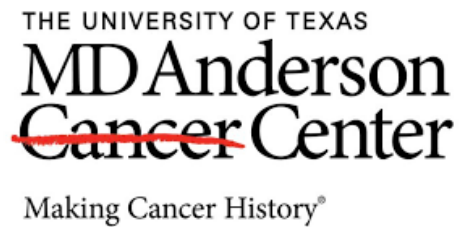
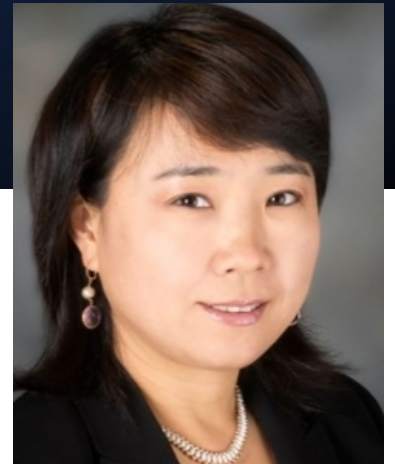


Cancer Immunotherapy Related Gastrointestinal Toxicities



Yinghong (Mimi) Wang MD PhD MSc
Professor, Gastroenterology and Hepatology
Director of Oncology-GI Toxicity Program
Director of Fecal Microbiota Transplantation
Deputy Division Head of Research, Internal Medicine
Chair of MD Anderson IOTOX Leaders Group



Initial Presentation

Symptom onset at outside hospital

- 1 month after completion of ICI therapy (pembrolizumab)
- 20+ BMs/day, mucus, bleeding, abd pain, fecal urgency



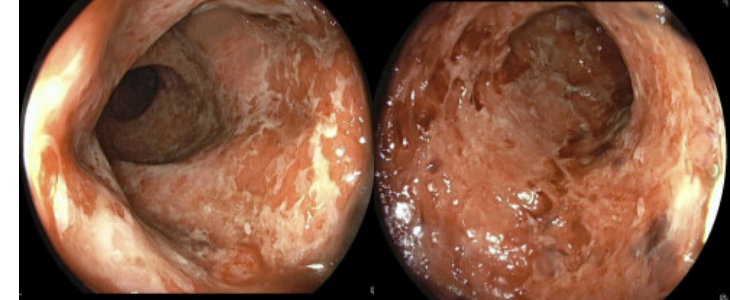
- Colonoscopy: diffuse area of friable mucosa with ulceration; Pathology: marked acute colitis
- Calprotectin 265, Stool culture, C. difficile, GI multiplex panel negative
- Hospitalized and treatment
 - IV methylprednisolone, Prednisone 80mg/day, then tapered to 40mg/day
 - Infliximab x 1st dose



- Symptoms only mildly improved: 10 BMs/day, mucus, bleeding
- Treatment: Infliximab x 2nd dose
- Presented to MD Anderson for 2nd opinion

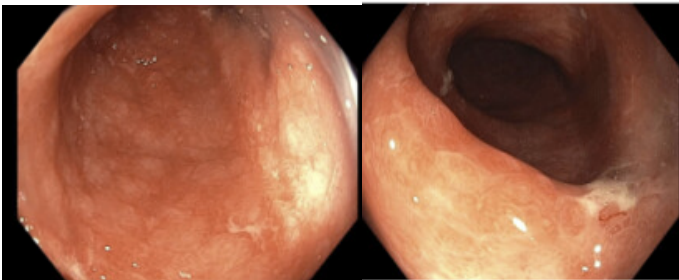
Disease Course

Still with 20+ BMs/day, excess flatulence, mucus, bleeding, urgency, abdominal cramping.



- Repeat colonoscopy: severe pancolitis with ulcerations
- Decision is to do fecal transplant treatment.

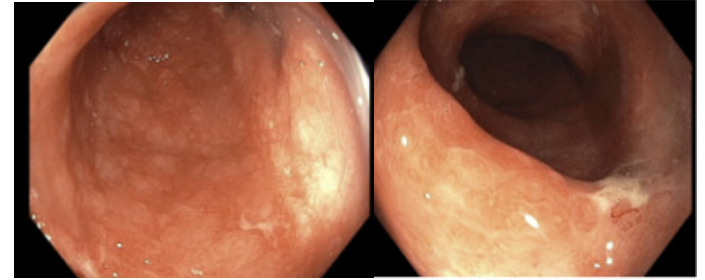
- Patient continued to have abdominal cramps, worsening diarrhea >25 BMs/day with mucus and blood, increased urgency
- Unable to return to MD Anderson, but hospitalized locally



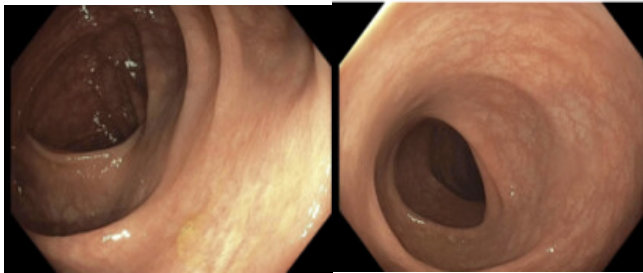
- Switched to vedolizumab x 5 doses with steroid
- Disease course wax and wane for months with remote MD Anderson management together with local team
- Repeat scope: improvement of colitis, but remaining ulcers

Disease Course

- Worsening diarrhea, blood, mucus, abdominal pain while on vedolizumab
- Persistent ulcers on repeat endoscopy

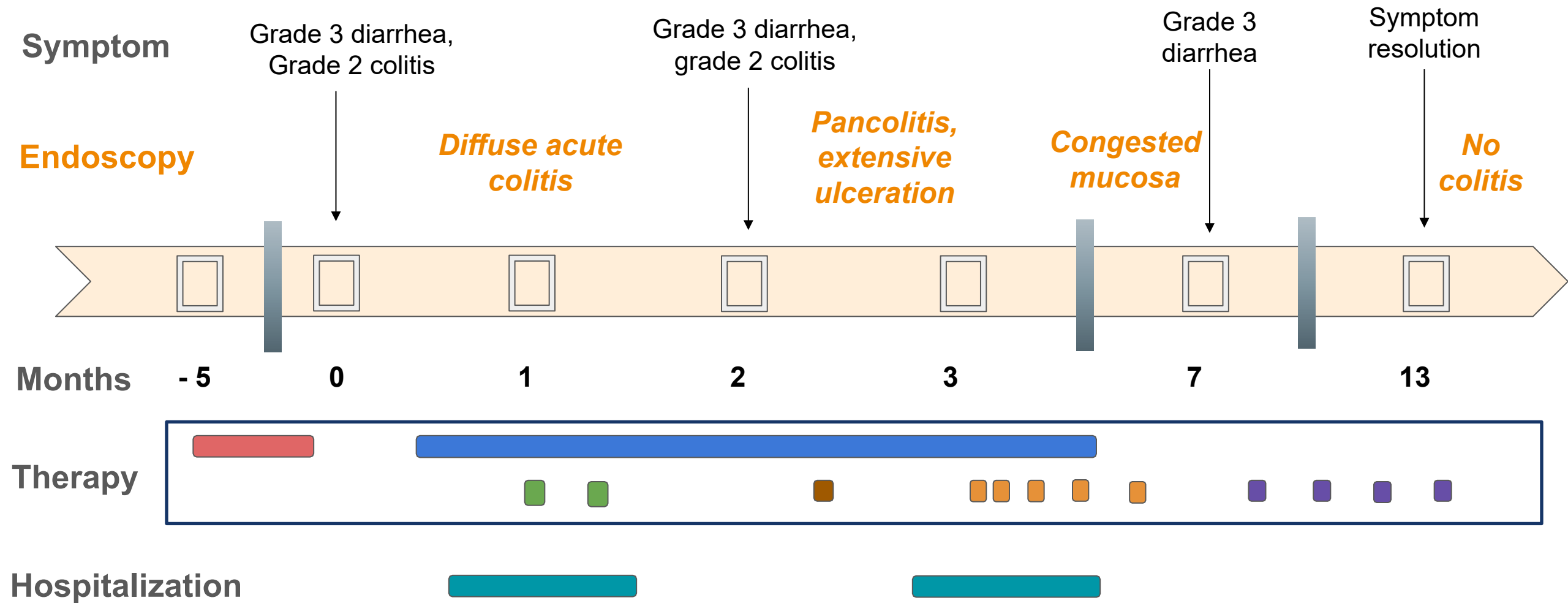


Started ustekinumab and continued for total 4 doses.



Patient achieved clinical remission and endoscopic mucosal healing.

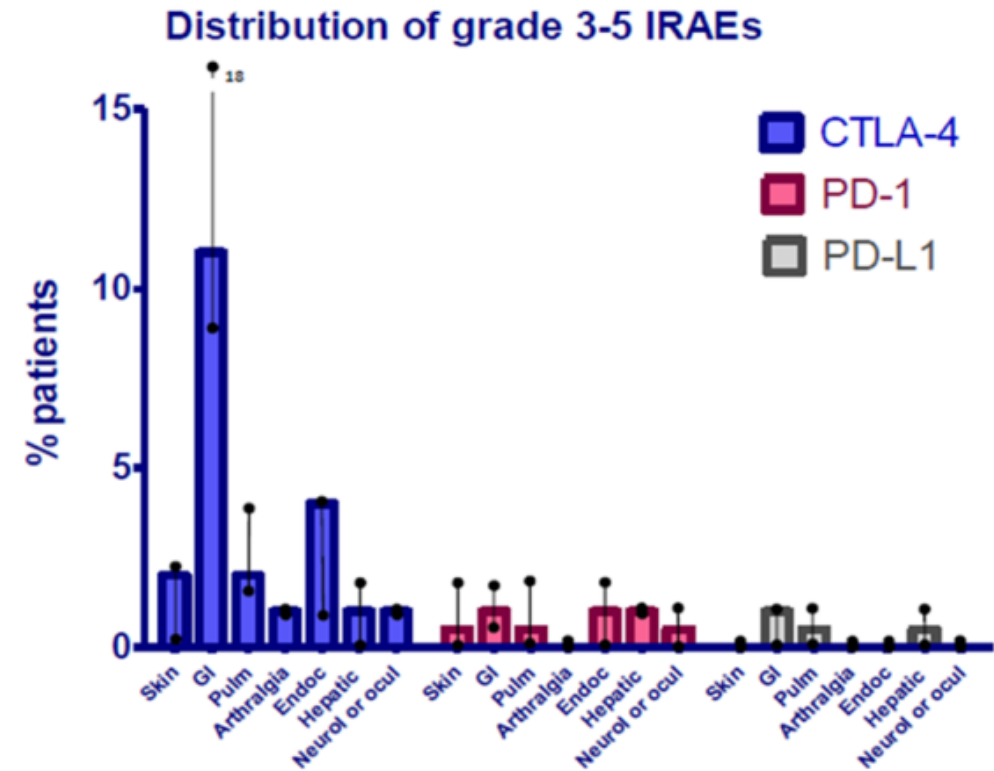
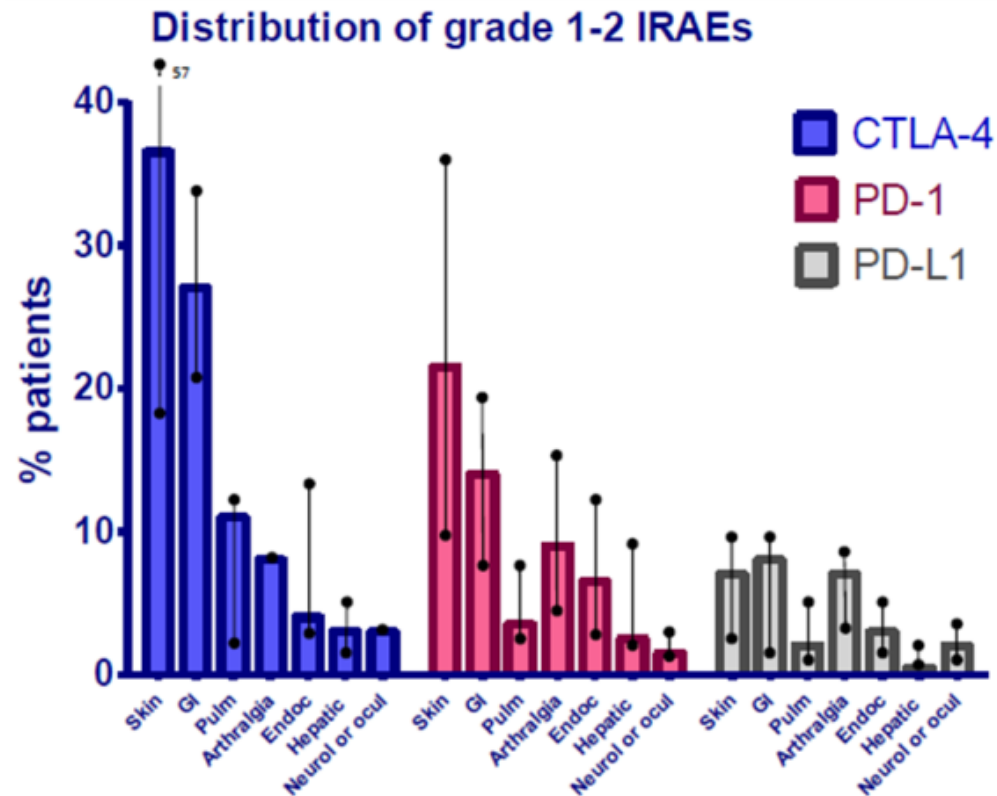
Case Summary



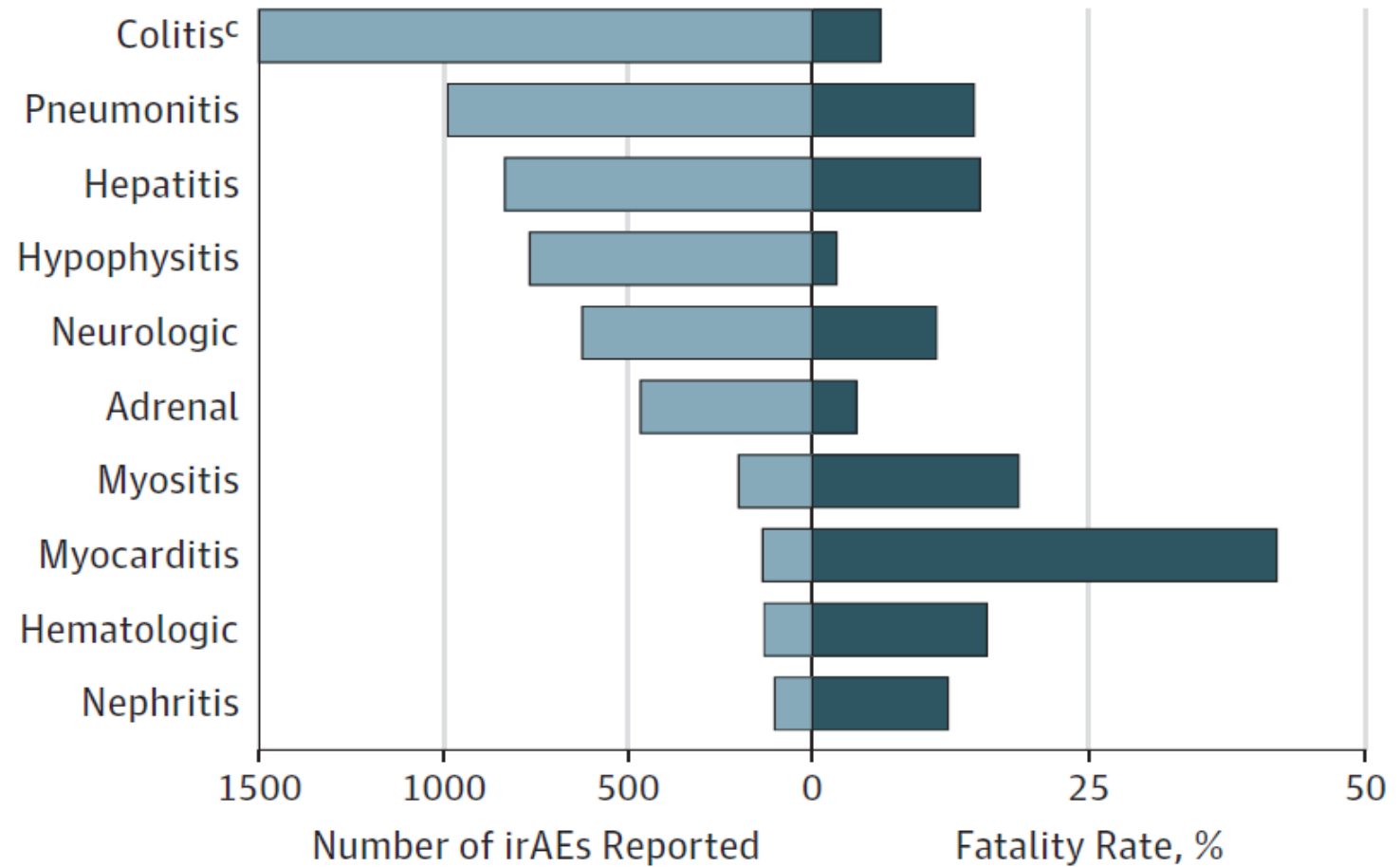
Pembrolizumab, Prednisone, Infliximab, FMT, Vedolizumab, Ustekinumab

Immune Related Adverse Events

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



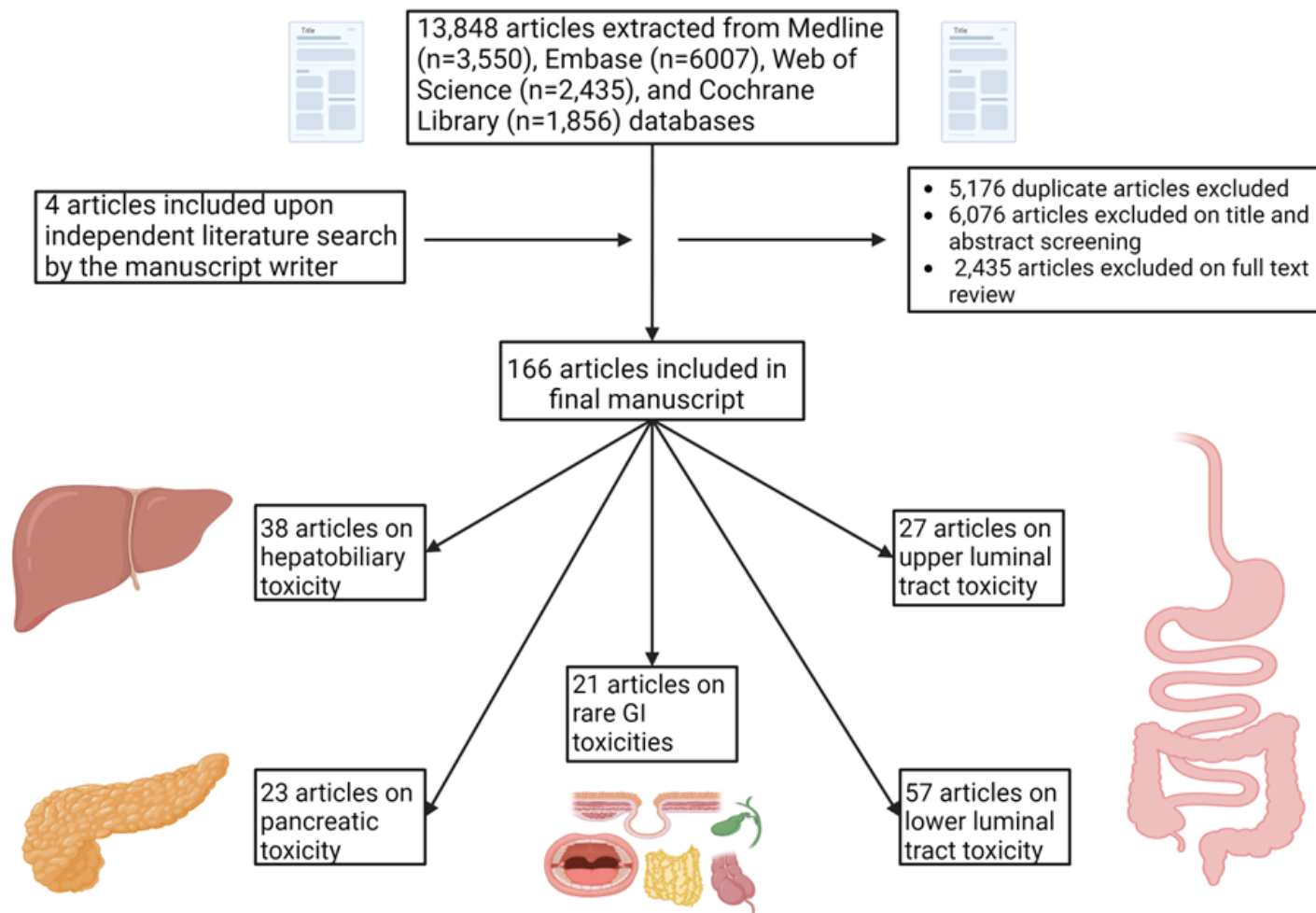
Fatalities from IrAEs by Organ Involved



Wang et al JAMA Oncol. 2018;4(12):1721-1728.

GI irAE Evidence Summary

Shatila, Wang et al, J Immunother Cancer. 2024 Nov 14;12(11):e009742. doi: 10.1136/jitc-2024-009742. PMID: 39542654.



Sites of GI, Liver, Pancreas Toxicities

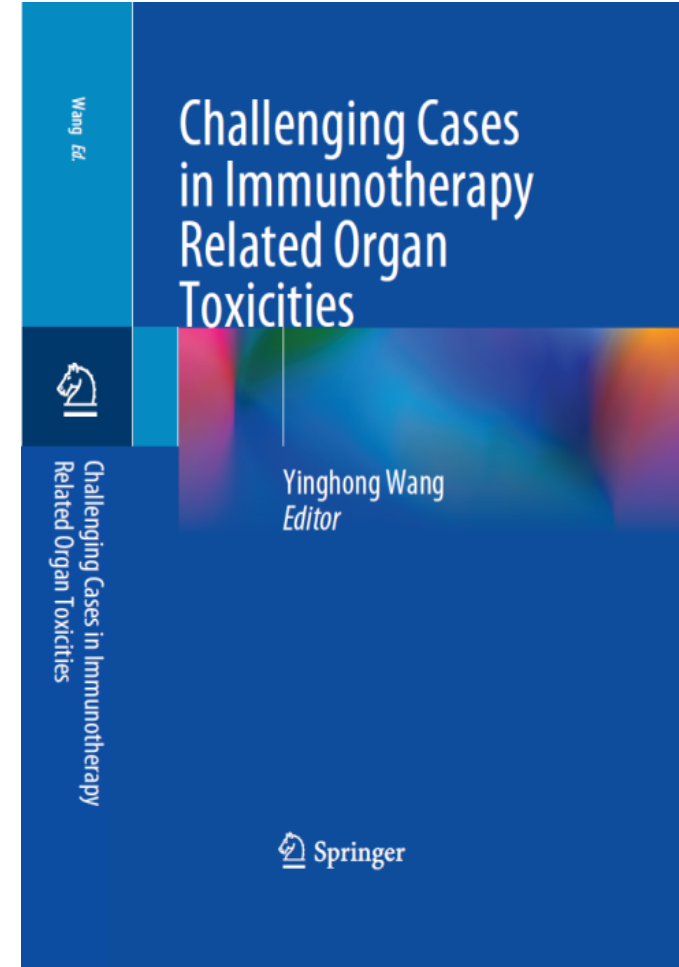
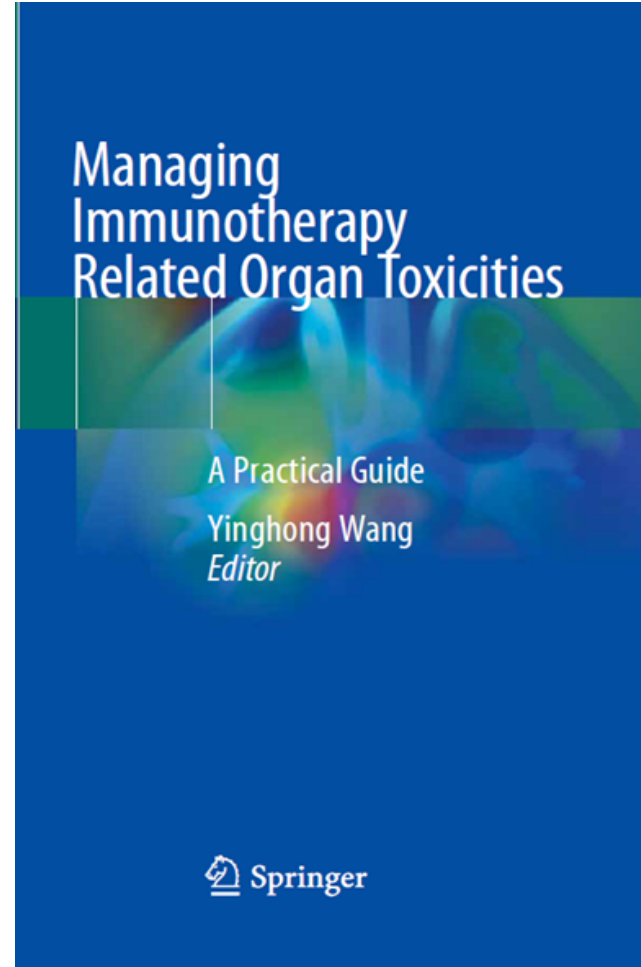


GI LUMINAL TOXICITIES	OTHER GI TOXICITIES	OTHERS
Mucositis	Cholecystitis	Hepatitis
Esophagitis	Appendicitis	Cholangiopathy
Gastroenteritis	Diverticulitis	Pancreatitis
Celiac	Mesenteritis	
Gastroparesis		
Constipation		
Pouchitis		
Pneumatosis Intestinalis		
GI perforation		
Colitis		

IOTOX Guidelines



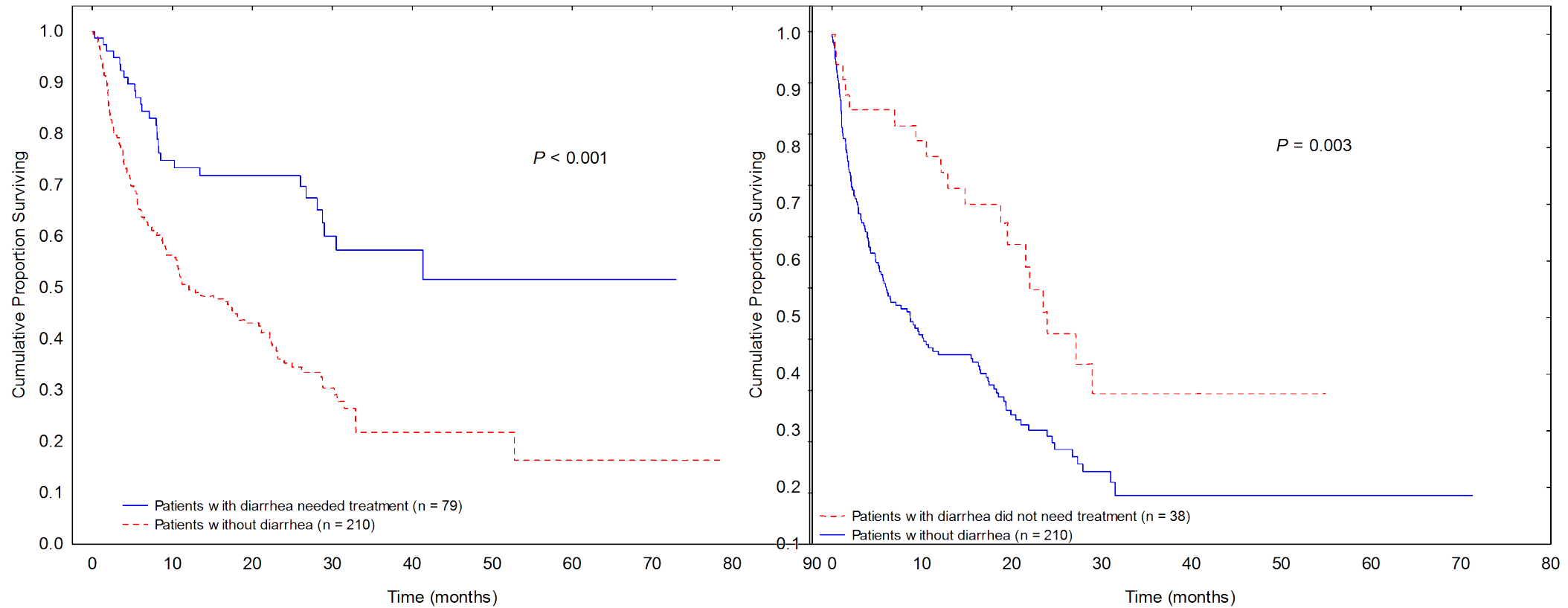
Society for Immunotherapy of Cancer



<https://link.springer.com/book/10.1007/978-3-031-00241-0>

<https://link.springer.com/book/10.1007/978-3-031-83533-9>

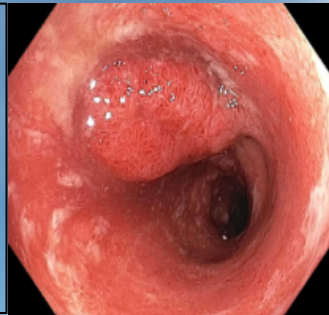
Overall Survival



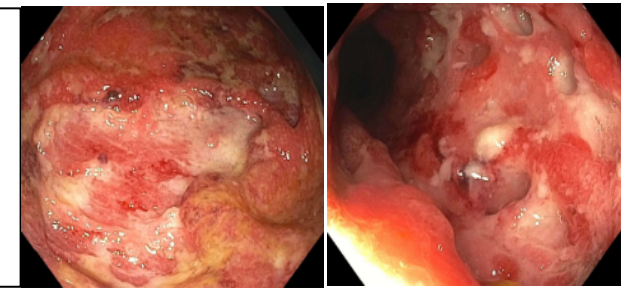
- *GI toxicity is associated with better overall survival.*
- *Goal is to control the GI toxicity and resume effective cancer treatment.*

Challenging Cases after ICI

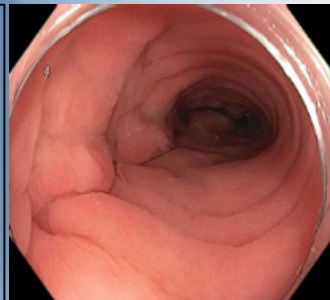
Diarrhea with >20 watery BM/day, history of ulcerative colitis



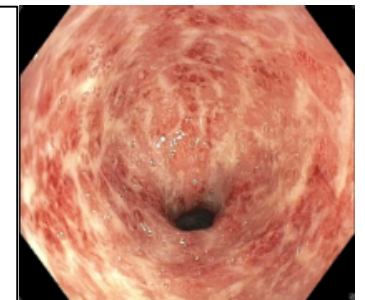
Bloody diarrhea leading to hospitalization that is steroid refractory.



Diarrhea with >30 watery BM/day



Persistent colitis despite IFX, VDZ after steroid, oncologist is pushing to resume ICI given cancer progression.



Clinical Presentations










Diarrhea

Watery, loose stools
Fecal incontinence
Urgency



Colitis

Bleeding
Mucus in stool
Abdominal pain
Fever

BRISTOL STOOL CHART			
	Type 1	Separate hard lumps	Very constipated
	Type 2	Lumpy and sausage like	Slightly constipated
	Type 3	A sausage shape with cracks in the surface	Normal
	Type 4	Like a smooth, soft sausage or snake	Normal
	Type 5	Soft blobs with clear-cut edges	Lacking fibre
	Type 6	Mushy consistency with ragged edges	Inflammation
	Type 7	Liquid consistency with no solid pieces	Inflammation



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

Routine Evaluations of Immunotherapy GI Toxicity



STOOL INFECTIOUS WORK UP



STOOL INFLAMMATORY MARKERS
(LACTOFERRIN, CALPROTECTIN)



COLONOSCOPY OR
SIGMOIDOSCOPY WITH BIOPSY

Stool Biomarkers

	Lactoferrin (+) N (%)	Lactoferrin (-) N (%)	Scope Findings	Calprotectin (SD)
Abnormal Scope	42 (70)	4 (36)	Ulcers	465 (363)
Normal Scope	18 (30)	7 (64)	Non-Ulcer Inflammation	213 (184)
Abnormal Histology	54 (90)	3 (27)	Normal	152 (133)
Normal Histology	6 (10)	8 (73)	P	0.006

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

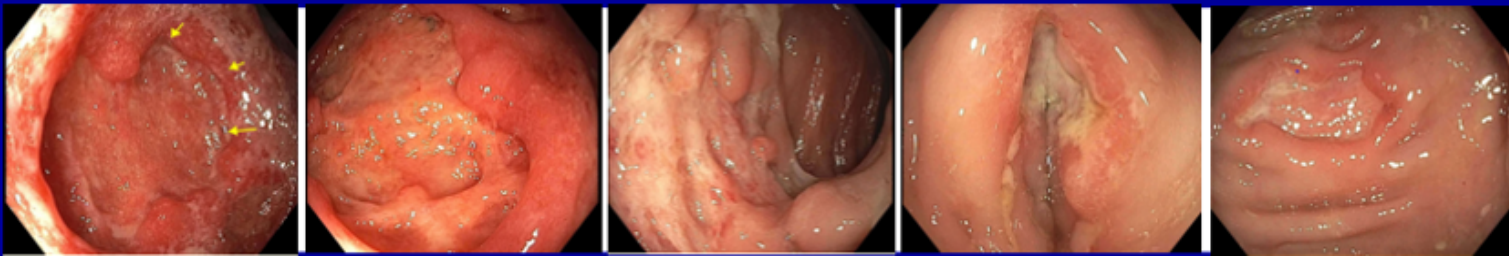
Sensitivity of calprotectin: endoscopic inflammation is 91.4%; for histologic inflammation is 86.4%

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

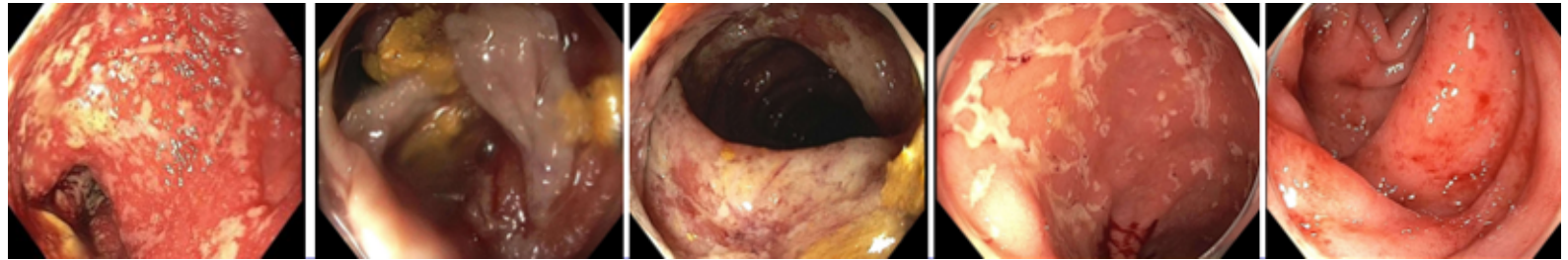
Wang et al J Immunother Cancer. 2018;6(1):95

Shatila, Wang et al submitted 06.2025

Endoscopy Features



Severe inflammation with large deep ulcers

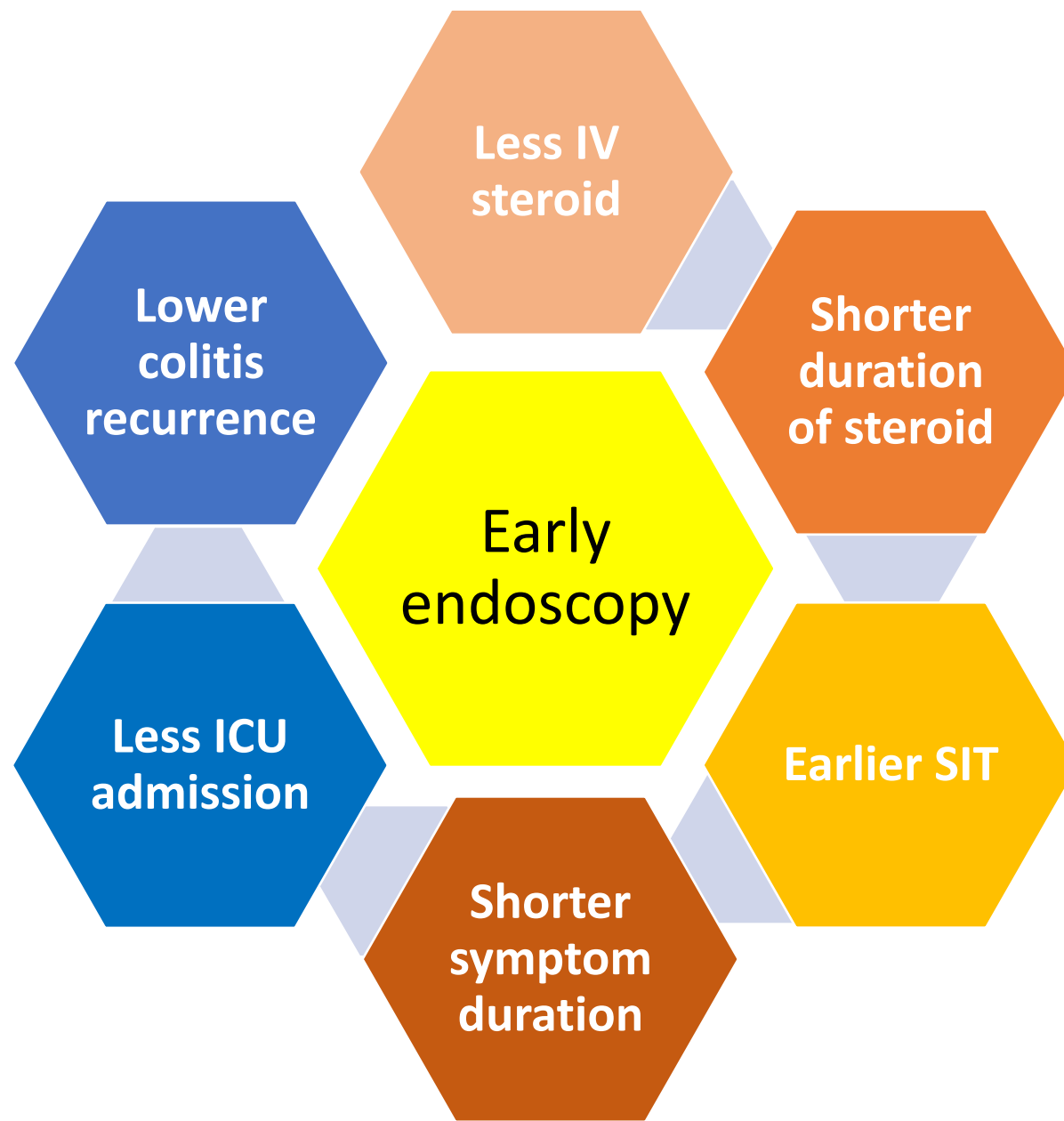


Moderate inflammation with erythema, exudate, superficial ulcers



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

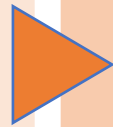
IMC has wide spectrum of endoscopic presentations from mild to severe level.



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

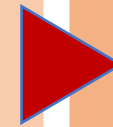
Colitis Disease Course

High risk
endoscopic
features
(multiple, large,
deep ulcers and
extensive
inflammation)



-More steroid
refractory
course

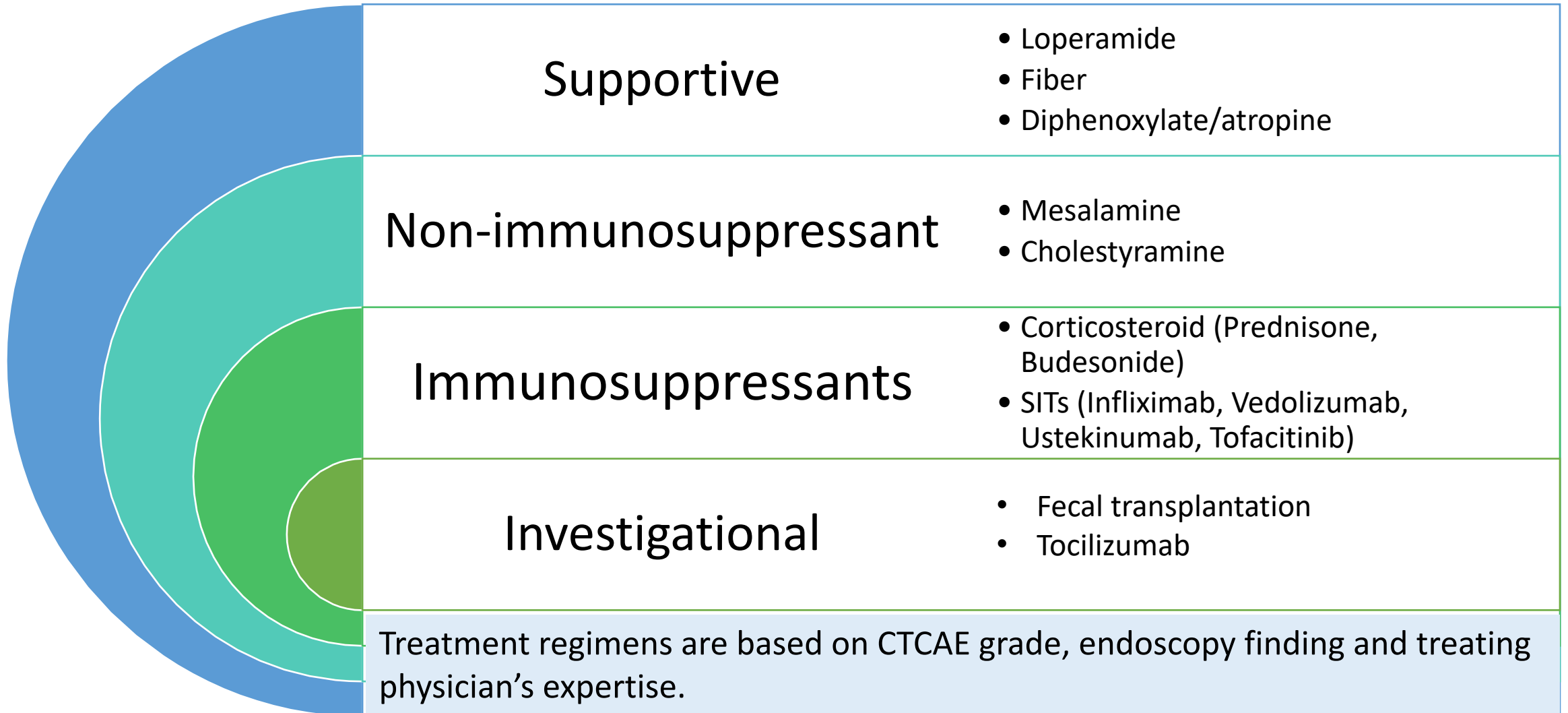
-More
immunosuppre
ssive
treatments



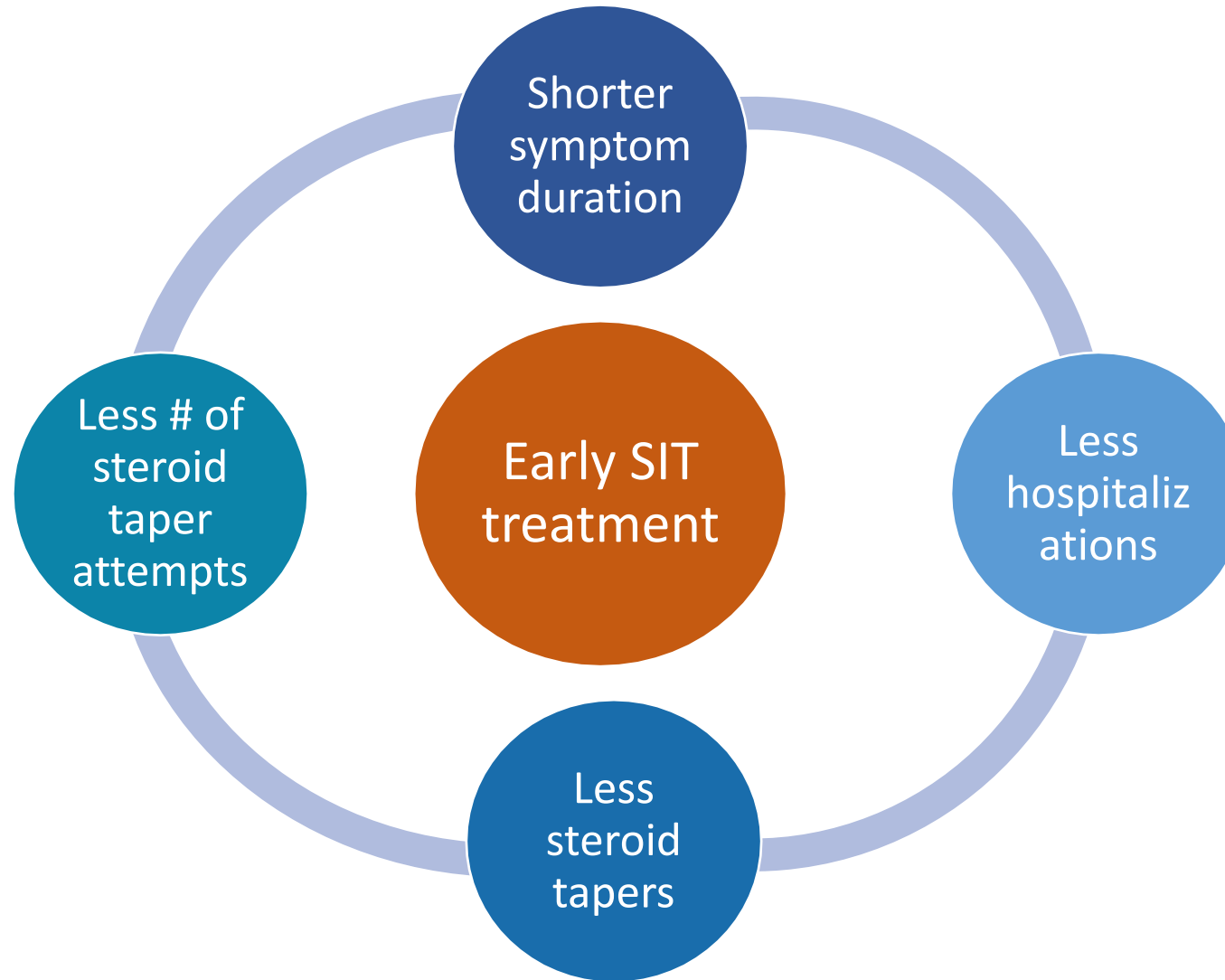
-More
hospitalization

-Longer
hospital stay

Treatments



Introduction of SIT



Comparison of IFX and VDZ

Infliximab (IFX)
TNF- α blocker

- Quicker effect onset in 13 days
- Response rate 88%
- Steroid duration 51 days
- Recurrence rate 29%

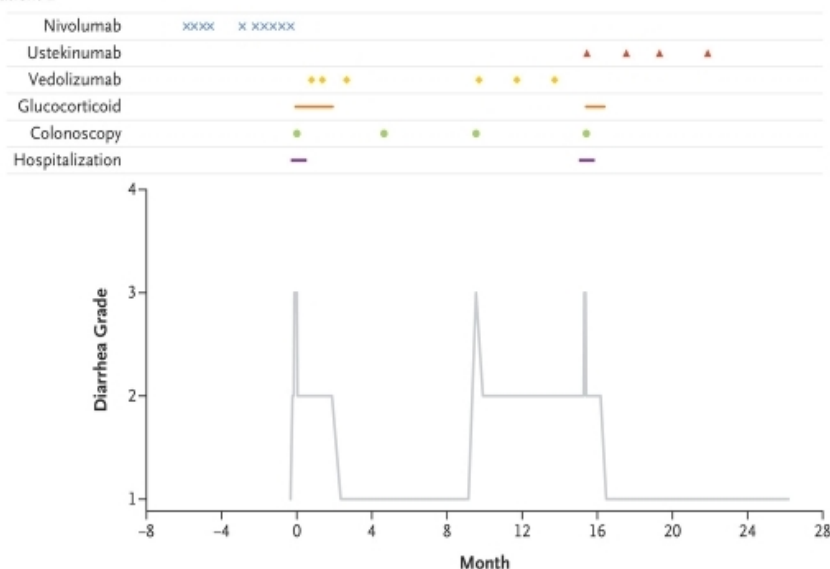
Vedolizumab (VDZ)
 α 4 β 7-integrin blocker

- Slower effect onset in 18 days
- Response rate 89%
- Steroid duration 35 days
- Recurrence rate 14%

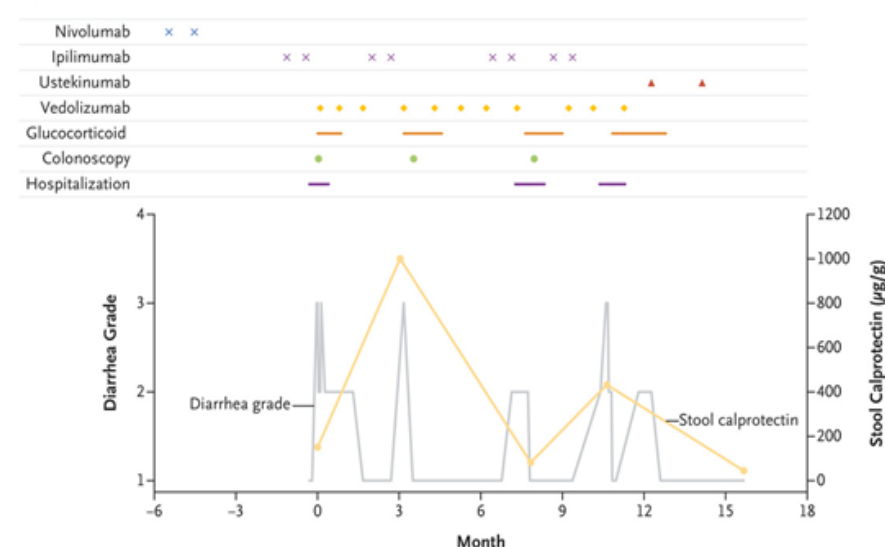
NCT 04407247: Randomized trial at MD Anderson is completed, data will be published soon.

Ustekinumab and Tofacitinib

A Patient 1



B Patient 2



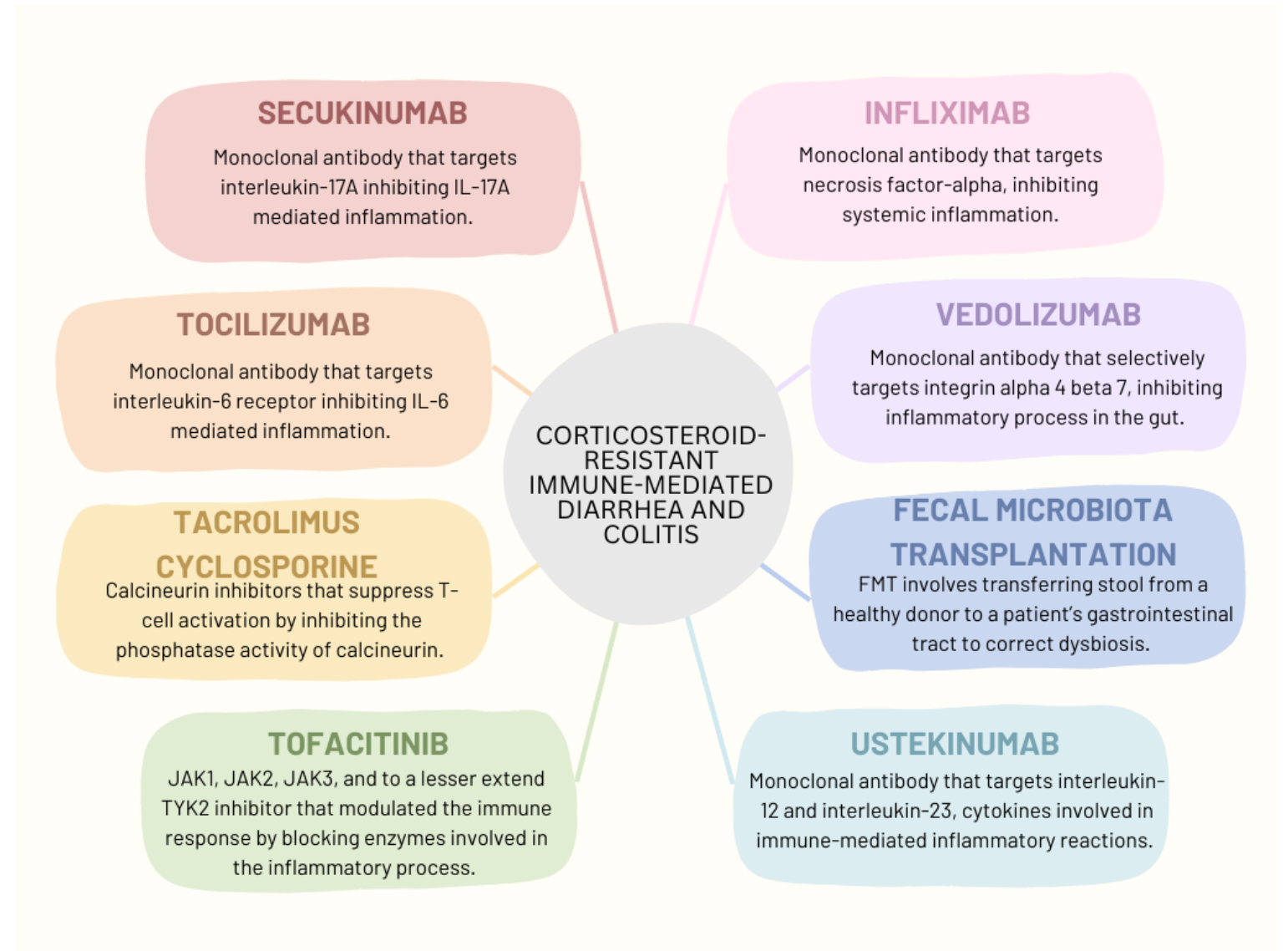
- Case series of 19 patients from MDACC and MSKCC achieved 68.4% efficacy from ustekinumab.
- Case series of 5 patients achieved clinical response/remission from tofacitinib.

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 Am J Gastroenterol. 2023;118(9):1679-1683.
 Esfahani et al N Engl J of Med 2020;382(24):2374-2375
 Bishu et al Gastro 2021;160(3):932-934.e3.

Options of different steroid-sparing agents

Cruz, Wang etc Immunotherapy.
2025 Mar;17(4):293-303. doi:
10.1080/1750743X.2025.247330
5.



Factors for Colitis Recurrence

Severe index event

High calprotectin level

Longer steroid treatment

Failure of steroid taper

SIT use

Multiple hospitalizations

- *Higher colitis recurrence*

Received >3 doses of SIT

Achieved endoscopic healing

Achieved histologic healing

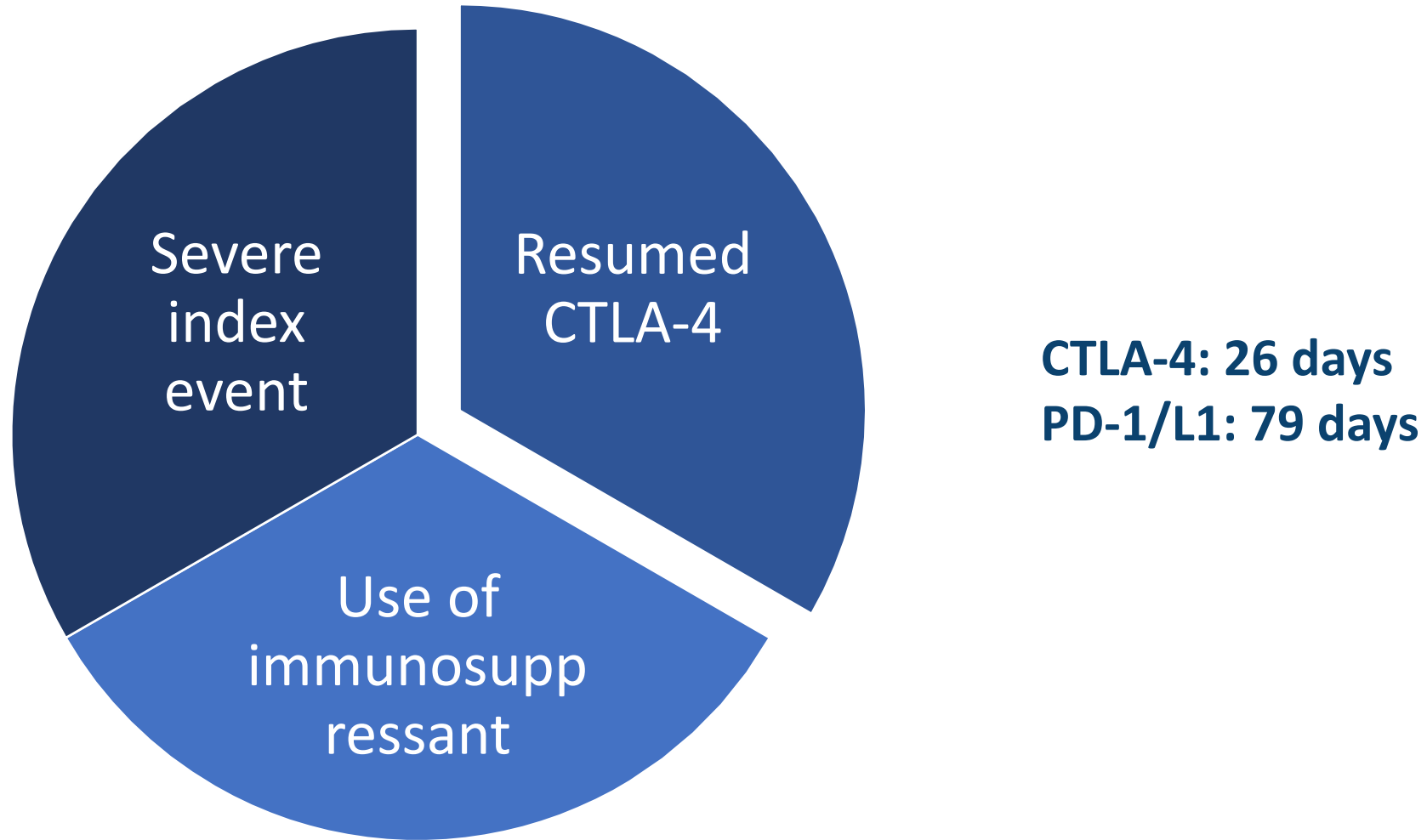
- *Lower colitis recurrence*

Calprotectin as Surrogate Marker

Endpoint	Cutoff value (mcg/g)	Specificity
Overall, N=77		
Endoscopic remission, N=46	≤116	94%
Histologic remission, N=24	≤80	85%

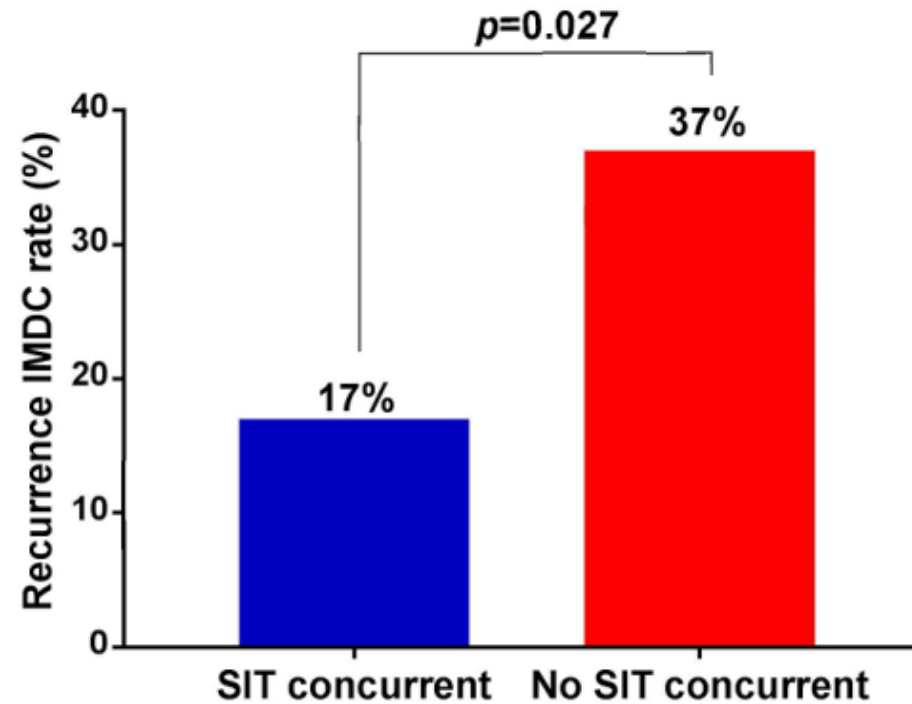
Fecal calprotectin can serve as surrogate marker to predict colitis remission and guide the treatment duration.

Factors of Colitis Recurrence Upon Resumption



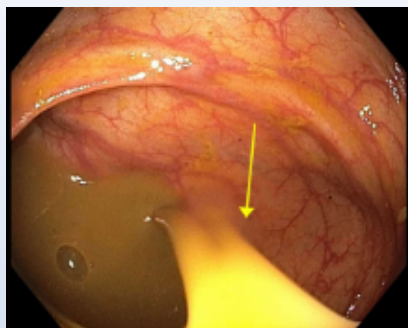
Abu-Sbeih, Wang et al J Clin Oncol. 2019;37(30):2738-2745.

IMC Management on ICI Resumption



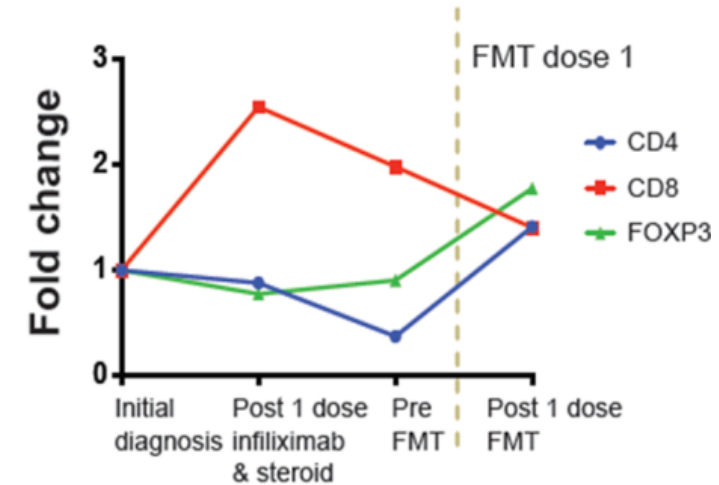
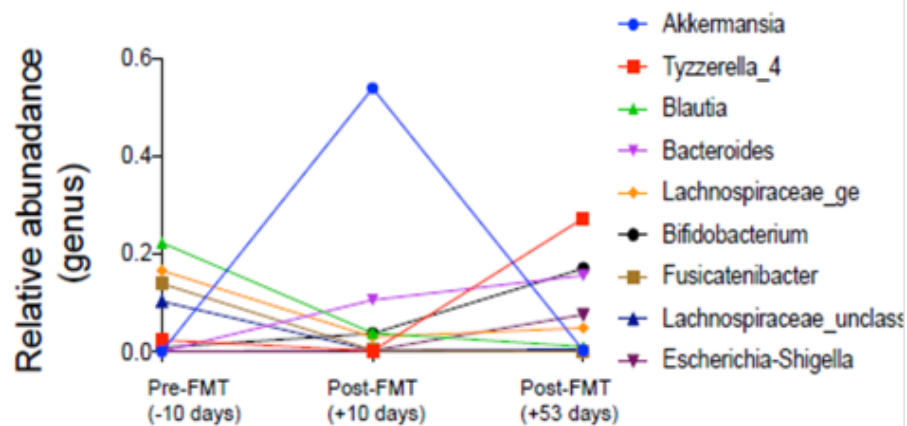
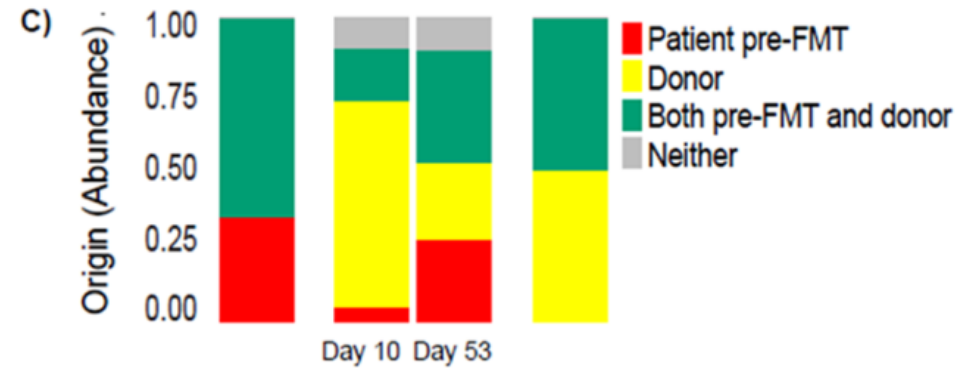
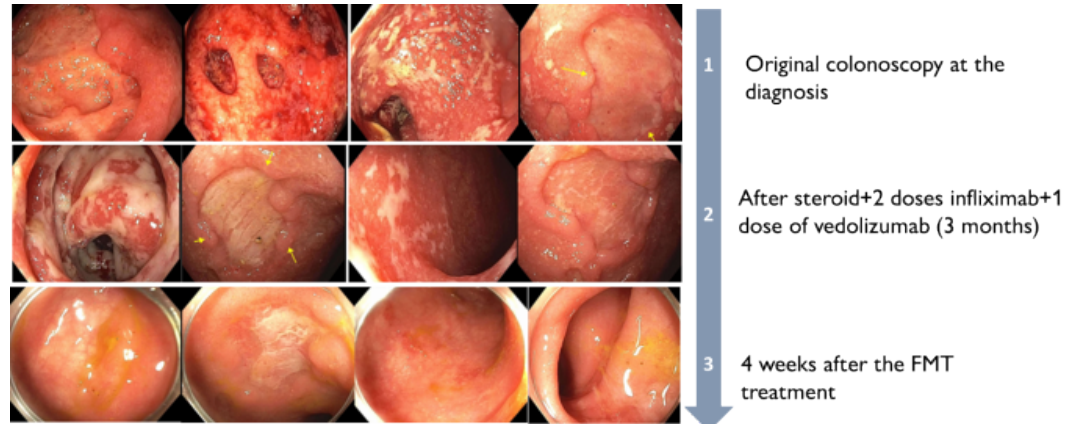
SIT: selective immunosuppressive therapy (infliximab or vedolizumab)

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



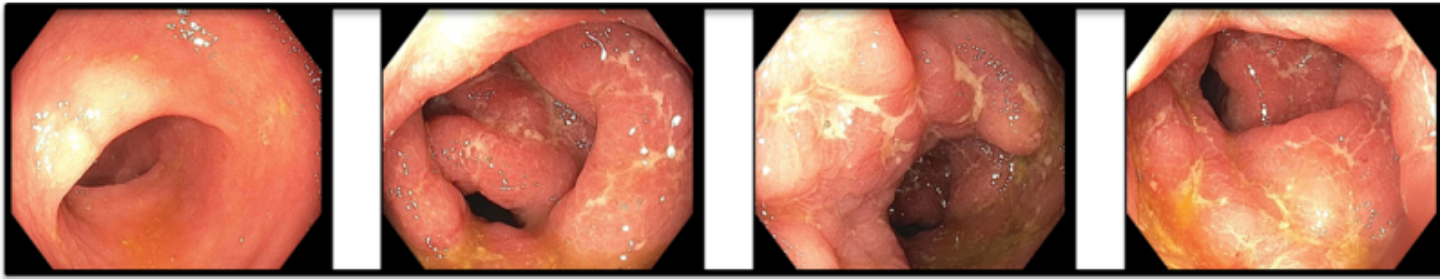
First FMT for ICI colitis in the universe
in 2017.

1st FMT Case

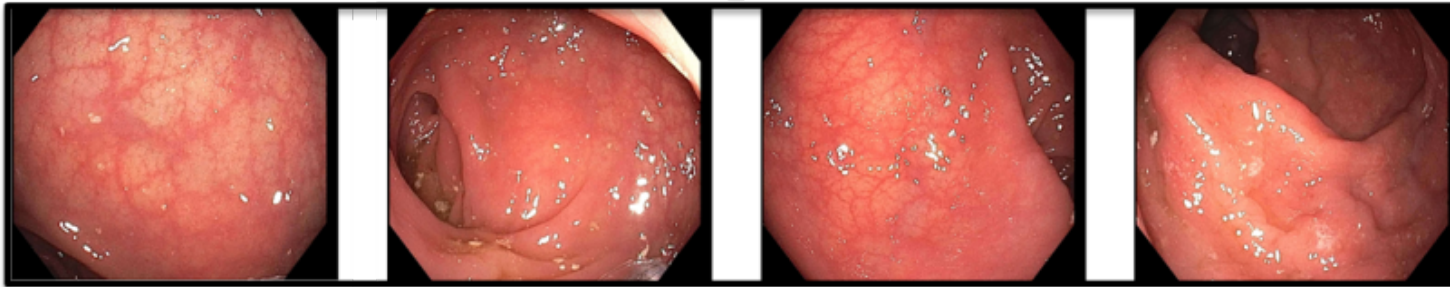


- Successful engraftment of donor's stool in recipient.
- Dramatic changes post FMT in recipient in gut microbiome and tissue immune profile.

1st Front Line FMT for ICI Colitis



ICI colitis onset

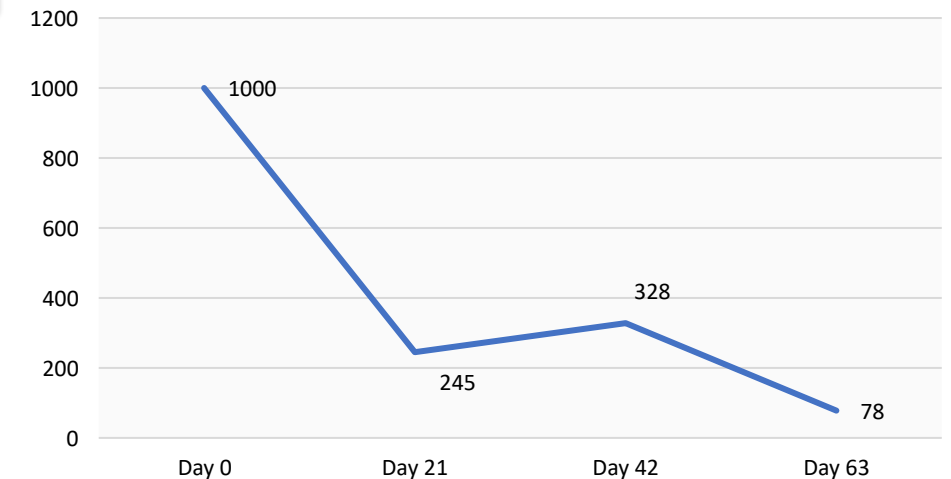


4 weeks later

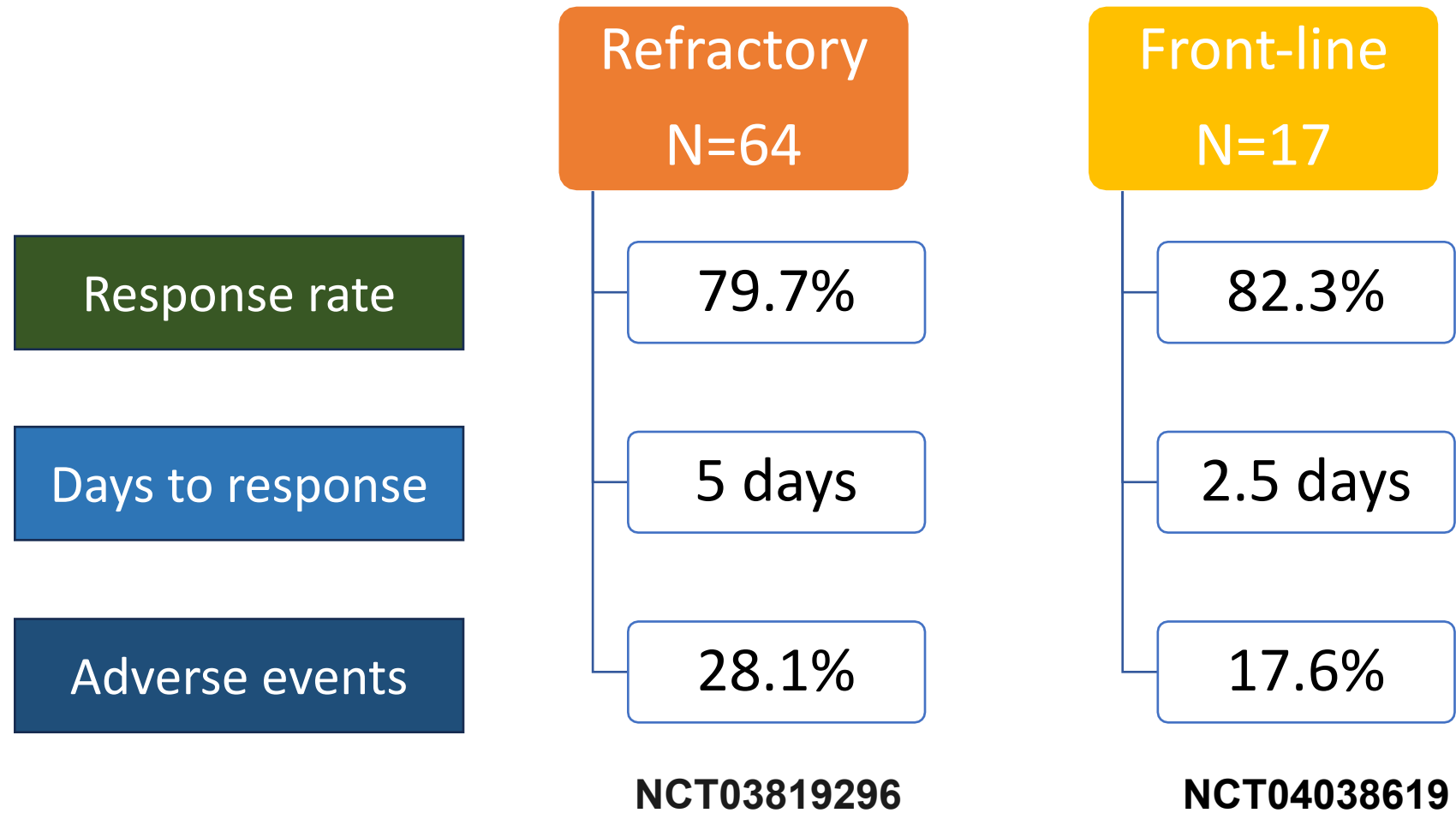
- Diarrhea resolved within 24 hours and sustained over 15 months.
- Resumed nivolumab x 2 doses after FMT followed by surgery.

First FMT for IMC as front-line treatment in the history with success.

Fecal Calprotectin Level

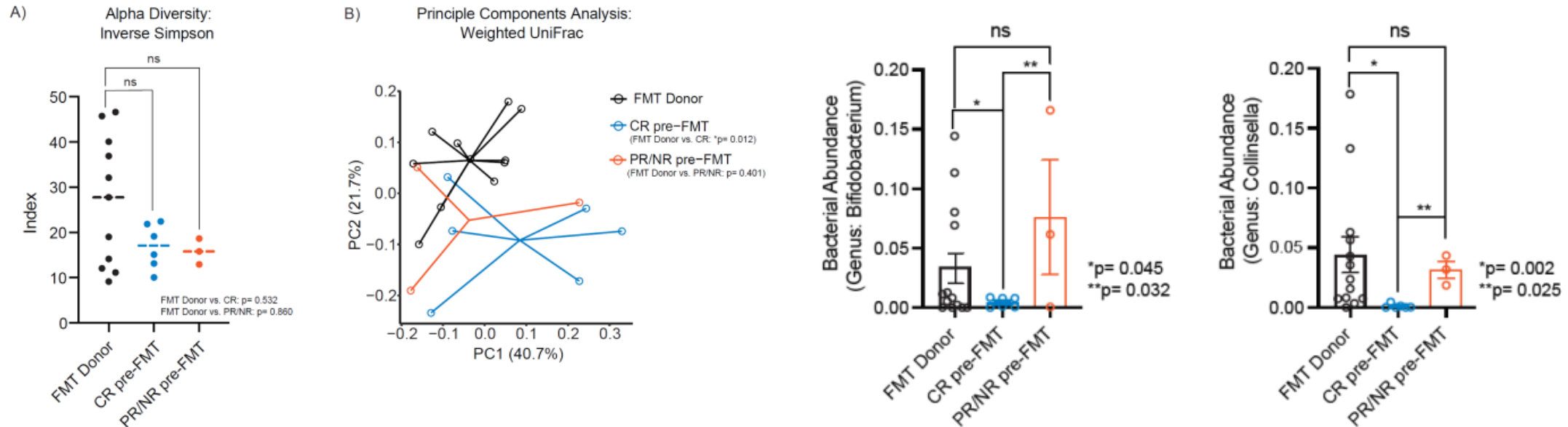


FMT Treatment for Immunotherapy Colitis



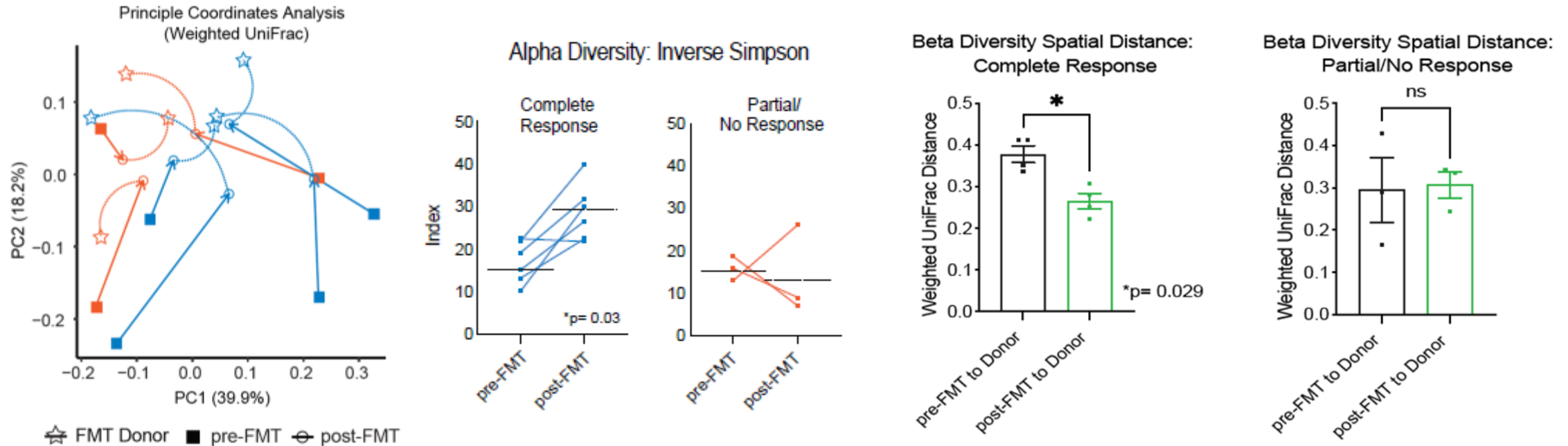
- Wang, Y, et al. Journal of Clinical Oncology, 2024. 42(16_suppl): p. 2660-2660.
- Wang, Y, et al. Journal of Clinical Oncology, 2024. 42(16_suppl): p. 2517-2517.

Microbiome Comparation between Donors and Recipients



- Donor stool was distinct from the stool of complete responders at pre-FMT baseline.
- Complete responders had greater dysbiosis pre-FMT than partial and non-responders.
- Composition showing reductions in the abundances of Bifidobacterium and Collinsella.

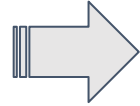
Diversity of Paired FMT Donors and Recipients



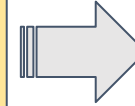
- Complete responders had more similar beta diversity of stool post-FMT to their donor.
- Complete responders had higher alpha diversity following FMT, while partial and non-responders did not.
- Partial and non-responders showed no substantial change in beta-diversity post-FMT to their donor.

Case Summary

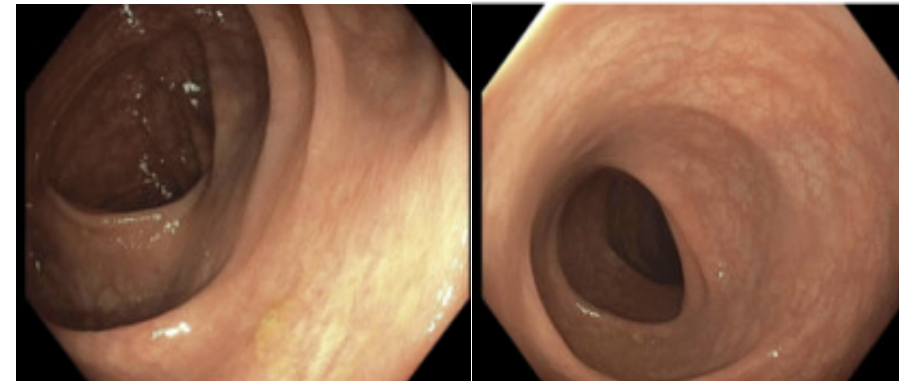
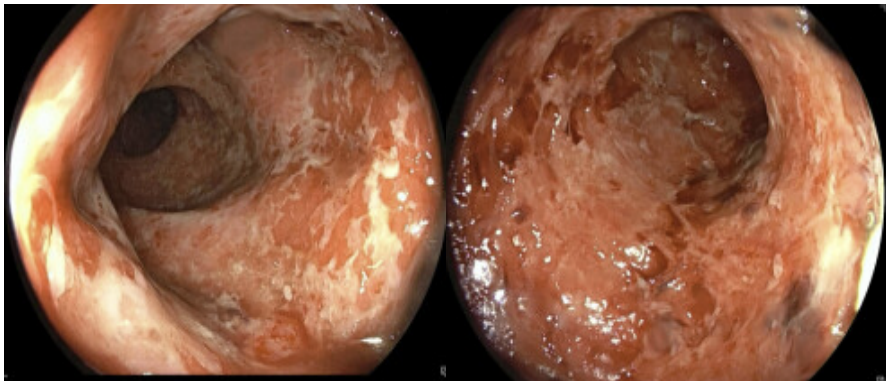
Severe ICI colitis:
Grade 3 diarrhea,
grade 2 colitis



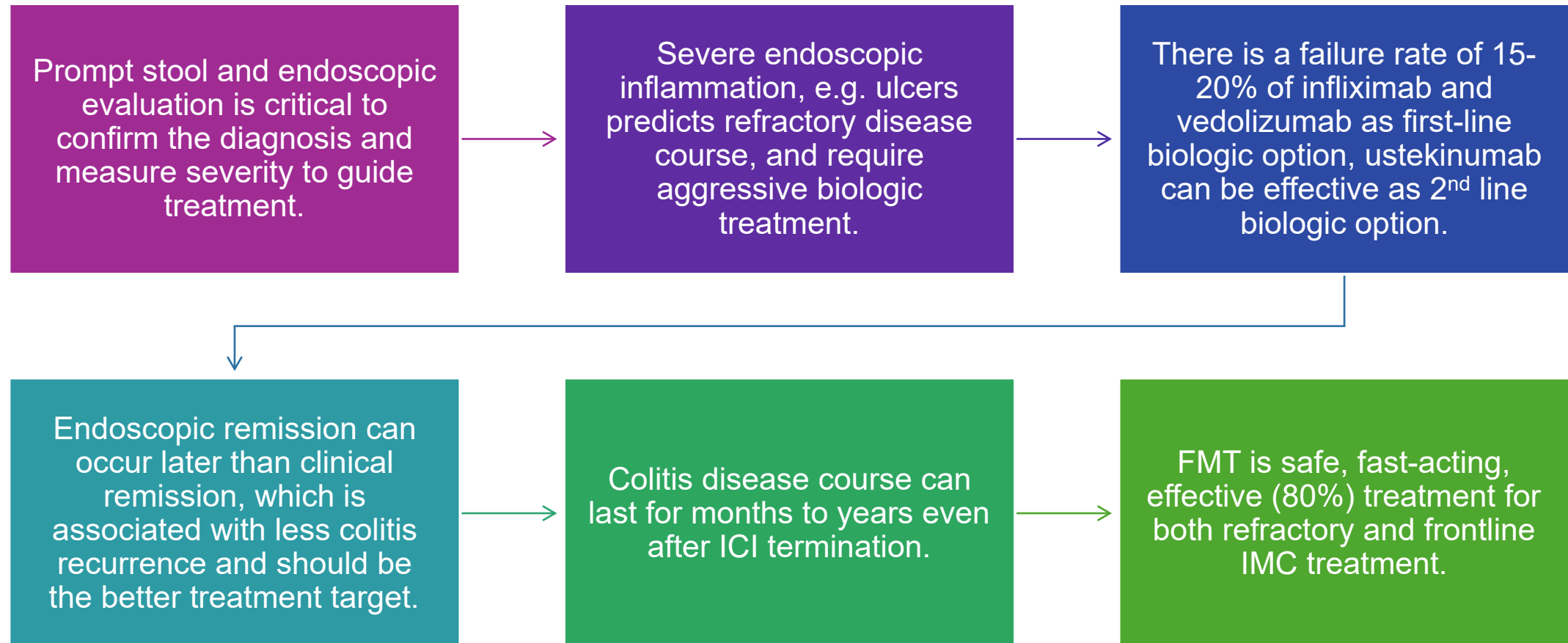
Refractory symptoms
despite glucocorticoids,
infliximab x2 doses,
FMT, and vedolizumab
x5 doses



Clinical and endoscopic
remission after
ustekinumab
(induction & x3
maintenance doses)



Take Home Points



Acknowledgements

MDACC GI research
team

IOTOX initiative, MDACC
oncology, ICT, ACCC,
Path, Radiology,
mbiome core, TMP-IL

BWH, CCF, DFCI, GTU,
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MSKCC, Mount Sinai,
Moffit, NCI, NYU,
Northwestern

OSU, Stanford, Swedish,
U Chicago, U Mich,
UPMC, UTH, UW,
Vanderbilt, Yale

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award