

Immunotherapy Side Effects

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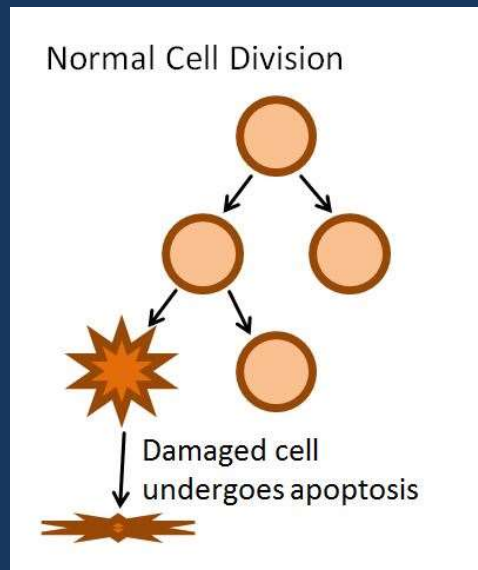
Disclosures

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

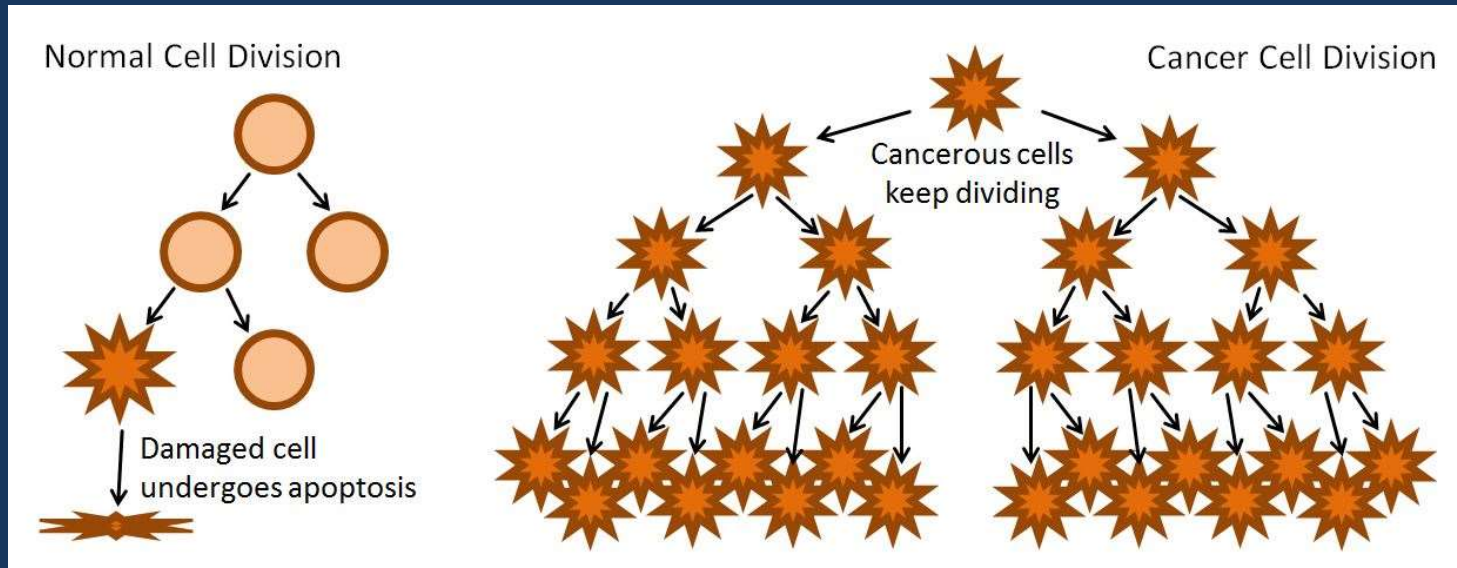
Honoraria: BMS and Merck

Institutional Support: RGenix, Infinity, BMS, Merck, Array BioPharma, Novartis

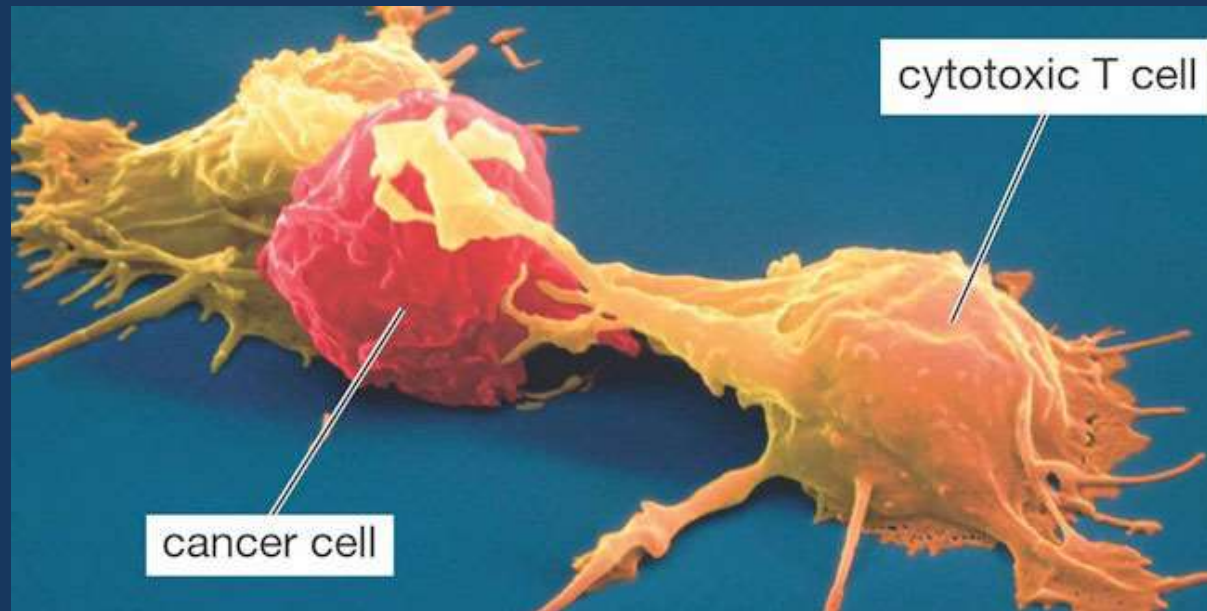
Cancer Treatment Side Effects Related to Inhibiting Dividing Cells



Cancer Treatment Side Effects Related to Inhibiting Dividing Cells

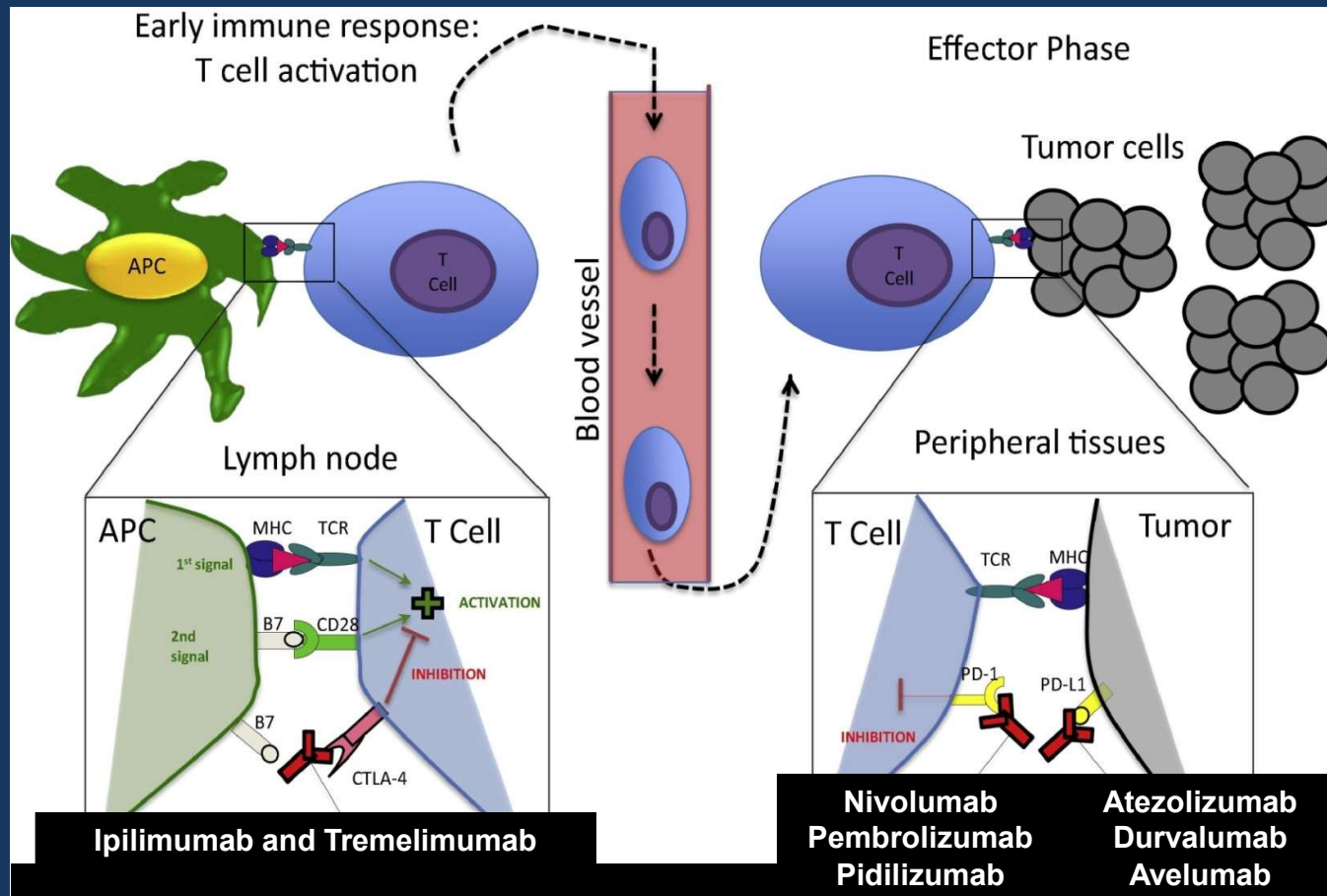


Immunotherapy = Immune cell kills a cancer cell



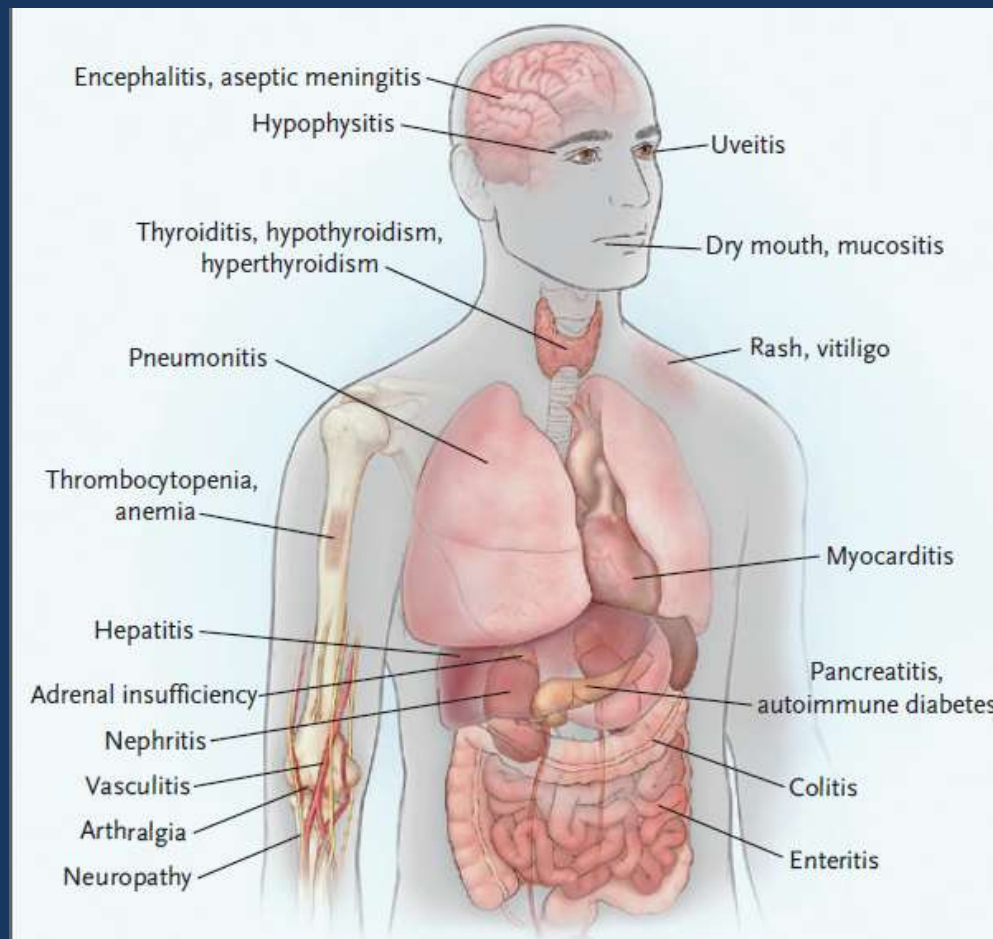
Immunotherapy does not directly
treat cancer, it only turns up
immune system

Blocking both CTLA-4 and PD-1



What kind of side
effects happen?

All organs can be involved



Postow, Sidlow, Hellmann *N Eng J Med* 2018

What do they
look like and why
do they happen?

Rash



Development of vitiligo



Related to outcomes with
PD-1?

Lo et al. *JAMA Oncol* 2015
Sanlorenzo M et al. *JAMA Dermatology* 2015

Development of vitiligo

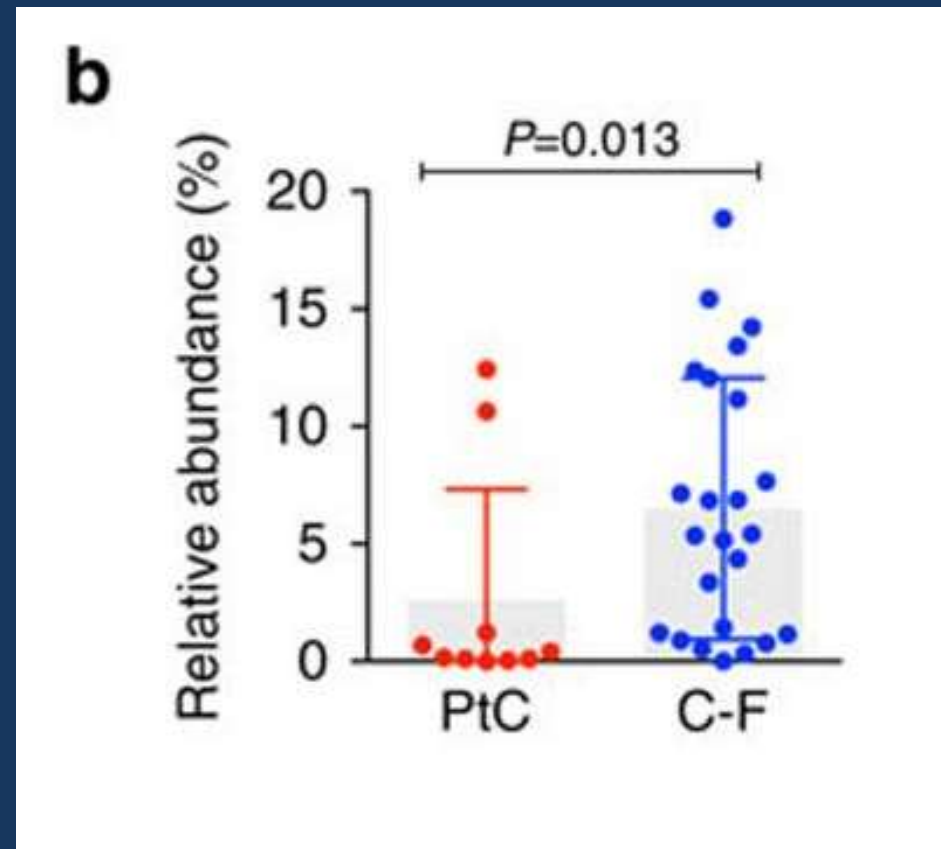
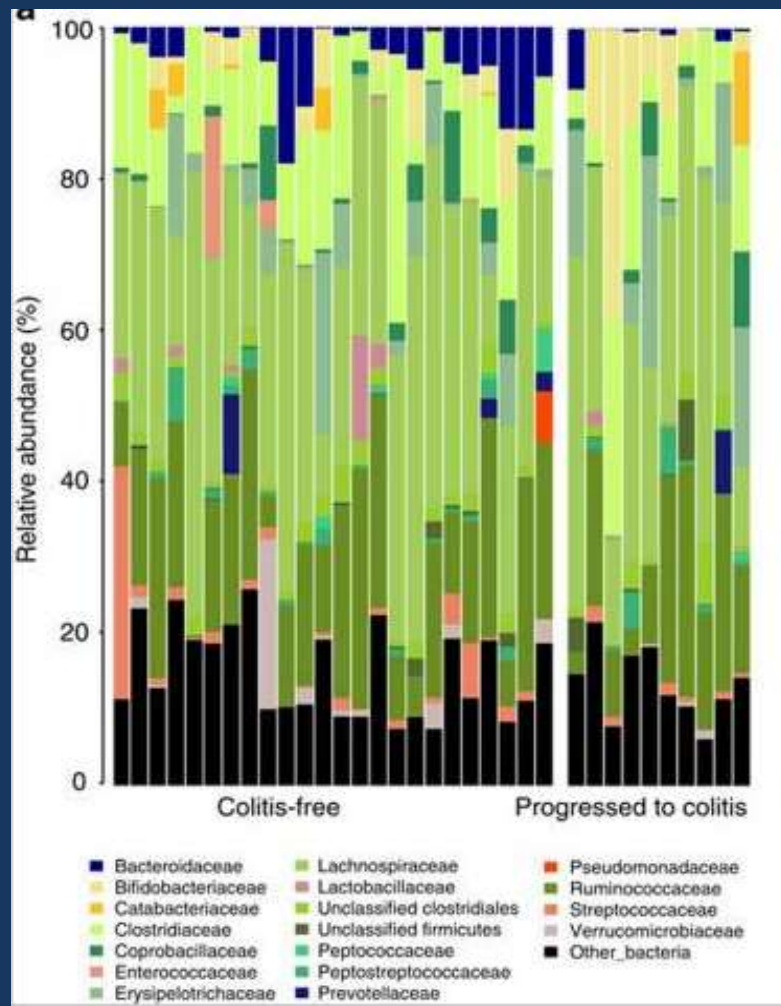


Diarrhea and Colitis



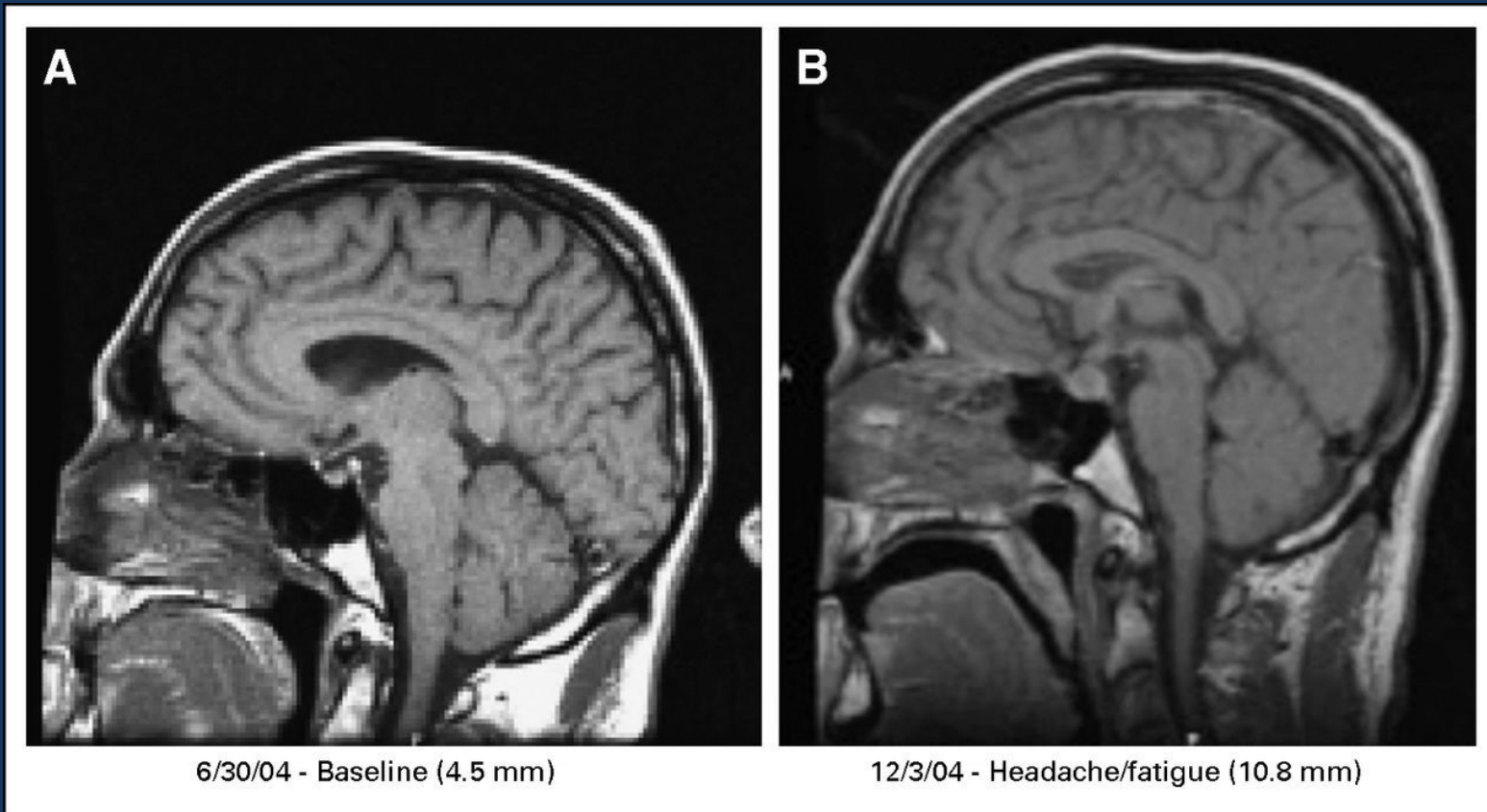
Slangen et al., *World J Gastrointest Pharmacol Ther*, 2013

Bacteroidetes is associated with less colitis



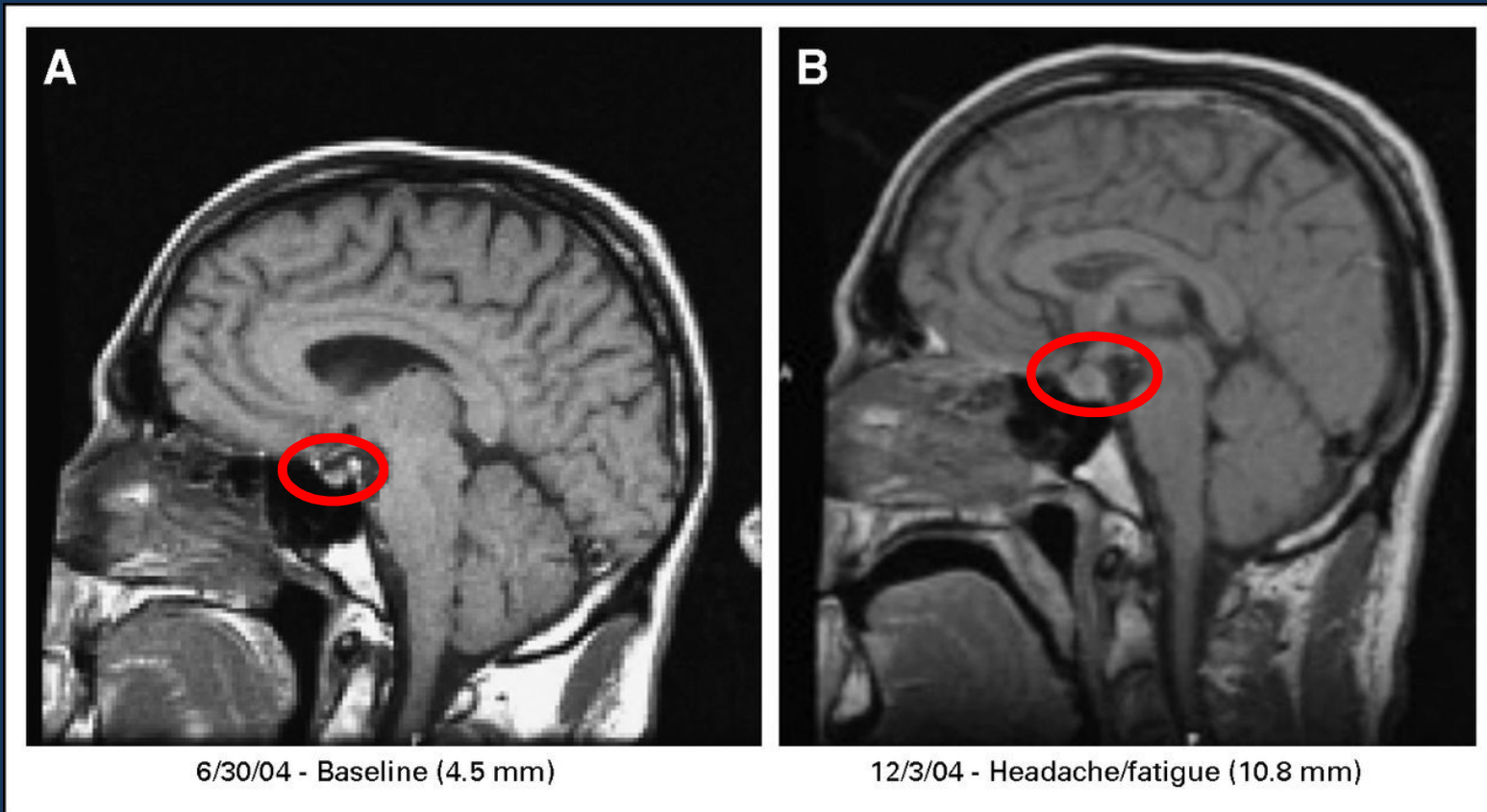
Dubin, et al. *Nat Commun* 2016

Headache/Fatigue is endocrinopathy until proven otherwise



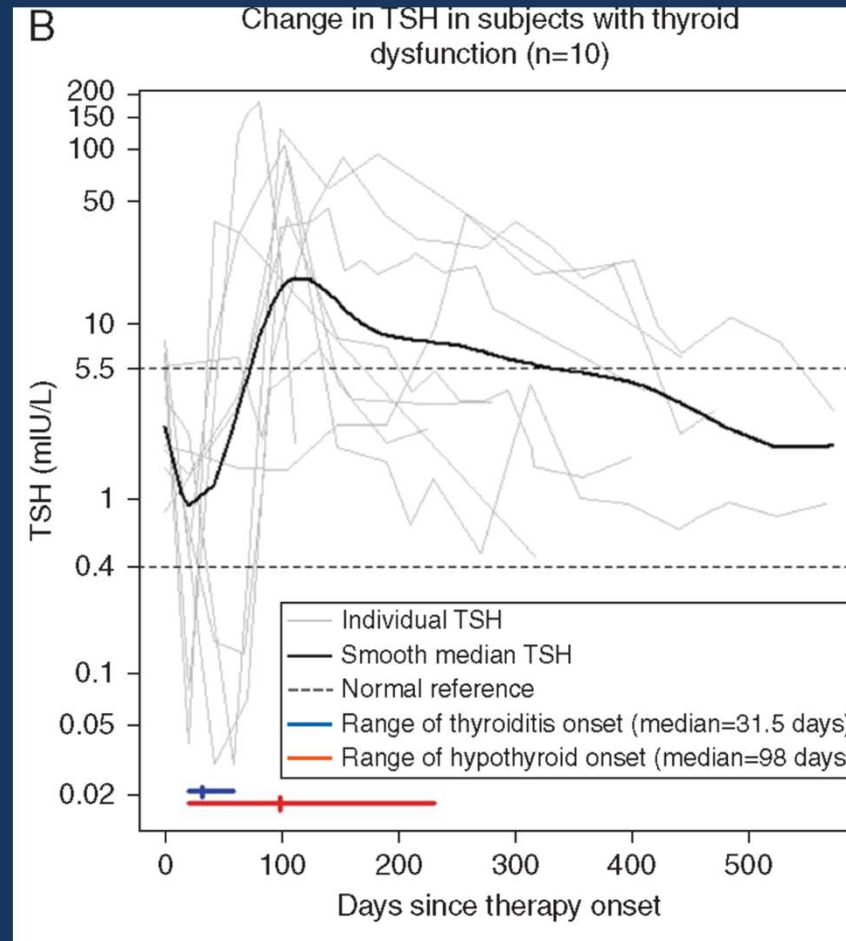
Weber et al. *JCO* 2012, reprinted from Blansfield *J Immunother* 2005

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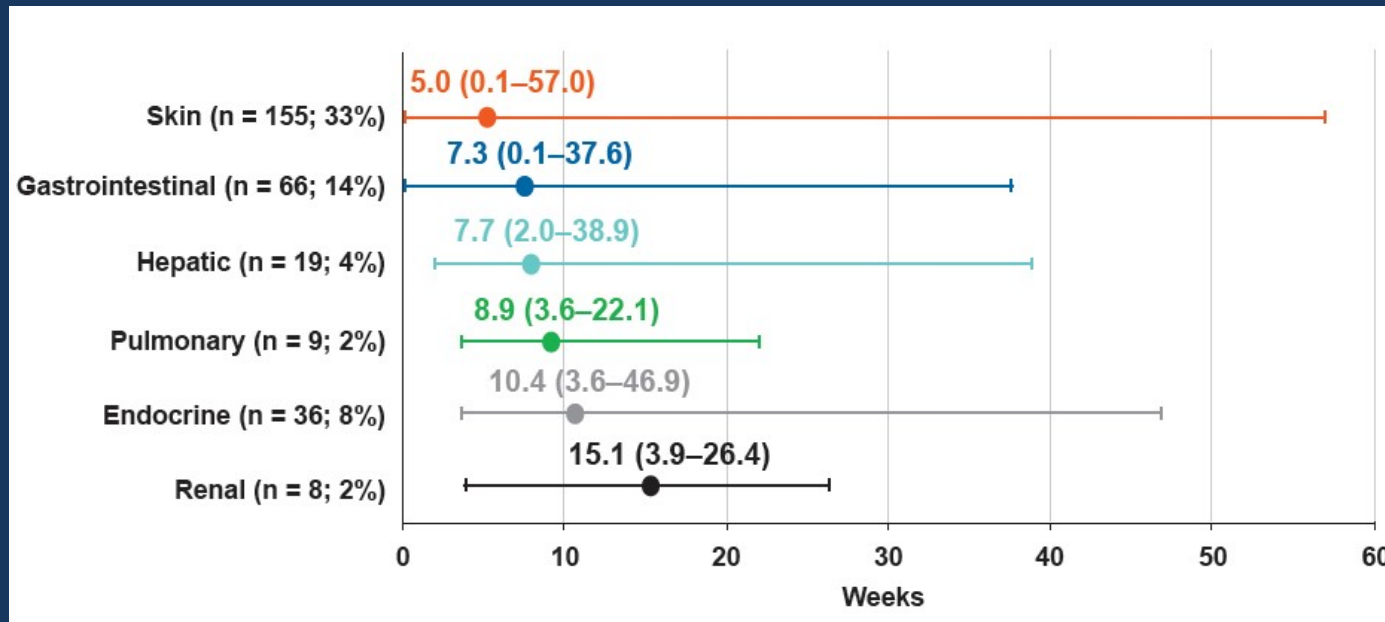
Often hyperthyroid (thyroiditis) then hypothyroid



Osorio et al. *Annals of Oncol* 2017

When do side
effects happen?

Most nivolumab side effects happen in first 3 months (Any Grade; N = 474)

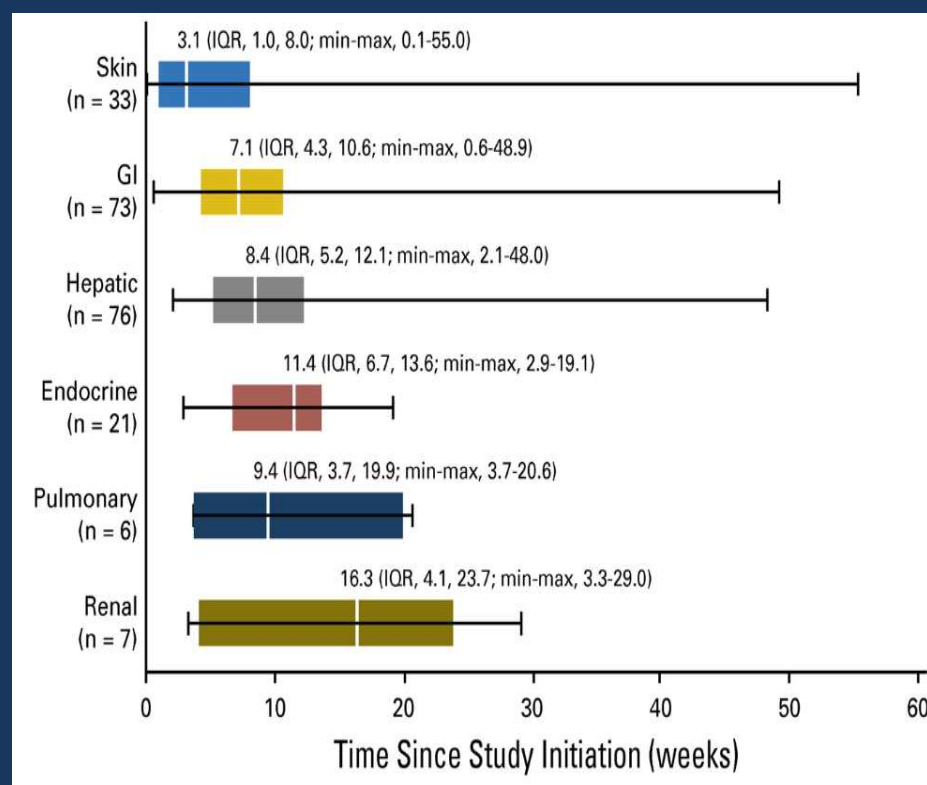


Circles indicate median and
bars indicate ranges

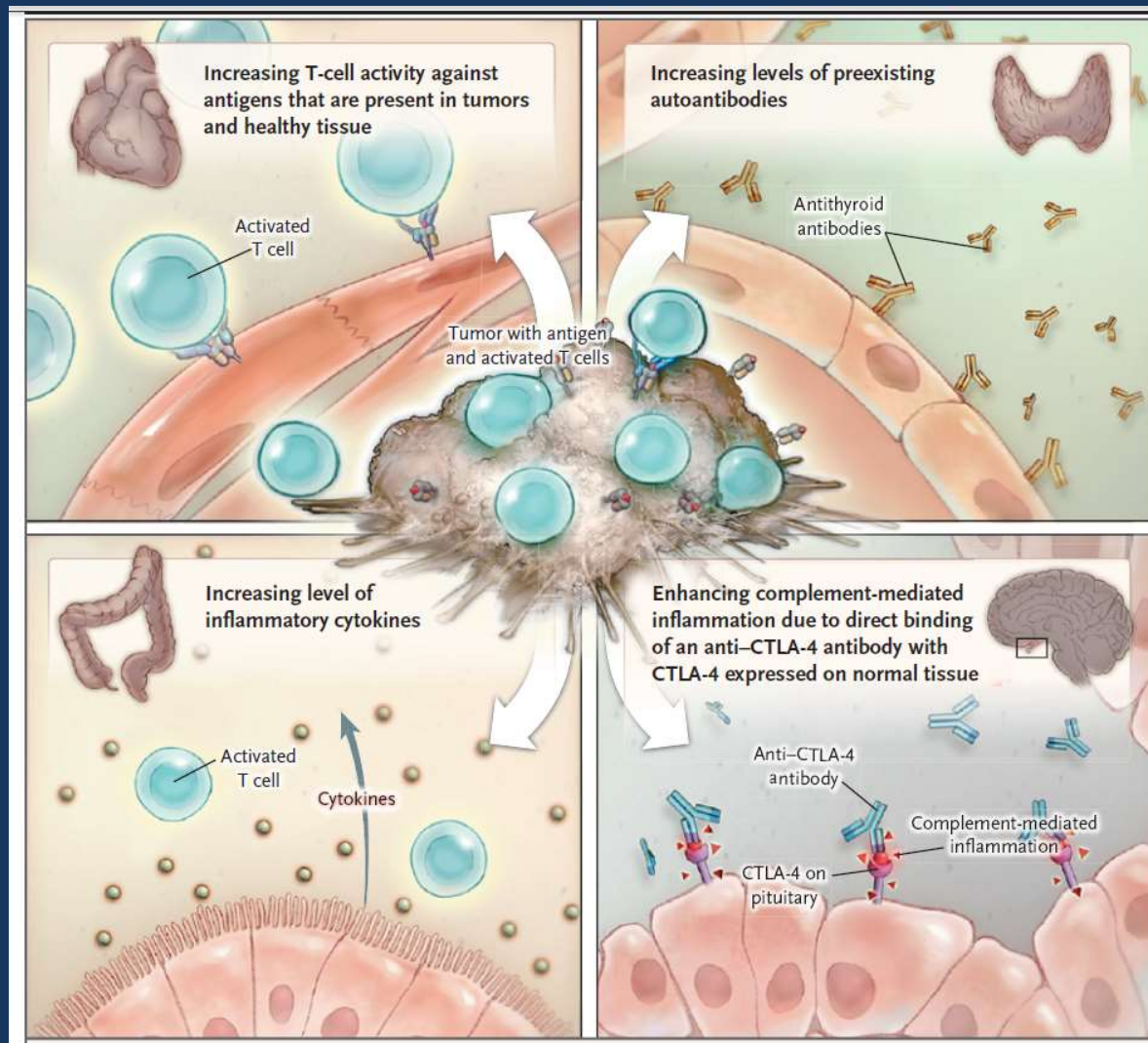
Weber et al. *Journal of Clin Oncol* 2016

Most nivolumab + ipilimumab side effects happen in first 3 months (Any Grade; N = 448)

Circles indicate median and bars indicate ranges

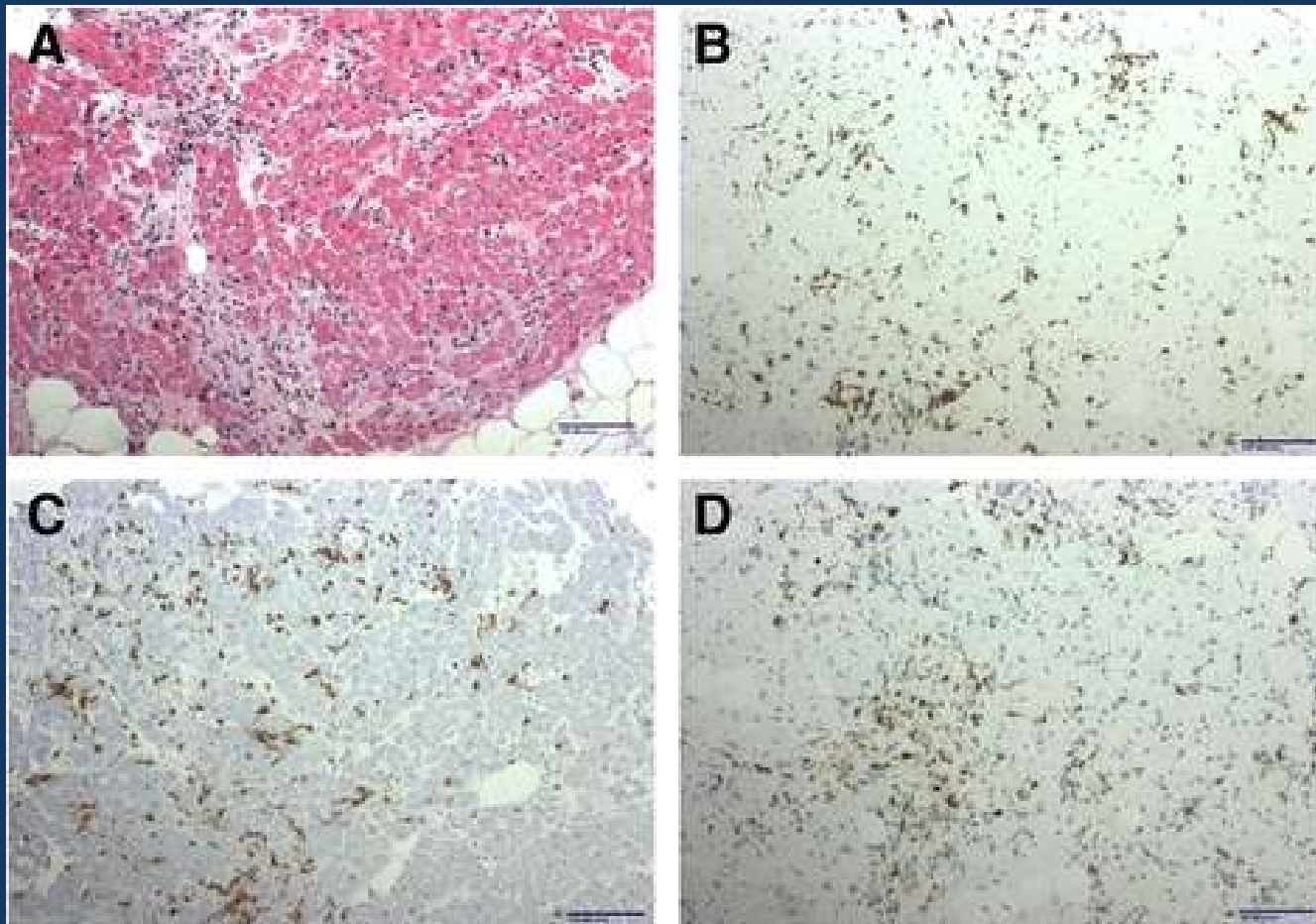


Sznol et al. *Journal of Clin Oncol* 2017



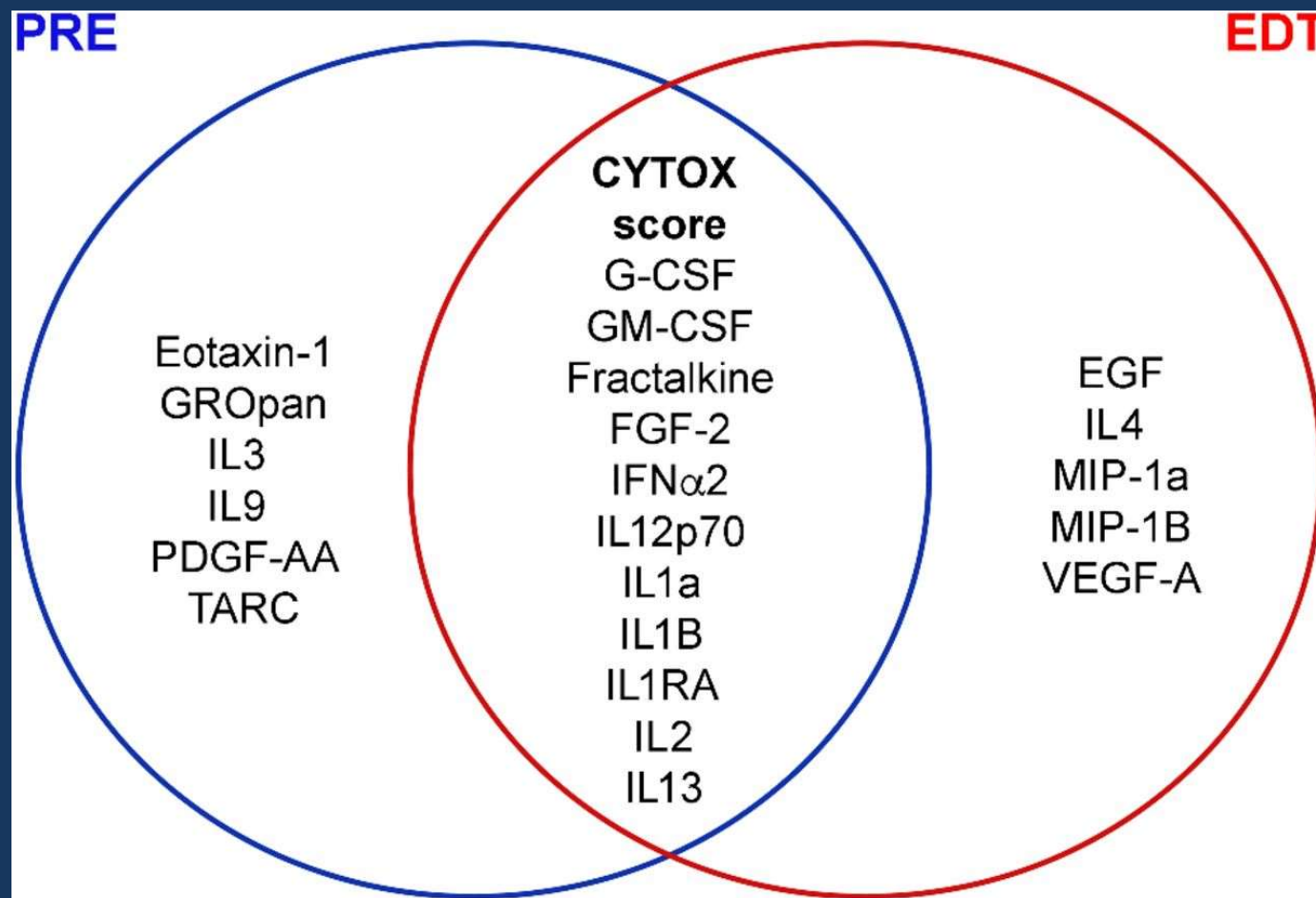
Postow, Sidlow, Hellmann *N Eng J Med* 2018

T cells infiltrating myocardium



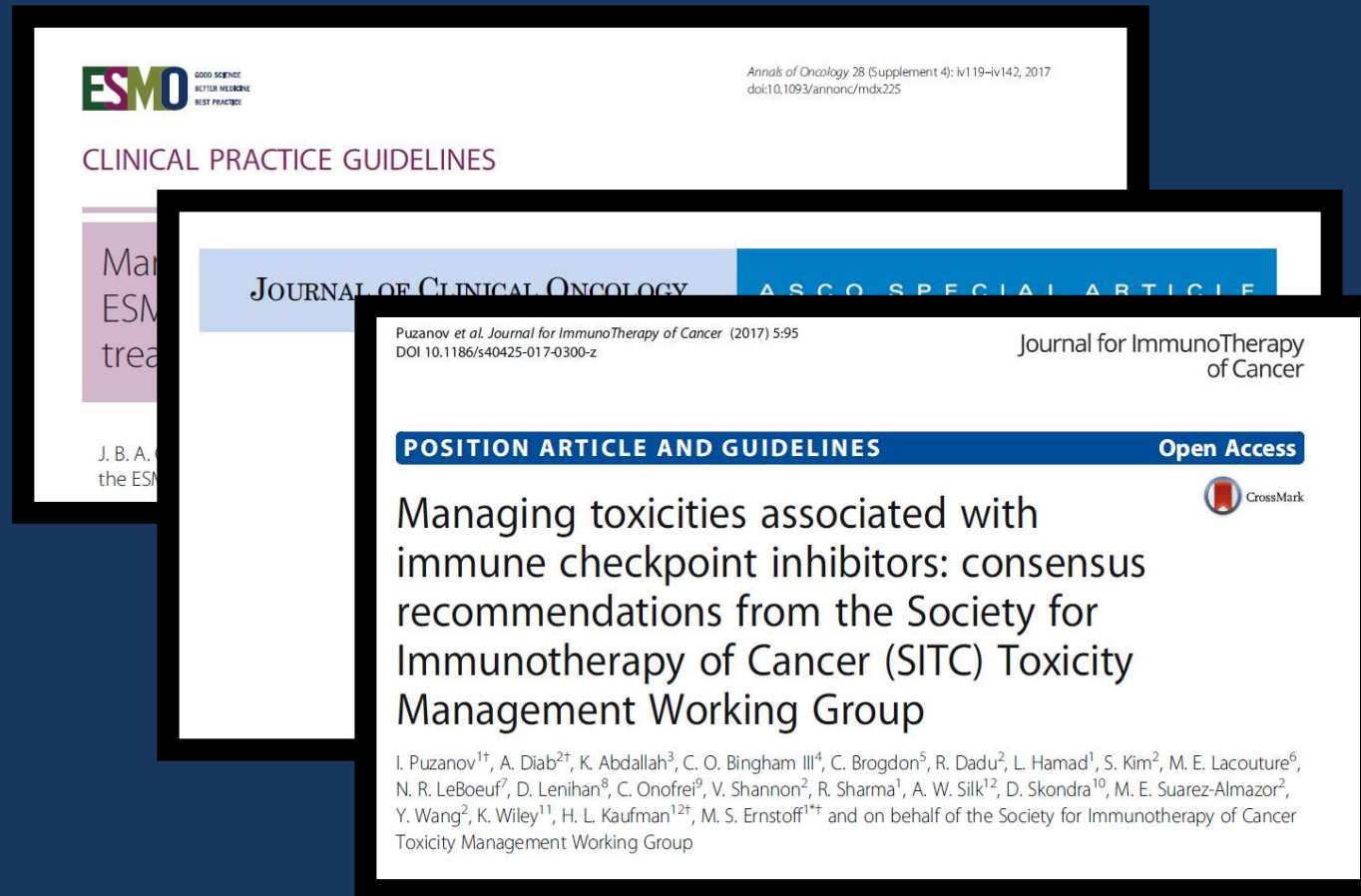
Norwood et al. *JITC* 2017

Peripheral cytokines associated with adverse events



What do I do if I have a problem?

Important Publications



Haanen et al. *Annals of Oncol* 2017, Brahmer et al *J Clin Oncol* 2018, Puzanov et al. *J Immunother Cancer* 2017

National Comprehensive Cancer Network (NCCN) Guidelines www.nccn.org



NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)
in partnership with the American Society of Clinical Oncology (ASCO)

Management of Immunotherapy-Related Toxicities

(Immune Checkpoint Inhibitor-Related Toxicities)

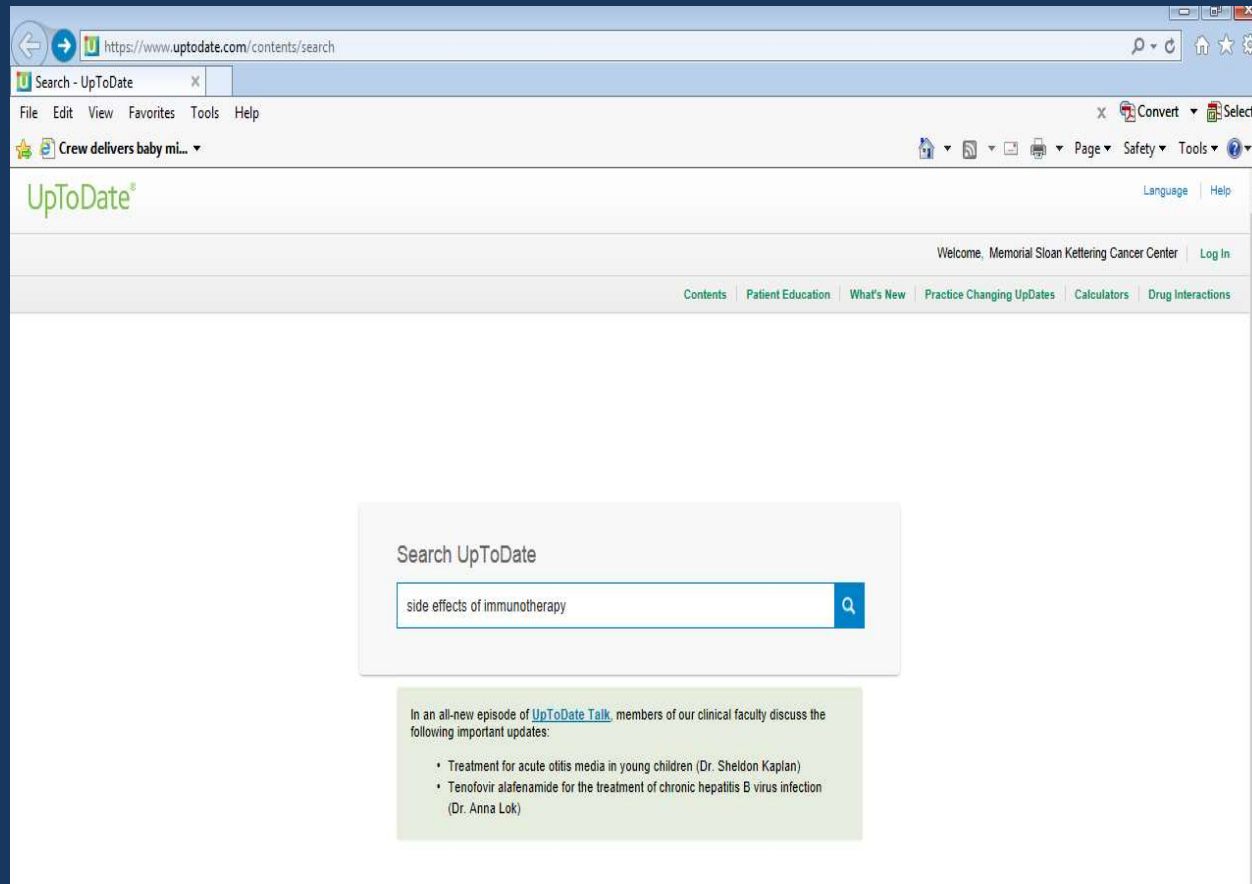
Version 1.2018 — February 14, 2018

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Does
immunosuppression
hurt immunotherapy
benefit?

Immunosuppression Does Not Seem to Affect Nivolumab Efficacy

Table 2. Impact of Treatment-Related Select AEs and IM Use on Response to Nivolumab Therapy

	All Patients (N = 576)	Any-Grade Treatment-Related Select AEs*				Grade 3 to 4 Treatment-Related Select AEs		Patients Receiving Systemic IM	
		Any (n = 255)	None (n = 321)	1-2 (n = 242)	≥ 3 (n = 13)	Yes (n = 18)	No (n = 558)	Yes (n = 114)	No (n = 462)
ORR, No. of patients (%)	181 (31.4)	124 (48.6)	57 (17.8)	113 (46.7)	11 (84.6)	5 (27.8)	176 (31.5)	34 (29.8)	147 (31.8)
95% CI	27.6 to 35.4	42.3 to 54.9	13.7 to 22.4	40.3 to 53.2	54.6 to 98.1	9.7 to 53.5	27.7 to 35.6	21.6 to 39.1	27.6 to 36.3
P		< .001		< .0001†	< .001†	1.00		.736	

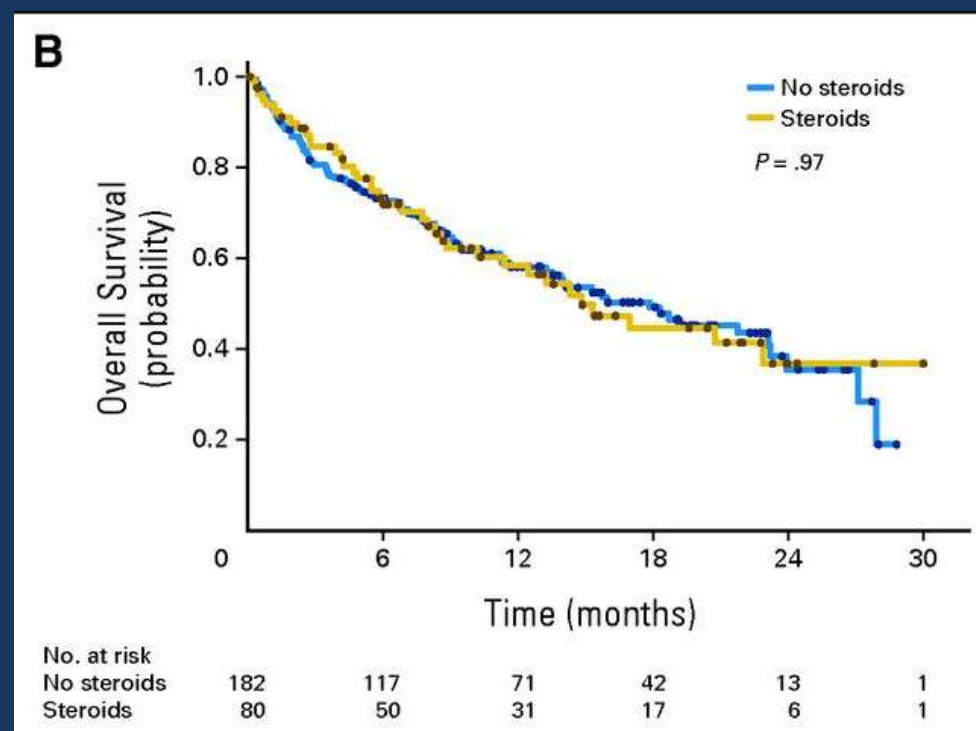
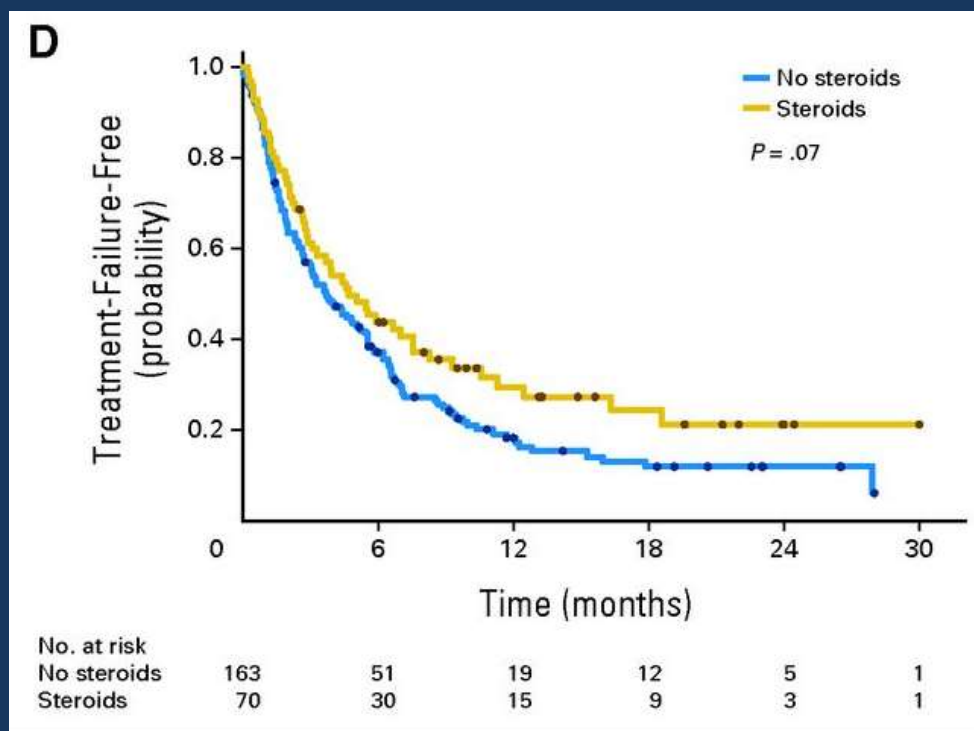
Abbreviations: AE, adverse event; IM, immune-modulating agent; ORR, objective response rate.

*Data in these columns are for patients with the indicated numbers of any-grade treatment-related select AEs: any AE, no AEs, 1-2 AEs, and ≥ 3 AEs.

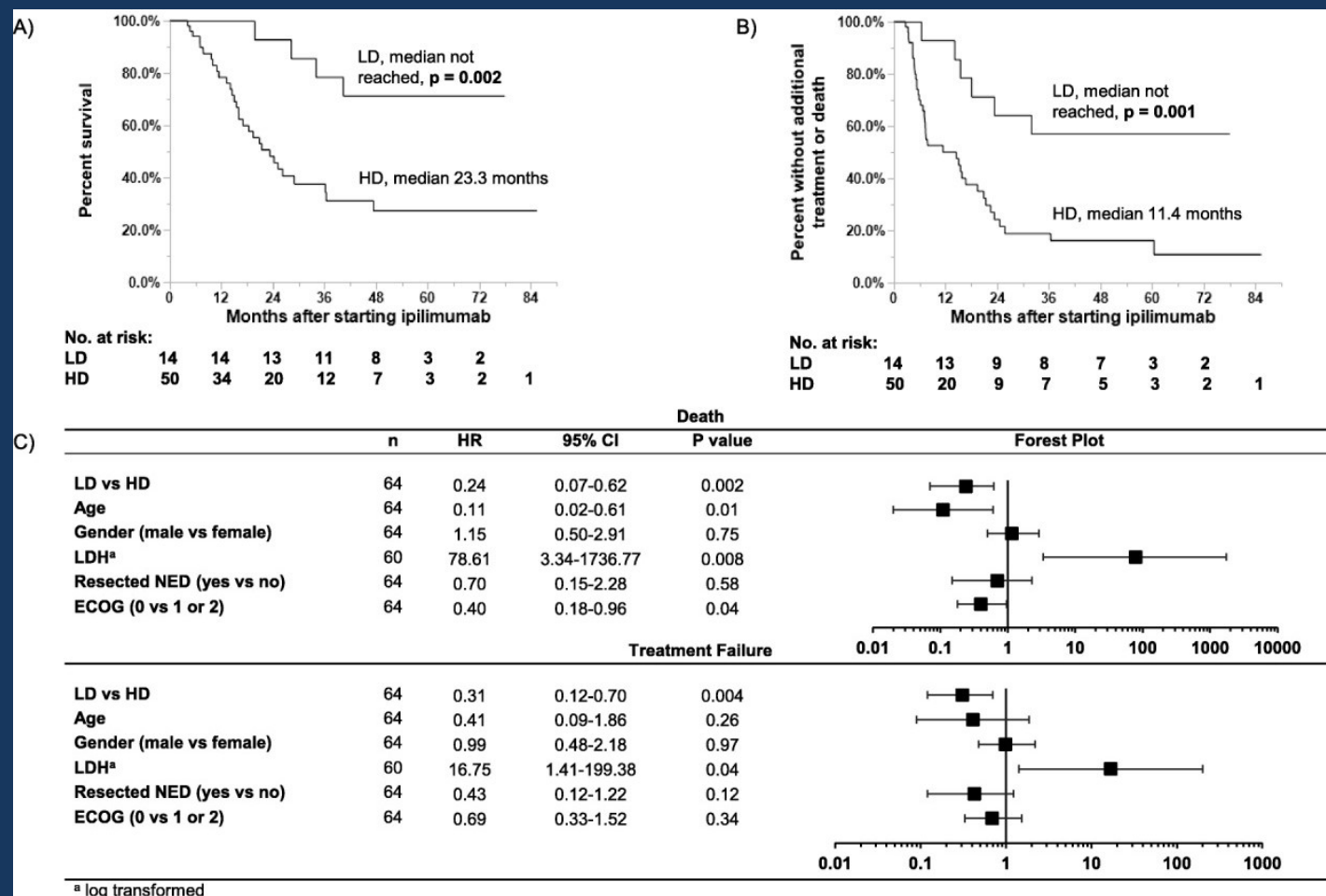
†Versus no treatment-related select AEs.

Weber JS, et al. *J Clin Oncol*. 2017.

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



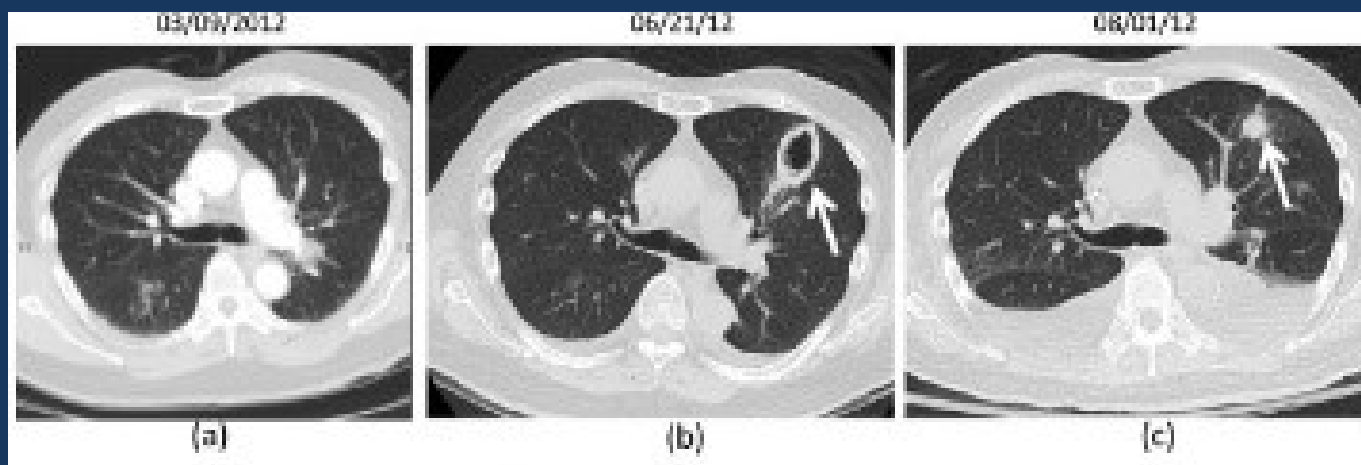
BUT High Dose Steroids (>7.5mg daily) for Ipilimumab Hypophysitis was Associated With Worse Outcomes (n = 98)



Faje AT, et al. *Cancer*. 2018.

What are the consequences of immunosuppression?

Opportunistic infections are possible



- 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?

Safety in patients with underlying autoimmunity

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

When is it safe to restart
immunotherapy after toxicity?

38 patients with NSCLC who discontinued PD1/PDL1 due to toxicity and retreated with PD-1

- 26% recurrence rate of same irAE that caused discontinuation
- 84% improved to grade 1 or resolved but some recurrent toxicities were severe with 2 treatment related deaths
- No clear association between intensity of prior toxicity and likelihood of recurrent toxicity
- No clear benefit to resuming PD-1 in patients who responded prior to initial toxicity

Future Questions

- How can subspecialty care be integrated into oncology care?
- What can immunotherapy side effects teach us about autoimmune disease?
- Long-term complications?