



## Review

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# Immune checkpoint blockade for cancer therapy: current progress and perspectives

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**Abstract:** Dysfunction of anti-tumor immune responses is crucial for cancer progression. Immune checkpoint blockade (ICB), which can potentiate T cell responses, is an effective strategy for the normalization of host anti-tumor immunity. In recent years, immune checkpoints, expressed on both tumor cells and immune cells, have been identified; some of them have exhibited potential druggability and have been approved by the US Food and Drug Administration (FDA) for clinical treatment. However, limited responses and immune-related adverse events (irAEs) cannot be ignored. This review outlines the development and applications of ICBs, potential strategies for overcoming resistance, and future directions for ICB-based cancer immunotherapy.

**Key words:** Immune checkpoint blockade; Cancer immunotherapy; Tumor immune evasion; Immune normalization

## 1 Introduction

Over the past century, cancer treatments have evolved from surgery, radiotherapy, and chemotherapy to the exciting realm of immunotherapy. Novel treatments keep pace with a deeper understanding of the immune response against tumors. At present, the main approaches to cancer immunotherapies include general immune stimulation, vaccination, immune checkpoint blockade (ICB), and adoptive T cell transfer (Li et al., 2019). The conventional strategies of cancer immunotherapy include harnessing immune effector cells and molecules to kill tumor cells directly or modulating intrinsic immune mechanisms to attack tumor cells indirectly (Sanmamed and Chen, 2018). However, “immune enhancement” strategies usually lead to non-negligible immune-related adverse events (irAEs). Nowadays, there is a shift toward normalization strategies, aiming to restore particular dysfunctional immune

responses that tumor cells employ for immune evasion (Dunn et al., 2002; Sanmamed and Chen, 2018).

Immune checkpoints are a collection of multiple inhibitory pathways balanced with co-stimulatory receptor activity to restrain T cell activation (Pardoll, 2012; Andrews et al., 2017). Continuous exposure to tumor antigens during cancer results in the rewriting of immune checkpoints on antigen-specific T cells, causing effector T cell unresponsiveness or exhaustion (Virgin et al., 2009; Zarour, 2016), a predominant mechanism mediating tumor immune escape. ICBs block immune checkpoints and function to reverse immune tolerance, which fulfills the normal anti-tumor immune responses of T cells. Additionally, antigen-presenting cells (APCs) of the myeloid lineage and myeloid cells in the tumor microenvironment (TME) also play an important role in modulating immune responses to cancer. Thus, the immune checkpoints of myeloid cells have also been developed (Park and Kim, 2019).

This review provides insights into the basic mechanisms of ICBs and recent clinical trials targeting immune checkpoints on T cells and myeloid cells. Additionally, it explores the mechanisms and strategies for overcoming immunotherapy resistance, offering perspectives for future immunotherapy developments.

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## 2 Blockade of T cell-based immune checkpoints

### 2.1 Cytotoxic T lymphocyte antigen-4

T cell activation requires a major histocompatibility complex (MHC)/antigen-T cell receptor (TCR) signal alongside a co-stimulatory signal (Chen and Flies, 2013). Cluster of differentiation 28 (CD28) is constitutively expressed on the cell surface of naive T cells, and provides a co-stimulatory signal for T cell activation upon ligation by B7-1 (CD80) or B7-2 (CD86) on APCs (Sansom, 2000). Cytotoxic T lymphocyte antigen-4 (CTLA-4), also known as CD152, is a global checkpoint molecule induced following T cell activation (Rudd et al., 2009). As a homologous protein of CD28, CTLA-4 competes with CD28 on T cells for binding to the same ligands with a much higher binding affinity, thereby blocking the T cell response (Rudd et al., 2009). Thus, CTLA-4 critically contributes to the dysfunction of T cell activation. In the TME, CTLA-4 mainly leads to the repression of CD4<sup>+</sup> T cell priming and the induction of regulatory T cell (Treg) activity (Linsley et al., 1996; Topalian et al., 2016).

A fully-humanized CTLA-4 immunoglobulin G1 (IgG1) monoclonal antibody (mAb), ipilimumab (Yervoy), was the first T cell-targeting antibody approved by the US Food and Drug Administration (FDA) in 2011 for patients with advanced melanoma to enhance anti-tumor immune response (Ribas and Wolchok, 2018). In addition to melanoma, the FDA also approved ipilimumab to treat advanced renal cell carcinoma (RCC) and microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) metastatic colorectal cancer (CRC) combined with nivolumab (anti-programmed cell death 1 (anti-PD-1)) (Rotte, 2019). There are approximately 834 clinical trials of ipilimumab in patients with lung cancer, gastrointestinal cancer, prostate cancer, and many other cancer types. It has been shown that ipilimumab can mediate objective tumor regression in nearly 15% of patients with metastatic melanoma and significantly improve median overall survival (OS) (Attia et al., 2005; Downey et al., 2007; Hodi et al., 2010). Meanwhile, in small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), the usage of ipilimumab is associated with improved OS and progression-free survival (PFS) compared with non-ipilimumab therapies (Xu et al., 2022).

However, ipilimumab treatment poses challenges due to the frequency of irAEs, which is correlated with

dosage (Wolchok et al., 2010). Therefore, ipilimumab is limited at the FDA-approved dose of 3 mg/kg to treat patients with melanoma. With the treatment of ipilimumab, irAEs occurred in nearly 60% of patients with unresectable stage III or IV melanoma. Although a large proportion of irAEs can be relieved by steroid administration (Weber et al., 2012), identifying predictive biomarkers, such as TME genes, tumor mutation burden (TMB), gastrointestinal irAEs, and CD39<sup>+</sup> tumor-resident cytotoxic T cells, is crucial for determining the potential benefit for patients and guiding personalized ipilimumab therapies (Abu-Sbeih et al., 2019; Krijgsman et al., 2021; Attrill et al., 2022).

### 2.2 Programmed cell death 1

PD-1, or CD279, discovered by Tasuku HONJO in 1992, is initially associated with apoptosis (Ishida et al., 1992). PD-1 engagement with its ligands, programmed death-ligand 1 (PD-L1, also known as CD274, B7H1) and PD-L2 (also known as B7-DC, CD273), transmits the co-inhibitory signals into the cell to constrain proliferation and cytokine production (Keir et al., 2008). In various human carcinomas, including lung cancer, ovarian cancer, CRC, and melanoma, PD-L1 and PD-L2 are broadly expressed on the surface of B cells, dendritic cells (DCs), macrophages, bone marrow-derived mast cells, and T cells (Dong et al., 2002; Francisco et al., 2010). Targeting PD-1 and/or PD-L1 is a promising option for tumor treatment. On average, 25% of patients with solid tumors and 40%–60% of patients with lymphomas earned benefits from anti-PD-1/PD-L1 therapy (Kim et al., 2022). Until now, the FDA has approved seven antibodies targeting PD-1/PD-L1, and we have counted the number of clinical trials on these approved immune checkpoint inhibitors (ICIs) (Table 1).

The objective response rate (ORR) diverges across types of cancer, with an ORR of 40.0% to nivolumab in previously untreated advanced melanoma (Robert et al., 2015) and 11.6% in recurrent SCLC (Ready et al., 2020). Given the unstable efficacy between patients, high costs, and severe irAEs, it is important to distinguish responders from non-responders by utilizing new biomarkers. High tumor mutational burden, MSI, and tumor PD-L1 expression were approved for diagnostic tests in clinical trials (Le et al., 2015; Reck et al., 2016; Yarchoan et al., 2017; Li et al.,

**Table 1** Number of clinical trials on commonly used immune checkpoint inhibitors

Target	Drug	Cancer type	Number of clinical trials				
			Phase I	Phase II	Phase III	Phase IV	
CTLA-4	Ipilimumab	Non-small cell lung cancer	35	53	16	1	
		Small cell lung cancer	10	14	2	0	
		Hepatocellular carcinoma	10	14	4	0	
		Melanoma	118	176	22	2	
		Breast cancer	16	20	1	0	
		Leukemia	17	6	0	0	
		Colorectal cancer	17	21	4	0	
		Prostate cancer	17	28	3	0	
		Gastric cancer	6	12	3	0	
	Tremelimumab	Non-small cell lung cancer	10	16	4	0	
		Small cell lung cancer	5	2	3	0	
		Hepatocellular carcinoma	4	14	2	0	
		Melanoma	10	8	1	0	
		Breast cancer	9	10	0	0	
		Colorectal cancer	8	10	0	0	
		Prostate cancer	5	7	0	0	
		Gastric cancer	3	4	0	0	
		Advanced solid cancer	2	2	0	0	
PD-1	Pembrolizumab	Non-small cell lung cancer	174	216	51	3	
		Small cell lung cancer	26	27	3	0	
		Melanoma	143	163	14	1	
		Gastric cancer	50	64	10	0	
		Esophageal cancer	33	46	10	0	
		Liver cancer	23	45	7	0	
		Breast cancer	95	122	9	0	
		Renal cell carcinoma	65	54	11	0	
		Squamous cell carcinoma of head and neck	86	133	12	1	
		Colorectal cancer	71	70	6	0	
		Cervical cancer	50	72	12	0	
		Merkel cell carcinoma	16	12	3	0	
		Lymphoma	68	79	1	0	
		Nivolumab	Non-small cell lung cancer	106	151	29	3
			Squamous cell carcinoma of head and neck	41	64	8	0
			Gastric cancer	25	31	9	0
			Esophageal cancer	16	29	6	0
			Small cell lung cancer	18	27	2	0
	Melanoma		116	163	24	2	
	Colorectal cancer		47	64	5	0	
	Liver cancer		36	52	7	1	
	Renal cell carcinoma		61	86	14	4	
	Lymphoma	63	75	5	0		

To be continued

Table 1 (continued)

Target	Drug	Cancer type	Number of clinical trials			
			Phase I	Phase II	Phase III	Phase IV
PD-1	Durvalumab	Non-small cell lung cancer	39	104	28	4
		Small cell lung cancer	9	27	7	0
		Urothelial cell carcinoma	5	11	1	1
	Cemiplimab	Non-small cell lung cancer	4	7	4	0
		Cutaneous squamous cell carcinoma	2	3	0	0
	Camrelizumab	Non-small cell lung cancer	2	17	5	0
		Liver cancer	7	26	9	0
	Sintilimab	Non-small cell lung cancer	9	32	7	0
	Tislelizumab	Non-small cell lung cancer	5	15	9	0
	PD-L1	Atezolizumab	Non-small cell lung cancer	40	92	25
Small cell lung cancer			14	31	8	0
Breast cancer			38	55	16	0
Urothelial cell carcinoma			11	22	2	0
Liver cancer			13	30	8	1
Avelumab		Urothelial cell carcinoma	6	9	0	0
		Renal cell carcinoma	9	11	4	0
		Merkel cell carcinoma	9	13	1	0

CTLA-4: T lymphocyte antigen-4; PD-1: programmed cell death 1; PD-L1: programmed death-ligand 1.

2022). Furthermore, inflammatory TME signatures, human leukocyte antigen (HLA) heterozygosity, and mutations are potential biomarkers for predicting responders, as supported by cumulative evidence (Chowell et al., 2018; Higgs et al., 2018). Additionally, intratumoral plasma cells can predict the OS of NSCLC patients treated with atezolizumab (Patil et al., 2022). High levels of CD8<sup>+</sup> tumor-infiltrating cells expressing PD-1 but not T cell immunoglobulin and mucin domain containing-3 (TIM-3) or lymphocyte-activation gene 3 (LAG-3) correlate with a better response to nivolumab than to everolimus (an mammalian target of rapamycin (mTOR) inhibitor) in patients with metastatic clear cell RCC (mccRCC) (Ficial et al., 2021). Moreover, <sup>89</sup>Zr-pembrolizumab positron emission tomography (PET) imaging can serve as a non-invasive approach with which to assess the clinical response to PD-1 blockade (Kok et al., 2022).

Restricted by the low response rate, anti-PD-1/PD-L1 therapy turns to combination strategies. One study integrating 4897 active trials for anti-PD-1/PD-L1 therapy revealed that 4062 (83%) trials combined chemotherapies, radiotherapies, targeted therapies, and immuno-oncology (I-O) therapies. Among them, vascular endothelial growth factor (VEGF)/VEGF receptor (VEGFR)-targeted therapy, chemotherapy, and CTLA-4

antibodies are the most prominent combination strategies (Upadhaya et al., 2022). In particular, nivolumab plus ipilimumab (anti-CTLA-4) is approved by the FDA for the treatment of melanoma, NSCLC, RCC, hepatocellular carcinoma (HCC), and CRC. This combination showed ameliorated PFS and median OS compared to monotherapy (Wolchok et al., 2022), although accompanied by a higher rate of irAEs (Geraud et al., 2021). Tumor-associated high endothelial venules (TA-HEVs) can be used to predict the response to and survival of patients treated with PD-1 and CTLA-4 blockades (Asrir et al., 2022). Additionally, in a phase II clinical trial, ramucirumab (an mAb that targets VEGFR2) plus pembrolizumab resulted in a longer OS than standard-of-care (SOC) in advanced NSCLC (Reckamp et al., 2022). Recently, a study has proven that the combination of CXCR4-targeted p53 messenger RNA (mRNA) nanoparticles and PD-1 blockade can suppress cancer cell growth by increasing the number of immune cells such as activated CD8<sup>+</sup> T cells and mature natural killer (NK) cells, and by increasing the levels of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-2 (IL-2), and IL-1 $\beta$  in HCC (Xiao et al., 2022). However, some positive preclinical results fail to be replicated in the clinic and in combination therapy with an increased risk of irAEs. Thus,

understanding tumor-induced adaptive immune resistance (AIR) and irAEs is crucial for guiding future immunotherapy. Therefore, we include Table 2 to show the incidence of some common all-grade potential irAEs in advanced melanoma patients after the use of some specific ICIs.

### 2.3 B7 homolog 3

B7 homolog 3 (B7-H3) (also known as CD276), a member of the B7-CD28 pathway family (Chapoval et al., 2001), is widely expressed on non-hematopoietic cells, including cancer cells (Lines et al., 2014b), and can be induced on some immune cells (Lines et al., 2014a). B7-H3 is overexpressed in many types of cancer, and is involved in proliferation, migration, and invasion during cancer development. Notably, the soluble form of B7-H3 is an effective biomarker for poor prognosis in patients with NSCLC, and is even better than traditional biomarkers such as carcinoembryonic antigen (CEA) (Lines et al., 2014b).

There are more than 20 clinical trials of B7-H3-targeting mAb-based immune checkpoint therapies. Different immunotherapeutic strategies have been used to target B7-H3. The first is B7-H3-targeting radioimmunotherapy; 8H9 (omburtamab), an mAb specific to B7-H3, is radiolabeled with iodine-131 (<sup>131</sup>I) for patients with neuroblastoma, peritoneal cancer, advanced central nervous system tumor, or leptomeningeal cancer in clinical trials (Janakiram et al., 2017). It is well-tolerated without dose-limiting toxicity (DLT) and has

low radiation exposure to normal organs in patients with B7-H3-expressing tumors (Modak et al., 2020). Another B7-H3-targeting strategy involves the novel Fc-enhanced mAbs, such as enoblituzumab (MGA271), an IgG1 mAb against B7-H3 with potent anti-tumor activity through antibody-dependent cell-mediated cytotoxicity (ADCC) (Janakiram et al., 2017). Enoblituzumab has been investigated in prostate cancer, NSCLC, melanoma, and other refractory cancers, and has produced results with good tolerance (Picarda et al., 2016). However, its combination with pembrolizumab (anti-PD-1) has shown potential in the treatment of metastatic NSCLC and recurrent/metastatic head and neck squamous cell carcinoma (HNSCC) along with irAEs, including infusion-related reactions (IRRs) and fatigue (Aggarwal et al., 2022). Other categories include: antibody–drug conjugates (ADCs), trials on MGC018; CD3-engaging bispecific antibodies (BsAbs), obridatamab (MGD009); and tri-specific killer engagers (TriKEs). All of them are ongoing to assess their efficacy (Kontos et al., 2021). The irAEs of these strategies still need further studies.

### 2.4 B7 homolog 4

B7 homolog 4 (B7-H4), another member of the B7 family, is also known as B7x, a V-set domain-containing T cell activation inhibitor 1 (VTCN1) or B7S1 (Choi et al., 2003). Its mRNA is detectable in most non-hematopoietic tissues, but its protein expression is limited to APCs and cancer cells such as NSCLC,

**Table 2 Incidence of some common all-grade potential irAEs in advanced melanoma patients after the use of some specific ICIs\***

irAEs	Incidence (%)			
	Ipilimumab	Nivolumab	Pembrolizumab	Ipilimumab+nivolumab
Rash	20.54	18.10	13.47	30.68
Pruritus	24.88	22.53	21.40	33.73
Vitiligo	2.39	9.13	7.69	8.61
Diarrhoea	27.74	17.68	11.14	35.69
Colitis	6.87	1.88	1.64	11.80
Hypothyroidism	2.05	7.09	8.15	16.37
Hyperthyroidism	0.88	3.17	3.83	10.59
Hypophysitis	2.58	0.31	1.64	10.86
Hepatitis	0.29	3.01	0.68	4.85
Hyperglycemia	0.75	0.58	5.57	2.60
Acute renal injury	0.31	0.04	0.26	0.52

irAEs: immune-related adverse events; ICIs: immune checkpoint inhibitors. \* Data are from Almutairi et al. (2020).

melanoma, stomach cancer, prostate cancer, and breast cancer, which can be induced by IL-6 and IL-10 (Ceeraz et al., 2013; Li et al., 2018). Its receptor is assumed to be the B and T lymphocyte attenuator (BTLA) (Watanabe et al., 2003). B7-H4 expression was confirmed to be associated with cancer cell stemness in prostate cancer (Li HY et al., 2020). The silence of B7-H4 expression in CRC can reduce the viability and migration of cells and inhibit the epithelial–mesenchymal transition (EMT) process (Li C et al., 2020; Yin et al., 2022).

FPA150 is the first B7-H4 antibody tested in an early phase I trial in combination with pembrolizumab (anti-PD-1) for patients with breast cancer, ovarian cancer, and endometrial cancer to evaluate its dosing, safety, tolerability, pharmacokinetics (PK), pharmacodynamics, and preliminary efficacy (Andrews et al., 2019). It appeared to be well tolerated, with grade 1 and grade 2 treatment-related adverse events (TRAEs), including 16.7% diarrhea and 13.8% fatigue (Wainberg et al., 2019). NC762, another B7-H4-targeting mAb, is still in clinical trials for ovarian cancer, NSCLC, and breast cancer. Additionally, B7-H4 and CD3-bispecific mAbs such as PF-07260437 and GEN1047 are being tested in the treatment of breast cancer, ovarian cancer, and some other advanced or metastatic solid tumors to evaluate their safety and tolerability to determine the recommended dose.

### 2.5 V-domain Ig suppressor of T cell activation

A new target for cancer immunotherapy is the Ig superfamily member V-domain Ig suppressor of T cell activation (VISTA), also named B7-H5, PD-1 homolog (PD-1H), differentiation of ESC-1 (Dies1), C10orf54, stress-induced secreted protein 1 (SISP1), or platelet receptor Gi24 precursor (Wang et al., 2011; Huang et al., 2020). VISTA is expressed mainly on hematopoietic cells, with the highest level observed in leukocytes and myeloid cells (Lines et al., 2014a; Wu et al., 2021). In addition, VISTA is implicated in various kinds of cancers, such as melanoma, NSCLC, pancreatic cancer, and prostate cancer (Huang et al., 2020). Endogenous VISTA has immuno-inhibitory effects both as a ligand on APCs and as a receptor on T cells (Flies et al., 2014). Some studies have shown that V-set and immunoglobulin domain-containing 3 (VSIG-3)/immunoglobulin superfamily 11 (IgSF11) is the ligand of VISTA, which contributes to the suppression of T

cell responses *in vitro* by enhancing IL-2, IL-17, and interferon- $\gamma$  (IFN- $\gamma$ ) production (Wang et al., 2019). Importantly, as an acidic pH-selective ligand for P-selectin glycoprotein ligand-1 (PSGL-1), VISTA specifically mediates immune suppression in the acidic TME (Johnston et al., 2019).

CA-170, an oral checkpoint antagonist of VISTA, has been confirmed to interfere with the suppression of T cell activation and cytokine production by VISTA (Musielak et al., 2019). The potential pharmacologically active dose of tumors expressing VISTA has been evaluated in a phase I clinical trial in lymphomas, mesothelioma, NSCLC, and triple negative breast cancer. CA-170 was found to induce grade 1 and grade 2 TRAEs, including fever, fatigue, chills, and nausea. Another phase II trial treated patients with non-squamous NSCLC with 400 mg CA-170, which showed superior efficacy, with a clinical benefit rate (CBR) of 75% and median PFS of 19.5 weeks (Radhakrishnan et al., 2019). The safety of JNJ-61610588, an IgG1 anti-VISTA mAb, was investigated in a phase I trial in treating patients with advanced cancer such as metastatic NSCLC. However, it was terminated because of obvious side effects (Eltanbouly et al., 2020).

### 2.6 T cell immunoglobulin and mucin domain containing-3

TIM-3, a member of the TIM family, was first discovered in 2002 and is considered a cell surface marker of T helper 1 (Th1) cells (Monney et al., 2002). Among the TIM family, TIM-3 has attracted the most attention because of its negative effects on Th1 responses and the production of proinflammatory cytokines, such as TNF and IFN- $\gamma$  (Das et al., 2017). TIM-3 is expressed on IFN- $\gamma$ -producing T cells, Tregs, myeloid cells, NK cells, and mast cells (Wolf et al., 2020). It plays an inhibitory role through binding to different ligands, including galectin 9, carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1), phosphatidylserine (PS), and high-mobility group box 1 (HMGB1) (Zhu et al., 2005; Chiba et al., 2012; Huang et al., 2015). The absence of TIM-3 activates the inflammasome to promote anti-tumor immunity (Dixon et al., 2021). TIM-3 is also expressed in many types of cancers, such as melanoma and NSCLC, with a trend toward poor clinical prognosis (Fourcade et al., 2010; Gao et al., 2012). Moreover, TIM-3 blockade can

reduce the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT)/mTOR signaling-mediated inhibition of NK cells in HCC (Tan et al., 2020), underscoring its significance in the immunotherapy of cancer patients.

Mechanistic insights into the inhibitory function of TIM-3 and potential therapeutic evidence of TIM-3 blockade in combination with anti-PD-1 therapy boost the development of anti-TIM-3-blocking antibodies. The first trial focused on TSR-022 (cobolimab), a humanized anti-TIM-3 IgG4 antibody designed by Tesaro, Inc., Waltham, USA (Murtaza et al., 2016). The combination treatment of TSR-022 and anti-PD-1 antibody dostarlimab (TSR-042) has been proven to increase clinical activity in patients with NSCLC who do not respond to anti-PD-1 or anti-PD-L1 treatment (Davar et al., 2018). The TIM-3-blocking antibodies, LY3321367 from Eli Lilly (Harding et al., 2019) and MGB453 (sabatolimab) from Novartis (Ahn, 2018), have both completed phase I clinical trial. LY3321367 reportedly leads to TRAEs including diarrhea, pruritus, fatigue, and anorexia, without DLTs (Harding et al., 2021). The combination of LY3321367 with LY3300054 (an anti-PD-L1 antibody) did not change the frequencies or types of TRAEs compared with LY3300054 monotherapy, but led to higher response rates (Hollebecque et al., 2021). Now dual targeting of TIM-3 and PD-1 by RO7121611 has been attempted for the treatment of metastatic solid tumors, NSCLS, and some other cancers (Gomes de Moraes et al., 2022).

### 2.7 Lymphocyte-activation gene 3

LAG-3 is the third clinically targeted antagonistic mAb inhibitory receptor (Andrews et al., 2017). LAG-3 is expressed on a subset of NK cells (Triebel et al., 1990), T cells (Triebel et al., 1990), thymus-derived Tregs (Huang et al., 2004), plasmacytoid DCs in mice (Workman et al., 2009), invariant natural killer T (NKT) cells, and B cells (Workman et al., 2002; Kisielow et al., 2005). In effector T cells, the cross-linking of LAG-3 and CD3/TCR complex suppresses TCR-induced T cell proliferation, cytokine production, and calcium flux (Hannier et al., 1998). LAG-3 plays an essential role in T cell homeostasis by directly suppressing T cells or indirectly inhibiting Tregs (Workman and Vignali, 2005).

There are over 20 antibodies targeting LAG-3, including soluble LAG-3-Ig fusion protein (IMP321), mAbs (relatlimab, sym022, TSR-033, REGN3767,

and LAG525), and BsAbs (MGD013, FD118, and XmAb22841). In a phase I/II study of LAG525 and anti-PD-1 spartalizumab (PDR001), the frequencies of TRAEs were 56% and 69% for LAG525 monotherapy and the combination strategy, respectively. TRAEs commonly had low severity, such as fatigue, gastrointestinal disease, and dermatosis (Schöffski et al., 2022). In phases II and III clinical trials, relatlimab plus nivolumab (anti-PD-1) significantly improved the median PFS compared with nivolumab alone (10.1 months vs. 4.6 months) in previously untreated patients with metastatic or unresectable melanoma. Of the patients receiving combination arms, 18.9% had grade 3 or 4 TRAEs (Tawbi et al., 2022). Subsequently, in March 2022, nivolumab plus relatlimab gained approval from the FDA for the treatment of unresectable or metastatic melanoma.

### 2.8 T cell immunoglobulin and ITIM domain

TIGIT (T cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif (ITIM) domain) is a surface protein that was identified in the human lymphocyte population as a member of the CD28 family in 2009 (Yu et al., 2009). TIGIT is expressed on activated T cells, NK cells, memory T cells, and a subset of Treg cells (Yu et al., 2009). The ligands of TIGIT—CD155 (poliovirus receptor (PVR)) and CD112 (PVR-like protein 2 (PVRL2), nectin-2)—which are expressed on APCs, T cells, and a variety of non-hematopoietic cell types including tumor cells, play a tremendous role in mediating immune inhibitory functions (Mendelsohn et al., 1989; Casado et al., 2009; Stanietsky et al., 2009; Yu et al., 2009; Levin et al., 2011).

TIGIT features a cytoplasmic tail containing an ITIM and an immunoglobulin tail tyrosine (ITT)-like motif which are conserved between mice and humans. TIGIT leads to a strong reduction in NK cell functions via its ITT-like domain (Stanietsky et al., 2009; Liu et al., 2013). The phosphorylated ITT-like domain binds to adaptor proteins, including Grb2 and  $\beta$ -arrestin 2, which further recruit Src homology 2 (SH2)-containing inositol phosphatase 1 (SHIP1) to suppress NK cell function via PI3K/mitogen-activated protein kinase (MAPK) signaling or nuclear factor- $\kappa$ B (NF- $\kappa$ B) signaling (Liu et al., 2013; Li et al., 2014). The activation of TIGIT negatively affects different facets of the functions of T cells, such as productive T cell activation

and proliferation, and the acquisition of effector functions (Yu et al., 2009; Joller et al., 2011). It targets the TCR signaling pathway, in which it downregulates the components of the TCR complex and phospholipase C  $\gamma$  (PLC $\gamma$ ), the central regulator of the TCR signaling cascade (Joller et al., 2011).

So far, there have been 75 clinical trials on TIGIT-related drugs; most of them are in phase I or II. Currently, there are four TIGIT mAbs in phase III trials, including tiragolumab, ociperlimab, vibostolimab, and domvanalimab. For example, the anti-TIGIT antibody vibostolimab, as a monotherapy or in combination with pembrolizumab (anti-PD-1), is in a first-in-human phase I study to cure patients with advanced solid tumors, including advanced NSCLC. TRAEs occurred in 62% of patients, and even 17% had grades 3 and 4 TRAEs. The most common TRAEs were pruritus (17%) and rash (14%) (Niu et al., 2021). Recently, a phase I trial of the combination of the anti-TIGIT antibodies etigilimab and nivolumab reported a notably increased median PFS of 57.5 d (Mettu et al., 2022).

## 2.9 B and T lymphocyte attenuator

BTLA, a co-inhibitor that is also known as B and T lymphocyte-associated protein or CD antigen CD272, is an Ig domain superfamily protein with cytoplasmic ITIM and an immunoreceptor tyrosine-based switch motif (ITSM). As discovered in 2003, BTLA is widely expressed on many immune cells, such as Th1 cells, bone marrow-derived CD11c<sup>+</sup> DCs, resting peripheral B cells, anergic T cells, and T follicular helper (Tfh) cells (Watanabe et al., 2003; Han et al., 2004; Hurchla et al., 2005; Loyet et al., 2005; Nurieva et al., 2008; M'Hidi et al., 2009). BTLA was also found in NSCLS, and its expression was positively correlated with PD-L1 expression, which showed a synergistic action (Li XM et al., 2020).

BTLA has some similarities with PD-1 and CTLA-4, as they are all Ig domain-containing inhibitory receptors (Watanabe et al., 2003). However, BTLA is unique because its ligand, herpesvirus entry mediator (HVEM), is a tumor necrosis factor receptor (TNFR) superfamily member rather than an Ig domain-containing protein (Gonzalez et al., 2005; Sedy et al., 2005). The BTLA/HVEM signaling functions bidirectionally in T cell regulation. Concerning *trans* interaction, both ITIM and ITSM of BTLA can be phosphorylated and recruit SH2 domain-containing protein tyrosine phosphatase

1/2 (SHP1/2) to inhibit both TCR and CD28 signaling after interacting with the cysteine-rich domain 1 (CRD1) region of HVEM, thus suppressing T cell function (Gavrieli et al., 2003; Watanabe et al., 2003; Sedy et al., 2005). Additionally, the *cis* interaction between HVEM and BTLA prevents HVEM from being activated by *trans* ligation and provides proinflammatory signals (Cheung et al., 2009).

Given the complexity of the BTLA/HVEM signaling pathway, whether or not the BTLA blockade can be used on immunotherapy seems to be a context-specific decision. It is reported that the BTLA/HVEM axis downregulated IFN- $\gamma$  production and NK cell-mediated cytotoxicity to promote NK cell immunosuppression in chronic lymphocytic leukemia (CLL), and the BTLA blockade worked in reversing the effects (Sordo-Bahamonde et al., 2021). JS004 is the first anti-BTLA mAb approved in clinical trials by the FDA, which intends to cure advanced unresectable or metastatic solid tumors (including lymphoma). In a phase I study of JS004 as a single agent or in combination with toripalimab (anti-PD-1) in relapsed/refractory lymphoma, 83.3% of patients experienced treatment emergent adverse events (TEAEs), with 18.8% experiencing TEAEs of grade 3 or higher (Ma et al., 2022). As a suppressor gene, miR-32 can inhibit the metastasis and proliferation of ovarian cancer cells by regulating the target gene *BTLA* (Zhang et al., 2020); however, no BTLA-targeted drug has yet been approved for tumor treatment by the FDA.

We summarize the clinical trials on current novel ICIs with corresponding phases and tumor types to give readers an intuitive sense of these ICIs (ClinicalTrials.gov) (Table 3).

## 3 Myeloid immune checkpoints

Knowledge about immune checkpoints expressed on myeloid cells has been expanding in recent years (Fig. 1), and they have been proven to critically suppress anti-tumor immune responses in the TME (Nakayama et al., 2009; Yao et al., 2009; Bally et al., 2015).

The first class of myeloid immune checkpoints acts as a “negative regulator,” of which PD-1 and TIM-3 are the most representative because of their impressive immunosuppressive function on T cells.

**Table 3 Clinical trials on novel immune checkpoint inhibitors**

Target	Drug	Clinical trial No.	Phase	Tumor type	
B7-H3	DS-7300a	NCT04145622	I, II	Advanced solid tumor, malignant solid tumor	
		Enoblituzumab	NCT04129320	II, III	Recurrent or metastatic HNSCC
	NCT04630769		I	Ovarian cancer, fallopian tube adenocarcinoma, primary peritoneal cavity cancer	
	NCT02923180		II	Prostate cancer	
	NCT02982941		I	Neuroblastoma, rhabdomyosarcoma, osteosarcoma, Ewing's sarcoma, Wilms' tumor, desmoplastic small round cell tumor	
	NCT05276609		I	Advanced solid tumor	
	HS-20093	NCT05293496	I	Advanced solid tumor, castration-resistant prostate cancer, malignant melanoma, pancreatic ductal carcinoma, hepatocellular cancer, epithelial ovarian cancer, RCC	
	MGC018	NCT03729596	I, II	HNSCC, triple negative breast cancer, melanoma, metastatic castration-resistant prostate cancer, NSCLC	
	MGA271				NCT01918930
		MGD009	NCT03406949	I	Advanced solid tumor
		MGA012	NCT02628535	I	Mesothelioma, bladder cancer, melanoma, HNSCC, NSCLC, clear cell RCC, ovarian cancer, thyroid cancer, breast cancer, pancreatic cancer, prostate cancer, colon cancer, soft tissue sarcoma
		MGD009			
		4SCAR-276	NCT04432649	I, II	Solid tumor
		131I-8H9	NCT01099644	I	Peritoneal cancer
			NCT00089245	I	Brain and central nervous system tumor, neuroblastoma, sarcoma
	NCT03275402		II, III	Neuroblastoma, central nervous system/leptomeningeal metastasis neuroblastoma, leptomeningeal metastasis	
B7-H4	PF-07260437	NCT05067972	I	Ovarian neoplasm, endometrial neoplasm, breast neoplasm	
	SGN-B7H4V	NCT05194072	I	Ovarian neoplasm, peritoneal neoplasm, fallopian tube neoplasm, triple negative breast neoplasm, HER2 negative breast neoplasm, hormone receptor positive breast neoplasm, endometrial neoplasm carcinoma, NSCLC, cholangiocarcinoma, gallbladder carcinoma	
	FPA150	NCT03514121	Early phase I	Breast cancer, ovarian cancer, endometrial cancer, advanced solid tumor	
	Pembrolizumab				
		HS-20089	NCT05263479	I	Advanced solid tumor
		GEN1047	NCT05180474	I, II	Breast cancer, uterine cancer, ovarian cancer, NSCLC, cervical cancer, and HNSCC, except for nasopharyngeal carcinoma, urothelial cancer, and cholangiocarcinoma
		NC762	NCT04875806	I, II	Advanced or metastatic solid tumor, ovarian cancer, NSCLC, breast cancer
VISTA	CA-170	NCT02671955	I	Advanced cancer	
	JNJ-61610588	NCT02812875	I	Advanced solid tumor or lymphoma	
	CI-8993	NCT04475523	I	Solid tumor	
TIM-3	Sabatolimab (MGB453)	NCT04812548	II	MDS	
		NCT04623216	I, II	AML	
		NCT04878432	II	MDS	
		NCT05367401	I, II	MDS, AML	
		NCT05201066	II	MDS, myelomonocytic leukemia	
	NCT04097821	I, II	Myelofibrosis		

To be continued

Table 3 (continued)

Target	Drug	Clinical trial No.	Phase	Tumor type	
TIM-3	Sabatolimab (MGB453)	NCT04150029	II	AML	
		NCT03946670	II	MDS	
		NCT04266301	III	MDS, myelomonocytic leukemia	
	Cobolimab (TSR-022)	NCT03680508	II	Adult primary liver cancer, advanced adult primary liver cancer, localized unresectable adult primary liver cancer	
		NCT04139902	II	Stage III melanoma, stage IV melanoma	
		NCT02817633	I	Neoplasm	
		NCT03307785	I	Neoplasm, metastatic cancer, advanced cancer, solid tumor, metastatic NSCLC, stage IIIB NSCLC	
	Sym023	NCT03489343	I	Metastatic cancer, solid tumor, lymphoma	
		NCT04641871	I	Metastatic cancer, solid tumor	
		NCT03311412	I	Metastatic cancer, solid tumor, lymphoma	
	BGBA425	NCT03744468	I, II	Locally advanced or metastatic solid tumor for phase 1 HNSCC, NSCLC and RCC for phase 2	
	LY3321367	NCT03099109	I	Solid tumor	
		NCT02791334	I	Solid tumor, microsatellite instability-high (MSI-H) solid tumor, cutaneous melanoma, pancreatic cancer, breast cancer (HR <sup>+</sup> HER2 <sup>-</sup> )	
	BMS-986258	NCT03446040	I, II	Advanced cancer	
	SHR-1702	NCT04443751	I	AML, MDS	
NCT03871855		I	Advanced solid tumor		
LAG-3	Eftilagimod Alpha (IMP32)	NCT03625323	II	NSCLC, HNSCC	
		NCT04811027	II	HNSCC	
		NCT02676869	I	Stage IV melanoma, stage III melanoma	
		NCT04252768	I	Metastatic breast cancer	
		NCT02614833	II	Adenocarcinoma, stage IV breast cancer	
		NCT03600090	I	Metastatic breast cancer	
		Relatlimab (BMS-936558)	NCT03743766	II	Melanoma
	NCT04552223		II	Metastatic uveal melanoma	
	NCT02061761		I, II	Hematologic neoplasm	
		NCT03623854	II	Metastatic or locally advanced/unresectable chordoma	
		NCT01968109	I, II	NSCLC, HNSCC, HCC, RCC, bladder cancer, gastric cancer, melanoma	
		Cemiplimab (REGN3767)	NCT04566978	I	Large B-cell lymphoma, DLBCL
			NCT03005782	I	Malignancy
	NCT04706715		I, II	Metastatic solid tumor	
	BI 754111	NCT05352672	III	Melanoma	
NCT03780725		I	Advanced NSCLC, HNSCC		
NCT03156114		I	Advanced solid tumors including NSCLC		
NCT03433898		I	Neoplasm		
Sym022	NCT03964233	I	Neoplasm		
	NCT03489369	I	Metastatic cancer, solid tumor, lymphoma		
	NCT04641871	I	Metastatic cancer, solid tumor		
	NCT03311412	I	Metastatic cancer, solid tumor, lymphoma		

To be continued

Table 3 (continued)

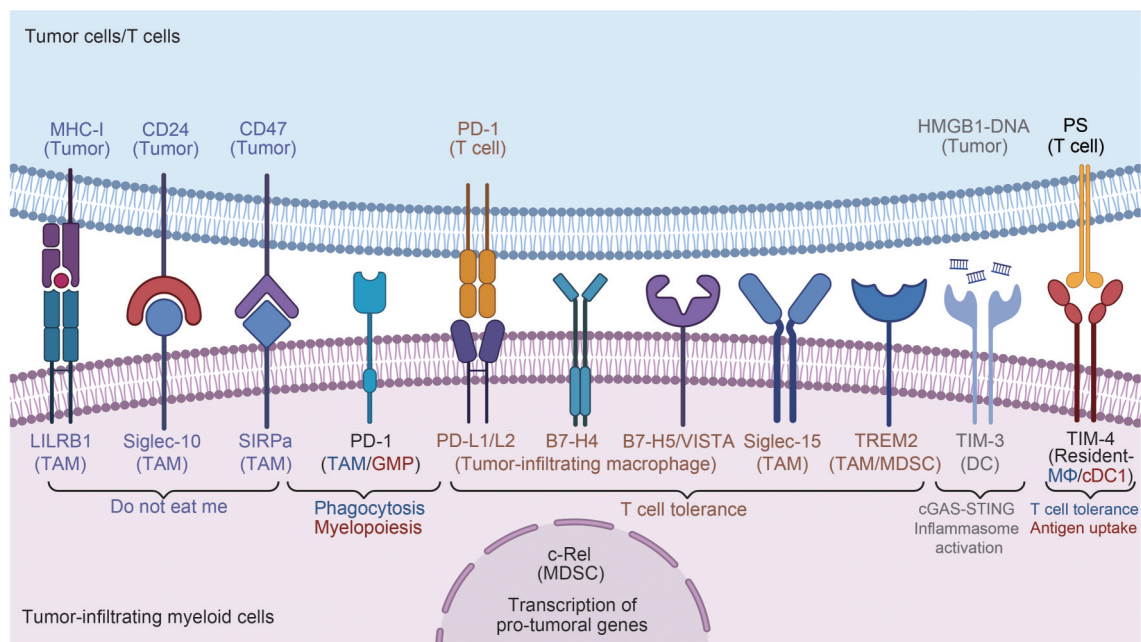
Target	Drug	Clinical trial No.	Phase	Tumor type		
LAG-3	MGD013	NCT04212221	I, II	Advanced HCC		
		NCT04653038	I	Unresectable recurrent or metastatic melanoma, untreated mucosal or acral lentiginous melanoma		
		NCT04178460	I	Gastric cancer, triple negative breast cancer, biliary tract carcinoma, endometrial carcinoma		
		NCT04129320	II, III	Head and neck cancer, HNSCC		
Favezelimab (MK-4280)		NCT03598608	I, II	Hodgkin disease, lymphoma (non-Hodgkin), lymphoma (B-cell)		
		NCT05064059	III	Colorectal cancer		
		NCT02720068	I	Neoplasm		
TSR-033		NCT03250832	I	Neoplasm		
TIGIT	Tiragolumab	NCT05251948	I, II	Gastric and gastroesophageal junction carcinoma		
		NCT03563716	II	NSCLC		
		NCT03708224	II	HNSCC		
		NCT04933227	II	Stomach neoplasm, gastric cancer, gastroesophageal junction adenocarcinoma		
		NCT05009069	II	Locally advanced rectal cancer		
		NCT04543617	III	Esophageal squamous cell carcinoma		
		NCT04256421	III	Small cell lung cancer		
		NCT04294810	III	NSCLC		
		JS006		NCT05061628	I	Advanced tumor
		IBI939		NCT04353830	I	Advanced malignant tumor
				NCT04672369	I	Advanced lung cancer
		BMS-986207		NCT04150965	I, II	Relapsed/refractory MM
				NCT04570839	I, II	Endometrial neoplasm, ovarian cancer, peritoneal cancer, fallopian tube cancer, HNSCC
		Etigilimab (MP-313M32)		NCT03119428	I	Locally advanced cancer, metastatic cancer
				NCT04761198	I, II	Advanced solid tumor, metastatic solid tumor
		COM902		NCT04354246	I	Advanced cancer, ovarian cancer, lung cancer, colon cancer, plasma cell neoplasm, MM, HNSCC
AZD2936		NCT04995523	I, II	NSCLC		
Ociperlimab		NCT04047862	I	Locally advanced and metastatic solid tumors		
		NCT04693234	II	Cervical cancer		
		NCT04732494	II	Esophageal squamous cell carcinoma		
		NCT04952597	II	Limited stage small cell lung cancer		
		NCT04866017	III	NSCLC		
HLX301		NCT05102214	I, II	Locally advanced or metastatic solid tumor, NSCLC		
		NCT05390528	I, II	Advanced tumor, lymphoma, metastatic tumor		
M6223		NCT04457778	I	Metastatic solid tumor		
		NCT05327530	II	Locally advanced or metastatic urothelial carcinoma		
BAT6021		NCT05120375	I	Solid tumor		
		NCT05073484	I	Advanced solid tumor		

To be continued

Table 3 (continued)

Target	Drug	Clinical trial No.	Phase	Tumor type
TIGIT	Domvanalimab	NCT03628677	I	Solid tumor
		NCT05130177	II	Melanoma
		NCT05329766	II	Gastrointestinal tract malignancy
		NCT04791839	II	NSCLC
		NCT04262856	II	Metastatic squamous or non-squamous NSCLC
		NCT04736173	III	Advanced or metastatic, squamous or non-squamous NSCLC
		EOS-448		NCT05060432
NCT05289492	I, II			Relapsed/refractory MM
NCT03739710	II			Neoplasm
BTLA	JS004	NCT04278859	I	Advanced solid tumor
		NCT04137900	I	Advanced unresectable solid tumor, metastatic solid tumor
		NCT04929080	I, II	HNSCC, nasopharyngeal carcinoma
		NCT04773951	I	Melanoma, RCC, urothelial carcinoma
		NCT04477772	I	Recurrent/refractory malignant lymphoma
		NCT05000684	I, II	Advanced lung cancer

B7-H3: B7 homolog 3; B7-H4: B7 homolog 4; VISTA: V-domain Ig suppressor of T cell activation; TIM-3: T cell immunoglobulin and mucin domain containing-3; LAG-3: lymphocyte-activation gene 3; TIGIT: T cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif (ITIM) domain; BTLA: B and T lymphocyte attenuator; HNSCC: head and neck squamous cell carcinoma; RCC: renal cell carcinoma; NSCLC: non-small cell lung cancer; MDS: myelodysplastic syndrome; AML: acute myeloid leukemia; HR: hormone receptor; HER2: human epidermal growth factor receptor 2; HCC: hepatocellular carcinoma; DLBCL: diffuse large B cell lymphoma; MM: multiple myeloma.



**Fig. 1** Immune checkpoints on tumor-infiltrating myeloid cells. Immune checkpoints in tumor-infiltrating myeloid cells have a variety of functions, which encompass the activation of the “do not eat me” signal, phagocytosis, myelopoiesis, T cell tolerance, inflammasome activation, antigen uptake, and transcription of pro-tumoral genes. MHC-I: major histocompatibility complex class I; CD24/47: cluster of differentiation 24/47; PD-1: programmed cell death-1; HMGB1: high-mobility group box 1; PS: phosphatidylserine; LILRB1: leukocyte immunoglobulin-like receptor B1; Siglec: sialic-acid-binding Ig-like lectin; SIRP $\alpha$ : signal regulatory protein  $\alpha$ ; PD-L1/L2: programmed death-ligand 1/2; B7-H4: B7 homolog 4; B7-H5: B7 homolog 5; VISTA: V-domain Ig suppressor of T cell activation; TREM2: triggering receptor expressed on myeloid cells 2; TIM-3/4: T cell immunoglobulin and mucin domain-containing protein 3/4; TAM: tumor-associated macrophage; GMP: granulocyte-monocyte progenitor; MDSC: myeloid-derived suppressor cell; DC: dendritic cell; M $\Phi$ : macrophage; cDC1: conventional dendritic cell 1; cGAS: cyclic GMP-AMP synthase; STING: stimulator of interferon gene; c-Rel: cellular reticuloendotheliosis oncogene homolog. Created in <https://BioRender.com>.

In macrophages, PD-1 expression is upregulated by Toll-like receptor (TLR)-induced NF- $\kappa$ B activation (Bally et al., 2015; Martinez et al., 2015; Voron et al., 2015). PD-1 expressed on DCs negatively regulates proinflammatory cytokine production (Yao et al., 2009). TIM-3 expressed on DCs competitively binds to dying cell-derived HMGB1, which can activate innate immune responses through TLRs and retinoic acid-inducible gene I (RIG-I) (Chiba et al., 2012).

The second class of myeloid immune checkpoints has a great impact on the phagocytosis of myeloid cells, including monocytes, macrophages, and neutrophils. Upon recognizing ligands on tumor cells, they can downregulate the clearing ability of myeloid cells. For instance, signal regulatory protein  $\alpha$  (SIRP $\alpha$ ) is a member of the SIRP-paired receptor family that has ITIMs. Upon the recognition of its ligand, CD47, SIRP $\alpha$  recruits SHP1/2, leading to the negative regulation of phagocytosis (Nakamura and Smyth, 2020). Another checkpoint is leukocyte immunoglobulin-like receptor (LILR), which belongs to the superfamily of paired receptors and can be divided into inhibitory LILRBs and activating LILRAs (Kuroki et al., 2012; Burshtyn and Morcos, 2016). Inhibitory LILRB1 and LILRB2 are well characterized to recognize classic MHC-I and non-classic MHC-I (Held and Mariuzza, 2008). LILRBs might also transmit a “do not eat me” signal in monocytes and macrophages. Blockade of LILRB1 unleashes tumor MHC-I-induced negative regulation of phagocytosis (Barkal et al., 2018). It is noted that sialic-acid-binding Ig-like lectin 10 (Siglec-10), which is a family of sialic acid-binding immunoglobulin-like receptors expressed on B cells, monocytes, and eosinophils in humans, can downregulate inflammatory responses through the recruitment of SHP1/2 when interacting with its ligand, CD24 (Chen et al., 2009, 2011; Macauley et al., 2014).

The third class contains several scavenger receptors on macrophages, such as scavenger receptor-A (SR-A), macrophage receptor with collagenous structure (MARCO), and common lymphatic endothelial and vascular endothelial receptor-1 (Clever-1, also known as stabilin-1 or fibroblast growth factor receptor-like 1 (FEEL1)) (Salmi et al., 2004; Arredouani et al., 2007). SR-A (also known as CD204) can recognize low-density lipoproteins (LDLs), heat shock proteins, proteoglycans, and various pathogen-associated molecular patterns (PAMPs). High expression levels of

SR-A on tumor-associated macrophages (TAMs) correlate with tumor invasiveness and angiogenesis in patients with lung and esophagus squamous carcinoma (Hirayama et al., 2012; Shigeoka et al., 2013).

Cellular reticuloendotheliosis oncogene homolog (c-Rel), a member of the NF- $\kappa$ B family, acts as an intracellular checkpoint by selectively activating pro-tumoral genes and deactivating anti-tumoral genes through a c-Rel enhanceosome. This results in the generation of myeloid-derived suppressor cells (MDSCs). Studies have shown that c-Rel deficiency in myeloid cells significantly reduced cancer growth in mice. Similarly, pharmaceutical inhibition of c-Rel also had the same effect. This suggests that c-Rel is a myeloid checkpoint that can be targeted for cancer treatment (Li T et al., 2020).

Some clinical trials have been carried out on these myeloid immune checkpoints. For example, anti-CD47 mAb (Hu5F9-G4) in combination with anti-CD20 mAb (rituximab) was tested in patients with relapsed and refractory B cell lymphoma (Advani et al., 2018). However, because myeloid subsets feature a high turnover rate, functional compensation, heterogeneity, and plasticity, targeting these immune checkpoints will be a great challenge.

#### 4 Secreted immune checkpoint

IL-18 is a member of the IL-1 cytokine family, which can promote the activity of effector T cells and NK cells to increase the production of IFN- $\gamma$ , thus inhibiting the proliferation of tumors (Srivastava et al., 2013; Yasuda et al., 2019). However, its decoy receptor IL-18-binding protein (IL-18BP) can neutralize IL-18 with higher affinity than the IL-18 receptor to reduce the induction of IFN- $\gamma$  and downregulate Th1 responses (Nakanishi et al., 2001). Studies also found that, after patients received treatment with recombinant human IL-18 (rhIL-18), IL-18 was neutralized by IL-18BP (Robertson et al., 2006, 2008). Because IL-18BP is prevalent in the TME and is often upregulated in tumors, it acts as a secreted checkpoint to be the barrier to IL-18 immunotherapy (Zhou et al., 2020). Decoy-resistant IL-18 (DR-18) is a variant created to avoid the inhibition of IL-18BP, but with full signaling capacity; it has been proven that DR-18 can drive potent tumor growth inhibition in mouse tumors, and

can elicit NK cell responses in MHC-I-deficient tumors. It may be a promising way to treat cold tumors, which are not sensitive to traditional immunotherapy, although its clinical safety and pleiotropy are still worthy of attention (Zhou et al., 2020).

## 5 Limitation of clinical application of immune checkpoint blockades

### 5.1 Factors influencing resistance to immune checkpoint blockade

Most cancer patients with primary resistance to ICB cannot benefit from this therapy. Some people who initially respond to treatment also obtain acquired resistance, and consequently have adverse outcomes (Sharma et al., 2017). The response to immune checkpoint therapy is influenced by both host-intrinsic and host-extrinsic factors. Host-intrinsic factors include tumor and TME, host genomics and epigenomics, systemic immunity, systemic factors, and microbiota. For host-extrinsic factors, environmental exposures, psychosocial factors, lifestyle, and microbial factors also have a significant impact on the patient's response to ICB. The interaction of these factors and the coevolution of cancer and anti-tumor immunity also impacts the therapy immensely (Morad et al., 2021). The IFN- $\gamma$  pathway plays a key role in primary and acquired resistance in checkpoint blockade therapy. T cells produce IFN- $\gamma$  once they recognize tumor antigens, which activates the Janus kinase (JAK)-signal transducer and activator of the transcription (STAT) pathway, and upregulates the downstream expression of chemokines, in particular C-X-C motif chemokine ligand 9 (CXCL9), CXCL10, and CXCL11, to attract T cell infiltration (Castro et al., 2018; Grasso et al., 2020). Cancer cells can mutate or silence the molecules involved in the IFN- $\gamma$  pathway to mediate immune escape (Benci et al., 2016).

It can be seen that abnormal cellular transduction signals, including the WNT/ $\beta$ -catenin pathway, PI3K/AKT pathway, and MAPK pathway, may be the factors leading to immunotherapy resistance (Barrueto et al., 2020). The activation of the melanoma-intrinsic WNT/ $\beta$ -catenin pathway can produce immunosuppressive cytokines, such as IL-10, and exclude T cell infiltration (Spranger et al., 2015). In melanoma cells, the soluble WNT agonist WNT5A can activate  $\beta$ -catenin

signaling in DCs, which induces downstream target indoleamine 2,3-dioxygenase 1 (IDO1) to catalyze the conversion of tryptophan into kynurenine. It promotes the development of Treg cells and results in the inhibition of effector T cell activity (Holtzhausen et al., 2015). PI3K can phosphorylate the metabolite phosphatidylinositol 4,5-bisphosphate (PIP2) to phosphatidylinositol 3,4,5-trisphosphate (PIP3). PIP3 acts as a second messenger and promotes AKT activation, thereby stimulating cell proliferation, inhibiting apoptosis, and promoting angiogenesis. However, the lipid phosphatase phosphatase and tensin homolog (PTEN) can dephosphorylate PIP3 and turn it back to PIP2, terminating the PI3K signaling pathway (Fresno Vara et al., 2004). Therefore, the loss of the lipid phosphatase PTEN in cancer can activate the PI3K/AKT pathway, thus reducing melanoma autophagic activity to facilitate the resistance to T cell-mediated tumor apoptosis (Peng et al., 2016). Ras can activate the Ras-Raf-mitogen-activated protein kinase kinase (MEK)-extracellular signal-regulated kinase 1/2 (ERK1/2)/MAPK phosphorylation cascade to regulate cell proliferation, survival, differentiation, and angiogenesis. Activating mutations of serine/threonine-protein kinase B-raf (BRAF) is common in different kinds of tumors, augmenting the expression of IL-6, IL-10, and VEGF to perform immunosuppressive functions (Sumimoto et al., 2006). In addition, a lack of neoantigens and the loss of antigen presentation can lead to the absence of tumor cell recognition, contributing to immunotherapy resistance (Barrueto et al., 2020). Meanwhile, the specialized components of the TME, such as MDSCs, Tregs, and exhausted T cells, are also associated with ICB resistance (Kalbasi and Ribas, 2020). Hyperprogressive disease (HPD), a phenomenon of accelerated tumor growth after the administration of checkpoint inhibitors, occurs with an incidence from 4% to 29% (Borcman et al., 2019), which will reduce survival durations (Champiat et al., 2017). However, the mechanism and predictive biomarkers of this phenomenon have not been well identified.

Genetic and epigenetic influences are significant factors impacting the response to ICB. Tumor cells can reduce HLA class I on their surface, thus influencing antigen presentation to escape immune recognition. Genetically, *HLA* loss of heterozygosity (LOH) or antigen-presentation machinery (APM) mutations can hinder antigen presentation (Rosenthal et al.,

2019). The loss of  $\beta$ -2 microglobulin (*B2M*) alleles, a component of HLA-I that maintains stability, can be observed only in ICB non-responders (Sade-Feldman et al., 2017). Epigenetically, tumor cells can regulate *HLA-I* gene expression through their promoter hypermethylation. This always leads to the inactivation of *HLA-A*, *HLA-B*, and *HLA-C* transcription (Ye et al., 2010). Histone methyltransferase EZH2 can be upregulated by intratumoral T cells and TNF- $\alpha$  in melanoma; then, it promotes the loss of immunogenicity and silences antigen presentation, resulting in immunotherapy-induced immune resistance in melanoma (Zingg et al., 2017).

Environment also matters—it has been reported that exposure to ultraviolet radiation and/or cigarette smoke can increase TMB and secondarily neoantigen levels, which may increase the response rate to ICB in melanoma and NSCLC, respectively (Morad et al., 2021). Environment is related to more things we are exposed to, such as sociological factors, lifestyle (diet, physical exercise, smoking, and alcohol consumption), and climate. More studies are needed to draw conclusions about the influences of these factors on the ICB response. However, our studies ignore the influences of the environment on ICB resistance, instead focusing on genetic factors.

## 5.2 Immune-related adverse events

Despite boosting antitumor immunity, an immune system that is excessively activated by ICB also introduces the development of irAEs, which range from skin pruritus to fatal events. The mechanisms of irAEs differ between various ICIs, and the precise mechanisms remain to be explored. However, the main mechanisms are as follows: the use of ICIs can activate T cells, impairing Tregs to increase the ratio of effector T cells in the TME. It can also increase the production of pro-inflammatory cytokines such as TNF, IFN- $\gamma$ , and IL-2, which always leads to colitis (Sullivan and Weber, 2022). Cross-reactivity between anti-tumor T cells and similar antigens on healthy cells might account for some irAEs, such as myocarditis (Johnson et al., 2016). Activated T cells mediated by ICIs can interact with B cells to produce autoantibodies. This usually happens in patients treated with CTLA-4 antibody but not with PD-1 or PD-L1 inhibitor, leading to irAEs such as hypophysitis. Additionally, complement can mediate injury directly from ICB (Sullivan and Weber, 2022).

irAEs can occur in nearly every organ, including the liver, lung, gastrointestinal and endocrinal organs, heart, and skin (Dolladille et al., 2020). An estimation of 36 phase II/III trials of ICBs showed a frequency of 54% to 76% for all adverse events (Xu et al., 2018). The clinical usage of combination therapy with nivolumab and ipilimumab is also constrained because of the high rate of severe irAEs (Pauken et al., 2019). Usually, grade 1 irAEs, referring to asymptomatic or mild symptoms, can be stopped temporarily or continued with close monitoring, without interventional treatment. However, patients with grade 2 or higher irAEs should stop ICIs and be referred to a specialist. Meanwhile, grade 2 irAEs mean that age-appropriate instrumental activities of daily living (ADL) are limited, and patients should be treated with glucocorticoids, except for endocrine irAEs (Brahmer et al., 2018), and prednisone is usually the first choice. Patients with grade 3 (where the symptoms are severe or medically significant but not immediately life-threatening) or 4 (showing life-threatening consequences) irAEs should initially be treated with steroids, such as starting methylprednisolone pulses (Torino et al., 2016). In addition, hormonal replacement can relieve endocrine irAEs (Sznol et al., 2017). More detailed management guidelines targeting specific organs can be found in other guidelines (Brahmer et al., 2018). Administering other drugs according to specific symptoms to manage irAEs is necessary for clinical applications (Martins et al., 2019), and potential predictive biomarkers, such as MHC, gut microbiota, and tumor-infiltrating lymphocytes (TILs), need to be improved (Mahadevan et al., 2021; Hone Lopez et al., 2022; Wang et al., 2022). Moreover, ICIs are expensive and their use can significantly increase costs. The financial burden limits access and may further strain healthcare resources in developing nations (Merchant et al., 2023).

## 6 Perspective

Immune checkpoint therapy aims to restore the function of tumor-infiltrating T cells. Hot tumors, characterized by high T cell infiltration, respond well to immune checkpoint therapy. In contrast, cold tumors, lacking T cell infiltration, respond weakly (Chen and Mellman, 2017). Cold tumors are also characterized by low mutational load, low MHC-I expression, low

PD-L1 expression, and the presence of immunosuppressive cell populations, including Tregs, TAMs, and MDSCs. Deficiencies in T cell priming and homing to the tumor bed contribute to the weak response. It is critical to find approaches to convert cold tumors to hot tumors for a better response and less resistance to immunotherapy. Key strategies include promoting T cell priming, promoting T cell expansion, and promoting T cell trafficking and infiltration (Liu and Sun, 2021).

Nowadays, many combination strategies have been developed to improve efficacy and overcome ICB resistance. Treatment with DNA methyltransferase inhibitors, individually or combined with histone deacetylase (HDAC) inhibitor to modulate epigenetic status, promotes antigen presentation (Luo et al., 2018). Other combination treatment strategies are also under investigation. Signal modulators, such as the combination of atezolizumab (anti-PD-L1) and BRAF/MEK inhibitors in melanoma, significantly increase PFS (NCT02908672). PI3K inhibitors and cyclin-dependent kinase 4/6 (CDK4/6) can reverse signal defects (Goel et al., 2017; Marijt et al., 2019). Cytokines like IL-2 or IL-12 can be introduced to increase the abundance of TIL, but usually with severe toxicity because of the systematic pro-inflammatory side effects (Panelli et al., 2004). Therefore, confining cytokines to the site of action may be an effective improvement measure. Anti-angiogenic agents, when combined with ICIs, have been proven to expand immune cell infiltration in tumors. For example, bevacizumab (anti-angiogenic agent) combined with atezolimumab (anti-PD-L1) has been approved by the FDA for the treatment of unresectable or metastatic HCC (Finn et al., 2020). Vaccines are another approach to increasing T cell infiltration. The CD103 conventional dendritic cell 1 (cDC1) vaccine, combined with CTLA-4 antibody, has been shown to control primary and metastatic melanoma and osteosarcoma in mice (Finn et al., 2020). Oncolytic viruses (OVs) can mediate the lysis of tumor cells directly or make tumor cells release antigens and activate an inflammatory response, thus inducing anti-tumor immune response. However, inadequate OV penetration and spread and host antiviral immunity are barriers to be overcome (Ma et al., 2023).

Combining ICB with other strategies, such as adoptive T cell transfer, radiation, chemotherapy, and intra-tumoral therapies, is being actively explored, with the aim of increasing the sensitivity of tumors to

immunotherapy (Meric-Bernstam et al., 2021). Furthermore, treatments based on cytokines, such as the therapeutic neutralization of interleukins, recombinant and engineered interleukins, TNF antagonists, and transforming growth factor- $\beta$  (TGF- $\beta$ ) inhibition, are promising targets for the modulation of the immune-related toxicities of other anti-tumor therapies, including ICBs (Briukhovetska et al., 2021; Propper and Balkwill, 2022). Because of the complexity of tumor types and individual patient differences, developing biomarkers—even biomarker panels to indicate the response and resistance to ICB monotherapy and combinatorial therapies—is crucial for guiding the selection of treatment and optimizing patient outcomes (Ganesan and Mehnert, 2020).

Patient adherence is one of the factors influencing efficacy. The complexity of combination strategies' precise compatibility, the irAEs of drugs, patients' anxiety, and even the loss of monitoring can lead to lower patient adherence. A clinical trial used the web application KidneyPRO to monitor and manage the toxicities of patients undergoing treatment with the new combination of axitinib/pembrolizumab for first-line RCC (NCT04764487). The application provided care adapted to irAEs quickly and personally, improving patient adherence and OS. A clinical trial investigated the ePRO follow-up of cancer patients treated with anti-PD-(L)1 therapies. These patients felt that electronic patient-reported outcome (ePRO) follow-up was easy to use and improved their cancer care, and the results showed good patient adherence and satisfaction (Iivanainen et al., 2020). In the long run, automated patient health management is poised to revolutionize the follow-up of cancer patients treated with ICB.

Comparative results have shown that immunotherapy monotherapy has a similar efficacy to that of chemotherapy, but the combination of immunotherapy and chemotherapy provides better efficacy, reducing the death rate (Wang et al., 2023). Several studies have demonstrated that ICIs are superior to other anti-cancer therapies (chemotherapy, targeted therapies, and other immunotherapy strategies) across various symptoms and in terms of health-related quality of life, despite the high rate of high-grade irAEs (Hall et al., 2019). However, the existing PRO cannot adequately assess the many toxicities patients experience after ICI therapy; therefore, it is necessary to develop new PRO

tools to capture the symptoms of patients treated with ICIs.

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### Author contributions

Qingqing WANG and Yin SHI determined the topic of the article, proposed this program, and reviewed and edited the manuscript. Hongying YE, Weijie LIAO, and Jiongli PAN collected the literature and wrote the manuscript. Hongying YE and Weijie LIAO summarized and drew the tables and pictures. All authors have read and approved the final manuscript.

### Compliance with ethics guidelines

Hongying YE, Weijie LIAO, Jiongli PAN, Yin SHI, and Qingqing WANG declare no competing interests.

This review does not contain any studies with human or animal subjects performed by any of the authors.

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