Society for Immunotherapy of Cancer

Advances in Cancer Immunotherapy™

Immunotherapy Toxicity Management

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Disclosures

- Consulting Fees: Exelixis, Aveo, Apricity Health, Clinigen
- I will be discussing non-FDA approved indications during my presentation.

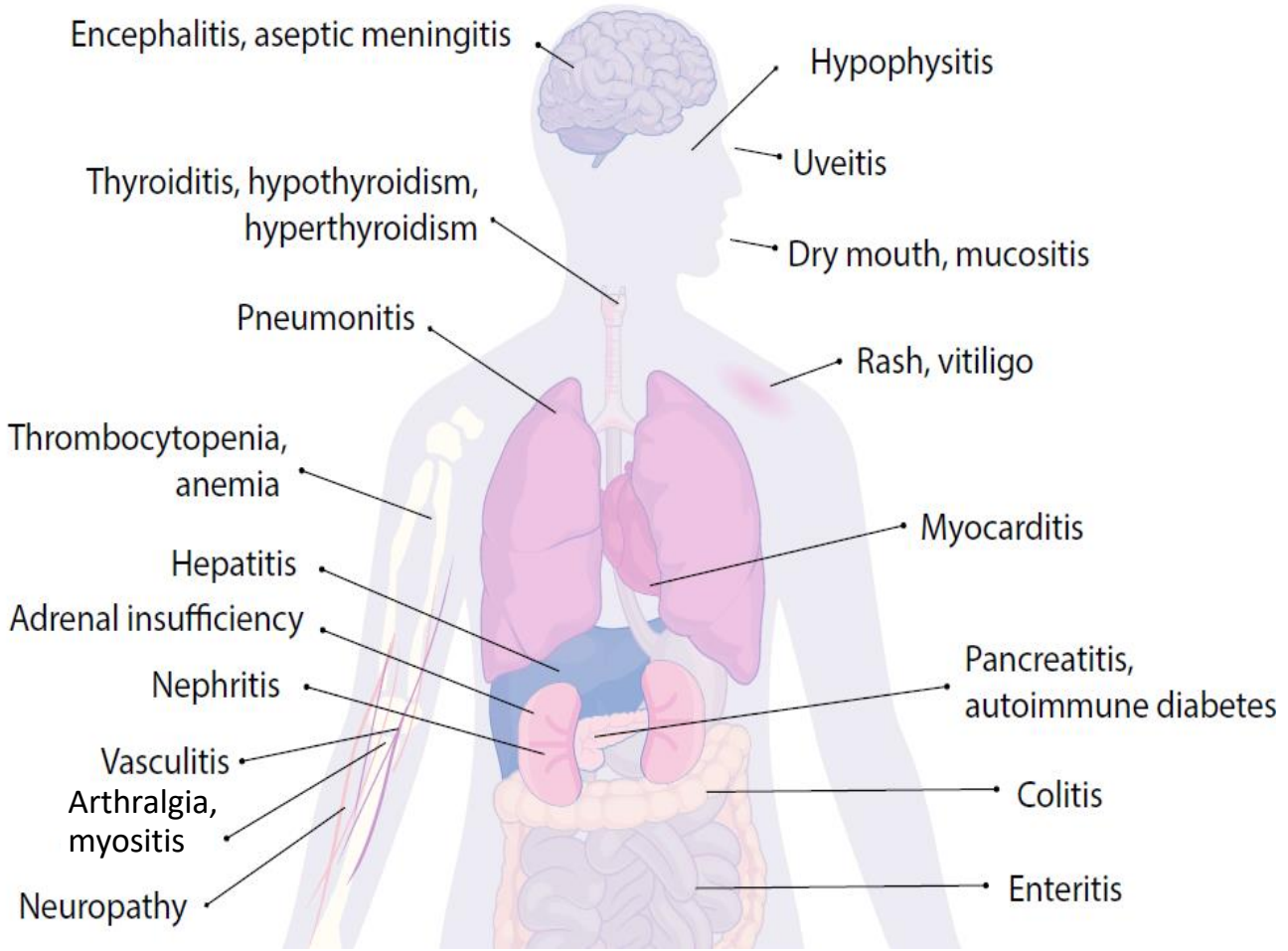
Immune related adverse events (irAEs)

- Critical to recognize irAEs early
- Prompt treatment to improve clinical outcomes
- Patient/caregiver education key
- Multidisciplinary team for management

The Spectrum of irAEs

1. "Taking the brakes off" the immune system can help the body fight cancer, but can also lead to toxicity from an activated immune system

2. Any organ system can be affected



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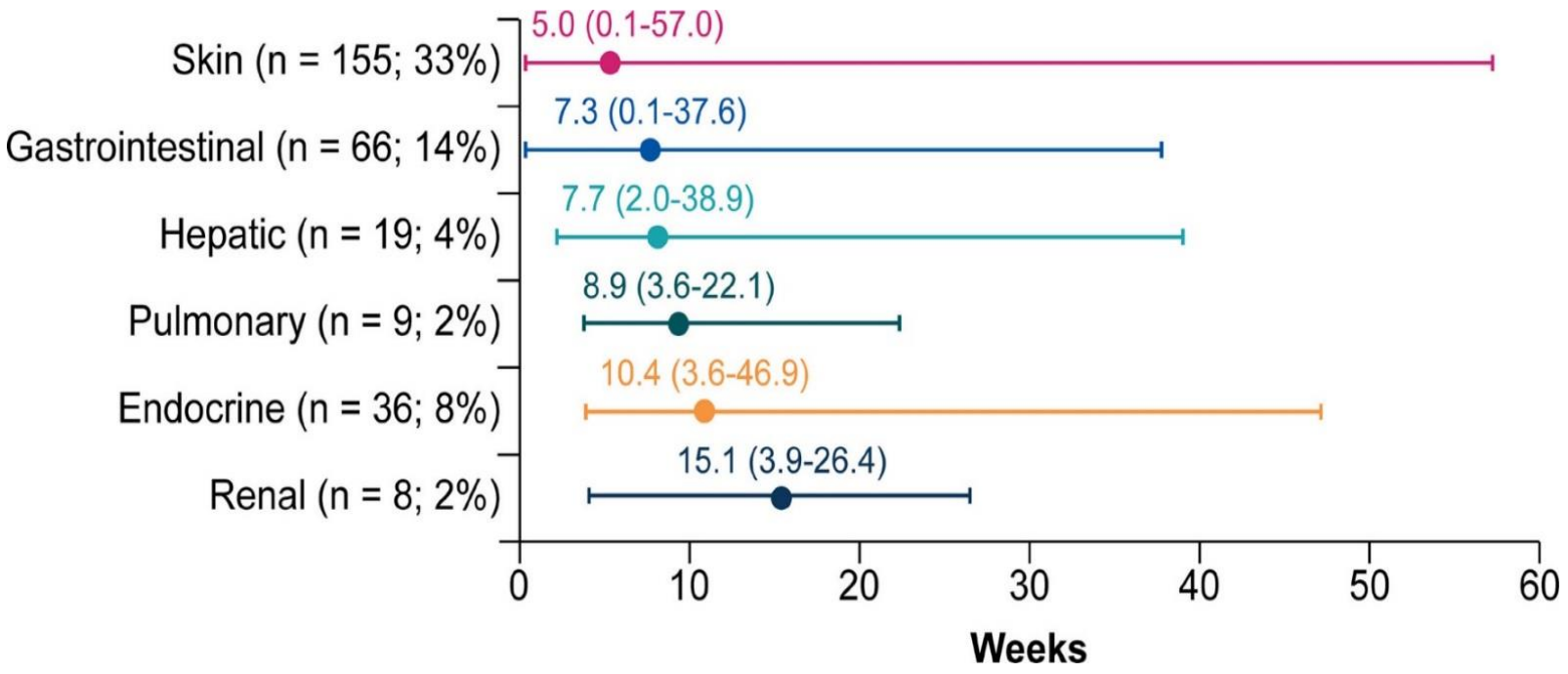
1. Postow MA et al. *N Engl J Med*. 2018;378:158-168. 2. Brahmer JR et al. *J Clin Oncol*. 2018;36:1714-1768.

Onset of irAEs



- Can be days to months after therapy initiation
- May occur even after treatment is discontinued
- Important to identify patients who are currently **OR** previously on ICI treatment

Pallin, Acad Emerg Med 2018
Puzanov and Diab, JITC 2017

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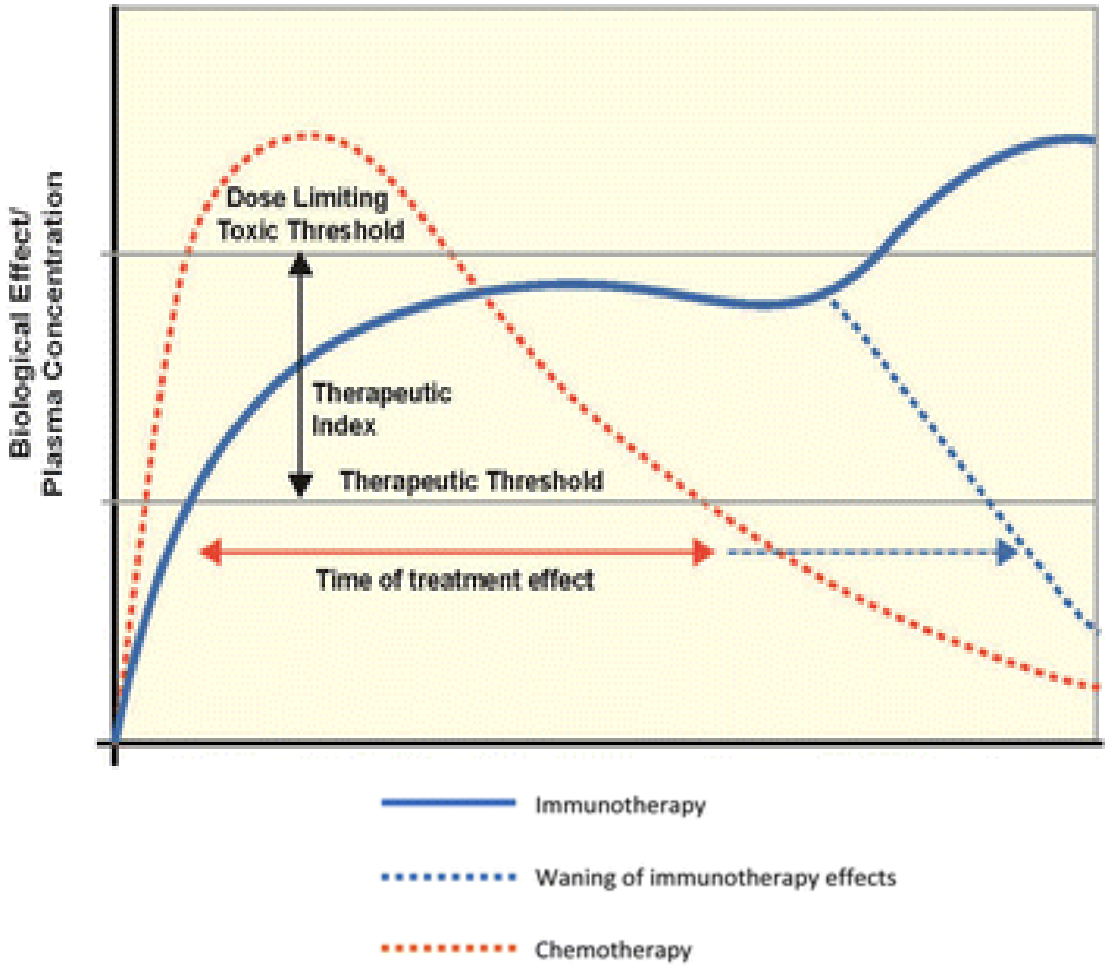
irAE Timing and Etiology

- Immune checkpoint inhibitor (ICI) toxicities often have delayed onset and prolonged duration in relation to chemotherapy toxicity
- Toxicities result from non-specific activation of the immune system and may mimic other medical conditions



Puzanov and Diab, JITC 2017

Incidence of irAEs

- Anti-CTLA-4 inhibitor (ipilimumab):
  - irAEs more common
  - Dose-dependent toxicities
- PD-1/PD-L1 inhibitors:
  - irAEs less common
  - Toxicities less dose-dependent
- Combination ipilimumab/nivolumab:
  - Higher incidence of irAEs vs single agent therapy

Puzanov and Diab, JITC 2017.
NCCN Guidelines. Management of immunotherapy-related toxicities. Version 2.2019.

Incidence of specific irAEs by ICI

Drug	Dermatitis	Colitis	Hepatitis	Endocrinopathies	Pneumonitis
	All grades (grade 3-4)				
Ipilimumab	14.5 (12)	10 (7)	5 (2)	10 (3)	<1
Ipilimumab/Nivolumab	30 (3)	26 (16)	13 (6)	35 (4)	6 (2.2)
Nivolumab	28 (1.5)	2.9 (0.7)	1.8 (0.7)	12 (0)	3.1 (1.1)
Pembrolizumab	20 (0.5)	1.7 (1.1)	0.7 (0.4)	12.5 (0.3)	3.4 (1.3)
Atezolizumab	17 (0.8)	1 (<1)	1.3 (<1)	5.9 (<1)	2.6 (<1)
Avelumab	15 (0.4)	1.5 (0.4)	0.9 (0.7)	6.5 (0.3)	1.2 (0.5)
Durvalumab	11 (1)	1.3 (0.3)	1.1 (0.6)	16.2 (0.1)	2.3 (0.5)

Puzanov and Diab, JITC 2017

irAE management

- Recognition
- Need for treatment based on severity (CTCAE grade)
- Resources/algorithms for irAEs
  - SITC/ASCO/NCCN/ESMO
  - Review article by Dr. Darnell and colleagues highlighting/synthesizing management recommendations of above organizations

Darnell EP et al. *Curr Oncol Rep.* 2020; 22:39.

CTCAE toxicity grading

- Refers to severity:
  - Grade 1 Mild
  - Grade 2 Moderate
  - Grade 3 Severe, but not immediately life-threatening
  - Grade 4 Life-threatening
  - Grade 5 Death related to AE

Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. Published: November 27, 2017, U.S. Dept. of Health and Human Services; National Institutes of Health; NCI

General Approach to Treatment

- Hold ICI for grade 2 or greater toxicity; start low dose steroids (prednisone 0.5 mg/kg) if sx's persist > 1 week
- Consider holding ICI for grade 1 cardiac, pulmonary or neuro irAEs
- 1st line for **MOST** grade 3-4 irAE's is systemic high-dose corticosteroids
- Endocrine toxicities managed with hormone replacement
- Some grade 1-2 irAEs may respond to topical steroids (dermatologic, ophthalmologic)
- Taper steroids slowly once symptoms improve to grade 1 or less
- Add other immunosuppression for steroid refractory irAEs

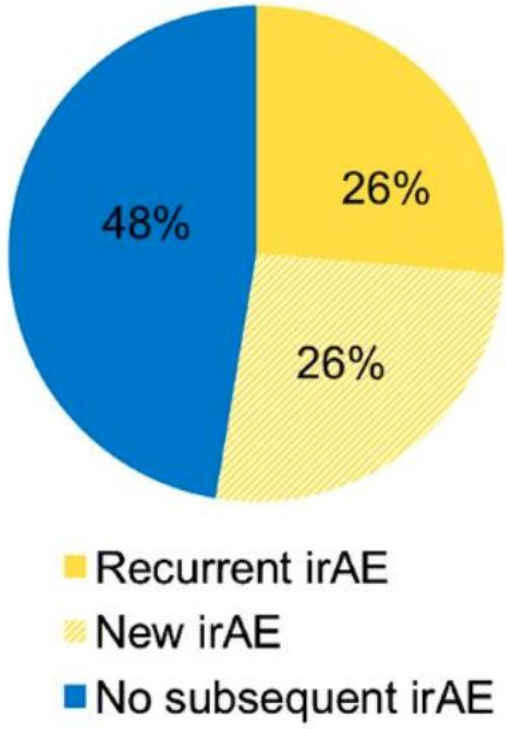
Additional immunosuppression

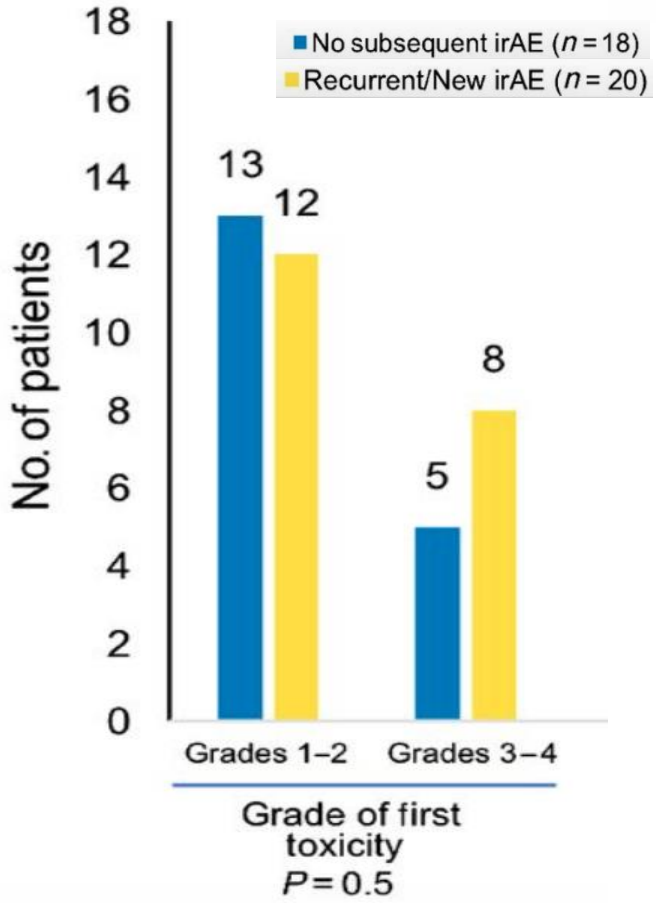
- Infliximab: anti-TNF-α mAb
  - Hepatotoxic so should NOT be used for immune-mediated hepatitis
  - Risk for hepatitis B and tuberculosis activation; obtain hepatitis serologies and TB testing prior to initiation
  - Dose: 5 mg/kg; 2nd dose may be administered after 2 weeks
- Vedolizumab: α4β7 integrin mAb
  - **Selective GI immunosuppression** → inhibits migration of T cells across endothelium into inflamed GI tissues
  - Dose: 300 mg; repeat dose at 2 and 6 weeks
- Others: mycophenolate, IVIG, tacrolimus

Abu-Sbeih H. JITC. 2018 Dec 5;6(1):142.
NCCN Guidelines. Management of immunotherapy-related toxicities. Version 2.2019.

Rechallenging with ICI after irAEs

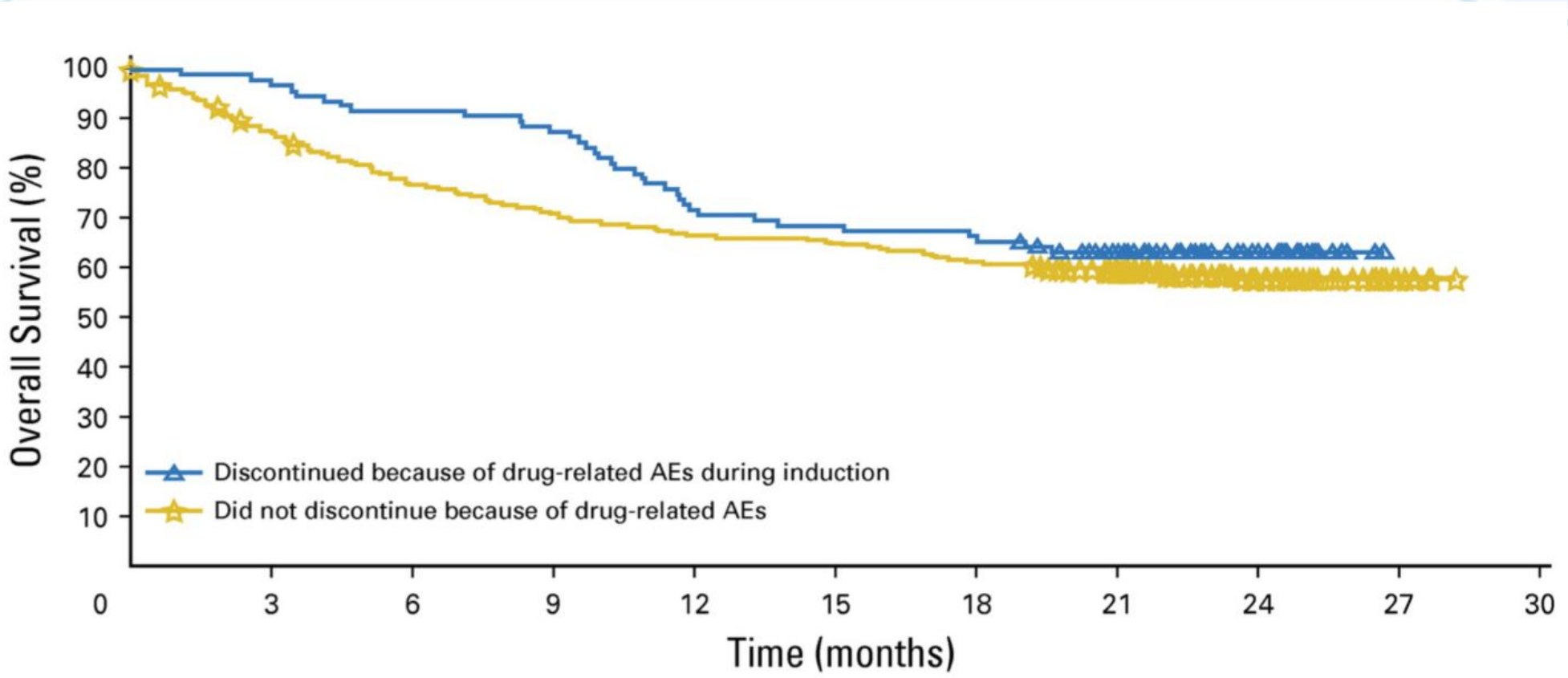
- Patients should not be rechallenged until irAE resolved to grade ≤1
- Re-challenge with anti-PD-1/L1 after anti-CTLA-4 ± anti-PD-1 likely safe
- Caution in re-challenging with same ICI in patients who previously had grade 3-4 irAEs





Santini FC. Cancer Immunol Res 2018.

Effect of irAEs on patient outcomes



No significant difference in survival in melanoma patients who discontinued ipilimumab + nivolumab due to irAEs versus those who did not discontinue treatment

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Schadendorf D. J Clin Oncol 2017 Dec; 35(35):3807-3814.

Special considerations

- Immunotherapy in patients with autoimmune disorders
- Immunotherapy in combination with other agents (chemotherapy or targeted therapy)
- Emerging data suggesting negative antitumor activity with high dose steroids
- Lack of randomized trials evaluating treatment of irAEs

Immune related adverse events: Key points

- Prompt recognition/treatment critical
- May affect any organ system
- High suspicion if new symptoms develop while on ICI's
- Communication b/t patient/caregiver and multidisciplinary oncology team is key
- Patient outcomes improve w/good toxicity management

Case Study 1

- 71 y.o. male with Stage IV RCC
- Received 2 doses of combination ipilimumab and nivolumab
- Presented w/abdominal pain; scans show disease regression
- Ipi/nivo held
- 10 days later, developed recurrent abdominal pain, N/V, diarrhea

Case Study 1, cont.

- What would be your plan?

A. Admit the patient for supportive care and further GI workup

B. Hydrate the patient and send him home with VNA and antiemetics/antidiarrheals with clinic visit in 3 days

C. Set up a GI consult and start steroids

D. Administer a 3rd dose of ipilimumab/nivolumab after IV hydration and antiemetics

Case Study 1, cont.

- Admitted and underwent CT showing small bowel enteritis
- Stool cultures negative; began IV solumedrol
- EGD = enteritis clinically with biopsy confirmation
- DC'ed to home with IV solumedrol after GI sx's and pain improved
- Transitioned to oral prednisone 2 mg/kg one week later w/continued improvement
- Developed recurrent diarrhea w/urgency and incontinence as prednisone tapered

Case Study 1, cont.

- What would be your next management step?
  - A. Set up infliximab infusion, continue antidiarrheals
  - B. Admit patient, restart IV fluids, resume IV steroids, obtain GI consult for infliximab
  - C. Continue steroid taper and BRAT diet while giving antidiarrheals
  - D. Set up outpatient IV fluids, IV steroids and GI consult

Case Study 1, cont.

- Admitted for IV hydration and IV solumedrol w/improvement
- GI consult with recommendation for infliximab
- DC'ed to home with IV solumedrol
- Received one dose of infliximab
- Transitioned to oral steroids 2 weeks later
- Slow taper of prednisone tolerated well
- Serial torso CT's show stable disease regression

Case Study 1 take home points

- Demonstrates challenge of severe irAEs
- Potential for negative clinical outcomes as immunotherapy indications and use become more widespread
- Highlights need for comprehensive patient and health care provider education

Case Study 2

- 76 y.o. female with Stage IV RCC
- Started single agent nivo with disease regression
- After one year of nivo, developed grade 2 transaminitis
- What would be your approach?

Case Study 2, cont.

- A. Continue immunotherapy and ask her to call with new GI symptoms
- B. Hold nivolumab and refer to hepatology
- C. Assess for symptoms of hepatitis, review meds for hepatotoxins, ETOH use, hold nivolumab
- D. Continue immunotherapy and have labs repeated in one week

Case Study 2, cont.

- Assess for symptoms – no N/V, anorexia, RUQ pain
- Evaluate hepatotoxic agents – atorvastatin held, acetaminophen and alcohol reduced
- Nivolumab held; weekly labs
- Transaminases improve to grade 1
- Nivo restarted
- Transaminases back to grade 2
- What would your approach be?

Case Study 2, cont.

- A. Continue nivolumab and watch LFT's closely
- B. Hold nivolumab and watch LFT's closely
- C. Continue nivolumab, refer to hepatology
- D. Permanently discontinue nivolumab

Case Study 2, cont.

- Nivo held
- Repeat labs show grade 3 LFT's
- Remains asymptomatic
- Management?
  - A. Continue nivolumab, hold hepatotoxins and avoid ETOH, hepatology consult
  - B. Hold nivolumab and check LFT's weekly
  - C. Hold nivolumab and obtain hepatology consult
  - D. Continue nivolumab and check LFT's weekly

Case Study 2, cont.

- Nivo held
- Hepatitis screen negative
- Urgent hepatology consult
- LFT's worsening
- Autoimmune markers sent (IgG, IgM, ANA, ASMA, AMA) – ANA positive
- Liver MRI shows fibrosis
- Liver bx shows plasma cell predominant hepatitis and necrosis c/w moderate to severe autoimmune hepatitis
- Remains asymptomatic

Case Study 2, cont.

- How would you manage this patient?
  - A. Begin prednisone 1-2 mg/kg/day, monitor LFT's every 2 days, close hepatology follow up, consider permanent discontinuation of nivo
  - B. Begin prednisone 0.5 mg/kg/day to start, monitor LFT's every 3 days, close hepatology follow up, consider permanent discontinuation of nivo
  - C. Admit to the hospital, begin IV methylprednisolone, daily LFT's, inpatient hepatology consult
  - D. Begin prednisone 0.5 mg/kg/day, monitor LFT's weekly, restart nivo when LFT's return to grade 1

Case Study 2, cont.

- Placed on prednisone 1.5 mg/kg daily
- PPI and PCP prophylaxis started
- LFT's return to grade 1 within 3 days
- LFT's return to normal within 3 weeks
- Slow steroid taper with normal LFT's
- Statin restarted
- Scans show no disease progression and nivo remains on hold