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Society for Immunotherapy of Cancer

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Gastrointestinal Toxicities of Checkpoint Blockade

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Disclosures

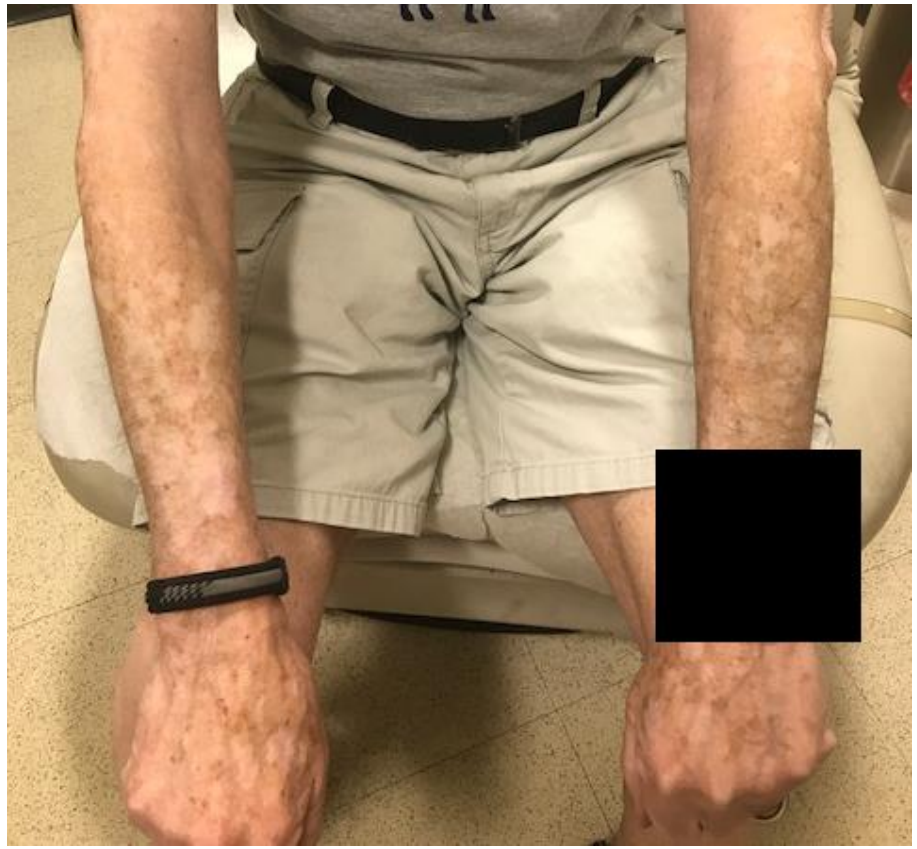
- I have several research/financial ties to Novartis Pharmaceutics, and have been a consultant for Tillots, Partners Therapeutics, and Genentech

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

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



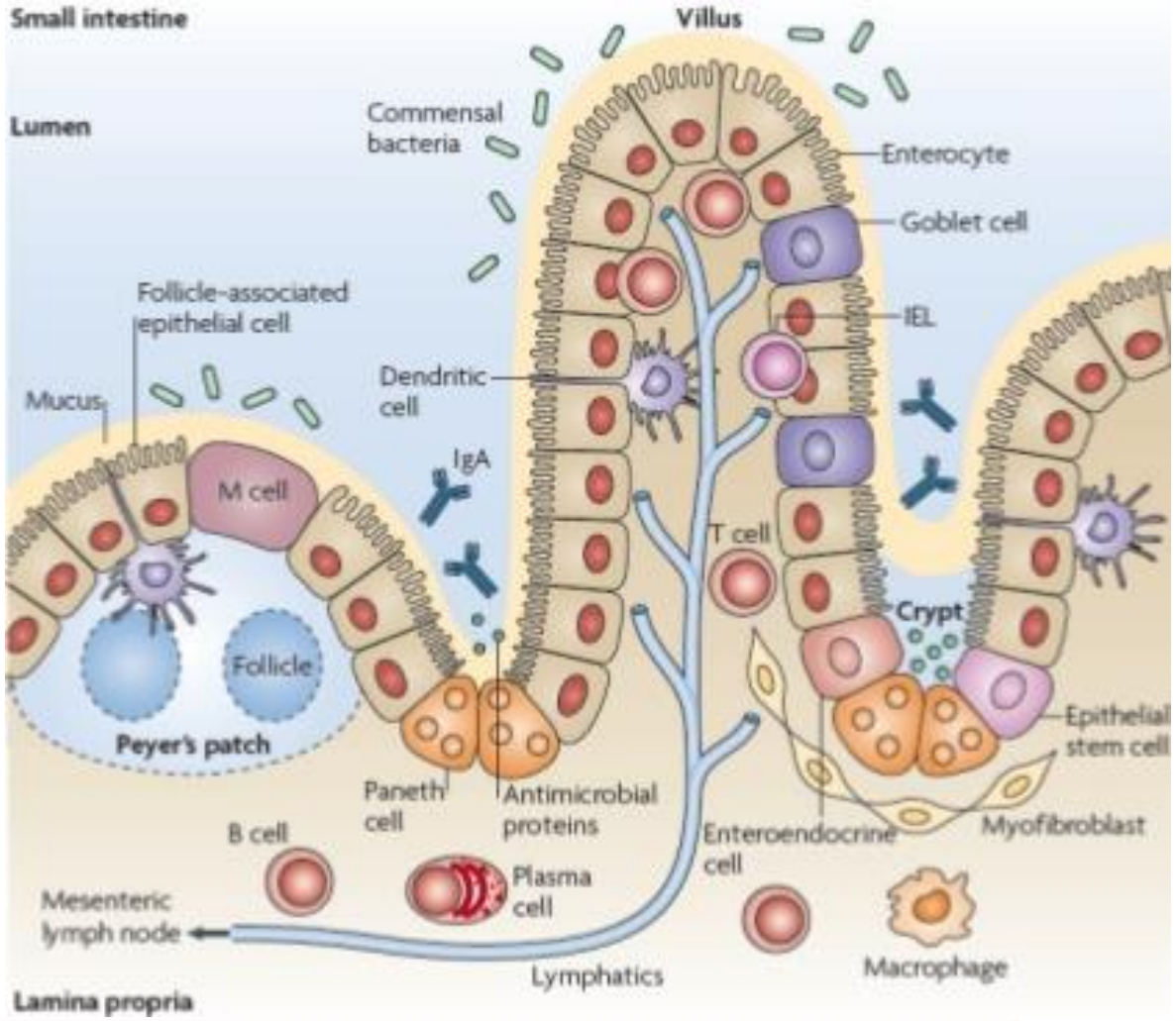
Immune-related adverse events are not just “side effects”

- 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

- Few irAEs are seen in animals models

The gut is the most immunologically complex barrier in the body



Careful immune regulation is essential

- Dietary proteins
- Commensal bacteria
- Pathogenic microorganisms
- Toxins

Abreu et al. Nat. Rev. Imm. 2010

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

	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

(Entero)colitis
Hepatitis
Pancreatitis

Dougan M. *Frontiers in Immunology*. 2017.

The spectrum is dependent on the pathway targeted

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Pulmonary				
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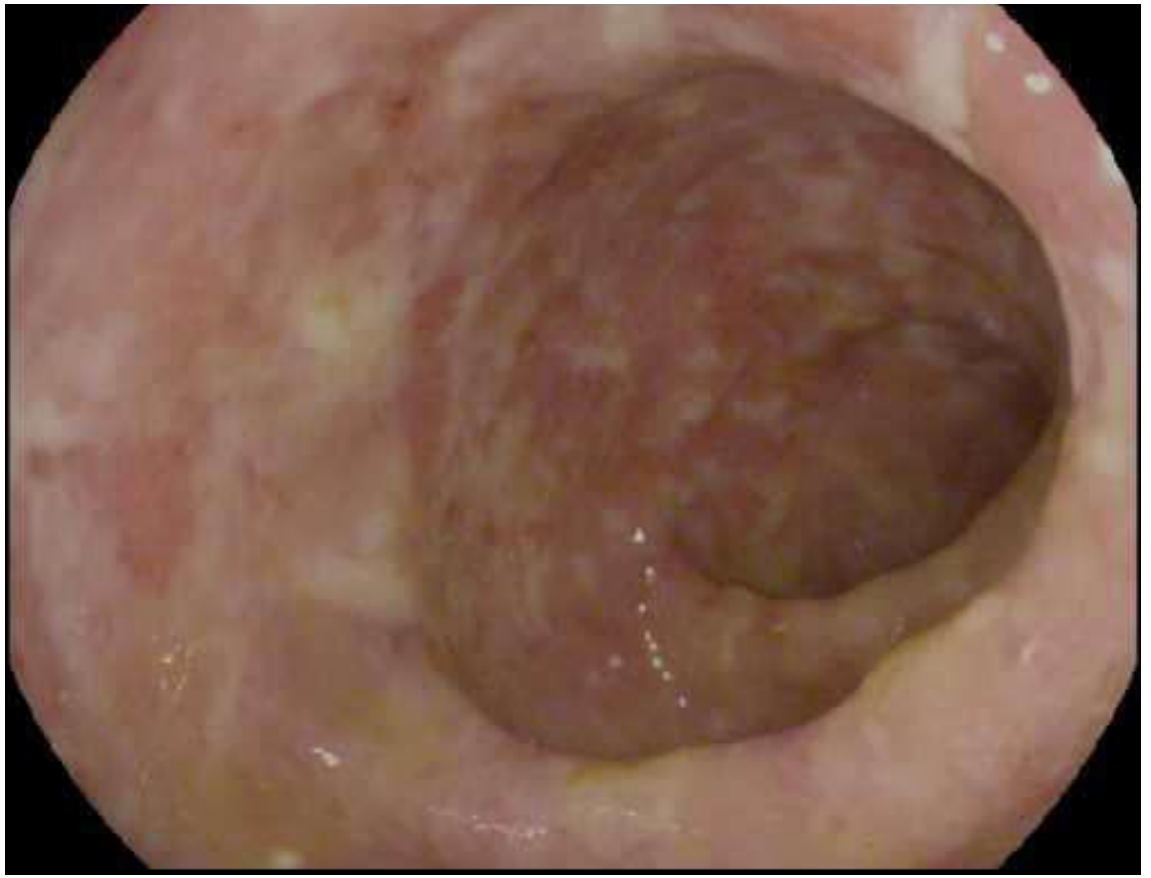
Enterocolitis

- (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



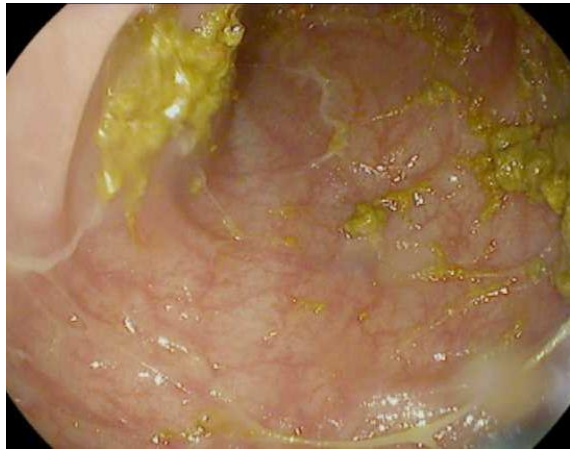
Endoscopy provides valuable diagnostic information

- Determine the severity and extent of inflammation

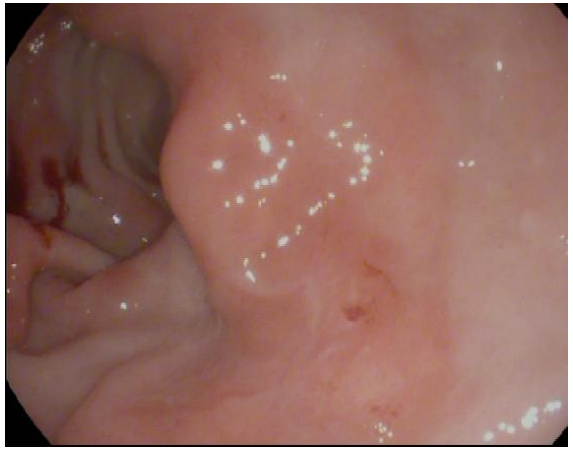
Mayo Endoscopic Score (adapted from ulcerative colitis)

- Determine the severity and extent of inflammation

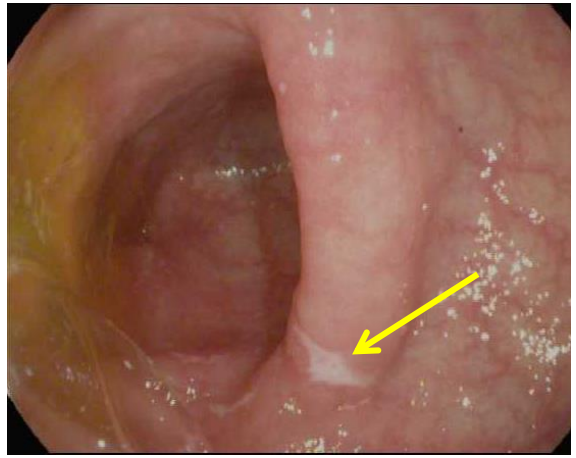
MES 0



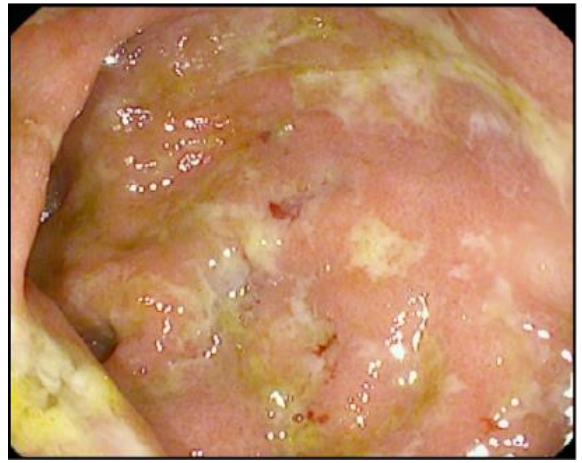
MES 1



MES 2



MES 3



Endoscopy provides valuable diagnostic information

- Determine the severity and extent of inflammation
- Diagnostic Accuracy – not all cases of suspected CPI enterocolitis are confirmed by endoscopy
- Therapy guided by this information may reduce steroid dose, and improves symptoms faster (Abu-Sbeih H et al. JITC. Sept 2018)
- **Does it affect tumor outcome?**

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%

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Enterocolitis and colitis are common

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A significant minority have stomach and small bowel inflammation

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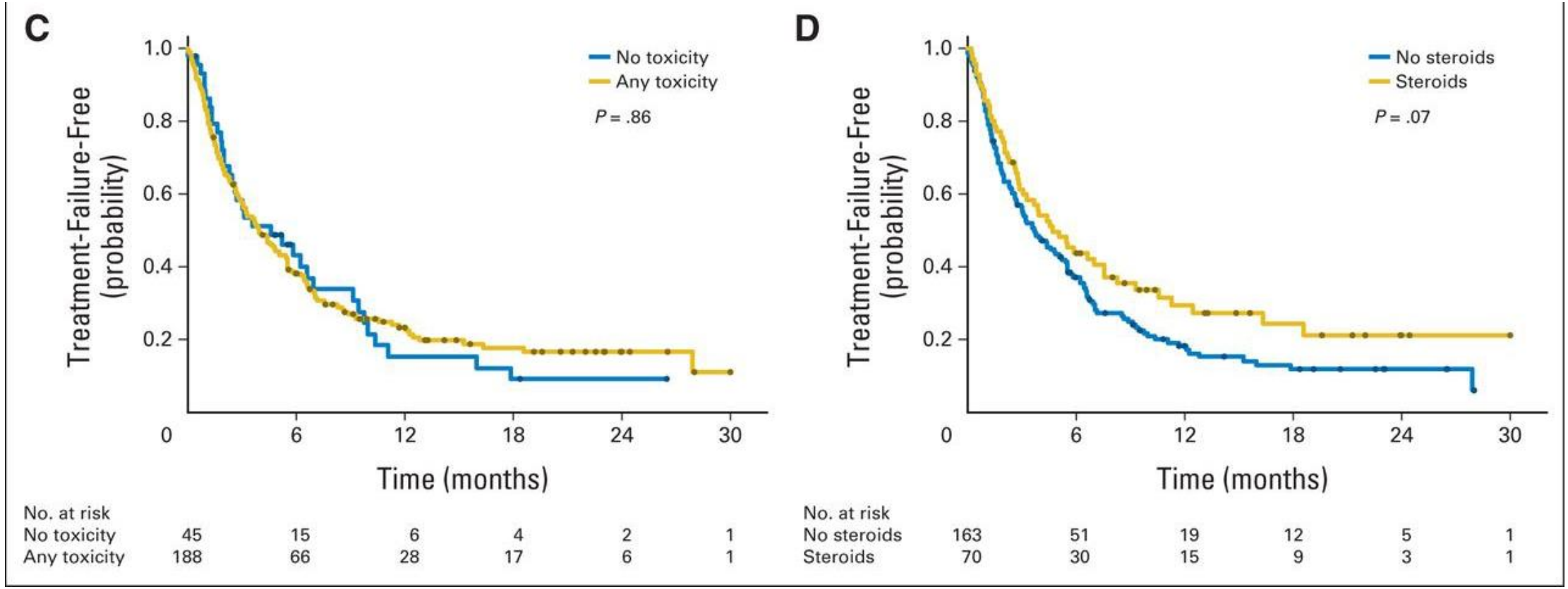
Managing immune toxicities to improve cancer therapy

- **Minimize morbidity/mortality from immune toxicities without inhibiting antitumor immunity**

- Without understanding the immune mechanisms of these toxicities, how do we make treatment decisions?

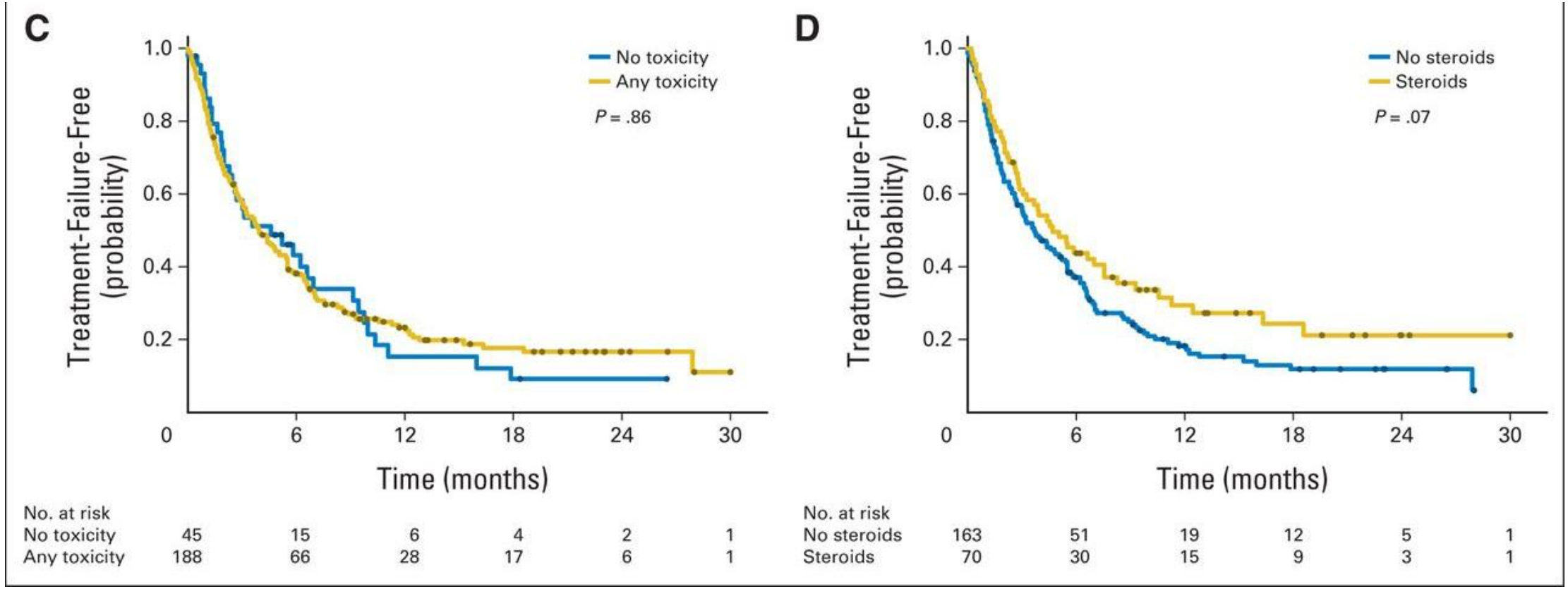
- Systemic glucocorticoids are effective in at least 2/3 of patients – is there a reason to develop more targeted treatment strategies?

Do systemic steroids impact antitumor immunity?



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

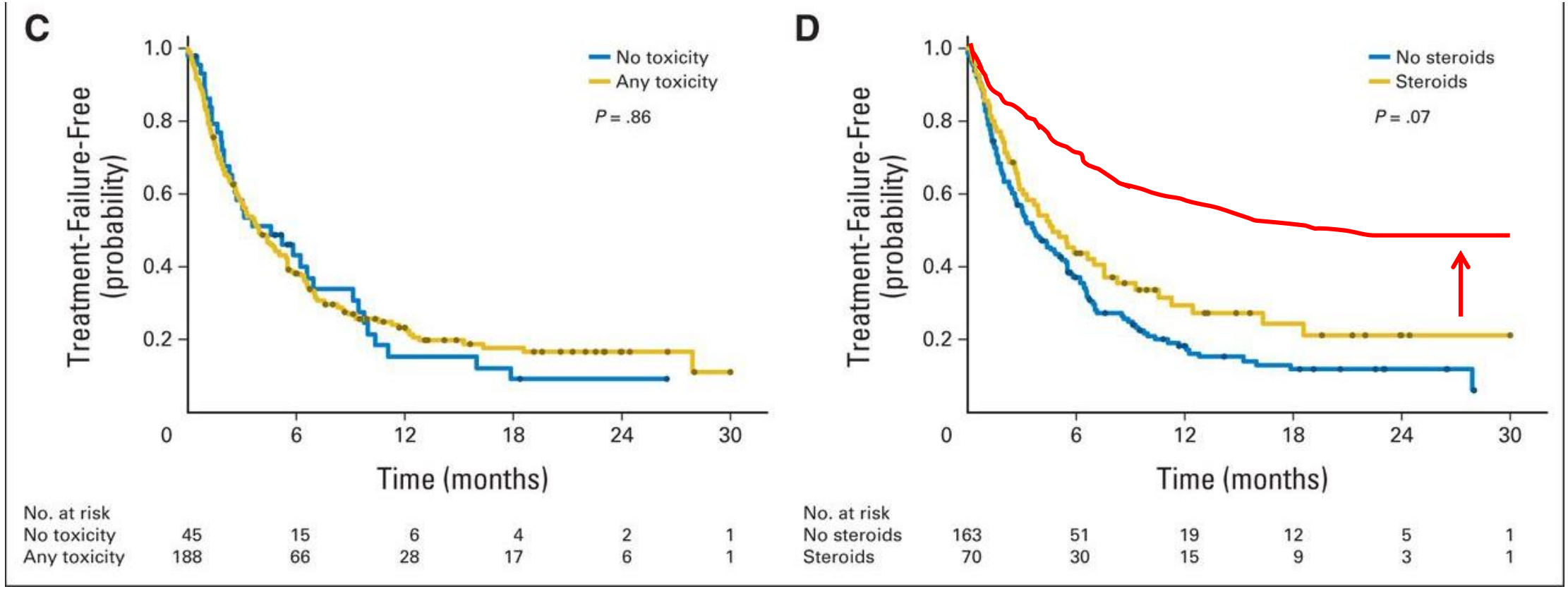
Do systemic steroids impact antitumor immunity?



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 have been better without steroids?



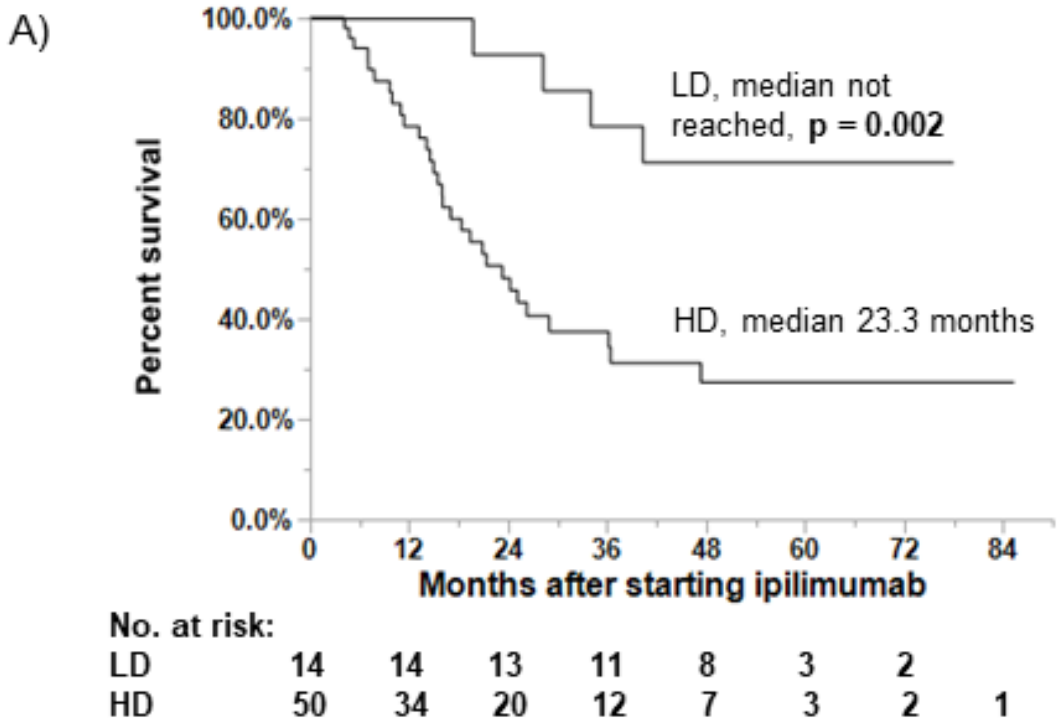
Horvat et al. JCO. 2009. Single center retrospective study

- Patients only received steroids if they had an adverse event
- Anyone with a serious adverse event got steroids

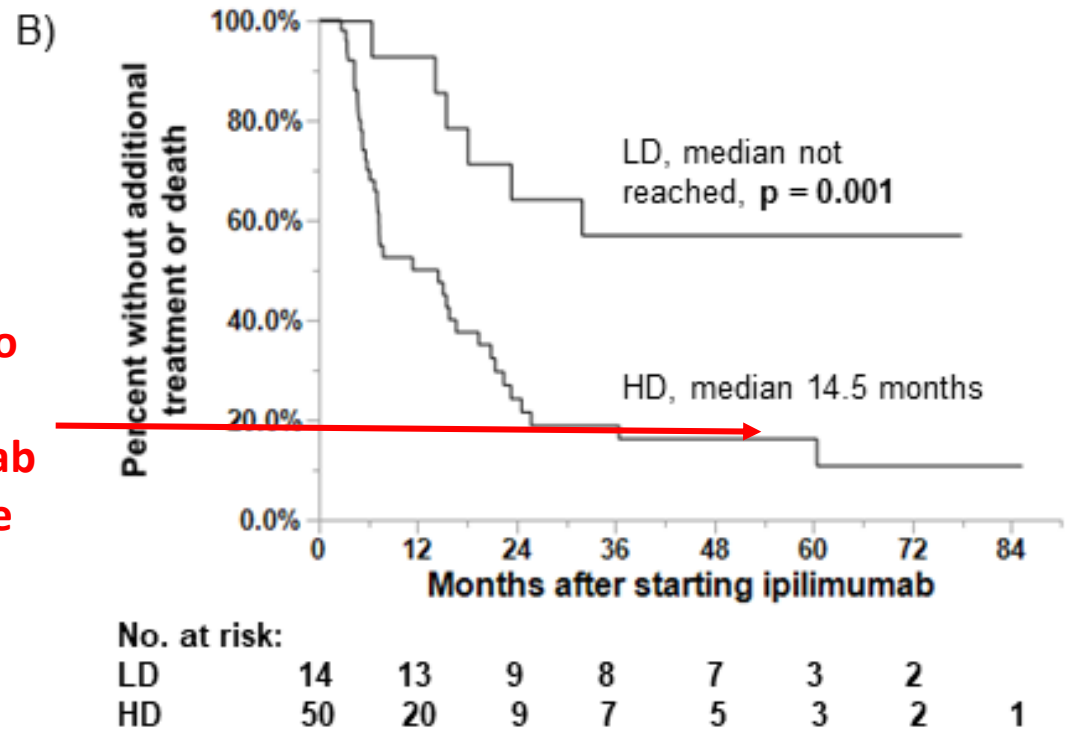
MGH data suggests steroids inhibit the antitumor response

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

overall survival



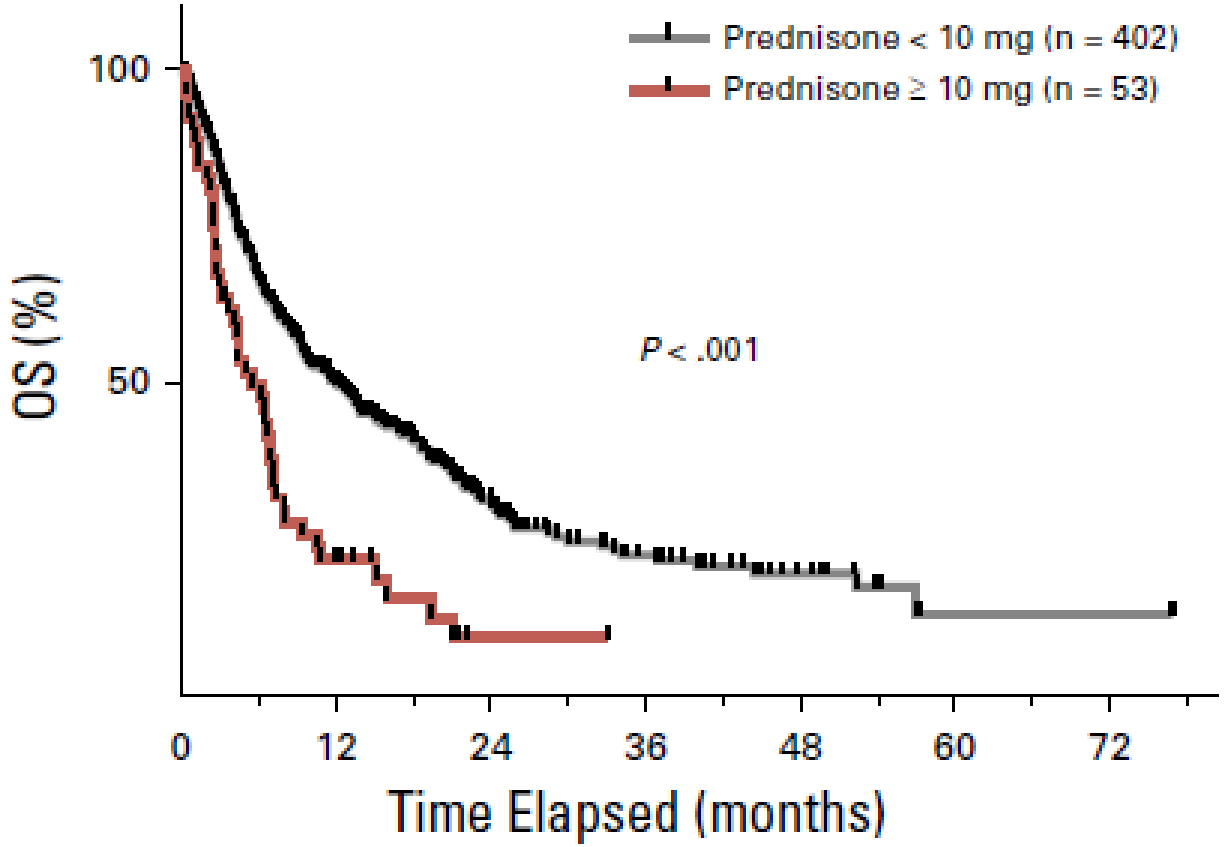
Time to treatment failure



Similar to average ipilimumab response

Alexander Faje et al., Cancer, 2018

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

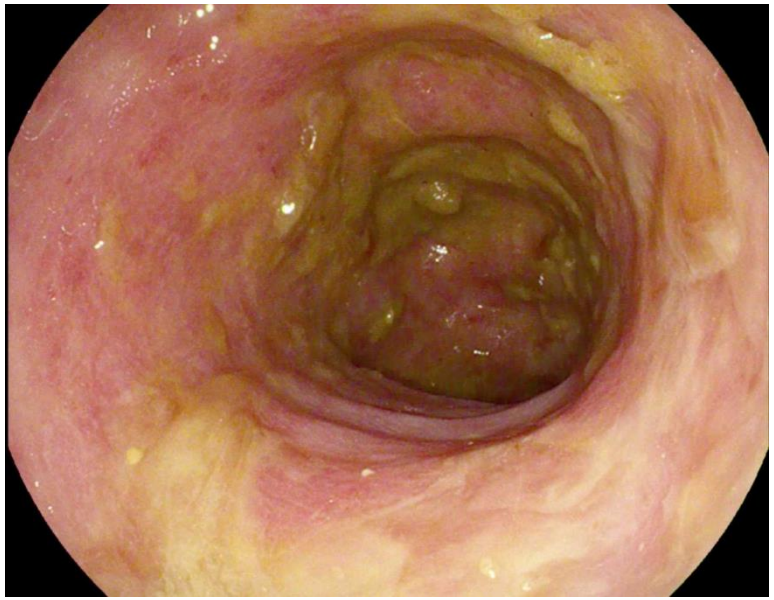


Arbour et al. JCO. 2018

What do we know about the mechanism driving checkpoint colitis?

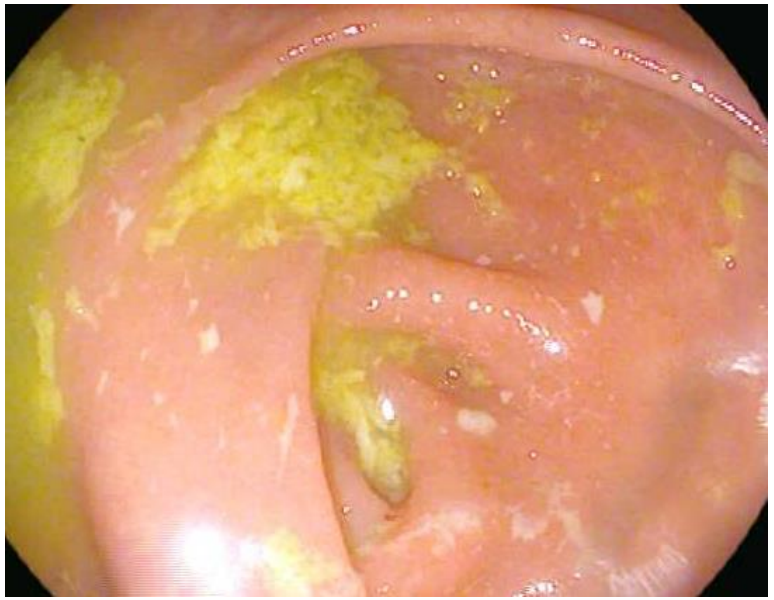
CTLA-4 and PD-1/PD-L1 have different regulatory roles in the gut

Ipilimumab colitis



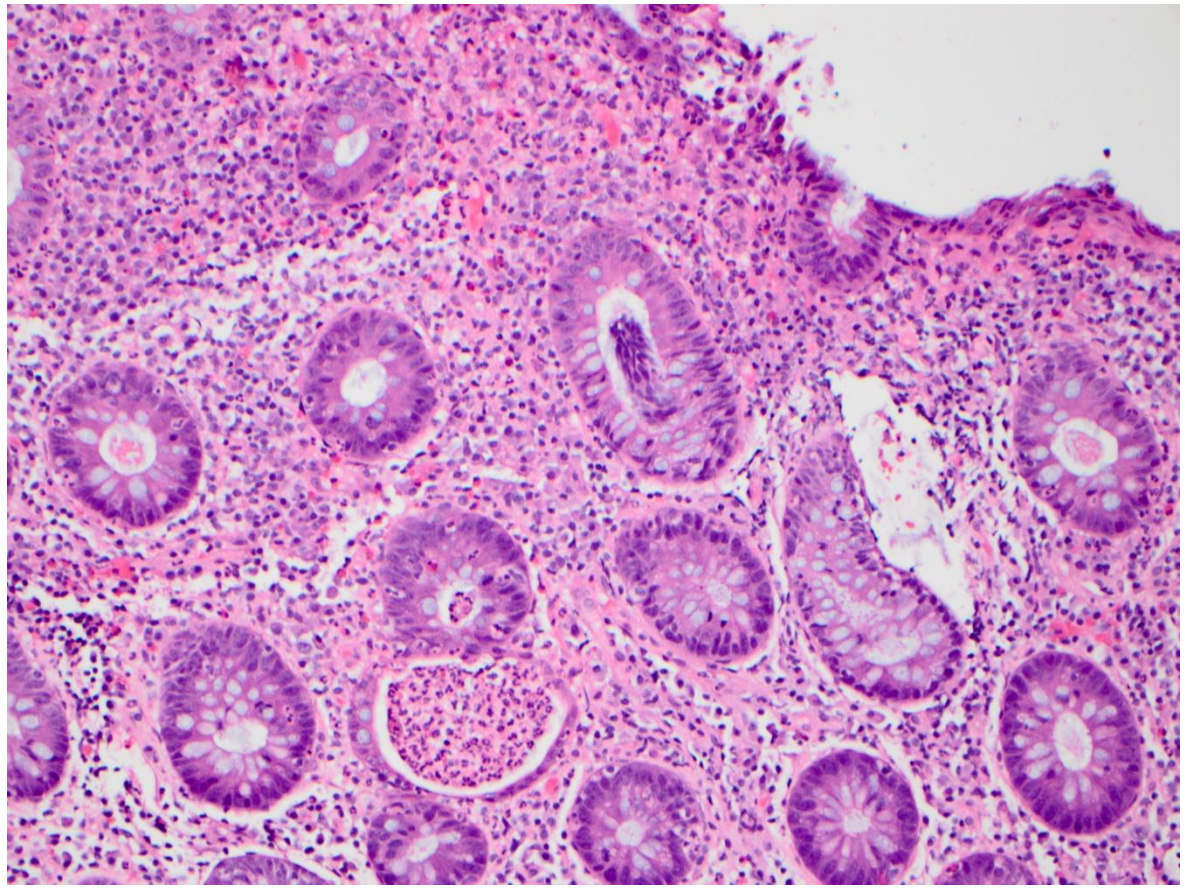
- More frequent and more severe
- Rapid onset
- Dose-dependent
- Rapidly resolves

PD1-blockade colitis



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

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

TNFα is likely a key driver of checkpoint colitis

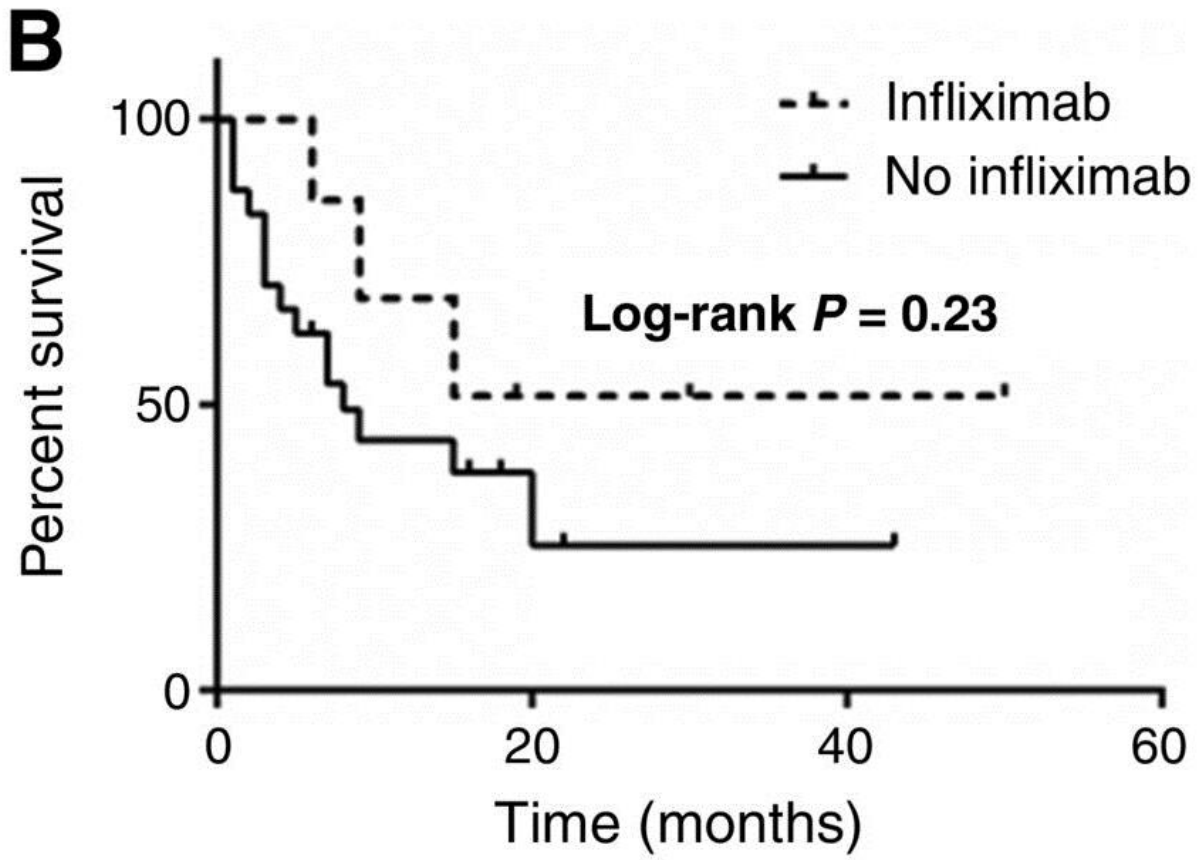
- Infliximab (anti-TNFα) is highly effective in ipilimumab and anti-PD1 mediated colitis
- We have a low threshold for using it (49% of our checkpoint colitis patients go on infliximab)
- In ipilimumab colitis, responses are within days (one dose is often sufficient)
  - Unlike in IBD, restoration of gut homeostasis is the norm

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)
- What do the MGH (melanoma) data show?
  - 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)

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

Overall survival, almost completely driven by the melanoma



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

Innate inflammation may promote tumor growth

ARTICLE

DOI: 10.1038/s41467-017-02358-7 OPEN

TNFα blockade overcomes resistance to anti-PD-1 in experimental melanoma

Florie Bertrand[1,2], Anne Montfort[1,2], Elie Marcheteau[1,2,3,4], Caroline Imbert[1,2,3,4], Julia Gilhodes[5], Thomas Filleron[5], Philippe Rochaix[5], Nathalie Andrieu-Abadie[1,2], Thierry Levade[1,2,3,4,6], Nicolas Meyer[1,3,4,7], Céline Colacios[1,2,3,4] & Bruno Ségui[1,2,3,4]

- It's a mouse model, true

- …but mice have correctly predicted much of what we have seen in immunotherapy thus far

Blockade of gut-homing integrins is effective for CPI enterocolitis

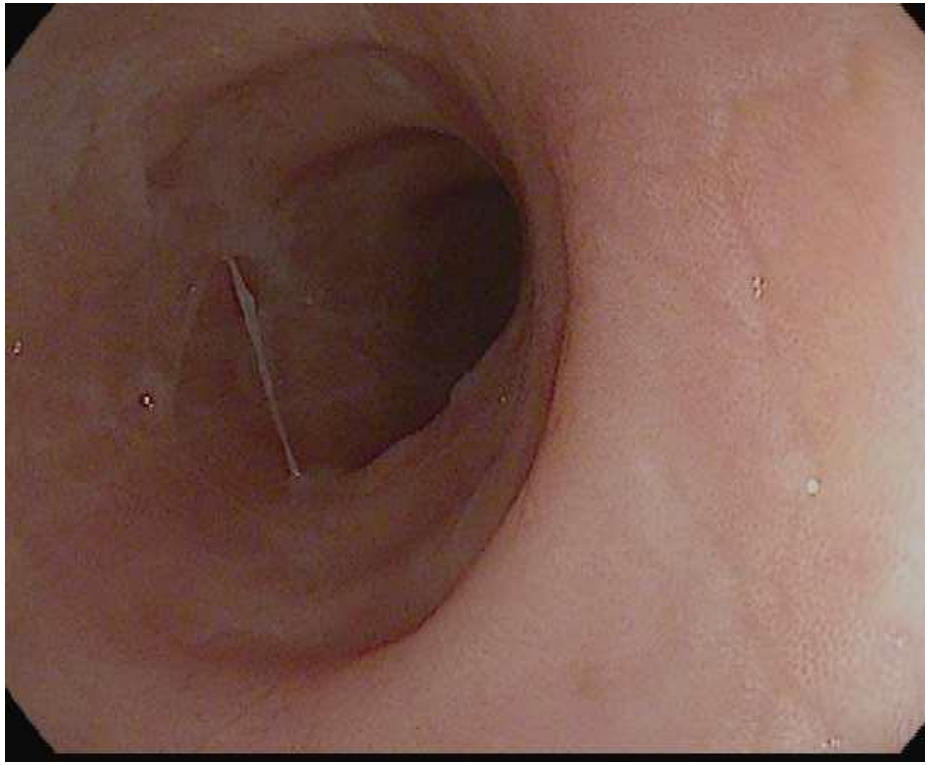
- Vedolizumab (anti-α4β7 integrin) is effective in CPI enterocolitis, indicating a role for trafficking of new T cells into the gut to drive inflammation (Abu-Sbeih et al. JITC. 2018)

- Vedolizumab will not influence the tumor microenvironment for most cancers

- For patients with primary GI malignancies (or GI metastases), inhibition of T cell trafficking to the gut will likely inhibit antitumor responses

Case 1: diarrhea on pembrolizumab

- M.C. 62 yoW on adjuvant nivolumab for resected melanoma
- Developed grade 2-3 diarrhea 5 months after starting therapy, 6 pound weight loss

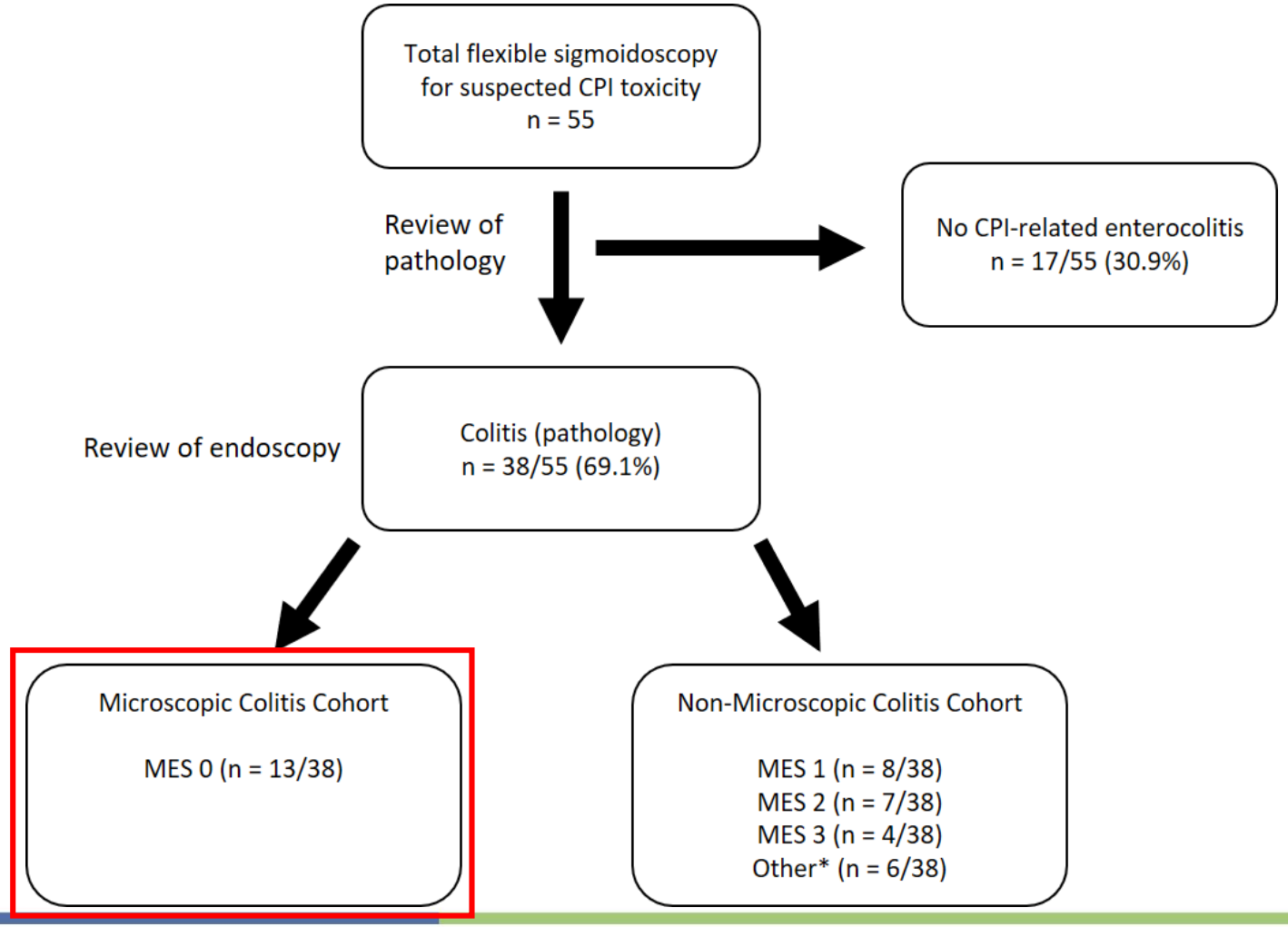


- Mild colonic edema
- No macroscopic evidence of colitis (MES 0)
- Treated with colonic formulation of budesonide and continued on nivolumab

Budesonide of checkpoint microscopic colitis

Michael Hughes, MD
PGY1 Johns Hopkins

Microscopic colitis is a common subgroup of CPI colitis



Hughes et al. JITC. Accepted.

Microscopic colitis responds to budesonide

		Overall	Microscopic colitis	Non-microscopic colitis	p-value
Interventions					
	Budesonide	15/38 (39.5%)	12/13 (92.3%)	3/25 (12.0%)	**<0.001***
	Any systemic glucocorticoids	25/38 (65.8%)	3/13 (23.1%)	22/25 (88.0%)	**<0.001***
	Systemic glucocorticoids < 1 mg/kg/d	14/38 (36.8%)	2/13 (15.4%)	12/25 (48.0%)	0.077
	Systemic glucocorticoids ≥ 1 mg/kg/d	12/38 (31.2%)	1/13 (7.7%)	11/25 (44.0%)	**0.030***

Hughes et al. JITC. Accepted.

Most patients avoid systemic glucocorticoids

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Hughes et al. JITC. Accepted.

Most patients are able to continue immunotherapy

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Time from symptom onset to initiation of glucocorticoids (days)					
	Mean +/- SD	32.4 +/- 37.1	33.2 +/- 26.0	32.0 +/- 42.7	
	Median	21.0	28.0	18.0	0.928
Proportion continuing CPI course		14/38 (10.5%)	10/13 (76.9%)	4/25 (16.0%)	**<0.001***
Proportion eventually discontinuing immunotherapy		29/38 (76.3%)	8/13 (61.5%)	21/25 (84.0%)	0.226
Average number of additional infusions#		3.0 +/- 5.7	5.8 +/- 6.8	1.6 +/- 4.5	**0.030***

Do CTLA-4 and PD-1 regulate IBD?

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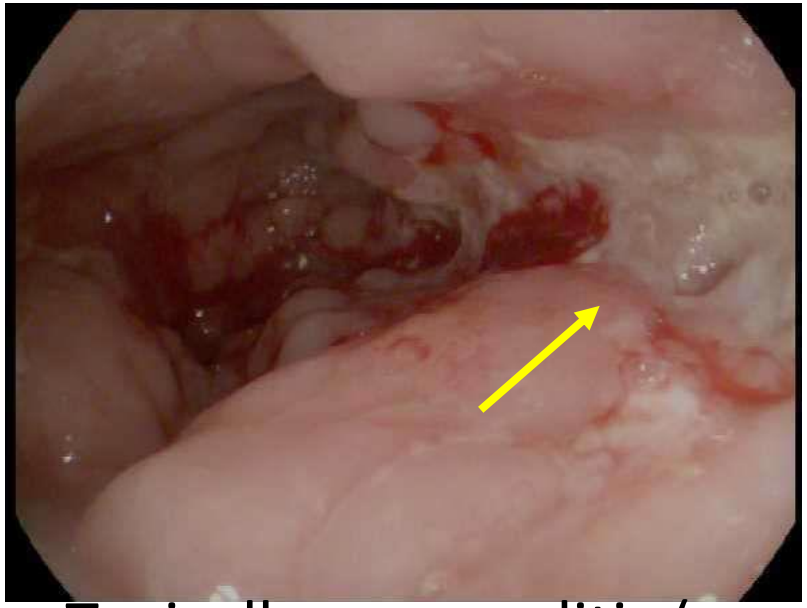
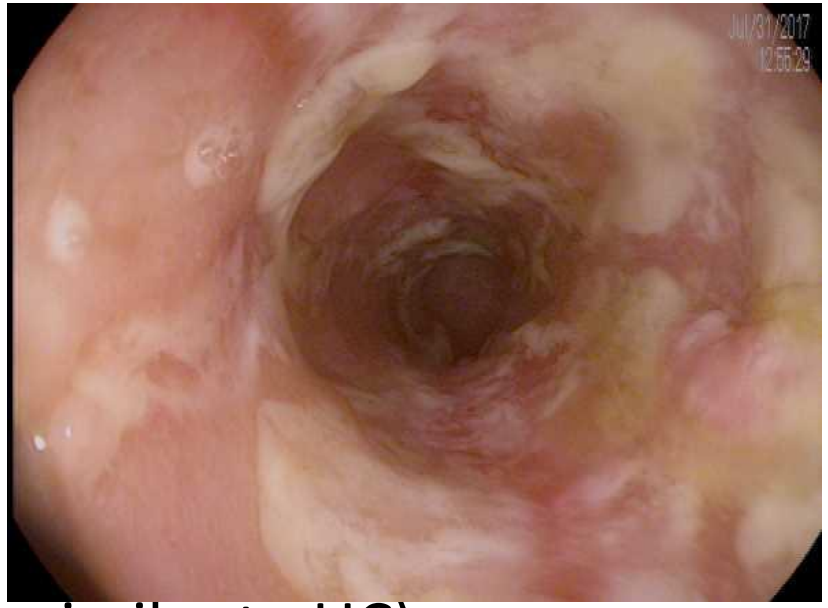
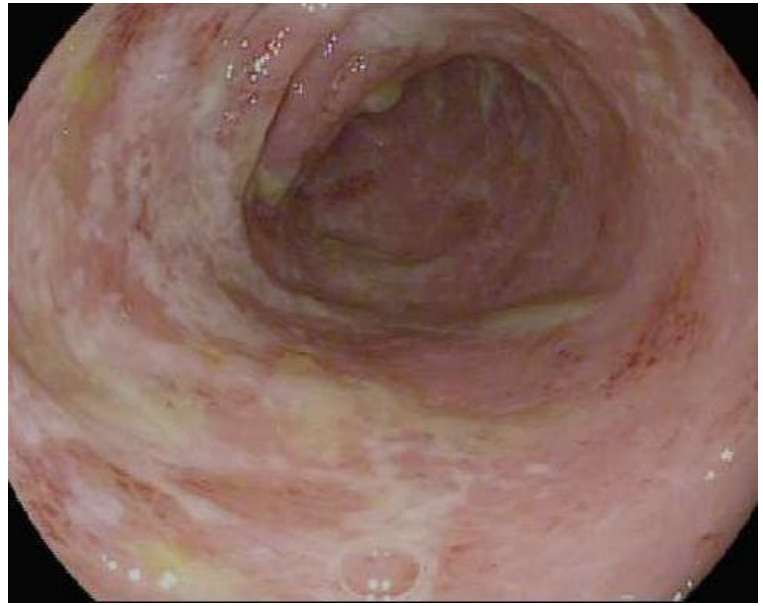
Crohn's Disease



Ulcerative Colitis



Checkpoint Colitis



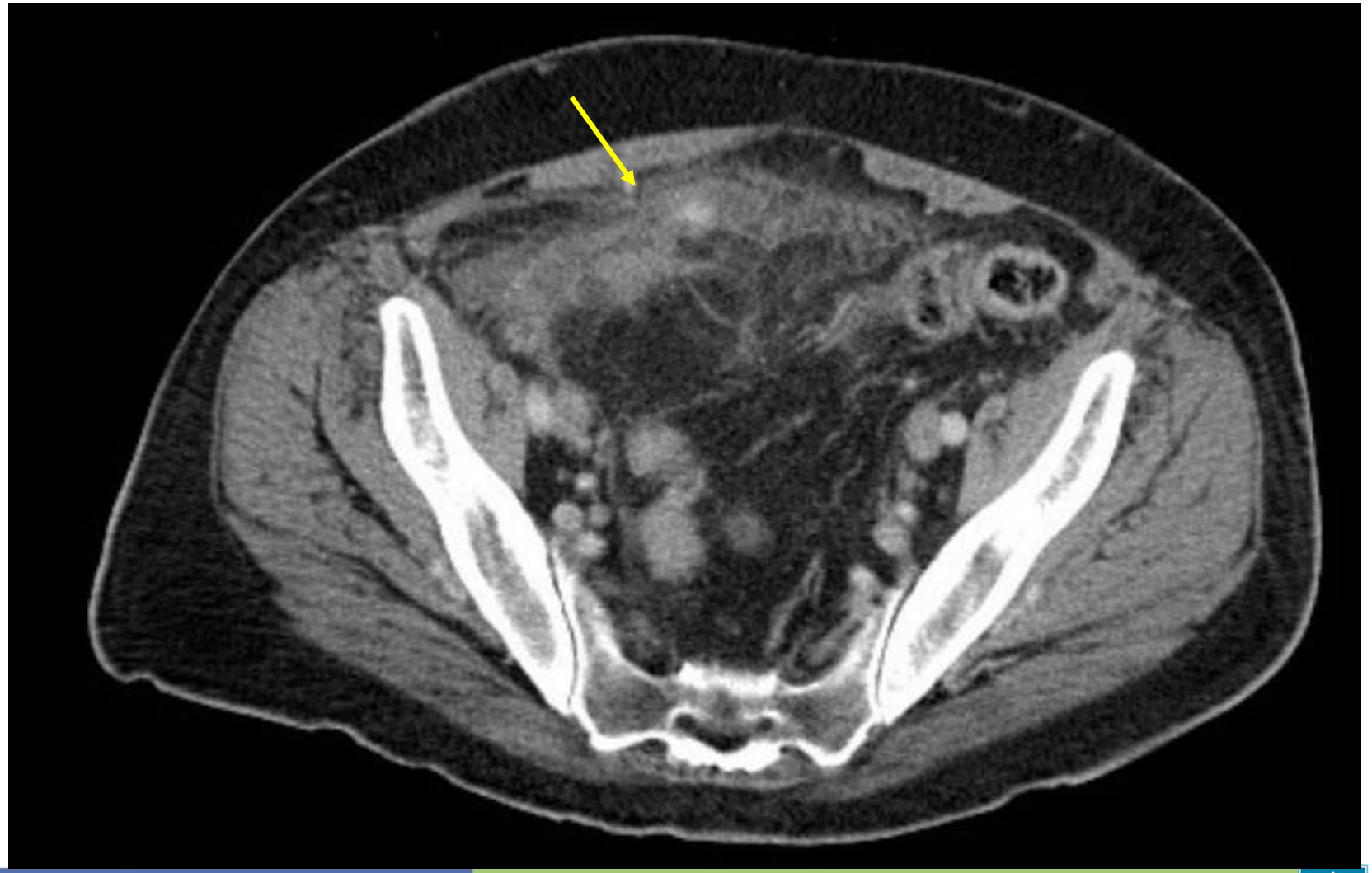
- Typically a pan colitis (more similar to UC)
- Deep ulcers and strictures are rare
- Fistulas don't seem to occur
- Typically a monophasic course

What happens when someone with IBD receives checkpoint blockade?

74 yo man w/ quiescent Crohn's disease off medication for many years with metastatic sarcoma.

- Initiated nivolumab (anti-PD-1) in early 2017
- 2 weeks after first dose presented to ED w/ LLQ pain

Checkpoint blockade can cause IBD reactivation



Checkpoint blockade can cause IBD reactivation

- Received steroids and antibiotics
- Nivolumab held
- Underwent ileocecal resection with no further complications
- Nivolumab was restarted and he is in remission 2 years later

This is one case – was this biology or bad luck?

- Collaboration across 14 centers with a total of 102 patients with IBD on checkpoint blockade

MD Anderson Cancer Center

Yinghong (Mimi) Wang, MD, PhD

Memorial Sloan Kettering Cancer Center

David Faleck, MD

Abu-Sbeih et al. JCO. Accepted.

sitc

MGH 1811 MASSACHUSETTS GENERAL HOSPITAL GASTROENTEROLOGY

Our cohort reflects the population of patients receiving immunotherapy

TABLE 1. Patient Characteristics

Characteristic	No. of Patients (%; N = 102)*
Median age at time of immunotherapy initiation, years (IQR)	65 (54-74)
Male sex	69 (68)
White race	94 (92)
Median Charlson comorbidity index (IQR)	10 (9-11)
Smoking	
Current	2 (2)
Previous	56 (55)
NSAID use	38 (37)
Cancer type	
Melanoma	45 (44)
Lung	23 (23)
GI	17 (17)
GU	7 (7)
Head and neck	4 (4)
Other	6 (6)
Cancer stage	
III	5 (5)
IV	97 (95)
Checkpoint inhibitor type	
CTLA-4	7 (7)
PD-1/PD-L1	85 (83)
Combination	10 (10)

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Patients had disproportionately mild IBD – selection bias

TABLE 2. Baseline IBD Data

Characteristic	No. of Patients (%; N = 102)*
Type of IBD	
Crohn disease	49 (48)
Ulcerative colitis	49 (48)
Unclassified	4 (4)
Median time from IBD diagnosis to immunotherapy initiation, years (IQR)	19 (8-28)
Median time from last active IBD episode to immunotherapy initiation, years (IQR)	5 (3-12)
IBD treatment at time of immunotherapy initiation	
Mesalamine	37 (36)
Immunosuppressive†	22 (22)
None	43 (42)
Severity of endoscopic findings of IBD before immunotherapy initiation (n = 48)	
Normal	29 (60)
Mild	12 (25)
Moderate	5 (10)
Severe	2 (4)

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Both CTLA-4 and PD-1 likely regulate IBD

TABLE 3. Characteristics of GI Adverse Events

Characteristic	No. of Patients (%; n = 42)*
Median time from immunotherapy to GI adverse event, days (IQR)	62 (33-123)
Highest grade of diarrhea (n = 41)	
1	5 (12)
2	15 (37)
3	15 (37)
4	6 (15)
Median duration of symptoms, days (IQR)	17 (9-35)
Hospitalizations	22 (52)
Median duration of hospitalization, days (IQR)	5 (3-9)
ICU admission	2 (5)
Mortality as a result of GI adverse event	0 (0)

GI Adverse Events
41% vs 11% in control cohort

21% had a serious event

None of the GI adverse events were fatal
Cancer specific mortality similar to published trials

Abu-Sbeih et al. JCO. Accepted.

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Summary of Key Points

- Corticosteroids may limit the treatment effect from CPIs
- Endoscopy can be useful for risk stratification (ulcerating disease), and for identifying patients who do not require systemic steroids (microscopic colitis)
- Microscopic colitis on CPIs can be treated with concurrent budesonide
- TNFα is a key regulator of CPI enterocolitis, and trafficking of T cells into the gut is required to maintain inflammation
- CTLA-4 and PD-1 colitis are not completely overlapping syndromes
- CTLA-4 and PD-(L)1 likely regulate remission in IBD

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