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

Abstract#296

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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 been shown to be a potent, reversible inhibitor of focal adhesion kinase (FAK) and proline-rich tyrosine-kinase-2.
- Blockade of FAK reduces tumor growth and metastasis through inhibition 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 while chemotherapy standard of care agents (SOC) enrich for CSCs.
- The ability of CSCs to survive exposure to chemotherapy but remain susceptible to novel drugs suggests a unique therapeutic approach whereby SOC may be combined or sequenced with targeted drugs to kill surviving CSCs, prevent tumor recurrence and metastasis.
- Defactinib is currently under clinical investigation in three solid tumor Phase 2 studies including a multinational registration directed trial in mesothelioma (COMMAND).
- In this study we evaluated the safety and pharmacokinetics of defactinib in Japanese subjects.

Fig 1: Targeting Cancer Stem Cells For a More Durable Clinical Response

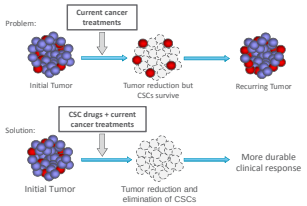
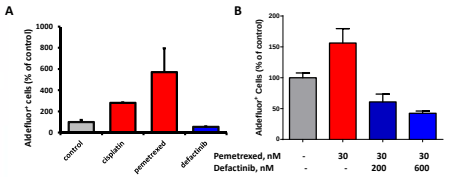


Fig 2: FAK Inhibitor Defactinib Reduces Enrichment of CSCs by Chemotherapy



A) Pemetrexed induces Aldefluor+ CSCs in H2052 mesothelioma cell line while defactinib selectively targets Aldefluor+ CSCs population. Cells were treated with 200 nM cisplatin, 100 nM pemetrexed or 200 nM defactinib for 4 days followed by an Aldefluor assay.

B) Defactinib diminishes mesothelioma Aldefluor+ CSCs induced by pemetrexed treatment when used in combination. H2052 mesothelioma cells were treated for 4 days, as doses indicated below the graph.

METHODS

- This is a single center, Phase I, open-label, dose-escalation study to investigate the safety and pharmacokinetics (PK) of defactinib in first-in-Asian (Japanese) subjects with non-hematologic malignancies.
- Defactinib was administered continuously at a starting dose of 200 mg BID. Following completion of this cohort the dose of defactinib was escalated in the second cohort to 400 mg BID (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 8 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.

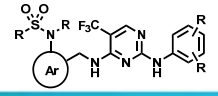
Secondary Objectives

- To define the maximum tolerated dose (if achieved), and to establish the recommended phase 2 dose of defactinib in Japanese subjects.
- To assess the pharmacokinetics, metabolism and elimination of defactinib in plasma and urine.
- To evaluate the efficacy (response rate and progression-free survival) of subjects treated with defactinib.

Table 1: Baseline demographics

	200 mg defactinib BID	400 mg defactinib BID	600 mg defactinib BID
Patients, n	3	3	3
Sex, n (%)			
Male	3 (100.0)	3 (100.0)	1 (33.3)
Female	0	0	2 (66.7)
Median age, years (range)	61.0 (54-67)	65.0 (61-75)	52.0 (38-71)
Diagnosis			
Colorectal	1	1	2
Esophageal	1	0	0
Lung	1	0	0
Mesothelioma	0	1	0
Thymic	0	0	1
Paget's Carcinoma	0	1	0
ECOG PS			
0	3 (100.0)	2 (66.7)	2 (66.7)
1	0	1 (33.3)	1 (33.3)
Prior systemic therapy regimens			
0	0	1	0
1	0	1	0
2	0	0	1
3	0	0	0
≥4	3	1	2

Fig 3: Defactinib



FAK Enzymatic IC_{50} = 24 nM
FAK Cellular EC_{50} = 28 nM

KEY INCLUSION CRITERIA

- Japanese descent with a histopathologically-confirmed diagnosis of a non-hematologic malignancy
- Age ≥ 20 years
- ECOG PS 0-1
- Creatinine ≤ 1.5x ULN or GFR of ≥ 50mL/min
- Total bilirubin ≤ 1.5x ULN; AST and ALT ≤ 3x ULN, or ≤ 5x ULN if liver involvement by tumor
- Hemoglobin ≥ 9.0 g/dL; platelets ≥ 100 x10^9 cells/L; ANC ≥ 1.5x10^9 cells/L
- Corrected QT interval (QTc) < 470 ms

KEY EXCLUSION CRITERIA

- Gastrointestinal (GI) condition which could interfere with swallowing or absorption
- Uncontrolled or severe concurrent medical condition (including uncontrolled brain metastases)
- History of upper gastrointestinal bleeding, ulceration, or perforation within 12 months
- Cancer-directed therapy within 28 days of the first dose of study drug or 5 half-lives
- Known history of malignant hypertension
- Known history of stroke or cerebrovascular accident within 6 months
- Known infection with HIV, AIDS, or Hepatitis A, B or C

SAFETY

- No DLTs or SAEs were observed at any dose cohort (200, 400 or 600 mg BID).
- All treatment emergent adverse events were grade 1 or 2 except for one grade 3 blood bilirubin increased experienced in one subject in the 200 mg BID cohort. No corresponding increase in AST or ALT was observed in this subject.

Table 2: Treatment-Emergent Adverse Events in ≥2 subjects

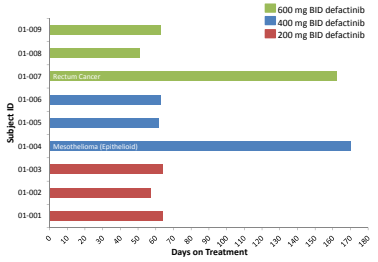
Adverse Event	200 mg defactinib BID (n=3)	400 mg defactinib BID (n=3)	600 mg defactinib BID (n=3)	Total (n=9)
Blood Bilirubin Increased	3 (100.0%)	2 (66.7%)	2 (66.7%)	7 (77.8%)
Fatigue	2 (66.7%)	1 (33.3%)	3 (100.0%)	6 (66.7%)
Decreased Appetite	2 (66.7%)	1 (33.3%)	1 (33.3%)	4 (44.4%)
Diarrhoea	0 (0.0%)	1 (33.3%)	2 (66.7%)	3 (33.3%)
Anaemia	0 (0.0%)	0 (0.0%)	2 (66.7%)	2 (22.2%)
AST Increased	1 (33.3%)	0 (0.0%)	1 (33.3%)	2 (22.2%)
Blood Alk Phos Increased	2 (66.7%)	0 (0.0%)	0 (0.0%)	2 (22.2%)
Cancer Pain	1 (33.3%)	1 (33.3%)	0 (0.0%)	2 (22.2%)
Headache	0 (0.0%)	1 (33.3%)	1 (33.3%)	2 (22.2%)
Nausea	1 (33.3%)	0 (0.0%)	1 (33.3%)	2 (22.2%)

DISCLOSURES

T. Shimizu, H. Aida, C. Hashii, K. Nakagawa report nothing to disclose;
A. Poli, L. Wilson, M. Keegan, M. Padval and J. Horobin are employees of Verastem.

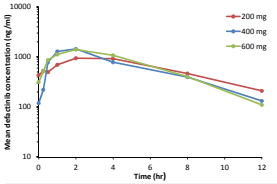
DURATION ON STUDY TREATMENT

Fig 4: Duration on Study Treatment



PHARMACOKINETICS

Fig 5: Defactinib Exposure in Japanese Subjects



- Defactinib exposure at the recommended phase 2 dose of 400 mg BID was consistent with that previously reported in non-Japanese subjects.
- Doses above 400 mg BID did not result in a significant increase in defactinib exposure.

CONCLUSIONS

- Defactinib was well tolerated at all dose levels investigated in this study.
- Most frequent treatment related AEs were grade 1/2 blood bilirubin increased, fatigue, decreased appetite and diarrhoea, consistent with AEs previously reported in non-Japanese subjects.
- PK analyses confirmed the exposure at the recommended phase 2 dose (RP2D) of 400 mg BID was comparable to that previously reported in non-Japanese subjects.
- Durable stable disease of approximately 24 weeks was confirmed in two patients (malignant mesothelioma and rectum cancer).
- Data from this study supports the entry of Japanese subjects at the RP2D into the ongoing multinational trial (COMMAND) of defactinib in malignant mesothelioma patients.
- The early execution of phase I studies in Japan facilitates the inclusion of Japanese subjects in global development programs simultaneously with the rest of world and may lead to a decrease in the Japanese drug lag.
- **Clinical trial registry number: NCT01943292**

Unlocked data as of October 2014.

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