Phase 2, Parallel-Arm Study of Receptor Tyrosine Kinase (RTK) Inhibitor MGCD265 in Patients (pts) with Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC) with Activating Genetic Alterations in Mesenchymal-Epithelial Transition Factor (*MET*)

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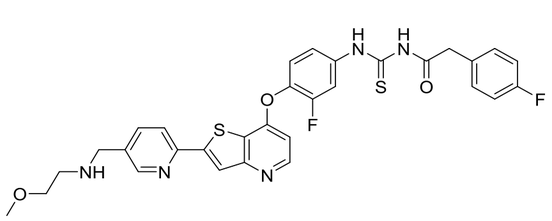
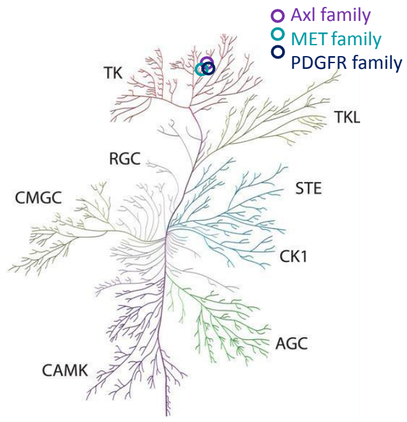
Background



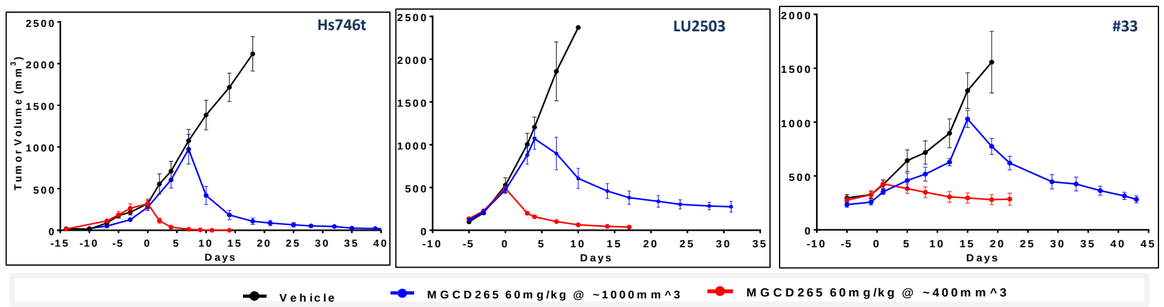
- MET signaling is dysregulated in ~7% of NSCLC through the following mechanisms:
  - *MET* gene amplification
  - *MET* exon 14 splice site mutations
  - Activating point mutations in *MET*
- These genetic alterations result in MET functioning as an oncogenic driver and promoting cancer development and progression[1]
- 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 (*MET*ex14del) 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 *MET*ex14del and *MET* amplification. Additionally, confirmed partial responses have been observed in patients with *MET*-altered NSCLC treated with MGCD265 in the Phase 1 setting[2]

- 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.



Gastric Xenograft Model with *MET* ex14del and *MET* Amplification

Lung Adenocarcinoma PDX Models with *MET* ex14del and increased *MET* Copy Number



Study Objectives

Primary Objectives:

- To determine the tumor response to MGCD265 in the selected patient population.

Secondary Objectives:

- 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

Study Design:

- Amethyst NSCLC is a global, open-label, parallel arm, Phase 2 trial evaluating the tumor response to MGCD265 in patients with locally advanced, unresectable or metastatic NSCLC exhibiting an activating genetic alteration of *MET*
- This Phase 2 parallel-arm-study will be conducted in four cohorts of patients having genetic tumor alterations activating *MET*:
  - *MET* activating mutation in tumor tissue,
  - *MET* gene amplification in tumor tissue,
  - *MET* activating mutation in ctDNA, and
  - *MET* gene amplification in ctDNA
- A Bayesian Predictive Probability Design will be applied separately to each cohort using the same assumptions.
  - Up to 45 patients may be enrolled in to each cohort
  - Assumptions of $p_0 = 0.20$, $p_1 = 0.40$; α constrained to <0.05, and power constrained to ≥0.90
  - Emerging tumor response data will be evaluated continuously after 10 patients in each cohort have had their first on-study disease assessment

Key Inclusion Criteria:

- Histologically-confirmed NSCLC with metastatic or unresectable, locally advanced disease
- Receipt of at least one prior platinum-containing chemotherapy regimen in the advanced disease setting
- Genetic *MET* alteration in tumor tissue or blood
- ECOG performance status 0, 1, or 2
- Adequate bone marrow and organ function

Key Exclusion Criteria:

- Prior treatment with a small molecule or antibody inhibitor of MET or HGF
- Prior positive test for *EGFR* mutation or *ALK* gene rearrangement
- Symptomatic or uncontrolled brain metastases
- Unstable angina pectoris, congestive heart failure of NYHA Class ≥ 3, or QTc > 480 msec

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

1. *Christensen JG, Burrows J, Salgia R. c-Met as a target for human cancer and characterization of inhibitors for therapeutic intervention. Cancer Lett. 2005;225(1):1-26. doi:10.1016/j.canlet.2004.09.044*
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)*

Study Trial Information: www.mirati.com