Priming the Immune System to Kill Cancer and Reverse Tolerance

Dr. Diwakar Davar
Assistant Professor, Melanoma and Phase I Therapeutics
Learning Objectives

• Describe the role of the immune system in cancer and cancer therapy.

• Distinguish between the different forms of immunotherapy presently approved for the treatment of advanced cancers.

• Understand the mechanisms behind the toxicities associated with anti-cancer immunotherapy.

• Describe the challenges and barriers to care associated with treating patients with immunotherapy.
• Describe the role of the immune system in cancer and cancer therapy.

• Distinguish between the different forms of immunotherapy presently approved for the treatment of advanced cancers.

• Understand the mechanisms behind the toxicities associated with anti-cancer immunotherapy.

• Describe the challenges and barriers to care associated with treating patients with immunotherapy.
Cancer patients develop spontaneous immune responses directed against tumor antigens \(^1,^2\).

Tumor antigen (TA)-specific cytotoxic T-lymphocytes (CTL) often fail to induce tumor rejection \(^3\).

There are numerous mechanisms of tumor-induced immunosuppression that contribute to the resistance of tumors to CTL responses \(^4\).

- PD-1/PD-L1 interactions play a key role in inhibiting the effector functions of TA-specific CD8\(^+\) T cells.
Cancer Immunosurveillance

• Cancer immunosurveillance
  – Advanced by Ehrlich, Burnet and Thomas
  – *It is by no means inconceivable that small accumulations of tumour cells may develop and because of their possession of new antigenic potentialities provoke an effective immunological reaction with regression of the tumour and no clinical hint of its existence.*

• Criticized by Stutman
  – Similar susceptibility of immunocompetent and nude mice to chemically induced cancer; *and* no difference in latency

---

• Cancer immunoediting
  – Elimination corresponds to immunosurveillance
  – Equilibrium represents process by which immune system iteratively selects and/or promotes tumor cell variants with increasing capacities to survive immune attack
  – Escape is process wherein immunologically sculpted tumor expands in an uncontrolled manner in the immunocompetent host

Dunn GP, Nature Immunology 2002
Cancer Immunotherapy and Breaking Immune Tolerance

Makkouk A, Cancer Res 2015
Role of Immune System in Cancer and Cancer Therapy - Summary

- Spontaneous anti-cancer immune responses occur early in the development of cancer and are detectable.
- Invasive cancer represents successful attempt by cancer at immunoediting.
- Tumors exploit tolerogenic mechanisms to evade immune system.
- Successful cancer immunotherapy requires breaking tolerance.
• Describe the role of the immune system in cancer and cancer therapy.

• **Distinguish between the different forms of immunotherapy presently approved for the treatment of advanced cancers.**

• Understand the mechanisms behind the toxicities associated with anti-cancer immunotherapy.

• Describe the challenges and barriers to care associated with treating patients with immunotherapy.
Immunotherapy In Cancer

1. Release of cancer cell antigens
   - Chemotherapy
   - Radiation therapy
   - Targeted therapy

2. Cancer antigen presentation
   - Vaccines
   - IFN-α
   - GM-CSF
   - Anti-CD40 (agonist)
   - TLR agonists

3. Priming and activation
   - Anti-CTLA4
   - Anti-CD137 (agonist)
   - Anti-OX40 (agonist)
   - Anti-CD27 (agonist)
   - IL-2
   - IL-12

4. Trafficking of T cells to tumors
5. Infiltration of T cells into tumors
   - Anti-VEGF

6. Recognition of cancer cells by T cells
   - CARs

7. Killing of cancer cells
   - Anti-PD-L1
   - Anti-PD-1
   - IDO inhibitors

Chen D, Immunity 2013
Ipilimumab in Melanoma

• CTLA-4 directed IgG1 monoclonal antibody

• Improved OS in 2 phase III trials:
  – gp100 vaccine comparator, pre-treated patients (MDX010-020 study)\(^1\)
  – Dacarbazine comparator, untreated patients (MDX010-024/CA184-024 study)

• Overall response rates: 10-15\(^\%\)\(^1^2\)

• Durable survival:
  – 22\(^\%\) (all patients), 26\(^\%\) (treatment-naïve patients), 20\(^\%\) (pre-treated patients)\(^3\)
  – 21\(^\%\) beginning at 3 years\(^3\)

\(^1\)Hodi FS, NEJM 2010; \(^2\)Robert C, NEJM 2011; \(^3\)Schadendorf D, JCO 2015
• IgG4 monoclonal antibody against PD-1

• Improved OS in multiple phase III trials:
  – Dacarbazine comparator, ipi pre-treated (CheckMate-037)\(^1\)
  – Dacarbazine comparator, untreated (CheckMate-066)\(^2\)
  – Ipilimumab comparator, untreated (KEYNOTE-006)\(^3\)

• Overall response rates: 30-45\%\(^1\)\(^-\)\(^3\)

\(^1\)Weber JS, Lancet Oncol 2015; \(^2\)Robert C, NEJM 2015; \(^3\)Robert C, NEJM 2015
PD-1 Blockade in Melanoma (2)

- **Durable survival:**
  - 35% 12-month PFS rate (nivolumab): equal efficacy in BRAF mutant/wild type patients

1Ribas A, JAMA Oncol 2016; 2Larkin J, JAMA Oncol 2015
• Pre-clinical data suggested synergy with concurrent inhibition\(^1\)

• Phase III trial of ipilimumab vs. nivolumab vs. ipi/nivo combination:
  - Higher ORR: 58% (ipi/nivo) vs. 44% (nivo) vs. 19% (ipi)
  - Improved PFS: 11.5 mths (ipi/nivo) vs. 6.9 (nivo) vs. 2.9 (ipi)
  - Considerable grade 3/4 AE with combination: 55% (ipi/nivo) vs. 16% (nivo) vs. 27% (ipi)

---

\(^1\)Das R, J Immunol 2015; \(^2\)Wolchok JD, NEJM 2013; \(^3\)Larkin J, NEJM 2015
# PD-1/PD-L1 Inhibitors Being Developed

<table>
<thead>
<tr>
<th>PD-1</th>
<th>Name</th>
<th>Type</th>
<th>Company</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nivolumab</td>
<td>Fully human IgG4 mAb</td>
<td>BMS</td>
<td>ph III</td>
</tr>
<tr>
<td></td>
<td>Pidilizumab</td>
<td>Humanized IgG1 mAb</td>
<td>Cure Tech</td>
<td>ph II</td>
</tr>
<tr>
<td></td>
<td>Pembrolizumab</td>
<td>Humanized IgG4 mAb</td>
<td>Merck</td>
<td>ph III</td>
</tr>
<tr>
<td></td>
<td>AMP-224</td>
<td>Recombinant PD-L2 Fc fusion protein</td>
<td>GSK</td>
<td>ph I</td>
</tr>
<tr>
<td>PD-L1</td>
<td>BMS-936559</td>
<td>Fully human IgG4 mAb</td>
<td>BMS</td>
<td>ph I</td>
</tr>
<tr>
<td></td>
<td>MEDI4736</td>
<td>Engineered human IgG1 mAb</td>
<td>MedImmune</td>
<td>ph III</td>
</tr>
<tr>
<td></td>
<td>MPDL3280A (Atezolizumab)</td>
<td>Engineered human IgG1 mAb</td>
<td>Genentech</td>
<td>ph III</td>
</tr>
<tr>
<td></td>
<td>MSB0010718C</td>
<td>Engineered human IgG1 mAb</td>
<td>EMD Serono</td>
<td>ph II</td>
</tr>
</tbody>
</table>
PD-1 Blockade in Other Cancers

Opdivo Approval History

- FDA approved: Yes (First approved December 22nd, 2014)
- Brand name: Opdivo
- Generic name: nivolumab
- Dosage form: Injection
- Company: Bristol-Myers Squibb Company
- Treatment for: Melanoma, Metastatic, Non-Small Cell Lung Cancer, Renal Cell Carcinoma, Hodgkin's Lymphoma, Head and Neck Cancer, Urothelial Carcinoma, Hepatocellular Carcinoma

Imfinzi Approval History

- FDA approved: Yes (First approved May 1st, 2017)
- Brand name: Imfinzi
- Generic name: durvalumab
- Dosage form: Injection
- Company: AstraZeneca
- Treatment for: Urothelial Carcinoma

Tecentriq Approval History

- FDA approved: Yes (First approved May 18th, 2016)
- Brand name: Tecentriq
- Generic name: atezolizumab
- Dosage form: Injection
- Company: Genentech, Inc.
- Treatment for: Bladder Cancer, Non-Small Cell Lung Cancer

Keytruda Approval History

- FDA approved: Yes (First approved September 4th, 2014)
- Brand name: Keytruda
- Generic name: pembrolizumab
- Dosage form: for Injection
- Company: Merck & Co., Inc.
- Treatment for: Melanoma, Metastatic, Non-Small Cell Lung Cancer, Head and Neck Cancer, Hodgkin's Lymphoma, Urothelial Carcinoma, Gastric Cancer

FDA Website
Impact of ICB in Cancer Immunotherapy

Ledford H, Nature 2016
Adoptive Cellular Therapy

First generation

Second generation

Third generation

Signal 1

Signal 2

Signal 1

Signal 1

Signal 2

Antigen-recognition domain

Signalling domains

Jackson HJ, Nat Rev Clin Oncol 2016
Improving CAR

- **a** ‘Armoured’ CARs
  - e.g. IL-12-secreting CAR T cells

- **b** Dual receptor/chemokine CARs
  - e.g. CAR T cells co-expressing tumour-specific CAR and chimeric cytokine receptor 4αβ

- **f** Targeting tumour vasculature
  - e.g. VEGFR-2-specific CAR T cells

- **c** NK cell-receptor CARs
  - e.g. NKG2-based CAR

- **e** B-cell eradication
  - e.g. infusion of tumour-targeted CAR T cells together with B-cell-specific CAR T cells

- **d** Combination therapy
  - e.g. CAR T cells and checkpoint blockade

Jackson HJ, Nat Rev Clin Oncol 2016
Different Forms of Immunotherapy Approved in Cancer

- PD-1/CTLA-4 ICB has transformed management of advanced melanoma and other cancers in general with **unprecedented durable remissions in a significant percentage** of treated patients.

- PD-1/PD-L1 ICB is currently approved for 9 malignancies.

- Chimeric antigen receptor (CAR) T-cell therapy is **very effective** in some patients with **refractory leukemias**. Long-term survival data is lacking.

- Other approved forms of cancer immunotherapy include vaccines (Sipuleucel-T in prostate cancer) and oncolytic viruses (T-vec in melanoma).
• Describe the role of the immune system in cancer and cancer therapy.

• Distinguish between the different forms of immunotherapy presently approved for the treatment of advanced cancers.

• Understand the mechanisms behind the toxicities associated with anti-cancer immunotherapy.

• Describe the challenges and barriers to care associated with treating patients with immunotherapy.
Toxicity Associated with Immunotherapy

• Unlike chemotherapy or targeted therapy, spectrum of toxicity associated with immunotherapy is unique and diverse.

• Spectrum of toxicities associated with immunotherapy are distinct between PD-1/CTLA-4 immune checkpoint inhibitors (ICB) and CAR.
Toxicity Associated with Immunotherapy – ICB

• Tolerance (central and peripheral) permits elimination of self-reactive T cells. Persistence of self-reactive T cells → autoimmune diseases.

• In the adult, peripheral tolerance either through anergy or inhibiting T cell activation (regulatory T cells or inhibitory receptors) prevents autoimmune disease.

• These inhibitory receptors include CTLA-4 and PD-1.

• Spectrum of toxicities primary revolve around autoimmune events.
## Toxicity Associated with Immunotherapy – ICB

<table>
<thead>
<tr>
<th>Select Treatment-Related AEs, %</th>
<th>Nivo + Ipi (n = 313)</th>
<th>Nivo (n = 313)</th>
<th>Ipi (n = 311)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3/4</td>
<td>All Grades</td>
</tr>
<tr>
<td>Any select AE</td>
<td>88</td>
<td>40</td>
<td>62</td>
</tr>
<tr>
<td>Skin</td>
<td>59</td>
<td>6</td>
<td>42</td>
</tr>
<tr>
<td>Pruritus</td>
<td>33</td>
<td>2</td>
<td>19</td>
</tr>
<tr>
<td>Rash</td>
<td>28</td>
<td>3</td>
<td>22</td>
</tr>
<tr>
<td>Maculopapular rash</td>
<td>12</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>46</td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>44</td>
<td>9</td>
<td>19</td>
</tr>
<tr>
<td>Colitis</td>
<td>12</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Hepatic</td>
<td>30</td>
<td>19</td>
<td>6</td>
</tr>
<tr>
<td>ALT increase</td>
<td>18</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>AST increase</td>
<td>15</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Endocrine</td>
<td>30</td>
<td>5</td>
<td>14</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>15</td>
<td>&lt; 1</td>
<td>9</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>7</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>6</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
Toxicity Associated with Immunotherapy – CAR

• Spectrum of toxicities with cellular therapies is wide.

• Commonly non-specific immune activation \(\rightarrow\) release of inflammatory cytokines.

• Includes anaphylaxis, “on-target, off-tumor” effects etc.
# Toxicity Associated with Immunotherapy – CAR

## Acute Lymphoblastic Leukemia (ALL)

<table>
<thead>
<tr>
<th>Study Group/Reference</th>
<th>Signaling Domains Targeted</th>
<th>Lymphodepleting Agent(s)</th>
<th>Population</th>
<th>Response Rate</th>
<th>CRS Rate</th>
<th>Neurologic Toxicity Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penn/CHOP Maude et al[4]</td>
<td>CD3ζ, 4-1BB&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Varied</td>
<td>N = 30 pediatric and adult patients</td>
<td>CR: 90%</td>
<td>Total: 100% 27% severe</td>
<td>Total: 43% Encephalopathy, aphasia, seizures (1 patient)</td>
</tr>
<tr>
<td>MSKCC Davila et al[1]</td>
<td>CD3ζ, CD28</td>
<td>Cyclophosphamide</td>
<td>N = 16 adults</td>
<td>CR: 88%</td>
<td>43% severe</td>
<td>Grade 3/4: 25% Encephalopathy, seizures</td>
</tr>
<tr>
<td>NCI Lee et al[3]</td>
<td>CD3ζ, CD28</td>
<td>Fludarabine/cyclophosphamide</td>
<td>N = 21 pediatric and adult patients</td>
<td>CR: 67% in intent-to-treat population</td>
<td>Total: 76% 28% severe</td>
<td>Total: 29% Hallucinations, dysphasia, encephalopathy</td>
</tr>
<tr>
<td>FHCRC Turtle et al[7]</td>
<td>CD3ζ, 4-1BB&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Cyclophosphamide and fludarabine/cyclophosphamide</td>
<td>N = 29 adults</td>
<td>CR: 93%</td>
<td>Total: 83% 23% severe</td>
<td>Severe neurotoxicity: 50% TRM: 1 patient</td>
</tr>
</tbody>
</table>

## Chronic Lymphocytic Leukemia (CLL) and Non-Hodgkin Lymphoma (NHL)

<table>
<thead>
<tr>
<th>Study Group/Reference</th>
<th>Signaling Domains Targeted</th>
<th>Lymphodepleting Agent(s)</th>
<th>Population</th>
<th>Response Rate</th>
<th>CRS Rate</th>
<th>Neurologic Toxicity Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penn Porter et al[6]</td>
<td>CD3ζ, 4-1BB&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Varied</td>
<td>N = 14 (CLL)</td>
<td>CR: 29% PR: 29%</td>
<td>Total: 64% 36% severe</td>
<td>Total: 43% Grade 4: 1 patient</td>
</tr>
</tbody>
</table>
Toxicity Associated with Immunotherapy

• With ICB, spectrum of toxicity primary revolves around development of autoimmune diseases.

• With CAR, toxicity involves early CRS (from immune activation) and neurologic toxicity (mechanism unknown).

• Spectrum of toxicities are distinct to what is seen with chemotherapy and can be fatal.

• With both ICB and CAR, early recognition of toxicity is critical both to initiate appropriate reversal agents, and to modify subsequent therapy.
• Describe the role of the immune system in cancer and cancer therapy.

• Distinguish between the different forms of immunotherapy presently approved for the treatment of advanced cancers.

• Understand the mechanisms behind the toxicities associated with anti-cancer immunotherapy.

• Describe the challenges and barriers to care associated with treating patients with immunotherapy.
Survival greater (median 2.7 vs. 1.5 yrs) in pts with actionable mutations treated with targeted therapy than standard therapy.

% of pts with actionable mutations treated with targeted therapy: 25%.

Kris MG, JAMA 2014
Financial Toxicity

Per infusion cost (1/patient): $475,000
Pricing model between Novartis and CMS “allows for full payment only when these patients respond to Kymriah by the end of the first month after treatment”

Average per-mg wholesale price: $28.78
Annual treatment cost for average patient: $103,220 or $206,440 for 2 years.
20% copay: $1,720 monthly.

Spot price of gold: $1,300/oz.
Barriers to Care

• Durable response rates previously unseen with either chemotherapy or targeted therapies → functional cures.

• Ongoing challenges include
  – Improving access: lifesaving therapies through early involvement of specialists
  – Improving toxicity: better understanding of immune-related adverse events
  – Reducing costs: shorter duration; patient optimization
Conclusions

• Cancer exploits defective immunosurveillance to grow and is sustained by tolerogenic mechanisms.

• PD-1 and CTLA-4 immune checkpoint blockade have transformed the management of cancer. CAR T cell therapy is effective in refractory hematologic malignancies including some leukemias.

• Toxicity profile of ICB and CAR products are unique and require high degree of suspicion.

• Multiple barriers to care exist including lack of knowledge and financial toxicity.
Questions

• Cancer patients spontaneously develop anti-cancer immune responses early that are detectable.
  – True or False
  – Answer: True

• Immune checkpoint blockade with PD-1/CTLA-4 inhibitors are potentially curative in advanced (stage IV) cancers including melanoma, lung cancer and kidney cancer.
  – True or False
  – Answer: True
Questions

• The spectrum of toxicities associated with immune checkpoint inhibitors (PD-1/CTLA-4 blocking antibodies) and/or chimeric antigen receptor T cells are identical to those seen with conventional chemotherapy.
  – True or False
  – Answer: False

• Immune therapies such as immune checkpoint inhibitors (PD-1/CTLA-4 blocking antibodies) and/or chimeric antigen receptor T cells are readily affordable.
  – True or False
  – Answer: False