**BACKGROUND**

Immune checkpoint inhibitor therapy (CIT) targeting the PD-1/PD-L1 pathway produces durable clinical responses in a subset of patients with NSCLC. Sitravatinib is an oral drug that inhibits RTKs, which regulate these immunosuppressive cell types implicated in resistance to CIT. Activating the TAM (TYRO3, AXL, MER) and split family (VEGFR2, c-KIT) RTKs has been associated with acquired resistance to CIT implicated in mediating an immunosuppressive tumor microenvironment, which has emerged as a potential resistance mechanism to CIT. Activation of the TAM (TYRO3, AXL, MER) and split family (VEGFR2, c-KIT) RTKs, which regulate these immunosuppressive cell types implicated in resistance to CIT, is the rationale behind this trial of sitravatinib plus nivolumab versus docetaxel in patients with advanced non-squamous NSCLC who previously experienced radiographic disease progression or on treatment with platinum-based chemotherapy in combination with CIT.

Combining sitravatinib with CIT is a rational approach to enhance the anti-tumor immune response and improving outcomes by overcoming resistance to CIT.

**STUDY OBJECTIVES**

**PRIMARY OBJECTIVE**

To compare overall survival (OS) in patients randomized to treatment with sitravatinib and nivolumab or docetaxel, after disease progression on or after platinum-based chemotherapy in combination with CIT.

**SECONDARY OBJECTIVES**

- To evaluate safety and tolerability of sitravatinib in combination with nivolumab.
- To evaluate secondary efficacy endpoints (including ORR, DOR, PFS per RECIST 1.1).
- To evaluate the pharmacokinetics (PK) of sitravatinib administered in combination with nivolumab.
- To evaluate health-related quality of life and lung cancer-specific symptoms.

**EXPLORATORY OBJECTIVES**

- To assess correlations of baseline tumor PD-L1 expression and gene alterations with treatment-related outcomes.

**METHODS**

**KEY INCLUSION CRITERIA**

- Histologically confirmed non-squamous NSCLC with metastatic or unresectable, locally advanced disease, not amenable to treatment with curative intent.
- Receipt of prior first-line treatment in the advanced disease setting with a platinum-based chemotherapy regimen in combination with a CIT (i.e., anti-PD-1/PD-L1 including nivolumab, pembrolizumab, or atezolizumab), with the result of radiographically documented progression of disease or on after the combination regimen.
- First-line treatment may have included maintenance therapy with a chemotherapy agent (e.g., pemetrexed) and/or a CIT.
- Duration of treatment on prior CIT at least 4 months.
- Adequate bone marrow and organ function.

**STUDY DESIGN**

This randomized (1:1), open-label, global multicenter Phase 3 study compares the efficacy and safety of sitravatinib in combination with nivolumab versus docetaxel in patients with advanced non-squamous NSCLC who previously experienced radiographic disease progression or on treatment with platinum-based chemotherapy in combination with CIT. Patient randomization is stratified based on:

- Duration of previous CIT treatment (< 9 months versus ≥ 9 months).
- Brain metastasis at baseline (presence or absence).
- ECOG Performance Status at baseline (0 versus 1).
- Duration of previous CIT treatment (< 9 months versus ≥ 9 months).
- Other assessments include patient reported outcomes (LCSS, EQ-5D), baseline tumor PD-L1 expression, gene alterations in tumor tissue and in circulating tumor DNA.

**STUDY ASSESSMENTS**

- Routine safety assessments performed throughout the study.
- Disease assessments per RECIST version 1.1.
- PK parameters evaluated after administration of sitravatinib in combination with nivolumab.
- Other assessments include patient reported outcomes (LCSS, EQ-5D), baseline tumor PD-L1 expression, gene alterations in tumor tissue and in circulating tumor DNA.

**SUMMARY**

- Activation of the TAM (TYRO3, AXL, MER) and split family (VEGFR2, c-KIT) RTKs has been implicated in mediating an immunosuppressive tumor microenvironment, which has emerged as a potential resistance mechanism to CIT.
- Sitravatinib is an oral drug that inhibits the TAM family and split family RTKs.
- Combining sitravatinib with CIT is a rational approach to enhance the anti-tumor immune response and overcome CIT resistance.
- This randomized Phase 3 study evaluating sitravatinib plus nivolumab versus docetaxel in non-squamous NSCLC after platinum-based chemotherapy is open for enrollment and recruitment is ongoing.

**REFERENCES**


**ACKNOWLEDGMENT**

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**STUDY TRIAL INFORMATION**

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