CITN Investigator Meeting:

Overview of anti-CD40 biology and initial clinical trials

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CD40 as a target for cancer therapy

- Member of the TNF receptor superfamily

- Broadly expressed by antigen presenting cells (APC) and other normal cells, including endothelium and platelets; certain tumor cells

- No intrinsic kinase or other signal transduction activity

Vonderheide, Clin Can Res, 2007
Drug formulations that target CD40

- **CD40L**
  - Recombinant trimer: rhCD40L (Immunex/Amgen)
  - CD40L gene therapy: Adeno-CD40L intratumoral (Weill Cornell)
  - Cell-based CD40L gene therapy: CLL (UCSD); leukemia (Baylor)
  - Ex vivo CD40L activated APCs: CD40-DC (Baylor) or CD40-B (Penn)

- **CD40 monoclonal antibody**
  - Antagonist: lucatumumab (Novartis/Xoma)
  - Weak agonist: dacetuzumab (Seattle Genetics/Genentech)
  - Agonist: Chi Lob 7/4 (Southampton, UK); CP-870,893 (Pfizer)
Potential mechanisms of action for CD40 mAb

- **Tumor CD40 dependent**
  - Fc-dependent cytotoxicity of CD40+ tumors (ADCC, CMC) – *IgG1*
  - Blockade of CD40L-CD40 growth signals – *antagonist*
  - Direct cytotoxicity of CD40+ tumors – *agonist*
  - Increase immunogenicity of CD40+ B cell tumor – *agonist*

- **Tumor CD40 independent**
  - Licensing of APC to induce anti-tumor T cell responses – *agonist*
  - Activation of macrophages to destroy tumor and tumor stroma – *agonist*
Potential downsides of agonist CD40 mAb

- Autoimmunity
- Promote tumor angiogenesis
- Thrombosis
- Cytokine release syndrome
- Hyper immune-stimulation; abolishment of long-term T cell responses to tumor or viral antigens; induction of tolerance
Chemotherapy can synergize with agonist CD40 mAb

Murine pancreas adenocarcinoma cell line

Tumor challenge
0  13  15 Days

-100%
-75%
-50%
-25%
0%
100%
200%
300%
400%

PBS
Gemcitabine
IgG2a

PBS
Gemcitabine
FGK45

PBS
Gemcitabine
FGK45

Percentage change in tumor volume relative to baseline

2 weeks
Chemotherapy can synergize with agonist CD40 mAb

- Tumor challenge
- Gemcitabine
- Anti-CD40 mAb (FGK45, agonist anti-mouse CD40 mAb)

Murine pancreas adenocarcinoma cell line

PBS + IgG2a vs. Gem + FGK45

CD3
Chemotherapy can synergize with agonist CD40 mAb

Murine pancreas adenocarcinoma cell line

Tumor challenge

0 13 15 Days

Gemcitabine

Anti-CD40 mAb

FGK45, agonist anti-mouse CD40 mAb

PBS + IgG2a

Gemcitabine + FGK45

Gemcitabine + GK1.5 (CD4)

Gemcitabine + 2.43 (CD8)

Percentage change in tumor volume relative to baseline

2 weeks
Targeted expression of mutated $\text{Kras}^{G12D}$ and $\text{p53}^{R172H}$ genes in pancreas via Cre-Lox approach ("KPC mice") \textit{Hingorani et al, Cancer Cell, 2005}

\textbf{Evaluating CD40 mAb in a genetically engineered mouse model of pancreatic ductal adenocarcinoma}

Targeted expression of mutated $\text{Kras}^{G12D}$ and $\text{p53}^{R172H}$ genes in pancreas via Cre-Lox approach ("KPC mice") \textit{Hingorani et al, Cancer Cell, 2005}
Treatment with CD40 mAb and gemcitabine in KPC mice

Beatty et al, Science, 2011
Treatment with CD40 mAb and gemcitabine in KPC mice

Beatty et al, Science, 2011
CD40-mediated tumor regression in the absence of tumor-infiltrating T cells

<table>
<thead>
<tr>
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<th>IgG2a Non-responder</th>
<th>FGK45 Non-responder</th>
<th>FGK45 Responder</th>
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CD40 mAb modulates the phenotype of tumor associated macrophages in the KPC model

No change in magnitude of macrophage infiltrate

Transient macrophage activation
CD40-mediated tumor regression is not observed after systemic depletion of macrophages.

Ultrasound assessment 14d after systemic treatment with 100 ug FGK45 or control IgG2a, compared to baseline.

CEL: Clodrinate encapsulated liposomes given every 4 days starting at day -2.
Macrophage-dependent stromal involution with CD40 mAb

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<th>FGK45 + CEL</th>
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18 hr
Modulation and trafficking of macrophages with CD40 mAb

FGK45 labeling detected by IHC
CP-870,893: agonist anti-CD40 mAb (Pfizer)

- Fully human IgG2 monoclonal antibody
  - Potent and selective agonist of the CD40 receptor
- Exhibits anti-tumor activity in xenograft models (Pfizer)
  Gladue et al, CII, 2011
- Activates human dendritic cells and B cells \textit{in vitro}
  Hunter et al, SJI, 2007; Carpenter et al, JTR, 2009

Baseline

48 hours

Purified peripheral blood B cells

CP-870,893 = 1 ug/ml

MFI=143

MFI=3573

CD86

CD86
Clinical trials with the agonist CD40 mAb CP-870,893

Completed

- First-in-human, dose-escalation single infusion for pts with refractory tumors
  - N=29 patients (Vonderheide et al, JCO, 2007)

- Repeated ‘single’ infusions (q8weeks) in pts with clinical benefit
  - N=7 patients (Vonderheide et al, JCO, 2007)

- Weekly infusion for pts with solid tumors
  - N=27 patients (Ruter et al, Cancer Biol Therapy, 2010)

- CP-870,893 with carboplatin and paclitaxel for pts with solid tumors
  - N=32 patients (Vonderheide, ASCO 2009)

- CP-870,893 with gemcitabine for pts with chemo-naïve advanced pancreas cancer
  - N=21 patients (Beatty et al, Science, 2011)
Clinical trials with the agonist CD40 mAb CP-870,893

Ongoing

- CP-870,893 with pemetrexed/cisplatin for pts with mesothelioma (first line)
  - N=12 patients treated so far (PI, Nowak; Univ Western Australia)

- Poly IC:LC and NYESO-1/gp100/MART peptides +/- CP-870,893 for patients with resected stage III or IV melanoma
  - N=15 patients treated so far (PI, Weber; sponsor, Moffitt Cancer Center)

- CP-870,893 with tremelimumab (anti-CTLA4) for pts with metastatic melanoma
  - N=10 patients treated so far (sponsor/PI, Vonderheide; Penn)

Total number of patients treated with CP-870,893 as of May 2011: 146
CP-870,893 toxicities

• **Cytokine release syndrome**
  – Transient chills, rigor, fever 30 min after infusion
  – Acute elevation of IL-6 and TNF-alpha (<500-1000 pg/ml)
  – Occurs in 30%-50% of patients (grade 1-2 at 0.1 mg/kg or higher)
  – Occasional patients with grade 3 CRS that defined MTD
  – Rate much lower with current prophylaxis (antihistamine, NSAID, acetaminophen, ondansetron)

• **No major autoimmune events**
  – No colitis, thyroiditis, hypophysitis, or dermatitis
  – 2 melanoma pts receiving CP-870,893 and Carbo/Taxol developed extensive vitiligo

• **Thrombosis**
  – DVT, PE, CVA have been observed (<5% of patients)

• **Same MTD in multiple dose-escalation studies**
  – 0.2 mg/kg
Laboratory abnormalities after CP-870,893

- Transient, dose-dependent increase in:
  - AST and ALT grade 1 or 2; very rarely grade 3
  - D-dimer elevation no signs of DIC

- Transient, dose-dependent decline in:
  - Abs lymphocyte count up to grade 3 or 4
  - Abs monocyte count not graded
  - Platelets never grade 3 or 4
Pharmacokinetics and pharmacodynamics of CP-870,893

- Serum half-life is <24hrs
  - Related to large in vivo sink of CD40 molecules
- No human-anti-human antibodies (HAHA)
- Pharmacodynamics
  - Acute, transient loss of CD19+ B cells in blood
  - Increase in %CD86+ and %CD54+ peripheral B cells
  - Obliterated by use of peri-infusional steroids
  - Diminished when given with CarboTaxol

Vonderheide et al, JCO, 2007
Immune impact of weekly dosing CP-870,893

B cell hyperstimulation

T cell depletion

PD effects after 1\textsuperscript{st}, 2\textsuperscript{nd}, and 4\textsuperscript{th} infusion relative to baseline at MTD or higher

End of study relative to baseline for 8 pts at MTD or higher

Ruter et al, CBT, 2010
### Summary of clinical responses with CP-870,893

<table>
<thead>
<tr>
<th>All dose levels</th>
<th>All patients</th>
<th>Melanoma</th>
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<tbody>
<tr>
<td>Single infusion</td>
<td>4/29 (14%)</td>
<td>4/15 (27%)</td>
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<tr>
<td>Weekly infusions</td>
<td>0/27 (0%)</td>
<td>0/11 (0%)</td>
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<tr>
<td>q3wk with CT*</td>
<td>6/29 (21%)</td>
<td>3/23 (13%)</td>
</tr>
<tr>
<td>q4wk with Gem**</td>
<td>5/21 (24%)</td>
<td>N/A</td>
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<td>4/16 (25%)</td>
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<td>Weekly infusion</td>
<td>0/19 (0%)</td>
<td>0/5 (0%)</td>
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<td>4/18 (22%)</td>
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* CT = carboplatin plus paclitaxel all solid tumors
** Gem = gemcitabine for pancreatic carcinoma
Clinical response from single infusion of CP-870,893

- FIH study: 29 patients evaluated by RECIST after single infusion
  - 4 Partial Responses, all melanoma, all at MTD
  - 7 Stable Disease

- 7 patients with SD or PR were retreated with CP-870,893
  - One melanoma patient had a near CR for 18 mo; then isolated LN recurrence, removed
  - Pt remains NED at 27+ mo since resection without other therapy (4 years since starting study)
Clinical response to Gem/CD40 in pancreatic cancer

Gemcitabine i.v. 1000 mg/m2 q week x3, then 1 week off
CP-870,893 i.v. 0.1 or 0.2 mg/kg on day 3 of every cycle

Beatty et al, Science, 2011
Clinical response to Gem/CD40 in pancreatic cancer

Best overall response

Patient number

Percentage change from baseline

Primary Lesion | Liver Metastasis | Liver Metastasis

Baseline

3.9 cm | 7.6 cm | 7.5 cm

End of Cycle 3

2.1 cm | Not seen | 4.0 cm

Pt 10031016
Clinical response to Gem/CD40 in pancreatic cancer

Percentage change from baseline

Best overall response

10031016
Liver Metastasis

10061003
Primary Tumor
Challenges for CP-870,893 drug development

- Understand and exploit mechanism(s) of action in pts with solid tumors
- Optimize dose and schedule appropriate for immune agonist
- Optimize route of administration
- Find the right combination for the right diseases
- Keep up the momentum
CP-870,893 for treatment of melanoma

In 2011, new landscape for experimental therapeutics w/ ipilimumab and PLX4032

1. Metastatic disease
   - Single agent – not recommended
   - Combination with:
     - Ipilimumab or tremelimumab – ongoing at Penn with treme
     - Cancer vaccine – ongoing at Moffitt
     - PLX4032
     - PLX4032 plus other targeted therapy
     - Other targeted therapy
     - TLR ligand
     - IFN
     - IL-2
     - Any of the above with Prevnar

2. Resected stage III (and IV)
   - Bring forward successful combination from (1)
1. Randomized phase II study of gemcitabine/abraxane with CP-870,893 for patients with chemotherapy naïve locally advanced or metastatic pancreatic cancer
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**CP-870,893 for treatment of pancreatic cancer**

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**Day**

- **1**
- **3**
- **8**
- **15**

**Gem Abraxane**

**CP-870,893**

**next 28 day cycle**

**ORR**

**PFS**

**OS**

**PET**

**next 28 day cycle**
CP-870,893 for treatment of pancreatic cancer

2. Phase II study of preoperative CP-870,893/gemcitabine followed by addition of CP-870,893 to standard of care adjuvant chemoradiation for patients with newly diagnosed resectable or borderline resectable pancreatic cancer.
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Randomize

Day 1

15

Gem CP-870,893 +/− GVAX

Lap

Resect 5FU/XRT

Tissue only SOC

TTP

OS

PET

CP-870,893 for treatment of pancreatic cancer