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

3

Buckets of cancer treatment

Chemotherapy | Hormone therapy | Target Therapy | Biologics | Immune therapy

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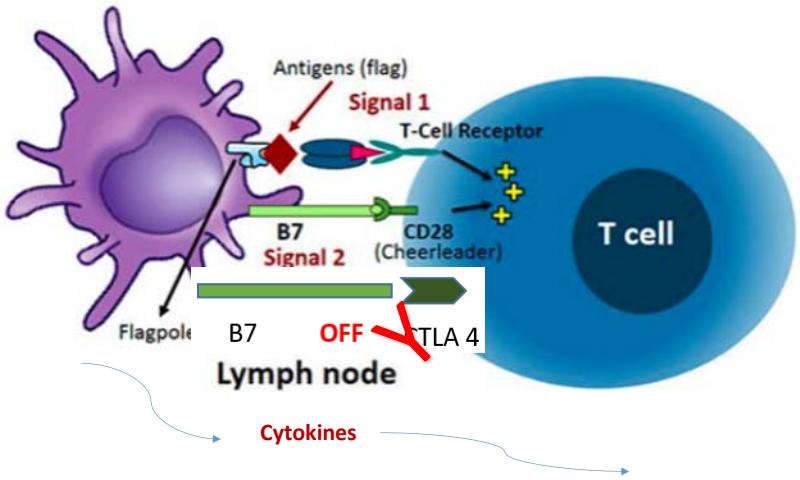
The revolution in cancer came when the check point in the immune system was discovered. We are going to focus on that today.

5

The Check Point away from the tumor.



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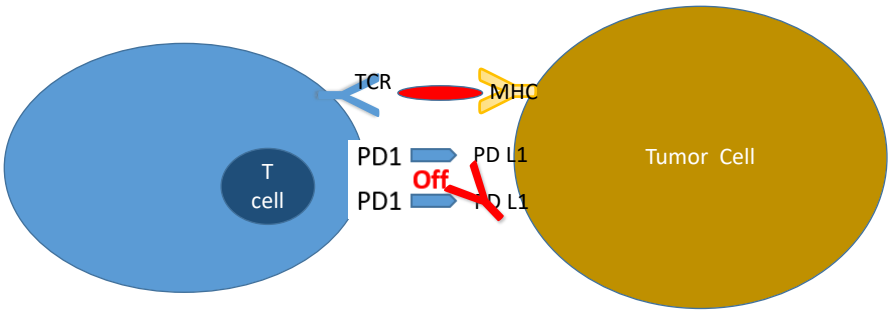
The Check Point at the tumor



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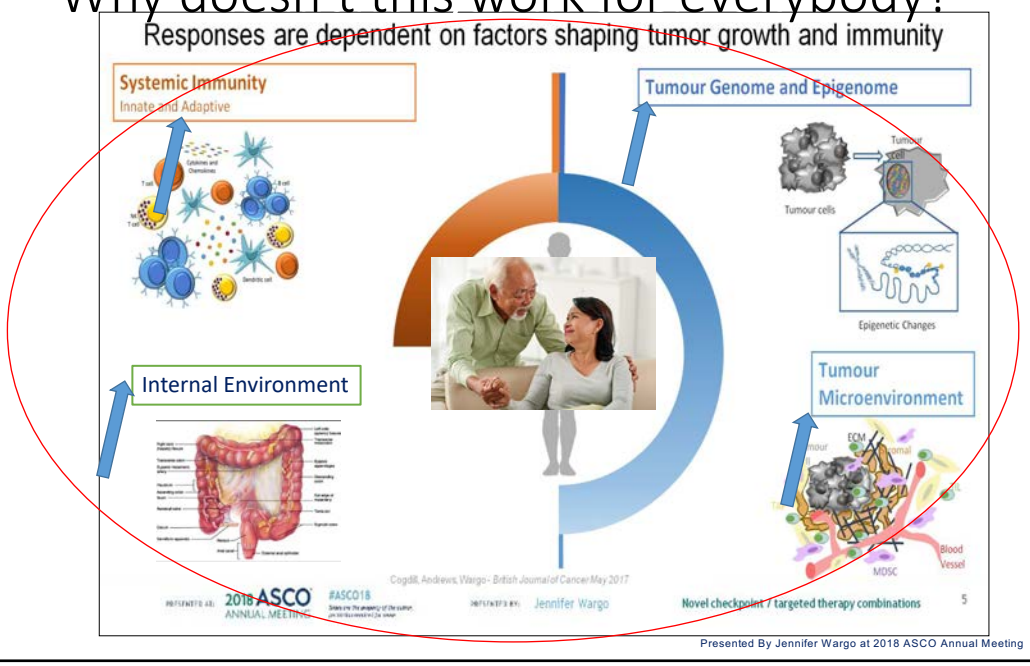
Why doesn't this work for everybody?



Presented By Jennifer Wargo at 2018 ASCO Annual Meeting

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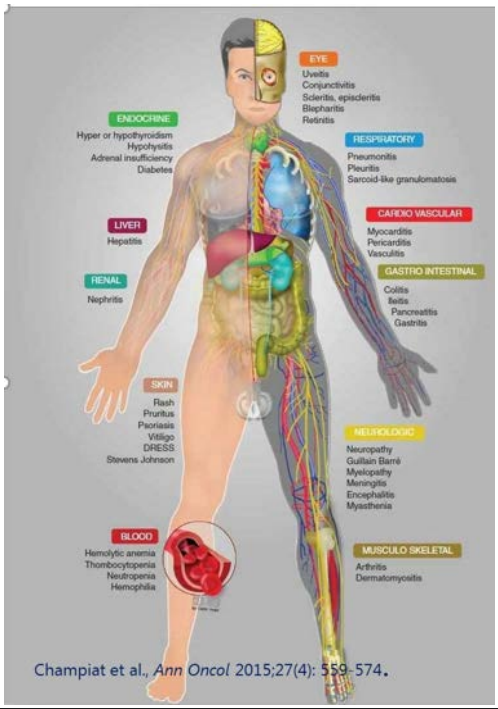

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These are the events we think about

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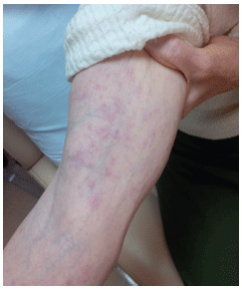
A 65 year old on pembrolizumab presents to the clinic for his second cycle of therapy. He has been feeling well. He has a mild macular rash here and there on the medial forearms. It is not pruritic. An example is shown in the photograph. Labs are normal. Can treatment be given today?



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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
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
National Cancer Institute

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

Electronic version is available at
https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

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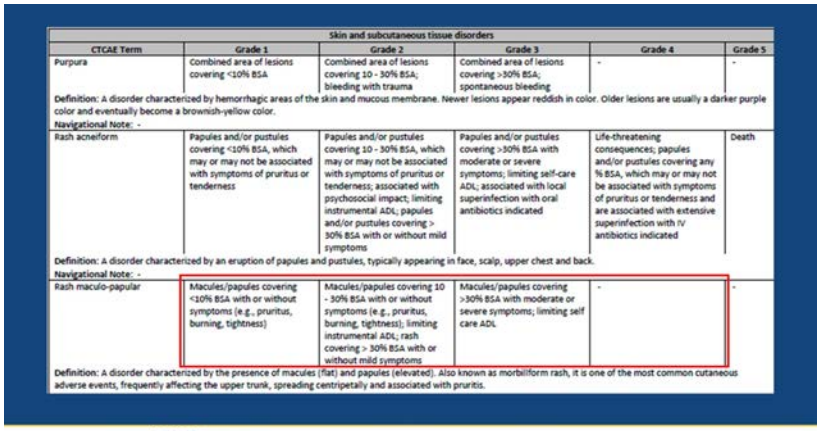
CTAE for Rash



Skin and subcutaneous tissue disorders					
CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Purpura	Combined area of lesions covering <10% BSA	Combined area of lesions covering 10 - 30% BSA; bleeding with trauma	Combined area of lesions covering >30% BSA; spontaneous bleeding	-	-
Definition: A disorder characterized by hemorrhagic areas of the skin and mucous membrane. Newer lesions appear reddish in color. Older lesions are usually a darker purple color and eventually become a brownish-yellow color.					
Navigational Note: -					
Rash acneiform	Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10 - 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL; papules and/or pustules covering > 30% BSA with or without mild symptoms	Papules and/or pustules covering >30% BSA with moderate or severe symptoms; limiting self-care ADL; associated with local superinfection with oral antibiotics indicated	Life-threatening consequences; papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated	Death
Definition: A disorder characterized by an eruption of papules and pustules, typically appearing in face, scalp, upper chest and back.					
Navigational Note: -					
Rash maculo-papular	Macules/papules covering <10% BSA with or without symptoms (e.g., pruritus, burning, tightness)	Macules/papules covering 10 - 30% BSA with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental ADL; rash covering > 30% BSA with or without mild symptoms	Macules/papules covering >30% BSA with moderate or severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by the presence of macules (flat) and papules (elevated). Also known as morbilliform rash, it is one of the most common cutaneous adverse events, frequently affecting the upper trunk, spreading centripetally and associated with pruritis.					

PRESENTED AT: 2019 ASCO ANNUAL MEETING #ASCO19 PRESENTED BY: Krista M. Rubin, MS, FNP-BC

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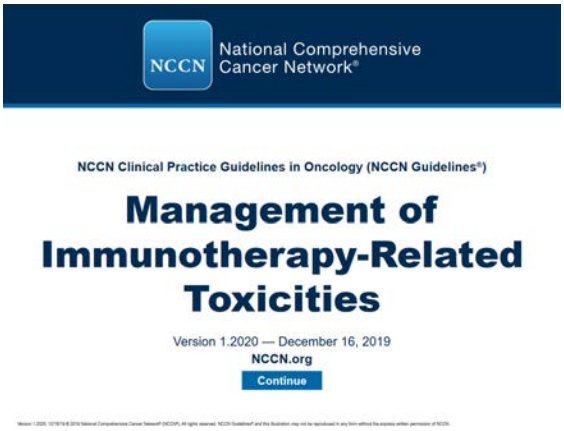
KEY CONCEPT #2: Use a consistent tool to manage these side effects.



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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 ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL	Increase of >=7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Definition: A disorder characterized by an increase in frequency and/or loose or watery bowel movements.

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General Principles of Management of IrAEs

Grade (CTCAE v4)	Management	Follow-up monitoring
Grade 1	• Continue immunotherapy • Treatment of symptoms	• Frequent monitoring • If worsening: treat as grade 2 or 3/4
Grade 2	• Delay immunotherapy • Treatment of symptoms	• Resume immunotherapy when symptoms improve to grade 1 • Consider glucocorticosteroids 0.5–1 mg/kg per day if symptoms persist more than 5–7 days • If worsening with steroids: treat as grade 3/4
Grade 3–4	• Discontinue immunotherapy except in patients with skin or endocrine toxicities • Initiate glucocorticosteroids 1–2 mg/kg per day • Consider hospitalization	• Continue glucocorticosteroids until grade 1 • Taper dose of steroids over at least one month • If persistent or worsening: consider alternative immunosuppressive therapy

Boutros Nat Rev Clin Oncol 2016

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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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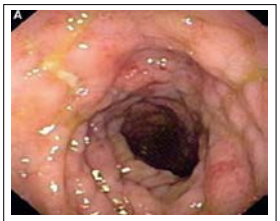
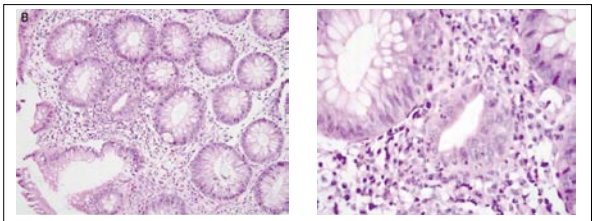
Diarrhea/Colitis

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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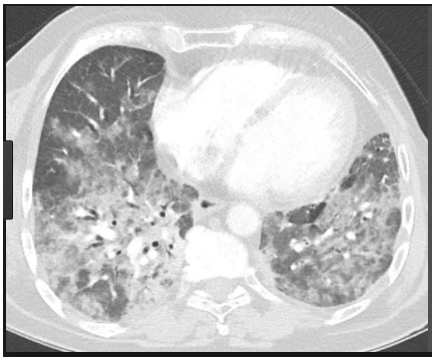
A 48 year old woman with COPD and metastatic adenocarcinoma of the lung to the lung is admitted with "pneumonia". Her cancer was diagnosed 6 months ago, and treated with monthly nivolumab. Three months into the treatment, scans showed stable disease. On presentation she has a room air 02 Sat of 85%, 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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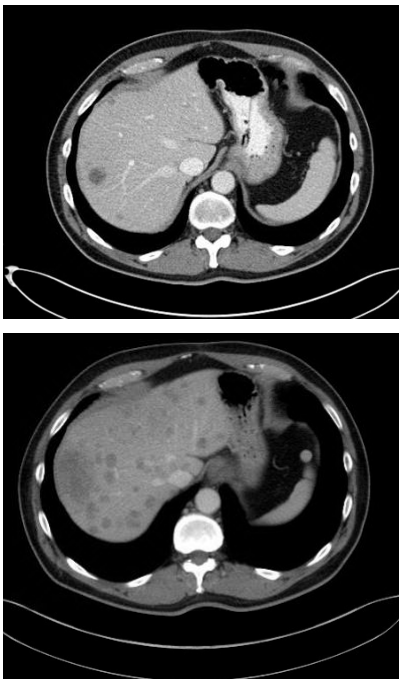
A 65 year old is on ipilimumab and nivolumab for metastatic melanoma to the liver. He has had two treatments when he presents for an unscheduled visit with right upper quadrant abdominal pain and bloating. No fever No diarrhea but his stools have become lighter in color. CBC shows a mildly elevated WBC 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

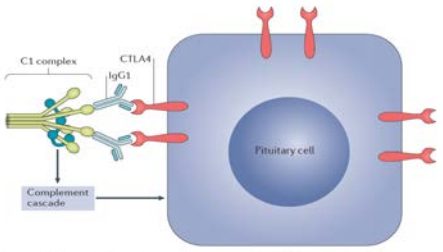

Figure 2 | **Normal pituitary tissues express ectopic CTLA4 protein.** Binding to cytotoxic T-lymphocyte antigen 4 (CTLA4) autoantibodies or ipilimumab IgG1 to native CTLA4 proteins on normal pituitary tissue is thought to lead to activation of the classic complement pathway.

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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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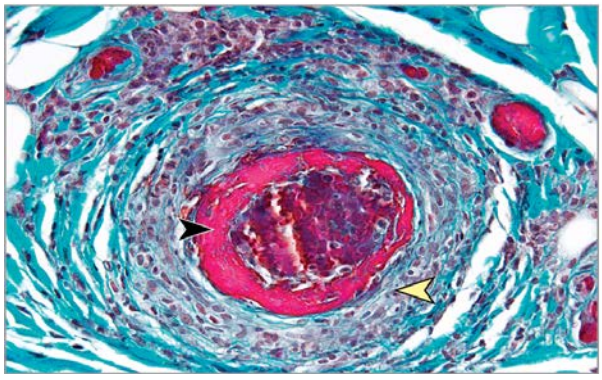
Neurotoxicity: Peripheral Neuropathy

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
- Arrythmia

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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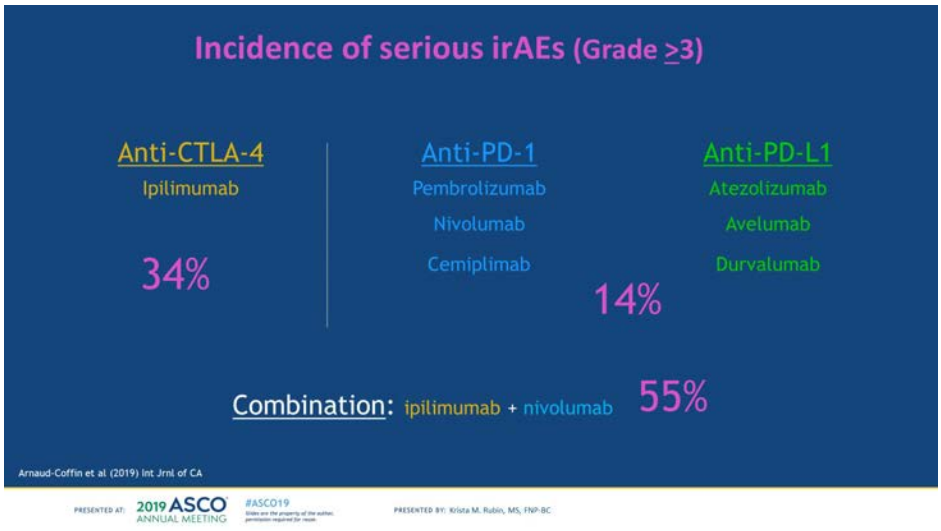
KEY CONCEPT 5: Combination CTLA 4 and PD1 inhibitors are more toxic than either alone.



Presented By Krista Rubin at 2019 ASCO Annual Meeting

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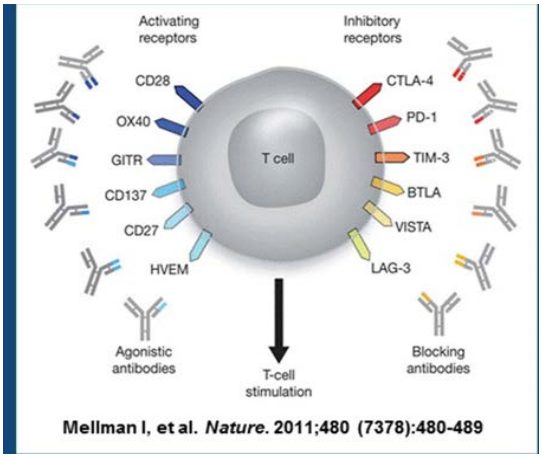
KEY CONCEPT 6:New combinations may change the side effect profile.



Immune Oncology Plus:
Chemotherapy
Radiation Therapy
Target Therapy
  VEGF inhibitors
Oncolytic Viral Therapy

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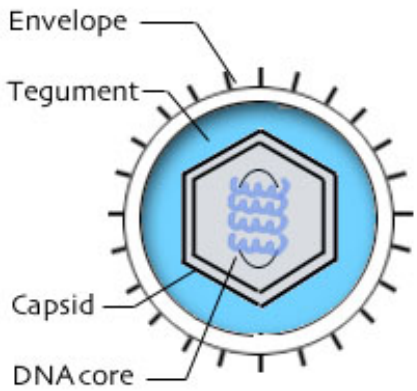
HSV Structure/ Talimogene Laheparepvec



Derived from HSV-1 strain JS1
ICP34.5 gene deleted
ICP47 gene deleted
hGM-CSF gene inserted, controlled by the human cytomegalovirus immediate early promoter

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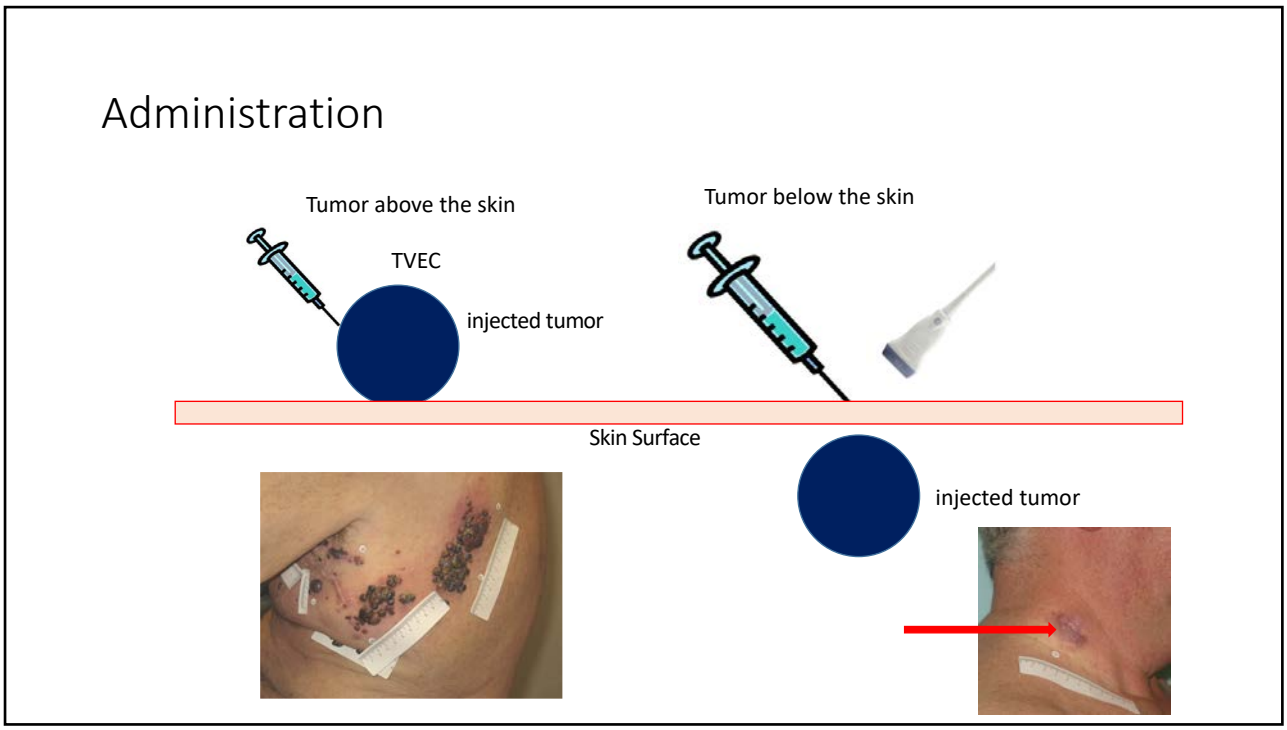
Administration
Tumor above the skin
TVEC
injected tumor
Tumor below the skin
Skin Surface
injected tumor

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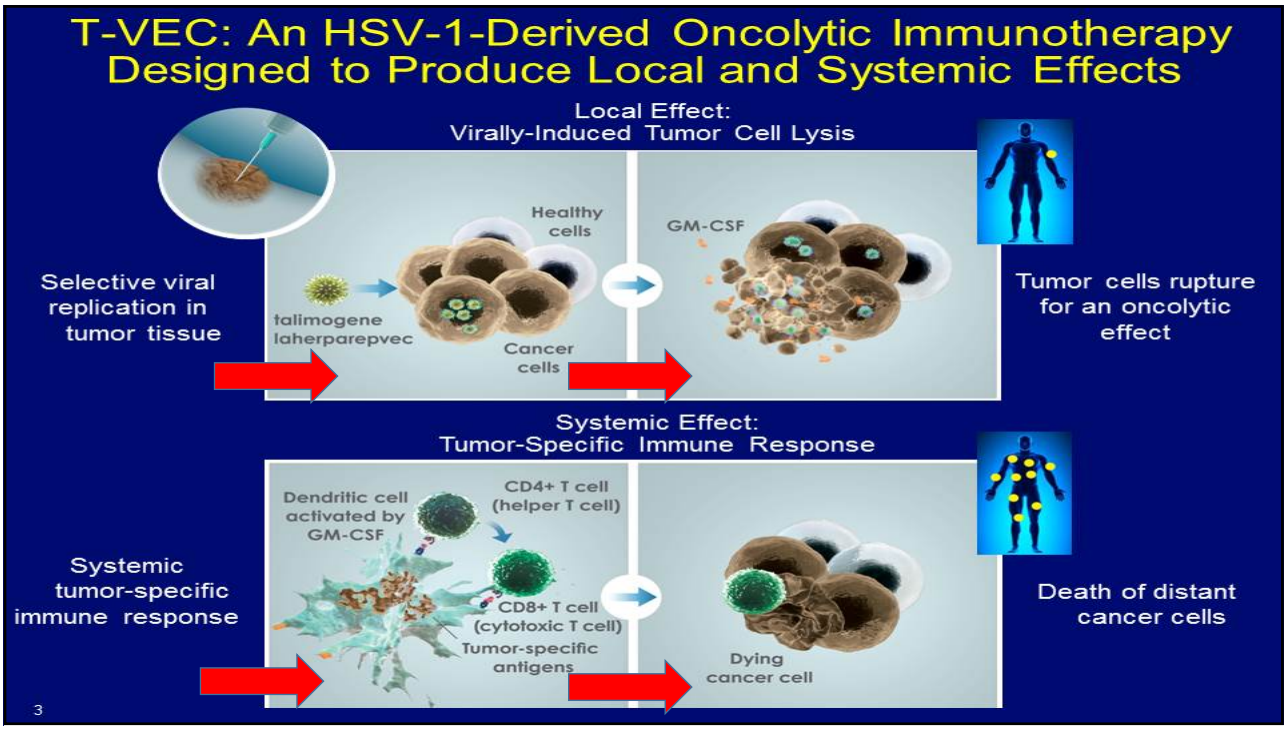
T-VEC: An HSV-1-Derived Oncolytic Immunotherapy Designed to Produce Local and Systemic Effects
Local Effect:
Virally-Induced Tumor Cell Lysis
Selective viral replication in tumor tissue
talimogene laherparepvec
Healthy cells
Cancer cells
GM-CSF
Tumor cells rupture for an oncolytic effect
Systemic Effect:
Tumor-Specific Immune Response
Systemic tumor-specific immune response
Dendritic cell activated by GM-CSF
CD4+ T cell (helper T cell)
CD8+ T cell (cytotoxic T cell)
Tumor-specific antigens
Dying cancer cell
Death of distant cancer cells
3

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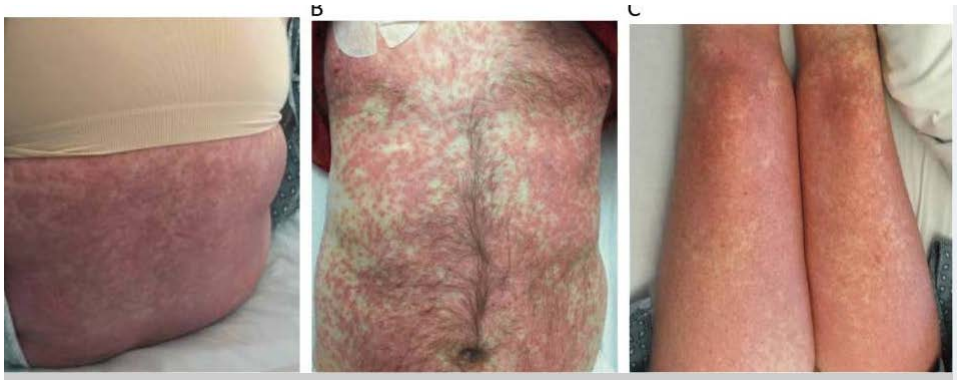
Here are three people who were treated with target therapy followed by PD1i. All three patients were clinically unstable.



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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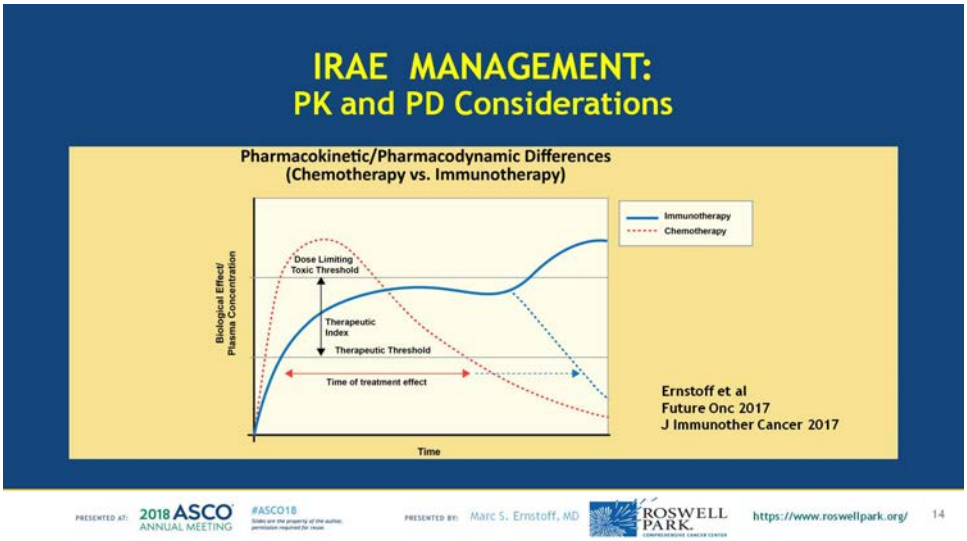

Presented By Marc Ernstoff at 2018 ASCO Annual Meeting

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KEY CONCEPT 10: Delayed Immune therapy side effects

- Literature search from 2008-2018search: 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, *JITC* 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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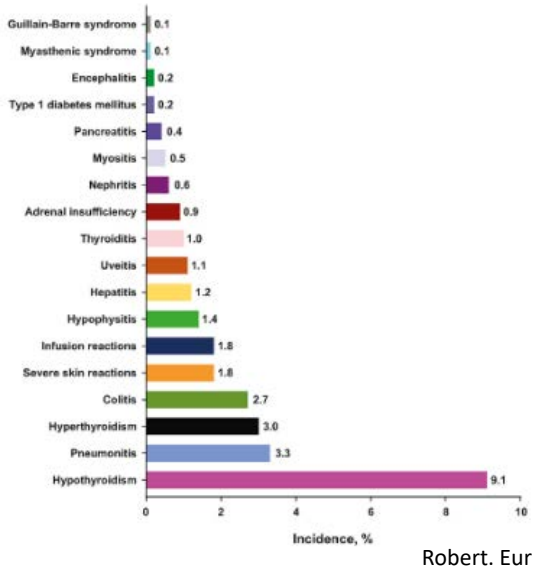
Long term safety of pembrolizumab in melanoma



Robert. Eur J of Cancer 144: 182-191, 2021

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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 Rumey C. Ishizawar

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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 PD1i'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 withs autoimmune disease).

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References

- Brahmer JR, Lacchetti C, Schneider BJ, et al: Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 36:1714-1768, 2018
- 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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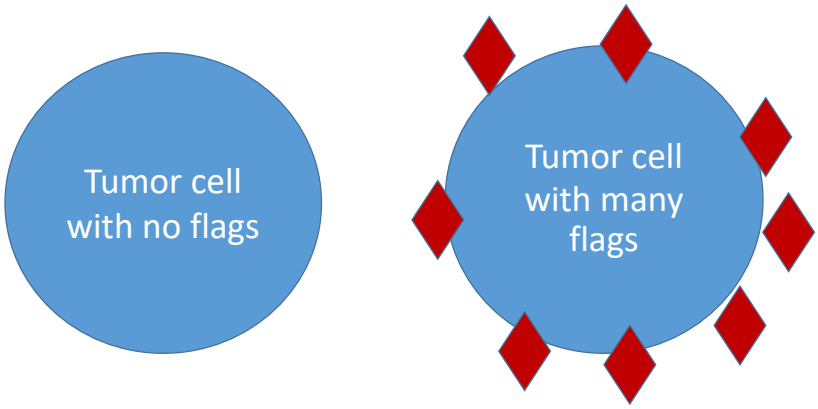
Key Concept #1: Some cancers look very foreign to the immune system so they can be seen more easily.



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

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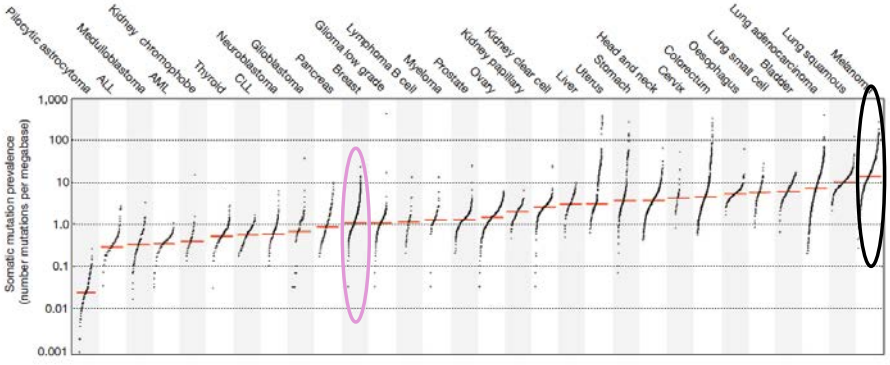
Key Concept #1: Cancers that look foreign have a high Mutational Load



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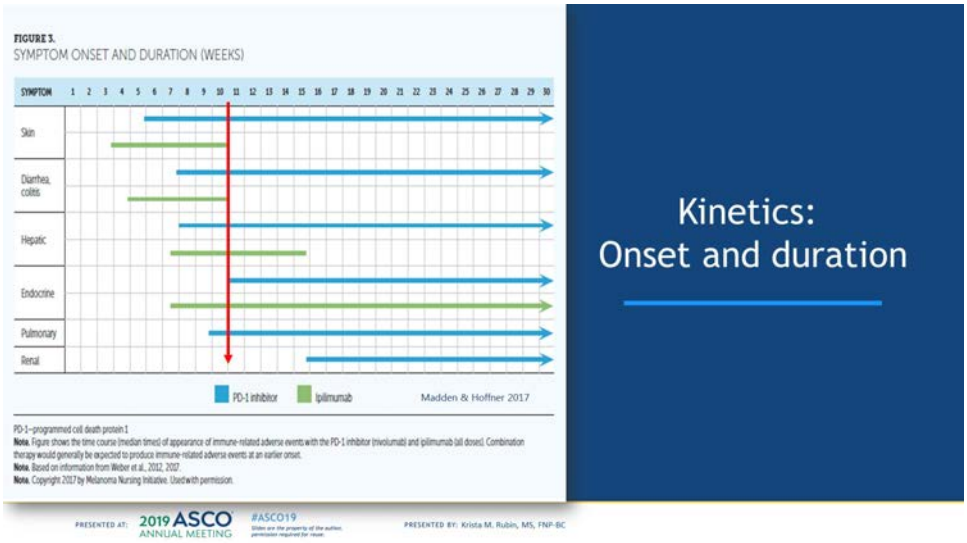

Presented By Krista Rubin at 2019 ASCO Annual Meeting

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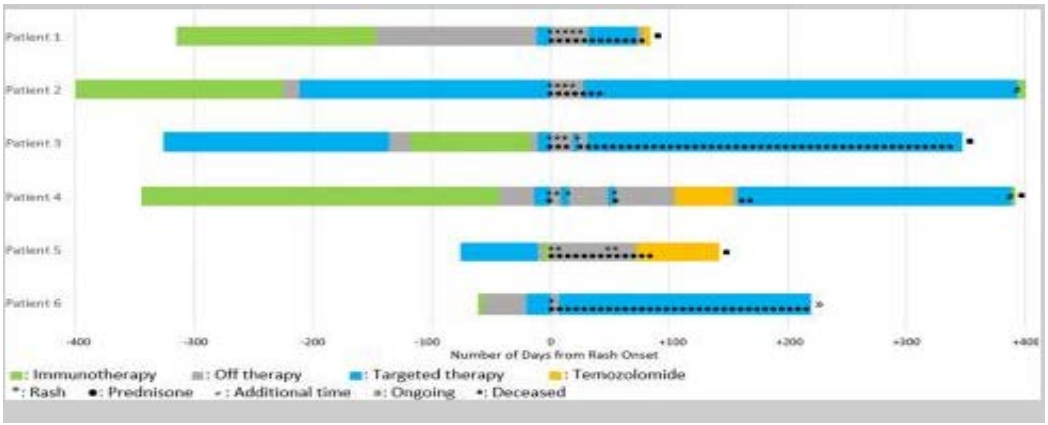
Cutaneous adverse reactions in B-RAF positive metastatic melanoma following sequential treatment with B-RAF/MEK inhibitors and immune checkpoint blockade or vice versa



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