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
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

<table>
<thead>
<tr>
<th>VS-6063</th>
<th>VS-4718</th>
</tr>
</thead>
<tbody>
<tr>
<td>![Chemical Structure]</td>
<td>![Chemical Structure]</td>
</tr>
<tr>
<td><strong>USAN name:</strong> defactinib</td>
<td><strong>Dosage:</strong> Oral BID</td>
</tr>
<tr>
<td><strong>Dosage:</strong> Oral, 400 mg BID</td>
<td><strong>FAK EC$_{50}$ = 6 nM</strong></td>
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<tr>
<td>• Ph I/II agent studied in 300+ patients to date with good safety profile</td>
<td><strong>PYK2 EC$_{50}$ = 20 nM</strong></td>
</tr>
<tr>
<td>FAK EC$_{50}$ = 15 nM</td>
<td><strong>FAK EC$_{50}$ = 15 nM</strong></td>
</tr>
<tr>
<td>PYK2 EC$_{50}$ = 95 nM</td>
<td><strong>PYK2 EC$_{50}$ = 95 nM</strong></td>
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</table>

![Graph](chart1)

![Graph](chart2)
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

Tumor burden

CD8+ T cells

T-regs

SCC 7.1 chemical carcinogen-induced skin cancer model
FAK Inhibitor reduces immunosuppressive MDSCs, M2 Macrophages and T-regs in tumors

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

- **Tumor burden**
  - Tumor Weight (grams)
  - Vehicle
  - VS-4718

- **Myeloid Derived Suppressor Cells**
  - Monocytes (Mo-MDSC)
  - Granulocytes (G-MDSC)

- **M2 Macrophages & Activation**
  - CD206^{Hi}/MHCII^{Low}
  - Relma^{*}

- **T-regs**
  - CD4^{+} FOXP3^{+}

**Study design (n = 6-7):**
- Day 0
- 10
- 20
- VS-4718
- Cryo
- RNA-Later (Cryo)

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

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

**Treatment with Verastem FAK inhibitor**

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

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

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**

![Graph showing tumor burden](image)

**Ratio: CD8 T cells/Tregs**

![Graph showing ratio CD8 T cells/Tregs](image)

MC38 colorectal cancer mouse model
FAK inhibition reduces stromal density & boosts T cell entry into pancreatic tumors

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

Transgenic Kras/p53 pancreatic model

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

## FAK Inhibitor Immuno-Oncology Trials Currently in Progress

<table>
<thead>
<tr>
<th>DEFACITINIB (FAK INHIBITOR)</th>
<th>PHASE 1 / 1B</th>
<th>PHASE 2</th>
<th>PHASE 3</th>
<th>COLLABORATOR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ovarian</strong>&lt;br&gt;With avelumab</td>
<td>Enrolling</td>
<td></td>
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<tr>
<td><strong>NSCLC, Pancreatic, Mesothelioma</strong>*&lt;br&gt;With pembrolizumab</td>
<td>Enrolling</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pancreatic, relapsed</strong>*&lt;br&gt;With pembrolizumab + gemcitabine</td>
<td>Dose-escalation complete; In expansion phase</td>
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</table>

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

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

Proliferating CD8+ T cells (CD3+ CD8+ Ki67+ DR+)

Macrophages (CD11b+ CD15-CD16- CD14+ CCR2low DR+)

Proliferating CTL to TAM Ratio

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
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
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

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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>PI3K-δ IC₁₀₀ (µM)</th>
<th>PI3K-γ IC₁₀₀ (µM)</th>
<th>Cₘₐₓ (ss) (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duvelisib</td>
<td>Dual PI3K-δ/PI3K-γ Inhibitor</td>
<td>0.4 ± 0.1</td>
<td>1.6 ± 0.2</td>
<td>2.5</td>
</tr>
<tr>
<td>Idelalisib</td>
<td>PI3K-δ Inhibitor</td>
<td>1.0 ± 0.2</td>
<td>9.4 ± 2.3</td>
<td>4.8</td>
</tr>
<tr>
<td>IPI-549</td>
<td>PI3K-γ Inhibitor</td>
<td>12 ± 0.5</td>
<td>0.5 ± 0.2</td>
<td>9.1</td>
</tr>
<tr>
<td>TGR-1202</td>
<td></td>
<td>25 ± 8</td>
<td>55 ± 16</td>
<td>9.2</td>
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</table>

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

- PI3K-gamma inhibition is known to reduce immunosuppressive myeloid cells

- 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\textsubscript{25-33} peptide in the presence of PI3K isoform-specific inhibitors
- Memory T cells (CD62L\textsuperscript{hi}CD44\textsuperscript{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
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)
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.
The Dual PI3K-δ/PI3K-γ Inhibitor Duvelisib Suppresses Immunosuppressive T-Reg Cells & Myeloid Cells in A20 B Cell Lymphoma Model

**Hypothesis:** Reduction of T regulatory cells (Tregs) through PI3K-δ inhibition

**Hypothesis:** Reduction of myeloid immunosuppressive cells through PI3K-γ inhibition
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!