Handling the Most Common Toxicities from IO: Endocrinopathies, Pneumonitis, Skin Rash/Pruritus, and Adrenal Insufficiency

Puerto Rico Winter Cancer Symposium

Jeanelle King, PA-C
Sylvester Comprehensive Cancer Center
Miami, FL

Disclosures

- I have received honoraria from Novartis, Array Biopharma, and Genentech
- I *will not* be discussing non-FDA approved indications during my presentation

Pre-test Question

72 year old man with metastatic NSCLC and COPD coming in to restart maintenance atezolizumab and bevacizumab after completing course of steroids for pneumonitis. He complains of overwhelming fatigue and general malaise. His vitals are: BP-74/56, P-98, RR-18, T-99.2F.

Based on his symptoms, what is your first course of action?

A. Resume prednisone at 40 mg

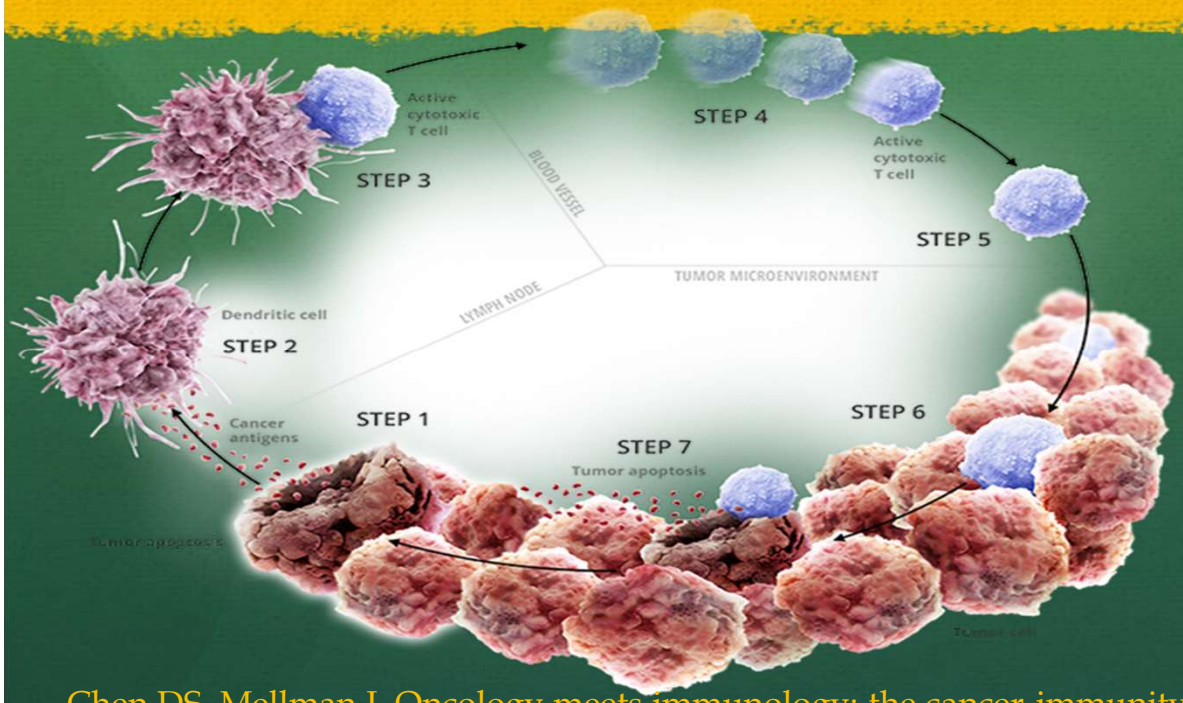
B. Give Rx for Medrol dose pack

C. Start IV methylprednisolone in clinic

Objectives

- Improve the early recognition, education and management of immune-related side effects in cancer immunotherapy patients
- Identify strategies for the management of toxicities

Cancer Immunity Cycle



The Cancer Immunity Cycle*

1. ACTIVATION of T cells by antigen-presenting dendritic cells

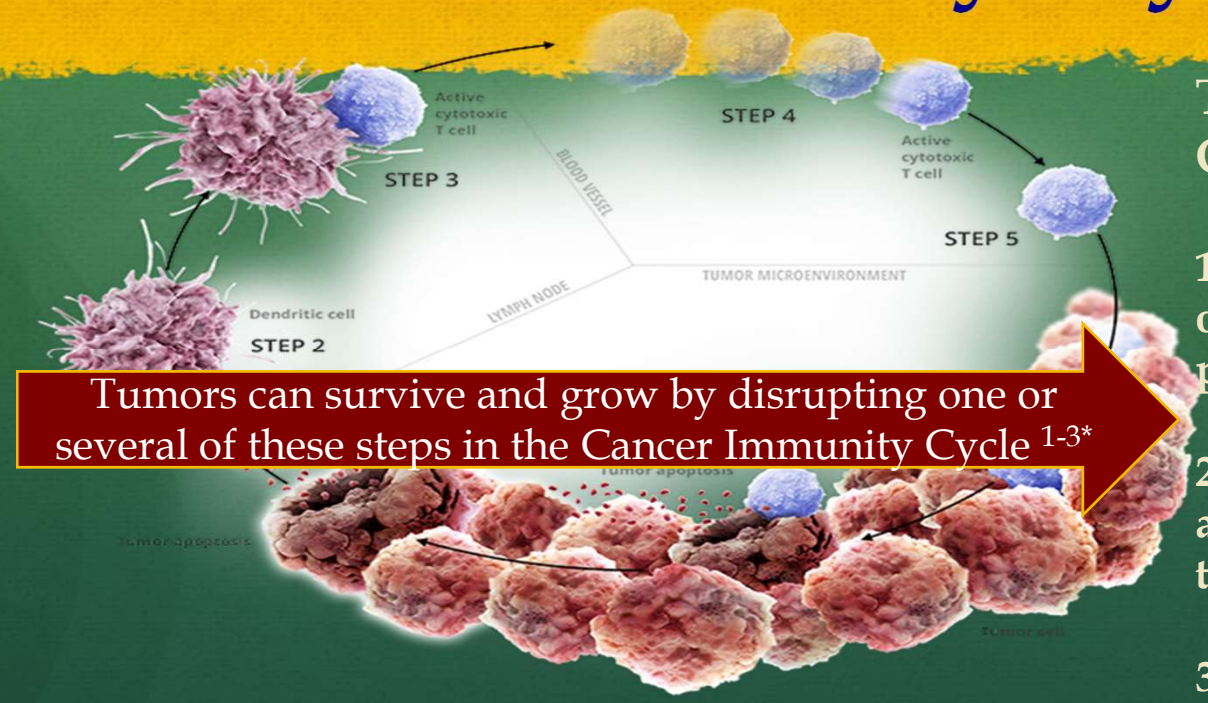
2. INFILTRATION of activated T cells into the tumor microenvironment

3. ELIMINATION of tumor cells by activated T cells

Chen DS, Mellman I. Oncology meets immunology: the cancer-immunity cycle. *Immunity*. 2013;39:1-10. PMID: 23890059

*Adapted from Genentech *Tecentriq*

Cancer Immunity Cycle



Tumors can survive and grow by disrupting one or several of these steps in the Cancer Immunity Cycle [1-3*]

The Cancer Immunity Cycle

1. ACTIVATION of cells by antigen-presenting dendritic cells

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3. ELIMINATION of tumor cells by activated T cells

*Chen DS, Mellman I. *Immunity*. 2013;39(1):1-10. **2.** Bhatia A, Kumar Y. *Cancer Microenviron*. 2011;4(2):209-217. **3.** Melero I et al. *Cancer Discov*. 2014;4(5):552-526.
*Adapted from Genentech *Tecentriq*

Checkpoint Inhibition

Checkpoint inhibition

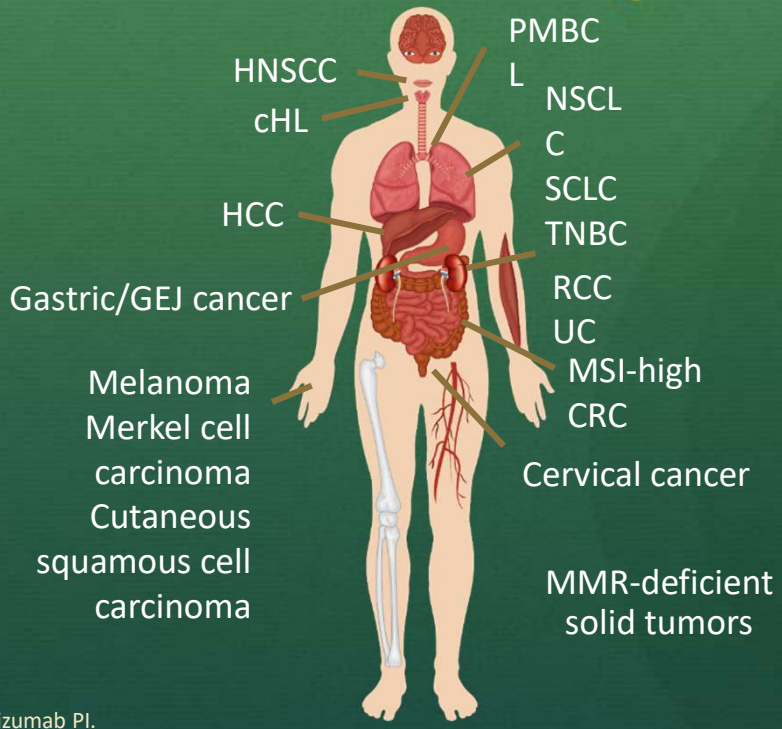
Immune checkpoints refer to inhibitory pathways hardwired into the immune system that are crucial for maintaining self tolerance and modulating the duration and amplitude of physiological immune responses in peripheral tissues in order to minimize collateral tissue damage.

Tumors recruit immune-checkpoint pathways as mechanisms of immune resistance, particularly against T cells that are specific for tumor antigens.

Pardoll, DM. *Nature Reviews Cancer* 12, 252-264

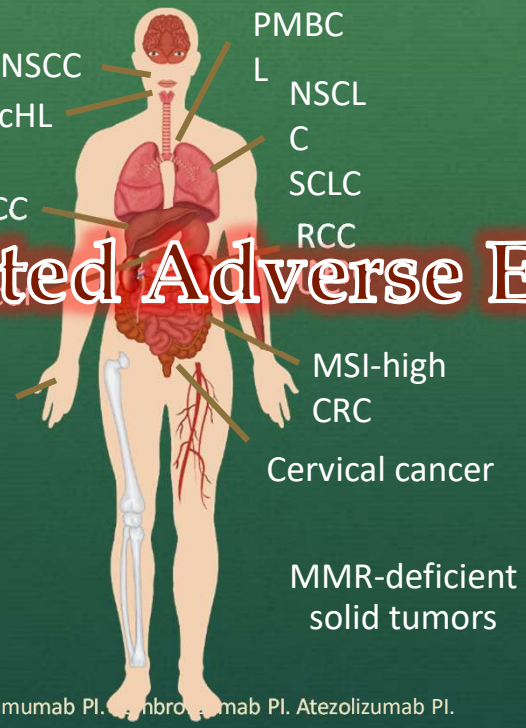
Immune Checkpoint Inhibitors FDA Approved in Multiple Cancers as of April 2019

- Number of patients treated with ICIs is growing
  - ICIs now approved as monotherapy, in combination with other ICIs, and in combination with chemotherapy
  - ICIs historically used in later-line metastatic disease
    - Moving into earlier lines of therapy and earlier stages of disease (eg, adjuvant tx for melanoma; tx for stage III NSCLC)
  - Patients may receive ICI therapy for years, as optimal duration is unknown
    - Initial strategy was continuing ICI until progression/toxicity or to 2 years



Michot. Eur J Cancer. 2016;54:139. Nivolumab PI. Ipilimumab PI. Pembrolizumab PI. Atezolizumab PI. Durvalumab PI. Avelumab PI. Cemiplimab-rwlc PI.

Immune Checkpoint Inhibitors FDA Approved in Multiple Cancers as of April 2019

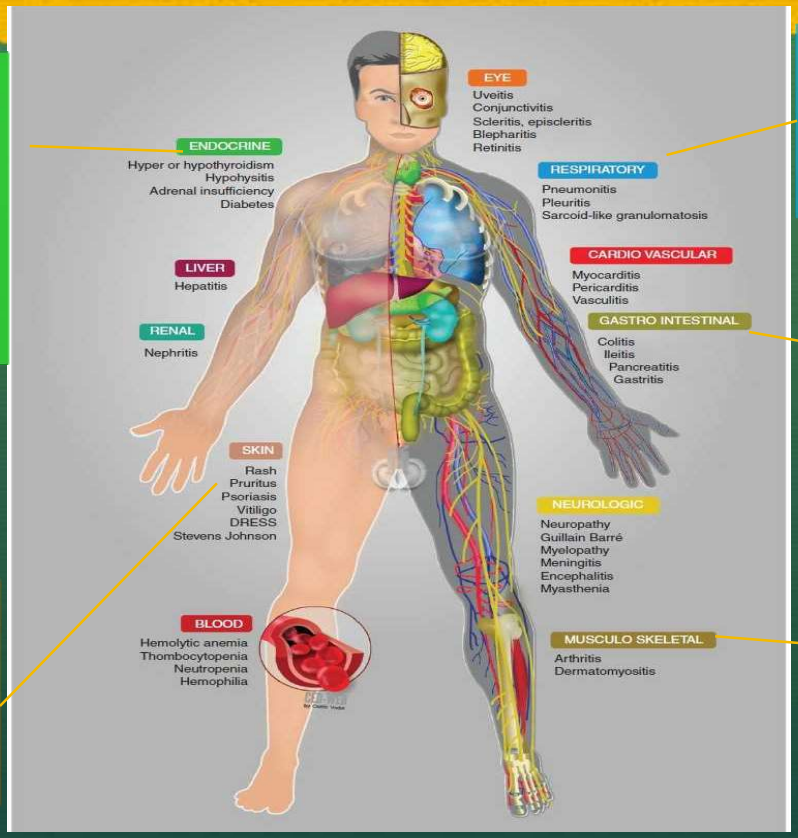


Immune-related Adverse Events (irAEs)

Michot. Eur J Cancer. 2016;54:139. Nivolumab PI. Ipilimumab PI. [illegible]mab PI. Atezolizumab PI. Durvalumab PI. Avelumab PI. Cemiplimab-rwlc PI.

Toxicity Spectrum: Immune-Related Adverse Events

Hypothyroid/Hyperthyroid
Hypophysitis
Adrenal insufficiency
Diabetes



Shortness of breath
Dyspnea on exertion
Cough

Colitis
Pancreatitis

Maculopapular rash
Pruritus
DRESS
Vitiligo (positive factor)

Arthritis

Guidelines

- ESMO
- SITC
- ASCO
- NCCN

Presented By Julie Brahmer at 2018 ASCO Annual Meeting

Most Common immune-related AEs

Affected Organ(s)	CTLA-4 Inhibitors	PD-1/PD-L1 Inhibitors
Skin		
Rash	24%	15%
Itching	25%-35%	13%-20%
Gastrointestinal Tract		
Diarrhea	27%-54%	Very low
Colitis	8%-22%	Very low
Lungs		
Cough/breathlessness	Very low	20%-40%
Pneumonitis	Very low	2%-4%
Liver	5%-10%	5%-10%
Endocrine Organs		
Thyroid effects	1%-5%	5%-10%
Hypophysitis	1%	Very rare

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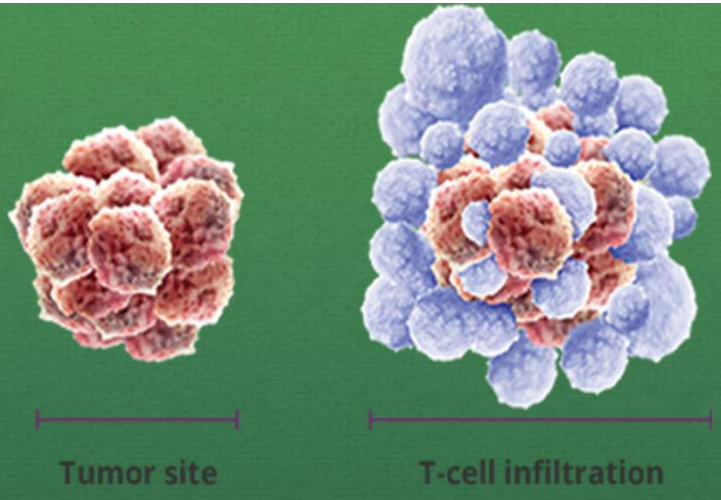
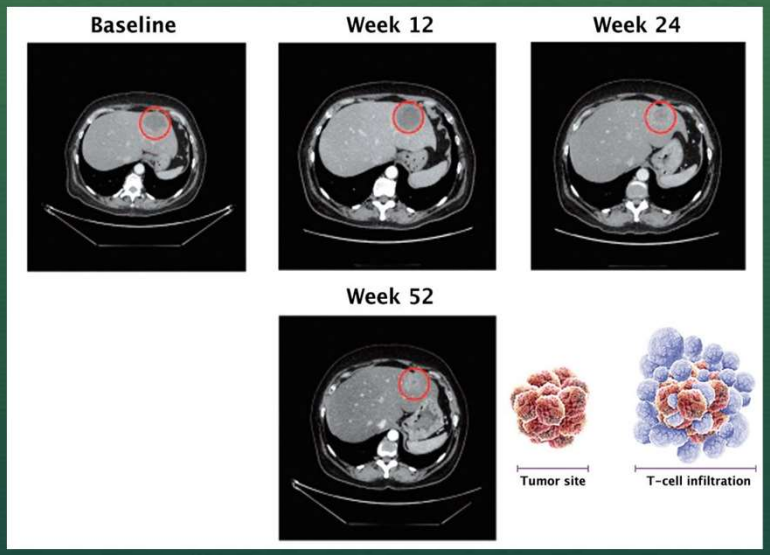
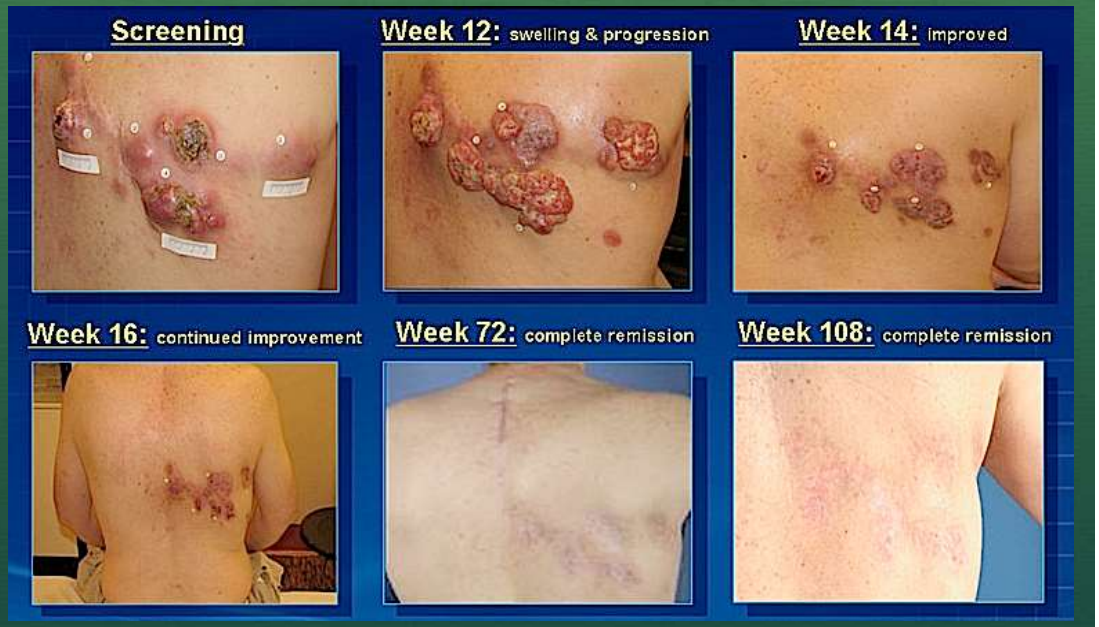
Inflammatory AEs from immunotherapy



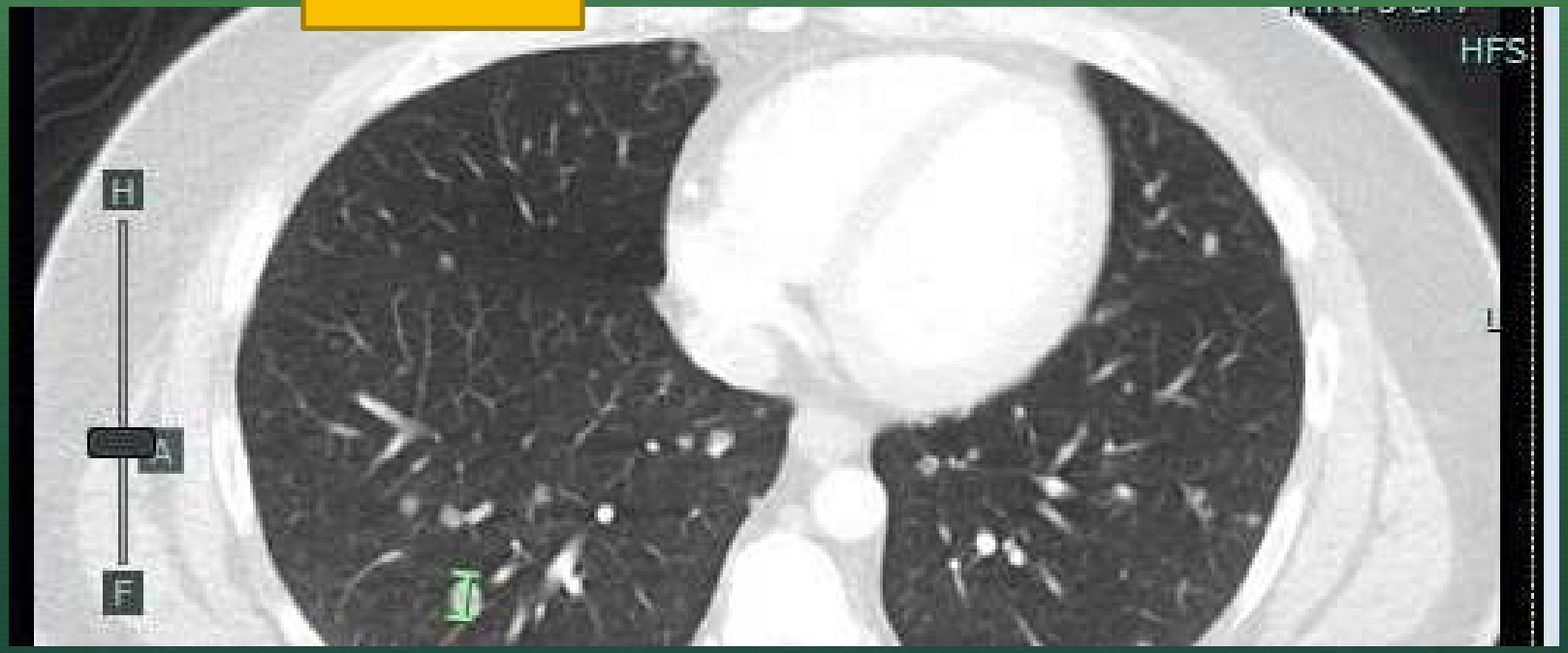




Case 1
Metastatic Melanoma

- 42 y/o male with stage IV metastatic melanoma to lung and skin.
- He was seen as a new patient for treatment options in Dec 2018; he was treatment naïve.

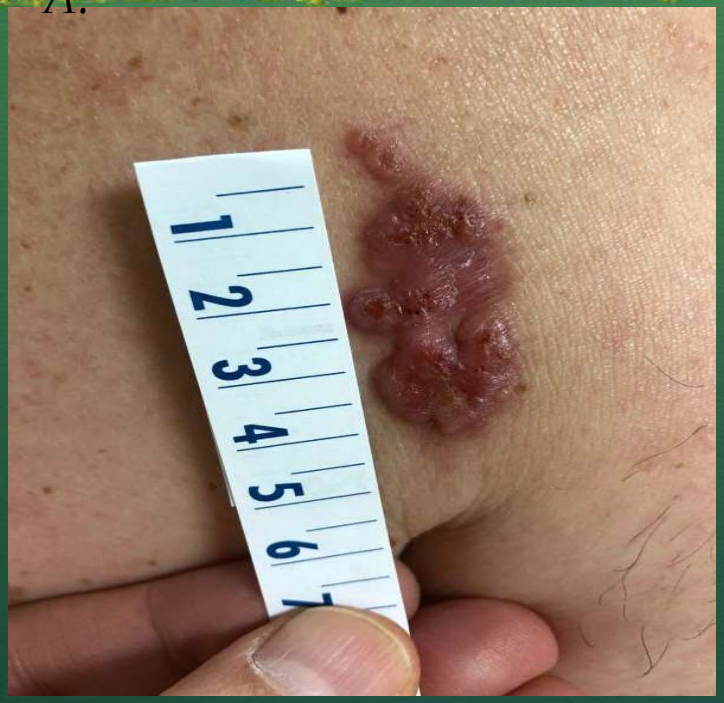
Case 1
Metastatic Melanoma



Pre-treatment CT of chest December 24, 2018

Case 1
Metastatic Melanoma

A.



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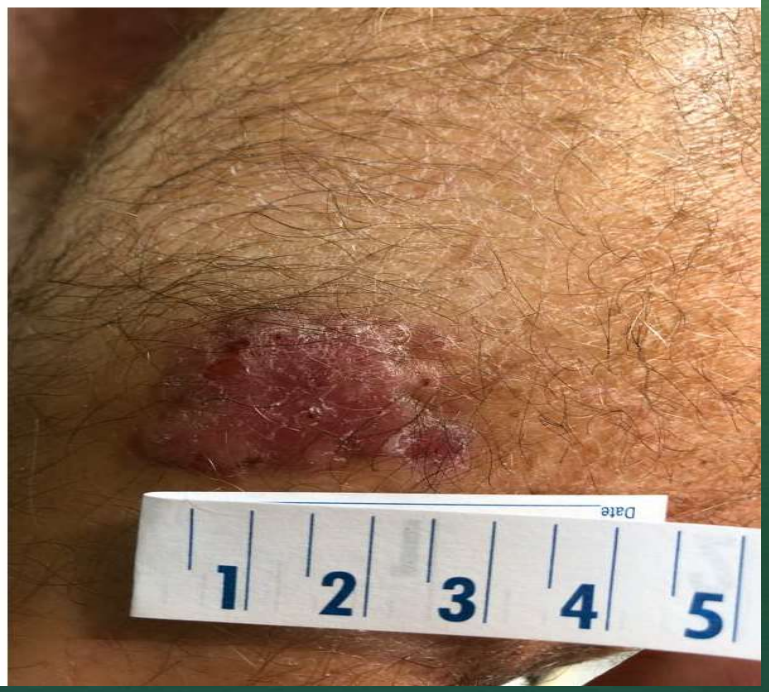


Images from December 18, 2018: A. Right anterior shoulder B. Left elbow

Case 1
Metastatic Melanoma

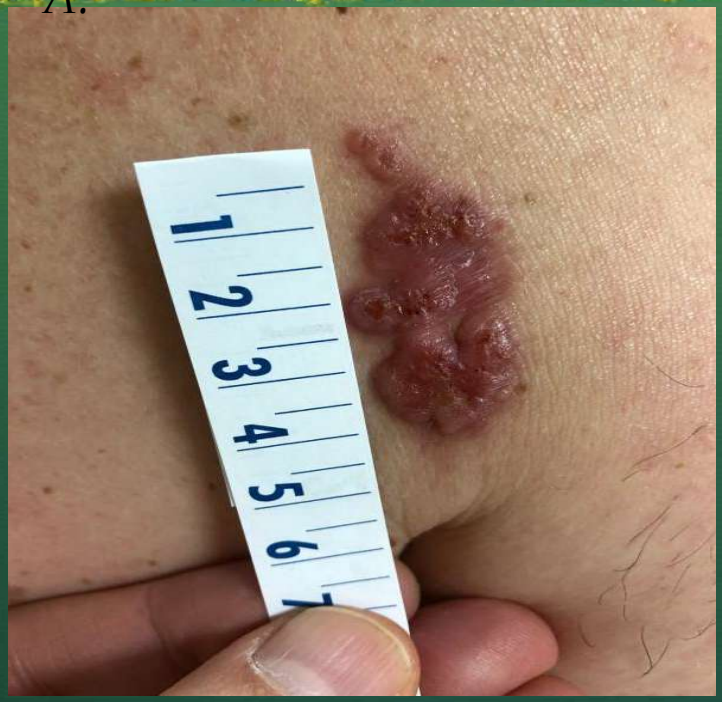
- He began treatment on ipilimumab (1 mg/kg) + nivolumab (3 mg/kg) on December 26, 2018.
- At 7 week FU, the patient reported that the skin lesions were decreasing, but he reported some AEs including: grade 1 arthralgias, grade 1 diarrhea, grade 1 fever (T max 101.5°F) and now **CHEST TIGHTNESS and COUGH.**

Case 1
Metastatic Melanoma

- Differential diagnoses:
  - Immune-mediated pneumonitis
  - Pneumonia
  - Disease progression
- Work-up:
  - Preliminary CXR→ inconclusive
  - Pulse oximetry (rest and after exertion)- 93% and 87%
  - CT Chest *

Case 1
Metastatic Melanoma

A.



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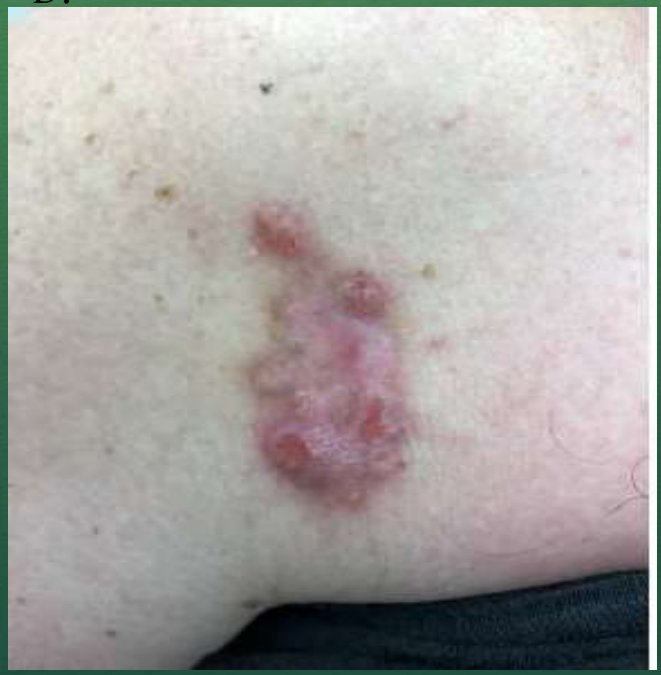
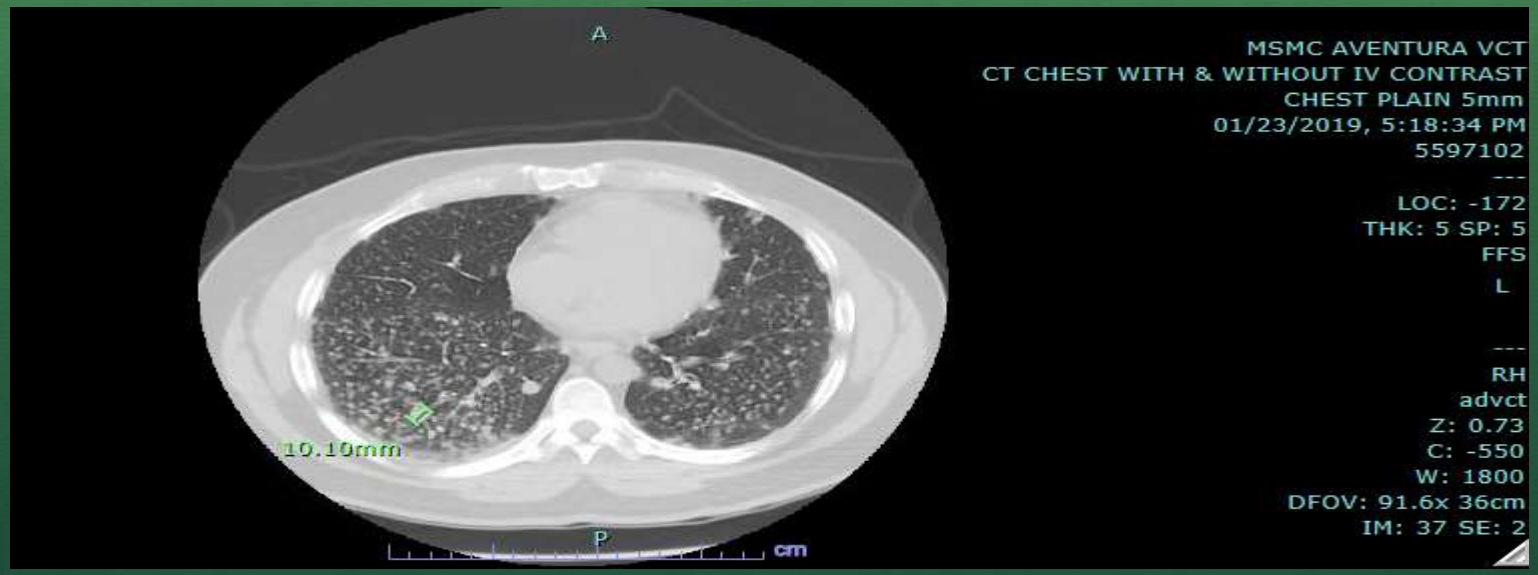


Images of Right ant. Shoulder from December 18, 2018 and January 29, 2019 respectively

Case 1
Metastatic Melanoma



Case 1
Metastatic Melanoma

- Treatment:

  -methylprednisolone 100 mg IV in clinic

  -Sent home with prednisone 80 mg and Zantac

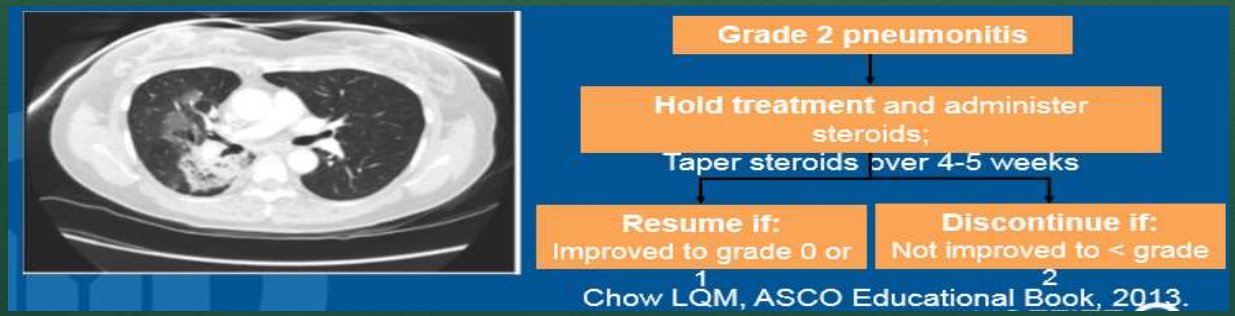
  -Pulmonary evaluation

Case 1
Metastatic Melanoma

- Ipilimumab and nivolumab were discontinued and the patient was started on targeted therapy with a BRAF and MEK inhibitor given the BRAF V600+ melanoma.

Pneumonitis is more common with anti-PD1/CTLA-4 combination therapy

- Important to address respiratory symptoms and check oxygen saturations at each visit
- On any patients where pneumonitis is suspected based on H&P or clinical exam, provider will hold treatment and order a CT scan of the chest.
- Specific management is necessary for grade 2 or greater pneumonitis.



Pulmonary side effects (pneumonitis)

Grade	Symptoms	Management
1	None; based on findings from x-ray examination.	Monitor every two to three days, tests to rule out other causes; checkpoint inhibitor treatment may be delayed.
2	Breathlessness, cough, chest pain.	Antibiotics (if infection suspected), oral corticosteroids if no improvement on antibiotics or no infection found, further tests (including CT scan and bronchoscopy); checkpoint inhibitor treatment will be withheld.
3/4	Worsening symptoms, difficulty breathing.	Hospital admission, intravenous corticosteroids, other stronger immunosuppressive drugs if no improvement; checkpoint inhibitor treatment must be discontinued permanently.

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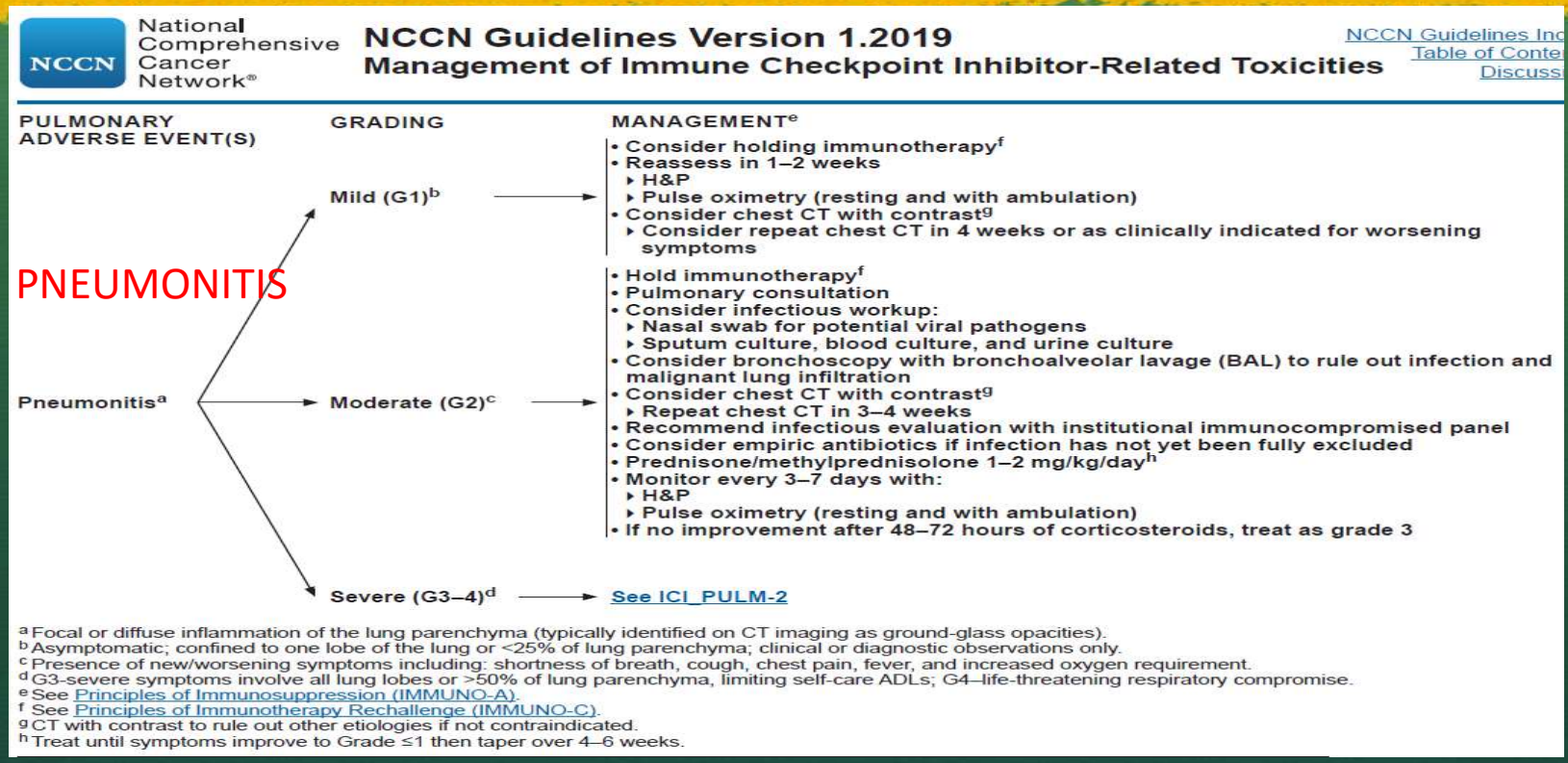
Case 1
Metastatic Melanoma



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PNEUMONITIS

PULMONARY ADVERSE EVENT(S)	GRADING	MANAGEMENT[e]
Pneumonitis[a]	Mild (G1)[b]	• Consider holding immunotherapy[f] • Reassess in 1–2 weeks ▸ H&P ▸ Pulse oximetry (resting and with ambulation) • Consider chest CT with contrast[g] ▸ Consider repeat chest CT in 4 weeks or as clinically indicated for worsening symptoms
	Moderate (G2)[c]	• Hold immunotherapy[f] • Pulmonary consultation • Consider infectious workup: ▸ Nasal swab for potential viral pathogens ▸ Sputum culture, blood culture, and urine culture • Consider bronchoscopy with bronchoalveolar lavage (BAL) to rule out infection and malignant lung infiltration • Consider chest CT with contrast[g] ▸ Repeat chest CT in 3–4 weeks • Recommend infectious evaluation with institutional immunocompromised panel • Consider empiric antibiotics if infection has not yet been fully excluded • Prednisone/methylprednisolone 1–2 mg/kg/day[h] • Monitor every 3–7 days with: ▸ H&P ▸ Pulse oximetry (resting and with ambulation) • If no improvement after 48–72 hours of corticosteroids, treat as grade 3
	Severe (G3–4)[d]	See ICI_PULM-2

[a] Focal or diffuse inflammation of the lung parenchyma (typically identified on CT imaging as ground-glass opacities).
[b] Asymptomatic; confined to one lobe of the lung or <25% of lung parenchyma; clinical or diagnostic observations only.
[c] Presence of new/worsening symptoms including: shortness of breath, cough, chest pain, fever, and increased oxygen requirement.
[d] G3-severe symptoms involve all lung lobes or >50% of lung parenchyma, limiting self-care ADLs; G4–life-threatening respiratory compromise.
[e] See Principles of Immunosuppression (IMMUNO-A).
[f] See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[g] CT with contrast to rule out other etiologies if not contraindicated.
[h] Treat until symptoms improve to Grade ≤1 then taper over 4–6 weeks.

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ASSESSMENT/ GRADING

MANAGEMENT[e]

PNEUMONITIS

Severe (G3–4)[d] pneumonitis[a] →

- **Permanently discontinue immunotherapy[f]**
- **Inpatient care**
- **Infectious workup:**
  - **Consider that patient may be immunocompromised**
  - **Nasal swab for potential viral pathogens**
  - **Sputum culture, blood culture, and urine culture**
- **Pulmonary and infectious disease consultation, consider PFTs**
- **Bronchoscopy with BAL to rule out infection and malignant lung infiltration**
- **Consider empiric antibiotics if infection has not yet been fully excluded**
- **Methylprednisolone 1–2 mg/kg/day. Assess response within 48 hours and plan taper over ≥6 weeks**
- **Consider adding any of the following if no improvement after 48 hours:**
  - **Infliximab 5 mg/kg IV, a second dose may be repeated 14 days later at the discretion of the treating provider**
  - **Mycophenolate mofetil 1–1.5g BID then taper in consultation with pulmonary service**
  - **Intravenous immunoglobulin (IVIG)[i]**

[a] Focal or diffuse inflammation of the lung parenchyma (typically identified on CT imaging as ground-glass opacities).
[d] G3-severe symptoms involve all lung lobes or >50% of lung parenchyma; limiting self-care ADL; G4–life-threatening respiratory compromise.
[e] See Principles of Immunosuppression (IMMUNO-A).
[f] See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[i] Total dosing should be 2 g/kg, administered in divided doses per package insert.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Case 2
Metastatic NSCLC

- 72 year old man with metastatic NSCLC and COPD coming in to restart maintenance atezolizumab and bevacizumab after completing course of steroids for pneumonitis. He complains of overwhelming fatigue and general malaise. His vitals are: BP-74/56, P-98, RR-18, T-99.2F.
- Based on his symptoms, what is your first course of action?

Case 2
Metastatic NSCLC

- Differential diagnoses:
  - Hyper of hypothyroidism
  - Treatment-related fatigue
  - Adrenal insufficiency
- Work-up:
  - STAT cortisol level
  - Thyroid function tests
  - Infectious workup-Blood cultures, CXR, urine culture

Case 2 *Metastatic NSCLC*

Parameter	Patient Value	Reference Range
Na, mEq/L	130 ↓	135-145
TSH, µU/mL	2.9	0.5-5.0
Free T4, ng/dL	0.8 ↓	0.9-2.3
AM cortisol, mcg/dL	0.6 ↓	5-25

ENDOCRINE ADVERSE EVENT(S)	ASSESSMENT/GRADING	MANAGEMENT[n,o]
Primary adrenal insufficiency[m]	• Evaluate cortisol level (AM) • Comprehensive metabolic panel (Na, K, CO_2, glucose), renin level	• Endocrine consultation ▸ Endocrine evaluation prior to surgery or any procedure • Hold immunotherapy[f] • Start corticosteroid first before other hormone replacement to avoid adrenal crisis • Steroid replacement[p,q] ▸ Hydrocortisone 20 mg in AM, 10 mg in PM, then slowly titrating doses down according to symptoms[r] OR ▸ Prednisone 7.5 mg or 10 mg starting dose, then reduce to 5 mg daily as appropriate AND ▸ Fludrocortisone can be started 0.1 mg every other day; then titrated up or down based on blood pressure, symptoms, lower-extremity edema, and labs • If hemodynamically unstable, inpatient care and initiate high-dose/stress-dose steroids • Patients with severe symptoms (hypotension) may require additional fluids (eg, normal saline often >2 L required) • Patient education regarding stress doses of hydrocortisone for infection, trauma, etc. ▸ Alert bracelet is recommended

[f] See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[m] Low morning cortisol (<5) with high ACTH (> reference range) with or without abnormal electrolytes and symptoms. Other criteria: 30- or 60-minute cortisol <18 after ACTH stimulation in the setting of low morning cortisol and high ACTH. Other abnormalities: hypotension, orthostatic hypotension, low Na, and high K.
[n] See Principles of Immunosuppression (IMMUNO-A).
[o] If severe acute symptoms (eg, headache/nausea/emesis, fevers), high-dose steroids as indicated until symptoms resolve (1–2 weeks) then rapid taper to physiologic replacement.
[p] If acutely ill, double or triple these doses for 24–48 hours (ie, sick day rules for fever >101, nausea/emesis, surgeries).
[q] Will require physiologic replacement steroids indefinitely.
[r] The goal for physiologic steroid replacement is to identify the lowest steroid dose needed to prevent symptoms of adrenal insufficiency. For many patients, this may be, for example, 10 mg in AM and 5 mg in PM, if tolerated.

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Case 2
Metastatic Melanoma

- Treatment:

  -Methylprednisolone 100 mg IV and well as IV normal saline in clinic

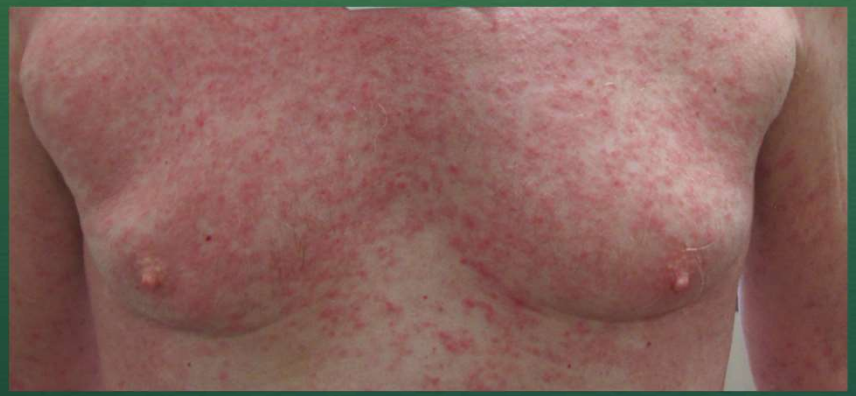
  -Sent home with hydrocortisone 20 mg BID

  -Immunotherapy resumed once symptoms resolved

  -Consider endocrinology consult

Case 3
Metastatic Melanoma

Mr. M.C. returns to clinic for evaluation prior to dose #4 of pembrolizumab.



He reports that for the past week he has had a pruritic rash on his chest, abdomen and arms. What next?

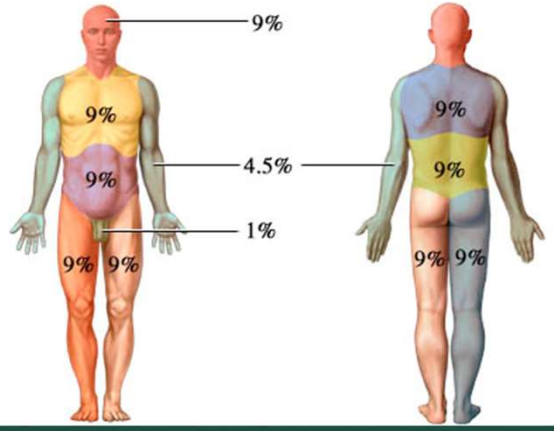
Rash/Pruritus

Anticipate/Prevent

- Skin toxicities can be seen in up to 58% of cases
- Autoimmune conditions can worsen
- Occupational/recreational activities (exposure to outdoors/high temps can worsen skin AEs)
- Possibility of developing hypopigmentation (vitiligo correlated to positive outcome)

Monitor

- New onset of rash
- New lesions
- Itching
- Sunburn
- Photosensitivity



Manage

- Educate patient about potential side effects
- Grade 1: topical OTC hydrocortisone / oral diphenhydramine
- Grade 1/2: triamcinolone or clobetasol cream, diphenhydramine or hydroxyzine
- Grade 2: consider holding treatment, oral corticosteroids
- Grade 3/4: discontinue agent

Skin side effects (rash/itching)

Grade	Symptoms	Management
1	Rash > 10% of BSA with or without symptoms.	Topical moisturizing cream/ointment, oral or topical antihistamines for itching (if present) and/or topical corticosteroid cream (mild strength); checkpoint inhibitor treatment can continue.
2	Rash covering 10%–30% of BSA with or without symptoms.	Topical moisturizing cream/ointment, oral or topical antihistamines for itching (if present) and/or topical corticosteroid cream (medium strength); checkpoint inhibitor treatment can continue.
	Self-help measures for Grade 1/2 (mild-to-moderate) symptoms are: avoid contact with skin irritants and exposure to sun	
3	Rash covering less than 30% of BSA with or without symptoms.	Topical moisturizing cream/ointment, oral or topical antihistamines for itching (if present) and/or topical corticosteroid cream (high strength); plus intravenous corticosteroids; checkpoint inhibitor treatment will be withheld, but may be restarted if symptoms reduce to Grade 1 or mild Grade 2.
4	Rash covering over 30% BSA with infection or other complications.	Intravenous corticosteroids and urgent specialist review; checkpoint inhibitor therapy must be discontinued permanently.

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SKIN

DERMATOLOGIC ADVERSE EVENT(S)	ASSESSMENT/GRADING	MANAGEMENT[e]
Pruritus[h]	• Total body skin exam, including mucosa • Assess for history of prior inflammatory dermatologic diseases	**Mild (G1)[i]** • Continue immunotherapy • Oral antihistamines • Treatment with moderate potency topical steroids to affected areas
		Moderate (G2)[j] • Continue immunotherapy with intensified antipruritic therapy[l] • Oral antihistamines • Treatment with high potency topical steroids to affected areas • Dermatology consultation
		Severe (G3)[k] • Hold immunotherapy[f] • Oral antihistamines • Prednisone/methylprednisolone 0.5–1 mg/kg/day[g] • Consider GABA agonists (gabapentin, pregabalin) • Consider aprepitant or omalizumab for refractory cases • Urgent dermatology consultation

[e] See Principles of Immunosuppression (IMMUNO-A).
[f] See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[g] Treat until symptoms improve to Grade ≤1 then taper over 4–6 weeks.
[h] Characterized by an intense itching sensation.
[i] Mild or localized.
[j] Intense or widespread; intermittent; skin changes from scratching (eg, edema, papulation, excoriations, lichenification, oozing/crusts); limiting iADLs.
[k] Intense or widespread; constant; limiting self-care ADLs or sleep. Assess serum IgE and histamine; consider oral antihistamines for increased histamine and omalizumab for increased IgE.
[l] Consider holding in select cases.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Vitiligo

Case 3 *Metastatic Merkel-cell carcinoma*

A 56-yr-old woman with metastatic Merkel Cell carcinoma has been on avelumab for 11 weeks when routine TSH returns high

- She reports increasing fatigue more than usual
- Additional testing reveals:

Lab	Value		Normal Range
TSH, MIU/L	22.850	↑	0.46-4.70
Free T4, ng/dL	0.2	↓	0.58-1.64
Free T3, pg/dL	105	↓	250-390

Which is the most appropriate course of action for this patient?

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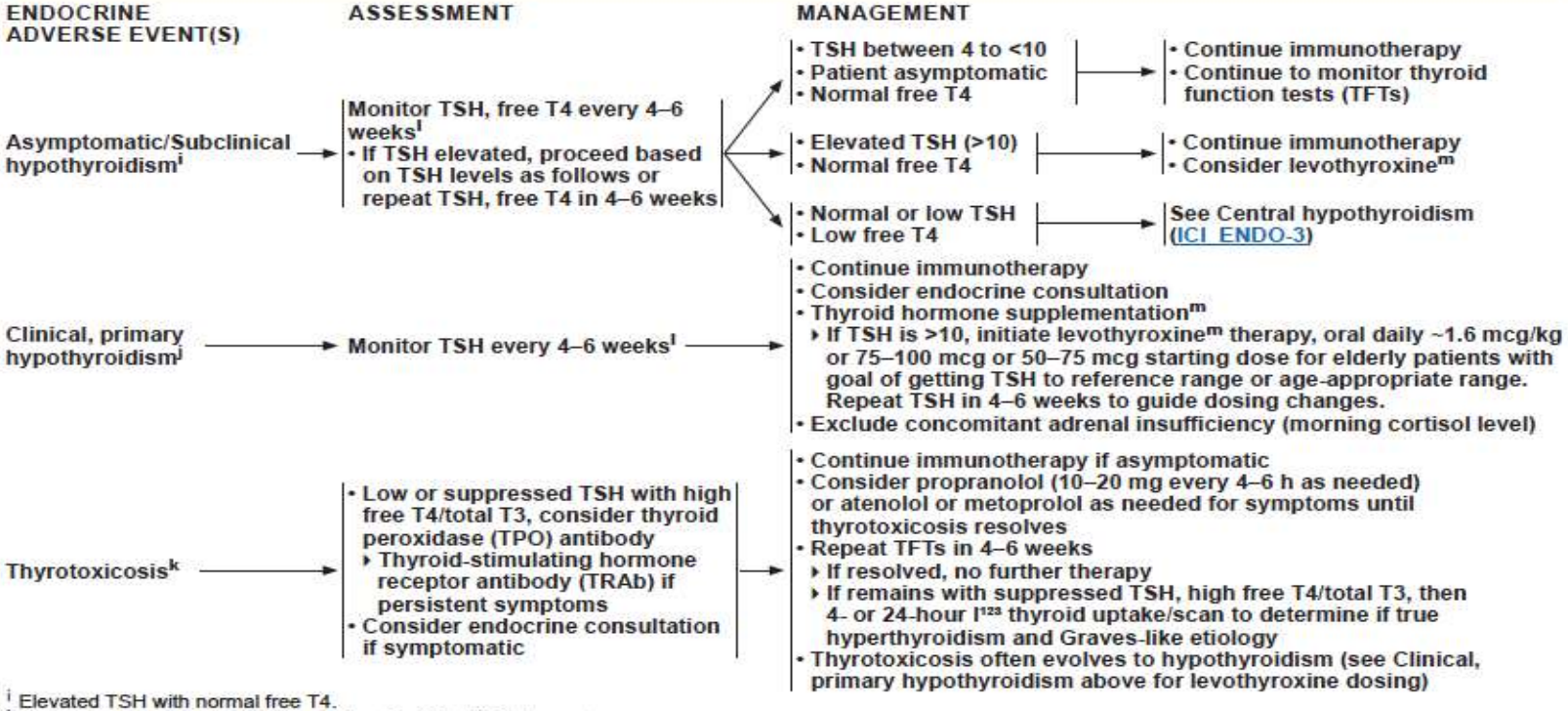

[i] Elevated TSH with normal free T4.
[j] Generally, elevated TSH (>10) with low free T4, clinical symptoms.
[k] Defined as suppressed TSH that may be: a) subclinical if free T4 normal, b) clinical if high free T4. The majority of suppressed TSH (<0.01) are due to transient or progressive painless thyroiditis.
[l] For patients without baseline thyroid function abnormalities or who are asymptomatic, can increase thyroid function testing interval to every 12–18 weeks as indicated.
[m] Levothyroxine oral daily ~1.6 mcg/kg with goal of getting TSH to reference range or age-appropriate range; reduce dose by 10% to avoid hyperthyroidism in patient populations that may be sensitive to thyroid supplementation (eg, elderly populations or patients with comorbidities).

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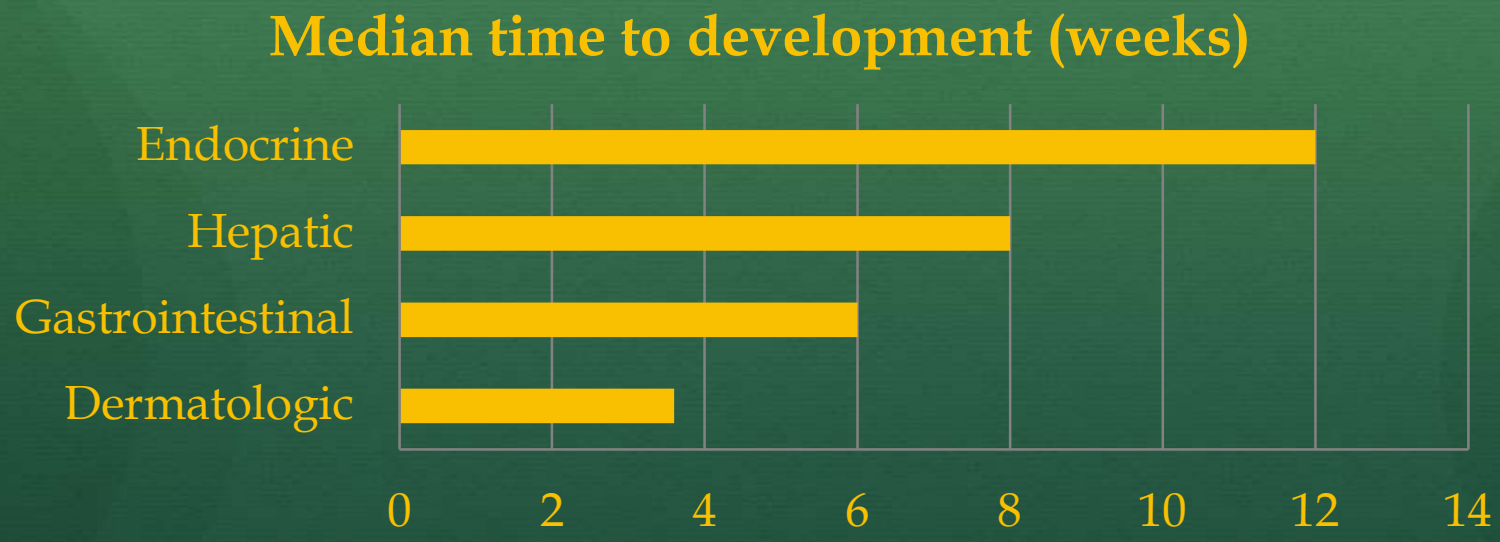
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Case 3 Metastatic *Merkel-cell carcin*oma

This patient has **symptomatic** hypothyroidism

- Begin thyroid replacement
- No endocrinology referral needed
- Continue to monitor thyroid function Q 6-8 weeks throughout therapy and thereafter
- Guidelines recommend HOLDING CPI until asymptomatic then resume avelumab

Immune checkpoint inhibitors-irAEs



Weber J et al, J clin Oncol 2012

General Principles of Toxicity Management

- Reversible toxicities when recognized quickly and treated appropriately
- Treatment may include:
    - Corticosteroids (initiate at 1 -2 mg/kg/day of prednisone or equivalent)
    - Consider other therapies if no improvement with corticosteroids; such as tumor necrosis alfa (TNF-α) antagonists (infliximab) for GI toxicities and mycophenolate mofetil in hepatotoxicity.
    - Dose delay, omission or discontinuation of the immunotherapy; should hold immunotherapy for grade ≥2
- Corticosteroids may require a long tapering duration to prevent recurrence of symptoms
- Re-challenge with checkpoint inhibitor may only be done, if clinically appropriate, once a patient is receiving 10 mg of oral prednisone or equivalent or less.

Villadolid J and Amin A. *Transl Lung Cancer Res* 2015; 4 (5): 560-575

Educate patients: constant communication of symptoms is essential sooner rather than later

- Updated safety information with 9 additional months of follow-up were consistent with the initial report

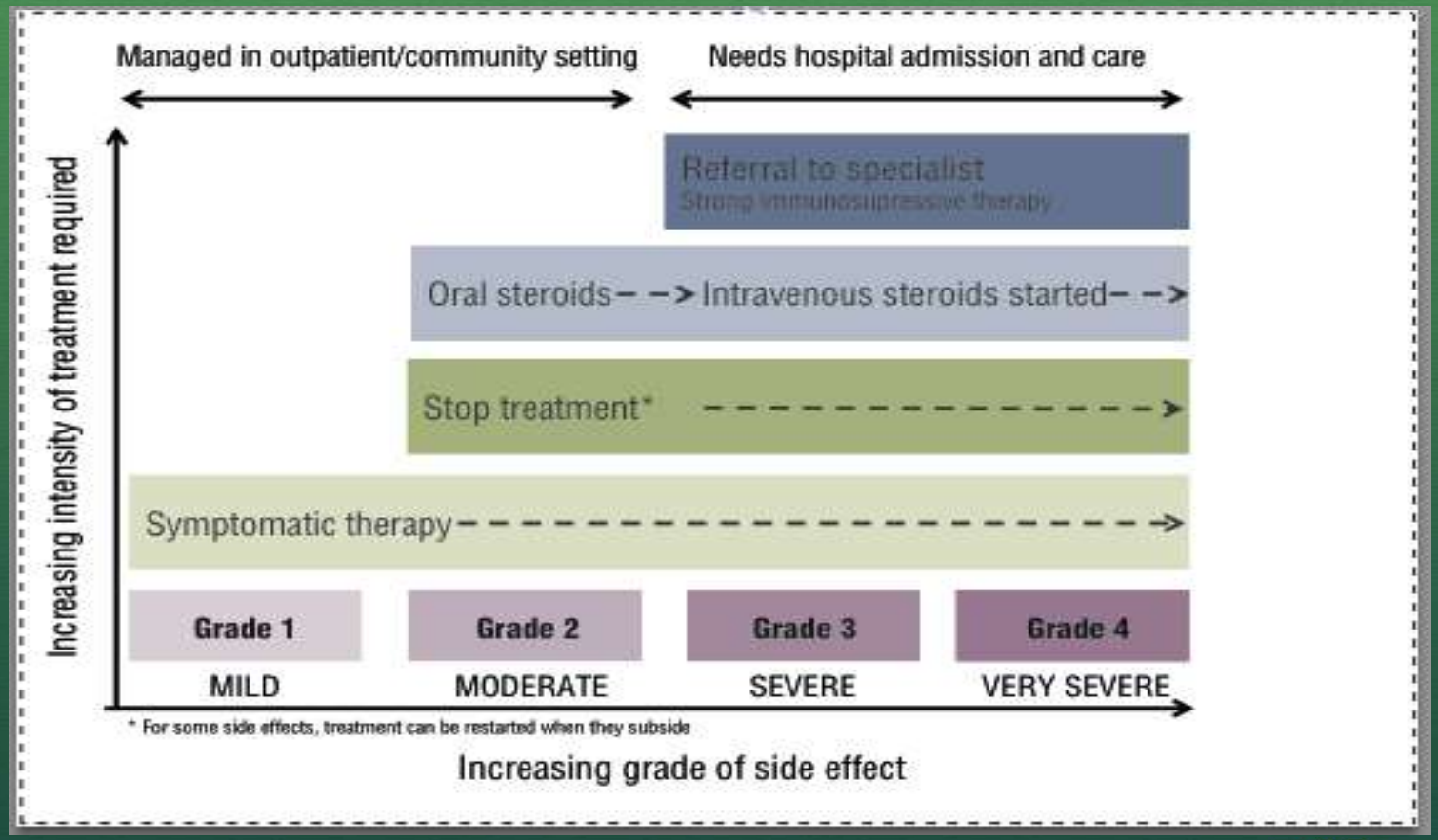
	NIVO+IPI (N=313)		NIVO (N=313)		IPI (N=311)	
Patients reporting event, %	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Treatment-related death*	0		0.3		0.3	

Grade 3/4 is life-threatening

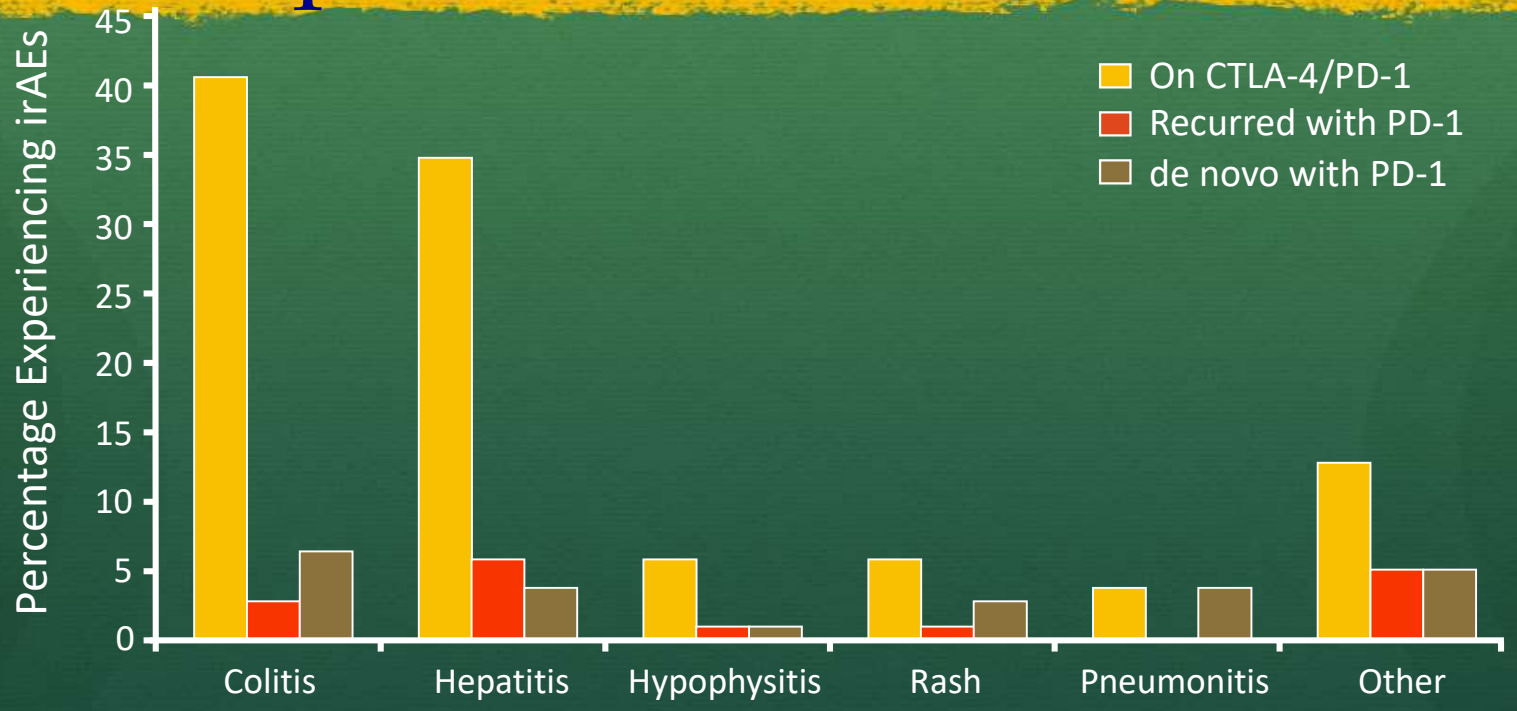
- 68.8% of patients who discontinued NIVO+IPI due to treatment-related AEs achieved a response

*One reported in the NIVO group (neutropenia) and one in the IPI group (colon perforation)

Database lock Nov 2015


Managed in outpatient/community setting
Needs hospital admission and care
Increasing intensity of treatment required
Referral to specialist
Strong immunosuppressive therapy
Oral steroids
Intravenous steroids started
Stop treatment*
Symptomatic therapy
Grade 1
Grade 2
Grade 3
Grade 4
MILD
MODERATE
SEVERE
VERY SEVERE
* For some side effects, treatment can be restarted when they subside
Increasing grade of side effect

Recurrent Toxicities With Resumption of Anti–PD-1



Pollack. Ann Oncol. 2018;29:250.

Clinically Significant irAEs After Resumption of Anti–PD-1

irAEs, n (%)	CTLA-4 + PD-1 Blockade		Anti–PD-1 Resumption (Recurrent or de Novo)	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Colitis	33 (41)	20 (25)	6 (8)	2 (3)
Hepatitis	29 (36)	19 (24)	8 (10)	5 (7)
Hypophysitis	5 (6)	2 (3)	2 (3)	1 (1)
Dermatitis/rash	5 (6)	3 (4)	6 (8)	2 (3)*
Pneumonitis	3 (4)	1 (1)	4 (5)	–
Elevated lipase	4 (5)†	4 (5)	3 (5)	2 (3)†
Nephritis	2 (3)	1 (1)	1 (1)	–
Neurologic	2 (3)	1 (1)	–	–
ITP	1 (1)	1 (1)	–	–
Other	7 (9)	2 (3)	8 (10)	2 (3)‡

- *Includes 1 patient with grade 5 Stevens-Johnson. †Both patients with clinical pancreatitis. ‡Grade 3 type 1 diabetes and grade 3 arthralgias.

Pollack. Ann Oncol. 2018;29:250.

Conclusion 1

- More patients are being treated with ICIs as indications expand to new malignancies, earlier lines of therapy, and earlier stages of disease
- ICIs can cause irAEs by activating immune cells in nontumor tissues
  - irAEs can occur after discontinuing ICI
- irAEs most commonly presenting to emergency department are diarrhea, colitis, dermatitis, pneumonitis, hypophysitis

Conclusion 2

- When a patient with cancer history presents to clinic:
  - Ask about immunotherapy treatment, wallet card, autoimmune conditions
  - Consult promptly with specialists for affected organ systems
  - Manage based on severity of symptoms by providing supportive care, holding/discontinuing immunotherapy, and administering corticosteroids, as appropriate
  - Make use of resources on identification and management of irAEs, including NCCN Guidelines, and ASCO guidelines

Questionnaire for nurses to guide discussions with patients on CPI therapy

Ask patients about their signs and symptoms	Yes answers may indicate the patient is experiencing an irAE
Are you experiencing any diarrhea, increased bowel movements, watery stools, or any cramping or pain in your belly?	Gastrointestinal irAEs
Have you been having a hard time sleeping or feeling sleepier than usual? Are you experiencing headaches, light-headedness, or changes in mood?	Endocrine irAEs
Does your skin feel itchy anywhere, or have you noticed any new rashes, or any changes in pigmentation?	Dermatologic irAEs
Have you noticed any weakness or trouble gripping or dropping things? Do you have tingling in your fingers or toes?	Neurologic irAEs
Have you noticed any changes in vision or problems with your eyes?	Ocular irAEs

Pre-test Question

Question 4:

72 year old man with metastatic NSCLC and COPD coming in to restart maintenance atezolizumab and bevacizumab after completing course of steroids for pneumonitis. He complains of overwhelming fatigue and general malaise. His vitals are: BP-74/56, P-98, RR-18, T-99.2F.

Based on his symptoms, what is your first course of action?

A. Resume prednisone 40 mg

B. Give Rx for Medrol dose pack

C. Start Methylprednisolone in clinic- This patient likely has primary adrenal insufficiency related to chronic steroid use from COPD as well as immunotherapy-related adrenal insufficiency. This is an ENDOCRINOLOGIC EMERGENCY. Because the patient was **hemodynamically unstable (BP),** the patient was given aggressive hydration and started on IV steroid replacement. Immunotherapy was held.

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2019
Management of Immune Checkpoint Inhibitor-Related Toxicities

NCCN Guidelines Index
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ENDOCRINE ADVERSE EVENT(S)	ASSESSMENT/GRADING	MANAGEMENT[n,o]
Primary adrenal insufficiency[m]	• Evaluate cortisol level (AM) • Comprehensive metabolic panel (Na, K, CO_2, glucose), renin level	• Endocrine consultation ▸ Endocrine evaluation prior to surgery or any procedure • Hold immunotherapy[f] • Start corticosteroid first before other hormone replacement to avoid adrenal crisis • Steroid replacement[p,q] ▸ Hydrocortisone 20 mg in AM, 10 mg in PM, then slowly titrating doses down according to symptoms[r] OR ▸ Prednisone 7.5 mg or 10 mg starting dose, then reduce to 5 mg daily as appropriate AND ▸ Fludrocortisone can be started 0.1 mg every other day; then titrated up or down based on blood pressure, symptoms, lower extremity edema, and labs • If hemodynamically unstable, inpatient care and initiate high-dose/stress-dose steroids • Patients with severe symptoms (hypotension) may require additional fluids (eg, normal saline often >2 L required) • Patient education regarding stress doses of hydrocortisone for infection, trauma, etc. ▸ Alert bracelet is recommended

[f] See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[m] Low morning cortisol (<5) with high ACTH (> reference range) with or without abnormal electrolytes and symptoms. Other criteria: 30- or 60-minute cortisol <18 after ACTH stimulation in the setting of low morning cortisol and high ACTH. Other abnormalities: hypotension, orthostatic hypotension, low Na, and high K.
[n] See Principles of Immunosuppression (IMMUNO-A).
[o] If severe acute symptoms (eg, headache/nausea/emesis, fevers), high-dose steroids as indicated until symptoms resolve (1–2 weeks) then rapid taper to physiologic replacement.
[p] If acutely ill, double or triple these doses for 24–48 hours (ie, sick day rules for fever >101, nausea/emesis, surgeries).
[q] Will require physiologic replacement steroids indefinitely.
[r] The goal for physiologic steroid replacement is to identify the lowest steroid dose needed to prevent symptoms of adrenal insufficiency. For many patients, this may be, for example, 10 mg in AM and 5 mg in PM, if tolerated.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Key Take Home Points

- Immune checkpoint blockade is associated with unique clinical features
  - irAEs → contemporary type of oncologic emergency
    - Can affect any organ system, anytime during therapy
    - Can mimic many other conditions
- ***Early recognition and effective management of irAEs is crucial to optimal use of checkpoint inhibitors***
  - Maintain high index of suspicion
  - Early communication with the entire care team
  - Have your stable of experts available to help you

Thank you