CD40 agonists in cancer immunotherapy

Robert H. Vonderheide, MD, DPhil

Abramson Cancer Center
Abramson Family Cancer Research Institute
Perelman School of Medicine
University of Pennsylvania
Disclosures

- Investigational use of CP-870,893
- Dr. Vonderheide reports receiving research funding from Pfizer and Roche
PD-1 + Your Pipeline Here = Future of Cancer Immunotherapy
Platform for cancer immunotherapy

- Negative checkpoint blockade
- Antigen delivery
- APC licensing
CD40 by the numbers

Rank on CITN list of investigational agents: 1
CD40 by the numbers

Rank on CITN list of investigational agents: 1

Number of actively enrolling agonist CD40 mAb cancer clinical trials: 0
CD40 by the numbers

Rank on CITN list of investigational agents: 1

Number of actively enrolling agonist CD40 mAb cancer clinical trials: 0

Number of years since a patient with pancreatic cancer was treated with CD40: 4
CD40 and the T cell hypothesis of tumor immunity

Vonderheide and Glennie, Clin Can Res, 2013
CD40 and the T cell hypothesis of tumor immunity

“Licensed APC”

Vonderheide and Glennie, Clin Can Res, 2013
### Agonist CD40 monoclonal antibodies in clinical trials

<table>
<thead>
<tr>
<th>mAb</th>
<th>CP-870,893</th>
<th>Dacetuzumab</th>
<th>Chi Lob 7/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Company/Institution</td>
<td>Pfizer/VLST</td>
<td>Seattle Genetics</td>
<td>Univ. of Southampton</td>
</tr>
<tr>
<td>Isotype</td>
<td>Fully human</td>
<td>Humanized</td>
<td>Chimeric</td>
</tr>
<tr>
<td>Maximum dose</td>
<td>0.2 mg/kg</td>
<td>Up to 12 mg/kg</td>
<td>Up to 160 mg total</td>
</tr>
<tr>
<td>Route of administration</td>
<td>i.v.</td>
<td>i.v.</td>
<td>i.v.</td>
</tr>
<tr>
<td>Dosing interval</td>
<td>Every 3–4 wks</td>
<td>Weekly</td>
<td>Weekly × 4</td>
</tr>
<tr>
<td>Toxicity</td>
<td>Mild-to-moderate cytokine release syndrome</td>
<td>Mild-to-moderate cytokine release syndrome</td>
<td>Noninfectious inflammatory eye disorders</td>
</tr>
<tr>
<td>Diseases targeted</td>
<td>Melanoma</td>
<td>Hematologic malignancies, especially NHL</td>
<td>Advanced solid tumors and lymphoma</td>
</tr>
<tr>
<td></td>
<td>Pancreatic carcinoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mesothelioma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical efficacy</td>
<td>Objective tumor responses reported in melanoma and pancreatic carcinoma (about 20%)</td>
<td>Objective tumor responses (in refractory and relapsed NHL, 12% as single agent; 47% with rituximab and gemcitabine)</td>
<td>Study to address is underway</td>
</tr>
<tr>
<td>Combinations explored</td>
<td>Chemotherapy</td>
<td>Chemotherapy</td>
<td>None yet</td>
</tr>
<tr>
<td></td>
<td>Melanoma vaccine</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tremelimumab</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**NOTE:** Only reagents showing agonistic activity are included and thus lucatumumab (Novartis) has not been discussed. Abbreviation: NHL, non-Hodgkin lymphoma.

*Vonderheide and Glennie, Clin Can Res, 2013*
Clinical trials with the agonist CD40 mAb CP-870,893

- **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 patients with clinical benefit**
  - N=7 patients (Vonderheide et al, JCO, 2007)

- **Weekly infusion for patients 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, OncoImmunology, 2013)

- **CP-870,893 with gemcitabine for chemo-naïve advanced pancreas cancer**

- **CP-870,893 with tremelimumab (anti-CTLA4) for pts with metastatic melanoma**
  - N=24 patients (sponsor/PI, Vonderheide; Penn)

*Overall tumor response rate is 20%-25% across studies (more than 130 patients)*
CD40 is a ‘proximal’ TNFR agonist

Ott et al, Clin Can Res, 2013
Chemotherapy/CD40 mAb as a vaccine in pancreas ca

KPC = _Kras^{G12D/+} Trp53^{R172H/+} Pdx-1 Cre_
Chemotherapy/CD40 mAb as a vaccine in pancreas ca

KPC = _Kras^{G12D/+} Trp53^{R172H/+} Pdx-1 Cre_

Carcinoma: CD45

Carcinoma: CD8
Chemotherapy/CD40 mAb as a vaccine in pancreas ca

Byrne and Vonderheide, UPenn; unpublished

If mice are first depleted of T cells, there are no regressions in Gem/nab-P/FGK45 mice (not shown)
Tumor infiltrating T cells after chemotherapy/CD40

% Treg

% CD4^+ cells that are FoxP3^+

Ratio CD4^+ Teff/Treg

Ratio CD8/Treg

Abrx = abraxane = nab-P

Byrne and Vonderheide, UPenn; unpublished
CD40/chemo plus checkpoint blockade

Rafi Winograd
Kate Byrne
unpublished
PD-L1 expression is independent of IFN-gamma and T cells

Rafi Winograd unpublished

Pancreatic cancer patient

Rafi Winograd unpublished
Gemcitabine and agonist CD40 mAb CP-870,893 in chemo-naïve metastatic pancreatic carcinoma

Partial response 24%
mPFS 5.2 mo
mOS 8.4 mo

Beatty et al, Science, 2011
CD40 mAb-mediated tumor regression in KPC mice is T cell-independent & macrophage-dependent

Beatty et al, Science, 2011
Macrophage-dependent stromal involution with CD40 mAb

- H&E
- Masson’s trichrome
- CD40-Mac IHC

IgG2a

CD40 mAb

CEL + CD40 mAb
Treatment with CD40 mAb enhances T cell function

CD4 T cells

% IFN-gamma secreting cells

nl spleen  KPC spleen  KPC Pancreas  KPC Pancreas d+7 FGK45  KPC Pancreas d+14 FGK45

CD8 T cells

% IFN-gamma secreting cells

nl spleen  KPC spleen  KPC Pancreas  KPC Pancreas d+7 FGK45  KPC Pancreas d+14 FGK45
Inducing a T cell response with Gem/CD40/CEL

<table>
<thead>
<tr>
<th>Rates of regression in KPC mice (%)</th>
<th>T cells in KPC tumor</th>
<th>Regression after T cell depltn (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0</td>
<td>No</td>
</tr>
<tr>
<td>Gem</td>
<td>0</td>
<td>No</td>
</tr>
<tr>
<td>Gem/CD40</td>
<td>30</td>
<td>No</td>
</tr>
<tr>
<td>CD40</td>
<td>30</td>
<td>No</td>
</tr>
<tr>
<td>CEL</td>
<td>0</td>
<td>No</td>
</tr>
<tr>
<td>CD40/CEL</td>
<td>0</td>
<td>No</td>
</tr>
<tr>
<td>Gem/CD40/CEL</td>
<td>67</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Beatty and Vonderheide, UPenn; submitted

CD3, day 14
Long-term remission of melanoma from CP-870,893

55 yr old woman with metastatic melanoma (Braf V600E), progressive despite chemotherapy and exp therapies, enrolled on first-in-human trial in 2005, received 10 doses of CP-870,893

_Bajor et al, Can Immunol Res, 2014_
Change in melanoma microenvironment after CP-870,893
TCR-beta deep sequencing of tumor infiltrating T cells

Emergence of a new T cell repertoire in the tumor after treatment with CD40 mAb

TQ = top quartile

TCR-beta deep sequencing reveals systemic T cell response years after resolution of disease

Issues for CD40 mAb clinical development

- Toxicity
- Formulation
- Dose and schedule
- Route of administration
- Optimal combination partners
- Drug availability
Does CD40 mAb need to be crosslinked?

Richman and Vonderheide, OncoImmunology, 2014
Richman and Vonderheide, Can Immunol Res, 2014
CD40 as neoadjuvant therapy in pancreatic cancer

Phase I study of preoperative RO7009789 +/- chemo for patients with newly diagnosed resectable pancreatic carcinoma or stage III melanoma

Arm A: RO7009789
Arm B: Gen/nP then RO7009789

Dx  ↓  Resect  ↓  Tissue and blood biomarkers
Day 1  15

Safety  DFS  OS

Gem/nP + RO7009789 x 4 cycles

observe
CITN working group view on priority trials

- As a adjuvant to T cell ‘vaccine’
  - With chemo (current trial)
  - With radiation
  - With anti-tumor mAb (trastuzumab, TDM-1)
  - With an tumor vaccine with defined antigens
- Get mechanistic for CITN trials
  - Window trial design (neoadjuvant pancreas, breast, bladder)
  - Metastatic with pre and post biopsies

All +/- PD-1
PD-1 + Your Pipeline Here = Future of Cancer Immunotherapy
It’s OK to say the ‘V’ word

Vaccine
Summary: CD40 mAb for cancer therapy

- Activates both innate and adaptive immunity
  - Licenses APC, triggers T cells
  - May be a critically important component for vaccination

- Established safety profile and reproducible clinical activity
  - Combination partner: chemotherapy, radiation, CTLA4, PD-1
## Acknowledgements

<table>
<thead>
<tr>
<th>Vonderheide Lab</th>
<th>Scientific collaborators</th>
<th>Current funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>David Bajor</td>
<td>Andy Minn</td>
<td>R01 CA 169520</td>
</tr>
<tr>
<td>Kate Byrne</td>
<td>John Wherry</td>
<td>R01 CA158186</td>
</tr>
<tr>
<td>Rafi Winograd</td>
<td>Christina Twyman</td>
<td>R01 CA111377</td>
</tr>
<tr>
<td>Andrew Rech</td>
<td>Michael Kalos</td>
<td>P30 CA016520</td>
</tr>
<tr>
<td>Lee Richman</td>
<td>Gregory Beatty</td>
<td>Breast Cancer Res Fnd</td>
</tr>
<tr>
<td>Rebecca Evans</td>
<td></td>
<td>SU2C</td>
</tr>
<tr>
<td>Ran Reshef</td>
<td>Clinical collaborators</td>
<td>PanCan Action Network</td>
</tr>
<tr>
<td>Tim Chao</td>
<td>Amit Maity</td>
<td></td>
</tr>
<tr>
<td>Nate Leissenring</td>
<td>Steve Hahn</td>
<td></td>
</tr>
<tr>
<td>Nune Markosyan</td>
<td>Lynn Schuchter</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tara Gangadhar</td>
<td></td>
</tr>
<tr>
<td>Mouse hospital</td>
<td>Rosemarie Mick</td>
<td></td>
</tr>
<tr>
<td>Cynthia Clendenin</td>
<td>George Xu</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cindy Desmarais (Adaptive)</td>
<td></td>
</tr>
</tbody>
</table>