Sistema Socio Sanitario

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Fondazione IRCCS Policlinico San Matteo

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GRAND ROUNDS CLINICI DEL MERCOLEDÌ

con il Policlinico San Matteo

Aula Magna "C. Golgi" & WEBINAR

TOSSICITÀ GASTROENTERICA INDOTTA DA IMMUNOTERAPIA

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ANAMNESI REMOTA

uomo, 83 anni, pensionato

Storia Clinica

- ✓ **Sospetto radiologico di neoplasia prostatica (in anamnesi IPB) per cui è in trattamento con analogo LHRH (ultimo PSA 10/2022: stabile)**
- ✓ **Esiti di colecistectomia per litiasi**
- ✓ **Pregressa gastroresezione subtotale per ulcera gastrica (1981)**
- ✓ **Plastica di laparocele**
- ✓ **Ipertensione arteriosa da circa dieci anni in trattamento farmacologico con sartani**
- ✓ **Polineuropatia sensitivo-motoria, assonale distale cui si sovrappongono segni di sofferenza poliradicolare cronica nei territori L1-L2 di dx e L3-L4 bilateralmente**

STORIA CLINICA: ANAMNESI ONCOLOGICA

Anamnesi oncologica

08/2012 Asportazione di lesione avambraccio destro →E.I.: **melanoma nodulare Clark III**
10/2013 Asportazione di lesione avambraccio dx sede di recidiva di melanoma
01/2014 Asportazione di lesione in avambraccio destro recidiva di melanoma

24/03/2014 Linfadenectomia ascellare sinistra (c/o Città di Pavia) E.I.: **micrometastasi** pluriembolica in 1 su 22

05/2014 Ricerca mutazioni BRAF: mutazione V600E a carico dell'esone 15

20/07/2016 PET: patologico accumulo dell'analogo radiomarcato del glucosio in corrispondenza della porzione anteriore dell'ala iliaca e della regione sovracetabolare destra con estensione ai muscoli ileopsoas, trasverso e obliquo interno di destra e di un nodulo di pertinenza peritoneale a livello del fianco di sinistra, reperti compatibili con lesioni di natura neoplastica.
08/2016 Biopsia spina iliaca anteriore dx E.I.: Diffusa infiltrazione di elementi marcatamente atipici con i caratteri morfologici e fenotipici (S100+, MelanA+, HMB45+) del **melanoma amelanotico**

09/2016 **Trattamento radiante palliativo** a livello dell'ala iliaca destra (dose totale 30 Gy in 10 frazioni, dal 5-9-16 al 15-9-16) 09/2016 Avvia terapia di supporto con Acido Zoledronico.

STORIA CLINICA: ANAMNESI ONCOLOGICA

Anamnesi oncologica

09/2017

TC TB con mdc: incremento del **tessuto patologico a livello dell'ala iliaca dx** fino a 60 mm circa su piano assiale. Aumentato di dimensioni il **linfonodo patologico** in sede femorale sinstra che presenta asse breve di 15 mm. Notevolmente aumentata la **formazione nodulare sottocutaneo a dx** che al controllo odierno presenta dimensioni fino a 28 mm

06/2023

TC TB con mdc: incremento dimensionale di **pressoché tutti i linfonodi presenti in sede ilo-mediastinica**, in particolare con formazione di pacchetto linfonodale confluente in sede sottocarenale, che ora presenta diametri assiali massimi di circa 17 x 37 x 48mm (vs 9 x 34 x 39mm), sospetti in senso patologico.

STORIA CLINICA: DIARREA

10/2023

Completati 4 cicli, 2 mesi, di terapia con Ipilimumab

Alla visita pre-infusione, riferita diarrea: 6-7 evacuazioni/die di feci liquide, senza sangue né muco, frequente causa di risveglio notturno. Calo ponderale di 3 kg. Dolore addominale severo. Non dispepsia, non nausea. Ipotensione con sincopi.

Terapia in corso

Oxatomide 30 mg 1 cp ore 22 se prurito
Prednisone 5 mg 1 cp ore 8-12
Ossicodone/Naloxone 5/2.5 mg 1 cp ore 10-22
Paracetamolo 1 g 1 cp ore 8-20
Omeprazolo 20 mg 1 cp ore 8-20
Enoxaparina 4000UI 1fl sc ore 20
Goserelin 10.8 mg 1 fl ogni 3 mesi
Loperamide 2 mg cpr, 1 cpr al bisogno

CTCAE definitions

Grade	Diarrhea	Colitis
1	Increase of <4 stools/d over baseline	Asymptomatic
2	Increase of >4–6 stools/d	Abdominal pain, mucous, and blood in the stools
3	Increase of ≥7 stools/d, incontinence, and limiting self-care activity of daily living	Severe pain, fever, peritoneal signs, and ileus
4	Life-threatening consequences (hemodynamic collapse)	Life-threatening consequences (perforation, ischemia, necrosis, bleeding, and toxic megacolon)
5	Death	Death

diarrea G3

STOP IPILIMUMAB, PROPOSTO RICOVERO CLINICO

STORIA CLINICA: WORK-UP

Management

- ✓ Coprocoltura per enteropatogeni (Salmonella, Shigella, Campylobacter)
- ✓ Esame coproparassitologico
- ✓ ricerca tossina C. difficile

NEGATIVI

- ✓ Calprotectina fecale > 2000 mcg/g

- ✓ Emocromo completo
- ✓ Pannello metabolico
- ✓ Albumina
- ✓ Indici di flogosi

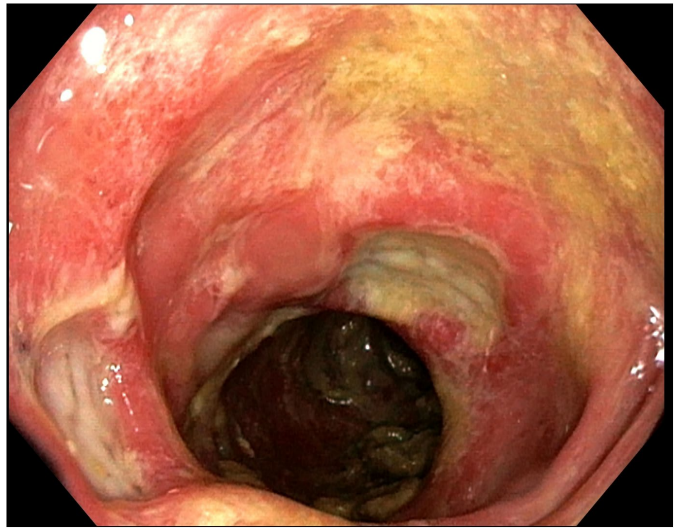
Hb 9.5, MCV 90 fL, WBC 6000, formula nei limiti, PLT 231000
Creatinina 1.48, AST/ALT 24/35, bilirubina totale 0,34
2.5 g/dL
PCR 15 mg/dL, procalcitonina < 0.5

Terapia

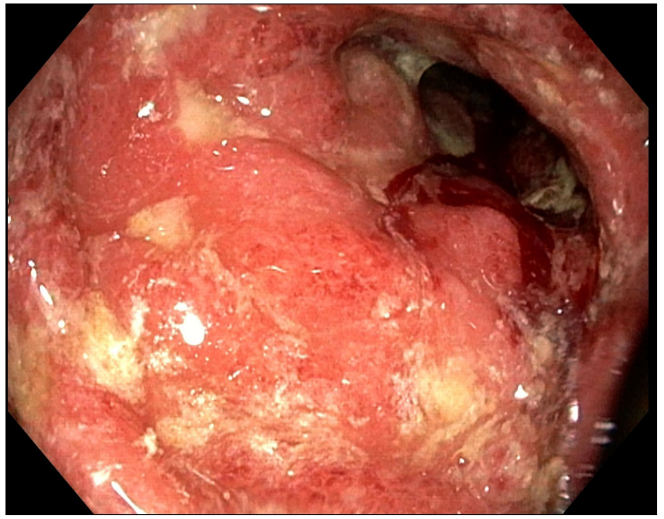
METILPREDNISOLONE 1 mg/kg

COLONSCOPIA

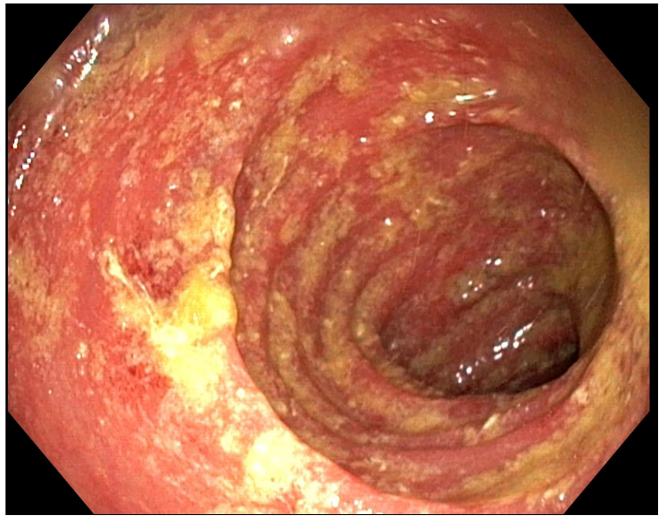
COLONSCOPIA



Colon trasverso



Colon discendente



sigma

A partire dal sigma si reperta iperemia diffusa della mucosa con multiple ulcere a stampo di dimensioni variabili da 5 mm fino a 15-20 mm con fondo fibrinoso fino al colon trasverso distale.

EI: flogosi linfogranulocitaria con modificazioni architetturali delle ghiandole; aspetti di aggressione granulocitaria intraepiteliale. Reperti coerenti con l'ipotesi clinica di colite da farmaco (riferita terapia con ipilimumab).

Conclusioni: colite severa tipo Crohn's-like indotta da immunoterapico

EVOLUZIONE CLINICA

EVOLUZIONE CLINICA

- ✓ Graduale riduzione del numero di evacuazioni fino a 1-2/die
- ✓ Calprotectina fecale: >2000->300
- ✓ PCR: 23->2

- ✓ In considerazione della severità del quadro endoscopico, eseguito screening per terapia immunomodulante (infliximab/vedolizumab):
  - ➢ Sierologie per HIV, HCV, HBV: negative
  - ➢ Quantiferon test: debomente positivo
  - ➢ RX torace: non focolai

- ✓ Condizioni cliniche stabili dopo décalage steroideo fino a prednisone 25 mg 1 cp x 2

- ✓ Paziente dimesso il 7/11 in terapia con prednisone 25 mg 1 cp ore 8 – 16 in décalage

TERAPIA

23/11: prima infusione di Infliximab 5 mg/kg off label

28/11 Sepsi da E. coli-> buona risposta a meropenem

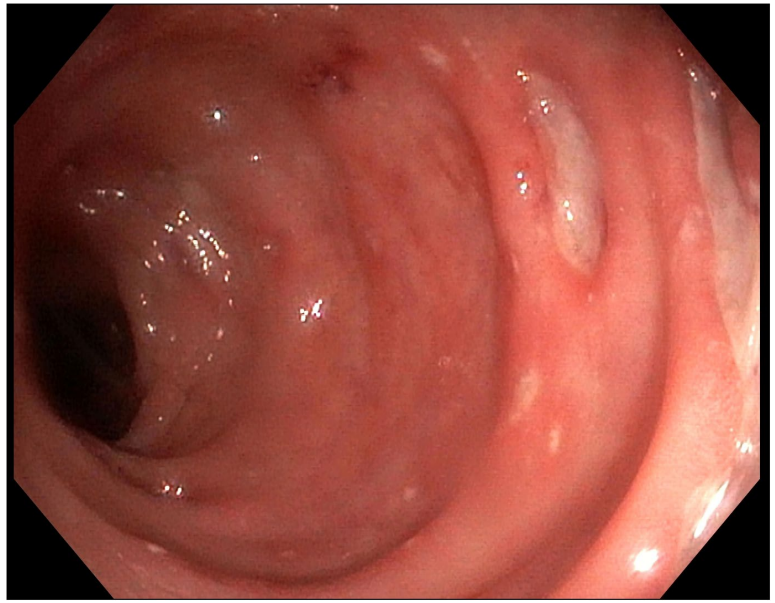
- ✓ Netto miglioramento clinico, con normalizzazione dell'alvo e degli indici di flogosi
  - ➢ PCR 2.3
  - ➢ Calprotectina fecale 500
  - ➢ Hb 10.2

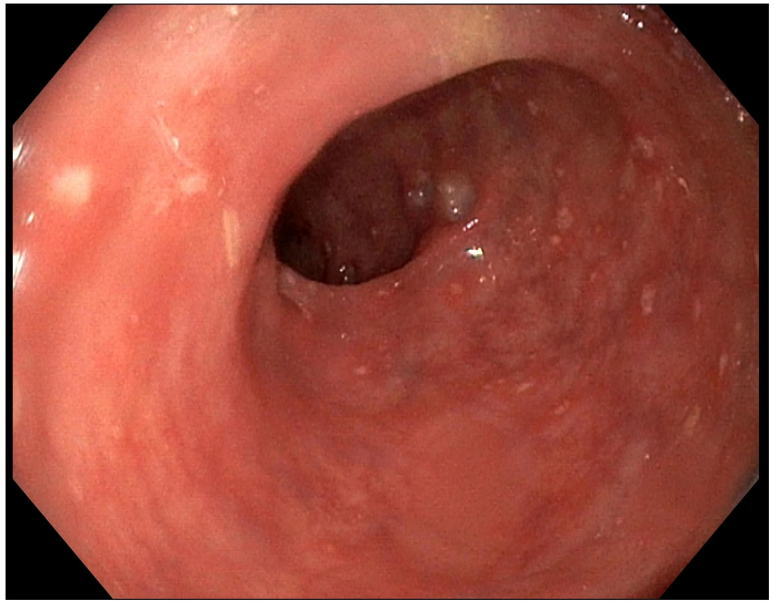
07/12 Dimesso

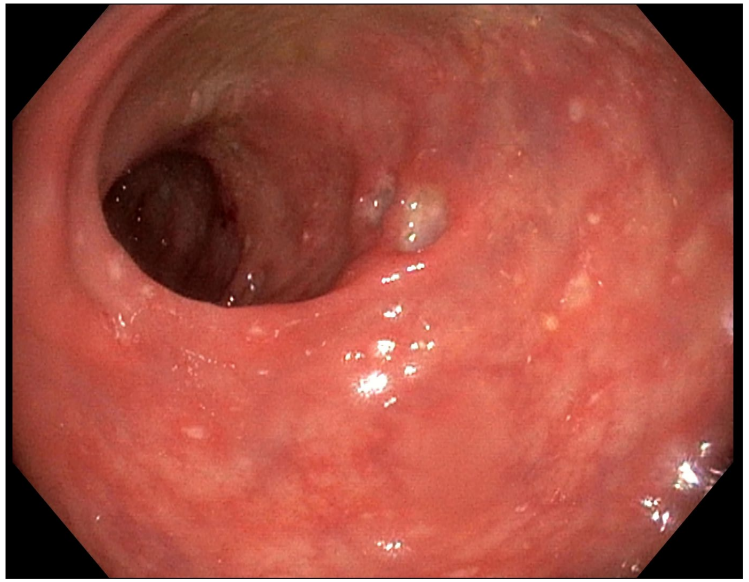
Infusioni di infliximab a 2 e 6 settimane; quindi ogni 4 settimane

COLONSCOPIA. FOLLOW-UP

COLONSCOPIA 30/01







Miglioramento del quadro flogistico e ulcerativo

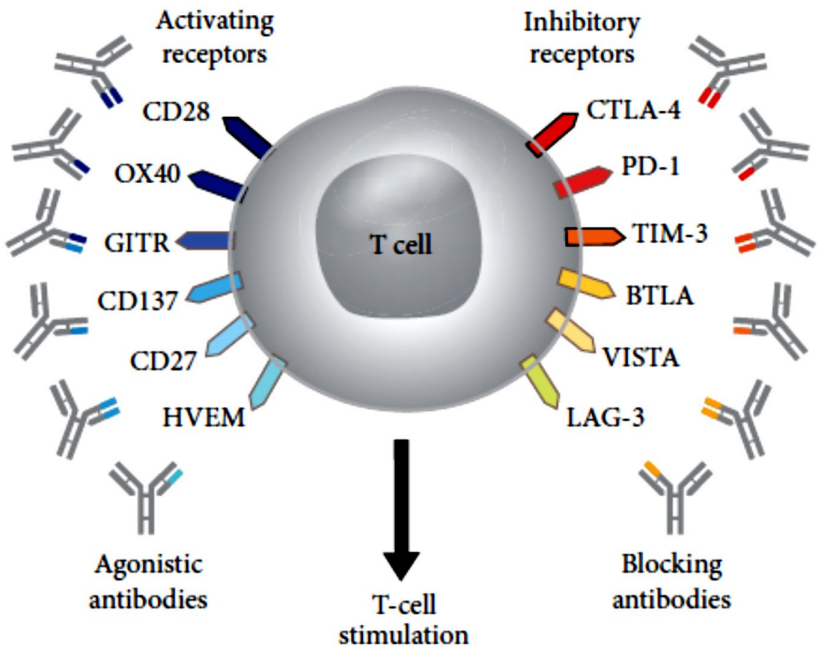
… AD OGGI …

Ed oggi…

- ✓ Prosegue infusioni di infliximab 5 mg/kg ogni 6-8 settimane
- ✓ Permane benessere clinico
- ✓ Ultima calprotectina fecale 150 mg/kg

Immunotherapy – a relatively new concept

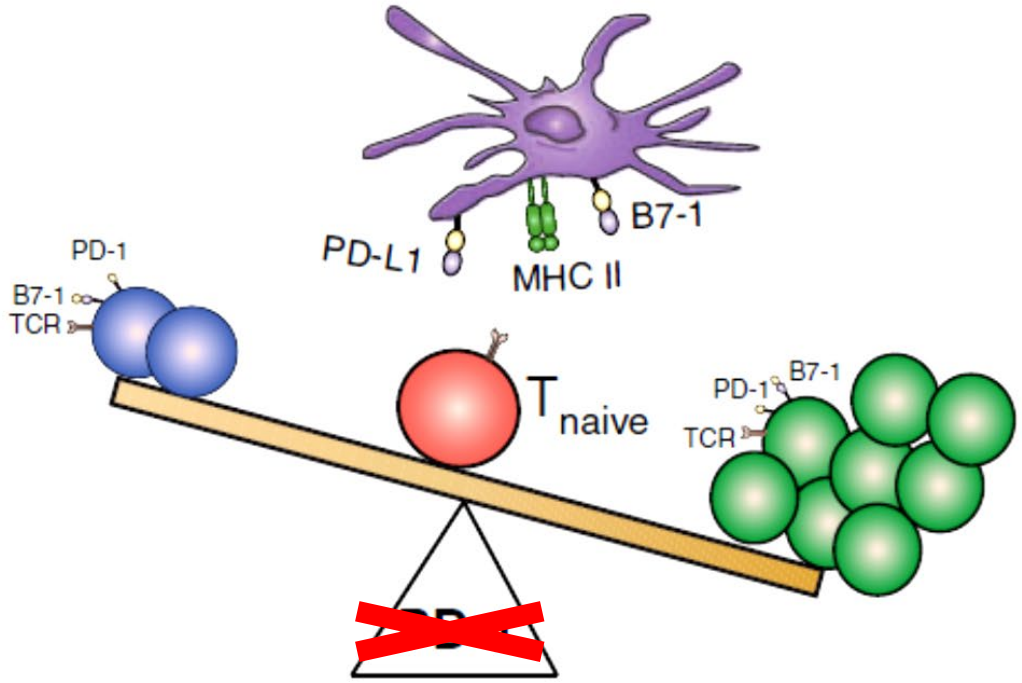
- Checkpoint inhibitors are **a type of immunotherapy** which act by blocking different checkpoint proteins
- They **enhance a defective/altered immune pathways**
- **The number and indications** for the use of these drugs **are dramatically increasing** in oncology



Tarhini et al. *Scientifica 2015*

Drug	Immune checkpoint target	Date of approval and indication
Ipilimumab	CTLA-4	Approved in 2011 Unresectable metastatic melanoma Approved in 2015 Adjuvant therapy with Stage III melanoma
Pembrolizumab	PD-1	Approved in 2014 Advanced or unresectable melanoma Approved in 2015 Metastatic NSCLC with PDL-1 expression and progression on or after platinum therapy Approved in 2016 Recurrent SCCHN
Nivolumab	PD-1	Approved in 2014 Unresectable or metastatic melanoma with progression after ipilimumab or BRAF inhibitor if BRAF V600 mutant Approved in 2015 NSCLC with progression after or on platinum therapy Metastatic RCC after prior anti-angiogenic therapy
Atezolizumab	PDL-1	Approved in 2015 NSCLC with progression after or on platinum therapy Approved in 2016 Urolthelial carcinoma with progression on or after platinum therapy

Programmed cell death 1 (PD-1)/programmed cell death-ligand 1 (PD-L1) signaling



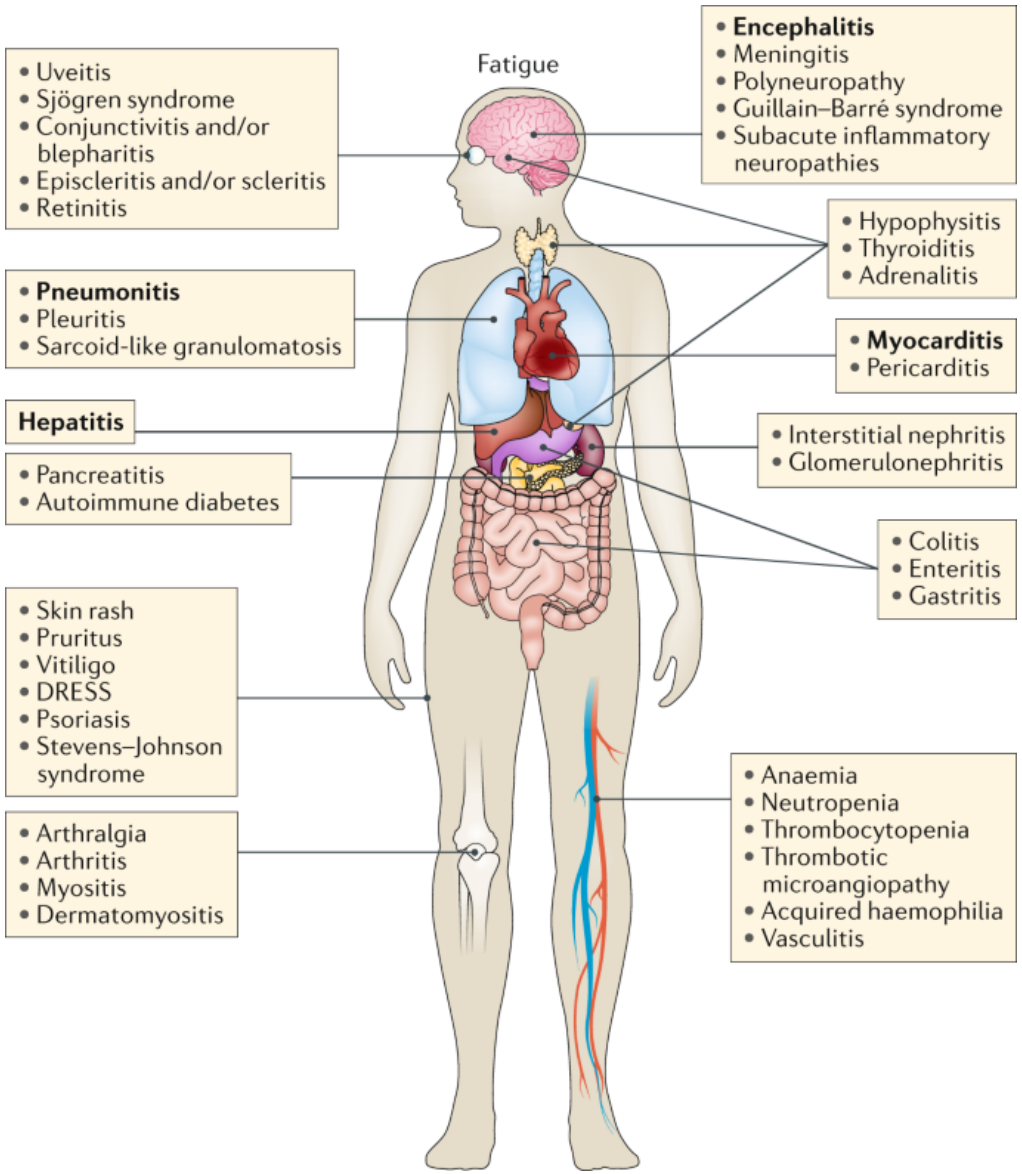
Immunity

Tolerance

Immune-mediated toxicity

Francisco LM et al. *Immunol Rev* 2010

Epidemiology of GI immune-mediated adverse events

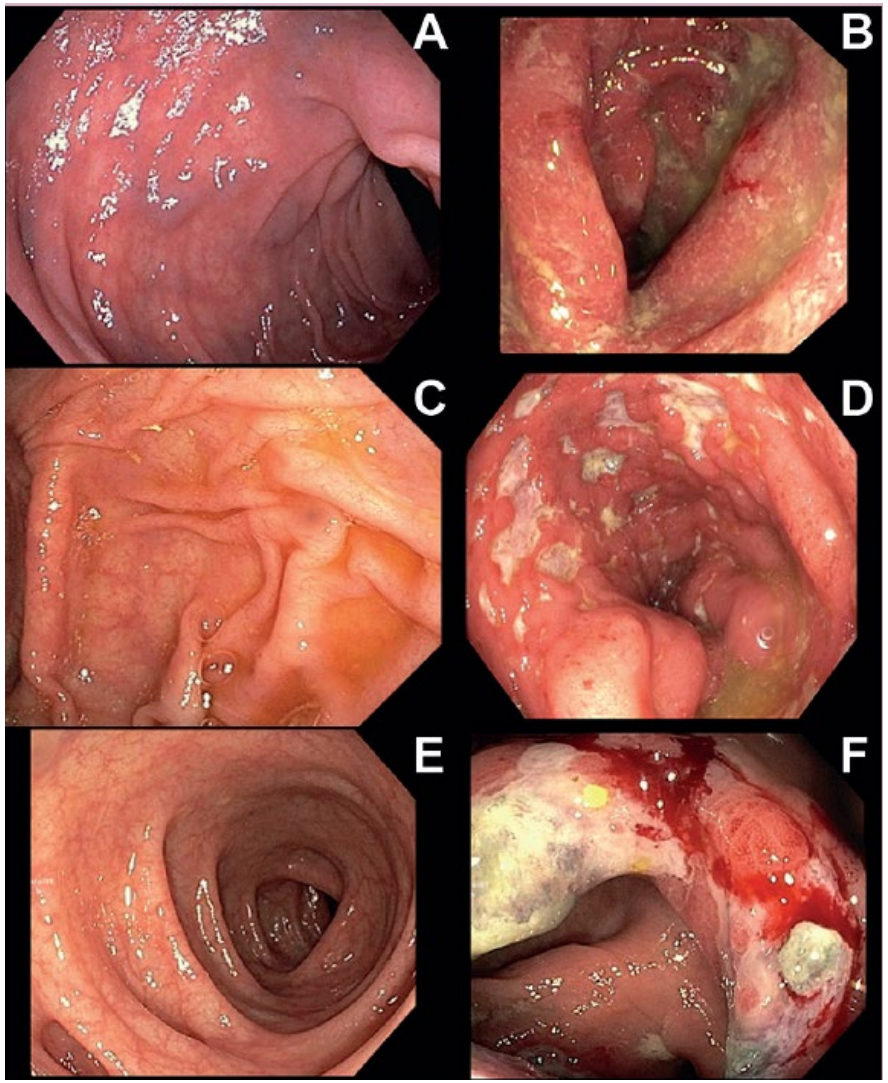


- **Immune-mediated adverse events occur in up to 40-60% of the cases**
- **Endocrinopathies are the most common (30-40%; thyroiditis, hypophysitis)**
- **Diarrhoea occurs in up to 30% of patients; a diagnosis of ileo-colitis/colitis is made in up to 15-20% of the cases; the incidence of overt hepatitis is likely lower**
- **Gastritis (erosive/ulcerous) and atrophic enteropathy are rare**
- **Exceptional (and doubtful) cases of pancreatitis have also been reported**

Martins et al. *Nat Rev Clinical Oncol 2019*

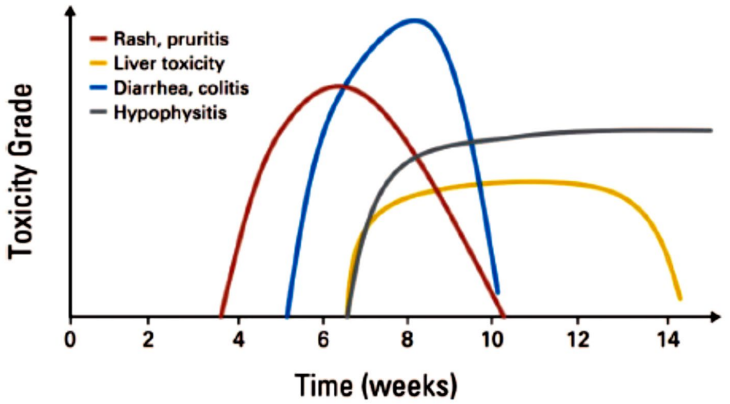
Immune check-point inhibitors ileo-colitis

- an inflammatory condition that involves the colon ± ileum, with different disease extension
- it may occur any time (even after a single dose, or many months later) after starting immunotherapy
- three different main types: unspecific, IBD-like (both resembling either Crohn's disease or ulcerative colitis), microscopic (both lymphocitic and collegenous)



Geukes Foppen et al. *ESMO Open* 2018

Median time of onset of ICI-related toxicity



Postow et al. *ASCO Educ Book 2015*

Basic diagnostic work-up for assessing patients with ICI entero-colitides

1. Full medical history, family history, pharmacology history
2. Type and characteristics of diarrhoea and other symptoms
3. Laboratory work-up: CBC, RCP, kidney/liver function, serum proteins, electrolytes
4. Faecal calprotectin, stool coltures/parasites, *C. difficile*
5. Exclude alternative, non-colonic, causes of diarrhoea/GI symptoms → TSH reflex, ACTH/cortisol; consider enteropathy if steathorrea/hypoalbuminaemia
6. Colonoscopy + ileoscopy and multiple biopsies and/or enteroscopy and/or videocapsule endoscopy and/or upper GI endoscopy; exclude CMV/EBV superimposed infection if treated with steroids
7. Imaging: US, entero-CT, entero-MRI (for complications)

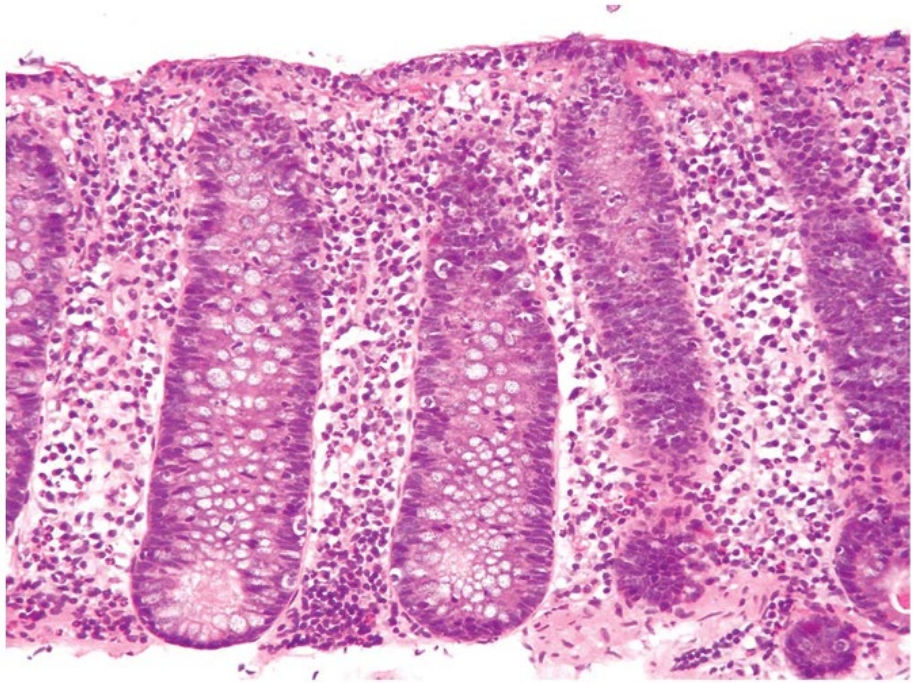
Microscopic colitis as a common form of ICI-induced colitis

Pembrolizumab-Induced Microscopic Colitis

Monjur Ahmed, MD, FRCP[1] and Gloria Francis, MD[1]

doi:10.1038/ajg.2018.8

- Histopatology does not differ from that of microscopic colitis of other aetiologies
- Both lymphocytic and collagenous colitis have been reported



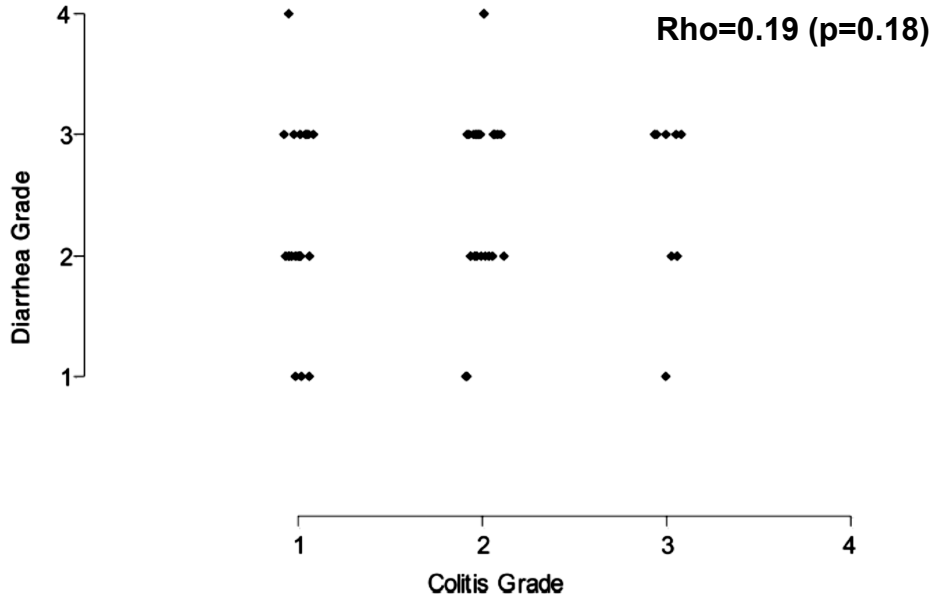
Dissociation between diarrhea severity and colitis severity in patients treated with ICI

	Colitis Grade 1 No. = 21	Colitis Grade 2–3 No. = 32	*P* value
Endoscopic findings, no. (%)			0.039
Inflammation	14 (67)	29 (91)	
Normal	7 (33)	3 (9)	
Histology features, no. (%)			1.000
Inflammation	19 (90)	29 (91)	
Normal	2 (10)	3 (9)	

Severity: combotherapy >> anti-CTL4 > anti-PD1

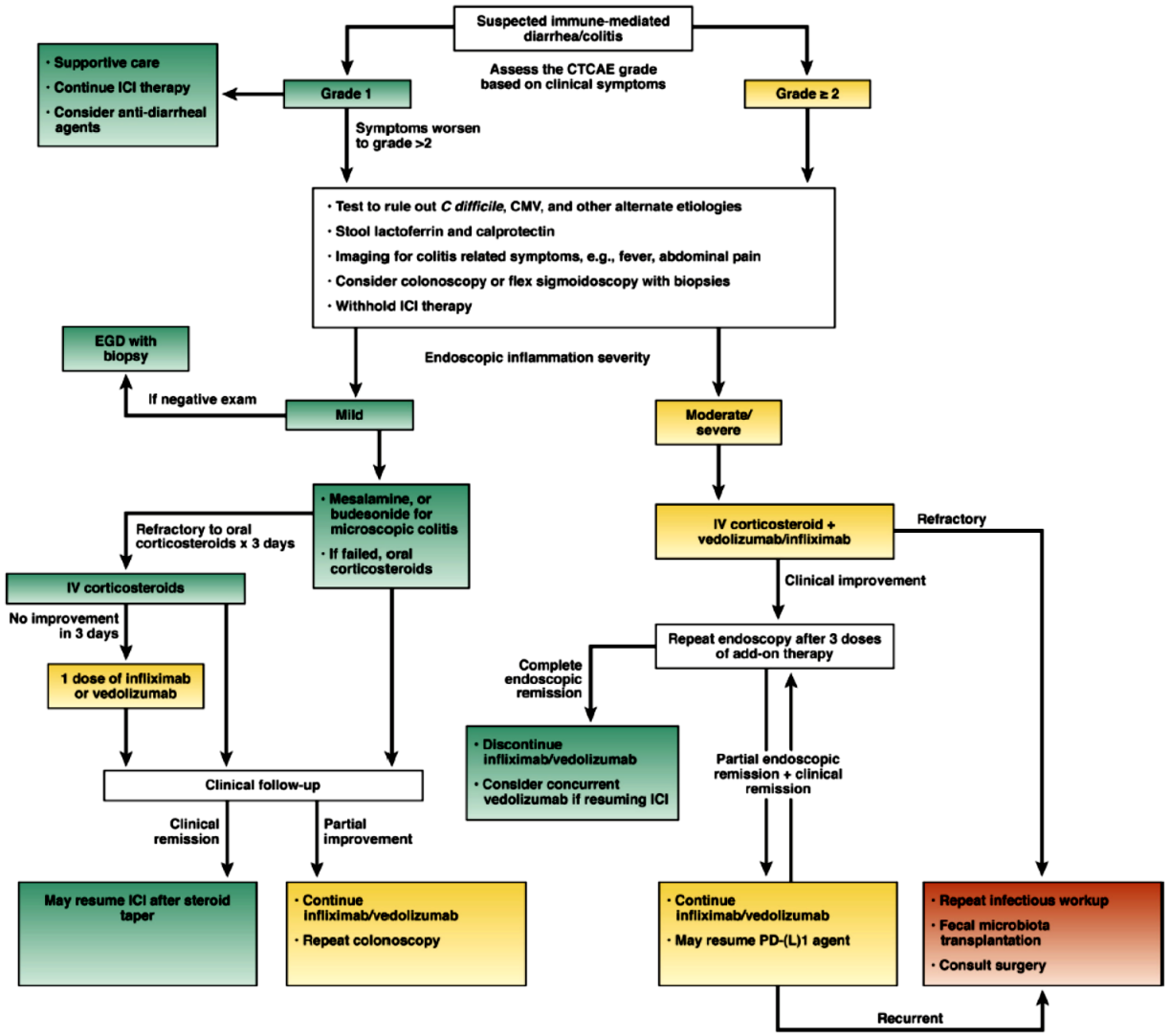
Severity: preexisting IBD > no-IBD

Severity: not influenced by tumor types



Wang et al. *Inflamm Bowel Dis* 2018

Management algorythm in checkpoint inhibitor-induced colitis



Dougan et al. *Gastroenterology 2021*

- The first line therapy for microscopic colitis and mild-to-moderate RCU-like colitis is budesonide MMX
- Systemic steroids, including hospitalization + iv steroids, must be considered if failure to budesonide occur, or in case of severe diarrhoea; NOT to be used as a first-line in all cases as they prompt ICI discontinuation
- There is no role for the use of mesalamine
- If iv steroids fail within 3-5 days, biologic agents are recommended
- Infliximab has the most solid available evidence
- Vedolizumab usually a second choice (may be first choice especially in case of anti-PDL1/PD1)
- Ustekinumab and fecal microbiome transplantation to be considered in selected cases (scarce evidence, but potentially promising)

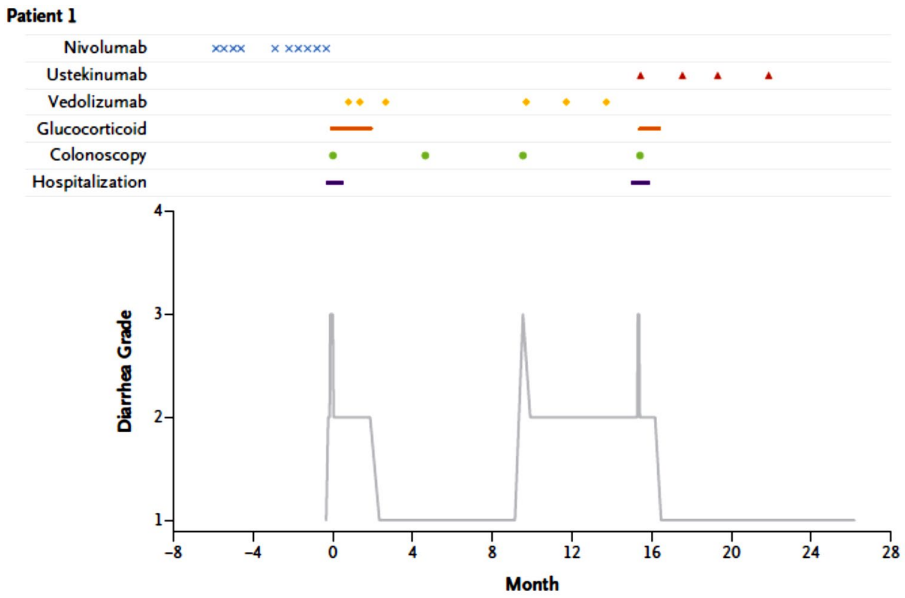
Efficacy and safety of vedolizumab or infliximab in a dual center observational study

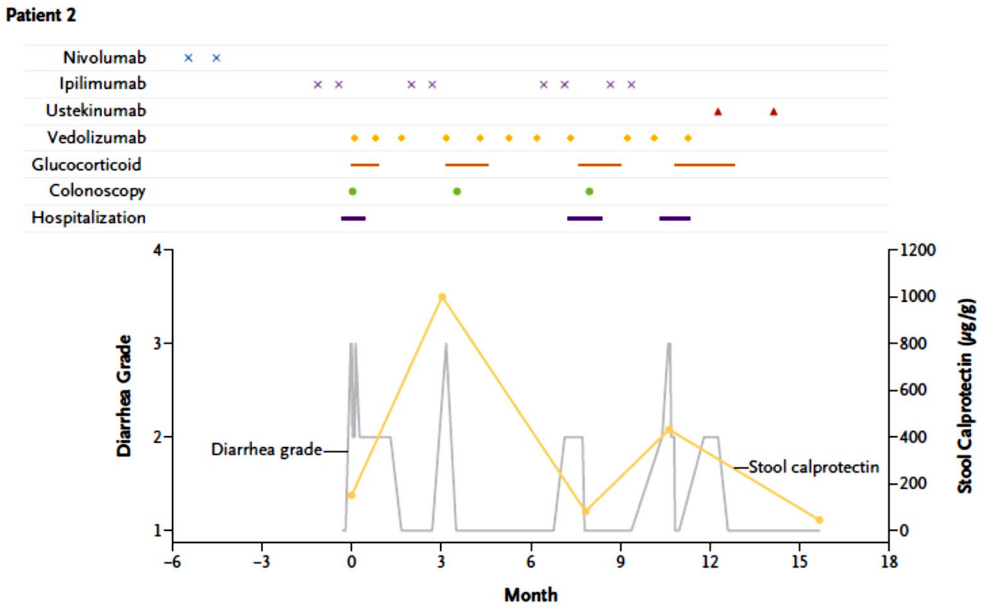
- a total of 184 patients (62 vedolizumab, 94 infliximab, 28 combined sequentially) were included
- the efficacy of achieving clinical remission of was similar (89% vs 88%, p=0.79) between the two groups
- compared with infliximab, the vedolizumab group had a shorter steroid exposure (35 vs 50 days, p<0.001), fewer hospitalizations (16% vs 28%, p=0.005), and a shorter hospital stay (median 10.5 vs 13.5 days, p=0.043), but a longer time to clinical response (17.5 vs 13 days, p=0.012)
- longer durations of immune checkpoint inhibitors treatment (OR 1.01, p=0.004) and steroid use (OR 1.02, p=0.043), and infliximab use alone (OR 2.51, p=0.039) were associated with higher colitis recurrence
- furthermore, ≥3 doses of biologic therapy (p=0.011), and fewer steroid tapering attempts (p=0.012) were associated with favorable overall survival

Zou et al. *J Immunother Canc 2021*

Ustekinumab might be promising biologic in refractory immune checkpoint inhibitor-induced colitis

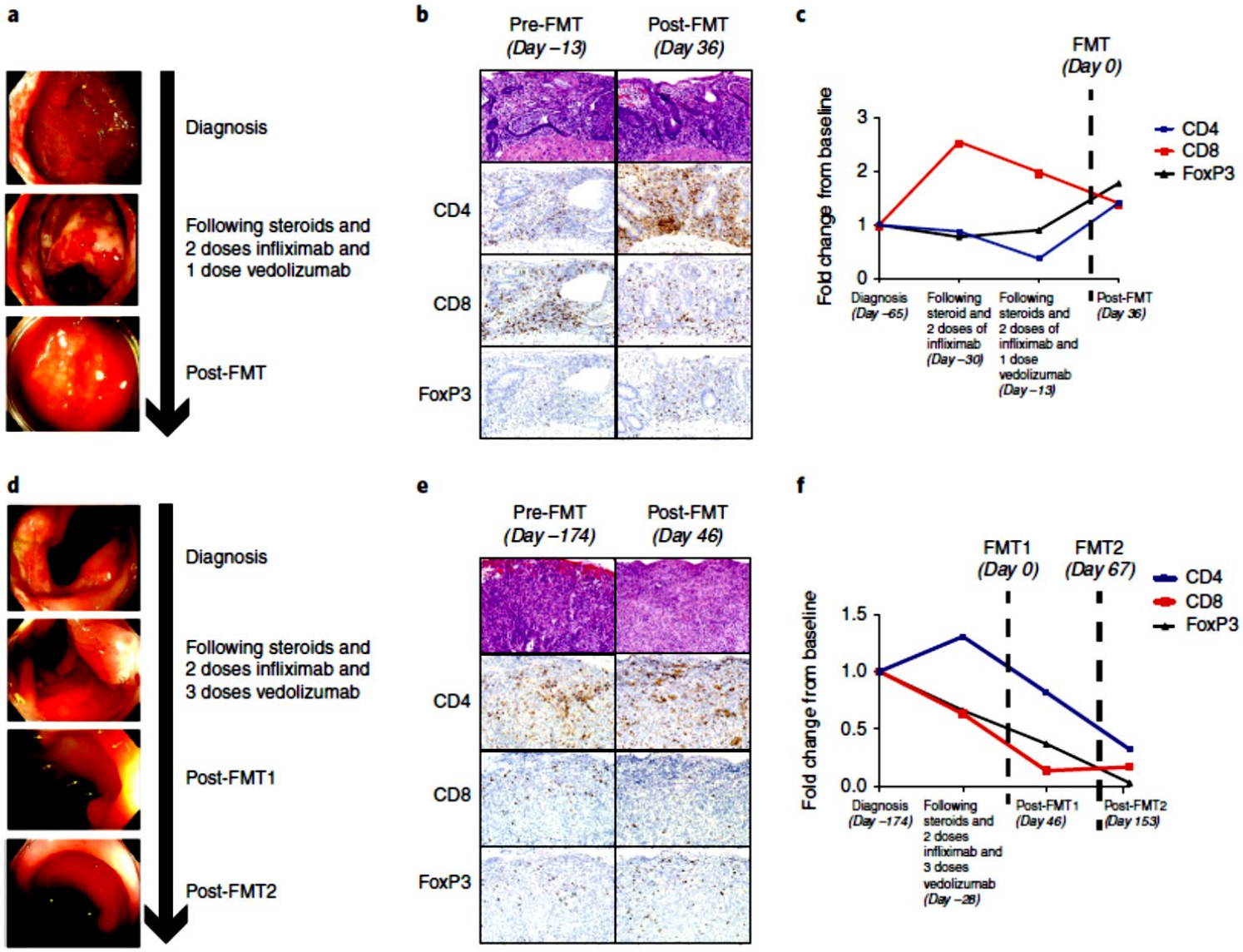
- two cases of vedolizumab or IFX/vedolizumab refractory colitis had complete response to ustekinumab





Thomas et al. *NEJM 2021*

Faecal microbiota transplantation as a safe and effective option in immune checkpoint inhibitor-induced colitis



Wang et al. Nat Med 2018

Long-term follow-up of checkpoint inhibitors-induced ileo-colitis

- No studies with a long-term follow-up are available
- Risk factors for the development of colitis are partially known
- Response to treatments are uncertain
- Long-term follow-up is uncertain

ECCO-endorsed study

Progetto di Ricerca Corrente

- The aim of this clinical research was to perform an **epidemiological study regarding a series of patients diagnosed with checkpoint inhibitors-induced enterocolitis or colitis**, with at least **1 year of clinical follow-up** after the first index colonoscopy
- **Retrospective** and prospective phase
- Any EU country can participate
- **Prof. Ribaldone, Dr. Vernero, Dr. Borrelli de Andreis**; Federico Sottotetti – IRCCS Maugeri Pavia; Edoardo Savarino – Università di Padova; Renato Cannizzaro; Maurizio Vecchi – Università di Milano; Flavio Caprioli – Università di Milano; Nicola Slivestris – Università di Messina; Andrea Magarotto – Istituto Tumori Milano; Giovanni Cammarota – Cattolica di Roma; Stefano Cascinu – San Raffaele Milano; Mihai Diculescu – Università di Bucarest; Tudor Stroie – Università di Bucarest; Adina Croitoru – Università di Bucarest; Pierre Ellul – Università di Malta; Ebbe Langholz - Københavns Universitet Danimarca; Jakob Benedict Seidelin - Københavns Universitet; Emilie Kristine Dahl - Københavns Universitet; Kalliopi Foteinogiannopoulou – Università di Creta; Ioannis Koutroubakis – Università di Creta; Maria Cappello – Università di Palermo; Gianluca Ianiro – Università Cattolica; Lobaton Ortega Triana – Ghent, Belgium; Jeroen Geldof; Piotr Eder - Poznan University Poland; Andreas Blesl - Graz, Austria; Taylan Kav - Ankara University, Turchia; Andrea Buda – Feltre; Daniela Pugliese – Gemelli; Alessandro Armuzzi - Humanitas; Roberto Gabbiadini – Humanitas; Arianna Dalbuono – Humanitas; Konstantinos Argyriou - Larissa, Grecia; Diana Carvalho - Lisbona, Portogallo; Hans Groechenig – Austira; Aranzazu Jaureguiamezaga – UZA Belgio; Lorenzo Bertani – Pisa

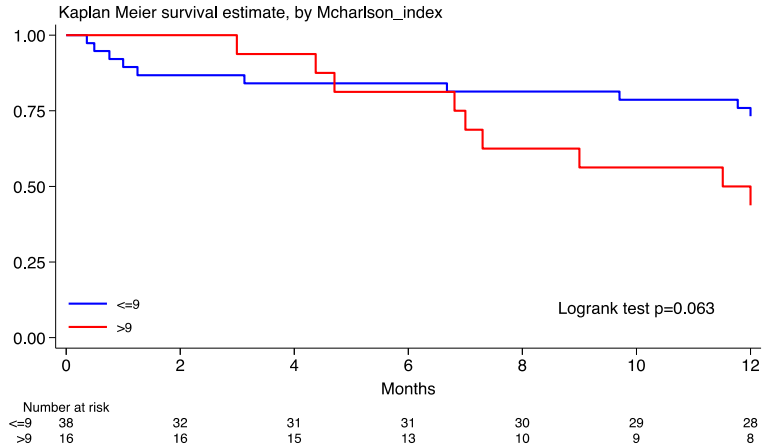
Preliminary results from the retrospective series. Baseline characteristics

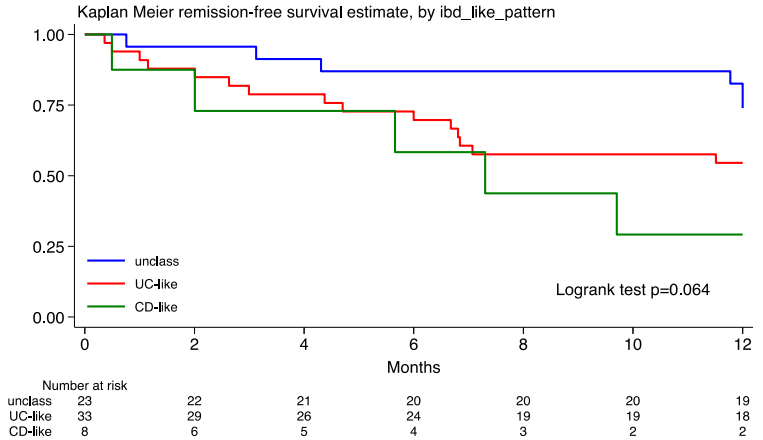
- **98 patients have been enrolled from 28 centres**

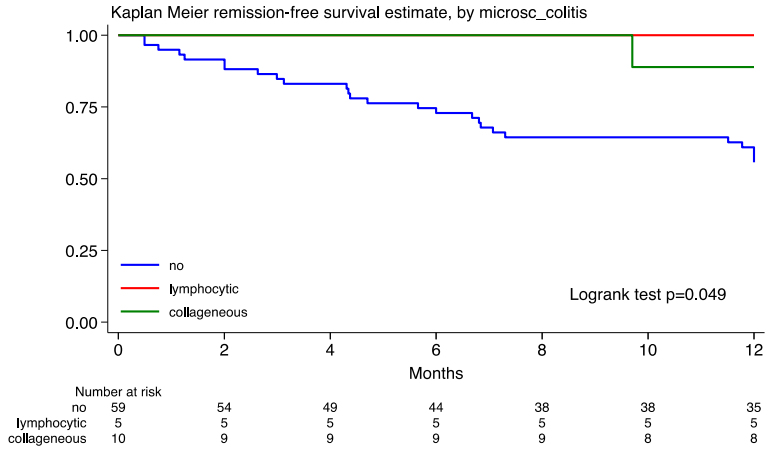
Total number of patients	98
Age, median (IQR)	65 (56-71)
Sex, female, n (%)	40 (40.8%)
Previous autoimmune disease, n (%)	13 (13.2%)
Cancer, localisation	Lung (41; 42.7%) Skin (30; 31.2%) Kidney (9; 9.3%) Colorectal (2; 2.1%) Others (14; 14.6%)
Time for developing colitis, median (IQR)	4 (3-7) months
Colitis pattern	UC-like (35; 35.7%) Microscopic (19; 19.4%) CD-like (11; 11.2%) Undetermined (33; 33.7%)
ICI discontinued due to colitis, n (%)	66 (67.3%)

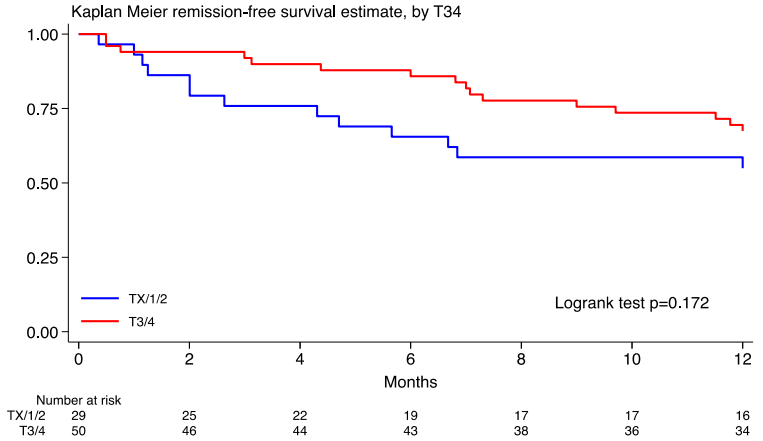
Preliminary results from a retrospective series. Outcomes

- Overall, **colitis remission** was reached in 39 (39.7%) cases within one year
- Despite most patients recovered from colitis, **only a minority** (18; 18.3%) **re-commenced the ICI**
- Four patients (4.0%) **died** from ileo-colitis after receiving third-line therapy, two underwent surgery



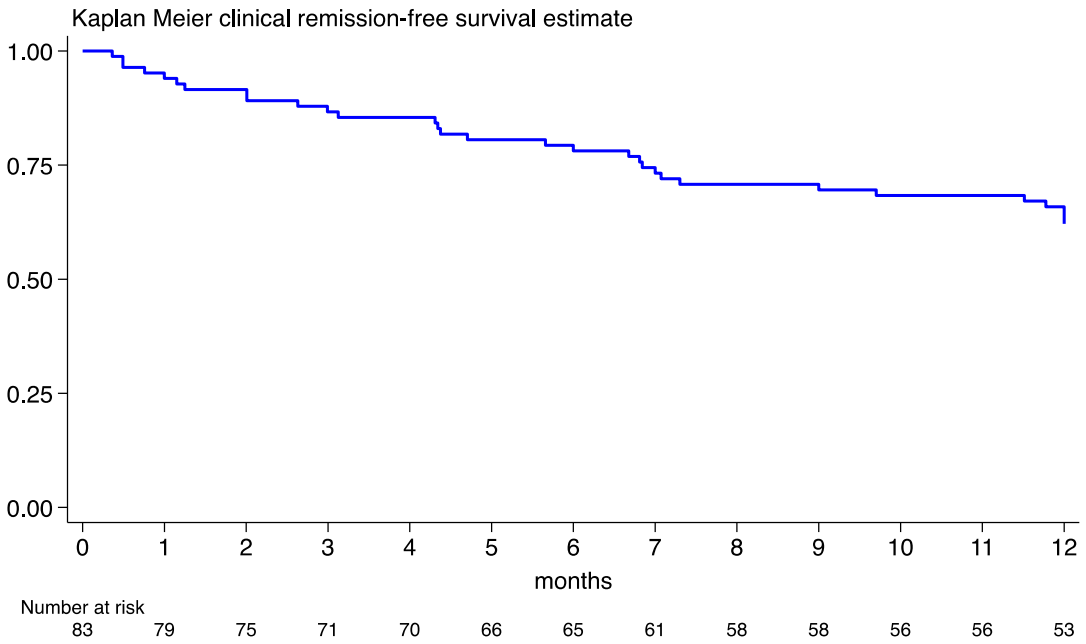




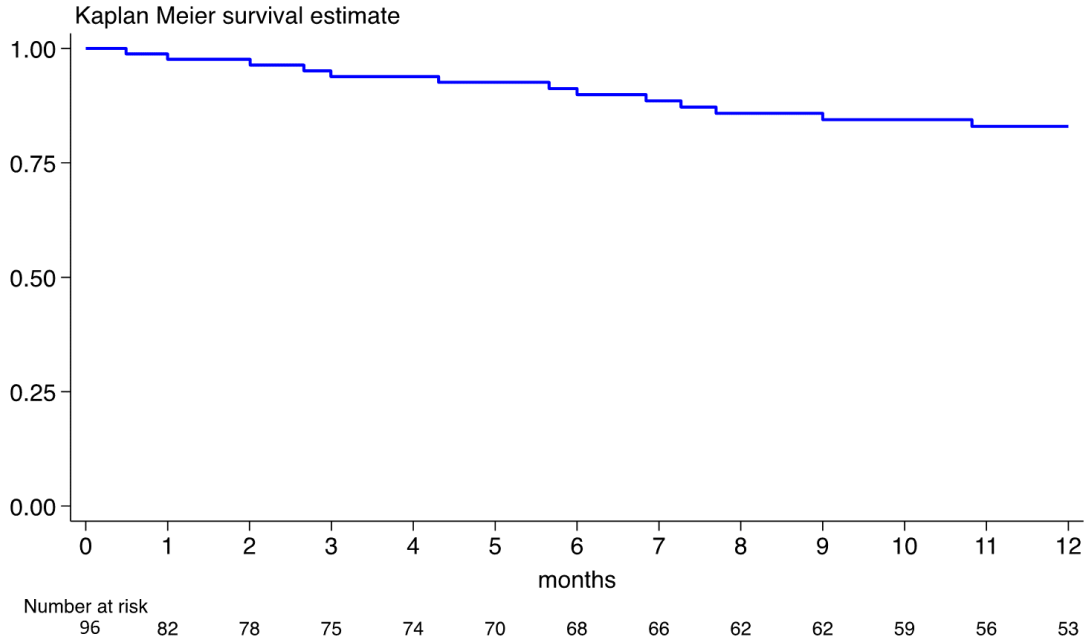


Preliminary results from a retrospective series. Outcomes

Clinical remission-free survival



Overall death



Immune check-point inhibitor (ICI)-induced colitis: take-home messages

- ICI-induced colitis or ileocolitis is a rather frequent (15-30%) complication that may occur any time after ICI commencement
- It may present with different clinical/endoscopic/histopathological forms
- Severity of diarrhoea and severity of colitis are often dissociated
- Steroid therapy is usually the first-line treatment
- Biologics are effective in most cases, but not devoid from complications or death
- The theraputic role of T-selective agents (tacrolimus, cyclosporine and ustekinumab) and FMT should be addressed
- Prevention of ICI-induced colitis after ICI recommencement is currently unknown

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