FAK inhibitor (VS-6063) Defactinib targets MPM Cancer Stem Cells

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Cancer Stem Cells

- Have the exclusive ability to self renew
- May exhibit an increased drug resistance

Can be identified by
- Aldehyde DeHydrogenase (ALDH1A2a and ALDH2)
- CD44 staining

ALDH+/CD44+ can identify most putative CSC
CSC resistance

- To all chemotherapeutic agents?
- In all types of tumors?
- Can this be overcome?
Cell lines of NSCLC, leukemia, MPM, breast cancer have been identified*

Resistance to cisplatin in 3 MPM cell lines confirmed*

FAK inhibitors can reverse this process

*Cortes-Dericks, BMC Cancer 2014, 14:304
Standard of Care Treatment Increases Cancer Stem Cells

Mesothelioma Cancer Stem Cells *in vitro*

Treatment of human MPM cell lines with pemetrexed enriches cancer stem cells

*Canino et al. Oncogene 2011*
The Current Therapy for Mesothelioma Enriches Cancer Stem Cells

Pemetrexed + platinum

Initial tumor → Disease control but CSCs are enriched → Recurring tumor
Is there proof in patients with MPM?
Experimental set-up

- Patients in the cis/pem +/- axitinib study
- Biopsies before treatment and after 3 courses by VATS
- Preparation of TMA constructs
ALDH1 CSC marker increases in mesothelioma following standard chemotherapy

- ALDH1 IHC in patients with MPM
- Paired samples are collected pre-treatment and post-treatment

N = 11
11 patients analyzed

*** P = 0.036, Paired t-test
Chemotherapy induction of CSC gene expression in mesothelioma

- Mesothelioma patient tumors from pre-treatment and post-standard-of-care were compared by RNA analysis.
- Induction of CSC gene expression (fold change >1) was observed in the post-treatment samples.

CSC markers in chemo-treated patients

N = 12
Problem:

More durable clinical response

Disease control but CSCs are enriched

Recurring tumor

Initial tumor

Goal of COMMAND:

CSC Agent

More durable clinical response

Initial tumor

Disease control but CSCs are enriched
FAK is Critical for Cancer Stem Cells

- FAK is a critical pathway for cancer stem cells and disease progression

Shibue et al, Cancer Discovery (2012) 2:706

- Cell mobility
- Proliferation
- Tumor initiation
VS-6063: Potent, Selective FAK Inhibitor

- Oral compound with good safety profile & initial signs of activity in Phase 1
- Reduces pFAK & CSCs in tumors from treated patients
- USAN name: defactinib
- Orphan designation in US and EU for mesothelioma
Switch maintenance with defactinib, phase II

N=372

- Unresectable MPM
- PR/SD after 4 cycles of chemo
- 4-6 weeks after last chemo

Stratify: Merlin status

Randomize

VS6063 400mg orally twice daily

Placebo twice daily

Primary Objectives: PFS and OS
Secondary Objective: QoL

Data will be analyzed based on Merlin status
CT scans every 6 weeks
Primary endpoint: Overall survival
Summary

- Mesothelioma has CSC
- FAK inhibitor reduces CSC
- The Phase II COMMAND study is ongoing to test FAK maintenance in MPM