A first-in-Asian phase 1 dose escalation study to evaluate the safety and pharmacokinetics of VS-6063 (defactinib), a focal adhesion kinase inhibitor in subjects with non-hematologic malignancies

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ABSTRACT

BACKGROUND AND RATIONALE

- To overcome the Japanese "drug lag" problem, early initiation of phase 1 studies in Japanese subjects and inclusion in global clinical trials of novel agents is desirable.
- Defactinib has shown to be a potent, reversible inhibitor of focal adhesion kinase (FAK) and positive effect against liver fibrosis.
- FAK is overexpressed on the cancer cells, which can lead to increased metastasis through activation of tumor cell survival, proliferation, and invasion as well as tumor angiogenesis.
- Treatment with FAK inhibitors has been demonstrated to reduce the proportion of cancer stem cells (CSCs) in a dose-dependent manner.

METHODS

- This is a single-center, phase Ia open-label, dose-escalation study to investigate the safety and pharmacokinetics (PK) of defactinib in East-Asian (Japanese) subjects with non-hematologic malignancies.
- Defactinib was administered continuously at a starting dose of 60 mg BD. Following completion of this cohort the dose of defactinib was escalated in the second cohort at 400 mg BD (the recommended phase 2 single agent dose) and then to 600 mg in the third dose cohort.
- Blood samples for defactinib pharmacokinetics were collected on Day 1 and 15.
- Response was assessed every 4 weeks, with subjects continuing treatment until disease progression or unacceptable toxicity.

STUDY OBJECTIVES

Primary Objectives:
- To assess the safety and tolerability of defactinib in Japanese subjects with non-hematologic malignancies.
- To define the maximum tolerated dose (MTD) achieved, and to establish the recommended phase 2 dose of defactinib in Japanese subjects.
- To assess the pharmacokinetics, immunogenicity, and elimination of defactinib in plasma and urine.
- To evaluate the efficacy (response rate and progression-free survival) of subjects treated with defactinib.

KEY INCLUSION CRITERIA

- Japanese descent with a histologically confirmed diagnosis of a non-hematologic malignancy.
- Age ≥ 20 years.
- AECG ≥ 24 hr.
- Patients with a 3.5 × 10^4 HR, ECOG 0–1.

KEY EXCLUSION CRITERIA

- Prior treatment with defactinib or defactinib-related agents.
- History of severe concurrent medical condition (including uncontrolled brain metastasis).
- Uncontrolled medical condition, including but not limited to, uncontrolled diabetes, hypertension, or pulmonary disease, etc.
- History of body system or organ dysfunction.
- History of current or unresolved gastric and/or duodenal ulcer, etc.
- History of moderate or severe gastrointestinal (GI) condition with delayed emptying, or absorption.
- History of severe concurrent medical condition (including concomitant brain metastasis).
- History of uncontrolled medical condition, including but not limited to, uncontrolled diabetes, hypertension, or pulmonary disease, etc.

SAFETY

- No SAEs were observed at any dose level.
- No treatment-related adverse events were grade 3 or 4 except for one grade 1 blood bilirubin increase.

PHARMACOKINETICS

- Defactinib exposure was consistent with that previously reported in non-Japanese subjects.
- Total AUC increased in a dose-proportional manner.
- Defactinib exposure was highest in the first cohort.

CONCLUSIONS

- Defactinib was well tolerated at all dose levels investigated in this study.
- Most frequent treatment-related AEs were grade 1/2 blood bilirubin increase, fatigue, decreased appetite, and diarrhea, consistent with AEs previously reported in non-Japanese subjects.
- PK analyses confirmed the exposure at the recommended phase 2 dose of VS-6063 (400 mg BD) was comparable to that previously reported in non-Japanese subjects.
- Preliminary anti-tumor activity was seen, although the sample size was small.

DISCLOSURES

- A. Reid, L. Wilson, M. Keegan, M. Redelis and L. Poli are employees of Verastem.