ImmunoScience Academy

Partnering for Education & Optimizing Treatment in ImmunoScience

Gastrointestinal Immune-Mediated Adverse Reactions

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Bristol Myers Squibb™

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Any organ system can be affected by inflammation[1–5]

Neurologic

- Neuropathy
- Myelopathy
- Guillain-Barré syndrome
- Myasthenia gravis-like syndrome
- Encephalitis
- Meningitis

Signs and symptoms, such as:
- Sensory alterations
- Headache
- Confusion
- Muscle weakness
- Numbness

Ocular

- Conjunctivitis
- Uveitis, retinitis, iritis
- Scleritis, episcleritis
- Blepharitis

Endocrine

- Hypo or hyperthyroidism
- Hypophysitis, hypopituitarism
- Adrenal insufficiency
- Type 1 diabetes

Signs and symptoms, such as:
- Fatigue
- Headache
- Mental status changes
- Abdominal pain
- Hypotension
- Abnormal thyroid function tests and/or serum chemistries
- Dehydration
- Hyponatremia

Cardiac

- Myocarditis
- Pericarditis
- Vasculitis

Signs and symptoms, such as:
- Non-specific symptoms[a] (eg, fatigue, muscle pain)

Dermatologic

- Dermatitis
- Psoriasis
- Vitiligo
- Toxic epidermal necrolysis
- Stevens-Johnson syndrome
- Oral candidiasis
- Maculopapular rash

Signs and symptoms, such as:
- Pruritus
- Rash
- Burning
- Tightness
- Generalized exfoliative dermatitis
- Full-thickness dermal ulceration
- Skin necrosis

Pulmonary

- Pneumonitis
- Pleuritis
- Interstitial lung disease

Signs and symptoms, such as:
- Radiographic changes
- Shortness of breath
- Chest pain
- New cough
- Fever

Infusion reactions

Signs and symptoms, such as:
- Chills or shaking
- Itching or rash
- Difficulty breathing

Musculoskeletal

- Arthralgia, arthritis
- Myalgia, myositis

Signs and symptoms, such as:
- Joint pain, swelling, erythema
- Muscle discomfort
- Muscle weakness

Hepatic

- Hepatitis

Signs and symptoms, such as:
- Abnormal liver function tests (eg, AST, ALT) or total bilirubin

Renal

- Nephritis

Signs and symptoms, such as:
- Gradually rising creatinine
- Hematuria
- Ankle edema

Gastrointestinal

- Colitis
- Ileitis
- Pancreatitis
- Gastritis
- Gastrointestinal perforation
- Esophagitis

Signs and symptoms, such as:
- Diarrhea, bowel perforation
- Abdominal pain
- Blood or mucus in stool
- Peritoneal signs
- Ileus
- Fever

IMARs can be severe or life-threatening if not identified early[6]

ALT, alanine aminotransferase; AST, aspartate aminotransferase; IMAR, immune-mediated adverse reaction. 1. Naidoo J et al. *J Clin Oncol* 2016;35:709–717.2. Naidoo J et al. *Ann Oncol* 2015;26:2375–2391. 3. Villadolid J et al. *Transl Lung Cancer Res* 2015;4:560–575. 4. Weber JS et al. *Oncologist* 2016;21:1230–1240. 5. Champiat S et al. *Ann Oncol* 2016;27:559–574. 6. Daniels GA et al. *Emerg Med J* 2019;36:369–377.

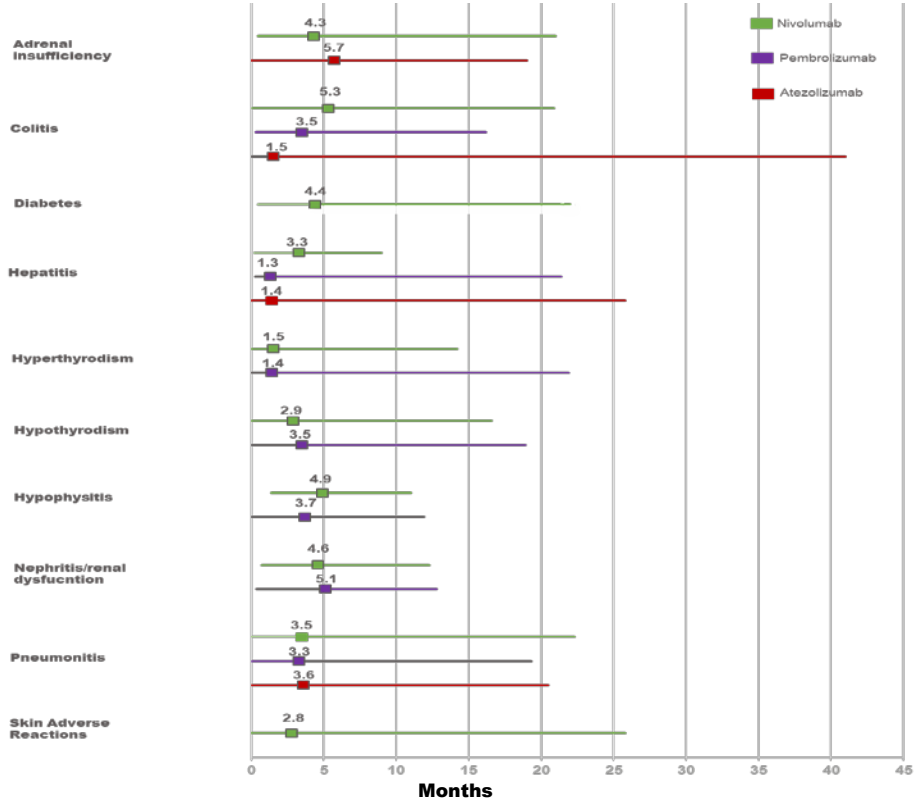
Signs and symptoms of gastrointestinal IMARs

- Signs and symptoms of gastrointestinal adverse reactions may include[1–4] :
  - Colitis
  - Enteritis
    - Diarrhea
    - Stools with blood or mucus
    - Abdominal pain
      - Cramps
      - in severe cases: signs of peritonitis
    - Nausea & anorexia & weight loss
    - Fever

IMAR, immune-Pract Res Clin mediated adverse reaction. 1. Naidoo J et al. *Ann Oncol* 2015;26:2375–2391. 2. Villadolid J et al. *Transl Lung Cancer Res* 2015;4:560–575. 3. Weber JS et al. *Oncologist* 2016;21:1230–1240. 4.Cheung VTF, Brain O. Best Gastroenterol. 2020 Oct-Dec;48-49:101703. doi: 10.1016/j.bpg.2020.101703. Epub 2020 Oct 23

Kinetics of appearance of IMARs

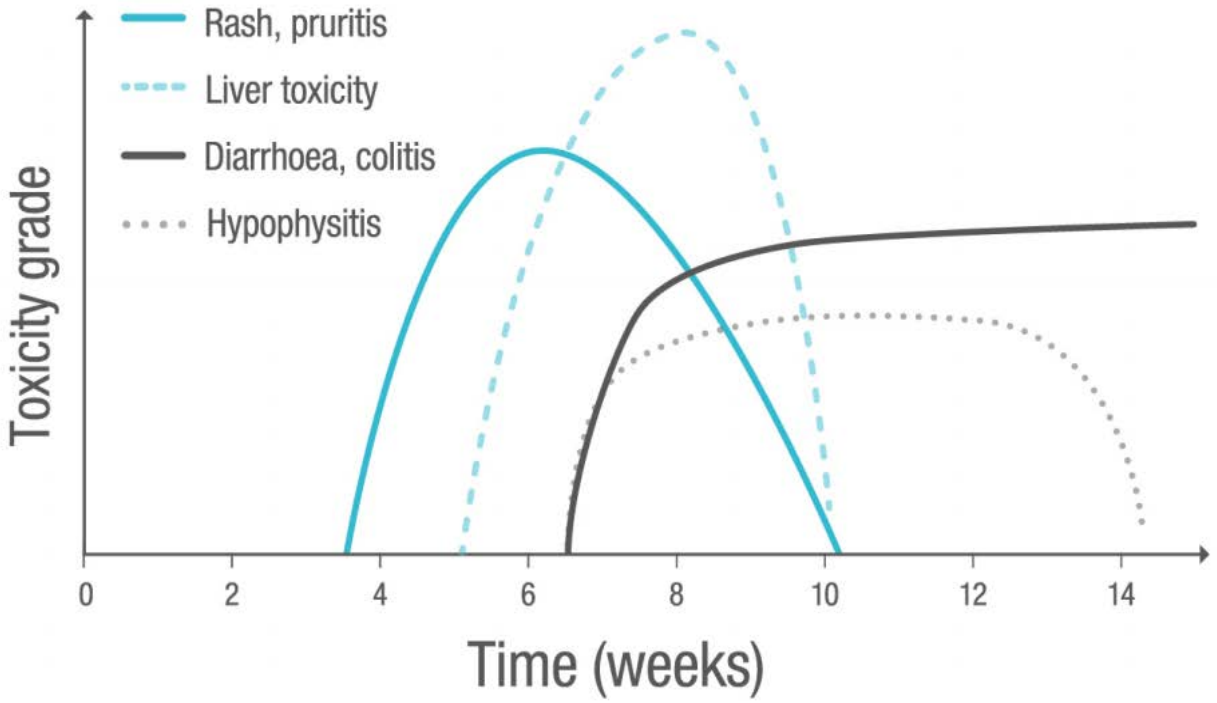
Median (range) IMAR symptom onset (months) following PD-1/PD-L1 inhibitor treatment across FDA-approved tumour types.



	Colitis	Hepatitis
Nivolumab	5.3 months (2 days to 20.9 months)	3.3 months (6 days to 9 months)
Pembrolizumab	3.5 months (10 days to 16.2 months)	1.3 months (8 days to 21.4 months)
Atezolizumab	1.5 months (1 day to 41 months)	1.4 months (1 day to 25.8 months)

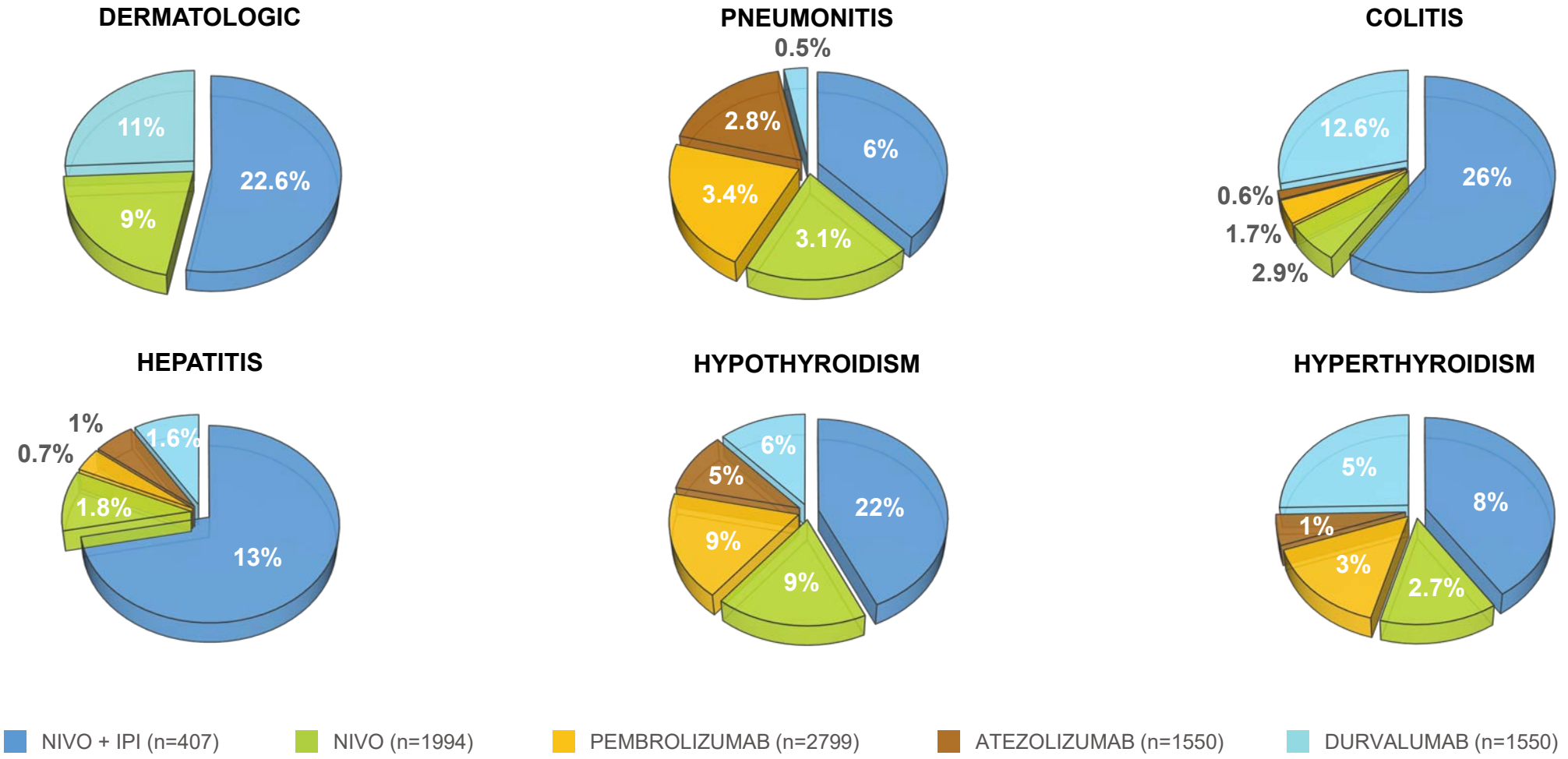
Adapted from Daniels GA, et al. Emerg Med J 2019;**36**:369–377

Timing of IMAR occurrence by toxicity grade following ipilimumab inhibitor treatment in melanoma



Adapted from Haanen JBAG et al. Ann Oncol 2017;28(suppl 4):iv119–iv142

Frequency of any-grade IMARs following ICI treatment



Adapted from Daniels GA, et al. Emerg Med J 2019;36:369–377.

Common Terminology Criteria for adverse events (CTCAE): grading of diarrhea and colitis

Common Terminology Criteria for adverse events (CTCAE) Version 5 (2017): grading of diarrhoea and colitis[ab]

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Diarrhea • A disorder characterized by an increase in frequency and/or loose or watery bowel movement	• Increase of < 4 stools per day over baseline • Mild increase in ostomy output compared with baseline	• Increase of 4–6 stools per day over baseline • Moderate increase in ostomy output compared with baseline • Limiting instrumental ADL	• Increase of ≥ 7 stools per day over baseline • Incontinence • Hospitalization indicated • Severe increase in ostomy output compared with baseline • Limited self-care ADL	• Life-threatening consequences • Urgent intervention indicated	Death
Colitis • A disorder characterized by inflammation of the colon	• Asymptomatic • Clinical or diagnostic observations only • Intervention not indicated	• Abdominal pain • Mucus or blood in stool	• Severe abdominal pain • Peritoneal signs	• Life-threatening consequences • Urgent intervention indicated	Death

ADL: activities of daily living;
a There is also a CTCAE definition of enterocolitis (inflammation of small and large intestines), which is very similar to colitis, except grade 3 enterocolitis includes severe or persistent abdominal pain, fever, ileus and peritoneal signs.
b CTCAE Version 4.0 published in 2009, is what most immunotherapy clinical trials have used. The main difference is that in version 4.0 and 4.03, definition of grade 3 colitis also included change in bowel habits and medical intervention indicated.

Cheung VTF, Brain O. Best Pract Res Clin Gastroenterol. 2020 Oct-Dec;48-49:101703. doi: 10.1016/j.bpg.2020.101703. Epub 2020 Oct 23

Endoscopic and histological features of ICP inhibitors enterocolitis

	Anti-CTLA-induced enterocolitis	Anti-PD-1/PD-L1-induced enterocolitis
Endoscopic features	Extensive (66-68%) Continuous (45-79%) Ileitis (20%)	Extensive (33%) Continuous (25%) Ileitis (11%) Normal (15-40%)
Histological features	Acute colitis with mixed inflammatory cell infiltrate in lamina propria; neutrophilic cryptitis; crypt abscesses; glandular destruction; erosions ofmucosal surface; ulceration;diffuse inflammation (75%); no basalplasmacytosis; no crypt architectural distortion; possible granulomas (7%): possible skip lesion	Acute active colitis with neutrophilic infiltrate and cryptitis; Lamina propria expansion; Increased apoptosis; Crypt dropout OR microscopic colitis (1/3 of patients); Lymphocytic colitis (>20 intra-epithelial lymphocytes per 100 surface epithelial cells) or collagenous colitis (thickened subepithelial collagen layer of>10mm)

Cheung VTF, Brain O. Best Pract Res Clin Gastroenterol. 2020 Oct-Dec;48-49:101703. doi: 10.1016/j.bpg.2020.101703. Epub 2020 Oct 23

Endoscopic and histological images of ICP inhibitors enterocolitis

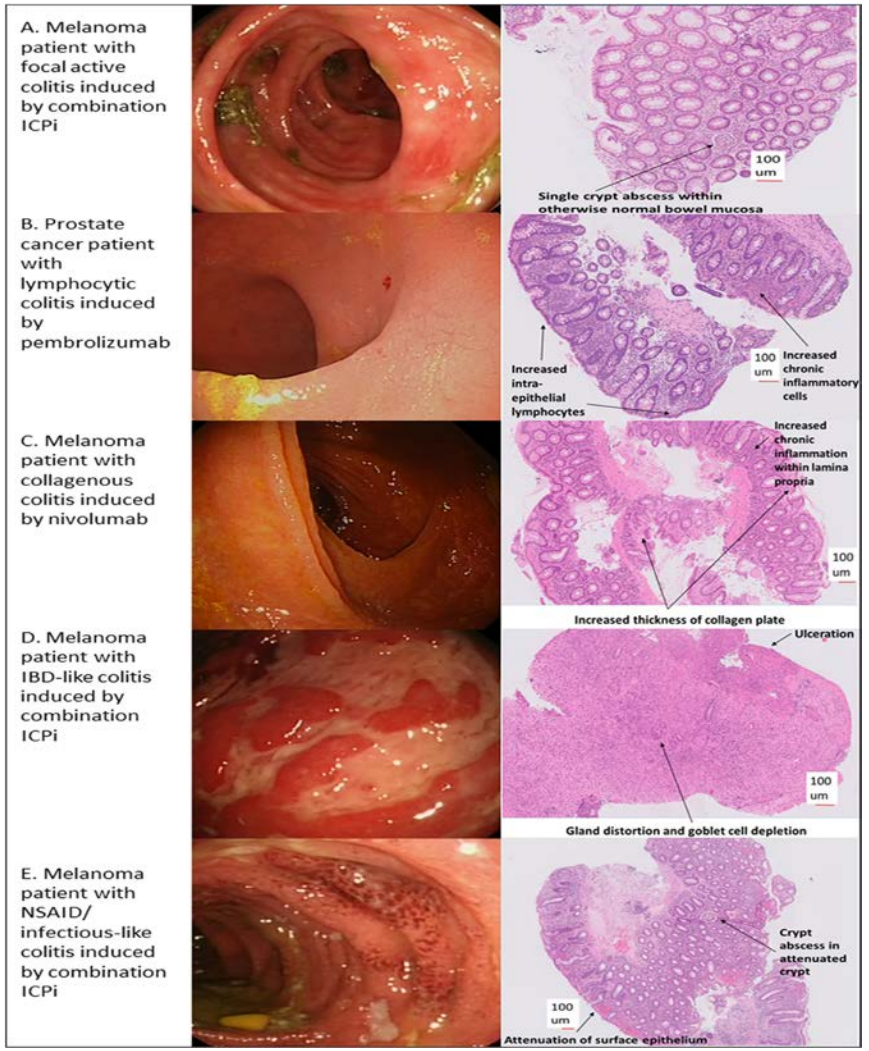
Focal active colitis: occasional foci of acute inflammation, in the absence of chronic inflammation or significant crypt injury

Lymphocytic colitis: increase in intraepithelial and lamina propria lymphocytes, in the abcence of crypty architectural distortion

Collagenous colitis: increase in thickness of the subepithelial collagen plate and increased lamina propria lymphocytes, in the absence of crypt architectural distortion

IBD-like: active chronic inflammation with goblet cell depletion and crypt architectural distortion

Non-steroidal anti-inflammatory drug (NSAID)/infectious like predominantly acute, superficial inflammation with attenuation of crypt and/or surface epithelium



red line indicates 100 µm

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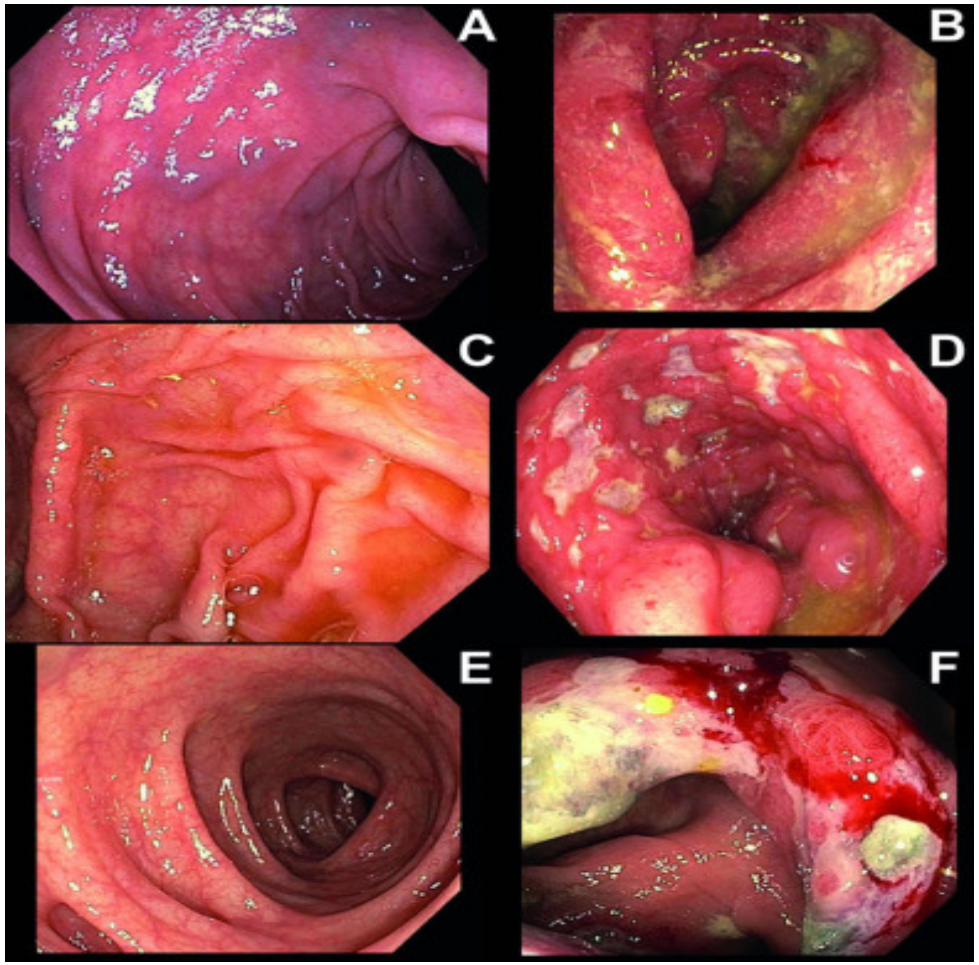
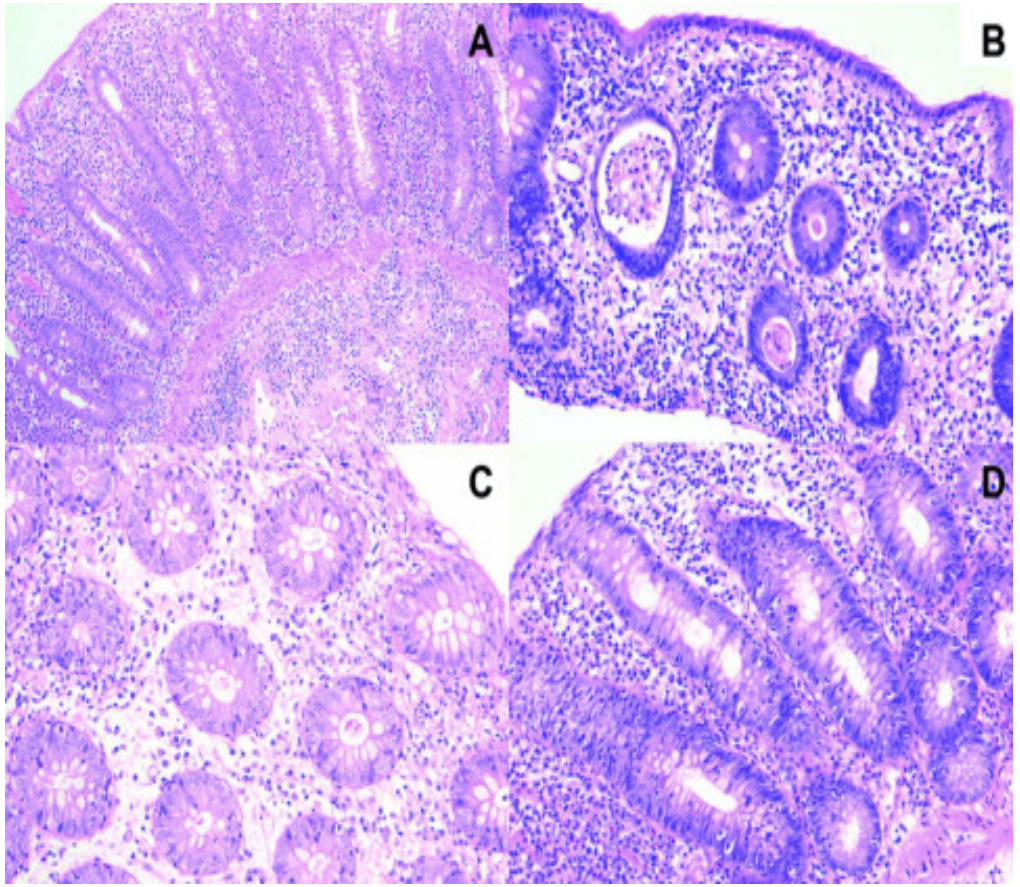
Immune-Checkpoint related colitis

Examples of differences in immune checkpoint inhibition-related colitis



Representative hematoxylin-eosin stained (HE) sections demonstrating immune checkpoint inhibition-related colitis

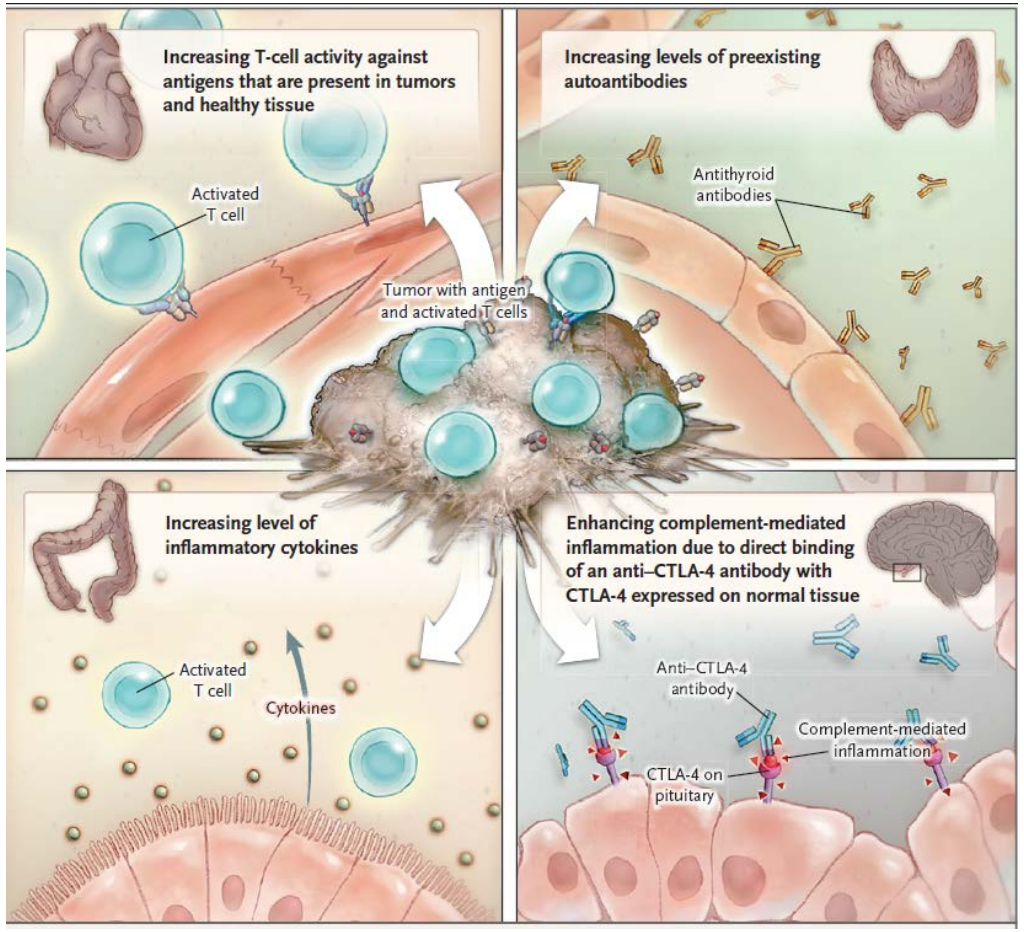


Geukes Foppen MH, et al. ESMO Open 2018;3:e000278. doi:10.1136/esmoopen-2017-000278

Potential mechanisms underlying checkpoint inhibitor–related IMARs[1,2]

T-cells reacting to antigens in healthy tissue
- Myocarditis
- Vitiligo

Cytokine-mediated
- Colitis
- Arthritis
- Skin – psoriasis, eczema



Reproduced with permission from Postow MA, et al.[1]

Antibody-mediated
- Thyroiditis
- Hemolytic anemia
- Skin - bullous pemphigoid
- Neurologic - myasthenia gravis, transverse myelitis, autoimmune encephalitis

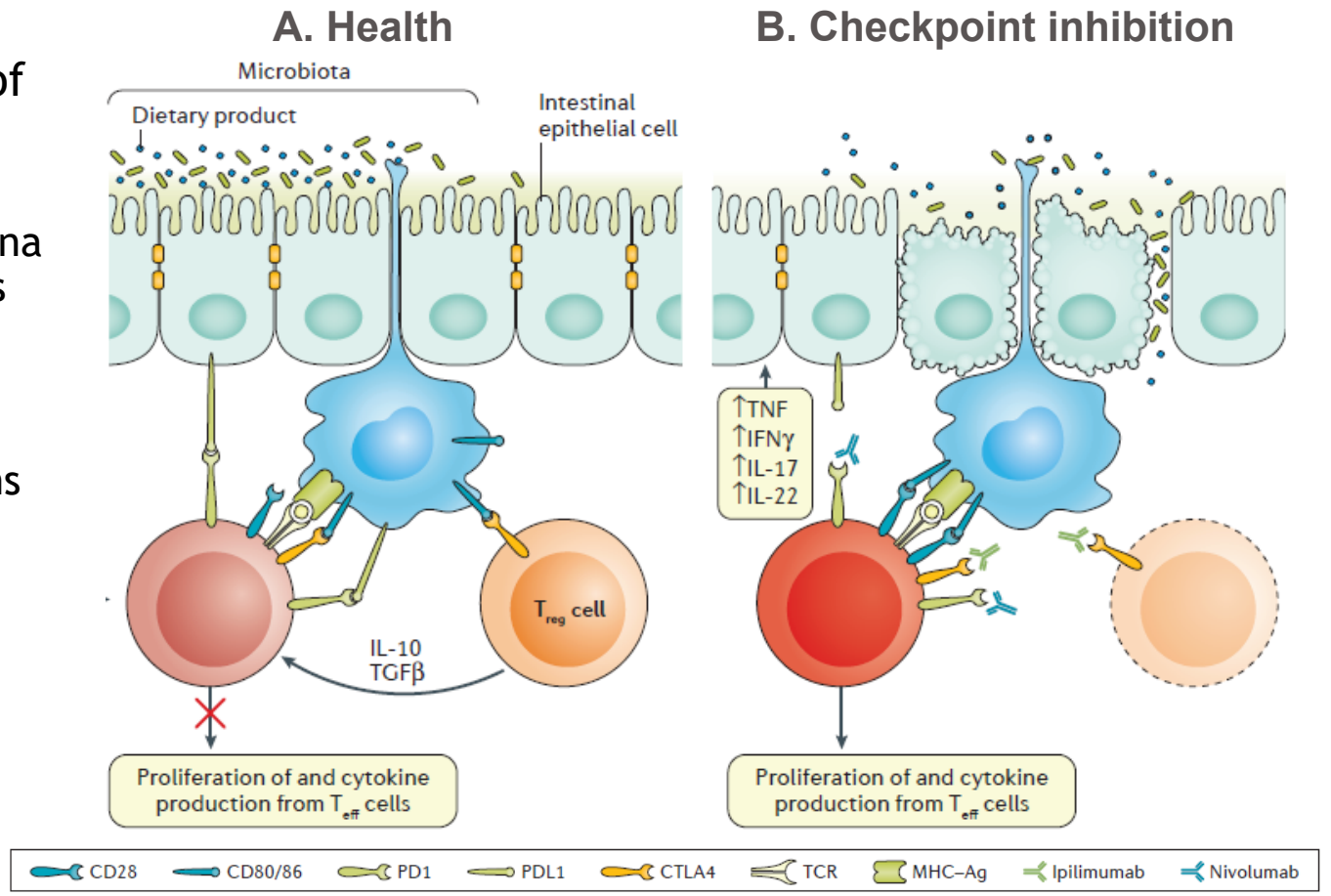
Expression of target (ex. CTLA-4) in normal tissue
- Pituitary toxicity - hypophysitis

IMARs result from increased or excessive immune activity, but the immunomodulatory cause may vary

ADCC, antibody-dependent cellular cytotoxicity; CTLA-4, cytotoxic T lymphocyte antigen 4; IMAR, immune-mediated adverse reaction.1. Postow MA et al. N Engl J Med 2018;378:158–168. 2. Esfahani K et al. Nat Rev Clin Oncol 2020;17:504–515.

Potential mechanisms of GI IMARs

- Under healthy conditions, the intestinal mucosa has been described to be in a state of equilibrium involving "physiological inflammation"[1,2] (see diagram A)[3]:
  - Commensal microorganisms that activate lamina propria DCs and macrophages to induce T cells through the production of interleukins
  - Microbiota-induced T_{reg} cells that attenuate intestinal damage caused by exaggerated immune responses against infectious pathogens
- CPI-associated immune enterocolitis may be due to loss of tolerance (see diagram B)[1]:
  - Hyperactivation of T_{eff} cells targeting luminal antigens (microbiota and dietary products)
  - Loss of functional T_{reg} cells



Reproduced with permission from *Nat Rev Gastroenterol Hepatol.*[1]

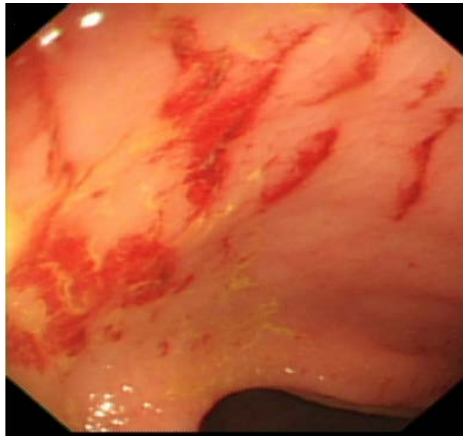
CD, cluster of differentiation; CPI, checkpoint inhibitor; CTLA-4, cytotoxic T lymphocyte antigen 4; DC, dendritic cell; IFN, interferon; IL, interleukin; GI, gastrointestinal; IMAR, immune-mediated adverse reaction; MHC, major histocompatibility complex; PD-1, programmed death-1; PD-L1, programmed death ligand 1; TCR, T-cell receptor; T_{eff}, effector T cells; TGF, transforming growth factor; TNF, tumor necrosis factor; T_{reg}, regulatory T cells. 1. Samaan MA et al. Nat Rev Gastroenterol Hepatol 2018;15:222–234. 2. Clemente JC et al. Cell 2012;148:1258–1270. 3. Kamada N et al. Nat Rev Immunol 2013;13:321–335.

Diarrhea and colitis: pathophysiology (1 of 2)

- Microscopic colitis is a chronic inflammatory disease of the colon
- Symptoms include chronic, non-bloody, watery diarrhea
- The diagnosis depends on characteristic histological findings
- Patients with microscopic colitis often have:
  - Bile acid malabsorption
  - Autoimmune conditions, including celiac disease
- The following factors are linked to increased risk:
  - Certain drug use: NSAIDs, proton-pump inhibitors, selective serotonin reuptake inhibitors
  - Smoking tobacco

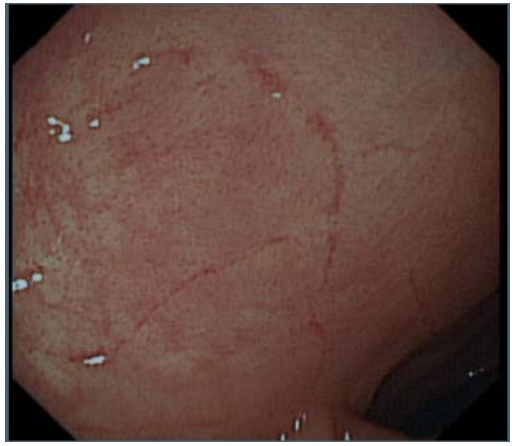
Endoscopic presentations of microscopic colitis[1]

A



A: Cat-scratch colon: haemorrhagic linear mucosal breaks/tears[1]

B

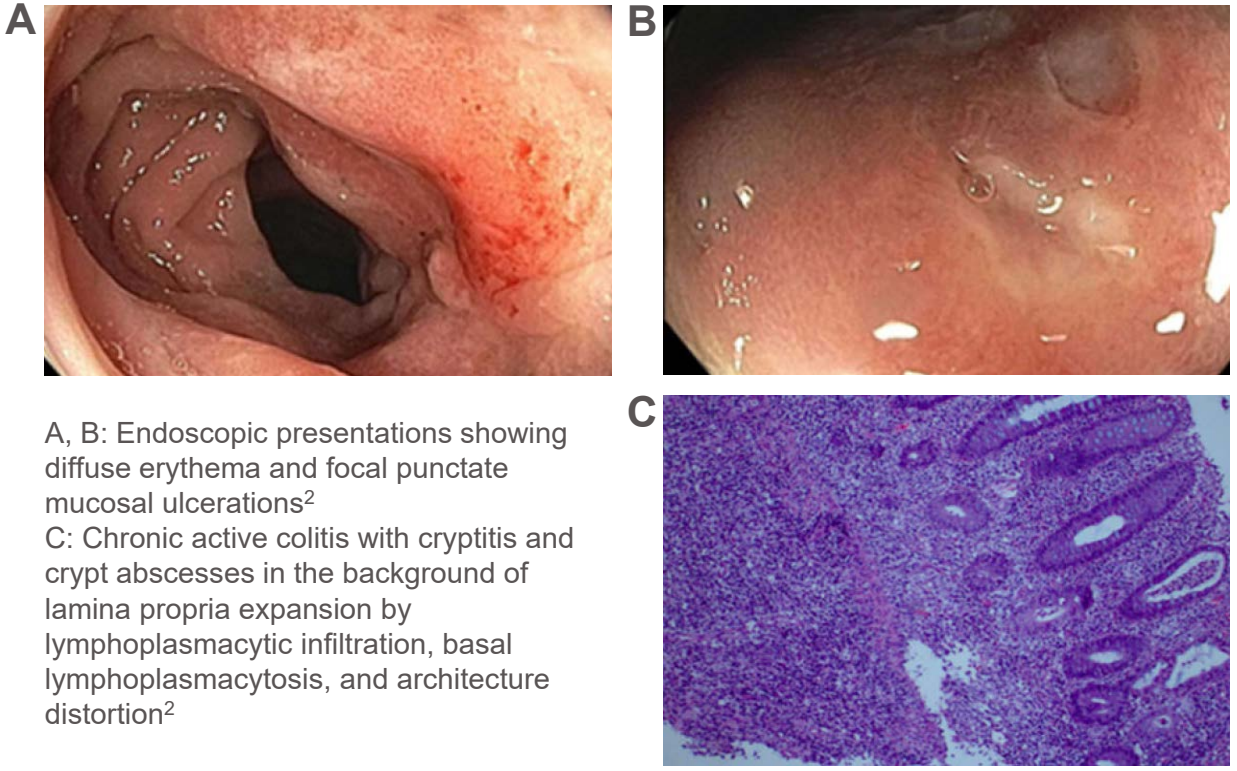


B: Cicatricial lesion: fine linear scar-like lesions, possibly the healed remnants of previous cat-scratch type lesions[1]

NSAID, nonsteroidal anti-inflammatory drugs; 1. Townsend T et al. Frontline Gastroenterol 2019;10:388–393

Diarrhea and colitis: pathophysiology (2 of 2)

- Under healthy conditions, the intestinal mucosa is in a state of “physiological inflammation”[1]
  - The main driver of ICI-associated enterocolitis is thought to be loss of immune tolerance
- Phenotypic variability and differences in severity suggest that other factors impact patient pathophysiological manifestations[1]
  - PK/PD
  - Intestinal dysbiosis
  - Smoking, diet, lifestyle
- To date, there are no predictive biomarkers for GI IMARs[1]
  - Patients with a markedly elevated fecal calprotectin level (> 250 µg/g) should go for prompt endoscopic evaluation and GI consultation
- Preliminary studies are exploring the role of gut microbiota in the pathophysiology of ICI-associated enterocolitis[1]



A, B: Endoscopic presentations showing diffuse erythema and focal punctate mucosal ulcerations[2]
C: Chronic active colitis with cryptitis and crypt abscesses in the background of lamina propria expansion by lymphoplasmacytic infiltration, basal lymphoplasmacytosis, and architecture distortion[2]

Reproduced with permission from *J Immunother Cancer.*[2]

GI, gastrointestinal; ICI, immune checkpoint inhibitor; IMAR, immune-mediated adverse reaction; PK/PD; pharmacokinetic/pharmacodynamic. 1. Samaan MA et al. Nat Rev Gastroenterol Hepatol 2018;15:222–234. 2. Abu-Sbeih H et al. J Immunother Cancer 2018;6:142.

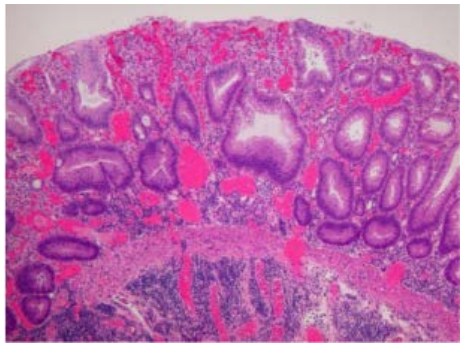
Importance of biopsy to detect microscopic colitis associated with GI IMARs

- ICI-related microscopic colitis has been found to require more aggressive treatment and result in increased morbidity and mortality in comparison to non-ICI-related microscopic colitis, highlighting the importance of this diagnosis[1]

Flexible sigmoidoscopy findings in patients discontinued due to GI IMARs[2,a]

	Had CS, %	Median CS duration, days	On CS at 3 months, %	Received anti-TNF, %	Duodenitis on gastroscopy, %
Macroscopy abnormality (± micro)	35/38 (92)	64	14/38 (37)	13/38 (34)	6/23 (26)
Microscopic abnormality only (ie, no macro change)	10/12 (83)	74	4/12 (33)	1/12 (8)	2/8 (25)
Normal FS	9/9 (100)	47	2/9 (22)	2/9 (22)	2/6 (33)
Unknown FS findings	5/6 (83)	n/a	n/a	1/6 (17)	n/a

Microscopic severe active colitis[3]



Expansion of lamina propria lymphoplasma cells, cryptitis, crypt destruction/dropout, and crypt architecture alteration

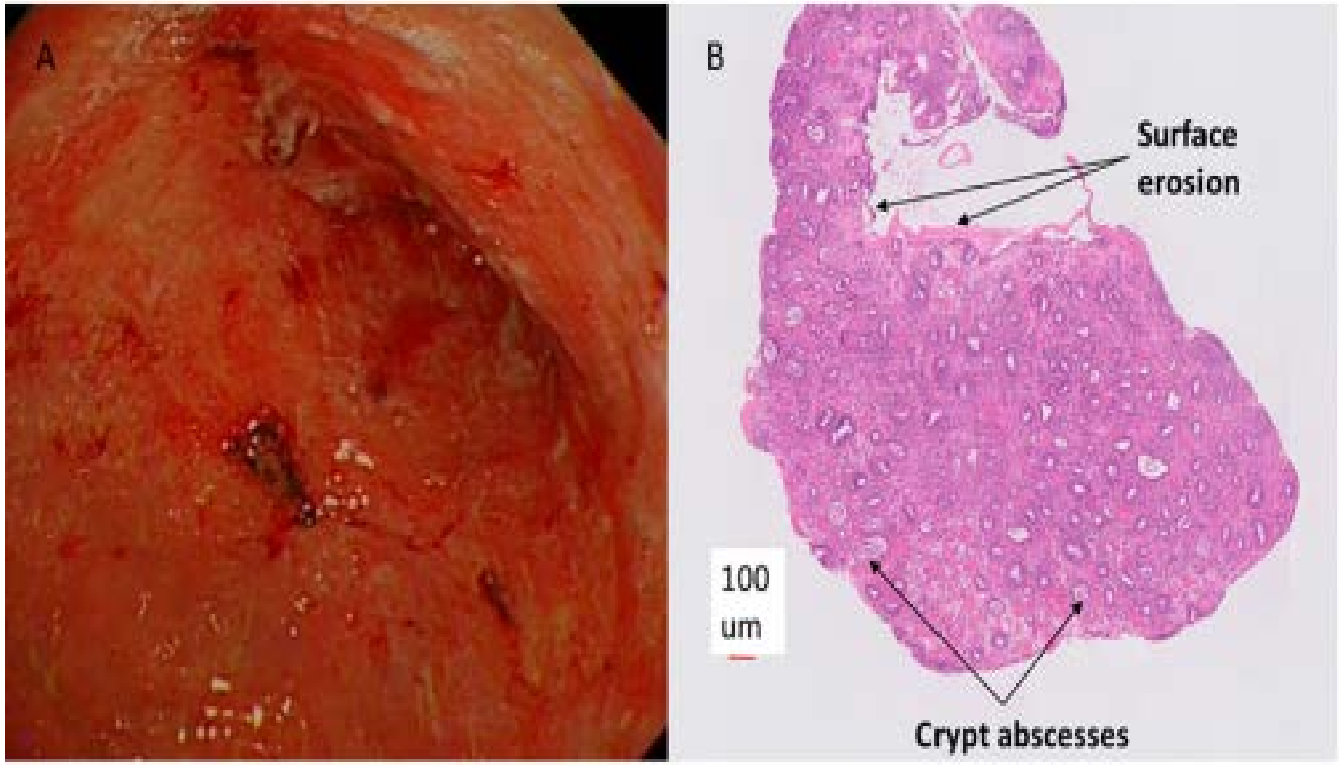
Reproduced with permission from *Ther Adv Gastroenterol*.[3]

- Four categories of GI IMARs are recognized: acute colitis, microscopic colitis, upper gastrointestinal tract inflammation, and pseudo-obstruction[2]
- 18% of patients had microscopic colitis, but this could be an underestimate[2]
  - Some patients did not have a biopsy following a "normal" macroscopic flexible sigmoidoscopy
  - Assessment of endoscopic changes alone, without biopsy, may miss this important subgroup of microscopic colitis

[a]Investigation of ir-D/C with flexible endoscopy was undertaken in 65/117 (56%) ir-D/C episodes. CS, corticosteroid; FS, flexible sigmoidoscopy; GI, gastrointestinal; ICI, immune checkpoint inhibitor; IMAR, immune-mediated adverse reaction; IPI, ipilimumab; ir-D/C, immune-related diarrhea/colitis; NIVO, nivolumab; PD-1, programmed death-1. 1. Choi K et al. Inflamm Bowel Dis 2019;25:385–393. 2. Favara DM, et al. ESMO Open 2020;5:e000585. 3. Shivaji UN et al. Ther Adv Gastroenterol 2019;12:1–15.

Immune checkpoint inhibitors induced gastritis

Endoscopic and histological features

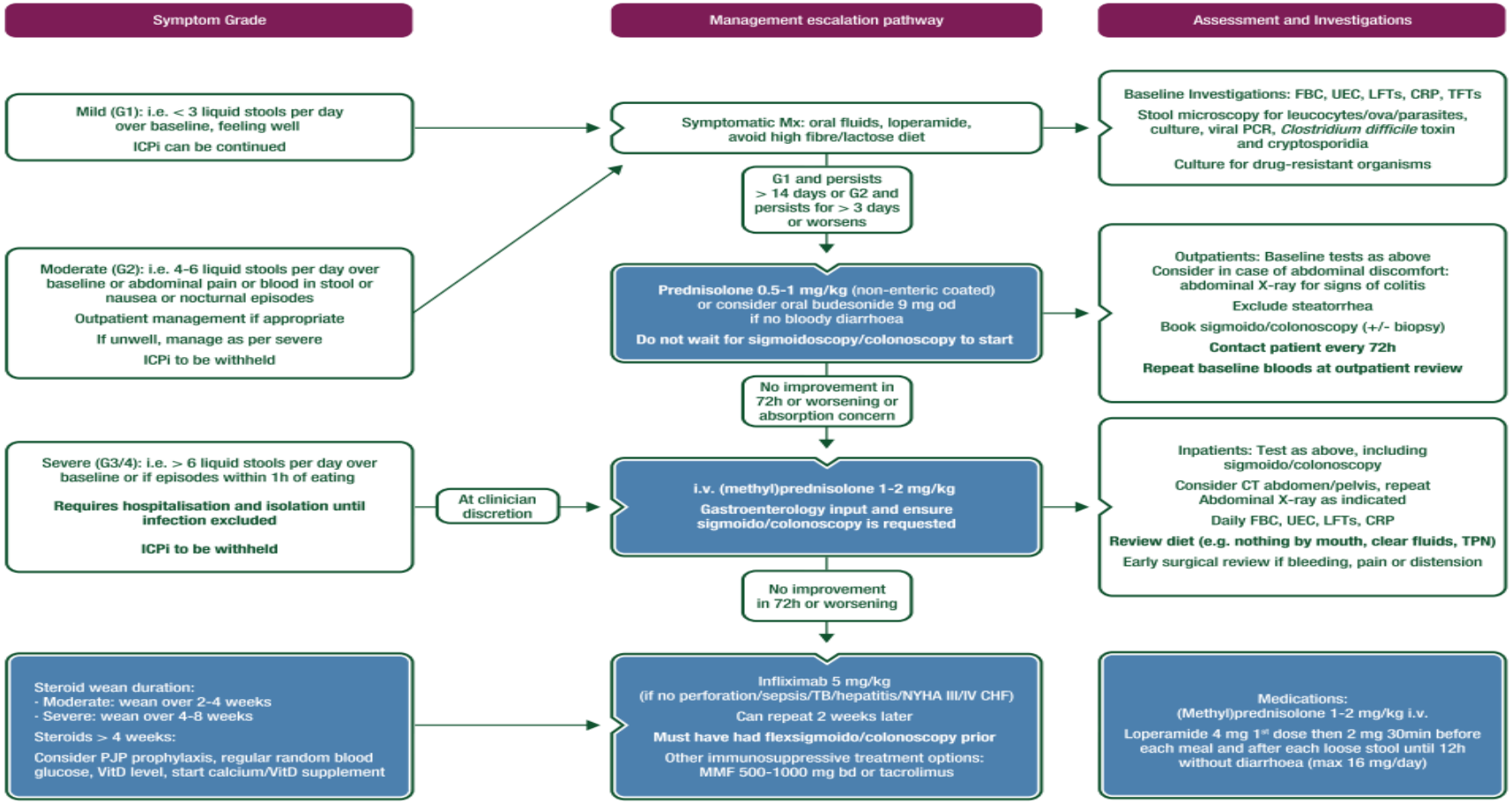


- Endoscopy: erythema, friability, hemorrhage, erosions, ulcerations, white exudates
- Histology:
  - ✓ stomach: chronic active gastritis with intraepithelial lymphocytosis and apoptosis
  - ✓ duodenum: may mimic coeliac disease with villous blunting & intraepithelial

Cheung VTF, Brain O. Best Pract Res Clin Gastroenterol. 2020 Oct-Dec;48-49:101703. doi: 10.1016/j.bpg.2020.101703. Epub 2020 Oct 23

Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

Management of diarrhoea and colitis



Haanen JBAG et al, ESMO Clinical Practice Guidelines, Ann Oncol. 2017 Jul 1;28(suppl_4):iv119-iv142. doi: 10.1093/annonc/mdx225.

Checkpoint inhibitor-associated diarrhea and colitis: management guidelines (grade 1–2)

White	Continue ICI
Yellow	Consider holding ICI
Orange	Hold/temporarily hold ICI
Red	Permanently discontinue ICI

Grade	NCCN Clinical Practice Guidelines In Oncology (NCCN Guidelines®)[1]	ASCO[2]	SITC[3]	ESMO[4]
1	< 4 ×/day over baseline, no colitis symptoms • Consider withholding ICI • Loperamide or diphenoxylate/ atropine for 2–3 days – If no improvement and not already done, obtain labs for infectious workup • Hydration • Close monitoring • If persistent or progressive symptoms, check lactoferrin/calprotectin – If positive, treat as grade 2 (below) – If negative and no infection, continue grade 1 management and add mesalamine, cholestyramine	< 4 ×/day over baseline; mild increase in ostomy output compared with baseline • Continue ICI or temporarily withhold ICI, and resume if toxicity does not exceed grade 1 • Monitor for dehydration and recommend dietary changes • Facilitate expedited phone contact with patient/caregiver • Consult gastroenterologist for prolonged grade 1 cases	≤ 4 ×/day, asymptomatic; clinical or diagnostic observations only; intervention not indicated • Continue ICI • Close follow up within 24–48 h • If symptoms persist, start routine stool and blood tests • Advise bland diet • Anti-diarrheal medication is optional but not highly recommended when infectious workup is negative	< 4 ×/day over baseline, feeling well • Continue ICI • Symptomatic treatment (fluids, loperamide, low fiber/lactose) • If grade 1 and persists > 14 days or worsens, give prednisolone 0.5–1 mg/kg or consider oral budesonide 9 mg daily if no bloody diarrhea
2	4–6 ×/day over baseline, colitis symptoms, not interfering with ADLs • Withhold ICI • Prednisone/ methylprednisolone[a] 1–2 mg/kg/day – Treat until symptoms improve to grade ≤ 1 then taper over 4–6 weeks • No response within 2–3 days: – Continue steroids – Consider adding infliximab or vedolizumab within 2 weeks[b,c,d] a IV steroid is preferred due to possible absorption impairment. bDuration of therapy with tumor necrosis factor alpha (TNF-alpha) blockers or integrin blocker is not clearly defined; evidence supports up to three doses (at weeks 0, 2, and 6) and is associated with reduced recurrence rates. Repeat endoscopy to assess endoscopic healing may be helpful to guide colitis treatment duration, but is optional. See Principles of Immunosuppression (IMMUNO-A). c An FDA-approved biosimilar is an appropriate substitute for infliximab. d Obtain TB test before receiving first dose of infliximab or vedolizumab. Treatment does not need to be held for results.	4–6 ×/day over baseline; moderate increase in ostomy output compared with baseline • Withhold ICI temporarily and consider permanently discontinuing CTLA-4 agents – may restart PD-1/PD-L1 agents if patient can recover to grade 1 or less • Concurrent immunosuppressants maintenance therapy (< 10 mg prednisone equivalent dose) may be offered only if clinically indicated in individual cases • Can include supportive care medications such as loperamide if infection has been ruled out • Consult gastroenterologist (grade 2 or higher) • Administer corticosteroids, unless diarrhea is transient, starting with initial dose of 1 mg/kg/day prednisone or equivalent. If improved to grade 1 or less, taper corticosteroids over at least 4–6 weeks before resuming treatment • EGD/colonoscopy, endoscopy evaluation highly recommended to stratify patients for early treatment with infliximab and to determine the safety of resuming PD-1/PD-L1 therapy (grade 2 or higher) • Stool inflammatory markers can be considered (lactoferrin and calprotectin) to differentiate functional vs inflammatory diarrhea, and use calprotectin to monitor treatment response (grade 2 or higher) • Repeat colonoscopy is optional for disease activity monitoring to achieve complete remission, especially if there is a plan to resume ICI (grade 2 or higher)	4–6 ×/day; abdominal pain; mucus/blood in stool • Withhold ICI • GI consultation if negative for infection. Outpatient stool and blood work; CRP, ESR, fecal calprotectin, lactoferrin, imaging and endoscopy are optional • **Diarrhea only:** observe for 2–3 days. If no improvement, start prednisone 1 mg/kg/day (or equivalent dose of methylprednisolone) • **Diarrhea & Colitis:** start prednisone 1 mg/kg/day and if no improvement in 48 h, increase dose to 2 mg/kg/day (or equivalent dose of methylprednisolone • If patient improves: – Tapering corticosteroid over 4–6 weeks may be needed – Resume ICI when corticosteroid is tapered to ≤ 10 mg/day and patient remains symptom-free (≤ grade 1) – Continue anti–PD-1 or anti–PD-L1 monotherapy – If using combination anti–CTLA-4/anti–PD-1, continue anti–PD-1 agent only	4–6 ×/day over baseline/ abdominal pain/blood in stool/nausea/nocturnal episodes • Withhold ICI • If grade 2 and persists for > 3 days or worsens, give prednisolone 0.5–1 mg/kg or consider oral budesonide 9 mg daily if no bloody diarrhea • Do not wait for sigmoido/ colonoscopy to start If no improvement in 72 h or absorption concern, treat as grade 3–4. Steroid wean duration: • Moderate: wean over 2–4 weeks • Severe: wean over 4–8 weeks

. ADL, activities of daily living; ASCO, American Society of Clinical Oncology; CRP, c-reactive protein; CTCAE, Common Terminology Criteria for Adverse Events; CTLA-4, cytotoxic T-lymphocyte-associated antigen; EGD, esophagogastroduodenoscopy; ESMO, European Society for Medical Oncology; ESR, erythrocyte sedimentation rate; GI, gastrointestinal; ICI, immune checkpoint inhibitor; IV, intravenous; NCCN, National Comprehensive Cancer Network® (NCCN®); PD-1, programmed death-1; PD-L1, programmed death ligand 1; SITC, Society for Immunotherapy of Cancer. 1.Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Management of Immunotherapy-Related Toxicities V.3.2021. Accessed June 14 2021. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. . 2. Brahmer JR et al. *J Clin Oncol* 2018;36:1714–1768. 3. Puzanov I et al. *J Immunother Cancer* 2017;5:95. 4. Haanen JBAG et al. *Ann Oncol* 2017;28(suppl 4):iv119–iv142.

Checkpoint inhibitor-associated diarrhea and colitis: management guidelines (grade 3–4)

White	Continue ICI
Yellow	Consider holding ICI
Orange	Hold/temporarily hold ICI
Red	Permanently discontinue ICI

Grade	NCCN Guidelines®[1]	ASCO[2]	SITC[3]	ESMO[4]
3	> 6 ×/day over baseline, colitis symptoms, interference with ADLs, hemodynamic instability, hospitalization, other serious complications • G3: Permanently discontinue anti–CTLA-4 Consider resuming anti–PD-1/PD-L1 after resolution of toxicity • G4: Permanently discontinue Immunotherapy agent responsible for toxicity • Consider inpatient care for provision of supportive care • IV methylprednisolone (1–2 mg/kg/day). If no response in 2 days: – Continue steroids, strongly consider adding infliximab or vedolizumab – Treat until symptoms improve to grade ≤ 1 then taper over 4–6 weeks (attempt < 4 weeks if infliximab or vedolizumab)[a-e]	≥ 7 ×/day over baseline, incontinence, hospitalization indicated, severe increase in ostomy output compared with baseline, limiting self-care ADL • Consider permanently discontinuing anti–CTLA-4, consider resuming anti–PD-1/PD-L1 if patient can recover to grade 1 or less • Administer corticosteroids (initial dose of 1–2 mg/kg/day prednisone or equivalent) • Consider hospitalization for patients with dehydration or electrolyte imbalance • If symptoms persist ≥ 3–5 days or recur after improvement, consider administering IV corticosteroid or non-corticosteroid (eg, infliximab) • Consider colonoscopy in cases where patients have been on immunosuppression and may be at risk for opportunistic infections as an independent cause for diarrhea (ie, Cytomegalovirus colitis) and for those who are anti-TNF or corticosteroid refractory • The use of vedolizumab may be considered in patients refractory to infliximab and/or contraindicated to TNF-α blocker	Diarrhea: ≥ 7 ×/day Colitis: severe abdominal pain; change in bowel habits; medical intervention indicated; peritoneal signs • Withhold ICI • Consider resuming ICI when corticosteroid is tapered to ≤ 10 mg/day and patient remains symptom-free (grade ≤ 1) • Consider hospitalization • Blood and stool infection work-up, inflammatory markers, imaging, endoscopy • Consult gastroenterologist • Start intravenous prednisone 1–2 mg/kg/day (or equivalent dose of methylprednisolone) immediately • If patient improves, follow instructions for 'If patient improves' for grade 2 • If refractory or no improvement on IV corticosteroid, start prednisone 2 mg/kg/day (or equivalent dose of methylprednisolone) for 3 days • Consider adding infliximab 5 mg/kg, which can be given again after two weeks if a second dose is needed (vedolizumab may also be used)	≥ 7 ×/day or life-threatening • Withhold ICI and hospitalize • IV methylprednisolone (1–2 mg/kg) • Consult gastroenterologist • Ensure sigmoido/colonoscopy If no improvement in 72 h or worsening: • Add infliximab 5 mg/kg (can repeat 2 weeks later) • Other immunosuppressant: mycophenolate 500–1000 mg or tacrolimus Steroid taper duration: • Moderate: wean over 2–4 weeks • Severe: wean over 4–8 weeks
4		Life-threatening consequences; urgent intervention indicated • Permanently discontinue ICI • Admit patient when clinically indicated, or outpatient with close monitoring • Administer 1–2 mg/kg/day methylprednisolone or equivalent until symptoms improved to grade 1 then start taper over 4–6 weeks • Consider early infliximab 5–10 mg/kg if symptoms refractory to corticosteroid within 2–3 days if infliximab-refractory, consider vedolizumab • Consider lower GI endoscopy if symptoms are refractory despite treatment or there is concern of new infections	Life-threatening consequences; urgent intervention indicated • Permanently discontinue ICI therapy • Hospitalize • Blood and stool infection workup, inflammatory markers, imaging, endoscopy • Consult gastroenterologist • Start intravenous prednisone 1–2 mg/kg/day (or equivalent dose of methylprednisolone) immediately • If patient improves, follow instructions for 'If patient improves' for grade 2 • If refractory or no improvement on IV corticosteroid, start prednisone 2 mg/kg/day (or equivalent dose of methylprednisolone) for 3 days • Consider adding infliximab 5 mg/kg, which can be given again after 2 weeks if a second dose is needed (vedolizumab may also be used)	

a Duration of therapy with tumor necrosis factor alpha (TNF-alpha) blockers or integrin blocker is not clearly defined; evidence supports up to three doses (at weeks 0, 2, and 6) and is associated with reduced recurrence rates. Repeat endoscopy to assess endoscopic healing may be helpful to guide colitis treatment duration, but is optional. See Principles of Immunosuppression (IMMUNO-A).
b An FDA-approved biosimilar is an appropriate substitute for infliximab.
c Obtain TB test before receiving first dose of infliximab or vedolizumab. Treatment does not need to be held for results.
d Consider tofacitinib for infliximab- or vedolizumab-refractory colitis (Esfahani K, et al. N Engl J Med 2020;382:2374-2375).
e Fecal transplantation may be considered for immunosuppressant-refractory colitis based on institutional availability and expertise.

ADL, activities of daily living; ASCO, American Society of Clinical Oncology; CTCAE, Common Terminology Criteria for Adverse Events; CTLA-4, cytotoxic T-lymphocyte-associated antigen; EGD, esophagogastroduodenoscopy ESMO, European Society for Medical Oncology; G, grade; GI, gastrointestinal; ICI, immune checkpoint inhibitor; IPI, ipilimumab; IV, intravenous; NCCN, National Comprehensive Cancer Network® (NCCN®); NIVO, nivolumab; PD-1, programmed death-1; PD-L1, programmed death ligand 1; SITC, Society for Immunotherapy of Cancer; TNF, tumor necrosis factor. 1.Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Management of Immunotherapy-Related Toxicities V.3.2021. Accessed June 14 2021. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.. 2. Brahmer JR et al. J Clin Oncol 2018;36:1714–1768. 3. Puzanov I et al. J Immunother Cancer 2017;5:95. 4. Haanen JBAG et al. Ann Oncol 2017;28(suppl 4):iv119–iv142.

Immune-related AEs: gastrointestinal

This slide is focused on CPi-related AEs The type, onset and severity of any immunotherapy-related AE varies. Always refer to appropriate guidelines and/or organ specialists for management strategies relating to different and specific types of immunotherapies

Incidence[1,2]

- Adverse events involving the gastrointestinal tract are common
- Grade 3/4 diarrhea/colitis was the most commonly observed serious adverse event reported across several trials involving CPIs

Onset[1]

- 6-7 weeks

Differential diagnosis[3]

- *Clostridium difficile*

Management of diarrhea and colitis[3]

Grade 2 (4–6 liquid stools/day over baseline)

- Withhold CPi
- Symptomatic management[a]
- Prednisolone 0.5–1 mg/kg/day or oral budesonide 9 mg od if symptoms persist for >3 days or worsen

Grade 3–4 (> 6 liquid stools/day over baseline)

- Hospitalization and isolation until infection excluded
- Withhold CPi
- Prednisolone 1–2 mg/kg/day
- Sigmoido/colonoscopy
- Infliximab if no improvement after 3 days

[a]Oral fluids, loperamide, avoid high fibre/lactose diet. od, once daily, CPI, checkpoint inhibitor.

.1. Gelao et al. Toxins 2014;6:914–33. 2. Hodi et al. N Engl J Med 2010;363:711–23. 3. Haanen JBAG et al. Ann Oncol. 2017;28(suppl_4):iv119–iv142.

Important factors for the management of GI IMARs

- Clinicians should be aware that using immunosuppressive agents to treat inflammation can increase risk of other GI pathology, such as small intestinal bacterial overgrowth or infective diarrhea
  - Symptoms could be viewed as failure of IMAR management
- Routine hematological and biochemical tests should be accompanied by stool examination for pathogens such as *Clostridium difficile*
- CTCAE v4 grading can underestimate the severity of symptoms and associated burdens for patients
- In addition to number of stools, clinicians should enquire about additional factors:
  - Time spent in restroom
  - Nocturnal bowel movements
  - Bowel urgency
  - Impact on QoL and ADL
- Corticosteroid-refractory patients are defined as those who do not improve with 3 days of IV corticosteroids
  - May start on infliximab 5 mg/kg (or vedolizumab)

ADL, activities of daily living; CTCAE; Common Terminology Criteria for Adverse Events; GI, gastrointestinal; IMAR, immune-mediated adverse reaction; IV, intravenous; QoL, quality of life.
Samaan MA et al. Nat Rev Gastroenterol Hepatol 2018;222–234.

Patients with corticosteroid-refractory GI IMARs

- Many patients with cancer may have GI IMARs that are corticosteroid-refractory[1,2]
  - Corticosteroids appear to effective for only 60-70% of patients who have enterocolitis as an IMAR
  - About a third of patients may require additional biologic agents such as infliximab or vedolizumab
- Retrospective studies suggest that colonic ulceration (involving severe inflammation) may be an important predictive factor associated with failure of corticosteroid treatment[3,4]
- CMV infection/reactivation has been reported in patients with corticosteroid-refractory, immune-mediated colitis[5]
- Addition or replacement with other immunosuppressive therapies should be considered in corticosteroid-refractory immune-mediated colitis if other causes are excluded[6-8]

CMV, cytomegalovirus; GI, gastrointestinal; IMAR, immune-mediated adverse reaction. 1. Favara DM et al. *ESMO Open* 2020;5:e000585. 2. Dougan M. *Curr Gastroenterol Rep* 2020;22:15. 3. Geukes Foppen MH et al. *ESMO Open* 2018;3:e000278. 4. Wang Y et al. *Inflamm Bowel Dis* 2018;24:1695-1705. 5. . Postow M. Toxicities associated with checkpoint inhibitor immunotherapy. topic last updated: May 25, 2021. Uptodate Accessed online on June 1st 2021. 6. . Brahmer JR et al. J Clin Oncol 2018;36:1714–1768. 7. Puzanov I et al. J Immunother Cancer 2017;5:95. 8. Haanen JBAG et al. Ann Oncol 2017;28(suppl 4):iv119–iv142

Additional treatments for corticosteroid-refractory GI IMARs

- Patients with corticosteroid-refractory GI IMARs require escalation to a biologic agent, such as infliximab or vedolizumab[1,2]
- Infliximab is successful in this setting, starting with an initial dose of 5 mg/kg[1]

Infliximab therapy for corticosteroid-refractory GI IMARs[1]		
Study population	**Dosage**	**Outcomes**
• Infliximab vs corticosteroids • 75 patients: 48% received infliximab	• 1–3 infusions of infliximab	• Infliximab + corticosteroids superior to corticosteroids alone • Resolution of diarrhea: 3 days vs 9 days • Duration of corticosteroid use: 35 days vs 51 days
• Case report (n = 1)	• Infliximab (5 mg/kg) single dose	• Symptom resolution in 2 days • Mucosal healing on endoscopy noted on day 7

- If patients are infliximab-refractory, then vedolizumab, an anti-integrin antibody, could be considered[3]
- Vedolizumab is also effective in those without multisystem involvement[1]
- Patients who had not received infliximab prior to vedolizumab had 95% clinical remission rate, and those that had previous exposure to infliximab had success rates as high as 67%[1]
- A recent retrospective study showed that, compared with infliximab, vedolizumab can significantly improve the disease course of IMDC, reduce steroid exposure, deliver equal efficacy of clinical remission, lower IMDC recurrence, and increase long-term OS[4]

GI, gastrointestinal; IMAR, immune-mediated adverse reaction; IMDC, immune-mediated diarrhea and colitis; OS, overall survival. 1. Shivaji UN et al. Ther Adv Gastroenterol 2019;12:1–15. 2. Dougan M. Curr Gastroenterol Rep 2020;22:15. 3. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Management of Immunotherapy-Related Toxicities V.1.2021. © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. 4. Zou F et al. Oral presentation at the Virtual American College of Gastroenterology Annual Scientific Meeting; October 23–28, 2020. Abstract S0136.

GI IMARs: key takeaways

- Key event underlying diarrhea and colitis may result from hyper-activated effector T cells[1]
  - Immune enterocolitis due to checkpoint inhibition is secondary to hyper-activated effector T cells targeting luminal antigens and to loss of functional regulatory T cells
- Consult a gastroenterologist who has experience in treating IMARs[2-4]
- Biopsies are necessary for the diagnosis of GI IMARs when patients present with macroscopically normal bowels but may have microscopic colitis[5]
- Around a third of patients with GI IMARs are corticosteroid-refractory and require immunosuppressive biologic agents, such as infliximab or vedolizumab[6]
- Cytomegalovirus infection/reactivation has been reported in patients with corticosteroid-refractory, immune-mediated colitis[7]

AE, adverse event; GI, gastrointestinal; IMAR, immune-mediated adverse reaction. 1. Samaan MA et al. Nat Rev Gastroenterol Hepatol 2018;222–234. 2. Brahmer JR et al. J Clin Oncol 2018;36:1714–1768. 3. Puzanov I et al. J Immunother Cancer 2017;5:95. 4. Haanen JBAG et al. Ann Oncol 2017;28(suppl 4):iv119–iv142. 5. Favara DM et al. ESMO Open 2020;5:e000585. 6. Shivaji UN et al. Ther Adv Gastroenterol 2019;12:1–15. 7. Postow M. Toxicities associated with checkpoint inhibitor immunotherapy. topic last updated: May 25, 2021. Up to date Accessed online on June 1st 2021