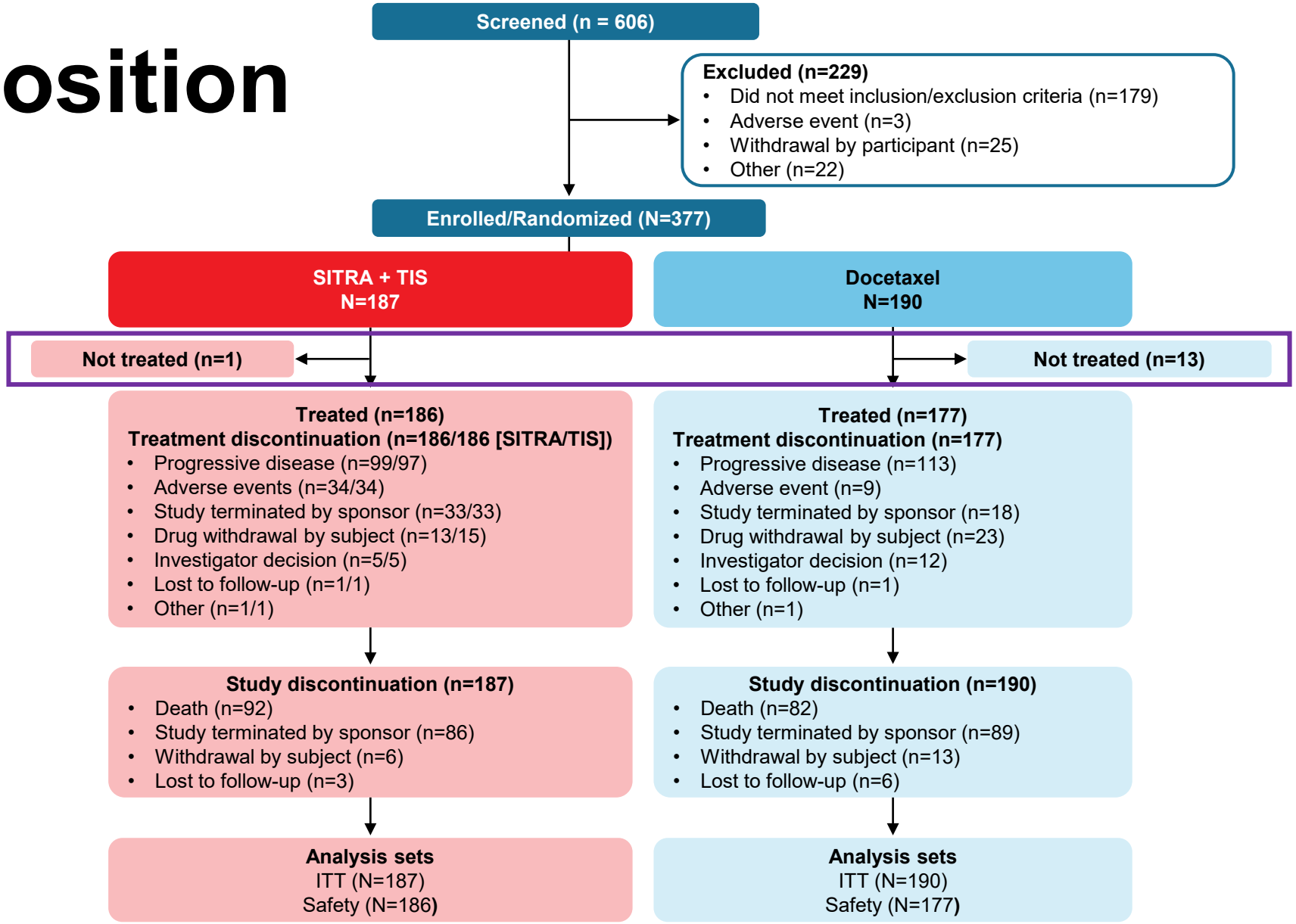
Study was terminated early on September 25, 2023, due to an imbalanced rate of serious/fatal pulmonary hemorrhage and an unfavorable risk-benefit assessment in the investigational arm

[a]Anti-PD-(L)1 antibody administered with or sequentially before or after platinum-based chemotherapy.
[b]Actual sample size; planned sample size was N=420.
Ab, antibody; *ALK*, anaplastic lymphoma kinase; *BRAF*, B-Raf proto-oncogene; DCR, disease control rate; DoR, duration of response; *EGFR*, epidermal growth factor receptor; IRC, Independent Review Committee; IV, intravenous; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PD-(L)1, programmed cell death protein-1/programmed death-ligand 1; PFS, progression-free survival; PO, oral; QD, once daily; Q3W, every 3 weeks; R, randomized; RECIST, Response Evaluation in Solid Tumors; *ROS1*, ROS Proto-Oncogene 1; TC, tumor cells; TIS, tislelizumab; SITRA, sitravatinib.

Patient Disposition

Median study follow-up

- **SITRA + TIS:** 8.0 months
- **Docetaxel:** 7.6 months



ITT, intent-to-treat; SITRA, sitravatinib; TIS, tislelizumab.

Baseline Characteristics (ITT Population)

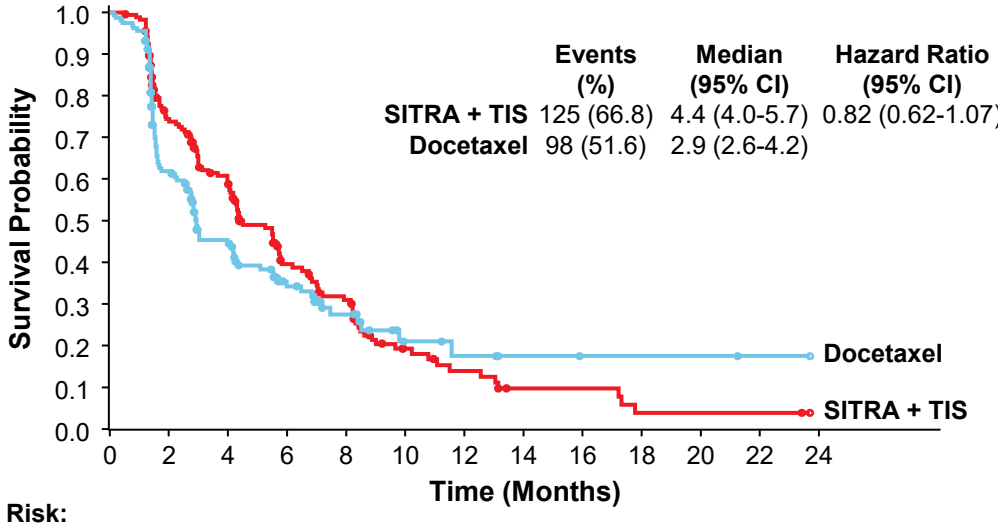
	SITRA + TIS N=187	Docetaxel N=190	Total N=377
Age, median (range), years	63.0 (29-76)	63.0 (34-79)	63.0 (29-79)
Gender, n (%)			
Male	153 (81.8)	151 (79.5)	304 (80.6)
Female	34 (18.2)	39 (20.5)	73 (19.4)
Race, n (%)			
Asian	175 (93.6)	177 (93.2)	352 (93.4)
White	12 (6.4)	13 (6.8)	25 (6.6)
ECOG performance status, n (%)			
0	47 (25.1)	46 (24.2)	93 (24.7)
1	140 (74.9)	144 (75.8)	284 (75.3)
Histology, n (%)			
Squamous	96 (51.3)	97 (51.1)	193 (51.2)
Non-squamous	91 (48.7)	93 (48.9)	184 (48.8)
PD-L1 expression status, n (%)			
≥1%	68 (36.4)	70 (36.8)	138 (36.6)
<1%	106 (56.7)	107 (56.3)	213 (56.5)
Not evaluable[a]	13 (7.0)	13 (6.8)	26 (6.9)
Number of lines of prior systemic therapy, n (%)			
1	142 (75.9)	140 (73.7)	282 (74.8)
2	45 (24.1)	50 (26.3)	95 (25.2)

[a]Patients with unevaluable PD-L1 expression status were included in the <1% TC group during randomization.
ECOG, Eastern Cooperative Oncology Group; ITT, intent-to-treat; PD-L1, programmed death-ligand 1; SITRA, sitravatinib; TC, tumor cells; TIS, tislelizumab.

PFS by IRC and by INV (ITT Population)

- The dual primary endpoint, PFS (IRC), was numerically longer with investigational therapy (median, 4.4 vs 2.9 months; HR, 0.82)
- PFS (INV), a secondary endpoint, was comparable with IRC-assessed PFS (median, 4.4 vs 2.9 months; HR, 0.64)

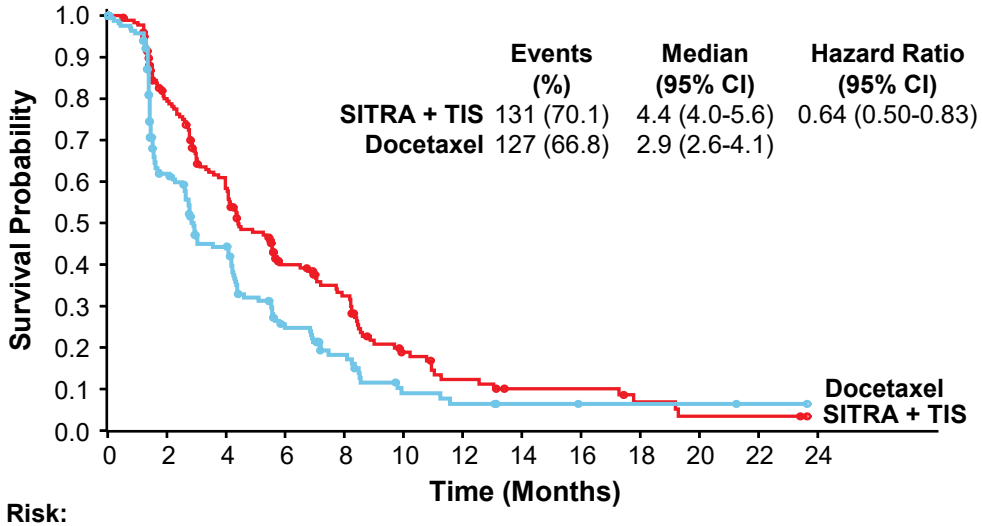
PFS by IRC



	Events (%)	Median (95% CI)	Hazard Ratio (95% CI)
SITRA + TIS	125 (66.8)	4.4 (4.0-5.7)	0.82 (0.62-1.07)
Docetaxel	98 (51.6)	2.9 (2.6-4.2)	

Number at Risk:													
SITRA + TIS	187	118	87	47	35	15	10	5	5	2	2	2	0
Docetaxel	190	84	53	30	17	7	5	3	2	2	2	1	0

PFS by INV



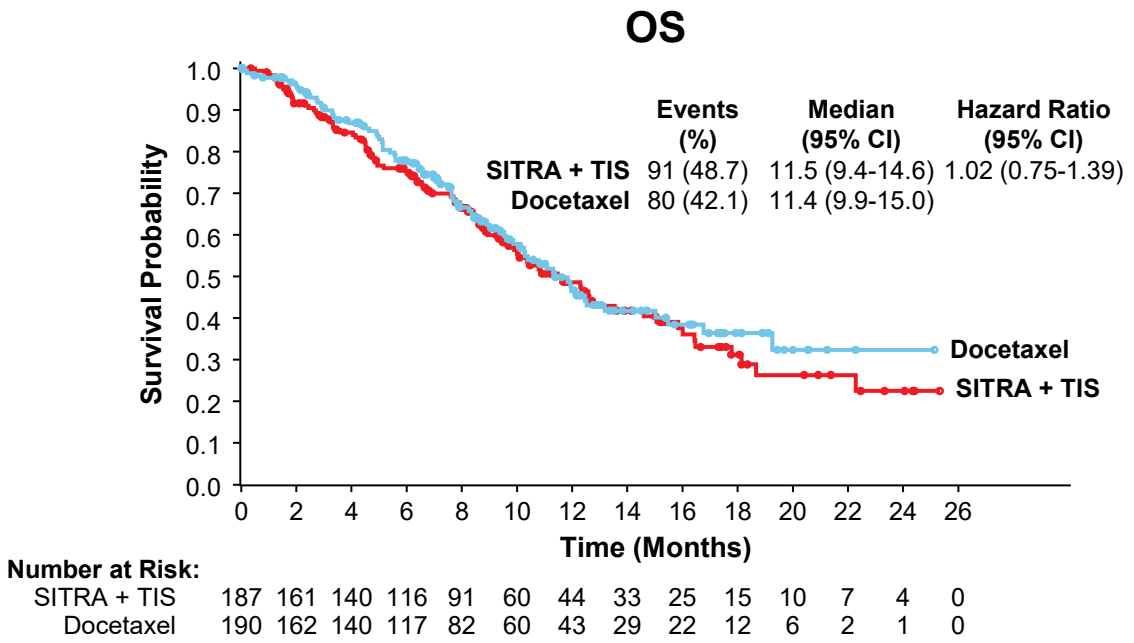
	Events (%)	Median (95% CI)	Hazard Ratio (95% CI)
SITRA + TIS	131 (70.1)	4.4 (4.0-5.6)	0.64 (0.50-0.83)
Docetaxel	127 (66.8)	2.9 (2.6-4.1)	

Number at Risk:													
SITRA + TIS	187	128	90	51	38	18	11	7	7	4	2	2	0
Docetaxel	190	91	60	29	17	7	5	3	2	2	2	1	0

[a]Median follow-up time was estimated by the reverse Kaplan-Meier method with 95% CIs estimated using the Brookmeyer and Crowley method.
CI, confidence interval; IRC, Independent Review Committee; INV, investigator; ITT, intent-to-treat; PFS, progression-free survival; SITRA, sitravatinib; TIS, tislelizumab.

OS (Dual Primary Endpoint; ITT Population)

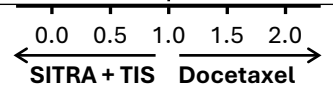
- At data cutoff (December 20, 2023), median follow-up time for OS was 11.7 months (SITRA + TIS) versus 11.4 months (docetaxel)[a]
- Median OS was similar in both arms (11.5 vs 11.4 months)



[a]Median follow-up time was estimated by the reverse Kaplan-Meier method with 95% CIs estimated using the Brookmeyer and Crowley method.
CI, confidence interval; ITT, intent-to-treat; OS, overall survival; SITRA, sitravatinib; TIS, tislelizumab.

OS Subgroup Analyses (ITT Population)

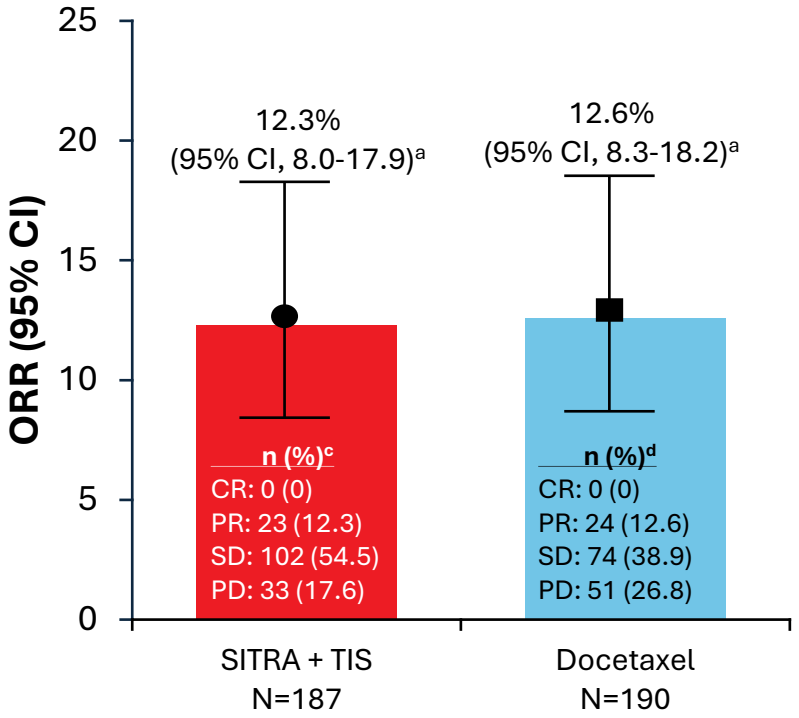
Subgroup	Event/Total SITRA + TIS	Event/Total Docetaxel	Hazard Ratio for Death (95% CI)	Hazard Radio (95% CI)
Overall	91/187	80/190		1.10 (0.82-1.49)
Age group				
<65 years	48/106	51/112		0.87 (0.59-1.29)
≥65 years	43/81	29/78		1.52 (0.94-2.44)
Sex				
Male	78/153	68/151		1.11 (0.80-1.54)
Female	13/34	12/39		1.13 (0.52-2.49)
Race				
Asian	82/175	73/177		1.08 (0.79-1.49)
Non-Asian	9/12	7/13		1.26 (0.47-3.41)
Geographic region				
China	81/174	72/175		1.07 (0.78-1.47)
Australia	10/13	8/15		1.56 (0.61-3.99)
ECOG performance status				
0	16/47	13/46		1.27 (0.61-2.64)
1	75/140	67/144		1.06 (0.76-1.47)
PD-L1 Expression				
≥1% TC	32/68	25/70		1.30 (0.77-2.20)
<1% TC	52/106	50/107		0.96 (0.65-1.41)
Not evaluable	7/13	5/13		1.45 (0.46-4.62)
Histological subtype				
Non-squamous	46/91	39/93		1.18 (0.77-1.81)
Squamous	45/96	41/97		1.01 (0.66-1.54)
Smoking Status				
Former/current smoker	71/131	60/132		1.17 (0.83-1.66)
Non-Smoker	20/56	20/58		0.95 (0.51-1.76)
Disease status at study entry				
Locally advanced	9/19	10/24		0.91 (0.37-2.25)
Metastatic	82/168	70/166		1.10 (0.80-1.52)
Number of lines of prior systemic therapy				
1	68/142	64/140		0.97 (0.69-1.36)
2	23/45	16/50		1.68 (0.89-3.19)



CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; OS, overall survival; PD-L1, programmed death-ligand 1; ITT, intent-to-treat; SITRA, sitravatinib; TC, tumor cells; TIS, tislelizumab.

Tumor Response (ITT Population)

- IRC-confirmed ORR was similar in both arms (12.3% vs 12.6%)



Category	SITRA + TIS N=187	Docetaxel N=190
Overall response rate by IRC, n (%)	23 (12.3)	24 (12.6)
95% CI (%)[a]	8.0-17.9	8.3-18.2
Disease control rate by IRC, n (%)	130 (69.5)	102 (53.7)
95% CI (%)[a]	62.4-76.0	46.3-60.9
Median duration of response by IRC (95% CI), months[b]	6.0 (3.2-8.5)	NR (5.4-NE)

Complete response and partial response were confirmed per RECIST v1.1.
[a]The 95% CI was estimated using the Clopper-Pearson method.
[b]The 95% CI was estimated using the Brookmeyer and Crowley method with log-log transformation.
[c]5 (2.7%) and 24 (12.8%) had non-CR/non-PD and could not be determined, respectively.
[d]4 (2.1%) and 37 (19.5%) had non-CR/non-PD and could not be determined, respectively.
CI, confidence interval; CR, complete response; ITT, intent-to-treat; IRC, Independent Review Committee; NE, not estimable; ORR, overall response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; SITRA, sitravatinib; TIS, tislelizumab.

Safety (Safety Population)

- Higher incidences of most categories of TEAEs in investigational arm
- Fatal hemoptysis was more common in investigational arm

	SITRA + TIS N=186 n (%)	Docetaxel N=177 n (%)
Patients with ≥1 TEAE	183 (98.4)	162 (91.5)
≥Grade 3	121 (65.1)	100 (56.5)
Serious	83 (44.6)	66 (37.3)
Leading to death[a]	15 (8.1)	5 (2.8)
Leading to treatment discontinuation	45 (24.2)	15 (8.5)
TEAEs leading to death in >1 patient[a]		
Death[b]	4 (2.2)	1 (0.6)
Pneumonia	3 (1.6)	2 (1.1)
Hemoptysis	3 (1.6)	0
Treatment-related[c]	3 (1.6)[d]	0

Adverse event grades were evaluated based on NCI-CTCAE Version 5.0.
[a]Death events due to disease under study are not included as a TEAE leading to death.
[b]For all 5 fatal TEAE cases where death was listed as the preferred term, all reported terms were "unexplained death".
[c]TEAEs that were considered by the Investigator to be related to study drug or TEAEs with a missing causality.
[d]IDMC reviewed and concluded the fatal events were confounded by squamous central NSCLC (n=2) and pre-existing hemoptysis at baseline (n=1).
NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events;
TEAE, treatment-emergent adverse event; SITRA, sitravatinib; TIS, tislelizumab.

TEAEs (Any Grade) Occurring in >25% in Any Arm	SITRA + TIS N=186 n (%)		Docetaxel N=177 n (%)	
	Any Grade	≥Grade 3	Any Grade	≥Grade 3
Aspartate aminotransferase increased	111 (59.7)	6 (3.2)	18 (10.2)	3 (1.7)
Alanine aminotransferase increased	97 (52.2)	5 (2.7)	17 (9.6)	4 (2.3)
Diarrhea	83 (44.6)	9 (4.8)	26 (14.7)	5 (2.8)
Blood creatine phosphokinase MB increased	74 (39.8)	5 (2.7)	3 (1.7)	0
Palmar-plantar erythrodysesthesia syndrome	68 (36.6)	12 (6.5)	0	0
Anemia	61 (32.8)	7 (3.8)	84 (47.5)	5 (2.8)
Hypoalbuminemia	58 (31.2)	1 (0.5)	41 (23.2)	0
Hypertension	56 (30.1)	25 (13.4)	6 (3.4)	2 (1.1)
Weight decreased	54 (29.0)	8 (4.3)	15 (8.5)	1 (0.6)
Decreased appetite	53 (28.5)	2 (1.1)	29 (16.4)	2 (1.1)
White blood cell count decreased	11 (5.9)	0	66 (37.3)	52 (29.4)
Neutrophil count decreased	10 (5.4)	1 (0.5)	59 (33.3)	51 (28.8)
Alopecia	5 (2.7)	0	59 (33.3)	0

Conclusions

In patients with locally advanced/metastatic NSCLC whose disease progressed following platinum-based chemotherapy and anti–PD-(L)1 antibody:

- IRC- and investigator-assessed PFS were numerically longer in investigational versus docetaxel arm
- No improvements of OS were observed
  - Data were immature with limited follow-up and event rates
  - Higher number of patients in the docetaxel arm who did not receive treatment may bring biases
  - Lack of survival benefit is consistent with other phase 3 studies of anti–PD-(L)1 and TKI combinations (LEAP-008, CONTACT-01, and SAPPHIRE) in NSCLC[1-3]
- There were higher incidences of ≥grade 3 TEAEs, serious TEAEs, and TEAEs leading to discontinuation and death in the investigation arm versus docetaxel
  - Patient population included squamous central NSCLC
- The study was terminated early based on unfavorable benefit: risk ratio

Acknowledgments

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IRC, Independent Review Committee; NSCLC, non-small cell lung cancer; OS, overall survival; PD-(L)1, programmed cell death protein-1/programmed death-ligand 1; PFS, progression-free survival; TEAE, treatment-emergent adverse event; TKI, tyrosine kinase inhibitor.

1. Borghaei H, et al. *Ann Oncol.* 2024;35:66-76. 2. Leighl N, et al. *Ann Oncol.* 2024;20(suppl_1):100535-100535. doi:101016/iotech/iotech100535. 3. Neal J, et al. *J Clin Oncol.* 2024; 42:2393-2403.