Digestive complications of immunotherapy: How to deal with them?

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Disclosures

- Speaker fees: Abbvie, Biogen, Ferring, Janssen, MSD, Pfizer, Pileje, Takeda, Tillotts

- Advisory boards: Amgen, Celltrion, Ferring, Janssen, Medtronic, Pfizer, Pharmacosmos, Roche, Tillotts

Frequency of enterocolitis in patients treated with anti CTLA-4 and/or anti PD-1

	Diarrhea	Colitis
Anti CTLA-4	30%	8%
Anti PD-1	13%	1%
Combotherapy		13.6%

✓Colonic perforation in 1% (melanoma) to 6% (renal cancer)

✓0.6 to 0.8% des patients die of GI Immune-related adverse events

Tandon J Immunoth 2018.
Wang DY Oncoimmunology 2017.
Khoja Ann Oncol.

Symptoms of enterocolitis

- Diarrhea and abdominal pain
- hematochezia and fever
- Severe acute colitis +/- dehydration, toxic megacolon, perforation and death, particularly in case of diagnosis delay

Symptoms of enterocolitis

- Diarrhea and abdominal pain

Differential diagnoses : infections, diverticulitis, intestinal metastases (particularly from NSCLC and melanoma).

case of diagnosis delay

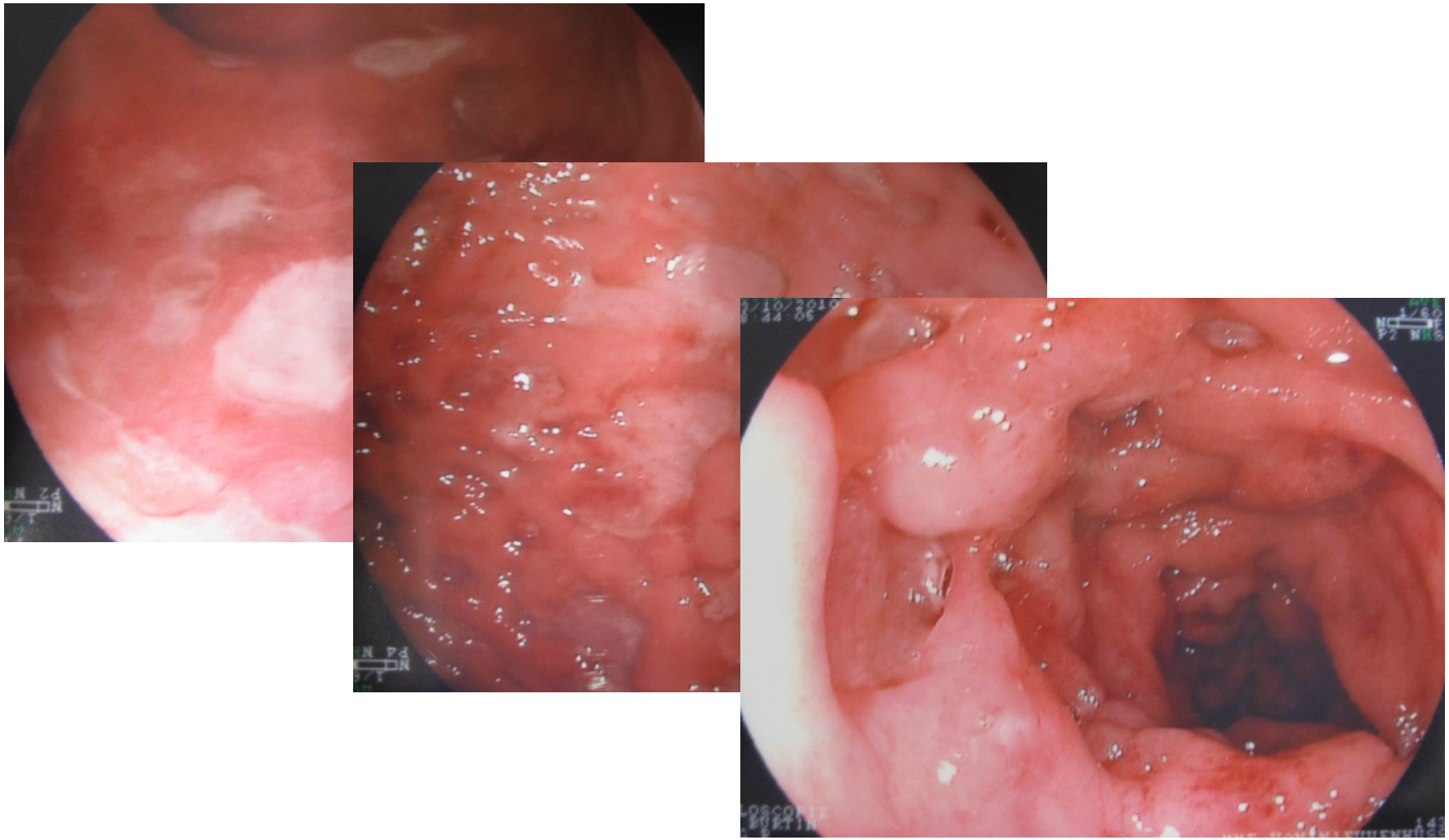
Blood and stool tests mandatory in patients with diarrhea under ICI

- Serum electrolytes and creatinine levels
- Complete blood count
- CRP
- Serum Albumin
- Interferon-g-release assay screening for tuberculosis, HBV and HIV serology (in patients with a severe form, who may need infliximab)
- Stool search for enteropathogens
- *Clostridioides difficile* toxin
- Fecal Calprotectine

Endoscopy of anti-CTLA-4-induced colitis

- Ulcerations

Journal of Crohn's and Colitis, 2016, 1–7



Endoscopy of anti-CTLA-4-induced colitis

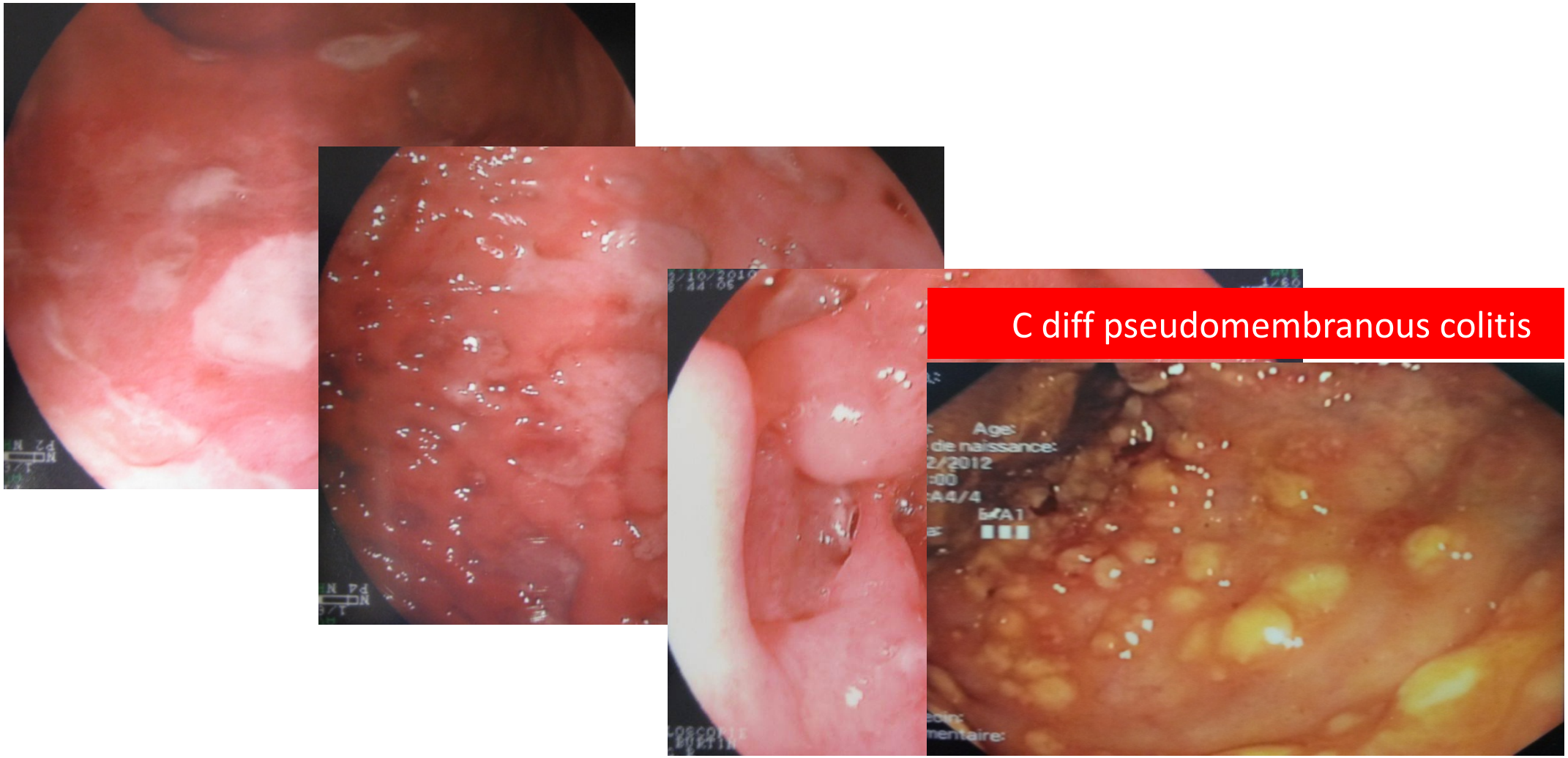
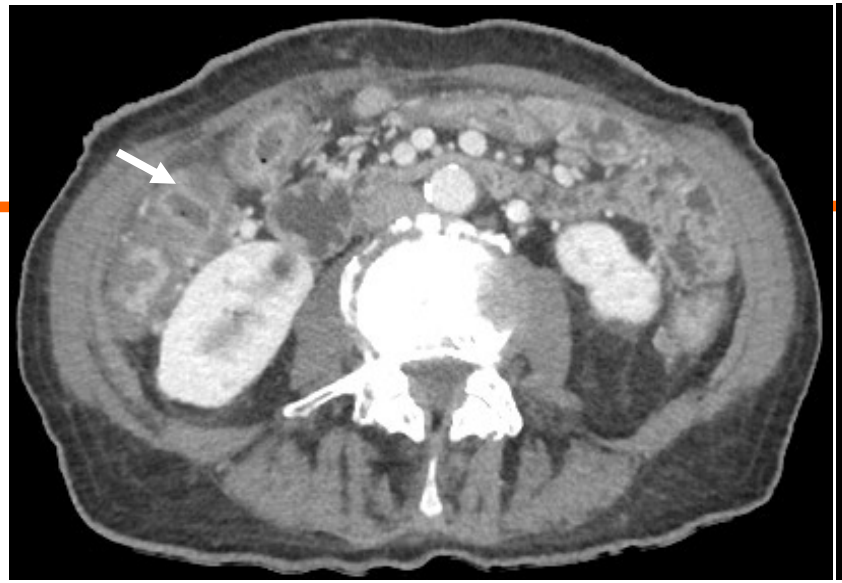
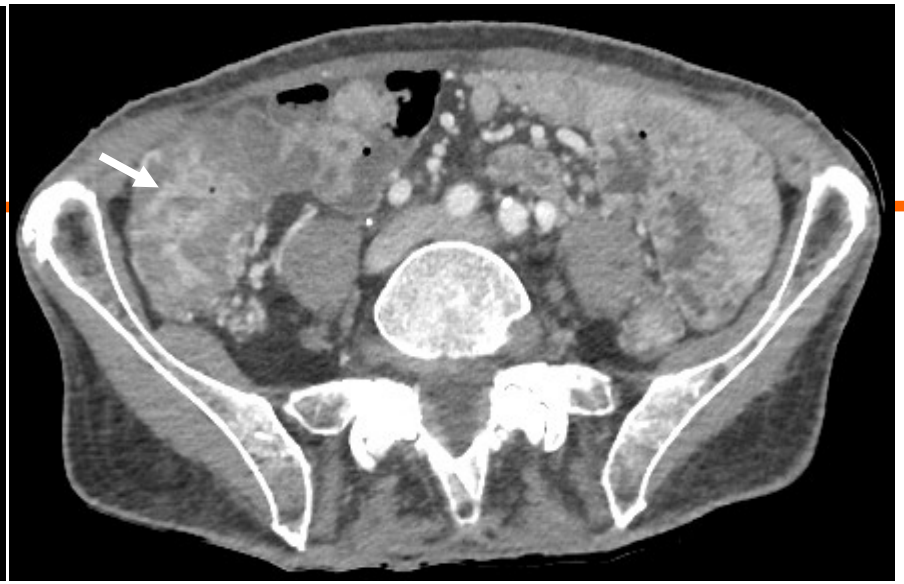


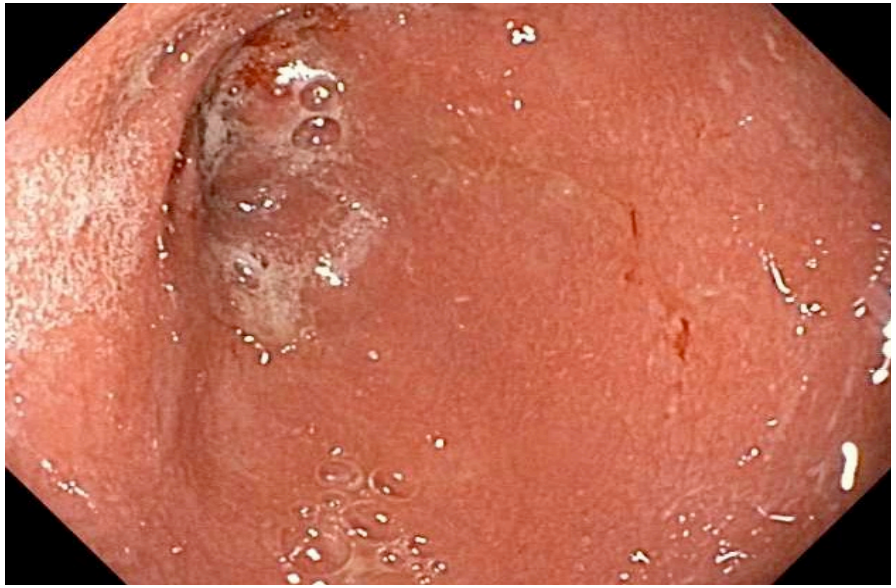
Table 3 Endoscopic features and association with symptoms and treatment management in 92 episodes of diarrhoea

Endoscopic features	Total No. (%)	Grade of diarrhoea* G2/G3 No. (%)	P value	Bloody stools no/yes No. (%)	P value	Need for infliximab no/yes No. (%)	P value
Endoscopic Mayo†							
0–1 (low)	60 (68)	21 (44)/27 (56)	0.84	47 (78)/13 (22)	<0.01	32 (53)/28 (47)	<0.01
2–3 (high)	28 (32)	12 (46)/14 (54)		13 (46)/15 (54)		6 (21)/22 (79)	
Total van der Heide score							
0–6 (low)	50 (54)	20 (49)/21 (51)	0.53	44 (88)/6 (12)	<0.01	29 (58)/21 (42)	<0.01
7–12 (high)	42 (46)	15 (42)/21 (58)		19 (45)/23 (55)		12 (29)/30 (71)	
Ulcers							
No	63 (69)	22 (44)/28 (56)	0.73	47 (75)/16 (25)	0.06	35 (56)/28 (44)	<0.01
Yes	29 (31)	13 (48)/14 (52)		16 (55)/13 (45)		6 (21)/23 (79)	
Pancolitis‡							
No	20 (32)	7 (50)/7 (50)	0.36	17 (85)/3 (15)	0.13	15 (75)/5 (25)	<0.01
Yes	42 (68)	14 (36)/25 (64)		28 (67)/14 (33)		10 (24)/32 (76)	

Geukes Foppen MH, *et al. ESMO Open* 2018;3:e000278. doi:10.1136/esmoopen-2017-000278

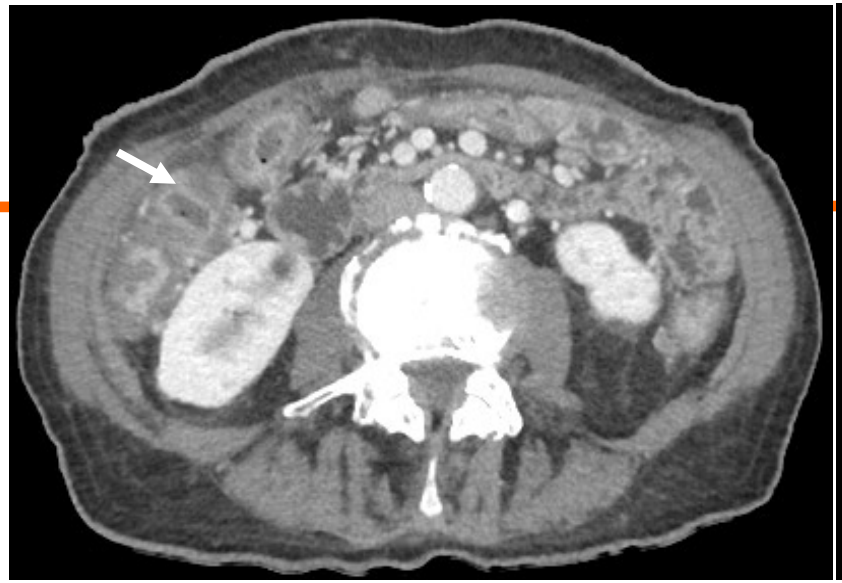


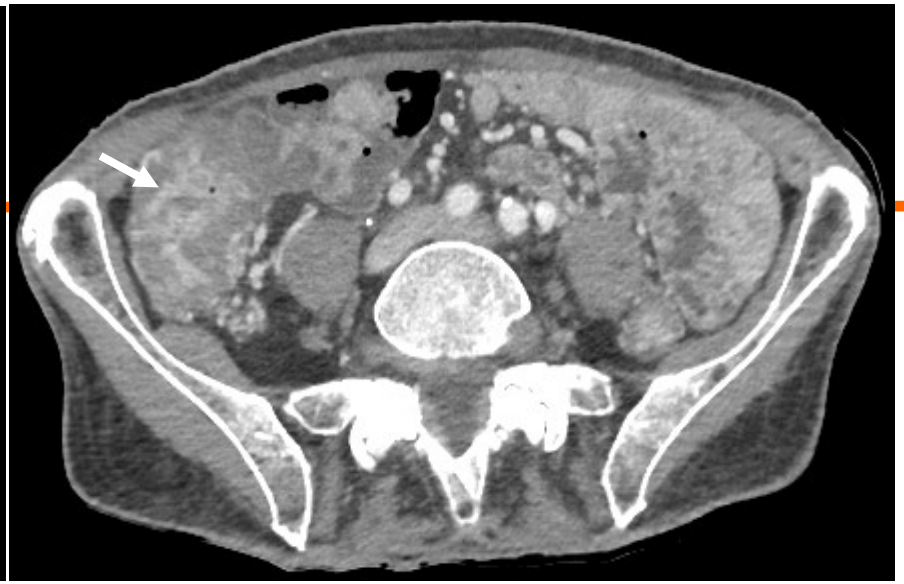




Abdominal tomodensitometry in a patient with anti-PD-1 induced colitis, showing thickening of the right colon wall (white arrow) and mucosal enhancement, as well as vessel engorgement.

Bottom anti-PD-1 induced colitis, with erythema, mild bleeding, loss of vascular pattern.





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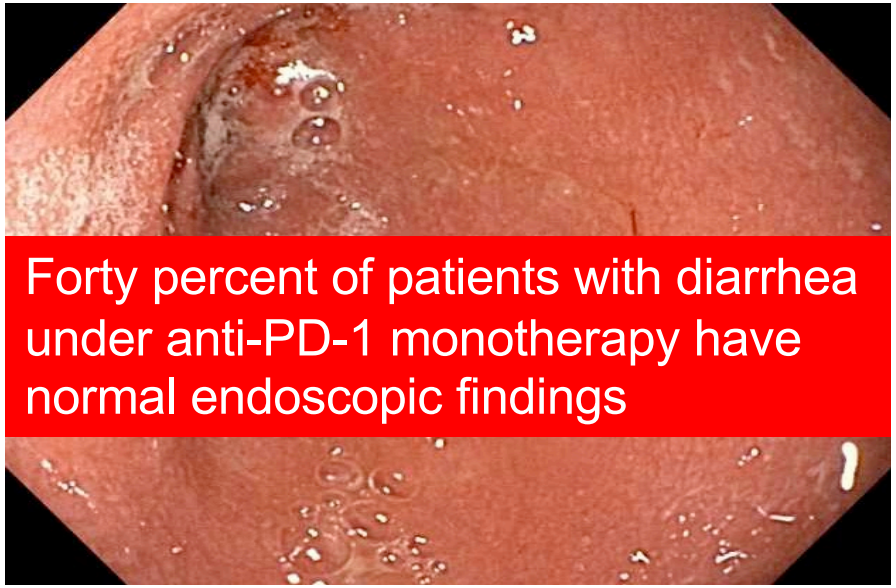


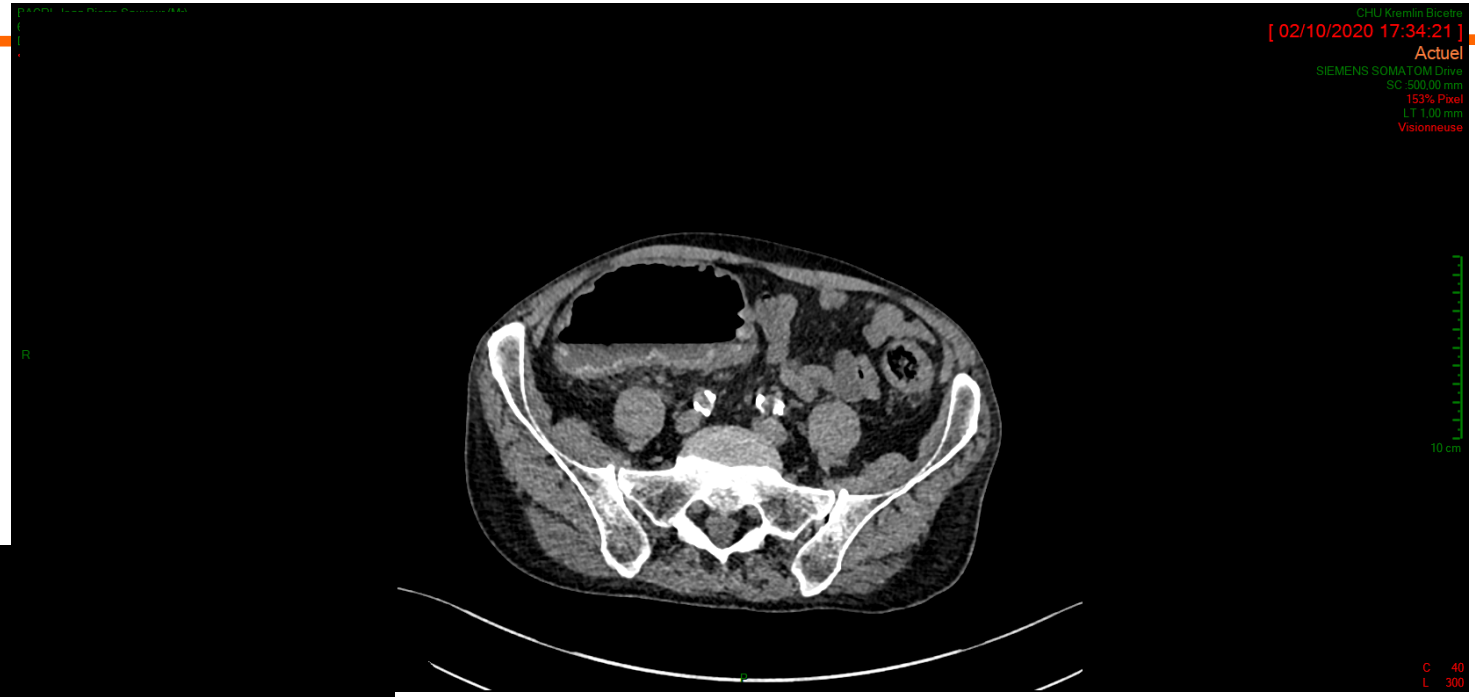
Forty percent of patients with diarrhea under anti-PD-1 monotherapy have normal endoscopic findings

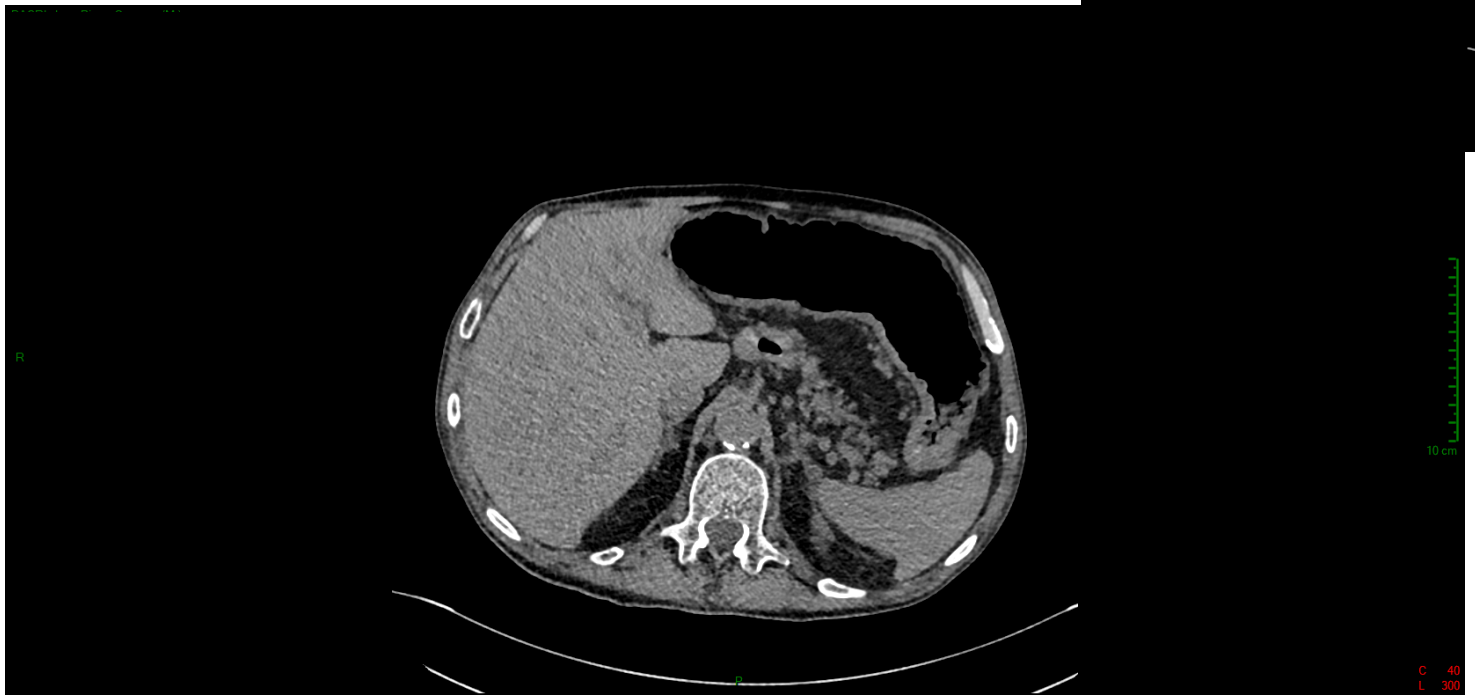
Imaging : abdominal CT scan

- Low sensitivity : not appropriate for diagnosis
- For severe colitis assessment : perforation, toxic megacolon and abscess
- Segmental or continuous thickening of bowel wall (SB or colon), mucosal contrast enhancement, comb sign

What is your diagnosis?

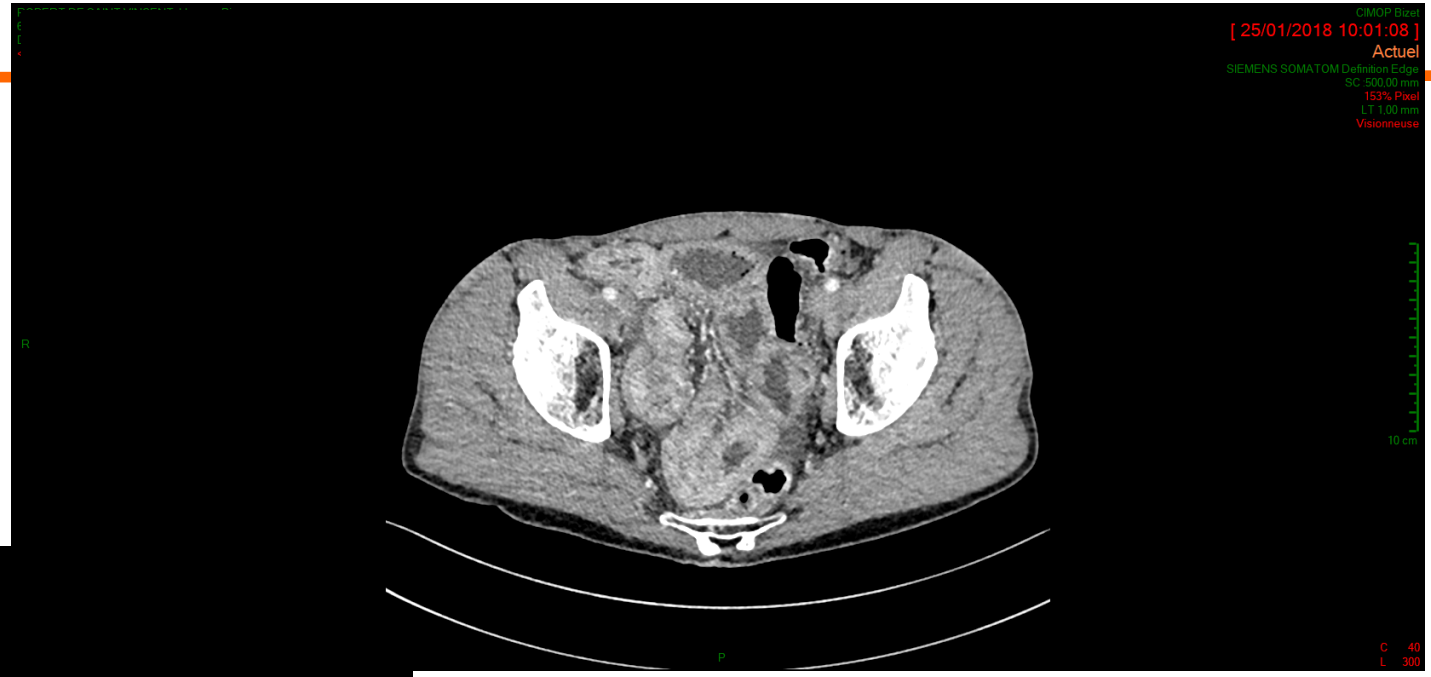
Man 70, bladder cancer, pembrolizumab, severe diarrhoea, corticosteroids for 1 month, no improvement

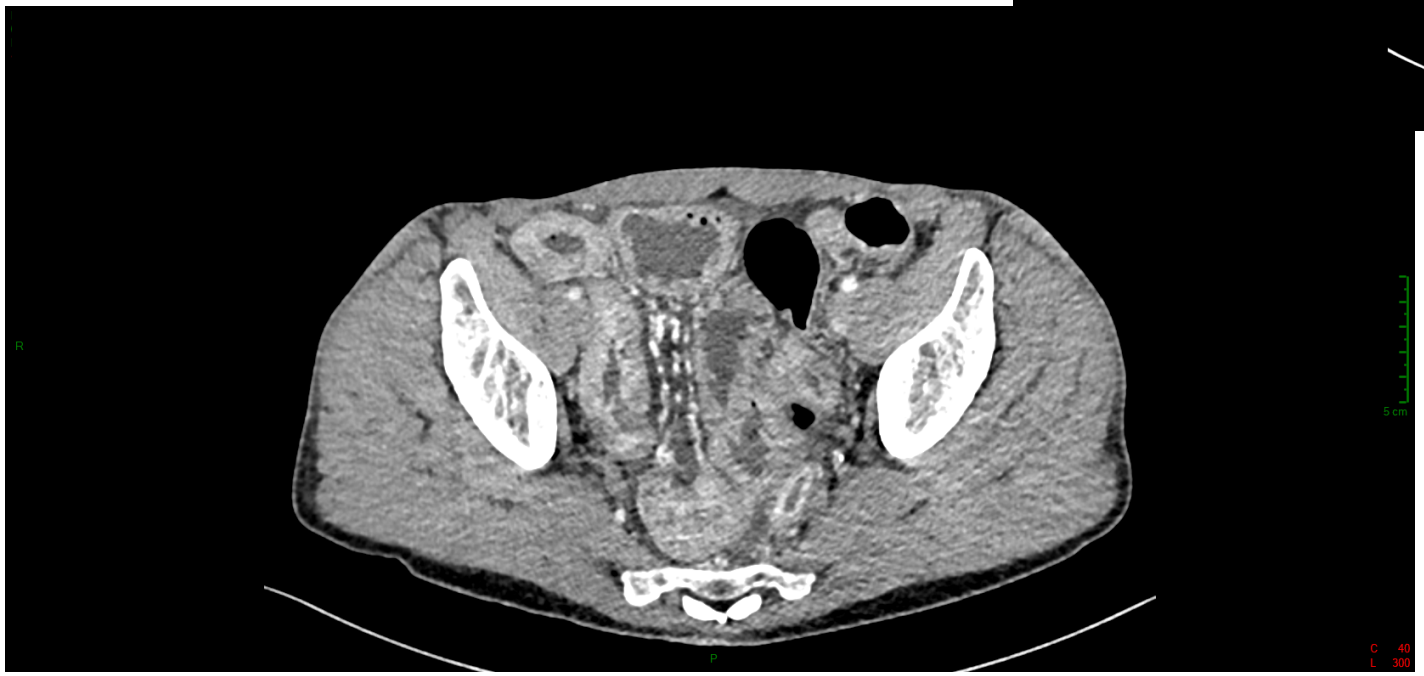




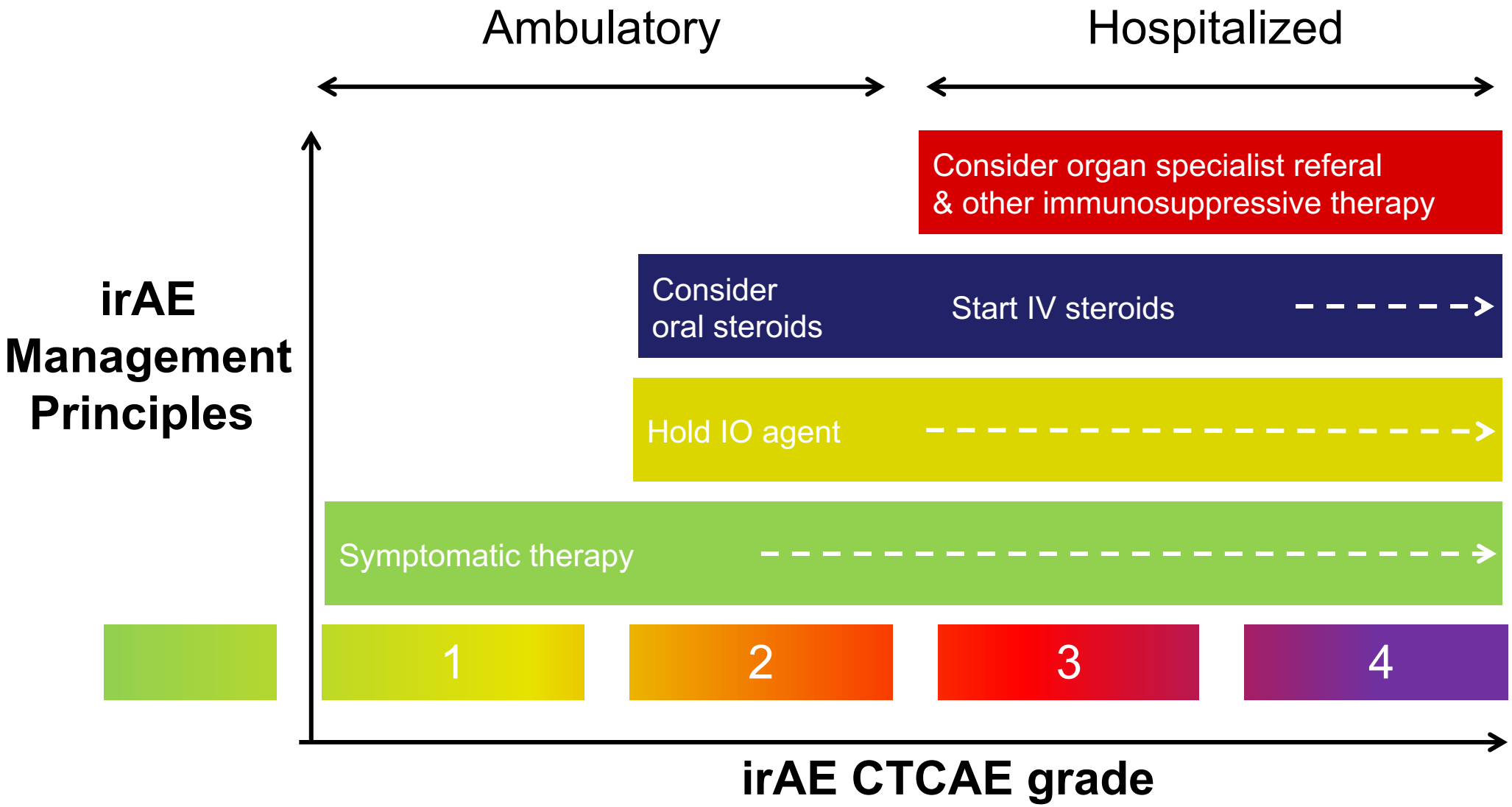
What is your diagnosis?

Man 60, NSCLC, durvalumab, abdominal pain, intestinal obstruction





General management strategies for irAEs



What is a severe diarrhea?

National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.

Gastrointestinal disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by frequent and watery bowel movements.					

Severe diarrhea = grade 3 or 4
grade 1 or 2 with dehydration, fever, tachycardia or hematochezia

Management of patients with non-severe diarrhea due to immune checkpoint inhibitors

- **Always**
- Loperamide
- Oral fluids
- Low fiber diet
- Continue immune checkpoint inhibitors
- Close follow-up

- **Persisting grade 1 diarrhea and intestinal inflammation (biopsies) or grade 2 diarrhea/colitis :**
  - Prednisolone 40 mg/d or budesonide 9 mg/d
  - Infliximab or rather, vedolizumab in refractory cases
  - Interruption of ICI. Can be resumed if needed

Management of a patient with a severe diarrhea due to ICI

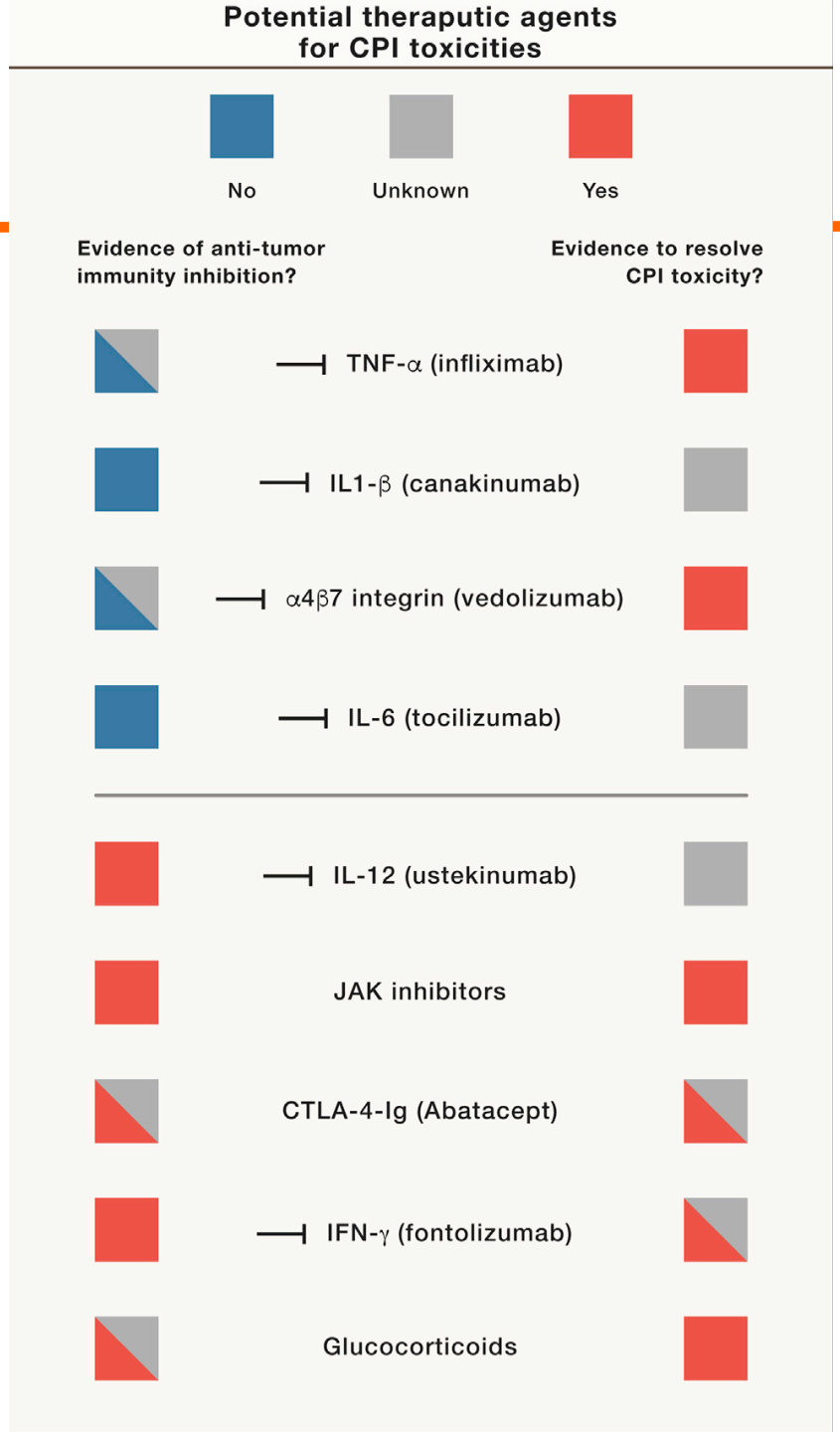
- Withdrawal of ICI
- Hospitalize
- IV steroids : 40-60 mg/d
- Close medical and surgical supervision
- D3 to D5 :
  - Responders: oral steroids with tapering over 4-8 weeks
  - Non responders:
    - Infliximab (5mg/kg à j1, j 14 et j 42) particularly if severe, extensive colitis, ulcerations and combination of anti CTLA-4 + anti PD1
    - Vedolizumab is an option (300 mg j1, d14 and d42). It is less rapidly active ; for moderate colitis

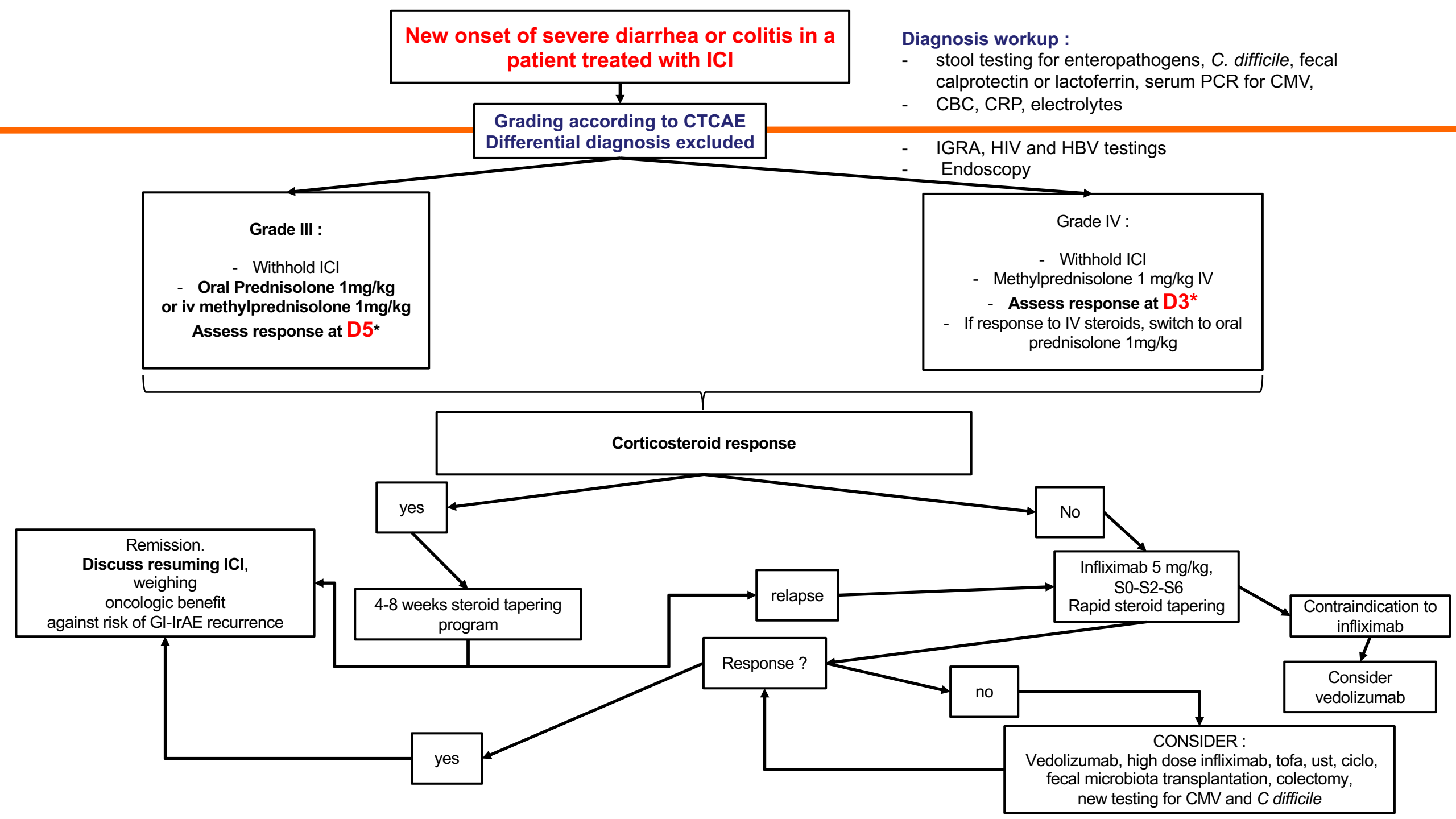
H. Abu-Sbeih, J Immunother Cancer, 6 (2018), 95; T.Z. Horvat, J Clin Oncol, 33 (2015), pp. 3193-3198; Nahar KJ, J Immunother Cancer 2020;8:e001488.; H. Abu-Sbeih, J Immunother Cancer, 6 (2018), p. 142

Management of a patient with a severe diarrhea due to ICI

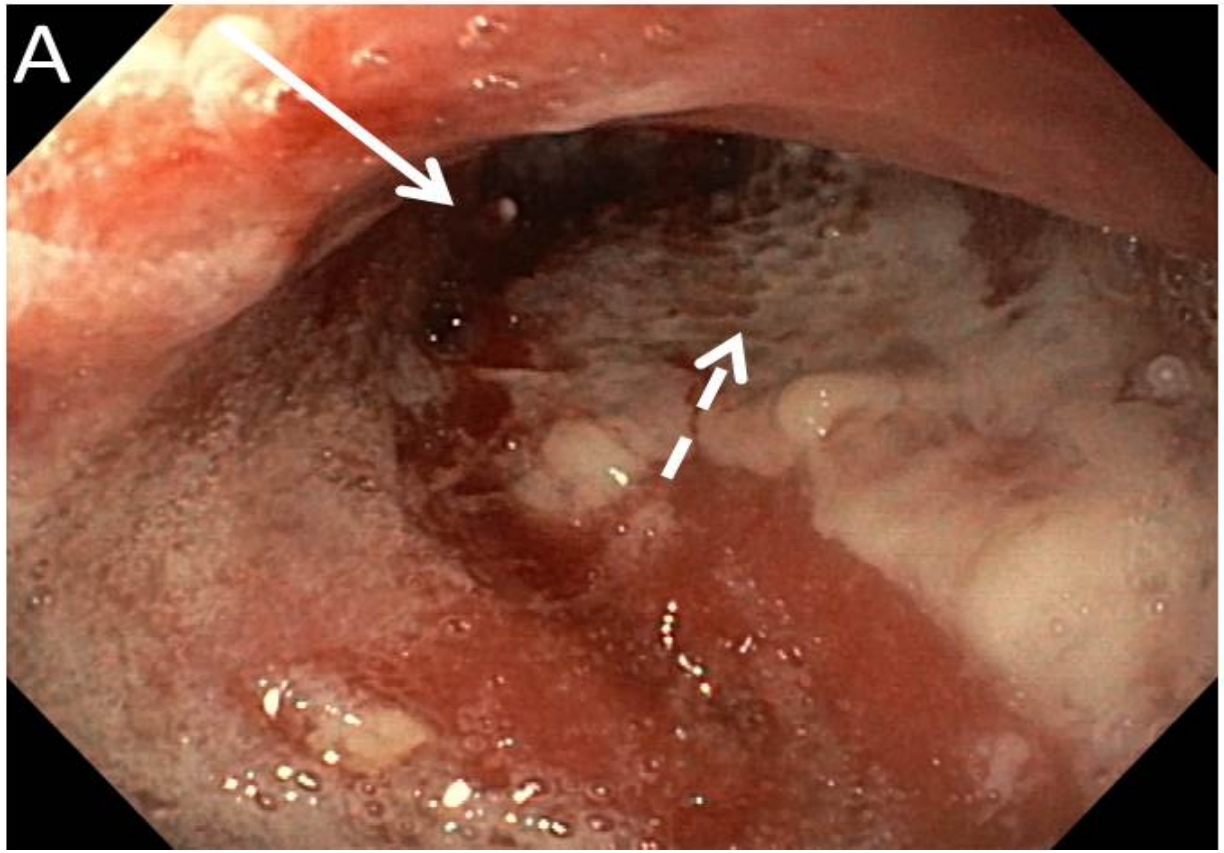
- 47% of patients respond to corticosteroids
- 41% need and respond to infliximab
- 11% of patients are infliximab-refractory ; case reports or small case series of successful fecal microbiota transplantation, ustekinumab, tofacitinib, calcineurin inhibitors and mycophenolate mofetil
- Surgery should be considered in patients with toxic megacolon and intra-abdominal abscesses; mandatory for intestinal perforation

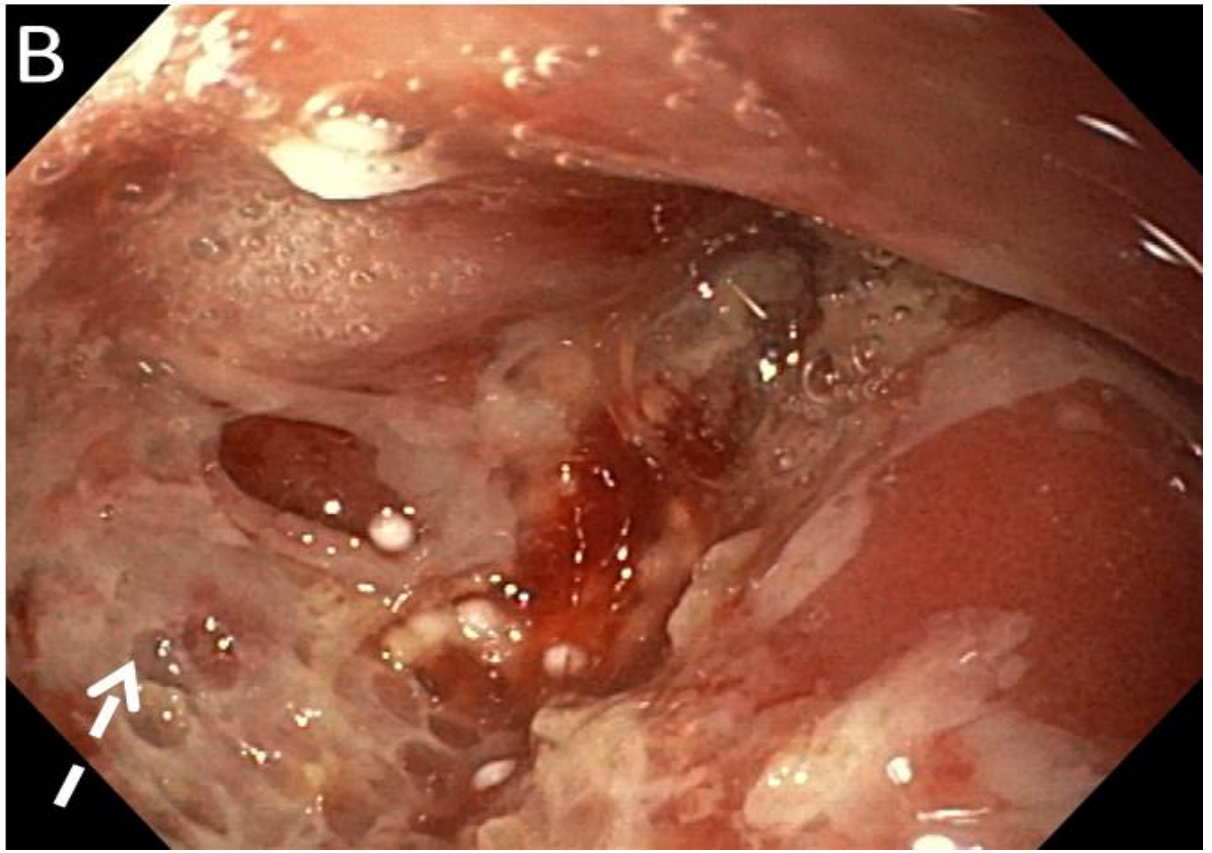
T.Z. Horvat, J Clin Oncol, 33 (2015), pp. 3193-3198


Potential theraputic agents
for CPI toxicities
No
Unknown
Yes
Evidence of anti-tumor immunity inhibition?
Evidence to resolve CPI toxicity?
TNF-α (infliximab)
IL1-β (canakinumab)
α4β7 integrin (vedolizumab)
IL-6 (tocilizumab)
IL-12 (ustekinumab)
JAK inhibitors
CTLA-4-Ig (Abatacept)
IFN-γ (fontolizumab)
Glucocorticoids


New onset of severe diarrhea or colitis in a patient treated with ICI
Diagnosis workup :
- stool testing for enteropathogens, C. difficile, fecal calprotectin or lactoferrin, serum PCR for CMV,
- CBC, CRP, electrolytes
Grading according to CTCAE
Differential diagnosis excluded
- IGRA, HIV and HBV testings
- Endoscopy
Grade III :
- Withhold ICI
- Oral Prednisolone 1mg/kg or iv methylprednisolone 1mg/kg
Assess response at D5*
Grade IV :
- Withhold ICI
- Methylprednisolone 1 mg/kg IV
- Assess response at D3*
- If response to IV steroids, switch to oral prednisolone 1mg/kg
Corticosteroid response
yes
No
Remission.
Discuss resuming ICI, weighing oncologic benefit against risk of GI-IrAE recurrence
4-8 weeks steroid tapering program
relapse
Infliximab 5 mg/kg, S0-S2-S6
Rapid steroid tapering
Contraindication to infliximab
Consider vedolizumab
Response ?
no
yes
CONSIDER :
Vedolizumab, high dose infliximab, tofa, ust, ciclo, fecal microbiota transplantation, colectomy, new testing for CMV and C difficile

Severe gastritis under anti PD-1





Inflammatory gastrointestinal diseases associated with PD-1 blockade antibodies

M. Collins[1,2†], J. M. Michot[3†], F. X. Danlos[3], C. Mussini[2,4], E. Soularue[1,2], C. Mateus[5], D. Loirat[6], A. Buisson[7], I. Rosa[8], O. Lambotte[2,9,10,11], S. Laghouati[12], N. Chaput[2,13], C. Coutzac[2,13], A. L. Voisin[12], J. C. Soria[3], A. Marabelle[3], S. Champiat[3], C. Robert[5] & F. Carbonnel[1,2*]

Annals of Oncology 0: 1–6, 2017
doi:10.1093/annonc/mdx403
Published online 3 October 2017

What is your diagnosis?

- Woman, 53 year-old, renal cancer since 2010
- …
- Janvier 2021 Axitinib and PEMBROLIZUMAB
- Juin 2021 : epigastric pain, nausea, vomiting. Metoclopramide and Omeprazole inefficient
- FOGD : erythema of the gastric body
- Histologie: acute superficial gastritis focal metaplasia

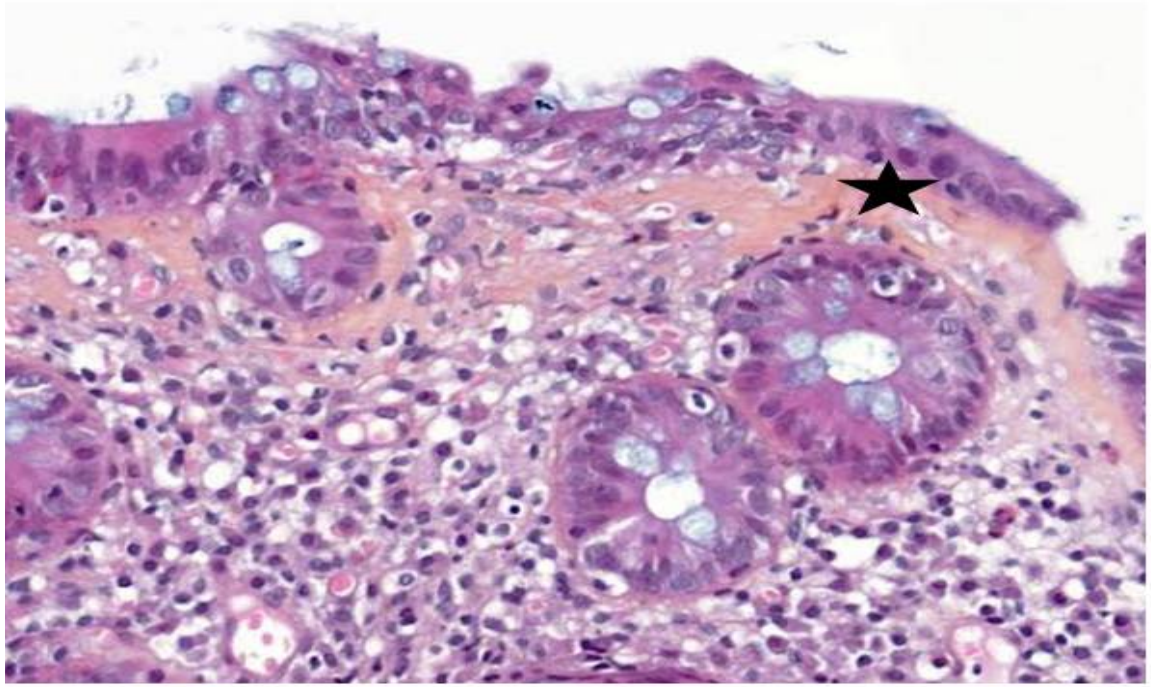
What is your diagnosis ?

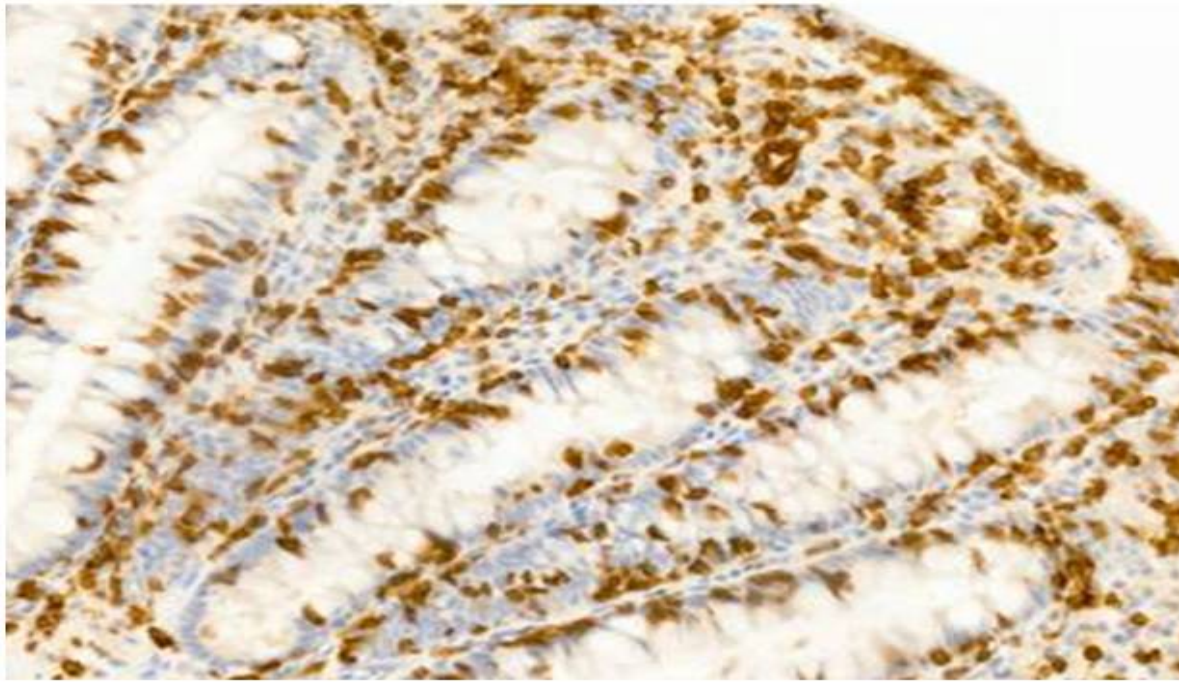
- Fasting cortisol serum level 8 AM < 10 µg/L the 28th and 30th August 2021.

  very low ACTH

- Diagnosis: Hypophysitis due to Pembrolizumab

Microscopic colitis under anti PD-1





Collagenous colitis

Lymphocytic colitis

Annals of Oncology 0: 1–6, 2017
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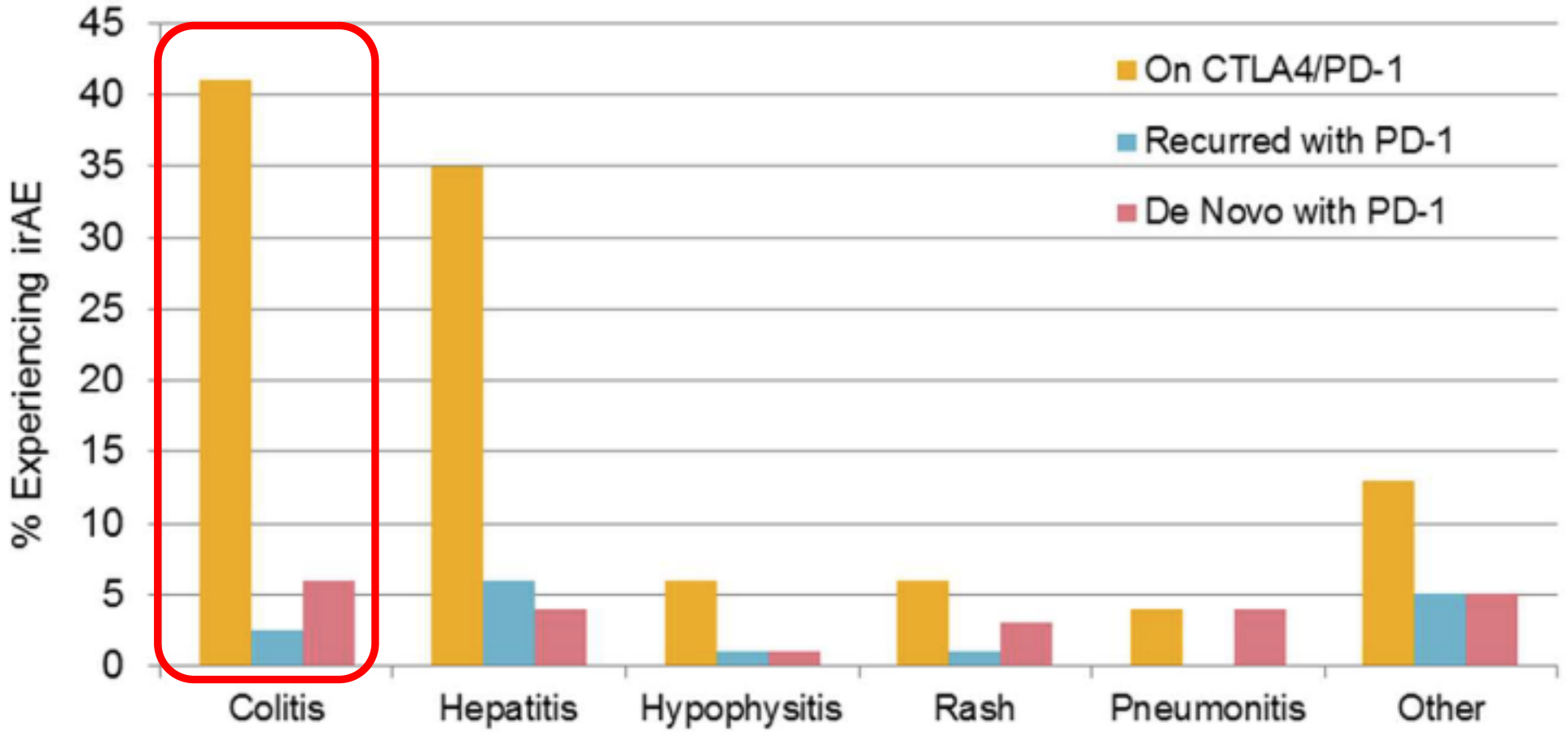
Other presentations

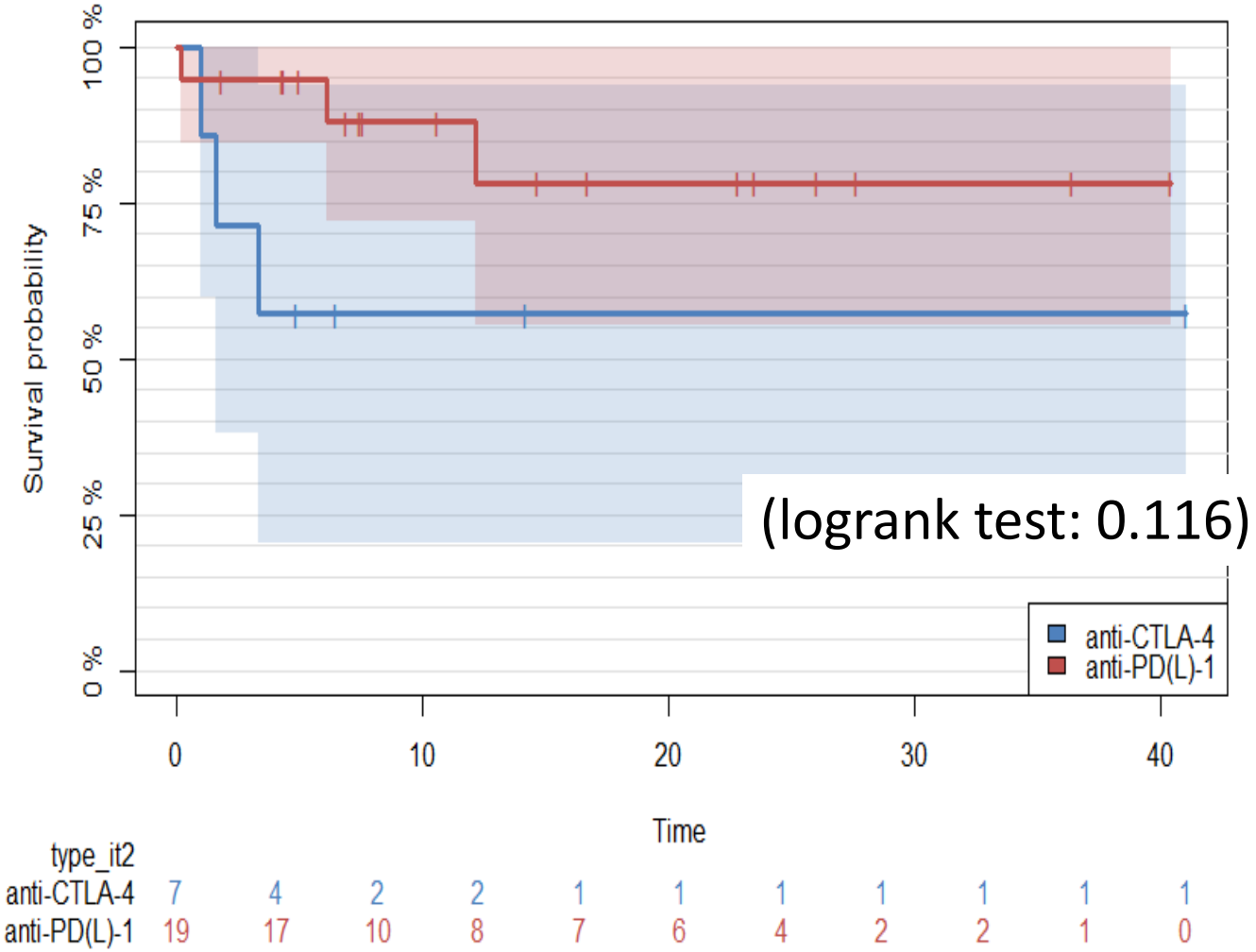
- Fissuring or fistulizing anal lesions similar with those observed in Crohn's disease have been reported. Two case reports have described enteric neuropathy induced by ipilimumab and revealed by severe constipation

IS IT SAFE TO RESUME IMMUNE CHECKPOINT INHIBITORS IN PATIENTS WHO HAD A GI IRAE ?

Risk of IrAE after resumption of anti PD-1 in patients who had an IrAE under combotherapy *(Pollack, Ann Oncol 2017)*



Risk of GI irAE after resuming an immune checkpoint inhibitor in patients who had a GI IrAE with a first ICI *(De Malet A, Eur J Cancer 2018)*



Risk of recurrent GI irAE after ICI resumption

- The risk of recurrence of GI IrAE after ICI resumption is 34%, with 5% grade 3 or 4 diarrhea, and 20% grade 2 or more colitis
- Risk factors for GI-irAE are the use of anti-CTLA-4 second line, the requirement for immunosuppressive therapy and long symptom duration for the first episode and first line use of anti-PD-1 before the initial ICI enterocolitis
- The decision to reintroduce ICI after initial GI irAE should be made on a case-by-case basis, and discussed within a multidisciplinary team
- Concurrent use of non-steroid immunosuppressant e.g. infliximab and vedolizumab could be considered to minimize the risk of recurrence at the time of resuming ICI

A. de Malet, Eur J Cancer, 106 (2019), pp. 106-114; Abu-Sbeih H, J Clin Oncol 2019; 37:2738-2745

Merci

TAKE-HOME MESSAGES

1. Main differential diagnoses of GI IRAE are infection and metastasis of the intestines (NSCLC, melanoma) or peritoneum

2. Management of severe colitis is based upon IV steroids, infliximab for non responders, and close medical and surgical supervision