Phase 2 Study of Sitravatinib in Combination with Nivolumab in Patients with Advanced or Metastatic Urothelial Carcinoma (UC) after Checkpoint Inhibitor Therapy (CIT)


BACKGROUND

Sitravatinib is hypothesized to sensitize tumors to immune checkpoint inhibitor therapy.

- TAM FAMILY
- SPLIT RTKs
- DDR 1/2
- MET

Checkpoint inhibitor therapy (CIT) produces overall survival benefits and durable clinical responses in a subset of patients with urothelial carcinoma (UC).

Sitravatinib in the Tumor Microenvironment

This study will use Predictive Probability Designs in each patient cohort. CIT-naïve patients may also be evaluated in separate cohorts.

Enrollment is stratified by prior receipt of platinum-based chemotherapy.

METHODS

- To evaluate clinical activity (Objective Response Rate, ORR) of the investigational agent sitravatinib in combination with nivolumab in advanced UC.

- To assess efficacy and tolerability of the combination.
- To evaluate secondary efficacy endpoints.
- To evaluate sitravatinib pharmacokinetics (PK).

EXPERIMENTAL OBJECTIVES

- To assess immune effects on circulating PD-L1 levels, immune cell populations and cytokines.
- To assess effect on tumor cell PD-L1 expression, tumor infiltrating immune cell populations and gene expression signatures.
- To assess correlation of tumor gene alterations in circulation and tumor tissue with treatment outcome.

METHODS

- This open-label Phase 2 study evaluates the tolerability and clinical activity of the investigational agent sitravatinib in combination with nivolumab in patients with advanced or metastatic UC who experienced disease progression on or after CIT as the most recent treatment.

- Patients receive oral sitravatinib once daily (QD) in combination with nivolumab.

- Prior therapies:
  - Brain metastases unless asymptomatic and treated.
  - Prior therapies:
    - Selected immunotherapies (does not apply to Cohorts 3 and 4).
    - Combination therapy with checkpoint inhibitor and cancer therapy having same mechanism of action as investigational agent.
    - Unacceptable toxicity on prior CIT.
    - Active or prior documented autoimmune disease.
    - Active or prior immunosuppressing agents.
    - Unstable angina pectoris, CHF ≥ NYHA Class 3.

- Dosing regimens and assessments

- Patients receive oral sitravatinib once daily (QD) in combination with intravenous nivolumab 240 mg every 2 weeks or 480 mg every 4 weeks.

- Routine safety assessments performed throughout the study.

- Disease assessments per RECIST version 1.1.
- Other assessments include safety, tolerability, PK and changes in PD-L1 expression, tumor and infiltrating immune cell populations, cytokines and gene expression signatures.

- Key inclusion criteria

- Histologically confirmed urothelial (transitional cell) carcinoma with metastatic disease or with unresectable, locally advanced disease.
- Eligible patients must have radiographic progression of disease on or after CIT as the most recent treatment.

- Other assessments include safety, tolerability, PK and changes in PD-L1 expression, tumor and infiltrating immune cell populations, cytokines and gene expression signatures.

- Clinical trial registry number: NCT03606174.

SUMMARY

- The combination of sitravatinib with nivolumab is a rational approach to restoring or enhancing the clinical activity of CIT in patients with immunotherapy resistant urothelial carcinoma.
- The study is open for enrollment and recruitment is ongoing.

REFERENCES