The renaissance of immunotherapy is a revolution for cancer patients

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The renaissance of immunotherapy is a revolution for cancer patients
Early data suggests that anti-PD-L1/PD-1 is active across a wide range of tumor types

- Melanoma: FDA approval
- NSCLC (squamous): FDA approval, 2nd line
- Renal cell carcinoma
- Breast cancer (e.g. TNBC)
- Metastatic bladder cancer
- Head & neck cancer
- Hodgkin's lymphoma

Response rates are modest, at ~10-30%

Broad activity but most patients do not benefit from single agent therapy
Using patient data to understand cancer immunity cycle

**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?
The cancer immunity cycle

*Immunosuppression as the rate limiting step to effective anti-tumor immunity*

1. Release of cancer cell antigens (cancer cell death)
2. Cancer antigen presentation (dendritic cells/ APCs)
3. Priming and activation (APCs & T cells)
4. Trafficking of T cells to tumors (CTLs)
5. Infiltration of T cells into tumors (CTLs, endothelial cells)
6. Recognition of cancer cells by T cells (CTLs, cancer cells)
7. Killing of cancer cells (Immune and cancer cells)

**Immuno-suppression**

- α-CTLA4 (ipilimumab)
- α-PD-L1/PD-1 (multiple)

Chen & Mellman (2013) *Immunity*
Combinations of immunotherapeutics

Increasing response rates by keeping cancer immunity cycle turning

- α-CTLA4*
- α-OX40*
- α-CD27*
- α-CD137
- α-GITR
- Vaccines*
- α-CD40*
- α-PDL1*/PD1
- α-CTLA4* (Treg)
- α-OX40* (Treg)
- α-LAG-3
- α-CTLA4* (Treg)
- α-TIGIT*
- α-CSF1R*
- α-KIR
- IDO inhibitor*

* = Genentech/Roche programs

Chen & Mellman (2013) *Immunity*
IDO (indoleamine di-oxygenase)
Another suppressor of effector T cells

Adaptive expression of PD-L1

IFN$\gamma$-mediated up-regulation of tumor PD-L1

Shp-2

MAPK PI3K pathways

CD8+ Cytotoxic T Lymphocyte (CTL)

Adaptive expression of IDO

IFN$\gamma$-mediated up-regulation of tumor IDO

Shp-2

IDO

MAPK PI3K pathways

CD8+ Cytotoxic T Lymphocyte (CTL)

Inhibition of effector T cell function

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.*

*IDO* (indoleamine 2,3-dioxygenase) is a second related target to TDO (tryptophan dioxygenase).

- **IDO**
  - Tumor cells
  - IFNγ activates IDO expression
  - Kynurenine
  - Enhance T reg
  - Enhance T reg
  - Supress T effectors

- **IDO**
  - Tumor cells
  - IFNγ activates IDO expression
  - Kynurenine
  - Enhance T reg
  - Enhance T reg
  - Supress T effectors

- **mTOR**
  - Free tryptophan
  - High
  - Promote translation

- **GCN2 kinase**
  - Uncharged Tryptophanol-tRNA
  - Stress response
  - Suppressive cytokines

*IDO* (indoleamine 2,3-dioxygenase) is a second related target to IDO. 

- **TDO (tryptophan dioxygenase)** is a second related target to IDO.
Early combination data shows promising efficacy
Phase I/II study of INCB024360 plus ipilimumab in melanoma

Gibney et al. ASCO 2014
**TIGIT**

*Model of TIGIT regulation of T cell responses*

- Human and murine tumor-infiltrating CD8⁺ T cells express high levels of TIGIT.
- Antibody coblockade of TIGIT and PDL1 elicits tumor rejection in preclinical models.
- TIGIT selectively limits the effector function of chronically stimulated CD8⁺ T cells.
- TIGIT interacts with CD226 in *cis* and disrupts CD226 homodimerization.

[Diagram of TIGIT regulation of T cell responses]
TIGIT

**TIGIT and PD-L1 combination effective in PD-L1 non-responsive model**

Tumor cell or DC

1. Competes with CD226 for PVR

2. Disrupts CD226 activation

3. Directly inhibits T cell in cis

- Control
- Anti-PD-L1
- TIGIT
- Anti-PD-L1 + TIGIT

Complete Remission (CR)

**Graph:**
- X-axis: Day
- Y-axis: Median Tumor Volume (mm$^3$)
- Log scale on both axes
OX40 function and potential in oncology

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

Increase in T\textsubscript{eff} cells by anti-OX40 may create need to combine with anti-PDL1

Anti-OX40 combined with anti-PDL1 in the MC38 model

Jeong Kim et al. AACR 2015
Combination with Avastin

*Increasing response rates by keeping cancer immunity cycle turning*

Chen & Mellman (2013) *Immunity*
Increases in CD8⁺ T cell infiltration and vasculature changes with treatments in RCC

<table>
<thead>
<tr>
<th>Pretreatment</th>
<th>Post Avastin</th>
<th>Post Avastin + aPD-L1</th>
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<tbody>
<tr>
<td>CD8 (T cells)</td>
<td></td>
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<tr>
<td>CD31 (vasculature)</td>
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</table>

Sznol et al. ASCO GU 2015
Anti-PDL1 in combination with Avastin

**Anti-VEGF combination:**
*preclinical data*

- Cloudman melanoma
- Control
- a-PD-L1
- a-VEGF
- a-PD-L1 + a-VEGF

**Combination of anti-PDL1 and Avastin** *(Ph1 data in renal cancer)*

Sznol et al. ASCO GU 2015
Combinations with chemotherapy

Induced inflammation & antigen release may enhance anti-PDL1 efficacy
Inflammation is necessary for response

**Inflamed**

- Can responses be improved?

20-30% patients
- T cells present in tumor
- Chemokines present (attract leukocytes)

Responsive to single agent immunotherapies

**Non-inflamed**

- Can we convert these to responsive?

70-80% patients
- Lack lymphocytic infiltrates

Non-responsive to single agent immunotherapies
Combinations with chemotherapy extend the benefit of anti-PDL1

- Platinum chemo increases number of CD8+ cells in animal models
- Compelling chemo+PD-L1 combination efficacy observed in phase 1 studies
- Broad phase 3 combination program initiated in 1L NSCLC and TNBC

Phase 1 chemo combination data to be presented at ASCO 2015
Not all patients may have pre-existing immunity: monitoring & promoting T cell responses

*ImmTACs and bispecific antibodies*
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
- T cell
- TCR
- Knob into holes
- Full-length IgG

Immune-mobilizing mTCR Against Cancer*

T-cell Dependent Bispecific

*In collaboration with Immunocore*
Not all patients may have pre-existing immunity: monitoring & promoting T cell responses

Vaccines:
- Endogenous
- Exogenous
Anti-PDL1 Phase Ia: indication response rates correlate with mutation frequency

Schumacher and Schreiber (2015) Science
Structural analysis suggests that only some mutations will be accessible to T cell receptors.

**Immunogenic solvent-exposed mutation**

<table>
<thead>
<tr>
<th>REPS1</th>
<th>AQLPNDVVL</th>
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<tbody>
<tr>
<td>ADPGK</td>
<td>ASMTNRELMM</td>
</tr>
<tr>
<td>FLU-NP</td>
<td>ASNENMETM</td>
</tr>
</tbody>
</table>

**Non-immunogenic mutation in MHC groove**

<table>
<thead>
<tr>
<th>Copine-1</th>
<th>SSPDSDLHLYL</th>
</tr>
</thead>
<tbody>
<tr>
<td>H60</td>
<td>SSVIGVWYL</td>
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Promise for a PHC vaccine?

Immunization with antigenic peptides regresses growth of established MC38 tumors

Strategic vision: lead by developing best in class combination therapies

**Combinations with immunotherapies**
- aCD40 ✔
- Vaccines, Oncolytic Viruses ✔ ✔
- aCTLA-4 ✔
- aOX40 ✔
- aCD27 ✔
- aCEA-IL2v ✔
- T Cell Bispecifics ✔
- ImmTACs Planned
- IDOi ✔ ✔
- aCSF1R ✔
- aTIGIT Planned
- Cytokines, anti-cytokines ✔

**Combinations with other agents**
- aVEGF ✔
- aCD38 ✔
- FGFR1 ✔
- EGFRi ✔ ✔
- ALKi Planned
- BRAFi ✔
- MEKi ✔
- BTKi ✔
- aCD20 ✔
- aHER2 ✔
- Chemo ✔ ✔
- HDAC ✔
- HDAC ✔
- A2V ✔

* Clinical development
* Preclinical development
* Partnered projects

Chen & Mellman (2013) *Immunity*
Doing now what patients need next