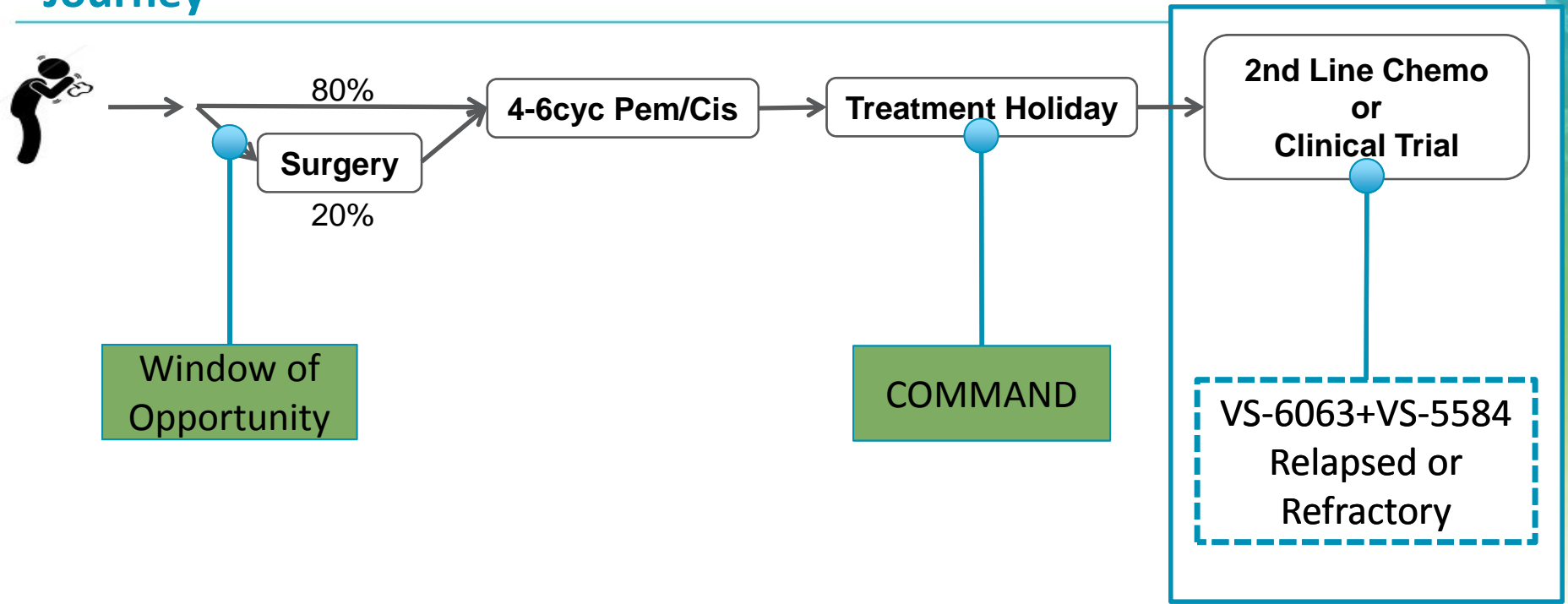




**CANCER STEM CELL INHIBITORS VS-6063 (DEFACTINIB) &  
VS-5584 EXHIBIT SYNERGISTIC ANTICANCER ACTIVITY IN  
PRECLINICAL MODELS OF MESOTHELIOMA**

**MITCHELL KEEGAN, VP DEVELOPMENT**

# Developing Potential Treatment Options Throughout the Patient Journey



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

Ongoing  
Planned

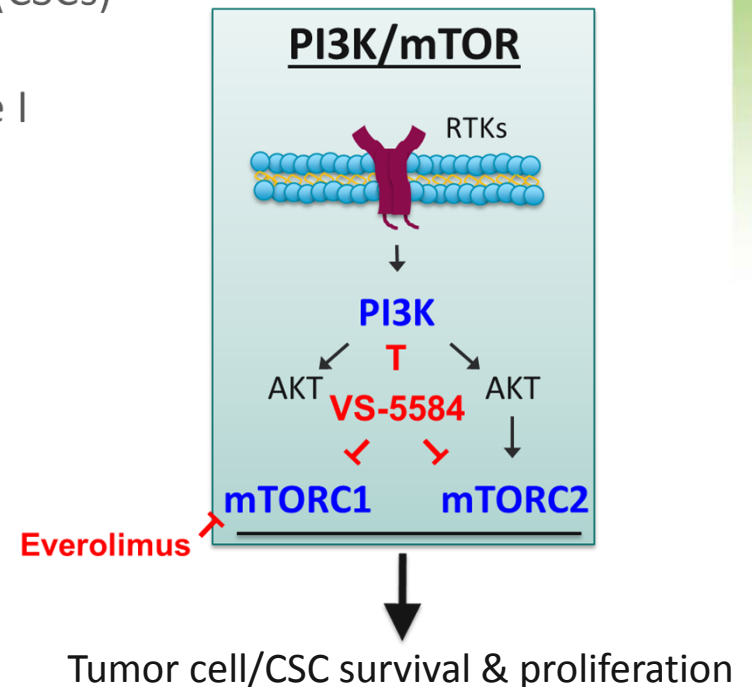
## Profiles of VS-6063 & VS-5584

### VS-6063 (Defactinib) FAK Kinase Inhibitor

- Potent, selective inhibitor of FAK & PYK2 tyrosine kinases
- Preferentially targets Cancer Stem Cells (CSCs)
- Various clinical trials in progress

### VS-5584 PI3K/mTOR Kinase Inhibitor

- Potent, selective inhibitor of PI3K & mTOR kinases
- Preferentially targets Cancer Stem Cells (CSCs)
- Phase I



## Rationale: Combination of VS-6063 (FAK) with VS-5584 (PI3K/mTOR) for the Treatment of Relapsed/Refractory Mesothelioma

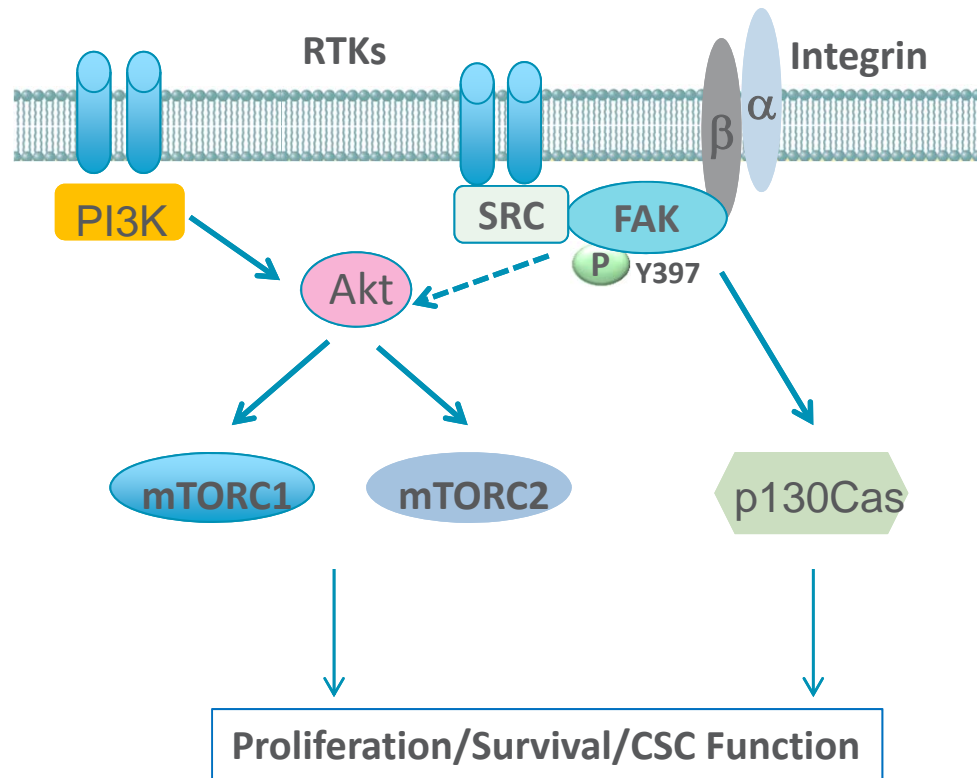
- Both VS-6063 & VS-5584 effectively target CSCs
- Pre-clinical models show synergy between VS-6063 and VS-5584

PI3K/mTOR dual inhibitor GDC-0980 showed 4 PRs among 33 mesothelioma patients in a phase 1 study *ECCO 2013*

IC<sub>50</sub> (nM)

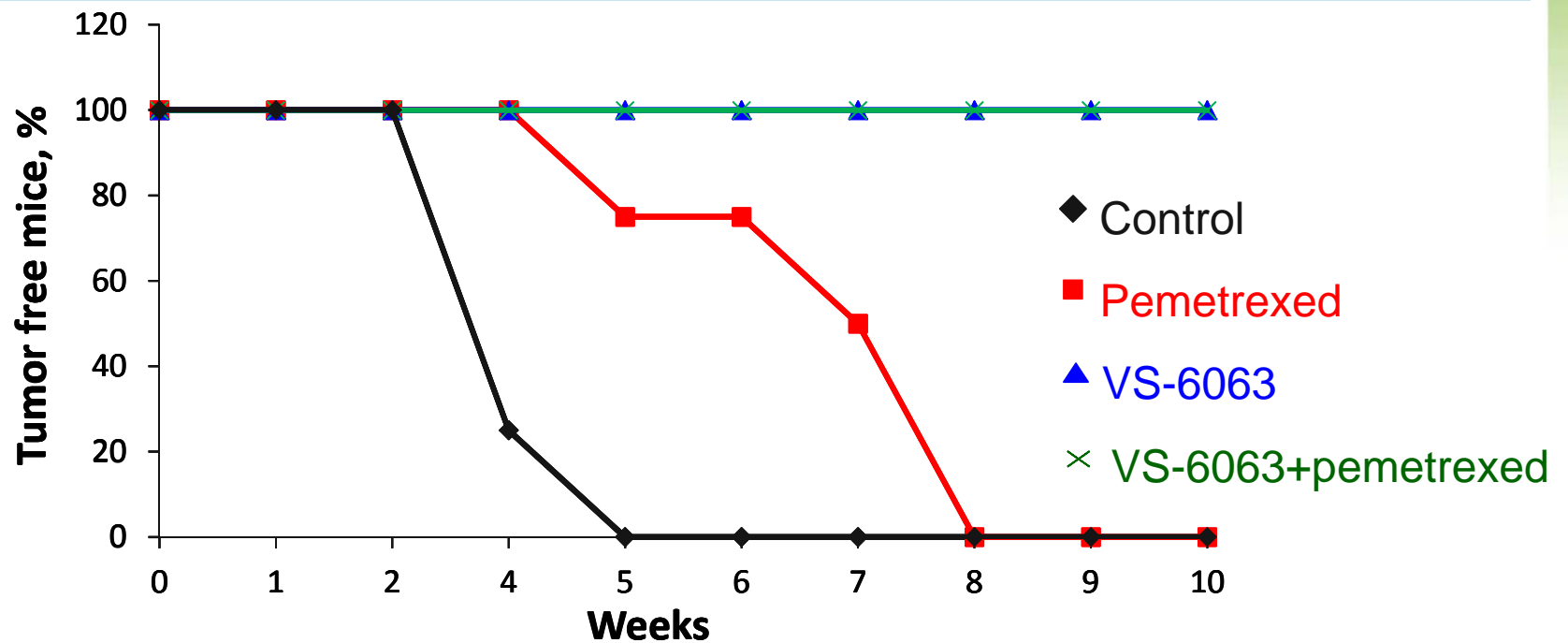
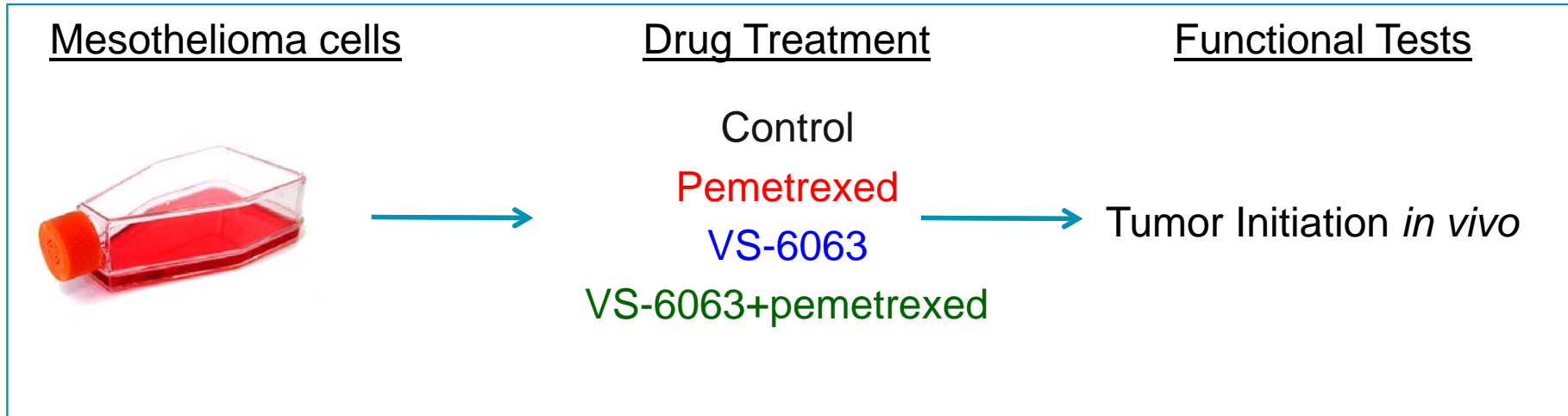
Compound	Company	mTOR	PI3K $\alpha$	PI3K $\beta$	PI3K $\gamma$	PI3K $\delta$
VS-5584	Verastem	3.4	2.6	21	2.7	3.0
GDC-0980	Genentech	5.5	6.6	31	6.5	13

## Rationale for Combining VS-5584 with FAK inhibitor: *Signal Cross Talk between FAK and PI3K/mTOR Pathways*

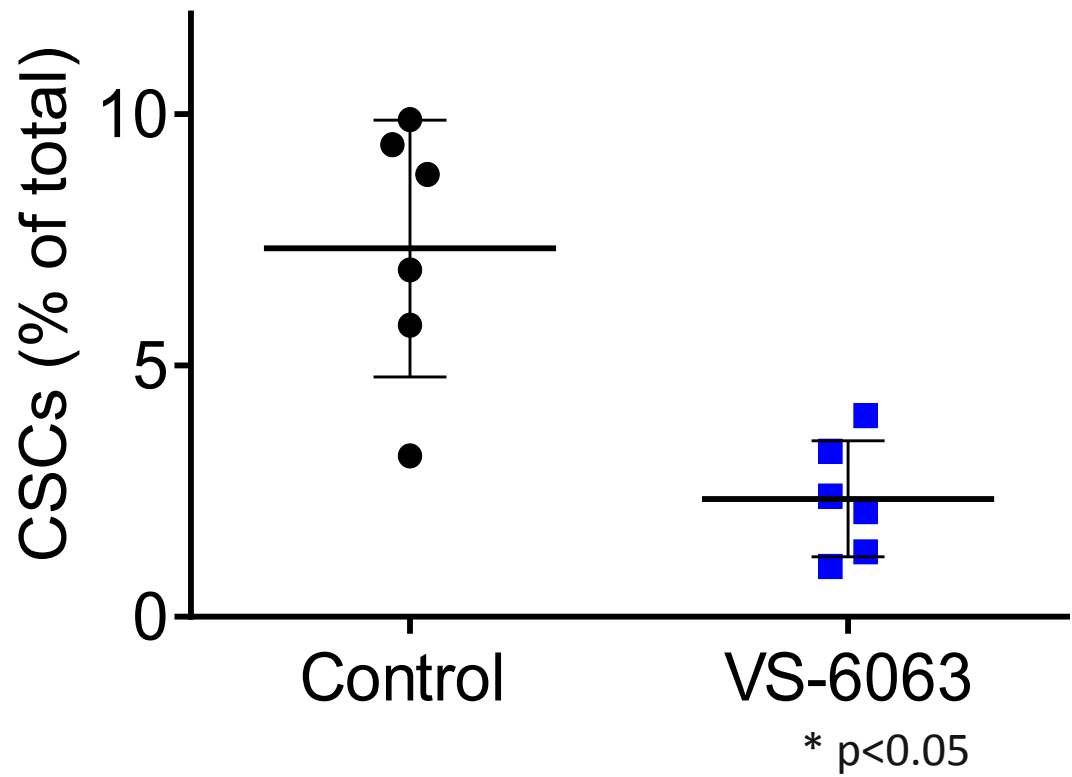
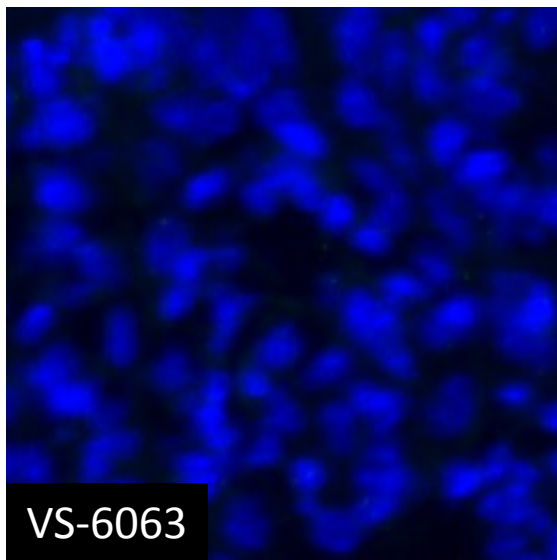
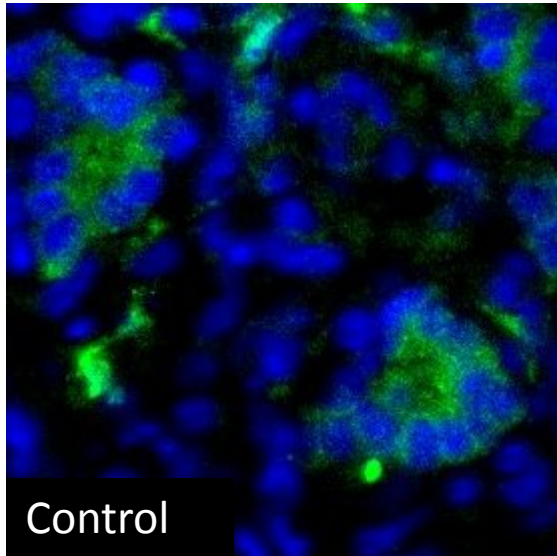


- FAK & PI3K/mTOR inhibition may combine for more robust shut down of AKT survival signaling

# VS-6063 Inhibits Tumor Initiation in Mouse Mesothelioma Models



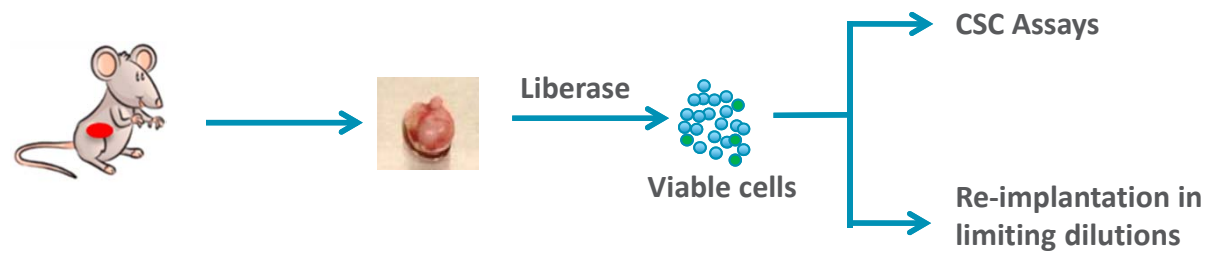
# Oral Administration of VS-6063 Targets Cancer Stem Cells in Mesothelioma Tumors Grown in Mouse Lungs



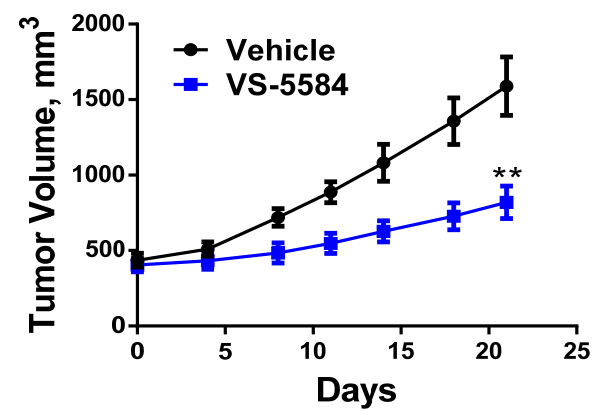
CSCs (ALDH+)  
DAPI

50 mg/kg, po BID x 2 wks

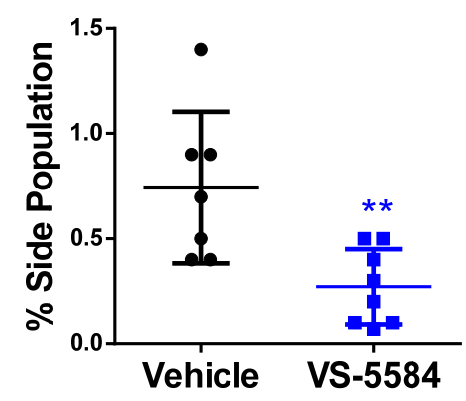
# VS-5584 Preferentially Targets CSCs: ~ 70-Fold Reduction in Tumor Initiating Frequency in a SCLC model



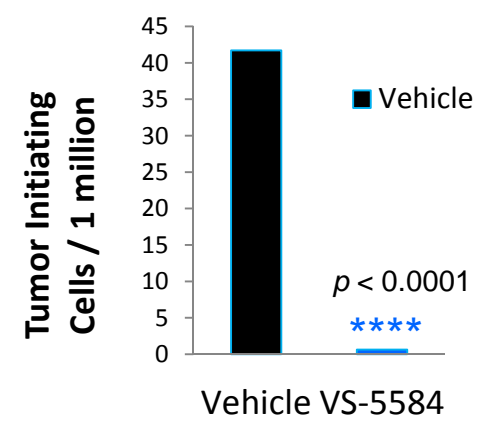
## Antitumor Efficacy



## SP CSC Assay



## Tumor Initiation

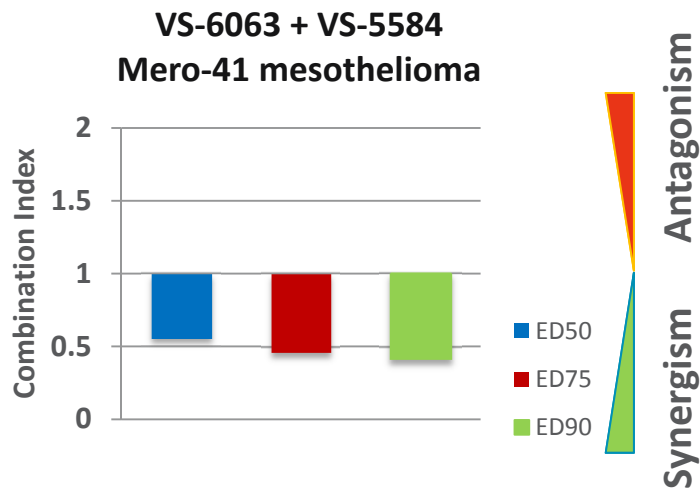


*H841 SCLC model*

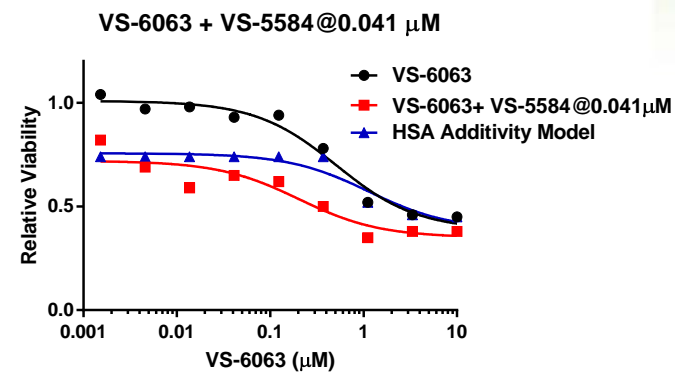
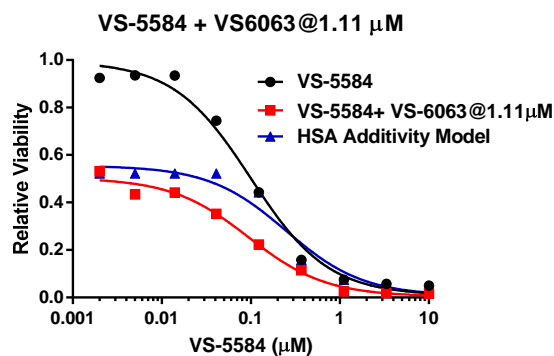
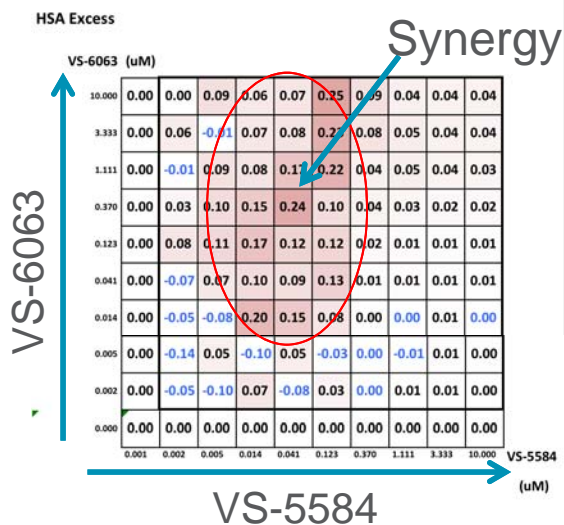


# VS-5584 and VS-6063 exhibit synergistic combination activity in mesothelioma cell lines *in vitro*

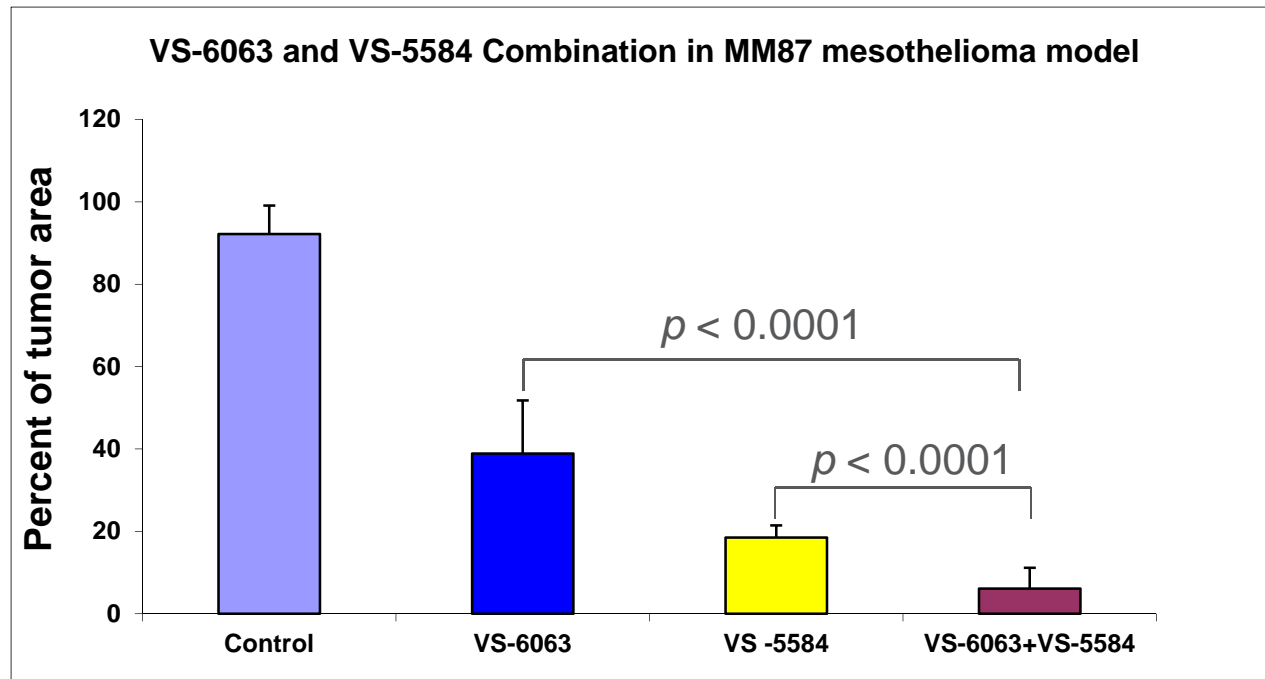
## Combination Index Analysis



## Highest Single Agent Analysis



## Enhanced Antitumor Efficacy of VS-5584 and VS-6063 Combination Compared to Single Agent in MM87 Mesothelioma *in vivo*



- Dosing started 11 days post MM87 cell injection with evidence of tumor burden. VS-6063, 50 mg/kg, po bid; VS-5584, 20 mg/kg (MWF) for 2 weeks
- Mesothelioma tumors grown in lungs
- 2 out of 10 mice were tumor free in the VS-6063 and VS-5584 combination group. No tumor free mice in other groups

J. Testa, Fox Chase

## Summary/Conclusions

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- 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 a planned Phase I combination study of VS-6063 & VS-5583 in patients with relapsed/refractory mesothelioma

## Acknowledgments

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- Joseph Testa