UNC CANCER NETWORK

CANCER TREATMENT IN NORTH CAROLINA **RESEARCH TO PRACTICE**

Live Lecture

March 25, 2020

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Sound Checks

Start Time

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UNC CANCER NETWORK

CANCER TREATMENT IN NORTH CAROLINA **RESEARCH TO PRACTICE**

March 25, 2020

Immune (check point) Related Adverse Events

Frances Collichio, MD

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OUR PRESENTER

Frances Collichio, MD

Frances Collichio, MD, is a UNC Lineberger Comprehensive Cancer Center member and Professor of Medicine at UNC-Chapel Hill in the Division of Hematology and Oncology.

Dr. Collichio has held several leadership positions in education the United States including a term on the American Society of Clinical Oncology (ASCO) Education Council, representative to the Association of Subspecialty Professors (ASP) of the Alliance of Academic Medicine (AAIM), and chair of the ASCO Oncology Training Program Committee.

Her academic mission is to advance training of physicians in the United States, particularly oncology trainees.

Dr. Collichio's clinical research mission is melanoma. She has been the principal investigator at UNC for more than 20 trials in melanoma.

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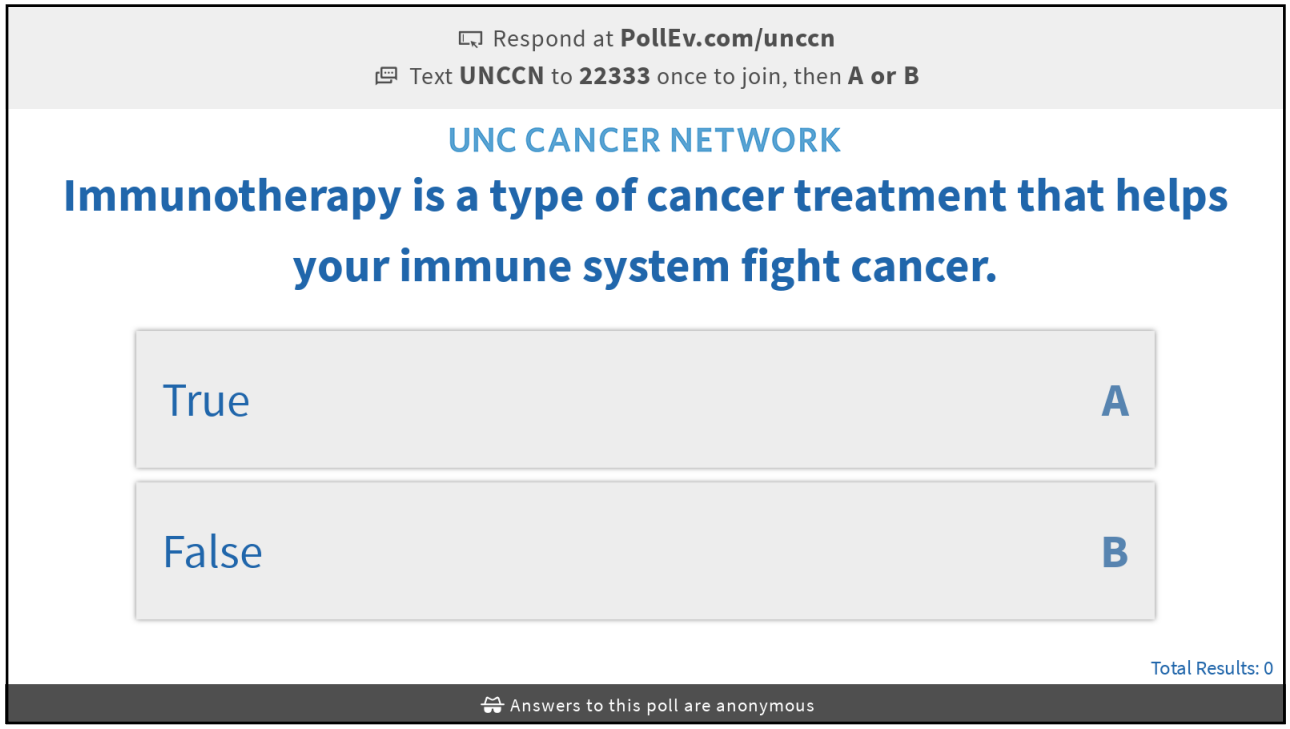

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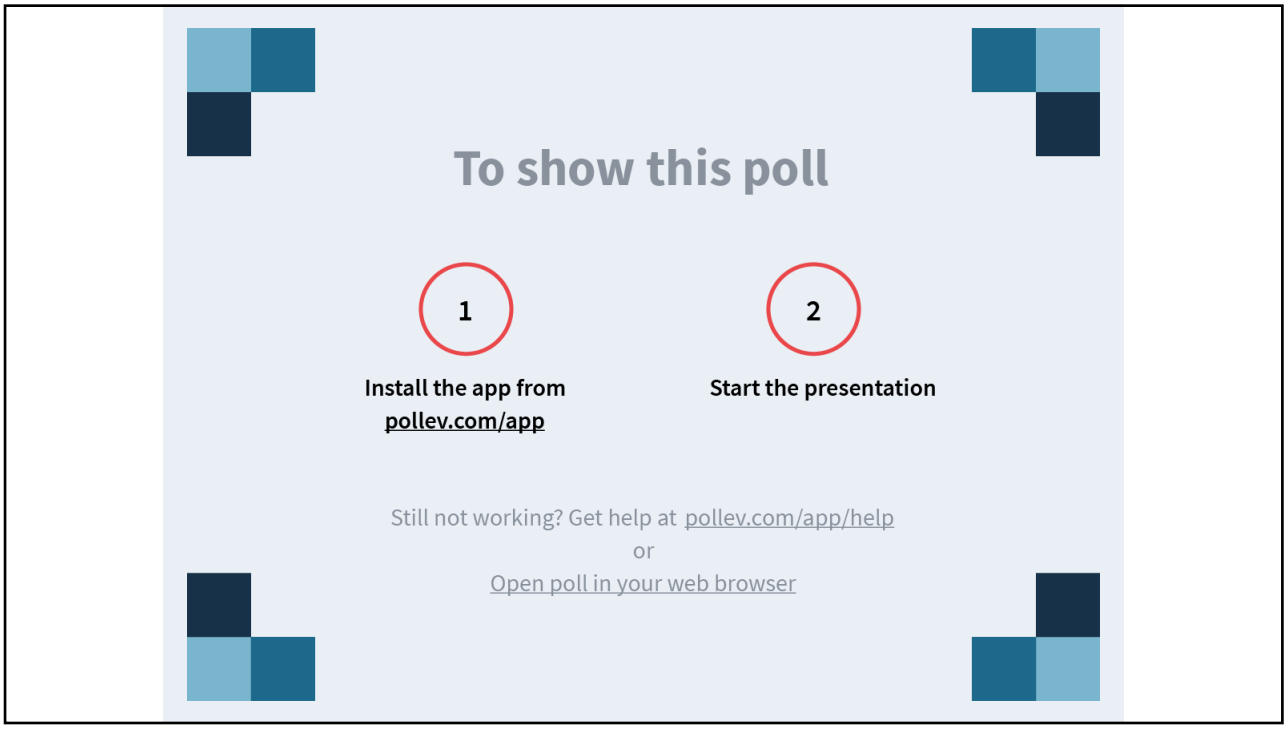

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Immune (check point) Related Adverse Events

Frances Collichio
Professor of Medicine
Division of Hematology/Oncology
The University of North Carolina, Chapel Hill

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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)

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Mechanism

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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.

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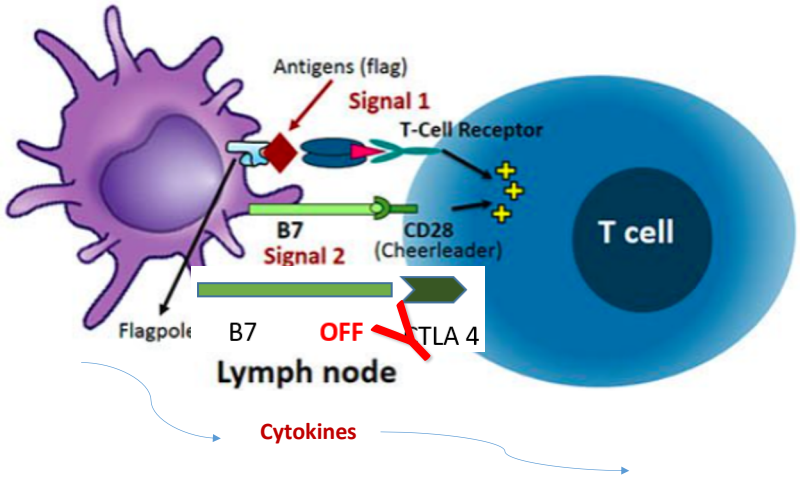
The Check Point away from the tumor.



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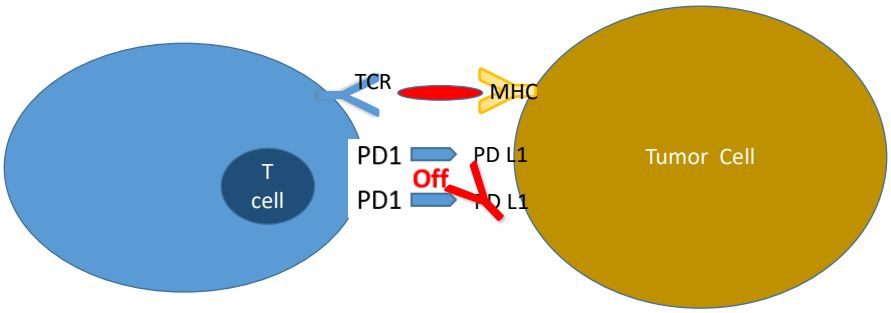
The Check Point at the tumor



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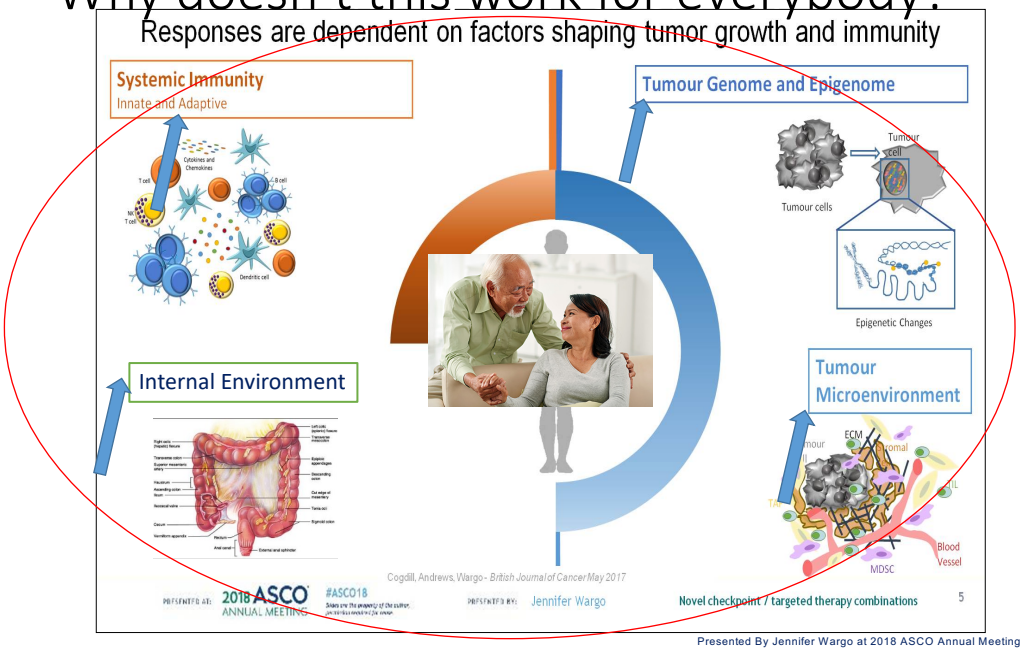
Why doesn't this work for everybody?



Presented By Jennifer Wargo at 2018 ASCO Annual Meeting

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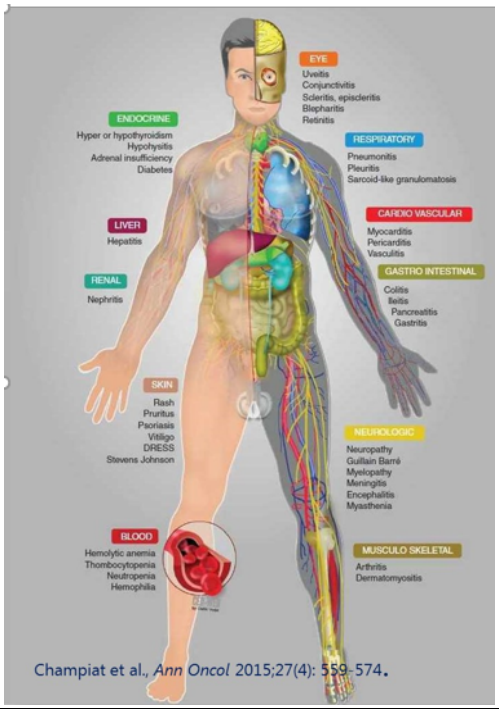

Champiat et al., *Ann Oncol* 2015;27(4): 559-574.

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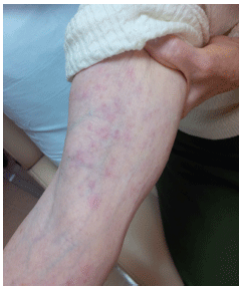
These are the events we think about

19

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 Slides are the property of the author, permission required for reuse.

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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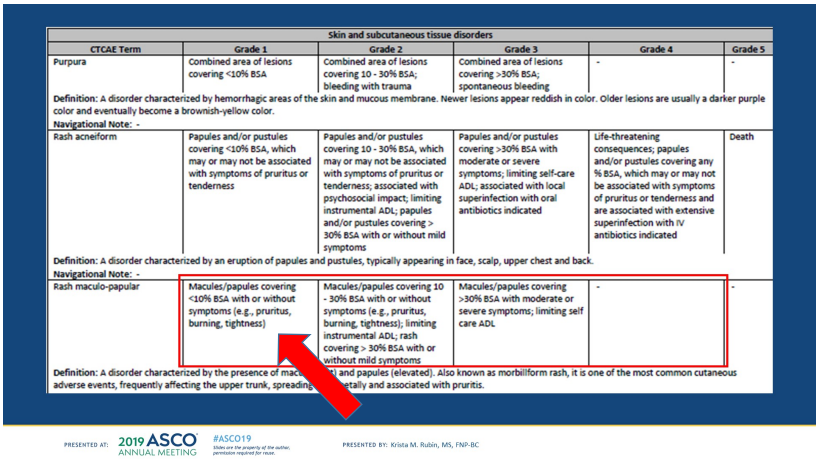
CTAE for Rash



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Definition: A disorder characterized by the presence of macules and papules (elevated). Also known as morbilliform rash, it is one of the most common cutaneous adverse events, frequently affecting the upper trunk, spreading centrally and associated with pruritis.					

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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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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 per day for the last two days. There was no associated abdominal pain, blood 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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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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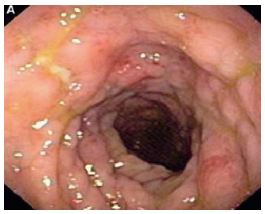
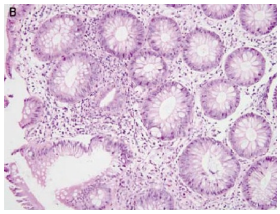
Diarrhea/Colitis

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: 1-2 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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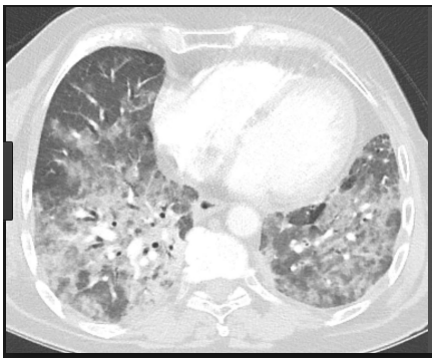
A 48 year old woman with COPD and metastatic adenocarcinoma of the lung to the lung is admitted with "pneumonia". Her cancer was diagnosed 6 months ago, and treated with monthly nivolumab. Three months into the treatment, scans showed stable disease. On presentation she has a room air 02 Sat of 85%, BP of 135/80 and Temp 99. CT scan is shown.



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What is the differential Diagnosis?

- Pneumonitis
- Atypical pneumonia
- Lymphangitic spread of the malignancy
- ARDS

Total Results: 0

Answers to this poll are anonymous

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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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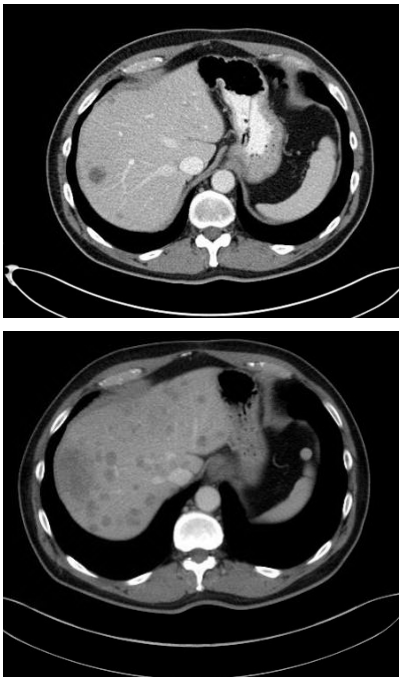
A 65 year old is on ipilimumab and nivolumab for metastatic melanoma to the liver. He has had two treatments when he presents for an unscheduled visit with right upper quadrant abdominal pain and bloating. No fever No diarrhea but his stools have become lighter in color. CBC shows a mildly elevated WBC 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?

- Progression of his disease
- Immune mediated liver toxicity
- Reactivation of Hepatitis B
- Both A and B

Total Results: 0

Answers to this poll are anonymous

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Hepatitis

- Incidence
  - 30% on combined anti-CTLA and anti PD1
  - 10% on anti PD1 alone
- 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. He states that it was harder to drive to clinic because his peripheral vision is "off". 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 5.2, chloride 99, CO2 26, creatinine 0.7, AST 26, ALT 62, Alk phos 61

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What other diagnostic studies can you order?

- Am Cortisol
- ACTH
- Thyroid Function Tests
- MRI brain with pituitary images
- All of the above

Answers to this poll are anonymous

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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

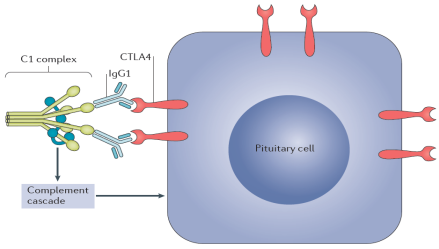

Figure 2 | **Normal pituitary tissues express ectopic CTLA4 protein.** Binding to cytotoxic T-lymphocyte antigen 4 (CTLA4) autoantibodies or ipilimumab IgG1 to native CTLA4 proteins on normal pituitary tissue is thought to lead to activation of the classic complement pathway.

43

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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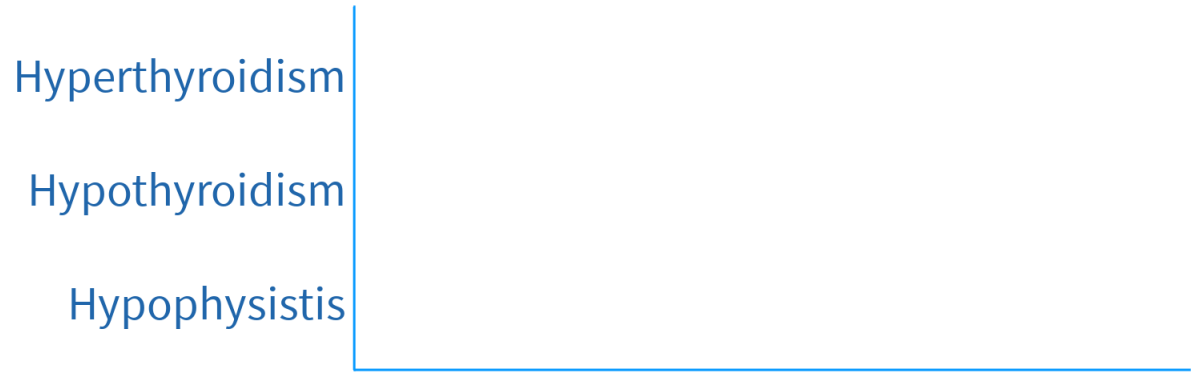
What is the diagnosis?



Answers to this poll are anonymous

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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

48

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

49

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 dry. There are no abnormal lesions. She has no cervical lymphadenopathy. There is fullness over the left parotid gland.

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The most likely diagnosis is:

Answers to this poll are anonymous

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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
  - Oral moisturizes
  - 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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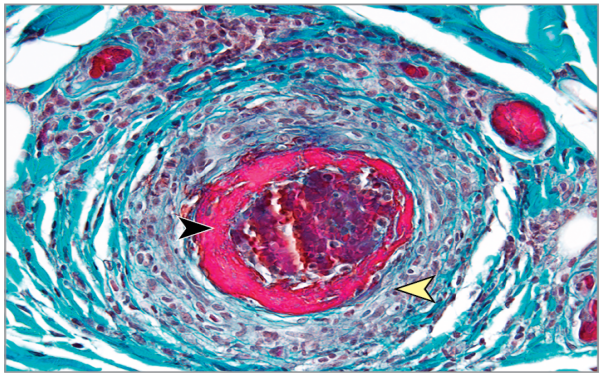
Neurotoxicity: Peripheral Neuropathy

Sural Nerve Biopsy Specimen



Teased Nerve Fiber Preparation

54

Rare Events

55

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

Incidence of serious irAEs (Grade ≥3)

Anti-CTLA-4	Anti-PD-1	Anti-PD-L1
Ipilimumab	Pembrolizumab	Atezolizumab
	Nivolumab	Avelumab
	Cemiplimab	Durvalumab
34%	14%	

Combination: ipilimumab + nivolumab 55%

Arnaud-Coffin et al (2019) Int Jrnl of CA

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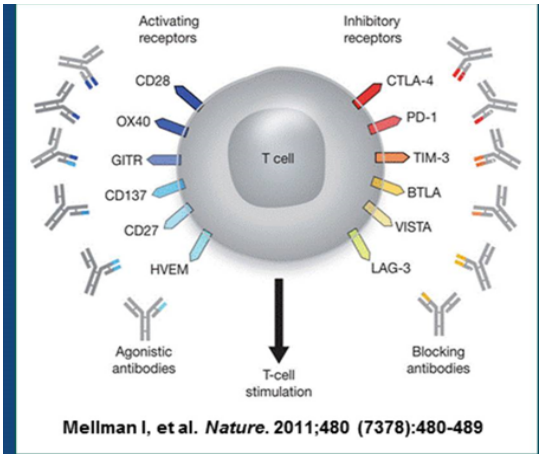
KEY CONCEPT 6:New combinations may change the side effect profile.



Mellman I, et al. *Nature*. 2011;480 (7378):480-489

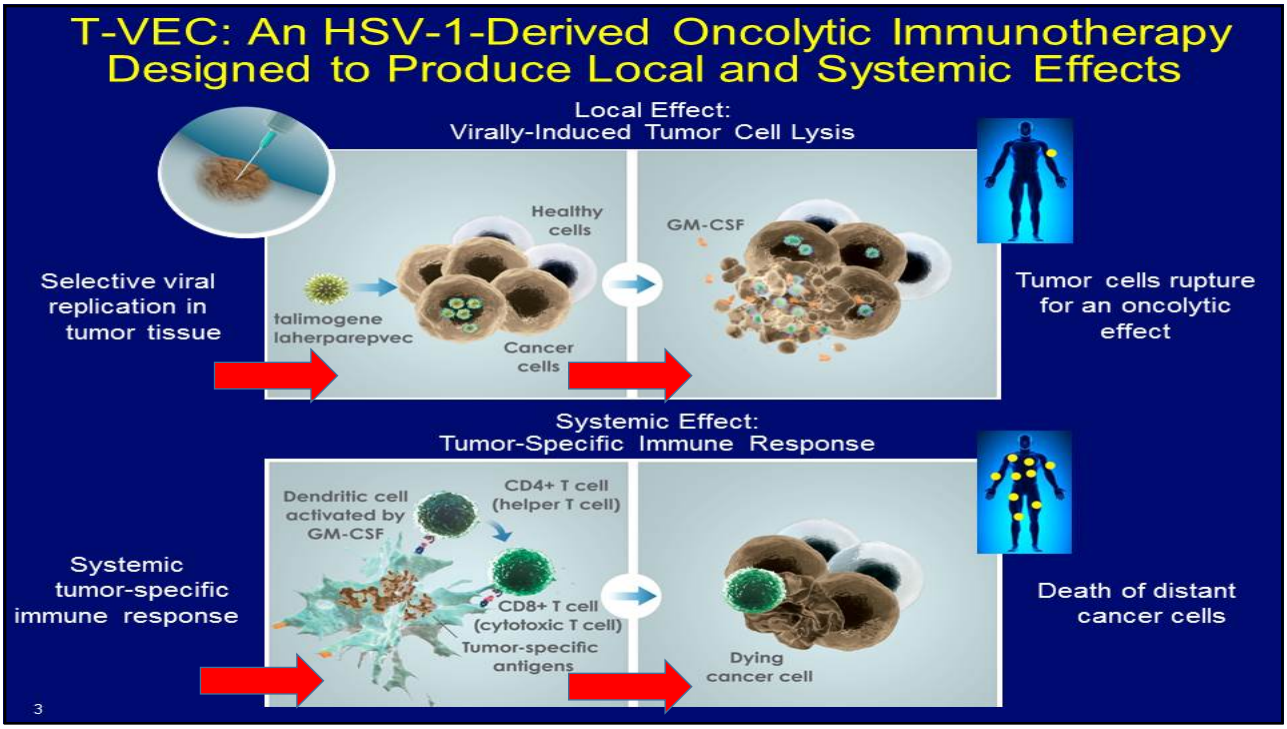
Immune Oncology Plus:
Chemotherapy
Radiation Therapy
Target Therapy
VEGF inhibitors

60

New combinations…

Oncolytic viral therapy

61



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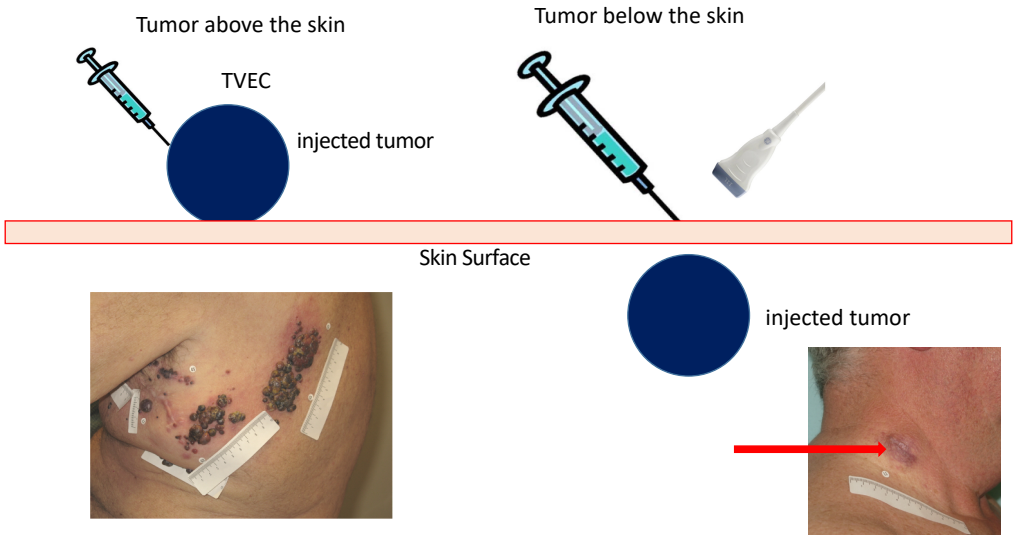
Administration



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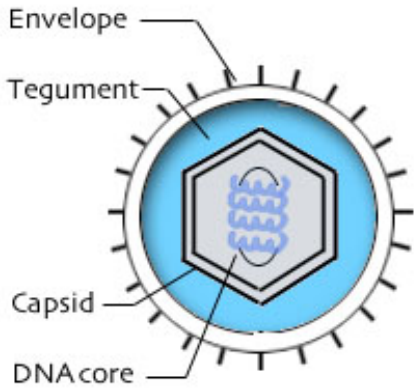
HSV Structure



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

64

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

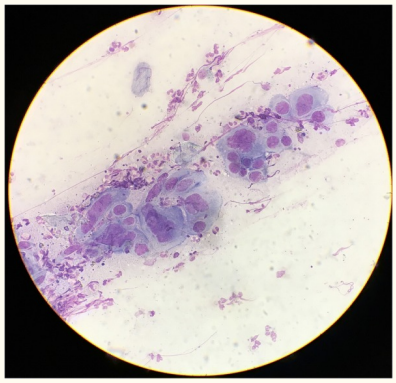
65

Beyond the usual toxicities…

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

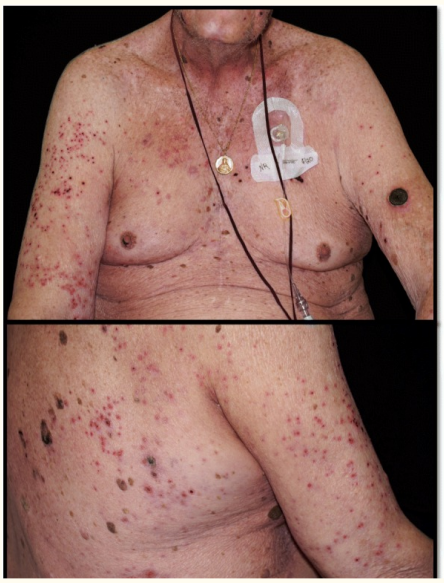
66

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



Giant cells with viral cytopathic effects

Varicelliform eruption



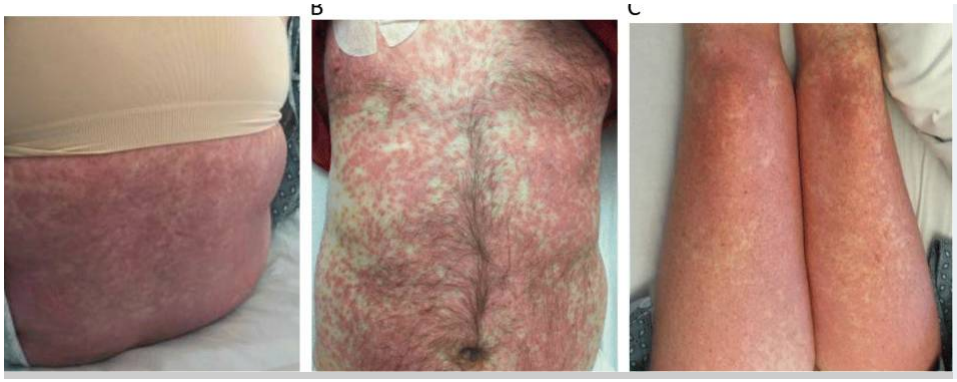
Miller DM J Immunother Cancer. 2018; 6: 122.

67

KEY CONCEPT 7: Sequencing may change the toxicity profile

68

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.

69

The management plan

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

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KEY CONCEPT 8: 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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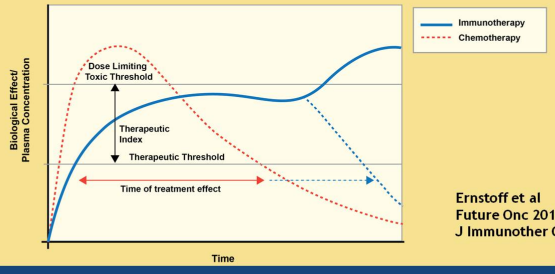
IRAE MANAGEMENT: PK and PD Considerations

Pharmacokinetic/Pharmacodynamic Differences (Chemotherapy vs. Immunotherapy)



Ernstoff et al
Future Onc 2017
J Immunother Cancer 2017

Presented By Marc Ernstoff at 2018 ASCO Annual Meeting

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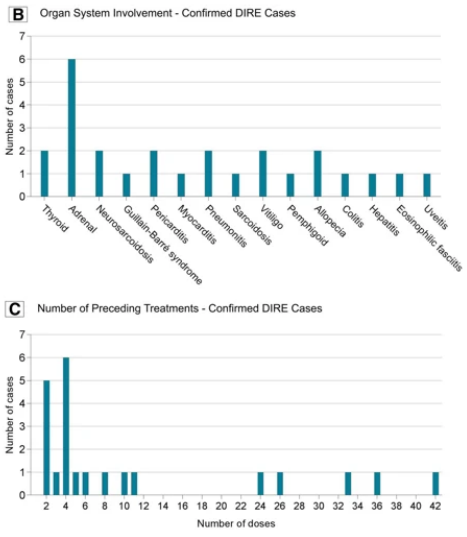
DIRE (Delayed Immune Related Adverse Events)

73

- Lit search: 367 case reports + 194 I-O clinical trials
- DIRE: irAE sequelae newly diagnosed ≥ 90 days following discontinuation of immunotherapy
- 23 confirmed DIRE cases + 16 additional suspected cases



Couey et al, *JITC* 2019

74

Closing remarks

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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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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 (DIRE), even long after the treatment is done.

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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
- National Cancer Institute. Division of Cancer Treatment and Diagnosis. https://ctep.cancer.gov/default.htm
- AIM Immuno-Oncology Essentials. https://aimwithimmunotherapy.org/
- Yan et al. Journal of Oncology Practice. Immuno-Oncology Essentials: Applications in Clinical Scenarios. Vol. 16, No. 2_suppl, February 1, 2020

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Thank you

Appointments for the Complex Skin Cancer Program:

984-974-8289

984-974-0000

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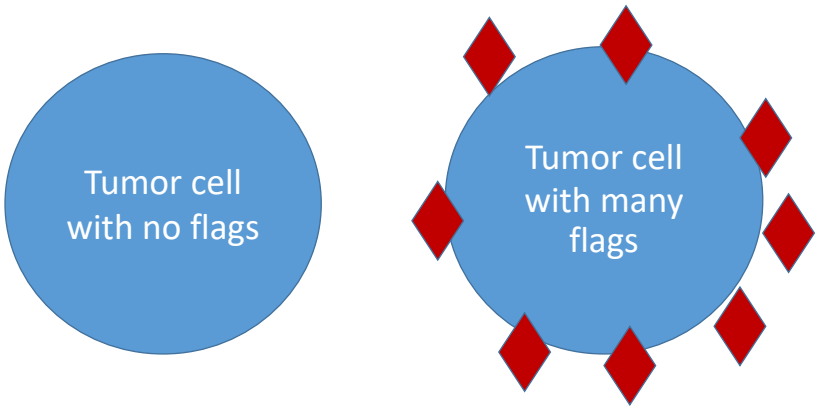
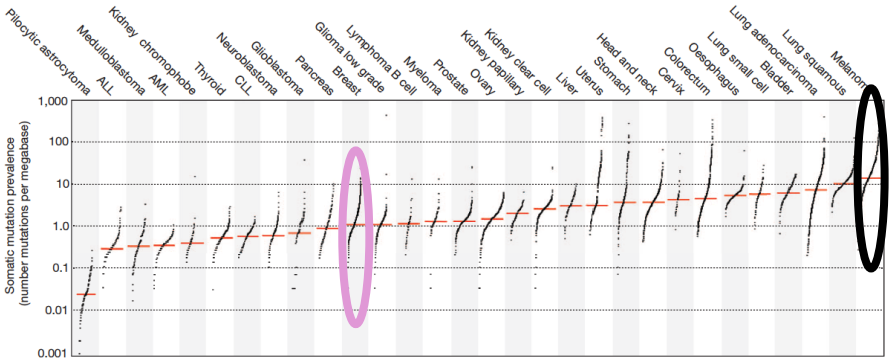
Key Concept #1: Some cancers look very foreign to the immune system so they can be seen more easily.



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

80

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



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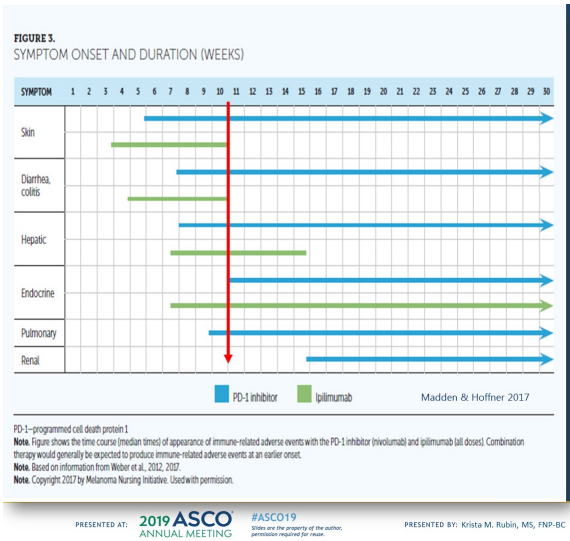
81



Kinetics: Onset and duration

Presented By Krista Rubin at 2019 ASCO Annual Meeting

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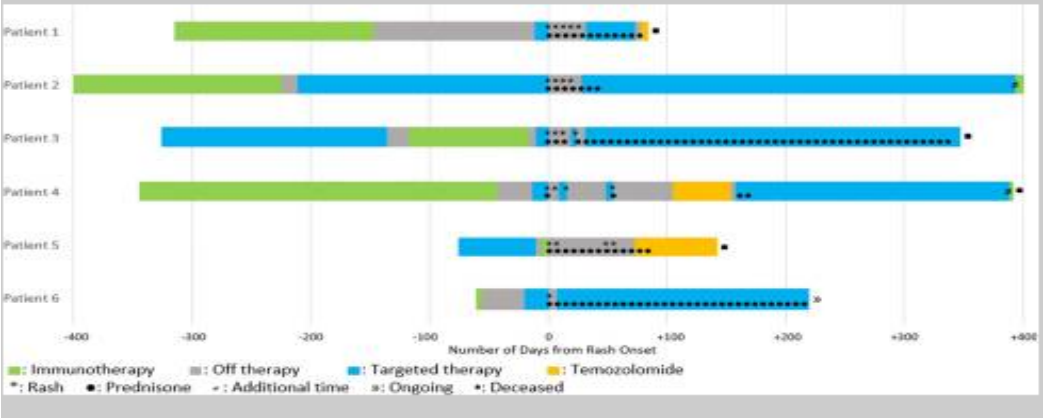
Cutaneous adverse reactions in B-RAF positive metastatic melanoma following sequential treatment with B-RAF/MEK inhibitors and immune checkpoint blockade or vice versa



Nagash J Immunother Cancer. 2019; 7: 4.

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Mary King, *Operational Coordinator*
Veneranda Obure, *A/V Support Engineer*
Jon Powell, PhD, *Continuing Education Specialist*

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CANCER TREATMENT IN NORTH CAROLINA **PATIENT CENTERED CARE**

Live Lecture

April 8

12:00 PM

Use of Opioids in Patients with Cancer in North Carolina

Amy M. Goetzinger, PhD

CANCER TREATMENT IN NORTH CAROLINA **RESEARCH TO PRACTICE**

Live Lecture

April 22

12:00 PM

Head and Neck Cancer Management in North Carolina: Updates for 2020

Siddharth Sheth, DO, MPH

For a complete listing and details on coming events visit:

www.unccn.org/events

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SELF-PACED, ONLINE COURSES

CANCER TREATMENT IN NORTH CAROLINA **PATIENT CENTERED CARE**

Self-Paced, Online Course

The Role of Patient Support Networks in Cancer Outcomes

Justin Yopp, PhD

CANCER TREATMENT IN NORTH CAROLINA **RESEARCH TO PRACTICE**

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Paola A. Gehrig, MD

Prostate Cancer Management in North Carolina: Updates for 2020

Young Whang, MD, PhD

Today's lecture will be available in *May 2020* as a ***FREE***, Self-Paced, Online Course

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