Pharmacology: Immunotherapies

Presented by: Alga S. Ramos Morales, PharmD, MS, BCPS
2019 Fall Rapid Integration Course
Mayo Clinic Florida, Jacksonville, FL
September 21, 2019
Disclosures

• I have nothing to disclose
Objectives

Discuss the definition and types of immunotherapy

Describe the indications for immunotherapy

Discuss monitoring and treatment of potential side effects

State patient resources available for education on immunotherapy
Agenda

- Definitions and History
- Checkpoint Inhibitors
- Management of Toxicities
- Cancer Vaccines
- CAR-T cell Therapy
- Monoclonal Antibodies
- Patient Resources
Immunotherapy

- Treatment that uses the body's own immune system to help fight cancer

Source: https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/immunotherapy.html
Mechanism of Action

- An efficient T-cell-mediated adaptive antitumor immune response requires two phases:
  - Priming phase (generation of antitumor T cells)
  - Effector phase (destruction of the cancer by T cells)

Source: https://clincancerres.aacrjournals.org/content/21/5/976
Immunotherapy

Types

Checkpoint Inhibitors

Cancer Vaccines

CAR-T cell

Monoclonal Antibodies
Checkpoint Inhibitors

PD-1 inhibitors

CTLA-4 inhibitors

Drug Classes

PD-L1 inhibitors

Others in research studies
Mechanism of Action

1. T-cell

2. CTLA-4

3. CD28

4. PD-L1

Nivolumab, pembrolizumab
Atezolizumab, durvalumab, avelumab
Ipilimumab, tremelimunab

## Nivolumab

<table>
<thead>
<tr>
<th>Indication</th>
<th>Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unresectable or metastatic melanoma</td>
<td>2014, 2nd line</td>
</tr>
<tr>
<td>Metastatic squamous NSCLC</td>
<td>2015</td>
</tr>
<tr>
<td>Metastatic NSCLC</td>
<td>2015</td>
</tr>
<tr>
<td>Advanced RCC</td>
<td>2015</td>
</tr>
<tr>
<td>Relapsed classical Hodgkin lymphoma (cHL)</td>
<td>2016</td>
</tr>
<tr>
<td>Recurrent/metastatic squamous cell carcinoma of the head and neck after disease progression</td>
<td>2016</td>
</tr>
<tr>
<td>Adjuvant treatment of patients with melanoma with involvement of lymph nodes or in patients with metastatic disease who have undergone complete resection</td>
<td>2017</td>
</tr>
<tr>
<td>Accelerated approval</td>
<td></td>
</tr>
<tr>
<td>MSI-H or dMMR metastatic colorectal after disease progression</td>
<td>2017</td>
</tr>
<tr>
<td>HCC</td>
<td>2017, 2nd line</td>
</tr>
<tr>
<td>Locally advanced or metastatic urothelial carcinoma after disease progression</td>
<td>2017</td>
</tr>
<tr>
<td>Metastatic SCLC with progression after platinum-based chemotherapy and at least one other line of therapy</td>
<td>2018</td>
</tr>
</tbody>
</table>
Nivolumab cont.

• Mechanism of Action: fully human immunoglobulin G4 (IgG4) monoclonal antibody that selectively inhibits programmed cell death-1 (PD-1) activity by binding to the PD-1 receptor to block the ligands PD-L1 and PD-L2 from binding; the negative PD-1 receptor signaling that regulates T-cell activation and proliferation is therefore disrupted

• Dosing:
  - 240 mg every 2 weeks
  - 480 mg every 4 weeks
  - 1 mg/kg every 3 weeks
  - 3 mg/kg every 2 or 3 weeks

• Warnings: complications of allogeneic HSCT after nivolumab

• ADRs: fatigue, rash, musculoskeletal pain, pruritus, diarrhea, nausea, asthenia, cough, dyspnea, constipation, decreased appetite, back pain, arthralgia, upper respiratory tract infection, pyrexia, headache, and abdominal pain

## Ipilimumab

<table>
<thead>
<tr>
<th>Indication</th>
<th>Year Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unresectable or metastatic melanoma</td>
<td>2011</td>
</tr>
<tr>
<td>Adjuvant treatment of certain patients with cutaneous melanoma</td>
<td>2015</td>
</tr>
</tbody>
</table>

- Monotherapy dosing: 3 mg/kg or 10 mg/kg over 90 mins every 3 weeks
- Binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands, CD80/CD86
- ADRs: fatigue, diarrhea, pruritus, rash, and colitis; common adverse reactions at the 10 mg/kg dose: nausea, vomiting, headache, weight loss, pyrexia, decreased appetite, and insomnia

---


## Nivolumab and ipilimumab

<table>
<thead>
<tr>
<th>Indication</th>
<th>Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unresectable or metastatic melanoma</td>
<td>2015</td>
</tr>
<tr>
<td>Intermediate or poor risk, previously untreated advanced renal cell carcinoma</td>
<td>2018</td>
</tr>
<tr>
<td>MSI-H or dMMR metastatic colorectal following treatment w/a fluoropyrimidine, oxaliplatin, irinotecan</td>
<td>2018</td>
</tr>
</tbody>
</table>

- **Dosing:**
  - Melanoma or CRC
    - 1 mg/kg followed by ipilimumab 3 mg/kg on the same day every 3 weeks for 4 doses, then 240 mg every 2 weeks or 480 mg every 4 weeks
  - RCC
    - 3 mg/kg followed by ipilimumab 1 mg/kg on the same day every 3 weeks for 4 doses, then 240 mg every 2 weeks or 480 mg every 4 weeks

- **ADRs:** fatigue, rash, diarrhea, nausea, pyrexia, musculoskeletal pain, pruritus, abdominal pain, vomiting, cough, arthralgia, decreased appetite, dyspnea, and upper respiratory infection

# Pembrolizumab

<table>
<thead>
<tr>
<th>Indication</th>
<th>Year Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unresectable or metastatic melanoma</td>
<td>2015, 1st line 2014, 2nd line</td>
</tr>
<tr>
<td>Recurrent/metastatic squamous cell carcinoma of the head and neck</td>
<td>2016</td>
</tr>
<tr>
<td>Metastatic NSCLC</td>
<td>2016, 1st line 2015-second line</td>
</tr>
<tr>
<td>Classical Hodgkin Lymphoma (cHL)</td>
<td>2017</td>
</tr>
<tr>
<td>Locally advanced or metastatic urothelial carcinoma</td>
<td>2017</td>
</tr>
<tr>
<td>Recurrent/metastatic cervical cancer, PD-L1 (CPS ≥1)</td>
<td>2018</td>
</tr>
<tr>
<td>Metastatic NSqNSCLC with no EGFR or ALK genomic tumor aberrations, in combination with pemetrexed and platinum</td>
<td>2018, 1st line</td>
</tr>
<tr>
<td>Require the use of an FDA-approved companion diagnostic test to determine PD-L1 levels in tumor tissue from patients with locally advanced or metastatic urothelial cancer who are cisplatin-ineligible</td>
<td>2018</td>
</tr>
<tr>
<td>In combination with carboplatin and either paclitaxel or nab-paclitaxel as first-line treatment of metastatic squamous non-small cell lung cancer (NSCLC)</td>
<td>2018, 1st line</td>
</tr>
<tr>
<td>Adjuvant treatment of patients with melanoma with involvement of lymph node(s) following complete resection</td>
<td>2019</td>
</tr>
<tr>
<td>First-line treatment of patients with stage III non-small cell lung cancer (NSCLC) who are not candidates for surgical resection or definitive chemoradiation or metastatic NSCLC. Patients’ tumors must have no EGFR or ALK genomic aberrations and express PD-L1 (Tumor Proportion Score [TPS] ≥1%) determined by an FDA-approved test</td>
<td>2019</td>
</tr>
</tbody>
</table>

Source: Keytruda (pembrolizumab) [prescribing information]. Whitehouse Station, NJ: Merck & Co Inc; June 2019.
Pembrolizumab cont.

### Accelerated approvals

<table>
<thead>
<tr>
<th>Indication</th>
<th>Approval Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>In combination with pemetrexed and carboplatin non-squamous NSCLC</td>
<td>2017, 1st line</td>
</tr>
<tr>
<td>MSI-H or dMMR solid tumors after disease progression</td>
<td>2017</td>
</tr>
<tr>
<td>Recurrent locally advanced/metastatic gastric/GEJ</td>
<td>2017, 1st line</td>
</tr>
<tr>
<td>Refractory primary mediastinal large B-cell lymphoma (PMBCL), or relapse</td>
<td>2018</td>
</tr>
<tr>
<td>after two or more prior lines of therapy</td>
<td></td>
</tr>
<tr>
<td>Hepatocellular carcinoma (HCC) patients who have been previously treated</td>
<td>2018</td>
</tr>
<tr>
<td>with sorafenib</td>
<td></td>
</tr>
<tr>
<td>Adult and pediatric patients with recurrent locally advanced or metastatic</td>
<td>2018</td>
</tr>
<tr>
<td>Merkel cell carcinoma (MCC)</td>
<td></td>
</tr>
</tbody>
</table>

- **Dosing:** 200 mg over 30 mins every 3 weeks
- **Warnings:** complications of allogeneic HSCT; treatment of patients with multiple myeloma with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials
- **ADRs:** fatigue, musculoskeletal pain, decreased appetite, pruritus, diarrhea, nausea, rash, pyrexia, cough, dyspnea, constipation, pain, and abdominal pain

Source: Keytruda (pembrolizumab) [prescribing information]. Whitehouse Station, NJ: Merck & Co Inc; June 2019.
# Atezolizumab

<table>
<thead>
<tr>
<th>Indication</th>
<th>Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Locally advanced or metastatic urothelial carcinoma after progression</td>
<td>2016</td>
</tr>
<tr>
<td>Metastatic NSCLC after disease progression</td>
<td>2016</td>
</tr>
<tr>
<td>Require to determine PD-L1 levels in tumor tissue from patients with locally advanced/metastatic urothelial cancer cisplatin-ineligible</td>
<td>2018</td>
</tr>
<tr>
<td>In combination with bevacizumab, paclitaxel, and carboplatin for the first-line treatment of patients with metastatic non-squamous, non-small cell lung cancer (NSq NSCLC) with no EGFR or ALK mutations</td>
<td>2018</td>
</tr>
<tr>
<td>PD-L1 positive unresectable locally advanced/metastatic triple-negative breast cancer</td>
<td>2019</td>
</tr>
<tr>
<td>In combination with carboplatin and etoposide, for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC)</td>
<td>2019</td>
</tr>
</tbody>
</table>

- *NEW Dosing Options*
  - 840 mg every 2 weeks
  - 1200 mg every 3 weeks
  - 1680 mg every 4 weeks

- ADRs: fatigue, decreased appetite, nausea, constipation, urinary tract infection, diarrhea, dyspnea, cough, and pyrexia

Source: Tecentriq (atezolizumab) [prescribing information]. South San Francisco, CA: Genentech Inc; May 2019.
Durvalumab

<table>
<thead>
<tr>
<th>Indication</th>
<th>Year Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accelerated approval</td>
<td></td>
</tr>
<tr>
<td>Locally advanced or metastatic urothelial carcinoma after disease progression</td>
<td>2017</td>
</tr>
<tr>
<td>Unresectable stage III NSCLC without progression following concurrent platinum-based chemotherapy &amp;RT</td>
<td>2018</td>
</tr>
</tbody>
</table>

- Dosing: 10 mg/kg every 2 weeks
- Administer over 60 minutes
- Advise females of reproductive potential to use effective contraception for at least 3 months after the last dose
- ADRs: Peripheral edema, fatigue, infection, musculoskeletal pain, constipation, decreased appetite, skin rash, nausea, dyspnea, lymphocytopenia, hypothyroidism, anemia, cough

Source: Imfinzi (durvalumab) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; July 2019
## Avelumab

<table>
<thead>
<tr>
<th>Indications</th>
<th>Year Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-line treatment, in combination with axitinib of patients with advanced renal cell carcinoma</td>
<td>2019</td>
</tr>
<tr>
<td>Accelerated approvals</td>
<td></td>
</tr>
<tr>
<td>Metastatic Merkel cell carcinoma (MCC)</td>
<td>2017</td>
</tr>
<tr>
<td>Locally advanced or metastatic urothelial carcinoma after disease progression</td>
<td>2017</td>
</tr>
</tbody>
</table>

- **Dosing**
  - Initially 10 mg/kg, NOW 800 mg once every 2 weeks
  - Infused over 60 minutes
  - In advanced RCC:
    - Use in combination with axitinib 5 mg twice daily
- **Premeds**
  - Acetaminophen and antihistamine prior to the first 4 infusions
- **ADRS**: fatigue, musculoskeletal pain, diarrhea, nausea, infusion-related reaction, rash, decreased appetite, and peripheral edema

Source: Bavencio (avelumab) [prescribing information]. Rockland, MA: EMD Serono Inc; May 2019.
Cemiplimab

<table>
<thead>
<tr>
<th>Indication</th>
<th>Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastatic cutaneous squamous cell carcinoma (CSCC) or locally advanced CSCC who are not candidates for curative surgery or curative radiation</td>
<td>2018</td>
</tr>
</tbody>
</table>

- Recombinant human monoclonal antibody that binds to PD-1 and blocks its interaction with PD-L1 and PD-L2
- Dose: 350 mg over 30 minutes every 3 weeks
- Warnings and precautions (similar to other IOs): Severe and Fatal Immune-Mediated Adverse Reaction; Infusion-Related Reactions; Embryo-Fetal Toxicity
- ADRs (incidence ≥ 20%): fatigue, rash and diarrhea

Source: Libtayo (cemiplimab-rwlc) [prescribing information]. Tarrytown, NY: Regeneron Pharmaceuticals, Inc; March 2019.
## Comparison of PD-1/PD-L1 Agents

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Atezolizumab</th>
<th>Avelumab</th>
<th>Cemiplimab</th>
<th>Durvalumab</th>
<th>Nivolumab</th>
<th>Pembrolizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indications</strong></td>
<td>Metastatic non-small cell lung cancer and locally advanced or metastatic urothelial carcinoma</td>
<td>First-line treatment, in combination with axitinib of patients with advanced renal cell carcinoma</td>
<td>Treatment of patients with metastatic cutaneous squamous cell carcinoma (CSCC) or locally advanced CSCC who are not candidates for curative surgery or curative radiation. <em><strong>Unique IO indication</strong></em></td>
<td>Unresectable, Stage III non-small cell lung cancer (NSCLC) whose carcinoma were not progressed following concurrent platinum-based chemotherapy and radiation therapy and locally advance or metastatic urothelial carcinoma. <em><strong>Unique IO indication</strong></em></td>
<td>Multiple indications</td>
<td>Multiple indications</td>
</tr>
<tr>
<td><strong>Mechanism of action</strong></td>
<td>PD-L1 inhibitor</td>
<td>PD-L1 inhibitor</td>
<td>PD-1 inhibitor</td>
<td>PD-L1 inhibitor</td>
<td>PD-1 inhibitor</td>
<td>PD-1 inhibitor</td>
</tr>
<tr>
<td><strong>Infusion time</strong></td>
<td>60 mins</td>
<td>60 mins</td>
<td>30 mins</td>
<td>60 mins</td>
<td>30 mins</td>
<td>30 mins</td>
</tr>
<tr>
<td><strong>Dosing frequency</strong></td>
<td>Every 3 weeks</td>
<td>Every 2 weeks</td>
<td>Every 3 weeks</td>
<td>Every 2 weeks</td>
<td>Every 2 weeks; every 3 weeks; every 4 weeks</td>
<td>Every 3 weeks</td>
</tr>
</tbody>
</table>

Source: Manufacturer PIs
Immune-Mediated Adverse Events (irAEs)

**Dermatological**
- Typically faintly erythematous, reticular and maculopapular rash
- Common irAE

**Endocrine**
- Often difficult diagnosis
- Non-specific (e.g. fatigue, nausea or headache)
- Thyroid function tests monitored frequently during treatment may diagnose issues before patients are symptomatic
- Hypothyroidism far more common than hyperthyroidism
- Typical management of hypothyroidism/hyperthyroidism
- Hypophysitis will likely require long-term levothyroxine and/or oral hydrocortisone supplementation

**Hepatic**
- Elevations in aspartate transaminase, alanine transaminase and occasionally bilirubin. Often asymptomatic
- Commonly discovered through frequent liver function test monitoring, which is a requirement of therapy
- **Important:** Rule out other causes before treating (e.g. viral/other drug-induced)

**Respiratory**
- Pneumonitis
- Relatively rare but potentially life threatening
- Shortness of breath, cough, chest infection
- Bronchoscopy may be required to rule out other infectious causes

**Gastrointestinal**
- Colitis
- Diarrhoea
- Abdominal pain
- Endoscopic/radiological evidence of inflammation
- Common irAE
- **Important:** Rule out other causes (e.g. infection)

- Mild symptoms can be managed with loperamide followed by oral or intravenous (IV) corticosteroids. More severe cases may require infliximab (6mg/kg)

Management of Toxicities

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Management of Immunotherapy-Related Toxicities

Version 2.2019 — April 8, 2019
NCCN.org

### Principles of Routine Monitoring

<table>
<thead>
<tr>
<th>Baseline Assessment</th>
<th>Monitoring Frequency</th>
<th>Evaluation for Abnormal Findings/Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical</strong></td>
<td>Clinical exam at each visit with adverse event (AE) symptom assessment</td>
<td>Follow-up testing based on findings, symptoms</td>
</tr>
<tr>
<td>Physical examination</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comprehensively patient history of any autoimmune/organ-specific disease, endocrinopathy, or infectious disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurologic examination</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bowel habits (typical frequency/consistency)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Imaging</strong></td>
<td>Periodic imaging as indicated</td>
<td>Follow-up testing as indicated based on imaging findings</td>
</tr>
<tr>
<td>CT imaging</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain MRI if indicated</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>General bloodwork</strong></td>
<td>Repeat every 2–3 weeks during immunotherapy, then in 6–12 weeks or as indicated</td>
<td>HbA1c for elevated glucose</td>
</tr>
<tr>
<td>CBC with differential</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comprehensive metabolic panel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infectious disease screening as indicated</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dermatologic</strong> (ICI_DERM-1)</td>
<td>Conduct/repeat as needed based on symptoms</td>
<td>Monitor affected BSA and lesion type; photographic documentation. Skin biopsy if indicated</td>
</tr>
<tr>
<td>Examination of skin and mucosa if history of immune-related skin disorder</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pancreatic</strong> (ICI_ENDO-1)</td>
<td>No routine monitoring needed if asymptomatic</td>
<td>Amylase, lipase, and consider abdominal imaging for suspected pancreatitis</td>
</tr>
<tr>
<td>Baseline testing is not required</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Thyroid</strong> (ICI_ENDO-2)</td>
<td>Every 4–6 weeks during immunotherapy, then follow-up every 12 weeks as indicated</td>
<td>Total T3 if abnormal thyroid function suspected. TPO antibodies if TSH is high, TRAbs if TSH is low</td>
</tr>
<tr>
<td>Thyroid-stimulating hormone (TSH), free thyroxine (T4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Adrenal/Pituitary</strong> (ICI_ENDO-3)</td>
<td>Luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone, adrenocorticotropic hormone (ACTH)</td>
<td></td>
</tr>
<tr>
<td>Adrenal: Serum cortisol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pituitary: TSH, free T4</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pulmonary</strong> (ICI_PULM-1)</td>
<td>Repeat oxygen saturation tests based on symptoms</td>
<td>Chest CT to evaluate for pneumonitis, biopsy if needed to exclude other causes</td>
</tr>
<tr>
<td>Oxygen saturation (resting and with ambulation)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary function tests (PFTs) for high-risk patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cardiovascular</strong> (ICI_CARDIO-1)</td>
<td>Consider periodic testing for those with abnormal baseline or symptoms</td>
<td>Individualized follow-up in consultation with cardiology as indicated</td>
</tr>
<tr>
<td>Individualized assessment in consultation with cardiology as indicated</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Musculoskeletal</strong> (ICI_MS-1)</td>
<td>No routine monitoring needed if asymptomatic</td>
<td>Consider rheumatology referral</td>
</tr>
<tr>
<td>Joint examination/functional assessment as needed for patients with pre-existing disease</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Infusion-Related Reactions

- **Mild (G1)**
  - Physical exam
  - Vital signs
  - Pulse oximetry
  - ECG (if chest pain or sustained tachycardia)
  - Treat per institutional guidelines
  - Consider hold or slow the rate of infusion
  - Continue immunotherapy
  - Consider premedication with acetaminophen and diphenhydramine with future infusions

- **Moderate (G2)**
  - Physical exam
  - Vital signs
  - Pulse oximetry
  - ECG (if chest pain or sustained tachycardia)
  - Treat per institutional guidelines
  - Consider hold or slow the rate of infusion
  - Continue immunotherapy
  - Consider premedication with acetaminophen and diphenhydramine with future infusions

- **Severe (G3–4)**
  - Physical exam
  - Vital signs
  - Pulse oximetry
  - ECG (if chest pain or sustained tachycardia)
  - Treat per institutional guidelines
  - Permanently discontinue immunotherapy
  - There are no data to guide the use of alternate immune checkpoint inhibitors

Maculopapular Rash

Mild (G1)" →
- Total body skin exam, including mucosa
- Assess for history of prior inflammatory dermatologic diseases
- Consider biopsy if unusual features

Moderate (G2)" →
- Topical emollient
- Oral antihistamine
- Treatment with moderate potency topical steroids to affected areas

Severe (G3–4)" →
- Hold immunotherapy"f
- Treatment with high potency topical steroids to affected areas
- Prednisone 0.5–1 mg/kg/day"g (increase dose up to 2 mg/kg/day if no improvement)
- Urgent dermatology consultation
- Consider inpatient care

"Continue immunotherapy
- Topical emollient
- Oral antihistamine
- Treatment with moderate potency topical steroids to affected areas

Pruritus

Mild (G1)
- Total body skin exam, including mucosa
- Assess for history of prior inflammatory dermatologic diseases

Moderate (G2)
- Continue immunotherapy with intensified antipruritic therapy
- Oral antihistamines
- Treatment with high potency topical steroids to affected areas
- Dermatology consultation

Severe (G3)
- Hold immunotherapy
- Oral antihistamines
- Prednisone/methylprednisolone 0.5–1 mg/kg/day
- Consider GABA agonists (gabapentin, pregabalin)
- Consider aprepitant or omalizumab for refractory cases
- Urgent dermatology consultation

Dermatitis and SJS

Gastrointestinal Effects

ADVERSE EVENT(S)

Mild (G1)\textsuperscript{b}
- Diarrhea
- Colitis\textsuperscript{a}

Moderate (G2)\textsuperscript{c}
- Stool evaluation to rule out infectious etiology\textsuperscript{e}
  - Nucleic acid amplification tests (NAATs) for GI pathogens/bacterial culture
  - C. difficile
  - Ova & parasites; molecular testing for Giardia and Cryptosporidium spp and E. histolytica; consider microsporidia, Cyclospora/isospora spp
  - Viral pathogens testing when available
  - Based on institutional availability, consider lactoferrin/calprotectin
  - Consider abdominal/pelvic CT with contrast
  - Consider GI consultation
  - Colonoscopy or flexible sigmoidoscopy ± esophagastroduodenoscopy (EGD) with biopsy

Severe (G3–4)\textsuperscript{d}

Consider holding immunotherapy\textsuperscript{g}
- Loperamide or diphenoxylate/atropine
- Hydration
- Close monitoring\textsuperscript{h}

Moderate (G2)\textsuperscript{c}
- Hold immunotherapy\textsuperscript{g}
- Prednisone/methylprednisolone\textsuperscript{f} 1 mg/kg/day\textsuperscript{j}
  - No response in 2–3 days:
    - Increase dose to 2 mg/kg/day\textsuperscript{j}
    - Consider adding infliximab\textsuperscript{k}

Severe (G3–4)\textsuperscript{d}
- G3: Discontinue anti-CTLA-4; consider resuming anti-PD-1/PD-L1 after resolution of toxicity\textsuperscript{g}
- G4: Permanently discontinue immunotherapy agent responsible for toxicity\textsuperscript{g}
- Consider inpatient care for provision of supportive care
- Intravenous (IV) methylprednisolone\textsuperscript{l} 2 mg/kg/day\textsuperscript{j}
  - No response in 2 days:
    - Continue steroids, consider adding infliximab\textsuperscript{k}
    - If infliximab-refractory, consider vedolizumab

Hepatic Effects

Pancreatic Effects

Assessment/Grading:
- Mild (G1)
  - Assess for signs/symptoms of pancreatitis
  - Abdominal CT with contrast
  - Consider MRCP if clinical suspicion of pancreatitis and no radiologic evidence on CT

- Moderate (G2)
  - Hold immunotherapy
  - Prednisone/methylprednisolone 0.5–1 mg/kg/day

- Severe (G3–4)
  - Permanently discontinue immunotherapy
  - Prednisone/methylprednisolone 1–2 mg/kg/day

Management:
- Consider gastroenterology referral
- Manage as per Elevation in amylase/lipase (asymptomatic) (ICI GI-4)

Endocrine Effects

Endocrine Effects

Pulmonary Effects

Renal Effects

RENAL ADVERSE EVENT(S)

Elevated serum creatinine/acute renal failure

ASSESSMENT/GRADING

Mild (G1) (Creatinine 1.5–2x above baseline; increase of ≥0.3 mg/dL)

• Limit/discontinue nephrotoxic medications and dose adjust to creatinine clearance
• Evaluate potential alternative etiologies (recent IV contrast, medications, fluid status, UTI)
• Spot urine protein/creatinine ratio

Moderate (G2) (Creatinine 2–3x above baseline)

• Hold immunotherapy
• Follow creatinine and urine protein every 3–7 days
• Nephrology consultation
• Start prednisone 0.5–1 mg/kg/day if other causes are ruled out
• For persistent G2 beyond 1 week, prednisone/methylprednisolone 1–2 mg/kg/day

Severe (G3) (Creatinine >3x baseline or >4.0 mg/dL)

• Life-threatening (G4) (Creatinine >6x baseline; dialysis indicated)

• Severe (G3) (Creatinine >3x baseline or >4.0 mg/dL)
• Consider inpatient care
• Prednisone/methylprednisolone 1–2 mg/kg/day
• Nephrology consultation
• Consider renal biopsy
• Consider adding one of the following if >G2 after 1 week of steroids:
  • Azathioprine
  • Cyclophosphamide (monthly)
  • Cyclosporine
  • Infliximab
  • Mycophenolate

MANAGEMENT

• Consider holding immunotherapy
• Follow creatinine and urine protein every 3–7 days

Ocular Effects

Peripheral Neuropathy

Cardiovascular Effects

CARDIOVASCULAR ADVERSE EVENT(S)

ASSESSMENT/GRADING

- Immediate cardiology consultation
- ECG
- Telemetry monitoring
- Cardiac biomarkers (creatine kinase and troponin)
- Inflammatory biomarkers
  - ESR
  - CRP
  - WBC count
- Cardiac MRI
- Evaluate for other causes:
  - Viral titers
  - Echocardiogram
  - Biopsy if severe symptoms

Severe (G3)\(^c\)

MANAGEMENT\(^e\)

- Permanently discontinue immunotherapy\(^f\)
- Consider methylprednisolone pulse dosing 1 g/day for 3–5 days
  - Treat until cardiac function returns to baseline, then taper over 4–6 weeks
  - Inpatient care

Life-threatening (G4)\(^d\)

- Permanently discontinue immunotherapy\(^f\)
- Consider methylprednisolone pulse dosing 1 g/day for 3–5 days
  - Treat until cardiac function returns to baseline, then taper over 4–6 weeks
- If no improvement within 24 hours on steroids, consider adding anti-thymocyte globulin (ATG). May also consider adding infliximab.
- Inpatient care

Musculoskeletal Effects

Case #1

1. XY is a 60 y/o female with Stage IV TNBC and showed PD-L1 > 1%. She was recently started on atezolizumab 840 mg Days 1 and 15 alongside nab-PACLitaxel 100 mg/m2 Days 1, 8, and 15 every 28 days.

What side effects concern you and how would you monitor?

   I. Increases in blood pressure; monitor BP at home and before infusion
   II. Hepatotoxicity; monitor LFTs prior to each dose
   III. Extravasation; monitor injection site during administration
   IV. Hypothyroidism or thyrotoxicosis; monitor TSH on Day 1 of each cycle
   V. II and IV
Case #1

1. XY is a 60 y/o female with Stage IV TNBC and showed PD-L1 > 1%. She was recently started on atezolizumab 840 mg Days 1 and 15 alongside nab-PACLitaxel 100 mg/m² Days 1, 8, and 15 every 28 days.

What side effects concern you and how would you monitor?

I. Increases in blood pressure; monitor BP at home and before infusion
II. Hepatotoxicity; monitor LFTs prior to each dose
III. Extravasation; monitor injection site during administration
IV. Hypothyroidism or thyrotoxicosis; monitor TSH on Day 1 of each cycle
V. II and IV
Cancer Vaccines

Source: https://clincancerres.aacrjournals.org/content/21/5/976
Sipuleucel-T

• Autologous cellular immunotherapy indicated for the treatment of asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer

• Designed to induce an immune response targeted against PAP, an antigen expressed in most prostate cancers

• Manufactured in several steps:
  - Leukapheres
  - Introduction of PAP-GM-CSF
    • Prostatic acid phosphatase (PAP)
    • Granulocyte-macrophage colony-stimulating factor (GM-CSF)

• Each dose contains a minimum of 50 million autologous CD54+ cells activated with PAP-GM-CSF

• Administered intravenously in a three-dose schedule at approximately two week intervals

• Each dose is preceded by the leukapheresis procedure approximately three days prior to the scheduled treatment

• ADRs: acute infusion reactions, chills, fatigue, fever, back pain, nausea, joint ache, and headache

Source: https://www.fda.gov/media/78511/download
https://www.provenge.com/Support/Your-PROVENGE-Experience
**Talimogene laherparepvec**

- Local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery

- **Genetically modified herpes simplex virus type 1** used to replicate within tumors and to produce the immune stimulatory protein GM-CSF causing tumor lysis

- Acyclovir or other antiviral agents may lessen its effectiveness

- Administer by injection into cutaneous, subcutaneous, and/or nodal lesions that are visible, palpable, or detectable by ultrasound guidance

- ADRs: fatigue, chills, pyrexia, nausea, influenza-like illness, and injection site pain

- Patients may also develop herpetic infections and should follow standard hygienic practices to prevent viral transmission

- Healthcare providers who are immunocompromised or pregnant should not prepare or administer and should not come into direct contact with injection sites, dressings, or body fluids of treated patients

Source: [https://www.fda.gov/media/94129/download](https://www.fda.gov/media/94129/download)
Cancer Preventing Vaccines

- Hepatitis B vaccines
  - Prevent liver cancer

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Age group/conditions</th>
<th>Recommended schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Single-agent</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recombivax HB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pediatric/adolescent formulation</td>
<td>18-19 years</td>
<td>0,1, and 6 months</td>
</tr>
<tr>
<td>Adult formulation</td>
<td>≥ 20 y/o</td>
<td>0,1, and 6 months</td>
</tr>
<tr>
<td>Dialysis formulation</td>
<td>≥ 20 y/o receiving dialysis</td>
<td>0,1, and 6 months</td>
</tr>
<tr>
<td>Engerix-B</td>
<td>18 through 19 years</td>
<td>0,1, and 6 months</td>
</tr>
<tr>
<td>Adult formulation</td>
<td>≥ 20 y/o</td>
<td>0,1, and 6 months</td>
</tr>
<tr>
<td>Dialysis formulation</td>
<td>≥ 20 y/o receiving hemodialysis</td>
<td>0,1,2, and 6 months</td>
</tr>
<tr>
<td>Heplisav-B</td>
<td>≥ 18 y/o</td>
<td>0 and 1 months</td>
</tr>
<tr>
<td><strong>Combination Vaccine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Twinrix (HepB-HepA vaccine)</td>
<td>≥ 18 y/o</td>
<td>Standard: 0,1, and 6 months; Accelerated: 0,7, and 21 to 30 days and 12 months</td>
</tr>
</tbody>
</table>

Source: [https://www.uptodate.com/contents/image?imageKey=ID%2F117603&topicKey=ID%2F3641&search=hepatitis%20b%20vaccine&rank=2~146&source=see_link](https://www.uptodate.com/contents/image?imageKey=ID%2F117603&topicKey=ID%2F3641&search=hepatitis%20b%20vaccine&rank=2~146&source=see_link)
Cancer Preventing Vaccines

• HPV vaccine
  - Prevents cervical and head & neck cancers
  - Now approved in patients up to 45 y/o

• ACIP/CDC Recommendations:
  - **Children and adults aged 9 through 26 years**
    ▪ HPV vaccination is routinely recommended at age 11 or 12 years
    ▪ Catch-up HPV vaccination recommended for persons through age 26 years
  - **Adults aged >26 years**
    ▪ Catch-up HPV vaccination is not recommended for all adults aged >26 years
    ▪ Shared clinical decision-making regarding HPV vaccination is recommended for some adults aged 27 through 45 years who are not adequately vaccinated
    ▪ HPV vaccines are not licensed for use in adults aged >45 years
  - **Immunocompromising conditions through age 26 years**
    ▪ 3-dose series HPV vaccine at 0, 1–2, 6 months

Source: https://www.cdc.gov/mmwr/volumes/68/wr/mm6832a3.htm#B1_down
https://www.cdc.gov/vaccines/schedules/hcp/imz/adult.html
2. BW is a 70 y/o male recently with an unresectable nodal melanoma lesion recurrent after initial surgery. He will be started on talimogene laherparepvec.

What precautions would you recommend BW to take while receiving this therapy?

I. May experience influenza-like illness, and injection site pain
II. Could develop herpetic infections and should follow standard hygienic practices to prevent viral transmission
III. Will need to adjust dose in renal or liver dysfunction
IV. This therapy is localized and therefore not associated with major toxicity
V. I and II

Source: Case #2
2. BW is a 70 y/o male recently with an unresectable nodal melanoma lesion recurrent after initial surgery. He will be started on talimogene laherparepvec. What precautions would you recommend BW to take while receiving this therapy?
   I. May experience influenza-like illness, and injection site pain
   II. Could develop herpetic infections and should follow standard hygienic practices to prevent viral transmission
   III. Will need to adjust dose in renal or liver dysfunction
   IV. This therapy is localized and therefore not associated with major toxicity
   V. I and II
CAR-T cell Therapy

Leukapheresis

Cell infusion

Clinical (Good Manufacturing Practice) cell-manufacturing facility

Activate T cells

Engineer T cells with virus encoding CAR

Expand CAR T cells

Harvest CAR T cells

Source: https://illustrated-glossary.nejm.org/index.html
Mechanism of Action

T cells are genetically engineered to express a CAR

Agent Comparison

**Mechanism:**
Anti CD-19

**Indication:**
Large B-cell Lymphoma

**Dosing:**
$2 \times 10^6$ CAR-positive viable T cells per kg body weight

---

**Mechanism:**
Anti CD-19

**Indications:**
ALL and Diffuse Large B-cell Lymphoma

**Dosing:**
ALL<br>≥ 25 y/o - 0.2 to 5 x $10^6$ T cells per kg body weight<br><25 y/o and >50 kg - 0.1 to 2.5 x $10^8$ T cells<br>DLBCL - 0.6 to 6 x $10^8$ T cells

---

Toxicities

Neurologic:
- Headaches
- Changes in level of consciousness
- Delirium
- Aphasia
- Apraxia
- Ataxia
- Hallucinations
- Tremor
- Dysmetria
- Myoclonus
- Facial nerve palsy
- Seizures

Hepatic:
- Transaminitis
- Hyperbilirubinemia

Hematologic:
- Anemia
- Thrombocytopenia
- Neutropenia
- Febrile neutropenia
- Lymphopenia
- B-cell aplasia
- Prolonged prothrombin time
- Prolonged activated partial thromboplastin time
- Elevated D-Dimer
- Hypofibrinogenemia
- Disseminated intravascular coagulation
- Hemophagocytic lymphohistiocytosis

Constitutional:
- Fevers
- Rigors
- Malaise
- Fatigue
- Anorexia
- Arthralgias

Cardiovascular:
- Tachycardia
- Widened pulse pressure
- Hypotension
- Arrhythmias
- Decreased left ventricular ejection fraction
- Troponinemia
- QT prolongation

Pulmonary:
- Tachypnea
- Hypoxia

Renal:
- Acute kidney injury
- Hyponatremia
- Hypokalemia
- Hypophosphatemia
- Tumor lysis syndrome

Gastrointestinal:
- Nausea
- Emesis
- Diarrhea

Musculoskeletal:
- Myalgias
- Elevated creatine kinase
- Weakness

Source: http://www.bloodjournal.org/content/127/26/3321?sso-checked=true
## Toxicities

<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Axicabtagene ciloleucel</strong>&lt;sup&gt;a&lt;/sup&gt; and <strong>tisagenlecleucel</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>CRS (CART-3)</strong></td>
</tr>
</tbody>
</table>
| • Typical time to onset: 2–3 days  
• Typical duration: 7–8 days  
• Manifestation may include fever, hypotension, tachycardia, hypoxia, and chills. CRS may be associated with cardiac, hepatic, and/or renal dysfunction.  
• Serious events may include atrial fibrillation and ventricular tachycardia, cardiac arrest, cardiac failure, renal insufficiency, capillary leak syndrome, hypotension, hypoxia, and hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS). |
| **Neurologic Toxicity (CART-4)** |
| • Typical time to onset: 4–10 days  
• Typical duration: 14–17 days  
• The most common neurologic toxicities include encephalopathy, headache, tremor, dizziness, aphasia, delirium, insomnia, anxiety, and autonomic neuropathy. Agitation, hyperactivity, or signs of psychosis can also occur.  
• Serious events including seizures, as well as fatal and serious cases of cerebral edema, have occurred. |
| **Hemophagocytic Lymphohistiocytosis/Macrophage-Activation Syndrome (HLH/MAS) During CRS (CART-3)** |
| • Criteria for considering HLH/MAS:  
  ◇ Rapidly rising and high ferritin (>5,000 ng/mL) with cytopenias in the context of CRS, especially if accompanied by any of the following:  
    ◇ Grade ≥ 3 increase in serum bilirubin, AST, ALT  
    ◇ Grade ≥ 3 oliguria or increase in serum creatinine  
    ◇ Grade ≥ 3 pulmonary edema  
  ◇ Presence of hemophagocytosis in bone marrow or organs based on histopathologic assessment of cell morphology and/or CD68 IHC. |
| **Miscellaneous** |
| • Patients may exhibit cytopenias for weeks to months following lymphodepleting chemotherapy and CAR T-cell therapy infusion.  
• Long-term B-cell aplasia and hypogammaglobulinemia can occur in patients with a complete remission after CAR T-cell therapy infusion. |
## Management of Toxicities

<table>
<thead>
<tr>
<th>CRS Grade</th>
<th>Anti-IL-6 Therapy</th>
<th>Corticosteroids&lt;sup&gt;11,11&lt;/sup&gt;</th>
<th>Additional Supportive Care</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade 1</strong>&lt;br&gt;Fever (≥ 38°C)</td>
<td>For prolonged CRS (&gt;3 days) in patients with significant symptoms and/or comorbidities, consider tocilizumab as per Grade 2</td>
<td>N/A</td>
<td>- Empiric broad-spectrum antibiotics, consider granulocyte colony-stimulating factor (G-CSF) if neutropenic&lt;br&gt;- Maintenance IV fluids for hydration&lt;br&gt;- Symptomatic management of organ toxicities</td>
</tr>
<tr>
<td><strong>Grade 2</strong>&lt;br&gt;Fever with hypotension not requiring vaspressors and/or hypoxia requiring low-flow nasal cannula&lt;sup&gt;9&lt;/sup&gt; or blow-by</td>
<td>Tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg/dose)&lt;sup&gt;8&lt;/sup&gt;. Repeat in 3 hours if no improvement; no more than 3 doses in 24 hours, with a maximum of 4 doses total</td>
<td>For persistent refractory hypotension after 1–2 doses of anti-IL-6 therapy:&lt;br&gt;Dexamethasone 10 mg IV every 6 hours (or equivalent)&lt;sup&gt;2&lt;/sup&gt;</td>
<td>- IV fluid bolus as needed&lt;br&gt;- For persistent refractory hypotension after two fluid boluses and anti-IL-6 therapy: Start vaspressors, consider transfer to intensive care unit (ICU), consider echocardiogram, and initiate other methods of hemodynamic monitoring&lt;br&gt;- Manage per Grade 3 if no improvement within 24 hours after starting anti-IL-6 therapy&lt;br&gt;- Symptomatic management of organ toxicities</td>
</tr>
<tr>
<td><strong>Grade 3</strong>&lt;br&gt;Fever with hypotension requiring a vasopressor with or without vasopressin and/or hypoxia requiring high-flow cannula&lt;sup&gt;9&lt;/sup&gt;, face mask, nonbreather mask, or Venturi mask.</td>
<td>Anti-IL-6 therapy as per Grade 2&lt;sup&gt;2&lt;/sup&gt; if maximum dose not reached within 24-hour period</td>
<td>Dexamethasone 10 mg IV every 6 hours (or equivalent)&lt;sup&gt;2&lt;/sup&gt;. If refractory, manage as grade 4</td>
<td>- Transfer to ICU, obtain echocardiogram, and perform hemodynamic monitoring&lt;br&gt;- Supplemental oxygen&lt;br&gt;- IV fluid bolus and vasopressors as needed&lt;br&gt;- Symptomatic management of organ toxicities</td>
</tr>
<tr>
<td><strong>Grade 4</strong>&lt;br&gt;Fever with hypotension requiring multiple vasopressors (excluding vasopressin) and/or hypoxia requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation).</td>
<td>Anti-IL-6 therapy as per Grade 2&lt;sup&gt;2&lt;/sup&gt; if maximum dose not reached within 24-hour period</td>
<td>Dexamethasone 10 mg IV every 6 hours (or equivalent)&lt;sup&gt;2&lt;/sup&gt;. If refractory, consider methylprednisolone 1000 mg/day IV&lt;sup&gt;k&lt;/sup&gt;</td>
<td>- ICU care and hemodynamic monitoring&lt;br&gt;- Mechanical ventilation as needed&lt;br&gt;- IV fluid bolus and vasopressors as needed&lt;br&gt;- Symptomatic management of organ toxicities</td>
</tr>
</tbody>
</table>

## Management of Toxicities

<table>
<thead>
<tr>
<th>Treatment by Grade</th>
<th>No Concurrent CRS</th>
<th>Additional Therapy if Concurrent CRS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade 1</strong></td>
<td>• Supportive care</td>
<td>Tocilizumab 8 mg/kg IV over 1 h (not to exceed 800 mg/dose)</td>
</tr>
</tbody>
</table>
| **Grade 2p**       | • Supportive care  
• Dexamethasone 10 mg IV x 1. Can repeat every 6 hours or methylprednisolone 1 mg/kg IV every 12 h if symptoms worsen. | Anti-IL-6 therapy as per Grade 1q  
Consider transferring patient to ICU if neurotoxicity associated with grade ≥2 CRS |
| **Grade 3p**       | • ICU care is recommended.  
• Dexamethasone 10 mg IV every 6 h or methylprednisolone, 1 mg/kg IV every 12 h  
• Consider repeat neuroimaging (CT or MRI) every 2–3 days if patient has persistent grade ≥3 neurotoxicity. | Anti-IL-6 therapy as per Grade 1q                                                                 |
| **Grade 4p**       | • ICU care, consider mechanical ventilation for airway protection.  
• High-dose corticosteroids1,k  
• Consider repeat neuroimaging (CT or MRI) every 2–3 days if patient has persistent grade ≥3 neurotoxicity.  
• Treat convulsive status epilepticus per institutional guidelines. | Anti-IL-6 therapy as per Grade 1q                                                                   |

Monoclonal antibodies

- Alemtuzumab
- Bevacizumab
- Blinatumumab
- Cetuximab
- Daratumumab
- Elotuzumab
- Gemtuzumab
- Ibritumomab tiuxetan w Y-90
- Obinutuzumab
- Ofatumumab
- Panitumumab
- Pertuzumab
- Rituximab
- Trastuzumab

Antibodies designed to attach to specific targets found on cancer cells.
These mark cancer cells so that they will be better seen and destroyed by the immune system.

CD20 Monoclonal Antibodies

- **Rituximab**
  - Treatment of CLL, NHL, RA, GPA (Wegener’s Granulomatosis), MPA, PV

- **Rituximab/hyaluronidase (Rituxan Hycela)**
  - **ONLY** given **subcutaneously in the abdomen**
  - Monitor for severe skin and mouth reactions
  - ADRS: Infusion site reactions (dose dependent), hypersensitivity, fatigue, infections, alopecia, tumor lysis syndrome, renal toxicity, nausea/vomiting, erythema, constipation

- **Obinutuzumab**
  - Treatment of chronic lymphocytic leukemia, treatment of follicular lymphoma
  - ADRS: Hepatitis B virus reactivation, tumor lysis syndrome, infusion reactions, neutropenia, thrombocytopenia, anemia, pyrexia, cough, nausea, diarrhea, fatigue, cough, constipation, vomiting, upper respiratory tract infection, decreased appetite, arthralgia, sinusitis, asthenia and urinary tract infection

- **Ofatumumab**
  - Treatment of chronic lymphocytic leukemia
  - ADRs: infusion reactions, neutropenia, leukopenia, pneumonia, pyrexia, cough, diarrhea, anemia, fatigue, dyspnea, rash, nausea, bronchitis, and upper respiratory tract infections

Screen for Hepatitis B prior to starting therapies
Hepatitis B virus (HBV) reactivation → Fulminant hepatitis, hepatic failure, and death

VEGF Monoclonal Antibodies

• Bevacizumab and bevacizumab-awwb

• Indications: Metastatic colorectal cancer; unresectable, locally advanced, recurrent or metastatic non-squamous non-small cell lung cancer; recurrent glioblastoma in adults; metastatic renal cell carcinoma; persistent, recurrent, or metastatic cervical cancer; epithelial ovarian, fallopian tube, or primary peritoneal cancer

• Mechanism of Action: Binds VEGF and prevents the interaction of VEGF to its receptors (Flt-1 and KDR) on the surface of endothelial cells

• Warnings:
  • Gastrointestinal Perforations and Fistula
  • Surgery and Wound Healing Complications
  • Hemorrhage
  • Arterial Thromboembolic Events (ATE)
  • Venous Thromboembolic Events (VTE)
  • Hypertension
  • Posterior Reversible Encephalopathy Syndrome (PRES)
  • Renal Injury and Proteinuria
  • Ovarian Failure
  • Congestive Heart Failure (CHF)

• ADRs: epistaxis, headache, hypertension, rhinitis, proteinuria, taste alteration, dry skin, rectal hemorrhage, lacrimation disorder, back pain and exfoliative dermatitis
# EGFR Monoclonal Antibodies

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Cetuximab</th>
<th>Panitumumab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indications</strong></td>
<td>SCCHN; and K-Ras Wild-type, EGFR-expressing CRC</td>
<td>Metastatic CRC in Ras Wild-type patients</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>400 mg/m(^2) followed by 250 mg/m(^2) weekly; OR 500 mg/m(^2) every 14 days</td>
<td>6 mg/kg every 14 days</td>
</tr>
<tr>
<td><strong>ADRs</strong></td>
<td>The most common adverse reactions (incidence ≥25%): cutaneous adverse reactions (including rash, pruritus, and nail changes), headache, diarrhea, and infection.</td>
<td>Most common adverse reactions (≥20%) of Vectibix as monotherapy are skin rash with variable presentations, paronychia, fatigue, nausea, and diarrhea.</td>
</tr>
<tr>
<td><strong>Rate</strong></td>
<td>400 or 500 mg/m(^2) dosing: 2 hours 250 mg/m(^2) dosing: 1 hour</td>
<td>≤1000 mg: 60 minutes &gt;1000 mg: 90 minutes</td>
</tr>
</tbody>
</table>

Erbitux (cetuximab) [prescribing information]. Indianapolis, IN: Eli Lilly and Company; April 2019.  
HER2 Monoclonal Antibodies

• Trastuzumab and trastuzumab-anns
  - Indications: treatment of HER2-overexpressing breast cancer, and HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma
  - Mechanism of action: inhibit the proliferation of human tumor cells that overexpress HER2
  - Monitor ejection fraction (EF) via ECHO or MUGA study
  - Warning: exacerbation of chemotherapy-induced neutropenia
  - ADRs: headache, diarrhea, nausea, and chills. Fever, infection, congestive heart failure, insomnia, cough, and rash. Neutropenia, fatigue, anemia, stomatitis, weight loss, upper respiratory tract infections, thrombocytopenia, mucosal inflammation, nasopharyngitis, and dysgeusia

• Pertuzumab
  • Indications: treatment of HER2-overexpressing breast cancer
  • Mechanism of action: targets the extracellular HER2 dimerization domain; binds to a different HER2 epitope than trastuzumab so that when pertuzumab is combined with trastuzumab, a more complete inhibition of HER2 signaling occurs
  • ADRs: diarrhea, alopecia, neutropenia, nausea, fatigue, rash, asthenia, constipation, fatigue, mucosal inflammation, vomiting, myalgia, anemia, and peripheral neuropathy
Other Monoclonal Antibodies

- **Blinatumomab → Anti-CD19/CD3**
  - Treatment of B-cell precursor acute lymphoblastic leukemia (ALL)
  - Mechanism of Action: bispecific CD19-directed CD3 T-cell engager (BiTE) that binds to CD19 expressed on the surface of cells of B-lineage origin and CD3 expressed on the surface of T cells
  - **BLACK BOX WARNING:** Neurotoxicity; Cytokine Release Syndrome
  - **ADRs:** infections (bacterial and pathogen unspecified), pyrexia, headache, infusion-related reactions, anemia, febrile neutropenia, thrombocytopenia, and neutropenia

- **Daratumumab → Anti-CD38**
  - Treatment for Multiple Myeloma
  - To prevent herpes zoster reactivation, initiate antiviral prophylaxis within 1 week after starting daratumumab and continue for 3 months following completion of treatment
  - Dosed on actual body weight
  - If cycle 1, ensure that type and screen is ordered with request for phenotype prior to administration
  - May result in a positive indirect antiglobulin test (indirect Coombs test)
  - **ADRs:** neutropenia, thrombocytopenia, edema, peripheral neuropathy

Darzalex (daratumumab) [prescribing information]. Horsham, PA: Janssen Biotech Inc; June 2019.
Other Monoclonal Antibodies

• Elotuzumab → Anti-SLAMF7
  - Indicated in combination for the treatment of multiple myeloma after one to three prior therapies
  - ADRS: Decreased or increase heart rate, fatigue, peripheral neuropathy, hyperglycemia, hypocalcemia, diarrhea, constipation, cough, fever

• Gemtuzumab → Anti-CD33
  - Treatment of newly-diagnosed CD33-positive acute myeloid leukemia (AML) in adults, and treatment of relapsed or refractory CD33-positive AML in adults and in pediatric patients 2 years and older
  - ADRs: tumor lysis syndrome, QT prolongation, hemorrhage, infection, fever, nausea, vomiting, constipation, headache, increased AST, increased ALT, rash, and mucositis

Mylotarg (gemtuzumab ozogamicin) [prescribing information]. Philadelphia, PA: Wyeth Pharmaceuticals; April 2018.
WW is a 67 y/o male that was recently diagnosed with advanced non squamous NSCLC w PD-L1 expression ≥ 1% and EGFR/ALK negative. His oncology team started him on atezolizumab 1,200 mg, bevacizumab 15 mg/kg, PACLitaxel 200 mg/m2, and CARBOplatin AUC 6 every 21 days for 4 cycles.

What side effects concern you and how would you monitor?

I. Increases in blood pressure; monitor BP at home and before infusion
II. Hepatotoxicity; monitor LFTs prior to each dose
III. Extravasation; monitor injection site during administration
IV. Hypothyroidism or thyrotoxicosis; monitor TSH on Day 1 of each cycle
V. All of the above
1. WW is a 67 y/o male that was recently diagnosed with advanced non squamous NSCLC w PD-L1 expression ≥ 1% and EGFR/ALK negative. His oncology team started him on atezolizumab 1,200 mg, bevacizumab 15 mg/kg, PACLitaxel 200 mg/m2, and CARBOplatin AUC 6 every 21 days for 4 cycles.

What side effects concern you and how would you monitor?

I. Increases in blood pressure; monitor BP at home and before infusion
II. Hepatotoxicity; monitor LFTs prior to each dose
III. Extravasation; monitor injection site during administration
IV. Hypothyroidism or thyrotoxicosis; monitor TSH on Day 1 of each cycle
V. **All of the above**
Patient Resources

https://www.sitcancer.org/connectedold/p/patient

https://www.accc-cancer.org/home/learn/immunotherapy/resource-detail/More-Information-Please-Online-Patient-Resources-in-Immuno-Oncology

https://www.cancerresearch.org/patients/free-resources-support-answers
Questions?