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A Phase 2 Study of Sitravatinib in Combination with Tislelizumab Versus Chemotherapy in Patients With Locally Advanced Unresectable or Metastatic Esophageal Squamous Cell Carcinoma That Progressed on or After Anti–PD-1/Anti–PD-L1 Antibody Therapy

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Background

- There is no established standard of care for second- or later-line therapy of patients with locally advanced unresectable or metastatic ESCC whose disease progressed on or after anti–PD-(L)1 therapy
- Sitravatinib is a selective TKI targeting TAM receptors (TYRO3, AXL, MERTK) and split tyrosine-kinase domain-containing receptors (VEGFR2, KIT) that can shift the immunosuppressive tumor microenvironment toward an immunostimulatory state[1-3]
- Tislelizumab is an anti-PD-1 monoclonal antibody designed to abrogate antibody-dependent phagocytosis, a potential mechanism of resistance[4]
- Combining sitravatinib and tislelizumab could potentially reverse resistance to PD-(L)1 inhibitors
- In the phase 1b SAFFRON-103 study, combination therapy with sitravatinib and tislelizumab had preliminary antitumor activity in patients with anti-PD-(L)1 resistant/refractory locally advanced/metastatic NSCLC and anti–PD-(L)1 refractory/resistant advanced melanoma[5,6]

Objective: To investigate the efficacy and safety of sitravatinib and tislelizumab administered as second- or third-line therapy in patients with locally advanced unresectable or metastatic ESCC whose disease progressed after prior systemic platinum-based chemotherapy and anti-PD-(L)1

Abbreviations: AXL, AXL receptor tyrosine kinase; ESCC, esophageal squamous cell carcinoma; 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-(L)1, programmed cell death protein-(ligand) 1; TKI, tyrosine kinase inhibitor; TYRO3, TYRO3 protein tyrosine kinase; VEGFR2, vascular endothelial growth factor receptor-2.

1. Du W et al. *JCI Insight.* 2018;3:2018;3:e124184. 2. Bauer T et al. *Invest New Drugs.* 2022;40:990-1000. 3. Patwardhan PP et al. *Oncotarget.* 2015;5:4093-4109. 4. Zhang, T et al. *Cancer Immunol Immunother.* 2018;67:1079–1090.
5. Zhao J et al. *J Immunother Cancer.* 2023;11:e006055. 6. Wang X et al. *Immunotherapy.* 2024;16:243–256.

Study Design

BGB-A317-Sitravatinib-203: An open-label, randomized, multicenter, phase 2 study (NCT05461794)

Key eligibility criteria

- Histologically or cytologically confirmed locally advanced unresectable or metastatic ESCC, not amenable to treatment with curative intent
- Confirmed disease progression on or after platinum-based chemotherapy doublet and anti-PD-(L)1 therapy
- Naive to VEGF(R)-targeted agents
- Received ≤2 lines of systemic treatment
- ECOG PS score ≤1

R 2:1:2 *China only*

Arm A (n=40)
Sitravatinib 100 mg PO QD
+
Tislelizumab 200 mg IV on D1[a]

Arm B (n=20)
Sitravatinib 100 mg PO QD

Arm C (n=40)
Docetaxel 75 mg/m^2 IV on D1[a] **OR**
Irinotecan 125 mg/m^2 IV on D1 and D8[a]

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

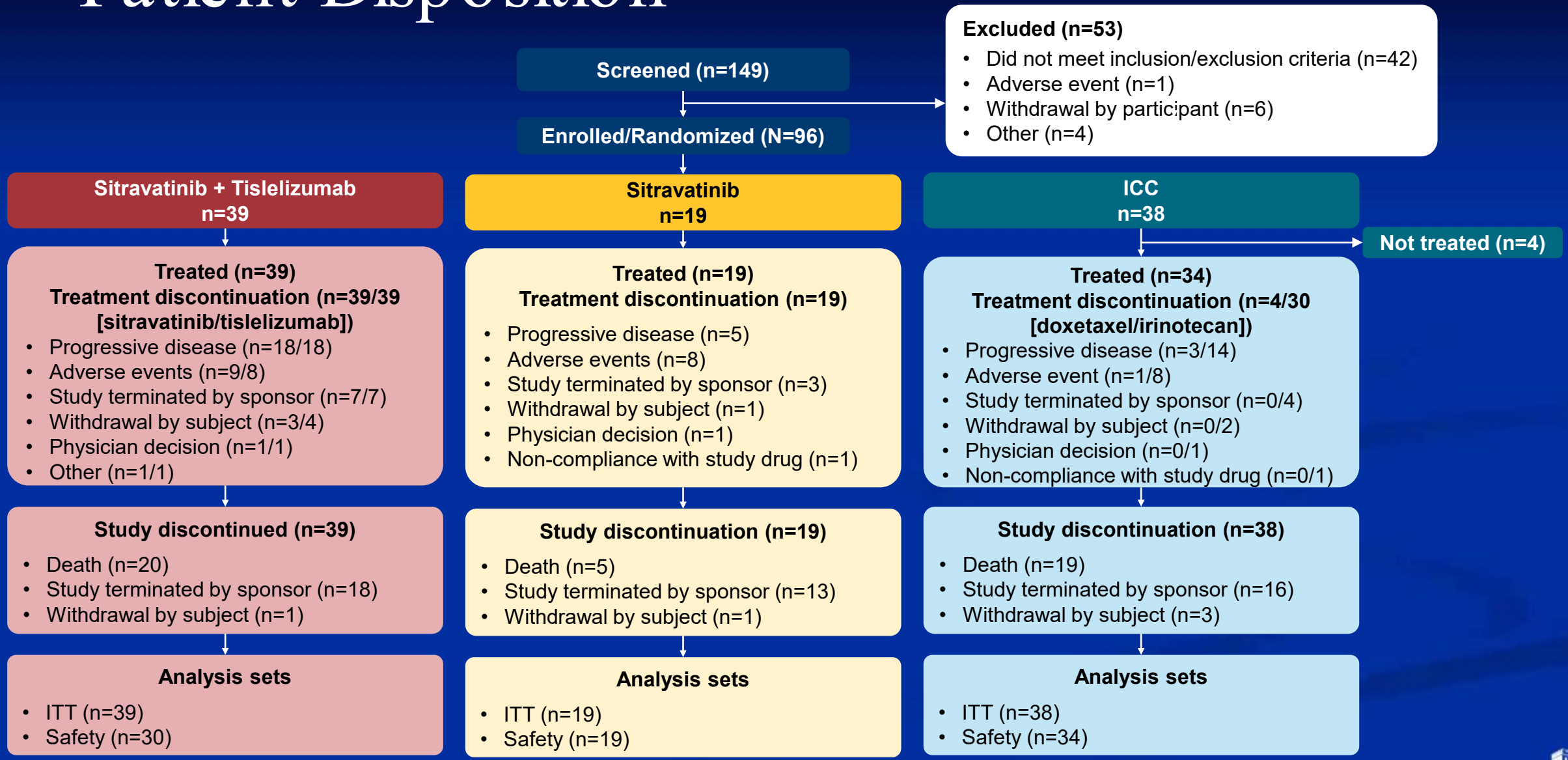
Primary endpoint
- ORR by INV in Arms A and C

Secondary endpoints
- DoR by INV in Arms A and C
- OS in Arms A and C
- DCR, CBR, and PFS by INV in Arms A and C
- ORR, DoR, DCR, CBR, and PFS by INV in Arms A and B
- Safety

Stratification factors
- PD-(L)1 expression status (TAP score[b]: ≥10% vs <10%)

[a]Cycle length is 21 days. [b]TAP score was determined visually by estimating the proportion of total tumor area covered by PD-L1 positive tumor cells and tumor-associated immune cells, assessed by the Ventana PD-L1 (SP263) assay.
Abbreviations: CBR, clinical benefit rate; D, Day; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ESCC, esophageal squamous cell carcinoma; INV, investigator; IV, intravenously; n, number of patients; ORR, overall response rate; OS, overall survival; PD-1, programmed cell death protein-1; PD-(L)1, programmed cell death protein-(ligand) 1; PFS, progression-free survival; PK, pharmacokinetics; PO, orally; QD, once daily; R, randomization ratio; TAP, tumor area positivity; VEGF(R), vascular endothelial growth factor (receptor).

Patient Disposition



Data cutoff: February 26, 2024. Study was terminated early on October 9, 2023 due to a modification of sponsor strategy.
Abbreviations: ICC, investigator-chosen chemotherapy; ITT, intent-to-treat.

Demographics and Baseline Characteristics

Characteristic	SITRA + TIS (n=39)	SITRA (n=19)	ICC (n=38)	Total (N=96)
Age (years)				
Mean (SD)	59.1 (7.73)	61.9 (7.87)	60.4 (8.06)	60.2 (7.87)
Min, max	37- 71	50- 73	46- 73	37- 73
Sex, n (%)				
Male	37 (94.9)	17 (89.5)	35 (92.1)	89 (92.7)
Race, n (%)				
Asian	39 (100.0)	19 (100.0)	38 (100.0)	96 (100.0)
Geographic region, n (%)				
China	39 (100.0)	19 (100.0)	38 (100.0)	96 (100.0)
ECOG performance status, n (%)				
0	5 (12.8)	3 (15.8)	9 (23.7)	17 (17.7)
1	34 (87.2)	16 (84.2)	29 (76.3)	79 (82.3)
PD- L1 TAP score from central lab, n (%)				
≥10%	6 (15.4)	3 (15.8)	5 (13.2)	14 (14.6)
<10%	33 (84.6)	16 (84.2)	33 (86.8)	82 (85.4)
Metastatic disease status at study entry, n (%)	35 (89.7)	16 (84.2)	34 (89.5)	85 (88.5)
Number of prior lines, n (%)				
1	23 (59.0)	11 (57.9)	24 (63.2)	58 (60.4)
2	15 (38.5)	8 (42.1)	13 (34.2)	36 (37.5)
≥3	1 (2.6)	0 (0.0)	1 (2.6)	2 (2.1)

Demographic and baseline characteristics, including TAP scores, were generally balanced across arms

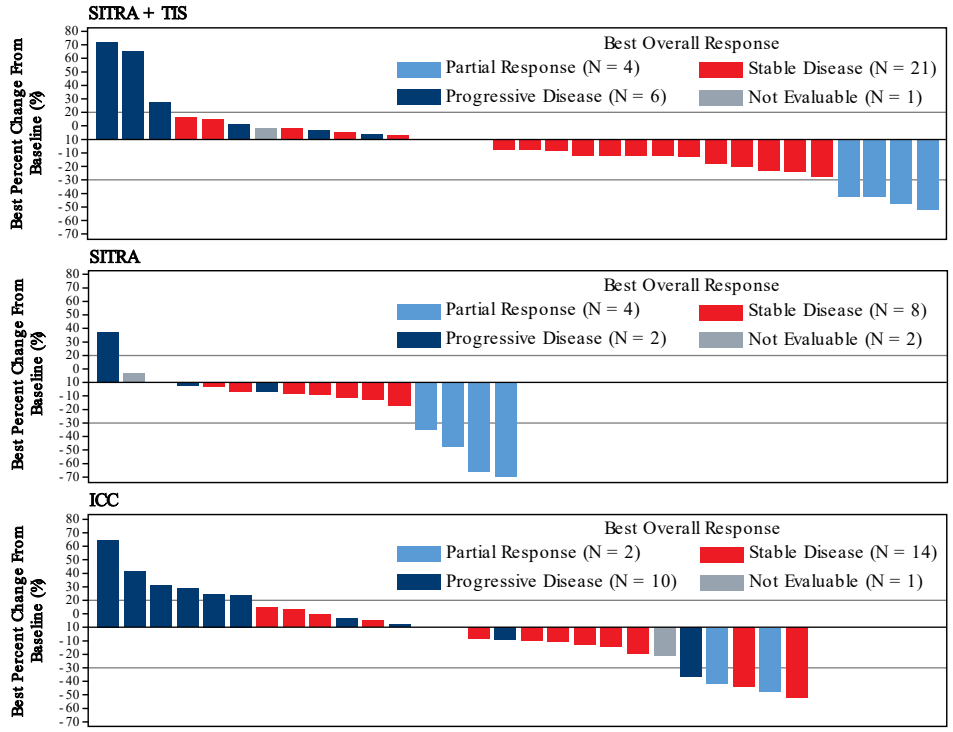
Data cutoff: Feb 26, 2024.
Baseline was defined as the last non-missing value prior to the first study drug administration or randomization (for untreated subjects).
Abbreviations: ECOG, Eastern Cooperative Oncology Group; ICC, investigator-chosen chemotherapy; PD-L1, programmed death-ligand 1; TAP, tumor area positivity; SD; standard deviation; SITRA, sitravatinib; TIS, tislelizumab.

Disease Response[a]

- At the data cutoff, the median follow-up times were 4.2, 5.3, and 4.4 months for SITRA + TIS, SITRA, and ICC, respectively

Response category	SITRA + TIS (n=39)	SITRA (n=19)	ICC (n=38)
Best overall response, n (%)			
Complete response	0 (0.0)	0 (0.0)	0 (0.0)
Partial response	4 (10.3)	4 (21.1)	2 (5.3)
Stable disease	21 (53.8)	8 (42.1)	14 (36.8)
Progressive disease	6 (15.4)	2 (10.5)	10 (26.3)
Could not be determined[b]	8 (20.5)	5 (26.3)	12 (31.6)
ORR, n (%)	4 (10.3)	4 (21.1)	2 (5.3)
95%CI (%)[c]	2.9-24.2	6.1-45.6	0.6-17.7
DCR, n (%)	25 (64.1)	12 (63.2)	16 (42.1)
95%CI (%)[c]	47.2-78.8	38.4-83.7	26.3-59.2
CBR, n (%)	7 (17.9)	5 (26.3)	2 (5.3)
95%CI (%)[c]	7.5-33.5	9.1-51.2	0.6-17.7

Best Percent Change in Target Lesion Size[d]

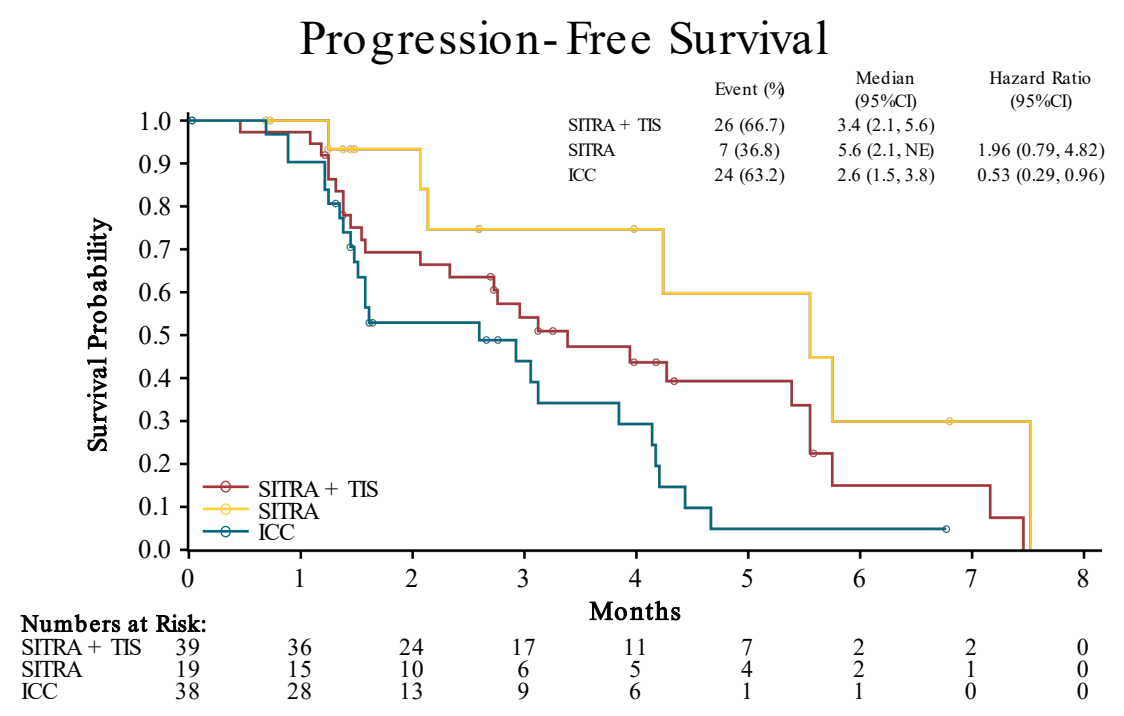


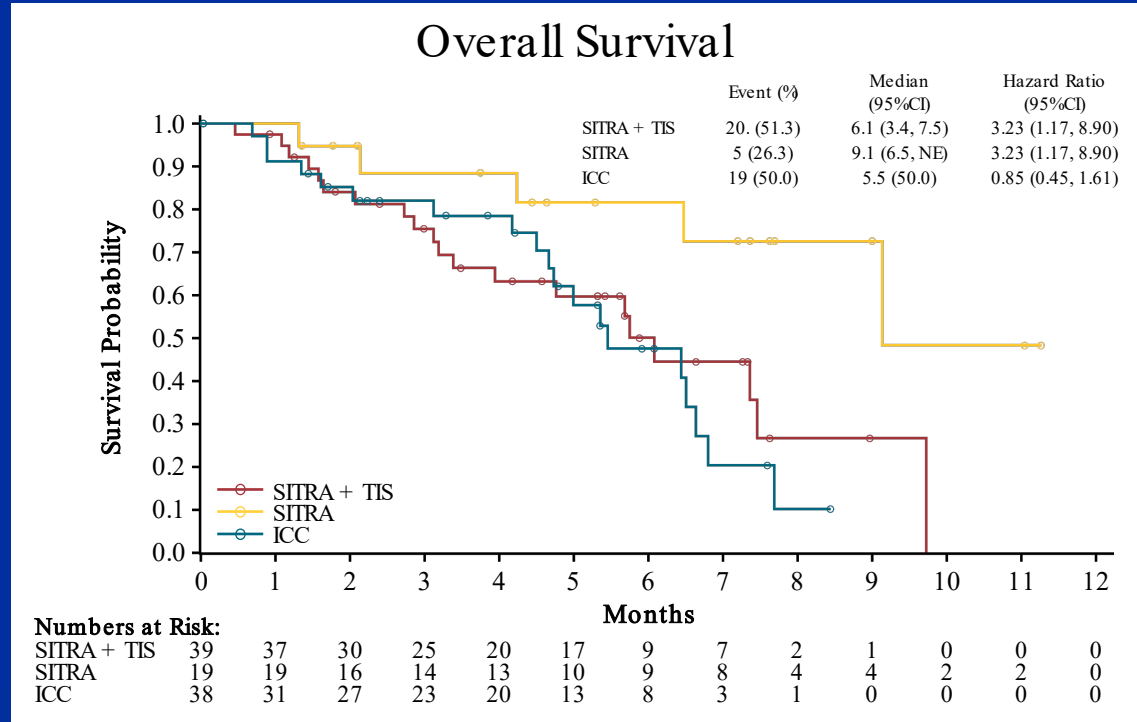
The confirmed ORR in the SITRA + TIS arm was numerically higher versus the ICC arm, but numerically lower versus the SITRA arm

Complete response and partial response were confirmed per RECIST v1.1.
Efficacy was assessed between Arm A and Arm C, while efficacy between Arm A and Arm B was only be assessed for efficacy contribution analysis of tislelizumab in the combination treatment.
[a]Investigator-confirmed per RECIST 1.1.
[b]The primary reason for undetermined best overall response was the absence of post-baseline tumor assessment due to study termination.
[c]The 95%CI was estimated using the Clopper-Pearson method.
[d]By best overall response with confirmation per investigator by treatment in the ITT analysis set.
Abbreviations: CBR, clinical benefit rate; CI, confidence interval; DCR, disease control rate; ICC, investigator-chosen chemotherapy; ITT, intent-to-treat; ORR, overall response rate; SITRA, sitravatinib; TIS, tislelizumab.

Overall Survival and Progression-Free Survival

- Median PFS and OS were numerically longer for SITRA + TIS versus ICC; both outcomes were numerically shorter for SITRA + TIS versus SITRA





Data cutoff: February 26, 2024.

Abbreviations: ICC, investigator-chosen chemotherapy; NE, not estimable; OS, overall survival; PFS, progression-free survival; SITRA, sitravatinib; TIS, tislelizumab.

Safety Overview

- The median RDI of SITRA was numerically higher in the SITRA arm versus the SITRA+TIS arm

Drug exposure	SITRA + TIS (n=39)	SITRA (n=19)	ICC (n=34)
Median duration of exposure, months			
SITRA	2.2	1.5	-
TIS	2.3	-	-
Docetaxel	-	-	1.4
Irinotecan	-	-	1.4
Median RDI, %			
SITRA	84.3	95.5	-
TIS	98.3	-	-
Docetaxel	-	-	98.6
Irinotecan	-	-	82.8

- The proportion of patients who experienced ≥1 serious TEAE was higher for SITRA+TIS versus SITRA or ICC

Patients, n (%)	SITRA + TIS (n=39)	SITRA (n=19)	ICC (n=34)
With ≥1 TEAE	39 (100.0)	19 (100.0)	34 (100.0)
≥Grade 3	26 (66.7)	14 (73.7)	24 (70.6)
Serious	22 (56.4)	6 (31.6)	15 (44.1)
Leading to death	1 (2.6)	0 (0.0)	0 (0.0)
Leading to treatment discontinuation	13 (33.3)	8 (42.1)	9 (26.5)
Leading to dose modification	29 (74.4)	13 (68.4)	21 (61.8)

Data cutoff: February 26, 2024.
Adverse events were classified based on MedDRA Version 26.0. and graded for severity using CTCAE v5.0. A TEAE was defined as an adverse event that had an onset date or a worsening in severity from baseline (pretreatment) on or after the first dose of study drug(s) up to 30 days following last dose of study drug(s) or initiation of a new anticancer therapy, whichever occurs first.
TRAEs included those events considered by the investigator to be related or with missing assessment of the causal relationship.
Patients with multiple events for a given Preferred Term were counted once at the Preferred Term levels.
Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; ICC, investigator-chosen chemotherapy; MedDRA, Medical Dictionary for Regulatory Activities; RDI, relative dose intensity; SITRA, sitravatinib; TEAE, treatment-emergent adverse event; TIS, tislelizumab; TRAE, treatment-related TEAE.

Adverse Events by Preferred Term

Adverse events with incidence >25%of patients in any arm	SITRA + TIS (n=39)		SITRA (n=19)		ICC (n=34)	
Patients, n (%)	Any Grade	≥Grade 3	Any Grade	≥Grade 3	Any Grade	≥Grade 3
With ≥1 TEAE	39 (100.0)	26 (66.7)	19 (100.0)	14 (73.7)	34 (100.0)	24 (70.6)
AST increased	16 (41.0)	1 (2.6)	9 (47.4)	0 (0.0)	2 (5.9)	0 (0.0)
ALT increased	13 (33.3)	0 (0.0)	6 (31.6)	0 (0.0)	4 (11.8)	0 (0.0)
Anemia	13 (33.3)	4 (10.3)	5 (26.3)	2 (10.5)	20 (58.8)	6 (17.6)
Hypoalbuminemia	11 (28.2)	1 (2.6)	6 (31.6)	0 (0.0)	9 (26.5)	0 (0.0)
Hypothyroidism	10 (25.6)	0 (0.0)	2 (10.5)	0 (0.0)	0 (0.0)	0 (0.0)
PPE syndrome	10 (25.6)	0 (0.0)	8 (42.1)	4 (21.1)	0 (0.0)	0 (0.0)
Weight decreased	10 (25.6)	1 (2.6)	7 (36.8)	1 (5.3)	9 (26.5)	0 (0.0)
Platelet count decreased	9 (23.1)	1 (2.6)	7 (36.8)	1 (5.3)	6 (17.6)	2 (5.9)
Decreased appetite	8 (20.5)	1 (2.6)	6 (31.6)	0 (0.0)	10 (29.4)	0 (0.0)
Hypertension	8 (20.5)	4 (10.3)	5 (26.3)	2 (10.5)	1 (2.9)	0 (0.0)
Hypokalemia	7 (17.9)	2 (5.1)	5 (26.3)	0 (0.0)	9 (26.5)	1 (2.9)
White blood cell count decreased	7 (17.9)	1 (2.6)	5 (26.3)	0 (0.0)	25 (73.5)	14 (41.2)
Neutrophil count decreased	3 (7.7)	0 (0.0)	5 (26.3)	1 (5.3)	22 (64.7)	13 (38.2)
Nausea	3 (7.7)	0 (0.0)	4 (21.1)	0 (0.0)	12 (35.3)	1 (2.9)

Data cutoff: February 26, 2024.

The most common Any Grade and ≥Grade 3 TEAEs are highlighted for each treatment arm.

Adverse events were classified based on MedDRA Version 26.0. and graded for severity using CTCAE v5.0. A TEAE was defined as an adverse event that had an onset date or a worsening in severity from baseline (pretreatment) on or after the first dose of study drug(s) up to 30 days following last dose of study drug(s) or initiation of a new anticancer therapy, whichever occurs first.

TRAES included those events considered by the investigator to be related or with missing assessment of the causal relationship. Patients with multiple events for a given Preferred Term were counted once at the Preferred Term levels.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; ICC, investigator-chosen chemotherapy; MedDRA, Medical Dictionary for Regulatory Activities; PPE, palmar-plantar erythrodysesthesia; SITRA, sitravatinib; TEAE, treatment-emergent adverse event; TIS, tislelizumab; TRAE, treatment-related TEAE.

Conclusions

- In this phase 2 trial, sitravatinib plus tislelizumab combination therapy and sitravatinib monotherapy demonstrated numerically favorable anti-tumor response in patients with ESCC who progressed on or after anti–PD-1/PD-Ll antibody therapy compared with ICC and were tolerable with acceptable safety profiles
- The survival benefit of sitravatinib monotherapy or in combination with tislelizumab remains to be determined
- As a result of early termination due to modification of sponsor strategy, the sample size was small and data were immature

Abbreviations: ESCC, esophageal squamous cell carcinoma; ICC, investigator-chosen chemotherapy; PD-1; programmed cell death protein-1 ; PD-Ll, programmed death-ligand 1.

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