Policy Issues in the Clinical Development and Use of Immunotherapy for Cancer
Cancer Immunotherapy Development

1890s
1st CA vaccine developed (Coley)

1976
1st study with BCG in bladder CA

1985
1st study with adoptive T cell transfer in CA

1990s
Discovery of checkpoint inhibitor (Allison)

1998
IL-2 (cytokine) approved for CA

2011
1st checkpoint inhibitor approved for CA

2014/2015
Approval of 2 anti-PD-1 antibodies for advanced melanoma and lung cancer

http://www.fightcancerwithimmunotherapy.com
Safety and tumor responses with lambrolizumab (aPD1 Merck) in melanoma
Tumor-Immune Interaction

GM-CSF, VEGF, IL-1β

TGFβ

IDO, IL-10

ARG1, iNOS

Vaccine

DC

PD-L1

TGFβ

IDO, IL-10

VEGF, IL-1β

IL-10

CD80

CD80

GM-CSF, VEGF, IL-1β

TGFβ

IDO, IL-10

ARG1, iNOS

Vaccine

DC

PD-L1

TGFβ

IDO, IL-10

VEGF, IL-1β

IL-10

CD80

CD80
Effective Therapeutic immune balance

Induction of immune response

Inhibition of suppression

Proinflammatory cytokines (IL-6 and TNF-α)

Tumor cells

IDO+ DC

Treg

MDSC

TAM

CTL

B cell

CD+ T cell

NK cell

IFN-γ
Immune Therapy

• Cancer Vaccines
• T cell Therapy
• Immune modulating agents, Large and Small
• combinations
Policy Issues

- What pre-clinical data is needed for clinical trials translation and what models are needed
Policy Issues

• What pre-clinical data is needed for clinical trials translation and what models are needed
  – What are the scenarios that preclinical applies or it does not?
  – What are tumor models needed?
Policy Issues

• What pre-clinical data is needed for clinical trials translation and what models are needed
• Challenges in trial design for immunotherapies and combinations
MPDL3280A (anti-PD-L1) in metastatic bladder cancer

Powles T et al. Nature 515(7528), 558-562 (2014)
MPDL3280A (anti-PD-L1) in metastatic bladder cancer

Powles T et al. Nature 515(7528), 558-562 (2014)
<table>
<thead>
<tr>
<th>Rank*</th>
<th>Agent</th>
<th>Agent Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>IL-15</td>
<td>T-Cell Growth Factor</td>
</tr>
<tr>
<td>2</td>
<td>Anti-Programmed Death-1 (PD1) and/or anti-B7-H1 (PD1 Ligand)</td>
<td>T-Cell Checkpoint Blockade Inhibitor</td>
</tr>
<tr>
<td>3</td>
<td>IL-12</td>
<td>Vaccine Adjuvant</td>
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<tr>
<td>4</td>
<td>Anti-CD40 and/or CD40L</td>
<td>Antigen Presenting Cell Stimulator</td>
</tr>
<tr>
<td>5</td>
<td>IL-7</td>
<td>T-Cell Growth Factor</td>
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<tr>
<td>6</td>
<td>CpG</td>
<td>Vaccine Adjuvant</td>
</tr>
<tr>
<td>7</td>
<td>1-Methyl Tryptophan</td>
<td>**T-cell Inhibitor</td>
</tr>
<tr>
<td>8</td>
<td>Anti-CD137 (anti-4-1BB)</td>
<td>T-Cell Stimulator</td>
</tr>
<tr>
<td>9</td>
<td>Anti-TGF-beta</td>
<td>Signaling Inhibitor</td>
</tr>
<tr>
<td>10</td>
<td>Anti-IL-10 Receptor and Anti-IL-10</td>
<td>Suppression Inhibitor</td>
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<tr>
<td>11</td>
<td>Flt3L</td>
<td>Dendritic Cell Growth Factor/Vaccine Adjuvant</td>
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<tr>
<td>12</td>
<td>Anti-Glucorticoid-Induced TNF Receptor (GITR)</td>
<td>T-cell Stimulator</td>
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<tr>
<td>13</td>
<td>CCL2 Adenovirus</td>
<td>T-Cell Attracting Chemokine</td>
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<tr>
<td>14</td>
<td>Monophosphoryl Lipid A (MPL)</td>
<td>Vaccine Adjuvant</td>
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<td>15</td>
<td>Poly I:C and/or Poly ICLC</td>
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<tr>
<td>16</td>
<td>Anti-OX40</td>
<td>T-Cell Stimulator</td>
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<tr>
<td>17</td>
<td>Anti-B7-H4</td>
<td>T-Cell Checkpoint Blockade Inhibitor</td>
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<tr>
<td>18</td>
<td>Resiquimod and/or 852A</td>
<td>Vaccine Adjuvant</td>
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<tr>
<td>19</td>
<td>LIGHT and/or LIGHT vector</td>
<td>T-Cell Stimulator</td>
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<tr>
<td>20</td>
<td>Anti-Lymphocyte Activation gene-3 (LAG-3)</td>
<td>T-Cell Checkpoint Blockade Inhibitor</td>
</tr>
</tbody>
</table>

NCI Immunotherapy Agent Workshop Proceedings
Combinational Immunotherapy

• Vaccines

• Immune Modulators
  – Immune Agonists
    • Stimulatory cytokines (IL-2, IL-12, IL-15, TLR etc..)
    • Co-stimulatory molecules (OX-40, GITR, 4-1BB)
  – Immune inhibitors
    • Check point inhibitors (CTLA4, PD1/PDL1, LAG3, TIM3, iDO)
    • Inhibitory cytokines/factors (IL-10, TGFb)

• Small Molecules

• T cell therapy

• Standard Therapy
  – Chemotherapy
  – Radiation Therapy
Challenges

• What pre clinical data would be needed to move with the combination?
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• Type of Combination/Schedule of combination
  Prediction of response
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• What clinical trial design?
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  – Time
• How to enable using combinations from different developers—pharm/bio
• Health Economics, “financial adverse” effect
Policy Issues

• What pre-clinical data is needed for clinical trials translation and what models are needed
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• Expanding opportunities for collaboration and information exchange
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• Challenges in trial design for immunotherapies and combinations
• Expanding opportunities for collaboration and information exchange
  – Infrastructure data integration and implementation for clinical data exchange
  – Trans-IT interoperability
  – Bio/pharma collaboration in the pre-competitive space
Policy Issues

• What pre-clinical data is needed for clinical trials translation and what models are needed
• Challenges in trial design for immunotherapies and combinations
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• Implementation in clinical practice
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• Challenges in trial design for immunotherapies and combinations
• Expanding opportunities for collaboration and information exchange
• Implementation in clinical practice
  – Technology assessment and scaling cellular therapies for clinical use
  – Adverse events in immunotherapy
  – Physician training needs for immunotherapy
Policy Issues

• What pre-clinical data is needed for clinical trials translation and what models are needed
• Challenges in trial design for immunotherapies and combinations
• Expanding opportunities for collaboration and information exchange
• Implementation in clinical practice
• Value of immunotherapy and combination therapies
Targeted Audience

- Policy makers
- Regulatory agency
- Funding agencies
- Drug Developers – pharm-bio industry
- Third party payers (CMS, PIC etc..)
- Advocacy Groups