JADPRO CE
Regional Education

From Inquiry to Investigation to Insight: Clinical Clarity in Non–Small Cell Lung Cancer

Managing Immune-Related Adverse Events

Program Chair

Beth Eaby-Sandy
MSN, CRNP
Abramson Cancer Center

Faculty

Tyler Beardslee, PharmD
Winship Cancer Institute at Emory University

Marianne Davies
DNP, ACNP, AOCNP®
Yale School of Nursing

Elizabeth Gilbert
MS, PA-C
Abramson Cancer Center

Rasheda Persinger, NP-C
Johns Hopkins Sidney Kimmel Cancer Center

Faculty Financial Disclosures

- **Ms. Eaby-Sandy** has served as a consultant and on speakers bureaus for AstraZeneca, Helsinn, Merck, and Takeda.
- **Dr. Beardslee** has served as a consultant for AstraZeneca and Herron, and on the speakers bureau for AstraZeneca.
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Learning Objective

- Apply clinical approaches to mitigate adverse events associated with targeted and ICI therapy

Audience Response Question

The strongest data to correlate immune-related adverse events with a survival advantage is in:

A. Patients with NSCLC receiving nivolumab
B. Patients with NSCLC receiving pembrolizumab
C. Patients with melanoma who experience pneumonitis but not skin rash
D. Patients with melanoma who experience colitis but not skin rash
E. Unsure

Audience Response Question

A patient with SCLC is receiving the combination of ipilimumab and nivolumab in the second-line setting after failure on platinum-based front-line chemotherapy. She develops worsening diarrhea with mucus in her stools and significant abdominal pain. IV steroids do not improve her symptoms and she is admitted to the hospital for IV hydration and symptom management.

She is given a dose of infliximab and finally it improves. She is labeled as having a grade 3 colitis requiring 1 dose of infliximab. According to the NCCN Guidelines, you should:

A. Permanently discontinue the immunotherapy

B. Consider restarting a PD-1 inhibitor but not the anti-CTLA drug once symptoms resolve

C. Consider restarting both the PD-1 inhibitor and the anti-CTLA drug once symptoms resolve

D. Consider restarting both the PD-1 inhibitor and the anti-CTLA drug, but only after a long steroid taper and all symptoms have resolved

E. Unsure

Do irAEs Correlate With Response to Treatment?

- Melanoma
  - Appears that skin toxicities may correlate with response; however, other irAEs may not as much
- NSCLC
  - Fairly significant data to support that any irAEs correlate with response to immune checkpoint inhibitors
  - In at least 3 studies, mainly in patients receiving nivolumab, presence of irAEs associated with significant improvements in OS
    - Median OS not reached vs. 11.1 months in no-irAEs arm, $p = .01$
- Head and neck cancer
  - Emerging data suggest there may be a correlation

NSCLC = non–small cell lung cancer; irAE = immune-related adverse event; OS = overall survival

Saleh, K. et al. *Immunotherapy.* 2019;11(4): 257–259; Haratani K, et al. *JAMA Oncol.* 2018;4(3):374–378; Foster CC, at al. *J Clin Oncol*. 2018;36(15 suppl.):6014–6014

The irAEs

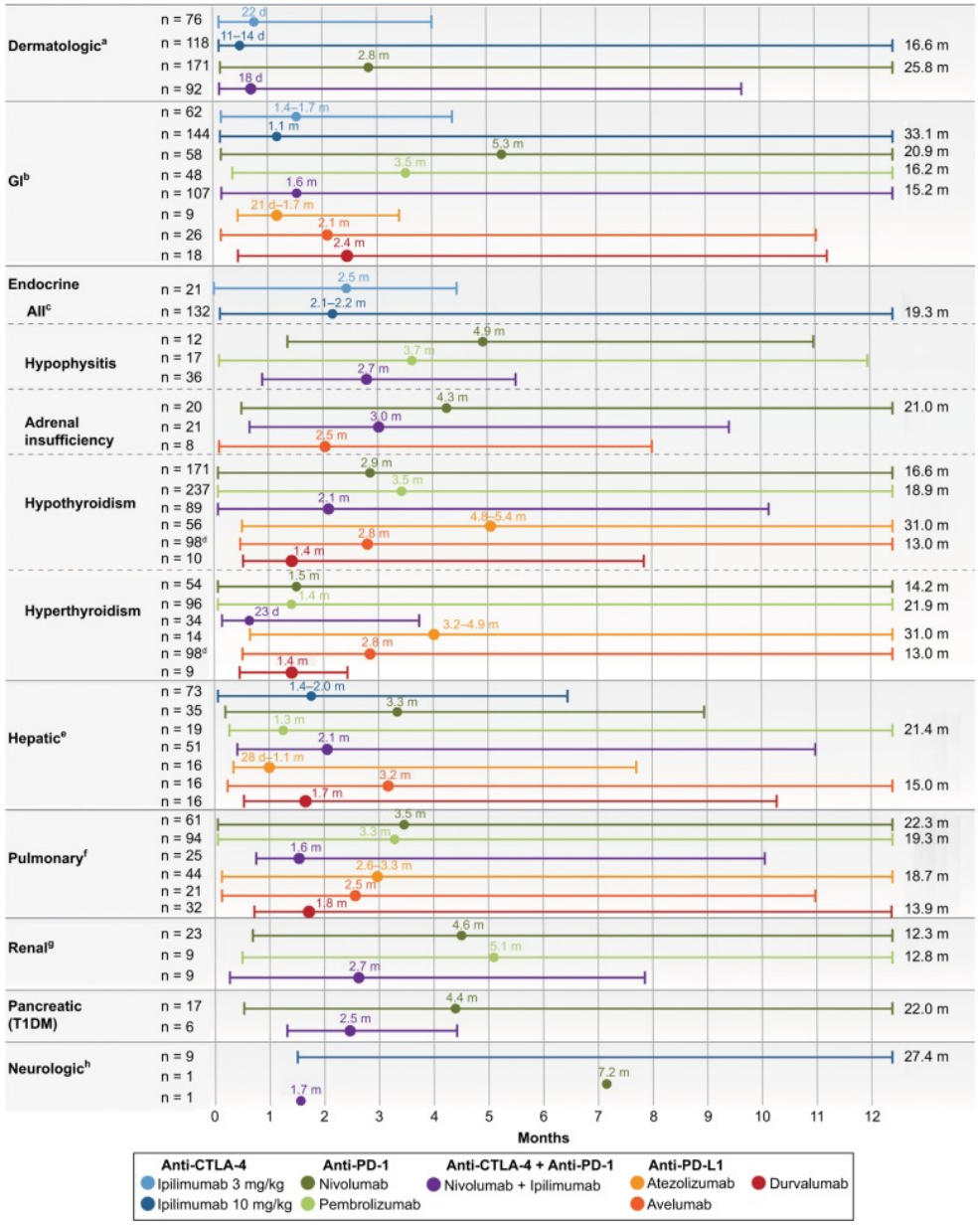
- Pneumonitis
- Colitis
- Dermatitis
- Hepatitis
- Nephritis
- Endocrinopathies
  - Hypo/hyperthyroid, adrenal insufficiency, hypophysitis, Type 1 diabetes
- Other

General Management Strategies of Immune-Mediated Toxicities

Grade	Treatment
1	• Supportive treatment, increased monitoring; if worsening, treat as grade 2 or as 3/4
2	• Delay treatment, consider glucocorticosteroids at 0.5–1 mg/kg daily if symptoms persist more than 5-7 days. If worsening, treat as grade 3/4 • May resume immunotherapy if toxicity returns to grade 1 or less after steroids tapered over a month
3/4	• Permanently discontinue immunotherapy (except endocrinopathies and skin toxicity) • Initiate glucocorticosteroids at 1–2 mg/kg daily; consider hospitalization • Taper steroids over at least a month • If persistent with steroids, consider alternative immunosuppressive agents (infliximab at 5 mg/kg)

Boutros C et al. *Nat Rev.* 2016;13:473-486

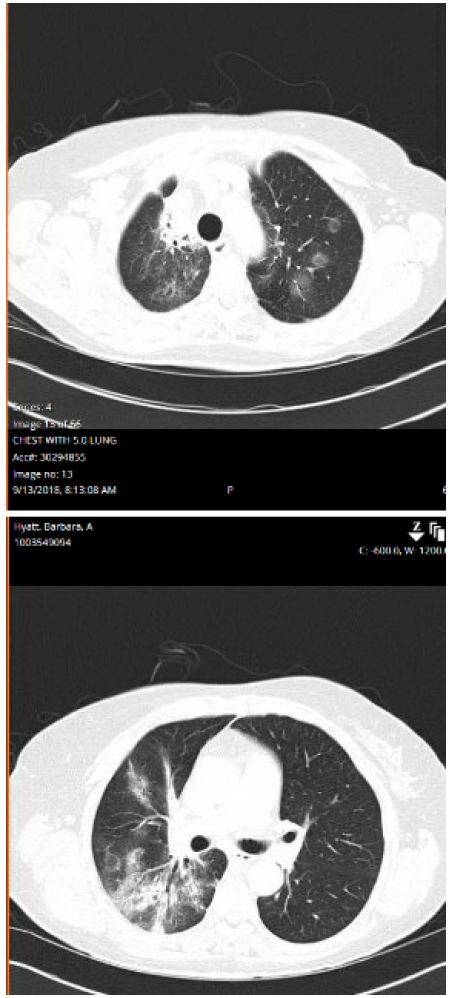
Time to Onset of Immune-Mediated Toxicities (Median and Range)



Davies, M. & Duffield, E. *ImmunoTargets and Therapy.* 2017;6:51–71.
https://doi.org/10.2147/ITT.S141577

Immune-Mediated Toxicities: Pneumonitis

Respiratory, thoracic and mediastinal disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Pneumonitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; oxygen indicated	Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by inflammation focally or diffusely affecting the lung parenchyma.					



Reason For Visit: 71-year-old female with locally advanced NSCLC. She was on a rad onc study "Pembrolizumab…on the pembrolizumab q3 week 100 mg dose, which finished 8/27/2018."

CT Chest 9/13/2018: Impression

1. Grossly stable atelectatic changes of the medial right upper lobe and soft tissue density along the bronchovascular bundle to the right hilum, in keeping with posttreatment changes of the primary malignancy.
2. Interval development of large area of groundglass opacity and consolidation in the superior segment of the right lower lobe, obstructive pneumonia versus tumor involvement.
3. Interval development of bilateral multifocal rim-enhancing groundglass lesions especially bilateral lung apices and right lung base, multifocal atypical infection versus metastases. Clinical and radiologic follow-up suggested.

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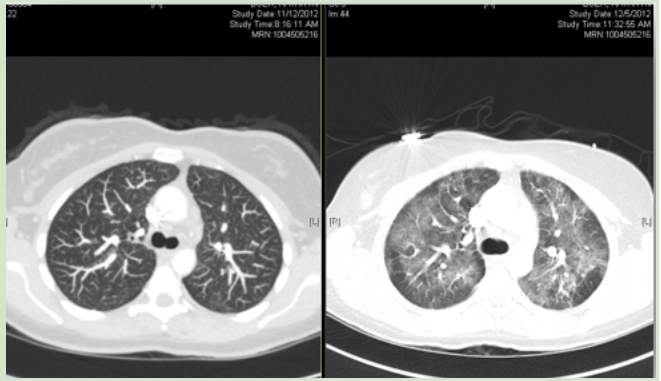
Pneumonitis Case Study (cont.)

Pneumonitis

- Significant on the CT chest from 9/13/2018. In retrospect was slightly visible starting on the 7/2018 CT chest.
- Surprisingly not symptomatic given the severity of the pneumonitis on the CT chest.
- What is the grade of pneumonitis in this patient?
- How would you manage this based on NCCN Guidelines?

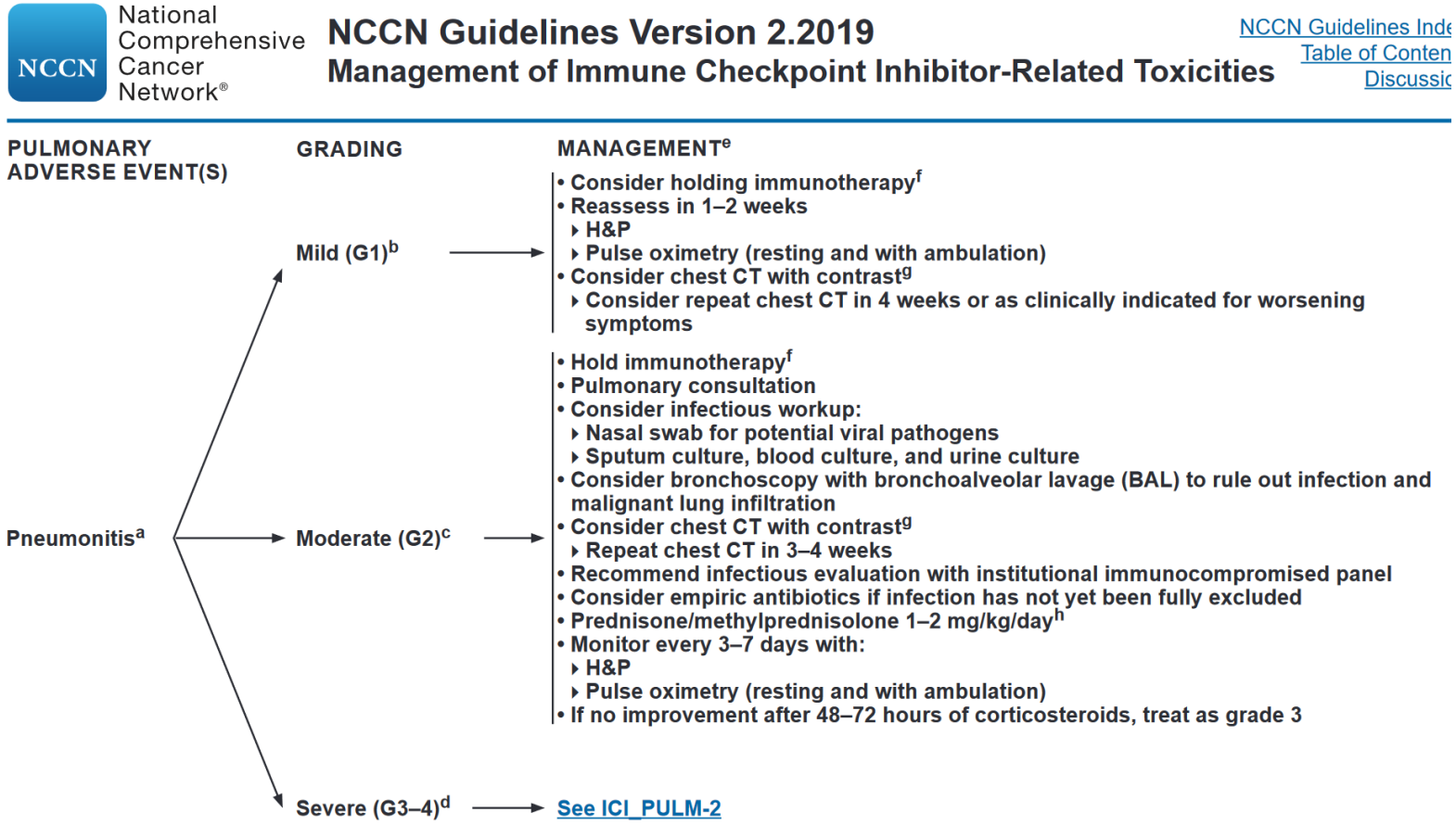
Rates of Pneumonitis Per Package Inserts

Toxicity	Drug	Any grade %
Pneumonitis 	Atezolizumab	2.5
	Nivolumab	3.1
	Pembrolizumab	3.4
	Ipilimumab	0
	Ipi (3 mg/kg) + nivo (1 mg/kg)	6
	Ipi (1 mg/kg) + nivo (3 mg/kg)	4.4

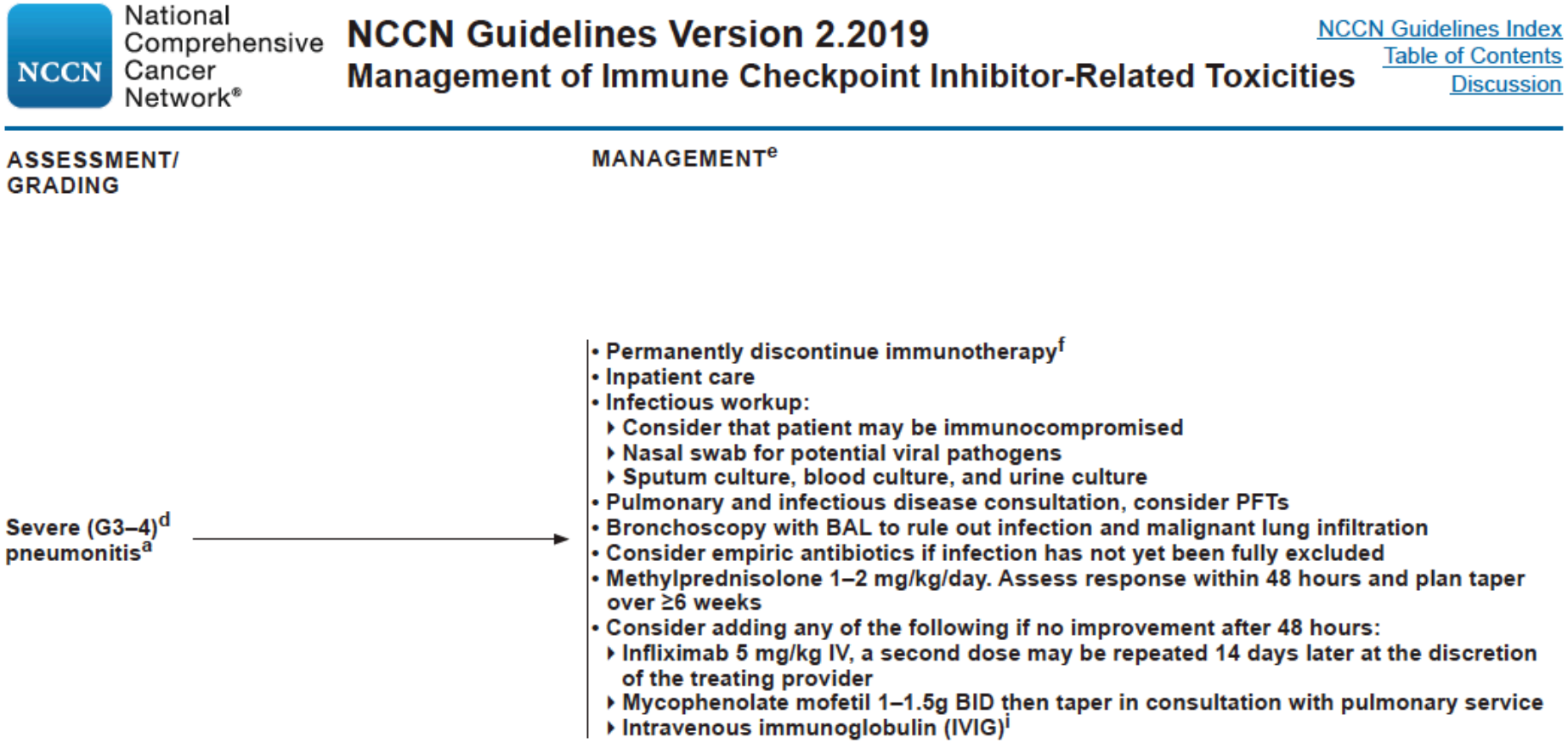
- However, in NSCLC, rates of pneumonitis are often at higher rates than in other disease sites: One retrospective analysis of 167 NSCLC patients receiving immunotherapy checkpoint inhibitors reported 13.2% of patients developed pneumonitis, 4.2% of which were grade 3/4.

Cho JY et al. *Lung Cancer 125 (2018) 150–156*

NCCN Guidelines for Pneumonitis Management



NCCN Guidelines for Pneumonitis Management (cont.)



National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2019
Management of Immune Checkpoint Inhibitor-Related Toxicities

NCCN Guidelines Index
Table of Contents
Discussion

ASSESSMENT/ GRADING	MANAGEMENT[e]

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]

ASCO Guidelines Slightly Differ

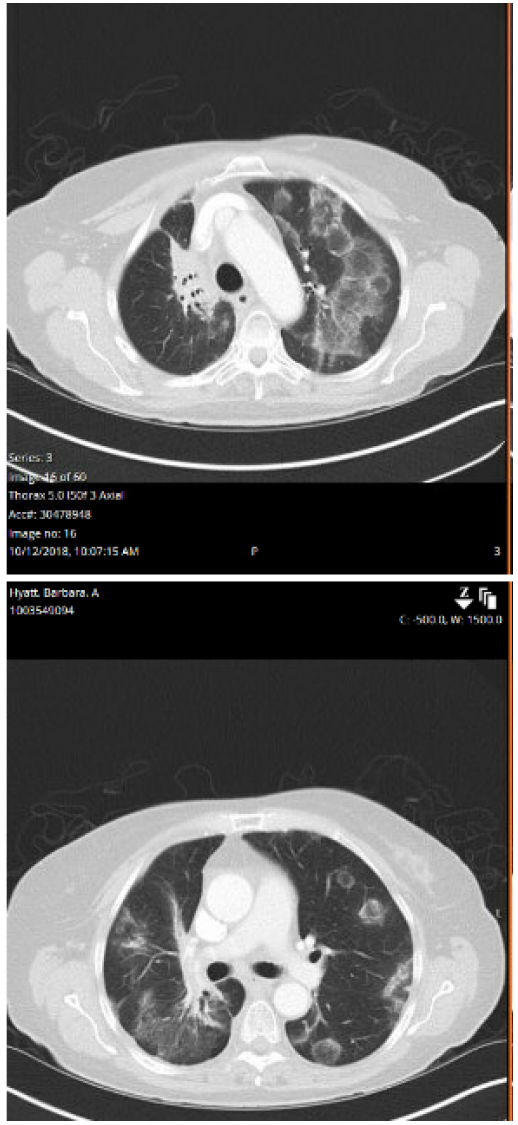
Table 3. Management of Lung irAEs in Patients Treated With ICPis

3.0 Lung Toxicities	
3.1 Pneumonitis	
Definition: Focal or diffuse inflammation of the lung parenchyma (typically identified on CT imaging) No symptomatic, pathologic, or radiographic features are pathognomonic for pneumonitis	
Diagnostic work-up Should include the following: CXR, CT, pulse oximetry For G2 or higher, may include the following infectious work-up: nasal swab, sputum culture and sensitivity, blood culture and sensitivity, urine culture and sensitivity	
Grading	**Management**
G1: Asymptomatic, confined to one lobe of the lung or < 25% of lung parenchyma, clinical or diagnostic observations only	Hold ICPi with radiographic evidence of pneumonitis progression May offer one repeat CT in 3-4 weeks; in patients who have had baseline testing, may offer a repeat spirometry/DLCO in 3-4 weeks May resume ICPi with radiographic evidence of improvement or resolution. If no improvement, should treat as G2 Monitor patients weekly with history and physical examination and pulse oximetry; may also offer CXR
G2: Symptomatic, involves more than one lobe of the lung or 25%-50% of lung parenchyma, medical intervention indicated, limiting instrumental ADL	Hold ICPi until resolution to G1 or less Prednisone 1-2 mg/kg/d and taper by 5-10 mg/wk over 4-6 weeks Consider bronchoscopy with BAL Consider empirical antibiotics Monitor every 3 days with history and physical examination and pulse oximetry, consider CXR; no clinical improvement after 48-72 hours of prednisone, treat as G3
G3: Severe symptoms, hospitalization required, involves all lung lobes or > 50% of lung parenchyma, limiting self-care ADL, oxygen indicated G4: Life-threatening respiratory compromise, urgent intervention indicated (intubation)	Permanently discontinue ICPi Empirical antibiotics; (methyl)prednisolone IV 1-2 mg/kg/d; no improvement after 48 hours, may add infliximab 5 mg/kg or mycophenolate mofetil IV 1 g twice a day or IVIG for 5 days or cyclophosphamide; taper corticosteroids over 4-6 weeks Pulmonary and infectious disease consults if necessary Bronchoscopy with BAL ± transbronchial biopsy Patients should be hospitalized for further management

Brahmer JR, 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*. 2018;36(17):1714–1768. https://doi.org/10.1200/JCO.2017.77.6385

Pneumonitis Case Study (cont.)

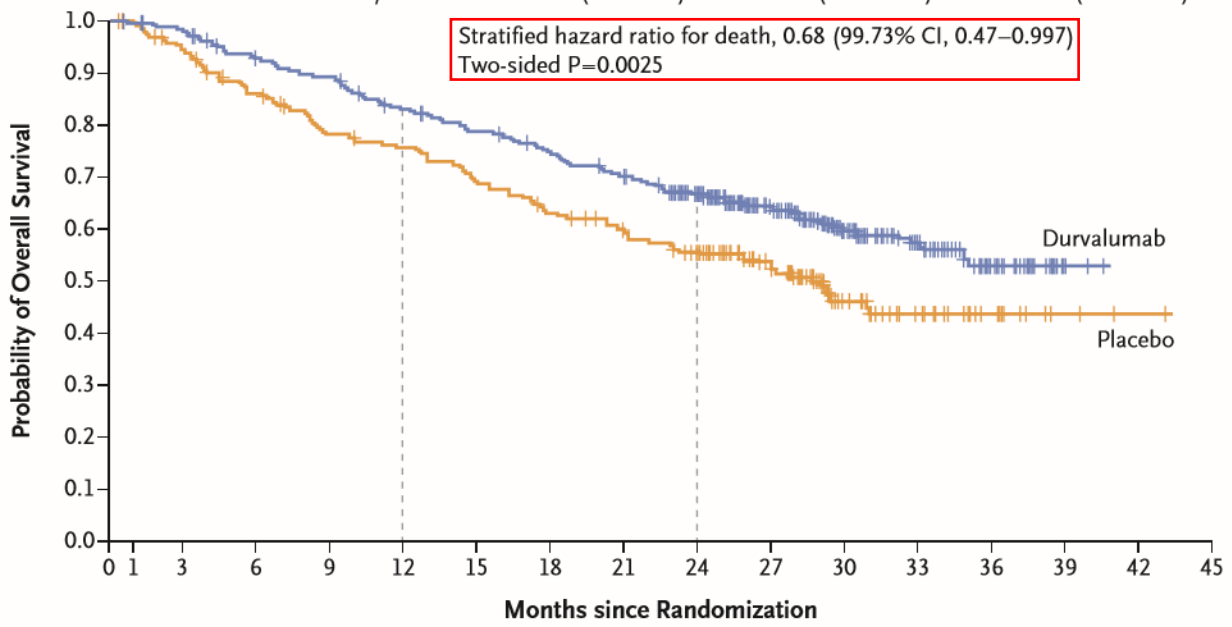
- The patient's last dose of pembrolizumab was held due to radiographic evidence of pneumonitis.
- However, after 10/12/2018 CT showed worsening pneumonitis, she did develop SOB and chills every evening. No fever, not hypoxic.
- Treated with prednisone 60 mg with slow taper, decreasing by 10 mg q5 days (currently at 50 mg today).
- Doing much better after a week on prednisone, SOB gone.
- Discussed at tumor board on 10/19/2018 and Ipulm did not feel a bronch was needed, appears to be consistent with pneumonitis.
- Ordered CT chest in a month to follow up on the pneumonitis.



SOB = shortness of breath

Durvalumab OS in PACIFIC trial

	No. of Events/ Total No. of Patients	Median Overall Survival (95% CI)	12-Mo Overall Survival Rate (95% CI)	24-Mo Overall Survival Rate (95% CI)
		mo	%	%
Durvalumab	183/476	NR (34.7–NR)	83.1 (79.4–86.2)	66.3 (61.7–70.4)
Placebo	116/237	28.7 (22.9–NR)	75.3 (69.2–80.4)	55.6 (48.9–61.8)



No. at Risk															
Durvalumab	476	464	431	415	385	364	343	319	274	210	115	57	23	2	0	0
Placebo	237	220	198	178	170	155	141	130	117	78	42	21	9	3	1	0

Figure 2. Overall Survival in the Intention-to-Treat Population.

- Toxicity concern
- Pneumonitis
  - All grades 34% vs. 25% in placebo arm
  - Grade 3/4 was 3.4% vs 3.0% in placebo arm

Antonia SJ, et al. *NEJM* 2018;379(24):2342-2350

Pearls for Managing Pneumonitis

- Need a CT chest to evaluate for pneumonitis
- Having a baseline pulse ox is important
- SOB, dry cough, and hypoxia can have other symptoms
- Manage high-dose prednisone and go from there
- Follow-up frequently recommended
- Repeat CT chest prior to restarting treatment

Immune-Mediated Toxicities: Colitis

Gastrointestinal disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Colitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Abdominal pain; mucus or blood in stool	Severe abdominal pain; change in bowel habits; medical intervention indicated; peritoneal signs	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the colon.					

Case study: 52-year-old female with stage III NSCLC, on durvalumab post concurrent chemotherapy and radiation.

- Today, pt has had 6 to 7 grainy, non-formed stools, varying in size. No dark, coffee colored stools today. Yesterday, x 1 stool with blood streak. All stools are mucous-y today.
- Loperamide taken twice today. Appears to have no effect.
- Abd pain right before BM but resolves after evacuation. Also reports vomiting.
- Low appetite. Drinking water as much as possible. Had about 30 oz water today.
- ABD CT 6/14/2019 showed near pancolitis (infectious vs. 2/2 abx vs. 2/2 immunotherapy). *C.diff* negative.
- What grade of colitis does this patient have? How should we manage?

ASCO Guidelines for Colitis Management

2.1 Colitis

Definition: A disorder characterized by inflammation of the colon

Diagnostic work-up

- G2
  - Work-up of blood (CBC, comprehensive metabolic panel, TSH, ESR, CRP), stool (culture, *Clostridium difficile*, parasite, CMV or other viral etiology, ova and parasite) should be performed
  - Consider testing for lactoferrin (for patient stratification to determine who needs more urgent endoscopy) and calprotectin (to follow up on disease activity)
  - Screening laboratories (HIV, hepatitis A and B, and blood quantiferon for TB) to prepare patients to start infliximab should be routinely done in patients at high risk for those infections and appropriately selected patients based on infectious disease expert's evaluation
  - Imaging (eg, CT scan of abdomen and pelvis and GI endoscopy with biopsy) should be considered as there is evidence showing that the presence of ulceration in the colon can predict a corticosteroid-refractory course, which may require early infliximab
  - Consider repeating endoscopy for patients who do not respond to immunosuppressive agents; repeating endoscopy for disease monitoring can be considered when clinically indicated and when planning to resume therapy
- G3-4
  - All the work-up listed for G2 (blood, stool, imaging, and scope with biopsy) should be completed immediately
  - Consider repeating endoscopy for patients who do not respond to immunosuppressive agents; repeating endoscopy for disease monitoring should only be considered when clinically indicated and when planning to resume ICPi

Brahmer JR, 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*. 2018;36(17):1714–1768. https://doi.org/10.1200/JCO.2017.77.6385

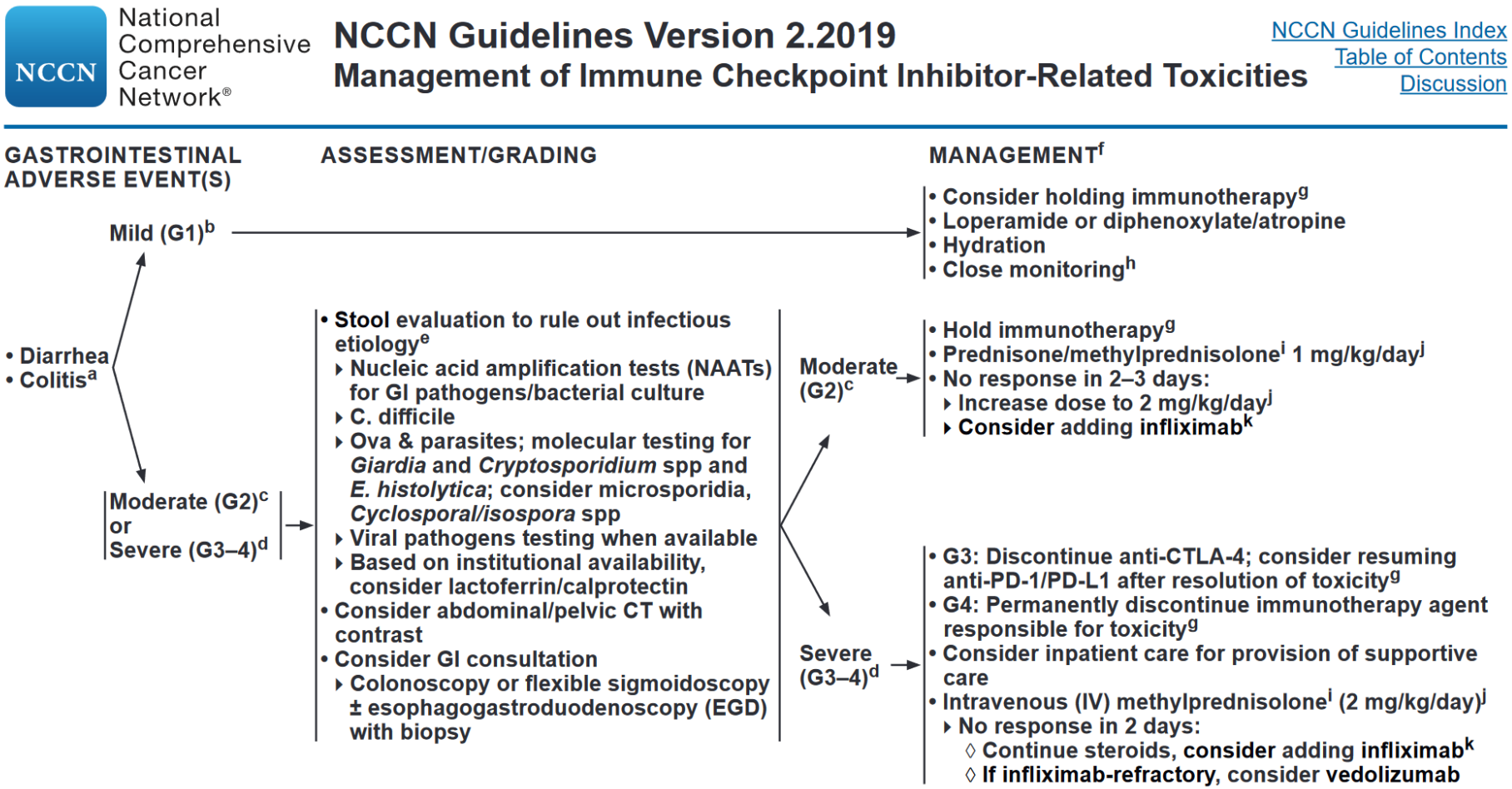
ASCO Guidelines for Colitis Management (cont.)

Grading (based on CTCAE for diarrhea, as most often used clinically)	Management
All patients	Counsel all patients to be aware of and inform their health care provider immediately if they experience: Abdominal pain, nausea, cramping, blood or mucus in stool or changes in bowel habits Fever, abdominal distention, obstipation, constipation For G2 or higher, consider permanently discontinuing CTLA-4 agents and may restart PD-1, PD-L1 agents if patient can recover to G1 or less; concurrent immunosuppressant maintenance therapy should be considered only if clinically indicated in individual cases
G1: Increase of fewer than four stools per day over baseline; mild increase in ostomy output compared with baseline	Continue ICPi; alternatively, ICPi may be held temporarily and resumed if toxicity does not exceed G1 Monitor for dehydration and recommend dietary changes Facilitate expedited phone contact with patient/caregiver May obtain gastroenterology consult for prolonged G1 cases
G2: Increase of four to six stools per day over baseline; moderate increase in ostomy output compared with baseline	Should hold ICPi temporarily until patient's symptoms recover to G1; can consider permanently discontinuing CTLA-4 agents and may restart PD-1, PD-L1 agents if patient can recover to G1 or less Concurrent immunosuppressant maintenance therapy (< 10 mg prednisone equivalent dose) may be offered only if clinically indicated in individual cases May also include supportive care with medications such as Imodium if infection has been ruled out Should consult with gastroenterology for G2 or higher Administer corticosteroids, unless diarrhea is transient, starting with initial dose of 1 mg/kg/day prednisone or equivalent When symptoms improve to G1 or less, taper corticosteroids over at least 4-6 weeks before resuming treatment, although resuming treatment while on low-dose corticosteroid may also be an option after an evaluation of the risks and benefits EGD/colonoscopy, endoscopy evaluation should be highly recommended for cases grade ≥ 2 to stratify patients for early treatment with infliximab based on the endoscopic findings and to determine the safety of resuming PD-1, PD-L1 therapy Stool inflammatory markers can be considered (lactoferrin and calprotectin) in cases of G2 or higher to differentiate functional *v* inflammatory diarrhea, and use calprotectin to monitor treatment response if provider prefers Repeat colonoscopy is optional for cases of G2 or higher for disease activity monitoring to achieve complete remission, especially if there is a plan to resume ICPi
G3: Increase of seven or more stools per day over baseline, incontinence, hospitalization indicated, severe increase in ostomy output compared with baseline, limiting self-care ADL	Should consider permanently discontinuing CTLA-4 agents and may restart PD-1, PD-L1 agents if patient can recover to G1 or less. Administer corticosteroids (initial dose of 1-2 mg/kg/d prednisone or equivalent) Consider hospitalization or outpatient facility for patients with dehydration or electrolyte imbalance If symptoms persist ≥ 3-5 days or recur after improvement, consider administering IV corticosteroid or noncorticosteroid (eg, infliximab) Consider colonoscopy in cases where patients have been on immunosuppression and may be at risk for opportunistic infections as an independent cause for diarrhea (ie, CMV colitis) and for those who are anti-TNF or corticosteroid refractory
G4: Life-threatening consequences; urgent intervention indicated	Permanently discontinue treatment Should admit patient when clinically indicated; patients managed as outpatients should be very closely monitored Administer 1-2 mg/kg/d methylprednisolone or equivalent until symptoms improve to G1, and then start taper over 4-6 weeks Consider early infliximab 5-10 mg/kg if symptoms refractory to corticosteroid within 2-3 days Consider lower GI endoscopy if symptoms are refractory despite treatment or there is concern of new infections

(continued on following page)

Brahmer JR, 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*. 2018;36(17):1714–1768. https://doi.org/10.1200/JCO.2017.77.6385

NCCN Guidelines on Colitis Management



Colitis Rates Per Package Inserts

Immune-mediated colitis

- Favoring related to durvalumab
- Ova and parasites and *C.diff* negative from 6/14
- CT A/P 6/14: Findings in keeping with near pancolitis
- Received IV fluids on 6/14; will give another 1L of NSS today
- Started 80 mg prednisone once daily with plan to taper, f/up in 2 days. If not improved, consider inpatient admission for IV steroids

Toxicity	Drug	Any Grade %
Colitis	Atezolizumab	IM diarrhea/colitis: 20
	Nivolumab	2.9
	Pembrolizumab	1.7
	Ipilimumab	7
	Ipilimumab (3 mg/kg) + nivolumab (1 mg/kg)	26
	Ipilimumab (1 mg/kg) + nivolumab (3 mg/kg)	10

Colitis Case Study (cont.)

- Interval history 6/19/19
  - Reports x 5 mucuous-y, non-bloody loose bowel movements today after taking 2 loperamide. Estimates about 10–12 BM in a full day. Also experiencing nausea today; decreased appetite but drinking water.
- Immune-mediated colitis
  - Related to durvalumab
  - O/P and culture from 6/14 negative for cryptosporidium and giardia. No other pathogens found.
  - *C.diff* negative from 6/14
  - CT A/P 6/14: A findings in keeping with near pancolitis. Could be infectious related to recent antibiotic use (*C. difficile*) or related to immunotherapy.
  - Received IV fluids on 6/17; will give another 1L of NSS today, though is hemodynamically stable.
  - Increased 80 mg daily prednisone to 100 mg daily orally. Methylprednisolone 125 mg IV given in clinic today. Also started budesonide 3 mg three times a day.
  - CMP and CBC ordered today; will follow-up and replete electrolytes if low
  - Pt will continue to take prednisone and budesonide over the remainder of the week and return to clinic on 6/24 to reassess colitis. Instructed pt to go to the ED if symptoms worsen.
  - In the process of pre-certing infliximab IV in case pt does not respond to additional immunosuppressive therapy. Pt has no s/sx of TB and has had multiple CT scans of the chest with no evidence of TB.
  - Colonoscopy scheduled for 6/26/19; no need for stat colonoscopy at this time given that pt is exhibiting hallmark signs of colitis and CT shows pancolitis. Will instruct pt to get colonoscopy if colitis does not resolve with additional immunosuppressive therapy.

Colitis Case Study (cont.)

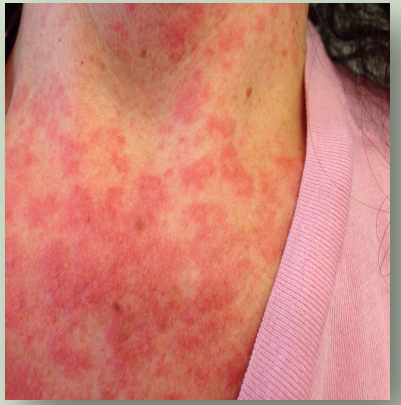
- Interval history 6/24/19
  - Reports stools are more formed but she is still having ~9 episodes per day. BRBPR when wiping but no signs of blood in the stools. Her abdomen is tender right before she needs to have a BM but resolves after BM.
  - Adequate fluid intake but low appetite. No N/V. No weight loss.
- Immune-mediated colitis
  - Related to durvalumab
  - Received IV fluids on 6/17; will give another 1L of NSS today, though is hemodynamically stable.
  - Increased 80 mg daily prednisone to 100 mg daily orally on 6/19. Methylprednisolone 125 mg IV given in clinic 6/19.
  - Originally planned to start budesonide po but insurance denied.
  - 6/24 f/u visit: stools more formed but pt still has ~9 stools per day. Also reported BRBPR upon wiping, which has existed since 6/12.
  - Give infliximab IV. Pt has no s/sx of TB and has had multiple CT scans of the chest with no evidence of TB. Given continued frequent stools even after prednisone increase, **will give infliximab 5 mg/kg IV and q2 weeks for max of 3 doses until colitis improves.**
  - Colonoscopy scheduled for 6/26/19 cancelled due to inflamed bowel, rescheduled for 7/17/2019.

Pearls for Managing Colitis

- Discuss bowel habits! Hallmarks of colitis; how does it differ from diarrhea
- Gold standard is colonoscopy, but Abd CT may show
- Often may need admission due to nature of colitis; however, can manage in the outpatient setting
- Most common in ipilimumab, especially in combination with nivolumab
- Need to instruct patients to call for symptoms; can be life-threatening

Immune-Mediated Toxicities: Rash/Dermatitis

Skin and subcutaneous tissue disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
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	Macules/papules covering >30% BSA with or without associated 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 pruritus.					

Toxicity	Drug	Any Grade %
Dermatitis 	Atezolizumab	NR
	Nivolumab	IM rash: 9
	Pembrolizumab	NR
	Ipilimumab	Grade 2 dermatitis: 12
		Grade 3–5 dermatitis: 2.5
	Ipilimumab (3 mg/kg) + Nivolumab (1 mg/kg)	IM rash: 22.6%
	Ipilimumab (1 mg/kg) + Nivolumab (3 mg/kg)	IM rash: 16%

CTCAE grading criteria V4.03, June 2014

ASCO Guidelines for Dermatologic Toxicity

Table 1. Management of Skin irAEs in Patients Treated With ICPis (continued)

1.0 Skin Toxicities	
Grading	**Management**
All grades	In cases of suspected SJS or any mucous membrane involvement, discontinue ICPi treatment and monitor closely for improvement, regardless of grade
G1: NA	For SCARs, there is no G1 category; if lower BSA is involved with bullae or erosions, there should remain a high concern that this reaction will progress to G3 or G4
G2: Morbilliform ("maculopapular") exanthem covering 10%-30% BSA with systemic symptoms, lymphadenopathy, or facial swelling	Hold ICPi and monitor patients closely every 3 days with G2 irAEs for progression to involvement of greater BSA and/or mucous membrane involvement Consider following patients closely using serial photography Initiate therapy with topical emollients, oral antihistamines, and medium- to high-strength topical corticosteroids Consider initiation of prednisone (or equivalent) 0.5-1 mg/kg tapered over at least 4 weeks
G3: Skin sloughing covering < 10% BSA with mucosal involvement associated signs (eg, erythema, purpura, epidermal detachment, mucous membrane detachment)	Hold ICPi therapy and consult with dermatology Treat skin with topical emollients and other petrolatum emollients, oral antihistamines, and high-strength topical corticosteroids; dimethicone may also be offered as an alternative to petrolatum Administer IV (methyl)prednisolone (or equivalent) 0.5-1 mg/kg and convert to oral corticosteroids on response, wean over at least 4 weeks Admit to burn and/or consult wound services with attention to supportive care, including fluid and electrolyte balance, minimizing insensible water losses, and preventing infection Given the immune mechanism of action of these medicines, use of immune suppression is warranted and should be offered For mucous membrane involvement of SJS or TEN, appropriate consulting services should be offered to guide management in preventing sequelae from scarring (eg, ophthalmology; ear, nose, and throat; urology; gynecology; etc, as appropriate)
G4: Skin erythema and blistering/sloughing covering ≥ 10% BSA with associated signs (eg, erythema, purpura, epidermal detachment, mucous membrane detachment) and/or systemic symptoms and concerning associated blood work abnormalities (eg, liver function test elevations in the setting of DRESS/DIHS)	Permanently discontinue ICPi Admit patient immediately to a burn unit or ICU with consulted dermatology and wound care services Consider further consultations based on management of mucosal surfaces (eg, ophthalmology; urology; gynecology; ear, nose, and throat surgery; etc) Initiate IV (methyl)prednisolone (or equivalent) 1-2 mg/kg, tapering when toxicity resolves to normal IVIG or cyclosporine may also be considered in severe or corticosteroid-unresponsive cases Consider pain/palliative consultation and/or admission in patients presenting with DRESS manifestations
Additional considerations: The usual prohibition of corticosteroids for SJS is not relevant here, as the underlying mechanism is a T-cell immunodirected toxicity. Adequate suppression is necessary with corticosteroids or other agents and may be prolonged in cases of DRESS/DIHS	

Brahmer JR, 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*. 2018;36(17):1714–1768. https://doi.org/10.1200/JCO.2017.77.6385

NCCN Guidelines for Dermatologic Toxicity: Rash

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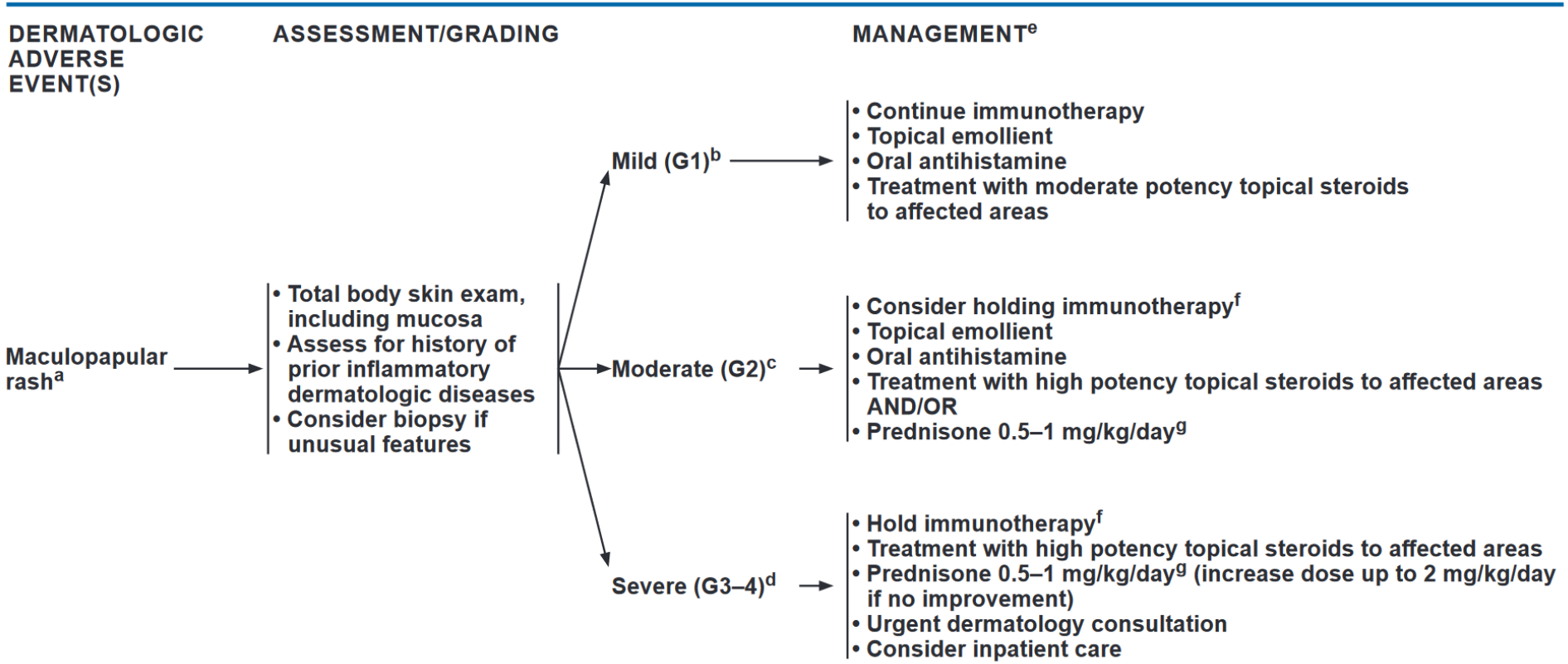
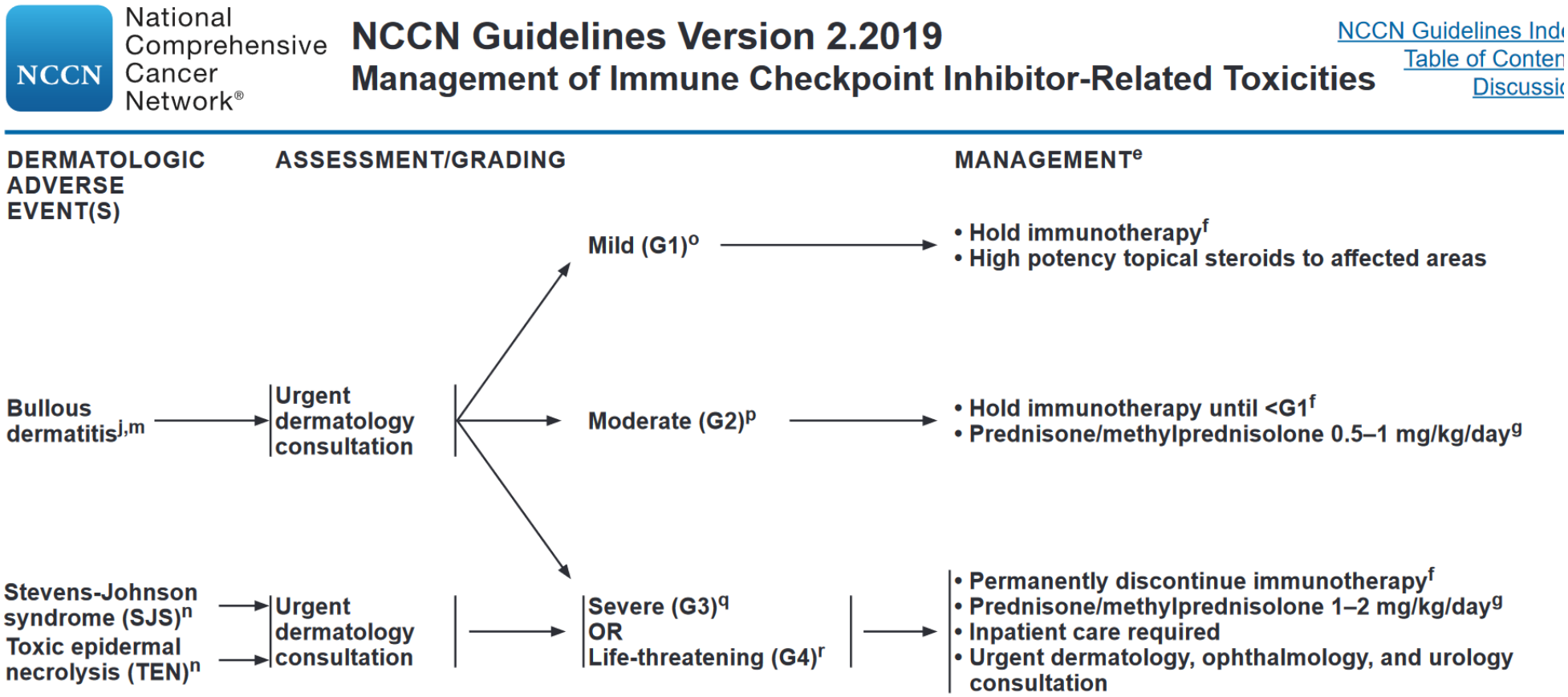
Management of Immune Checkpoint Inhibitor-Related Toxicities

NCCN Guidelines Index
Table of Contents
Discussion

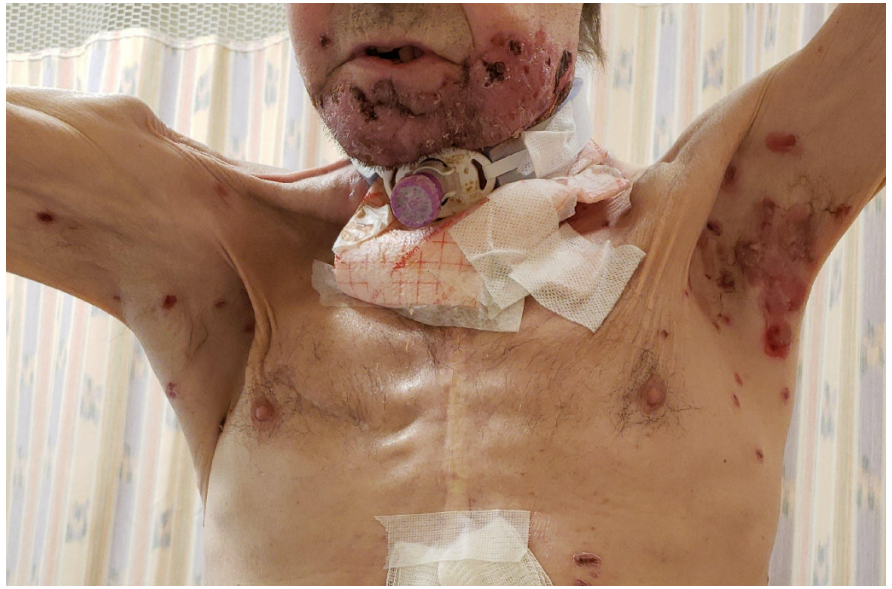


NCCN Guidelines for Dermatologic Toxicity: Blistering

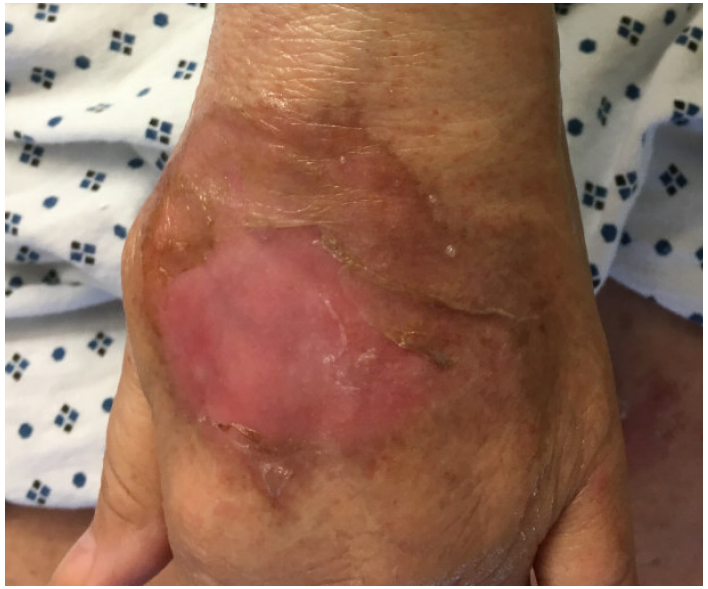


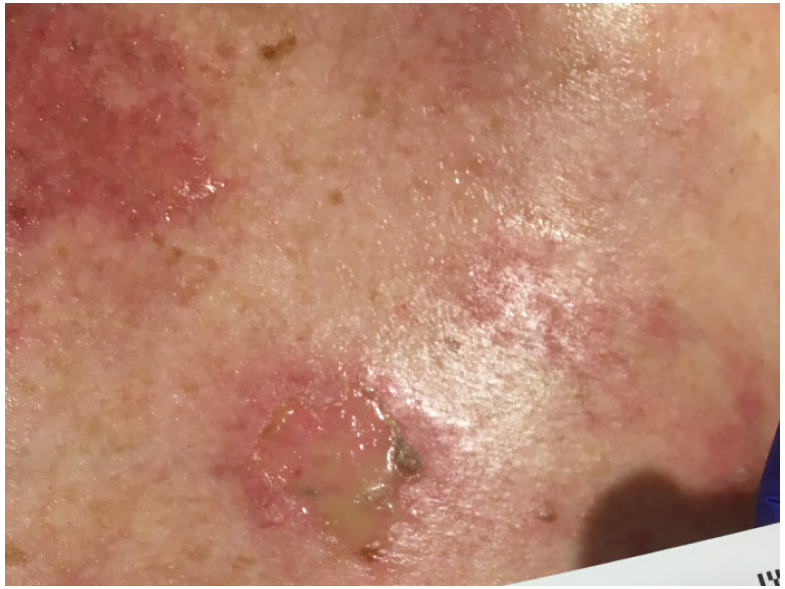
Blistering Dermatitis From Immunotherapy

Bullous pemphigoid from pembrolizumab in a head and neck cancer patient



SJS from pembrolizumab in NSCLC patient





Images courtesy of Beth Eaby-Sandy, Abramson Cancer Center, Hospital of the University of Pennsylvania

Endocrinopathies: The Most Common irAE

- Hypothyroidism: 10%–20% across clinical trials, TSH elevated
  - Check T4
  - Treat with levothyroxine for TSH over 10 or if symptomatic
  - Symptoms: fatigue, weight gain, cold intolerance, constipation, dry skin
- Hyperthyroidism (thyrotoxicosis): much less common, suppressed TSH
  - Symptoms: tachycardia, appetite change, insomnia, diarrhea, irritability, increased sweating
  - Treatment based on symptoms; consult endocrine
  - Beta blocker if indicated

NCCN Guidelines for Hypothyroidism

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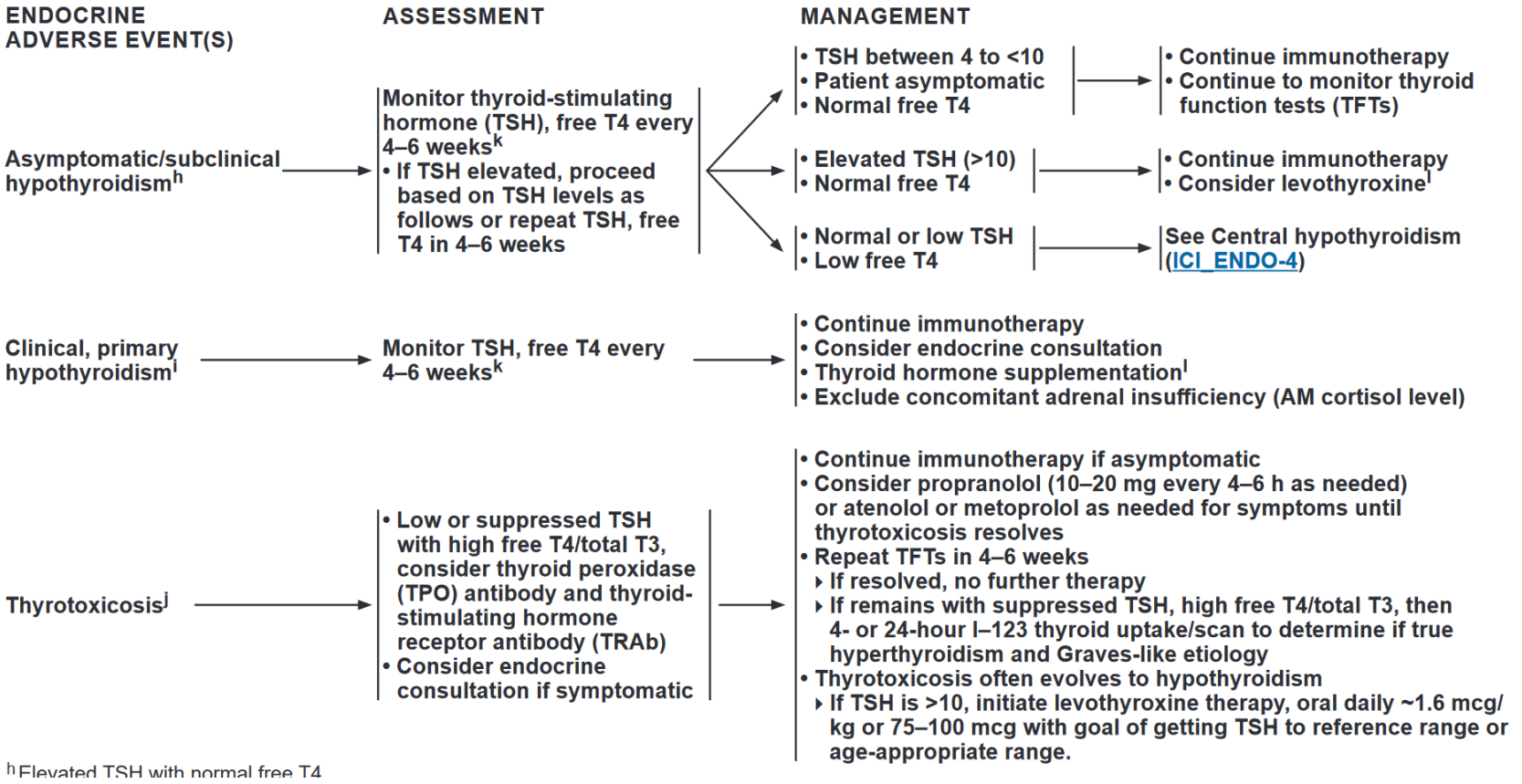
Management of Immune Checkpoint Inhibitor-Related Toxicities

NCCN Guidelines Index
Table of Contents
Discussion



[h] Elevated TSH with normal free T4

Endocrinopathies: The Most Common irAE (cont.)

- Adrenal insufficiency
  - Symptoms: severe fatigue, hypotension, dizziness, nausea/vomiting
  - Treatable and may continue therapy often
  - Endocrine labs
- Hypophysitis
  - Similar symptoms to adrenal insufficiency
  - Treatment very similar as well
  - Need MRI brain with pituitary cuts to diagnose and labs
- Type 1 diabetes: rare, less than 1%
  - Very high blood sugar in patient with no history of hyperglycemia, usually quite symptomatic
  - Will need insulin for the rest of their life
  - Need endocrine consult

NCCN Guidelines for Adrenal Insufficiency

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Management of Immune Checkpoint Inhibitor-Related Toxicities

NCCN Guidelines Index
Table of Contents
Discussion

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

NCCN Guidelines for Hypophysitis

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Management of Immune Checkpoint Inhibitor-Related Toxicities

NCCN Guidelines Index
Table of Contents
Discussion

ENDOCRINE ADVERSE EVENT(S)	ASSESSMENT	MANAGEMENT[n]
Central hypothyroidism[s]	• Evaluate cortisol (AM), FSH, LH, TSH, free T4, DHEA-S • Estradiol testing in women • Testosterone testing in men • Consider MRI of pituitary if confirmed central thyroid/ adrenal insufficiency	• Consider holding immunotherapy until no longer symptomatic[f] • Treat as hypophysitis (below)
Hypophysitis[t]	• Evaluate cortisol (AM), FSH, LH, TSH, free T4, testosterone in men, estrogen in premenopausal women • MRI brain ± contrast with pituitary/sellar cuts, if symptomatic	• Consider endocrine consultation • Hold immunotherapy until acute symptoms resolve[f,t] • If symptomatic, prednisone/methylprednisolone 1–2 mg/kg/day[o] • Hormone replacement as indicated[u] • Patient education regarding stress doses of hydrocortisone for infection, trauma, etc. ▸ Alert bracelet is recommended

Pearls for Managing Endocrinopathy

- When these occur, they will be on the hormone supplementation for the rest of their lives
- Remember to get baseline TSH at minimum
- Other than hypothyroidism, these are rare; however, the symptoms are usually profound
- Many of these patients can remain on treatment without even holding drug, or brief hold and restart

Immune-Mediated Toxicities of PD-1, PD-L1 Inhibitors, and Anti-CTLA4

- Hepatitis
  - Elevation of LFTs, transaminitis
  - Grade 3/4 around 1%–3% over all drugs
- Nephritis
  - Changes in renal function: creatinine/BUN
  - Grade 3/4 around 1%–3% over all drugs
- Neuromuscular toxicities
  - Very uncommon, peripheral neuropathy and others, encephalitis. 1 fatal case of Guillian-Barré syndrome reported with ipilimumab
- Rare toxicities
  - Occular (uveitis), pancreatitis, myocarditis, polymyositis, autoimmune pancytopenias, acquired hemophilia, and many others!

More General Side Effects of Immunotherapy Checkpoint Inhibitors

- Nausea
  - Unclear etiology, rare grade 3/4, manage accordingly
- Diarrhea
  - Minor, no colitis hallmarks
  - May treat with loperamide; however, high alert for colitis risk
- Arthritis/myalgias
  - Obvious inflammation of joints
  - Can use NSAIDs in eligible patients, low-dose steroids
- Fatigue
  - Not exactly etiology, the cancer?

Treatment of Patients With Underlying Autoimmune Disease

- There are no contraindications to the immune checkpoint inhibitors; that being said…
  - Solid organ transplant patients
    - In patients with prior renal transplant where an immune checkpoint inhibitor was used, out of 5 published case studies, 4 out of 5 patients rejected their transplanted kidney
  - Low- or high-grade autoimmune disease
    - Rheumatoid arthritis
    - Scleroderma
    - Lupus
    - Many others: What medications are they on? How symptomatic are they of their autoimmune disease?

Brahmer JR, 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*. 2018;36(17):1714–1768. https://doi.org/10.1200/JCO.2017.77.6385

Rechallenging After irAEs

- Rates of recurrent irAEs after rechallenge are generally acceptable
- 55% of the patients developed same or new irAE
- Study specific to colitis
  - In 167 patients with colitis, 1/3 developed recurrent colitis after resumption of the immunotherapy
  - It was more common to develop recurrent colitis when resuming anti-CTLA drug as opposed to PD-1 or PD-L1 inhibitor

Table 3. Characteristics of the Immune-Related Adverse Events After Anti–PD-1 or Anti–PD-L1 Rechallenge

Toxic Effect	No./No. (%)[a]	
	Same irAE After Rechallenge (n = 17)	New irAE After Rechallenge (n = 5)
Pneumonitis	1/5 (20)	1/5 (20)
Hepatitis	3/5 (60)	0/5 (0)
Colitis	3/5 (60)[b]	0/5 (0)
Arthralgia	5/6 (83)[c]	1/6 (15)
Lipase elevation	0/3 (0)	2/3 (67)
Grade 4 neutropenia	2/3 (67)	0/3 (0)
Skin	3/7 (43)[b]	1/7 (14)

Simonaggio A, et al. Pub online ahead of print. *JAMA Oncol*. 2019. https://doi.org/10.1001/jamaoncol.2019.1022
Abu-Sbeih H, et al. Pub online ahead of print. *JCO*. 2019. https://doi.org/10.1200/JCO.19.00320

Clinical Pearls

- How do we educate patients about irAEs?
- These drugs are the future of oncology
- Must continue to understand toxicity
- More research to try to predict irAEs?

Audience Response Question

The strongest data to correlate immune-related adverse events with a survival advantage is in:

A. Patients with NSCLC receiving nivolumab
B. Patients with NSCLC receiving pembrolizumab
C. Patients with melanoma who experience pneumonitis but not skin rash
D. Patients with melanoma who experience colitis but not skin rash
E. Unsure

Audience Response Question

A patient with SCLC is receiving the combination of ipilimumab and nivolumab in the second-line setting after failure on platinum-based front-line chemotherapy. She develops worsening diarrhea with mucus in her stools and significant abdominal pain. IV steroids do not improve her symptoms and she is admitted to the hospital for IV hydration and symptom management.

She is given a dose of infliximab and finally it improves. She is labeled as having a grade 3 colitis requiring 1 dose of infliximab. According to the NCCN Guidelines, you should:

A. Permanently discontinue the immunotherapy

B. Consider restarting a PD-1 inhibitor but not the anti-CTLA drug once symptoms resolve

C. Consider restarting both the PD-1 inhibitor and the anti-CTLA drug once symptoms resolve

D. Consider restarting both the PD-1 inhibitor and the anti-CTLA drug, but only after a long steroid taper and all symptoms have resolved

E. Unsure

Questions?