

FAK INHIBITOR DEFACTINIB (VS-6063) TARGETS MESOTHELIOMA CANCER STEM CELLS

Rationale for maintenance therapy after conventional therapy

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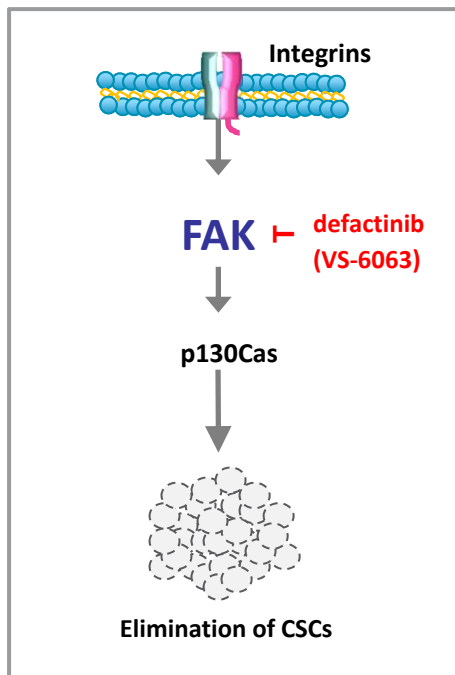


Disclosure

- I am an employee and stockholder of Verastem Inc.
- I will be discussing investigational drugs



Focal Adhesion Kinase: Key roles in cancer stem cell biology & tumor microenvironment



Focal Adhesion Kinase (FAK)

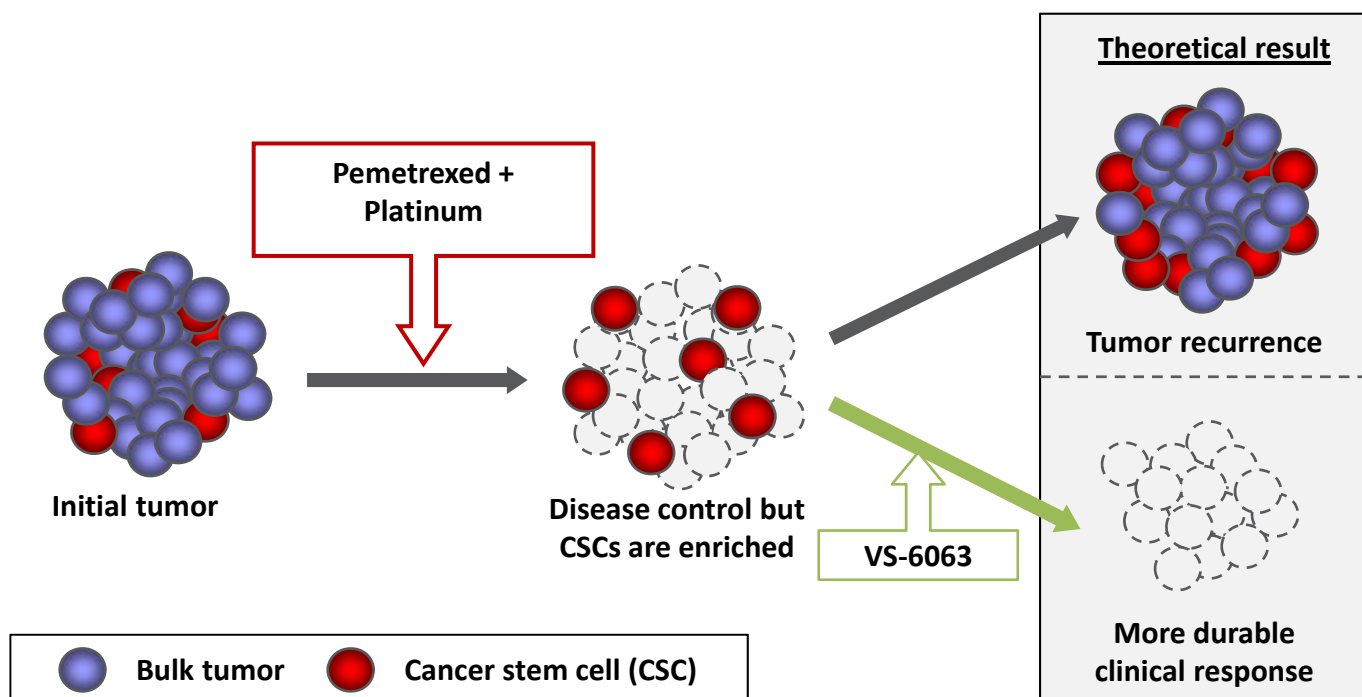
- Non-receptor tyrosine kinase
- Mediates proliferation & survival signaling downstream of integrin & growth factor receptors
- Key roles in Cancer Stem Cell biology & stromal interactions

Defactinib (VS-6063) – FAK inhibitor

- Registration-directed trial in mesothelioma
- Phase 2 trial in mt Kras NSCLC
- Phase 1/2 combination trial with paclitaxel in ovarian cancer



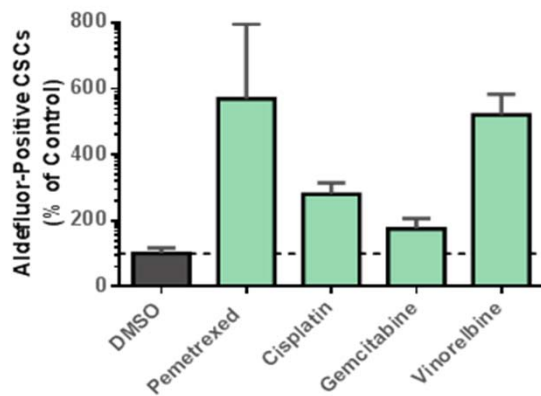
Importance of targeting cancer stem cells for a durable response



Standard-of-care chemotherapy enriches cancer stem cells in both mesothelioma cell lines and patient tumors

Mesothelioma CSCs *in vitro*

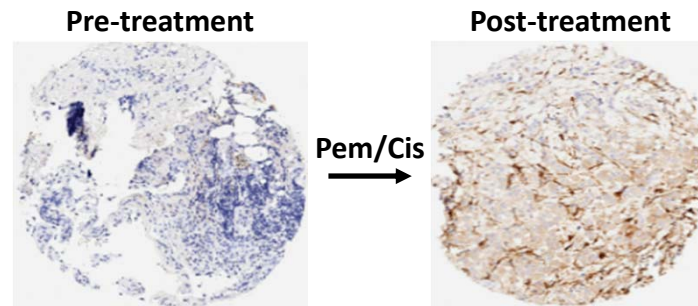
H2052 cell line



MPM cells treated with SOC chemotherapies are enriched for cancer stem cells

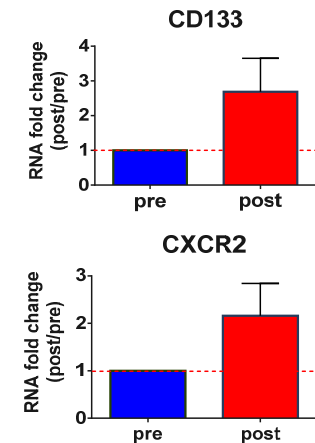
Mesothelioma CSCs *in vivo*

Paired patient biopsies



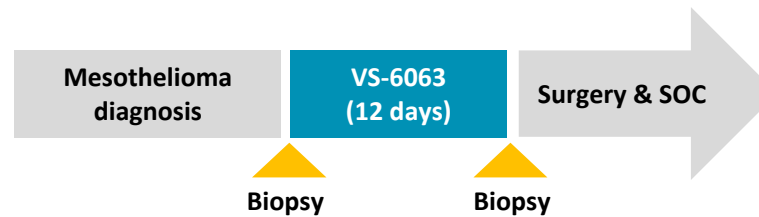
Brown = ALDH+ (cancer stem cells)

Treatment of MPM tumors with SOC chemotherapy enriches cancer stem cells

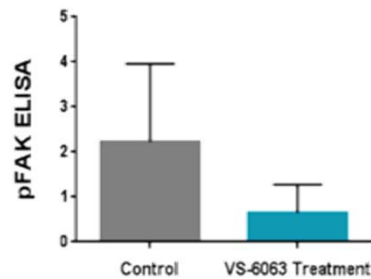


12 day VS-6063 treatment reduces pFAK & CSC markers in tumors of mesothelioma patients

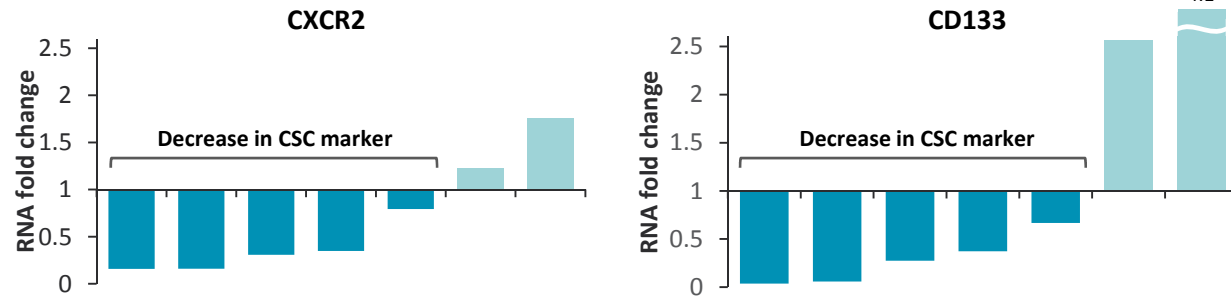
Phase 2 “Window of Opportunity”:



Tumor pFAK



Cancer Stem Cells (CXCR2+/CD133+)

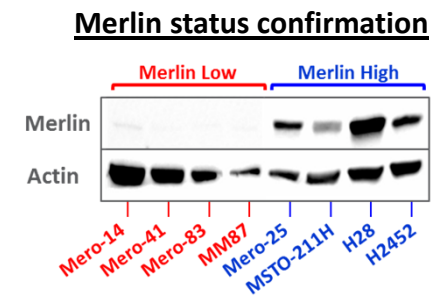
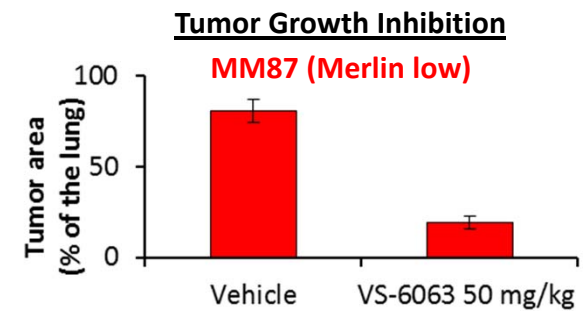
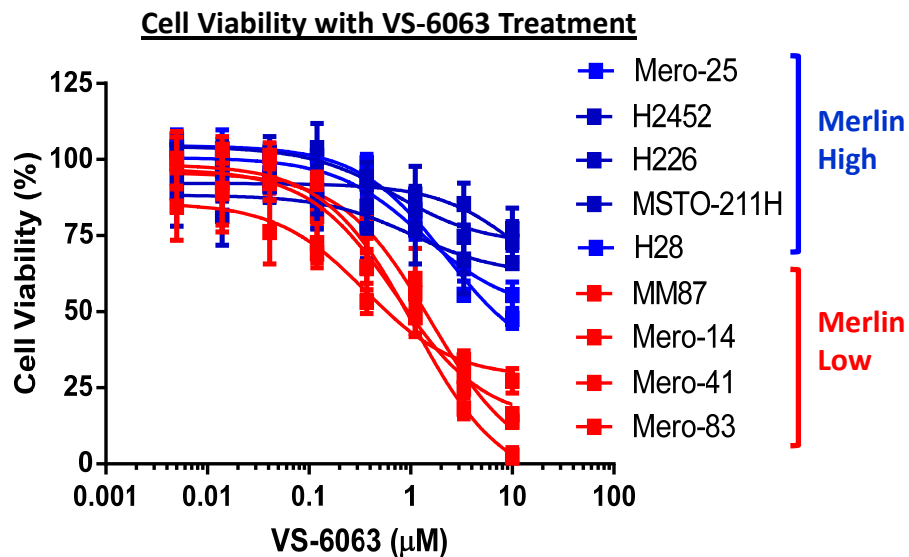


Change from baseline (normalized to 1)
using matched samples from individual patients



Low merlin expression increases sensitivity to VS-6063 in mesothelioma models

Approximately 40-50% of mesothelioma tumors have low merlin

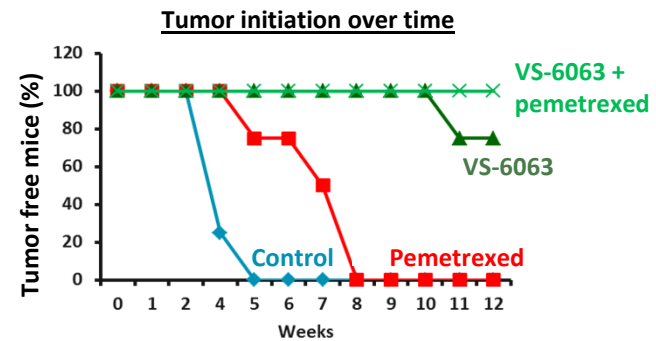
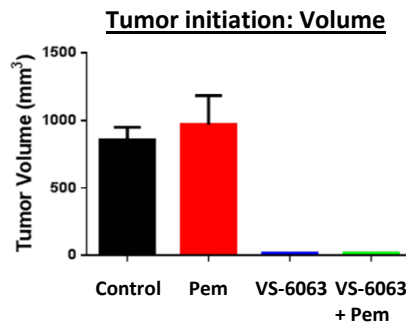


Source: Shapiro et al., Science Transl Med 6:237, 2014

VS-6063 reduces CSCs & tumor-initiating potential in both merlin-low & merlin-high mesothelioma tumor models

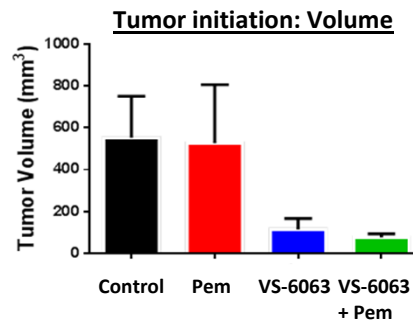
Merlin-high mesothelioma (H28)

Treatment with VS-6063 reduces tumor initiating capability

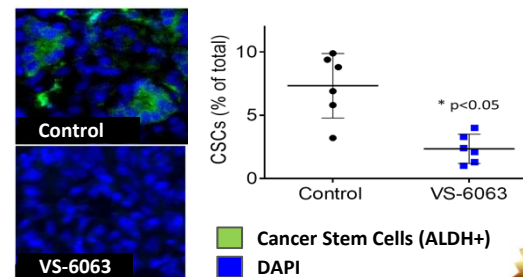


Merlin-low mesothelioma (MM87)

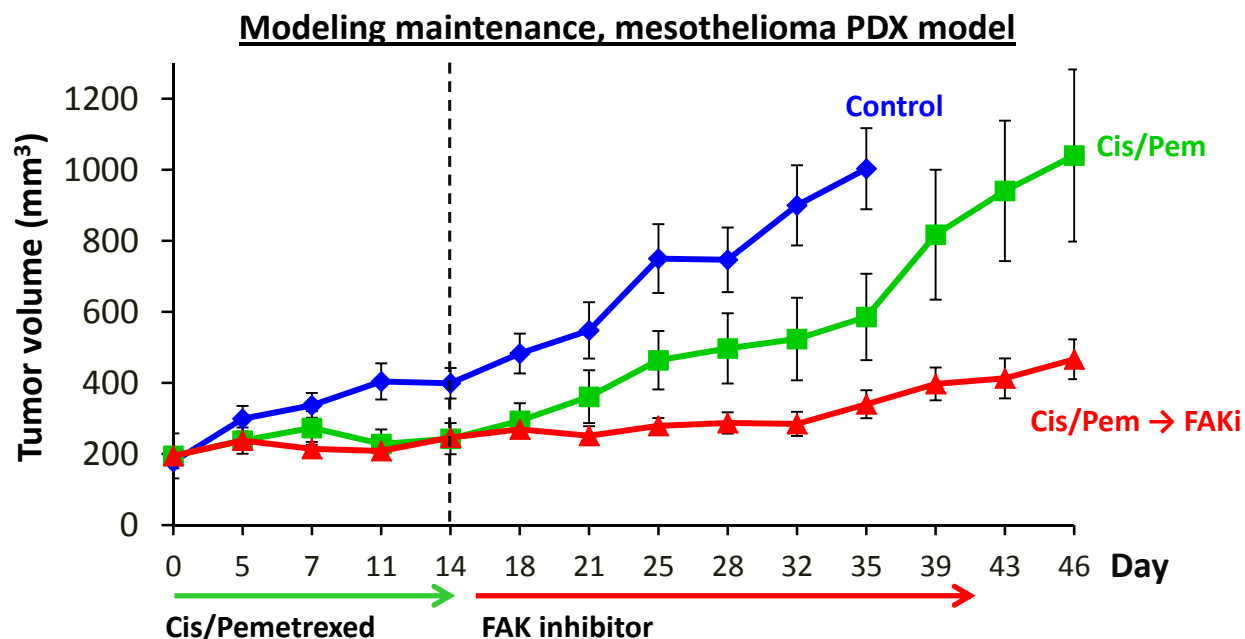
Treatment with VS-6063 reduces tumor initiating capability and ALDH+ CSCs



Cancer stem cells in VS-6063-treated tumor

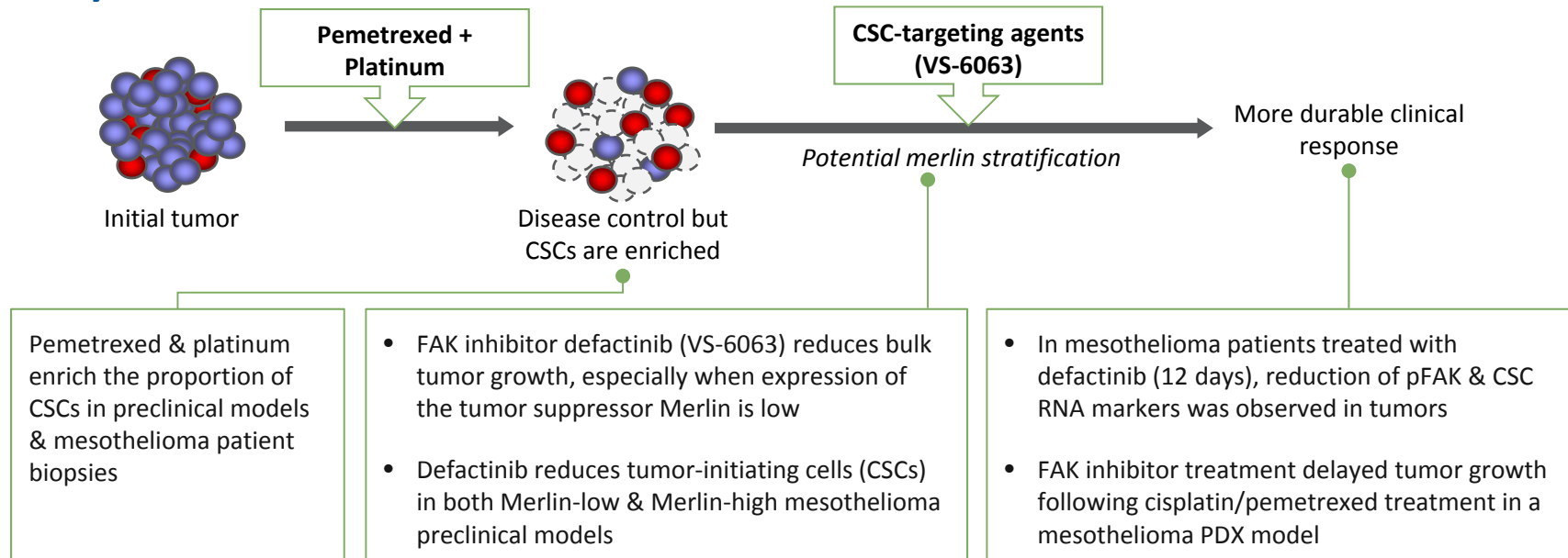


FAK inhibitor extends duration of antitumor efficacy following standard of care chemotherapy in mesothelioma



Source: Shapiro et al., Science Transl Med 6:237, 2014

Summary & conclusions



These data provide rationale for the current clinical testing of defactinib in a maintenance setting to potentially prolong response following front line chemotherapy in mesothelioma patients

