Immune (check point) Related Adverse Events

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Outline

- Mechanism of check point inhibitors
- Events we think about
- Events that are common and we don't think about them
- Rare Events

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Mechanism

3

Buckets of cancer treatment

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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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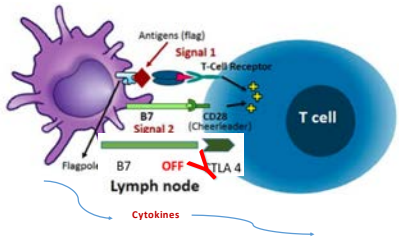
The Check Point away from the tumor.



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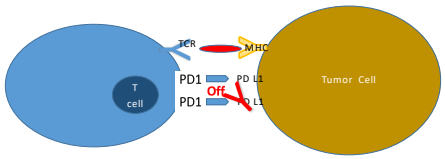
The Check Point at the tumor



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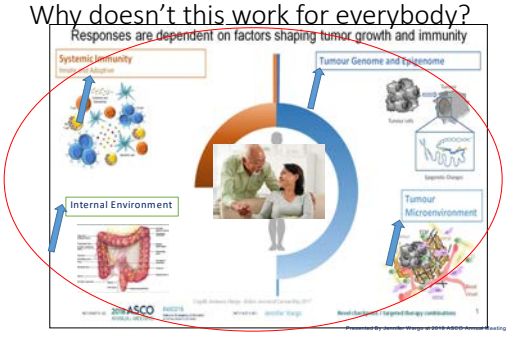
Why doesn't this work for everybody?



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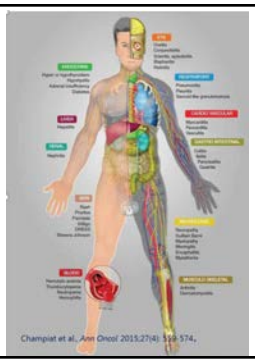

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These are the events we think about

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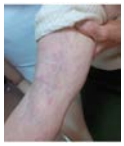
A 65 year old on pembrolizumab presents to the clinic for his second cycle of therapy. He has been feeling well. He has a mild macular rash here and there on the medial forearms. It is not pruritic. An example is shown in the photograph. Labs are normal. Can treatment be given today?



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

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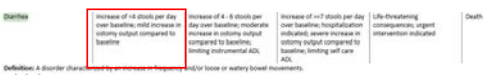
A 28 year old man is on ipilimumab (3mg/kg) and nivolumab (1mg/kg) every three weeks for metastatic melanoma to the lung. When he presented to the clinic before the start of his second cycle he reported that he had three loose stools for two days. There was no associated abdominal pain, bleeding in the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

On exam he appears well and VS are normal.

Can you give him the treatment today?



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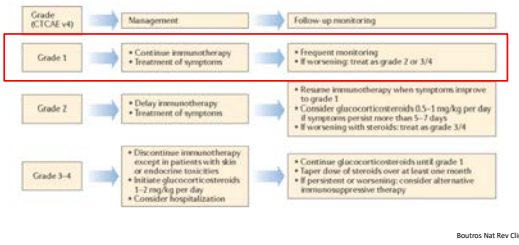
General Principles of Management of IrAEs



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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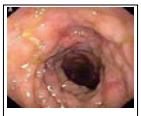
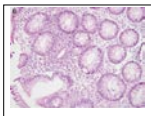
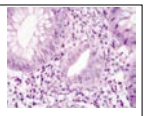
Diarrhea/Colitis

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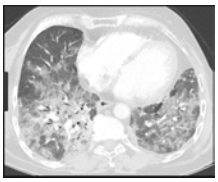
A 48 year old woman with COPD and metastatic adenocarcinoma of the lung to the lung is admitted with "pneumonia". Her cancer was diagnosed 6 months ago, and treated with monthly nivolumab. Three months into the treatment, scans showed stable disease. On presentation she has a room air 02 Sat of 85%,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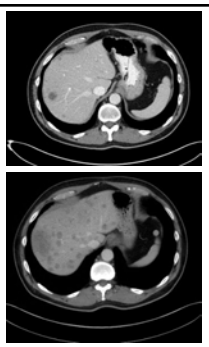
A 65 year old is on ipilimumab and nivolumab for metastatic melanoma to the liver. He has had two treatments when he presents for an unscheduled visit with right upper quadrant abdominal pain and bloating. No fever No diarrhea but his stools have become lighter in color. CBC shows a mildly elevated WBC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

A. Progression of his disease
B. Immune mediated liver toxicity
C. Reactivation of Hepatitis B
D. Both A and B

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Hepatitis

- Incidence
  - 2 to 9% on anti-CTLA therapy alone
  - 0.5% 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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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, WBC 11.3, Hg 14, Platelet 308

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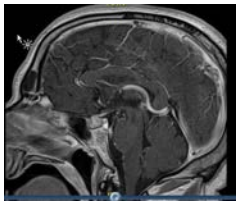
What other diagnostic studies can you order?

A. Am Cortisol
B. ACTH
C. Thyroid Function Tests
D. MRI brain with pituitary images
E. All of the above



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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

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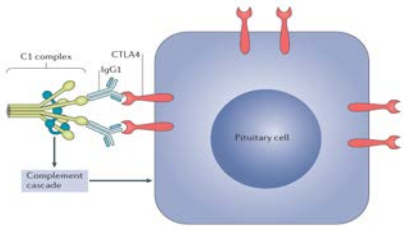

Figure 2 | **Normal pituitary tissues express ectopic CTLA4 protein.** Binding to cytotoxic T-lymphocyte antigen 4 (CTLA4) autoantibodies or ipilimumab IgG1 to native CTLA4 proteins on normal pituitary tissue is thought to lead to activation of the classic complement pathway.

Byun et al. Nature Reviews. January 2017

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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)

What is the diagnosis?

A. Hyperthyroidism
B. Hypothyroidism
C. Hypophysistis

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Endocrinopathies

- Hypophysitis (typically by CTLA4 antibodies)
- Hypothyroidism 4-6% PD1 antibodies
- Hyperthyroidism 1 to 5% of PD1 antibodies
- Diabetes ---rare. ---possibly d/t T1DM specific autoantibodies (GAD65)

- 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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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. The most likely diagnosis is:

A. Mucositis
B. Thrush
C. Metastasis to the parotid gland
D. Sicca Syndrome.

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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 a 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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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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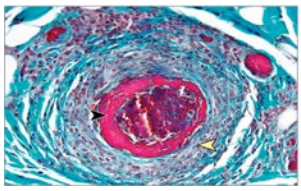
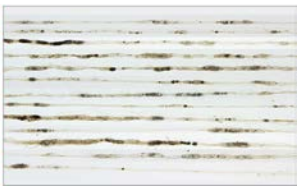
Neurotoxicity: Peripheral Neuropathy

Sural Nerve Biopsy Specimen



Teased Nerve Fiber Preparation



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Rare Events

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

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A 81 year old chemistry professor is treated with ipi/nivo for RCC metastatic to the lung. He is admitted to the ICU with chest pain and diagnosed with myocarditis. After stabilizing his heart and transferring the pt to the floor, his nurse calls the doctor for "abnormal breathing". It is observed that the pt is using his abdominal mm to breathe. His voice is weak and he states that he has difficulty swallowing.

The pt went back to the ICU

Serum-negative myasthenia gravis was diagnosed

Treated with 1000 mg methylprednisolone i.v. for 3 d, tapered to 80 mg per day

Pyridostigmine 30 mg BID G tube

Plasmapheresis.

The pt was intubated for airway protection but he rapidly deteriorated and passed away on day 8.

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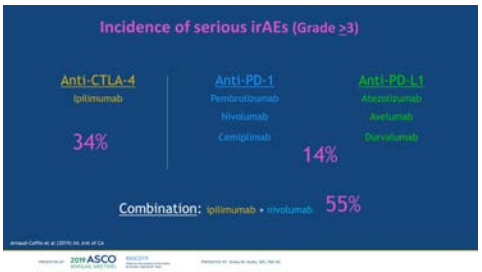

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KEY CONCEPT 5:New combinations may change the side effect profile.

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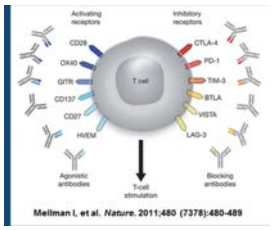
New Combinations



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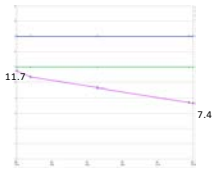
- 60 year old with metastatic melanoma previously treated with IL2, Ipilimumab, nivolumab, Dabrafenib/Trametinib. Currently on pembrolizumab and a CD40 agonist study drug.
- Developed acute normocytic anemia with normal iron studies, low haptoglobin, and elevated LDH.
- The DAT was negative. This can be the case in up to 10% of cases of AIHA.
- The pt improved after the CD 40 agonist and pembrolizumab were stopped and she was treated with prednisone.



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New combinations…

Oncolytic viral therapy

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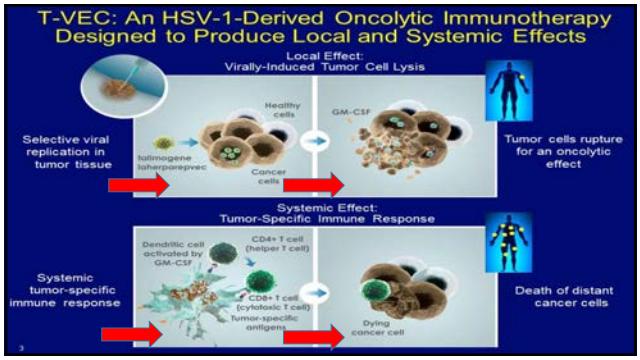

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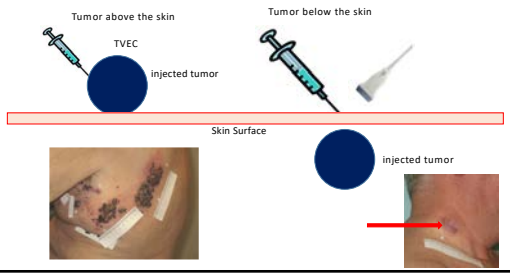
Administration



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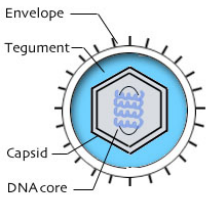
HSV Structure



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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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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Beyond the usual toxicities…

But caution as oncolytic therapy could be included in patients with complex conditions.

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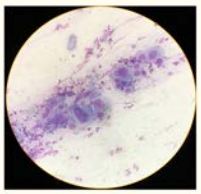
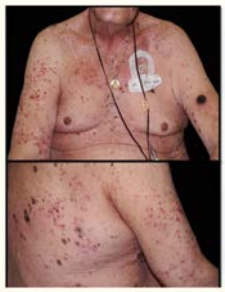
Varicelliform eruption in a patient with melanoma and cutaneous anaplastic NHL treated with TVEC and nivolumab



Giant cells with viral cytopathic effects

Varicelliform eruption



Miller DM J Immunother Cancer. 2018; 6: 122.

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KEY CONCEPT 6: Sequencing may change the toxicity profile

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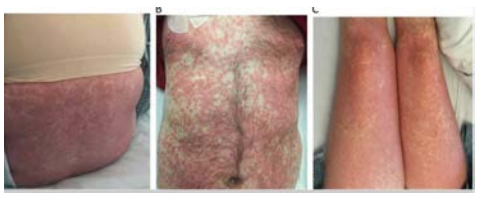
Here are three people who were treated with target therapy followed by PD1i. All three patients were clinically unstable.



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 7: 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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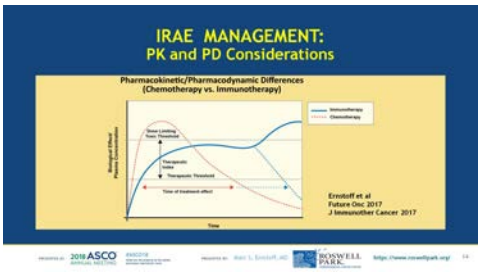

Presented By Marc Ernstoff at 2018 ASCO Annual Meeting

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KEY CONCEPT 9

- 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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Closing remarks

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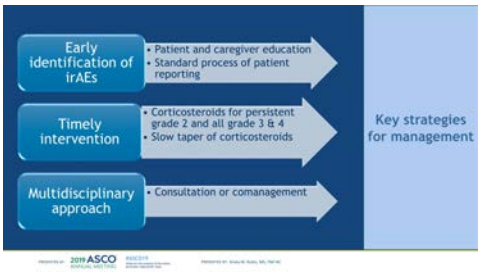

Presented By Krista Rubin at 2019 ASCO Annual Meeting

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KEYs in one stroke

- Use the Common Toxicity Criteria for Adverse Events to Grade toxicity
- Management is based on the grade.
- 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
- Don't forget the rare but important risks to the CNS and heart.
- IrAES can be permanent, and recurrent, even long after the treatment is done.

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Thank you

Appointments for the Complex Skin Cancer Program:
984-974-8289
984-974-0000

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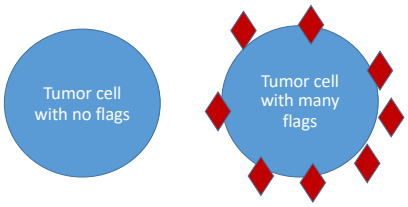
Key Concept #1: Some cancers look very foreign to the immune system so they can be seen more easily.



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

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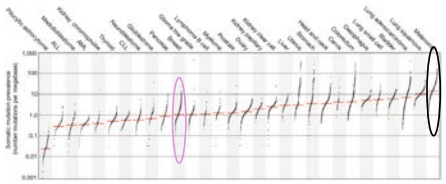
Key Concept #1: Cancers that look foreign have a high Mutational Load



22 AUGUST 2013 | VOL 500 | NATURE | 415

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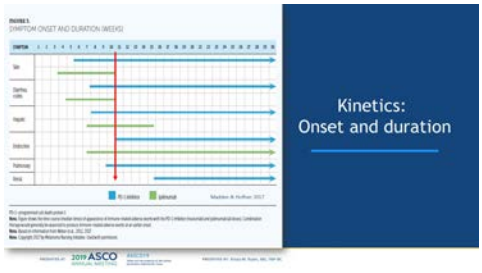

Presented By Krista Rubin at 2019 ASCO Annual Meeting

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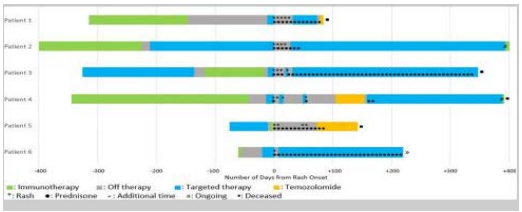
Cutaneous adverse reactions in B-RAF positive metastatic melanoma following sequential treatment with B-RAF/MEK inhibitors and immune checkpoint blockade or vice versa



Nagash J Immunother Cancer. 2019; 7: 4.

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