What all physicians need to know about irAEs

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Financial Disclosures

- Alexa Meara: Abbvie, Ampel, Genentech, Aurinia,GSK, Chemocentryx

- Presentation will include discussion of off-label use of drugs

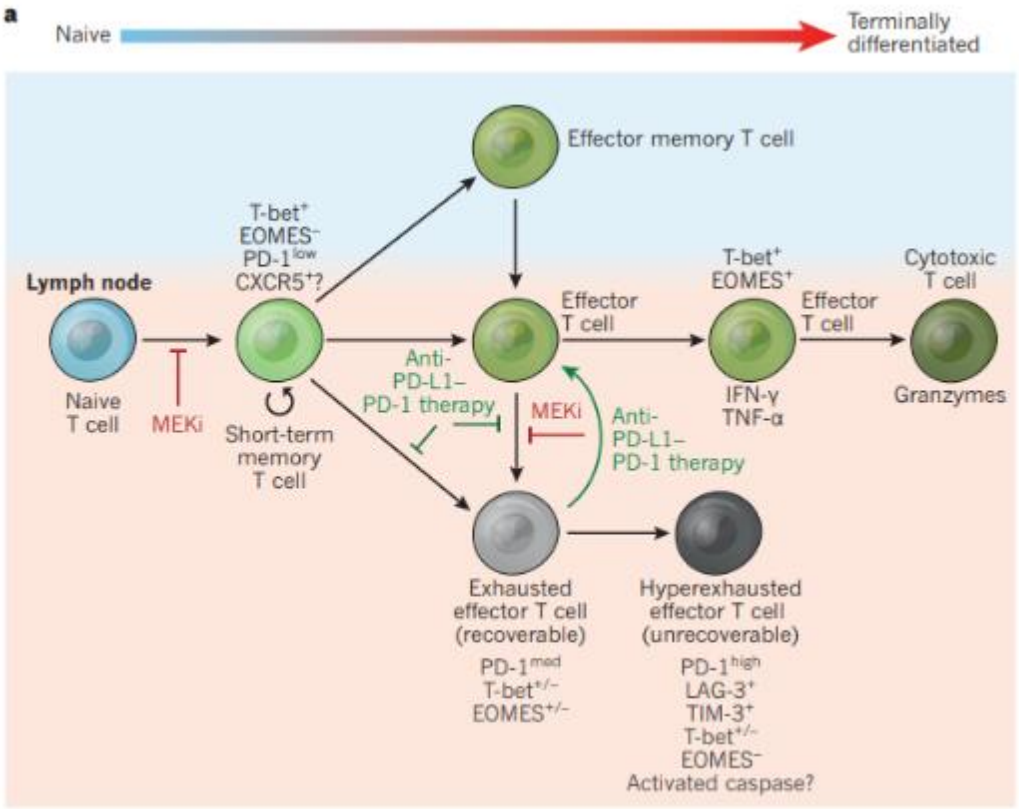
Objectives

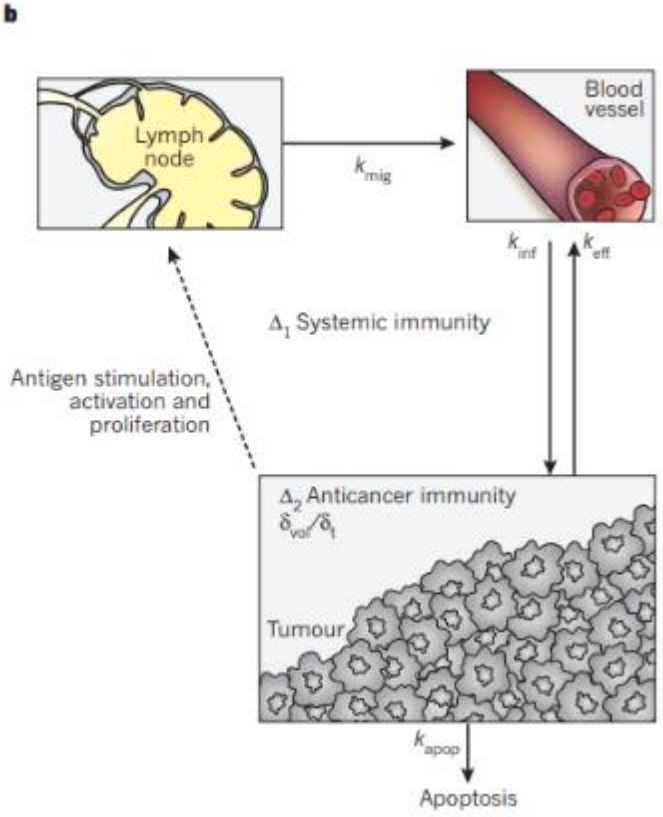
- Review the incidence and clinical implications of common immune related adverse events in patients treated with immune checkpoint inhibitors.
- Review and understand the mechanism of action of agents used to treat irAE
- Review irAE treatments

Outline

- Background: Cancer immunity and checkpoint inhibitors
- Overview of immune related adverse events
- OSU experience
- Background of DMARD type drugs
- Specific agents and role in irAE
- Treatments for irAEs
- Future directions and opportunities

Background: Cancer immunotherapy





Chen DS, *Nature* 2017

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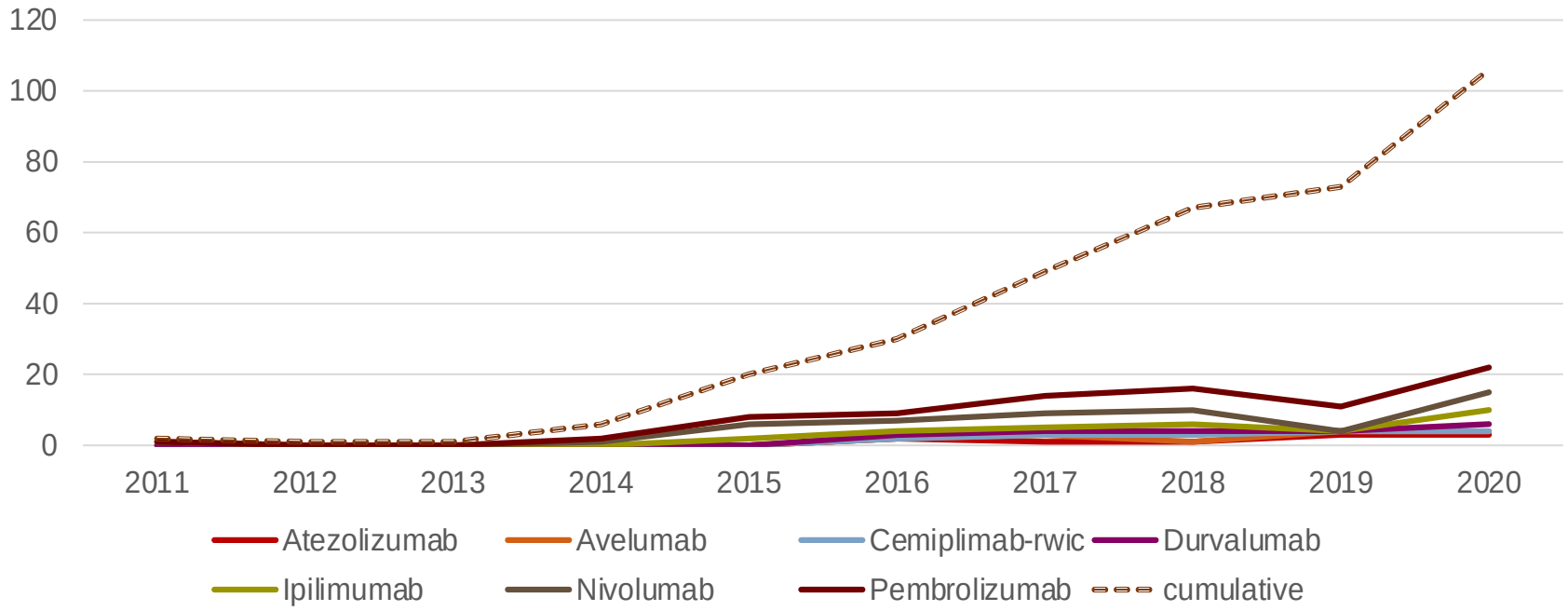
FDA Approvals - Checkpoint Inhibitors

Drug category	Name	Cancer Types
PD-1 monoclonal antibodies	Pembrolizumab	Melanoma, lung, head & neck, urothelial, gastric, lymphomas, cervix, MSI high cancers
	Nivolumab	Melanoma, lung, kidney, head & neck, liver, bladder, lymphomas, MSI high cancers
PD-L1 antibodies	Atezolizumab Avelumab Durvalumab	Lung, urothelial cancers Merkel cell carcinoma, urothelial
CTLA-4 antibodies	Ipilimumab	Melanoma
Combination	Ipilimumab + Nivolumab	Melanoma, renal cell carcinoma, MSI high colorectal, ?NSCLC

Approval for ICIs by Year

Figure 2: Number of Indications by Each Immune Check Point Inhibitors By Year



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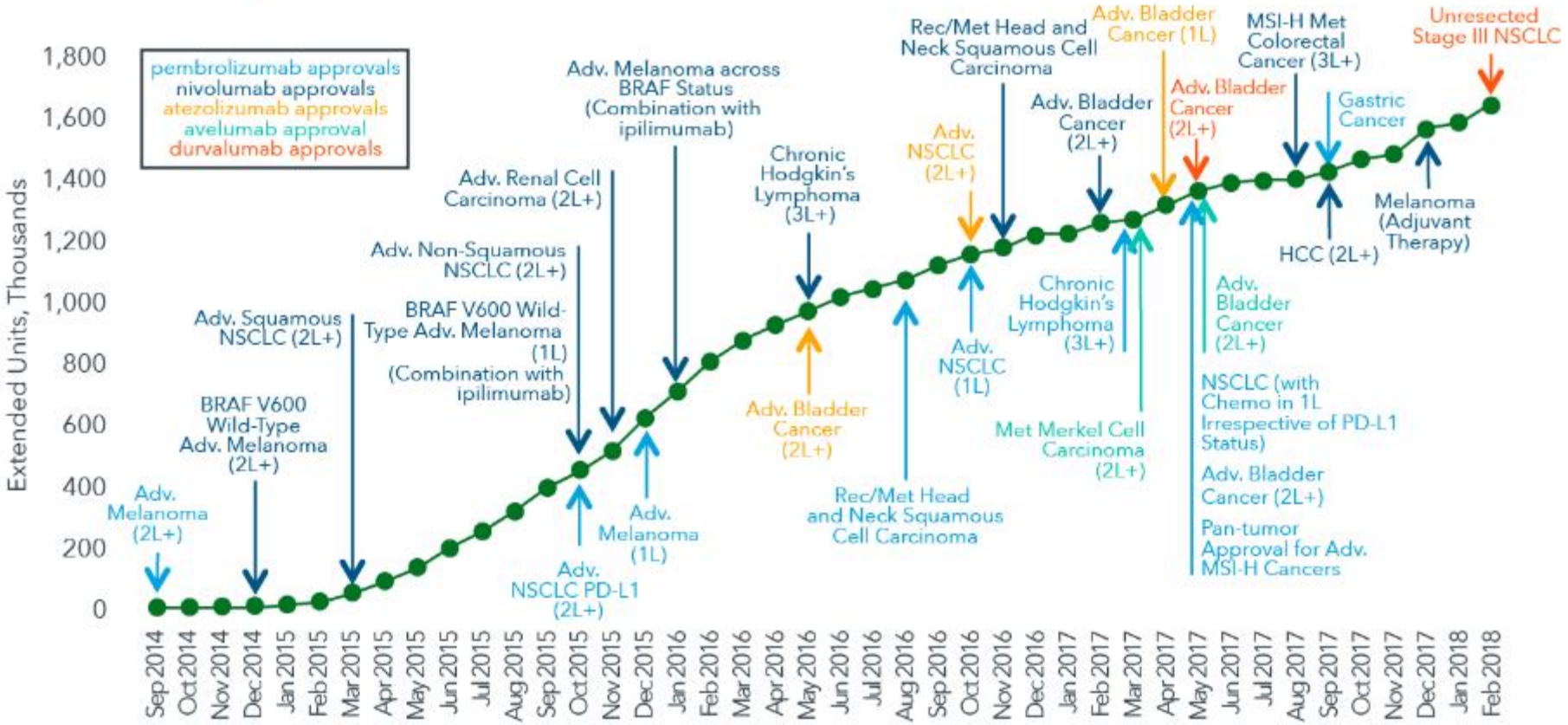
Immuno-Oncology PD-1 and PD-L1 Inhibitor Uptake in the United States

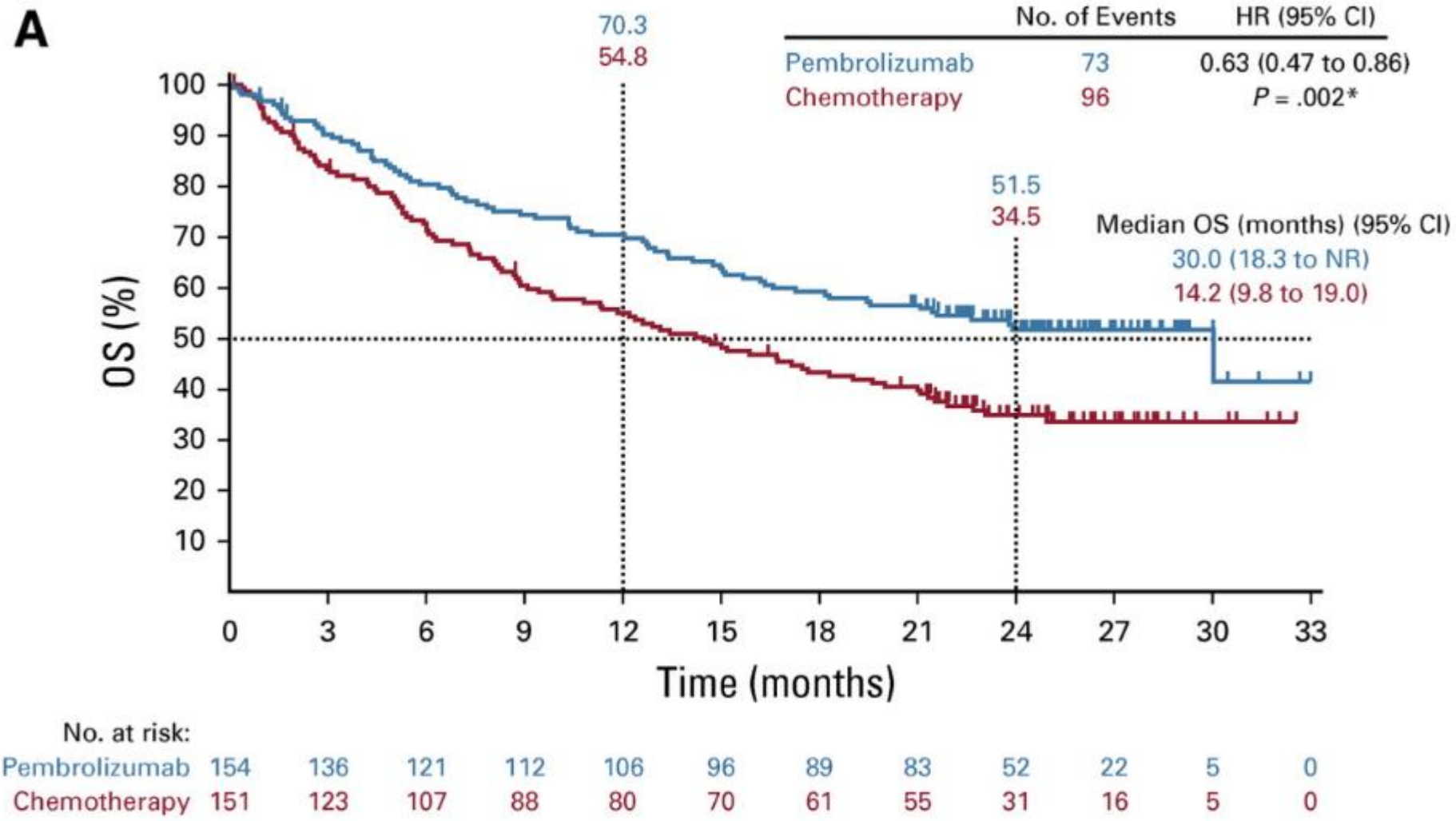


Source: U.S. FDA, IQVIA, National Sales Perspectives, Feb 2018; IQVIA Institute, Apr 2018

Notes: Met = metastatic; rec/met = recurrent/metastatic; 1L+ = 1st line; 2L+ = 2nd line; HCC = hepatocellular carcinoma.

Report: Global Oncology Trends 2018: Innovation, Expansion and Disruption. IQVIA Institute for Human Data Science, May 2018

Long term survival from KN 24



Reck M et al, *JCO* 2019

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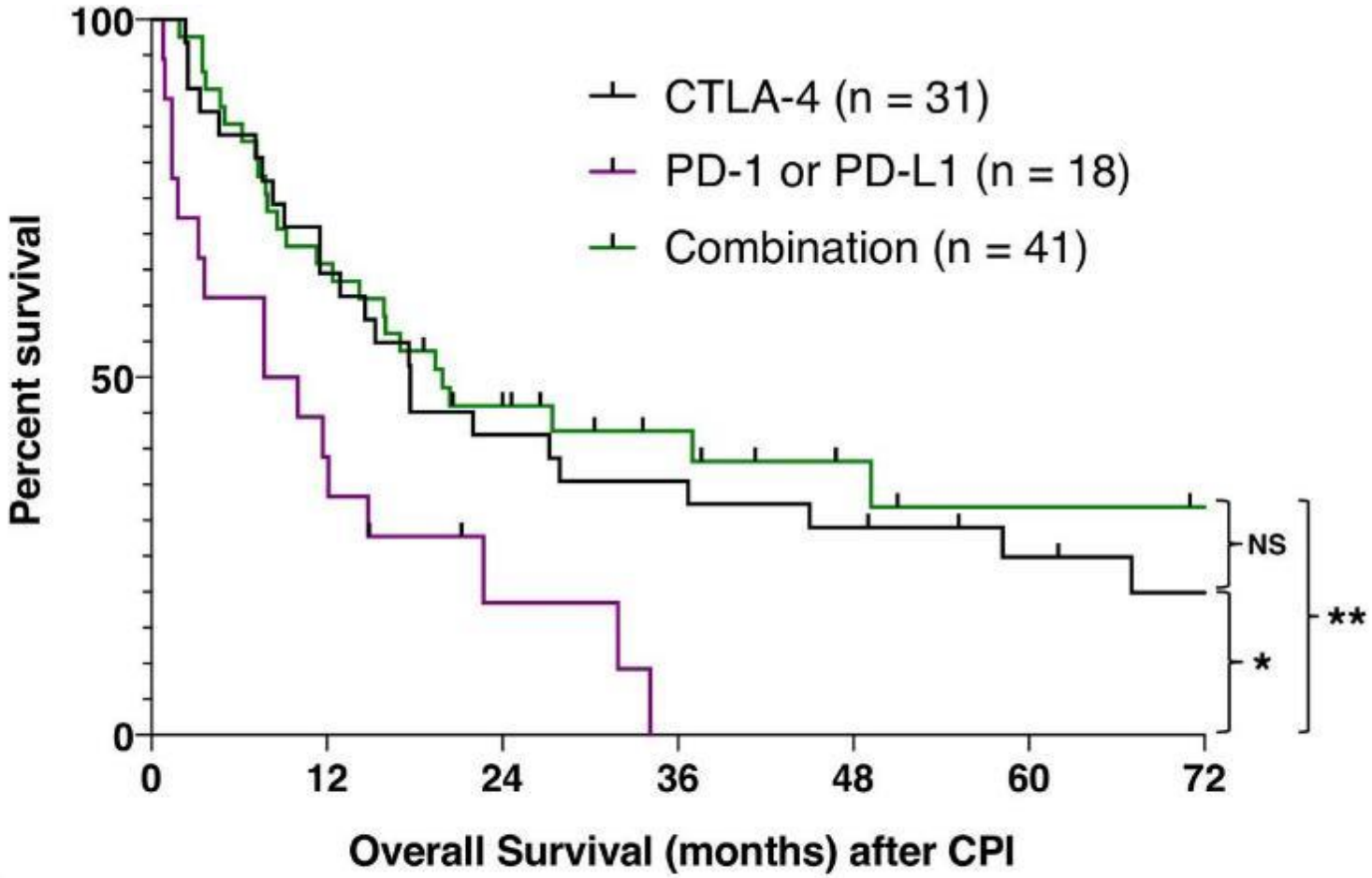
Survival in patients receiving ICI in Melanoma



At risk							
CTLA-4	31	20	13	11	9	6	4
PD-1/PD-L1	18	7	2	0	0	0	0
Combination	41	27	17	10	6	4	3

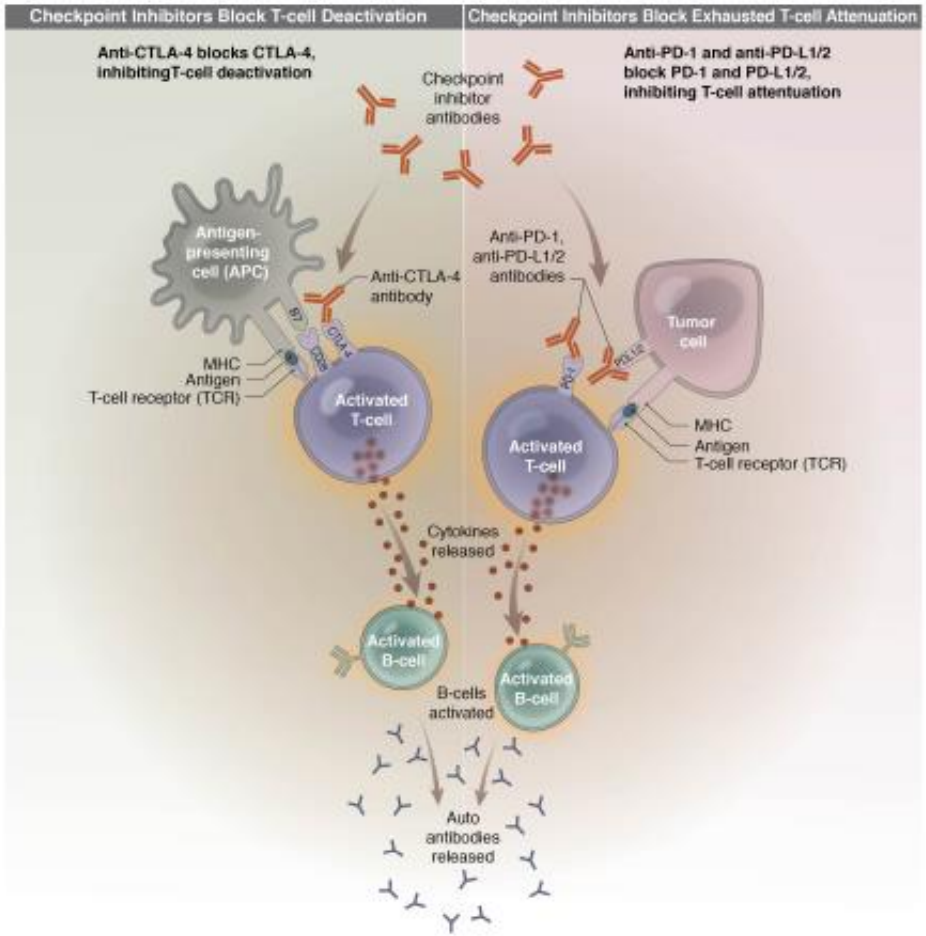
Polling Question

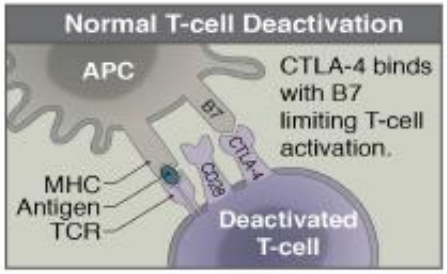
- What percentage of patients exposed to immunotherapy develop any irAE?
  - A. 10%
  - B. 30%
  - C. 50%
  - D. 80%

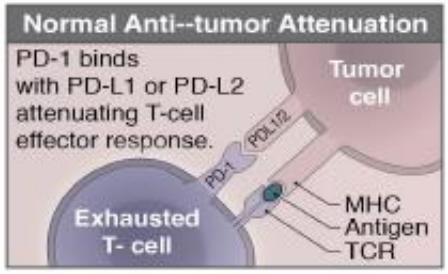
Immune related adverse events (irAE)

- Unique set of side effects/toxicities from immunotherapies such as ICI
- Differ significantly from cytotoxic chemotherapy
- Require high clinical suspicion and early testing
- Require new monitoring and screening protocols
- Patient education is key

The Development of irAE's after receiving ICI's







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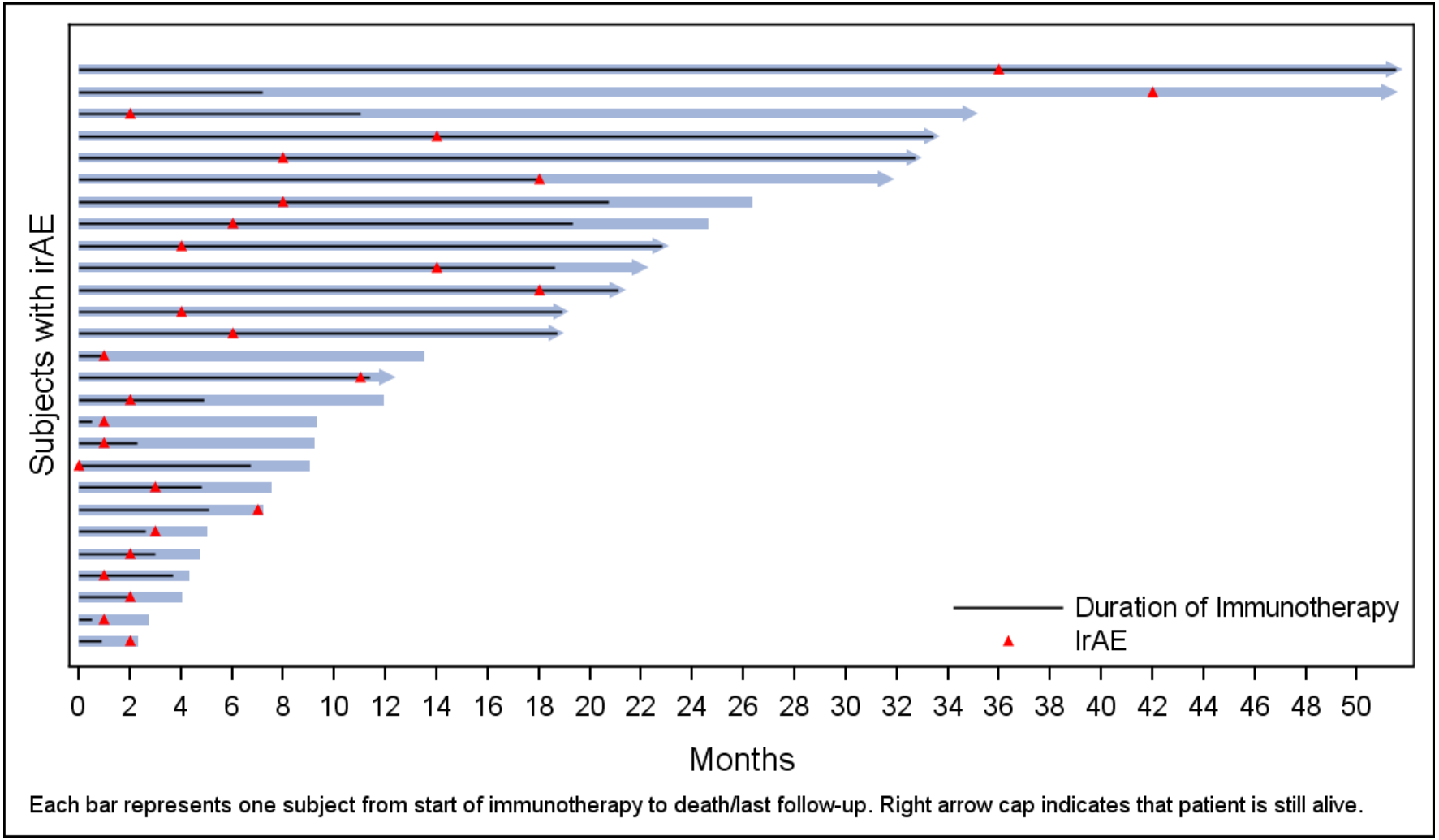

Owen DH et al, *Clin Lung Cancer* 2018

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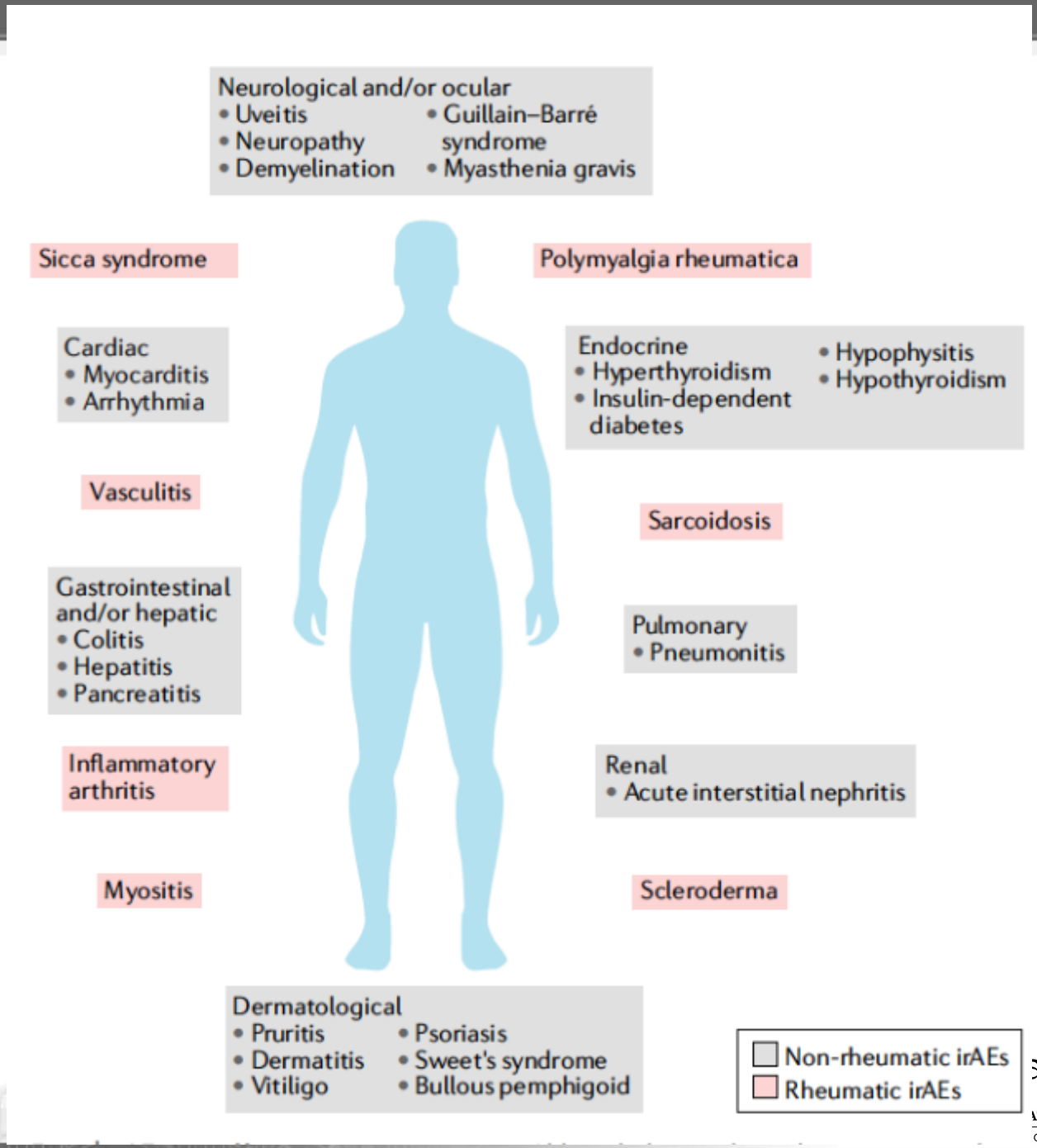
Different Types of irAEs

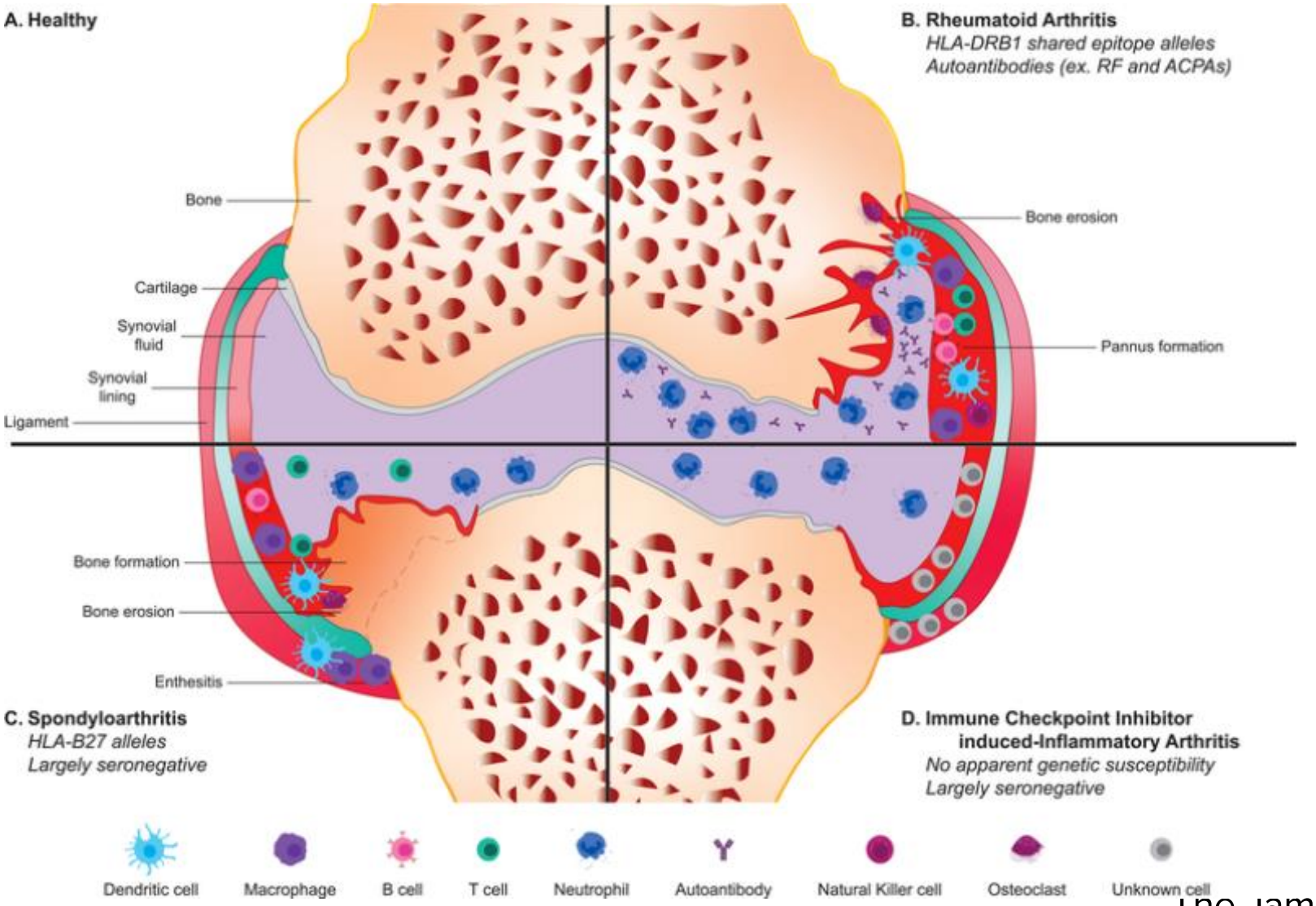


Calabrese, Nature, 2018

Inflammatory Arthritis

- Inflammatory arthritis about 3-7.5% of irAEs for PD-1/PD-L1
- Often reactive like arthritis syndrome
- Often between 5-24 months
- More commonly seronegative
- Persists after chemotherapy stopped
  - 10% persist to chronic inflammatory arthritis

Immunologic Features of Inflammatory Arthritis



Cappelli, L *Immuno Rev, 2020*

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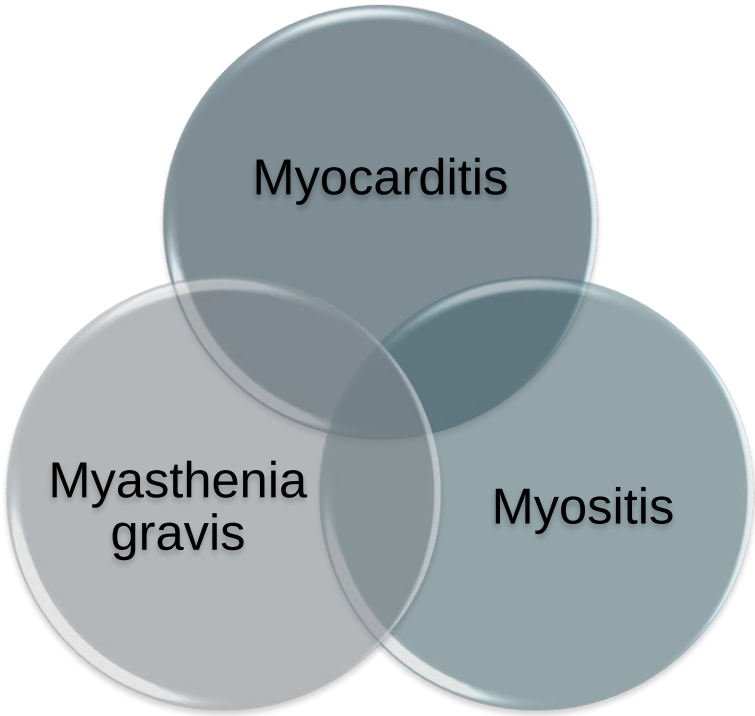
Polymyalgia Rheumatica

- Often atypical
- Under reported
- Requires for more aggressive therapy than traditional PMR.
- Two cases of CPI-related PMR with concurrent giant cell arteritis

Overlap Myopathy Syndromes

- Overlap of myocarditis, myositis, and myasthenia gravis
- 38 patients with monastic skin cancers treated with ICIs
- 32% had concomitant myocarditis
- Autoantibodies are negative
- Cytotoxic T cell infiltration
- Most deadly

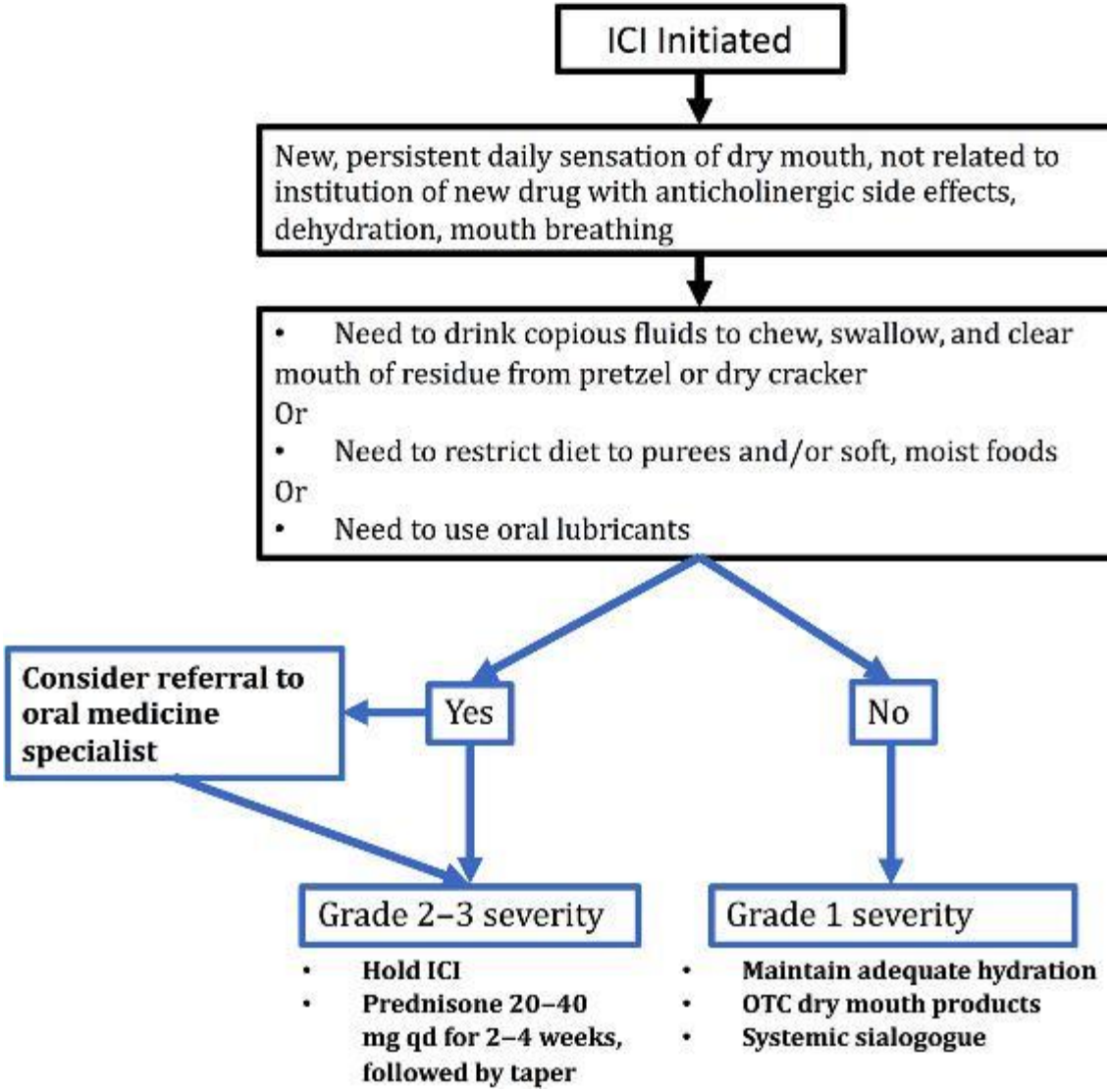


Moreired al, Eur J cancer 2018, Naidoo et al, JNCCN 2019

Sicca Syndrome

- Common with PD-1 inhibitors
- Biopsies of salivary gland similar to Sjogren's patients
- Negative to traditional autoantibodies
- Hypothesis: cytotoxic T cell damaging the salivary epithelium

Sicca Syndrome



The Oncologist, Volume: 24, Issue: 9, Pages: 1259-1269, First published: 17 April 2019, DOI: (10.1634/theoncologist.2018-0823)

Colitis

- Most common with CTLA-4 inhibitors
  - 30-40% of patients
- Onset with in the first 2 weeks if CPI therapy
- Must rule out infection

Pneumonitis

- Most common with PD-1 therapy
- Most common with lung cancer patients
- Severe and life threatening
- Often patient are oxygen dependent post therapy with stable cancer

Other IrAEs

Glomerulonephritis

- Often Acute interstitial nephritis most common
- Improves with corticosteroids and CPI withdrawal

Autoimmune Hepatitis

- 1/3 of patient CTLA-4 blockade
- Improves with corticosteroids
- Does not require CPI withdrawal

Neurological

- Often vague complaints
- <15% have serious encephalitis, Guillain-Barre, neuropathy
- May require CPI withdrawal

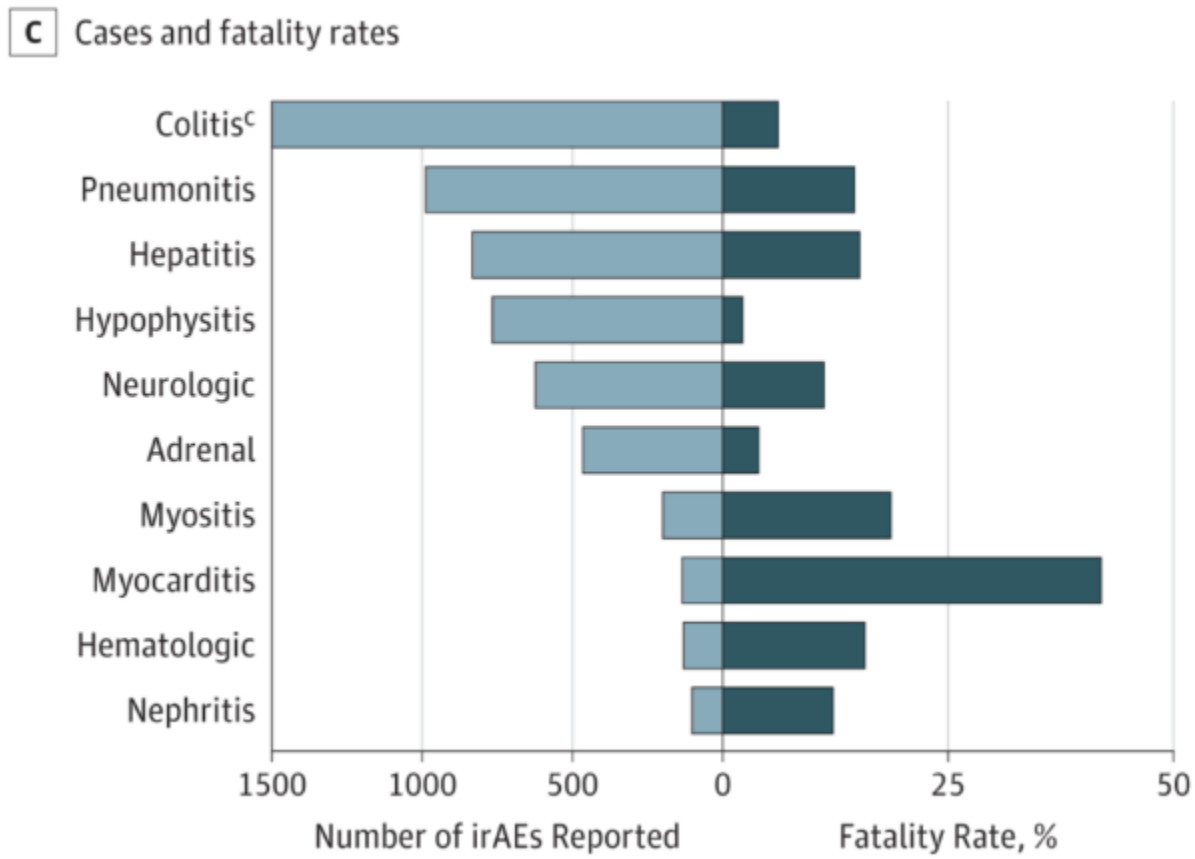
Dermatologic

- Most common and often not serious
- Improves with corticosteroids
- Does not require CPI withdrawal

Endocrine

- Do not require biologics or DMARDs
- Hypophysitis is a common IRAE with use of anti-CTLA-4
- Watch TSH level
- If hypophysitis is suspected, the substitution of a corticotropin deficiency is an emergency.
  - MRI must be performed if a hypophysitis is suspected and monitored during the first 3 months, especially to rule out the differential diagnosis of cerebral metastasis.
- High-dose GC should not be systematically given
- Immunotherapy should not be stopped
- Gonadotropin and thyrotropin defects should recover, unlike corticotropin deficiencies
- A multidisciplinary long-term follow-up with an endocrinologist and an oncologist is needed in cases of hypophysitis.

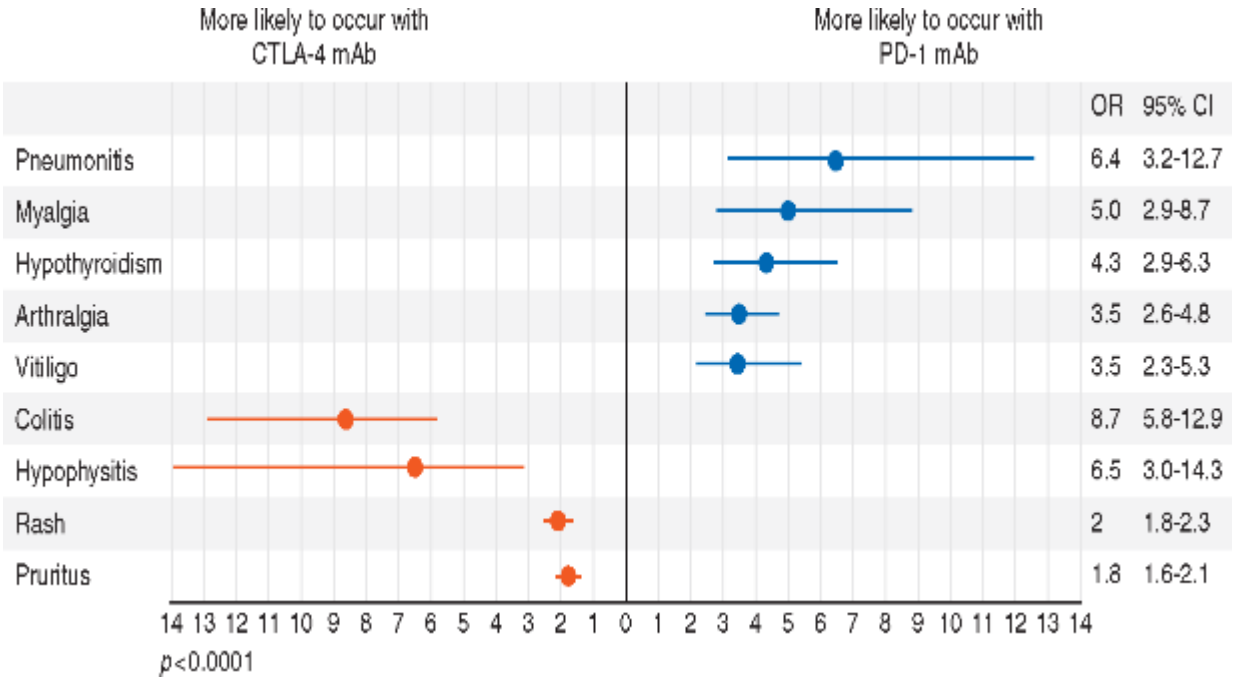
Delayed Recognition of IO Toxicity: Life-Threatening or Fatal



Wang DY, Salem J, Cohen JV, et al. Fatal Toxic Effects Associated With Immune Checkpoint Inhibitors: A Systematic Review and Meta-analysis. *JAMA Oncol.* 2018;4(12):1721–1728.

Serious Toxicity Varies by Type of Immunotherapy

- Figure 2. The odds ratio (OR) of different immune-related adverse events (all grades) comparing PD-1/PD-L1 versus CTLA4



OXFORD UNIVERSITY PRESS

Annals of Oncology, Volume 28, Issue 10, October 2017, Pages 2377–2385.

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Fatal Events – More Early but can be Late

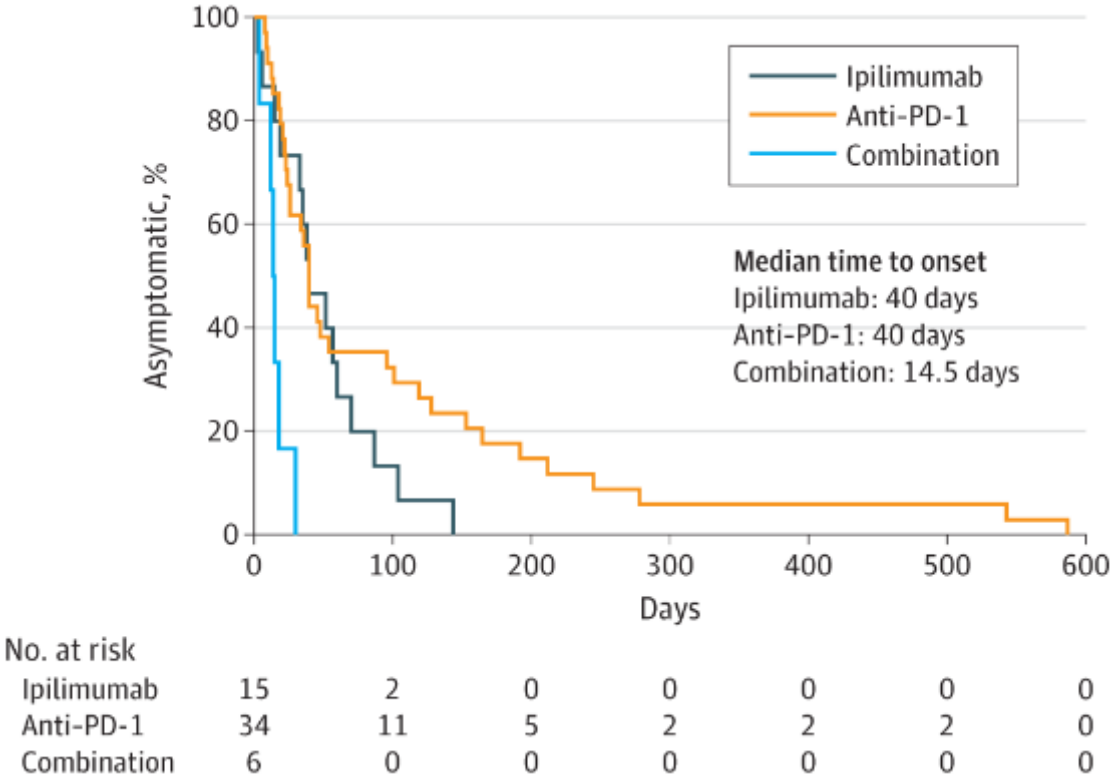

Figure 2: Time to Symptom Onset of Fatal Toxic Effects by ICI Regimen

JAMA Network

Wang DY, Salem J, Cohen JV, et al. Fatal Toxic Effects Associated With Immune Checkpoint Inhibitors: A Systematic Review and Meta-analysis. *JAMA Oncol.* 2018;4(12):1721–1728.

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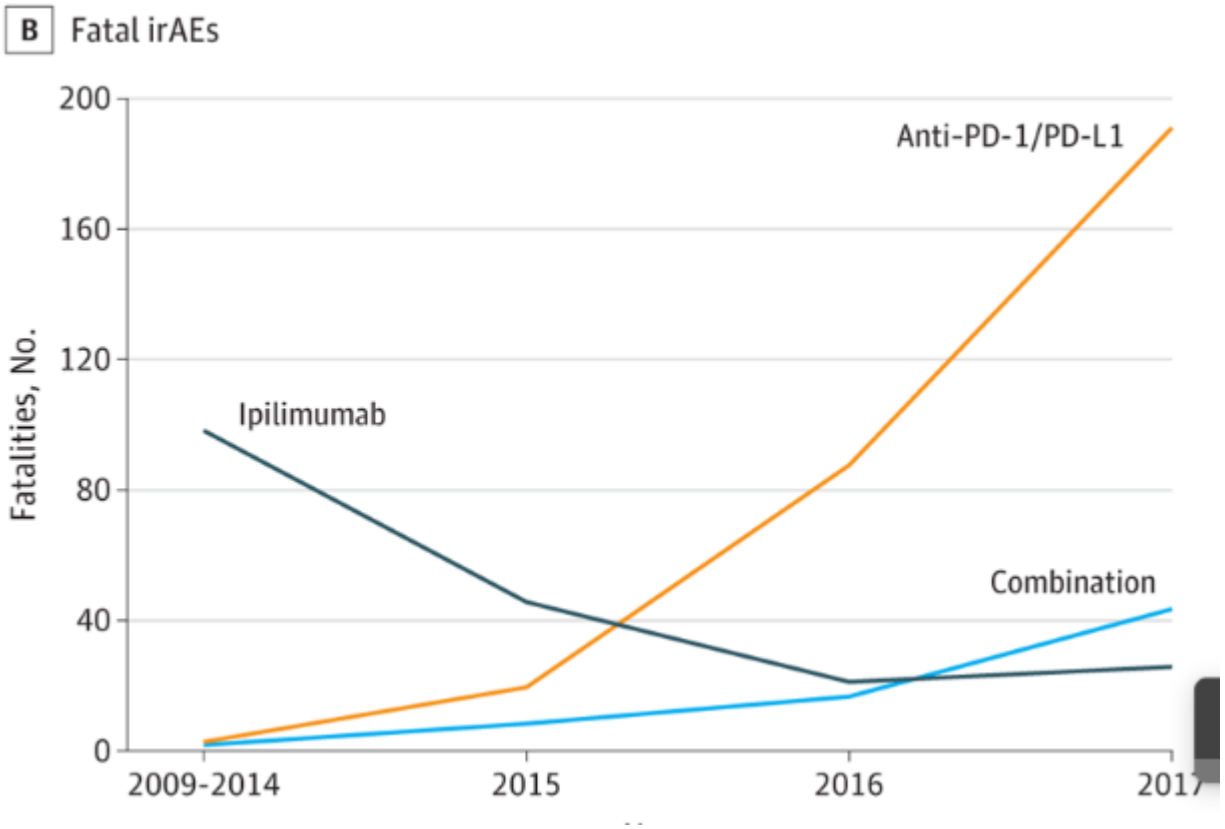
Immune AE are serious



Wang DY, Salem J, Cohen JV, et al. Fatal Toxic Effects Associated With Immune Checkpoint Inhibitors: A Systematic Review and Meta-analysis. *JAMA Oncol.* 2018;4(12):1721–1728.

Consequences of Immunotherapy

- Side effects can be expected in any organs through an autoimmune mechanism
- Early recognition is key
- What are the appropriate treatments?

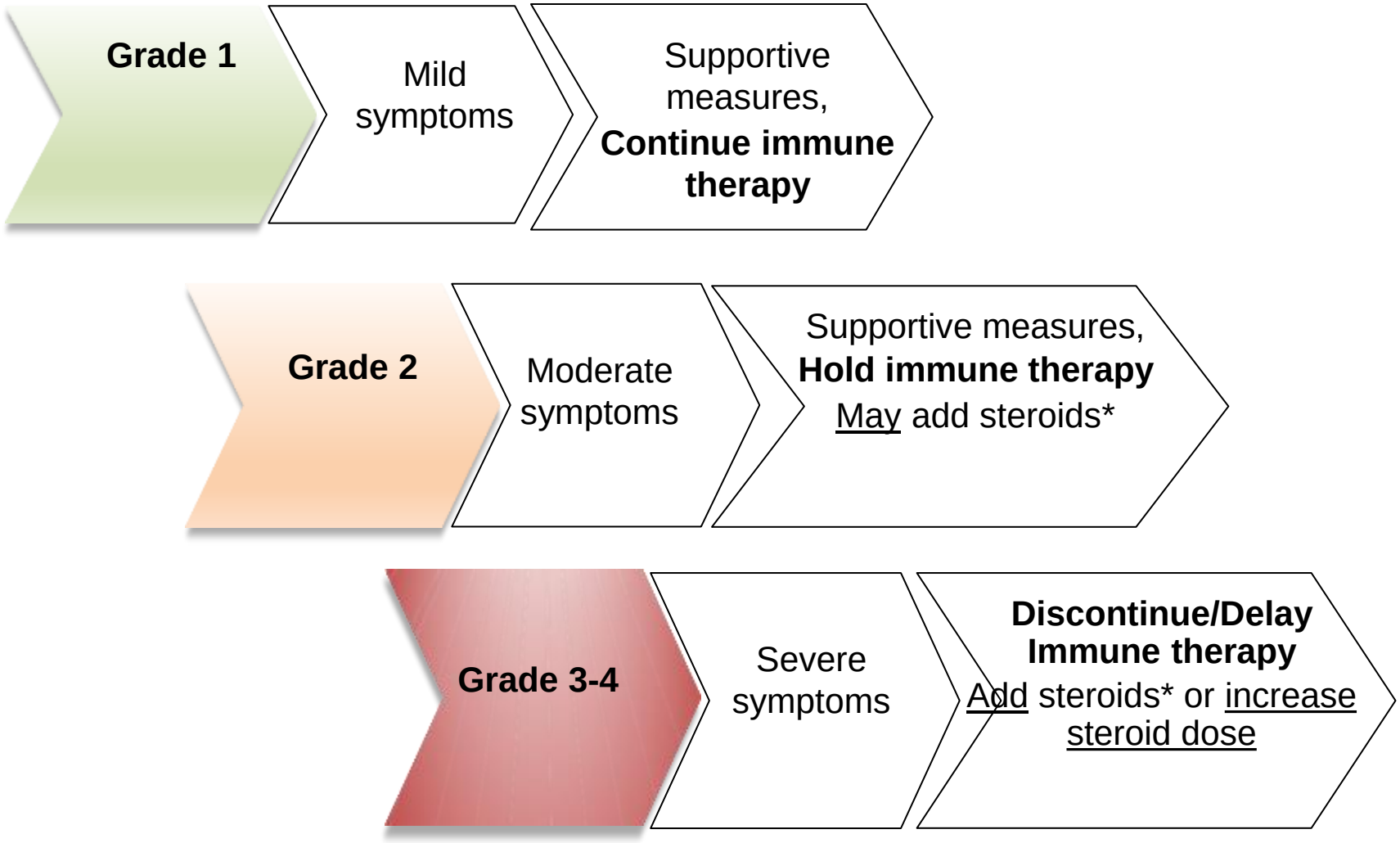
Polling Question

- Can your irAE become a permanent autoimmune disease?
  A. True
  B. False

General Thoughts on Immunotherapy and Immune Related Adverse Events (irAEs)

- Immunotherapy is very effective in about 25% of oncology patients
- Serious irAEs do occur – probably more frequently than reported in clinical trials
- Understanding of these irAEs continues to evolve
- Positive correlation between irAEs and clinical benefit is exploratory
  - May simply be a marker for duration of therapy
- irAEs can be permanent and lethal
- Risks factors for irAE undefined although underlying cancer and PMH likely play a role

Immunotherapy Toxicities – General Management

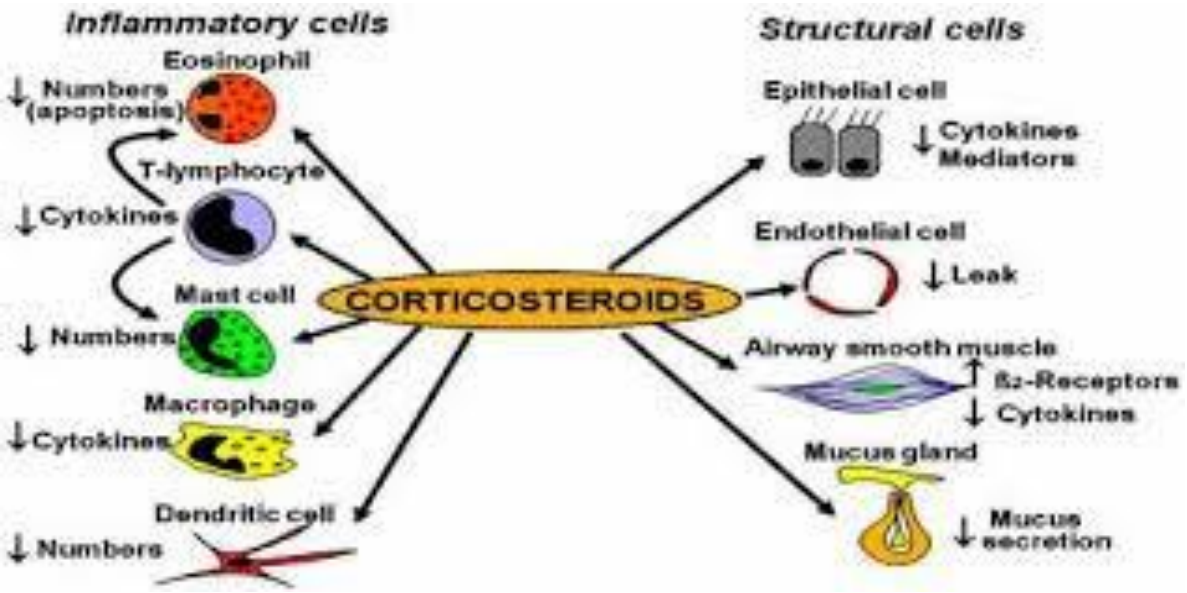


General Approach to irAEs

- Main stay of treatment: Steroids
- Dose 1 to 2 mg/kg initially
- Methylprednisolone if inpatient
- Taper should be very slow, over a minimum of 4 weeks, but likely 8-12 weeks otherwise symptoms recur
- Consider prophylactic antibiotics and GI ppx if steroids > 1 month
- Start patients immediately as soon as clinical suspicion
- Can manage many patients as outpatient

First Line Treatments

- Corticosteroids: IV corticosteroids
  - Grade 1-2 0.5-1 mg/kg
  - Grade 3 1-2 mg/kg
  - Grade 4 1-2 mg/kg



Recommendations from SITC: General Corticosteroid Recommendations

Grade of immune-related AE (CTCAE/equivalent)	Corticosteroid management	Additional notes
1	• Corticosteroids not usually indicated	• Continue immunotherapy
2	• If indicated, start oral prednisone 0.5-1 mg/kg/day if patient can take oral medication. • If IV required, start methylprednisolone 0.5-1 mg/kg/day IV • If no improvement in 2–3 days, increase corticosteroid dose to 2 mg/kg/day • Once improved to ≤grade 1 AE, start 4–6 week steroid taper	• Hold immunotherapy during corticosteroid use • Continue immunotherapy once resolved to ≤grade 1 and off corticosteroids • Start proton pump inhibitor for GI prophylaxis
3	• Start prednisone 1-2 mg/kg/day (or equivalent dose of methylprednisolone) • If no improvement in 2–3 days, add additional/alternative immune suppressant • Once improved to ≤ grade 1, start 4–6-week steroid taper • Provide supportive treatment as needed	• Hold immunotherapy; if symptoms do not improve in 4–6 weeks, discontinue immunotherapy • Consider intravenous corticosteroids • Start proton pump inhibitor for GI prophylaxis • Add PCP prophylaxis if more than 3 weeks of immunosuppression expected (>30 mg prednisone or equivalent/day)
4	• Start prednisone 1-2 mg/kg/day (or equivalent dose of methylprednisolone) • If no improvement in 2–3 days, add additional/alternative immune suppressant, e.g., infliximab • Provide supportive care as needed	• Discontinue immunotherapy • Continue intravenous corticosteroids • Start proton pump inhibitor for GI prophylaxis • Add PCP prophylaxis if more than 3 weeks of immunosuppression expected (>30 mg prednisone or equivalent/day)

Note: For steroid-refractory cases and/or when steroid sparing is desirable, management should be coordinated with disease specialists. AE, adverse event

NCCN Guidelines Version 1.2019
Management of Immune Checkpoint Inhibitor-Related Toxicities

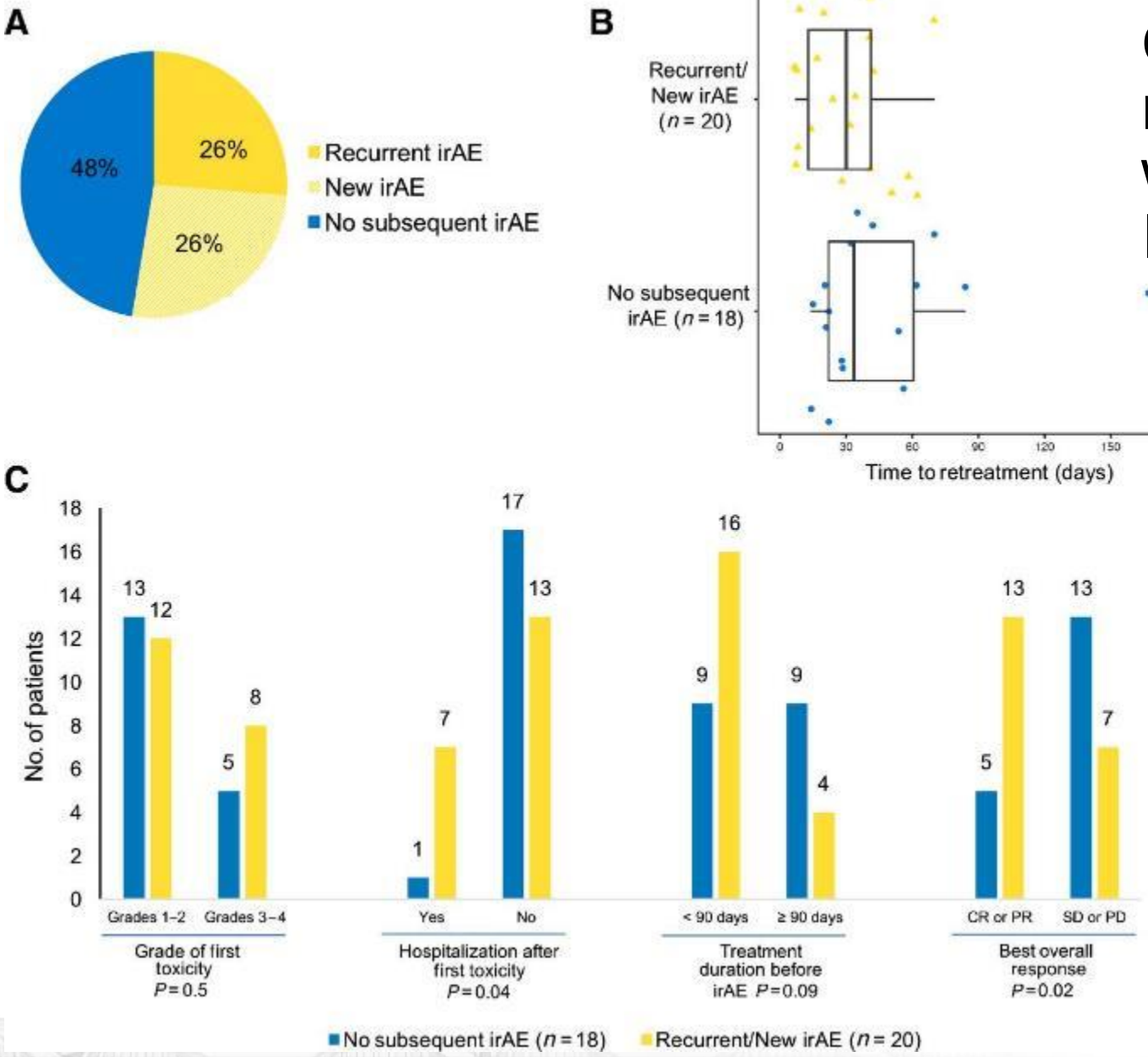
PRINCIPLES OF ROUTINE MONITORING

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.

NCCN/ASCO Guidelines

- These guidelines are specific to the type of irAE
- In general, the work up consists of holding immunotherapy
  - Ruling out infections
  - Starting corticosteroids
- When the symptoms persistent despite corticosteroids that is when the DMARDs or biologics are used
  - Dependent on irAE
  - Dependent on the organ involved
  - Dependent on the guideline
  - Minimal evidence

Can we rechallenge with ICI after IrAEs?



Fernando C. Santini et al. Cancer Immunol Res 2018;6:1093-1099

Summary Table: Targeted therapy of rheumatic irAEs:			
Targeted Therapy	Anti-tumor effect of the Targeted Therapy	Safety Concerns for the Targeted therapy	IrAEs that have been Treated by Targeted Therapy
TNF	No data so far[14]	Infections	Colitis[4] IA[5]
IL-6	May improve PD-1	Perforation Infections	IA[15] PMR[16] GCA[17]
IL-1	No data	Infection	MAS[18]
IL-17	Mixed data[19]	Infection[20] Unmask Colitis[20]	Spondyloarthropathy psoriasis
B-cell	No data	Infections	Grade 4 irAEs [21]
Jaki	Mixed data[22]	Infections[23] Thrombosis	Unknown
Abatacept	Theory only	Infection	Myocarditis[24]

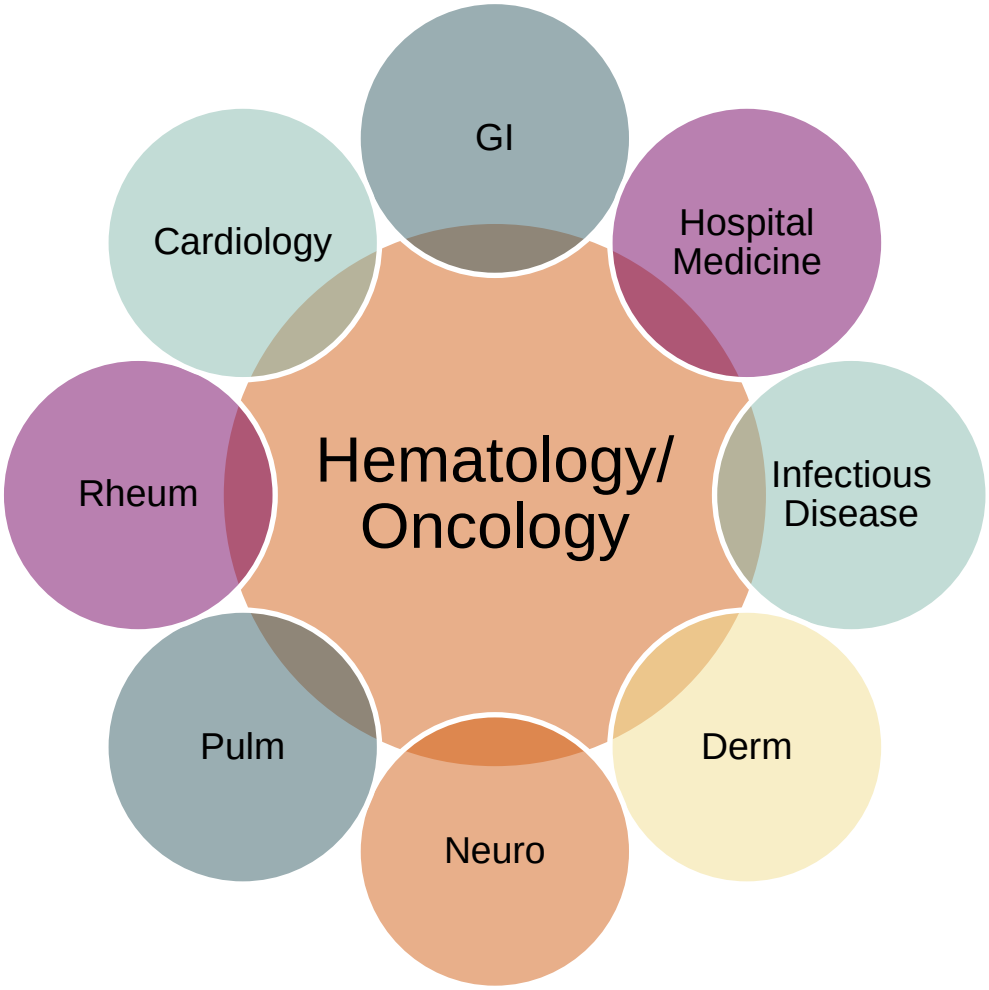
irAE: immune related adverse events, TNF: tumor necrosis factor, JAKi: janus kinase inhibitors, IL: interleukin, IA: inflammatory arthritis, PMR: polymyalgia rheumatica, GCA: giant cell arteritis, MAS: macrophage activation syndrome

Generic (Brand) name	Therapeutic agent	Type of irAE Treated
Abatacept (Orencia)	A fusion protein composed of the Fc region of the immunoglobulin IgG1 fused to the extracellular domain of CTLA-4.	Myocarditis
Infliximab (Remicade)	Chimeric Monoclonal AB with high affinity to the soluble (free floating in the blood) and transmembrane (located on the outer membranes of T cells and similar immune cells) forms of TNF-α	Colitis Arthritis
IVIG	Pooled immunoglobulin (IgG) from several thousand healthy donors. IVIg consists of antibodies to external antigens and naturally occurring autoantibodies (NAbs) with germline or close to germline configurations	Pneumonitis Neurotoxicity
Mycophenolate mofetil (Cellcept)	MPA depletes guanosine nucleotides preferentially in T and B lymphocytes and inhibits their proliferation, thereby suppressing cell-mediated immune responses and antibody formation.	Hepatitis Pneumonitis Neurotoxicity
Methotrexate	Antimetabolite of the antifolate type. It is thought to affect cancer and rheumatoid arthritis by two different pathways. For cancer, **methotrexate** competitively inhibits dihydrofolate reductase (DHFR), an enzyme that participates in the tetrahydrofolate synthesis.	Arthritis
Tocilizumab (Actemra)	humanized anti IL-6 receptor monoclonal antibody and binds specifically to IL-6 receptors.	CAR2

Unknown

- Do biologics or DMARDs affect the anti-tumor effect of ICIs
  - It is believed corticosteroids do not
- The dogmas has been to avoid certain DMARDs and biologics in patients with previous cancers (not exposed to ICI) due to high risk of recurrence
- Do patients with pre-existing autoimmune disease have different responses to ICIs?
- irAEs occur at different organs and depend on the cancer being treated

Multi-Disciplinary Management is Crucial



Thank You