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 related spectrum of RTKs including:
 - RET, TRK and DDR family members
 - Split RTK families including VEGFR, PDGFR and KIT
 - MET and TAM family
- RTKs inhibited by MGCD516 are genetically altered in a variety of cancers functioning as oncogenic drivers and involved in tumor resistance mechanisms.
- MGCD516 has demonstrated cytoreductive anti-tumor activity and tumor regression in preclinical tumor models displaying:
 - RET Rearrangement
 - TRK Rearrangement
 - Chromosome 4q12 amplification (PDGFRA, KIT, KDR gene loci)



- NSCLC exhibiting genetic alteration of MET, AXL, RET, DDR2, and NTRK family have been reported
 - RET rearrangements in lung adenocarcinoma (2%)
 - NTRK family rearrangements and mutations (up to 2%)
 - DDR2 mutations in lung SCC
 - Chromosome 4 amplicon (KIT/PDGFRA/KDR) (2-3%)
 - Negative regulators for MET, AXL, PDGFR/KIT signaling: CBL mutations (2-4%)

Study Objectives

Primary Objectives:

- To characterize safety and tolerability profile 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 design².
- 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_τ*). This study *p_τ*=0.3 and n=30.
 - All dose-escalation decisions pre-calculated before start of trial.

Dose Expansion:

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

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:

- Concurrent uncontrolled illness
- Significant cardiac abnormality within past 12 months, such as MI or CHF ≥ Class 3
- QTc interval > 450msec; LVEF < 50%
- Uncontrolled arterial hypertension
- · Recent history of significant hemoptysis / hemorrhage
- Symptomatic or uncontrolled brain metastases
- 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 using RECIST version 1.1.
- · PK parameters evaluated after single and repeated administrations.
- · PD Biomarkers soluble (s)MET, sVEGFR2, VEGFA and sAXL explored in plasma samples.

Summary

Dose Escalation Phase 1:

- · Started in September 2014.
- · First three cohorts (10mg, 20mg and 40mg MGCD516 QD) completed without DLTs.
- Cohort 4, 80mg: 1 DLT, Grade 3 palmar plantar erythrodysesthesia syndrome.
- Cohort 5, 110mg: Started May 2015 and is ongoing.

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.
- 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.