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Review

Immune checkpoint blockade and its combination therapy with small-molecule inhibitors for cancer treatment

Manni Wang, Yu Liu, Yuan Cheng, Yuquan Wei, Xiawei Wei*

Laboratory of Aging Research and Nanotoxicology, State Key Laboratory of Biotherapy and Cancer Center, National Clinical Research Center for Geriatrics, West China Hospital, Sichuan University, No. 17, Block 3, Southern Renmin Road, Chengdu, Sichuan 610041, PR China

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ABSTRACT

Initially understood for its physiological maintenance of self-tolerance, the immune checkpoint molecule has recently been recognized as a promising anti-cancer target. There has been considerable interest in the biology and the action mechanism of the immune checkpoint therapy, and their incorporation with other therapeutic regimens. Recently the small-molecule inhibitor (SMI) has been identified as an attractive combination partner for immune checkpoint inhibitors (ICIs) and is becoming a novel direction for the field of combination drug design. In this review, we provide a systematic discussion of the biology and function of major immune checkpoint molecules, and their interactions with corresponding targeting agents. With both preclinical studies and clinical trials, we especially highlight the ICI + SMI combination, with its recent advances as well as its application challenges.

1. Introduction

The immune checkpoint system has been recognized as a promising therapeutic target in cancer treatment [1]. Initially understood for its physiological maintenance of self-tolerance, immune checkpoint molecules protect tissues from the damage caused by the immune system during pathogenic infections [2,3]. However, taking advantages of this immune suppression mechanism, tumor cells evade immune clearance activities mediated by CD4+ and CD8+ T cells. It has been suggested that high expression of inhibitory receptors on antigen-specific T cells within the tumor microenvironment leads to immune unresponsiveness, decreased cell proliferation and reduced cytokine secretion [4,5]. With the participance of regulatory T cells (Tregs) in immune suppression and immune tolerance, the elimination of cancer cells appears to be even more challenging [6,7]. Previous reports have emphasized the application of T cells in the manipulation of endogenous anti-tumor immunity. The immune response of T cells is initiated through antigen recognition by the T cell receptor (TCR), the magnitude of which is balanced by co-stimulatory and inhibitory signals [8]. CD8+ effector T cells, also referred to as cytotoxic T lymphocytes (CTLs), are able to selectively recognize and kill antigen-expressing cells, whereas CD4+ helper T cells can integrate diverse immune responses[9]. Thus, by targeting immune-suppressive receptors expressed on activated T cells and natural killer (NK) cells, novel immune therapies have aimed to release this immune suppression and reactivate cytotoxic T cells to attack tumor cells. Although cytotoxic T lymphocyte antigen 4 (CTLA-4), and programmed cell death 1/programmed cell death 1 ligand (PD-1/PDL-1) are the 2 furthest-studied immune checkpoints, many other

Abbreviations: Small-molecule inhibitor, (SMI); immune checkpoint inhibitor, (ICI); regulatory T cells, (Treg); T cell receptor, (TCR); cytotoxic T lymphocytes, (CTL); natural killer, (NK); cytotoxic T lymphocyte antigen 4, (CTLA-4); programmed cell death 1, (PD-1); programmed cell death 1 ligand, (PD-L1); dendritic cells, (DC); immunohistochemistry, (IHC); antigen-presenting cells, (APC); Lymphocyte activation gene 3, (LAG3); tumor-associated macrophages, (TAM); chimeric antigen receptors, (CAR); TIM-3, (T cell membrane protein 3); T helper 1, (TH1); VISTA, (V-domain immunoglobulin suppressor of T-cell activation); KIR, (killer cell immunoglobulin-like receptor); A2aR, (A2a adenosine receptor); TIGIT, (T cell immunoglobulin and ITIM domains); DR3, (Death receptor 3); TNF-like ligand 1A, (TL1A); lymphoid tissue inducer cells, (LTi); GITR, (glucocorticoid-induced tumor necrosis factor receptor-related protein); ICOS, (inducible T-cell co-stimulator); T follicular helper cells, (Tfh); monoclonal antibodies, (mAb); HNSCC, (squamous cell carcinoma of the head and neck); colorectal cancers, (CRC); microsatellite instability, (MSI); mismatch repair gene, (MMR); acute myeloid leukemia, (AML); chronic lymphocytic leukemia, (CLL); non-Hodgkin's lymphoma, (NHL); diffuse large B-cell lymphoma, (DLBCL); PFS, (progression-free survival); infusion-related reaction, (IRR); metastatic renal cell carcinoma, (mRCC); myeloid derived suppressor cell, (MDSC); DNA methyltransferase inhibitor, (DNMTi); histone deacetylase, (HDAC); Indoleamine 2,3-dioxygenase 1, (IDO1); 1-methyl-tryptophan, (1-MT); PARP, (poly ADP ribose polymerase); Mantle cell lymphoma, (MCL); chemokine receptor 4, (CXCR4); TGFβ, (transforming growth factor-beta)

* Corresponding author.
E-mail address: xiaweiwei@scu.edu.cn (X. Wei).

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checkpoints are currently being investigated for their potentials to improve the anti-tumor immunity.

There has been considerable interest in the biology and the action mechanism of the immune checkpoint inhibitor (ICI), and their incorporation with other therapeutic regimens. Recently the small-molecule inhibitor (SMI) has been identified as an attractive combination partner for ICIs and is gradually becoming an important direction for the field of combination drug design. In this review, we provide a systematic discussion of the biology and function of major immune checkpoint molecules, and their interactions with corresponding targeting agents. With ongoing clinical trials presented below, an expanding repertoire of ICIs combined with SMIs will soon be developed to increase the clinical efficacy of the immune checkpoint therapy.

2. The expression profiles and action mechanism of immune checkpoint molecules

2.1. PD-1 and its ligands

Programmed cell death-1 (PD-1), also known as CD279, is one of the most comprehensively-studied immune checkpoints that suppress the excessive immune response and thus prevent autoimmunity [10]. It is a member of the immunoglobulin superfamily and the extended CD28/CTLA-4 family [11]. One thing that makes PD-1 different from other members of CD28/CTLA-4 family is the lack of an extracellular cysteine residue avoiding the formation of covalent dimers [12]. Though the precise structure of human PD-1/PD-L1 and PD-1/PD-L2 complexes remains incompletely defined, some studies have suggested a high degree of similarity between mouse and human PD-1 as for the structure and the way of ligand-binding [13–15]. More efforts are warranted to figure out the crystal structures of human PD-1 and the PD-1/PD-L1 and PD-1/PD-L2 complexes to provide additional targeting options.

PD-1 can be expressed on a broad panel of immune cells including T lymphocytes (CD4− CD8− thymocytes and peripheral CD4+ and CD8+ T cells), B lymphocytes, natural killer (NK) T cells, activated monocytes, and dendritic cells (DCs) [12,16,17]. Persistent stimulation and deficient CD4+ T cell can lead to T cell exhaustion[18] and the malfunction of exhausted CD8 T cells results in reduced secretion of cytolysins and inflammatory cytokines[19,20]. PD-1 is also expressed on the CD4+ regulatory T cell (Treg) which is also known as the immune suppressor T cell. Along with CD3 and TGF-β, the ligation of PD-1 receptor on Tregs promotes the de novo transformation of naive CD4+ T cells to Tregs which enhances immune suppression [21,22]. This simultaneous inhibition by PD-1 including a reduced function of effector T cells and an increased function of immunosuppresive T cells effectively manipulates the over-activation of T cells. In addition to T cells, PD-1 expression can also be observed on B cells which is usually undetectable at the early stages and then elevated during the course of differentiation [23]. Previous research has identified an enhanced antigen-specific antibody response following the use of PD-1 blockade on B cells, suggesting the role of PD-1 in inhibiting B cell clonal responses [24]. Some recent researches applied the immunohistochemistry (IHC)-based bioassays to detect PD expression at protein and mRNA levels, but failed to reach a consensus on the cut-off points. Further assessments of PD expression on tumor cells and tumor-infiltrating T cells are needed to help shape clinical decisions [25–27].

The ligands of PD-1 include PD-L1 (also known as B7-H1, CD274) [10,28] and PD-L2 (also known as B7-DC, CD273) [29,30]. However, apart from PD-1, PD-L1 can also bind to B7-1 (CD80) [31] and PD-L2 can bind to repulsive guidance molecule B (RGMb) [32]. The expression of PD-L1 on T cells, B cells, endothelial and epithelial cells can be upregulated by cytokines such as IFN-γ and TNF-α, which helps maintain the peripheral tolerance [17]. Unlike PD-L1, the expression of which can be induced on both hematopoietic and non-hematopoietic cells, PD-L2 is strictly expressed on DCs, macrophages, mast cells, and certain B cells in response to IL-4 and IFN [33]. Although recent researches have demonstrated that PD-L1 may deliver a negative signal for T cell proliferation and activation [10], the exact mechanism of the inhibition of PD-L1 and PD-L2 in T cell activity is yet to be elucidated. It may involve the increased programmed cell death caused by the binding of PD-1 to PD-L1 [12]. One study found that PD-1 antibodies could not prevent either co-stimulation or apoptosis of T cells, suggesting that co-stimulation and apoptosis by PD-L1 might be mediated by other receptors rather than PD-1 [34].

2.2. CTLA-4

CTLA-4 (cytotoxic T-lymphocyte-associated antigen 4), also known as CD152, is constitutively expressed on regulatory T cells and upregulated on activated CD8+ effector T cells. It functions through binding to its ligands, CD80 (B7-1) or CD86 (B7-2) on the surface of antigen-presenting cells (APC) [35,36]. The process of T-cell activation involves multiple activating signals. CD28, which is expressed on T cells, binds to the same ligands of CTLA-4, offering an important co-stimulatory signal for further T cell activation after the TCR signaling [37–39]. Given that CTLA4 has higher affinity than CD28 to their mutual ligands, the competitive binding between CTLA-4 and B7-1/B7-2 diminishes the CD82-mediated T cell activation [40–42]. Additionally, CTLA-4/B7 ligation actively produces inhibitory signals that antagonize the stimulatory signals by CD28/B7 or TCR/MHC binding [43,44]. This inhibition by CTLA4 to keep T cell activation in check is well illustrated by the immune hyper-activation observed in CTLA-4-knockout mice [45,46]. Several mechanisms have been proposed for this immune suppression, one of which involves the disruption of cell-cycle progression by CTLA-4 [47,48]. Another possible explanation is that CTLA-4 increases T cell motility leading to unstable conjugation between T cells and APCs, ultimately suppressing cell proliferation and cytokine production [49].

On the other hand, CTLA-4 is also involved in the immune regulation of CD4+ T cells. Though CTLA4 is expressed on activated CD8+ effector T cells, it appears to act through two major subtypes of CD4+ T cells: down-regulating the activity of helper T cells and amplifying immunosuppression of Tregs [50–52]. Treg cells are able to control effector T cells through the down-regulation of B7 ligands for co-stimulation [51,53–55]. Previous studies also reported that the Treg-specific CTLA4 knockout or blockade could dramatically decrease the regulation of both auto-immunity and anti-tumor immunity [51,52]. Therefore, in the light of mechanism of CTLA4 inhibition, both enhancement of CTLA-4/B7 binding and inhibition of Treg-dependent immunosuppression can be potential cancer treatment.

2.3. Other immune checkpoint molecules

CTLA-4 and PD-1 represent the two furthest-studied immune checkpoints, and at the same time many other immune checkpoint molecules are being investigated as potential therapeutic targets to improve anti-tumor responses. The overview of multiple co-stimulatory and inhibitory immune checkpoint molecules that regulate T cell responses and their ligand-receptor interactions are presented in Table 1 and Fig. 1.

Lymphocyte activation gene 3 (LAG3 or CD223) has been described as one of the immune inhibitory receptors (IRs) expressed on activated human T and NK cells[56]. It not only acts as an enhancement of Treg cells [57,58], but also inhibits the function of CD8+ effector T cells [59]. In this way, LAG3 works as a negative regulator to prevent the exacerbation of a number of autoimmunity diseases. Persistent co-expression with other inhibitory receptors such as PD1 in tolerogenic environments leads to a state of immune exhaustion, characterized by decreased proliferation, cytokine release and cytolytic activities [60–62]. Noteworthy, PD1 and LAG3 are often simultaneously expressed on tumor-infiltrating CD4+ and CD8+ T cells in melanoma, colon adenocarcinoma and fibrosarcoma[63]. It is therefore

Table 1
The function of the immune checkpoint pathway discussed in this review, and the development of its related target therapy.

Immune checkpoint	Function	Target therapy	Development status[a]	Clinical trials[b]
CTLA-4	Inhibitory	Ipilimumab	FDA approved for melanoma; RCC and MCC (with nivolumab)	NCT01515189, NCT02279732, NCT00324155, NCT01450761, NCT02279732, NCT01057810
		Tremelimumab	Phase III trial in multiple solid malignancies in combination with durvalumab	NCT00257205, NCT03084471, NCT02453282, NCT03703297
PD-1	Inhibitory	Nivolumab	FDA approved for melanoma; HCC; HNSCC; RCC; UC; HL; MCC; NSCLC	NCT02596035, NCT02066636, NCT03635983, NCT03195491,
		Pembrolizumab	FDA approved for cervical cancer; Gastric or gastroesophageal junction cancer; PMBCL; Melanoma; UC; HL; NSCLC; HNSCC	NCT03553836, NCT03486873, NCT03260894, NCT03062358, NCT02684292, NCT03358472, NCT02494583
		Pidilizumab	Phase II trial in DLBCL and myeloma	NCT02077959, NCT00532259
		AMP-224	Phase I trial in multiple cancers including MCC	NCT02298946, NCT01352884
		TSR-042	Phase III trial in ovarian cancer (with niraparib) and pahse I trial in solid tumors (with bevacizumab)	NCT02715284, NCT03602859, NCT03307785, NCT03574779
PD-L1	Inhibitory	BMS-936559	Phase I trial in melanoma and hematogic malignancies	NCT02028403, NCT00729664
		Atezolizumab	FDA approved for bladder cancer; Lung cancer; UC	NCT02928406, NCT03148418, NCT03285763, NCT03125902
		Durvalumab	FDA approved for NSCLC; Bladder Cancer	NCT03706690, NCT03084471, NCT02516241, NCT03164616
		Avelumab	FDA approved for UC; Merkel Cell Carcinoma; Ovarian Cancer (with entinostat)	NCT02926196, NCT02625623, NCT02603432, NCT02999087
		CA-170	Phase I trial in advanced solid tumors or lymphomas	NCT02812875, NCT01288911
		BMS-936559	Phase II trial in gastric cancer, RCC and hematologic neoplasms	NCT02028403, NCT00729664
		BMS-1001	No clinical trial available	
		BMS-1166	No clinical trial available	
LAG3	Inhibitory	IMP321	Phase I/II trial in breast cancer, melanoma,RCC	NCT02614833, NCT00351949, NCT02676869
		BMS-986016	Phase II trial in hematogic malignancies as monotherapy, and in RCC, gastric cancer and NSCLC in combination with nivolumab	NCT02061761, NCT03493932, NCT03642067, NCT03607890
B7-H3	Inhibitory	Enoblituzumab	Phase I/II trial in prostate cancer, melanoma, head and neck Cancer	NCT02982941, NCT02475213
B7-H4	Inhibitory			
VISTA	Inhibitory	JNJ-61610588	Phase I clinical trial terminated	NCT02671955
		CA-170	Phase I trial in advanced solid tumors or lymphomas	NCT02812875, NCT01288911
KIR	Inhibitory	Lirilumab	Phase I/II trial in multiple solid tumors (with nivolumab) and CLL (with rituximab) and hematological malignancies	NCT03341936, NCT02481297, NCT02399917, NCT02252263
		IPH2101	Phase II clinical trial in multiple myeloma	NCT00999830, NCT01248455
A2aR	Inhibitory	NIR178	Phase II clinical trial in multiple solid tumors and DLBCL (with anti-PD-1)	NCT03549000, NCT03207867, NCT03742349
		AZD4635	Phase II clinical trial in NSCLC (with oleclumab)	NCT02740985, NCT03381274, NCT03710434
TIGIT	Inhibitory	MTIG7192A	Phase I/II trial in advanced tumors (with atezolizumab)	NCT02794571, NCT03563716
		OMP-313 M32	Phase I trial in advanced tumors (with nivolumab)	NCT03119428
TIM3	Inhibitory	MBG453	Phase II trial in advanced malignancies	NCT03066648, NCT02608268
		TSR-022	Phase I trial in multiple solid tumors	NCT03680508, HYPERLINK NCT02817633, NCT03307785
4-1BB	Co-stimulatory	Urelumab	Phase II trial in solid tumors and NHL (with nivolumab) and CLL (rituximab)	NCT02253992, NCT01471210, NCT01775631
		Utomilumab	Phase III trial in DLBCL and phase II trial in inmultiple malignancies (with avelumab)	NCT03258008, NCT03440567, NCT02951156
OX40	Co-stimulatory	INCAGN01949	Phase II trial terminated	NCT02923349, NCT03241173
		PF-04518600	Phase II trial in AML, kidney cancer and other malignancies (with other immunotherapy)	NCT03092856, NCT03390296, NCT03217747, NCT03636503
		MEDI0562	Phase I/II trial in ovarian cancer, HNSCC and head and neck cancer	NCT03336606, NCT02318394, NCT02705482, NCT03267589
CD27	Co-stimulatory	Varlilumab	Phase II trial in solid tumors (with nivolumab) and B-cell Lymphoma (with rituximab)	NCT03307746, NCT02335918, NCT02270372 NCT03688178, NCT03038672
CD70	Co-stimulatory	ARGX-110	Phase I/II trial in advanced malignancies	NCT03030612, NCT02759250, NCT01813539
DR3	Co-stimulatory			
GITR	Co-stimulatory	MK-4166	Phase I trial in solid tumors (with pembrolizumab)	NCT02132754, NCT03707457
		TRX518	Phase I trial in malignant melanoma as monotheray or with pembrolizumab/nivolumab	NCT02628574, NCT01239134
		INCAGN01876	Phase I/II trial in advanced malignancies as monotheray or with ipilimumab/nivolumab	NCT02697591, NCT03277352, NCT03126110
ICOS	Co-stimulatory	BMS-986226	Phase II trial in solid tumors alone or in combination With nivolumab or ipilimumab	NCT03251924

PD-1 (programmed cell death-1), CTLA4 (cytotoxic T-lymphocyte-associated antigen 4), FDA (US Food and Drug Administration), LAG3 (lymphocyte activation gene 3), PD-L1 (PD-1 ligand), TIM-3 (T cell membrane protein 3), VISTA (V-domain immunoglobulin suppressor of T-cell activation), KIR (killer cell immunoglobulin-like receptor), A2aR (A2a adenosine receptor), DR3 (Death receptor 3), ICOS (inducible T-cell costimulator), NSCLC (non-small cell lung cancer), CHL (classical Hodgkin lymphoma), HNSCC (squamous cell carcinoma of the head and neck), RCC (renal cell carcinoma), urothelial carcinoma (UC), HCC (hepatocellular carcinoma), CRC (colorectal cancer), MCC (metastactic colorectal cancer), PMBCL (primary mediastinal large B-cell lymphoma),UC (urothelial carcinoma), HL(Hodgkin lymphoma), DLBCL (diffuse large B-cell lymphoma), CLL (chronic Lymphocytic Leukemia), NHL (non-Hodgkin's lymphoma), AML(acute myeloid leukemia).

[a] As of August 2018.

[b] Only represent partial list of all relevant clinical trials.

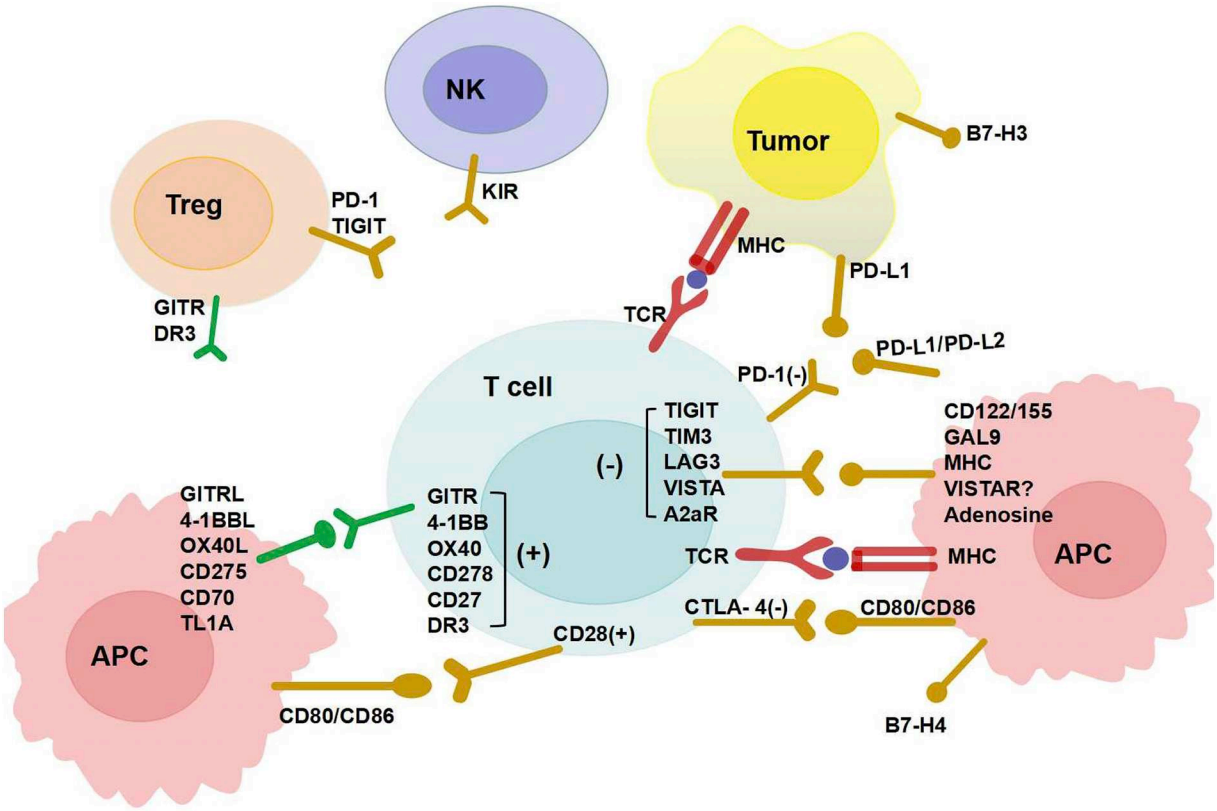

Fig. 1. Simplified overview of multiple co-stimulatory and inhibitory immune checkpoint molecules that regulate T cell responses and their ligand-receptor interactions.

Antigen-presenting cells (APCs) take up tumor antigens and regulate T cell responses through the interaction between the major histocompatibility complex (MHC) and the T cell receptor (TCR). Activated T cells upregulate inhibitory checkpoints such as CTLA-4 and PD-1 and suppresses T cell responses. Immune checkpoint therapies either block inhibitory immune checkpoint molecules, or upregulate co-stimulatory immune checkpoint molecules to enhance T cell responses. PD-1 (programmed cell death-1), CTLA4 (cytotoxic T-lymphocyte-associated antigen 4), FDA (US Food and Drug Administration), LAG3 (lymphocyte activation gene 3), PD-L1 (PD-1 ligand), TIM-3 (T cell membrane protein 3), VISTA (V-domain immunoglobulin suppressor of T-cell activation), KIR (killer cell immunoglobulin-like receptor), A2aR (A2a adenosine receptor), DR3 (Death receptor 3), ICOS (inducible T-cell costimulator), NSCLC (non-small cell lung cancer), CHL (classical Hodgkin lymphoma), HNSCC (squamous cell carcinoma of the head and neck), RCC (renal cell carcinoma), urothelial carcinoma (UC), HCC (hepatocellular carcinoma), CRC (colorectal cancer), MCC (metastactic colorectal cancer), PMBCL (primary mediastinal large B-cell lymphoma),UC (urothelial carcinoma), HL(Hodgkin lymphoma), DLBCL (diffuse large B-cell lymphoma), CLL (chronic Lymphocytic Leukemia), NHL (non-Hodgkin's lymphoma), AML(acute myeloid leukemia).

hypothesized that co-targeting PD1 and LAG3 could reverse the exhaustion of tumor-specific CD8+ T cells. Experiment results validated this coordinate T cell inhibition by PD1 and LAG3 with Pd1−/−LAG3−/− double-knockout mice, which rejected tumors in a T cell-dependent manner and ultimately developed autoimmune presentations [63]. LAG3 is highly homologous to CD4 in structure with adjacent gene location on chromosome[56] and shares the same ligand, MHC class II molecules, with CD4 but with a significantly higher affinity [64,65]. Given that the LAG3 cytoplasmic tailless mutants do not bind to MHC class II, the cytoplasmic domain of LAG3 is considered crucial to pass down the inhibitory signals [66,67]. Other ligands for LAG3 include Galectin-3 which is expressed on various cells except for the tumor cells and its ligation with LAG3 may modulate the anti-tumor immune response [68,69]. The interaction between LAG3 and another potential ligand, LSECtin, appears to reduce IFNγ production by antigen-specific effector T cells in melanoma microenvironment [70]. It is therefore reasonable to speculate that many more alternative ligands exist which may broaden the efficacy of LAG3 in or outside the immune system.

B7-H3, a member of the B7 family that is highly expressed on tumor cells[71–74], is able to inhibit CD4 T cell activation and effector cytokine production[75]. Due to the participance of B7-H3 in cancer immune escape [76], B7-H3 expression is suggestive of decreased number of T cells in the tumor microenvironment[77], tumor invasion [78] and metastasis[79], and poor prognosis[72] [80–82]. However, some studies have suggested the opposite conclusions that B7-H3 is actually a co-stimulatory molecule. It has been observed that B7-H3 promotes T-cell proliferation and IFN-γ production [83] and its overexpression on tumor cells can enhance anti-tumor immune reactions [84]. Despite this controversy, B7-H3 has mostly been considered as a down-regulator of the immune response. Enoblituzumab (MGA271) is an engineered anti-B7-H3 mAb(monoclonal antibody) with potent cellular cytotoxicity in various tumor types [85]. High level of B7-H3 expression is closely correlated with high percentage of FOXP3+ Tregs in NSCLC patients, predicting poor prognosis [86]. This leads to the hypothesis that co-targeting B7-H3 expression and Tregs can be a potential treatment strategy for cancer patients. Moreover, due to the high homology of B7-H3 to B7-H1, the concomitant blockade of B7-H1 and B7-H3 can be of great feasibility.

B7-H4 is another member of B7 family and is 25% homologous with other B7 molecules [87]. Previous studies on hH4, a human B7-H4 mAb, failed to detect surface B7-H4 expression on human T cells, B cells, monocytes or DCs [88]. Given that B7-H4 shuttles between the nucleus and cytoplasm [8], it is challenging to precisely evaluate cell surface B7-H4 expression on tumor cells and immune cells. Also, the different methodologies used in previous literature makes it difficult to reach a consensus on B7-H4 expression [89–91]. Recent studies explore the correlation between B7-H4 expression and tumor-associated macrophages (TAMs). Tregs promote the production of IL-6 and IL-10 by TAMs within the tumor microenvironment which in turn increases B7-

H4 expression on TAMs surface [89,91–93]. Moreover, IL-10 produced by TAMs could also enhance B7-H4 expression on tumor cells [91]. Growing evidence demonstrates that after binding to the unknown receptor on activated $CD4^+$ and $CD8^+$ T cells, B7-H4 impairs the T-cell function through cell cycle arrest, proliferation inhibition and decreased IL-2 secretion [94]. B7-H4 also takes part in tumor metastasis by facilitating local immune escape. In a metastatic breast cancer model, B7-H4 deficient mice have less infiltration of immunosuppressive cells such as TAMs and Tregs [95]. Though currently no clinical studies have specifically targeted B7-H4, some studies are addressing the design of anti-B7-H4-specific chimeric antigen receptors (CARs). CAR T cells have been successfully used in treating B-cell malignancies [96,97], but is not effective in some cancer types due to the lack of T-cell co-stimulatory domains in the CAR and the existence of inhibitory molecules such as B7-H4 [98,99]. It is therefore feasible to use CAR T-cell treatment to target B7-H4-expressing tumor cells or TAMs, and consequently clear immune suppressing cells from the tumor microenvironment.

TIM-3 (T cell membrane protein 3), on the other hand, inhibits T helper 1 (TH1) cell responses [100] and its antibodies have been found to potently enhance the anti-tumor immunity [101]. Previous studies have detected the co-expression of TIM-3 and PD-1 on tumor-infiltrating lymphocytes and have found that the simultaneous blockade of these two pathways could significantly augment anti-tumor immune responses where the inhibition of individual pathway displayed very modest effects [102–104].

VISTA (V-domain immunoglobulin suppressor of T-cell activation) is a recently-identified immune-checkpoint molecule with strong inhibitory activities in T-cell activation both in vitro and in vivo [105] [106]. VISTA is constitutively expressed on myeloid cells, CD4+, CD8+ T cells, and Foxp3 + CD4+ Treg cells. Antibodies targeting VISTA can induce autoimmune disease progression in the encephalomyelitis model, and boost anti-tumor immunity in multiple murine tumor models [107]. Although cells can often co-express multiple immune-checkpoint regulators, experimental evidence suggest that, VISTA and the PD-1/PD-L1 pathways nonredundantly control T-cell activation, indicating the potential of co-targeting these two pathways to promote the anti-tumor immunity [108].

KIR (killer cell immunoglobulin-like receptor) is an inhibitory receptor for classical MHC class I molecules (HLA-A, HLA-B, and HLA-C) and was initially regarded as crucial regulators of the killing activity of NK cells [109]. Preclinical studies reported that the anti-KIR mAb IPH2101 could augment NK-cell-mediated killing of tumor cells [110], and a phase I clinical study suggested the promising safety profile of an anti-KIR antibody lirilumab that potently blocked KIR [111]. The actual role of each individual KIR in NK cells and T cells remains poorly defined and recent researches mainly focus on the genetic analyses regarding the polymorphism of KIR and HLA (human leukocyte antigen) genes. The KIR gene is highly polymorphic and binds to different HLA, suggesting the functional balance underlying these selections [112]. Considering the diversity KIR, it is still unclear which of the large group of receptors to be targeted in order to block the NK cell-specific immune suppression.

A2aR (A2a adenosine receptor) is expressed on a variety of immune cell subsets and endothelial cells. It suppresses the immune activity of T cells partly by driving CD4+ T cells to express FOXP3 and to develop into Treg cells [113]. An accumulation of literature has identified the role of A2aR signaling in immune tolerance, which prevents tissue destruction during the T-cell-mediated inflammation [113–115]. Extracellular adenosines generated from tissue breakdown and hypoxia bind to A2a adenosine receptors, which is considered an important signaling pathway to protect tissues from the inflammatory injury [116–118]. In tumor models, A2aR−/− mice presented significantly stronger tumor rejection and better survival [119]. Clinical benefits and manageable toxicities of the A2AR antagonist NIR178 (PBF-509) were observed in clinical trials of NSCLC patients irrespective of their PD-L1 status [120]. AZD4635 is another potent and selective A2aR inhibitor and is able to reduce tumor burden and promote anti-tumor immune responses[121]. Moreover, combination of A2aR blockade with other immunotherapy displays stronger efficacy on tumor control [122] [123].

TIGIT (T cell immunoglobulin and ITIM domains) is a co-inhibitory receptor preferentially expressed on immune cells including NK, effector T, memory T cells and Tregs [124–128]. The two TIGIT ligands CD155 (PVR) and CD112 (PVRL2, nectin-2) are widely expressed on APCs, T cells and tumor cells [129,130]. This pathway resembles the B7-CD28-CTLA-4 pathway in that both positive and negative signals exist and form a balance of immune reaction. CD226 (DNAM-1) is the positive counterpart of TIGIT that binds to the same ligands and provides a co-stimulatory signal that enhances anti-tumor responses [131–133]. It was suggested that TIGIT not only can compete with CD226 for ligands but can also bind to CD226 directly to impair its homodimerization process [134]. A recent study found that TIGIT inhibition alone could restore CD8+ T cell immunity against multiple myeloma [135] and co-targeting TIGIT and other checkpoint receptors could be a promising anti-cancer therapy [136]. A growing number of clinical trials are currently assessing the combination of TIGIT blockade with ICIs in the treatment of advanced malignancies.

In addition to inhibitory immune checkpoint molecules, a number of co-stimulatory receptors are being studied. 4-1BB (CD137) positively regulates T-cell-mediated immunity by binding to its major ligand 4-1BBL [137]. Though 4-1BB was initially conceived to only be expressed on activated T cells, growing evidence demonstrates the wide distribution of 4-1BB on DCs, activated monocytes and NK cells [138–142]. 4-1BB/4-1BBL signaling ultimately leads to the increased production of IL-2 and IFN-γ, and the activity of antiapoptotic Bcl-2 family which prevents activation-induced T-cell death (AICD) [143–146]. This enhanced cytotoxicity effect of T-cell by 4-1BB was further verified with the observation that anti-4-1BB mAbs resulted in tumor clearance in several tumor models [147]. Two agonist antibodies of 4-1BB, urelumab and utomilumab, are currently under clinical evaluation with promising preliminary results in patients with lymphoma [148,149].

OX40 (CD134), a member of the tumor necrosis factor-receptor superfamily [150], is another co-stimulatory checkpoint molecule expressed on activated CD4+ and CD8+ T cells [151–153]. The binding of OX40 to its ligand OX40L promotes T cell proliferation, cytokine production and survival of antigen-specific memory T cells [154,155]. OX40 expression on colorectal cancer infiltrating cells is suggestive of favorable prognosis[156], and OX40-targeting immunotherapy may therefore be clinically beneficial[157,158].

The CD27/CD70 co-stimulatory system is an important immune regulator. CD27 is transiently elevated upon the activation of T cells, then sheds from the surface of activated T cells and becomes circulating soluble CD27, a hallmark of T-cell activation [159]. CD70 is the ligand for CD27 and exclusively expressed on various activated immune cells including DCs and NK cells [159–161]. Unlike other tumor necrosis factor receptor (TNFR) family members that have a proapoptotic death domain, CD27 and other co-stimulatory TNFRs carry certain motifs that can bind to adaptor molecules associated with the NF-κB and JNK signaling pathways [162]. These signaling pathways counteract apoptosis which helps co-stimulatory TNFRs provide survival signals in activated T cells [163–166]. Similar immune enhancement can be observed in CD70-expressing B cells that boosts anti-tumor response of $CD8^+$ T cells [167]. Moreover, unlike other co-stimulatory TNFRs that are only synthesized after T cell activation, CD27 is already expressed on naive $CD4^+$ and $CD8^+$ T cells [168,169].

DR3 (Death receptor 3) is a member of the TNFR superfamily. It is mainly expressed on Tregs, lymphoid tissue inducer cells (LTi), and NK cells, whereas its ligand TNF-like ligand 1A (TL1A) is expressed on endothelial cells and APCs [170]. Although it is referred to as a death receptor, DR3 signaling does not directly targets cell death. Similar to

another TNFR member CD27, it does not have a death-domain and it mediates cell death through NF-κB signaling pathways [171]. The activation of DR3/TL1A system could elicit pathogenic inflammation in several models [172]. This observation was validated by the use of αDR3, an agonistic mAb of DR3 which could promote Tregs expansion and hence prevent the occurrence of inflammation [173]. Though the mechanism of DR3/TL1A co-stimulation varies between T cell subtypes, it mainly increases IL-2 secretion and promotes T cell proliferation in an IL-2-dependent manner [174–176]. TL1A and DR3-deficient T cells have very subtle stimulation which requires the presence of antigen-presenting cells, suggesting that TL1A production by T cells is not sufficient to co-stimulate T cell activation [175].

The third member of the TNFR superfamily, GITR (glucocorticoid-induced tumor necrosis factor receptor-related protein) or TNFRSF18, is expressed on human NK cells and T cells [177–181] and the expression is markedly elevated upon T-cell activation. After binding to its ligand (GITR-L) expressed on APCs [182–184], GITR initiates a co-stimulatory signal that promotes the anti-tumor immune responses of antigen-specific T cells [185,186]. The GITR-L fusion protein (GITRL-FP) has recently been identified as a therapeutic strategy that augments anti-tumor responses in the presence of tumor-specific CD8 T cells [187] and when combined with murine OX40L-FP, this effect is further enhanced compared with the monotherapy [188]. Agonist anti-GITR antibodies such as a novel anti-GITR mAb MK-4166, have been found to suppress tumor growth or clear established tumors in mouse models[189–196], but whether human GITR agonists can achieve the same results needs to be further testified in human clinical trials [197]. Moreover, the co-administration of aGITR and aPD-1 mAbs in combination with a peptide vaccine significantly reduces tumor growth in the murine tumor model, pointing to the potential of dual aGITR/aPD-1 combination with cancer vaccines to combat poorly immunogenic tumors [198]. Currently several clinical trials are ongoing to evaluated the efficacy and safety of GITR agonists in combination with immune checkpoint inhibitors.

ICOS (inducible T-cell co-stimulator or CD278) is an inducible co-stimulatory member of the CD28 super-family, primarily expressed on activated CD4 cells. It promotes T-cell proliferation and cytokine production via ligation to its receptor ICOSL expressed on DCs, B cells and macrophages [199,200]. However, ICOS does not increase IL-2 production potentially leading to less co-stimulation potency than CD28 [201]. ICOS also plays a non-overlapping role in the functional differentiation of T follicular helper cells (Tfh), Th2 and Th17 lymphocytes [202–204]. A recent study provided new insights to the ICOS-related immune response by transfecting ICOS-specific siRNA into human T cells, and found that ICOS-mediated PI3K signaling was required for T-bet expression which controlled the Th1 genetic program for effective anti-tumor responses induced by anti-CTLA-4 therapy [205]. Therefore, ICOS may be an attractive target to enhance Th1 anti-tumor responses. When used as the vaccination or combined with CTLA-4 blockade, CD4 cells start to express ICOS, which promotes CTL-mediated anti-tumor immune response with the co-stimulation of natural ligands or agonist antibodies of ICOS [206]. No clinical trials have been performed to date to test the use of agonist ICOS antibodies in cancer, but this pathway has already been applied to the treatment of hypersensitivity and autoimmune diseases [207] [208].

3. Mechanisms and clinical applications of immune checkpoint therapy

The clinical success of anti-CTLA4 therapy, followed by preliminary application of anti-PD1 therapy, has encouraged more studies on the potential anti-tumor effect of an individual's endogenous immune system. Based on the action of mechanism stated above, the principle of immune checkpoint therapy is either to block inhibitory immune checkpoint molecules and the following transmission of the inhibitory signal, or to induce co-stimulatory checkpoint signals, boosting the anti-tumor immunity. Herein we discuss recent advances in the development of immune checkpoint therapy for cancer including single use of monoclonal antibodies (mAb), small molecule inhibitors and the combined therapy with other anti-tumor agents.

3.1. Immune checkpoint antibodies

3.1.1. CTLA-4 antibodies

Antibodies that inhibit CTLA4 counteract the inhibitory effects of CTLA-4 on anti-tumor or anti-self-antigen immune reactions resulting in immune stimulation. Previous studies suggested the striking anti-tumor activity of CTLA4 mAb monotherapy in mice [209–213]. However, in some tumor models, tumors with poor immunogenicity only respond to the combination of anti-CTLA4 with the GM-CSF-transduced vaccine rather than single use of anti-CTLA4 [214–216], suggesting that CTLA4 antibody alone can not induce a substantial immune reaction in poorly immunogenic tumors. Based on the preclinical evidence, two fully humanized CTLA4 antibodies, ipilimumab and tremelimumab, are now under clinical investigations.

Ipilimumab (MDX-010) was approved by US Food and Drug Administration (FDA) for the treatment of melanoma patients in 2011. A phase III clinical trial assessing the use of ipilimumab in prostate cancer has recently been completed. In this study, patients with castrate-resistant prostate cancer displayed progression though treated with chemotherapy and the observed survival benefit for patients receiving ipilimumab lacked statistical significance [217]. Two phase III clinical trials investigated the efficacy of ipilimumab in advanced melanoma and reported better overall survival in patients treated with ipilimumab [218,219]. Patients with ipilimumab monotherapy even showed better overall response rate than peptide vaccine plus ipilimumab. This anti-tumor response observed in melanoma patients was durable, with some of the treated patients living for more than 10 years [220].

One of the most common immune-related adverse events (irAEs) of ipilimumab is enterocolitis, with approximately 15% of ipilimumab-treating patients presenting grade III/IV enterocolitis [221]. Normally the ipilimumab-related colitis can be readily managed with the early use of corticosteroids and anti-TNF therapy, which does reduce the treatment efficacy of ipilimumab [222]. Other frequently observed irAEs include rash, hepatitis, hypophysitis, uveitis, pancreatitis and leucopenia [223–227]. In a phase I study, all responding patients with metastatic melanoma presented grade III/IV irAEs, whereas only 27% of non-responders had the same symptoms [228]. An increasing number of studies have found that grade III/IV toxicity is modestly correlated with higher rates of clinical response [229–231]. However, it does not necessarily mean that high grade irAEs guarantee effective responses.

Tremelimumab (CP-675206) is another CTLA4 inhibitory mAb undergoing a series of clinical trials in cancer patients. Though the first phase I dose escalation trial suggested a durable tumor response in melanoma patients with a follow-up of 10 years [232], a phase II study evaluating different dosing regimens of tremelimumab in metastatic melanoma revealed no significant difference in terms of response rate or survival [233]. Dacarbazine (DTIC) was the standard chemotherapy for patients with metastatic melanoma. A randomized phase III study compared tremelimumab with DTIC and demonstrated no significant survival benefit or increased response rates [234]. A more recent phase III trial also failed to demonstrate prognosis superiority of tremelimumab over standard chemotherapy in patients with metastatic melanoma [235]. On the other hand, a phase I dose escalation trial showed that tremelimumab plus gemcitabine were safe and brought prolonged OS in patients with metastatic pancreatic cancer [236]. The most common adverse events were skin rash and diarrhea, and the incidence increased with the administration of 10 mg/kg every 28 days, leading to the selection of 15 mg/kg every 90 days as the pivotal trial dosing regimen.

Numerous efforts have been undertaken to identify biomarkers that

predict clinical responses to anti-CTLA4 therapy. A retrospective study detected a better survival and a persistent increase in CD4+ high-ICOS T cells in melanoma patients treated with ipilimumab [237]. A similar association between anti-CTLA-4 therapy and marker expression could be observed in the cases of HLA-DR on CD4+ and CD8+ T cells and CD45RO on memory T cells, the expression levels of which are elevated after treatment with ipilimumab or tremelimumab [230,238,239]. The T helper 17 (Th17) cell, as a special subtype of CD4+ T cells, is characterized by its active role in promoting anti-tumor immunity [240–242]. Meanwhile, previous reports have emphasized that the CTLA-4 blockade can potentiate Th17 differentiation which provides a possible mechanism for CTLA-4 activities [243]. It was further supported by the fact that metastatic melanoma patients treated with tremelimumab, either alone or in combination with peptide pulsed DCs, exhibited increased number of Th17 cells [244]. Moreover, a phase II study identified the association of Th17 cells frequency with tumor relapse [245]. Advanced melanoma patients treated with ipilimumab had higher levels of Th17 cells and were less prone to tumor relapse. More future studies are warranted to establish a clear association between the pretreatment biomarker and clinical response to CTLA-4 blockade.

3.1.2. PD-1/PD-L1 antibodies

Nivolumab (MDX-1106 or BMS-936558) is a fully human IgG4 mAb to PD-1 with high-affinity, and has been approved by FDA for the treatment of a broad panel of malignancies including melanoma, NSCLC (non-small cell lung cancer), classical Hodgkin lymphoma, HNSCC (squamous cell carcinoma of the head and neck), RCC (renal cell carcinoma), urothelial carcinoma (UC), HCC (hepatocellular carcinoma), and CRC (colorectal cancer) [246–252][253]. An in vitro study of melanoma demonstrated that nivolumab added into human vaccine could enhance the expansion and functional capacity of CD8+ T cells that were specific to melanoma antigens [254]. Later in a randomized phase III study, nivolumab was found to correlate with higher rates of objective response than chemotherapy in ipilimumab-refractory melanoma patients [255]. Nivolumab has displayed good safety profile and long-lasting efficacy in a number of advanced solid tumors [256] [257] [246,258] and is currently under clinical trials in more cancer types. A phase II trial tested the efficacy of nivolumab in platinum-resistant ovarian cancer and suggested promising results [259]. Up to date, more than 350 trials have been registered to evaluate the efficacy and safety of nivolumab.

Pembrolizumab (MK-3475, lambrolizumab) is a humanized IgG4 PD-1 blocking mAb [260,261] approved by the FDA in 2014 for the treatment of advanced, unresectable or drug-resistant melanoma and metastatic non-small cell lung cancer. It is the first approved immunotherapy for NSCLC patients relapsed after chemotherapy. A phase I clinical trial evaluated the single use of pembrolizumab in patients with non-small cell lung cancer and found that the toxicity of pembrolizumab was well tolerated, with low rates of high grade adverse events. Moreover, in this study, a remarkably curative effect was observed in patients with higher expression of PD-L1 [262]. Pembrolizumab inhibits the ligation of PD-L1 to PD-1 and consequently exposes tumor cells to be recognized and killed by T cells, suggesting that PD-L1 expression levels can be used to determine the suitability of pembrolizumab [263]. A phase I clinical trial demonstrated that pembrolizumab could lead to a high rate of sustained tumor regression in patients with ipilimumab-pretreated melanoma [261]. In this study, doses ranged from 2 mg/kg every three weeks to 10 mg/kg every two weeks, with the highest response rate and highest AE frequency observed in the cohort of 10 mg/kg every two weeks. The AEs were mostly low grades, indicating good tolerability. Noteworthy, tumor biopsies in the regressing parts of tumors demonstrated highly infiltrating CTLs, reinforcing the proposed action mechanism of PD-1 blockade. However, although the cutoff for PD-L1 positivity was low, the anti-tumor activity could still be observed in tumors with low PD-L1 expression, which casted doubt upon the previous conclusion that PD-L1 expression could be used as a biomarker to predict the response to pembrolizumab.

Pembrolizumab has now been approved by FDA for the treatment of five more types of advanced malignancies including HNSCC (squamous cell carcinoma of the head and neck), urothelial carcinoma, Hodgkin's lymphoma[264], and gastric cancer[265], and has also demonstrated efficacy in Ewing's sarcoma and refractory large cell lymphoma of the mediastinum[266,267]. One special indication approved by FDA is any type of malignancy with high microsatellite instability (MSI) or mismatch repair gene (MMR) deficiency. A phase II study assessed the clinical efficacy of single agent pembrolizumab in progressive tumors with or without MMR deficiency [268], and found that MMR-deficient tumors were more sensitive to pembrolizumab regardless of their origin. MSI colorectal cancers (CRCs) have been observed with elevated expression of immune checkpoints including PD-1 and PD-L1 on tumor infiltrating lymphocytes, suggesting the potential mechanism of the efficacy of pembrolizumab in MMR-deficient tumors [269].

Pidilizumab (CT-011) is a humanized IgG-1 recombinant mAb and is also the first PD-1-targeting mAb to be tested in clinical trials [270]. It was initially conceived to bind B lymphoblastoid cell lines in mice, stimulating murine lymphocytes to inhibit tumor activity [271]. Pidilizumab is especially potent in various advanced hematological malignancies, which has been reported in the first phase I trial of pidilizumab involving patients with acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), non-Hodgkin's lymphoma (NHL), Hodgkin's lymphoma and multiple myeloma. In this study, pidilizumab exhibited durable response and good tolerance, and was later followed by two phase II clinical trials [272,273]. Furthermore, pidilizumab is the first drug used for the treatment of diffuse large B-cell lymphoma (DLBCL) [274], leading to the approval of FDA to initiate of the pivotal phase II trial in patients with DLBCL. These early success allows the investigation on the efficacy of pidilizumab in patients with autologous hematopoietic stem cell transplantation (AHSCT) [275]. Post-AHSCT DLBCL patients that were treated with pidilizumab displayed positive responses and prolonged PFS (progression-free survival) suggesting that PD-1 blockade with pidilizumab after AHSCT may be a promising therapeutic strategy for DLBCL [273]. Pidilizumab has also been studied in combination with rituximab in recurrent follicular lymphoma and displays effectiveness and good tolerance [272]. In addition to its efficacy in hematological malignancies, in a phase II clinical trial, pidilizumab could also bring clinical benefits to patients with metastatic melanoma [276]. The ipilimumab treatment history was used to stratify refractory melanoma patients and ultimately did not demonstrate significant association with response rates. The treatment was well tolerated, and the 1-year OS rate in each dose cohort was similar to that of nivolumab. Noteworthy, pidilizumab treatment has led to lower response rates in melanoma compared with nivolumab or pembrolizumab, suggesting the anti-tumor activity of pidilizumab being more specific to hematologic malignancies. Pidilizumab remains an investigational agent with a partial clinical hold on new drug application recently, which according to FDA, is not related to any safety concerns.

AMP-224 (B7-DC-Ig) is a recombinant fusion protein with the PD-L2 extracellular domain and Fc region that specifically targets PD-1 [277]. Preliminary evidence suggested that the murine form of this fusion protein could amplify the therapeutic efficacy of vaccines when combined with cyclophosphamide [278]. Unlike pembrolizumab or nivolumab that largely act by directly blocking the PD-1/PD-L1 interaction, AMP-224 decreases PD-1 overexpression on exhausted effector T cells and replenishes the T cell pool with functional T cells. Ongoing clinical trials (NCT01352884, NCT02013804) are underway to assess the safety and efficacy of AMP-224 in patients with advanced cancers [279], but it remains unclear whether these trials are moving forward considering the high rates of infusion reactions and lack of efficacy compared with other PD-1 blockade [280].

Atezolizumab (MPDL3280A) has been approved for the treatment of

advanced NSCLC and urothelial carcinoma, and exhibits acceptable tolerance and remarkable efficacy in several other solids tumors [281–286]. Atezolizumab selectively binds to PD-L1, other than PD-L2, to inhibit the downstream PD-L1/PD-1 pathway [287]. It was also suggested that across multiple cancer types, responses to atezolizumab could be seen in patients with high levels of PD-L1 expression on tumor infiltrating immune cells, indicating the underlying action mechanism of atezolizumab that the immune suppression by PD-L1 of patients was re-invigorated by antibody treatment [288]. A phase II clinical trial found that atezolizumab was more effective in UC patients with higher levels of PD-L1 expression on immune cells [281]. A phase I study reported the promising anti-tumor activity of atezolizumab in metastatic renal cell carcinoma (RCC) and the potential of PD-1 as a predictive and pharmacodynamic biomarker, with a higher response rate observed in patients with higher expression levels of PD-1 on tumor infiltrating immune cells [289]. Moreover, responses to atezolizumab were also correlated with other biomarkers in baseline tumor tissues, such as T-helper type 1 gene expression, CTLA4 expression and CX3CL1 deficiency [288].

Durvalumab (MEDI4736) is a humanized PD-L1 mAb with T cell dependent anti-tumor activity [290] and has been approved for treatment of advanced urothelial carcinoma[261]. In line with atezolizumab and durvalumab, it selectively blocks the interaction of PD-L1 with PD-1 and CD80, sparing PD-L2, and therefore prevents the previously-observed AEs of PD-L2 blockade [291–293]. Durvalumab is now being tested in various types of advanced solid tumors including NSCLC and melanoma and brings remarkable tumor shrinkage [294]. A recent study of durvalumab as consolidation therapy for stage III NSCLC suggested a significantly prolonged PFS in durvalumab cohort compared with the placebo cohort, and the occurrence of AEs were similar in two arms [295]. A phase I/II trial demonstrated desirable efficacy with acceptable safety profile in pretreated UC patients [296]. Moreover, this study also identified a subgroup of PD-L1-positive patients with favorable survival, suggesting the correlation of PD-L1 expression with treatment outcomes of durvalumab.

Avelumab (MSB0010718C) shares the same binding pattern with durvalumab and atezolizumab, specifically targeting PD-L1 and sparing PD-L2. As shown in the preclinical research, antibody-dependent cellular cytotoxicity (ADCC) is considered a potential mechanism of avelumab efficacy [297]. Previous reports have emphasized the promising clinical activity and manageable safety profile of avelumab in patients with refractory advanced solid tumors [298][299]. It has been approved for the treatment of advanced Merkel cell cancer and advanced UC [300,301]. Despite the rarity of Merkel cell carcinoma, more than 40% of patients present recurrence after initial treatment [302]. It was reported that avelumab monotherapy was well tolerated and induced a rapid and durable response in patients with chemotherapy-refractory Merkel cell carcinoma [301]. In another dose-expansion cohort trial, high grade adverse events of avelumab occurred in 44% of patients with advanced platinum-treated NSCLC [303]. The most common AEs included fatigue, infusion-related reaction (IRR) and nausea.

BMS-936559 (MDX-1105) is a fully human and PD-L1–specific mAb [304]. In a phase I trial beginning in 2008, BMS-936559 successfully induced tumor regression with an objective response rate of 6–17%, and led to durably stable disease in patients with multiple advanced cancers including non–small-cell lung cancer, melanoma, and renal-cell cancer [305]. BMS-936559 also displayed good safety profile with irAEs including rash, diarrhea, and endocrine disorders [306], mostly being grade 1 or 2 and manageable with treatment interruption or glucocorticoids. Though the preliminary trials present promising results, BMS-936559 does not appear to be further studied or developed by the manufacturer.

3.1.3. Other immune checkpoint inhibitors

Despite the remarkable progress made in the development of anti-CTLA-4 and anti-PD-1 antibodies, other immune checkpoint inhibitors are also currently under clinical investigation. The inhibitors described below only represent a partial list of all immune checkpoints agents.

LAG-3 is an inhibitory receptor and its antagonistic mAbs (e.g. BMS-986016) and fusion proteins (e.g. IMP321) are currently at different stages of evaluation. Clinical trials of BMS-986016 were initiated in 2013 including its combinational use with nivolumab. IMP321 was tested as monotherapy in patients with renal cell carcinoma and showed good tolerance and stabilization of disease in some patients [307]. IMP321 was further assessed in combination with paclitaxel chemotherapy in metastatic breast cancers and presented an objective response rate of 50% [308].

As for the co-stimulatory immune checkpoints, 9B12, a murine antibody of OX40, was tested in a phase I clinical trial which demonstrated acceptable toxicity and anti-tumor efficacy in a subset of patients with advanced cancers [157]. An OX40 mAb, MEDI6469 later entered clinical trials as either monotherapy or combination therapy to treat solid tumors and aggressive B-cell lymphomas. Urelumab (BMS-663513) is a fully humanized mAb of 41BB with encouraging anti-tumor activities in clinical trials of melanoma, renal cell carcinoma and ovarian cancer. However, with the obvious toxicity at higher doses, this drug needs further evaluation [309].

3.2. Small-molecule immune checkpoint inhibitors

Currently there are no small-molecule checkpoint inhibitors available on the market. Compared with that of monoclonal antibodies, the development of small-molecule therapy in the field of immune checkpoint blockade is lagging behind mainly due to the flat and highly hydrophobic PD-1/PD-L1 interaction surface that makes it difficult to act on [310]. CA-170, the first-in-class small molecule targeting both PD-1/PD-L1 and VISTA pathways has demonstrated clinical benefits in preliminary studies and is expecting the initiation of a phase II trial [311]. BMS-1001 and BMS-1166 represent two newly developed small-molecule compounds that bind to human PD-L1 and inhibits the PD-1/PD-L1 interaction in experiments with isolated proteins [312]. Based on this observation, BMS-1001 and BMS-1166 may attenuate the inhibitory effect of PD-L1 on TCR-mediated activation of T cells.

Although a large number of monoclonal antibodies targeting immune checkpoints have been developed, their high cost, instability and potential immune related toxicities have turned research interest to the investigation of small-molecule inhibitors. Compared with antibodies, small-molecule drugs can achieve higher concentration in the tumor microenvironment due to their relatively smaller weight and size. Moreover, small molecules do not induce immune rejection, which helps control adverse events. Therefore, it is of paramount importance to explore more small-molecule ICIs for cancer treatment.

3.3. Combination therapy

Combining ICIs with other treatments has long been perceived as an attractive field of research. Such strategies render cancer cells more immunogenicity via the release of immune-stimulating antigens by other treatments such as chemotherapy and radiation therapy [313].

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3.3.1. Combination of multiple checkpoint inhibitors

Based on the different inhibitory pathways of CTLA-4 and PD-1 on T cells, the combination therapy that targets both pathways may therefore augment the activity of each other by overcoming the limitations of each monotherapy. One proposed mechanism is that CTLA-4 inhibitors increase the number of T cells and IFN-γ level in the tumor microenvironment, which in turn induces PD-L1 expression and therefore better utilizes the benefit from anti-PD-1 and anti-PDL1 therapies. The combination of CTLA-4 and PD-1/PD-L1 blockade has exhibited anti-tumor efficacy in a preclinical models [314]. Ongoing clinical trials on the combination of ipilimumab or tremelimumab with nivolumab

highlight the encouraging efficacy in various cancer types including metastatic melanoma, advanced NSCLC and metastatic renal cell carcinoma (mRCC) [315–318]. One study found that ipilimumab/nivolumab combination therapy led to similar response with nivolumab monotherapy in PD-L1-positive patients, but acted more effectively in PD-L1-negative patients [247]. Recently, the tumor mutation burden has been reported to be a potential predictor for response to ipilimumab/nivolumab combination therapy in patients with NSCLC [319]. For example, nivolumab/ipilimumab combination can improve PFS of patients with unresectable or metastatic melanoma, and has now been approved for its treatment [320,321].

Compelling preclinical data suggest that the combination of durvalumab and tremelimumab simultaneously targets two nonredundant pathways to exert a synergistic effect[322]. A phase I dose-escalation study assessed this combination in patients with advanced NSCLC and reported manageable toxicity and anti-tumor activity irrespective of the PD-L1 status [323]. Currently the durvalumab/tremelimumab combination is under clinical investigation in unresectable HCC population [324].

Another synergistic blockade which targets LAG3 and PD1 can promote anti-tumor immunity in an ovarian cancer model by increasing the infiltration of CD4+ and CD8+ T cells, and IFNγ/TNFα-producing CD8+ T cells [325]. In a lymphoma model on the other hand, 100% of mice became tumor-free after receiving the dual blockade of anti-LAG3 and anti-PD-1, whereas only 50% of mice treated with the anti-PD1 monotherapy cleared their tumors and anti-LAG3 monotherapy mice only showed delayed tumor growth [325]. In a model of recurrent melanoma, concomitant inhibition of LAG3 and PD1 led to marked tumor regression [326]. All the above preclinical data indicates the synergistic interaction between LAG3 and PD1 which is still on the way to clinical trials.

3.3.2. Combination with chemotherapy, radiotherapy and surgery

In an attempt to achieve the maximal efficacy of cytotoxic chemotherapy, many studies are addressing the contribution of immune system in chemotherapy, with PD inhibitors recently being clinically evaluated in combination with chemotherapeutic agents [327]. Some chemotherapies can induce the immunogenicity of tumor cells, while some others are able to eliminate immunosuppressive cells within the tumor microenvironment. A study tested the safety and toxicity of nivolumab plus platinum-based doublet chemotherapy (PT-DC) as first-line treatment for advanced NSCLC and demonstrated promising anti-tumor activity, with a 2-year OS rate of 62% [328]. However, the AE-related treatment discontinuation was greater in the nivolumab/PT-DC combination, which warranted further evaluation. Meanwhile, pembrolizumab was also studied in combination with the carboplatin/pemetrexed-based DC for advanced NSCLC patients with no prior history of chemotherapy and no EGFR or ALK mutations [329]. The objective response rate (ORR) was significantly higher in the combination group compared with that of the pemetrexed group, whereas the occurrence of adverse events was similar. The achieved clinical success of this combination modality has led to the approval by FDA as first-line treatment for metastatic non-squamous NSCLC. For patients of early stages, a recent trial has been initiated to compare the nivolumab plus chemotherapy compared to chemotherapy alone in the treatment of early stage NSCLC and the outcome is expected to be reported in 2023 (NCT02998528).

A growing body of literature has demonstrated that local radiotherapy (RT) elicits the abscopal effect partially mediated by radiation-induced immunogenic cell death (ICD), leading to the anti-tumor T cell response [330]. It now becomes clear that RT can induce an adaptive immune response against malignant cells, mediating potent anti-tumor activities on non-irradiated lesions [331–333]. Based on substantial preclinical and clinical observations [334–337], we can assume that the additional use of radiotherapy can convert the unresponsiveness to CTLA-4 inhibitors and several clinical trials are under way to test radiotherapy plus ipilimumab [338–340]. Apart from ipilimumab, a wide range of mAbs aganist immune checkpoint regulators such as PD-1/PD-L1, are now under evaluation in combination with RT.

The CTLA-4 inihibitor ipilimumab has been approved by FDA as post-surgical adjuvant therapy for stage III melanoma. It is therefore intriguing to speculate that whether surgeries have immune modulatory functions on cancer patients, with the removal of the immunosuppressive tumor burden which allows for immune re-activation [341]. Previous studies has suggested that the addition of surgery into immune therapy can improve the survival of patients with metastatic RCC [342]. Several studies are assessing the combination of surgery and immune checkpoint blockade, such as the ongoing clinical trials assessing the effectiveness of the pre-surgical and post-surgical nivolumab/ipilimumab treatment for recurrent/advanced melanoma (NCT02736123, NCT02977052). These observations, along with the results yet to be published, establish a rationale for clinical application to add ICIs into the surgical treatment.

4. Combination of immune checkpoint therapy with small molecule inhibitors of other pathways

An increasing number of studies in recent years focus on the development of the combination therapy of ICIs with SMIs that target various pathways. Under certain circumstances, the lower production costs, higher tumor penetration, amenability of oral administration and immunogenicity-free property make small molecules superior over therapeutic antibodies [343]. However, the development of small-molecule therapy in the field of immune checkpoint blockade is lagging behind mainly due to the flat and highly hydrophobic PD-1/PD-L1 interaction surface that makes it difficult to act on [310]. Furthermore, SMIs produce rapid responses, but usually with limited duration, which can be prolonged through combining with ICIs. It is challenging to generalize the various functions of these SMIs, which largely depends on their targeting pathways. Herein in this review, we describe the advances of immune checkpoint therapies in combination with small molecule therapies, with already marketed drugs of both kinds and those under clinical assessment (Table 2).

4.1. EGFR (epidermal growth factor receptor) inhibitors

Although the EGFR TKI (tyrosine kinase inhibitor) can produce a rapid immune response in advanced EGFR mutant NSCLC, the modest response duration is its major problem. On the contrary, ICIs can induce durable anti-tumor activities but usually with low response rates. Therefore, combining of these two types of drugs may be a promising therapeutic option to overcome each other's limitations. The activation of EGFR pathway is potentially associated with tumor PD-L1 status based on a series of preclinical evidence that activating EGFR mutation can up-regulate PD-L1 expression in NSCLC, suggesting the potentially higher sensitivity of EGFR-mutant patients to anti-PD-1 therapy [344–346]. The correlation between high expression of PD-L1 and activating EGFR mutations was first identified with surgical specimens of NSCLC and was further validated by later publications [346,347], leading to the hypothesis that ICIs are especially effective in EGFR mutant NSCLC. However, recent studies have suggested the poor performance of ICIs among EGFR-mutant tumors, with lower response rates compared with EGFR wild-type NSCLC patients [348,349]. Given that a higher mutation burden is correlated with better clinical outcomes after ICI treatment [350,351], mechanisms underlying this diminished effect appear to involve the lower mutational load in EGFR-mutant tumors compared with EGFR wild-type NSCLC [352]. The low response rate was also considered to be attributed to the overexpression of CD73 in EGFR mutant NSCLC and the consequent immunosuppressive tumor microenvironment [353].

In addition to earlier discussion that activating EGFR mutation can up-regulate PD-L1 expression, EGFR TKIs were found to down-regulate

Table 2
Combination therapies of immune checkpoint inhibitors with small-molecule inhibtors.

Checkpoint inhibitor	Small-molecule inhibitor	Target	Population	Phase	Clinical trials
Nivolumab	Erlotinib	PD-1 + EGFR	NSCLC	II	NCT02039674
	Bevacizumab	PD-1 + VEGF	Metastatic RCC	I	NCT02210117
	Bevacizumab	PD-1 + VEGF	Peritoneal cancer, ovarian cancer, fallopian tube cancer	II	NCT02873962
	Temsirolimus	PD-1 + mTOR	Metastatic RCC	I/II	NCT02423954
	Bevacizumab	PD-1 + VEGF	Melanoma	I/II	NCT03167177
	Bevacizumab	PD-1 + VEGF	NSCLC	I/II	NCT03169738
	Axitinib	PD-1 + VEGFR	RCC	I/II	NCT03172754
	Axitinib	PD-1 + VEGFR	RCC	II	NCT03595124
	Vemurafenib, cobimetinib	PD-1 + BRAF,MEK	BRAF V600E/K mutated melanoma	II	NCT02968303
	Azacitidine	PD-1 + DNMT	NSCLC	II	NCT01928576
	IDO Peptide	PD-1 + IDO1	Metastatic melanoma	I/II	NCT03047928
	Indoximod	PD-1 + IDO1	Advanced melanoma	I/II	NCT02073123
	BMS-986205	PD-1 + IDO1	Advanced solid tumors	I/II	NCT03459222
	Galunisertib	PD-1 + TGFβR	Advanced solid tumors	I/II	NCT02423343
	TRX518	PD-1 + GITR	Malignant melanoma	I	NCT02628574
	INCAGN01876	PD-1 + GITR	Advanced malignancies	I/II	NCT03126110
	OMP-313 M32	PD-1 + TIGIT	Advanced malignancies	I	NCT03119428
Pembrolizumab	Pazopanib	PD-1 + VEGFR	Advanced RCC	I/II	NCT02014636
	Axitinib	PD-1 + VEGFR	Advanced RCC	I	NCT02133742
	Ziv-Aflibercept	PD-1 + VEGF	Advanced solid tumors	I	NCT02298959
	Gefitinib	PD-1 + EGFR	NSCLC	I/II	NCT02039674
	Bevacizumab	PD-1 + VEGF	Metastatic RCC	Ib/II	NCT02348008
	Bevacizumab	PD-1 + VEGF	Melanoma, NSCLC	II	NCT02681549
	Axitinib	PD-1 + VEGFR	RCC	III	NCT02853331
	Tenalisib	PD-1 + PI3K	CHL	I/II	NCT03471351
	Idelalisib	PD-1 + PI3K	NSCLC	I/II	NCT03257722
	INCB050465	PD-1 + PI3K	Advanced solid tumors	I	NCT02646748
	Binimetinib	PD-1 + MEK	Metastatic CRC	I	NCT03374254
	Binimetinib, encorafenib	PD-1 + BRAF,MEK	Malignant melanoma	I/II	NCT02902042
	Azacitidine	PD-1 + DNMT	Advanced solid tumors	I/II	NCT02959437
	Azacitidine	PD-1 + DNMT	Advanced melanoma	II	NCT02816021
	Azacitidine	PD-1 + DNMT	Carcinoma, NSCLC	II	NCT02546986
	Vorinostat	PD-1 + HDAC	RCC, urinary bladder neoplasms	I	NCT02619253
	Epacadostat	PD-1 + IDO1	GIST	II	NCT03291054
	Epacadostat	PD-1 + IDO1	Metastatic endometrial carcinoma	II	NCT03310567
	Epacadostat	PD-1 + IDO1	Urothelial carcinoma	III	NCT03361865
	Epacadostat	PD-1 + IDO1	Solid tumors	I/II	NCT02959437
	Epacadostat	PD-1 + IDO1	SCCHN	II	NCT03325465
	Epacadostat	PD-1 + IDO1	Head and neck cancer	III	NCT03358472
	Epacadostat	PD-1 + IDO1	UC	III	NCT03374488
	Epacadostat	PD-1 + IDO1	Advanced solid tumors	I/II	NCT03085914
	Epacadostat	PD-1 + IDO1	Metastatic pancreatic cancer	II	NCT03006302
	Epacadostat	PD-1 + IDO1	Metastatic NSCLC	II	NCT03322540
	Epacadostat	PD-1 + IDO1	RCC	III	NCT03260894
	Epacadostat	PD-1 + IDO1	Ovarian cancer	II	NCT03602586
	Indoximod	PD-1 + IDO1	Advanced melanoma	I/II	NCT02073123
	Niraparib	PD-1 + PARP	Advanced triple-negative BC, ovarian cancer	I/II	NCT02657889
	Ibrutinib	PD-1 + BTK	CLL	II	NCT03514017
	Ibrutinib	PD-1 + BTK	CLL, NHL	II	NCT02332980
	Ibrutinib	PD-1 + BTK	Refractory NHL	I	NCT02950220
	Ibrutinib	PD-1 + BTK	CRC	I/II	NCT03332498
	MK-4166	PD-1 + GITR	Advanced solid tumors	I	NCT02132754
	TRX518	PD-1 + GITR	Malignant melanoma	I	NCT02628574
PDR001	Dabrafenib, trametinib	PD-1 + BRAF,MEK	Melanoma	III	NCT02967692
	Everolimus	PD-1 + mTOR	Solid tumors	I	NCT02890069
	MBG453, decitabine	PD-1 + TIM-3 + DNMT	AML	I	NCT03066648
	NIS793	PD-1 + TGFβ	Solid tumors	I	NCT02947165
	Panobinostat	PD-1 + HDAC	Multiple tumors	I	NCT02890069
TSR-042	Bevacizumab	PD-1 + VEGF	Solid tumors	I	NCT03307785
	Bevacizumab	PD-1 + VEGF	Recurrent ovarian cancer	II	NCT03574779
	Bevacizumab	PD-1 + VEGF	Solid tumors and metastatic cancer	I	NCT03307785
	Bevacizumab	PD-1 + VEGF	Ovarian cnavcer	II	NCT03574779
	Decitabine	PD-1 + DNMT	Hodgkin lymphoma	I/II	NCT03250962
	Niraparib	PD-1 + PARP	Ovarian Cancer	II	NCT03574779
	Niraparib	PD-1 + PARP	Ovarian Cancer	III	NCT03602859
	Niraparib	PD-1 + PARP	Solid tumors	I	NCT03307785
Anti-PD-1 antibody	Decitabine	PD-1 + DNMT	Multiple maligancies	I/II	NCT02961101
	Niraparib	PD-1 + PARP	Lung neoplasms	II	NCT03308942
BGB-A317	BGB-290	PD-1 + PARP	Solid tumors	I	NCT02660034

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Table 2 (*continued*)

Checkpoint inhibitor	Small-molecule inhibitor	Target	Population	Phase	Clinical trials
JS001	Axitinib	PD-1 + VEGFR	Advanced kidney cancer and melanoma	I	NCT03086174
SHR-1210	SHR7390	PD-1 + MEK	Solid tumors	I	NCT03182673
	Decitabine	PD-1 + DNMT	Primary mediastinal large B-cell lymphoma	I/II	NCT03346642
	SHR9146	PD-1 + IDO1	Advanced solid tumors	I	NCT03491631
Avelumab	Axitinib	PD-L1 + VEGFR	Advanced RCC	I	NCT02493751
	Axitinib	PD-L1 + VEGFR	NSCLC	II	NCT03386929
	Axitinib	PD-L1 + VEGFR	Carcinoma, HCC	I	NCT03289533
	Axitinib	PD-L1 + VEGFR	UC, NSCLC	II	NCT03472560
	Axitinib	PD-L1 + VEGFR	Glioblastoma	II	NCT03291314
	Axitinib	PD-L1 + VEGFR	RCC	III	NCT02684006
	Bevacizumab	PD-L1 + VEGF	Merkel Cell Carcinoma	I/II	NCT03167164
	Bevacizumab	PD-L1 + VEGF	Melanoma	I/II	NCT03167177
	Bevacizumab	PD-L1 + VEGF	NSCLC	I/II	NCT03169738
	Bevacizumab	PD-L1 + VEGF	HNSCC	I/II	NCT03169764
	Bevacizumab	PD-L1 + VEGF	UC	I/II	NCT03197571
	Bevacizumab	PD-L1 + VEGF	SCC	I/II	NCT03387111
	Bevacizumab	PD-L1 + VEGF	Pancreatic cancer	I/II	NCT03136406
	Bevacizumab	PD-L1 + VEGF	Triple negative BC	I/II	NCT03175666
	Bevacizumab	PD-L1 + VEGF	NHL	I/II	NCT03169790
	Bevacizumab	PD-L1 + VEGF	Metastatic RCC	II	NCT03186326
	Talazoparib	PD-L1 + PARP	Advanced solid tumors	II	NCT03330405
Atezolizumab	Erlotinib	PD-L1 + EGFR	NSCLC	Ib	NCT02013219
	Bevacizumab	PD-L1 + VEGF	Solid tumors	I	NCT02174172
	Bevacizumab	PD-L1 + VEGF	Ovarian cancer, fallopian tube cancer, peritoneal neoplasms	III	NCT03038100
	Bevacizumab	PD-L1 + VEGF	Ovarian neoplasms	II	NCT02659384
	Bevacizumab	PD-L1 + VEGF	CRR with mismatch repair deficiency	III	NCT02997228
	Bevacizumab	PD-L1 + VEGF	Ovarian Cancer	III	NCT02891824
	Bevacizumab	PD-L1 + VEGF	Metastatic RCC	I	NCT03063762
	Bevacizumab	PD-L1 + VEGF	Ovarian cancer, fallopian tube cancer, peritoneal neoplasms	II/III	NCT02839707
	Bevacizumab	PD-L1 + VEGF	Breast neoplasms	I/II	NCT03280563
	Bevacizumab	PD-L1 + VEGF	UC	II	NCT03272217
	Bevacizumab	PD-L1 + VEGF	Advanced non-clear cell kidney cancer	II	NCT02724878
	Guadecitabine	PD-L1 + DNMT	CML	I/II	NCT02935361
	MTIG7192A	PD-L1 + TIGIT	Advanced tumors	I	NCT02794571
	MTIG7192A	PD-L1 + TIGIT	NSCLC	II	NCT03563716
Durvalumab	Gefitinib	PD-L1 + EGFR	NSCLC	I	NCT02088112
	Osimertinib	PD-L1 + EGFR	NSCLC	I	NCT02143466
	Osimertinib	PD-L1 + EGFR	T790 M mutation positive tumors	III	NCT02454933
	Bevacizumab	PD-L1 + VEGF	Solid tumors	I/II	NCT02734004
	Bevacizumab	PD-L1 + VEGF	Colorectal or pancreatic adenocarcinoma	I/II	NCT03376659
	Bevacizumab	PD-L1 + VEGF	Metastatic breast cancer	I	NCT02802098
	Bevacizumab	PD-L1 + VEGF	Glioblastoma	II	NCT02336165
	Guadecitabine	PD-L1 + DNMT	Solid tumors	I/II	NCT03308396
	Azacitidine	PD-L1 + DNMT	Lymphoma	I/II	NCT03161223
	Olaparib	PD-L1 + PARP	Triple negative BC	II	NCT02849496
	Olaparib	PD-L1 + PARP	Advanced solid tumors	I/II	NCT02734004
	Olaparib	PD-L1 + PARP	Advanced solid tumors	I/II	NCT02484404
	Olaparib	PD-L1 + PARP	Cancer with BRCA1/BRCA2 Mutation	I/II	NCT02953457
	Ibrutinib	PD-L1 + PARP	Refractory solid tumors	I/II	NCT02403271
Atezolizumab	Bevacizumab	PD-L1 + VEGF	Advanced RCC	I/II	NCT03024437
	Bevacizumab	PD-L1 + VEGF	Advanced RCC	II	NCT01984242
	Bevacizumab	PD-L1 + VEGF	Solid tumors	I	NCT02715531
	Bevacizumab	PD-L1 + VEGF	NSCLC	III	NCT02366143
	Bevacizumab	PD-L1 + VEGF	RCC	III	NCT02420821
	Bevacizumab	PD-L1 + VEGF	MSI-like CRR	II	NCT02982694
	Bevacizumab	PD-L1 + VEGF	Cancer	I	NCT01633970
	Bevacizumab	PD-L1 + VEGF	ER+, HER2- BC	II	NCT03395899
	Bevacizumab	PD-L1 + VEGF	Metastatic cervical cancer	II	NCT02921269
	Bevacizumab	PD-L1 + VEGF	Cervical carcinoma	III	NCT03556839
	Bevacizumab	PD-L1 + VEGF	Advanced ovarian cancer	II	NCT02659384
	GDC-0919	PD-L1 + IDO1	Solid tumors	I	NCT02471846
Anti-PD-L1/TGFβ fusion protein AM7824		PD-L1 + TGFβ	Advanced triple-negative BC	I	NCT03579472
		PD-L1 + TGFβ	BC	I	NCT03524170
LY3300054	LY3381916	PD-L1 + IDO1	Solid tumors	I	NCT03343613
Tremelimumab	Bevacizumab	CTLA-4 + VEGF	Colorectal cancer, liver metastases	I	NCT02754856
	Azacitidine	CTLA-4 + HDAC	Head and neck cancer	I/II	NCT03019003
	BMS-986205	CTLA-4 + IDO1	Advanced tumors	I/II	NCT03459222

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Table 2 (*continued*)

Checkpoint inhibitor	Small-molecule inhibitor	Target	Population	Phase	Clinical trials
Ipilimumab	Dabrafenib, trametinib	CTLA-4 + BRAF,MEK	Melanoma with BRAF V600E Mutation	I	NCT01940809
	Dabrafenib + / − trametinib	CTLA-4 + BRAF,MEK	Unresectable or metastatic melanoma	I	NCT01767454
	Vemurafenib, cobimetinib	CTLA-4 + BRAF,MEK	Melanoma with BRAF V600E Mutation	II	NCT02968303
	Entinostat	CTLA-4 + HDAC	Solid tumors	I	NCT02453620
	SGI-110	CTLA-4 + DMNT	Metastatic melanoma	I	NCT02608437
	Decitabine	CTLA-4 + DMNT	AML	I	NCT02890329
	INCAGN01876	PD-1 + GITR	Advanced malignancies	I/II	NCT03126110
	BMS-986205	CTLA-4 + IDO1	Advanced tumors	I/II	NCT03459222
	Indoximod	CTLA-4 + IDO1	Advanced melanoma	I/II	NCT02073123
	BMS-986205	CTLA-4 + IDO1	Advanced solid tumors	I/II	NCT03459222

PD-1 (programmed cell death-1), PD-L1 (PD-1 ligand), CTLA4 (cytotoxic T-lymphocyte-associated antigen 4), EGFR (epidermal growth factor receptor), VEGF (vascular endothelial growth factor), PARP (poly ADP ribose polymerase), DNMT (DNA methyltransferase), HDAC (histone deacetylase), IDO1 (indoleamine 2,3-dioxygenase 1), BTK (Bruton's tyrosine kinase), TGFβ (transforming growth factor-beta), NSCLC (non-small cell lung cancer), CHL (classical Hodgkin lymphoma), SCC (squamous cell carcinoma), HNSCC (squamous cell carcinoma of the head and neck), RCC (renal cell carcinoma), urothelial carcinoma (UC), HCC (hepatocellular carcinoma), CRC (colorectal cancer), UC (urothelial carcinoma), HL(Hodgkin lymphoma), CLL (chronic lymphocytic leukemia), NHL (non-Hodgkin's lymphoma), AML(acute myeloid leukemia), CML (chronic myelomonocytic leukemia), BC (breast cancer), GIST (gastrointestinal stromal tumors).

PD-L1 expression and exert an immune stimulatory effect [354,355]. EGFR TKIs such as erlotinib and gefitinib, can up-regulate the antigen presenting molecules, and enhance T cell-mediated killing and the susceptibility to NK cell-mediated lysis [356,357]. However, EGFR TKIs have also demonstrated immune suppressive activities. For example, erlotinib was found to disrupt T-cell-mediated immune response by inhibiting T-cell proliferation and activation [358], and at the same time, increase the circulating myeloid derived suppressor cells (MDSCs) which are considered to participate in tumor progression [359].

Researches on novel therapeutic approaches combining ICIs and EGFR TKIs have been conducted to improve the survival outcome of patients with EGFR mutant NSCLC. In a phase I trial, the gefitinib/durvalumab combination therapy exhibited a manageable safety profile and a promising objective response in TKI naive NSCLC patients that harbor EGFR mutations, supporting the subsequent in-depth studies on this combination [360]. Similar results could also be observed with the combination of erlotinib and atezolizumab in EGFR TKI naïve patients [361]. On the other hand, for patients that have previously been treated with EGFR TKIs and later developed drug resistance, erlotinib plus nivolumab can lead to an ORR of 15% and a 24-week PFS rate of 47% [362]. However, such strategies are limited due to the overlapping toxicities when used in combination. One example is osimertinib which exhibits significantly improved PFS compared with its EGFR TKI companions (e.g. erlotinib, gefitinib) in patients with EGFR-mutant advanced NSCLC [363]. Several trials have assessed osimertinib in combination with durvalumab (NCT02454933, NCT02143466), but are currently suspended for safety concerns. Further work will therefore aims to overcome adverse events induced by EGFR TKIs and ICIs, and search for the optimal dose of each agent.

4.2. VEGF (vascular endothelial growth factor)/VEGFR inhibitors

Previous studies showed that tumors could induce the sprouting of new blood vessels which is essential for tumor growth beyond 2–3 mm [364]. Anti-VEGF/VEGFR therapies including bevacizumab, sunitinib and axitinib not only inhibit sprouting angiogenesis, but also reduce the number of immunosuppressive cells including Tregs and MDSCs and promote T cell infiltration into the tumor microenvironment [365–371]. Furthermore, as demonstrated in preclinical mouse models, this T-cell infiltration could be enhanced by the concomitant inhibition of the VEGF and PD-1 pathways in a synergistic manner [372]. Another study has compared the concomitant use of anti-VEGF agent bevacizumab plus ipilimumab, with ipilimumab monotherapy for the treatment of metastatic melanoma patients. Compared with the monotherapy, the bevacizumab/ipilimumab combination can be safely administered and can influence the inflammation process, lymphocyte trafficking and immune regulation [373,374].

Recent clinical studies have suggested that the combination of PD-1/PD-L1 inhibitors (nivolumab or pembrolizumab) and anti-VEGF kinase inhibitors (sunitinib or pazopanib) has demonstrated promising anti-tumor activities in advanced RCC [375,376]. Preliminary results of a phase I study evaluated axitinib, a highly potent and selective inhibitor against the VEGFRs [377], in combination with the PD-L1 inhibitor avelumab, which exhibited anti-tumor efficacy with an acceptable safety profile in untreated RCC patients [378]. Similar efficacy and safety profile can be observed in the combination regime of axitinib and pembrolizumab in patients with untreated advanced RCC [379]. To identify whether the anti-VEGF/ICI combination acts better than a sequence of VEGF pathway inhibitors, a phase III trial has been initiated to compare axitinib/pembrolizumab combination with sunitinib monotherapy (NCT02853331) [380]. Of all the treatment combinations tested in clinical trials, the most intensively studied one is bevacizumab plus atezolizumab. A phase I trial assessed two different dosing regimens of this combination which were both well tolerated in entire solid tumor cohorts [381]. This combination was further tested in a phase II trial and phase III trial in comparison with each single agent in advanced RCC patients (NCT02420821, NCT01984242). On the other hand, the first clinically tested combination of CTLA-4 inhibitor tremelimumab and sunitinib was poorly tolerated, with the most common AE being renal failure [382]. The combination treatment of renal cell carcinoma has involved PD-1/PD-L1 inhibitors along with small-molecule kinase inhibitors, many of which are multi-kinase inhibitors with a wide range of unavoidable side effects [383]. Future studies are warranted to unravel the biology of anti-VEGF plus checkpoint inhibitor combinations to refine the toxicity profile and determine appropriate regimens for each subset of patients.

4.3. PI3K and MAPK pathway inhibitors

Previous studies have suggested that both PI3K-Akt-mTOR and RAS/RAF/MEK/MAPK pathways take part in the regulation of PD-L1 expression [384,385], indicating the potential of PI3K inhibitors (PI3Kis) and MEK inhibitors (MEKis) to combine with target therapies that modulate T cell functions. The BRAF inhibitor vemurafenib can increase the expression of T cell antigens in melanoma and thus promote the immune response of T cells [386,387]. Likewise, the PI3K-Akt-mTOR pathway is also involved in developing resistance to T cell-mediated killing by elevating the expression of anti-apoptotic proteins [388,389]. The PI3K pathway can be activated through the loss of the tumor suppressor protein PTEN, which frequently occurs in tumors with

the BRAFV600E mutation [390,391]. Although PTEN loss can attenuate the tumor response to BRAFis, it can also be overcome by the additional inhibition of PI3K-Akt-mTOR pathway [392,393].

Previous reports have emphasized the simultaneous blocking of CTLA-4 + PD-1/PD-L1 or BRAF + MEK, and each pair of combination has all been verified of anti-tumor activities in the treatment of advanced melanoma [321,394,395], leading to the notion of combining ICIs with BRAF/MEK inhibitors. It has been reported that MEK inhibitors before or after checkpoint inhibitor therapy could increase the survival benefit in patients with NRAS mutant melanoma [396]. Meanwhile, an enhanced anti-tumor efficacy of anti-PD-1 therapy has been observed when synergistically working with the BRAFi and MEKi in a BRAFV600E-mutated melanoma model [397]. Likewise, in a CT26 mouse colorectal carcinoma model, MEKis act more effectively in combination with anti-CTLA-4, anti-PD-1, and anti-PD-L1 blockade [398,399]. A more recent study suggested that when combined with PD-1 inhibitors, the short-term dual blockade of BRAF and MEK could promote tumor immune infiltration and improve tumor control in a CD8 T-cell-dependent way, which might be more effective than continuous combination therapy. The above experimental evidence provides a potential rationale for clinical testing of BRAF and/or MEK inhibition in combination with ICIs. To further validate this hypothesis, a phase II study is now under way to assess the pembrolizumab in combination with intermittent versus continuous use of BRAFi + MEKi (dabrafenib + trametinib) in patients with advanced melanoma (NCT02625337). Meanwhile, long-term analyses are needed to assess the potential cumulative toxicity of the combination therapy of each single agent [386,400]. Another concern is the systemic shutdown of PI3K and MAPK pathways caused by the T cell exhaustion, which then limits the effect of PD-1/PD-L1 inhibitors [33,401].

Some studies on the other hand, have shifted the interest to developing simultaneous inhibition of immune checkpoints and PI3K-Akt-mTOR pathway. In an in vitro model of peripheral T-cell non-Hodgkin lymphoma, the combination of Aurora kinase inhibitor alisertib and anti-PD-L1 agent led to a tumor growth inhibition of 90%, and the addition of a pan-PI3K inhibitor PF-04691502 into the combination achieved a 100% TGI [402]. To determine whether PI3K blockade interacts with immune checkpoint therapies, PI3Kγ inhibitors plus anti-PD-1 was administered and resulted in long-term tumor regression in in mice [403]. The selective targeting of PI3K–γ with a small molecule inhibitor IPI-549 (NCT02637531), can restore the tumor microenvironment and overcome resistance to ICIs by inducing cytotoxic T cell-mediated tumor regression [404]. This observation introduces an attractive strategy combining PI3Kis with ICIs to prevent resistance to immune checkpoint blockade. One or two agents targeting the PI3K-Akt-mTOR pathway could be a potential combination partner for immune checkpoint blockade [405], but it remains incompletely defined which combination is the most effective one.

4.4. DNMT (DNA methyltransferase) inhibitors and HDAC (histone deacetylase) inhibitors

As discussed earlier that the immune checkpoint therapy has achieved remarkable success in various caner types. However, the response of ovarian cancer to anti–PD-L1 antibody is limited, in contrast to the potent efficacy in melanoma, NSCLC and RCC. Novel therapeutic strategies are therefore needed to reverse the immune suppressive microenvironment of ovarian cancer. Given the frequent occurrence of DNA methylation alterations in HCC which are essential to the onset of disease progression [406–408], DNA methyltransferase inhibitors (DNMTis) have recently emerged to reverse the DNA hypermethylation and its related gene silencing. 5′-aza-2′deoxycytidine (decitabine) and 5-azacytidine (azacitidine) represent the first generation of DNMTis approved by FDA. Compared with DNMTi single treatment, the addition of an HDACis to DNMTis can largely enhance the above changes in immune microenvironment. HDACis are now used as a novel therapeutic approach for treatment hematological malignancies [409]. Likewise, DNMTis have also exhibited remarkable efficacy in the treatment of hematological malignancies including chronic myelomonocytic leukemia (CMML) and acute myeloid leukemia (AML) [410–412] and are recently evaluated in clinical trials for the treatment of solid tumors [413–415].

An accumulation of recent literatures have suggested that DNMTis can up-regulate various genes involved in the immune activities during cancer development [416–419] One example is the up-regulation of viral defense gene signature in both tumor and immune cells, leading to increased production of IFN [416,418]. Through the IFN signaling pathway, DNMTi azacitidine enhances the immune system by increasing the number of CD45+ immune cells and activated CD8+ T and NK cells in the tumor microenvironment, as well as reducing tumor burden and the number of immune suppressor cells in the tumor microenvironment [420]. However, the effect of HDACis such as panobinostat, vorinostat and entinostat, on immune cells remains poorly-defined. It has been suggested that HDACis induce an effective response of the immune system mainly composed of B cells [421]. Panobinostat not only elevates the level of the co-stimulatory molecule OX-40 on T cells but also stimulates an immune response through B cells [422]. Moreover, blocking HDACs decreases the number of cells associated with immune tolerance, reactivating the immune system to clear tumors [423].

With the exploration of the anti-tumor effectiveness of DNMTis or HDACis combined with immune checkpoint blockade, azacitidine/anti-CTLA4 combination display more effective tumor growth than monotherapy in the mouse model of melanoma [416]. Synergy of decitabine with anti-CTLA-4 therapy can also decrease tumor burden and improve the survival in the mouse model [424]. One possible mechanism for the enhancement of immune checkpoint therapy by DNMTis is the upregulation of immune suppressing molecules on tumor cellsincluding PD-L1, PD-L2, PD-1, and CTLA-4 on CMML, AML patients and NSCLC cell lines [413,425]. Recently, a triple combination of DNMTi/HDACi with anti-PD-1 agents exhibits promising anti-tumor effects and survival benefits in ovarian cancer. The synergy of anti-PD1 antibody nivolumab or pembrolizumab with azacitidine will be evaluated in advanced/metastatic NSCLC patients (NCT01928576, NTC02546986). And likewise, in a phase II study, decitabine plus nivolumab treatment will be compared for efficacy in NSCLC patients with nivolumab monotherapy (NCT02664181). The potential of pembrolizumab + entinostat combination is currently under assessment to treat metastatic eye melanoma, which includes the PFS and clinical beneficial rate as evaluation parameters (NCT02697630).

4.5. IDO1 (indoleamine 2,3-dioxygenase 1) inhibitors

Indoleamine 2,3-dioxygenase 1(IDO1) has long been identified with its role in immunosuppression, tolerance and tumor escape [426–428]. IDO1 is an intracellular enzyme involved in the first and rate-limiting step of tryptophan degradation along with two other enzymes, indoleamine 2,3-dioxygenase 2 (IDO2) and tryptophan 2,3-dioxygenase 2 (TDO) [429]. This IDO1-mediated depletion of tryptophan and downstream production of kynurenin renders tumor cells the ability to escape immune surveillance through the suppression of T cell activation [430]. IDO expression has not only been found in a wide variety of tumor cells [431,432], but also on a subset of DCs in tumor-draining lymph nodes [433]. CTLA-4 enhances IDO expression on regulatory DCs, which turns DCs into a quiescent state and thus impairs its ability to present antigens to T cells [434]. Moreover, IDO-expressing DCs prompt the transition of CD4C T cells into Tregs, which further suppresses anti-tumor activities of the immune system [435].

In recent years, IDO1 blockade is emerging as a novel anti-cancer therapy. Three small-molecule inhibitors of IDO1: 1-methyl-tryptophan (1-MT), NLG919 and epacadostat, are now being evaluated for treatment of a number of cancers including NSCLC and melanoma

[436–438]. Preclinical studies have reported that the IDO1 inhibitor 1-methyl-DL-tryptophan (1-MT) can promote T cell-dependent anti-tumor immunity and mediate tumor regression when combined with chemotherapy [439–441]. Recently a newly-devised small-molecule IDO1 inhibitor, LW106 has been found to potently control tumor outgrowth [442]. Given that IDO1 inhibitors lack effectiveness when used as single agent in cancer treatment, a recent study focuses on the combination of IDO inhibitors with the immune checkpoint blockade.

INCB024360 (Epacadostat) is a second generation IDO inhibitor [437] being tested in combination with ipilimumab in patients with advanced melanoma (NCT01604889) [443]. Preliminary results showed that the adverse events were reversible with steroids and treatment discontinuation, and that 6 out of 8 patients had their tumor reduced form imaging, suggesting the effectiveness of the IDO inhibitor/CTLA4 inhibitor combination in advanced melanoma. In another phase I/II trial of advanced melanoma, the D isomer of 1-MT indoximod combined with ipilimumab demonstrated encouraging anti-tumor activities without severe AEs (NCT02073123) [444].

4.6. PARP (poly ADP ribose polymerase) inhibitors

PARP (poly ADP ribose polymerase) takes part in DNA base excision repair, the inhibition of which has been proven highly effective in the treatment of tumors with germline mutation of DNA repair genes [445]. Hence the PARP inhibitor (PARPi) olaparib, was later approved by the FDA in 2014 for the treatment of advanced ovarian cancer with germline BRCA-mutation [446]. Another PARPi niraparib was later approved by the FDA for the treatment of recurrent platinum-sensitive ovarian cancer based on its marked prolongation of PFS [447].

Recently the interplay between PARP inhibition and immune checkpoint axis has been detected that PARPis can up-regulate PD-L1 expression in breast tumor cells both in vivo and in vitro [448]. Furthermore, PD-L1 inhibition could re-sensitize PARPi-treated tumor cells to T cell killing and the combination of PARPis with PD-L1 inhibitors demonstrated the highest efficacy in vivo compared with each agent used. Similar observation was reported in the combination regimen of PARPi and CTLA-4 blockade, leading to long-term survival in the BRCA1-deficient ovarian cancer model [449]. Mechanistically, such combination could induce anti-tumor immune responses and IFNγ production within the tumor microenvironment [449].

All the above preclinical data supports the combination of PARP inhibition with immune checkpoint therapy for cancer treatment [450]. The first report on the concomitant use of PD-L1 inhibitor durvalumab and PARPi olaparib has suggested that this combination therapy potently controls disease progression [451]. The subsequent phase II trial of durvalumab plus olaparib with biomarker evaluation is currently ongoing in patents with gBRCAm (germline BRCA mutated) platinum-sensitive relapsed ovarian cancer (NCT02734004). Thus PARPis/ICIs are intriguing combination therapy under investigation that can potentially deliver considerable benefit to patients of more cancer types [450].

4.7. Bruton's tyrosine kinase inhibitors

Depending on their expression on different cell lines, the Tec kinase family comprises a group of non-receptor kinases including the Bruton's tyrosine kinase (BTK), bone marrow-expressed kinase (BMX), redundant resting lymphocyte kinase (RLK) and IL-2 inducible T-Cell kinase (ITK). BTK is mostly expressed on, but not limited to B Cells, and ITK is mainly expressed on T Cells [452,453]. Ibrutinib (PCI-32765) is a small molecule that not only targets BTK which is essential for the survival of malignant B cells, but also blocks ITK to shift the Th1/Th2 balance and subsequently boosts antitumor immune activities [454,455]. It has been proven effective for the treatment of certain hematological malignancies including CLL, Mantle cell lymphoma (MCL) and Waldenstrom's Macroglobulinemia.

The synergistic anti-tumor activity of ibrutinib plus immune-checkpoint inhibitors has also been investigated in preclinical models and its promising therapeutic outcome does not result from the direct action against tumor cells, but rather from their effects on the immune system. Ibrutinib not only increases CD8+ T cells, decreases the cytokine secretion of MDSCs, but also impairs the inhibitory function of immune checkpoint molecules such as the PD1/PD-L1 and CTLA-4 axis on tumor infiltrating lymphocytes [456]. A recent study reported both in vivo and vitro antitumor activities of ibrutinib/anti–PD-L1 combination in A20 lymphoma and J558 myeloma models which highly expressed BTK [457]. In two solid tumor models with no BTK expression, 4 T1-breast cancer and CT26-colon cancer, the combination therapy also induced a delay in tumor growth and improved survival outcomes compared with each individual agent [457]. These preclinical evidences have indicated the necessity to test ICIs/ibrutinib combination in the clinic not only for the treatment of hematologic malignancies, but also solid tumors that do not even express BTK.

To date, such combinations are currently being explored in multiple clinical trials. Ibrutinib has been evaluated in combination with PD-1 blockade durvalumab in a number of refractory or relapsed solid tumors including NSCLC, breast cancer and pancreatic cancer (NCT02403271). This trial has been completed, but the results have not yet been published (clinicaltrials.gov). Other phase I/II studies assess the applicability and efficacy of ibrutinib in combination with nivolumab in patients with relapsed metastatic RCC (NCT02899078) or with pembrolizumab in patients with stage III-IV melanoma (NCT03021460). Though both ibrutinib and ICIs are well tolerated as single agents, one obstacle of developing this combination is the optimal dosing, timing, and sequencing of treatment.

4.8. Other small-molecule inhibitors

The chemokine receptor 4 (CXCR4), also referred to as “fusin”, is one of the most intensively-studied chemokine receptors and is known for its unique interactions with the endogenous ligand CXCL12 (or chemokine stromal cell-derived factor-1) [458] [459,460]. Multiple downstream signaling pathways can be activated upon the ligation of CXCL12 with CXCR4, leading to various responses including calcium release from intracellular storage, gene transcription, chemotaxis and cell proliferation [461]. The increase of intracellular Ca^{2+} then activates the MAPK pathway which further contributes to cell migration [462,463]. Meanwhile, CXCR4 also activates the PI3K pathway and phosphorylate multiple focal adhesion components [464,465]. After the homodimerization of CXCR4, the JAK/STAT pathway, along with other pathways, promotes the morphological change of cells for the chemotactic response [463,466]. Previous research found that in patients with hepatocellular carcinoma (HCC), the sorafenib treatment could induce tissue hypoxia and increased CXCR4 expression and the inhibition of the CXCR4 pathway impaired tumor growth despite the persistent tissue hypoxia [467]. More recently, a murine HCC model was used to identify CXCR4 inhibitors in combination with PD-1 blockade on tumor growth, pulmonary metastasis and the immune microenvironment following sorafenib treatment [468]. In this study, the addition of the anti-PD-1 agent into CXCR4 antagonist AMD3100 plus sorafenib therapy acts through promoting the infiltration of CD8 T cells. Although the preclinical results appear promising, it is challenging to translate this triple combination therapy into the clinic.

Mps1 (Monopolar spindle 1), also known as TTK protein kinase, is a dual-specificity kinase expressed in proliferating cells during mitosis [469]. It serves as a core component of the spindle assembly checkpoint (SAC), a surveillance mechanism that prevents chromosome mis-segregation [470]. The overexpression of Mps1 has been detected in various human cancers, and is reported to be associated with poor prognosis [471–473]. The inhibition of Mps1 can result in the premature exit of cells from normal mitosis process and thus cause chromosome mis-segregation, aneuploidy and eventually cell death [474–477]. CFI-

402257 is a selective Mps1 kinase inhibitor with consistent depletion of Mps1 in various human cancer cell lines [474,475,477]. A recent study suggested that in a mouse colon cancer model, the combination of CFI-402257 with the anti-PD-1 therapy could improve survival outcomes and lead to tumor regression, pointing to the feasibility of combination therapy of ICIs and Mps1 blockade [478].

TGFβ (transforming growth factor-beta) has long been identified as a pharmacological target based on its participance in tumor growth, survival and metastasis. The aim of the TGFβ-targeting strategies including antibodies, vaccines, antisense oligonucleotides and small-molecule inhibitors [479,480], is to inhibit the tumor-boosting effects of TGFβ, and at the same time keep its tumor-suppression function. Galunisertib (LY2157299 monohydrate) is a small-molecule inhibitor of TGFβ receptor I (TGFβRI) and is well-tolerated and active in patients with glioblastoma and pancreatic cancer [481,482]. To investigate the potential of galunisertib to work synergistically with ICIs, clinical trials (NCT02423343, NCT02734160) are ongoing to test this combination in patients with NSCLC, HCC and pancreatic cancer. A more recent study highlights the potential synergistic effects of co-targeting TGFβ and immune checkpoint pathway [483]. The combination of galunisertib with PD-L1 blockade has been found to more potently inhibit tumor growth in colon carcinoma models compared with anti-PD-L1 monotherapy through the upregulation of anti-tumor immune related genes.

5. Conclusions and future prospects

The clinical application of immune checkpoint therapies is rapidly expanding and revolutionizing anti-cancer immunotherapy. In this review, we provide an in-depth discussion of the biology and function of major immune checkpoint molecules, and their interactions with corresponding targeting agents. Furthermore, SMI + ICI combination has recently been identified as a novel direction in the field of combination drug design. The combinations discussed above only represent a partial list of SMI + ICI combination therapies, and with the increasing number of clinical trials, an expanding repertoire of this combination will rapidly be developed. Despite the durable efficacy that has been achieved with combination therapies, it is challenging to avoid both the overlapped and non-overlapped toxicities caused by two or more classes of drugs. Another challenge is the identification of potential biomarkers that can predict the clinical response to immune checkpoint therapies, such as high-ICOS expression as described above. Overall, the combination therapy of immune checkpoint inhibitors, especially with small-molecule inhibitors is an attractive strategy to improve therapeutic efficacy and more future studies are needed to identify more treatment options.

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Declarations of interest

None.

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