Pharmacology: Immunotherapies

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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

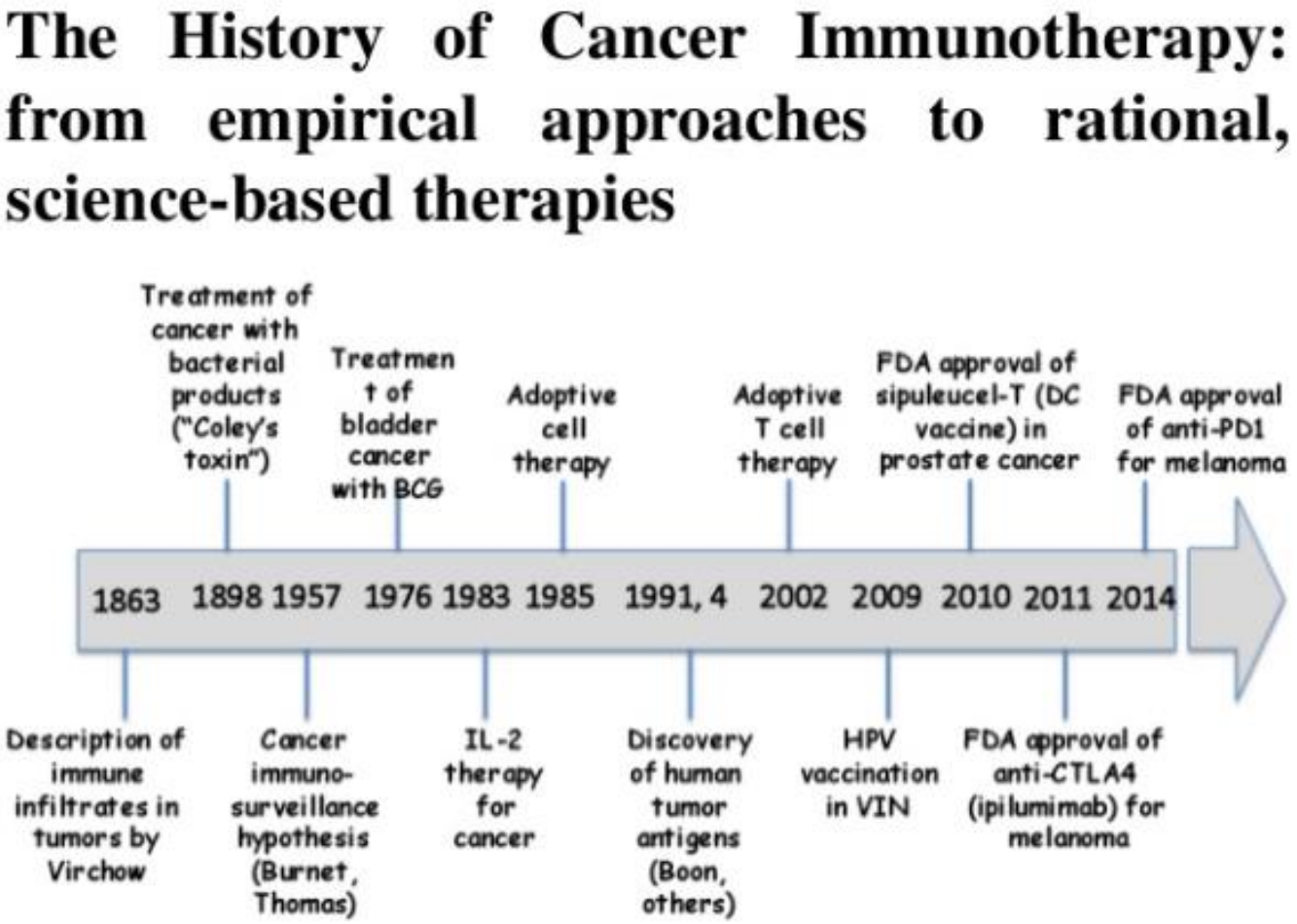
Source:

Agenda

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

Immunotherapy

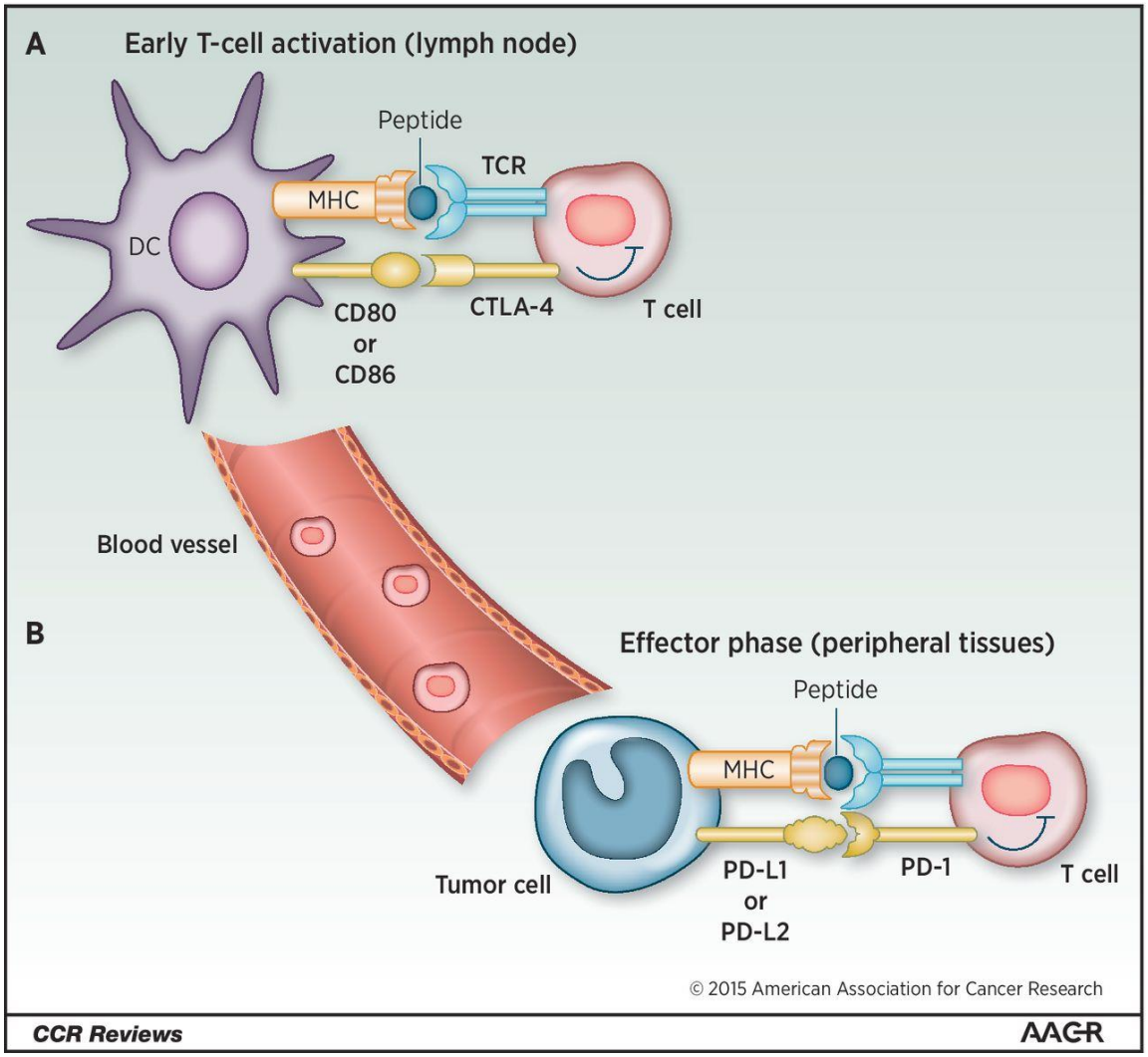
- Treatment that uses the body's own immune system to help fight cancer



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

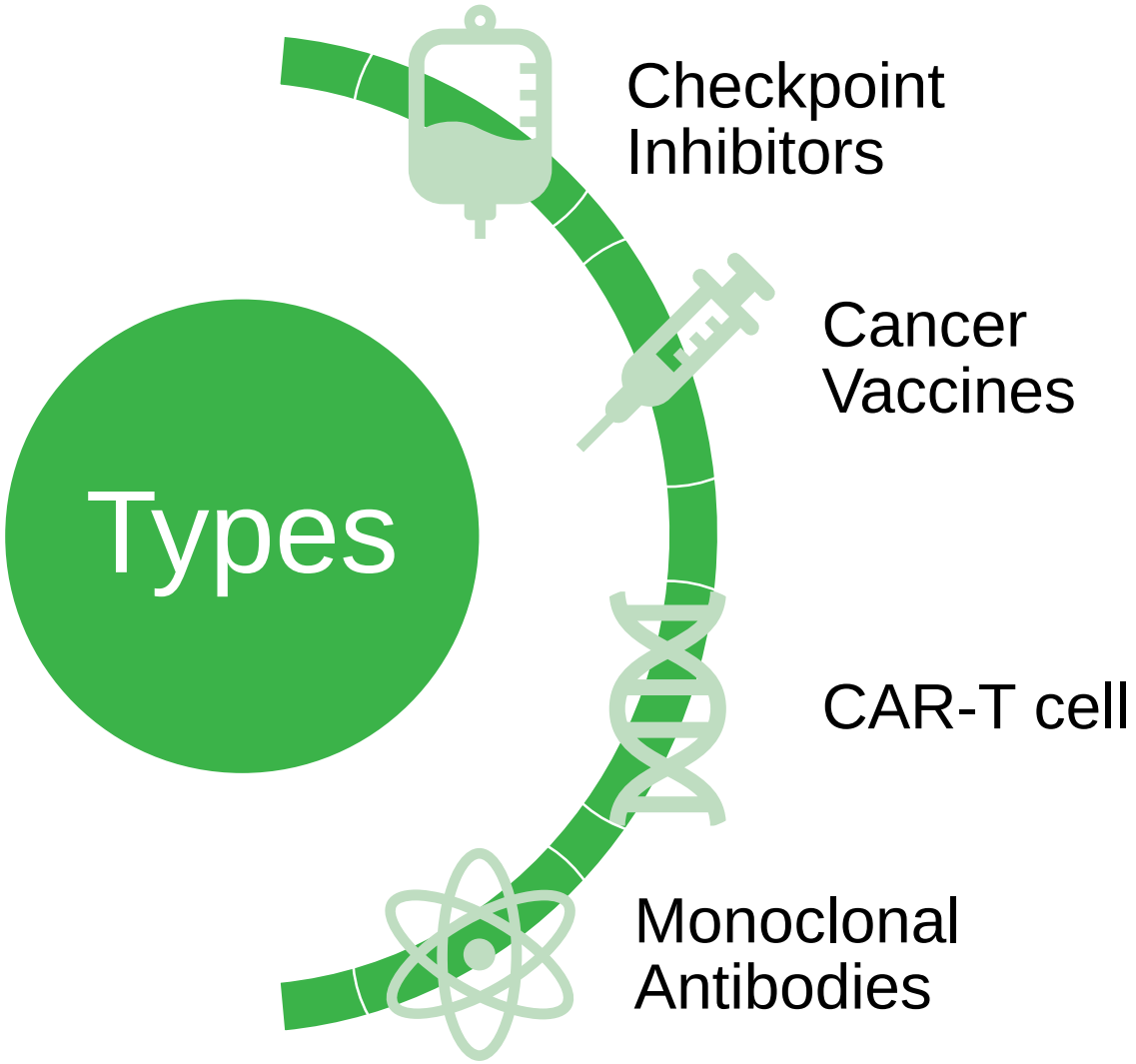
Mechanism of Action

- 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)

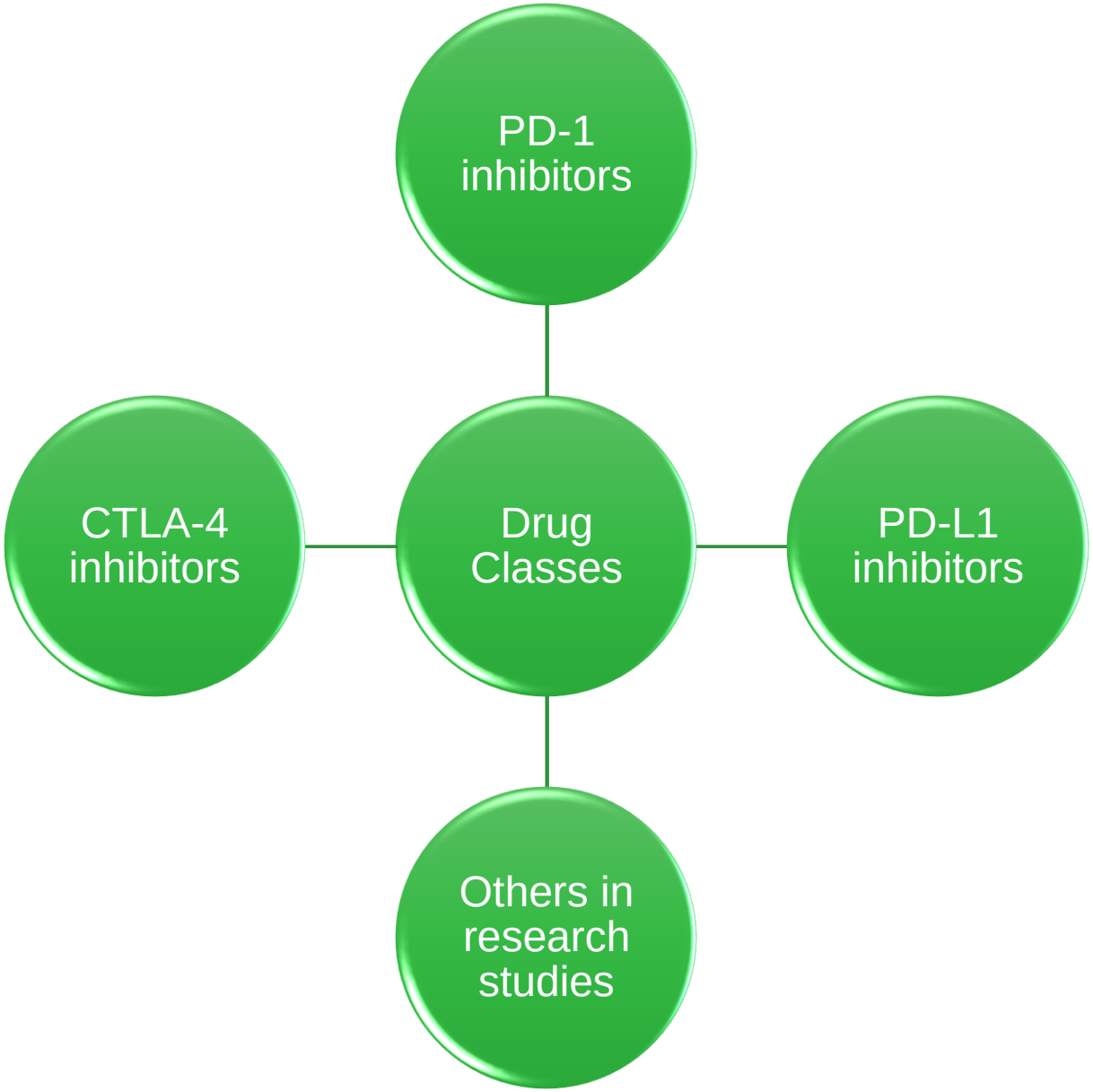


Source: https://clincancerres.aacrjournals.org/content/21/5/976

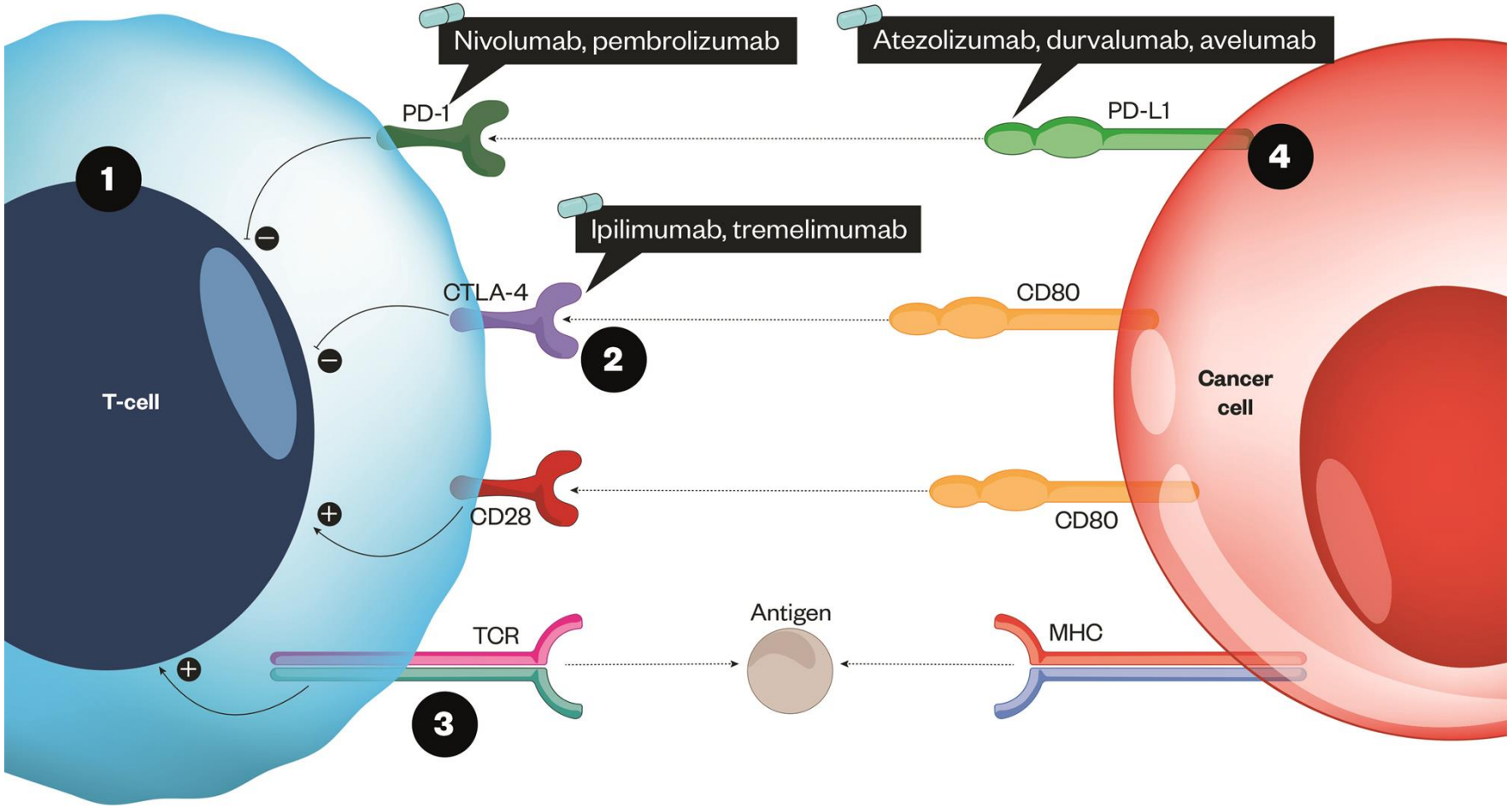
Immunotherapy



Checkpoint Inhibitors



Mechanism of Action



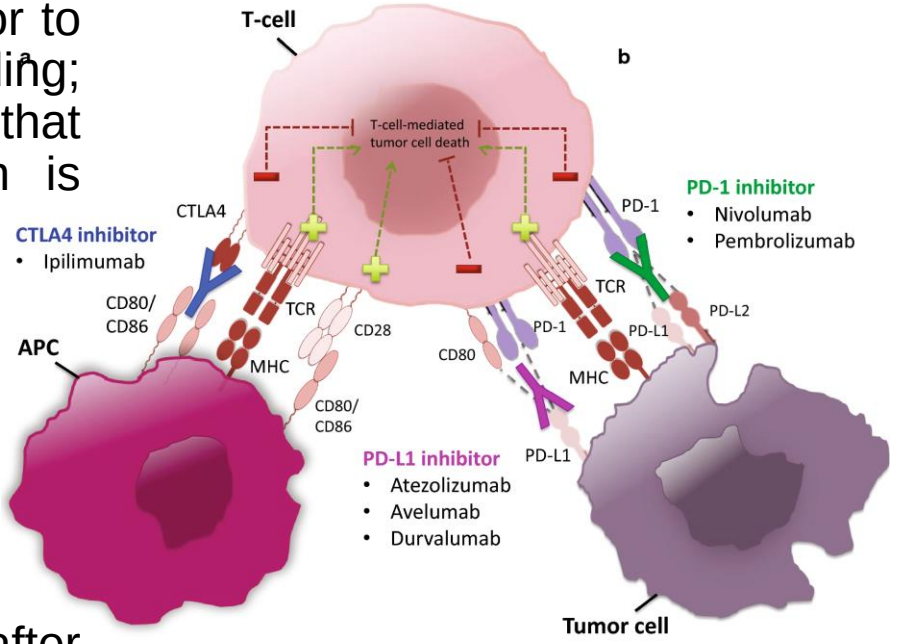
Source: https://www.pharmaceutical-journal.com/learning/learning-article/immune-checkpoint-inhibitors-in-cancer-pharmacology-and-toxicities/20204831.article?firstPass=false

Nivolumab

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

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

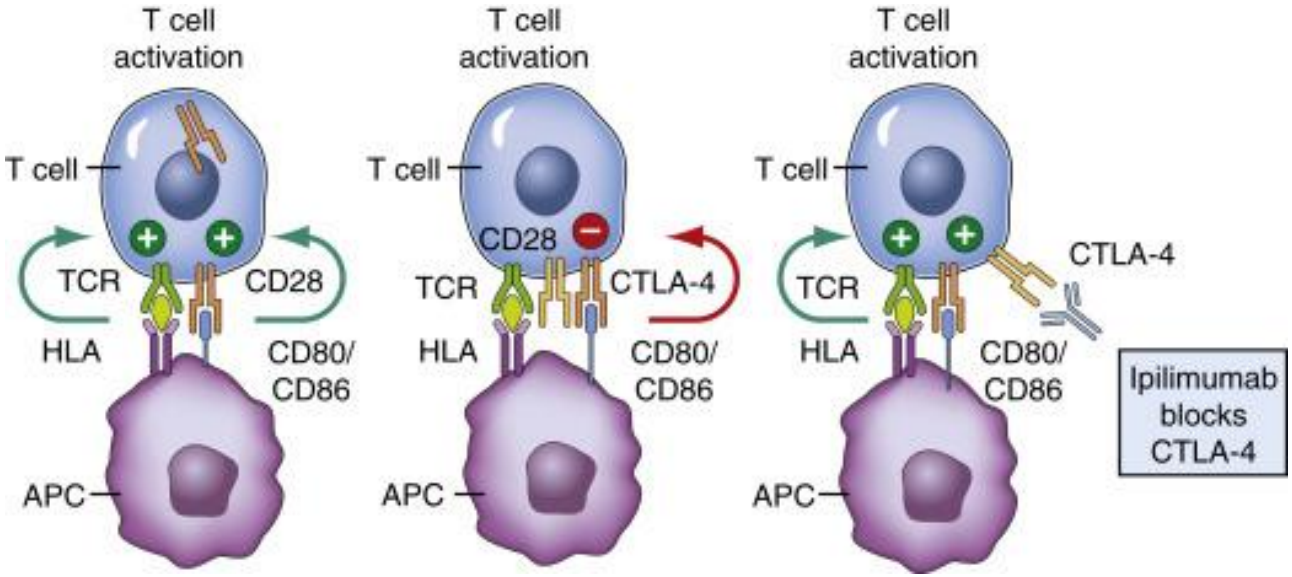


Source: Opdivo (nivolumab) [prescribing information]. Princeton, NJ: Bristol-Myers Squibb; May 2019.

Ipilimumab

Indication	Year Approved
Unresectable or metastatic melanoma	2011
Adjuvant treatment of certain patients with cutaneous melanoma	2015

- 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



Source: R. Bryan Bell, Zipei Feng, Carlo B. Bifulco, , et al. Immunotherapy. Oral, Head and Neck Oncology and Reconstructive Surgery. 2018, Pages 314-340
Yervoy (ipilimumab) [prescribing information]. Princeton, NJ: Bristol-Myers Squibb; May 2019.

Nivolumab and ipilimumab

Indication	Approved
Unresectable or metastatic melanoma	2015
Intermediate or poor risk, previously untreated advanced renal cell carcinoma	2018
MSI-H or dMMR metastatic colorectal following treatment w/a fluoropyrimidine, oxaliplatin, irinotecan	2018

- 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

Source: Yervoy (ipilimumab) [prescribing information]. Princeton, NJ: Bristol-Myers Squibb; May 2019.
Opdivo (nivolumab) [prescribing information]. Princeton, NJ: Bristol-Myers Squibb; May 2019.

Pembrolizumab

Indication	Year Approved
Unresectable or metastatic melanoma	2015, 1rst line 2014, 2nd line
Recurrent/metastatic squamous cell carcinoma of the head and neck	2016
Metastatic NSCLC	2016, 1rst line 2015-second line
Classical Hodgkin Lymphoma (cHL)	2017
Locally advanced or metastatic urothelial carcinoma	2017
Recurrent/metastatic cervical cancer, PD-L1 (CPS ≥1)	2018
Metastatic NSqNSCLC with no EGFR or ALK genomic tumor aberrations, in combination with pemetrexed and platinum	2018, 1rst line
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	2018
In combination with carboplatin and either paclitaxel or nab-paclitaxel as first-line treatment of metastatic squamous non-small cell lung cancer (NSCLC)	2018, 1rst line
Adjuvant treatment of patients with melanoma with involvement of lymph node(s) following complete resection	2019
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	2019

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

Pembrolizumab cont.

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

- 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-L1blocking 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

Indication	Approved
Locally advanced or metastatic urothelial carcinoma after progression	2016
Metastatic NSCLC after disease progression	2016
Require to determine PD-L1 levels in tumor tissue from patients with locally advanced/metastatic urothelial cancer cisplatin-ineligible	2018
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	2018
PD-L1 positive unresectable locally advanced/metastatic triple-negative breast cancer	2019
In combination with carboplatin and etoposide, for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC)	2019

- *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

Indication	Year Approved
Accelerated approval	
Locally advanced or metastatic urothelial carcinoma after disease progression	2017
Unresectable stage III NSCLC without progression following concurrent platinum-based chemotherapy &RT	2018

- 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

Indications	Year Approved
First-line treatment, in combination with axitinib of patients with advanced renal cell carcinoma	2019
Accelerated approvals	
Metastatic Merkel cell carcinoma (MCC)	2017
Locally advanced or metastatic urothelial carcinoma after disease progression	2017

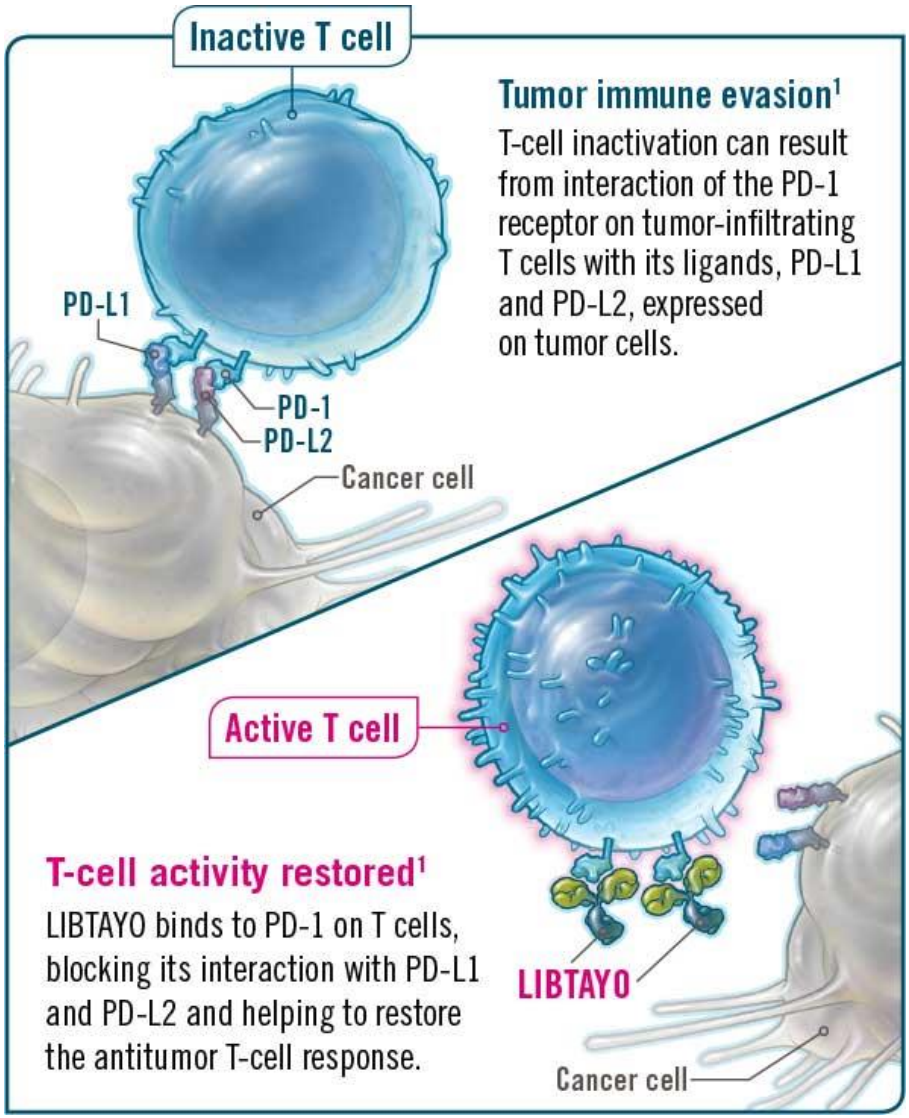
- Dosing Initially 10 mg/kg, NOW 800 mg once every 2 weeks
- Infused over 60 minutes
- In advanced RCC:
  - Use in combination with axitinib 5 mg twice daily
- Premeds:
  - Acetaminophen and antihistamine prior to the first 4 infusions
- ADRS: fatigue, musculoskeletal pain, diarrhea, nausea, infusion-related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

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

Cemiplimab

Indication	Approved
Metastatic cutaneous squamous cell carcinoma (CSCC) or locally advanced CSCC who are not candidates for curative surgery or curative radiation	2018

- 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



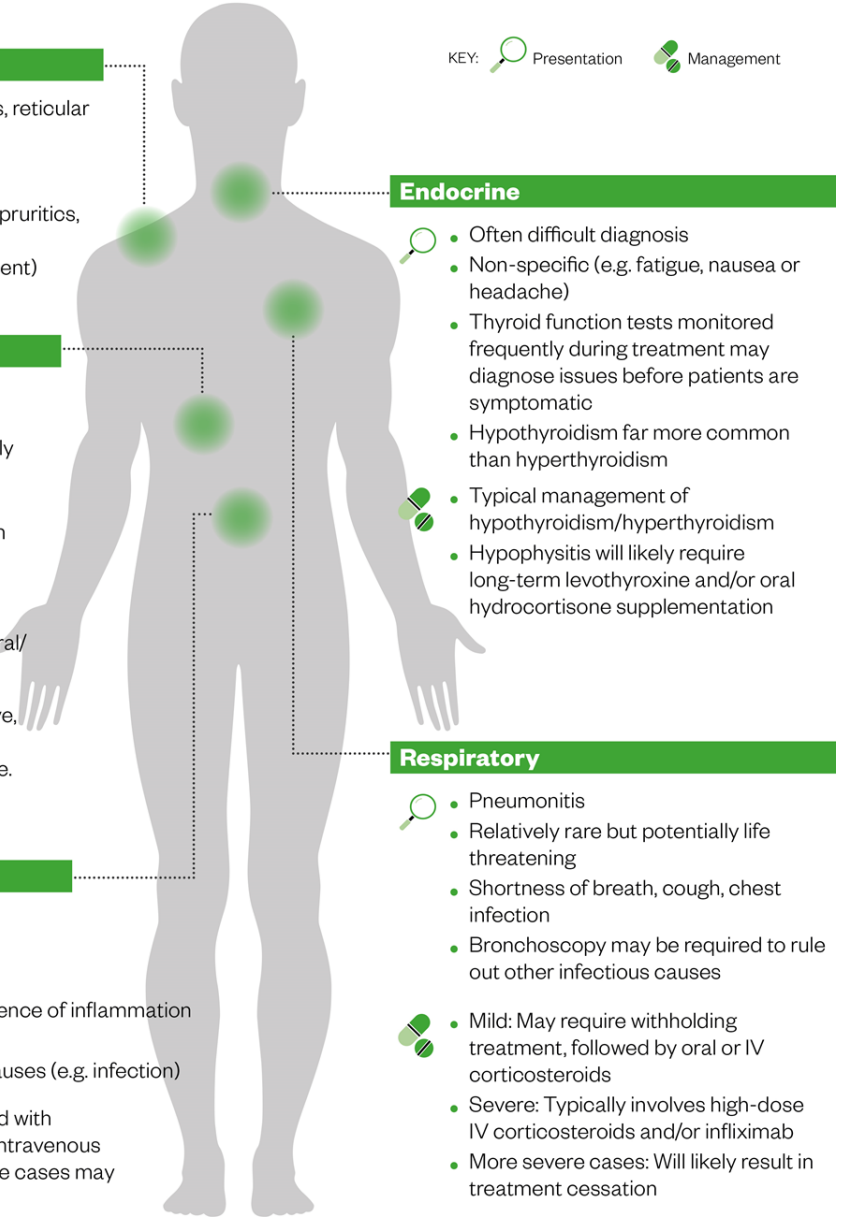
Source: Libtayo (cemiplimab-rwlc) [prescribing information]. Tarrytown, NY: Regeneron Pharmaceuticals, Inc; March 2019.

Comparison of PD-1/PD-L1 Agents

Comparison	Atezolizumab	Avelumab	Cemiplimab	Durvalumab	Nivolumab	Pembrolizumab
Indications	Metastatic non-small cell lung cancer and locally advanced or metastatic urothelial carcinoma	First-line treatment, in combination with axitinib of patients with advanced renal cell carcinoma Metastatic Merkel cell carcinoma (MCC) Locally advanced or metastatic urothelial carcinoma after disease progression	Treatment of patients with metastatic cutaneous squamous cell carcinoma (CSCC) or locally advanced CSCC who are not candidates for curative surgery or curative radiation. ***Unique IO indication***	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. ***Unique IO indication***	Multiple indications	Multiple indications
Mechanism of action	PD-L1 inhibitor	PD-L1 inhibitor	PD-1 inhibitor	PD-L1 inhibitor	PD-1 inhibitor	PD-1 inhibitor
Infusion time	60 mins	60 mins	30 mins	60 mins	30 mins	30 mins
Dosing frequency	Every 3 weeks	Every 2 weeks	Every 3 weeks	Every 2 weeks	Every 2 weeks; every 3 weeks; every 4 weeks	Every 3 weeks

Source: Manufacturer PIs

Immune-Mediated Adverse Events (irAEs)



Source: https://www.pharmaceutical-journal.com/learning/learning-article/immune-checkpoint-inhibitors-in-cancer-pharmacology-and-toxicities/20204831.article?firstPass=false

Management of Toxicities

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Management of Immunotherapy-Related Toxicities

Version 2.2019 — April 8, 2019

NCCN.org

Continue

Source: https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf

Monitoring

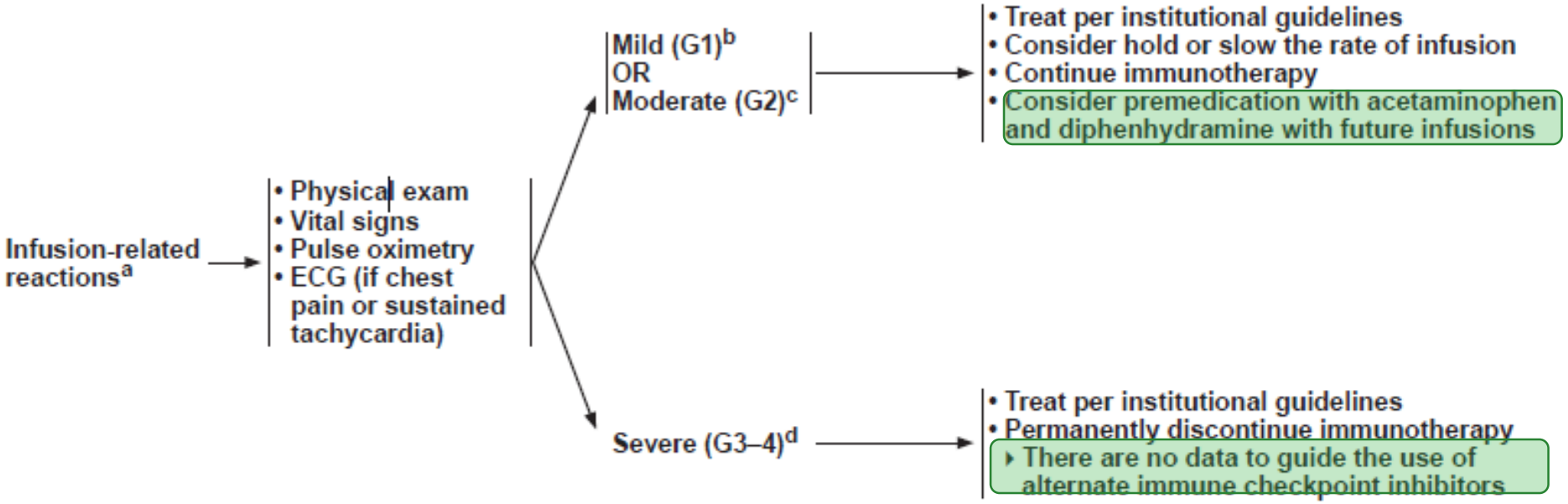
Cancer Treatment Centers of America

PRINCIPLES OF ROUTINE MONITORING

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

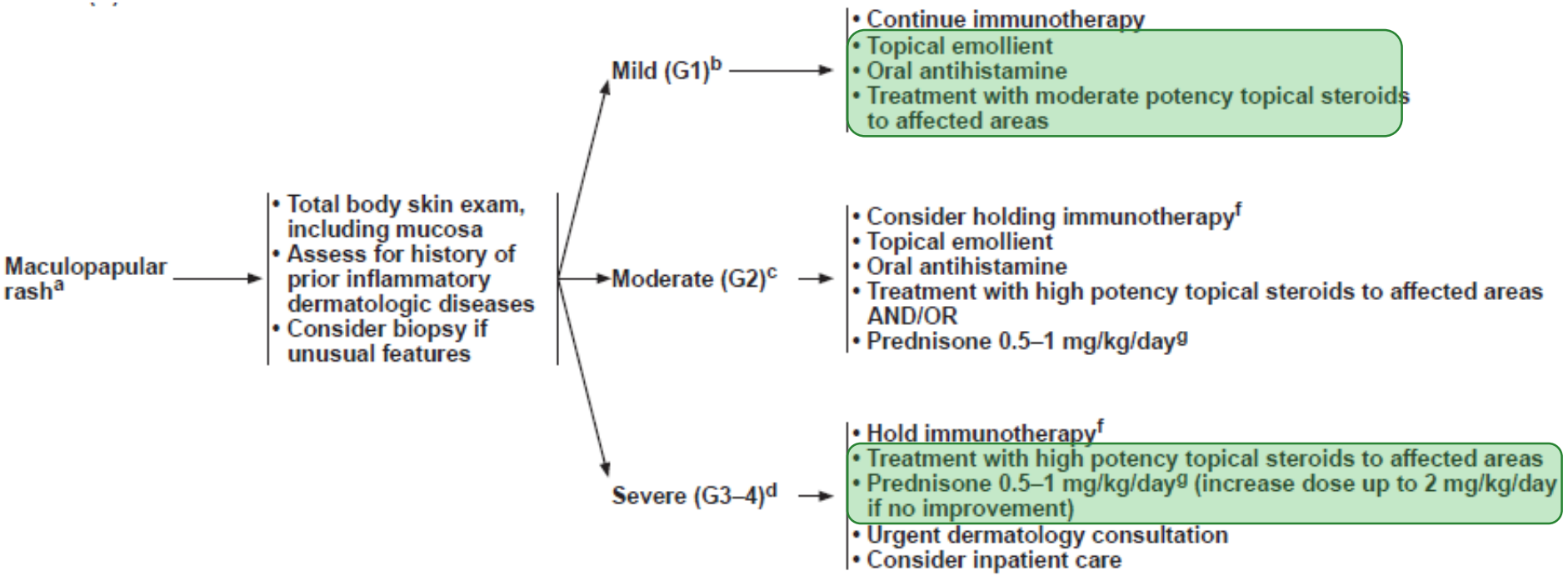
Source: https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf

Infusion-Related Reactions



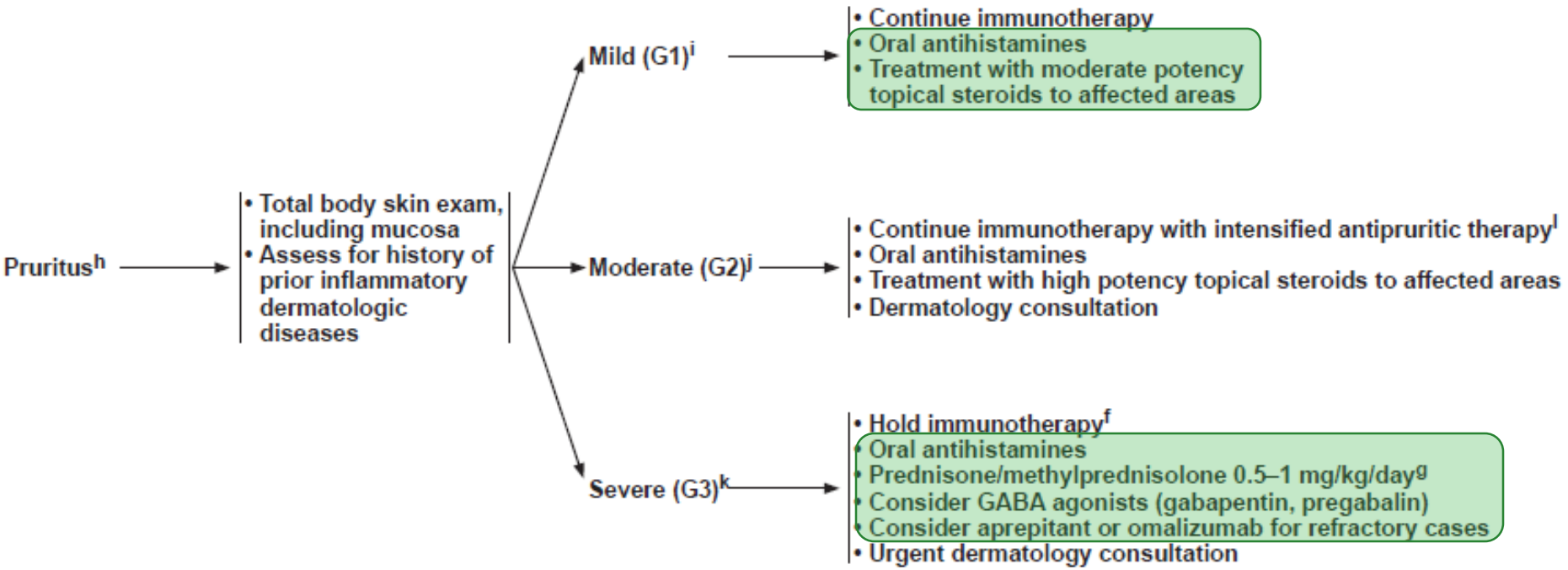
Source: https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf

Maculopapular Rash



Source: https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf

Pruritus



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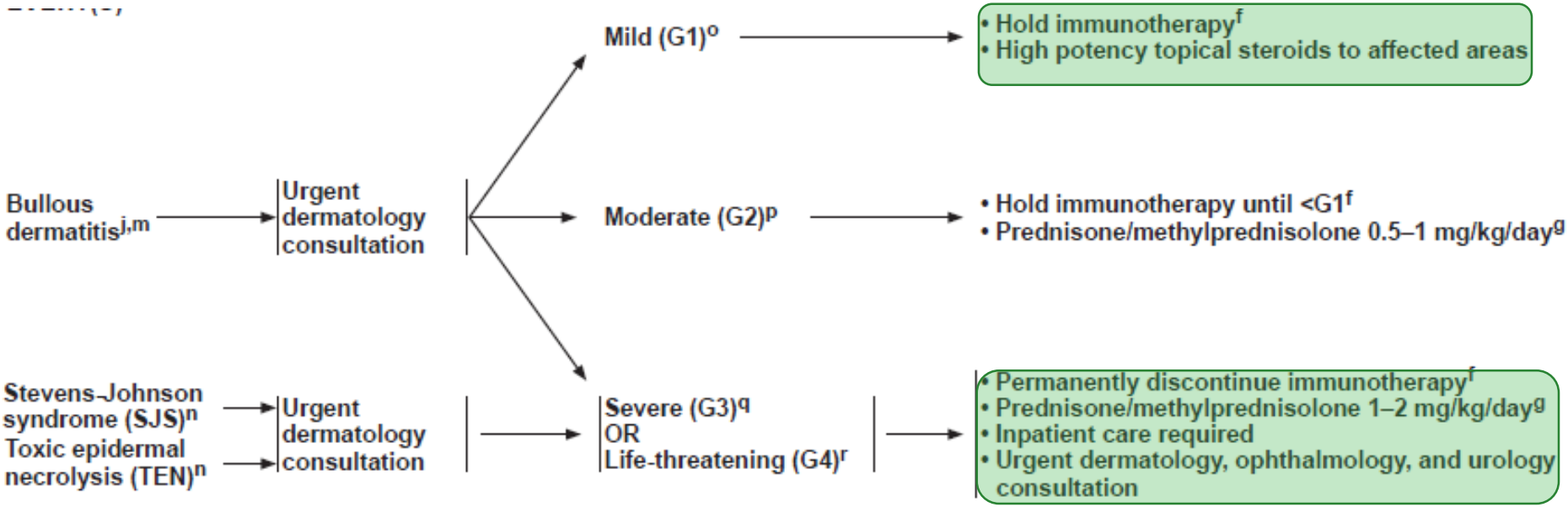
Dermatitis and SJS



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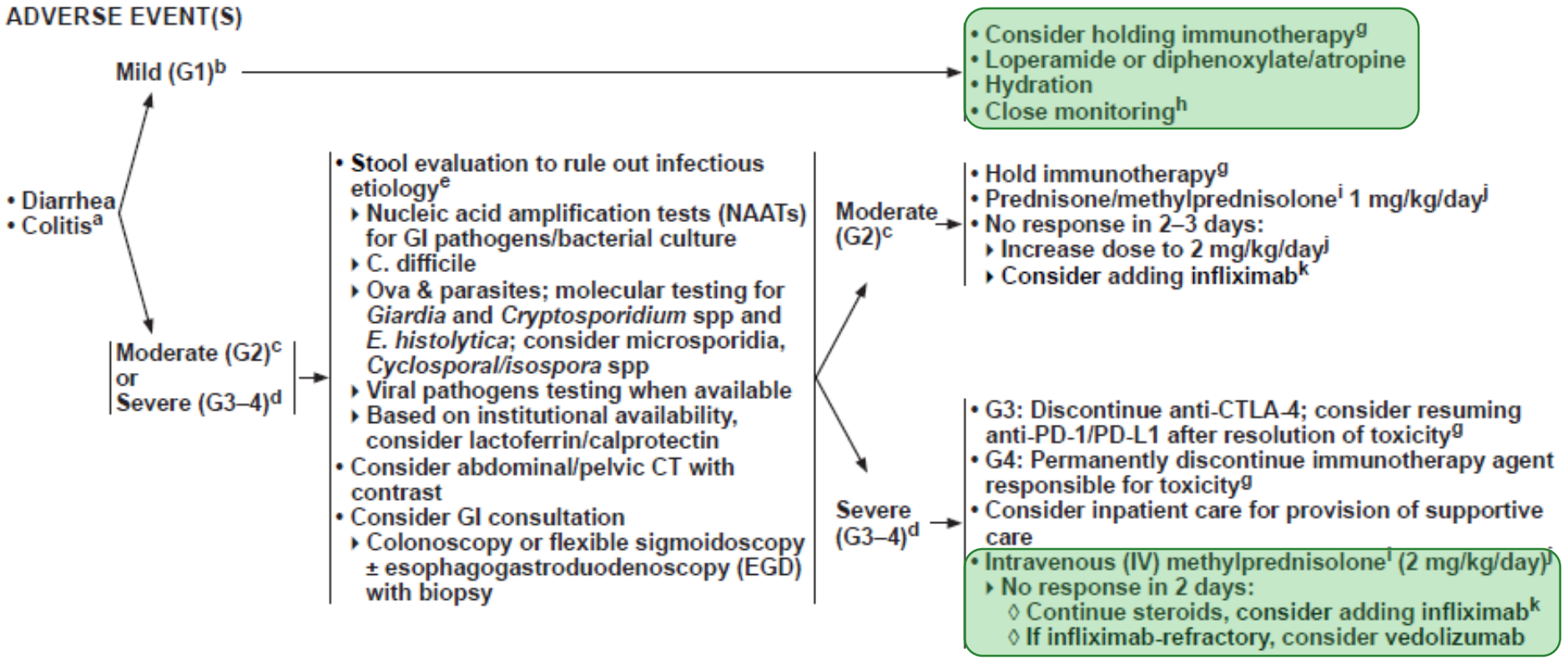
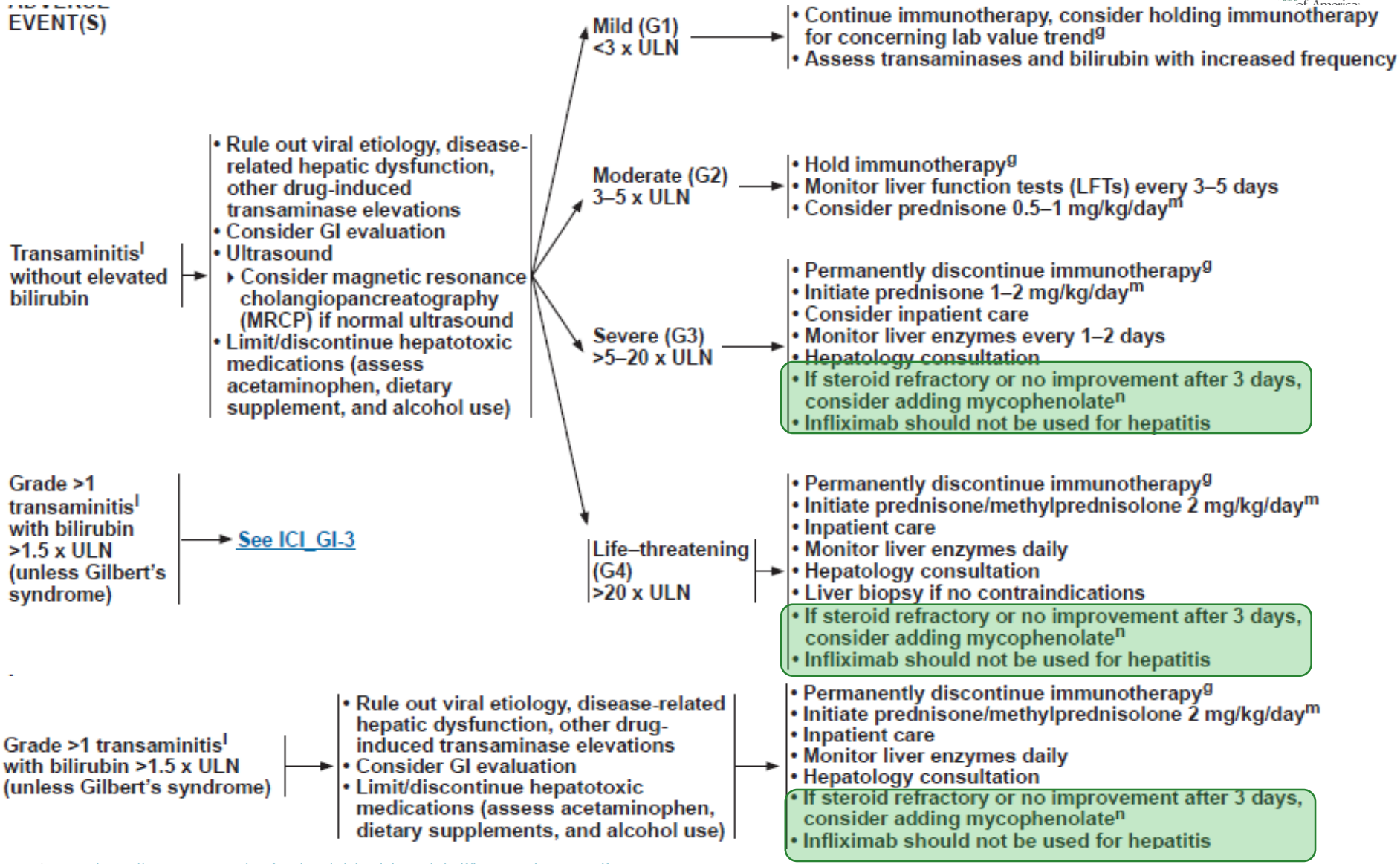
Gastrointestinal Effects



Source: https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf

Hepatic Effects



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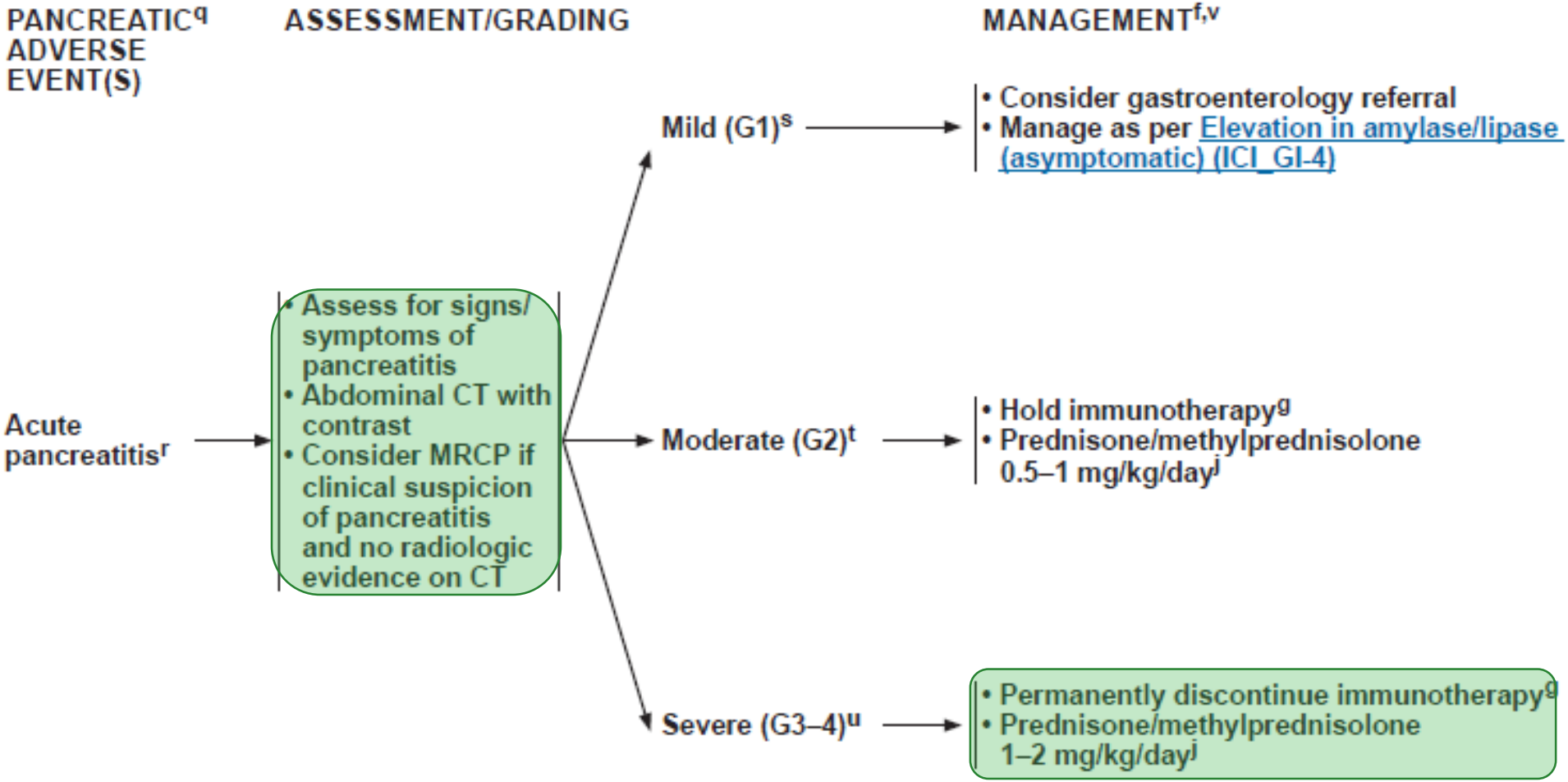
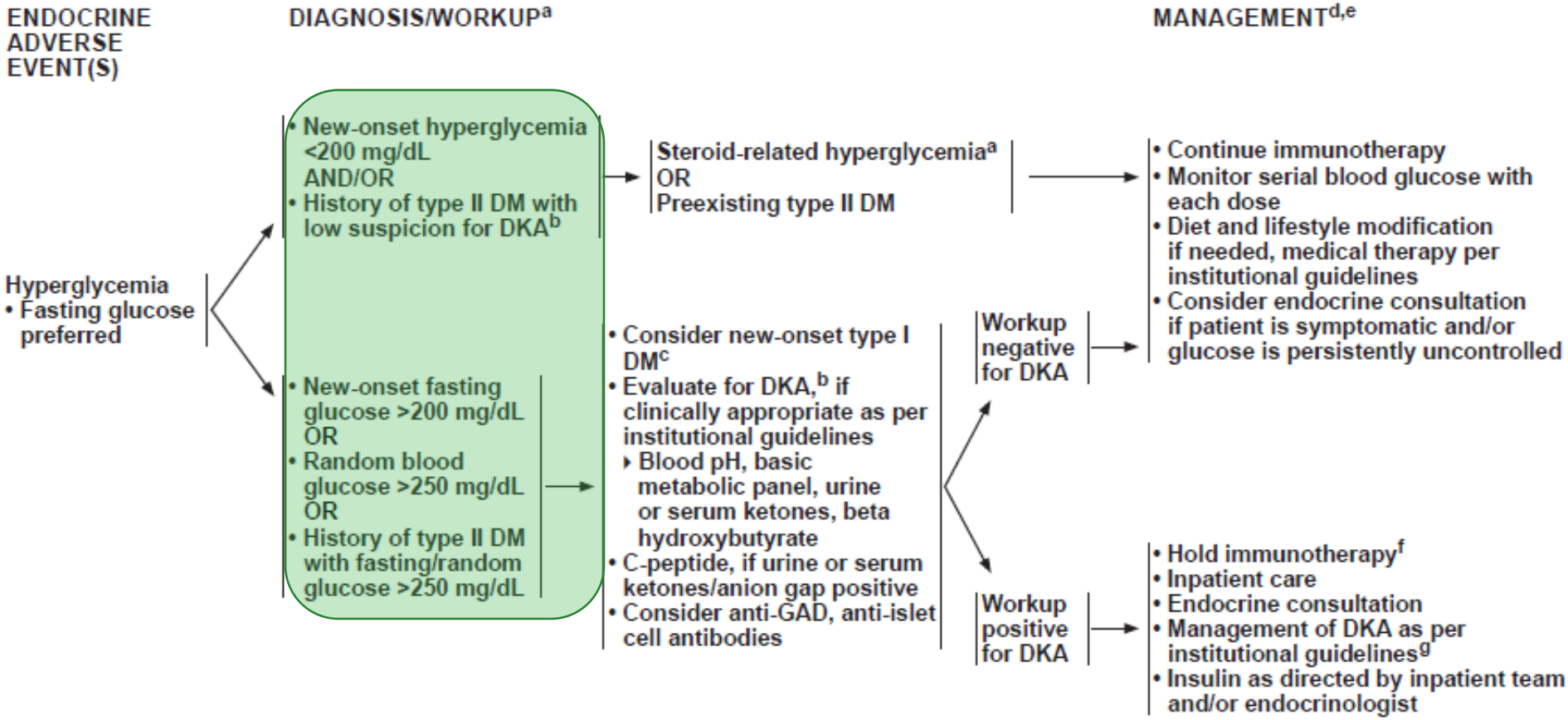
Pancreatic Effects



Source: https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf

Endocrine Effects



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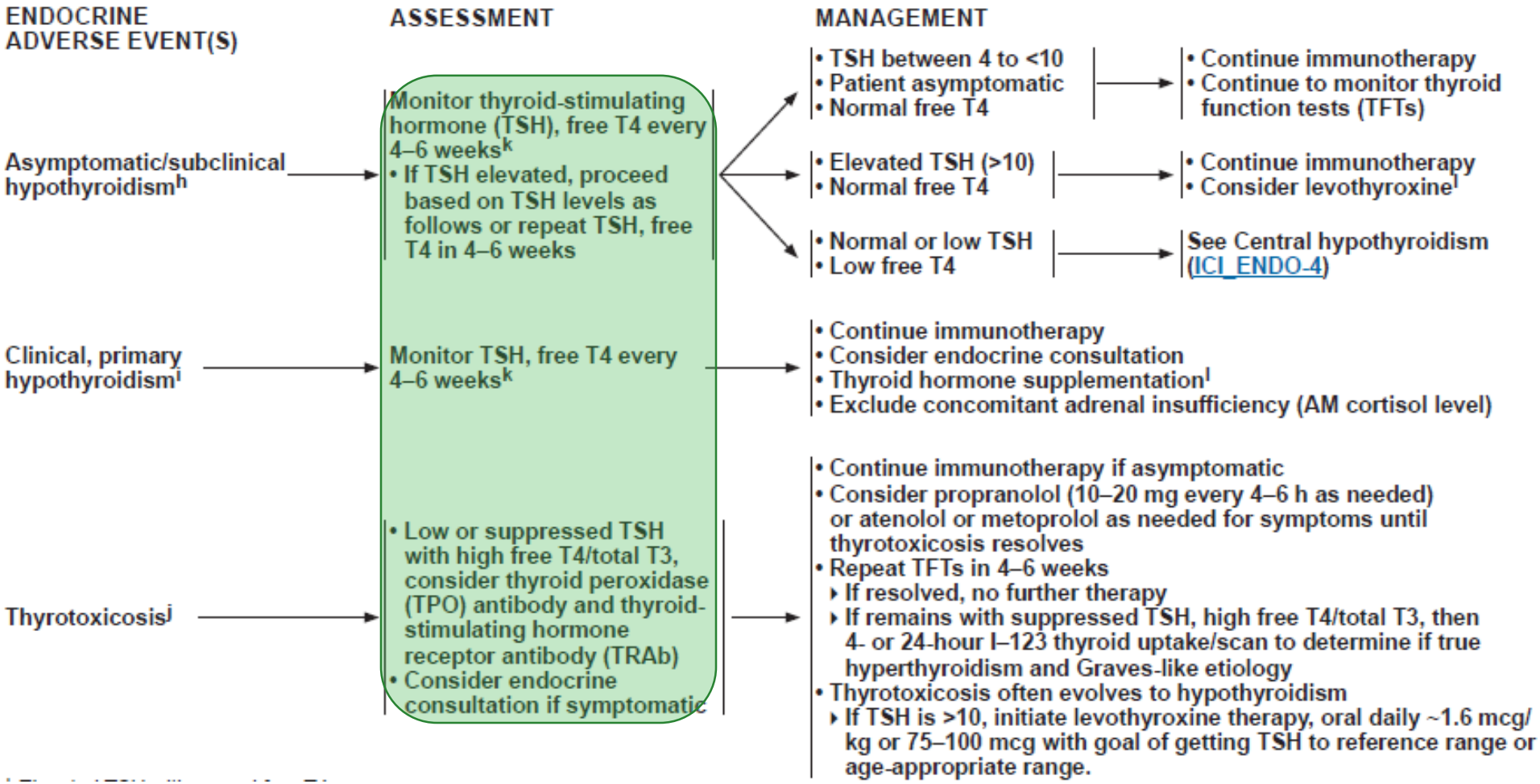
Endocrine Effects



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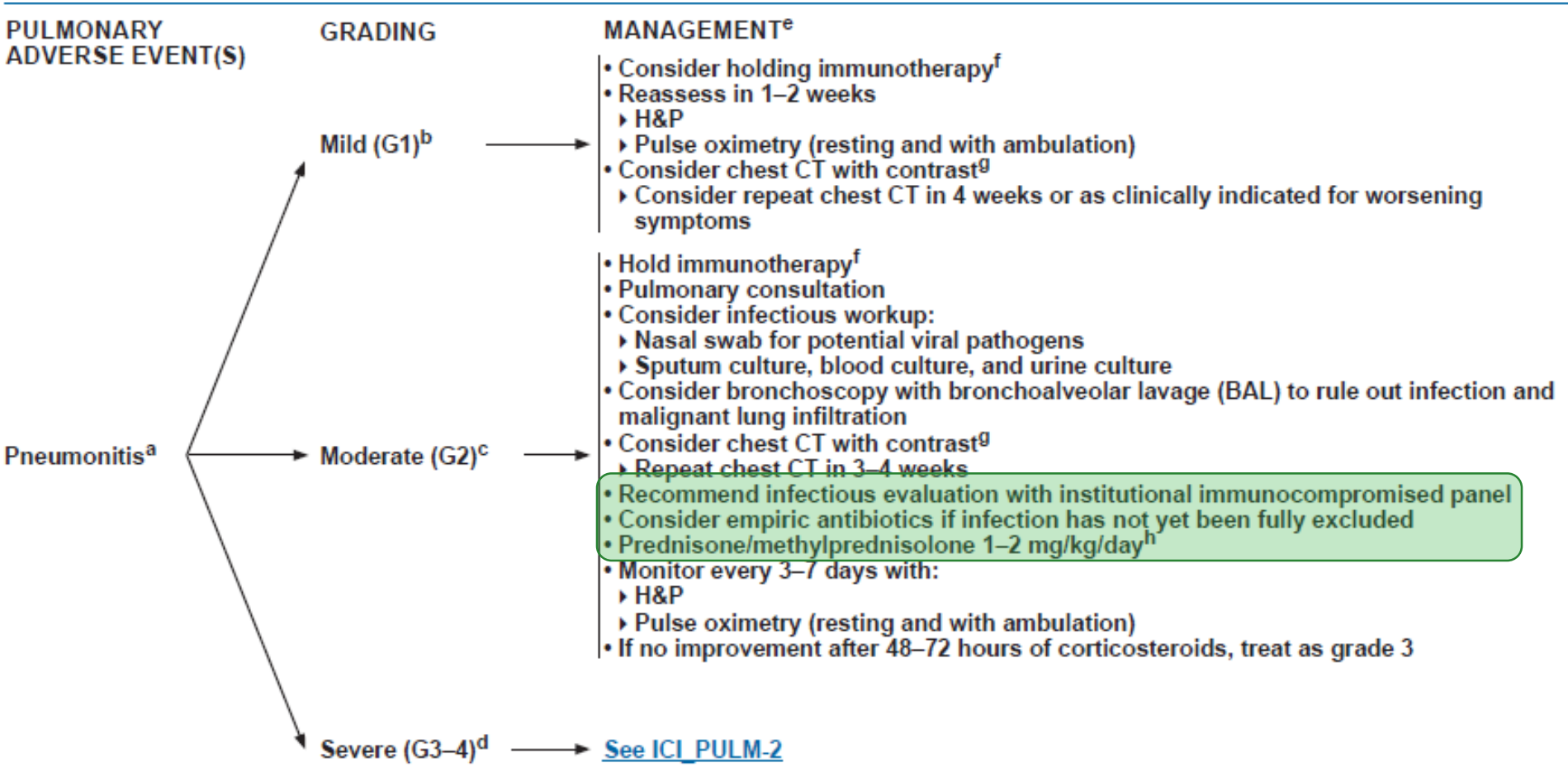
Pulmonary Effects



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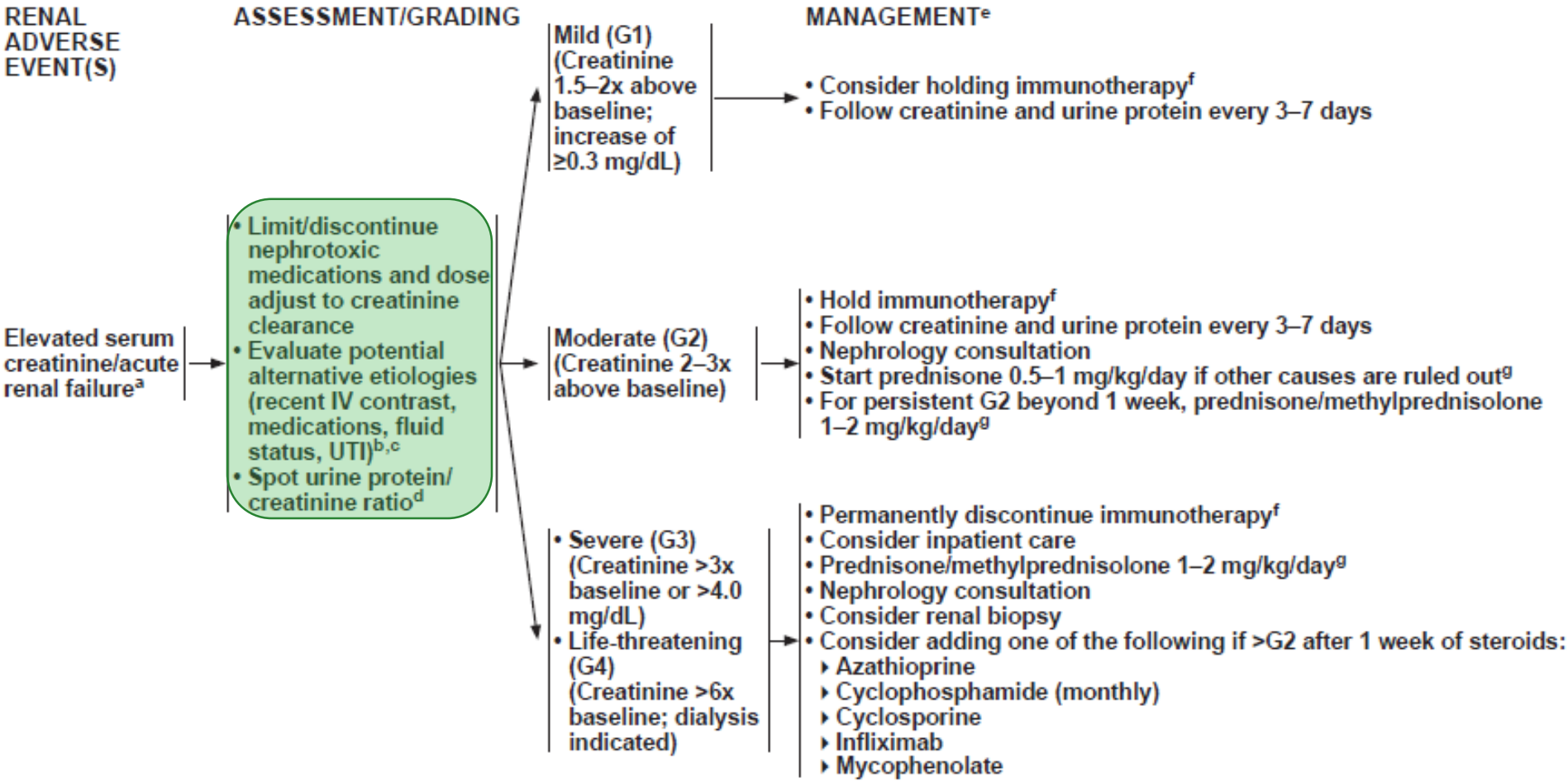
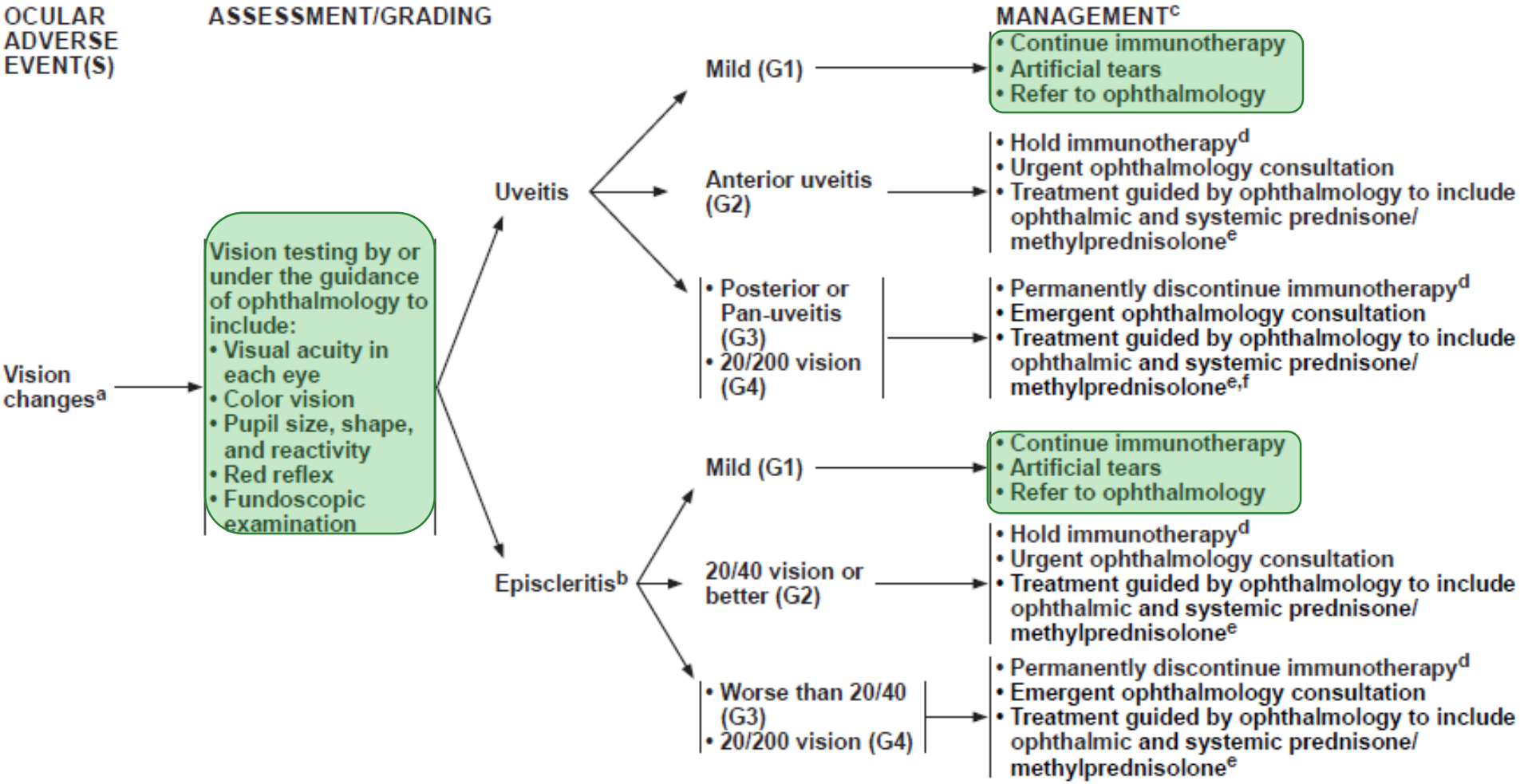
Renal Effects



Source: https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf

Ocular Effects



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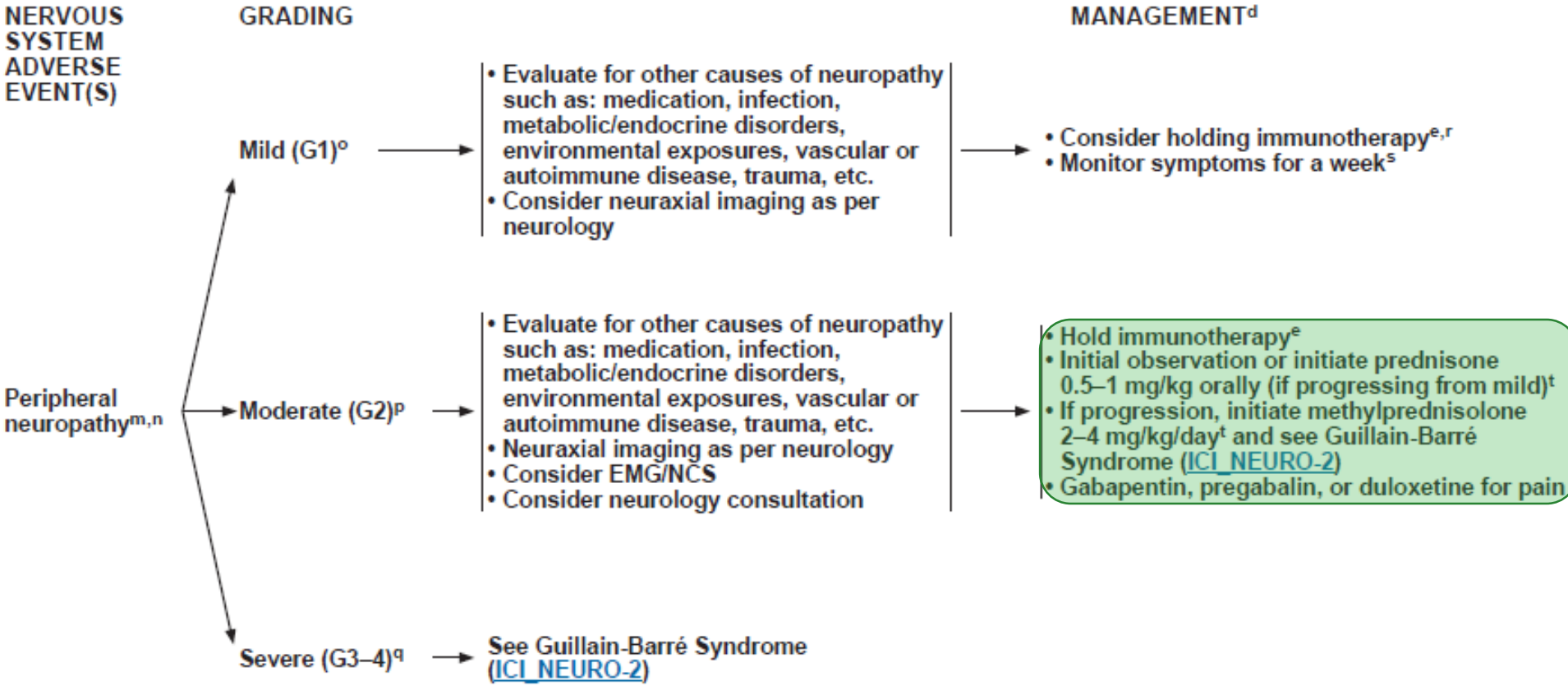
Peripheral Neuropathy



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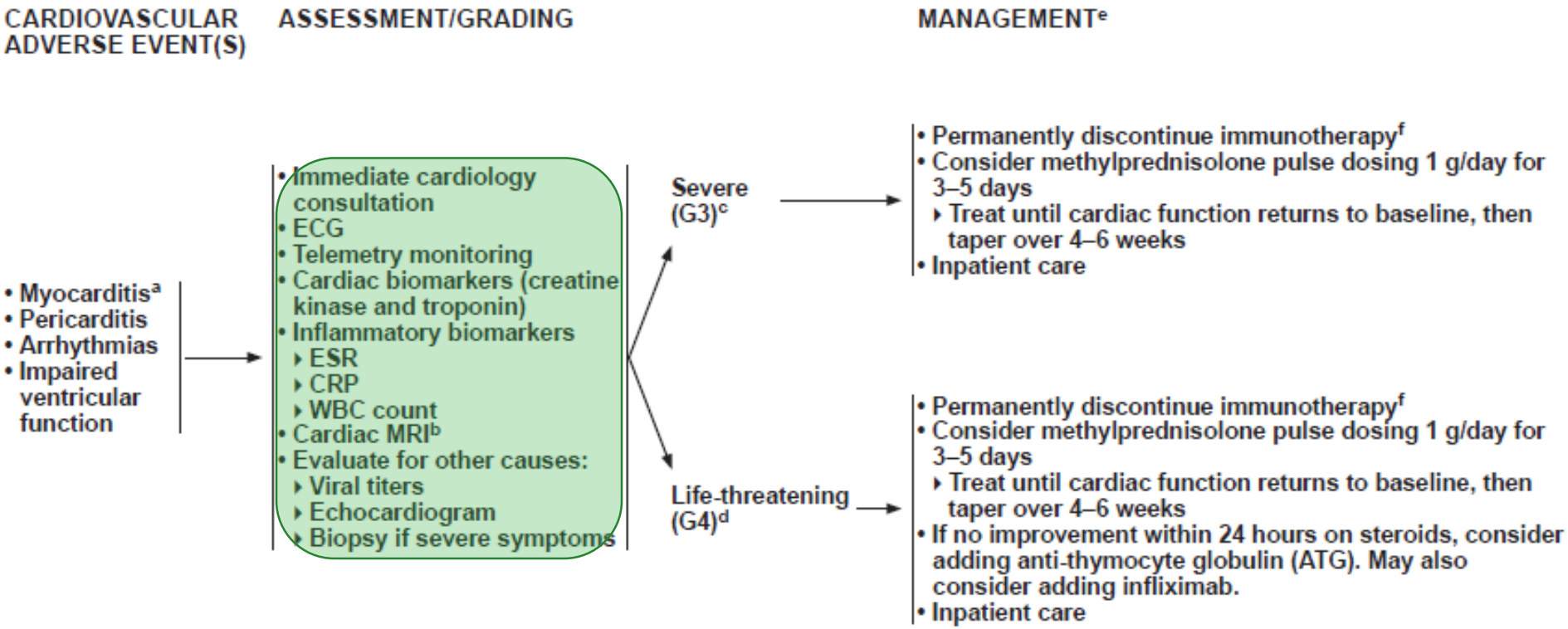
Cardiovascular Effects



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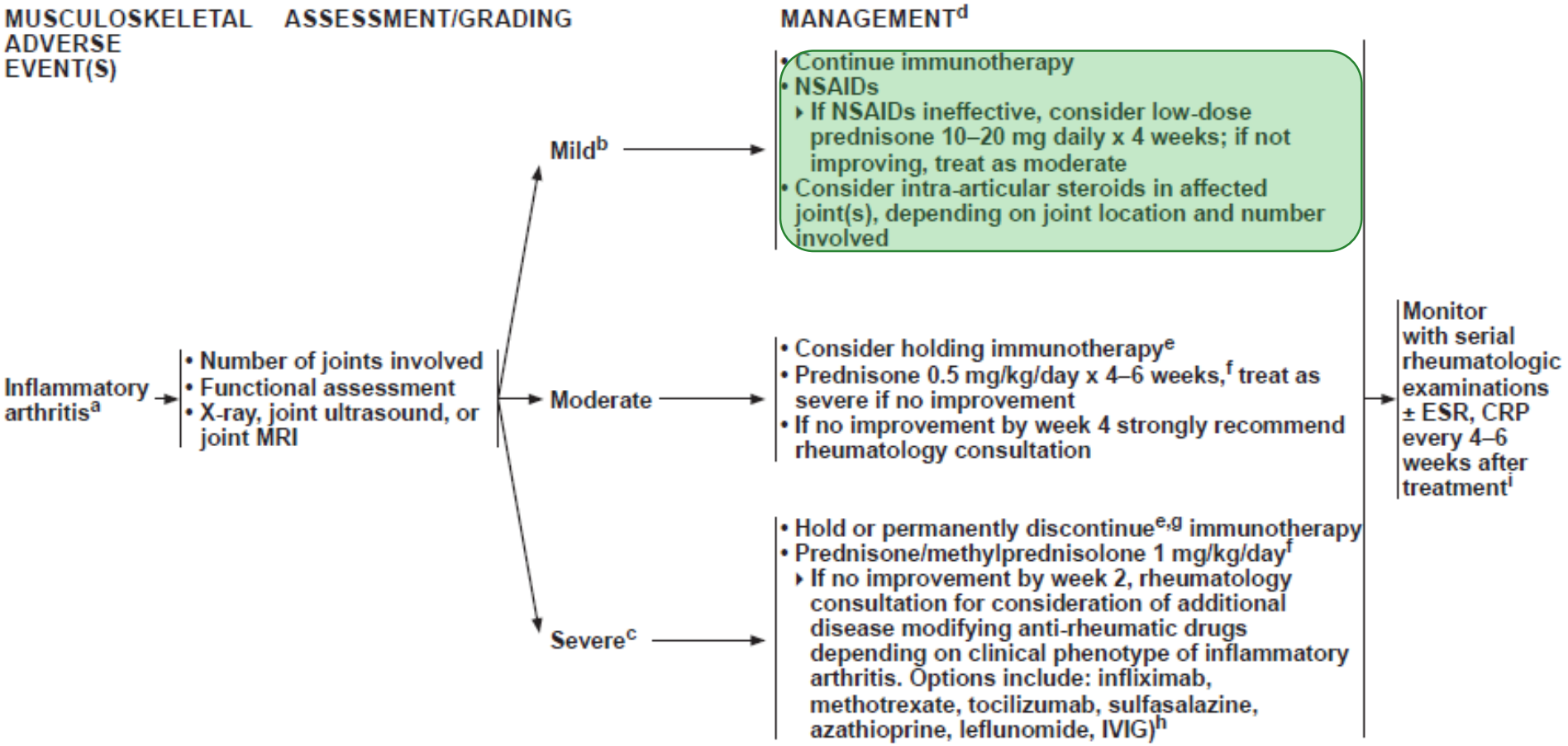
Musculoskeletal Effects



Source: https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf

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

Source:

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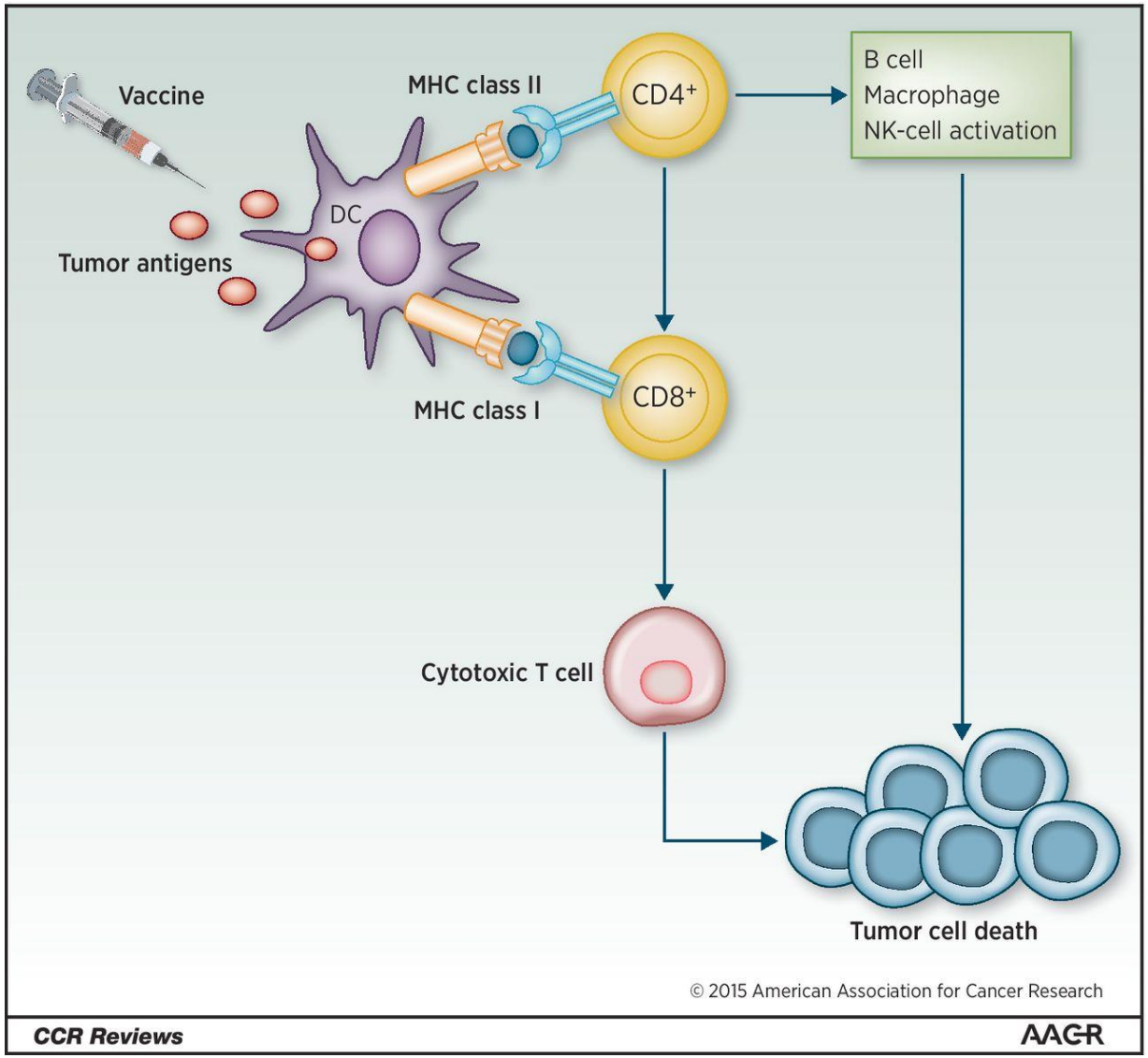
   V. II and IV

Source:

Cancer Vaccines



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

Sipuleucel-T

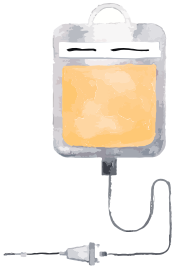
- Autologous cellular immunotherapy indicated for the treatment of asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer
- Designed to induce an immune response targeted against PAP, an antigen expressed in most prostate cancers
- Manufactured in several 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

Cancer Treatment Centers of America

Day 1–Cell Collection

Personal dose is manufactured



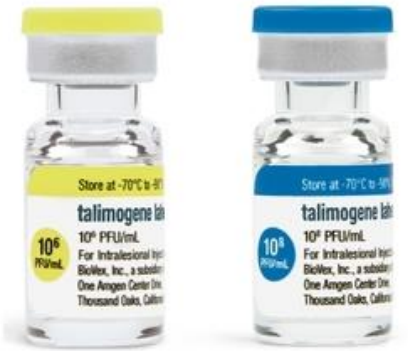
Day 3 or 4–Patient is Infused

Process repeated 2 more times

6 Appointments and Your Treatment is Complete

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

Cancer Preventing Vaccines

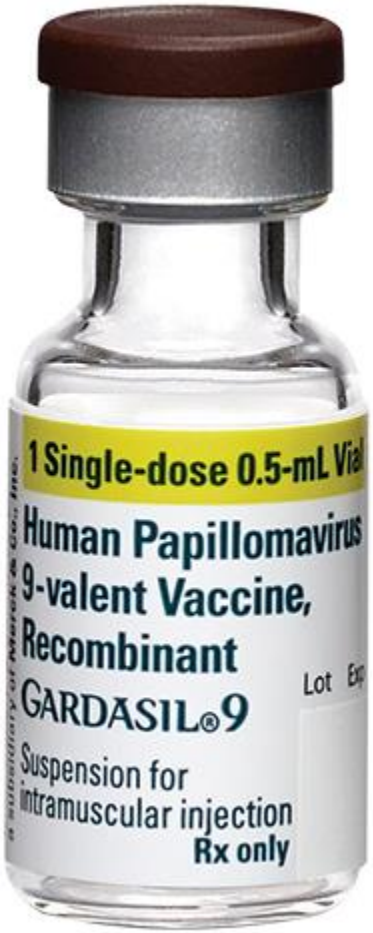
- Hepatitis B vaccines
  - Prevent liver cancer

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

Source: 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

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

Source:

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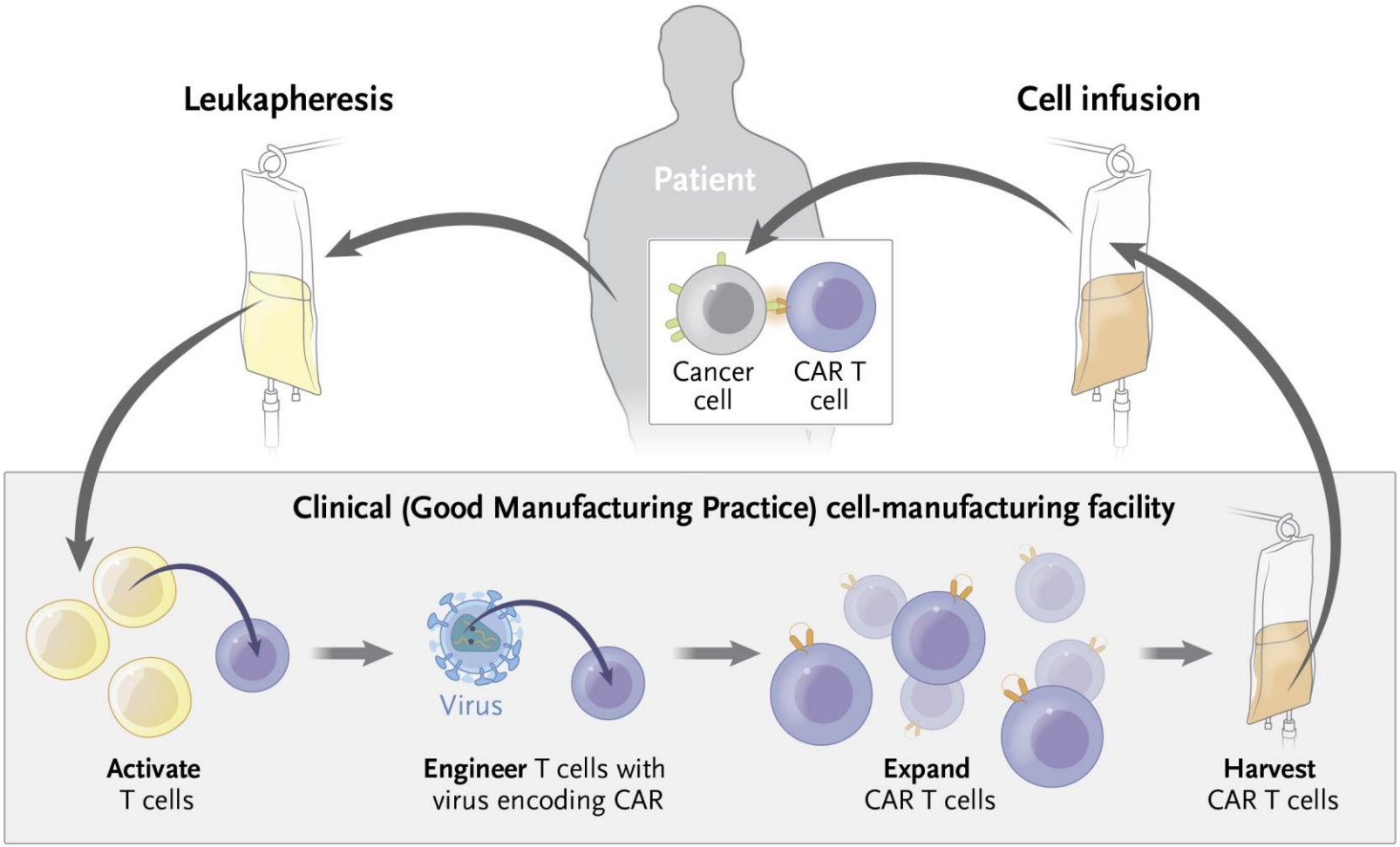
Source:

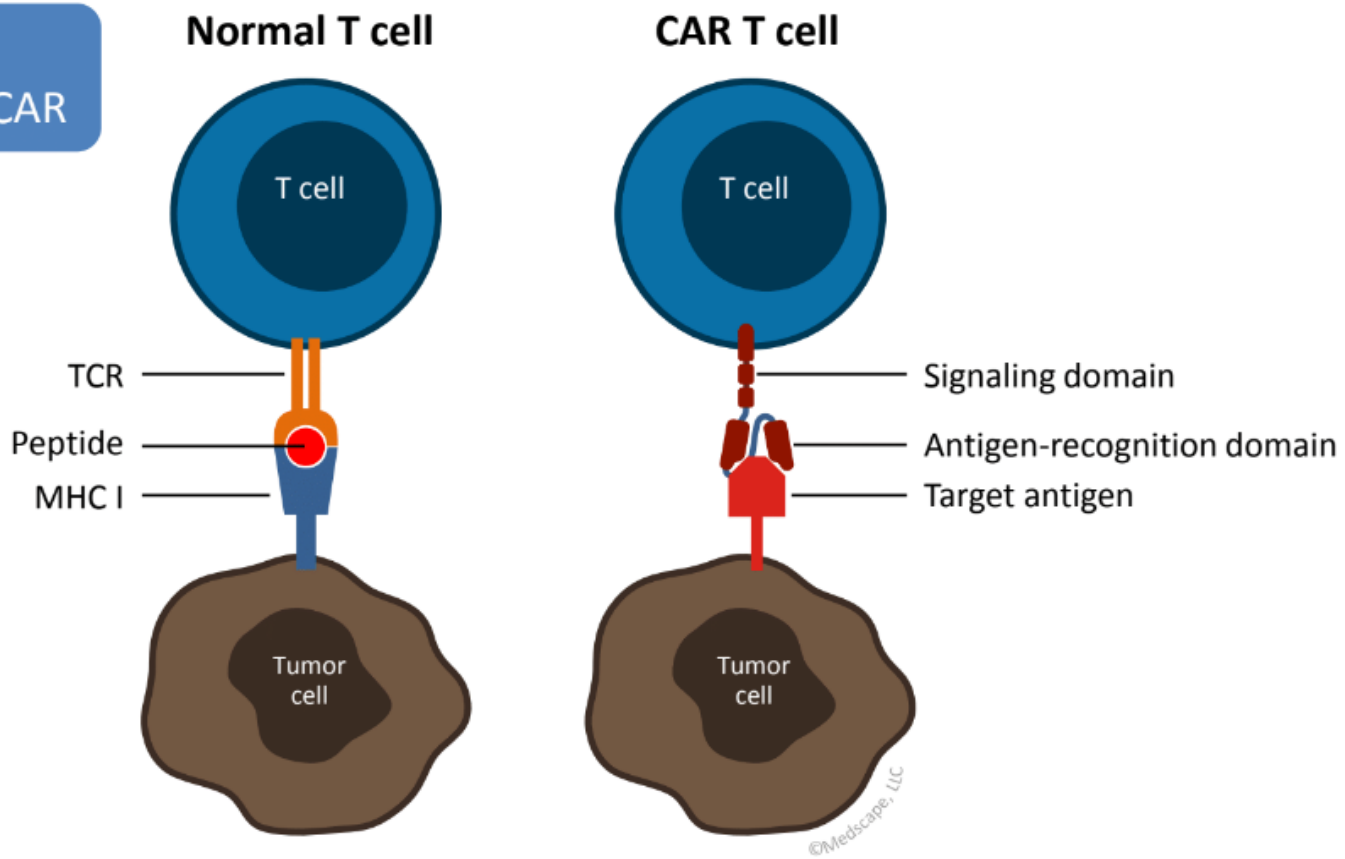
CAR-T cell Therapy



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

Mechanism of Action

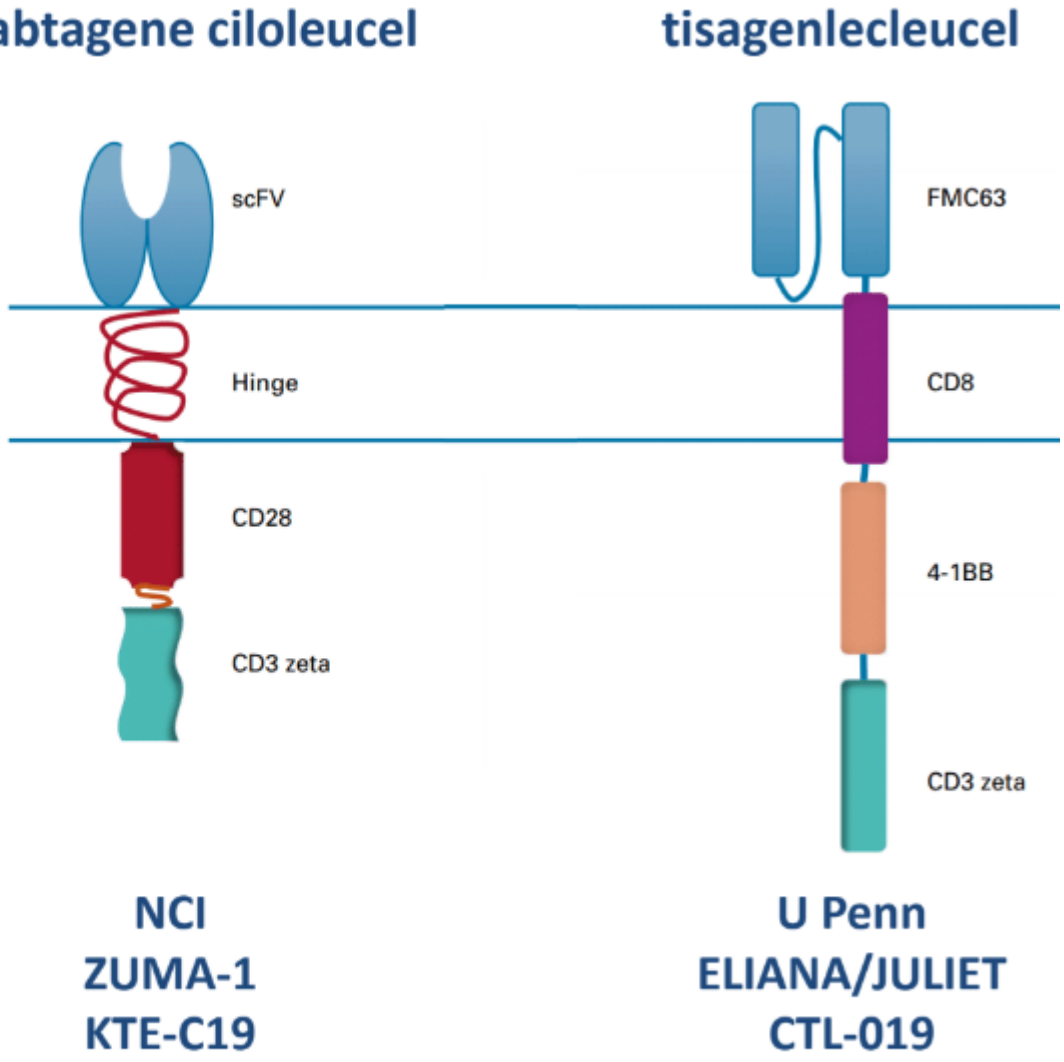
T cells are genetically engineered to express a CAR



Hinrichs CS, et al. *Nat Biotechnol.* 2013;31:999-1008.

Agent Comparison

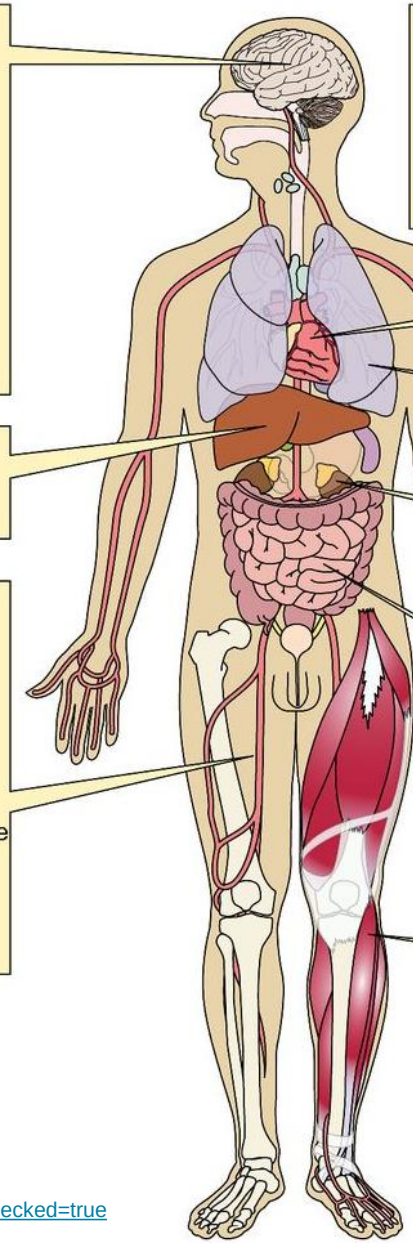
Mechanism:
Anti CD-19
Indication:
Large B-cell Lymphoma
Dosing:
2×10^6 CAR-positive viable T cells per kg body weight



Jacobson C, JCO. 2018; DOI: 10.1200/JCO.18. 01457.

Mechanism:
Anti CD-19
Indications:
ALL
and
Diffuse Large B-cell Lymphoma
Dosing:
<u>ALL</u>
≥ 25 y/o - 0.2 to 5 x 10^6 T cells per kg body weight
<25 y/o and >50 kg - 0.1 to 2.5 x 10^8 T cells
<u>DLBCL</u>
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

	Axicabtagene ciloleucel[a] and tisagenlecleucel[b]
CRS (CART-3)	• 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.

Source: https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf

Management of Toxicities

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

Source: https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf

Management of Toxicities

Treatment by Grade	No Concurrent CRS	Additional Therapy if Concurrent CRS
Grade 1	• Supportive care	Tocilizumab 8 mg/kg IV over 1 h (not to exceed 800 mg/dose)[q]
Grade 2[p]	• 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 1[q] Consider transferring patient to ICU if neurotoxicity associated with grade ≥2 CRS
Grade 3[p]	• ICU care is recommended. • Dexamethasone 10 mg IV every 6 h or methylprednisolone, 1 mg/kg IV every 12 h[l] • Consider repeat neuroimaging (CT or MRI) every 2–3 days if patient has persistent grade ≥3 neurotoxicity.	Anti-IL-6 therapy as per Grade 1[q]
Grade 4[p]	• ICU care, consider mechanical ventilation for airway protection. • High-dose corticosteroids[l,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 1[q]

Source: https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf

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

Source: https://www.ons.org/sites/default/files/2018-10/0676_sample.pdf

CD20 Monoclonal Antibodies

- Rituximab
  - Treatment of CLL, NHL, RA, GPA (Wegener's Granulomatosis), MPA, PV
- Rituximab/hyaluronidase (Rituxan Hycela)
  - **ONLY** given **<u>subcutaneously in the abdomen</u>**
  - Monitor for severe skin and mouth reactions
  - ADRS
- Obinut
  - Treatm
  - 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

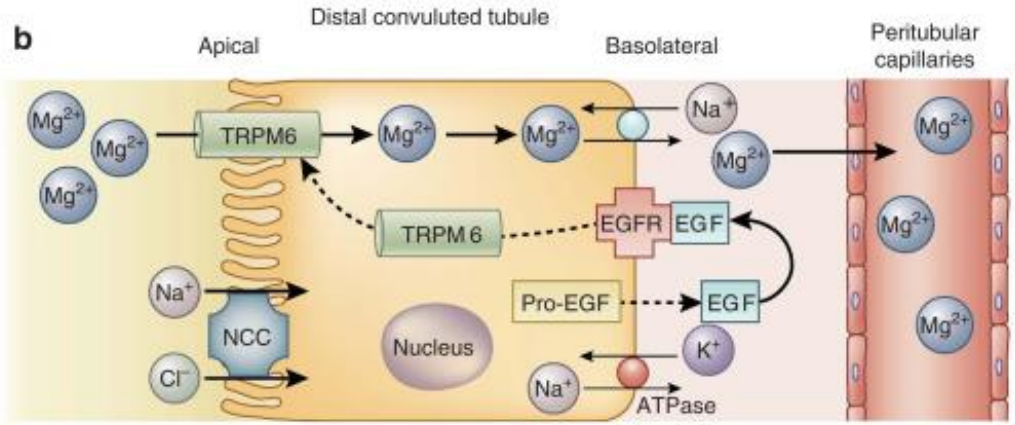
Source: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm

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

Generic Name	Cetuximab	Panitumumab
Indications	SCCHN; and K-Ras Wild-type, EGFR-expressing CRC	Metastatic CRC in Ras Wild-type patients
Dosing	400 mg/m2 followed by 250 mg/m2 weekly; OR 500 mg/m2 every 14 days	6 mg/kg every 14 days
ADRs	The most common adverse reactions (incidence ≥25%): cutaneous adverse reactions (including rash, pruritus, and nail changes), headache, diarrhea, and infection.	Most common adverse reactions (≥ 20%) of Vectibix as monotherapy are skin rash with variable presentations, paronychia, fatigue, nausea, and diarrhea.
Rate	400 or 500 mg/m2 dosing: 2 hours 250 mg/m2 dosing: 1 hour	≤1000 mg: 60 minutes >1000 mg: 90 minutes



Source: https://www.sciencedirect.com/science/article/pii/S0085253815558018

Erbitux (cetuximab) [prescribing information]. Indianapolis, IN: Eli Lilly and Company; April 2019.
Vectibix (panitumumab) [prescribing information]. Thousand Oaks, CA: Amgen; June 2017.

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

- Blinatumumab → 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

Source: Blincyto (blinatumomab) [prescribing information]. Thousand Oaks, CA: Amgen Inc; April 2019.
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

Source: Empliciti (elotuzumab) [prescribing information]. Princeton, NJ: Bristol-Myers Squibb; November 2018.
Mylotarg (gemtuzumab ozogamicin) [prescribing information]. Philadelphia, PA: Wyeth Pharmaceuticals; April 2018.

Case #3

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

Source:

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Source:

Patient Resources

Cancer Treatment Centers of America

sitc Cancer Immunotherapy connect ED

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

ACCC
Association of Community Cancer Centers

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

CANCER RESEARCH INSTITUTE

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

Questions?