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Society for Immunotherapy of Cancer

SITC
2017

Checkpoint Blockade and Gut Homeostasis

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Society for Immunotherapy of Cancer

#SITC2017

Presenter Disclosure Information

Michael Dougan, MD, PhD

The following relationships exist related to this presentation:

*Novartis, Research Funding
Tocagen, Consulting Fees*

irAEs are not just side effects

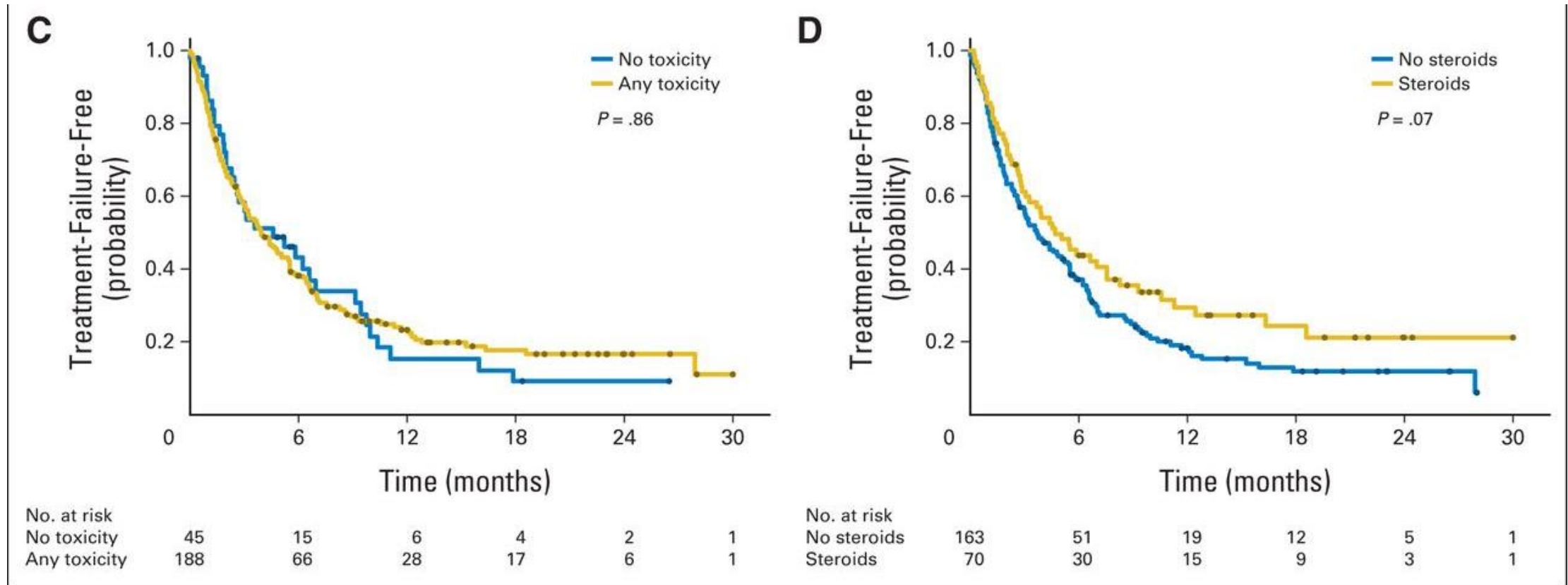
- Window into the biology of immune regulation in humans
- Potential insight into “sporadic” autoimmunity
- Likely complex relationship to antitumor response



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
- Likely to be increasingly important with combination treatments

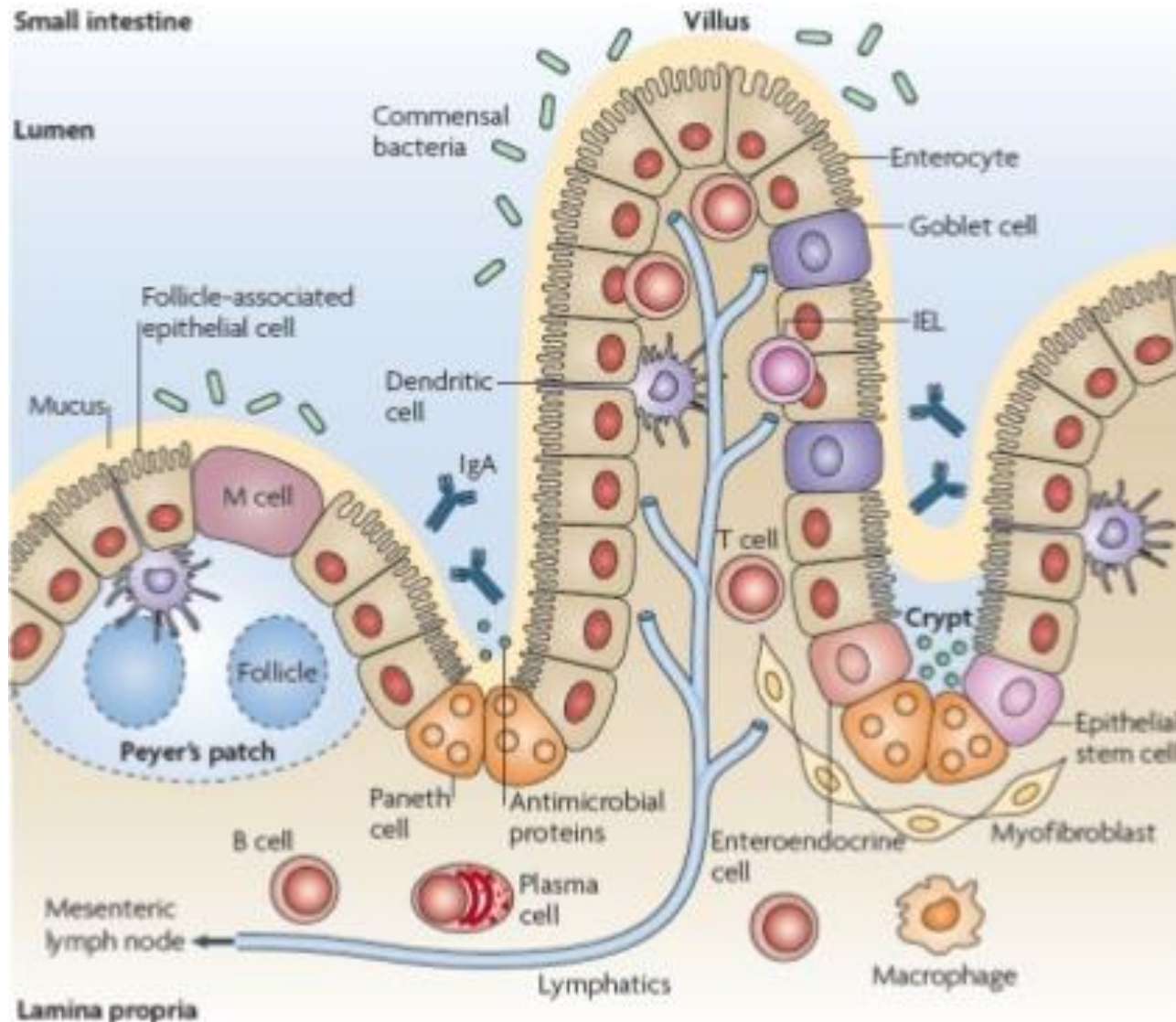
Is it important to avoid steroids?



Horvat et al. JCO. 2009. Single center retrospective study

- Of course, the limitation here is that patients only got steroids if they had an adverse event
- And anyone with a serious adverse event got steroids
- Could this response be better with alternate immune suppression?

The gut is a complex barrier



- Careful immune regulation is essential to the gut
 - Dietary antigens
 - Commensal bacteria
 - Pathogenic microorganisms
 - Toxins

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

Common Toxicities of Checkpoint Blockade (all grades)				
	Ipilimumab	anti-PD-1*	anti-PD-L1**	ipilimumab + anti-PD1*
Constitutional				
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
Dermatologic				
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
Gastrointestinal				
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 - 6.4		13 - 15.3
Decrease 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
Increase Lipase	14 - 17	0.6		13 - 18
Musculoskeletal				
Arthralgia	5 - 9	2.8 - 14	6 - 10	10.5 - 11
Endocrine				
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
Pulmonary				
Pneumonitis	0 - 1.8	0.4 - 5.8	4	9 - 11

*nivolumab and pembrolizumab **atezolizumab and durvalumab

And some rare...

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*nivolumab and pembrolizumab **atezolizumab and durvalumab

- Gastritis
- Cholangitis
- Celiac disease

Some immune-mediated diseases are not seen

- IgE-mediated food allergies
- Eosinophilic esophagitis
- Eosinophilic gastrointestinal diseases
- Does this tell us something about the role of CTLA-4 and PD-1/PD-L1 in the regulation of these (probably related) diseases?

Checkpoint blockade induced enterocolitis

Dougan M. *Frontiers in Immunology*. In Press.



- By far the most common GI toxicity
 - Up to 20% of patients on combination therapy
- Range of severity
- Likely responsible for most treatment related diarrhea

Colitis

Clinical Features

Dougan M. *Frontiers in Immunology*. In Press.

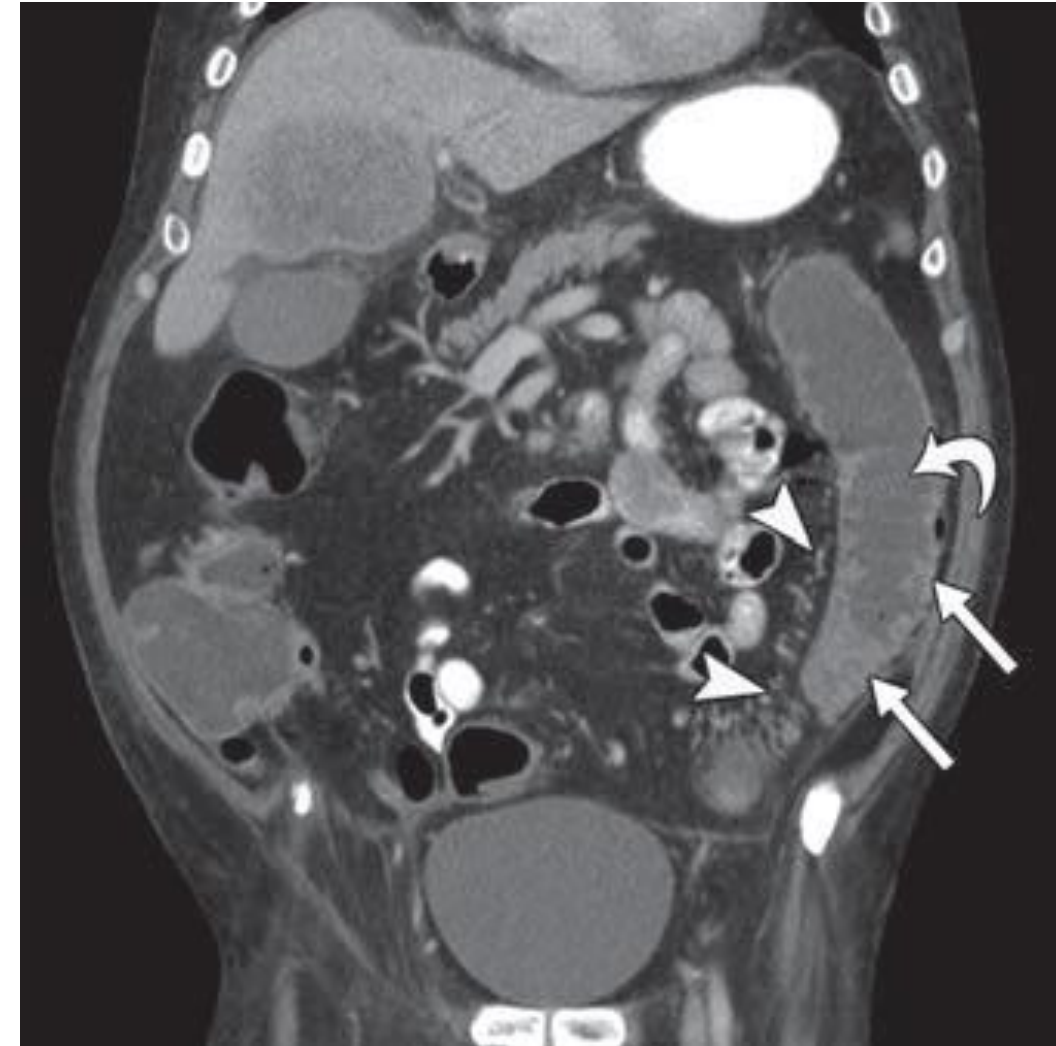


- Watery diarrhea >> pain or cramping
- Urgency without incontinence
- Blood is rare
- Can be accompanied by nausea/vomiting

Colitis

Initial workup of checkpoint blockade induced enterocolitis

- Exclude infections: stool culture, test for *C. Difficile*
- CT scans are useful in some patients
 - looking for perforation or other potentially surgical complications



Kim et al. Am J
Roentgenol. 2013.

PD1 Blockade in Crohns

- 74 yoM w/ quiescent Crohn's
- Asymptomatic off medication for many years
- 2 weeks after starting PD1 blockade p/w perforation from reactivated disease



Checkpoint blockade in patients with IBD

Original Investigation

Ipilimumab Therapy in Patients With Advanced Melanoma and Preexisting Autoimmune Disorders

Douglas B. Johnson, MD; Ryan J. Sullivan, MD; Patrick A. Ott, MD, PhD; Matteo S. Carlino, MBBS; Nikhil I. Khushalani, MD; Fei Ye, PhD; Alexander Guminski, MD, PhD; Igor Puzanov, MD; Donald P. Lawrence, MD; Elizabeth I. Buchbinder, MD; Tejaswi Mudigonda, BS; Kristen Spencer, DO; Carolin Bender, MD; Jenny Lee, MBBS; Howard L. Kaufman, MD; Alexander M. Menzies, MBBS; Jessica C. Hassel, MD; Janice M. Mehnert, MD; Jeffrey A. Sosman, MD; Georgina V. Long, MBBS; Joseph I. Clark, MD

- 6 patients with pre-existing IBD (quiescent)
- 2 cases of colitis (33%)
- Higher than average risk (5-10%)

Initial workup of checkpoint blockade induced enterocolitis

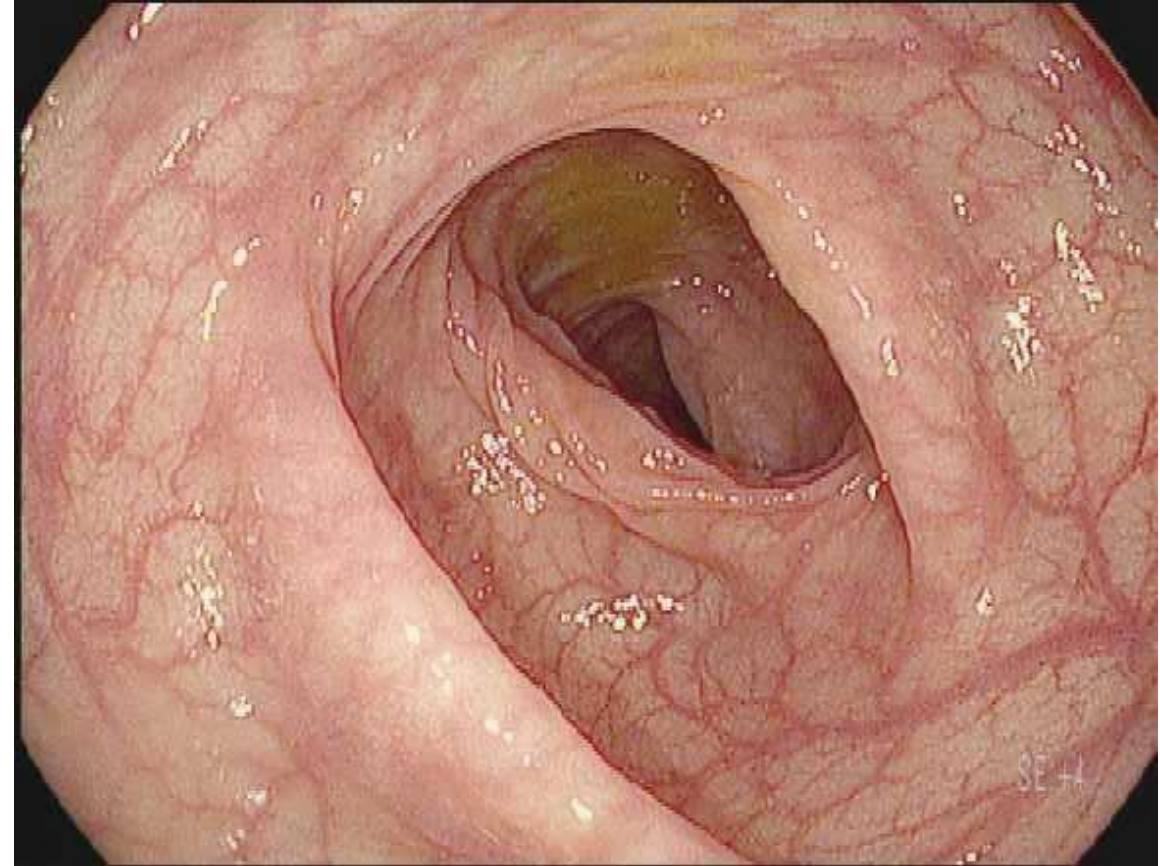
- Exclude infections: stool culture, test for *C. Difficile*
- CT scans are useful in some patients
 - looking for perforation or other potentially surgical complications
- Endoscopy should be considered for:
 - Grade 3/4 toxicity
 - Atypical presentations
 - Failure to respond to treatment

Endoscopic Appearance

Dougan M. *Frontiers in Immunology*. In Press.



Colitis



Normal

Extent of Disease: UC type pattern

Dougan M. *Frontiers in Immunology*. In Press.



Typically a pan-colitis but with regional variability

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

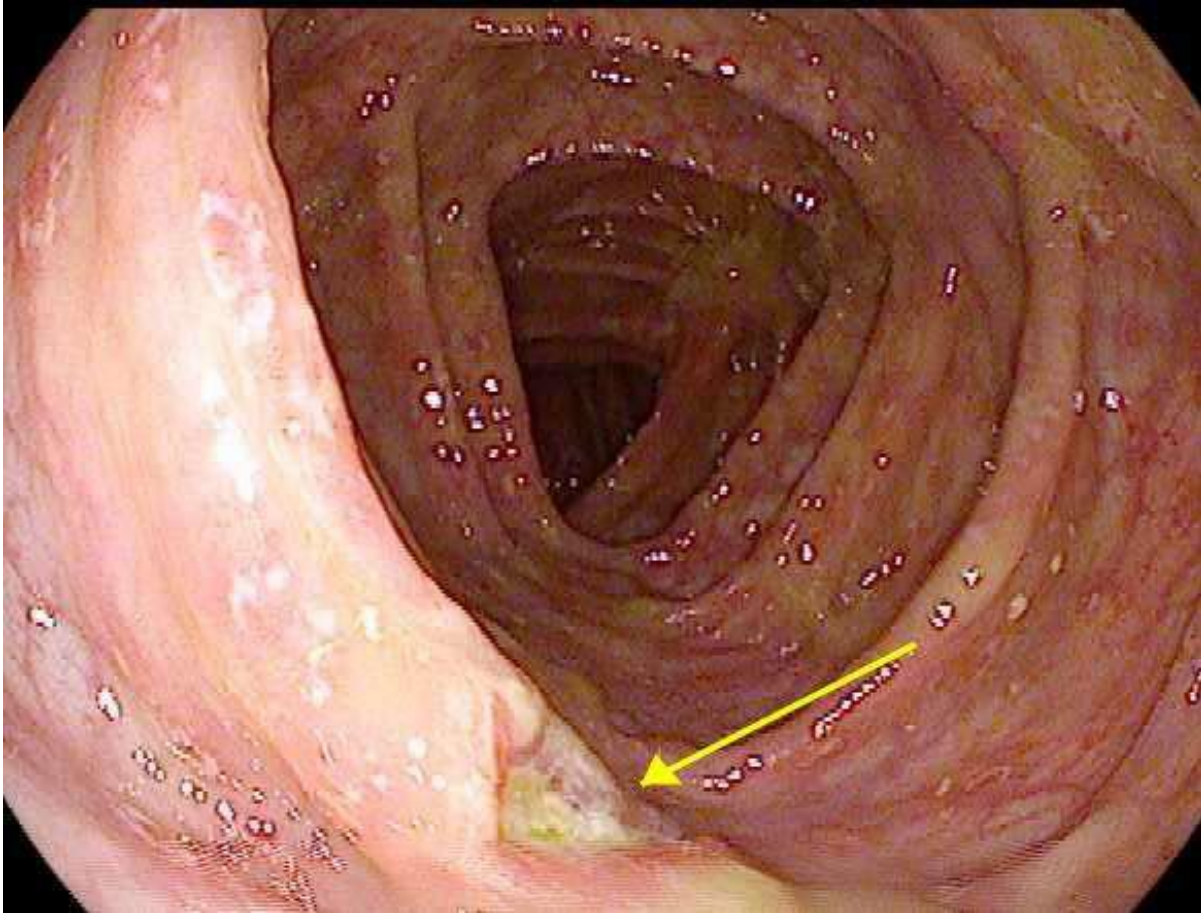
Site of inflammation (*n/N*, %)

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.

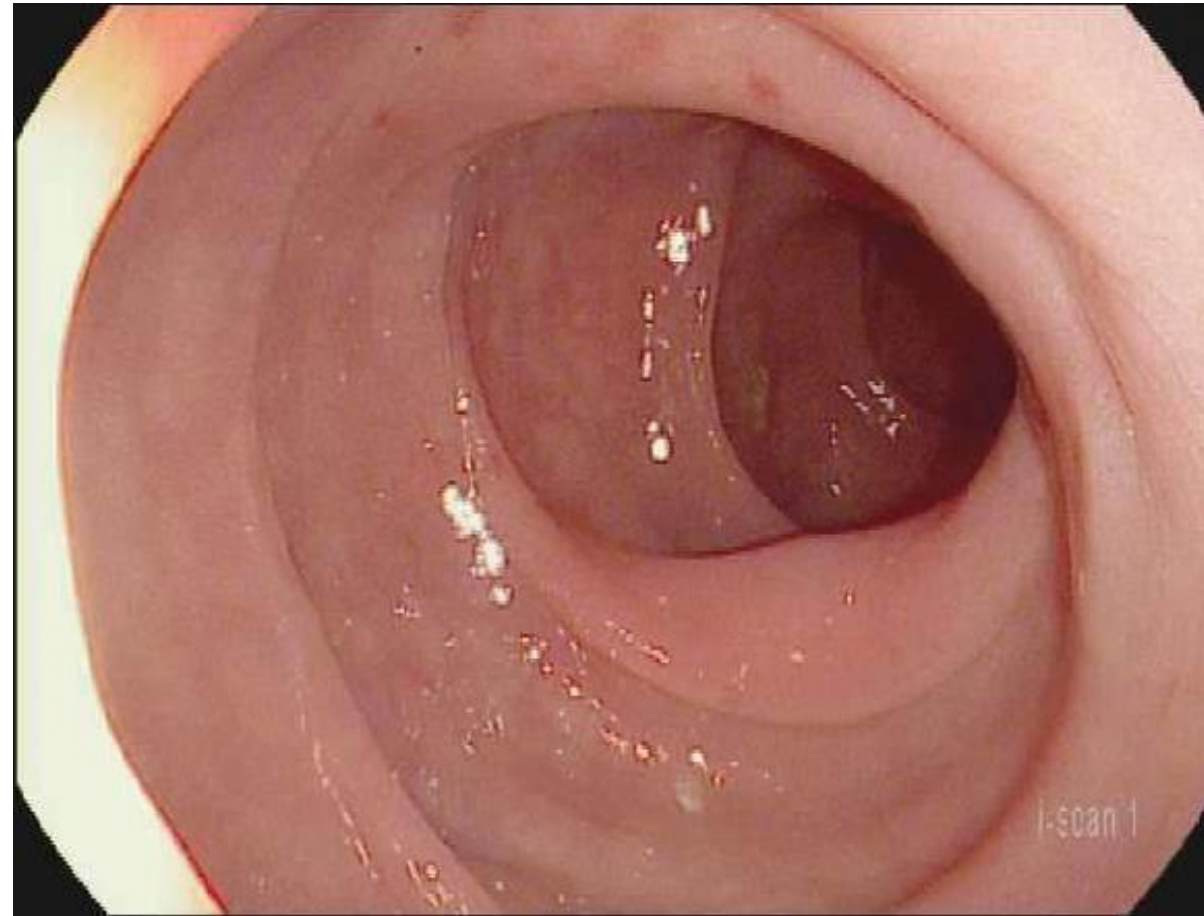
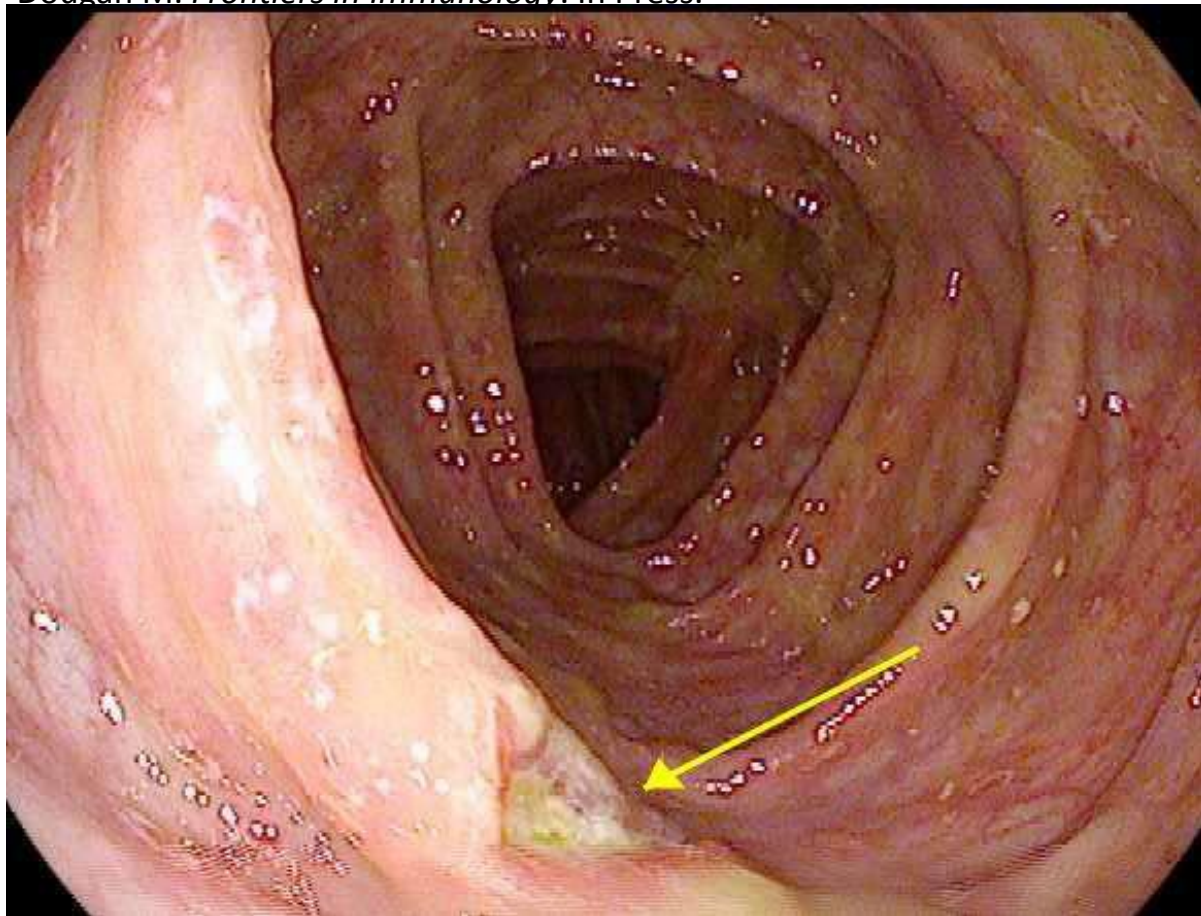
Crohns type disease does occur

Dougan M. *Frontiers in Immunology*. In Press.



Microscopic (lymphocytic) colitis

Dougan M. *Frontiers in Immunology*. In Press.



Microscopic colitis does not require treatment discontinuation, and typically responds to budesonide

Comparison of checkpoint colitis to IBD

Crohn's Disease



Ulcerative Colitis



Checkpoint Colitis



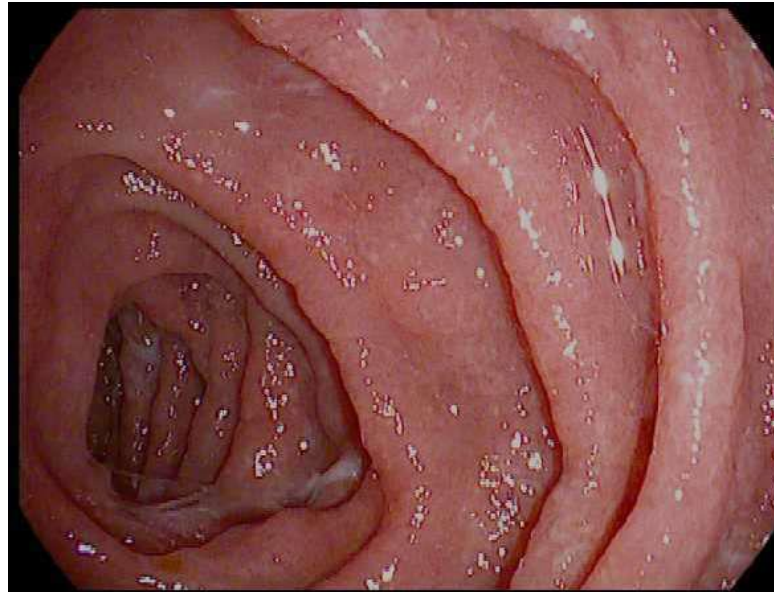
- Deep ulcers (characteristic of Crohn's) are rare
- Segmental colitis is rare (similar to UC)
- Fistulas, strictures, and small bowel obstructions don't occur
- Onset with ipilimumab is acute (rare in IBD), but nivo/pembro can be indolent
- Healing appears to be complete with resolution of inflammation

Comparison of checkpoint colitis to IBD

Gastritis



Enteritis (duodenum)



Dougan M. *Frontiers in Immunology*. In Press.

- Enteritis is common (25% or more), only seen in Crohn's
- Diarrhea disproportionate to colonic disease severity (enteritis?)
- Both of these occur exclusively in Crohn's and rarely involve the entire stomach or small bowel

Not all adverse symptoms are adverse events

73 yo woman w/ uveal melanoma metastatic to the liver on ipilimumab
p/w epigastric pain and reflux

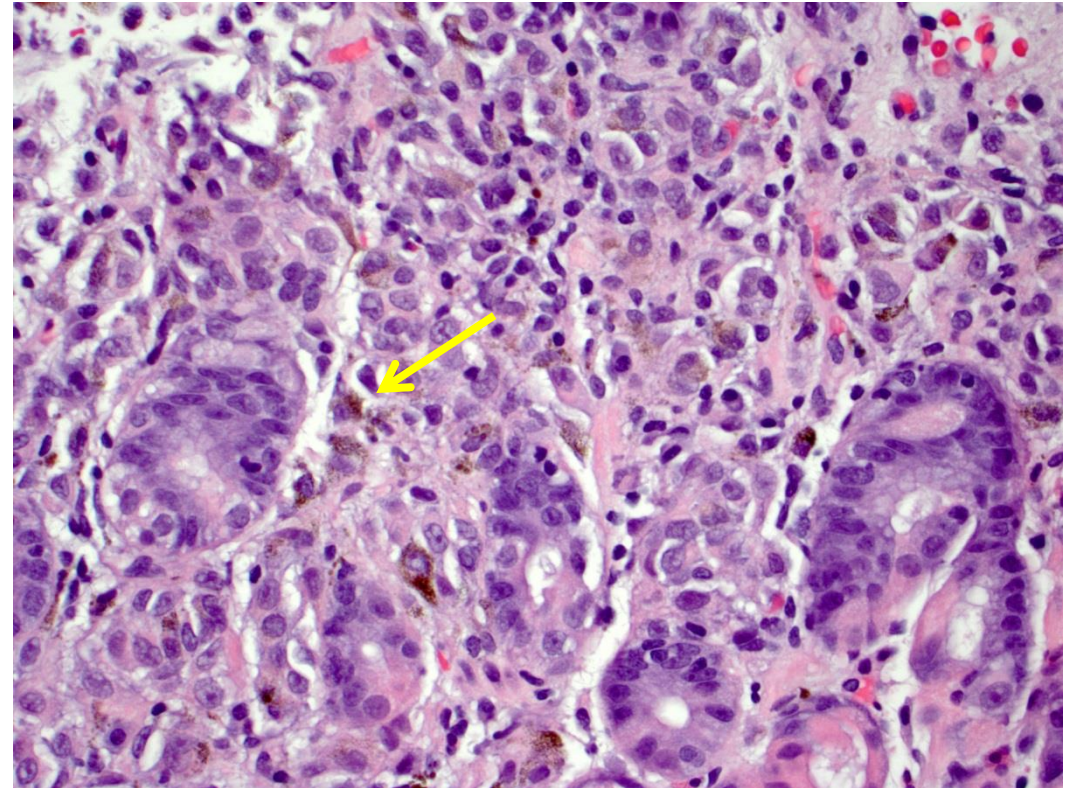
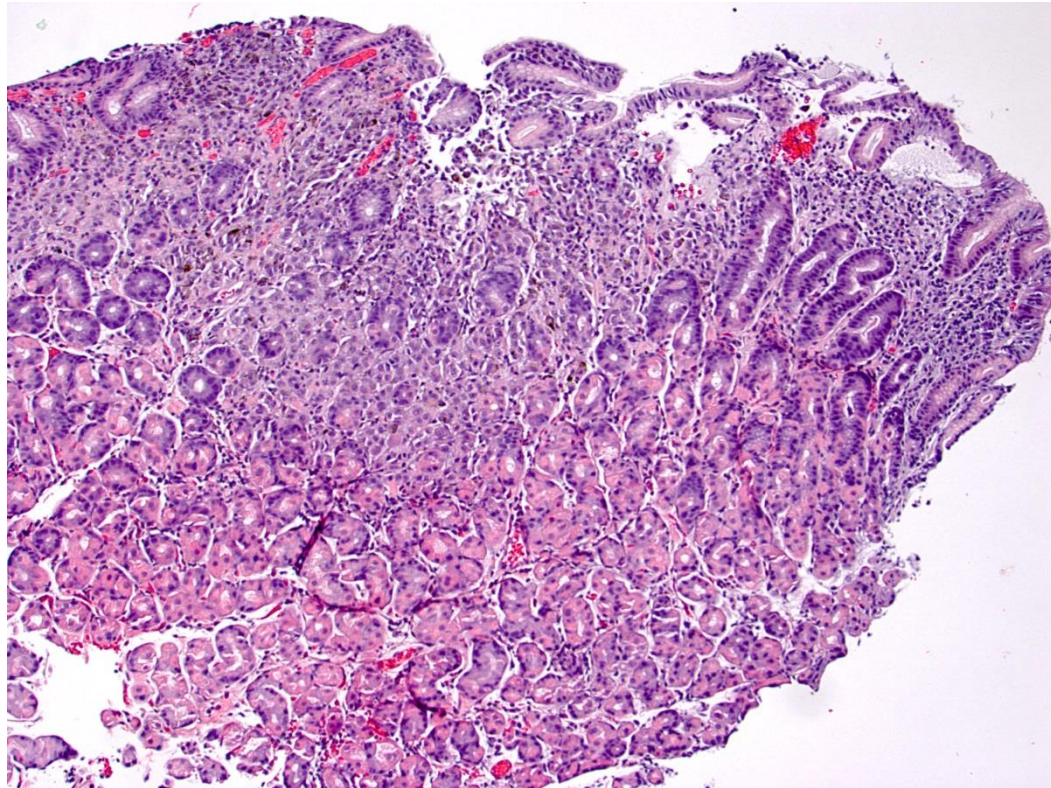
- Non responsive to high dose PPI
- No prior history of GERD
- Symptoms onset shortly after initiation of ipilimumab

Endoscopy (normal)

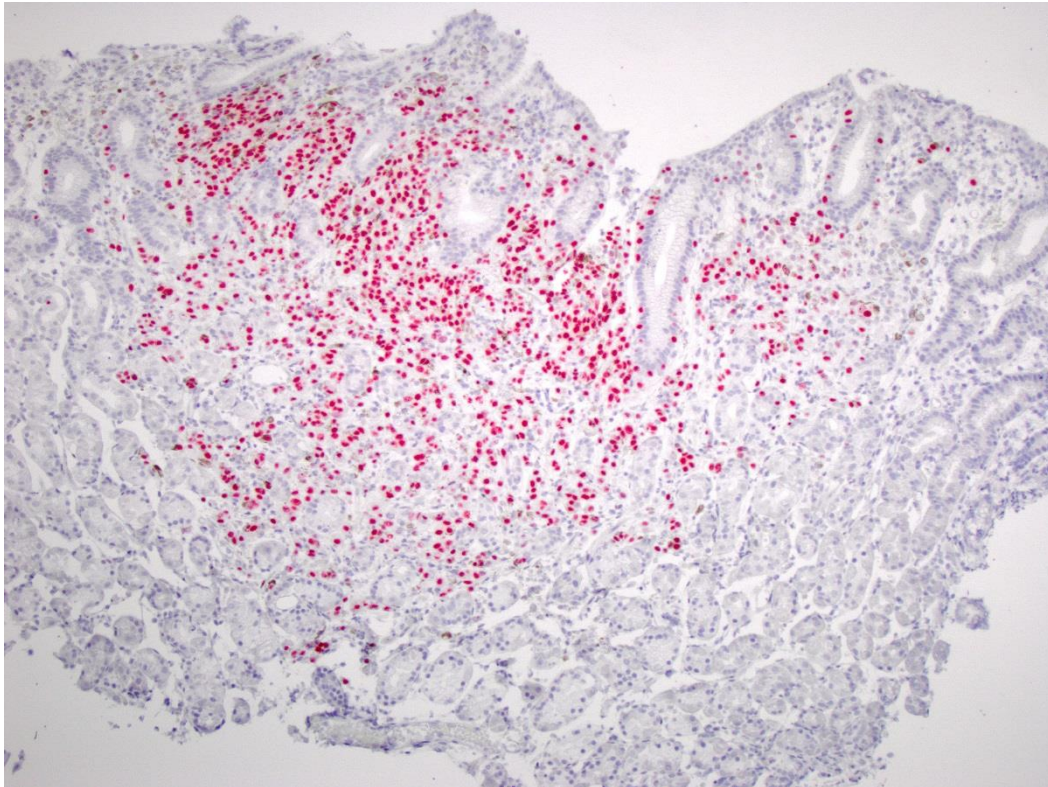


Pathology

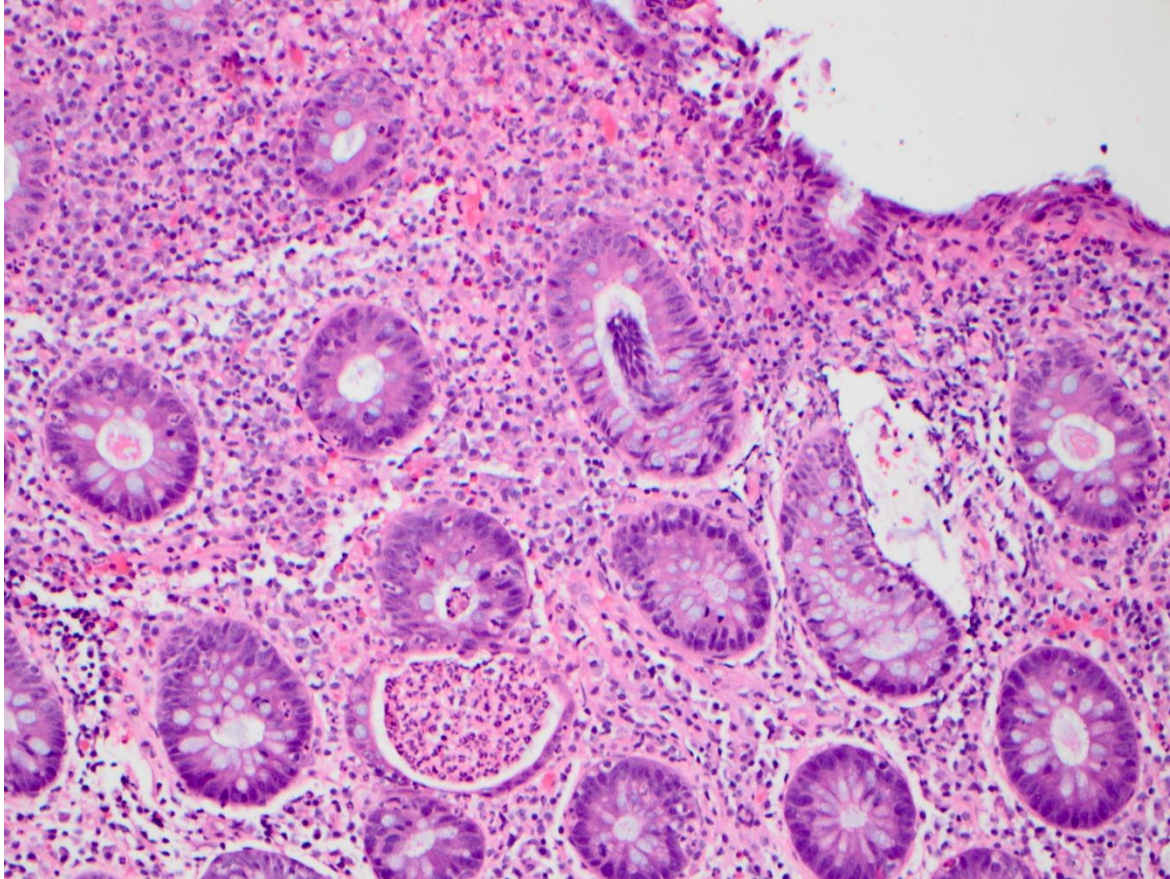
melanocytes



S100 Positive: melanoma

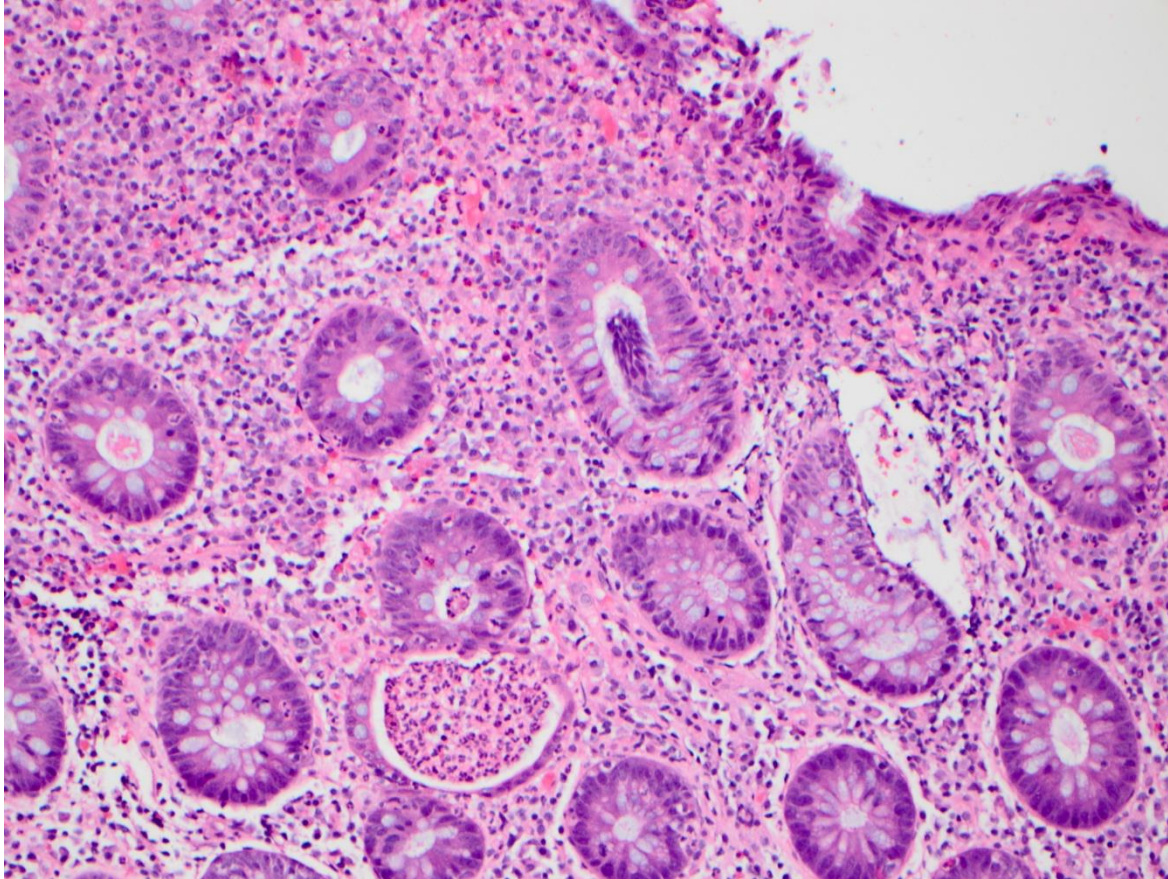


Histology of Typical Checkpoint Colitis



- Lymphocytic and neutrophilic infiltrate
- Prominent epithelial apoptosis
- Crypt abscesses, rare granulomas reported
- Preserved crypt architecture

Histology of Typical Checkpoint Colitis



- **Lymphocytic and neutrophilic infiltrate**
- **Prominent epithelial apoptosis**
- Crypt abscesses, rare granulomas reported
- Preserved crypt architecture

Treatment of Grade 3/4 Ipilimumab/Nivolumab colitis

- Most patients respond to systemic steroids, and can be weaned over a period of several weeks
- Large case series reported 12/41 ($<1/3$) patients to be steroid refractory (Beck et al. JCO. 2006)
- no rigorous studies of appropriate steroid dose
- Anecdotally, most patients appear to respond to 40-60 mg prednisone daily – some require IV steroids

Steroid Refractory Colitis

- Infliximab is highly effective in steroid refractory disease
 - Several small cases series (Beck et al. JCO. 2006), isolated patients in other trials
- Indications for infliximab
 - No/minimal response to steroids after 2 days
 - Recurrence on steroid taper
 - Preventing hospitalization in patients with rapidly escalating symptoms
- Responses typically occur within days
 - Many patients with ipilimumab colitis require only 1 dose (very few more than 3)

Concern about anti-TNF α therapy in melanoma

Risk of Melanoma and Nonmelanoma Skin Cancer Among Patients With Inflammatory Bowel Disease

MILLIE D. LONG,^{*,‡} CHRISTOPHER F. MARTIN,^{*,‡} CLARE A. PIPKIN,[§] HANS H. HERFARTH,^{*,‡} ROBERT S. SANDLER,^{*,‡} and MICHAEL D. KAPPELMAN^{‡,||}

Gastroenterology 2012

Medication ^a	IBD overall	
	Melanoma	NMSC
Any use		
5-ASA	1.06 (0.77–1.45)	0.99 (0.92–1.08)
Biologic	1.88 (1.08–3.29)	1.14 (0.95–1.36)
Thiopurine	1.10 (0.72–1.67)	1.85 (1.66–2.05)

- Retrospective, nested case-control study with >100,000 patients with IBD
- Small increased RR of melanoma in IBD patients treated with anti-TNF α
- More recent large meta-analyses have not demonstrated this association

Response to checkpoint blockade depends on antigen presentation and interferon responses

Mutations Associated with Acquired Resistance to PD-1 Blockade in Melanoma

Jesse M. Zaretsky, B.S., Angel Garcia-Diaz, Ph.D., Daniel S. Shin, M.D., Helena Escuin-Ordinas, Ph.D., Willy Hugo, Ph.D., Siwen Hu-Lieskovan, M.D., Ph.D., Davis Y. Torrejon, M.D., Gabriel Abril-Rodriguez, M.Sc., Salemiz Sandoval, Ph.D., Lucas Barthly, M.Sc., Justin Saco, B.S., Blanca Homet Moreno, M.D., Riccardo Mezzadra, M.Sc., Bartosz Chmielowski, M.D., Ph.D., Kathleen Ruchalski, M.D., I. Peter Shintaku, Ph.D., Phillip J. Sanchez, Ph.D., Cristina Puig-Saus, Ph.D., Grace Cherry, R.N., N.P., Elizabeth Seja, B.A., Xiangju Kong, M.Sc., Jia Pang, B.S., Beata Berent-Maoz, Ph.D., Begoña Comin-Anduix, Ph.D., Thomas G. Graeber, Ph.D., Paul C. Tumeh, M.D., Ton N.M. Schumacher, Ph.D., Roger S. Lo, M.D., Ph.D., and Antoni Ribas, M.D., Ph.D.

- Mutations in interferon signaling
- Class I MHC presentation (CD8 T cells)

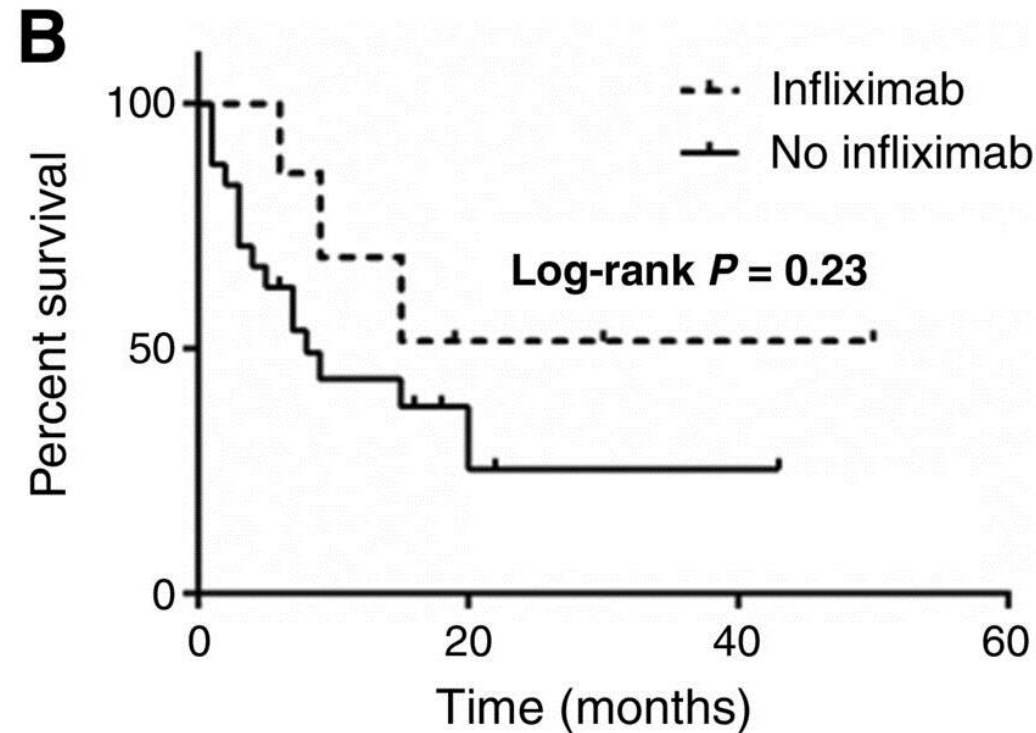
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- Subsequent analyses have confirmed this
- Correlates of efficacy show similar findings
- TNF α does not correlate with response/resistance
- Suggests mechanistic difference between the two immune reactions

Infliximab is associated with a trend toward increased survival in patients with ipilimumab associated diarrhea



Eduar Arriola et al. Clin Cancer Res 2015;21:5642-5643

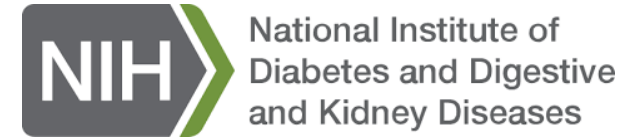
Resistance to infliximab

- We have seen this very rarely at MGH
 - The question is not addressed adequately in the literature
- Most cases appear to be infectious (C Diff >> CMV, aspergillus)
 - We always rescope, and obtain biopsies
- Where infections are rigorously excluded and colitis is still macroscopically severe other options include:
 - bowel rest (TPN)
 - vedolizumab (integrin inhibitor)
 - CTLA-4-Ig
 - Surgery

Next steps

- Mechanistic studies focusing on the immune mechanisms of colonic inflammation
 - Identify new targets
 - Understand the relationship to antitumor response
- Trials of novel therapeutic strategies
 - Integrin inhibitors
 - Anti-cytokine therapies
- Endoscopy/pathology based treatment guidelines
 - Drug specific?

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- **Lee Kaplan**

Novartis

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