IMMUNE CHECKPOINT INHIBITORS

Josie Garnoc, MSN, RN, CRNI, OCN
KEY PLAYERS IN THE IMMUNE RESPONSE
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B Lymphocytes

- Humoral immunity: plasma cell precursors, immunoglobulins
- Cell–mediated immunity: interaction with T cells
KEY PLAYERS IN THE IMMUNE RESPONSE
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T-Lymphocytes

- Coordinate immune response (Regulatory)
- Cell–mediated immunity
- Maintain cytotoxic T cell response and express CD4 (CTLA–4)
KEY PLAYERS IN THE IMMUNE RESPONSE

- T_FH cell
  - Bcl6
  - BILmp-1
- IL-10
- T_FR cell
- CXCR5
- CD28
- CD40L
- TCR
- MHC-II
- IL-21R
- B7
- ICOS
- ICOSL
- PD-1
- PDL-1
- CD40
- IL-21R
- Memory B cell
- Plasma cell
Influence T cell reactivity

Enhanced antitumor response

- CTLA–4 inhibitor: more T cells activated, longer activation period. Increased number of antitumor T cells.
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- PD1 inhibitor: prevent activated T cells from being turned off, prolong, enhance antitumor response.
  - prevents binding of PDL-1, PDL-2
FIGURE 1. Mechanism of Action of PD-1/PD-L1 and CTLA-4 Antibodies

PD-1 AND CTLA-4 PATHWAYS

CTLA-4 PATHWAY INHIBITION

PD-1 PATHWAY INHIBITION

TUMOR CELL

ACTIVATED T CELL

APG

T CELL
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- CTLA4 inhibitor
  - ipilimumab (Yervoy)

  - Unresectable or metastatic melanoma: 3mg/kg IV infusion over 90 minutes every 3 weeks X 4

  - Adjuvant treatment melanoma: 10mg/kg IV infusion over 90 minutes every 3 weeks X 4 then 10mg/kg every 12 weeks up to 3 years
PD-1 inhibitors:
- nivolumab (Opdivo)
  - Melanoma (single agent): 240mg IV infusion over 90 minutes every 2 weeks until disease progression or unacceptable toxicity
  - Melanoma in combination with ipilimumab: 1mg/kg IV infusion over 60 minutes followed by ipilimumab every 3 weeks X 4. Then as single agent
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- NSCLC, renal cell, urothelial CA: 240mg IV infusion over 90 minutes every 2 weeks until disease progression or unacceptable toxicity

- Classical Hodgkin lymphoma, squamous cell CA head/neck: 3mg/kg IV infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity
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- pembrolizumab (Keytruda)
  - Melanoma: 2mg/kg IV infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity
  
  - Metastatic NSCLC, head/neck squamous cell CA and classical Hodgkin lymphoma: 200mg IV infusion over 30 minutes every 2 weeks until disease progression or unacceptable toxicity up to 24 months without disease progression
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PDL–1 inhibitors:

- atezolizumab (Tecentriq)
  - metastatic urothelial CA, local or advanced not eligible for cisplatin chemo or progression during/after cisplatin chemotherapy or within 12 months neoadjuvant or adjuvant chemotherapy
  - NSCLC, metastatic or progression during or after cisplatin chemotherapy with ALK or EGFR aberrations use FDA approved TX prior
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- atezolizumab:
  - Usual dose: 1,200mg IV infusion over 60 minutes every 3 weeks until disease progression or unacceptable toxicity
  - If first dose tolerated, subsequent infusions over 30 minutes.
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- avelumab (Bavencio)
- Premedication: antihistamine/acetaminophen
  1st 4 doses
  - Merkel cell; metastatic: 10mg/kg IV infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity
  - Urothelial: 10mg/kg IV infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity
Durvalumab (Imfinzi)
- Urothelial: 10mg/kg IV infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity
  - NSCLC local advanced (NCCN): beginning within 6 weeks after chemotherapy, continue up to 12 months or disease progression or unacceptable toxicity.
  - Beyond 12 months if at end of 12 months progression during follow up.
Unique side effects:

- "IRAES": immune related adverse events
  - Dermatological
  - Gastrointestinal
  - Endocrine
  - Pulmonary
  - Renal
  - Ocular
  - Hematological
  - Cardiovascular
  - Neurological
  - Musculoskeletal
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- Novel toxicity profile: immune based etiology
- T cells systemic: any organ/tissues impacted
- Symptom assessment/evaluation R/T grade essential with each infusion
- Patient/Caregiver education R/T “irAEs” & report
Immunotherapy Toxicity Assessment Questions

- **GENERAL**
  - Are you having difficulty performing your normal activities? Yes No
  - Have you had constant or unusual headaches? Yes No
  - Have you felt drowsy or extremely tired? Yes No
  - Have you felt dizzy or fainted? Yes No
  - Have you had changes in mood or behavior, such as decreased sex drive, irritability, or forgetfulness? Yes No
  - Have you felt cold? Yes No
  - Have you gained or lost weight? Yes No
  - Have you had hair loss? Yes No
  - Has your voice gotten deeper? Yes No
  - Have you noticed your skin or eyes turning yellow? Yes No
  - Are you experiencing increased thirst? Yes No
  - Are you urinating more or less often than usual? Yes No
  - Is your urine bloody, dark, or tea-colored? Yes No
  - Do you bleed or bruise more easily than normal? Yes No
  - Do you have swelling in your ankles? Yes No
  - Have you had severe or constant muscle or joint pain? Yes No
  - Have you had severe muscle weakness? Yes No
  - Have you been running a fever? Yes No
  - Have you had changes in your eyesight? Yes No
  - Have you started taking any new medications (prescription, nonprescription, or herbal)? If yes, which and how often? Yes No
  - Have you experienced any weakness? Yes No
**IMMUNE CHECKPOINT INHIBITORS**

**Immunotherapy Toxicity Assessment Questions**

- **PULMONARY**
  - Do you have a new cough or one that has worsened? Yes No
  - Are you having chest pain? Yes No
  - Are you having trouble breathing or shortness of breath? Yes No

- **GASTROINTESTINAL**
  - Are you severely nauseous and/or vomiting? Yes No
  - Do you have a loss of appetite or have you felt less hungry than usual? Yes No
  - How many bowel movements are you having each day?
  - Is this different than normal? If yes, how? Yes No
  - Are your stools loose or watery, or do they have a foul smell? Yes No
  - Have you seen blood or mucous in your stools? Yes No
  - Are your stools dark, tarry, or sticky? Yes No
  - Are you having painful bowel movements? Yes No
  - Are you having pain or tenderness around your belly? If yes, where? Yes No
IMMUNE CHECKPOINT INHIBITORS

**Immunotherapy Toxicity Assessment Questions**

- **NEUROLOGIC**
  - Have you experienced any periods of confusion? Yes No
  - Have you lost consciousness at any point? Yes No
  - Have you had any stiffness in your neck? Yes No
  - Have you had any seizures? Yes No
  - Have you had any sudden changes in your mood, perception, judgment, or memory? Yes No

- **SKIN**
  - Have you had a rash or itching? Yes No
  - Have you had any skin blisters or ulcers in your mouth or other mucous membranes? Yes No

- **GENERAL**
  - Have you had eye pain or redness? Yes No
  - Has your skin peeled? Yes No
  - Are you having numbness or tingling in your hands or feet? Yes No
  - Are you having unusual weakness of your legs, arms, or face? Yes No
IMMUNE CHECKPOINT INHIBITORS

Immunotherapy Toxicity Assessment Questions

- **INFUSION REACTIONS**
  - Have you experienced chills or shaking after receiving a dose of OPDIVO? Yes No
  - Have you experienced itching or rash after receiving a dose of OPDIVO? Yes No
  - Have you experienced flushing after receiving a dose of OPDIVO? Yes No
  - Have you had difficulty breathing after receiving a dose of OPDIVO? Yes No
  - Have you experienced dizziness after receiving a dose of OPDIVO? Yes No
  - Have you had a fever after receiving a dose of OPDIVO? Yes No
  - Have you felt like passing out after receiving a dose of OPDIVO? Yes No
## IMMUNE CHECKPOINT INHIBITORS

<table>
<thead>
<tr>
<th>System</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye</td>
<td>Uveitis, Conjunctivitis, Blepharitis, Retinitis</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Hyper/hypothyroidism, Hypohysitis, Adrenal insufficiency, Diabetes</td>
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<tr>
<td>Liver</td>
<td>Hepatitis</td>
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</tbody>
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<tbody>
<tr>
<td>Renal</td>
<td>Nephritis</td>
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<tr>
<td>Respiratory</td>
<td>Pneumonitis Pleuritis Sarcoid–like granulomatosis</td>
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<tr>
<td>Cardiovascular</td>
<td>Myocarditis Pericarditis Vasculitis</td>
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<tr>
<td>Gastrointestinal</td>
<td>Colitis Ileitis Pancreatitis Gastritis</td>
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<tr>
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<td>Pruritus</td>
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<td>Psoriasis</td>
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<td>Vitiligo</td>
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<td>Stevens Johnson</td>
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<td>Neurologic</td>
<td>Neuropathy</td>
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<td>Guillain Barre’</td>
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<td>Myelopathy</td>
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<td>Encephalitis</td>
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<td>Myasthenia</td>
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<td>Musculoskeletal</td>
<td>Arthritis</td>
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<td>Dermatomyositis</td>
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<td>Blood</td>
<td>Hemolytic Anemia</td>
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<td>Thrombocytopenia</td>
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<td>Neutropenia</td>
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<td>Hemophilia</td>
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# Managing Immune–Medicated Adverse Reactions

<table>
<thead>
<tr>
<th></th>
<th>GRADE 1</th>
<th>GRADE 2</th>
<th>GRADE 3–4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PD1, PDL–1</strong></td>
<td>Continue treatment</td>
<td>Withhold TX</td>
<td>Grade 3 withhold until Grade 0–1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Grade 4 permanently DC</td>
</tr>
<tr>
<td><strong>PD–1 + CTLA–4</strong></td>
<td>Continue treatment</td>
<td>Withhold TX until Grade 0–1</td>
<td>Permanently DC</td>
</tr>
<tr>
<td><strong>Symptomatic Treatment</strong></td>
<td>Administer</td>
<td>Administer</td>
<td></td>
</tr>
<tr>
<td><strong>Steroids (Prednisone equivalents)</strong></td>
<td>SX worsen or persist &gt; 5 days or recur 0.5–1.0mg/kg/day</td>
<td></td>
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</tr>
<tr>
<td><strong>Additional Testing</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>Follow-up</strong></td>
<td>Close monitoring for worsening SX</td>
<td>If improved: Resume TX</td>
<td>1–2mg/kg/day</td>
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<tr>
<td></td>
<td>Educate patient to report worsening SX immediately</td>
<td>Taper steroids over at least 1 month before resuming TX</td>
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<tr>
<td></td>
<td>SX worsen or persist &gt; 3–5 days with oral steroids: TX as Grades 3–4</td>
<td>If SX worsen or persist &gt; 3–5 days with oral steroids: TX as Grades 3–4</td>
<td>Consider system specific testing Consult specialist</td>
</tr>
</tbody>
</table>
Financial Toxicity:

- **ipilimumab**– 200mg/40ml  $33,924.92
  - induction 3mg/kg q 3 wks X4, 10mg/kg q 3 wks X4 then q 12 weeks up to 3 years

- **nivolumab**– 100mg/10ml  $3,100.00
  - monotherapy 240mg q 2 wks (DP/UT)
  - with CTLA-4  1mg/k q 3 wks X 4 the single agent

- **pembrolizumab**– 100mg/4ml  $5,497.00
  - Melanoma 2mg/kg q 3 wks (DP/UT)
  - NSCLC, Head/Neck Squam/Hodgins 240mg q 2week (DP/UT) up to 24 months without DP
Financial Toxicity:
  o atezolizumab– 1200mg/20ml  $10,344.00
    –1200mg q 3 wks until DP/UT
  
  o avelumab– 200mg/10ml  $1,831.17
    –10mg/kg q 2 wks until DP/UT
  
  o durvalumab– 500mg/10ml  $4,174.57
    –10mg/kg q 2 wks until DP/UT
IMMUNE CHECKPOINT INHIBITORS

- Financial Toxicity:
  - Financial Representative
  - Copay Assistance/Free drug programs
  - Social Work Referral
NCI: 1.7 million new cases of cancer diagnosed annually

FDA oral immunotherapy: etinostat (Syndex)
- Histone deacetylase inhibitor: affects number/activity of myeloid suppressor cells and regulatory T cells theoretically boost the body’s immune response to therapy with weekly dosing
Mab–drug conjugates: link mab with cytotoxic small–molecule drug.
- cemiplimab: PD–1 IV for cutaneous squamous cell with metastatic disease
  - CTLA–4 + PD1 for other malignancies
  - Combination immunotherapies + cytotoxic chemotherapy for improved cytotoxic effect, improved immunity
References

- Cousin, S, Senechal, J. & Italiano, A; Toxicity profiles of immunotherapy, Pharmacy and Therapeutics: 181 92018) 91–100.
- Esin, Ece, Clinical applications of immunotherapy combination methods and new opportunities for the future, BioMed Research International, 2017, Article ID 1623679, 10 pages
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Questions?