Incidence and Management of Unique Toxicities Associated with Checkpoint Inhibitors; Autoimmune Contraindications to Treatment

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Disclosures

Advisory Committee	AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Exelixis Inc, Genentech BioOncology, Horizon Pharma, Inovio Pharmaceuticals Inc, Lilly, Novartis, Pfizer Inc, Roche Laboratories Inc
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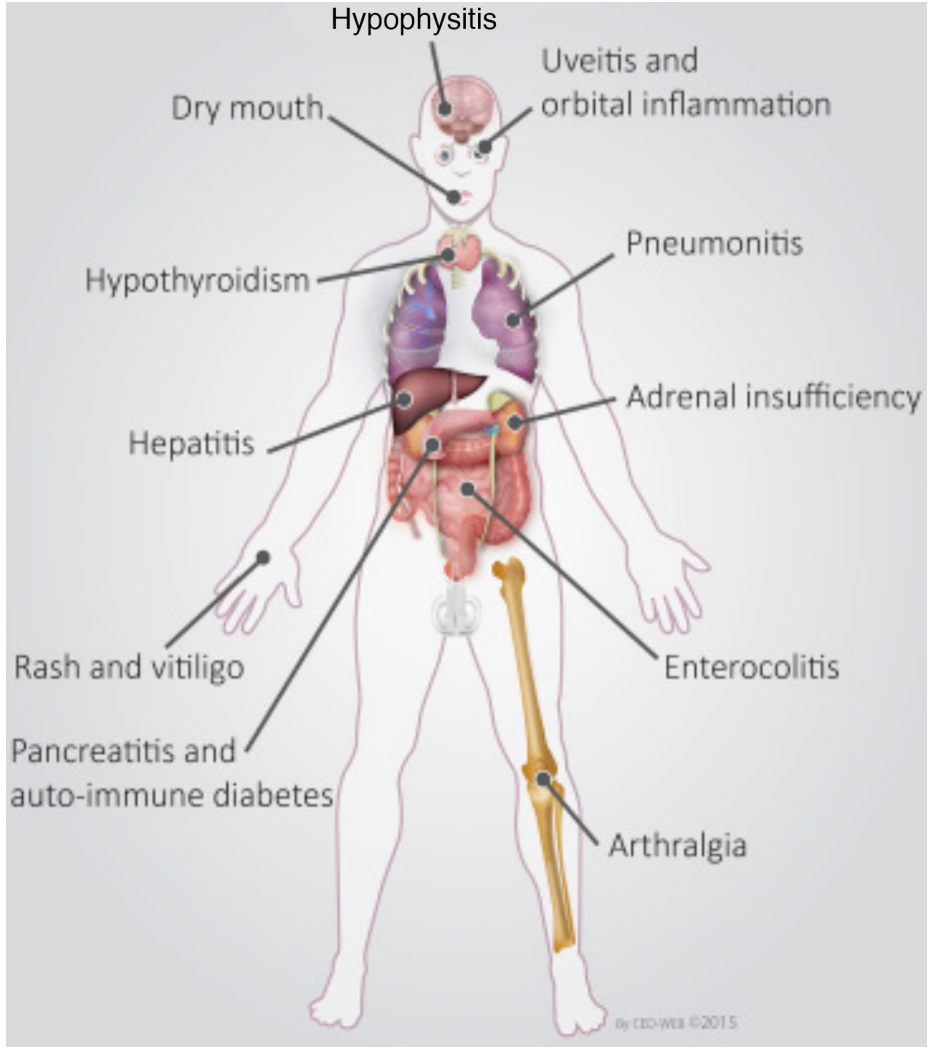
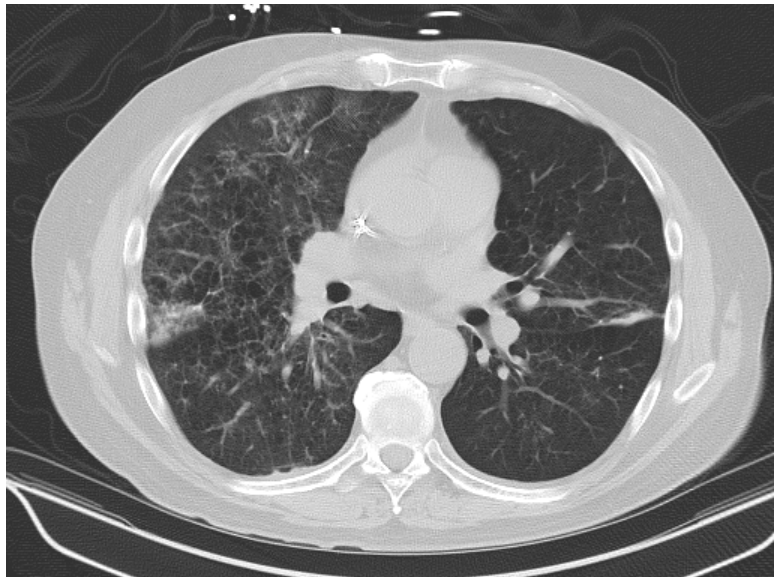
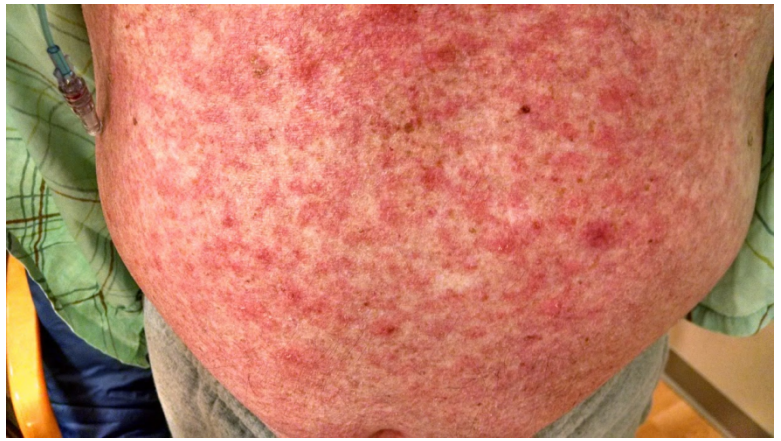
Autoimmune toxicities seen with checkpoint inhibitors







Photos: E Plimack

Minchot JM et al. *Eur J Cancer* 2016;54:139-148.

Managing autoimmune AEs

- Most autoimmune toxicities are reversible with immunosuppression (steroids)
- Typically start at high dose IV and then taper over 1-3 months
  - Exception: Adrenal insufficiency and hypothyroidism need replacement hydrocortisone/levothyroxine, not immune suppressive doses of steroids.
- No evidence that intervening with steroids curtails the antitumor efficacy of the agent

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

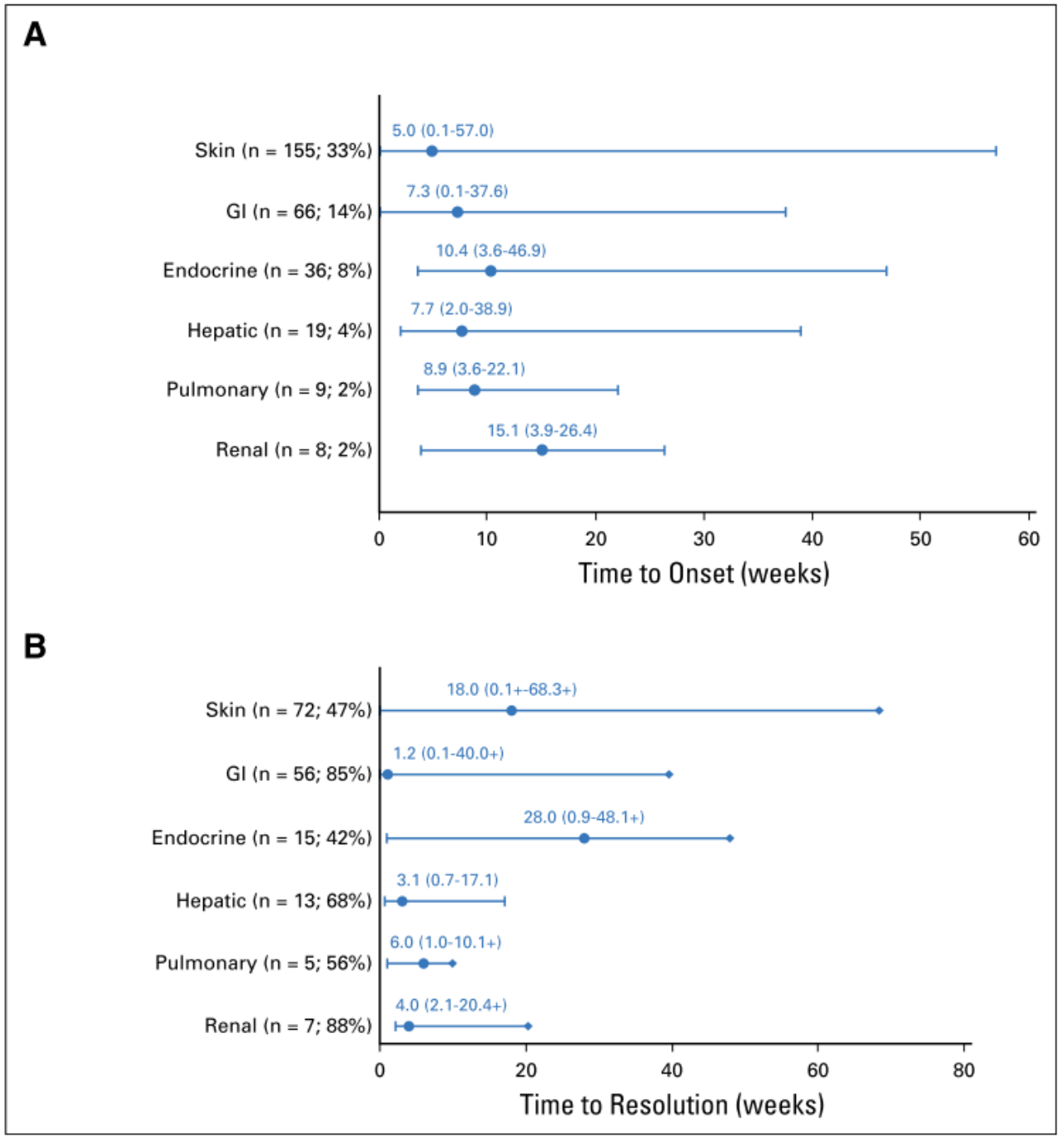
Safety Profile of Nivolumab Monotherapy: A Pooled Analysis of Patients With Advanced Melanoma

Jeffrey S. Weber, F. Stephen Hodi, Jedd D. Wolchok, Suzanne L. Topalian, Dirk Schadendorf, James Larkin, Mario Sznol, Georgina V. Long, Hewei Li, Ian M. Waxman, Joel Jiang, and Caroline Robert

576 patients with melanoma treated on four studies with single agent nivolumab

- 10% severe (grade 3/4) treatment-related adverse effects
- 24% received systemic immunomodulatory drugs (i.e. steroids) to treat adverse effects
  - Receipt of IMs had no effect on response rate
    - 29.8% for those who received IMs versus 31.8 % who did not
- Adjusting for number of doses, response rate was higher in pts who experienced treatment related AEs
  - Treatment related AEs predict efficacy?
  - Responding patients get more drug and are more prone to AEs?

Weber, Jeffrey S., et al. "Safety Profile of Nivolumab Monotherapy: A Pooled Analysis of Patients With Advanced Melanoma." *Journal of Clinical Oncology* (2016)



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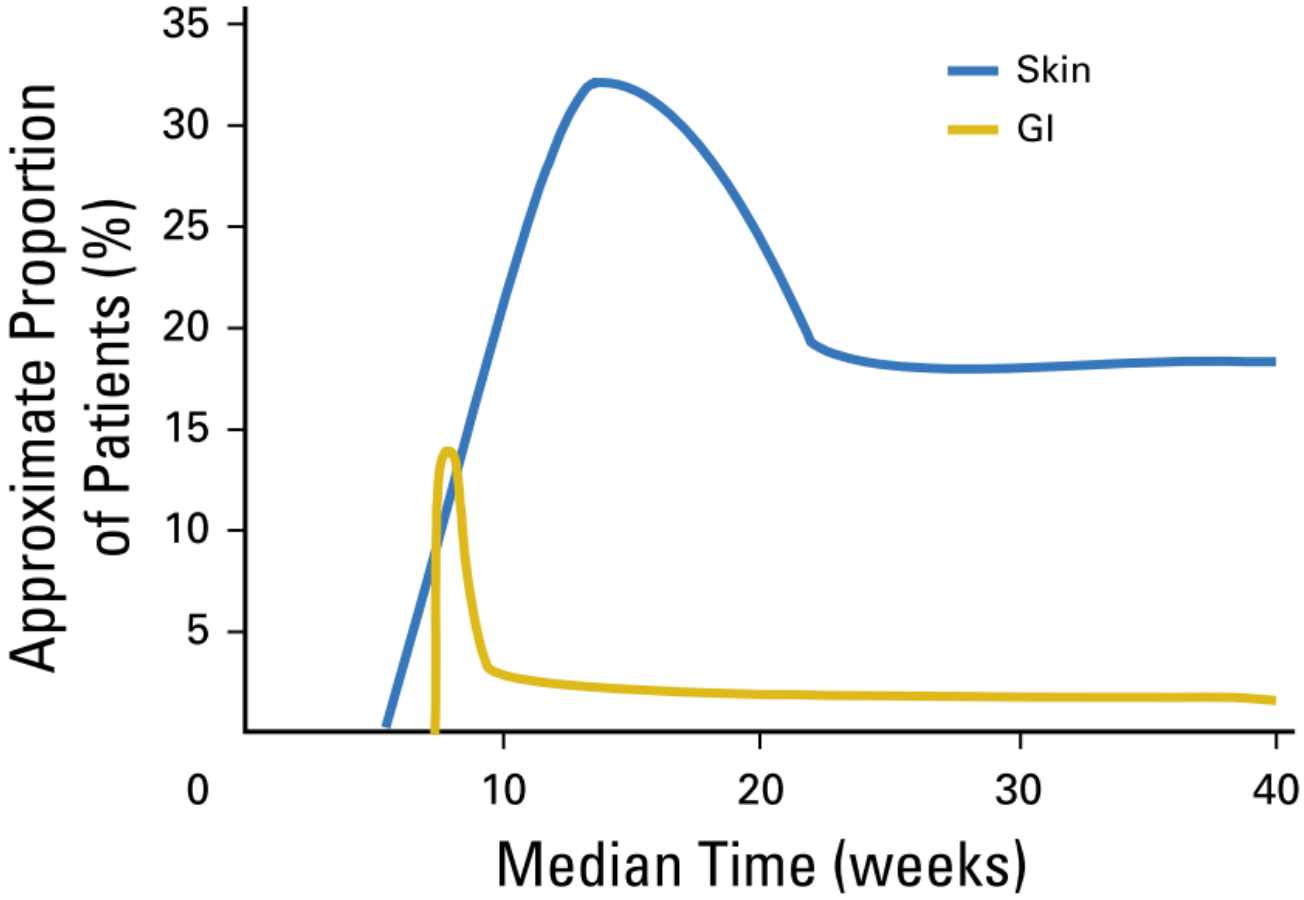
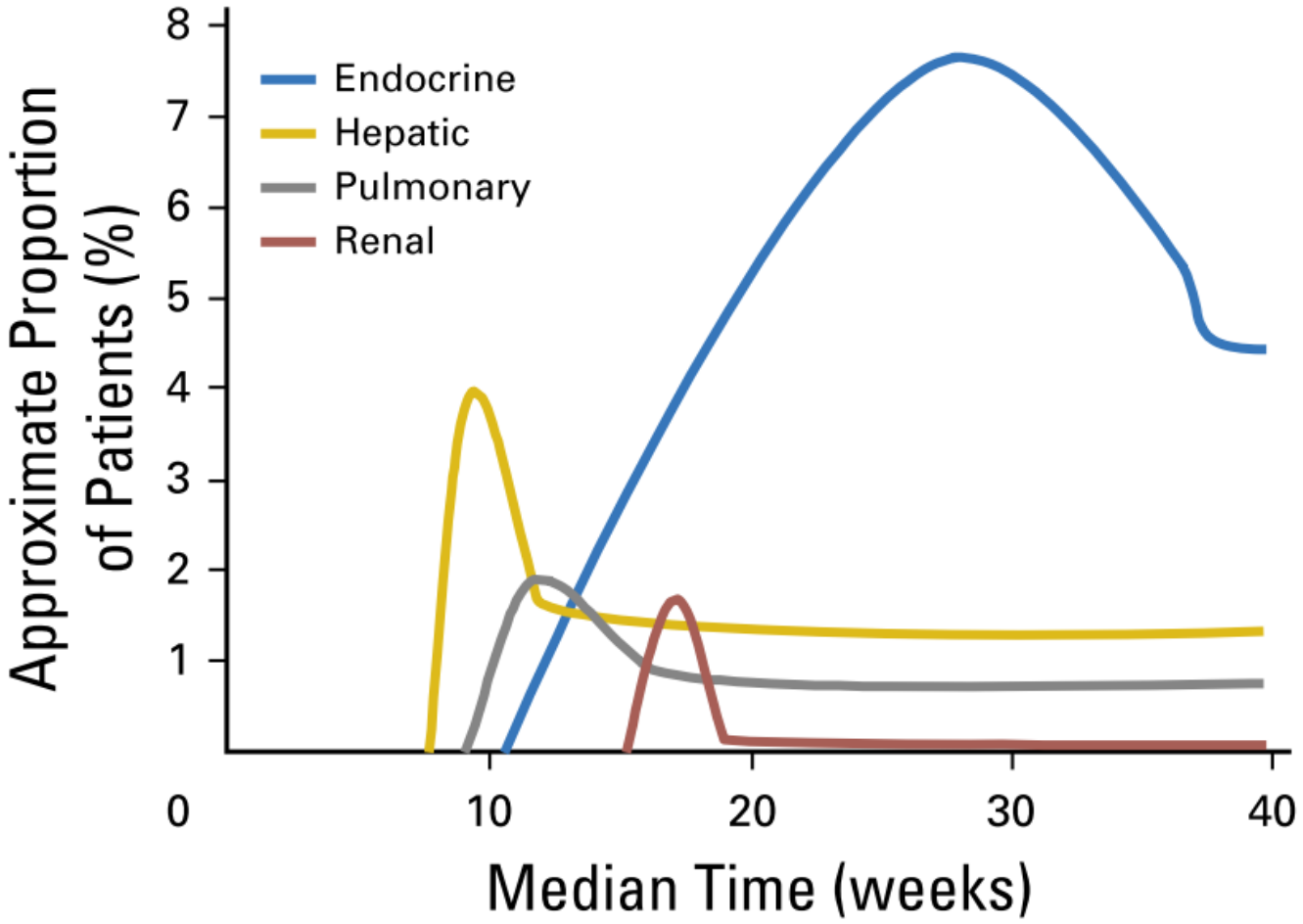
Kinetics of onset and resolution of skin and GI treatment related toxicity



Weber, Jeffrey S., et al. "Safety Profile of Nivolumab Monotherapy: A Pooled Analysis of Patients With Advanced Melanoma." *Journal of Clinical Oncology* (2016)

Kinetics of onset and resolution of endocrine, hepatic, pulmonary and renal treatment related toxicity



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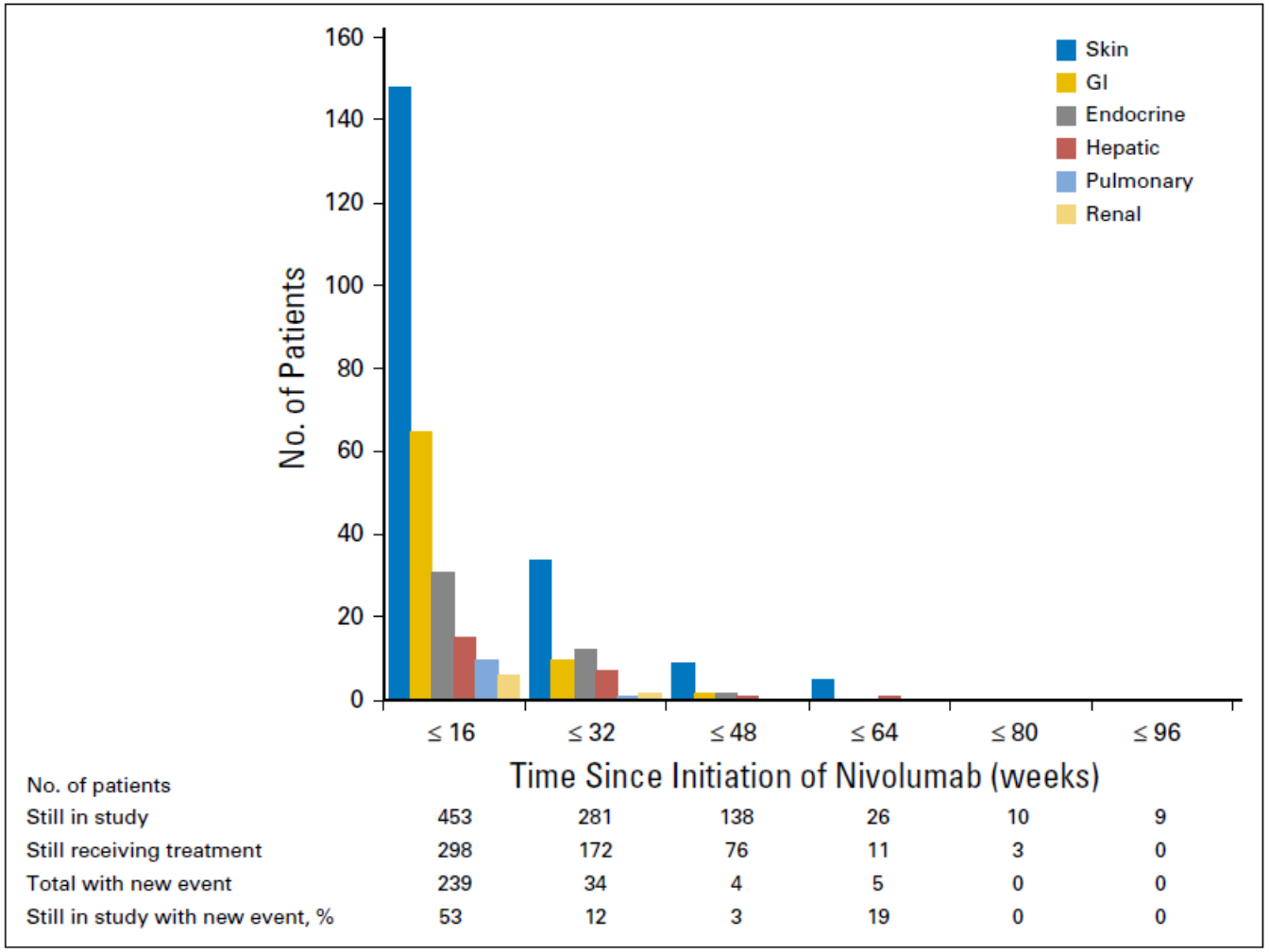
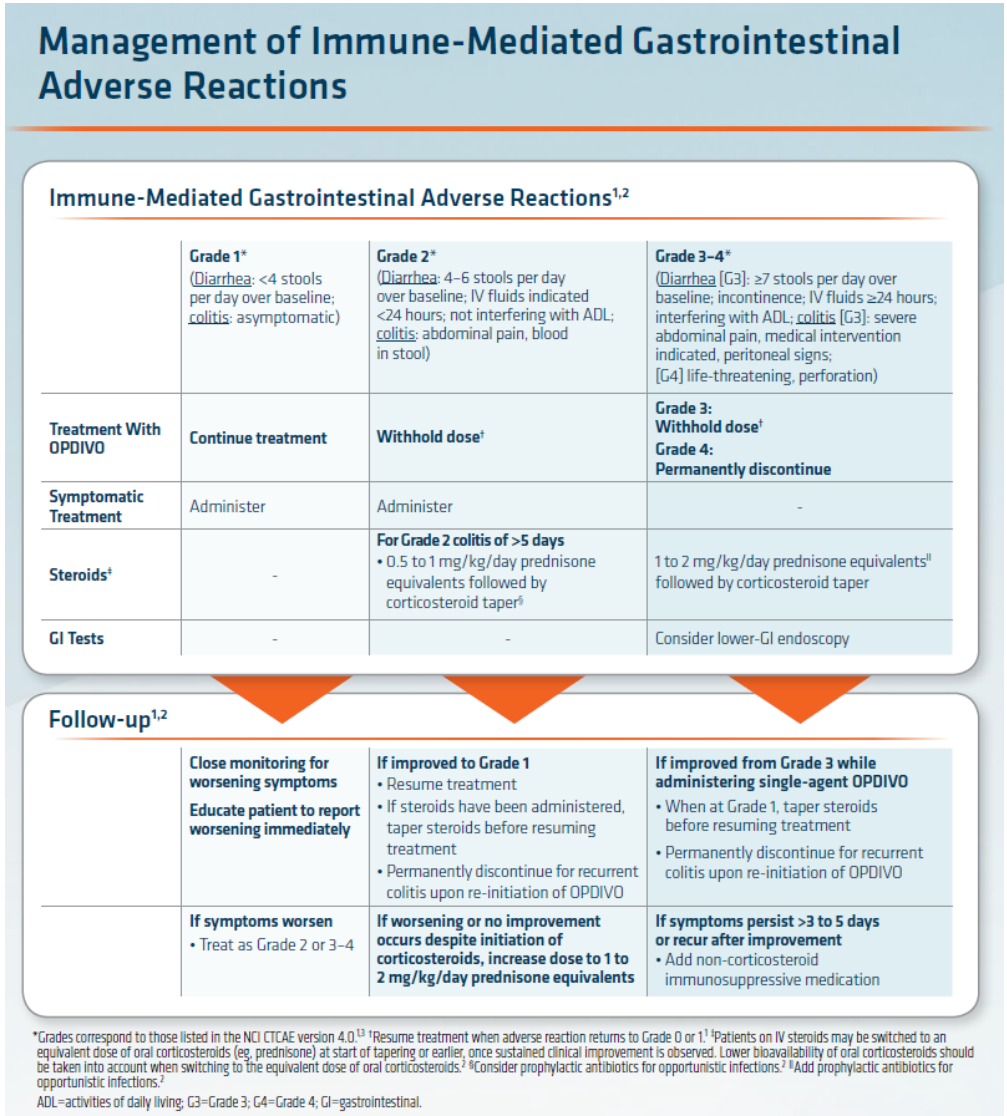
Occurrence of new treatment-related select adverse events of any grade over time



No. of patients						
Still in study	453	281	138	26	10	9
Still receiving treatment	298	172	76	11	3	0
Total with new event	239	34	4	5	0	0
Still in study with new event, %	53	12	3	19	0	0

Weber, Jeffrey S., et al. "Safety Profile of Nivolumab Monotherapy: A Pooled Analysis of Patients With Advanced Melanoma." *Journal of Clinical Oncology* (2016)

Detailed treatment algorithms were used for AE management in clinical trials. These are available online



Management of Immune-Mediated Gastrointestinal Adverse Reactions

Immune-Mediated Gastrointestinal Adverse Reactions[1,2]

	Grade 1* (Diarrhea: <4 stools per day over baseline; colitis: asymptomatic)	Grade 2* (Diarrhea: 4–6 stools per day over baseline; IV fluids indicated <24 hours; not interfering with ADL; colitis: abdominal pain, blood in stool)	Grade 3–4* (Diarrhea [G3]: ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hours; interfering with ADL; colitis [G3]: severe abdominal pain, medical intervention indicated, peritoneal signs; [G4] life-threatening, perforation)
Treatment With OPDIVO	**Continue treatment**	**Withhold dose†**	**Grade 3: Withhold dose† Grade 4: Permanently discontinue**
Symptomatic Treatment	Administer	Administer	-
Steroids‡	-	**For Grade 2 colitis of >5 days** • 0.5 to 1 mg/kg/day prednisone equivalents followed by corticosteroid taper§	1 to 2 mg/kg/day prednisone equivalents‖ followed by corticosteroid taper
GI Tests	-	-	Consider lower-GI endoscopy

Follow-up[1,2]

	Close monitoring for worsening symptoms **Educate patient to report worsening immediately**	**If improved to Grade 1** • Resume treatment • If steroids have been administered, taper steroids before resuming treatment • Permanently discontinue for recurrent colitis upon re-initiation of OPDIVO	**If improved from Grade 3 while administering single-agent OPDIVO** • When at Grade 1, taper steroids before resuming treatment • Permanently discontinue for recurrent colitis upon re-initiation of OPDIVO
	If symptoms worsen • Treat as Grade 2 or 3–4	**If worsening or no improvement occurs despite initiation of corticosteroids, increase dose to 1 to 2 mg/kg/day prednisone equivalents**	**If symptoms persist >3 to 5 days or recur after improvement** • Add non-corticosteroid immunosuppressive medication

*Grades correspond to those listed in the NCI CTCAE version 4.0.[13] †Resume treatment when adverse reaction returns to Grade 0 or 1.[1] ‡Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.[2] §Consider prophylactic antibiotics for opportunistic infections.[2] ‖Add prophylactic antibiotics for opportunistic infections.[2]

ADL=activities of daily living; G3=Grade 3; G4=Grade 4; GI=gastrointestinal.

Source: BMS website

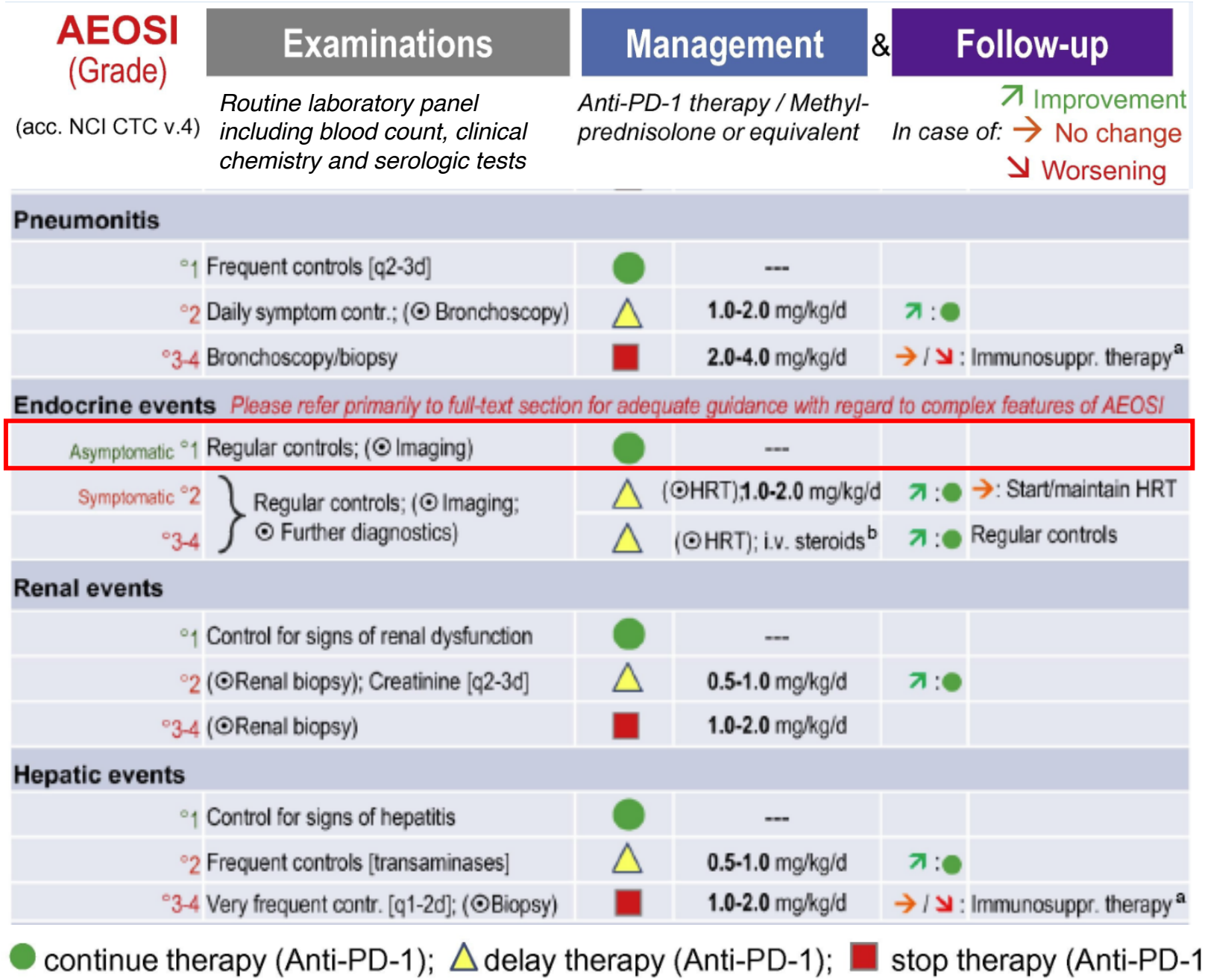
Management algorithms

AEOSI (Grade) (acc. NCI CTC v.4)	Examinations	Management	& Follow-up
	Routine laboratory panel including blood count, clinical chemistry and serologic tests	*Anti-PD-1 therapy / Methyl-prednisolone or equivalent* [a]	*In case of:* ↗ Improvement → No change ↘ Worsening
Skin events			
°1		●	Topical steroid [b]
°2		●	Topical steroid [b]
°3-4	(⊙Skin biopsy)	△ or ■	**1.0-2.0** mg/kg/d ↗ : ●
Diarrhea/Colitis			
°1	Stool test on pathogens	●	--- [c]
°2	(⊙ Colonoscopy)	△	**0.5-1.0** mg/kg/d → : ■
°3-4	Colonoscopy	■	**1.0-2.0** mg/kg/d → / ↘ : Infliximab *Cave!* [d]

● continue therapy (Anti-PD-1); △ delay therapy (Anti-PD-1); ■ stop therapy (Anti-PD-1);

[a] Following symptom improvement/resolution, a corticosteroid taper of at least 1 month should be initiated.
[b] For persistent rash or pruritus, urea-containing ointments or oral antipruritics or topical steroids may be used.
[c] Use of antidiarrheal drugs (loperamide), oral hydration and electrolyte supplements is recommended.
[d] *Cave*: Use of immunosuppressive therapy (ie, in patients refractory to steroids after 3-5 days) is not indicated in cases of sepsis or supposed/manifest perforation; exclude other causes.

Eigentler TK, et al. Diagnosis, monitoring and management of immune-related adverse drug reactions of anti-PD-1 antibody therapy. *Cancer Treatment Reviews* 2016



AEOSI (Grade) (acc. NCI CTC v.4)	Examinations: *Routine laboratory panel including blood count, clinical chemistry and serologic tests*	Management: *Anti-PD-1 therapy / Methyl-prednisolone or equivalent*	Follow-up: ↗ Improvement / In case of: → No change / ↘ Worsening
Pneumonitis			
°1	Frequent controls [q2-3d]	●	---
°2	Daily symptom contr.; (⊙ Bronchoscopy)	△	**1.0-2.0** mg/kg/d; ↗ : ●
°3-4	Bronchoscopy/biopsy	■	**2.0-4.0** mg/kg/d; → / ↘ : Immunosuppr. therapy[a]
Endocrine events	*Please refer primarily to full-text section for adequate guidance with regard to complex features of AEOSI*		
Asymptomatic °1	Regular controls; (⊙ Imaging)	●	---
Symptomatic °2	Regular controls; (⊙ Imaging; ⊙ Further diagnostics)	△	(⊙HRT)**1.0-2.0** mg/kg/d; ↗ : ●; →: Start/maintain HRT
°3-4		△	(⊙HRT); i.v. steroids[b]; ↗ : ●; Regular controls
Renal events			
°1	Control for signs of renal dysfunction	●	---
°2	(⊙Renal biopsy); Creatinine [q2-3d]	△	**0.5-1.0** mg/kg/d; ↗ : ●
°3-4	(⊙Renal biopsy)	■	**1.0-2.0** mg/kg/d
Hepatic events			
°1	Control for signs of hepatitis	●	---
°2	Frequent controls [transaminases]	△	**0.5-1.0** mg/kg/d; ↗ : ●
°3-4	Very frequent contr. [q1-2d]; (⊙Biopsy)	■	**1.0-2.0** mg/kg/d; → / ↘ : Immunosuppr. therapy[a]

● continue therapy (Anti-PD-1); △ delay therapy (Anti-PD-1); ■ stop therapy (Anti-PD-1);

[a] Use should be guided by clinical response; in severe cases, mycophenolate mofetil might be used.
[b] A stress test with steroids with mineralocorticoid activity might be indicated.

Eigentler TK et al. Diagnosis, monitoring and management of immune-related adverse drug reactions of anti-PD-1 antibody therapy. *Cancer Treatment Reviews* 2016

Autoimmune disease is a general contraindication to checkpoint inhibitors

- Studies excluded patients with a history of autoimmune disease
  - lupus, psoriasis, Crohn's disease/UC, multiple sclerosis etc
- Rationale: Propensity towards autoimmunity portends increased risk of related or unrelated autoimmune AEs.
- Minimizing risk of autoimmune AEs is critical in early disease states (NMIBC), or in the adjuvant setting where risk/benefit is not yet established.

Exceptions:

- Vitiligo, hypothyroid state unless proven due to autoimmune etiology

Checkpoint Inhibitors and Patients with Preexisting Autoimmune Diseases (AD)

- Scope of the problem: 20-50 million people in the United States with active AD
  - 24.6% of lung cancer patients have concurrent diagnosis of AD
- Knowledge is limited because patients with AD are not included in clinical trials. Exclusion criteria in prior studies include
  - Active AD that required systemic treatment in the past 2 years
  - Chronic use of steroids or other immunosuppressants
  - Previous history of pneumonitis
  - Any evidence of clinical autoimmunity
- Anecdotal observations suggest CI use may be safe
- Risk/benefit discussion with patients

Kyi C et al. *J Immuno Ther Cancer* 2014;2(1):35; Johnson DB et al. *JAMA Oncol* 2016;2:234-40; Khan SA et al. *Proc ASCO* 2016;Abstract 9039; Menzies AM et al. *Ann Oncol* 2017;28(2):368-76.

Toxicity of Anti-PD-1 Antibodies in Patients with Preexisting Autoimmune Disorders

Retrospective study of 52 patients with melanoma and preexisting AD

Immune toxicity characteristic (N = 52)	Number (%)
Flare of AD on anti-PD-1	
Yes	20 (38%)
No	32 (62%)
Median time to flare	38 days
Grade of flare	
Grade 1-2	17 (33%)
Grade 3	3 (6%)
Grade 4	0 (0%)

- Anti-PD-1 antibodies induced relatively frequent immune toxicities that were often mild and easily managed without the need for treatment discontinuation.

Menzies AM et al. *Ann Oncol* 2017;28(2):368-76.