Gastrointestinal Toxicities of Checkpoint Blockade

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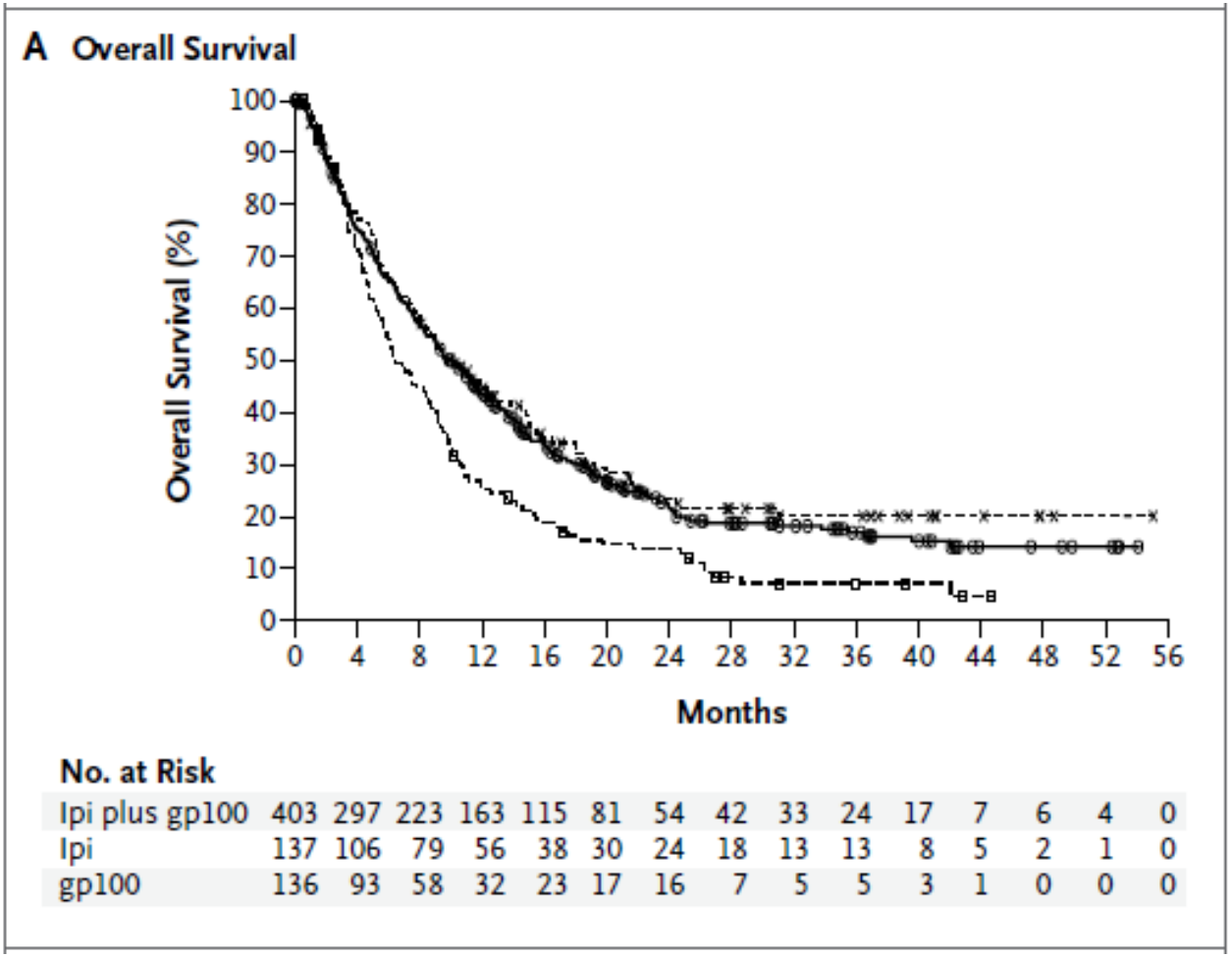
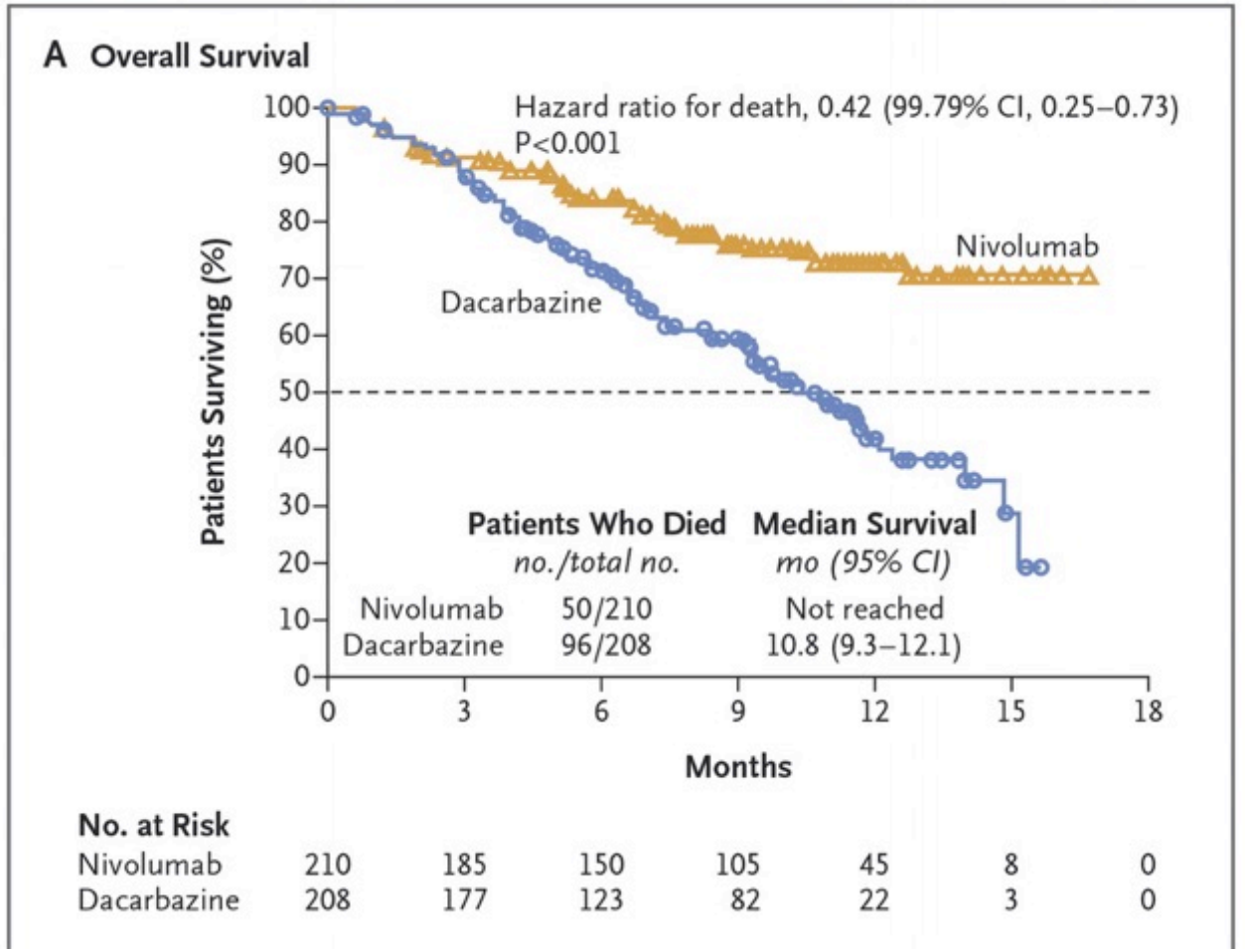
Disclosures

- Novartis Pharmaceutics
- Tocagen

- I will be talking about non FDA approved indications for infliximab (and other anti-TNF medications), and vedolizumab

Immune therapy for melanoma is highly effective





Current metastatic melanoma 3-yr survival is now 40% (compared to <5% before 2011)

Hodi et al. NEJM. 2011; Robert et al. NEJM. 2015.

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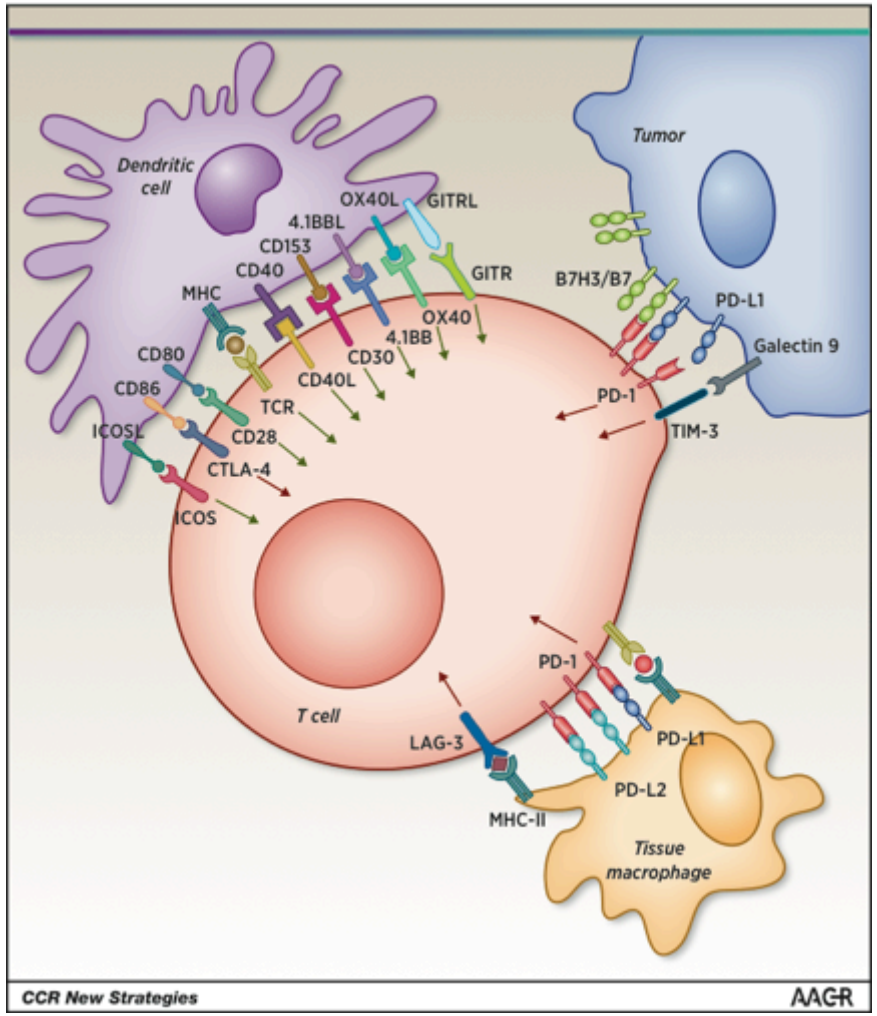
Immune therapy for cancer

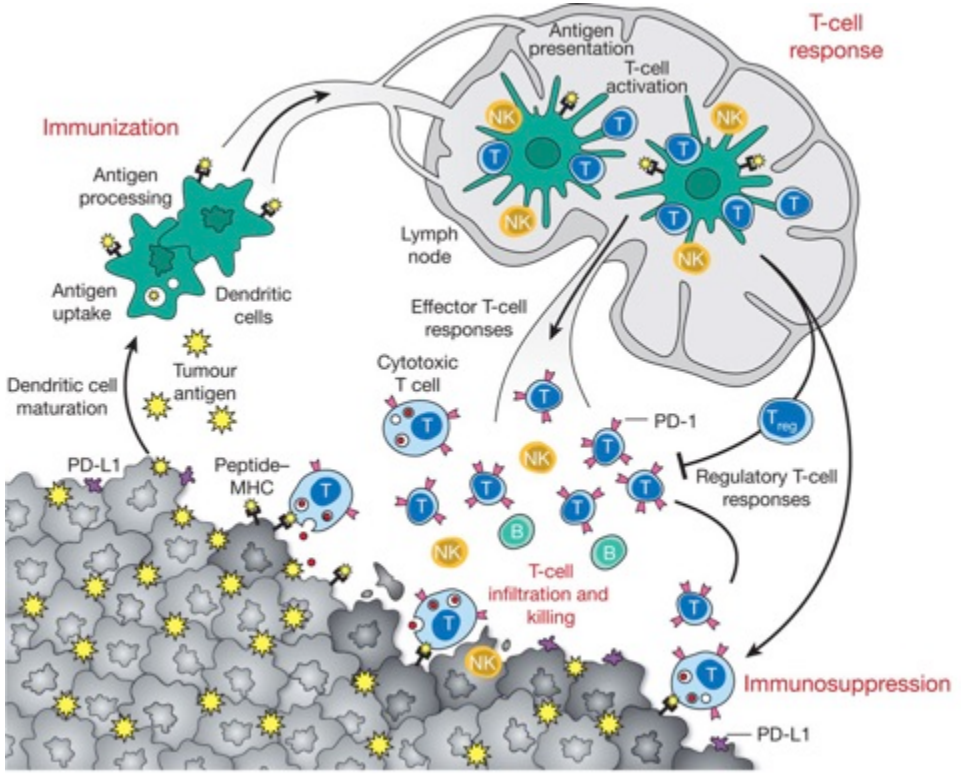


- Developing tumors are recognized by adaptive immunity (e.g. mutated tumor proteins)
- Regulatory pathways (PD1/PDL1, CTLA-4) inhibit nascent antitumor responses
- Blockade of regulatory “checkpoints” has proven highly effective at activating adaptive responses against diverse malignancies
- Current treatments are only effective in a minority of patients with cancer

Sullivan and Flaherty. Clin Cancer Res. 2015

Expanding the reach of immunotherapy

- Diagnostics to monitor/predict response
- Combination and tumor directed immune therapies
- Modulation of innate immunity
- Prediction and management of immune-related adverse events (irAEs)



Mellamn, Coukos & Dranoff. Nature. 2011

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Expanding the reach of immunotherapy

- Diagnostics to monitor/predict response
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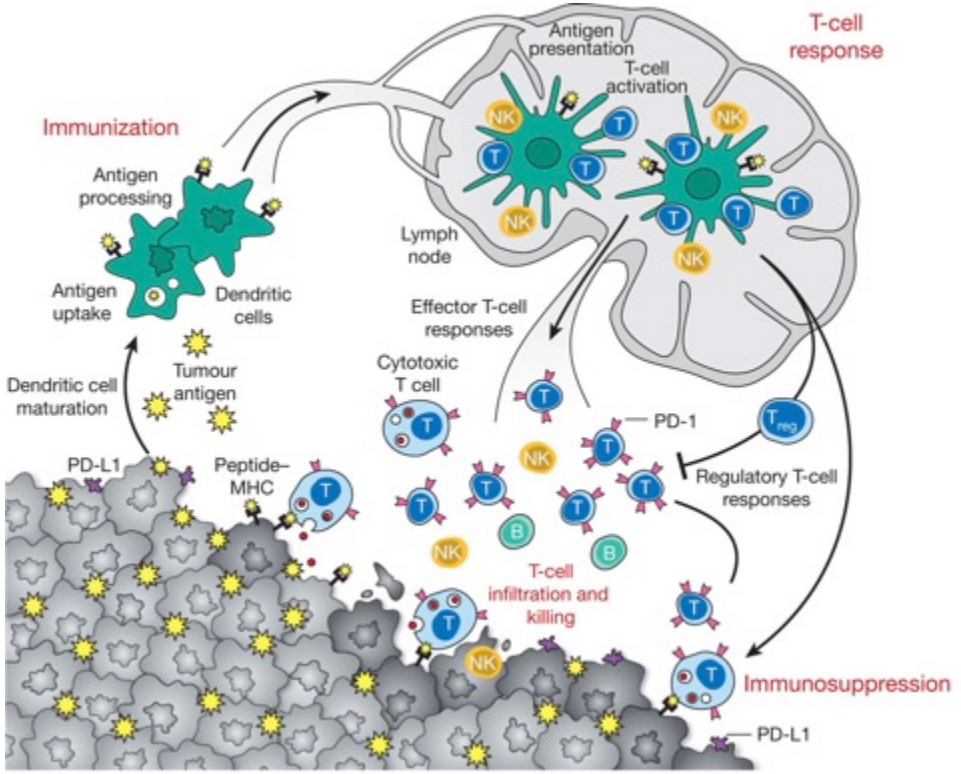
- **Prediction and management of immune-related adverse events (irAEs)**



Mellamn, Coukos & Dranoff. Nature. 2011

Immune-related adverse events 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

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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

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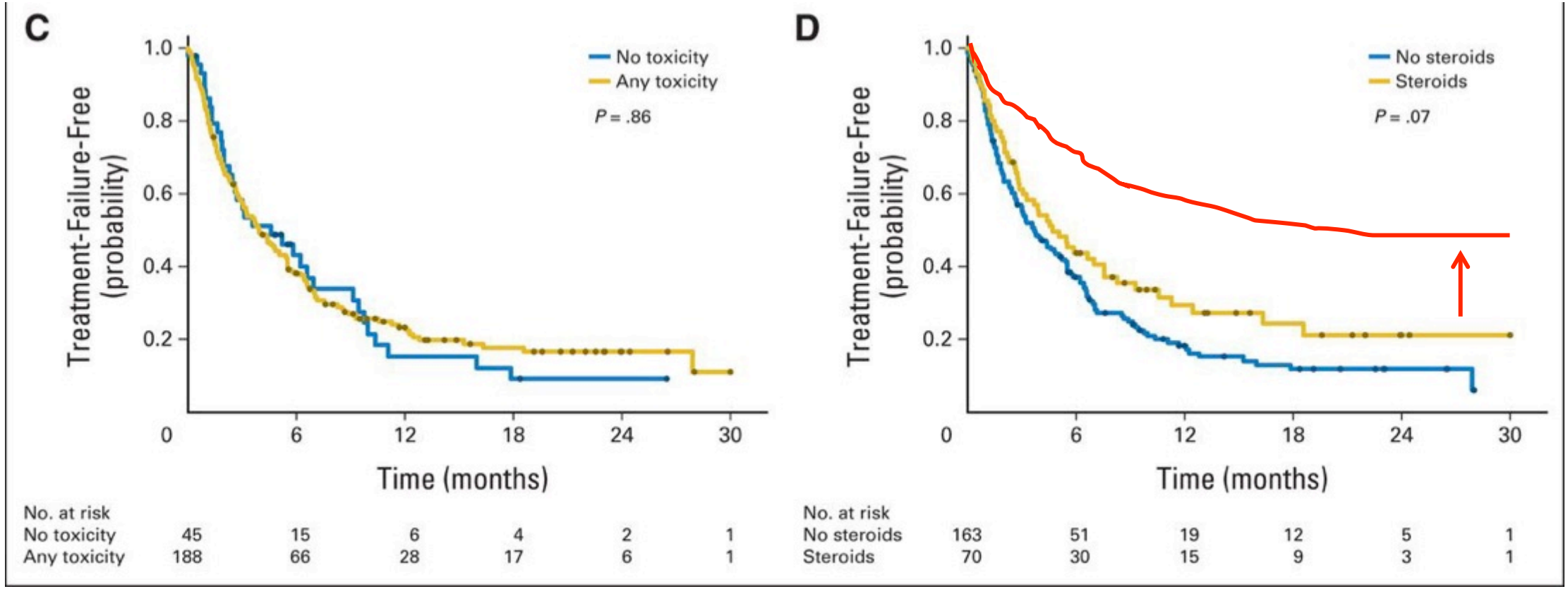
Is it important to avoid steroids?



Horvat et al. JCO. 2009. 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?

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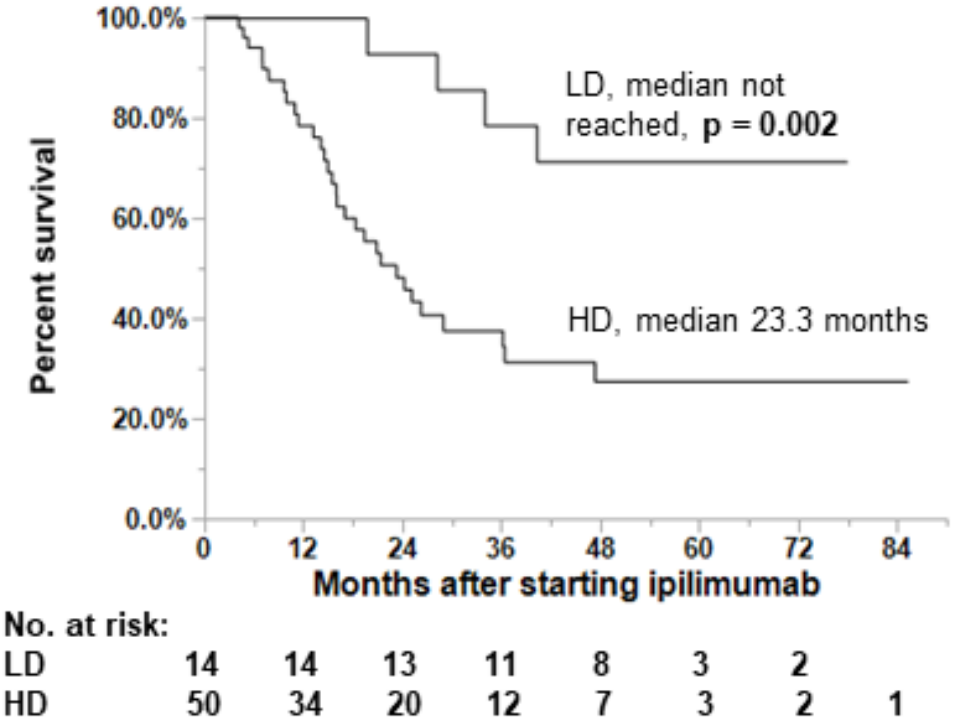
MGH data suggests steroids inhibit the antitumor response

Metastatic melanoma treated with ipilimumab
All patients in the analysis developed hypophysitis

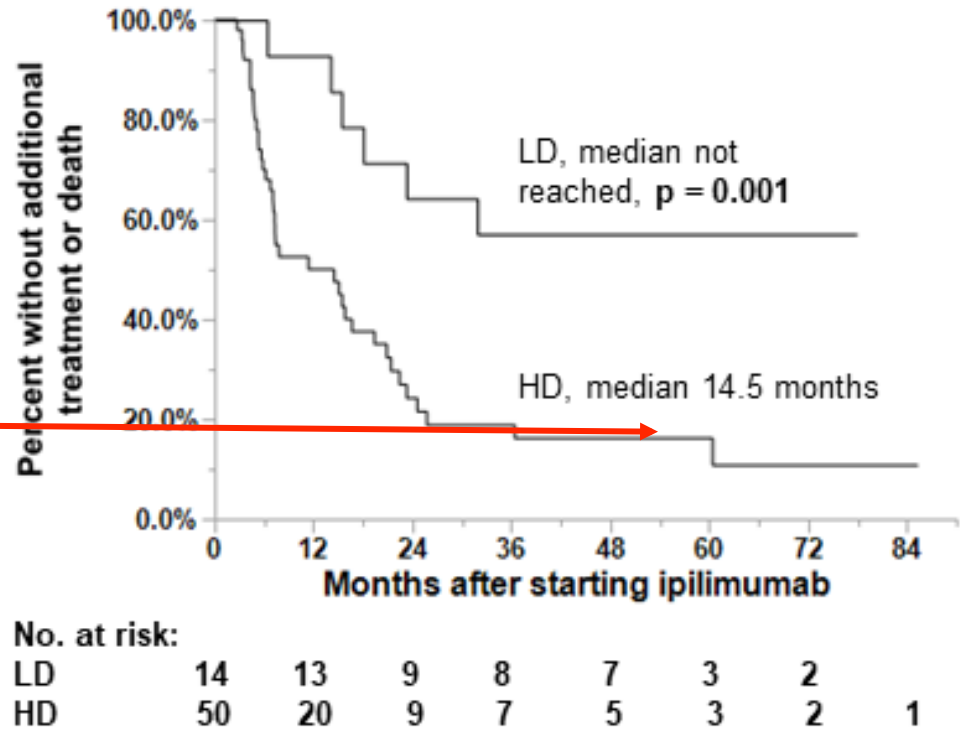
overall survival

A)



Time to treatment failure

B)



Similar to average ipilimumab response

Alexander Faje, Cancer, 2018

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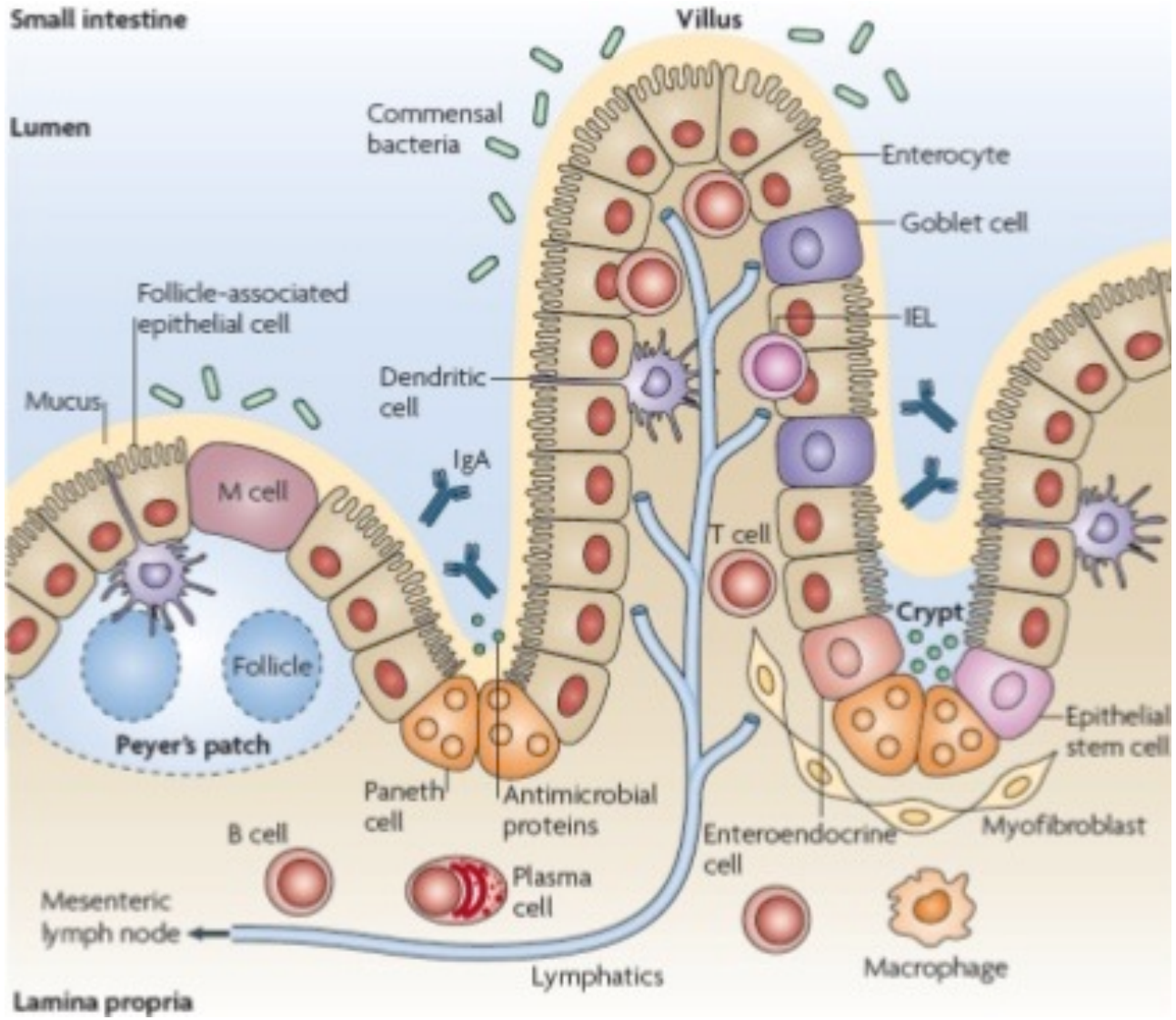
The gut is a complex barrier



Abreu et al. Nat. Rev. Imm. 2010

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

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

(Entero)colitis
Hepatitis
Pancreatitis

	Ipilimumab	αPD-1[a]	αPD-L1[b]	Ipilimumab + αPD-1
Common toxicities of checkpoint blockade (all grades)				
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 (GI)				
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
Musculoskeletal				
Arthalgia	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

Dougan M. *Frontiers in Immunology*. 2017.

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And some rare ones…

Gastritis
Cholangitis
Celiac

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The spectrum is dependent on the pathway targeted

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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?

Enterocolitis

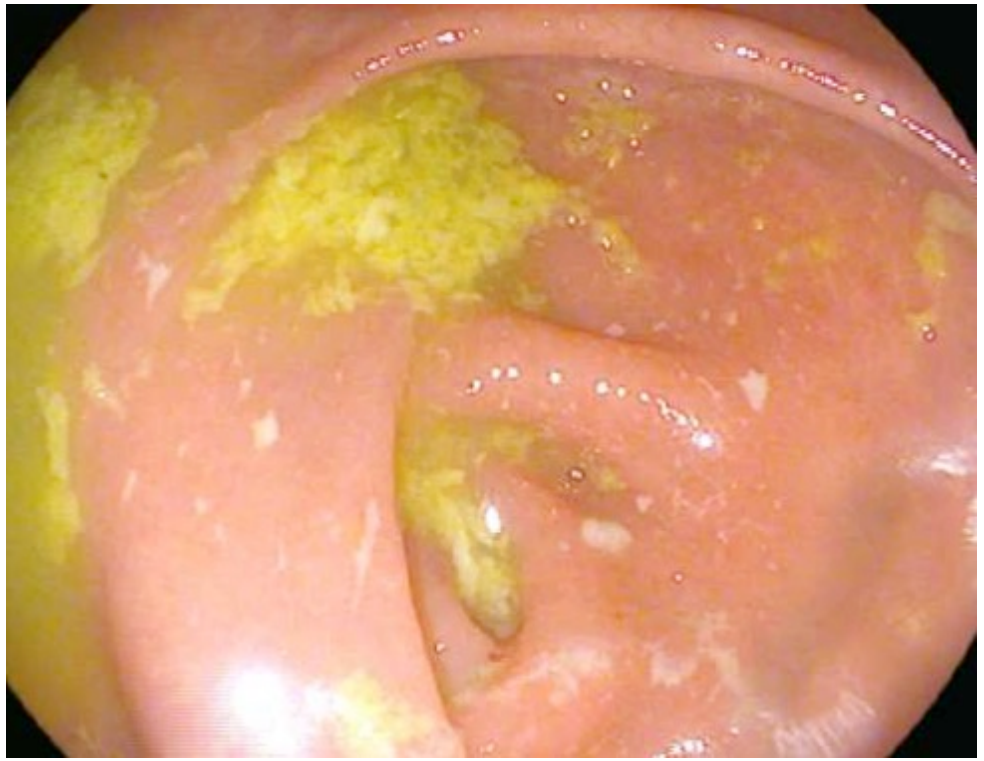
- Enterocolitis is by far the most common GI toxicity from current checkpoint blocking antibodies
- Range of severity (many patients have indolent disease)
- Likely responsible for most treatment related diarrhea
- Often isolated to the colon, but can involve the GI tract from stomach to rectum

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

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Clinical Features

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Colitis

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

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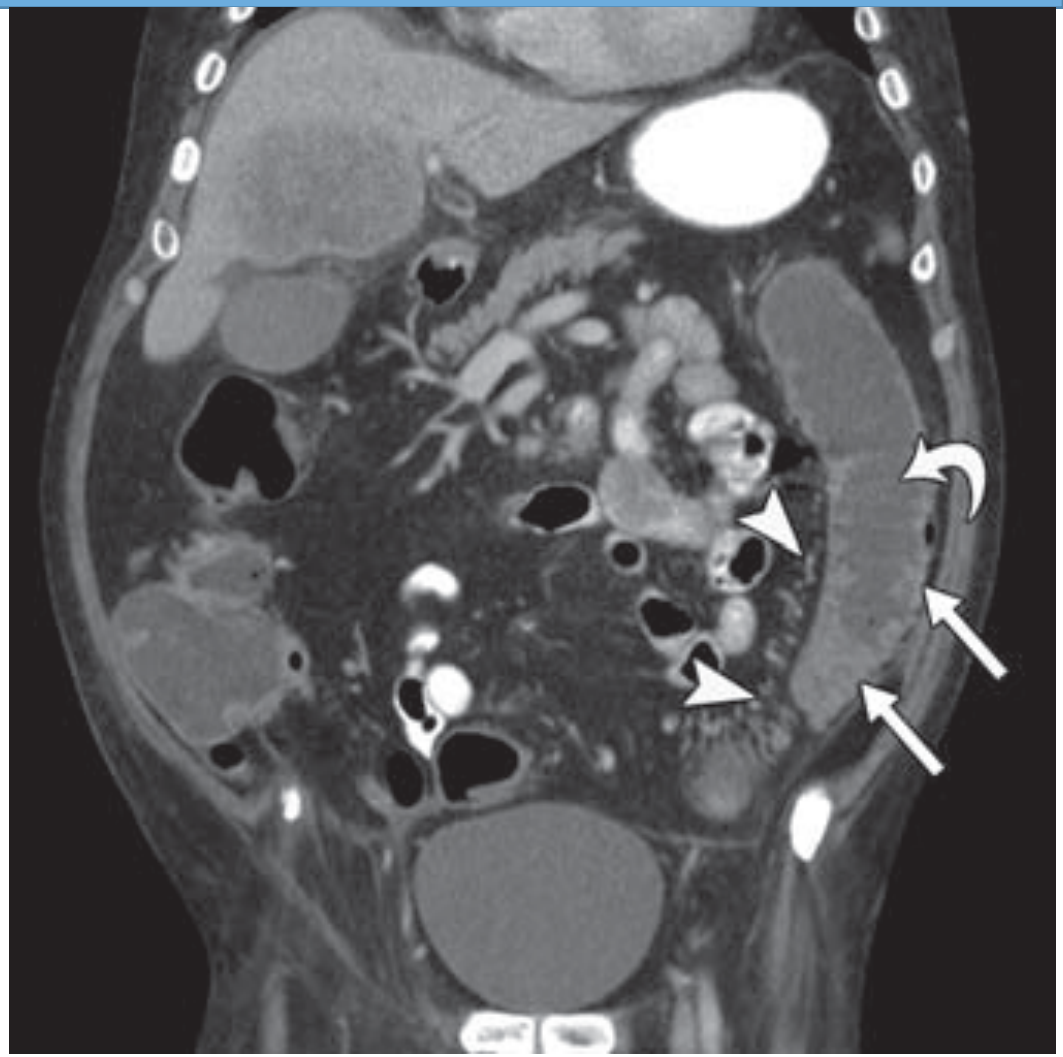
Initial workup of checkpoint blockade induced enterocolitis

- 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.

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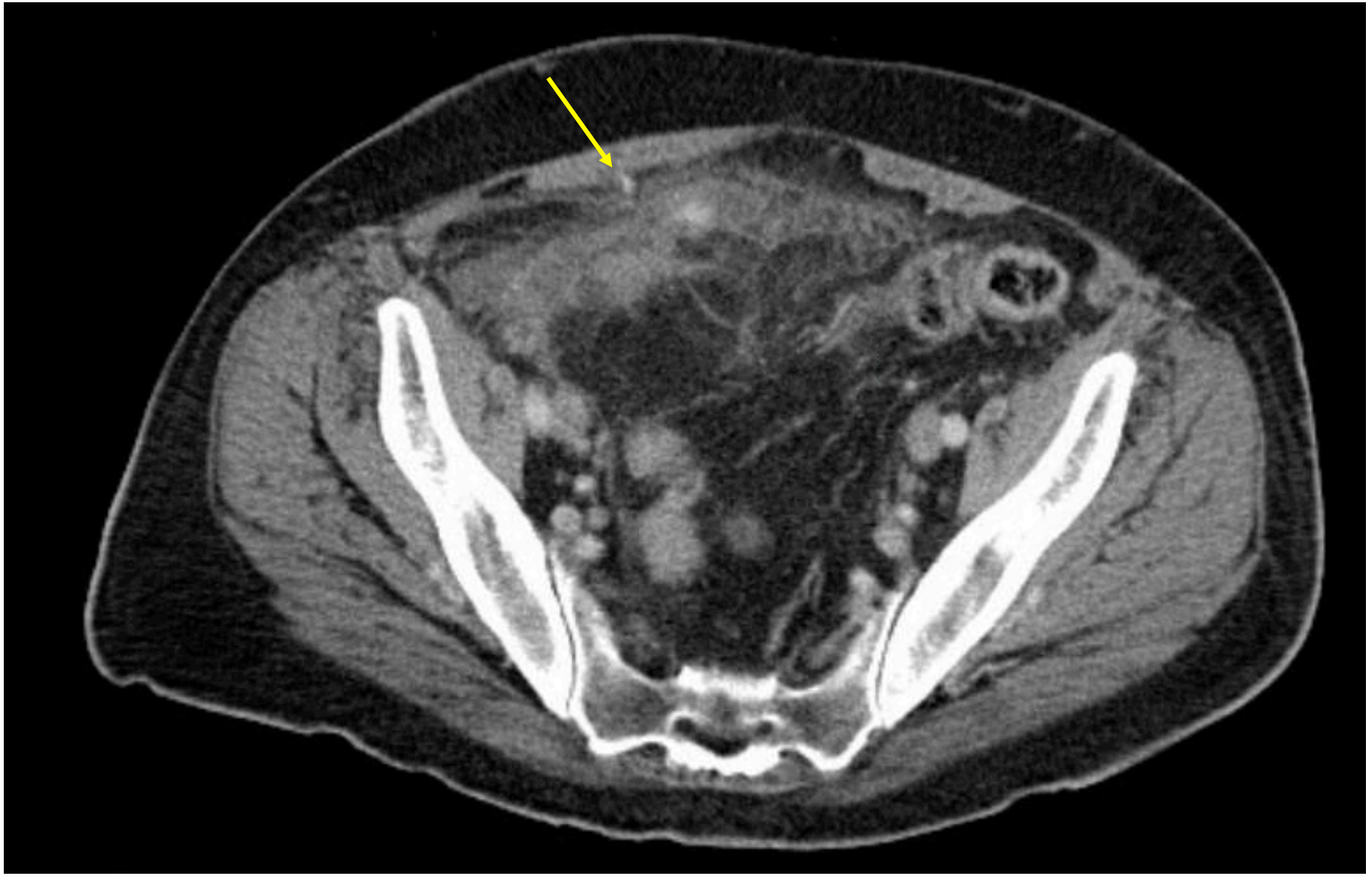
PD-1 blockade in Crohn's

- 74 yoM w/ quiescent Crohn's and metastatic sarcoma on nivolumab
- Asymptomatic off medication for many years
- two weeks after starting PD-1 blockade p/w severe abdominal pain

Checkpoint blockade can cause IBD reactivation



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Checkpoint blockade can cause IBD reactivation

- Received steroids and antibiotics
- Nivolumab held
- Underwent ileocecal resection with no further complications

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%)
- I have seen several of these patients and they tend to be more difficult to treat

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PD-1 blockade may have less of an effect on IBD

Safety of Programmed Death–1 Pathway Inhibitors Among Patients With Non–Small-Cell Lung Cancer and Preexisting Autoimmune Disorders

Giulia C. Leonardi, Justin F. Gainor, Mehmet Altan, Sasha Kravets, Suzanne E. Dahlberg, Lydia Gedmintas, Roxana Azimi, Hira Rizvi, Jonathan W. Riess, Matthew D. Hellmann, and Mark M. Awad

- Two retrospective studies comprising 12 patients with UC or Crohn's treated with PD-1/PD-L1

- Few patient details in the study, but all had minimal/no evidence of ongoing disease

- None flared while on PD-1 blockade, but they had a higher incidence of unrelated irAEs

Menzies et al. Ann. Oncol. 2017; Leonardi et al. JCO. 2018

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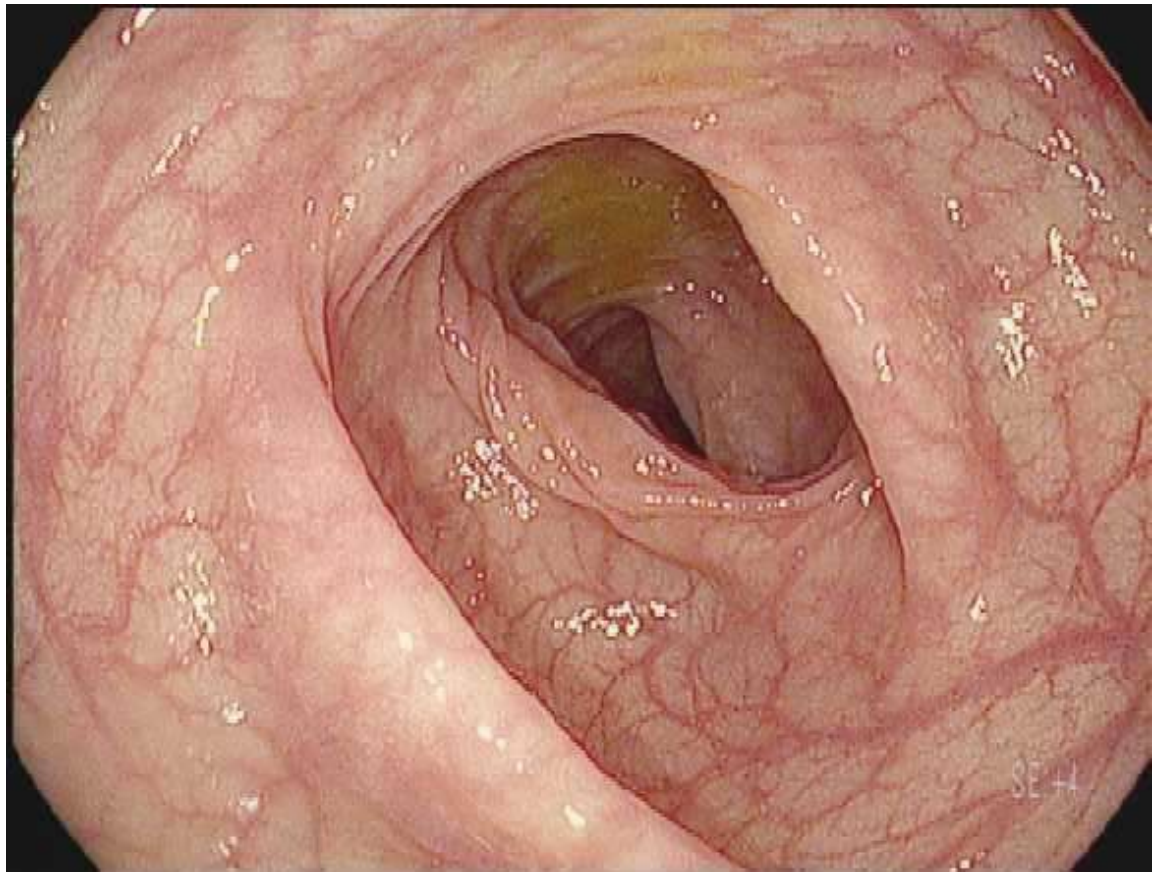
Endoscopic Appearance

Colitis

Normal



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Who needs to undergo endoscopy

- 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
- Diarrhea on investigational combinations, or other drugs that cause diarrhea

Extent of disease: UC type pattern

Dougan M. *Frontiers in Immunology*. 2017.

- Typically a pan-colitis
- 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.

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Crohns type disease does occur

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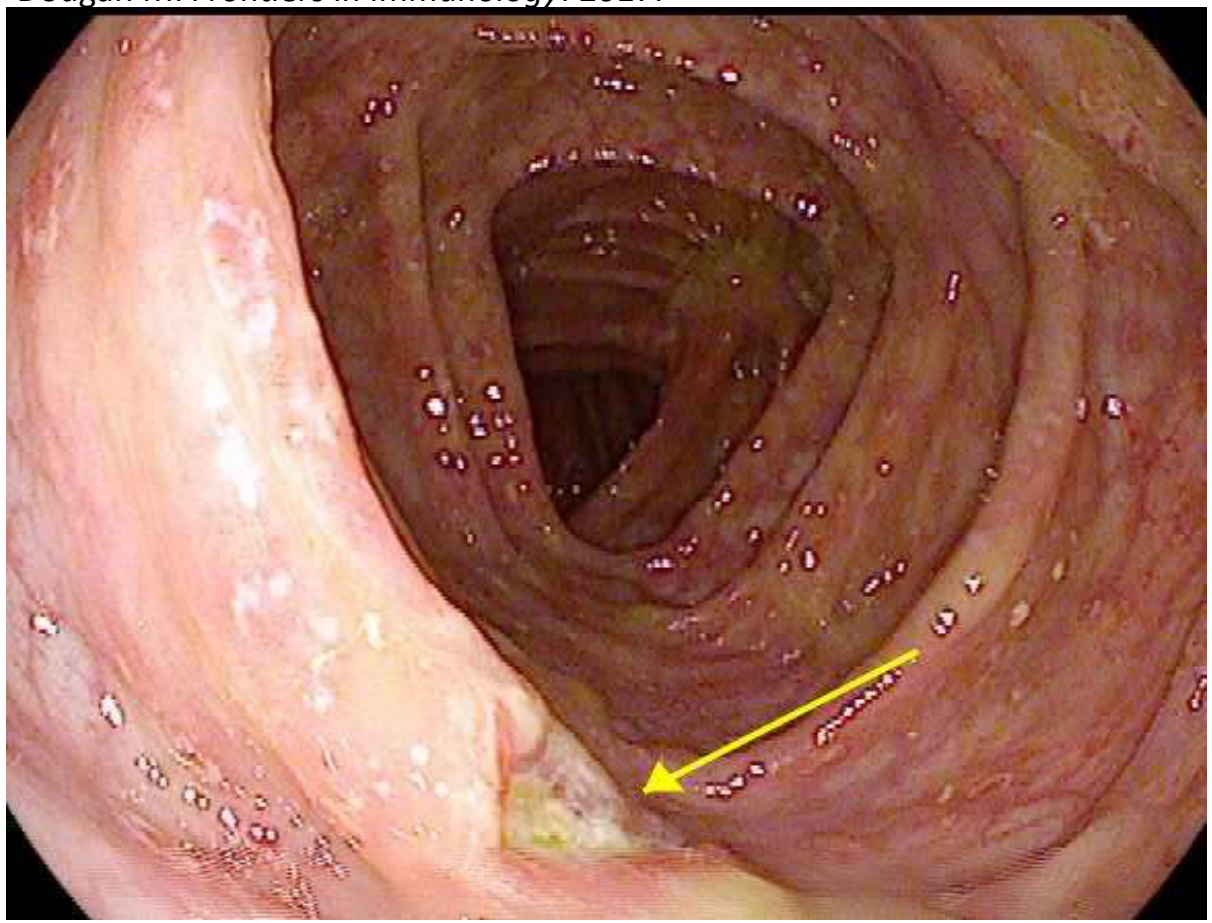

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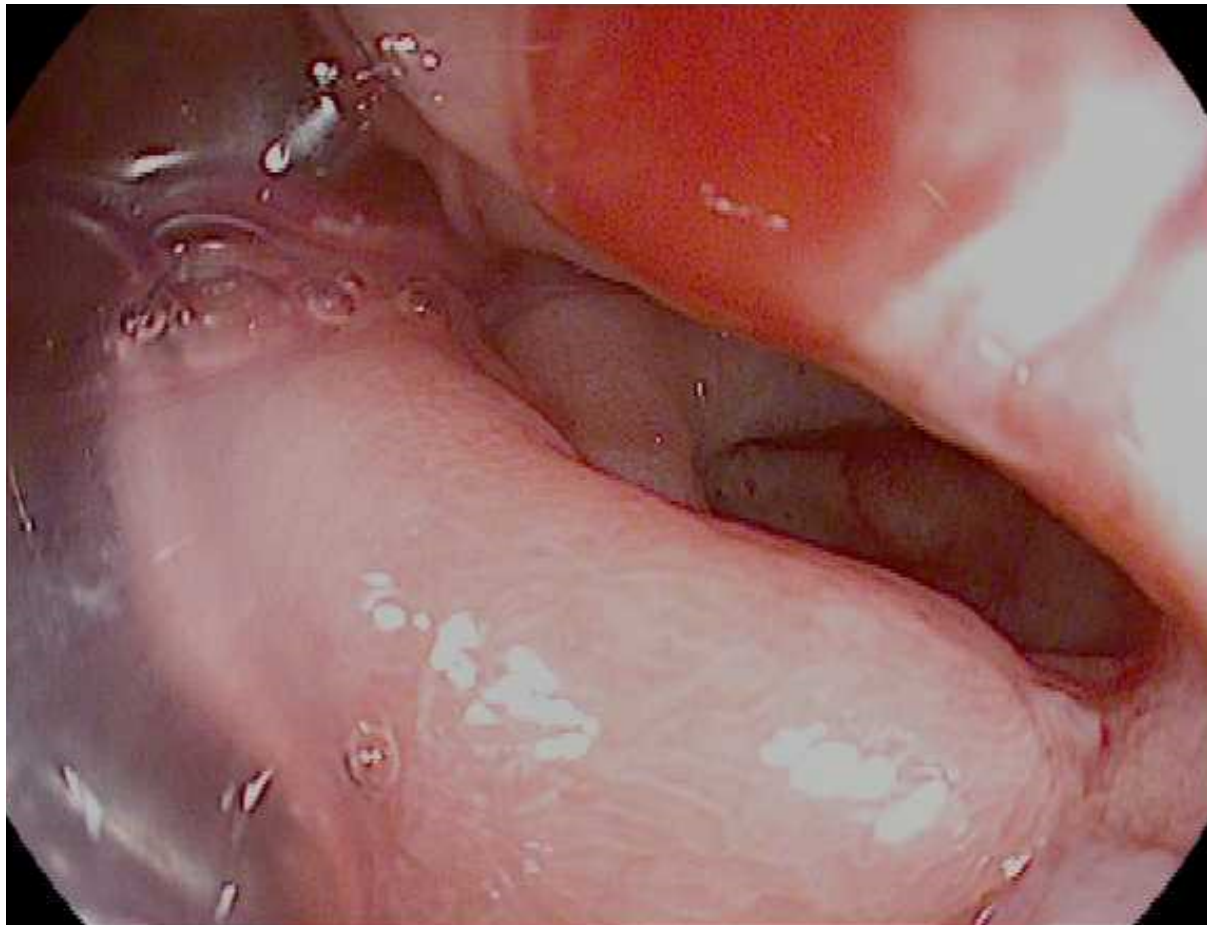
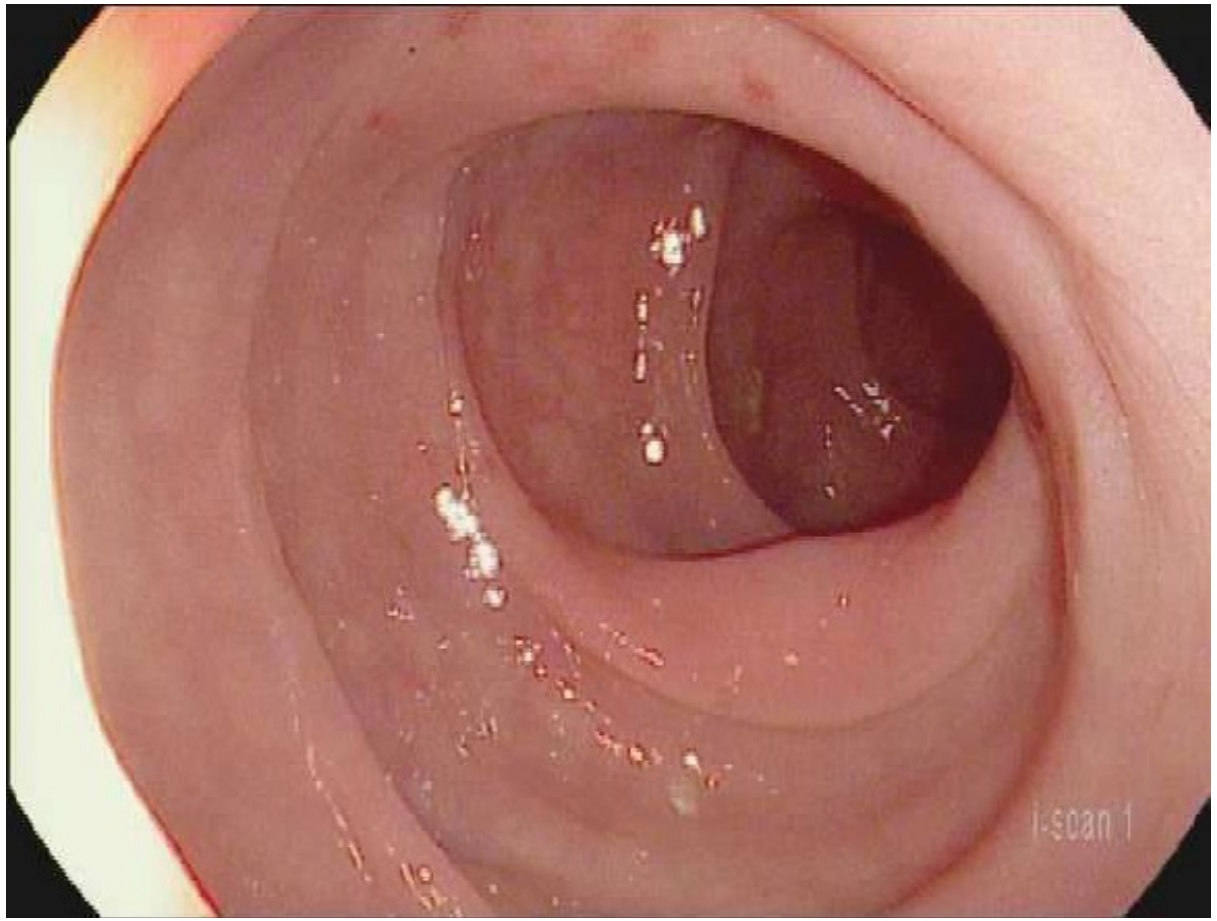
Crohns type disease does occur



- Nivolumab (13 months)
  - previously treated with ipilimumab/nivolumab, and BRAF/MEKi
- Rare (on the order of 1%)
- This patient was treated with infliximab and a duodenal stent

Microscopic colitis



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- Can be high grade based on diarrhea criteria
- Responds to budesonide
- Does not require discontinuation of checkpoint blockade
- More common with anti-PD-1

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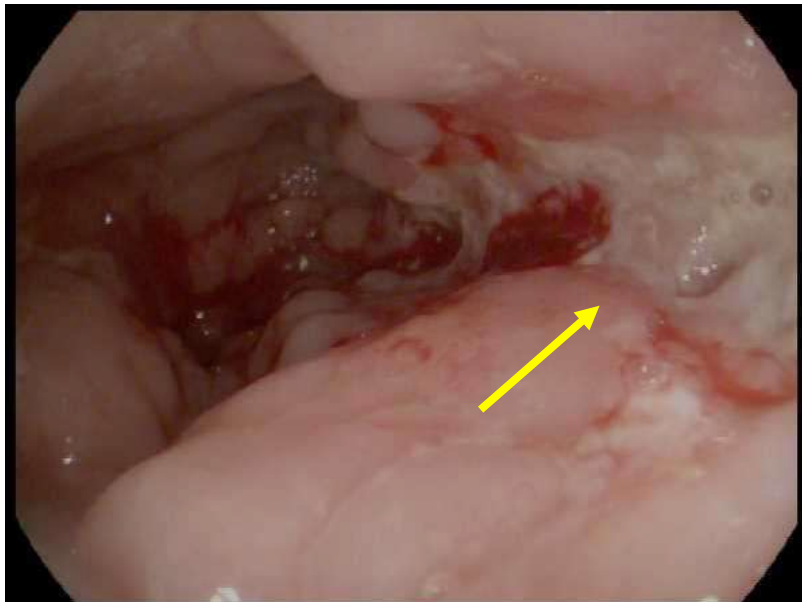
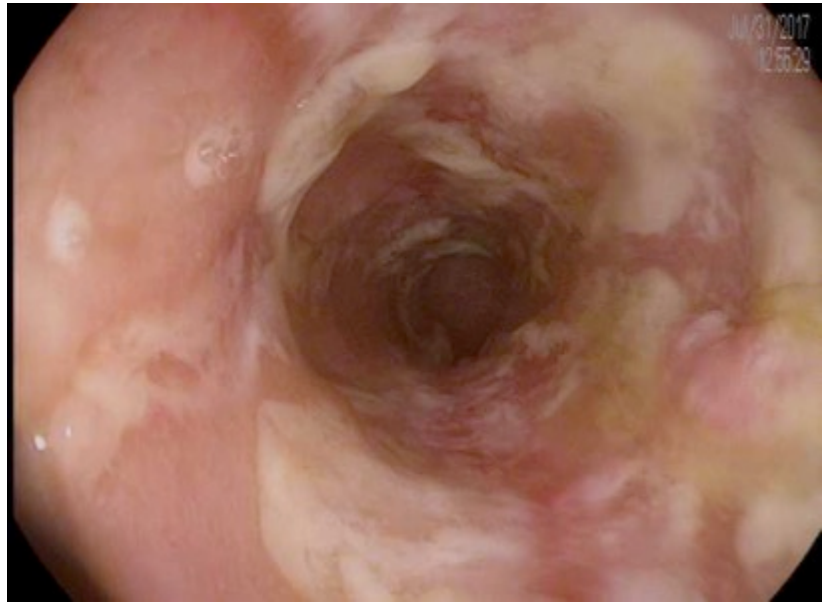
How similar is checkpoint colitis to IBD?

Crohn's Disease



Ulcerative Colitis



Checkpoint Colitis

- Typically a pan colitis (more similar to UC)
- Deep ulcers and strictures are rare
- Fistulas don't seem to occur
- Typically a monophasic course

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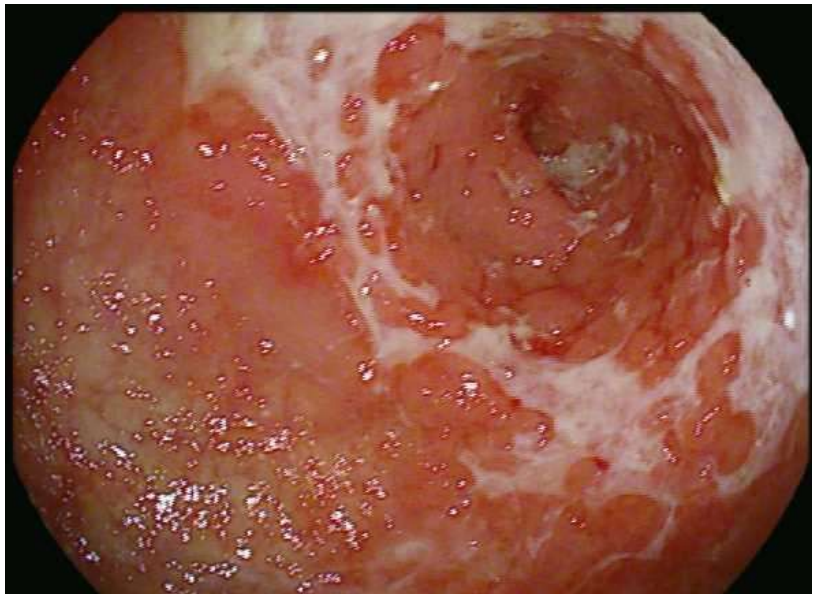
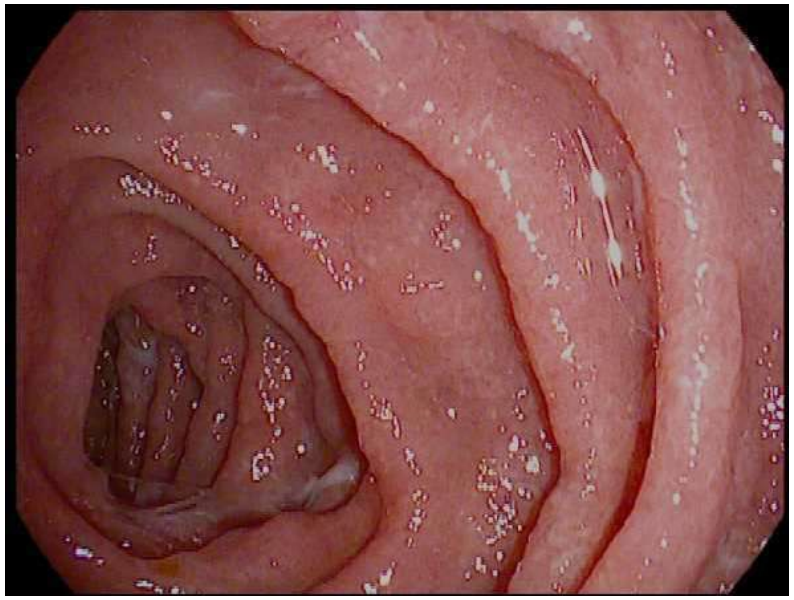
Upper GI manifestations would be rare in IBD

Gastritis



Enteritis (duodenum)



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- 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

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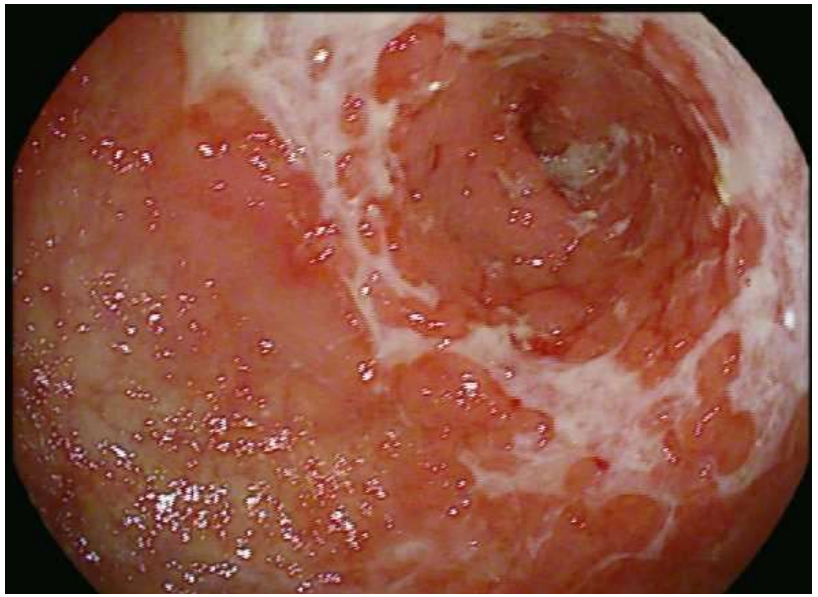
Checkpoint induced Celiac Disease

Gastritis



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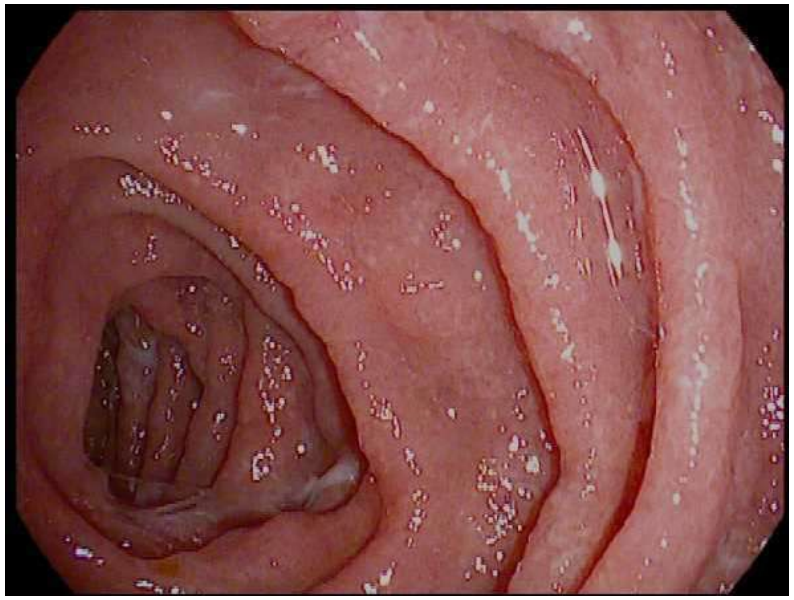
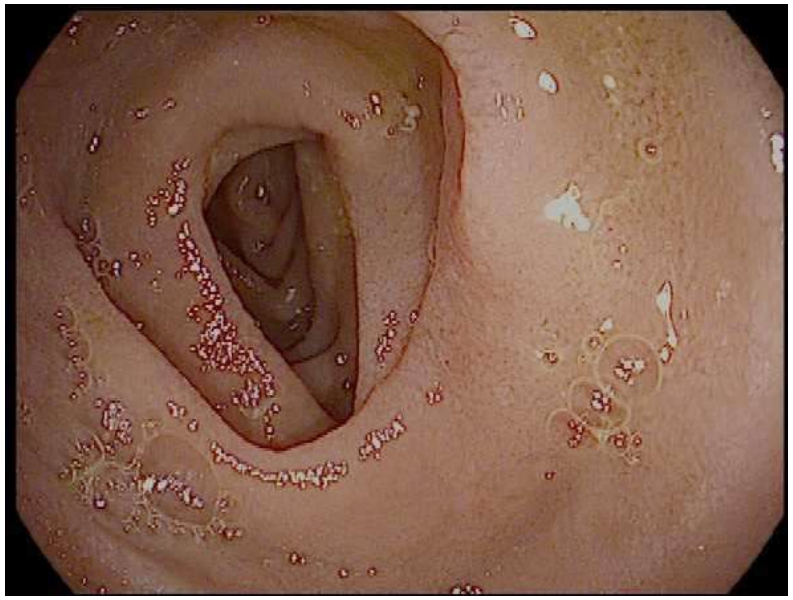


Celiac



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- Approximately 5% of cases of immunotherapy induced diarrhea
- Responds to a gluten free diet
- Variable response to steroids
- May be (partially) reversible

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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

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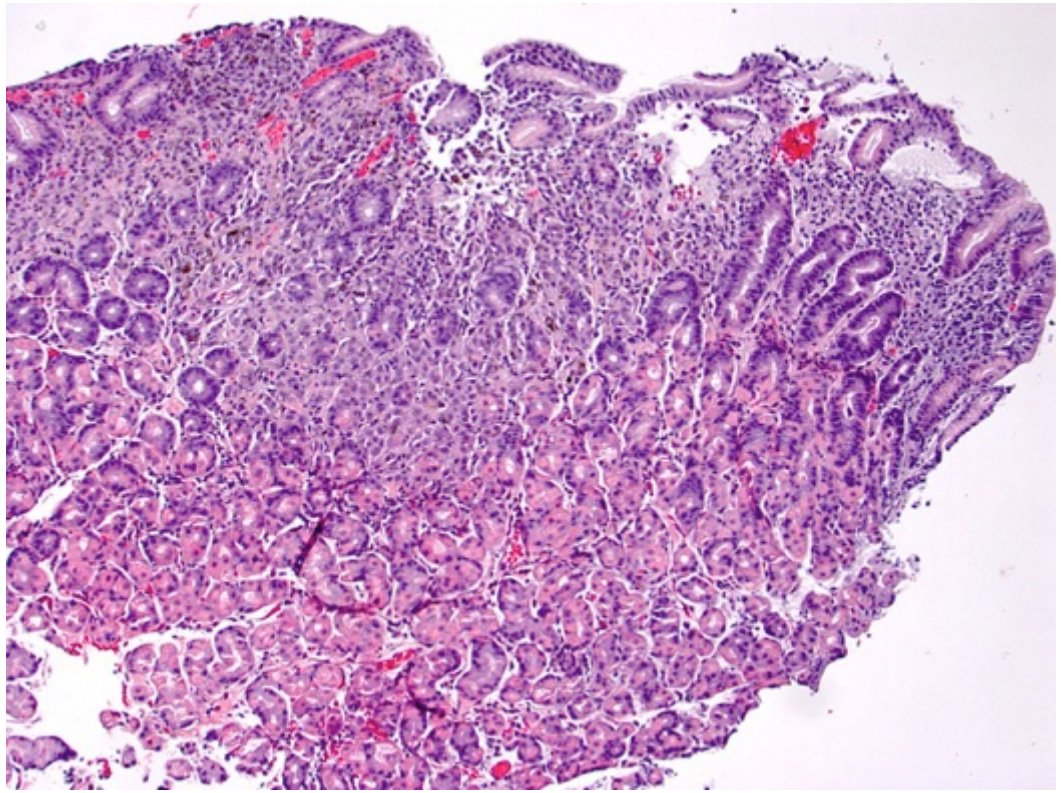
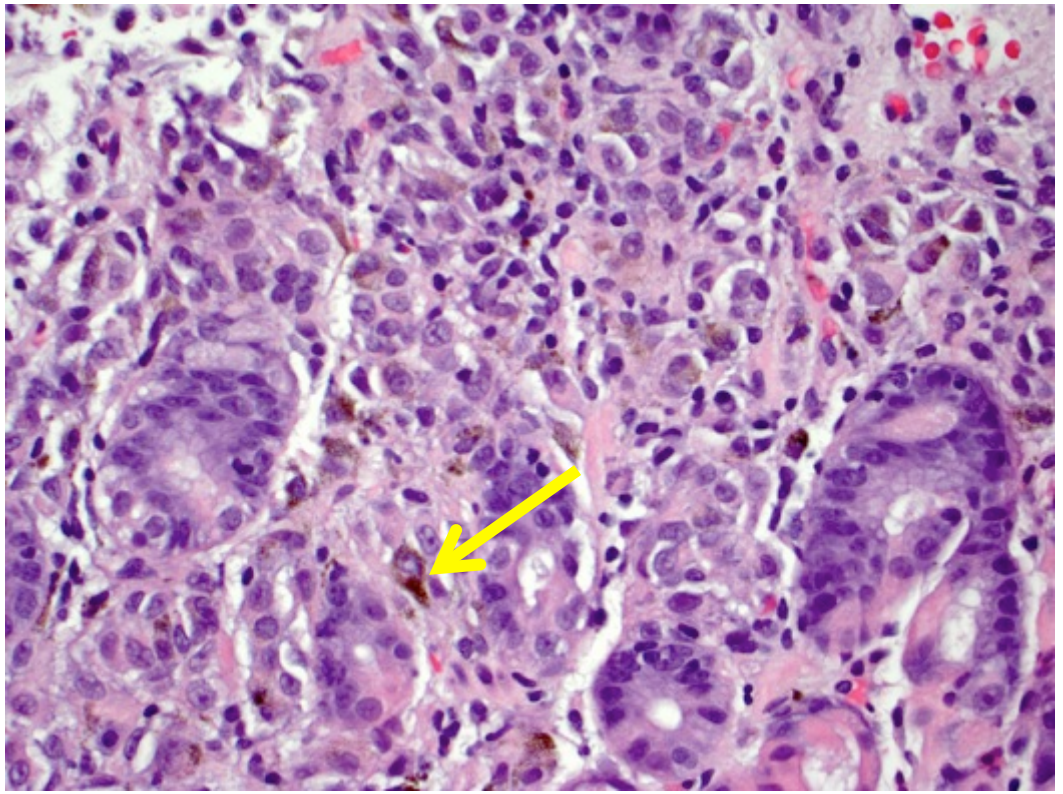
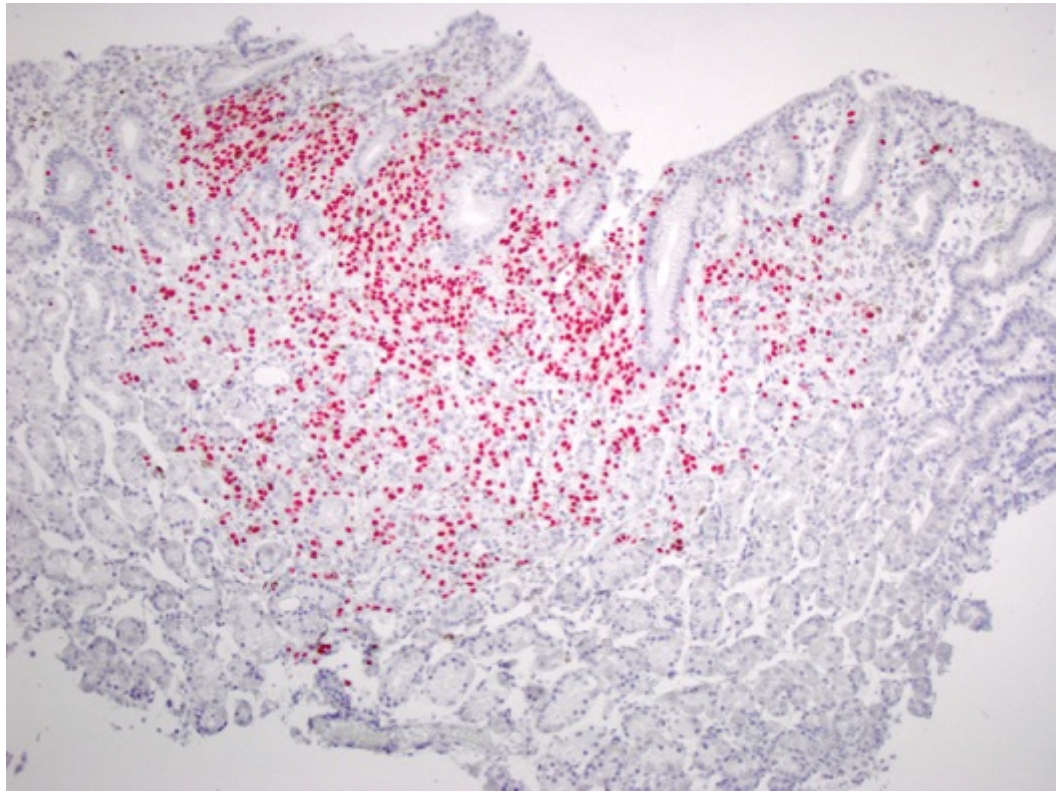
Pathology



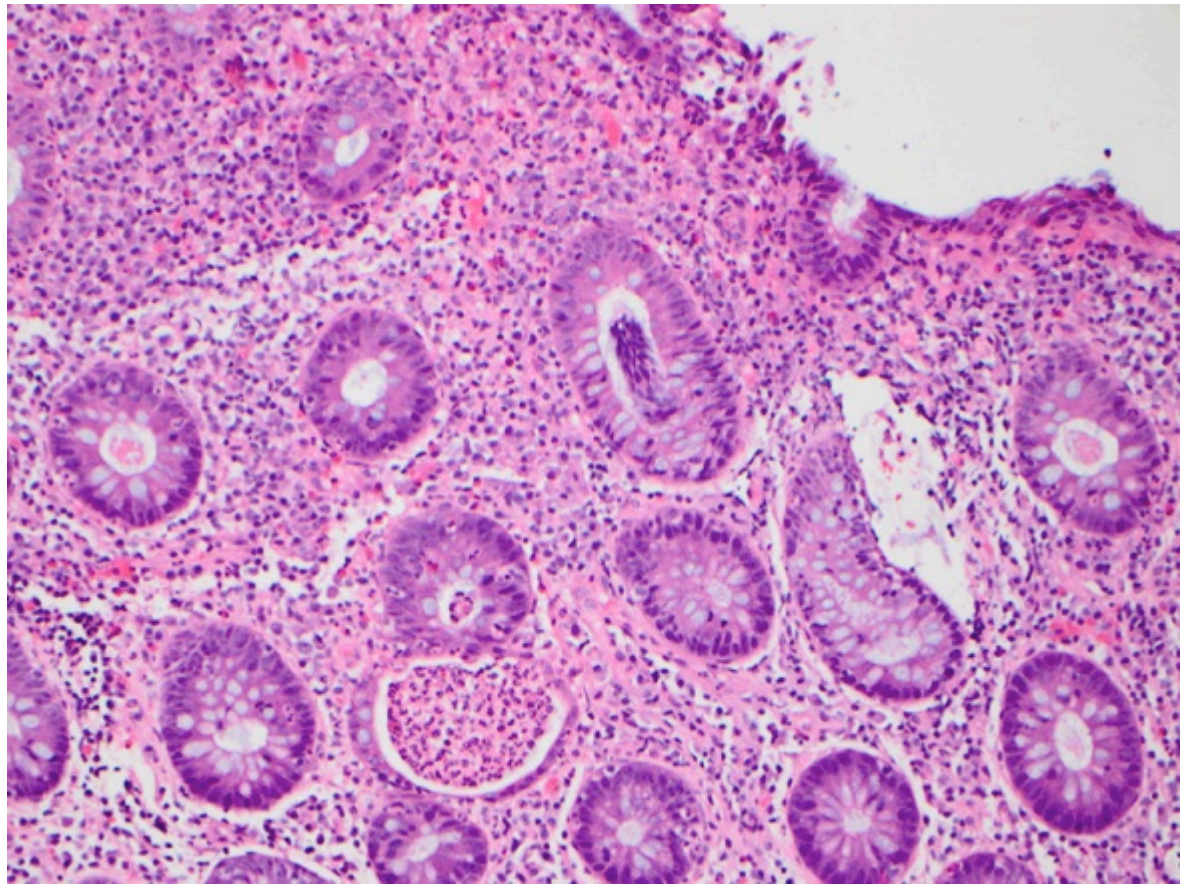
melanocytes



S100 positive: melanoma



Histology of Typical Checkpoint Colitis



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

Treatment of grade 3/4 checkpoint 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)
  - MGH and other recent experience closer to 50% inadequate response
  - PD-1 blockade may be more likely to be refractory

- No rigorous studies of steroid dose
  - 1-2 mg/kg IV solumedrol, 40-60 mg oral prednisone

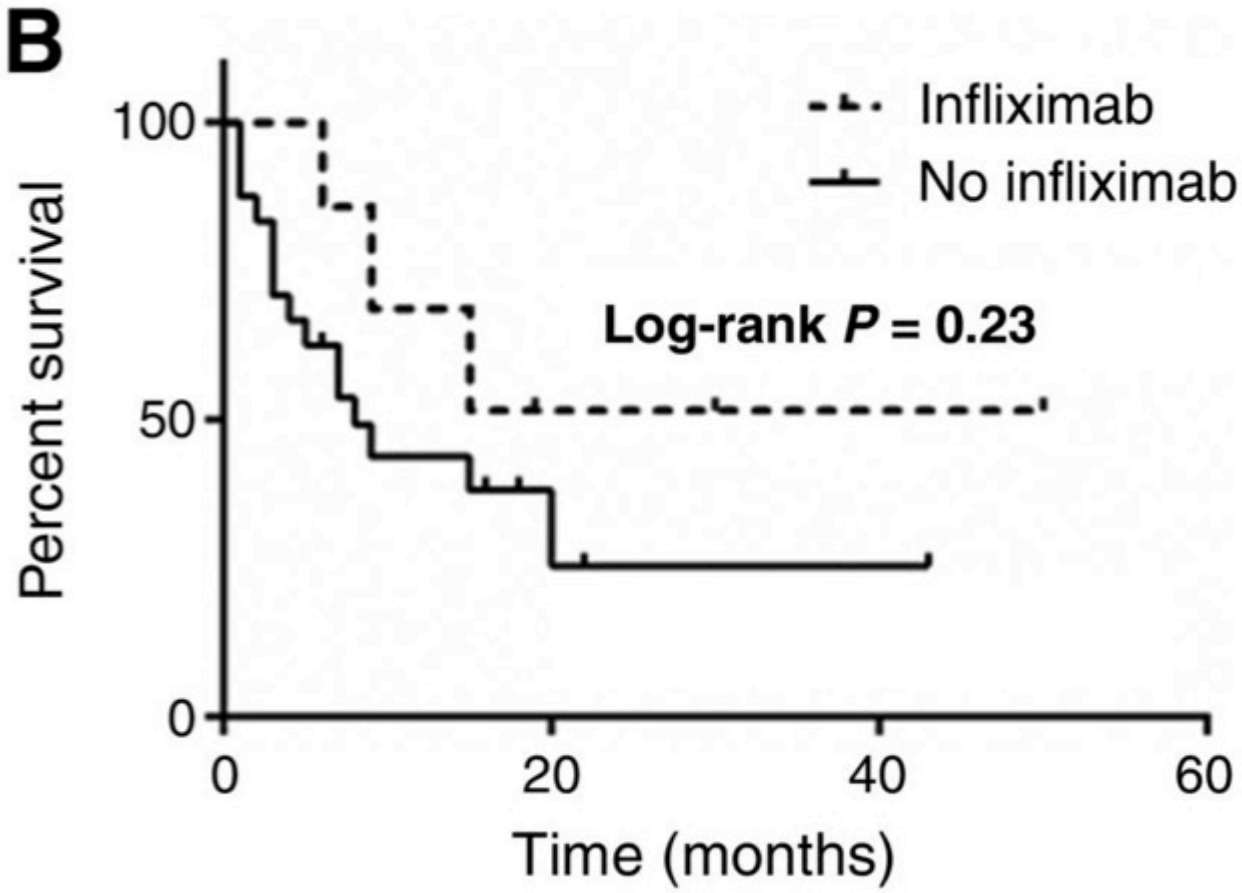
TNFα is a key mediator of checkpoint colitis

- Infliximab is highly effective in steroid refractory disease
  - Several small cases series (Beck et al. JCO. 2006), multiple other reports, incorporated into all guidelines

- Indications for infliximab
  - No/minimal response to steroids after 2-3 days
  - Recurrence on steroid taper
  - Colonic ulcers on endoscopy (?)

- Responses typically occur within days (1-3 doses)
  - PD-1 blockade colitis is more likely to be refractory

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



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

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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
  - Microbiome (?)

- Endoscopy/pathology based treatment guidelines
  - Drug specific?

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