Phase 3 Trial of Sitravatinib plus Nivolumab vs Docetaxel for Treatment of NSCLC after Platinum-Based Chemoimmunotherapy

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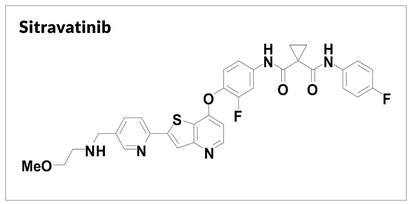
BACKGROUND

Sitravatinib: A Spectrum-selective Receptor Tyrosine Kinase Inhibitor

- Sitravatinib is an oral drug that inhibits a spectrum of related receptor tyrosine kinases (RTKs) including:
  - TAM family (TYRO3, AXL, MER)
    - Cellular IC_{50}: 1 nM
  - Split family (VEGFR, PDGFR, KIT)
    - Cellular IC_{50}: 5-10 nM

Sitravatinib



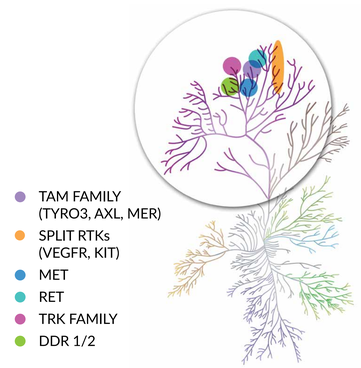


Figure 1. Kinase tree with magnified inset of the tyrosine kinases, showing sitravatinib targets in colored regions

- Immune checkpoint inhibitor therapy (CIT) targeting the PD-1/PD-L1 pathway produces durable clinical responses in a subset of patients with NSCLC
- Putative mechanisms of resistance to CIT include the recruitment of immunosuppressive myeloid-derived suppressor cells (MDSCs), regulatory T cells (Tregs), and M2-polarized macrophages within the tumor microenvironment
- Sitravatinib inhibits the TAM (TYRO3, AXL, MER) family and split family (VEGFR2, c-KIT) RTKs, which regulate these immunosuppressive cell types implicated in resistance in CIT-refractory patients
- Combination of sitravatinib with CIT is a rational approach to augmenting the anti-tumor immune response and improving outcomes by overcoming resistance to CIT
- Promising clinical activity has been observed in an ongoing phase 2 study of sitravatinib plus nivolumab in patients with NSCLC progressing on or after prior CIT

Sitravatinib in the Tumor Microenvironment

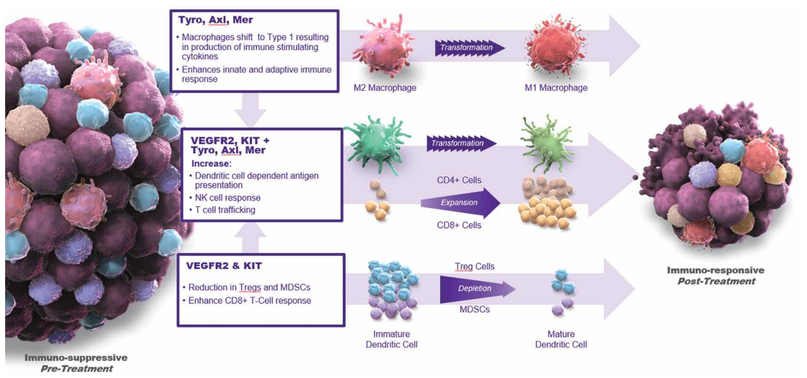


Figure 2. Sitravatinib in the Tumor Microenvironment
Sitravatinib is hypothesized to sensitize tumors to immune checkpoint inhibitor therapy

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 sitravatib 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

- 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 on or after 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)
  - ECOG Performance Status at baseline (0 versus 1)
  - Brain metastasis at baseline (presence or absence)
- Independent Data Monitoring Committee (IDMC) established to review safety at regular intervals and efficacy data at planned interim analyses

STUDY DESIGN

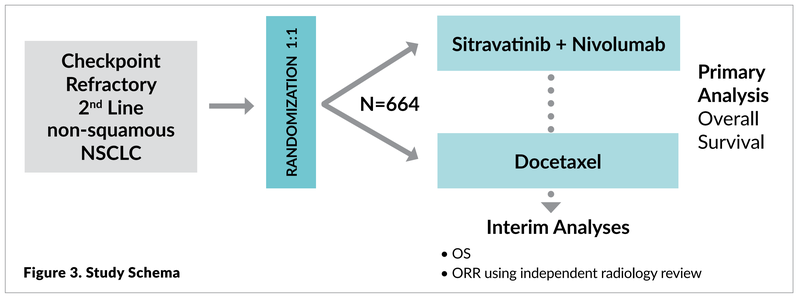


Figure 3. Study Schema

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 on or 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

METHODS

KEY EXCLUSION CRITERIA

- Discontinuation of prior treatment with CIT more than 90 days prior to the date of randomization
- Receipt of systemic cancer therapy since discontinuation of CIT, with the exception of maintenance chemotherapy in the first-line treatment setting
- Active brain metastases, unless treated, asymptomatic and considered neurologically stable
- Prior therapies:
  - Other immunotherapies including anti-CTLA-4, anti-OX40 and anti–CD137
  - Cancer therapy having the same mechanism of action as sitravatinib (e.g., tyrosine kinase inhibitor with a similar target profile or bevacizumab)
- Unacceptable toxicity on prior CIT
- Known history of tumors that test positive for *EGFR*, *ROS1*, *ALK* mutations or ALK fusions

STUDY TREATMENTS

- **SITRAVATINIB + NIVOLUMAB ARM**
  - Cycle length 28 days
  - Oral sitravatinib once daily at 120mg in combination with intravenous Nivolumab* 240mg every 2 weeks or 480mg every 4 weeks
- **DOCETAXEL ARM**
  - Cycle length 21 days
  - Intravenous docetaxel 75mg/m^2 every 3 weeks

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 chemoimmunotherapy is open for enrollment and recruitment is ongoing
- Clinical trial registry number: NCT03906071

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Study Trial Information:
www.mirati.com