**COMMAND: A Phase 2 Randomized, Double-blind, Placebo-Controlled, Multicenter Study of Defactinib as Maintenance Therapy in Subjects with Malignant Pleural Mesothelioma which has Not Progressed on at least 4 Cycles of Pemetrexed/Platinum Therapy**

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**BACKGROUND**

**Defactinib (VS-6063)**
- Defactinib targets cancer stem cells (CSCs) through the inhibition of focal adhesion kinase (FAK).
- CSCs are tumor cells resistant to standard therapies and capable of seeding new tumors resulting in tumor recurrence and metastasis (Fig 1).
- SOCs agents for treatment of malignant pleural mesothelioma (MPM) have been shown in preclinical models to increase the proportion of CSCs (Fig 2).
- Defactinib PK and toxicity profile previously characterized in Phase 1 studies in advanced solid tumors.

**Merlin (NF2) in Mesothelioma**
- 40-50% of patients with MPM have loss or low levels of the tumor suppressor gene encoding the moesin-erzin-radixin-like protein (merlin).
- Merlin regulates FAK and plays a role in cell adhesion, invasion, and motility.
- Merlin-low mesothelioma cell lines are more sensitive to defactinib than merlin-high cell lines in vitro and in vivo (Fig 2).

**OBJECTIVES**

- **Primary Efficacy Objectives**
  - Progression free survival
  - Overall survival

- **Secondary Efficacy Objectives**
  - Quality of Life using LCS5-Meso
  - Objective response rate

- **Exploratory Efficacy Objectives**
  - Determine time to new lesions
  - Evaluate the relationship of defactinib PK and outcome
  - Population PK

**COMMAND STUDY DESIGN**

- **Key Endpoints**
  - PFS
  - OS
  - QoL
- **Key Inclusion Criteria**
  - Histological proof of MPM (and merlin status)
  - Measurable or evaluable disease per RECIST v1.1
  - One prior regimen (≥4 cycles) pem/cis or pem/carbo with a documented ongoing response (PR or SD)
  - KPS ≥70%
- **Key Exclusion Criteria**
  - History of upper GI bleed, ulceration or perforation
  - Major surgery within 28 days
  - Gilbert’s syndrome
  - Serious active infection
  - History of malignancy within 5 years

**STUDY STATUS**

- Currently enrolling in 15 countries worldwide
- 324 patients accrued as of August 28, 2015

**SUMMARY**

- COMMAND is open and actively accruing at > 72 centers worldwide
- IHC assay has been validated for the determination of merlin in patient biopsies
- For additional information see www.COMMANDmeso.com

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