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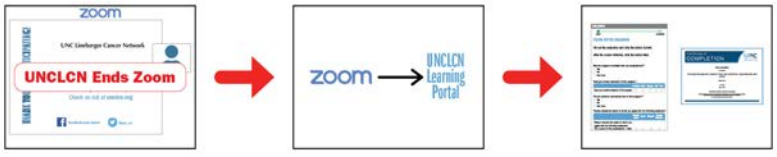

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Our Presenter

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 medical education in the United States. She has been part of the Complex Skin Cancer Program at UNC. Melanoma led way for treatments with immune check point inhibitors.

The focus of her talk is on the side effects of these agents. She has given this talk to us before but it remains and essential part of oncology education, so we are pleased to have her speak again.

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Our Presenter

9

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1. IF you have toddlers in your life, then packs of applesauce and yogurt are treats. You can make the package tops into art such as mobiles, helicopters, and bugs.

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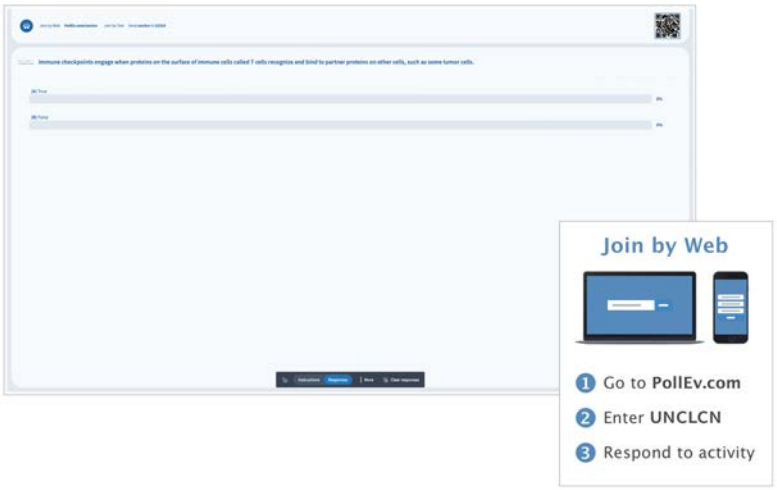
Sample Poll Everywhere Question



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Immune (check point) Related Adverse Events

Frances Collichio
Professor of Medicine
frances_collichio@med.unc.edu
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
  - Combination therapy and increased toxicity
  - Delayed Immune Related Events (DIRE)
- Rechallenge
- Test your knowledge

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Buckets of systemic cancer treatment

Chemotherapy

Antibody drug conjugates

Hormone therapy

Target Therapy

Biologics

Immune therapy

Immune check point
Interleukin 2
Interferon
CAR-T, BiTE

Oncolytic viral 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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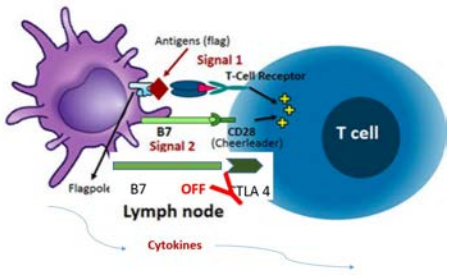
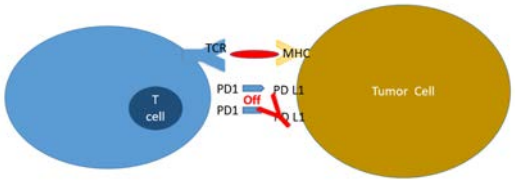
Mechanism of the check point and inhibitors

Away from the tumor



At the tumor



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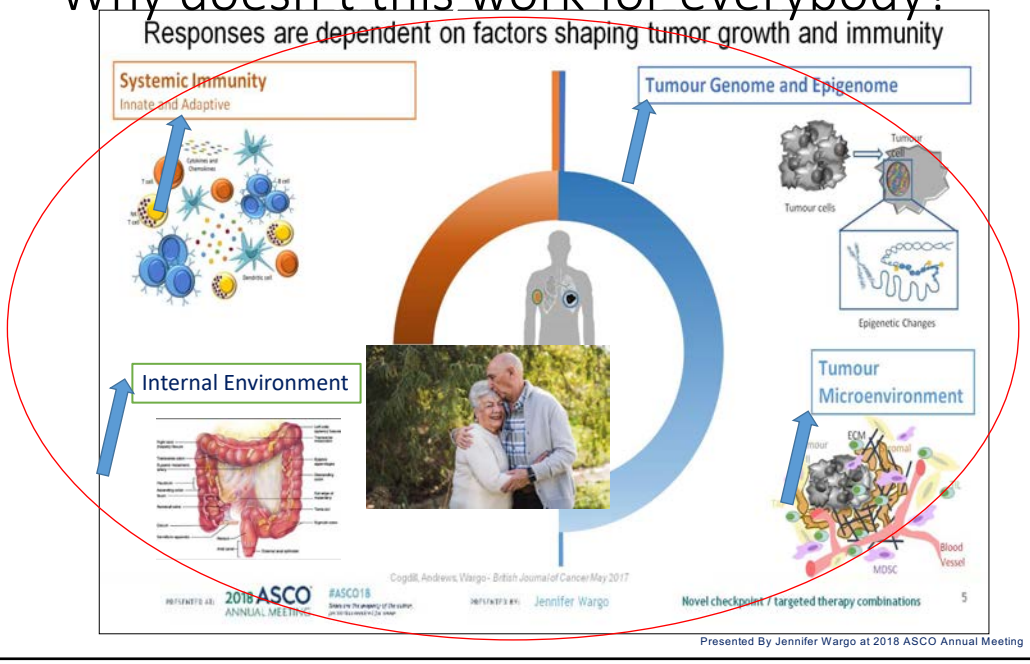
Why doesn't this work for everybody?



Presented By Jennifer Wargo at 2018 ASCO Annual Meeting

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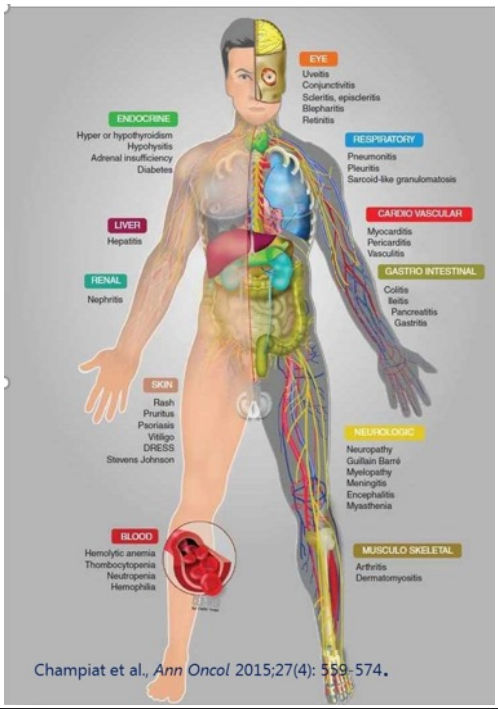

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These are the events we think about

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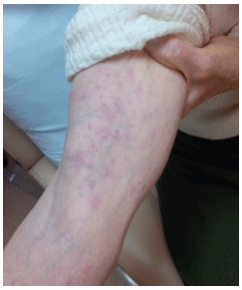
Case 1

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 itchy rash. It shows up as patches on his arms and legs. 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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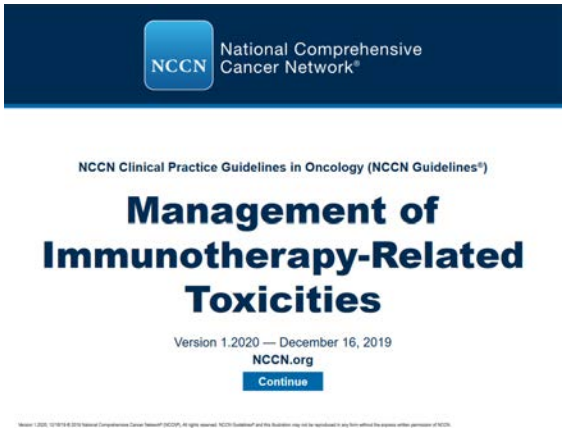
KEY CONCEPT #2: Use a consistent tool to manage these side effects.



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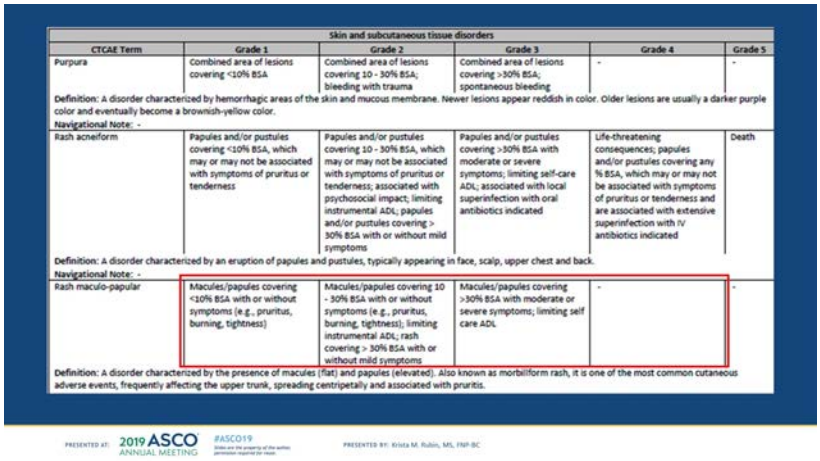
CTAE for Rash



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.					

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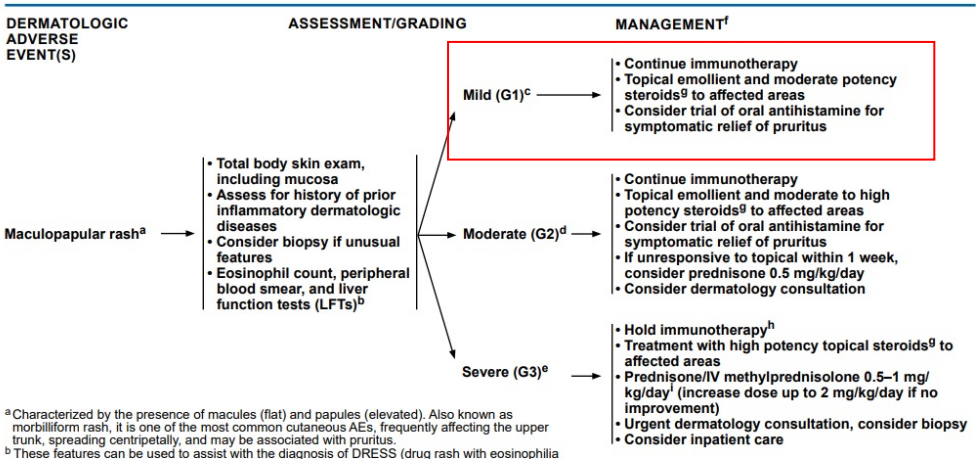
NCCN guidelines for Rash



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Case 2

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 the last 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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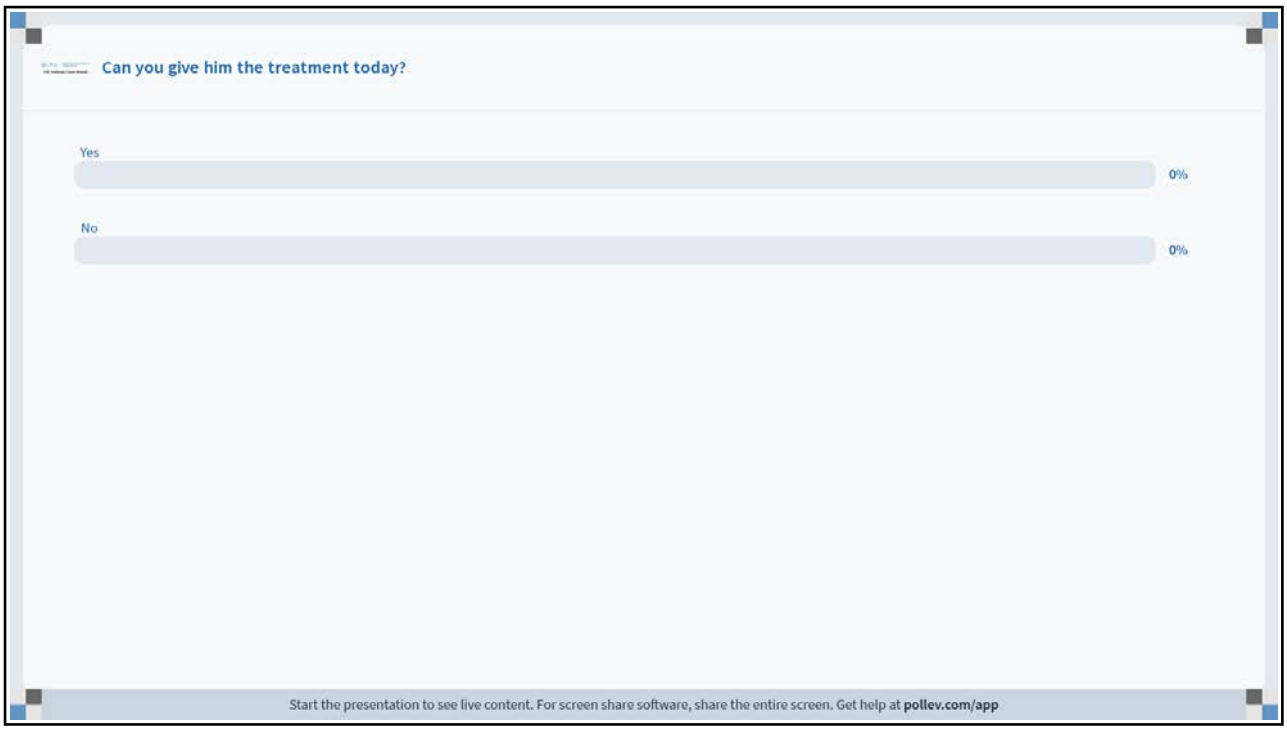

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The patient received his treatment and two days later he called with to report 7 watery bowel movements in the last 24 hours. He was told to come to clinic for care and on the drive over, he felt feverish and had chills.

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

34

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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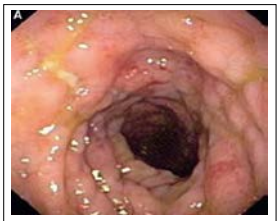
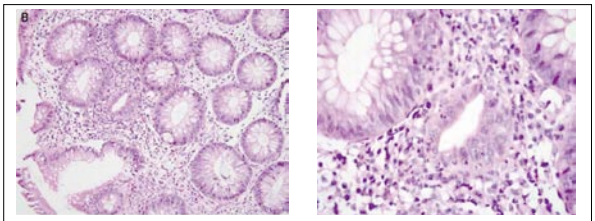
Diarrhea/Colitis

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 cellular infiltrates in the crypt epithelium (right)

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

36

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What is the management plan?

- Management
  - NPO, advance diet
  - High dose steroids (IV)
  - If no improvement after 1-2 days:
    - Infliximab [1-2 infusions] or vedolizumab [3 infusions]

Zou Immunother Cancer 2021
https://pubmed.ncbi.nlm.nih.gov/34789551/

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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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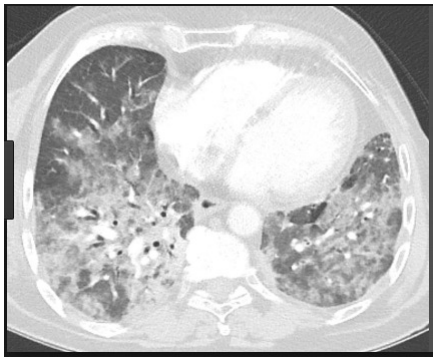
Case 3

A 48-year-old woman with COPD was diagnosed with metastatic adenocarcinoma of the lung, no targetable mutations, PDL1 greater than 50%. She starts treatment with atezolizumab and one week after the second cycle, is seen in the Emergency Department for shortness of breath. The patient is in respiratory distress with room air 02 Sat of 85%, BP of 135/80, a Temperature of 101F. A cross section of her CT scan is shown.



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Pneumonitis

- Grade 3 occurs in 1.6 % of pts with melanoma, 4% with lung cancer
- Risk factors still need to be elucidated but pts w lung ca and underlying COPD +- smoking are at increased risk.
- Variable onset 2-12 months
- 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

Nishino. Jama Oncol 2016

41

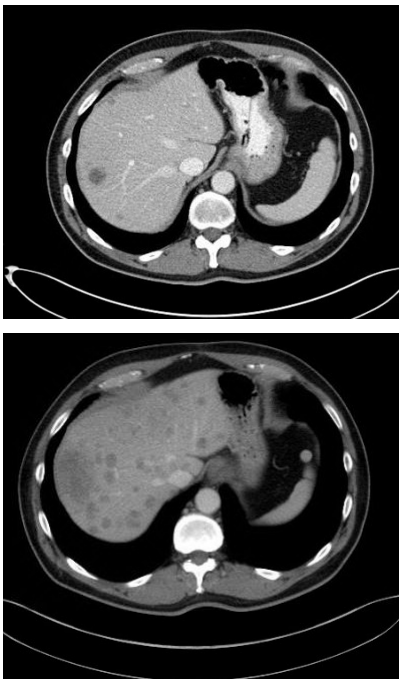
NCCN guidelines for grade 3/4 pneumonitis

ASSESSMENT/ GRADING	MANAGEMENT[f]
Severe (G3–4)[e] pneumonitis[a] →	• Discontinue immunotherapy[g] • Inpatient care • Pulmonary and infectious disease consultation • Minimally invasive evaluation ▸ Infectious workup: ▸ Consider that the patient may be immunocompromised ◊ Nasal swab for potential viral pathogens[j] ◊ Sputum culture (including bacterial, fungal, and AFB), blood culture, and urine antigen test (pneumococcus, legionella) ◊ Consider cardiac evaluation to exclude cardiac causes for clinical presentation • Invasive evaluation ▸ Bronchoscopy with BAL (send for institutional immunocompromised panel[k]) if feasible to rule out infection and malignant lung infiltration and consider transbronchial lung biopsy if feasible and clinically indicated • Consider empiric broad-spectrum antibiotics (including coverage for atypical pathogens) if infection has not yet been fully excluded • IV methylprednisolone 1–2 mg/kg/day. Assess response within 48 hours and plan taper over ≥6 weeks[f] • Consider adding any of the following if no improvement after 48 hours[o]: ▸ IV infliximab[p] 5 mg/kg, a second dose may be repeated 14 days later at the discretion of the treating provider ▸ IVIG[q] ▸ Mycophenolate mofetil 1–1.5 g BID then taper in consultation with pulmonary service[r]

42

Case 4

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 or diarrhea. WBC is 12.5 with a normal differential. AST 340, Alt 410, Alk phos 167, Total Bili 0.5, Protein 6.2, Albumin 3.8. The top CT is baseline, the bottom is current.



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What is the most likely diagnosis?

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

1. Advise against alcohol
2. Check for other liver toxins (Hold statins)
3. Check hepatic function, INR, bili
4. Check for Hep A, B, C
5. Consider other viral infections in immunocompromised hosts
6. US doppler or CT esp if alkphos or direct bili are high

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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.
- Mycophenolate mofetil (MMF) (500–1000 mg p.o. twice a day) or azathioprine (1–2 mg/kg/day).

Likhitsup Curr Opin Gastroenterol 2024 Feb 16

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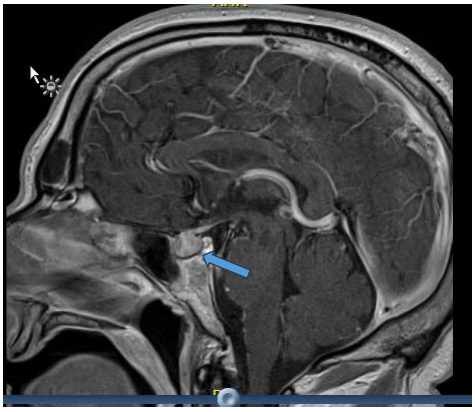
Case 5

A 52-year-old with advanced renal cell cancer on ipilimumab and nivolumab presents with headache and peripheral vision loss 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. Normal serum labs



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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
  - Check a morning cortisol
  - Low ACTH, Low TSH (and low T4).
- Concern
  - Adrenal Crisis
  - Adrenal insufficiency associated with hypophysitis is usually permanent

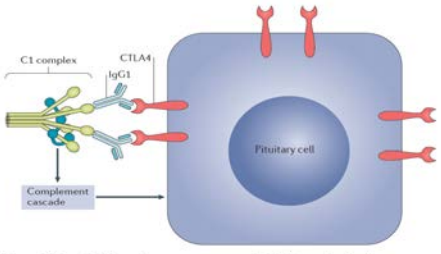

Figure 2 | **Normal pituitary tissues express ectopic CTLA4 protein.** Binding to cytotoxic T-lymphocyte antigen 4 (CTLA4) autoantibodies or ipilimumab IgG1 to native CTLA4 proteins on normal pituitary tissue is thought to lead to activation of the classic complement pathway.

Tsoli Cancer Manag Res 2020

48

Case 6

- A 64-year-old man on pembrolizumab for lung cancer presents for his third cycle. He is an avid jogger, but lately he cannot run because he is “shaky”. His exam, CBC and CMP are normal. You send him to infusion and while waiting for the chair, the thyroid labs return.

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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

- Consider an endocrine consult
- Beta blockers for tremor or tachycardia
- Consider Graves disease in persistent cases: + Anti-thyroperoxidase antibodies and anti-thyroglobulin antibodies, Radioactive iodine uptake

51

Rheumatologic

- Inflammatory arthritis
- Myositis
- Polymyalgia Rheumatica
- Vasculitis

52

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

54

Case 7

54-year-old patient with NSSLC metastatic to liver on carboplatin, pemetrexate and pembrolizumab 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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The most likely diagnosis is:

Mucositis 0%

Thrush 0%

Metastasis to the parotid gland 0%

Sicca Syndrome 0%

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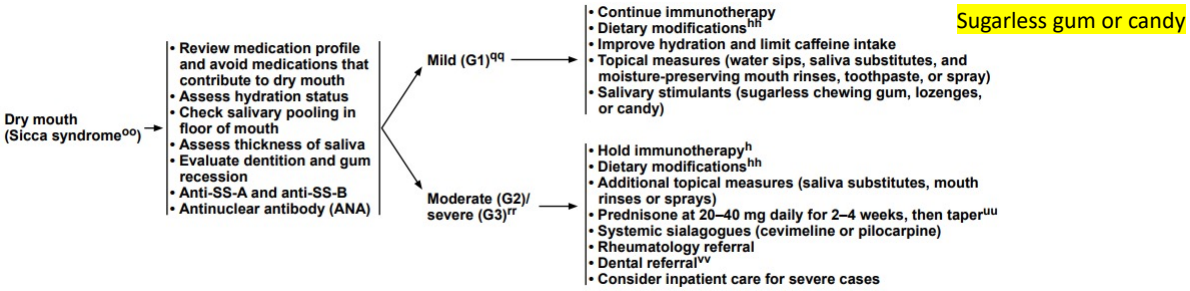
Sicca Syndrome



Sugarless gum or candy

57

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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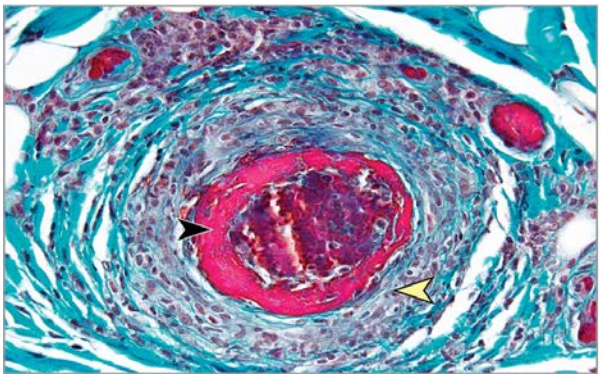
Neurotoxicity: Peripheral Neuropathy

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, nervous system, and pancreas (type 1 diabetes)

60

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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Case 7: Don't forget this one in informed consent!

A 54- year -old with triple negative metastatic breast cancer and CPS score greater than 10, is treated with paclitaxel and pembrolizumab for two months when she is brought to the ED with acute onset confusion. Blood glucose is 350 mg/dl, serum bicarbonate is 14. A stat non contrast CT scan of the head is normal. Tox screen and alcohol level are normal. The arterial pH is 7.29.

1. Sepsis
2. Diabetic ketoacidosis
3. Aldehyde toxicity

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Type 1 Diabetes

- Incidence from PD1 inhibitors: 0.1-0.86%
  - Majority with PD1 inhibitors or in combination
- Acute onset, and often with DKA
- Rx DKA per institutional standard
- Low C peptide = Type 1 DM (destruction of the beta cells)
  - Anti-GAD and HLA DR4 are not helpful for the dx
- Permanent
- Rx with insulin

Chen, X et al. Diabetes Care. 2022
Prelato V Lo, Reviews in Endocrine and Metabolic Disorders 2020

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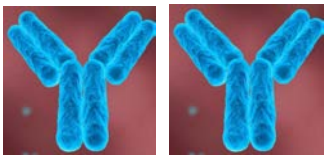
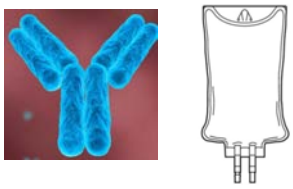
KEY CONCEPT #5: Combination therapy has more side effects than either therapy alone.

Dual check point inhibitors

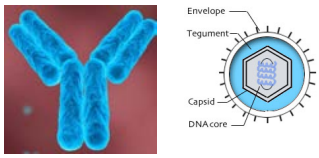


Check point inhibitor and chemo

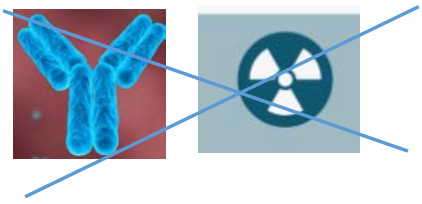


Checkpoint and Target Rx

Check point inhibitor and oncolytic virus



But not check point inhibitor and radiation.



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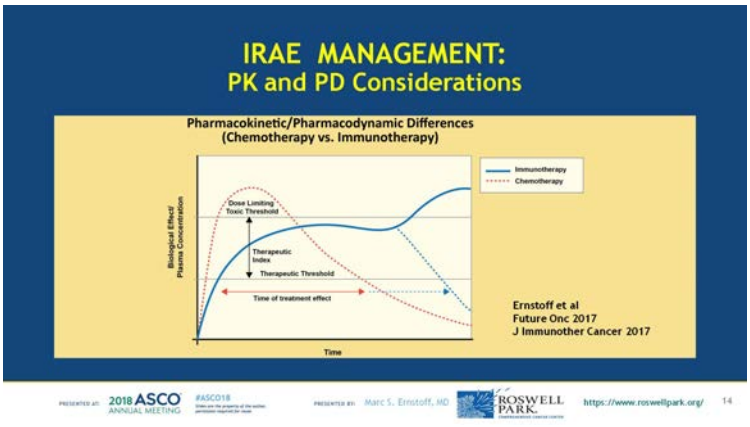
Chemo versus ICIs

- Chemotherapy side effects can be severe, but they can be more predictable than check point inhibitors.
- Immune check point inhibitors side effects can be unpredictable, persistent, recurrent



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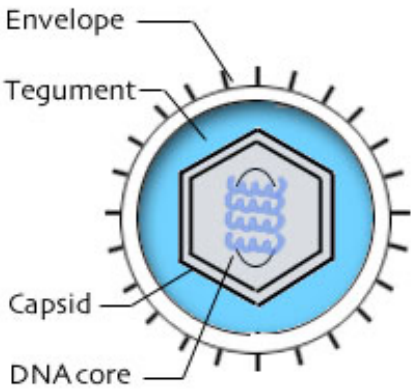
HSV Structure/ Talimogene Laheparepvec



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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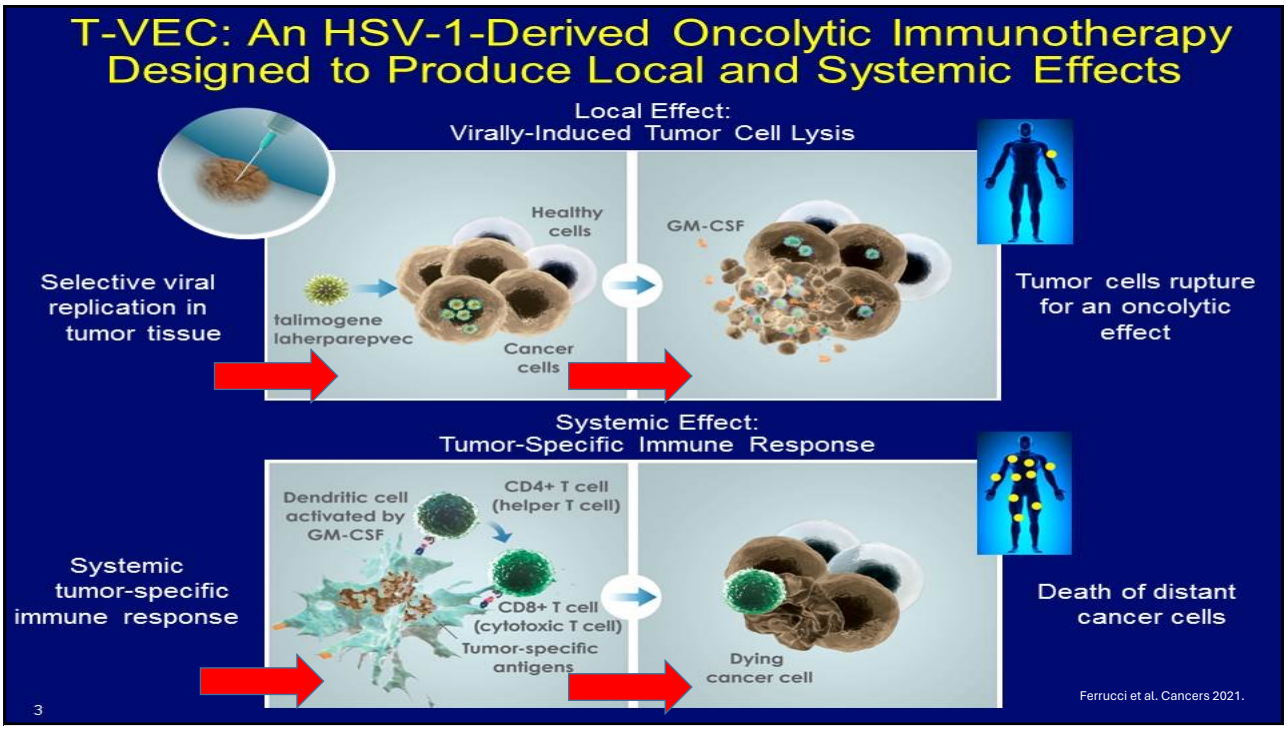

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Safety

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

- Side effects are of each agent

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Key Concept #6: Delayed Immune Related Adverse Events, DIRE

- 82-year-old treated with an oncolytic virus and cemiplimab for locally advanced, non resectable SCC of the scalp. Three years into maintenance cemiplimab she has increased fatigue and abnormal liver enzymes. She drinks one glass of wine a night and has acetaminophen prn.

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DIRE

- Greater than 12 months on immune check point therapy
- Multiple case reports
- Endocrine, skin and lung are most common
- Liver as well

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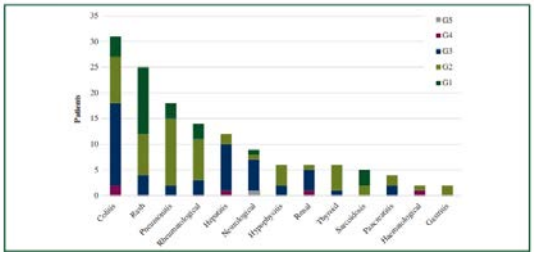
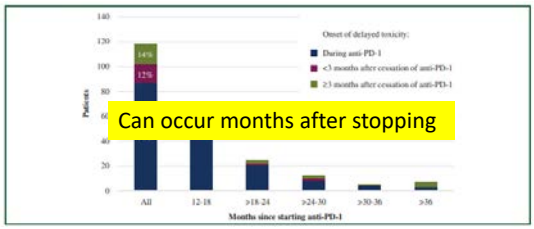
DIRE; study in melanoma patients.

Type of delayed immune Rx side effect



Timing of side effect



Can occur months after stopping

Owen CN et al. Annals Oncology. Jul;32(7):917-925. 2021

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KEY CONCEPT #7: Patients with underlying autoimmune disease have an increased chance of IrAEs

Underlying autoimmune disease is worse 1/3 of the time.

Increased risk of high grade irAEs in 2/3s.

Weigh the benefit versus the risk.

BMC Rheumatol. 2022 Nov 8;6(1):64

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Rechallenge

- A talk of its own
- Risk/Benefit with the patient
- If dual agent, eg ipi/nivo, can resume the PD 1 inhibitor upon recovery
- Endocrinopathies, replace hormones
- Low grade eye, continue steroid drops
- Severe Aes, neuro/heart---NO

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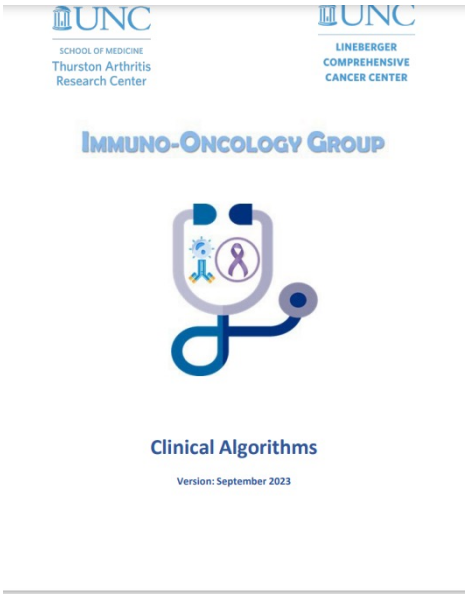
KEY CONCEPT #8

- ICI management requires a team approach.
- UNC has a multidisciplinary team for this. It is led by Dr Rumey Ishizawar



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Closing remarks

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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 the disease, the patient, sequence, combination, new agents, pre-existing autoimmune disease.
- Don't forget the rare but important risks to the CNS, heart and pancreas.
- IrAES can be permanent and delayed (DIRE).
- For prescribers, discuss risk/benefit especially in specific context (Goals of care) and populations (patients withs autoimmune disease).

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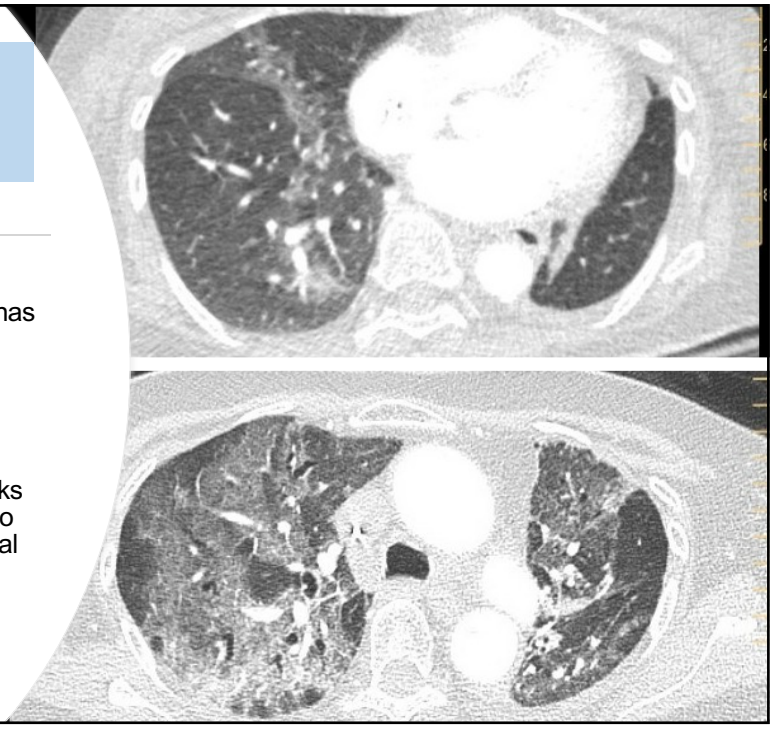
Test your knowledge

A 71- year-old female who had never smoked, is on treatment for hepatitis B, has metastatic adenocarcinoma of the lung, *KRAS G12*A mutant, PDL1 10%, treated with carboplatin/pemetrexate has new disease in the celiac nodes and bones after two years of treatment.

Pembrolizumab was stopped and 4 weeks later she is started on nab-paclitaxel. Two weeks later she is admitted to the hospital for hypoxia. The CT is shown. She is placed on high flow oxygen.



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What is the differential diagnosis

1. Immune check point inhibitor pneumonitis
2. Chemotherapy induced pneumonitis
3. SARs-COV-2 pneumonia
4. Atypical bacterial infection
5. Fungal infection

Hiba. Radiol Case Rep 2022
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9411188/

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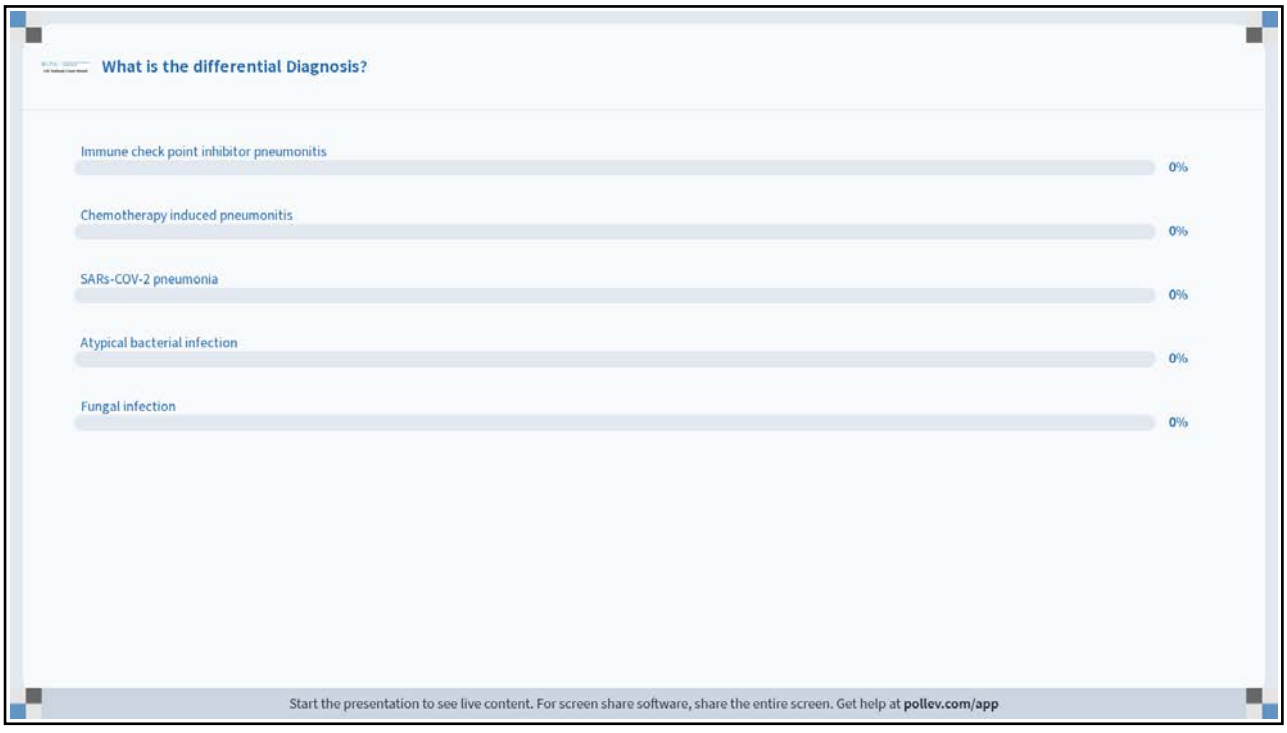

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The song ***Back Rhodes*** written and performed by **Don Poe**

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