Society for Immunotherapy of Cancer

Cancer Immunotherapy GUIDELINES

Practical Management Pearls for Immune Checkpoint Inhibitor-related Adverse Events

September 16, 2021

11:30 a.m. – 12:30 p.m. ET

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(as of 6/7/21)

Moderators

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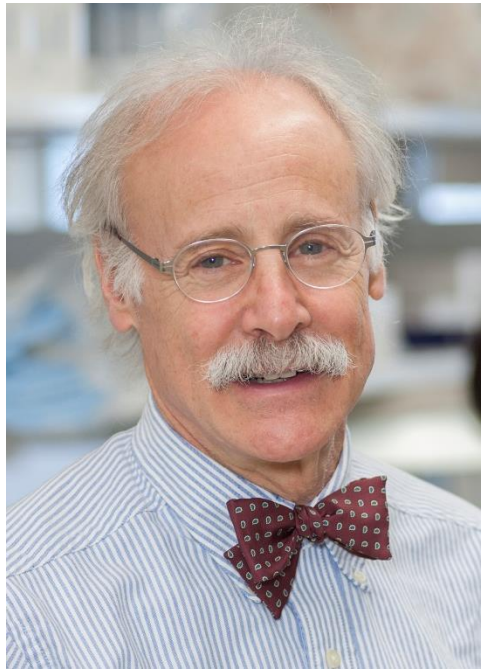

Marc S. Ernstoff, MD –
National Institute of Health

Presenters

David E. Gerber, MD – *Harold C. Simmons Comprehensive Cancer Center, UT Southwestern*

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Learning objectives

- Identify and manage difficult and severe immune-related adverse events from checkpoint inhibitor treatment
- Outline management approaches for steroid-refractory irAEs
- Properly identify the causative agent of adverse events in settings of immunotherapy combinations or sequencing
- Describe areas of controversy in irAE management

Open access Position article and guidelines

Journal for ImmunoTherapy of Cancer

Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune checkpoint inhibitor-related adverse events

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Guideline development

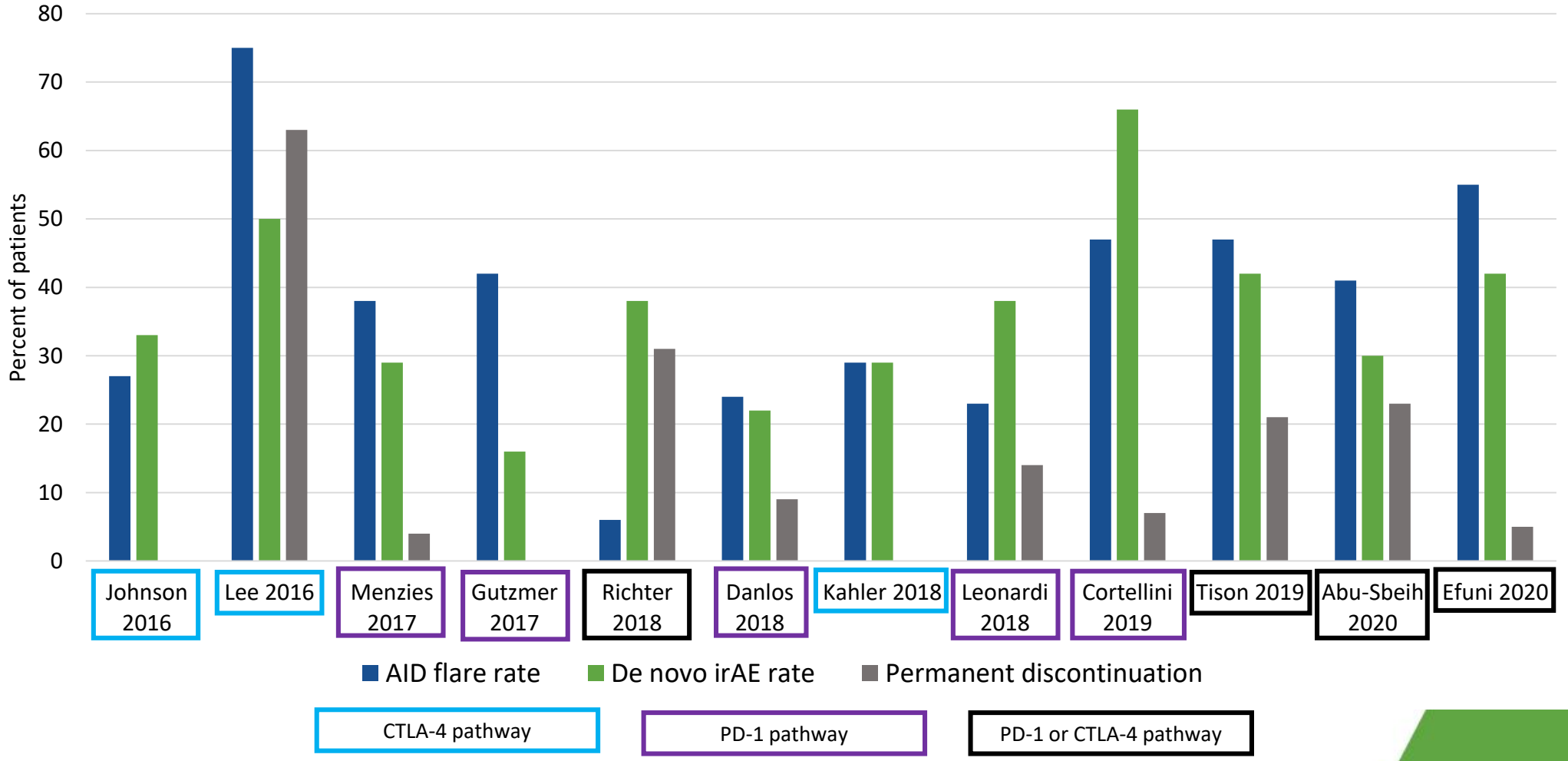
- Developed according to the Institute of Medicine's Standards for Developing Trustworthy Clinical Practice Guidelines
- Panel consisted of 23 experts in the field
- Recommendations are based upon published literature evidence, or clinical evidence where appropriate
- Consensus was defined at 75% approval among voting members

Webinar outline

Clinical questions in ICI toxicities:

- ICIs in high-risk populations (autoimmunity)
- Dose, duration and supportive care with steroids
- Steroid-resistant toxicities
- Difficult-to-diagnose irAEs
- Determining how each agent contributes to toxicity in combination therapy
- ICI re-challenge

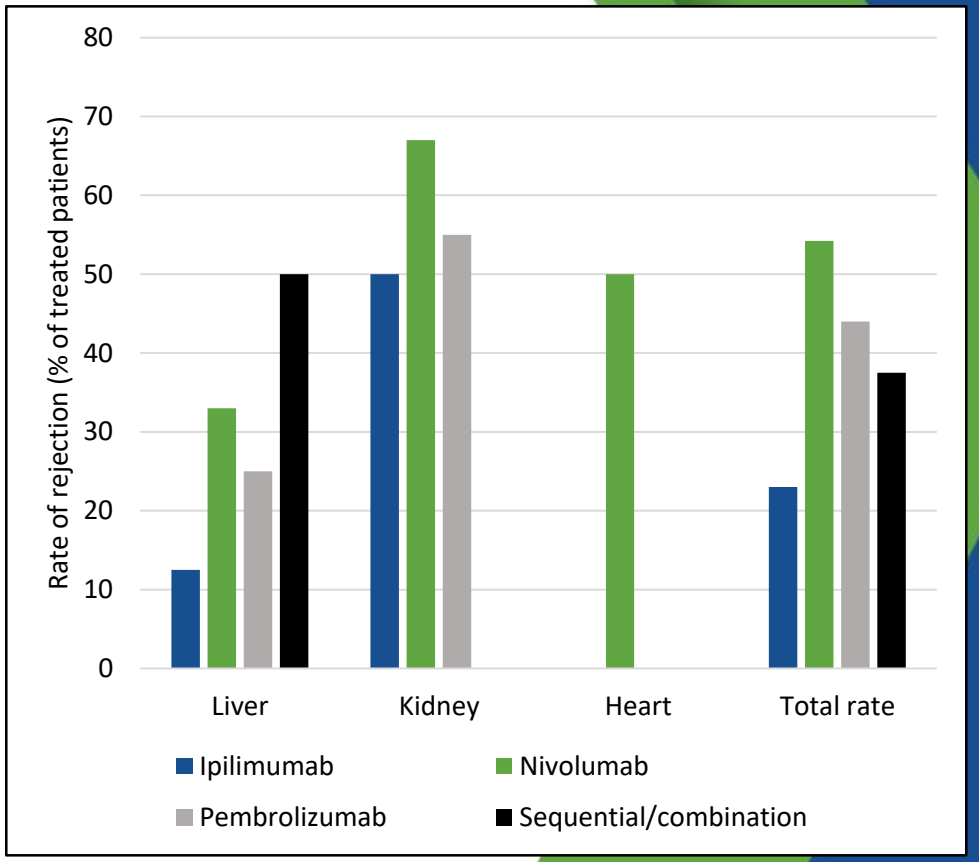
Patients with pre-existing autoimmune disorders



Boland, J Immunother Cancer 2020

ICI use in patients with solid organ or stem cell transplants

- Patients who relapse after allogeneic SCT:
  - Ipilimumab: 32% response (10 mg/kg); 14% GVHD; 21% irAEs
  - Anti-PD-1: 77% response; 26% died due to new-onset GVHD
- Solid organ data is limited; most is in renal SOT patients
  - One retrospective study (n=39) reported graft loss in 81% and death in 46%
  - Also reported rapid time to rejection with median onset of 21 days
- PD-1 pathway appears to be more critical in allograft immune tolerance compared to CTLA-4 pathway



Davids MS. NEJM 2016; Haverkos BM. Blood 2017
Abdel-Wahab. JITC 2019; Kumar V. Oncologist 2020

Practical pearls for high-risk patients

- Patient with underlying autoimmune disease can receive immune checkpoint therapy especially if their autoimmunity requires ≤ 10mg prednisone/day and is clinically under good control.
- Patients frequently have an increase in organ specific toxicities, but these are largely manageable
- Risk of organ-rejection and GvHD is great in those with prior organ transplant and allogeneic BMT, but this is not uniform

Dosing of steroids

- In general:
  - Grade 2 irAEs: 0.5-1 mg/kg/day oral prednisone or IV methylprednisolone or equivalent
  - Grade 3-4 irAEs: 1-2 mg/kg/oral prednisone or day IV methylprednisolone equivalent
- Patients should have significant clinical improvement within the initial 2-3 days. If no improvement is observed either increase dose of steroids up to 2mg/kg/day or add a second line immunosuppressive agent.
- Whenever second line immunosuppression is planned again re-evaluate for other causes of the toxicities (GI, liver or other organs).
- For myocarditis and CNS toxicities strongly consider higher dosage of methylprednisolone of 1 gm/day from 3-5 days

Brahmer, J Immunother Cancer 2021

Supportive care with steroids

- When beginning corticosteroid therapy, patients should be specifically counseled about potential toxicities, including hyperglycemia, mood disturbances, insomnia, gastritis, weight gain, and opportunistic infections
- There is potential for overlapping toxicities from steroids and ICIs (diabetes, musculoskeletal)
- Infection prophylaxis may vary by institutional practice, but must be considered early on in steroid therapy

Brahmer, J Immunother Cancer 2021

Steroid-Resistant immune-related adverse events

Steroid-refractory colitis

High-grade colitis

Initial: prednisone 1-2 mg/kg/day

Grade 4: IV corticosteroids

If no improvement within 3-5 days:

Administer infliximab. If necessary can give up to 3 doses of infliximab (5 mg/kg) at 0, 2, and 6 weeks.

If symptoms persist after two doses of infliximab:

Hold the third dose of infliximab

Administer up to 3 doses of vedolizumab (300 mg) at 0, 2, and 6 weeks

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Steroid-refractory hepatitis

High-grade hepatitis

Grade 2 hepatitis
Initial: IV or po predisone 0.5-1.0 mg/kg/day

Grade 3-4 hepatitis
Initial prednisone 1.0-2.0 mg/kg/day

If no improvement within 3-5 days:

Administer Mycophenolate mofetil
Initial at 500mg BID
then 1000mg BID

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Steroid-refractory pneumonitis

High-grade pneumonitis

Grade 2: 1-2 mg/kg/day prednisone

Grade 3+: 1-2 mg/kg/day methylprednisolone

If no improvement within 72 hours:

- **Mycophenolate mofetil**: 1-1.5 g twice daily (LE: 3)
- **hdIVIG**: 2 g/kg in divided doses over 2-5 days (LE: 4)
- **Infliximab**: 5 mg/kg, one dose with optional second dose 2 wk later (LE: 4)
- **Cyclophosphamide**: 600 mg/m^2 for 6 infusions (LE: 3)
- **Tocilizumab**: 4 mg/kg (LE: 4)

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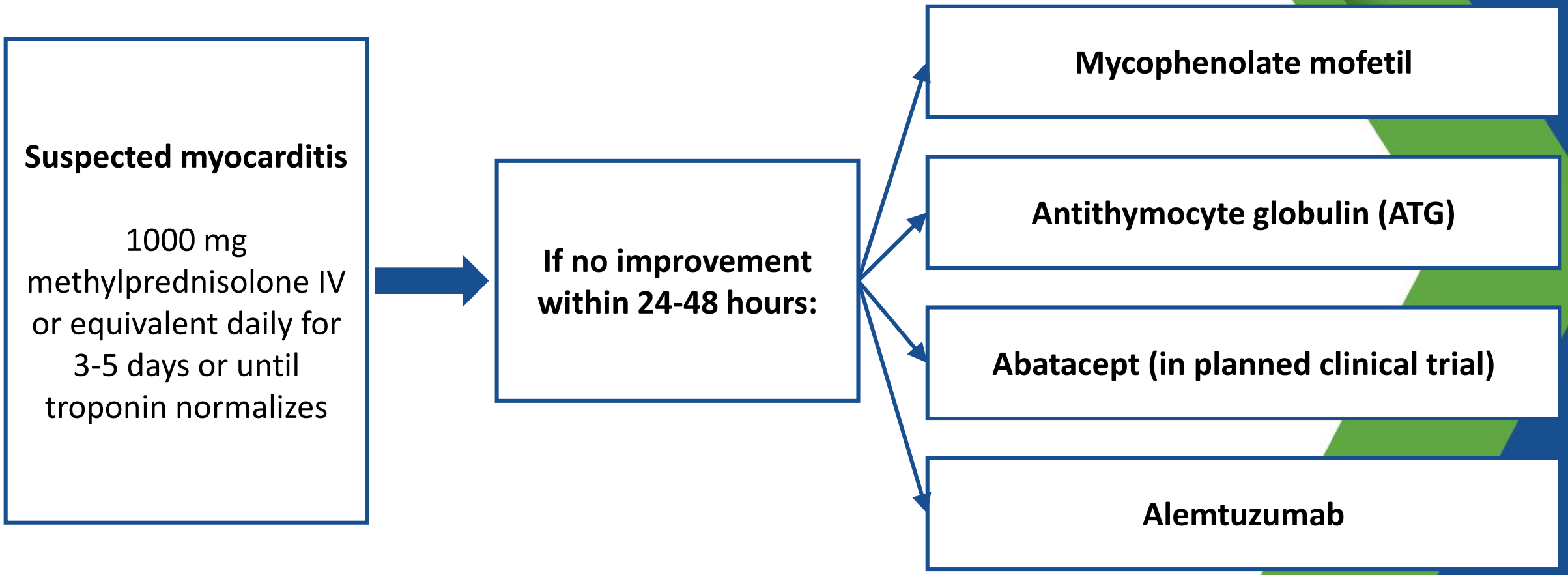
Steroid-refractory myocarditis



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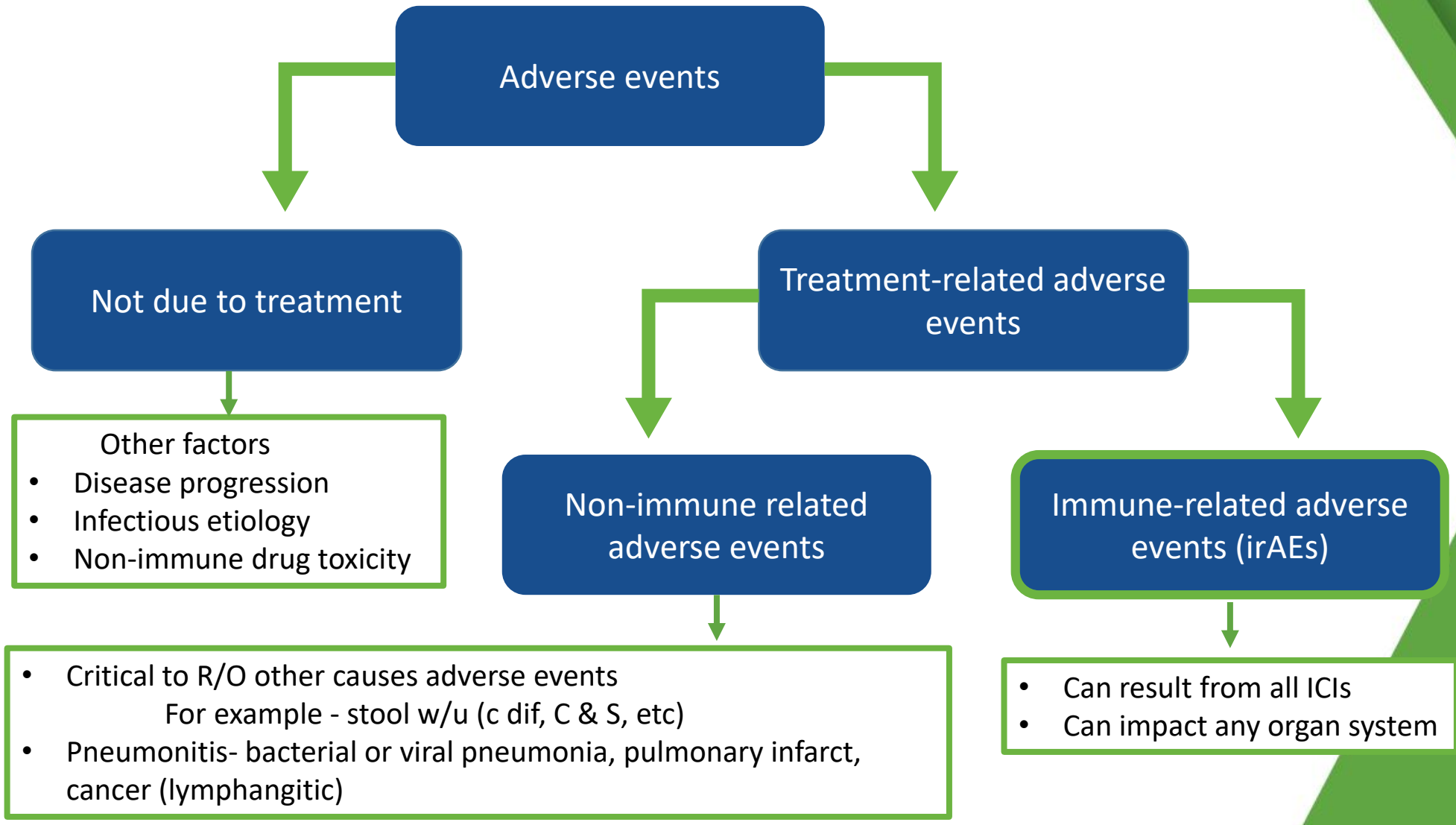
Steroids and second-line immunosuppressives

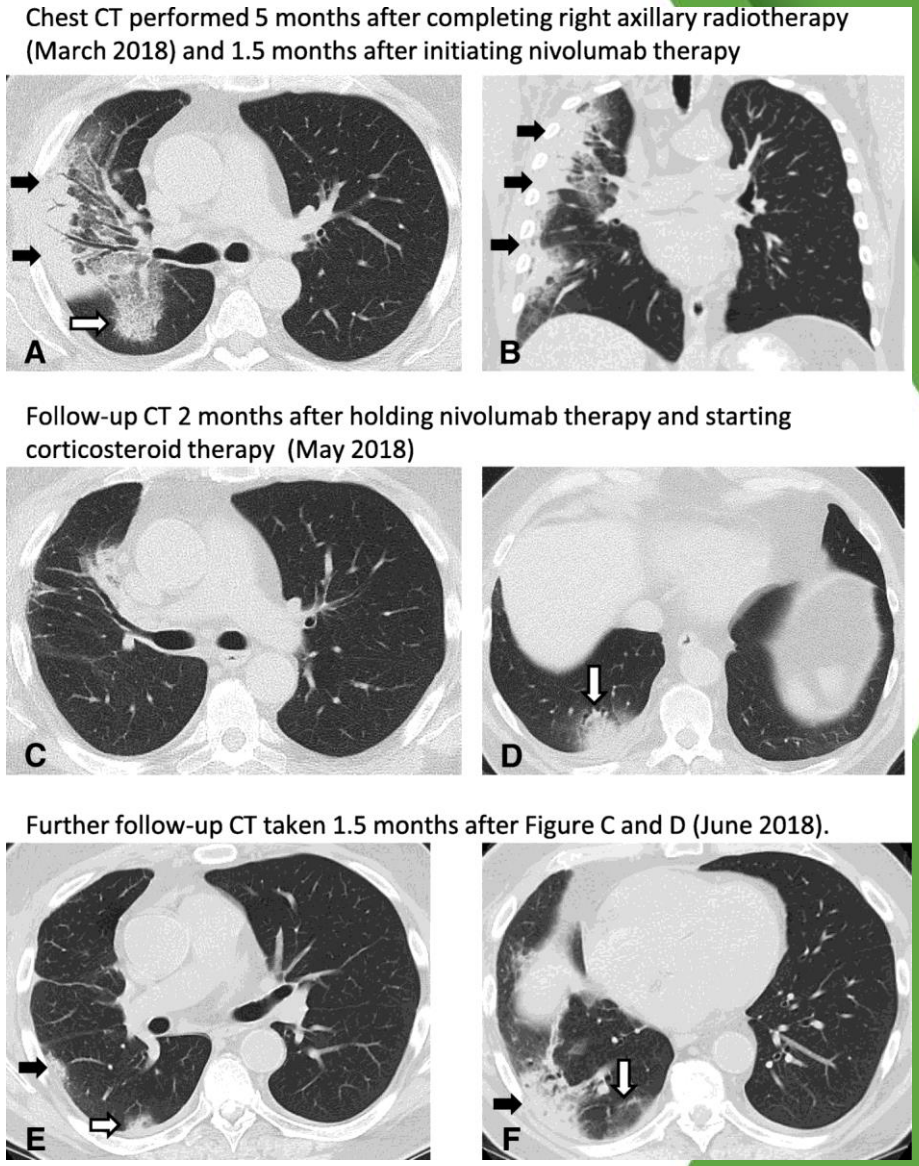
- If a patient is started on steroid treatment for an irAE but then warrants second-line immunosuppression, how do you handle the steroids (taper, etc)?
  - Once irAE is controlled then taper steroids over 2-4 week period
- Are there any precautions one should take at this time?
- Does this preclude further immune checkpoint therapy?

Types of adverse events



Pneumonitis: immune- or radiation-associated?

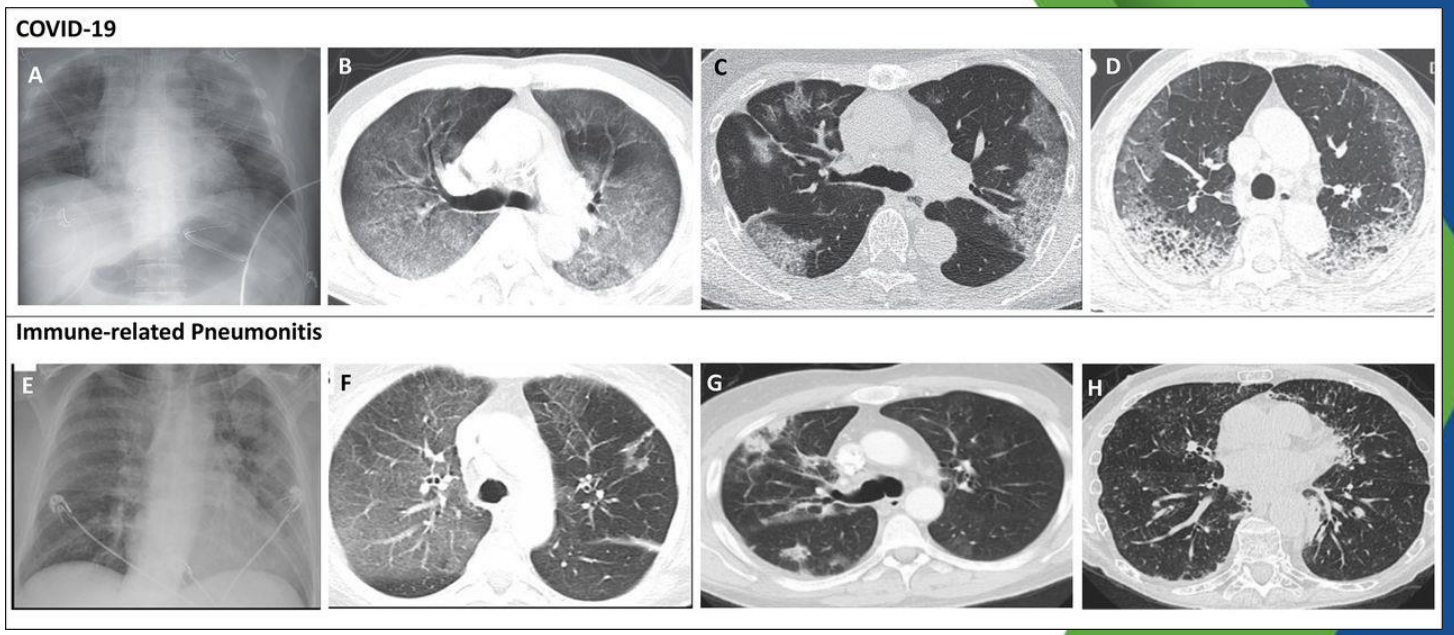
- Imaging findings may be similar
- Patients with prior thoracic radiotherapy may have pre-existing lung changes
- Immune-mediated pneumonitis should respond to immunosuppression



Schoenfeld, J Immunother Cancer 2019

COVID-19

- Imaging findings of pneumonitis from ICIs may be similar to those of severe COVID-19 infection
- Management of the two conditions are different, making accurate diagnosis critical



Naidoo, J Immunother Cancer 2020

Determining which Agent in Combination Therapy: (other ICI or TKI, or Ctx) is the etiology of the toxicity

- Some chemotherapy or targeted therapy AEs may have similar presentation to irAEs, so identifying the causative agent is important for proper treatment
  - Gastrointestinal and dermatologic events also common with taxanes and VEGFR inhibitors, but root causes are different
- Pembrolizumab + axitinib (approved for RCC) tends to cause higher incidence of grade 3+ irAE. TKI and ICI toxicities overlap especially diarrhea, other toxicities are very different
- Several clinical trials of IO + targeted therapies were discontinued due to high rates of toxicity

Brahmer, J Immunother Cancer 2021

Practical pearls for combination treatment toxicities

- Differences in timing of onset
- Chronic and irregular inconsistent clinical course
- Stop targeted agent first and look for immediate resolution
- Many toxicities are unique to each agent
  - TKI- hypertension, palmer-plantar dyserythrodysethesia, irregular diarrhea
  - Immune checkpoint inhibitor- hypophysitis, pneumonitis, encephalitis

Myasthenia gravis an irAE with a high morbidity/mortality

Diagnoisis

- Not very common, but high potential for patient fatality
- Patients may present with:
  - Fatigable or fluctuating muscle weakness, often in proximal muscles
  - Ptosis
  - Facial weakness
  - Difficulty swallowing
  - Respiratory compromise
- May co-occur with myositis and/or myocarditis

Management

- Discontinue ICIs
- Frequent pulmonary assessments
- Corticosteroids and pyridostigmine with IVIG or PLEX
- Grade 3+: hospital admission and potential ICU-level monitoring

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Immune checkpoint therapy can be resumed in some cases….

- Hypophysitis with physiologic hormone replacement therapy
- Thyroiditis without thyrotoxicosis
- Colitis/ diarrhea grade 2-3 controlled with steroids over 4-6 weeks
  - Even consider after Colitis/diarrhea with infliximab given and rapid response??
  - Can resume therapy as long as steroid taper << 12 weeks
  - Can consider repeat colonoscopy prior to g
- Hepatitis with AST, ALT < 8 x ULN, Direct bilirubin elevation , 2xULN?
  - Use of mycophenalate largely should be a situation where treatment should not be resumed
- Grade 2 pneumonitis, completely resolved
- Patients recovered from combination of anti-CTLA-4 and anti PD-1 now proceeding to single agent anti-PD-1

Endocrinopathies are unique

- Continuation of treatment is generally free from additional problems
- These toxicities are generally
- Many have non-specific and/or overlapping cancer-related symptoms (fatigue, headache, malaise)
- Usually late-onset
- Assumed to be long-lasting or chronic
- Include:
  - Primary or secondary **thyroid dysfunction**
  - **Hypophysitis**
  - **Secondary adrenal insufficiency** (primary AI is exceedingly rare)
  - **Type 1 diabetes mellitus** (rare but life threatening)

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Clinical Scenarios where retreatment is likely too high a risk

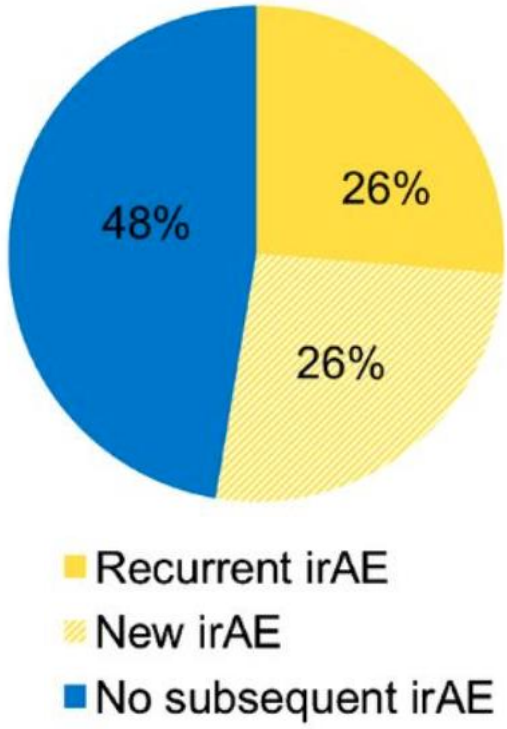
Myocarditis, completely resolved

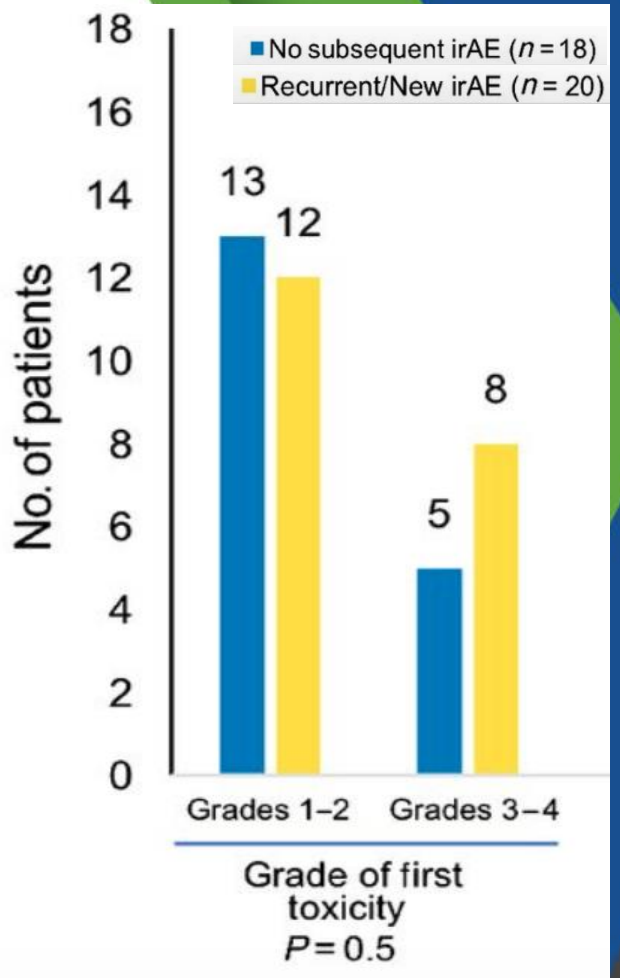
- Retreatment could easily be fatal
- Frequently myocarditis can leave long standing cardiac abnormal function or electrophysiologic status

- Myasthenia gravis, completely resolved
  - Potential recurrence can lead to persistent deficit or be fatal
  - Consider association with myocarditis and myositis
  - Can lead to respiratory depression or failure

Re-challenging with ICIs after irAEs

- Patients should not be re-challenged 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

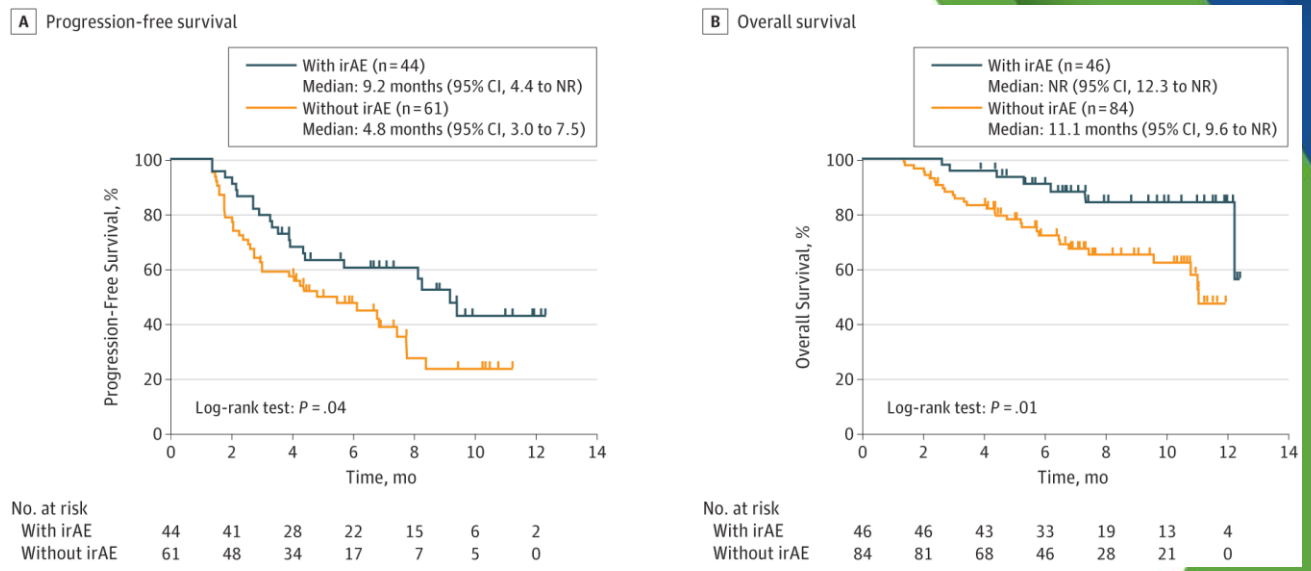


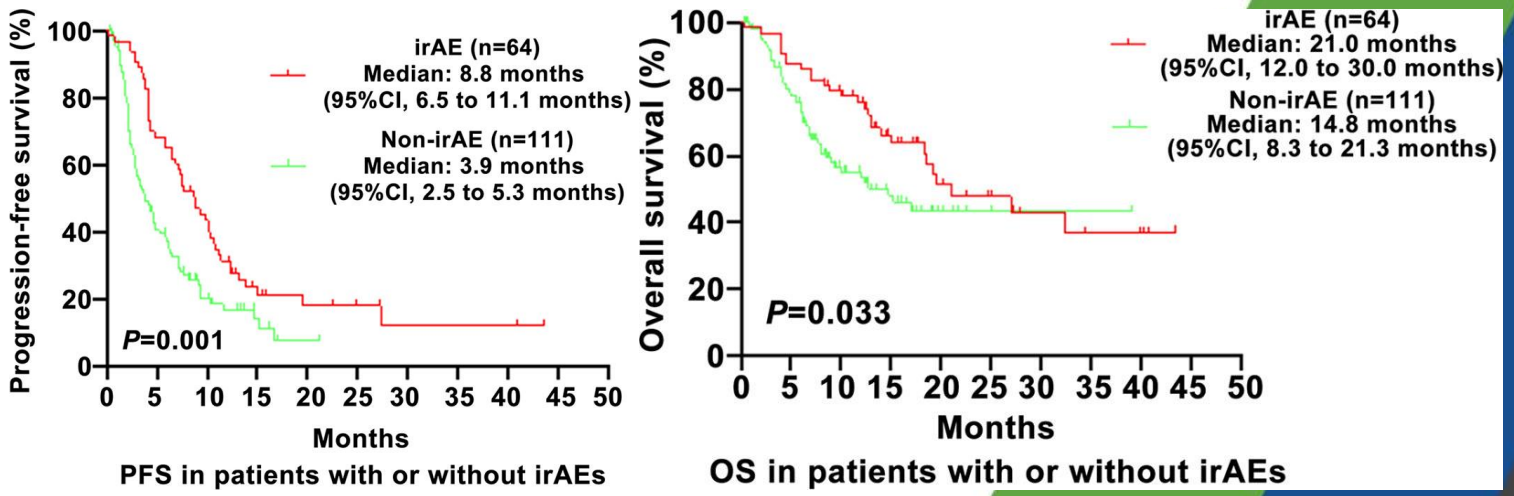


Santini FC. Cancer Immunol Res 2018.

Association of irAEs and survival

- Some studies associate irAE development with PFS or OS
- Certain types of irAE may correlate more with outcomes
- This trend is not consistent across settings, agents or studies





Haratani, JAMA Oncol 2018
Chen, Front Oncol 2021

Conclusions

- Do not continue to administer front line steroids alone if no response in 3-5 days but instead switch to higher dose of steroids or second line immunosuppression
- Immune checkpoint inhibitors can be given to patients with autoimmune disease especially if controlled with caution
- Generally all irAE are treated with high dose steroids but
  - Endocrine toxicities generally are simply treated with replacement of hormonal deficit in most situations except in specific situations
  - Situations include patients with severe headache from enlarged pituitary or thyrotoxicosis and local effects
  - Myocarditis and severe neurologic toxicities are frequently treated with 1gm methylprednisolone x 3-5 days
- Always evaluate patients for other causes of toxicities even after steroids are ineffective.
- Retreatment is feasible in some situations but not all.

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Case Studies in Immune Checkpoint Inhibitor-related Adverse Events

October 6, 2021, 7 – 8 p.m. ET

Learn more and register at:
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Practical Management Pearls for Immunotherapy for the Treatment of Urothelial Cancer

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