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)
- SOC agents for treatment of malignant pleural mesothelioma (MPM) have been shown in pre-clinical 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-ezrin-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)

Fig 1: Targeting Cancer Stem Cells as Maintenance Therapy

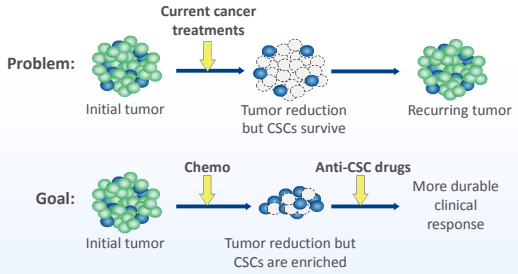
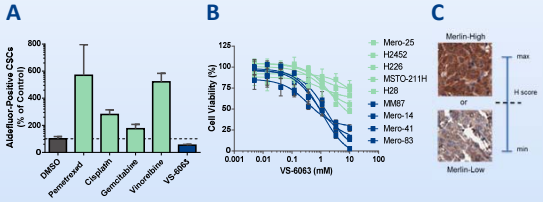


Fig 2: Defactinib Kills Cancer Stem Cells and is More Potent in Merlin-low Cell Lines

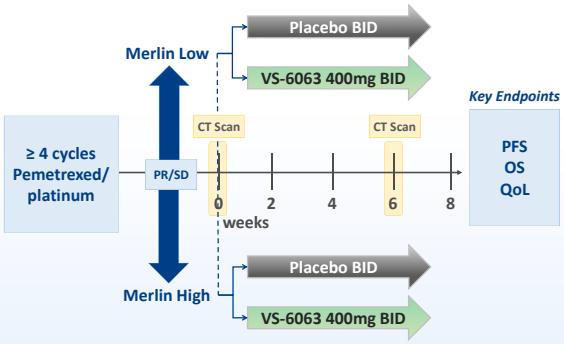


[A] Inhibition of Aldefluor-positive mesothelioma CSCs by defactinib in contrast to induction by chemotherapy.

[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.

COMMAND STUDY DESIGN



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

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 lesions
- Evaluate the relationship of defactinib PK and outcome
- Population PK

KEY ELIGIBILITY 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

- 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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Clinical Trial Registry Number NCT01870609