

Immune Related Adverse Events (irAE) from Checkpoint Inhibitor Immunotherapy

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Memorial Sloan Kettering Cancer Center

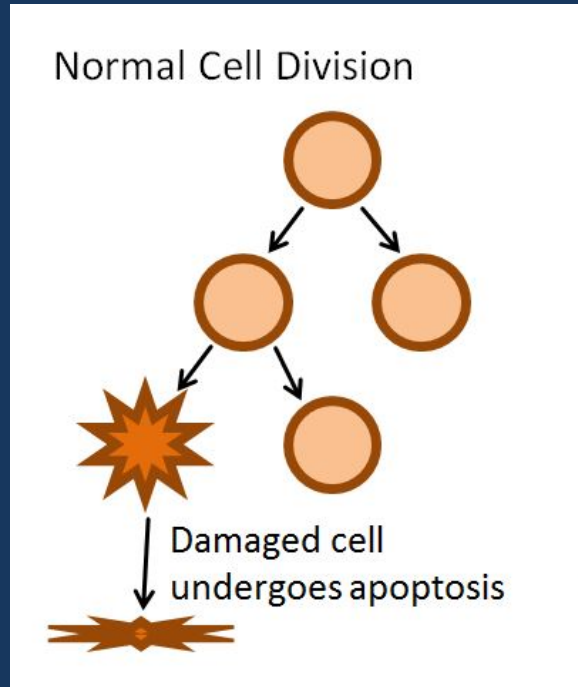
Disclosures

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

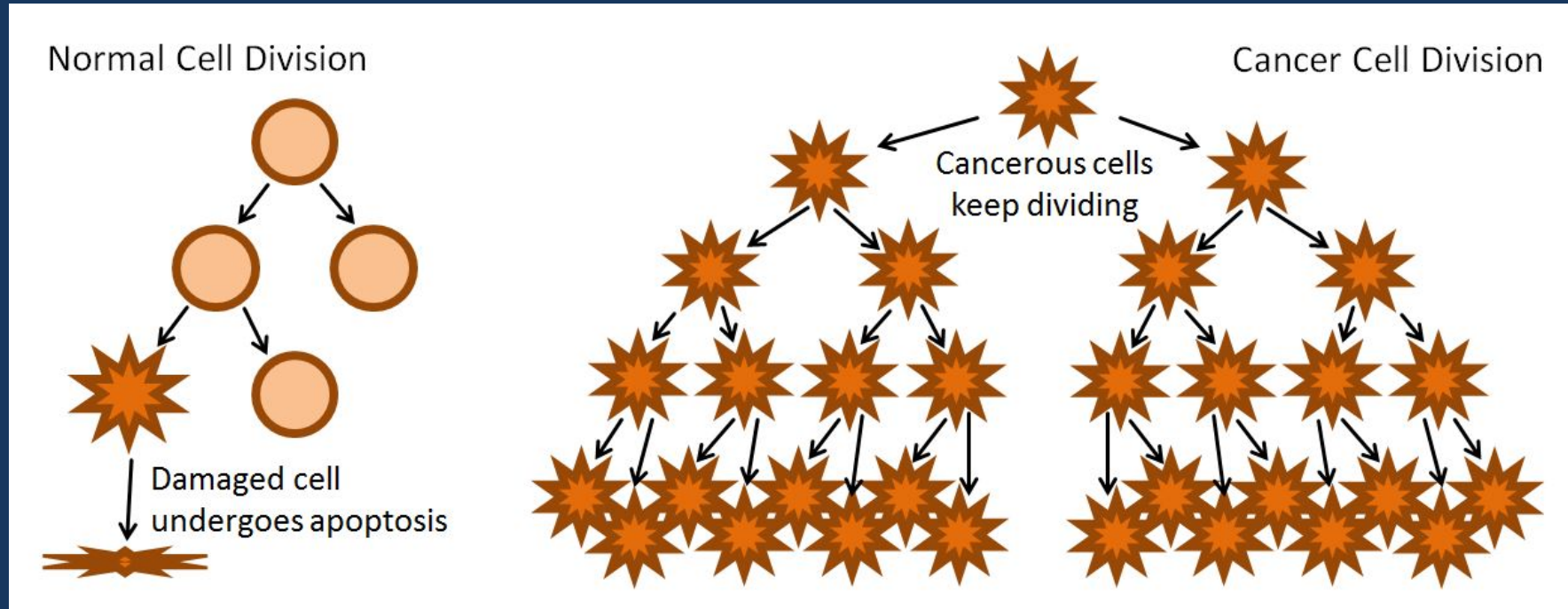
Honoraria: BMS and Merck

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

Cancer historically understood as disorder of dividing cells

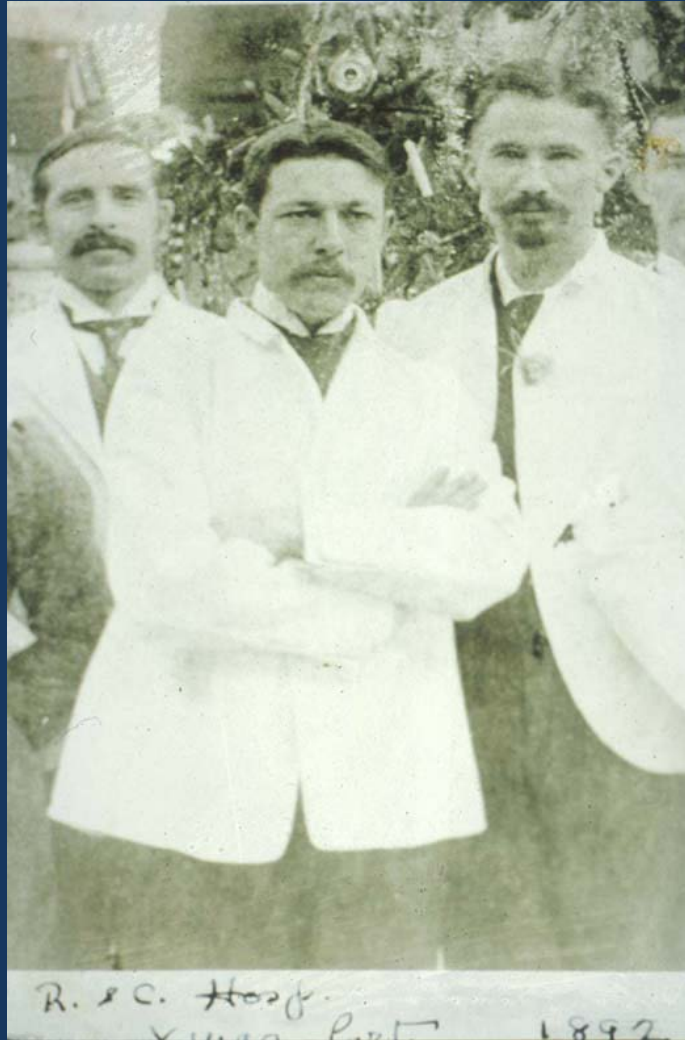


Cancer historically understood as disorder of dividing cells

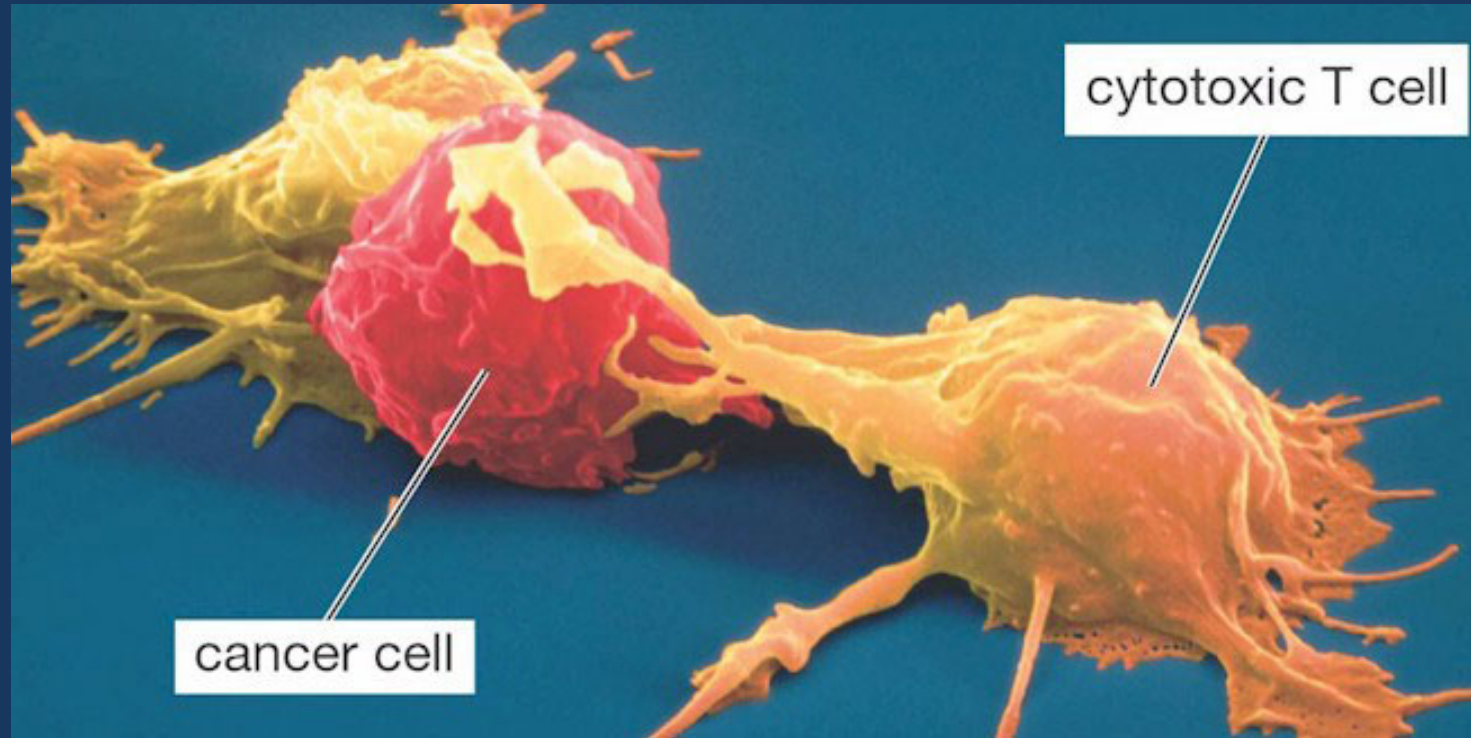


Oncologists stop dividing cells

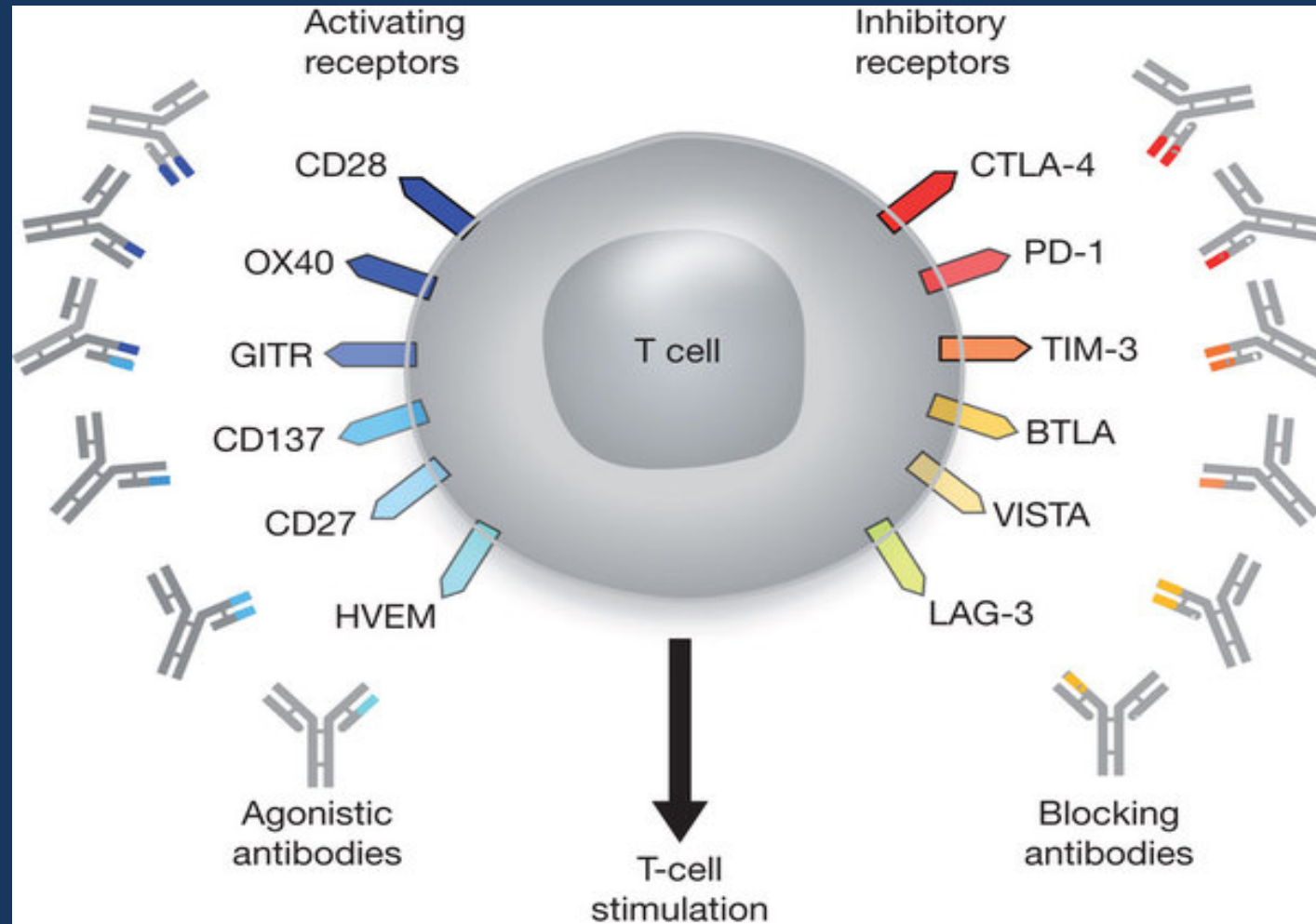
What happened in 1891?



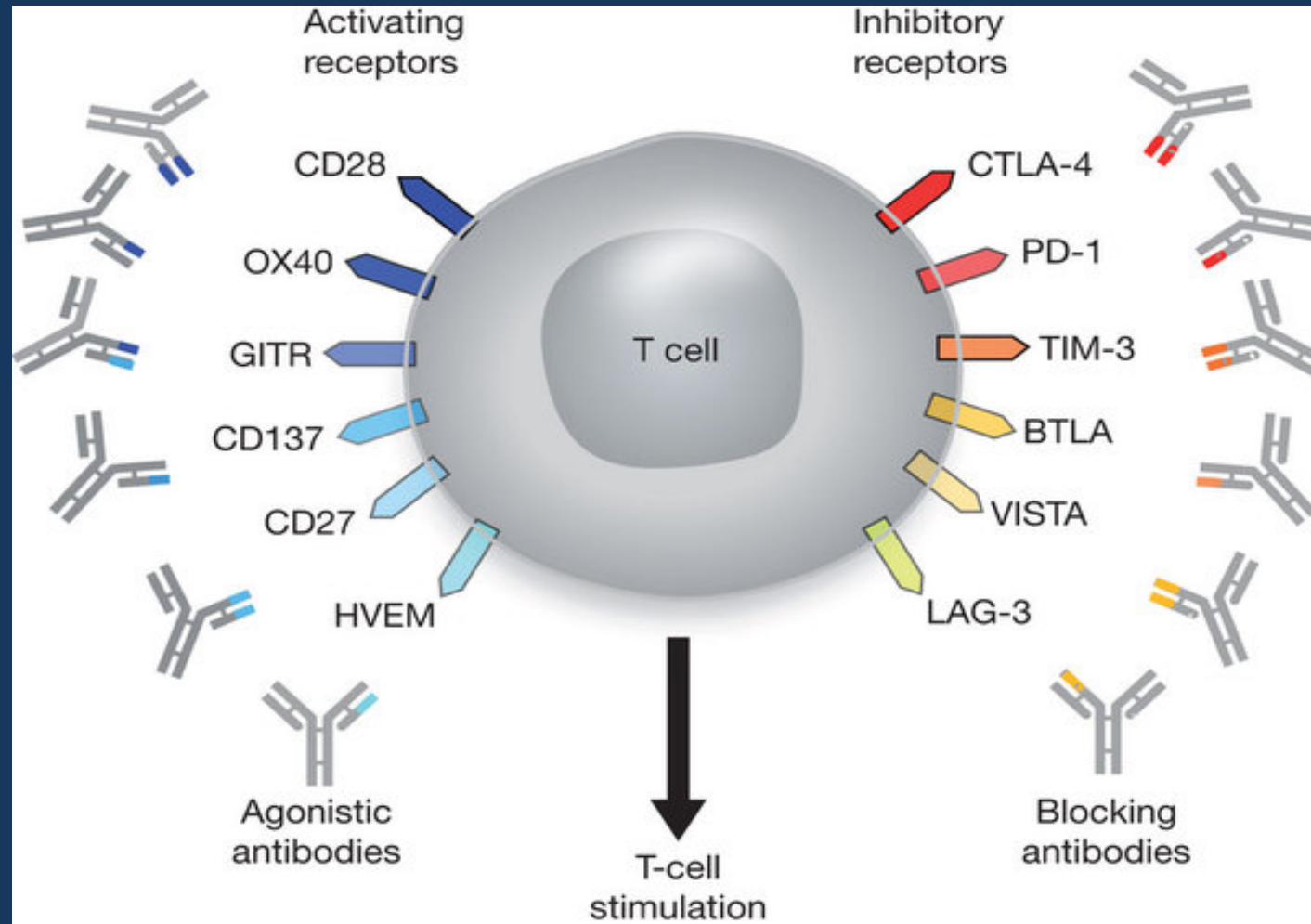
Immunotherapy = Immune cell kills a cancer cell



Ways to enhance T cell attack

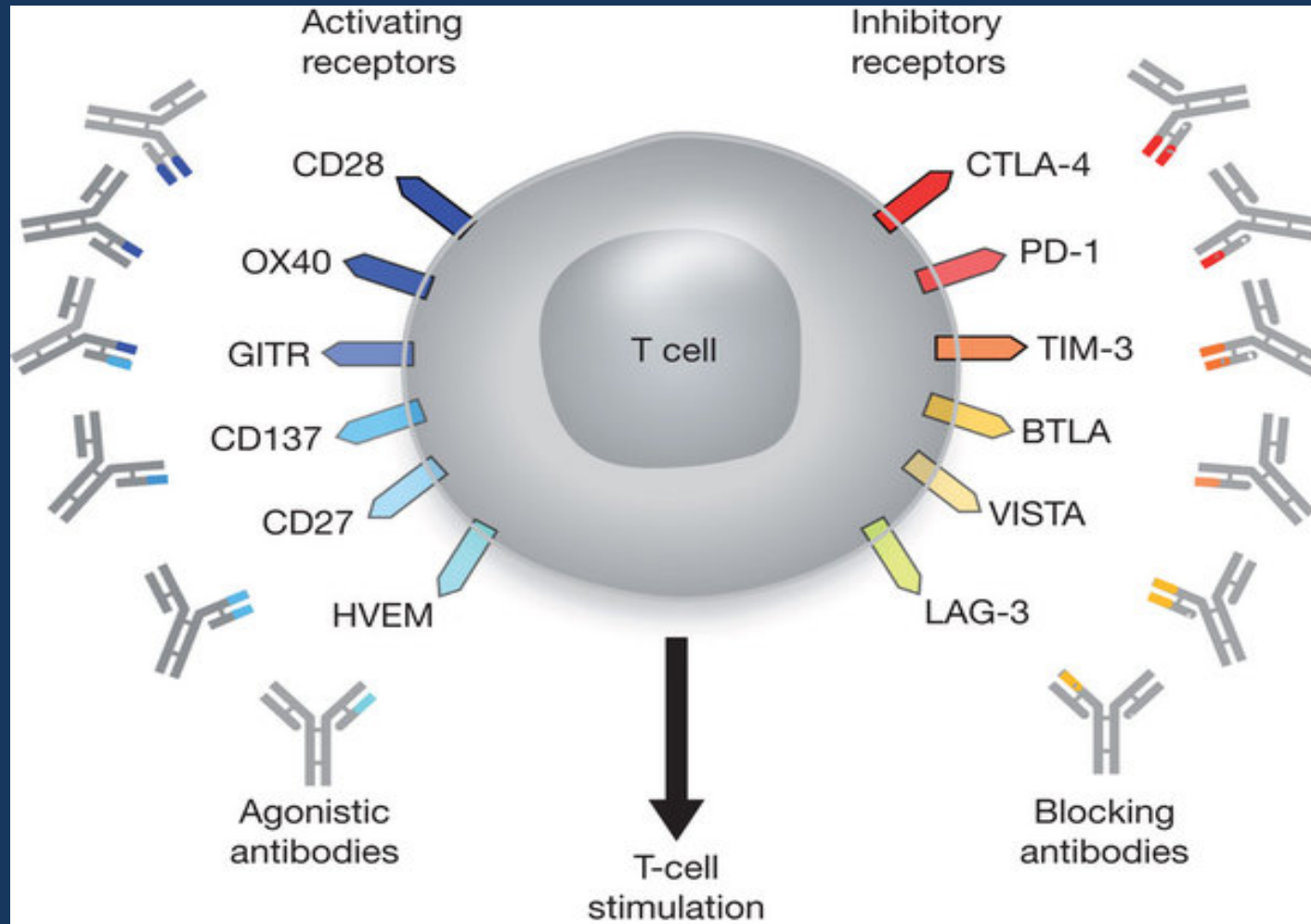


Ways to enhance T cell attack



Turning up The Activating

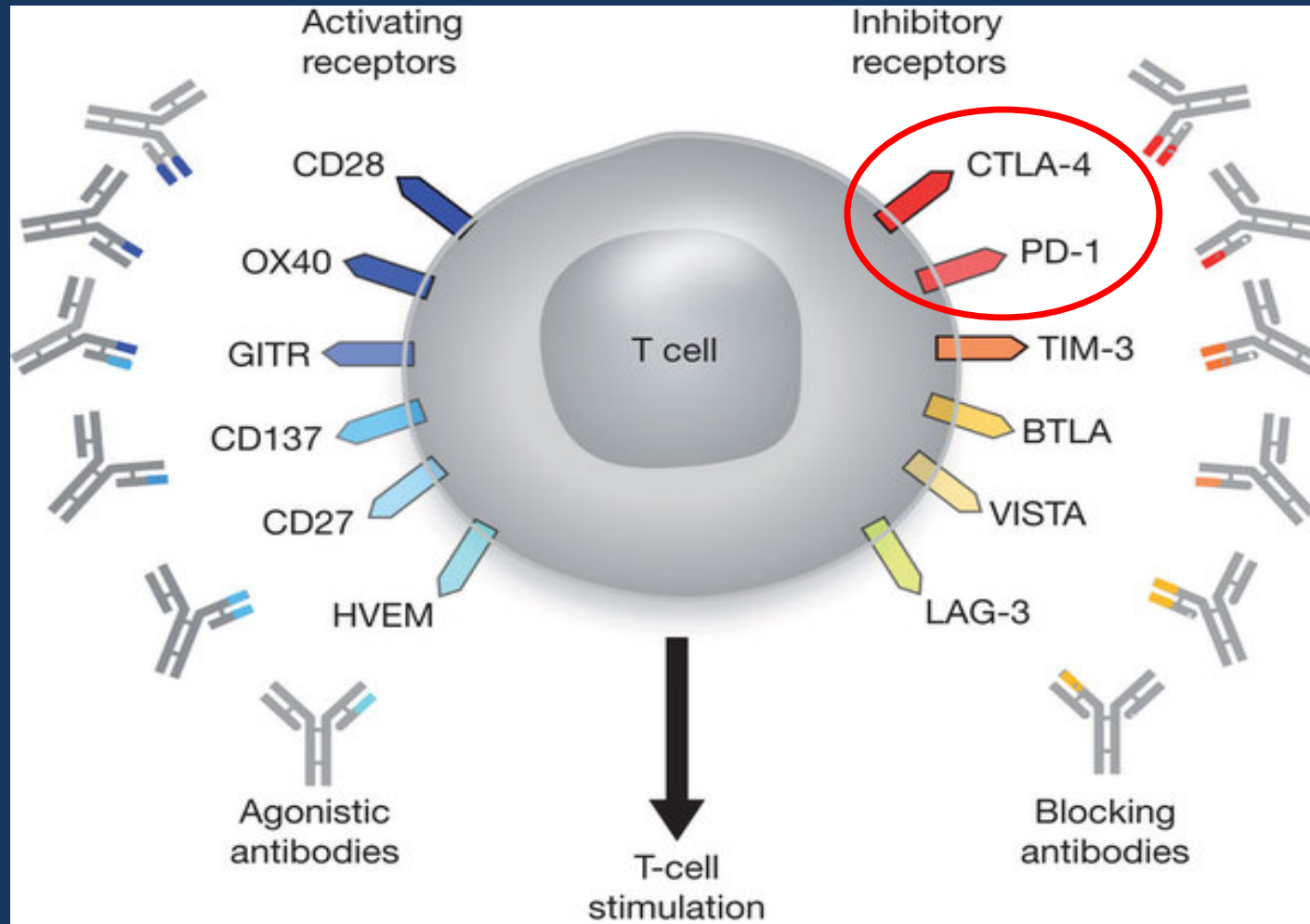
Ways to enhance T cell attack



Turning up The Activating

Blocking the Inhibiting

FDA Approved Targets



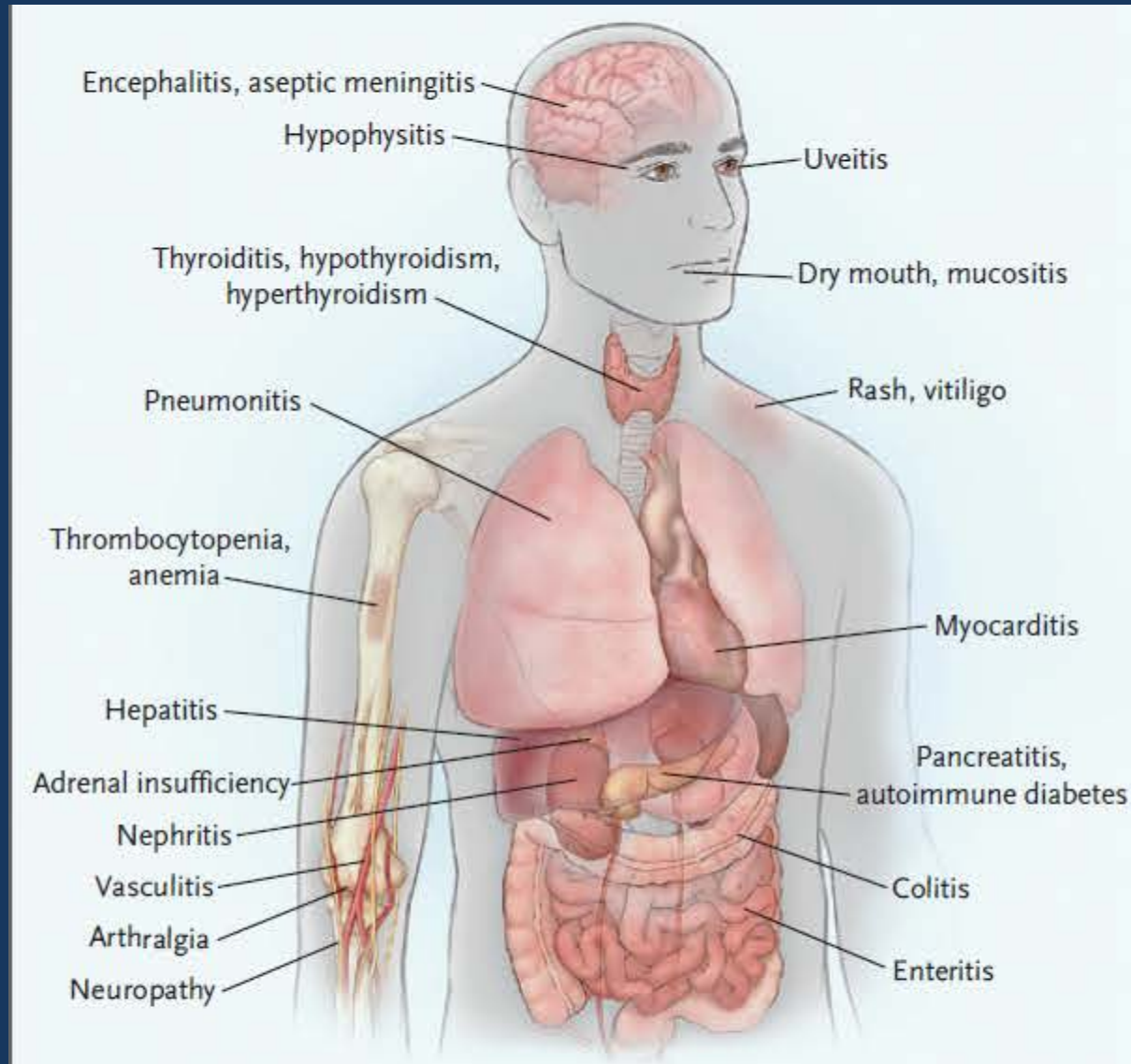
Turning up The Activating

Blocking the Inhibiting

Oncologists turn up immune
system

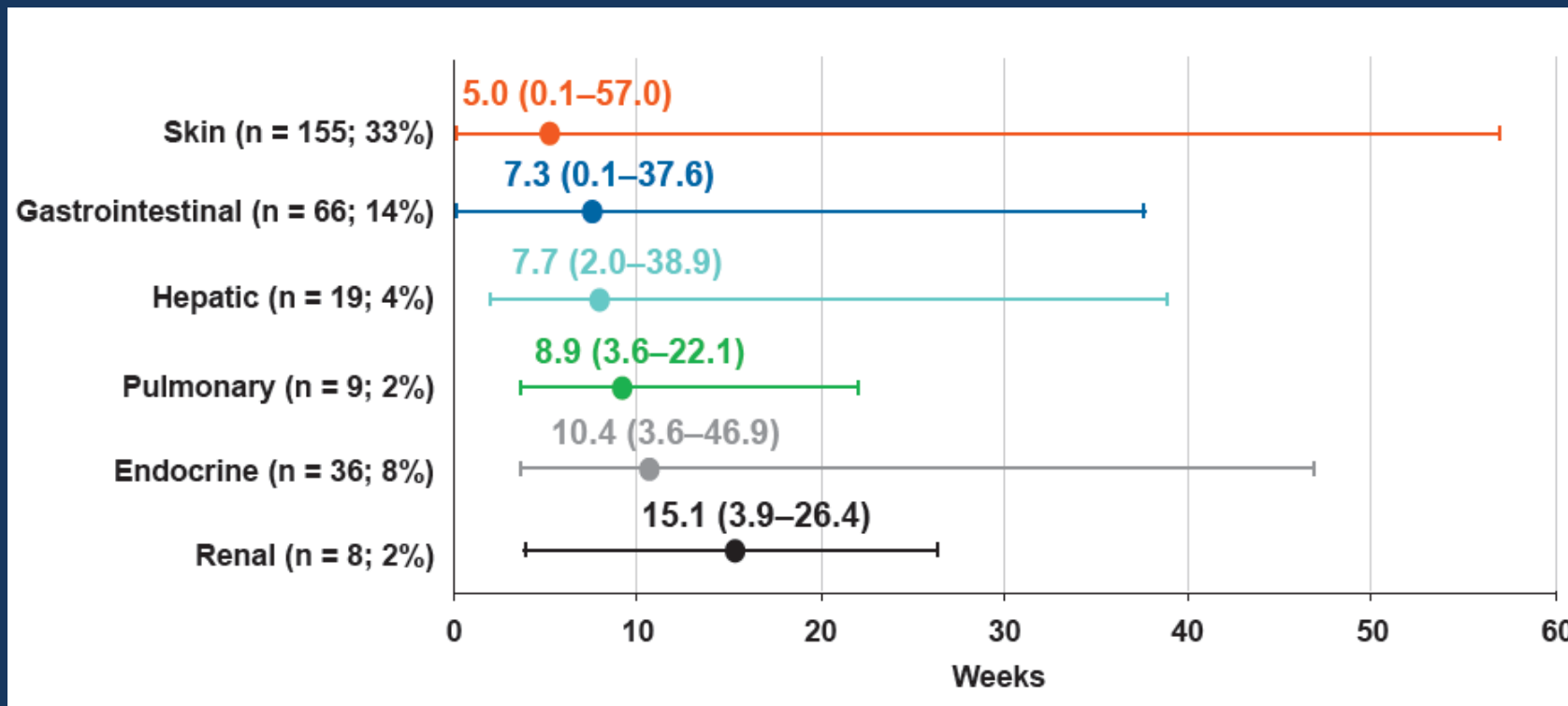
What kind of side effects happen?

All organs can be involved



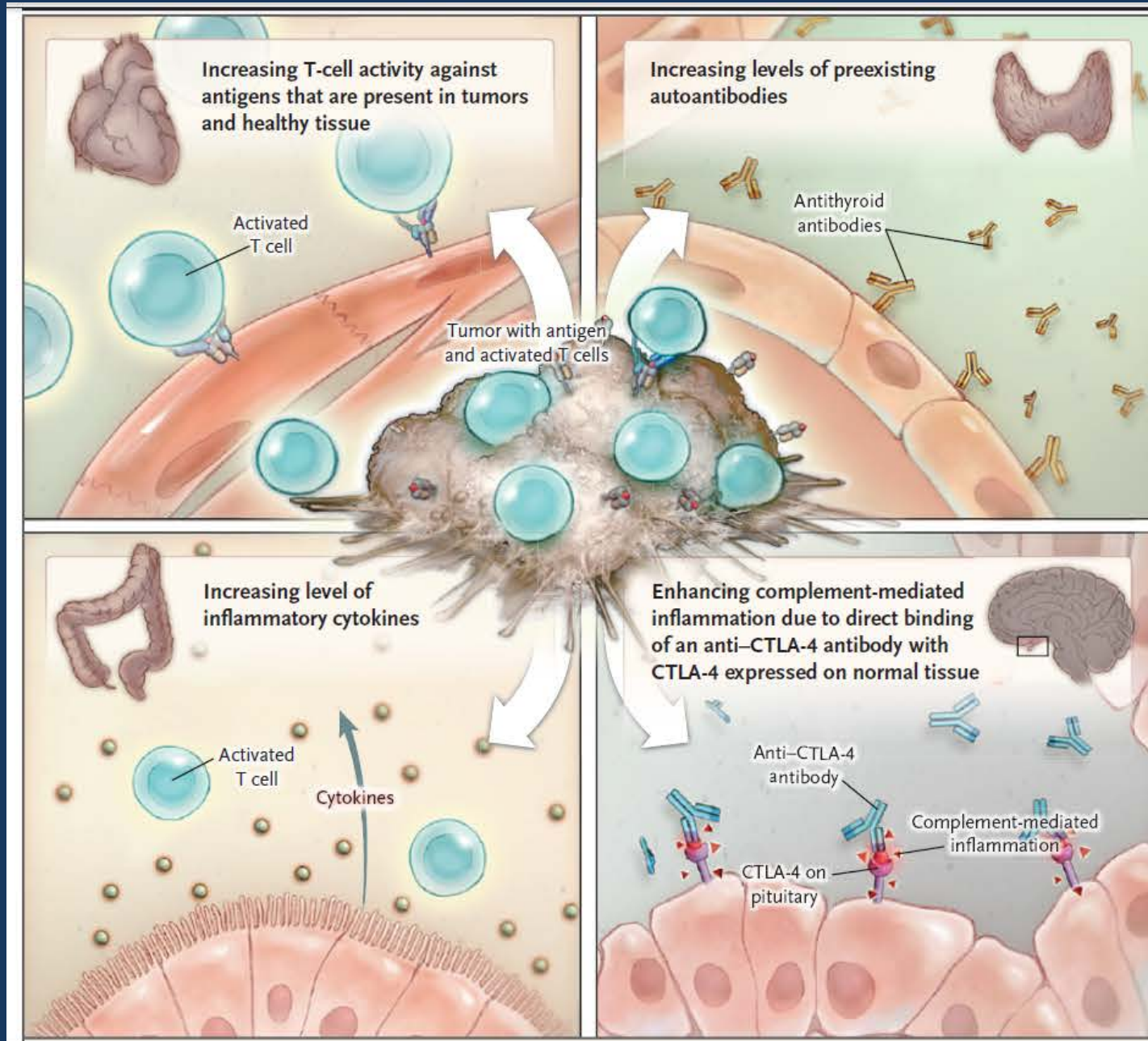
When do side
effects happen?

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

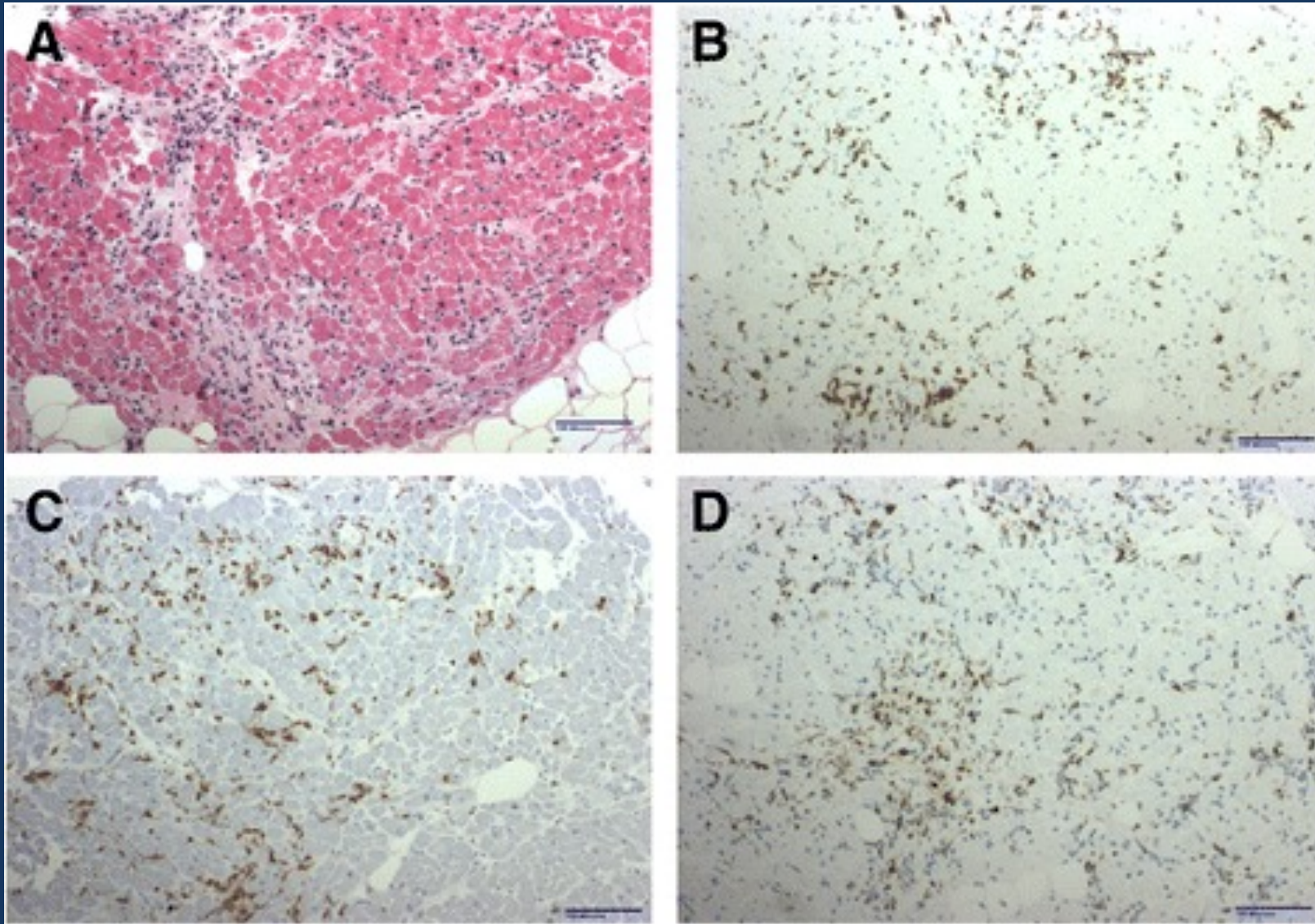


Circles indicate median and
bars indicate ranges

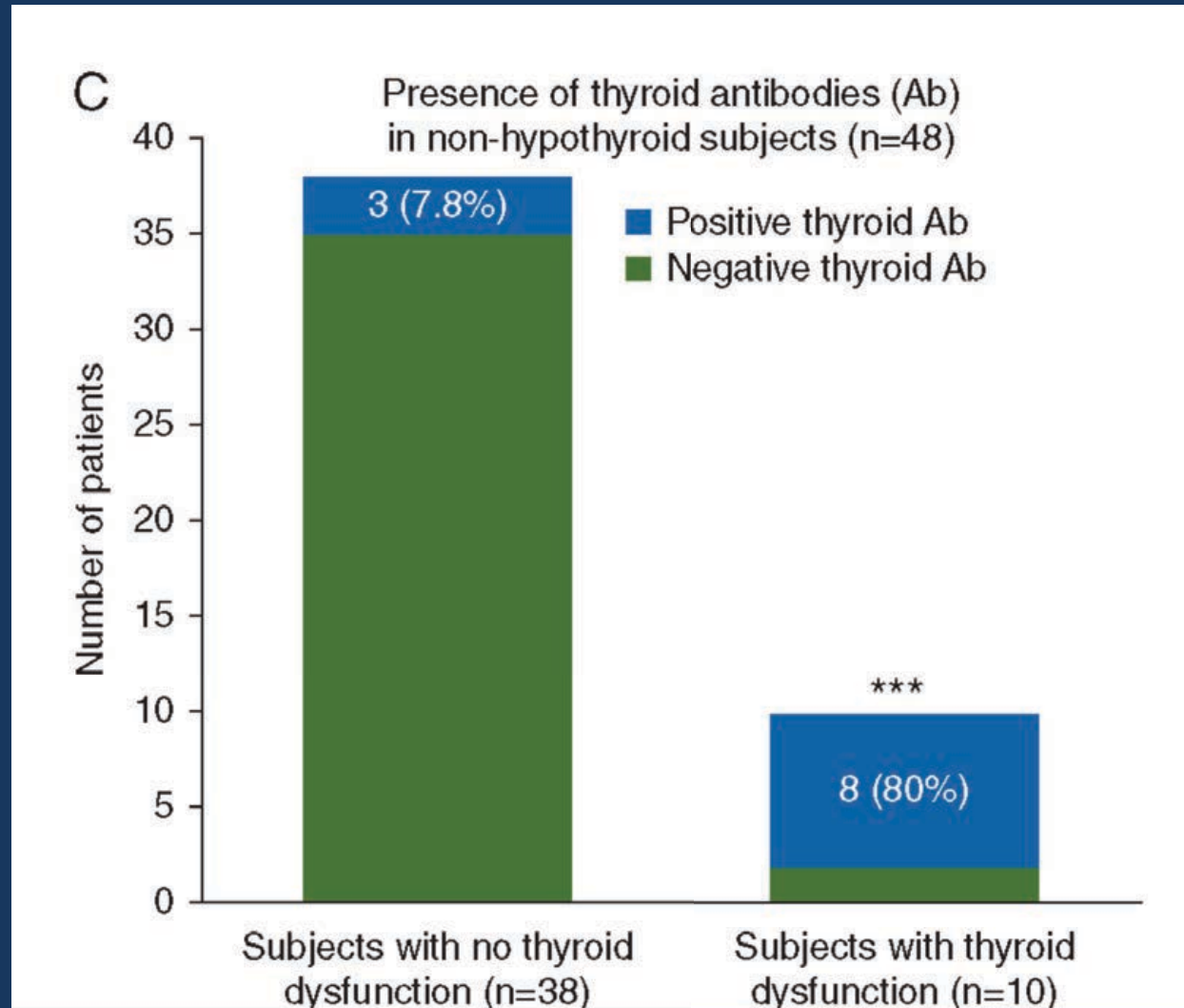
Why do side
effects happen?



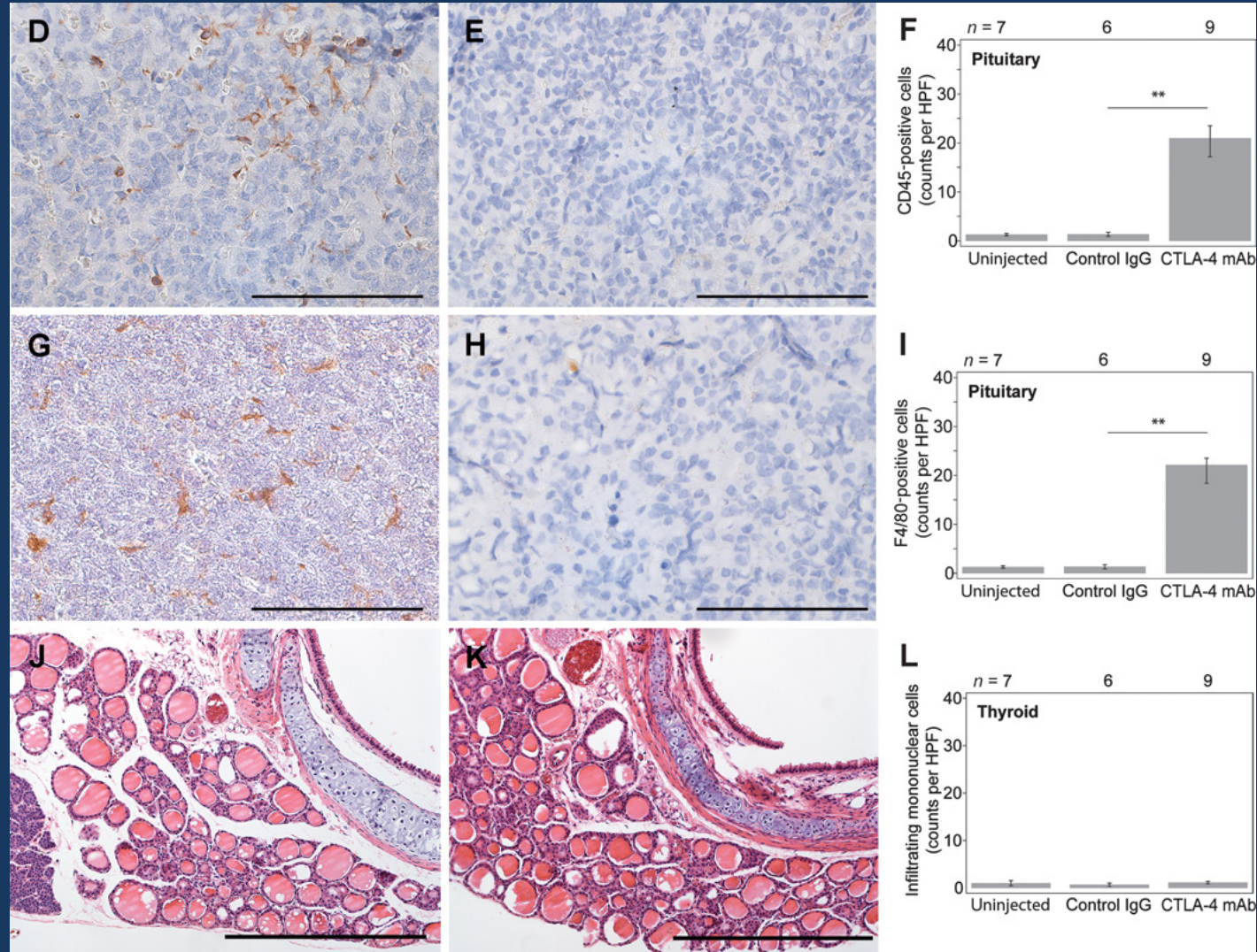
T cells infiltrating myocardium



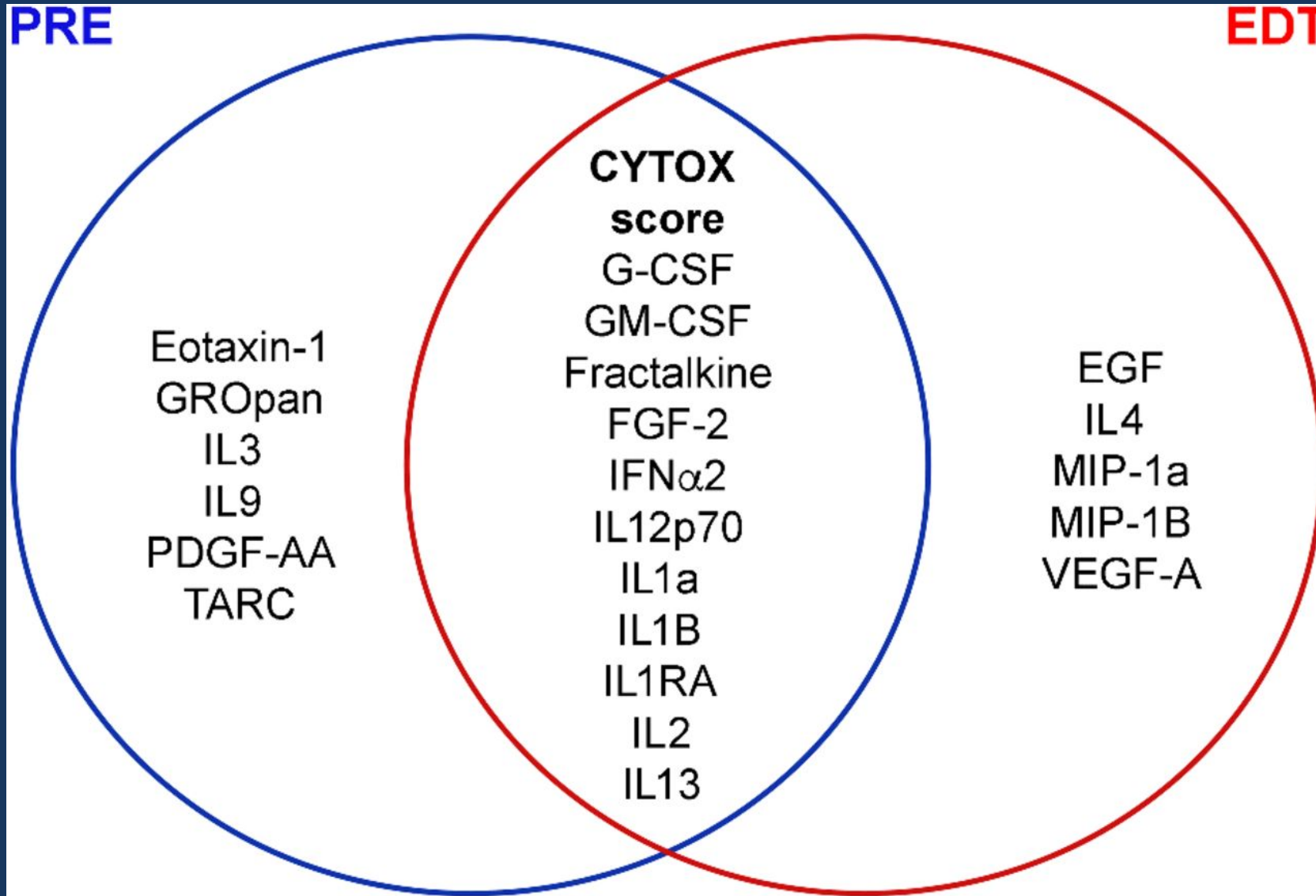
Thyroid dysfunction associated with antibodies (i.e. anti-thyroglobulin)



Hematopoietic cell infiltration of the pituitary gland in mice injected with a CTLA-4 blocking antibody




Peripheral cytokines associated with adverse events



What do I do if I have a problem?

Important Publications



Annals of Oncology 28 (Supplement 4): iv119-iv142, 2017
doi:10.1093/annonc/mdx225

CLINICAL PRACTICE GUIDELINES

Managing ESMT
treat

J. B. A.
the ES

JOURNAL OF CLINICAL ONCOLOGY ASCO SPECIAL ARTICLE

Puzanov et al. *Journal for Immunotherapy of Cancer* (2017) 5:95
DOI 10.1186/s40425-017-0300-z

Journal for Immunotherapy
of Cancer

POSITION ARTICLE AND GUIDELINES **Open Access**

 CrossMark

Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group

I. Puzanov^{1†}, A. Diab^{2†}, K. Abdallah³, C. O. Bingham III⁴, C. Brogdon⁵, R. Dadu², L. Hamad¹, S. Kim², M. E. Lacouture⁶, N. R. LeBoeuf⁷, D. Lenihan⁸, C. Onofrei⁹, V. Shannon², R. Sharma¹, A. W. Silk¹², D. Skondra¹⁰, M. E. Suarez-Almazor², Y. Wang², K. Wiley¹¹, H. L. Kaufman^{12†}, M. S. Ernstoff^{1*†} and on behalf of the Society for Immunotherapy of Cancer Toxicity Management Working Group

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

NCCN.org

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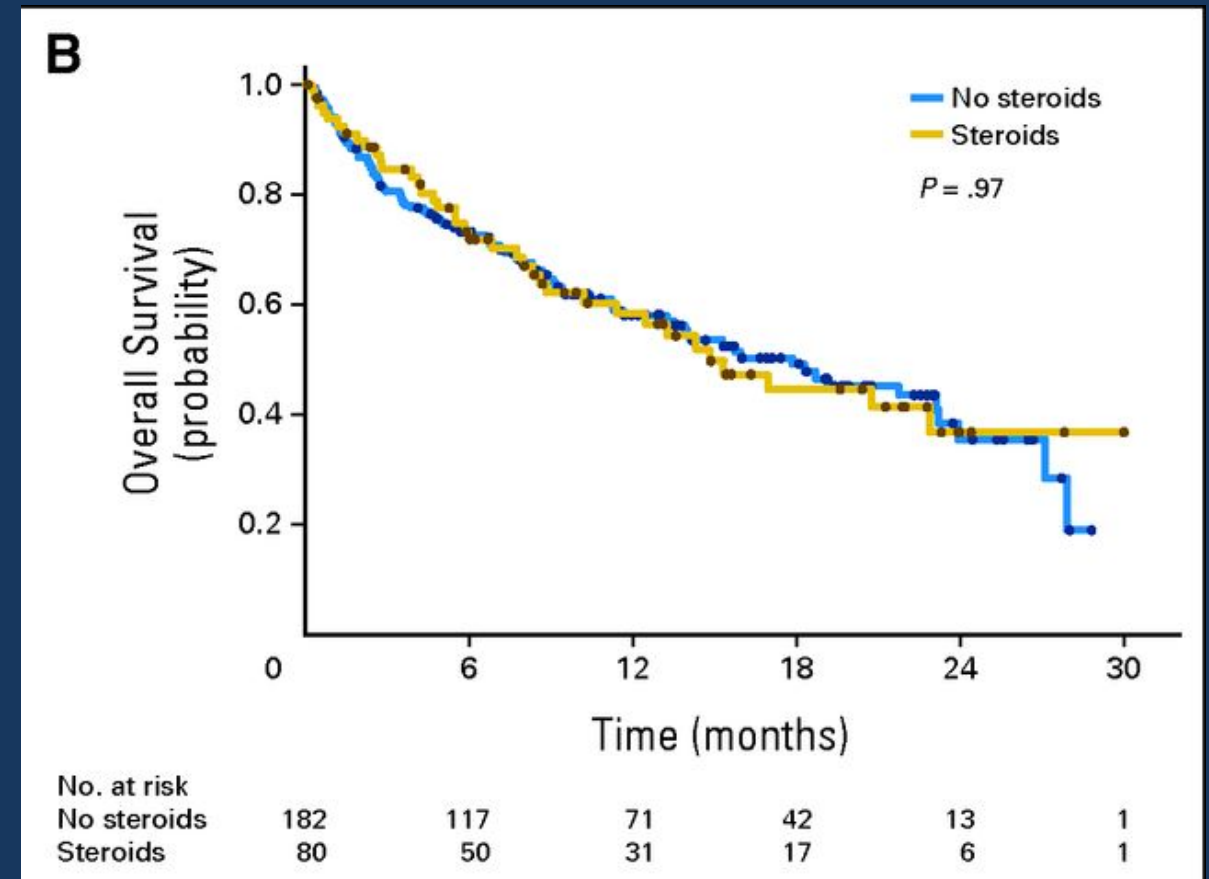
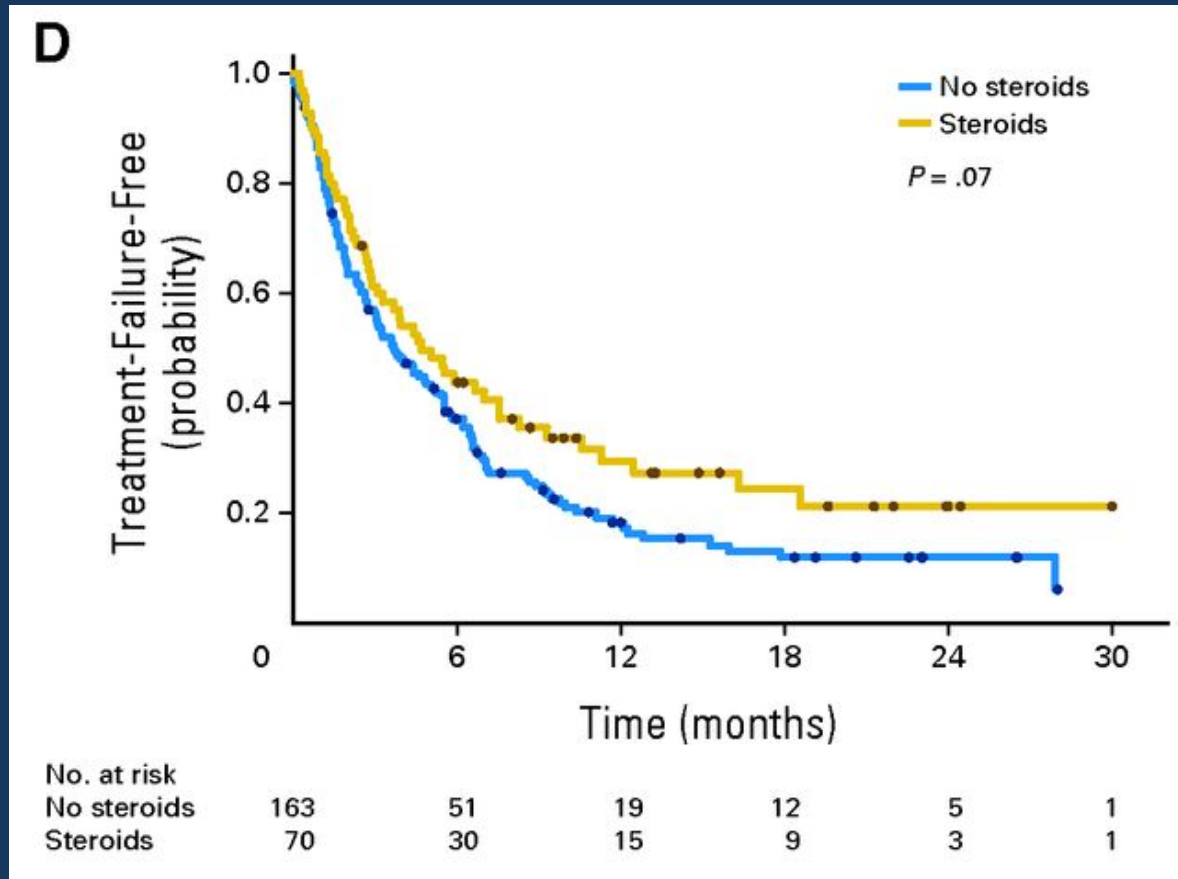
side effects of immunotherapy

In an all-new episode of [UpToDate Talk](#), members of our clinical faculty discuss the following important updates:

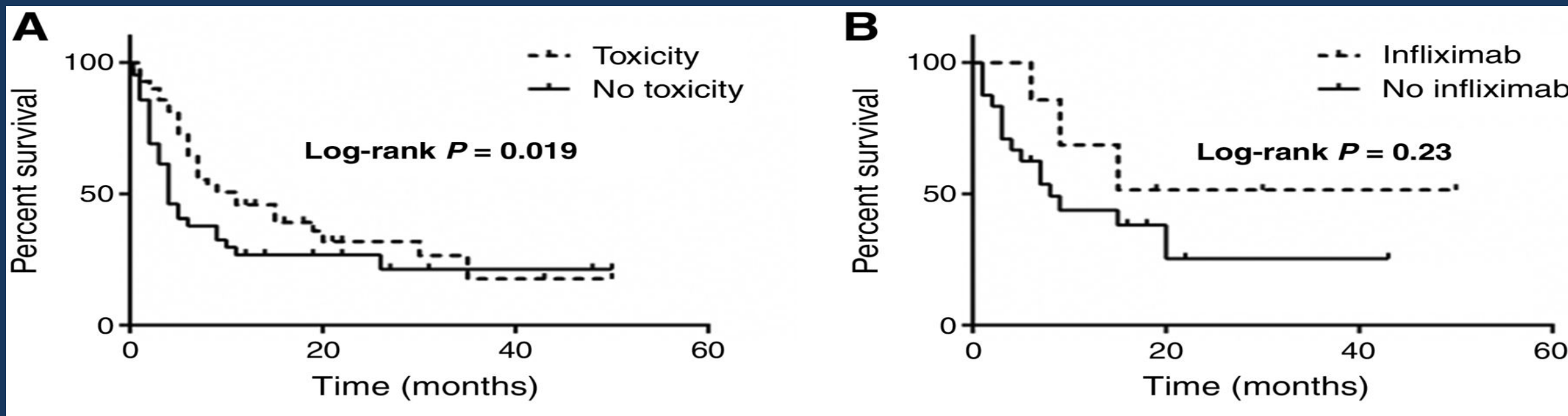
- Treatment for acute otitis media in young children (Dr. Sheldon Kaplan)
- Tenofovir alafenamide for the treatment of chronic hepatitis B virus infection (Dr. Anna Lok)

Does immunosuppression
hurt immunotherapy
benefit?

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



Infliximab does not seem to affect efficacy of ipilimumab



Retrospective study of 113 patients

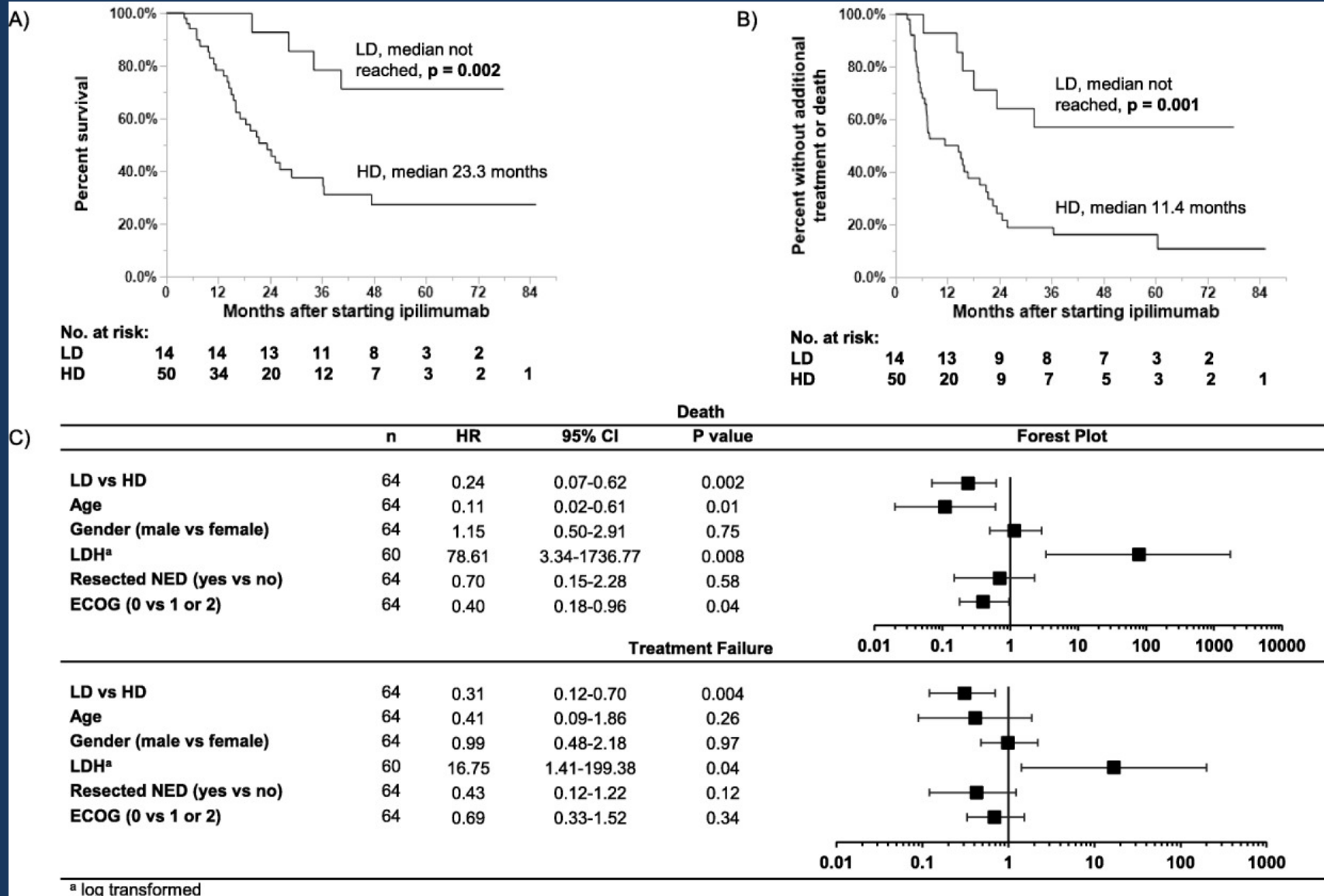
32 patients with diarrhea (19 patients Grade ≥ 2 diarrhea)

29 patients received steroids

7 patients had infliximab

Arriola et al. *Clin Cancer Res* 2015

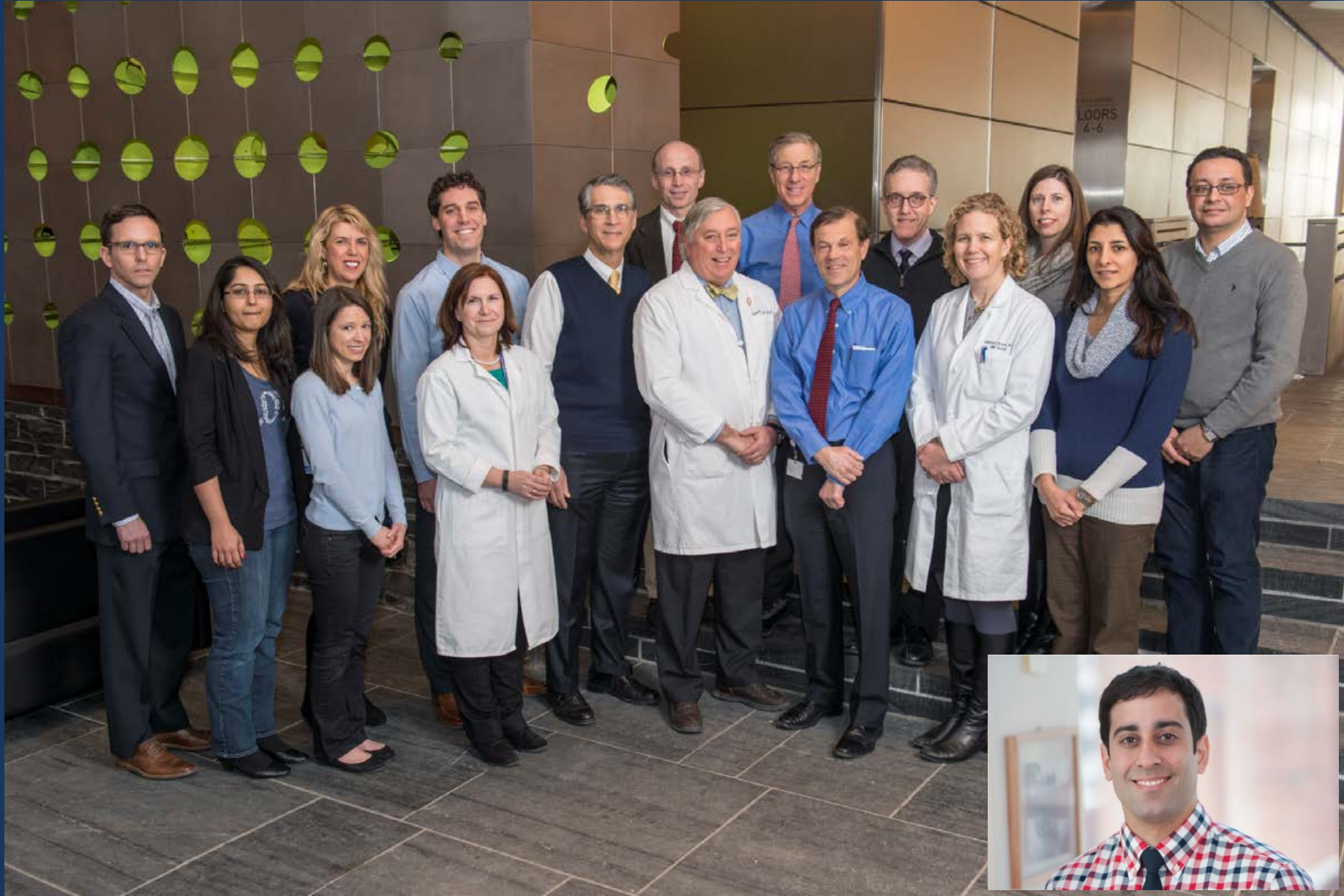
BUT high dose steroids (>7.5mg daily) for ipilimumab hypophysitis was associated with worse outcomes (n=98)



Future Questions

- Can mechanism based immunosuppression mitigate toxicity from steroids?
- What can toxicities teach us about autoimmune diseases?
- Long-term complications?

Thank you!



Back-up slides in case of
questions

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

When is it safe to restart
immunotherapy after toxicity?

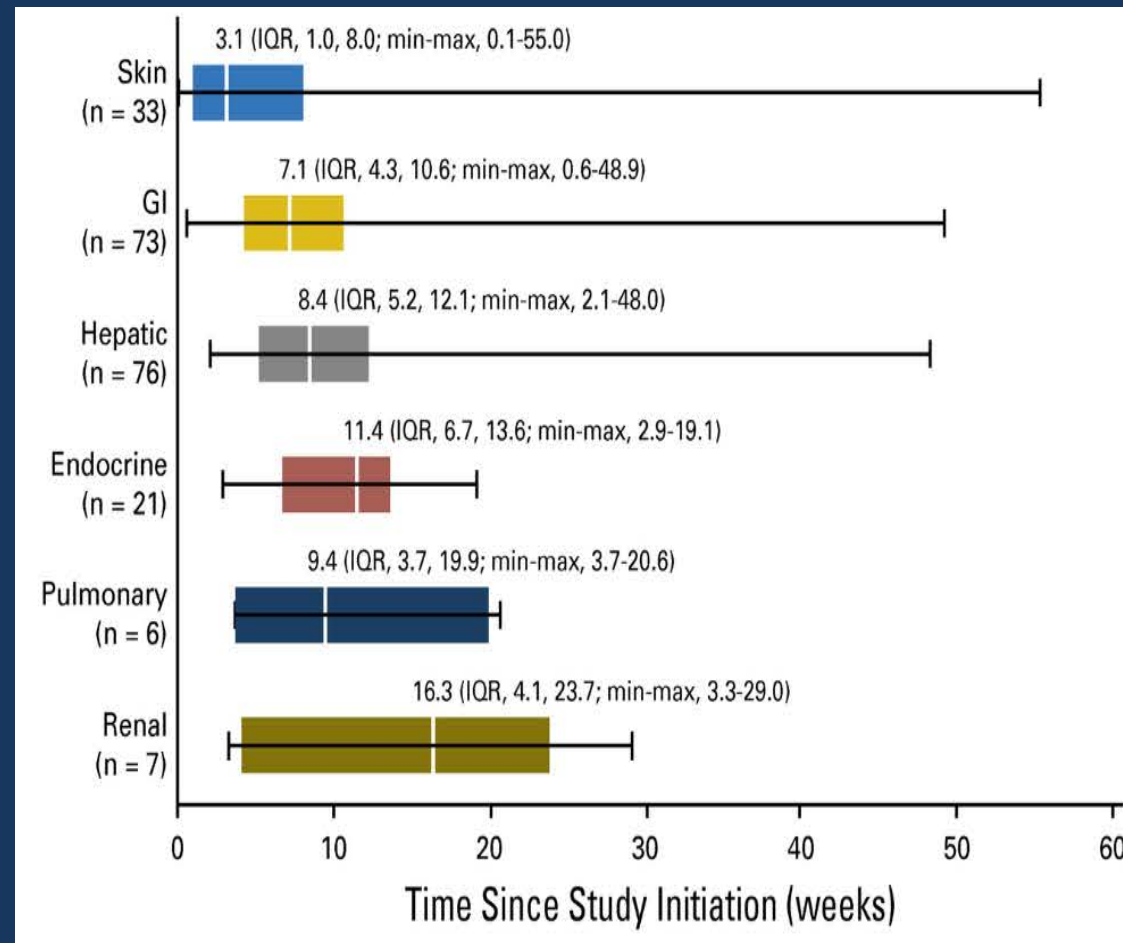
38 patients with NSCLC who discontinued PD1/PDL1 due to toxicity and retreated with PD-1

- 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

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]
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)

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



Circles indicate median and bars indicate ranges

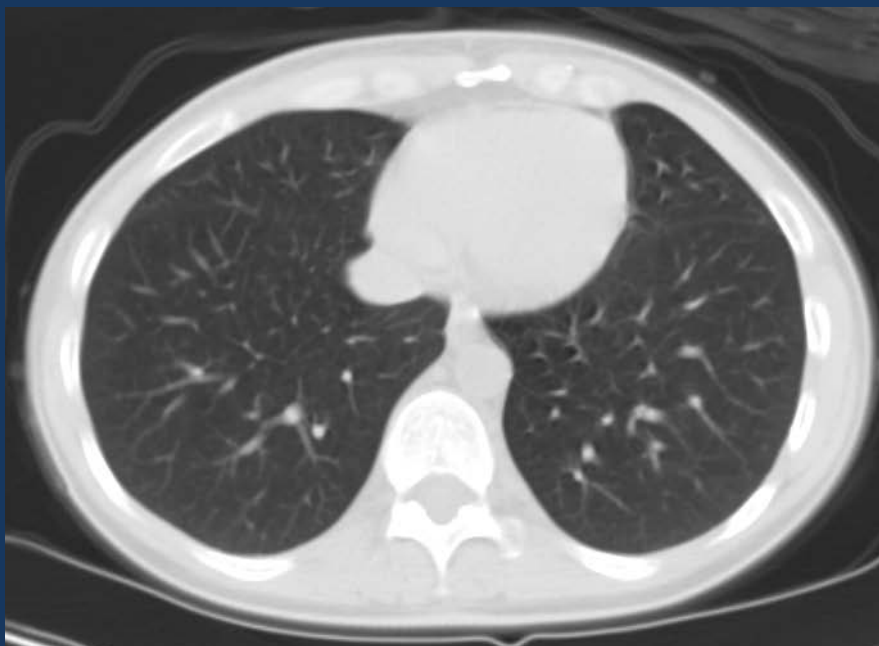
80 patients who discontinued CTLA4+PD1 due to toxicity of whom 77 (96% required steroids) [1]

- 18% recurrence rate of same irAE that caused discontinuation
- Some recurrent toxicities were severe
- No clear association between recurrent toxicity and prior steroid duration or use of additional immunosuppression
- Some association with lower recurrent toxicity risk with being off steroids and time since prior toxicity

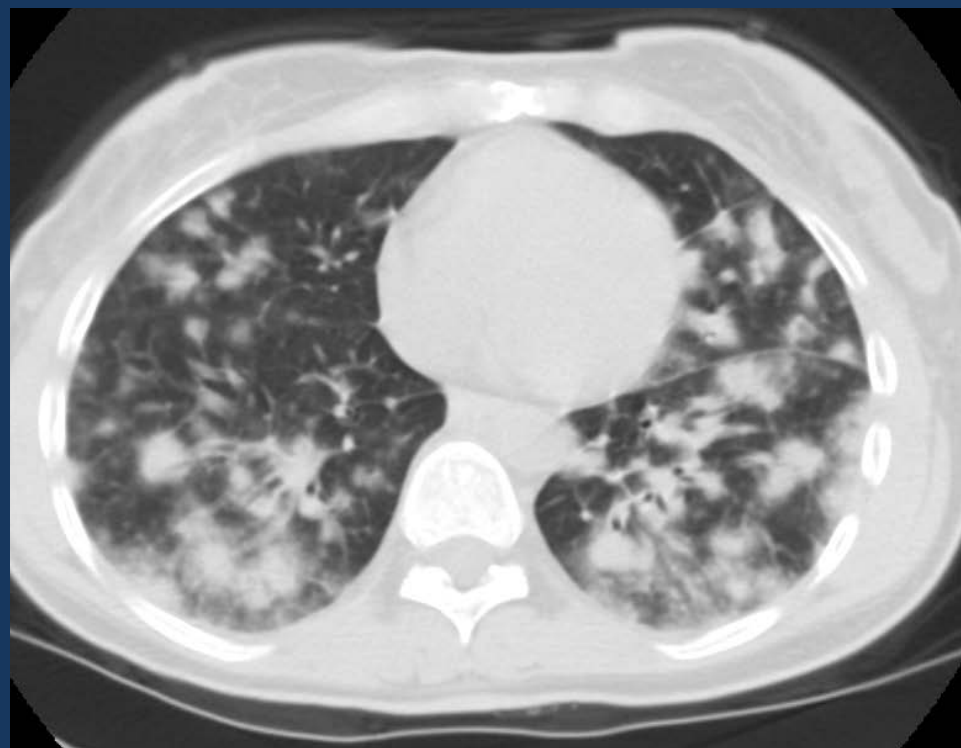
[1] Pollack, Betof, et al. *Ann of Oncol* 2017

[2] Santini et al. *Cancer Immunol Res* 2018

Pneumonitis



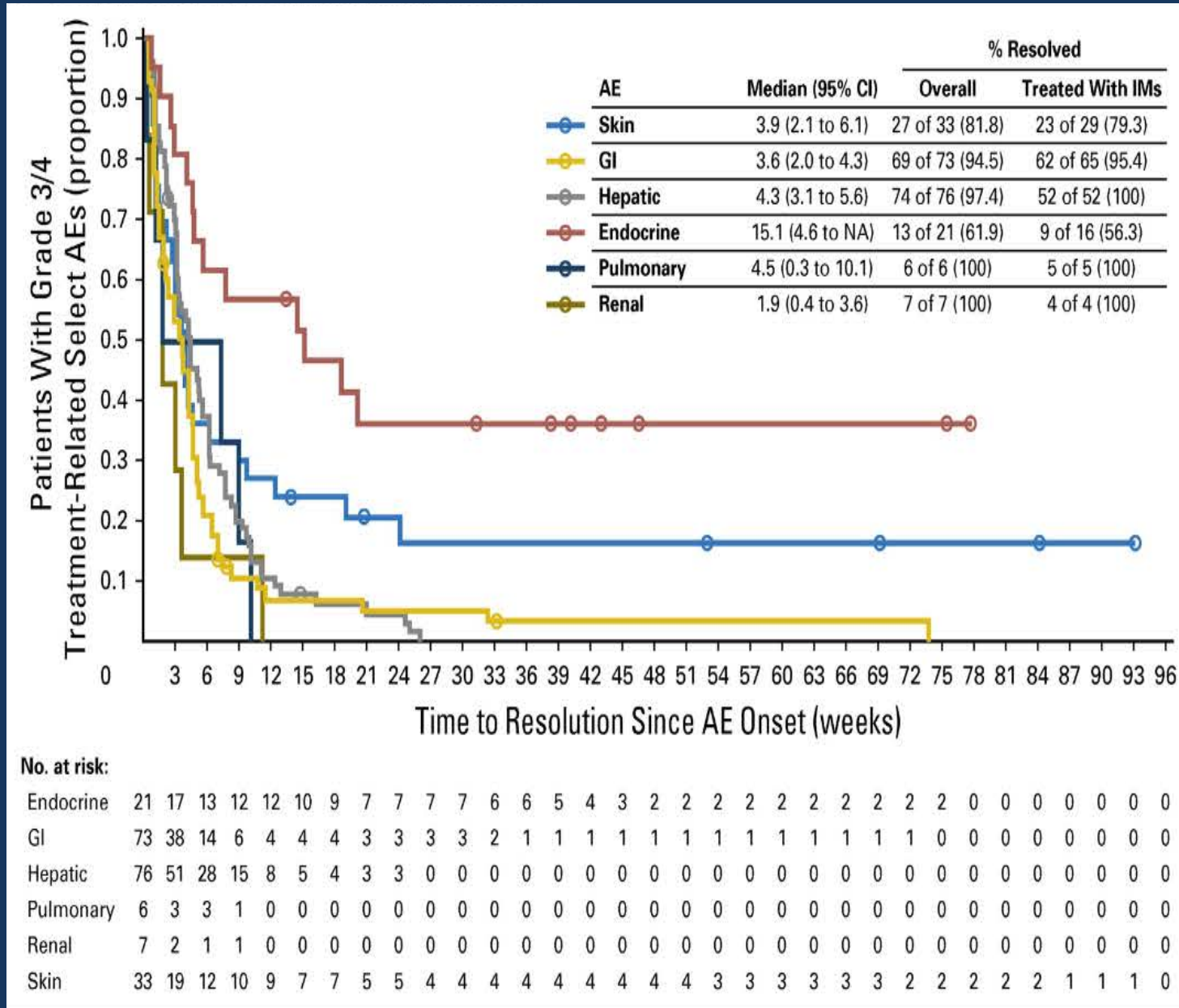
2/21/2011



3/30/2011

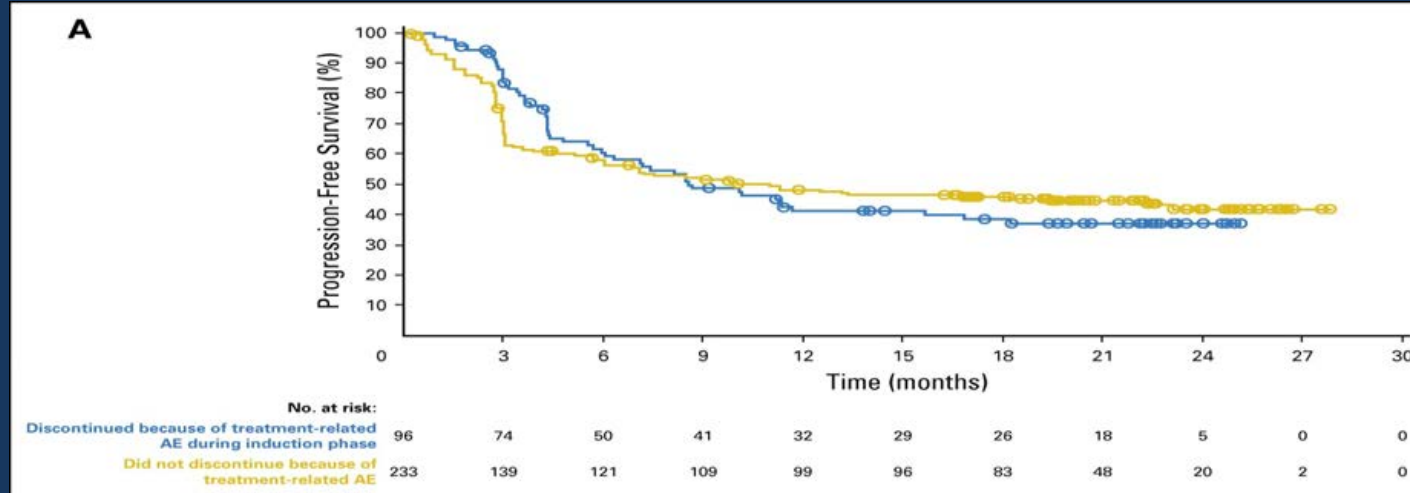
Two doses of ipilimumab and four of nivolumab

Most side effects resolve



Sznol et al.
*Journal of Clin
 Oncol* 2017

Outcomes look similar in patients who discontinue due to toxicity vs. those who continue treatment longer



Outcomes look similar in patients who discontinue due to toxicity vs. those who continue treatment longer

