

Management of Immune Checkpoint Inhibitors Related Colitis

Yinghong (Mimi) Wang, MD, PhD

Director of Inflammatory Bowel Disorders

Director of Fecal Microbiota Transplantation

Department of Gastroenterology, Hepatology and Nutrition

Case Presentation

60s yo woman with stage IV lung cancer with metastasis



Atezolizumab maintenance (~17 doses)



Developed grade 3 diarrhea/colitis, responded to one course of steroid



Resumed atezolizumab → colitis progression



Received 2nd course of steroid + vedolizumab x1 with good response



allergic reaction: cough, sinus congestion, joint pain/swelling

Started on Ustekinumab x 2 (similar allergic reaction)



Recurrent diarrhea and cancer progression → fecal transplantation



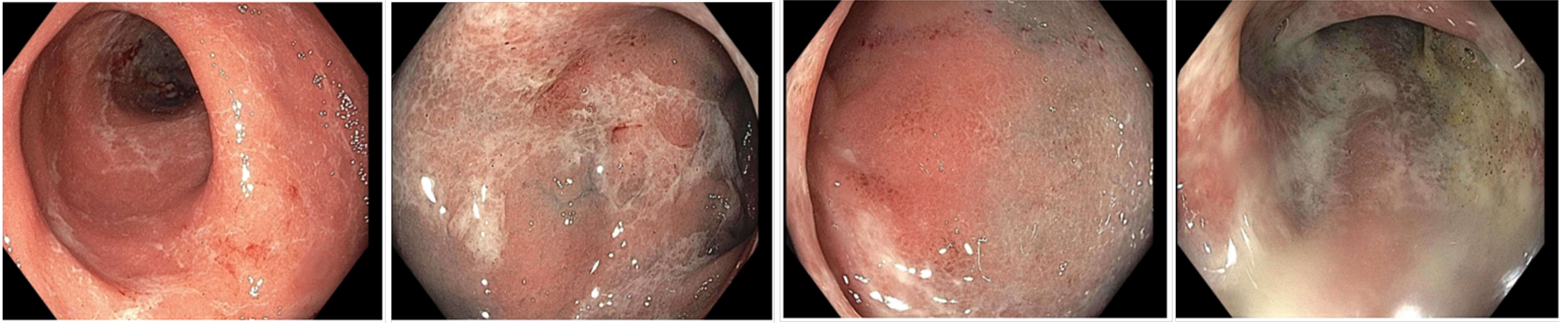
Resumed atezolizumab 2 weeks after for 15 doses



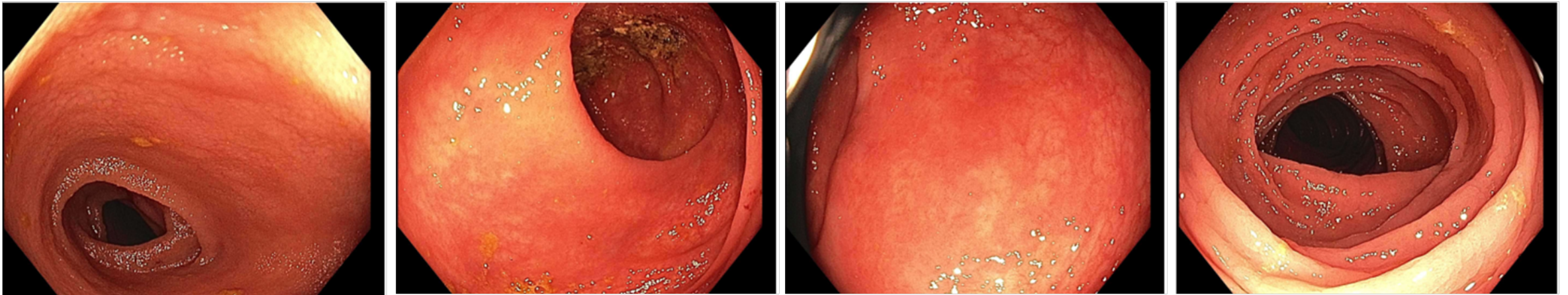
Remain colitis free for 11 months



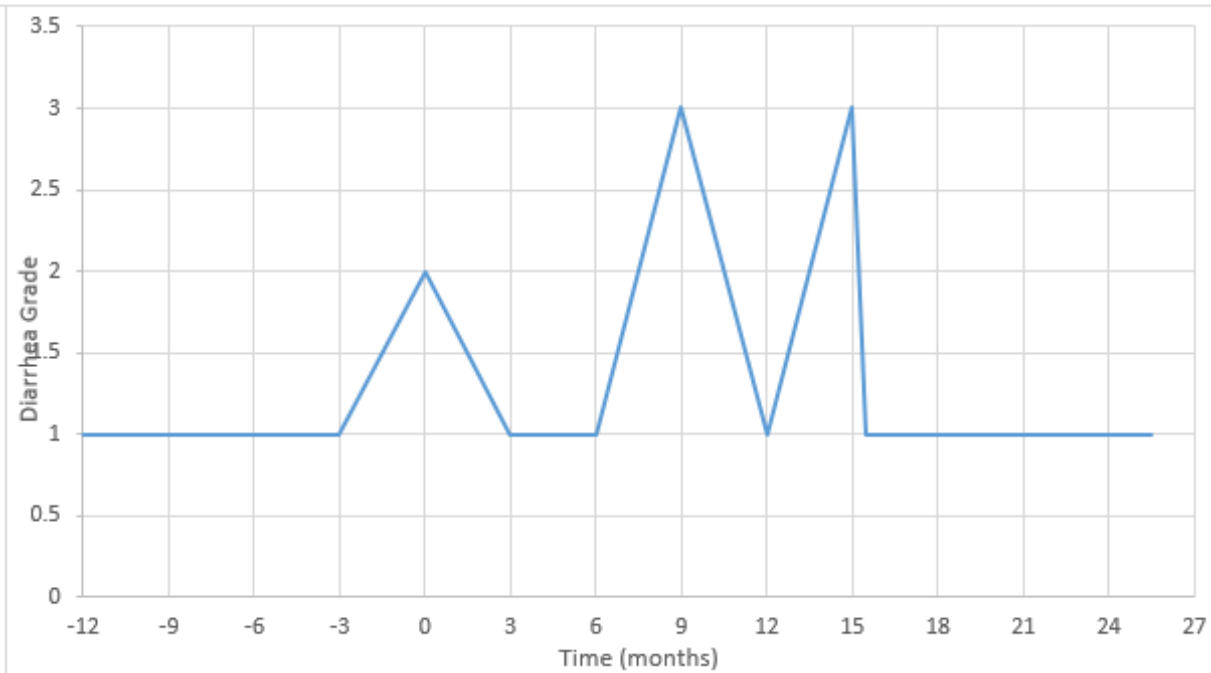
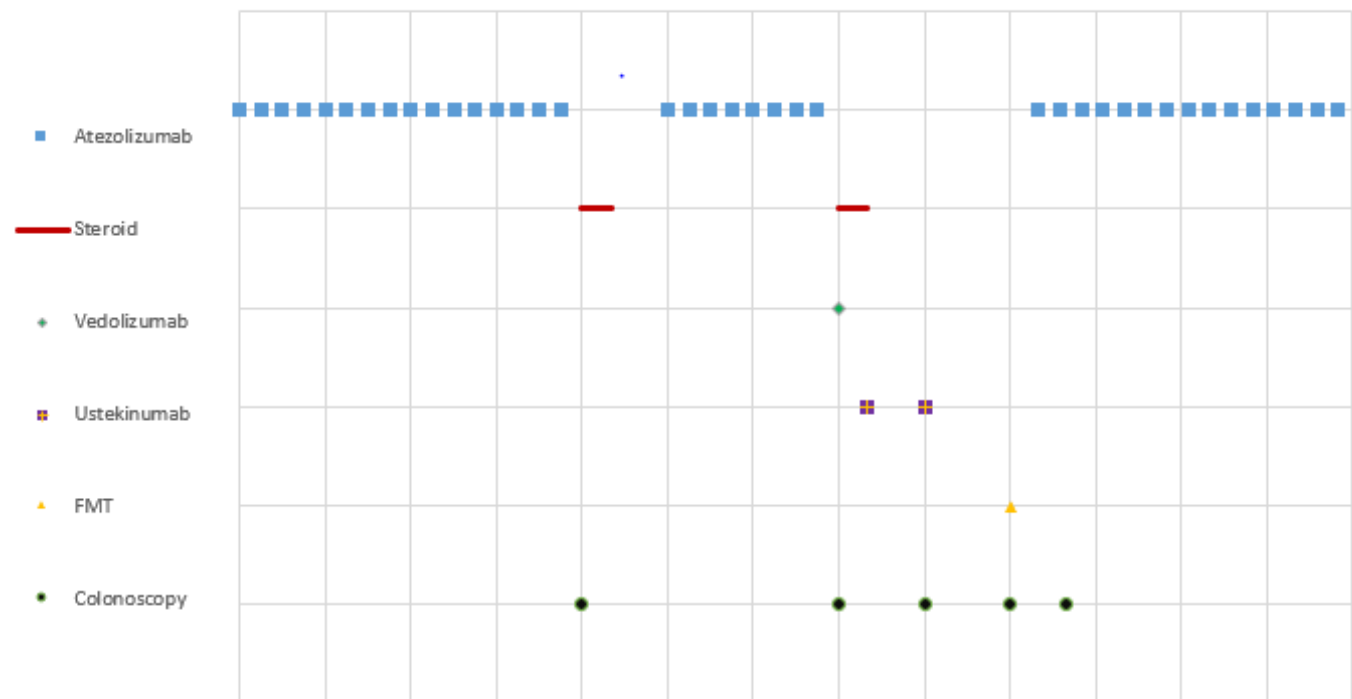
Cancer in remission



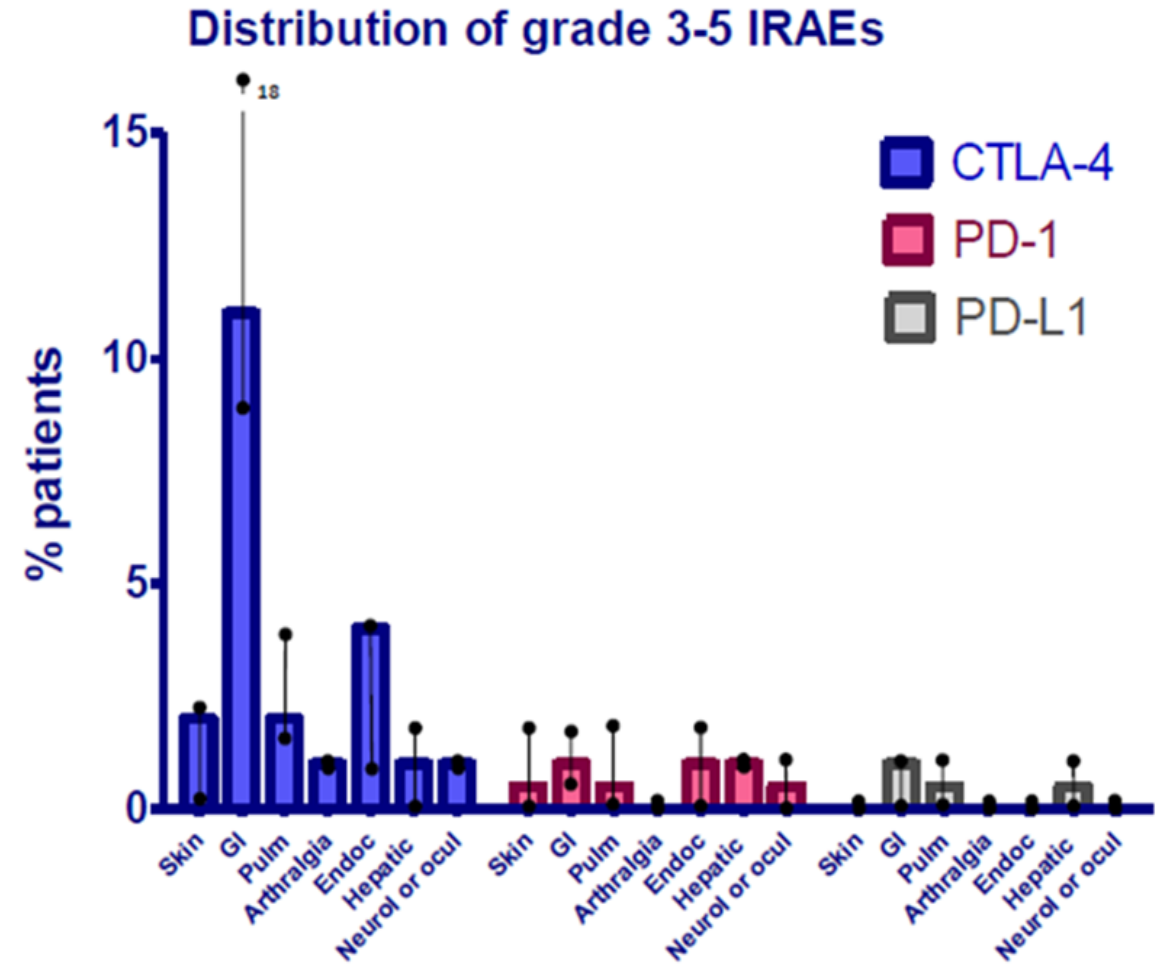
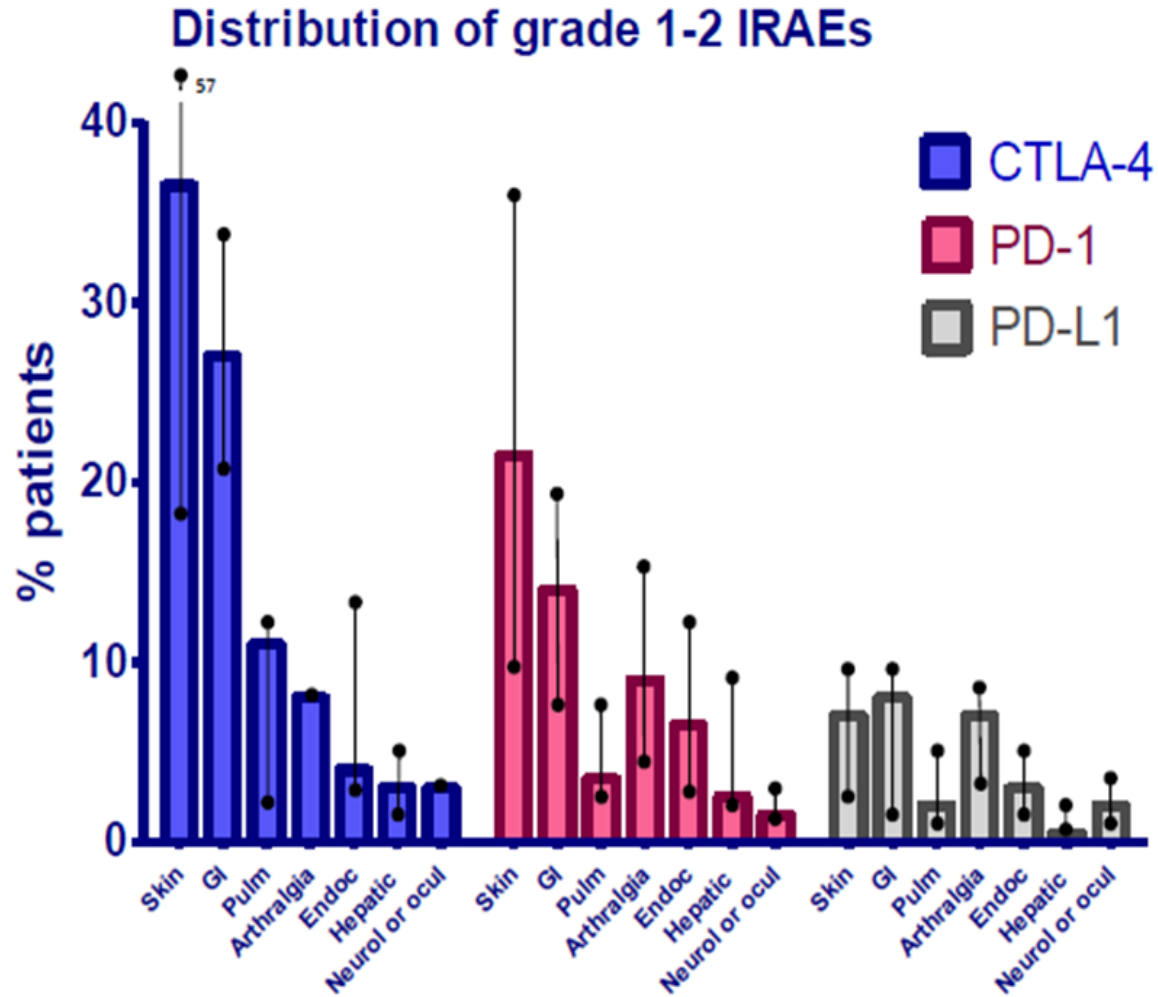
Diagnosis of ICI colitis



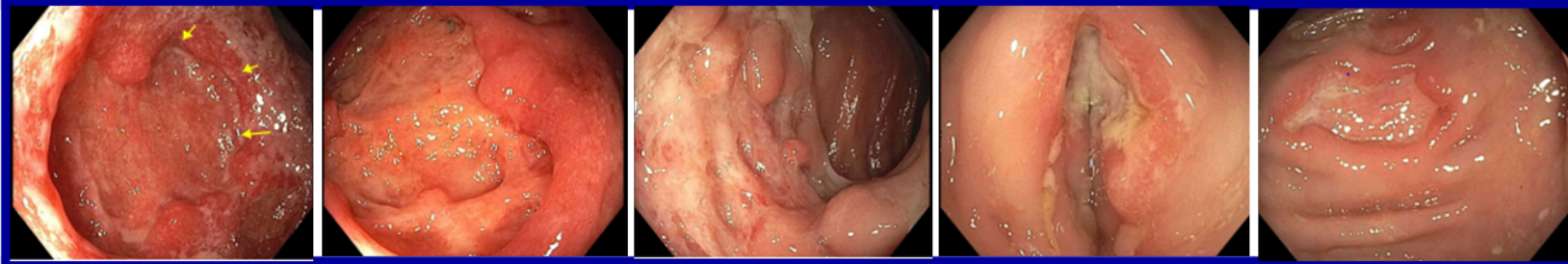
After FMT



Distribution of irAEs



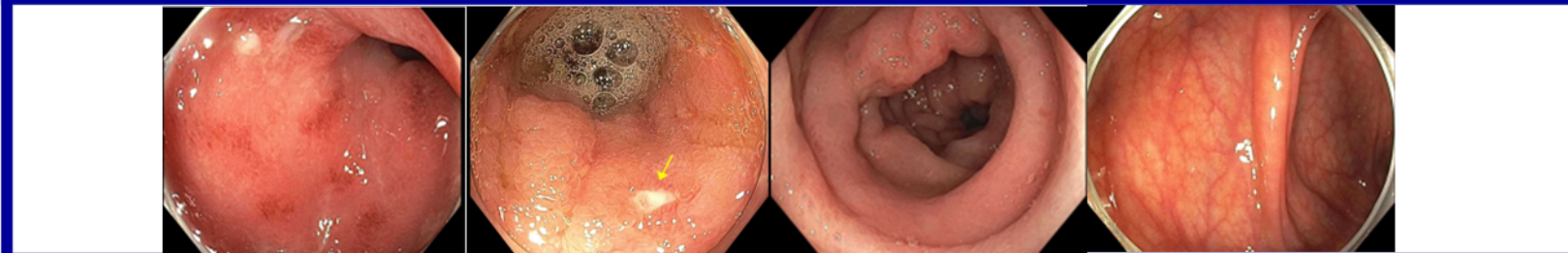
Endoscopy Presentations



Severe inflammation with large deep ulcerated mucosa

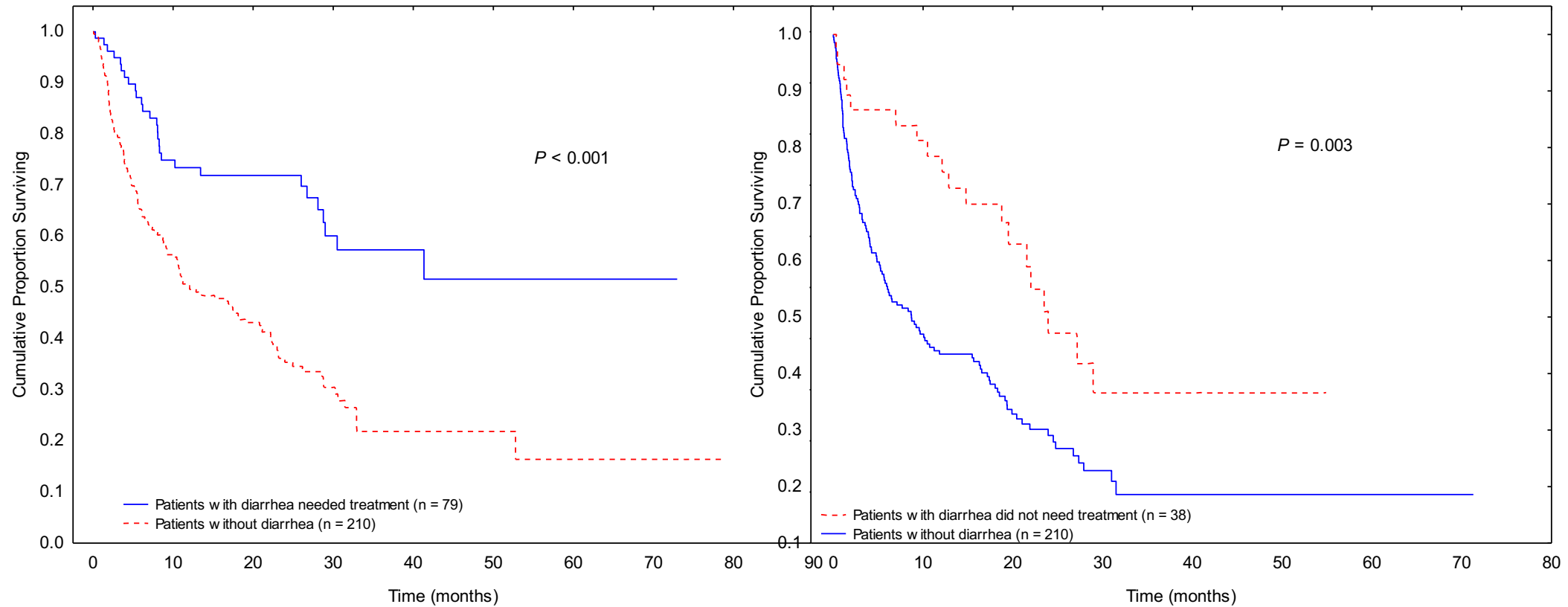


Moderate to severe inflammation with diffuse/patchy erythema, superficial ulcers, exudate, LOV



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

Overall Survival with GI Toxicity



Role of Endoscopy and Pathology in Evaluation and Outcome

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

^aHigh-risk endoscopic features; deep ulcers >2 mm in depth, large ulcers > 1 cm, multiple ulcers, extensive involvement

Timing of Endoscopy and Clinical Outcomes

Characteristic	> 7 days of onset N = 89	≤ 7 days of onset N = 93	P value
IV steroids, n (%)	46 (66.7)	37 (56.9)	0.287
Duration of symptoms (days, SD)	47 (104)	19 (47)	0.026
Duration of steroid (days, SD)	74 (90)	49 (43)	0.053
Infliximab/vedolizumab, n (%)	26 (29.2)	27 (29.0)	1.000
Duration from onset to first infliximab/vedolizumab dose (days, SD)	23 (17)	14 (17)	0.154
Outcomes, n (%)			
Hospitalization	58 (65.2)	74 (79.6)	0.032
Duration of hospitalization (days, SD)	9 (7)	6 (7)	0.068
ICU admission	4 (4.5)	3 (3.2)	0.856
Recurrence	60 (67.4)	71 (76.3)	0.191

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

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

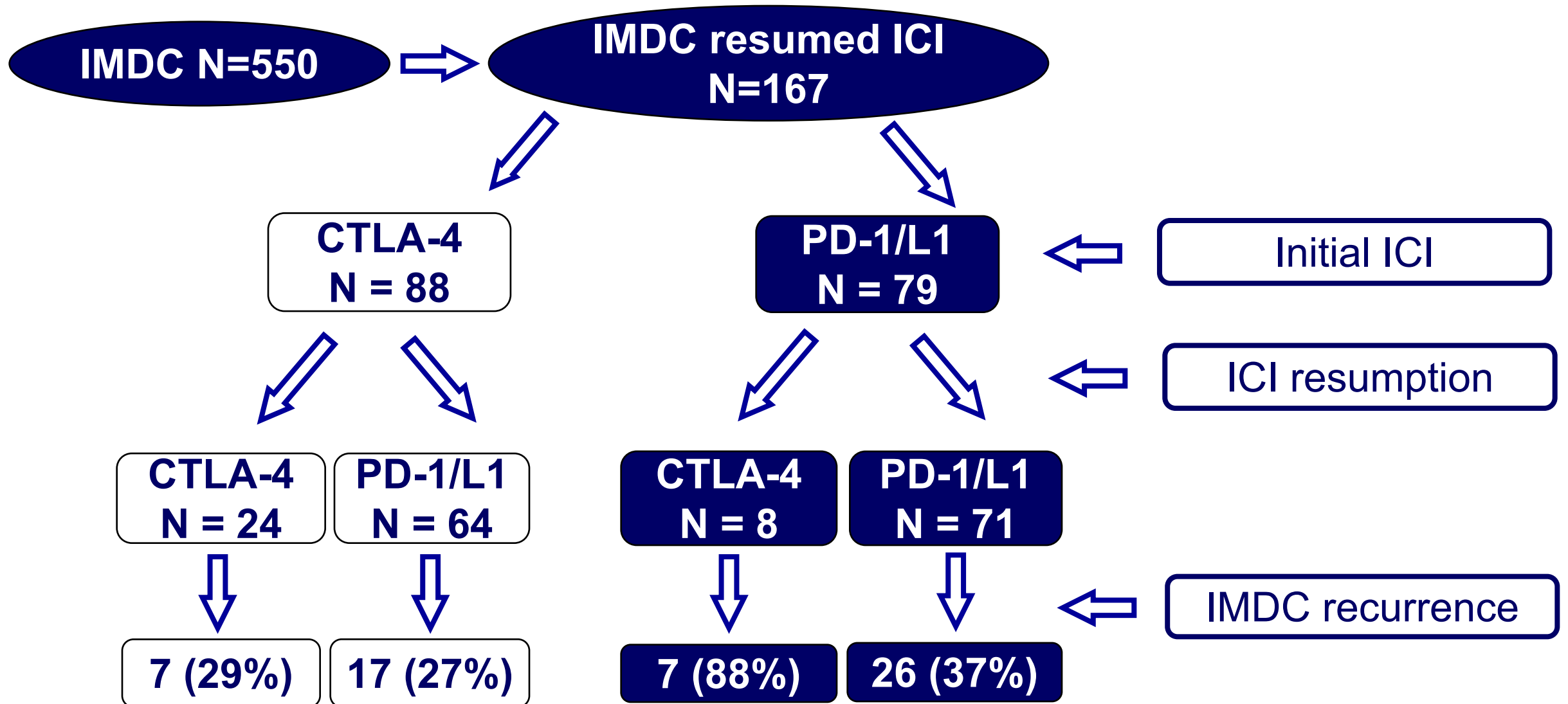
SIT: Selected immunosuppressive therapy (infliximab or vedolizumab)

ICI Resumption Post ICI Colitis

Design and Population

- Retrospective (01/2010 -11/2018)
- Six centers (5-US and 1-Italy)
- 167 adult cancer patients
- Resumed ICI after IMDC

Incidence



Patients' Characteristics

Characteristic	No. of patients (%)
Cancer type	
Melanoma	90 (54)
NSCLC	27 (16)
GU	17 (10)
Initial ICI type	
Anti-CTLA-4	88 (53)
Anti-PD-1/L1	79 (47)
Grade of diarrhea, 3-4	62 (38)
Grade of colitis, 3-4	45 (33)
Received steroid	113 (68)
Received infliximab/vedolizumab add-on	24 (14)
Median days of symptoms	12 (5-28)

Characteristics of Recurrent IMDC

Characteristic	Anti-CTLA-4 N = 32	Anti-PD-1/L1 N = 135	P
IMDC recurrence	14 (44)	43 (33)	0.30
Days to IMDC recurrence	26 (2-43)	79 (27-141)	0.02
Recurrent IMDC 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

Characteristics of Recurrent IMDC

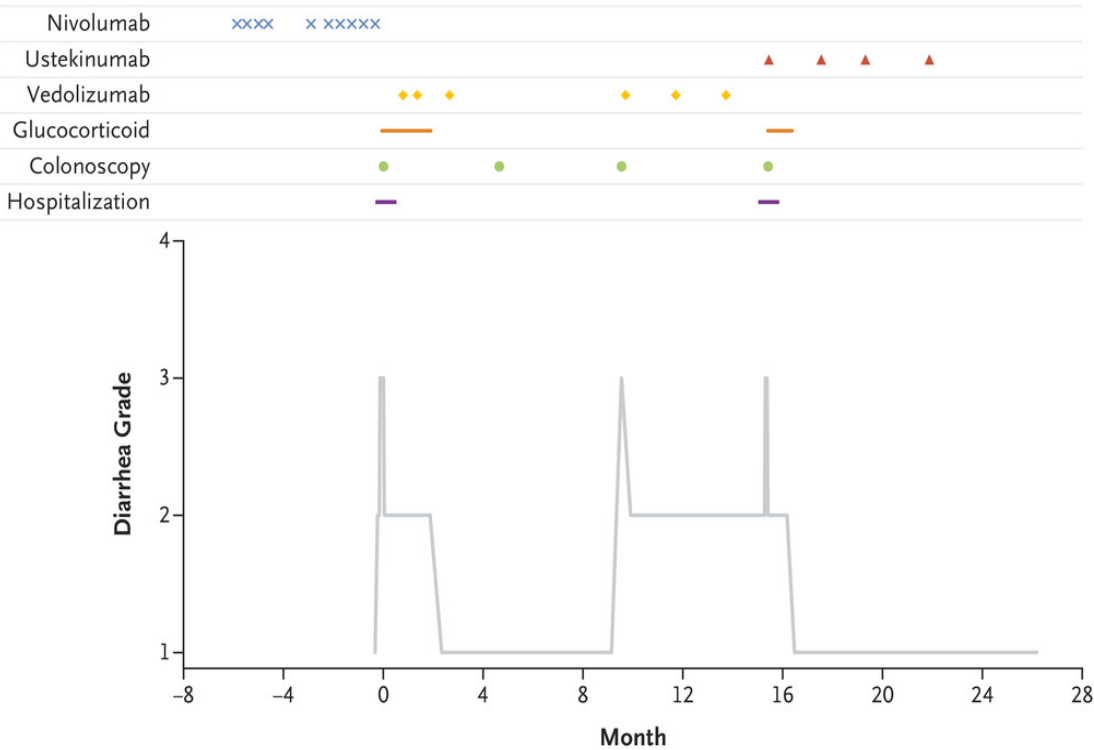
Characteristic	IMS N = 47	No IMS N = 10	P value
Treatment			< 0.01
Steroid	39 (83)	0 (0)	
Infliximab/vedolizumab	6 (13)	1 (10)	
Grade of diarrhea			< 0.01
2	38 (81)	2 (20)	
3-4	6 (13)	0 (0)	

Multivariate Analysis for Recurrence

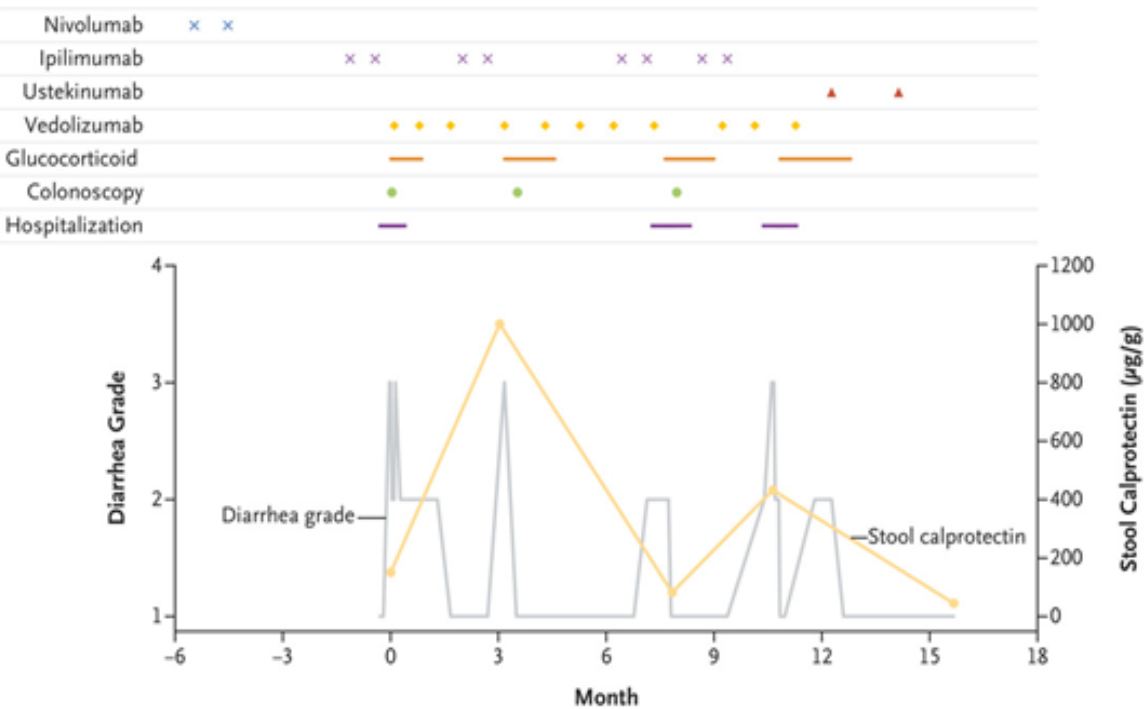
Covariate	OR	95% CI	P
Initial anti–PD-1/L1	3.45	1.59-7.69	0.01
Resumed anti–PD-1/L1	0.30	0.11-0.81	0.02
Grade of initial diarrhea			
2	1.19	0.37-3.80	0.78
3	2.19	0.66-7.29	0.20
Immunosuppressant initially	3.22	1.08-9.62	0.02
Duration of initial IMDC	1.01	1.00-1.03	0.03

Ustekinumab (anti IL-12/23) Therapy for Refractory IMDC

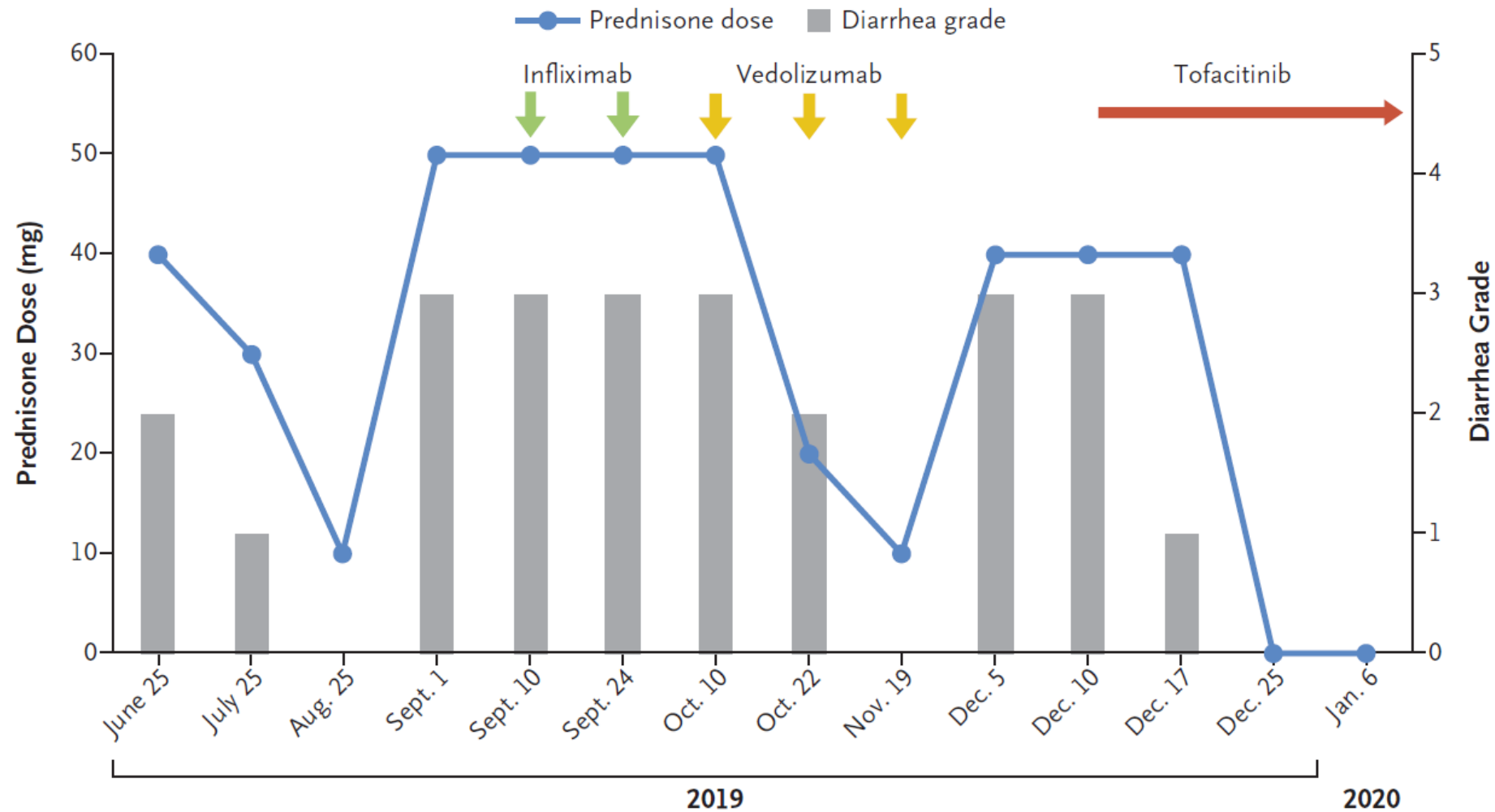
A Patient 1



B Patient 2

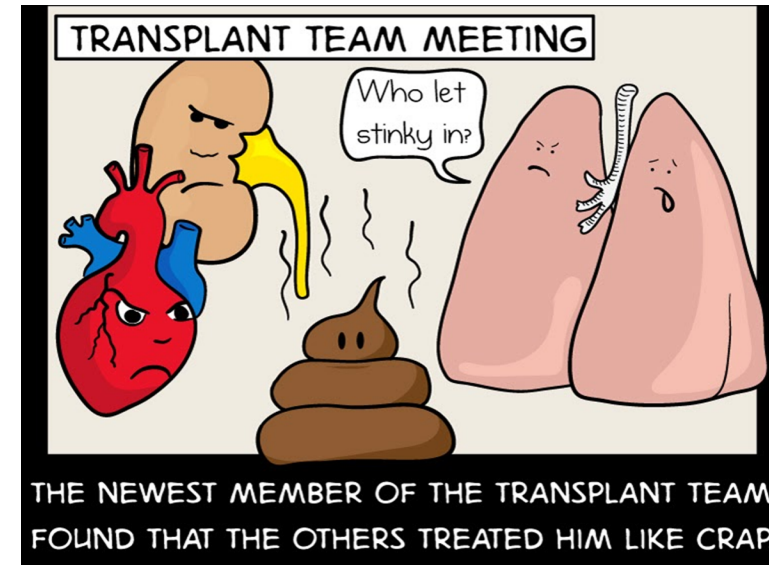
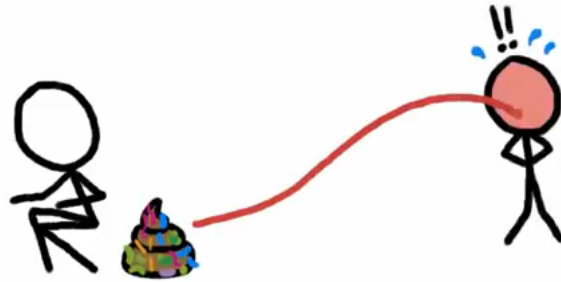


Tofacitinib (JAK inhibitor) for IMDC

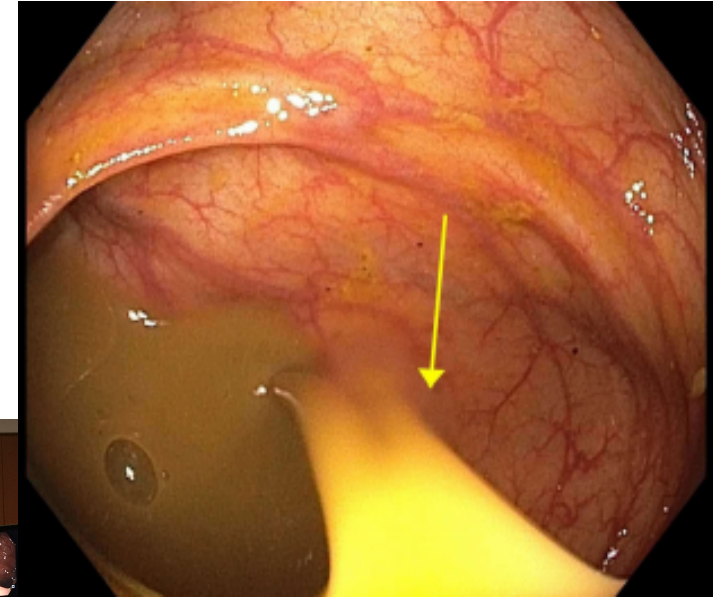


Why FMT could work in ICI colitis?

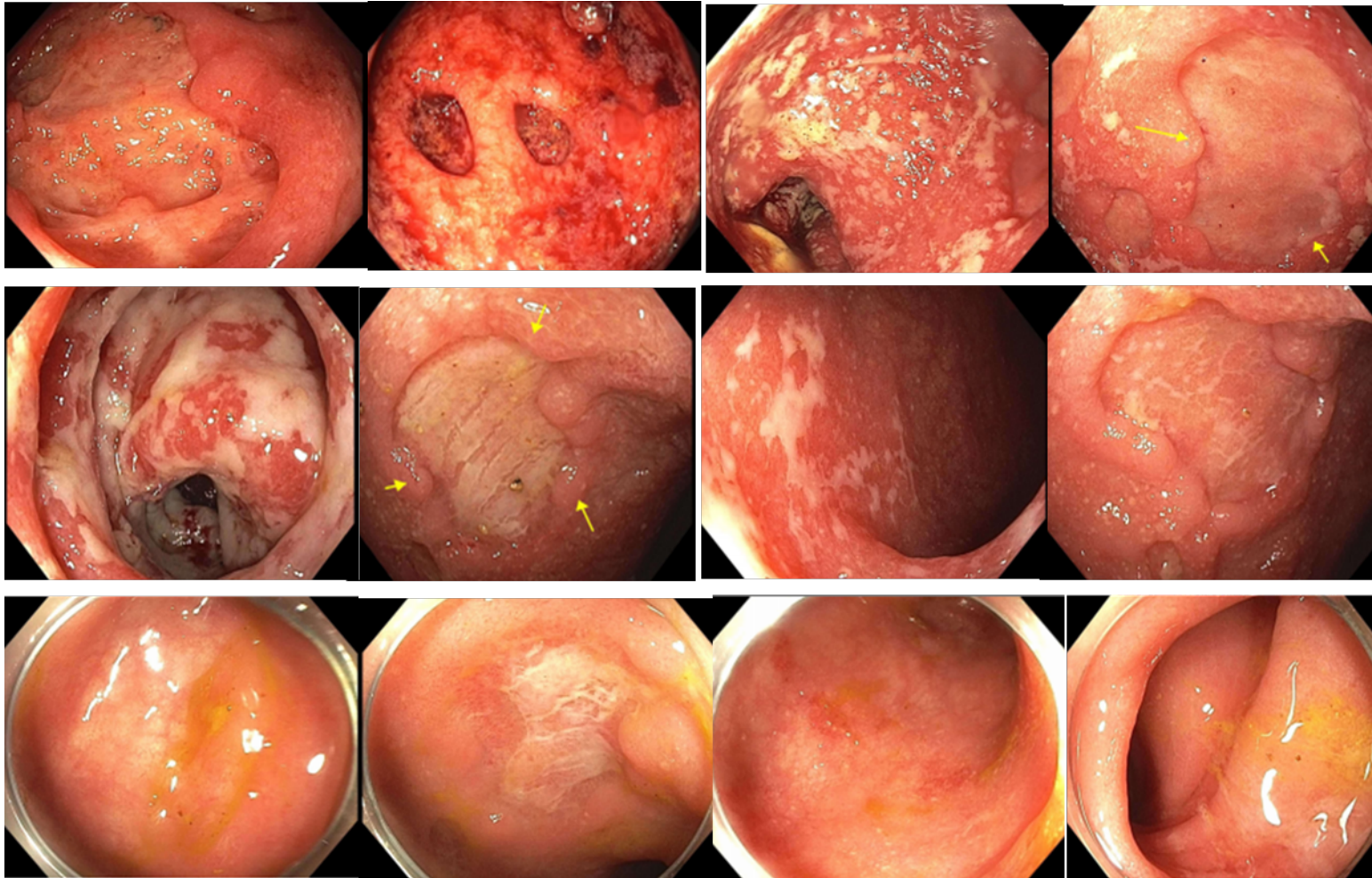
Fecal microbiota transplantation



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



1st FMT Case

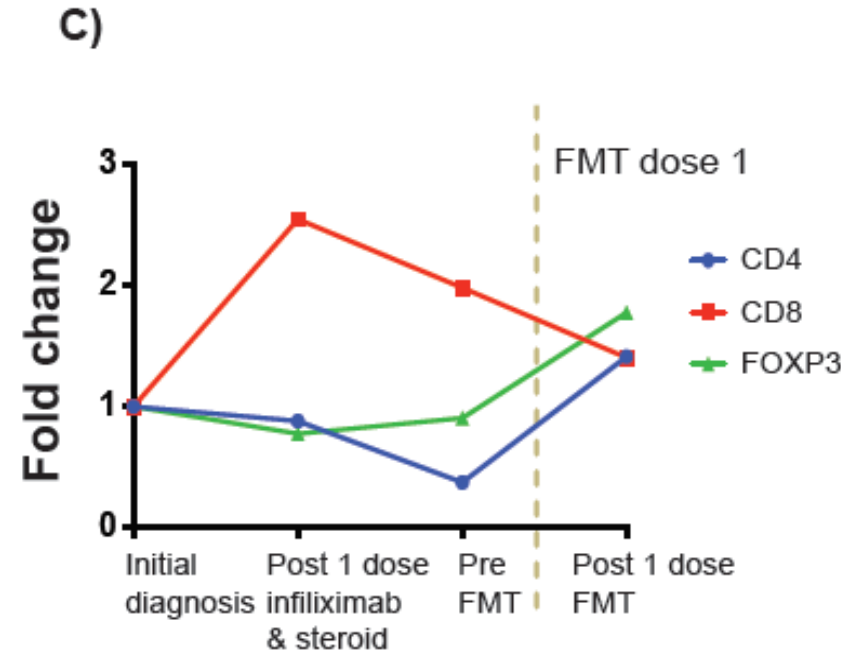
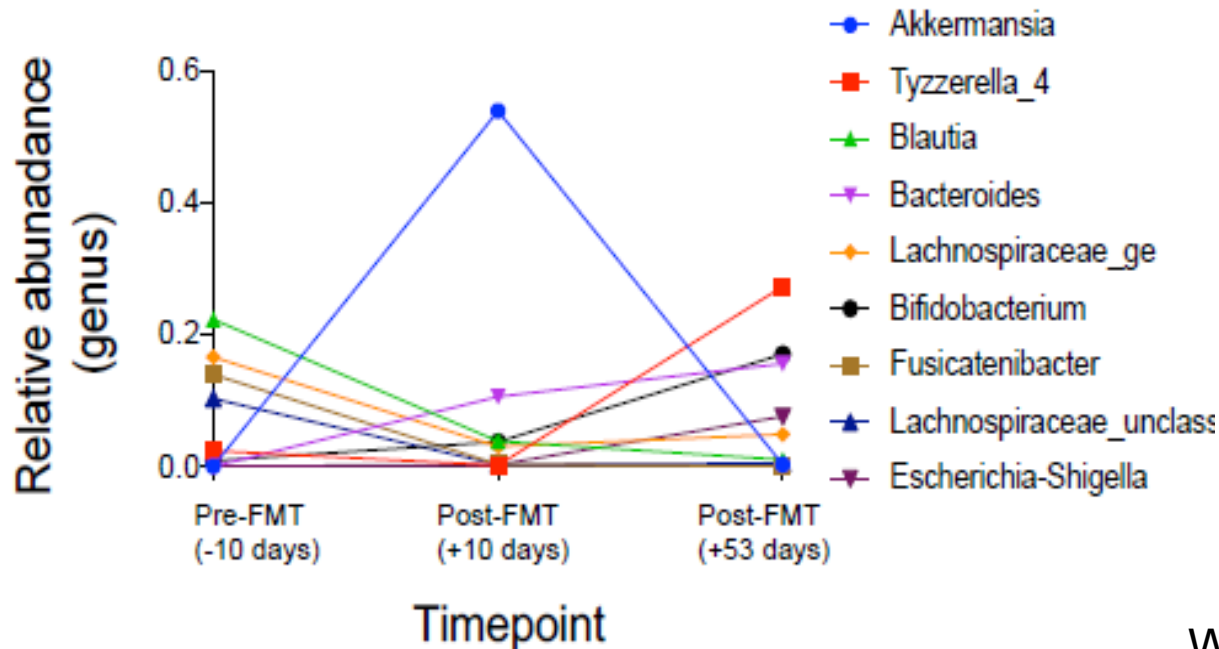
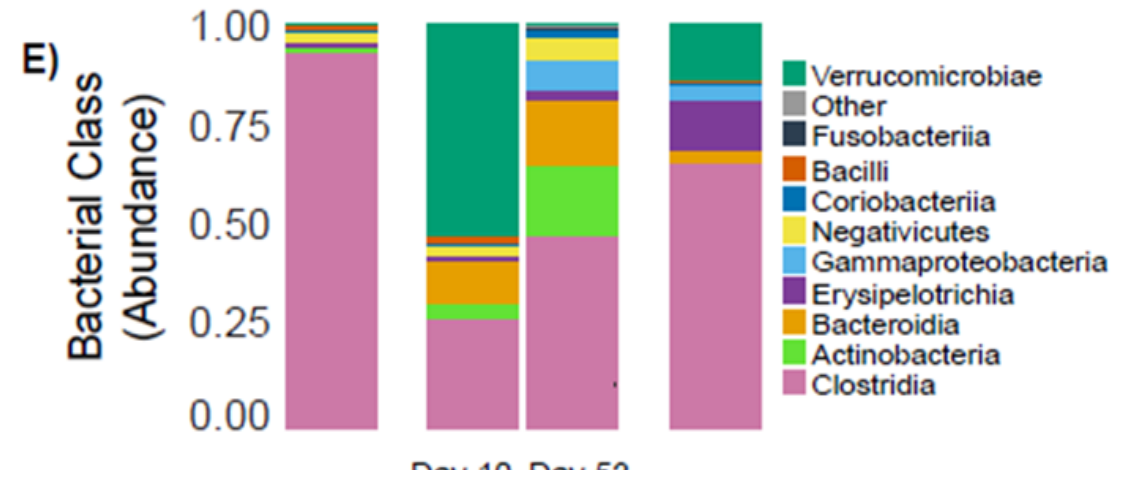
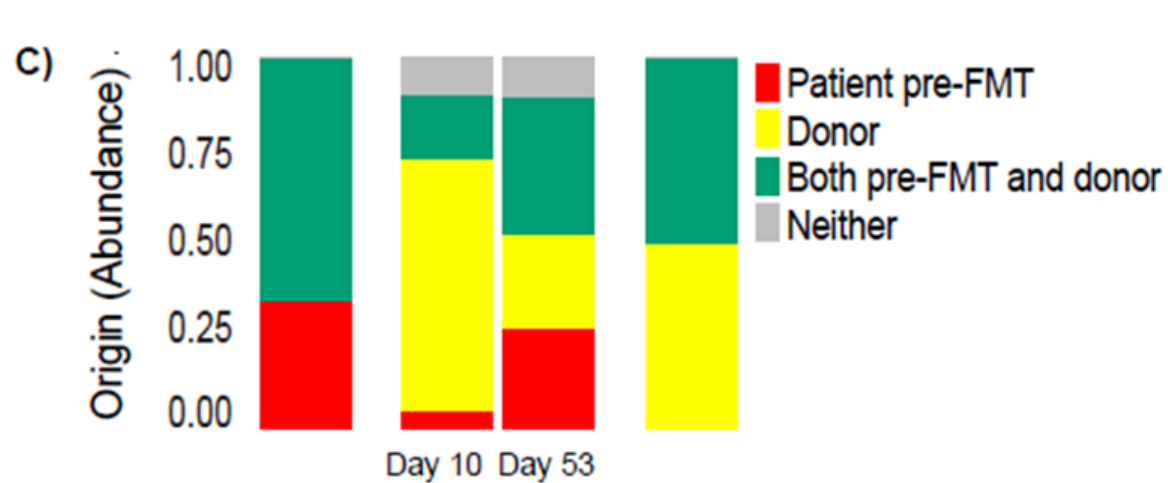


1 Original colonoscopy at the diagnosis

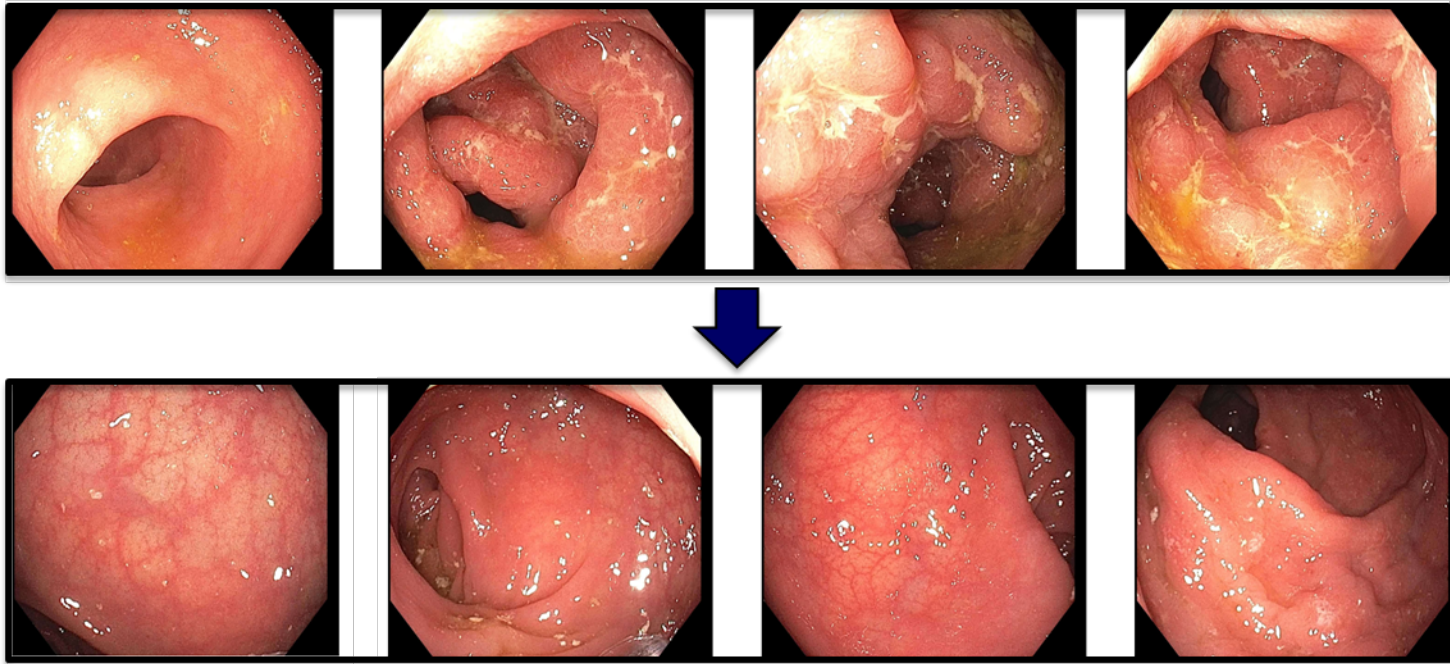
2 After steroid+2 doses infliximab+1 dose of vedolizumab (3 months)

3 4 weeks after the FMT treatment

Stool Metagenomic Analysis and IHC



ICI Resumption Post Front Line FMT for ICI Colitis

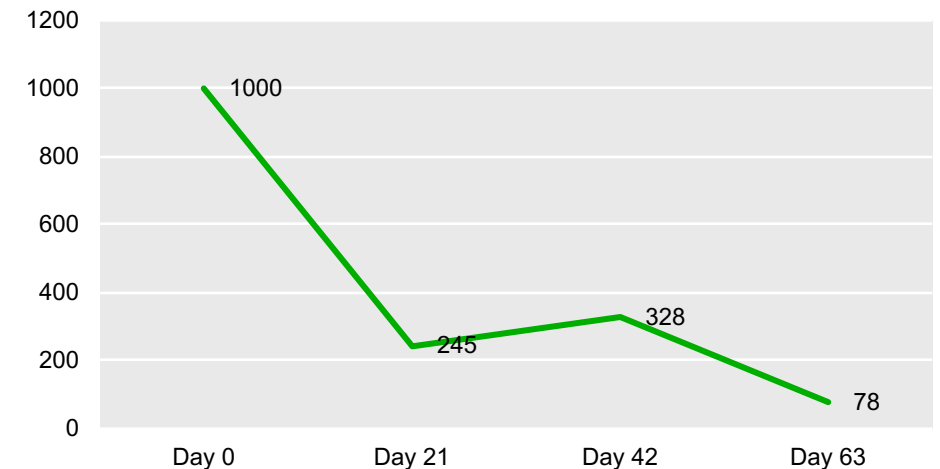


ICI colitis onset

4 weeks later

- Diarrhea resolved within 24 hours, and sustained over 7 months.
- Resumed nivolumab x 2 doses after FMT followed by surgery.

Fecal Calprotectin Level



MD Anderson Study: FMT Cases for Refractory ICI colitis

Characteristic	Data (N=12)
Median time from initial GI AE to FMT– days (IQR)	89 (58-386)
Highest grade of diarrhea (3-4) – no. (%)	16 (100%)
Highest grade of colitis (3-4)– no. (%)	6 (50%)
Treatment of GI adverse event – no. (%)	
Steroid	12 (100%)
Infliximab/vedolizumab added	12 (100%)
Number of cases achieved symptom improvement after FMT, no (%)	10 (83%)
Median time from FMT to symptom improvement– days (IQR)	14 (9-16)
FMT related serious AE within 7 and 30 days —no (%)	0
Resumed cancer treatment after FMT—no (%)	4 (33%)

MD Anderson ICI Colitis Clinical Trials

- Fecal transplant trials
 - #1 For ICI colitis refractory to medical treatments
 - #2 Front line FMT treatment
- Randomized clinical trial of infliximab and vedolizumab for ICI colitis

Additional Information

MD Anderson colitis management algorithm:

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

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

Acknowledgements

- [Research team](#)

Anusha Thomas, Hao Chi Zhang, Fangwen Zou, Weijie Ma, Hamzah Abu-Sbeih, Jake Jacob, Kavea Pannerselvam, Shruti Khurana, Barbara Dutra, Mostafa Eyada, David Szafron, Rajan Amin, Andrew Kuang, Victor Garcia-Rodriguez, Aaron Isaac, Kevin Yu, Shaleen Vasavada, Miho Kono, Krishnavathana Varatharajalu

- [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)