This study will assess the clinical activity of the combination in the neoadjuvant setting and investigate potential immune-based mechanisms of sitravatinib and nivolumab.

**STUDY OBJECTIVES**

- **PRIMARY OBJECTIVE**
  - To evaluate the preoperative clinical activity (point in time objective response) of the combination of sitravatinib and nivolumab in patients with locally-advanced clear cell carcinoma undergoing nephrectomy.

- **SECONDARY OBJECTIVES**
  - To evaluate the safety and tolerability of the combination regimen in the selected population.
  - To characterize the baseline tumor-related immune profile in patients with RCC.
  - To determine the immune effects of sitravatinib and the combination regimen in patients with ccRCC.
  - To evaluate the pharmacokinetics (PK) of sitravatinib administered daily alone and in combination with nivolumab in patients with ccRCC.
  - To characterize the time to surgery.
  - To evaluate secondary efficacy endpoints with the combination regimen in the selected population.

- **EXPLORATORY OBJECTIVE**
  - To evaluate changes in gene expression and the T-cell repertoire in response to therapy in patients with ccRCC.

**METHODS**

- **This study (S16-002) is an open-label, non-randomized, preoperative window of opportunity Phase 2 study of sitravatinib and nivolumab in the neoadjuvant setting for the treatment of patients with locally advanced ccRCC undergoing nephrectomy. Approximately 25 patients with a clinical diagnosis of locally advanced renal tumor will be enrolled into this study in order to identify a total of 18 clinical activity evaluable patients with clear cell histology and detect the primary endpoint of percentage of patients with ccRCC achieving a point in time objective response (either CR or PR) prior to surgery with the combination treatment.**

- **The study is designed to assess the clinical activity of this combination in the neoadjuvant setting and investigate potential immune-based mechanisms of sitravatinib and nivolumab.**

**ON-STUDY ASSESSMENTS**

- **Routine safety assessments** performed throughout the study.

**KEY INCLUSION CRITERIA**

- Imaging results consistent with locally-advanced RCC without evidence of metastatic disease.
- Candidate for partial or radical nephrectomy that extirpates all tumor tissue as part of treatment plan.
- Measurable disease as per RECIST version 1.1.
- ECOG performance status 0 or 1.
- Adequate bone marrow and organ function.

**KEY EXCLUSION CRITERIA**

- Prior systemic anti-tumor treatment for RCC.
- Patients who are receiving any other investigational agents.
- Clinical status indicating that immediate surgery (within 6 weeks) is warranted regardless of whether neoadjuvant therapy is to be administered, as assessed by the treating surgeon.
- Inability to undergo baseline tumor biopsy.
- Active or prior documented autoimmune disease or immunocompromising condition.
- Uncontrolled hypertension.

**REFERENCES**

2. Du W et al. JCI Insight. 2018 Nov 2;3(15).