Mechanistic Relationships Between Fibrosis and Cancer

Seth Porter
A Circuitous Path of Drug Development

Pre-clinical studies in pancreatic cancer

Clinical trial in pancreatic cancer

First FG-3019 IPF clinical trial

Randomized Ph 2 IPF trial

Open-label Ph 2 IPF trial

Studies in radiation-induced pulmonary fibrosis
Elevated CTGF Promotes Diversion of Normal Tissue Healing Toward Fibrosis

Adapted from Wynn (2007) J Clin Invest 117:524-529
Persistent Proliferation of Myofibroblasts has Similarities to Cancer


**FIGURE 5.** The myofibroblast march in idiopathic pulmonary fibrosis and cancer.
Pamrevlumab in Pancreatic Cancer Clinical Study
CTGF Expression is Elevated in Pancreatic Cancer

- CTGF mRNA is expressed in tumor and stromal cells
- CTGF expression is stronger in stroma
- In vitro, CTGF expression is stronger in stromal cells than in tumor cells
- PDAC tumors are very desmoplastic


Phase 1/2 Clinical Trial in Pancreatic Cancer

Design

• Escalating doses of pamrevlumab (FG-3019) combined with chemotherapy (gemcitabine and erlotinib)

Trial Endpoints

• Safety
• Efficacy: PFS, OS, tumor response by RECIST and CA19.9
• FG-3019 pharmacokinetics and pharmacodynamics

Inclusion Criteria

• Untreated Stage 3 or 4 PDAC (88% stage 4)
• ECOG 0 or 1 (60% ECOG 1)
Open-label, Dose-Escalation Study of Pamrevlumab in Combination with Gemcitabine and Erlotinib

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Dose (mg/kg)</th>
<th>Freq</th>
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<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>Q2W</td>
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<tr>
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<td>Q2W</td>
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<tr>
<td>3</td>
<td>15</td>
<td>Q2W</td>
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<tr>
<td>4</td>
<td>25</td>
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<tr>
<td>5</td>
<td>35</td>
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<tr>
<td>6</td>
<td>45</td>
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<tr>
<td>7</td>
<td>17.5</td>
<td>QW</td>
</tr>
<tr>
<td>8</td>
<td>22.5</td>
<td>QW</td>
</tr>
</tbody>
</table>

FG-3019 Infusions

Treatment continued until disease progression
Improved 1-Year Overall Survival Rate with Higher FG-3019 Doses and Exposure

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Dose mg/kg Freq</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>3 Q2W</td>
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<tr>
<td>2</td>
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<td>45 Q2W</td>
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<td>7</td>
<td>17.5 QW</td>
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<tr>
<td>8</td>
<td>22.5 QW</td>
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</table>
Improved OS with Higher FG-3019 Exposure and Low Baseline Plasma CTGF

### FG-3019 Day 15 C\textsubscript{min}

<table>
<thead>
<tr>
<th>FG-3019 C\textsubscript{min} (Day 15) ≥150 μg/mL</th>
<th>n</th>
<th>Median OS (Months)</th>
<th>1-Year OS Rate</th>
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</thead>
<tbody>
<tr>
<td>No (37)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (38)</td>
<td></td>
<td>9.0</td>
<td>34.2%</td>
</tr>
<tr>
<td>p value</td>
<td>0.0255 (Log Rank Test)</td>
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<td></td>
</tr>
</tbody>
</table>

### Baseline [CTGF]

<table>
<thead>
<tr>
<th>BL [CTGF] ≥10 ng/mL</th>
<th>n</th>
<th>Median OS (Months)</th>
<th>1-Year OS Rate</th>
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<tbody>
<tr>
<td>No (36)</td>
<td></td>
<td>10.1</td>
<td>30.6%</td>
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<tr>
<td>Yes (39)</td>
<td></td>
<td>4.4</td>
<td>15.4%</td>
</tr>
<tr>
<td>p value</td>
<td>0.028 (Log Rank Test)</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>0.17 Fisher’s</td>
<td></td>
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</table>
Pamrevlumab in Pancreatic Cancer Mouse Study

**LSL-Kras$^{G12D/+}$;LSL-Trp53$^{R172H/+}$;Pdx-1-Cre (KPC) mouse model**

- Generated with conditional mutations in both the Kras oncogene and the p53 tumor-suppressor gene
- Analogous to common genetic mutations found in PDAC patients
- Resistant to chemotherapy
KPC Mouse: Elevated Expression of CTGF

B

![Graph showing CTGF levels in normal pancreas and PDA tissue.](image)

D

<table>
<thead>
<tr>
<th>Protein</th>
<th>KPC tumor cells</th>
<th>CAFs</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTGF</td>
<td><img src="image" alt="Image of CTGF expression" /></td>
<td><img src="image" alt="Image of CTGF expression" /></td>
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<tr>
<td>SMA</td>
<td><img src="image" alt="Image of SMA expression" /></td>
<td><img src="image" alt="Image of SMA expression" /></td>
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<tr>
<td>E-cadherin</td>
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<td><img src="image" alt="Image of E-cadherin expression" /></td>
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<tr>
<td>HSP90</td>
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<td><img src="image" alt="Image of HSP90 expression" /></td>
</tr>
</tbody>
</table>

Neesse, PNAS (2013) 110:12325
KPC Mouse: Efficacy

- FG-3019 in combination with gemcitabine
  - Slowed tumor growth
  - Inhibited formation of ascites
  - Decreased metastatic burden (ns)
  - Increased survival

Tumor Volume

Survival

Metastasis

Ascites

Neesse, PNAS (2013) 110:12325
FG-3019 promoted tumor cell apoptosis and decreased expression of survival gene XIAP.

Neesse, PNAS (2013) 110:12325
Pamrevlumab in Pancreatic Cancer

In an open label Phase 1/2 clinical trial:

• Pamrevlumab in combination with chemo enhanced survival in a dose/exposure dependent manner
• Elevated baseline CTGF correlated with poorer survival

In the KPC mouse model of pancreatic cancer:

• Pamrevlumab in combination with chemo:
  • Enhanced survival
  • Reduced metastases
  • Increased tumor apoptosis
  • Decreased expression of survival gene XIAP
IAP Antagonists for Cancer Therapy

- XIAP inhibits caspase-3/-7
- Smac and DIABLO are inhibitors of XIAP
- Smac mimetics are being developed for cancer

Wang in L. Current Topics in Microbiology and Immunology (2011), 348, 89
Pamrevlumab in Pulmonary Fibrosis
Mouse Radiation-Induced Fibrosis Study
FG-3019 Reversed Lung Density and Impacted Survival Gene Expression

- Administration of pamrevlumab beginning 16 weeks after irradiation altered progression of lung density.
- Irradiated, untreated group (orange triangles) have progressive increases in lung density.
- Lung density of therapeutic treatment group (green squares) increased until administration of FG-3019 began at 16 weeks, and then began to decrease.

**Diablo Expression**
- Diablo Expression, 18wks (normalized to no RT controls)
- ns, p<0.05

**Survivin (Birc5)**
- Survivin (Birc5) Expression, 18wks (normalized to no RT controls)
- p<0.001, p<0.001
Pamrevlumab in IPF Clinical Study
Phase 2A Clinical Trial in IPF

- Cohort 1: FVC 45-85% predicted, 15 mg/kg Q3W
- Cohort 2: FVC ≥ 55% predicted, 30 mg/kg Q3W
- DLCO ≥30% predicted
- ≥10% to <50% parenchymal fibrosis and <25% honeycombing
- 15 or 30 mg/kg Q3W for 45 weeks
- HRCT at 24 and 48 weeks
- PFTs at 12, 24, 36, and 48 weeks
- PROs at 24 and 48 weeks
Phase 2A Clinical Trial in IPF: Change in Quantitative HRCT

$$\Delta \text{CAD} = \% \text{ change from BL in Computer-Aided Detection scores assessed at } 24 \& 48 \text{ weeks}$$

- QLF
- QILD

Week 24 Placebo Treated IPF Patients

Independently UCLA study
Phase 2A Clinical Trial in IPF: Changes in FVC Correlate with Changes in Quantitative HRCT

Correlation of fibrosis change with FVC change

Categorical change of FVC change

Correlation of fibrosis change with FVC change

<table>
<thead>
<tr>
<th>Fibrosis subtype</th>
<th>Week</th>
<th>p-value</th>
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<tbody>
<tr>
<td>QLF</td>
<td>24</td>
<td>&lt;0.0001</td>
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<tr>
<td>QLF</td>
<td>48</td>
<td>&lt;0.001</td>
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<tr>
<td>GG</td>
<td>48</td>
<td>0.074</td>
</tr>
<tr>
<td>QILD</td>
<td>48</td>
<td>&lt;0.001</td>
</tr>
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∆ Fibrosis* > 0
Pamrevlumab in Pulmonary Fibrosis

In an open label Phase 2 IPF clinical trial:
- Pamrevlumab appeared to reduce fibrosis in ~25% of completers by quantitative HRCT
- Changes in FVC correlated with changes in fibrosis

In the radiation-induced fibrosis mouse model of lung fibrosis
- Pamrevlumab
  - Reduced lung density by HRCT
  - Improved pulmonary function
  - Improved survival
  - Decreased expression of survival gene Birc5 and increased XIAP inhibitor (DIABLO)
Studies in Apoptosis in Lung Mesenchymal Cells
Activation and Inhibition of XIAP in Mouse Lung Fibroblasts

Targeting Inhibitor of Apoptosis Proteins Protects from Bleomycin-Induced Lung Injury

TGFβ increased the expression of XIAP and cIAPs in fibroblasts

Smac mimetic (XIAP inhibitor) reduced collagen expression and increased apoptosis in bleo lung injury model

XIAP is Elevated in Human IPF Lung Fibroblasts

- Absence of XIAP staining in healthy control lung
- Localization of XIAP to fibroblast-like cells within established fibrosis and fibroblastic foci in IPF lung

Human IPF Fibroblasts Have Elevated Gene Expression of CTGF and XIAP


Transcriptome of Cultured Lung Fibroblasts in IPF: Meta-Analysis of Publically Available Microarray Datasets …


X-Linked Inhibitor of Apoptosis Regulates Lung Fibroblast Resistance to Fas-Mediated Apoptosis
1. CTGF is elevated in pancreatic cancer (and others) and in fibrosis
2. CTGF appears to elevate expression of survival genes (XIAP)
3. Survival genes (XIAP) play a critical role in preventing apoptosis of cancer cells and myofibroblasts
4. Reduced expression of survival genes can make cancer cells susceptible to chemotherapy and can enable cessation/reversal of fibrosis
5. Blockade of CTGF can reduce expression of survival genes and provide clinical benefit in pancreatic cancer and IPF
6. CTGF affects other aspects of disease biology in both cancer and IPF
Acknowledgements

- KPC mouse model of PDAC
  - David Tuveson laboratory, Cold Spring Harbor
- Pulmonary fibrosis animal studies
  - Peter Huber laboratory, Univ. Heidelberg
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