Immune modulators

Naiyer Rizvi, MD
Complete metabolic response after 6 weeks of therapy to anti-PD-L1 in NSCLC
Hypothetical goals of I-O therapies

Goal 1: biomarker selection for durable benefit

Survival vs. Time

- Control
- Targeted therapies

Goal 2: rationale design of combination I-O therapy

Survival vs. Time

- Immune checkpoint blockade
- Combinations/sequencing

Cancer Elimination

TUMOR

perforin
granzyme

cytokines

Activated T cell

T cell clonal expansion

Resting T cell

LYMPH NODE

TCR

CD28

Dendritic cell

Tumor antigen

MHC

B7

Courtesy of Scott Gettinger
Multiple mechanisms of immune escape

Immune Modulators

Vasaturo et al Front Immunol. 2013
Immune modulators

Press the gas pedal

Receptor agonists

+ CTLA-4
PD-1
B7-H1
BTLA
LAG-3
TGF-β
IL-10

Release the brakes

Receptor antagonists

- CD137
CD40
OX40
GITR
CD27

Melero et al CCR 2013
CTLA-4 vs PD-1: Distinct Immune Checkpoints

Naive/resting T cell

CTLA-4 to cell surface

Tissue

Inflammation

CTLA-4

APC

B7.1/2

CD28

Signal 1

APC

Costim. ligand

Costim. receptor

T-cell priming

Traffic to periphery

PD-L1

PD-1

Experience T cell

Immune checkpoint blockade
## Clinical Development of Inhibitors of PD-1 Immune Checkpoint

<table>
<thead>
<tr>
<th>Target</th>
<th>Antibody</th>
<th>Molecule</th>
<th>Development stage</th>
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<tbody>
<tr>
<td>CTLA-4</td>
<td>Ipilimumab</td>
<td>Human IgG1</td>
<td>MEL 2011</td>
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<tr>
<td></td>
<td>Tremelimumab</td>
<td>Human IgG2</td>
<td>Phase 3</td>
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<tr>
<td>PD-1</td>
<td>Nivolumab</td>
<td>Human IgG4</td>
<td>MEL, NSCLC, RCC 2015</td>
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<tr>
<td></td>
<td>Pembrolizumab</td>
<td>Humanized IgG4</td>
<td>MEL, PD-L1 + NSCLC 2015</td>
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<td></td>
<td>PDR001</td>
<td>Humanized IgG4</td>
<td>Phase 1</td>
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<td></td>
<td>REGN2810</td>
<td>Human IgG4</td>
<td>Phase I</td>
</tr>
<tr>
<td>PD-L1</td>
<td>MEDI-4736</td>
<td>Engineered human IgG1</td>
<td>Phase 3</td>
</tr>
<tr>
<td></td>
<td>MPDL-3280A</td>
<td>Engineered human IgG1</td>
<td>Phase 3</td>
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<tr>
<td></td>
<td>MSB0010718C</td>
<td>Human IgG1</td>
<td>Phase 3</td>
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</table>
Ipilimumab: Pooled Survival Analysis from Phase II/III Trials in Advanced Melanoma

![Graph showing overall survival for Ipilimumab]

Dirk Schadendorf et al. JCO doi:10.1200/JCO.2014.56.2736
Durable responses off treatment:
Ongoing responses after discontinuation of nivolumab in NSCLC

Gettinger et al JCO 2015
# Immune checkpoint blockade activity

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab</th>
<th>Pembro</th>
<th>MEDI4736</th>
<th>MPDL3280 A</th>
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<tr>
<td>Melanoma</td>
<td>35%</td>
<td>27%</td>
<td></td>
<td>30%</td>
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<tr>
<td>NSCLC</td>
<td>19%</td>
<td>21%</td>
<td>16%</td>
<td>23%</td>
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<tr>
<td>RCC</td>
<td>20%</td>
<td></td>
<td></td>
<td>14%</td>
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<tr>
<td>Bladder</td>
<td></td>
<td>24%</td>
<td></td>
<td>26%</td>
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<tr>
<td>Ovarian</td>
<td></td>
<td></td>
<td>23%</td>
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<tr>
<td>Breast</td>
<td></td>
<td>19%</td>
<td></td>
<td>33%</td>
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<tr>
<td>Gastric</td>
<td></td>
<td>31%</td>
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<tr>
<td>SCCHN</td>
<td>20%</td>
<td>14%</td>
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</table>

Adapted from Sunshine and Taube, Current Opinion in Pharmacology, 2015
Patient Selection?
<table>
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<tbody>
<tr>
<td>Diagnostic partner</td>
<td>Dako</td>
<td>Dako</td>
<td>Ventana</td>
<td>Ventana</td>
<td>Dako</td>
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<tr>
<td>Clones</td>
<td>22C3</td>
<td>28-8</td>
<td>SP263</td>
<td>SP142</td>
<td>?</td>
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<tr>
<td>Machines Utilized</td>
<td>Link 48</td>
<td>Link 48</td>
<td>BenchMark ULTRA</td>
<td>BenchMark ULTRA</td>
<td>?</td>
</tr>
<tr>
<td>Compartment</td>
<td>TM</td>
<td>TM</td>
<td>TM</td>
<td>TC/IC</td>
<td>?</td>
</tr>
<tr>
<td>Variables</td>
<td>% of cells</td>
<td>% of cells</td>
<td>% of cells</td>
<td>% of cells</td>
<td>?</td>
</tr>
<tr>
<td>Definition of positive</td>
<td>PD-L1(+): &gt;1% Strong(+): &gt;50%</td>
<td>PD-L1(+): &gt;1% Strong(+): &gt;5%</td>
<td>PD-L1(+): ≥25%</td>
<td>TC / IC 3(+)</td>
<td>TC / IC 3(+)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TC / IC 2(+)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TC / IC 1(+)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TC / IC 0(−)</td>
<td></td>
</tr>
</tbody>
</table>
Association of PD-L1 expression with response to anti-PD-1/PD-L1 therapy

Adapted from Sunshine and Taube, Current Opinion in Pharmacology, 2015
Intratumoral Heterogeneity of PD-L1 Expression in NSCLC

McLaughlin et al, JAMA Oncol 2016
Nivolumab OS in non-squamous NSCLC

Symbols represent censored observations.

Borghaei et al NEJM 2015
Pembrolizumab in NSCLC
OS in Subgroups ≥1%

**PD-L1 tumor proportion score**
- 50%: 204/442, Favor Pembrolizumab
- 1%-49%: 317/591, Favor Pembrolizumab

**Tumor sample**
- Archival: 266/455, 0.70 (0.54-0.89)
- New: 255/578, 0.64 (0.50-0.83)

**Histology**
- Squamous: 128/222, 0.74 (0.50-1.09)
- Adenocarcinoma: 333/708, 0.63 (0.50-0.79)

**EGFR status**
- Mutant: 46/86, 0.88 (0.45-1.70)
- Wild type: 447/875, 0.66 (0.55-0.80)

Herbst et al, Lancet 2015
## PD-L1 testing: PROS and CONS

<table>
<thead>
<tr>
<th>Benefits</th>
<th>(main) Challenges</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commercially available assays</td>
<td>Benefit demonstrated in PD-L1 negatives</td>
</tr>
<tr>
<td>Inform single agent vs. combination therapies</td>
<td>Different PD-L1 expression cut-off used</td>
</tr>
<tr>
<td>Help decide in overall treatment decisions</td>
<td>Core biopsies not always available</td>
</tr>
<tr>
<td>Help interpret pseudoprogression</td>
<td>Poor correlation between biopsy and surgical specimen</td>
</tr>
<tr>
<td></td>
<td>Lack of harmonization of PD-L1 assays</td>
</tr>
</tbody>
</table>
Mutational Landscape

Alexandrov et al, Nature 2013
Mutational Load and Clinical Response to CTLA-4 Blockade in Melanoma

Long-Term Benefit (n=11)

Minimal or No Benefit (n=14)

- $P=0.01$ by Mann-Whitney test

Survival (% of patients)

- $>100$ mutations (N=17)
- $\leq 100$ mutations (N=8)

- $P=0.04$ by log-rank test

Mutational Burden, MSI, and Response to Anti-PD-1 Therapy

MSI+ 1782 mutations
MSI- 73 mutations

Le et al, NEJM 2015
Mutation Burden Determines Sensitivity to PD-1 Blockade in NSCLC

*Partial or stable response lasting >6 months.

Targeted gene panel to estimate mutation load

Campesato et al, Oncotarget 2015
Response of a Large Chest-Wall Melanoma Metastasis to One Dose of Ipilimumab plus Nivolumab.
## Combination Immune Checkpoint Blockade

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab + Ipilimumab</th>
<th>MEDI4736 + TREME</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Melanoma</strong></td>
<td>57.6%</td>
<td></td>
</tr>
<tr>
<td><strong>Renal</strong></td>
<td>29-39%</td>
<td></td>
</tr>
<tr>
<td><strong>SCLC</strong></td>
<td>32%</td>
<td>31-39%</td>
</tr>
<tr>
<td><strong>NSCLC</strong></td>
<td></td>
<td>23%</td>
</tr>
<tr>
<td><strong>ORR, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PFS</strong></td>
<td>11.5 months</td>
<td>8 months</td>
</tr>
<tr>
<td><strong>Cut Off</strong></td>
<td>5%</td>
<td>1%</td>
</tr>
<tr>
<td><strong>ORR in PD-L1 +</strong></td>
<td>72.1%</td>
<td>48%</td>
</tr>
<tr>
<td><strong>ORR in PD-L1 -</strong></td>
<td>57.5%</td>
<td>0-22%</td>
</tr>
</tbody>
</table>

Combined versus single agent immune checkpoint blockade in untreated melanoma

Larkin et al, NEJM
Novel biomarkers

<table>
<thead>
<tr>
<th>Monitoring strategy</th>
<th>Immunologically-unresponsive tumor</th>
<th>Immunologically-responsive tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole exome sequencing</td>
<td>Low mutational burden</td>
<td>High mutational burden</td>
</tr>
<tr>
<td>Gene signature/patterns</td>
<td>↓ activation signature</td>
<td>↑ activation signature</td>
</tr>
<tr>
<td>Epigenetic modification</td>
<td>↑ Treg/CD3 ratio, ↓ CD3 cells</td>
<td>↑ Treg/CD3 ratio, ↑ CD3 cells</td>
</tr>
<tr>
<td>Protein microarray</td>
<td>Poor general antibody response</td>
<td>Robust general antibody response</td>
</tr>
<tr>
<td>B/T-cell receptor repertoire</td>
<td>Low CD3 count, Low clonality</td>
<td>High CD3 count, High clonality</td>
</tr>
<tr>
<td>Flow/Mass cytometry</td>
<td>↓ effector cells, ↓ T-eff/T-reg ratio</td>
<td>↑ effector cells, ↑ suppressor cells</td>
</tr>
<tr>
<td>Multicolor IHC</td>
<td>Low PD-L1 on tumor and tumor-infiltrating immune cells</td>
<td>High PD-L1 on tumor and tumor-infiltrating immune cell</td>
</tr>
</tbody>
</table>

| Therapeutic strategy        | Vaccination, ablation, radiotherapy, chemotherapy, oncolytic therapy, adaptive cellular therapy first | Immune checkpoint blockade therapies and other immunotherapies first |

Legend:
- Blood vessel
- Lymph node
- Live tumor
- Dying tumor
- Naive T-cell
- Memory T-cell
- Immature dendritic cell
- Mature dendritic cell
Personalized combination strategies

- Co-stimulatory mAbs targeting: CD137, OX40, CD40, GITR
- Conventional agents inducing immunogenic cell death: Chemotherapy, Radiotherapy, Anti-angiogenics, Targeted therapies
- Other checkpoint inhibitory molecules: CTLA4, LAG3, TIM3, BTLA, TIGIT
- Cancer vaccines considering individual neoantigens
- Functional modification of immunosuppressive enzymes such as: IDO1, iNOS
- T\textsubscript{Reg} cell targeting or inhibition
- Adoptive cell therapy
- Myeloid cell modulation

PD\textsubscript{1} or PDL\textsubscript{1} blockade

Melero Nature Reviews Cancer 2015