Immunotherapy in Oncology

Michelle Ranaghan, MSN, RN, CRNI OCN
Clinical Specialist
Dana- Farber Cancer Institute
Boston, MA

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Objectives

- Identify the types of Immunotherapy used in Oncology
- Understand the basics of Immunotherapy
- List appropriate monitoring for Immunotherapy
- Identify common adverse reactions of Immunotherapy
- Understand the nurse's role in management of adverse reactions with Immunotherapy

Pillars of Cancer Therapy

- Chemotherapy
- Surgery
- Radiation
- Targeted Therapies
- Immunotherapy

Poll Time: Question 1

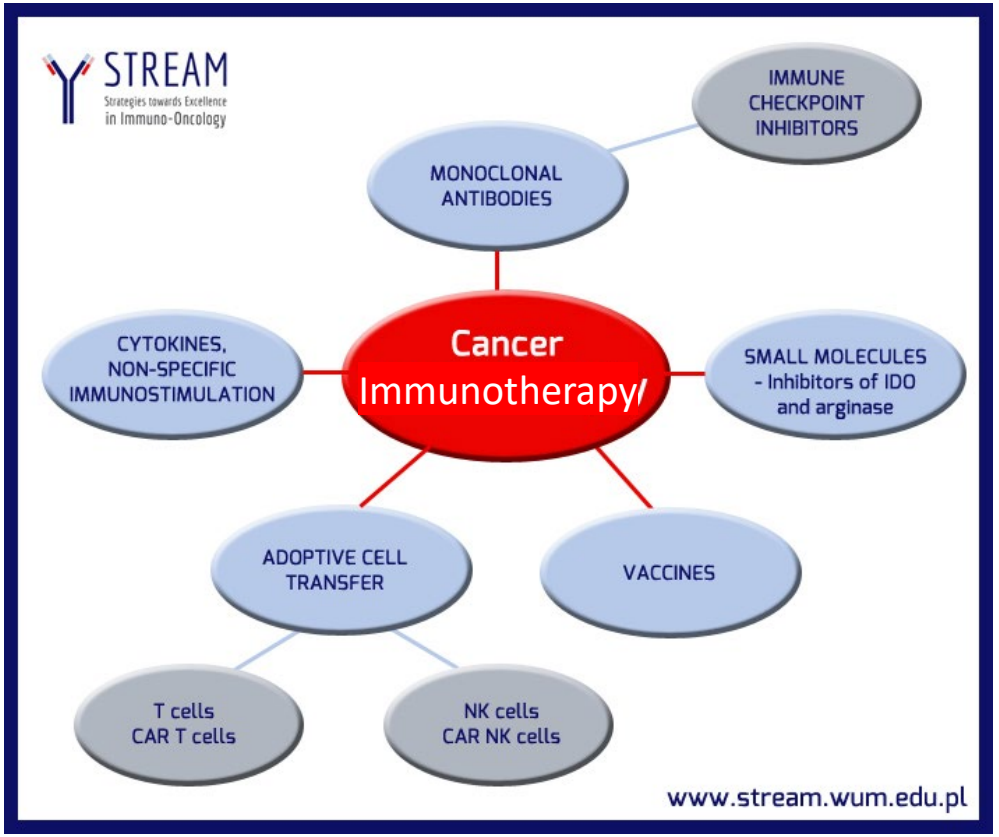
- Which of the following describes you?

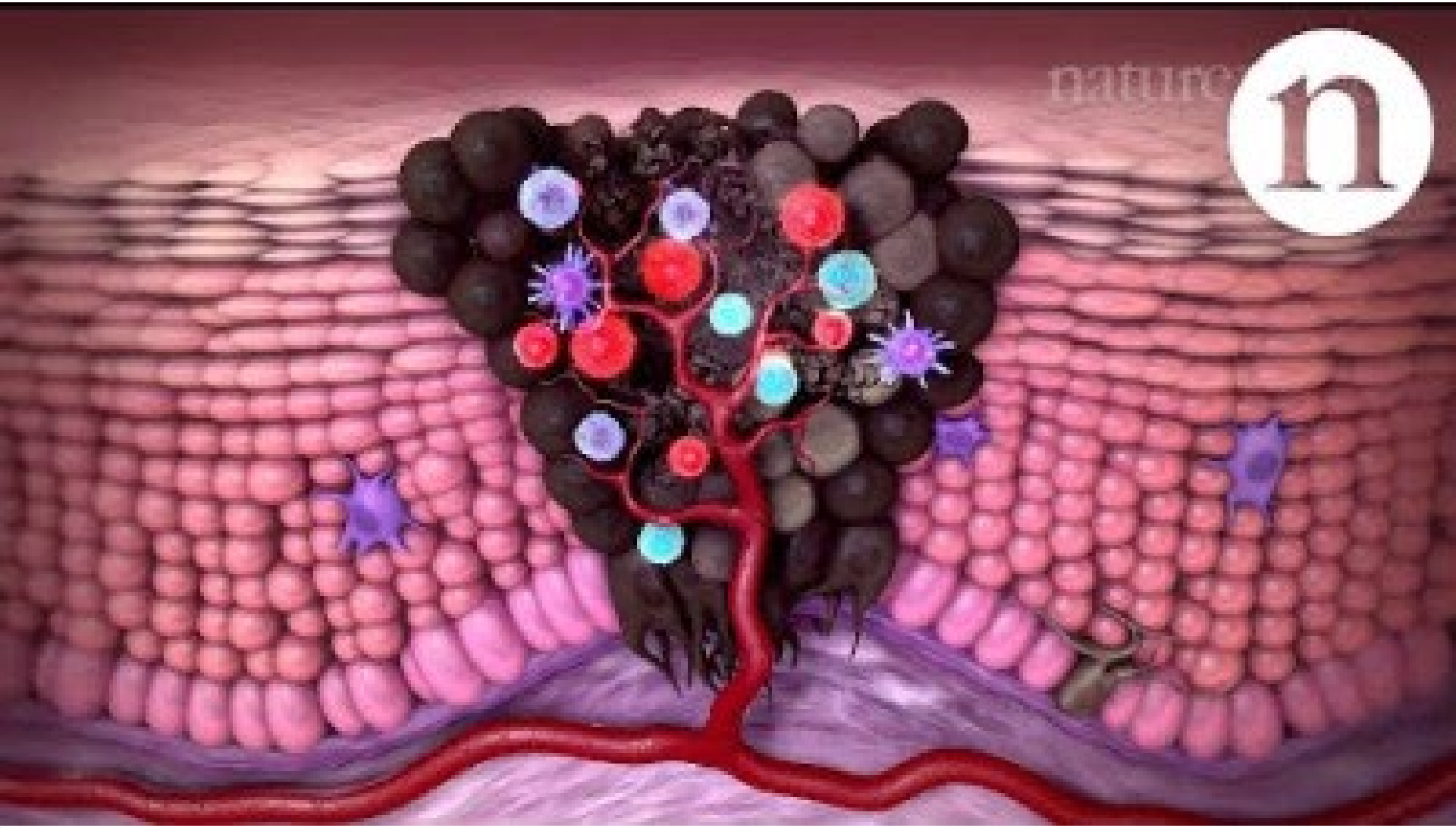
I administer immunotherapy or take care of patients receiving immunotherapy...

- Never
- Rarely (less than once a month)
- Often (at least monthly)
- All the time (at least weekly)

Types of Immunotherapy

- Monoclonal Antibodies
  - Checkpoint inhibitors
- Cytokines
- Small Molecules
  - Inhibit specific targets
- Vaccines
- Adoptive Cell Transfer
  - CAR T and CAR NK cells
  - Tumor-Infiltrating Lymphocytes





- Tumour Immunology: https://www.youtube.com/watch?v=K09xzIQ8zsg (5:03)

Monoclonal Antibodies

- -mabs
  - Used when receptor targets are overexpressed on the outside of the cancer cells
- -ibs
  - Small molecule inhibitors
  - Targets processes inside and outside the cell
  - Target proteins that code for growth or inhibit growth

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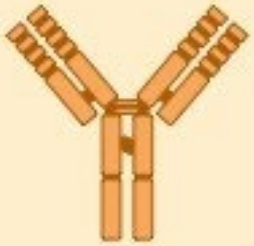
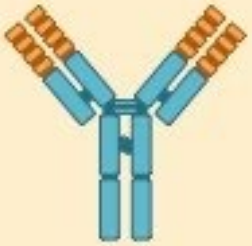
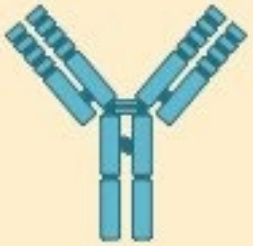
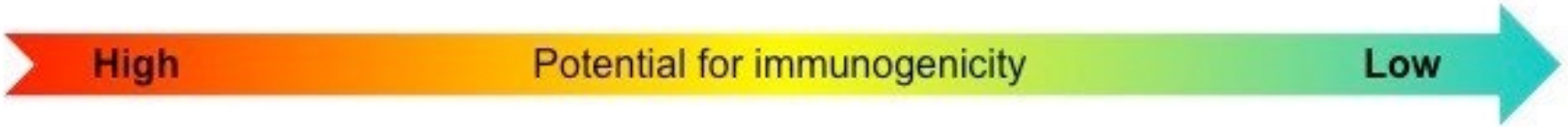
Monoclonal Antibodies -mabs

- Naturally produced in the body
- Response to Antigens
- Synthetic
  - Attach to receptors on the outside of cells
  - Prevent the receptors from interacting with signaling molecules
  - Deliver radioactive molecules or toxins to the inside of cells through attachment receptors
  - Activate the body's natural immune response

Three Types of -mabs

Type:	Murine (0% human)	Chimeric (65% human)	Humanised (>90% human)	Human (100% human)
				
Suffix:	–omab	–ximab	–zumab	–umab



- -ximab
  (Ritu*ximab*)
- -zumab
  (Bevaci*zumab*)
- -umab
  (Ipilim*umab*)

https://ib.bioninja.com.au/higher-level/topic-11-animal-physiology/111-antibody-production-and/monoclonal-antibodies.html

Poll Time: Question 2

- Monoclonal antibodies with the suffix **-zumab,** refers to an antibody that is approximately __ % human a.k.a. "_____"

  - 65%, chimeric
  - 90%, humanized
  - 100%, human

Poll Time: Question 3

- Monoclonal antibodies with the suffix **-ximab**, refer to an antibody that is approximately __ % human a.k.a. "_____"

  - 65%, chimeric
  - 90%, humanized
  - 100%, human

Poll Time: Question 4

- Monoclonal antibodies with the suffix **-umab**, refer to an antibody that is approximately __ % human a.k.a. "_____"

  - 65%, chimeric
  - 90%, humanized
  - 100%, human

Three Types of -ibs

- Tyrosine Kinase Inhibitors-tinib
  (e.g. Ima*tinib*)
- Protease Inhibitors-zomib
  (e.g. Borte*zomib*)
- Cyclin-Dependent Kinase Inhibition-ciclib
  (e.g. Palbo*ciclib*)

-mabs and -ibs

- Additional stems describe where the immunotherapy is targeting
  - **Tu**-tumor (e.g. Ri **TU** ximab)
  - **Ci**-circulatory (e.g. Beva **CI** zumab)
  - **Li**-immune system (e.g. Ipi **LI** mumab)

Monoclonal Antibodies Common Side Effects

- Infusion Reaction
- Diarrhea
- Nausea/Vomiting
- Rash
- Hyperglycemia
- Cough
- Constipation
- Peripheral Edema
- Decreased Appetite
- Increase Triglycerides
- Insomnia
- Abdominal Pain
- Back Pain
- Dizziness

Monoclonal Antibodies Serious Adverse Events

- Anaphylaxis
- Hypotension
- Serious Infections
- Serum Sickness
- Autoimmune Thyroiditis
- Cancer
- CHF
- Bleeding
- Hepatitis
- Gastrointestinal Perforation
- Neutropenia
- Blood Clots

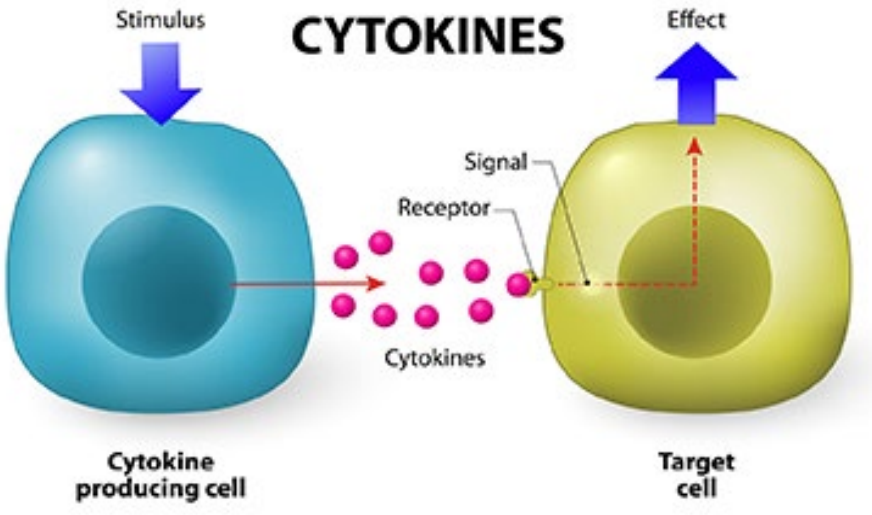
Poll Time: Question 3

- Which of the following are NOT common side effects of -mabs and -ibs?

  - Rash
  - Alopecia
  - Peripheral Neuropathy
  - Infusion Reaction
  - Dizziness
  - Cough

Cytokines

- A group of proteins secreted by cells of the immune system that act as chemical messengers
- Cytokines released from one cell affect the actions of other cells by binding to receptors (mailboxes) on their surface
- Synthesized and given in larger doses
- Types:
  - Interleukin 2 (IL-2)
  - Interferon-alpha (IFN-alpha)



https://www.integrativepro.com/Resources/Integrative-Blog/2016/Closer-Look-Cytokines

Cytokines

- Approved to treat:
  - Leukemia
  - Lymphoma
  - Melanoma
  - Bladder Cancer
  - Renal Cell carcinoma
- May stimulate the growth of immune cells
  - Depression
  - Flu-like symptoms
  - Profound fatigue
  - Cytokine Storm

Poll Time: Question 5

- Cytokines, such as IL-2 and IFN-alpha, do NOT have any serious potential side effects.

- TRUE or FALSE

Immune Checkpoints

- Immune checkpoint pathways regulate activation of T cells at various stages in the immune response[1]
- Killer T cells find and destroy cells that are cancerous or have been infected by germs
- Helper T cells direct the immune response

1. Buchbinder EI, Desai A. CTLA-4 and PD-1 pathways: similarities, differences, and implications of their inhibition. *Am J Clin Oncol.* 2016;39:98-106.

Immune Checkpoint Proteins

- Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) pathway
- Programmed cell death protein (PD-1)
- Programmed death ligand (PD-L1)

CTLA-4 Pathway

- CTLA-4 pathway provides a negative signal to T cells
- Blocking the pathway promotes T cell activation which may cause an antitumor immune response.[1-3]

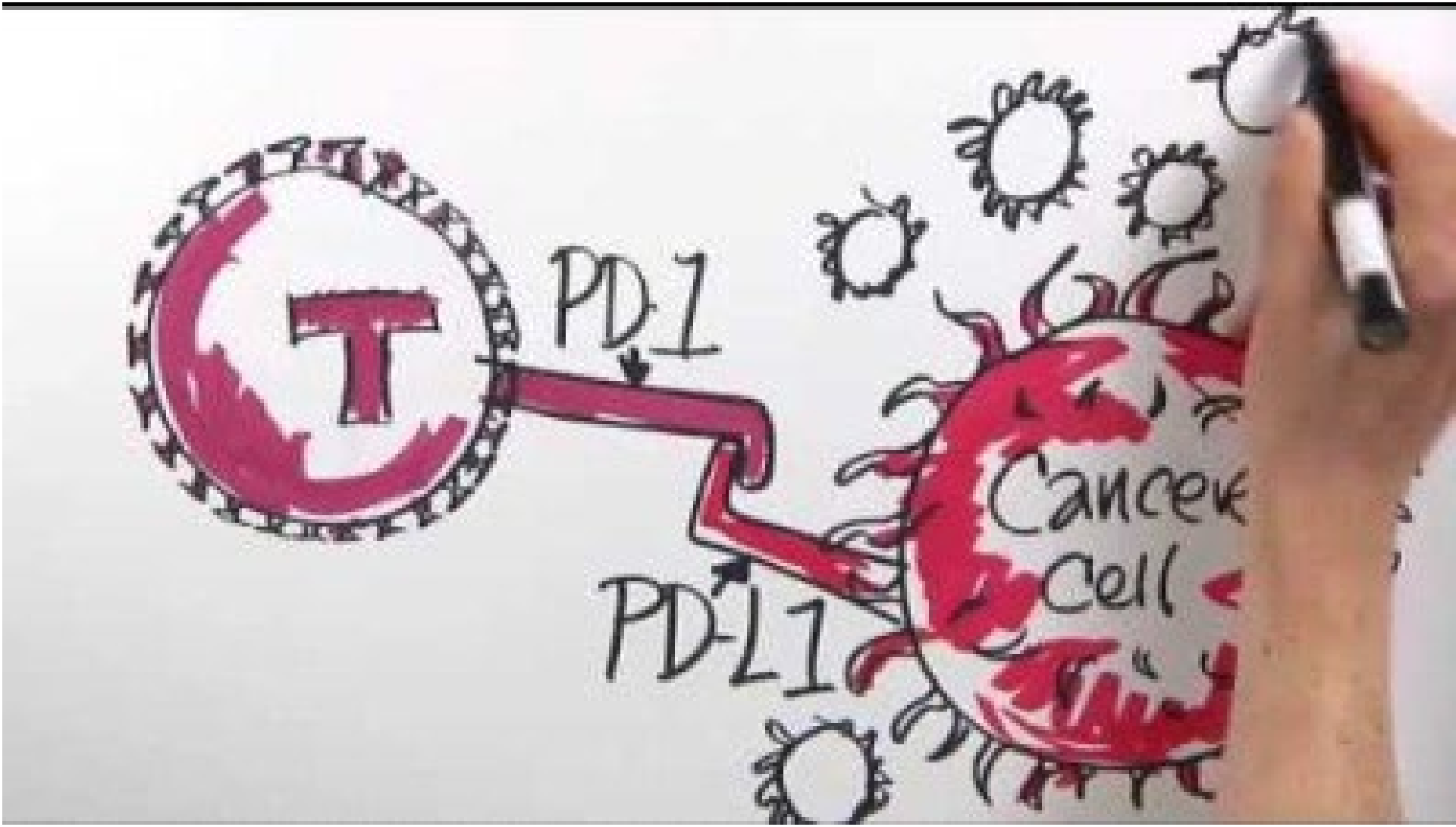
1. Intlekofer AM, Thompson CB. At the bench: preclinical rationale for CTLA-4 and PD-1 blockade as cancer immunotherapy. *J Leukoc Biol*. 2013;94(1):25-39.
2.Gardner D, Jeffery LE, Sansom DM. Understanding the CD28/CTLA-4 (CD152) pathway and its implications for costimulatory blockade. *Am J Transplant*. 2014;14(9):1985-1991.
3. Egen JG, Kuhns MS, Allison JP. CTLA-4: new insights into its biological function and use in tumor immunotherapy. *Nat Immunol*. 2002;3(7):611-618.

Anti-CTLA-4

- Ipilimumab (Yervoy®)
- FDA approved for use in:
  - Stage IV and unresectable melanoma in adult and pediatric patients > 12 y.o.
  - Adjuvant treatment of cutaneous melanoma patients w/positive lymph nodes >1 mm, s/p lymph node dissection
  - Melanoma, colorectal, NSCLC, HCC and RCC (intermediate or poor risk) in combination with nivolumab

https://packageinserts.bms.com/pi/pi_yervoy.pdf - As of 2/2022

PD-1/PD-L1 Video



- Dana-Farber Science Illustrated: Ihttps://www.youtube.com/watch?v=AbmEt_E8kfo (1:05)

PD-1 Inhibitors

- Nivolumab (Opdivo)
- Pembrolizumab (Keytruda)
- Cemiplimab (Libayo)
- Dostarlimab (Jemperli)

Nivolumab (Opdivo®) FDA Approved Use

- Melanoma
- Stage IV NSCLC
- SCLC
- Renal cell cancer (RCC)
- Colorectal Cancer
- Esophageal SCC & adenocarcinoma
- Classical Hodgkin's lymphoma (chL)
- Head & Neck squamous cell carcinoma (HNSCC)
- Urothelial carcinoma
- Hepatocellular carcinoma (HCC)
- Pleural Mesothelioma
- Gastric Cancers

https://packageinserts.bms.com/pi/pi_opdivo.pdf - as of 5/2022

Pembrolizumab (Keytruda®) FDA Approved Use

- Unresectable or metastatic melanoma
- Merkel Cell Carcinoma
- Metastatic NSCLC
- Metastatic SCLC
- cHL
- PMBCL
- Microsatellite Instability-High Grade Cancer
- HNSCC
- Gastric cancer
- Esophageal cancer
- Cervical cancer
- Endometrial Carcinoma
- Urothelial carcinoma
- RCC
- HCC
- NEW: Triple Negative Breast Cancer

https://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf - as of 4/2019

Cemiplimab (Libtayo) FDA Approved Use

- First treatment ever approved for Advanced Cutaneous Squamous Cell Carcinoma
- Locally advanced CSCC not amenable to surgery or radiation
- Basal Cell Carcinoma
- Metastatic NSCLC (high PD-L1expression)

https://www.regeneron.com/downloads/libtayo_fpi.pdf - as of 2/2021

Dostarlimab (Jemperli) FDA Approved Use

- Endometrial CA
- NEW in 2021: mismatch repair deficient solid tumors

https://gskpro.com/content/dam/global/hcpportal/en_US/Prescribing_Information/Jemperli/pdf/JEMPERLI-PI-MG.PDF - updated 4/2021

PD-L1 Pathway

- Programmed cell death ligand-1 (PD-L1) pathway causes T-cell exhaustion[1-5]
  - PD-L1 is frequently expressed on tumor cells
  - PD-L1 binds to PD-1 which is expressed on activated T cells, causing T-cell exhaustion and dysfunction
- PD-L1 blockade prevents T-cell exhaustion leading to antitumor activity[1-5]

1. Stewart R, Morrow M, Hammond SA, et al. Identification and characterization of MEDI4736, an antagonistic anti-PD-L1 monoclonal antibody. *Cancer Immunol Res*. 2015;3:1052-1062.
2. Ibrahim R, Stewart R, Shalabi A. PD-L1 blockade for cancer treatment: MEDI4736. *Semin Oncol*. 2015;42:474-483.
3. Sznol M, Chen L. Antagonist antibodies to PD-1 and B7-H1 (PD-L1) in the treatment of advanced human cancer. *Clin Cancer Res*. 2013;19:1021-1034.
4. Chen DS, Irving BA, Hodi FS. Molecular pathways: next-generation immunotherapy—inhibiting programmed death-ligand 1 and programmed death-1. *Clin Cancer Res*. 2012;18:6580-6587.
5. Chen L, Flies DB. Molecular mechanisms of T cell co-stimulation and co-inhibition. *Nat Rev Immunol.* 2013;13:227-242

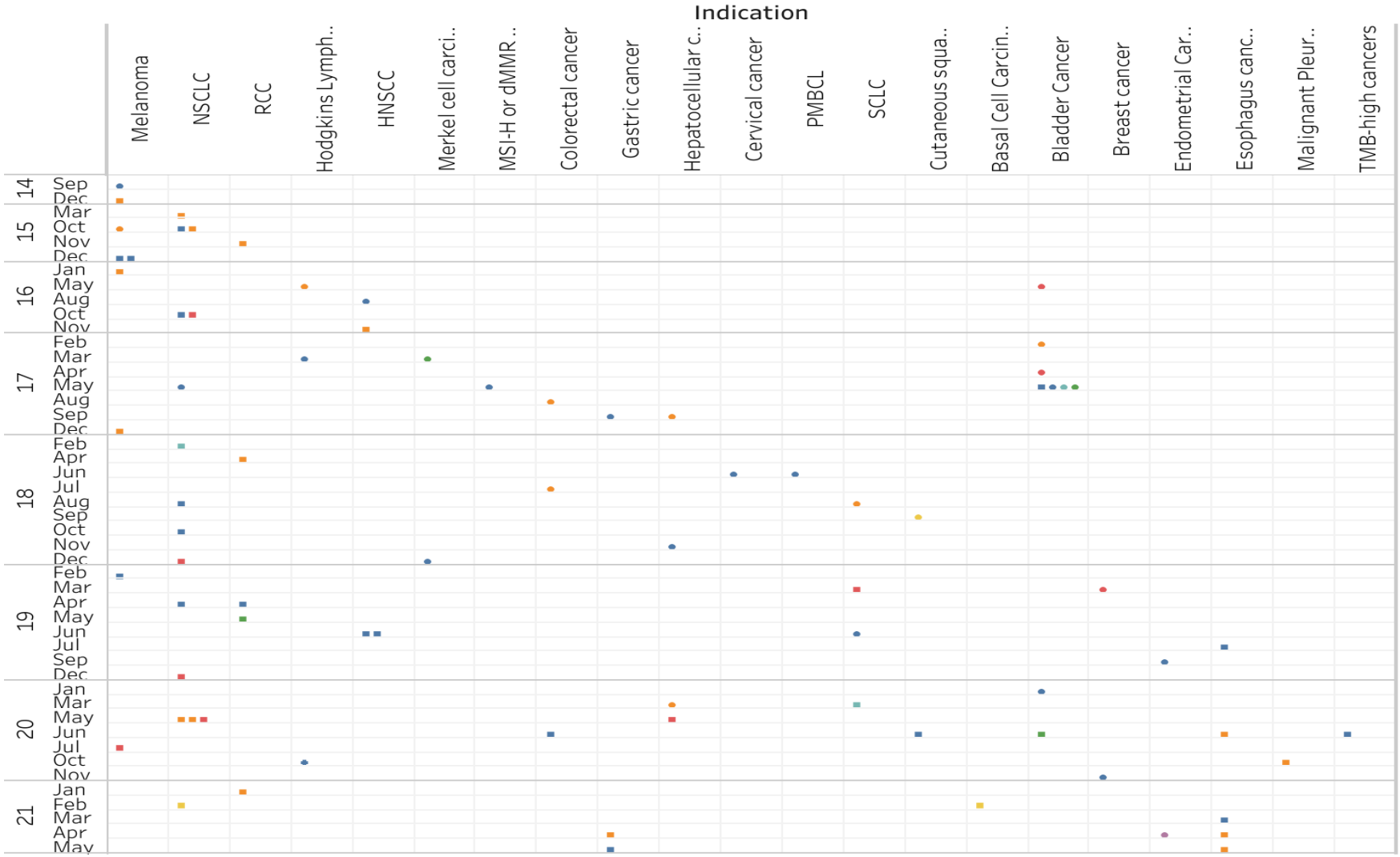
PD-L1 Inhibitors

- Avelumab (Bavencio)
- Durvalumab (Imfinzi)
- Atezolizumab (Tecentriq)

Timeline of Anti-PD-1/L1 Antibody Approvals by the FDA

Updated May 20, 2021

Sources: CRI, CRI Analytics, and FDA



CANCER RESEARCH INSTITUTE®

The Anna-Maria Kellen Clinical Accelerator

https://www.cancerresearch.org/scientists/immuno-oncology-landscape/fda-approval-timeline-of-active-immunotherapies -

Avelumab (Bavencio®) FDA Approved Use

- Merkel cell carcinoma in adults and pediatric patients>12 y.o.
- Urothelial carcinoma
- Advanced RCC (in combination with axitinib)

https://www.emdserono.com/us-en/pi/bavencio-pi.pdf - Updated 11/2020

Durvalumab (Imfinzi®) FDA Approved Use

- Stage III unresectable NSCLC

- ~~Urothelial carcinoma~~

https://www.azpicentral.com/imfinzi/imfinzi.pdf#page=1 - Updated 2/2021

Atezolizumab (Tecentriq®) FDA Approved Use

- Urothelial carcinoma
- NSCLC
- Triple-Negative Breast Cancer
- SCLC
- Hepatocellular Carcinoma
- Melanoma
- Bladder (Pending)

https://www.gene.com/download/pdf/tecentriq_prescribing.pdf – Updated 4/2021

Combination Therapy Ipilimumab/Nivolumab

- FDA approved for use in:
  - Melanoma
  - RCC (poor risk)
  - Some colorectal
  - HCC
  - NSCLC
  - Pleural Mesothelioma

➢ Side effect profile higher

https://packageinserts.bms.com/pi/pi_yervoy.pdf – As of June 2020

Other Combination Therapy

- Avelumab (PD-L1) + Axitinib (TKI)
  - Advanced RCC
- Atezolizumab + Bevacizumab
  - HCC
- Atezolizumab + Cobimetinib + Vemurafenib
  - Melanoma
- Pembrolizumab + Lenvatinib
  - Endometrial
  - RCC

Poll Time: Question 6

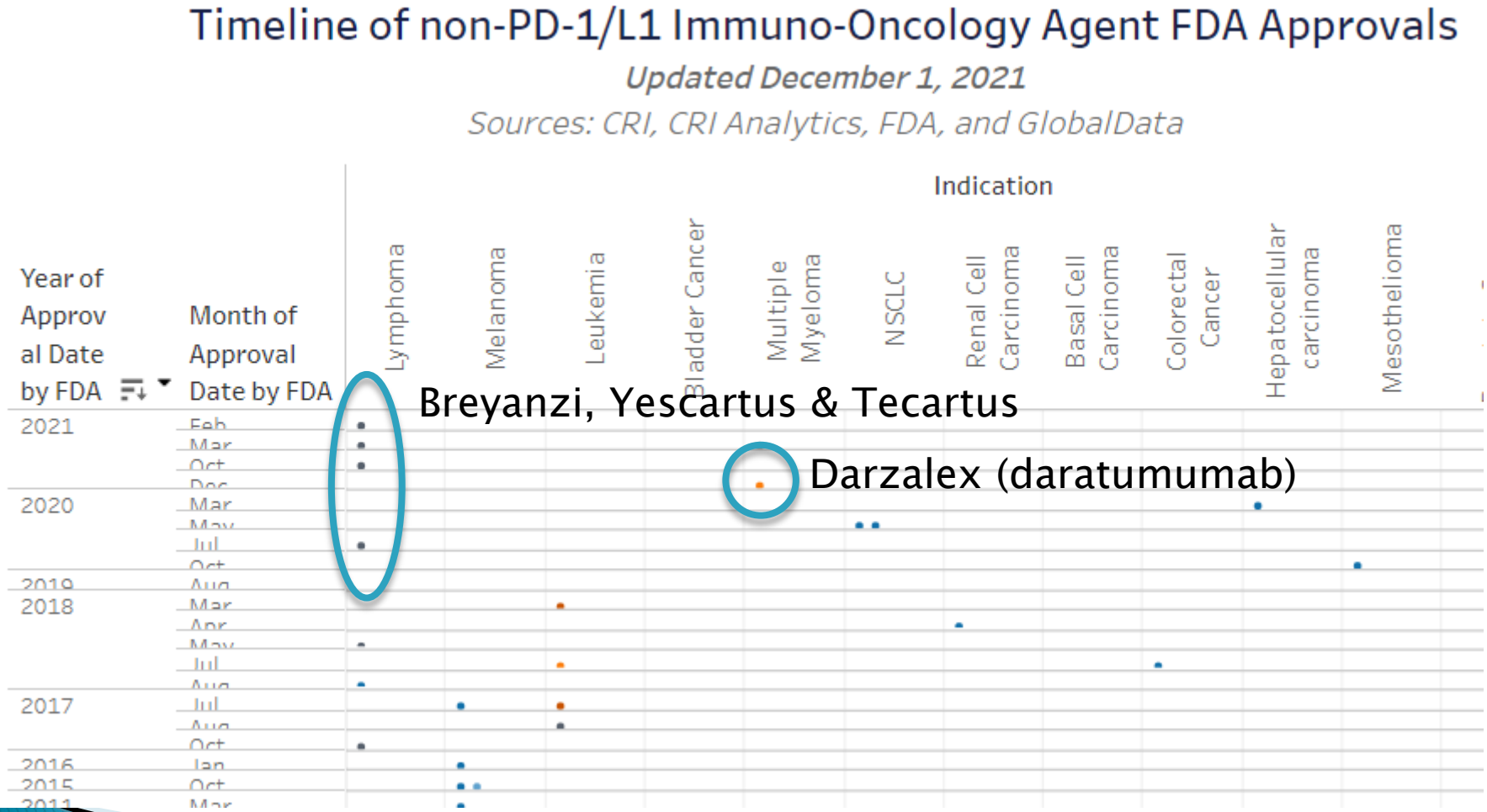
- Patient's who receive PD-1 inhibitors must also receive PD-L1 inhibitors for treatment to work.

- TRUE or FALSE

Checkpoint Inhibitors Unique Features

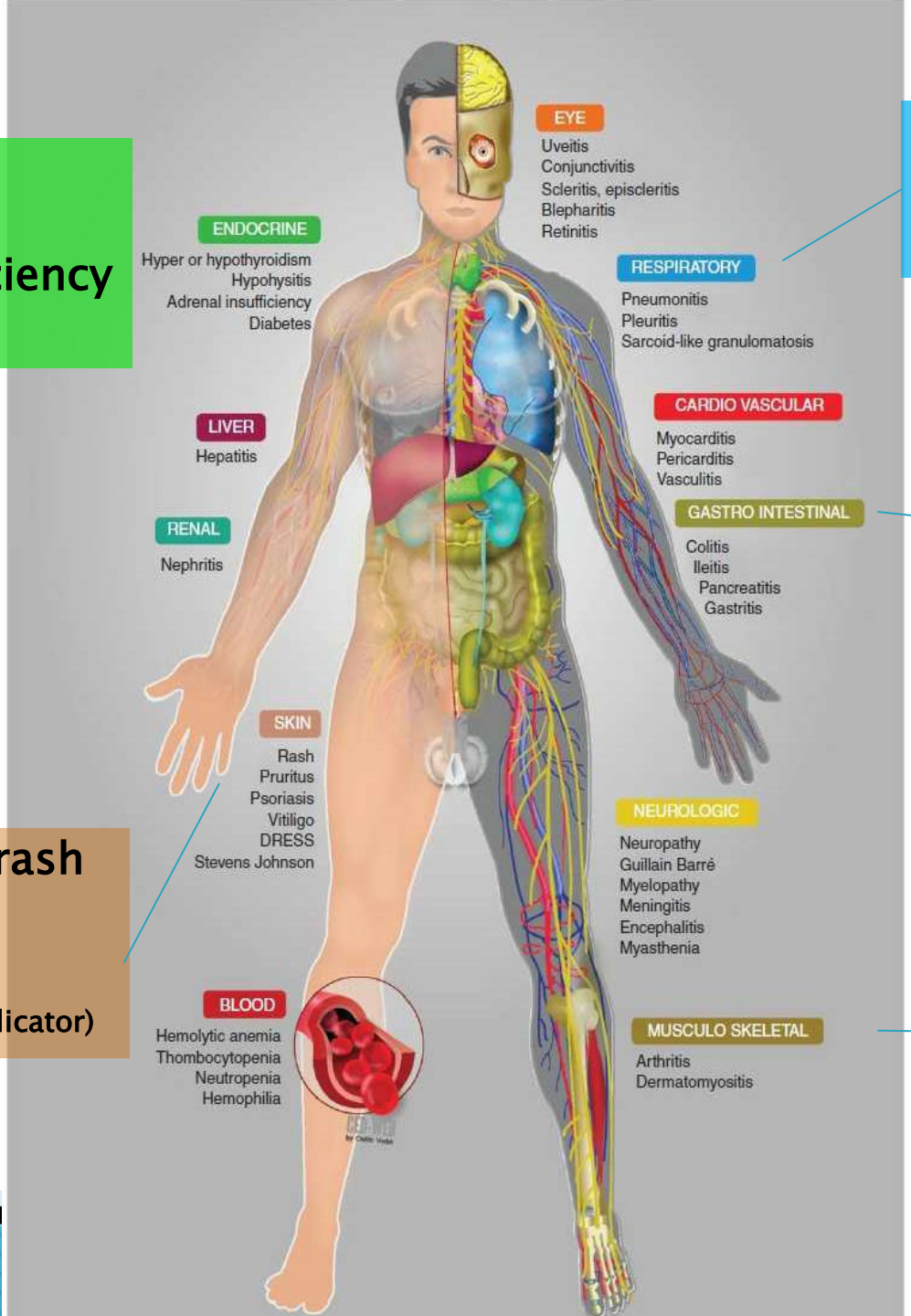
- Responses take more time
- Pseudo-progression may occur
- Autoimmune conditions need to be considered
- May induce durable responses or stabilize disease long term

Adoptive Cell Transfer and Immunomodulators



https://www.cancerresearch.org/scientists/immuno-oncology-landscape/fda-approval-timeline-of-active-immunotherapies
Retrieved 4/7/2022

Hypothyroid
Hypophysitis
Adrenal insufficiency
Diabetes



Shortness of breath
Dyspnea on exertion
Cough

Colitis
Pancreatitis

Maculopapular rash
Pruritus
DRESS
Vitiligo (positive indicator)

Arthritis

Immunotherapy Toxicities

- Immune related adverse events (irAEs) are critical
- Any organ system may be involved
- EARLY RECOGNITION and PROMPT TREATMENT is KEY (often steroids)
- Hold treatment if irAEs develop
- May develop any time during or after treatment
- Anti-tumor benefit persists even with steroid use
- Algorithms are available

Immune Related Adverse Events

- **Communication is key**
- Multidisciplinary team effort
- Patient/family education critical
- Other health care providers may not be familiar with them

NCCN Guidelines: Immune Checkpoint Inhibitors

When a patient should contact their provider right away!

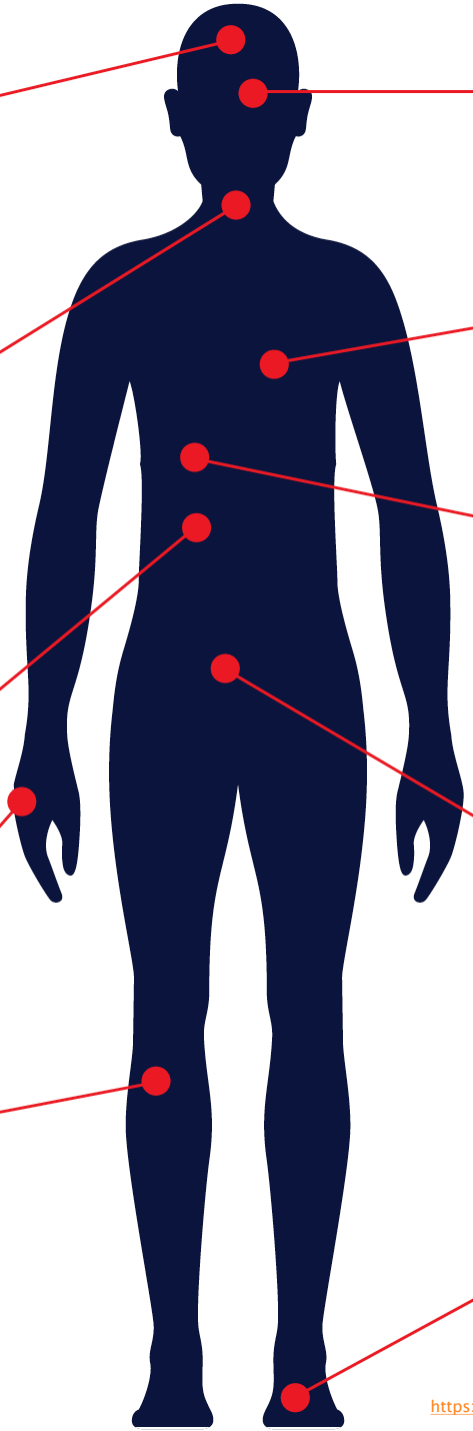
Brain inflammation (encephalitis)
Fever; confusion; changes in mood or behavior; neck stiffness; seizures; extreme sensitivity to light.

Hormone gland problems (especially the thyroid, pituitary, adrenal glands, pancreas)
Persistent or unusual headaches; extreme tiredness; weight loss or gain; rapid heartbeat; increased sweating; hair loss; constipation; dizziness or fainting.

Kidney problems
Decrease in the amount of urine; blood in the urine.

Skin problems
Rashes; itching; blistering; painful sores or ulcers.

Joint or muscle problems
Severe or persistent muscle or joint pain; severe muscle weakness.



Eye problems
Blurry or double vision or other vision problems; eye pain or redness.

Lung problems (pneumonitis)
New or worsening cough; shortness of breath.

Liver problems (hepatitis)
Yellowing of the skin or the whites of the eyes; severe nausea or vomiting; pain on the right side of the stomach area; dark urine; bleeding or bruising more easily than normal.

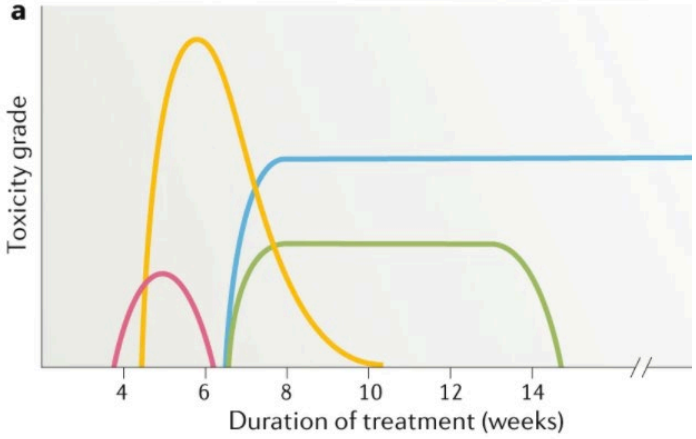
Intestinal problems (colitis)
Diarrhea or more bowel movements than usual; stools that have blood or are dark, tarry, or sticky; severe stomach-area pain.

Nerve problems
Numbness or tingling in hands or feet; unusual weakness in legs, arms, or face.

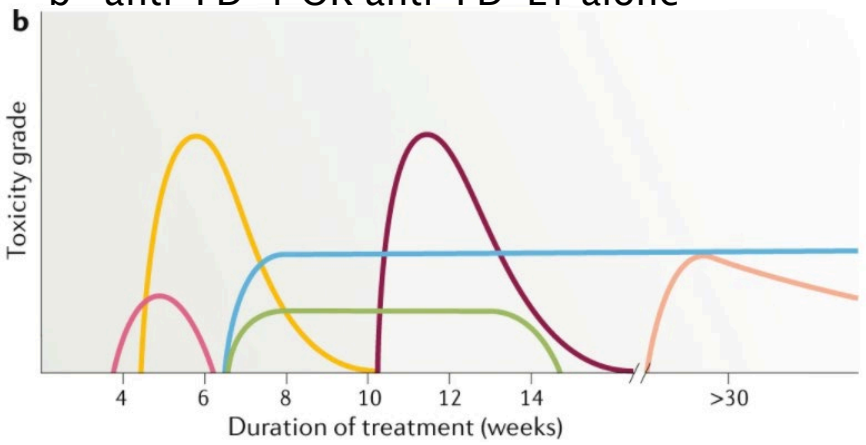
https://www.nccn.org/images/pdf/Immunotherapy_Infographic.pdf

Immune checkpoint inhibitors–irAEs

a– ipilimumab alone



b– anti–PD–1 OR anti–PD–L1 alone



Colitis

Endocrinopathy

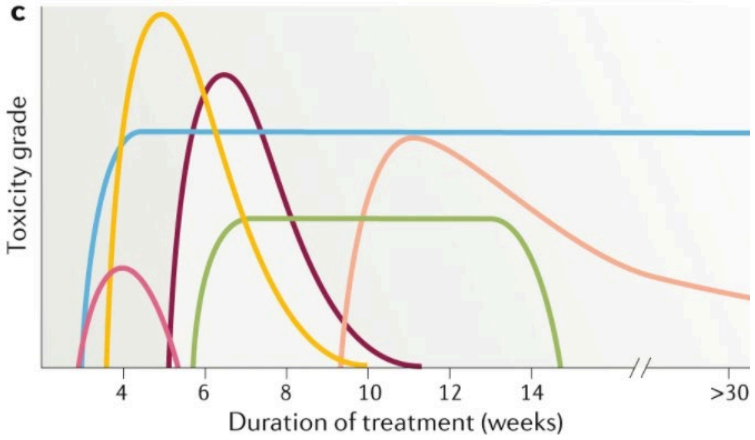
Liver toxicity

Skin, rash or pruritus

Pneumonitis

Nephritis

c– ipilimumab AND anti–PD–1 combination therapy

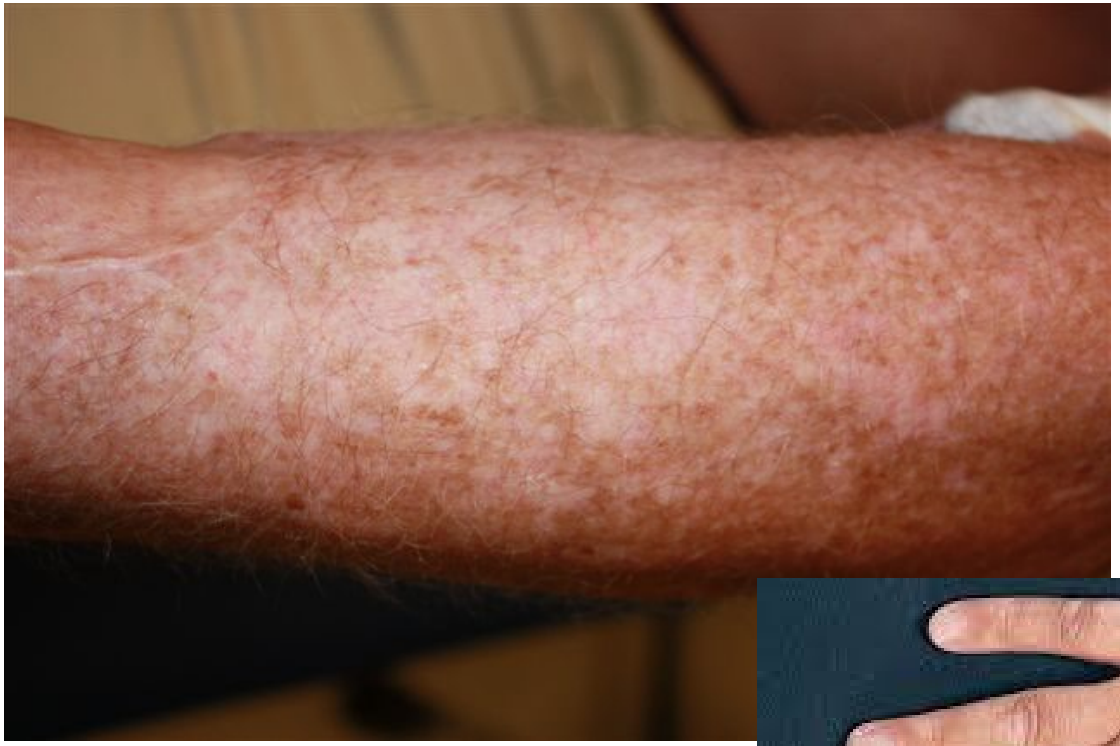


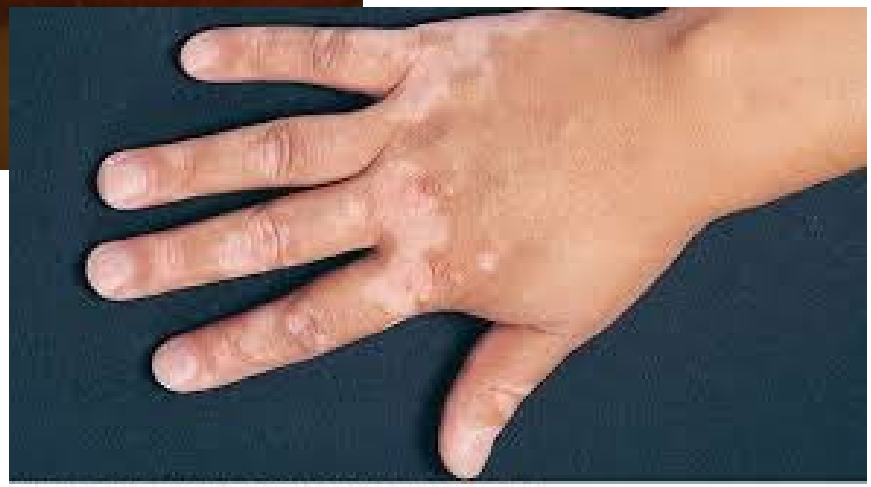
https://www.nature.com/articles/s41571-019-0218-0/figures/1

Dermatologic AEs

- Rash (maculopapular/erythematous)
- Pruritis/dry skin
- Vitiligo
- Median time to onset 3 weeks
- Severity based on BSA involved and sx's
- Grade 1-2 (mild to moderate) events most common
- Rare grade 3-4 (severe) events
  - Stevens-Johnson syndrome (SJS)
  - Toxic epidermal necrolysis (TEN)

Vitiligo



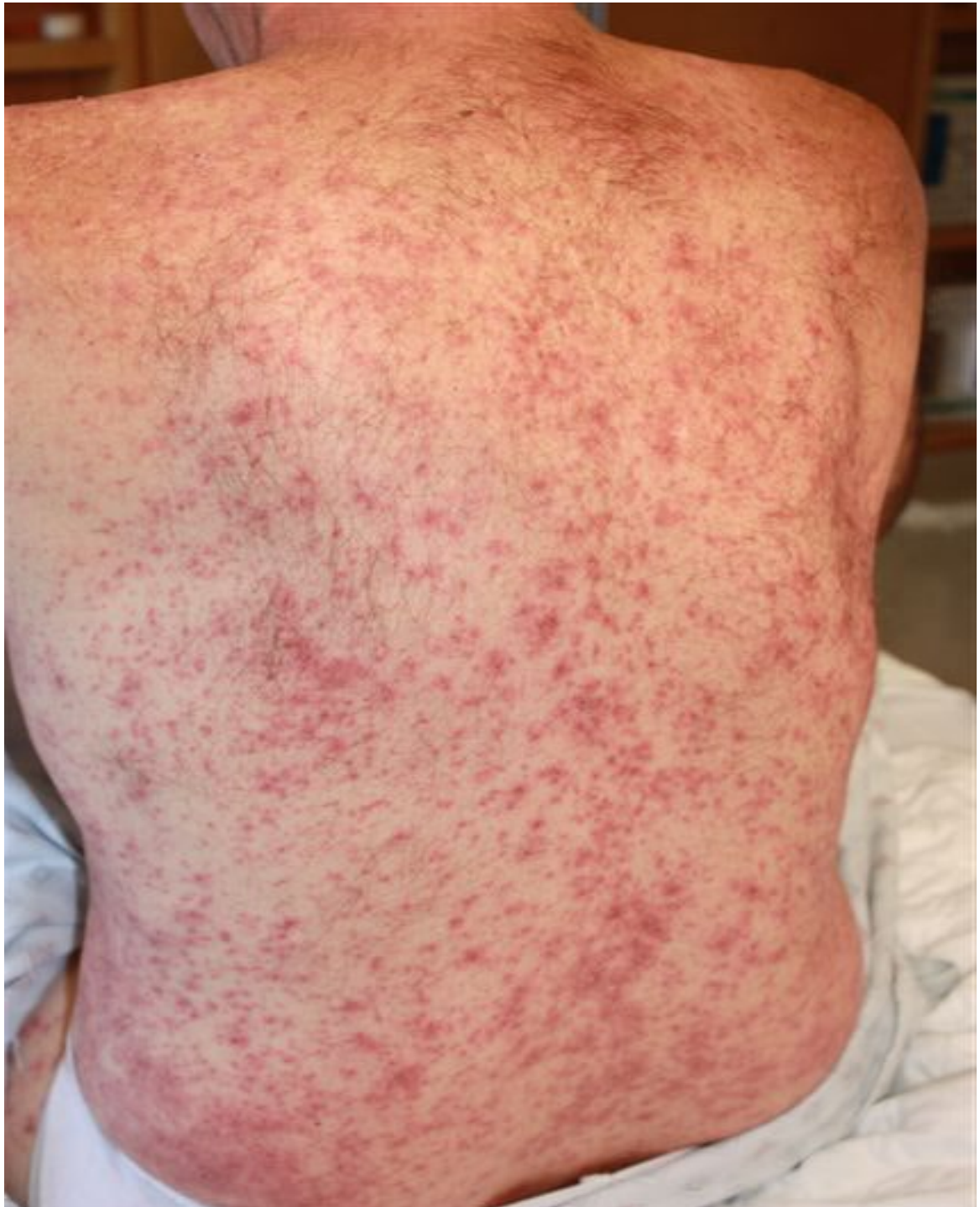


Melanoma Case Study

- 53 y.o. male with hx of melanoma of the lower abdomen with melanoma present in bilateral groin nodes, s/p bilateral groin dissection.
- Developed left groin and left iliac lymphadenopathy (LAD) one year later. Had surgical resection confirming melanoma. XRT and interferon considered, but quickly developed new SQ nodules. PET showed FDG uptake in a left pelvic LN felt to be unresectable.
- Began ipilimumab therapy.

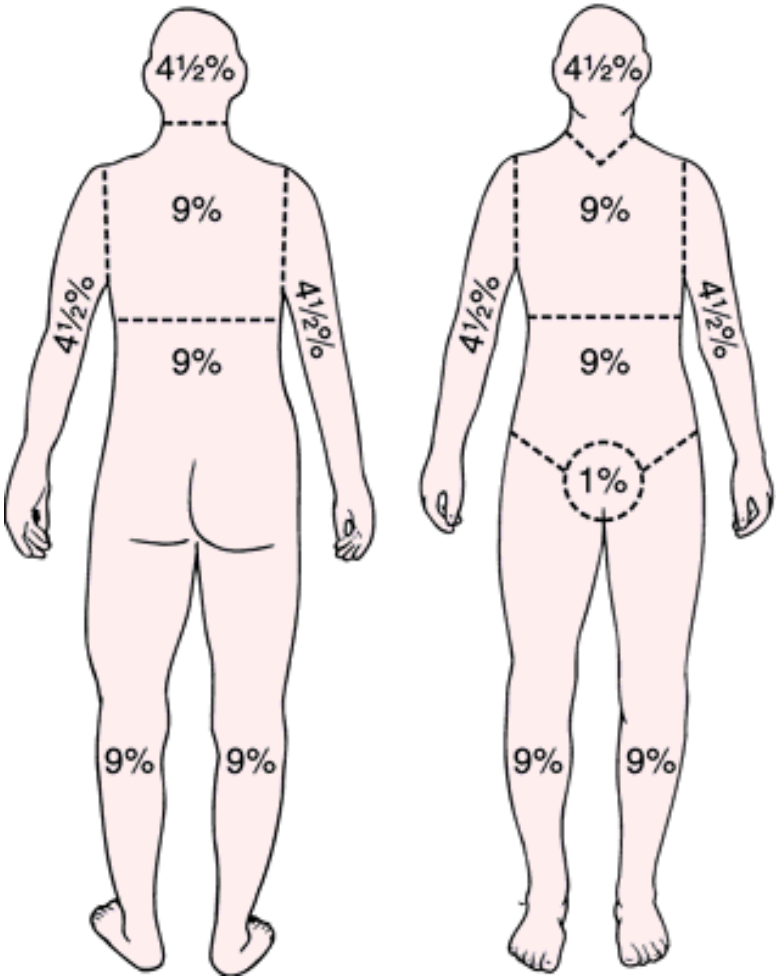
Melanoma Case Study (contd)

- Presents to clinic for 4th dose and notes pruritic rash, present for one week. Interrupting sleep.
- On physical exam, maculopapular rash covers back, arms and upper legs.



Poll Time: Question 7

- How would you grade this AE?
- **Mild** (Grade 1) – macules covering <10% BSA +/- symptoms (e.g., pruritis, burning, tightness)
- **Moderate** (Grade 2) – macules covering 10-30% BSA, +/- symptoms, limiting ADLs
- **Severe** (Grade 3/4) – macules covering >30% BSA, +/- symptoms, limiting ADLs



https://medical-dictionary.thefreedictionary.com/rule+of+nines

Rash Management Strategies:

- Emollients
- Anti-pruritics
- Sun avoidance
- Hold treatment based on severity
- Topical steroids for grade 1 or 2
- Systemic steroids for persistent rashes ≥ grade 2

Melanoma Case Study (contd)

- 53 y.o. male with hx of melanoma on ipilimumab with new rash

- Ipilimumab held and steroids started. Rash improved. Weaned off steroids over one month. Further ipilimumab held.

Melanoma Case Study (contd)

- Scans show disease progression.
- Started nivolumab therapy.
- Short interval scans at 6 weeks show significant disease regression.
- Nivolumab continued for 6 months with no evidence of melanoma on scans.

Melanoma Case Study (contd)

- Calls to report diarrhea (4-6 stools above baseline) with associated cramping and blood in stools.
- Seen in clinic. Appears non-toxic and well-hydrated. Labs WNL.
- Stools for C diff and O&P sent, negative.

Poll Time: Question 8

- What do you expect the treatment for this patient to be?
- Anti-diarrheals, BRAT diet and continue nivolumab on schedule
- Oral steroids, anti-diarrheals and continue nivolumab on schedule
- Oral Steroids and hold nivolumab

Melanoma Case Study (contd)

- Nivolumab held and started on steroids 1 mg/kg.
- Colonoscopy shows inflammation. Biopsy shows active colitis.
- GI symptoms improve on steroids which are slowly weaned off.
- Nivolumab discontinued. Subsequent scans continue to show no melanoma recurrence.

Diarrhea/Colitis

- Communication is key
- Monitor for diarrhea, abdominal pain, cramping, blood or mucus in stool
- Median time to onset is 6-7 weeks
- Hold therapy and start steroids for grade 2 or above
- Infliximab if refractory to steroids after 3-5 days
- Grade 3-4 events ~ 10% with ipilimumab, less with nivolumab and pembrolizumab ~ 1-2%
- Deaths reported in trials from bowel perforation, sepsis

Endocrine AE's

- Hypophysitis/hypothyroidism most common
- Adrenal insufficiency rare, but serious
- Median time to onset 11 weeks
- Symptoms are nonspecific:
  - Fatigue, headache, mental status changes, hypotension, vision changes, abnormal TFT's or serum chemistries
- Check TFT's, ACTH, cortisol, LH, FSH, GH, prolactin
- Treatment often includes long term hormone supplementation

Immune-Mediated Pneumonitis

- Acute Interstitial Pneumonitis
- Organizing Inflammatory Pneumonia
  - Cough
  - Dyspnea
  - URI
  - Hypoxia
  - CT findings-ground glass opacities

- Management:
  - Hold Therapy
  - Rule out infection-bronchoscopy
  - May need to biopsy if concern is for disease progression
  - Antibiotics vs immunosuppression

Hepatotoxicity

- Often asymptomatic with transaminase (ALT/AST) elevation
- Total bilirubin rarely elevated
- Fever occasionally associated
- Hold therapy for grade 2 toxicity or >
- Rule out viral or drug induced causes
- Corticosteroids for prolonged grade 2 or >sx's
- Mycophenolate if refractory to steroids
- Avoid infliximab

Tisotumab-vedotin (Tivdak®)

- Newly approved immunotherapy that targets tissue factor (TF) bound to microtubule inhibitor
  - Antibody-Drug Conjugate (ADC)
  - Indication: Cervical Cancer
  - Significant Ocular Toxicity

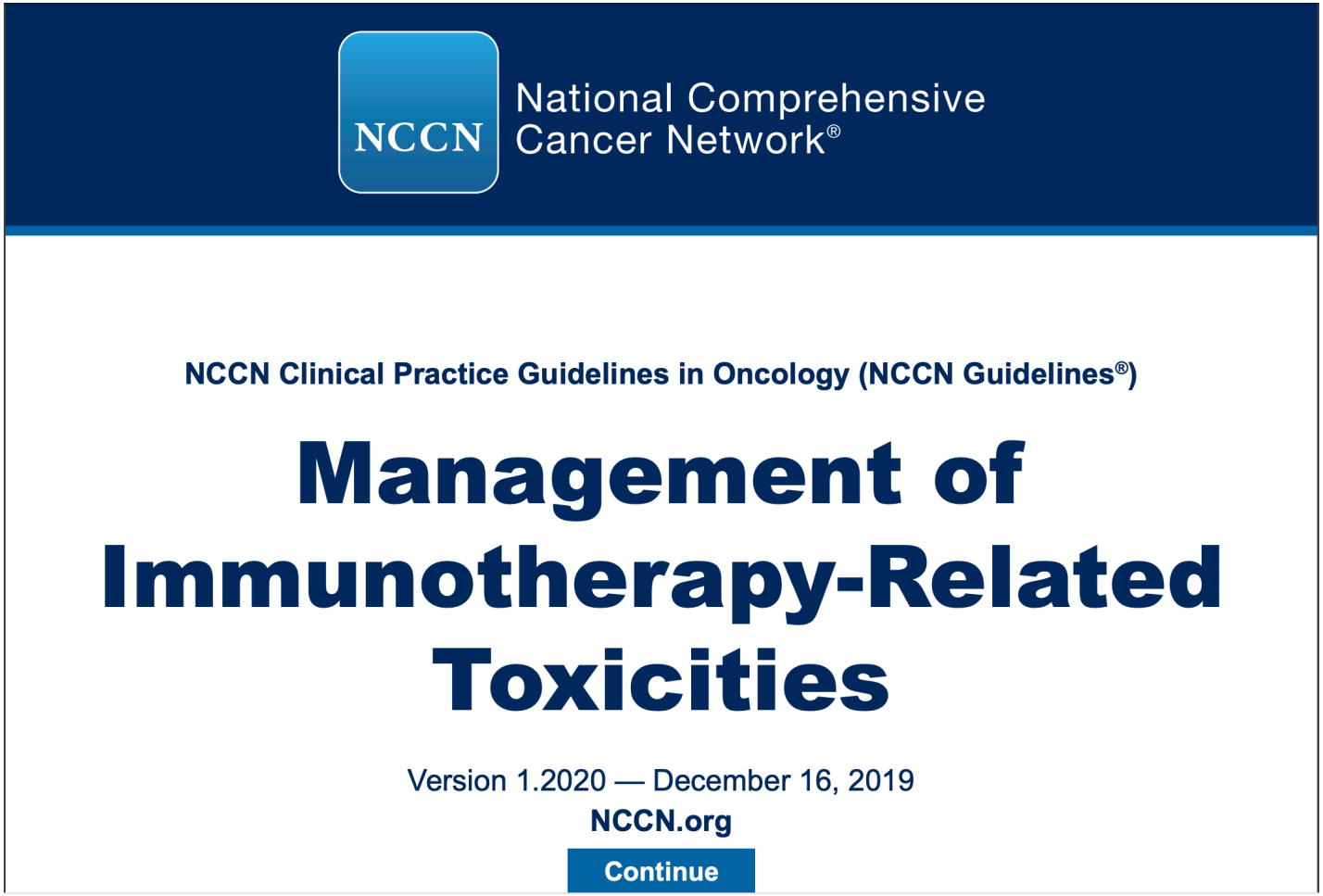
2.2 PREMEDICATION AND REQUIRED EYE CARE

Adhere to the following recommendations to reduce the risk of ocular adverse reactions *[see Warnings and Precautions (5.1)]*.

- Ophthalmic exam: Conduct an ophthalmic exam including visual acuity and slit lamp exam at baseline, prior to each dose, and as clinically indicated.
- Topical corticosteroid eye drops: The initial prescription and all renewals of any corticosteroid medication should be made only after examination with a slit lamp. Administer first drop in each eye prior to each infusion. Instruct patients to continue to administer eye drops in each eye as prescribed for 72 hours after each infusion.
- Topical ocular vasoconstrictor drops: Administer in each eye immediately prior to each infusion.
- Cold packs: Use cooling eye pads during the infusion of TIVDAK.
- Topical lubricating eye drops: Instruct patients to administer for the duration of therapy and for 30 days after the last dose of TIVDAK.
- Contact lenses: Advise patients to avoid wearing contact lenses unless advised by their eye care provider for the entire duration of therapy.

https://www.tivdakhcp.com/Tivdak_Large_Print_Tabbed_PI.pdf

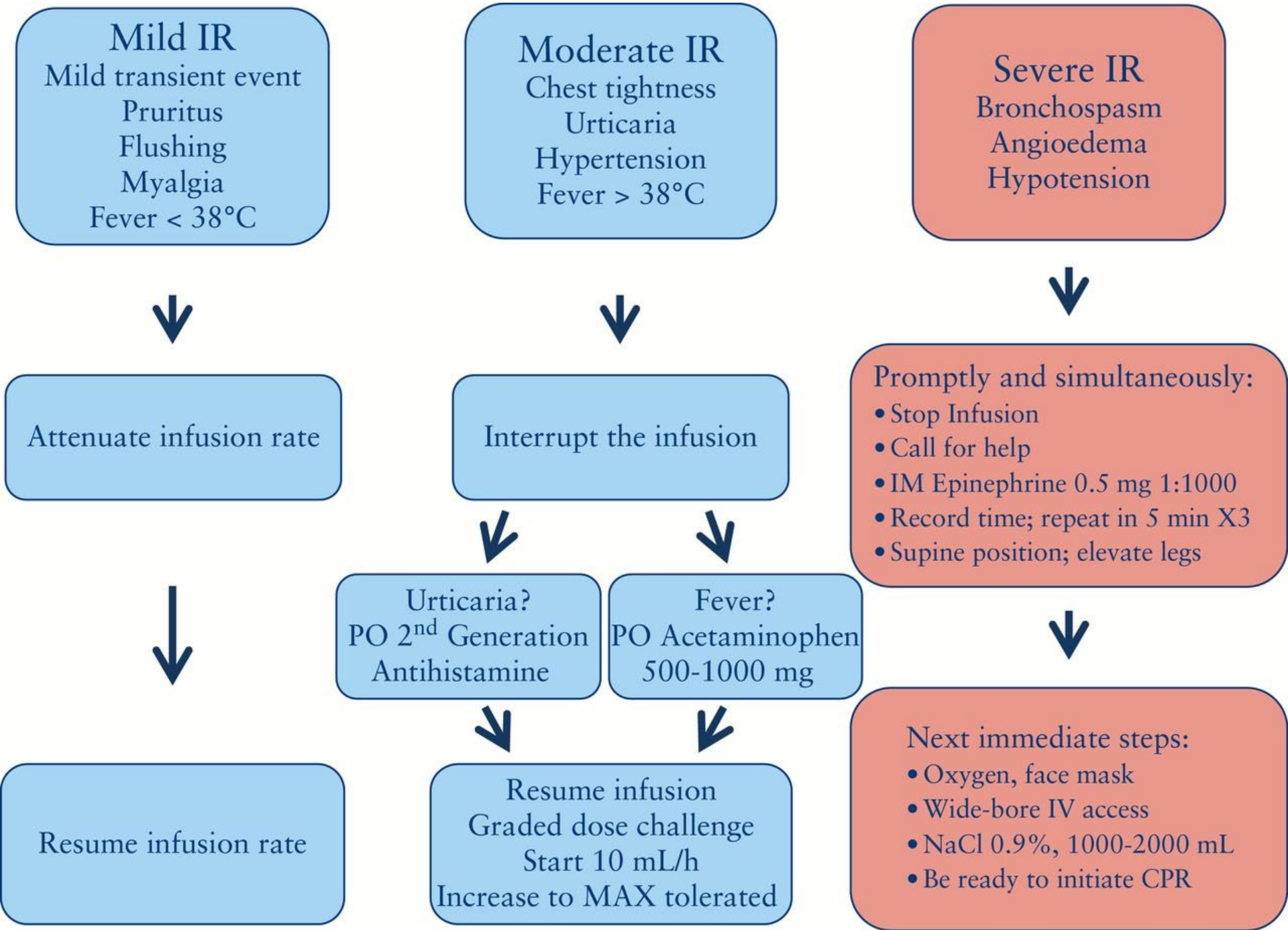
NCCN Guidelines: Management of Immune Checkpoint Inhibitors



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

Infusion Reactions

- Usually seen in first infusion
- Most able to complete infusion
- Use of Pre-medications
  - Varies among agents
  - histamine H1-receptor antagonists
  - histamine H2-receptor antagonists
  - corticosteroids
  - antipyretics


Mild IR
Mild transient event
Pruritus
Flushing
Myalgia
Fever < 38°C
Moderate IR
Chest tightness
Urticaria
Hypertension
Fever > 38°C
Severe IR
Bronchospasm
Angioedema
Hypotension
Attenuate infusion rate
Interrupt the infusion
Promptly and simultaneously:
• Stop Infusion
• Call for help
• IM Epinephrine 0.5 mg 1:1000
• Record time; repeat in 5 min X3
• Supine position; elevate legs
Urticaria?
PO 2nd Generation
Antihistamine
Fever?
PO Acetaminophen
500-1000 mg
Resume infusion rate
Resume infusion
Graded dose challenge
Start 10 mL/h
Increase to MAX tolerated
Next immediate steps:
• Oxygen, face mask
• Wide-bore IV access
• NaCl 0.9%, 1000-2000 mL
• Be ready to initiate CPR

Rare AE's

- Diabetes mellitus
- Kidney/nephritis
- Ocular
- Neurologic
  - Sensory/motor neuropathy
  - Guillain-Barré syndrome, myasthenia gravis, encephalitis
- Cardiac/myocarditis
- Hematologic
- Rheumatologic
- Musculoskeletal

Conclusions

- New immune therapy approaches are being developed
- Unique side effects may be seen
- Toxicity management is critical to success
- Nurses are a pivotal part of the team due to need for good communication and prompt recognition of side effects

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