Verastem Oncology

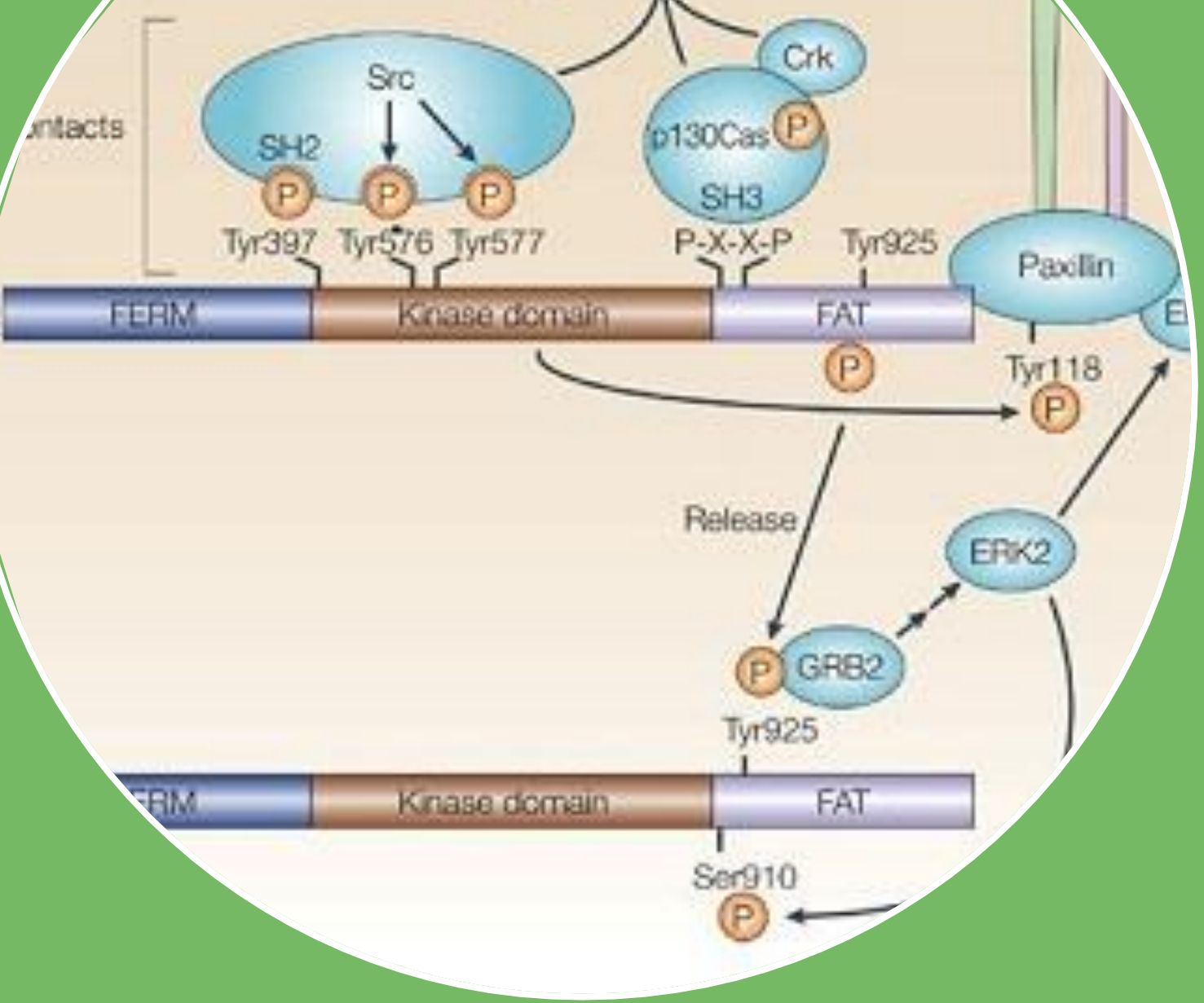
Immunologic Effects of Clinical Stage FAK & PI3K-Delta/Gamma Inhibitors

Jonathan Pachter, Ph.D - Chief Scientific Officer

3rd Annual Immuno-Oncology Congress, May 24, 2018

Disclosures

- I am an employee and stockholder of Verastem
- I will discuss investigational use of defactinib (FAK inhibitor) and duvelisib (PI3K-δ/γ inhibitor)



FAK Inhibitor Program

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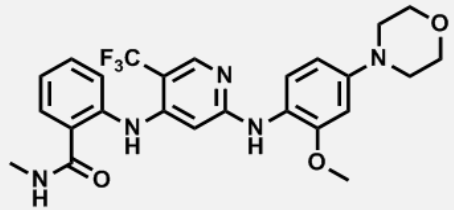
FAK is critical for multiple aspects of tumor progression

- Focal Adhesion Kinase (FAK) is a non-receptor tyrosine kinase that mediates signaling downstream of integrins & growth factor receptors
- Cancer Stem Cell Function, Drug Resistance & Metastasis
  - FAK is essential for survival & tumor-initiating capability of CSCs
  - Metastasis: FAK plays important roles in tumor cell migration, invasion & EMT which are all critical for the metastatic process
- Immuno-Oncology/Tumor Microenvironment
  - FAK inhibition reduces immune suppressive cell populations in the tumor microenvironment: Tregs, M2 tumor-associated macrophages, MDSCs
  - FAK inhibition reduces stromal density: Facilitates entry of cytotoxic T cells into tumor

Verastem FAK/PYK2 inhibitor program

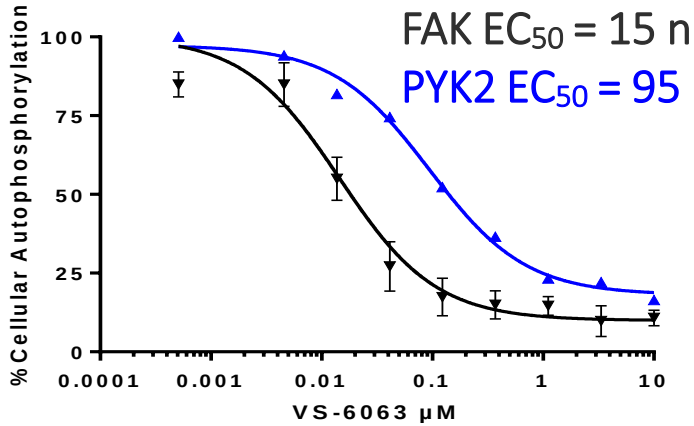
VS-6063



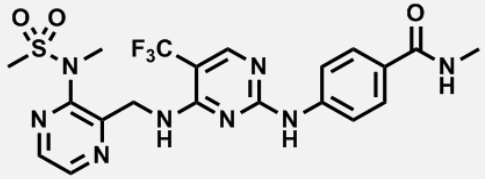
USAN name: **defactinib**

Dosage: Oral, 400 mg BID

- Ph I/II agent studied in 300+ patients to date with good safety profile

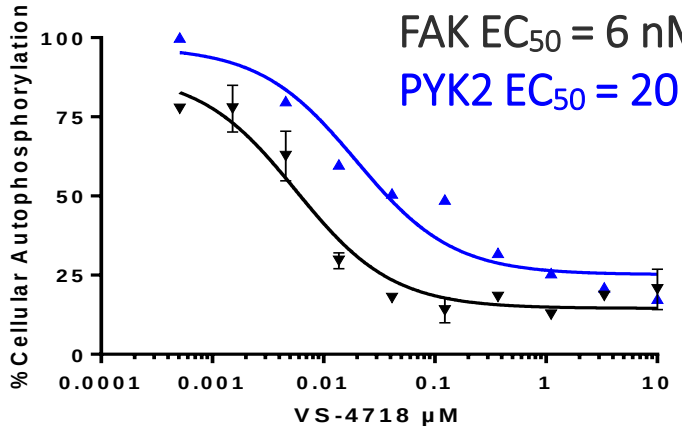


VS-4718

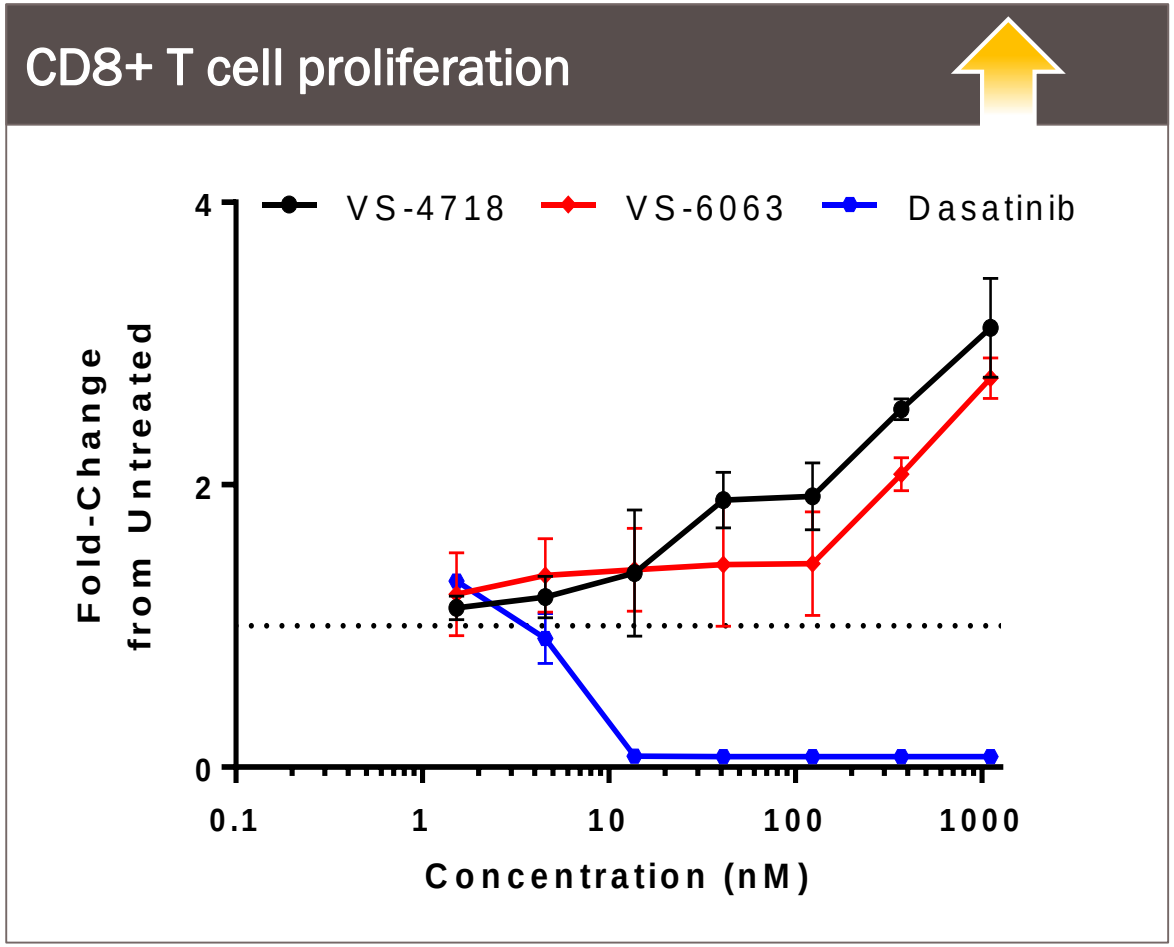


Dosage: Oral BID

- Extensive preclinical proof-of-concept research conducted
- Similar to VS-6063 in potency vs. FAK & PYK2



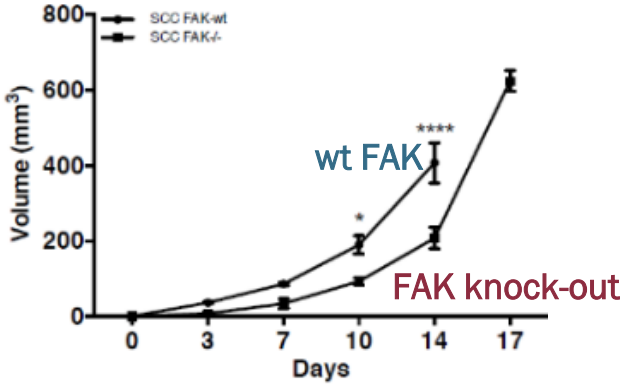
FAK inhibitors stimulate T cell proliferation in contrast to other protein kinase inhibitors



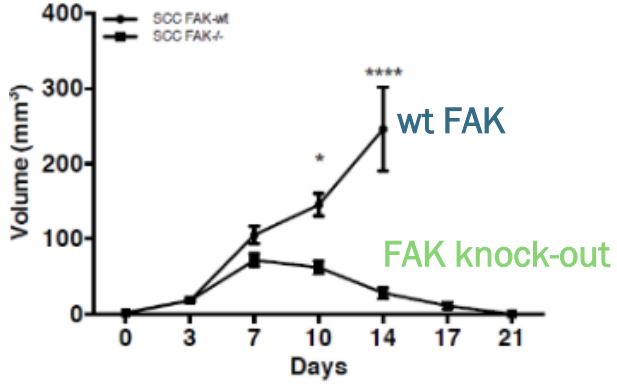
- FAK inhibitor treatment, human lymphocytes from healthy donors
- VS-4718 & VS-6063 also induced dose-dependent reduction of exhaustion markers (LAG3, PD-1) on human CD8+ T cells

FAK knockout or FAK inhibitor induces tumor regression through T cell-dependent mechanism

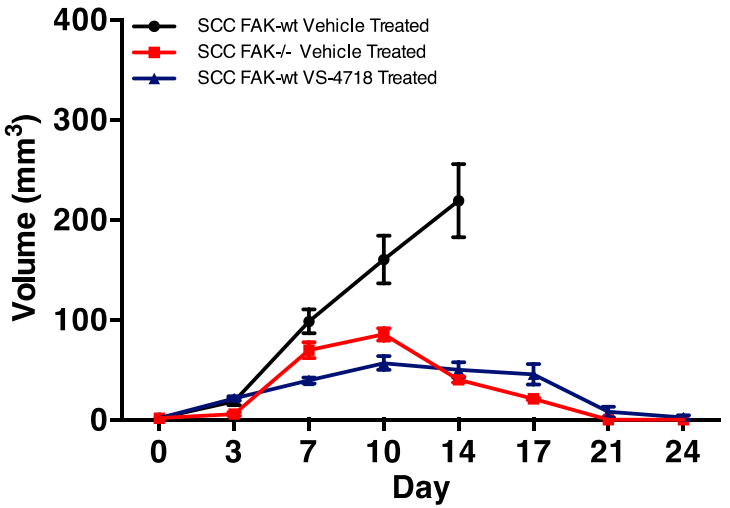
Immune-deficient CD-1 nude mice



Immune-competent FVB mice

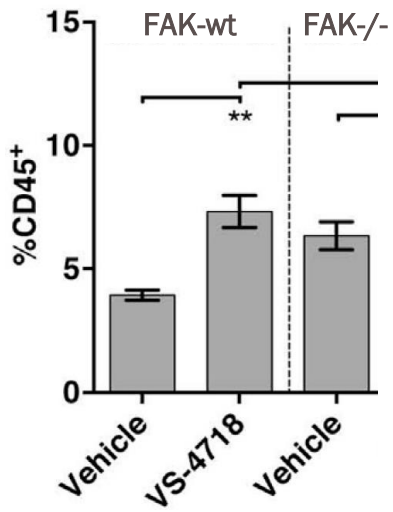


Tumor burden



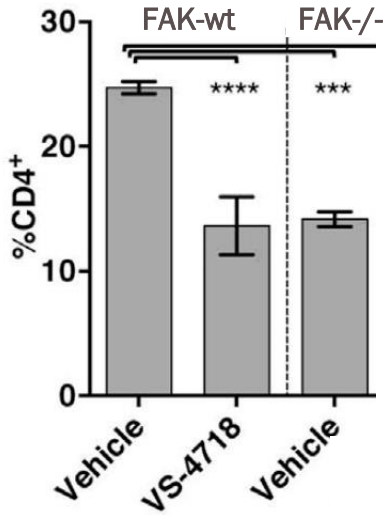
CD8+ T cells

CD45+ CD3+ CD4- CD8+



T-regs

CD4+ FoxP3+ CD25+



SCC 7.1 chemical carcinogen-induced skin cancer model

Serrels et al. (2015) *Cell* 163: 160-173

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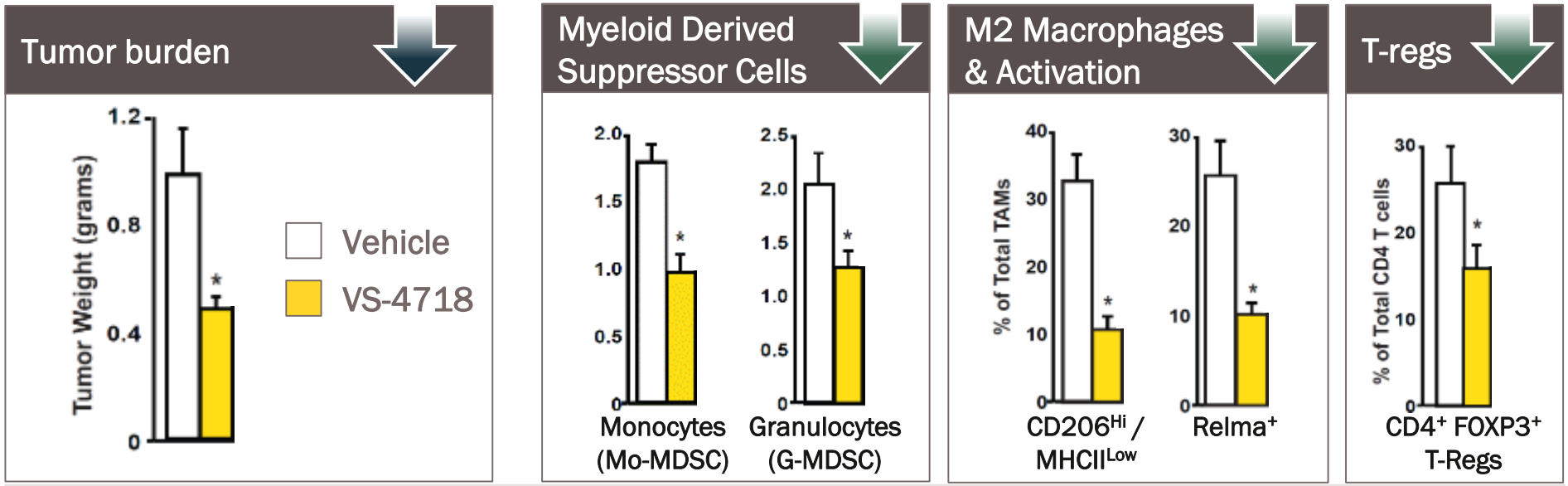
FAK Inhibitor reduces immunosuppressive MDSCs, M2 Macrophages and T-regs in tumors

FAK inhibitor treatment, KRas-INK orthotopic pancreatic cancer model:



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

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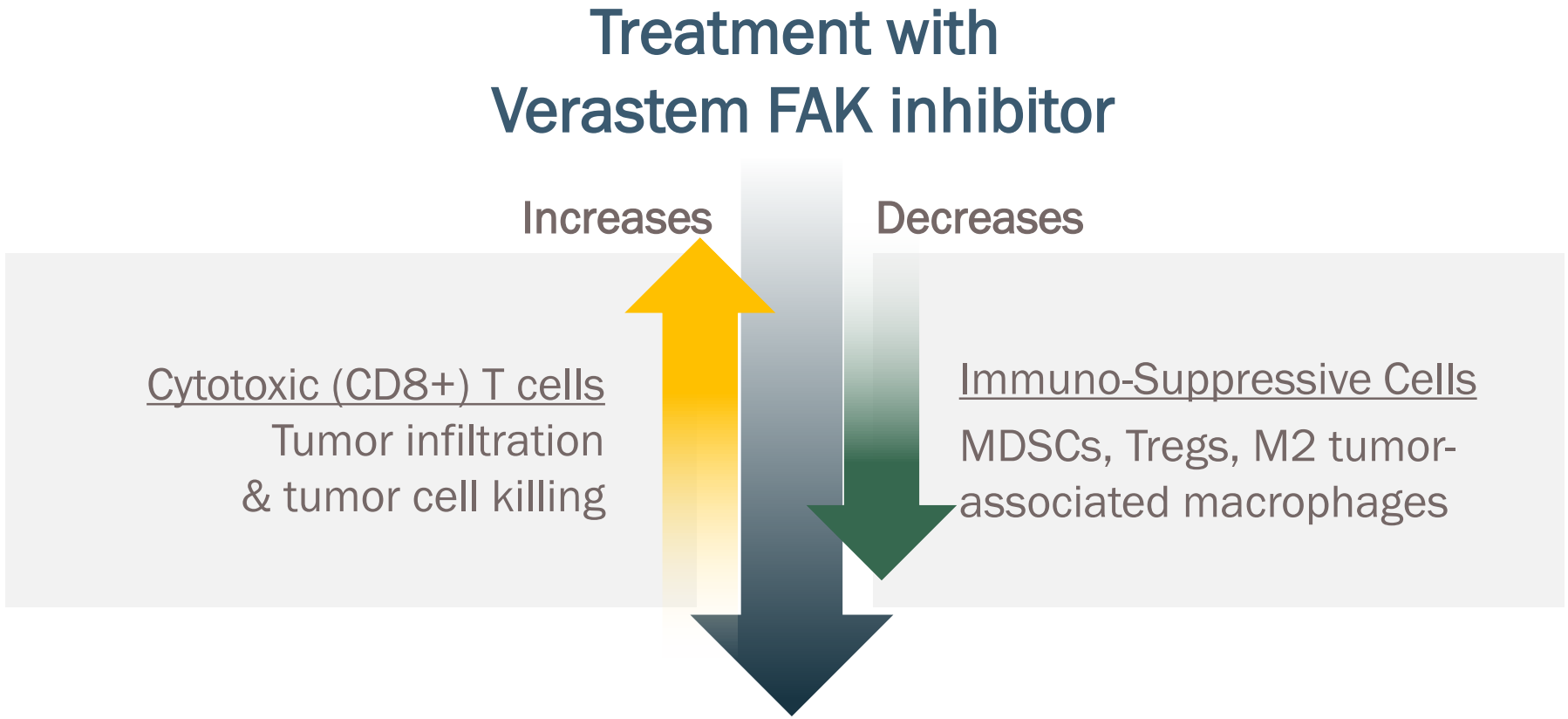
Jiang et al. (2016) *Nature Med.* 163: 851-860

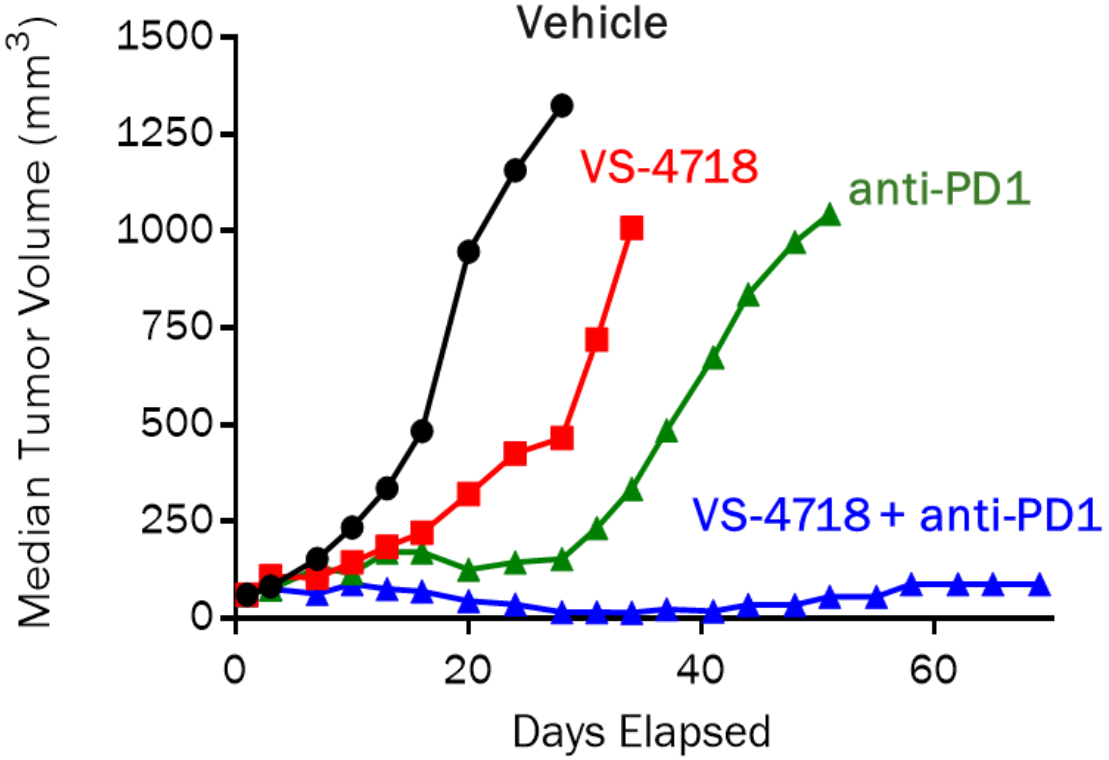
FAK inhibitor treatment creates a more favorable tumor immune microenvironment for T cell-directed anti-cancer therapeutics



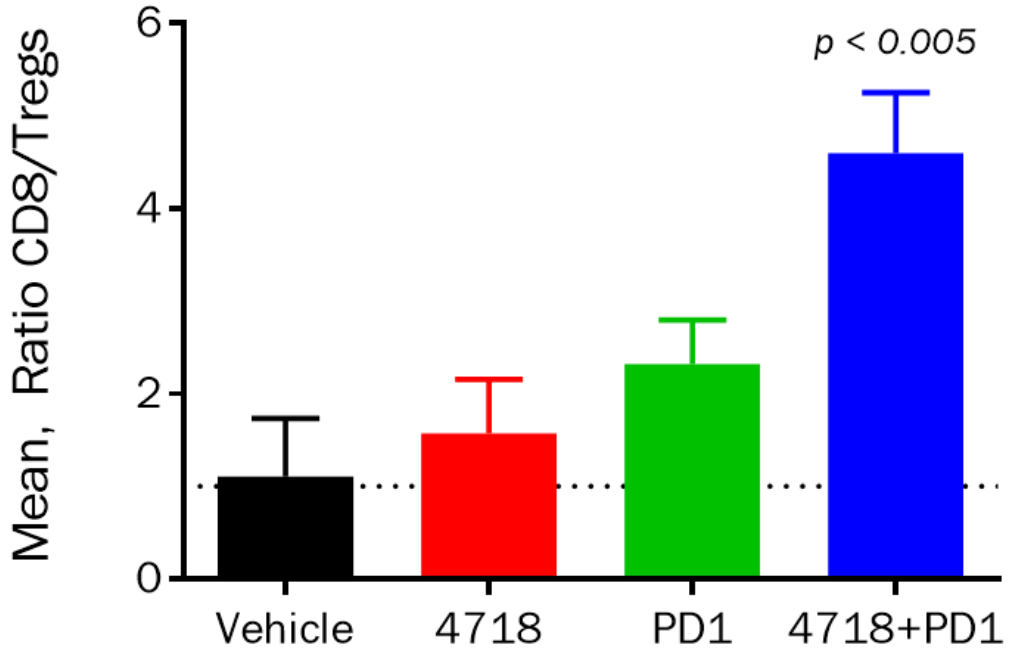
More favorable tumor microenvironment for enhanced efficacy of Immuno-Oncology therapeutics

FAK inhibitor potentiates efficacy of anti-PD-1 in MC38 model & correlates with decreased Tregs & increased CD8+ T cells

Tumor burden



Ratio: CD8 T cells/Tregs



MC38 colorectal cancer mouse model

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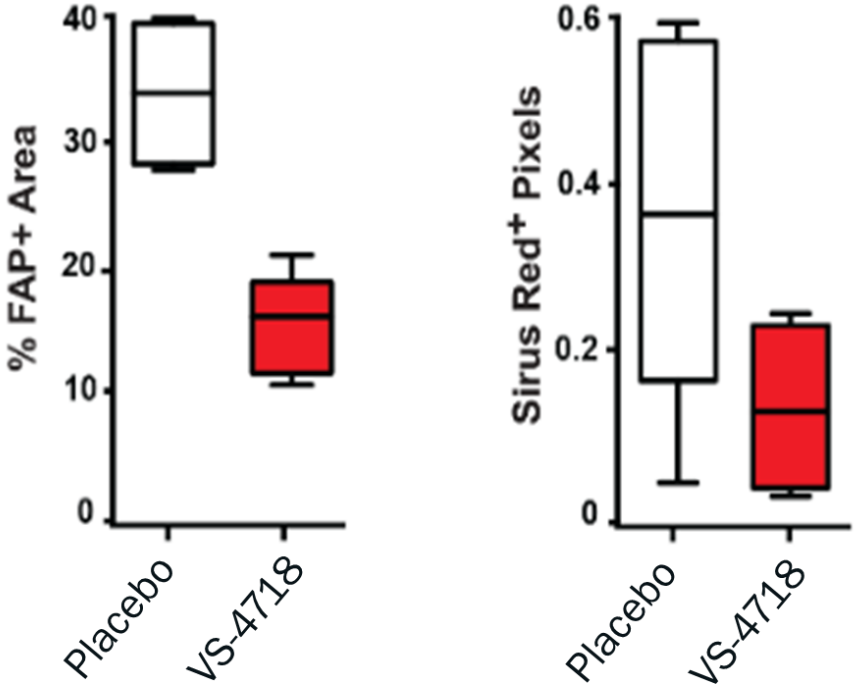
FAK inhibition reduces stromal density & boosts T cell entry into pancreatic tumors

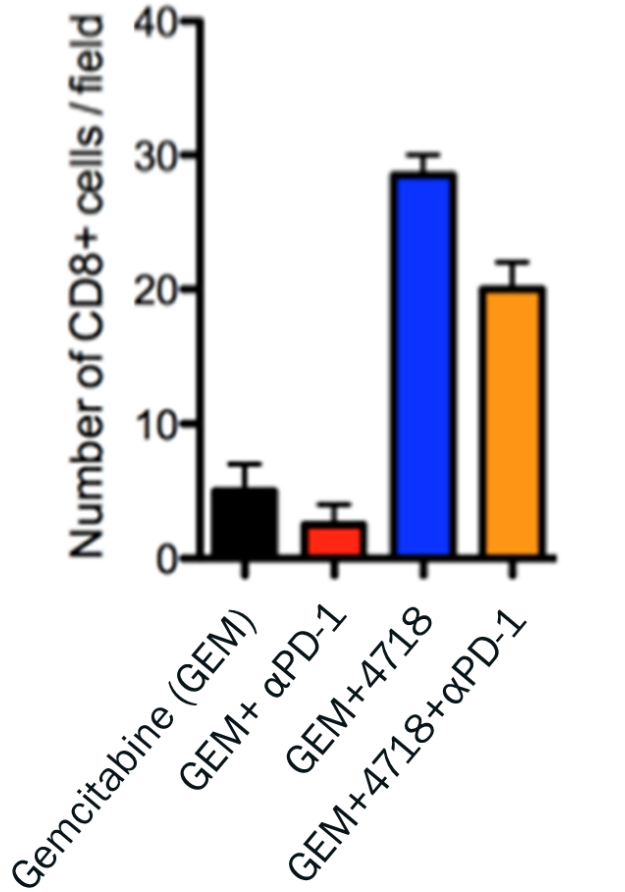
Fibroblasts

Extracellular Matrix

Cytotoxic CD8+ T cells



STROMAL DENSITY COMPONENTS



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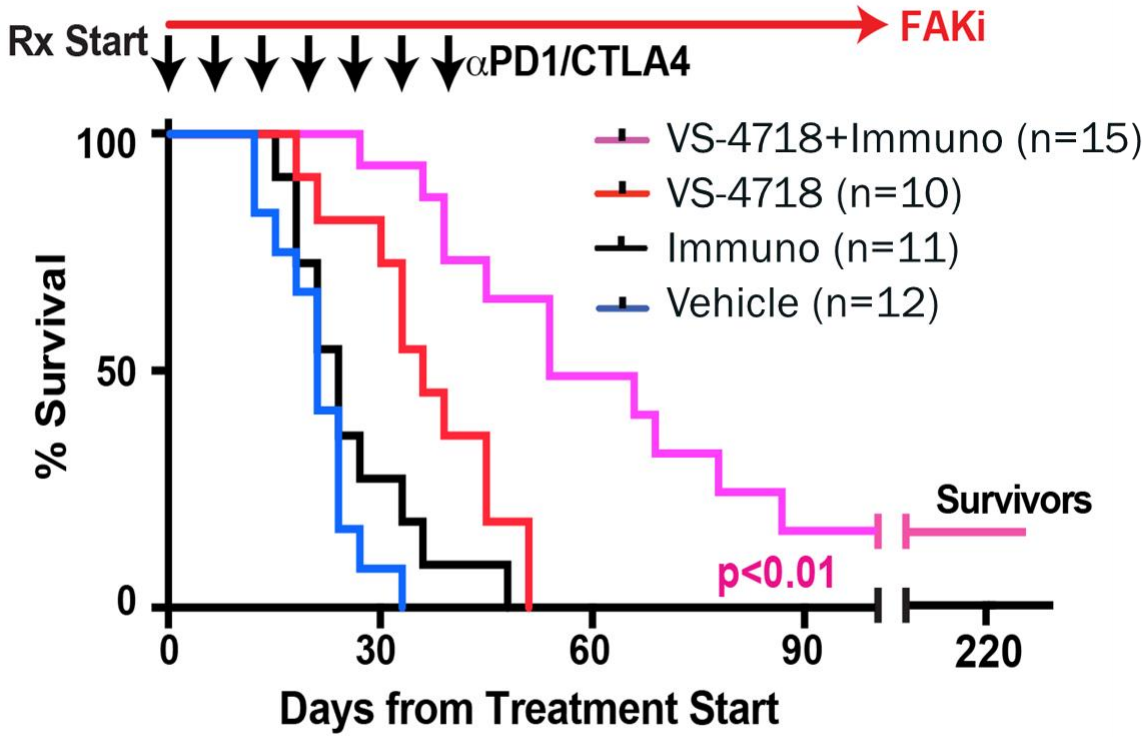
Jiang et al. (2016) ***Nature Med.*** 163: 851-860

FAK Inhibitor addition to checkpoint cocktail increases CD8+ T Cell entry into Pancreatic tumors enabling long term survival

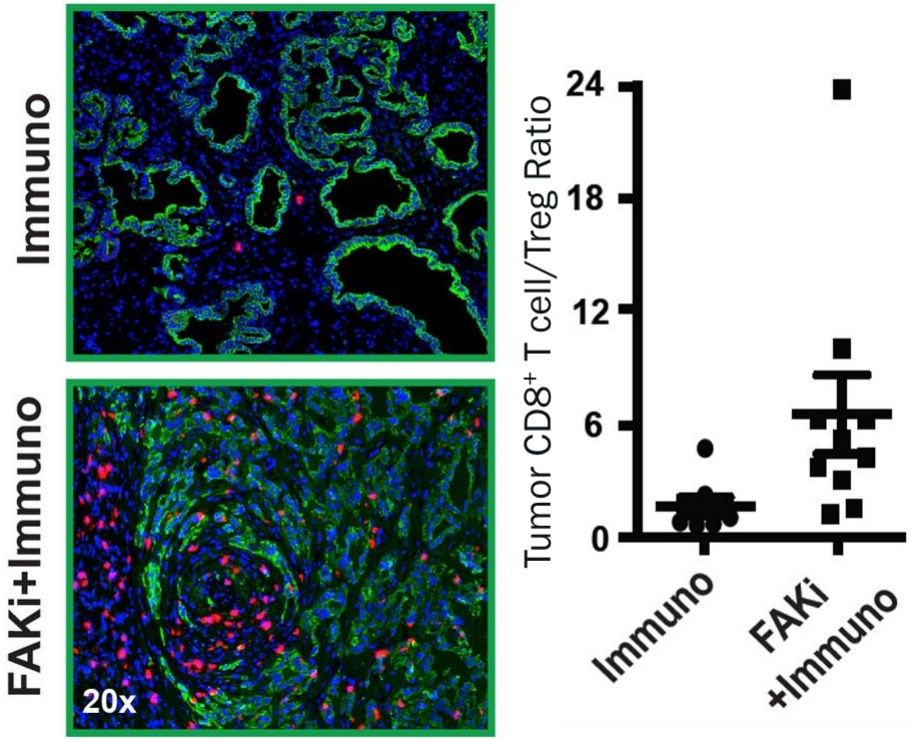
Extended survival



Transgenic Kras/p53 pancreatic model

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

CD8+ T cell infiltration into tumor



CD8+ T cell infiltration

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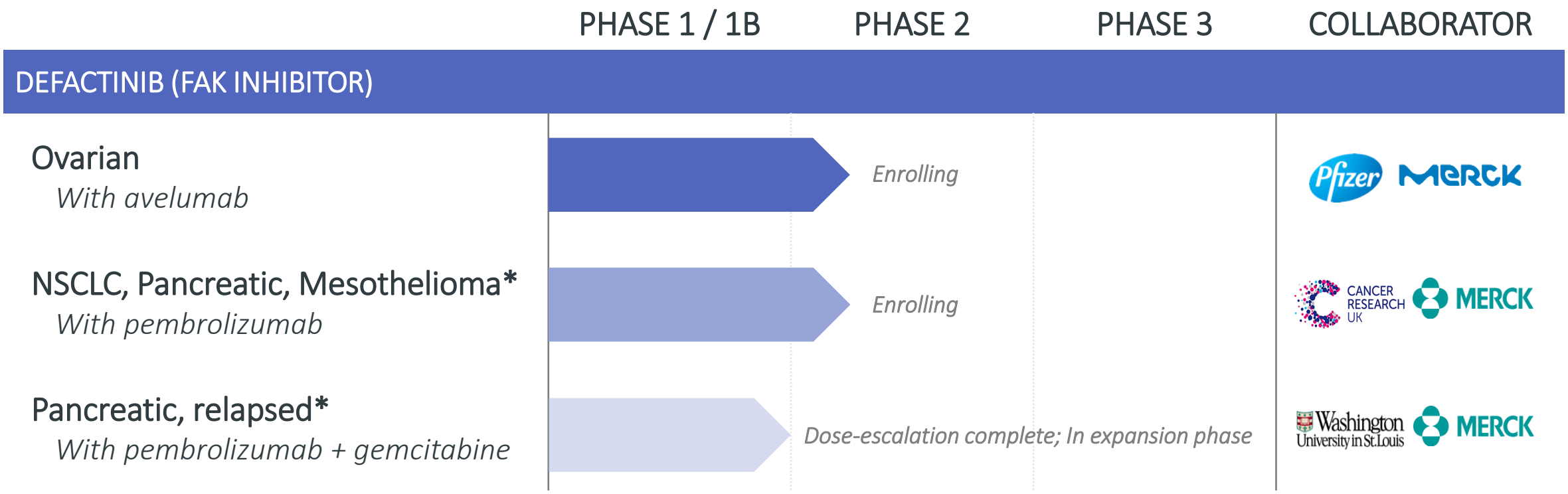
Jiang et al. (2016) ***Nature Med.*** 163: 851-860

FAK Inhibitor Immuno-Oncology Trials Currently in Progress



Defactinib is an investigational agent available for clinical trial use only. Safety and efficacy have not been established.

Pembrolizumab = anti-PD1
Avelumab = anti-PD-L1
* = Investigator Sponsored Trial (IST)

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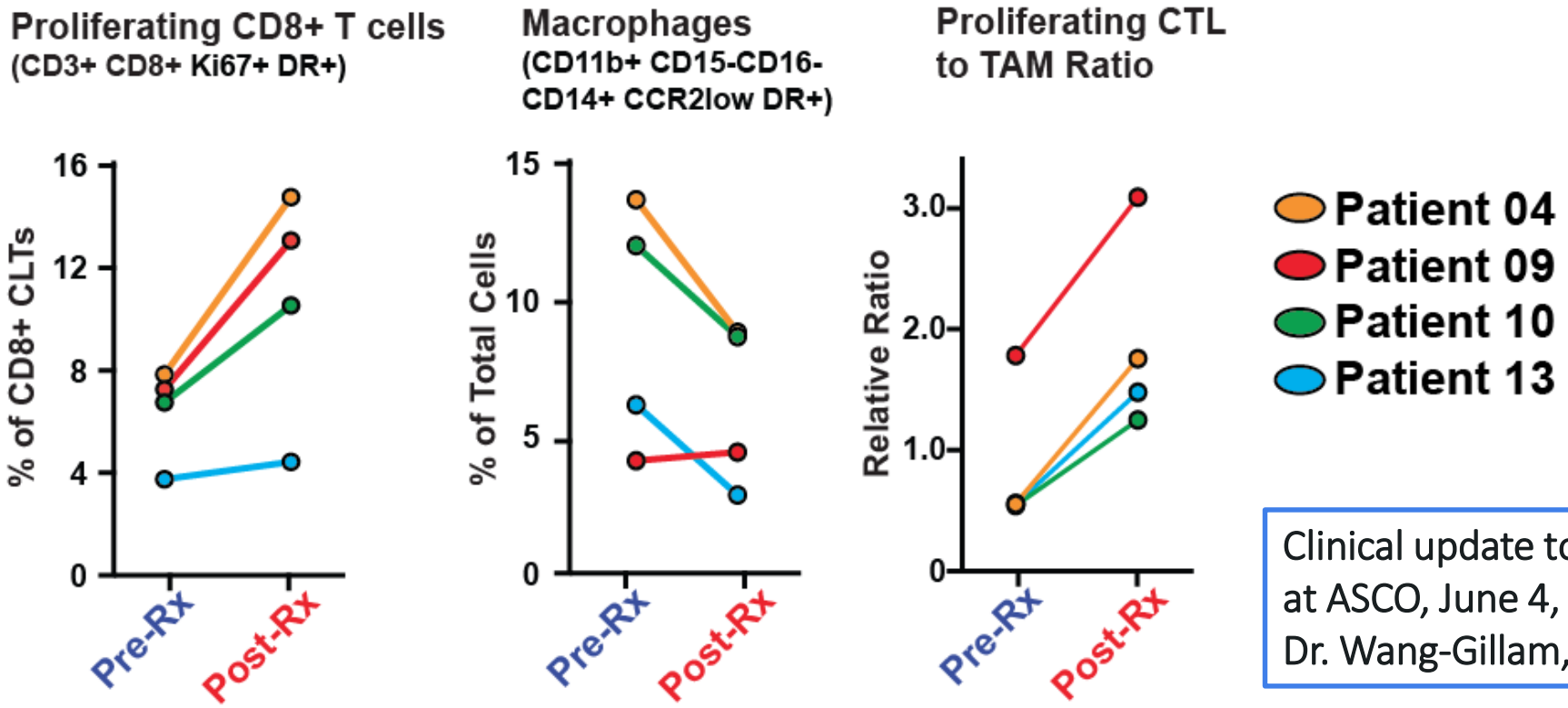
Early Biomarker Results From Pancreatic Cancer Biopsies (Metastases) Pre-Treatment vs. Post-Cycle 2

Defactinib (FAKi) + Pembrolizumab (anti-PD-1) + Gemcitabine



Clinical update to be presented at ASCO, June 4, 2018
Dr. Wang-Gillam, Abstract 2561

Andrea Wang-Gillam, David DeNardo, Washington University, St. Louis
Investigator-Initiated Phase Ib Study NCT02546531

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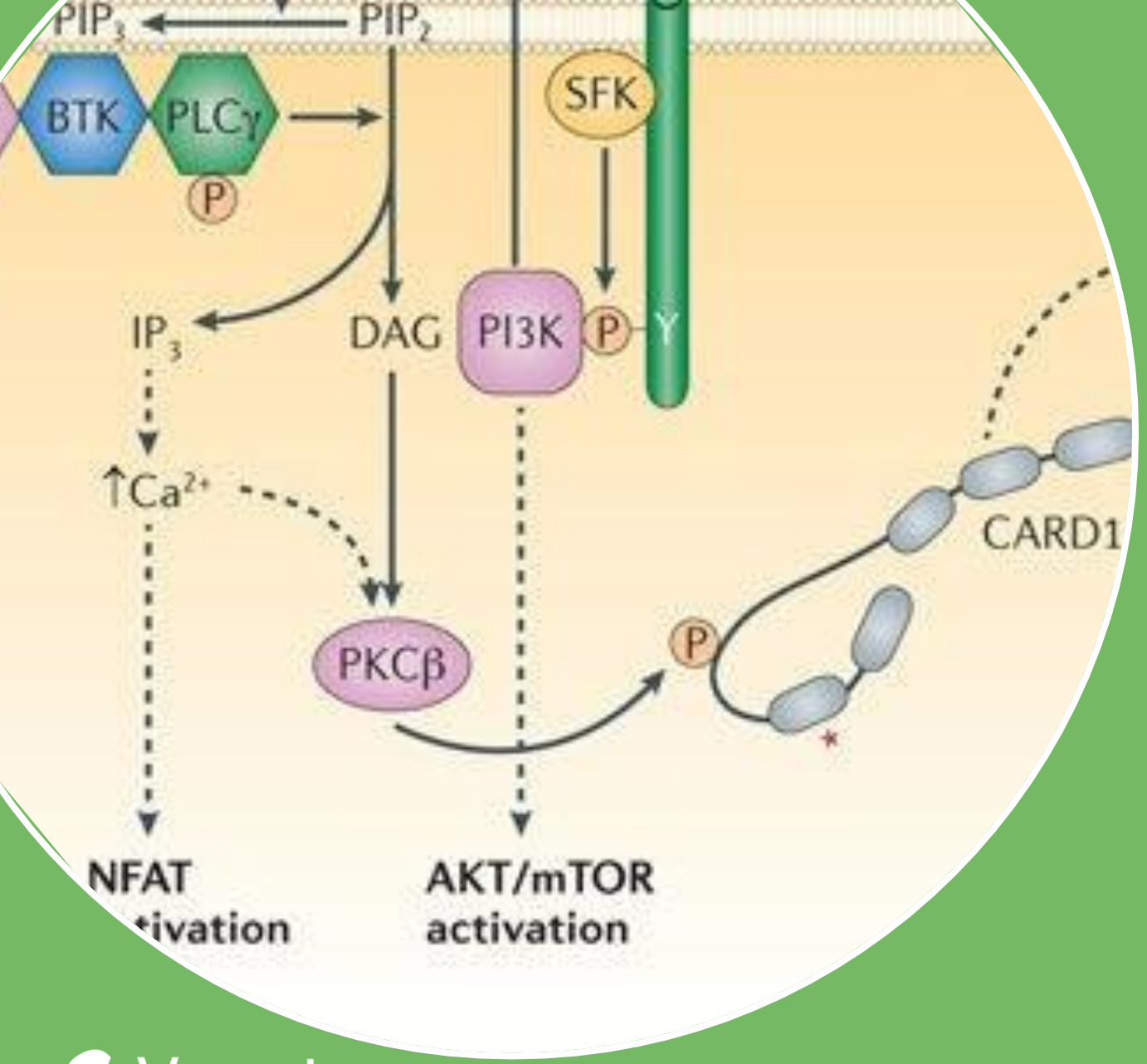
Summary & Conclusions: FAK

- FAK inhibition (pharmacological or genetic) induces full tumor regression in a skin cancer model through a T cell-mediated mechanism
- FAK inhibitor modulates the tumor microenvironment to enhance efficacy of immuno-oncology therapeutics
  - Increased $CD8^+$ T cells in tumor
  - Decreased immunosuppressive cells (Tregs, MDSCs, M2 TAMs)
  - Reduced stromal density to enable T cell infiltration
- FAK inhibitor extends survival in response to PD-1 inhibitor in multiple syngeneic and transgenic models
- Clinical evaluation of FAK inhibitor + anti-PD-1 (pembrolizumab) or anti-PD-L1 (avelumab) ongoing in multiple solid tumor types



Duvelisib

Oral PI3K-Delta/Gamma Inhibitor

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Duvelisib: Oral PI3K-Delta/Gamma Inhibitor

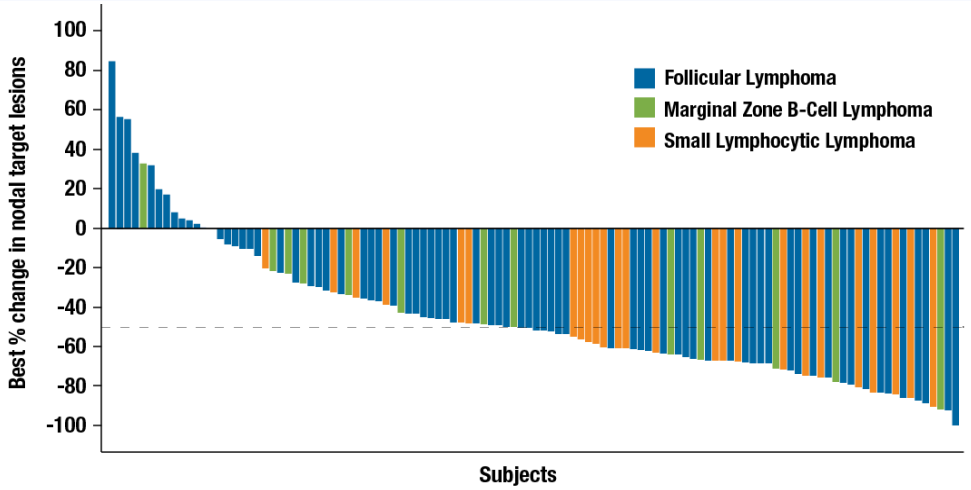
- Potent, selective inhibitor of PI3K-delta & PI3K-gamma isoforms
- Active as monotherapy in iNHL, CLL & T-cell lymphoma
- Positive Phase 3 data in CLL/SLL (DUO) & Phase 2 data in iNHL (DYNAMO)
- NDA filed (Feb 2018) for relapsed/refractory CLL/SLL & FL
  - Priority Review with Oct. 5, 2018 PDUFA date

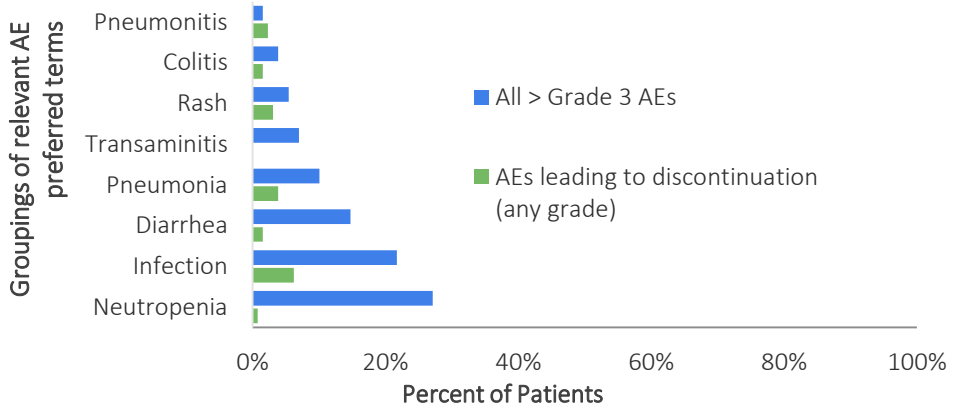
Clinically Active with Well-Characterized and Manageable Safety Profile

More than 500 patients treated to date with duvelisib across all oncology clinical trials

DYNAMO™

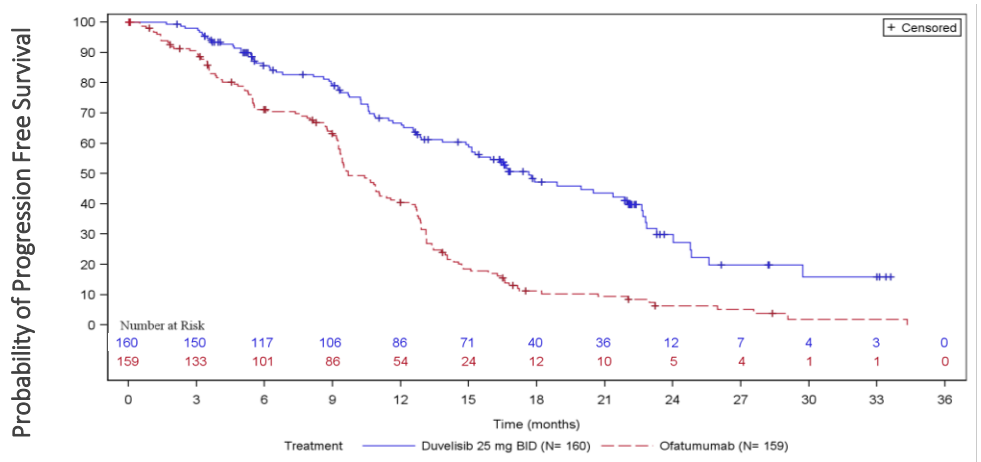
Positive Phase 2 Trial of Duvelisib Monotherapy in Double Refractory iNHL Patients (n = 129)

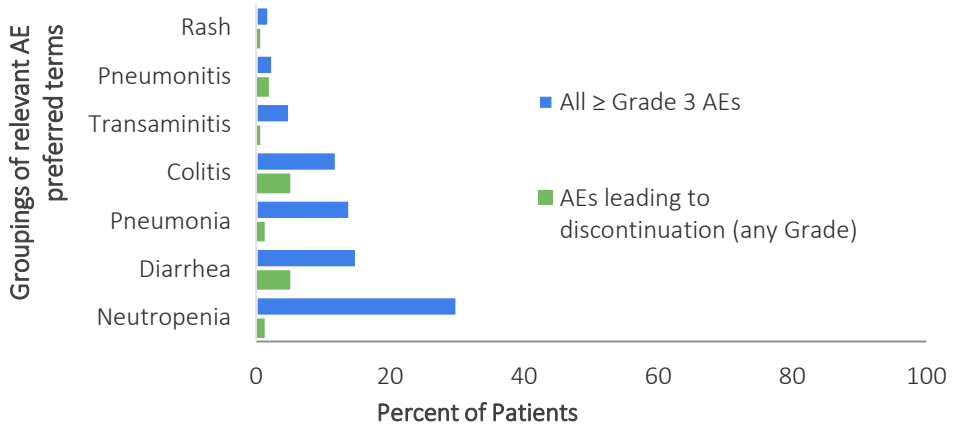




DUO™

Positive Phase 3 Trial of Duvelisib Monotherapy vs. Ofatumumab in R/R CLL/SLL patients (n = 319)





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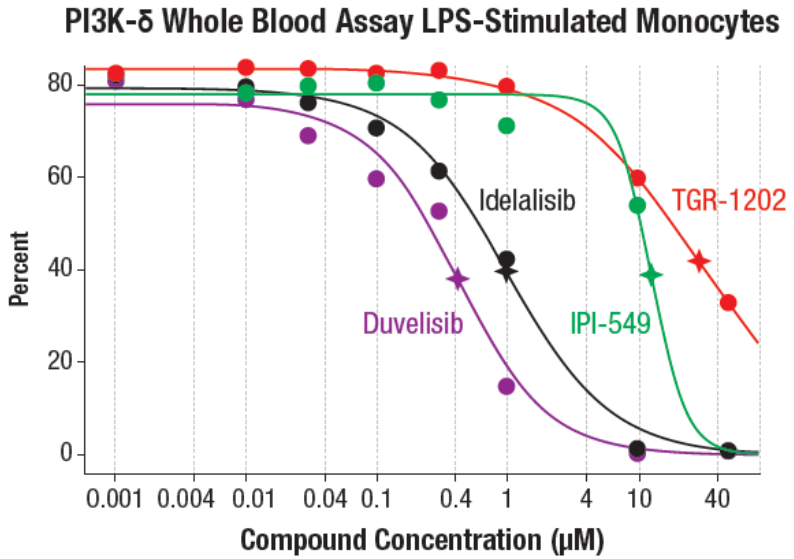
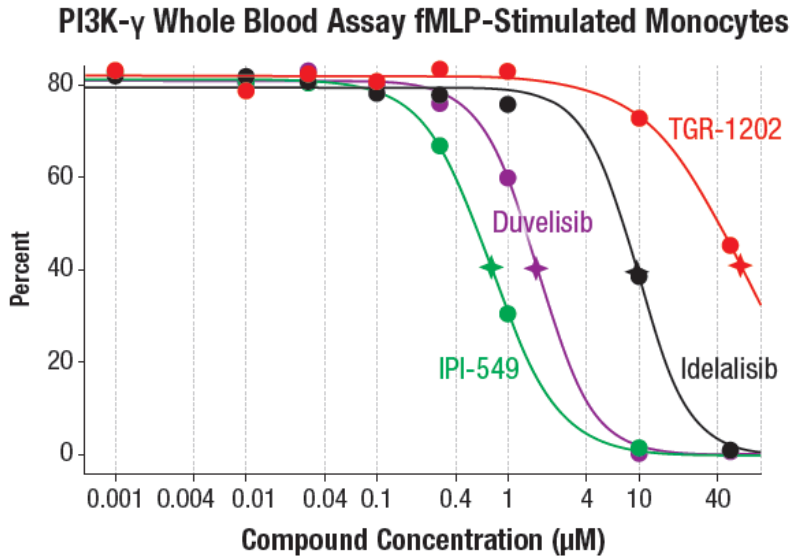
Duvelisib is an investigational agent available for clinical trial use only. Safety and efficacy have not been established.

Duvelisib: Unique Dual Inhibitor of PI3K-Delta & PI3K-Gamma





Drug	Mechanism of Action	PI3K-δ IC_{50} (μM)	PI3K-γ IC_{50} (μM)	C_{max} (ss) (μM)
Duvelisib	Dual PI3K-δ/PI3K-γ Inhibitor	0.4 ± 0.1	1.6 ± 0.2	2.5
Idelalisib	PI3K-δ Inhibitor	1.0 ± 0.2	9.4 ± 2.3	4.8
IPI-549	PI3K-γ Inhibitor	12 ± 0.5	0.5 ± 0.2	9.1
TGR-1202		25 ± 8	55 ± 16	9.2

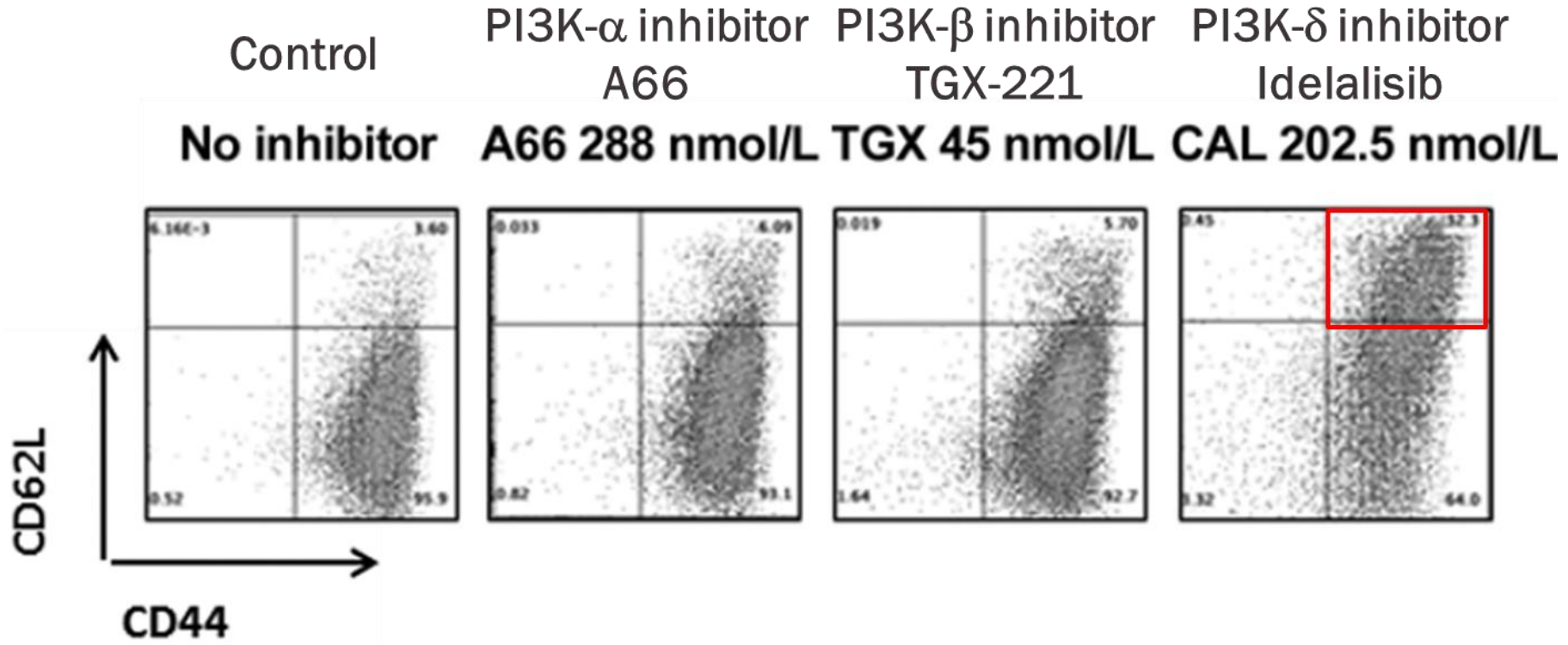
- Duvelisib human PK. C_{max} @ 25 mg BID (RP2D) = 1062 ng/ml; MW = 417 g/mol
- Idelalisib human PK from Webb, ASH 2010. C_{max} @ 150 mg BID (RP2D) = 2000 ng/ml; MW = 415 g/mol
- IPI-549 human PK from Hong, SITC 2017. $C_{max\text{-}ss}$ @ 60 mg QD (RP2D) = 4800 ng/ml, MW = 529 g/mol
- TGR-1202 human PK from Burris, Lancet Oncol 2018. $C_{max\text{-}ss}$ @ 800 mg QD (RP2D) = 5276 ng/ml; MW = 572

CONCEPT:

Benefit of Dual Inhibition of PI3K-Delta & PI3K-Gamma for Immuno-Oncology

- Duvelisib is clinically active as a monotherapy in B cell malignancies
  - O'Brien ASH 2014; Flinn ASH 2014; Flinn ASH 2016; Flinn ASH 2017
- PI3K-delta inhibition is known to reduce immunosuppressive Tregs
  - Ali, Nature 2014
- PI3K-gamma inhibition is known to reduce immunosuppressive myeloid cells
  - Kaneda, Nature, 2016; De Henau, Nature, 2016
- Duvelisib may potentiate efficacy of various Immuno-Oncology agents
  - Checkpoint inhibitors, co-stimulatory antibodies, CAR-T

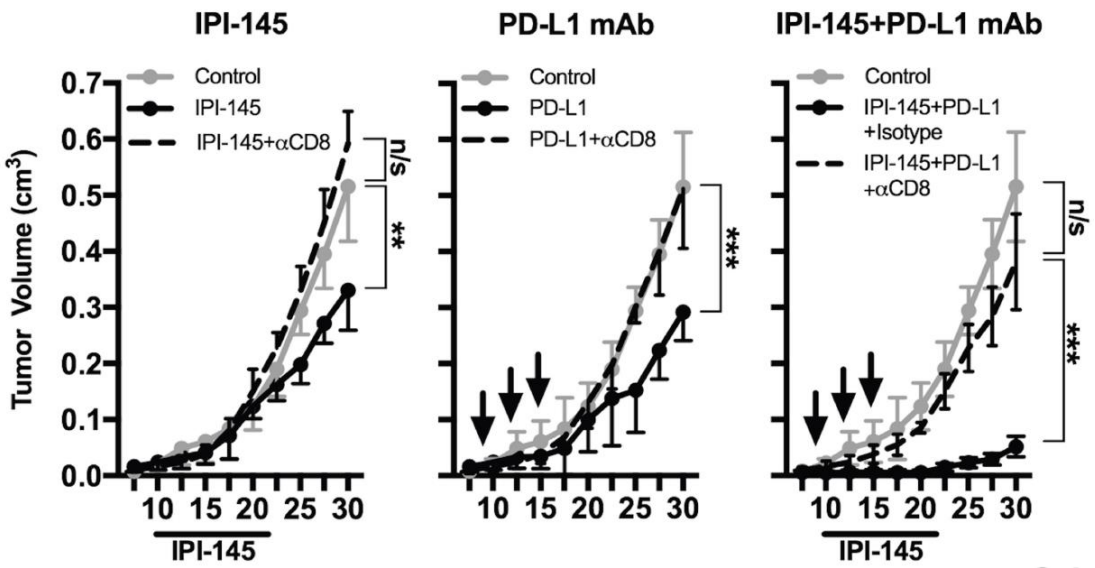
PI3K-Delta Inhibition Enhances Memory T Cells

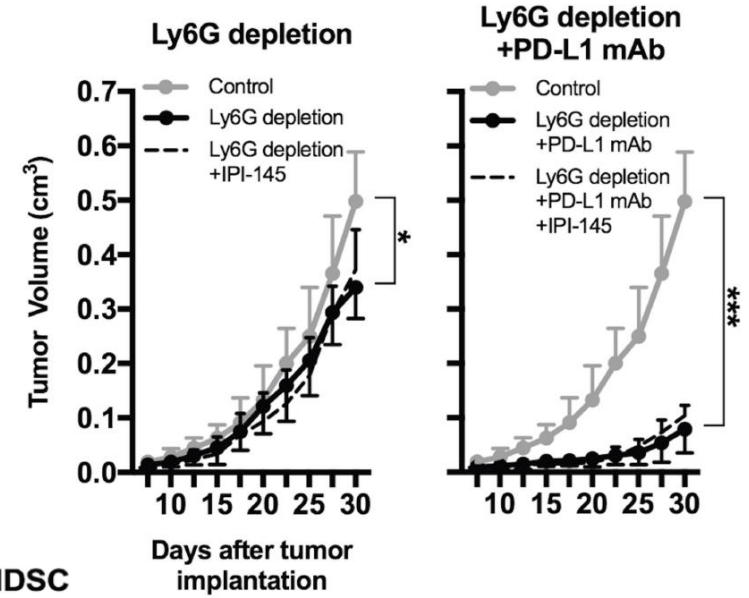


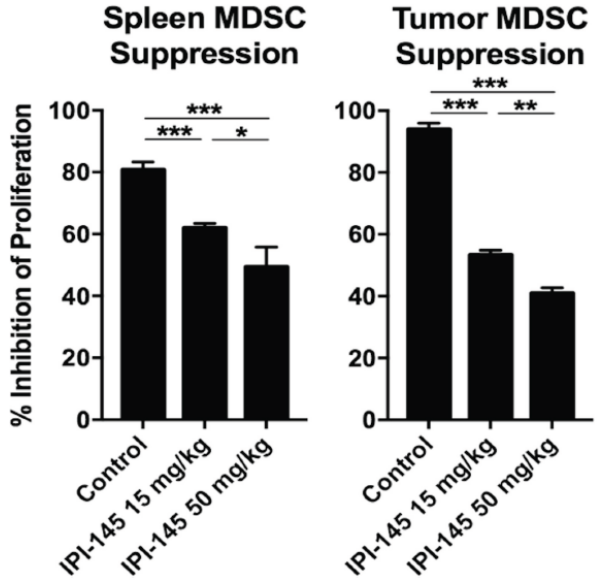
- Tumor antigen-specific $CD8^+$ T cells from pMel-1 mice were activated by $gp100_{25\text{-}33}$ peptide in the presence of PI3K isoform-specific inhibitors
- Memory T cells ($CD62L^{hi}CD44^{hi}$) were quantified by flow cytometry

Abu Eid et al., Cancer Res 2017

Duvelisib Inhibits HNSCC Tumor Growth Through Depletion of Immunosuppressive MDSCs







Davis, Cancer Res 2017

IPI-145 = Duvelisib

Suggests potential for duvelisib + anti-PD-1/PD-L1 for solid tumors

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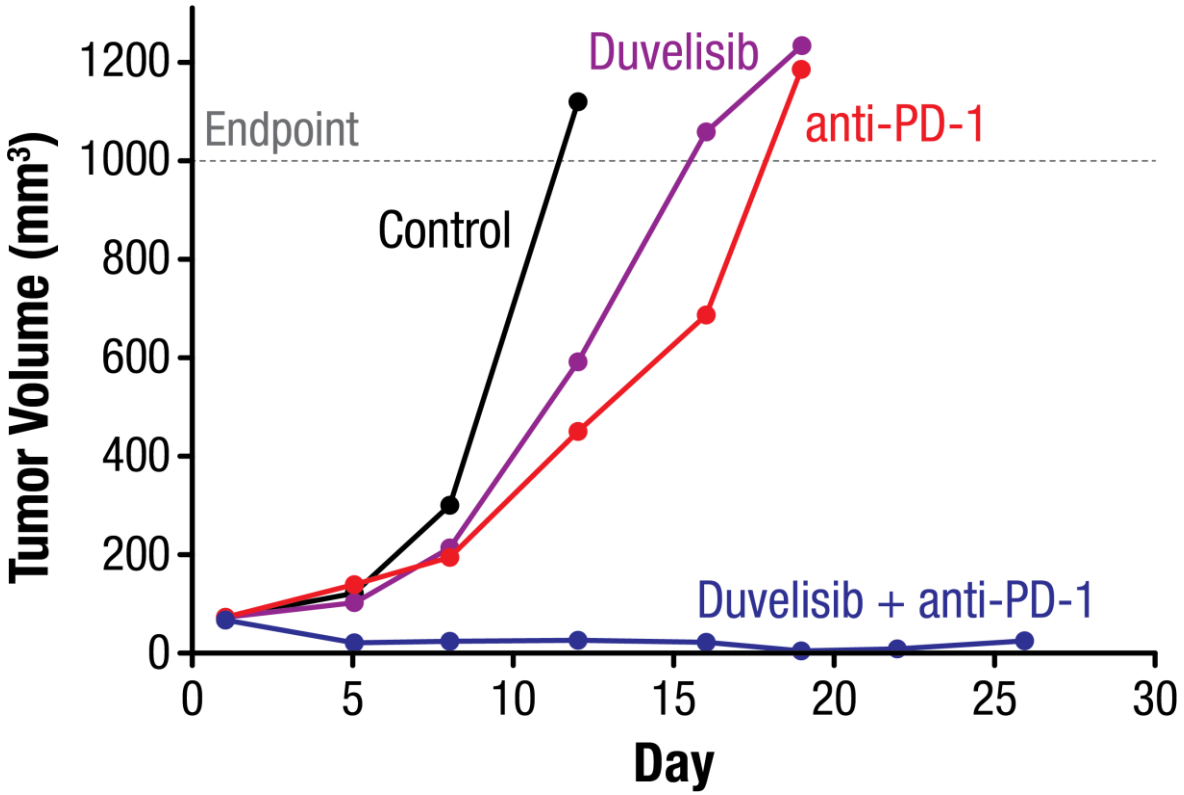
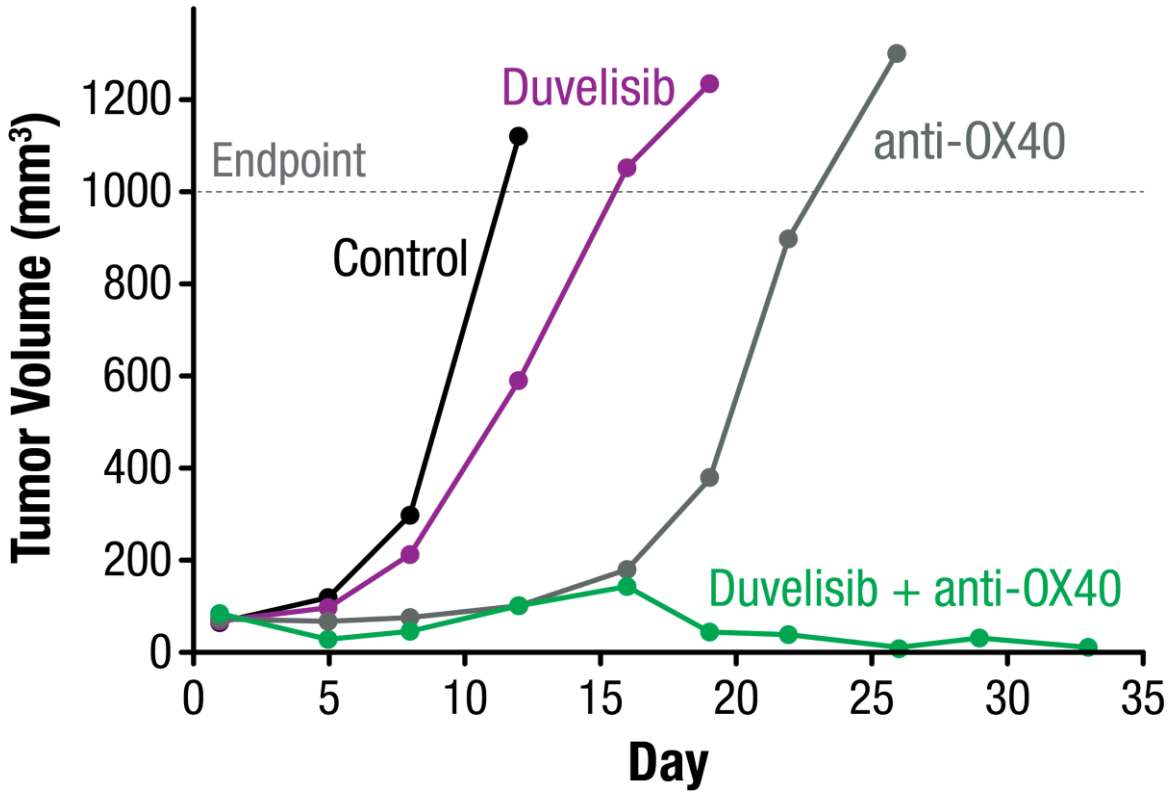
Duvelisib is Synergistic with PD-1 and OX40 Antibodies in B Cell Lymphoma (A20) Preclinical Model

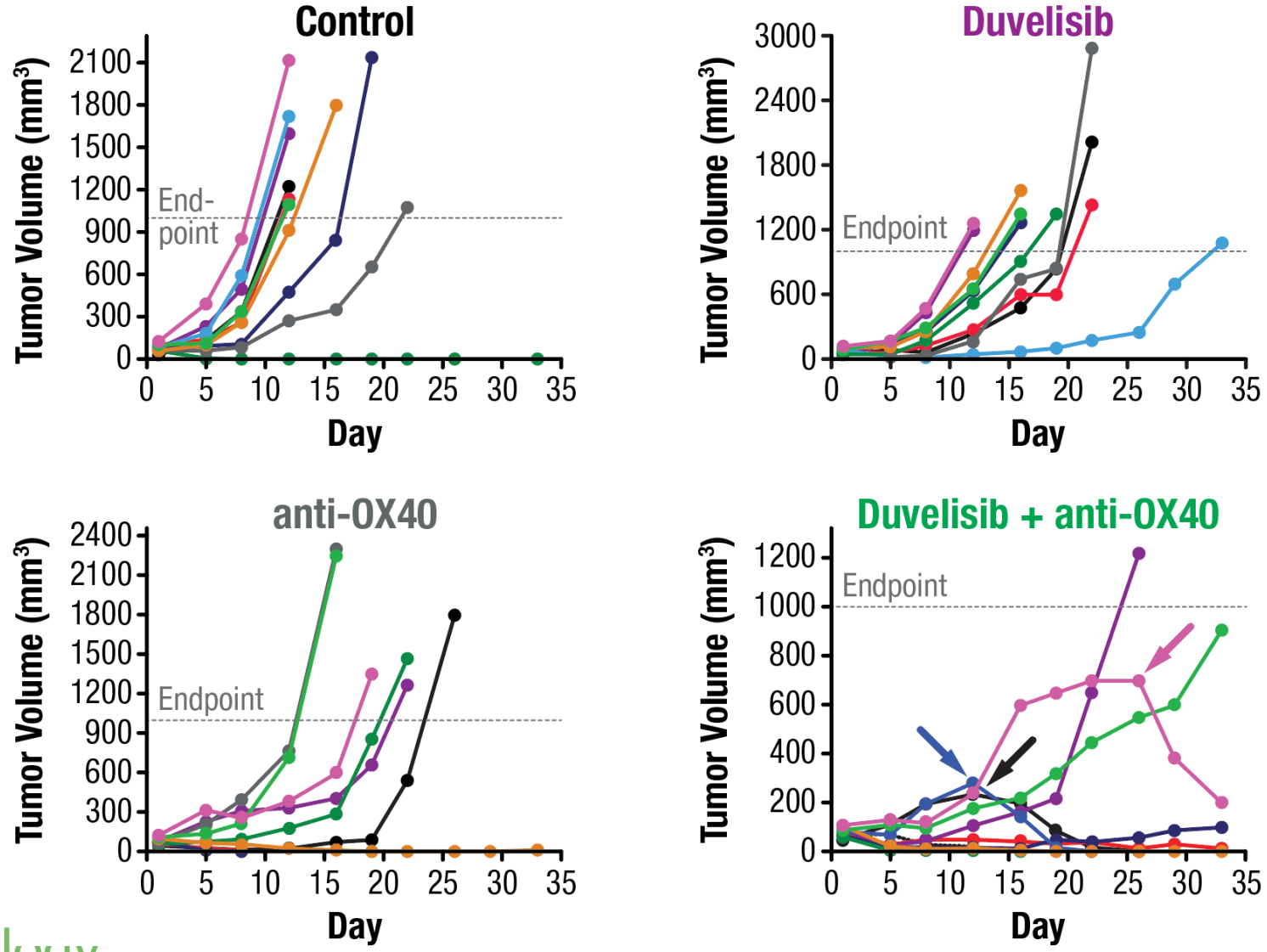




- Duvelisib @ 50 mg/kg po, BID
- Anti-PD-1 @ 100 mg/mouse ip, biweekly x 2

- Duvelisib @ 50 mg/kg po, BID
- Anti-OX40 @ 100 µg/mouse ip, biweekly x 2

Individual Mice: Duvelisib + Anti-OX40 Combo Induces Dramatic Tumor Regressions in B-Cell Lymphoma model (A20)



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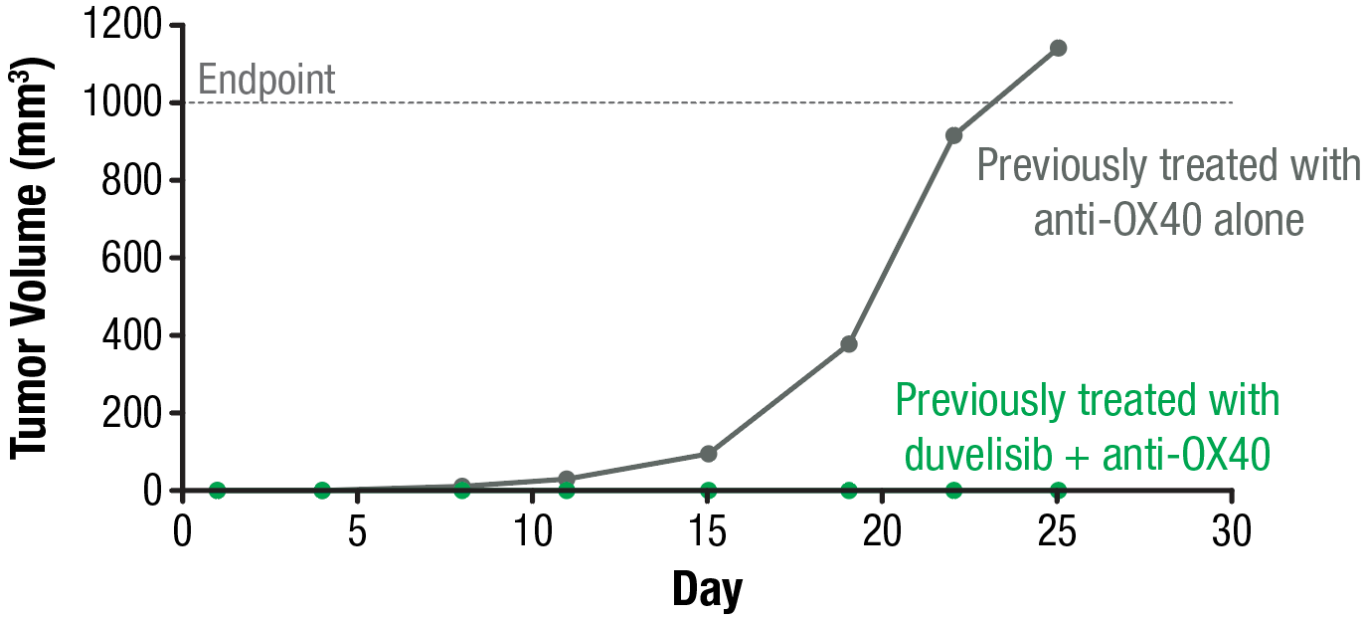
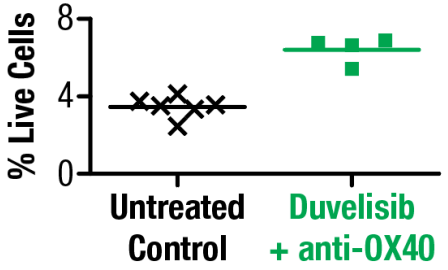
Duvelisib + Anti-OX40 Induces Immune Memory, in Contrast to Anti-OX40 Alone

Mice bearing A20 tumors were treated with anti-OX40 alone or anti-OX40 + duvelisib

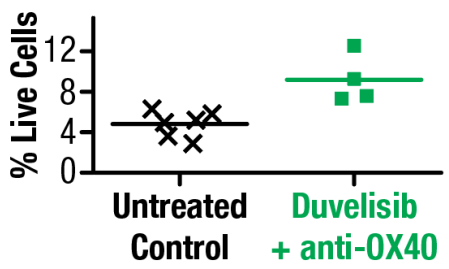
On day 44, all mice with no detectable tumor from the anti-OX40 (n = 2) and anti-OX40 + duvelisib (n = 5) groups were re-injected with A20 B-cell lymphoma cells in the opposite flank with no further treatment to assess immune memory



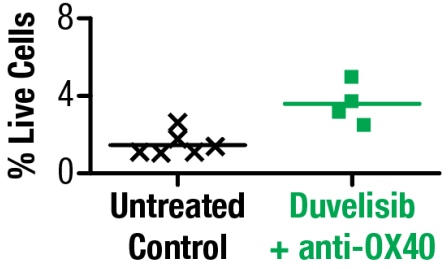
Blood: Memory CD8⁺ T Cells
$CD45^{+}CD19^{-}CD3^{+}CD8^{+}CD44^{hi}CD62L^{lo}$



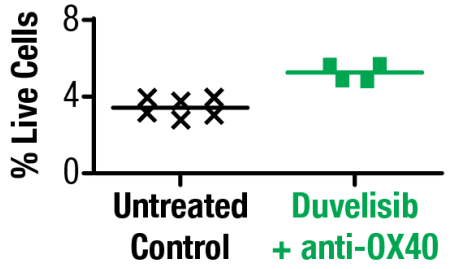
Spleen: Memory CD8⁺ T Cells
$CD45^{+}CD19^{-}CD3^{+}CD8^{+}CD44^{hi}CD62L^{lo}$



Blood: Memory CD4⁺ T Cells
$CD45^{+}CD19^{-}CD3^{+}CD4^{+}CD44^{hi}CD62L^{lo}$



Spleen: Memory CD4⁺ T Cells
$CD45^{+}CD19^{-}CD3^{+}CD4^{+}CD44^{hi}CD62L^{lo}$



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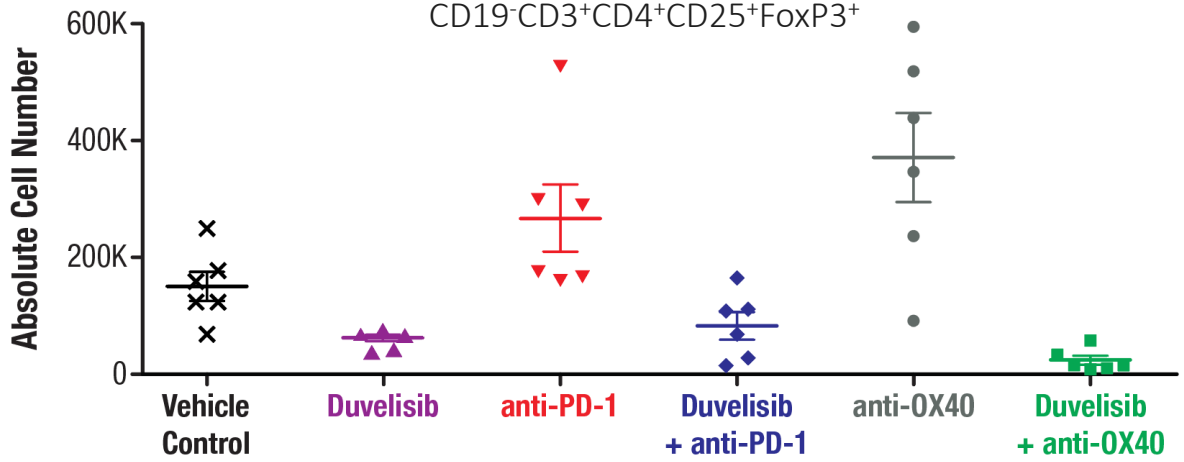
The Dual PI3K-δ/PI3K-γ Inhibitor Duvelisib Suppresses Immunosuppressive T-Regs & Myeloid Cells in A20 B Cell Lymphoma Model

Tumor Tregs

$CD19^{-}CD3^{+}CD4^{+}CD25^{+}FoxP3^{+}$

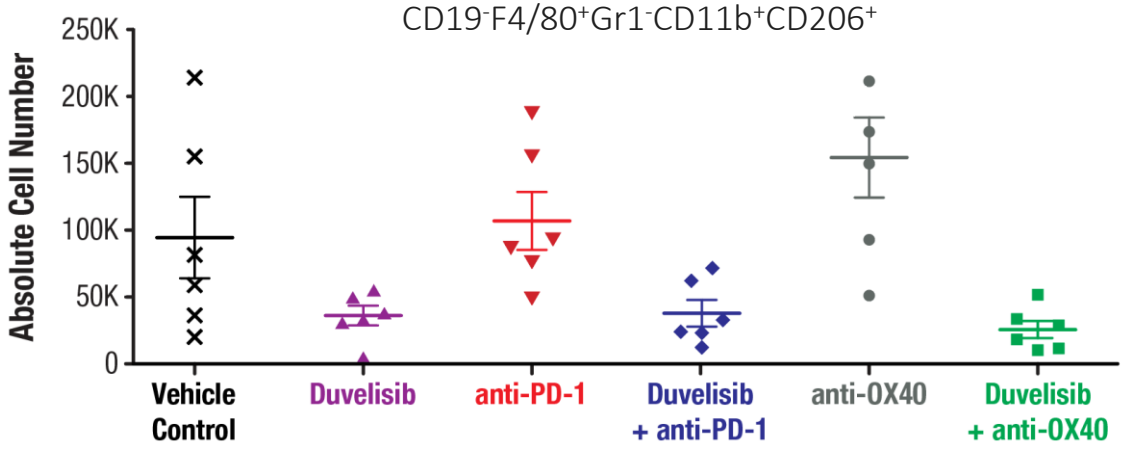


Hypothesis: Reduction of Tregs through PI3K-delta inhibition

Hypothesis: Reduction of myeloid immunosuppressive cells through PI3K-gamma inhibition

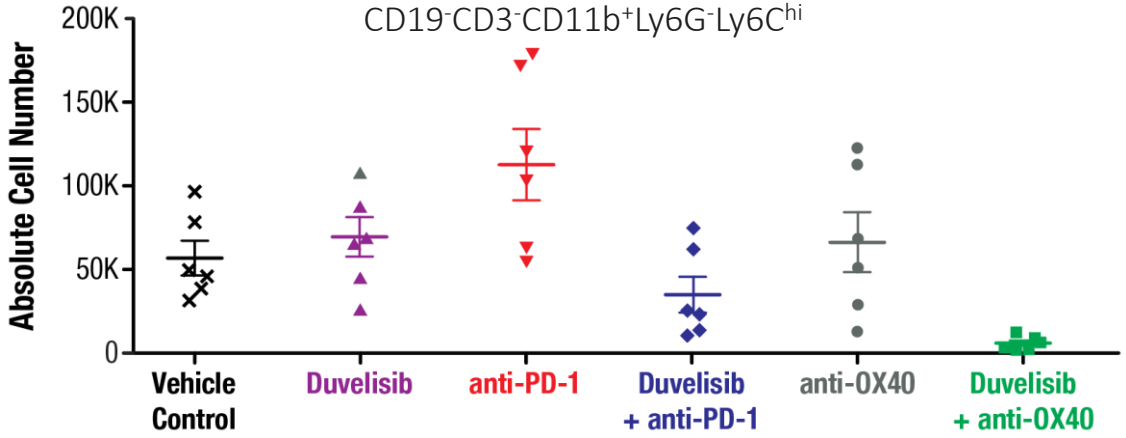
M2 Tumor-Associated Macrophages

$CD19^{-}F4/80^{+}Gr1^{-}CD11b^{+}CD206^{+}$



Tumor Monocytic MDSCs

$CD19^{-}CD3^{-}CD11b^{+}Ly6G^{-}Ly6C^{hi}$



Verastem Oncology

Summary & Conclusions: Duvelisib

- Duvelisib is a dual inhibitor of PI3K-δ and PI3K-γ
  - PI3K-δ inhibition reported to reduce Tregs & enrich memory T cells
  - PI3K-γ inhibition reported to reduce myeloid immunosuppressive cells
- Duvelisib is clinically active as monotherapy in B cell malignancies
  - Positive Phase 3 data in CLL/SLL (DUO)
  - Positive Phase 2 data in iNHL (DYNAMO)
- In a syngeneic mouse model of B cell lymphoma (A20)
  - Duvelisib synergized with anti-PD-1 or anti-OX40 mAbs in induction of tumor growth inhibition
  - Duvelisib reduced both Tregs and myeloid immunosuppressive cells
  - Duvelisib in combination with anti-OX40 induced immune memory
    - Increased memory T cells in blood & spleen; No tumor growth following inoculation on contralateral side
- These data support potential clinical combination of duvelisib with checkpoint or co-stimulatory mAbs

Thanks for your attention!