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## Immune checkpoint inhibitor-mediated colitis in gastrointestinal malignancies and inflammatory bowel disease

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### Abstract

Immune checkpoint inhibitors (ICI) have markedly changed the landscape of cancer therapy. By re-invigorating the immune system against tumors, ICI provide novel therapeutic options for a broad variety of malignancies, including many gastrointestinal (GI) cancers. However, these therapies can also induce autoimmune-like side effects in healthy tissue across the body. One of the most common of these side effects is ICI-mediated colitis and diarrhea (IMC). Here, we review the incidence and risk of IMC in ICI therapy, with a focus on what is known regarding IMC in patients with GI malignancies. We also discuss data available on the use of ICI and risk of IMC in patients with pre-existing inflammatory bowel disease, as these patients may have increased risk of IMC due to their underlying intestinal pathology.

**Key Words:** Immune checkpoint inhibitors; Cytotoxic T-lymphocyte antigen 4; Programmed cell death protein-1; Inflammatory bowel disease; Gastrointestinal cancer

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**Core Tip:** Immune checkpoint inhibitor-mediated colitis and diarrhea (IMC) is a common immune-related adverse event with immune checkpoint inhibitor (ICI) therapy. The risk of IMC is most strongly associated with type of ICI used, but race, malignancy, and vitamin D use may also contribute to the risk of developing IMC. IMC incidence in gastrointestinal cancers appears comparable to other malignancies, but this is hampered by lack of a consistent definition for IMC and confounding by

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contemporaneous chemotherapy. Although patients with inflammatory bowel disease (IBD) are often excluded from treatment with ICI, available data suggest that they have increased risk of diarrhea and/or colitis compared to patients without IBD.

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## INTRODUCTION

### *Mechanisms of immune checkpoint blockade and use in cancer therapy*

Immune checkpoint inhibitors (ICIs) are powerful novel therapies against a variety of solid and hematologic malignancies. Since the approval of the first ICI in 2011, they have become first-line options for some metastatic malignancies, such as melanoma, and are now approved as second- and third-line options for many other cancers, including gastrointestinal (GI) malignancies[1,2]. These drugs target and block inhibitory molecules on the surface of leukocytes to induce a potent T cell anti-tumor response, ideally leading to tumor regression[3-5].

T cell activation, whether for anti-tumor immunity or to mount a response to infection, requires not only stimulation through the T cell receptor (TCR), but also co-stimulation from B7-1 (CD80) and B7-2 (CD86) molecules on antigen presenting cells [6]. These molecules bind to CD28 on the T lymphocyte and act as a necessary second signal (signal 2) to mount an adaptive immune response. However, cytotoxic T lymphocyte-associated protein-4 (CTLA-4) expression on T cells can block signal 2, due to its higher affinity for B7-1/B7-2[7-9]. As a result, peripheral immune tolerance is induced.

Another mechanism of peripheral immune tolerance is through the programmed cell death-1 (PD-1)/programmed cell death ligand-1 (PD-L1) pathway. Binding of PD-1 on the T cell membrane to PD-L1 on antigen presenting cells is thought to attenuate TCR signaling[10]. It is possible that PD-1/PD-L1 engagement may also lead to decreased signaling through CD28, and decrease activation of signal 2 as CTLA-4 does [11]. This pathway is thereby a distinct mechanism from CTLA-4 signaling which promotes immune tolerance. Blockade of either (or both) of these pathways can therefore lead to an upregulated immune response, particularly against tumors which can express neo-antigens and provide ample targets for T cells[1,12].

All of the currently Food and Drug Administration (FDA)-approved ICI target molecules within one of these two pathways. The earliest ICI to be approved was ipilimumab, an antibody targeting CTLA-4, for the treatment of metastatic melanoma in 2011[2]. In 2014 FDA approval was extended to two antibodies which target PD-L1, nivolumab and pembrolizumab[2]. Atezolizumab, in a third class of ICI which targets PD-L1, was approved for urothelial carcinoma in 2016[2]. A variety of ICI are now approved for a broad spectrum of malignancies, from renal cell carcinoma (RCC) to non-small cell lung cancer (NSCLC) to Hodgkin lymphoma. ICI are approved for GI malignancies as well, including nivolumab for hepatocellular carcinoma (HCC) and pembrolizumab for gastric and gastroesophageal junction (GEJ) carcinoma[2].

### *Immune-related adverse events with ICI*

Despite the promising benefits of ICI therapy, patients frequently develop autoimmune-like effects, termed immune-related adverse events (irAE), likely due to overall non-antigen specific activation of the immune system following checkpoint blockade. These irAE can affect any organ system, causing autoimmune diseases ranging from vitiligo to hypophysitis to colitis[13].

The specific mechanisms of irAE remain unclear, but are thought to be related to removal of key peripheral tolerance pathways normally maintained by immune checkpoints, resulting in inflammation in several non-tumor tissues[13]. Some studies have speculated that anti-PD-1 treatment may modulate humoral immunity to enhance pre-existing anti-thyroid antibodies, in the case of ICI-induced hypothyroidism[14]. In a report from one patient with myocarditis, similar T cell clones

were found in myocardium and tumor[15]. In addition, the rate of vitiligo in patients treated with ICI for melanoma is higher compared to other tumor types[16]. These findings suggest that there may be cross-reactivity between tumor antigens and self-antigens that arises when immune checkpoints are removed.

Beyond cross-reactivity of antigens, there is some evidence that in the colon immune checkpoint blockade may shift the balance of regulatory T cells, responsible for peripheral immune tolerance, and Th17 cells, which produce interleukin (IL)-17 that can drive inflammation. For example, one study has found increased serum IL-17 in patients with colitis due to ICI[17]. In mouse models, administration of recombinant PD-L1 protein decreases the number of IL-17-producing cells in the colon and ameliorates colitis[18]. Meanwhile, mutations in the *Ctla4* gene in both humans and mice are associated with colitis[19]. Overall, it is currently speculated that loss of CTLA-4 and/or PD-1 may lead to decrease activation of regulatory T cells and increased activation of effector T cells, leading to unchecked inflammation in the colon and elsewhere[20].

Cytotoxic CD8+ T cells may also play a role in the development of ICI-mediated colitis and diarrhea (IMC). A recent analysis of single-cell RNA sequences from patients with IMC revealed that tissue resident memory CD8+ T were more likely to have expanded into inflammatory populations within colon tissue compared to patients without IMC[21]. These findings suggest that activation or alteration of CD8+ T cell populations may also be a potential mechanism of colitis due to checkpoint inhibitors.

Clinically, the severity of irAE can be highly variable, and is typically evaluated using the common terminology criteria for adverse events (CTCAE), which ranges from minimal symptoms or lab abnormalities at grade 1 to death of the patient at grade 5[22]. For GI irAE, specifically colitis, symptoms range from loose stools fewer than four per day above baseline, to ileus, perforation, or death[22]. The grading scheme for colitis is outlined in Table 1.

In this review, we discuss the development of diarrhea and colitis in patients treated with ICI, the emerging use of ICI for GI malignancies, and the data available on the occurrence of diarrhea and colitis in patients treated with ICI for GI malignancies. We also review currently available data on the use of ICI in patients with underlying inflammatory bowel disease (IBD), given the potential increased risk of GI irAE in these patients.

## IMC

### **Incidence of IMC**

One of the most common irAE following ICI use is IMC. Early clinical data on the use of ipilimumab, the most commonly used anti-CTLA-4 antibody, indicated that colitis was the most prevalent high grade (grade 3 or 4) irAE among patients with melanoma and RCC[23]. In this cohort, 24 of 137 (18%) of patients with melanoma and 17 of 61 (28%) of patients with RCC developed grade 3-4 colitis.

Following FDA approval for ipilimumab in 2011[2] as well as the introduction of anti-PD-1 and anti-PD-L1 agents, several retrospective cohort studies and meta-analyses have evaluated the frequency of IMC (Table 2). Overall, the rate of IMC (including both diarrhea and colitis) has been reported as 35-40% with anti-CTLA-4, 11%-17% with anti-PD-1, and 32% with a combination of both classes[24]. In the published meta-analyses of IMC which distinguish between diarrhea and colitis, the rates of diarrhea in patients treated with ICI are substantially higher than colitis. For example, Khoja *et al*[25] found that diarrhea occurred in 30.2% of patients treated with anti-CTLA-4, 12.1% with anti-PD-1, and 7.3% with anti-PD-L1. Colitis was less common than diarrhea in these patients, occurring at a rate of 5.7% with anti-CTLA-4, 0.7% with anti-PD-1, and 0% with anti-PD-L1. These findings also demonstrate that rates of IMC, inclusive of both diarrhea and colitis, are substantially more common with anti-CTLA-4 use compared to anti-PD-1 or anti-PD-L1.

Another study by Soularue *et al*[26] found that diarrhea due to anti-CTLA-4 treatment occurred in 30.2%-35.4% of patients *vs* 12.1%-13.7% of patients treated with anti-PD-1, while 5.7%-9.1% of patients treated with anti-CTLA-4 and 0.7%-1.6% of patients treated with anti-PD-1 developed colitis. A third study also found that diarrhea occurred in 35.4% of patients treated with anti-CTLA-4 compared to 13.7% of patients treated with anti-PD-1, with an overall relative risk (RR) of 0.58 [95% confidence interval (CI): 0.43-0.77] for diarrhea with anti-PD-1 treatment *vs* anti-CTLA-4[27]. In this study, colitis occurred in 11% of patients treated with anti-CTLA-4 and

Table 1 Common terminology criteria for adverse events

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

2% of patients treated with anti-PD-1, with an RR of 0.16 (95%CI: 0.05-0.51) for anti-PD-1 *vs* anti-CTLA-4. Another study by Komaki *et al*[28] also found an increased risk for colitis in patients treated with anti-CTLA-4, with 8.4% of patients treated with anti-CTLA-4 developing colitis (RR 11.39 compared to standard chemotherapy, 95%CI: 6.3-20.59), while only 0.87% of patients treated with anti-PD-1 developed colitis, which was not significantly higher than standard chemotherapy (RR 2.49, 95%CI: 0.49-12.68) [28]. Interestingly, although the risk of developing diarrhea with anti-CTLA-4 treatment was significantly higher compared to standard chemotherapy and occurred in 40% of patients treated with anti-CTLA-4 (RR 2.10, 95%CI: 1.62-2.73), only 10.7% of patients treated with anti-PD-1 or anti-PD-L1 developed diarrhea; the risk of diarrhea in these patients was significantly lower compared to standard chemotherapy (RR 0.64, 95%CI: 0.42-0.98).

The finding that patients treated with anti-CTLA-4 experience significantly higher rates of IMC *vs* anti-PD-1 or anti-PD-L1 treatment is consistent across the aforementioned studies as well as others. A study by Wang *et al*[29] found that while overall the rate of colitis in patients treated with any ICI was 2.4%, the rate was 9.1% in patients treated with anti-CTLA-4 *vs* 1.4% for anti-PD-1 and 1.0% for anti-PD-L1. In another study, in which the overall rate of colitis was 2.3% across all ICI, the RR of colitis with anti-CTLA-4 use *vs* anti-PD-1/anti-PD-L1 use was higher, although it did not reach statistical significance ( $P = 0.054$ )[30]. Specifically, these authors found a RR of 11.3 (95%CI 6.05-21.1) for anti-CTLA-4 and 3.36 (95%CI: 1.36-8.33) with anti-PD-1/anti-PD-L1 compared to chemotherapy. However, in this study the rate of severe colitis (grade 3 or higher) was significantly increased ( $P = 0.021$ ) with anti-CTLA-4 treatment, with a RR of 22.5 (95%CI: 6.37-79.4) *vs* chemotherapy, compared to RR of 2.47 (95%CI: 0.9-6.72) with anti-PD-1/anti-PD-L1.

These studies and others have also examined the incidence of IMC in patients treated with combination therapy (anti-CTLA-4 plus anti-PD-1). Some work has suggested that the rate of IMC in combination therapy may be higher than in either class of ICI alone. For example, Wang *et al*[29] found that the rate of colitis was 13.6% in combination therapy compared to 9.1% with anti-CTLA-4 and 1%-1.4% for anti-PD-1/anti-PD-L1, as above. Similarly, Tandon *et al*[27] found that combination therapy was associated with diarrhea in 44.2% of patients and colitis in 14.5% of patients, *vs* 35.4% and 11.0% for diarrhea and colitis, respectively, in anti-CTLA-4 monotherapy and 13.7% and 2% in anti-PD-1 monotherapy[27]. However, these differences reached significance only for diarrhea in patients treated with combination therapy *vs* anti-CTLA-4 alone (RR 1.31, 95%CI: 1.09-1.57). Zhang *et al*[31] evaluated the incidence of irAE, including IMC, in patients treated with combination nivolumab and ipilimumab, *vs* either of these agents alone. They found that the overall incidence of diarrhea was 32.7%, with a RR of 1.95 for combination therapy *vs* monotherapy (95%CI: 1.54-2.46). Similarly, the rate of colitis overall was 14.2% but was again significantly increased in combination therapy compared to monotherapy (RR 4.45, 95%CI: 3.04-6.51). Overall, these studies suggest that the rate of IMC, particularly diarrhea, may be higher in patients treated with combination ICI therapy *vs* a single ICI agent.

In addition to evaluating different classes and combinations of ICI, two meta-analyses have also specifically evaluated the rates of IMC for anti-PD-1 and anti-PD-L1 therapies. Baxi *et al* found the overall rate of colitis to be 0.7% across all anti-PD-1 and anti-PD-L1, with a RR of 2.88 *vs* non-ICI therapies (95%CI: 1.3-6.37)[32]. This included a rate of 1.1% in pembrolizumab, 0.3% in nivolumab, and 0.5% in atezolizumab. Although the incidence of diarrhea was 18.5% with these agents, it was not significantly different than patients treated with standard therapy (RR 0.78, 95%CI: 0.57-1.05). A second meta-analysis by Wang *et al*[33] similarly found that the incidence

Table 2 Meta-analyses of immune checkpoint inhibitor-mediated colitis and diarrhea with immune checkpoint inhibitor use

Meta-analysis	No. of studies	ICI targets	Malignancies	GI malignancy	Trial Phase	Diarrhea (incidence, %)			Colitis (incidence, %)						
Ref.						Total	Anti-CTLA-4	Combo <sup>1</sup>	Anti-PD-1	Anti-PD-L1	Total	Anti-CTLA-4	Combo <sup>1</sup>	Anti-PD-1	Anti-PD-L1
Khoja <i>et al</i> [25], 2017	48	CTLA-4	Melanoma	Colorectal	1-3		30.2		12.1	7.3		5.7		0.7	0.0
		PD-1	Solid tumors	GEJ											
		PD-L1		Liver											
				Pancreas											
Wang <i>et al</i> [29], 2017	34	CTLA-4	Melanoma	None	1-3		7.9 <sup>2</sup>	9.2 <sup>2</sup>	1.3 <sup>2</sup>	0.3 <sup>2</sup>	2.4	9.1	13.6	1.4	1.0
		Combination <sup>†</sup>	Solid tumors												
		PD-1													
		PD-L1													
De Velasco <i>et al</i> [30], 2017	21	CTLA-4	Melanoma	None	2-3						2.3				
		PD-1	Solid tumors												
		PD-L1													
Wang <i>et al</i> [33], 2017	46	PD-1	Melanoma	Colorectal	1-3	4-13					1.0				
		PD-L1	Solid tumors	Gastric											
			Hematologic												
Zhang <i>et al</i> [31], 2018	11	CTLA-4	Melanoma	None	1-3		17 <sup>3</sup>	32.7	17 <sup>3</sup>			2.9 <sup>3</sup>	14.2	2.9 <sup>3</sup>	
		Combination <sup>†</sup>	Sarcoma												
		PD-1	Solid tumors												
Tandon <i>et al</i> [27], 2018	18	CTLA-4	Melanoma	None	1-3		35.4	44.2	13.7			11.0	14.5	2.0	
		Combination <sup>†</sup>													

Baxi <i>et al</i> [32], 2018	13	PD-1										
		PD-1	Melanoma	None	2-3				0.7		0.3-1.1	0.5
Komaki <i>et al</i> [28], 2018	22	PD-L1	Solid tumors									
		CTLA-4	Melanoma	None	2-3	40.0		9.9	10.7	8.4	0.9	
		PD-1	Solid tumors									
Bishay <i>et al</i> [34], 2020	27	PD-L1										
		Combination <sup>1</sup>	NSCLC	None	1-3		13.2-40.4	9.1	11.0		7.3-12.1	0.9
		PD-1										
Yang <i>et al</i> [35], 2020	10	PD-L1										
		CTLA-4	Melanoma	None	2-3	31.5		30.0	7.6	5.8	2.3	
		PD-1	NSCLC									
Yao <i>et al</i> [36], 2020	40	PD-L1	Breast									
		CTLA-4	Melanoma	Colorectal	2-3					8.1	14.5	1.4 <sup>4</sup>
		Combination <sup>1</sup>	Solid tumors	Gastric/GEJ								1.4 <sup>4</sup>
		PD-1		HCC								
		PD-L1										

<sup>1</sup>Combination anti-cytotoxic T-lymphocyte antigen 4 plus anti-programmed cell death protein-1.

<sup>2</sup>Grade 3-4 diarrhea only.

<sup>3</sup>Did not distinguish between monotherapy with ipilimumab or nivolumab.

<sup>4</sup>Combined incidence with programmed cell death protein-1 and programmed cell death-ligand 1.

ICI: Immune checkpoint inhibitor; IMC: Immune checkpoint inhibitor-mediated colitis and diarrhea; CTLA-4: Cytotoxic T-lymphocyte antigen 4; PD-1: Programmed cell death protein-1; PD-L1: Programmed cell death-ligand 1; GEJ: Gastroesophageal junction; NSCLC: Non-small cell lung cancer; HCC: Hepatocellular carcinoma.

of colitis in patients across all anti-PD-1 and anti-PD-L1 was approximately 1%. Interestingly, while rates of diarrhea were similar with nivolumab at 10%-13%, the incidence of diarrhea was much lower with pembrolizumab, at less than 4%. These findings along with the work above suggest that while colitis seems to be significantly more prevalent in patients treated with anti-PD-1 or anti-PD-L1 compared to chemotherapy, rates of diarrhea may not be significantly higher[28,32].

In addition to the above meta-analyses, three new studies have also examined the rates of IMC in patients treated with a variety of ICI. In a meta-analysis of IMC in patients with NSCLC, Bishay *et al*[34] found that the rate of diarrhea was 40.4% in patients treated with a combination of anti-CTLA-4 and anti-PD-L1, 13.2% in patients treated with combination anti-CTLA-4 and anti-PD-1, 11.0% in patients treated with anti-PD-L1 alone, and 9.1% in patients treated with anti-PD-1 alone[34]. The risk of diarrhea in patients treated with combination therapy was higher than with anti-PD-1 monotherapy, with a RR of 1.51 (95% CI: 1.11-2.06). Although the RR of colitis in these patients was not compared directly, the incidence of colitis was higher in combination therapy (7.3%-12.1%) *vs* anti-PD-1/anti-PD-L1 monotherapy (0.4%-0.9%). A second new study compared the rates of GI irAE in patients treated with ICI and chemotherapy *vs* chemotherapy alone across a variety of malignancies, and also found an increased risk of diarrhea and colitis[35]. As prior studies have shown, treatment with anti-CTLA-4 was associated with a significant risk of diarrhea (RR 2.23, 95% CI: 1.9-2.63) and colitis (RR 28.39, 95% CI: 5.59-144.24) compared to chemotherapy alone, with an incidence of 31.4% and 5.8% for diarrhea and colitis, respectively. Interestingly, this study found that the risk of diarrhea in anti-PD-1 treatment was significantly higher than with chemotherapy, with an incidence of 30% and a RR of 1.38 (95% CI: 1.13-1.68), although the risk with anti-PD-L1 was not higher (RR 0.82, 95% CI: 0.43-1.59). As suggested by prior work, although the incidence of colitis with anti-PD-1 was low at 2.3%, this was still significantly increased over the risk of colitis with chemotherapy alone (RR 2.9, 95% CI: 1.02-8.21). Finally, Yao *et al*[36] found that the risk of colitis with either anti-CTLA-4 or anti-PD-1/PD-L1 was significantly increased compared to placebo, chemotherapy, or targeted therapy, except for anti-PD-1/PD-L1 *vs* targeted therapy (RR 0.89, 95% CI: 0.06-13.98). While the risk of colitis with combination therapy was significantly increased compared to treatment with anti-PD-1/PD-L1 alone (RR 9.25, 95% CI: 3.34-25.64), the risk was not significantly higher compared to treatment with anti-CTLA-4 alone (RR 1.16, 95% CI: 0.79-1.70).

Based on these studies, the incidence of diarrhea with ICI treatment spans 4%-30% for anti-PD-1/PD-L1, 30.2%-40% for anti-CTLA-4, and 13.2%-44.2% for combination therapy. The incidence of colitis appears to be 0%-2.3% for anti-PD-1/PD-L1, 5.7%-11% for anti-CTLA-4, and 7.3%-14.5% for combination therapy. Rates of diarrhea are consistently higher than rates of colitis across all classes of ICI in these studies. In general, the risk of IMC (both diarrhea and colitis) is higher with anti-CTLA-4 or combination therapy compared to anti-PD-1/PD-L1, but the data are mixed regarding whether IMC risk is higher in combination compared to anti-CTLA-4 monotherapy or whether risk is similar with both treatments. For the most part, rates of colitis are greater with any ICI compared to chemotherapy, with the exception of the one study above which did not find a significantly increased rate of colitis with anti-PD-1[28]. However, findings are mixed for the incidence of diarrhea following ICI compared to chemotherapy, which may be significantly higher with anti-CTLA-4 or combination therapy but possibly similar or even lower for anti-PD-1/PD-L1.

Unfortunately, most clinical studies focused on safety and use of ICI have not included information on endoscopy in those patients who develop diarrhea or colitis. As noted in multiple meta-analyses of IMC which incorporate these studies, lack of information on endoscopy is a significant limitation on accurate estimates of the rate of IMC[27,36]. As the CTCAE for diarrhea and colitis does not require endoscopic assessment (Table 1), it is probable that many of these patients do not undergo endoscopy to confirm diagnosis of IMC[22].

In cohort studies focused on IMC, patients were more likely to be included only if they had endoscopic and/or histologic confirmation of colonic inflammation. Across thirteen cohort studies of IMC, encompassing 863 patients, 626 (72.5%) underwent endoscopy to confirm the diagnosis, ranging from 40%-100% of patients within each study[23,37-48]. However, because patients with symptoms of IMC but without endoscopy were frequently excluded from these studies, the ability to extract information on IMC incidence from this literature is limited.

### **Risk factors for developing IMC**

Overall, the aforementioned meta-analyses have suggested that a major risk factor for development of IMC is the type of ICI used, and whether multiple types of ICI are used in combination. Several retrospective cohort studies have been performed to identify other clinical factors which may contribute to the development of IMC (Table 3). One such factor is likely to be the dose of ICI, at least for anti-CTLA-4. Two studies have shown that a higher dose of ipilimumab (10 mg/kg *vs* 3 mg/kg) is associated with a significant increase in risk of colitis (RR 1.83-2.01)[49,50]. In contrast, higher doses of anti-PD-1 and anti-PD-L1 do not seem to be significantly associated with increased

**Table 3 Risk factors for immune checkpoint inhibitor-mediated colitis and diarrhea**

Ref.	Number of patients	ICI targets	Malignancies	GI malignancies	Risk factors for IMC	OR or RR	95%CI	Fisher's exact <i>P</i> value
Wolchok <i>et al</i> [49], 2010	217	CTLA-4	Melanoma	None	High dose ipilimumab	2.01	0.52-7.82	
Ascierto <i>et al</i> [50], 2017	727	CTLA-4	Melanoma	None	High dose ipilimumab	1.83	1.07-0.14	
Wang <i>et al</i> [46], 2018	327	CTLA-4	Melanoma	None	Race (Caucasian)	5.76	2.03-16.36	
		Combination <sup>1</sup>	Solid tumors		Cancer stage IV <i>vs</i> stage III	0.09	0.03-0.30	
		PD-1	Hematologic		Melanoma	1.96	1.04-3.67	
		PD-L1			Ipilimumab or combination <sup>1</sup>	2.23	1.03-4.81	
Abu-Sbeih <i>et al</i> [53], 2019	346	CTLA-4	Melanoma	None	Race (Caucasian)	NA	NA	0.023
		Combination <sup>1</sup>			Lower mean lactate dehydrogenase	NA	NA	0.011
		PD-1						
		PD-L1						
Grover <i>et al</i> [40], 2020	213	CTLA-4	Melanoma	None	Combination <sup>1</sup> <i>vs</i> pembrolizumab	3.34	1.1-9.8	
		Combination <sup>1</sup>			CTLA-4 <i>vs</i> PD-1	7.14	2.2-25.0	
		PD-1			Neutrophil-to-lymphocyte ratio $\geq 5$	0.34	0.1-0.9	
					Vitamin D intake	0.35	0.1-0.9	0.03
					Pneumococcal pneumonia vaccine	NA	NA	0.05
					Influenza or pneumonia vaccine	NA	NA	0.05

<sup>1</sup>Combination anti- cytotoxic T-lymphocyte antigen 4 plus anti-programmed cell death protein-1.

ICI: Immune checkpoint inhibitor; IMC: Immune checkpoint inhibitor-mediated colitis and diarrhea; CTLA-4: Cytotoxic T-lymphocyte antigen 4; PD-1: Programmed cell death protein-1; PD-L1: Programmed cell death-ligand 1; OR: Odds ratio; RR: Relative risk; CI: Confidence interval; NA: Not available.

risk of IMC[51,52].

Beyond dose of ICI, several studies have identified additional factors which may be associated with development of IMC. One retrospective cohort study found that across a variety of malignancies treated with ICI, white race, melanoma (versus solid tumors or hematologic malignancies), and stage 3 (versus stage 4) tumors were associated with increased risk of IMC[46]. In concordance with the meta-analyses previously reviewed, this study also found that the use of ipilimumab was significantly associated with IMC. Interestingly, they also found that diarrhea was significantly ( $P < 0.001$ ) associated with increased overall survival (OS) within their cohort. A later study at the same institution, evaluating only patients with melanoma, similarly found that development of IMC was associated with improved OS [hazard ratio (HR) 0.53, 95%CI: 0.37-0.76] and progression-free survival (PFS) (HR 0.53, 95%CI: 0.36-0.78)[53]. As in the previous study, those who developed IMC were significantly ( $P = 0.023$ ) more likely to be white. This study also found that a lower serum lactate dehydrogenase was associated with increased risk of IMC (536 IU/L *vs* 582 IU/L,  $P = 0.011$ ). Another study performed a retrospective analysis of irAE reported to the FDA, and found that while the incidence of IMC was higher with combination ICI *vs* anti-PD-1 monotherapy, the incidence of IMC in patients treated with anti-CTLA-4 alone was higher[54]. In this study, there was also a slight predilection for male over female patients to develop IMC, as 53.5% of patients with IMC were male, *vs* 33.2% female and 13.3% unknown. A study by Shah *et al* suggested that age may be related to risk of different irAE; within this cohort of melanoma patients treated with anti-PD-1, the authors found colitis in patients with a significantly lower median age (64 years)

compared to pneumonitis (median age 66) and myocarditis (median age 69)[55]. Finally, a recent study found that vitamin D supplementation at the time of ICI initiation was associated with a lower risk of IMC in melanoma patients [odds ratio (OR) 0.35, 95%CI: 0.1-0.9][40]. This study similarly showed that use of anti-CTLA-4 or combination ICI was associated with a significantly higher rate of IMC *vs* anti-PD-1 monotherapy. Interestingly, another factor which seemed to be significantly associated with IMC was receiving the pneumococcal pneumonia vaccine within 3 mo prior to starting ICI, as 35.1% of patients who developed IMC received this vaccine *vs* only 19.9% of patients who did not develop IMC ( $P = 0.05$ ). Overall, these studies suggest that while type of ICI is one of the strongest predictive factors for development of IMC, primary malignancy, race, sex, age, vitamin D supplementation, pneumococcal pneumonia vaccine exposure, and potentially other factors may contribute to the risk of IMC.

### Diagnosis and management of IMC

The diagnostic evaluation and treatment of IMC has recently been reviewed and an in-depth analysis is beyond the scope of this discussion[56-58]. In brief, the diagnosis of IMC begins with an assessment of symptoms (Table 1), followed by evaluation to rule out other causes of diarrhea and colitis, including infection and ischemia. Typically, endoscopic evaluation (either a colonoscopy or flexible sigmoidoscopy) is recommended to directly evaluate for both overt and microscopic colitis (via biopsy) for grade 2 or higher IMC.

Several guidelines from both Oncology and Gastroenterology societies have recently emerged to direct therapy of IMC[57-61]. For grade 1 diarrhea and/or colitis, supportive therapy is recommended, including anti-diarrheal medications, dietary modifications, and hydration. For higher grade IMC, many guidelines recommend temporary cessation of ICI and treatment with steroids, which appears to be effective in 87.5% of patients[37]. Permanent discontinuation of anti-CTLA-4 is recommended with grade 3 IMC, and discontinuation of all ICI is recommended for grade 4 colitis[58,62].

If a patient does not respond to steroids in 2-3 d, current recommendations are to advance to an anti-inflammatory biologic, typically the anti-tumor necrosis factor antibody infliximab[56-58]. The anti-integrin antibody vedolizumab is emerging as an alternative to infliximab, particularly in those with concomitant hepatitis who should not receive infliximab[57,63,64]. There are also case reports of the use of the small molecule Janus kinase inhibitor tofacitinib[65] and fecal microbiota transplantation[66] in IMC refractory to the above therapeutic options. Finally, case reports have suggested that budesonide may be an option for treatment of microscopic colitis due to ICI[67].

Emerging data from recent studies may help guide initial evaluation of IMC as well as options for management. One case series found that of eleven patients referred to their center for diarrhea and concern for IMC, the seven patients with endoscopic evidence of IMC had significantly higher episodes of diarrhea per day (7.7 times *vs* 3.0 times per day), suggesting that number of bowel movements per day may be a useful tool for screening patients who may have immune-mediated colitis *vs* other causes of diarrhea[48]. Another recent case series of eight patients found that on colonoscopy, three had findings predominantly in the right colon[41], suggesting that a full colonoscopy may be important for endoscopic evaluation and diagnosis of IMC, even though it has previously been suggested that inflammation is typically contiguous beginning in the rectum and therefore flexible sigmoidoscopy would be sufficient for the diagnosis of IMC[43].

In addition to advances in diagnosis, several studies have examined treatment response and outcomes in IMC. One recent retrospective cohort study evaluated outcomes in IMC due to treatment with anti-PD-1 monotherapy *vs* combination therapy in melanoma[47]. As several prior studies have found, the incidence of IMC was much lower with monotherapy compared to combination immunotherapy (3% *vs* 24%). Furthermore, patients treated with combination therapy developed IMC substantially faster compared to monotherapy, at a median of 7.2 wk following first ICI infusion with combination therapy (range 0.7-51 wk) and a median of 25.4 wk with monotherapy (range 0.6-119.9 wk). Finally, steroid duration and maximum dose were significantly lower in patients who received anti-PD-1 alone, with a median of four weeks *vs* six weeks for combination therapy ( $P = 0.0065$ ) and 1 mg/kg prednisone equivalents *vs* 1.5 mg/kg in combination therapy ( $P = 0.0015$ ). Another recent retrospective study of melanoma patients found that high-grade IMC (grade 3-4) was associated with an increased risk of steroid-associated side effects, such as infection or mood changes, possibly due to a need for increased steroid dose or duration in these patients[38]. A case series of nine patients treated with anti-PD-1 for solid tumors

noted that two of these patients developed a relapse of symptoms when steroids were tapered, while one developed secondary cytomegalovirus colitis, and two eventually required infliximab after failure of steroid treatment[44]. Overall, these findings suggest that combination anti-CTLA-4/anti-PD-1 therapy as well as more severe IMC on initial presentation may require prolonged or higher-dose steroid treatment, which in turn may be associated with more severe side effects from steroid use.

Reports to date suggest that early decisions on escalation of IMC treatment beyond steroids may lead to better outcomes for patients. However, very little data exist regarding this issue. A retrospective study found that a higher endoscopic severity score, presence of ulcers, and pancolitis was associated with a greater likelihood of escalation to infliximab therapy, suggesting that endoscopic appearance may be a helpful predictive tool for determining early biologic therapy[39]. A second retrospective study on patients admitted to the hospital for IMC management found that 50% of these patients required second-line therapy, predominantly infliximab[42]. Within this cohort, the need for treatment escalation was significantly associated with the use of ipilimumab ( $P = 0.010$ ), stage III tumors ( $P = 0.011$ ), absence of GI metastases ( $P = 0.028$ ), hypoalbuminemia ( $P = 0.005$ ), relative lymphopenia ( $P = 0.027$ ), and decreased LDH ( $P = 0.026$ ). Therefore, patients with these clinical characteristics and laboratory findings may benefit from earlier or even up-front treatment with a biologic. Ongoing prospective studies are currently underway to evaluate whether this may apply to certain patients with IMC (NCT04407247)[57].

## ICIS AND IMC IN GI MALIGNANCY

Despite the abundance of retrospective studies on IMC, only a few have included data on patients with GI malignancies. This limitation is likely due to the relatively recent approval of ICI for GI malignancies. In 2017, the FDA approved the use of anti-PD-1 therapies in gastric and GEJ cancers and HCC[2]. That same year, the FDA also approved the use of ICI for cancers with high levels of microsatellite instability (MSI-H)[68]. The rationale behind this approval was that MSI-H is believed to increase mutational rates within the tumor, which in turn leads to an increase in the type and abundance of tumor neoantigens which provide novel targets for CD8-positive anti-tumor T cells and other components of the immune system[1]. This type of anti-tumor immunity is boosted by the use of ICI, and therefore may lead to a stronger response to ICI. In other words, MSI-H tumors, including GI cancers, are likely to be more susceptible targets for ICI therapy compared to tumors that do not have substantial MSI-H.

With approval of ICI for these tumors, more recent studies on IMC have included patients with GI malignancies. Of the meta-analyses discussed above, only two included studies in patients with GI cancers[33,36]. Muro *et al*[69] included data from a phase 1b trial of pembrolizumab, an anti-PD-1 antibody, in gastric cancer (KEYNOTE-012). This study reported only a single case of grade 1 colitis among 39 patients. The meta-analysis from Yao *et al*[36] included the ATTRACTION-2 trial, a phase 3 study of nivolumab, also an anti-PD-1 antibody, in patients with gastric and GEJ cancers[70]. Rates of IMC in this trial were comparable to data on the use of anti-PD-1 in other studies, with diarrhea occurring in 7% and colitis in 1% of patients. A second study on gastric and GEJ cancers was included in the meta-analyses, specifically KEYNOTE-061, a phase 3 study with pembrolizumab[71]. Comparable to the findings in ATTRACTION-2, this study reported an incidence of diarrhea and colitis of 5% and 1%, respectively. Yao *et al*[36] also included a single study on the use of pembrolizumab in HCC, the KEYNOTE-240 study, which reported a higher rate of diarrhea at 17.2%, but again a comparable rate of colitis at 1.4%[72]. The meta-analysis also included a single study with atezolizumab (anti-PD-L1) in colorectal cancer (CRC)[73]. The IMblaze370 study found that atezolizumab was associated with diarrhea in 18% of patients; rates of colitis were not reported. These findings preliminarily suggest that rates of IMC in patients with GI malignancies treated with anti-PD-1 and anti-PD-L1 are comparable to the rates seen in other malignancies. Since studies have suggested that tumor type may be associated with the development of IMC, it will be important to continue evaluating whether specific GI malignancies are higher risk[46].

The use of ICIs in GI cancers has been recently reviewed in depth, including a review of the major clinical trials for all ICI across all GI malignancies[74]. All classes of ICI (anti-CTLA-4, anti-PD-1, and anti-PD-L1) have been trialed in GI malignancies individually, in combination, and combined with both conventional chemotherapy and tyrosine kinase inhibitors. Here, we review these trials by malignancy and

evaluate the data on rates of IMC reported in these studies.

### CRC

Several recent reviews have highlighted the use of ICI in MSI-H CRC[74-76]. In agreement with findings in other malignancies, these reviews note that diarrhea and colitis are relatively common side effects of ICI therapy in CRC patients. Interestingly, one of the early phase I trials of anti-PD-1 included 14 CRC patients, although the only reported episode of colitis in that trial occurred in a patient with melanoma[77]. Since this early trial, several phase 2 and phase 3 trials have recently reported the efficacy and side effect profile of multiple ICI in MSI-H CRC (Table 4).

The earliest published phase 2 trial of ICI in MSI-H CRC was the Checkmate-142 trial examining nivolumab[78]. This was an open-label trial that included 74 patients who had either not tolerated or progressed with at least one prior treatment. After a mean follow up of 12 mo, 31.3% of patients had an objective treatment response and 69% had disease control for at least 12 wk. Of the 74 patients enrolled, 15 (20%) experienced grade 1-2 diarrhea and one (1%) experienced grade 3 diarrhea. Only one patient (1%) experienced colitis.

The first published phase 3 trial of an ICI in CRC was the IMblaze 370 trial, which evaluated the efficacy of atezolizumab, an anti-PD-L1[73]. This study specifically evaluated atezolizumab with or without cobimetinib, an inhibitor of the MAP kinase pathway, in comparison to regorafenib, a multi-kinase inhibitor. Unfortunately, the trial failed to meet the primary endpoint of improved OS in either atezolizumab group *vs* the group treated with regorafenib, demonstrating a 2%-3% objective response rate in the two atezolizumab groups. Diarrhea was the most common adverse event in the combination group, with grade 1-2 diarrhea in 54% and grade 3 diarrhea in 11% of patients. Diarrhea was substantially less common in the atezolizumab monotherapy group, with 18% of patients experiencing grade 1-2 diarrhea and only 1% grade 3. Colitis was not reported in this study.

In addition to nivolumab and atezolizumab, two recent trials have highlighted the use of pembrolizumab in MSI-H CRC. The KEYNOTE-164 trial was an open-label phase 2 trial of pembrolizumab in patients who had been exposed to at least two prior lines of standard therapy[79]. Across two independent cohorts, the objective response rate was 33%. 12.1% of patients experienced grade 1-2 diarrhea, and no patients developed grade 3 or higher diarrhea. 1.6% of patients developed grade 1-2 colitis and one patient (0.81%) developed grade 3-4 colitis. The KEYNOTE-177 trial was a phase 3 trial comparing pembrolizumab to chemotherapy in treatment-naïve patients[80]. This study reported a significantly improved overall response rate with ICI, demonstrating response in 43.8% of patients treated with pembrolizumab compared to 33.1% with chemotherapy. Interestingly, diarrhea was less common in the pembrolizumab group, with an incidence of 44% at any grade (6% grade 3 or higher) compared to 62% any grade (11% grade 3 or higher) in patients who received chemotherapy. However, the incidence of colitis was 7% at any grade and 3% grade 3 or higher in patients with pembrolizumab, while there were zero cases amongst patients given chemotherapy.

Finally, one recent study evaluated the use of combination ipilimumab and nivolumab in MSI-H CRC. The GERCOR NIPICOL study was a phase 2 trial in patients who had previously received standard chemotherapy, with an overall response rate of 59.7%[81]. In the trial, 35.1% of patients experienced diarrhea, with 3.5% experiencing grade 3 or higher. Diarrhea was the second-most common adverse event of any grade, after fatigue. Colitis was not reported in this study.

Overall, these studies are generally in line with prior reported rates of IMC. Rates of diarrhea ranged from 12.1% to 44% of patients, with higher rates (35.1%) in patients treated with combination ICI therapy, as expected. However, diarrhea was unexpectedly frequent amongst treatment-naïve patients in the KEYNOTE-177 trial, at a rate of 44%, which was much higher than typically observed for single-agent anti-PD-1 therapy[80]. Colitis was also observed at 7%, which is more typical of the higher rates characteristic of anti-CTLA-4 therapy. These findings suggest that prior chemotherapy treatment could be protective against, or perhaps mask, IMC in CRC patients treated with anti-PD-1.

### Gastric and GEJ cancer

Two retrospective studies evaluated irAE in patients with gastric and GEJ cancers, which included data on diarrhea and colitis. Masuda *et al* studied the incidence of irAE in patients with gastric cancer treated with nivolumab and found that five of 65 patients (7.7%) developed IMC, which was also the most common irAE in this study [82]. Intriguingly, the investigators found that development of any irAE was significantly associated with improved OS in a multivariate analysis (HR 9.54, 95%CI:

Table 4 Immune checkpoint inhibitor-mediated colitis and diarrhea in gastrointestinal malignancies

	Ref.	Number of Patients	Trial phase	Type of study	Therapies	Objective response rate (%)	Incidence of diarrhea (%)	Incidence of colitis (%)
<b>Colorectal cancer</b>								
Checkmate-142	Overman <i>et al</i> [78], 2017	74	Phase 2	Open-label	Nivolumab	31.3	21.6	1
IMblaze 370	Eng <i>et al</i> [73], 2019	363	Phase 3	RCT	Atezolizumab plus cobimetinib	3	65.3	-
					Atezolizumab	2	18.9	-
					Regorafenib	2	37.5	-
KEYNOTE-164	Le <i>et al</i> [79], 2020	124	Phase 2	Open-label	Pembrolizumab	33	12.1	2.4
KEYNOTE-177	André <i>et al</i> [80], 2020	307	Phase 3	Open-label	Pembrolizumab	43.8	44	7
					5-FU based therapy with or without bevacizumab or cetuximab	33.1	62	0
GERCOR NIPICOL	Cohen <i>et al</i> [81], 2020	57	Phase 2	Open-label	Ipilimumab plus nivolumab	59.7	35.1	-
<b>Gastric and GEJ cancer</b>								
	Masuda <i>et al</i> [82], 2019	65	NA	Retrospective cohort	Nivolumab	6.7	7.7 <sup>1</sup>	7.7 <sup>1</sup>
	Chen <i>et al</i> [83], 2019	2003	Phase 1b-3	Meta-analysis	Nivolumab	9.9	8.2	0.9
					Pembrolizumab			
					Avelumab			
					Ipilimumab			
					Tremelimumab			
Checkmate-032	Janjigian <i>et al</i> [84], 2018	160	Phase 1/2	Open-label	Nivolumab 1 mg/kg and ipilimumab 3 mg/kg	24	31	-
					Nivolumab 3 mg/kg and ipilimumab 1 mg/kg	8	10	-
					Nivolumab 3 mg/kg	12	15	-
Attraction-2	Kang <i>et al</i> [70], 2017	493	Phase 3	RCT	Nivolumab	11.2	7	1
					Placebo	0	2	0
Attraction-4	Boku <i>et al</i> [85], 2019	39	Phase 2	Open-label	Nivolumab plus S-1 and oxaliplatin	57.1	66.7	-
					Nivolumab plus capecitabine and oxaliplatin	76.5	44.4	-
KEYNOTE-012	Muro <i>et al</i> [69], 2016	39	Phase 1b	Open-label	Pembrolizumab	33.3	-	3
KEYNOTE-059	Fuchs <i>et al</i> [86], 2018	259	Phase 2	Open-label	Pembrolizumab	11.6	6.6	-
KEYNOTE-061	Shitara <i>et al</i> [71], 2018	570	Phase 3	Open-label	Pembrolizumab	16	5	1
					Paclitaxel	14	14	1
	Bang <i>et al</i> [87], 2017	114	Phase 2	Open-label	Ipilimumab	1.8	24.6	5.3
					Best supportive care	7	6.7	0

	Ralph <i>et al</i> [88], 2010	12 <sup>2</sup>	Phase 2	Open-label	Tremelimumab	0	22.2 <sup>2</sup>	5.6 <sup>2</sup>
JAVELIN Gastric 300	Bang <i>et al</i> [89], 2018	371	Phase 3	Open-label	Avelumab	2.2	6	-
					Chemotherapy (physician's choice)	4.3	26.6	-
<b>Esophageal cancer</b>								
	Ralph <i>et al</i> [88], 2010	6 <sup>3</sup>	Phase 2	Open-label	Tremelimumab	16.7	22.2 <sup>2</sup>	5.6 <sup>2</sup>
Attraction-3	Kato <i>et al</i> [90], 2019	419	Phase 3	Open-label	Nivolumab	19	10.5	-
					Chemotherapy (physician's choice)	22	9.6	-
KEYNOTE-180	Shah <i>et al</i> [91], 2019	121	Phase 2	Open-label	Pembrolizumab	9.9	5.8	-
KEYNOTE-181	Kojima <i>et al</i> [92], 2020	628	Phase 3	Open-label	Pembrolizumab	16.7	5.4	-
					Chemotherapy (physician's choice)	7.4	20.3	-
<b>Hepatocellular carcinoma</b>								
Checkmate-040	El-Khoueiry <i>et al</i> [93], 2017	262	Phase 1/2	Open-label	Nivolumab	15-20	10	-
Checkmate-040	Yau <i>et al</i> [94], 2020	148	Phase 1/2	Open-label	Nivolumab 1 mg/kg and ipilimumab 3 mg/kg (4 doses)	32	24	10
					Nivolumab 3 mg/kg and ipilimumab 1 mg/kg (4 doses)	27	12	2
					Nivolumab 3 mg/kg and ipilimumab 1 mg/kg (every 6 wk)	29	17	2
KEYNOTE-224	Zhu <i>et al</i> [95], 2018	104	Phase 2	Open-label	Pembrolizumab	17	11	2
KEYNOTE-240	Finn <i>et al</i> [72], 2020	413	Phase 3	RCT	Pembrolizumab	18.3	17.2	1.4
					Placebo	4.4	15.7	1.5
IMbrave 150	Finn <i>et al</i> [96], 2020	501	Phase 3	Open-label	Atezolizumab plus bevacizumab	33.2	18.8	-
					Sorafenib	13.3	49.4	-
<b>Biliary tract cancers</b>								
	Ueno <i>et al</i> [98], 2019	60	Phase 1	Open-label	Nivolumab	3	-	-
					Nivolumab plus gemcitabine and cisplatin	37	-	-
KEYNOTE-028	Piha-Paul <i>et al</i> [99], 2020	24	Phase 1b	Open-label	Pembrolizumab	13	8.3	4.2
KEYNOTE-158	Piha-Paul <i>et al</i> [99], 2020	104	Phase 2	Open-label	Pembrolizumab	5.8	6.7	1
	Klein <i>et al</i> [100], 2020	33	Phase 2	Open-label	Ipilimumab plus nivolumab	23	6 <sup>1</sup>	6 <sup>1</sup>
<b>Pancreatic cancer</b>								
KEYNOTE-158	Marabelle <i>et al</i> [101], 2020	22	Phase 2	Open-label	Pembrolizumab	18.2	12 <sup>2</sup>	3.9 <sup>2</sup>
	Royal <i>et al</i> [102], 2010	27	Phase 2	Open-label	Ipilimumab	0	-	3.7

O'Reilly <i>et al</i> [102], 2019	65	Phase 2	Open-label	Durvalumab	0	6	-
				Durvalumab plus tremelimumab	3.1	13	-

<sup>1</sup>Reported as combined diarrhea/colitis.

<sup>2</sup>Combined rates across all malignancies in study.

<sup>3</sup>Also included 12 patients with gastric and gastroesophageal junction cancer.

ICI: Immune checkpoint inhibitor; IMC: Immune checkpoint inhibitor-mediated colitis and diarrhea; CTLA-4: Cytotoxic T-lymphocyte antigen 4; PD-1: Programmed cell death protein-1; PD-L1: Programmed cell death-ligand 1; RCT: Randomized controlled trial; 5-FU: 5-Fluorouracil; S-1: Tegafur-gimeracil-oteracil potassium; GEJ: Gastroesophageal junction; NA: Not available.

3.34-27.3), which is consistent with data from retrospective studies of IMC in other tumor types. A recent meta-analysis of nine phase 1b to phase 3 trials in patients with gastric and GEJ cancer treated with ICI demonstrated a 6.2%-21.9% incidence of diarrhea and a 0.8%-5.3% incidence of colitis, which is similar to rates seen in studies of other malignancies[83]. These studies, although not focused on IMC, suggest that the rates and clinical implications of IMC may be similar in patients with gastric and GEJ cancer compared to other malignancies.

Three studies on nivolumab in gastric and GEJ cancer found a wide range of IMC rates. The Checkmate-032 phase 2 trial compared nivolumab and combination ipilimumab/nivolumab following failure of at least one chemotherapy regimen, and found a 12% objective response rate in the nivolumab monotherapy arm, with 15% of patients in that arm developing diarrhea[84]. The Attraction-2 phase 3 trial compared nivolumab to placebo in patients who had failed two or more chemotherapy regimens and found an overall 11.2% response rate in the nivolumab arm, with a 7% incidence of diarrhea and a 1% incidence of colitis[70]. Finally, the Attraction-4 phase 2 trial examined chemotherapy-naïve patients treated with nivolumab, oxaliplatin, and either capecitabine or S-1[85]. The rate of diarrhea was quite high in both arms, at 56.4% overall, with 7.7% of patients developing grade 3 or 4 diarrhea. Colitis was not reported in this study. The objective response rates were high, at 57.1% in patients who received combination therapy with S-1 and 76.5% in patients who received capecitabine. Rates of diarrhea in the Checkmate-032 and Attraction-2 trials are comparable to rates of diarrhea for anti-PD-1 therapy in other malignancies; it is possible that the increased rate in the Attraction-4 trial may be due to combination with chemotherapy or may be related to its use in treatment-naïve patients.

Three trials with pembrolizumab in gastric and GEJ cancer patients evaluated both treatment response and rates of IMC. As noted above, the KEYNOTE-012 phase 1b study included patients with gastric and GEJ cancers, demonstrating a response rate of 33.3% and a 3% incidence of colitis[69]. The KEYNOTE-059 phase 2 study found a response rate of 11.6% in patients who had progressed on two or more regimens of standard chemotherapy[86]. In this study, 6.6% of patients developed diarrhea, of which 1.2% were grade 3. Colitis was not reported in this study. Shitara *et al* compared pembrolizumab to paclitaxel in the KEYNOTE-061 phase 3 trial for second-line therapy for gastric and GEJ cancers[71]. No significant difference in OS was found between the two groups in this study. Patients treated with pembrolizumab had a 5% incidence of diarrhea and a 1% incidence of colitis, which was generally lower than the paclitaxel arm (15% and 1% for diarrhea and colitis, respectively). Overall, these studies suggest that rates of IMC may be comparable or slightly lower with the use of pembrolizumab in gastric and GEJ cancers compared to other malignancies.

Several studies have examined the use of anti-CTLA-4 in gastric and GEJ malignancies. The Checkmate-032 trial cited earlier also included two arms with combination ipilimumab and nivolumab in addition to nivolumab monotherapy[84]. The use of a higher dose of ipilimumab (3 mg/kg, along with 1 mg/kg nivolumab) had a much higher objective response rate of 24%, compared to 8% with lower dose ipilimumab (1 mg/kg with 3 mg/kg nivolumab). However, the higher dose ipilimumab was also associated with a substantially higher incidence of diarrhea, at 31% compared to 10% with lower dose ipilimumab. There has also been a phase 2 trial comparing ipilimumab monotherapy to best supportive care in patients who responded to first-line chemotherapy[87]. Neither PFS nor OS were significantly different between these two groups. In the ipilimumab group, which received a very high dose of ipilimumab at 10 mg/kg, 24.6% developed diarrhea and 5.3% developed colitis. Finally, one early phase 2 study of tremelimumab in 12 patients with gastric and GEJ cancer (as well as six patients with esophageal cancer) found that no patients with

gastric or GEJ cancer had an objective response to the therapy[88]. Among all patients in this study, four (22.2%) developed diarrhea, and one died after developing colonic perforation due to IMC. The results from these studies are variable, but overall suggest anti-CTLA-4 monotherapy may not have a role in the treatment of gastric and GEJ cancer. Although in other malignancies the dose of anti-CTLA-4 was positively correlated to rate of IMC, it is unclear if this holds true in gastric and GEJ cancers, since IMC was less common with very high dose ipilimumab (10 mg/kg) in one study compared to a lower dose (3 mg/kg) in another study[84,87].

Lastly, a phase 3 study examined the use of avelumab, an anti-PD-L1 antibody, in gastric and GEJ cancers[89]. The JAVELIN Gastric 300 study was a randomized trial comparing avelumab to chemotherapy in patients who had failed two or more prior therapies. There were no significant differences in either median OS or median PFS with avelumab *vs* chemotherapy. Diarrhea occurred in 6% of the patients given avelumab, *vs* 26.6% of patients given chemotherapy; rates of colitis were not noted. Therefore, the rate of IMC with anti-PD-L1 in gastric and GEJ tumors appears to be comparable to the rate reported for other malignancies.

Overall, these studies suggest that rates of IMC are roughly comparable for patients with gastric and GEJ malignancies compared to other cancers, particularly for pembrolizumab and anti-PD-L1 (Table 4). There appears to be an increased rate of IMC in some studies using nivolumab in gastric and GEJ cancer compared to other malignancies; however, this may be confounded either by concomitant chemotherapy and/or by evaluation in treatment-naïve patients. Data on the rates of IMC with anti-CTLA-4 therapy in these patients are highly variable and may also be related to dose of anti-CTLA-4 and/or exposure to prior therapies.

### **Esophageal cancer**

Several studies have examined the use of anti-PD-1 in patients with esophageal cancer, including both esophageal adenocarcinoma (EAC) and esophageal squamous cell carcinoma (ESCC) (Table 4). The Attraction-3 phase 3 trial compared nivolumab to chemotherapy in patients with ESCC who had failed at least one trial of chemotherapy [90]. Objective response was similar in the nivolumab group compared to the chemotherapy group (19% *vs* 22%, respectively). Grade 1-2 diarrhea occurred in 10% of the nivolumab group compared to 9% of the chemotherapy group, and grade 3 or higher diarrhea occurred in 1% of both groups. Colitis was not reported in this study. Rates of IMC therefore may be similar with nivolumab in ESCC compared to other malignancies.

Two studies have evaluated the use of pembrolizumab in esophageal cancer. The KEYNOTE-180 trial was a phase 2 study of patients with either EAC and ESCC who had progressive disease after two or more prior therapies[91]. The objective response rate in this study was 9.9%. Rates of IMC were similar compared to studies with pembrolizumab in other malignancies, with a 4.9% incidence of grade 1-2 diarrhea and 0.8% incidence of grade 3-5 diarrhea; colitis was not reported in this study. The later KEYNOTE-181 phase 3 trial compared pembrolizumab to chemotherapy in EAC and ESCC patients who had progressed on one prior line of treatment[92]. The rate of diarrhea in this study was similarly 5.4% for all grades, with an incidence of only 0.6% for grade 3 or higher. Again, colitis was not reported.

There are very limited data on the use of anti-CTLA-4 in patients with esophageal cancer. One early phase 2 study with tremelimumab referenced earlier included a group of patients with esophageal cancer[88]. Out of six patients with esophageal cancer in this study, one had partial response with an OS of over 30 mo, two had stable disease with OS of 5-12 mo, and three had progressive disease with an OS of 1.7-2.7 mo. As mentioned above, one patient in the entire study developed colitis (5.6%), and 22.2% of patients overall developed diarrhea. These data are quite limited but suggest that the use of anti-CTLA-4 in patients with esophageal cancer may not be associated with substantially different rates of IMC compared to other malignancies. All together, these findings suggest that rates of IMC appear to be similar in esophageal cancer compared to other malignancies based on data available to date.

### **HCC**

There has been increasing interest in the use of ICI for HCC (Table 4). The Checkmate-040 phase 1 and 2 studies with nivolumab and ipilimumab plus nivolumab provided early data on the safety and efficacy of these ICI in patients with HCC[93,94]. The first Checkmate-040 trial with nivolumab monotherapy found an objective response rate of 15%-20% across groups[93]. 10% of patients in this study developed diarrhea. The second study, which used combination nivolumab and ipilimumab in three different dosing regimens, found an objective response of 27%-32% across all three arms of the

study[94]. The incidence of diarrhea was 17.8% across all arms of the study, with higher rates occurring in the arm with 3 mg/kg ipilimumab (24%) compared to the two arms with 1 mg/kg ipilimumab (12% and 17%, respectively). Rates of colitis requiring immunosuppressive treatment were similar to rates seen in other malignancies, with an incidence of 10% in patients who received the higher dose of ipilimumab and 2% in the other groups. Overall, these data for HCC are consistent with rates of IMC reported for combination therapy and nivolumab monotherapy in patients with other cancers.

Two studies examined the safety and efficacy of pembrolizumab in patients with HCC. The KEYNOTE-224 study was a phase 2 trial evaluating pembrolizumab in patients with HCC who had previously received the tyrosine kinase inhibitor sorafenib[95]. The study had an objective response rate of 17%. Similar to other malignancies, there was an 11% rate of diarrhea and a 2% rate of colitis. Building on these findings, the KEYNOTE-240 phase 3 trial evaluated pembrolizumab in patients with HCC[72]. Patients previously treated with sorafenib were randomized to receive either pembrolizumab or placebo, with an objective response of 18.3% in the pembrolizumab group *vs* 4.4% in the placebo group. 17.2% and 1.4% of patients in the pembrolizumab arm developed diarrhea and colitis, respectively, *vs* 15.7% and 1.5% in the placebo arm, respectively. Similar rates of diarrhea in anti-PD-1 and comparators have been reported for other malignancies as well, although a comparable rate of colitis with placebo is unusual and perhaps denotes an increased baseline risk of colitis in patients with HCC compared to other tumor types[28,32].

Finally, one very recent phase 1b study evaluated the use of atezolizumab with the anti-vascular endothelial growth factor antibody bevacizumab in HCC[96]. The IMbrave150 study compared atezolizumab and bevacizumab combination to sorafenib in patients with unresectable HCC who had received prior systemic therapy. The combination arm had a 33.2% objective response rate, which was significantly higher ( $P < 0.001$ ) than the objective response rate in the sorafenib arm at 13.3%. 18.8% of patients in the combination therapy group developed diarrhea. This was higher than some studies of atezolizumab in other malignancies[25,34], although comparable to rates in CRC[73], but much lower than the 49.4% of patients in the sorafenib group.

In general, the data from these studies in HCC suggest that some ICI, including anti-CTLA-4, are associated with similar rates of IMC compared to other malignancies, while others, notably atezolizumab, are associated with an increased incidence of IMC. It remains unclear if this observation is related to underlying tumor type or other confounding factors. Of note, bevacizumab, which was used in the IMbrave150 trial combined with atezolizumab, has been associated with colitis, and its use could explain the observed rate of IMC in this study[97].

### **Biliary tract cancers**

The use of ICI in biliary tract cancers is in its infancy, as only a few recent phase 1 and phase 2 trials have been published (Table 4). A phase 1 study comparing nivolumab with or without cisplatin plus gemcitabine showed limited success in biliary tract cancers, with a 3% objective response in the monotherapy group and 37% objective response with combination therapy[98]. No diarrhea or colitis was reported in this study. A recent sub-group analysis of patients with biliary tract cancer who received pembrolizumab as part of the phase 1b KEYNOTE-028 and phase 2 KEYNOTE-158 trials found an objective response rate of 13% and 5.8%, respectively[99]. There was an 8.3% incidence of diarrhea among patients with biliary tract cancer in the KEYNOTE-028 trial and 6.7% in the KEYNOTE-158 trial. The 1% rate of colitis in the phase 2 trial was comparable to studies using pembrolizumab in other malignancies. Although the 4.2% rate of colitis in the phase 1b trial was much higher than studies in other cancers, this was likely due to the small sample size (24 patients total, one of which developed colitis). Finally, there has been one published subgroup analysis of patients with biliary tract cancers from a phase 2 trial of combination ipilimumab and nivolumab, where patients received a low dose of ipilimumab at 1 mg/kg along with 3 mg/kg of nivolumab[100]. A total of 6% of patients developed IMC (both diarrhea and colitis), with 3% developing grade 1-2 IMC and 3% developing grade 3-4. Overall, the data are limited for biliary tract cancers, but preliminary studies suggest these patients develop IMC at similar rates to other malignancies.

### **Pancreatic cancer**

Data are similarly limited on the use of ICI in patients with pancreatic cancer (Table 4). As with biliary tract cancers, there were patients with pancreatic cancer included in the phase 2 KEYNOTE-158 trial with pembrolizumab. A recent subgroup analysis of this study focused on non-CRC patients found that among the 22 patients with pancreatic

cancer from this trial, there was an objective response rate of 18.2% [101]. Across all patients included in the subgroup analysis, 12% developed diarrhea and 3.9% developed colitis, although these data were not separated by tumor type.

Only a few limited studies have focused exclusively on ICI treatment of patients with pancreatic cancer. A phase 2 study with ipilimumab found that zero out of 27 patients enrolled had a primary response to treatment, although one patient had a delayed response [102]. Unlike the KEYNOTE-158 trial, patients in this study by Royal *et al* [102] were not selected for MSI-H tumors, which as above are predicted to exhibit improved response to ICI therapy. Out of the 27 patients in this study, only one case of grade 3 or higher colitis was reported. A recent phase 2 study examined the anti-PD-L1 antibody durvalumab with or without tremelimumab in pancreatic cancer patients [103]. This study enrolled patients regardless of MSI status who had received only one prior line of chemotherapy and had similarly poor outcomes, with an objective response rate of 3.1% in the combination arm and 0% in the durvalumab monotherapy arm. Similar to data in other malignancies, there was a 13% reported incidence of diarrhea in the combination therapy group and 6% in the durvalumab monotherapy group.

## ICIS AND GI IRAE IN PATIENTS WITH IBD

### *Malignancy in patients with IBD*

IBD is a chronic relapsing-remitting immune-mediated enteropathy thought to occur with environmental triggers in genetically susceptible individuals [104]. IBD consists of Crohn's disease (CD) and ulcerative colitis (UC), each with distinct phenotypes and clinical courses and each increasing in incidence and prevalence worldwide [105,106]. Chronic inflammation and increased turnover of intestinal stem cells increases the risk of CRC in IBD [107], and there is a considerable body of literature devoted to understanding GI cancers in IBD patients [108]. This has led to the widespread use of CRC surveillance regimens for IBD patients based on regular colonoscopy, but screening for extraintestinal malignancies in IBD is sometimes overlooked. Nevertheless, IBD is associated with systemic inflammation beyond the GI tract, raising the risk for a variety of malignancies. Further, IBD patients are treated chronically with immunosuppressive and immunomodulatory medications, which enhance the risk for certain cancers. For instance, a recent study demonstrated that CD is associated with an increased risk of melanoma and cervical cancer, and that use of immunosuppressive thiopurine medications further increased the risk of lymphoma and nonmelanoma skin cancers [109]. Despite extensive evidence for increased risk of skin and other cancers in IBD, there remains a low frequency of dermatologic care and surveillance for other extraintestinal malignancies in IBD patients overall, suggesting that many IBD patients may unfortunately become increasingly common candidates for ICI therapy [110].

### *ICI use in patients with IBD*

Use of ICI therapies in IBD patients has been variable and frequently reported with only small sample sizes. Although IBD patients have been included in some ICI trials, there are insufficient numbers to draw definitive conclusions from these studies alone, and patients were also highly selected based on various criteria, which would further complicate extrapolation of results related to this small subgroup. Early after regulatory approval, clinicians were often reluctant to use ICI in patients with IBD or other auto-inflammatory and autoimmune conditions, as serious and sometimes life-threatening toxicities became increasingly recognized. More recently, experts have come to appreciate that the benefits of ICI therapy may outweigh the potential risks in these conditions [111]. To date, reports on GI irAE prevalence and outcomes in IBD patients treated with ICI have largely been sporadic and based upon small cohorts [112-114], with a single very recent meta-analysis of twelve studies to date [115]. With increasing use of ICI in these populations, evidence-based approaches are needed for better prediction, monitoring, and treatment of GI irAE in IBD patients.

### *GI irAE in IBD patients following ICI therapy*

Understanding GI irAE in IBD patients treated with ICI is of great clinical significance, as these adverse events are common and associated with major morbidity and mortality. GI irAE encompass diarrhea and colitis as IMC as well as upper GI tract manifestations, such as nausea, vomiting, gastritis, and small bowel inflammation. As the number of IBD patients continues to grow and more of these patients are

diagnosed with cancer which may be treated with ICI, it is vital to understand the incidence, prevalence, and characteristics of GI irAE in IBD patients[58]. Unlike the literature on ICI use in patients with other autoimmune and auto-inflammatory conditions, which shows consistently increased incidence of disease exacerbation or relapse and effective management with standard treatment for these conditions[116-118], literature on ICI in IBD has primarily focused on prevalence of GI irAE *via* retrospective cohort studies[112-114]. Major concerns in IBD are whether patients are at increased risk of GI irAE and/or flares of their underlying IBD, whether those GI irAE can be managed with conventional medical therapy, and whether ICI treatment must be discontinued following a GI irAE in an IBD patient. Since limited numbers of IBD patients have been treated with ICI to date and inconsistent definitions of GI irAE have been used across studies, reports have often been without clear or generalizable findings on incidence and with limited information on associated clinical characteristics and outcomes. Nevertheless, increased prevalence of GI irAE in IBD patients treated with ICI compared to the general population treated with ICI has emerged as a clear pattern from these reports.

In IBD patients treated with ICI, GI irAE most frequently consist of diarrhea and/or colitis, which can be difficult to distinguish from underlying IBD, and less frequently include more severe conditions such as bowel perforation, toxic megacolon, and others. Inconsistent definitions of IMC and IBD flare across studies have complicated understanding of underlying pathophysiology, furthered by additional contributing factors such as pre-ICI IBD activity, superimposed infection, and effects of other medications in the setting of polypharmacy. While these heterogeneous features and small cohort sizes have so far precluded identification of generalizable characteristics associated with IBD exacerbation following ICI treatment and outcomes, the data demonstrate overall increased rates of IBD exacerbation following ICI treatment (roughly 40% [115]; Table 5) compared to rates of IMC in the general population treated with ICI (9.1%-35.4% for diarrhea and 0.7-13.6% for colitis) [58].

Of IBD patients with an exacerbation following ICI therapy, many require corticosteroids, biologics, and/or other immunomodulatory therapy[115]. Approximately 35% of these patients discontinued ICI[115]. We recently found that exacerbation of IBD was also associated with an increased rate of GI-related hospitalization, half the time requiring surgery. While patients may in some cases be managed with medical therapy consistent with typical IBD treatment[61,119], clearly IBD patients on ICI are a vulnerable population requiring close monitoring and prompt intervention upon disease exacerbation. Newer IBD therapies, such as vedolizumab, may be especially helpful for IMC or disease exacerbation in IBD patients treated with ICI, as suggested by recent reports[63,120-122]. Vitamin D intake, which has been associated with reduced risk of IMC in the general population treated with ICI, should also be investigated as a potential modifiable risk factor, especially in patients with IBD who are at increased risk of developing IMC or disease exacerbation and may already be taking vitamin D for their IBD[40]. As IBD patients who develop cancer are increasingly treated with ICI, the field will benefit dramatically from a more concerted effort to identify risk factors for IBD exacerbations, and ideally next-generation checkpoint inhibitors will be increasingly tuned to reduce the risk of irAE.

## CONCLUSION

IMC is among the most common irAE observed with ICI therapy[23,24]. However, the incidence appears to vary widely across studies, with variation due in part to whether the definition of IMC includes diarrhea, colitis, or both. Although the National Cancer Institute has established separate grading schemes for immune-related diarrhea and colitis[22], studies do not consistently differentiate these two side effects, leading to discrepancies in how events are reported in both prospective studies aimed at evaluating ICI safety as well as retrospective studies seeking to analyze irAE rates. Due to these challenges, we included both diarrhea and colitis in the definition of IMC used here and have attempted to differentiate the two whenever possible. Furthermore, as the diagnosis and management of IMC evolve, the incidence of true immune-mediated colitis may shift as more patients undergo endoscopic evaluation for their symptoms[24,57,58].

Despite these limitations, there are clear patterns of risk for IMC that emerge across multiple studies. The use of anti-CTLA-4 as well as combination therapy with anti-CTLA-4 plus anti-PD-1 is consistently associated with higher rates of IMC, including colitis specifically[25-29,35]. Higher doses of anti-CTLA-4, particularly ipilimumab, are

**Table 5 Selected retrospective studies reporting prevalence of gastrointestinal immune-related adverse events in inflammatory bowel disease patients treated with all immune checkpoint inhibitor regimens**

Ref.	Number of IBD patients	Single or multi center	Prevalence of GI irAE (%)
Abu-Sbeih <i>et al</i> [112], 2020	102	Multi	41.2
Grover <i>et al</i> [113], 2020	21	Single	28.0
Braga Neto <i>et al</i> [114], 2021	13	Single	30.7
Meserve <i>et al</i> [115], 2021	193 across 12 studies	Meta-analysis	40.0

IBD: Inflammatory bowel disease; GI: Gastrointestinal; irAE: Immune-related adverse events.

consistently associated with higher rates of IMC[49,50]. The relevance of other risk factors, such as race, sex, primary malignancy, and vitamin D supplementation, is less clear and may be limited by small sample sizes or patient population selection (*e.g.*, inclusion of only melanoma patients). More work is needed to identify risk factors across the spectrum of ICI and malignancies using clear definitions of IMC in order to elucidate risks factors that may help predict which patients will develop this irAE. Identification of these risk factors may also allow us to identify pathophysiological mechanisms underlying IMC, understanding of which could improve our ability to diagnosis and manage this condition without compromising treatment of the patient's malignancy.

Understanding individual risk factors for IMC and other GI irAE is particularly pertinent for patients with GI malignancies. Although ICI are thought to amplify the immune response to neoantigens present within tumor tissue[12], there is a potential risk of engaging healthy tissue of a similar origin to the primary malignancy. For example, patients with melanoma develop higher rates of ICI-related vitiligo compared to those with other cancers[25]. Similarly, patients with GI malignancies may be at higher risk of non-irAE side effects from cancer therapy, such as diarrhea, nausea, and vomiting, due to the location of their primary tumor. It is therefore more difficult, yet critical, to properly diagnose GI irAE in these patients, as immunosuppression should only be considered for true immune-related events. Our review of IMC rates in patients with GI malignancies highlights this point, as colitis in particular appears to be under-reported compared to diarrhea, a symptom more likely than colitis to be related to concomitant chemotherapy or non-ICI causes rather than an immune-mediated process.

Patients with IBD also represent a vulnerable population where appropriate diagnosis and management of GI irAE is critical, especially for IMC. Diagnosis of IMC in patients with underlying IBD is especially challenging, as symptoms, endoscopic appearance, and pathology may be exquisitely similar to active IBD. Initial management of both IBD flares and IMC is currently similar, but decisions on length of treatment, when to escalate therapy, and whether up-front biologic therapy is appropriate are ongoing areas of study in IMC and may ultimately differ from guidelines for IBD treatment[56-58,63-66]. There is much work to be done on elucidating the underlying pathophysiology of IMC and how it differs from IBD, which will enhance our diagnostic evaluation and inform management of these two related yet distinct conditions.

Future work on IMC should continue to focus on identifying those at higher risk for the condition and defining appropriate management. As steroid and infliximab use may be associated with worse cancer outcomes[123,124], treating IMC only when appropriate and only for as long as needed may ultimately improve our ability to treat cancers with ICI. An understanding of risk factors for IMC may also provide insight into the mechanisms underlying this condition, which will direct development of novel treatments for IMC and may also expand our arsenal of immune checkpoint targets.

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