Advances in Cancer Immunotherapy: A Focus on Nurses

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- Marianne Davies: no financial disclosures

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Learning Objectives/Poll

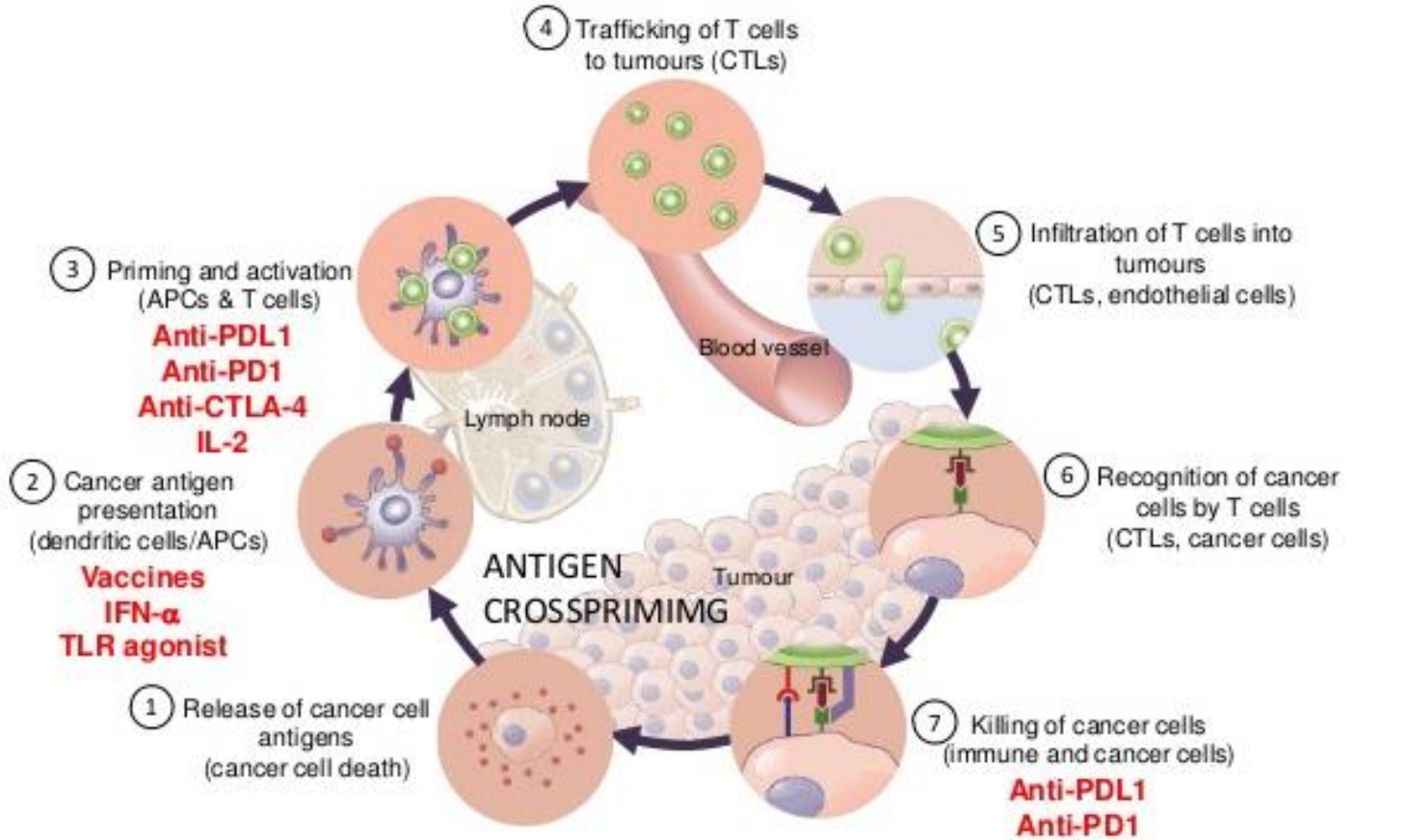
Please rate your level of understanding on the below learning objectives in the poll on your screen.

- Describe the expanding landscape of immune checkpoint immunotherapy
- Identify available patient education resources for cancer immunotherapy immune-related adverse events.
- Distinguish the mechanisms of immune-related adverse reactions from cancer immunotherapy treatment
- Recognize and properly triage immune related adverse events related to cancer immunotherapy

It is recommended to hold ICI therapy for Grade 2 colitis. Grade 2 colitis is described as:

A. Watery diarrhea
B. 1-3 stools over baseline
C. 4-6 stools over baseline
D. Blood or mucus in the stool

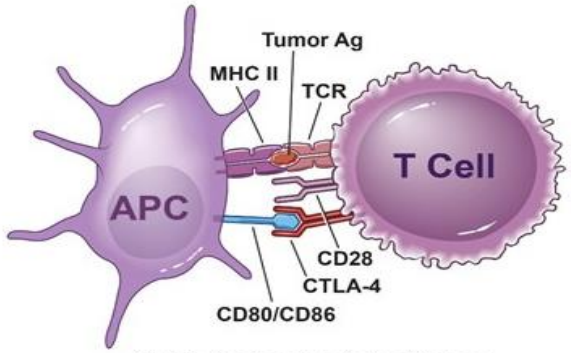
Adaptive Immune System



Chen & Mellman. Immunity 2013

CTLA-4 and PD-1/PD-L1 Checkpoint Blockade

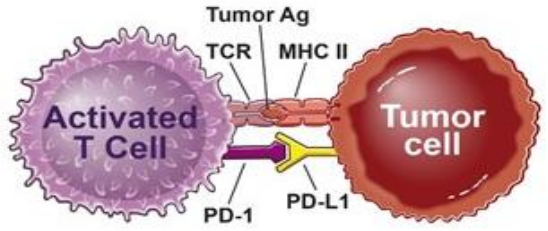
- **PRIMING PHASE**: Lymph Node
- **EFFECTOR PHASE**: Peripheral Tissue



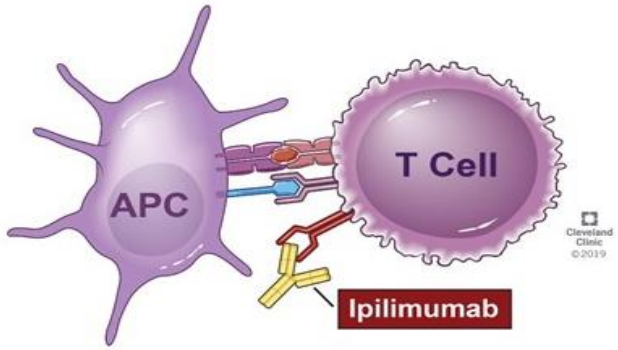
CTLA-4 checkpoint pathway

T-Cell Migration

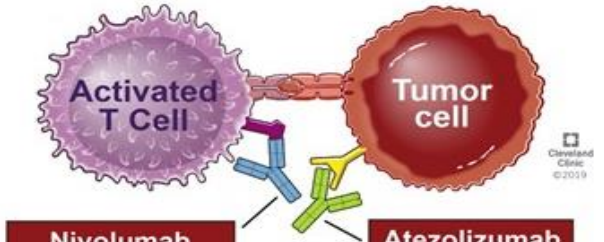
Activation



PD-1 checkpoint pathway



Monoclonal antibody binds to CTLA-4, blocking interaction of CD80/CD86



Monoclonal antibody blocks PD-1

Monoclonal antibody blocks PD-L1

Cemiplimab
Dostarlimab

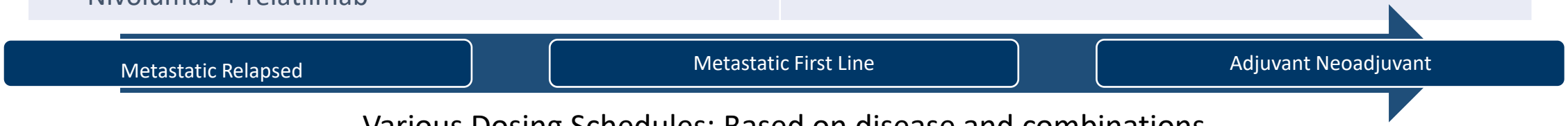
Adapted from: Ribas A. *N Engl J Med*. 2012;366(26):2517-2519.

ICPI & Combinations

PD-1	PD-L1	CTLA-4	LAG-4
• Nivolumab • Pembrolizumab • Cemiplimab • Dostarlimab	• Atezolizumab • Avelumab • Durvalumab	• Ipilimumab • Tremelimumab	• Relatimab

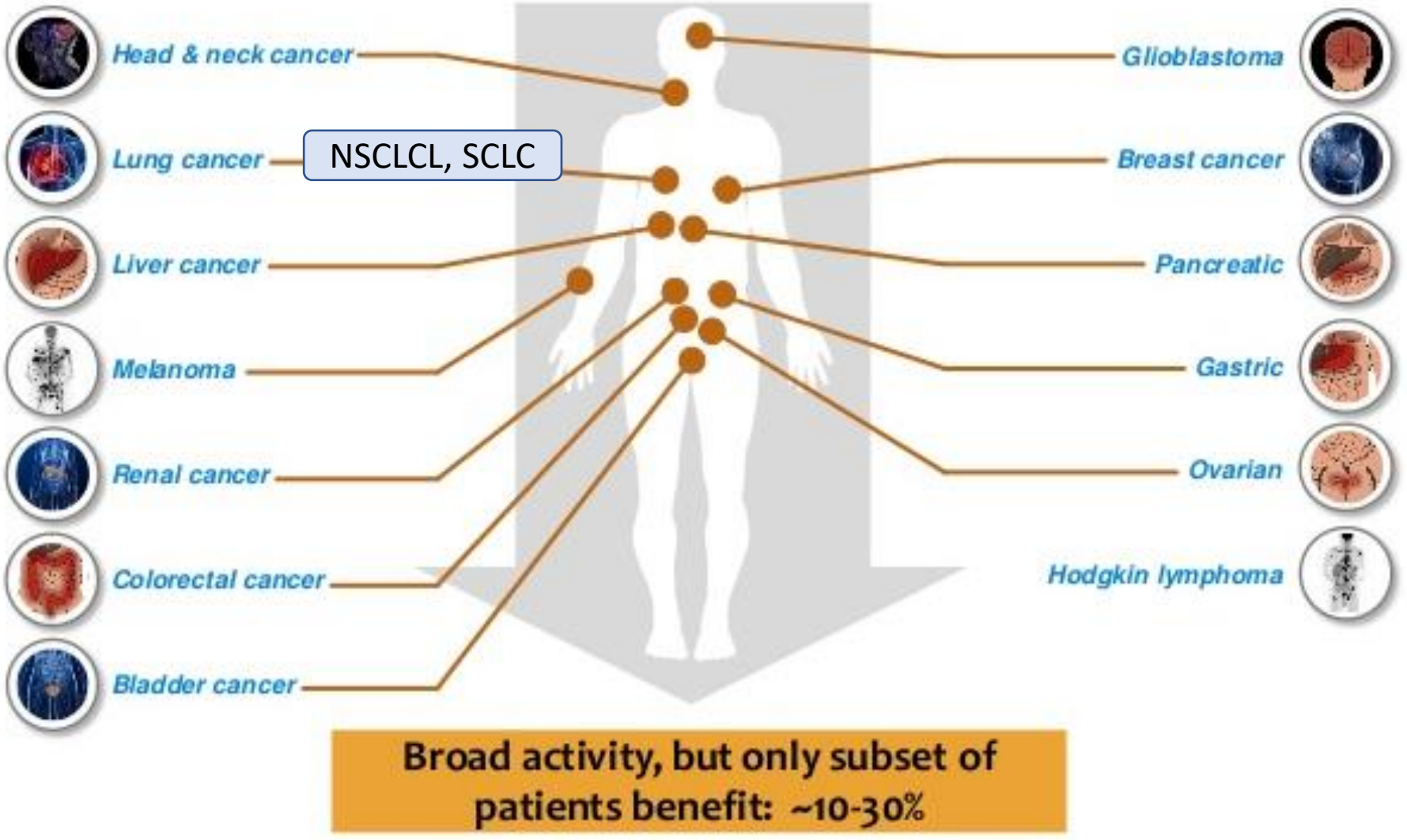
Approved Combinations

- Atezolizumab + bevacizumab
- Atezolizumab + chemotherapy +/- bevacizumab
- Avelumab + axitinib
- Durvalumab + chemotherapy
- Nivolumab + relatlimab
- Nivolumab + ipilimumab (+/-) limited chemotherapy
- Pembrolizumab + chemotherapy
- Pembrolizumab + axitinib
- Pembrolizumab + lenvatanib



Various Dosing Schedules: Based on disease and combinations

Approvals



Merkel Cell

Cutaneous Sq Cell

Mesothelioma

Cervical

Esophageal

Hodgkin's Lymphoma

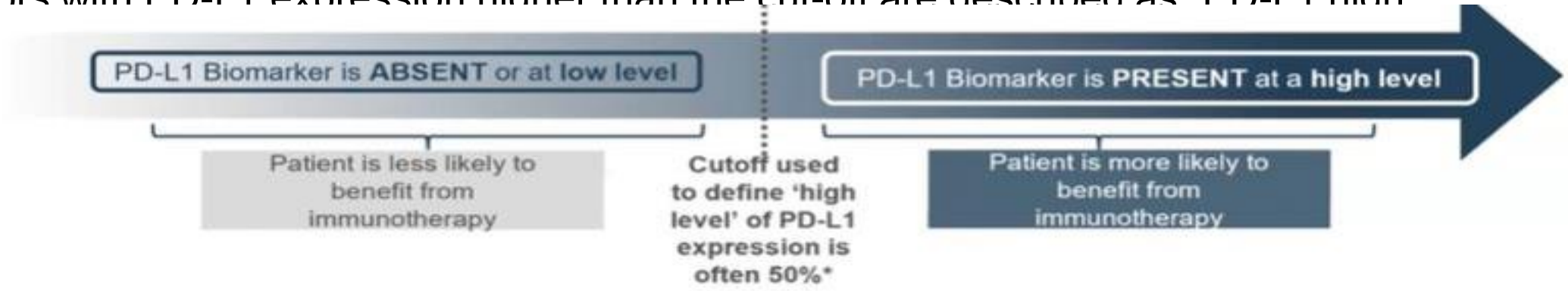
Primary mediastinal large-B cell Lymphoma

Microsatellite instability High or mismatch repair deficient cancers

PD-L1 Expression: Defining the Level of Expression

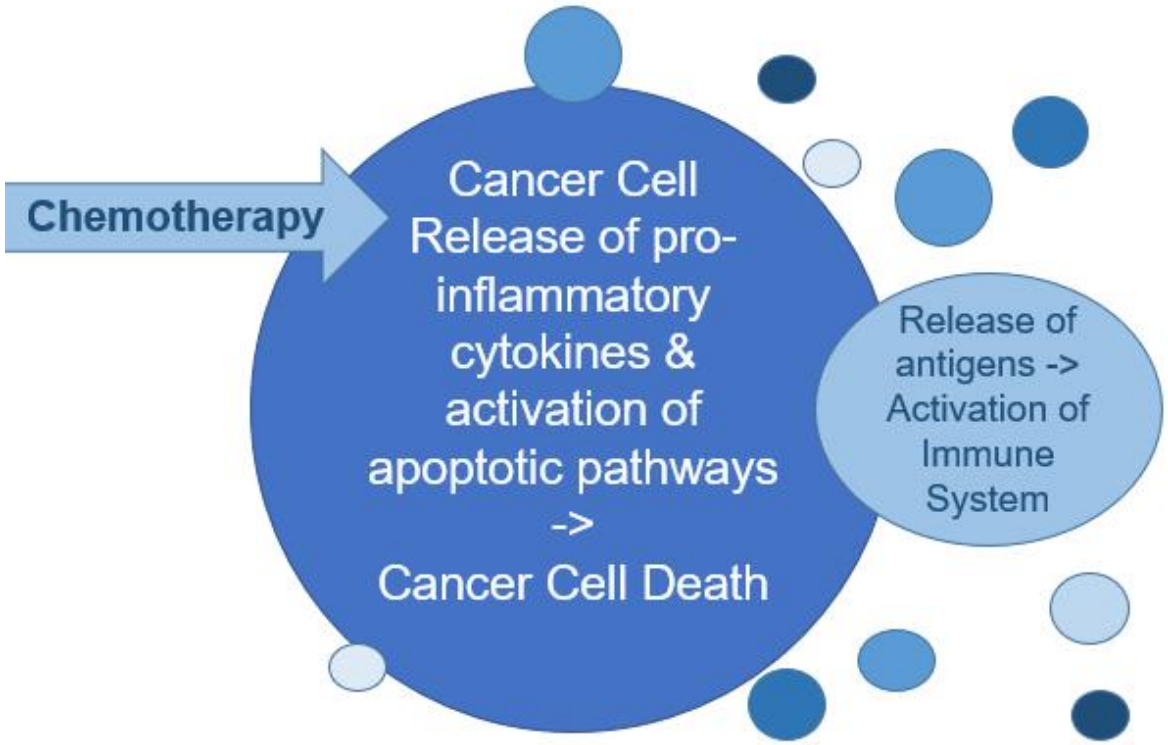
- The expression of PD-L1 on tumor cells can be used to determine how well a patient might benefit from treatment with a PD-L1 inhibitor

- With PD-L1 testing, the dynamic nature of PD-L1 expression means that a "**cut-off**" is more appropriate to define the level of expression at which PD-L1 inhibitor treatment may be beneficial; tumors with PD-L1 expression higher than the cut-off are described as "PD-L1 high"

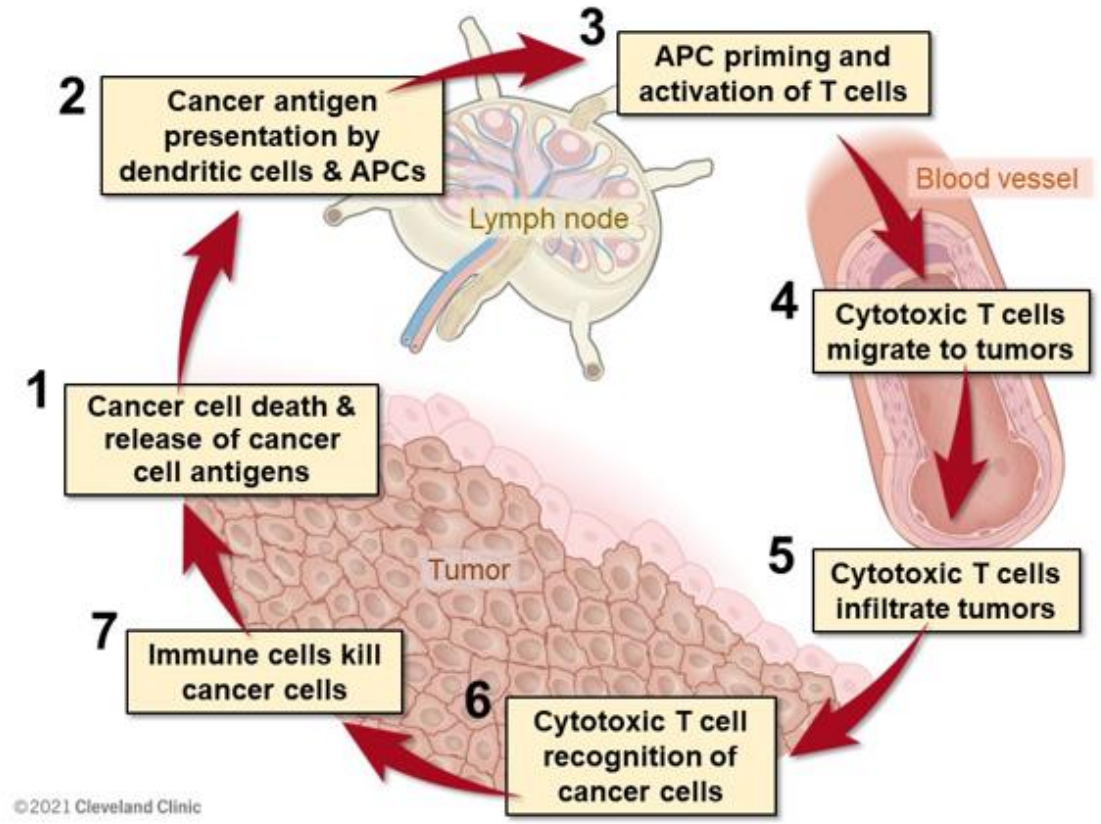


Rational for Combination Therapy

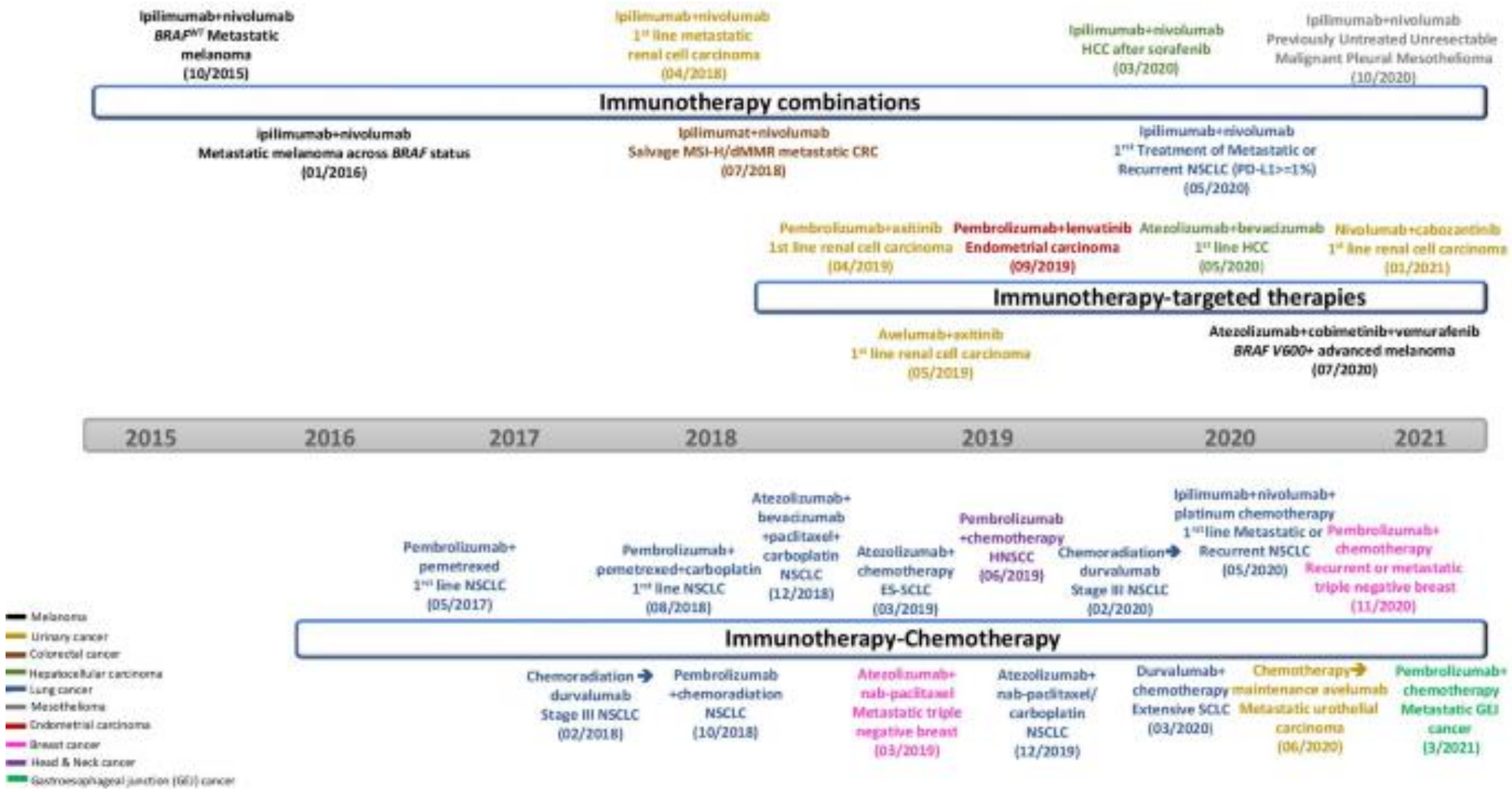
Chemotherapy: MOA-Priming



Immune Checkpoint: MOA



Adapted From: Chen & Mellman (2013).Immunity. 39



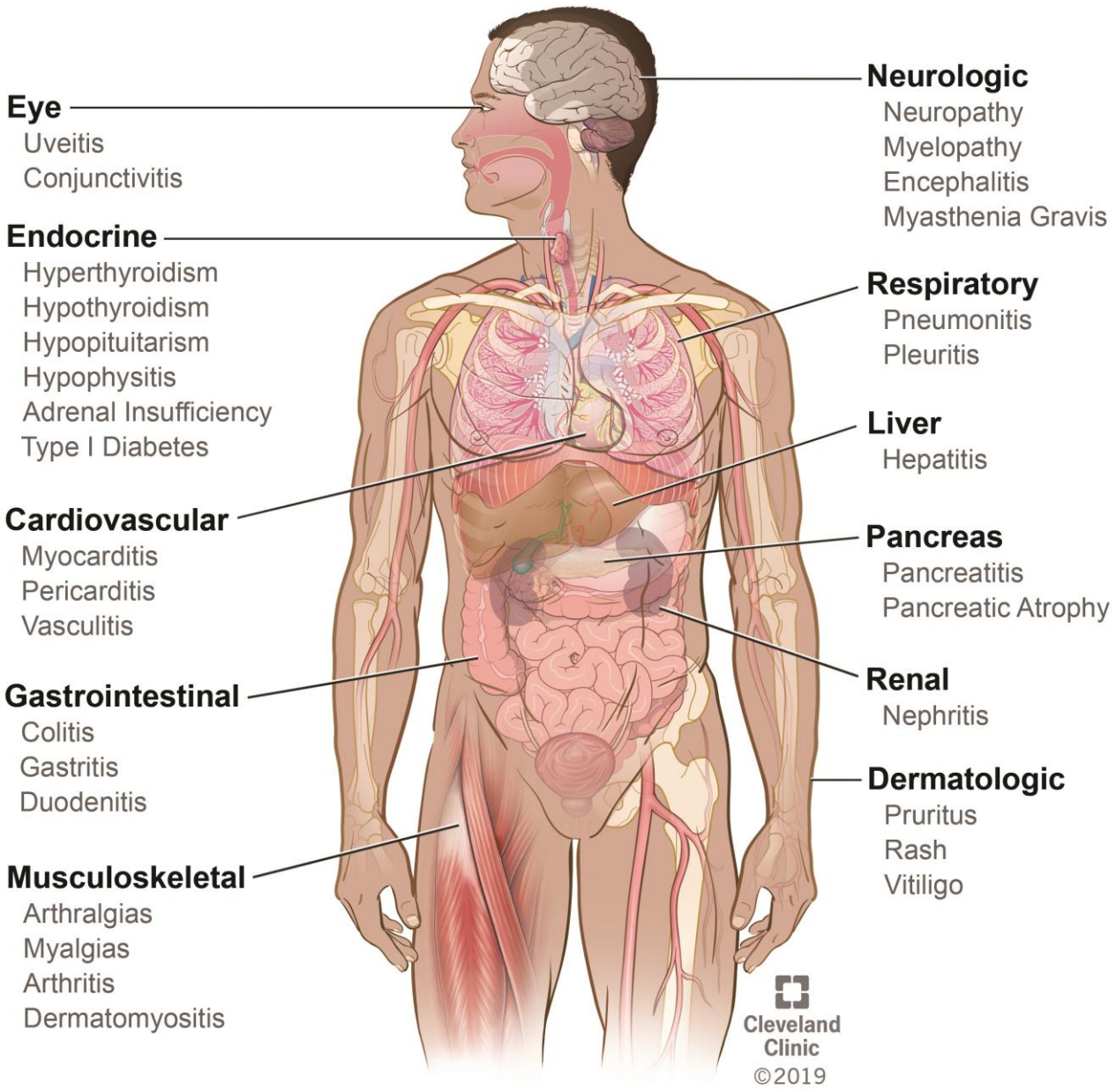
Immune Related Adverse Events (irAEs)

Organs Affected

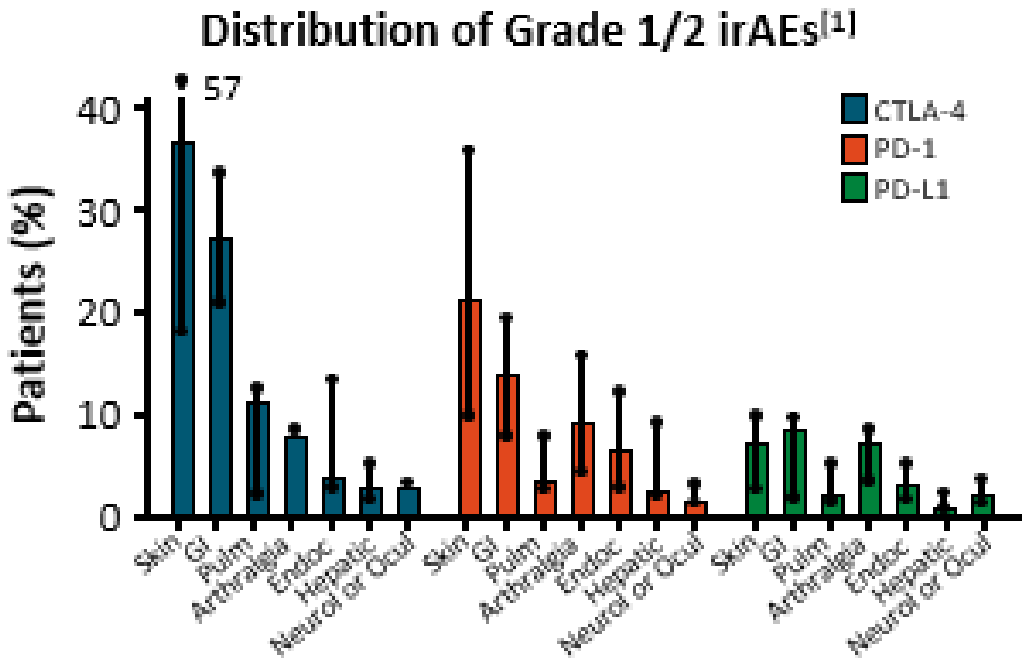
- May affect one or many organs
- Concurrently or sequentially

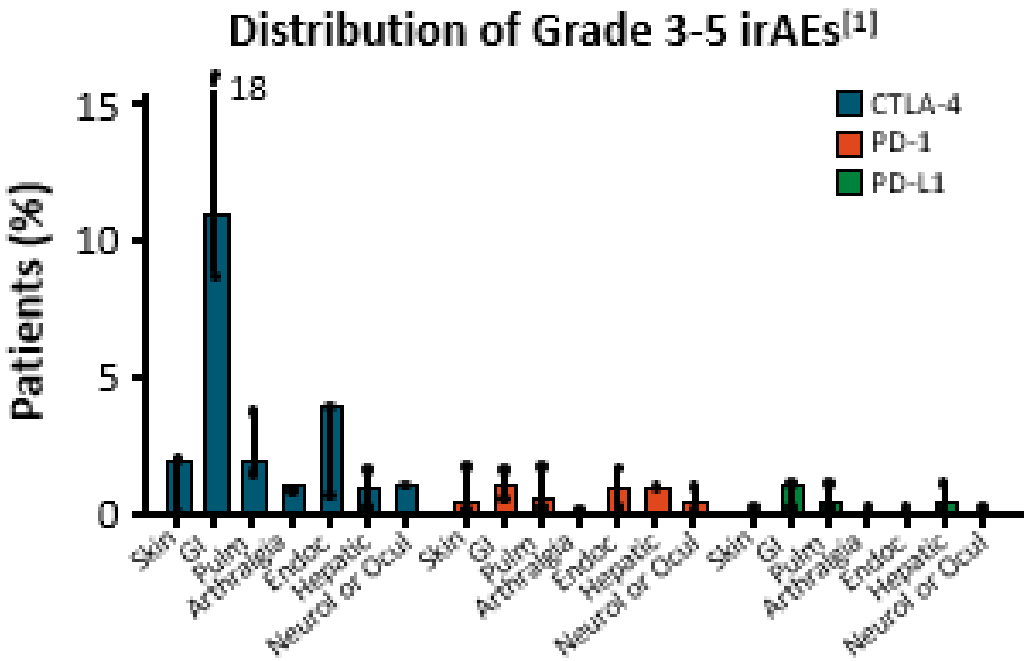
Severity

- Incidence/severity higher in anti-CTLA-4 agents
- High grade AE to one class does not preclude safe administration to another class



Frequency of irAEs

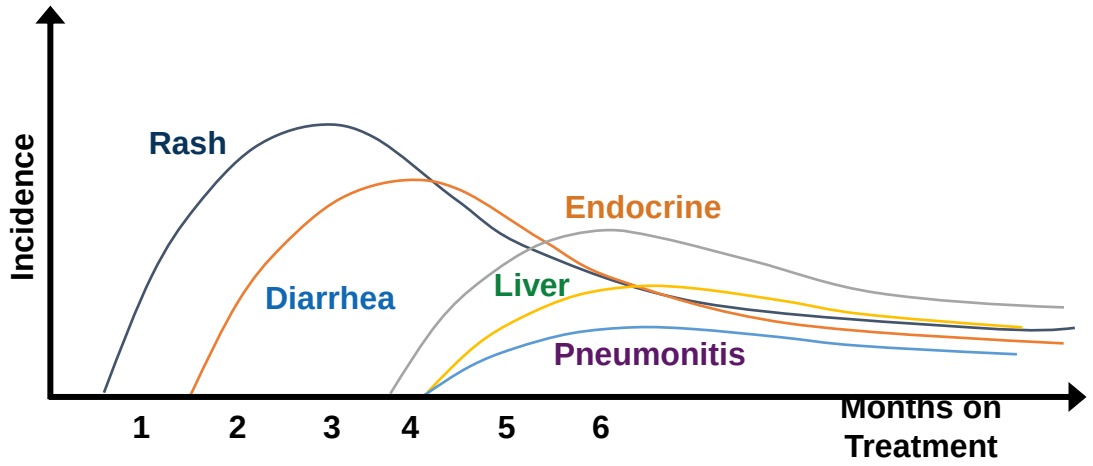




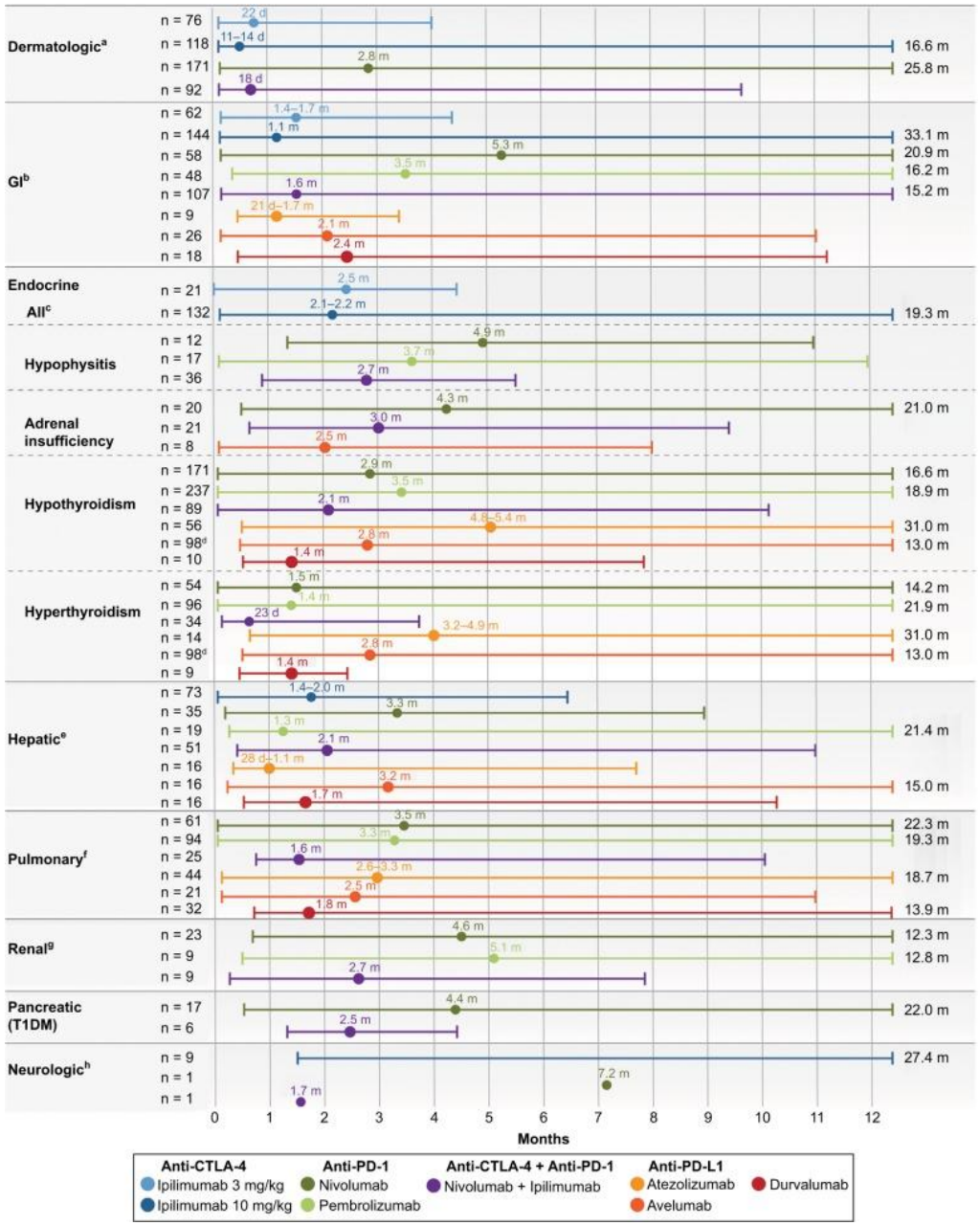
Michot. 2016. Eur J Cancer 54:139

Immune-related Adverse Events (irAEs)

- Onset
  - Median onset is 5-12 weeks after initiation
    - Within days of first dose
    - After months of treatment
    - After discontinuation of therapy



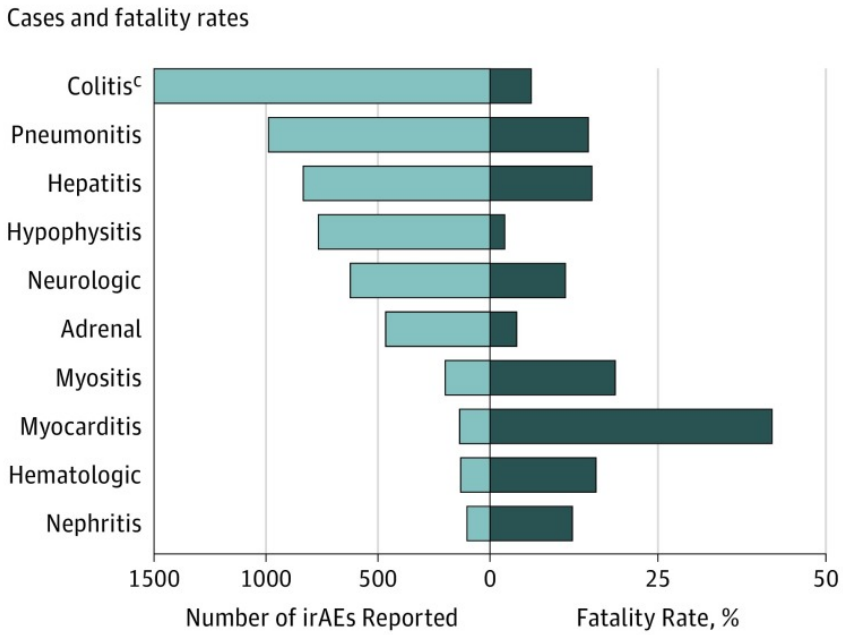
Haanen JB, et al. Ann Oncol. 2017;28:iv119-iv142; Postow MA, et al. N Engl J Med. 2018;378:158-168;

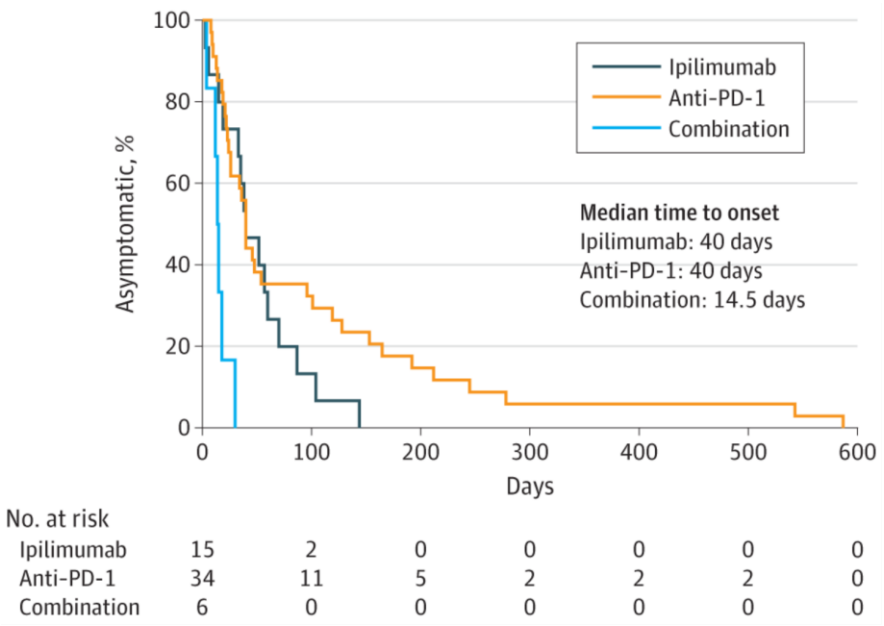


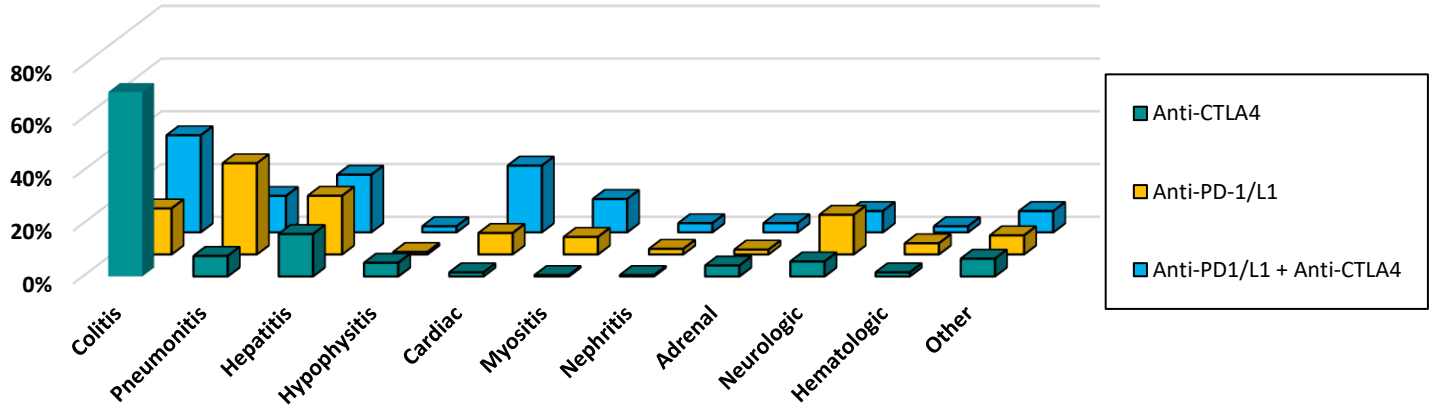
Davies, M. & Duffield, E. (2017). Safety of checkpoint inhibitors for cancer treatment: strategies for patient monitoring and management of immune-mediated adverse events. *ImmunoTargets and Therapy*. 6:51-71

Fatal irAEs

- Chemotherapy Fatalities: 1.4%
- ICB Fatality rates vary: 0.25%-1.1%



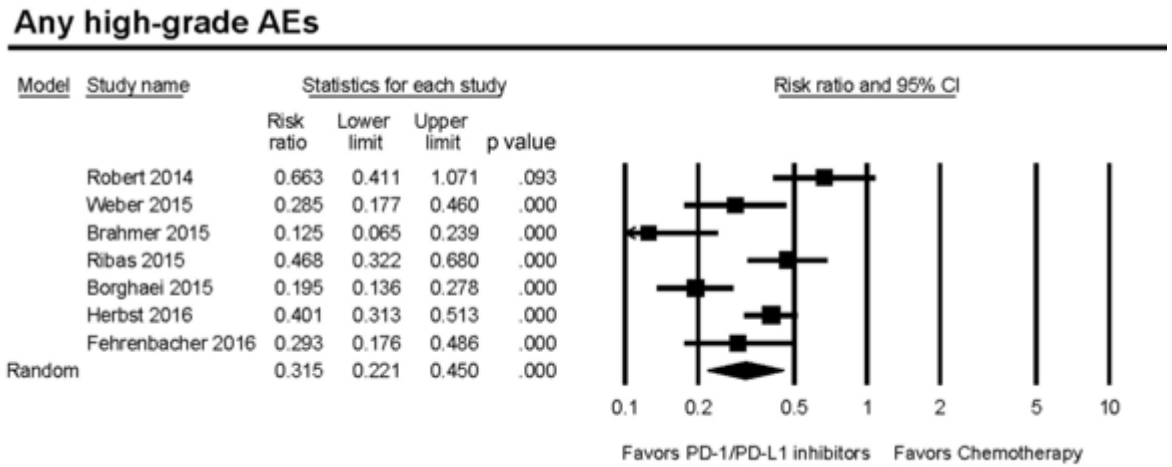




Wang et al. 2018. JAMA Oncol. ; Nishijima et al. 2017. The Oncologist

irAEs Differ from Chemotherapy AEs

	Chemotherapy	Immunotherapy
Incidence (moderate/sever Aes)	Almost all patients	Majority Without
AE profile	Well described	Variable
Affected Organs	Few organs affected	Any Organ
Time Course	Well Established	Variable (even after end of tx)
	Predictable	**Relatively Unpredictable**



Lower total AEs* (67.6% vs 82.9%)
Lower high-grade AEs* (11.4% vs 35.7%)
Lower treatment discontinuation* (4.5% vs 11.1%)
Lower treatment-related deaths (0.6% vs 1.4%)

*Statistically Significant

Nishijima et al 2017. The Oncologist

Preparing Patients for Therapy

- Patient Assessment
  - Evaluate for Auto-immune risks
    - Auto-immune diagnosis
    - Prior organ transplantation
      - Risk of graft loss
  - Medication reconciliation: including OTC and herbal
    - Immunosuppressants, immune stimulants, immune modulating

- Baseline review of systems
- Physical Examination
- Laboratory Evaluation
  - Complete blood count
  - Comprehensive Metabolic Panel
  - Thyroid Panel
  - Lipase
  - Troponin
  - CK

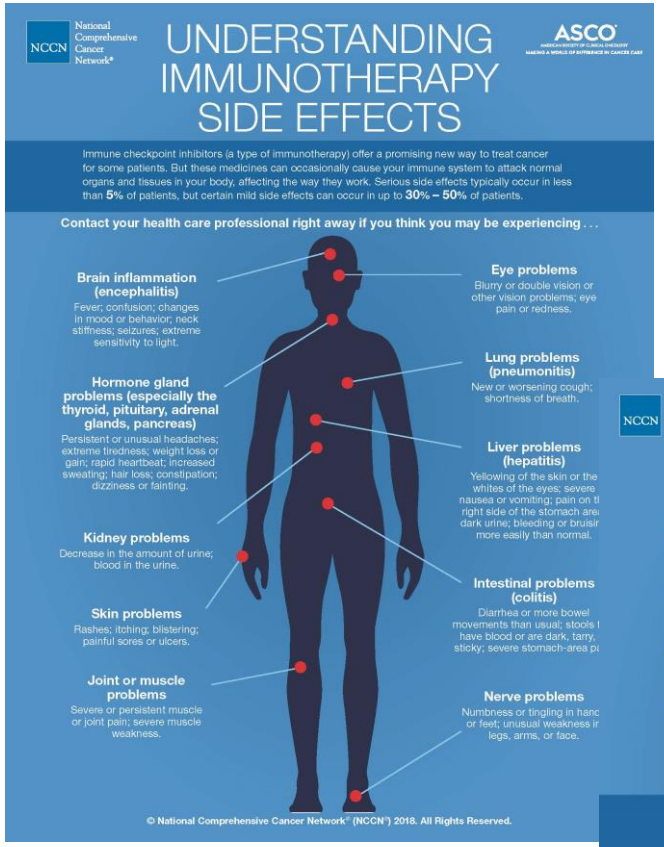
Preparing Patients for Therapy: Education

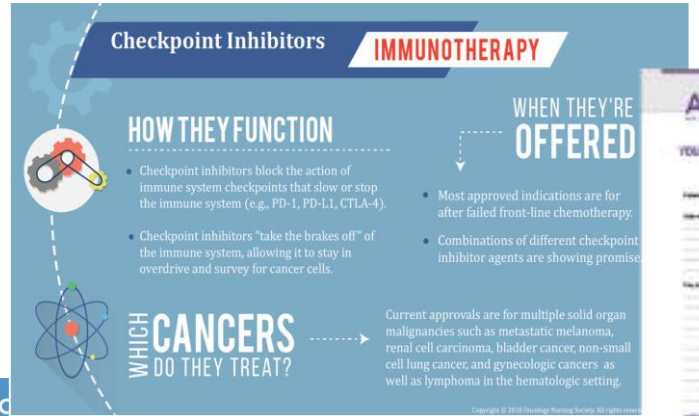
- How the immune system works
- Potential IrAEs
- Mechanism of IRAEs
- Timing of onset
- Signs & symptoms to report
- Expectation of treatment

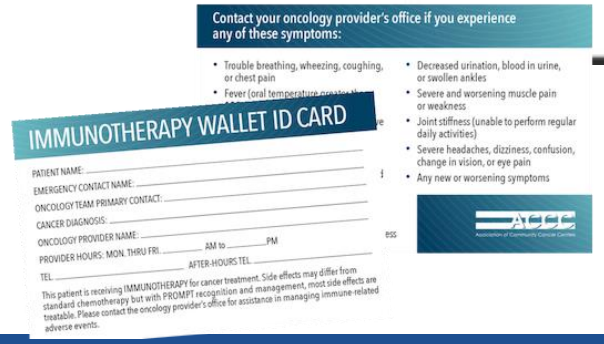
* Consider language, culture, literacy, timing and access

- Different AE profile than chemotherapy
- Onset of the AE may help to diagnose etiology
- irAEs can overlap and/or worsen with subsequent therapies
- New irAEs can develop during subsequent therapies
  - Can be latent irAEs

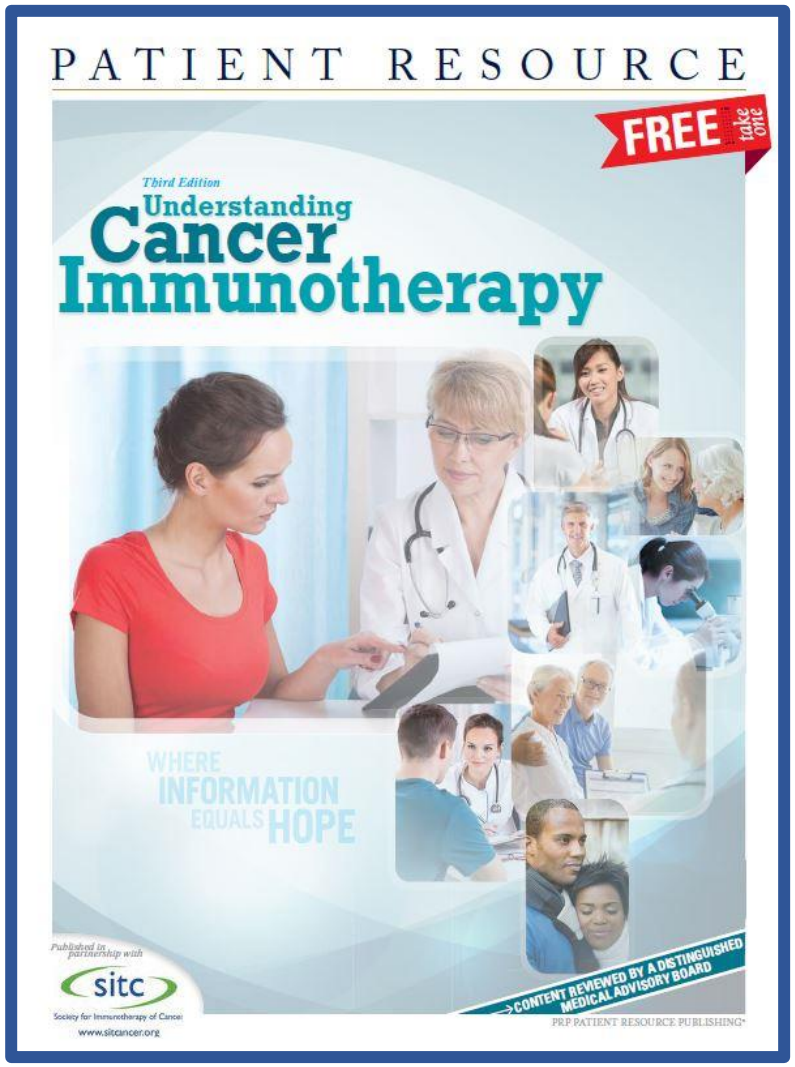
Patient Education Resources

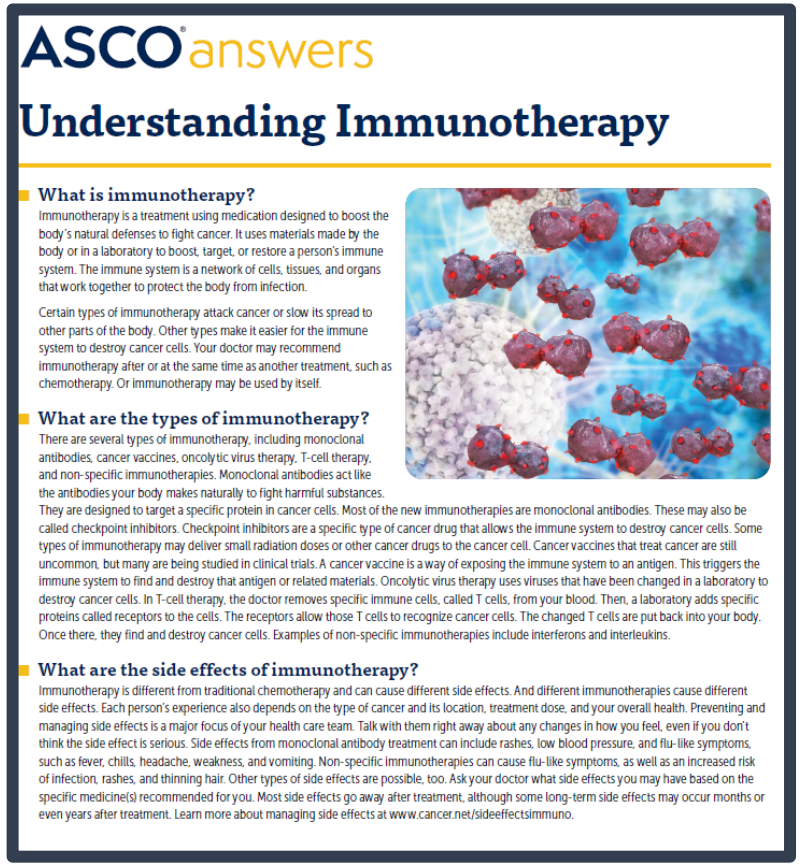






Patient Education Resources





ASCO answers

Understanding Immunotherapy

What is immunotherapy?

Immunotherapy is a treatment using medication designed to boost the body's natural defenses to fight cancer. It uses materials made by the body or in a laboratory to boost, target, or restore a person's immune system. The immune system is a network of cells, tissues, and organs that work together to protect the body from infection.

Certain types of immunotherapy attack cancer or slow its spread to other parts of the body. Other types make it easier for the immune system to destroy cancer cells. Your doctor may recommend immunotherapy after or at the same time as another treatment, such as chemotherapy. Or immunotherapy may be used by itself.

What are the types of immunotherapy?

There are several types of immunotherapy, including monoclonal antibodies, cancer vaccines, oncolytic virus therapy, T-cell therapy, and non-specific immunotherapies. Monoclonal antibodies act like the antibodies your body makes naturally to fight harmful substances. They are designed to target a specific protein in cancer cells. Most of the new immunotherapies are monoclonal antibodies. These may also be called checkpoint inhibitors. Checkpoint inhibitors are a specific type of cancer drug that allows the immune system to destroy cancer cells. Some types of immunotherapy may deliver small radiation doses or other cancer drugs to the cancer cell. Cancer vaccines that treat cancer are still uncommon, but many are being studied in clinical trials. A cancer vaccine is a way of exposing the immune system to an antigen. This triggers the immune system to find and destroy that antigen or related materials. Oncolytic virus therapy uses viruses that have been changed in a laboratory to destroy cancer cells. In T-cell therapy, the doctor removes specific immune cells, called T cells, from your blood. Then, a laboratory adds specific proteins called receptors to the cells. The receptors allow those T cells to recognize cancer cells. The changed T cells are put back into your body. Once there, they find and destroy cancer cells. Examples of non-specific immunotherapies include interferons and interleukins.

What are the side effects of immunotherapy?

Immunotherapy is different from traditional chemotherapy and can cause different side effects. And different immunotherapies cause different side effects. Each person's experience also depends on the type of cancer and its location, treatment dose, and your overall health. Preventing and managing side effects is a major focus of your health care team. Talk with them right away about any changes in how you feel, even if you don't think the side effect is serious. Side effects from monoclonal antibody treatment can include rashes, low blood pressure, and flu-like symptoms, such as fever, chills, headache, weakness, and vomiting. Non-specific immunotherapies can cause flu-like symptoms, as well as an increased risk of infection, rashes, and thinning hair. Other types of side effects are possible, too. Ask your doctor what side effects you may have based on the specific medicine(s) recommended for you. Most side effects go away after treatment, although some long-term side effects may occur months or even years after treatment. Learn more about managing side effects at www.cancer.net/sideeffectsimmuno.

Questions to ask the health care team

Regular communication is important for making informed decisions about your health care. It can be helpful to bring someone along to your appointments to take notes. Consider asking your health care team the following questions:

- What type of immunotherapy do you recommend and why?
- What is the goal of this treatment? To destroy cancer cells? To slow down the spread of cancer to other parts of the body?
- What immunotherapy clinical trials are available for me? Where are they located, and how do I find out more about them?
- Will immunotherapy be my only treatment or will other treatments be a part of my treatment plan?
- How will the treatment be given?
- How often will I receive this treatment? How long does each treatment session take?
- Where will I receive treatment?
- What will I experience when I receive this treatment?
- What can I do to get ready for this treatment?
- What are the possible short-term and long-term side effects of this treatment?
- How can those side effects be avoided or managed?
- How soon should I let you know about changes in how I'm feeling?
- How will this treatment affect my daily life? Will I be able to work, exercise, and perform my usual activities?
- If I'm worried about managing the costs of cancer care, who can help me?
- If I have a question or problem, who should I call?

Find more questions to ask the health care team at www.cancer.net/immunotherapy. For a digital list of questions, download Cancer.Net's free mobile app at www.cancer.net/app.

Words to know

Antibodies: Proteins that fight infection.

Antigens: Harmful substances that cause your body to make antibodies.

Biologic therapy: Another name for immunotherapy.

Clinical trial: A research study that tests a new treatment or drug.

Intravenous immunotherapy: Medication given directly into a vein.

Medical oncologist: A doctor who specializes in treating cancer with medication.

Oncolytic virus therapy: A treatment that uses genetically modified viruses to destroy cancer cells.

Oral immunotherapy: Medication swallowed as a pill, capsule, or liquid.

Radioimmunotherapy: An immunotherapy treatment that delivers radiation directly to cancer cells.

Side effects: Problems that happen during or after treatment. These could be from the cancer or how the treatment affects your body.

Targeted therapy: Treatment that targets a cancer's specific genes, proteins, or the tissue environment that contributes to cancer.

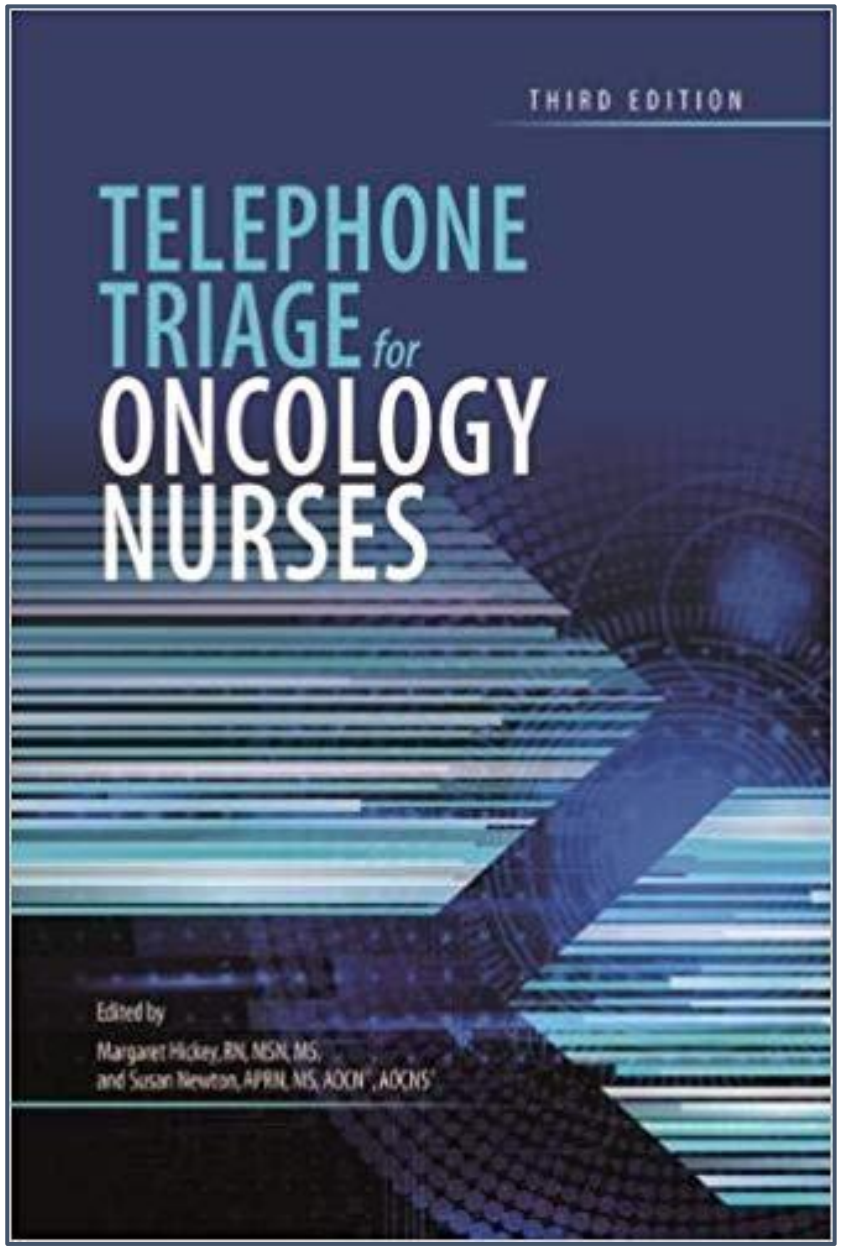
T-cell therapy: A treatment that modifies a patient's own T cells to destroy cancer cells.

Health Care Professionals: To order more printed copies, please call 888-273-3508 or visit www.cancer.net/estore.

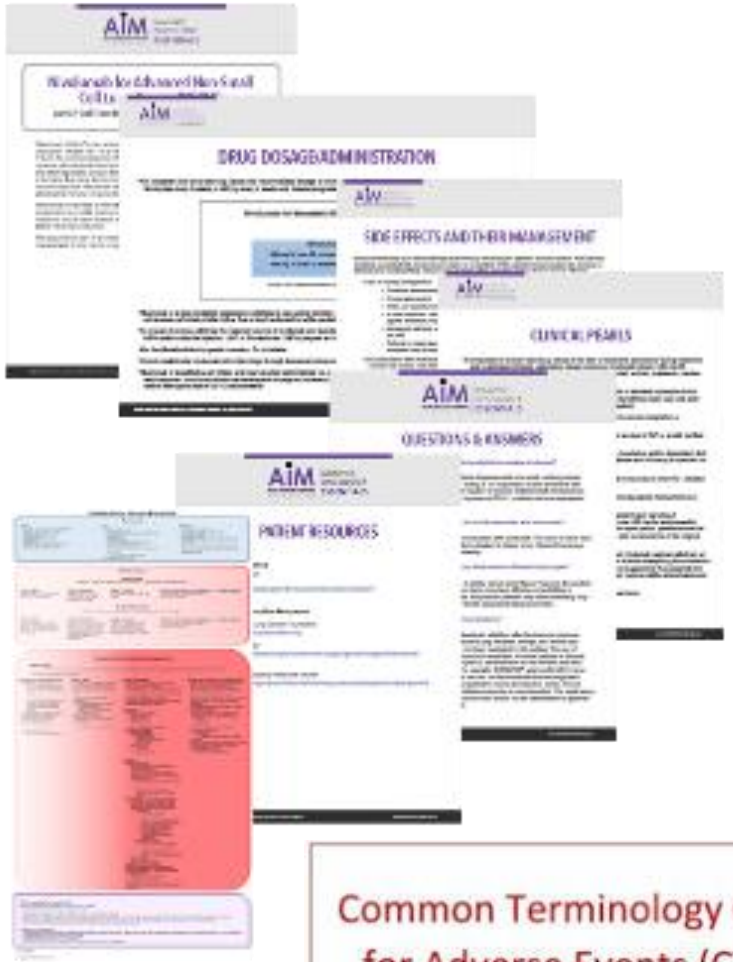
MADE AVAILABLE THROUGH

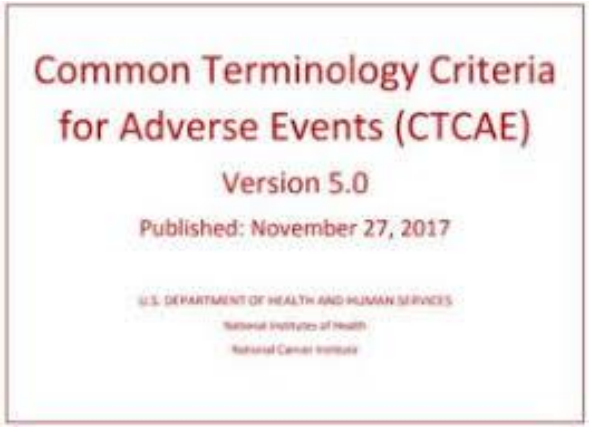
Professional Resources

- All staff must be educated on triage
- Educate patients on the telephone triage process
- Provides tool to distinguish patients who can be treated at home and those that need formal evaluation or hospitalization
- Early identification of symptoms may minimize severity of IRAE

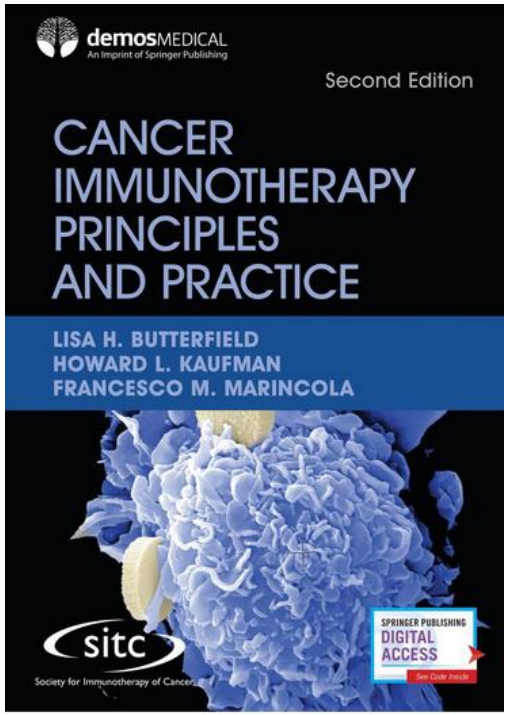


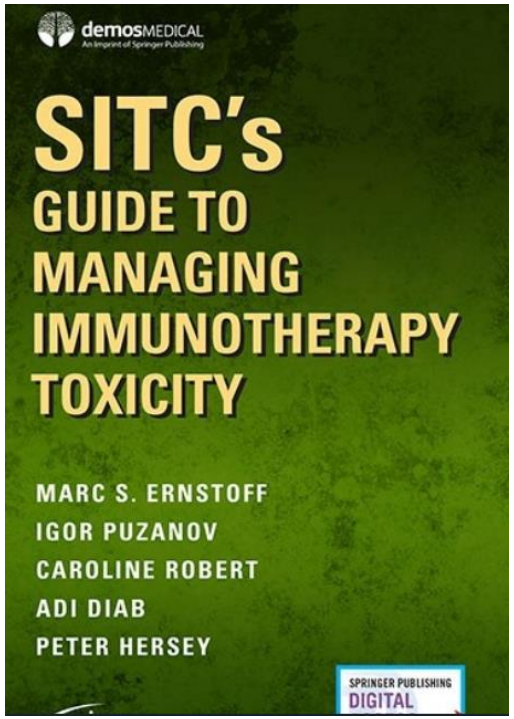
Professional Resources
Clinical Practice Guidelines (CPGs)





SITC Professional Resources

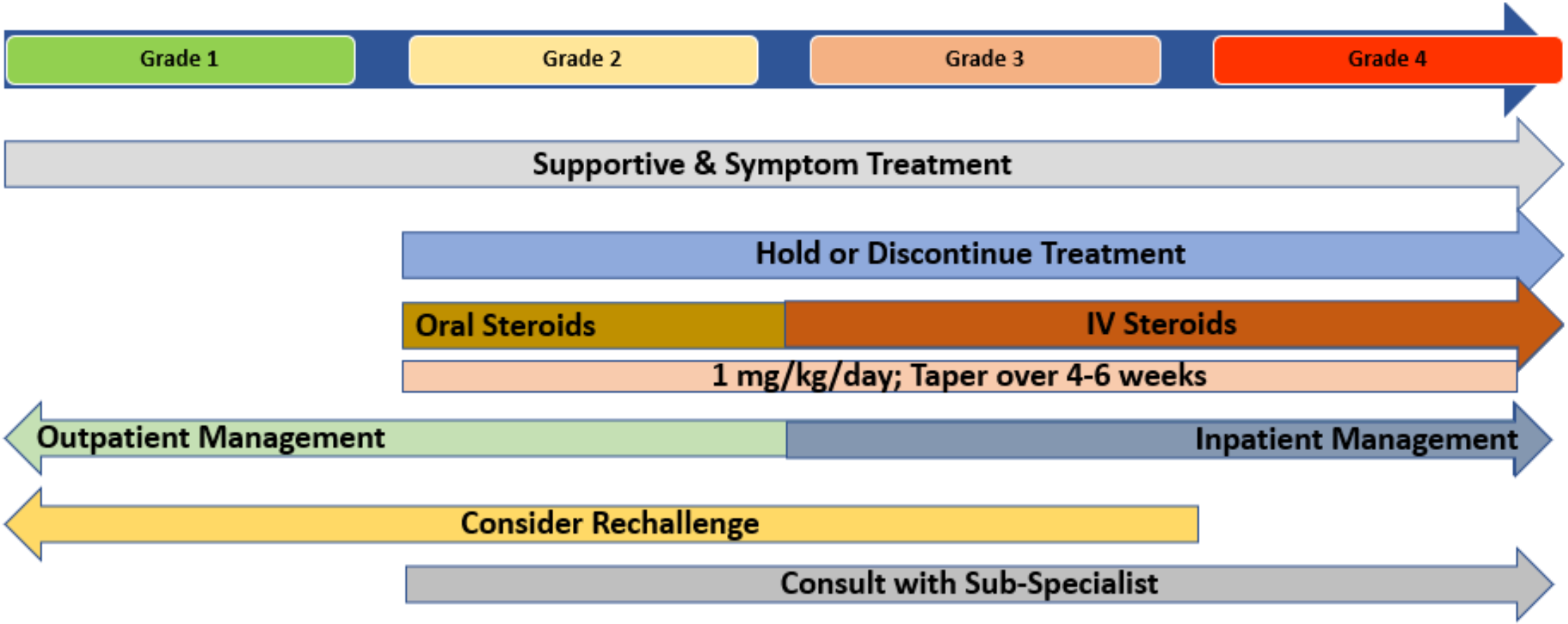




- Acute Leukemia
- Breast Cancer
- Gastrointestinal
- ICI-related adverse events
- Head & Neck Squamous Cell
- Lung & Mesothelioma
- Gynecologic
- Hepatocellular
- Lymphoma
- Melanoma
- Multiple Myeloma
- Renal Cell
- Prostate
- Urothelial
- Non-Melanoma Skin

General Management of irAEs.

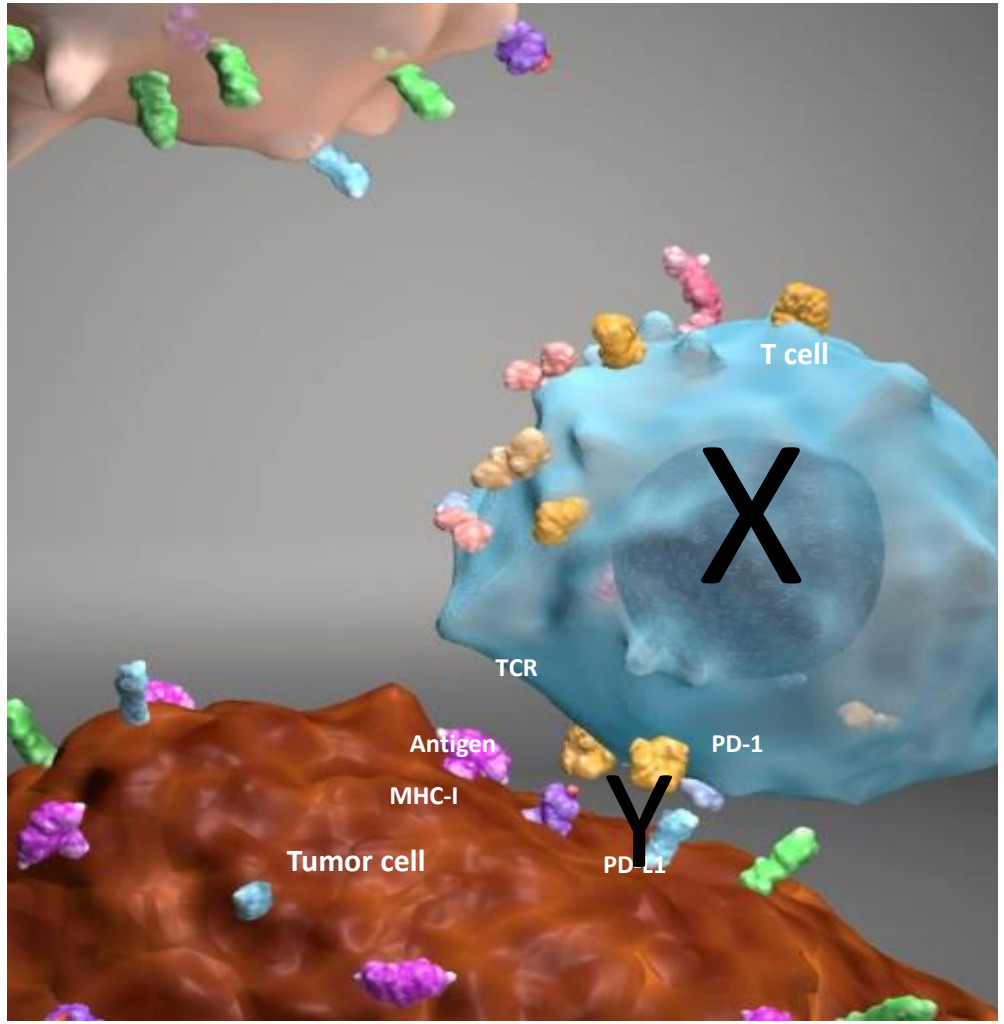
Common Terminology Criteria for Adverse Events (CTCAE)
Version 5.0
Published: November 27, 2017
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES



Davies M (2023); Adapted from NCCN, SITC, & ASCO Guidelines

Why do IRAE's happen to patients on immunotherapy?

- Explain to patients it is due to overactive T-cell activity
  - Can mimick auto-immune diseases
- May help them understand importance to call
- Educate patients on the common areas to be affected:
  - In NSCLC, rates of pneumonitis tend to be higher, 7-13%
  - Rates of colitis higher in CTLA-4 containing regimens.



Zhai X, Zhang J, Tian Y, et al. Cancer Biol Med (2020). 17(3):599-611; IRAE- Immune-related adverse event

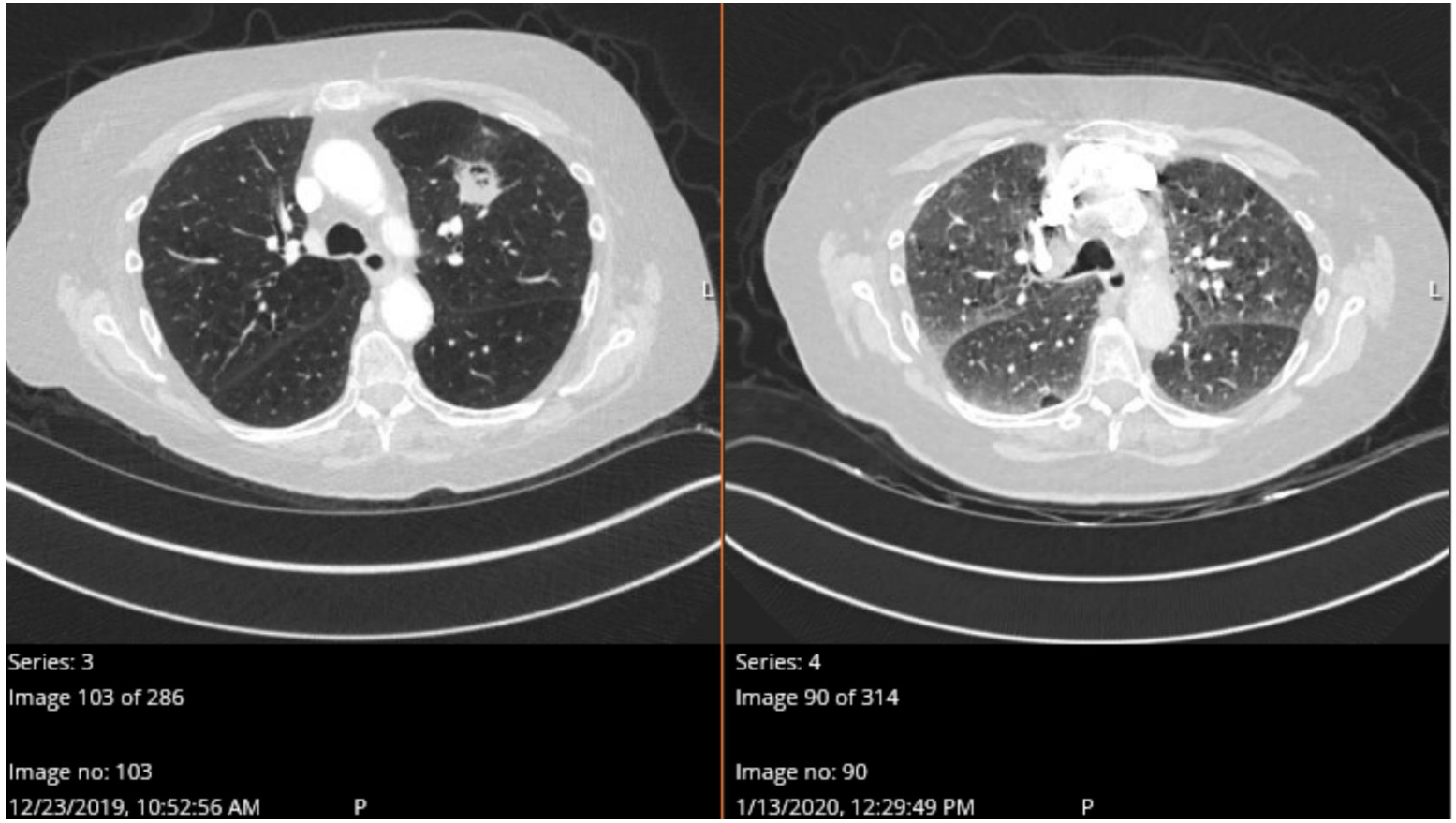
Early Detection Key

- If we can detect these IRAE's earlier, (grade 1 or 2), and manage them, better chance to stay on therapy and less risk of severe toxicity to patients.
- Once toxicity is grade 3, and definitely for grade 4, requires permanent discontinuation of immunotherapy.
- For patients receiving immunotherapy, consider all reported symptoms or side effects as related to immunotherapy until you can reasonably determine it is not. (Anything on the body can be inflamed)

Pneumonitis: What you will find, when to bring them in?

- Sometimes called ILD
- Inflammation of the pulmonary tissues from T-cell assault
- Symptoms are acute onset SOB over 1-2 days; dry irritating cough; hypoxia

After 1 treatment with Pembrolizumab



ILD= Interstitial Lung Disease

Pneumonitis:

- Rates of pneumonitis are higher in patients with lung cancer 13-19% as opposed to 3-5% rates reported across other disease sites.
- Can occur at any time
- Differentials: PE, Pleural effusion, Pneumonia
- Must get a CT chest to evaluate
- Treatment promptly with prednisone at around 1-2mg/kg and taper slowly over 4-6 weeks. It is good to get a repeat CT chest prior to resuming immunotherapy to be sure the pneumonitis has resolved/improved.

Suresh K, et al. J Thoracic Oncol. 2018;13(12) 1930-1939. https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf; ICI_PULM-1

Colitis: How to evaluate, when to bring them in, what is “diarrhea” vs “colitis”

- First question: how many stools per day over your baseline?
  - This establishes your grading of diarrhea
- Workup:
  - Do you need to confirm with diagnostics when symptoms present?
  - CT abdomen can show pancolitis in more severe cases
  - Do not recommend scope at first, especially when inflamed bowel
  - Fecal calprotectin (and other r/o stool specimens if/when indicated)

Diarrhea	Description
Grade 1	<4 stools over baseline
Grade 2	4-6 stools over baseline
Grade 3	> 7 stools over baseline
Grade 4	Life threatening

Colitis	Description
Grade 1	Asymptomatic; diagnostic findings only
Grade 2	Abdominal pain; blood or mucus in the stool
Grade 3	Severe abdominal pain; peritoneal signs
Grade 4	Life Threatening

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf

Colitis/Diarrhea:

- Diarrhea vs Colitis occurs in:
  - 44% and 16% in combined ICI regimens, respectively
  - 11% and 1% in PD-1/L1 regimens, respectively
- Colitis is more serious and diarrhea can lead to colitis
- Treatment is with high dose prednisone, again 1-2mg/kg, consider IV
- Upon resumption of the immunotherapy, about 34% experienced recurrence of colitis
- Consider infliximab or Vedolizumab if not responsive to prednisone

Brahmer JR et al. Journal for ImmunoTherapy of Cancer 2021;9:e002435.doi:10.1136/jitc-2021-002435; https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf; ICI_GI-2

Nephritis/Hepatitis: The paper toxicity?!

Nephritis

- Usually not symptomatic initially
- Sharp rise in Creat;
- Not gradual

12/29/2022 9:32:00 AM	Final	Creatinine	1.65H	mg/dL	0.64-1.27
12/12/2022 10:13:00 AM	Final	Creatinine	1.93H	mg/dL	0.64-1.27
12/12/2022 10:13:00 AM	Final	Creatinine	1.91H	mg/dL	0.64-1.27
11/28/2022 1:41:00 PM	Final	Creatinine	2.72H	mg/dL	0.64-1.27
11/28/2022 1:41:00 PM	Final	Creatinine	2.72H	mg/dL	0.64-1.27
11/25/2022 4:14:00 AM	Final	Creatinine	4.02H	mg/dL	0.64-1.27
11/24/2022 5:02:00 AM	Final	Creatinine	4.37H	mg/dL	0.64-1.27
11/23/2022 5:01:00 AM	Final	Creatinine	4.78H	mg/dL	0.64-1.27
11/22/2022 12:17:00 PM	Final	Creatinine	5.33H	mg/dL	0.64-1.27
11/22/2022 12:17:00 PM	Final	Creatinine	5.4H	mg/dL	0.6-1.0
11/21/2022 3:13:00 PM	Final	Creatinine	5.82H	mg/dL	0.64-1.27

Hepatitis

- Usually not symptomatic initially
- Sharp rise in LFT's;
- Not gradual

Collected Date/Time	Sts	Test	Value	Units	Range
12/21/2021 1:59:00 PM	Final	ALT	25	U/L	17-63
12/13/2021 10:55:00 AM	Final	ALT	40	U/L	17-63
11/30/2021 9:00:00 AM	Final	ALT	15L	U/L	17-63
11/5/2021 11:06:00 AM	Final	ALT	24	U/L	17-63
10/10/2021 3:04:00 AM	Final	ALT	147H	U/L	17-63
10/9/2021 10:34:00 AM	Final	ALT	180H	U/L	17-63
10/5/2021 1:46:00 PM	Final	ALT	212H	U/L	17-63
9/14/2021 1:14:00 PM	Final	ALT	23	U/L	17-63
8/30/2021 1:42:00 PM	Final	ALT	37	U/L	17-63
8/25/2021 10:04:00 AM	Final	ALT	52	U/L	17-63
8/17/2021 1:08:00 PM	Final	ALT	23	U/L	17-63
7/27/2021 2:09:00 PM	Final	ALT	34	U/L	17-63

Nephritis/Hepatitis: The paper toxicity?!

- Usually not something patients will call in with since not usually “feeling” it
- Don’t forget to be checking these labs each with each treatment, can happen at any time
- Prompt treatment with prednisone; IV hydration likely in order for the nephritis cases
- Recheck labs in a week or less, follow up quickly to be sure steroids are helping

Hypo/Hyperthyroidism: Paper toxicity versus Symptomatic

Hypothyroidism

- TSH is high, T4 (thyroxine) is low
- Most times not symptomatic, but can be: Sluggish, gaining weight, sensitivity to cold, slow movements/thoughts
- Treatment is replacement of thyroid hormone with levothyroxine
- If asymptomatic, can wait till TSH is over 10 to initiate therapy.

Hyperthyroidism

- TSH is low, T4 is high
- usually just watch it and they become hypothyroid eventually
- If symptomatic: weight loss, jittery, hyperactive, tachycardia
- endocrine consult, consider treating symptoms such as tachycardia, etc.

https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf; ICI_ENDO-2

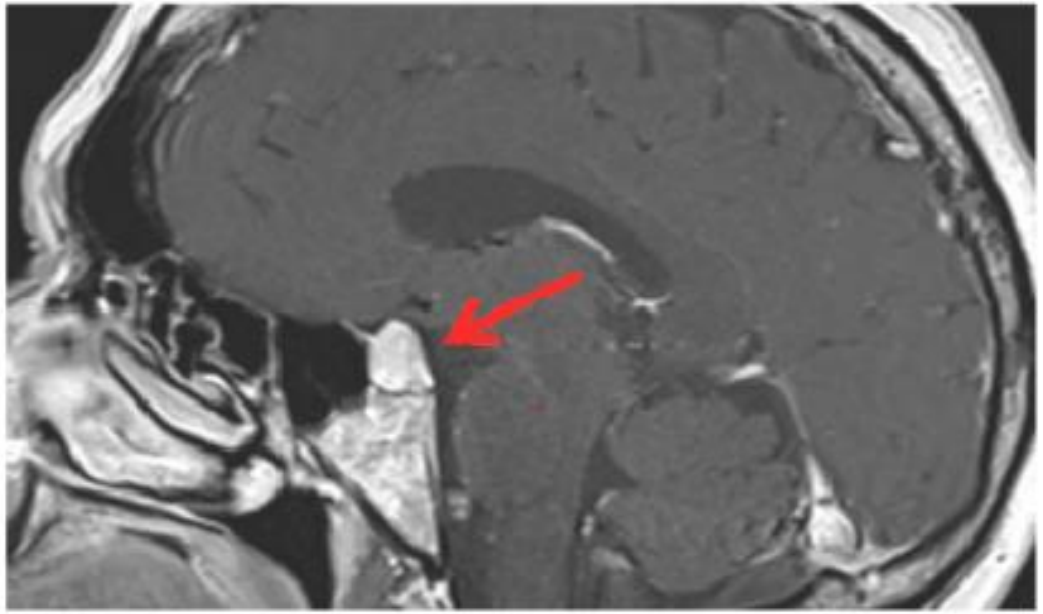
Hypophysitis/Adrenal Insufficiency

- The pituitary gland becomes inflamed due to overactive T-cell activity
- Thus, in turn, it does not send signals to the adrenal glands to produce cortisol (causing secondary AI). Can also contribute to hypothyroidism.
  - 6.4% in combination ICI
  - 3.2% anti-CTLA4
  - 1-5% in PD-1/PD-L1 therapy*
- Symptoms: very, very fatigued, hypotensive, anorexia
- Labs: check cortisol (9am preferred…); ACTH can be useful as well. Put the cortisol level into context.
- MRI brain (with pituitary cuts)- sometimes will show enlarged pituitary gland.
- Consult with Endocrine, can be tricky

Johnson et al. J Natl Compr Canc Netw 2023;21(3):281–287. doi: 10.6004/jnccn.2022.7098; *Observational studies

Hypophysitis/Adrenal Insufficiency

- Bring patient in, get labs, likely needs IV hydration, stop BP meds if hypotensive
- Replace cortisol with oral (or acutely IV) hydrocortisone.
- Corticosteroids only if inflammation is causing neurologic issues.



Mahzari M, et al. *Clinical Medicine Insights: Endocrinology and Diabetes*. 2015:8 21–28 doi:10.4137/CMED.S22469

Dermatitis:

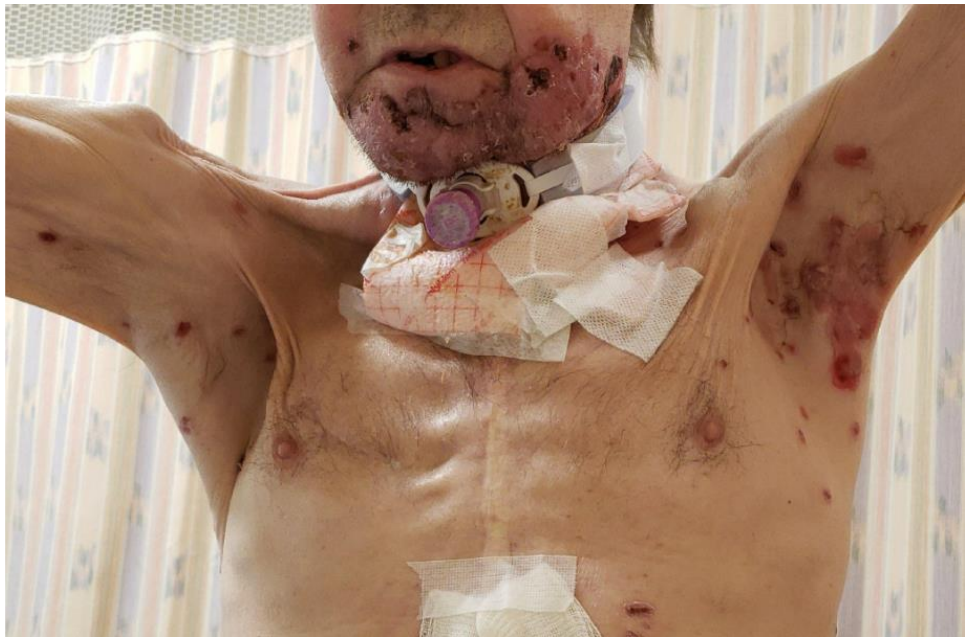
- Overactive T-cells cause skin eruptions.
- Mostly mild rashes
- More common with anti-CTLA4 regimens and in patients with melanoma
- Grading is hard, there are 2 categories, bullous dermatitis and Rash acneiform

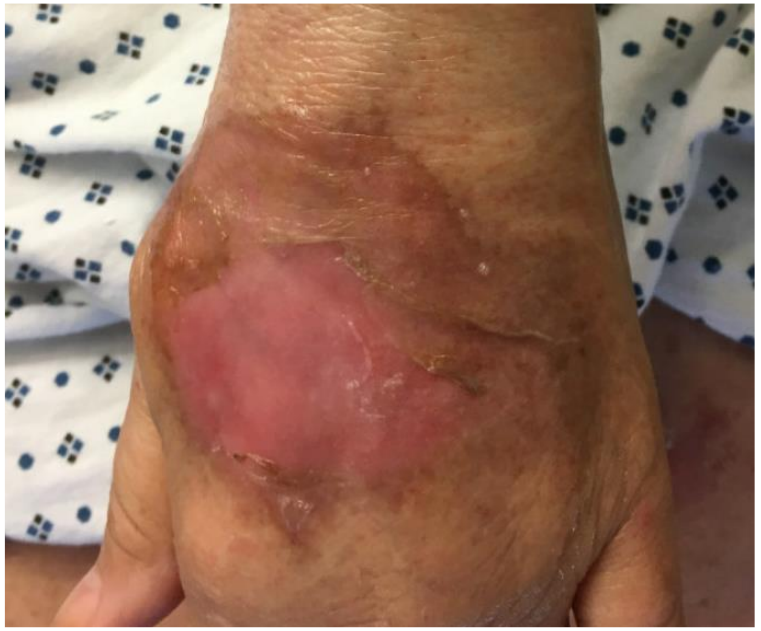
Rash (acneiform)	Description
Grade 1	<10% BSA
Grade 2	10-30% BSA
Grade 3	> 30% BSA
Grade 4	Life threatening

Bullous Dermatitis	Description
Grade 1	<10% BSA blisters
Grade 2	10-30% BSA blisters
Grade 3	> 30% BSA blisters
Grade 4	Life threatening

Dermatitis:

- More severe reactions can occur
- Grade 3 sometimes can be rechallenged, but not cases of SJS or BP
- Use of topical steroids is common, even for grade 2 rashes. Often will continue immunotherapy for grade 1 and 2 if patient is not bothered by the rash
- Rashes can be of all sorts: eczema; psoriatic; papular; pustular; red/edema





SJS: Steven-Johnson Syndrome; BP: Bullous Pemphigoid

It is recommended to hold ICI therapy for Grade 2 colitis. Grade 2 colitis is described as:

A. Watery diarrhea
B. 1-3 stools over baseline
C. 4-6 stools over baseline
D. Blood or mucus in the stool

Learning Objectives/Poll

Please rate your level of understanding on the below learning objectives in the poll on your screen.

- Describe the expanding landscape of immune checkpoint immunotherapy
- Identify available patient education resources for cancer immunotherapy immune-related adverse events.
- Distinguish the mechanisms of immune-related adverse reactions from cancer immunotherapy treatment
- Recognize and properly triage immune related adverse events related to cancer immunotherapy