

Immune (check point)
Related Adverse Events 2021

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Outline

- Mechanism of check point inhibitors
- Immune Related Adverse Events (irAEs)
 - Events we think about
 - Events that are common and we don't think about them
 - Rare Events
 - Delayed Immune Related Events (DIRE)
- Situations that may increase toxicity

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Mechanism

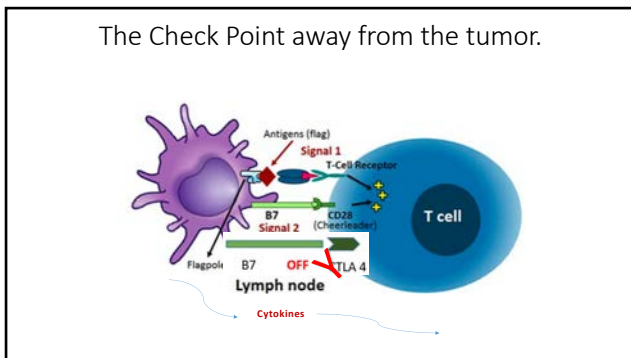
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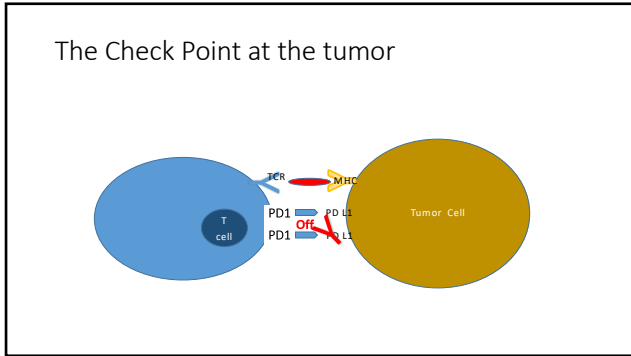
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The revolution in cancer came when the check point in the immune system was discovered. We are going to focus on that today.

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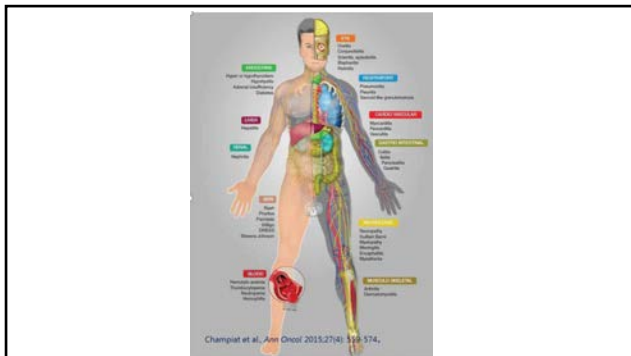
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These are the events we think about

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A 65 year old on pembrolizumab presents to the clinic for his second cycle of therapy. He has been feeling well. He has a mild macular rash here and there on the medial forearms. It is not pruritic. An example is shown in the photograph. Labs are normal. Can treatment be given today?



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KEY CONCEPT #1: Use a consistent tool to grade these side effects.

Determining *degree* of toxicity is key to management

Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 Published November 27, 2017	Grade 1: Mild, asymptomatic, no intervention required Grade 2: Moderate, local or non-invasive intervention required Grade 3: Severe or medically significant, but not life-threatening Grade 4: Life-threatening consequences; urgent intervention required Grade 5: Death related to AE
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Electronic version is available at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

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CTAE for Rash

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KEY CONCEPT #2: Use a consistent tool to manage these side effects.

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A 28 year old man is on ipilimumab (3mg/kg) and nivolumab (1mg/kg) every three weeks for metastatic melanoma to the lung. When he presented to the clinic before the start of his second cycle he reported that he had three loose stools for two days. There was no associated abdominal pain, bleeding in the stool or fever.

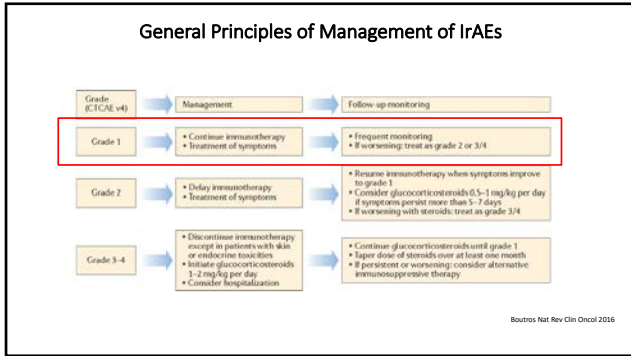
On exam he appears well and VS are normal.

Can you give him the treatment today?

Diarrhea	Increase of ≥ 4 stools per day over baseline; mild increase in colostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in colostomy output compared to baseline; moderate ADL	Increase of ≥ 7 stools per day over baseline; hospitalization indicated; severe increase in colostomy output compared to baseline; limiting self care	Life threatening consequences; urgent intervention indicated	Death
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Definition: A disorder characterized by an increase in frequency of stools or loose or watery bowel movements.

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The patient is admitted overnight for work up and IVF and he does well. He had only one loose stool in the hospital so he is discharged the next day. Two days later at his scheduled post hospital follow up he states that he had 7 watery bowel movements in the last 24 hours. On the two hour drive to clinic he felt feverish and had chills.

Temp 101.5. HR 140. The patient is flushed. Abdominal exam is slightly tender but no rebound.

WBC 12.5. Hg 11.5. Platelets 175. ANC 10. ALC 0.8. Lactate normal. Comprehensive metabolic parameters (CMP) are normal

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What is the diagnostic plan?

- Stool cultures
- C Difficile testing
- Stool calprotectin
- CT scan
- GI consult
- Colonoscopy
- Quantiferon Gold
- Hepatitis Serology
- Pan Endocrine labs

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What is the management plan?

- Management
 - NPO, advance diet
 - High dose steroids (IV)
 - Infliximab or vedolizumab if the patient is not improved after 48 to 72 hours

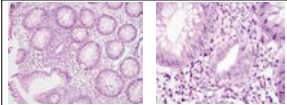
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Diarrhea/Colitis

Immune-related colitis in a patient with metastatic melanoma treated with ipilimumab



Colonoscopic view of bowel edema and ulceration in the descending colon



Histopathologic analyses show focal active colitis (left) with crypt destruction, loss of goblet cells, and neutrophilic infiltrates in the crypt epithelium (right)

Maker AV, et al. Ann Surg Oncol 2005;12:1005-16

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Diarrhea/Colitis

- Mild (Grade 1): <4 stools/day above baseline
 - Bland diet
 - Some recommend: loperamide +/- diphenoxylate/atropine
 - May delay ipilimumab until symptoms improve
- Moderate (Grade 2): > or + to 4 to 6 stools/day
 - Consider colonoscopy,
 - 1-2mg/kg/d of methylprednisolone
 - Hold immunotherapy
 - If no response, continue treatment per grade >=3
- Severe (Grade >=3): >=7 stools/day
 - High dose steroids: 1 mg/kg of methylprednisolone or equivalent
 - Discontinue immunotherapy
 - If unresolved in 48 to 72 hours consider infliximab

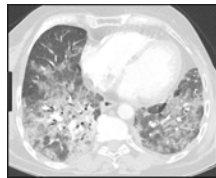
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KEY CONCEPT 3: Steroids need to work quickly

- Patients who benefit from corticosteroids usually do so in a few days.
- If symptoms do not improve in a few days, particularly after IV steroids, consider further immunosuppression.

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A 48 year old woman with COPD and metastatic adenocarcinoma of the lung is admitted with "pneumonia". Her cancer was diagnosed 6 months ago, and treated with monthly nivolumab. Three months into the treatment, scans showed stable disease. On presentation she has a room air O2 Sat of 85%, BP of 135/80 and Temp 99. CT scan is shown.



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What is the differential Diagnosis?

- Lymphangitic spread of the malignancy
- Atypical pneumonia
 - (COVID)
- ARDS
- Pneumonitis

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Pneumonitis

Diagnostic

- CXR and /or CT scan
- Radiographic findings of ground glass lesions and /or disseminated nodular infiltrates
- Bronchoscopy
- PFTs
- Blood gas

Management

- Steroids---IV for grade 3 (like this case)
- Albuterol Nebulizers.
- Oxygen
- Prophylactic antibiotics and antifungals for patients on high dose steroids
- Add mycophenolate, cyclophosphamide, IVIG, or infliximab if the pt does not improve

NCCN January 2019

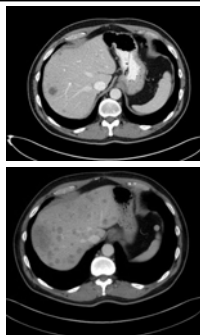
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Pneumonitis

- Occurs in 1 -2 % of pts with melanoma but 3 to 4% (or more) with lung cancer
- Time to onset 9 to 19 weeks (earlier with Nivolumab than pembrolizumab)
- Symptoms
 - Dry, unproductive cough
 - Dyspnea
 - Cyanosis (late)
 - Fatigue
- Differential Diagnosis
 - Infection
 - Allergies
 - Lymphangitic spread of cancer
 - Cardiac (Pericarditis)
- Later diagnosis may lead to chronic, irreversible lung disease

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A 65 year old is on ipilimumab and nivolumab for metastatic melanoma to the liver. He has had two treatments when he presents for an unscheduled visit with right upper quadrant abdominal pain and bloating. No fever No diarrhea but his stools have become lighter in color. CBC shows a mildly elevated WBC otherwise it is normal. AST 340, Alt 410, Alk phos 810, Total Bili 0.5, Protein 6.2, Albumin 3.8.



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Immune Related Hepatitis

- Incidence
 - 30% on combined anti-CTLA and anti PD1
 - 10% on anti PD1 alone
 - Higher incidence in the combination regimens, 15 -18% and 6 to 8% grade 3 to 4.
- Time
 - 8 to 12 weeks in single agent regimens
 - Sooner in the combination
 - A waxing and waning picture may be seen with hepatitis induced by anti-CTLA-4
- Symptoms and signs
 - Usually based on elevated LFTs
 - Bloating, pain, dyspepsia, jaundice, nausea
 - Biopsy shows lymphocytic infiltrate

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Immune Related Hepatitis Treatment

- Grades 3 to 4 hepatotoxicity treat with high-dose intravenous corticosteroids for 24 to 48 hours, followed by an oral steroid taper over not less than 30 days.
- Infliximab, because of its potential for hepatotoxicity, should be avoided in this setting.
- Can use Mycophenolate 1500 mg Bid.

Weber et al. J Clin Oncol 30:2691-2697. © 2012

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A 52 year old with advanced renal cell cancer on ipilimumab and nivolumab presents with neck pain and headache two weeks after his first cycle of treatment. Prior to starting the treatment he had a normal MRI of the brain.

On exam, 150/91, 37.2, 88, 96% resting comfortably. No focal neurologic findings.

Labs: 10am WBC 10.7, Hg 14.2, platelet 319, ALC 2.2, Na 129, K 4.8, chloride 99, CO2 26, creatinine 0.7, AST 26, ALT 62, Alk phos 61

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Hypophysitis

- Rare:
 - 0.4 to 17% on CTLA4 antibody therapy
 - Less than 1% in PD1 antibody therapy
- Timing (more common 11 weeks after the first dose of ipilimumab)
- Presentation
 - Headache, fatigue, MM weakness, visual field
 - Hyponatremia
 - Low ACTH, and Low TSH.
- Concern
 - Adrenal Crisis
 - Adrenal insufficiency associated with hypophysitis is usually permanent
- Secondary hypothyroidism and gonadal axis recovery can occur

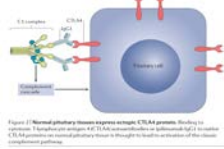


Figure 1 | Normal pituitary function requires CTLA4 protein. Binding to B7-1 inhibits the costimulatory signal that T cells receive from an antigen-presenting cell (APC). CTLA4 protein is expressed on the surface of T cells and binds to B7-1 on APCs, inhibiting the costimulatory signal. CTLA4 protein is also expressed on the surface of pituitary cells, where it binds to B7-1 on APCs, inhibiting the costimulatory signal.

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A 54 year old man on ipi/nivo for melanoma metastatic to the brain presents for his third cycle. He has been "shaky" lately.

BP 134/74. HR 110. Temp 37.1 Exam is otherwise normal.

CBC and CMP are normal.

You send him up to infusion, waiting the TSH to come back.

60 minutes later you see the following labs.

- TSH < 0.015 (0.600-3.300 iIU/mL)
- Free T4 4.65 (0.71-1.40 ng/dl)

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Endocrinopathies

- Hypophysitis (typically by CTLA4 antibodies)
- Hypothyroidism 4-6% PD1 antibodies
- Hyperthyroidism 1 to 5% of PD1 antibodies
- Diabetes ---rare. ---due to direct destruction of the endocrine pancreas---pretreatment Hemoglobin A1c
- PDL1 has a slightly lower incidence of endocrinopathy.

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Thyroid

Hypothyroid: High TSH, Low FT4
High TSH and nl FT4 in subclinical

Hyperthyroid: Low TSH, high FT4, high FT3
Low TSH and nl FT4 in subclinical

Graves disease: + Anti-thyroperoxidase antibodies and anti-thyroglobulin antibodies, Radioactive iodine uptake

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Thyroid Treatments

- Hypothyroid: Levothyroxine
 - Watch subclinical
- Hyperthyroid:
 - In severe thyrotoxicosis before progression to hypothyroidism, administering corticosteroid could be done
 - Beta blockers for tremor or tachycardia
 - Endocrine consult

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Rheumatologic

- Inflammatory arthritis
- Myositis
- Polymyalgia Rheumatica
- Vasculitities

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Nephritis

- Nephritis: Not common but difficult to diagnosis. UA is a more appropriate screening test than Cr.
- Guidelines are creatinine driven
- Gold standard is a kidney biopsy

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Events that are common and we don't think about them

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54 year old patient with NSSLC metastatic to liver on nivolumab presents for her third cycle of treatment. She is doing well but complains of pain in the left side of her mouth. On examination her oral mucosa is pink and there are no abnormal lesions. Her lips are dry. She has no cervical lymphadenopathy. There is fullness over the left parotid gland.

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Oral Mucosa

- May include mucositis, gingivitis, and sicca (Sjogren) syndrome.
- Approximate 5% of patients on check point inhibitors have symptoms of dry mouth
 - More common with the anti-PD1 agents
- Work up
 - Antinuclear antibodies (ANA)
 - Screen for Sjogren syndrome (SSA/SSB)
- Management
 - Oral corticosteroid rinses
 - Pilocarpine chloro hydrate
 - Viscous Lidocaine
 - Good oral hygiene.

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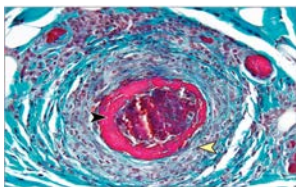
Arthralgia

- The typical adult with OA
- The young person with an injury from a skiing accident
 - Gosh, my joints hurt more than they used to
 - NSAIDS
 - Integrate care with orthopedics
 - Steroid injections

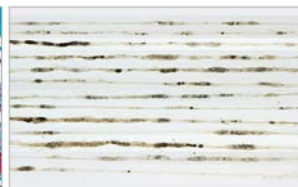
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Neurotoxicity: Peripheral Neuropathy

Sural Nerve Biopsy Specimen



Teased Nerve Fiber Preparation



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Rare but Important Events

KEY CONCEPT 4: Do not forget the rare but serious side effects to the heart and nervous system

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Cardiac

- Myocarditis
- Pericardial disease
 - Pericarditis
 - Pericardial effusion
 - Cardiac tamponade
- Arrhythmia

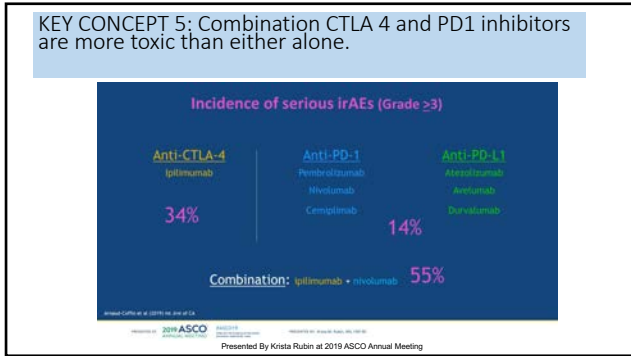
Pirozzi . Curr Oncol Rep. 2021;23(2):13

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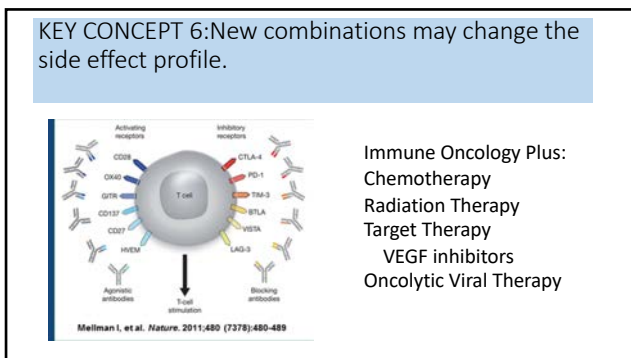
Severe Neurologic toxicities

- Encephalopathy
- Meningitis
- Myasthenia Gravis
- Guillian Barre
- Transverse Myelitis

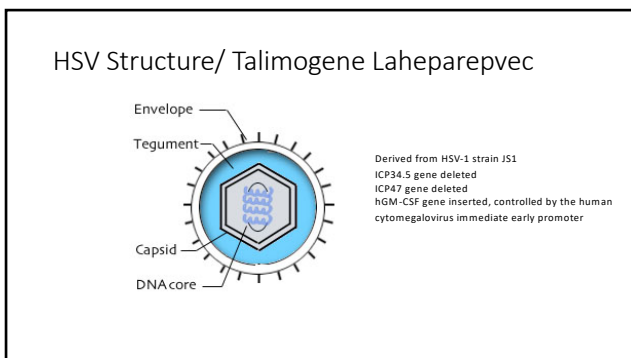
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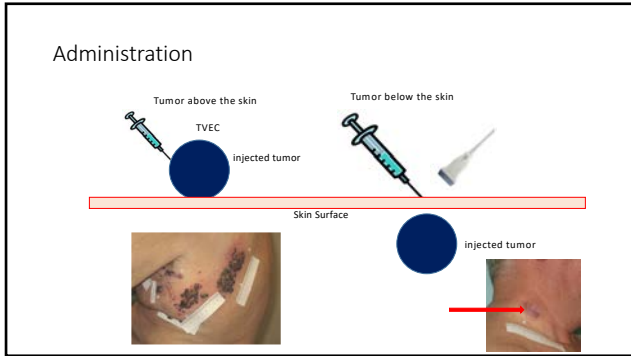
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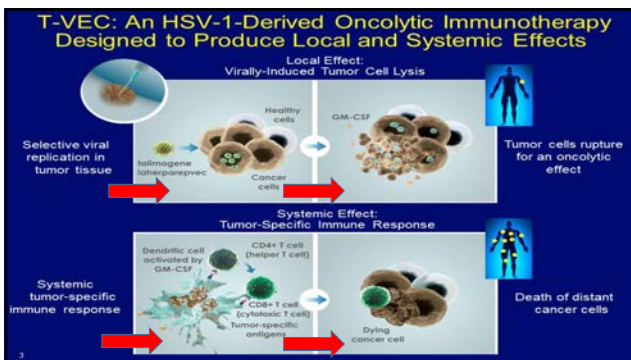
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Safety

TVEC as a single agent

- Flu like side effects for 1 to 2 days, usually after the first and second cycle.

TVEC and check point inhibitors

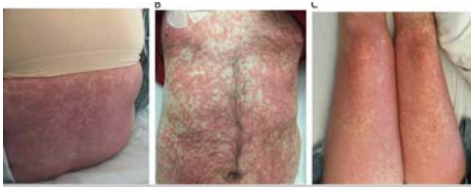
- No additive side effects were seen

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KEY CONCEPT 7: Sequencing may change the toxicity profile

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Here are three people who were treated with target therapy followed by PD1i. All three patients were clinically unstable.



[Nagash, J Immunother Cancer, 2019; 7: 4.](#)

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The management plan

- Dermatology Consult
- Burn Unit (considered)
- Steroids
- Mycophenolate (considered)

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KEY CONCEPT 8: Patients with underlying autoimmune disease have an increased chance of IrAEs

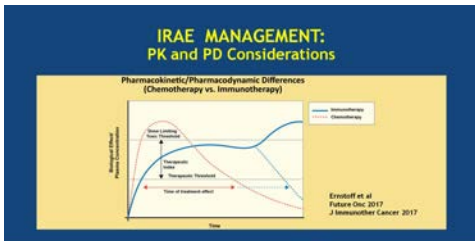
- Underlying auto immune disease is worse 1/3 of the time.
- Increased risk of high grade irAEs in 2/3s.
- Weigh the benefit versus the risk.

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KEY CONCEPT 9: Chemo versus I/O

- Chemotherapy side effects can be severe, but they can be more predictable than I/O
- I/O side effects can be unpredictable, persistent, recurrent

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KEY CONCEPT 10: Delayed Immune therapy side effects

- Literature search from 2008-2018 search: 367 case reports + 194 I-O clinical trials.
 - DIRE: irAE sequelae newly diagnosed ≥ 90 days following discontinuation of immunotherapy (1)
- Delayed Immune thrombocytopenia (2)
- Delayed Diabetic Ketoacidosis (3)

1. Couey et al, *JTC* 2019
2. *J Oncol Pharm Pract*. 2021 Jan 12
3. *J Emerg Med*. 2020 Oct 20

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Immunotherapy treatment in patients who contract SARs-COV2 is complex

Immune Rx may help COVID+ pt



Virus specific T cells may help viral clearance
May be helpful in early phase COVID infection

Immune Rx may hurt COVID + pt.



Activation of T cells may cause more inflammation

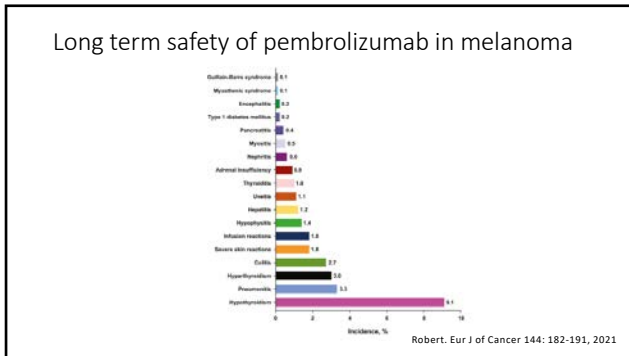


Maio M, et al. *Clin Cancer Res*. 2020.

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Closing remarks

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KEY CONCEPT 11

- I/O management requires a team approach.
- UNC has a multidisciplinary team for this. It is led by Dr Rumei C. Ishizawa

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KEYs in one stroke

- Use the Common Toxicity Criteria for Adverse Events to Grade toxicity.
- Use a tool to manage side effects based on grade such as NCCN.org.
- Patients usually respond to steroids in a few days; if they don't, move to more aggressive management.
- Good PS pts who are treated with PD1's have a low risk of grade 3.
- Toxicity risk depends on sequence, combination, new agents, pre-existing autoimmune disease.
- Don't forget the rare but important risks to the CNS and heart.
- IrAES can be permanent, and delayed (DIRE), even long after the treatment is done.
- For prescribers, discuss risk/benefit especially in specific contest (COVID pandemic) and populations (patients with autoimmune disease).

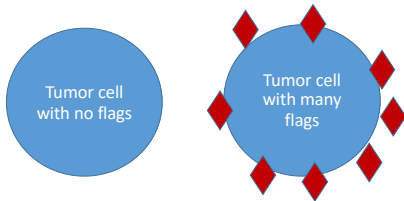
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- National Comprehensive Cancer Network: Management of immunotherapy-related toxicities, v.2, 2019. https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf [Google Scholar](#)

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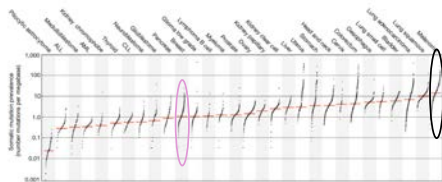
Key Concept #1: Some cancers look very foreign to the immune system so they can be seen more easily.



The more mutations in the cancer, the easier it is to see them.

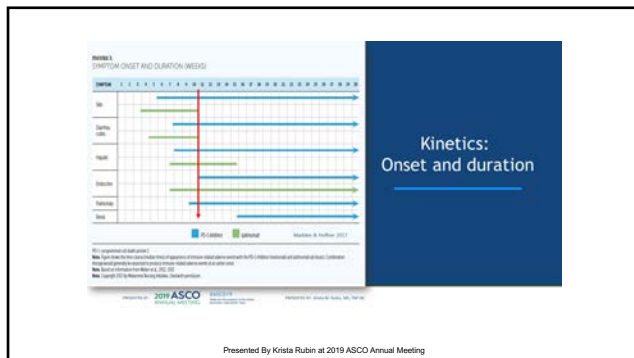
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Key Concept #1: Cancers that look foreign have a high Mutational Load

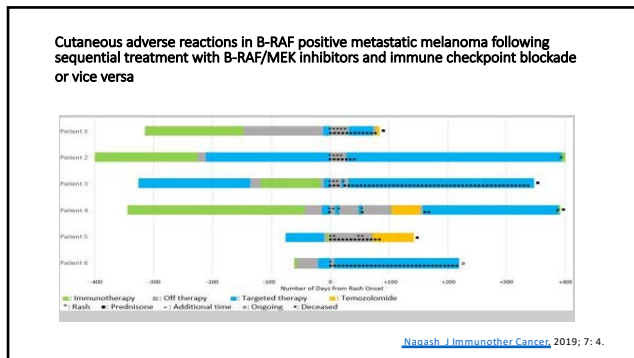


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