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Immune checkpoint inhibitors: From friend to foe

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ABSTRACT

Immune checkpoints are crucial in regulating the activation of cell-mediated and humoral immune responses. However, cancer cells hijack this mechanism to evade the immune surveillance and anti-cancer response. Typically, receptors like PD-1 and CTLA4, expressed on immune cells, prevent the activation and differentiation of T cells. They also inhibit the development of autoimmune reactions. However, ligands such as PD-L1 for the receptor PD-1 are also expressed on the surface of cancer cells that help prevent the activation of anti-cancer immune responses by blocking the signalling pathways mediated by PD-1 and CTLA4. Immune checkpoint inhibitors (ICIs) have promising therapeutic efficacy for treating several cancers by activating T cells and their differentiation into effector cells against tumours. Nonetheless, hyperactivated immune cells usually contribute to detrimental issues, also known as immune-related adverse effects (IrAE). IrAEs have been observed in multiple organs, leading to neurological issues, colitis, endocrine dysfunction, renal issues, hepatitis, pneumonitis, and dermatitis. The interplay between hyperactivated T cells and Treg cells helps in orchestrating the development of autoimmunity. Moreover, the crosstalk between proinflammatory interleukins and the development of autoantibodies also mediates the multiorgan effects of ICIs in cancer patients. IrAEs are generally managed by terminating the ICI therapy, reducing the ICI dose, and by using corticosteroids to subvert inflammation. Therefore, the present review aims to delineate the impacts of ICIs on the development of autoimmune diseases and inflammatory outcomes in cancer patients. In addition, mechanistic insight involving immune cells, cytokines, and autoantibodies for ICI-mediated IrAEs will also be discussed with updated findings in this field.

1. Introduction

Immune checkpoints are critical regulatory mediators that control the activation of immune cells and autoimmunity to block detrimental impacts on their own cells and organs. However, cancer cells exploit this mechanism to block anti-cancer effects and favour their growth and metastasis. Programmed cell death-1 (PD-1) is an important receptor and a key component of the immune checkpoint expressed in the immune cells, particularly in the T cells. The receptor suppresses the inactivation of T cells and, therefore, regulates the entire immune homeostasis. Structurally, the PD-1 is a transmembrane receptor composed of an extracellular IgV-like domain, a transmembrane domain, and an intracellular immunoreceptor tyrosine-based inhibitory motif. Programmed cell death-Ligand 1 (PD-L1) is a protein ligand expressed on the surface of antigen-presenting cells such as dendritic cells and macrophages. However, cancer cells can also express PD-L1 to control the activation of immune cells. Interaction of PD-L1 with PD-1 results in the inhibition of T cell activation and prevention of autoimmune disease by maintaining self-tolerance. Cancer cells also take advantage of this system by expressing the PD-L1 on their surface and suppressing the activation of immune response against them. Thus, this outcome favours immune suppression for the progression of the tumor environment. Deletion of PD or PD-L1 results in several health effects at later stages of life. These adverse effects range from cardiomyopathy to arthritis [1].

Similar to PD-1, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) is a crucial component of the immune checkpoint that governs the activation of T cells. CTLA-4 is a transmembrane receptor with an extracellular, transmembrane and intracellular domain. This receptor is specifically expressed on immune cells like regulatory T cells (Treg), activator T cells, dendritic cells, and macrophages. Ligands for CTLA-4 include B7–1 (CD80) and B7–2 (CD86). Interaction between the ligand and protein triggers a signalling cascade that results to the inactivation of T cells and immune response. Cancer cells also hijack this pathway to suppress anti-cancer immune activation to favour cancer progression and metastasis.

Therefore, targeting the immune checkpoints offers a promising therapeutic strategy to control tumour development and progression. In light of this, several immune checkpoint blockers (ICB) have been

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developed to target cancer progression. ICBs such as nivolumab and pembrolizumab have been synthesized to target PD-1, while other ICBs such as atezolizumab and durvalumab have been designed to target PD-L1. All of these ICBs block the interactions between PD-1 and PD-L1 to activate T cells and an effective anti-cancer immune response. ICBs like ipilimumab target CTLA-4 and prevent T cell inactivation. By triggering the activation of T cells, ICBs have shown promising results as therapeutic agents to treat various types of cancers, such as melanoma, lung cancer, renal cancer, and lymphoma. Clinical trials have improved overall survival and response rates compared to conventional chemotherapy. The efficiency of ICBs may be enhanced when combined with other traditional therapeutic strategies.

Despite several therapeutic benefits, ICBs can induce immune-related adverse effects (IrAEs), such as the onset of inflammation and autoimmune diseases. More specifically, ICBs may promote dermatitis, colitis, hepatitis, lung inflammation, and nephritis. Other toxicity, such as inflammation in the nervous system, endocrine glands, and the gastrointestinal system, can also be promoted by hyperactivated immune response following treatment with ICBs. Of note, fetal toxicity can be associated with 0.4–1.2 % of cases [2]. Blocking PD-1 or PD-L1 by different agents in clinically relevant doses can produce high-grade toxicity in 10–15 % of patients. However, the figure may exceed 38.6 and 57.9 % in cancer patients, when CTLA-4 is blocked by ipilimumab at doses of 3 mg/kg or 10 mg/kg, respectively [3]. ICB-mediated IrAE usually occurs during the first three months of treatment. However, the adverse immune effects may also occur several months after the therapy ends [4]. Organs more severely impacted include the liver, skin, kidney, and gastrointestinal tract. Pre-existing autoimmunity in joints and the thyroid also worsens the effects of IrAE. Therefore, careful observation and management of ICB-mediated IrAEs are inevitable for effective treatment of cancer. In addition, research focusing on identifying biomarkers of ICB-induced toxicity and developing strategies for effective management is currently warranted. Exploring new targets such as TIGIT, TIM-3, and LAG-3 can overcome the resistance and help minimize existing toxicities. The development of ICI-mediated IrAEs can result in the termination of immunotherapy in patients. In some cases, overstimulated immune responses can be treated with a suppressant or corticosteroid. However, the application of immunosuppressants can interfere with the anti-tumour responses of the immune system. However, in some cases, patients may become unresponsive to the steroid treatment, resulting in chronic disease. In these patients, lifelong therapy with immunosuppressants and hormones may be required as treatment measures [5].

Hence, the present review aims to discuss the latest advancements in ICIs and their application in cancer treatment. The present study also delineates the IrAEs and their biomarkers following treatment with ICIs in cancer patients. Moreover, an underlying mechanism for the onset of IrAEs following ICI-administration in cancer patients will also be illuminated.

2. Literature search strategy

Scientific databases such as Scopus and PubChem were employed to search the relevant literature for qualitative synthesis of the present review. Search terms like “immune checkpoint inhibitors and immune-related adverse effects”, “immune checkpoint inhibitors and cutaneous toxicity”, “immune checkpoint inhibitors and colitis”, “immune checkpoint inhibitors and neurotoxicity”, “immune checkpoint inhibitors and endocrine dysfunction”, “immune checkpoint inhibitors and myocarditis”, “immune checkpoint inhibitors and rheumatological issues”, “immune checkpoint inhibitors and pulmonary toxicity”, “immune checkpoint inhibitors and autoantibody and cytokines”, “immune checkpoint inhibitors and immune-related adverse effects and biomarkers” were used. Relevant articles were screened based on title and abstract. Only relevant articles were accessed and used for the qualitative synthesis of the review. Articles like encyclopaedia, editorials, letter to the editor, and viewpoints were not considered for inclusion. Only the articles published in English were taken into the consideration.

3. Interplay between ICIs and IrAEs

Monoclonal antibodies like nivolumab, dostarlimab, cemiplimab, and pembrolizumab are the ICIs for the PD-1, expressed on the T cells. Other monoclonal antibodies, such as avelumab, durvalumab, and atezolizumab, function as inhibitors for the PD-L1 expressed on the cell surface of the antigen-presenting cells as well as cancer cells. Ipilimumab acts as the ICI of the CTLA-4. Interactions between immune checkpoint mediators are essential to regulate T cell activation and prevent autoimmunity. However, binding of ICI with the receptors and their ligands could break the interactions and signalling pathways, leading to the activation of T cells and the immune response. This immune response also plays a critical role in blocking cancer progression and metastasis. However, ICI-mediated hyperactivation of the immune response and hyperinflammation could be detrimental to the self-organisms, causing the IrAEs. Studies have suggested a positive correlation between the therapeutic responses and the incidence of IrAEs. Sometimes, the ICI-mediated antitumor activities and onset of autoimmune response can be mechanistically linked to each other. For instance, the occurrence of an autoimmune reaction against the melanocytes can be a reliable indicator of antitumor activity in patients with melanoma [6]. Targeting certain proinflammatory cytokines, such as IL6, implicated in ICI-mediated autoimmune response, can be effective to minimize anti-host responses of the hyperactivated immune system [7].

It is worth mentioning that IrAE can be influenced by both tumor-related and tumor-independent factors. In a patient suffering from hepatocellular carcinoma, treatment with nivolumab resulted in the onset of insulin-dependent diabetes and ketoacidosis. However, the patient did not have any earlier history of diabetes [8]. Similar onset of autoimmune diabetes mellitus in patients with lung cancer has also been found after treatment with nivolumab. The development of islet autoantibodies might have a critical role in such immune-linked adverse outcomes [9]. Generally, the ICI for CTLA-4 is also associated with the development of skin rashes, colitis, and hypophysitis. However, in the case of inhibitors for PD-1 and PD- L1, the most common adverse outcomes have been reported to be thyroid issues and pneumonia. Therefore, the combined adverse effects of CTLA-4 and PD-1/PD-L1 are commonly attributed to the endocrine and cutaneous issues [10]. Studies have suggested that the development of IrAE can be governed by several factors, such as age, gender, existing autoimmune diseases, and the type of ICI used [11].

Due to the possibilities of adverse outcomes, only 20–40 % of the patients benefit from the treatment employing various ICIs. In comparison, around 40 % of these patients suffer from auto-immune related side effects, mainly associated with rheumatological, hepatic, cardiac, and gastrointestinal ailments [12–14]. Therefore, PD-1 and CTLA-4 play a critical role in maintaining peripheral tolerance and suppression of autoimmunity and exacerbated inflammatory responses. However, implications of various ICIs either in suppression of the PD-1-mediated signaling or blockage of the CTLA-4 functions could propagate to the manifestation of IrAEs. Therefore, in cancer patients, the development of adverse effects in multiple organs is suggestive of a strong correlation between the use of ICI and the IrAEs (Fig. 1).

4. ICIs and their targets

PD-1 is a major protein in the immune checkpoint that belongs to the type I transmembrane glycoprotein. It contains a single extracellular domain, a transmembrane domain, and a cytoplasmic domain. The cytoplasmic domain of PD-1 has an immunoreceptor tyrosine-based switch motif (ITSM) and an immunoreceptor tyrosine-based inhibitory motif (ITIM) [15]. PD-1 is generally expressed on activated T cells. However, they can also be found in myeloid cells, neutrophils, dendritic

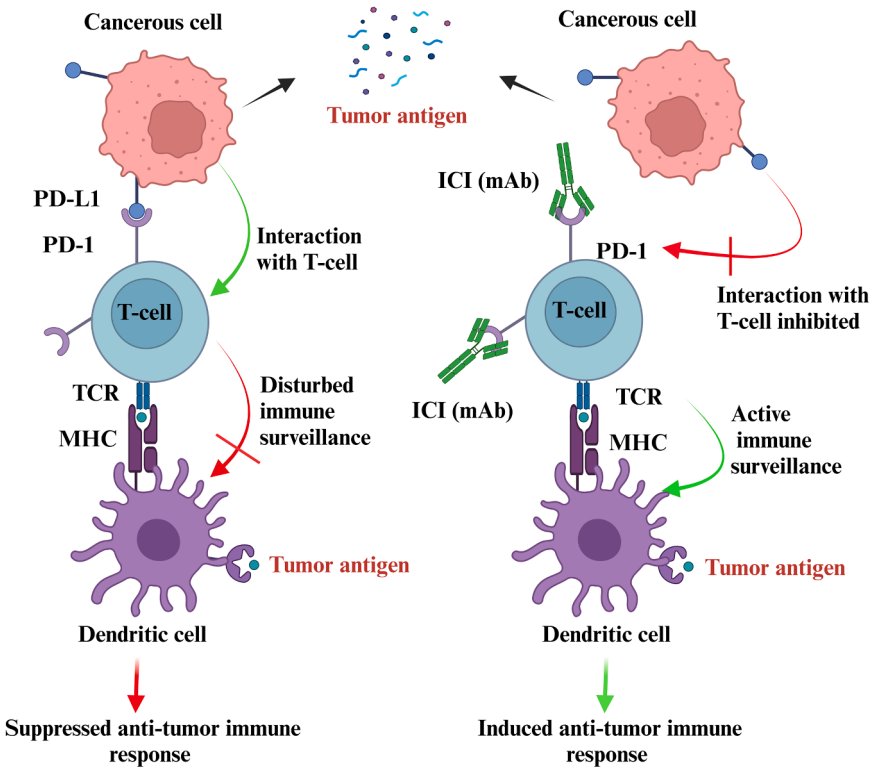

Fig. 1. Immune response regulation by ICIs. Cancer cells express ligands for the PD-1 expressed on the T cells. PD-L1 of cancer cells interacts with the PD-1 on T cells to block the subsequent signalling required to activate anti-tumour response. However, ICIs exhibit competitive binding for PD-1, and they prevent the PD-L1 on cancer cells from interacting with the PD-1. This results in the activation of an anti-tumour immune response mediated by various subsets of T cells.

cells, and natural killer cells. The predominant ligand for PD-1 is PD-L1 and is found in T cells, mast cells, macrophages, B cells, and dendritic cells. When PD-L1 binds to its receptor PD-1, the ITSM and ITIM get phosphorylated at their tyrosine residues, leading to the recruitment of Src homology 2 domain-containing tyrosine phosphatase 2 (SHP2). The activated PD-1 forms clusters with the T cells receptor and triggers dephosphorylation of the T cells receptor leading to suppression in T cells activation. SHP-2 dephosphorylates the downstream signalling molecules such as ZAP70, PI3K, and Ras, resulting in the down-regulation of AP-1, NFAT, and NF-κB, which are involved in the activation of T cell receptors, proliferation, and functions of effector cells. This pathway can be hijacked by tumour cells expressing PD-L1 to evade immune surveillance.

Monoclonal antibodies have been developed to block the PD-1/PD-L1 pathway to induce an anti-cancer immune response. Nivolumab was the first anti-PD-1 monoclonal antibody that was approved by FDA against metastatic melanoma due to high survival rates [16]. Later, another monoclonal antibody, such as pembrolizumab, was developed as an anti-PD-1 agent to treat advanced melanoma due to its manageable IrAE. Other anti-PD-1 antibodies include toripalimab, dostarlimab, and cemiplimab that are effective in targeting various tumours [17,18]. Monoclonal antibodies targeting PDL1 include durvalumab, atezolizumab, and avelumab that targets local metastatic cancers [19]. Antibodies such as durvalumab, envafolimab, and sugemalimab have shown improvement in treating non-small-cell lung cancer (Table 1).

CD28 is the receptor found in APCs and binds with the ligands CD80 and CD86 to induce T cell activation and proliferation. However, CTLA-4, a transmembrane receptor, has higher binding affinity for CD80 and CD86 than CD28. Therefore, the binding of CTLA-4 with the CD80/86 prevents CD28 from interacting with the ligands, leading to the suppression of T cell activation. Targeting CTLA-4 with monoclonal antibodies is also a promising therapeutic strategy against carcinomas. Ipilimumab and tremelimumab are the major monoclonal antibodies used to target CTLA-4b [20,21]. Tremelimumab is a humanized IgG2 monoclonal immunoglobulin that has been used to increase the response of T cells against tumours. The activation of effector T cells is orchestrated by complex interactions. Interaction between CD28 of T cells and CD80/CD86 of APC triggers signalling employed in the activation of

Table 1
ICI, their target molecules, and applications.

ICI	Target molecule	Used in cancer	Reference
PD1	Pembrolizumab	Non–small cell lung cancer	[168]
	Nivolumab	Stage III-B or IV Squamous non–small cell lung cancer	[169]
	Cemiplimab	Metastatic cutaneous squamous cell carcinoma	[170]
PD-L1	Atezolizumab	Non–small cell lung cancer	[171]
	Avelumab	Metastatic Merkel cell carcinoma	[172]
	Durvalumab	Non-small-cell lung cancer	[173]
CTLA4	Ipilimumab	Malignant melanoma	[174]
	Tremelimumab	Advanced biliary tract carcinoma	[175]
LAG−3	Relatlimab	Melanoma	[176]
TIM−3	Sabatolimab	Myeloid cells neoplasms	[22]
	Cobolimab	Malignant carcinoma	[177]

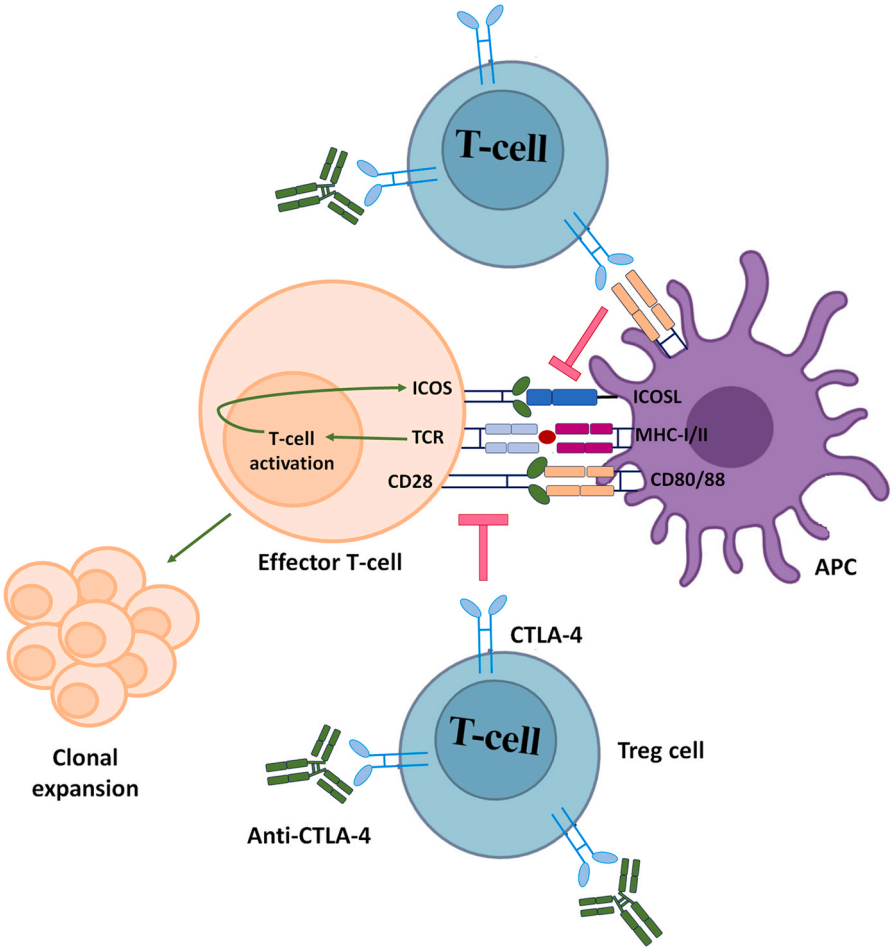

Fig. 2. Activation of effector T cells. Interaction between the CD28 of T cells and CD80/CD86 of APC is essential for activation of effector T cells. CTLA-4 has higher affinity for CD80/CD86 and therefore inhibits the differentiation of T cells by decreasing IL2 expression and promoting the expression of IL-2Rα (CD25) on activated T cells. Effector T cells are differentiated using clonal proliferation.

effector T cells. CTLA-4 has a greater affinity for CD80/CD86 and therefore blocks the T cell differentiation by decreasing IL2 expression and promoting the expression of IL-2Rα (CD25) on activated T cells. The multiplication of effector T cells occurs through clonal proliferation (Fig. 2). Tregs orchestrate the down-regulation of anti-tumour immunity by expressing CTLA-4 on their surface. CTLA-4 of Tregs interacts with the CD80/CD86 to impair the antigen presentation by APCs. This, in turn, enables the tumour cells to escape anti-tumor immunity. Through PKC signalling, Tregs decline the expression of CD80/CD86. Moreover, the population of Tregs increases through CD28 co-stimulatory signals to reduce CD80 and CD86 expression. Therefore, ICIs aid in Treg population reduction and preservation of effector T cell activities to augment anti-tumour immunity (Fig. 3).

Other important immune checkpoint proteins include LAG-3 (CD223) and TIM-3 (CD366), which can be blocked by monoclonal antibodies to treat metastatic carcinoma. Relatlimab is a monoclonal antibody used against LAG-3 to restore T cell function. Sabatolimab is a humanized IgG4 antibody used against the TIM-3 to manage myeloid cell neoplasms [22]. Another antibody used against the TIM-3 is cobolimab that helps activate T cells function (Fig. 4).

5. ICI-mediated adverse effects

5.1. ICI-mediated cutaneous toxicity

ICI-mediated adverse effects on skin-related issues following treatment with ICI are common in patients. Approximately 30–50 % of patients face inflammatory and blistering dermal issues. However, these skin-related issues are generally mild and do not require the termination of ICI-based treatment. Notably, the onset of dermal issues can occur within four weeks of treatment with ICIs. Nonetheless, the period may vary from 2 to 150 weeks [23,24]. Further, the skin-associated complications can be much higher (up to 60 %) in the case of treatment with anti-CTLA-4 compared to the treatments with anti-PD-L1 or anti-PD-1 inhibitors. With the use of ICIs for PD-1 and PD-L1, skin-related adverse effects may be found in 20 % of the patients [25]. The higher dermal issues (59–72 %) are frequently detected in cases of combination therapy with the anti-CTLA-4 and anti-PD-L1 or anti-PD-1 inhibitors [26].

The extract mechanism of ICI-mediated dermatologic toxicity is not clear. However, some studies suggest the differential distribution of lymphocytes in the dermal tissues of patients recovered through biopsies. In a study, patients with melanoma who underwent treatment with ICI for PD-1 suffered from detrimental cutaneous reactions. Biopsies of samples have revealed excessive accumulation of $CD8^+$ T cells at the dermo-epidermal junctions. Results were suggestive of the fact that $CD8^+$ T-cells might have released cytotoxic factors through exocytosis that resulted in the lysis of keratinocytes. Moreover, the expression of genes such as CCL27, NURR1, GLY, FASLG, and PRF1 associated with cutaneous inflammation was upregulated in patients who underwent anti-PD-1 therapy. Moreover, genes such as PI3, SPRR2B, GZMB, CXCL9, CXCL10, and CXCL11, involved in cellular toxicity, have been over-expressed in the cutaneous tissue of the patient compared to the healthy subjects [27]. In another investigation, immune

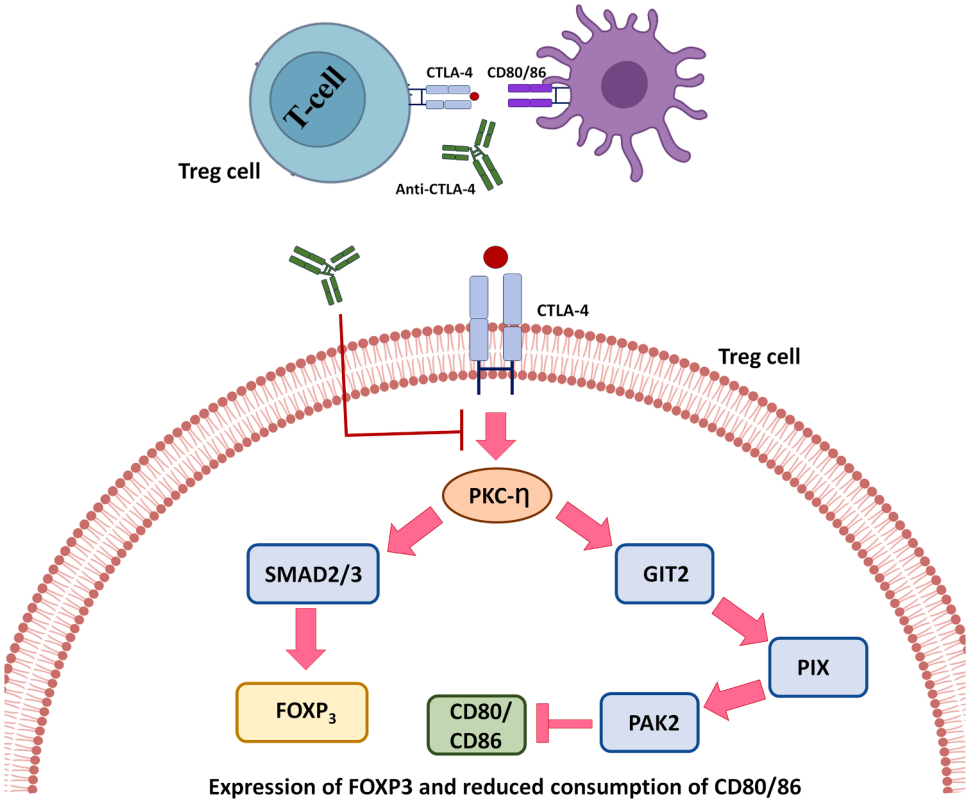

Fig. 3. Regulation of Treg and effector T cell activity by ICIs. Tregs orchestrate the suppression of anti-tumour immunity by expressing the CTLA-4 on their surface. CTLA-4 of Tregs interacts with the CD80/CD86 to disrupt the activities of APCs. This in turn impairs the antigen presentation by the APCs enabling the tumour cells to escape anti-tumour immunity. Tregs through PKC signalling is associated with the depletion of CD80/CD86. Moreover, Tregs also expand their population through CD28 costimulatory signals to deplete CD80 and CD86 expression. Therefore, ICIs aid in depletion of Tregs and preservation of effector T cell activities to augment anti-tumour immunity.

cells, such as $CD3^+$ lymphocytes and Foxp3 Treg cells, were invariably present in the skin tissues of patients with melanoma [28]. These immune infiltrates might be linked to adverse effects on the skin. Patients treated with ICI have suffered from lichenoid dermatitis characterized by the upregulation of various genes, including TLR2 and TLR4. Moreover, elevated numbers of $CD14^+$ and $CD16^+$ monocytes were apparent compared to the control samples of benign lichenoid keratosis. These changes were suggestive of TLR-mediated cascades that might have contributed to lichenoid dermatitis in patients who underwent ICI therapy [29]. Studies have also correlated cutaneous toxicity with cytokine levels. In a study, patients undergoing ICI therapy developed skin rashes along with increased levels of serum angiopoietin-1 (Ang-1) and CD40L, indicating their potential contribution to skin-related toxicities [30]. Moreover, in another study, elevated levels of cytokines such as serum IL-6 and IL-10 were also associated with cutaneous toxicities. In these patients undergoing ICI therapy, comparatively higher numbers of allergenic eosinophils and Ig E were also evident to cause severe skin-related issues [31]. Studies have also suggested the involvement of a complement system in skin tissue damage. Patients treated with anti-PD-1 and anti-PD-L1 have developed an autoimmune disease called bollous skin disorders. In these subjects, IgG and complement protein 3 were much higher than the basal levels, suggesting the potential implications of the complement system and membrane attack complex in skin damage [32]. These studies suggest that both the mediators of innate and adaptive immunity are involved in cutaneous toxicity in cancer patients undergoing ICI therapy.

5.2. *ICI-mediated colitis*

ICIs, particularly those targeting CTLA-4 and PD-1/PD-L1, have been associated with an increased risk of developing colitis, a type of inflammatory bowel disease. Immune-mediated colitis mainly occurs when the exacerbated immune response triggered by anti-CTLA-4 and anti-PD-1/anti-PD-L1-based therapies mistakenly targets the healthy tissues of the gastrointestinal tract. Approximately 8–27 % of cases suffer from ICI-mediated colitis, while up to 54 % of cases have been reported with ICI-associated diarrhea [33]. However, the type of ICI regimens is the crucial factor for such toxicities. The exact mechanisms underlying ICI-induced colitis are yet to be delineated. However, it may involve the disruption of immune homeostasis in the gut, leading to an imbalance between effector T cells and regulatory T cells. This imbalance triggers an inflammatory cascade characterized by increased cytokine production, activation of immune cells, and tissue injuries.

Excessive infiltration of $CD8^+$ has been detected in the lamina propria of the colon in ICI-mediated colitis [34]. The increase in the number of $CD8^+$ lymphocytes has been corrected with the severity of the colitis. In particular, tissue-resident memory ($CD69^+CD103^+$; TRM) cells can be the contributing factor for the elevated numbers of T cells in the colon [34]. Moreover, the differentiation of Trm cells into cytotoxic T cells results in their abundance and exacerbated cytotoxicity in the colon [34]. Higher proportions of $CD8^+$ in ICI-mediated colon have been associated with the increased expression of genes such as LAG-3, TIM-3, TIGIT, CTLA-4, and PDCD1 implicated in the immune checkpoints. Moreover, other genes, such as PRF1, GZMB, and HLA-DR, were also activated in subjects with ICI-mediated colitis [35]. IFN-γ also has implications in ICI-mediated colitis, as these inflammatory mediators contribute to the apoptosis of colonic cells along with the disruption of colonic vasculature.

In patients with ICI colitis, mucosal Treg cells can have higher numbers as a protective measure against inflammation. These cells can

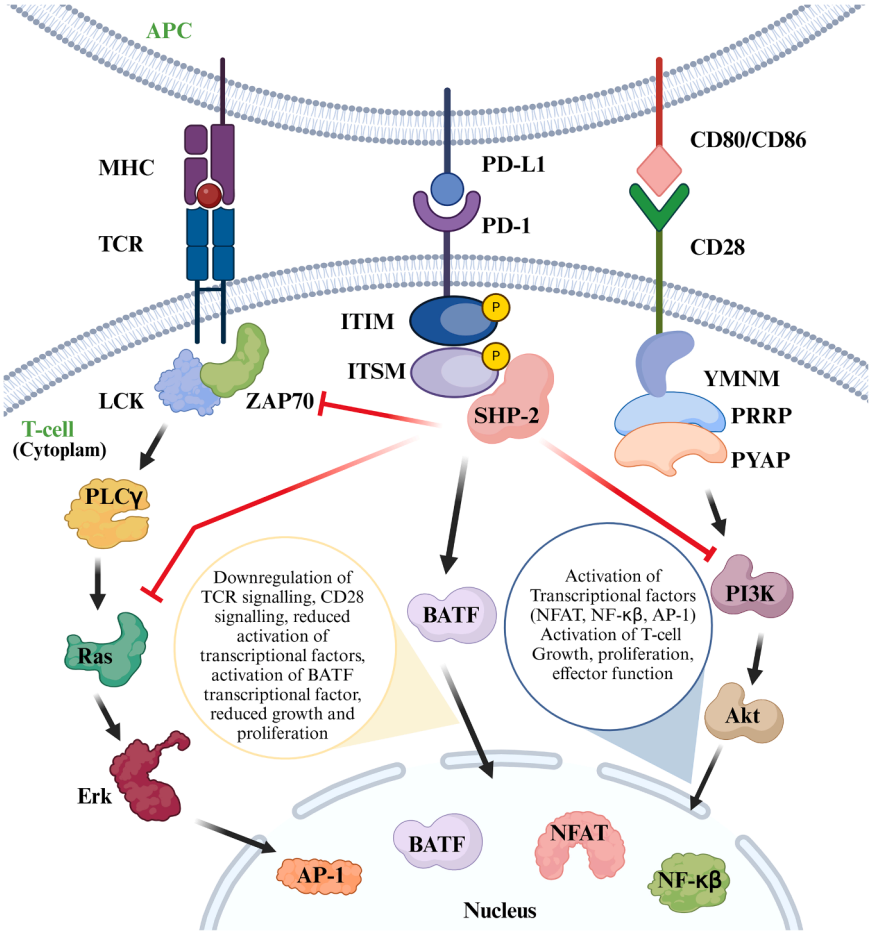

Fig. 4. Sub-cellular events leading to various immune responses. TCR interacts with the MHC on the APCs, activating the PLCγ/Ras/Erl-mediated signalling cascade. Similarly, interactions between CD28 and CD80/86 lead to the activation of the PI3K/Akt pathway. These signalling cascades activate transcription factors (AP-1, NFAT, NF-κβ) that promote growth, proliferation, and effector T cell functions. However, interaction of PD-1 with PD-L1 activates BATF that downregulates T cell proliferation and functions.

produce anti-inflammatory cytokines such as IL-10 and TGFβ to counteract the tissue damage [36]. Moreover, Treg cells have Th1-like characteristics and express CXCR3, IL12RB2, and STAT1, which may suppress effector cells producing IFN-γ. However, these counteracting measures might not be sufficient to curb the inflammatory and cytotoxic toxicities caused by ICI therapy. Therefore, the interplay between Treg and T cells ($CD8^{+}$) provides the underlying mechanistic route to develop ICI-mediated colitis in patients.

Major symptoms of ICI-induced colitis typically include diarrhea (92–100 %), abdominal discomfort (55–82 %), and haematochezia (55–64 %,) [37,38]. In severe cases, colitis might also lead to life-threatening health complications, such as bowel perforation and sepsis. Endoscopic examination has revealed the inflammation predominantly in the left colon, however it can also be found in other parts of the colon [39]. ICI-induced inflammation in the colon can result in loss of vascular pattern, edema, erythema, erosion, friability, and ulcerations. In case of chronic colitis, histopathological symptoms include crypt distortion and basal lymphocytic infiltration while in case of acute colitis, histopathology is characterized by abscesses, cryptitis, and neutrophilic infiltration [39]. In a study involving 1478 patients with ICI-treated cancer, the incidence rate of colitis was 3.5 % in patients treated with nivolumab and ipilimumab. However, in such cases, the mild symptoms of colitis were improved with supportive care [40]. Some common histopathologic manifestations are associated with ICI-mediated colitis. These include ischemic colitis, microscopic colitis (collagenous or lymphocytic), acute active colitis, and chronic active colitis. The mechanism for pathological manifestation encompasses autoimmune-type dysregulation and alteration of gut microbiome [41].

The incidence of ICI-induced colitis varies depending on the specific ICI used for the therapy. Generally, CTLA-4 inhibitors (e.g., ipilimumab) have a greater chance to induce colitis compared to PD-1/PD-L1 inhibitors [33]. Management of ICI-mediated colitis typically encompasses the application of corticosteroids and immunosuppressive agents, and, in some cases, discontinuation of ICI treatment may be required. Early recognition and therapeutic intervention are crucial to prevent long-term gastrointestinal damage caused by ICI-mediated colitis. Studies are needed to identify biomarkers of ICI-induced colitis and to develop strategies for mitigating this toxicity and associated IrAEs.

5.3. *ICI-mediated neurotoxicity*

ICIs have been documented to cause neurotoxicities in patients undergoing anti-PD-1/anti-PD-L1 and anti-CTLA-4 monoclonal antibodies. Such neurotoxicity is rare and found only in 1–6 % of patients treated with ICIs. Nonetheless, ICI-mediated neurotoxicity can be comparatively more fatal and accounts for up to 15 % of total ICI-related fatalities [42,43]. ICI-mediated neurotoxicity includes meningitis, encephalitis, Guillain-Barré syndrome, myasthenia gravis, and neuropathy. The underlying mechanism of neurotoxicity might involve ICI-induced disruption of immune homeostasis in the central nervous system (CNS) and the activation of auto-reactive T cells along with inflammatory mediators. PD-1/PD-L1 inhibitors (6.1 %), more commonly associated with neurotoxicity than CTLA-4 inhibitors (3.8 %). Nevertheless, the incidence percentage of neurotoxicity with the combined treatment

of ipilimumab and nivolumab has been reported in 12–14 % of patients. Of note, neurotoxicity usually occurs in 4 weeks. However, the symptoms may occur from 1 to 68 weeks [33]. In a study, 18 patients treated with ICIs such as nivolumab, pembrolizumab, atezolizumab, or ipilimumab for various malignancies have suffered from neurotoxicity. In these patients, a wide spectrum of neurologic effects such as myasthenia gravis (MG) (17 %) with concurrent myositis (6 %), aseptic meningitis (6 %), sensorimotor polyneuropathy (11 %), central demyelinating disorder (28 %), and hypophysitis (17 %) have been detected [44].

General symptoms of ICI-induced neurotoxicity include headache, confusion, seizures, weakness, and sensory dysfunctions. In severe cases, neurotoxicity can be associated with severe health issues, such as cerebral edema and status epilepticus in patients. The underlying immunological mechanism of ICI-induced neurotoxicity is vague. However, both the humoral and cell-mediated immunity can be associated with neurological issues. Patients treated with two cycles of pembrolizumab have been reported to develop transverse myelitis. Specifically, elevated levels of B cell chemoattractant, CXCL13, IgG, and $CD8^+$ plasma cells have been detected in samples of cerebrospinal fluid. Moreover, the formation of autoreactive antibodies was also apparent. These findings were suggestive of humoral immunity-mediated development of transverse myelitis in pembrolizumab-treated patients [45]. Notably, in a cohort study, approximately 63 % of patients with ICI-induced neurotoxicity were found to have auto-antibodies for neuromuscular tissues [46]. Moreover, the formation of auto-antibodies targeting the intracellular and surface antigens has been detected in around 45 % of the patients with ICI-induced toxicity [46]. In an *in vivo* study, mice treated with anti-PD-1 exhibited increased CD^{3+}, CD^{4+}, $CD^{4+}CD^{69+}$, and $CD^{4+}CD^{154+}$ T cells in their brain. Moreover, the microglial activation was also apparent, suggesting their active role in ICI-mediated neurotoxicity [47].

The severity of ICI-mediated neurotoxicity can be governed by several risk factors, such as the presence of pre-existing autoimmune disorders, brain metastases, and agents used for ICI-based therapy. Management typically involves the suppression of inflammation and tissue injuries using corticosteroids and immunosuppressive drugs. Early detection of ICI-induced neurotoxicity can be helpful in effective management without terminating the ICI therapy. Therefore, identifying potential biomarkers for ICI-induced neurotoxicity could be the major research need to enhance the safety of ICIs for individual or combinational therapy in cancer patients.

5.4. ICI-mediated endocrine dysfunction

ICI agents can potentially target the endocrine glands. In the majority of cases, the thyroid gland is vulnerable to ICI-mediated toxicities. Around 10 % of patients receiving anti-PD-1 and anti-PD-L1 antibodies suffer from hypothyroidism. However, the percentage of incidence can reach up to 20 % in patients undergoing combined therapy with ipilimumab and nivolumab. In some cases, thyrotoxicosis, characterized by hypersecretion of thyroid hormone, can also be an outcome following ICI therapy. Moreover, thyrotoxicosis can be asymptomatic [48]. The onset of thyrotoxicosis is temporary. Nonetheless, the proceeding hypersecretion of thyroid hormone can become a life-long condition [49,50].

The immunological basis of ICI-mediated thyroiditis is still unclear. However, certain studies indicate the involvement of inflammatory cytokines in the adverse effect outcome. In anti-PD-1 and anti-CTLA-4 treated mice, higher levels of IL17A were detected in the thyroid tissue of the mice. Moreover, Th17 and Tc17 cell cytokines were also elevated in mice treated with ICIs. Interestingly, the application of anti-IL17A antibodies helped reduce ICI-induced thyroid toxicity [51]. In another study, ICI treatment resulted in the accumulation of $CD8^+$ T cells, $CD4^+$ T cells, and macrophages in the tissues of thyroid glands. Moreover, infiltration of $ROR\gamma^+$ T cells in thyroid tissues was also apparently visible, suggesting the importance of these cells in proinflammatory cytokine production and tissue damage in thyroid glands [51].

Hypophysitis is a type of IrAE that occur commonly in ipilimumab-based therapy compared to treatment with anti-PD-1 and anti-PD-L1 antibodies, with a median onset of approximately 26 weeks [52]. Patients developing hypophysitis generally suffer from pituitary inflammation and symptoms of secondary adrenal insufficiency. Though the inflammatory outcome is transient, hypopituitarism can be long-lasting and often requires hormonal treatment [53]. Generally, the major manifestations of hypophysitis in patients include nausea, fatigue, asthenia, headache, nausea, weakness, and lethargy [54]. In some cases, visual disturbance may be seen. However, this outcome is not common, as in the majority of cases, swelling in the pituitary gland does not interfere with the optic chiasma [55].

In a study, anti-GNAL and anti-ITM2B antibodies have been detected in patients after treatment with ICI and were found 1.7–2.5 folds much higher compared to pretreated samples. Moreover, the anti-GNAL antibodies were comparatively higher in patients with hypophysitis than the individuals without hypophysitis. Therefore, it can be suggested that individuals with higher levels of anti-GAL antibodies can be at higher risk of developing hypophysitis after treatment with single or combinational ICIs [56].

Other endocrine toxicities can also be associated with the pancreas and the adrenal glands. In a study involving 76 patients, pancreatic autoantibodies were detected. Autoantibodies were found in varying percentages. For instance, anti-insulinoma-associated protein-2 (anti-IA2) antibodies were prevalent in 12 % of patients, and 19 % of patients had anti-insulin antibodies. Moreover, anti-ZnT8 antibodies were noted in 10 % of patients, while anti-glutamic acid decarboxylase 65 (anti-GAD65) antibodies were detected in 58 % of patients [57]. Notably, $CD4^+$ and $CD8^+$ T cells have been reported to be present in peri-islet regions of the pancreas. However, higher numbers of $CD45^+$ have been detected in the pancreatic exocrine region. Expression of inflammatory cytokines such as IFN-γ and TNF-α has also been found in pancreatic tissues, suggesting their potential role in inflammatory outcomes in the pancreas following ICI therapy. Interestingly, treatment with anti–IFN–γ and anti–TNF–α were effective in blocking the ICI-mediated diabetes mellitus in mice [58]. Therefore, pancreatic dysfunction could be attributed to the apoptotic changes in the Islet of Langerhans, thereby adversely impacting insulin secretion, leading to the manifestation of diabetes mellitus [59]. Development of autoantibodies and inflammation against the adrenal cortical tissues can result in adrenal insufficiency with hyposecretion of adrenal hormones.

5.5. Myocarditis induced by ICIs

ICIs have been associated with myocarditis, which is rare, affecting 1 % of patients, but potentially life-threatening inflammatory conditions affecting the cardiac muscle with a fatality rate of 39.7 % [60]. Patients treated with ICIs can suffer from myocarditis depending upon several factors, such as underlying inflammatory conditions, cardiovascular diseases, and the dose and type of ICIs being used in therapy. In a study involving 709 patients with lung cancer, around 5.5 % of patients treated with durvalumab suffered from cardiac adverse effects [61]. Of note, cardiac adverse effects have a higher incidence rate in cases of combined therapy (such as ipilimumab and nivolumab), in old-age patients (above 75 years old), and in female patients.

ICIs usually destroy the cardiac muscles via autoimmune reactions that can be triggered following the occurrence of an imbalance between effector T cells and regulatory T cells. Moreover, exacerbated synthesis of proinflammatory cytokines can also result in myocardial tissue injuries through apoptotic-cascade activation. Clinical presentation of ICI-mediated mycarditis includes chest pain, shortness of breath, fatigue, electrocardiogram changes, elevated troponin, natriuretic peptides, and creatine kinase levels [62,63]. Moreover, patients with fulminant disease may manifest with cardiac shock, arrhythmias, and even cardiac

arrest [63]. Histological investigation has revealed that ICI treatment favours myocardial necrosis and lymphocyte infiltration. More specifically, $CD8^+$ cell infiltration is comparatively higher in inflammatory tissues of the myocardium. Depletion of $CD8^+$ T cells has been associated with reduced cardiac adverse effects caused by ICI treatment. Therefore, it is apparent that $CD8^+$ T cells act as the major driver in the development of myocarditis [64]. In a study, patients who developed ICI-induced myocarditis had higher CD45RA re-expressing $CD8^+$ T cells. These cells are highly cytotoxic and express different chemokines, such as CCL4 and CCL5 [65].

Treatment of patients with engineered T cells targeting the immune checkpoint protein, MAGEA3, have been reported to inflict carditis, cardiac shock, and ultimately death. The findings suggested that the engineered T cells had an off-target cross-reactivity with titin, which is a cardiac myofilament protein [66]. This cross-reactivity might be the reason for inflammatory outcomes in the heart. In a study, PD-1-deficient mice have been found to develop dilated cardiomyopathy and premature death. In these mice, cardiomyopathy was found to be promoted by IgG antibodies [1]. These IgG immunoglobulins can recognize cardiac troponin I. Therefore, studies suggest that ICI-mediated myocarditis is typically governed by $CD8^+$ T cells, IgG antibodies for cardiac troponin I, and macrophages.

Therefore, inhibitors blocking the activity of CTLA-4, PD-1, or PD-L1 can activate autoimmunity against the cardiac tissue by triggering inflammatory cascades and necrotic changes. These autoimmune and inflammatory outcomes together contribute to the development of ventricular arrhythmias, myocarditis, acute myocardial infarction, and conduction disease. Moreover, inhibition of PD-L1 has the potential to exacerbate the pre-existing cardiac diseases, which can further escalate the cardiac toxicity.

Mostly, the myocarditis is associated with the early stage of ICI therapy. However, it can be fulminant [67]. As per a recent multivariate investigation, there is a 3-fold increased chance of cardiovascular events after starting ICI therapy. In this study, it has been demonstrated that around 2.32 % of patients were reported with cardiovascular issues before the commencement of ICI therapy. However, it was increased to 4.2 % after the initiation of ICI treatment [68]. Notably, ICI therapy was linked to higher rates of atherosclerosis and aortic plaque progression. Takotsubo (stress-induced) cardiomyopathy has been reported in patients treated with ICIs. In a cohort study involving 30 patients with cardiac issues, around 14 % of patients had clinical signs of stress-induced cardiomyopathy [69]. Moreover, the incidence of Takotsubo cardiomyopathy was much higher in patients receiving combination therapy involving ICI and chemotherapy [70].

Management involves discontinuing ICI therapy, administering corticosteroids, immunosuppressive therapy, and cardiac supportive care, with regular monitoring of ECGs, troponin levels, and cardiac imaging. Multidisciplinary care could be more effective.

5.6. Rheumatological adverse effects

Inflammatory arthritis is one of the most common outcomes in patients undergoing ICI-based therapy. However, this adverse effect is more common in patients treated with anti-PD-1/PD-L1 antibodies than those receiving anti-CTLA-4 monoclonal antibody therapy. Nonetheless, treatment with more than one type of antibody can be more detrimental compared to monotherapy [71]. Studies have suggested that the incidence rate of inflammatory arthritis could vary from 2 % to 7 % [72]. Moreover, the median time for the onset of inflammatory arthritis could be 38 weeks from its first infusion. Notably, the onset of inflammatory arthritis could be more disturbing with the occurrence of joint swelling and stiffness followed by joint damage and erosion of bones [73]. Other complications include polymyositis, polymyalgia rheumatica, and Sjögren syndrome in patients treated with ICIs. Rheumatoid arthritis can persist even 6–12 months after cessation of the ICI treatment. The application of non-steroidal anti-inflammatory drugs and disease-modifying anti-rheumatic drugs could help minimize the inflammatory symptoms in such patients suffering from rheumatoid arthritis. However, some patients may suffer from severe health issues, and in such cases adoption of biologic therapy employing TNF inhibitors and IL-6 receptor inhibitors may be required to minimize the inflammatory issues [74].

In a study, it was found that patients with pre-existing rheumatoid arthritis can have similar risks for morbidity and severe IrAEs compared to patients without pre-existing rheumatoid arthritis. However, patients may suffer from mild immune-related issues having pre-existing rheumatoid arthritis [75]. Application of Nivolumab (anti-PD-1 antagonist) can be associated with increased PD-1 expression in early and established rheumatoid arthritis synovial tissue. Moreover, infiltration of $CD4^+$ and $CD8^+$ T cells has been detected in synovial tissue. Notably, serum PD-1 levels were upregulated in auto-antibody-positive patients with rheumatoid arthritis. Therefore, therapeutic intervention with agonistic PD-1 antibodies can effectively manage rheumatoid arthritis [76]. TNF inhibitors also have potential scopes for reducing inflammation and treating ICI-mediated inflammatory rheumatoid arthritis. Moreover, c-reactive proteins can also be prevalent in patients undergoing combined ICI therapy. Most of the patients with knee arthritis and reactive arthritis-like symptoms can be treated with corticosteroids. However, in some cases, treatment with TNF inhibitors and/or methotrexate may be required. Notably, the application of TNF inhibitors is not associated with further tumour progression [77]. Side effects of ICI therapy include musculoskeletal issues, but these issues can be resolved after the termination of the therapy. In some cases, HQ, MTX, anti-TNF-alpha, and anti-IL-6 drugs can be more effective in replacement to steroid-based conventional medications. Certain immune markers have been investigated that play a crucial role in the development of ICI-mediated rheumatoid arthritis. In a study, samples of blood and synovial fluid have been investigated to explore the major immune hallmarks of IrAE-associated arthritis. Results revealed an apparent Th1-$CD8^+$ T cell axis in blood and joints with inflammatory changes. $CXCR3^{hi}$ $CD8^+$ T cells and $CX3CR1^{hi}$ $CD8^+$ T cells sharing TCR repertoires were detected in synovial fluid and blood, respectively. The study further indicated that CXCL9/10/11/16 expressed on myeloid cells helped migrate blood $CX3CR1^{hi}$ $CD8^+$ T cells into the joints. Moreover, Th17 and transient Th1/Th17 cell signatures are also enhanced in the case of combined therapy with PD-1 and CTLA-4, suggesting their possible contribution to rheumatoid arthritis progression [78].

However, further investigations are warranted to explore the efficient early detection and management to curb rheumatoid arthritis in patients treated with ICIs.

5.7. ICI-mediated pulmonary toxicity

ICI therapy has been associated with pulmonary toxicity. Having a pre-existing history of pulmonary diseases and combined ICI therapy are the risk factors that trigger pulmotoxicity. Clinical presentation of pulmotoxicity includes cough, pneumonitis, interstitial lung disease, and acute respiratory distress syndrome. Major symptoms may include dyspnoea, chest pain, fatigue, and fever. Typically, the immune disruption in lung tissue caused by inflammatory cytokines and activated T cells plays a critical role in ICI-mediated pulmonary toxicity. Studies have documented that treatment with anti-PD antibodies could reduce the pulmonary fibrosis caused by the ICI treatment [79]. Treatment with anti-PD-1 can fuel the development of immune-mediated alveolar interstitial lung diseases, which can occur in 3 % of patients undergoing anti-PD-1 therapy. Such immune reactions in pulmonary tissues can exacerbate the existing alveolar-interstitial lung disease [80]. In a retrospective study involving 2826 cancer patients receiving PD-1 inhibitors, approximately 3.5 % of patients were identified with interstitial lung disease. Notably, interstitial lung disease was found mainly in males with a median age of 59. Moreover, smokers were more susceptible to the disease. This immune-related adverse effect was

predominantly characterized by the occurrence of ground-glass opacities (81.3 %). In addition, hypersensitivity pneumonitis and organizing pneumonia were also frequent [81]. In a cohort study involving 199 advanced non-lung cancer patients, it was noted that patients with pre-existing interstitial lung issues and undergoing anti-PD-1 antibody-mediated monotherapy have an increased chance of acquiring ICI-mediated interstitial lung disease [82].

In another study, patients undergoing treatment with pembrolizumab or nivolumab have been identified with interstitial lung disease. Some patients suffered from hypoxemic respiratory failure caused by interstitial lung disease or ICI-mediated pneumonitis. However, cancer patients having interstitial lung disease and undergoing ICI-therapy are mostly more likely to die from cancer-related problems than from interstitial lung disease [83]. Studies have suggested some of the soluble immunological biomarkers of ICI-mediated interstitial lung disease. These biomarkers include CXCL9, MMP-1, IL-6, and IL-19. Among them, IL-19 may be considered a causal and prognostic factor for ICI-mediated interstitial lung disease [84]. In another investigation, patients treated with ICIs such as pembrolizumab, ipilimumab, or both, and durvalumab who developed pneumonitis served as the case group. The bronchoalveolar lavage fluid (BALF) examination has revealed a higher number of lymphocytes than the control group. Moreover, elevated levels of IL-6 in BALF further indicated its potential role in the pathophysiology of ICI-mediated pneumonitis [85].

TIM-3, TIGIT, and LAG-3 are negative regulators of anti-tumour responses. $TIM3^{+}PD\text{-}1^{+}$ Tumour-infiltrating lymphocytes (TILs) are the dysfunctional lymphocytes that cannot produce IL-2, TNF, and IFN-γ. Moreover, TIM-3 is also associated with the cell death of $CD8^{+}$ TILs. Therefore, the expression of TIM-3 is increased in the case of cancer cells. Several clinical trials are underway to investigate the efficacy of anti-TIM3 antibodies. In a study, the expression profiles of immune checkpoint proteins such as PD-1, TIM-3, TIGIT, LAG-3, and PD-L1 in T cells were examined in BALF of patients with ICI-mediated interstitial lung disease. Notably, BALF of patients with ICI-mediated interstitial lung disease contained higher proportions of $CD8^{+}$ T cells expressing immune checkpoint proteins such as PD-1 and TIM-3 or TIGIT. Moreover, an increased presence of $PD\text{-}1^{+}PD\text{-}L1^{+}$ cells among $CD8^{+}$ T cells in BALF of fatal cases of the ICI-mediated interstitial lung disease was also apparent, which might have implications in the development of fatal outcomes [86]. In another study, the BALF of patients suffering from ICI-mediated pneumonitis had exacerbated levels of $CD4^{+}$ T cells, increased expression of IL1β, and higher levels of T cell chemoattractant. Moreover, evidence of type I polarization and decreased expression of PD-1 and CTLA-4 in Treg was also detected. These findings were suggestive of an activated inflammatory cascade that contributed to the disease progression [87]. Therefore, a complex interplay between the T cells and interleukins and T cell attractants plays a critical role in the development of ICI-mediated lung disease (Fig. 5; Table 2).

6. TIM3, LAG3, and TIGIT as promising immunotherapy targets

TIM3, LAG3, and TIGIT are emerging immunotherapy targets, offering potential for combination therapy with existing checkpoint inhibitors to enhance anti-tumour immunity. TIM3, expressed on exhausted T cells, binds to galectin-9 and suppresses T cell function. It has been suggested that the co-blockade of TIM3 and PD-1 may lead to tumour regression and enhance the anticancer effects of T cells in individuals with advanced cancers [88]. LAG3, a receptor, inhibits T cell expansion and function, and is often co-expressed with PD-1 on exhausted T cells. Signalling through LAG3 is mediated by a disintegrin

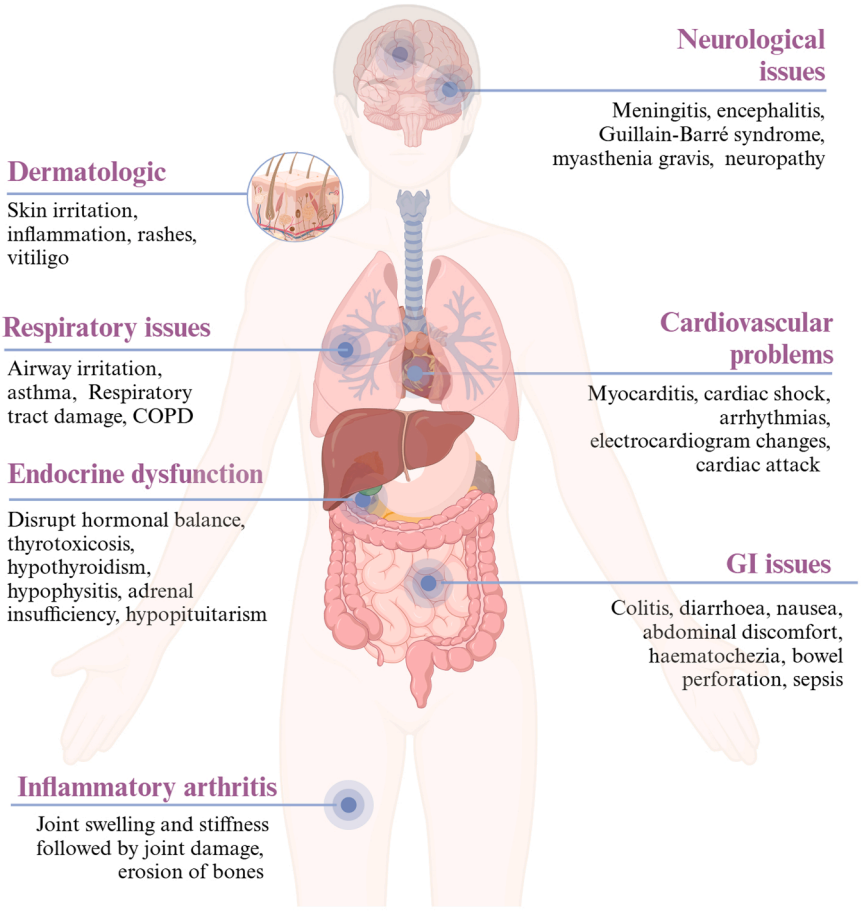

Fig. 5. ICI-mediated immune-related adverse effects in cancer patients.

Table 2
ICI-mediated IrAEs in cancer patients.

Type of study	Number of patients used in the study	Cancer type	ICI used	Target of ICIs	IrAEs	Reference
Retrospective cohort study	105	Esophageal cancer, urothelial cancer, gastric cancer, lung cancer, melanoma, liver cancer	Nivolumab, pembrolizumab, ipilimumab	PD−1, CTLA	hypothyroidism/ hyperthyroidism, Hematologic, Immune-related pneumonia, Gastrointestinal symptom	[178]
Phase III randomized clinical trial	655	Advanced melanoma	Tremelimumab	CTLA−4	Pruritus, rash, diarrhea,	[179]
Pooled Analysis of Randomized Phase II and III Trials	409	Advanced Melanoma	Nivolumab and Ipilimumab	PD−1, CTLA	GI disorder, hepatoiliary disorder, respiratory issues, endocrine disorders	[180]
Retrospective cohort study	134	Non-Small-Cell Lung Cancer	Nivolumab	PD−1	Dermatologic and endocrine effects	[181]
Cohort study	318	Advanced Melanoma	Ipilimumab	PD−1	Cutaneous impacts	[182]
Meta-analysis	7060	Head and neck cancer and lung cancer	Nivolumab, pembrolizumab, durvalumab, atezolizumab, ipilimumab	PD−1/ L1, CTLA	Endocrine effects	[183]
Cohort study	319	Stage IV Melanoma	Nivolumab, ipilimumab	PD−1, CTLA	IrAE included hematological (51.1 %, 163 patients), renal (28.8 %, 92 patients), hepatobiliary (25.4 %, 81 patients) and endocrine (24.1 %, 77 patients) effects.	[184]
Retrospective study	190	Metastatic melanoma	Nivolumab or pembrolizumab	PD−1	Endocrine, cutaneous, rheumatologic, gastrointestinal effects	[185]
Cohort study	26	Advanced Cutaneous Squamous-Cell Carcinoma	Cemiplimab	PD−1	Rash, constipation, fatigue. diarrhea, nausea	[186]
Cohort study	87	Non-squamous nonsmall cell lung cancer	Pembrolizumab	PD−1	Inflammatory effects	[168]
Cohort study	23	Advanced biliary tract cancer	Durvalumab and tremelimumab	PD1/PD-L1	Lymphopenia, AST increase, pruritus, fatigue, and anemia.	[175]

and metalloprotease domain-containing protein-10 (ADAM10)- and ADAM17-mediated cell surface shedding. A study has shown that LAG3 mutants are resistant to PD-1 blockage and fail to mount anti-tumour effects. LAG3 mutants limit the capacity of $CD4^+$ T conventional cells (Tconvs) to provide $CD8^+$ T cell help [89]. TIGIT suppresses T-cell function and promotes immune tolerance. Targeting these receptors with monoclonal antibodies or small molecules has shown promising results in preclinical and early clinical studies.

Several anti-TIM3 antibodies are under various phases of clinical trials. In a study, the safety, tolerability, and efficacy of anti-TIM3 antibody TSR-022 have been examined (arm 1 A). This study also included combination therapy, such as combining anti-PD-1 antibodies nivolumab (arm 1B) or dostarlimab (arm 1 C). Patients of arm 1 A exhibited 4.3 % of treatment-related adverse effects (TRAE) of grade 3. 28.6 % of patients in arm 1B, and 14.5 % of patients in arm 1 C demonstrated grade 3 or worse TRAE. Combination therapy, including

Table 3
Clinical trials associated with the of new-generation ICIs (LAG-3, TIM-3, TIGIT inhibitors).

New generation ICI	Phase	Drug	Purpose of the trial	Name of the company	NCT number
TIM3	2	MBG453	Combined study involving sabatolimab with venetoclax and azacitidine.	Novartis Pharmaceuticals	NCT04812548
LAG3	1 and 2	BMS−986016	Assessment of anti-TIGIT, anti-LAG3, and elotuzumab.	BMS (New York, NY, USA)	NCT04150965
TIGIT	1 and 2	Tiragolumab	Assessment of single and combined-immunotherapy in patients with advanced liver cancers (Morpheus-Liver).	Roche (Basel, Switzerland)	NCT04524871
TIM3	1	MBG453	Evaluation of drug combinations in low-risk MDS patients.	Novartis Pharmaceuticals	NCT04810611
LAG3	2	BMS−986016	Analysis of relatlimab and nivolumab in paticipants with microsatellite stable advanced CRC	BMS (New York, NY, USA)	NCT03642067
TIM3	1	TSR−022	Evaluation of efficacy of TSR−022 in patients with advanced solid tumors.	Tesaro (Waltham, MA, USA)	NCT02817633
TIM3	1	Sym023	Evaluation of efficacy of Sym023 in patients with advanced solid tumor malignancies or lymphomas.	Symphogen A/S (Copenhagen, Denmark)	NCT03489343
LAG3	1	BMS−986016	Assessment of anti-LAG3 alone and in combination with nivolumab in participants with recurrent GBM	BMS (New York, NY, USA)	NCT02658981
LAG3	1	REGN3767	Evaluation of REGN3767 (anti-LAG3) with or without REGN2810 (anti-PD−1) in advanced cancers	Regeneron Pharmaceuticals (Tarrytown, NY, USA)	NCT03005782
TIGIT	1	OMP−313M32	Assessment of OMP−313M32 in patients with advanced or metastatic solid tumors.	OncoMed Pharmaceuticals (Redwood City, CA, USA)	NCT03119428
LAG3	1	MGD013	Analysis of **effectiveness** of MGD013 in participants with unresectable or metastatic neoplasms.	MacroGenics (Rockville, MD, USA)	NCT03219268
TIGIT	1 and 2	Tiragolumab	Assessment of single and combined-immunotherapy in patients with urothelial carcinoma.	Roche (Basel, Switzerland)	NCT03869190
TIM3	1	LY3415244	Evaluation of efficacy of LY3415244 in participants with advanced solid tumors	Eli Lilly and Company (Indianapolis, IN, USA)	NCT03752177
TIGIT	2	MTIG7192A	Assessment of effectiveness of MTIG7192A with atezolizumab in patients with metastatic NSCLC.	Genentech (San Francisco, CA, USA)	NCT03563716

TSR-022 and dostarlimab was better tolerated and found with anti-tumour activity [90]. In a phase 1 clinical trial, another anti-TIM3 antibody LY3321367 (Eli Lilly) has been evaluated alone or in combination with the anti-PD-L1 antibody. Preliminary investigation has suggested that LY3321367 is well tolerated as monotherapy [91]. MBG453 (Novartis), another anti-TIM3 antibody is being investigated under phase 1–3 clinical trials alone and in combination with anti-PD-1 agents or chemotherapy drugs. MBG453 with decitabine is safe, durable, and well-tolerated in acute myeloid leukaemia patients. TRAE included neutropenia, febrile neutropenia, anaemia, and thrombocytopenia [92, 93]. A soluble LAG3 protein, IMP321 has been investigated for its benefits in metastatic breast cancer patients. IMP321 was used in combination with chemotherapy agent paclitaxel and the majority of breast cancer patients were clinically benefited [94]. In another clinical trial, combination therapy involving IMP321 and gemcitabine, a chemotherapy drug, showed no adverse effects in the case of pancreatic cancer [95]. There are anti-TIGIT antibodies such as AB154, IBI939, MK-7684, tiragolumab, COM902, etc., that have been evaluated through clinical trials. AB154 can block the TIGIT at sub-nanomolar concentrations. AB154 is under phase 2 clinical trial and exhibits a favorable safety profile for NSCLC [96]. MK-7684 monotherapy or combination therapy using KEYTRUDA is well tolerated. In an investigation, around 56 % of patients receiving MK-7684 monotherapy and 62 % of patients receiving combination therapy exhibited TRAE. Monotherapy was found to be safer [97]. IrAEs have been detected in case of patients treated with OMP-313M32 or etigilimab. However, in the case of patients with stable disease, early signs of efficacy have been detected [98] (Table 3).

7. Mechanistic insights on ICI-mediated toxicity

The application of ICIs in cancer patients is associated with IrAEs on several organs, ranging from the GI tract to neurological issues. A complex interplay between immune cells, autoantibodies, and cytokines constitutes the mechanism for ICI-mediated adverse effects.

7.1. Role of immune cells in IrAEs

The autoimmune cascades are predominantly orchestrated by several T cells, such as cytotoxic T cells, Th cells, and Treg cells. Th cells differentiate into Th1, Th2, and Treg cells. All of these cells are characterized by specific cytokines driving the specific autoimmune responses. Th1 cells typically secrete IFNγ, TNFα, IL-1β, and IL12, which play a critical role in the activation of macrophages. However, Th2 subsets secrete several interleukins such as IL-4, IL-5, IL-10, and IL-13 that help in the maturation of B cells [99]. The Th1/Th2 paradigm helps regulate autoimmunity by counteracting their functions. For instance, the cytokines released from Th1 and Th17 subsets help enhance the antigen-presenting capacity of macrophages. Moreover, cytokines released from these two cells help promote inflammatory responses, leading to a number of inflammatory diseases, including rheumatoid arthritis following ICI treatment. Th1 and Th17 cell functions regulate the production and functions of Treg. In contrast, Treg releases immunosuppressive cytokines such as TGFβ and IL10 that facilitate tissue repair following autoimmune reactions in the body. Regulatory B cells also secrete IL-10 that prevents the release of inflammatory cytokines from the dendritic cells and also impairs the development of Th1 and Th17 cells, ultimately contributing to the suppression of autoimmunity. Cytokines released from the Th2 cells help downregulate the proinflammatory function of macrophages. The imbalance in these cytokines regulates the outcome of autoimmune reactions.

Studies have suggested the crosslinks between the $CD8^+$ T cells and a number of health issues associated with the IrAEs. Moreover, ICIs can affect the expansion of T cell and B cell repertoire. However, Treg expressing IL-2 receptor γ-chain are typically involved in suppressing the autoimmune cascades. In a study involving 6 patients treated with ICI and who developed hypophysitis, it was observed that patients treated with ICI alone had predominant infiltration of T cells, whereas patients receiving additional therapy had increased T cell and B cell populations. Notably, type 2 macrophages were predominant in the inflammatory cell population in these patients, suggesting that these macrophages play a critical role in the development of inflammatory outcomes in ICI-treated patients [100]. Moreover, low levels of Treg cells further contribute to the intense inflammatory responses. The major drivers of autoimmunity are B cells and T cells. Specifically, T cells can directly harm the healthy self-tissues or act as helper cells for B cells to secrete soluble autoantibodies. Moreover, the innate immune system can also regulate the autoimmune responses by triggering the autoreactive T cells through the dendritic cells. Tissue damage is primarily mediated by the Th cells that work via the induction of transcription factors, T-bet and Signal Transducer and Activator of Transcription 4 (STAT4). The expression of IFNγ by Th cells mainly triggers the cytotoxic responses in autoimmune diseases. Moreover, CXCL10 also promotes dendritic cells to secrete IFNγ.

7.2. Implication of autoantibodies

Autoantibodies are produced by the leakage of peripheral and central tolerance mechanisms. This allowed the maturation of autoantibody-secreting plasma cells from B cells. Application of anti-PD-1/anti-PD-L1 or CTLA-4, individually or in combined form, can activate the T cells and their proliferation in various subsets. This activation is required for a better immune response against the cancer cells. However, hyperactivated immune responses can fuel the production of autoantibodies that harm the healthy cells of multiple organs. The effects of exacerbated immune response can lead to a number of IrAEs associated with acute and chronic diseases. In a cohort study, the development of autoantibodies was examined in 133 ipilimumab-treated melanoma patients. Results demonstrated that, sera of some patients were detected with the autoantibodies for the thyroid gland, leading to thyroid dysfunction. These autoantibodies could also be used as markers for ICI-mediated toxicities [101].

Autoantibodies have been reported in patients with ICI-mediated endocrinopathies. Anti-BP180 is seen in cases of skin-related adverse effects. Patients with myositis/myasthenia/myocarditis are also reported with autoantibodies. Moreover, patients suffering from ICI-mediated arthritis are shown to have circulating rheumatoid factors or cyclic citrullinated peptide antibodies. However, autoantibodies such as antinuclear antibodies in hepatitis patients and perinuclear anti-neutrophil cytoplasmic antibodies in colitis patients have also been detected, suggesting their potential implications in adverse effects induced by ICIs [102]. Fold change increase in autoantibodies such as anti-cyclic citrullinated peptide, rheumatoid factor, and antinuclear antibody have been noted over 6 weeks of developing organ-specific IrAEs. This suggests the implications of humoral and cellular immunity in the development and pathogenesis of IrAE [103]. In a cohort study containing serum samples from 29 cancer patients, neuromuscular autoantibodies were detected in 63 % of patients with IrAE. Moreover, 45 % of patients with IrAE have been detected with the brain-reactive autoantibodies targeting intracellular (anti-GFAP, -Zic4, -septin complex), surface (anti-$GABA_BR$, -NMDAR, -myelin), or unknown antigens. These results suggest that neuromuscular autoantibodies can be used as a marker to predict the life-threatening neuromuscular diseases caused by ICI administration.

ICI-induced autoimmune encephalitis in patients has been associated with the anti-Ma2 antibodies targeting the intracellular proteins. Antibodies for acetylcholine receptors are also linked to the development of myasthenia gravis as IrAE [104].

Therefore, autoantibodies have a strong association with the development of ICI-mediated adverse effects and pathogenesis of diseases in cancer patients, suggesting the interplay between cellular and humoral immunity (Fig. 6).

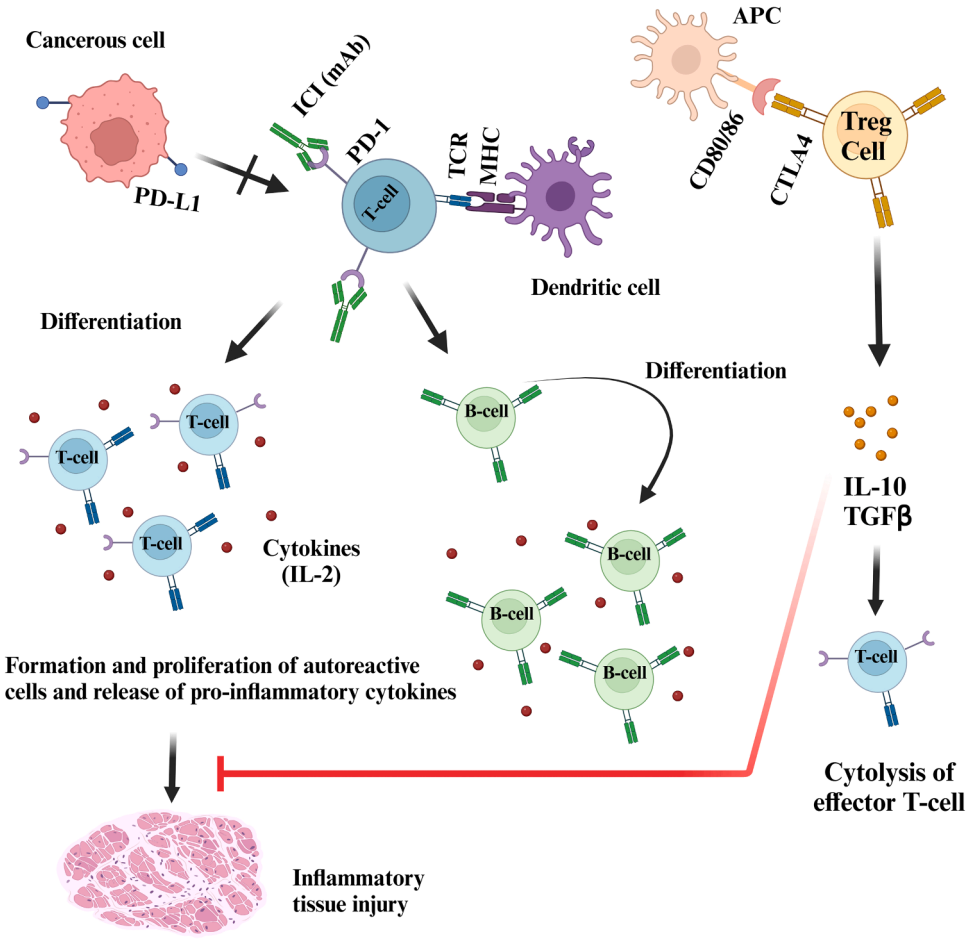

Fig. 6. Production of ICI-mediated autoimmune cells and proinflammatory cytokines. The binding between ICI mAb and PD-1 prevents the binding of PD-L1 expressed on cancer cells to the PD-1. It triggers the activation of T cells, followed by their differentiation and secretion of proinflammatory cytokines (IL-2). These outcomes are responsible for inflammatory tissue damage. However, Treg cells have immunosuppressive action. They release IL-10 and TGFβ, leading to the cytolysis of effector T cells.

7.3. Impacts of cytokines

Cytokines are small, soluble molecules that are released from the immune cells upon activation. They have both proinflammatory and anti-inflammatory functions. A wide range of cytokines have been characterized that orchestrate the immune functions against microbes and cancer cells. Moreover, cytokines play a pivotal role in the onset and pathogenesis of autoimmune responses. Typically, the IL-2, TNF, and IFN catalyse the autoimmune orchestra essential for the proinflammatory outcome. IL-12 is expressed on the APCs and are critical for differentiation and expansion of Th1 cells, responsible for organ specific autoimmunity. Studies involving animal models have documented that the development of autoimmune reactions is attributed to the aberrant IL-12 production by the APCs. However, IFN typically control the proinflammatory reactions. Specifically, type I IFN has been implicated in the suppression of autoimmune diseases associated with Th1-mediated pathogenesis. Nonetheless, type 2 IFN (IFN-γ) promotes the Suppressors Of Cytokine Signaling (SOCS) that counteract the proinflammatory signaling. IL-12 also favours the differentiation of cytotoxic T cells, effectors from $CD8^+$ T lymphocytes that further promote the autoimmune reactions.

In a study involving 45 patients with metastatic melanoma and suffering from ICI-mediated IrAE, it was found that the levels of serum C-reactive proteins and IL-6 were apparently upregulated, suggesting their correlation with the onset of IrAE [105].

In another study involving 98 patients who are undergoing single or combined therapy with anti-PD-1 and/or CTLA-4 inhibitors, the expression of 65 cytokines was assessed to understand the implications of cytokines in ICI-mediated IrAE. These patients were treated with nivolumab or pembrolizumab (anti-PD-1) and/ ipilimumab (anti-CTLA-4). Notably, 11 cytokines were found upregulated in these patients with severe IrAEs. These cytokines included fractalkine, Fibroblast Growth Factor-2 (FGF-2), IFN-α2, IL-12p70, IL-1a, IL-1B, IL-1RA, IL-2, and IL-13, Granulocyte Colony-Stimulating Factor (G-CSF), and Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF) [106]. However, disruption in the expression of these cytokines is not linked to the anti-tumor efficiency of the anti-PD-1 or anti-CTLA-4 inhibitors.

IL-1β and IL-2 are important cytokines that have potent inflammatory activities. These molecules are involved in cell proliferation, differentiation, and apoptosis. In addition, they also contribute to the development of autoimmune reactions in the body [107,108]. Studies involving 223 lung cancer patients have revealed that, in peripheral blood, the baseline IL-1β and IL-2 levels were linked to the development of IrAE in lung cancer patients. Moreover, during the treatment with ICI, levels of IL-5, IFN-α and IFN-γ had a strong correlation with the immune adverse effects. However, cytokines such as IL-6, IL-8, IL-10, and IL-17 contributed to the immunotherapy efficacy for the lung cancer patients [109]. These findings suggest that the interplay between a number of cytokines helps promote the development of IrAE during the treatment.

C–X–C motif chemokine 10 (CXCL10) is a cytokine belonging to the CXC chemokine family. These molecules bind to their CXCR3 receptor to

mediate chemotaxis, angiotaxis, cellular differentiation l, and apoptosis. Moreover, they have been associated with inflammatory diseases [110]. In a study involving a cohort of patients suffering from renal cell carcinoma, the plasma levels of CXCL10 were higher. More specifically, the CXCL10 level was greater in patients with renal cell carcinoma with grade 2 or higher IrAE [111].

8. Mechanism of resistance to ICIs

Resistance to ICIs can occur through various mechanisms, including primary and acquired resistance. Primary resistance refers to the inherent inability of ICIs to elicit a response in certain patients, often due to a lack of tumour antigenicity, impaired antigen presentation, or an immunosuppressive tumour microenvironment. Acquired resistance, on the other hand, develops over time in patients who initially respond to ICIs, but eventually experience disease progression. Mechanisms of acquired resistance include genetic alterations in the tumour, such as mutations in the IFN-γ pathway or the antigen presentation machinery, as well as epigenetic changes that suppress anti-tumour immunity. Additionally, the upregulation of alternative immune checkpoints, such as TIM-3 or LAG-3, can also contribute to acquired resistance to ICIs. Therefore, the molecular interactions between the cancer cells and the immune system are continuous. Primary, adaptive, and acquired resistance may contribute to evasion of cancer immunotherapy [112]. Further understanding the various sub-classes of the immune microenvironment can help gain better clinical outcomes [113].

Immune exhaustion triggered by immunometabolism plays a crucial role in cancer. Exhausted T cells express immune checkpoints that determine cancer prognosis. ICIs can hinder immune exhaustion and hence reinvigorate immune cells to enhance the anti-tumour microenvironment [114]. Tumour cells can modulate the tumour microenvironment to evade the anti-tumour response. In addition, loss of MHC and hindrance in IFN-γ signaling can lead to resistance to ICI therapy. T cell activation is crucial to impart anti-tumour response. Loss of MHC is associated with the T cell inactivation leading to the failure of antigen presentation. Resistance to ICI is also induced by a noninflamed tumour microenvironment following reduced chemokines. Neoantigens play a crucial role in the activation of anti-tumour responses. Neoantigens are essential for the activation of T cell-mediated responses. However, the loss of neoantigens in cancer cells results in resistance to ICIs [115,116]. Cancer cells can also hinder antigen presentation by APCs through the secretion of Vascular Endothelial Growth Factor (VEGF) or prostaglandin E2 (PGE2) or activation of WNT/β-catenin signaling pathway [117,118]. Another factor that contributes to the ICI resistance is the loss of MHC molecules on cancer cells. It has been suggested that loss of heterozygosity in MHC-I genes results in immune escape of cancer cells, which can further contribute to the resistance to ICI therapy [119]. Several chemokines such as CXCL9, CXCL10, CXCL11, and CCL5 are the essential mediators that govern the migration and infiltration of T cells into the tumour microenvironment, leading to anti-tumour activity. WNT/β-catenin, PTEN, LKB1, and EGFR pathways are associated with disruption in the production of these chemokines and hence contribute to the ICI resistance [120–122]. SNF2-family DNA translocase SMARCAL1 acts as a factor that favours immune evasion by cancer cells. It limits DNA damage to surpass cGAS-STING-dependent signalling during the growth of cancer cells. Moreover, this factor cooperates with the AP-1 family member JUN to maintain chromatin accessibility at a PD-L1 transcriptional regulatory element, thereby promoting PD-L1 expression in cancer cells. These mechanisms are favoured by SMARCAL1 to evade anti-cancer effects of the immune system [123]. Metabolic programming of tumour cells can promote immune evasion. Metabolic immune suppression of effector cells and induction of regulatory cells are mediated by altered nutrients and signals in the tumour microenvironment, leading to weak anti-cancer effects of immune cells [124].

Various immune suppressive myeloid-derived suppressor cells (MDSCs), tumour-associated macrophages (TAMs), Treg cells, and CAFs are also associated with ICI resistance, as these cells interfere with the T cell effector functions. Treg cells, through IL-2 and binding CD80/CD86 suppress T cell effector functions. Anti-PD-1 mAbs have been associated with the activation of PD-1^+ Treg cells and PD-$1^+$$CD8^+$ T cells, which contribute to the ICI resistance [125]. Therefore, unveiling the mechanism of ICI resistance is essential to curb the resistance to ICI therapy in cancer patients.

9. Recent advances in ICI therapy and combination strategies

Tumour-infiltrating lymphocytes (TILs) play a crucial role in cancer immunotherapy, and their presence and characteristics have been linked to the efficacy of ICIs. TILs are the immune cells that enter the tumour microenvironment, where they can recognize and target cancer cells. High levels of TILs, particularly $CD8^+$ T cells, in the tumour microenvironment are associated with improved responses to ICIs, such as PD-1/PD-L1 inhibitors. ICIs help activate and proliferate TILs, leading to enhanced anti-tumour immunity.

In a study, lifileucel, a one-time autologous TIL cell therapy, has been investigated for its efficacy against advanced melanoma in patients. Lifileucel demonstrated high efficacy in patients with advanced tumour burden and melanoma. Lifileucel reported to have durable responses and a favorable safety profile [126]. Further, in a phase 2 multicenter study, lifileucel was found effective in metastatic non–small cell lung cancer refractory to prior therapy [127]. In metastasized malignant melanomas, TIL has been associated with improved survival. Interestingly, in the case of BRAF V600E/K mutated metastasized malignant melanomas, TILs result in improved survival [128]. Japanese patients who underwent TIL-adoptive cell therapy (ACT) exhibited variable responses against melanoma. Several factors like MAPK signalling, Wnt/β-catenin, VEGF, TGF-β, and epithelial-to-mesenchymal transition might have influenced the efficiency of TIL-ACT [129].

The combination of metabolic checkpoint inhibitors, such as IDO and ARG1 inhibitors, with ICIs has emerged as a promising therapeutic strategy in cancer treatment. Metabolic checkpoint inhibitors target enzymes involved in the metabolism of essential amino acids, thereby reversing immune suppression and enhancing anti-tumour immunity. When combined with ICIs, such as PD-1/PD-L1 and CTLA-4 inhibitors, this dual approach has shown improved treatment outcomes and increased patient response rates. Abrine, an inhibitor of IDO1, has shown promising response against hepatocellular carcinoma. Abrine and anti-PD-1 antibody and abrine can synergistically suppress tumour growth by down-regulating the $Foxp3^+$ Treg cells, up-regulating the $CD4^+$ or $CD8^+$ T cells, and inhibiting the expression of PD-L1, CD47, and IDO1 [130]. Similarly, ARG1/2 plays a crucial role in immune suppression against tumours. A novel ARG1/2 inhibitor - OAT-1746 improves the anti-tumour effects of PD-1 against gliomas by changing the immunosuppressive microenvironment [131]. Suppression of ARG1 activity significantly reduces the migration and metastatic colonization of colon cancer cells [132].

ICI-mediated therapy in cancer patients has raised serious concerns due to exacerbated inflammation that further complicates the issue. Therefore, combination therapy employing agents that target interleukins is under consideration. Inhibitors of inflammatory cytokines could help to reduce further health complications [133]. However, certain interleukins, such as IL-2 have been suggested to improve the anti-tumour effects of $CD8^+$ T cells. Moreover, IL-2 can also enhance ICI therapy against cancer [134]. High-dose IL-2 treatment can be used for renal cell carcinoma and melanoma [135]. Therefore, combination therapy including IL-2 can promote the anti-tumour microenvironment in patients (Table 4).

10. Biomarkers linked to ICI therapy

In recent years, the role of biomarkers in predicting response to ICI therapy is increasingly investigated. Several important biomarkers, such

Table 4
Response to ICIs in different cancers.

ICIs used	No. of patients	Cancer type	Response outcomes	Reference
Atezolizumab, pembrolizumab, and Nivolumab	178	Melanoma, urothelial cell carcinoma, and non-small cell lung cancer	Overall survival (37.3 vs 7.8 months, $p < 0.0001$), Progression-free survival (7.9 vs 2.6 months, $p < 0.0001$)	[187]
Anti PD−1	114	Head and neck squamous cell carcinoma	Overall survival (12.5 vs 6.8 months, $p = .0007$), Progression-free survival (6.9 vs 2.1 months, $p = .0004$)	[188]
Anti-PD-L1 or Anti-PD−1	52	Urothelial cell carcinoma	Overall survival (21.91 vs 6.47 months, $p = .004$)	[189]
Anti-PD−1	90	Renal cell carcinoma	Overall survival (hazard ratio 0.38; 95 % confidence interval 0.18–0.79; $p = .01$)	[190]
Nivolumab	576	Melanoma	Overall response rate (48.6 % vs 17.8 %, $p < .001$)	[2]
Anti-PD−1	61	Gastrointestinal carcinoma	Overall survival (32.4 vs 8.5 months, $p = .0036$), Progression-free survival (32.4 vs 4.8 months, $p = .0001$)	[191]
Nivolumab	389	Renal cell carcinoma	Overall survival (hazard ratio.57; 95 % confidence interval.35–.93; $p = .02$)	[192]
Anti-PD−1	173	Melanoma	Overall survival (hazard ratio 0.39; 95 % confidence interval 0.18–0.81; $p = .007$), Progression-free survival (hazard ratio 0.47; 95 % confidence interval 0.26–0.86; $p = .016$)	[193]
Anti-PD-L1 and anti-PD−1	270	Non-small cell lung cancer	Overall survival (hazard ratio 0.29; 95 % confidence interval 0.18–0.46; $p = .001$), Progression-free survival (hazard ratio 0.42; 95 % confidence interval 0.32–0.57; $p < .001$)	[194]
Nivolumab	195	Non-small cell lung cancer	Overall survival (hazard ratio 0.33; 95 % confidence interval 0.23–0.47; $p < .001$), Progression-free survival (hazard ratio 0.41; 95 % confidence interval 0.3–0.57; $p < .001$)	[195]

as tumour mutational burden (TMB), microsatellite instability (MSI), gene expression profiling (GEP), PD-L1 expression, and the gut microbiome, are promising in predicting response to ICI in cancer patients. Studies have reported the positive correlation between high TMB and the response to ICI in cancer patients. In a study, high median TMB were detected in respondents treated with nivolumab. Moreover, further results have suggested that TMB may be used as imperfect biomarkers for overall survival and progression-free survival in cancer patients. Andrews et al. [136] have used a deidentified nationwide (US-based) melanoma clinicogenomic database to examine the reliability on TMB to predict ICI response. Results have suggested that high TMB is associated with real-world progression-free survival and overall survival in patients treated with mono and dual ICIs. The overall response rate in MSI-H and TMB-H patients has been assessed. There have been 50.0 % and 64.1 % overall response rates in MSI-H and TMB-H patients, respectively, who received only immunotherapy. In addition, for patients with both TMB-H and MSI-H, the overall response rate was found to be 50 %, with the disease control rate as 75 % [137]. In another cohort study involving 674 patients, there was a significant relationship between TMB-H and higher survival rates in ICI-treated patients [138]. Tissue TMB-high status has been associated with the robust responses to pembrolizumab monotherapy. Therefore, tissue TMB can be used as a biomarker of response to pembrolizumab monotherapy in patients with previously treated recurrent or metastatic advanced solid tumours [139]. Therefore, these studies suggest the promising scopes of TMB and MSI in predicting responses to ICI therapy.

Mismatch repair-deficient (dMMR) tumours displaying microsatellite instability have been suggested to predict progression-free survival in patients with metastatic colorectal cancer following anti-PD-1 therapy [140]. GEP is becoming increasingly popular to predict the outcome of ICI therapy. Two important GEPs, such as IFN-γ signatures and TIS (tumour inflammation signature) have promising scopes in selecting NSCLC patients who would benefit from the ICI therapies [141].

Differential gene expression is mainly linked to antigen processing and presentation. In another investigation, gene expression profile was analysed to detect a differential set of genes that were linked to ICI therapy in metastatic renal cell carcinoma patients. Interestingly, a set of 14 genes was found to be associated with the responder patients treated with ipilimumab and/or nivolumab. In the case of patients with advanced NSCLC, six gene signatures (Lung Tumour Score – LungTS have been suggested that discriminated patients with low and high risk of death. The study involved a cohort of 66 Brazilian patients and a validation cohort composed of 54 Spanish patients [142]. The majority of these patients were treated with nivolumab. Therefore, gene expression profiling is a promising approach to screen patients who can respond better to ICI therapy.

Accumulating evidence suggests that, in addition to cellular, genetic, and molecular markers, gut microbiomes could act as potential biomarkers for ICI therapy. Various bacterial species can be used as potential markers for anti-PD-1 or anti-CTLA-4 therapy efficacy in patients with melanoma [143]. In a study, *Phascolarctobacterium* was abundant in patients with clinical benefit from the immune checkpoint blockade and was also positively associated with the prolonged progression-free survival. However, the abundance of *Dialister* was associated with reduced progression-free survival and progressive disease [144]. In another investigation, it was addressed that a reduced number of Bacteroidetes is associated with colitis [145]. Moreover, patients with anti-PD-1 refractory metastatic melanoma showed improved response rates when fecal microbiota transplant (FMT) from patients with anti-PD-1 responsive disease was performed. Another study has shown that the status of gut microbiome can vary in ICI responders and non-responders. Bacterial species *Coprococcus comes* and *Faecalibacterium prausnitzii* were abundant in responders of ≥ 2 cancer types or from ≥ 3 cohorts. The gut microbiome may modulate the $CD8^+$ T cell activity to influence the efficacy of ICI therapy [146]. The gut microbiome can influence the response to PD-1-based therapy. In a study, oral supplementation with *Akkermansia muciniphila* after fecal microbiota transplantation using nonresponder faeces restored the efficacy of PD-1 blockade. Increased efficacy was achieved in an IL-12-dependent manner by promoting the recruitment of CCR9 +CXCR3 +CD4 + T lymphocytes into the mouse tumour beds [147].

11. Strategies for the mitigation of IrAEs

Strategies to mitigate IrAEs caused by ICIs include careful patient selection, baseline assessments, and regular monitoring during treatment. Identifying high-risk patients and implementing prophylactic measures, such as corticosteroids, can help prevent severe irAEs. Additionally, establishing standardized grading systems and management guidelines for IrAEs can facilitate timely and effective interventions. Diagnosis of organ-specific toxicity is essential as the management of IrAEs varies from organ to organ. Schneider et al. [33] have discussed strategies to control IrAEs. According to them, ICI therapy can be continued in case of grade-1 toxicity. However, the therapy may be

discontinued in the majority of grade-2 toxicities. Corticosteroid treatment may be initiated to revert grade-2 toxicity to grade-1. In case of grade-3 toxicity, ICI therapy should be terminated, followed by high-dose administration of corticosteroids (initial dose 0.5–1 mg/kg/day prednisone or equivalent) and should be tapered over 4–6 weeks. In patients diagnosed with grade-4 toxicity, ICI therapy should be permanently discontinued except for endocrinopathies that have been treated through hormonal replacement. Early detection of IrAEs can help reverse the detrimental outcome. Biomarkers can aid in early detection and suitable intervention. An increase in the levels of CD177 and CEACAM1 has been considered as the biomarkers of colitis after treatment with ipilimumab [148]. FDI has approved biomarkers like PD-L1, microsatellite instability (MSI), and tumour mutational burden (TMB), which are currently used in the selection of patients for ICI therapy in clinical settings [149,150]. Gene signature biomarkers such as melanocytic plasticity signature (MPS), T cell dysfunction and exclusion gene signature (TIDE), T cell inflamed gene expression profile (GEP), and B cell focused gene signature have been compared and MPS gene signature is found better and superior to the PD-L1 and TMB [149]. Blood count monitoring can also be used as an effective biomarker of early IrAEs. For instance, neutrophil-to-lymphocyte ratio > 2.3 and platelet-to-lymphocyte ratio > 165 have been associated with the increased risk of IrAEs in patients treated with pembrolizumab [151]. Changes in non-cardiac biomarkers such as aspartate aminotransferase, alanine aminotransferase, and creatine phosphokinase also help diagnose ICI-mediated myocarditis in patients [152]. Treatment using corticosteroids can produce severe adverse effects. In such cases, the administration of corticosteroids is usually terminated. IL-6 receptor inhibitor tocilizumab, CD20 inhibitor rituximab, and TNF-α inhibitor infliximab are preferred biological agents [33]. Infliximab antibodies target TNF-α and can reduce inflammation by modulation of cytokine pathways. However, administration of infliximab can be associated with heart failure and hence should be used with caution in patients diagnosed with ICI-mediated myocarditis [153]. In clinical settings, patients treated with rituximab had reduced neurological issues [154,155]. Moreover, rituximab had inhibitory effects on the reactivation of primary membranous nephropathy induced by ICI therapy [156]. Rituximab has been used in combination with the PD-1 inhibitors to improve the conditions of follicular lymphoma, as the effectiveness of the drug has been confirmed in several clinical trials. Tocilizumab has inhibitory effects on IL-6, and it helps mitigate the IrAEs associated with the digestive and respiratory systems [157,158]. Studies have reported that therapy using tocilizumab notably alleviates clinical symptoms of steroid-refractory IrAEs [157]. The drug has therapeutic effects on cancer-associated cachexia and can be synergistically used along with ICI therapy [159].

Therefore, combining ICIs with other immunomodulatory agents or using alternative dosing schedules may help minimize IrAEs. Furthermore, developing personalized treatment strategies based on individual patient profiles is a promising area of investigation. Future research should focus on elucidating the underlying mechanisms of IrAEs, identifying novel biomarkers, and developing more targeted and effective therapies to mitigate these adverse effects. Moreover, studies examining the impact of ICIs on the gut microbiome and their potential role in IrAEs are warranted. Ultimately, a multidisciplinary approach involving oncologists, immunologists, and other healthcare professionals is essential to optimize ICI therapy and minimize IrAEs.

12. ICI cost and accessibility

ICI therapy is available for the treatment of several cancers. However, their adoption is limited due to financial burdens on patients. Generally, ICIs like cabozantinib plus atezolizumab, pembrolizumab plus lenvatinib, tislelizumab, durvalumab, camrelizumab plus rivoceranib, and atezolizumab plus bevacizumab are costly compared to tyrosine kinase inhibitors or other ICIs.

The cost-effectiveness of the therapy may vary depending on the type of ICI used and the country. For instance, in a study, the adoption of nivolumab for ICI-based therapy was considered costly in the US for the treatment of hepatocellular carcinoma. Nevertheless, the combination therapy involving atezolizumab plus bevacizumab has been considered cost-effective in the US [160,161]. Notably, atezolizumab and bevacizumab are not considered cost-effective in Thailand and France. In China, several regimens, such as sintilimab plus bevacizumab/bevacizumab biosimilar, are considered cost-effective [162,163]. Nonetheless, some regimens like cabozantinib plus atezolizumab are not cost-effective in China [162]. Studies have demonstrated that combination therapy involving ICIs and chemotherapy is more cost-effective compared to subsequent ICI therapy after chemotherapy in patients with metastatic urothelial carcinoma [164]. Studies have also reviewed the cost-effectiveness of ICI therapies and concluded that ICI therapy may not be cost-effective compared to conventional chemotherapy approaches [165]. However, several factors such as overall survival, long-term outcome, and combination therapy might be influential factors for the choice of drugs for particular patients. Another investigation compared the incremental cost-effectiveness ratio of ICI with that of sorafenib. Analysis of five studies has revealed that ICI has a higher incremental cost-effectiveness ratio compared to sorafenib in patients with hepatocellular carcinoma. The outcome of the study suggested that ICI was not a cost-effective option when compared to the drug, sorafenib, for the treatment of patients with hepatocellular carcinoma [166]. In another study, sequential and combination ICI therapy were analysed for their cost-effectiveness in patients with melanoma. Combination therapy employing PD-1/PD-L1 and anti-CTLA was costly and also toxic to patients. Nonetheless, sequential therapy commencing with the PD-1/PD-L1 was comparatively more cost-effective [167]. Healthcare disparities in ICI therapy persist, limiting access to these life-saving treatments for certain populations. Communities, particularly in rural and low-income areas, face barriers to adopting ICI therapy due to limited access to specialized cancer centres, inadequate healthcare infrastructure, and disparities in insurance coverage and reimbursement policies. Sometimes, systemic inequalities and biases within the healthcare system further reduce access to ICI therapy. As a result, some populations often receive delayed or inadequate treatment, ultimately affecting disease outcomes and survival rates. In a study, it has been demonstrated that non-Hispanic (NH)-Black patients receive ICI therapy 15 % less compared with their NH-White counterparts [164]. This study suggests racial/ethnic disparities in the utilisation of ICI therapy. Such disparity requires further interventions so that access to ICI therapy can be optimized.

13. Conclusion

In essence, cancer cells employ a complex array of strategies to hijack the PD-1/PD-L1 and CTLA-4-mediated signalling to mask the anticancer immune response. It helps in tumour progression. Recent advances in immune checkpoint inhibition have shown promising clinical outcomes. However, the development of autoimmune diseases and inflammatory reactions poses significant challenges to their safe application in cancer patients. Elucidating the mechanism of immune response modulation by emerging ICIs and identifying promising biomarkers for ICI-mediated immunotoxicity can help better manage the IrAEs, associated with this immunotherapy. Implementation of combination therapy along with the use of anti-inflammatory drugs with fewer side effects can also help mitigate the adverse effects of ICIs in patients. Moreover, searching for novel ICIs and in-depth understanding of tumour microenvironment are crucial for the effective management of IrAEs in cancer patients.

CRediT authorship contribution statement

Prem Rajak: Writing – review & editing, Writing – original draft,

Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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No data was used for the research described in the article.

References

[1] H. Nishimura, T. Okazaki, Y. Tanaka, K. Nakatani, M. Hara, A. Matsumori, S. Sasayama, A. Mizoguchi, H. Hiai, N. Minato, T. Honjo, Autoimmune dilated cardiomyopathy in PD-1 receptor-deficient mice, Science 291 (2001) 319–322, https://doi.org/10.1126/science.291.5502.319.

[2] J.S. Weber, F.S. Hodi, J.D. Wolchok, S.L. Topalian, D. Schadendorf, J. Larkin, M. Sznol, G.V. Long, H. Li, I.M. Waxman, J. Jiang, C. Robert, Safety profile of nivolumab monotherapy: a pooled analysis of patients with advanced melanoma, JCO 35 (2017) 785–792, https://doi.org/10.1200/JCO.2015.66.1389.

[3] A.A. Tarhini, S.J. Lee, F.S. Hodi, U.N.M. Rao, G.I. Cohen, O. Hamid, L. F. Hutchins, J.A. Sosman, H.M. Kluger, Z. Eroglu, H.B. Koon, D.P. Lawrence, K. L. Kendra, D.R. Minor, C.B. Lee, M.R. Albertini, L.E. Flaherty, T.M. Petrella, H. Streicher, V.K. Sondak, J.M. Kirkwood, Phase III study of adjuvant Ipilimumab (3 or 10 mg/kg) versus high-dose interferon alfa-2b for resected high-risk melanoma: North American Intergroup E1609, JCO 38 (2020) 567–575, https://doi.org/10.1200/JCO.19.01381.

[4] J. Weber, M. Mandala, M. Del Vecchio, H.J. Gogas, A.M. Arance, C.L. Cowey, S. Dalle, M. Schenker, V. Chiarion-Sileni, I. Marquez-Rodas, J.-J. Grob, M. O. Butler, M.R. Middleton, M. Maio, V. Atkinson, P. Queirolo, R. Gonzalez, R. R. Kudchadkar, M. Smylie, N. Meyer, L. Mortier, M.B. Atkins, G.V. Long, S. Bhatia, C. Lebbé, P. Rutkowski, K. Yokota, N. Yamazaki, T.M. Kim, V. De Pril, J. Sabater, A. Qureshi, J. Larkin, P.A. Ascierto, Adjuvant nivolumab versus ipilimumab in resected stage III or IV melanoma, N. Engl. J. Med 377 (2017) 1824–1835, https://doi.org/10.1056/NEJMoa1709030.

[5] M. Conroy, J. Naidoo, Immune-related adverse events and the balancing act of immunotherapy, Nat. Commun. 13 (2022) 392, https://doi.org/10.1038/s41467-022-27960-2.

[6] M. Guida, S. Strippoli, M. Maule, P. Quaglino, A. Ramondetta, V. Chiaron Sileni, G. Antonini Cappellini, P. Queirolo, L. Ridolfi, M. Del Vecchio, E. Cocorocchio, A. M. Di Giacomo, L. Festino, B. Merelli, M. Occelli, S. Brugnara, A. Minisini, S. Sava, S. Tommasi, S. De Summa, Immune checkpoint inhibitor associated vitiligo and its impact on survival in patients with metastatic melanoma: an Italian Melanoma Intergroup study, ESMO Open 6 (2021) 100064, https://doi.org/10.1016/j.esmoop.2021.100064.

[7] D.H. Johnson, Y. Hailemichael, W.C. Foo, K.R. Hess, et al., Interleukin-6 is potential target to de-couple checkpoint inhibitor-induced colitis from antitumor immunity, J. Clin. Oncol. 37 (2019) 2616.

[8] I.A. Harsch, P.C. Konturek, Acute-onset diabetes mellitus with ketoacidosis in a nivolumab-treated patient with hepatocellular carcinoma, Wiadomosci Lek. 71 (2018) 945–948.

[9] J.L. Godwin, S. Jaggi, I. Sirisena, P. Sharda, A.D. Rao, R. Mehra, C. Veloski, Nivolumab-induced autoimmune diabetes mellitus presenting as diabetic ketoacidosis in a patient with metastatic lung cancer, J. Immunother. Cancer 5 (2017) 40, https://doi.org/10.1186/s40425-017-0245-2.

[10] L. Khoja, D. Day, T. Wei-Wu Chen, L.L. Siu, A.R. Hansen, Tumour- and class-specific patterns of immune-related adverse events of immune checkpoint inhibitors: a systematic review, Ann. Oncol. 28 (2017) 2377–2385, https://doi.org/10.1093/annonc/mdx286.

[11] M. Issa, J. Tang, Y. Guo, C. Coss, T.A. Mace, J. Bischof, M. Phelps, C.J. Presley, D. H. Owen, Risk factors and predictors of immune-related adverse events: implications for patients with non-small cell lung cancer, Expert Rev. Anticancer Ther. 22 (2022) 861–874, https://doi.org/10.1080/14737140.2022.2094772.

[12] D.B. Johnson, A. Manouchehri, A.M. Haugh, H.T. Quach, J.M. Balko, B. Lebrun-Vignes, A. Mammen, J.J. Moslehi, J.-E. Salem, Neurologic toxicity associated with immune checkpoint inhibitors: a pharmacovigilance study, J. Immunother. Cancer 7 (2019) 134, https://doi.org/10.1186/s40425-019-0617-x.

[13] L. Hountondji, C. Ferreira De Matos, F. Lebossé, X. Quantin, C. Lesage, P. Palassin, V. Rivet, S. Faure, G.-P. Pageaux, É . Assenat, L. Alric, A. Zahhaf, D. Larrey, P. Witkowski Durand Viel, B. Riviere, S. Janick, S. Dalle, A.T.J. Maria, T. Comont, L. Meunier, Clinical pattern of checkpoint inhibitor-induced liver injury in a multicentre cohort, JHEP Rep. 5 (2023) 100719, https://doi.org/10.1016/j.jhepr.2023.100719.

[14] A. Bobircă, F. Bobircă, I. Ancuta, A. Florescu, V. Pădureanu, D.N. Florescu, R. Pădureanu, A. Florescu, A.E. Mușetescu, Rheumatic immune-related adverse events—a consequence of immune checkpoint inhibitor therapy, Biology 10 (2021) 561, https://doi.org/10.3390/biology10060561.

[15] K.C. Ohaegbulam, A. Assal, E. Lazar-Molnar, Y. Yao, X. Zang, Human cancer immunotherapy with antibodies to the PD-1 and PD-L1 pathway, Trends Mol. Med. 21 (2015) 24–33, https://doi.org/10.1016/j.molmed.2014.10.009.

[16] L.J. Scott, Nivolumab: a review in advanced melanoma, Drugs 75 (2015) 1413–1424, https://doi.org/10.1007/s40265-015-0442-6.

[17] A. Lee, S. Duggan, E.D. Deeks, Cemiplimab: a review in advanced cutaneous squamous cell carcinoma, Drugs 80 (2020) 813–819, https://doi.org/10.1007/s40265-020-01302-2.

[18] T. André, D. Berton, G. Curigliano, R. Sabatier, A.V. Tinker, A. Oaknin, S. Ellard, F. De Braud, H.-T. Arkenau, J. Trigo, A. Gravina, R. Kristeleit, V. Moreno, C. Abdeddaim, Y.-A. Vano, V. Samouëlian, R. Miller, V. Boni, A.A. Torres, L. Gilbert, J. Brown, N. Dewal, C. Dabrowski, G. Antony, E. Zografos, J. Veneris, S. Banerjee, Antitumor activity and safety of dostarlimab monotherapy in patients with mismatch repair deficient solid tumors: a nonrandomized controlled trial, JAMA Netw. Open 6 (2023) e2341165, https://doi.org/10.1001/jamanetworkopen.2023.41165.

[19] T. Powles, M. Kockx, A. Rodriguez-Vida, I. Duran, S.J. Crabb, M.S. Van Der Heijden, B. Szabados, A.F. Pous, G. Gravis, U.A. Herranz, A. Protheroe, A. Ravaud, D. Maillet, M.J. Mendez, C. Suarez, M. Linch, A. Prendergast, P.-J. Van Dam, D. Stanoeva, S. Daelemans, S. Mariathasan, J.S. Tea, K. Mousa, R. Banchereau, D. Castellano, Clinical efficacy and biomarker analysis of neoadjuvant atezolizumab in operable urothelial carcinoma in the ABACUS trial, Nat. Med. 25 (2019) 1706–1714, https://doi.org/10.1038/s41591-019-0628-7.

[20] J. Larkin, V. Chiarion-Sileni, R. Gonzalez, J.-J. Grob, P. Rutkowski, C.D. Lao, C. L. Cowey, D. Schadendorf, J. Wagstaff, R. Dummer, P.F. Ferrucci, M. Smylie, D. Hogg, A. Hill, I. Márquez-Rodas, J. Haanen, M. Guidoboni, M. Maio, P. Schöffski, M.S. Carlino, C. Lebbé, G. McArthur, P.A. Ascierto, G.A. Daniels, G. V. Long, L. Bastholt, J.I. Rizzo, A. Balogh, A. Moshyk, F.S. Hodi, J.D. Wolchok, Five-year survival with combined nivolumab and ipilimumab in advanced melanoma, N. Engl. J. Med 381 (2019) 1535–1546, https://doi.org/10.1056/NEJMoa1910836.

[21] C. Robert, J. Schachter, G.V. Long, A. Arance, J.J. Grob, L. Mortier, A. Daud, M. S. Carlino, C. McNeil, M. Lotem, J. Larkin, P. Lorigan, B. Neyns, C.U. Blank, O. Hamid, C. Mateus, R. Shapira-Frommer, M. Kosh, H. Zhou, N. Ibrahim, S. Ebbinghaus, A. Ribas, Pembrolizumab versus Ipilimumab in advanced melanoma, N. Engl. J. Med. 372 (2015) 2521–2532, https://doi.org/10.1056/NEJMoa1503093.

[22] S. Schwartz, N. Patel, T. Longmire, P. Jayaraman, X. Jiang, H. Lu, L. Baker, J. Velez, R. Ramesh, A.-S. Wavreille, M. Verneret, H. Fan, T. Hu, F. Xu, J. Taraszka, M. Pelletier, J. Miyashiro, M. Rinne, G. Dranoff, C. Sabatos-Peyton, V. Cremasco, Characterization of sabatolimab, a novel immunotherapy with immuno-myeloid activity directed against TIM-3 receptor, Immunother. Adv. 2 (2022) ltac019, https://doi.org/10.1093/immadv/ltac019.

[23] V. Sibaud, Dermatologic reactions to immune checkpoint inhibitors: skin toxicities and immunotherapy, Am. J. Clin. Dermatol. 19 (2018) 345–361, https://doi.org/10.1007/s40257-017-0336-3.

[24] S.-Q. Tang, L.-L. Tang, Y.-P. Mao, W.-F. Li, L. Chen, Y. Zhang, Y. Guo, Q. Liu, Y. Sun, C. Xu, J. Ma, The pattern of time to onset and resolution of immune-related adverse events caused by immune checkpoint inhibitors in cancer: a pooled analysis of 23 clinical trials and 8,436 patients, Cancer Res. Treat. 53 (2021) 339–354, https://doi.org/10.4143/crt.2020.790.

[25] M.G. Lechner, M.I. Cheng, A.Y. Patel, A.T. Hoang, N. Yakobian, M. Astourian, M. S. Pioso, E.D. Rodriguez, E.C. McCarthy, W. Hugo, T.E. Angell, A. Drakaki, A. Ribas, M.A. Su, Inhibition of IL-17A protects against thyroid immune-related adverse events while preserving checkpoint inhibitor antitumor efficacy, J. Immunol. 209 (2022) 696–709, https://doi.org/10.4049/jimmunol.2200244.

[26] L.K. Collins, M.S. Chapman, J.B. Carter, F.H. Samie, Cutaneous adverse effects of the immune checkpoint inhibitors, Curr. Probl. Cancer 41 (2017) 125–128, https://doi.org/10.1016/j.currproblcancer.2016.12.001.

[27] S.M. Goldinger, P. Stieger, B. Meier, S. Micaletto, E. Contassot, L.E. French, R. Dummer, Cytotoxic cutaneous adverse drug reactions during anti-PD-1 therapy, Clin. Cancer Res. 22 (2016) 4023–4029, https://doi.org/10.1158/1078-0432.CCR-15-2872.

[28] R.E. Perret, N. Josselin, A. Knol, A. Khammari, J. Cassecuel, L. Peuvrel, B. Dreno, Supported by GESTIM Nantes group of cutaneous adverse events induced by anticancer drugs, Histopathological aspects of cutaneous erythematous-papular eruptions induced by immune checkpoint inhibitors for the treatment of metastatic melanoma, Int. J. Dermatol. 56 (2017) 527–533, https://doi.org/10.1111/ijd.13540.

[29] J.L. Curry, A. Reuben, R. Szczepaniak-Sloane, J. Ning, D.R. Milton, C.H. Lee, C. Hudgens, S. George, C. Torres-Cabala, D. Johnson, S. Subramanya, J.A. Wargo, K. Mudaliar, I.I. Wistuba, V.G. Prieto, A. Diab, M.T. Tetzlaff, Gene expression profiling of lichenoid dermatitis immune-related adverse event from immune checkpoint inhibitors reveals increased $CD14^{+}$ and $CD16^{+}$ monocytes driving an innate immune response, J. Cutan. Pathol. 46 (2019) 627–636, https://doi.org/10.1111/cup.13454.

[30] K. Tyan, J. Baginska, M. Brainard, A. Giobbie-Hurder, M. Severgnini, M. Manos, R. Haq, E.I. Buchbinder, P.A. Ott, F.S. Hodi, O.E. Rahma, Cytokine changes during immune-related adverse events and corticosteroid treatment in melanoma patients receiving immune checkpoint inhibitors, Cancer Immunol. Immunother. 70 (2021) 2209–2221, https://doi.org/10.1007/s00262-021-02855-1.

[31] G.S. Phillips, J. Wu, M.D. Hellmann, M.A. Postow, N.A. Rizvi, A. Freites-Martinez, D. Chan, S. Dusza, R.J. Motzer, J.E. Rosenberg, M.K. Callahan, P.B. Chapman, L. Geskin, A.T. Lopez, V.A. Reed, G. Fabbrocini, M.C. Annunziata, O. Kukoyi, A. Pabani, C.-H. Yang, W.-H. Chung, A. Markova, M.E. Lacouture, Treatment outcomes of immune-related cutaneous adverse events, JCO 37 (2019) 2746–2758, https://doi.org/10.1200/JCO.18.02141.

[32] J. Naidoo, K. Schindler, C. Querfeld, K. Busam, J. Cunningham, D.B. Page, M. A. Postow, A. Weinstein, A.S. Lucas, K.T. Ciccolini, E.A. Quigley, A.M. Lesokhin, P.K. Paik, J.E. Chaft, N.H. Segal, S.P. D'Angelo, M.A. Dickson, J.D. Wolchok, M. E. Lacouture, Autoimmune bullous skin disorders with immune checkpoint inhibitors targeting PD-1 and PD-L1, Cancer Immunol. Res. 4 (2016) 383–389, https://doi.org/10.1158/2326-6066.CIR-15-0123.

[33] B.J. Schneider, J. Naidoo, B.D. Santomasso, C. Lacchetti, S. Adkins, M. Anadkat, M.B. Atkins, K.J. Brassil, J.M. Caterino, I. Chau, M.J. Davies, M.S. Ernstoff, L. Fecher, M. Ghosh, I. Jaiyesimi, J.S. Mammen, A. Naing, L.J. Nastoupil, T. Phillips, L.D. Porter, C.A. Reichner, C. Seigel, J.-M. Song, A. Spira, M. Suarez-Almazor, U. Swami, J.A. Thompson, P. Vikas, Y. Wang, J.S. Weber, P. Funchain, K. Bollin, Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: ASCO guideline update, JCO 39 (2021) 4073–4126, https://doi.org/10.1200/JCO.21.01440.

[34] A.M. Luoma, S. Suo, H.L. Williams, T. Sharova, K. Sullivan, M. Manos, P. Bowling, F.S. Hodi, O. Rahma, R.J. Sullivan, G.M. Boland, J.A. Nowak, S.K. Dougan, M. Dougan, G.-C. Yuan, K.W. Wucherpfennig, Molecular pathways of colon inflammation induced by cancer immunotherapy, Cell 182 (2020) 655–671.e22, https://doi.org/10.1016/j.cell.2020.06.001.

[35] S.C. Sasson, S.M. Slevin, V.T.F. Cheung, I. Nassiri, A. Olsson-Brown, E. Fryer, R. C. Ferreira, D. Trzupek, T. Gupta, L. Al-Hillawi, M. Issaias, A. Easton, L. Campo, M.E.B. FitzPatrick, J. Adams, M. Chitnis, A. Protheroe, M. Tuthill, N. Coupe, A. Simmons, M. Payne, M.R. Middleton, S.P.L. Travis, B.P. Fairfax, P. Klenerman, O. Brain, Interferon-gamma–producing CD8+ tissue resident memory T cells are a targetable hallmark of immune checkpoint inhibitor–colitis, Gastroenterology 161 (2021) 1229–1244.e9, https://doi.org/10.1053/j.gastro.2021.06.025.

[36] M.F. Neurath, Cytokines in inflammatory bowel disease, Nat. Rev. Immunol. 14 (2014) 329–342, https://doi.org/10.1038/nri3661.

[37] G. Bamias, I. Delladetsima, M. Perdiki, S.I. Siakavellas, D. Goukos, G. V. Papatheodoridis, G.L. Daikos, H. Gogas, Immunological characteristics of colitis associated with anti-CTLA-4 antibody therapy, Cancer Investig. 35 (2017) 443–455, https://doi.org/10.1080/07357907.2017.1324032.

[38] L. Marthey, C. Mateus, C. Mussini, M. Nachury, S. Nancey, F. Grange, C. Zallot, L. Peyrin-Biroulet, J.F. Rahier, M. Bourdier De Beauregard, L. Mortier, C. Coutzac, E. Soularue, E. Lanoy, N. Kapel, D. Planchard, N. Chaput, C. Robert, F. Carbonnel, Cancer immunotherapy with anti-CTLA-4 monoclonal antibodies induces an inflammatory bowel disease, ECCOJC 10 (2016) 395–401, https://doi.org/10.1093/ecco-jcc/jjv227.

[39] Y. Wang, H. Abu-Sbeih, E. Mao, N. Ali, W. Qiao, V.A. Trinh, C. Zobniw, D. H. Johnson, R. Samdani, P. Lum, G. Shuttlesworth, B. Blechacz, R. Bresalier, E. Miller, S. Thirumurthi, D. Richards, G. Raju, J. Stroehlein, A. Diab, Endoscopic and histologic features of immune checkpoint inhibitor-related colitis, Inflamm. Bowel Dis. 24 (2018) 1695–1705, https://doi.org/10.1093/ibd/izy104.

[40] T.K. Kim, H.S. Lee, E.S. Kim, Incidence and risk factors of immune checkpoint inhibitor-induced colitis in Korean patients with cancer, Korean J. Intern. Med. 40 (2025) 49–56, https://doi.org/10.3904/kjim.2024.135.

[41] B.L. Sun, A.S. Elliott, D. Nolte, X. Sun, Immune checkpoint inhibitor–related colitis in patients on immunotherapy for cancer, Am. J. Clin. Pathol. 162 (2024) 17–27, https://doi.org/10.1093/ajcp/aqae002.

[42] V. Albarrán, J. Chamorro, D.I. Rosero, C. Saavedra, A. Soria, A. Carrato, P. Gajate, Neurologic toxicity of immune checkpoint inhibitors: a review of literature, Front. Pharm. 13 (2022) 774170, https://doi.org/10.3389/fphar.2022.774170.

[43] E. Sechi, A. Zekeridou, Neurologic complications of immune checkpoint inhibitors in thoracic malignancies, J. Thorac. Oncol. 16 (2021) 381–394, https://doi.org/10.1016/j.jtho.2020.11.005.

[44] S.L. Duong, F.J. Barbiero, R.J. Nowak, J.M. Baehring, Neurotoxicities associated with immune checkpoint inhibitor therapy, J. Neurooncol. 152 (2021) 265–277, https://doi.org/10.1007/s11060-021-03695-w.

[45] S. Charabi, L. Engell-Noerregaard, A.C. Nilsson, C. Stenör, Case report: longitudinal extensive transverse myelitis with novel autoantibodies following two rounds of Pembrolizumab, Front. Neurol. 12 (2021) 655283, https://doi.org/10.3389/fneur.2021.655283.

[46] L. Müller-Jensen, S. Knauss, L. Ginesta Roque, C. Schinke, S.K. Maierhof, F. Bartels, C. Finke, K. Rentzsch, C. Ulrich, R. Mohr, W. Stenzel, M. Endres, W. Boehmerle, P. Huehnchen, Autoantibody profiles in patients with immune checkpoint inhibitor-induced neurological immune related adverse events, Front. Immunol. 14 (2023) 1108116, https://doi.org/10.3389/fimmu.2023.1108116.

[47] J.M. Vinnakota, R.C. Adams, D. Athanassopoulos, D. Schmidt, F. Biavasco, A. Zähringer, D. Erny, M. Schwabenland, M. Langenbach, V. Wenger, H. Salié, J. Cook, O. Mossad, G. Andrieux, R. Dersch, S. Rauer, S. Duquesne, G. Monaco, P. Wolf, T. Blank, P. Häne, M. Greter, B. Becher, P. Henneke, D. Pfeifer, B. R. Blazar, J. Duyster, M. Boerries, N. Köhler, C.M. Chhatbar, B. Bengsch, M. Prinz, R. Zeiser, Anti–PD-1 cancer immunotherapy induces central nervous system immune-related adverse events by microglia activation, Sci. Transl. Med. 16 (2024) eadj9672, https://doi.org/10.1126/scitranslmed.adj9672.

[48] C.A. Muir, et al., Thyroid immune-related adverse events following immune checkpoint inhibitor treatment, J. Clin. Endocrinol. Metab. 106 (2021) e3704–e3713.

[49] C. Ma, F.S. Hodi, A. Giobbie-Hurder, X. Wang, J. Zhou, A. Zhang, Y. Zhou, F. Mao, T.E. Angell, C.P. Andrews, J. Hu, R. Barroso-Sousa, U.B. Kaiser, S.M. Tolaney, L. Min, The impact of high-dose glucocorticoids on the outcome of immune-checkpoint inhibitor–related thyroid disorders, Cancer Immunol. Res. 7 (2019) 1214–1220, https://doi.org/10.1158/2326-6066.CIR-18-0613.

[50] H. Lee, F.S. Hodi, A. Giobbie-Hurder, P.A. Ott, E.I. Buchbinder, R. Haq, S. Tolaney, R. Barroso-Sousa, K. Zhang, H. Donahue, M. Davis, M.E. Gargano, K. M. Kelley, R.S. Carroll, U.B. Kaiser, L. Min, Characterization of thyroid disorders in patients receiving immune checkpoint inhibition therapy, Cancer Immunol. Res. 5 (2017) 1133–1140, https://doi.org/10.1158/2326-6066.CIR-17-0208.

[51] M.G. Lechner, N. Yakobian, A. Patel, E. Rodriguez, T.E. Angell, A. Drakaki, P. Famini, S.S. Praw, A. Ribas, M.A. Su, Identification of RORg+T cells as key players in thyroid autoimmunity from checkpoint immunotherapy, J. Endocr. Soc. 5 (2021) A839–A840, https://doi.org/10.1210/jendso/bvab048.1714.

[52] A. Faje, K. Reynolds, L. Zubiri, D. Lawrence, J.V. Cohen, R.J. Sullivan, L. Nachtigall, N. Tritos, Hypophysitis secondary to nivolumab and pembrolizumab is a clinical entity distinct from ipilimumab-associated hypophysitis, Eur. J. Endocrinol. 181 (2019) 211–219, https://doi.org/10.1530/EJE-19-0238.

[53] J. Garon-Czmil, N. Petitpain, F. Rouby, M. Sassier, S. Babai, M. Yéléhé-Okouma, G. Weryha, M. Klein, P. Gillet, Immune check point inhibitors-induced hypophysitis: a retrospective analysis of the French Pharmacovigilance database, Sci. Rep. 9 (2019) 19419, https://doi.org/10.1038/s41598-019-56026-5.

[54] T. Dillard, C.G. Yedinak, J. Alumkal, M. Fleseriu, Anti-CTLA-4 antibody therapy associated autoimmune hypophysitis: serious immune related adverse events across a spectrum of cancer subtypes, Pituitary 13 (2010) 29–38, https://doi.org/10.1007/s11102-009-0193-z.

[55] J.A. Blansfield, K.E. Beck, K. Tran, J.C. Yang, M.S. Hughes, U.S. Kammula, R. E. Royal, S.L. Topalian, L.R. Haworth, C. Levy, S.A. Rosenberg, R.M. Sherry, Cytotoxic T-lymphocyte-associated antigen-4 blockage can induce autoimmune hypophysitis in patients with metastatic melanoma and renal cancer, J. Immunother. 28 (2005) 593–598, https://doi.org/10.1097/01.cji.0000178913.41256.06.

[56] S.A. Tahir, J. Gao, Y. Miura, J. Blando, R.S.S. Tidwell, H. Zhao, S.K. Subudhi, H. Tawbi, E. Keung, J. Wargo, J.P. Allison, P. Sharma, Autoimmune antibodies correlate with immune checkpoint therapy-induced toxicities, Proc. Natl. Acad. Sci. USA 116 (2019) 22246–22251, https://doi.org/10.1073/pnas.1908079116.

[57] R. Jeun, P.C. Iyer, C. Best, V. Lavis, J.M. Varghese, S. Yedururi, V. Brady, I. C. Glitza Oliva, R. Dadu, D.R. Milton, K. Brock, S. Thosani, Clinical outcomes of immune checkpoint inhibitor diabetes mellitus at a comprehensive cancer center, Immunotherapy 15 (2023) 417–428, https://doi.org/10.2217/imt-2021-0316.

[58] A.L. Perdigoto, S. Deng, K.C. Du, M. Kuchroo, D.B. Burkhardt, A. Tong, G. Israel, M.E. Robert, S.P. Weisberg, N. Kirkiles-Smith, A.M. Stamatouli, H.M. Kluger, Z. Quandt, A. Young, M.-L. Yang, M.J. Mamula, J.S. Pober, M.S. Anderson, S. Krishnaswamy, K.C. Herold, Immune cells and their inflammatory mediators modify β cells and cause checkpoint inhibitor–induced diabetes, JCI Insight 7 (2022) e156330, https://doi.org/10.1172/jci.insight.156330.

[59] J.J. Wright, A.C. Powers, D.B. Johnson, Endocrine toxicities of immune checkpoint inhibitors, Nat. Rev. Endocrinol. 17 (2021) 389–399, https://doi.org/10.1038/s41574-021-00484-3.

[60] D.Y. Wang, J.-E. Salem, J.V. Cohen, S. Chandra, C. Menzer, F. Ye, S. Zhao, S. Das, K.E. Beckermann, L. Ha, W.K. Rathmell, K.K. Ancell, J.M. Balko, C. Bowman, E. J. Davis, D.D. Chism, L. Horn, G.V. Long, M.S. Carlino, B. Lebrun-Vignes, Z. Eroglu, J.C. Hassel, A.M. Menzies, J.A. Sosman, R.J. Sullivan, J.J. Moslehi, D. B. Johnson, Fatal toxic effects associated with immune checkpoint inhibitors: a systematic review and meta-analysis, JAMA Oncol. 4 (2018) 1721, https://doi.org/10.1001/jamaoncol.2018.3923.

[61] S.J. Antonia, A. Villegas, D. Daniel, D. Vicente, S. Murakami, R. Hui, T. Yokoi, A. Chiappori, K.H. Lee, M. De Wit, B.C. Cho, M. Bourhaba, X. Quantin, T. Tokito, T. Mekhail, D. Planchard, Y.-C. Kim, C.S. Karapetis, S. Hiret, G. Ostoros, K. Kubota, J.E. Gray, L. Paz-Ares, J. De Castro Carpeño, C. Wadsworth, G. Melillo, H. Jiang, Y. Huang, P.A. Dennis, M. Özgüroğlu, Durvalumab after chemoradiotherapy in stage III non–small-cell lung cancer, N. Engl. J. Med. 377 (2017) 1919–1929, https://doi.org/10.1056/NEJMoa1709937.

[62] S. Ganatra, T.G. Neilan, Immune checkpoint inhibitor-associated myocarditis, Oncologist 23 (2018) 879–886, https://doi.org/10.1634/theoncologist.2018-0130.

[63] L. Zhang, K.L. Reynolds, A.R. Lyon, N. Palaskas, T.G. Neilan, The evolving immunotherapy landscape and the epidemiology, diagnosis, and management of cardiotoxicity, JACC: CardioOncol. 3 (2021) 35–47, https://doi.org/10.1016/j.jaccao.2020.11.012.

[64] M.L. Axelrod, W.C. Meijers, E.M. Screever, J. Qin, M.G. Carroll, X. Sun, E. Tannous, Y. Zhang, A. Sugiura, B.C. Taylor, A. Hanna, S. Zhang, K. Amancherla, W. Tai, J.J. Wright, S.C. Wei, S.R. Opalenik, A.L. Toren, J. C. Rathmell, P.B. Ferrell, E.J. Phillips, S. Mallal, D.B. Johnson, J.P. Allison, J. J. Moslehi, J.M. Balko, T cells specific for α-myosin drive immunotherapy-related myocarditis, Nature 611 (2022) 818–826, https://doi.org/10.1038/s41586-022-05432-3.

[65] H. Zhu, F.X. Galdos, D. Lee, S. Waliany, Y.V. Huang, J. Ryan, K. Dang, J.W. Neal, H.A. Wakelee, S.A. Reddy, S. Srinivas, L.-L. Lin, R.M. Witteles, H.T. Maecker, M. M. Davis, P.K. Nguyen, S.M. Wu, Identification of pathogenic immune cell subsets associated with checkpoint inhibitor–induced myocarditis, Circulation 146 (2022) 316–335, https://doi.org/10.1161/CIRCULATIONAHA.121.056730.

[66] G.P. Linette, E.A. Stadtmauer, M.V. Maus, A.P. Rapoport, B.L. Levine, L. Emery, L. Litzky, A. Bagg, B.M. Carreno, P.J. Cimino, G.K. Binder-Scholl, D.P. Smethurst, A.B. Gerry, N.J. Pumphrey, A.D. Bennett, J.E. Brewer, J. Dukes, J. Harper, H. K. Tayton-Martin, B.K. Jakobsen, N.J. Hassan, M. Kalos, C.H. June, Cardiovascular toxicity and titin cross-reactivity of affinity-enhanced T cells in

myeloma and melanoma, Blood 122 (2013) 863–871, https://doi.org/10.1182/blood-2013-03-490565.
[67] R.P. Patel, R. Parikh, K.S. Gunturu, R.Z. Tariq, S.S. Dani, S. Ganatra, A. Nohria, Cardiotoxicity of immune checkpoint inhibitors, Curr. Oncol. Rep. 23 (2021) 79, https://doi.org/10.1007/s11912-021-01070-6.
[68] Z.D. Drobni, R.M. Alvi, J. Taron, A. Zafar, S.P. Murphy, P.K. Rambarat, R. C. Mosarla, C. Lee, D.A. Zlotoff, V.K. Raghu, S.E. Hartmann, H.K. Gilman, J. Gong, L. Zubiri, R.J. Sullivan, K.L. Reynolds, T. Mayrhofer, L. Zhang, U. Hoffmann, T. G. Neilan, Association between immune checkpoint inhibitors with cardiovascular events and atherosclerotic plaque, Circulation 142 (2020) 2299–2311, https://doi.org/10.1161/CIRCULATIONAHA.120.049981.
[69] J. Naidoo, D.B. Page, B.T. Li, L.C. Connell, K. Schindler, M.E. Lacouture, M. A. Postow, J.D. Wolchok, Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint antibodies, Ann. Oncol. 26 (2015) 2375–2391, https://doi.org/10.1093/annonc/mdv383.
[70] S. Ederhy, J. Cautela, Y. Ancedy, M. Escudier, F. Thuny, A. Cohen, Takotsubo-like syndrome in cancer patients treated with immune checkpoint inhibitors, JACC: Cardiovasc. Imag. 11 (2018) 1187–1190, https://doi.org/10.1016/j.jcmg.2017.11.036.
[71] M.D. Richter, C. Crowson, L.A. Kottschade, H.D. Finnes, S.N. Markovic, U. Thanarajasingam, Rheumatic syndromes associated with immune checkpoint inhibitors: a single-center cohort of sixty-one patients, Arthritis Rheumatol. 71 (2019) 468–475, https://doi.org/10.1002/art.40745.
[72] A. Cunningham-Bussel, J. Wang, L.C. Prisco, L.W. Martin, K.M.M. Vanni, A. Zaccardelli, M. Nasrallah, L. Gedmintas, L.A. MacFarlane, N.A. Shadick, M. M. Awad, O. Rahma, N.R. LeBoeuf, E.M. Gravallese, J.A. Sparks, Predictors of rheumatic immune-related adverse events and de novo inflammatory arthritis after immune checkpoint inhibitor treatment for cancer, Arthritis Rheumatol. 74 (2022) 527–540, https://doi.org/10.1002/art.41949.
[73] X. Pundole, N. Abdel-Wahab, M.E. Suarez-Almazor, Arthritis risk with immune checkpoint inhibitor therapy for cancer, Curr. Opin. Rheumatol. 31 (2019) 293–299, https://doi.org/10.1097/BOR.0000000000000601.
[74] S. Jeurling, L.C. Cappelli, Treatment of immune checkpoint inhibitor-induced inflammatory arthritis, Curr. Opin. Rheumatol. 32 (2020) 315–320, https://doi.org/10.1097/BOR.0000000000000701.
[75] K.R. McCarter, T. Wolfgang, S. Arabelovic, X. Wang, K. Yoshida, E.P. Banasiak, G. Qian, E.N. Kowalski, K.M.M. Vanni, N.R. LeBoeuf, E.I. Buchbinder, L. Gedmintas, L.A. MacFarlane, D.A. Rao, N.A. Shadick, E.M. Gravallese, J. A. Sparks, Mortality and immune-related adverse events after immune checkpoint inhibitor initiation for cancer among patients with pre-existing rheumatoid arthritis: a retrospective, comparative, cohort study, Lancet Rheumatol. 5 (2023) e274–e283, https://doi.org/10.1016/S2665-9913(23)00064-4.
[76] Y. Guo, A.M. Walsh, M. Canavan, M.D. Wechalekar, S. Cole, X. Yin, B. Scott, M. Loza, C. Orr, T. McGarry, M. Bombardieri, F. Humby, S.M. Proudman, C. Pitzalis, M.D. Smith, J.R. Friedman, I. Anderson, L. Madakamutil, D.J. Veale, U. Fearon, S. Nagpal, Immune checkpoint inhibitor PD-1 pathway is down-regulated in synovium at various stages of rheumatoid arthritis disease progression, PLoS ONE 13 (2018) e0192704, https://doi.org/10.1371/journal.pone.0192704.
[77] L.C. Cappelli, J.R. Brahmer, P.M. Forde, D.T. Le, E.J. Lipson, J. Naidoo, L. Zheng, C.O. Bingham, A.A. Shah, Clinical presentation of immune checkpoint inhibitor-induced inflammatory arthritis differs by immunotherapy regimen, Semin. Arthritis Rheum. 48 (2018) 553–557, https://doi.org/10.1016/j.semarthrit.2018.02.011.
[78] S.T. Kim, Y. Chu, M. Misoi, M.E. Suarez-Almazor, J.H. Tayar, H. Lu, M. Buni, J. Kramer, E. Rodriguez, Z. Hussain, S.S. Neelapu, J. Wang, A.Y. Shah, N. M. Tannir, M.T. Campbell, D.L. Gibbons, T. Cascone, C. Lu, G.R. Blumenschein, M. Altan, B. Lim, V. Valero, M.E. Loghin, J. Tu, S.N. Westin, A. Naing, G. Garcia-Manero, N. Abdel-Wahab, H.A. Tawbi, P. Hwu, I.C.G. Oliva, M.A. Davies, S. P. Patel, J. Zou, A. Futreal, A. Diab, L. Wang, R. Nurieva, Distinct molecular and immune hallmarks of inflammatory arthritis induced by immune checkpoint inhibitors for cancer therapy, Nat. Commun. 13 (2022) 1970, https://doi.org/10.1038/s41467-022-29539-3.
[79] L.J. Celada, J.A. Kropski, J.D. Herazo-Maya, W. Luo, A. Creecy, A.T. Abad, O. S. Chioma, G. Lee, N.E. Hassell, G.I. Shaginurova, Y. Wang, J.E. Johnson, A. Kerrigan, W.R. Mason, R.P. Baughman, G.D. Ayers, G.R. Bernard, D.A. Culver, C.G. Montgomery, T.M. Maher, P.L. Molyneaux, I. Noth, S.E. Mutsaers, C. M. Prele, R. Stokes Peebles, D.C. Newcomb, N. Kaminski, T.S. Blackwell, L. Van Kaer, W.P. Drake, PD-1 up-regulation on $CD4^+$ T cells promotes pulmonary fibrosis through STAT3-mediated IL-17A and TGF-β1 production, Sci. Transl. Med. 10 (2018) eaar8356, https://doi.org/10.1126/scitranslmed.aar8356.
[80] B. Duchemann, J. Pluvy, B. Crestani, G. Zalcman, H. Nunes, Immune checkpoint blockade for patients with lung cancer and idiopathic pulmonary fibrosis, Eur. J. Cancer 145 (2021) 179–182, https://doi.org/10.1016/j.ejca.2020.12.016.
[81] M. Delaunay, J. Cadranel, A. Lusque, N. Meyer, V. Gounant, D. Moro-Sibilot, J.-M. Michot, J. Raimbourg, N. Girard, F. Guisier, D. Planchard, A.-C. Metivier, P. Tomasini, E. Dansin, M. Pérol, M. Campana, O. Gautschi, M. Früh, J.-D. Fumet, C. Audigier-Valette, S. Couraud, S. Dalle, M.-T. Leccia, M. Jaffro, S. Collot, G. Prévot, J. Milia, J. Mazieres, Immune-checkpoint inhibitors associated with interstitial lung disease in cancer patients, Eur. Respir. J. 50 (2017) 1700050, https://doi.org/10.1183/13993003.00050-2017.
[82] K. Shimoji, T. Masuda, K. Yamaguchi, S. Sakamoto, Y. Horimasu, T. Nakashima, S. Miyamoto, H. Iwamoto, K. Fujitaka, H. Hamada, S. Takeno, M. Hide, J. Teishima, H. Ohdan, N. Hattori, Association of preexisting interstitial lung abnormalities with immune checkpoint inhibitor–induced interstitial lung disease among patients with nonlung cancers, JAMA Netw. Open 3 (2020) e2022906, https://doi.org/10.1001/jamanetworkopen.2020.22906.
[83] I.A. Dobre, A.J. Frank, K.M. D'Silva, et al., Outcomes of patients with interstitial lung disease receiving programmed cell death 1 inhibitors: a retrospective case series, Clin. Lung Cancer 22 (2021) e738–e744, https://doi.org/10.1016/j.cllc.2021.01.014.
[84] D. Murata, K. Azuma, K. Murotani, N. Matsuo, G. Matama, T. Tokito, T. Sasada, T. Hoshino, Survival and soluble immune mediators of immune checkpoint inhibitor-induced interstitial lung disease in patients with non-small cell lung cancer, Lung Cancer 184 (2023) 107351, https://doi.org/10.1016/j.lungcan.2023.107351.
[85] B. Kowalski, A. Valaperti, P. Bezel, U.C. Steiner, D. Scholtze, S. Wieser, M. Vonow-Eisenring, A. Widmer, M. Kohler, D. Franzen, Analysis of cytokines in serum and bronchoalveolar lavage fluid in patients with immune-checkpoint inhibitor-associated pneumonitis: a cross-sectional case–control study, J. Cancer Res. Clin. Oncol. 148 (2022) 1711–1720, https://doi.org/10.1007/s00432-021-03750-z.
[86] K. Suzuki, T. Yanagihara, K. Matsumoto, H. Kusaba, T. Yamauchi, Y. Ikematsu, K. Tanaka, K. Otsubo, H. Inoue, Y. Yoneshima, E. Iwama, M. Arimura-Omori, E. Harada, N. Hamada, I. Okamoto, Y. Nakanishi, Immune-checkpoint profiles for T cells in bronchoalveolar lavage fluid of patients with immune-checkpoint inhibitor-related interstitial lung disease, Int. Immunol. 32 (2020) 547–557, https://doi.org/10.1093/intimm/dxaa022.
[87] K. Suresh, J. Naidoo, Q. Zhong, Y. Xiong, J. Mammen, M.V. De Flores, L. Cappelli, A. Balaji, T. Palmer, P.M. Forde, V. Anagnostou, D.S. Ettinger, K.A. Marrone, R. J. Kelly, C.L. Hann, B. Levy, J.L. Feliciano, C.-T. Lin, D. Feller-Kopman, A. D. Lerner, H. Lee, M. Shafiq, L. Yarmus, E.J. Lipson, M. Soloski, J.R. Brahmer, S. K. Danoff, F. D'Alessio, The alveolar immune cell landscape is dysregulated in checkpoint inhibitor pneumonitis, J. Clin. Investig. 129 (2019) 4305–4315, https://doi.org/10.1172/JCI128654.
[88] Y. Wolf, A.C. Anderson, V.K. Kuchroo, TIM3 comes of age as an inhibitory receptor, Nat. Rev. Immunol. 20 (2020) 173–185, https://doi.org/10.1038/s41577-019-0224-6.
[89] L.P. Andrews, A. Somasundaram, J.M. Moskovitz, A.L. Szymczak-Workman, C. Liu, A.R. Cillo, H. Lin, D.P. Normolle, K.D. Moynihan, I. Taniuchi, D.J. Irvine, J.M. Kirkwood, E.J. Lipson, R.L. Ferris, T.C. Bruno, C.J. Workman, D.A.A. Vignali, Resistance to PD1 blockade in the absence of metalloprotease-mediated LAG3 shedding, Sci. Immunol. 5 (2020) eabc2728, https://doi.org/10.1126/sciimmunol.abc2728.
[90] G.S. Falchook, A. Ribas, D. Davar, Z. Eroglu, J.S. Wang, J.J. Luke, E.P. Hamilton, B. Di Pace, T. Wang, S. Ghosh, A. Dhar, T. Borgovan, A. Waszak, P. LoRusso, Phase 1 trial of TIM-3 inhibitor cobolimab monotherapy and in combination with PD-1 inhibitors nivolumab or dostarlimab (AMBER), JCO 40 (2022) 2504, https://doi.org/10.1200/JCO.2022.40.16_suppl.2504.
[91] J.J. Harding, A. Patnaik, V. Moreno, M. Stein, A.M. Jankowska, N. Velez De Mendizabal, Z. Tina Liu, M. Koneru, E. Calvo, A phase Ia/Ib study of an anti-TIM-3 antibody (LY3321367) monotherapy or in combination with an anti-PD-L1 antibody (LY3300054): Interim safety, efficacy, and pharmacokinetic findings in advanced cancers, JCO 37 (2019) 12, https://doi.org/10.1200/JCO.2019.37.8_suppl.12.
[92] U. Borate, J. Esteve, K. Porkka, S. Knapper, N. Vey, S. Scholl, G. Garcia-Manero, M. Wermke, J. Janssen, E. Traer, C.C. Chua, R. Narayan, N. Tovar, M. Kontro, O. Ottmann, H. Sun, T. Longmire, S. Szpakowski, S. Liao, A. Patel, M.L. Rinne, A. Brunner, A.H. Wei, Phase Ib study of the anti-TIM-3 antibody MBG453 in combination with decitabine in patients with high-risk myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML), Blood 134 (2019) 570, https://doi.org/10.1182/blood-2019-128178.
[93] A.M. Brunner, J. Esteve, K. Porkka, S. Knapper, E. Traer, S. Scholl, G. Garcia-Manero, N. Vey, M. Wermke, J. Janssen, R. Narayan, S. Loo, M. Kontro, O. Ottmann, P. Naidu, M. Pelletier, M. Han, A. Lewandowski, N. Zhang, A. Mohammed, M.L. Rinne, U. Borate, A.H. Wei, N. Tovar, Efficacy and safety of sabatolimab (MBG453) in combination with hypomethylating agents (HMAs) in patients (Pts) with very high/high-risk myelodysplastic syndrome (vHR/HR-MDS) and acute myeloid leukemia (AML): final analysis from a phase Ib study, Blood 138 (2021) 244, https://doi.org/10.1182/blood-2021-146039.
[94] C. Brignone, M. Gutierrez, F. Mefti, E. Brain, R. Jarcau, F. Cvitkovic, N. Bousetta, J. Medioni, J. Gligorov, C. Grygar, M. Marcu, F. Triebel, First-line chemoimmunotherapy in metastatic breast carcinoma: combination of paclitaxel and IMP321 (LAG-3Ig) enhances immune responses and antitumor activity, J. Transl. Med. 8 (2010) 71, https://doi.org/10.1186/1479-5876-8-71.
[95] A. Wang-Gillam, S. Plambeck-Suess, P. Goedegebuure, P.O. Simon, J.B. Mitchem, J.R. Hornick, S. Sorscher, J. Picus, R. Suresh, A.C. Lockhart, B. Tan, W. G. Hawkins, A phase I study of IMP321 and gemcitabine as the front-line therapy in patients with advanced pancreatic adenocarcinoma, Invest. N. Drugs 31 (2013) 707–713, https://doi.org/10.1007/s10637-012-9866-y.
[96] M.L. Johnson, W. Fox, Y.-G. Lee, K.H. Lee, H.K. Ahn, Y.-C. Kim, K.-Y. Lee, J.-S. Lee, X. He, C. Park, D. Pomponio, T. Dang, P.H. Phuong, D.S.A. Nuyten, A. M. Hegde, R. Joshi, ARC-7: Randomized phase 2 study of domvanalimab + zimberelimab ± etrumadenant versus zimberelimab in first-line, metastatic, PD-L1-high non-small cell lung cancer (NSCLC), JCO 40 (2022) 397600, https://doi.org/10.1200/JCO.2022.40.36_suppl.397600.
[97] J. Niu, C. Maurice-Dror, D.H. Lee, D.-W. Kim, A. Nagrial, M. Voskoboynik, H. C. Chung, K. Mileham, U. Vaishampayan, D. Rasco, T. Golan, T.M. Bauer, A. Jimeno, V. Chung, E. Chartash, M. Lala, Q. Chen, J.A. Healy, M.-J. Ahn, First-in-human phase 1 study of the anti-TIGIT antibody vibostolimab as monotherapy or with pembrolizumab for advanced solid tumors, including non-small-cell lung

cancer★, Ann. Oncol. 33 (2022) 169–180, https://doi.org/10.1016/j.annonc.2021.11.002.
[98] N.B. Mettu, S.V. Ulahannan, J.C. Bendell, I. Garrido-Laguna, J.H. Strickler, K. N. Moore, R. Stagg, A.M. Kapoun, L. Faoro, S. Sharma, A phase 1a/b open-label, dose-escalation study of etigilimab alone or in combination with nivolumab in patients with locally advanced or metastatic solid tumors, Clin. Cancer Res. 28 (2022) 882–892, https://doi.org/10.1158/1078-0432.CCR-21-2780.
[99] J. Wang, J. Wakeham, R. Harkness, Z. Xing, Macrophages are a significant source of type 1 cytokines during mycobacterial infection, J. Clin. Invest. 103 (1999) 1023–1029, https://doi.org/10.1172/JCI6224.
[100] D. Mihic-Probst, M. Reinehr, S. Dettwiler, I. Kolm, C. Britschgi, K. Kudura, E. M. Maggio, D. Lenggenhager, E.J. Rushing, The role of macrophages type 2 and T-regs in immune checkpoint inhibitor related adverse events, Immunobiology 225 (2020) 152009, https://doi.org/10.1016/j.imbio.2020.152009.
[101] E.C. De Moel, E.A. Rozeman, E.H. Kapiteijn, E.M.E. Verdegaal, A. Grummels, J. A. Bakker, T.W.J. Huizinga, J.B. Haanen, R.E.M. Toes, D. Van Der Woude, Autoantibody development under treatment with immune-checkpoint inhibitors, Cancer Immunol. Res. 7 (2019) 6–11, https://doi.org/10.1158/2326-6066.CIR-18-0245.
[102] N. Ghosh, K.K. Chan, B. Jivanelli, A.R. Bass, Autoantibodies in patients with immune-related adverse events from checkpoint inhibitors: a systematic literature review, J. Clin. Rheuma 28 (2022) e498–e505, https://doi.org/10.1097/RHU.0000000000001777.
[103] N. Ghosh, M. Postow, C. Zhu, D. Jannat-Khah, Q.-Z. Li, G. Vitone, K.K. Chan, A. R. Bass, Lower baseline autoantibody levels are associated with immune-related adverse events from immune checkpoint inhibition, J. Immunother. Cancer 10 (2022) e004008, https://doi.org/10.1136/jitc-2021-004008.
[104] M. Seki, S. Kitano, S. Suzuki, Neurological disorders associated with immune checkpoint inhibitors: an association with autoantibodies, Cancer Immunol. Immunother. 71 (2022) 769–775, https://doi.org/10.1007/s00262-021-03053-9.
[105] B. Husain, M.C. Kirchberger, M. Erdmann, S. Schüpferling, A.-R. Abolhassani, W. Fröhlich, C. Berking, L. Heinzerling, Inflammatory markers in autoimmunity induced by checkpoint inhibitors, J. Cancer Res Clin. Oncol. 147 (2021) 1623–1630, https://doi.org/10.1007/s00432-021-03550-5.
[106] S.Y. Lim, J.H. Lee, T.N. Gide, A.M. Menzies, A. Guminski, M.S. Carlino, E.J. Breen, J.Y.H. Yang, S. Ghazanfar, R.F. Kefford, R.A. Scolyer, G.V. Long, H. Rizos, Circulating cytokines predict immune-related toxicity in melanoma patients receiving anti-PD-1–based immunotherapy, Clin. Cancer Res. 25 (2019) 1557–1563, https://doi.org/10.1158/1078-0432.CCR-18-2795.
[107] R. Zhao, H. Zhou, S.B. Su, A critical role for interleukin-1β in the progression of autoimmune diseases, Int. Immunopharmacol. 17 (2013) 658–669, https://doi.org/10.1016/j.intimp.2013.08.012.
[108] C. De Rham, S. Ferrari-Lacraz, S. Jendly, G. Schneiter, J.-M. Dayer, J. Villard, The proinflammatory cytokines IL-2, IL-15 and IL-21 modulate the repertoire of mature human natural killer cell receptors, Arthritis Res. Ther. 9 (2007) R125, https://doi.org/10.1186/ar2336.
[109] N. Zhao, Y. Yi, W. Cao, X. Fu, N. Mei, C. Li, Serum cytokine levels for predicting immune-related adverse events and the clinical response in lung cancer treated with immunotherapy, Front. Oncol. 12 (2022) 923531, https://doi.org/10.3389/fonc.2022.923531.
[110] M. Liu, S. Guo, J.M. Hibbert, V. Jain, N. Singh, N.O. Wilson, J.K. Stiles, CXCL10/IP-10 in infectious diseases pathogenesis and potential therapeutic implications, Cytokine Growth Factor Rev. (2011) S1359610111000293, https://doi.org/10.1016/j.cytogfr.2011.06.001.
[111] Y. Miura, T. Motoshima, T. Anami, H. Yano, R. Mito, C. Pan, S. Urakami, K. Kinowaki, H. Tsukamoto, R. Kurahashi, Y. Murakami, J. Yatsuda, Y. Fujiwara, T. Kamba, Y. Komohara, Predictive value of CXCL10 for the occurrence of immune-related adverse events in patient with renal cell carcinoma, Microbiol. Immunol. 67 (2023) 345–354, https://doi.org/10.1111/1348-0421.13067.
[112] P. Sharma, S. Hu-Lieskovan, J.A. Wargo, A. Ribas, Primary, adaptive, and acquired resistance to cancer immunotherapy, Cell 168 (2017) 707–723, https://doi.org/10.1016/j.cell.2017.01.017.
[113] M. Binnewies, E.W. Roberts, K. Kersten, V. Chan, D.F. Fearon, M. Merad, L. M. Coussens, D.I. Gabrilovich, S. Ostrand-Rosenberg, C.C. Hedrick, R. H. Vonderheide, M.J. Pittet, R.K. Jain, W. Zou, T.K. Howcroft, E.C. Woodhouse, R. A. Weinberg, M.F. Krummel, Understanding the tumor immune microenvironment (TIME) for effective therapy, Nat. Med 24 (2018) 541–550, https://doi.org/10.1038/s41591-018-0014-x.
[114] M.H. Kazemi, A. Najafi, J. Karami, F. Ghazizadeh, H. Yousefi, R. Falak, E. Safari, Immune and metabolic checkpoints blockade: dual wielding against tumors, Int. Immunopharmacol. 94 (2021) 107461, https://doi.org/10.1016/j.intimp.2021.107461.
[115] The TRACERx consortium, R. Rosenthal, E.L. Cadieux, R. Salgado, M.A. Bakir, D. A. Moore, C.T. Hiley, T. Lund, M. Tanić, J.L. Reading, K. Joshi, J.Y. Henry, E. Ghorani, G.A. Wilson, N.J. Birkbak, M. Jamal-Hanjani, S. Veeriah, Z. Szallasi, S. Loi, M.D. Hellmann, A. Feber, B. Chain, J. Herrero, S.A. Quezada, J. Demeulemeester, P. Van Loo, S. Beck, N. McGranahan, C. Swanton, Neoantigen-directed immune escape in lung cancer evolution, Nature 567 (2019) 479–485, https://doi.org/10.1038/s41586-019-1032-7.
[116] V. Anagnostou, K.N. Smith, P.M. Forde, N. Niknafs, R. Bhattacharya, J. White, T. Zhang, V. Adleff, J. Phallen, N. Wali, C. Hruban, V.B. Guthrie, K. Rodgers, J. Naidoo, H. Kang, W. Sharfman, C. Georgiades, F. Verde, P. Illei, Q.K. Li, E. Gabrielson, M.V. Brock, C.A. Zahnow, S.B. Baylin, R.B. Scharpf, J.R. Brahmer, R. Karchin, D.M. Pardoll, V.E. Velculescu, Evolution of neoantigen landscape during immune checkpoint blockade in non–small cell lung cancer, Cancer Discov. 7 (2017) 264–276, https://doi.org/10.1158/2159-8290.CD-16-0828.
[117] M. Ruiz De Galarreta, E. Bresnahan, P. Molina-Sánchez, K.E. Lindblad, B. Maier, D. Sia, M. Puigvehi, V. Miguela, M. Casanova-Acebes, M. Dhainaut, C. Villacorta-Martin, A.D. Singhi, A. Moghe, J. Von Felden, L. Tal Grinspan, S. Wang, A. O. Kamphorst, S.P. Monga, B.D. Brown, A. Villanueva, J.M. Llovet, M. Merad, A. Lujambio, β-catenin activation promotes immune escape and resistance to anti–PD-1 therapy in hepatocellular carcinoma, Cancer Discov. 9 (2019) 1124–1141, https://doi.org/10.1158/2159-8290.CD-19-0074.
[118] E. Bonavita, C.P. Bromley, G. Jonsson, V.S. Pelly, S. Sahoo, K. Walwyn-Brown, S. Mensurado, A. Moeini, E. Flanagan, C.R. Bell, S.-C. Chiang, C.P. Chikkanna-Gowda, N. Rogers, B. Silva-Santos, S. Jaillon, A. Mantovani, C. Reis E Sousa, N. Guerra, D.M. Davis, S. Zelenay, Antagonistic inflammatory phenotypes dictate tumor fate and response to immune checkpoint blockade, Immunity 53 (2020) 1215–1229.e8, https://doi.org/10.1016/j.immuni.2020.10.020.
[119] J.H. Lee, E. Shklovskaya, S.Y. Lim, M.S. Carlino, A.M. Menzies, A. Stewart, B. Pedersen, M. Irvine, S. Alavi, J.Y.H. Yang, D. Strbenac, R.P.M. Saw, J. F. Thompson, J.S. Wilmott, R.A. Scolyer, G.V. Long, R.F. Kefford, H. Rizos, Transcriptional downregulation of MHC class I and melanoma de- differentiation in resistance to PD-1 inhibition, Nat. Commun. 11 (2020) 1897, https://doi.org/10.1038/s41467-020-15726-7.
[120] W. Peng, J.Q. Chen, C. Liu, S. Malu, C. Creasy, M.T. Tetzlaff, C. Xu, J.A. McKenzie, C. Zhang, X. Liang, L.J. Williams, W. Deng, G. Chen, R. Mbofung, A.J. Lazar, C. A. Torres-Cabala, Z.A. Cooper, P.-L. Chen, T.N. Tieu, S. Spranger, X. Yu, C. Bernatchez, M.-A. Forget, C. Haymaker, R. Amaria, J.L. McQuade, I.C. Glitza, T. Cascone, H.S. Li, L.N. Kwong, T.P. Heffernan, J. Hu, R.L. Bassett, M. W. Bosenberg, S.E. Woodman, W.W. Overwijk, G. Lizée, J. Roszik, T.F. Gajewski, J.A. Wargo, J.E. Gershenwald, L. Radvanyi, M.A. Davies, P. Hwu, Loss of PTEN promotes resistance to T cell–mediated immunotherapy, Cancer Discov. 6 (2016) 202–216, https://doi.org/10.1158/2159-8290.CD-15-0283.
[121] E. Sugiyama, Y. Togashi, Y. Takeuchi, S. Shinya, Y. Tada, K. Kataoka, K. Tane, E. Sato, G. Ishii, K. Goto, Y. Shintani, M. Okumura, M. Tsuboi, H. Nishikawa, Blockade of EGFR improves responsiveness to PD-1 blockade in *EGFR* -mutated non–small cell lung cancer, Sci. Immunol. 5 (2020) eaav3937, https://doi.org/10.1126/sciimmunol.aav3937.
[122] F. Skoulidis, M.E. Goldberg, D.M. Greenawalt, M.D. Hellmann, M.M. Awad, J. F. Gainor, A.B. Schrock, R.J. Hartmaier, S.E. Trabucco, L. Gay, S.M. Ali, J. A. Elvin, G. Singal, J.S. Ross, D. Fabrizio, P.M. Szabo, H. Chang, A. Sasson, S. Srinivasan, S. Kirov, J. Szustakowski, P. Vitazka, R. Edwards, J.A. Bufill, N. Sharma, S.-H.I. Ou, N. Peled, D.R. Spigel, H. Rizvi, E.J. Aguilar, B.W. Carter, J. Erasmus, D.F. Halpenny, A.J. Plodkowski, N.M. Long, M. Nishino, W. L. Denning, A. Galan-Cobo, H. Hamdi, T. Hirz, P. Tong, J. Wang, J. Rodriguez-Canales, P.A. Villalobos, E.R. Parra, N. Kalhor, L.M. Sholl, J.L. Sauter, A. A. Jungbluth, M. Mino-Kenudson, R. Azimi, Y.Y. Elamin, J. Zhang, G.C. Leonardi, F. Jiang, K.-K. Wong, J.J. Lee, V.A. Papadimitrakopoulou, I.I. Wistuba, V. A. Miller, G.M. Frampton, J.D. Wolchok, A.T. Shaw, P.A. Jänne, P.J. Stephens, C. M. Rudin, W.J. Geese, L.A. Albacker, J.V. Heymach, *STK11/LKB1* mutations and PD-1 inhibitor resistance in *KRAS* -mutant lung adenocarcinoma, Cancer Discov. 8 (2018) 822–835, https://doi.org/10.1158/2159-8290.CD-18-0099.
[123] G. Leuzzi, A. Vasciaveo, A. Taglialatela, X. Chen, T.M. Firestone, A.R. Hickman, W. Mao, T. Thakar, A. Vaitsiankova, J.-W. Huang, R. Cuella-Martin, S. B. Hayward, J.S. Kesner, A. Ghasemzadeh, T.S. Nambiar, P. Ho, A. Rialdi, M. Hebrard, Y. Li, J. Gao, S. Gopinath, O.A. Adeleke, B.J. Venters, C.G. Drake, R. Baer, B. Izar, E. Guccione, M.-C. Keogh, R. Guerois, L. Sun, C. Lu, A. Califano, A. Ciccia, SMARCAL1 is a dual regulator of innate immune signaling and PD-L1 expression that promotes tumor immune evasion, Cell 187 (2024) 861–881.e32, https://doi.org/10.1016/j.cell.2024.01.008.
[124] E.N. Arner, J.C. Rathmell, Metabolic programming and immune suppression in the tumor microenvironment, Cancer Cell 41 (2023) 421–433, https://doi.org/10.1016/j.ccell.2023.01.009.
[125] S. Kumagai, Y. Togashi, T. Kamada, E. Sugiyama, H. Nishinakamura, Y. Takeuchi, K. Vitaly, K. Itahashi, Y. Maeda, S. Matsui, T. Shibahara, Y. Yamashita, T. Irie, A. Tsuge, S. Fukuoka, A. Kawazoe, H. Udagawa, K. Kirita, K. Aokage, G. Ishii, T. Kuwata, K. Nakama, M. Kawazu, T. Ueno, N. Yamazaki, K. Goto, M. Tsuboi, H. Mano, T. Doi, K. Shitara, H. Nishikawa, The PD-1 expression balance between effector and regulatory T cells predicts the clinical efficacy of PD-1 blockade therapies, Nat. Immunol. 21 (2020) 1346–1358, https://doi.org/10.1038/s41590-020-0769-3.
[126] J. Chesney, K.D. Lewis, H. Kluger, O. Hamid, E. Whitman, S. Thomas, M. Wermke, M. Cusnir, E. Domingo-Musibay, G.Q. Phan, J.M. Kirkwood, J.C. Hassel, M. Orloff, J. Larkin, J. Weber, A.J.S. Furness, N.I. Khushalani, T. Medina, M. E. Egger, F. Graf Finckenstein, M. Jagasia, P. Hari, G. Sulur, W. Shi, X. Wu, A. Sarnaik, Efficacy and safety of lifileucel, a one-time autologous tumor-infiltrating lymphocyte (TIL) cell therapy, in patients with advanced melanoma after progression on immune checkpoint inhibitors and targeted therapies: pooled analysis of consecutive cohorts of the C-144-01 study, J. Immunother. Cancer 10 (2022) e005755, https://doi.org/10.1136/jitc-2022-005755.
[127] A.J. Schoenfeld, S.M. Lee, B. Doger De Spéville, S.N. Gettinger, S. Häfliger, A. Sukari, S. Papa, J.F. Rodríguez-Moreno, F. Graf Finckenstein, R. Fiaz, M. Catlett, G. Chen, R. Qi, E.L. Masteller, V. Gontcharova, K. He, Lifileucel, an autologous tumor-infiltrating lymphocyte monotherapy, in patients with advanced non–small cell lung cancer resistant to immune checkpoint inhibitors, Cancer Discov. 14 (2024) 1389–1402, https://doi.org/10.1158/2159-8290.CD-23-1334.
[128] S. Klein, C. Mauch, K. Brinker, K.-W. Noh, S. Knez, R. Büttner, A. Quaas, D. Helbig, Tumor infiltrating lymphocyte clusters are associated with response to immune checkpoint inhibition in BRAF V600E/K mutated malignant melanomas, Sci. Rep. 11 (2021) 1834, https://doi.org/10.1038/s41598-021-81330-4.

[129] Hirai, T. Funakoshi, H. Kamijuku, K. Fukuda, M. Mori, M. Sakurai, Y. Koda, J. Kato, T. Mori, N. Watanabe, S. Noji, T. Yaguchi, T. Iwata, S. Ohta, T. Fujita, R. Tanosaki, M. Handa, S. Okamoto, M. Amagai, Y. Kawakami, Adoptive cell therapy using tumor-infiltrating lymphocytes for melanoma refractory to immune-checkpoint inhibitors, Cancer Sci. 112 (2021) 3163–3172, https://doi.org/10.1111/cas.15009.
[130] X. Liang, H. Gao, J. Xiao, S. Han, J. He, R. Yuan, S. Yang, C. Yao, Abrine, an IDO1 inhibitor, suppresses the immune escape and enhances the immunotherapy of anti-PD-1 antibody in hepatocellular carcinoma, Front. Immunol. 14 (2023) 1185985, https://doi.org/10.3389/fimmu.2023.1185985.
[131] P. Pilanc, K. Wojnicki, A.-J. Roura, S. Cyranowski, A. Ellert-Miklaszewska, N. Ochocka, B. Gielniewski, M.M. Grzybowski, R. Błaszczyk, P.S. Stańczak, P. Dobrzański, B. Kaminska, A novel oral arginase 1/2 inhibitor enhances the antitumor effect of PD-1 inhibition in murine experimental gliomas by altering the immunosuppressive environment, Front. Oncol. 11 (2021) 703465, https://doi.org/10.3389/fonc.2021.703465.
[132] X. Wang, H. Xiang, Y. Toyoshima, W. Shen, S. Shichi, H. Nakamoto, S. Kimura, K. Sugiyama, S. Homma, Y. Miyagi, A. Taketomi, H. Kitamura, Arginase-1 inhibition reduces migration ability and metastatic colonization of colon cancer cells, Cancer Metab. 11 (1) (2023), https://doi.org/10.1186/s40170-022-00301-z.
[133] K. Mortezaee, J. Majidpoor, Checkpoint inhibitor/interleukin-based combination therapy of cancer, Cancer Med. 11 (2022) 2934–2943, https://doi.org/10.1002/cam4.4659.
[134] S.J. Im, K. Lee, S.-J. Ha, Harnessing IL-2 for immunotherapy against cancer and chronic infection: a historical perspective and emerging trends, Exp. Mol. Med. 56 (2024) 1900–1908, https://doi.org/10.1038/s12276-024-01301-3.
[135] S. Rokade, A.M. Damani, M. Oft, J. Emmerich, IL-2 based cancer immunotherapies: an evolving paradigm, Front. Immunol. 15 (2024) 1433989, https://doi.org/10.3389/fimmu.2024.1433989.
[136] M.C. Andrews, G. Li, R.P. Graf, V.A. Fisher, J. Mitchell, A. Aboosaiedi, H. O'Rourke, M. Shackleton, M. Iddawela, G.R. Oxnard, R.S.P. Huang, Predictive impact of tumor mutational burden on real-world outcomes of first-line immune checkpoint inhibition in metastatic melanoma, JCO Precis Oncol. (2024) e2300640, https://doi.org/10.1200/PO.23.00640.
[137] M. Palmeri, J. Mehnert, A.W. Silk, S.K. Jabbour, et al., Real-world application of tumor mutational burden-high (TMB-high) and microsatellite instability (MSI) confirms their utility as immunotherapy biomarkers, ESMO Open 7 (2022) 100336, https://doi.org/10.1016/j.esmoop.2021.100336.
[138] C. Aggarwal, R. Ben-Shachar, Y. Gao, S.W. Hyun, Z. Rivers, C. Epstein, K. Kaneva, C. Sangli, H. Nimeiri, J. Patel, Assessment of tumor mutational burden and outcomes in patients with diverse advanced cancers treated with immunotherapy, JAMA Netw. Open 6 (2023) e2311181, https://doi.org/10.1001/jamanetworkopen.2023.11181.
[139] A. Marabelle, M. Fakih, J. Lopez, M. Shah, et al., Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study, Lancet Oncol. 21 (2020) 1353–1365, https://doi.org/10.1016/S1470-2045(20)30445-9.
[140] T. Ratovomanana, R. Nicolle, R. Cohen, A. Diehl, A. Siret, Q. Letourneur, O. Buhard, A. Perrier, E. Guillerm, F. Coulet, P. Cervera, P. Benusiglio, K. Labrèche, R. Colle, A. Collura, E. Despras, P. Le Rouzic, F. Renaud, J. Cros, A. Alentorn, M. Touat, M. Ayadi, P. Bourgoin, C. Prunier, C. Tournigand, C.D. L. Fouchardière, D. Tougeron, V. Jonchère, J. Bennouna, A. De Reynies, J.-F. Fléjou, M. Svrcek, T. André, A. Duval, Prediction of response to immune checkpoint blockade in patients with metastatic colorectal cancer with microsatellite instability, Ann. Oncol. 34 (2023) 703–713, https://doi.org/10.1016/j.annonc.2023.05.010.
[141] P. De Marchi, L.F. Leal, L.S. Da Silva, R.D.O. Cavagna, F.A.F. Da Silva, V.D. Da Silva, E.C. Da Silva, A.O. Saito, V.C.C. De Lima, R.M. Reis, Gene expression profiles (GEPs) of immuno-oncologic pathways as predictors of response to checkpoint inhibitors in advanced NSCLC, Transl. Oncol. 39 (2024) 101818, https://doi.org/10.1016/j.tranon.2023.101818.
[142] P. De Marchi, L. Ferro Leal, L.S. Da Silva, R. De Oliveira Cavagna, F.A. Ferreira Da Silva, V.D. Da Silva, E.C. Da Silva, A.O. Saito, C. Aguado, J. Bracht, M. Gonzalez-Cao, A. Giménez-Capitán, C. Pedraz, D.D.S. Sá, M.A. Molina Vila, V.C. Cordeiro De Lima, R.M. Reis, LungTS: A new gene expression signature for prediction of response to checkpoint inhibitors in non-small cell lung cancer, JCO 40 (2022) e21143, https://doi.org/10.1200/JCO.2022.40.16_suppl.e21143.
[143] K. Tomela, B. Pietrzak, M. Schmidt, A. Mackiewicz, The tumor and host immune signature, and the gut microbiota as predictive biomarkers for immune checkpoint inhibitor response in melanoma patients, Life 10 (2020) 219, https://doi.org/10.3390/life10100219.
[144] F. Zhang, M. Ferrero, N. Dong, G. D'Auria, M. Reyes-Prieto, A. Herreros-Pomares, S. Calabuig-Fariñas, E. Duréndez, F. Aparisi, A. Blasco, C. García, C. Camps, E. Jantus-Lewintre, R. Sirera, Analysis of the gut microbiota: an emerging source of biomarkers for immune checkpoint blockade therapy in non-small cell lung cancer, Cancers 13 (2021) 2514, https://doi.org/10.3390/cancers13112514.
[145] B. Oh, F. Boyle, N. Pavlakis, S. Clarke, T. Eade, G. Hruby, G. Lamoury, S. Carroll, M. Morgia, A. Kneebone, M. Stevens, W. Liu, B. Corless, M. Molloy, B. Kong, T. Libermann, D. Rosenthal, M. Back, The gut microbiome and cancer immunotherapy: can we use the gut microbiome as a predictive biomarker for clinical response in cancer immunotherapy? Cancers 13 (2021) 4824, https://doi.org/10.3390/cancers13194824.
[146] Y. Lin, M. Xie, H.C.-H. Lau, R. Zeng, R. Zhang, L. Wang, Q. Li, Y. Wang, D. Chen, L. Jiang, W. Damsky, J. Yu, Effects of gut microbiota on immune checkpoint inhibitors in multi-cancer and as microbial biomarkers for predicting therapeutic response, Med 6 (2025) 100530, https://doi.org/10.1016/j.medj.2024.10.007.
[147] B. Routy, E. Le Chatelier, L. Derosa, C.P.M. Duong, M.T. Alou, R. Daillère, A. Fluckiger, M. Messaoudene, C. Rauber, M.P. Roberti, M. Fidelle, C. Flament, V. Poirier-Colame, P. Opolon, C. Klein, K. Iribarren, L. Mondragón, N. Jacquelot, B. Qu, G. Ferrere, C. Clémenson, L. Mezquita, J.R. Masip, C. Naltet, S. Brosseau, C. Kaderbhai, C. Richard, H. Rizvi, F. Levenez, N. Galleron, B. Quinquis, N. Pons, B. Ryffel, V. Minard-Colin, P. Gonin, J.-C. Soria, E. Deutsch, Y. Loriot, F. Ghiringhelli, G. Zalcman, F. Goldwasser, B. Escudier, M.D. Hellmann, A. Eggermont, D. Raoult, L. Albiges, G. Kroemer, L. Zitvogel, Gut microbiome influences efficacy of PD-1–based immunotherapy against epithelial tumors, Science 359 (2018) 91–97, https://doi.org/10.1126/science.aan3706.
[148] V. Shahabi, D. Berman, S.D. Chasalow, L. Wang, Z. Tsuchihashi, B. Hu, L. Panting, M. Jure-Kunkel, R.-R. Ji, Gene expression profiling of whole blood in ipilimumab-treated patients for identification of potential biomarkers of immune-related gastrointestinal adverse events, J. Transl. Med. 11 (2013) 75, https://doi.org/10.1186/1479-5876-11-75.
[149] Y. Wang, Z. Tong, W. Zhang, W. Zhang, A. Buzdin, X. Mu, Q. Yan, X. Zhao, H.-H. Chang, M. Duhon, X. Zhou, G. Zhao, H. Chen, X. Li, FDA-approved and emerging next generation predictive biomarkers for immune checkpoint inhibitors in cancer patients, Front. Oncol. 11 (2021) 683419, https://doi.org/10.3389/fonc.2021.683419.
[150] J.D. Twomey, B. Zhang, Cancer immunotherapy update: FDA-approved checkpoint inhibitors and companion diagnostics, AAPS J. 23 (2021) 39, https://doi.org/10.1208/s12248-021-00574-0.
[151] S. Egami, H. Kawazoe, H. Hashimoto, R. Uozumi, T. Arami, N. Sakiyama, Y. Ohe, H. Nakada, T. Aomori, S. Ikemura, K. Fukunaga, M. Yamaguchi, T. Nakamura, Peripheral blood biomarkers predict immune-related adverse events in non-small cell lung cancer patients treated with pembrolizumab: a multicenter retrospective study, J. Cancer 12 (2021) 2105–2112, https://doi.org/10.7150/jca.53242.
[152] A. Vasbinder, Y. Chen, A. Procureur, A. Gradone, T.U. Azam, D. Perry, H. Shadid, E. Anderson, T. Catalan, P. Blakely, N. Nelapudi, M. Fardous, M.C. Bretagne, S. K. Adie, K.T. Pogue, M. Leja, S. Yentz, B. Schneider, L.A. Fecher, C.D. Lao, J.-E. Salem, S.S. Hayek, Biomarker trends, incidence, and outcomes of immune checkpoint inhibitor–induced myocarditis, JACC: CardioOncol. 4 (2022) 689–700, https://doi.org/10.1016/j.jaccao.2022.11.004.
[153] X. Liu, W. Wu, L. Fang, Y. Liu, W. Chen, TNF-α inhibitors and other biologic agents for the treatment of immune checkpoint inhibitor-induced myocarditis, Front. Immunol. 13 (2022) 922782, https://doi.org/10.3389/fimmu.2022.922782.
[154] S.A. Muley, B. Jacobsen, G. Parry, U. Usman, E. Ortega, D. Walk, J. Allen, M. Pasnoor, M. Varon, M.M. Dimachkie, Rituximab in refractory chronic inflammatory demyelinating polyneuropathy, Muscle Nerve 61 (2020) 575–579, https://doi.org/10.1002/mus.26804.
[155] E. Chauvet, G. Blanchard Rohner, V. Manel, E. Delmont, J. Boucraut, S. Garcia-Tarodo, Autoantibodies to a nodal isoform of neurofascin in pediatric chronic inflammatory demyelinating polyneuropathy, Child Neurol. Open 10 (2023) 2329048X221149618, https://doi.org/10.1177/2329048X221149618.
[156] J.S. Lin, D.Y. Wang, O. Mamlouk, W.F. Glass, M. Abdelrahim, C. Yee, A. Abudayyeh, Immune checkpoint inhibitor associated reactivation of primary membranous nephropathy responsive to rituximab, J. Immunother. Cancer 8 (2020) e001287, https://doi.org/10.1136/jitc-2020-001287.
[157] C.R. Stroud, A. Hegde, C. Cherry, A.R. Naqash, N. Sharma, S. Addepalli, S. Cherukuri, T. Parent, J. Hardin, P. Walker, Tocilizumab for the management of immune mediated adverse events secondary to PD-1 blockade, J. Oncol. Pharm. Pr. 25 (2019) 551–557, https://doi.org/10.1177/1078155217745144.
[158] L. Moi, H. Bouchaab, N. Mederos, T. Nguyen-Ngoc, M. Perreau, C. Fenwick, J. Vaucher, C. Sempoux, S. Peters, M. Obeid, Personalized cytokine-directed therapy with tocilizumab for refractory immune checkpoint inhibitor–related cholangiohepatitis, J. Thorac. Oncol. 16 (2021) 318–326, https://doi.org/10.1016/j.jtho.2020.09.007.
[159] A.S. Laino, D. Woods, M. Vassallo, X. Qian, H. Tang, M. Wind-Rotolo, J. Weber, Serum interleukin-6 and C-reactive protein are associated with survival in melanoma patients receiving immune checkpoint inhibition, J. Immunother. Cancer 8 (2020) e000842, https://doi.org/10.1136/jitc-2020-000842.
[160] Y. Li, X. Liang, H. Li, X. Chen, Atezolizumab plus bevacizumab versus nivolumab as first-line treatment for advanced or unresectable hepatocellular carcinoma: a cost-effectiveness analysis, Cancer 128 (2022) 3995–4003, https://doi.org/10.1002/cncr.34457.
[161] Y. Li, X. Liang, H. Li, T. Yang, S. Guo, X. Chen, Nivolumab versus sorafenib as first-line therapy for advanced hepatocellular carcinoma: a cost-effectiveness analysis, Front. Pharm. 13 (2022) 906956, https://doi.org/10.3389/fphar.2022.906956.
[162] K. Liu, Y. Zhu, H. Zhu, Immunotherapy or targeted therapy as the first-line strategies for unresectable hepatocellular carcinoma: a network meta-analysis and cost-effectiveness analysis, Front. Immunol. 13 (2023) 1103055, https://doi.org/10.3389/fimmu.2022.1103055.
[163] T. Zhou, Y. Cao, X. Wang, L. Yang, Z. Wang, A. Ma, H. Li, Economic evaluation of sintilimab plus bevacizumab versus sorafenib as a first-line treatment for unresectable hepatocellular carcinoma, Adv. Ther. 39 (2022) 2165–2177, https://doi.org/10.1007/s12325-022-02079-4.
[164] L.-Y. Yang, J.-R. Li, C.-S. Chen, C.-L. Cheng, S.-C. Hung, K.-Y. Chiu, C.-K. Yang, C.-Y. Hsu, S.-S. Wang, Cost-effectiveness of immune checkpoint inhibitors in treating metastatic urothelial cancer, Front. Pharm. 15 (2024) 1281654, https://doi.org/10.3389/fphar.2024.1281654.

[165] A.S. Walia, R.F. Sweis, P.K. Agarwal, A.K. Kader, P.K. Modi, Cost-effectiveness of immune checkpoint inhibitors in urothelial carcinoma—a review, Cancers 14 (2021) 73, https://doi.org/10.3390/cancers14010073.
[166] Z.S. Dawood, Z.J. Brown, Y. Endo, E.S. Katayama, M.M. Munir, L. Alaimo, S. M. Ruff, H.A. Lima, S. Woldesenbet, T.M. Pawlik, Cost effectiveness of immune checkpoint inhibitors for treatment of Hepatocellular Carcinoma: a systematic review and Meta-analysis, Surg. Oncol. 51 (2023) 102013, https://doi.org/10.1016/j.suronc.2023.102013.
[167] C.G. Kohn, S.B. Zeichner, Q. Chen, A.J. Montero, D.A. Goldstein, C.R. Flowers, Cost-effectiveness of immune checkpoint inhibition in *BRAF* wild-type advanced melanoma, JCO 35 (2017) 1194–1202, https://doi.org/10.1200/JCO.2016.69.6336.
[168] G. Wu, Therapeutic effects of pembrolizumab combined with paclitaxel and cisplatin chemotherapy on advanced non-squamous non-small cell lung cancer and influencing factors, Ijps 83 (2021), https://doi.org/10.36468/pharmaceutical-sciences.757.
[169] C. Rolfo, C. Caglevic, M. Santarpia, A. Araujo, E. Giovannetti, C.D. Gallardo, P. Pauwels, M. Mahave, Immunotherapy in NSCLC: A Promising and Revolutionary Weapon, in: A. Naing, J. Hajjar (Eds.), Immunotherapy, Springer International Publishing, Cham, 2017, pp. 97–125, https://doi.org/10.1007/978-3-319-53156-4_5.
[170] M.R. Migden, N.I. Khushalani, A.L.S. Chang, K.D. Lewis, C.D. Schmults, L. Hernandez-Aya, F. Meier, D. Schadendorf, A. Guminski, A. Hauschild, D. J. Wong, G.A. Daniels, C. Berking, V. Jankovic, E. Stankevich, J. Booth, S. Li, D. M. Weinreich, G.D. Yancopoulos, I. Lowy, M.G. Fury, D. Rischin, Cemiplimab in locally advanced cutaneous squamous cell carcinoma: results from an open-label, phase 2, single-arm trial, Lancet Oncol. 21 (2020) 294–305, https://doi.org/10.1016/S1470-2045(19)30728-4.
[171] J.-X. Li, J.-M. Huang, Z.-B. Jiang, R.-Z. Li, A. Sun, E. Lai-Han Leung, P.-Y. Yan, Current clinical progress of PD-1/PD-L1 immunotherapy and potential combination treatment in non–small cell lung cancer, Integr. Cancer Ther. 18 (2019) 1534735419890020, https://doi.org/10.1177/1534735419890020.
[172] M. Shirley, Avelumab: a review in metastatic merkel cell carcinoma, Targ. Oncol. 13 (2018) 409–416, https://doi.org/10.1007/s11523-018-0571-4.
[173] L. Paz-Ares, A. Spira, D. Raben, D. Planchard, B.C. Cho, M. Özgüroğlu, D. Daniel, A. Villegas, D. Vicente, R. Hui, S. Murakami, D. Spigel, S. Senan, C.J. Langer, B. A. Perez, A.-M. Boothman, H. Broadhurst, C. Wadsworth, P.A. Dennis, S. J. Antonia, C. Faivre-Finn, Outcomes with durvalumab by tumour PD-L1 expression in unresectable, stage III non-small-cell lung cancer in the PACIFIC trial, Ann. Oncol. 31 (2020) 798–806, https://doi.org/10.1016/j.annonc.2020.03.287.
[174] M. Mansh, Ipilimumab and cancer immunotherapy: a new hope for advanced stage melanoma, Yale J. Biol. Med. 84 (2011) 381–389.
[175] C. Monge, C. Xie, Y. Myojin, K.L. Coffman-D'Annibale, D. Hrones, G. Brar, S. Wang, A. Budhu, W.D. Figg, M. Cam, R. Finney, E.B. Levy, D.E. Kleiner, S. M. Steinberg, X.W. Wang, B. Redd, B.J. Wood, T.F. Greten, Combined immune checkpoint inhibition with durvalumab and tremelimumab with and without radiofrequency ablation in patients with advanced biliary tract carcinoma, Cancer Med. 13 (2024) e6912, https://doi.org/10.1002/cam4.6912.
[176] J. Su, Y. Fu, Z. Cui, Z. Abidin, J. Yuan, X. Zhang, R. Li, C. Zhao, Relatlimab: a novel drug targeting immune checkpoint LAG-3 in melanoma therapy, Front. Pharm. 14 (2024) 1349081, https://doi.org/10.3389/fphar.2023.1349081.
[177] A.L. Gomes De Morais, S. Cerdá, M. De Miguel, New checkpoint inhibitors on the road: targeting TIM-3 in solid tumors, Curr. Oncol. Rep. 24 (2022) 651–658, https://doi.org/10.1007/s11912-022-01218-y.
[178] R. Bai, N. Chen, X. Chen, L. Li, W. Song, W. Li, Y. Zhao, Y. Zhang, F. Han, Z. Lyu, J. Cui, Analysis of characteristics and predictive factors of immune checkpoint inhibitor-related adverse events, Cancer Biol. Med. 18 (2021) 1118–1133, https://doi.org/10.20892/j.issn.2095-3941.2021.0052.
[179] A. Ribas, R. Kefford, M.A. Marshall, C.J.A. Punt, J.B. Haanen, M. Marmol, C. Garbe, H. Gogas, J. Schachter, G. Linette, P. Lorigan, K.L. Kendra, M. Maio, U. Trefzer, M. Smylie, G.A. McArthur, B. Dreno, P.D. Nathan, J. Mackiewicz, J. M. Kirkwood, J. Gomez-Navarro, B. Huang, D. Pavlov, A. Hauschild, Phase III randomized clinical trial comparing tremelimumab with standard-of-care chemotherapy in patients with advanced melanoma, JCO 31 (2013) 616–622, https://doi.org/10.1200/JCO.2012.44.6112.
[180] D. Schadendorf, J.D. Wolchok, F.S. Hodi, V. Chiarion-Sileni, R. Gonzalez, P. Rutkowski, J.-J. Grob, C.L. Cowey, C.D. Lao, J. Chesney, C. Robert, K. Grossmann, D. McDermott, D. Walker, R. Bhore, J. Larkin, M.A. Postow, Efficacy and safety outcomes in patients with advanced melanoma who discontinued treatment with nivolumab and ipilimumab because of adverse events: a pooled analysis of randomized phase II and III trials, JCO 35 (2017) 3807–3814, https://doi.org/10.1200/JCO.2017.73.2289.
[181] K. Haratani, H. Hayashi, Y. Chiba, K. Kudo, K. Yonesaka, R. Kato, H. Kaneda, Y. Hasegawa, K. Tanaka, M. Takeda, K. Nakagawa, Association of immune-related adverse events with nivolumab efficacy in non–small-cell lung cancer, JAMA Oncol. 4 (2018) 374, https://doi.org/10.1001/jamaoncol.2017.2925.
[182] H.T. Quach, A.K. Dewan, E.J. Davis, K.K. Ancell, R. Fan, F. Ye, D.B. Johnson, Association of anti–programmed cell death 1 cutaneous toxic effects with outcomes in patients with advanced melanoma, JAMA Oncol. 5 (2019) 906, https://doi.org/10.1001/jamaoncol.2019.0046.
[183] C.J. Gomes-Lima, J. Kwagyan, F. King, S.J. Fernandez, K.D. Burman, I. Veytsman, A comprehensive meta-analysis of endocrine immune-related adverse events of immune checkpoint inhibitors and outcomes in head and neck cancer and lung cancer, JCO 37 (2019) e14096, https://doi.org/10.1200/JCO.2019.37.15_suppl.e14096.
[184] L.M. Serna-Higuita, T. Amaral, A. Forschner, U. Leiter, L. Flatz, O. Seeber, I. Thomas, C. Garbe, T.K. Eigentler, P. Martus, Association between immune-related adverse events and survival in 319 stage IV melanoma patients treated with PD-1-based immunotherapy: an approach based on clinical chemistry, Cancers 13 (2021) 6141, https://doi.org/10.3390/cancers13236141.
[185] M.L. Bastacky, H. Wang, D. Fortman, Z. Rahman, G.P. Mascara, T. Brenner, Y. G. Najjar, J.J. Luke, J.M. Kirkwood, H.M. Zarour, D. Davar, Immune-related adverse events in PD-1 treated melanoma and impact upon anti-tumor efficacy: a real world analysis, Front. Oncol. 11 (2021) 749064, https://doi.org/10.3389/fonc.2021.749064.
[186] M.R. Migden, D. Rischin, C.D. Schmults, A. Guminski, et al., PD-1 blockade with cemiplimab in advanced cutaneous squamous-cell carcinoma, N. Engl. J. Med. 379 (2018) 341–351, https://doi.org/10.1056/NEJMoa1805131.
[187] M. Riudavets, A. Barba, P. Maroto, I.G. Sullivan, G. Anguera, D. Páez, L. Del Carpio, A. Callejo, C. Gonzalez Blanco, E. Garcia Planellas, D. Castillo, C. Facundo, I. Genua, C. Martin Lorente, A. Virgili, A. Sebio, O. Gallego, A. Lopez-Pousa, A. Barnadas, M. Majem, Correlation between immune-related adverse events (irAEs) and efficacy in patients with solid tumors treated with immune-checkpoints inhibitors (ICIs), JCO 36 (2018) 3064, https://doi.org/10.1200/JCO.2018.36.15_suppl.3064.
[188] C.C. Foster, M.A. Couey, S.E. Kochanny, A. Khattri, et al., Immune-related adverse events are associated with improved response, progression-free survival, and overall survival for patients with head and neck cancer receiving immune checkpoint inhibitors, Cancer 127 (2021) 4565–4573, https://doi.org/10.1002/cncr.33780.
[189] R. Morales-Barrera, C. Suarez Rodriguez, M. Gonzalez, J. Ros, M.E. Semidey, E. Serra Hernandez, J. Mateo, C. Fernández Sáez, F. Lozano, R. Mast, S. Roche, A. Quintana, S. Gutiérrez Fernández, C. Serrano, C. Valverde, I. De Torres, X. Maldonado, J. Morote, J. Carles, Impact of immune-related adverse events on survival in patients with metastastic urothelial carcinoma treated with immune-checkpoint inhibitors, JCO 37 (2019) 4531, https://doi.org/10.1200/JCO.2019.37.15_suppl.4531.
[190] R. Elias, F. Yan, N. Singla, N. Levonyack, J. Formella, A. Christie, P. Kapur, A. I. Bowman, H.J. Hammers, R. Hannan, J. Brugarolas, Immune-related adverse events are associated with improved outcomes in ICI-treated renal cell carcinoma patients, JCO 37 (2019) 645, https://doi.org/10.1200/JCO.2019.37.7_suppl.645.
[191] S. Das, K.K. Ciombor, S. Haraldsdottir, Y.S. Pumpalova, I.H. Sahin, Y. Shyr, S.-K. Chu, E.P.-Y. Lin, C.-Y. Hsu, L.W. Goff, D.B. Cardin, M.A. Bilen, J. Berlin, C. Wu, Immune checkpoint inhibitors (ICIs) in gastrointestinal (GI) cancer: Immune-related adverse events (IRAEs) and efficacy, JCO 37 (2019) 4116, https://doi.org/10.1200/JCO.2019.37.15_suppl.4116.
[192] E. Verzoni, G. Cartenì, E. Cortesi, D. Giannarelli, A. De Giglio, R. Sabbatini, S. Buti, S. Rossetti, F. Cognetti, F. Rastelli, A. Sobrero, D. Turci, C.N. Sternberg, C. Porta, F. Cappuzzo, G. Tortora, D. Tassinari, S. Panni, A. Pazzola, G. Surico, A. Raimondi, U. De Giorgi, G. Procopio, Real-world efficacy and safety of nivolumab in previously-treated metastatic renal cell carcinoma, and association between immune-related adverse events and survival: the Italian expanded access program, J. Immunother. Cancer 7 (2019) 99, https://doi.org/10.1186/s40425-019-0579-z.
[193] A. Indini, L. Di Guardo, C. Cimminiello, M. Prisciandaro, G. Randon, F. De Braud, M. Del Vecchio, Immune-related adverse events correlate with improved survival in patients undergoing anti-PD1 immunotherapy for metastatic melanoma, J. Cancer Res Clin. Oncol. 145 (2019) 511–521, https://doi.org/10.1007/s00432-018-2819-x.
[194] M. Grangeon, P. Tomasini, S. Chaleat, A. Jeanson, M. Souquet-Bressand, N. Khobta, J. Bermudez, Y. Trigui, L. Greillier, M. Blanchon, M. Boucekine, C. Mascaux, F. Barlesi, Association between immune-related adverse events and efficacy of immune checkpoint inhibitors in non–small-cell lung cancer, Clin. Lung Cancer 20 (2019) 201–207, https://doi.org/10.1016/j.cllc.2018.10.002.
[195] B. Ricciuti, C. Genova, A. De Giglio, M. Bassanelli, M.G. Dal Bello, G. Metro, M. Brambilla, S. Baglivo, F. Grossi, R. Chiari, Impact of immune-related adverse events on survival in patients with advanced non-small cell lung cancer treated with nivolumab: long-term outcomes from a multi-institutional analysis, J. Cancer Res. Clin. Oncol. 145 (2019) 479–485, https://doi.org/10.1007/s00432-018-2805-3.