**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 (see Fig 1).
- SOC agents used for the treatment of malignant pleural mesothelioma (MPM) have been shown in pre-clinical models to increase the proportion of CSCs (see Fig 2).
- The PK and toxicity profile of defactinib has been previously characterized in Phase 1 studies in patients with advanced solid tumors.
- ~50% of patients with MPM have loss or low levels of the tumor suppressor gene encoding the moesin-exrin-radixin-like protein (merlin).
- Merlin regulates FAK and plays a role in cell adhesion, invasion and cell motility.
- Merlin-low mesothelioma cell lines are more sensitive to defactinib than merlin-high cell lines in vitro and in vivo (see Fig 2).

**Figure 1: Targeting Cancer Stem Cells as Maintenance Therapy**

Problem: Current cancer treatments
- Initial tumor
- Tumor reduction but CSCs survive

Goal: More durable clinical response
- Initial tumor
- Tumor reduction but CSCs are enriched

**Figure 2: Defactinib Kills Cancer Stem Cells and is More Potent in Merlin-low Cell Lines**

(A) Inhibition of Aldefluor-positive mesothelioma CSCs by defactinib in contrast to induction by chemotherapy. (B) Cell viability analysis of merlin high (green) or merlin low (blue) MPM cell lines treated with defactinib. (C) Immunohistochemistry for merlin expression in MPM patient biopsies. An H-score is used for stratification.

**OBJECTIVES**

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

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

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

**COMMAND STUDY DESIGN**

 Patients stratified by tumor merlin status, assessed by IHC.
- Treatment until progression
- Interval analysis at 128 progression events
- Central review of CT scan

**KEY ENTRY CRITERIA**

**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**

Enrolling now in many countries worldwide

**SUMMARY**

- Study is open and actively accruing at multiple centers
- Accrual is expected to be completed in second half of 2015 for PFS endpoint
- IHC assay has been validated for the determination of merlin in patient biopsies
- For additional information see www.COMMANDmeso.com

**PRESENTED AT**

2014 iMig annual meeting 21-24 October in Cape Town, South Africa

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