

# Gastrointestinal Toxicities of Checkpoint Blockade

Michael Dougan, MD, PhD

Director of the Immunotherapy Mucosal Toxicities Program

Assistant Professor of Medicine

Division of Gastroenterology

Massachusetts General Hospital

22 June 2019



MASSACHUSETTS  
GENERAL HOSPITAL

GASTROENTEROLOGY

# Disclosures

- Novartis (research funding), Genentech (consulting), Tillots (consulting), Moderna (consulting)
- I will be talking about non FDA approved indications for infliximab (and other anti-TNF medications), and vedolizumab



MASSACHUSETTS  
GENERAL HOSPITAL

GASTROENTEROLOGY

# Immune-related adverse events are not just “side effects”

- Window into the biology of immune regulation in humans
  - In vivo immune receptor blockade
  - The side effects are the “phenotype”
- Potential insight into “sporadic” autoimmunity
  - Well-defined system
  - timing and nature of the immune perturbation is known



# Managing immune toxicities to improve cancer therapy

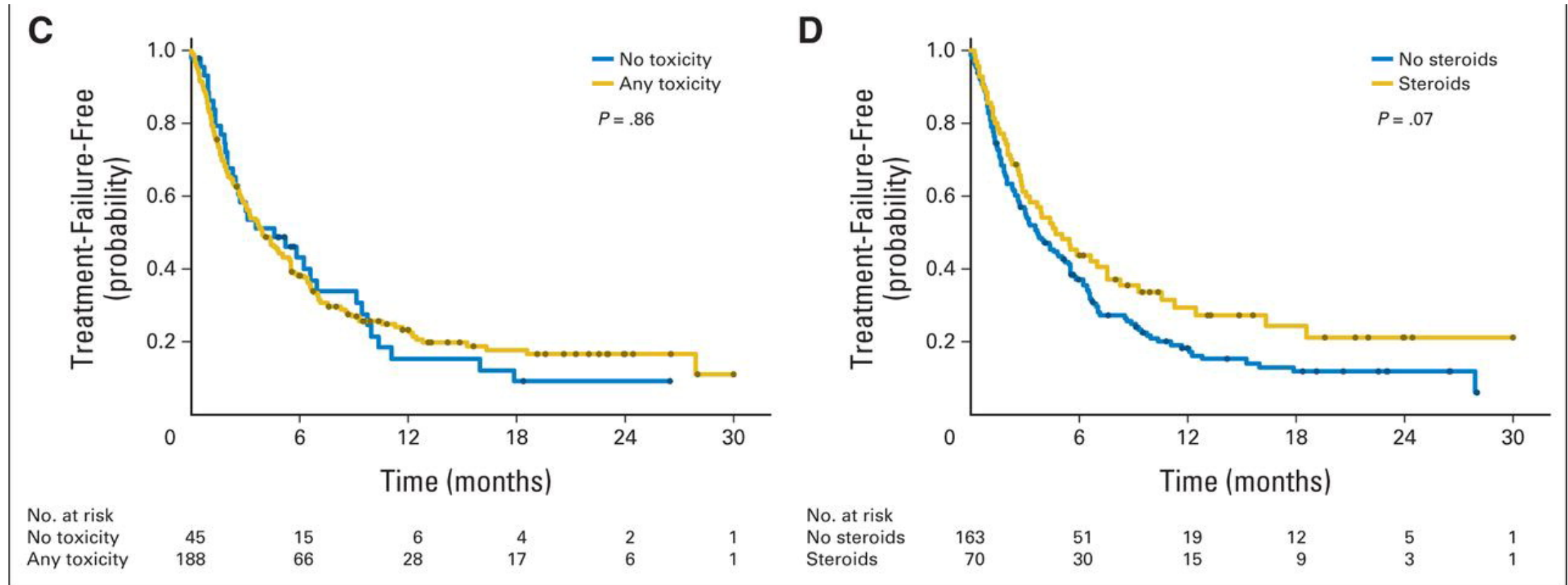
- Minimize morbidity/mortality from immune toxicities **without inhibiting antitumor immunity**
- Novel therapeutics to avoid steroids
- Concurrent treatments
- Prophylactic/preventative treatments in high risk patients
- Increasingly important with combination treatments



MASSACHUSETTS  
GENERAL HOSPITAL

GASTROENTEROLOGY

# Is it important to avoid steroids?



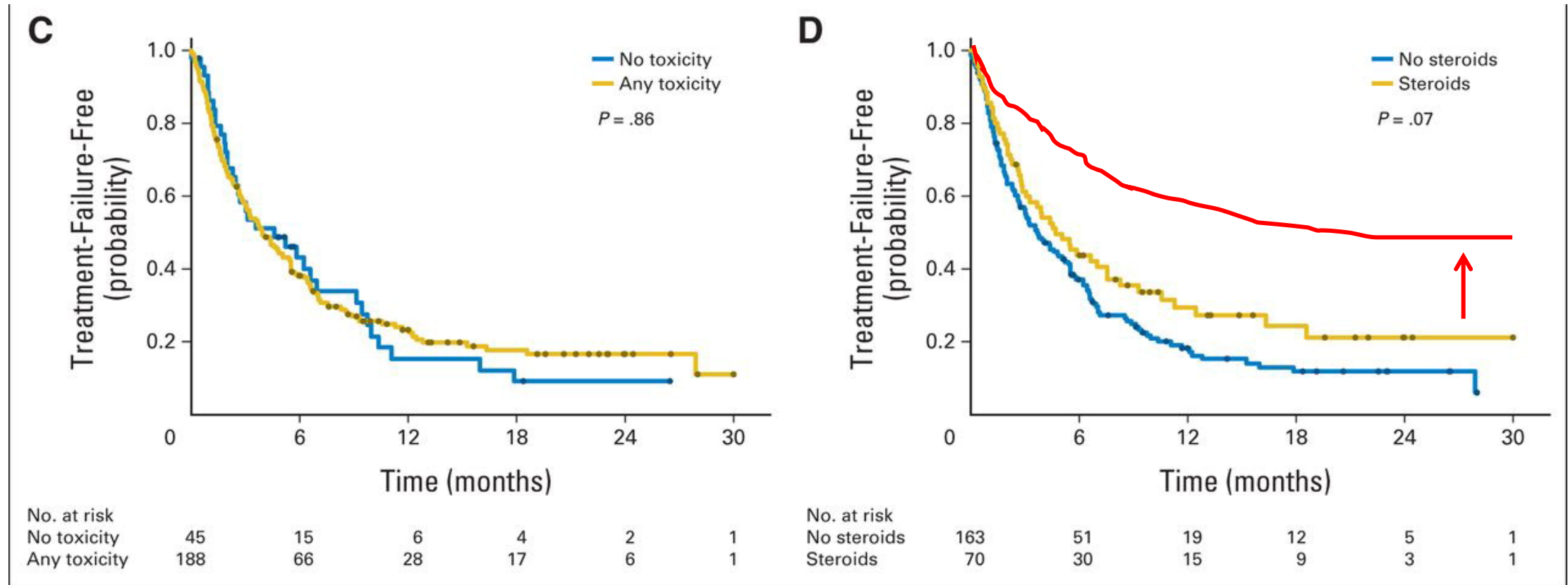
Horvat et al. JCO. 2015. Single center retrospective study



MASSACHUSETTS  
GENERAL HOSPITAL

GASTROENTEROLOGY

# Is it important to avoid steroids?



Horvat et al. JCO. 2015. Single center retrospective study

- Patients only received steroids if they had an adverse event
- Anyone with a serious adverse event got steroids
- Could this response be better with alternate immune suppression?

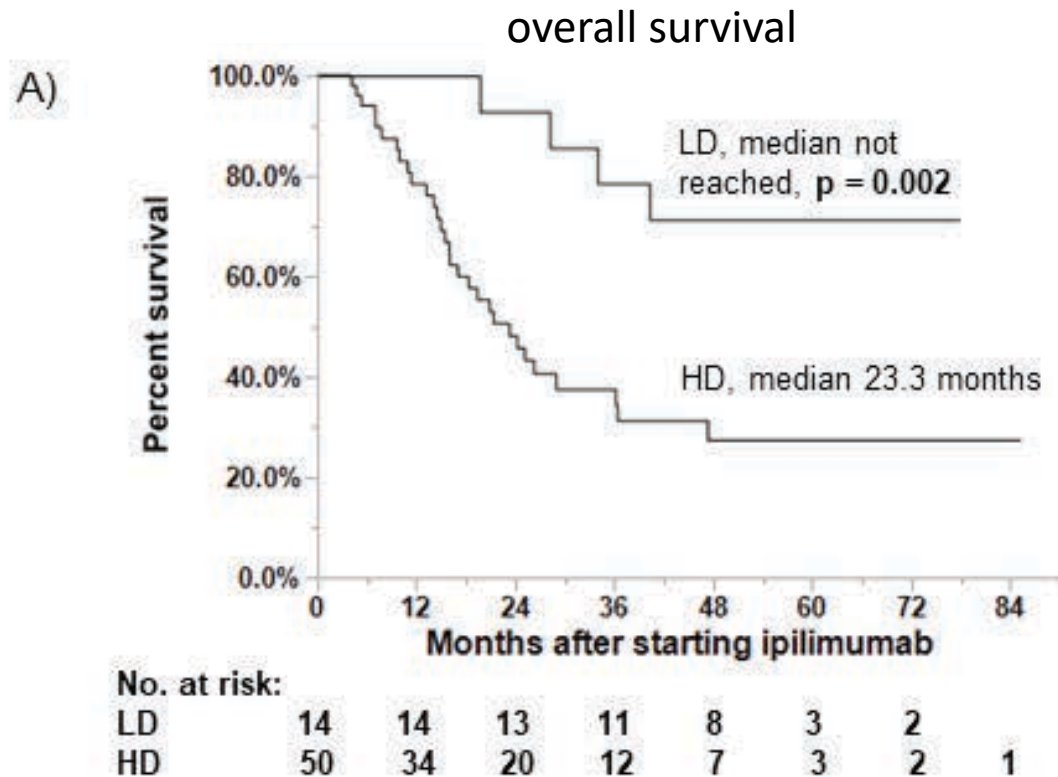


MASSACHUSETTS  
GENERAL HOSPITAL

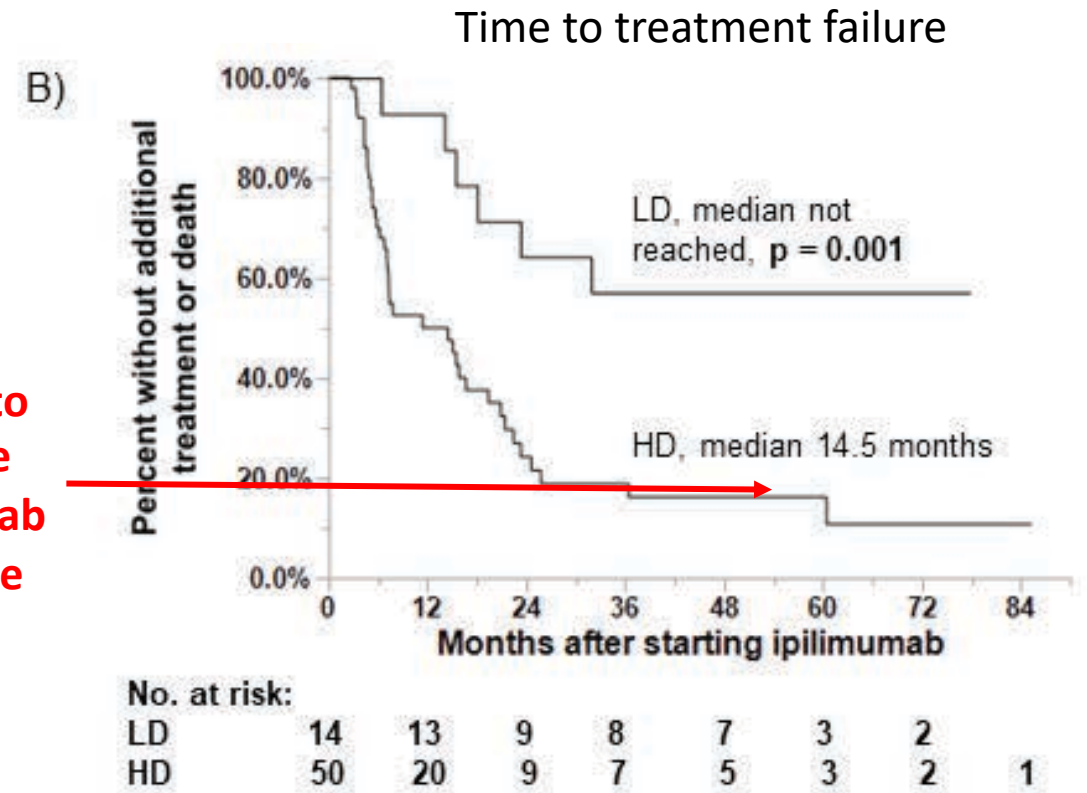
GASTROENTEROLOGY

# Steroids may inhibit the antitumor response

Metastatic melanoma treated with ipilimumab  
(all patients in the analysis developed hypophysitis)



Similar to  
average  
ipilimumab  
response

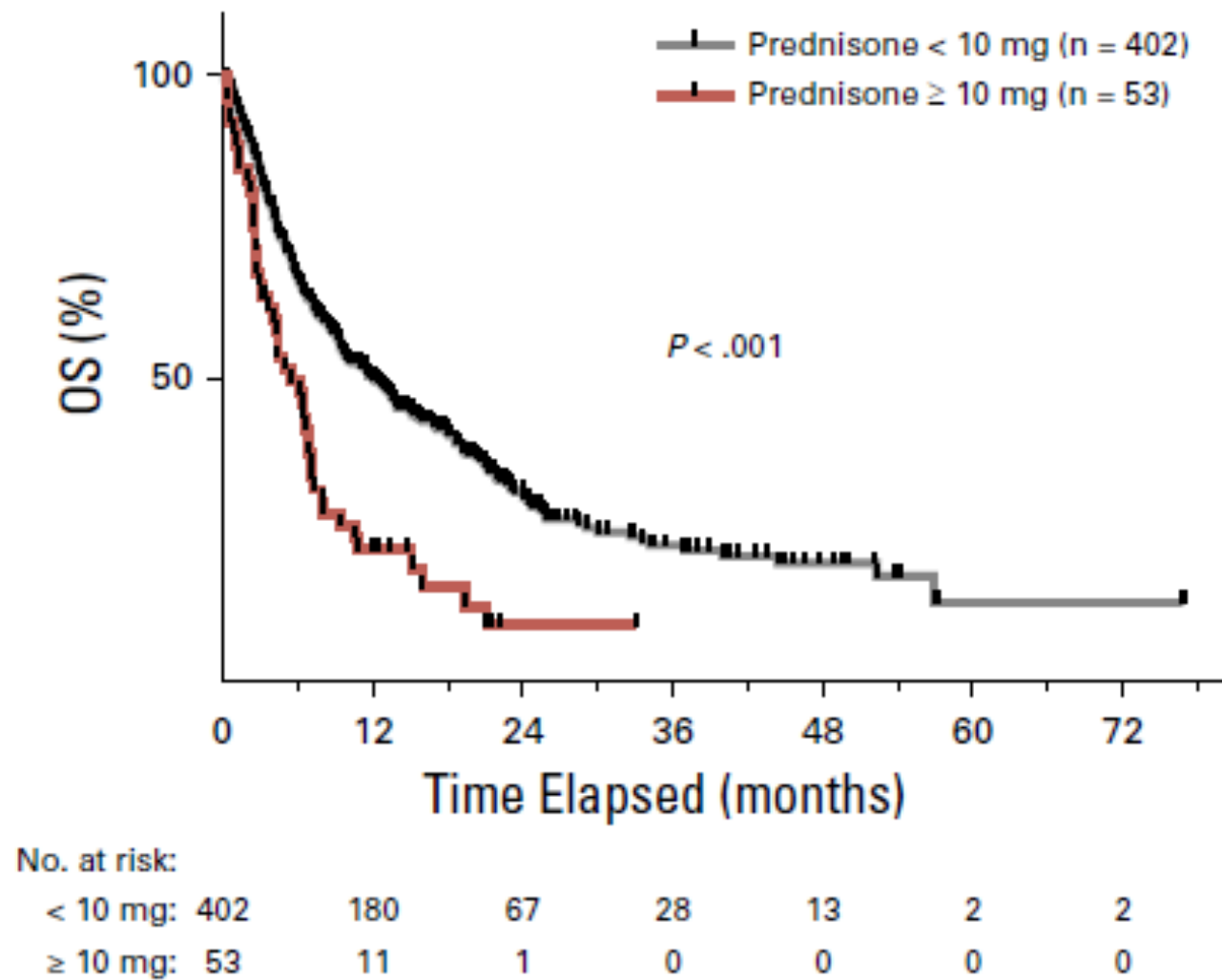


MASSACHUSETTS  
GENERAL HOSPITAL

GASTROENTEROLOGY

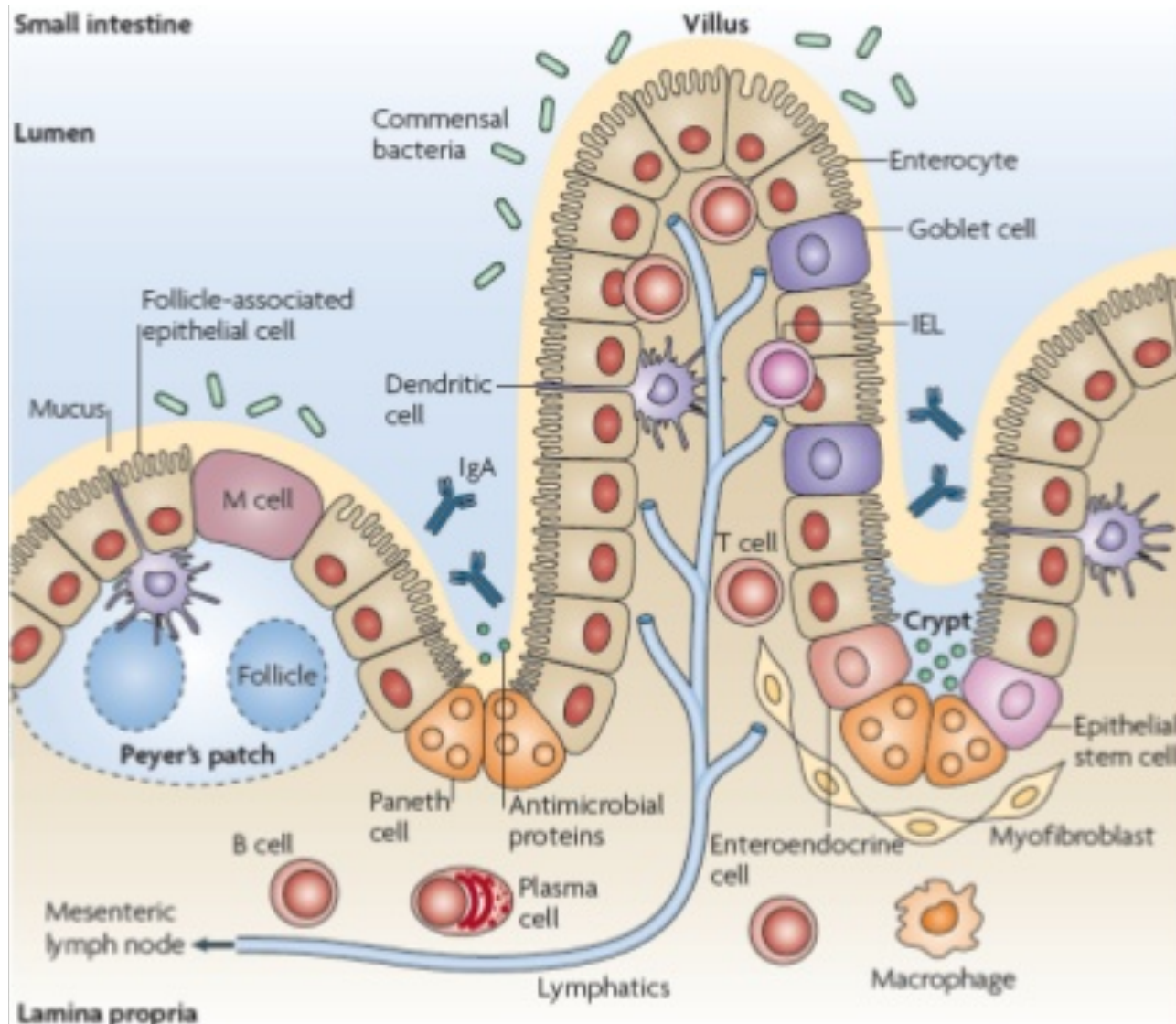


# Baseline steroids are associated with decreased survival after immunotherapy for lung cancer





# The gut is the most immunologically complex barrier in the body



Careful immune regulation is essential

- Dietary proteins
- Commensal bacteria
- Pathogenic microorganisms
- Toxins



MASSACHUSETTS  
GENERAL HOSPITAL

GASTROENTEROLOGY

# Disruption of immune homeostasis leads to a wide-spectrum of common GI toxicities

(Entero)colitis  
Hepatitis

	Ipilimumab	$\alpha$ PD-1 <sup>a</sup>	$\alpha$ PD-L1 <sup>b</sup>	Ipilimumab + $\alpha$ PD-1
<b>Common toxicities of checkpoint blockade (all grades)</b>				
<b>Constitutional</b>				
Fatigue	15.2–48	10.4–34.2	13.1–25	35.1–39
Asthenia	6.3–11	4.8–11.5	6.6	9
Pyrexia	6.8–15	4.2–10.4	6.6–8	18–20
<b>Dermatologic</b>				
Pruritus	26–35.4	8.5–20	8–10	33.2–40
Rash	14.5–32.8	0.9–25.9	8	40.3–41
<b>Gastrointestinal (GI)</b>				
Diarrhea	22.7–37	7.5–19.2	9.8–15	44.1–45
Nausea	8.6–24	5.7–16.5	6.6–17	21–25.9
Vomiting	7–11	2.6–16.4		13–15.3
Decreased appetite	9–12.5	1.9–10.9	8–8.2	12–17.9
Constipation	9	2–10.7		8–11
Colitis	8.2–11.6	0.9–3.6	2	18–23
Hepatitis	1.2–3.9	1.1–3.8	4	15.3–27
Increased lipase	14–17	0.6		13–18
<b>Musculoskeletal</b>				
Arthralgia	5–9	2.8–14	6–10	10.5–11
<b>Endocrine</b>				
Hypothyroidism	1–15	4.8–11	5–8	15.3–17
Hyperthyroidism	2.3–4.2	3.2–7.8		
Hypophysitis	2–2.3	0.4–0.7		12–13
Adrenal insufficiency	0–2	0.4		5
<b>Pulmonary</b>				
Pneumonitis	0–1.8	0.4–5.8	4	9–11

Dougan M. *Frontiers in Immunology*. 2017.



MASSACHUSETTS  
GENERAL HOSPITAL

GASTROENTEROLOGY

# The spectrum is dependent on the pathway targeted

	Ipilimumab	$\alpha$ PD-1 <sup>a</sup>	$\alpha$ PD-L1 <sup>b</sup>	Ipilimumab + $\alpha$ PD-1
<b>Common toxicities of checkpoint blockade (all grades)</b>				
<b>Constitutional</b>				
Fatigue	15.2–48	10.4–34.2	13.1–25	35.1–39
Asthenia	6.3–11	4.8–11.5	6.6	9
Pyrexia	6.8–15	4.2–10.4	6.6–8	18–20
<b>Dermatologic</b>				
Pruritus	26–35.4	8.5–20	8–10	33.2–40
Rash	14.5–32.8	0.9–25.9	8	40.3–41
<b>Gastrointestinal (GI)</b>				
Diarrhea	22.7–37	7.5–19.2	9.8–15	44.1–45
Nausea	8.6–24	5.7–16.5	6.6–17	21–25.9
Vomiting	7–11	2.6–16.4		13–15.3
Decreased appetite	9–12.5	1.9–10.9	8–8.2	12–17.9
Constipation	9	2–10.7		8–11
Colitis	8.2–11.6	0.9–3.6	2	18–23
Hepatitis	1.2–3.9	1.1–3.8	4	15.3–27
Increased lipase	14–17	0.6		13–18
<b>Musculoskeletal</b>				
Arthralgia	5–9	2.8–14	6–10	10.5–11
<b>Endocrine</b>				
Hypothyroidism	1–15	4.8–11	5–8	15.3–17
Hyperthyroidism	2.3–4.2	3.2–7.8		
Hypophysitis	2–2.3	0.4–0.7		12–13
Adrenal insufficiency	0–2	0.4		5
<b>Pulmonary</b>				
Pneumonitis	0–1.8	0.4–5.8	4	9–11

Dougan M. *Frontiers in Immunology*. 2017.



MASSACHUSETTS  
GENERAL HOSPITAL

GASTROENTEROLOGY

# Enterocolitis

- (Entero)colitis is the most common GI toxicity from current checkpoint blocking antibodies (CTLA-4, PD-1, PD-L1)
- Range of severity (many patients have indolent disease)
- Likely responsible for most treatment related diarrhea
- Often isolated to the colon, but can involve the GI tract from stomach to rectum



Dougan M. *Frontiers in Immunology*. 2017.



MASSACHUSETTS  
GENERAL HOSPITAL

GASTROENTEROLOGY



# Enterocolitis

- Watery diarrhea >> pain or cramping
- Urgency
- Bleeding is rare (often unrelated – hemorrhoids, metastatic disease)
- Can be accompanied by nausea/vomiting (enteritis)



Dougan M. *Frontiers in Immunology*. 2017.



MASSACHUSETTS  
GENERAL HOSPITAL

GASTROENTEROLOGY

# Not all patients with suspected colitis have inflammation

	N	% total	% inflammation
Total	80	100%	-
Mucosal Inflammation	63	78.8%	100%
Colitis	43	53.3%	68.3%
Enterocolitis	6	7.5%	9.5%
(Gastro)enteritis	11	13.8%	17.5%
Celiac	1	1.3%	1.6%
Other Inflammation	2	2.5%	3.2%



# Not all patients with suspected colitis have inflammation

	N	% total	% inflammation
Total	80	100%	-
Mucosal Inflammation	63	<b>78.8%</b>	100%
Colitis	43	53.3%	68.3%
Enterocolitis	6	7.5%	9.5%
(Gastro)enteritis	11	13.8%	17.5%
Celiac	1	1.3%	1.6%
Other Inflammation	2	2.5%	3.2%

- Endoscopy is the best way to diagnose mucosal inflammation



MASSACHUSETTS  
GENERAL HOSPITAL

GASTROENTEROLOGY



# What type of endoscopic exam is sufficient?



MASSACHUSETTS  
GENERAL HOSPITAL

GASTROENTEROLOGY

# Checkpoint colitis: pancolitis with regional variability

Dougan M. *Frontiers in Immunology*. 2017.



**Table 2.** Site of inflammation on colonoscopies of patients with anti-CTLA-4 enterocolitis. Variation in the denominator is due to incomplete colonoscopy.

Site of inflammation (n/N, %)		
Ileum	5/25	20
Ascending colon	27/33	82
Transverse	28/35	80
Descending colon	35/38	92
Sigmoid colon	36/38	95
Rectum	32/39	82
Extensive colitis	23/35	66
Patchy distribution	18/33	55

Marthey et al. *J Crohns Colitis* 2016.

- Flex sigs are usually sufficient (~95% sensitive for colitis when present)



MASSACHUSETTS  
GENERAL HOSPITAL

GASTROENTEROLOGY

# Enterocolitis is common

	N	% total	% inflammation
Total	80	100%	-
Mucosal Inflammation	63	78.8%	100%
Colitis	43	53.3%	68.3%
Enterocolitis	6	7.5%	9.5%
(Gastro)enteritis	11	13.8%	17.5%
Celiac	1	1.3%	1.6%
Other Inflammation	2	2.5%	3.2%



# A significant minority for upper inflammation

	N	% total	% inflammation
Total	80	100%	-
Mucosal Inflammation	63	78.8%	100%
Colitis	43	53.3%	68.3%
Enterocolitis	6	7.5%	9.5%
(Gastro)enteritis	11	13.8%	17.5%
Celiac	1	1.3%	1.6%
Other Inflammation	2	2.5%	3.2%

- Open question: the role for EGD in evaluation?



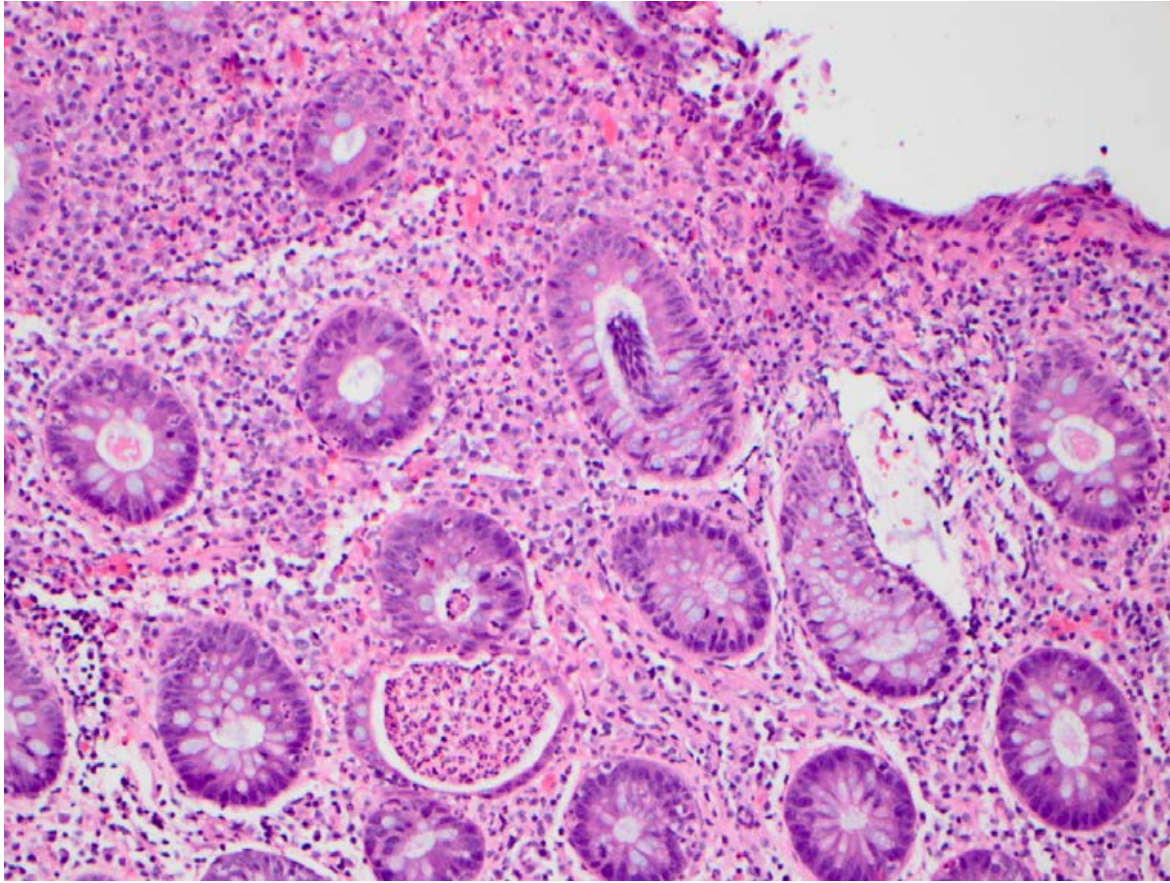
# When should endoscopy be considered?

- Grade 3/4 diarrhea and anyone who is sick enough to be admitted
- Persistent grade 2 disease (sometimes even grade 1)
- Atypical symptoms: bleeding, pain, fevers
- Atypical onset: months after discontinuation of immunotherapy, <7 days after starting, rapid escalation
- Prior to initiation of steroids?
- Diarrhea on investigational combinations, or other drugs that cause diarrhea?
- To guide the decision to re-challenge?





# Microscopic appearance



- Lymphocytic and neutrophilic infiltrate
- T cells appear to be the key drivers (unclear target)
- Prominent epithelial apoptosis
- Preserved crypts
- We will have an incomplete picture of the cellular infiltrate



MASSACHUSETTS  
GENERAL HOSPITAL

GASTROENTEROLOGY

# CTLA-4 and PD-1/PD-L1 have different regulatory roles in the gut

Ipilimumab colitis



- More frequent and more severe
- Rapid onset
- Dose-dependent
- Rapidly resolves

PD1-blockade colitis



- more microscopic inflammation
- Indolent course
- Dose-independent (?)
- Slow resolution



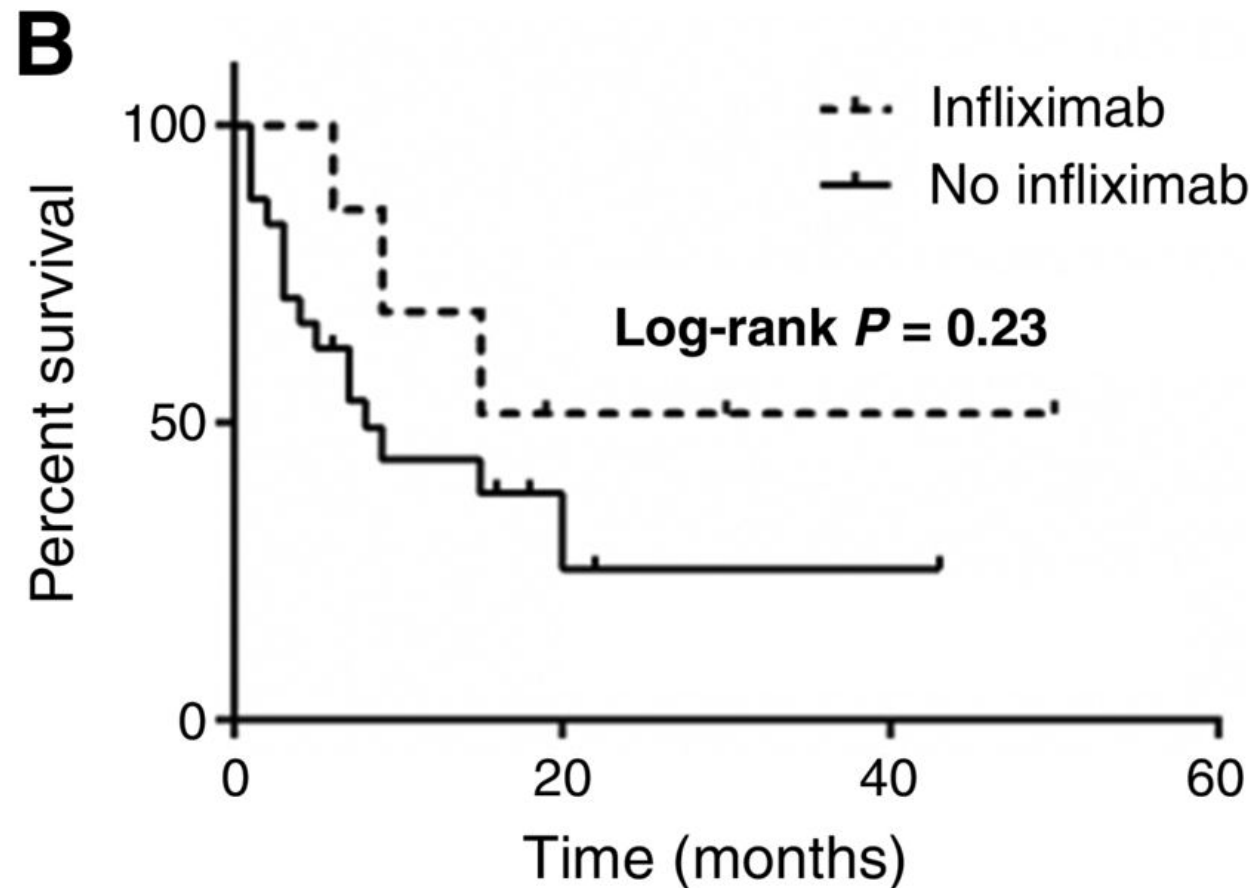
# TNF $\alpha$ is likely a key driver of checkpoint colitis

- Most patients with checkpoint colitis respond to steroids
  - 30-40% of severe cases are steroid refractory
- Infliximab (anti-TNF $\alpha$ ) is highly effective in ipilimumab and anti-PD1 mediated colitis
  - Suggests a critical functional role for this cytokine in disease pathogenesis
- We have a low threshold for using it (41% of our checkpoint colitis patients go on infliximab)
  - Similar rates for ipilimumab and anti-PD-1 colitis, but ipilimumab colitis seems to respond faster
- Vedolizumab also appears to be effective in some patients (Abu-Sbeih et al. JITC. 2018)
  - Trafficking of new T cells into the gut probably plays a role in maintaining inflammation



# Infliximab does not altered overall survival

Overall survival, almost completely driven by the melanoma



MASSACHUSETTS  
GENERAL HOSPITAL

GASTROENTEROLOGY

# Can we predict who is going to need infliximab?

- All current data are retrospective
- Two published case series found an association with **colonic ulceration** (Wang et al. *IBD*. 2018, Geukes et al. *ESMO Open*. 2018)
- In our MGH cohort of 49 patients with detailed endoscopic and oncologic clinical data:
  - Mayo Endoscopic Score is higher in patients who need infliximab (1.14 vs 2.26 out of 3,  $p = 0.001$ )
  - No association with CTCAE grade (2.05 vs 1.95)
  - MES 3 (ulcers) is associated with an increased need for infliximab ( $p < 0.009$ )
  - No association with rectal bleeding
  - Patients with enteritis tend to get infliximab more often ( $p = 0.08$ )
  - No association with pathway inhibited (PD-1 vs CTLA-4)



# What if patients don't respond to infliximab?

- This question has not been adequately addressed in the literature
  - Best data is for vedolizumab (Abu-Sbeih et al. JITC. 2018)
- We have rarely addressed it at MGH
  - Some cases appear to be infectious (C Diff >> CMV, aspergillus)
  - I always rescope
- What other options do we have?
  - Surgery
  - Ustekinumab (anti-IL-12/23 p40)
  - Other cytokine inhibitors (anti-IL-1beta, IL-6)
  - JAK inhibitors, CTLA-4-Ig (likely inhibit antitumor responses)
  - FMT?

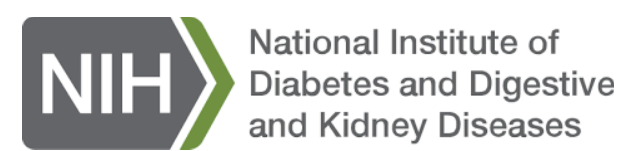


# Summary of Key Points

- Corticosteroids may limit the treatment effect from checkpoint blockade
- Endoscopy can be useful for risk stratification (ulcerating disease), and for identifying patients who do not require systemic steroids
- A significant fraction of patients with mucosal inflammation on checkpoint blockade have isolated enteritis (~20%)
- CTLA-4 and PD-1 colitis are not completely overlapping syndromes
- TNF- $\alpha$  appears to be a key mediator of checkpoint colitis



# Acknowledgements



Funded by the AGA Research Foundation



## **MGH Cancer Center**

Kerry Reynolds  
Alexandra-Chloe Villani  
Ryan Sullivan  
Justine Cohen  
Leyre Zubiri  
Meghan Mooridian  
Donald Lawrence  
Keith Flaherty  
Riley Fadden  
Krista Rubin  
Genevieve Boland  
Tatyana Sharova  
Maclean Sellers

## **MGH GI**

Molly Thomas  
Md Aladdin Bhuyian  
Andy Chan  
Ramnik Xavier

## **NIH/CTEP**

Elad Sharon

## **MD Anderson Cancer Center**

Hussein Tawbi  
Yinghong (Mimi) Wang

## **Dana-Farber Cancer Institute**

Stephanie Dougan  
Kai Wucherpennig  
Adrienne Louma  
Lestat Ali  
Osama Rahma  
Elizabeth Buchbinder  
Stephen Hodi  
Patrick Ott  
Jonathan Schoenfeld

## **MIT/Koch**

Michael Birnbaum

## **Memorial Sloan-Kettering**

David Faleck

## **Novartis**

Glenn Dranoff



MASSACHUSETTS  
GENERAL HOSPITAL

GASTROENTEROLOGY