Adverse events induced by immune checkpoint inhibitors

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Abstract

Immune checkpoint inhibitors have revolutionized the treatments of cancers but are also associated with immune related adverse events that can interfere with their use. The types and severity of adverse events vary with checkpoint inhibitors. A single mechanism of pathogenesis has not emerged: postulated mechanisms involve direct effects of the checkpoint inhibitor, emergence of autoantibodies or autoreactive T cells, and destruction by toxic effects of activated T cells. Several host factors such as genotypes, preexisting autoimmune disease, inflammatory responses and others may have predictive value. Ongoing investigations seek to identify ways of modulating the autoimmunity without affecting the anti-tumor response with agents that are specific for the autoimmune mechanisms.

Introduction:

Checkpoint inhibitor (CPI) immunotherapy has altered the landscape of cancer treatment, demonstrating efficacy and improved survival in a growing number of advanced malignancies [1,2]. Monoclonal antibodies (mAbs) targeting immune checkpoint molecules such as programmed cell death 1 (PD-1) or its ligand programmed cell death ligand 1 (PD-L1) and cytotoxic T-lymphocyte antigen 4 (CTLA-4), release the inhibition of immune cells resulting in tumor cell destruction and control of tumor growth. A consequence of immune system activation by CPI therapy is the development of immune-related adverse events (irAE), which can affect most organ systems and, in some cases, can be life threatening. In this review, we focus on mechanisms, risk factors and predictors of these irAEs and current and emerging treatment options with consideration of their impact on tumor responses.

Overview of CPI-induced irAEs:

The development of irAEs following CPI therapy is relatively common [3]. The incidence of irAEs following anti-CTLA-4 is estimated to be 72% for any irAE and 24–34% for high grade irAE with a dose dependent effect on risk [4–6]. Estimates for anti-PD-1 or anti-PD-L1 related irAEs are 66–74% for any event and 14%–21% for higher grade irAEs [5–7]. With combination therapies, such as anti-CTLA-4 and anti-PD-1, the frequency is higher

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than with monotherapies (88–94.9% for any event and 41–59% for high grade events) and more often leads to discontinuation of treatment [6,8,9].

The most common irAEs involve the skin, gastrointestinal tract, liver, endocrine organs and lungs [5,9]. However, there are differences in the frequency of the irAEs in individual organs based on type of CPI treatment. For example, hypophysitis, colitis and rash are more frequent with anti-CTLA-4 therapy, but pneumonitis, thyroid dysfunction and diabetes are more frequently seen with anti-PD-1 [5,10–14].

The time to onset of autoimmune complications is variable, depending on the organ affected and the type of treatment. Complications can occur after a single dose of CPI and as early as within days of treatment, but the median time to onset following CPI start is typically within weeks to months. The earliest complications to develop are dermatological, followed by gastrointestinal, hepatic, endocrine, lung and renal complications [9].

In general, the irAEs occur with all tumors suggesting that side effects are dependent on the CPI itself and the host rather than the tumor. One notable exception is CPI-induced vitiligo which develops preferentially in patients receiving CPIs for melanoma [15,16] and may be related to melanocyte antigens shared with tumors. In addition, the risk of CPI-induced colitis/diarrhea is increased in melanoma patients treated with anti-PD-1 compared to patients with non-small cell lung cancer (NSCLC) and renal cell carcinoma (RCC) [13,17].

Fatal irAEs tend to occur early in treatment and the incidence depends on the type of treatment: 0.36% for anti-PD-1, 0.38% for anti-PD-L1, 1.08% for anti-CTLA-4 and 1.23% for combination of anti-PD-1/PD-L1 plus anti-CTLA-4 [18]. The frequencies and type of fatal events depend on treatment modality: Colitis is the most common fatality with anti-CTLA-4, pneumonitis with anti-PD-1/PD-L1, and colitis and cardiac complications with combination therapy [18]. Fatality rates were 39.7% for myocarditis, 5% for colitis and 2% for endocrine events.

Although the clinical features of some irAEs share similarities with their spontaneous autoimmune counterparts, there are often notable differences [3]. For example, diabetic ketoacidosis may be the presenting scenario with CPI-induced diabetes (CPI-DM), similar to type 1 diabetes (T1D), and patients may have low to undetectable C-peptide suggesting beta cell destruction [10]. However, other features are distinguishing. For example, the progression of beta cell failure is more rapid with CPI-DM and autoantibodies are less common [10,14]. Hyperthyroidism may be found at presentation with CPI-induced thyroiditis, but it typically progresses to hypothyroidism rather than remitting, and the kinetics of progression are more rapid compared to other causes of thyroiditis [19]. Other irAEs, such as colitis, are fully reversible, thus differing from inflammatory bowel disease, and the histologic picture is also different [17].

General mechanisms of irAEs:

The reasons why some patients develop particular complications and others do not remain largely unknown. Several mechanisms have been proposed to play a role in the development

of CPI-induced irAEs, including autoreactive T cells, B cells/autoantibodies, complement, cytokines/chemokines, and the microbiome (Figure 1).

Autoreactive T cells have been postulated to play a role in the development of CPI-induced irAEs. In patients with fulminant myocarditis from checkpoint blockade, histopathological analysis of myocardial and skeletal tissue showed CD4+ and CD8+ T cell infiltrate but not CD20+ cells or antibody deposits [20]. In some patients with CPI-induced DM an increase in beta cell antigen reactive CD8+T cells was increased in the circulation[21]. T cell infiltrates have been implicated in several other CPI-induced irAEs including colitis, dermatological complications, nephritis, liver injury, sicca syndrome and pneumonitis, in several cases with a predominance of CD4+ T cells [22,23]. A role for Th1 and Th17 cells has been proposed for CPI-induced colitis [22,24].

There is also evidence for a role for humoral immunity in CPI-induced irAEs. Das et al identified a role for early B cell changes in irAEs in melanoma patients treated with checkpoint blockade [25]. These changes included a reduction in circulating B cells and an increase in CD21lo PD-1+ B cells and plasmablasts with changes preceding and correlated with frequency and timing of adverse events. Autoantibodies implicated in spontaneous autoimmune diseases have been identified in CPI-induced adverse events but their role remains unclear. For example, in patients who develop thyroid dysfunction, autoantibodies (thyroglobulin and/or thyroid peroxidase antibodies) are only detected in 18–70% of patients whereas in Hashimoto's thyroiditis they are present 90–95% of the time [19,26,27]. There is some evidence that the presence of thyroid autoantibodies at baseline may increase the risk of CPI-induced thyroid dysfunction [28–30]. Similarly, in spontaneous T1D, beta cell reactive autoantibodies are detected in >90% of individuals, but only present in about 50% of patients with CPI-DM [10,14,31]. Approximately half of patients with CPI-induced myasthenia gravis (MG) have anti-acetylcholine receptor antibodies [32]. Patients with CPI-induced inflammatory arthritis are more likely to be rheumatoid factor (RF) and cyclic citrullinated peptide negative compared to rheumatoid arthritis patients [33]. In most cases, there is lack of data regarding whether autoantibodies are present prior to CPI initiation. One study profiled baseline antibodies in melanoma patients treated with CPIs and identified antibody signatures predictive of irAEs, including those targeting TNFα signaling pathways [34]. Another study examining preexisting autoantibodies (RF, antithyroglobulin, thyroid peroxidase, and anti-nuclear antibody) in patients with NSCLC treated with anti-PD-1 found that autoantibodies were more common in patients who developed irAEs[30]. Skin iRAEs, for example, were more frequent in patients who were positive for RF factor at baseline.

Shared antigens between tumor and tissue may lead to stimulation of autoreactive cells. There was evidence of shared T cell clones in the cardiac muscle, skeletal muscle and tumor supporting a role for autoreactive T cells in the development of myocarditis that develop due to shared antigens [20]. In patients with lung cancer who develop skin toxicities, shared T cell antigens were detected in the skin and tumor and were able to stimulate T cells *in vitro* [35]. Likewise, vitiligo is a frequent event in patients with melanoma treated with CPIs [16].

A unique mechanism has been postulated to lead to hypophysitis in anti-CTLA-4 treated patients. Iwama et al found that human anterior pituitary cells express CTLA-4 and in a

mouse model of anti-CTLA-4 induced hypophysitis these cells became sites of anti-CTLA-4 binding and subsequent complement deposition and immune cell infiltration. Patients with CPI-induced hypophysitis developed anti-pituitary antibodies whereas patients without hypophysitis did not [36]. Pathology from patients with CPI-induced hypophysitis confirmed CTLA-4 expression on pituitary cells and implicated both IgG and T cell mediated processes in pituitary destruction. The currently proposed mechanism involves binding of anti-CTLA-4 to pituitary cells, complement activation with macrophage/phagocyte infiltration, enhanced antigen presentation and infiltration of B and T cells, leading to endocrine cell destruction [37].

Certain cytokines and chemokines, have been implicated in tumor response and development of toxicities in patients treated with CPIs. Baseline IL-17 levels were found to be associated with subsequent development of colitis [38]. Increased levels of IL-17 were found in patients with colitis and the rise and fall in levels were temporally correlated with the development and resolution of the complication respectively [39]. Elevated IL-6 and IL-10 have been identified in patients with dermatological irAEs[40]. Elevated IL-1β, IL-2, and GM-CSF at baseline and early decrease in IL-8, G-CSF, and MCP-1 were associated with development of thyroid dysfunction[41].

The microbiome has been suggested to play a role in both tumor response and the development of irAE [42–44]. Patients treated with anti-CTLA-4 for melanoma with baseline gut microbiome enriched for *Faecalibacterium* and other Firmicutes had better tumor response and longer progression-free survival and to a lesser extent overall survival. These subjects also had more frequent colitis whereas those enriched for *Bacteroidetes* had less frequent colitis [43]. A prospective study of patients with melanoma undergoing anti-CTLA-4 treatment, also found that patients with abundant pre-inflammation *Bacteroidetes phylum* were less likely to develop CPI-induced colitis [44]. Similarly, tumor response to anti-PD-L1 can also be modulated by the microbiome [42]. Although the anti-tumor efficacy has been linked, there have not been clear ties between the microbiome and irAEs.

There is an emerging interest in tissue-resident memory T (Trm) cells in cancer and evidence that these cells may be targets of CPIs in the tumor microenvironment and influence anti-tumor response as well as irAEs [45]. Finally, CTLA-4 on Tregs is an important modulator of Treg function [46]. Although there is mixed data on the effects of anti-CTLA-4 on eliminating or modulating Tregs in the tumor microenvironment [47], given that Tregs represent an important gatekeeper for the prevention of autoimmunity, a potential role for Tregs in CPI-induced irAEs warrants further investigation.

Risk factors/predictors of autoimmunity (Table 1):

Genetic factors may affect the development of irAEs following CPIs. A number of studies have identified a significant HLA-DR4 predominance in patients who develop CPI-DM [10,14]. Other organ specific HLA associations include HLA-DRB1*04: 05 in patients with CPI-induced inflammatory arthritis [33] and HLA-DRB1*11:01 and pruritis [48]. There may be an interaction between HLA genotypes, primary cancer, and the CPI.

Cancer patients with underlying autoimmune disease were not initially included in clinical trials and therefore their risk of developing irAEs or exacerbation of their underlying autoimmune disease were not well understood. irAEs may be more frequent in patients with underlying autoimmune disease [49,50]. There is evidence that onset of irAEs may occur faster in patients with underlying autoimmune disease [50] suggesting that close monitoring of these patients early in the treatment course is warranted. Although most autoimmune flares and irAEs could be managed without discontinuation of therapy, fatalities are possible [51]. Studies regarding risk of autoimmune flares or irAEs in patients whose autoimmune disease is active vs inactive at the start of CPI have been conflicting [49,51]. In general, it is advisable that patients with underlying autoimmunity, especially when the exacerbation of which could produce significant morbidity and even mortality (ie inflammatory bowel disease (IBD)) should be managed by multidisciplinary teams with careful consideration of alternative therapies, risks and benefits.

Adverse events and treatment response:

Studies have thus far been conflicting regarding whether the development of irAEs and/or their severity may predict tumor response. Although not all have shown an association of irAEs with improved tumor response [52], several reports suggest that patients who develop irAEs, including for example endocrine complications and vitiligo in patients with melanoma, have better tumor response rates and improved survival [12,53–56]. Importantly, in large, randomized trials, patients who discontinue CPIs due to toxicity are more likely to respond than patients without clinically meaningful irAEs [57]. Our analysis in patients with CPI-DM showed that the majority of patients had at least partial tumor response but numbers were too small to make statistical inferences[10].

Management:

Management of irAEs depends on the type of adverse event, its mechanism, and severity. Due to lack of trials to guide management, treatment decisions are primarily based on data from retrospective studies and expert consensus [12]. In general, low grade irAEs do not require cessation of therapy and may not require immunosuppressive therapy whereas higher grade adverse events may require both.

Glucocorticoids are the most frequent first line anti-inflammatory agent used in patients with CPI-induced irAEs and are effective in most cases. In deciding to treat patients with glucocorticoids it is important to consider potential side effects of steroid treatment and potential impact on anti-tumor response. Several studies have demonstrated that response rates and/or survival are not affected by the need for steroids to treat irAEs [52,53,58]. A recent systematic review and meta-analysis found that steroids used to mitigate irAEs, as opposed to symptomatic or supportive care, did not negatively impact survival [58]. However, steroids at the start of or early in the course of CPI treatment may negatively impact outcomes [59–62]. Patients with lung cancer treated with anti-PD-1 on >10mg daily of prednisone at baseline had worse outcomes compared to patients on low dose steroids at baseline, although steroid indication seems to play a role [59,63].

Depending on severity, duration, and response of adverse events to steroids, other immunosuppressive agents may be required. In cases of severe irAEs refractory to steroids, infliximab, a mAb targeting TNFα, has emerged as an alternate therapeutic agent that has been used successfully to treat several irAEs (e.g., colitis, rashes, pneumonitis, ocular complications, myocarditis, among others)[12]. Infliximab, which has been used in the treatment of IBD, has been particularly useful in cases of CPI-induced colitis refractory to glucocorticoids [17,64,65]. In murine models, prophylactic TNFα blockade also eliminated colitis without affecting anti-tumor response [66]. *In vitro* studies suggest that infliximab had a minor impact on the activation of tumor specific tumor-infiltrating lymphocytes (TILs) whereas even low doses of steroids had a negative impact on anti-tumor effects of TILs [67]. Notably, the efficacy of infliximab in treating colitis points to a potential role for TNFα in CPI-induced colitis. (Table 2)

While most CPI-induced irAEs resolve, endocrine adverse events are unique in that they are largely irreversible. Glucocorticoids have not been shown to reverse endocrine complications and in the case of hypophysitis, high dose steroids may worsen clinical outcomes [54,73]. One case report suggested that infliximab may be efficacious in reversing CPI-DM. Reversal of diabetes occurred in the setting of infliximab treatment for oligoarthritis but the patient had been on steroids, mixed meal tolerance test showed both impaired insulin secretion and peripheral resistance, and the patient was not documented to be insulinopenic [74]. Thus, it is not clear that this was a typical case of CPI-DM and the potential benefit of infliximab for this complication remains uncertain. Inflammatory arthritis is also unique in that the complication often persists and requires long term immunosuppression [72]. Treatment modalities include steroids in the majority of patients and in some cases conventional synthetic or biological disease-modifying antirheumatic drugs.

The decision to resume CPI treatment following an irAE depends on the severity of the complication, the stage of the malignancy and availability of alternate therapies. Studies to date show that it is possible to retreat with CPIs following complications. However, there should be careful consideration of risks and benefits given patients can have recurrence or development of new toxicities and some cases of fatality have been reported with retreatment [1,75]. Furthermore, some patients who have had treatment success and require cessation of therapy due to irAEs may not need to restart CPIs due to ongoing benefit from therapy [76].

There is currently no known treatment modality to prevent CPI-induced irAEs. Budesonide treatment was not protective in anti-CTLA-4 induced colitis [77]. While one study showed that baseline steroids prior to CPI start was protective against the development of irAEs, as mentioned previously baseline prednisone at doses >10mg daily may negatively impact survival[59].

Potential emerging/future therapies:

As our understanding of the mechanisms underlying CPI-induced irAEs grows, our ability to offer patients more targeted therapies for these complications with limited impact on tumor responses is essential. Emerging therapies have been shown in some cases to successfully

treat irAEs, but in general the efficacy and impact on tumor responses of these therapies remains unknown. Myocarditis has the highest fatality rates amongst irAEs and thus understanding the mechanisms underlying this complication and identifying additional treatment modalities is of great interest. Alemtuzumab (anti-CD52) and abatacept (CTLA-4 agonist) have recently been used to successfully treat glucocorticoid refractory myocarditis[78,79]. A concern with abatacept is potential for infectious complications and possible tumor progression. After one month of treatment with abatacept there was no evidence of tumor progression in the treated patient, but further studies are needed to better understand the efficacy on myocarditis reversal and possible effects on tumor growth. Interestingly, abatacept has also been used successfully to treat CPI-induced worsening of MG [80]. Anti-CD52 leads to T cell depletion (as well as other peripheral immune cells) and although it led to resolution of a potentially fatal complication its impact on tumor response is not known.

Vedolizumab, a gut specific anti-integrin α4β7 antibody, that is used for treatment of IBD is emerging as a promising potential treatment option for patients with CPI-induced colitis. Small studies have shown that vedolizumab leads to colitis remission in patients with CPI-induced colitis that is steroid refractory with favorable outcomes and good safety profiles [68,69]. Furthermore, early introduction of selective immunosuppressive agents such as infliximab and vedolizumab may be associated with more favorable clinical outcomes [70]. A patient with Crohn's disease was successfully treated for advanced melanoma with concurrent anti-PD-1 and vedolizumab without autoimmune disease flare [71]. Whether selective inhibition of T cell migration to other tissues affected by CPIs is feasible is not yet known.

A preclinical model suggests that B cell targeted therapies may potentially be used to treat irAEs without impacting anti-tumor activity [81]. Rituximab, an antibody targeting CD20, has been used as an alternate or additional therapy in steroid refractory neurological complications of CPIs, such as encephalitis and MG, [82,83], bullous pemphigoid-like skin disease [40], renal vasculitis[84], and hematological complications[85]. Intravenous immunoglobulins have also been used [12,85]. Tocilizumab, an IL-6 receptor antagonist, has been used in patients, mostly with lung cancer, treated with anti-PD-1 and with steroid refractory irAEs[86]. Clinical improvement was noted in 79.4% of patients but further work is necessary to better understand the efficacy and impact on clinical course of this inhibitor. Tocilizumab has also been used to successfully treat severe CPI-induced inflammatory arthritis[87]. A case of a patient with preexisting autoimmunity on anti-PD-1 for colon cancer developed skin and GI complications that were successfully reversed with IL-17 blockade [88]. However, IL-17 blockade led to tumor progression. A patient with melanoma and with anti-PD-1 induced psoriasiform dermatological complication responded to IL-17A blockade without altering the patient's tumor response [89].

Manipulation of the gut microbiome may be a potential mechanism for preventing the development of colitis. Fecal transplant has been successfully used for the treatment of refractory CPI-induced colitis, possibly through a Treg mediated process [90]. However, there is evidence that higher gut microbiome diversity is associated with improved tumor

response [91] and antibiotic consumption is associated with reduced response to anti-PD-1 treatment [92]; microbiome manipulation could potentially impact cancer course.

Conclusions:

Autoimmune side effects of CPIs are frequent and, in some cases, can have significant morbidity and even mortality. The pathophysiology of the irAEs is related to the mechanisms of action of the CPIs but the organ(s) affected vary according to the CPI and other patient factors including HLA. Many of the irAEs resolve or can be treated with brief courses of glucocorticoids. Others, including endocrine and cardiac irAEs may be permanent or have dire consequences. Further studies may identify immediate causes of the irAEs or may identify those individuals at highest risk to avoid morbidity and potentially prevent the onset without affecting the anti-tumor response.

Acknowledgements

Abbreviations:

CPI	checkpoint inhibitor
CTLA-4	cytotoxic T-lymphocyte antigen 4
DM	diabetes
G-CSF	granulocyte colony-stimulating factor
GM-CSF	granulocyte-macrophage colony-stimulating factor
HLA	human leukocyte antigen
IBD	inflammatory bowel disease
irAE	immune-related adverse event
mAb	monoclonal antibody
MCP-1	monocyte chemoattractant protein-1
MG	myasthenia gravis
NSCLC	non-small cell lung cancer
PD-1	programmed cell death 1

PD-L1	programmed cell death ligand 1
RCC	renal cell carcinoma
RF	rheumatoid factor
T1D	type 1 diabetes
TIL	tumor-infiltrating lymphocytes
Trm	tissue-resident memory T cell

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Highlights

- Adverse events are frequent with checkpoint inhibitors and occurs with all tumor types

- A single mechanism has not emerged as explaining all of these adverse events

- Host factors such as genotype and microbiome may affect risk of the adverse events

- Studies are identifying ways to stop adverse events without impeding tumor response
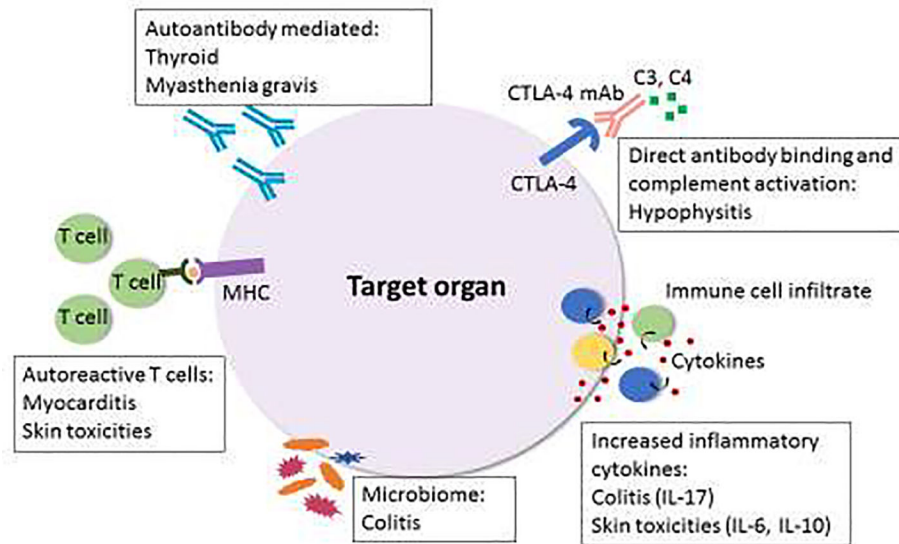
Figure 1. Potential mechanisms of CPI-induced immune related adverse events.
Mechanisms of irAEs vary depending on the organ system affected and type of CPI. The pathophysiology of irAEs remains largely unknown but postulated mechanism are shown. Although frequency of autoantibodies is lower than in spontaneous autoimmune disease, autoantibodies may paly a role in some autoimmune complications, including thyroid dysfunction where presence of autoantibodies at baseline increases risk of this complication. Direct CTLA-4 mAb binding to pituitary cells and complement activation may lead to hypophysitis. Inflammatory cytokines also seem to play a role in the development of certain irAEs. T cell mediated processes, in particular autoreactive T cells, may be involved in the development of myocarditis and skin toxicities. The microbiome may impact risk of developing irAEs, such as colitis, and may also be mechanistically important.

Table 1:

Predictors of adverse events following checkpoint inhibitor therapy

Genotype	• High risk T1D HLA alleles, such as HLA-DR4, in patients with CPI-induced DM [10, 14] • HLA-DRB1*04:05 association with CPI-induced inflammatory arthritis [33] • HLA-DRB1*11:01 association with CPI-induced pruritis [48]
History of autoimmune disease	• irAEs may be more frequent and occur sooner in patients with underlying autoimmune disease [49, 50]
Baseline autoantibodies	• Presence of thyroid autoantibodies at baseline increase risk of thyroid dysfunction [28–30] • Skin irAEs may be more frequent in patients with positive RF at baseline [30] • Baseline autoantibody signatures, such as those targeting TNFα signaling pathways may be predictive of irAEs [34]
Cytokine levels	• Baseline IL-17 levels may predict CPI-induced colitis [38] • IL-1β, IL-2, and GM-CSF at baseline and early decreases in IL-8, G-CSF, and MCP-1 predict thyroid dysfunction [41] • Cytokine toxicity score predictive of severe irAEs [93]
Immune cell changes	• Reduction in circulating B cells, increase in CD21lo PD-1+ B cells and plasmablasts precede adverse events [25] • Neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio may predict appearance of irAEs [94]
Microbiome	• Baseline microbiome enriched for *Faecalibacterium* predictive of colitis [43] • Abundance of *Bacteroidetes phylum* may be protective for development of colitis [44]
Tumor burden	• High tumor burden in NSCLC associated with higher risk of severe irAEs [95]

Abbreviations: DM: diabetes, G-CSF: granulocyte colony-stimulating factor, GM-CSF: granulocyte-macrophage colony-stimulating factor, HLA: human leukocyte antigen, irAE: immune-related adverse event, MCP-1: monocyte chemoattractant protein-1, NSCLC: non-small cell lung cancer, RF: rheumatoid factor, T1D: type 1 diabetes

Table 2:

Therapies for checkpoint inhibitor related adverse events

Drug name	Mechanism of action	Examples of efficacy in reversing irAE	Effect on tumor response	Clinical trial
Routinely used immunosuppressants:				
Glucocorticoids	Anti-inflammatory agent	• 1st line therapy for most irAEs. • Not effective for reversing endocrinopathies.	• Some studies suggest that tumor response and survival are not affected by steroids [52, 53, 58] whereas others show possible negative impact [54, 59–63]. • *In vitro* data suggests negative impact on anti-tumor effects of TILs [67].	
Infliximab	TNFα mAb	• Colitis [17, 64] • May be safer and result in faster resolution of symptoms compared to steroids for colitis [64,65]. • Others: Myocarditis, pneumonitis, uveitis [12]	• No known negative impact on tumor response [64,65]. • Preclinical studies suggest that anti-tumor response is maintained [66,67].	
Emerging and potential future therapeutic options:				
Vedolizumab	Gut specific integrin α4β7 mAb	• Colitis [68–70] • Potential benefit in preventing autoimmune flares in patients with IBD? [71]	Clinical outcomes favorable [69, 71].	NCT04407247: Comparison of vedolizumab vs infliximab for clinical remission/response of CPI-induced diarrhea/ colitis
Alemtuzumab	CD52 mAb	Myocarditis [78]	Unknown	
Abatacept	CTLA-4 agonist	• Myocarditis [79] • CPI-induced worsening of myasthenia gravis (MG) [80]	No tumor progression at 1 month [79]	
Rituximab	CD20 mAb	Neurological complications (eg encephalitis and MG), bullous pemphigoid-like skin disease, renal vasculitis, hematological complications [12, 40, 82–85]	Mixed: progression, partial and complete responses reported [82–84]	NCT03719131: Comparison of irAEs in patients on CPIs with or without rituximab
Tocilizumab	IL-6 receptor antagonist	• Pneumonitis, serum sickness/SIRS, cerebritis, colitis, pancreatitis and coagulopathy [86] • Inflammatory arthritis [87]	• No statistically significant difference in overall survival but limited by small size and with trend towards worse survival with increased doses of tocilizumab [86]. • 1/3 patients maintained durable anti-tumor response [87].	NCT03601611: Benefit of tocilizumab on diarrhea and/ or colitis and/ or arthritis induced by CPIs
Secukinumab	IL-17A mAb	• Psoriatic rash and colitis [88] • Psoriasiform dermatological complication [89]	Tumor progression occurred in one patient [88] but in the other there was no impact on tumor response [89].	
Fecal transplant	Possibly due to increased Tregs and decreased effector T cells [90]	Colitis [90]	Unknown	• NCT04038619: Phase I trial of fecal transplant for CPI-induced colitis/ diarrhea • NCT04163289:

Drug name	Mechanism of action	Examples of efficacy in reversing irAE	Effect on tumor response	Clinical trial
				Preventing irAEs using fecal transplant

Not included are other immunosuppressants occasionally used/recommended for treatment of irAEs such as mycophenolate mofetil, tacrolimus, cyclophosphamide, intravenous immunoglobulin, and anti-thymocyte globulin [12].

Abbreviations: IBD: inflammatory bowel disease, irAE: Immune related adverse event, mAb: monoclonal antibody, MG: myasthenia gravis, SIRS: systemic inflammatory response syndrome, TIL: tumor-infiltrating lymphocytes