A First-in-Human Phase 1 Study of Receptor Tyrosine Kinase (RTK) Inhibitor MGCD516 in Patients with Advanced Solid Tumors

2575

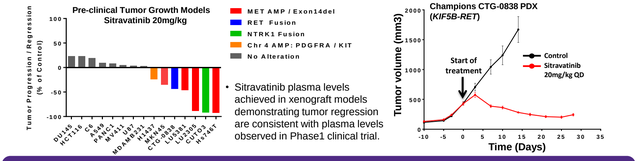
Todd M. Bauer[1], Douglas Adkins[2], Gary K. Schwartz[3], Theresa L. Werner[4], Ajjai S. Alva[5], David S. Hong[6], Richard D. Carvajal[3], Mansoor N. Saleh[7], Lyudmila Bazhenova[8], Sanjay Goel[9], Keith D. Eaton[10], Robert D. Siegel[11], Ding Wang[12], Richard C. Lauer[13], Saskia Neuteboom[14], Demiana Faltaos[14], Isan Chen[14], James Christensen[14], Richard Chao[14], Rebecca Suk Heist[15]

[1]Sarah Cannon Research Institute/Tennessee Oncology, PLLC, Nashville, TN; [2]Washington University School of Medicine, St. Louis, MO; [3]Columbia University Medical Center, New York, NY; [4]The Huntsman Cancer Institute, Salt Lake City, UT; [5]University of Michigan, Ann Arbor, MI; [6]The University of Texas MD Anderson Cancer Center, Houston, TX; [7]University of Alabama, Birmingham, AL; [8]University of California San Diego Moores Cancer Center, La Jolla, CA; [9]Montefiore Einstein Center for Cancer Care, Bronx, NY; [10]University of Washington, Seattle, WA; [11]Bon Secours St. Francis Cancer Center, Greenville, SC; [12]Henry Ford Health Systems, Detroit, MI; [13]University of New Mexico Comprehensive Cancer Center, Albuquerque, NM;[14]Mirati Therapeutics, San Diego, CA; [15]Massachusetts General Hospital Cancer Center, Boston, MA

Background

- MGCD516 (Sitravatinib) is an oral drug that inhibits a spectrum of related 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.
- Targets of sitravatinib are genetically altered in a variety of cancers:
  - Function as oncogenic drivers; have a potential role in tumor resistance mechanisms.
    - Several targets of sitravatinib are dysregulated in NSCLC
      - *RET* rearrangements in lung adenocarcinoma (2%)
      - Chromosome 4 amplicon (*KIT/PDGFRA/KDR*) (2-3%)
      - *CBL* loss of function mutations (2-4%); CBL is negative regulator for MET, AXL, PDGFR/KIT signaling
      - *NTRK* family rearrangements and mutations (up to 2%)
      - *DDR2* mutations in lung squamous cell carcinoma.
  - Mediate suppression of tumor immunity (MERTK, Axl).
- Sitravatinib demonstrates tumor growth inhibition across patient-derived xenograft models, with frank tumor regression occurring predominantly in NSCLC models driven by dysregulated sitravatinib RTK targets (Figure 1).

Figure 1. Sitravatinib Induces Significant Tumor Regression in Genetically Defined Lung Cancer Models



- Sitravatinib plasma levels achieved in xenograft models demonstrating tumor regression are consistent with plasma levels observed in Phase1 clinical trial.

Study Objectives

Primary Objectives:
- To characterize the safety profile and tolerability of sitravatinib
- To characterize the PK of sitravatinib
- To evaluate the clinical activity of sitravatinib in patients selected based upon diagnosis and/or tumor gene alteration.

Secondary Objectives:
- To characterize sitravatinib metabolites
- To explore potential PD markers in blood plasma
- To identify sitravatinib dose and regimen for investigation of clinical activity
- To explore use of tumor molecular markers for selection of patients with increased potential for response to sitravatinib.

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.

Dose Escalation:
- Phase 1: Explore dose/regimen and define viable Phase 1b dose using the mTPI design[1]. 3 to 5 molecularly unselected patients are enrolled per dose level cohort.

Dose Expansion:
- Phase 1b: Evaluation of sitravatinib in selected patient populations:
  - Tumors with a Molecular Profile of interest:
    - NSCLC with genetic alteration in *RET, NTRK, DDR2, MET, AXL, KDR, PDGFRA, KIT, CBL*
    - Any solid tumor malignancy with genetic alteration of sitravatinib RTK targets or of *CBL*.
  - mRCC refractory to VEGF pathway inhibitors (simultaneously targeting MET and VEGFR).
  - CRPC with bone metastases.

Key Entry Criteria:
- Advanced metastatic or unresectable solid tumor malignancy
- ECOG performance status 0,1 or 2
- Adequate bone marrow and organ function
- No symptomatic or uncontrolled brain metastases
- Expansion Phase 1b:
  - Selected diagnosis or displaying tumor genetic alteration of sitravatinib RTK targets or of *CBL*.

Dosing Regimen and Assessments:
- Patients receive oral sitravatinib once daily (QD) in cycles of 21 days
- Routine safety assessments performed throughout the study
- Disease assessments every 6 to 9 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.

Results

Patient Characteristics and Disposition:
- As of 20 Apr 2016, 52 patients (pts) have been enrolled (Table 1)
  - 32 molecularly unselected pts in the Phase 1 dose escalation
  - 8 pts with qualifying mutated, amplified or rearranged tumor RTK genes (Table 2), 4 RCC and 8 CRPC pts in Phase 1b.
- Treatment has been discontinued in 31 (60%) pts; primary reasons were disease progression (n=17), clinical progression (n=6), withdrawal by subject (n=4), adverse events (n=2), and other (n=2).

Table 1. Patient and Disease Characteristics

Baseline Characteristics, N=52		n (%)
Age	Median (range)	64 (27-85) years
Gender	Female / Male	22/30 (42%/58%)
Race	White	42 (81%)
	Black	2 (4%)
	Asian	2 (4%)
	Other/Unknown	6 (12%)
Performance Status	ECOG 0 / ECOG 1	21 (40%) / 31 (60%)
Primary Diagnosis	Prostate Cancer	11 (21%)
	Renal Cell Carcinoma	7 (13%)
	Non-small Cell Lung Cancer	6 (12%)
	Soft Tissue Sarcoma	6 (12%)
	Colon Cancer	5 (10%)
	Endometrial Carcinoma	3 (6%)
	Other	14 (27%)

Table 2. Phase 1b Patients with Altered Sitravatinib Targets in Tumor Tissue

Phase 1b Qualifying Altered Tumor Genes		
Gene	**Tumor Type**	**n**
RET	NSCLC	3
	Colorectal Cancer	1
	Thyroid Carcinoma	1
KDR	Angiosarcoma	1
MET	Adenoid Cystic Carcinoma	1
AXL	Bladder Cancer	1

Dose Escalation and Dose Limiting Toxicity:
- 32 pts were enrolled in the dose escalation phase. Doses ranged from 10-200 mg QD on a 21-day, continuous dosing regimen. 1 DLT was reported at 80 mg, and 3 DLTs were observed at 200 mg, exceeding the MTD (Table 3).
- Phase 1b dose: 150 mg QD in cycles of 21 days.

Table 3. Dose Levels and Dose Limiting Toxicity.

Dose Level, QD	Evaluable Patients, n	DLT
10 mg	4	None
20 mg	4	None
40 mg	5	None
80 mg	6*	1 Grade 3 Palmar-plantar erythrodysesthesia
110 mg	3*	None
150 mg	4	None
200 mg	3*	Grade 2 Neuropathy, Fatigue, Mucositis (1pt each)

*1 patient not evaluable for DLTs in this cohort

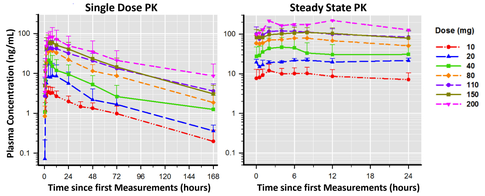
Safety:
- As of 20 Apr 2016, the most frequently reported treatment-related AEs (all grades, >15%) were fatigue, diarrhea, hypertension, nausea, decreased appetite and vomiting (Table 4).
- No treatment-related grade 5 AEs have been reported.
- One treatment-related grade 4 AE (febrile neutropenia) was reported and resolved within 5 days; pt has subsequently received 4+ months of treatment and remains on study.

Table 4. Treatment-related Adverse Events in >15% of the Patients

Treatment-related AEs Preferred Term	All Grades AEs All Dose Levels (N=51)	Grade 3 AEs All Dose Levels (N=51)	Grade 4 AEs All Dose Levels (N=51)
Fatigue	17 (33%)	1 (2%)	0
Diarrhea	14 (28%)	2 (4%)	0
Hypertension	12 (24%)	7 (14%)	0
Nausea	10 (20%)	0 (0%)	0
Decreased Appetite	9 (18%)	0 (0%)	0
Vomiting	8 (16%)	0 (0%)	0

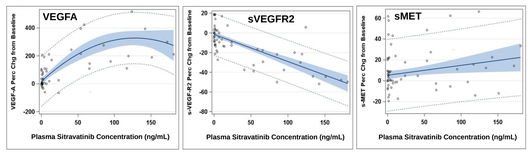
Clinical Pharmacokinetics Summary:
- PK parameters were evaluated for 32 pts in dose escalation and 12 pts in Phase1b.
- Plasma exposure levels increased dose proportionally.
- After single dose administration, median t_{max} was 3 to 9 hours; mean $t_{½}$ ranged from 40-53 hours.
- Steady state PK was reached in 11-15 days.
- Drug accumulation observed after multiple dosing and averaged 2.6-fold for C_{max} and 3.1-fold for AUC_{0-24}.
- 150 mg QD dose resulted in a steady state geometric mean C_{avg}, C_{max} and AUC of 88.9 ng/mL, 111 ng/mL and 2133 ng•h/mL, respectively.

Figure 2. Sitravatinib Plasma Concentrations Following Single Dose and Multiple Dose Administration



Clinical Pharmacodynamic Summary:
- VEGFA, sVEGFR2 and sMET levels in human plasma have been utilized as PD target modulation markers for VEGFR or MET inhibitors, respectively.
- Sitravatinib showed plasma concentration-dependent modulation of each biomarker.
- The mean prediction (95% CI) percent change from baseline in biomarker modulation with exposure (Figure 3), approached: VEGFA (400% increase), sVEGFR2 (60% decrease) and sMET (35% increase), consistent with VEGFR and MET inhibition.

Figure 3. Pharmacodynamic Biomarkers in Patient Plasma



Linear regression (sVEGFR2 and sMET), quadratic regression (VEGFA) with 95% Confidence Interval indicated by shaded area

Clinical Activity:
- In Phase 1 molecularly unselected pts, prolonged stable disease was observed with 7 pts completing at least 6 cycles of treatment, including 1pt with hepatocellular carcinoma completing 15 cycles and 2 pts (renal cell carcinoma; thymoma) receiving treatment in C9 and C12, respectively as of 1 May 2016.
- In Phase 1b, decreases in target lesions have been reported (Figure 4); a confirmed PR has been observed in clear cell renal cell carcinoma (Figure 5); and significant bone scintigraphy response was observed in a patient with CRPC.

Figure 4. Phase 1b Activity in Evaluable Patients at 150 mg Dose Level

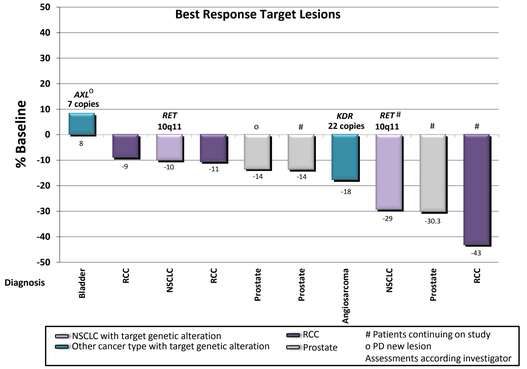
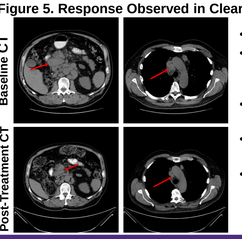


Figure 5. Response Observed in Clear Cell RCC



- 68 year old male with clear cell RCC.
- Previously underwent right nephrectomy followed by treatment with sunitinib, capecitabine, and thrice weekly, subcutaneous interferon injections.
- Entered the study with abdominal and mediastinal lymphadenopathy.
- Achieved a partial response at week 9, which was confirmed at week 15.
- Pt continuing on study in week 24, as of 10 May 2016.

Conclusions

- Sitravatinib (MGCD516) is a potent inhibitor of several RTKs that act as oncogenic drivers.
- Phase 1 dose escalation has been completed with recommended Phase 1b dose of 150 mg QD.
- Pharmacokinetics are linear, long elimination half life (40-53 hours), 3-fold drug accumulation with steady state reached in 11-15 days.
- Pharmacodynamic biomarkers demonstrate target modulation.
- Tolerable safety profile with manageable AEs consistent with on-target inhibition.
- Clinical activity has been demonstrated in clear cell RCC, NSCLC and CRPC.
- Further evaluation of sitravatinib is warranted in pts with refractory RCC and in selected pts with NSCLC and other tumors harboring genetic alteration in *RET, NTRK, DDR2, CBL,* or Chromosome 4 amplicon.

References:

1. Modified Toxicity Probability Interval Design: A Safer and More Reliable Method than the 3+3 Design for Practical Phase I Trials, 2013 *Journal of Clinical Oncology 31:1785-1791.*