ACCC
Association of Community Cancer Centers

PROJECT ECHO®: TELE-MENTORING TO MANAGE IMMUNE-RELATED ADVERSE EVENTS IN PATIENTS RECEIVING CANCER IMMUNOTHERAPIES

Gastroenterology Toxicities with Immune Checkpoint Inhibitors

WELCOME AND INTRODUCTIONS

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FACULTY DISCLOSURES

Jocelyn E. Mohs, PharmD, BCOP has no relevant financial relationships.

Yinghong Wang, MD, PhD is a consultant with Sorriso, MabQuest, Sanarentero, AzurRx, and received research grant from Gateway, Adopt A Scientist, Moonshot, HESI, Sabin Fellowship.

Ryan M. Weight, DO, MS is a consultant and speaker with Immunocore and Castle Biosciences INC and is a consultant for Novartis and Pfizer.

Laura S. Wood, RN, MSN, OCN is a speaker for BMS, Eisai, EMD Serono, Exelixis, Merck and Pfizer.

LEARNING OBJECTIVES

At the end of this educational program, participants should be able to:

- Apply evidence-based practices for the monitoring and management of immune-related adverse events (irAEs) in patients receiving cancer immunotherapies
- Improve coordination and communication with non-oncology specialists and with patients/caregivers to manage irAEs in patients receiving cancer immunotherapies
- Review strategies for providing equitable care for underserved patients receiving cancer immunotherapies

SUPPORT STATEMENT

This activity is supported by an educational grant from BMS.

POLLING QUESTION #1

Compared to patients without GI toxicity, the development of GI irAEs is associated with:

A. Worse overall and progression-free survival, the more severe GI irAE, the worse survival.
B. Improved overall and progression-free survival, the more severe GI irAE, the better survival.
C. No difference in survival

POLLING QUESTION #2

Which of the following statements is correct regarding the evaluation of ICI colitis?

A. If the stool infection for diarrhea work up is positive for infection, this is most likely the cause of symptom, which should be adequately treated and steroid should be avoided in this situation.
B. For ICI related colitis, endoscopy should be avoided given the higher risk of perforation.
C. Early endoscopy evaluation and the colitis severity measurement on endoscopy will provide more accurate guidance on the treatment strategy.
D. Abdominal imaging will provide high yield for patients with new onset of diarrhea symptom after ICI treatment and should be considered as part of the routine evaluation.

POLLING QUESTION #3

Which of the following endoscopic features would be most concerning for more severe disease?

A. Ulceration
B. Congestion
C. Normal findings on gross examination
D. Loss of vasculature

POLLING QUESTION #4

What do you need to know about immune checkpoint inhibitors (ICI) re-challenge in patients with ICI colitis?

A. Since steroid is required for the index colitis event, ICI re-challenge should not be considered.
B. The recurrence rate of colitis is low, ICI re-challenge can always be considered if clinically indicated at any time.
C. Since CTLA-4 agent is found to be associated with higher level of GI toxicity, re-challenge should be only limited to PD-1/PD-L1 agent.
D. Despite recurrence rate of 35% on ICI re-challenge, once the colitis is under adequate treatment with remission, ICI can still be restarted, preferably with PD-1/L1 monotherapy

Goals of irAE Management

- Provide effective treatment early to control irAEs and avoid complications
- Minimize irAE recurrence
- Facilitate ICI resumption or continuation of other cancer treatment

MANAGEMENT OF GASTROINTESTINAL IMMUNE-RELATED TOXICITIES

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irAE Guidelines

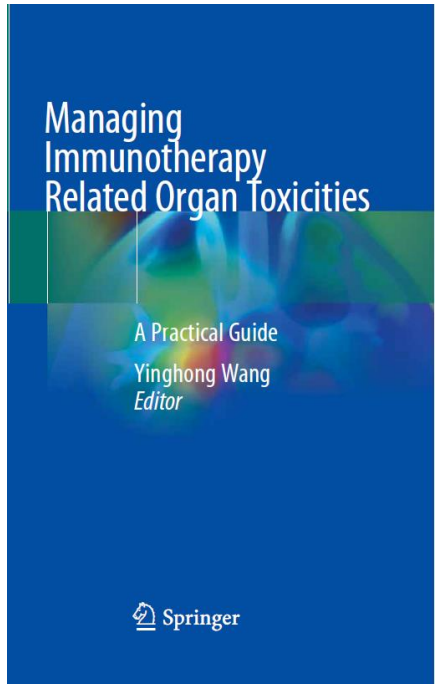
ASCO Guidelines

ESMO

SOCIETY FOR IMMUNOTHERAPY OF CANCER

sitc
Cancer Immunotherapy
CONNECT

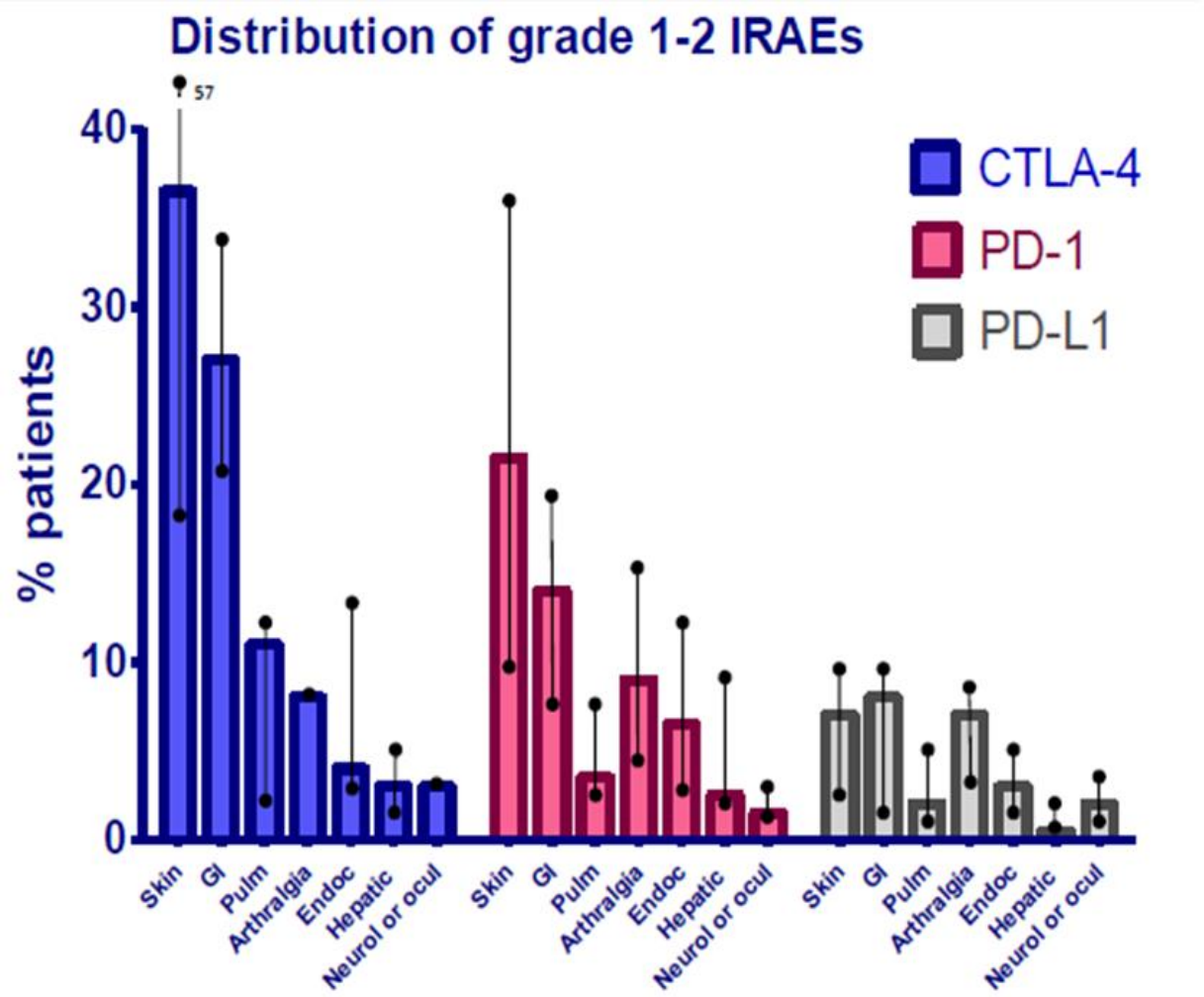
aga American Gastroenterological Association

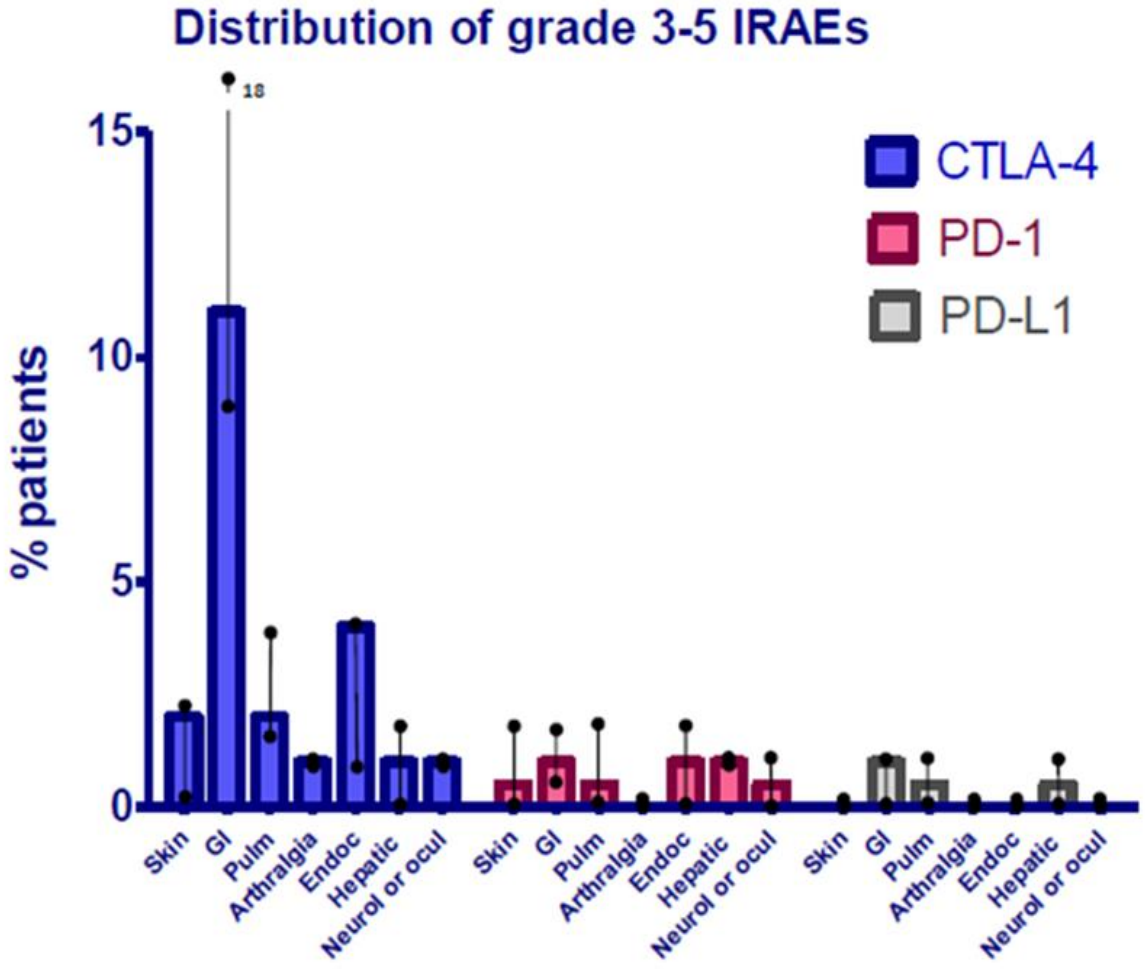


Immune Related Gastrointestinal Toxicities

GI Luminal	Extra GI Luminal
Mucositis	Hepatitis
Esophagitis	Pancreatitis
Gastroenteritis	Cholecystitis
Colitis	Appendicitis

Distribution of irAEs





Michot et al European Journal of Cancer 54 (2016) 139-148

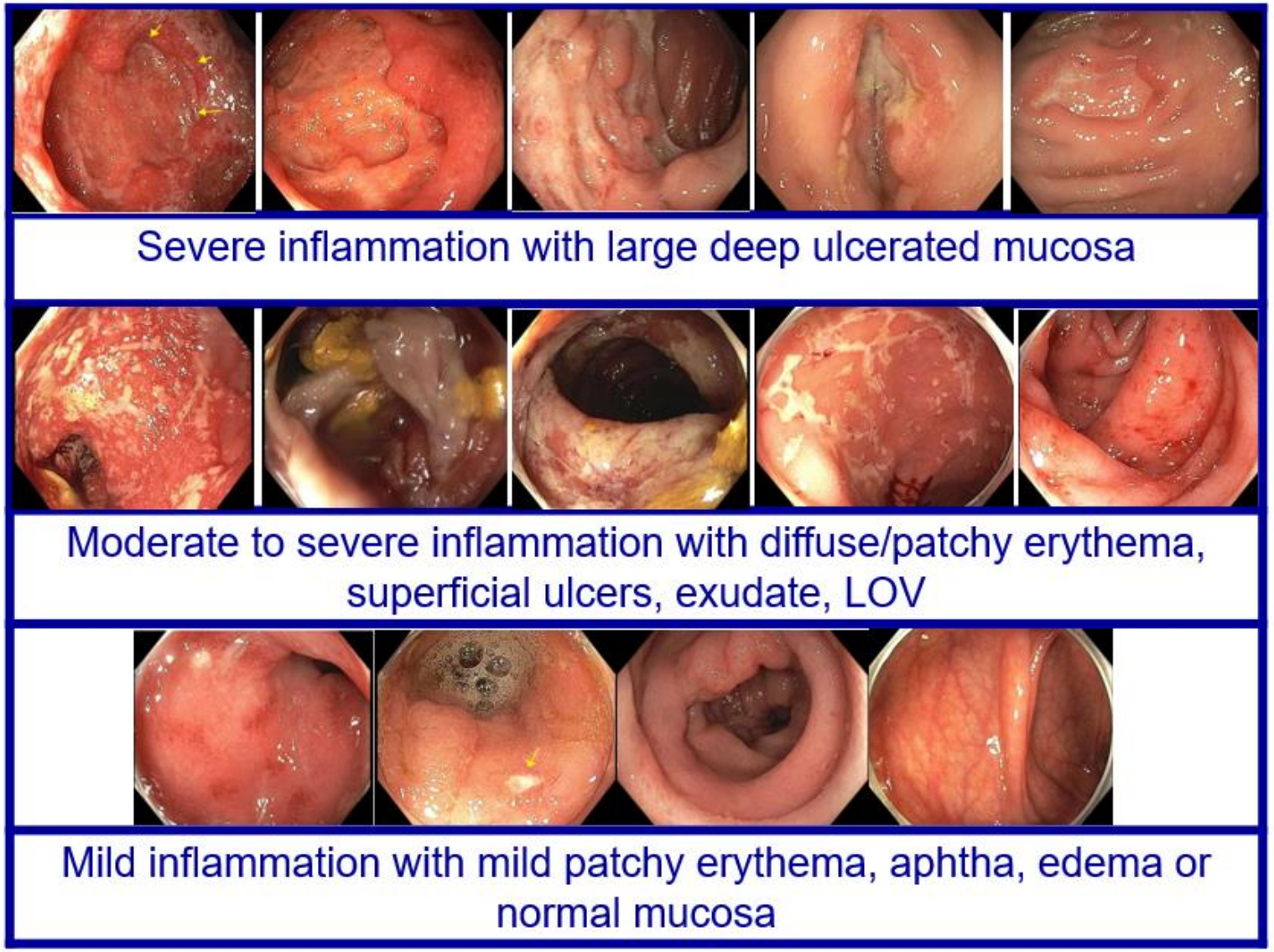
Clinical Presentations

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Diarrhea	Increase of <4 stools/day over baseline, mild increase in ostomy output above baseline	Increase of 4-6 stools/day above baseline, moderate increase in ostomy output, limiting instrumental daily activities	Increase of > 7 stools/day above baseline, Hospitalization, severe increase of ostomy output, limited self-care ADL	Life-threatening consequence, urgent intervention indicated	Death
Colitis	Asymptomatic, clinical or diagnostic observation, intervention not indicated	Abdominal pain, mucus or blood in stool	Severe abdominal pain, peritoneal sign	Life-threatening consequence, urgent intervention indicated	Death

Time of onset: first ICI dose ⟷ 1 year after last dose; majority in 2-3 months.

https://ctep.cancer.gov

Endoscopy Presentations



Wang et al Inflamm Bowel Dis. 2018 Jul 12;24(8):1695-1705.

Stool Biomarkers and Its Sensitivity

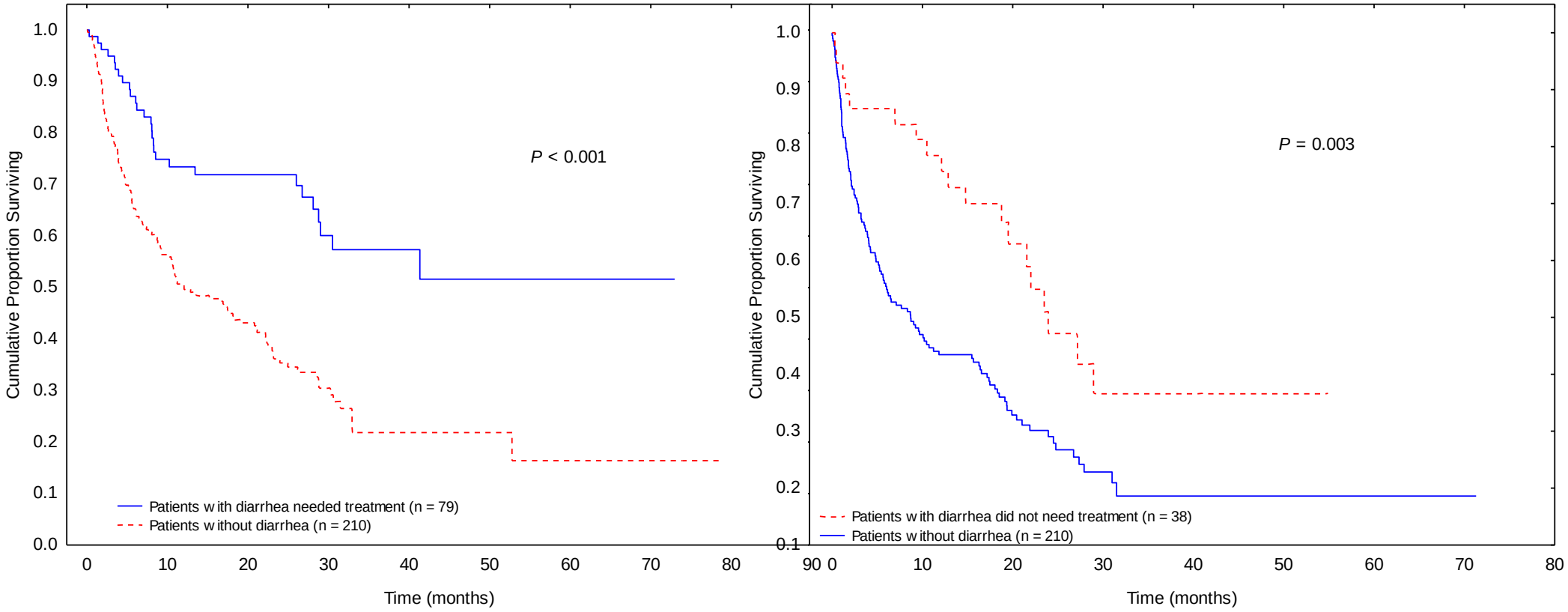
	Lactoferrin (+) N (%)	Lactoferrin (-) N (%)
Abnormal Scope	42 (70)	4 (36)
Normal Scope	18 (30)	7 (64)
Abnormal Histology	54 (90)	3 (27)
Normal Histology	6 (10)	8 (73)

Scope Findings	Calprotectin (SD)
Ulcers	465 (363)
Non-Ulcer Inflammation	213 (184)
Normal	152 (133)
P	0.006

Sensitivity of lactoferrin for endoscopic inflammation is 70%
Sensitivity of lactoferrin for histologic inflammation is 90%

Wang et al J Immunother Cancer. 2018 Sep 25;6(1):95

Overall Survival with GI Toxicity



Wang et al J Immunother Cancer. 2018 May 11;6(1):37.

Endoscopic Features and Outcomes

Characteristic	High-risk features N = 71	No high-risk features N = 111	P value
Duration of symptoms (days, SD)	41 (106)	27 (60)	0.301
IV steroids, n (%)	41 (66.1)	42 (58.3)	0.378
Infliximab/vedolizumab, n (%)	30 (46.2)	12 (15.8)	< 0.001
Mean duration from dx to first recurrence (days, SD)	140 (147)	144 (121)	0.902
Outcomes, n (%)			
Hospitalization	58 (81.7)	74 (66.7)	0.028
Duration of hospitalization (days, SD)	9 (8)	6 (5)	0.016
Recurrence	20 (28.2)	31 (27.9)	1.000
Repeat endoscopy	18 (25.4)	18 (16.2)	0.181

[a]High-risk endoscopic features; deep ulcers >2 mm in depth, large ulcers > 1 cm, multiple ulcers, extensive involvement

Abu-Sbeih, Wang et al J Immunother Cancer. 2018 Sep 25;6(1):95

Timing of Endoscopy and Clinical Outcomes

Characteristic	>30 days of onset N = 40	≤30 days of onset N = 142	P value
IV steroids, n (%)	23 (57.5)	60 (42.3)	0.054
Duration of symptoms (days, SD)	54 (92)	26 (77)	0.062
Duration of steroid (days, SD)	87 (120)	53 (41)	0.019
Infliximab/vedolizumab, n (%)	8 (22.9)	34 (32.1)	0.395
Duration from onset to first infliximab/vedolizumab dose (days, SD)	31 (23)	15 (14)	0.030
Outcomes, n (%)			
Hospitalization	27 (67.5)	105 (73.9)	0.428
Duration of hospitalization (days, SD)	9 (7)	7 (6)	0.138
ICU admission	4 (10)	3 (2.1)	0.072
Recurrence	20 (50.0)	31 (21.8)	0.001

Abu-Sbeih, Wang et al J Immunother Cancer. 2018 Sep 25;6(1):95

Timing of SIT and Clinical Outcomes of ICI colitis

Covariate	≤ 10 days of onset N = 44	> 10 days of onset N = 40	P value
High-risk endoscopic features initially, n (%)	17 (55)	23 (70)	0.302
Duration of symptoms, mean days (SD)	25 (32)	50 (40)	0.002
Multiple hospitalization, n (%)	13 (30)	22 (55)	0.026
Duration of hospitalization, mean days, (SD)	10 (8)	12 (8)	0.321
Failed steroid taper after SIT, n (%)	9 (23)	19 (49)	0.033
# of attempts at steroids taper, median (IQR)	1 (1-4)	2 (1-4)	< 0.001
Overall duration of steroids, mean days (SD)	64 (38)	82 (51)	0.092
Recurrent diarrhea, n (%)	8 (18)	8 (20)	1.000
Infectious adverse events, n (%)	16 (36)	9 (23)	0.233

SIT: Selected immunosuppressive therapy

Abu-Sbeih, Wang et al J Immunother Cancer. 2019 Apr 2;7(1):93.

Univariate Analysis for Recurrence

Characteristics	OR (95% CI)	P
Colitis grade 3-4	1.79 (0.59-3.38)	0.299
Multiple hospitalization	26.25 (3.22-213.82)	0.002
Failed steroid tapering after SIT	4.07 (1.29-12.88)	0.017
Infliximab	12.57 (1.57-100.57)	0.017
No. of SIT infusions ≥3	0.09 (0.01-0.72)	0.023
Endoscopic remission	0.15 (0.03-0.79)	0.025
Histologic remission	0.18 (0.04-0.88)	0.033
Number of steroids tapering attempts	3.35 (1.68-6.69)	0.001
Duration from onset to SIT	1.00 (0.98-1.03)	0.774
Overall duration of steroids	1.01 (1.00-1.03)	0.022
Calprotectin after SIT	1.01 (1.00-1.01)	0.014
Duration of hospitalization	1.14 (1.05-1.23)	0.001
Duration of symptoms	1.02 (1.01-1.03)	0.008

Abu-Sbeih, Wang et al J Immunother Cancer. 2019 Apr 2;7(1):93.

Calprotectin Predicts Endoscopic and Histologic Remission

Endpoint	Cutoff value, mcg/g	Specificity	Sensitivity	NPV	PPV
Overall, n=77					
Endoscopic remission, n=46	≤116	94%	46%	0.54	0.91
Histologic remission, n=24	≤80	85%	21%	0.70	0.38
Clinical remission group, n=65					
Endoscopic remission, n=46	≤140	89%	78%	0.63	0.95
Histologic remission, n=24	≤80	80%	21%	0.63	0.38

Zou, Wang et al. J Immunother Cancer 2021 Jan;9(1):e002058. PMID: 33436487

Clinical Characteristics Between VDZ and IFX

Characteristic	VDZ alone n=62	IFX alone n=94	P
Diarrhea grade 3-4 –no. (%)	42(68)	61(65)	0.583
Colitis grade 3-4 –no. (%)	32(52)	37(39)	0.246
Median days from IMDC to first dose of SIT, n=156	11 (9-48)	23 (19-37)	<0·001
Days from first dose of SIT to symptoms remission, n=138	18 (10-40)	13 (8-29)	0·012
Number dose of SIT, ≥3– no. (%)	41 (66)	17 (18)	<0·001
Median days of steroids for initial IMDC, n=156	35 (27-43)	51 (41-68)	<0·001
Median hospital stay, – days (IQR), n=107	10 (5-15)	14 (8-19.8)	0·043
No. of steroid tapering attempts prior to SIT use, n=156	1 (1-3)	2 (2-3)	0·016
Colitis outcomes at last follow up			
IMDC recurrence, – no. (%)	8 (14)	27 (29)	0·007
Clinical remission, – no. (%)	55 (89)	83 (88)	0·785

VDZ: vedolizumab; IFX: infliximab

Zou et al, J Immunother Cancer. 2021 Nov;9(11):e003277

Recurrent ICI Colitis Upon ICI Resumption

Characteristic	Anti–CTLA-4 N = 32	Anti–PD-1/L1 N = 135	P
ICI colitis recurrence	14 (44)	43 (33)	0.30
Days to ICI colitis recurrence	26 (2-43)	79 (27-141)	0.02
Recurrent ICI colitis treatment			0.31
Steroid	8 (25)	31 (23)	
Infliximab/vedolizumab	3 (9)	4 (3)	
Grade of diarrhea			0.50
2	11 (34)	29 (22)	
3-4	1 (3)	5 (4)	
Grade of colitis, 2-3	6 (19)	20 (15)	0.39

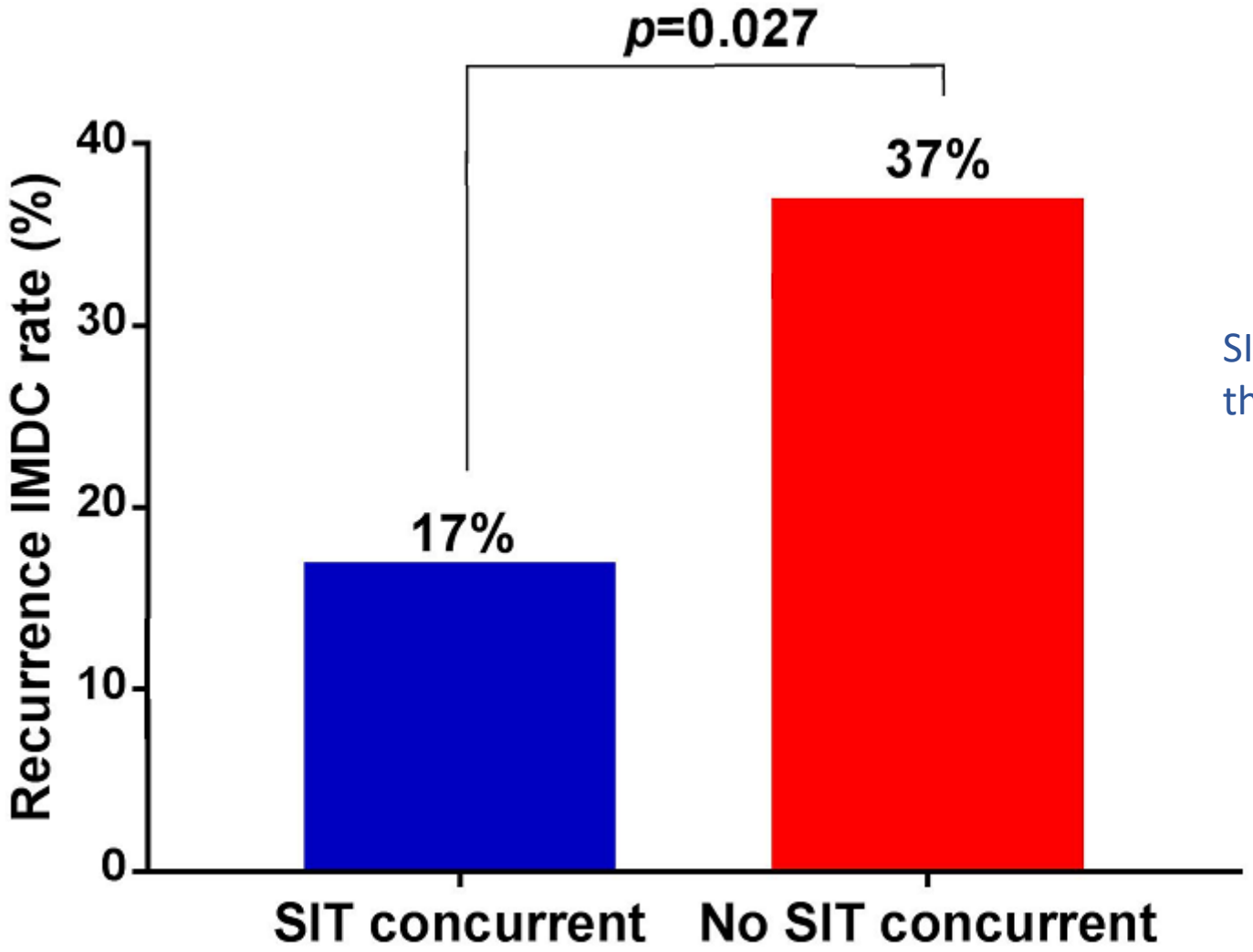
Abu-Sbeih, Wang et al J Clin Oncol. 2019 Oct 20;37(30):2738-2745.

Multivariate Analysis for Colitis Recurrence

Covariate	OR	95% CI	P
Initial anti–PD-1/L1	3.45	1.59-7.69	0.01
Resumed anti–PD-1/L1	0.30	0.11-0.81	0.02
Grade of initial diarrhea			
2	1.19	0.37-3.80	0.78
3	2.19	0.66-7.29	0.20
Immunosuppressant initially	3.22	1.08-9.62	0.02
Duration of initial colitis	1.01	1.00-1.03	0.03

Abu-Sbeih, Wang et al J Clin Oncol. 2019 Oct 20;37(30):2738-2745.

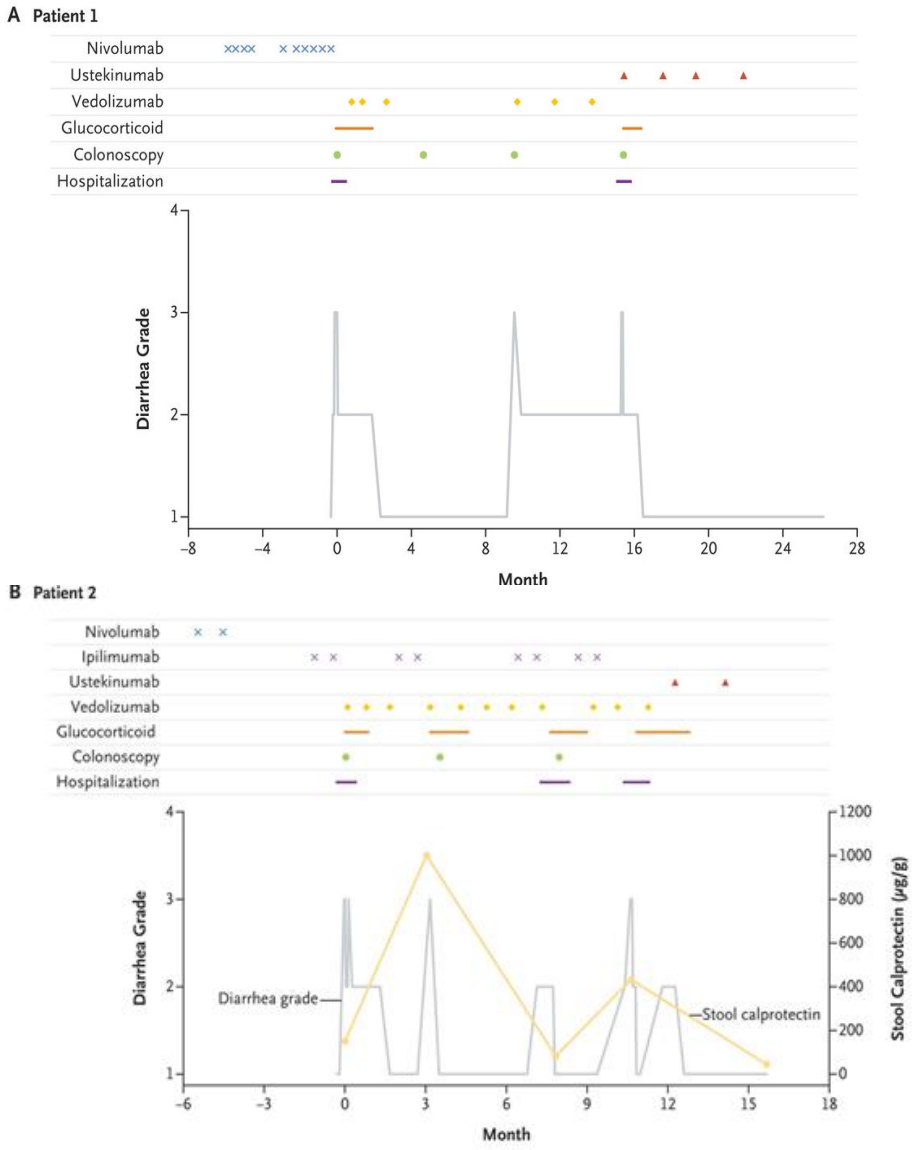
ICI Colitis Management on ICI Resumption



SIT: selective immunosuppressive therapy (infliximab or vedolizumab)

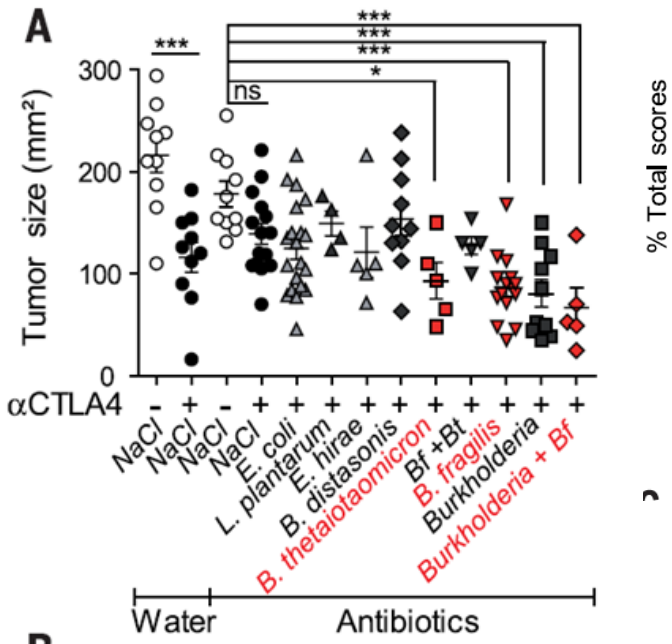
Zou et al. Gastroenterology 2021; 160 (6): Suppl. S-711

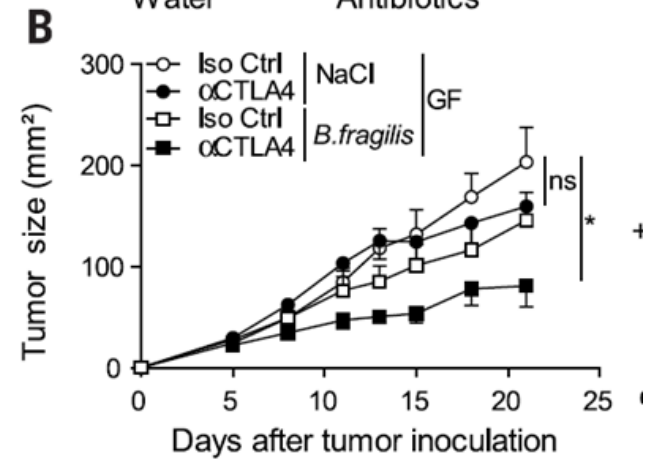
Ustekinumab and Tofacitinib Therapy for Refractory ICI Colitis

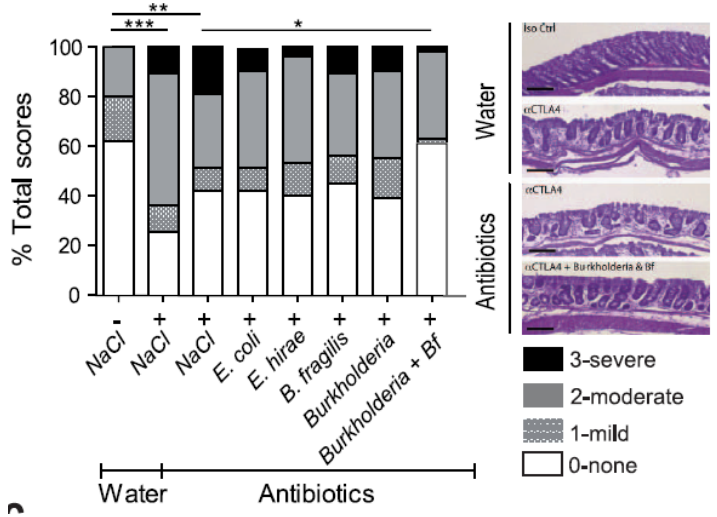


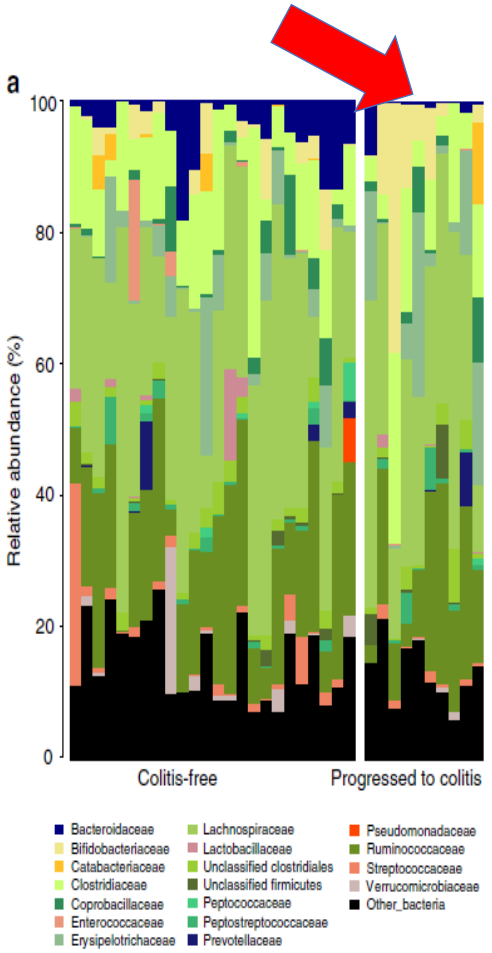
- 5 patients have been reported to achieve clinical response/remission to tofacitinib after failing infliximab or vedolizumab and steroid.
- More evidence is imperative in terms of safety in cancer patients from using these agents.

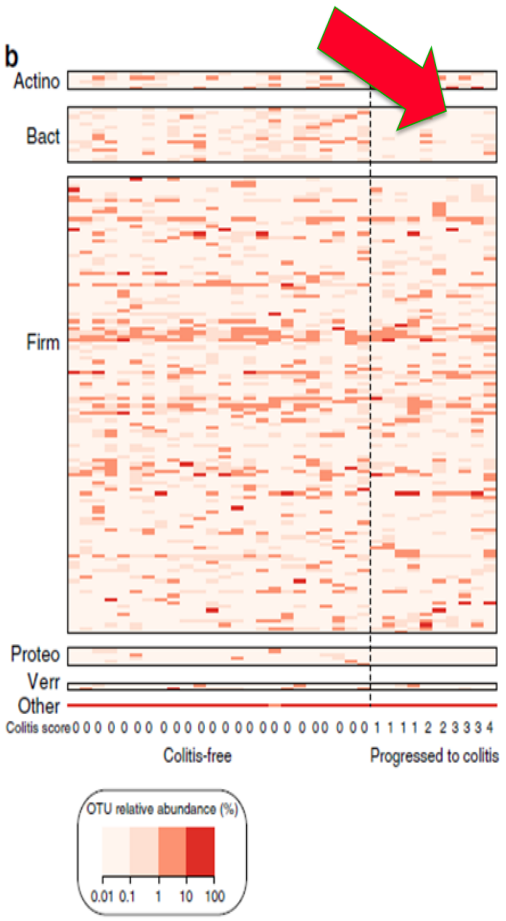
Thomas and Wang et al N Engl J Med 2021 Feb 11;384(6):581-583
Esfahani et al New England Journal of Medicine 2020 382;24
Bishu et al Gastroenterology. 2021;160(3):932-934.e3.





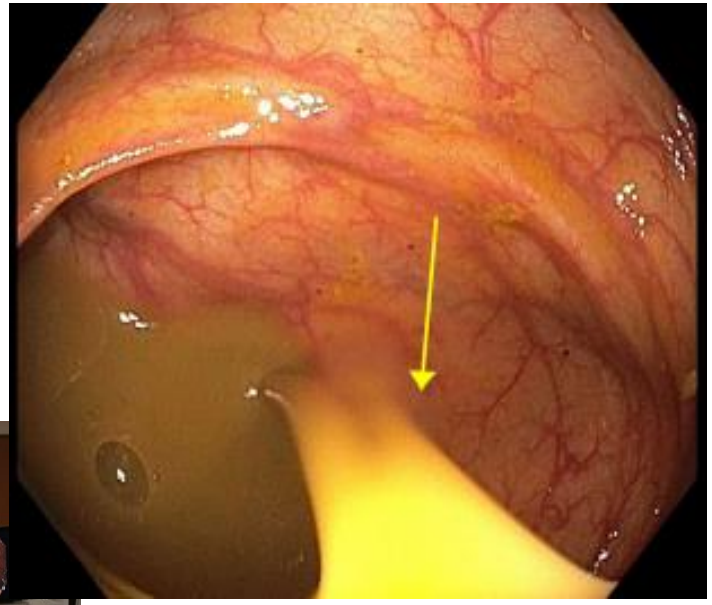




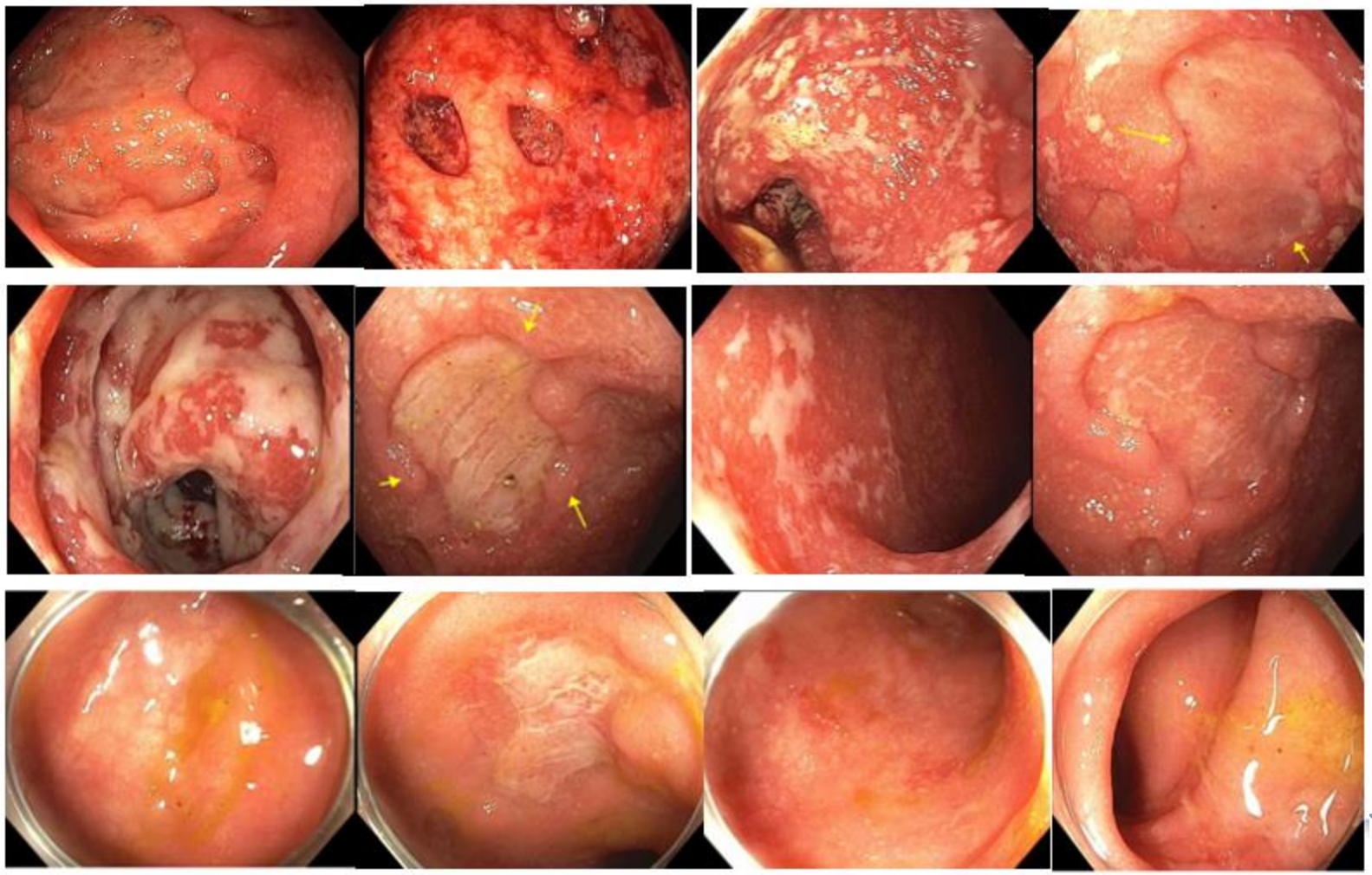


Vetizou M et al Science 2015; 350:1079–1084
Dubin K et al Nature communications | 7:10391 | DOI: 10.1038/ncomms10391

1st Fecal Microbiota Transplantation at MDACC 06/13/2017



1st FMT Case



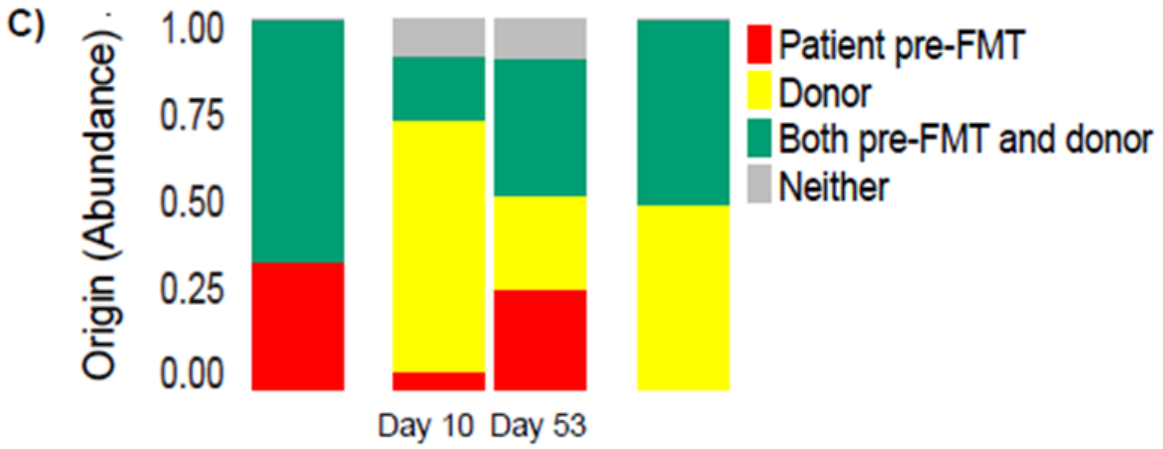
1 **Original colonoscopy at the diagnosis**

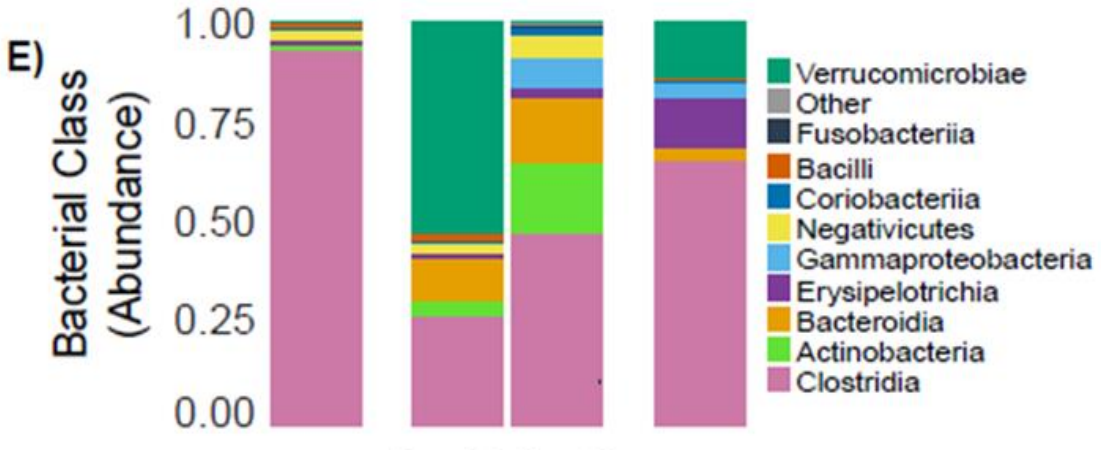
2 **After steroid+2 doses infliximab+1 dose of vedolizumab (3 months)**

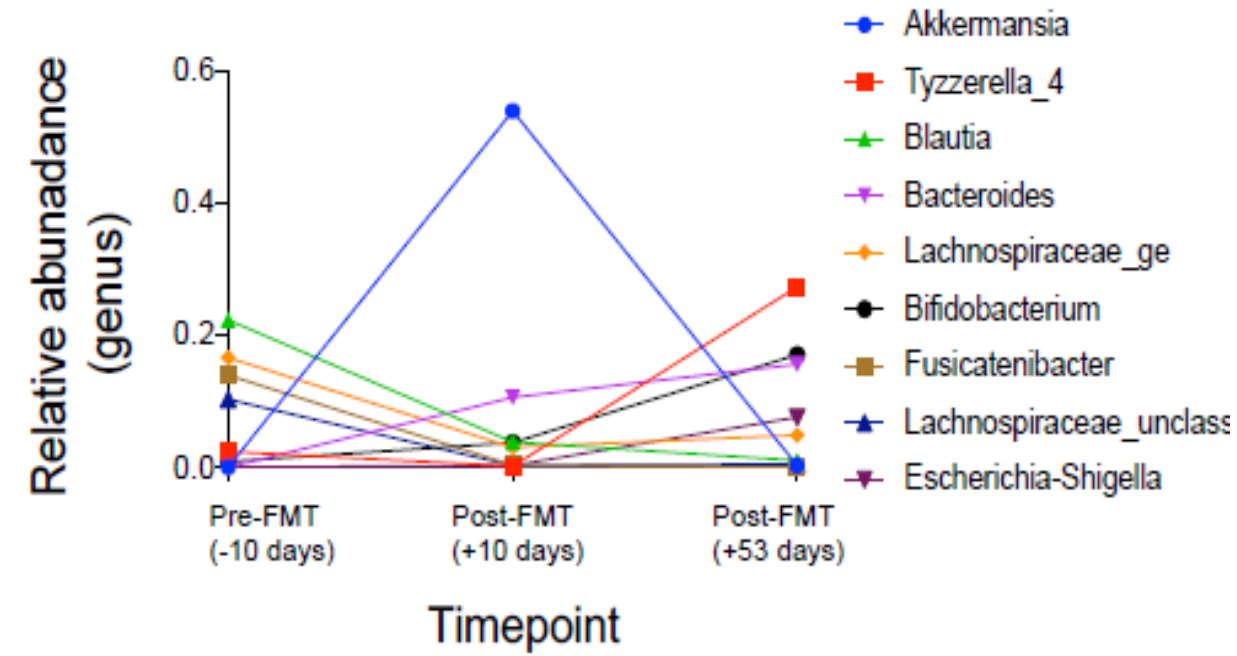
3 **4 weeks after the FMT treatment**

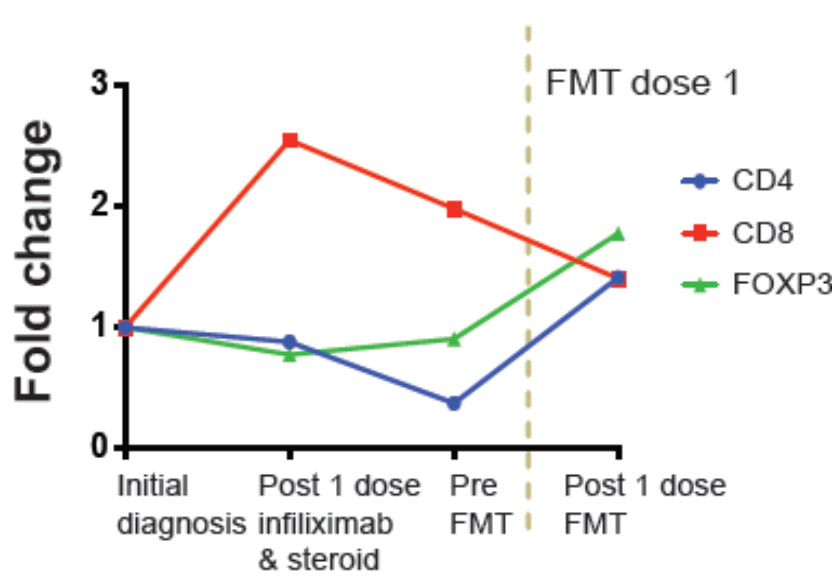
Wang et al Nature Medicine, 2019 Jan;25(1):188

Stool Metagenomic Analysis and IHC



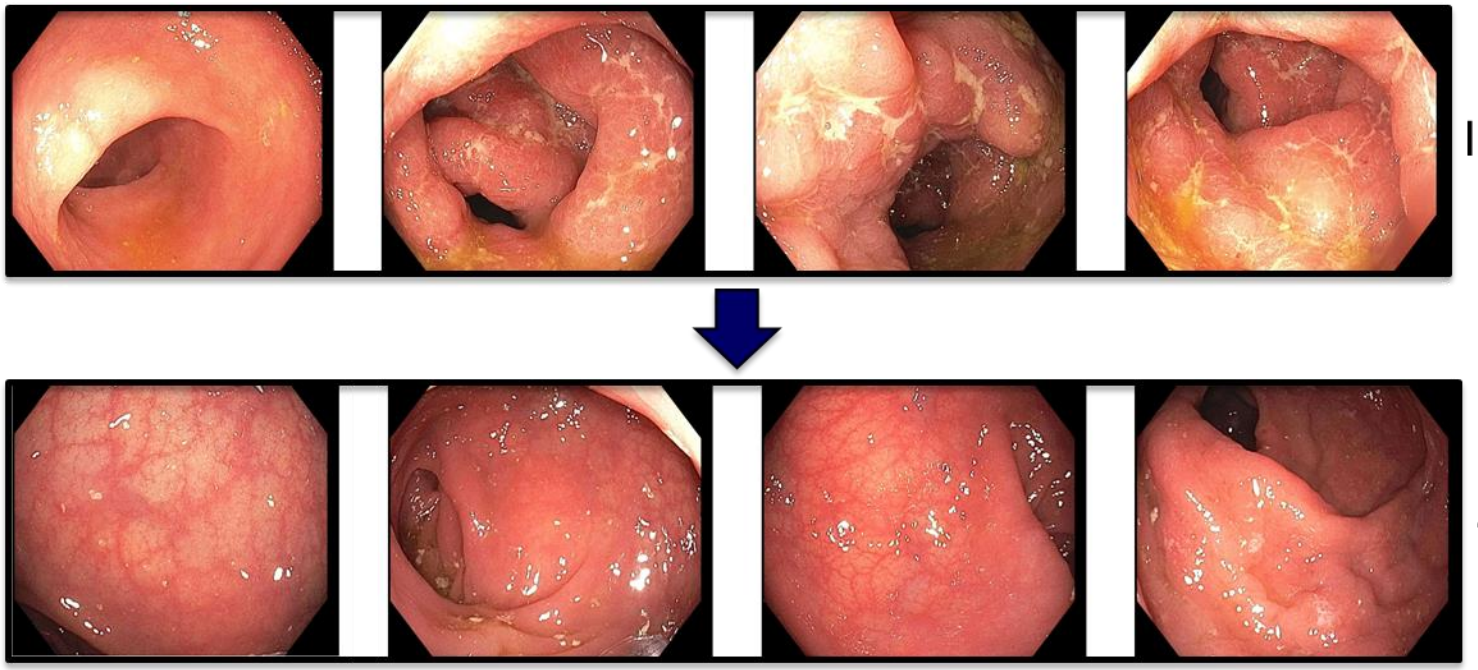






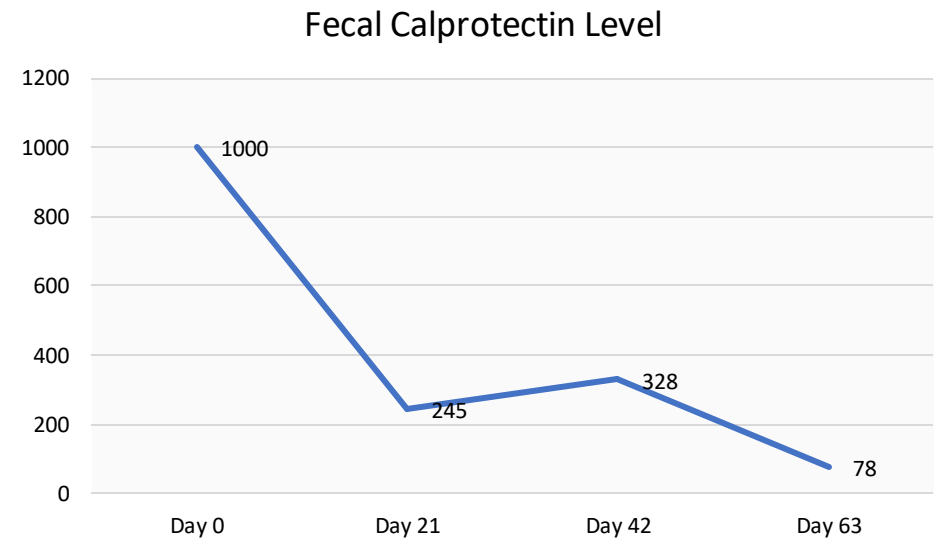
Wang et al Nature Medicine, 2019 Jan;25(1):188

ICI Resumption Post Front Line FMT for ICI Colitis



ICI colitis onset

4 weeks later



- Diarrhea resolved within 24 hours, and sustained over 15 months.
- Resumed nivolumab x 2 doses after FMT followed by surgery.

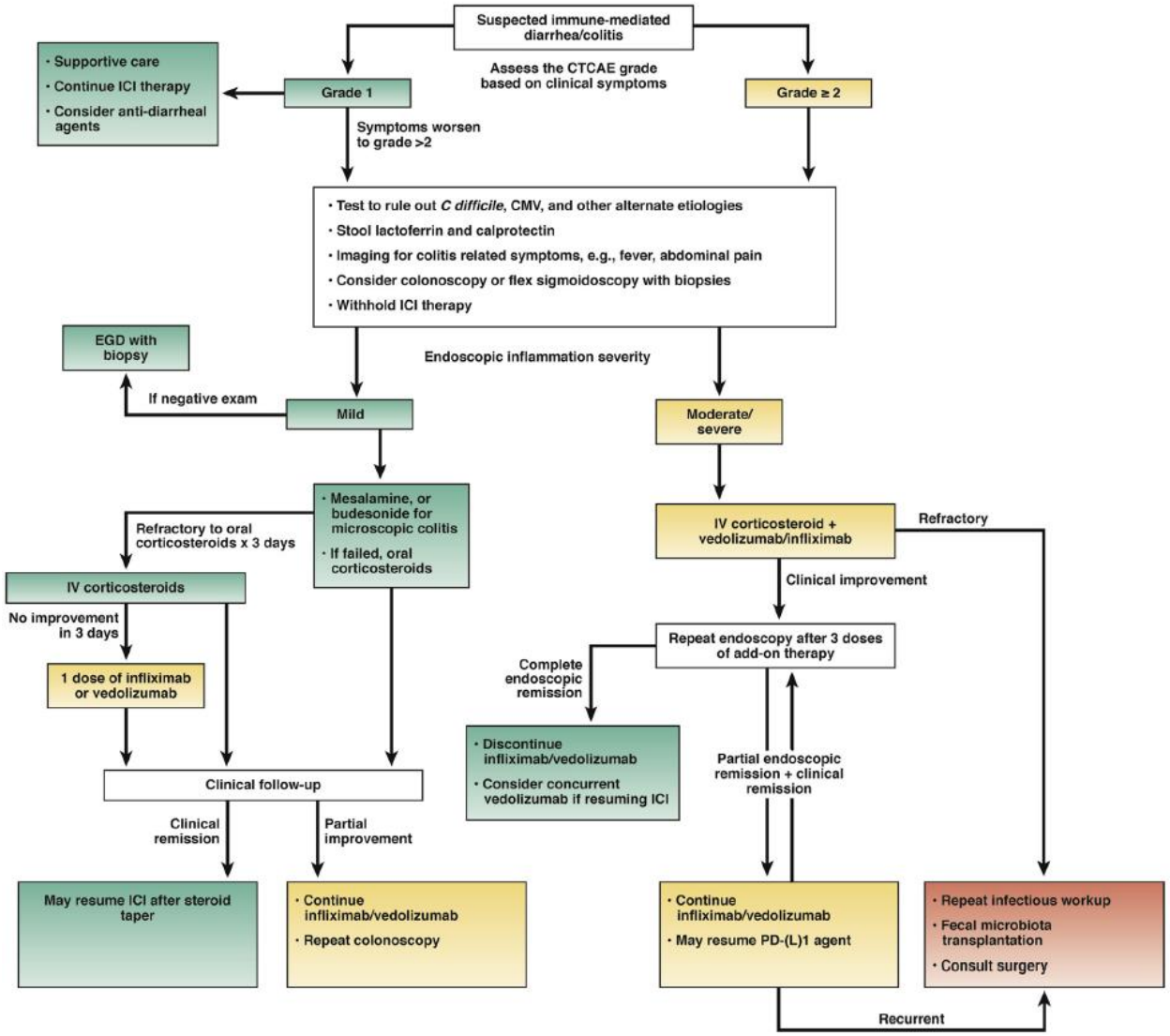
Annals of Internal Medicine, in press, 2022

FMT Cases for Refractory ICI colitis

FMT characteristic and outcome (N=37)	
Median time from initial IMC to FMT– days (IQR)	121 (75-226)
Symptom improvement after FMT, all patients – no (%)	31 (83.7%)
Median days from FMT to symptom improvement (IQR), n=37	5 (2-10)
FMT-related adverse events within 7 days –no (%)	6 (16.2%)
FMT-related adverse events within 30 days –no (%)	2 (5.4%)
Resumed cancer treatment after FMT – no (%)	11 (29.7%)
Clinical remission of colitis at the end of the study period	35 (94.6%)

Thomas et al The American Journal of Gastroenterology. 2021,116:S68-S69.

AGA Guideline



Dougan, Wang, et al. AGA Clinical Practice Update on Diagnosis and Management of Immune Checkpoint Inhibitor Colitis and Hepatitis: Expert Review. Gastroenterology 2021;160:1384–1393.

Additional Information

MD Anderson colitis management algorithm:

https://www.mdanderson.org/content/dam/mdanderson/documents/for-physicians/algorithms/clinical-management/clin-management-immune-mediated-colitis-web-algorithm.pdf

Managing Immunotherapy Related Organ Toxicities, A Practical Guide
https://link.springer.com/book/10.1007/978-3-031-00241-0

For referral of potential candidate for trial, pls email GIColitisTrials@mdanderson.org
For referral of colitis patient for SOC, pls contact me at ywang59@mdanderson.org

Other Extra-GI Luminal AEs

	Hepatitis and cholangiopathy	Pancreatitis	Esophago-Gastroenteritis	Appendicitis and Cholecystitis
Incidence	11-29%	0.6-4%	Uncommon	Rare-0.6%
Clinical Presentations	-Malaise -Abdominal pain -Fever -Nausea/vomiting -Jaundice	-Nausea/vomiting -Abdominal pain -Fever	-Nausea/vomiting -Abdominal pain -Indigestion -GI bleed	-Nausea/vomiting -Abdominal pain -Fever
Evaluation	-Blood work -Imaging -Liver biopsy	-Blood work -Imaging	-EGD -Imaging	-Imaging
Medication	-Steroid (prednisone, budesonide) -Cellcept -Azathioprine -ATG	-IV hydration -Pain control	-Proton pump inhibitor -H2-blocker -Steroid -SIT	-Antibiotics -Surgery -Percutaneous drainage

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- MDA collaborators

GHN, GU onc, Melanoma, Endocrine onc, Head/neck/lung onc, Genomic medicine, Pathology, Emergency medicine, Investigational Cancer Therapeutics, Radiology, Biostat

- External collaborators (USA)

Cleveland Clinic, Dana-Farber Cancer Institute, Georgetown Univ, Johns Hopkins Univ, Massachusetts General Hosp, Memorial Sloan Kettering, National Cancer Institute, Ohio State Univ, UT Public Health, Vanderbilt Univ, Yale, Univ of Washington, Univ of Michigan

- External collaborators (Outside USA)

Univ of Perugia (Italy), King's College of London (UK), Imperial College of London (UK), University of Liverpool (UK), Chelsea and Westminster Hospital (UK), Universität München (Germany), Sheba Medical Center (Israel), Peter MacCallum Cancer Center (Australia)

CASE STUDY

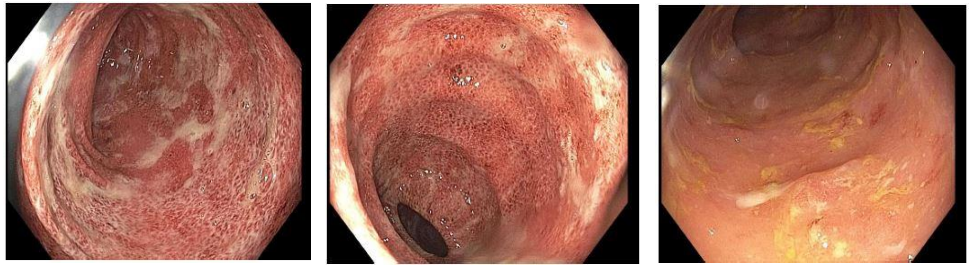
Case Presentation

- 69-year old female with metastatic lung cancer, treated with multiple lines of chemotherapy.
- Received atezolizumab maintenance therapy with good tumor response.
- Developed significant diarrhea (CTCAE grade 2; > 7 times/day with mucus in the stool).

Evaluation

Laboratory work-up		
Test	Purpose	Value
GI Multiplex	Rule out infection	Negative
C. difficile	Rule out infection	Negative
Lactoferrin	Inflammatory Marker	Positive
Calprotectin	Inflammatory Marker	234

Endoscopic Findings



Erythema, congestion, loss of vasculature, friability, ulceration, and extensive inflammation

Pathologic Findings

Intraepithelial neutrophils, crypt abscesses, apoptotic bodies, crypt architectural distortion, Paneth cell metaplasia

Treatments

Options include:

- Antidiarrheals → loperamide, cholestyramine

  Patient was treated with loperamide with no effect.

- Anti-inflammatory medication → mesalamine

  Patient was treated with mesalamine with only slight improvement in symptoms.

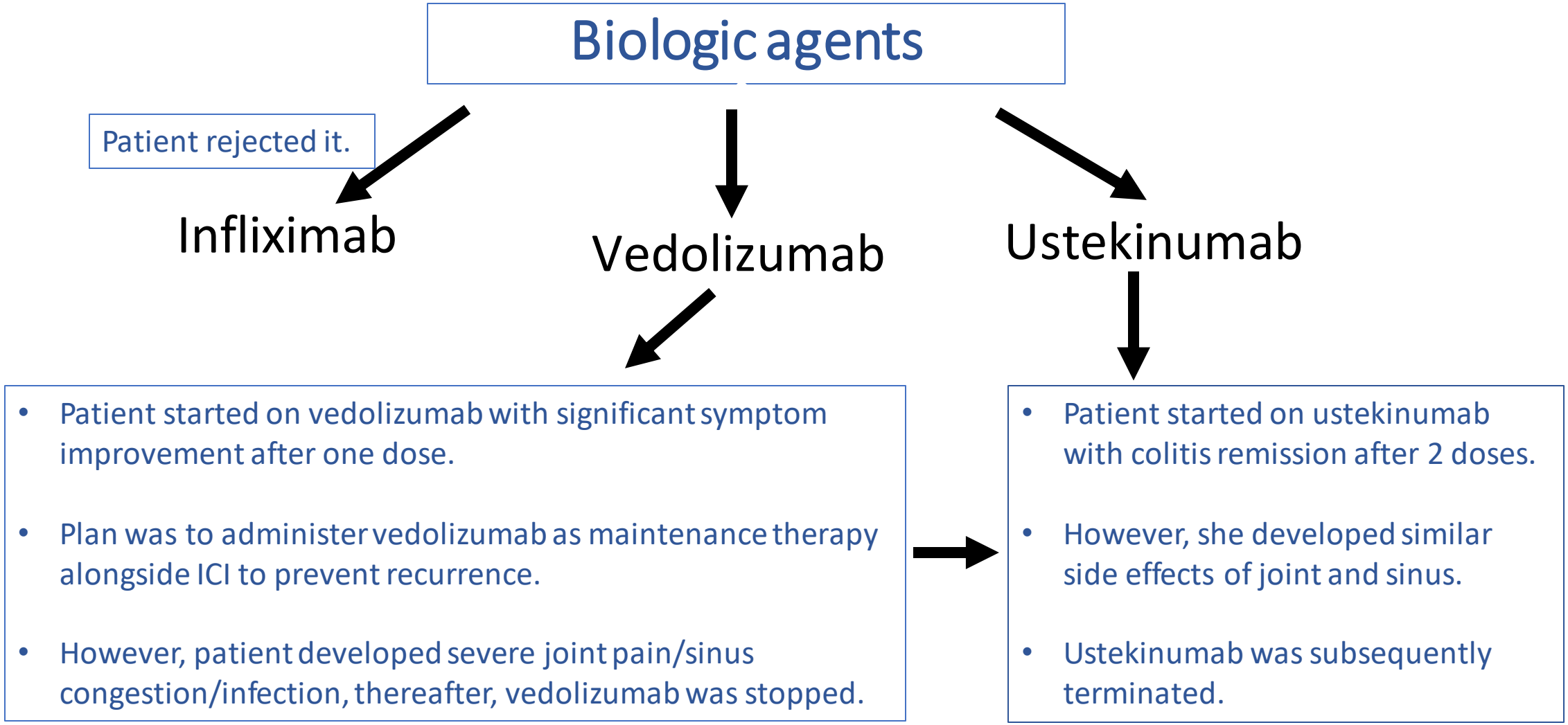
- Corticosteroids → prednisone, budesonide

  Patient received a course of oral prednisone at 1mg/kg with good clinical response.

Patient Course

- Diarrhea symptoms resolved following the steroid taper, and patient was maintained on mesalamine.
- Atezolizumab was resumed with improvement in her oncologic status.
- Patient presented with recurrent grade 2 diarrhea 9 months after ICI resumption.
- Repeat colonoscopy showed erythema, friability, ulceration, and inflammatory exudate.

Next Line of Treatment?

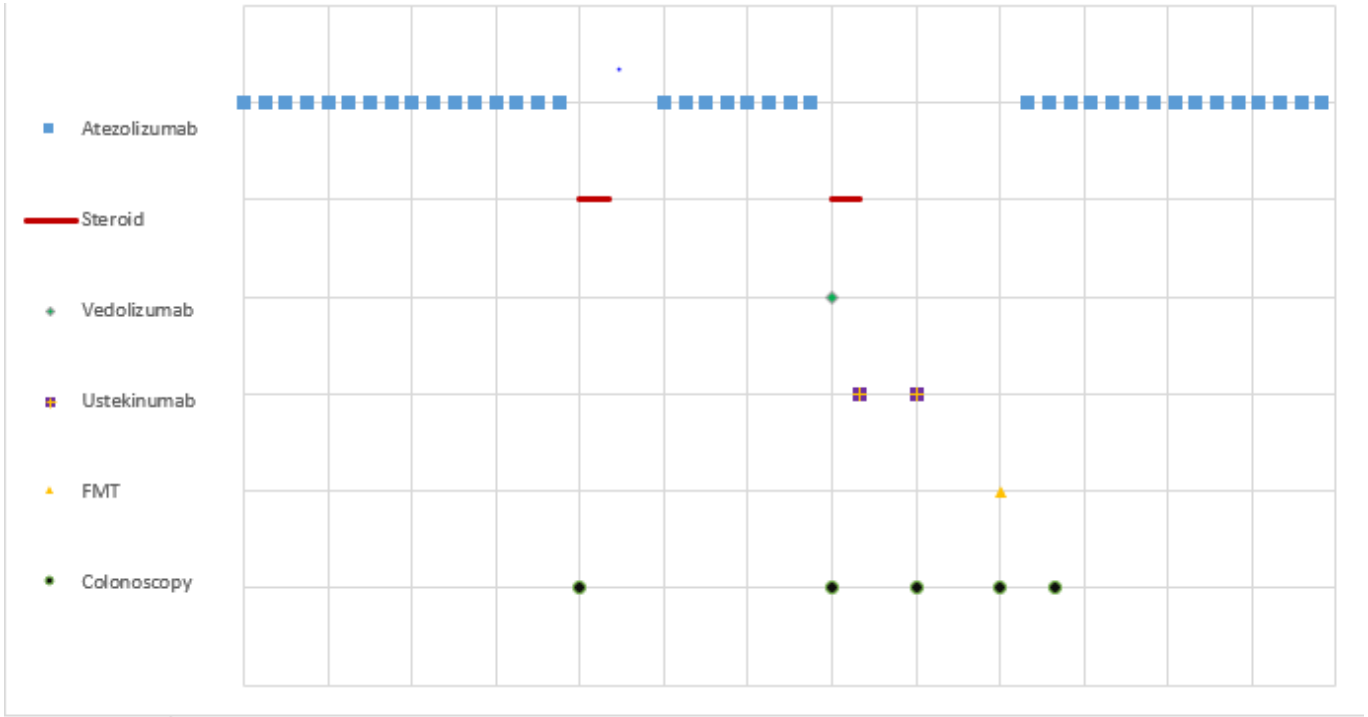


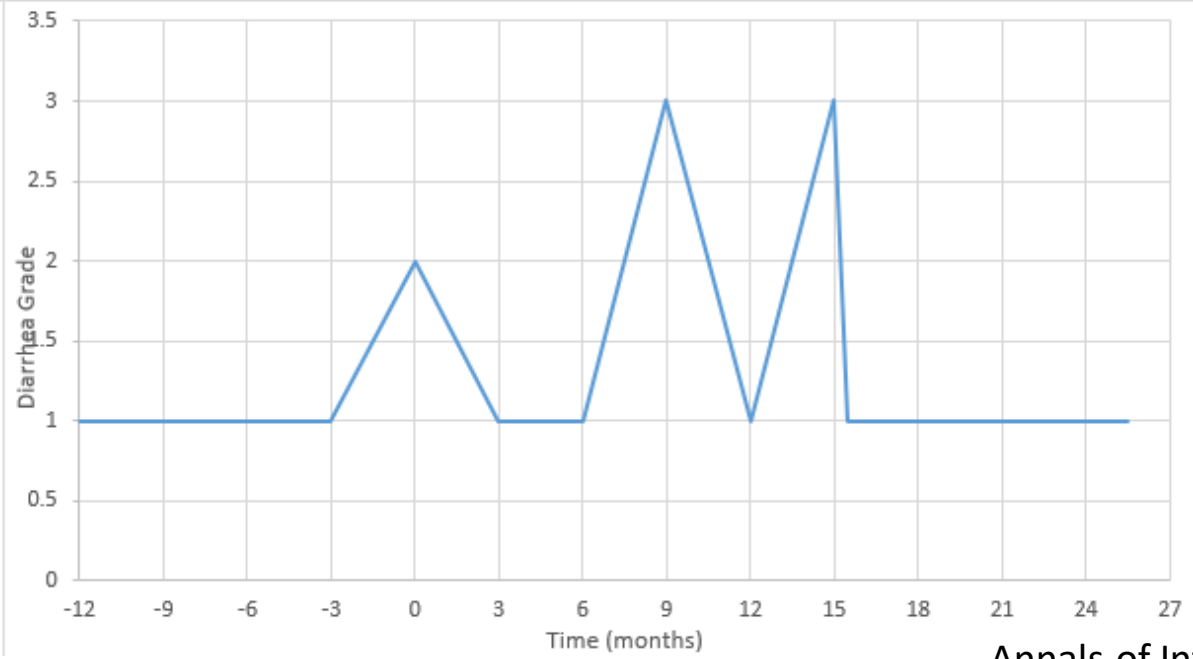
Cancer Progression

- Patient had cancer progression 3 months after previous events with a recurrence of her colitis (CTCAE Grade 3 this time).
- Oncology team urgently want to restart immunotherapy, but are also deeply concerned about the ongoing colitis.
- Is it a hopeless case?

Fecal Microbiota Transplantation

- Patient received fecal transplant treatment via colonoscopy
- Within one week, patient had resolution of their colitis symptoms
- Atezolizumab was safely restarted 2 weeks after FMT and continued for 12 months, with an uneventful treatment course.
- Both clinical and endoscopic remission of colitis was achieved, and patient's cancer was stable with minimal lymphadenopathy.





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Final Summary

- Stool inflammatory markers can be useful to screen and monitor colitis status.
- Endoscopy with biopsy can provide more accurate severity assessment for colitis than CTCAE.
- High risk endoscopic features are associated with more refractory colitis disease course.
- Early introduction of steroid-sparing immunosuppressant agents can have high efficacy in treating aggressive colitis.
- Endoscopic remission is associated with lower colitis recurrence, should be considered as the treatment target.
- Incidence of ICI colitis predicts better overall survival.
- Fecal transplant can be an effective treatment for refractory colitis by altering the microbiome.

QUESTIONS

ACCC
Association of Community Cancer Centers

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