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REVIEW

Small-molecule agents for cancer immunotherapy

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Abstract Cancer immunotherapy, exemplified by the remarkable clinical benefits of the immune checkpoint blockade and chimeric antigen receptor T-cell therapy, is revolutionizing cancer therapy. They induce long-term tumor regression and overall survival benefit in many types of cancer. With the advances in our knowledge about the tumor immune microenvironment, remarkable progress has been made in the development of small-molecule drugs for immunotherapy. Small molecules targeting

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Oncogenic signaling;
Metabolic pathways;
Cytokine/chemokine signaling;
Antitumor immunity;
Tumor immune microenvironment

PRR-associated pathways, immune checkpoints, oncogenic signaling, metabolic pathways, cytokine/chemokine signaling, and immune-related kinases have been extensively investigated. Monotherapy of small-molecule immunotherapeutic drugs and their combinations with other antitumor modalities are under active clinical investigations to overcome immune tolerance and circumvent immune checkpoint inhibitor resistance. Here, we review the latest development of small-molecule agents for cancer immunotherapy by targeting defined pathways and highlighting their progress in recent clinical investigations.

1. Introduction

Cancer immunotherapy, which aims to control and eradicate tumors by reestablishing normal antitumor immune responses, has emerged as a strategy for cancer treatment with enormous potential. The history of cancer immunotherapy could be traced back to 1891 upon an important observation made by Dr. William B. Coley, widely accepted as the "Father of Immunotherapy". He found that certain bacterial infections in cancer patients could lead to tumor regression or even complete remission by causing necrosis[1,2]. This astonishing discovery has attracted scientists worldwide to investigate novel strategies to combat cancer. In 1986, the US Food and Drug Administration (FDA) approved an antitumor cytokine called interferon-α (IFNα) as the first immunotherapeutic agent for hairy cell leukemia[3]. After decades of exploration, the development of ipilimumab (a CTLA-4 monoclonal antibody) and chimeric antigen receptor (CAR) T cell therapy marked a significant breakthrough in the field of cancer immunotherapy in 2013, indicating that cancer treatment has entered the era of immunotherapy[4]. The advent of cancer immunotherapy has revolutionized cancer treatment, substantially prolonged the survival of cancer patients, and improved their quality of life.

Cancer immunotherapy is comprised of cancer vaccines, adoptive cellular immunotherapy (*e.g.*, CAR-T cell therapy), immunomodulators (*e.g.*, cytokines), and immune checkpoint inhibitors (ICIs), with ICIs being the most widely used and promising drugs. ICIs such as anti-PD-1/PD-L1 antibodies and anti-CTLA4 antibodies show clinical benefits in a range of cancer types, including non-small cell lung cancer (NSCLC), melanoma, renal carcinoma, and breast cancer[5−7]. However, only 20%−30% of patients respond to ICIs and the majority of patients fail to benefit from these agents. The low response rates of ICIs are often due to poor tissue permeability and single-target inhibition. In addition, the long half-life and inherent immunogenicity of ICIs could contribute to high rates of immune-related adverse events. ICIs also have several other drawbacks such as high costs and intravenous or subcutaneous route of administration[8,9]. These clinical challenges hamper the widespread application of ICIs and it is urgent to develop other strategies to improve the clinical efficacy of cancer immunotherapy. To this end, small-molecule agents targeting tumor immunity have been developed for their oral bioavailability, short half-life, membrane permeability, extensive tissue penetration, low immunogenicity, and manageable adverse events, which lead to more potent antitumor activity and safer clinical application[8]. Improved understanding of tumor immunology has led to the development of small-molecule immunotherapeutics, which could activate or reactivate the immune system to attack cancer cells. Numerous small-molecule agents implicated in pattern recognition receptor-associated pathways, immune checkpoints, oncogenic signaling, metabolic pathways, cytokine/chemokine signaling, and immune-related kinases have been studied in the past few years. A substantial number of small-molecule drugs have entered clinical trials and some of them have received clinical approval for cancer treatment.

This review summarizes the recent advancements in the development of small molecule-based cancer immunotherapy, with special emphasis on those under clinical investigation and on the market (Tables 1 and 2).

2. Small-molecule agents targeting PRR-associated pathways

2.1. *Targeting cGAS−STING pathway*

Pattern recognition receptors (PRRs) play a central role in immune responses against various pathogen and damage-associated molecular patterns (PAMPs and DAMPs). Their activation elicits signaling cascades that lead to the initiation of cell-autonomous defense mechanisms, as well as the production of soluble mediators, such as type I interferon (IFN) and pro-inflammatory cytokines. By inducing the expression of IFN-stimulated genes, type I IFNs boost cell-autonomous defense mechanisms in an autocrine manner, and activate the adaptive immune system. Cytosolic DNA is a potent activator of a type I IFN response. Cyclic GMP−AMP synthase (cGAS)-stimulator of IFN genes (STING) axis is one of the most notable pathways that recognizes cytosolic DNA to drive activation of IFN and other inflammatory cytokines[10]. Activation of cGAS−STING in tumor cells may serve as a barrier to early neoplastic progression through the upregulation of inflammatory genes. Tumor DNA can also be released and transferred into the cytosol of dendritic cells (DCs) and macrophages. The accumulation of tumor DNA activates STING−IRF3-induced IFN signaling to enforce tumor-antigen presentation on DCs and macrophages that cross-prime $CD8^+$ T cells for antitumor immunity (Fig. 1). The critical role of cGAS−STING signaling in antitumor immunity has sparked the development of pharmacologic agonists aiming to boost anti-tumor immunity or enhance the effects of existing immunotherapies. Over ten natural and synthetic STING agonists have undergone clinical development (Fig. 2A)[11]. Although generally not toxic, the first generation of STING agonists, cyclic dinucleotides (CDNs), are structurally unstable and only exhibit very modest activity *via* intratumoral delivery. The development of next-generation STING agonists, mainly novel CDNs and non-CDNs, with improved potency and

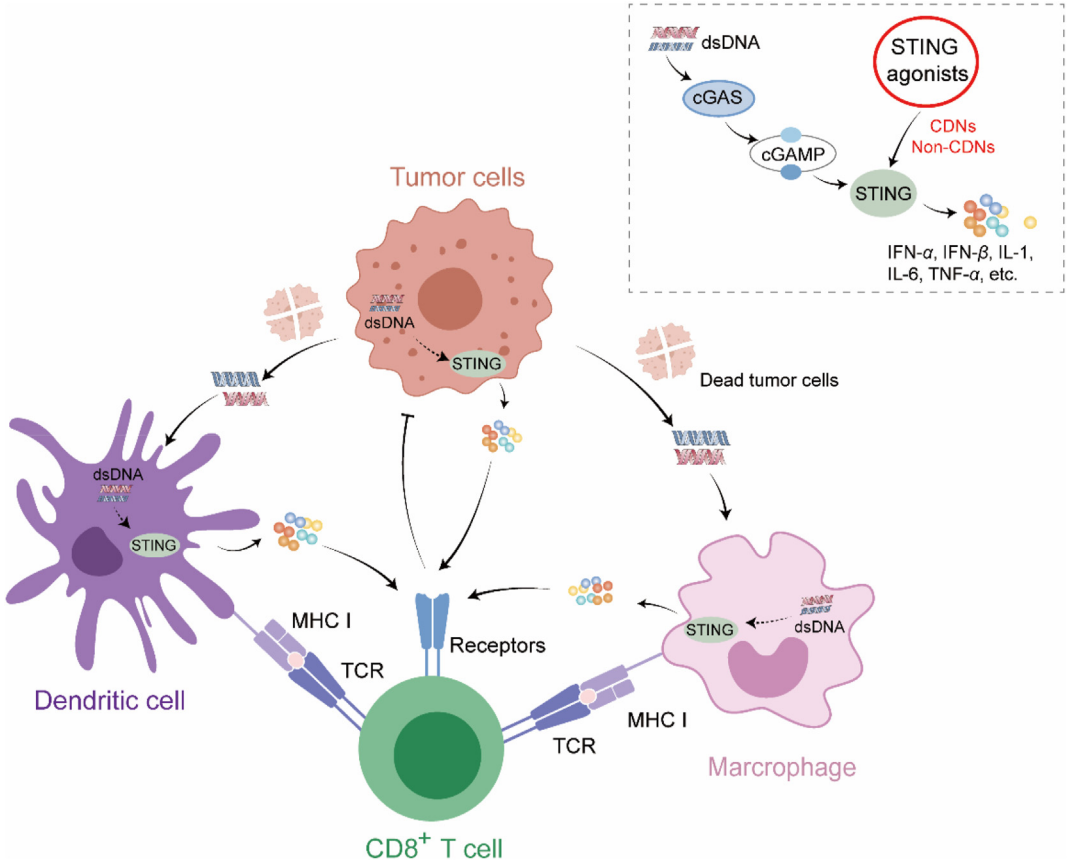

Figure 1 cGAS−STING signaling in antitumor immunity. Cytosolic DNA is a potent activator of type I IFN response. cGAS−STING pathway recognizes cytosolic DNA and induces the secretion of type I IFNs and other pro-inflammatory cytokines. Tumor cells are often replete with cytosolic DNA derived from genomic, mitochondrial, and exogenous origins. Activation of cGAS−STING in tumor cells may serve as a barrier to early neoplastic progression through the upregulation of inflammatory genes, which can recruit immune cells. Additionally, tumoral DNA is thought to be transferred and released into the cytosol of dendritic cells and macrophages. The accumulation of tumoral DNA, in turn, activates STING-induced IFN signaling to enforce tumor-antigen presentation on dendritic cells and macrophages that cross-prime $CD8^+$ T cells for antitumor immunity. Created with BioRender.com.

properties enabling their stability for systemic delivery, represents the research direction in the field[11−13]. Extensive investigations are also invested to combine STING agonists with different classes of therapies in particular anti-PD-1/PD-L1 antibodies, as it has been shown that STING activation is accompanied by the upregulation of immune inhibitory factors including PD-L1.

2.1.1. CDNs

The development of STING agonists was initially inspired by cyclic GMP−AMP (cGAMP), the endogenous ligand of STING. Modified CDNs are designed to mimic cGAMP. ADU-S100 was the first STING agonist to reach the clinical stage for cancer immunotherapeutic potentials. In its first-in-human trial, intratumoral administration of ADU-S100 demonstrated good tolerability among patients with advanced/metastatic solid tumors and lymphomas. However, its clinical efficacy was very modest, with only one confirmed partial response in Merkel cell carcinoma[14]. ADU-S100 was also investigated in combination with other ICIs, including spartalizumab and pembrolizumab, which was well tolerated but only minimal anti-tumor responses were observed[14].

MK-1454 (Ulevostinag) is a rationally designed CDN based on the scaffold of 2′,3′-cGAMP, and ADU-S100. MK-1454 exhibited high affinity to human wild-type STING and its second-most prevalent variant (R71H-G230A-R293Q) with K_d values at single-digit nanomole or even lower. MK-1454 exhibited robust potency in cell-based assays and possessed a binding mode and kinetic binding profiles that closely resembled those of 2′,3′-cGAMP[15]. It is currently undergoing investigation in clinical trials (NCT 03010176, NCT04220866), both as a monotherapy and in combination therapy.

2.1.2. Next-generation CDNs

To avoid the necessity for intratumoral delivery of early-generation CDNs, recent efforts have concentrated on developing STING agonists with stable physical properties suitable for systemic administration.

BMS-986301 is a next-generation CDN standing out for its promising preclinical results[16]. In a phase I trial targeting patients with advanced solid cancers (NCT03956680), BMS-986301 is evaluated either as monotherapy or in combination with nivolumab (Opdivo) and ipilimumab. SB11285 is a second-generation STING agonist that allows intravenous administration. The combination of SB11285 and cyclophosphamide was reported to produce a significant synergistic anti-tumor effect[17]. An ongoing phase I non-randomized, dose escalation study (NCT04096638) is currently evaluating SB11285 as monotherapy or in combination with

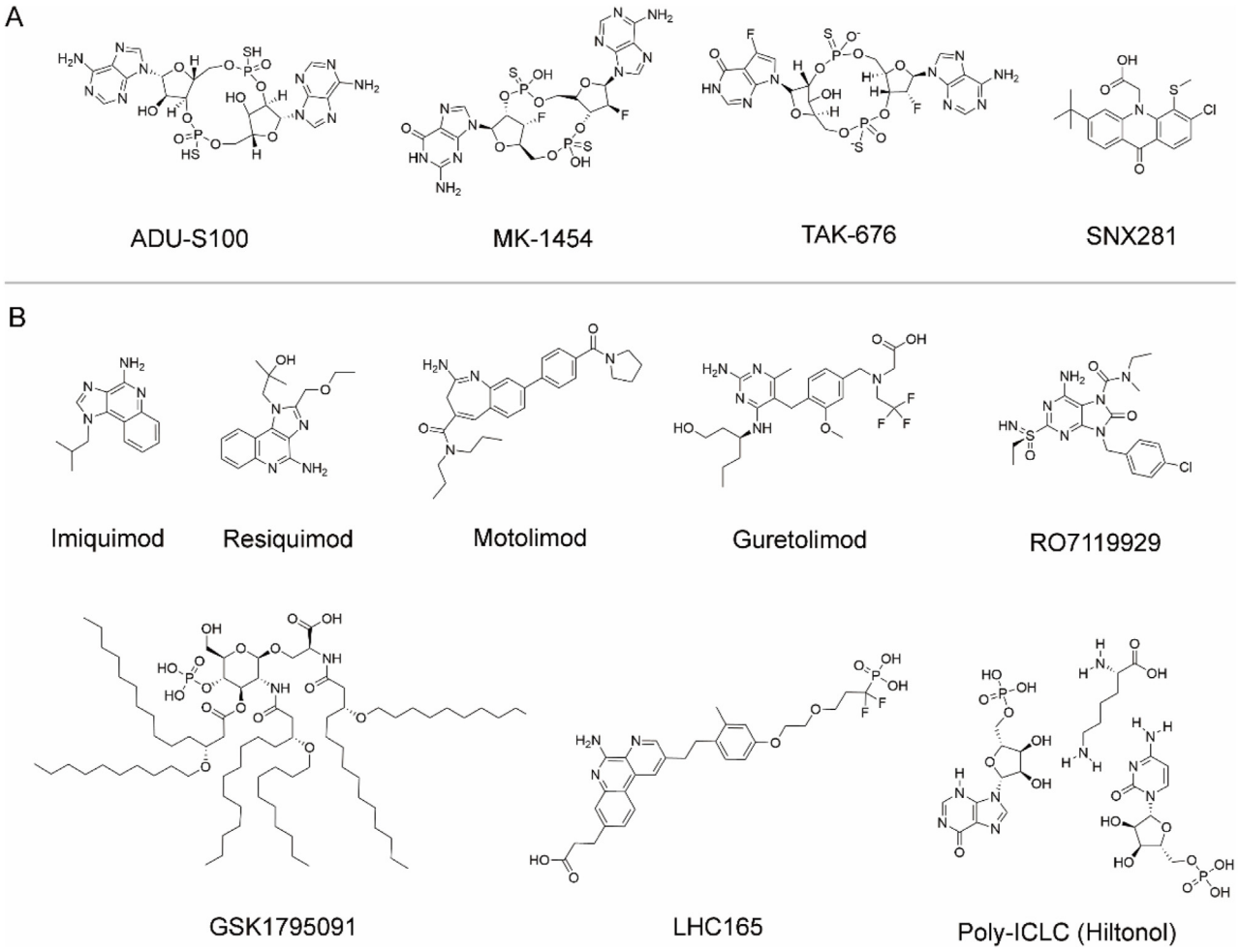

Figure 2 PRR-associated pathway agonists. (A) Representative STING agonists. ADU-S100, MK-1454, and TAK-676 are cyclic dinucleotides (CDNs) while SNX281 is non-CDN. (B) Representative TLR agonists. GSK1795091 is a TLR4 agonist and poly-ICLC (Hiltonol) is a TLR3 agonist, and the others are TLR7 agonists.

atezolizumab for intravenous use in patients with advanced solid tumors. TAK-676 is another synthetic STING agonist designed for intravenous administration, which has been demonstrated to activate the STING signaling pathway and type I IFNs in a dose-dependent manner. TAK-676 exhibited remarkable effects in activating both innate and adaptive immune activity, as demonstrated in multiple syngeneic tumor models spanning various tumor types[18]. Currently, TAK-676 is being investigated in cancer patients with locally advanced or metastatic solid tumors, either as a monotherapy or in combination with various treatments including ICIs, radiation, and chemotherapy (NCT04420884, NCT04879849).

BI 1387446, a BI-STING compound, has progressed to clinical testing and is currently being evaluated in the first-in-human trial in patients with advanced, unresectable, and/or metastatic solid tumors (NCT04147234). The primary objective of this trial is to determine the maximum tolerated dose and assess the tolerability of a single intratumoral injection of BI 1387446, either as a monotherapy or in combination with BI 754091 (an anti-PD1 monoclonal antibody).

2.1.3. Non-CDNs

In addition to novel CDNs, an increasing number of small molecule non-CDNs STING agonists with drug-like physicochemical properties have been reported, including the first orally available STING agonist MSA-2[19] and a non-nucleotide cGAMP mimetic SR-717[20], yet very few have entered the clinical stage.

GSK3745417 is a small molecule non-CDN with a dimeric amidobenzimidazole (ABZI) scaffold. This class of compounds was developed by linking two symmetry-related ABZI-based compounds to create linked ABZIs (diABZIs) to produce a synergistic antitumor effect. This novel dimeric design not only resolved the challenge of drug administration but also extended the therapeutic potentials, thus representing a milestone in the development of next-generation STING agonists[20,21]. Intravenous administration of GSK3745417 in syngeneic tumor models exhibited satisfactory plasma exposure and durable tumor regression. GSK3745417 is currently being investigated in a phase I dose-escalation study as monotherapy or in combination with dostarlimab in patients with relapsed/refractory solid tumors (NCT03843359, NCT05424380).

E7766 is a macrocycle-bridged STING agonist that structurally features a transannular macrocyclic bridge between the nucleic acid bases in CDNs, thereby effectively locking a bioactive U-shaped conformation. E7766 demonstrates enhanced stability and STING affinity due to the conformational rigidity provided by its unique macrocycle bridge, resulting in increased efficacy

compared to conventional STING agonists. Furthermore, E7766 exhibits broad pan-genotypic activity across all major human STING variants. Currently, an ongoing phase I/Ib clinical trial (NCT04144140) is assessing the efficacy of intratumorally administered E7766 as a monotherapy in patients with advanced solid tumors and lymphomas[22].

SNX281 is a small molecule STING agonist rationally designed by a multifaceted computational approach. SNX281 was created by using a unique self-dimerizing mechanism in the STING binding site, where the constituting ligands form dimers to resemble approximately the size and shape of a cyclic dinucleotide. Upon activation, it induces a large-scale conformational change of the STING protein. Preclinical data indicated that SNX281 exhibited adequate systemic bioavailability, and it was found to trigger STING-mediated cytokine release, strong induction of type I IFN, potent antitumor activity, durable immune memory, and single-dose tumor elimination in mouse models[23]. It is currently under investigation in a first-in-human clinical trial (NCT04609579) as a single agent or in combination with pembrolizumab for treating advanced solid tumors and lymphomas.

A few other non-CDN agonists are also currently under clinical investigation, though very limited information has been reported. IMSA101 is a small molecule analog of cGAMP. In preclinical studies, IMSA101 stimulated the production of IFNs and cytokines, generated long-term memory immunity to tumors, and demonstrated robust tumor growth inhibition as a single agent or in combination with anti-PD-L1 monoclonal antibody in multiple mouse models. A dose escalation (phase I) and dose expansion (phase IIa) study (NCT04020185) of intratumoral IMSA101 treatment alone or in combination with ICIs has been recruiting patients since 2019. MK-2118 is another non-CDN STING agonist whose structure has not been reported. In a clinical trial focusing on patients with advanced solid tumors or lymphomas (NCT03249792), SNX281 is being investigated, either intratumorally or subcutaneously injected as a monotherapy and in combination with pembrolizumab. KL340399 and HG381 are new-generation non-CDN STING agonists developed in China. They are currently under clinical investigation in phase I trials (NCT05549804, NCT04998422) to evaluate their safety, tolerability, pharmacokinetic profile, and antitumor efficacy in patients with advanced solid tumors.

2.1.4. *STING agonists with facilitated delivery*

Despite the substantial progress in designing novel cGAS−STING agonists, their biological efficacies are hindered by stability and delivery problems. Recently, novel delivery systems, including nanocarriers, microparticles, and hydrogels, have been developed to improve the pharmaceutical properties (*e.g.*, excessive hydrophilicity, vulnerability to enzymatic degradation, and being negatively charged) of novel STING agonists.

Exosome-based formulation is believed to promote targeted antitumor immunity while minimizing off-target toxicity due to systemic elevation of toxic cytokines. CDK-002 is a novel exosome formulation loaded with an agonist of STING and it expresses high levels of glycoprotein prostaglandin F2 receptor negative regulator (PTGFRN). PTGFRN expression on the surface of the exosome facilitates specific uptake in tumor-resident antigen-presenting cells (APCs) and enhances systemic APC-mediated antitumor immune response. According to the information released by Codiak BioSciences, intratumoral administration of CDK-002 activates the innate immune response locally, thereby increasing the production of pro-inflammatory cytokines (including IFNs), enhancing the cross-presentation of tumor-associated antigens (TAAs) by DCs, and inducing a cytotoxic T-lymphocyte (CTL)-mediated immune response against cancer cells. A first-in-human, phase I/II open-label, multicenter, dose escalation, safety, pharmacodynamic, and pharmacokinetic study of CDK-002 (NCT04592484) has been initiated in patients with advanced/metastatic, recurrent, injectable solid tumors progressed following standard of care treatment.

2.2. *Targeting Toll-like receptor pathways*

Toll-like receptors (TLRs) family is one of the best-characterized PRRs responsible for sensing invading pathogens outside of the cell and in intracellular endosomes and lysosomes. Human TLR family consists of 10 receptors (TLR1-10), grouped into two major categories: surface TLRs (TLR1, TLR2, TLR4, TLR5, TLR6, and TLR10) that reside on the plasma membrane and bind to microbial-derived ligands, and intracellular endosomal TLRs (TLR3, TLR7, TLR8, and TLR9) that are nucleic acid-sensing TLRs. TLR4 is found both on the plasma membrane and in the intracellular compartments[24−26]. Responding to DNA/RNA derived from pathogens and dead cells, TLR signaling is activated to induce the production of pro-inflammatory cytokines or type I IFN and the activated TLRs expressed on DCs also contribute to T cell activation, thereby bridging between innate and adaptive immunity (Fig. 3).

Given the central role of TLRs in innate immunity and their important role in adaptive immunity, tremendous efforts have been invested in identifying TLR agonists to enhance antitumor immune response, particularly in the context of therapeutic vaccine potential in cancer. Different TLRs are amenable to the intervention *via* different types of agents (Fig. 2B). Cell surface TLRs can be targeted by small molecules and antibodies whereas the intracellular nucleic-acid sensing TLRs could be targeted by modified oligonucleotides. To date, agonists for several TLRs, including TLR3, TLR4, TLR7, TLR8, and TLR9, have been tested clinically either alone or in combination with other therapies to strengthen the immune system in cancer therapy[24,27,28].

2.2.1. *Intracellular TLR agonists*

Imiquimod is an immune response modifier, which has been clinically approved for actinic keratosis, external genital warts, and basal cell carcinoma. It acts through a TLR7−MYD88-dependent pathway and has also been extensively investigated in a broad spectrum of cancer patients, mostly in combination with different types of cancer treatments, including tumor vaccines, chemotherapy, targeted therapies, and ICIs. Most recently, a phase I trial showed that the combination of topical imiquimod and IDH1 peptide vaccine resulted in immune responses in 93.3% of *IDH1* R132H-mutated patients with grade I adverse effects[29]. In prostate cancer, the combination of topical imiquimod and different tumor vaccines also produced a promising antitumor effect[30]. Resiquimod (R848) and motolimod (VTX-2337) are second-generation derivatives of imiquimod. Resiquimod has been investigated in combination with tumor vaccine and/or other adjuvants for the treatment of melanoma and brain tumors, but it did not successfully induce a consistent antigen-specific $CD8^+$ T cell response. Motolimod was tested in patients with ovarian cancer or other squamous cell carcinoma in different combination regimens. Among them, motolimod was shown to augment the clinical responses of patients with advanced head and neck squamous cell

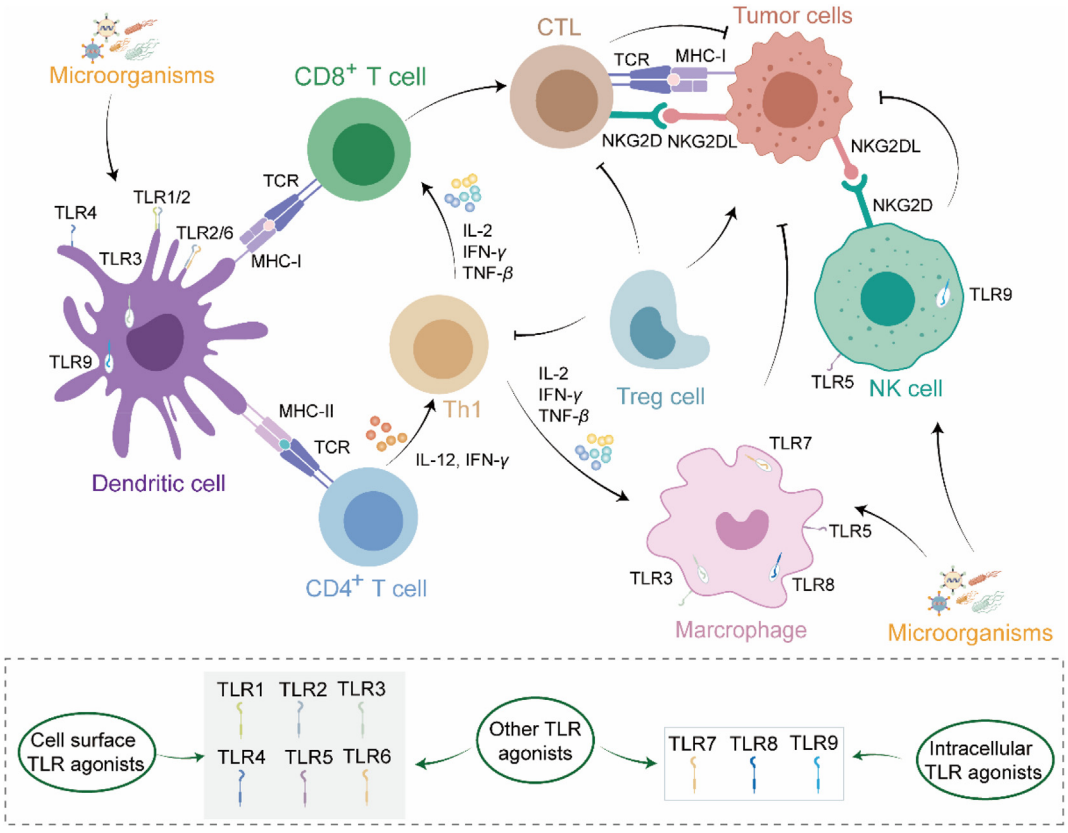

Figure 3 The roles of TLR in anti-infection and antitumor immunity. Innate immune cells (*e.g.*, macrophages, dendritic cells, and NK cells) recognize the PAMP of microorganisms through PRRs such as TLRs. Macrophages kill bacteria and viruses *via* phagocytosis, whereas dendritic cells process the foreign antigens and present them to T cells through the TCR−MHC complex. Activated $CD4^+$ T cells secrete cytokines to exert an immunoregulatory effect on $CD8^+$ T cells and the latter differentiate into cytotoxic T cells to execute the cell-killing effect. PAMP, pathogen-associated molecular pattern; PRR, pattern recognition receptor; TLRs, Toll-like receptors. Created with BioRender.com.

carcinoma (HNSCC) who received epidermal growth factor receptor inhibitor cetuximab[31].

TLR9 is recognized as a first-line host defense against pathogens by recognizing DNA comprising unmethylated CpG motifs present in viruses and bacteria. CpG oligonucleotides (ODNs) can activate innate immunity by binding to TLR9 and trigger Th1-mediated immune responses. It has been hypothesized that the introduction of unmethylated CpG ODNs into tumor lesions may reinvigorate the tumor microenvironment (TME) and subsequently reverse therapeutic resistance to PD-1 blockade immunotherapy. Currently, the most extensively investigated TLR9 agonists in the clinic are SD-101, CMP-001, and IMO-2125. CMP-001 (Vidutolimod) is a virus-like particle containing a CpG-A TLR9 agonist. A recent phase Ib study (NCT02680184) showed that CMP-001 could reverse PD-1 blockade resistance by triggering a strong IFN response to induce and attract antitumor T cells. Among patients with advanced melanoma previously treated with pembrolizumab, 25% of patients had a partial (7 of 11) or complete (4 of 11) response to therapy, and responses were seen not only in the injected tumors but also in noninjected tumors, including visceral sites[32,33]. IMO-2125, also known as tilsotolimod, is a CpG-C TLR9 agonist that effectively activates DCs, induces type I IFN signaling, and upregulates multiple immune checkpoint pathways in cancer patients. In a phase Ib/II study, the combination of ipilimumab and IMO-2125 in 25 patients with advanced melanoma achieved a response rate of 36%[34]. However, a follow-up phase III trial evaluating the combination of ipilimumab with or without intralesional IMO-2125 did not improve the overall response rate (ORR), with 8.8% in the combination group *versus* 8.6% in ipilimumab alone group (NCT03445533).

2.2.2. *Cell surface TLR agonists*

TLR2 is a cell surface innate immune sensor that recognizes diverse ligands from external pathogens. TLR2 agonists, including triacylated lipopeptides, synthetic chemical compounds, glucomannan polysaccharides, naturally extracted compounds, and inactivated viruses, have been investigated to boost the antitumor response. In preclinical studies, TLR2 agonists alone or in combination with tumor vaccines, immune checkpoint inhibition, chemotherapy, photodynamic therapy (PDT), or adoptive cell transfusion, have been shown to activate immune responses. To date, there are only a limited number of clinical trials investigating TLR2 agonists for cancer immunotherapy. Amplivant, a synthetic TLR2 ligand that can be directly conjugated to tumor peptide antigens, represents the most promising one. In preclinical studies, amplivant-conjugation to antigens led to enhanced antigen presentation by DCs and T-cell priming, thereby inducing effective antitumor responses. Moreover, amplivant-conjugated synthetic long peptides (SLPs) have been shown to generate immune responses that are 100 times higher compared to unconjugated SLPs. In the first-in-human phase I clinical trial, amplivant-conjugated human papillomavirus (HPV) 16-SLP was administered as an intradermal therapeutic anticancer

vaccine, and it was found to induce robust HPV16-specific T-cell immunity in patients with HPV16 positive malignancies[35].

Among immune cells, TLR3 is expressed only in myeloid DCs, macrophages, and mast cells. TLR3 is known to localize both at the cell surface and in endosomes in mast cells and macrophages, but only in endosomes in myeloid DCs. TLR3 plays an important role in antiviral host response. Polyinosinic:polycytidylic acid (Poly (I:C)), a mismatched double-stranded RNA with one strand being a polymer of inosinic acid and the other a polymer of cytidylic acid, has been used as an immunostimulant. Poly (I:C) has been used in most immunotherapeutic studies as the TLR3-targeting agent because of its known interaction with TLR3. To date, three investigational TLR3 agonists, poly-ICLC (Hiltonol), rintatolimod (Ampligen), and BO-112 have progressed to clinical trials. Poly-ICLC is currently under active clinical investigation in combination with traditional therapies (surgery, chemotherapy, or radiotherapy) and immunotherapies (tumor vaccine, immune co-stimulation, or ICB) (NCT01976585, NCT03380871).

TLR4 is an important PRR that activates both innate and adaptive immune cells. TLR4 agonists under investigation for enhancing cancer immunotherapy include LPS, lipid A derivatives, polysaccharides, and protein TLR4 agonists. Monophosphoryl lipid A (MPLA) is the first TLR4 agonist approved as an adjuvant for hepatitis B vaccine. GLA-SE is a synthetic TLR4 agonist, which is composed of a glucopyranosyl lipid A-stable oil-in-water emulsion. The immune stimulatory activity of GLA-SE has been widely studied in lymphoma, skin cancers, sarcoma, lung cancer, and colorectal cancer. In a phase I trial (NCT02035657), intratumoral administration of G100 containing GLA-SE was well-tolerated as an adjuvant to surgery and radiotherapy, and it exhibited notable clinical efficacy in Merkel cell carcinoma with increased intratumoral infiltration of $CD8^+$ and $CD4^+$ T cells, activation of immune-related genes and local tumor regression[36].

2.2.3. *Other TLR agonists*

In addition to single TLR activation, multi-TLR agonists are also under clinical investigation for cancer therapy. Bacillus Calmette-Guérin (BCG), an attenuated live *Mycobacterium bovis* simultaneously activating TLR2, TLR4, and TLR9, is the most studied multi-TLR agonist. Initially developed as a vaccine for tuberculosis, BCG has evolved to become a gold-standard adjuvant immunotherapy for patients with high-risk non-muscle-invasive bladder cancer. BCG was shown to induce a non-specific enhancement of the innate immune system, creating a heterologous immunological memory termed trained immunity[37]. Currently, BCG is being tested in bladder carcinoma patients in combination with other treatments, including anti-PD-1/PD-L1 antibodies, small molecule inhibitors, and a neoantigen-encoding gene vaccine. In a completed clinical trial (NCT02753309), the combination of rapamycin and BCG was well tolerated in patients with high-grade non-muscle invasive bladder carcinoma and it induced antigen-specific $\gamma\delta$ T cell response as well as urinary cytokine production[38]. BCG was also investigated for the treatment of lower urinary tract carcinoma (NCT00794950). Besides malignancies in the urinary system, the combination of BCG and other cancer treatment modalities such as chemotherapy, radiofrequency ablation, and GM-CSF has also been investigated in the treatment of liver metastases from colorectal cancer (NCT04062721).

3. Small-molecule agents targeting immune checkpoints

3.1. *Targeting PD-1/PD-L1 signaling*

3.1.1. *PD-1/PD-L1 signaling in immune-oncology*

Programmed cell death protein 1 (PD-1) is an immunosuppressive molecule predominantly expressed by activated T cells and induces immunosuppressive signals through binding to its ligands, mainly programmed cell death-ligand 1 (PD-L1). The binding of PD-L1 to PD-1 triggers the phosphorylation of PD-1 and suppresses T cell receptor (TCR) and co-stimulatory signaling, resulting in the inhibition of T cell activation and function. Upregulation of PD-L1 expression mediated by cancer cells in TME fosters cancer immune escape, leading to limited antitumor responses of cytotoxic T cells. The blockade of the PD-1/PD-L1 signaling by ICIs represents an attractive strategy for cancer treatment. Numerous PD-1/PD-L1 ICIs exhibited potent antitumor efficacy by potentiating T cell-mediated antitumor immunity in clinical trials. However, currently clinically approved ICIs are monoclonal antibodies that have several disadvantages, such as poor tissue permeability, high rate of immune-related adverse events, and intravenous or subcutaneous routes of administration, thus hindering the widespread application of ICIs[8]. Conversely, small-molecule agents can overcome these drawbacks and exert more effective anticancer activity with fewer adverse effects.

In consideration of the intrinsic limitations of monoclonal antibodies, numerous small molecule inhibitors targeting PD-1/PD-L1 signaling were developed and some of them have entered clinical trials (Fig. 4)[39]. These small molecule agents inhibit PD-1/PD-L1-mediated immunosuppressive signal by preventing the binding of PD-1 to PD-L1, regulating PD-L1 expression, or various other mechanisms.

3.1.2. *Interfering with the interaction of PD-1 and PD-L1*

INCB086550 is a small-molecule inhibitor targeting PD-L1 that potently contributed to PD-L1 dimerization and internalization, selectively interfered with the PD-1/PD-L1 interaction *in vitro*, and delayed tumor growth in $CD34^+$ humanized mice[40]. Two clinical trials have been initiated to investigate INCB086550 in cancer patients (NCT03762447, NCT04629339).

IMMH-010 is an oral PD-L1 inhibitor, which could be rapidly metabolized to YPD-29B, and exhibited remarkable antitumor efficacy in xenograft mouse models of colon cancer and melanoma[41]. Currently, IMMH-010 is under clinical evaluation in advanced patients with solid tumors (NCT04343859). ASC61 is another small molecule PD-L1 inhibitor, which has received the investigational new drug approval for the treatment of advanced solid tumors. A phase I clinical study is underway to assess its safety (NCT05287399). GS-4224 (evixapodlin) was developed by Gilead Sciences for treating advanced solid tumors, however, the phase I study (NCT04049617) of GS-4224 was terminated for unknown reasons. Additionally, other PD-L1 inhibitors including MAX-10181 (NCT05196360, NCT04122339) and BPI-371153 (NCT05341557) are being studied in phase I clinical trials.

3.1.3. *Regulating PD-L1 expression*

The expression of PD-L1 is reported to be regulated by various mechanisms involved in transcriptional regulation, translational regulation, and epigenetic regulation. Multiple oncogenic signaling

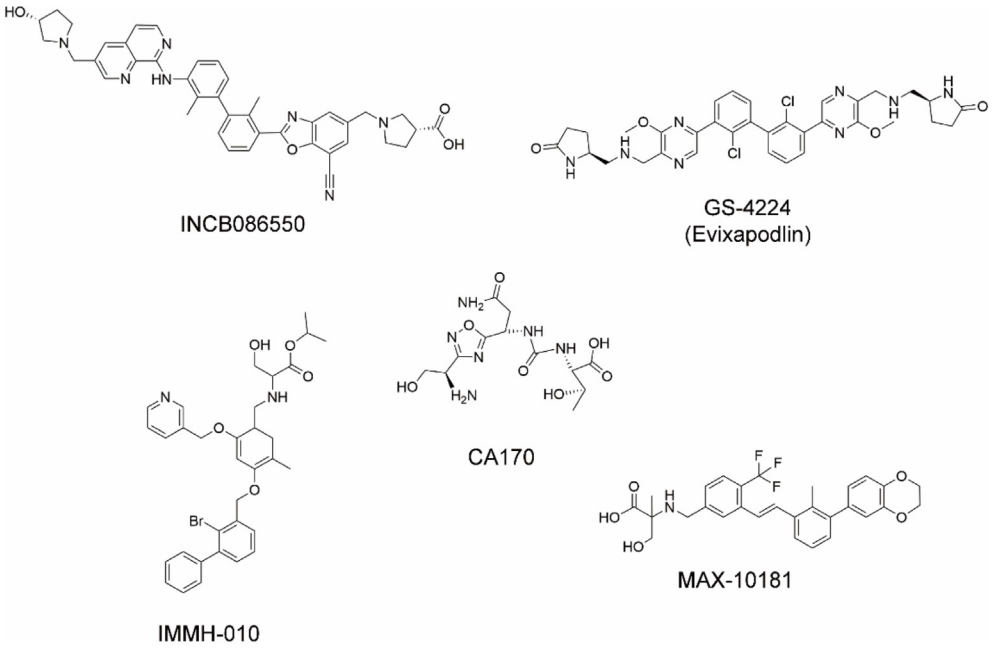

Figure 4 Small-molecule immune checkpoint inhibitors. The PD-L1 inhibitors (INCB086550, GS-4224, IMMH-010, and MAX-10181) can interfere with the interaction of PD-1 and PD-L1, contributing to the inhibition of immunosuppressive signal. CA170 is a small-molecule inhibitor targeting both PD-L1 and VISTA.

pathways consisting of JAK/STATs, RAS/RAF/MEK/ERK, PI3K/AKT/mTOR, and WNT/β-catenin were reported to have pivotal roles in regulating PD-L1 expression. PI3K/AKT/mTOR can increase PD-L1 expression through transcription factors including STAT3 and YAP1/TAZ, and mTOR-mediated translational regulation[8]. Activation of the AKT-mTOR pathway upregulated PD-L1 expression in NSCLC cells at the translational level, whereas rapamycin (mTOR inhibitor) inhibited PD-L1 expression by decreasing protein synthesis and increasing lysosomal protein degradation[42]. Furthermore, the combination therapy of rapamycin and anti-PD-1 markedly decreased tumor growth in a mouse model of lung cancer, with the increase of $CD3^+$ T cells and reduction of $FoxP3^+$ Tregs[42]. MAPK signaling can transcriptionally upregulate PD-L1 *via* AP1 and STAT3. EGF or IFNγ-induced activation of MAPK signaling increased the PD-L1 mRNA and protein, and sel umetinib (MEK1/2 inhibitor) prevented the upregulation of PD-L1 in lung adenocarcinoma cells[43]. Small-molecule inhibitors targeting JAK−STATs (fedratinib, ruxolitinib, and tofacitinib) were also reported to downregulate PD-L1 expression in breast cancer cells and NSCLC cells[44]. Downregulation of PD-L1 expression through inhibition of oncogenic pathways could simultaneously suppress sustaining proliferative signaling and improve the immunosuppressive TME, contributing to enhanced antitumor efficacy.

In addition, epigenetic regulation also has an impact on PD-L1 expression. DNA global hypomethylation fosters PD-L1 expression while DNA hypermethylation within the PD-L1 promoter inhibits PD-L1 expression[45]. DNA hypomethylating agents (azacytidine and decitabine) could upregulate PD-L1 expression and potentiate the efficacy of anti-PD-L1 antibodies in several mouse models of cancer, such as NSCLC, gastric cancer, and colorectal cancer[46,47]. Histone acetylation at the PD-L1 promoter region also participates in the regulation of PD-L1 expression. Histone deacetylase (HDAC) inhibitors including belinostat, panobinostat, vorinostat, and romidepsin could increase PD-L1 expression and enhance the efficacy of anti-PD-1/PD-L1 antibodies *in vivo*[48−50]. Upregulation of PD-L1 mediated by epigenetic regulation potenti ally gives rise to enhanced antitumor efficacy of anti-PD-1/PD-L1 antibodies *via* increasing the proportion of cancer cells' response to these antibodies. Currently, extensive clinical trials are underway to investigate the potential benefits of HDAC inhibitors combined with ICIs (NCT05068427, NCT03765229, and NCT04651127). Small-molecule drugs that regulate PD-L1 expression have many application prospects in cancer immunotherapy, however, it is worth noting that the mechanisms of action of these agents and options of drug combination rely on the cellular context and cancer types. Further clinical trials are warranted to broaden this promising research area.

3.2. *Targeting VISTA signaling*

V-domain immunoglobulin suppressor of T-cell activation (VISTA) is one of the immune checkpoint proteins that suppress T-cell response against cancer. VISTA, a member of the B7 protein family, shares 22% sequence similarity with PD-L1[51]. The extracellular domain of VISTA contains two typical cysteines conserved in immunoglobulin-like proteins, and four unique cysteines only conserved in VISTA orthologs but absent in other B7 family members[52]. VISTA is abundantly expressed on myeloid and lymphoid cells[53,54]. The expression of VISTA on the $\gamma\delta$ T cells and naïve $CD4^+$ T cells blocks their auto-reactivation, thereby preventing T cell activation without foreign antigenic stimulation[55]. The binding of VISTA to its ligand can reduce the pro-inflammatory cytokines IL-2, TNF-α, and IFN-γ while increasing the anti-inflammatory cytokines and mediators. Deficiency or blockade of VISTA can greatly regulate the TME to a more pro-inflammatory myeloid phenotype, which is conducive to tumor-responsive T cell infiltration[52,56,57]. Therefore, VISTA-targeting therapy may potentiate the anticancer effect of immunotherapy[57].

CA170 is an oral small-molecule antagonist targeting both PD-L1 and VISTA[58]. The drug molecule consists of L-serine, D-asparagine, and L-threonine, partially linked by diacylhydrazine and urea linker moieties. The *in vitro* inhibitory effect (EC_{50}) of CA170 on PD-L1 and VISTA was found to be 66 nmol/L and 83 nmol/L, respectively. As a single agent, CA170 was taken orally once daily and significantly suppressed tumor growth and metastasis in mouse models of melanoma cells B16F10 and colorectal cells MC38[59]. CA170 was shown to rescue IFN-γ released from human PBMC blocked by the recombinant PD-L1, PD-L2 and VISTA. In a completed phase I study, CA170 was well tolerated at an oral dose of 50−1200 mg and it displayed a dose proportional plasma half-life of 4−9.5 h[60]. In a phase II study, CA-170 also demonstrated exciting clinical activity, including an ORR of 30% in Hodgkin lymphoma (based on *Lugano criteria*), and a clinical benefit rate of >85% at a daily dose of 400 mg and progression-free survival (PFS) of 19.6 weeks (PFS with best supportive care was approximately 8 weeks in a cross-study comparison) in advanced non-squamous NSCLC[61]. Notably, the development of lung cancer was completely inhibited by CA170 in combination with the major histocompatibility complex (MHC) class II-directed KRAS oncogene peptide vaccines. CA170 enhanced the tumor infiltration of $CD8^+$ T cell and their effector functions by reducing the tumor infiltration of regulatory T (Treg) cells and myeloid-derived suppressor cells, and the KRAS vaccine mainly induced $CD4^+$ effector T cells expansion[62].

4. Small-molecule agents targeting cytokine and chemokine pathways

Cytokine and chemokine are important regulatory molecules in the TME and both play pleiotropic effects on cancer cells and immune cells. The cytokine and chemokine pathways are activated upon the binding of cytokine and chemokine to their corresponding receptors, which has an impact on tumor growth, proliferation, metastasis, and the function of immune cells. Thus, targeting immunoregulatory cytokines and chemokine contributes to enhanced antitumor immunity.

4.1. Targeting TGF-β signaling

TGF-β is a powerful regulatory cytokine that maintains immune homeostasis and tolerance *via* controlling lymphocyte proliferation, differentiation, and survival. TGF-β contains three isoforms. TGF-β1 is primarily involved in immunomodulation, whereas TGF-β2 and TGF-β3 play important roles in regulating cellular environments[63]. TGF-β1 and TGF-β3 are released from their latent complexes after the Arg−Gly−Asp motif interacts with integrins αvβ6 or αvβ8. The three isoforms of TGF-β are the ligands for the TGF-β receptor 1 (TβR1, ALK5) and TGF-β receptor 2 (TβR2) combination. TGF-β plays a critical dual role in the progression of cancer. In the early or primary stages of cancer, TGF-β can act as a tumor suppressor by inducing cell cycle arrest and promoting apoptosis. Cancer cells use TGF-β to initiate immune evasion, growth factor production, differentiation into an invasive phenotype, and metastatic dissemination, or establishme nt and expansion of metastatic colonies when cancer cells lose the tumor suppressor effect of TGF-β[64]. The direct effects of TGF-β on tumor cells and the indirect effects of TGF-β on tumor growth by creating a favorable microenvironment suggest that blocking TGF-β signaling is a beneficial response. Therefore, TGF-β inhibitors are expected to potentiate ICIs, especially in cancer types growing in TGF-β-rich environments. The development of small molecule inhibitors of TGF-β is an important complement to influence the tumor microenvironment. The initial TGF-β small-molecule inhibitor starts by targeting TβR1 (Fig. 5A)[65].

Galunisertib (LY2157299 monohydrate) is a potent small molecule inhibitor of TGFβR1 that specifically blocks the phosphorylation of SMAD2. Oral administration of 75 mg/kg twice daily of galunisertib was shown to significantly delay tumor growth of human lung cancer Calu6 xenograft model, human breast cancer MX1 xenograft model, and murine breast cancer 4T1 syngeneic model[66]. Galunisertib also exhibited good anticancer activity in preclinical models of myelodysplastic syndromes and acceptable side effects in phase I studies of solid tumors (NCT02008318)[67]. However, in a phase Ib clinical trial investigating the combination of galunisertib and ramucirumab (a VEGFR2 monoclonal antibody) to treat advanced hepatocellular carcinoma (HCC), the results did not endorse the preclinical hypothesis that inhibition of TGF-β signal transduction could enhance the efficacy of VEGF-targeted therapy (NCT01246986)[68]. In a phase IIa study investigating the combination of galunisertib and standard temozolomide-based radiochemotherapy (TMZ/RTX) to treat newly diagnosed malignant gliomas, the antitumor efficacy was found to be modest for the drug combination of galunisertib plus TMZ/RTX *vs.* TMZ/RTX (median overall survival (18.2 *vs.* 17.9 months), median PFS (7.6 *vs.* 11.5 months), and disease control rate (80% *vs.* 56%), respectively)[69]. In a recent phase Ib study for metastatic pancreatic cancer patients (NCT02734160), the combination of galunisertinib (150 mg twice daily) and durvalumab (anti-PD-L1 monoclonal antibody; 1500 mg Q4W) was well tolerated but clinical efficacy was limited[70]. The disease control rate for the drug combination was 25.0%. Median overall survival (OS) was 5.72 months, and PFS was 1.87 months. As the patients were not selected by using predictive biomarkers of TGF-β inhibition, the clinical benefit achieved by this study was limited[70]. In another phase II clinical trial, the combination of galunisertib and neoadjuvant chemoradiotherapy was well tolerated and was shown to increase the complete response rate to 32% in patients with locally advanced rectal cancer (NCT02688712)[71], thus advocating further evaluation in larger randomized clinical trials. The results of a phase Ib/II study of galunisertib combined with nivolumab in NSCLC showed that the combination was well tolerated and observed in a subset of patients in stage II NSCLC to the initial effect (NCT02423343)[72]. In another phase II study of patients with recurrent glioblastoma, galunisertib in combination with lomustine failed to demonstrate an improvement in OS over lomustine alone (NCT01582269)[73].

LY3200882 is an orally active ATP-competitive TGFβ-R1 inhibitor derived from galunisertib. It exhibited potent antitumor activity in a mouse model of triple-negative breast cancer, and its activity was associated with an increase in tumor-infiltrating lymphocytes. In immunosuppressive assays, LY3200882 was shown to rescue TGF-β1 inhibitory or T-modulating cells to inhibit naïve T cell activity and recover proliferation. In addition, LY3200882 also showed anti-metastatic activity in the intravenous mouse triple-negative breast cancer EMT6-LM2 model. Moreover, LY3200882 could also enhance the antitumor effect of checkpoint inhibition therapy (anti-PD-L1 monoclonal antibody) in the homologous mouse model of colorectal cancer[74]. A phase I multicenter clinical trial of oral LY3200882 was carried out, which included dose escalation, monotherapy extension for grade 4 gliomas, and

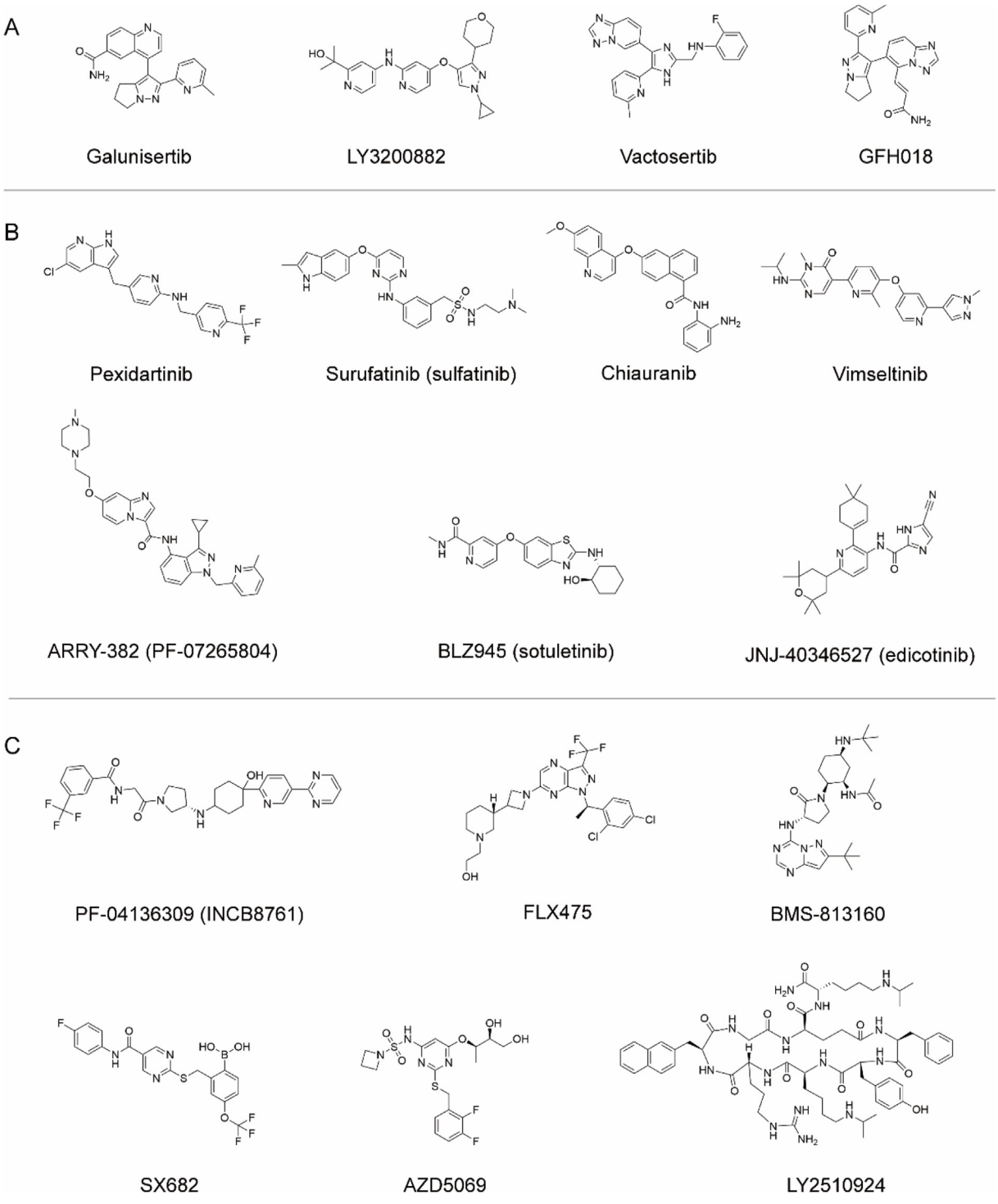

Figure 5 Cytokine and chemokine pathways inhibitors. (A) Chemical structures of representative TβR1 (ALK5) inhibitors. (B) Chemical structures of representative CSF1R inhibitors. (C) Chemical structures of representative chemokine receptor antagonists, including CCR2 antagonist (PF-04136309), CCR4 antagonist (FLX475), CCR5 antagonist (BMS-813160), CXCR1/2 antagonist (SX682), CXCR2 antagonist (AZD5069) and CXCR4 antagonist (LY2510924).

combined therapy for solid tumors (LY3200882 plus PD-L1 inhibitor LY3300054), squamous cell carcinoma of head and neck (LY3200882, *cis*-platinum and radiotherapy), and pancreatic cancer (LY3200882, nab-paclitaxel and gemcitabine) (NCT02937272). Most (93.5%) of patients experienced an adverse event in $\geq$1 treatment, of which 39.6% were associated with LY3200882[75].

Vactosertib (TEW 7197) is another small-molecule inhibitor of TGFβ-R1. The combination of vactosertib and a PRMT5 inhibitor

T1-44 could significantly reduce tumor size and invasion of surrounding tissues, and significantly improve long-term survival of the C57BL/6 mouse model of syngeneic orthotopic pancreatic ductal adenocarcinoma (PDAC)[76]. In other models including breast cancer, melanoma, and prostate cancer, vactosertib treatment abated cancer cell migration, invasion, and metastasis[77−79]. In a phase Ib/IIa clinical trial, the combination of vactosertib and pembrolizumab also showed promising antitumor efficacy and manageable safety in metastatic colorectal cancer patients who previously received chemotherapy[80]. Co-treatment of vactosertib with radiotherapy can enhance the treatment outcome of breast cancer by inhibiting epithelial−mesenchymal transition, reactive oxygen species stress generation, cancer cell stemness, and metastasis to other organs. Clinical trials of vactosertib plus other chemotherapies are being performed in patients with multiple cancer types, such as gastric cancer (NCT03698825), colorectal or gastric cancer (NCT03724851), desmoid tumor (NCT03802084), NSCLC (NCT03732274), and multiple myeloma (NCT03143 985)[81].

GFH018 is a small molecule inhibiting TGF-βR1 kinase. It is also a potent immune modulator by inhibiting Treg cell induction and reversal of the M2 phenotype to M1, thereby increasing the production of pro-inflammatory cytokines. GFH018 exhibits potent antitumor efficacy in several syngeneic mouse models as monotherapy or combinational therapy with anti-PD-L1 antibodies[82]. Currently, the combination of GFH018 and toripalimab is being investigated in patients with advanced solid tumors in an ongoing phase Ib/II clinical trial (NCT04914286).

AVID200 is a TGFβ1 trap that binds to TGFβ1 and *TGF*β3, but not TGFβ2. AVID200 has been investigated in a phase I study (NCT03895112) which recruited 12 patients with myelofibrosis who were resistant, intolerant, or unsuitable for ruxolitinib and had grade 2+ myelofibrosis and platelet count $>25 \times 10^9$/L. During dose escalation, 8 patients had grade 3/4 side effects, the majority of which were hematologic (anemia, thrombocytopenia), but dose-limiting toxicity (DLTs) did not occur. The spleen size was reduced by more than 50% in 2 patients, and the total symptom score improved by 50% in 5 patients. Interestingly, platelet counts improved in 8 patients, with a median increase of 48%[83].

4.2. *Targeting CSF1/CSF1R pathway*

Colony stimulating factor 1 receptor (CSF1R) belongs to a member of the receptor tyrosine kinases family which is predominantly expressed in myeloid cells, such as DCs, macrophages, monocytes, microglia, and osteoclasts[84]. CSF1 activates CSF1R-mediated downstream signaling pathways and promotes the differentiation of hematopoietic stem/progenitor cells (HSPC) into heterogeneous populations of myeloid cells. However, abnormal activation of CSF1R signaling contributes to inflammatory diseases, neurodegenerative diseases, and cancer[84−86]. The CSF1/CSF1R pathway has attracted increasing attention for its roles in regulating the proliferation, migration, and survival of macrophages, and influencing immune function. Tumor-associated macrophages (TAMs) are recognized to exert immunosuppressive effects in the TME to promote tumor survival and metastasis. The function of CSF1R in modulating TAMs has been well-documented and pharmacological inhibition of CSF1R represents a novel therapeutic strategy for cancer therapy. CSF1R-targeted small-molecule inhibitors as monotherapy and combination treatment are currently in clinical development (Fig. 5B).

Pexidartinib (PLX3397) is an oral CSF1R inhibitor harboring activity against FLT3 and c-KIT, which received FDA approval for the treatment of adult patients with tenosynovial giant cell tumor (TGCT) based on positive results from the phase III ENLIVEN study[87]. In the ENLIVEN study recruiting 120 TGCT patients, pexidartinib achieved a higher ORR (39% *vs*. 0%) and improved patient symptoms compared with placebo[88]. However, severe adverse events were more common in the pexidartinib cohort than the placebo cohort (13% *vs*. 2%), and cholestatic hepatotoxicity was identified as a pexidartinib treatment-associated risk. CSF1R is primarily expressed in microglia in the central nervous system and it was reported that depletion of the microglia reduces tumor burden and invasive capacity. A phase II trial assessed the antitumor effect of pexidartinib in recurrent glioblastoma, however, the results showed no clinical efficacy from the pexidartinib monotherapy cohort[89]. The follow-up evaluation of the pexidartinib drug combination was suggested. Additionally, the safety and tolerability of pexidartinib plus sirolimus to target TAMs were evaluated in soft tissue sarcomas in a phase I study[90]. This combination therapy was well-tolerated, which supports further investigation to determine its clinical efficacy. Besides adult patients, pexidartinib was also well-tolerated in pediatric patients with leukemia and neurofibroma (NCT02390752). Moreover, pexidartinib monotherapy or combination treatment is being investigated in various cancers.

Surufatinib (sulfatinib, HMPL-012) is a kinase inhibitor that selectively targets CSF-1R, FGFR1, and VEGFR 1/2/3. The phase III SANET-ep trial investigated the efficacy of surufatinib among patients diagnosed with extrapancreatic neuroendocrine tumors (NETs)[91]. Surufatinib achieved a markedly longer PFS of 9.2 months *vs*. 3.8 months than placebo in advanced extrapancreatic NETs, with a favorable benefit-to-risk profile. Similarly, another phase III SANET-p study also showed that surufatinib could significantly prolong the median PFS (10.9 *vs*. 3.7 months) compared with a placebo for treating advanced pancreatic NETs[92]. Results from the two trials also revealed that the quality of life of these patients in the surufatinib group was similar to the placebo group except for diarrhea, which advocated the clinical application of surufatinib as a novel treatment option in such a patient population. Based on the promising results of these trials, surufatinib received its first approval in China for treating extrapancreatic NETs in 2020. Surufatinib as either monotherapy or combinatorial therapy is currently under investigation in patients with thyroid cancer, ovarian cancer, breast cancer, and other types of solid tumors (Tables 1 and 2).

Chiauranib is a novel multitargeted inhibitor that simultaneously inhibits CSF1R, VEGFR1-3, PDGFRα, and c-Kit, which has activity against tumor growth, angiogenesis, and chronic inflammation. In preclinical studies, chiauranib presented antitumor potential in mouse models of multiple cancers, including colorectal cancer, non-Hodgkin lymphoma (NHL), acute myeloid leukemia (AML) and HCC. A phase I trial revealed that chiauranib demonstrated favorable pharmacokinetic traits and an acceptable safety profile with potential antitumor effect among patients with refractory advanced solid tumors[93]. Chiauranib monotherapy has entered phase III assessment for patients with small cell lung cancer (SCLC) after two lines of chemotherapy (NCT04830813). Additionally, chiauranib is also under active clinical investigation in a range of cancers as monotherapy or combination therapy.

Compared with pexidartinib, vimseltinib (DCC-3014) has been shown to exhibit significantly improved selectivity to CSF1R and

Table 1 Small-molecule agents under clinical development in immuno-oncology.

Target pathway	Agent	Company	Function	Stage	NCT number
cGAS/STING	ADU-S100/MIW815	Chinook Therapeutics	CDN agonist	Phase I	NCT02675439
	BMS-986301	Bristol-Myers Squibb	CDN agonist	Phase I	NCT03956680
	SB-11285	F-star Therapeutics	CDN agonist	Phase I	NCT04096638
	TAK-676	Takeda	CDN agonist	Phase I	NCT04420884
	BI 1387446	Boehringer Ingelheim	CDN agonist	Phase I	NCT04147234
	GSK3745417	GlaxoSmithKline	Non-CDN agonist	Phase I	NCT03843359
	E7766	Eisai	Macrocycle-bridged CDN	Phase I	NCT04144140
	SNX281	Stingthera	Non-CDN agonist	Phase I	NCT04609579
	MK-2118	Merck Sharp & Dohme	Non-CDN agonist	Phase I	NCT03249792
	IMSA101	ImmuneSensor Therapeutics	cGAMP analogue	Phase I/IIa	NCT04020185
	KL340399	Sichuan Kelun	Non-CDN agonist	Phase I	NCT05387928, NCT05549804
	HG381	HitGen	Non-CDN agonist	Phase I	NCT04998422
	CDK-002 (exoSTING)	Codiak BioSciences	Exsome agonist	Phase I/II	NCT04592484
TLRs	Amplivant	Leiden University	TLR2 agonist	Phase I	NCT02821494
	Poly-ICLC (Hiltonol)	Oncovir	TLR3 agonist	Phase II	NCT02423863
	IDC-G305	Immune Design	TLR4 agonist	Phase I	NCT02015416
	Entolimod	Roswell Park Cancer Institute	TLR5 agonist	Phase I	NCT01527136
	Mobilan (M-VM3)	Panacela Labs	TLR5 agonist	Phase I	NCT02654938
	Imiquimod	Medical University of Graz, United States	TLR7 agonist	Phase III	NCT01861535
				Phase II/III	NCT02130323
		Naval Medical Center,		Phase III	NCT02059499
		VA Office of Research and Development,		Phase III	NCT05212246
				Phase II	NCT03233412
		Barretos Cancer		Phase II	NCT00899574
		Hospital, NYU		Phase II	NCT00941811
		Langone Health		Phase I	NCT04883645
		Medical University of Vienna, Medical University of South Carolina			
	TMX-101	Telormedix SA	TLR7 agonist	Phase II	NCT01731652
	DSP-0509	Sumitomo Pharma Oncology	TLR7 agonist	Phase I/II	NCT03416335
	BNT411	BioNTech SE	TLR7 agonist	Phase I/II	NCT04101357
	RO7119929	Hoffmann-La Roche	TLR7 agonist	Phase I	NCT04338685
	LHC165	Novartis	TLR7 agonist	Phase I	NCT03301896
	Motolimod (VTX-2337)	Celgene	TLR8 agonist	Phase I	NCT03906526
	Tilsotolimod (IMO-2125)	A.J.M. van den Eertwegh	TLR9 agonist	Phase II	NCT04126876
	Lefitolimod (MGN 1703)	Mologen	TLR9 agonist	Phase II	NCT02200081
	1018 ISS	Dynavax	TLR9 agonist	Phase I	NCT00403052
	BCG	Southwest Oncology Group	Multi-TLR agonist	Phase III	NCT03091660
PD-1/PD-L1	GS-4224	Gilead Sciences	PD-L1 antagonist	Phase I	NCT04049617
	INCB086550	Incyte	PD-L1 antagonist	Phase I	NCT03762447
				Phase II	NCT04629339
	ASC61	Gannex Pharma	PD-L1 antagonist	Phase I	NCT05287399
	IMMH-010	Tianjin Chasesun Pharmaceutical	PD-L1 antagonist	Phase I	NCT04343859
	MAX-10181	Maxinovel Pty	PD-L1 antagonist	Phase I	NCT05196360
				Phase I	NCT04122339
	BPI-371153	Betta Pharmaceuticals	PD-L1 antagonist	Phase I	NCT05341557
VISTA	CA170	BMS & Aurigene	PD-L1/VISTA antagonist	Phase I	NCT02812875
TβRI	Galunisertib	Eli Lilly & Co.	TβRI inhibitor	Phase I/II	NCT02408744
				Phase I/II	NCT03470350

Table 1 (*continued*)

Target pathway	Agent	Company	Function	Stage	NCT number
				Phase I	NCT02304419
				Phase I	NCT01722825
	Vactosertib	Ewha Womans University	TβRI inhibitor	Phase I	NCT03074006
				Phase I/II	NCT03698825
				Phase II	NCT04103645
	LY3200882	Eli Lilly & Co.	TβRI inhibitor	Phase I/II	NCT04031872
	TP-0184	Tolero Pharmaceuticals Inc.	TβRI inhibitor	Phase I/II	NCT04623996
				Phase I	NCT03429218
	GFH018	Genfleet	TβRI inhibitor	Phase I	NCT05051241
CSF1R	Pexidartinib	Daiichi Sankyo	CSF1R, c-KIT, FLT3	Phase III	NCT04488822
	Surufatinib	Hutchison Medipharma	CSF-1R, VEGFR1−3, FGFR1	Phase II	NCT05171439
				Phase II	NCT02614495
				Phase III	NCT02588170
	Chiauranib	Chipscreen Biosciences	CSF1R, VEGFR1−3, PDGFRα, c-Kit	Phase I/II	NCT03166891
				Phase I/II	NCT03245190
				Phase II	NCT05497843
				Phase III	NCT04830813
	Vimseltinib	Deciphera Pharmaceuticals	CSF1R inhibitor	Phase I/II	NCT03069469
				Phase III	NCT05059262
	JNJ-40346527	Johnson Pharmaceuticals	CSF1R inhibitor	Phase I	NCT03177460
				Phase I	NCT01572519
				Phase II	NCT03557970
	ARRY-382	Array Biopharma	CSF1R inhibitor	Phase I	NCT01316822
Chemokine receptor	Plozalizumab	Millennium Pharmaceuticals	CCR2 antagonist	Phase I	NCT02723006
	BMS-813160	Bristol-Myers Squibb	CCR2/5 antagonist	Phase I/II	NCT03496662
				Phase I/II	NCT03767582
Arginine metabolism	INCB001158	Incyte	ARG1 antagonist	Phase II	NCT02903914
				Phase II	NCT03910530
IDO1	Epacadostat	Incyte	IDO1 inhibitor	Phase III	NCT02752074
				Phase III	NCT03361865
	Indoximod	NewLink	IDO1 inhibitor	Phase II	NCT01560923
	Linrodostat	Flexus/BMS	IDO1 inhibitor	Phase III	NCT03329846
Prostaglandin pathway	SC-58635	Pfizer	COX2 inhibitor	Phase III	NCT02429427
				Phase II	NCT00527982
				Phase II	NCT01158534
				Phase II	NCT00499655
	ONO-4578	Ono Pharmaceutical Co., Ltd.	EP4 antagonist	Phase I	NCT03155061
	E7046	Adlai Nortye Biopharma Co., Ltd.	EP4 antagonist	Phase I	NCT02540291
				Phase I	NCT04432857
Adenosine receptor	Arcus	Arcus Biosciences	CD73 inhibitor	Phase II	NCT04660812
				Phase II	NCT04381832
	ORIC-533	ORIC Pharmaceuticals	CD73 inhibitor	Phase I	NCT05227144
	CS3005	CStone Pharmaceuticals	A2aR inhibitor	Phase I	NCT04233060
	EXS21546	Exscientia Limited	A2aR inhibitor	Phase I	NCT04727138
	INCB106385	Incyte Corporation	A2aR inhibitor	Phase I	NCT04580485
	TT-10	Tarus Therapeutics	A2aR inhibitor	Phase I/II	NCT04969315
	Ciforadenant	Corvus	A2aR inhibitor	Phase I	NCT03454451
				Phase I	NCT02655822
				Phase I/II	NCT05501054
	Inupadenant	iTeos	A2aR inhibitor	Phase I	NCT05117177
				Phase II	NCT05403385
				Phase I/II	NCT05060432
	AZD4635	AstraZeneca	A2aR inhibitor	Phase I/II	NCT03381274
				Phase I	NCT04478513
	Taminadenant (PBF-509, NIR178)	Novartis Pharmaceuticals	A2aR inhibitor	Phase I	NCT02403193
				Phase I	NCT03786484
				Phase II	NCT03207867
	Preladenant (MK-3814, SCH-420814)	Merck	A2aR inhibitor	Phase Ib/II	NCT03099161

(*continued on next page*)

Table 1 (*continued*)

Target pathway	Agent	Company	Function	Stage	NCT number
	Etrumadenant	Arcus	A2aR/A2bR inhibitor	Phase II	NCT05177770
					NCT04262856
PI3K	Eganelisib	Infinity Pharmaceuticals	PI3Kγ inhibitor	Phase II	NCT03795610
	Idelalisib	Gilead Sciences	PI3Kδ inhibitor	Phase II	NCT01282424
				Phase II	NCT01393106
	Umbralisib	TG Therapeutics	PI3Kδ/CK1ε inhibitor	Phase II	NCT02742090
	Parsaclisib	Incyte	PI3Kδ inhibitor	Phase II	NCT04434937
				Phase II	NCT02998476
	Zandelisib	MEI Pharma	PI3Kδ inhibitor	Phase II	NCT03768505
	Linperlisib	Shanghai YingLi Pharmaceutical	PI3Kδ inhibitor	Phase II	NCT05274997
	Copanlisib	Bayer	PI3Kα/δ inhibitor	Phase III	NCT02369016
	Taselisib	Roche Group	PI3Kα/δ inhibitor	Phase II	NCT02785913
	Duvelisib	Verastem	PI3Kγ/δ inhibitor	Phase III	NCT02004522
	Tenalisib	Rhizen Pharmaceuticals	PI3Kγ/δ inhibitor	Phase II	NCT03711578
				Phase II	NCT04204057
				Phase II	NCT05021900
	Buparlisib	Adlai Nortye	Pan-PI3K inhibitor	Phase II	NCT01790932
	Pictilisib	Roche; Genentech	Pan-PI3K inhibitor	Phase I	NCT00876109
JAK	Ruxolitinib	Incyte	JAK1/2 inhibitor	Phase II	NCT03153982
				Phase II	NCT03722407
				Phase III	NCT00952289
				Phase III	NCT00934544
	Fedratinib	TargeGen	JAK2 inhibitor	Phase II	NCT05177211
				Phase III	NCT01437787
				Phase II	NCT01523171
	Pacritinib	Cell Therapeutics	JAK2 inhibitor	Phase I/II	NCT04520269
				Phase II	NCT04635059
				Phase II	NCT02277093
				Phase III	NCT01773187
				Phase III	NCT02055781
	Momelotinib	Sierra Oncology	JAK1/2 inhibitor	Phase III	NCT01969838
				Phase III	NCT02101268
				Phase III	NCT04173494
HPK-1	CFI-402411	Treadwell Therapeutics, Inc.	HPK-1 inhibitor	Phase I/II	NCT04521413
	BGB-15025	BeiGene	HPK-1 inhibitor	Phase I	NCT04649385
	PF-07265028	Pfizer	HPK-1 inhibitor	Phase I	NCT05233436
	PRJ1-3024	Zhuhai Yufan Biotechnologies Co.	HPK-1 inhibitor	Phase I/II	NCT05315167
	NDI-101150	Nimbus Saturn, Inc.	HPK-1 inhibitor	Phase I/II	NCT05128487
RON	BMS 777607	Bristol-Myers Squibb	RON/c-Met inhibitor	Phase I/II	NCT00605618
	(ASLAN002)	Aslan Pharmaceuticals	RON/c-Met inhibitor	Phase I	NCT01721148
RORγt	LYC-55716	Lycera	RORγt agonist	Phase II	NCT02929862
Bromodomain	ABBV-075	AbbVie	Bromodomain inhibitor	Phase I	NCT02391480
	Alobresib	Gilead Sciences	Bromodomain inhibitor	Phase I/II	NCT02607228
				Phase I	NCT02392611
	BAY 1238097	Bayer	Bromodomain inhibitor	Phase I	NCT02369029
	Birabresib	Merck Sharp & Dohme LLC	Bromodomain inhibitor	Phase I	NCT02698189
				Phase I	NCT02698176
				Phase II	NCT02296476
				Phase I	NCT02259114
				Phase I	NCT01713582
	BMS-986158	Bristol-Myers Squibb	Bromodomain inhibitor	Phase I/II	NCT02419417
	BMS-986378	Bristol-Myers Squibb	Bromodomain inhibitor	Phase I	NCT03936465
	CC-90010	Celgene	Bromodomain inhibitor	Phase I	NCT03220347
	CCS1477	CellCentric Ltd.	Bromodomain	Phase I/II	NCT04068597

Table 1 (*continued*)

Target pathway	Agent	Company	Function	Stage	NCT number
			inhibitor	Phase I/II	NCT03568656
	CPI-0610	Constellation Pharmaceuticals	Bromodomain inhibitor	Phase II	NCT02986919
				Phase I/II	NCT02158858
				Phase I	NCT02157636
				Phase I	NCT01949883
	GSK2820151	GlaxoSmithKline	Bromodomain inhibitor	Phase I	NCT02630251
	GSK525762	GlaxoSmithKline	Bromodomain inhibitor	Phase II	NCT01943851
				Phase I	NCT01587703
	INCB054329	Incyte Corporation	Bromodomain inhibitor	Phase I/II	NCT02431260
	INCB057643	Incyte Corporation	Bromodomain inhibitor	Phase I/II	NCT02711137
	RO6870810	Hoffmann-La Roche	Bromodomain inhibitor	Phase I	NCT03068351
				Phase I	NCT02308761
				Phase I	NCT01987362
	SYHA1801	CSPC ZhongQi Pharmaceutical Technology Co., Ltd.	Bromodomain inhibitor	Phase I	NCT04309968
	TQB3617	Chia Tai Tianqing Pharmaceutical Group Co., Ltd.	Bromodomain inhibitor	Phase I	NCT05110807
	ZEN003694	Zenith Epigenetics	Bromodomain inhibitor	Phase II	NCT05607108
				Phase I	NCT02705469
DHODH	RP7214	Rhizen Pharmaceuticals SA	DHODH inhibitor	Phase I/II	NCT05246384
	BAY2402234	Bayer	DHODH inhibitor	Phase I	NCT03404726
	AG-636	Agios Pharmaceuticals, Inc.	DHODH inhibitor	Phase I	NCT03834584
	ASLAN003	Aslan Pharmaceuticals	DHODH inhibitor	Phase II	NCT03451084
	Leflunomide	Joseph Sparano, Icahn School of Medicine at Mount Sinai	DHODH inhibitor	Phase I/II	NCT03709446
		University Hospital, Basel, Switzerland		Not applicable	NCT05605587
		City of Hope Medical Center, National Cancer Institute (NCI)		Phase I/II	NCT02509052
	PTC299	PTC Therapeutics	DHODH inhibitor	Phase I	NCT03761069

more durable suppression of CSF1R activity *in vitro* and *in vivo*. Vimseltinib was also found to significantly suppress tumor growth in mouse models of tumors. Vimseltinib is currently being studied as monotherapy in TGCT and combined with avelumab (anti-PD-L1 antibody) for sarcoma in various ongoing clinical trials at different stages (NCT03069469, NCT05059262, NCT04242238).

In a phase I/II trial (NCT02880371), while combination therapy of the CSF1R-selective inhibitor ARRY-382 (PF-07265804) with pembrolizumab was well-tolerated, it only exhibited limited clinical benefit in cancer patients, which resulted in premature termination of the study[94]. Similarly, another selective inhibitor of CSF-1R, JNJ-40346527 (edicotinib) also showed limited clinical activity against refractory or relapsed Hodgkin lymphoma in phase I/II trial[95]. Additionally, BLZ945 (sotuletinib) alone and combination therapy with spartalizumab (anti-PD-1 antibody) are underway to be assessed in advanced solid tumors (NCT02829723).

Collectively, CSF1R inhibitors represent a novel category of immunomodulatory drugs, however, the clinical efficacy is limited because of the existence of other immunosuppressive molecules and cells in TME. The combination of CSF1R inhibitors with chemotherapy, anti-angiogenic drugs, or immunotherapy may provide better clinical outcomes and they are under clinical evaluation.

4.3. *Targeting chemokine receptors*

Chemokines and their receptors are important mediators of immune cell trafficking, which play a central role in the composition of TME, proliferation, and metastasis of cancer cells[96]. Leukocyte recruitment and activation, angiogenesis, cancer cell proliferation, and metastasis are regulated by chemokines and their receptors. The precise movement of immune cells, such as leukocyte recruitment, was controlled by the spatial and temporal expression of chemokines. Chemokines can directly stimulate the growth of cancer cells *via* activating various signaling pathways, including PI3K/AKT/NF-κB and MAPK/ERK pathways. Importantly, the chemokine/chemokine receptor pathways have pleiotropic effects on tumor cells and immune cells. Some exert antitumor function by inducing the activation and differentiation of immunostimulatory cells while

Table 2 Small-molecule agents in combinational therapies.

Target	Agent	Combination	NCT number	Indication	Status/phase
cGAS/STING	ADU-S100	+Ipilimumab	NCT02675439	Advanced/metastatic solid tumors	Phase I, Terminated
		+PDR001	NCT03172936	Advanced solid tumors or lymphomas	Phase I, Terminated
		+Pembrolizumab	NCT03937141	Head and neck squamous cell carcinoma	Phase II, Terminated
	MK-1454	+Pembrolizumab	NCT03010176	Advanced solid tumors or lymphomas	Phase I, Completed
		+Pembrolizumab	NCT04220866	Head and neck squamous cell carcinoma	Phase II, Completed
	BMS-986301	+Nivolumab +Ipilimumab	NCT03956680	Advanced solid tumors	Phase I, Active, not recruiting
	SB 11285	+Atezolizumab	NCT04096638	Solid tumors	Phase I, Recruiting
	TAK-676	+Radiation +Pembrolizumab	NCT04879849	Non-small cell lung cancer, Triple negative breast cancer, Head and neck squamous cell carcinoma	Phase I, Recruiting
		+Pembrolizumab /Chemotherapy	NCT04420884	Advanced solid tumors	Phase I, Recruiting
	BI 1387446	+BI 754091	NCT04147234	Advanced solid tumors	Phase I, Active, not recruiting
	GSK3745417	+Dostarlimab	NCT03843359	Advanced solid tumors	Phase I, Active, not recruiting
	SNX281	+Pembrolizumab	NCT04609579	Advanced solid tumors, lymphomas	Phase I, Recruiting
	MK-2118	+Pembrolizumab	NCT03249792	Advanced solid tumors, lymphomas	Phase I, Completed
	IMSA101	+ICIs	NCT04020185	Advanced solid tumors	Phase I/II, Recruiting
TLRs	XS15	+Multi-peptide vaccine +Ibrutinib	NCT04688385	Chronic lymphocytic lymphoma	Phase I, Recruiting
	Poly-ICLC (Hiltonol)	+Vaccine +GM-CSF +Chemotherapy	NCT02873819	Squamous cell carcinoma of the oral cavity	Phase II, Completed
		+Vaccine	NCT01204684	Brain tumors	Phase II, Active, not recruiting
		+Vaccine +IFA	NCT01079741	Melanoma	Phase I/II, Completed
		+Vaccine +Bevacizumab	NCT02078648	Glioblastoma	Phase I/II, Completed
		+Durvalumab +Tremelimumab	NCT02643303	Solid tumors	Phase I/II, Completed
		+Vaccine +Tetanus peptide +IFA	NCT02126579	Melanoma	Phase I/II, Unknown
		+Vaccine +GuaDecitabine +Atezolizumab	NCT03206047	Recurrent ovarian, Fallopian tube, Primary peritoneal cancer	Phase I/II, Active, not recruiting
		+rhuFlt3L /CDX-301 +Radiotherapy	NCT01976585	B-cell lymphoma	Phase I/II, Completed
		+Vaccine +Anti-CD40	NCT04364230	Melanoma	Phase I/II, Recruiting
		+Pembrolizumab	NCT02834052	Metastatic Colorectal cancer	Phase I/II, Completed
		+Vaccine +Chemotherapy	NCT01834248	Acute myeloid leukemia, Myelodysplastic syndrome	Phase I, Completed
		+Vaccine +Nivolumab	NCT03358719	Acute myeloid leukemia	Phase I, Completed

	+Chemotherapy +Vaccine +Pembrolizumab	NCT03380871	Lung cancer	Phase I, Completed
	+Chemotherapy +Vaccine +IFA	NCT01585350	Melanoma	Phase I, Completed
	+Vaccine	NCT01677962	Pancreatic adenocarcinoma	Phase I, Completed
	+Vaccine	NCT02721043	Solid tumors	Phase I, Completed
	+Lenalidomide +Vaccine +Nivolumab	NCT02897765	Solid tumors	Phase I, Completed
	+Vaccines +Tadalafil	NCT02544880	HNSCC	Phase I, Completed
	+Vaccine +Citarinostat +Lenalidomide	NCT02886065	Multiple myeloma	Phase I, Completed
	+Vaccine +Durvalumab	NCT02826434	Breast cancer	Phase I, Active, not recruiting
	+Vaccine +Pembrolizuma	NCT03362060	Breast cancer	Phase I, Active, not recruiting
	+Peptide vaccine +anti-CD27	NCT02924038	Glioma	Phase I, Active, not recruiting
	+Vaccine +Nivolumab	NCT02960230	Glioma	Phase I/II, Active, not recruiting
	+Vaccine /neoadjuvant	NCT02549833	Glioma	Phase I, Active, not recruiting
	+Vaccine	NCT03300817	Lung cancer	Phase I, Active, not recruiting
	+Neoadjuvant	NCT03262103	Prostate cancer	Phase I, Completed
Rintatolimod	+Vaccines +IFA	NCT01312389	Recurrent ovarian, Fallopian tube, Primary peritoneal cancer	Phase I/II, Terminated
	+Chemokine	NCT03403634	Colorectal cancer with liver metastasis	Phase II, Completed
	+Pembrolizumab +Chemotherapy	NCT03734692	Recurrent platinum-sensitive ovarian cancer	Phase I/II, Recruiting
	+IFNα-2b	NCT04379518	Cancer patients with mild or moderate COVID-19 infection	Phase I/II, Suspended
BO-112	+Pembrolizumab	NCT04570332	Melanoma	Phase II, Active, not recruiting
GLA-SE (G100)	+Vaccine	NCT02320305	Melanoma	Phase I, Active, not recruiting
	+Radiotherapy	NCT02035657	Merkel cell carcinoma	Phase I, Completed
	+Radiotherapy	NCT02180698	Sarcoma	Phase I, Completed
GSK1795091	+Pembrolizumab /GSK3174998 /GSK3359609	NCT03447314	Solid tumors	Phase I, Completed

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Table 2 (*continued*)

Target	Agent	Combination	NCT number	Indication	Status/phase
	TriMix DC	+Vaccine	NCT01530698	Melanoma	Phase I/II, Completed
	Imiquimod	+Paracetamol +Iidocaine	NCT02385188	Vulvar Paget disease	Phase III, Completed
		+Curettage	NCT02242929	Basal cell carcinoma	Phase III, Active, not recruiting
		+Radiation or +Chemotherapy	NCT01421017	Breast cancer	Phase II, Completed
		+Sonidegib	NCT03534947	Basal cell carcinoma	Phase II, Recruiting
		+Vaccine	NCT02864147	Cervical intraepithelial neoplasia	Phase II, Active, not recruiting
		+Vaccine +Lenalidomide	NCT02802943	Chronic lymphocytic lymphoma	Phase II, Completed
		+Vaccine	NCT03180684	VIN2/3 and vulvar HSIL	Phase II, Completed
		+Vaccine +Chemotherapy +Sargramostim	NCT02276300	Gastric cancer, Breast cancer	Phase I, Completed
		+Chemotherapy/ Radiotherapy/Vaccine	NCT01678352	Glioma (grade II)	Phase I, Completed
		+Vaccine	NCT02454634	Glioma	Phase I, Completed
		+Vaccine +IFA	NCT02293707	Prostate carcinoma	Phase II, Completed
		+Vaccines +Chemotherapy	NCT02234921	Prostate carcinoma	Phase I, Completed
		+Surgery	NCT05055050	Bladder cancer	Phase I, Recruiting
		+Zalifrelimab	NCT05375903	Recurrent bladder cancer	Phase I, Recruiting
		+Chemotherapy	NCT03196180	CIN	Phase I, Active, not recruiting
		+Ultrasound ablation/ Pembrolizumab/ Atezolizumab	NCT04116320	Solid tumors	Phase I, Recruiting
		+Vaccine +Chemotherapy +Nivolumab +Pembrolizumab	NCT03872947	Solid tumors	Phase I, Recruiting
		+Chemotherapy	NCT03370406	Squamous cell carcinoma	Phase I, Recruiting
		+Vaccine +Toripalimab +GM-CSF	NCT04072900	Melanoma	Phase I, Unknown
		+Pembrolizumab	NCT03276832	Melanoma	Phase I, Active, not recruiting
		+Vaccine +hP1A8	NCT04642937	Recurrent glioblastoma	Phase I, Active, not recruiting
		+Vaccine +Atezolizumab	NCT04808245	H3-mutated glioma	Phase I, Recruiting
	SHR2150	+Chemotherapy +anti-PD-1/anti-CD47	NCT04588324	Metastatic solid tumors	Phase I/II, Unknown
	DSP-0509	+Pembrolizumab	NCT03416335	Tumors	Phase I/II, Completed
	BNT411	+Chemotherapy /Atezolizumab	NCT04101357	Solid tumors	Phase I/II, Recruiting

RO7119929	+Tocilizumab	NCT04338685	Hepatocellular carcinoma, Biliary tract cancer	Phase I/II, Completed
LHC165	+PDR001	NCT03301896	Solid tumors	Phase I/II, Terminated
Resiquimod	+Vaccine	NCT01204684	Brain tumors	Phase II, Active, not recruiting
	+Vaccine +IFA	NCT00821652	Melanoma	Phase I/II, Completed
	+Vaccine/IFA	NCT02126579	Melanoma	Phase I/II, Unknown
Motolimod (VTX-2337)	+Chemotherapy	NCT01666444	Epithelial ovarian cancer, Fallopian tube cancer, Primary peritoneal cancer	Phase II, Completed
	+Chemotherapy +Cetuximab	NCT01836029	Squamous cell carcinoma of the head and neck	Phase II, Completed
	+Durvalumab +Chemotherapy	NCT02431559	Ovarian cancer	Phase I/II, Completed
	+Nivolumab	NCT03906526	Head and neck squamous cell carcinoma	Phase I, Terminated
	+Cetuximab	NCT01334177	Squamous cell cancer of head and neck	Phase I, Completed
	+chemotherapy	NCT01294293	Epithelial ovarian cancer, Fallopian tube cancer, Primary peritoneal cancer	Phase I, Completed
CMP-001	+Nivolumab	NCT04695977	Melanoma	Phase II/III, Active, not recruiting
	+Avelumab +Utomilumab +PF-04518600	NCT02554812	Advanced cancer	Phase I/II, Terminated
	+Nivolumab	NCT04401995	Melanoma	Phase II, Recruiting
	+Pembrolizumab	NCT04708418	Melanoma	Phase II, Recruiting
	+Pembrolizumab	NCT04633278	Head and neck squamous cell carcinoma	Phase II, Active, not recruiting
	+Nivolumab	NCT04698187	Melanoma	Phase II, Active, not recruiting
	+Cemiplimab-rwlc	NCT04916002	Multiple tumor types	Phase II, Recruiting
	+Radiotherapy	NCT04807192	Triple-negative breast cancer	Phase II, Recruiting
	+Nivolumab	NCT03618641	Melanoma, Lymphoma	Phase II, Active, not recruiting
	+Ipilimumab +Anti-OX40	NCT04387071	Advanced pancreatic cancer, Solid tumors	Phase I/II, Terminated
	+Pembrolizumab	NCT03983668	Lymphoma	Phase I/II, Recruiting
SD-101	+Pembrolizumab +Radiotherapy	NCT03007732	Prostate cancer	Phase II, Active, not recruiting
	+Ipilimumab +Radiotherapy	NCT02254772	Lymphoma	Phase I/II, Completed
	+Epacadostat +Radiotherapy	NCT03322384	Solid tumors, lymphoma	Phase I/II, Completed
	+Ibrutinib +Radiotherapy	NCT02927964	Lymphoma	Phase I/II, Active, not recruiting
	+BMS-986178 +Radiotherapy	NCT03410901	Lymphoma	Phase I, Active, not recruiting
	+Nivolumab +Radiotherapy	NCT04050085	Pancreatic adenocarcinoma	Phase I, Active, not recruiting
	+BMS 986178	NCT03831295	Solid tumors	Phase I, Active, not recruiting
	+Nivolumab/Ipilimumab	NCT04935229	Liver metastatic uveal melanoma	Phase I, Recruiting

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Table 2 (*continued*)

Target	Agent	Combination	NCT number	Indication	Status/phase
	PF-03152676	+Vaccine +ACT +Rituximab +Chemotherapy +Filgrastim	NCT00490529	Mantle cell lymphoma	Phase II, Completed
	CpG7910	+Radiotherapy	NCT00185965	Recurrent lymphomas	Phase I/II, Completed
	Tilsotolimod (IMO-2125)	+Ipilimumab +Nivolumab	NCT03865082	Advanced solid tumors	Phase II, Active, not recruiting
		+Ipilimumab +Nivolumab	NCT04270864	Advanced solid tumors	Phase I, Active, not recruiting
	Lefitolimod (MGN1703)	+Ipilimumab	NCT02668770	Melanoma	Phase I, Active, not recruiting
	BCG	+Lenalidomide	NCT01373294	Bladder cancer	Phase II, Completed
		+Vaccine	NCT02015104	Bladder cancer	Phase II, Completed
		+Sunitinib	NCT00794950	Lower urinary tract urothelial carcinoma	Phase II, Completed
		+Nivolumab/BMS-986205	NCT03519256	Bladder cancer	Phase II, Terminated
		+ALT803	NCT03022825	Bladder cancer	Phase II/III, Recruiting
		+Atezolizumab	NCT02792192	Bladder cancer	Phase I/II, Terminated
		+ALT803	NCT02138734	Bladder cancer	Phase I/II, Recruiting
		+Durvalumab	NCT03317158	Bladder cancer	Phase I/II, Recruiting
		+Rapamycin	NCT02753309	Bladder cancer	Phase I, Completed
		+Pembrolizumab	NCT02808143	Bladder cancer	Phase I, Active, not recruiting
		+Chemotherapy +RFA +GM-CSF	NCT04062721	CRC with liver metastasis	Phase I, Not yet recruiting
VISTA	CA170	+Enzalutamide +Bicalutamide	NCT01288911	Prostatic neoplasms	Phase II, Completed
TβRI	Galunisertib	+Durvalumab	NCT02734160	Pancreatic cancer	Phase I, Completed
		+Nivolumab	NCT02423343	Non-small cell lung cancer, Hepatocellular carcinoma	Phase I/II, Completed
		+Enzalutamide	NCT02452008	Prostate cancer	Phase II, Recruiting
		+Sorafenib	NCT02240433	Hepatocellular carcinoma	Phase I, Completed
		+Capecitabine	NCT05700656	Colorectal cancer	Phase I/II, Not yet recruiting
		+Lomustine	NCT01582269	Glioblastoma	Phase II, Active, not recruiting
		+Paclitaxel +Carboplatin	NCT03206177	Ovarian carcinosarcoma	Phase I, Active, not recruiting
	Vactosertib	+Pomalidomide	NCT03143985	Multiple myeloma	Phase I, Active, not recruiting
		+Durvalumab	NCT04893252	Stomach neoplasm	Phase II, Recruiting
		+Paclitaxel	NCT03698825	Metastatic gastric cancer	Phase I/II, Unknown
		+Durvalumab	NCT03732274	Non-small cell lung cancer	Phase I/II, Unknown
		+Pembrolizumab	NCT03724851	Metastatic colorectal or gastric cancer	Phase I/II, Active, not recruiting
	LY3200882	+Pembrolizumab	NCT04158700	Advanced cancer	Phase I/II, Withdrawn
		+Capecitabine	NCT04031872	Colorectal cancer	Phase I/II, Unknown
	GFH018	+Toripalimab	NCT04914286	Advanced solid tumor	Phase I/II, Recruiting
	YL-13027	+Sintilimab	NCT05457517	Solid tumors	Phase I/II, Recruiting

CSF1R, c-KIT, FLT3	Pexidartinib	+Binimetinib	NCT03158103	Gastrointestinal stromal tumor	Phase I, Completed
		+Paclitaxel	NCT01525602	Solid tumors	Phase I, Completed
		+Durvalumab	NCT02777710	Solid tumors	Phase I, Completed
		+Sunitinib	NCT02401815	Gastrointestinal stromal tumor	Phase I/II, Completed
		+Radiation +Temozolomide	NCT01790503	Glioblastoma	Phase I/II, Completed
		+Pembrolizumab	NCT02452424	Solid tumors	Phase I/II, Terminated
		+Sirolimus	NCT02584647	Sarcoma	Phase I/II, Recruiting
CSF-1R, VEGFR1−3, FGFR1	Surufatinib	+Tislelizumab	NCT05746728	Breast cancer	Phase I/II, Not yet recruiting
		+Gemcitabine	NCT05093322	Solid tumors	Phase I/II, Active, not recruiting
		+Pamiparib	NCT05652283	Ovarian cancer	Phase II, Recruiting
		+Envafolimab	NCT05722977	Sarcoma	Phase II, Not yet recruiting
		+Vinorelbine	NCT04922658	Non-small cell lung cancer	Phase II, Recruiting
		+Toripalimab	NCT05030246	Solid tumors	Phase II, Recruiting
		+Capecitabine	NCT03873532	Biliary tract cancer	Phase II/III, Unknown
		+Toripalimab	NCT05015621	Neuroendocrine carcinoma	Phase III, Recruiting
CSF1R, VEGFR1−3, PDGFRα, c-Kit	Chiauranib	+Capecitabine	NCT05336721	Breast cancer	Phase II, Recruiting
		+Etoposide +Paclitaxel	NCT03901118	Ovarian cancer	Phase II, Completed
CSF1R	Vimseltinib	+Avelumab	NCT04242238	Sarcoma	Phase I, Active, not recruiting
		+Pembrolizumab	NCT02880371	Solid tumors	Phase I/II, Terminated
		+Spartalizumab	NCT02829723	Solid tumors	Phase I/II, Terminated
CCR5	Leronlimab	+Carboplatin	NCT03838367	Triple negative breast neoplasms	Phase I/II, Active, not recruiting
	Maraviroc	+Pembrolizumab	NCT03274804	Metastatic colorectal cancer	Phase I, Completed
		+Chemotherapy	NCT03631407	Colorectal neoplasms	Phase II, Completed
	Vicriviroc	+Pembrolizumab	NCT03631407	Colorectal neoplasms	Phase II, Completed
	MK-7690	+Pembrolizumab	NCT00976378	Microsatellite stable colorectal cancer	Phase I, Completed
CCR2/5	BMS-813160	+Nivolumab	NCT04123379	Non-small cell lung cancer, Hepatocellular carcinoma	Phase II, Recruiting
CXCL8	BMS-986253	+Nivolumab	NCT03689699	Prostate cancer	Phase I/II, Active, not recruiting
			NCT04050462	Hepatocellular carcinoma	Phase II, Active, not recruiting
			NCT03400332	Melanoma	Phase I/II, recruiting
			NCT04572451	Melanoma, Renal cell carcinoma, Unresectable solid tumors	Phase I, recruiting
			NCT04123379	Non-small cell lung cancer, Hepatocellular carcinoma	Phase II, Recruiting
			NCT04848116	Head and neck squamous cell carcinoma	Phase II, Recruiting
ARG1	INCB001158	+Pembrolizumab	NCT02903914	Advanced/metastatic solid tumors	Phase I/II, Completed
IDO1	Epacadostat	+Pembrolizumab	NCT02752074	Metastatic melanoma	Phase III, Completed
		+Pembrolizumab	NCT03361865	Urothelial carcinoma	Phase III, Completed
Prostaglandin pathway	Celecoxib (SC-58635)	+Toripalimab	NCT03926338	Colorectal cancer	Phase I/II, Recruiting
		+5-fluorouracil /oxaliplatin /leucovorin	NCT01150045	Colorectal cancer	Phase III, Active, not recruiting
		+Atorvastatin	NCT01220973	Prostate cancer	Phase II, Completed
		+Erlotinib hydrochloride	NCT00499655	Non-small cell lung cancer	Phase II, Completed

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Table 2 (*continued*)

Target	Agent	Combination	NCT number	Indication	Status/phase
	ONO-4578	+Nivolumab	NCT03155061	Advanced or metastatic solid tumors	Phase I, Active, not recruiting
	E7046	+Pelvic radiotherapy + Capecitabine/ folinic acid/5-FU/oxaliplatin (mFOLFOX-6)	NCT03152370	Rectal cancer	Phase I, Completed
		+Atezolizumab	NCT04975958	Locally advanced solid tumor	Phase I, Recruiting
		+Pembrolizumab	NCT04432857	Advanced solid tumors	Phase I, Recruiting
	CR6086	+Balstilimab	NCT05205330	Colorectal cancer	Phase I/II, Active, not recruiting
A2aR	Etrumadenant	+Zimberelimab +Domvanalimab	NCT04791839	Lung cancer	Phase II, Recruiting
	Ciforadenant	+CPI-006	NCT03454451	Non-small cell lung cancer, Renal cell cancer, Colorectal cancer	Phase I, Active, not recruiting
		+Atezolizumab	NCT02655822	Renal cell cancer, Prostate cancer	Phase I, Completed
		+lpilimumab/nivolumab	NCT05501054	Renal cell carcinoma	Phase I/II, Recruiting
	Inupadenant	+Chemotherapy	NCT05403385	Non-small cell lung cancer	Phase II, Recruiting
	taminadenant	+PDR001	NCT02403193	Non-small cell lung cancer	Phase I, Completed
		+DFF332/spartalizumab	NCT04895748	Renal cell carcinoma	Phase I, Recruiting
	AZD4635	+Durvalumab +Oleclumab	NCT04089553	Prostate cancer	Phase II, Active, not recruiting
PI3Kα	Alpelisib	+Fulvestrant	NCT02437318	Breast cancer	Phase III, Active, not recruiting
		+Trastuzumab +Pertuzumab	NCT04208178	Breast cancer	Phase III, Recruiting
		+Olaparib	NCT04729387	Ovarian cancer	Phase III, Recruiting
		+Capecitabine	NCT04753203	Colorectal cancer	Phase I/II, Not yet recruiting
		+Paclitaxel	NCT04526470	Gastric cancer	Phase I/II, Recruiting
		+Tipifarnib	NCT04997902	Head and neck squamous cell carcinoma	Phase I/II, Recruiting
	Inavolisib	+Giredestrant	NCT05708235	Breast cancer	Phase II, Not yet recruiting
		+Fulvestrant	NCT05646862	Breast cancer	Phase III, Recruiting
		+Palbociclib +Fulvestrant	NCT04191499	Breast cancer	Phase II/III, Recruiting
	Serabelisib	+Sapanisertib +Paclitaxel	NCT03154294	Solid Tumors	Phase I, Active, not recruiting
		+Cisplatin +Nab Paclitaxel	NCT03193853	Triple-negative breast cancer	Phase II, Active, not recruiting
PI3Kγ	Eganelisib	+Etrumadenant +PLD	NCT03719326	Triple-negative breast cancer	Phase I, Completed
		+Nivolumab	NCT03980041	Urothelial carcinoma	Phase II, Completed
		+Atezolizumab +Nab-paclitaxel/ bevacizumab	NCT03961698	Triple-negative breast cancer, Renal cell carcinoma	Phase II, Active, not recruiting
PI3Kδ	Idelalisib	+Lenalidomide	NCT01838434	Mantle cell lymphoma	Phase I, Completed
		+Entospletinib	NCT01796470	Chronic lymphocytic lymphoma, Mantle cell lymphoma	Phase II, Terminated
		+Obinutuzumab	NCT03890289	Follicular lymphoma	Phase II, Active, not recruiting
		+Rituximab	NCT01539512	Chronic lymphocytic lymphoma	Phase III, Completed
		+Bendamustine +Rituximab	NCT01569295	Chronic lymphocytic lymphoma	Phase III, Completed

		+Ofatumumab	NCT01659021	Chronic lymphocytic lymphoma	Phase III, Terminated
PI3Kδ/CK1ε	Umbralisib	+Brentuximab vedotin	NCT02164006	Hodgkin's lymphoma	Phase I, Completed
		+Ibrutinib	NCT02268851	Chronic lymphocytic lymphoma, Mantle cell lymphoma	Phase I, Active, not recruiting
		+Ublituximab	NCT02006485	Chronic lymphocytic lymphoma, Non-Hodgkin lymphoma	Phase I, Completed
		+Ublituximab +Ibrutinib	NCT02006485	Chronic lymphocytic lymphoma, Non-Hodgkin lymphoma	Phase I, Completed
		+Rituximab	NCT03919175	Follicular lymphoma, Marginal zone lymphoma	Phase II, Recruiting
		+Pembrolizumab	NCT03283137	Non-Hodgkin lymphoma, Chronic lymphocytic lymphoma	Phase I, Active, not recruiting
PI3Kδ	Parsaclisib	+Romidepsin	NCT04774068	T-cell lymphoma	Phase I, Recruiting
		+CHOP	NCT05238064	Peripheral T-cell lymphoma	Phase I/II, Not yet recruiting
		+Tafasitamab	NCT04809467	Chronic lymphocytic lymphoma, Non-Hodgkin lymphoma	Phase I/II, Active, not recruiting
		+Itacitinib	NCT04509700	B-cell malignancy	Phase II, Recruiting
		+Ibrutinib	NCT04551066	Myelofibrosis	Phase III, Recruiting
	Zandelisib	+Tazemetostat	NCT05604417	Follicular lymphoma	Phase I/II, Not yet recruiting
		+Rituximab/Venetoclax	NCT05209308	Chronic lymphocytic lymphoma	Phase II, Withdrawn
		+Rituximab	NCT04745832	Follicular lymphoma, Non-Hodgkin lymphoma	Phase III, Active, not recruiting
	Linperlisib	+Camrelizumab	NCT05429398	Solid tumor	Phase I, Not yet recruiting
		+Azacitidine	NCT05559008	Peripheral T-cell lymphoma	Phase I/II, Recruiting
PI3Kα/δ	Copanlisib	+Durvalumab	NCT04895579	Non-small cell lung cancer	Phase I, Recruiting
		+Trastuzumab	NCT02705859	Breast cancer	Phase I, Completed
		+Venetoclax	NCT04939272	Mantle cell lymphoma	Phase I/II, Recruiting
		+Nivolumab	NCT03711058	Colorectal cancer	Phase I/II, Active, not recruiting
		+Avelumab	NCT05687721	Bladder cancer	Phase I/II, Not yet recruiting
		+Rituximab	NCT03474744	Marginal zone lymphoma	Phase II, Recruiting
		+Obinutuzumab	NCT05387616	Follicular lymphoma	Phase II, Recruiting
		+R-CHOP	NCT02626455	Non-Hodgkin lymphoma	Phase III, Active, not recruiting
		+Rituximab	NCT02367040	Non-Hodgkin lymphoma	Phase III, Active, not recruiting
	Taselisib	+Letrozole	NCT02273973	Breast cancer	Phase II, Completed
		+Fulvestrant	NCT02340221	Breast cancer	Phase III, Terminated
PI3Kγ/δ	Duvelisib	+Romidepsin	NCT02783625	T-cell lymphoma	Phase I, Active, not recruiting
		+Bortezomib	NCT03534323	Chronic lymphocytic lymphoma	Phase I/II, Recruiting
		+Venetoclax	NCT04688658	Melanoma	Phase I/II, Recruiting
		+Nivolumab	NCT05057247	Head and neck squamous cell carcinoma	Phase II, Recruiting
		+Docetaxel	NCT02576275	Non-Hodgkin lymphoma	Phase III, Withdrawn
		+Rituximab +Bendamustine	NCT02204982	Follicular lymphoma	Phase III, Terminated
	Tenalisib	+Pembrolizumab	NCT03471351	Hodgkin lymphoma	Phase I, Terminated
		+Romidepsin	NCT03770000	T-cell lymphoma	Phase I/II, Completed
Pan-PI3K	Buparlisib	+Ibrutinib	NCT02756247	Lymphoma	Phase I, Completed
		+Bevacizumab	NCT01283048	Renal cell carcinoma	Phase I, Completed
		+Panitumumab	NCT01591421	Colorectal cancer	Phase I/II, Completed
		+Bevacizumab	NCT01349660	Glioblastoma	Phase I/II, Completed
		+Erlotinib	NCT01487265	Non-small cell lung cancer	Phase II, Completed
		+Paclitaxel	NCT01852292	Head and neck squamous cell carcinoma	Phase II, Terminated

(*continued on next page*)

Table 2 (*continued*)

Target	Agent	Combination	NCT number	Indication	Status/phase
		+Tamoxifen	NCT02404844	Breast cancer	Phase II, Completed
		+Fulvestrant	NCT01633060	Breast cancer	Phase III, Terminated
		+Paclitaxel	NCT04338399	Head and neck squamous cell carcinoma	Phase III, Recruiting
	Pictilisib	+Fulvestrant	NCT01437566	Breast cancer	Phase II, Completed
		+Paclitaxel	NCT01740336	Breast cancer	Phase II, Completed
JAK1/2	Ruxolitinib	+Venetoclax	NCT03874052	Acute myeloid leukemia	Phase I, Active, not recruiting
		+Umbralisib	NCT02493530	Myelofibrosis	Phase I, Active, not recruiting
		+Radiation; +Radiation/temozolomide	NCT03514069	Glioma/Glioblastoma	Phase I, Active, not recruiting
		+Ibrutinib	NCT02912754	Chronic lymphocytic lymphoma	Phase I/II, Unknown
		+Nilotinib	NCT02973711	Chronic myelomonocytic leukemia	Phase I/II, Withdrawn
		+Nivolumab	NCT03681561	Hodgkin lymphoma	Phase I/II, Active, not recruiting
		+Decitabine	NCT02076191	Myeloproliferative neoplasm	Phase I/II, Completed
		+Trastuzumab	NCT02066532	Breast cancer	Phase I/II, Completed
		+Erlotinib	NCT02155465	Lung cancer	Phase I/II, Completed
		+Capecitabine	NCT01423604	Pancreatic cancer	Phase II, Completed
		+Navitoclax	NCT04468984	Myelofibrosis	Phase III, Recruiting
	Momelotinib	+Capecitabine +Capecitabine/oxaliplatin	NCT02244489	Pancreatic ductal adenocarcinoma	Phase I, Terminated
		+Erlotinib	NCT02206763	Non-small cell lung cancer	Phase I, Terminated
		+Pembrolizumab	NCT05436990	Melanoma	Phase II, Not yet recruiting
		+Durvalumab	NCT04064190	Urothelial carcinoma	Phase II, Not yet recruiting
		+Durvalumab	NCT04893252	Gastric cancer	Phase II, Recruiting
JAK2	Fedratinib	+Decitabine	NCT05524857	Myeloproliferative neoplasm	Phase I, Recruiting
		+Ivosideni +Enasidenib	NCT04955938	Myeloproliferative neoplasm	Phase I, Recruiting
		+Nivolumab	NCT05393674	Myelofibrosis	Phase II, Recruiting
	Pacritinib	+Ibrutinib	NCT02677948	Chronic lymphocytic lymphoma, Small lymphocytic lymphoma	Phase I/II, Withdrawn
		+Decitabine +Cytarabine	NCT02532010	Acute myeloid leukemia	Phase II, Terminated
HPK1	CFI-402411	+Pembrolizumab	NCT04521413	Advanced solid tumors	Phase I/II, Recruiting
	BGB-15025	+Tislelizumab	NCT04649385	Advanced solid tumors	Phase I, Recruiting
	PF-07265028	+Sasanlimab	NCT05233436	Advanced solid tumors	Phase I, Recruiting
	NDI-101150	+Pembrolizumab	NCT05128487	Solid tumors	Phase I/II, Recruiting
RORγt	LYC-55716	+Pembrolizumab	NCT03396497	Non-small cell lung cancer	Phase I, Unknown
Bromodomain	ZEN003694	+Nab-paclitaxel +Pembrolizumab	NCT05422794	Metastatic triple-negative breast cancer	Phase I, Recruiting
		+Abemaciclib	NCT05372640	Malignant solid neoplasm, NUT carcinoma	Phase I, Suspended
		+Talazoparib	NCT05071937	Recurrent ovarian cancer	Phase II, Recruiting
			NCT03901469	Triple-negative breast cancer	Phase II, Recruiting
			NCT05327010	Malignant solid neoplasm, Ovarian carcinoma	Phase II, Recruiting
		+Binimetinib	NCT05111561	Solid tumors	Phase I, Recruiting
		+Entinostat	NCT05053971	Advanced/refractory solid tumors	Phase I/II, Recruiting
		+Etoposide +Cisplatin	NCT05019716	NUT carcinoma	Phase I/II, Recruiting

	+Enzalutamide	NCT04986423	Metastatic prostate cancer	Phase II, Recruiting
		NCT02711956	Metastatic prostate cancer	Phase I/II, Completed
	+Ipilimumab	NCT04840589	Solid tumors	Phase I, Recruiting
	+Nivolumab			
	+Enzalutamide	NCT04471974	Metastatic prostate cancer	Phase II, Recruiting
	+Pembrolizumab			
	+Trametinib	NCT03266159	Solid tumors	Phase II, Withdrawn
	+Selumentinib	NCT05253131	Sarcoma	Phase II, Not yet recruiting
	+Durvalumab			
	+Etoposide	NCT04116359	NUT carcinoma	Phase I/II, Withdrawn
	+Cisplatin			
	+Azacitidine	NCT04022785	Myelodysplastic syndrome, Acute myeloid leukemia	Phase I, Completed
	+Nivolumab	NCT03059147	Advanced hepatocellular carcinoma	Phase I, Terminated
	+Exemestane	NCT02983604	Advanced breast cancer	Phase I/II, Terminated
	+Fulvestrant			
	+Pembrolizumab	NCT02959437	Advanced solid tumors	Phase I/II, Terminated
	+Epacadostat			
	+Azacitidine	NCT02303782	Acute myeloid leukemia	Phase I/II, Withdrawn
	+AZA/VEN	NCT04609826	Acute myeloid leukemia, Myelodysplastic syndromes, Chronic myelomonocytic leukemia	Phase I, Active, not recruiting
	+Ribavirin	NCT03760666	Acute myeloid leukemia	Phase I/II, Terminated

Azacitidine				
OTX015				
JNJ-74856665				
Brequinar				

thers suppress antitumor immune response (Fig. 6). There have been many studies involving chemokines and their receptors which could be used as therapeutic targets in solid tumors. Numerous chemokines/chemokine receptors-targeted drug candidates that focus on hematological or solid tumors are under clinical trials as monotherapy or in combination with anti-PD1/PD-L1 (Fig. 5C). Two antagonists, plerixafor and maraviroc, have been approved for clinical use. Other chemokine receptor antagonists including cenicriviroc, balixafortide, and motixafortide are in various phases of clinical trials.

4.3.1. *CCR2 antagonists*

The chemokine CCL2 is an important mediator of chemotaxis secreted by myeloid cells in tumors. The CCL2/CCR2 signaling axis promotes tumor cell proliferation and invasiveness, and recruits immunosuppressive cells[97]. Thus, cancer treatment has been increasingly concerned with blocking or inhibiting the CCL2/CCR2 signaling axis.

PF-04136309 (INCB8761) is a potent, selective, and orally bioavailable CCR2 antagonist. Researchers previously found that when PF-04136309 was combined with FOLFIRINOX chemotherapy, the partial response rate was higher (49%), as compared to FOLFIRINOX chemotherapy alone in patients with locally advanced (PDAC). Interestingly, the clinical benefit achieved by PF-04136309 was associated with the accumulation of $CCR2^{+}$ inflammatory monocytes in the bone marrow[98]. On the other hand, the combination of PF-04136309 and nab-paclitaxel plus gemcitabine was well tolerated in patients with metastatic PDAC, but without significant clinical benefit in another phase Ib trial (NCT02732938)[99].

CCX872, also known as CCX872-B, is a potent and orally active CCR2 antagonist. It improved the efficacy of the anti-PD-1 treatment in a preclinical setting. Combination therapy of CCX872 with FOLFIRINOX leads to enhanced tumor response in locally advanced PDAC patients[100].

As a small molecule CCR2/5 dual antagonist, BMS-813160 is now in phase I/II trials (NCT03496662, NCT03767582)[101].

4.3.2. *CCR4 antagonists*

The CC chemokine receptor 4 (CCR4) is important for regulating immune balance and it is mainly expressed in Th2 and Treg cells, which respond to CCL17 and CCL22[102]. Recent studies demonstrated that CCR4 blockade could limit the immunosuppressive functions of Tregs, thus making it a promising strategy for enhancing cancer immunotherapy. While numerous preclinical studies supported the emerging role of CCR4 as an immunotherapy target, there were only limited clinical studies conducted in this area in solid tumors.

FLX475 is a highly potent CCR4 antagonist that blocks the recruitment of Tregs to tumors. A phase II clinical trial has been initiated to evaluate the safety and antitumor activity of FLX475 alone or in combination with ipilimumab in subjects with advanced melanoma (NCT04894994). This trial was recently terminated due to the changes in the clinical landscape and no data have been released. Another two clinical studies (NCT04768686, NCT03674567) are underway to investigate the combination of FLX475 and pembrolizumab in patients with advanced cancer including gastric cancer.

4.3.3. *CCR5 antagonists*

The CC chemokine receptor 5 (CCR5) plays a key role in the recruitment of immune cells to sites of inflammation by directing

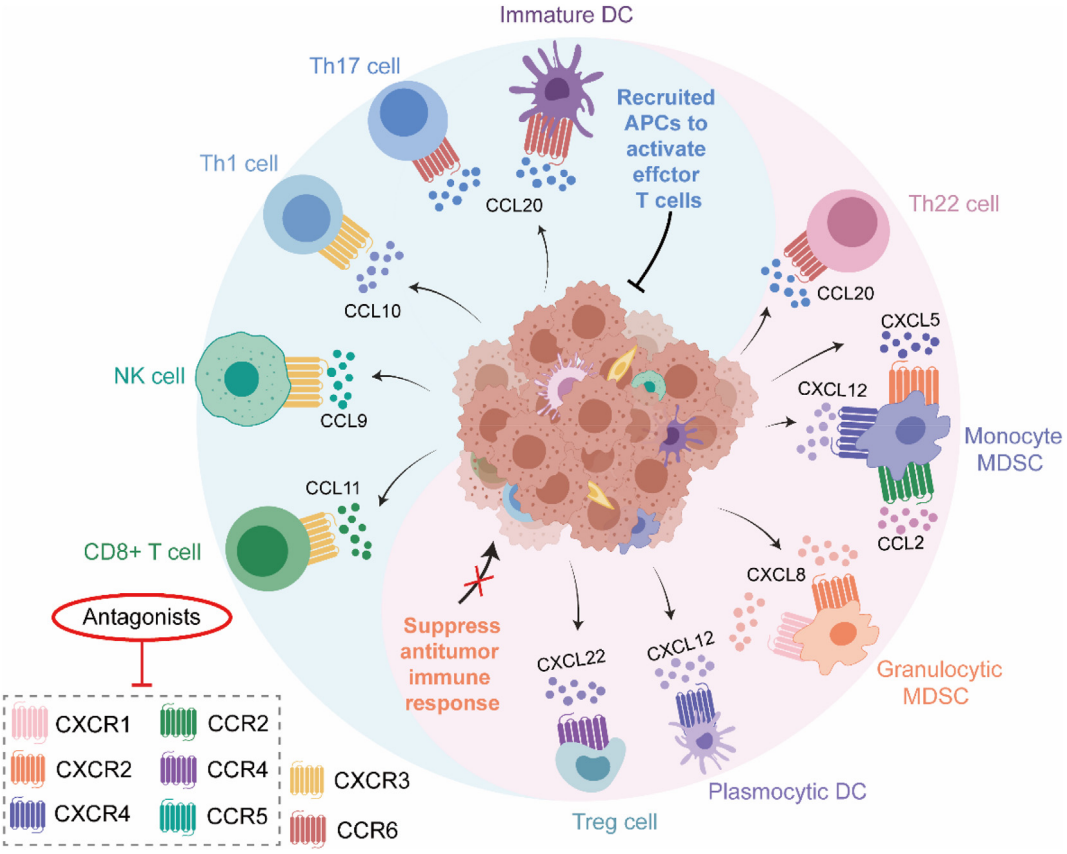

Figure 6 Chemokines and chemokine receptors in the tumor microenvironment. Chemokines are known to play dual roles in the TME. Some chemokines recruit T cells and NK cells to exert antitumor immunity, whereas other chemokines recruit Treg and MDSCs to impair immune activity. The effect of chemokines on diverse immune cell populations reflects their complex biological function. Created with BioRender.com.

immune cell migration along the chemokine gradient. It is activated by several chemokine ligands, including CCL3, CCL4, CCL5 and CCL8. In cancer biology, the CCR5 signaling pathway is primarily involved in immune surveillance, and it promotes tumor growth, stimulates angiogenesis, and suppresses tumor metabolic reprogramming and tumor stem cell proliferation[103].

CCR5 antagonists, including maraviroc and vicriviroc, combined with pembrolizumab in patients with microsatellite stable (MSS) CRC are currently under clinical investigation (NCT03274804, NCT03631407)[104,105], which showed that the OS was extended when maraviroc combined with pembrolizumab in such group of patients.

BMS-813160 is a CCR2/CCR5 dual antagonist with potential immunomodulatory and antineoplastic activities. A phase II trial is currently ongoing to evaluate the efficacy of BMS-813160 (CCR2/5-inhibitor) or BMS-986253 (anti-IL-8 antibody) in combination with nivolumab for NSCLC or HCC (NCT04123379)[106]. The combination of BMS-813160 and nivolumab is also being evaluated for patients with PDAC, microsatellite-stable colon cancer, and primary liver cancer (NCT04123379)[101]. Meanwhile, a phase I/II trial of neoadjuvant and adjuvant nivolumab and BMS-813160 with or without the GVAX vaccine is also under active investigation for locally advanced PDAC (NCT03767582).

4.3.4. CXCR1/2 antagonists

The chemokine receptors 1 and 2 (CXCR1/2) play a crucial role in angiogenesis, inflammation, chemotaxis of inhibitory myeloid cells, and tumor cell survival. As one of the major CXCR1/2 ligands, IL-8 (CXCL8) was overexpressed in solid tumors to promote tumor growth. Importantly, high serum IL-8 level was found to correlate well with poor response to ICIs. Therefore, inhibition of the IL-8/IL-8 receptor axis has been proposed as an emerging strategy to potentiate ICI efficacy. A series of clinical trials are underway to evaluate the safety and efficacy of combination therapy of anti-PD-1 antibody and IL-8 receptor antagonist, including SX682 (CXCR1/2 antagonist), navarixin (CXCR1/2 antagonist) and AZD5069 (CXCR2 antagonist) (NCT04599140, NCT03473925, and NCT02499328) in patients with advanced/metastatic solid tumors. Additionally, reparixin is an investigational allosteric inhibitor of CXCR1/2. The combination of reparixin and paclitaxel was shown to be safe, with demonstrated responses, in patients with HER2-negative metastatic breast cancer (NCT02001974)[107].

4.3.5. CXCR4 antagonists

CXCR4, a chemokine receptor, is widely expressed in immune response cells. It modulates various cellular functions, including cell migration, chemotaxis, differentiation, proliferation, and apoptosis, thus contributing to its vital role in both cancer development and progression[108,109]. A CXCR4 antagonist, plerixafor, has received FDA approval for autologous transplantation in lymphoma and multiple myeloma patients[110].

A few other novel CXCR4 antagonists have also been developed for cancer therapy. LY2510924 is a potent CXCR4

antagonist under investigation in clinical studies. The combination of LY2510924 and sunitinib was tolerated but it did not improve the efficacy of sunitinib alone in patients with metastatic renal cell carcinoma (NCT01391130) in a phase II study[111]. Recently, the maximum tolerated dose (MTD), safety, and tolerability of the combination of LY2510924 and durvalumab were also evaluated in a phase Ia study in patients with advanced (metastatic and/or unresectable) solid tumors. The recommended dose showed acceptable safety and tolerability[112].

BL-8040 (motixafortide) is a novel selective inhibitor of the CXCR4 chemokine receptor. A multi-center phase IIa trial of BL-8040 in combination with pembrolizumab and chemotherapy was completed. Compared with pembrolizumab, BL-8040 incr eased $CD8^+$ effector T cell tumor infiltration in pancreatic cancer patients. The study revealed that CXCR4 blockade gave rise to clinical efficacy and safety benefits in metastatic PDAC (NCT02826486)[113].

5. Small-molecule agents targeting metabolic pathways

The accelerated proliferation of tumor cells in the TME demands a substantial supply of nutrition, resulting in the shortage of nutrients and accumulation of metabolites. The depletion of nutrients and increased harmful metabolites will impair immune cell differentiation and their normal physiological function, collectively disrupting antitumor immunity. Several key enzymes that modulate important metabolic pathways in the TME have been investigated in clinical trials. Some of the representative metabolic pathway inhibitors are summarized in Fig. 7.

5.1. *Targeting arginine metabolism*

Arginase, an enzyme containing manganese, carries out the last step of the urea cycle, which aims to eliminate harmful ammonia from the body. This process involves converting L-arginine into L-ornithine and urea. It has two isoforms, namely ARG1 and ARG2[114]. Increased expression of arginase may deplete arginine, which is associated with malfunction of T cells. Reduced concentration of arginine could suppress the mTORC1 activity of T cells and impair their normal function in immune response[115]. Furthermore, arginine depletion can lead to the arrest of T cell cycle progression at the G0−G1 phase, a decrease in IFN-γ levels, and disruption of TCR signaling[116]. Moreover, the depletion of arginine could also activate the NF-κB-GCN2/eIF2α pathway in lymphocytes and suppress its protein synthesis and proliferation[117]. Importantly, it has been shown that supplementation of arginine could rescue the proliferation and anti-tumor response of T cells[118]. The underlying mechanism of the immunosuppressive role of arginine metabolism is summarized in Fig. 8.

In the TME, ARG1 is mainly expressed in myeloid-derived suppressor cells (MDSCs)[119]. It has been reported that the overexpression of ARG1 in MDSCs can effectively suppress the responses of T cells ($CD4^+$ and $CD8^+$) and NK cells and create an immunosuppressive microenvironment that promotes tumor growth in PDAC patients[120]. Furthermore, research has demonstrated that inhibiting ARG1 expression in MDSCs can effectively restore T cell function and enhance the antitumor immune response against multiple myeloma[116]. In ovarian cancer patients, extracellular vehicles (EVs) containing ARG1 were detected in the plasma and ascites[121]. Tumor-secreted EVs were additionally discovered in the lymph nodes, where they were observed to hinder the proliferation of T cells. Significantly, when these patients were administered arginase inhibitors as part of their treatment, the population of $CD4^+$ and $CD8^+$ T cells was restored, and the growth of tumors was slower. This represents the initial report documenting the transfer of a metabolic checkpoint molecule through tumor-derived extracellular vesicles over a long distance.

The upregulation of ARG2 has been observed in cancer cells, T cells, and DCs. This overexpression of ARG2 was identified in various types of cancer, resulting in arginine depletion within the TME. Consequently, the normal functions of T cells are suppressed[122]. Moreover, the overexpression of ARG2 in T cells was known to retard their cell proliferation and thus leading to immunosuppression[123]. Conversely, downregulation of ARG2 expression in T cells could restore their antitumor activity, though the extracellular level of arginine was not significantly altered. On the other hand, the antitumor response from DCs was also impaired by ARG2 overexpression[124]. To this end, DCs are known to produce microRNA-155 (miR155) to activate the antitumor effect of T cells. When ARG2 is overexpressed in DCs, the expression of miR155 is suppressed to mediate cell cycle arrest of T cells.

Considering the critical role of arginase in immunosuppression, numerous arginase inhibitors have been designed and investigated to enhance the outcome of cancer immunotherapy by promoting the proliferation of T cells and NK cells. The most established arginase inhibitors include arginine homologs (*e.g.*, nor-NOHA) and boronic acid derivatives (*e.g.*, numidargistat). Numidargistat (CB-1158, INCB01158) demonstrated the ability to inhibit MDSC-mediated immunosuppression of T cell proliferation *in vitro*, both as a standalone treatment and in combination with other cancer therapies[124]. To date, two clinical trials of phase I/II have been initiated to test the effectiveness of numidargistat as a monotherapy and in combination with pembrolizumab, an anti-PD-1 monoclonal antibody in the treatment of various cancer types (NCT02903914; NCT03910530).

5.2. *Targeting indoleamine 2,3-dioxygenase 1 (IDO1)*

L-Tryptophan (Trp) is an essential amino acid that is exclusively acquired through the diet. Trp metabolism is involved in the regulation of immunity and its aberrant regulation could cause cancer. IDOs (indoleamine 2,3-dioxygenases), as well as TDO (tryptophan 2,3-dioxygenase), are enzymes involved in the process of tryptophan deoxygenation, converting tryptophan into kynurenine. IDO1 is the most fully characterized and it is overexpressed in the vast majority of cancers[125]. Functionally, IDO1 plays a pivotal role in cancer immune escape *via* depleting tryptophan in the TME, which leads to T-cell anergy and apoptosis *via* the General Control Nonderepressible 2 (GCN2) pathway. In addition, the accumulation of the downstream products of IDO1 including kynurenine and quinolinic acid could induce the differentiation of naïve $CD4^+$ T cells towards the immunosuppressive form of T cells ($CD3^+CD4^+CD25^+FOXP3^+$ Treg) (Fig. 9). On the other hand, IDO1 overexpression could cause immunosuppression in a non-enzymatic manner mediated by MDSCs. Furthermore, IDO1 overexpression is known to cause resistance to immune checkpoint inhibitors. For example, overexpression of CTLA-4 by Treg could cause the upregulation of IDO1 expression in DCs[126]. PD-1 expression in T cells can be upregulated by IDO1 overexpression through aryl hydrocarbon receptor activation[127]. When both CTLA-4 and PD-1 expression were inhibited in

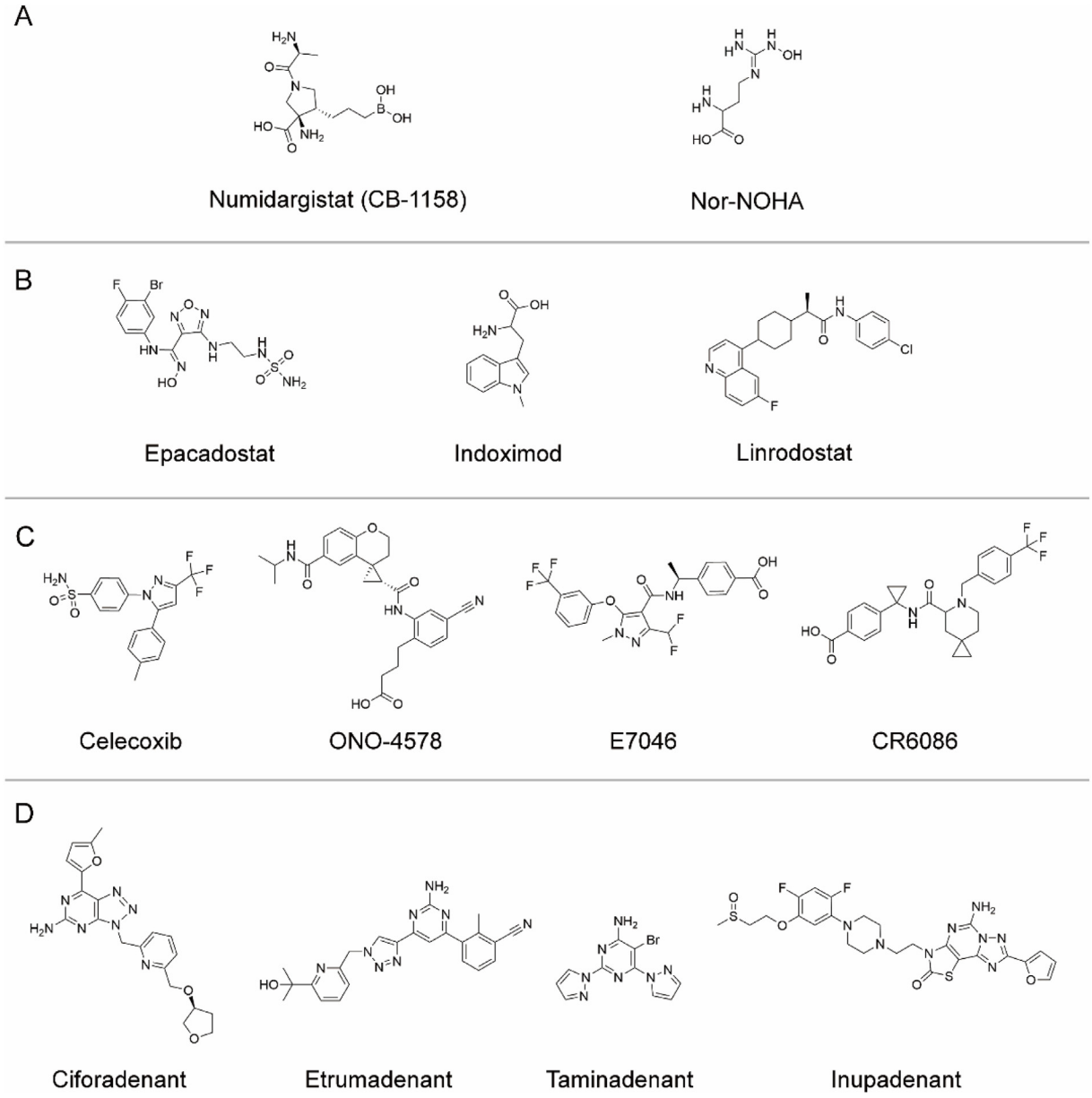

Figure 7 Metabolic pathway inhibitors. (A) Representative arginase inhibitors. Arginase inhibitors include boronic acid derivatives (numidargistat) and arginine homologs (nor-NOHA). (B) Representative IDO1 inhibitors. (C) Representative prostaglandin pathway inhibitors. Prostaglandin pathway inhibitors are comprised of COX-2 inhibitors (celecoxib) and EP4 antagonists (ONO-4578, E7046 and CR6086). (D) Representative adenosine pathway inhibitors.

glioblastoma-bearing mice, the expression of IDO1 was found upregulated[128]. A comprehensive analysis of data from The Cancer Genome Atlas (TCGA) demonstrated a strong correlation between the expression of IDO1 and several other immune checkpoints including PD-L1, PD-L2, CD39, and FoxP3[129]. Since the overexpression of IDO1 is often correlated with other immune checkpoints, IDO1 inhibitor was often used in combination with other cancer immunotherapy to achieve better treatment outcomes.

Early phase I/II clinical trials suggested that administering an IDO1 inhibitor as a standalone treatment showed limited effectiveness in cancer therapy. Nonetheless, clinical studies have shown that combining an IDO1 inhibitor with other cancer therapies produced a synergistic effect. This was evidenced by enhanced suppression of tumor growth and prolonged survival of patients[130]. Indoximod (D-1-MT), epacadostat (INCB024360), IDO1 vaccines, and other IDO1 inhibitors have progressed to various phases of clinical trials[130–132]. In a phase II clinical trial (NCT02178722), the combined therapy of epacadostat, an IDO1 inhibitor, and the anti-PD-1 monoclonal antibody pembrolizumab exhibited promising efficacy in treating various types of solid tumors. Unfortunately, the combination of epacadostat and pembrolizumab did not show a significant improvement in antitumor efficacy in phase III clinical trials conducted in patients with metastatic melanoma (NCT02752074) or urothelial carcinoma (NCT03361865).

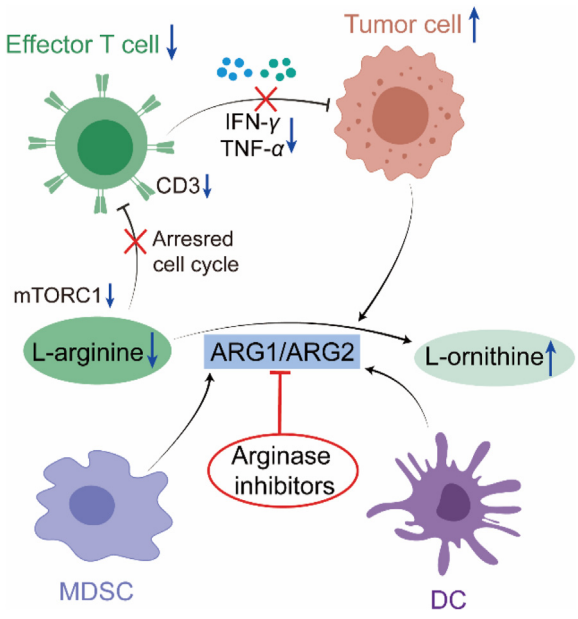

Figure 8 Overexpression of ARG1 and ARG2 leads to arginine depletion and T-cell dysfunction. The arginases ARG1 and ARG2 are expressed by MDSCs and DCs/tumor cells, respectively. The overexpression of ARG1 and ARG2 in TME results in arginine depletion, which could lead to T-cell dysfunction. Arginine depletion can suppress the mTORC1 activity of T cells, arrest cell cycle progression of T cells at the G0−G1 phase, diminish the production of IFN-γ, and disrupt TCR signaling. MDSCs, myeloid-derived suppressor cells; DCs, dendritic cells; TME, tumor microenvironment. Created with BioRender.com.

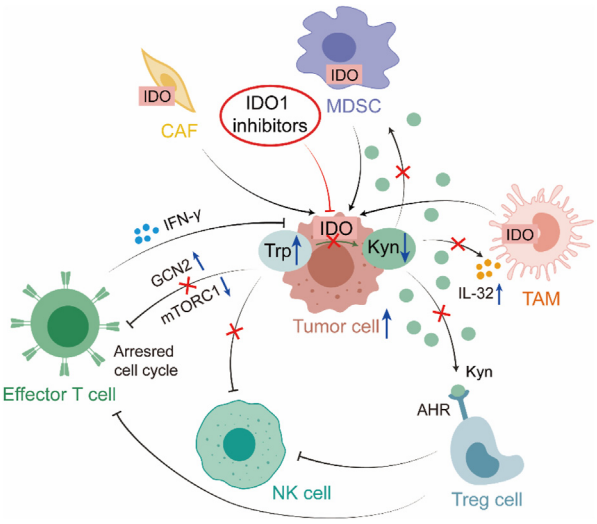

Figure 9 The role of IDO1 in immunosuppression. IDO1 is expressed in tumor cells, MDSCs, CAF, and TAM. Overexpression of IDO1 leads to the depletion of tryptophan in the TME, thereby triggering the activation of GCN2 signaling, inhibiting mTORC1 activity, and retarding cell cycle progression of T cells. Meanwhile, the accumulation of kynurenine, a metabolite produced by IDO1, can induce the generation of Treg cells and contribute to immunosuppression mediated by MDSCs and TAM. MDSCs, myeloid-derived suppressor cells; CAF, cancer-associated fibroblasts; TAM, tumor-associated macrophage. Created with BioRender.com.

5.3. *Targeting prostaglandin pathway*

Cyclooxygenase (COX) is the key enzyme catalyzing the biosynthesis of prostaglandins (PGs), which are important mediators of inflammation in various diseases. Two isoforms of COX enzymes, COX-1 and COX-2, have been identified. COX-2 is an established target of nonsteroidal anti-inflammatory drugs (NSAIDs) which also represents a novel molecular target for cancer therapy. Previous research has reported that constitutive IDO1 expression is driven by COX2 and mediates intrinsic immune resistance in many cancer types. Prostaglandin E2 (PGE2) is the primary metabolite of arachidonic acid generated by COX-2 and it regulates many biological functions including inflammatory activation and triggers a range of cellular responses through binding to one or more of its four prostaglandin E (EP) receptors (EP1, EP2, EP3, and EP4). In addition, EP receptors are also coupled to heterotrimeric G proteins which initiate intracellular signaling cascades, such as MAPK, NF-κB, glycogen synthase kinase 3β (GSK3β)-β catenin, Src−EGFR−Akt−mTOR, and EP4−PKA−CREB pathways, thereby facilitating tumor progression[133].

Importantly, COX-2/PGE2 signaling is recognized for its significant contribution in shaping an immunosuppressive TME[134]. COX-2 is released into the TME by cancer-associated fibroblasts (CAFs), alternatively activated macrophage type 2 (M2) cells, as well as tumor cells. Kabir et al.[135] showed that COX-2 and PGE2 were overexpressed in senescent CAFs, which contributed to tumor progression. The release of COX-2 from M2 cells favors tumor angiogenesis, invasion, and metastasis[136−138]. In tumor cells, the activation of MAPK, EGF, and KRAS signals, as well as inflammation and hypoxia, can upregulate COX-2 expression by upregulation of PTGS2 (Fig. 10)[139]. COX-2 overexpression and over-activity can induce upregulation of the immunosuppressor cells including MDSCs, and TAMs, thus the manipulation of which could be exploited to enhance or suppress immune responses in cancer[140]. Tumor-derived PGE2 is known to diminish the viability and chemokine production of NK cells, which is accompanied by down-regulating chemokine receptor expression in type 1 DCs (cDC1)[141]. Moreover, tumor production of PGE2 acts selectively on EP2 and EP4 receptors in NK cells, subsequently preventing the switch of inflammatory TME from cold to hot, and promoting immune evasion[142]. These studies demonstrate the potential of targeting PG pathways to improve immune checkpoint blockade efficacy against cancer.

5.3.1. *COX-2 inhibitors*

Celecoxib is a potent and selective COX-2 inhibitor approved by the FDA in 1998 for treating familial adenomatous polyposis. It has also been investigated for its effect on immunity and metabolism in the TME in different cancer types in clinical trials, mainly as adjuvant treatment combined with other checkpoint inhibitors. However, clinical outcomes from these drug combinations were mostly unsatisfactory. In a recent phase III trial, the effects of adding celecoxib to standard adjuvant chemotherapy for 3 years, compared to a placebo, did not yield a significant improvement in disease-free survival for patients with resected stage III colon cancer. Another phase III trial also showed no significant clinical benefit after a two-year treatment period with celecoxib compared to placebo as adjuvant treatment of HER2-

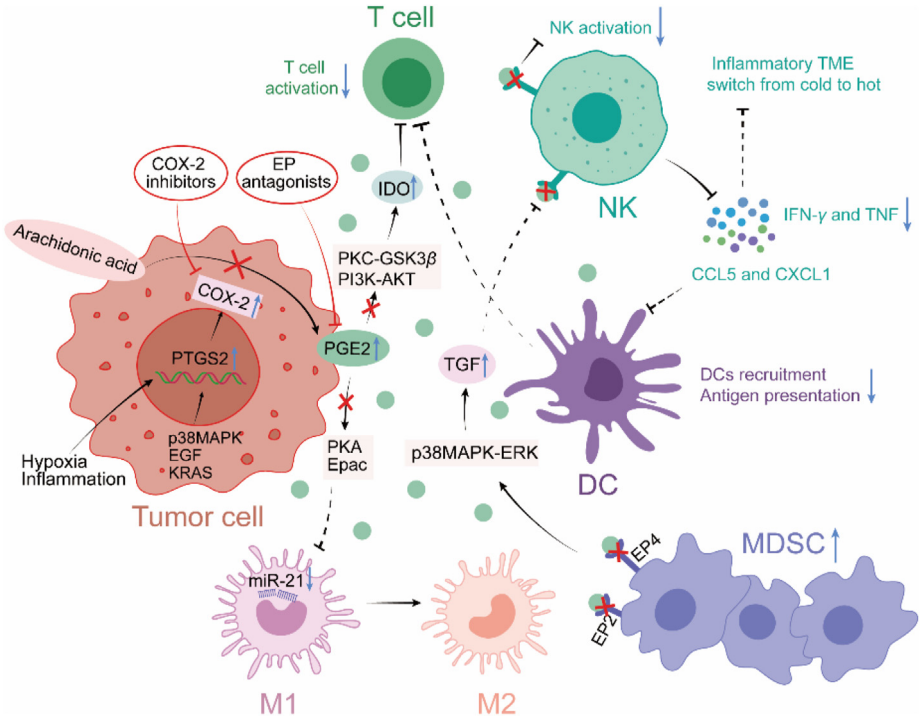

Figure 10 The role of COX-2/PGE2 signaling in promoting immunosuppressive tumor microenvironment. Hypoxia, inflammation, and intrinsic factors within the tumor contribute to the upregulation of COX-2 and the excessive production of PGE2 in tumor cells, thus creating an immunosuppressive tumor microenvironment through diverse mechanisms. COX-2/PGE2 signaling is associated with the accumulation of MDSCs and M2 polarization of macrophages. Additionally, the COX-2/PGE2 signaling pathway suppresses the recruitment of DCs and hampers the activation of NK cells and T cells. MDSCs, myeloid-derived suppressor cells; DCs, dendritic cells. Created with BioRender.com.

negative breast cancer[143,144]. A few other ongoing clinical trials are investigating the combination of celecoxib and other treatment modalities. A phase I/II study is trying to confirm whether neoadjuvant PD-1 blockade with toripalimab, with or without the addition of celecoxib, could potentially serve as a more effective therapeutic approach for patients with mismatch repair deficient or microsatellite instability-high, locally advanced colorectal cancer[145].

5.3.2. *EP4 antagonist*

As PGE2 regulates immune cell function, the modulation of EP receptor signaling pathways has emerged as attractive targets to enhance cancer immunotherapy. Among the four EP receptors, the EP4 receptor has been identified as a particularly useful cancer target. In patients with advanced or metastatic solid tumors, ONO-4578, a highly selective EP4 antagonist, exhibited potent antitumor activity and it was well tolerated when used in combination with nivolumab[146]. In a preclinical study, ONO4578 demonstrated potent antitumor activity and it was also shown to reduce infiltration of M2 macrophages in tumor xenografts in experimental mice. A phase I study is ongoing to research the combination of nivolumab with ONO-4578 in advanced or metastatic solid tumors (NCT03155061).

E7046 (AN0025), a novel EP4 receptor-specific antagonist, was found to exhibit manageable tolerability, immunomodulatory properties, and durable disease control (≥18 weeks) in patients with advanced malignancies[147]. A phase Ib, open-label, multicenter study (NCT03152370) of E7046 in combination with radiotherapy or chemoradiotherapy in patients with rectal cancer has been conducted recently, but the findings have not been released. There is another ongoing phase I trial that investigates the combination of E7046 and atezolizumab in locally advanced solid tumors.

CR6086 is another potent EP4 antagonist, which displays considerable immunomodulation activity. A phase I/Ib study is currently underway to evaluate the efficacy of CR6086 in combination with balstilimab (PD-1 inhibitor), focusing on patients with pretreated mismatch-repair-proficient and microsatellite stable metastatic colorectal cancer (NCT05205330).

5.4. *Targeting adenosine signaling*

Adenosine signaling derived from the A2a receptor (A2aR) triggers the cAMP/PKA/CREB pathway through typical G proteins, which is emerging as an important checkpoint of the immune response. Adenosine signaling is mediated *via* G-protein coupled adenosine receptors (A1R, A2aR, A2bR, A3R) and modulates human immunity. Adenosine is mainly produced by ectonucleotidases (CD39 and CD73) dephosphorylating extracellular ATP. It has been reported that the adenosine pathway was activated in the tumor microenvironment and inhibited the function of $CD8^+$ T cells, natural killer (NK) cells, and macrophages (Fig. 11)[148]. Besides, adenosine stimulates DCs to secrete immunosuppressive factors like IL-10, TGFβ, arginase, and IDO[149].

The A2a receptor (A2aR) is a typical GPCR with a high affinity for adenosine. It is expressed on T cells, B cells, natural killer T (NKT) cells, monocytes, macrophages, DCs, and NK cells. When the A2aR signaling pathway is activated in $CD4^+$ T cells, less IL-2 or IFN-γ is secreted, and CD28 is suppressed in these cells. Adenosine signaling can be inhibited by targeting

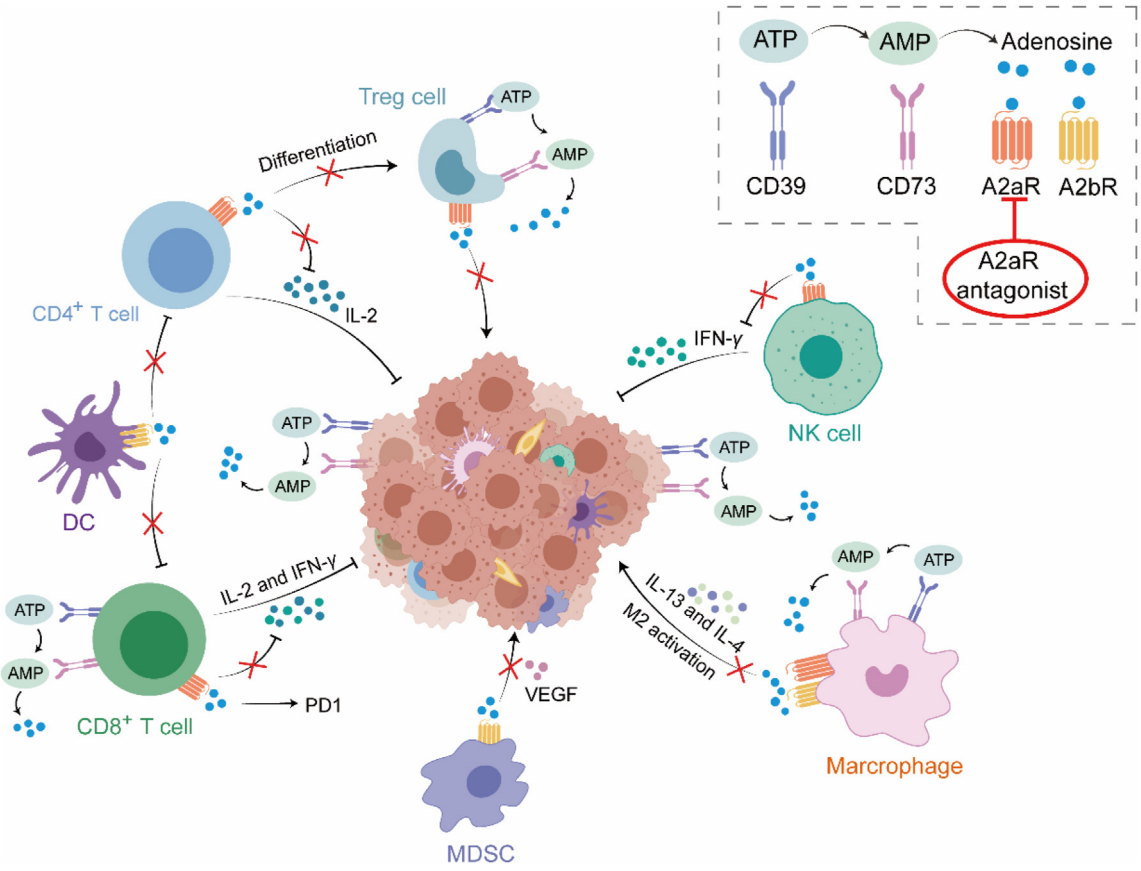

Figure 11 The activation of adenosine signaling pathway in the tumor microenvironment. Adenosine signal inhibits the function of $CD4^+$ T cells, $CD8^+$ T cells, and NK cells by reducing the production of immune factors including IL-2 and IFN-γ. Adenosine also promotes the secretion of immunosuppressive factors such as IL-13 and IL-14. Therefore, the activation of the adenosine signaling pathway in TME promotes the formation of an immunosuppressive TME. Created with BioRender.com.

CD73 and CD39 in TME, as well as blocking A2a and A2b receptors to enhance the anti-tumor immune response. In combination with other immune checkpoint inhibitors such as PD-L1, TIM-3, or CTLA-4, A2aR antagonists have been shown to potentiate anti-tumor immunity[150]. To this end, some small-molecule A2aR antagonists including ciforadenant, imaradenant, etrumadenant, and taminadenant have been developed.

Ciforadenant (CPI-444), a potent, selective, oral A2aR antagonist, alone or in combination with anti-PD-1/PD-L1 was shown to potently restrain tumor growth in multiple preclinical tumor models[151,152]. In clinical studies, ciforadenant combined with anti-PD-1/PD-L1 can increase the number of $CD8^+$ T cells in tumor tissues of patients with renal cell carcinoma (RCC), including patients who had progressed on PD-(L)1 inhibitors[153]. Additionally, ciforadenant plus CPI-006 in adult subjects with advanced cancers is in progress in phase I/Ib open-label trial (NCT03454451). Among patients with metastatic castration-resistant prostate cancer, colorectal cancer, or relapsed/refractory solid tumors, another A2aR antagonist, imaradenant (AZD4635) monotherapy (75−200 mg twice daily or 125 mg once daily) and in combination with anti-PD-1/PD-L1 inhibitors exhibited good tolerance[154].

Etrumadenant, also known as AB928, is a selective A2aR and A2bR dual antagonist developed by Arcus Company. When combined with docetaxel or zimberelimab, etrumadenant was shown to produce clinical benefits for patients with metastatic castration-resistant prostate cancer[155,156]. Furthermore, updated results from the ARC-3 study showed that the combination of etrumadenant and modified FOLFOX chemotherapy was well tolerated and associated with a substantial disease control rate in metastatic colorectal cancer patients[157].

Last but not least, taminadenant (NIR178; PBF509), a potent selective A2aR antagonist, combined with spartalizumab (PDR001) was well tolerated in patients with advanced NSCLC. However, no clinical benefit was observed in this study (NCT02403193)[158].

6. Small-molecule agents targeting oncogenic pathways

It has long been known that oncogenic pathways provide sustaining proliferative signaling for cancer cells and reprogram cellular metabolism, contributing to their rapid growth. In addition, it is reported that oncogenic pathways also play a crucial role in immunomodulation, which influences the biological function of immune cells and shapes the immunosuppressive environment.

6.1. Targeting PI3K-mediated signaling

The phosphatidylinositol 3-kinase (PI3K) family can be divided into class I, class II, and class III PI3Ks based on their structure and mode of regulation. The class I PI3Ks are comprised of

PI3Kα, PI3Kβ, PI3Kγ, and PI3Kδ, and each of them contains a regulatory subunit and a catalytic subunit. PI3Kα and PI3Kβ are present in a broad spectrum of cell types, whereas PI3Kγ and PI3Kδ are predominantly enriched in leukocytes. The PI3K pathway is often abnormally activated in cancer and contributes to tumor initiation and progression. Additionally, the PI3K pathway is also implicated in the development, differentiation, and activation of lymphocytes, regulating the biological function of the immune system[159]. Hyperactive PI3Kδ signaling induced by gain-of-function mutations in *PIK3CD* and *PIK3R1* leads to activated PI3Kδ syndrome (APDS), a primary combined immunodeficiency syndrome[160]. It is well known that macrophages play dual roles in inflammation and cancer, and an interesting study demonstrated that PI3Kγ signaling controls the molecular switch between immunostimulatory and immunosuppressive transcriptional programs in macrophages *via* AKT and mTOR[161]. Furthermore, oncogenic mutations in *PIK3CA* (encoding PI3Kα) have pleiotropic effects in solid tumors. On the one hand, activating *PIK3CA* mutations provides sustaining proliferative signaling for cancer cells; on the other hand, paracrine effects induced by *PIK3CA* mutations in cancer cells perhaps contribute to immune suppression through secretion of cytokines and chemokines and depletion of metabolic nutrients in the stroma[162–164]. Owing to the important role of PI3K signaling in immunity and cancer, inhibition of class I PI3Ks becomes a hotspot of drug development. Besides targeting tumor cell-intrinsic PI3K activity, increasing evidence underlines the potential of PI3K inhibitors in cancer immunotherapy (Fig. 12)[165]. PI3K inhibitors, particularly PI3Kα and PI3Kδ inhibitors, have achieved great progress in recent years and more than a dozen of PI3K inhibitors have entered clinical trials, which could be employed to reshape the TME and enhance antitumor immunity (Fig. 13A)[166]. Importantly, several drugs have received FDA approval for the clinical application of solid tumors and hematologic malignancies.

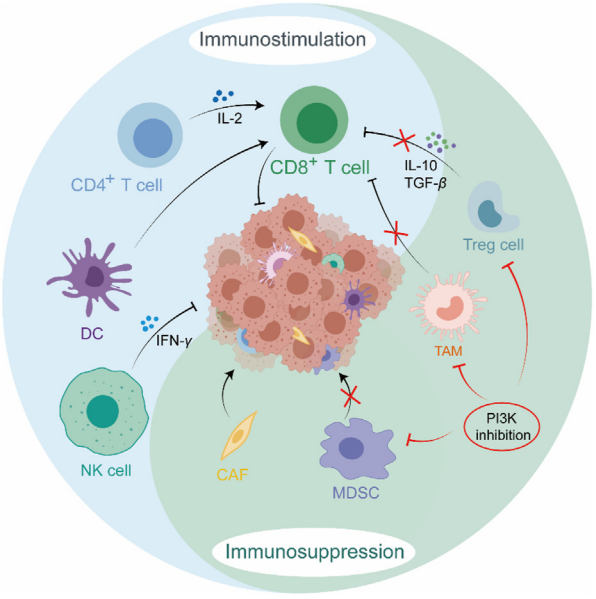

Figure 12 The role of PI3K inhibition in antitumor immunity. PI3K signaling not only provides the sustaining proliferative signaling for tumor cells but also has an important role in the regulation of immune components in the TME. Thus, PI3K inhibition can suppress tumor growth and inhibit the tumor-promoting function of immunosuppressive cells, contributing to enhanced antitumor immunity. Created with BioRender.com.

6.1.1. *PI3Kα inhibitors*

Alpelisib is a potent PI3Kα-selective inhibitor and the first clinically approved PI3Kα inhibitor. PIK3CA activation mutations are frequent in breast cancer and they could be used as a predictive biomarker for anticancer activity of PI3Kα inhibitors. In HER2-negative, estrogen receptor (ER)-positive breast cancer, PIK3CA mutations occur in approximately 40% of cases. It was reported that PI3Kα-selective inhibitors enhance ER function and dependence on estrogen in ER-positive breast cancer[167]. Therefore, hormone-responsive breast cancer is particularly responsive to the antitumor effect of PI3Kα inhibitors.

The phase III SOLAR-1 trial compared the effect of alpelisib plus fulvestrant (ER antagonist) with placebo plus fulvestrant in HER2-negative, ER-positive, PIK3CA-mutated, advanced breast cancer patients who had received prior endocrine therapy. The alpelisib−fulvestrant group achieved a longer PFS (11.0 *vs.* 5.7 months) than the placebo group, which subsequently led to FDA approval of the drug combination[168]. According to the final results from the SOLAR-1 study, the median OS was 39.3 months and 31.4 months in the combination group and placebo group, respectively[169]. Furthermore, alpelisib−fulvestrant combination was also found to significantly prolong median OS (37.2 *vs.* 22.8 months) in patients with lung and/or liver metastases.

The success of alpelisib fosters the development of other PI3Kα-selective inhibitors. Inavolisib is another recently developed PI3Kα-selective inhibitor that induces the selective degradation of PI3K mutant p110α protein (encoded by *PIK3CA*) and has 300-fold selectivity over the other class I PI3K isoforms[170]. This unique mechanism of action of inavolisib has little effect on wild-type p110α protein, which retains normal physiological function mediated by PI3K signaling. In early-phase clinical trials, inavolisib demonstrated antitumor efficacy with an acceptable safety profile in PIK3CA-mutated breast cancer patients. The antitumor efficacy of inavolisib in combination with fulvestrant and alpelisib combined with fulvestrant is studied in an ongoing clinical trial of PIK3CA-mutated, HER2-negative, hormone receptor (HR)-positive, locally advanced or metastatic breast cancer patients (NCT05646862). Besides, the combinations of inavolisib with other anticancer agents are also under active clinical investigation in other solid tumors (NCT04449874, NCT03006172, NCT04929223, and NCT04931342).

Serabelisib (TAK-117/MLN1117/INK1117) is another selective PI3Kα inhibitor. While serabelisib as single-agent therapy was shown to produce only limited efficacy in a phase I study, combination therapies involving serabelisib were evaluated[171]. Mechanistically, the simultaneous inhibition of PI3K and mTOR may produce more remarkable inhibition on the PI3K/AKT/mTOR pathway than the individual PI3K or mTOR inhibition alone. Serabelisib combined with sapanisertib (mTORC1/2 inhibitor) was reported to produce a synergistic antitumor effect in the preclinical model of bladder cancer. However, in a completed phase II trial (NCT02725268), the dual PI3K/mTOR inhibition by sapanisertib and serabelisib failed to prolong PFS (3.1 *vs.* 3.6 months) compared with sapanisertib alone in advanced RCC patients after antiangiogenic therapy[172]. The three-drug combination treatment (serabelisib plus sapanisertib and paclitaxel) is being evaluated in patients with advanced solid tumors. In a phase I trial (NCT03154294), such a regimen presented preliminary remarkable efficacy and manageable safety profile, with a PFS of 11 months.

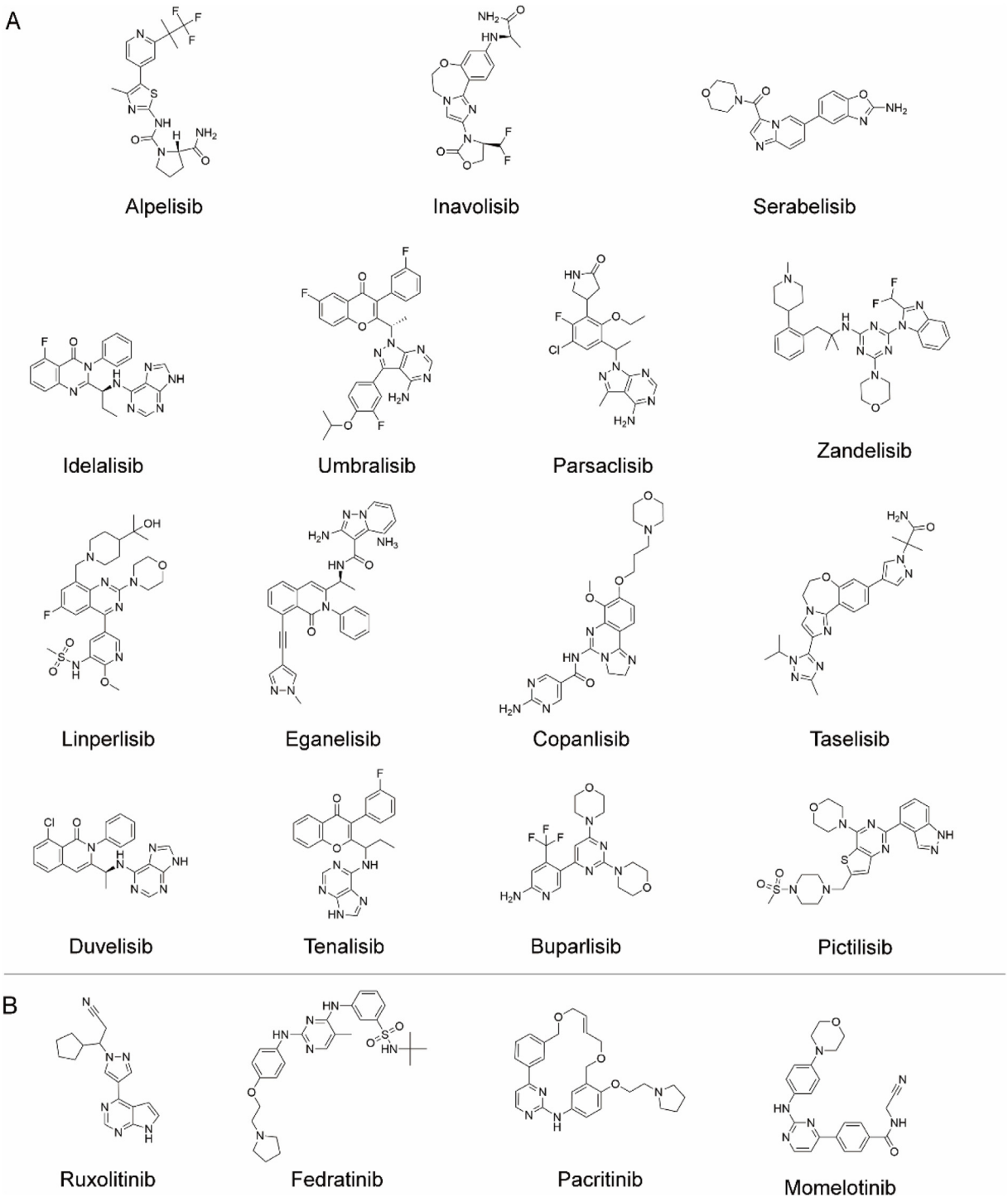

Figure 13 Oncogenic pathway inhibitors. (A) Representative PI3K inhibitors. PI3K inhibitors consist of PI3Kα inhibitors (alpelisib, inavolisib and serabelisib), PI3Kδ inhibitors (idelalisib, umbralisib, parsaclisib, zandelisib and linperlisib), PI3Kγ inhibitor (eganelisib), dual PI3K inhibitors (copanlisib, taselisib, duvelisib and tenalisib) and pan-PI3K inhibitors (buparlisib and pictilisib). (B) Representative JAK inhibitors. JAK inhibitors include ruxolitinib, fedratinib, momelotinib, and pacritinib.

6.1.2. PI3Kδ inhibitors

Idelalisib (GS-1101/CAL-101) is a selective inhibitor of the PI3Kδ subunit, which was reported to inhibit B cell receptor (BCR) signaling in malignant B cells. It is the first PI3Kδ inhibitor approved for treating relapsed follicular lymphoma (FL) and chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) based on promising results of idelalisib monotherapy and combination therapy with rituximab[173,174]. Idelalisib monotherapy showed a PFS of 11 months and a response rate of 57% in indolent NHL patients, and neutropenia is the most common $\geq$grade 3 adverse event. Idelalisib plus rituximab (anti-CD20 antibody) significantly improved PFS (19.4 months *vs*. 6.5

months) and OS (40.6 months *vs*. 34.6 months) compared with rituximab alone in relapsed CLL, with a favorable safety profile[175]. Furthermore, the addition of idelalisib to bendamustine (chemotherapeutic drug) and rituximab achieved a longer PFS of 20.8 months *vs*. 11.1 months than bendamustine combined with rituximab in relapsed or refractory CLL patients[176]. However, serious adverse events were more frequent (68% *vs*. 44%) in the idelalisib group than in the placebo group, and an increased risk of infection (39% *vs*. 25%) was observed in the idelalisib group. Similarly, idelalisib plus the second-generation anti-CD20 antibody ofatumumab also exhibited a better PFS of 16.3 months *vs*. 8.0 months than the ofatumumab group in patients with relapsed CLL[177]. The exciting results obtained from these clinical trials supported the clinical application of idelalisib in combination with an anti-CD20 antibody for treating relapsed CLL.

Umbralisib (TGR-1202) is another approved PI3Kδ inhibitor for treating relapsed or refractory marginal zone lymphoma (MZL), CLL, and FL adult patients. The safety and efficacy of umbralisib monotherapy in lymphoma and leukemia were assessed in several clinical trials (NCT01767766, NCT02793583, and NCT02742090), which demonstrated its superior clinical efficacy and a relatively low incidence of side effects. Given that the combination treatment of PI3Kδ inhibitor with anti-CD20 antibody exerts a potent antitumor effect in B-cell malignancies, umbralisib combined with CD20-directed monoclonal antibody was also studied. In a phase 1/1b study (NCT02535286), the promising clinical efficacy of umbralisib plus ublituximab (anti-CD20 antibody) showed that the median duration of response (DOR) was 20 months and ORR was 46%[178]. Additionally, it was reported that both PI3Kδ and Bruton tyrosine kinase (BTK) are implicated in the BCR pathway, thus, dual PI3Kδ and BTK blockade could be an efficacious antitumor strategy[159,160]. Another phase I trial (NCT02268851) demonstrated umbralisib plus ibrutinib (BTK inhibitor) was well-tolerated in B-cell malignancies, suggesting BTKi and PI3Kδi doublet treatment should be assessed in further investigations. In addition, the safety and efficacy of umbralisib, ublituximab, and ibrutinib combination therapy are being studied in an ongoing phase I trial (NCT02006485), which will provide better insight into this triplet combination in the management of CLL and NHL[179].

Parsaclisib (INCB50465) is a highly selective PI3Kδ inhibitor investigated in multiple studies of B cell malignancies (NCT02018861, NCT02998476, and NCT04509700). Parsaclisib monotherapy or combined with chemotherapy or JAK1 inhibitor for the treatment of relapsed or refractory B-cell malignancies was assessed in a phase I/II study. Parsaclisib monotherapy showed antitumor activity in relapsed or refractory B-cell NHL with ORR of 30% in diffuse large B-cell lymphoma (DLBCL), 67% in mantle cell lymphoma (MCL), 71% in FL and 78% in MZL[180]. Additionally, parsaclisib was also underway in a range of solid tumors in combination with different agents including immunotherapy and targeted therapy (NCT02559492, NCT04551066).

Other PI3Kδ inhibitors including zandelisib (ME-401), linperlisib (YY-20394), AMG319, and IOA-244 are in different stages of clinical investigation. Zandelisib as monotherapy or combined with rituximab is currently investigated in a phase I trial of relapsed or refractory B-cell malignancies (NCT02914938). Linperlisib showed promising preliminary efficacy with ORR of 64.0% and 79.8% in a phase I (NCT03757000) and a phase II (NCT04370405) study, respectively[181,182].

6.1.3. *PI3Kγ inhibitors*

Compared with PI3Kδ inhibitors, fewer drug candidates were developed to target PI3Kγ, and no PI3Kγ-selective inhibitors have received regulatory approval for treating cancer patients, indicating the distinct biological functions of PI3Kγ and PI3Kδ in tumors. Kaneda et al.[161] demonstrated that PI3Kγ promotes immune suppression through the production of immune-suppressive macrophages (M2) in the TME. Eganelisib (IPI-549), the only PI3Kγ-selective inhibitor studied in clinical trials, can reprogram the TME and foster the transformation of M2 into antitumor macrophages (M1)[183]. Additionally, eganelisib overcame resistance to immune checkpoint blockade (ICB) among patients with high infiltration of immunosuppressive myeloid cells by targeting PI3Kγ in myeloid cells[184]. Notably, eganelisib synergizes with anti-PD1 to promote tumor regression and improve survival in mouse models. Based on these preclinical studies, eganelisib monotherapy or in combination with ICB or chemotherapy are currently under clinical investigation in different cancer types (NCT03795610, NCT02637531, and NCT03961698).

6.1.4. *Dual PI3K inhibitors*

Besides selective inhibitors targeting individual PI3K isoforms, dual PI3K inhibitors have also been developed. Simultaneous inhibition of PI3Kδ and PI3Kγ was reported to enhance antitumor cytotoxicity by promoting human CAR-T cell epigenetic and metabolic reprogramming[185,186]. Moreover, the combination of PI3Kδ/γ inhibition and irradiation was also found to potentiate effector $CD8^+$ T cell-dependent antitumor immunity[185,186]. Therefore, dual PI3K inhibitors are expected to give rise to more potent inhibition of PI3K signaling and they represent promising antitumor therapeutic strategies.

Copanlisib is a pan-class I PI3K inhibitor that exhibits predominant activity against the p110α and p110δ isoforms and is also considered a PI3Kα/δ inhibitor. Dreyling et al.[187] demonstrated that copanlisib monotherapy achieved ORR of 43.7% *vs*. 27.1% and median PFS of 294 days *vs*. 70 days in the indolent lymphoma and the aggressive lymphoma, respectively. Similarly, the median PFS was 11.2 months and the ORR was 59% in indolent lymphoma patients who received copanlisib after two or more lines of therapy. Furthermore, gene expression analysis indicated that the high response rate of copanlisib was related to the high expression of PI3K and BCR signaling genes[188]. The two studies both demonstrated the antitumor activity and well-tolerated safety profile of copanlisib monotherapy in indolent lymphoma. On account of the promising results of these studies, copanlisib received the FDA accelerated approval for the treatment of relapsed FL adult patients who have been previously treated with at least two systemic therapies. Combination therapy of copanlisib and gemcitabine was also an effective treatment option with ORR of 72% and PFS of 6.9 months in relapsed/refractory peripheral T cell lymphoma patients[189]. Notably, a phase III study investigated copanlisib combined with rituximab *vs*. placebo in combination with rituximab in relapsed indolent NHL patients. Copanlisib plus rituximab showed a more substantial clinical benefit as reflected by a significantly higher median PFS (21.5 months *vs*. 13.8 months) than the placebo group. However, it is noteworthy that more serious adverse events (47% *vs*. 18%) were reported in the combination group than in the placebo group, and the most frequent grade 3−4 adverse events were hyperglycemia (56% *vs*. 8%) and hypertension (40% *vs*. 9%)[190].

Taselisib is a potent dual PI3Kα/δ inhibitor. Similar to inavolisib, taselisib was also known to promote the degradation of the mutated p110α isoform. The early-stage trials suggested that the combination therapy of taselisib and estrogen receptor (ER) antagonist (*e.g.*, fulvestrant and tamoxifen) had preliminary evidence of antitumor activity in ER-positive advanced or metastatic breast cancer (NCT02285179, NCT01296555). On account of these studies, the phase III SANDPIPER study was conducted to assess the clinical efficacy of taselisib combined with fulvestrant. The combination treatment of taselisib and fulvestrant was found to improve PFS (7.4 *vs*. 5.4 months) compared with the placebo cohort in PIK3CA-mutant, HER2-negative, ER-positive advanced breast cancer. However, such a combination regimen has limited clinical utility because of modest clinical benefit and considerable serious adverse events, resulting in the termination of its clinical development[191]. Similar results were also observed in other PIK3CA-mutant cancers including NSCLC, head and neck squamous, and cervical cancer.

Duvelisib is a dual PI3Kγ/δ inhibitor that was clinically approved for treating adult patients with relapsed or refractory FL, CLL, and SLL. In the phase II DYNAMO trial (NCT01882803), duvelisib monotherapy exhibited clinically meaningful activity with a median PFS of 9.5 months and an ORR of 47.3% in patients with refractory indolent NHL. Furthermore, in the phase III DUO study, compared to ofatumumab, duvelisib demonstrated a longer PFS of 13.3 months *vs*. 9.9 months and a better ORR of 74% *vs*. 45% in relapsed or refractory SLL/CLL patients (NCT02004522)[192]. Apart from duvelisib monotherapy, combination treatments are also under active clinical investigations in a range of cancer types. Duvelisib plus rituximab or bendamustine/rituximab achieved a median PFS of 13.7 months and an ORR of 71.8% in NHL or CLL patients, and the clinical efficacy of such regimen should be further studied.

Tenalisib (RP6530) is another dual PI3Kγ/δ inhibitor. Given that the PI3Kγ and PI3Kδ isoforms are overexpressed in Hodgkin lymphoma cells within the TME, the antitumor activity of tenalisib against Hodgkin lymphoma was investigated *in vitro* and *in vivo*. Tenalisib inhibited the proliferation of Hodgkin lymphoma cells and transformed macrophages from an M2-like phenotype to an M1-like state, resulting in tumor regression[193]. Currently, tenalisib monotherapy and its combination with romidepsin are being investigated in several clinical trials (NCT03711578, NCT05021900, and NCT03770000).

6.1.5. *Pan-PI3K inhibitors*

Activation of the PI3K pathway is known to confer resistance of hormone receptor (HR)-positive breast cancer to endocrine therapy. Thus, a combination treatment of PI3K inhibitor and endocrine therapy could be a feasible and efficacious option for HER2-negative, HR-positive advanced breast cancer. Buparlisib, a pan-PI3K inhibitor, was shown to potently inhibit all class I PI3K. Buparlisib plus fulvestrant presented a better median PFS of 6.9 months *vs*. 5.0 months and 3.9 months *vs*. 1.8 months than placebo plus fulvestrant in such patients group in the BELLE-2 and BELLE-3 trials, respectively (NCT01610284, NCT01633060). However, safety concerns for the buparlisib−fulvestrant combination in both trials, due to the low selectivity of buparlisib to PI3K inhibition, have halted its further clinical development. Moreover, the combination of buparlisib and paclitaxel also failed to improve PFS (9.1 *vs*. 9.2 months) compared to paclitaxel plus placebo in HER2-negative breast cancer, whereas this combination improved PFS (4.6 *vs*. 3.5 months) in head and neck squamous cell carcinoma (HNSCC)[194,195]. Thus, buparlisib plus paclitaxel is being investigated in a phase III trial for the treatment of HNSCC (NCT04338399). Similar to buparlisib, another pan-PI3K inhibitor pictilisib combined with paclitaxel or fulvestrant did not improve PFS (6.6 months *vs*. 5.1 months and 8.2 months *vs*. 7.8 months) of HR-positive breast cancer, respectively (NCT01437566, NCT01740336). Collectively, these clinical studies indicate that pan-PI3K inhibitors exert limited antitumor efficacy with toxicity related to their non-selective PI3K inhibition.

6.2. *Targeting JAK-mediated signaling*

The Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway plays a critical role in inflammation, hematopoiesis, adipogenesis, tissue repair, and immune responses. Multiple cytokines, growth factors, and hormones exert biological function through the JAK−STAT pathway. However, the aberrant activation of JAK/STAT signaling contributes to inflammatory and immune-mediated diseases, as well as malignancies[196,197]. For example, elevated IL-6 produced in the TME leads to hyperactivation of JAK/STAT3 signaling, resulting in the proliferation, invasiveness, and metastasis of cancer cells. In addition, IL-6-mediated JAK/STAT3 also exerts negative regulatory effects on DCs, NK cells, and effector T cells, but positively regulates Treg cells and MDSCs, collectively promoting an immunosuppressive TME[198]. In consideration of the regulatory function of JAK/STAT signaling in the immune system and its tumor-promoting effect in tumor development, targeting the JAK/STAT pathway has emerged as a useful therapeutic regimen in cancer treatment. Currently, over a dozen JAK inhibitors are under different stages of clinical development, and some of them have been approved for the treatment of a heterogeneous group of disorders, including autoimmune diseases and hematological malignancies[199,200]. Clinical applications of many JAK inhibitors mainly focus on inflammatory and autoimmune diseases, including ulcerative colitis, systemic lupus erythematosus, and rheumatoid arthritis[199]. Several JAK inhibitors (ruxolitinib, fedratinib, momelotinib, and pacritinib) have received FDA approval for treating myeloproliferative neoplasms (MPN) on account of promising results in clinical trials (Fig. 13B)[201−203]. In this section, we mainly focus on the JAK inhibitors involved in MPN. Myelofibrosis is a kind of MPN associated with the activation of the JAK2-mediated signaling pathway.

Ruxolitinib is a selective and potent JAK1/2 inhibitor that showed clinically significant activity against myelofibrosis in early-stage clinical studies. The phase III COMFORT-I and COMFORT-II studies demonstrated that ruxolitinib exhibited substantial clinical benefits in patients with myelofibrosis, contributing to its accelerated drug approval[201,204]. In the COMFORT-I trial, 41.9% of patients in the ruxolitinib group achieved a reduction in spleen volume $\geq$35% at 6 months compared to 0.7% in the placebo group. More patients treated with ruxolitinib (45.9% *vs*. 5.3%) showed an improvement in myelofibrosis-related symptoms at 24 weeks, and significant OS benefit was observed in the ruxolitinib group. Similarly, the favorable antitumor efficacy of ruxolitinib was also observed in the COMFORT-II trial, which evaluated the safety and efficacy of ruxolitinib in patients with myelofibrosis compared to the best available therapy (BAT). Ruxolitinib showed a marked and durable reduction in splenomegaly with a decrease of 56% in length and improved symptoms associated with myelofibrosis. Moreover,

the addition of navitoclax (Bcl-2 inhibitor) to ruxolitinib also resulted in improvement in spleen volume, hemoglobin, and bone marrow fibrosis[205]. Besides myelofibrosis, ruxolitinib monotherapy and in combination with chemotherapy, immunotherapy or targeted therapy are under active clinical investigations in different clinical stages for a range of cancers, including breast cancer, lung cancer, and pancreatic cancer.

Fedratinib is a potent JAK2-selective inhibitor approved for first-line and second-line therapy of myelofibrosis. The JAKARTA study demonstrated that 400 mg and 500 mg fedratinib were more effective than placebo in patients with myelofibrosis, which substantially decreased splenomegaly and symptom burden[202]. The phase II JAKARTA-2 trial investigated the efficacy of fedratinib in patients with myelofibrosis who received ruxolitinib, indicating that 55% of patients achieved spleen responses[206]. However, it is noteworthy that fedratinib treatment was related to an increased risk of Wernicke's encephalopathy, thus, considerations should be taken for dose adjustment and more closely monitoring.

Pacritinib is another approved JAK2 inhibitor for myelofibrosis. Pacritinib is focused on AML and myelofibrosis patients because of its high selectivity against the *JAK2* V617F and *FLT3* D835Y mutants frequently observed in AML and MPN. The two PERSIST-1 and PERSIST-2 studies compared the clinical efficacy of pacritinib with BAT in myelofibrosis[203,207]. Pacritinib exhibited superior efficacy to BAT in terms of symptom improvement and spleen volume reduction. Additionally, pacritinib 200 mg twice daily is more effective than pacritinib 400 mg once daily in improving hemoglobin and reducing transfusion burden. Pacritinib has also been evaluated in several other types of cancers, including breast cancer, prostate cancer, and colorectal cancer.

Momelotinib, a potent JAK1/2 inhibitor, was evaluated in two phase III trials for the treatment of myelofibrosis[208,209]. The SIMPLIFY-1 study assessed the safety and efficacy of momelotinib compared to ruxolitinib in myelofibrosis patients who never received JAK inhibitors. Momelotinib was non-inferior to ruxolitinib in terms of spleen response, and the results demonstrated that 26.5% of patients in the momelotinib cohort and 29% of patients in the ruxolitinib cohort achieved $\geq$35% spleen volume reduction. However, the SIMPLIFY 2 trial suggested that momelotinib was not superior to BAT (mainly ruxolitinib) in myelofibrosis patients previously receiving ruxolitinib for the reduction of spleen volume by $\geq$ 35%. Anemia is a common symptom of myelofibrosis and momelotinib can improve anemia with reductions in symptoms and splenomegaly. Thus, the phase III study (MOMENTUM) investigated the clinical benefits of momelotinib in patients with anemia and myelofibrosis. Momelotinib was shown to produce clinically significant improvements in spleen response, anemia, and myelofibrosis-associated symptoms than the traditional danazol treatment, which supported momelotinib as an effective treatment option in patients with myelofibrosis, especially in those with anemia[210]. Moreover, the exciting clinical outcome also led to FDA approval of momelotinib for patients with anemia and myelofibrosis in the first-line and second-line settings.

Taken together, JAK inhibitors generally exhibit clinical efficacy for the treatment of myelofibrosis. However, given the complexity of myeloproliferative neoplasms, JAK inhibitor monotherapy appears inadequate and its combination with other anticancer modalities should be developed. With the accumulating knowledge of JAK−STAT pathway in tumor biology, more JAK inhibitors will be developed and their full potential in cancer therapy could be realized in the future.

7. Small-molecule agents targeting immune-related kinases

7.1. Targeting hematopoietic progenitor kinase 1 (HPK1)

A member of the MAP4Ks family of human STE20-like protein serine/threonine kinases is the hematopoietic progenitor cell kinase 1 (HPK1), also known as mitogen-activated protein kinase kinase kinase kinase 1 (MAP4K1)[211]. Numerous studies have demonstrated that HPK1, which functions as a negative regulator of T cell, B cell, and DC-mediated immune responses, collaborates with several signal adaptor proteins to transmit signals to downstream cellular events, controlling the stress response, signal transduction, cell proliferation and apoptosis[212−216]. Previous investigations have demonstrated that HPK1 participates in practically every phase of the cancer immune cycle as a negative regulator. Inhibiting tumor growth is one of the effects of impaired HPK1 kinase activity, which also improves T cell signaling, virus clearance, and cytokine release. A recent study analyzed that HPK1 kinase activity inhibits immune function in a variety of cells, including $CD4^+$ T cells, $CD8^+$ T cells, and DCs, and confirmed that inactivation of its kinase domain is sufficient to induce an antitumor immune response[217]. Hernandez et al.[217] identified the kinase-dependent effects of HPK1 in CD1 T cells by using HPK1 kinase-dead (HPK1.kd) knock-in mice. It has been demonstrated that the intrinsically increased T cell receptor signaling and cytokine release are caused by the loss of HPK1 kinase activity. In response to tumor challenges, HPK1.kd mice showed enhanced tumor growth inhibition and increased CD8 T cell function. Interestingly, the simultaneous blockade of PD-L1 and HPK1 was found to further enhance the function of effector T cells, thus providing better anti-tumor immunity than single-target blockade. These researches suggest that HPK1 is a promising target for cancer immunotherapy.

There is currently no drug on the market worldwide that targets HPK1, but several small molecule inhibitors have entered clinical trials.

7.1.1. CFI-402411-based combinational therapy

CFI-402411, an HPK1 inhibitor currently being investigated in phase II clinical trials for treating advanced solid tumors, has shown promising antitumor activities in mouse models of solid and hematologic malignancies when used as monotherapy or in combination with checkpoint inhibitors. For example, CFI-402411 is effective as a single agent and acts synergistically with anti-PD1 antibodies in CT26 tumor-bearing mice. Intriguingly, experimental tumor rechallenges after prior complete remission failed to result in tumor regrowth in mice treated with HPK1 inhibitors, indicating the immune memory induced by HPK1 inhibitors[218]. The safety and tolerability of CFI-402411 alone or in combination with pembrolizumab in patients with advanced solid tumors are being assessed in a first-in-human study (NCT04521413).

7.1.2. BGB-15025-based combinational therapy

BGB-15025 is another HPK1 inhibitor currently under phase I clinical investigation for advanced solid tumor (NCT04649385)

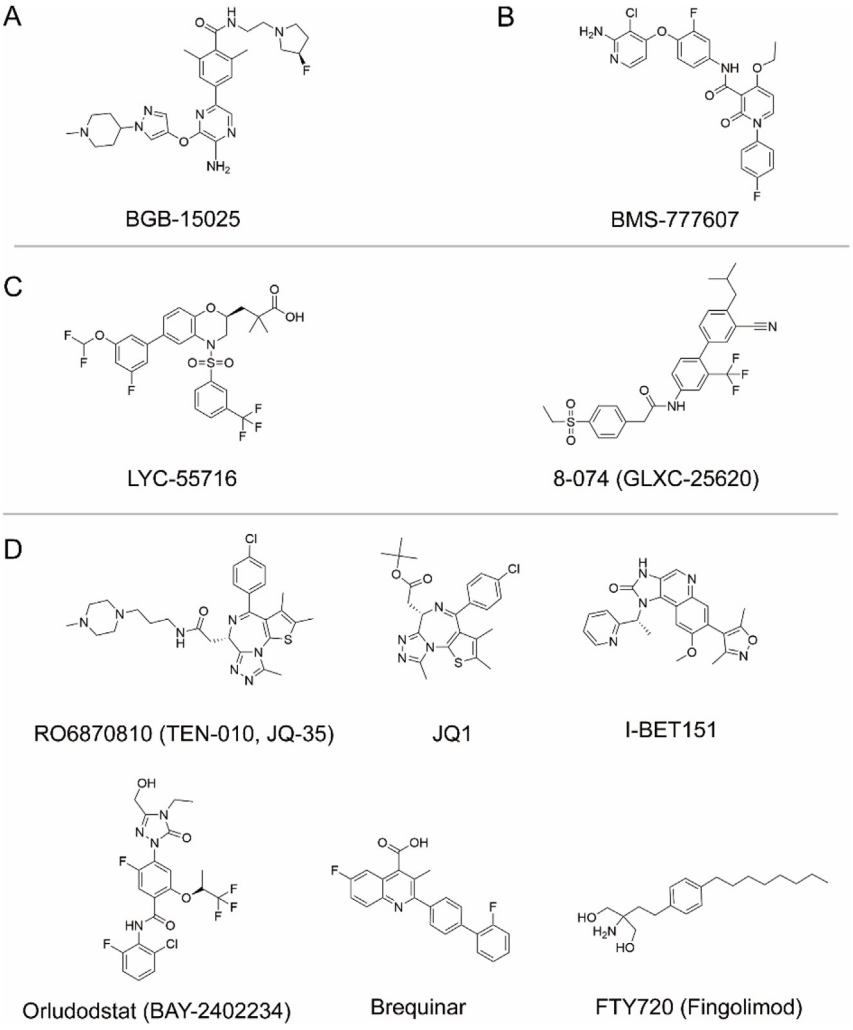

Figure 14 Representative inhibitors targeting immune-associated kinases, RORγt, and other targets. (A) Representative HPK1 inhibitor. (B) Representative RON inhibitor. (C) Representative RORγt inhibitors. (D) Representative inhibitors targeting other immunotherapy targets, including BET inhibitors (RO6870810, JQ1, and I-BET151), DHODH inhibitors (orludodstat and brequinar), and S1PR1 modulator (FTY720).

(Fig. 14A), which aimed to examine the safety, pharmacokinetics, and preliminary anticancer efficacy of BGB-15025 alone and in combination with tislelizumab (anti-PD1 monoclonal antibody) in patients with advanced solid tumors.

7.1.3. PF-07265028-based combinational therapy

For advanced or metastatic solid tumors, the HPK1 inhibitor PF-07265028 is presently being tested in a phase I clinical study (NCT05233436). This study's goal was to assess the effectiveness and safety of PF-07265028 monotherapy and in combination with sasanlimab (anti-PD-1 monoclonal antibody), establishing the maximum tolerated dosage (MTD) of PF-07265028. The suggested dose of PF-07265028 was chosen for monotherapy and combination therapy to assess the clinical efficacy of these treatments in future investigations.

7.1.4. PRJ1-3024-based combinational therapy

PRJ1-3024 is being tested in a phase II clinical trial for advanced solid tumors (NCT05315167). This study is designed to determine the MTD of PRJ1-3024 and assess its safety, tolerability, pharmacokinetics, and pharmacodynamics among patients with advanced solid tumors.

7.1.5. NDI-101150-based combinational therapy

Another HPK1 inhibitor, NDI-101150, is being studied in a phase I/II clinical trial (NCT05128487). The study was performed to evaluate the safety and initial antitumor activity of NDI-101150 as monotherapy or in combination with pembrolizumab in adult patients with advanced solid tumors. In addition, the MTD and recommended phase II dose were also identified.

7.1.6. GRC-54276-based combinational therapy

The HPK1 inhibitor, GRC-54276 is being investigated for advanced solid tumors and lymphomas in a phase I clinical study (NCT05878691). This research was conducted to evaluate the efficacy of GRC-54276 alone and in combination with pembrolizumab or atezolizumab (an anti-PD-L1 antibody) in patients with advanced solid tumors and lymphomas. Additionally, the MTD and suggested phase II doses of GRC-54276 alone and in combination with pembrolizumab or atezolizumab will also be determined.

7.1.7. *RGT-264-based combinational therapy*

RGT-264 is an HPK1 inhibitor being tested in a phase I clinical trial for advanced solid tumors (NCT05764915). This trial assesses the preliminary effectiveness, pharmacokinetics, safety, and tolerability of RGT-264 phosphate tablets in patients with advanced solid tumors. Besides, the MTD and the phase II dose advised for monotherapy were also evaluated.

7.2. *Targeting RON signaling*

Receptor tyrosine kinases (RTKs) have a significant impact on various cellular processes including cell growth, proliferation, differentiation, migration, metabolism, and cell cycle progression in cancer[219,220]. Recepteur d'origine nantais (RON, also known as macrophage stimulating 1 receptor, MST1R) expressed by epithelial-derived cells, osteoclasts, and macrophages, is an RTK of the Met proto-oncogene family which is a subfamily of RTKs containing another member, c-Mesenchymal−epithelial transition factor (c-Met)[221]. Macrophage-stimulating protein (MSP, also known as human macrophage stimulating 1, MST1, or mouse hepatocyte growth factor-like protein, HGFL) is currently recognized as the sole identified specific ligand of RON according to receptor binding, crosslinking, phosphorylation and induction of cell migration[222].

The expression of RON was reported to be substantially higher in cancer cells than in normal epithelial cells. Crystal structure analysis revealed that one MSP molecule interacts with two RON semaphorins (SEMA)[223]. Interestingly, while ligand-dependent activation of RON occurs classically in normal tissues, RON can be activated by ligand-independent dimerization mainly in RON-overexpressing cancers[222]. Moreover, the activation of RON requires the presence of CD44, especially the v6-containing isoforms as coreceptors, which are also overexpressed in tumors[224]. Currently, RON overexpression has been observed in many primary tumors due to numerous mechanisms. RON transcription could be enhanced by additional transcription factors including NF-κB and HIF-1α in cancer cells[225,226]. Meanwhile, the methylation patterns in the RON promoter could be altered to favor transcription. Interestingly, RON overexpression is often accompanied by the generation of multiple RON isoforms. Among all discovered RON isoforms, RONΔ165, RONΔ160, and RONΔ155 were identified from primary human colorectal adenocarcinomas to drive cancer progression[227], and the short-form Ron (sf RON) was shown to contribute to breast cancer pathogenesis[228].

RON signaling activates downstream pathways such as P13K−AKT, RAS−ERK, and MAPK pathways, which subsequently stimulate distinct signaling cascades that are crucial for epithelial-to-mesenchymal transition, including TGFβ, STAT, β-catenin, and NF-κB pathways to facilitate carcinogenesis[222]. The remarkable crosstalk of active RON signaling with other oncogenic signaling pathways as a result of RON overexpression in tumors highlights its importance in tumorigenesis[229]. Furthermore, RON-activated signaling in stromal cells, especially TAM in the TME also contributes to tumor growth and invasiveness[230]. Recently, RON activation was shown to block antitumor $CD8^+$ T cell response and thus contributed to immunotherapy resistance and metastasis[231]. Moreover, aberrant RON activation (*via* overexpression of RON protein or multiple RON isoforms) and MSP-RON signaling has been reported to induce and promote tumor survival, growth, metastasis, and chemoresistance in various cancers[228,232−235].

Given the significant role of RON signaling in cancer progression, targeting RON signaling has emerged as an attractive strategy for cancer therapy. Previous studies have demonstrated the antitumor effect by inhibition of RON signaling alone. Recently, accumulating evidence suggested that the combination of multi-tyrosine kinase inhibitors and RON inhibition may produce a more pronounced antitumor efficacy than targeting RON alone[236]. It is noteworthy that specific inhibitors of RON alone have not been discovered because RON shares similar protein structures with c-Met and various other RTKs[237]. Therefore, studies about small-molecule dual inhibitors of RON and c-Met were mainly reported in the literatures and they were mainly focused on the blockade of the HGF-c-Met signaling[146,147]. RON signaling was proposed as a co-therapeutic target due to its relatively weak kinase activities.

BMS-777607 (ASLAN002) is a selective inhibitor of RON kinase that has advanced into clinical trials because of its preclinical favorable pharmacokinetic and safety profiles and robust efficacy *in vivo* (Fig. 14B)[238]. The combination of BMS-777607 and anti-PD-1 was reported to significantly decrease tumor growth and incidence of lung metastasis *vs*. either monotherapy alone in a mouse model of triple-negative breast cancer[239]. Breast cancer cells are known to secrete high levels of MSP and activate the MSP-RON signaling to cause bone destruction. To this end, BMS-777607 was shown in a first-in-human clinical trial to reduce bone destruction and alter markers of bone turnover, which provided a rationale to target RON for breast cancer therapy[240]. However, Sharma et al.[241] reported that BMS-777607 could increase resistance to cytotoxic chemotherapy agents by inducing polyploidy in breast cancer cell lines[242]. These studies pointed to the potential clinical application and complications when using RON kinase inhibitors for cancer treatment.

In a phase I multiple ascending dose study among patients with advanced or metastatic solid tumors, BMS-777607 was well tolerated and 300 mg twice daily was determined as the recommended dose for future phase II studies (RP2D)[243]. Another phase I/II trial (NCT00605618) investigating multiple ascending doses of BMS-777607 in patients with advanced or metastatic solid tumors is also ongoing.

8. Targeting RORγt

RORγt, a crucial transcription factor in the RORs (Retinoic acid receptor-related orphan receptors) family[244], has been demonstrated to undergo sumoylation, which in turn facilitates the differentiation of naïve $CD4^+$ T cells, leading to the generation of Th17 cells[245]. The differentiated Th17 cells could produce interleukin (IL)-17 and activate the anti-tumor response of $CD8^+$ T cells (Fig. 15)[246]. $CD8^+$ T cells are of utmost importance in tumor immunotherapy, as they fulfill crucial roles among all types of immune cells[247]. Unfortunately, the tumor microenvironment often employs various immune escape mechanisms that result in the suppression of the normal anti-tumor functions of $CD8^+$ T cells[248]. Given that RORγt agonists have been demonstrated to activate RORγt signaling, facilitate the generation of Th17 cells, and promote the activation of $CD8^+$ T cells, they have emerged as a novel strategy in immunotherapy (Fig. 14C)[249]. RORγt is a particularly attractive target among all IL-17 regulators (*e.g.*, STAT3, IRF4, and BATF) because RORγt has a canonical NR ligand binding domain (LBD) that is readily accessible for the binding of small molecules[250].

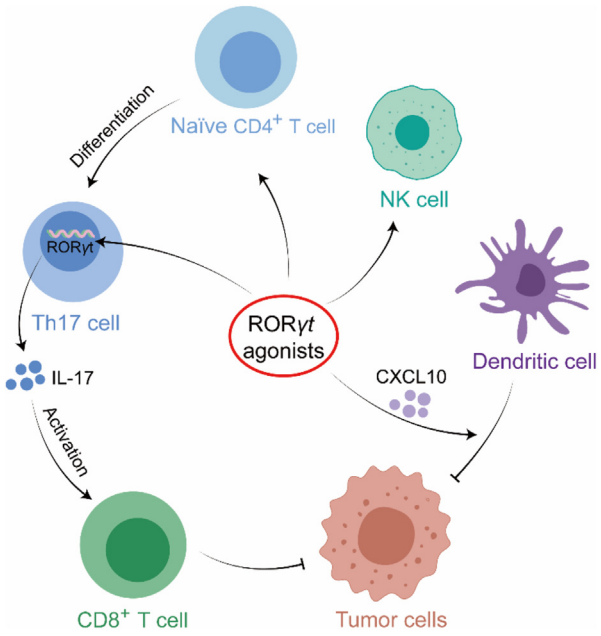

Figure 15 The role of RORγt agonists in antitumor immunity. RORγt agonists have been demonstrated to upregulate the expression of CXCL10 in DCs, increase the population of $CD8^+$ T cells, and activate NK cells. Moreover, it can promote the differentiation of $CD4^+$ T cells into Th17 cells, which subsequently secrete IL-17 to activate $CD8^+$ T cells. MDSCs, myeloid-derived suppressor cells; DCs, dendritic cells. Created with BioRender.com.

A recent study has revealed an alternative mechanism of RORγt agonists to potentiate immunotherapy[249]. The RORγt agonist (8-074) has been observed to upregulate CXCL10 expression in DCs and enhance the population of $CD8^+$ T cells. In transwell experiments, elevated CXCL10 expression was shown to enhance the migration of $CD8^+$ T cells. Crucially, the utilization of RORγt agonists has demonstrated the ability to significantly improve the effectiveness of anti-PD-1 immunotherapy. The enhancement effect of 8-074 was dependent on CXCL10 because the abundance and migration of $CD8^+$ T cells were not affected if CXCL10 was neutralized in the tumor microenvironment.

The most commonly used RORγt agonists include steroids (*e.g.*, cholesterol and desmosterol), synthetic aryl amide, and thiazole amide[244]. LYC-55716 is a first-in-class oral RORγt agonist currently in phase II clinical evaluation to test its efficacy against metastatic cancers (NCT02929862). Furthermore, the effectiveness of LYC-55716 as a monotherapy and in combination with pembrolizumab is also under active clinical investigation for the treatment of NSCLC (NCT03396497).

9. Small-molecule agents targeting other immunotherapy targets

9.1. *Bromodomain inhibitors*

The bromodomain is a protein domain that can recognize and bind to acetylated lysine residues present in various proteins important for cellular functions. Abnormal acetylation levels and dysfunction of the bromodomain-containing proteins could lead to dysregulation of gene transcription, which is associated with the development of various disorders including malignant tumors and inflammation. Among the protein families containing bromodomain, BET proteins, and CBP/p300 proteins are currently the most studied.

BET (Bromodomain and extra terminal) proteins, including BRD2, BRD3, BRD4, and BRDT, are involved in various biological processes and related to tumor development[251]. BET inhibitors exhibited potential antitumor effects, and some of them are under assessment in ongoing clinical trials. In the phase Ib study (NCT03255096), the combination of the BET inhibitor (RO6870810) and venetoclax with or without rituximab for the treatment of DLBCL showed an ORR of 38.5% and a complete response rate of 20.5%[252]. In another phase I clinical study of RO6870810 alone for the treatment of NUT carcinoma, other solid tumors, and DLBCL, the ORRs were 25% (2/8), 2% (1/47), and 11% (2/19), respectively[253]. Studies have also shown that BET bromodomain inhibitors JQ1 and I-BET151 can upregulate MICA to activate NK cells and regulate antitumor immunity[254]. Moreover, JQ1 was also reported to attenuate T regulatory cell suppressive function and synergize with the HDAC6 inhibitor ricolinostat to promote immune-mediated tumor growth arrest in NSCLC[255]. Furthermore, the combination of ricolinostat and JQ1 showed a significant inhibitory effect on SCLC tumor growth and this effect depended on NK cells[256].

CBP (cAMP-responsive element-binding protein-binding protein) and p300 (E1A-associated protein p300) are highly homologous, so they are generally referred to as CBP/p300. CBP/p300 belongs to the histone acetyltransferase family. The bromodomain inhibitor CBP30 selectively inhibits CBP/p300 and reduces the secretion of cytokines such as IL-17A[257]. Other CBP/p300 bromodomain inhibitors CPI703 and CPI644 were also found to inhibit the differentiation of Treg cells and the cytokine secretion of Th17 cells, possibly related to the regulation of FOXP3 acetylation[258]. In addition, the bromodomain inhibitor GNE-781 can downregulate MYC and FOXP3, thereby inhibiting the function of Treg cells to enhance antitumor immunity[259].

9.2. *DHODH inhibitors*

Dihydroorotate dehydrogenase (DHODH) is a key enzyme in the synthesis of pyrimidine nucleotides, which catalyzes the fourth step in the *de novo* pathway of pyrimidine nucleotide synthesis[260]. It is located on the inner mitochondrial membrane. Pyrimidine nucleotides can be synthesized by two pathways, the salvage pathway and the *de novo* pathway. In quiescent and fully differentiated cells, pyrimidine nucleotides are mainly synthesized by the salvage pathway. On the other hand, in rapidly proliferating cells such as malignant tumor cells and activated immune cells, the *de novo* pathway is activated as the demand for pyrimidine nucleotides increases to support cell proliferation. Therefore, the inhibition of DHODH may be exploited as a novel therapeutic strategy to inhibit abnormal cell proliferation.

DHODH inhibitors can inhibit the proliferation of activated lymphocytes by blocking the synthesis of pyrimidine nucleotides. Therefore, DHODH inhibitors are currently mainly used as immunosuppressants for the treatment of autoimmune diseases such as rheumatoid arthritis and multiple sclerosis[261,262]. The FDA has approved leflunomide and teriflunomide for clinical use.

In the field of cancer, DHODH inhibitors have also emerged as novel anticancer agents. *In vivo* and *in vitro* experiments showed that orludodstat (BAY2402234) can inhibit proliferation and

induce differentiation in AML, which supported the initiation of phase I clinical trial (NCT03404726) to evaluate its safety, tolerability, maximum tolerated dose, and pharmacological active dose in AML, myelodysplastic syndrome, and chronic myeloid leukemia[263]. Brequinar has also been reported to induce differentiation of AML cells[264]. Recent preclinical studies suggested that DHODH inhibitors may also play a role in melanoma, glioblastoma, SCLC, neuroblastoma, and other tumors[265−268]. In addition, the anticancer effect of DHODH inhibitors was shown to be related to the upregulation of p53 levels and ferroptosis[269,270]. Most recently, DHODH inhibitors were also reported to enhance the anti-tumor effect of ICI by inhibiting MDSCs[271].

9.3. S1PR modulators

S1P (sphingosine-1-phosphate) receptors are a class of transmembrane G protein-coupled receptors, including five subtypes, that exert various effects by binding to their natural ligand S1P. It is an important regulator in inflammation, angiogenesis, vascular permeability, cancer growth, and metastasis. S1P receptor agonists are currently mainly used as immunosuppressive agents for autoimmune diseases, organ transplantation, etc.

FTY720 is a sphingosine analog, which has been clinically approved for the treatment of multiple sclerosis. It can activate all S1PRs except S1P2 after phosphorylation by sphingosine kinase[272]. Furthermore, FTY720 may act as a functional inhibitor of S1P1 by mediating the internalization of S1PRs, so its action may be bidirectional[273]. By targeting S1PRs, FTY720 can increase the retention of lymphocytes in lymph nodes and exert immunosuppressive effects[274]. In addition, FTY720 was also reported to exhibit antitumor activity, but these effects are likely independent of S1PRs and may involve other pathways such as SPHK5, PP2A6, etc.[275−277]. Representative small-molecule agents targeting these targets are summarized in Fig. 14D.

10. Conclusion and future perspective

ICIs, especially monoclonal antibodies that target PD-1/PD-L1 and CTLA-4, have significantly advanced cancer treatment and substantially improved patient outcomes. Unfortunately, only 30%−40% of patients benefit from ICIs, and resistance to ICI therapy is common. Accumulating evidence indicates that combination therapy with ICIs and other therapeutic means could significantly improve the therapeutic efficacy. Small molecule-based immunomodulators targeting various intracellular pathways have gained significant advances recently and can provide complementary or alternative therapies with ICIs or chemotherapy. An increasing number of small molecules that target PRR-associated pathways, immune checkpoint, oncogenic signaling, metabolic pathways, etc. have been developed, hoping to provide new treatment options for patients who progressed from prior immunotherapy as well as patients who appear unresponsive to ICI therapy. Multiple clinical studies are ongoing for small-molecule immunomodulators alone or in combination with ICIs in a variety of cancer types.

By comparison with mAbs, immunomodulatory small-molecule inhibitors have several advantages, such as better organ or tumor penetration, higher stability, and the ability to cross cell membranes. Although quite optimistic, dozens of clinical trials evaluating different types of immunomodulators have failed to provide solid evidence of patient benefit. The major drawback is the disappointing clinical efficacy, and this may be due to a lack of predictive biomarkers to better select appropriate patients. For instance, results from ECHO-301, the first large phase III trial to evaluate epacadostat combined with pembrolizumab for the treatment of advanced melanoma showed no benefit[278]. Possible causes including its impact on the TME are not well understood and lack of direct evidence for target inhibition. The anti-tumor efficacy of immunomodulatory small molecule inhibitors depends on cancer types and the tumor microenvironment. Specific molecular changes or mutations may affect therapeutic efficacy, and identifying specific genes/proteins and understanding the molecular mechanism of action will help to improve the efficacy of current immunomodulators.

Another drawback is adverse side effects caused by off-target toxicity or “cytokine storm”. Recently, the phase I trial of XMT-2056 (a HER2-targeted immunosynthen STING-agonist antibody−drug conjugate) has been suspended due to serious adverse events (NCT05514717). Both continuous activation of the cGAS−STING pathway and systemic administration of TLR agonists can lead to excessive production of cytokines, causing severe toxicity. In light of existing problems, the development of small-molecule immuno-oncology drugs is still in a premature state, further optimization is needed to increase efficiency, specificity, and safety, to expand its clinical application.

Although there are some disadvantages, the potential of immunomodulatory small molecule inhibitors did show great clinical benefit in several tumor types. Lenvatinib plus pembrolizumab significantly prolonged the survival of patients with advanced RCC (NCT02811861). In patients with unresectable HCC, treatment with the combination of camrelizumab and rivoceranib demonstrated a strong improvement in survival outcome (NCT03764293). These small molecules possess unique properties to increase the efficacy of cancer immunotherapy strategies while eliminating immunosuppression and tolerance. In this review, we summarized clinical trials of small-molecule immunomodulators alone or in combination with other treatments for cancer therapy. A synergistic antitumor effect could be achieved by some combinations. Currently, the FDA has approved 16 different immunomodulators including 9 checkpoint inhibitors (7 targeting the PD1/PD-L1 signaling pathway, 1 targeting the CD28/CTLA-4 pathway, and 1 targeting LAG-3), 4 cytokines (3 targeting the IFNAR1/2 pathway and 1 targeting the IL-2/IL-2R pathway), 2 immune adjuvants (1 targeting TLR7 and another targeting TLR3), and pexidartinib (a small molecule with immunomodulatory properties targeting KIT, CSF1R, and FLT3 pathways) for the treatment of different cancer types. Among them, it is encouraging to see that two TLR agonists (imiquimod and Poly ICLC), have been approved by the FDA as adjuvants for the clinical treatment of basal cell carcinoma and squamous cell carcinoma. Lenvatinib plus pembrolizumab has been approved for first-line treatment of adult patients with advanced RCC. The combination therapy of rivoceranib and camrelizumab was approved by the China NMPA as a first-line treatment for liver cancer and the application for FDA approval was reviewed.

In summary, with increasing research in TME and reliable biomarkers in guiding clinical immuno-oncology, more effective new molecules and combination strategies are expected.

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Author contributions

Liwu Fu conceived the study and revised the manuscript. Kenneth Kin Wah To, Jianye Zhang, Zhi Shi, Zeping Hu and Min Huang revised the manuscript. Fang Wang, Kai Fu, Yujue Wang, Can Pan, Zeyu Liu, Xiaopeng Li, Yu Lu and Chenglai Xia retrieved the related literatures and wrote the manuscript. Kai Fu, Can Pan and Yujue Wang created the pictures. Fang Wang, Kai Fu, Yujue Wang, Xueping Wang and Chuan Yang retrieved the clinical trials and produced the tables. All authors have read and approved this version of manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

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