**SAFFRON-301: Tislelizumab plus sitravatinib in advanced/metastatic NSCLC progressing on/after chemotherapy and anti–PD-(L)1**

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**ABSTRACT**

**Introduction**: There are limited treatment options for patients with advanced NSCLC who were previously treated with chemotherapy and/or anti–programmed cell death protein-1 (PD-1)/–programmed death-ligand 1 (PD-L1) antibodies. Tislelizumab (TIS) is an anti–PD-1 antibody. Sitravatinib (sitra) is a receptor tyrosine kinase inhibitor that can shift the immunosuppressive tumor microenvironment toward an immunostimulatory state. Combining sitravatinib with tislelizumab may potentially overcome initial checkpoint inhibitor resistance. We present efficacy/safety results from an open-label, randomized, phase 3 trial evaluating TIS plus sitra versus docetaxel (doc) in patients with previously treated locally advanced/metastatic NSCLC (NCT04921358).

**Methods**: Adults (≥18 years) with unresectable locally advanced/metastatic histologically or cytologically confirmed NSCLC (ECOG PS ≤1), who were previously treated with ≤2 lines of systemic chemotherapy and anti–PD-(L)1 antibodies were eligible. Patients were randomized (1:1) to TIS 200 mg intravenously once every 3 weeks (Q3W) in combination with sitra 100 mg orally once daily (TIS+sitra) or doc 75 mg/m$^2$ intravenously Q3W. Patients were treated until disease progression, intolerable toxicity, death, or consent withdrawal. Co-primary endpoints were overall survival (OS) and independent-review committee (IRC)-assessed progression-free survival (PFS). Secondary endpoints included IRC-assessed objective response rate (ORR) by RECIST v1.1 and treatment-emergent adverse events (TEAEs).

**Results**: As of Dec 20, 2023, 187 and 190 patients were randomized to TIS+sitra and doc, respectively (median age [TIS+sitra/doc]: 63.0/63.0 years; median follow-up: 8.0/7.6 months). Most patients (TIS+sitra/doc) were male (81.8%/79.5%), Asian (93.6%/93.2%), had an ECOG PS 1 (74.9%/75.8%), had received 1 line of prior chemotherapy (75.9%/73.7%), and had metastatic disease (77.0%/74.2%). Median OS (95% confidence interval [CI]) was 11.5 (9.4–14.6) and 11.4 (9.9–15.0) months with TIS+sitra and doc, respectively; hazard ratio (HR) (95% CI), 1.02 (0.75–1.39). Median IRC-assessed PFS (95% CI) was 4.4 (4.0–5.7) (TIS+sitra) and 2.9 (2.6–4.2) months (doc); HR (95% CI): 0.82 (0.62–1.07). IRC-assessed ORR (95% CI) was 12.3% (8.0%–17.9%) (TIS+sitra) and 12.6% (8.3%–18.2%) (doc). The incidences of TEAEs was higher with TIS+sitra than doc (**Table**). Grade ≥3 TEAEs occurring in ≥5% of TIS+sitra or doc groups were (TIS+sitra/doc): hypertension (13.4%/1.1%), pneumonia (9.1%/8.5%), palmar-plantar erythrodysesthesia syndrome (6.5%/0%), hypokalemia

(5.4%/2.3%), white blood cell count decreased (0%/29.4%), neutrophil count decreased (0.5%/28.8%), neutropenia (0.5%/7.3%), and febrile neutropenia (0%/5.6%). The trial was terminated due to safety risks/unfavorable benefit-risk analysis.

**Conclusions**: In patients with previously treated advanced/metastatic NSCLC, TIS+sitra showed similar efficacy to doc and was associated with a higher incidence of TEAE.

**Table**

| **Patients with treatment-emergent adverse events, n (%)** | **Tislelizumab + sitravatinib (N = 186)** | **Docetaxel (N = 177)** |
|---|---|---|
| Any | 183 (98.4) | 162 (91.5) |
| Grade ≥3 | 121 (65.1) | 100 (56.5) |
| Serious | 83 (44.6) | 66 (37.3) |
| Leading to death | 15 (8.1) | 5 (2.8) |
| Leading to treatment discontinuation (any component) | 45 (24.2) | 15 (8.5) |
| Any Immune-mediated AEs | 91 (48.9) | 18 (10.2) |
| Grade ≥3 | 18 (9.7) | 4 (2.3) |