Immunotherapy: what primary care providers need to know

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Conflict of Interest

- None

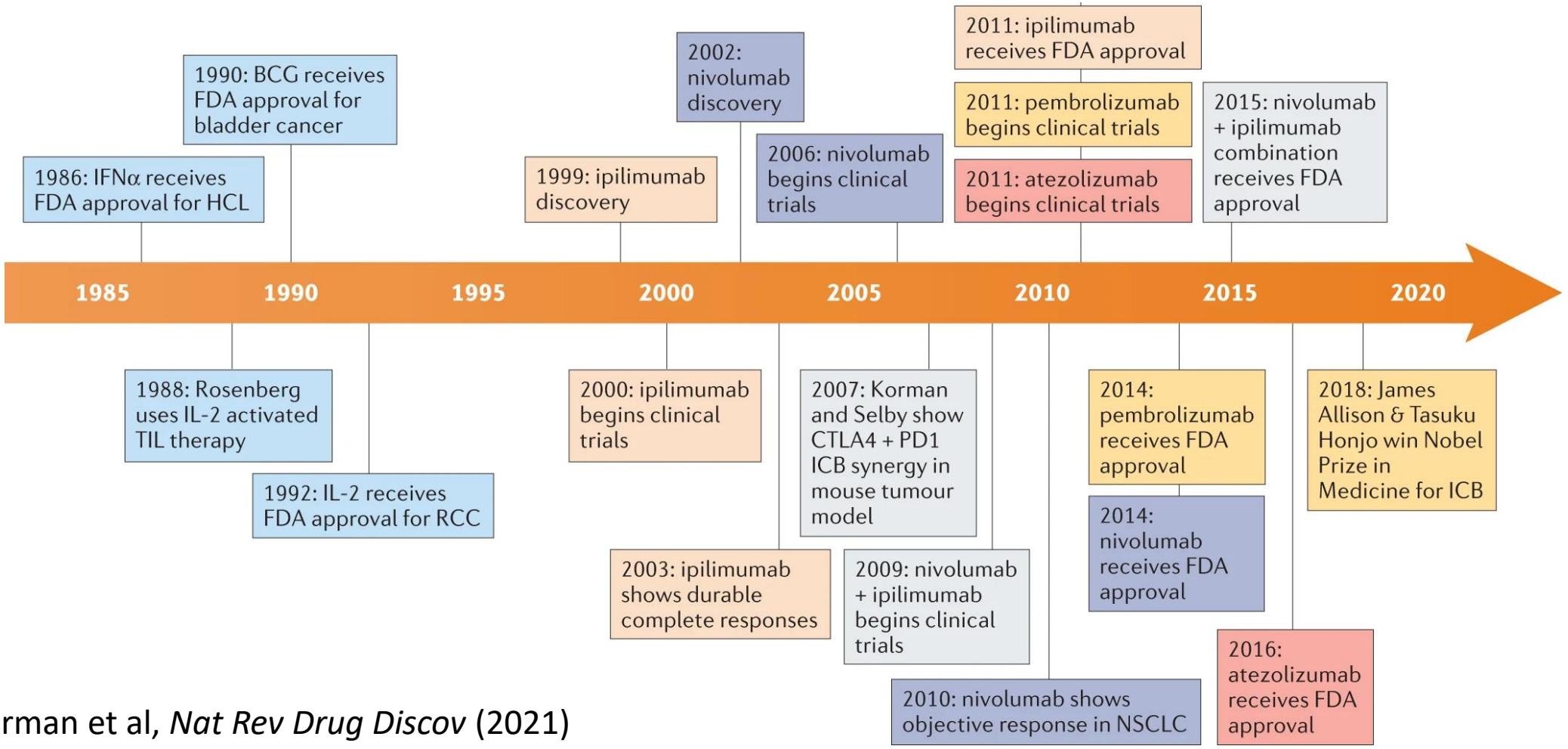
Learning Objectives

- Learn the basics of immunotherapy
- Identify adverse events
- Identify special situations

Agenda

- History
- What is special about these drugs
- Indications
- Mechanism of Action
- Types of immunotherapy
- Predictors of response
- Adverse Effects
- Challenging situations

Milestones in discovery and development of immunotherapeutics



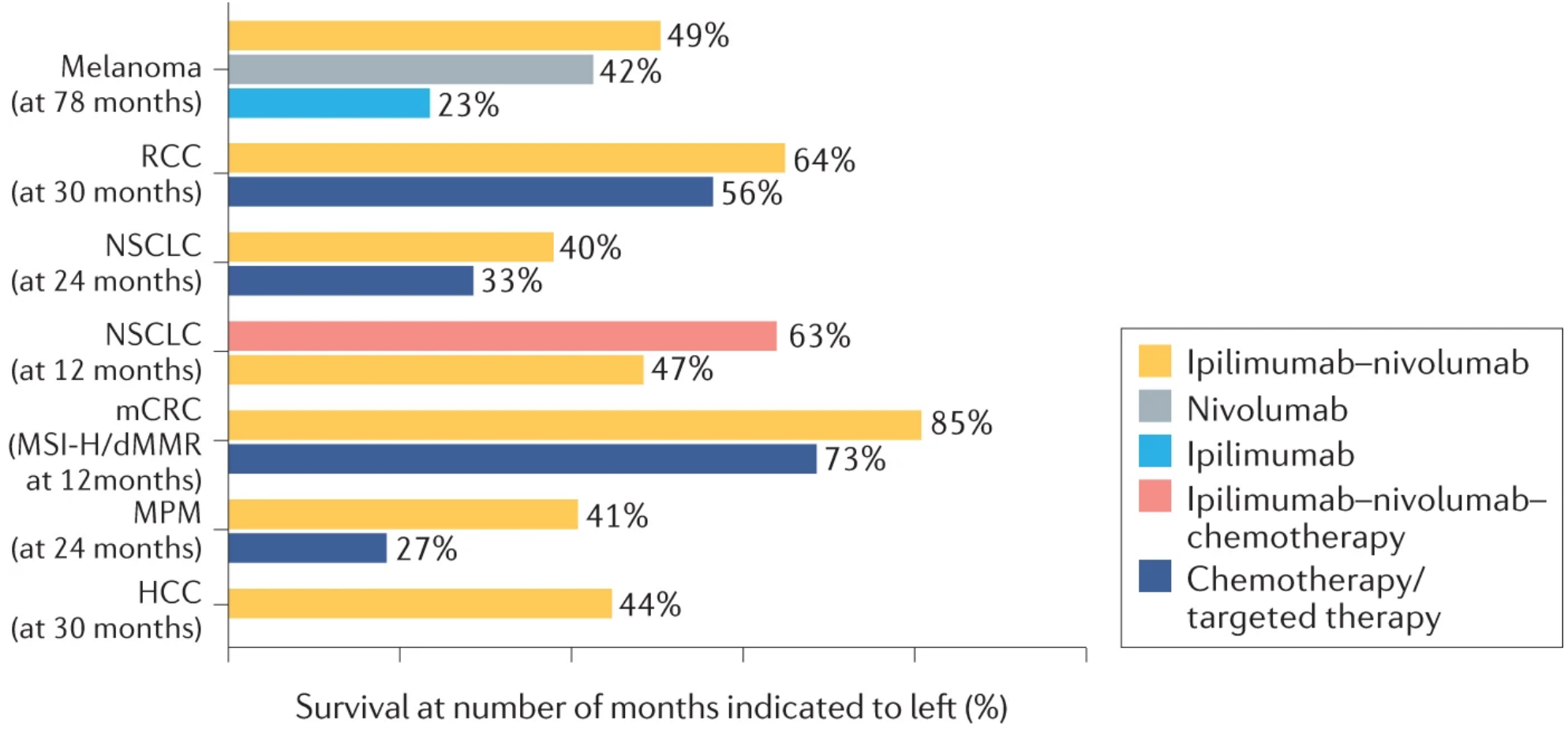
Korman et al, *Nat Rev Drug Discov* (2021)

Congratulations to James P. Allison & Tasuku Honjo

for winning
The 2018 Nobel Prize in
Physiology or Medicine

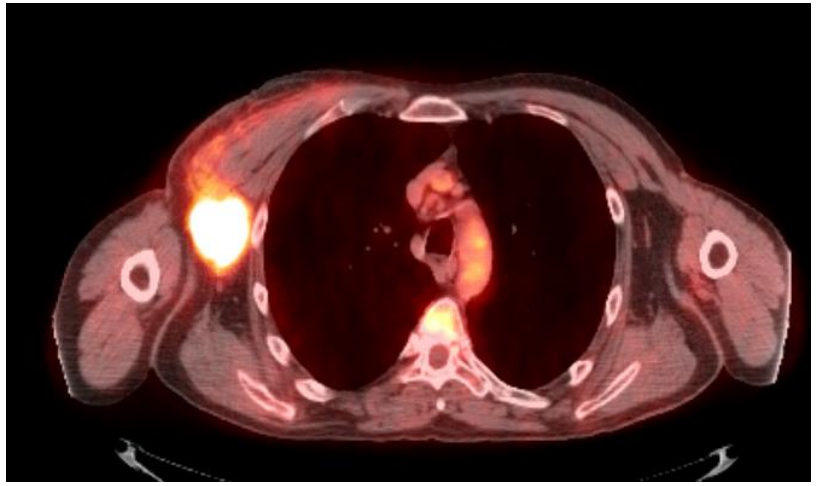
What’s special about these drugs

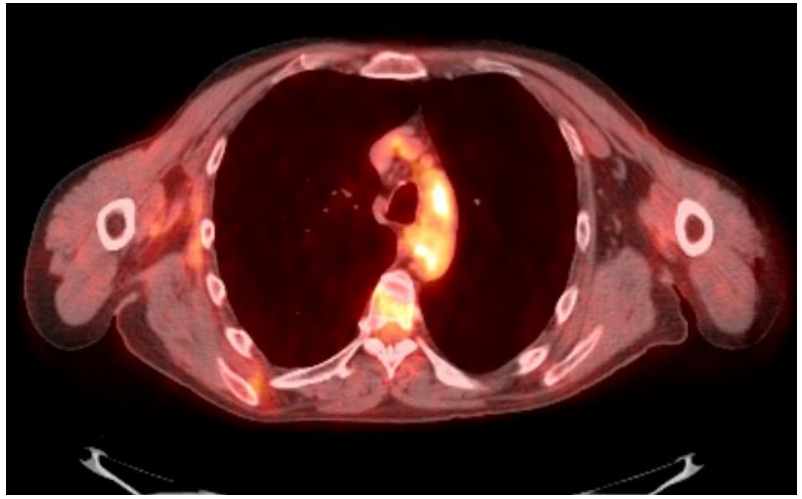
Prognosis

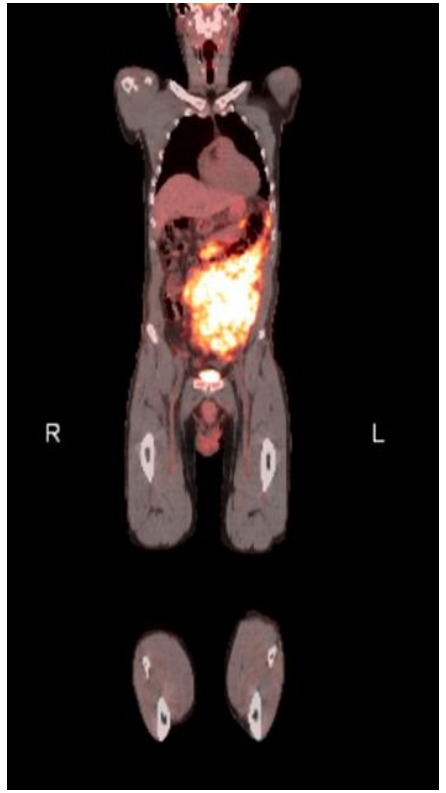


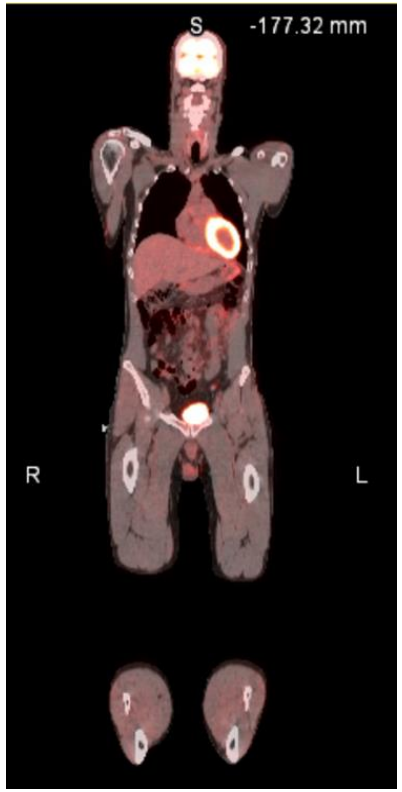
Korman et al, Nat Rev Drug Discov (2021)

Examples: melanoma









U.S. FDA APPROVED IMMUNE-CHECKPOINT INHIBITORS

Squamous Cell Head & Neck Cancer
2L after platinum chemo: nivolumab or pembrolizumab
1L with platinum chemo- pembrolizumab

Malignant Melanoma
Adjuvant ipilimumab, nivolumab, or pembrolizumab
1L ipilimumab, nivolumab, or pembrolizumab
1L combination nivolumab + ipilimumab

Merkel Cell Carcinoma
2L avelumab or pembrolizumab

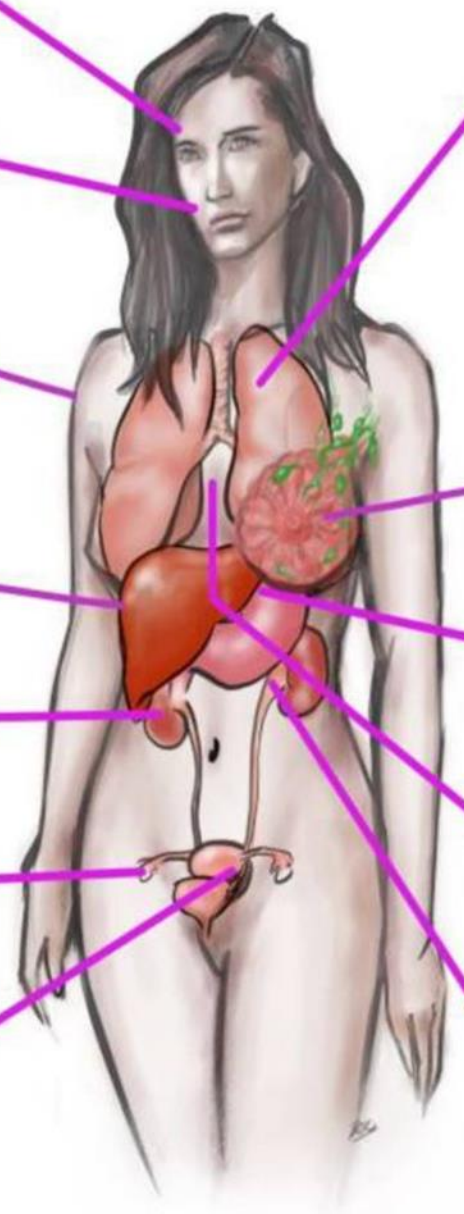
Cutaneous Squamous Cell Carcinoma
1L cemiplimab

Hepatocellular Carcinoma
2L nivolumab or pembrolizumab after sorafenib

Adv. Renal Cell Carcinoma
1L nivolumab plus ipilimumab
2L nivolumab after anti-angiogenic therapy

MSI-H or dMMR Cancers
2L nivolumab in CRC
2L nivolumab plus ipilimumab in CRC
2L pembrolizumab in any MSI-H/dMMR cancer

Cervical Cancer
2L pembrolizumab CPS≧1



Small Cell Lung Cancer
1L with chemo: Atezolizumab
2L after platinum chemo: nivolumab

Non-Small Cell Lung Cancer
Unresectable Stage III- durvalumab after chemoradiation
1L pembrolizumab TPS≧50%
1L non-squamous NSCLC
- pembrolizumab + pemetrexed & platinum
- atezolizumab + bevacizumab, paclitaxel & carboplatin

1L squamous NSCLC
- pembrolizumab + carboplatin & (nab-)paclitaxel in

2L pembrolizumab TPS≧1%
2L atezolizumab or nivolumab

Triple-Negative Breast Cancer
1L atezolizumab + paclitaxel protein-bound PD-L1≧1%

Gastric & GEJ Carcinoma
2l dMMR or MSI-H: gastric and GEJ
2L pembrolizumab CPS≧10: esophageal & GEJ
3L pembrolizumab CPS≧1: gastric

Classical Hodkin Lymphoma
Post-transplant (Auto or Allo) and 2L in
Transplant-ineligible: pembrolizumab

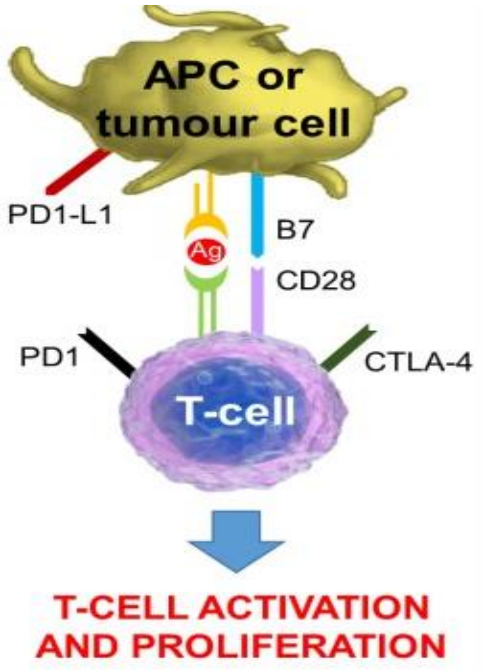
PMBCL
R/R (3L) pembrolizumab

Locally Adv. or Met. Urothelial Cancer
1L pembrolizumab, atezolizumab
1L/2L after platinum salt:
- Pembrolizumab, atezolizumab, avelumab, durvalumab, or nivolumab

Vaddepally et al. *Cancers* 2020

Immunity against cancer

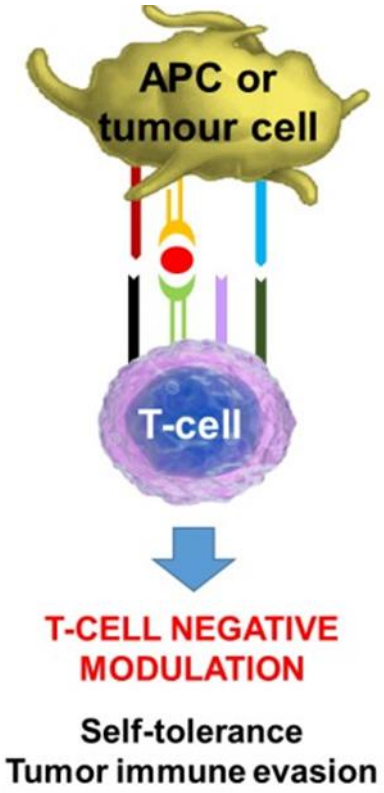
- Successful anti-tumor immune responses require:
  - Generation of tumor-reactive CD8 T cells
  - Recognition of MHC-bound tumor antigen providing the first signal for T-cell activation and full T-cell activation follows the engagement of the **co-stimulatory CD28 receptor on T cells by B7 on the APC**
  - Tumor-specific CD8 T cells subsequently differentiate into effector T-cells, undergo clonal expansion, traffic to the tumor microenvironment and ultimately kill tumor cells via release of cytolytic effector molecules (e.g., granzyme A/B and perforin).
- For long-term immunologic memory (and presumably durable disease control), a subset of effector T cells must differentiate into effector memory T cells



Jenkins et al., BJC 2018

What are Immune checkpoints?

- Immune checkpoints play a role in maintaining immunologic homeostasis
  - Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)
    - inhibits an immune response by attenuating T-cell activation at a proximal step in the immune response → binds B7
    - Lacking it leads to lympho-proliferation
  - Programmed Death-1 (PD-1)
    - inhibit T cells at later stages of the immune response in peripheral tissues
    - PD-L1 is made by tumor cells, and PD-1 is on the corresponding T cells
    - Lacking it leads to autoimmunity, including arthritis and cardiomyopathy
  - Lymphocyte activation gene-3 (LAG-3)
    - LAG-3 acts synergistically with PD-1 to suppress antitumor immunity & autoimmunity
    - LAG-3 selectively binds to stable pMHC II and inhibits the activation of $CD4^+$ T cells

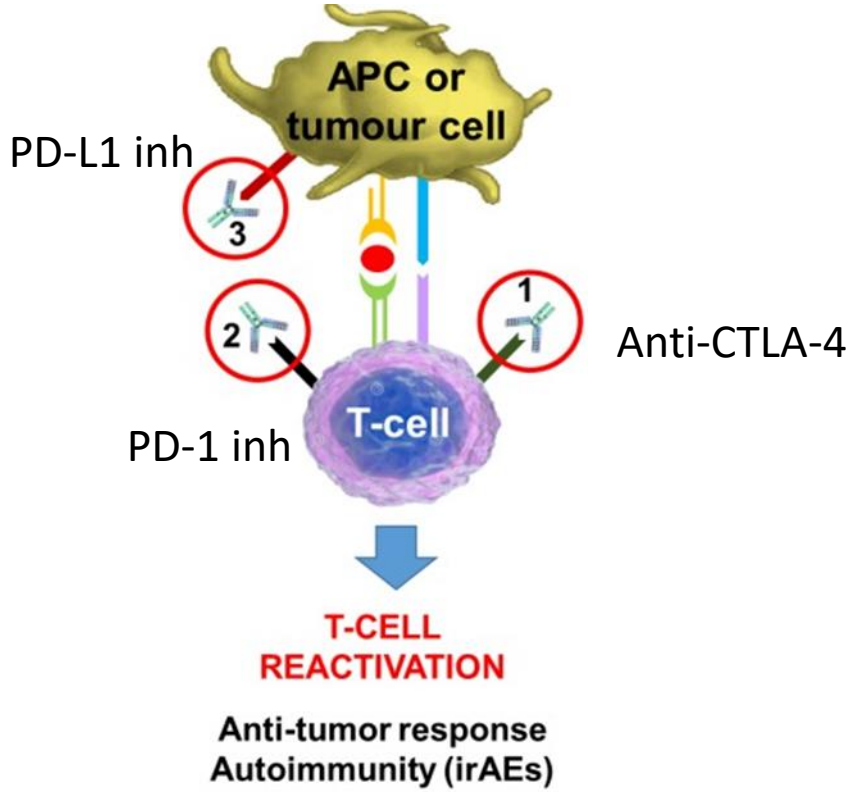


Immune checkpoints and cancer

- Main role in body is to modulate the immune system and avoid self destruction
- Cancer Cells hijack those pathways and use this system to protect self and evade the body defenses
- Immune Checkpoint Inhibitors
  - Monoclonal antibodies targeting immune checkpoints to restore antitumor immunity, thus reversing immune escape or evasion and promoting tumor cell death.

Immune Checkpoint Inhibitors

- Such antibodies include those targeting:
  - **CTLA-4 (cytotoxic T lymphocyte associated protein 4)**
    - Ipilimumab (Yervoy)
  - **PD-1 (programmed cell death protein 1)**
    - Nivolumab (Opdivo)
    - Pembrolizumab (Keytruda)
    - Cemiplimab (Libtayo)
  - **PD-L1 (programmed cell death ligand 1)**
    - Atezolizumab (Tecentriq)
    - Avelumab (Bavencio)
    - Durvalumab (Imfinzi)
  - **LAG-3 (Lymphocyte activation gene-3)**
    - Relatlimab (Opdualag in combination with Nivolumab)
  - **Tissue Factor (TF) inhibitor:**
    - Tisotumab vedotin-tftv (Tivdak)

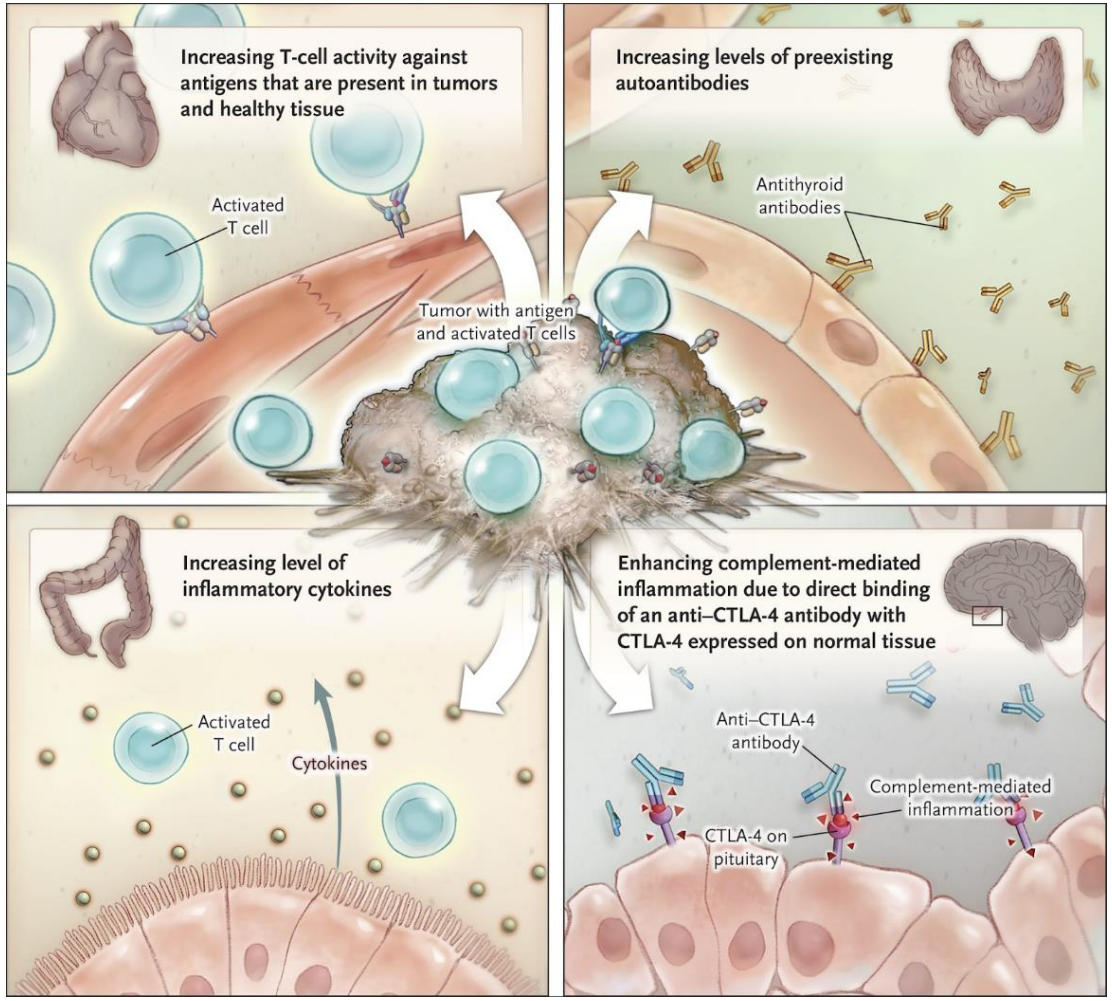


Predictors of response to checkpoint inhibitors

- PD- L1 - Programmed Cell death ligand 1
  - Expression on tumor cells leads to immune tolerance and ability to evade innate immune response
  - Different companion diagnostic assays for each drug and different clinical cut offs for PDL-1+ per assay
  - 2 forms of testing :
    - The proportion score (TPS) = (number of PD-L1 positive tumor cells/total number of tumor cells) X100
    - Combined positive score (CPS) = (number of all PD-L1 positive cells[tumor cells, macrophages, and lymphocytes]/ total number of tumor cells) X100.
  - Not a perfect marker for predicting tumor responses to ICIs (Some with negative PD-L1 may benefit from PD-1/PD-L1 inhibitors).
    - This maybe in part due to the heterogeneous pattern of PD-L1 expression in tumors
- TMB - Tumor mutational burden
  - The presence of high TMB [>10 somatic mutations per megabase (Mb) of coding DNA] is associated with high neoantigen load that trigger activation of T cells and anti-tumor immune responses
  - High TMB (TMB ≥ 20 mutations/mb): an independent predictor for favorable clinical outcome to ICIs irrespective of PD-L1 expression level
  - TMB in tissue samples can be measured using:
    - Whole exome sequencing (WES): allows detection of somatic mutations in the entire exome, high cost, needs larger amount of DNA and longer time for data analysis and interpretation
    - Targeted next-generation sequencing (NGS) of smaller gene panel that is comparable to WES AND is less expensive and complex.
  - TMB analysis in liquid biopsy using targeted NGS panels is difficult because circulating tumor DNA is only a small fraction of the cfDNA
- MSI- Microsatellite instability/Mismatch Repair deficiency - FDA's approval in May 2017
  - Microsatellite instability (MSI) results from the defective functions of mismatch repair proteins, including MLH1, MSH2, MSH3, MSH6, PMS1, and PMS2.

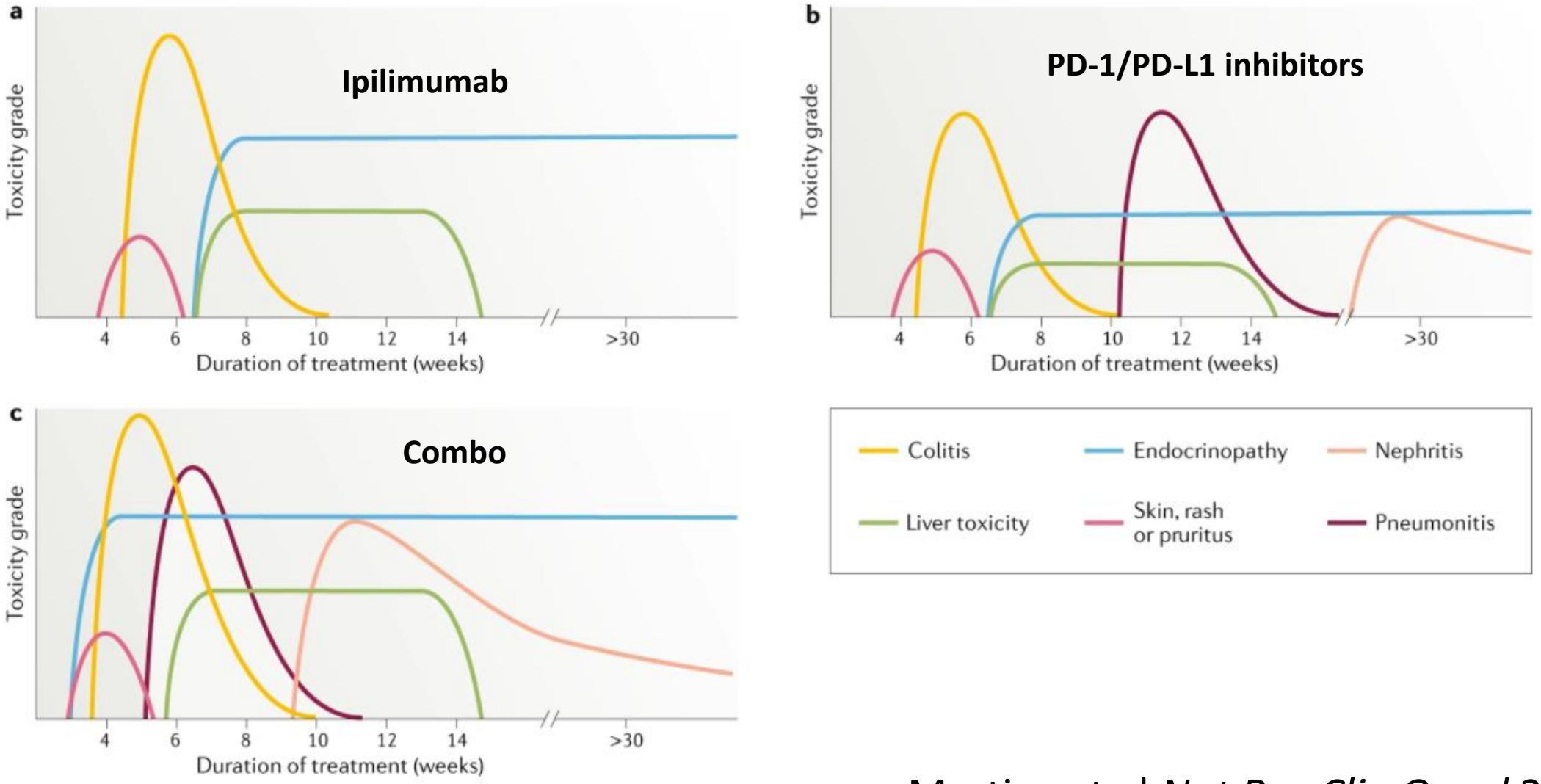
Immune-Related Adverse Events

Why Do Immune-Related Adverse Events Occur?

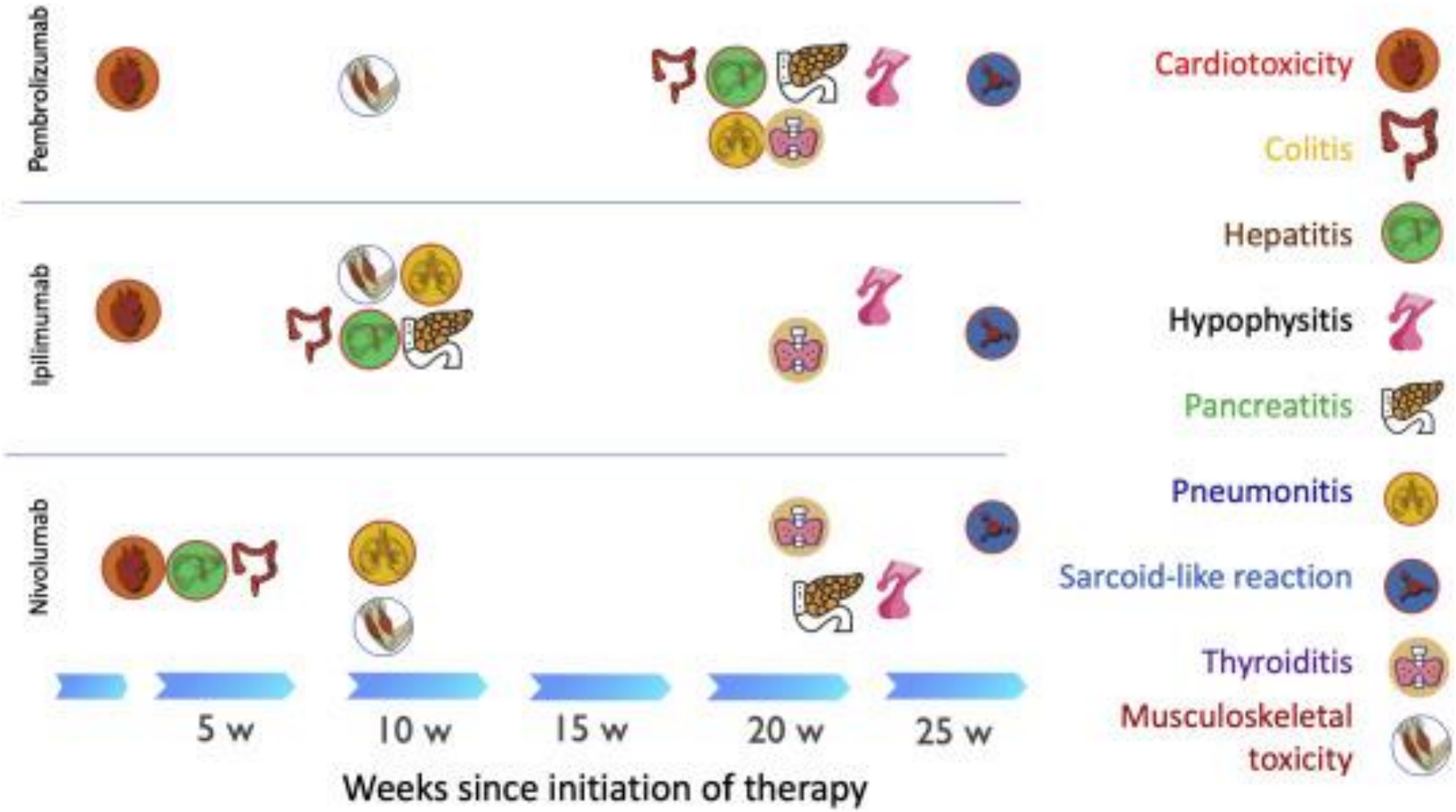


Postow et al. NEJM 2018

When Do Immune-Related Adverse Events Occur?

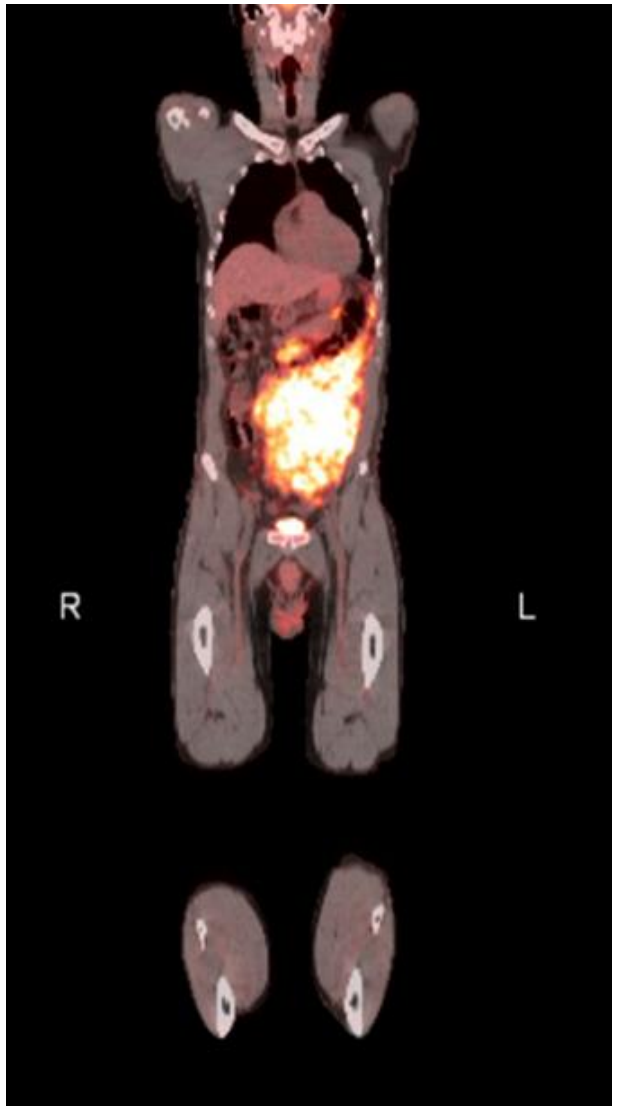


Martins et al *Nat Rev Clin Oncol* 2019


Pembrolizumab
Ipilimumab
Nivolumab
5 w
10 w
15 w
20 w
25 w
Weeks since initiation of therapy
Cardiotoxicity
Colitis
Hepatitis
Hypophysitis
Pancreatitis
Pneumonitis
Sarcoid-like reaction
Thyroiditis
Musculoskeletal toxicity

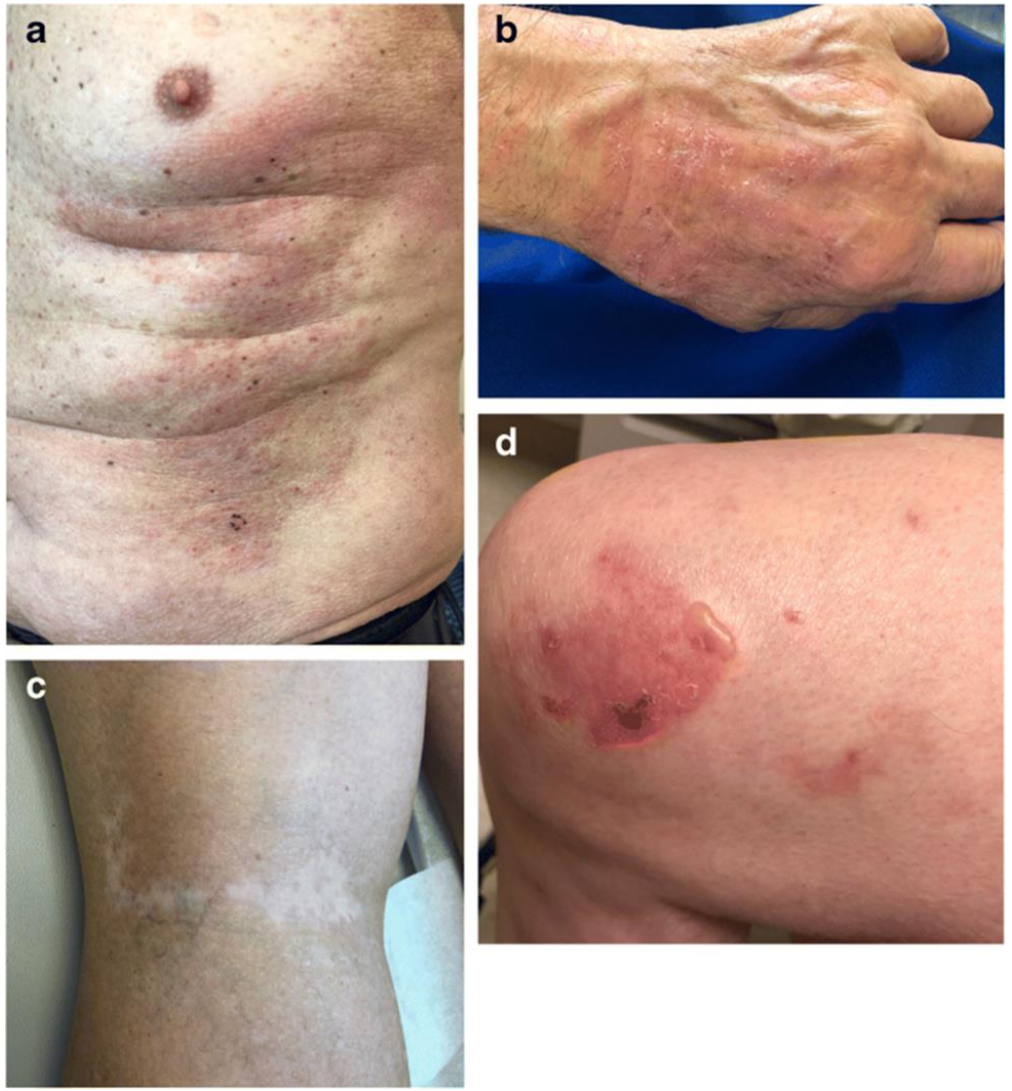
Case: George is a 55 year old with metastatic melanoma

- Started on combination immunotherapy using ipilimumab and nivolumab every 3 weeks
- 1 week prior to his next dose he presents to clinic c/o a rash and itching



Dermatologic Reactions to Immune Checkpoint Inhibitors

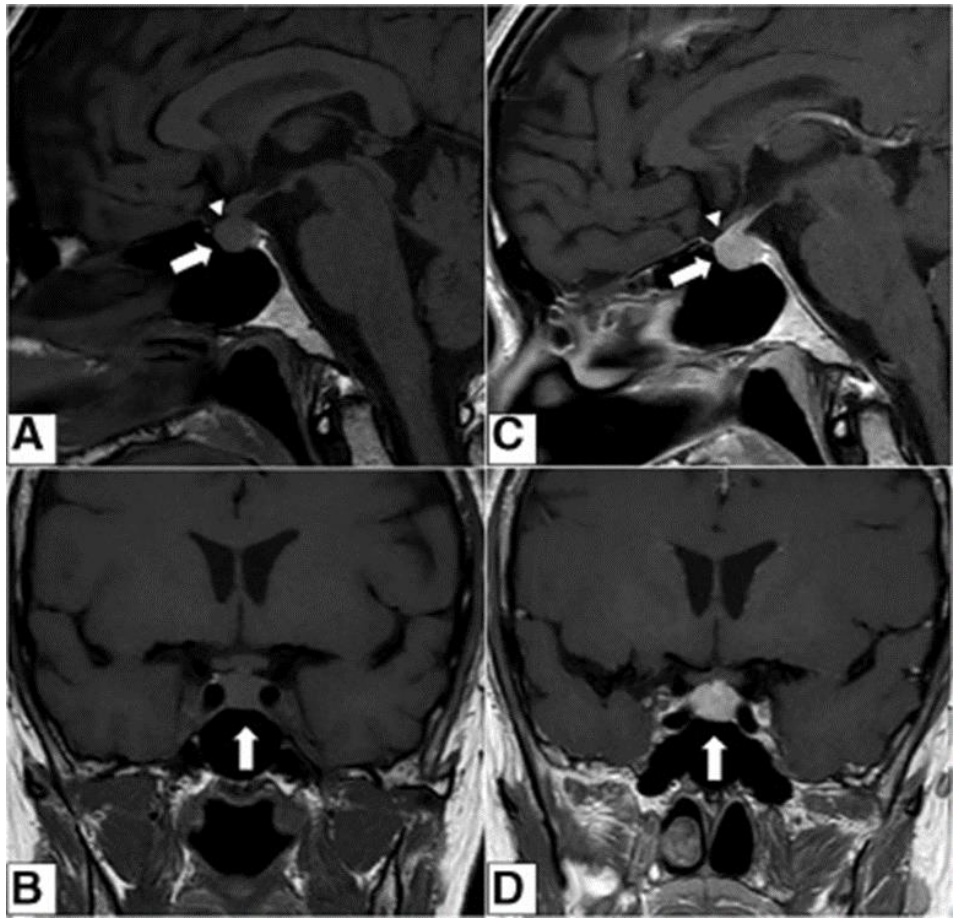
- Most prevalent irAE
- Mostly self-limiting maculopapular rashes and pruritus.
- Less common manifestations: lichenoid reactions, vitiligo, bullous pemphigoid, alopecia, and mucosal lesions
- Rarer side effects: scleroderma, fascitis, and dermatomyositis
- Management:
  - Early recognition is critical in mitigating the severity of the lesions
  - Topical corticosteroids
  - Severe reactions: systemic treatment or discontinuation of immunotherapy.



Ebia et al, Current Dermatology Reports 2018

Case : George returns to clinic 1 week after his second dose

- Severe central throbbing headache
- He denied any fever, chills, vision changes, diplopia, weakness, numbness of the extremities, hearing loss, tinnitus, or gait changes
- Unremarkable exam
- Work up:
  - CT head negative
  - MRI brain



Solinas et al. *Seminars in oncology 2018*

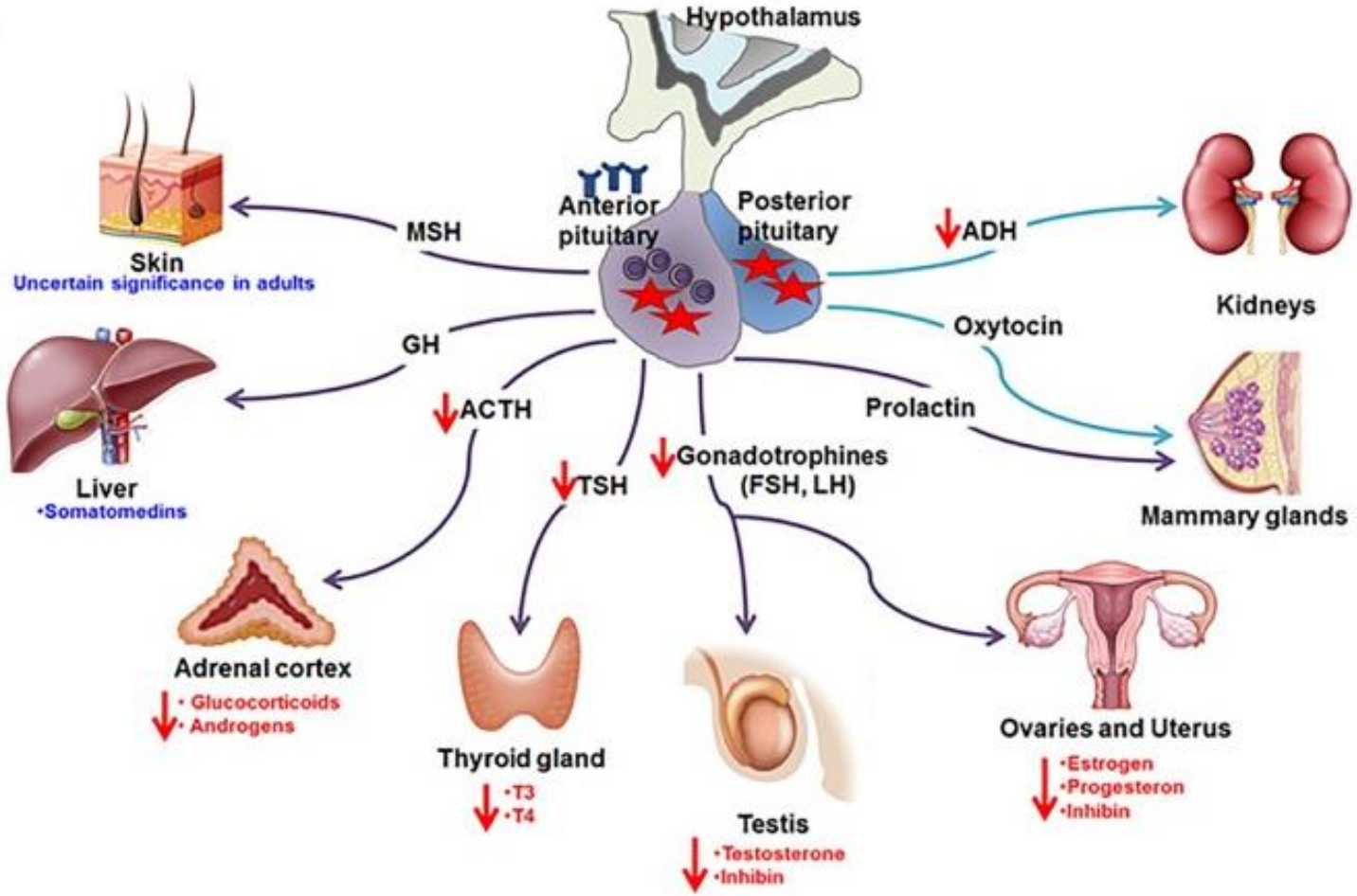
What do you suspect ? and what's the next step?

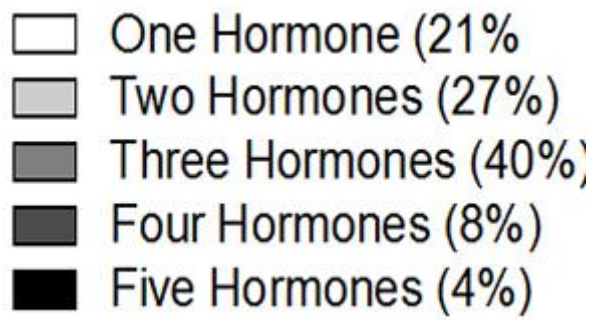
- Check – TSH, Free T4, morning cortisol, ACTH, FSH, and LH, sex hormones

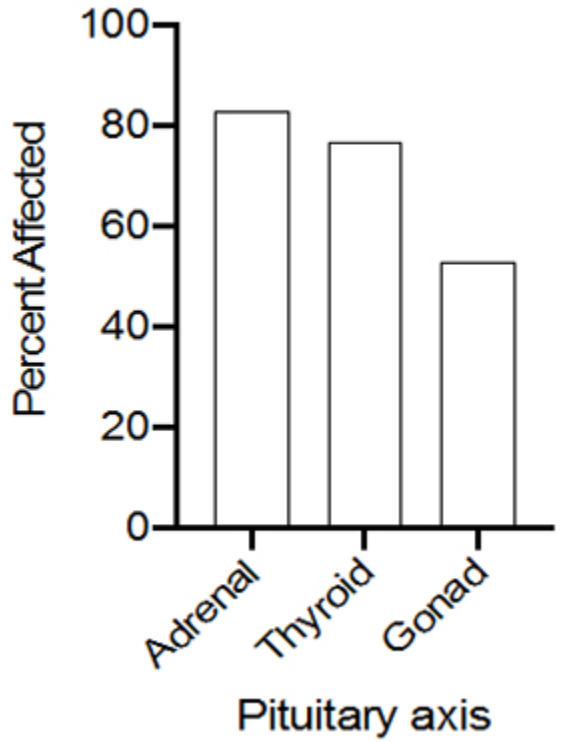
Hypophysitis (inflammation of the pituitary gland)

- Rare condition outside the context of ICI.
  - Occurs in up to 18% of patients on anti-CTLA-4 based therapy
  - Rare with single agent PD-1/PD-L1 inhibitors
  - More frequently in men and older patients
- Type II hypersensitivity reaction
  - Pituitary glands express CTLA-4, which were targets for CTLA-4 inhibitors
  - Result in complement deposition
- In contrast to thyroid disorders, most patients present w clinical symptoms
  - Most often have headache and fatigue
  - Other symptoms: confusion, weakness, hallucinations, memory loss, labile mood, anorexia, & hyponatremia
  - Visual disturbances (rare)
  - Diabetes insipidus (rare)

Hypophysitis







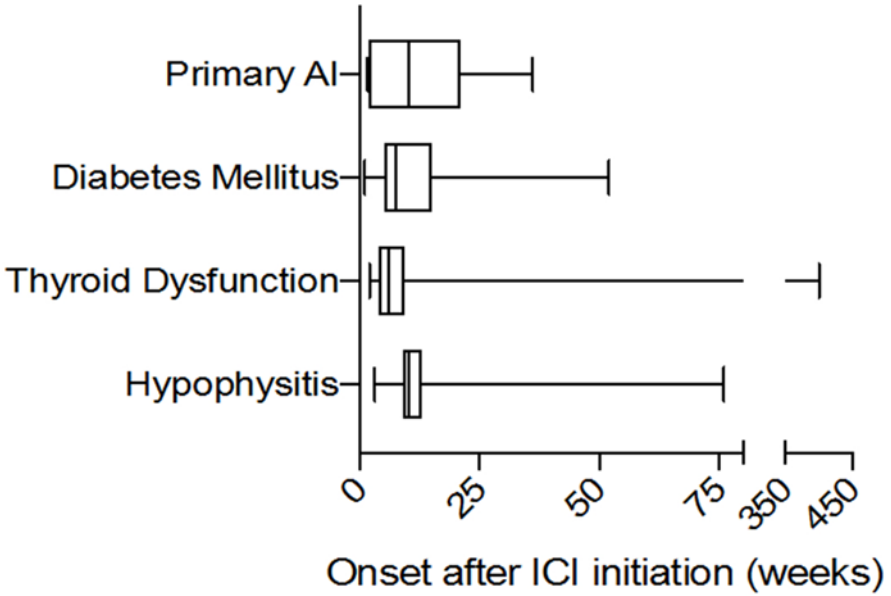
Martins et al, *Nature Reviews Clinical Oncology* 2019

Hypophysitis (inflammation of the pituitary gland)

- Treatment
  - Hold Immunotherapy
  - Start replacement therapy
  - Oral prednisone (1-2 mg/kg/day) should be started for severe persistent headache or visual symptoms
  - In most cases, the Immunotherapy can be continued along with long-term hormone replacement therapy.

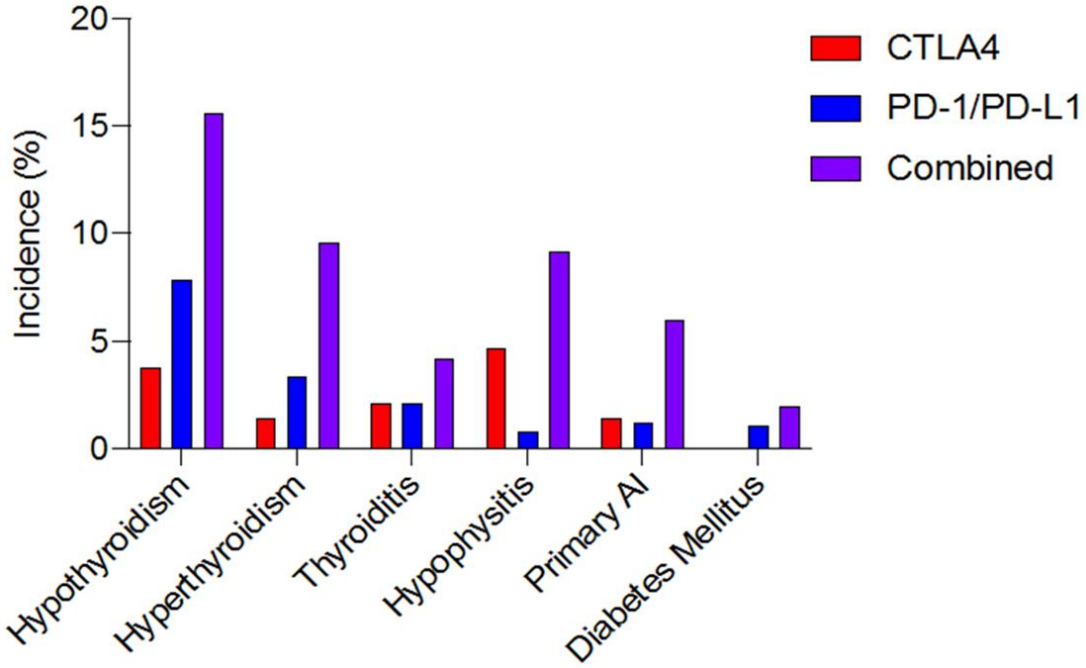
Endocrinopathies

- Asymptomatic or non-specific symptoms → timely diagnosis requires a high index of suspicion
  - Symptom can overlap with underlying disease
  - Rarely fatal (ex DKA) but can have dramatic effects on a patient's QoL
- Incidence:
  - Up to 40% of treated patients
  - Many endocrine disorders do not resolve, require lifelong replacement
- Median time to onset: Variable but typically within 6months (early for thyroid, late for others)



Organs affected

- Thyroid: Hypothyroid but may be preceded by transient thyroiditis-induced thyrotoxicosis
- Pituitary (panhypopituitarism or hypophysitis)
- Adrenal (primary adrenal insufficiency)
- Beta cells of the pancreatic islets (insulin-deficient diabetes, may present as DKA)
  - Rare <1% but may also present as exacerbation of underlying type 2 diabetes
  - Mostly with PD-1/PD-L1 inhibitors
- Rare: Primary hypoparathyroidism, diabetes insipidus, syndrome of inappropriate anti-diuretic hormone, and Cushing's disease (ACTH-dependent cortisol excess)



Nat Rev Endocrinol. 2021 Jul; 17(7): 389–399.

Diagnosis

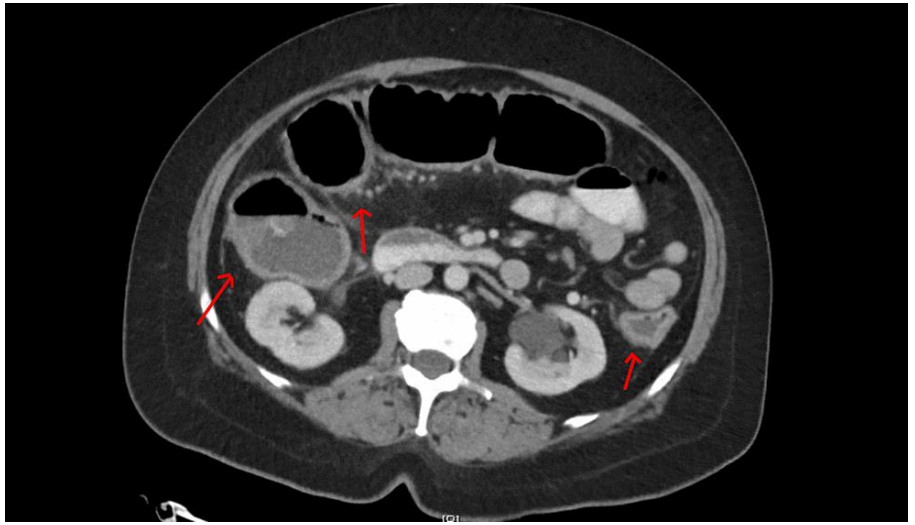
- Thyroid: TSH and FT4 every 8 weeks or sooner
- Pituitary : Monitoring not standard – use if Ipi
  - A low morning cortisol (< 5 mcg/dL) and low ACTH are indicative of secondary adrenal insufficiency
  - Low TSH and low free T4 indicative of secondary hypothyroidism
  - Low sex hormones, FSH, and LH indicative of secondary hypogonadism
  - Patients with headaches should have brain imaging, preferably brain MRI with pituitary windows.
    - May have enlarged pituitary (may be called radiographically as a “pituitary adenoma” or an empty sella).
    - Normal brain imaging does not rule out hypopituitarism/hypophysitis
- Adrenal:
  - Morning cortisol and ACTH levels
  - If mineralocorticoid-producing cells are affected, metabolic acidosis and hyperkalemia
- DM:
  - Random glucose monitoring at every cycle of ICI is the primary monitoring strategy.

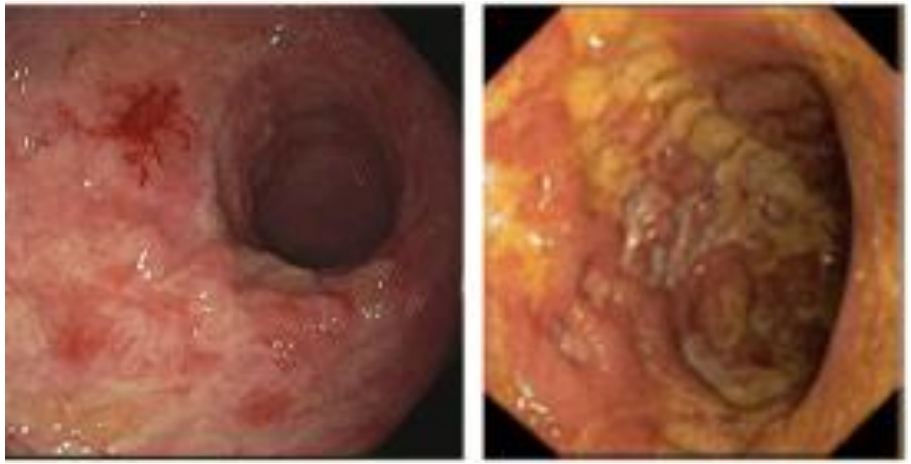
Management

- High-dose steroids are not indicated, as no evidence suggests that steroids will assist with gland function
- Patients may continue to receive their immunotherapy
  - May delay if severe symptoms
- Thyroid
  - HypoT4 – thyroid replacement (low dose in elderly)
  - HyperT4 - generally supportive with beta blockers for tachycardia; Tx Graves
- Pituitary
  - Replacement of affected hormone deficiencies
  - High doses of steroids with rapid taper over 1-2weeks if severe compressive symptoms from the hypophysitis (e.g. severe headaches or vision changes)
- Adrenal
  - Don’t delay treatment while awaiting confirmatory testing or subtype classification.
  - Treatment consists of glucocorticoid and mineralocorticoid replacement
- Diabetes Mellitus
  - Patients almost certainly will require lifelong insulin replacement therapy

Case: George continues treatment with ipilimumab and nivolumab

- c/o diarrhea and hematochezia.
- Reports NSAID use
- He was hospitalized and started on intravenous fluids.
- Stool studies were negative for *Clostridium difficile* toxin, *Salmonella, Shigella,* Shiga toxins 1 and 2*, Campylobacter, Escherichia coli O157:H7*, ova, and parasites.
- Evaluation: CT scans, endoscopic evaluation





GI Toxicity

- Among the most common AEs leading to discontinuation of checkpoint inhibitors.

	Diarrhea		Colitis		Hepatic Transaminase Elevation	
Characteristics	**Any Grade, %**	**Grade 3/4, %**	**Any Grade, %**	**Grade 3/4, %**	**Any Grade, %**	**Grade 3/4, %**
Timing of onset, weeks	6–8				8–12	
Anti–CTLA-4 mono-therapy	23–33	3–6	8–12	7–9	1–7	0–2
Anti–PD-1/PD-L1 mono-therapy	11–19	1–3	1–4	< 1–3	1–6	1–3
Combination anti–CTLA-4 and anti–PD-1/ PD-L1	44–45	9–11	12–26	8–17	13–30	6–19

Work up

- Any Grade
  - Fecal lactoferrin/calprotectin surrogate measure for intestinal inflammation.
  - Stool cultures: bacterial pathogens(*Salmonella*, *Shigella*, *Campylobacter*, *Yersinia*, *Vibrio*, and *Aeromomas*), *Clostridium difficile* infection, rotavirus, norovirus, *Escherichia coli* O157:H7/shiga toxin
  - Testing for ova and parasites, *Cryptosporidium*, and *Giardia (* risk factors or recent travel to endemic areas).
  - Multiplex molecular panel
- Grade 2 is an increase of 4 to 6 stools a day.
  - Endoscopy to establish dx & r/o CMV infection and ischemic colitis
    - Any bloody diarrhea or Grade 2 or above
  - Abdominal CT scan if G2 with pain or Gr 3-4 diarrhea - can rule out complications, including bowel perforation, abscess, and toxic megacolon

ASCO *Educational Book* 38 (2018) 13-19; NCCN 2022.

Management

- Hold immunotherapy unless mild Gr 1
  - Discontinue for G4, may restart PD-L1- after stopping CTLA-4 for G3
- Close monitoring, anti-diarrheals, dietary modifications
- Grade 2 or higher
  - Admit for Grade 3-4
  - Supportive care
  - GI consultation
  - Prednisone 1-2mg/kg/day or equivalent
  - Consider adding – Infliximab or Vedolizumab

Steroid-refractory:
Vedolizumab or Infliximab

- Selective immunosuppressive therapy (SIT)
- IFX is a chimeric antitumor necrosis factor-alpha (TNFα) monoclonal antibody that acts by **dampening TNFα's role in the immune response.**
- VDZ is a gut-selective humanized anti-$\alpha_4\beta_7$ monoclonal antibody that binds to the gut leukocyte adhesion molecule $\alpha_4\beta_7$-integrin and prevents lymphocyte infiltration in the gut
- Both SITs are approved for treating inflammatory bowel disease (IBD)

Hepatotoxicity

- Variable presentation
- Mostly mild asymptomatic transaminitis (elevation in ALT/AST – less likely hyperbilirubinemia) to symptomatic disease with fever, fatigue, or jaundice and rarely fulminant hepatitis
- Onset: 8 -12 weeks after initiation of treatment but can start as early as 8 days
- Up to 6-7% of patients during monotherapy ad up to 30% for combo
- Rates of grade 3 or 4 toxicity are lower unless given combination therapy

Diagnosis

- Patients being treated with immunotherapy require monitoring of liver tests before therapy.
- Diagnostic evaluation should rule out other alternative etiologies
  - R/o viral etiology (hepatitis, EBV, CMV, HSV, VAZ, HIV), disease related hepatic dysfunction (ceruloplasmin, alpha1-AT, mitochondrial AB M2, smooth ms AB) or drug related issues
  - Imaging with abdominal CT or ultrasound
    - Imaging to rule out presence of metastatic disease, and vascular obstruction
    - May be normal in mild cases but in more severe cases, hepatomegaly, peri-portal edema, attenuated liver parenchyma, and peri-portal lymphadenopathy may be present.
  - Biopsy: Histologic changes associated with ipilimumab-induced hepatitis are non-specific , include a pattern of hepatocellular injury with panlobular hepatitis, with less bile duct injury
    - Similar findings to patients with acute viral and autoimmune hepatitis.

Management

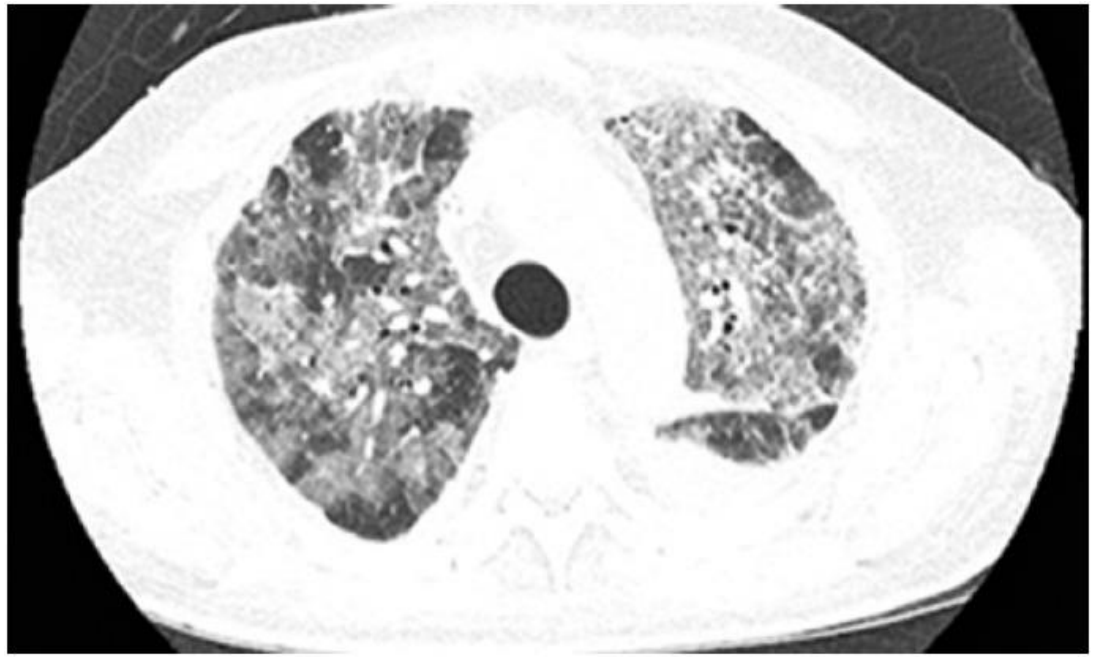
- Limit or discontinue any hepatotoxic medications
  - ex acetaminophen, dietary supplements and alcohol use
- Hold therapy and consider starting steroids for any AST/ALT elevation 3-5X UNL – continue until <=Gr 1 then taper over a month
- If no improvement at 3 days, severe elevation >5X or concomitant elevated total bilirubin
  - Inpatient care
  - HD steroids – add Mycophenolate and possibly anti-thymocyte globulin (ATG)
  - Consider biopsy
  - No role for Infliximab because of risk of hepatotoxicity

Pancreatic enzyme elevation and pancreatitis

- Incidence rate
  - Up 15% will have grade 3/4 enzyme elevation
  - Acute pancreatitis is less common
- R/o other causes of elevations in pancreatic enzymes:
  - Other tissue sources
  - pancreatic duct obstruction from metastatic disease
  - renal failure (which can delay clearance of these enzymes).
- Patients with pancreatic enzyme elevations without abdominal pain or evidence of acute pancreatitis on abdominal imaging (contrast enhanced abdominal CT scan or MRI) can be monitored clinically without the need for immunosuppressive therapy.
- Immunosuppression with corticosteroids should be reserved for patients with pancreatitis because of checkpoint inhibitors.

Case: George continues treatment but prior to his 4th cycle of Ipi/Nivo he reports

- Fatigue and dyspnea
- Physical examination:
  - O2 sat 83% RA
  - CBC revealed leukocytosis
  - CT chest revealed bilateral infiltrates and pleural effusion without signs of pulmonary thromboembolism.
  - He was started on antibiotic therapy with ceftriaxone and azithromycin with no improvement

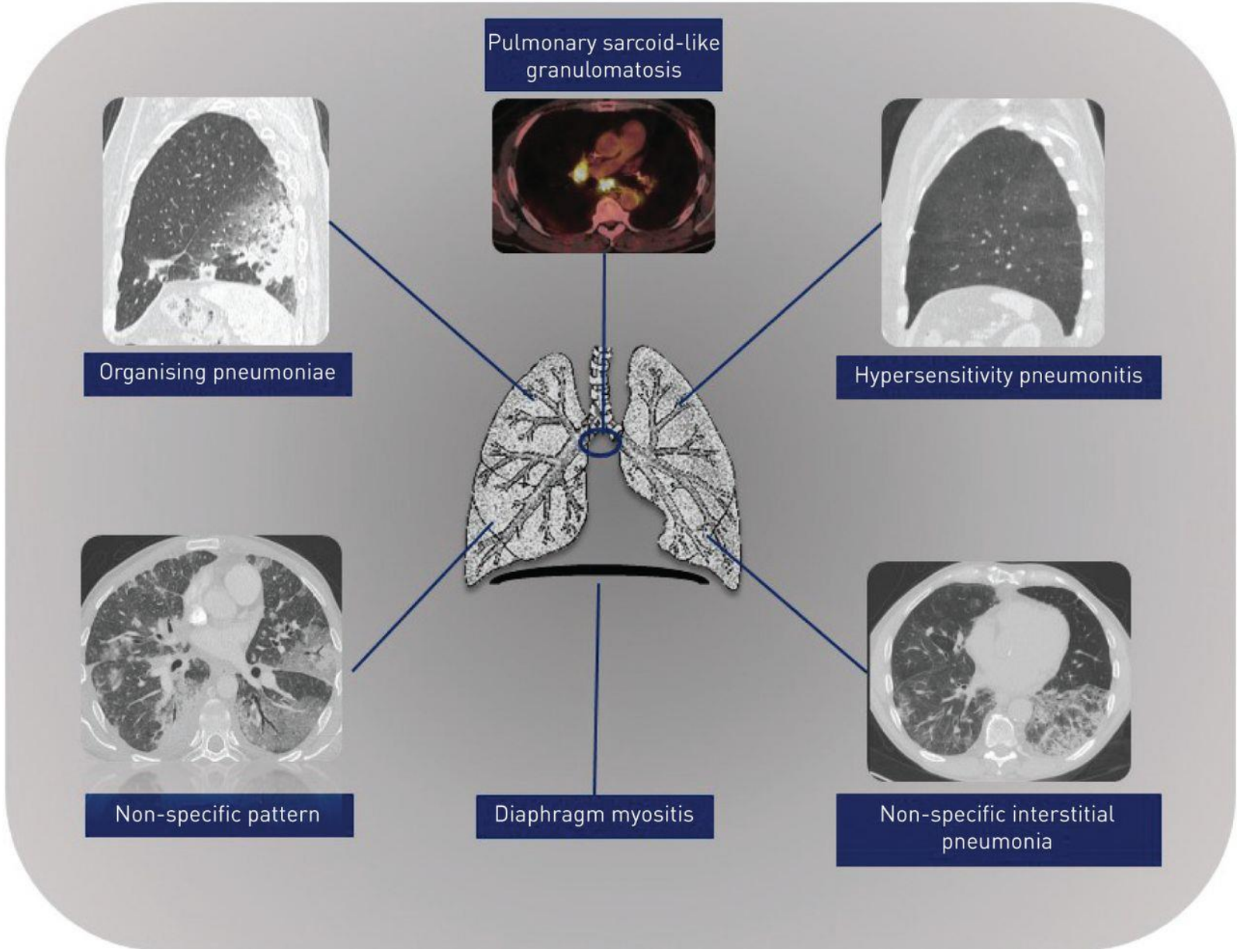


Delaunay et al, European respiratory review 2019

Pulmonary toxicity

- Incidence:
  - All grades 2.7% - grade 3-4 0.8%
  - Higher IR with combination Nivo/Ipi
  - No biomarker predicting the occurrence of lung toxicity has been identified
- Median time to onset was 2.3 months
- Symptoms: fatigue, cough, dyspnea, hypoxemia
- Differential diagnosis:
  - Infection, allergy, cardiac causes (myocarditis)
  - Other drug toxicity

Patterns



Nishino et al. Clin Cancer Res 2016

Workup and management

- Work up
  - Infectious work up
  - Chest x-ray and/or CT scan
  - PFT (pulmonary function testing)/ABGs
  - Pulmonary consultation and Bronchoscopy (if diagnosis in doubt)
- Management
  - Hold Therapy
  - Broad spectrum antibiotics
  - High dose steroids – plan to taper over 6 weeks
    - Add antibiotic/antifungal prophylaxis during high-dose steroid
  - May add Infliximab, IVIG and Mycophenolate in severe cases
  - May re-challenge in after resolution of grade 2 not 3/4

Case: George completed induction and started on maintenance Nivolumab – and completed 3 cycles

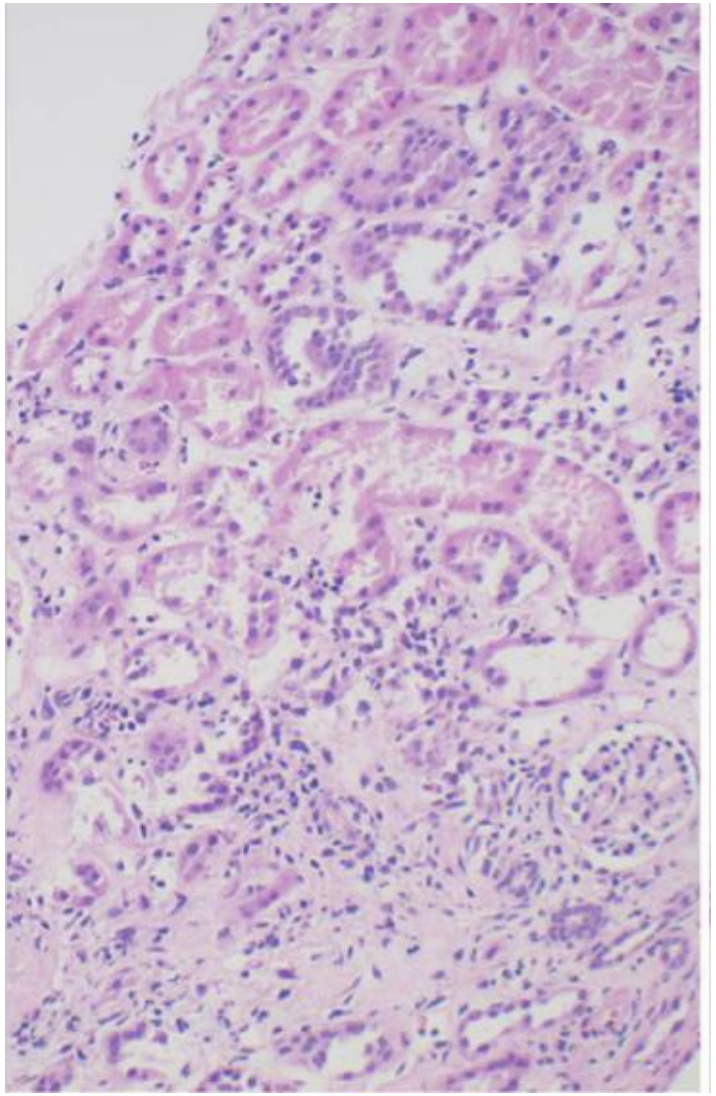
- Sx: Fatigue and decreased urine output
- Labs:
  - Baseline S. Creatinine: 0.60 mg/dL (GFR>89)
  - Current cycle: 2 mg/dL (GFR 35).

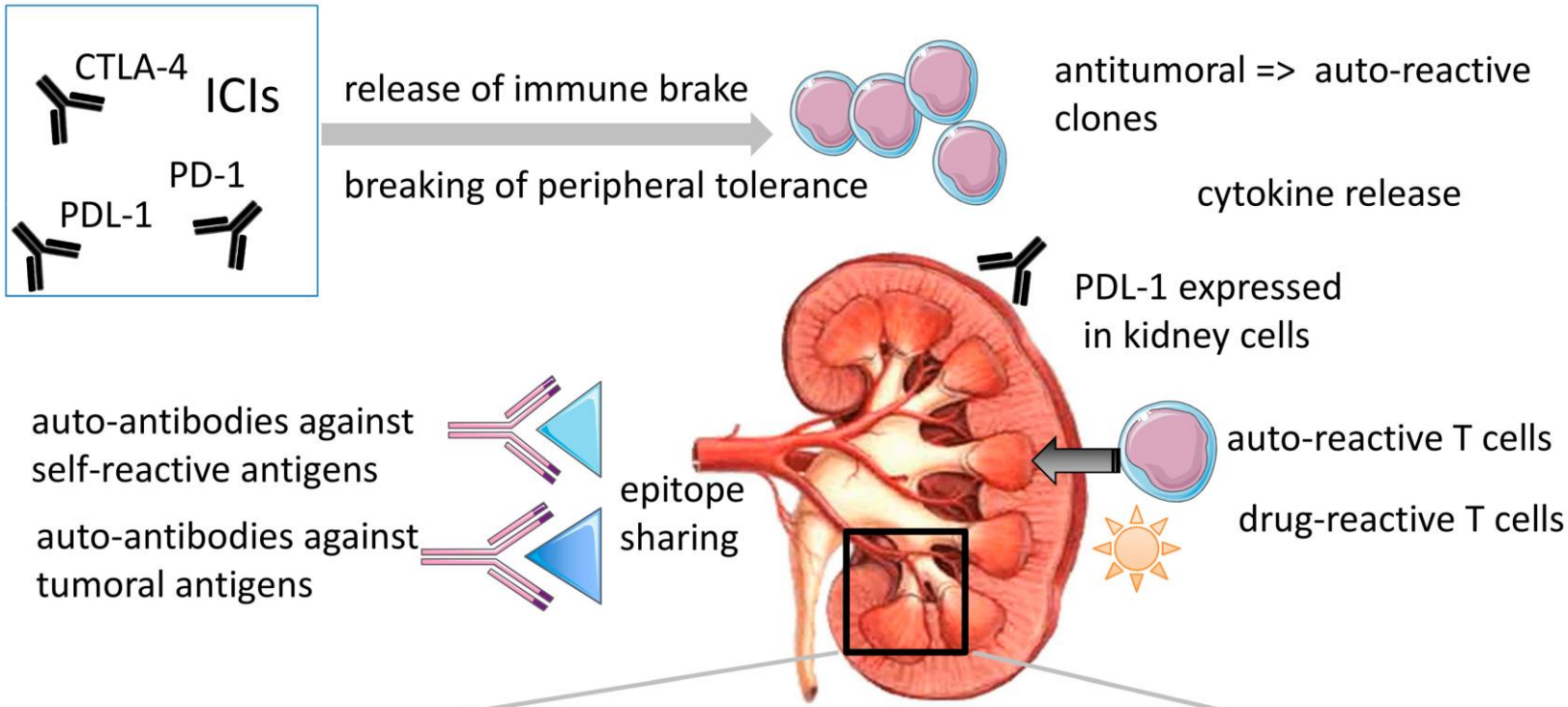
Work up of AKI

- History and exam:
  - R/o dehydration
  - Drug effects: Chemotherapies such as platinums, anti-VEGF, Iodine contrast, bisphosphonates, exposure to PPI
  - Evaluate for other irAEs
- Renal evaluation: urine culture, protein, hematuria
  - Na 137 , K 3.6 , HCO3 23, and urea nitrogen 38 mg/dL.
  - Urinalysis: 69 RBCs/HPF, 14 WBCs/HPF, 0-2 hyaline casts, and no urine eosinophils.
- Kidney imaging
  - showed improvement in disease burden and no evidence of obstruction

- Kidney biopsy
  - showed diffuse lymphocytic infiltrates, mild interstitial fibrosis and tubular atrophy, thought to represent medication-related injury

- Diagnosis:
  - **Acute interstitial nephritis (AIN)- immunotherapy-induced**





Ipilimumab (alone or in combination)	1021 (4.5%)
Ipilimumab (combined with nivolumab)	686 (5.9%)
tremelimumab	22 (5.4%)
pembrolizumab	1397 (4.7%)
nivolumab	2350 (4.5%)
cemiplimab	50 (7.6%)
atezolizumab	431 (5.3%)
avelumab	82 (6.3%)
durvalumab	116 (2.7%)
relatlimab	5 (7.7%)
Tiragolumab	0 (0%)
Enoblituzumab	0 (0%)

Belliere et al, *Diagnostics 2021*

Management of ICI related AKI - ATIN

- Stop ICI
- Stop PPI and avoid any nephron-toxins
- Corticosteroids (after biopsy if possible) + PCP Prophylaxis
  - Renal response to first-line treatment is very important
  - ORR 85% (CR 40%) - no response in 15%
  - Poor Prognosis
    - Failure to achieve kidney recovery was independently associated with higher mortality.
    - Concomitant extrarenal immune-related adverse events
- Renal replacement therapy (RRT) was required in 25%.
  - ORR 73 % (CR 31%) - 19% remained dialysis-dependent
- Immune suppressive therapies: Anti-TNF, Rituximab, Mycophenolic acid
- Rechallenge:
  - No data are available on class switching.
  - A key point for the rechallenge is the identification of any drug associated with the first AKI episode.
    - Prognosis is better if the co-medication has been interrupted.

Fatigue

- Very Common
- Non-specific
- Assess for depression, poor sleep, poor nutrition and lack physical activity
- Work up to r/o hormone deficiencies such as thyroid, cortisol and sex hormones
- Evaluate pulmonary and cardiac toxicity
- Consider a short course of low dose steroids (2weeks)
- If severe and affecting ADLs – may stop

Cardiac

- Incidence of myocarditis: 0.09 % - higher with combinations 0.06%
- 50% of ICI-associated myocarditis cases were fatal.
- Others:
  - Myocarditis, conduction disease with heart block and ventricular arrhythmias are the most common reported toxicities
  - Less: acute myocardial infarction, non-inflammatory LVSD, Takotsubo syndrome and pericarditis
- Treatment requires immunosuppression and appropriate cardiac therapies.
- Baseline cardiac assessment is advised for all patients scheduled to receive ICIs, and surveillance strategies may be considered for individuals at higher risk based on their ICI treatment strategy and past medical history (cardiovascular and autoimmune).

Lyon et al, *The Lancet* 2018

Inflammatory arthritis

- Joint pain, joint swelling, morning stiffness
- Consider labs – ANA, anti-CCP, CRP, ESR, RF
- Consider imaging
- Management depends on severity of symptoms
  - Mild – continue ICI, NSAIDs, IA joint injections, Prednisone 10-20mg X2-4weeks
  - Moderate – Hold ICI, Prednisone 0.5mg/kg/day
  - Severe i.e. affecting ADLs or joint erosions – Hold ICI, Prednsione 1mg/kg/day
    - If fail to improve by week 1 or can't taper by week 2 then Rheumatology consult – may add MTX, Infliximab, Plaquanil etc..

Myalgias or Myositis (muscle weakness)

- R/o PMR/GCA
- Monitor serial aldolase/CK
- Hold ICI
- Consider muscle biopsy
- Prednisone 1-2mg/kg/day
- Rheumatology consult
- Consider IVIG, Plasmapheresis, Infliximab, Rituximab

Neurological Conditions

- Myasthenia gravis – Discontinue ICI
- Guillain-Barre Syndrome- Discontinue ICI, Inpatient, start IVIG
- Peripheral neuropathy – Evaluate for other causes, hold ICI, add steroids
- Aseptic meningitis
- Encephalitis
- Transverse myelitis
- Vision changes: uveitis, episcleritis, scleritis

Hematological Complications

- Most common are thrombocytopenia, hemolytic and aplastic anemias
- Less common: agranulocytosis and neutropenia
- ICIs-induced thrombocytopenia
  - 25–29% of hematological irAEs
  - Mechanism is unclear
  - R/o drug-induced thrombocytopenia (heparin/HITT, chemotherapy, etc.), infections, hematological malignancies (myelodysplastic syndrome, etc.)
  - Steroids are generally effective in severe thrombocytopenia, IVIG

Omar et al., Front Immunol 2020

Challenging Situations

- Autoimmunity
  - Treatment with either anti-PD-1 or ipilimumab is feasible particularly in view of progressive, metastatic cancer
  - Avoid combinations and monitor closely
  - 30% experienced an autoimmune flare in 1 study

- Transplant
  - Immune checkpoint inhibitors in this setting are considered exceedingly high risk to produce catastrophic post-transplant complications by breaking immune tolerance.
    - Ipilimumab appears to have superior safety in this setting

Johnson et al, Cancer 2017

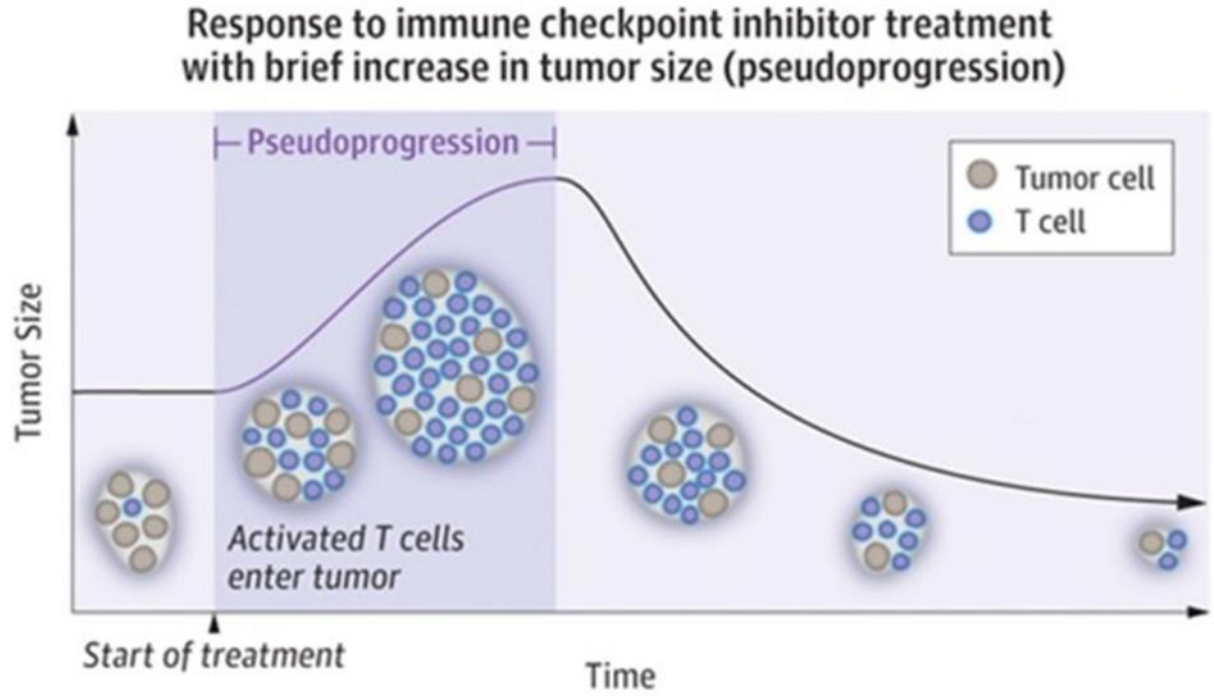
Challenging cases

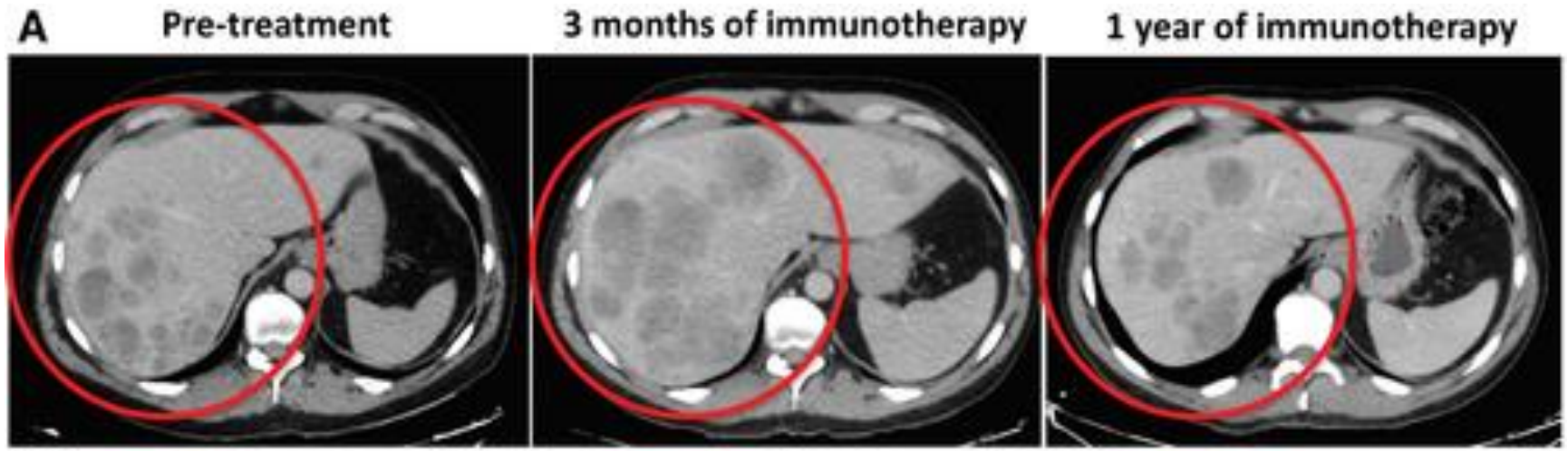
- Pregnancy
  - PD-1/PD-L1 interactions appear to play a key role in maintaining fetal tolerance
    - Placenta is often used as a positive control for PD-L1 expression given its strong and ubiquitous expression
  - In animal studies, anti-PD-1/PD-L1 clearly increased the risks of spontaneous abortions.
  - Anti-PD-1 agents are categorized as pregnancy category D by the Food and Drug Administration, whereas ipilimumab is pregnancy category C (due to the less clear role of the CTLA-4 axis in fetal immune tolerance).

Johnson et al, Cancer 2017

Pseudo-progression: “immune unconfirmed progressive disease” (iUPD)

- Incidence variable
  - Melanoma and NSCLC have produced the most documented cases of pseudo-progression : 10-25% and 6-17%
- It may happen at any time during and after the start of ICIs treatment, but especially at around 12 weeks
- Biopsy of lesions showed immune cell infiltration, necrosis and edema
- Potential serological markers : ctDNA, IL-8 to help differentiate
- **Caution should be taken in abandoning therapy early**


Response to immune checkpoint inhibitor treatment
with brief increase in tumor size (pseudoprogression)
Pseudoprogression
Tumor cell
T cell
Tumor Size
Activated T cells
enter tumor
Start of treatment
Time


A
Pre-treatment
3 months of immunotherapy
1 year of immunotherapy

Impact of corticosteroids on the efficacy of immunotherapy

- No formal prospective studies testing immunosuppressive
- Retrospective studies:
  - Outcomes for patients whose irAEs were treated with immunosuppression were not worse compared to who did not receive immunosuppressive agents
  - Possible worse outcomes if:
    - at baseline steroid intake is > 10mg Prednisone
    - or use of steroids in the **adjuvant setting**
- Attempt to wean patients to replacement doses of corticosteroids (≤10 mg of prednisone daily or equivalent) prior to starting immune checkpoint inhibitors whenever possible

Aldea et al, *European journal of cancer 2020*

Effect on the immune system

- Immune Checkpoint inhibitors can help the body have better immune reactions against cancer cells
- Sometimes they change the way the immune system works
- May be at risk for having a weaker immune system and getting infections

SARS-COV2, COVID-19

- Results of multiple registries including TERAVOLT, the CCC19 & Memorial Sloan Kettering Cancer Center, demonstrated that patients treated with ICIs alone, without chemotherapy, had outcomes equivalent or better to those receiving other cancer treatments.
- Could the combination of vaccine and ICI boost the immunological stimulation with potential reciprocal benefits?
  - ICI therapy results in a constant and variable increase of all COVID-19 vaccination side effects, which is cause for alarm
  - Tumor hyper-progression (THP) or tumor flare, can cause a potentially fatal locoregional progression of the disease

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Thank you

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