Society for Immunotherapy of Cancer

Cancer Immunotherapy GUIDELINES

Case Studies in Immune Checkpoint Inhibitor-related Adverse Events

October 6, 2021

7 – 8 p.m. ET

The Practical Management Pearls and Case Studies Webinars are part of the Cancer Immunotherapy Clinical Practice Guidelines Advanced Webinar Series supported, in part, by grants from Amgen and Merck & Co., Inc. (as of 9/15/2021).

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Moderators

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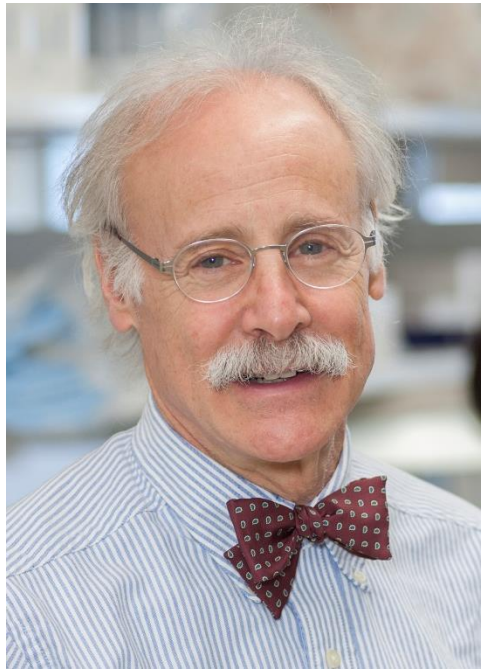
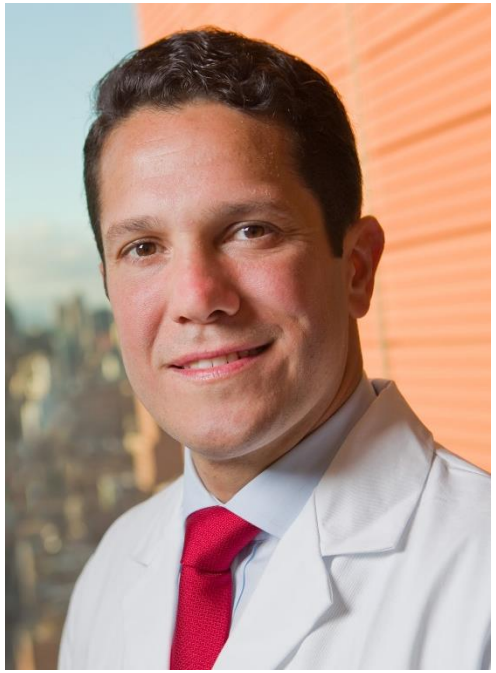


Marc S. Ernstoff, MD –
National Institute of Health

Presenters

Laura Cappelli, MD, MHS, MS – *Johns Hopkins University*

Bianca D. Santomasso, MD, PhD – *Memorial Sloan Kettering Cancer Center*



Mario Lacouture, MD – *Memorial Sloan Kettering Cancer Center*

Learning objectives

- Outline considerations for treating high-risk patients with immune checkpoint inhibitors
- Determine appropriate management of patients with multiple or sequential irAEs
- Identify management strategies for uncommon and/or steroid refractory immune-related toxicities

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

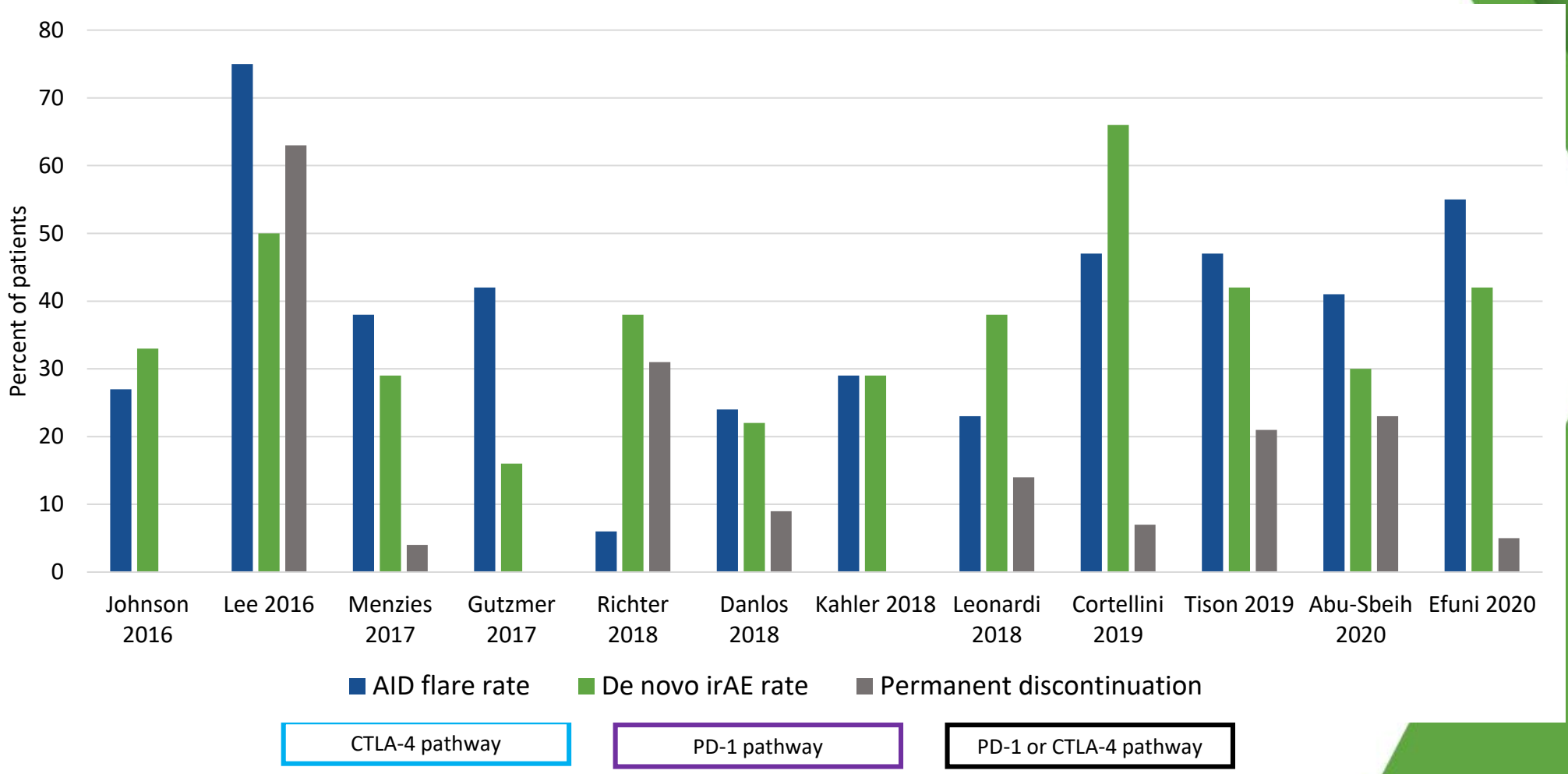
Case 1 – Pre-existing autoimmunity

- A patient with newly diagnosed metastatic non-squamous NSCLC is being considered for treatment with anti-PD-1 therapy.
- The patient tells you they had lupus, but do not have their medical records with details of the disease or treatment.
- How would you decide how to treat this patient's cancer?

Considerations for treating patients with pre-existing autoimmunity

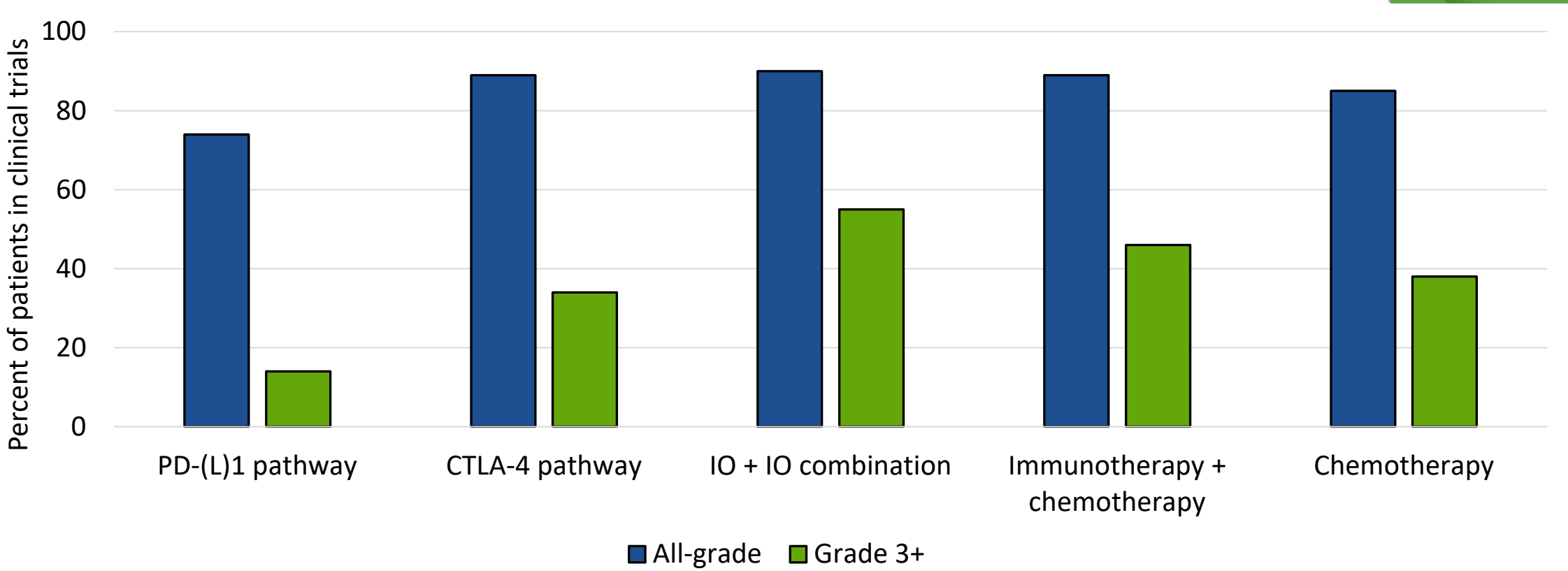
- Disease activity (current)
- Past severity of disease/characteristics of flares in the past
- Systemic or organ-limited disease
- Current medication/s for autoimmune disease
- Urgency of cancer treatment
- Alternative cancer treatment options

Patients with pre-existing autoimmune disorders



Boland, J Immunother Cancer 2020

Expected toxicities with different regimens

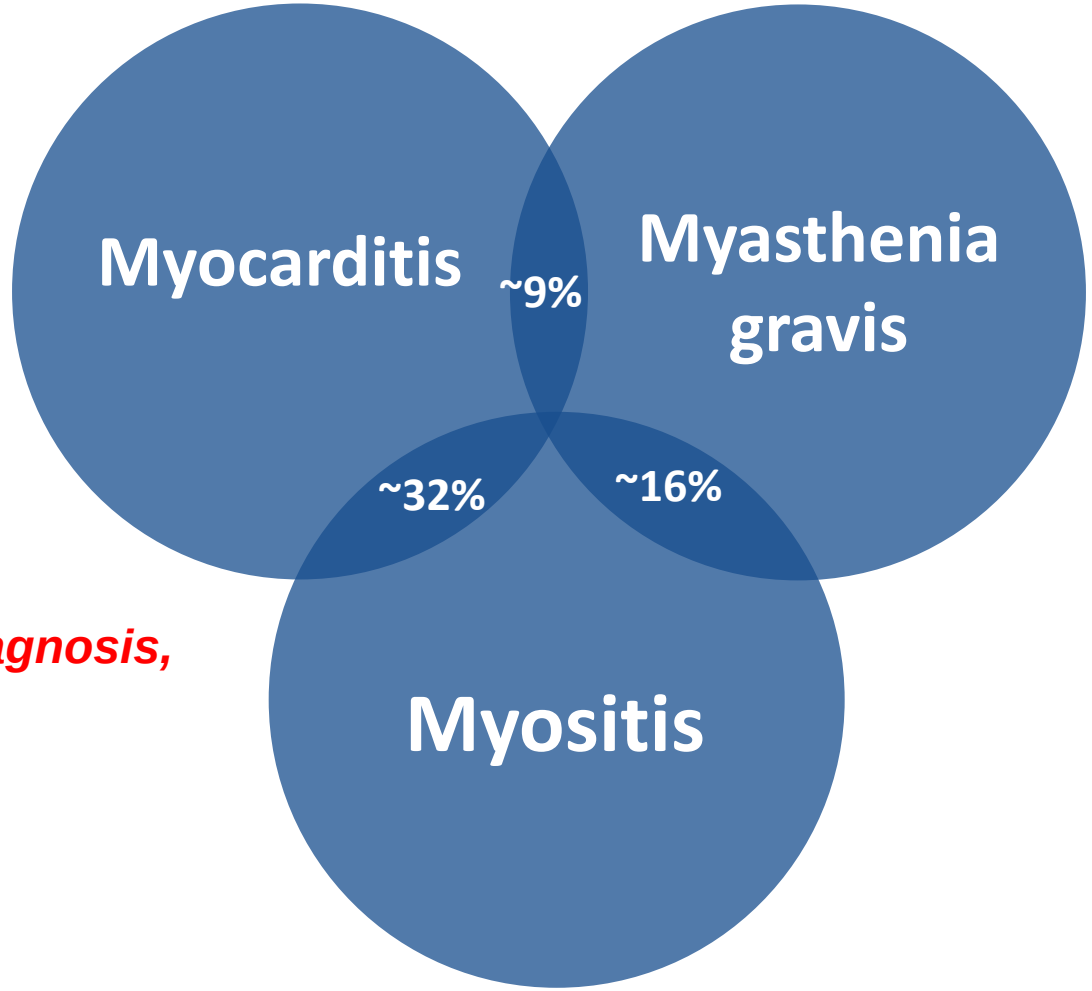


Wang, Front Pharmacol 2017.
Kelly, Cancer 2018.
Bertrand, BMC Med 2015.

Case 2

- 65 yo man with recurrent metastatic urothelial cancer starts anti-PDL1 monotherapy
- One week after 3rd dose of anti-PDL1, he develops new hoarse voice, double vision, ptosis.
- He is noted to have severe right greater than left upper lid ptosis. Weakness of right eye elevation and bilateral globe abduction. Hoarse voice and dysphagia. Reports limbs feel ”tired.” He is able to walk normally.
- MRI brain is negative
- Labs are notable for elevated AST/ALT, CPK, and aldolase. AChR binding blocking modulating and MuSK abs are negative. Clinical suspicion is for immune-related myasthenia gravis and myositis
- The immune checkpoint inhibitor is held. He is admitted to the hospital. He starts prednisone 1 mg/kg daily along with pyridostigmine and IVIG 0.4G/kg/day x 5 days.

Overlapping toxicities



When you encounter one diagnosis, send workup for all 3

Moreira et al, *Eur J Cancer* 2019
Johnson, J Immunother Cancer 2019

Myasthenia gravis

Diagnosis

- 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

Management

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

Brahmer, J Immunother Cancer 2021

Myositis

Diagnosis

- Diagnostic tests include CK, ESR, CRP, antibody tests, aldolase, troponin, EKG, nerve conduction, and EMG, given high suspicion of concurrent myocarditis or myasthenia gravis
- Biopsy may be considered
- Consultation with rheumatologist and/or neurologist

Management

- Grade 2: oral corticosteroids and analgesia with acetaminophen/NSAIDs
- Grade 3: ICIs held; corticosteroids at 1-2 mg/kg; potential hospitalization
- Additional treatment options include methotrexate, azathioprine, mycophenolate mofetil and IVIG

Brahmer, J Immunother Cancer 2021

Myocarditis

Diagnosis

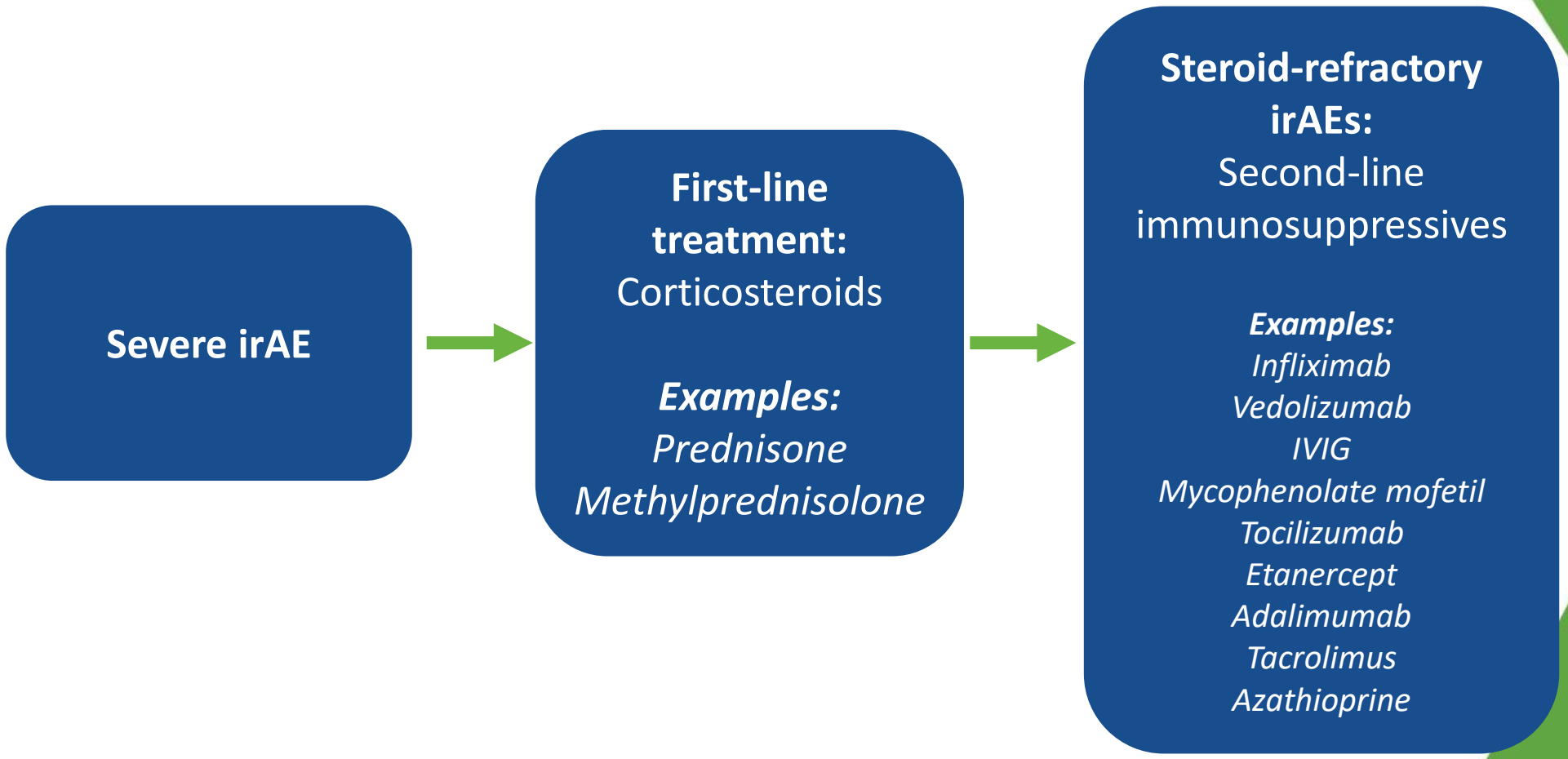
- Rapid diagnosis and management is critical
- Consult with a cardiologist
- Diagnostic techniques include:
  - Troponin levels (elevated in almost all patients with myocarditis)
  - EKG
  - Cardiac MRI
  - Endomyocardial biopsy

Management

- Discontinuation of ICIs and hospitalization
- Initial high-dose corticosteroids, typically 1 g/day IV methylprednisolone
- Steroid-resistant myocarditis may benefit from anti-thymocyte globulin, mycophenolate mofetil, abatacept or alemtuzumab

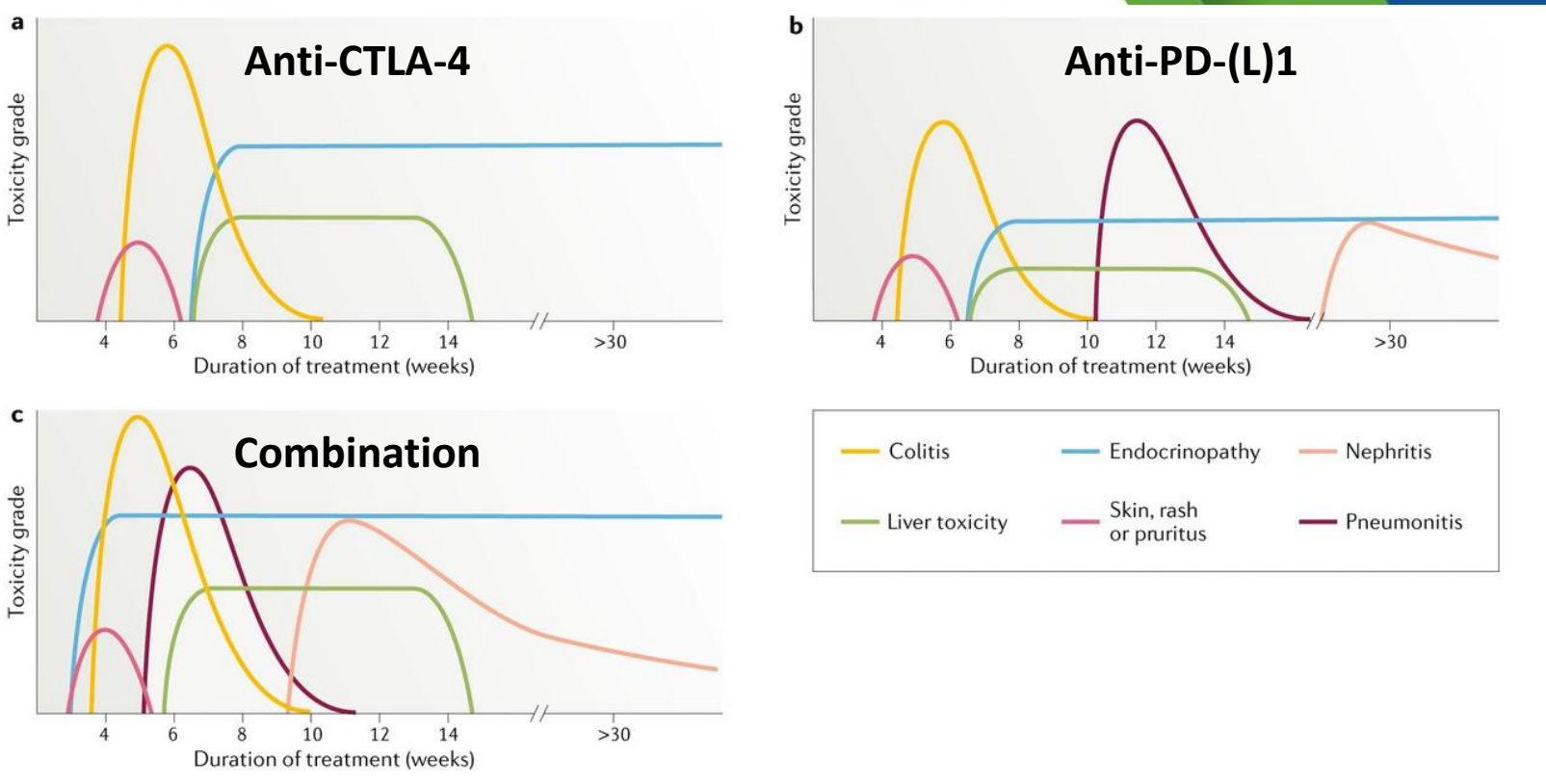
Bonaca, Circulation 2019
Brahmer, J Immunother Cancer 2021

Types of immunosuppressive agents



Kinetics of irAEs

- Can be days to months after therapy initiation
- Very early or very late AEs may warrant special concern
- May occur even after treatment is discontinued



Martins, Nat Rev Clin Oncol 2019

Determining causative agent in combination therapy

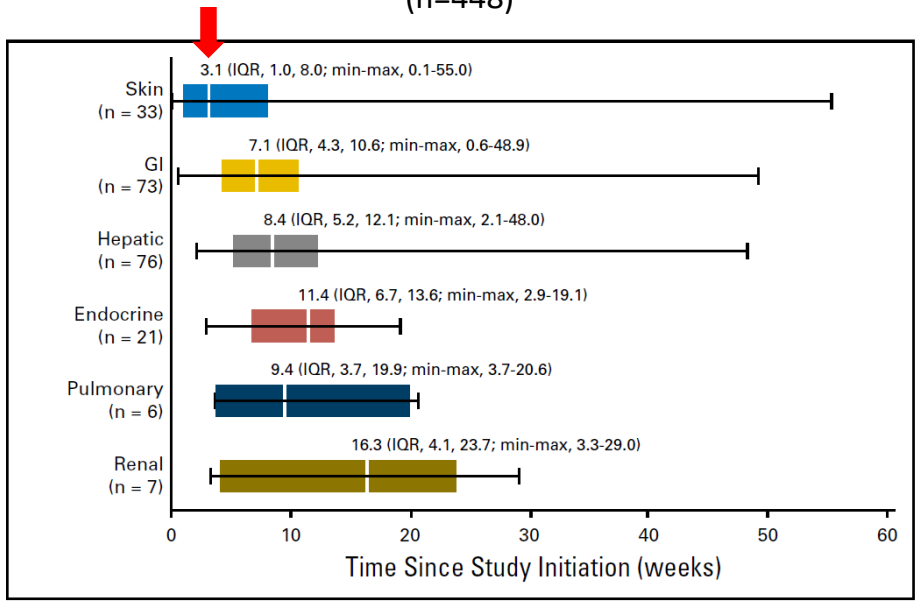
- Toxicities typically mirror individual monotherapies
- Some chemotherapy or targeted therapy AEs may have similar presentation to irAEs, so identifying the causative agent is important for proper treatment
  - Gastrointestinal and dermatologic events also common with taxanes and VEGFR inhibitors, but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

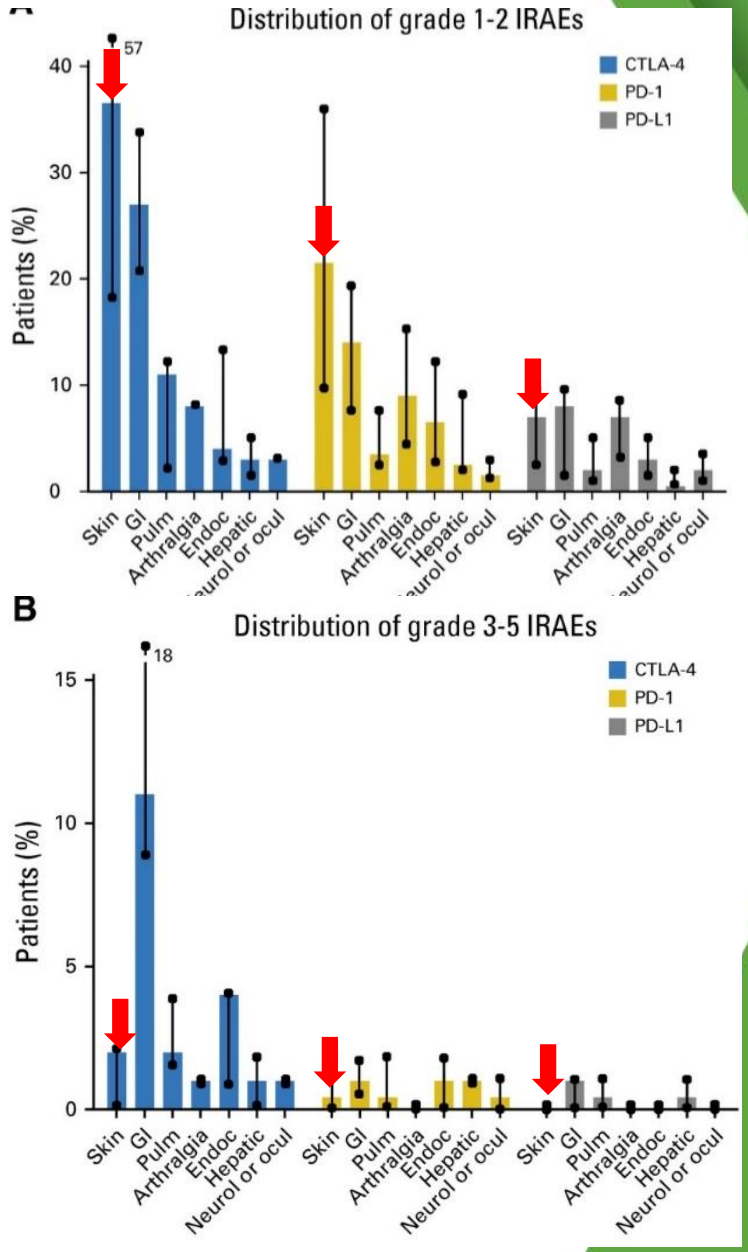
Brahmer, J Immunother Cancer 2021

Case 3 – Steroid-refractory irAEs

Skin is First and Frequent in Immune-Related Adverse Events

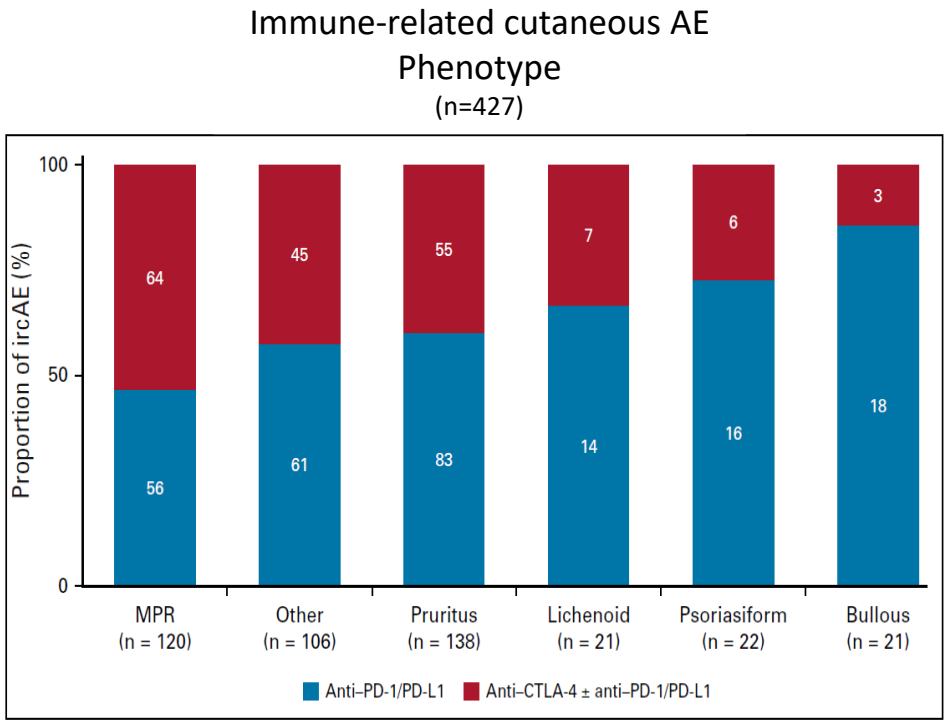
Ipilimumab+Nivolumab
Severe AE
(n=448)



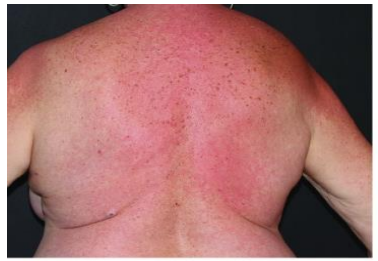


Sznol et al, *J Clin Oncol* 2017; Schmid et al; Michot et al *Eur J of Cancer* 2016

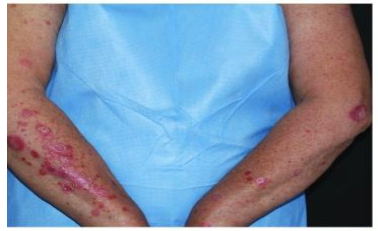
Dermatologic Evaluation Yields Various Rash Types



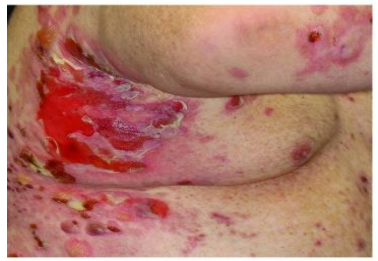
Maculopapular rash



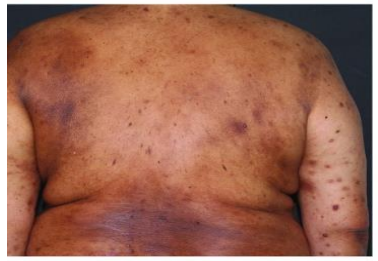
Psoriasiform rash



Bullous pemphigoid



Eczematous rash

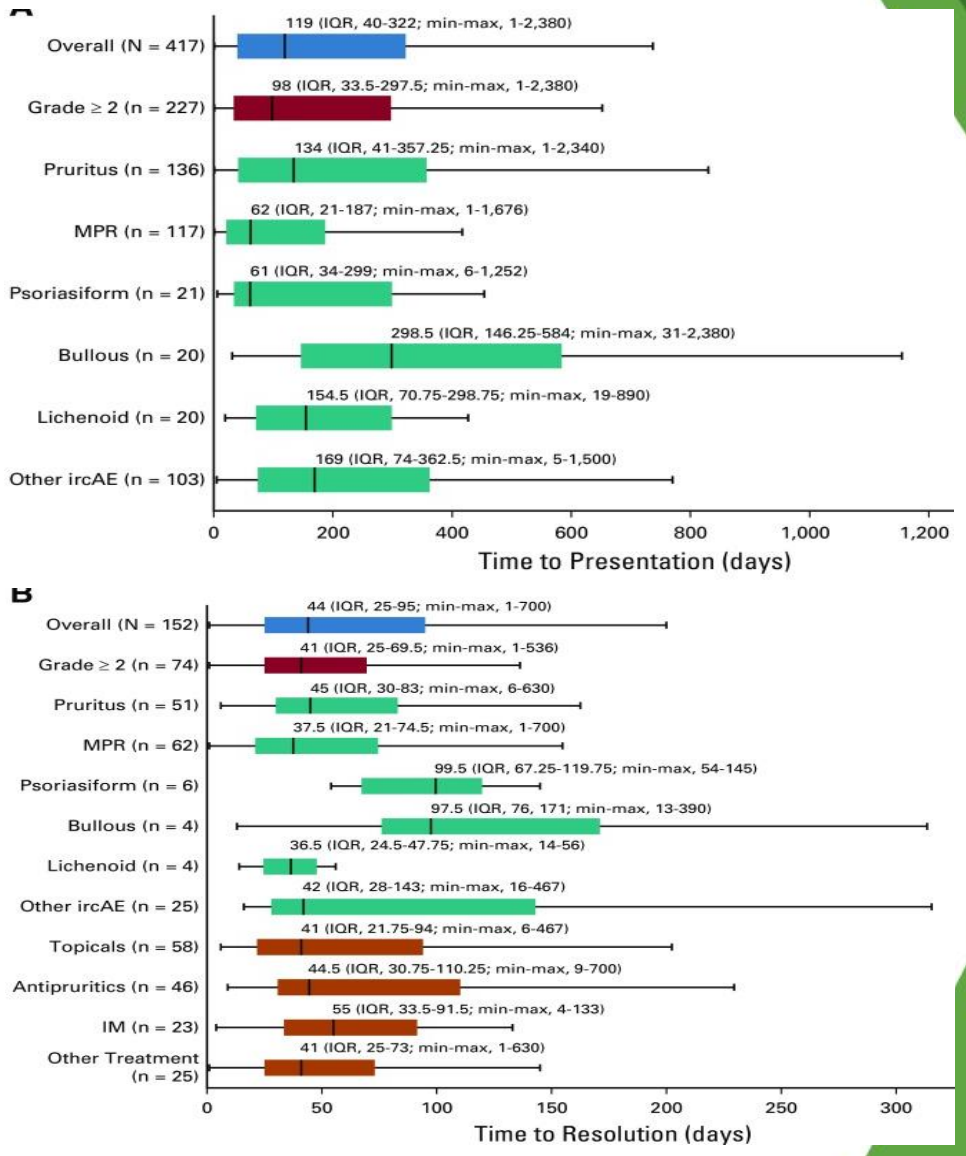


Phillips and Wu,et al, *J Clin Oncol* 2019; Geisler et al, *J Am Acad Dermatol* 2020

Treatment Outcomes and Duration of Dermatologic irAEs

PD-1/L1 ± CTLA-4 (n=482)

Characteristic	No. (%)
CTCAE v4.0 grade at presentation to dermatology	(n = 397)
Grade 0/1	164 (41)
Grade 2	183 (46)
Grade 3/4	50 (13)
Outcome‖	(n = 331)
Significant improvement	151 (46)
Moderate improvement	103 (31)
No improvement	77 (23)

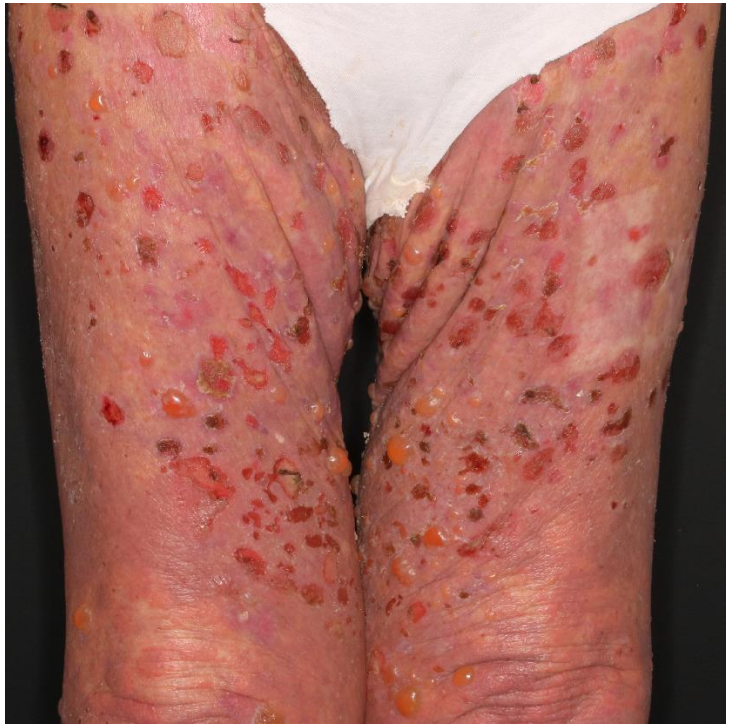


Santini et al, *Cancer Immunol Res* 2018; Phillips and Wu et al, *J Clin Oncol* 2019

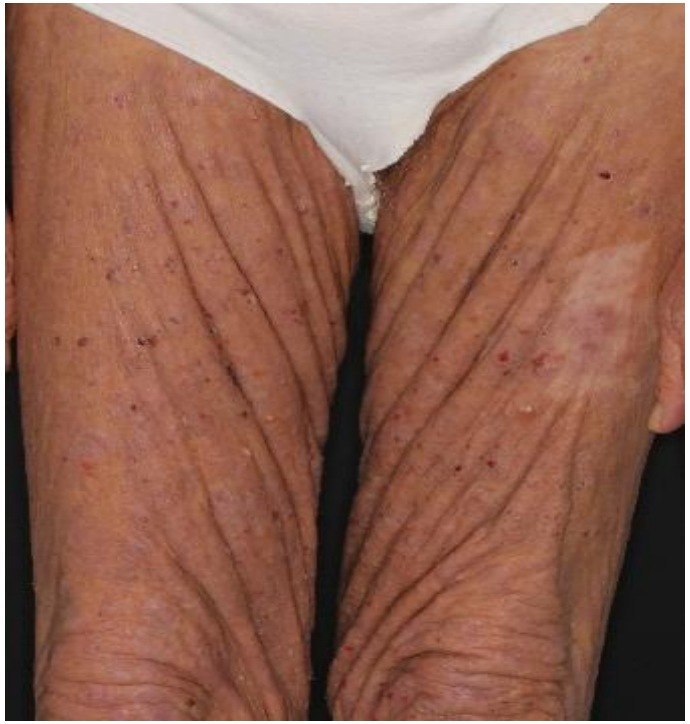
Targeting IO Autoimmunity: IgE Blockade

- 58 y/o woman; melanoma sp ipilimumab+nivolumab→nivolumab
  - Bullous pemphigoid treated with prednisone, MMF, rituximab

Baseline

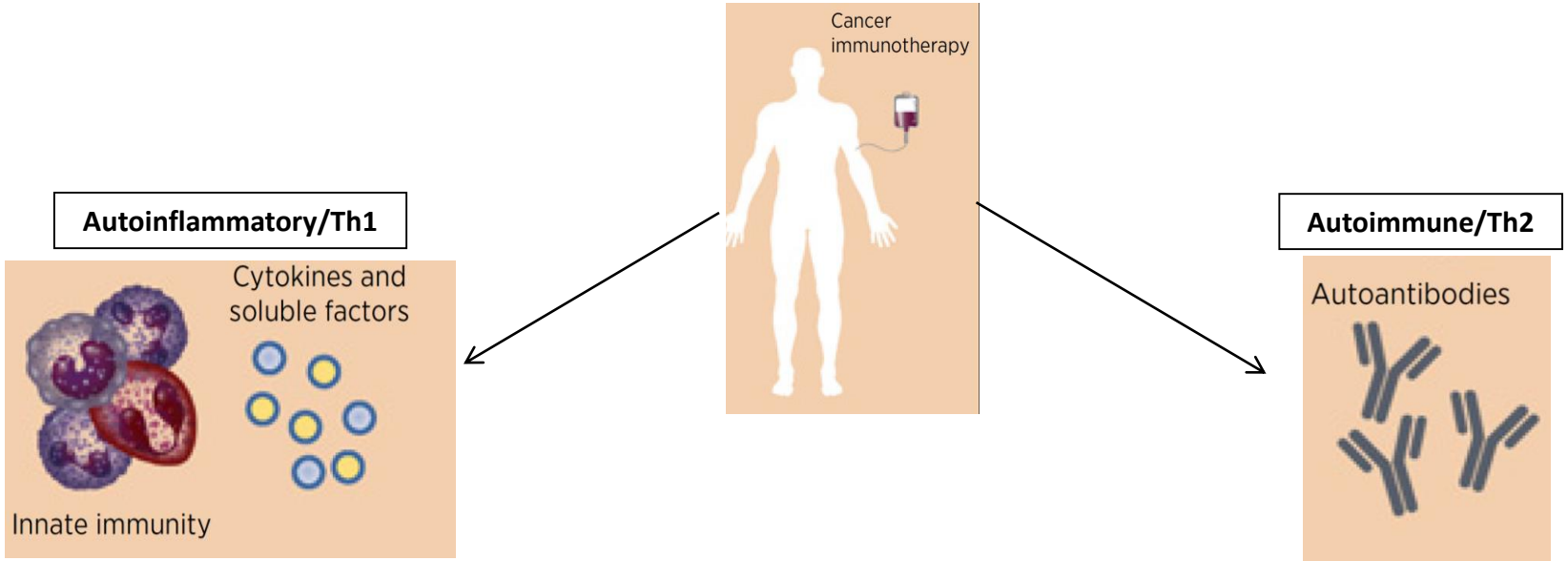


Omalizumab (1)



Barrios et al, *Ann Oncol* 2020

Polarized Immune Responses in Cutaneous Complications of IO

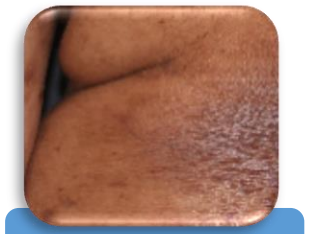


↑ $CD8^{+}$T cells
↑ IL-6
↑Neutrophils
↑Eosinophils

↑ BP Abs
↑IgE
$CD19^{lo}$ B cells

Young et al, *Cancer Immunol Res* 2018

Management of ircAE: Phenotype-Endotype



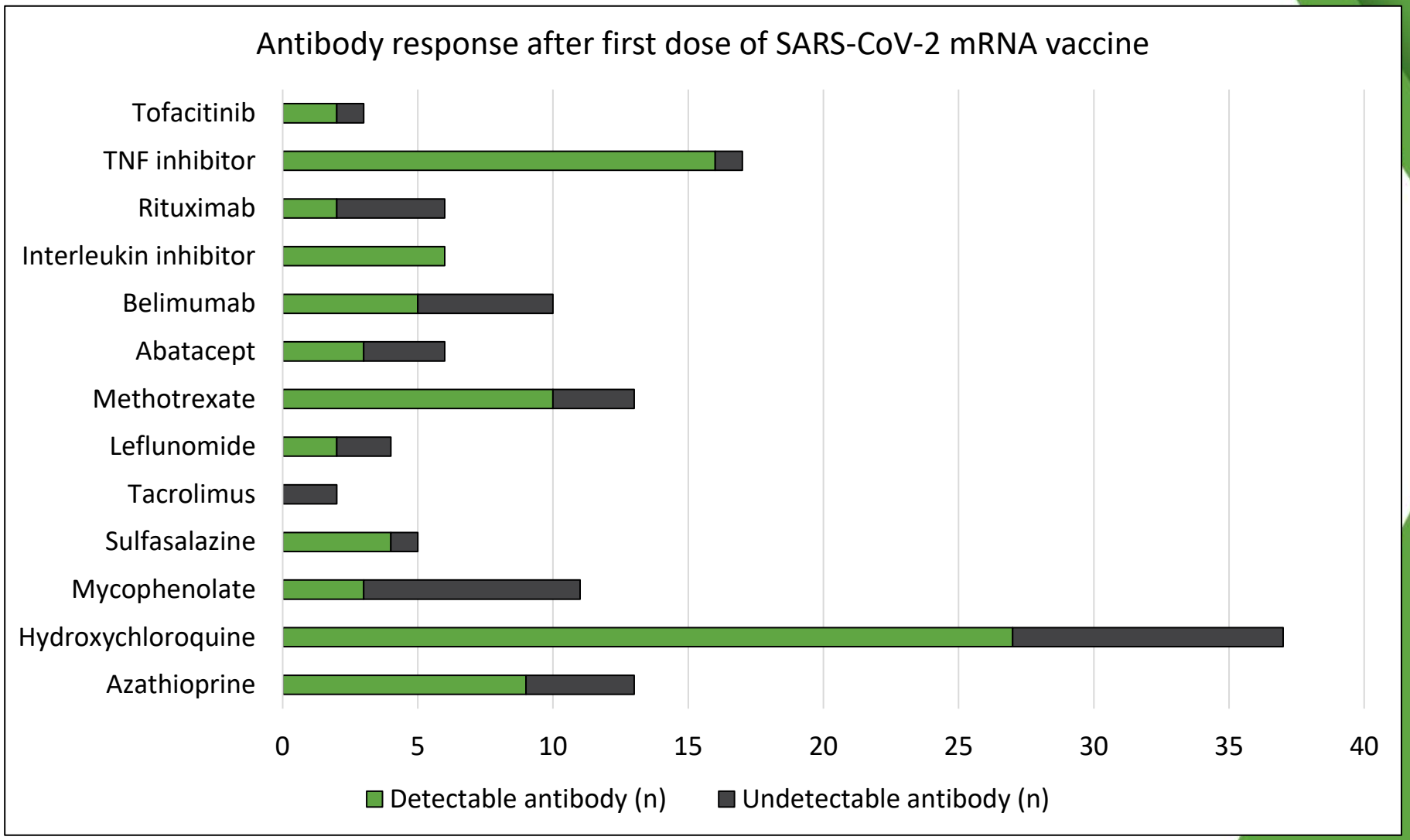
	Psoriasis	Blisters	Eczema	Pruritus
Biomarker	TNFα, IL-6	Dsg 1/3 BP180/230	IL-4 Eosinophils	IgE
Histology	Neutorphils	IgA/C/M	Eosinophils	Eosinophils
Therapy	Infliximab Tocilizumab	**Rituximab**	**Benralizumab**	Omalizumab

Phillips and Wu et al, *J Clin Oncol* 2019

Side effects of immunosuppression

- Steroids come with their own side effects, like hypertension, metabolic dysfunction, insomnia, etc
- Infection prophylaxis should be considered for vulnerable patients
- Patients with current or prior immunosuppressive therapy may have reduced response to vaccination

Vaccines and immunosuppressives



Boyarksky, Annals of Rheumatic Diseases 2021

Case #4

- 45 yo woman with metastatic melanoma treated with ipilimumab and nivolumab
- Develops multiple irAEs: colitis, hypophysitis
- After steroid taper-> joint pain and stiffness
- Diagnosed with inflammatory arthritis and started on methotrexate with partial improvement
- TNF-inhibitor added with good response
- After ~1 year TNF-inhibitor loses efficacy-> switch TNF-I
- Maintains CR from melanoma 5 years later but requires immunosuppression for inflammatory arthritis

Managing chronic irAEs

- Chronic irAEs reported in pneumonitis, hepatitis, inflammatory arthritis, dermatologic conditions
- Patient now essentially has chronic autoimmune disease WITH comorbid malignancy
- Important to have a specialist involved and regular communication with the patient's oncologist
- Steroid sparing immunosuppression is key given risk of side effects with long term steroids

Conclusions

- Pre-existing autoimmune disease is heterogeneous and understanding the nuances of your patient's history will help you determine the safety of ICI therapy
- Be aware of overlapping or concomitant irAEs
- Corticosteroid resistant/refractory irAEs are frequent and there are targeted therapies that may be effective
- Treatment of chronic irAEs requires partnership between the oncologist and relevant specialists

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Practical Management Pearls for Immunotherapy for the Treatment of Urothelial Cancer

October 13, 2021, 4 – 5 p.m. ET

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October 13, 2021, 6:30 – 7:30 p.m. ET

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Questions or comments: connectED@sitcancer.org

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