The renaissance of immunotherapy is a revolution for cancer patients and for oncology

Ira Mellman, Ph.D.
Vice President, Cancer Immunology, Genentech
The renaissance of immunotherapy is a revolution for cancer patients
Traditional drug development
Is linear development path the best approach?
Cancer immunotherapy requires a cyclical “learning organization”

Late Development
- FIR
- BIRCH
- POPLAR
- OAK
  - PII 1/2L Dx+ ORR
  - PII Dx+ ORR
  - PII 2L+ Dx+/− vs. Doce OS
  - PIII 2L+ Dx+/− vs. Doce OS

Early Development
- PD-L1 negative
- PD-L1 positive (IC)

Post-Launched

Research

Cancer Immunotherapy Strategy Group (CITS)
## Cancer immunotherapy at Genentech/Roche

### Pipeline overview

<table>
<thead>
<tr>
<th>Pre-clinical</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
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<tbody>
<tr>
<td><strong>ImmTAC</strong></td>
<td>Anti-PDL1 Solid tumors</td>
<td>Anti-PDL1 NSCLC (Dx+)</td>
<td>Anti-PDL1 NSCLC 2/3 L</td>
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<tr>
<td><strong>Neg. Regulator NME 1</strong></td>
<td>Anti-PDL1+Avastin Solid tumors</td>
<td>Anti-PDL1 NSCLC</td>
<td>Anti-PDL1 Bladder</td>
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<td><strong>IMA 942</strong></td>
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<td><strong>Anti-cytokine NME 2</strong></td>
<td>Anti-PDL1+Zelboraf Met. Melanoma</td>
<td>Anti-PDL1</td>
<td>Anti-PDL1 NSCLC 1L Dx+</td>
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<tr>
<td><strong>T-cell bispecific</strong></td>
<td>Anti-PDL1+Tarceva NSCLC</td>
<td>CSF1R huMAb PVNS</td>
<td><strong>Anti-PDL1 trials</strong></td>
</tr>
</tbody>
</table>

- **Anti-PDL1**
- **Stimulator**
- **Inhibitor**
- **Trial planned**

Note: Anti-PDL1 is listed as MPDL3280A in clinicaltrials.gov
Mechanistic basis of cancer immunotherapy

The Cancer Immunity Cycle

*Immunosuppression is the rate limiting step to effective anti-tumor immunity*
Targeting immuno-supression
PD-1/PD-L1 pathway

- PD-1/PD-L1 interaction inhibits T cell activation, attenuates target killing: **prevents overstimulation of T cells during acute virus infection**
- A large percentage of tumors also up-regulate PD-L1 and evade killing by T cells
- Blocking PD-1 binding restores effector T cell activity
Targeting PD-L1 produces dramatic responses in many cancers (lung)

64-year-old male with squamous NSCLC s/p R lobectomy; cisplatin + gemcitabine, docetaxel, erlotinib; PD-L1 positive

Herbst et al. MPDL3280A Anti-PDL1 Phase I ASCO 2013

Hospital Universitario Vall d’Hebron (Cruz/Tabernero).
Patients with clinical benefit rarely progress

Herbst et al., (2013) *J Clin Oncol.* 31, (suppl; abstr 3000)

Patients dosed at 1–20 mg/kg prior to Aug 1, 2012 with at least 1 post-baseline evaluable tumor assessment; data cutoff Feb 1, 2013.
PD-L1 positive kidney cancer patient with rapid response to MDL3280A

51-year-old male with RCC s/p L nephrectomy, sunitinib, XRT T9, temsirolimus

Biomarkers at baseline

Biomarkers at week 4 post C1D1

MPDL3280A Phase Ia response correlates with expression of PD-L1 on tumor infiltrating cells (bladder cancer)

<table>
<thead>
<tr>
<th>PD-L1 IHC (IC)</th>
<th>ORR, Best Response % (95% CI)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>IHC 3 (n = 10)</td>
<td>60% (27, 85)</td>
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<tr>
<td>IHC 2 (n = 23)</td>
<td>48% (27, 68)</td>
<td>52% (34, 69)</td>
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<tr>
<td>IHC 1 (n = 24)</td>
<td>17% (6, 37)</td>
<td>14% (6, 28)</td>
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<tr>
<td>IHC 0 (n = 12)</td>
<td>8% (0, 35)</td>
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</table>

Summary of ORR in UBC

Using patient data to understand cancer immunity and find new treatments

**MPDL3280A Phase 1 Data: Urothelial Bladder Cancer Patients**

**Progressive Disease (PD)**
Why do many patients not respond?
- No pre-existing immunity?

**Stable disease (SD)**
What combinations will promote PRs & CRs?
- Insufficient T cell immunity?
- Multiple negative regulators?

**Monotherapy durable responses (PR/CR)**
What are the drivers of single agent response?
How can PRs be enhanced to CRs?
- Insufficient T cell immunity?
- Multiple negative regulators?

Comprehensive approach to biomarker discovery

Genentech ImmunoChip

Multi-parametric immunofluorescence

Multi-channel fluorescence activated cell sorting

T-Cell Receptor Repertoire

Multiplex cytokine assay

Molecular Imaging

Genentech ImmunoChip

Multi-parametric immunofluorescence

Multi-channel fluorescence activated cell sorting

T-Cell Receptor Repertoire

Multiplex cytokine assay

Molecular Imaging
On-treatment biomarker profile defines response and lack of response

PD-L1 patient immune biomarker analysis guides research and clinical development

Compounds moving into clinic
- Negative regulator NME1
- Positive regulator: OX40

Activating receptors
- CD28
- GITR
- CD137*
- CD27*
- ICOS
- HVEM
- NKG2D
- CD226
- 2B4
- CD96

Inhibitory receptors
- CTLA-4*
- PD-1*
- TIM-3
- BTLA
- VISTA
- LAG-3*
- CD96

Targets elevated in non-responders

T cell stimulation
Example: NME1 is a negative regulator discovered from biomarker analysis

Negative regulator combines in PD-L1 non-responsive model
Positive regulator targeting two steps in the cycle

Anti-OX40

Accelerate T cell response to antigen

anti-OX40

Anti-PDL1

Inhibit T regs

anti-OX40
OX40 function and potential in oncology

Promote antigen dependent effector T cell activation and T regulatory cell inhibition

Rationale for targeting OX40

- Dual mode of action:
  - Co-stimulation of effector T cells
  - Inhibition of regulatory T cells
- Reduced risk of toxicity
- Complementary MoA to blocking inhibitory receptors
- Potential to overcome suppressive signals from multiple inhibitory receptors

Potential for activity in multiple tumor types

Pre-clinical efficacy and durability of response

OX40 is expressed in a variety of tumors

Colorectal cancer

Breast cancer

Anti-OX40 increases intratumor $T_{eff}$ cells while depleting $T_{regs}$

Increase in intratumoral $T_{eff}$ cells (CD4+CD8)

Decrease in intratumoral $T_{reg}$ cells (FoxP3+)

IFN-γ Fold Change (Rel to Avg Control)

FoxP3/CD4(%)
Anti-OX40 can induce durable responses and immunity as a single agent

Pre-clinical efficacy and generation of tumor-specific immunity

**Primary Tumor Challenge (EMT6)**

- Control
- Anti-mouse OX40

**Re-challenge (EMT6 or CT26)**

- CT26 Secondary
- EMT6 Secondary
- EMT6 Primary

Tumor Volume (mm$^3$) vs. day

*Treatment* vs. *No Treatment*
Increase in $T_{eff}$ cells by anti-OX40 may create need to combine with anti-PDL1
**IDO (indoleamine di-oxygenase)**

*Another suppressor of effector T cells*

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**Adaptive expression of PD-L1**

- **Tumor cell**
  - IFN-γ-mediated up-regulation of tumor PD-L1
  - IFN-γ-activated receptor (IFN-R)
  - MHC I
  - PD-L1
  - PD-1
  - Shp-2
  - MAPK, PI3K pathways
  - CD8+ Cytotoxic T Lymphocyte (CTL)

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**Adaptive expression of IDO**

- **Tumor cell**
  - IFN-γ-mediated up-regulation of tumor IDO
  - IFN-γ-activated receptor (IFN-R)
  - MHC I
  - PD-L1
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  - Shp-2
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Inhibition of effector T cell function

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Georgia Hatzivassiliou, Yichin Liu
IDO mediates T cell suppression by reducing extracellular tryptophan and increasing kynurenine

*IDO* mediates T cell suppression by reducing extracellular tryptophan and increasing kynurenine.

- **Dendritic cells**:
  - High mTOR
  - Promote translation
  - mTOR

- **Tumor cells**:
  - Uncharged Tryptophanol-tRNA
  - GCN2 kinase
  - Stress response
  - Tumor cells
  - T DO (tryptophan dioxygenase) is a second related target to IDO

- **Kynurenine**:
  - arylhydrocarbon receptor
  - Enhance T reg
  - FoxP3
  - Suppress T effectors

- **Macrophages**:
  - Suppress T effectors

*IDO* activates IFNγ, which activates IDO expression.
Not all patients may have pre-existing immunity: ImmTACs and bispecific antibodies as alternatives to CAR-T cells
Recruiting T cells to cancer cells
*ImmTACs and bispecific antibodies*

**Targeting intracellular tumor markers**

- Cancer cell
- ImmTAC
- Redirected T cell
- Kill

**Targeting extracellular tumor markers**

- Cancer cell
- Tumor antigen
- Knob into holes
- Full-length IgG
- T cell

*Immune-mobilizing mTCR Against Cancer*

*T-cell Dependent Bispecific*

*In collaboration with Immunocore*
Not all patients may have pre-existing immunity: Patient data defines a path to rational vaccines

Cancer antigen presentation (dendritic cells/APCs)

Vaccines:
- Endogenous
- Exogenous

Recognition of cancer cells by T cells (CTLs, cancer cells)

ImmTACs Bispecifics

Structural analysis suggests that only some mutations will be accessible to T cell receptors.

**Immunogenic solvent-exposed mutation**

- REPS1: AQLPNDVVL
- ADPGK: ASMTNRELM
- FLU–NP: ASNENMETM

**Non-immunogenic mutation in MHC groove**

- Copine-1: SSPDSDLHYL
- H60: SSVIGVWYL

Mutated peptides predicted to be immunogenic induce CD8 T cell responses upon immunization

Prime/boost immunization
elongated peptides + anti-CD40 + pIC

T cell response measured 7d after boost (MHCI dextramer staining)

Prediction of immunogenicity

Promise for a PHC vaccine?

Immunization with antigenic peptides regresses growth of established MC38 tumors

14–0584: mutated MHCI MC38 peptide vaccine; MC–38
Overlay Fits Tumor Volume

Building a portfolio based on the emerging appreciation of the cancer immunity cycle

Substantial investment in developing PD-L1 combinations with in house and partnered molecules

<table>
<thead>
<tr>
<th>Immunotherapies</th>
<th>Roche/GNE (PD-L1 inhibitor)</th>
<th>BMS (PD-1 inhibitor)</th>
<th>Merck (PD-1 inhibitor)</th>
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P Partnered external combo
✓ Internal combo

Sources: TrialTrove, company presentations, clinicaltrials.gov

Last updated: 3 Dec 2014
Genentech’s competitive advantage: Lead the field by focusing on the science

- Identification and validation of new targets & combinations based on our understanding of cancer immunity cycle
- An ever-expanding patient biomarker database
- Diverse, innovative portfolio
- Leverage small molecule expertise
- Leverage oncology expertise
- A uniquely integrated team, from Research to Late Stage…and back