An Brief Overview of Current Immunotherapy Strategies in the Treatment of Advanced Cancer

Suzanne McGettigan, CRNP AOCN® ANP-BC
Nurse Practitioner
Abramson Cancer Center
University of Pennsylvania
Philadelphia, PA
Objectives

• Understand the mechanism of action of currently approved therapies.
• Identify Immune Related Adverse Events (IRAEs)
• Recognize symptoms of the most common IRAEs and management strategies
History of Cancer Care

- **Radiotherapy**: 1890s-presenter
- **Surgery**: ancient times-present
- **Traditional Chemotherapy**: 1940s-present
- **Precision Therapy**: 1998-present
- **Immunotherapy**: 1997-present
Role of the Immune System in Cancer

- Immunosuppression linked with cancer development
- Tumor Infiltrating Lymphocytes in the primary tumor correlated with improved prognosis

- Tumors develop when the immune system fails to recognize and eliminate cells that no longer follow the rules
  - Active immunosuppression by the cancer
  - Loss of antigen expression on the cancer
  - Exploitation of immune checkpoint pathways
  - T cell exhaustion

Immunotherapy Categories

- Cytokines
  - Interferon
  - Interleukin

- Check Point Inhibitors
  - Programmed Death Receptor-1
  - Programmed Death Receptor Ligand-1
  - Cytotoxic T-Lymphocyte-Associated Antigen 4

- Oncolytic Virus Therapy

- CAR T-cell Therapy
  - Chimeric Antigen Receptor T-cells

- BiSpecific T-Cell engagers
  - BiTES
Check Point Inhibitors
# PD-1, PD-L1, and CTLA-4 Therapies

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Blocks PD-1</th>
<th>Blocks PD-L1</th>
<th>Blocks CTLA-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atezolizumab</td>
<td>Tecentriq</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Avelumab</td>
<td>Bevencia</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Durvalumab</td>
<td>Imvinzi</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>Yervoy</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>Opdivo</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>Keytruda</td>
<td></td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>
Currently Approved Indications for Checkpoint Inhibitor Therapy

• **Melanoma**
  - Ipilimumab (Adjuvant, metastatic)
  - Pembrolizumab (Any line)
  - Nivolumab (Adjuvant, metastatic)

• **Non-small cell lung cancer**
  - Pembrolizumab (1\textsuperscript{st} and 2\textsuperscript{nd} line)
  - Nivolumab (2\textsuperscript{nd} line)
  - Atezolizumab (2\textsuperscript{nd} line)
  - Durvalumab (Adjuvant)

• **Bladder cancer**
  - Pembrolizumab (2\textsuperscript{nd} line)
  - Atezolizumab (2\textsuperscript{nd} line or cisplatin ineligible)
  - Nivolumab (2\textsuperscript{nd} line)
  - Avelumab (2\textsuperscript{nd} line)
  - Durvalumab (2\textsuperscript{nd} line)

• **Kidney cancer (Renal Cell)**
  - Nivolumab + Ipilimumab (1\textsuperscript{st} line)
  - Nivolumab (2\textsuperscript{nd} line)

• **Head and neck cancer**
  - Nivolumab
  - Pembrolizumab

• **Hodgkin lymphoma/B-cell lymphoma**
  - Nivolumab
  - Pembrolizumab

• **Merkel cell carcinoma**
  - Avelumab

• **Liver cancer (Hepatocellular)**
  - Nivolumab

• **Gastric cancer**
  - Pembrolizumab

• **Colorectal cancer, MSI high**
  - Nivolumab

• **MSI-high cancer (any lineage)**
  - Pembrolizumab

• **Cervical Cancer**
  - Pembrolizumab
CTLA-4 and PD-1/PD-L1 Checkpoint Blockade for Cancer Treatment

Check Point inhibitors: Patient selection

- Consideration to individual characteristics
  - Tumor burden
  - Mutation status
  - ECOG Performance status
  - Organ function
  - Auto-immune disease
Immune response criteria

- Immune-related response criteria (irRC) were developed to evaluate antitumor responses with immunotherapy
  - Atypical response patterns noted with CTLA-4, PD-1 blockade
  - Conventional response criteria such as RECIST v1.1 do not provide a complete evaluation of immunotherapy benefit
- A new lesion does not automatically confirm progressive disease
- Mixed responses can be seen
- Treatment can continue beyond progression in the absence of obvious clinical decline
Melanoma patient on pembrolizumab

Baseline
Week 4
Week 24
Week 60
Lung cancer patient on pembrolizumab
Immune mediated adverse events (AEs)

- Related to mechanism of action
- Wide range of incidence and severity among approved and investigational approaches

- Immune mediated toxicity should be considered in the differential of any new symptom, involving any organ system
Immune-related Adverse Events: CTLA-4, PD-L, and PD-L1 therapies

- **Neurologic**
  - Autoimmune neuropathy
  - Guillain-Barre
  - Myasthenia gravis–like syndrome

- **Eye**
  - Uveitis
  - Iritis

- **Endocrine**
  - Hyperthyroidism
  - Hypothyroidism
  - Hypophysitis

- **Hepatic**
  - Hepatitis

- **Gastrointestinal**
  - Diarrhea
  - Colitis
  - GI perforation

- **Pulmonary**
  - Pneumonitis
  - Interstitial lung disease
  - Acute interstitial pneumonitis

- **Renal**
  - Nephritis, autoimmune
  - Renal failure

- **Dermatologic**
  - Rash
  - Pruritus
  - Dermatitis

- **Muscle / Joint**
  - Myalgias
  - Arthralgias

<table>
<thead>
<tr>
<th>Organ system</th>
<th>Ipilimumab</th>
<th>Nivolumab</th>
<th>Pembrolizumab</th>
<th>Ipi / Nivo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade</td>
<td>Grade 3/4</td>
<td>Any grade</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Rash</td>
<td>14-33%</td>
<td>1-2%</td>
<td>15-26%</td>
<td>0-1%</td>
</tr>
<tr>
<td>Pruritis</td>
<td>24-35%</td>
<td>&lt;1%</td>
<td>14%</td>
<td>0%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>23-33%</td>
<td>3-6%</td>
<td>11-19%</td>
<td>1-2%</td>
</tr>
<tr>
<td>Colitis</td>
<td>8-12%</td>
<td>5-9%</td>
<td>1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>1%</td>
<td>&lt;1%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>&lt;1-2%</td>
<td>&lt;1%</td>
<td>1-2%</td>
<td>0-&lt;1%</td>
</tr>
<tr>
<td>Renal</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>13-22%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>2-4%</td>
<td>0%</td>
<td>4-9%</td>
<td>0%</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>1-2%</td>
<td>&lt;1%</td>
<td>2-4%</td>
<td>0%</td>
</tr>
<tr>
<td>Hypophysitis</td>
<td>2-4%</td>
<td>2%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Any Immune Mediated</td>
<td>93%</td>
<td>24%</td>
<td>68%</td>
<td>12%</td>
</tr>
</tbody>
</table>
Other Immune Mediated Toxicities Reported

- **Ipilimumab**: nephritis, pneumonitis, meningitis, pericarditis, uveitis, iritis, and hemolytic anemia, myocarditis, angiopathy, temporal arteritis, vasculitis, polymyalgia rheumatica, conjunctivitis, blepharitis, episcleritis, scleritis, leukocytoclastic vasculitis, erythema multiforme, psoriasis, pancreatitis, arthritis, autoimmune thyroiditis, sarcoidosis, neurosensory hypoacusis, autoimmune central neuropathy (encephalitis), myositis, polymyositis, and ocular myositis.

- **Nivolumab**: uveitis, pancreatitis, facial and abducens nerve paresis, demyelination, autoimmune neuropathy, motor dysfunction, and vasculitis. diabetic ketoacidosis and myasthenic syndrome.

- **Pembrolizumab**: exfoliative dermatitis, uveitis, arthritis, myositis, pancreatitis, hemolytic anemia, and partial seizures arising in a patient with inflammatory foci in brain parenchyma, severe dermatitis including bullous pemphigoid, myasthenic syndrome, optic neuritis, and rhabdomyolysis.

- **Ipi/Nivo**: Guillain-Barré syndrome and hypopituitarism. uveitis, sarcoidosis, duodenitis, pancreatitis, and gastritis
Timing of IRAEs following Ipilimumab

Weber JCO 2012
Timing of IRAEs following Nivolumab

(Any Grade; N = 474)

- Median time to onset for treatment-related select AEs ranged from 5.0 weeks for skin AEs to 15.1 weeks for renal AEs

Circles represent median; bars signify ranges.
Timing of IRAEs after Ipi/Nivo

### Incidence and onset of immune-mediated adverse reactions

<table>
<thead>
<tr>
<th>Condition</th>
<th>All Grades n (%)</th>
<th>Median Time to Onset (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonitis</td>
<td>25 (6)</td>
<td>1.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>range: 24 days - 10.1 months</td>
</tr>
<tr>
<td>Colitis</td>
<td>107 (26)</td>
<td>1.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>range: 3 days - 15.2 months</td>
</tr>
<tr>
<td>Hepatitis, including liver function test elevations</td>
<td>51 (13)</td>
<td>2.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>range: 15 days - 11 months</td>
</tr>
<tr>
<td>Endocrinopathies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypophysitis</td>
<td>36 (9)</td>
<td>2.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>range: 27 days - 5.5 months</td>
</tr>
<tr>
<td>Adrenal Insufficiency</td>
<td>21 (5)</td>
<td>8.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>range: 21 days - 9.4 months</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>89 (22)</td>
<td>2.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>range: 1 day - 10.1 months</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>34 (8)</td>
<td>2.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>range: 3 days - 3.7 months</td>
</tr>
<tr>
<td>Type 1 diabetes mellitus</td>
<td>6 (1.5)</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>range: 1.3 - 4.4 months</td>
</tr>
<tr>
<td>Nephritis and Renal Dysfunction</td>
<td>9 (2.2)</td>
<td>2.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>range: 9 days - 7.9 months</td>
</tr>
<tr>
<td>Skin Adverse Reactions</td>
<td>92 (22.6)</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>range: 1 day - 9.7 months</td>
</tr>
</tbody>
</table>

*OPDIVO = YERVOY Regimen (n=407)
General Management

- Early Recognition is KEY
  - Patient education

- Rule out non-inflammatory etiologies

- Assess severity of symptom
  - mild, tolerable reactions, continue treatment.
    - Treat symptomatically
  - moderate reactions
    - hold Immunotherapy
    - initiate systemic corticosteroids (0.5-1 mg/kg/day of prednisone or equivalent)
    - When symptom is resolved or back to baseline, begin slow steroid taper over at least one month.
    - Resume therapy once patient is off steroid without recurrence of symptoms.
  - Severe symptoms:
    - permanently discontinue therapy
    - Initiate systemic corticosteroids (1-2 mg/kg/day of prednisone or equivalent)
    - If steroid-refractory, consider alternate/additional immune modulating therapy (infliximab, mycophenylate)
Colitis

- Recognition:
  - Early recognition is essential to prevent complications including perforation
  - Endoscopic evaluation may be indicated

- Management:
  - Mild: monitor symptoms closely; Initiate supportive care
  - Moderate: hold therapy, initiate systemic corticosteroids (1-2 mg/kg/day of prednisone or equivalent). Once diarrhea/colitis sx back to baseline or grade 1, begin slow steroid taper over at least one month. Can consider resuming therapy.
  - Severe: hold/discontinue immunotherapy. May require hospitalization for further management. Initiate systemic corticosteroids (1-2 mg/kg/day of prednisone or equivalent). Once diarrhea/colitis sx back to baseline or grade 1, begin slow steroid taper over at least one month.

- Additional Care:
  - IV corticosteroids may be required
  - Infliximab has been utilized successfully for steroid refractory enterocolitis.
Immune Mediated Hepatitis

• Evaluate LFTs prior to each dose
• Presentation: most commonly asymptomatic elevation in AST/ALT, less frequently elevation of T Bili

• Management:
  • Mild: monitor LFTs closely
  • Moderate: hold therapy, initiate systemic corticosteroids (1-2 mg/kg/day of prednisone or equivalent). Once LFTs back to baseline or grade 1, begin slow steroid taper
  • Severe: hold/discontinue immunotherapy. May require hospitalization for further management. Initiate systemic corticosteroids (1-2 mg/kg/day of prednisone or equivalent). Once LFTs back to baseline or grade 1, begin slow steroid taper
  • Mycophenylate has been utilized in steroid refractory hepatitis.
Immune Mediated Pneumonitis

- Typical presentation: new SOB, DOE, cough, upper respiratory symptoms, wheezing, chest pain, hypoxia
- Diagnosis: CT chest
- Management:
  - Mild (radiographic findings only): no intervention. Monitor CT chest closely throughout therapy
  - Moderate: hold immunotherapy. Initiate systemic corticosteroids (1-2 mg/kg/day prednisone or equivalent). Once symptoms have resolved, begin slow taper. Once patient has completed taper, resume immunotherapy.
  - Severe: discontinue immunotherapy. May require hospitalization for further management. Initiate systemic corticosteroids (2-4 mg/kg/day prednisone or equivalent). Once symptoms have resolved, begin slow taper. Once patient has completed taper, resume immunotherapy.

- Less common pulmonary toxicities: sarcoidosis, inflammatory pneumonia
Immune Mediated Endocrinopathies

• Most common organs affected:
  • Pituitary
  • Thyroid
  • Adrenal Glands

• Less Common:
  • Pancreas
    • Type 1 diabetes—a abrupt onset
    • Pancreatic insufficiency

• Presenting symptoms may be vague
Oncolytic Viral Immunotherapy
Oncolytic Virus Immunotherapy

• Utilize native or genetically modified viruses that selectively replicate within tumor cells
• Do not require defined antigens to be included in the vector
  • Tumor-associated antigens may be released by dying tumor cells
• Directly kill tumor cells

Talimogene Laherparepvec (T-VEC, Imlygic®)

• Herpes simplex virus (HSV-1) modified to replicate specifically within tumor cells leading to cell lysis

• Cell lysis leads to release of tumor cell antigens which stimulate anti-tumor immune response.

• Indication:

• Local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma following surgical resection

Administration

- Intratumoral injection
- Pregnant HCPs should not be involved in preparation or administration

Patient Education with T-VEC

• Injection site care
  • Avoid touching or scratching treatment sites
  • Keep treatment site covered with airtight and watertight dressings for at least 1 week
    • Until treatment site is no longer weeping or oozing
  • Replace loose dressing immediately
  • Discard dressings in a sealed plastic bag

• Notify oncology team immediately
  • Pain, burning, or blister around mouth, fingers, ears, or genitals
  • Eye pain, photophobia, eye drainage, blurry vision

Seery V. *Clin J Oncol Nurs.* 2017;21(suppl):76-86.
CAR-T Therapy
CAR-T Cells

• Adoptive cell therapy utilizing own T-cells to fight cancer

• Immune cells or antibodies can be produced in the laboratory and then given to patients to treat cancer.

• Current therapies:
  • Axicabtagene ciloleucel (Yescarta)
  • Tisagenlecleucel (Kymriah)
Anatomy of a Chimeric Antigen Receptor

• Gene transfer technology is used to stably express CARs on T-cells, conferring novel antigen specificity

• CARs combine antigen recognition domain (anti-CD19) with intracellular signaling domain

• Intracellular signaling domain:
  • Same functionality as endogenous T-cells
  • Co-stimulatory endodomain mediates potent anti-cancer effects and promotes persistence
CAR-T Cells: Autologous Approach
But Not Without Toxicity

On-target toxicities\(^1,2\):
- Tumor lysis syndrome
- B-cell aplasia
- Hypogammaglobulinemia

Off target toxicities\(^1,2\):
- Cytokine Release Syndrome (CRS)
  - Discussed on next slide
- CNS toxicity
  - Causative pathophysiology of these neurologic side effects is unknown
  - Neurologic toxicity has been reversible in a majority of cases

---

Cytokine Release Syndrome (CRS)

- Correlates with:
  - CAR-T19 activation and expansion
  - Dramatic cytokine elevations (very high levels of IL6, IL10, IFNγ, CRP, ferritin)
  - Almost all responding patients developed a CRS

- Clinical syndrome:
  - Onset 1-14 days after infusion
  - Duration 1-10 days
  - Monitor VS, ferritin level, and CRP level
  - Fevers come first and get very high (105°F/41°C)
  - Myalgias, fatigue, anorexia
  - Capillary leak, hypoxia and hypotension
    - May require ICU support
  - Associated with HLH/macrophage activation syndrome
    - Altered mental status, seizures, DIC
    - Ferritin >500,000

- Self-limited or anti-cytokine intervention (Tocilizumab)
“The Antidote”: Tocilizumab

• Humanized monoclonal antibody to IL-6 which can rapidly reverse CRS\(^1\)

• Ensure that 2 doses of tocilizumab are available prior to infusion of CAR-T cells

• Monitor patients at least daily for 7 days at the certified healthcare facility following infusion.

• Monitor patients for signs or symptoms of CRS for 4 weeks after infusion.

• At the first sign of CRS, institute treatment with supportive care, tocilizumab or tocilizumab and corticosteroids as indicated.

Temperature Response to Tocilizumab

Source: Patricia Mangan, RN, MSN, CRNP
BiTEs

Bispecific T-Cell Engagers
BiTE: Bispecific T-cell Engagers

Blinatumomab

- A constructed monoclonial antibody known as bispecific T-cell engagers (BiTEs)
- Exert action selectively and direct the human immune system to act against tumor cells
- Blinatumomab targets CD19
- FDA approved 12/2014 for treatment of relapsed refractory Ph-B-cell

- Side Effects:
  - CRS
  - Neurotoxicity

Summary

• Immunotherapy offer new treatment options for patient with advanced cancers, offering high rates of clinical benefit

• IRAEs are unique
  • Recognition is key by both patients and health care providers.
  • Requires a new skill set for all oncology providers involved in the care of these patients.
  • Patients who develop these toxicities require quick intervention with corticosteroid therapy to prevent progression.
Thank you.