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

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Background

- MGCD516 is an oral drug that inhibits a spectrum of related RTKs including:
  - RET, TRK and DDR family members
  - Split RTK families including VEGFR, PDGFR and KIT
  - MET and TAM family (including Axl and Mer)
- RTKs inhibited by MGCD516 are genetically altered in a variety of cancers where they function as oncogenic drivers and play a potential role in tumor resistance mechanisms.
- MGCD516 has demonstrated cytoreductive anti-tumor activity in preclinical tumor models with:
  - *RET* Rearrangement
  - *TRK* Rearrangement
  - Chromosome 4q12 amplification *(PDGFRA, KIT, KDR gene loci)*

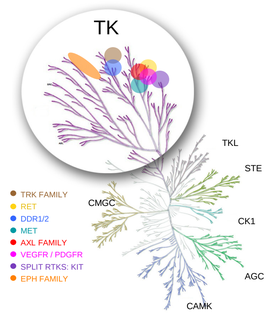
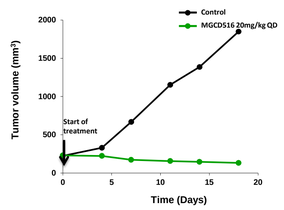


Figure 1. Kinase Tree With Magnified Inset of the Tyrosine Kinases Showing MGCD516 Targets in Colored Regions

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



B. CUTO3 Xenograft (*MPRIP-NTRK1*)

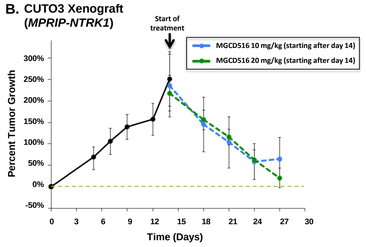


Figure 2. Potent Cytoreductive Activity of MGCD516 in PDX Models Driven by *RET* and by *NTRK1*. A. In a *KIF5B-RET* NSCLC model, 43% tumor regression was observed on Day 18[1]. B. In a *MPRIP-NTRK1* NSCLC model, mice were treated after day 14 with either 10 or 20 mg/kg MGCD516, resulting in tumor regression[2].

- NSCLC exhibiting genetic alteration of MGCD516 RTK targets have been reported
  - *RET* rearrangements in lung adenocarcinoma (2%)
  - *NTRK* family rearrangements and mutations (up to 2%)
  - *DDR2* mutations in lung squamous cell carcinoma
  - Chromosome 4 amplicon (*KIT/PDGFRA/KDR*) (2-3%)
  - Negative regulators for MET, AXL, PDGFR/KIT signaling: *CBL* mutations (2-4%)
- TAM and Split family RTKs mediate tumor immune surveillance, suggesting the utility of MGCD516 in combination with immune checkpoint inhibitors.
- In RCC, MET and HGF act as key resistance factors to VEGFR TKIs, and simultaneous inhibition of MET and VEGFR family members may circumvent resistance.

Study Objectives

Primary Objectives:

- To characterize the safety profile and tolerability of MGCD516
- To characterize the PK of MGCD516

Secondary Objectives:

- To characterize MGCD516 metabolites
- To explore potential PD markers in blood plasma
- To identify MGCD516 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 MGCD516

Methods

Study Design:

- Multi-center, open label Phase 1/1b study evaluating Safety, PK, Metabolism, PD and Clinical activity of MGCD516 in patients with advanced solid tumor malignancies.

Dose Escalation:

- Phase 1: Explore dose/regimen and define MTD/viable Phase 1b dose using the mTPI design[3]. 3 to 5 unselected patients are enrolled per dose level cohort.
  - mTPI design:
    - Bayesian statistical framework.
    - Beta/binomial model to compute posterior probabilities of underdosing, proper dosing or overdosing as compared to target toxicity probability (p_T). This study p_T=0.3 and n=30.
    - All dose-escalation decisions calculated before start of trial.

Dose Expansion:

- Phase1b: Evaluation of MGCD516 in stratified patient populations:
  - Tumor Molecular Profile of interest
    - NSCLC with genetic alteration in *RET, NTRK, DDR2, MET, AXL, PDGFRA, KIT, CBL*
    - Any solid tumor type with genetic alteration of MGCD516 RTK targets.
  - Selected Diagnosis (simultaneously targeting MET and VEGFR)
    - mRCC refractory to VEGF pathway inhibitors

Key Inclusion Criteria:

- Advanced metastatic or unresectable solid tumor malignancy
- ECOG performance status 0 or 1
- Adequate bone marrow and organ function
- Expansion Phase1b:
  - Selected diagnosis or displaying tumor genetic alteration of MGCD516 RTK target loci

Key Exclusion Criteria:

- Symptomatic or uncontrolled brain metastases
- Significant cardiovascular abnormality such as MI or CHF ≥ Class 3 within past 12 months, QTc interval > 450msec, LVEF < 50%, or uncontrolled arterial hypertension
- Recent history of significant hemoptysis / hemorrhage
- Expansion Phase1b:
  - Prior therapy targeting tumor molecular marker of interest

Dosing Regimen and Assessments:

- Patients receive oral MGCD516 once daily (QD) in cycles of 21 days.
- Routine safety assessments performed throughout the study.
- Disease assessments every 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 26 Aug 2015, 28 unselected patients (pts) have been enrolled in the dose escalation phase (Table 1.)
- Treatment has been discontinued in 19 (68%) pts; primary reasons were Disease Progression (n=10), Symptomatic Deterioration (n=2), Withdrawal by Subject (n=1), Adverse Events (n=0), and Other (n=6).

Table 1. Patient and Disease Characteristics.

Baseline Characteristics, N=28		n (%)
Age	Median (range)	60 (27-85) years
Gender	Female / Male	16/12 (57%/43%)
Race	White	20 (71%)
	Black	1 (4%)
	Asian	2 (7%)
	Other/Unknown	5 (18%)
Performance Status	ECOG 0 / ECOG 1	15 (54%) / 13 (46%)
Primary Diagnosis	Soft Tissue Sarcoma	5 (18%)
	Colon Cancer	4 (14%)
	Endometrial Cancer	3 (11%)
	Non-small Cell Lung Cancer	3 (11%)
	Prostate Cancer	3 (11%)
	Renal Cell Carcinoma	2 (7%)
	Other (1 each)	8 (29%)

Dose Escalation and Dose Limiting Toxicity:

- 28 pts have been enrolled into 6 different dose level cohorts, receiving a single dose for PK profiling followed by continuous, QD MGCD516 administration.
- Starting dose was 10 mg with dose escalation steps of 100% until observation of 1 DLT (Grade 3 Palmar Plantar Erythrodysesthesia) at 80 mg. Subsequent dose escalation steps were in smaller increments; no DLTs were observed at the 110 and 150 mg dose level (Table 2.)

Table 2. 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	Ongoing	

*1 patient not evaluable for DLTs in this cohort

Safety:

- As of 26 Aug 2015, the most frequently reported AEs (all grades, > 25%) regardless of drug relationship were: fatigue, diarrhea, cough, hypertension, nausea and vomiting (Table 3.)
- Treatment related Grade 3 AE in >1pt observed: hypertension in 3 pts (11%).
- No treatment related SAEs or treatment related Grade 4/5 AEs have been reported.

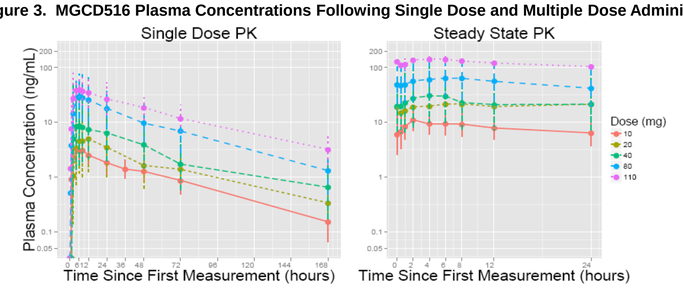
Table 3. Treatment-Emergent Adverse Events (TEAEs) in > 15% of the patients

All Causality AEs, Preferred Term	Total AEs All Dose Levels (N=28)	Grade 3 AEs All Dose Levels (N=28)	Grade 4 AEs All Dose Levels (N=28)
Fatigue	12 (43%)	2 (7%)	0
Diarrhea	10 (36%)	2 (7%)	0
Cough	8 (29%)	0	0
Hypertension	8 (29%)	4 (14%)	0
Nausea	8 (29%)	1 (4%)	0
Vomiting	8 (29%)	1 (4%)	0
Decreased Appetite	5 (18%)	1 (4%)	0
Dyspnea	5 (18%)	1 (4%)	0

Clinical Pharmacokinetics Summary:

- Single Dose PK parameters were evaluated for 24 pts and Steady State PK parameters for 20 pts.
- Plasma exposure levels increased dose proportionally.
- After single administration, median t_{max} was 3 to 9 hours; mean $t_{½}$ ranged from 40-53 hours.
- Steady state PK is reached in 11-15 days.
- Drug accumulation observed after multiple dosing, averaged 4.2-fold for C_{max} and 4.7-fold for AUC_{0-24}.
- At 110 mg dose level, mean C_{avg}, C_{max} and AUC at steady state were 123 ng/mL, 151 ng/mL and 2950 ng•h/mL respectively.

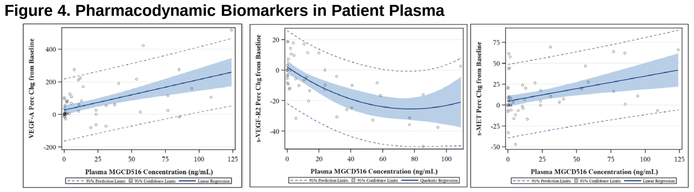
Figure 3. MGCD516 Plasma Concentrations Following Single Dose and Multiple Dose Administration



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.
- MGCD516 showed plasma concentration dependent modulation of each biomarker.
- Biomarker modulation observed (Figure 4.): VEGFA (300% increase), sVEGFR2 (35% decrease) and sMET (60% increase), approached near maximal modulation levels (based on historical RTKi data).

Figure 4. Pharmacodynamic Biomarkers in Patient Plasma



Linear regression (VEGF-A and sMET), quadratic regression (sVEGF-R2) with 95% Confidence Interval indicated by shaded area

Clinical Activity in Unselected Patients during Phase 1 Dose Escalation:

- Prolonged stable disease has been observed with 6 pts completing at least 5 cycles of treatment, including 1pt with liposarcoma completing 8 cycles and 2 pts (renal cell carcinoma; hepatocellular carcinoma) receiving treatment in C7 and C9, respectively as of 4 Sep 2015.

Conclusions

- Phase 1 dose escalation ongoing in unselected patients, currently evaluating dose level of 200 mg QD.
- Tolerable safety profile with manageable AEs consistent with target inhibition.
- Pharmacokinetics show linearity, long elimination half life (40-53 hours), 4-5 fold drug accumulation with steady state reached in 11-15 days.
- Clinical exposure levels of MGCD516 have reached levels where tumor response in RTK-target-driven nonclinical tumor models has been observed.
- Pharmacodynamic biomarkers illustrate target modulation.
- Selected patients with NSCLC or other tumors and with genetic alteration in *RET, NTRK, DDR2, CBL,* or Chromosome 4 amplicon or patients with treatment-refractory metastatic RCC will be recruited in Phase 1b expansion cohorts to evaluate clinical activity.

References:

1. "Preclinical Development of Novel Small Molecule Inhibitors of Receptor Tyrosine Kinases Involved in Resistance to Targeted Therapies" presented at the GTC 8th Protein Tyrosine Kinase Meeting. July 8-9, 2013, Boston, MA.
2. Doebele et al, 2015, presented at IASLC World Conference on Lung Cancer (MINI14.04). September 6-9, 2015 Denver, CO.
3. 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.*