**Background**

- MGCD265 is an oral, potent, small molecule RTK inhibitor of MET and Axl, which are important for mediating signals for cell growth, survival, and migration.
- MGCD265 binds to MET within a hydrophobic pocket induced in the DFG "out" conformation and thus inhibits both wild-type and mutant species including those harboring mutations in the activation loop.
- MET signaling is dysregulated in ~7% of NSCLC through the following mechanisms:
  - MET gene amplification
  - MET exon 14 splice site mutations
  - Activating point mutations in MET
- These genetic alterations result in MET functioning as an oncogenic driver and promoting cancer development and progression.
- The MET gene is highly amplified (>8 gene copies) in 2-3% of NSCLC resulting in increased expression and ligand-independent activation of MET-dependent signaling
- MET splice site mutations resulting in the deletion of exon 14 (METex14del) represent a novel class of genetic alterations. Exon 14 encodes the Y1003 CBL ubiquitin ligase regulatory binding site that mediates CBL-dependent MET degradation and signal attenuation. Deletion of this region of the MET protein results in sustained activation and downstream signaling. MET mutant variants are also frequently further dysregulated through selective gene copy gains or amplification of the MET mutant allele.
- MGCD265 has demonstrated anti-tumor efficacy with robust tumor regression in xenograft models of METex14del and MET amplification. Additionally, confirmed partial responses have been observed in patients with MET-altered NSCLC treated with MGCD265 in the Phase 1 setting.

**Study Objectives**

- To determine the tumor response to MGCD265 in the selected patient population.
- To evaluate the safety and tolerability of MGCD265 in the selected population
- To evaluate secondary efficacy endpoints with MGCD265 treatment in the selected population
- To assess correlation between selected tumor gene alterations using different analytical techniques in tumor tissue and ctDNA
- To assess change in genetic alteration status in ctDNA with MGCD265 treatment over time in the selected population

**Methods**

**Dosing Regimen and Assessments:**
- Patients receive oral MGCD265 twice daily (BID) 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 administration
- ctDNA collection at key time points throughout study

**Summary**

- MGCD265 is a potent and selective inhibitor of MET
- MGCD265’s unique binding mode inhibits wild-type and a broad range of mutant MET species
- The Amethyst NSCLC trial evaluates the activity of MGCD265 in patients with NSCLC with genetic alterations in MET
- Enrollment began in April 2016 and is ongoing in the United States, Canada, South Korea, Taiwan, Australia, Hungary, and Italy

**References**

2. Phase I study of receptor tyrosine kinase (RTK) inhibitor, MGCD265, in patients (pts) with advanced solid tumors. J Clin Oncol 33, 2015 (suppl; abstr 2589)

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Study Trial Information: www.mirati.com