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Immune checkpoint inhibitor-related gastrointestinal toxicity in patients with malignancy involving the luminal gastrointestinal tract and its impact on cancer outcomes

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Abstract

Background Immune checkpoint inhibitors (ICI) are known to cause immune-related adverse events (irAE) with the gastrointestinal (GI) tract among the most affected. Our knowledge of GI irAE in patients with luminal GI malignancies is poor. We aimed to characterize the incidence, clinical features, treatment, and outcomes of these GI irAEs.

Methods This was a retrospective study of patients with malignancies involving the luminal GI tract and GI irAEs at MD Anderson Cancer Center from January 2010 to June 2020. Clinical data were collected and analyzed.

Results Eighteen patients with luminal GI tract malignancies treated with ICIs had evidence of GI irAEs based on clinical symptoms and/or histology. The predominant GI irAE symptom was diarrhea (78%). Ten had non-ulcerative inflammation (56%) and 5 had ulcerative inflammation (28%) on endoscopy. Histologically, 3 patients (17%) had evidence of acute inflammation, 4 (22%) had chronic inflammation, and 9 (50%) had both. Ten patients (56%) received immunosuppressant treatment, which included steroids alone (n=2, 20%), steroids with biologics (infliximab or vedolizumab) (n=7, 70%), or biologics alone (n=1, 10%), with clinical remission in all cases. Of the 6 patients who previously had stable or ICI-responsive cancer and received immunosuppressants, none developed progression of GI luminal malignancy during the study period.

Conclusions GI irAEs occurred in 2.4% of patients treated with ICI for cancer involving the luminal GI tract. Immunosuppressant therapies (e.g., vedolizumab) appear to be effective for GI irAEs, showing no association with further GI luminal cancer progression, recurrence, or a subsequent poor response to ICI therapy.

Keywords Immune checkpoint inhibitor, GI luminal malignancy, colitis, outcome

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Introduction

Immune checkpoint inhibitor (ICI) therapy has revolutionized cancer care and the management of advanced malignancies. Immune checkpoints, the body's innate mechanism to control the immune response and prevent autoimmunity, are often exploited by tumors to escape immune surveillance. ICI therapy blocks these checkpoints and enables the body's own immune system to respond to malignancies. ICI therapy targets cytotoxic T lymphocyte-associated antigen 4 (CLTA-4) or programmed death receptor/ligand 1 (PD-1/L1), boosting T cell-mediated immune responses and antitumor effects. The first ICI therapy approved by the US Food and Drug Administration (FDA) was for the treatment of advanced melanoma using anti-CTLA-4 antibodies. Since then, multiple

ICI agents have been approved for various cancers, and combination therapy with 2 ICI agents has emerged as a new treatment option for advanced malignancies [1]. Recently, anti-PD-1 antibodies, such as pembrolizumab and nivolumab, have been approved by the FDA specifically for gastrointestinal (GI) malignancies such as gastric adenocarcinoma and mismatch repair-deficient solid tumors. Pembrolizumab has also been approved for hepatocellular carcinomas. Exploration into more applications of ICIs in other GI malignancies is currently ongoing in various clinical trials [1-4].

Despite the efficacy of ICI therapy, this class of medications is often associated with several immune-related adverse events (irAEs) that may affect almost any organ system [5]. Combinations of different types of ICI agents have also been shown to increase the risk of irAEs [6,7]. These irAEs often involve multiple systems, and GI toxicities are among the most frequently reported adverse events of ICI therapy. The incidence of colitis is reported to range from 8-27%, while the incidence of diarrhea alone has been reported to be as high as 54% among patients started on ICI therapy [6]. The symptoms of GI irAEs include, but are not limited to, diarrhea, abdominal pain, nausea, cramping, blood or mucus in stool, changes in bowel habits, fever, abdominal distension, obstipation and constipation [8]. Currently, management of ICI toxicity is driven by the severity of the irAE, graded by the Common Terminology Criteria for Adverse Events (CTCAE) [9]. Initial management of GI irAEs starts with a comprehensive evaluation (laboratory tests, radiologic imaging and endoscopy with biopsies) to rule out possible alternative etiologies of GI symptoms and determine the severity of the irAE [8-10]. Identifying high-risk endoscopic features and active histologic inflammation with early endoscopic evaluation is important, as these are markers of disease severity and bear significant clinical implications [11,12]. Additionally, clinical symptoms often do not correlate with endoscopic and histologic findings. Hence, early endoscopic evaluation becomes of utmost importance when evaluating for GI irAEs, as high-risk endoscopic features (i.e., ulcers or extensive inflammation) are likely to reflect steroid-refractory disease [13]. Once ICI-related toxicity is established, the severity of illness is used to determine the need for pausing or stopping ICI therapy, initiation of immunosuppression with corticosteroids, or use of biologic therapy with immunosuppressants, such as tumor necrosis factor (TNF)-α inhibitor (infliximab) or anti-integrin antibodies (vedolizumab). Early introduction of immunosuppressive therapy has been associated with favorable outcomes in patients with ICI-related colitis [14]. Anecdotal case reports also suggest therapies such as ustekinumab, tofacitinib and fecal microbiota transplantation (FMT) may be successful against ICI-related colitis refractory to routinely used immunosuppression [15-17].

Among these immunosuppressants, targeted biologic therapies are of particular interest for GI irAEs because of their specific mechanisms of action. Vedolizumab is an α4β7 integrin monoclonal antibody that is primarily gut selective in action. It prevents leukocyte binding to the endothelial surface and extravasation into the affected tissue, enabling selective GI immunosuppression [18]. It has been used as a first-line treatment for moderate to severe inflammatory bowel disease (IBD), as it offers a targeted, gut-selective mechanism of action without any clear increase in the risk of serious systemic opportunistic infections or other common complications associated with chronic diseases that typically require lifelong therapy [19,20]. Alternatively, infliximab is a chimeric IgG1 monoclonal antibody that binds with high affinity to TNF-α, neutralizing its biologic activity [21]. Infliximab was the first anti-TNF agent approved for use in IBD. Although infliximab is generally well-tolerated, adverse events of infliximab therapy that have been well recognized include drug-induced lupus, serious infection and malignancy from long-term use [22,23].

Interestingly, the existing literature has shown that the development of irAEs caused by ICI is associated with clinical benefits in terms of progression-free survival and overall survival [24,25]. Thus, it has been hypothesized that irAEs can be used as a biomarker to assess ICI response [26]. At the same time, the use of immunosuppressants for irAEs has often been limited by the concern that these treatments could counteract the therapeutic effect of ICIs, compromising future cancer outcomes. Moreover, despite the better safety profile of vedolizumab compared with infliximab in IBD and limited studies showing the efficacy of vedolizumab against ICI-related colitis, the efficacy and safety of vedolizumab among patients with luminal GI malignancy has not been studied [18]. To address these gaps and shed light on the impact of GI irAEs and their treatment, this study presents a retrospective case series evaluating the outcomes of GI irAEs and cancer in patients who underwent ICI therapy for malignancies involving the luminal GI tract. Our primary aim was to assess the incidence, characteristics, treatment, and outcomes of GI irAEs among this population. The secondary aim was to assess the outcomes of GI malignancy in this population after immunosuppressant treatments.

Patients and methods

Patient selection

We retrospectively studied patients with primary GI malignancies, or non-GI malignancy with metastasis involving the luminal GI tract, treated with ICIs at The University of Texas MD Anderson Cancer Center between January 2010 and June 2020 and in whom a GI irAE was diagnosed. Patients were included if they met the following criteria: older than 18 years; GI symptoms between the time of the first ICI dose and 6 months after the last dose; and upper or lower endoscopy with histology evaluation performed for GI symptoms.

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Endoscopic evaluation in this cohort was performed based on the following criteria: new onset of CTCAE grade ≥2 diarrhea or colitis from baseline GI malignancy; positive stool inflammatory markers (i.e., lactoferrin and calprotectin); imaging evidence of GI inflammation; and/or significant upper GI symptoms (e.g., nausea, vomiting, epigastric pain) with high clinical suspicion for GI irAE. Patients with other identifiable etiologies of GI symptoms or inflammation, including reflux, surgical anastomosis ischemia, preexisting inflammatory bowel condition, and infections (such as *Clostridioides difficile* and cytomegalovirus detected via stool studies and/or colon pathology) were excluded. GI irAE symptoms outside the window of the study period and GI toxicity related to non-ICI chemotherapy regimens were also excluded.

Data collection

Clinical and oncologic data

Baseline demographic data (including age, sex, race), oncology variables (GI luminal cancer location, cancer type and stage, ICI received, and surgery), GI irAE presentations, medical treatment received and outcomes were extracted from institutional electronic medical records and pharmacy databases. Diarrhea and colitis severity were graded by CTCAE version 5.0. Medical treatments for the GI irAEs were categorized as non-immunosuppressive therapy and immunosuppressive therapy. Non-immunosuppressive therapy included, but was not limited to, aggressive hydration, bland diet, loperamide, diphenoxylate/atropine, mesalamine and/or cholestyramine. The patients given immunosuppressive therapy were further stratified into those who received steroids only and those who received additional biologics (infliximab or vedolizumab). Clinical remission of GI irAE symptoms was defined as a sustained resolution of symptoms during the study period. Cancer status at GI irAE onset and at last follow up after GI irAE treatment was evaluated based on the Response Evaluation Criteria in Solid Tumors guidelines (version 1.1). Cancer outcomes in those who received immunosuppressive therapy were followed up and classified into stable/remission, GI luminal cancer progression, or extra-luminal cancer progression. Patients' vital status and survival at the last follow up were also recorded.

Endoscopic and histological evaluation

Endoscopic findings included the presence of mucosal ulcerations, non-ulcerative inflammation (erythema, exudate, loss of normal vascularity, atrophy), or normal appearance. Histological patterns comprised acute, chronic, acute and chronic inflammation, or no histologic inflammation. Details of the features in each category have been described previously [11]. Endoscopic remission was defined as a resolution of ulceration/non-ulcer inflammation on repeat endoscopy, and histological remission was defined as a resolution of active histological inflammation.

Ethical considerations

All patient data were in compliance with the Health Insurance Portability and Accountability Act confidentiality requirements.

Results

Patient baseline characteristics

Of the 12,051 patients who received ICI treatment between January 2010 and June 2020, 764 had primary GI malignancies or non-GI malignancy with metastasis involving the luminal GI tract confirmed by GI pathology. Of this sample, 18 patients had evidence of GI irAEs, based on clinical symptoms, and underwent endoscopy and histology evaluation after exclusion of other etiologies. The patient selection flowchart and baseline demographic characteristics are shown in Table 1 and Supplementary Fig. 1. The median age was 63 years, and the majority of patients were white women. The esophagus (33%) was the most common location of malignancies and

Table 1 General patient characteristics

Patient characteristics	No. (%), n=18
Age, median (interquartile range)	63 (37-80)
Male sex	8 (44)
Race	
White	16 (89)
Other	2 (11)
GI luminal cancer location (primary + metastatic)[a]	
Esophageal	6 (33)
Stomach	2 (11)
Duodenum	2 (11)
Jejunum	2 (11)
Colon	3 (17)
Rectum	2 (11)
Jejunum + ileum + colon	1 (6)
Disease stage	
Metastatic	18 (100)
Cancer type	
Adenocarcinoma	10 (56)
Squamous	1 (6)
Neuroendocrine	3 (17)
Melanoma metastasis only	3 (17)
Concomitant adenocarcinoma and melanoma	1 (6)
Checkpoint inhibitor received	
PD-1/L1[b]	10 (56)
CTLA-4 and PD-1/L1 combined[c]	8 (44)

Values are shown as no. (%) except where otherwise indicated

[a]Melanoma metastasis accounted for 4 patients

[b]PD-1/L1 include pembrolizumab, nivolumab, and atezolizumab

[c]Ipilimumab with nivolumab

GI, gastrointestinal; PD-1/L1, programmed death 1/programmed death 1 ligand; CTLA-4, cytotoxic T lymphocyte-associated antigen 4

the rectum (12%) was the least common site. A majority of the malignancies, regardless of location, were adenocarcinoma (56%), followed by neuroendocrine (17%) and squamous cell (6%) cancers. Fifteen patients had primary GI malignancy, while the remainder had metastasis in the luminal GI tract from non-GI primary malignancy. Four patients (22%) had prior surgical removal of primary GI malignancy before ICI initiation. ICI regimens included PD-1/L1 monotherapy (56%) and combination therapy with both PD-1/L1 and CTLA-4 inhibitors (44%). Six patients (33%) restarted ICI treatment after their GI irAE was resolved.

GI irAE characteristics

The most common presenting symptoms were diarrhea (78%), abdominal pain (33%), nausea/vomiting (11%), dysphagia (11%), and GI bleeding (6%) (Table 2). These symptoms were not attributable to the primary or secondary GI malignancy. The median duration from ICI initiation to the development of symptoms was 67 days. The most common types of GI irAE were isolated colitis (44%), enterocolitis (22%), and isolated gastritis (22%). Diarrhea and colitis each had a median CTCAE grade of 2. All 18 patients underwent endoscopic evaluation for GI irAE-related symptoms: 8 (44%) patients underwent colonoscopy only, 5 (28%) underwent esophagogastroduodenoscopy only, and 4 (22%) underwent both esophagogastroduodenoscopy and colonoscopy. Erythema (56%) and ulceration (28%) were the most frequently identified features on endoscopy. Notably, 3 patients (17%) had a normal endoscopic evaluation. Histological samples were also obtained from all patients: 3 (17%) had evidence of acute inflammation, 4 (22%) had chronic inflammation, 9 (50%) had evidence of both acute and chronic inflammation, while 2 patients (11%) had no histological inflammation.

Table 2 GI immune-related adverse events characteristics

GI immune-related adverse events	No. (%), n=18
Time to symptoms from ICI initiation, days, median (interquartile range), n=13	67 (24-150)
Clinical symptoms [a]	
Diarrhea	14 (78)
Abdominal pain	6 (33)
Nausea/vomiting	2 (11)
GI bleeding	1 (6)
Dysphagia	2 (11)
Organ involvement	
Isolated gastritis	4 (22)
Isolated enteritis	1 (6)
Isolated colitis	8 (44)
Gastroenteritis	1 (6)
Enterocolitis	4 (22)
EGD	5 (28)
Colonoscopy	8 (44)
Sigmoidoscopy	1 (6)
EGD + colonoscopy	4 (22)
Endoscopic presentation [b]	
Normal	3 (17)
Erythema	10 (56)
Ulceration	5 (28)
Exudate	1 (6)
Loss of normal vascularity	4 (22)
Atrophy	1 (6)
Histological features	
Acute inflammation	3 (17)
Chronic inflammation	4 (22)
Acute and chronic inflammation	9 (50)
No histological inflammation	2 (11)
Duration of follow up from GI irAE to last follow up, months, median (IQR), n=18	14 (5-19)

Values are shown as no. (%) except where otherwise indicated

[a]Seven patients presented with 2 or more clinical symptoms

[b]Eight patients had 2 or more endoscopic features

GI, gastrointestinal; EGD, esophagogastroduodenoscopy; ICI, immune checkpoint inhibitors; irAE, immune-related adverse events; IQR, interquartile range

GI irAE treatment and outcomes at last follow up

Among these 18 patients with GI irAEs, non-immunosuppressive therapy was administered in 8 patients (44%), while 10 patients (56%) had severe GI irAEs that required immunosuppressive therapy (Table 3). Of the 8 patients treated with non-immunosuppressive therapy, 4 patients (50%) had their ICI paused and the remaining 4 patients received supportive care for symptom control. Among those who received immunosuppressive therapy, 2 received steroids only, and 8 received steroids plus biologics, primarily vedolizumab (7 received vedolizumab only; 1 received infliximab followed by vedolizumab). Steroids used included budesonide extended-release, prednisone or methylprednisolone. ICI treatment was paused in all patients who received immunosuppressive therapy. The median durations of steroid treatment were 40 days with monotherapy and 46 days with steroids plus biologics. Patients who received non-immunosuppressive therapy had a 100% clinical remission rate; endoscopic remission was seen in 14%, and no patients showed histologic remission at the last follow up. Patients who received immunosuppressive therapy had a 100% clinical remission rate, with 63% and 40% endoscopic and histologic remission rates, respectively. Within the immunosuppressant-treated group, those who received steroids plus biologics had higher rates of endoscopic remission (71%) and histologic remission (50%) than did those who received steroids alone (0% for both endoscopic and histologic remission).

Notably, one patient in the cohort received FMT in addition to immunosuppressants for treatment of refractory ICI colitis. The patient was a 36-year-old man with stage IV colon cancer who received 3 doses of combination ipilimumab and nivolumab before the diagnosis of ICI colitis, after which his ICI medication was paused. He had severe diffuse colitis with ulcerations in the entire colon, in addition to a large circumferential ascending colon tumor with luminal

Table 3 GI irAE therapy and outcomes at last follow up

Therapy	Follow-up duration, months, median (IQR)	Duration of steroid treatment, days, median (IQR)	Clinical remission, no. (%)	Endoscopic remission, no. (%)[b]	Histological remission, no. (%)[c]	ICI resumed, no. (%)
Non-IMS therapy, n=8	14 (6-26)		8 (100)	1 (14)	0	3 (38)
IMS therapy, n=10	10 (5-18)		10 (100)	5 (63)	4 (40)	3 (30)
Steroids alone, n=2		40 (N/A)	2 (100)	0	0	0
Steroids and biologics,[a] n=8		46 (39-86)	8 (100)	5 (71)	4 (50)	3 (38)

[a]Seven patients were treated with vedolizumab; 1 patient was treated with infliximab and vedolizumab

[b]Only patients with abnormal endoscopy at the onset of GI irAE were included for this calculation

[c]Only patients with abnormal histology at the onset of GI irAE were included for this calculation

GI irAE, gastrointestinal immune-related adverse event; ICI, immune checkpoint inhibitor; IQR, interquartile range; IMS, immunosuppressant; N/A, not applicable

stricture. His GI irAEs did not respond to steroid treatment initially, and he was started on vedolizumab. However, his diarrhea and abdominal pain persisted; FMT was given as a compassionate treatment for his symptoms, but there was no significant improvement. During the ICI pause, the patient had a right hemicolectomy owing to colonic obstruction caused by the tumor. Postoperatively, the patient resumed nivolumab monotherapy along with concurrent vedolizumab. At the last follow up 20 months later, the patient had stable cancer in extra-intestinal lymph nodes only. He was taken off ICI therapy and vedolizumab with regular monitoring for cancer through imaging only. Colonoscopy confirmed the resolution of colitis after therapy completion.

When the characteristics of patients were compared between the immunosuppressant-treated group and the non-immunosuppressant–treated group, certain differences were identified (Supplementary Table 1). The immunosuppressant-treated group had more diverse cancer types, a higher proportion of colonic distribution of malignancy, more frequent use of combined CTLA-4 and PD-1/L1 agents, more lower GI tract toxicity, more diarrhea-predominant symptoms, and a higher proportion of chronic active histological inflammation. Among the 18 patients, 6 (33%) resumed ICI therapy after GI irAE, all without recurrence of GI irAE. Most of those who did not resume ICI therapy had their treatment discontinued because of cancer progression. Patients' characteristics of GI irAEs were also summarized based on the location of the GI lumen (Supplementary Table 2).

Cancer outcomes after immunosuppressive therapy in patients who previously had stable or ICI-responsive disease

Among the 10 patients who received immunosuppressive therapy, 4 patients (40%) were in cancer remission or had a response to ICI, and 2 (20%) had stable disease at the time of GI irAE occurrence (Table 4). None of these 6 patients developed GI luminal malignancy progression after immunosuppressive treatment during the study period. One (17%) had progression of extra-luminal metastases 30 days after initiation of steroids and vedolizumab. Notably, 1 of these patients underwent successful surgical resection of primary GI malignancy before initiation of ICI. Three of these patients resumed ICI after resolution of GI IrAEs.

Discussion

ICIs have been proven to significantly improve overall survival and delay tumor progression in patients with melanoma, non-small cell lung cancer and other types of cancer, while their benefit in the case of luminal GI cancers still needs more extensive studies [12]. We undertook a descriptive analysis to understand the impact of GI irAEs and immunosuppressants on outcomes among patients with luminal GI cancer. Our small-scale study suggests that vedolizumab combined with short-term steroid therapy is an effective treatment for severe GI irAEs, yielding high rates of clinical, endoscopic and histological remission. Additionally, treatment of GI irAEs with vedolizumab was not associated with GI luminal cancer progression, recurrence, or a subsequent poor response to ICI therapy.

The current practice in patients with GI irAEs refractory to corticosteroid therapy is treatment with selective immunosuppression: i.e., infliximab or vedolizumab [9]. However, there is concern that systemic immunosuppression for treatment of irAEs could counteract the effect of ICIs and possibly jeopardize the response to cancer treatment. Despite the high efficacy of the anti-TNF agent infliximab, recent literature has demonstrated an association between anti-TNF treatment and worse overall survival in melanoma patients who developed irAEs [27,28]. This observation is in accord with studies that have shown an increased risk of lymphoma and melanoma in IBD patients on infliximab [29,30]. Confounding factors, such as duration and cumulative dose of steroid used, should be taken into consideration when interpreting the data of these studies, and further evidence is still needed for clarification and confirmation.

On the other hand, vedolizumab, a gut-targeted $\alpha 4\beta 7$ integrin antibody approved for the treatment of IBD, has been shown to be a safer and more favorable option over other immunosuppressants in multiple studies [18,19].

Table 4 Cancer outcomes after immunosuppressive therapy in patients who previously had stable or immune checkpoint inhibitor-responsive disease

Therapy	Remission, response, or stable no. (%)	GI luminal progression or recurrence,[a] no. (%)	Extra-luminal progression,[a] no. (%)
Steroids alone, n=2	2 (100)	0	0
Steroids with biologics			
Infliximab, n=1	1 (100)	0	0
Vedolizumab, n=3	2 (66)	0	1 (33)

[a] Progression of malignancy occurring more than 30 days after initiation of irAE therapy

GI, gastrointestinal

Additionally, in post-marketing safety data published 4 years after its approval, vedolizumab continued to display a favorable safety profile in cancer risk and serious complications [31]. Given its unique mechanism of action and favorable safety profile in treating IBD, vedolizumab has also been recognized and increasingly used in the realm of ICI GI toxicity, with high efficacy against ICI colitis. To date, favorable evidence suggests a minimal risk of this therapy interfering with ICIs or jeopardizing cancer outcome compared to infliximab [28].

As the use of ICI for malignancies involving the GI tract has been mainly in clinical trials, cases with GI irAEs in this population are still very limited, as is the current literature on the use of vedolizumab for GI irAE management in this particular population. Our small case series is a start towards filling the gaps in our knowledge of this field. Among our 18 patients with GI luminal malignancies, we observed the consistent efficacy of vedolizumab against GI irAEs, as well as negligible evidence of luminal cancer progression and recurrence. Our findings thus disfavor the hypothesis that GI-targeted immunosuppression can contribute to luminal cancer progression by reversing the effect of ICIs in the GI tract. One explanation for these findings is that the scope of the inflammatory cascade from ICIs could be far beyond the effect of vedolizumab, which reserves adequate therapeutic benefit for the tumor in the GI tract. Further studies with larger sample sizes are needed to confirm these initial findings.

Four patients in our cohort had surgical resection of the primary GI malignancy before ICI initiation. Of these 4 patients, 2 subsequently received immunosuppressive therapy for their GI irAE. One of the patients had primary esophageal cancer with gastric involvement and underwent gastrectomy with aborted esophagectomy due to intraoperative bleeding. The other patient underwent a hemicolectomy for colon cancer before initiation of nivolumab. It can be inferred that, since the luminal cancer was resected before ICI therapy, GI-targeted immunosuppression carried less of a risk of triggering cancer progression or tempering ICI response within the GI tract. Moreover, luminal cancer recurrence was not observed in our cohort within the study period. In addition to the eradication or reduction of the GI luminal tumor burden before ICI, the limited follow-up duration in our study may not allow adequate time for the negative impact of immunosuppressants to manifest. The outcomes of these cases present the possibility that removing the luminal cancer burden in selected patients in the context of GI irAEs could be a practical strategy to maximize treatment options and therapeutic benefit.

In cases of GI irAE refractory to routine selective immunosuppression, FMT may serve as an attractive therapeutic alternative. FMT has been well studied and shown high efficacy for the treatment of recurrent *Clostridioides difficile* infection [32]. Emerging data support its therapeutic benefit against ICI colitis, with efficacy reaching 73% among refractory cases [33]. Most interestingly, 2 prospective FMT clinical trials demonstrated an improved cancer response among melanoma patients who had previously not shown a response to ICI therapy and subsequently received FMT from melanoma responders [34,35]. Based on these studies, it has been hypothesized that FMT increases intra-tumoral immune activity by shifting microbiome composition toward taxa that respond to immunotherapy. Given its favorable safety profile in the existing literature, even in the immunocompromised patient population, and given its high efficacy in treating GI irAEs, FMT could be considered as an alternative treatment option for patients with GI luminal malignancies [36]. This option will not only abate the counteracting effect of immunosuppressants toward ICIs within the GI tract but also potentially benefit cancer response. Upcoming prospective FMT trials at MD Anderson Cancer Center will further assess its efficacy in treating ICI colitis and its impact on cancer response.

The current study had some limitations. First, it was a single-center retrospective study with a small sample size. Second, a small number of patients had prior surgical resection of the primary GI malignancy, which could also have been a confounding factor for the better outcomes that we observed. Third, only patients who received endoscopy evaluation for GI irAE were included in this study (2.4%), which could have led to selection bias for moderate-to-severe patients only, underestimating the real incidence of GI irAE among this population. Fourth, since many different cancer types were included in our study, primary vs. metastatic, we were not able to do subgroup analysis to further evaluate the outcome of GI irAE and cancer in each group. Fifth, variations in treatments for cancer and GI irAE may also have confounded our findings. Finally, given that some patients with GI malignancy received an ICI in clinical trials, the short follow-up duration could have contributed to the favorable outcome of our cohort.

In conclusion, GI irAEs occur in 2.4% of patients with cancer involving the luminal GI tract who receive ICI and who undergo

endoscopy evaluation. Lower GI tract irAEs are more prevalent and often respond well to immunosuppressant therapies. Vedolizumab combined with a short course of steroids is an effective treatment for severe GI irAEs, with high rates of clinical, endoscopic and histological remission. Additionally, treatment of GI irAEs with vedolizumab appears to be safe and not associated with further GI luminal cancer progression, recurrence, or subsequent poor response to ICI therapy. As ICI therapy continues to evolve, future studies with larger sample sizes are warranted to further delineate the utility of various irAE treatment options and their impact on cancer outcomes in this population.

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Summary Box

What is already known:

- The use of immune checkpoint inhibitors (ICI) is associated with gastrointestinal (GI) immune-related adverse events (irAE)
- Endoscopic and histological evaluation for GI irAE is critical in addition to assessment of clinical severity
- The treatment of GI irAE in patients with luminal GI malignancy involvement has not been well described

What the new findings are:

- Vedolizumab combined with a short course of steroids is an effective treatment for severe GI irAEs
- Treatment of GI irAEs with vedolizumab is relatively safe and not associated with further GI luminal cancer progression, recurrence, or subsequent poor response to ICI therapy

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Supplementary material

Supplementary Table 1 Characteristics of GI irAE immunosuppressive vs. non-immunosuppressive treatment groups

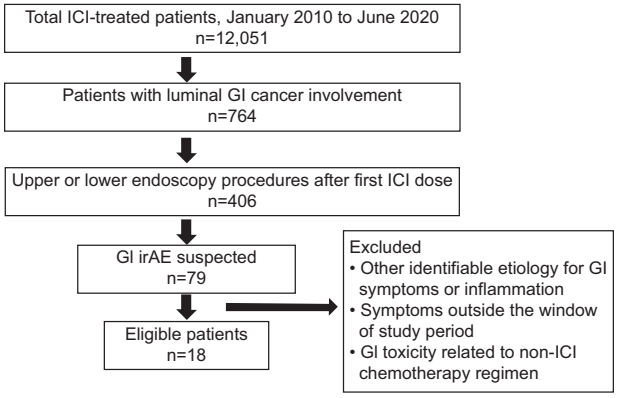
	IMS[a] no. (%), n=10	Non-IMS, no. (%), n=8
Primary malignancy type		
Adenocarcinoma only	4 (40)	6 (75)
Squamous	1 (10)	0
Neuroendocrine	1 (10)	2 (25)
Melanoma metastasis only	3 (30)	0
Concomitant adenocarcinoma and melanoma	1 (10)	0
Malignancy location		
Esophageal	4 (40)	2 (25)
Stomach	1 (10)	1 (12)
Duodenum	0	2 (25)
Jejunum	0	2 (25)
Colon	3 (30)	0
Rectum	2 (20)	0
Jejunum + ileum + colon	0	1 (12)
Prior surgical removal of primary malignancy	2 (20)	2 (25)
ICI type		
PD-1/L1[b]	3 (30)	7 (88)
CTLA-4 + PD-1/L1 Combined[c]	7 (70)	1 (12)
irAE location		
Isolated gastritis	0	4 (50)
Isolated enteritis	0	1 (12)
Isolated colitis	5 (50)	3 (38)
Gastroenteritis	1 (10)	0
Enterocolitis	4 (40)	0
irAE clinical presentation		
Diarrhea only	6 (60)	2 (25)
Diarrhea with other symptoms	4 (40)	2 (25)
Symptoms other than diarrhea only	0	3 (38)
Asymptomatic	0	1 (12)
Endoscopic presentation		
Normal	2 (20)	1 (12)
Non-ulcerative inflammation	5 (50)	5 (63)
Ulcerative inflammation	3 (30)	2 (25)
Histologic features		
Acute inflammation	1 (10)	2 (25)
Chronic inflammation	1 (10)	3 (38)
Acute + chronic inflammation	8 (80)	1 (12)
No histologic inflammation	0	2 (25)
irAE outcomes		
Clinical remission	10 (100)	8 (100)
Cancer status at time of GI irAE		
Remission or response	5 (50)	2 (25)
Stable	2 (20)	5 (63)
GI luminal progression	2 (20)	0
Extra-luminal progression	1 (10)	1 (12)
Resumed ICI after resolution of GI irAE	3 (30)	3 (38)

[a]Steroids, infliximab/vedolizumab/combination, or both

[b]PD-1/L1 include pembrolizumab, nivolumab, and atezolizumab

[c]Ipilimumab with nivolumab

GI irAE, gastrointestinal immune-related adverse event; ICI, immune checkpoint inhibitor; IMS, immunosuppressant; PD-1/L1, programmed death 1/programmed death 1 ligand; CTLA-4, cytotoxic T lymphocyte-associated antigen 4



Supplementary Figure 1 Patient selection flowchart
ICI, immune checkpoint inhibitor; GI, gastrointestinal; GI irAE, gastrointestinal immune-related adverse event

Supplementary Table 2 GI irAE characteristics based on anatomical location

Characteristics	Isolated gastritis no. (%), n=4	Isolated enteritis no. (%), n=1	Isolated colitis no. (%), n=8	Gastroenteritis no. (%), n=1	Enterocolitis no. (%), n=4
ICI type					
PD-1/L1	4 (100)	0	4 (50)	0	2 (50)
CTLA-4 + PD-1/L1 combined	0	1 (100)	4 (50)	1 (100)	2 (50)
Endoscopic presentation					
Normal	2 (50)	0	2 (25)	0	0
Non-ulcerative inflammation	1 (25)	0	5 (63)	1 (100)	2 (50)
Ulcerative inflammation	1 (25)	1 (100)	1 (12)	0	2 (50)
Histologic features					
Acute inflammation	1 (25)	0	1 (12)	0	1 (25)
Chronic inflammation	1 (25)	0	2 (25)	0	0
Acute + chronic inflammation	0	1 (100)	4 (50)	1 (100)	3 (75)
No histologic inflammation	2 (50)	0	1 (12)	0	0

GI irAE, gastrointestinal immune-related adverse event; PD-1/L1, programmed death 1/programmed death 1 ligand; CTLA-4, cytotoxic T lymphocyte-associated antigen 4