The following relationships exist related to this presentation:

**Employee of Genentech, a member of the Roche Group**

*I will not be discussing the off-label usage of any Genentech or Roche approved drugs*
What’s Up with Immunotherapy?

Unlike most traditional anti-cancer therapy...

...Immunotherapy relies on the function of immune cells

Chemotherapy (tubulin stabilizing agent epothilone)

Oncogene Target (bRAF mutated melanoma)

Tumor Cell Target (Her2neu expressing breast cancer)

Mellman et al. 2011

Prota 2013

Hsieh 2012
Relying on an Intact Immune System

Need to understand a complex network of cells, compartments and cytokines

Smith, BioTechniques 2012

Bodenmiller, Nature BioTech 2012

BMC Genomics 2008
# Immunotherapy vs Targeted Therapy

<table>
<thead>
<tr>
<th></th>
<th>Targeted Therapy</th>
<th>Immunotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Example:</strong></td>
<td>bRAF-targeted tx</td>
<td>Anti-CTLA4</td>
</tr>
<tr>
<td><strong>Biology</strong></td>
<td>Block bRAF-mediated signaling</td>
<td>Complex (enhanced priming? Clear Tregs?)</td>
</tr>
<tr>
<td><strong>Relevance</strong></td>
<td>High prevalence of mutation in melanoma</td>
<td>CTLA4 expressed on many cell types; not on tumors</td>
</tr>
<tr>
<td><strong>Pre-clinical</strong></td>
<td>High throughput human tumor cell line screening</td>
<td>Limited number of syngeneic models; variability in vivo efficacy</td>
</tr>
<tr>
<td><strong>Biomarker</strong></td>
<td>Presence of mutation</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>MTD, MTD-1</td>
<td>3mg/kg vs 10mg/kg? 4 doses? More?</td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td>AEs manageable with decreased dose</td>
<td>irAEs, delayed and persistent; may require steroids or more potent immune suppression</td>
</tr>
<tr>
<td><strong>PD</strong></td>
<td>Inhibition of MAPK signaling, ORR</td>
<td>Complex; immune infiltrates? Changes in T cell subsets? irAEs?</td>
</tr>
<tr>
<td><strong>Endpoints</strong></td>
<td>OS, PFS, ORR</td>
<td>OS? Tail of curve? ORR?</td>
</tr>
</tbody>
</table>
Drug Development Cycle

Duration: 10-15 Years
Cost: >1 billion US Dollars

- Biologic plausibility
- Pre-clinical activity
- Biomarker ID
- Acceptable tox

- Dose & schedule
- Safety
- PD biomarkers
  - Estimate efficacy
  - Evaluate predictive biomarker
    - Confirm efficacy
    - Validate predictive biomarker

5,000-10,000 compounds
5 compounds
1 FDA Approval

DiMasi 2003
Herper 2012
Drug Development Cycle: Pre-clinical

- **Target ID**
- **Drug Discovery**
- **Pre-Clinical**
- **Clinical Trials**
- **FDA Review**
- **Lg-scale MFG**

**IND**
- Phase I
- Phase II
- Phase III

**NDA**

- **FDA Review**
- **Lg-scale MFG**

5,000-10,000 compounds

Cost: >1 billion US Dollars

- Biologic plausibility
- Pre-clinical activity
- Biomarker ID
- Acceptable tox

Duration: 10-15 Years

Complex biology/biomarkers
Challenging pre-clinical models
How Well Do Pre-clinical Models Predict Human Immunobiology?

- Intact immune system required
- Limited syngeneic models
- Immunogenicity of antigens
- Tumor immune microenvironment differences?
- Intrinsic vs adaptive immune suppression
- Variability in models
- Genetic diversity vs human tumors

Complex biology/biomarkers
Challenging pre-clinical models
Drug Development Cycle: Early Clinical Development

- **Target ID**: 5,000-10,000 compounds
- **Drug Discovery**: 5 compounds
- **Pre-Clinical**: 1 FDA Approval

**Duration**: 10-15 Years
**Cost**: >1 billion US Dollars

- Dose & schedule
- Safety
- PD biomarkers

**Starting dose**
**Dose and schedule**
Immunotherapy Dose and Schedule Can Be Challenging

Starting Dose:
• MABEL vs NOAEL
• Minimal efficacious dose
• Maximum tolerated dose

Schedule:
Persistent immune activation may complicate identification of a schedule
• Single dose?
• 4 doses
• Dose for 1 year?
• Dose until PD or CR?
• Tx duration confounded by pseudoprogression

Endpoint: Long term OS
• Long time to endpoint
• May require large studies to evaluate the tail on the curve

Hodi et al 2010
www.dlsweb.rmit.edu.au
Drug Development Cycle: Clinical Development

<table>
<thead>
<tr>
<th>Stage</th>
<th>Duration</th>
<th>Cost</th>
<th>Compounds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target ID</td>
<td>3-6 Years</td>
<td></td>
<td>5,000-10,000 compounds</td>
</tr>
<tr>
<td>Drug Discovery</td>
<td>3-6 Years</td>
<td></td>
<td>5,000-10,000 compounds</td>
</tr>
<tr>
<td>Pre-Clinical</td>
<td>6-7 Years</td>
<td>&gt;1 billion US Dollars</td>
<td>5 compounds</td>
</tr>
<tr>
<td>Clinical Trials</td>
<td>6-7 Years</td>
<td></td>
<td>5 compounds</td>
</tr>
<tr>
<td>IND</td>
<td>1-2 Years</td>
<td></td>
<td>1 FDA Approval</td>
</tr>
<tr>
<td>FDA Review</td>
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<td></td>
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<tr>
<td>Lg-scale MFG</td>
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<tr>
<td>Post Marketing Phase IV</td>
<td></td>
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</tbody>
</table>

- Estimate efficacy
- Evaluate predictive biomarker

Duration: 10-15 Years
Cost: >1 billion US Dollars
Biomarkers: Non-invasive

- Obvious advantages to being able to easily assess a dynamic immune related biology
- Challenge related to whether tumor biology is adequately reflected in blood
- Use of imaging as a biomarker for immunotherapy will likely require additional technology development

Kurdziel et al 2007
Njemini et al 2007
Gattinoni et al 2011
Biomarkers: Tumor Tissue

Metastatic Cancer Natural History

Time 0 Years
Location Primary

Adjuvant

PFS
OS

Dynamic immune environment
Differences between archival and met
Changes in immunogenicity
Changes following SOC therapy
Changes following immunotherapy

1L 2L 3L

Metastatic samples likely to be limited to a small core bx

Primary samples likely to be large resection sample

Representative IHC images
1NME Drug Development

Duration: 10-15 Years
Cost: >1 billion US Dollars

- Biologic plausibility
- Pre-clinical activity
- Biomarker ID
- Acceptable tox
- Dose & schedule
- Safety
- PD biomarkers
  - Estimate efficacy
  - Evaluate predictive biomarker
  - Confirm efficacy
  - Validate predictive biomarker

5,000-10,000 compounds
5 compounds
1 FDA Approval
2NME Drug Development

Duration: 10-15 Years
Cost: >1 billion US Dollars

- Strong combo rationale
- Pre-clinical combo activity @ tolerable doses
- Non-overlapping organ tox
- Biomarkers for combo activity
- Both drugs available

- Dose & schedule of the combo: multiple potential MTDs
- Safety: distinguish from monotx?
- PD biomarkers for combo

- Estimate efficacy in multiarm study
- Evaluate predictive biomarker for 1 or both
  - Confirm efficacy- contribution?
  - Validate predictive biomarker

5,000-10,000 compounds
5 compounds
1 FDA Approval
2NME Drug Development

Duration: 10-15 Years
Cost: >1 billion US Dollars

Combinations that show high activity with good safety in early testing should be accelerated in their development.