



SITC 2017

November 8-12
NATIONAL HARBOR
MARYLAND
Gaylord National Hotel
& Convention Center



Society for Immunotherapy of Cancer

November 8-12 • NATIONAL HARBOR, MD

SITC
2017

General Concepts of Toxicity Management

Michael Postow

Melanoma and Immunotherapeutics Service

Memorial Sloan Kettering Cancer Center



Society for Immunotherapy of Cancer

#SITC2017

Presenter Disclosure Information

Michael Postow

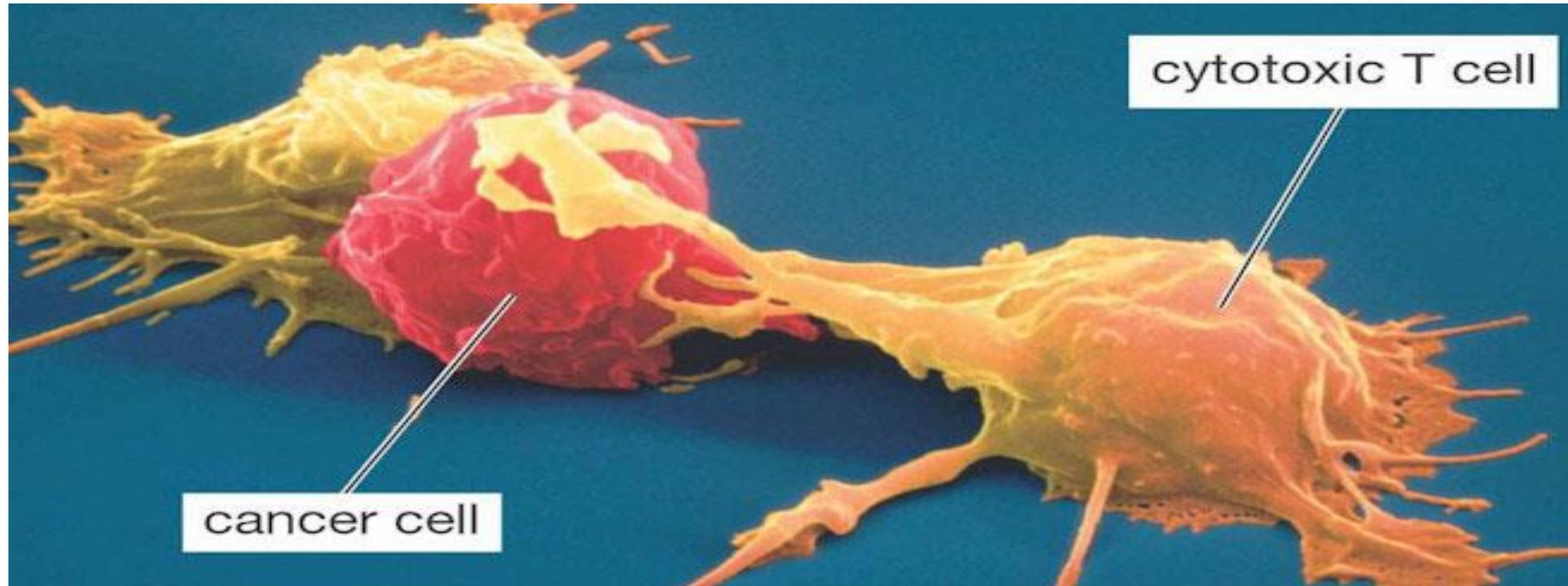
The following relationships exist related to this presentation:

Advisory Board: Array BioPharma, BMS, Incyte, Merck, NewLink Genetics, Novartis

Honoraria: BMS and Merck

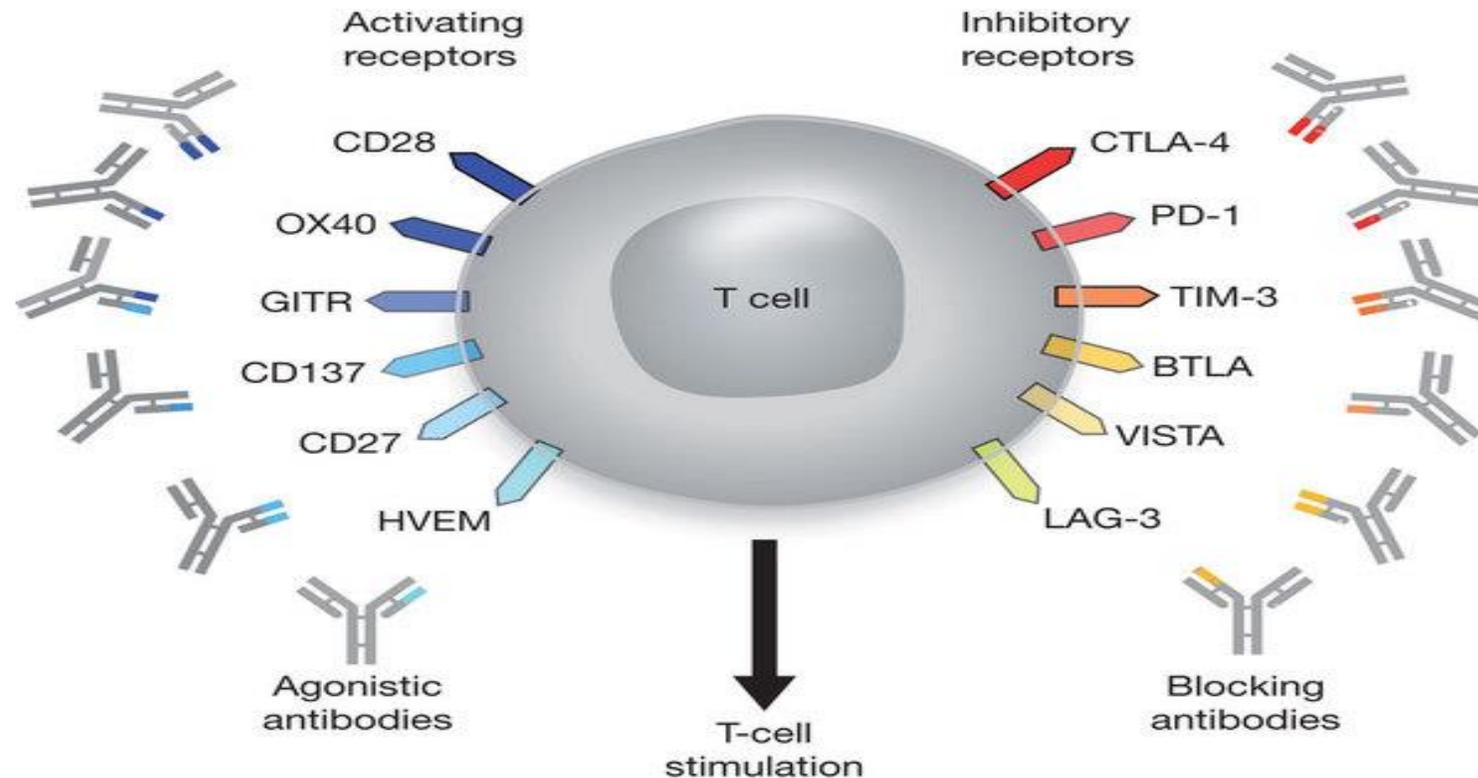


Immunotherapy = T cell kills a cancer cell





Ways to keep the T cells “active”

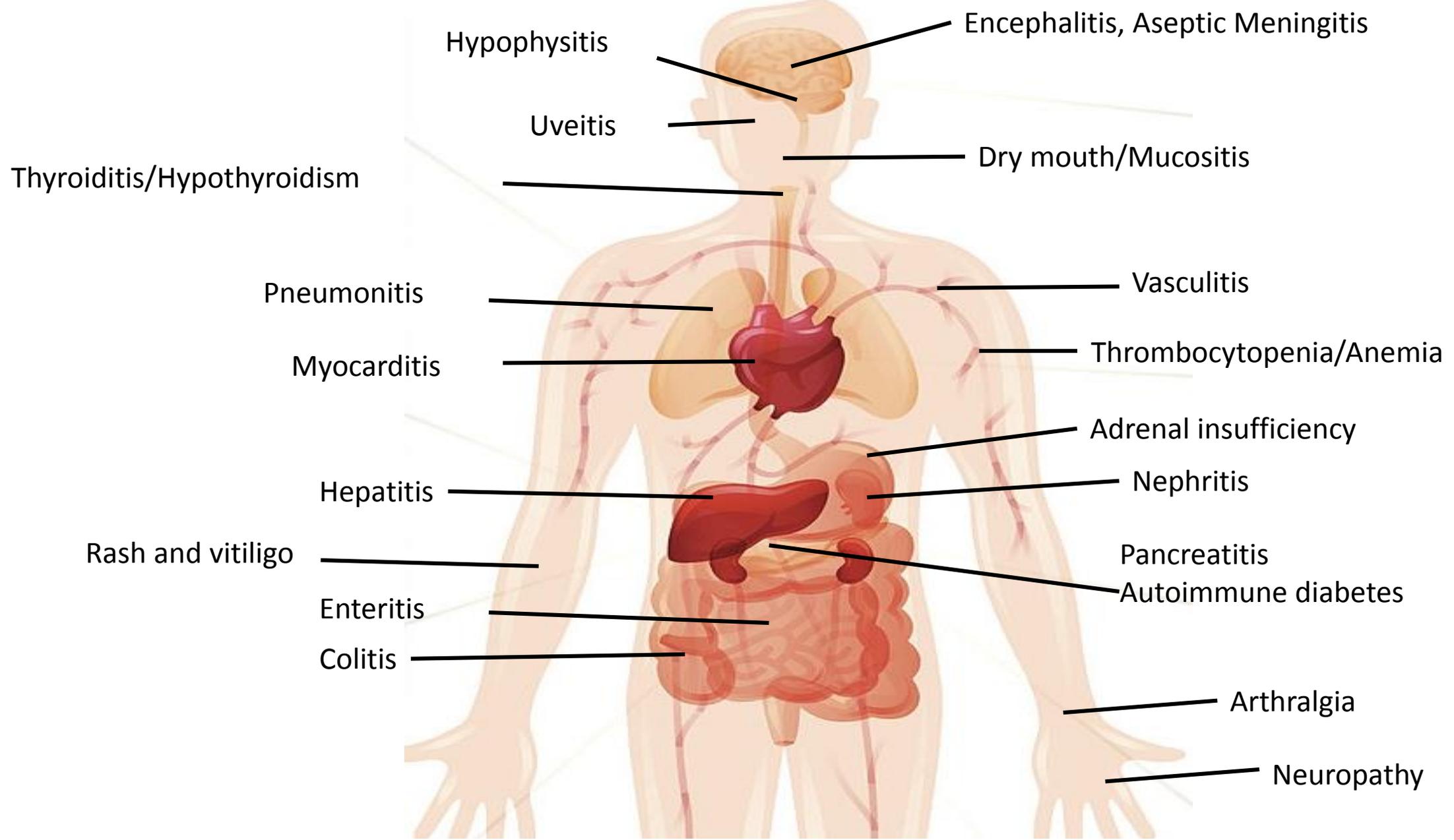


Turning up The Activating

Blocking the Inhibiting



What are the side effects?



Rash is usually on the trunk or proximal limbs and rarely face



Sanlorenzo M et al. *JAMA Dermatology* 2015

More severe rashes need systemic steroids



Vitiligo



Related to better PD-1 outcomes?

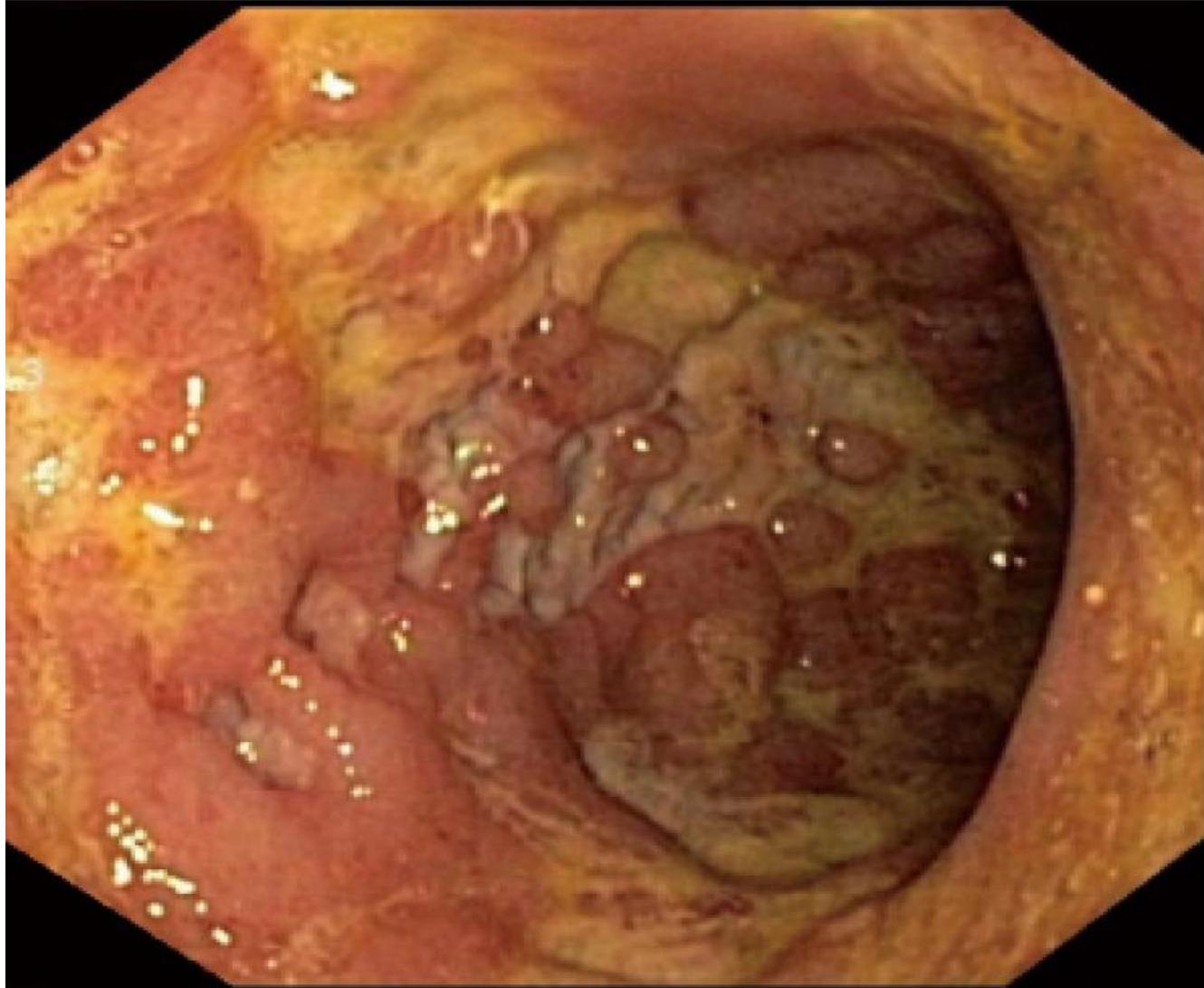
Lo et al. *JAMA Oncol* 2015

Sanlorenzo M et al. *JAMA Dermatology* 2015

Vitiligo

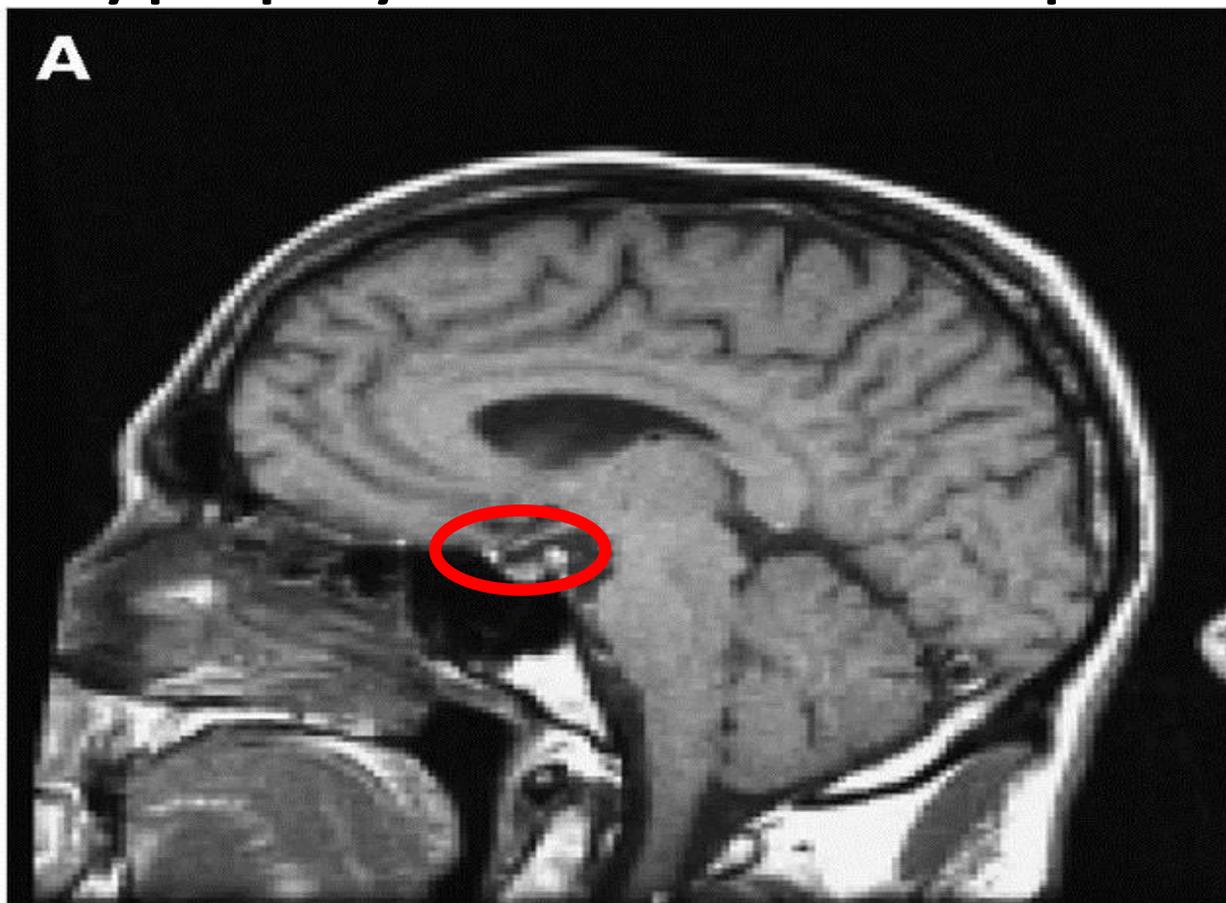


Diarrhea and Colitis

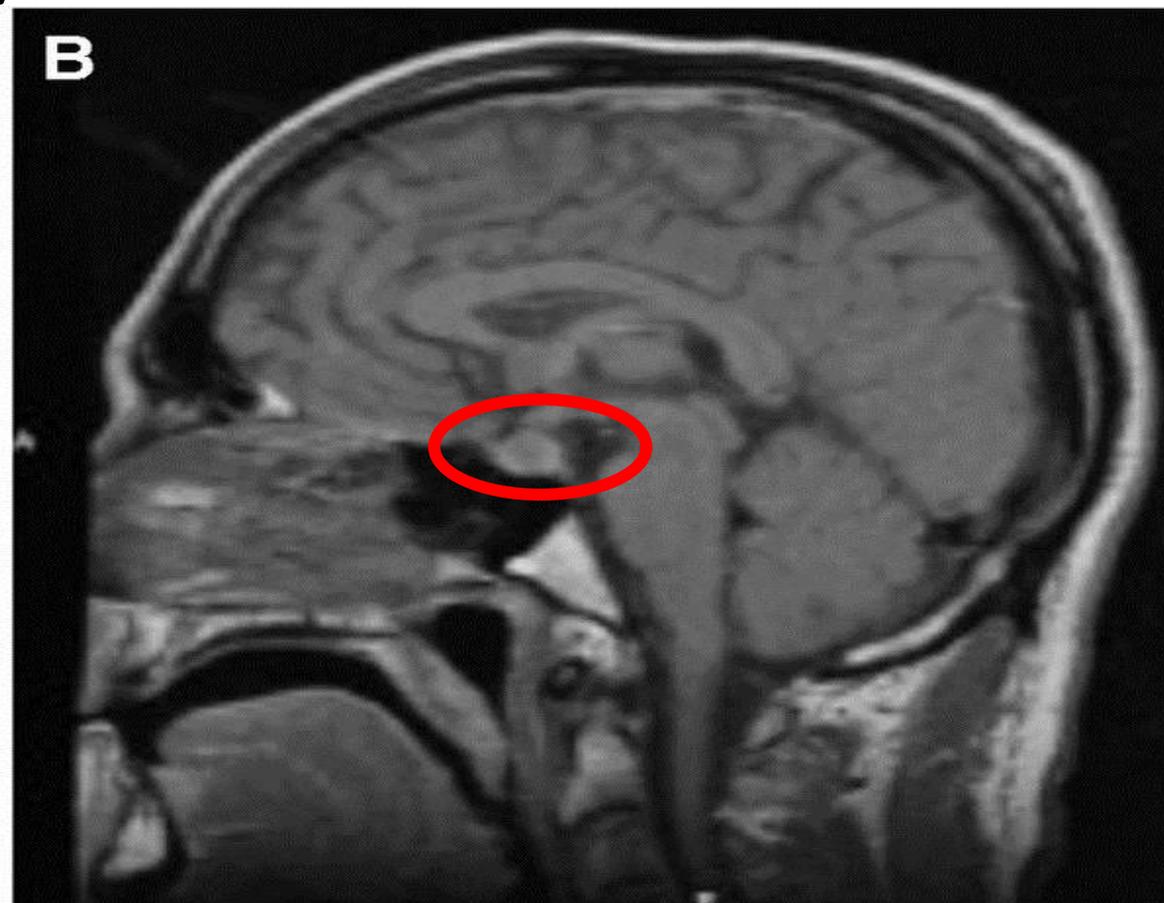


Slangen et al., *World J Gastrointest Pharmacol Ther*, 2013

Hypophysitis Endocrinopathy



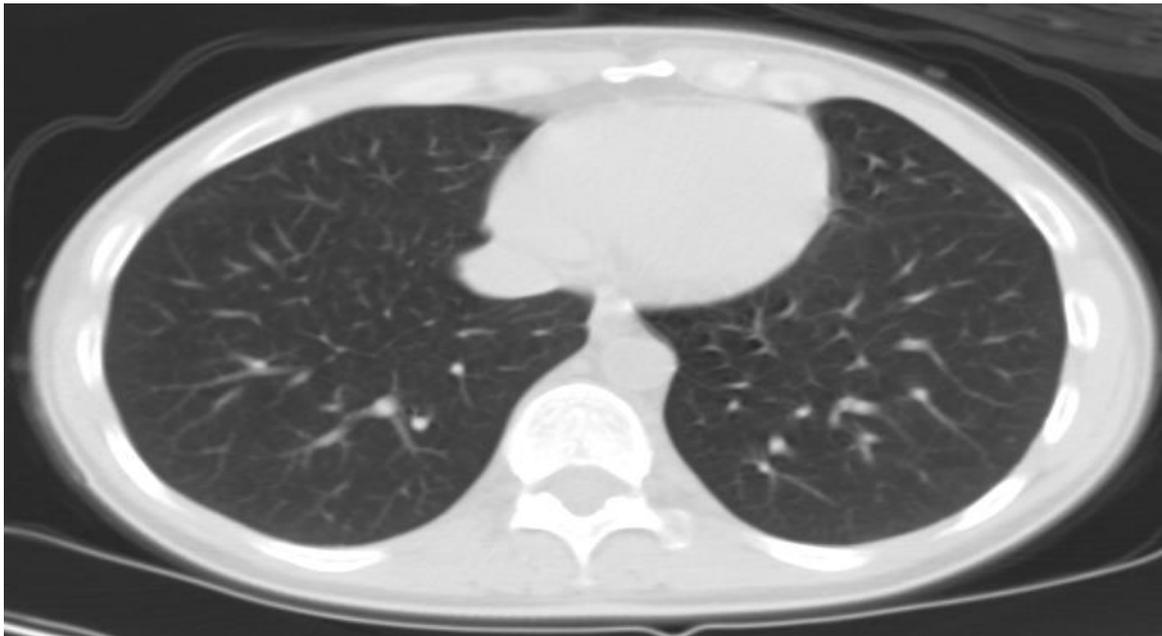
6/30/04 - Baseline (4.5 mm)



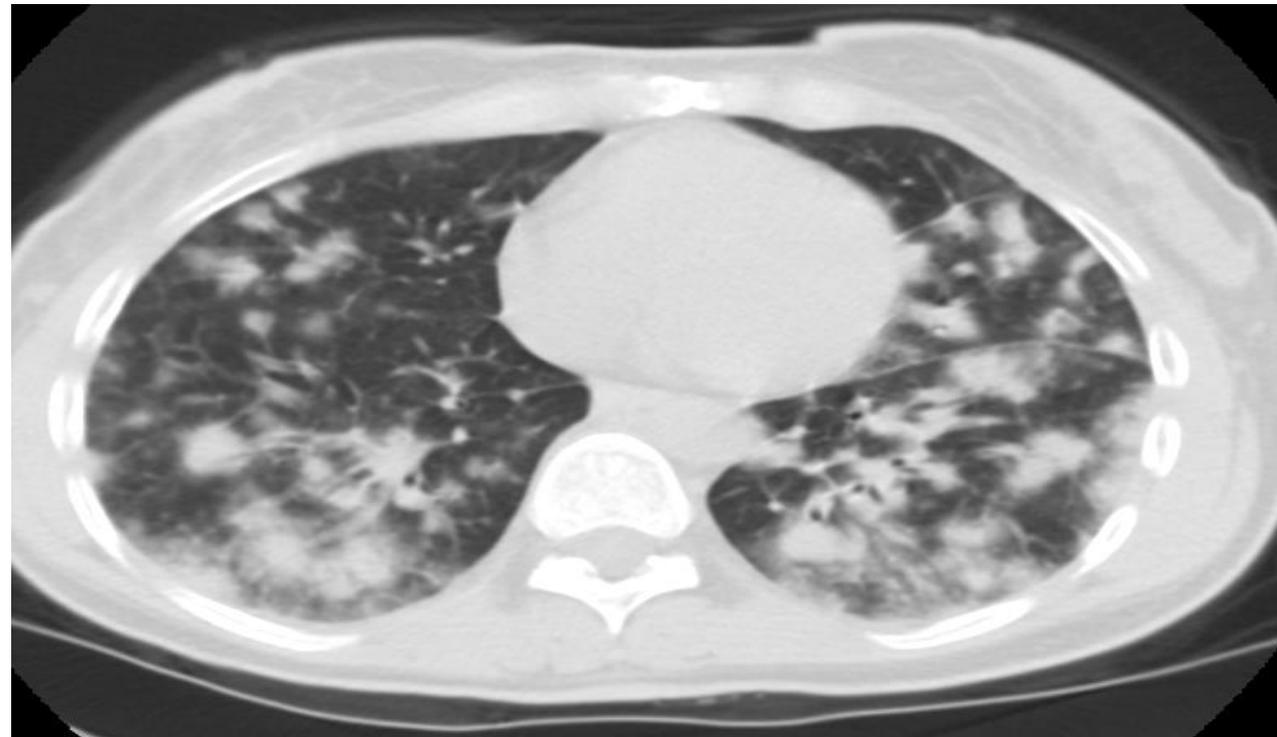
12/3/04 - Headache/fatigue (10.8 mm)

Weber et al. *JCO* 2012, reprinted from Blansfield *J Immunother* 2005

Pneumonitis

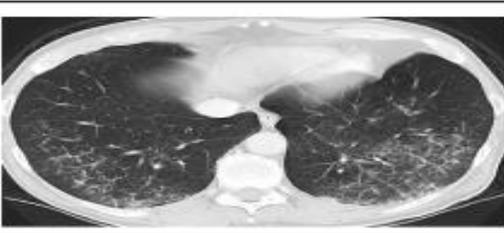
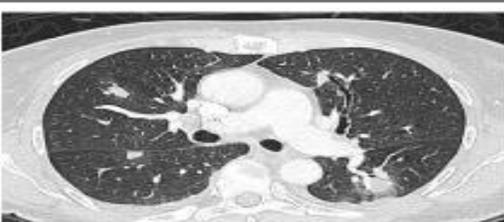


2/21/2011

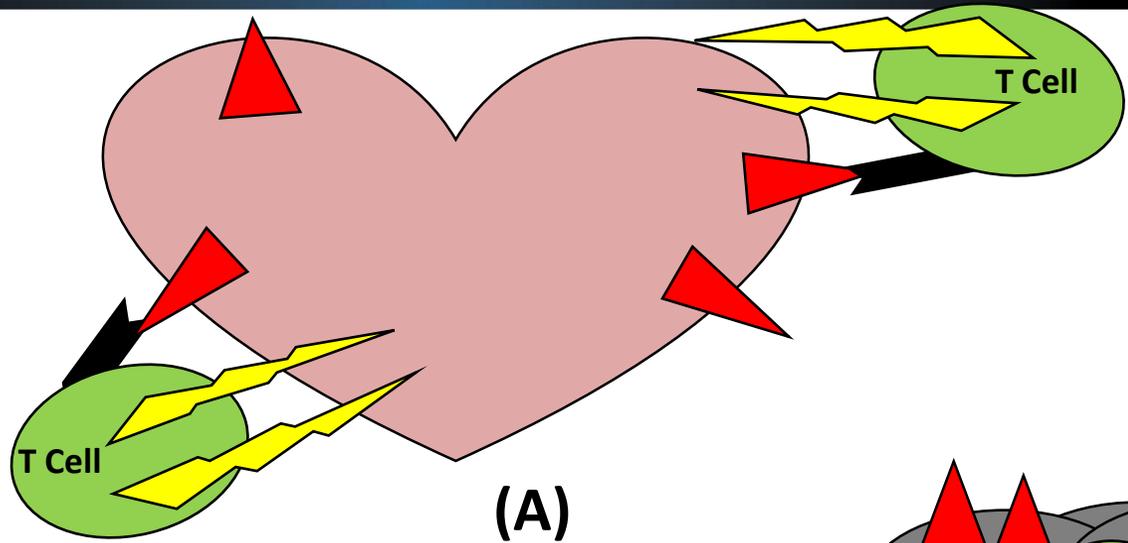


3/30/2011

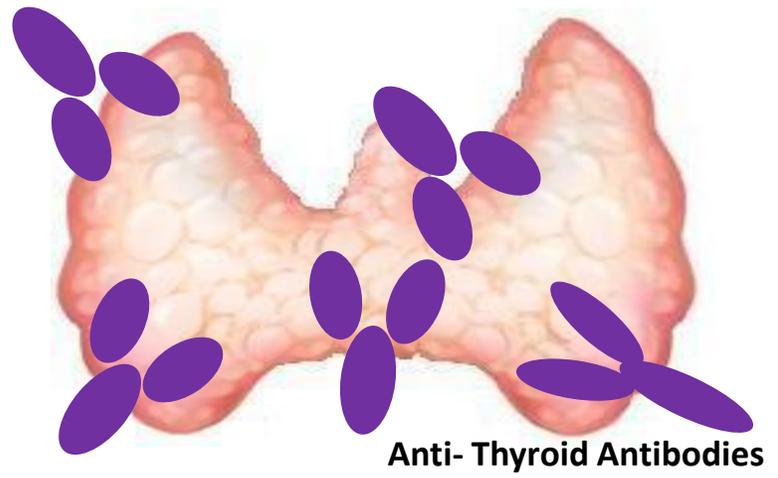
Two doses of ipilimumab and four of nivolumab

Radiologic Subtypes	Representative Image	Description
<p>Cryptogenic organizing pneumonia-like (n = 5, 19%)</p>		<p>Discrete patchy or confluent consolidation with or without air bronchograms Predominantly peripheral or subpleural distribution</p>
<p>Ground glass opacities (n = 10, 37%)</p>		<p>Discrete focal areas of increased attenuation Preserved bronchovascular markings</p>
<p>Interstitial (n = 6, 22%)</p>		<p>Increased interstitial markings, interlobular septal thickening Peribronchovascular infiltration, subpleural reticulation Honeycomb pattern in severe patient cases</p>
<p>Hypersensitivity (n = 2, 7%)</p>		<p>Centrilobular nodules Bronchiolitis-like appearance Tree-in-bud micronodularity</p>
<p>Pneumonitis not otherwise specified (n = 4, 15%)</p>		<p>Mixture of nodular and other subtypes Not clearly fitting into other subtype classifications</p>

Diverse Pneumonitis Presentations

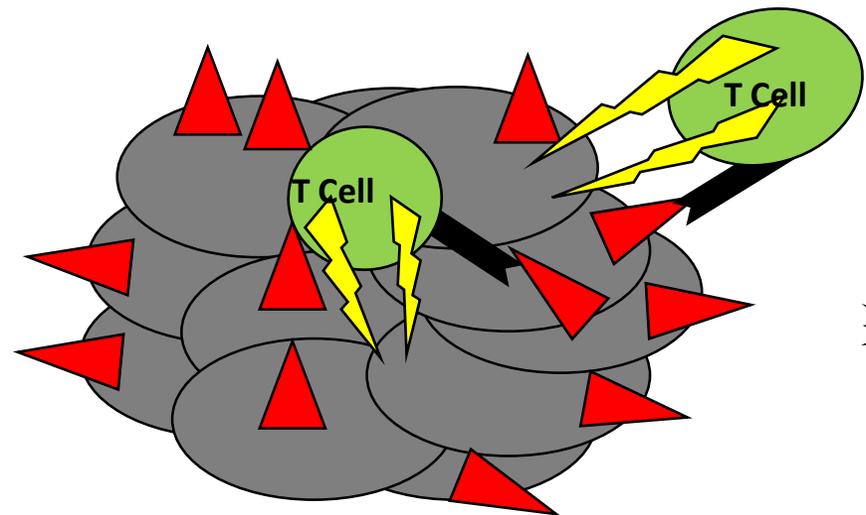


(A)

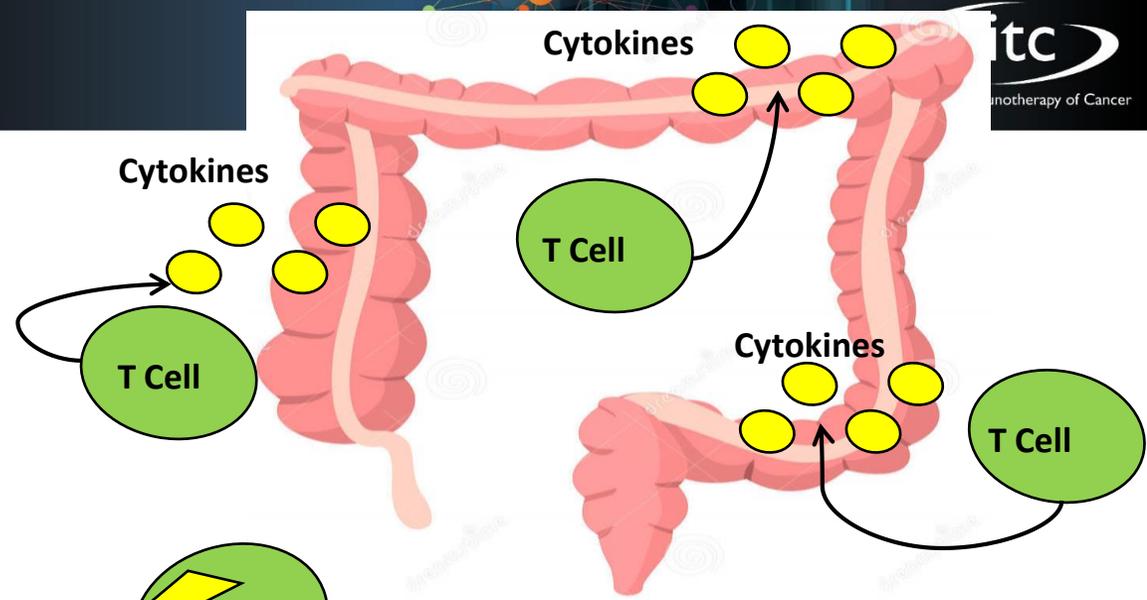


Anti-Thyroid Antibodies

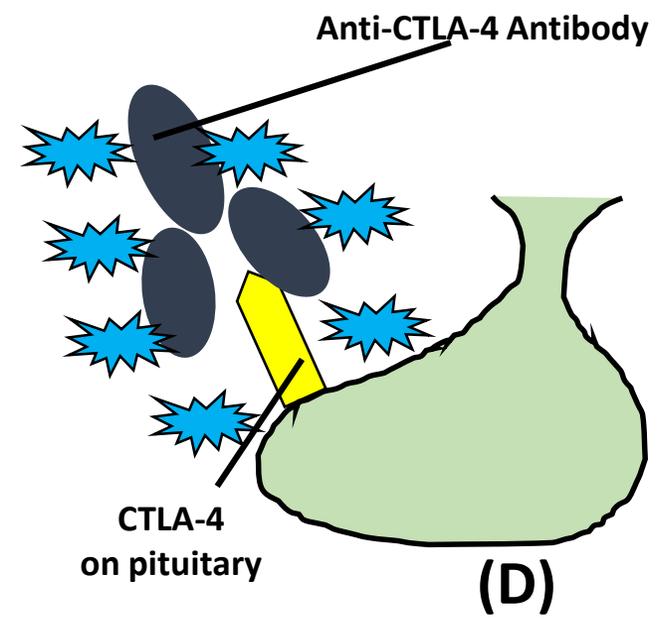
(B)



Tumor with antigen



(C)



CTLA-4 on pituitary

(D)

What to say to patients?

1. Immunotherapy causes inflammatory type reactions that can affect any organ that last from weeks to months .
2. Effects on hormones may be permanent and require supplements.
3. You may need steroid creams or to take steroids by mouth or other immunosuppressant drugs.
4. Most side effects can be dealt with at home.

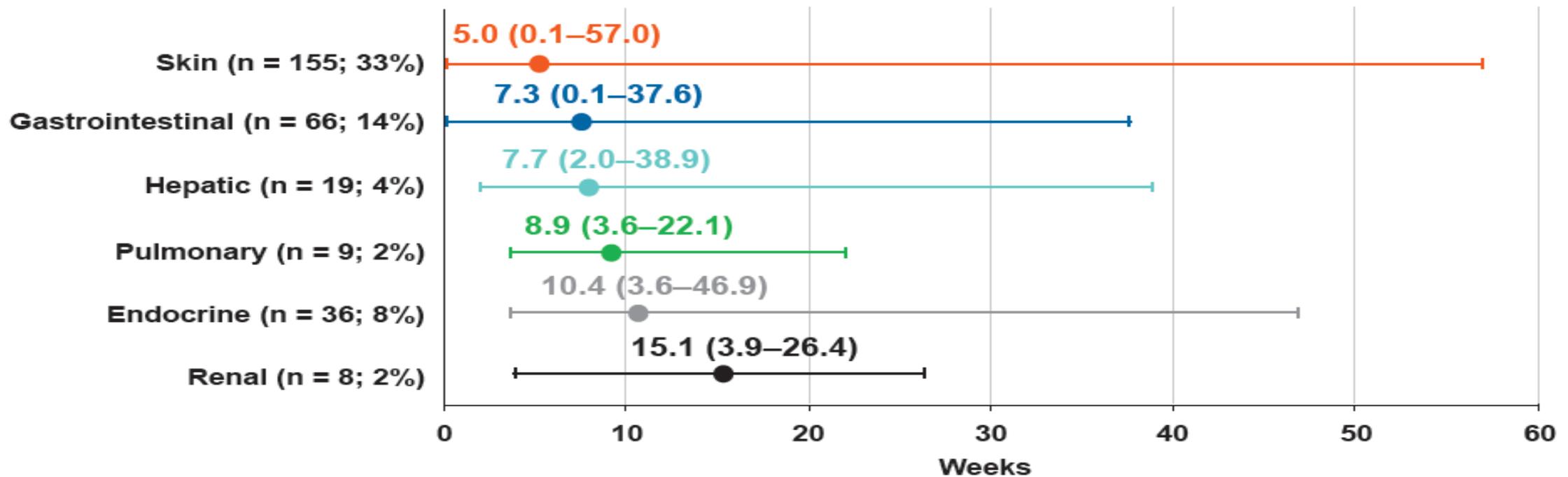
Most common side effects

1. **PD-1:** Rash, Tired, Achy joints
2. **Combination ipilimumab + PD-1:** Diarrhea, inflammation of liver, rash

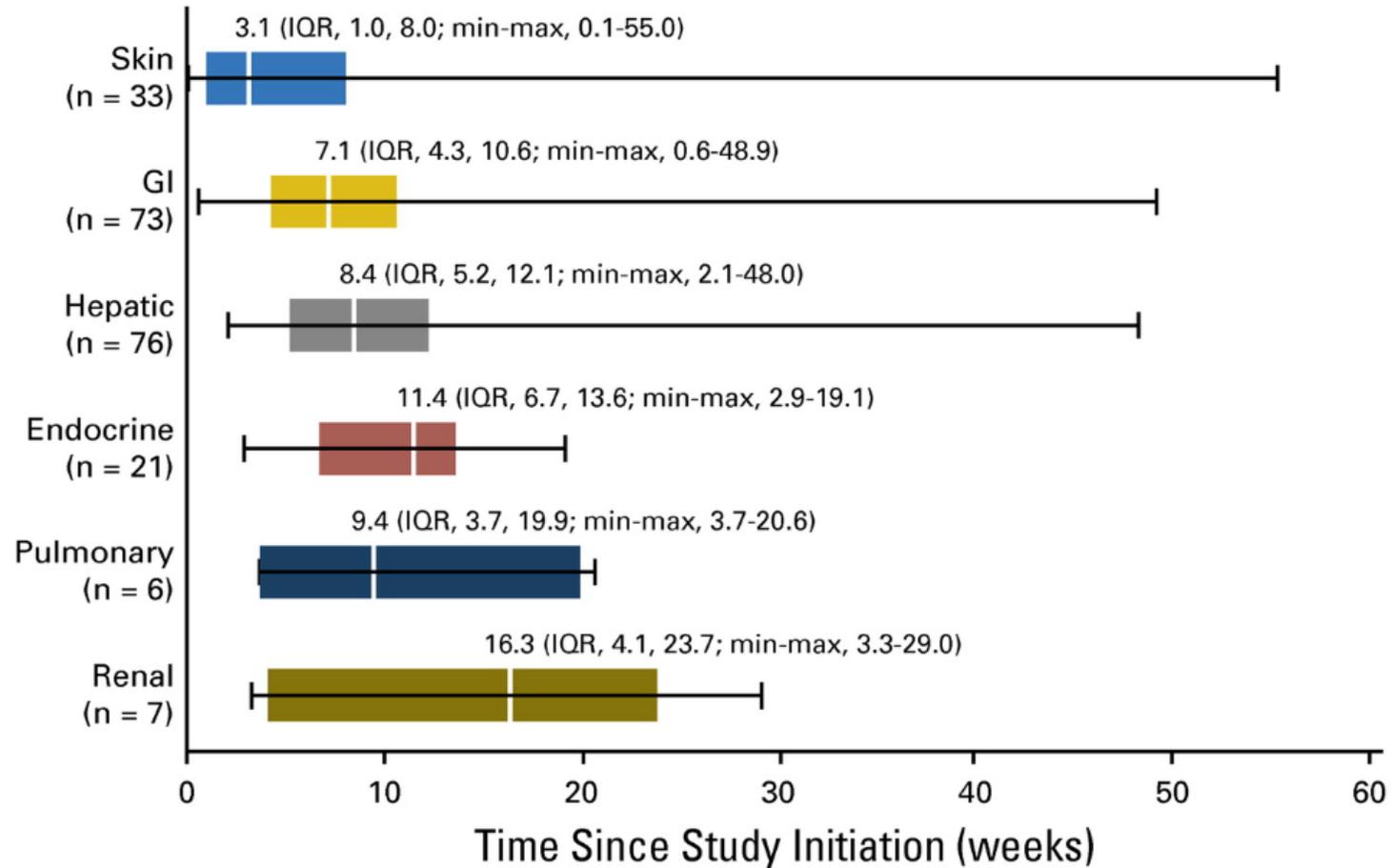


When do they happen?

Time to Onset of Select Treatment-related AEs for Nivolumab (Any Grade; N = 474)

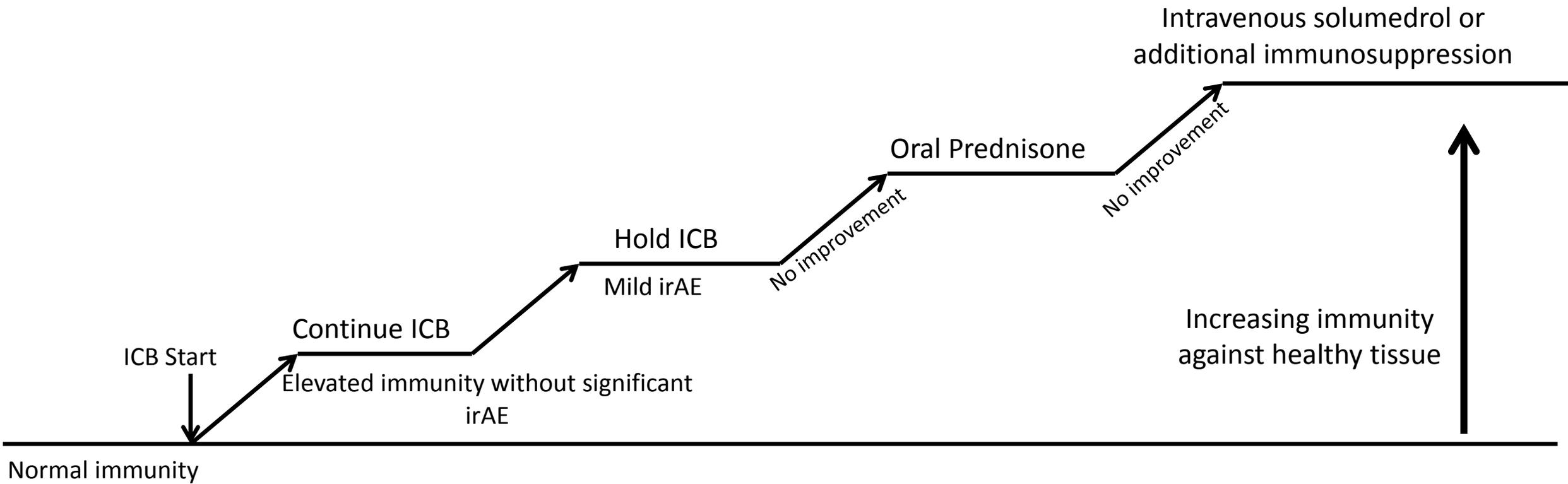


Time to Onset of Select Treatment-related AEs for Nivolumab + Ipilimumab



Sznol et al. *Journal of Clin Oncol* 2017

What do you do if they happen?

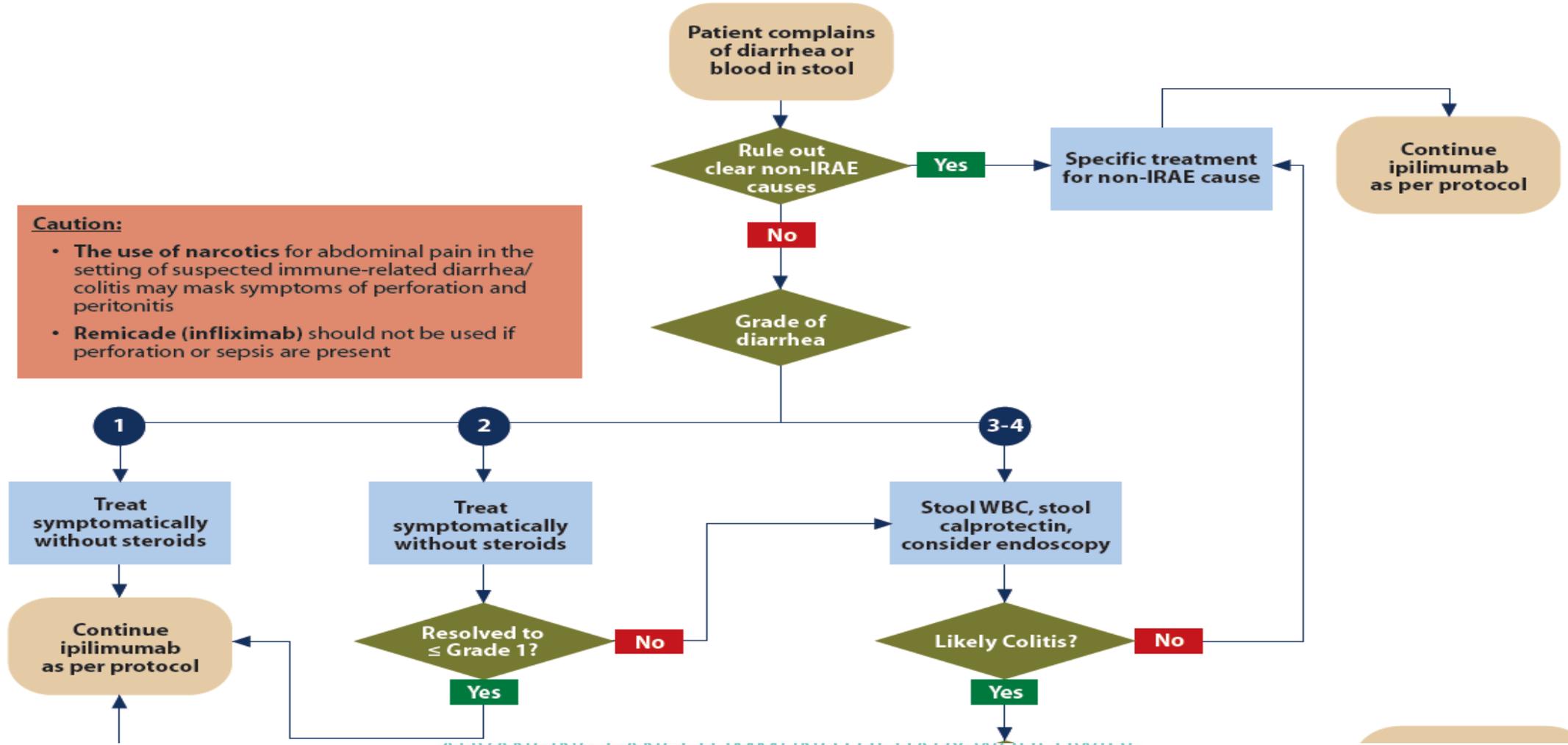


ipilimumab

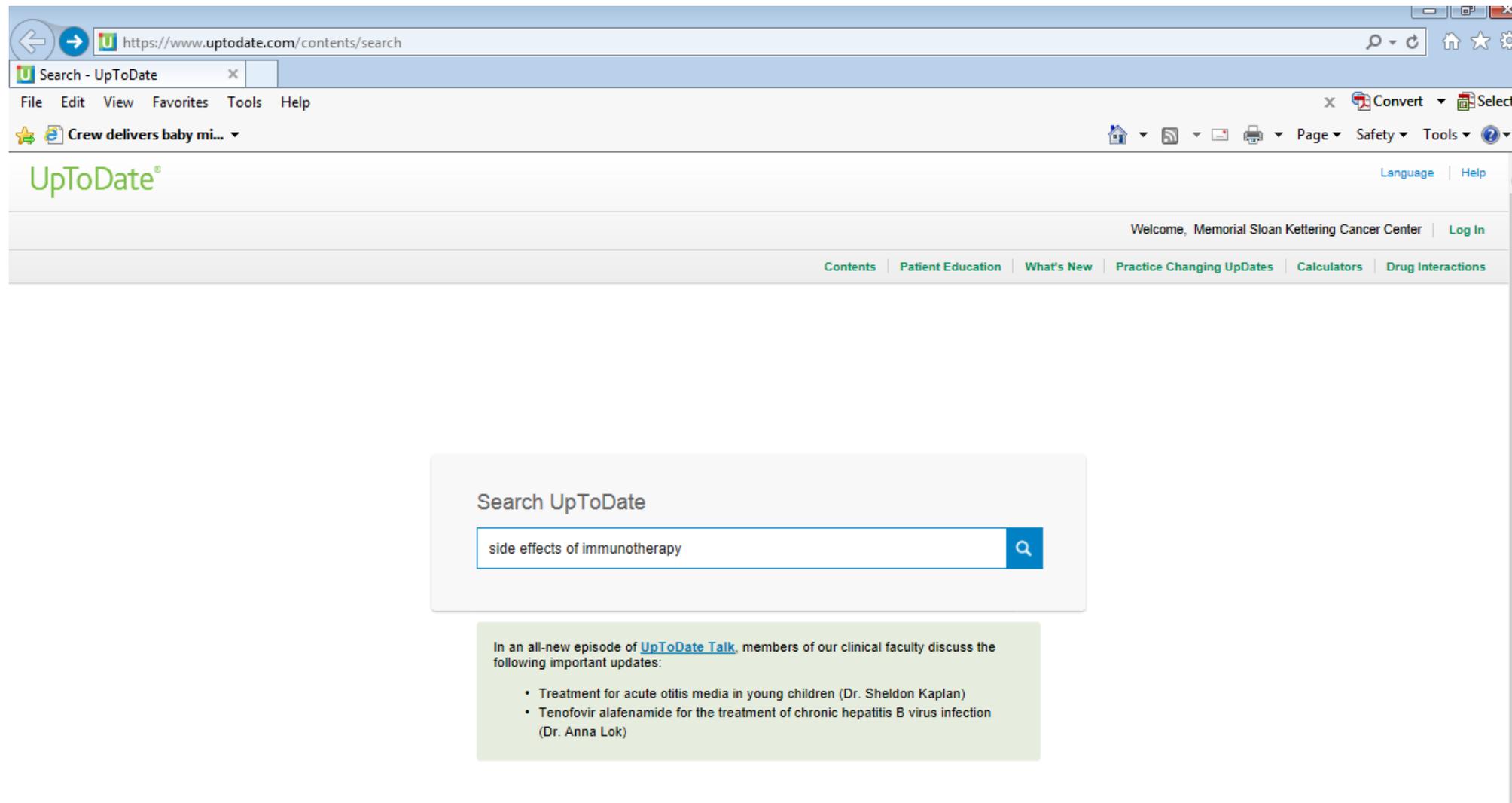
DIARRRHEA MANAGEMENT ALGORITHM

Caution:

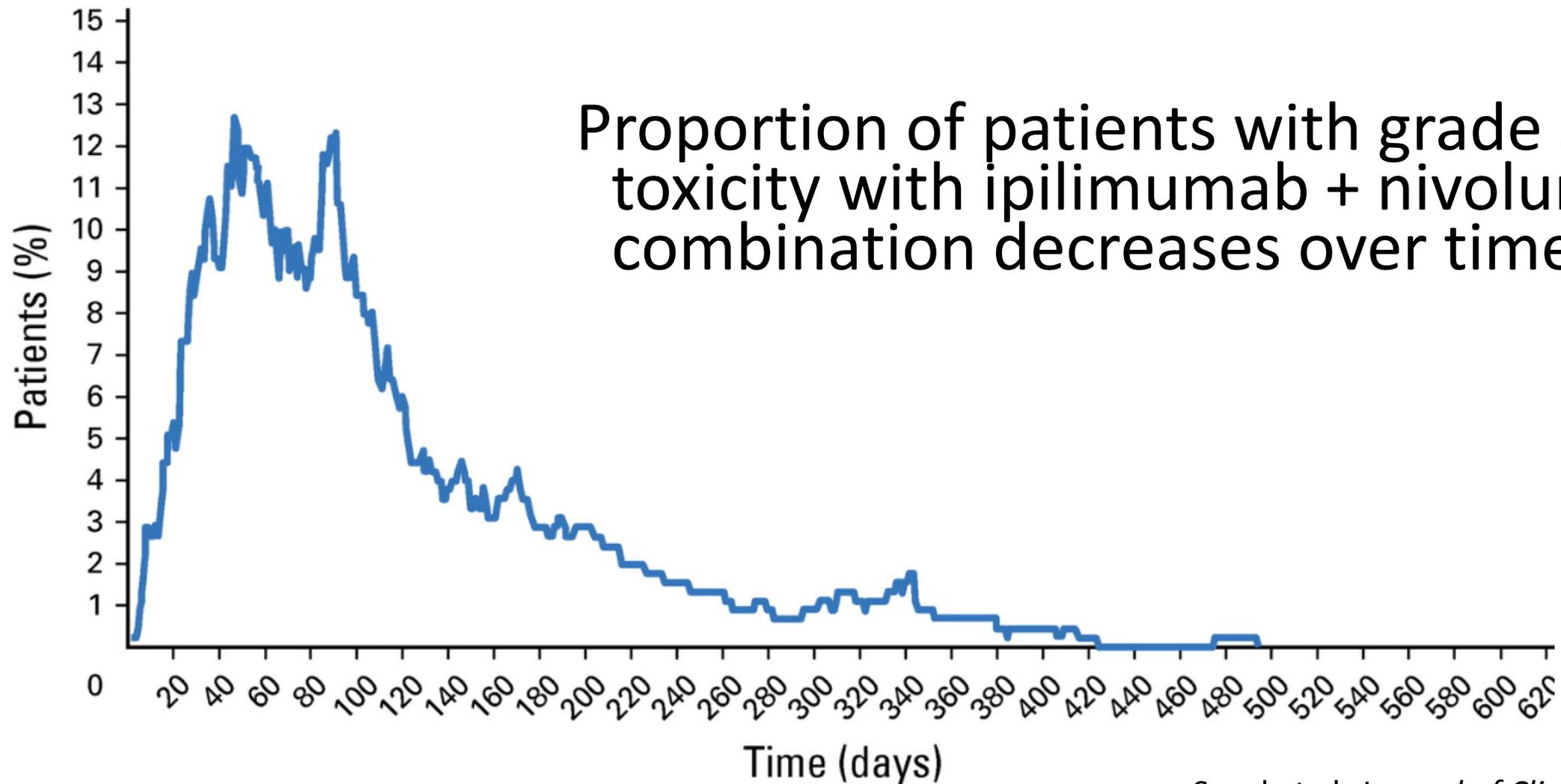
- The use of narcotics for abdominal pain in the setting of suspected immune-related diarrhea/colitis may mask symptoms of perforation and peritonitis
- Remicade (infliximab) should not be used if perforation or sepsis are present



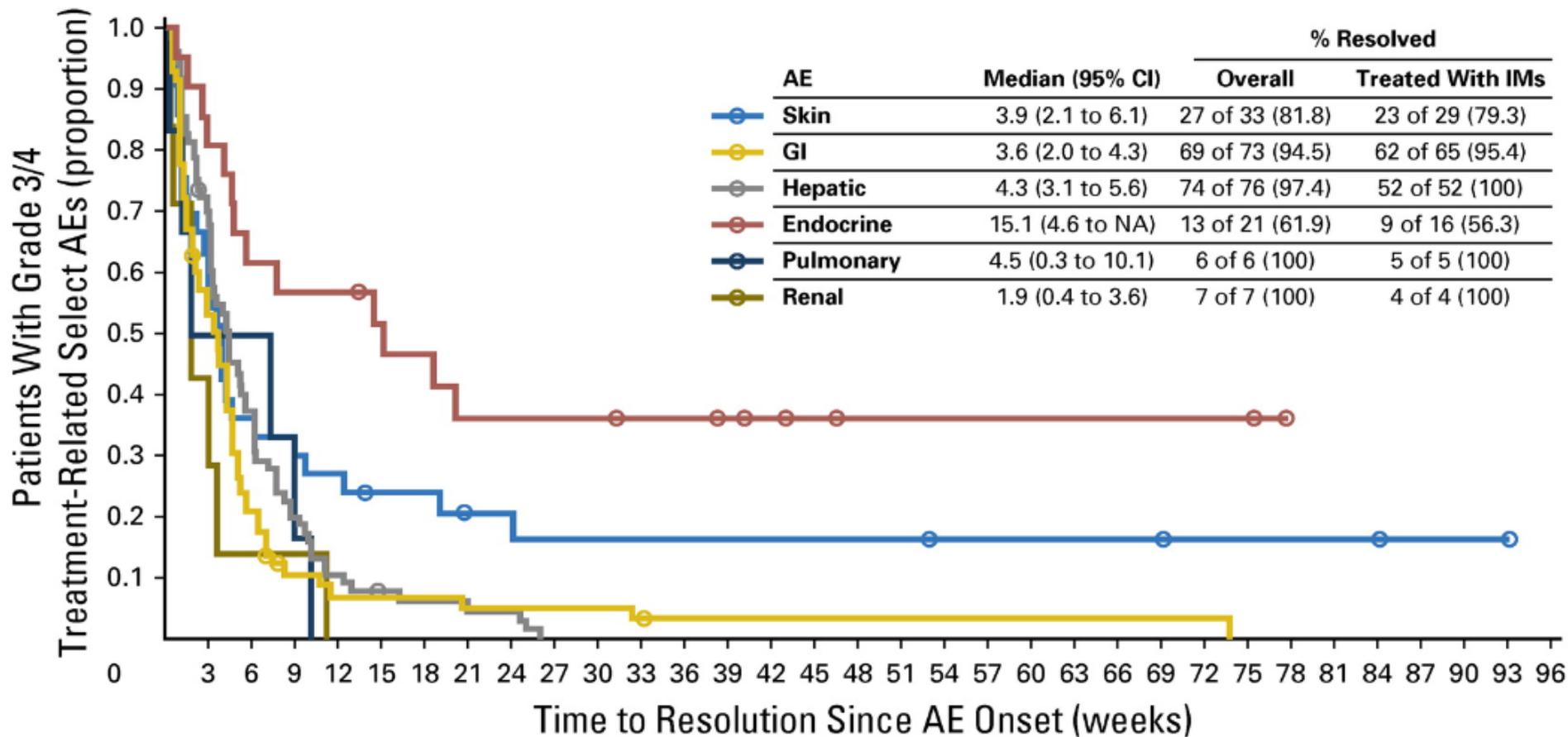
www.uptodate.com



The screenshot shows a web browser window displaying the UpToDate website. The address bar shows the URL <https://www.uptodate.com/contents/search>. The browser's menu bar includes File, Edit, View, Favorites, Tools, and Help. The UpToDate logo is visible in the top left of the page content. A navigation bar at the top right contains links for Language and Help. Below this, a welcome message for Memorial Sloan Kettering Cancer Center is displayed with a Log In link. A horizontal menu lists various site sections: Contents, Patient Education, What's New, Practice Changing UpDates, Calculators, and Drug Interactions. The main content area features a search box titled "Search UpToDate" with the text "side effects of immunotherapy" entered. Below the search box, a green callout box highlights a new episode of "UpToDate Talk" with the following text: "In an all-new episode of [UpToDate Talk](#), members of our clinical faculty discuss the following important updates:" followed by a bulleted list of two topics: "Treatment for acute otitis media in young children (Dr. Sheldon Kaplan)" and "Tenofovir alafenamide for the treatment of chronic hepatitis B virus infection (Dr. Anna Lok)".



Sznol et al. *Journal of Clin Oncol* 2017



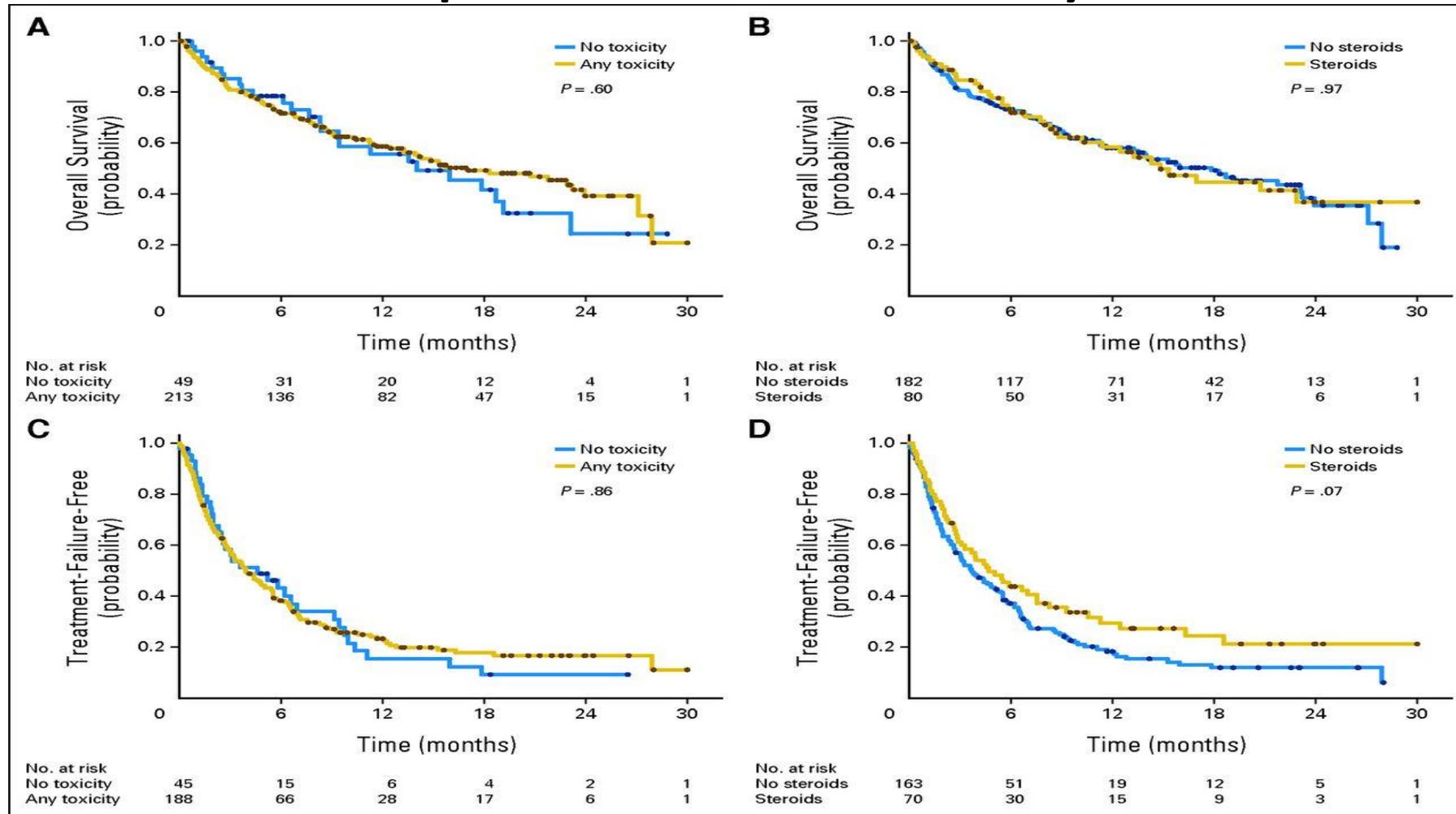
No. at risk:

Endocrine	21	17	13	12	12	10	9	7	7	7	7	6	6	5	4	3	2	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0		
GI	73	38	14	6	4	4	4	3	3	3	3	2	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0			
Hepatic	76	51	28	15	8	5	4	3	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			
Pulmonary	6	3	3	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			
Renal	7	2	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			
Skin	33	19	12	10	9	7	7	5	5	4	4	4	4	4	4	4	4	4	4	3	3	3	3	3	3	2	2	2	2	2	1	1	1	0

Sznol et al. *Journal of Clin Oncol* 2017

Does immunosuppression blunt immunotherapy favorable effect?

Steroids (to treat side effects) do not seem to affect ipilimumab efficacy



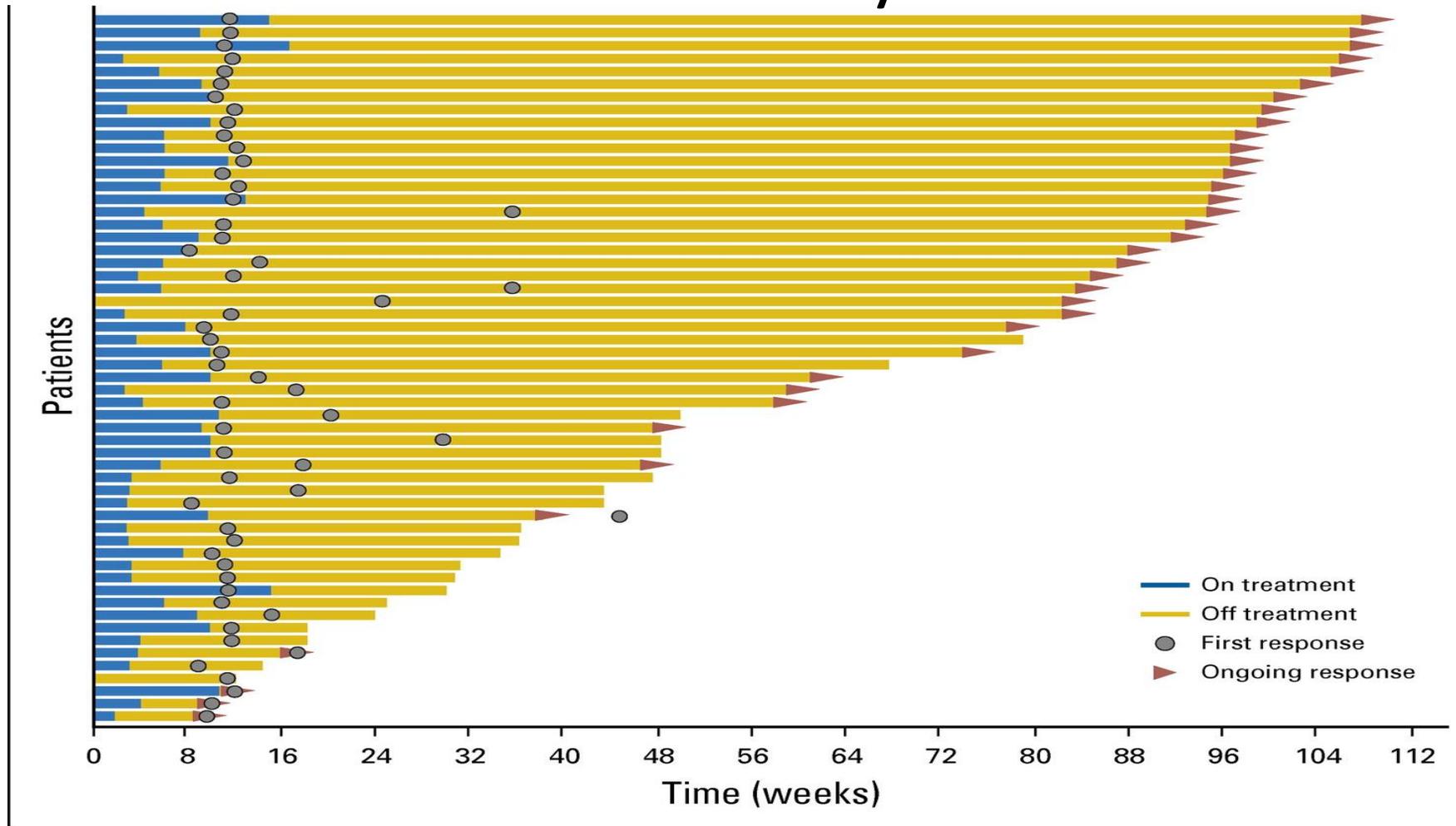
Immunosuppression does not seem to affect nivolumab efficacy

	NIVO monotherapy with immunosuppression to treat a side effect N = 139	NIVO monotherapy without immunosuppression to treat a side effect N = 437
ORR, n (%), [95% CI]	40 (28.8) [21.4–37.1]	141 (32.3) [27.9–36.9]
BOR, n (%)		
CR	7 (5.0)	22 (5.0)
PR	33 (23.7)	119 (27.2)
SD	31 (22.3)	102 (23.3)
PD	63 (45.3)	173 (39.6)
Not evaluable	5 (3.6)	21 (4.8)
Median duration of response, mo (95% CI)	NR (9.3–NR)	22.0 (22.0–NR)
Median time to response, mo (range)	2.1 (1.2–8.8)	2.1 (1.4–9.2)

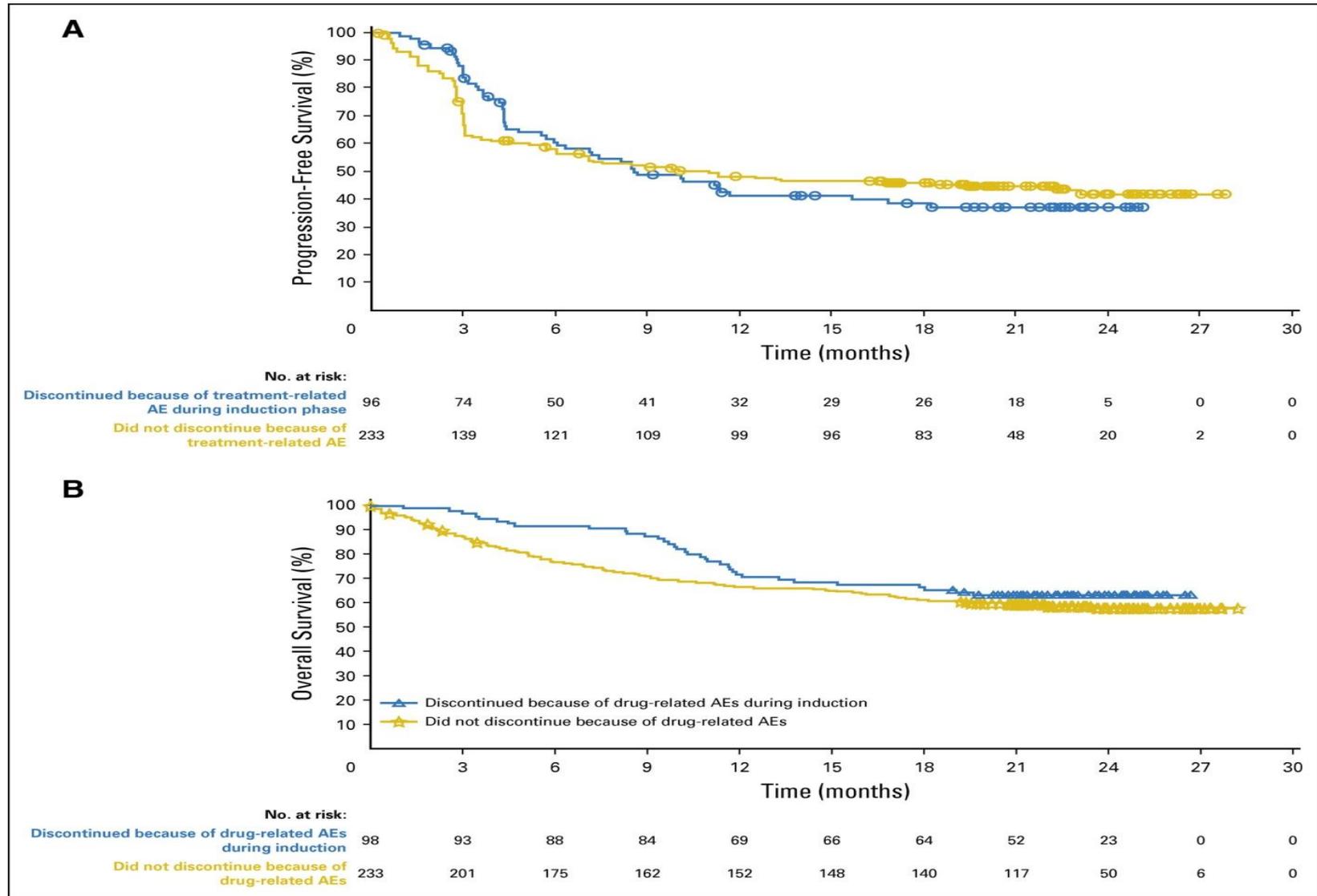
Weber et al. *Journal of Clin Oncol* 2016

Does stopping immunotherapy hurt patient outcomes?

Most responses continue after stopping immunotherapy due to toxicity

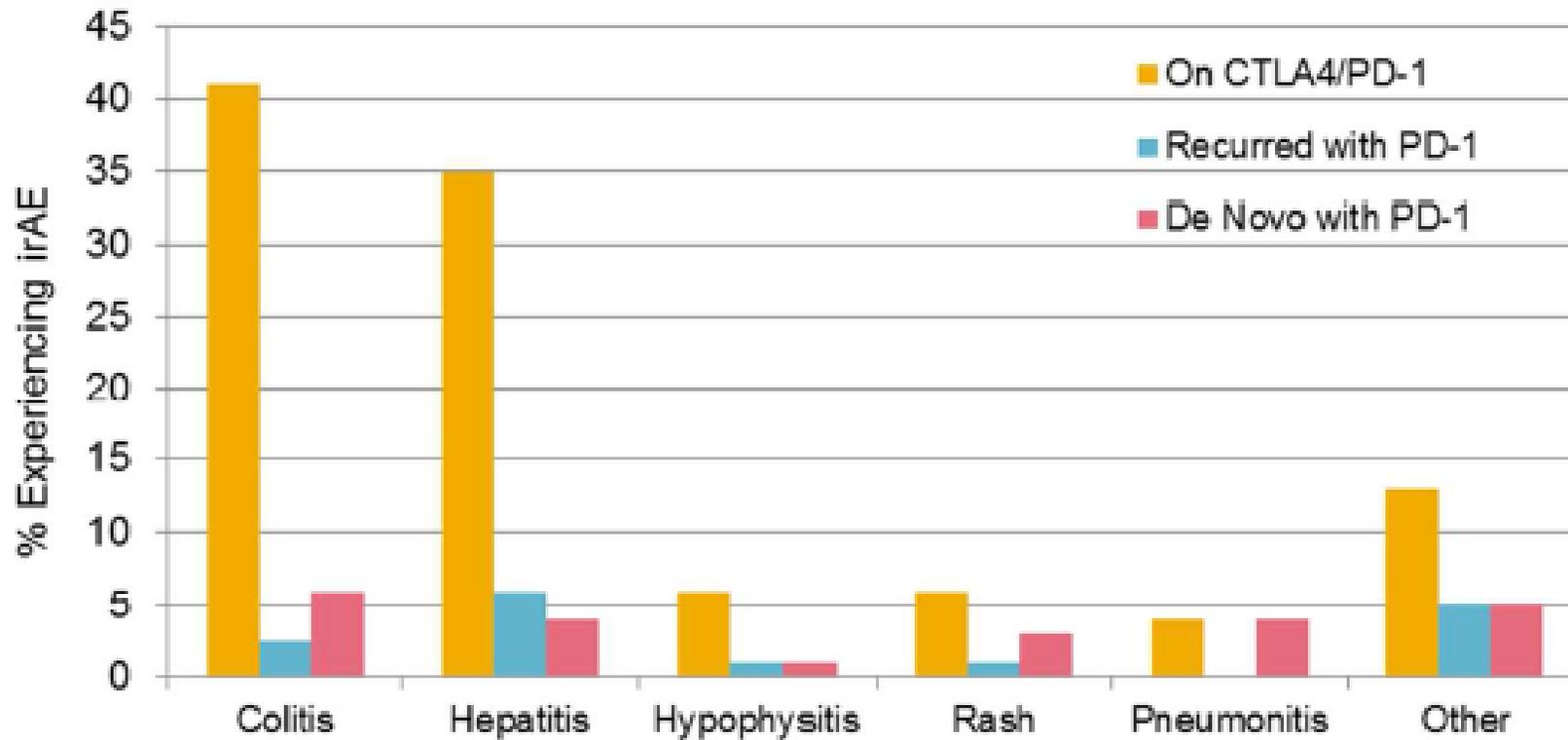


PFS and OS in patients stopping due to toxicity is not worse than patients who continue



Is it safe to restart immunotherapy after toxicity resolution?

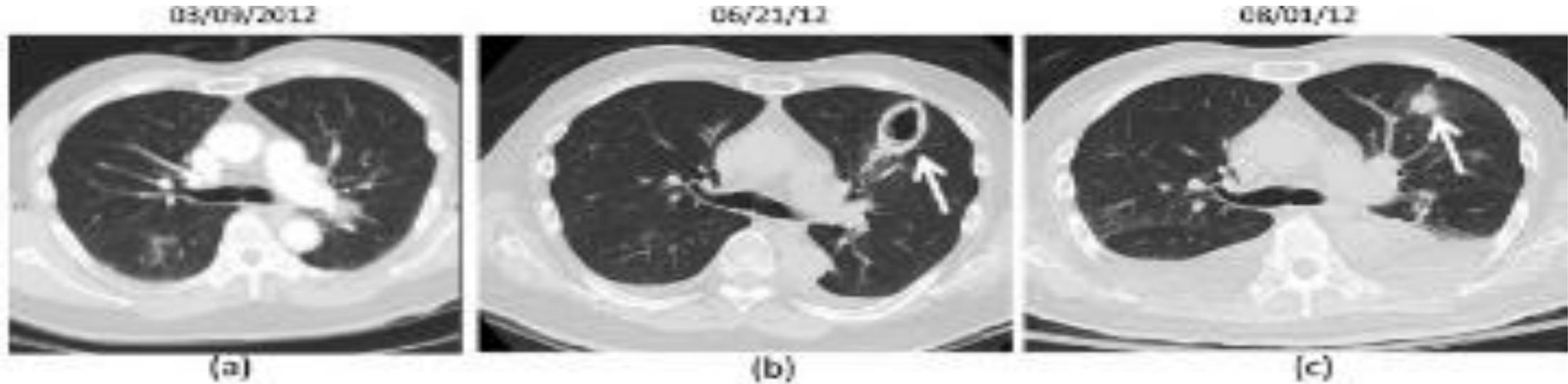
Toxicity profiles in patients restarting PD-1 after ipilimumab + PD-1 combination toxicity





What are risks of immunosuppression?

Possibility of Opportunistic Infection



- Ipilimumab diarrhea treated with prednisone and infliximab, subsequent *Aspergillus fumigatus* infection treated with voriconazole
- Consider prophylaxis for PCP (Bactrim, atovaquone) in patients on 20mg of prednisone for at least 4 weeks (Category 2B from NCCN)

What about safety in patients with autoimmune conditions?

1. Knowledge is limited since patients with autoimmunity not included in clinical trials
2. Retrospective studies suggest it may be safe
3. Risk/benefit discussion with patients

Kyi and Postow *JITC* 2014
Johnson et al. *JAMA Oncol* 2016
Menzies et al. *Annals of Onc* 2017

Future Questions

- Should patients stop after response?
- What are long-term complications?
- Preventative therapies for high risk patients?
- Mechanistic studies for specific treatments?