Inclusion Criteria:
- CMY
- CM
- K
- Y
- C

Secondary Objectives:
- Inhibition of FAK signaling leads to significant reduction of pancreatic tumor growth in animal models. Tumors treated with FAK inhibitors displayed markedly reduced tumor fibrosis and decreased immunosuppressive myeloid cells.
- FAK inhibition renders PDAC tumors responsive to chemo- and immunotherapy.

Primary Objective:
- To determine the RIPD of defactinib combined with pembrolizumab and gemcitabine in patients with advanced cancer.

Secondary Objectives:
- To determine the safety and toxicity profile of the triple drug combination.
- To evaluate the objective response rate (ORR) and treatment duration.
- To assess the progression-free survival (PFS), overall survival (OS), and immune-related PFS.

Exploratory Objectives:
- To determine the impact of this regimen on tumor microenvironment.

Focal adhesion kinase (FAK) is a cytosolic tyrosine kinase identified in 1990. The binding of integrin to extracellular matrix triggers FAK phosphorylation which activates multiple signaling pathways.

FAK phosphorylation is elevated in various cancer types. FAK signaling can induce an immunosuppressive microenvironment. FAK activation is consistently hyperactivated in pancreatic adenocarcinoma (PDAC), and FAK signaling is associated with poor clinical outcome.

FAK inhibition leads to significant reduction of pancreatic tumor growth in animal models. Tumors treated with FAK inhibitors displayed markedly reduced tumor fibrosis and decreased immunosuppressive myeloid cells.

FAK inhibition renders PDAC tumors responsive to chemo- and immunotherapy.

FAK inhibition leads to significant reduction of pancreatic tumor growth in animal models. Tumors treated with FAK inhibitors displayed markedly reduced tumor fibrosis and decreased immunosuppressive myeloid cells.

FAK inhibition renders PDAC tumors responsive to chemo- and immunotherapy.

Background

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FAK inhibition renders PDAC tumors responsive to chemo- and immunotherapy.

Secondary Objectives:
- Inhibition of FAK signaling leads to significant reduction of pancreatic tumor growth in animal models. Tumors treated with FAK inhibitors displayed markedly reduced tumor fibrosis and decreased immunosuppressive myeloid cells.
- FAK inhibition renders PDAC tumors responsive to chemo- and immunotherapy.

Results (Dose Escalation Cohorts)

Phase I Study of Defactinib Combined with Pembrolizumab and Gemcitabine in Advanced Cancer
Andrea Wang-Gillam1, A. Craig Lockhart2, Benjamin Tan1, Rama Suresh3, Kian-Huat Lim3, Lee Ratner1, Ashely Morton1, Jess Huffman1, Samantha Marquez1, Nicolas Boice1, David DeNardo3
1Division of Oncology, Washington University School of Medicine, St. Louis, MO; 2Division of Medical Oncology, University of Miami, Miami, FL.

Trial Design:
- Dose escalation cohort:
  - 3+1 dose escalation design (Table 1)

Study Design

Results (Dose Escalation Cohorts)

Primary Objectives:
- To determine the RP2D of defactinib combined with pembrolizumab and gemcitabine in patients with advanced cancer.

Secondary Objectives:
- To determine the safety and toxicity profile of the triple drug combination.
- To evaluate the objective response rate (ORR) and treatment duration.
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Exploratory Objectives:
- To determine the impact of this regimen on tumor microenvironment.

This study is funded by Precision Medicine Research Associates and Barnes Jewish Foundation in St. Louis.

Table 2. Baseline Characteristics

<table>
<thead>
<tr>
<th>Age</th>
<th>Gender</th>
<th>Race</th>
<th>ECOG</th>
<th>Prior Type</th>
<th>Pancreatic cancer</th>
<th>Biliary cancer</th>
<th>Other</th>
<th>Number of Prior Lines</th>
<th>Median, Range</th>
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<tr>
<td>67</td>
<td>Female</td>
<td>16 (88%)</td>
<td>1 (5%)</td>
<td>1 (5%)</td>
<td>1 (5%)</td>
<td>1 (5%)</td>
<td>1 (5%)</td>
<td>2 (1-4)</td>
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Table 3. Treatment-Emergent Adverse Events

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<th>Grade 3</th>
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</thead>
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<td>Fatigue</td>
<td>6 (30%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>5 (25%)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (20%)</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (15%)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (10%)</td>
<td>0</td>
</tr>
<tr>
<td>Mucositis</td>
<td>2 (10%)</td>
<td>0</td>
</tr>
<tr>
<td>Fever</td>
<td>2 (10%)</td>
<td>0</td>
</tr>
<tr>
<td>CTD</td>
<td>2 (10%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Results (Dose Escalation Cohorts)

Figure 1: Inhibition of FAK with chemotherapy and immunotherapy prolong survival. Tumor growth curve and Kaplan-Meier survival analysis of KP tumor-bearing mice treated with various combinations. [Jiang et al. Nat Medicine 2016]

Figure 2: Time on study (days) Efficacy data are available for 15 evaluable patients for dose escalation cohorts A, Level 1-3: Red, level 2-4: Green, level 3-4: Yellow, level 4-5: Blue, level 5: Purple. B: Patients with PDAC treatment.

Table 4. Treatment Response*

<table>
<thead>
<tr>
<th>Response</th>
<th>N (%)</th>
<th>ORR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>1 (11%)</td>
<td>15%</td>
</tr>
</tbody>
</table>

Table 4. Treatment Response*

<table>
<thead>
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<th>Response</th>
<th>N (%)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>1 (11%)</td>
<td>15%</td>
</tr>
</tbody>
</table>

Figure 3. Immune infiltrates in response to treatment in pancreatic cancer patients. Flow cytometry analysis of paired PDAC tissue biopsies at Pre-treatment (Pre) and Cycle 2 Day 1 (Post) (N = 8 patients). Treatment-induced increases in proinflammatory KEF+CD8+ T cells and decreasing FOXP3+ T-Regulatory cells and Tumor-associated macrophages (TAMs) are observed in the majority of patient samples. The increase in the ratio of KEF+CD8+ T cells to TAMs is observed in a subset of patients. Co-expression of PD-L1 in response to treatment indicates that KEF+CD8+ T cells are responding to tumors.

Conclusions

The triple drug regimen is well tolerated, and the dose level 5 is the RP2D dose.

Median time on therapy was 12 days for evaluable patients and 15 days for PDAC patients.

One (13%) PR and 3 (36%) SD were seen in heavily pretreated PDAC patients.

Paired biopsies showed increased proliferating CD8+ T cells and reduced Tregs and macrophages with treatment.

Expansion cohort in PDAC is ongoing and may be worthy of further study.

References


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