PI3K/MTOR KINASE INHIBITOR VS-5584

NON-CONFIDENTIAL SUMMARY

APRIL 2015

Novel Drugs Targeting Cancer Stem Cells

Verastem: Company Summary

- Verastem (VSTM) is a publically traded Biotech company based in Boston, MA
- Founded in 2010 by Bob Weinberg (Whitehead Institute, MIT) & Eric Lander (Broad Institute)
- Focused on development of small molecule anticancer drugs that target Cancer Stem Cells (CSCs)
- Clinical programs:
  - VS-5584 is a selective dual PI3K/mTOR kinase inhibitor (Phase 1)
  - VS-6063 (lead program) is a selective inhibitor of FAK & PYK2 protein kinases
    - Multiple phase 1 & 2 clinical trials in various solid tumor indications including the registration directed COMMAND study in Malignant Pleural Mesothelioma
  - VS-4718 is a structurally distinct FAK & PYK2 inhibitor (Phase 1)

Verastem Objectives for CRUK Combinations Alliance

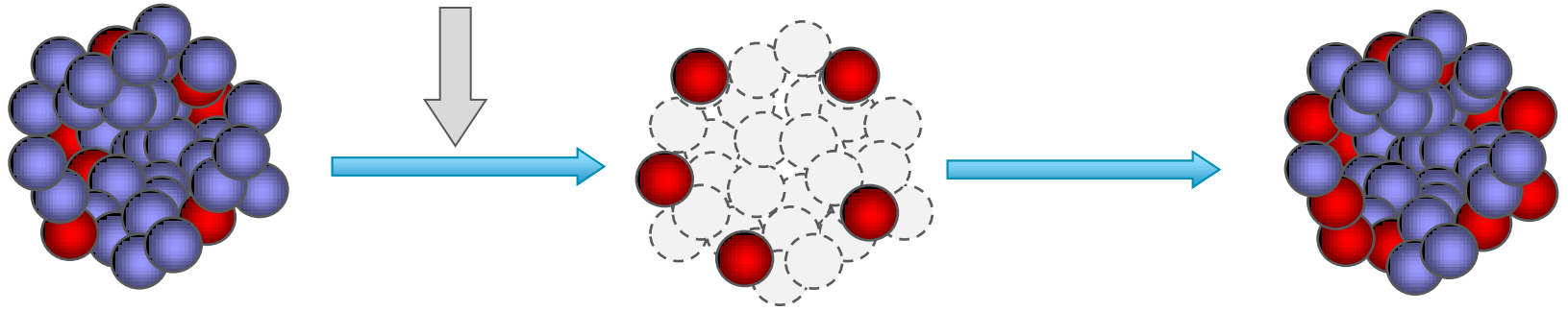
- Combine VS-5584 with novel agents
  - Phase 1 combination study with FAK inhibitor VS-6063 currently enrolling in mesothelioma
- Selected combinations of interest with VS-5584
  - PARP inhibitors
  - Androgen receptor antagonists
  - Aromatase inhibitors
- Selected indications of interest
  - SCLC
  - Ovarian cancer
  - ER positive and Triple Negative Breast Cancer
- Open to additional novel combos and indications with strong scientific rationale

Scientific Rationale

Targeting Cancer Stem Cells for a Durable Clinical Response

Problem:

Current cancer treatments



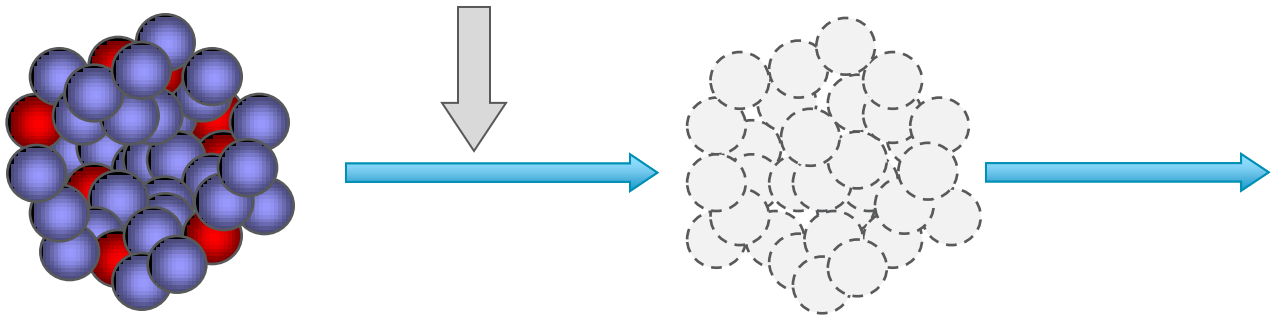
Initial tumor

Tumor Reduction but CSCs Survive

Recurring Tumor

Solution:

CSC drugs + current cancer treatments



Initial tumor

Tumor Reduction and Elimination of CSCs

Durable Clinical Response

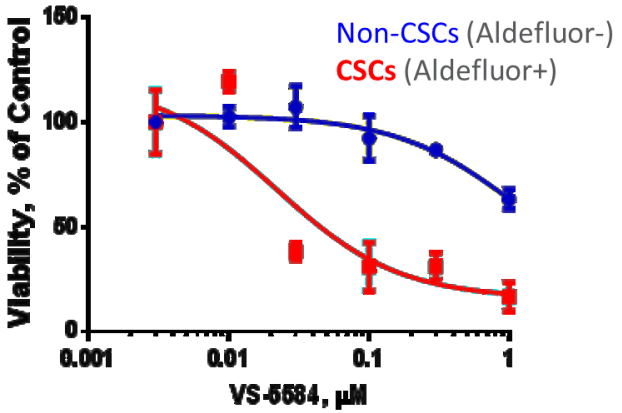
VS-5584 Highlights

- PI3K/mTOR dual kinase inhibitor
  - Equipotent against mTORC1, mTORC2 and all four PI3K class I isoforms
  - Highly selective vs. other protein & lipid kinases
- Preferentially targets cancer stem cells *in vitro* & *in vivo*
- Broad, robust anti-tumor activity in xenograft & PDX models
- Phase I dose escalation in progress in patients with solid tumors
  - 3x/week intermittant dosing schedule

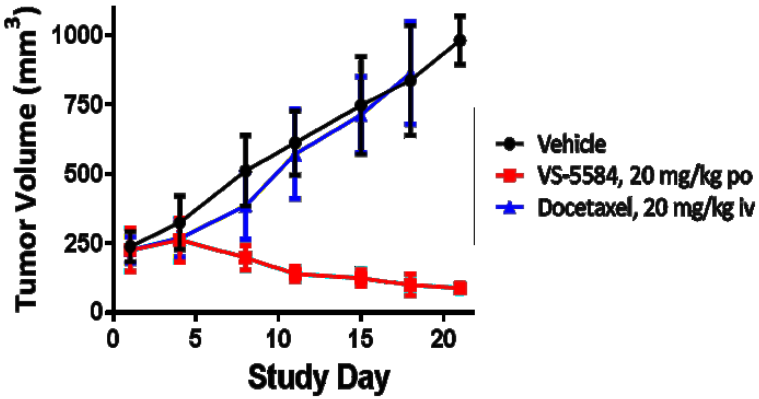
PI3K Isoform IC_{50} (nM)

mTOR	Alpha	Beta	Delta	Gamma
3.4	2.6	21	3.0	2.7

Preferential Inhibition of CSCs

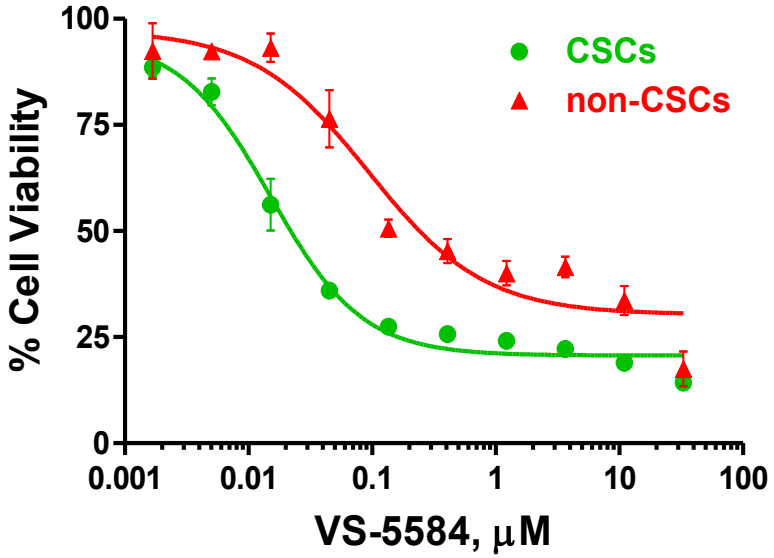


Chemo-Resistant TNBC PDX

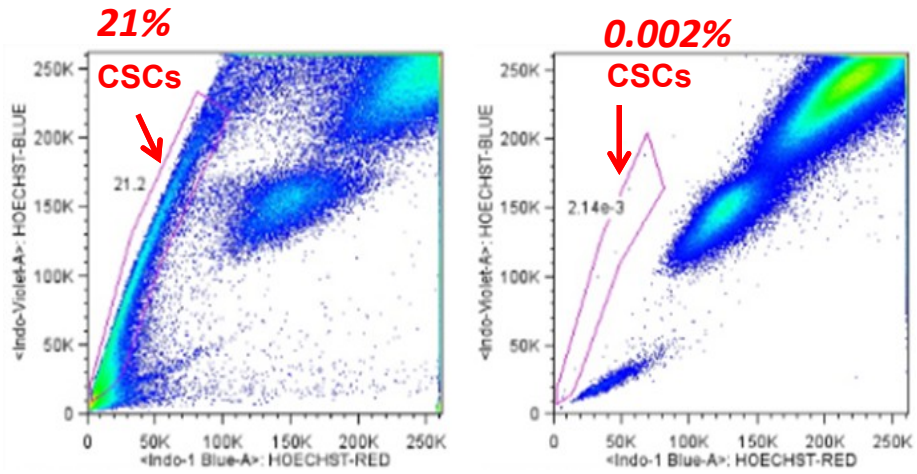


Inhibition of PI3K/mTOR Targets Cancer Stem Cells in Multiple Assays

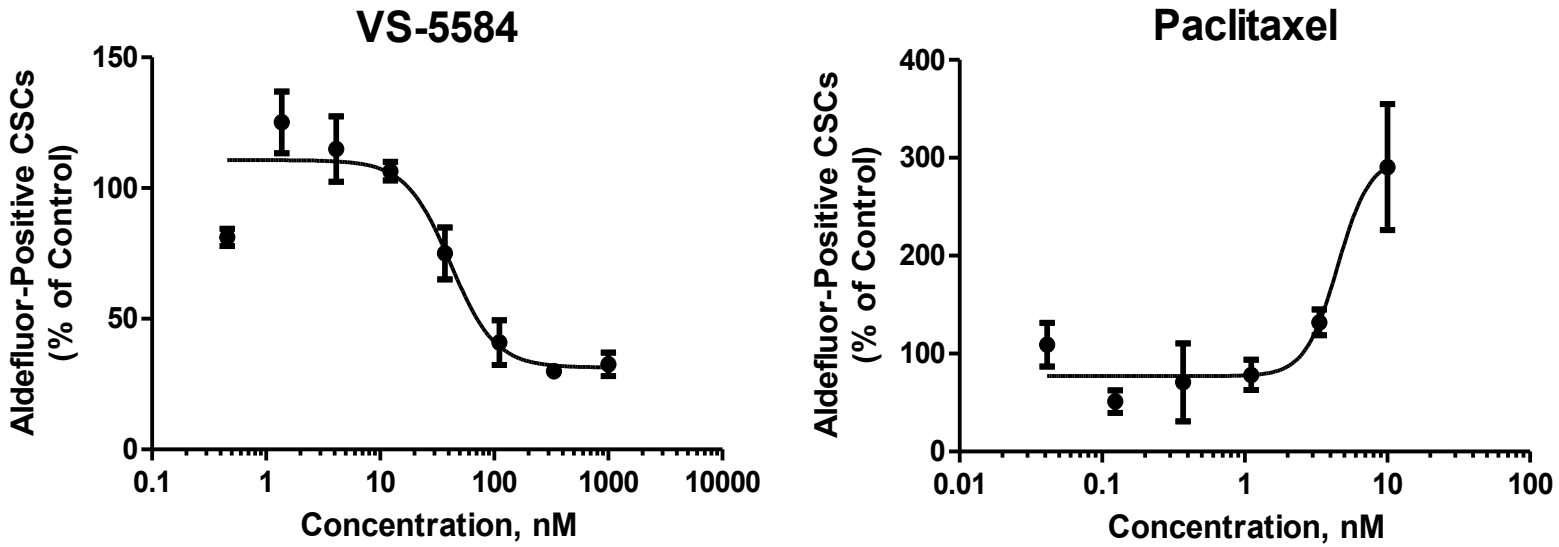
HMLE CSC Assay



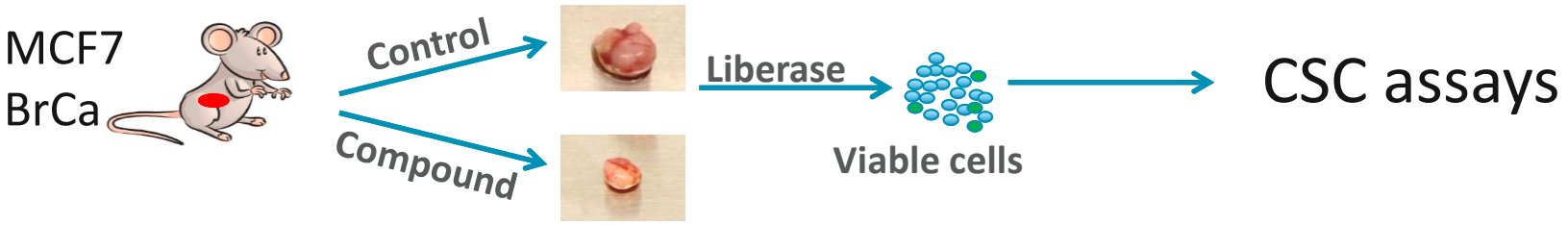
Dye Exclusion CSC Assay



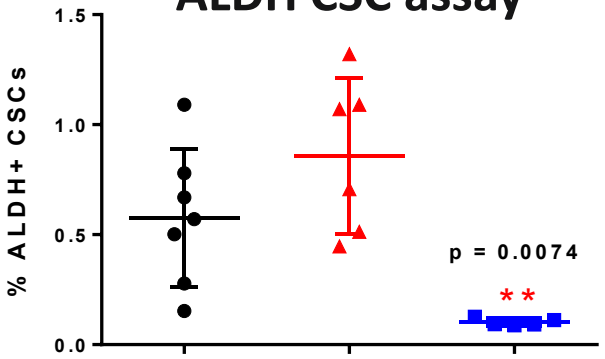
Aldefluor CSC Assay



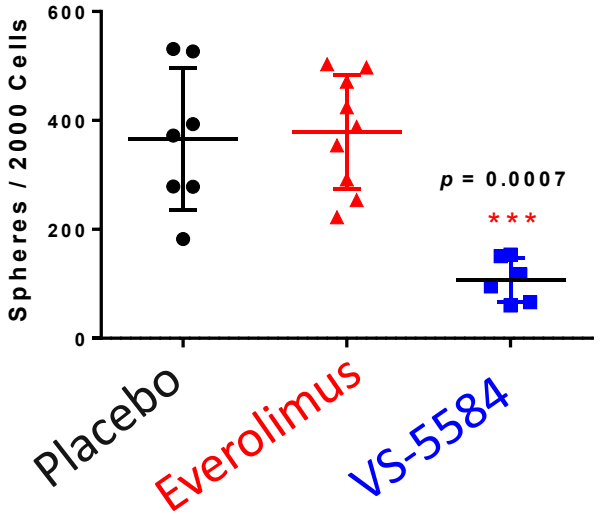
VS-5584 Reduces CSCs in MCF7 Breast Cancer Model: Contrast to mTORC1 Inhibitor Everolimus



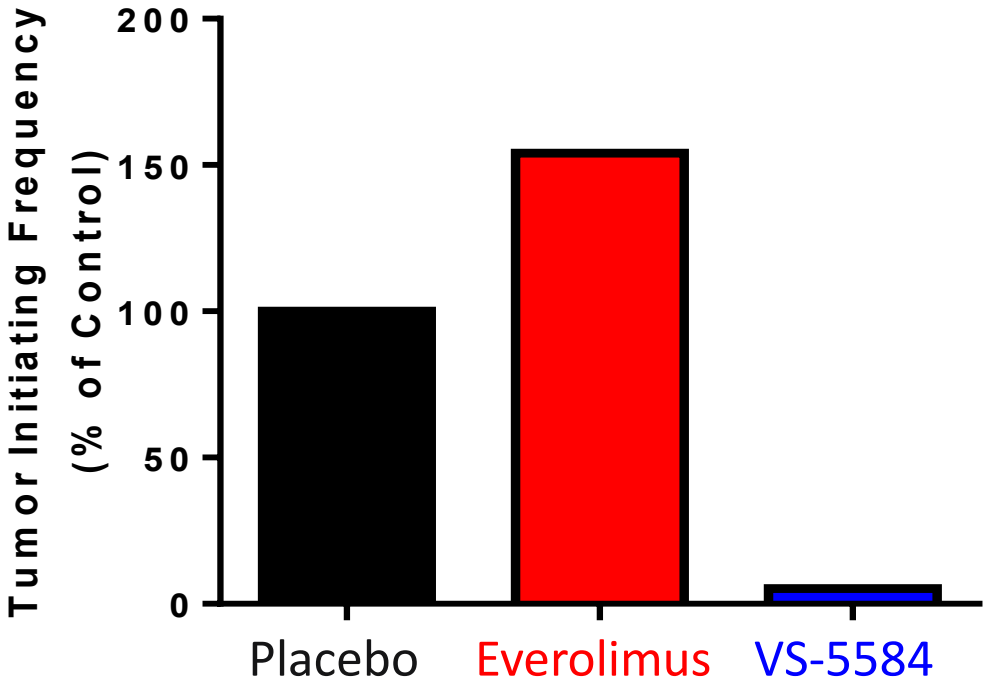
ALDH CSC assay



2º Tumorspheres

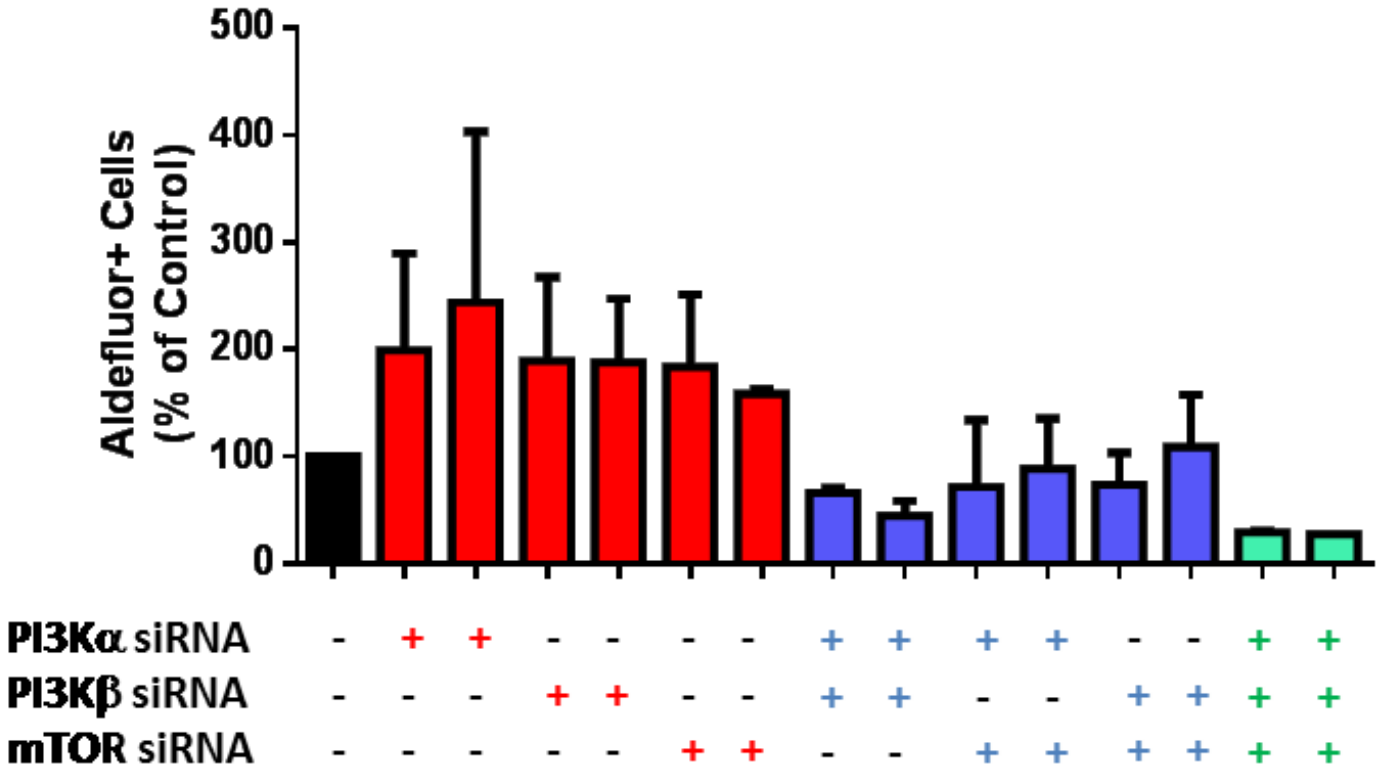


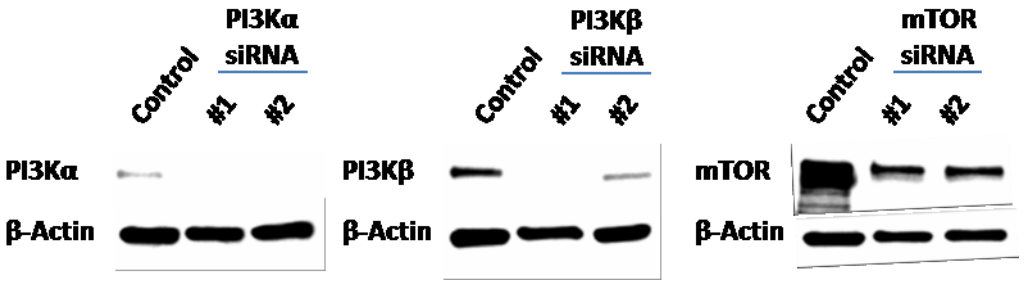
Tumor Initiation in 2º Mice



Kolev et al. (2015) Cancer Res 75: 446

Combined Inhibition of PI3K and mTOR is Critical for CSC Targeting Phenocopies VS-5584





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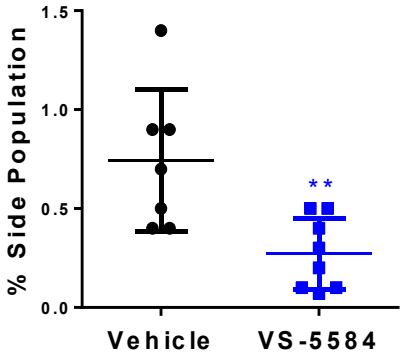
VS-5584 Preferentially Targets CSCs & Extends Efficacy of Chemotherapy in SCLC Models

Blockade of Tumor Initiating Capacity

- Mice bearing SCLC xenograft tumors treated with VS-5584 20 mg/kg, po, 3x/wk
  - Viable cells dissociated & CSCs tested

↓ CSCs
Hoechst Dye Exclusion



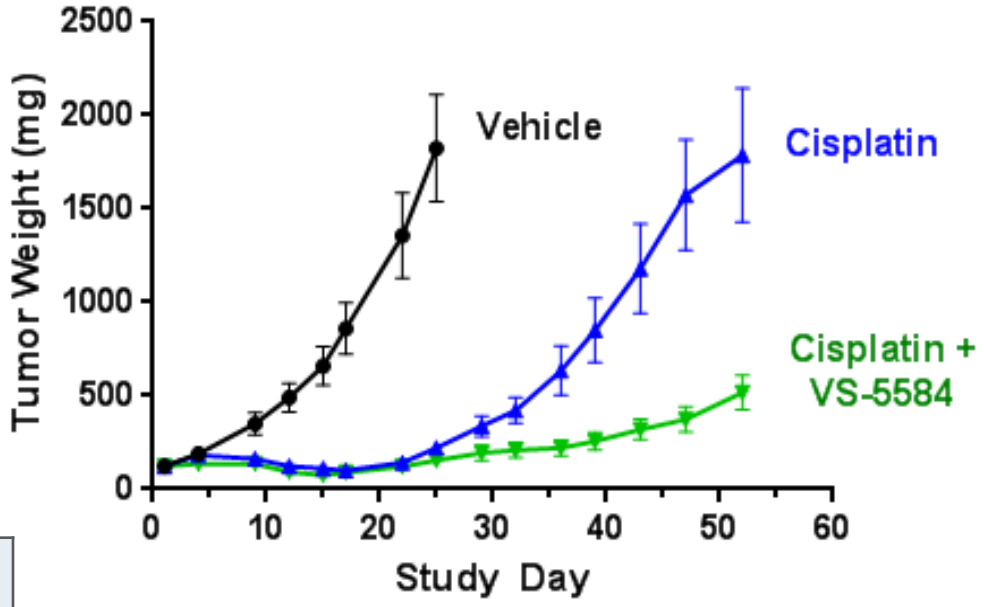
↓ Tumor-Initiating Potential in 2° Mice

# Cells	Control	VS-5584
1,000,000	4(4)	2(4)
100,000	2(3)	0(3)
10,000	2(3)	0(3)
1,000	1(3)	0(3)
TIF	1/24,000	1/1,615,000
p	$5x10^{-6}$	

70-fold decrease in TIF

NCI-H841 SCLC xenograft model

VS-5584 Extends Cisplatin Efficacy in SCLC Xenograft Model



Cisplatin

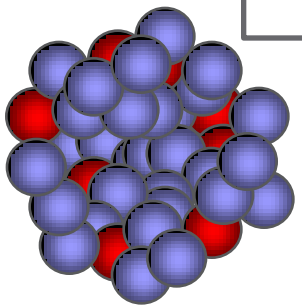
VS-5584

H69 SCLC xenograft model

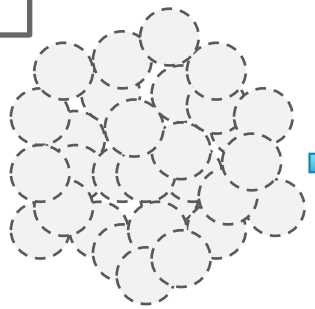
Potential Clinical Trial Designs for Drugs Targeting Cancer Stem Cells

Concurrent:

CSC Drugs + Chemo



Initial Tumor



Tumor Reduction & Elimination of CSCs

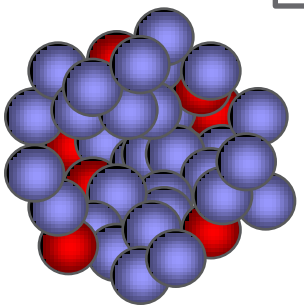
Theoretical Result

More Durable Clinical Response

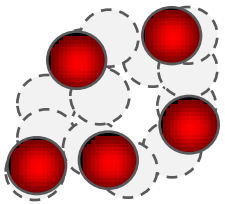
SCLC

Maintenance:

Cisplatin + Etoposide



Initial Tumor



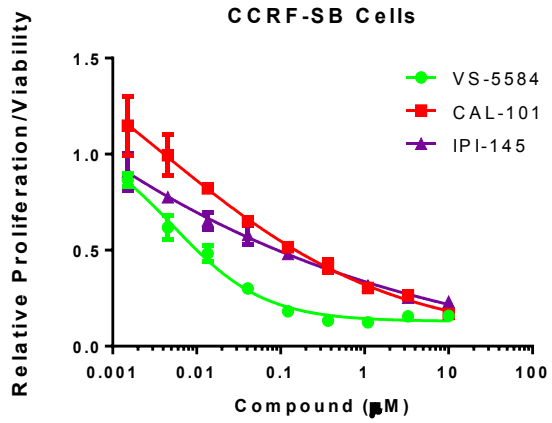
Tumor Reduction but CSCs are Enriched

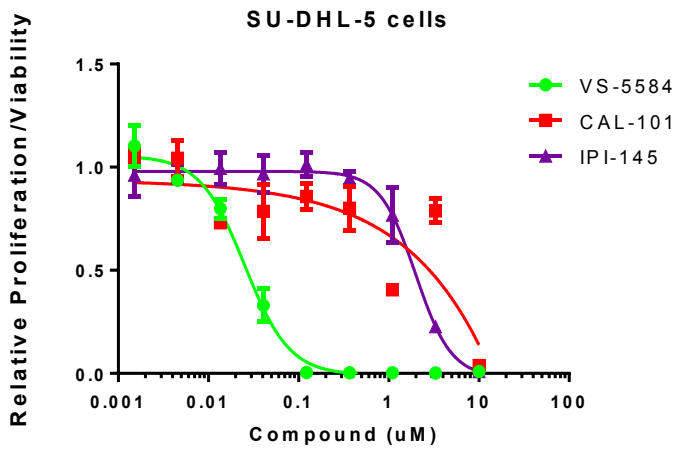
VS-5584

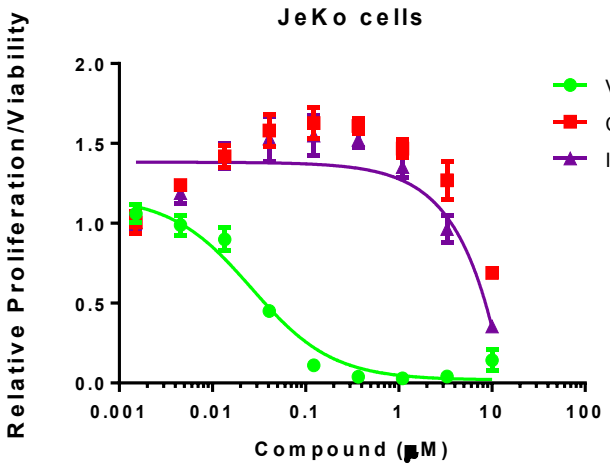
More Durable Clinical Response

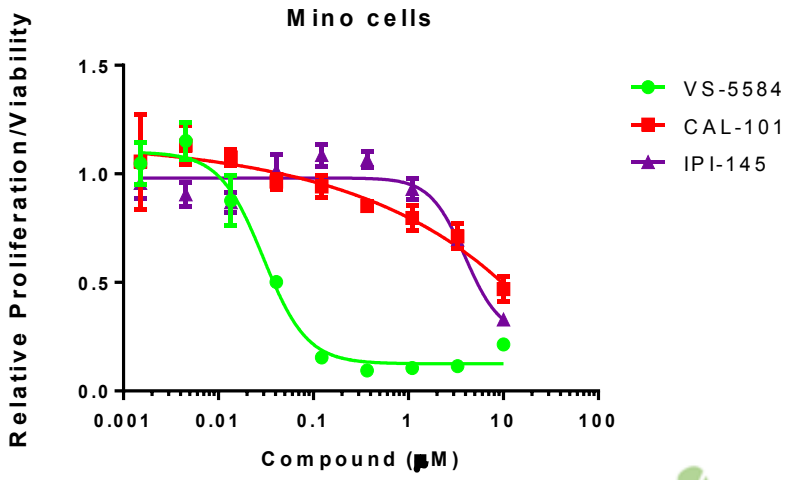
VS-5584 is More Potent than PI3K-delta Inhibitors Against the Proliferation & Survival of B-cell Leukemia/Lymphoma *in vitro*

	mTOR	PI3Kα	PI3Kβ	PI3Kγ	PI3Kδ
VS-5584	3.4	2.6	21	**2.7**	**3.0**
CAL-101	> 10,000	8500	840	**550**	**11**
IPI-145		1600	85	**27**	**2.5**









Phase 1 Single Agent Dose Escalation

VS-5584: Phase 1 Dose Finding and Safety Study in Solid Tumors

Design

- Phase 1 dose escalation study in solid tumors

Status

- Generally well tolerated to date and the expected on-target effects are clinically manageable
- MTD has not yet been reached
- Expect to report preliminary data in H2 2015

Sites

- Royal Marsden Hospital (UK) – Dr. Udai Banerji
- Scottsdale Healthcare (AZ – US) – Dr. Jasgit Sachdev
- Sarah Cannon Research Institute (TN – US) – Dr. Howard Burris
- Memorial Sloan Kettering Cancer Center (NY – US) – Dr. Anna Varghese
- Cedars-Sinai Medical Center (CA – US) – Dr. Monica Mita

Observations

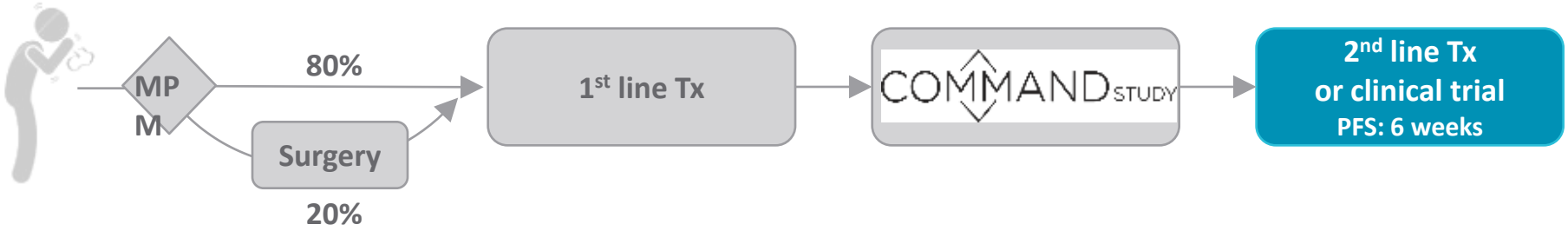
- Well within active dose range based on PD biomarker measurements
- Initial clinical activity in multiple tumors including mesothelioma
- Disease control of 6 months or more has been observed

**Unlocked, in-progress data as of 5 Jan 2015*

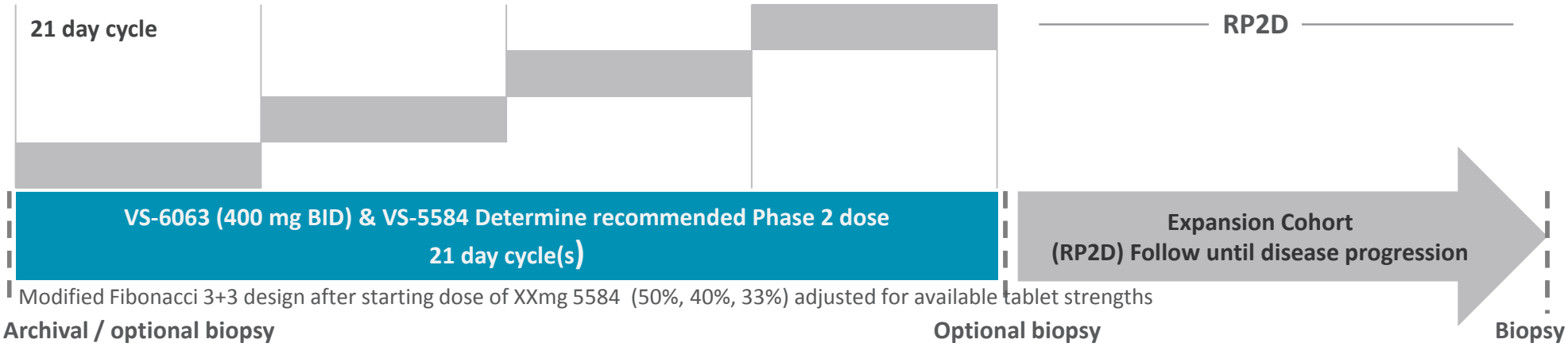
Mesothelioma: VS-5584/VS-6063 Combination Study in Relapsed Mesothelioma

VS-5584 and VS-6063 mesothelioma combo, Phase 1

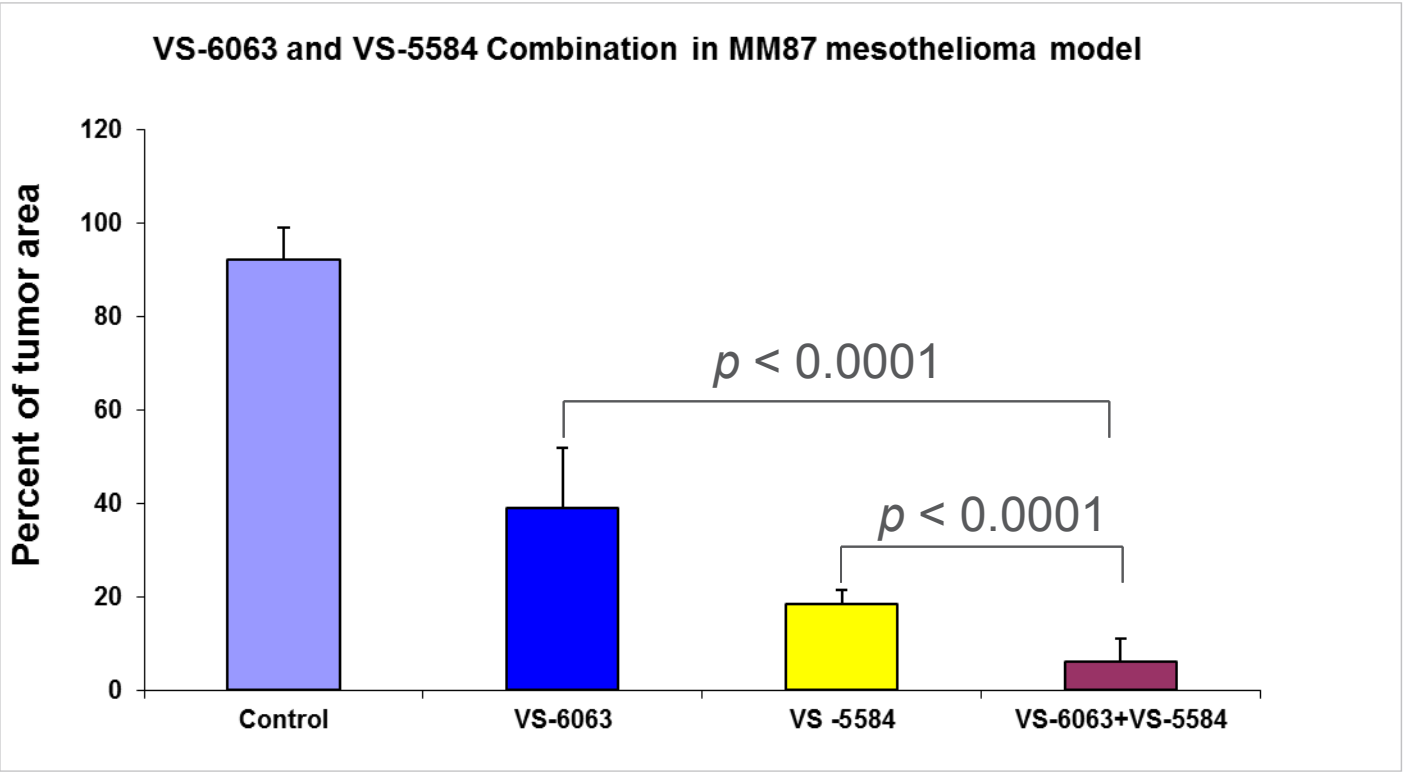
Phase 1 dose finding and safety study in solid tumors



Rationale	• Strong pre-clinical data demonstrating synergy of VS-5584 and VS-6063 in pre-clinical mesothelioma models • 3 FAKi's have demonstrated SD in meso patients with relapsed disease • PI3k/mTOR inhibitor GDC-0980 demonstrated ORR in meso patients with relapsed disease
Goals	• Safety of combination • Biomarker analysis (assess target proteins in tumor and genomic analysis, PRP for pharmacodynamics) • Assess potential activity in mesothelioma
Investigators	• Dr. Banerji , Royal Marsden (UK) • Dr. Fennell, University of Leicester (UK) • Dr. Kindler, University of Chicago (IL) • Dr. Zauderer, Memorial Sloan Kettering (NY)



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

Source: J. Testa, Fox Chase

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Verastem Team

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Breakthrough designation for Entinostat

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Cofounder: Alnara (now Lilly), OvaScience (OVAS)

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PharMetrics (now IMS), Axion

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Harvard Medical School/HHMI

Eric Winer, M.D.
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