Immune Checkpoint Inhibitors: The New Breakout Stars in Cancer Treatment
Introductions

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Immune Checkpoints

- With normal function, immune checkpoints:
  - Control excessive immune activation
  - Prevent autoimmunity
  - Protecting tissues from damage during an immune response to a pathogenic infection

- T cell activity governed by:
  - Ligand-receptor interactions
  - Balancing co-stimulatory and inhibitory signals
  - Immune checkpoints

Basic illustration of immunologic synapses between T cells and dendritic cells
Immune Checkpoints

- In many cancers, immune checkpoints also appear to be a means by which tumors evade the immune system.
- CTLA-4 can be abnormally expressed, allowing malignant cells to go unnoticed by T cells.
- Abnormal expression of PD-L1 can occur on malignant cells inhibiting the recognition of tumor antigens by antigen-presenting cells.

Abnormal expression of receptors on malignant cells can occur.
Clinical Trials with IO Products

- PD-1: 177
- PD-L1: 178
- CTLA-4: 11
- PD-1 + CTLA-4: 14
- PD-L1 + CTLA-4: 75

Clinicaltrials.gov (Data retrieved 30 March, 2016)
Indications Pursued with Checkpoint Inhibitors
Pembrolizumab or Ipilimumab or CTLA-4

- Melanoma
- NSCLC
- Head and Neck
- Breast
- Lymphoma
- Other (3 or less studies)
- Renal
- Ovarian
- Bladder
- Colorectal
- Prostate
- Pancreatic
- Multiple myeloma
- Brain
- SCLC
- AML/MDS

Clinicaltrials.gov (Data retrieved 30 March, 2016)
Clinical Trial Stages
Pembrolizumab or Ipilimumab or CTLA-4

Phases of All Clinical Stage
n = 414

Phase 0: 33
Phase 1: 14
Phase 2: 213
Phase 3: 163

Clinicaltrials.gov (Data retrieved 30 March, 2016)
# History of FDA Approval

## History of FDA Approval of Immune Checkpoint Inhibitors

<table>
<thead>
<tr>
<th>Date</th>
<th>Event Description</th>
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<tbody>
<tr>
<td>Mar 2011</td>
<td>Ipilimumab (Yervoy®), CTLA-4 checkpoint inhibitor, approved for treatment of refractory or advanced metastatic melanoma</td>
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<tr>
<td>Sept 2014</td>
<td>Pembrolizumab (Keytruda®), PD-1 checkpoint inhibitor, granted accelerated approval for treatment of metastatic or unresectable melanoma that did not respond to other treatments</td>
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<td>Dec 2014</td>
<td>Nivolumab (Opdivo®), PD-1 checkpoint inhibitor, approved for treatment of metastatic or unresectable melanoma</td>
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<tr>
<td>Oct 2015</td>
<td>Nivolumab (Opdivo®) approved use expanded for treatment of advanced (metastatic) squamous non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy</td>
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<tr>
<td>Oct 2015</td>
<td>Pembrolizumab (Keytruda®) granted accelerated approval for treatment of advanced, unresponsive, PD-L1-positive NSCLC</td>
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<tr>
<td>Oct 2015</td>
<td>Ipilimumab (Yervoy®) approved as adjuvant therapy with stage III melanoma to reduce risk of postoperative recurrence</td>
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<tr>
<td>Nov 2015</td>
<td>Nivolumab (Opdivo®) approved use expanded for previously treated metastatic renal cell carcinoma</td>
</tr>
<tr>
<td>Dec 2015</td>
<td>Pembrolizumab (Keytruda®) approved use expanded to first-line treatment of metastatic or unresectable melanoma</td>
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How Do We Save Our Investment?

- PD-1 & PD-L1 inhibitors have been the favored starlets
  - More durable responses
  - Treatment more tolerable
  - Response with PD-1/PD-L1 blockade is relatively rapid
  - Provided hope for those that have otherwise appeared to resist treatment

- However...
  - Performance can be unreliable
  - Potentially short-lived response
  - High levels of toxicity linked to autoimmune processes

- We love their performances when they’re on target, but we can’t rely on these relatively young stars to consistently deliver

- How do we save our investment & make these stars available?
Where To From Here?

- Why not...
  - Utilize consistently performing character stars as standard treatment
  - Bring back older stars (cytokines)
  - Introduce newer stars as discovered?
- Pair treatments with traits complementary to immune checkpoint inhibitors with combination therapies that have immunotherapy component

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<th>Driving higher &amp; longer responses:</th>
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<tr>
<td>Directly stimulating cytotoxic T cells</td>
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<td>Blocking tumor-expressed immunoinhibitory factors</td>
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<tr>
<td>Inhibiting regulatory T cells</td>
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<tr>
<td>Blocking inhibition of NK cell activity</td>
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<tr>
<td>Blocking activity of soluble factors produced by stromal myeloid and mesenchymal cells</td>
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</table>
Research has involved PD-1 and PD-L1 inhibitors administered with:
- Cytotoxic chemotherapy
- Radiation therapy
- CTLA-4 inhibitors
- Small-molecule inhibitors (VEGFR tyrosine kinase inhibitors sunitinib and paxopanib)

PD-1 or PD-L1 blockage served as backbone of many trials - subtle role in peripheral tolerance maintenance, inflammation regulation

Use of anti-PD-1 agent specifically as primary therapeutic:
- Fewer side effects
- Produce good response rates in more tumor types
Combination therapy with chemotherapy

- Ex: Prelim results from trial combining atezolizumab (anti-PD-L1) and chemotherapy (nab-paclitaxel) to treat TNBC
  - ORR 67% (9 patients not previously treated)
  - Overall ORR 42%

- Important considerations:
  - Dose
  - Timing
  - Mechanism of action
Combination therapy with radiation

- Synergy between immune checkpoint inhibitors and radiation?
- Particularly useful for patients with no pre-existing antitumor immunity
- Tumor cell death induced by radiation can activate tumor-specific immune responses
- Tumor cell phenotype modulated, cells more susceptible to immune-mediated death by cytotoxic T cells
- Ex: combined nivolumab and radiation therapy in patients with melanoma metastasized to brain
  - Better disease control (91% after 6 mos, 85% after 12 mos; compared to avg 4-5 mos)
  - Prolonged OS (median OS 11.8 and 12 mos from initiation of stereotactic radiation and nivolumab in patients with unresected disease; median OS not reached for patients with resected disease)
  - No treatment-related neurologic toxicities or scalp reactions

Old Stars: Cytokines

- Interferon (IFN) first approved in 1986 for cancer treatment
- Interleukin (IL) family
  - Regulates immune system, acts as growth factor
  - Initially approved in 1992 for melanoma & kidney cancer
  - Effective in metastatic melanomas & metastatic renal cell carcinoma
    - Recent study reporting an OS at 2 years of 60.6% in 91 patients
  - However...
    - Severe toxic effects are common
    - Overall cure rate only 6%
- Older agents might help further research of newer stars
- Number of trials exploring combined use of cytokines with immune checkpoint inhibitors
Old Stars: Vaccines

- Use of vaccines to activate response in patients without pre-existing anti-tumor response might amplify response to checkpoint inhibition
- Combination might induce tumor regression

Study examples:

- Therapies (IMCgp100) that recruit cells to tumor (combination with this vaccine currently being studied for melanoma)
- Phase II study (NCT01096602) for acute myelogenous leukemia
Combinations of New Stars: 1st Generation

Study examples:

- New anti-PD-1s (PDR001): first-in-human Phase I/II study for melanoma, NSCLC, TNBC, & other solid tumors
- Ipilimumab and nivolumab combination for treatment of BRAF V600 wild-type unresectable or metastatic melanoma
- Combination of anti-PD-1 agent with anti-PD-L1 agent

- Combination approach might stimulate antitumor immunological memory, combining higher response rate of targeted drug & longer-lasting response of immunotherapies
- Significantly more toxicities experienced
- Considerations with combined immune checkpoint therapy:
  - Sequence
  - Doses
Combinations of New Stars: 2\textsuperscript{nd} Generation

- Targeted at large number of receptors and ligands that help control immune response at various levels
- Use of these second-generation inhibitors is being extensively investigated as monotherapy
- The future: combination with existing and newly studied PD-1 inhibitors appears to further enhance antitumor immunity

Study examples:

\begin{itemize}
  \item LAG-3, a CD-4 homologue
  \item TIM-3, inhibits T helper 1 cell responses
  \item CPI-444, blocks binding of adenosine to A2A receptor
  \item 4-1BB, immune-stimulatory receptor
  \item CDX-1127, anti-CD27 drug
  \item APX005M, anti-CD40 agent
  \item HCD122/lucatumumab, anti-CD40 agent
  \item SGN-40, anti-CD40
  \item ADC-1013, anti-CD40 antibody
  \item MEDI6469, anti-OX40 agent
  \item MEDI0562, anti-OX40 agent
\end{itemize}
Combination With Other Targeted Drugs

- Enhance tumor response by forcing tumors to upregulate immune checkpoints that can be targeted in combination therapy
- “Prime” tumors to be sensitive to destruction by activated T cells
- Correct sequence is important
  - It has been suggested that targeted therapy should be administered first to prime T cell response

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<td>Vascular endothelial growth factor (VEGF)-VEGF receptor (VEGFR) inhibitors</td>
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<td>RAF inhibitors</td>
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<td>Antibodies targeted at receptor tyrosine kinases</td>
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<td>Epigenetic therapies</td>
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Who will benefit?

The search for appropriate and reliable biomarkers is ongoing:

- Prospectively identify best candidates for a particular treatment
- Monitor patient’s response to treatment

Immune checkpoint pathways

- Primarily in tumor microenvironment, key ligand and receptor expression in tumor biopsies
- Might help identify dominant pathway(s) within tumor

Study examples:

Therapies (IMCgp100) that recruit cells to tumor (combination with this vaccine currently being studied for melanoma)

Phase II study (NCT01096602) for acute myelogenous leukemia