

THE CANCER STEM CELL INHIBITORS VS-6063 AND VS-5584 EXHIBIT SYNERGISTIC ANTICANCER ACTIVITY IN PRECLINICAL MODELS OF MESOTHELIOMA

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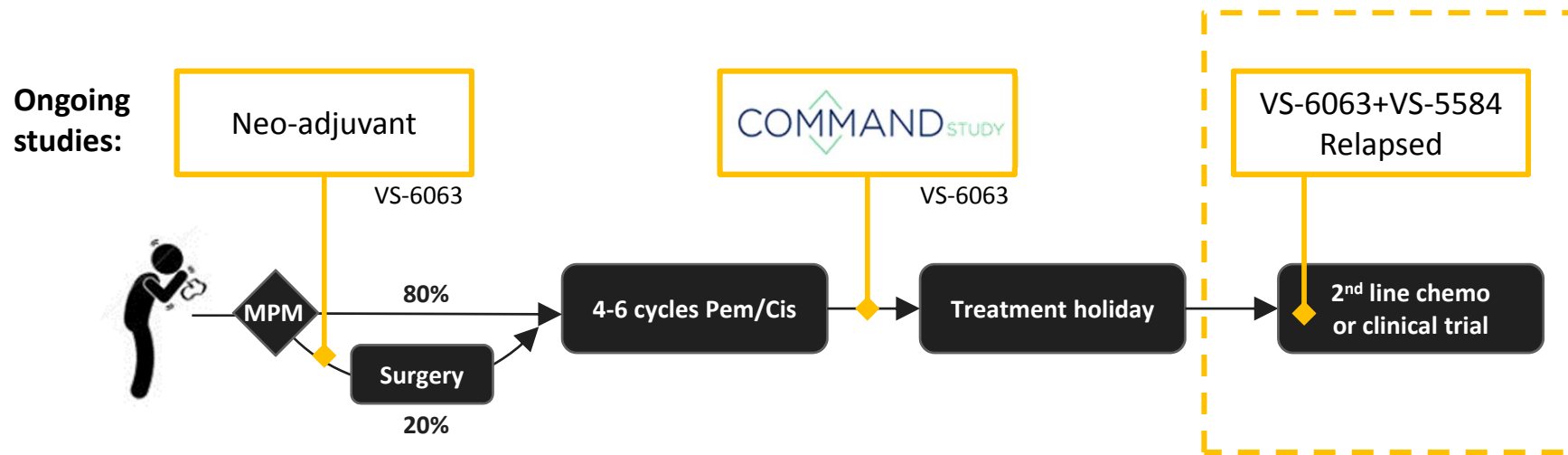


Disclosure

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



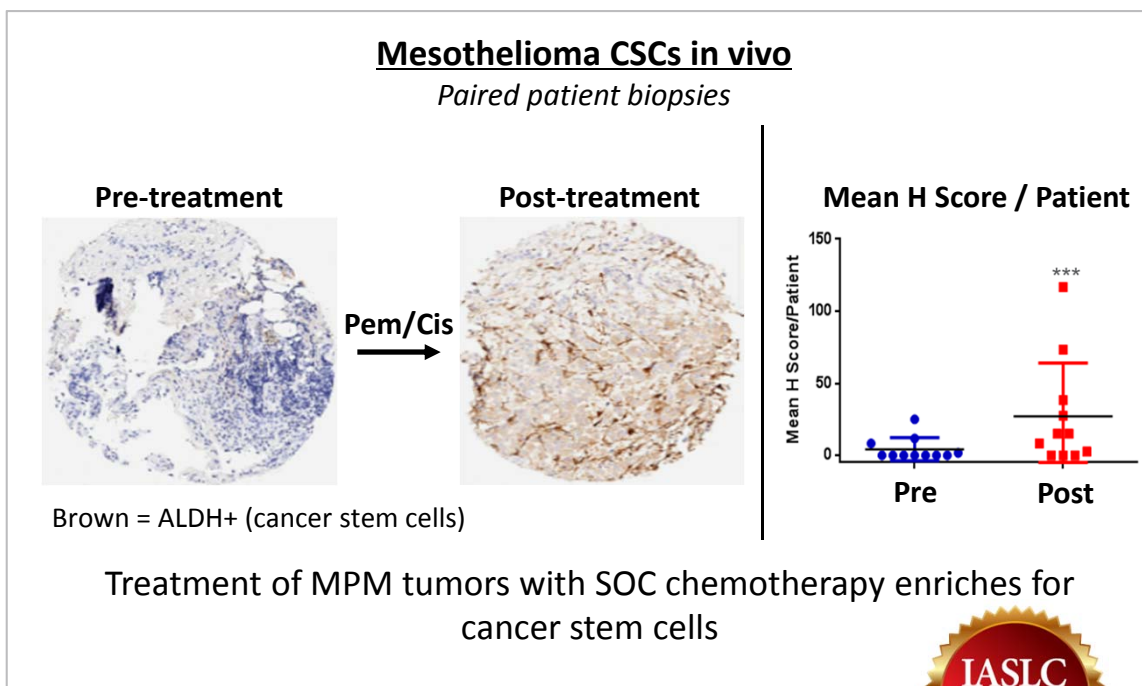
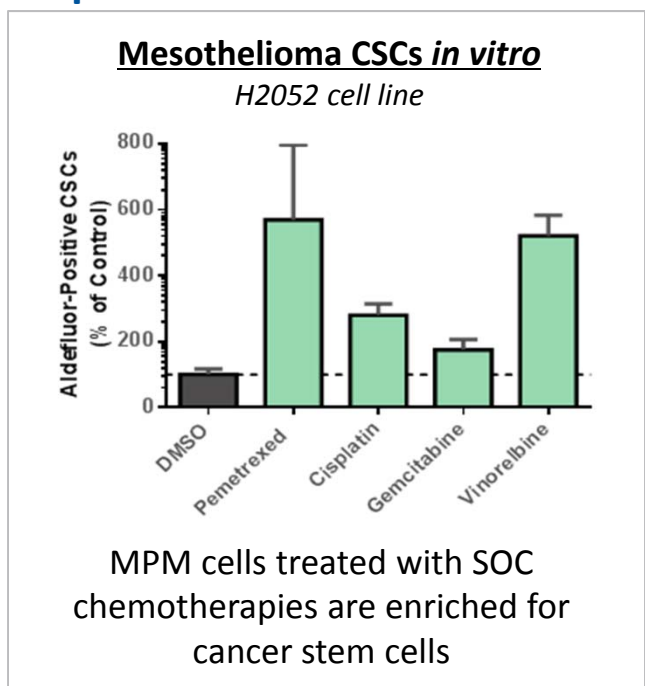
Developing potential treatment options throughout the mesothelioma patient journey



We want to maximize the potential treatment options for patients with mesothelioma



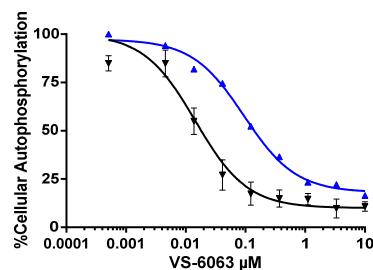
Standard-of-care chemotherapy enriches cancer stem cells in both mesothelioma cell lines and patient tumors



Profiles of VS-6063 & VS-5584

VS-6063 (defactinib)

- Potent, selective inhibitor of FAK & PYK2 tyrosine kinases
- Preferentially targets Cancer Stem Cells (CSCs)
- Lead compound, studied in 300+ patients to date with good safety profile
- Ongoing registration-directed trial in mesothelioma
- Orphan designation in US and EU for mesothelioma

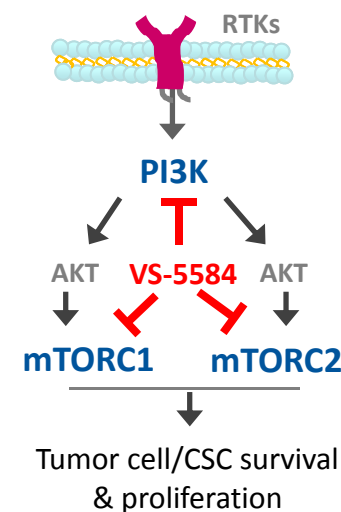


FAK $EC_{50} = 15$ nM
 PYK2 $EC_{50} = 95$ nM

VS-5584

- Potent, selective inhibitor of PI3K & mTOR kinases
- Preferentially targets Cancer Stem Cells (CSCs)
- Currently in Phase 1 with intermittent dosing schedule (3x weekly)

mTOR IC_{50} (nM)	PI3K isoform IC_{50} (nM)			
	α	β	δ	γ
3.4	2.6	21	3.0	2.7

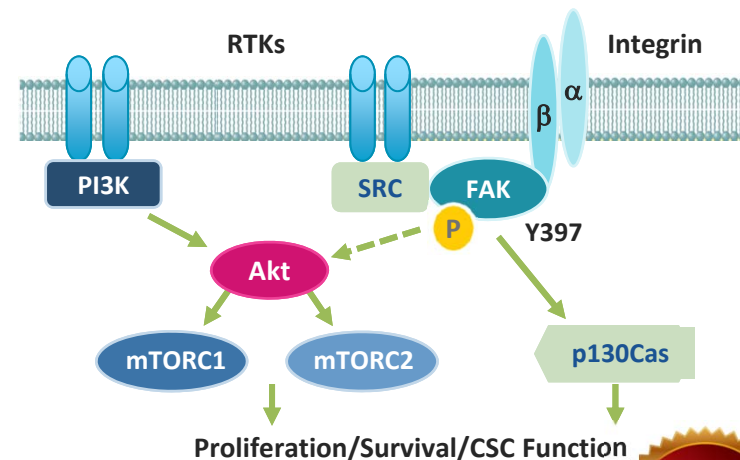


Rationale: Combination of VS-6063 (FAK) with VS-5584 (PI3K/mTOR) for the treatment of relapsed/refractory mesothelioma

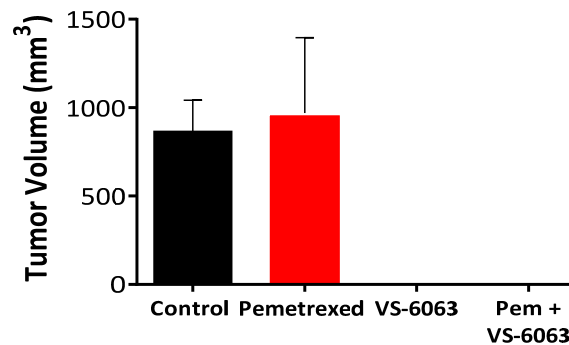
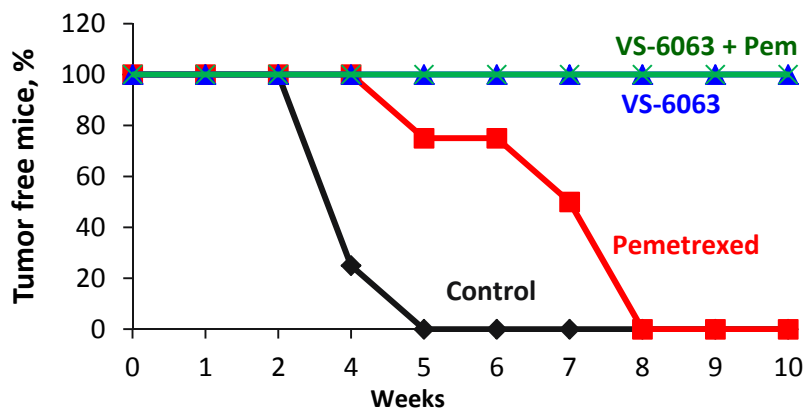
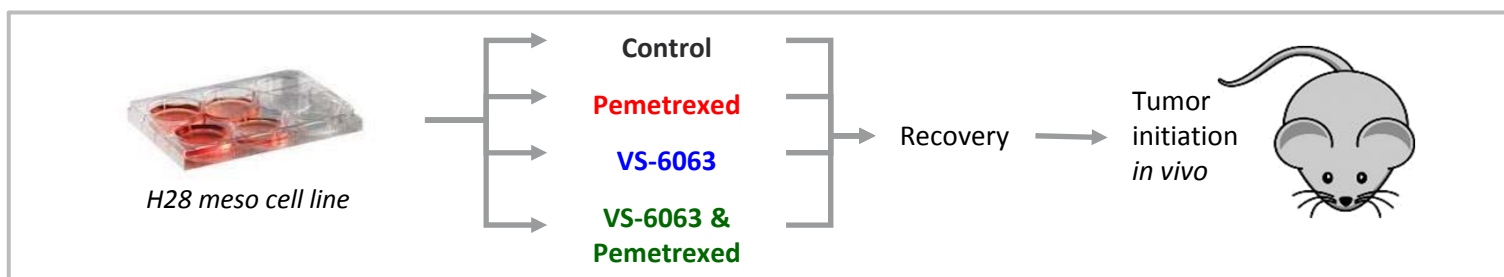
Both FAK & PI3K/mTOR inhibitors have shown early signs of clinical activity in mesothelioma

- 29 patients evaluated by GSK with their FAK inhibitor in Phase 1: Treatment resulted in median PFS of 4.5 months (vs. 6 weeks)
- 1 patient in VS-6063 Phase 1 in Japanese subjects: Symptom improvement and PFS of 5.6 months
- PI3K/mTOR dual inhibitor GDC-0980 showed 4 PRs among 33 mesothelioma patients in a Phase 1 study (*ECCO 2013*)

FAK & PI3K/mTOR inhibition may combine for more robust shut down of AKT survival signaling



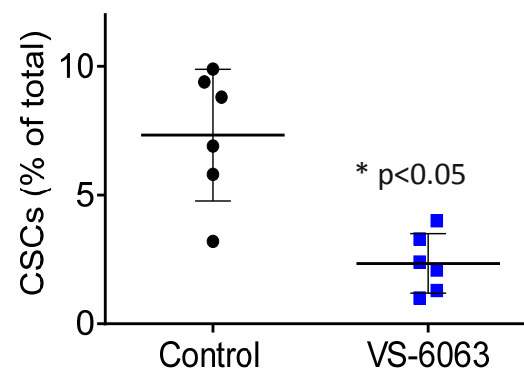
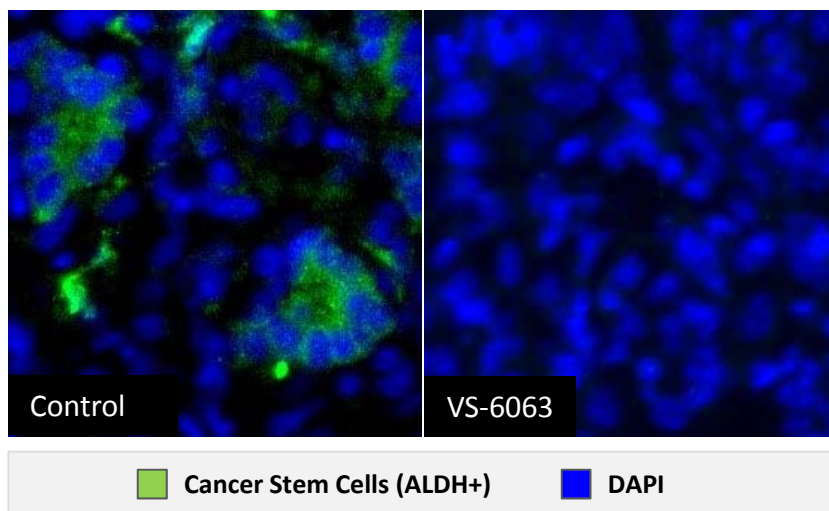
VS-6063 inhibits tumor initiation in mouse mesothelioma models



Oral administration of VS-6063 targets cancer stem cells in mesothelioma tumors grown in mouse lungs

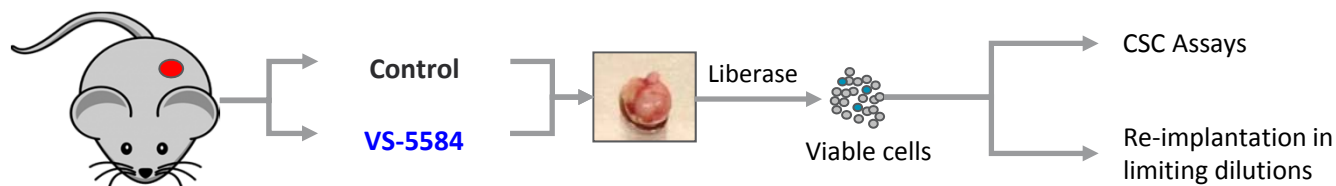
VS-6063 treatment, MM87 mesothelioma xenograft model:

50 mg/kg, po BID x 2 wks

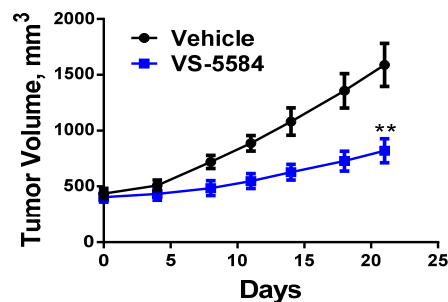


VS-5584 preferentially targets CSCs: ~ 70-fold reduction in tumor initiating frequency in a SCLC model

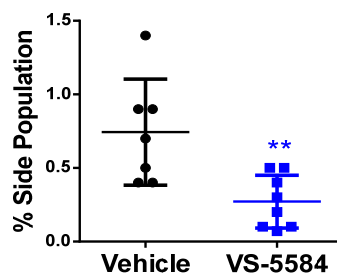
VS-5584 treatment, H841 SCLC model:



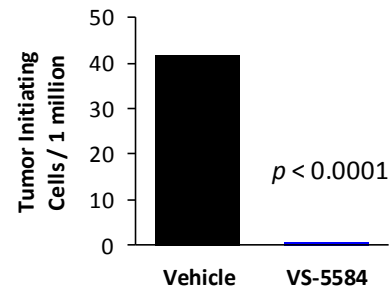
Antitumor Efficacy



SP CSC Assay

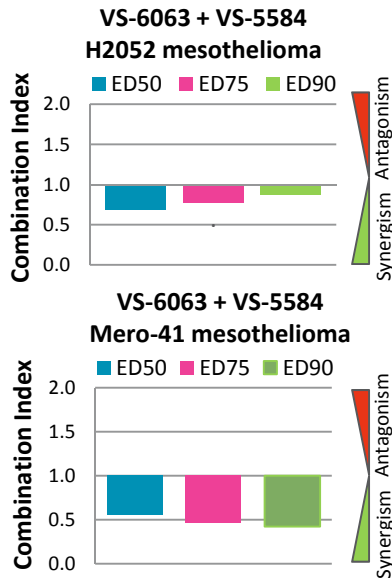


Tumor Initiation

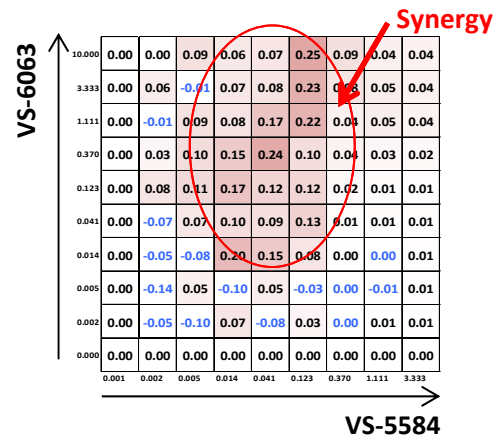


VS-5584 & VS-6063 exhibit synergistic combination activity in mesothelioma cell lines *in vitro*

Combination Index Analysis

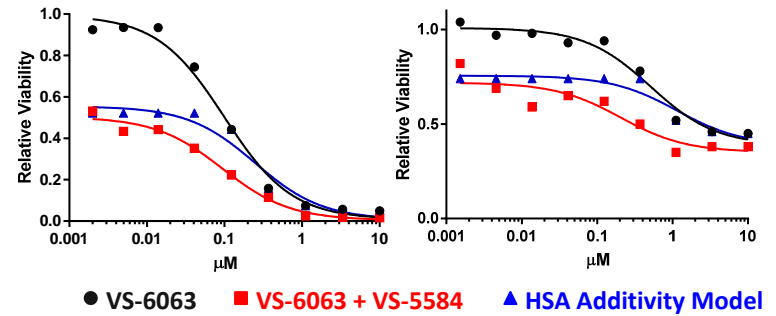


Highest Single Agent Analysis

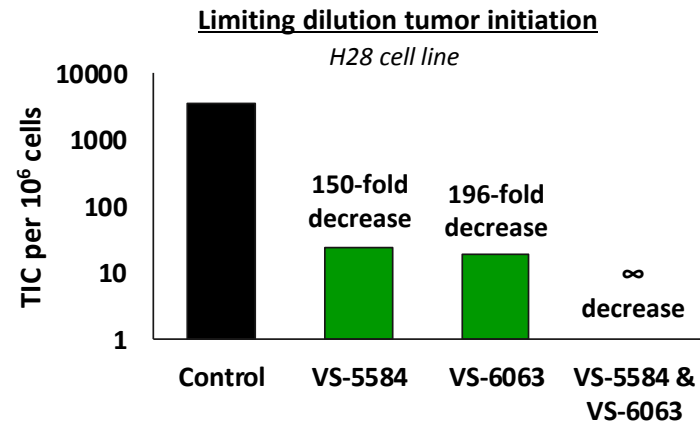
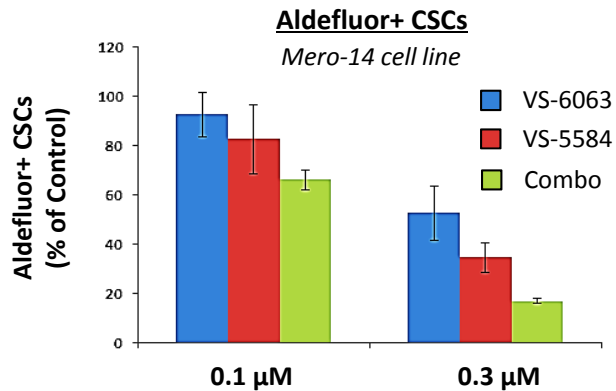
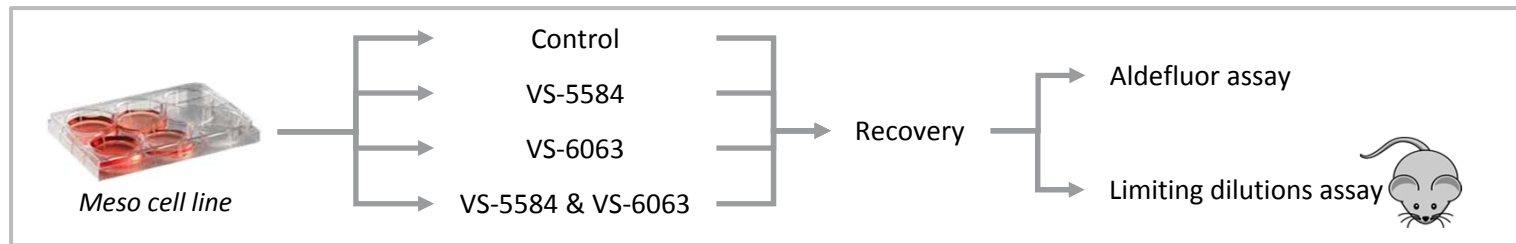


VS-5584 + VS-6063 @ 1.11 μM

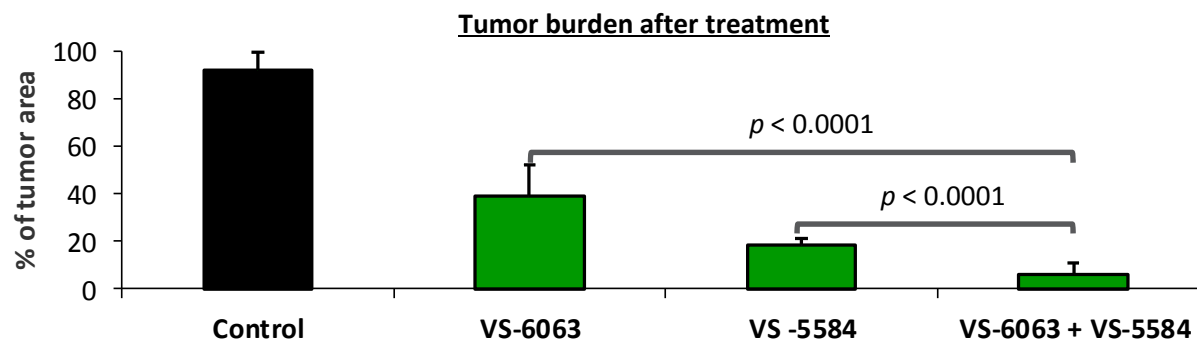
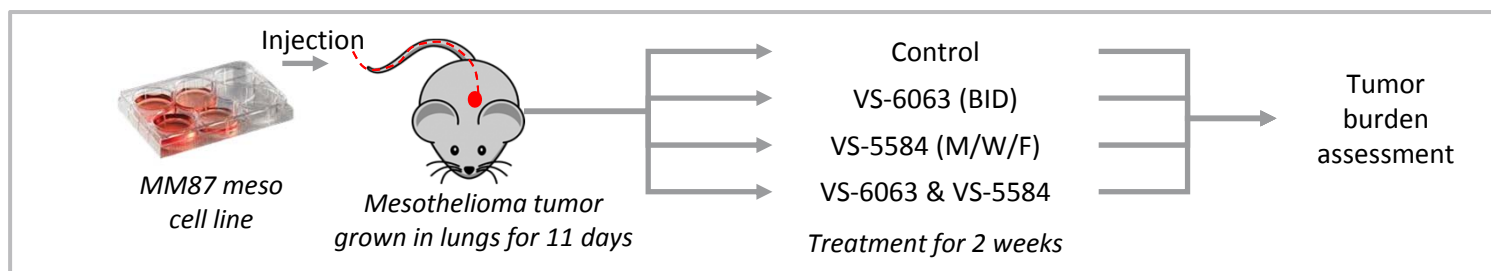
VS-5584 + VS-6063 @ 0.41 μM



Synergistic combination of VS-5584 and VS-6063 for targeting tumor initiating cells



Synergistic combination of VS-5584 and VS-6063 for enhanced anti-tumor efficacy compared to single agent in orthotopic meso model



- 2 out of 10 mice tumor free in the VS-6063 + VS-5584 combination group
- No tumor free mice in other groups



Summary & conclusions

- VS-6063 (defactinib) is a potent/selective FAK kinase inhibitor
- VS-5584 is a potent/selective inhibitor of PI3K & mTORC1/2
- Both agents preferentially target CSCs and also reduce bulk tumor growth in preclinical mesothelioma models
- Synergistic activity of VS-6063 & VS-5584 on CSCs & bulk tumor has been observed in preclinical models
- These data support an ongoing Phase I combination study of VS-6063 & VS-5583 in patients with relapsed/refractory mesothelioma
 - Additional study details will be presented at Poster #P2.08-008

