VS-4718 FAK INHIBITOR

NON-CONFIDENTIAL SUMMARY

DECEMBER 2015

Verastem Company Summary

- Verastem (VSTM) is a publically traded Biotechnology company based in Boston, MA
  - Founded in 2010 by Robert Weinberg (MIT) & Eric Lander (Broad Institute)
- Focused on development of small molecule anticancer drugs that target the tumor microenvironment for durable response
  - Cancer Stem Cells (CSCs)
  - Immune cell modulation
  - Tumor stromal density

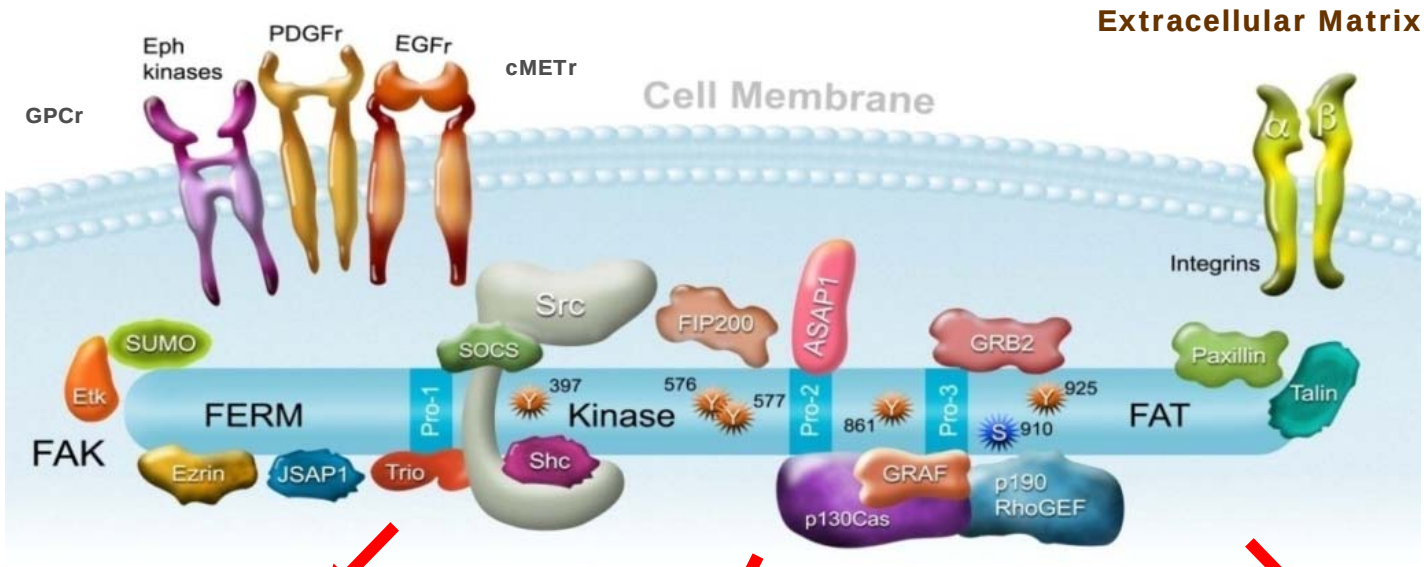
VS-4718 Objectives for CRUK Combinations Alliance

- Update on VS-4718 Development path
  - VS-4718 is an oral small molecule FAK/PYK2 kinase inhibitor
  - Phase 1 dose finding study nearing completion to define RP2D
  - Phase 1 combination study of VS-4718 with gemcitabine/Nab-paclitaxel in 1st line pancreatic cancer in progress
- Explore selected combinations of interest with VS-4718
  - Immune checkpoint inhibitors
  - Other immuno-oncology agents
  - Targeted agents of other classes
- Open to additional novel combinations and indications with strong scientific rationale

VS-4718 Scientific Rationale

FAK as an Anti-Cancer Target

- FAK (Focal Adhesion Kinase) is a non-receptor tyrosine kinase activated in response to Integrin and Growth Factor receptor stimulation
- FAK activation triggers signaling pathways essential for tumor cell proliferation, survival, migration, invasion, angiogenesis and resistance to chemo- & radiation therapy
- FAK inhibition blocks both primary tumor growth & metastasis



Focal adhesion contacts

Motility

Inplantation / Invasion

Anti-apoptosis / Anti-anoikis (survival)

Angiogenesis

Cell adhesion Drug resistance

Brunton VG & Frame MC. *Curr Opin Pharmacol*. 2008;8:427
Schlaepfer DD et al. *Biochim Biophys Acta*. 2004;1692:77

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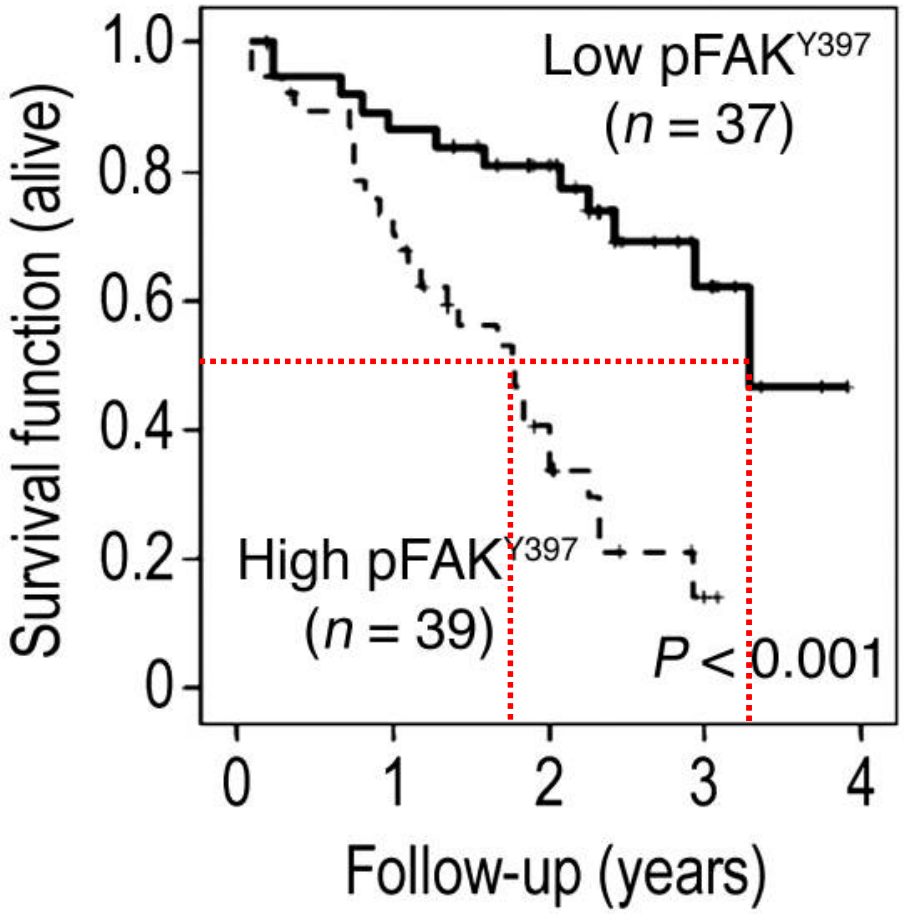
FAK is Highly Expressed in Advanced Stages of Cancer

Tissue	Normal	Benign	Pre-Invasive	Invasive	Metastatic	Reference
Breast		-		+++	++++	*Lancet* 342:1024, 1993.
	+/-			+++	++++	*Cancer Res* 55: 2752, 1995.
		+	+++	+++		*Clin Cancer Res* 6: 2417, 2000.
	+/-			+/+++		*J Gastroenterol* 8: 613, 2002.
Colon	-	+		++++	+++++	*Lancet* 342:1024, 1993.
	+	-	+++	+++	+++	*Cancer Res* 55: 2752,1995.
	+				+++	*Ann Surg Oncol* 4: 264, 1997.
		+	+++	+++		*Clin Cancer Res* 6: 2417, 2000.
	+			+++	++	*Clin Cancer Res* 7: 3106, 2001.
	+/-			++/+++		*J Gastroenterol* 8: 613, 2002.
Thyroid	+	+		+/+++	++++	*Ann Surg Oncol* 3: 100, 1996.
Prostate	+/-	+		+	+++	*Int J Cancer* 68: 164, 1996.
	++	+++	+++	+++	+++	*Prostate* 53: 124, 2002.
Head-Neck	-/++		+++	+/++++		*Head Neck* 20: 634, 1998.
Liver	-			+++		*Clin Cancer Res* 10: 2812, 2004
	+			+++++		*Br J Cancer* 85: 228, 2001.
	+/-			++/+++		*J Gastroenterol* 8: 613, 2002.
Stomach	+/-			++/+++		*J Gastroenterol* 8: 613, 2002.
Ovary	+			++++		*Cancer* 86: 1551, 1999.
Glioma	-	-	+	-	+++++	*Pediatr Neurosurg* 33: 49, 2000.
	-		-	+	++	*J Cell Sci* 113: 421, 2000.
		-	++	++	++	*Cancer Res* 61: 5688, 2001.
	+			+++		*Cancer Res* 62: 2699, 2002.

High pFAK Correlates with Poor Prognosis in Ovarian Cancer

- High tumor FAK and pFAK expression correlate with poor survival (*Sood et al., J Clin Invest 2010*)



VS-4718 is a potent FAK/PYK2 inhibitor

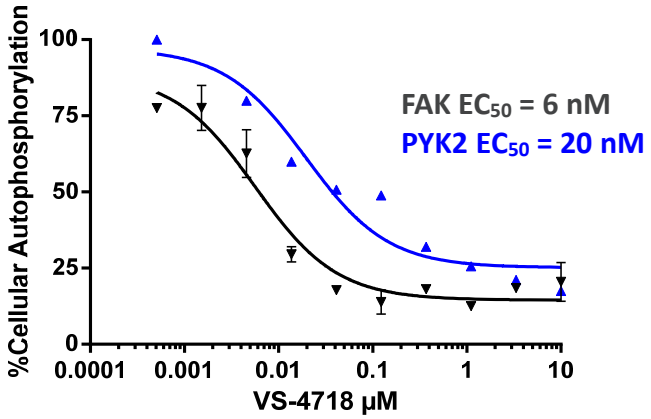
- VS-4718 FAK/PYK2 dual kinase inhibitor (orally available)

Biochemical Assay:

In vitro Inhibition of:	IC_{50} (nM)
Recombinant Focal Adhesion Kinase[1]	22

[1]Z-Lyte Kinase Assay

Cellular Assay:



- Preferentially targets cancer stem cells *in vitro* & *in vivo*
- Strong preclinical rationale for an Immuno-oncology role
- Broad, robust anti-tumor efficacy in xenograft, PDX & syngeneic models
- Phase I dose escalation nearing completion to define RP2D
  - Generally well tolerated to date and the expected on-target effects are clinically manageable

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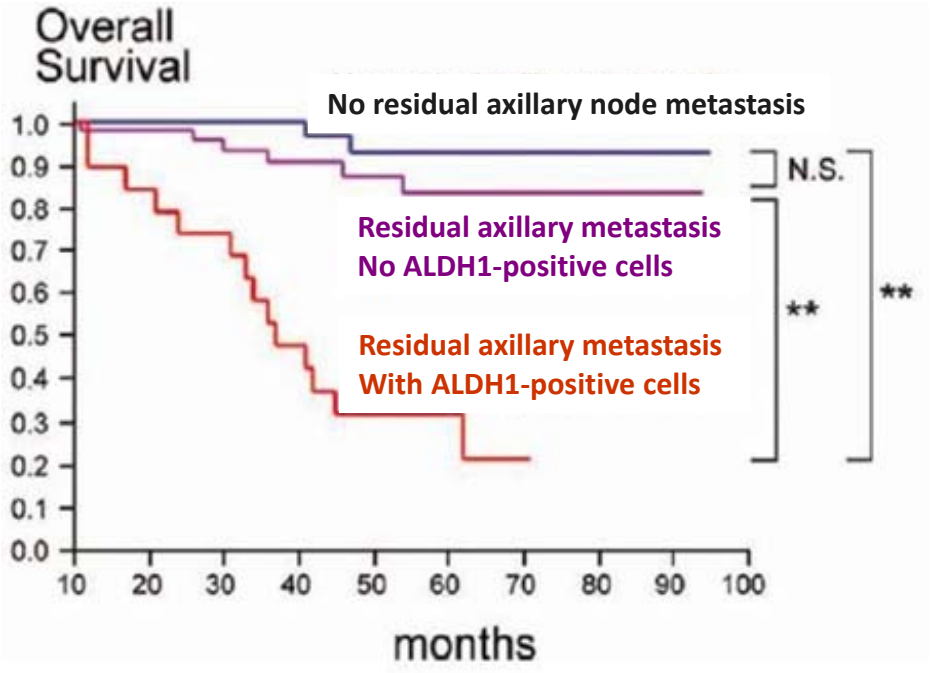
VS-4718 Preferentially Targets Cancer Stem Cells (CSCs)

Cancer Stem Cells (CSCs) in the tumor microenvironment

- Tumors are heterogeneous in composition
  - Bulk tumor (may be effectively targeted by chemotherapy)
  - Cancer stem cells (CSCs)
    - Resistant to chemotherapy and enriched by chemotherapy
    - Mediate cancer recurrence & metastasis
    - Functionally defined by their tumor-initiating capability
    - May be identified by specific markers (e.g. ALDH; CD133; SOX2)
  - Absence of CSC markers in residual tumor are indicators of good prognosis



- N = 115 patients with confirmed lymph node metastases at diagnosis
- Standard neoadjuvant chemotherapy: AC x 4 followed by weekly PTX x 12
- ALDH1 assessed by IHC
- ** $p<0.001$

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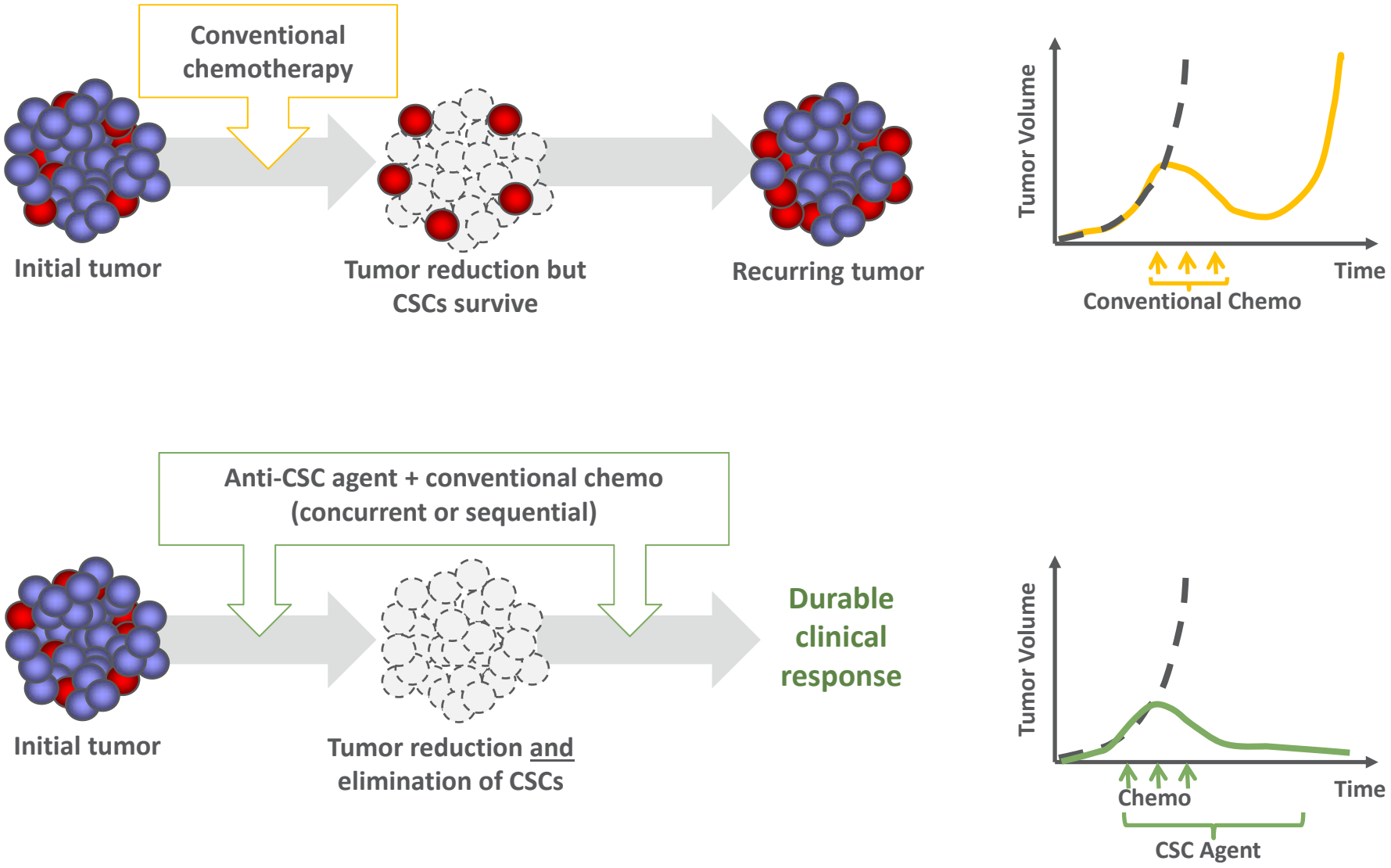
Targeting Cancer Stem Cells for a Durable Clinical Response



VS-4718 combinations are potentially important to target both cancer stem cells & bulk tumor for a more durable clinical response

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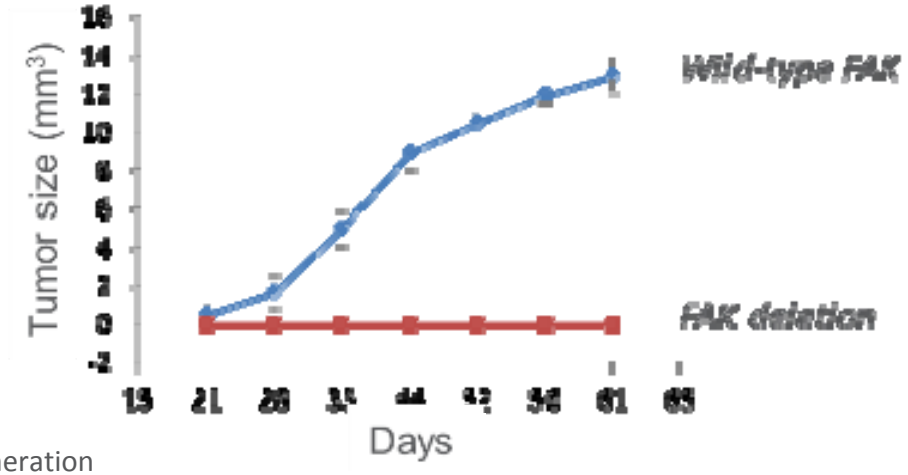
FAK is critical for Cancer Stem Cell tumor-initiating capability

Luo et al., Cancer Res 2009

Targeted deletion of FAK eliminates tumor initiating capability

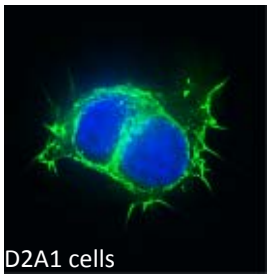
FAK deletion,
no tumor

FAK wt,
tumor generation



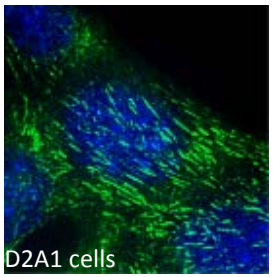
Shibue et al. Cancer Discovery 2012

FAK is critical for cancer cells undergoing EMT (epithelial-mesenchymal transition) to become CSCs capable of generating macrometastases



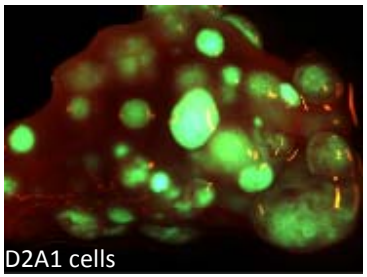
Cell mobility

FAK



Proliferation

FAK



Tumor initiation

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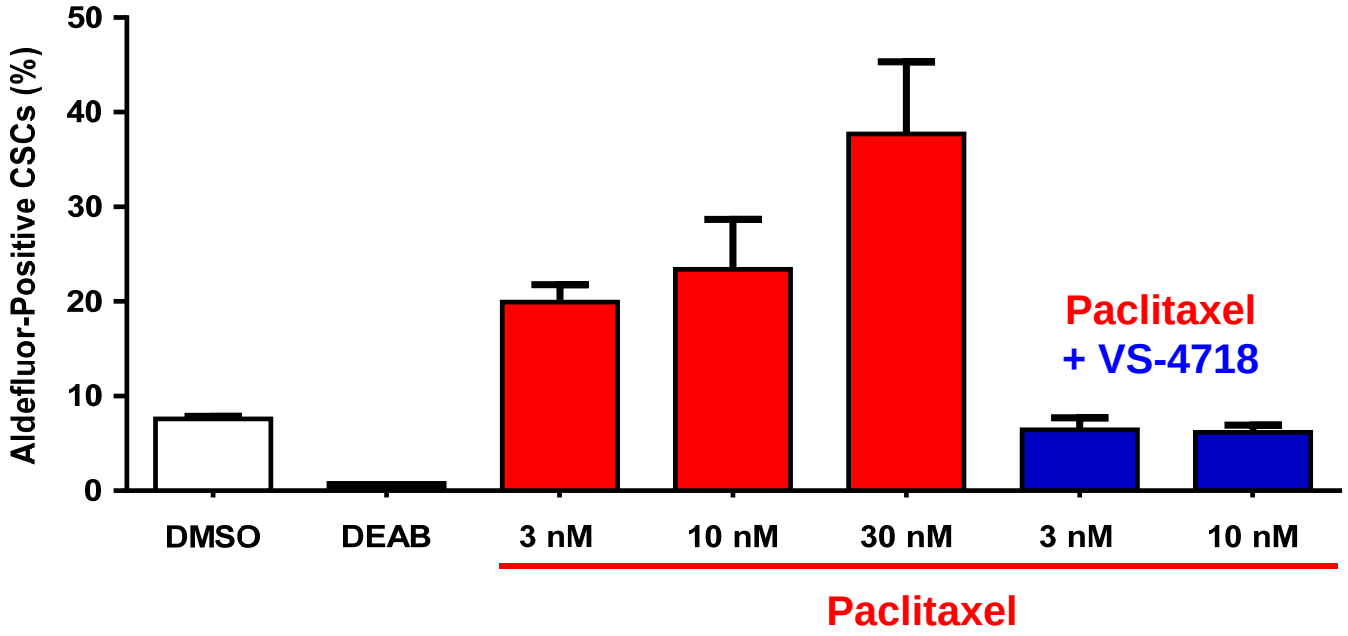
VS-4718 blocks enrichment of CSCs by standard of care chemotherapy

MDA-MB-231 TNBC cell line:



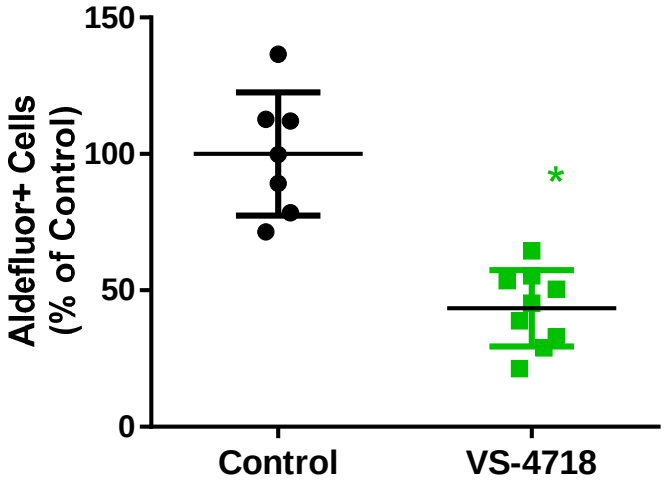
- Standard of care (SoC) chemotherapy agents enrich CSCs
- Single agent FAK inhibitor decreases the proportion of CSCs
- FAK inhibitor in combination with SoC chemotherapy blocks CSC enrichment

VS-4718 preferentially targets CSCs *in vivo*

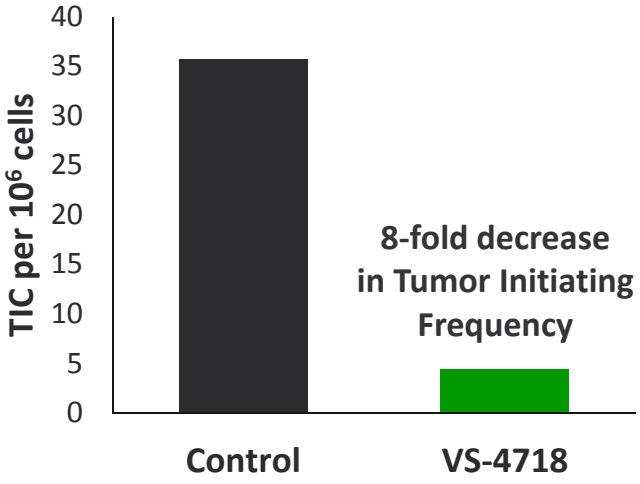
VS-4718 treatment, MDA-MB-231 TNBC model:

Treatment → Harvest tumors → Dissociation → Viable cells → Aldefluor assay; Re-implantation in limiting dilutions

CSC Population (Aldefluor +)

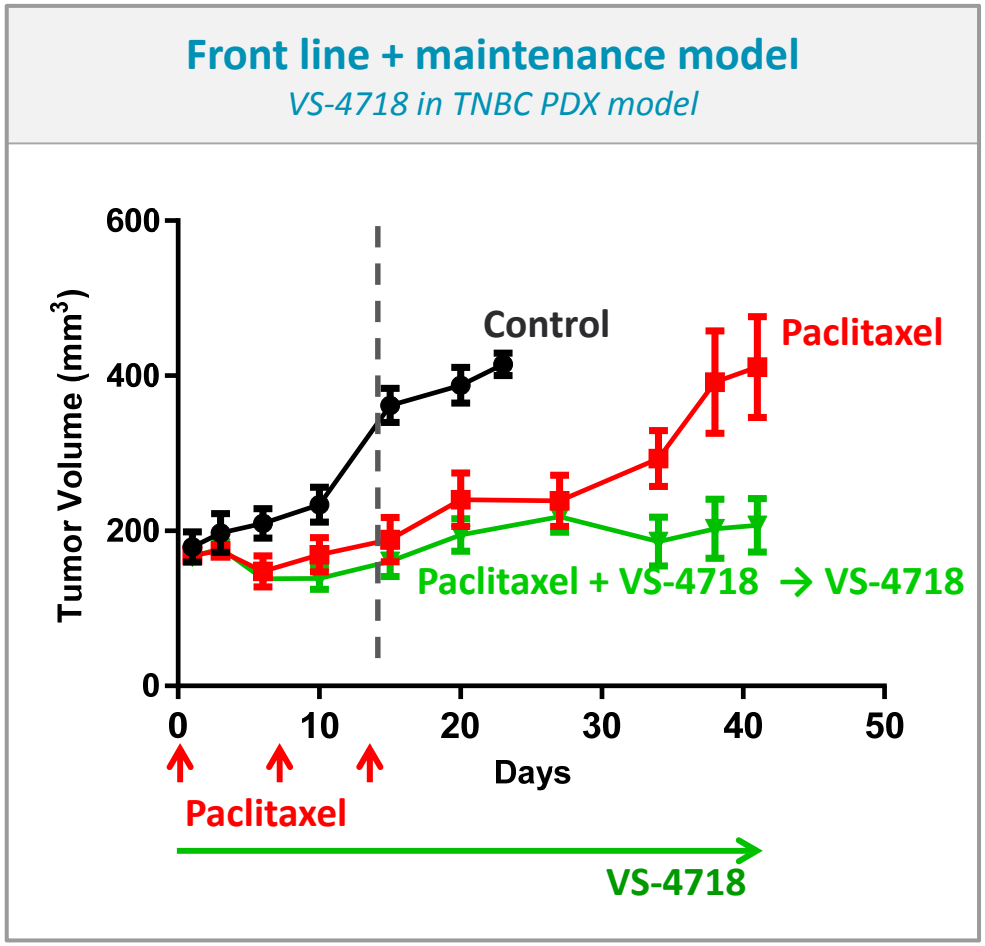


Limiting Dilution Assay##



The Limiting Dilution assay is a gold-standard functional assay for cancer stem cells

VS-4718 extends efficacy after discontinuation of chemotherapy



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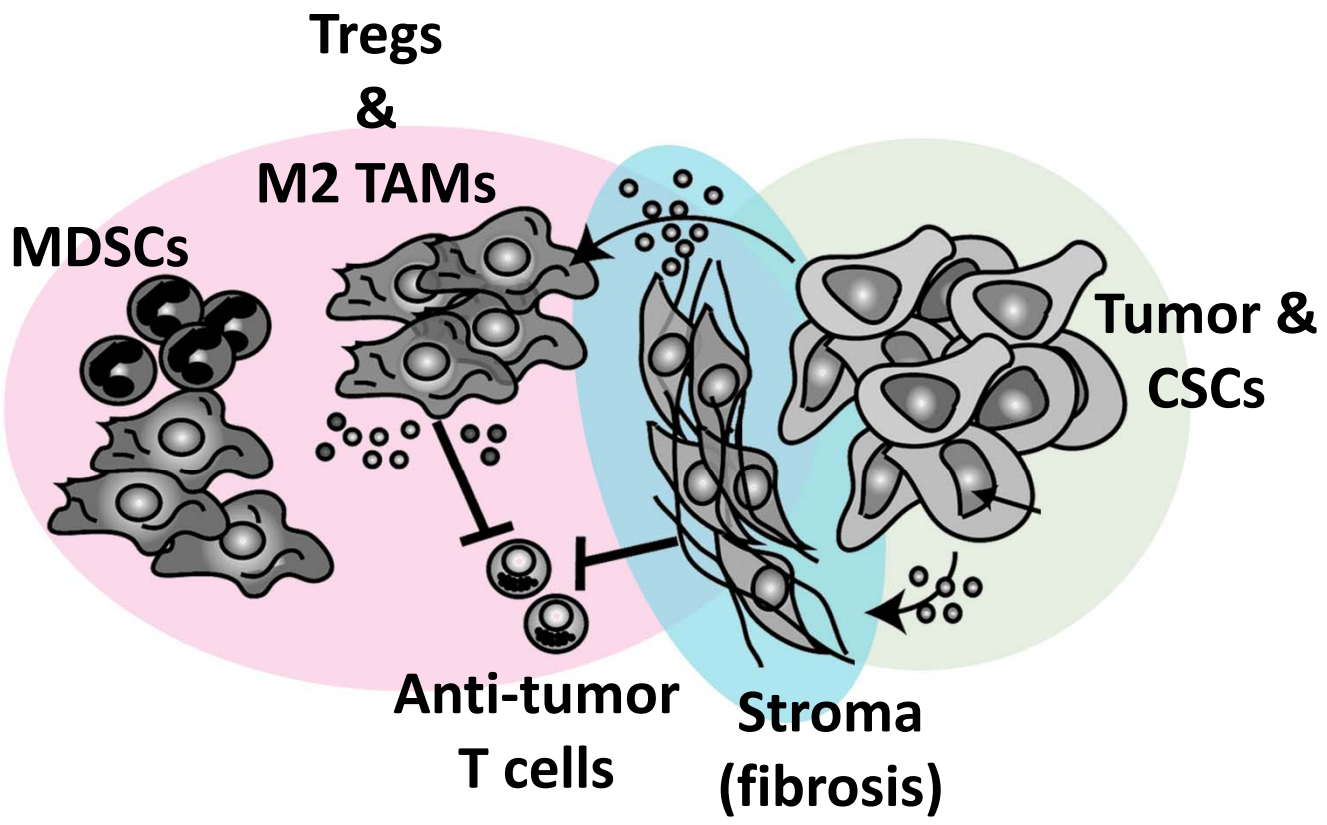
Immuno-Oncology role for VS-4718

Potential modulation of the immunosuppressive tumor microenvironment by FAK inhibitors



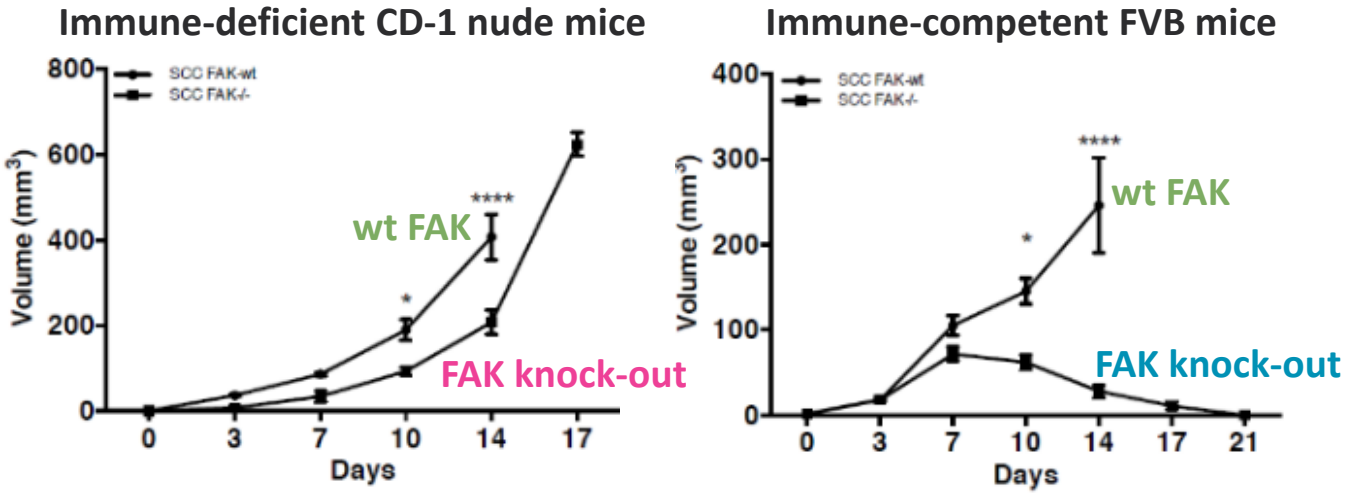
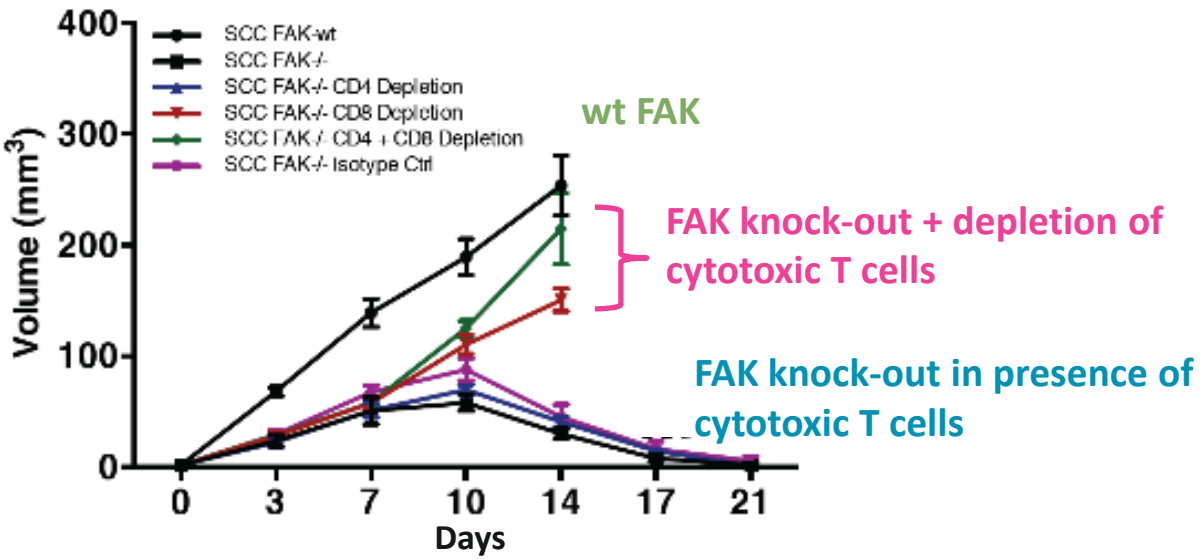
Modulate Tumor Immune Cell Populations
to enhance efficacy of immuno-therapeutics

Reduce Stromal Density
to improve drug & CD8+ T cell penetration To tumor

Reduce Cancer Stem Cells
in addition to bulk tumor for more durable response

FAK knockout-induced bulk tumor regression is dependent on the presence of CD8+ T cells

FAK knockout, SCC 7.1 cell line:

Tumor reduction through FAK knock-out is dependent on the presence of an immuno-competent setting	
Specifically, FAK knock-out mediated tumor reduction is dependent on the presence of cytotoxic (CD8+) T cells	

Serrels et al. (2015) *Cell* 163: 160

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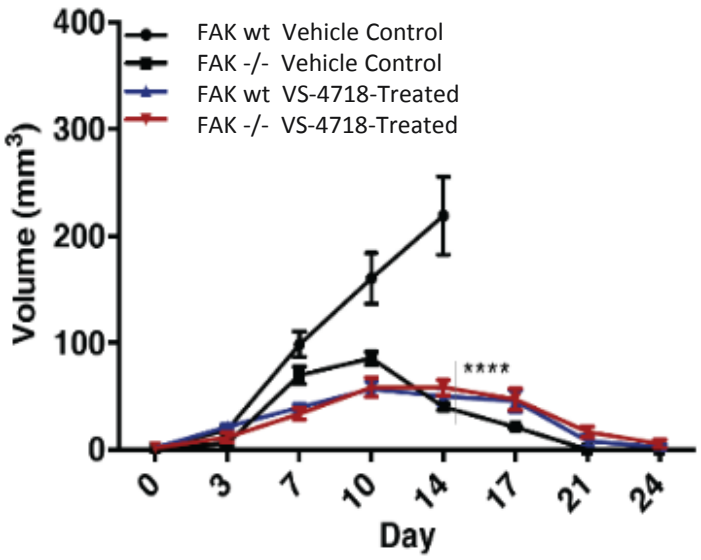
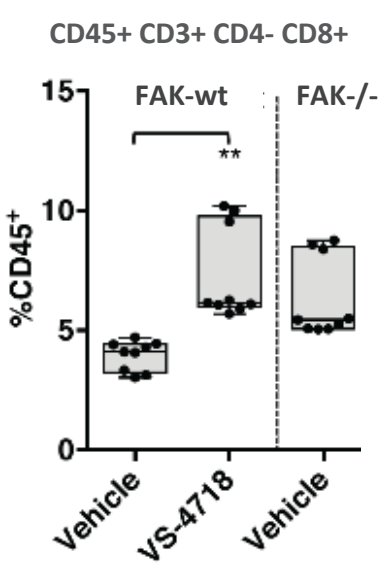
Treatment with FAK inhibitor replicates tumor regression, and correlates with increase in cytotoxic T cells & reduction in immunosuppressive Tregs

FAK knockout vs. FAK inhibitor treatment, SCC 7.1 cell line:

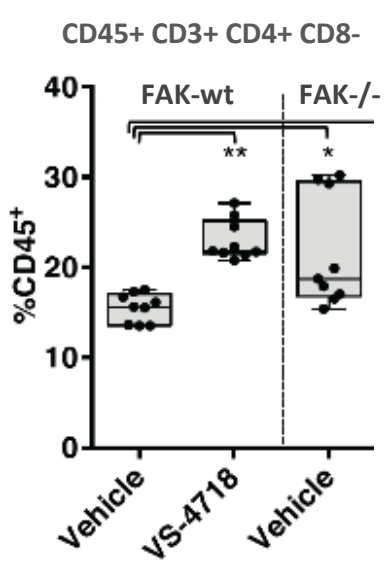
Tumor burden



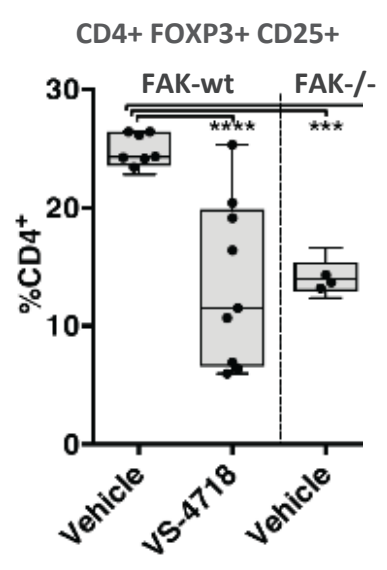
CD8+ T cells



CD4+ T cells



T-regs



FAK knock-out mediated tumor regression is replicated with FAK inhibitor treatment

In both FAK knockout cells and FAK-wt cells treated with FAK inhibitor, reduction in tumor burden is correlated with increase in T cells and reduction in immunosuppressive T-regs

Serrels et al. (2015) *Cell* 163: 160

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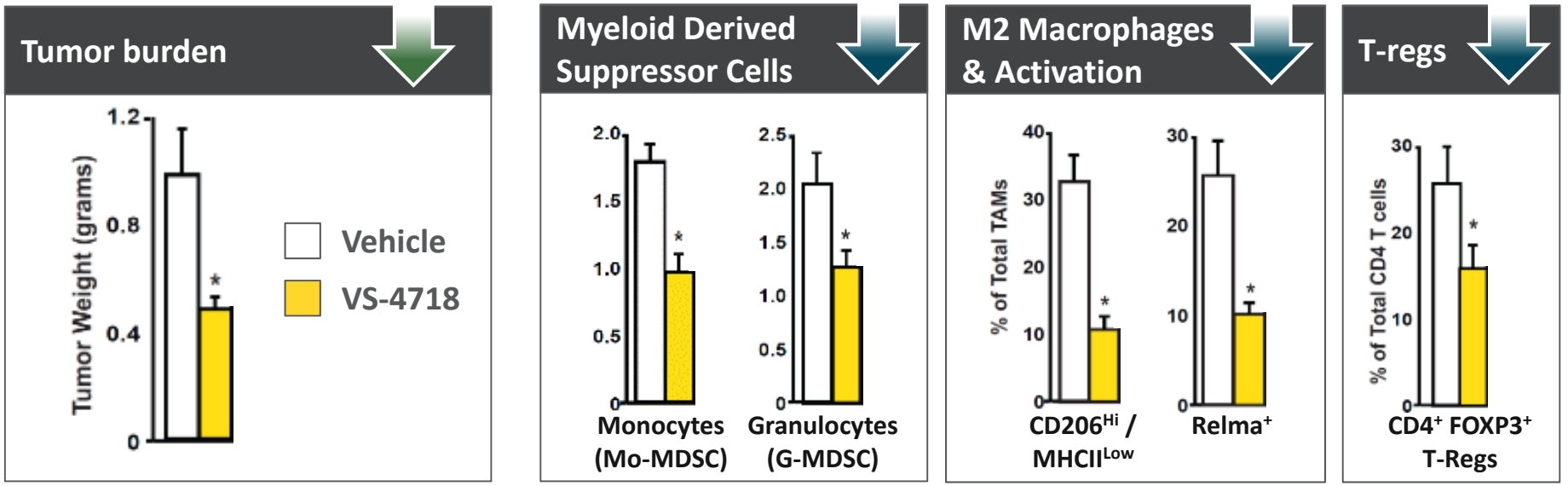
VS-4718 treatment reduces immunosuppressive MDSCs, M2 Macrophages & Tregs in tumor microenvironment

VS-4718 treatment, KRas-INK orthotopic pancreatic cancer model**:



Study design (n = 6-7):

Day 0 → 10 → 20

VS-4718

Flow cytometry
Cryo
RNA-Later (Cryo)

** Similar reductions in tumor MDSCs, TAMs & T-regs observed in skin, lung & breast cancer models

Source: D DeNardo, Washington University

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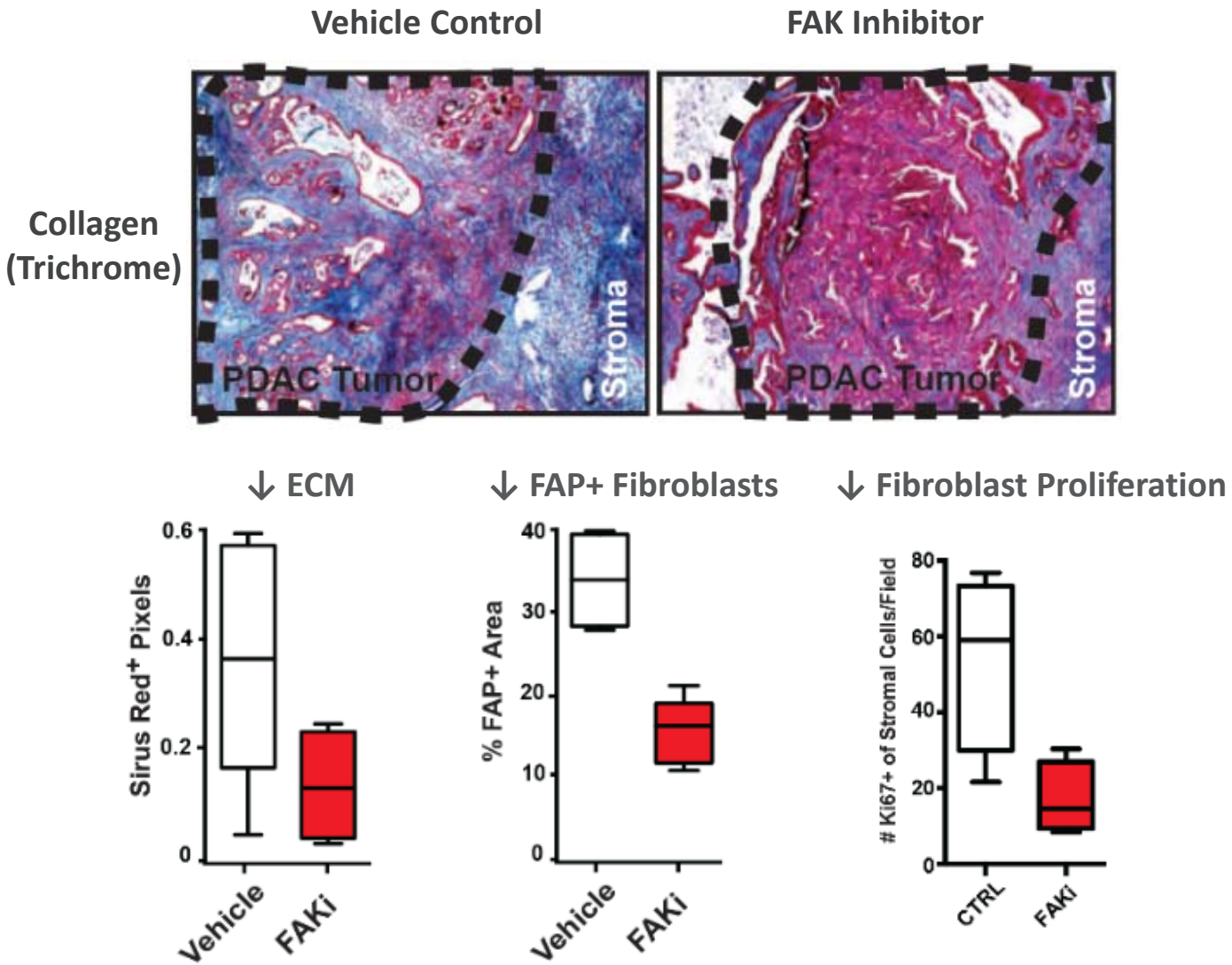
VS-4718 reduces stromal density in pancreatic cancer transgenic model

VS-4718, PDAC transgenic model:



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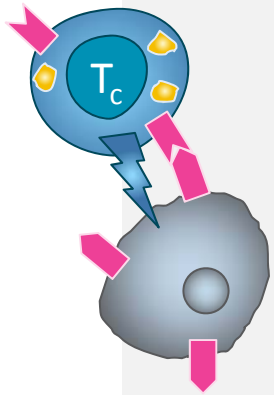
FAK inhibitor modulation creates a more favorable tumor immune microenvironment for checkpoint inhibitor efficacy

Treatment with Verastem FAK inhibitor



Increases

Cytotoxic (CD8+) T cells
Tumor infiltration
& tumor cell killing

Checkpoint inhibitor target presentation
Tumor PD-L1

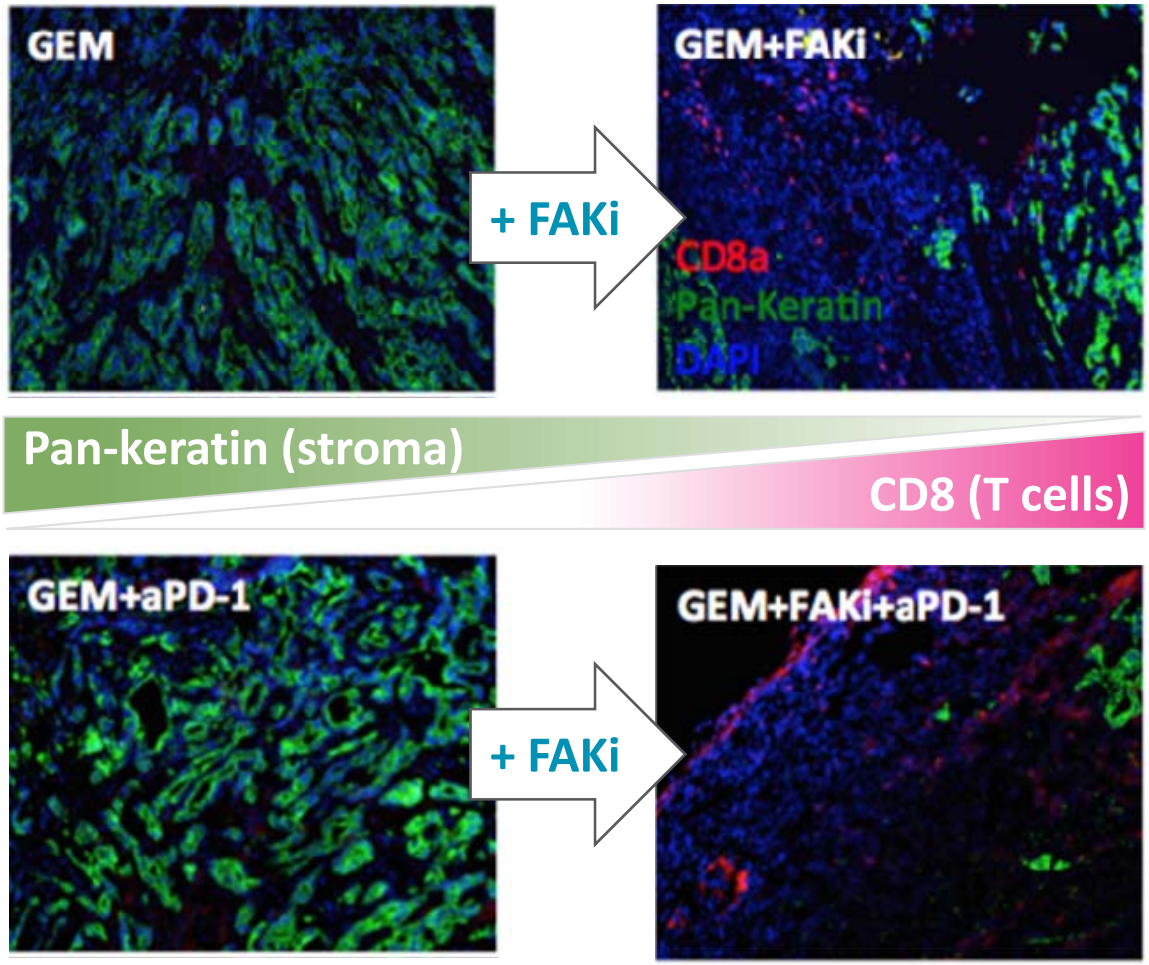
Decreases

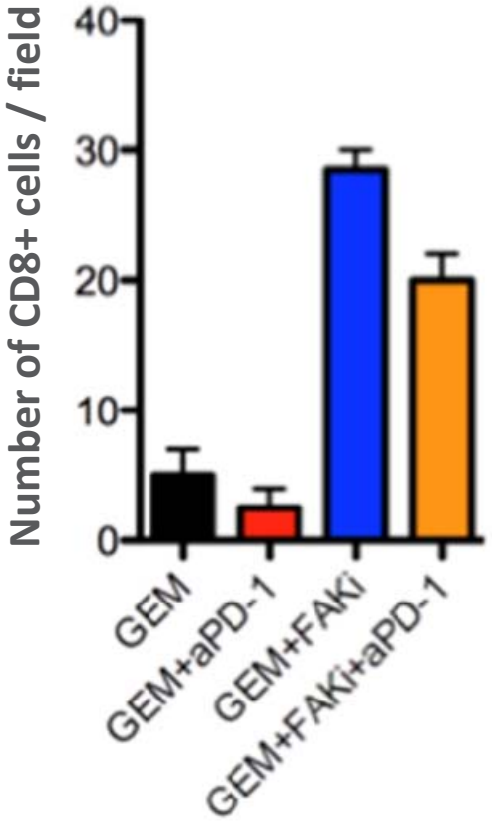
Immuno-Suppressive Cells
MDSCs, Tregs, M2 tumor-associated macrophages

More favorable tumor microenvironment for enhanced efficacy of Immuno-Oncology therapeutics

VS-4718 added to gemcitabine or gemcitabine + anti-PD-1 alters stroma and boosts CD8+ T cell entry

VS-4718, Kras/p53 pancreatic tumors:





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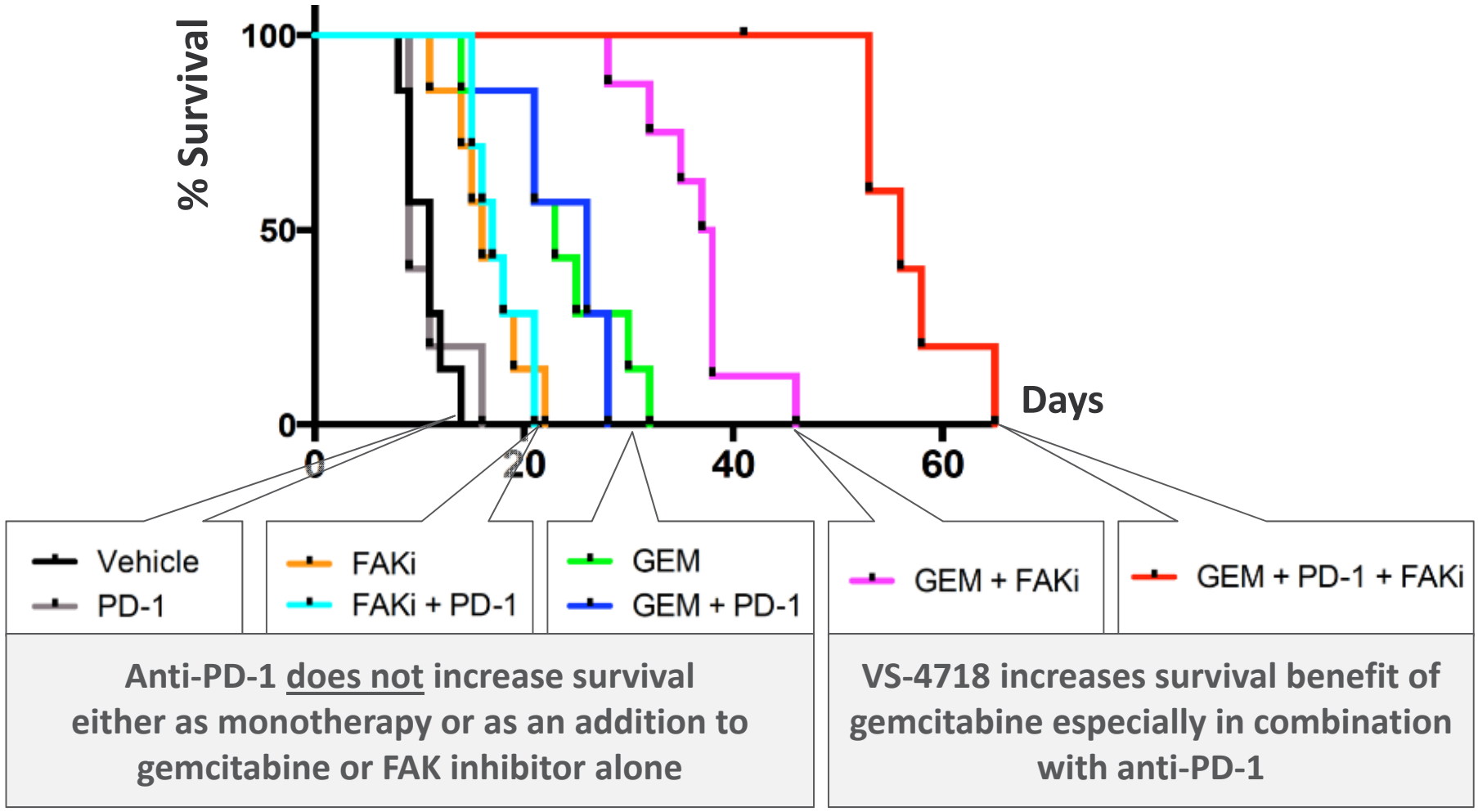
VS-4718 opens potential for anti-PD-(L)1 in pancreatic cancer

KRas/p53 s.c KPC pancreatic cancer mouse model:



Anti-PD-1 does not increase survival either as monotherapy or as an addition to gemcitabine or FAK inhibitor alone

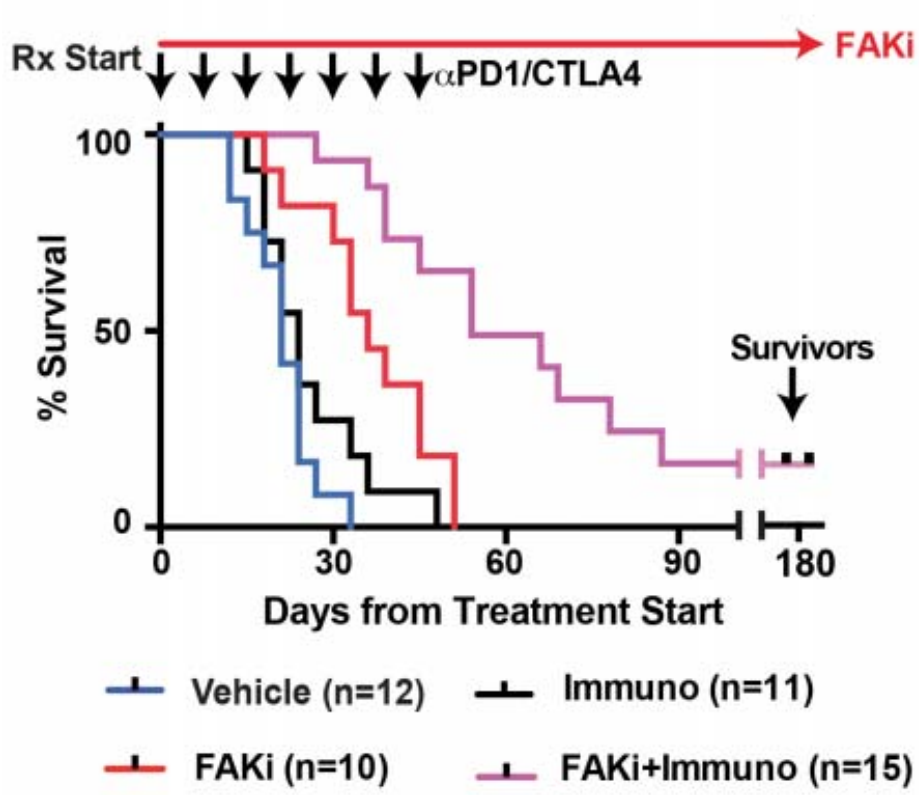
VS-4718 increases survival benefit of gemcitabine especially in combination with anti-PD-1

Source: D. DeNardo, Wash U

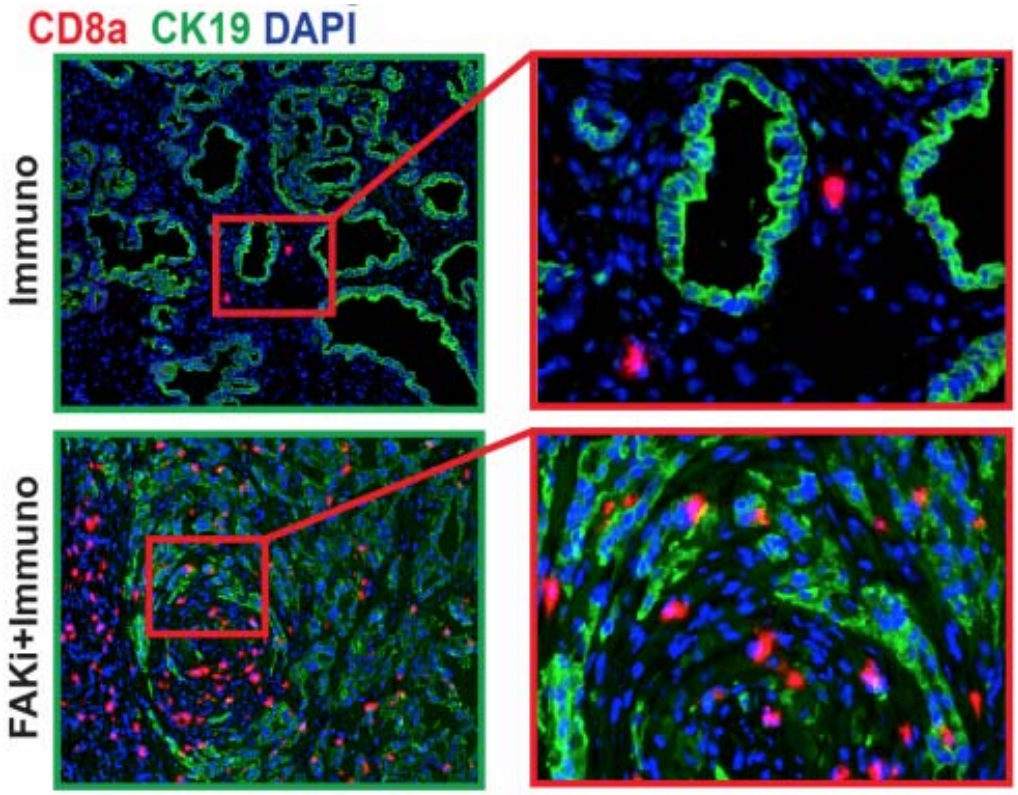
Combination benefit retained in difficult-to-treat KPPC transgenic model

FAK inhibitor treatment, KPPC transgenic pancreatic cancer model:

Extended Survival



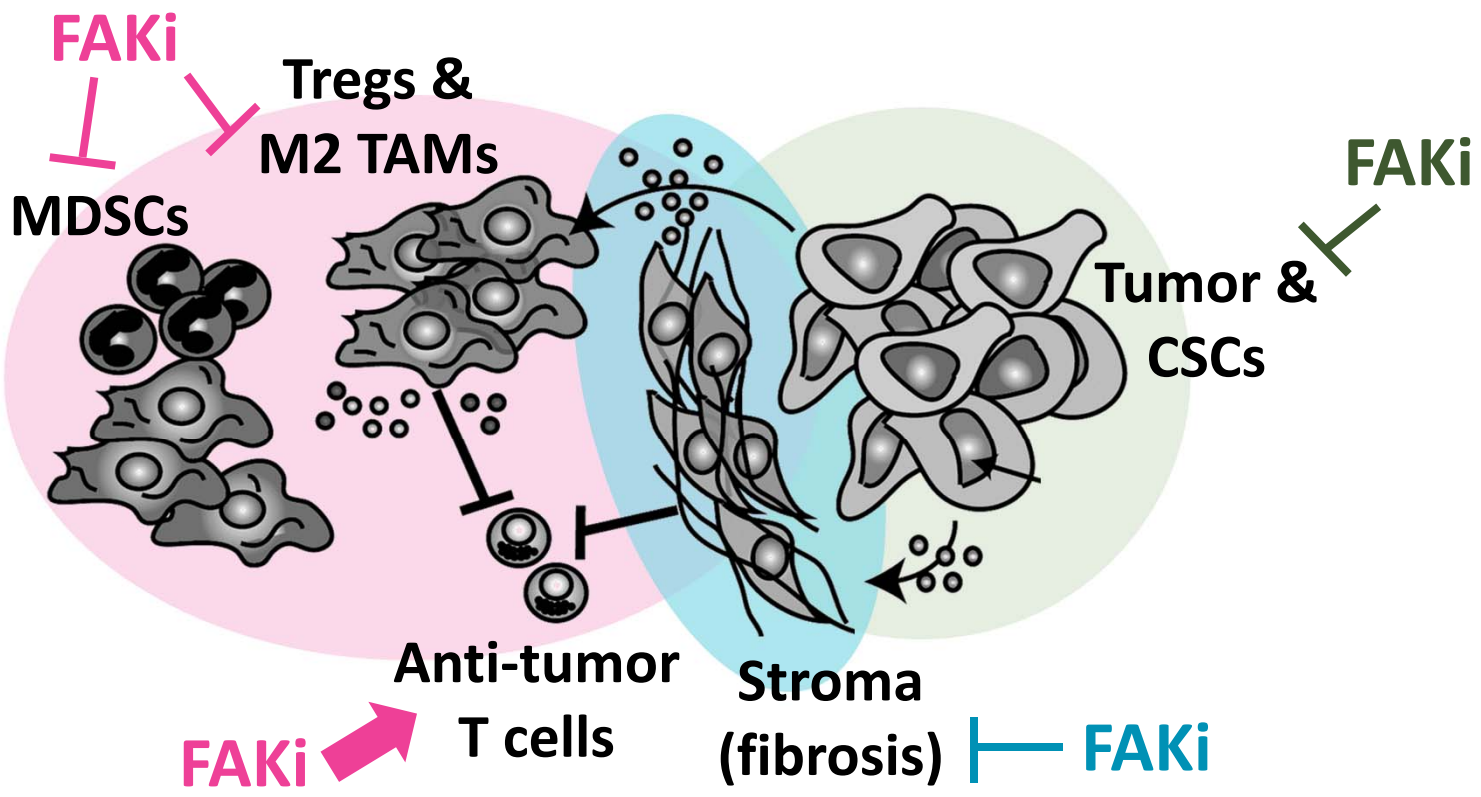
Entry of CD8+ Cytotoxic T cells into Tumor



"Immuno" = anti-PD-1 + anti-CTLA-4 + GEM (25 mg/kg)

Source: D DeNardo, Washington University

The VS-4718 mechanism-of-action creates a favorable tumor microenvironment for increased efficacy of immuno-therapeutics



Modulate Tumor Immune Cell Populations
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Reduce Stromal Density
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Reduce Cancer Stem Cells
in addition to bulk tumor for more durable response

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VS-4718 Clinical Development

VS-4718-101 Phase 1 Dose Finding and Safety Study in Solid Tumors

- VS-4718-101 (NCT01849744) dose finding to define RP2D
- Dose Proportional PK during the dose escalation
  - Exposures are sufficient for sustained target coverage (>target EC_{50})
- Safety & PD
  - Generally well tolerated to date and the expected on-target effects are clinically manageable
- Additional data can be shared under confidentiality

Combination with Gemcitabine/Nab-paclitaxel in pancreatic cancer

- VS-4718-103 Primary Objectives
  - To determine the recommended Phase 2 dose (RP2D) of VS-4718 in combination with nab-paclitaxel and gemcitabine in subjects with advanced cancer and subjects with untreated advanced pancreatic cancer
  - To assess the safety and tolerability of VS-4718 in combination with nab-paclitaxel and gemcitabine in subjects with advanced cancer and subjects with untreated advanced pancreatic cancer
- Status
  - Study initiated in September, 2015
  - Dose escalation Cohort 1 underway

VS-4718 Objectives for CRUK Combinations Alliance

- Update on VS-4718 Development path
  - VS-4718 is an oral small molecule FAK/PYK2 kinase inhibitor
  - Phase 1 dose finding study nearing completion to define RP2D
  - Phase 1 combination study of VS-4718 with gemcitabine/Nab-paclitaxel in 1st line pancreatic cancer in progress
- Explore selected combinations of interest with VS-4718
  - Immune checkpoint inhibitors
  - Other immuno-oncology agents
  - Targeted agents of other classes
- Open to additional novel combinations and indications with strong scientific rationale

Verastem Team

Executive Management

Robert Forrester
President/CEO, BOD
CEO/CFO, CombinatoRx/COLY
MeesPierson, Barclays, UBS

Lou Vaickus, M.D., FACP
Interim Chief Medical Officer
VP, Head of Clinical Development Vertex
Tolerx, Sunovion, EMD Serono

Christoph Westphal, M.D., Ph.D.
Executive Chairman of BOD, Cofounder
Cofounder/CEO: MNTA, ALNY, XLRN, SIRT, VSTM
Cofounder: Alnara (now Lilly), OvaScience (OVAS)

Jonathan Pachter, Ph.D.
VP, Head of Research
Head of Cancer Biology, OSI (now Astellas)
Schering-Plough (now Merck)

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Chief Financial Officer
CFO, Genzyme Transgenics Corporation (GTC)

Daniel Paterson
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PharMetrics (now IMS), Axion

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CEO Karyopharm (KPTI), former CMO Onyx

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Scientific Advisory Board

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Peter Elliott, Ph.D.
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Millennium (co-developed Velcade®)

Phil Sharp, Ph.D.
MIT – 1993 Nobel Prize in Medicine
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Broad Institute/MIT/HMS
Pioneer of Human Genome Project

Chris Walsh, Ph.D.
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Joseph (Yossi) Schlessinger, Ph.D.
Yale Medical School
Cofounder: Sugen (Pfizer), Plexxikon (Daiichi-Sankyo)

Translational Research

José Baselga, M.D., Ph.D.
Physician in Chief; MSKCC
Senior Medical Advisor

Max Wicha, M.D.
Director – University of Michigan
Comprehensive Cancer Center

George Daley, M.D., Ph.D.
Director – Stem Cell Program
Harvard Medical School/HHMI

Eric Winer, M.D.
Director – Breast Oncology Center
Dana Farber Cancer Institute/HMS

Published information on VS-4718 as a CSC agent

- **Publications:**
  - Shapiro et al. (2014) Merlin deficiency predicts for FAK inhibitor sensitivity: A synthetic lethal relationship. SCIENCE TRANSLATIONAL MEDICINE 6: 237ra68.
  - Meads et al. (2015) Targeting PYK2 Mediate Microenvironment-Specific Myeloma Cell Death. ONCOGENE
  - Zhang et al. (2015) Proline-rich Tyrosine Kinase (Pyk2) Promotes Tumor Progression in Multiple Myeloma. BLOOD 124: 2675.

- **AACR, San Antonio Breast Cancer Symposium, EORTC presentations**
  - Weaver et al. Minisymposium at AACR 2015; Targeting Cancer Stem Cells to Impede Tumor Progression
  - Kolev et al. FAK and PI3K/mTOR inhibitors target cancer stem cells: Implications for SCLC treatment strategies, AACR 2015
  - Kolev et al. FAK inhibitors VS-6063 and VS-4718 target cancer stem cells: Implications for TNBC sequential and combination therapies, SABCS 2014
  - Kolev et al. Pharmacological and Genetic Inhibition of FAK Attenuates Cancer Stem Cell Function *In Vitro* and *In Vivo* , AACR 2013
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