ASCO Gastrointestinal Cancers Symposium

Gastroenterology Toxicities with Immune Checkpoint Inhibitors

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FACULTY DISCLOSURES

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

GI Toxicities

GI Luminal Toxicities	Other GI Toxicities
Mucositis	Cholecystitis
Esophagitis	Appendicitis
Gastroenteritis	Diverticulitis
Colitis	

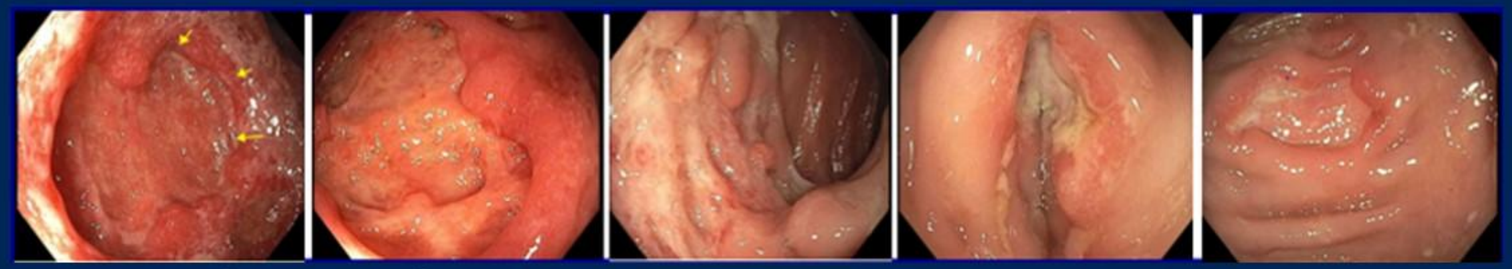
Clinical Presentations

	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

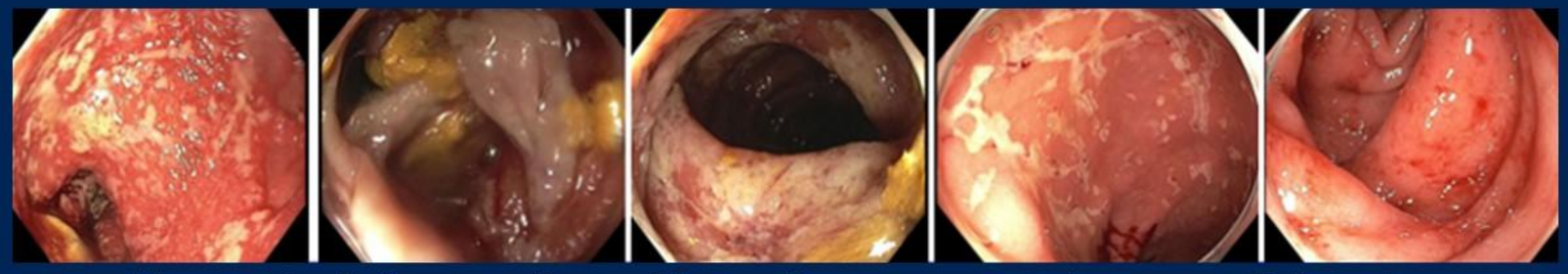
Time of onset: first ICI dose → 1 year after last dose; majority in 2-3 months.

https://ctep.cancer.gov

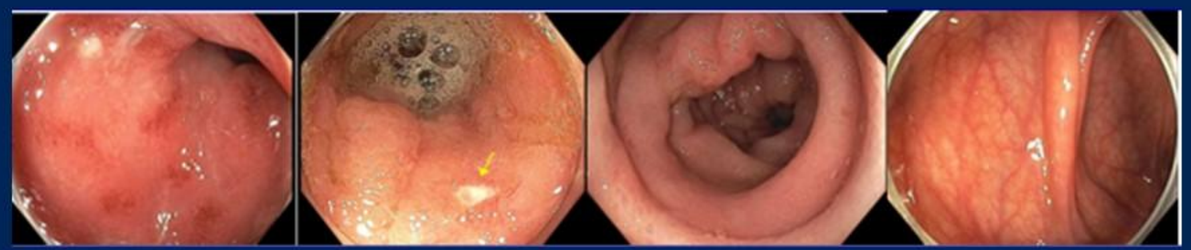
Endoscopy Presentations



Severe inflammation with large deep ulcers



Moderate inflammation with erythema, exudate, superficial ulcers



Mild inflammation with patchy erythema, aphtha, edema, or normal mucosa

IMC has wide spectrum of endoscopic presentations from mild to severe level.

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

Stool Biomarkers

	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)

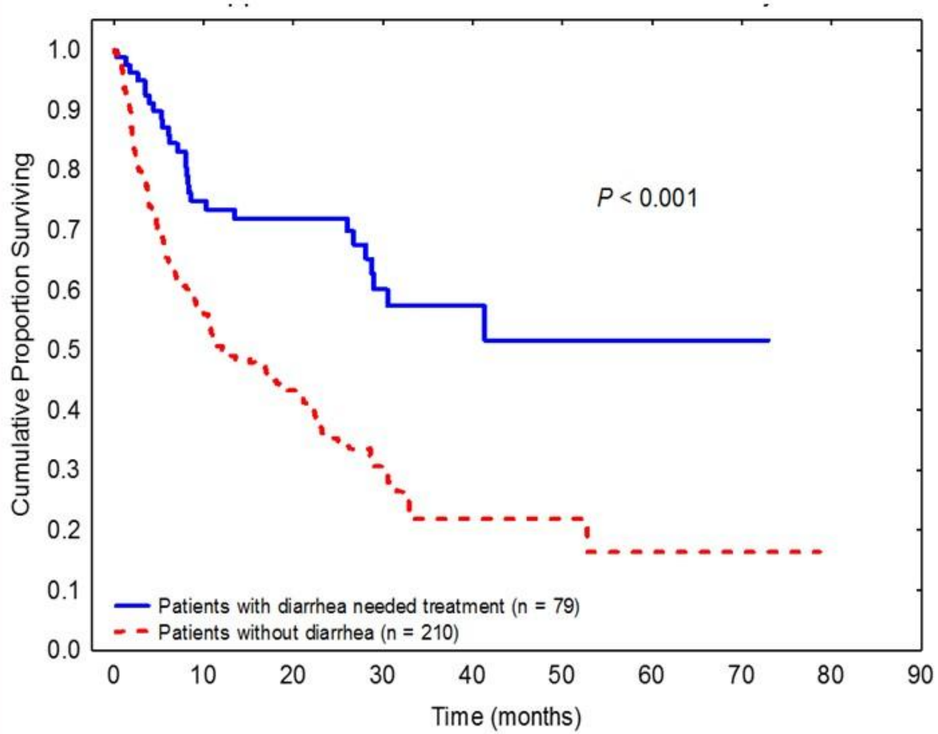
Scope Findings	Calprotectin (SD)
Ulcers	465 (363)
Non-Ulcer Inflammation	213 (184)
Normal	152 (133)
P	0.006

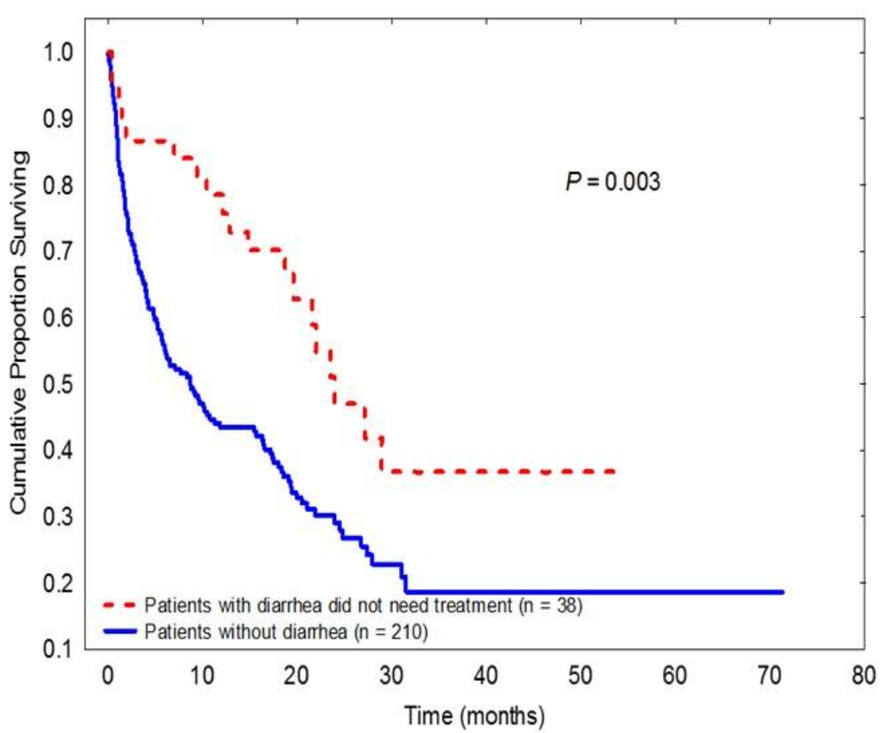
Sensitivity of lactoferrin for endoscopic inflammation is 70%.
Sensitivity of lactoferrin for histologic inflammation is 90%.

Stool biomarkers can serve as screening tool for colitis and surrogate marker for colitis disease monitoring.

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

Overall Survival





- *GI toxicity is associated with better overall survival.*
- *Goal is to control the GI toxicity and resume effective cancer treatment.*

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

Endoscopic Features

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
SIT: 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

High risk endoscopic features are predictive of steroid refractory colitis disease course.

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

Timing of Endoscopy

Characteristic	>30 days of onset N = 40	≤30 days of onset N = 142	P
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
SIT: Infliximab/vedolizumab, n (%)	8 (22.9)	34 (32.1)	0.395
Mean days from onset to first SIT dose	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

Early endoscopy to assess IMC severity can guide the SIT treatment and improve colitis disease course.

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

Factors 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
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
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

- *Endoscopic remission could decrease the recurrence of colitis.*
- *It serves as better treatment target rather than clinical remission.*

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

Timing of SIT

Covariate	≤ 10 days of onset N = 44	> 10 days of onset N = 40	P
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 (infliximab and vedolizumab)

Early SIT treatment can improve colitis disease course and decrease steroid exposure.

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

Calprotectin as Surrogate Marker

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

Fecal calprotectin can serve as surrogate marker to predict colitis remission and guide the treatment duration.

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

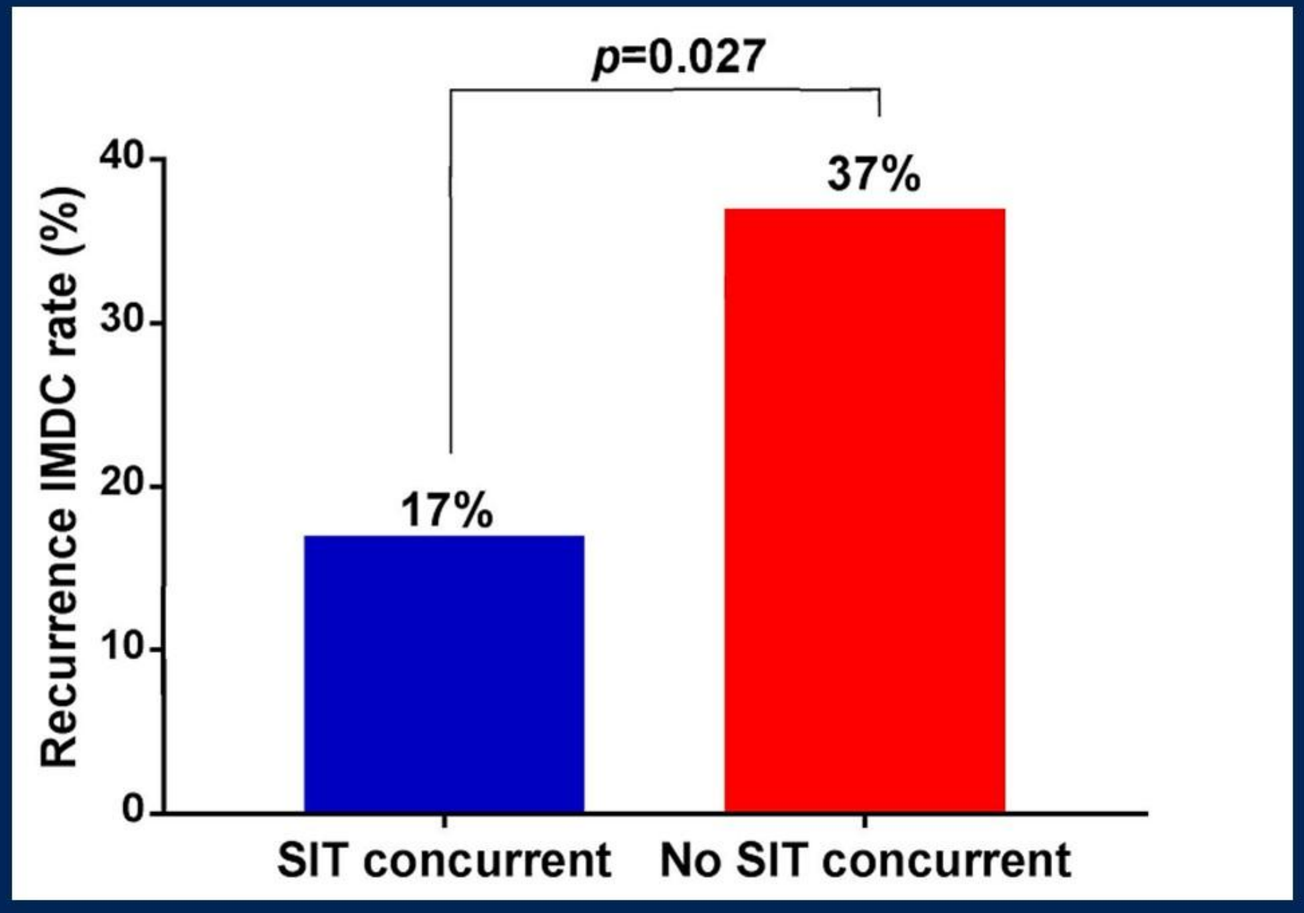
Factors of Colitis Recurrence

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

Severe index IMC event and CTLA-4 on resumption are associated with higher risk of colitis recurrence.

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

IMC Management on ICI Resumption



SIT: selective immunosuppressive therapy

(infliximab or vedolizumab)

Zou et al. Gastroenterology 2021;160 (6): Suppl. S-711
Badran et al. Gastroenterology 2022;162 (7): Suppl. S-79

Concurrent SIT treatment could effectively reduce IMC recurrence upon ICI resumption.

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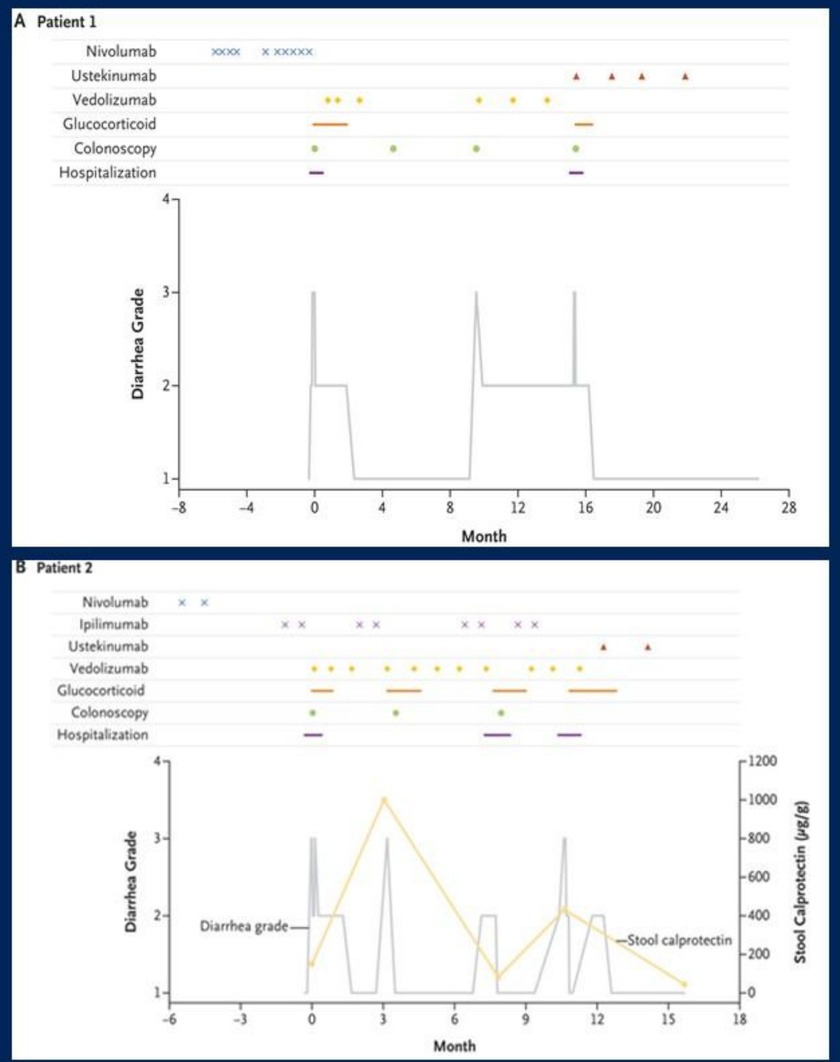
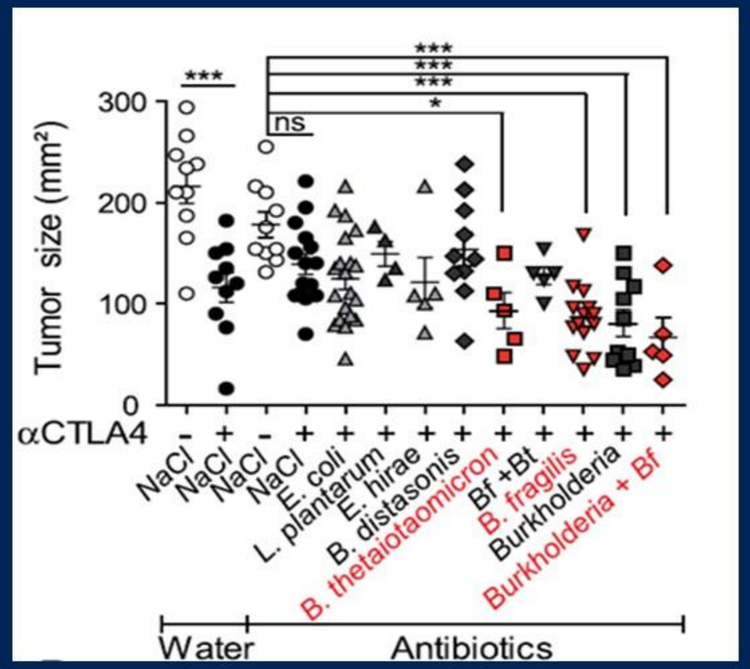
Ustekinumab and Tofacitinib

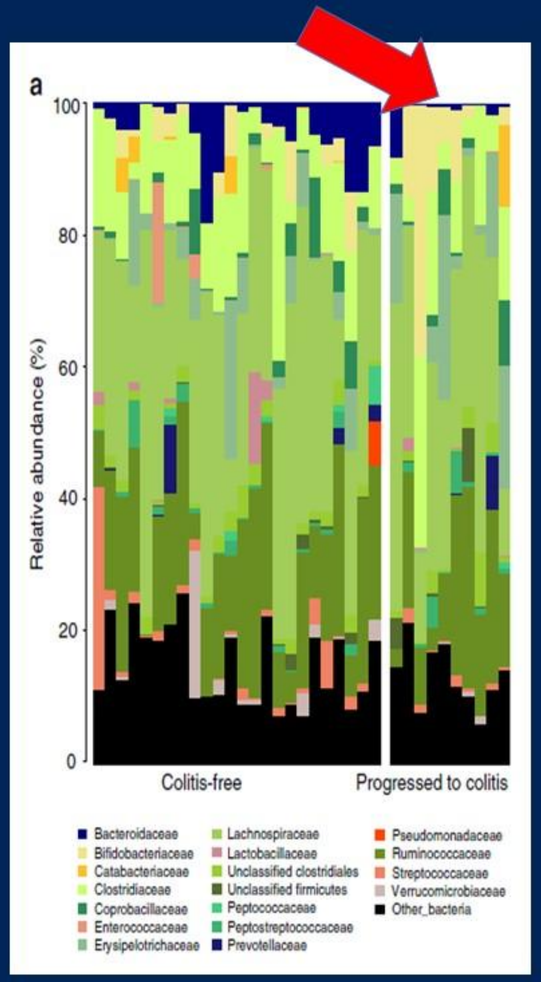


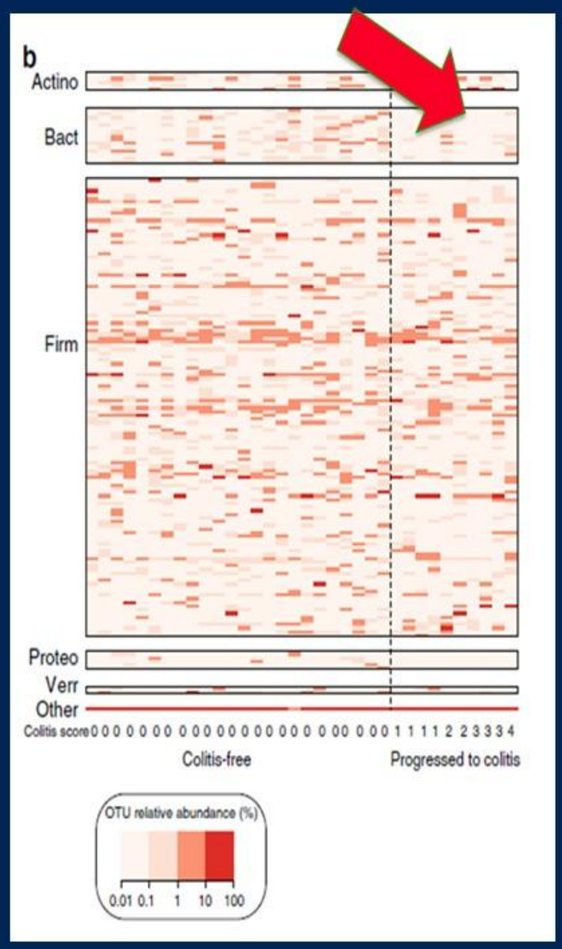
- 5 patients have been reported to achieve clinical response/remission to tofacitinib after failing infliximab or vedolizumab and steroid.
- More evidence is imperative in terms of safety in cancer patients from using these agents.

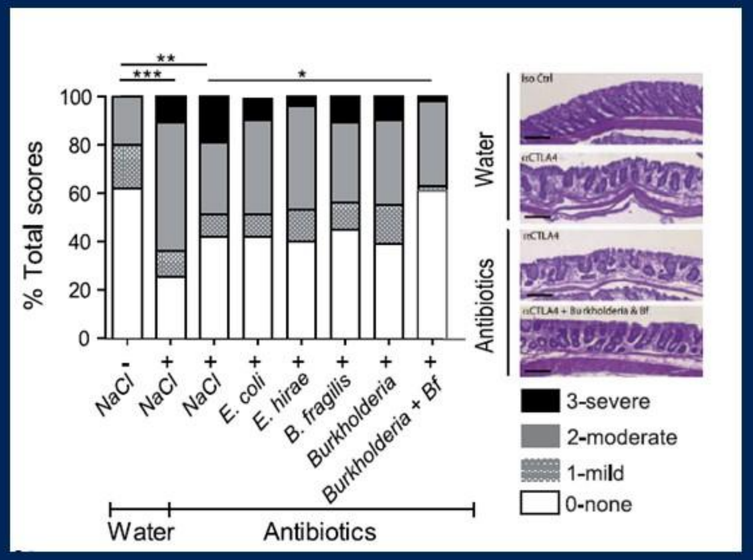
Ustekinumab and tofacitinib could be effective in refractory IMC.

Thomas and Wang et al N Engl J Med 2021;384(6):581-583
Thomas and Wang et al The Am J of Gastroenterol 2022; 117(10S):e635
Esfahani et al N Engl J of Med 2020;382(24):2374-2375
Bishu et al Gastro 2021;160(3):932-934.e3.



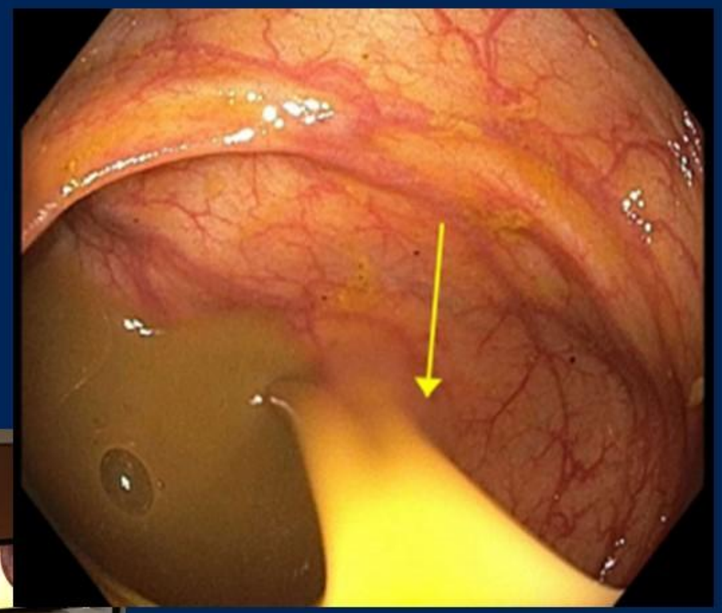




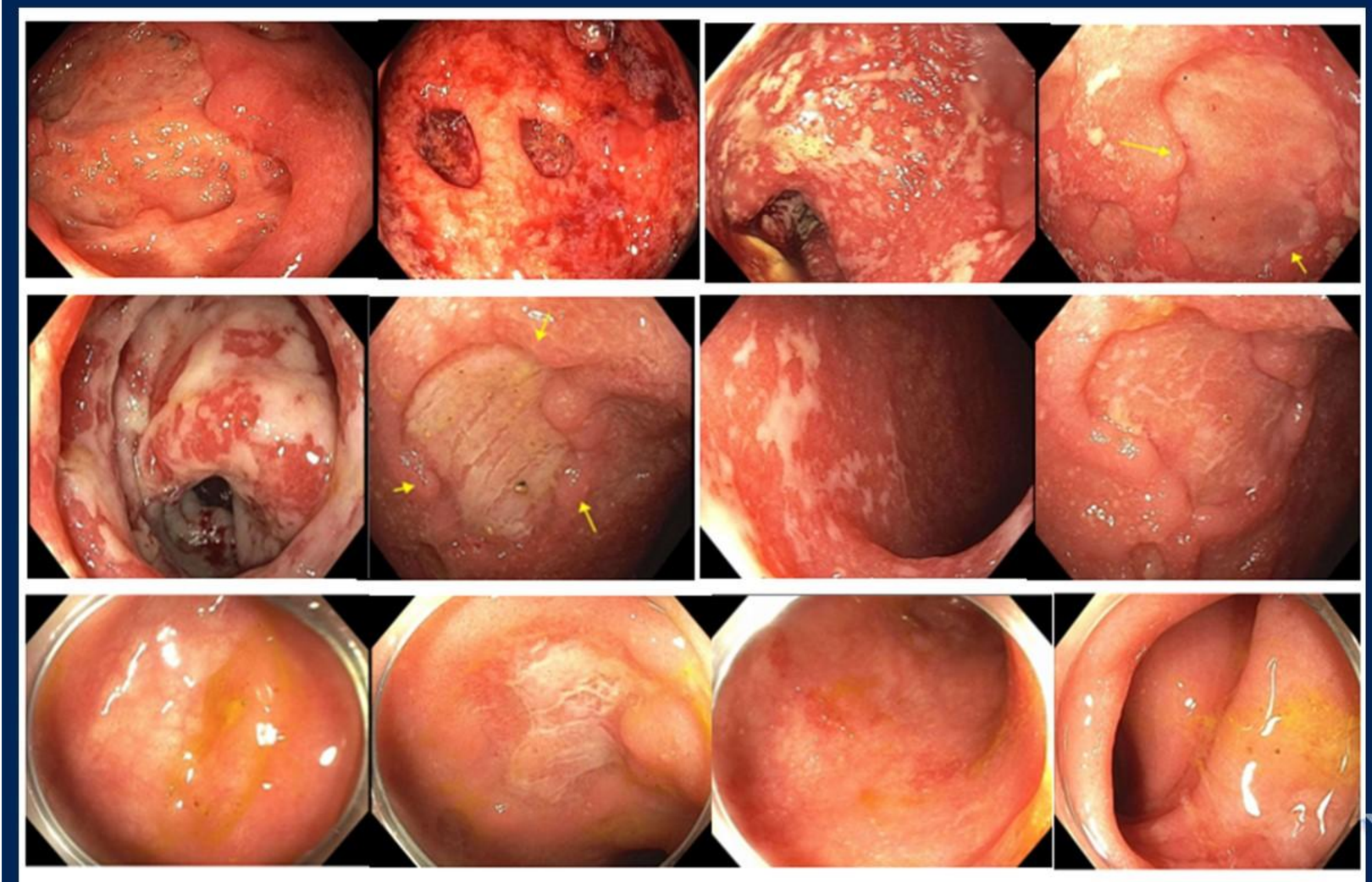


Vetizou M et al Science 2015; 350:1079–1084
Dubin K et al Nature communications 2016; 7:10391

1st Fecal Transplant at MDACC 06/2017



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

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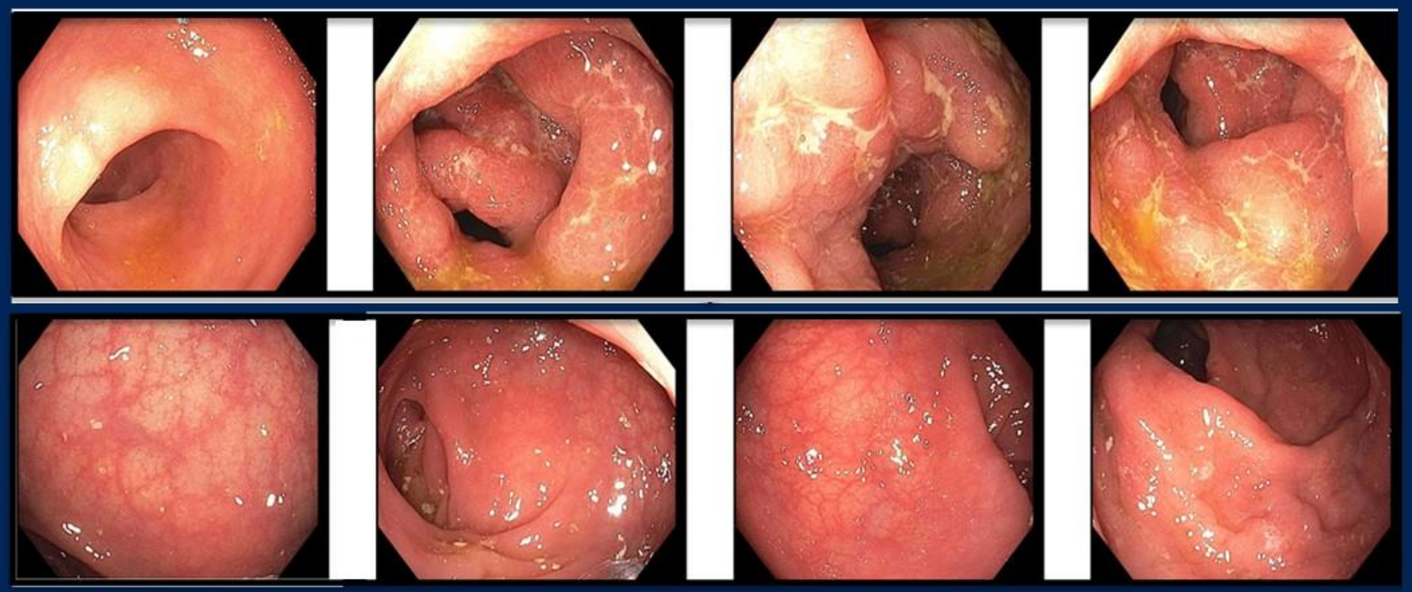
Front Line FMT for IMC

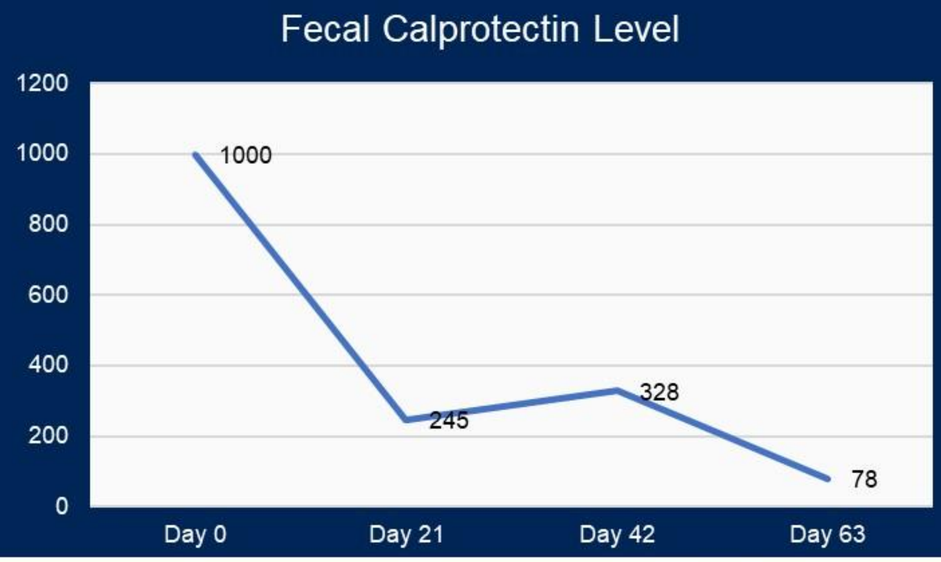


Time of colitis diagnosis

4 weeks after FMT

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

Amin and Wang et al Annals of Internal Medicine,
https://www.acpjournals.org/doi/10.7326/aimcc.2022.0490



FMT for Refractory IMC

FMT characteristic and outcome (N=37)	
Median time from initial IMC to FMT– days (IQR)	121 (75-226)
Symptom improvement after FMT– 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%)

FMT can be alternative strategy for IMC as compassionate or front line treatment with efficacy of 75-83%.

Wang et al The Am J of Gastroenterol 2022;117(10S):e508-e509.

Conclusions/Take-Away

- 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.

Acknowledgements

- Research team

Anusha Thomas, Hao Chi Zhang, Malek Shatila, Krishnavathana Varatharajalu, Fangwen Zou, Weijie Ma, Tenglong Tang, Hamzah Abu-Sbeih, Jake Jacob, Kavea Pannerselvam, Shruti Khurana, Barbara Dutra, Mostafa Eyada, David Szafron, Yantong Cui, Zane Peng, Brandon Zhao, Alice Saji, Maneera Chopra, Rajan Amin, Andrew Kuang, Victor Garcia-Rodriguez, Aaron Isaac, Kevin Yu, Shaleen Vasavada, Miho Kono, Antony Mathew, Austin Thomas, Antonio Pizuorno, Cythia Liu, Andrew Kuang, Gabriel Sperling, Farzin Ashaghi, Sidra Naz, Muhammad Vohra, Cyril Mazhuvanchery

- 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)