International Immunopharmacology 67 (2019) 160–175

Contents lists available at ScienceDirect

International Immunopharmacology

journal homepage: www.elsevier.com/locate/intimp

Review

Checkpoint-modulating immunotherapies in tumor treatment: Targets, drugs, and mechanisms

Lu Sun[a], Lixia Chen[a,*], Hua Li[a,b,*]

[a] Wuya College of Innovation, Key Laboratory of Structure-Based Drug Design & Discovery, Ministry of Education, Shenyang Pharmaceutical University, Shenyang 110016, China

[b] Hubei Key Laboratory of Natural Medicinal Chemistry and Resource Evaluation, School of Pharmacy, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China

ARTICLE INFO

Keywords:
Tumor
Immunotherapy
Checkpoint blockade
Targets

ABSTRACT

Tumor immunotherapy, as a new treatment of cancer, has been developing on the basis of tumor immunology. Tumor immunotherapy stimulates and enhances the function of immune system in human bodies, in order to control and kill tumor cells. It is often used as an adjuvant therapy combined with surgery, chemotherapy, radiotherapy and other conventional methods. Cancer immunotherapies involve cells, antibodies and cytokines, etc. Some immunotherapies are widely used to activate the immune system, while some others precisely target at different tumor antigens. With the development of tumor immunotherapy, immune regulation activities of small molecules and biological agents have been gradually becoming a hot research area these years. In this review, we summarize the therapeutic targets, drugs, biologics, and their mechanisms in tumor immunotherapies.

1. Introduction

Despite advances have been made in the treatment of cancer, cancer therapy is always a challenge for human. There are three main forms of cancer treatment: surgery, chemotherapy and radiation, while these conventional methods showed many deficiencies. Other treatments are therefore urgently required, such as immunotherapy which targets and eliminates malignant cells by activating immune system.

Compared with traditional therapies, the biggest advantage of tumor immunotherapy is that these drugs do not attack tumor cells directly, but stimulate and enhance the function of immune system, which will particularly benefit people whose immune functions have been damaged by radiation therapy or chemotherapy. Therefore, tumor immunotherapy is gaining increasing attention in recent years and shows good potency in treating cancers, which has been recognized as the fourth mode of cancer therapy all over the world. In this review, we summarize the therapeutic targets (Fig. 1), drugs, biologics, and their mechanisms in tumor immunotherapies.

2. Tumors and immune system

Tumor cells will experience interactions with the immune system. They can avoid the control and destruction of the immune system by a series of complex and overlapping mechanisms, sequentially damaging the key components involved in effective anti-tumor response. Similar to the cellular adaptive immune response targeting infectious agents, T cells and dendritic cells (DCs) are also involved in anti-tumor immunity [1].

DC is an important element of the tumor immunotherapy, known as full-time antigen presenting cell, with the strongest and unique ability to activate resting T cells in vivo. It is also a key link of initiating, controlling and maintaining the immune response. Tumor antigens are presented by DCs to activate $CD4^+$ helper T cells or $CD8^+$ cytotoxic T lymphocytes (CTLs) in the context of major histocompatibility complex class II (MHC II), MHC I [1], respectively. Helper T lymphocytes can be divided into two groups based on the types of cytokines secreted: Th1 and Th2, differentiating from the native T lymphocytes (Th0) [2]. Th1 effector cells secrete cytokine IL-2, IFN-γ and TNF-α, which mainly regulate cellular immunity, including anti-tumor immunity. In the meantime, Th2 effector cells secrete IL-4, IL-5, IL-6, IL-10, IL-13, mediating humoral immunity and promoting the production of antibody [3]. In normal conditions, Th1 and Th2 cytokines maintain a relative balance, which is important to human immune system. However, when dysfunction occurs, the balance is disturbed, causing the variation of Th1/Th2 equilibrium [4], which may result in many diseases and cause immunosuppression [5]. The imbalance of Th1/Th2 has been widely observed in many types of tumors and advanced cancers. In the tumor microenvironment, the variation of Th1/Th2 will significantly

* Corresponding authors.
E-mail addresses: syzyclx@163.com (L. Chen), li_hua@hust.edu.cn (H. Li).

https://doi.org/10.1016/j.intimp.2018.12.006
Received 18 October 2018; Received in revised form 20 November 2018; Accepted 3 December 2018
Available online 12 December 2018

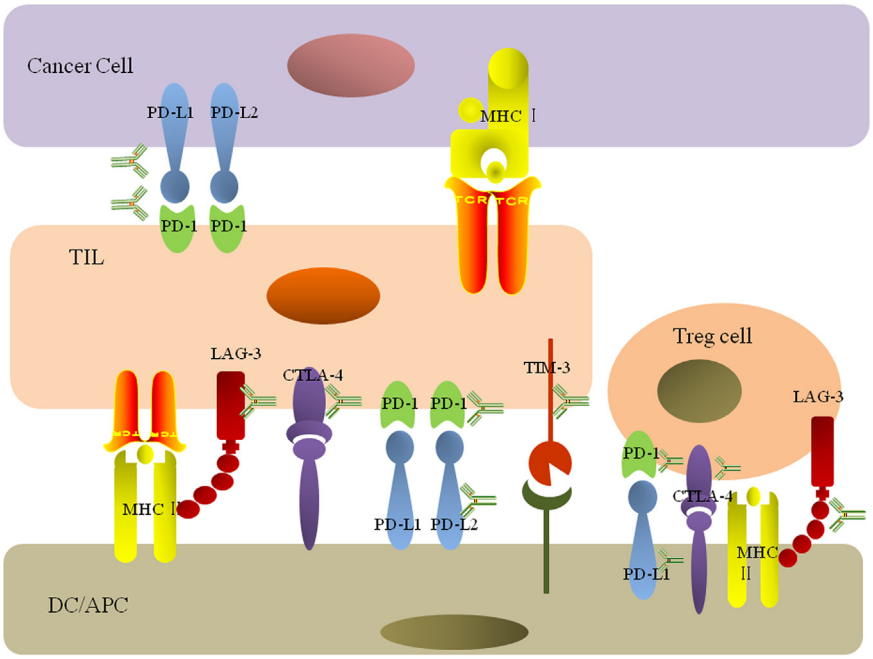


Fig. 1. Potential targets in tumor immunotherapy.

increase the ratio of $CD8^+/CD25^+$ cells [6]. These cells will be activated by Th1 cytokines and then developed into mature CTL [7], an important effector cell in anti-tumor immunity.

3. Checkpoint blockade: the research hotspot in tumor immunotherapy

Regarded as a novel strategy to treat cancer by regulating patients' immune responses, immunotherapy has been studied for many years. As the research continues, checkpoint blockade has caught more attentions.

Great complexity and specificity of immune system requires many rules and checkpoints to prevent autoimmunity and to “brake” immune response. Tumor cells show more changes in genetics and epigenetics than normal cells, which can theoretically produce sufficient amounts of antigens so that the immune system can distinguish them and trigger immune responses. However, immunosuppression makes it difficult to produce an effective immune response against tumor cells [8]. These suppression signals are so-called immune checkpoints.

On the one hand, these suppression signals are involved in maintaining the immune tolerance of auto antigen, avoiding autoimmune diseases and injuries caused by excessive activation of immune response [9]. On the other hand, tumor cells can escape from immune recognition by suppressing the activation of T cell through immune checkpoints. Up to now, several molecular mechanisms of tumor cells' escape from the immune recognition have been defined, such as tumor infiltrating macrophages which may limit activation and proliferation of T cell by interfering with amino-acid metabolism [10]. Therefore, activating T cells through different strategies is the important focus of tumor immunotherapy, among which blockade of immune checkpoints is one of the most effective strategies.

In recent years, immunocheckpoint blockade has revolutionized the way to treat cancer. Traditional cytotoxic chemotherapy drugs interfere with the proliferation and differentiation of normal cells and malignant cells by the common molecular mechanism. As a result, they can directly damage cancer cells, but not specifically. While, immunotherapy indirectly affects cancer cells by regulating the function of immune system [11]. Studies have shown that immunotherapy has significant effects on the prognosis of patients, including sustained responses and prolonged survival. Herein, several specific immune checkpoint targets will be introduced as follows. They include some classic immune checkpoints such as CTLA-4 and some atypical checkpoints which differ from the former but still work by regulating the immune system, such as CD122 and ICOS.

3.1. CTLA-4: scientific turning point for cancer immunotherapy

The turning point of cancer immunotherapy derived from an understanding that T cell immune response is controlled by switches, so called “immune checkpoints”, which can protect the body from potential destructive immune responses. CD28 cytotoxic T lymphocyte associated antigen 4 (CTLA-4) [12], the main switch, is a receptor that inhibits the activation of T cells and plays an important role in the initiation of immune response [13,14].

The suppression of T cell caused by CTLA-4 is achieved by two mechanisms: the competitive antagonism and direct negation of CD28 signal [15]. In the early response of T cell, CD28 was involved in initiating a synergistic signal cascade through B7 family, which was necessary to activate the T cell receptor (TCR). CTLA-4 can compete with CD28, and CTLA-4 has greater affinity for B7-1/B7-2 than CD28 [15–17]. The second mechanism of T cell inactivation mediated by CTLA-4 is to transmit the inhibitory signal through its cytoplasmic tail l [15]. The evidence of this mechanism is derived from the cross-linking of antibodies to CTLA-4 and TCR in the non-restrictive CD28 synergistic stimulus, which can induce arrest of cell cycle and inhibition of IL-2 [18,19]. CTLA-4 signals inhibit the production of cytokines by inhibiting accumulation of AP-1, NF-κB and NFAT in the nucleus of the activated T cells [20,21]. It can also regulate cell proliferation by inhibiting the degradation of cyclin D3, cyclin dependent kinase 4 and 6, and cell cycle inhibitor p27 [22].

In addition to the direct effects on TCR/CD28 signals, the other two processes in T cell activation may be directly or indirectly affected by CTLA-4 signals. One is to regulate signaling molecules and the availability of cell surface antigen receptors through Cbl-b. A recent study showed that CD28 and CTLA-4 regulate the activation and proliferation of T cells through E3 ubiquitin ligase Cbl-b [23]. Therefore, CD28 and CTLA-4 can control the threshold of T cell activation by regulating the expression of Cbl-b. The other function of CTLA-4 is that it may affect

Table 1
Potential agents targeting CTLA-4.

Highest phase	Code name	Generic name	Brand name/ structure	Product category	Therapeutic group	Mechanism of action
Phase I	M-834	Abatacept		Fc fusion proteins Follow-on Products Polypeptides, from 41 AA	Treatment of autoimmune diseases	T-Lymphocyte Activation Antigen CD80 (B7-1) Ligands CD86 (B7-2) Ligands
Phase I	MK-1308				Solid Tumors Therapy	Immune Checkpoint Inhibitors CTLA-4 Inhibitors
Phase I	CS-1002			Cancer Immunotherapy Human Monoclonal Antibodies	Solid Tumors Therapy	Immune Checkpoint Inhibitors Anti-CD152 (CTLA-4)
Phase I	BCD-145			Cancer Immunotherapy Monoclonal Antibodies	Melanoma Therapy	Immune Checkpoint Inhibitors Anti-CD152 (CTLA-4)
Phase I	MEDI-5752			Bispecific Antibodies Cancer Immunotherapy Humanized Monoclonal Antibodies	Solid Tumors Therapy	Immune Checkpoint Inhibitors Anti-CD152 (CTLA-4) Anti-PD-1
Phase II	AGEN-1884			Cancer Immunotherapy Human Monoclonal Antibodies	Non-Small Cell Lung Cancer/Cervical Cancer/Solid Tumors Therapy Oncolytic Drugs	Immune Checkpoint Inhibitors Anti-CD152 (CTLA-4)
Phase III	4.1.1 CP-642570 CP-675206 CT-4.1.1 MEDI-1123 PF-06753388	Ticilimumab (former INN; former USAN) Tremelimumab (Prop INN; USAN)		Cancer Immunotherapy Human Monoclonal Antibodies	Prostate Cancer/Small Cell Lung Cancer/Sarcoma/Multiple Myeloma/Non-Small Cell Lung Cancer/Endocrine Cancer/Lymphoma/Gastric Cancer/Melanoma/ Bladder Cancer/Breast Cancer/Ovarian Cancer/Pancreatic Cancer/Female Reproductive System Cancer/Colorectal Cancer/Osteosarcoma/Glioblastoma Multiforme/Liver Cancer/Head and Neck Cancer/Solid Tumors Therapy Oncolytic Drugs Digestive/Gastrointestinal Cancer Therapy Therapy Cancer of Unspecified Body Location/System Immunostimulants Renal Cancer Therapy	Immune Checkpoint Inhibitors Anti-CD152 (CTLA-4)
Launched-2006	BMS-188667 BMS-188667SC CTLA4-Ig ONO-4164 ONO-4164SC	Abatacept (USAN; Rec INN)	Orencia	Fc fusion proteins Polypeptides, from 41 AA	Agents for Nephritis/Psoriatic Arthritis/Myasthenia Gravis/Systemic Lupus Erythematosus/Vasculitis, Rheumatoid Arthritis/Type 1 Diabetes/Scleroderma/ Inflammatory Bowel Disease/Multiple Sclerosis; Treatment of Renal Diseases/Interstitial Lung Diseases/Ankylosing Spondylitis/ Idiopathic Inflammatory/Autoimmune Diseases Myopathies; Multiple Myeloma/Asthma Therapy Immunosuppressants, Ophthalmic Drugs Dermatologic Drugs	T-Lymphocyte Activation Antigen CD80 (B7-1) Ligands CD86 (B7-2) Ligands
Launched-2011	10D1 BMS-734016 MAb 10D14 MDX-010 MDX-CTLA4 MDX-101 (formerly)	Ipilimumab (USAN; Rec INN)	Yervoy	Cancer Immunotherapy Human Monoclonal Antibodies	Non-Hodgkin's Lymphoma/Multiple Myeloma/Small Cell Lung Cancer/Prostate Cancer/Sarcoma/Myelodysplastic Syndrome/Kaposi's Sarcoma/Endocrine Cancer/ Non-Small Cell Lung Cancer/Lymphoma/Neurologic Cancer/Cervical Cancer/ Melanoma/Skin Cancer/Gastric Cancer/Breast Cancer/Bladder Cancer/Ovarian Cancer/Renal Cancer/Colorectal Cancer/Myeloid Leukemia/Glioblastoma Multiforme/Head and Neck Cancer/Liver Cancer Therapy; Respiratory/Thoracic Cancer Therapy; Anti-HIV Agents Cancer of Unspecified Body Location/System Pancreatic Cancer Therapy; Digestive/Gastrointestinal Cancer Therapy	Immune Checkpoint Inhibitors Anti-CD152 (CTLA-4)
Launched-2011	BMS-224818 L104EA29YIg LEA-029 LEA29Y	Belatacept (Prop INN; USAN)	Nulojix	Fc fusion proteins Polypeptides, from 41 AA	Immunosuppressants Treatment of Transplant Rejection/Rheumatoid Arthritis	T-Lymphocyte Activation Antigen CD80 (B7–1) Ligands CD86 (B7–2) Ligands

cytoskeletal recombination by regulating the activity of small G protein Rap1. CD28 co-stimulation is associated with the inhibition of Rap1 activity, increasing activation level of extracellular signal regulation kinase (ERK) [24]. CTLA-4 has been shown to activate Rap1, suggesting that CTLA-4 can inhibit the activation of T cells by regulating the CD28 dependent activity of Rap [25]. Ipilimumab, a kind of antibody that can inhibit interaction of CTLA-4 and its ligands CD80 and CD86, had been approved in the treatment of advanced melanoma, with a raised survival rate in the patients group in clinical research [26–28]. Some other related drugs are listed in Table 1.

3.2. PD-1: an effective immune checkpoint in the combination therapy to treat cancer by mediating the immune system

PD-1 (programmed cell death protein-1) is a kind of important immunosuppressive transmembrane protein expressing on the surface of the T cells. PD-1 mainly restricts the activities of T cells in chronic inflammation, infection or cancer. It has two ligands, PD-L1 and PD-L2, which are related proteins found in antigen presenting cells and cancer cells. Tumor cells express PD-L1 or PD-L2, which can help tumor cells escape from the immune system by attaching to PD-1 protein on the surface of T cells. When ligands bind to PD-1, T cells cannot detect tumor cells and the signal of attacking tumor cells will be blocked. Meanwhile, PD-1 reduces the threshold of apoptosis and induces anergy of immune system through the passivated T cell receptor signal, which usually leads to the depletion of T cell [29,30].

In some tumor cells, the up-regulation of PD-L1 has been detected, leading to the inhibition of T cells which is correspondingly beneficial to the survival of tumor cells [31]. When the activated T cells begin to exhibit co-inhibitory PD-1 receptors in tumor cells, $CD4^+$ T helper cells and cytotoxic $CD8^+$ T cells release IFN-γ, which further increase the expression of PD-L1. PD-1 also combines with PD-L2 specially in dendritic cells and macrophages, indicating that PD-L2 can be activated in lymphatic organs, while PD-L1 can promote the self-tolerance of surrounding tissues. In TME, these cellular functions are inactivated when $PD\text{-}L1^+$ cells meet tumor specific $PD\text{-}1^+/CD8^+$ T cells [32]. Agents targeting PD-1 can block this pathway (interaction between PD-1 and PD-L1), induce immune responses and inhibit the growth of tumor cells [33].

The blockade of PD-1 and PD-1/PD-L1 pathway has been confirmed to be connected with prolonging survival of tumor cells in mice by enhancing phagocytosis of tumor associated macrophages and reducing tumor growth through a macrophage-dependent way. The expression of PD-1 interferes with different types of immune cells, including dendritic cells, natural killer cells, B cells and T cells. Besides cells mentioned above, macrophages are also involved, suggesting that expression of PD-1 is a general system for blocking immunity through adaptive and innate immune systems [34]. Although the expression of PD-L1 is generally considered to be a negative prognostic factor, it is clearly related to the positive results of PD-1/PD-L1 blocking antibody therapy for tumors [35]. The initial clinical trial tested antibodies that block the interaction of PD-1/PD-L1, using IgG4 human anti-PD-1 antibody (known as BMS-936558), later nivolumab (Opdivo; Bristol Myers Squibb, Princeton, NJ) in melanoma, lung cancers, colon cancers and renal cancers [36]. CTLA-4 blocking antibody ipilimumab combining with nivolumab was evaluated in the phase I, randomized phase II and randomized phase III studies [37–39]. MPDL3280A (Atezolizumab; Genentech), an IgG1 engineered antibody against PD-L1, has been evaluated in further studies of lung cancer [40]. An initial randomized phase II study of atezolizumab versus taxane in previously treated patients demonstrated promising outcomes [41]. Some other related drugs are listed in Table 2.

3.3. TIM3:Potential immune checkpoint with inhibitory activities of T cells

The pathophysiological inhibition of T cells' activities may be dominant in malignant tumors. The purpose of tumor immunotherapy is to alleviate the inhibition of effector T cells, so that effector T cells can eliminate the tumors. Molecules with inhibitory activities of T cells [42], T-cell immunoglobulin and mucin domain 3 (TIM3), has gained considerable attention recently. TIM3 was reported to be expressed in IFN-γ-secreting helper 1 (Th1) cells, DCs, monocytes, CD8 and other lymphocyte subsets [43,44]. The combination of galectin-9 and TIM3 leads to the death of Th1 cells, indicating that TIM3 is involved in the negative regulation of Th1 reaction [45].

The blockade of TIM3 has been shown to increase IFN-γ-secreting T cells [46]. Whereas monocytes and macrophages expressing TIM3 are associated with the phagocytosis of apoptotic cells. In addition to binding galectin-9, TIM3 is also reported to be the receptor of apoptotic cells. The agents with anti-TIM3 effects will therefore cause the death of tumor cells and the cross-lineage expression of tumor antigen in DC [47].

The anti-TIM3 treatment facilitates the generation of effector T cells by activating T-cell phenotype, increasing production of cytokines, promoting proliferation and transcriptional processes associated with T cell differentiation. Anti-TIM3 agent induces differentiation of CD8 T cell by activating mTORC1, concretely, by increasing the level of phosphorylated S6 protein and rhebl1 transcript. Activation of mTORC1 has been demonstrated to enhance the effects and differentiation of CD8 T cell. In the stimulus of antigen, TIM3 directly affects the differentiation of T cell through mTOR pathway [48]. TIM3 regulates innate immune response mediated by toll-like receptor (TLR) dependent on HMGB1, but not on galectin-9. High expressed TIM3 binds to HMGB1 specifically in the tumor infiltrating DCs, and reduces the transfer of nucleic acid into DC cells in dead tumor cells, which will inhibit the anti-tumor immune response caused by nucleic acid. The agents targeting TIM3 pathway have shown good results in the preclinical tumor model [49], and blocking the TIM3 pathway is a good strategy for anti-tumor immunity.

Currently, two types of TIM3 antagonised monoclonal antibodies (MBG453 and TSR-022) are in early clinical trials. MGB453 (Novartis, Basel, Switzerland), the safety and efficacy was first to be evaluated in human as a single agent or combined with PD-1 mAbs in patients with late malignant tumor. TSR-022 (American Waltham TESARO), as a single agent, is being evaluated again in Phase I trials in patients with advanced solid tumors, which will drive exploration of the safety and clinical activity of TSR-022 as a single therapy or a combination therapy with anti-PD-1 antibody in patients with some types of tumors. These trials will be closely watched, with great interest in the safety and efficacy results to evaluate whether TIM3 may be the next important focus in immunocheckpoint targets. Some other related drugs are listed in Table 3.

3.4. LAG-3: another immunomodulator similar to PD-1

The inhibitory receptors (IRs) are the key factors of controlling and shaping hosts' immune response. The lack of co-inhibition will break the self-tolerance, while the long-term utilization of inhibitory pathways is the main obstacle to effective anti-tumor immunity [50–52]. The tumor infiltrating lymphocytes (TILs) up-regulate various inhibitory receptors and exhibit an exhausted T cell phenotype after chronic antigenic stimulation [52]. Lymphocyte activation gene-3 (LAG-3) has recently been reported as the potential IR in clinic. LAG-3 is expressed in activated T cells, which essentially limits the proliferation, expansion and viability of normal T cells [53–56]. LAG-3 and other inhibitory receptors also have high expression in the regulatory T cells [57–60], which is a key suppressor group of T cells that inhibits autoimmunity but restricts anti-tumor immunity [61,62].

LAG-3 is reported as another immunomodulator similar to PD-1, inhibiting anti-tumor immunity and promoting tumor escape [63]. Firstly, LAG-3 is commonly expressed with several inhibitory receptors, such as PD-1, TIM3, BTLA and KLRG1 [63]. Secondly, in human lung,

Table 2
Potential agents targeting PD-1.

Highest phase	Code name	Generic name	Brand name/ structure	Product category	Therapeutic group	Mechanism of action
Phase I	CK-301			Cancer Immunotherapy Human Monoclonal Antibodies	Small Cell Lung Cancer/Non-Small Cell Lung Cancer/Lymphoma/ Skin Cancer/Renal Cancer/Melanoma/Genitourinary Cancer/ Hematological Cancer/Head and Neck Cancer Therapy Respiratory/Thoracic Cancer Therapy Oncolytic Drugs	Immune Checkpoint Inhibitors Anti-PD-L1 (CD274)
Phase I	KA-2507				Melanoma/Solid Tumors Therapy	Histone Deacetylase 6 (HDAC6) Inhibitors Apoptosis Inducers Epigenetic Modifier Modulators
Phase I	AUPM-170 CA-170			Cancer Immunotherapy	Lymphoma/Solid Tumors Therapy Oncolytic Drugs Cancer Immunotherapy	Immune Checkpoint Inhibitors V-Type Immunoglobulin Domain-Containing Suppressor of T-Cell Activation (VISTA, VSIR) Antagonists Programmed Cell Death 1 Ligand 1 (PD-L1; CD274) Antagonists
Phase I	BMS-189 BMS-986189 PD-L1-Milla			Polypeptides, from 10 AA to 40 AA	Treatment of Sepsis	Immune Checkpoint Inhibitors Programmed Cell Death 1 Ligand 1 (PD-L1; CD274) Antagonists
Phase I	LY-3300054			Cancer Immunotherapy Monoclonal Antibodies	Solid Tumors Therapy	Immune Checkpoint Inhibitors Anti-PD-L1 (CD274)
Phase I	CBT-502 TQB-2450			Cancer Immunotherapy Humanized Monoclonal Antibodies	Melanoma/Colorectal Cancer/Solid Tumors Therapy	Immune Checkpoint Inhibitors Anti-PD-L1 (CD274)
Phase I	CS-1001 WBP-3155			Cancer Immunotherapy Humanized Monoclonal Antibodies	Lymphoma/Solid Tumors Therapy	Immune Checkpoint Inhibitors Anti-PD-L1 (CD274)
Phase I	FAZ-053			Cancer Immunotherapy Monoclonal Antibodies	Endocrine Cancer/Non-Small Cell Lung Cancer/Breast Cancer/ Female Reproductive System Cancer/Solid Tumors Therapy	Immune Checkpoint Inhibitors Anti-PD-L1 (CD274)
Phase I		Zeushield cytotoxic T lymphocytes		Cancer Immunotherapy Chimeric Antigen Receptor (CAR)-Modified T Cells	Non-Small Cell Lung Cancer Therapy	Drugs Targeting CD86 (B7-2) Drugs Targeting Programmed Cell Death 1 Ligand 1 (PD-L1; CD274) Drugs Targeting CD80 (B7-1)
Phase I	FS-118 FS118 mAb2 LAG-3/PD-L1 mAb2			Antibodies Antibody-Derived Binding Proteins Bispecific Antibodies Cancer Immunotherapy	Oncolytic Drugs Colorectal Cancer Therapy	Immune Checkpoint Inhibitors Anti-PD-L1 (CD274) Anti-CD223 (Lymphocyte Activation Gene 3 Protein: LAG-3)
Phase I	HTI-1088 SHR-1316			Cancer Immunotherapy Humanized Monoclonal Antibodies	Solid Tumors Therapy	Immune Checkpoint Inhibitors Anti-PD-L1 (CD274)
Phase I	Sym-021			Cancer Immunotherapy Humanized Monoclonal Antibodies	Lymphoma/Solid Tumors Therapy	Immune Checkpoint Inhibitors Anti-PD-1
Phase I	MSB-2311			Cancer Immunotherapy Humanized Monoclonal Antibodies	Solid Tumors Therapy	Immune Checkpoint Inhibitors Anti-PD-L1 (CD274)
Phase I	Pd-1-pik			Antibodies Stem Cell Therapy	Glioblastoma Multiforme Therapy	Immune Checkpoint Inhibitors Anti-PD-1
Phase I/II	ARB-1598 CMP-001 CYT-003 CYT-003-QbG-10 CYT003-QbG10 QbG10			Cancer Immunotherapy Recombinant proteins Vaccines Virus-Like Particle Vaccines	Drugs for Allergic Rhinitis Anti-Hepatitis B Virus Drugs Asthma/Non-Small Cell Lung Cancer/Melanoma Therapy Agents for Atopic Dermatitis	Toll-Like Receptor 9 (TLR9) Agonists Signal Transduction Modulators

(*continued on next page*)

Table 2 (*continued*)

Highest phase	Code name	Generic name	Brand name/ structure	Product category	Therapeutic group	Mechanism of action
Phase I/II	BMS-936559 MDX-1105			Cancer Immunotherapy Human Monoclonal Antibodies	Treatment of Septic Shock/Sepsis, Anti-HIV Agents Solid Tumors Therapy	Immune Checkpoint Inhibitors Anti-PD-L1 (CD274)
Phase I/II	CX-072			Antibodies Cancer Immunotherapy Prodrugs	Lymphoma/Solid Tumors Therapy	Immune Checkpoint Inhibitors Anti-PD-L1 (CD274)
Phase I/II	IO102/IO103 peptide vaccine PD-L1/IDO peptide vaccine			Cancer Immunotherapy Cancer Vaccines Peptide Vaccines Polypeptides, from 41 AA	Melanoma Therapy	
Phase I/II	Ad5 [E1-, E2b-]-Brachyury ETBX-051			Cancer Immunotherapy Cancer Vaccines Recombinant Vector Vaccines	Prostate Cancer/Non-Small Cell Lung Cancer/Melanoma/Breast Cancer/Bladder Cancer/Colorectal Cancer/Squamous Cell Carcinoma/Head and Neck Cancer Therapy Oncolytic Drugs	
Phase I/II	Ad5 [E1-, E2b-]-MUC1		ETBX-061	Cancer Immunotherapy Cancer Vaccines Recombinant Vector Vaccines	Prostate Cancer/Non-Small Cell Lung Cancer/Melanoma/Breast Cancer/Colorectal Cancer/Squamous Cell Carcinoma/Non-Hodgkin's Lymphoma/Head and Neck Cancer Therapy	
Phase I/II	BGB-A333			Cancer Immunotherapy Humanized Monoclonal Antibodies	Solid Tumors Therapy	Anti-PD-L1 (CD274)
Phase I/II	TI-1007 TriCAR-T-CD19			Cancer Immunotherapy Chimeric Antigen Receptor (CAR)-Modified T Cells	Non-Hodgkin's Lymphoma Therapy	Drugs Targeting B-Lymphocyte Antigen CD19
Phase II	MK-7123 SCH-527123	Navarixin (Prop INN; USAN)			Treatment of Chronic Obstructive Pulmonary Diseases (COPD), Prostate Cancer/Non-Small Cell Lung Cancer/Colorectal Cancer Therapy Anti-allergy/Anti-asthmatic Drugs Anti-arthritic Drugs Antipsoriatics	Signal Transduction Modulators Chemokine CXCR2 (IL-8 beta Receptor) Antagonists Chemokine CXCR1 (IL-8 alpha Receptor) Antagonists Apoptosis Inducers Angiogenesis Inhibitors
Phase II	M-7824 MSB-0011359C			Bispecific Antibodies Cancer Immunotherapy Fusion Proteins Polypeptides, from 41 AA	Anti-Papilloma Virus Drugs Prostate Cancer/Gastric Cancer/Pancreatic Cancer/Colorectal Cancer/Solid Tumors Therapy	Immune Checkpoint Inhibitors Anti-TGFbeta2 Signal Transduction Modulators Anti-PD-L1 (CD274)
Phase II/III	MVA-Muc1-IL-2 TG-4010			Cancer Immunotherapy Cancer Vaccines IL-2 Recombinant Vector Vaccines	Prostate Cancer/Non-Small Cell Lung Cancer/Breast Cancer/ Renal Cancer Therapy	Anti-CD227 (MUC1)
Phase III	AM-0010 PEG-IL-10 PEG-hIL-10 PEGrhIL-10 5Z9850I25F (UNII code)	Pegilodecakin (Prop INN; USAN)		Cancer Immunotherapy IL-10 PEGylated Drugs Polypeptides, from 41 AA	Treatment of Pancreatic Fibrosis/Transplant Rejection/ Interstitial Lung Diseases/Inflammatory; Agents for Bowel Disease/Lipoprotein Disorders; Non-Small Cell Lung Cancer/ Atherosclerosis/Solid Tumors Therapy	
Phase III	IND-14205	Gemogenovatucel-T	FANG Vigil	Autologous Cellular Vaccines Cancer Immunotherapy Cancer Vaccines	Sarcoma/Non-Small Cell Lung Cancer/Melanoma/Breast Cancer/ Ovarian Cancer/Female Reproductive System Cancer/Colorectal Cancer Therapy Oncolytic Drugs	
Launched-2014	MK-3475 SCH-900475 h409A11	Lambrolizumab (former INN; former USAN) Pembrolizumab (USAN; Rec INN)	Keytruda	Cancer Immunotherapy Humanized Monoclonal Antibodies	Respiratory/Thoracic Cancer Therapy Multiple Myeloma/Lymphocytic Leukemia/Small Cell Lung Cancer/Sarcoma/Prostate Cancer/Myelodysplastic Syndrome/ Endocrine Cancer/Lymphoma/Non-Small Cell Lung Cancer/Basal Cell Carcinoma/Neurologic Cancer/Cervical Cancer/ Premalignant Conditions/Melanoma/Skin Cancer/Bladder	Immune Checkpoint Inhibitors Anti-PD-1

(*continued on next page*)

Table 2 (*continued*)

Highest phase	Code name	Generic name	Brand name/ structure	Product category	Therapeutic group	Mechanism of action
					Cancer/Gastric Cancer/Breast Cancer/Ovarian Cancer/Female Reproductive System Cancer/Genitourinary Cancer/Renal Cancer/Liver Cancer/Colorectal Cancer/Myeloid Leukemia/Solid Tumors/Head and Neck Cancer/Non-Hodgkin's Lymphoma/ Pancreatic Cancer Therapy Anti-Papilloma Virus Drugs Oncolytic Drugs Digestive/Gastrointestinal Cancer Therapy Cancer of Unspecified Body Location/System Glioblastoma Multiforme Therapy	
Launched-2016	MPDL-3280A RG-7446 RO-5541267 52CMI0WC3Y (UNII code)	Atezolizumab (USAN; Rec INN)	Tecentriq	Cancer Immunotherapy Humanized Monoclonal Antibodies	Prostate Cancer/Sarcoma/Small Cell Lung Cancer/ Myelodysplastic Syndrome/Lymphocytic Leukemia/Multiple Myeloma/Non-Small Cell Lung Cancer/Lymphoma/Endocrine Cancer/Cervical Cancer/Leukemia/Melanoma/Gastric Cancer/ Bladder Cancer/Breast Cancer/Ovarian Cancer/Pancreatic Cancer/Colorectal Cancer/Glioblastoma Multiforme/ Genitourinary Cancer/Renal Cancer/Myeloid Leukemia/Liver Cancer/Head and Neck Cancer/Solid Tumors/Non-Hodgkin's Lymphoma Therapy Oncolytic Drugs Digestive/Gastrointestinal Cancer Therapy	Immune Checkpoint Inhibitors Anti-PD-L1 (CD274)
Launched-2017	MK-4827	Niraparib (USAN; Rec INN)	Zejula	Radiosensitizers	Prostate Cancer/Non-Small Cell Lung Cancer/Neurologic Cancer/ Melanoma/Breast Cancer/Ovarian Cancer/Bladder Cancer/ Female Reproductive System Cancer/Pancreatic Cancer/ Glioblastoma Multiforme/Renal Cancer/Solid Tumors Therapy Oncolytic Drugs Digestive/Gastrointestinal Cancer Therapy	Poly(ADP-ribose) Polymerase 1 (PARP-1; ARTD1) Inhibitors Signal Transduction Modulators Poly(ADP-ribose) Polymerase 2 (PARP-2; ARTD2) Inhibitors
Launched-2017	28X28X9OKV (UNII code) MEDI-4736	Durvalumab (USAN; Rec INN)	Imfinzi	Cancer Immunotherapy Human Monoclonal Antibodies	Prostate Cancer/Small Cell Lung Cancer/Respiratory/Thoracic Cancer Therapy Endocrine Cancer/Lymphoma/Non-Small Cell Lung Cancer/ Female Reproductive System Cancer/Pancreatic Cancer/ Colorectal Cancer/Osteosarcoma/Hematological Cancer/Renal Cancer/Myeloid Leukemia/Glioblastoma Multiforme/Non-Hodgkin's Lymphoma/Hematopoiesis Disorders/Solid Tumors/ Liver Cancer/Head and Neck Cancer Therapy Gastric Cancer/ Bladder Cancer/Breast Cancer/Ovarian Cancer/Cervical Cancer/ Melanoma/Sarcoma/Lymphocytic Leukemia/Myelodysplastic Syndrome/Multiple Myeloma Therapy Anti-Papilloma Virus Drugs Oncolytic Drugs Digestive/Gastrointestinal Cancer Therapy	Immune Checkpoint Inhibitors Anti-PD-L1 (CD274)
Launched-2017	MSB-0010682 MSB-0010718C PF-06834635 KXG2PJ551I (UNII code)	Avelumab (USAN; Rec INN)	Bavencio	Cancer Immunotherapy Human Monoclonal Antibodies	Small Cell Lung Cancer/Sarcoma Respiratory cancer/Thoracic Cancer/Non-Small Cell Lung Cancer/Endocrine Cancer/ Lymphoma/Neurologic Cancer/Skin Cancer/Gastric Cancer/ Melanoma/Bladder Cancer/Colorectal Cancer/Hematological Cancer/Myeloid Leukemia/Non-Hodgkin's Lymphoma/Head and Neck Cancer/Solid Tumors/Liver Cancer/Female Reproductive System Cancer/Pancreatic Cancer/Glioblastoma Multiforme/ Osteosarcoma/Angiosarcoma/Genitourinary Cancer/Renal Cancer/Breast Cancer/Ovarian Cancer Therapy Anti-Papilloma Virus Drugs Oncolytic Drugs Digestive/Gastrointestinal Cancer Therapy	Immune Checkpoint Inhibitors Anti-PD-L1 (CD274)

Table 3
Potential agents targeting TIM3.

Highest phase	Code name	Generic name	Brand name/ structure	Product category	Therapeutic group	Mechanism of action
Biological Testing	L3B			Murine Monoclonal Antibodies	Asthma Therapy Anti-HIV Agents Anti-allergy/Anti-asthmatic Drugs Treatment of Sepsis Anti-Hepatitis Virus Drugs Treatment of Autoimmune Diseases	Immune Checkpoint Inhibitors Anti-TIM3 (Hepatitis A Virus Cellular Receptor 2)
Biological Testing	TIM3 TCB			Bispecific Antibodies Cancer Immunotherapy Humanized Monoclonal Antibodies	Oncolytic Drugs	Immune Checkpoint Inhibitors Signal Transduction Modulators Anti-TIM3 (Hepatitis A Virus Cellular Receptor 2) Anti-CD3
Biological Testing	FMab-31 Anti-CD20-HC N-TIM3			Cancer Immunotherapy Fusion Proteins Immunoconjugates Monoclonal Antibodies Polypeptides, from 41 AA	Oncolytic Drugs	Anti-CD20
Preclinical	TIM3-Apt1 TIM3Apt1			Aptamers Cancer Immunotherapy Single stranded oligoribonucleotide (RNA)	Colorectal Cancer Therapy	Immune Checkpoint Inhibitors Anti-TIM3 (Hepatitis A Virus Cellular Receptor 2)
Preclinical	CA-327			Cancer Immunotherapy	Oncolytic Drugs Cancer Immunotherapy	Immune Checkpoint Inhibitors Drugs Targeting Hepatitis A Virus Cellular Receptor 2 (HAVCR2; TIM3) Anti-PD-L1 (CD274)
Preclinical	AUPM-327 PM-327			Cancer Immunotherapy	Cancer Immunotherapy	Immune Checkpoint Inhibitors Drugs Targeting Hepatitis A Virus Cellular Receptor 2 (HAVCR2; TIM3) Drugs Targeting Programmed Cell Death 1 Ligand 1 (PD-L1; CD274)

breast, ovarian and colon cancer, LAG-3 expresses in tumor infiltrating lymphocytes (TILs) [64–67], and its expression frequency in TILs is significantly associated with the expression frequency of PD-1 in TILs and PD-L1-expressing tumor cells [65]. Thirdly, expression of LAG-3 is related to tumor prognosis, for example, LAG-3 positive or LAG-3/PD-1 double positive can predict poor prognosis in non-small cell lung cancer, while serum level of soluble LAG-3 can predict better prognosis of breast cancer [65,68]. Fourthly, the inhibition of LAG-3 and PD-1/PD-L1 pathway can significantly improve the function of $CD4^+$ T cells and TILs [69,70].

Preclinical studies found that the inhibition of LAG-3 was able to restore the cytotoxicity of T cells and enhance the effect of anti-tumor. Meanwhile, inhibition of LAG-3 can also reduce the function of regulatory T cells, so that LAG-3 is considered to be a more attractive target than other immune checkpoint proteins. Relatlimab, also known as BMS-986016, developed by BMS, is a monoclonal antibody targeting LAG-3. In the clinical 1/2a trial named ca224-020, the PD-1 inhibitor Opdivo developed by BMS and Relatlimab were used to treat solid-tumor patients. These patients in the clinical trial included those had no response or resistance to PD-1/PD-L1 immunotherapy. According to the latest published data at the annual meeting of the ESMO, objective response rate (ORR) of Relatlimab and Opdivo combination therapy in patients expressing LAG-3 in immune cells around tumor was 18%, meanwhile the ORR of patients expressing LAG-3 in immune cells around tumor < 1% was 5%. This result confirms that LAG-3 is an effective target. In addition, the safety of the LAG-3/Opdivo combination therapy is similar to that of Opdivo monotherapy. Some other related drugs are listed in Table 4.

3.5. CD122: also known as Interleukin-2 receptor (IL-2R), IL-2 receptor subunit β with high affinity, IL-2 receptor subunit β, and IL-2Rβ

IL-2 is a secreted glycoprotein with a molecular weight of 15–18 kDa. As a cytokine, IL-2 is mainly produced by antigen-activated T cells. It promotes the proliferation, differentiation and survival of T lymphocytes, the lytic activity of natural killer cells (NK) in the innate immune defense [71–75]. Activated T cells stimulate the secretion of IL-2, and IL-2 is subsequently used as a factor in the growth of natural killer (NK) cells, natural killer T (NKT) cells, and B cells, because of the high affinity for the IL-2 receptor in these cells. Therefore, IL-2 drives the proliferation of activated T cells until it is exhausted.

IL-2 works by binding to the dimer receptor, which is composed of IL-2β (CD122) and a common cytokine receptor γ_c (CD132) or trimer receptor (consisting of IL-2α, IL-2β and CD132) [76]. The effect of IL-2 regulating the immune system is pleiotropic and contextual, which could be an activator or an inhibitor. IL-2 binds to heterodimeric IL-2Rβγ receptor at high doses, leading to desired expansion of tumor killing $CD8^+$ memory effector T (CD8 T) cells [77]. IL-2 also binds to its heterotrimeric receptor IL-2Rαβγ, and expands immunosuppressive $CD4^+$ $CD25^+$ regulatory T cells (Tregs). It can also stimulate the proliferation and activation of Tregs. These cells continue to express high affinity heterotrimeric IL-2Rαβγ. Activation of Tregs may exacerbate immunosuppression and impair the expected anti-tumor effect. Expansion of Tregs represents an undesirable effect of IL-2 for cancer immunotherapy [29,77–82]. As a cytokine, IL-2 is an endogenous agonist of IL-2 pathway and a stimulating factor of $CD8^+$ T cells (CD8 T), NK cells [83]. However, it is not widely used due to its association with over activation of the immune system. High expression of IL-2Rα and IL-2Rβγ in Tregs enable these cells to consume IL-2 more effectively than in CD4, CD8, and NK cells, even at low levels.

Although IL-2 Rα isn't expressed by native T cells, its expression can quickly identify and trigger IL-2/IL-2Rα feedback loop [84]. $CD8^+CD122^+$ T cells can inhibit response of T cells. Agents targeting CD122 impair tumor growth in syngeneic solid tumor models, and immune microenvironment in tumor cells has been changed when treated with these agents. These agents restrict tumor growth through a

Table 4
Potential agents targeting LAG-3.

Highest phase	Code name	Generic name	Brand name/ structure	Product category	Therapeutic group	Mechanism of action
Preclinical	C9B7W			Cancer Immunotherapy Murine Monoclonal Antibodies	Sarcoma Therapy	Immune Checkpoint Inhibitors Anti-CD223 (Lymphocyte Activation Gene 3 Protein: LAG-3)
Preclinical	IMP-761			Agonist Antibodies Humanized Monoclonal Antibodies	Treatment of Other Autoimmune Disorders	Immune Checkpoint Inhibitors Anti-CD223 (Lymphocyte Activation Gene 3 Protein: LAG-3)
Preclinical	28G10			Cancer Immunotherapy Murine Monoclonal Antibodies	Renal Cancer Therapy	Immune Checkpoint Inhibitors Anti-CD223 (Lymphocyte Activation Gene 3 Protein: LAG-3)
Preclinical	H4sH15482P			Cancer Immunotherapy Human Monoclonal Antibodies	Oncolytic Drugs	Immune Checkpoint Inhibitors Anti-CD223 (Lymphocyte Activation Gene 3 Protein: LAG-3)
Preclinical	28G10-mG1 c28G10 c28G10-mG1-[D265A]			Cancer Immunotherapy Chimeric Monoclonal Antibodies	Oncolytic Drugs	Immune Checkpoint Inhibitors Anti-CD223 (Lymphocyte Activation Gene 3 Protein: LAG-3)
Preclinical	XmAb-22841			Bispecific Antibodies Cancer Immunotherapy	Oncolytic Drugs	Immune Checkpoint Inhibitors Anti-CD152 (CTLA-4) Anti-CD223 (Lymphocyte Activation Gene 3 Protein: LAG-3)
Preclinical	CB-213			Cancer Immunotherapy Fusion Proteins Polypeptides, from 41 AA Single-Domain Antibodies	Oncolytic Drugs	Immune Checkpoint Inhibitors Anti-PD-1 Anti-CD223 (Lymphocyte Activation Gene 3 Protein: LAG-3)
Phase I	IMP-731 ImmuTune IMP-731			Chimeric Monoclonal Antibodies	Treatment of Autoimmune Diseases	Immune Checkpoint Inhibitors Anti-CD223 (Lymphocyte Activation Gene 3 Protein: LAG-3)
Phase I	2831781 GSK-2831781			Monoclonal Antibodies	Anti-psoriatics	Immune Checkpoint Inhibitors Anti-CD223 (Lymphocyte Activation Gene 3 Protein: LAG-3)
Phase I	MGD-013			Bispecific Antibodies Cancer Immunotherapy Diabodies	Hematological Cancer/Solid Tumors Therapy	Immune Checkpoint Inhibitors Anti-PD-1 Anti-CD223 (Lymphocyte Activation Gene 3 Protein: LAG-3)
Phase I	TSR-033			Cancer Immunotherapy Humanized Monoclonal Antibodies	Oncolytic Drugs Solid Tumors Therapy	Immune Checkpoint Inhibitors Anti-CD223 (Lymphocyte Activation Gene 3 Protein: LAG-3)
Phase I	MK-4280			Cancer Immunotherapy Humanized Monoclonal Antibodies	Solid Tumors Therapy	Immune Checkpoint Inhibitors Anti-CD223 (Lymphocyte Activation Gene 3 Protein: LAG-3)
Phase I	BI-754111			Cancer Immunotherapy Humanized Monoclonal Antibodies	Non-Small Cell Lung Cancer/Non-Hodgkin's Lymphoma/Solid Tumors Therapy	Immune Checkpoint Inhibitors Anti-CD223 (Lymphocyte Activation Gene 3 Protein: LAG-3)
Phase I	REGN-3767			Cancer Immunotherapy Human Monoclonal Antibodies	Oncolytic Drugs	Immune Checkpoint Inhibitors Anti-CD223 (Lymphocyte Activation Gene 3 Protein: LAG-3)
Phase I	FS-118 FS118 mAb2 LAG-3/PD-L1 mAb2			Antibodies Antibody-Derived Binding Proteins Bispecific Antibodies Cancer Immunotherapy	Oncolytic Drugs Colorectal Cancer Therapy	Immune Checkpoint Inhibitors Anti-PD-L1 (CD274) Anti-CD223 (Lymphocyte Activation Gene 3 Protein: LAG-3)
Phase I	Sym-022			Cancer Immunotherapy Human Monoclonal Antibodies	Lymphoma/Solid Tumors Therapy Oncolytic Drugs	Immune Checkpoint Inhibitors Anti-CD223 (Lymphocyte Activation Gene 3 Protein: LAG-3)

(*continued on next page*)

Table 4 (*continued*)

Highest phase	Code name	Generic name	Brand name/ structure	Product category	Therapeutic group	Mechanism of action
Phase II	IMP-321 LAG-3Ig	Eftilagimod alfa (Rec INN)	ImmuFact	Cancer Immunotherapy Cancer Vaccines Fc fusion proteins Polypeptides, from 41 AA	Melanoma/Breast Cancer/Pancreatic Cancer/Renal Cancer/Solid Tumors Therapy Immunostimulants	
Phase II	IMP-701 ImmuTune IMP-701 LAG-525			Cancer Immunotherapy Humanized Monoclonal Antibodies Monoclonal Antibodies	Small Cell Lung Cancer/Prostate Cancer/Sarcoma/Non-Small Cell Lung Cancer/ Endocrine Cancer/Gastric Cancer/Melanoma/Breast Cancer/Ovarian Cancer/ Renal Cancer/Non-Hodgkin's Lymphoma/Solid Tumors Therapy Respiratory/Thoracic Cancer Therapy Oncolytic Drugs Anti-infectives (Not Specified) Digestive/Gastrointestinal Cancer Therapy	Immune Checkpoint Inhibitors Anti-CD223 (Lymphocyte Activation Gene 3 Protein: LAG-3)
Phase II/III	BMS-986016 ONO-4482 AF75XOF6W3 (UNII code)	Relatlimab (USAN)		Cancer Immunotherapy Human Monoclonal Antibodies	Lymphocytic Leukemia/Non-Small Cell Lung Cancer/Lymphoma/Neurologic Cancer/Melanoma/Gastric Cancer/Renal Cancer/Solid Tumors/Non-Hodgkin's Lymphoma Therapy	Immune Checkpoint Inhibitors Anti-CD223 (Lymphocyte Activation Gene 3 Protein: LAG-3)

Table 5
Potential agents targeting CD122.

Highest phase	Code name	Generic name	Brand name/structure	Product category	Therapeutic group	Mechanism of action
Biological Testing	P2C4/P1A3			Agonist Antibodies Bispecific Antibodies Cancer Immunotherapy Single-Chain V-Domain Antibody Fragment (scFv)	Oncolytic Drugs	Anti-IL-2RB (Interleukin-2 Receptor Subunit beta; CD122) Anti-IL-2RG (Cytokine Receptor Common Subunit gamma; CD132)
Preclinical	HuABC-2			Humanized Monoclonal Antibodies	Immunosuppressants Dermatologic Drugs	Anti-IL-2RB (Interleukin-2 Receptor Subunit beta; CD122)

mechanism that does not involve $CD4^+$ Tregs but significantly increases the percentage of tumor infiltrating $CD8^+$ T cells and decrease the percentage of infiltrated $CD8^+CD122^+$ T cells. NKTR-214, an IL-2 polymer binding, is beneficial to the balance of immune activation under the immunosuppression of tumor cells. By combination with anti–CTLA-4 antibody, NKTR-214 provides durable immunity to resist tumor. NKTR-214, a highly "combinable cytokine", is more like a cytokine than an antibody, stimulating the immune system directly through cytokines (IL-2) [85]. Some other related drugs are listed in Table 5.

3.6. ICOS: blockade of ICOS will deplete the regulatory T cells to enhance anti-tumor immunity

Regulatory T cells (Tregs) are subgroups of T cells, which usually lead to immunosuppression and can mediate the immune escape of tumors [86–88]. It has been confirmed that a large number of Tregs exist in tumor tissues and peripheral blood. The high concentration of Tregs is closely related to the severity and prognosis of the tumor [89]. ICOS, a kind of important stimulus molecular, is related to proliferation and activation of T cells, affecting the functions of Th1 and Th2 cells, playing a role in the synergy of T/B cells, and generating antibodies [90].

$Foxp3^+$ natural Tregs can be divided into two subgroups, depending on whether they express co-stimulator (ICOS) or not [91]. Among the both subgroups, $ICOS^+$ Tregs have stronger survival, proliferative ability, and stronger inhibitory activity than $ICOS^-$ Tregs [92]. In addition, $ICOS^+$ Tregs, not $ICOS^-$ Tregs, are closely related to the progression and prognosis of tumors [93]. Some studies have shown that the attenuation of Tregs combining with activation of tumor-specific effector T cells can improve the anti-cancer efficacy [94]. ICOS signal promotes the function and proliferation of Tregs, on the contrary, blocking the ICOS signal may inhibit the function of Tregs [95].

Antagonist targeting ICOS effectively reduces tumor infiltrating Tregs, which is consistent with the enhancement of anti-tumor immunity. CD28 mediates the proliferation and activation of effector T cells, thus ICOS, as a member of the co-stimulating molecules in CD28, plays an important role in activating T cells [96]. Blockade of ICOS may not have a significant effect on proliferation and activation of CD8 or CD4 T cell. Instead, it may inhibit the function of Tregs and reduce the concentration of Tregs. Immunoregulation targeting ICOS has therefore exhibited clinical significance for the long-term tolerance of autoimmune diseases and transplantation immunity [96].

The main candidate of Jounce, JTX-2011, is a monoclonal antibody that binds to and activates ICOS on the surface of T cells. Preclinical study data support JTX-2011 may have a dual action mechanism: stimulate the anti-tumor effector T cells and reduce the immune suppression regulatory T cells in tumor microenvironment. The company has been developing JTX-2011 to treat solid tumors as a single drug or to combine it with other therapies. Besides JTX-2011, the agonist GSK3359609 [97] also targets and binds with ICOS in tumor infiltrating $CD4^+$ T cells. This stimulates the proliferation of $ICOS^+$ T cells, enhances the survival of cytotoxic T lymphocytes (CTL), and increases CTL mediated immune response to tumor cells. Some other related drugs are listed in Table 6.

4. Summary

The innate immune system is the nonspecific frontier line of immune defense. It contains a large number of components:antigen presenting cells (APC), dendritic cells, mast cells, tissue cells, and macrophages. In contrast, the adaptive immune system induces the production of helper $CD4^+$ T cells, cytotoxic $CD8^+$ T cells and antibody-releasing plasma cells [32]. When tumor antigens are captured and processed by dendritic cells in tumor microenvironment, the anticancer T cell reaction is produced. These dendritic cells spread to lymph nodes where the most primitive T cells become effector T cells and kill cancer cells. So that antitumour immunotherapy is potential and can be used to treat many different types of cancer.

Although some immunotherapy mechanisms have been reported, few immunotherapies are currently approved as standard ways to treat cancers. At present, the immunotherapies of tumor mainly include the following main methods: cytokines, cellular therapies, checkpoint blockade, and tumor vaccines.

In the past decade, progress has been made in the application of monoclonal antibodies (mAbs), regulation of the immune response and cell therapy to treat cancer. So far, the United States has approved three antibody treatments for immunological checkpoints. More and more patients will benefit from immuno-mediated mAb treatment over the next few years [86]. The remarkable clinical results observed in the immunotherapy trials since 2010 have aroused great interest of public in this possible treatment [98]. Clinical trials using checkpoint blockade inhibitors to treat patients with metastatic melanoma [99–102] and NSCLC [39,103] and trials using CAR T cells to treat relapsed or refractory B-ALL [104–107] has been reported.

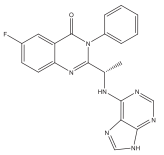
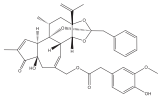
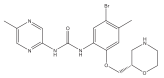
Immunotherapy can enhance the anti-tumor immunity of hosts and cause a lasting response in subgroups of patients with multiple tumor types. Blockade of the immune checkpoint is an effective strategy to relieve the inhibition of T cells. Cancer immunotherapy has changed the types of cancer in modern oncology. Immunotherapy with checkpoint inhibitors has significantly improved the clinical efficacy of some patients, but not all patients. This may be due to individual differences in tumor immunogenicity and immunosuppressive tumor microenvironment [108]. It is effective, however, it is also limited by its specificity. Therefore, it might be irrational to use the inhibitors of checkpoints as single agents. Combined treatment of different mechanisms may better regulate the immune system to promote anti-tumor response [108].

The rising trend in development of immunotherapies is to investigate combination therapies. Immunotherapies are commonly being tested for rational combinations with chemotherapies, targeted therapies or with other therapies. Targeted therapy can inhibit tumor growth factors and can cause important but transient clinical responses. These agents, such as some tyrosine kinase inhibitors (TKIs) [1], are often designed to destroy cancer cells by targeting specific genetic changes in these cells. With the development of modern molecular biology and genetic engineering technology, innate immunity targets and their drugs (for example, natural killer (NK) cell-targeting therapies) are gaining great interest [109,110]. Moreover, traditional chemotherapeutic drugs also have significant immunoregulatory effects. So the combination therapies will be an important direction for future study. Such meaningful synergistic effects of strategies are extremely expected [111–113].

For combination therapy, researches may be based on the understanding of the potential mechanisms of action, anticipated clinical profiles, and potential synergistic activities of the agents involved. The effects of the drugs are associated with the types of drugs, dosages, methods of administration, time that patients will be treated. Combination of different therapies doesn't mean adding different agents simply. The final effects of these combinations might exceed the expectations because the pharmacodynamics, efficacy and safety of individual agents may be different from the simple added effects of both agents. These choices of combination should be depended on the development of basic study [114].

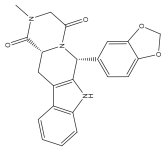
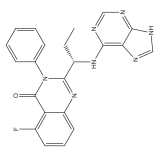
Further study may still be needed for the best combination of different tumor immune therapies and other therapies to treat patients. With the continuous improvement of precision medicine, individualized treatment options will be provided for each patient. Overall, we have to admit that the field is developing rapidly, the direction is clear, and the prospects for the development of cancer drug have never been much better.

Table 6
Potential agents targeting ICOS.

Highest phase	Code name	Generic name	Brand name/structure	Product category	Therapeutic group	Mechanism of action
Phase I	IC-14			Monoclonal Antibodies	Treatment of Septic Shock/Acute Respiratory Distress Syndrome (ARDS) Agents for Amyotrophic Lateral Sclerosis/Respiratory Disorders (Not Specified)	Anti-CD14
Phase I	IC-776				Antipsoriatics	Integrin alphaLbeta2 (LFA-1) Antagonists Signal Transduction Modulators
Phase I	CAL-120 GS-9820	Acalisib (Rec INN)			Hematological Cancer/Solid Tumors Therapy	Signal Transduction Modulators Phosphatidylinositol 3-Kinase delta (PI3Kdelta) Inhibitors
Phase I	MEDI-570			Cancer Immunotherapy Monoclonal Antibodies	Agents for Systemic Lupus Erythematosus, Non-Hodgkin's Lymphoma Therapy	Anti-ICOS
Phase I	AMG-570			Antibodies Bispecific Antibodies	Treatment of Rheumatoid Arthritis, Agents for Systemic Lupus Erythematosus	Anti-TNFSF13B (Tumor Necrosis Factor Ligand Superfamily Member 13B; BLyS) Signal Transduction Modulators Anti-ICOSLG (ICOS Ligand; B7-H2; B7RP-1)
Phase I	MEDI-0700			Bispecific Antibodies Monoclonal Antibodies	Agents for Systemic Lupus Erythematosus	Anti-TNFSF13B (Tumor Necrosis Factor Ligand Superfamily Member 13B; BLyS) Signal Transduction Modulators Anti-ICOSLG (ICOS Ligand; B7-H2; B7RP-1)
Phase I/II	ICM-3			Monoclonal Antibodies	Antipsoriatics	
Phase I/II	RTX RTX-107	(+)-Resiniferatoxin Resiniferatoxin			Analgesic Drugs Treatment of Neuropathic Pain, Urologic Drugs	TRPV1 (Vanilloid VR1 Receptor) Agonists
Phase I/II	3359609 GSK-3359609			Agonist Antibodies Cancer Immunotherapy	Solid Tumors Therapy	Anti-ICOS
Phase II	EOS-200-4 M-200	Volociximab (USAN; Rec INN)		Cancer Immunotherapy Chimeric Monoclonal Antibodies	Treatment of Age-Related Macular Degeneration, Non-Small Cell Lung Cancer/Melanoma/Ovarian Cancer/Pancreatic Cancer/Renal Cancer/ Solid Tumors Therapy	Anti-CD49e/CD29 (integrin alpha5beta1) Signal Transduction Modulators Angiogenesis Inhibitors
Phase II	AMG-557 MEDI-5872	Prezalumab (Rec INN)		Human Monoclonal Antibodies	Agents for Sjogren's Syndrome, Antipsoriatics Agents for Systemic Lupus Erythematosus	Anti-ICOSLG (ICOS Ligand; B7-H2; B7RP-1)
Phase II	IC-83 LY-2603618	Rabusertib (USAN; Rec INN)			Non-Small Cell Lung Cancer/Pancreatic Cancer Therapy	Checkpoint Kinase 1 (Chk1) Inhibitors Cytochrome P450 CYP3A4 Inhibitors Cytochrome P450 CYP2D6 Inhibitors Signal Transduction Modulators
Phase II	JTX-2011			Agonist Antibodies Cancer Immunotherapy Humanized Monoclonal Antibodies	Non-Small Cell Lung Cancer/Melanoma/Gastric Cancer/Breast Cancer/Head and Neck Cancer Therapy	Anti-ICOS
Phase III	23F2G Hu23F2G	Rovelizumab (USAN; Rec INN)	LeukArrest	Chimeric Monoclonal Antibodies	Treatment of Ischemic Stroke	Anti-CD11a/CD18 (LFA-1) Signal Transduction Modulators
Launched-2000	ABT-SLV-176		Androgel ReLibra Testogel	Androgens Steroids	Prostate Cancer Therapy Treatment of Female Sexual Dysfunction/Hypogonadism Male Contraceptives/Alzheimer's Dementia	Androgen Receptor Agonists Signal Transduction Modulators
Launched-2003	GF-196960 IC-351 INT-0007 INT-007 INT-007/06 LY-450190	Tadalafil (USAN; Rec INN)	Adcirca Cialis Extrinsa PharmFilm Tadalafil		Benign Prostatic Hyperplasia/Head and Neck Cancer Therapy Treatment of Female Sexual Dysfunction/Diabetic Complications Hypertension/Erectile Dysfunction Raynaud's Phenomenon/Cardiovascular Diseases (Not Specified)/ Vascular Dementia/Pulmonary Hypertension/Muscular Dystrophy	Signal Transduction Modulators Phosphodiesterase PDE5A Inhibitors

(*continued on next page*)

Table 6 (*continued*)

Highest phase	Code name	Generic name	Brand name/structure	Product category	Therapeutic group	Mechanism of action
			Zalutia			
						
Launched-2014	CAL-101 GS-1101	Idelalisib (USAN; Rec INN)	Zydelig		Oncolytic Drugs for Allergic Rhinitis Lymphocytic Leukemia/Pancreatic Cancer/Hematological Cancer/ Non-Hodgkin's Lymphoma/Hematopoiesis Disorders/Non-Small Cell Lung Cancer/Lymphoma Therapy Treatment of Amyloidosis/Inflammation	Cytochrome P450 CYP3A4 Inhibitors Signal Transduction Modulators P-Glycoprotein (MDR-1; ABCB1) Inhibitors Breast Cancer-Resistant Protein (BCRP; ABCG2) Inhibitors Neutrophil Elastase (Leukocyte Elastase) Release Inhibitors Apoptosis Inducers Phosphatidylinositol 3-Kinase delta (PI3Kdelta) Inhibitors
						

Acknowledgement

This paper received funding from National Natural Foundation of China (NSFC) (grant number 81473254, 81773637, 81773594, U170311), the Fundamental Research Fund for the Central Universities (grant number 2017KFYXJJ151).

References

[1] G. Alatrash, H. Jakher, P.D. Stafford, E.A. Mittendorf, Cancer immunotherapies, their safety and toxicity, Expert Opin. Drug Saf. 12 (2013) 631–645, https://doi.org/10.1517/14740338.2013.795944.
[2] D.H. Fowler, Rapamycin-resistant effector T-cell therapy, Immunol. Rev. 257 (2014) 210–225, https://doi.org/10.1111/imr.12127.
[3] W. Xu, M. Celeridad, S. Sankar, D.R. Webb, B.L. Bennett, CC-4047 promotes Th1 cell differentiation and reprograms polarized human Th2 cells by enhancing transcription factor T-bet, Clin. Immunol. 128 (2008) 392–399, https://doi.org/10.1016/j.clim.2008.04.009.
[4] P. Kidd, Th1/Th2 balance: the hypothesis, its limitations, and implications for health and disease, Altern. Med. Rev. 8 (2003) 223–246.
[5] J. Matsuzaki, T. Tsuji, I. Imazeki, H. Ikeda, T. Nishimura, Immunosteroid as a regulator for Th1/Th2 balance: its possible role in autoimmune diseases, Autoimmunity 38 (2005) 369–375, https://doi.org/10.1080/08916930500124122.
[6] D. Liao, Y. Luo, D. Markowitz, R. Xiang, R.A. Reisfeld, Cancer associated fibroblasts promote tumor growth and metastasis by modulating the tumor immune microenvironment in a 4t1 murine breast cancer model, PLoS One 4 (2009) e7965, , https://doi.org/10.1371/journal.pone.0007965.
[7] H. Ubukata, G. Motohashi, T. Tabuchi, H. Nagata, S. Konishi, T. Tabuchi, Evaluations of interferon-γ/interleukin-4 ratio and neutrophil/lymphocyte ratio as prognostic indicators in gastric cancer patients, J. Surg. Oncol. 102 (2010) 742–747, https://doi.org/10.1002/jso.21725.
[8] G.T. Motz, G. Coukos, Deciphering and reversing tumor immune suppression, Immunity 39 (2013) 61–73, https://doi.org/10.1016/j.immuni.2013.07.005.
[9] D.M. Pardoll, The blockade of immune checkpoints in cancer immunotherapy, Nat. Rev. Cancer 12 (2012) 252–264, https://doi.org/10.1038/nrc3239.
[10] A. Poggi, A. Musso, I. Dapino, M.R. Zocchi, Mechanisms of tumor escape from immune system: role of mesenchymal stromal cells, Immunol. Lett. 159 (2014) 55–72, https://doi.org/10.1016/j.imlet.2014.03.001.
[11] C.O. Starnes, Coley's toxins in perspective, Nature 357 (1992) 11–12, https://doi.org/10.1038/357011a0.
[12] A. Hoos, Development of immuno-oncology drugs — from CTLA4 to PD1 to the next generations, Nat. Rev. Drug Discov. 15 (2016) 235–247, https://doi.org/10.1038/nrd.2015.35.
[13] C.A. Chambers, M.S. Kuhns, J.G. Egen, J.P. Allison, Ctla-4-mediated I nhibition in regulation of T cell responses: mechanisms and manipulation in tumor immunotherapy, Annu. Rev. Immunol. 19 (2001) 565–594, https://doi.org/10.1146/annurev.immunol.19.1.565.
[14] W.A. Teft, M.G. Kirchhof, J. Madrenas, A molecular perspective of ctla-4 function, Annu. Rev. Immunol. 24 (2006) 65–97, https://doi.org/10.1146/annurev.immunol.24.021605.090535.
[15] B.M. Carreno, F. Bennett, T.A. Chau, V. Ling, D. Luxenberg, J. Jussif, M.L. Baroja, J. Madrenas, Ctla-4 (Cd152) can inhibit t cell activation by two different mechanisms depending on its level of cell surface expression, J. Immunol. 165 (2000) 1352–1356, https://doi.org/10.4049/jimmunol.165.3.1352.
[16] J.L. Greene, G.M. Leytze, J. Emswiler, R. Peach, J. Bajorath, W. Cosand, P.S. Linsley, Covalent dimerization of cd28/ctla-4 and oligomerization of cd80/cd86 regulate t cell costimulatory interactions, J. Biol. Chem. 271 (1996) 26762–26771, https://doi.org/10.1074/jbc.271.43.26762.
[17] H.T. Leung, J. Bradshaw, J.S. Cleaveland, P.S. Linsley, Cytotoxic t lymphocyte-associated molecule-4, a high avidity receptor for cd80 and cd86, contains an intracellular localization motif in its cytoplasmic tail, J. Biol. Chem. 270 (1995) 25107–25114, https://doi.org/10.1074/jbc.270.42.25107.
[18] M.L. Baroja, D. Luxenberg, T. Chau, V. Ling, C.A. Strathdee, B.M. Carreno, J. Madrenas, The inhibitory function of ctla-4 does not require its tyrosine phosphorylation, J. Immunol. 164 (2000) 49–55, https://doi.org/10.4049/jimmunol.164.1.49.
[19] M.F. Krummel, CTLA-4 engagement inhibits IL-2 accumulation and cell cycle progression upon activation of resting T cells, J. Exp. Med. 183 (1996) 2533–2540, https://doi.org/10.1084/jem.183.6.2533.
[20] J.H. Fraser, M. Rincón, K.D. McCoy, G. Le Gros, CTLA4 ligation attenuates AP-1, NFAT and NF-κB activity in activated T cells, Eur. J. Immunol. 29 (1999) 838–844, https://doi.org/10.1002/(SICI)1521-4141(199903)29:03<838::AID-IMMU838>3.0.CO;2-P.
[21] C. Olsson, K. Riebeck, M. Dohlsten, E. Michaëlsson, Ctla-4 ligation suppresses cd28-induced nf-κb and ap-1 activity in mouse t cell blasts, J. Biol. Chem. 274 (1999) 14400–14405, https://doi.org/10.1074/jbc.274.20.14400.
[22] M.C. Brunner, C.A. Chambers, F.K. Chan, et al., CTLA-4-mediated inhibition of early events of T cell proliferation, J. Immunol. 162 (1999) 5813–5820.
[23] D. Li, I. Gal, C. Vermes, M.-L. Alegre, A.S.F. Chong, L. Chen, Q. Shao, V. Adarichev, X. Xu, T. Koreny, K. Mikecz, A. Finnegan, T.T. Glant, J. Zhang, Cutting edge: cbl-b: one of the key molecules tuning cd28- and ctla-4-mediated t cell costimulation, J. Immunol. 173 (2004) 7135–7139, https://doi.org/10.4049/jimmunol.173.12.

7135.
[24] K.D. Carey, T.J. Dillon, J.M. Schmitt, A.M. Baird, A.D. Holdorf, D.B. Straus, A.S. Shaw, P.J.S. Stork, Cd28 and the tyrosine kinase lck stimulate mitogen-activated protein kinase activity in t cells via inhibition of the small g protein rap1, Mol. Cell. Biol. 20 (2000) 8409–8419, https://doi.org/10.1128/MCB.20.22.8409-8419.2000.
[25] T.J. Dillon, K.D. Carey, S.A. Wetzel, D.C. Parker, P.J.S. Stork, Regulation of the small gtpase rap1 and extracellular signal-regulated kinases by the costimulatory molecule ctla-4, Mol. Cell. Biol. 25 (2005) 4117–4128, https://doi.org/10.1128/MCB.25.10.4117-4128.2005.
[26] F.S. Hodi, S.J. O'Day, D.F. McDermott, R.W. Weber, J.A. Sosman, J.B. Haanen, R. Gonzalez, C. Robert, D. Schadendorf, J.C. Hassel, W. Akerley, A.J.M. van den Eertwegh, J. Lutzky, P. Lorigan, J.M. Vaubel, G.P. Linette, D. Hogg, C.H. Ottensmeier, C. Lebbé, C. Peschel, I. Quirt, J.I. Clark, J.D. Wolchok, J.S. Weber, J. Tian, M.J. Yellin, G.M. Nichol, A. Hoos, W.J. Urba, Improved survival with ipilimumab in patients with metastatic melanoma, N. Engl. J. Med. 363 (2010) 711–723, https://doi.org/10.1056/NEJMoa1003466.
[27] C. Robert, L. Thomas, I. Bondarenko, S. O'Day, J. Weber, C. Garbe, C. Lebbe, J.-F. Baurain, A. Testori, J.-J. Grob, N. Davidson, J. Richards, M. Maio, A. Hauschild, W.H. Miller, P. Gascon, M. Lotem, K. Harmankaya, R. Ibrahim, S. Francis, T.-T. Chen, R. Humphrey, A. Hoos, J.D. Wolchok, Ipilimumab plus dacarbazine for previously untreated metastatic melanoma, N. Engl. J. Med. 364 (2011) 2517–2526, https://doi.org/10.1056/NEJMoa1104621.
[28] D. Schadendorf, F.S. Hodi, C. Robert, J.S. Weber, K. Margolin, O. Hamid, D. Patt, T.-T. Chen, D.M. Berman, J.D. Wolchok, Pooled analysis of long-term survival data from phase ii and phase III trials of ipilimumab in unresectable or metastatic melanoma, J. Clin. Oncol. 33 (2015) 1889–1894, https://doi.org/10.1200/JCO.2014.56.2736.
[29] M.A. Curran, W. Montalvo, H. Yagita, J.P. Allison, PD-1 and CTLA-4 combination blockade expands infiltrating T cells and reduces regulatory T and myeloid cells within B16 melanoma tumors, Proc. Natl. Acad. Sci. 107 (2010) 4275–4280, https://doi.org/10.1073/pnas.0915174107.
[30] Y. Iwai, M. Ishida, Y. Tanaka, T. Okazaki, T. Honjo, N. Minato, Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade, Proc. Natl. Acad. Sci. 99 (2002) 12293–12297, https://doi.org/10.1073/pnas.192461099.
[31] T. Yamazaki, H. Akiba, H. Iwai, H. Matsuda, M. Aoki, Y. Tanno, T. Shin, H. Tsuchiya, D.M. Pardoll, K. Okumura, M. Azuma, H. Yagita, Expression of programmed death 1 ligands by murine t cells and apc, J. Immunol. 169 (2002) 5538–5545, https://doi.org/10.4049/jimmunol.169.10.5538.
[32] A. Marchetti, A. Di Lorito, F. Buttitta, Why anti-PD1/PDL1 therapy is so effective? Another piece in the puzzle, J. Thorac. Dis. 9 (2017) 4863–4866, https://doi.org/10.21037/jtd.2017.11.105.
[33] D.J. Byun, J.D. Wolchok, L.M. Rosenberg, M. Girotra, Cancer immunotherapy — immune checkpoint blockade and associated endocrinopathies, Nat. Rev. Endocrinol. 13 (2017) 195–207, https://doi.org/10.1038/nrendo.2016.205.
[34] S.R. Gordon, R.L. Maute, B.W. Dulken, G. Hutter, B.M. George, M.N. McCracken, R. Gupta, J.M. Tsai, R. Sinha, D. Corey, A.M. Ring, A.J. Connolly, I.L. Weissman, PD-1 expression by tumour-associated macrophages inhibits phagocytosis and tumour immunity, Nature 545 (2017) 495–499, https://doi.org/10.1038/nature22396.
[35] A.V. Balar, J.S. Weber, PD-1 and PD-L1 antibodies in cancer: current status and future directions, Cancer Immunol. Immunother. 66 (2017) 551–564, https://doi.org/10.1007/s00262-017-1954-6.
[36] J.R. Brahmer, C.G. Drake, I. Wollner, J.D. Powderly, J. Picus, W.H. Sharfman, E. Stankevich, A. Pons, T.M. Salay, T.L. McMiller, M.M. Gilson, C. Wang, M. Selby, J.M. Taube, R. Anders, L. Chen, A.J. Korman, D.M. Pardoll, I. Lowy, S.L. Topalian, Phase i study of single-agent anti–programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates, J. Clin. Oncol. 28 (2010) 3167–3175, https://doi.org/10.1200/JCO.2009.26.7609.
[37] J.D. Wolchok, H. Kluger, M.K. Callahan, M.A. Postow, N.A. Rizvi, A.M. Lesokhin, N.H. Segal, C.E. Ariyan, R.-A. Gordon, K. Reed, M.M. Burke, A. Caldwell, S.A. Kronenberg, B.U. Agunwamba, X. Zhang, I. Lowy, H.D. Inzunza, W. Feely, C.E. Horak, Q. Hong, A.J. Korman, J.M. Wigginton, A. Gupta, M. Sznol, Nivolumab plus ipilimumab in advanced melanoma, N. Engl. J. Med. 369 (2013) 122–133, https://doi.org/10.1056/NEJMoa1302369.
[38] M.A. Postow, J. Chesney, A.C. Pavlick, C. Robert, K. Grossmann, D. McDermott, G.P. Linette, N. Meyer, J.K. Giguere, S.S. Agarwala, M. Shaheen, M.S. Ernstoff, D. Minor, A.K. Salama, M. Taylor, P.A. Ott, L.M. Rollin, C. Horak, P. Gagnier, J.D. Wolchok, F.S. Hodi, Nivolumab and ipilimumab versus ipilimumab in untreated melanoma, N. Engl. J. Med. 372 (2015) 2006–2017, https://doi.org/10.1056/NEJMoa1414428.
[39] J. Larkin, V. Chiarion-Sileni, R. Gonzalez, J.J. Grob, C.L. Cowey, C.D. Lao, D. Schadendorf, R. Dummer, M. Smylie, P. Rutkowski, P.F. Ferrucci, A. Hill, J. Wagstaff, M.S. Carlino, J.B. Haanen, M. Maio, I. Marquez-Rodas, G.A. McArthur, P.A. Ascierto, G.V. Long, M.K. Callahan, M.A. Postow, K. Grossmann, M. Sznol, B. Dreno, L. Bastholt, A. Yang, L.M. Rollin, C. Horak, F.S. Hodi, J.D. Wolchok, Combined nivolumab and ipilimumab or monotherapy in untreated melanoma, N. Engl. J. Med. 373 (2015) 23–34, https://doi.org/10.1056/NEJMoa1504030.
[40] R.S. Herbst, J.-C. Soria, M. Kowanetz, G.D. Fine, O. Hamid, M.S. Gordon, J.A. Sosman, D.F. McDermott, J.D. Powderly, S.N. Gettinger, H.E.K. Kohrt, L. Horn, D.P. Lawrence, S. Rost, M. Leabman, Y. Xiao, A. Mokatrin, H. Koeppen, P.S. Hegde, I. Mellman, D.S. Chen, F.S. Hodi, Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients, Nature 515 (2014) 563–567, https://doi.org/10.1038/nature14011.
[41] L. Fehrenbacher, A. Spira, M. Ballinger, M. Kowanetz, J. Vansteenkiste, J. Mazieres, K. Park, D. Smith, A. Artal-Cortes, C. Lewanski, F. Braiteh, D. Waterkamp, P. He, W. Zou, D.S. Chen, J. Yi, A. Sandler, A. Rittmeyer, Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (Poplar): a multicentre, open-label, phase 2 randomised controlled trial, Lancet 387 (2016) 1837–1846, https://doi.org/10.1016/S0140-6736(16)00587-0.
[42] G.J. Freeman, J.M. Casasnovas, D.T. Umetsu, R.H. DeKruyff, Tim genes: a family of cell surface phosphatidylserine receptors that regulate innate and adaptive immunity: tim genes: a family of ptdser receptors, Immunol. Rev. 235 (2010) 172–189, https://doi.org/10.1111/j.0105-2896.2010.00903.x.
[43] L. Monney, C.A. Sabatos, J.L. Gaglia, A. Ryu, H. Waldner, T. Chernova, S. Manning, E.A. Greenfield, A.J. Coyle, R.A. Sobel, G.J. Freeman, V.K. Kuchroo, Th1-specific cell surface protein Tim-3 regulates macrophage activation and severity of an autoimmune disease, Nature 415 (2002) 536–541, https://doi.org/10.1038/415536a.
[44] A.C. Anderson, D.E. Anderson, L. Bregoli, W.D. Hastings, N. Kassam, C. Lei, R. Chandwaskar, J. Karman, E.W. Su, M. Hirashima, J.N. Bruce, L.P. Kane, V.K. Kuchroo, D.A. Hafler, Promotion of tissue inflammation by the immune receptor tim-3 expressed on innate immune cells, Science 318 (2007) 1141–1143, https://doi.org/10.1126/science.1148536.
[45] C. Zhu, A.C. Anderson, A. Schubart, H. Xiong, J. Imitola, S.J. Khoury, X.X. Zheng, T.B. Strom, V.K. Kuchroo, The Tim-3 ligand galectin-9 negatively regulates T helper type 1 immunity, Nat. Immunol. 6 (2005) 1245–1252, https://doi.org/10.1038/ni1271.
[46] C.A. Sabatos, S. Chakravarti, E. Cha, A. Schubart, A. Sánchez-Fueyo, X.X. Zheng, A.J. Coyle, T.B. Strom, G.J. Freeman, V.K. Kuchroo, Interaction of Tim-3 and Tim-3 ligand regulates T helper type 1 responses and induction of peripheral tolerance, Nat. Immunol. 4 (2003) 1102–1110, https://doi.org/10.1038/ni988.
[47] M. Nakayama, H. Akiba, K. Takeda, Y. Kojima, M. Hashiguchi, M. Azuma, H. Yagita, K. Okumura, Tim-3 mediates phagocytosis of apoptotic cells and cross-presentation, Blood 113 (2009) 3821–3830, https://doi.org/10.1182/blood-2008-10-185884.
[48] N.C. Sabins, O. Chornoguz, K. Leander, F. Kaplan, R. Carter, M. Kinder, K. Bachman, R. Verona, S. Shen, V. Bhargava, S. Santulli-Marotto, Tim-3 engagement promotes effector memory t cell differentiation of human antigen-specific cd8 t cells by activating mtorc1, J. Immunol. 199 (2017) 4091–4102, https://doi.org/10.4049/jimmunol.1701030.
[49] S. Chiba, M. Baghdadi, H. Akiba, H. Yoshiyama, I. Kinoshita, H. Dosaka-Akita, Y. Fujioka, Y. Ohba, J.V. Gorman, J.D. Colgan, M. Hirashima, T. Uede, A. Takaoka, H. Yagita, M. Jinushi, Tumor-infiltrating DCs suppress nucleic acid–mediated innate immune responses through interactions between the receptor TIM-3 and the alarmin HMGB1, Nat. Immunol. 13 (2012) 832–842, https://doi.org/10.1038/ni.2376.
[50] Q. Zhang, D.A.A. Vignali, Co-stimulatory and co-inhibitory pathways in autoimmunity, Immunity 44 (2016) 1034–1051, https://doi.org/10.1016/j.immuni.2016.04.017.
[51] M.K. Callahan, M.A. Postow, J.D. Wolchok, Targeting t cell co-receptors for cancer therapy, Immunity 44 (2016) 1069–1078, https://doi.org/10.1016/j.immuni.2016.04.023.
[52] S.L. Topalian, C.G. Drake, D.M. Pardoll, Immune checkpoint blockade: a common denominator approach to cancer therapy, Cancer Cell 27 (2015) 450–461, https://doi.org/10.1016/j.ccell.2015.03.001.
[53] A.C. Anderson, N. Joller, V.K. Kuchroo, Lag-3, tim-3, and tigit: co-inhibitory receptors with specialized functions in immune regulation, Immunity 44 (2016) 989–1004, https://doi.org/10.1016/j.immuni.2016.05.001.
[54] C.J. Workman, D.A.A. Vignali, The CD4-related molecule, LAG-3 (Cd223), regulates the expansion of activated T cells, Eur. J. Immunol. 33 (2003) 970–979, https://doi.org/10.1002/eji.200323382.
[55] C.J. Workman, L.S. Cauley, I.-J. Kim, M.A. Blackman, D.L. Woodland, D.A.A. Vignali, Lymphocyte activation gene-3 (Cd223) regulates the size of the expanding t cell population following antigen activation in vivo, J. Immunol. 172 (2004) 5450–5455, https://doi.org/10.4049/jimmunol.172.9.5450.
[56] C.J. Workman, D.A.A. Vignali, Negative regulation of t cell homeostasis by lymphocyte activation gene-3(Cd223), J. Immunol. 174 (2005) 688–695, https://doi.org/10.4049/jimmunol.174.2.688.
[57] C.-T. Huang, C.J. Workman, D. Flies, X. Pan, A.L. Marson, G. Zhou, E.L. Hipkiss, S. Ravi, J. Kowalski, H.I. Levitsky, J.D. Powell, D.M. Pardoll, C.G. Drake, D.A.A. Vignali, Role of lag-3 in regulatory t cells, Immunity 21 (2004) 503–513, https://doi.org/10.1016/j.immuni.2004.08.010.
[58] N. Gagliani, C.F. Magnani, S. Huber, M.E. Gianolini, M. Pala, P. Licona-Limon, B. Guo, D.R. Herbert, A. Bulfone, F. Trentini, C. Di Serio, R. Bacchetta, M. Andreani, L. Brockmann, S. Gregori, R.A. Flavell, M.-G. Roncarolo, Coexpression of CD49b and LAG-3 identifies human and mouse T regulatory type 1 cells, Nat. Med. 19 (2013) 739–746, https://doi.org/10.1038/nm.3179.
[59] B. Liang, C. Workman, J. Lee, C. Chew, B.M. Dale, L. Colonna, M. Flores, N. Li, E. Schweighoffer, S. Greenberg, V. Tybulewicz, D. Vignali, R. Clynes, Regulatory t cells inhibit dendritic cells by lymphocyte activation gene-3 engagement of mhc class II, J. Immunol. 180 (2008) 5916–5926, https://doi.org/10.4049/jimmunol.180.9.5916.
[60] F.A. Schildberg, S.R. Klein, G.J. Freeman, A.H. Sharpe, Coinhibitory pathways in the b7-cd28 ligand-receptor family, Immunity 44 (2016) 955–972, https://doi.org/10.1016/j.immuni.2016.05.002.
[61] D.A.A. Vignali, L.W. Collison, C.J. Workman, How regulatory T cells work, Nat. Rev. Immunol. 8 (2008) 523–532, https://doi.org/10.1038/nri2343.
[62] S. Sakaguchi, T. Yamaguchi, T. Nomura, M. Ono, Regulatory t cells and immune

tolerance, Cell 133 (2008) 775–787, https://doi.org/10.1016/j.cell.2008.05.009.
[63] L. Baitsch, P. Baumgaertner, E. Devêvre, S.K. Raghav, A. Legat, L. Barba, S. Wieckowski, H. Bouzourene, B. Deplancke, P. Romero, N. Rufer, D.E. Speiser, Exhaustion of tumor-specific CD8+ T cells in metastases from melanoma patients, J. Clin. Investig. 121 (2011) 2350–2360, https://doi.org/10.1172/JCI46102.
[64] J. Matsuzaki, S. Gnjatic, P. Mhawech-Fauceglia, A. Beck, A. Miller, T. Tsuji, C. Eppolito, F. Qian, S. Lele, P. Shrikant, L.J. Old, K. Odunsi, Tumor-infiltrating NY-ESO-1–specific CD8+ T cells are negatively regulated by LAG-3 and PD-1 in human ovarian cancer, Proc. Natl. Acad. Sci. 107 (2010) 7875–7880, https://doi.org/10.1073/pnas.1003345107.
[65] Y. He, H. Yu, L. Rozeboom, C.J. Rivard, K. Ellison, R. Dziadziuszko, K. Suda, S. Ren, C. Wu, L. Hou, C. Zhou, F.R. Hirsch, Lag-3 protein expression in non–small cell lung cancer and its relationship with pd-1/pd-l1 and tumor-infiltrating lymphocytes, J. Thorac. Oncol. 12 (2017) 814–823, https://doi.org/10.1016/j.jtho.2017.01.019.
[66] N.L. Losa, M. Cruise, A. Tam, E. Wick, E. Hechenbleikner, J.M. Taube, R. Blosser, H. Fan, H. Wang, B. Luber, M. Zhang, N. Papadopoulos, K. Kinzler, B. Vogelstein, C. Sears, R.A. Anders, D. Pardoll, F. Housseau, N. Siegel, The vigorous immune microenvironment of microsatellite instable colon cancer is balanced by multiple counter-inhibitory checkpoints, J. Immunother. Cancer 3 (2015) P410, https://doi.org/10.1186/2051-1426-3-S2-P410.
[67] G. Bottai, C. Raschioni, A. Losurdo, L. Di Tommaso, C. Tinterri, R. Torrisi, J.S. Reis-Filho, M. Roncalli, C. Sotiriou, A. Santoro, A. Mantovani, S. Loi, L. Santarpia, An immune stratification reveals a subset of PD-1/LAG-3 double-positive triple-negative breast cancers, Breast Cancer Res. 18 (2016), https://doi.org/10.1186/s13058-016-0783-4.
[68] F. Triebel, K. Hacene, M.-F. Pichon, A soluble lymphocyte activation gene-3 (Slag-3) protein as a prognostic factor in human breast cancer expressing estrogen or progesterone receptors, Cancer Lett. 235 (2006) 147–153, https://doi.org/10.1016/j.canlet.2005.04.015.
[69] N.S. Butler, J. Moebius, L.L. Pewe, B. Traore, O.K. Doumbo, L.T. Tygrett, T.J. Waldschmidt, P.D. Crompton, J.T. Harty, Therapeutic blockade of PD-L1 and LAG-3 rapidly clears established blood-stage Plasmodium infection, Nat. Immunol. 13 (2012) 188–195, https://doi.org/10.1038/ni.2180.
[70] L.T. Nguyen, P.S. Ohashi, Clinical blockade of PD1 and LAG3 – potential mechanisms of action, Nat. Rev. Immunol. 15 (2014) 45–56.
[71] S. Gillis, Interleukin 2: biology and biochemistry, J. Clin. Immunol. 3 (1983) 1–13, https://doi.org/10.1007/BF00919133.
[72] R.B. Herberman, Natural killer cells, Annu. Rev. Med. 37 (1986) 347–352, https://doi.org/10.1146/annurev.me.37.020186.002023.
[73] Y.S. Choi, Differentiation and apoptosis of human germinal center B-lymphocytes, Immunol. Res. 16 (1997) 161–174, https://doi.org/10.1007/BF02786360.
[74] M.H. Oppenheim, M.T. Lotze, Interleukin-2: solid-tumor therapy, Oncology 51 (1994) 154–169.
[75] K. Somersalo, Migratory functions of natural killer cells, Nat. Immun. 15 (1996) 117–133.
[76] D.J. Stauber, E.W. Debler, P.A. Horton, K.A. Smith, I.A. Wilson, Crystal structure of the IL-2 signaling complex: paradigm for a heterotrimeric cytokine receptor, Proc. Natl. Acad. Sci. 103 (2006) 2788–2793, https://doi.org/10.1073/pnas.0511161103.
[77] O. Boyman, J. Sprent, The role of interleukin-2 during homeostasis and activation of the immune system, Nat. Rev. Immunol. 12 (2012) 180–190, https://doi.org/10.1038/nri3156.
[78] X. Wang, Structure of the quaternary complex of interleukin-2 with its α, β, and γc receptors, Science 310 (2005) 1159–1163, https://doi.org/10.1126/science.1117893.
[79] K. Margolin, Cytokine therapy in cancer, Expert. Opin. Biol. Ther. 8 (2008) 1495–1505, https://doi.org/10.1517/14712598.8.10.1495.
[80] T.F. Gajewski, S.-R. Woo, Y. Zha, R. Spaapen, Y. Zheng, L. Corrales, S. Spranger, Cancer immunotherapy strategies based on overcoming barriers within the tumor microenvironment, Curr. Opin. Immunol. 25 (2013) 268–276, https://doi.org/10.1016/j.coi.2013.02.009.
[81] P. Zhou, X. Zheng, H. Zhang, Y. Liu, P. Zheng, B7 blockade alters the balance between regulatory t cells and tumor-reactive t cells for immunotherapy of cancer, Clin. Cancer Res. 15 (2009) 960–970, https://doi.org/10.1158/1078-0432.CCR-08-1611.
[82] H.Y. Wang, D.A. Lee, G. Peng, Z. Guo, Y. Li, Y. Kiniwa, E.M. Shevach, R.-F. Wang, Tumor-specific human CD4+ regulatory t cells and their ligands, Immunity 20 (2004) 107–118, https://doi.org/10.1016/S1074-7613(03)00359-5.
[83] G.C. Sim, L. Radvanyi, The IL-2 cytokine family in cancer immunotherapy, Cytokine Growth Factor Rev. 25 (2014) 377–390, https://doi.org/10.1016/j.cytogfr.2014.07.018.
[84] T.R. Malek, The biology of interleukin-2, Annu. Rev. Immunol. 26 (2008) 453–479, https://doi.org/10.1146/annurev.immunol.26.021607.090357.
[85] D.H. Charych, U. Hoch, J.L. Langowski, S.R. Lee, M.K. Addepalli, P.B. Kirk, D. Sheng, X. Liu, P.W. Sims, L.A. VanderVeen, C.F. Ali, T.K. Chang, M. Konakova, R.L. Pena, R.S. Kanhere, Y.M. Kirksey, C. Ji, Y. Wang, J. Huang, T.D. Sweeney, S.S. Kantak, S.K. Doberstein, Nktr-214, an engineered cytokine with biased il2 receptor binding, increased tumor exposure, and marked efficacy in mouse tumor models, Clin. Cancer Res. 22 (2016) 680–690, https://doi.org/10.1158/1078-0432.CCR-15-1631.
[86] S. Sakaguchi, Regulatory T cells, Cell 101 (2000) 455–458, https://doi.org/10.1016/S0092-8674(00)80856-9.
[87] J.D. Fontenot, A.Y. Rudensky, A well adapted regulatory contrivance: regulatory T cell development and the forkhead family transcription factor FOXP3, Nat. Immunol. 6 (2005) 331–337, https://doi.org/10.1038/ni1179.
[88] S. Sakaguchi, M. Miyara, C.M. Costantino, D.A. Hafler, FOXP3+ regulatory T cells in the human immune system, Nat. Rev. Immunol. 10 (2010) 490–500, https://doi.org/10.1038/nri2785.
[89] A.M. Miller, K. Lundberg, V. Ozenci, A.H. Banham, M. Hellstrom, L. Egevad, P. Pisa, CD4+CD25HIGH T cells are enriched in the tumor and peripheral blood of prostate cancer patients, J. Immunol. 177 (2006) 7398–7405, https://doi.org/10.4049/jimmunol.177.10.7398.
[90] S. Guedan, A.D. Posey, C. Shaw, A. Wing, T. Da, P.R. Patel, S.E. McGettigan, V. Casado-Medrano, O.U. Kawalekar, M. Uribe-Herranz, D. Song, J.J. Melenhorst, S.F. Lacey, J. Scholler, B. Keith, R.M. Young, C.H. June, Enhancing CAR T cell persistence through ICOS and 4-1BB costimulation, JCI Insight 3 (2018), https://doi.org/10.1172/jci.insight.96976.
[91] T. Ito, S. Hanabuchi, Y.-H. Wang, W.R. Park, K. Arima, L. Bover, F.X.-F. Qin, M. Gilliet, Y.-J. Liu, Two functional subsets of FOXP3+ regulatory t cells in human thymus and periphery, Immunity 28 (2008) 870–880, https://doi.org/10.1016/j.immuni.2008.03.018.
[92] Y. Chen, S. Shen, B.K. Gorentla, J. Gao, X.-P. Zhong, Murine regulatory t cells contain hyperproliferative and death-prone subsets with differential icos expression, J. Immunol. 188 (2012) 1698–1707, https://doi.org/10.4049/jimmunol.1102448.
[93] H. Nagase, T. Takeoka, S. Urakawa, A. Morimoto-Okazawa, A. Kawashima, K. Iwahori, S. Takiguchi, H. Nishikawa, E. Sato, S. Sakaguchi, M. Mori, Y. Doki, H. Wada, ICOS + Foxp3 + TILs in gastric cancer are prognostic markers and effector regulatory T cells associated with H elicobacter pylori: unique expression of ICOS on TREGS in gastric cancer, Int. J. Cancer 140 (2017) 686–695, https://doi.org/10.1002/ijc.30475.
[94] Y. Takeuchi, H. Nishikawa, Roles of regulatory T cells in cancer immunity, Int. Immunol. 28 (2016) 401–409, https://doi.org/10.1093/intimm/dxw025.
[95] C. Menetrier-Caux, M. Gobert, C. Caux, Differences in tumor regulatory t-cell localization and activation status impact patient outcome, Cancer Res. 69 (2009) 7895–7898, https://doi.org/10.1158/0008-5472.CAN-09-1642.
[96] L. Mo, Q. Chen, X. Zhang, X. Shi, L. Wei, D. Zheng, H. Li, J. Gao, J. Li, Z. Hu, Depletion of regulatory T cells by anti-ICOS antibody enhances anti-tumor immunity of tumor cell vaccine in prostate cancer, Vaccine 35 (2017) 5932–5938, https://doi.org/10.1016/j.vaccine.2017.08.093.
[97] L.F. Tremble, M.A. O'Brien, P.F. Forde, D.M. Soden, ICOS activation in combination with electrochemotherapy generates effective anti-cancer immunological responses in murine models of primary, secondary and metastatic disease, Cancer Lett. 420 (2018) 109–115, https://doi.org/10.1016/j.canlet.2018.01.081.
[98] D.N. Khalil, E.L. Smith, R.J. Brentjens, J.D. Wolchok, The future of cancer treatment: immunomodulation, CARs and combination immunotherapy, Nat. Rev. Clin. Oncol. 13 (2016) 273–290, https://doi.org/10.1038/nrclinonc.2016.25.
[99] P.B. Chapman, A. Hauschild, C. Robert, J.B. Haanen, P. Ascierto, J. Larkin, R. Dummer, C. Garbe, A. Testori, M. Maio, D. Hogg, P. Lorigan, C. Lebbe, T. Jouary, D. Schadendorf, A. Ribas, S.J. O'Day, J.A. Sosman, J.M. Kirkwood, A.M.M. Eggermont, B. Dreno, K. Nolop, J. Li, B. Nelson, J. Hou, R.J. Lee, K.T. Flaherty, G.A. McArthur, Improved survival with vemurafenib in melanoma with braf v600e mutation, N. Engl. J. Med. 364 (2011) 2507–2516, https://doi.org/10.1056/NEJMoa1103782.
[100] C. Robert, B. Karaszewska, J. Schachter, P. Rutkowski, A. Mackiewicz, D. Stroiakovski, M. Lichinitser, R. Dummer, F. Grange, L. Mortier, V. Chiarion-Sileni, K. Drucis, I. Krajsova, A. Hauschild, P. Lorigan, P. Wolter, G.V. Long, K. Flaherty, P. Nathan, A. Ribas, A.-M. Martin, P. Sun, W. Crist, J. Legos, S.D. Rubin, S.M. Little, D. Schadendorf, Improved overall survival in melanoma with combined dabrafenib and trametinib, N. Engl. J. Med. 372 (2015) 30–39, https://doi.org/10.1056/NEJMoa1412690.
[101] C. Robert, G.V. Long, B. Brady, C. Dutriaux, M. Maio, L. Mortier, J.C. Hassel, P. Rutkowski, C. McNeil, E. Kalinka-Warzocha, K.J. Savage, M.M. Hernberg, C. Lebbé, J. Charles, C. Mihalcioiu, V. Chiarion-Sileni, C. Mauch, F. Cognetti, A. Arance, H. Schmidt, D. Schadendorf, H. Gogas, L. Lundgren-Eriksson, C. Horak, B. Sharkey, I.M. Waxman, V. Atkinson, P.A. Ascierto, Nivolumab in previously untreated melanoma without braf mutation, N. Engl. J. Med. 372 (2015) 320–330, https://doi.org/10.1056/NEJMoa1412082.
[102] C. Robert, J. Schachter, G.V. Long, A. Arance, J.J. Grob, L. Mortier, A. Daud, M.S. Carlino, C. McNeil, M. Lotem, J. Larkin, P. Lorigan, B. Neyns, C.U. Blank, O. Hamid, C. Mateus, R. Shapira-Frommer, M. Kosh, H. Zhou, N. Ibrahim, S. Ebbinghaus, A. Ribas, Pembrolizumab versus ipilimumab in advanced melanoma, N. Engl. J. Med. 372 (2015) 2521–2532, https://doi.org/10.1056/NEJMoa1503093.
[103] P.B. Chapman, S.P. D'Angelo, J.D. Wolchok, Rapid eradication of a bulky melanoma mass with one dose of immunotherapy, N. Engl. J. Med. 372 (2015) 2073–2074, https://doi.org/10.1056/NEJMc1501894.
[104] J. Brahmer, K.L. Reckamp, P. Baas, L. Crinò, W.E.E. Eberhardt, E. Poddubskaya, S. Antonia, A. Pluzanski, E.E. Vokes, E. Holgado, D. Waterhouse, N. Ready, J. Gainor, O. Arén Frontera, L. Havel, M. Steins, M.C. Garassino, J.G. Aerts, M. Domine, L. Paz-Ares, M. Reck, C. Baudelet, C.T. Harbison, B. Lestini, D.R. Spigel, Nivolumab versus docetaxel in advanced squamous-cell non–small-cell lung cancer, N. Engl. J. Med. 373 (2015) 123–135, https://doi.org/10.1056/NEJMoa1504627.
[105] E.B. Garon, N.A. Rizvi, R. Hui, N. Leighl, A.S. Balmanoukian, J.P. Eder, A. Patnaik, C. Aggarwal, M. Gubens, L. Horn, E. Carcereny, M.-J. Ahn, E. Felip, J.-S. Lee, M.D. Hellmann, O. Hamid, J.W. Goldman, J.-C. Soria, M. Dolled-Filhart, R.Z. Rutledge, J. Zhang, J.K. Lunceford, R. Rangwala, G.M. Lubiniecki, C. Roach, K. Emancipator, L. Gandhi, Pembrolizumab for the treatment of non–small-cell lung cancer, N. Engl. J. Med. 372 (2015) 2018–2028, https://doi.org/10.1056/NEJMoa1501824.

[106] M.L. Davila, I. Riviere, X. Wang, S. Bartido, J. Park, K. Curran, S.S. Chung, J. Stefanski, O. Borquez-Ojeda, M. Olszewska, J. Qu, T. Wasielewska, Q. He, M. Fink, H. Shinglot, M. Youssif, M. Satter, Y. Wang, J. Hosey, H. Quintanilla, E. Halton, Y. Bernal, D.C.G. Bouhassira, M.E. Arcila, M. Gonen, G.J. Roboz, P. Maslak, D. Douer, M.G. Frattini, S. Giralt, M. Sadelain, R. Brentjens, Efficacy and toxicity management of 19-28z car t cell therapy in b cell acute lymphoblastic leukemia, Sci. Transl. Med. 6 (2014) 224ra25, https://doi.org/10.1126/scitranslmed.3008226.

[107] S.L. Maude, N. Frey, P.A. Shaw, R. Aplenc, D.M. Barrett, N.J. Bunin, A. Chew, V.E. Gonzalez, Z. Zheng, S.F. Lacey, Y.D. Mahnke, J.J. Melenhorst, S.R. Rheingold, A. Shen, D.T. Teachey, B.L. Levine, C.H. June, D.L. Porter, S.A. Grupp, Chimeric antigen receptor t cells for sustained remissions in leukemia, N. Engl. J. Med. 371 (2014) 1507–1517, https://doi.org/10.1056/NEJMoa1407222.

[108] J.A. Marin-Acevedo, A.E. Soyano, B. Dholaria, K.L. Knutson, Y. Lou, Cancer immunotherapy beyond immune checkpoint inhibitors, J. Hematol. Oncol. 11 (2018), https://doi.org/10.1186/s13045-017-0552-6.

[109] L.L. Lanier, Nkg2d receptor and its ligands in host defense, Cancer Immunol. Res. 3 (2015) 575–582, https://doi.org/10.1158/2326-6066.CIR-15-0098.

[110] J. Zhang, F. Basher, J.D. Wu, Nkg2d ligands in tumor immunity: two sides of a coin, Front. Immunol. 6 (2015), https://doi.org/10.3389/fimmu.2015.00097.

[111] D.W. Lee, et al., T cells expressing CD19 chimeric antigen receptors for acute lymphoblastic leukaemia in children and young adults: a phase 1 dose-escalation trial, Lancet 385 (2014) 517–528.

[112] M. Vanneman, G. Dranoff, Combining immunotherapy and targeted therapies in cancer treatment, Nat. Rev. Cancer 12 (2012) 237–251.

[113] L. Liu, et al., The BRAF and MEK inhibitors dabrafenib and trametinib: effects on immune function and in combination with immunomodulatory antibodies targeting PD1, PD-L1 and CTLA-4, Clin. Cancer Res. 21 (2015) 1639–1651.

[114] A. Hoos, R. Ibrahim, A. Korman, K. Abdallah, D. Berman, V. Shahabi, K. Chin, R. Canetta, R. Humphrey, Development of ipilimumab: contribution to a new paradigm for cancer immunotherapy, Semin. Oncol. 37 (2010) 533–546, https://doi.org/10.1053/j.seminoncol.2010.09.015.