A study of MGCD516, a receptor tyrosine kinase (RTK) inhibitor, in molecularly selected patients with NSCLC or other advanced solid tumors

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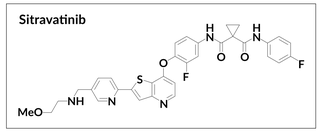
BACKGROUND

- MGCD516 (Sitravatinib) is an oral drug that inhibits a spectrum of related receptor tyrosine kinases (RTKs) including:
  - TAM family (Axl and MERTK) and split family RTKs (VEGFR2 and PDGFRA):
    - Target cellular potency range < 10 nmol/L
  - RET, MET, DDR2, TrkA:
    - Target cellular potency range 10-25 nmol/L



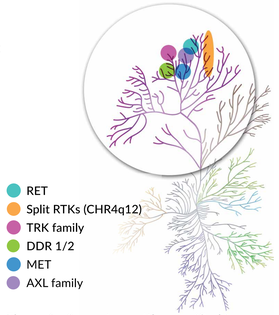


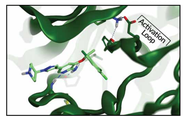
Figure 1. Kinase tree with magnified inset of the tyrosine kinases showing sitravatinib targets in colored regions

- RTKs inhibited by sitravatinib are genetically altered in a variety of cancers:
  - Function as oncogenic drivers
  - Have a potential role in tumor resistance mechanisms
  - Mediate suppression of tumor immunity
- Several RTK targets of sitravatinib are dysregulated in non-small cell lung cancer (NSCLC):
  - RET rearrangements in lung adenocarcinoma (2%)
  - Chromosome 4 amplicon (KIT/PDGFRA/KDR) (2-3%)
  - NTRK family rearrangements and mutations (up to 2%)
  - DDR2 mutations in lung squamous cell carcinoma
  - CBL loss of function mutations (2-4%); CBL is an ubiquitin ligase involved in MET, AXL, PDGFR/KIT degradation and signal attenuation

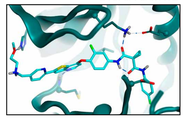
Sitravatinib's Binding Mode

- Binds as a DFG-out Type II kinase inhibitor
- Inhibits the RET gatekeeper mutation variant V804M associated with theoretical resistance to RET inhibitors
- Inhibits NTRK1 resistance mutation variants including G595R and G667C implicated in acquired resistance to NTRK family inhibitors in clinical studies
- Inhibits MET mutation variants, including D1228H/N and Y1230A/C/D/H, implicated in intrinsic and/or acquired resistance to Class I MET inhibitors in both preclinical and clinical studies

Crizotinib



Sitravatinib



- Sitravatinib demonstrates tumor growth inhibition across patient-derived xenograft models, with tumor regression occurring predominantly in NSCLC models driven by dysregulated sitravatinib RTK targets (Figure 2A and 2B).

Pre-Clinical Tumor Growth Models Sitravatinib 20mg/kg

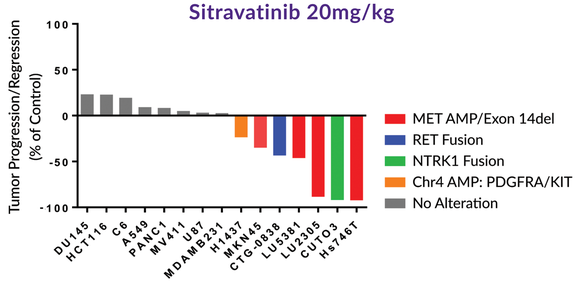


Figure 2A.
Sitravatinib induces significant tumor regression in genetically defined cancer models

Champions CTG-0838 PDX *(KIF5B-RET)*

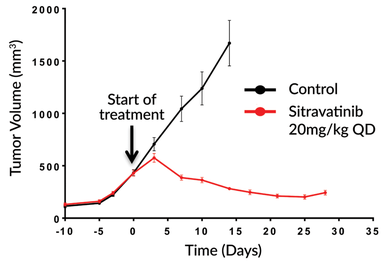


Figure 2B.
Potent anti-tumor activity of sitravatinib in PDX NSCLC model driven by *KIF5B-RET* fusion

STUDY OBJECTIVES

PRIMARY OBJECTIVE:

- To characterize the safety profile of sitravatinib
- To characterize the pharmacokinetic (PK) parameters of sitravatinib
- To evaluate the clinical activity of sitravatinib in patients selected by diagnosis and/or tumor gene alteration

SECONDARY OBJECTIVES:

- To characterize sitravatinib metabolites
- To explore potential pharmacodynamic (PD) markers in plasma
- To identify sitravatinib dose and regimen for further investigation of clinical activity
- To explore use of tumor molecular markers for selection of patients with increased potential for response to sitravatinib

EXPLORATORY OBJECTIVES:

- To assess the change in genetic alteration status in circulating tumor DNA (ctDNA) upon sitravatinib treatment in the selected population

METHODS

STUDY DESIGN:

- Multi-center, open label Phase 1/1b study evaluating safety, PK, metabolism, PD, and clinical activity of sitravatinib in patients with advanced solid tumor malignancies (NCT02219711)

PHASE 1 DOSE ESCALATION:

- Explore dose/regimen and select Phase 1b dose using the mTPI design[1] (completed).

PHASE 1B DOSE EXPANSION:

- Evaluate sitravatinib in selected patient populations:
  - Tumors harboring genetic alterations resulting in dysregulation of sitravatinib's RTK targets:
    - NSCLC with activating genetic alteration in *RET, KDR, PDGFRA, KIT, NTRK, DDR2, MET, AXL*, or with loss of function mutation in *CBL*
    - Any solid tumor malignancy with genetic alteration of sitravatinib RTK targets or *CBL*
  - mRCC refractory to VEGF pathway inhibitors (simultaneously targeting MET and VEGFR)
  - CRPC with bone metastases
- An optimal Simon 2-stage study design will be applied to each molecularly selected Phase1b cohort, assuming $p_0 = 0.15$ and $p_1 = 0.35$
  - Stage 1: 8 patients
  - Stage 2: Additional 16 patients to a total of 24 patients Potential to expand up to 70 patients

KEY INCLUSION CRITERIA:

- Histologically confirmed advanced metastatic or unresectable solid tumor malignancy
- Selected diagnosis or displaying tumor genetic alteration of sitravatinib RTK targets or *CBL*
- ECOG performance status 0, 1 or 2
- Adequate bone marrow and organ function

KEY EXCLUSION CRITERIA:

- Concurrent uncontrolled illness
- Significant cardiac abnormality within past 6 months, such as myocardial infarction or congestive heart failure of NYHA Class ≥ 3
- QTc interval > 480msec; LVEF < 40%
- Uncontrolled arterial hypertension
- Recent history of significant hemoptysis / hemorrhage
- Symptomatic or uncontrolled brain metastases
- Prior therapy targeting tumor molecular marker of interest

DOSING REGIMEN AND ASSESSMENTS:

- Patients receive oral sitravatinib at 150mg once daily (QD) in continuous 21 day cycles
- Routine safety assessments performed throughout the study
- Disease assessments every 6 weeks using RECIST version 1.1
- PK parameters evaluated after single and repeated administrations
- PD biomarkers soluble (s)MET, sVEGFR2, VEGFA explored in plasma samples
- ctDNA collection at several time points throughout the study

SUMMARY

- Sitravatinib is a potent inhibitor of several RTKs that act as oncogenic drivers
  - Has demonstrated anti-tumor activity in NSCLC models driven by dysregulated sitravatinib RTK targets
  - Binds in DFG-out binding mode resulting in inhibition of mutations implicated in resistance to RET, MET and TRK inhibitors
- This Phase 1b study evaluates sitravatinib in molecularly selected patients with NSCLC or other tumor types harboring:
  - Activating genetic alteration in *RET, NTRK, DDR2, MET* or *AXL*
  - Amplification of Chromosome 4q12 (*KDR/PDGFR/KIT*)
  - Loss of function mutations of *CBL*
- Enrollment is currently ongoing in the United States, with expansion to South Korea and potentially Europe in 2017

REFERENCES

1. Ji Y, Wang SJ, Modified toxicity probability interval design: a safer and more reliable method than the 3 + 3 design for practical phase I trials, *Journal of Clinical Oncology*, 2013, 31:1785-1791

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Study Trial Information: **www.mirati.com**