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Emerging targets in cancer immunotherapy

Authors: Samantha Burugu, Amanda R. Dancsok, and Torsten O. Nielsen

Affiliation: Department of Pathology & Laboratory Medicine, University of British Columbia Hospital, Koerner Pavilion, #G-227 2211 Wesbrook Mall, Vancouver, BC V6T 2B5

Corresponding Author: Dr. Torsten O. Nielsen, Pathology & Laboratory Medicine, Anatomical Pathology JPN 1401, 855 W. 12th Avenue, Vancouver BC, CANADA, V5Z 1M9, Email: torsten@mail.ubc.ca, Tel: +1.604.875.4111 x66768, Fax: +1.604.875.4797

Abstract

The first generation of immune checkpoint inhibitors (anti-CTLA-4 and anti-PD-1/PD-L1) targeted natural immune homeostasis pathways, co-opted by cancers, to drive anti-tumor immune responses. These agents led to unprecedented results in patients with previously incurable metastatic disease and may become first-line therapies for some advanced cancers. However, these agents are efficacious in only a minority of patients. Newer strategies are becoming available that target additional immunomodulatory mechanisms to activate patients' own anti-tumor immune responses. Herein, we present a succinct summary of emerging immune targets with reported pre-clinical efficacy that have progressed to active investigation in clinical trials. These emerging targets include co-inhibitory and co-stimulatory markers of the innate and adaptive immune system. In this review, we discuss: 1) T lymphocyte markers: Lymphocyte Activation Gene 3 [LAG-3], T-cell Immunoglobulinand Mucin-domain-containing molecule 3 [TIM-3], V-domain containing Ig Suppressor of T cell Activation [VISTA], T cell ImmunoGlobulin and ITIM domain [TIGIT], B7-H3, Inducible T-cell Co-stimulator [ICOS/ICOSL], CD27/CD70, and Glucocorticoid-Induced TNF Receptor [GITR]; 2) macrophage markers: CD47/Signal-Regulatory Protein alpha [SIRPα] and Indoleamine-2,3-Dioxygenase [IDO]; and 3) natural killer cell markers: CD94/NKG2A and the Killer Immunoglobulin-like receptor [KIR] family. Finally, we briefly highlight combination strategies and potential biomarkers of response and resistance to these cancer immunotherapies.

Keywords (up to 5): immuno-oncology, checkpoints, tumor-infiltrating lymphocytes, macrophages, Natural Killer

1. Introduction

Cancer immunotherapy is now considered a pillar of cancer treatment, alongside surgery, chemotherapy, and radiation. Ipilimumab and nivolumab/pembrolizumab are among the earliest immune checkpoint inhibitors (targeting CTLA-4 and PD-1, respectively) and are now moving from second-line to become first-line therapies of choice in advanced non-small cell lung cancer and melanoma [1,2]. Treatment with these agents can induce resistance through upregulation of additional immune checkpoints, highlighting a need for new antitumor immune activating agents [3]. Emerging drugs target not only lymphocytes associated with adaptive immunity − via blockade of immune-inhibitory checkpoints or as agonists of immunostimulatory pathways − but also innate immune processes mediated by macrophages and natural killer (NK) cells, pathways of broad relevance across many types of solid and hematopoietic cancers (markers summarized in Fig. 1). The following emerging immune targets in cancer immunotherapy were selected based on their advanced stage of development in preclinical/clinical studies and on the limited number of review articles available describing some of these targets.

2. Adaptive Immunity

2.1. Inhibitory lymphocyte receptors

2.1.1. LAG-3

Lymphocyte Activation Gene 3 (LAG-3) is a surface receptor expressed on activated T cells, an exhaustion marker with immunosuppressive activity. Major histocompatibility complex class II (MHC-II) is a ligand for LAG-3; additional ligands (e.g., L-selectin and galectin-3) have also been identified [4]. Regulatory T cells (Tregs) expressing LAG-3 have enhanced suppressive activity, whereas cytotoxic CD8+ T cells expressing LAG-3 have reduced proliferation rates and effector cytokine production in cancer and autoimmune diabetes [5–7]. A splice variant of LAG-3 cleaved by metalloproteinases and secreted in the cellular microenvironment has immune-activating properties when bound to MHC-II on antigen presenting cells [8].

LAG-3+ tumor-infiltrating lymphocytes (TILs) have been reported in melanoma, colon, pancreatic, breast, lung, hematopoietic, and head and neck cancer patients [9–15], in association with aggressive clinical features. Antibody-based LAG-3 blockade in multiple cancer mouse models restores CD8+ effector T cells and diminishes Treg populations, an effect enhanced when combined with anti-PD-1 [16,17]. A recent study in a metastatic ovarian cancer mouse model showed that LAG-3 blockade leads to upregulation of other immune checkpoints (PD-1, CTLA-4, and TIM-3), and combination therapy targeting LAG-3, PD-1, and CTLA-4 increases functional cytotoxic T cell levels while reducing Tregs and myeloid-derived suppressor cells [18].

Multiple early phase clinical trials are testing antagonistic LAG-3 agents in combination with anti-PD-1 and/or anti-CTLA-4 therapy (Table 1). In view of the activating properties of soluble secreted LAG-3, a soluble agonist LAG-3 antibody (IMP321) was tested in advanced solid malignancies as a single agent [19], and demonstrated sufficient tolerability and efficacy to warrant advancement to phase II.

2.1.2. TIM-3

T-cell Immunoglobulin- and Mucin-domain-containing molecule 3 (TIM-3) is an immune-inhibitory molecule first identified on CD4+ Th1 (helper) T-cells and CD8+ Tc1 (cytotoxic) T-cells [20], then later on Th17 T-cells [21], regulatory T-cells [22,23], and innate immune cells [24–26]. TIM-3 is activated primarily by its widely-expressed ligand, galectin-9 [27], leading to effector T-cell death through calcium influx, cellular aggregation, and apoptosis [28]. When TIM-3 signalling is active, interferon-producing T-cells become exhausted, resulting in Th1

suppression and immune tolerance [28–30]. TIM-3 expression is commonly observed during chronic infection, as a characteristic marker of exhausted T cells [31–35].

In cancer, tumor-infiltrating lymphocytes expressing TIM-3 have been observed in melanoma [36,37], non-Hodgkin lymphoma [38], lung, [22], gastric [39,40], and other cancers [41–44]. In these studies, Tim-3 is co-expressed with PD-1 and associated with effector T-cell exhaustion and dysfunction. This phenomenon is also observed in mouse models of solid [45] and hematologic [46] cancers, where Tim3 + PD1 + CD8+ T-cells exhibit an exhausted phenotype characterized by reduced proliferation and defective production of IL-2, TNFα, and IFN-γ. In contrast, TIM-3 positive Treg display increased expression of effector molecules and are more immunosuppressive than their TIM-3 negative counterparts [47,48].

Inhibition of TIM-3 alone tends to have little effect on tumor growth in pre-clinical mouse models, despite some evidence supporting a reversal of immune cell exhaustion [36,45,49–51]. However, combined targeting of PD-1 and TIM-3 leads to a substantial reduction in tumor growth − better than either pathway alone − in numerous preclinical in vivo models [36,45,46,51], supporting the concept that malignant cells become resistant to PD-1 checkpoint blockade by activating another immune checkpoint. Indeed, mouse models partially responsive to PD-L1 inhibition upregulated TIM-3 expression in resistant tumors [43,52], and addition of TIM-3 blockade was successful in overcoming that resistance. Upregulation of TIM-3 has also been observed in patients receiving PD-L1 monotherapy, suggesting it may represent a form of adaptive resistance to this therapy [52]. Four early phase clinical trials are underway that attempt to combine anti PD-L1 therapy with agents targeting TIM-3 (Table 1).

2.1.3. TIGIT

TIGIT (T cell Immunoglobulin and ITIM domain) is a transmembrane protein receptor that acts as an immune checkpoint on T and NK cells by way of two immunoreceptor tyrosine-based inhibitory motifs (ITIM) in its cytoplasmic tail [53]. There are two prominent TIGIT ligands (CD155 and CD112), mostly expressed on antigen presenting cells, and one recently-discovered ligand called nectin-2 [54]. TIGIT immunosuppressive actions appear to mimic CTLA-4 interactions with the B7 cell surface receptor. Binding of CD155 to CD226 (a receptor on T and NK cells) leads to activation of effector functions which are inhibited when CD155 binds to TIGIT instead [53].

Mice with TIGIT deficiency are sensitive to autoimmune arthritis [55]. In cancer, TIGIT blockade leads to tumor regression, increased survival, and resistance to tumor re-challenge in melanoma and colon cancer mouse models [56,57]. High expression of TIGIT mRNA and increased levels of TIGIT+ lymphocytes by flow cytometry have been reported in human renal cell carcinoma, melanoma, lung, breast, and esophageal cancers. [10,56,58–62]

In melanoma, NY-ESO-1-specific TIGIT+ CD8+ T cells co-express other immune checkpoint markers, such as PD-1 and TIM-3 [59]. Blockade of TIGIT and PD-1 in vitro increased IFN-γ and TNF-α production from tumor-specific CD8+ T cells. A population of early effector TILs that express TIGIT and other inhibitory receptors (LAG-3, TIM-3, and PD-1) but retain their functional phenotype has been reported in lung cancer patients [10]. TIGIT gene expression is demonstrable among a subset of basal-like breast cancers where, like other biomarkers of immune recognition, it is associated with improved survival in what is otherwise an aggressive disease [62]. TIGIT inhibitors are still in early phase development, but at least two agents (MTIG7192A, OMP-313M32) are being investigated in human trials (Table 1).

2.1.4. B7-H3

B7-H3 (CD276) is a member of the B7 superfamily of immune modulatory ligands, closely related to B7-H1 (PD-L1), B7-DC (PD-L2), B7-H2 (ICOS-L), and CTLA-4 ligands B7-1/B7-2 (CD80/CD86) [63]. The role of B7-H3 in immune regulation is controversial [64], as early studies described it as immune co-stimulator [63,65–72], but subsequent studies have shown a co-inhibitory role [73–81].

B7-H3 is highly expressed in normal tissues, [63]. and has been shown to be overexpressed in melanoma [82] and numerous carcinomas [83–88]; in most cases, expression is associated with worse outcomes. Enoblituzumab (MGA271), a monoclonal antibody targeting B7-H3, inhibits tumor growth in renal and bladder carcinoma xenografts [89] and is currently being investigated in at least four phase 1 clinical trials, including in combinations with pembrolizumab or ipilimumab. Preliminary single agent results (NCT01391143) report good tolerability and tumor shrinkage (2–69% at 12 weeks) across several tumor types [90]. A monoclonal antibody against B7-H3 labeled with iodine-131 for intratumoral delivery of radiation has shown promise in preclinical studies [91,92] and is being investigated in phase 1 trials. MGD009, a dual-affinity re-targeting protein bispecific for B7-H3 and CD3 [93] is at a similar stage of development (Table 1).

2.1.5. VISTA

V-domain containing Ig Suppressor of T cell Activation (VISTA, aka PD-1H, DD1α; gene name DIES1) is a recently-discovered immune regulator protein with a similar structure to the B7 Ig superfamily that includes PD-L1, [94,95] expressed in lymphoid organs and on myeloid cells [96–98]. VISTA functions as an immunosuppressive receptor and ligand on T-cells by decreasing IFN-γ and TNFα, blocking T-cell proliferation, and increasing the conversion of naïve T-cells into regulatory T-cells [98].

In mouse models, blocking VISTA increases immune infiltration in tumors while preferentially decreasing myeloid-derived suppressor cells [96]. Combining anti-VISTA and anti-PDL1 agents decreases tumor size and increases survival [99]. In humans, VISTA+ TILs were reported in 46% of gastric cancer patients, with a small percentage of tumor cells also expressing VISTA [100]. Recently, Oliveira P et al. showed that epigenetic factors can regulate VISTA expression in gastric cancer cell lines and that VISTA is associated with the epithelial-mesenchymal transition phenotype [101]. In oral squamous cell carcinoma patients, VISTA expression associates with poor overall survival in patients with low CD8+ TILS [102]. VISTA+ TILs and macrophages are upregulated in prostate cancer and melanoma patients following ipilimumab (anti-CTLA-4) treatment, with a greater percentage of VISTA+ macrophages being of the immunosuppressive M2 phenotype [103], suggesting that VISTA may represent a compensatory resistance mechanism. As of this writing, only phase 1 clinical trials of anti-VISTA agents are open (Table 1), with combination strategies anticipated once safety is established.

2.2. Costimulatory lymphocyte receptors

2.2.1. ICOS and ICOS-L

Inducible T-cell Costimulator (ICOS, CD278, H4, AILIM) is a receptor in the CD28 family of B7-binding proteins [104–106], expressed primarily by activated T cells [107–110]. Upon binding of ligand ICOS-L (B7-H2, B7 h, GL50, B7RP-1, LICOS, KIAA0653) − expressed mainly on antigen presenting cells [111–118] − ICOS enhances Th1 and Th2 function largely through augmented production of effector cytokines (IL-4, IL-5, IL-10, IL-21, IFNγ, TNFα) [104,108,110,119,120].

Expression of ICOS and ICOS-L has been observed in human cancers, with variable prognostic implications [121–128]. Mice and human clinical trial patients treated with anti-CTLA-4 or anti-PD-1 agents exhibit an increased treatment response in the presence of ICOS-hi T cells [129–135], suggesting the latter may be a marker of clinical benefit [131,136]. ICOS knockout mice do not respond well to anti-CTLA-4 therapy [137], whereas concomitant CTLA-4 blockade and ICOS stimulation has a superior anti-tumor effect [129]. Together, these results suggest that the ICOS pathway is critical for effective response to CTLA-4 (and perhaps other immune checkpoint) inhibition. Similar to TIM-3, it is unlikely that ICOS-agonists will be pursued as a monotherapy, as they do not independently induce a cytotoxic immune response [138]. Based on encouraging results in preclinical animal models [139], an ICOS agonist antibody JTX-2011 is being investigated in the phase 1 ICONIC clinical trial in combination with nivolumab (NCT02904226), and has so far been well-tolerated [140]; ICOS agonist GSK3359609 is also being evaluated in phase I trials (INDUCE-1, NCT02723955) in combination with pembrolizumab (Table 1).

2.2.2. CD27 and CD70

Members of the tumor necrosis factor (TNF) receptor superfamily contribute to immune upregulation by a mechanism of action different from B7/CD28 co-stimulatory interactions. One well-known member, CD27, is expressed exclusively on lymphocytes [141–144]. Even naïve CD4+ and CD8+ T-cells express low levels CD27; upon activation, CD27 is strongly upregulated on cell surfaces [145] and shed in a soluble form [146,147]. CD27 signalling is limited by the degree of expression of its ligand CD70, which is restricted to T cells, B cells, and dendritic cells following activation of an antigen receptor [148–151]. CD27/CD70 signalling boosts T-cell clonal expansion and survival [152–158], promotes effector and memory T-cell differentiation [152,154,157,159–166], and enhances activation and function of B and NK cells [151,167–172].

In a transgenic mouse model, forced expression of CD70 constitutively activates the CD27/CD70 axis, upregulating effector T cells [173] and protecting against tumor development [174]. CD27 agonist therapy also prevents tumor formation or progression in immunocompetent preclinical mouse models [171,175–179]. Varlilumab, a CD27 agonist, is being investigated in multiple early phase clinical trials alone and in combination with anti-PD-1 (Table 1). Preliminary results report that varlilumab treatment upregulates chemokine production, T-cell stimulation, and Treg depletion; 8/31 melanoma/renal cell carcinoma patients had stable disease (SD) at 3 months [180], and of 15 lymphoma patients in a different study, there was 1 partial response (77% reduction) and 3 SD [181]. The related strategy of targeting CD70 is the subject of three antibody-drug conjugates and one monoclonal antibody undergoing clinical trials (Table 1). MDX-1203 (NCT00944905) was well-tolerated and achieved SD in 16/23 (69%) of patients. [182]. SGN-75, an antibody-drug conjugate linking an anti-CD70 antibody with cytotoxic agent monomethyl auristatin F (NCT01015911), was also well-tolerated and elicited responses in renal cell carcinomas and lymphomas; however, development was discontinued in favour of a new antibody drug conjugate, SGNeCD70A, in which an anti-CD70 antibody is conjugated to pyrrolobenzodiazepine (NCT02216890).

2.2.3. GITR

Glucocorticoid-Induced TNF Receptor (GITR) is a type II transmembrane receptor, a member of the TNFR superfamily, constitutively expressed on regulatory T cells and induced on activated CD8+ and CD4+ T cells. GITR binding to GITR-L (expressed on antigen presenting cells) inhibits Treg activity [183,184] while stimulating effector T cells [185], making GITR activation an attractive strategy for cancer immunotherapy.

Many preclinical reports on GITR anti-tumor in vivo activity have used a murine GITR agonist IgG1 monoclonal antibody (DTA-1) in solid cancer mouse models [186–193]. GITR agonism, in addition to depleting and inhibiting Tregs (similar to CTLA-4 antagonists and OX40 agonists), suppresses myeloid derived suppressor cells and IL-10 production [191]. Combining of GITR agonists with other immune modulating agents leads to additive antitumor effects [187,188,192,193]. One of the most interesting finding from these studies is that GITR agonists suppress tumor growth and increase survival not only in immunogenic tumor models (colon, bladder, lung, melanoma) but also in poorly immunogenic tumors (breast, B16 melanoma mouse model, ovarian), putting GITR agonists in a unique position in comparison to other immune checkpoint inhibitors for which pre-existing immunity appears a prerequisite for the agents to work. By immunohistochemistry or flow cytometry, GITR expression has been reported in many human solid cancers [194–199]. In breast and endometrial cancer patients, GITR expression on Tregs is higher in TILs than in the peripheral blood [195,197]. The prognostic value of GITR+ TILs has yet to be investigated in detail. At least four GITR agonists are being investigated alone and in combinations with other checkpoint inhibitors in early phase clinical trials (Table 1).

3. Innate Immunity

3.1. Macrophage Checkpoints

3.1.1. CD47 and SIRPα

CD47, first identified as Integrin-Associated Protein (IAP) [200–203], is a cell-surface immunoglobulin that negatively regulates anti-tumor immunity through suppression of phagocytosis. Expressed ubiquitously in normal tissues [204], CD47 functions in part to protect viable erythrocytes from phagocytosis [205–210]. Signalling occurs by interaction with its ligand SIRPα (signal-regulatory protein alpha), a cell-surface immunoglobulin mainly expressed by macrophages and dendritic cells [211]. Activation of SIRPα by CD47 suppresses phagocytosis by preventing myosin-II accumulation at the phagocytic synapse [212] and suppressing the respiratory burst [213]. T-cell activation is secondarily decreased as an indirect result of reduced tumor cell ingestion by antigen-presenting cells; [214] furthermore, activation of CD47 on naïve T-cells promotes the formation of Tregs [215,216] and inhibits formation of T helper 1 effector cells. [217]

Overexpression of CD47 has been observed across most cancers [218–225], suggesting that malignant cells exploit the CD47/SIRPα “don’t eat me” signal to evade phagocytosis. In translational studies, high CD47 mRNA expression levels correlate with poor clinical outcomes. [223,225–233] In vitro, CD47/SIRPα blockade induces phagocytosis of cancer cells by human and mouse macrophages [221–223,225,226]. Anti-CD47 monoclonal antibodies have impressive activity in xenograft models [221–226,234,235], although because human CD47 binds exceptionally well to the SIRPα of the NOD-scid-IL2Rgammanull mice used [236,237], some studies may overestimate the degree of efficacy [238].

Many early phase clinical trials are in progress targeting the CD47/ SIRPα axis (Table 1). Toxicity data has been presented for NCT02216409, a trial investigating anti-CD47 antibody Hu5F9-G4, [235] which was well-tolerated in 16 patients with advanced solid tumors.

3.1.2. IDO

Indoleamine-2,3-dioxygenase (IDO) is an intracellular enzyme, which − in the immune compartment − is found in macrophages and dendritic cells [239–242], where it catalyzes the first, rate-limiting step of tryptophan catabolism [243–245]. In converting tryptophan to kynurenine, IDO impacts immune surveillance in two ways: 1) depletion of tryptophan impairs T-cell proliferation due to amino acid insufficiency [246–248], and 2) kynurenine induces apoptosis

of Th1 cells [249] and promotes differentiation of naïve T cells to regulatory T cells [250]. This generates an immune-privileged environment, as seen in the placenta, where IDO was first isolated [251].

Numerous cancer types have been shown to constitutively express IDO [239,252]. Transfecting cell lines with IDO prevents their rejection in tumor antigen-immunized mice [252], an effect reversible with IDO inhibitors. Pharmacological inhibition of IDO has been shown in numerous mouse tumor models to stimulate a robust T cell response and inhibit tumor progression [253,254]. The tumor suppressor BIN1, which controls expression of IDO, is deficient in numerous cancers [255–259]; BIN1 knockout induces higher levels of IFNγ-stimulated IDO expression and results in larger tumors in immunocompetent mouse models compared to controls [260].

There are presently four small molecule inhibitors of IDO under investigation in clinical trials. One of these, epacadostat, is registered to 20 clinical trials, including one phase 3 trial, and in patients with advanced malignancies, stable disease ≥16 weeks was observed in 7/52 patients (no objective response). [261] In combination with anti-PD-1 agent pembrolizumab, reductions in tumor burden were observed in 15/19 patients with advanced solid malignancies, including 2 complete responses in melanoma patients [262].

3.2. Natural Killer Cell Checkpoints

3.2.1. KIR family

The Killer Immunoglobulin-like Receptor (KIR) family is composed of highly polymorphic genes expressed on the cellular membrane of most NK and some T cells. Some KIR family members (KIR2DL1-3, KIR3DL1) are associated with inhibitory functions, through binding to MHC molecules (HLA-C/HLA-B) [263]. KIR expression on NK cells represents one mechanism to educate NK cells against self-recognition [264,265]. Strong interactions between inhibitory KIR receptors and HLA ligands can overcome NK activation signals [266].

Due to their highly polymorphic nature [267], various KIR genes and ligands influence disease risk, including autoimmunity and cancer [268–276]. Combinations of KIR genes and particular ligands have been associated with cancer risk [268,271–273,277]. Activating KIR genes (KIR2DS2, KIR2DS3, and KIR2DS4) are associated with improved survival in colorectal cancer and glioblastoma patients [274,276]. In mouse models, engineered chimeric antigen receptors expressing NK-activating KIR2DS2 show higher efficacy than conventional co-stimulatory molecules [278,279].

Despite promising pre-clinical results, a phase 1/2 myeloma trial investigating single agent IPH2101, an antibody inhibitor of KIR2DL1, 2, and 3 (IPH2101), showed no disease responses [280]. A follow-up correlative study showed that patient peripheral blood mononuclear cells treated in vitro with IPH2101 led to KIR2DL1 removal on NK cells by trogocytosis from FcγRI-expressing antigen presenting cells [281]. Accordingly, there was a decrease of NK cell cytotoxic activity that could explain the failure to activate NK cells in trial patients. Another KIR2DL1/2/3 inhibitor (IPH2102, lirilumab) is currently in phase 1/2 clinical trials in advanced solid and hematologic malignancies, in combination with PD-1 or CTLA-4 blockade (Table 1). Preliminary results report an encouraging objective response rate of 24% in advanced head and neck cancer patients treated with lirilumab in combination with anti-PD1 (nivolumab) [282].

3.2.2. CD94/NKG2A

CD94 is an invariant chain receptor that, on NK cells, can form an inhibitory heterodimer with the C type lectin like family member NKG2A or an activating heterodimer with NKG2C or E

[283]. T cells can also express CD94/NKG2A receptor (albeit to a lesser degree compared to NK cells), where it functions as a predominant inhibitory checkpoint [284]. Binding to MHC class I (HLA-E) mediates the inhibitory function of CD94/NKG2A following TCR engagement [284]. The CD94/NKG2A-HLA-E interaction can be blocked by targeting ERAP-1, a protein required to provide functional ligands for CD94/ NKG2A on HLA-E molecules [285].

NKG2A blockade can improve antibody-dependent cell cytotoxicity [286], and solid cancers that overexpress HLA-E are associated with poor prognosis [287–289], supporting CD94/NKG2A as an active target for cancer immunotherapy [290]. Indeed, multiple studies report the presence of CD94/NKG2A+ cells in cancer patients [287–289,291–297]. Blood samples from early-stage colorectal cancer patients show elevated frequency of NKG2A+ NK cells with lower cytotoxic activity compared to samples from healthy controls [297]. NKG2A expression on NK cells is higher in tumors versus from peripheral blood of lung and cervical cancer patients [293,295]. In a small cohort of oral cancer patients, a higher frequency of NKG2A+ NK infiltrating in the tumor region compared to normal mucosa was reported [291]. The highest expression of NKG2A+ NK cells was observed in nests of cancer with low CD8 + TILs that were negative for Ki67. In hepatocellular carcinoma, greater numbers of NKG2A+ NK cells are found in the intratumoral compared to peritumoral regions [289]. These findings support the relevance of NKG2A inhibitory mechanisms as an important immune evasion pathway in human tumors [291]. There are at least six phase 1/2 clinical trials investigating the IPH2201 antibody targeting NKG2A in various advanced stage cancer patients, some in combination with PD-L1 inhibitors (Table 1).

4. Discussion

The success of early immune checkpoint inhibitors targeting CTLA-4 and PD-1/PD-L1 has led to a surge in research and development of resources devoted to cancer immunotherapy. How these emerging targets and drugs will be incorporated into the clinical practice is one of the major focuses of clinical cancer research today. There is evidence for additive anti-tumor activity but also higher adverse effects of strategies combining CTLA-4 and PD-1 checkpoint inhibitors [1,2]. Many agents listed in this review are being evaluated in combination with PD-1 and/or CTLA-4 inhibitors (Table 1), with unresolved issues including not only efficacy and toxicity, but also optimal sequential delivery in patients and identification of predictive biomarkers of response.

At present, few predictive biomarkers of response to immune checkpoint inhibitors are in use. The best tests to support PD-1/PD-L1 agents are a subject of great controversy, and most new agents do not have validated companion biomarkers. However, inflamed tumors are associated with an elevated response to immune checkpoint inhibitors, and frequently comprise tumors with a high mutational load or with microsatellite instability[13,298], the latter now considered an FDA-approved biomarker for pembrolizumab independent of tumor site or histology. Immune response profiling by next generation panel sequencing or technologies such as NanoString may also prove useful in this regard and are a subject of active research in clinical trial correlative science studies. In contrast, immune-desert (so-called “cold”) tumors have only modest responses to immune checkpoint inhibitors and may need to be treated using immunostimulatory approaches [299]. Clinical trial designs that include assessment of immune biomarkers (e.g., T cell receptor sequencing), access to early on-treatment biopsies for immune monitoring, and identification of peripheral blood biomarkers that correlate with the tumor immune microenvironment may help to address these issues.

5. Conclusions

This field is rapidly advancing and extremely active for drug development and clinical trials. Toxicities still need to be determined, particularly of combination strategies, which risk enhanced autoimmune side effects. Given limited resources and patients available for clinical trials, emerging agents with acceptable toxicity will need to be prioritized based on factors including not

only the strength of evidence implicating their role in cancer immuno-oncology, but also their frequency of expression in areas of clinical need not well-served by existing agents. While many of these agents may not ultimately find a place in the growing armamentarium of anticancer immuno-oncology drugs, the pathways under investigation are so many, and the early data so promising, that it is likely that several truly effective new treatment strategies will emerge.

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Figure legend

FIGURE 1. Overview of emerging targets for cancer immunotherapy. Immune inhibitory interactions are marked in red, and immune co-stimulatory interactions are marked in green.

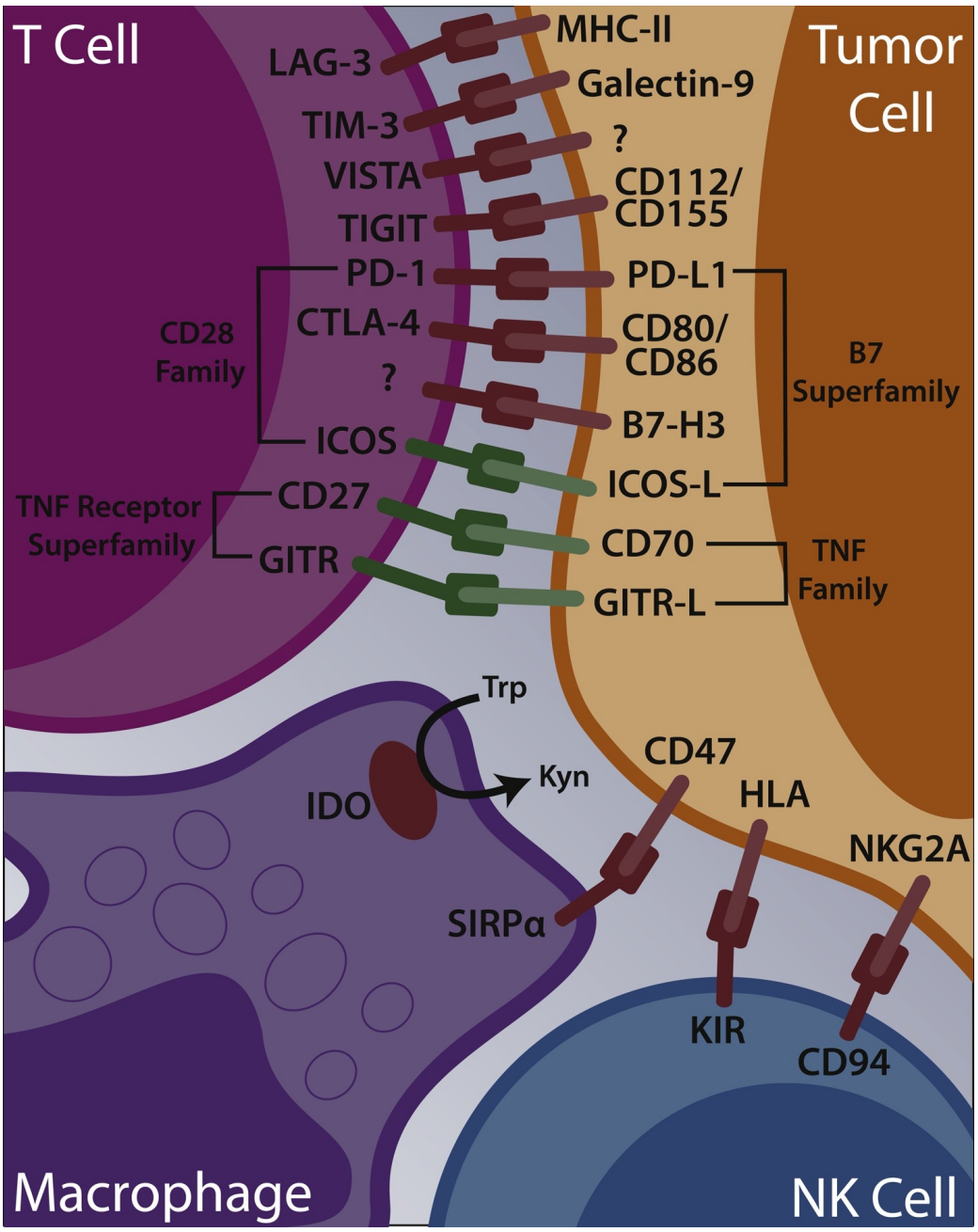

Table 1. A summary of past and current clinical trials in cancer for immune checkpoint agents

Target	Agent(s)	Mechanism of Action	Other agents	Identifier	Phase	Disease(s)	Sponsor
LAG3	IMP321	Monoclonal soluble LAG-3 agonist antibody	Paclitaxel	NCT00349934	1	Metastatic breast cancer	Immuntep S.A; Umanis
			Paclitaxel	NCT02614833	2	Metastatic breast cancer	Immuntep S.A; Prima BioMed Ltd
			-	NCT00351949	1	Metastatic Renal Cell Carcinoma	Immuntep S.A; Umanis
			Anti-PD-1	NCT02676869	1	Advanced melanoma	Prima BioMed Ltd
	LAG525	Monoclonal anti-LAG-3 antibody	Anti-PD-1	NCT02460224	1/2	Advanced solid malignancies	Novartis Pharmaceuticals
	BMS986016	Monoclonal anti-LAG-3 antibody	Anti-PD-1	NCT01968109	1/2	Advanced solid and hematologic malignancies	Bristol-Myers Squibb
			Anti-PD-1	NCT02061761	1/2	hematologic malignancies	
			Anti PD-1	NCT02060188	2	Colorectal cancer	
			Anti-PD-1	NCT02488759	1/2	Virus-associated tumors	
			Anti-PD-1	NCT02935634	2	Advanced gastric cancer	
			Anti-PD-1	NCT02750514	2	Advanced NSCLC	
			Anti-PD-1	NCT02996110	2	Advanced RCC	
			Anti-PD-1	NCT02658981	1	Recurrent brain neoplasms	Bristol-Myers Squibb
			Anti-PD-1	NCT02966548	1	Advanced solid malignancies	Bristol-Myers Squibb; Ono Pharmaceutical Co. Ltd
	REGN3767	Monoclonal anti-LAG-3 antibody	Anti-PD-1	NCT03005782	1	Malignancies (progressed without any available therapy and are immune checkpoint naive)	Regeneron Pharmaceuticals; Sanofi
TIM-3	TSR-022	Monoclonal anti-TIM-3 antibody	Anti-PD-1	NCT02817633	1	Advanced solid malignancies	Tesaro, Inc.
	LY3321367	Monoclonal anti-TIM-3 antibody	Anti-PD-L1	NCT03099109	1	Advanced relapsed/refractory solid malignancies	Eli Lilly and Company
	MBG453	Monoclonal anti-TIM-3 antibody	Anti-PD-1	NCT02608268	1-1b/ 2	Advanced/metastatic solid malignancies	Novartis Pharmaceuticals
			Anti-PD-1	NCT03066648	1	Acute myeloid leukemia or high-risk myelodysplastic syndrome	
TIGIT	OMP-313M32	Monoclonal anti-TIGIT antibody	-	NCT03119428	1	Advanced and metastatic solid tumors	OncoMed Pharmaceuticals, Inc
	MTIG7192A/RG6058	Monoclonal anti-TIGIT antibody	Anti-PD-L1	NCT02794571	1	Advanced and metastatic solid tumors	Genentech
VISTA	JNJ-510588	Monoclonal anti-VISTA antibody	-	NCT02671955	1	Advanced and metastatic solid tumors	Janssen Research & Development
	CA-170	Small molecule targeting PD-L1,	-	NCT02812875	1	Advanced solid and hematologic malignancies	Curis, Inc.

Target	Agent(s)	Mechanism of Action	Other agents	Identifier	Phase	Disease(s)	Sponsor
		PD-L2, and VISTA					
B7-H3	Enoblituzumab (MGA271)	Monoclonal anti-B7-H3 antibody	-	NCT02982941	1	B7-H3-expressing relapsed or refractory solid malignancies	MacroGenics
			Anti-PD-1	NCT02475213	1	B7-H3-expressing melanoma, squamous cell cancer of the head and neck, non-small cell lung cancer and other B7-H3-expressing cancers	
			Anti-CTLA-4	NCT02381314	1	B7-H3-expressing melanoma, squamous cell cancer of the head and neck, non-small cell lung cancer and other B7-H3-expressing cancers	
			-	NCT01391143	1	Refractory Cancer	
	^{131}I-8H9	Monoclonal anti-B7-H3 antibody radiolabeled with iodine-131	-	NCT01099644	1	Desmoplastic small round cell tumors and other solid tumors involving the peritoneum	Memorial Sloan Kettering Cancer Centre
			-	NCT01502917	1	Non-progressive diffuse pontine gliomas	
			-	NCT00089245	1	Refractory/recurrent/advanced CNS or leptomeningeal cancer	
	MGD009	B7-H3 x CD3 Dual-Affinity Re-Targeting (DART) Protein	-	NCT02628535	1	Unresectable or metastatic B7-H3-expressing neoplasms	MacroGenics
ICOS	JTX-2011	Monoclonal anti-ICOS agonist antibody	Anti-PD-1	NCT02904226	1/2	Advanced solid malignancies	Jounce Therapeutics, Inc.
	GSK3359609	Monoclonal anti-ICOS agonist antibody	Anti-PD-1	NCT02723955	1	Advanced solid malignancies	GlaxoSmithKline
GITR	TRX518	Monoclonal anti-GITR antibody	-	NCT01239134	1	Unresectable and metastatic solid malignancies	Leap Therapeutics, Inc.; Cancer Research Institute
	MEDI1873	Monoclonal anti-GITR antibody	-	NCT02583165	1	Advanced solid malignancies	MedImmune LLC
	GWN323	Monoclonal anti-GITR antibody	Anti-PD-1	NCT02740270	1	Advanced solid and hematologic malignancies	Novartis Pharmaceuticals
	INCAGN01876	Monoclonal anti-GITR antibody	-	NCT02697591	1/2	Advanced and metastatic solid tumors	Incyte Corporation
			Anti-PD-1 and/or anti-CTLA-4	NCT03126110	1/2	Advanced and metastatic solid tumors	

Target	Agent(s)	Mechanism of Action	Other agents	Identifier	Phase	Disease(s)	Sponsor
CD27/ CD70	Varlilumab (CDX-1127)	Monoclonal anti-CD27 agonist antibody	Anti-PD-1	NCT02335918	1/2	Advanced refractory solid malignancies	Celldex Therapeutics
			-	NCT01460134	1	Selected refractory or relapsed hematologic or solid malignancies	
			ONT-10 (Cascadian Therapeutics, Inc.)	NCT02270372	1	Advanced ovarian or breast cancer	
			IMA950 vaccine, poly-ICLC	NCT02924038	1	WHO grade II low-grade glioma	University of California
			Anti-PD1	NCT03038672	2	Relapsed or refractory aggressive B-cell lymphomas	National Cancer Institute (US)
	SGN-CD70A	Anti-CD70 monoclonal antibody conjugated to pyrrolobenzodiazepine (cytotoxic DNA minor-groove crosslinking agent)	-	NCT02216890	1	CD70-Positive Malignancies	Seattle Genetics, Inc.
	Vorsetuzumab mafodotin (SGN-75)	Anti-CD70 monoclonal antibody conjugated to monomethyl auristatin F (cytotoxic agent)	-	NCT01015911	1	CD70-positive relapsed or refractory non-Hodgkin lymphoma or metastatic renal cell carcinoma	Seattle Genetics, Inc.
	ARGX-110	Monoclonal anti-CD70 antibody	-	NCT01813539	1	Advanced malignancies expressing CD70	arGEN-X BVBA
			-	NCT02759250	1	Nasopharyngeal carcinoma	
	BMS-936561 (MDX-1203)	Anti-CD70 monoclonal antibody conjugated to a rachelmycin prodrug	-	NCT00944905	1	Renal cell carcinoma or non-hodgkin's lymphoma	Bristol-Myers Squibb
CD47/ SIRPα	Hu5F9-G4	Monoclonal anti-CD47 antibody	-	NCT02216409	1	Advanced solid malignancies	Forty Seven, Inc.
			-	NCT02678338	1	Relapsed/refractory acute myeloid leukemia	
			Cetuximab (EGFR inhibitor)	NCT02953782	1b/2	Solid malignancies and advanced colorectal cancer	

Target	Agent(s)	Mechanism of Action	Other agents	Identifier	Phase	Disease(s)	Sponsor
			Rituximab (CD20 inhibitor)	NCT02953509	1b/2	Relapsed/refractory B-cell non-Hodgkin's lymphoma	
	TTI-621	Recombinant SIRPα-Fc fusion protein (wild-type CD47-binding domain of SIRPα fused to Fc domain of IgG1)	-	NCT02890368	1	Relapsed/refractory solid malignancies and mycosis fungoides	Trillium Therapeutics, Inc.
			Anti-PD-1, Rituximab (CD20 inhibitor)	NCT02663518	1a/1b	Hematologic malignancies	
	CC-90002	Monoclonal anti-CD47 antibody	Rituximab (CD20 inhibitor)	NCT02367196	1	Advanced solid and hematologic malignancies	Celgene
			-	NCT02641002	1	Acute myeloid leukemia and high-risk myelodysplastic syndrome	
	ALX148	Recombinant SIRPα-Fc fusion protein (engineered high-affinity CD47-binding domains of SIRPα, fused to Fc domain of IgG4)	Anti-PD-L1, Trastuzumab (HER2 inhibitor)	NCT03013218	1	Advanced solid malignancies and lymphoma	Alexo Therapeutics, Inc
IDO	Epacadostat (INCB024360)	Small-molecule inhibitor of IDO-1	-	NCT01195311	1	Advanced malignancies	InCyte CorporationInCyte Corporation
			Anti-PD-1	NCT02178722	1/2	Selected cancers	
			Anti-PD-1	NCT02327078	1/2	Select advanced cancers	
			Anti-PD-L1	NCT02298153	1	Non-Small cell lung cancer, previously treated stage IV urothelial carcinoma	
			Azacitidine, Anti-PD-1	NCT02959437	1/2	Advanced solid tumors, and previously treated stage IIIB/IV non-small cell lung cancer and stage IV colorectal cancer	
			Anti-PD-L1	NCT02318277	1/2	Selected advanced solid tumors	
			Anti-PD-1 Oxaliplatin Leucovorin 5-Fluorouracil Gemcitabine nab-Paclitaxel Carboplatin Paclitaxel Pemetrexed Cyclophospha	NCT03085914	1/2	Advanced or Metastatic Solid Tumors	

Target	Agent(s)	Mechanism of Action	Other agents	Identifier	Phase	Disease(s)	Sponsor
			mide				
			Anti-PD-1	NCT02752074	3	Unresectable or metastatic melanoma	
			Anti-PD-1	NCT02862457	1	Advanced solid tumors	Merck Sharp & Dohme Corp.
			INCB039110 (JAK-1 inhibitor), INCB050465 (PI3K-delta inhibitor)	NCT02559492	1	Advanced or metastatic solid tumors	H. Lee Moffitt Cancer Center and Research Institut
			-	NCT01822691	2	Myelodysplastic syndrome	
			Multipeptide Melanoma Vaccine (MELITAC 12.1)	NCT01961115	2	Advanced melanoma	Fred Hutchinson Cancer Research Center
			-	NCT02042430	pilot	Newly diagnosed stage III-IV epithelial ovarian, fallopian tube, or primary peritoneal cancer	National Cancer Institute (US)
			Survivin vaccine DPX-Survivac, Cyclophospha mide	NCT02785250	1b	Recurrent ovarian, fallopian tube, or peritoneal cancer	ImmunoVaccine Technologies, Inc.
			CDX-1401 vaccine (DEC-205/NY-ESO-1 fusion protein), Poly-ICLC	NCT02166905	1/2b	NY-ESO-1 or LAGE-1 expressing epithelial ovarian, fallopian tube, or primary peritoneal carcinoma in remission	Roswell Park Cancer Institute
			Anti-PD-1 CRS-207 (listeria-based vaccine) GVAX (pancreas vaccine) Cyclophospha mide	NCT03006302	2	Metastatic pancreatic cancer	Sidney Kimmel Comprehensive Cancer Center
			Anti-PD-1 CRS-207 (listeria-based vaccine)	NCT02575807	1/2	Platinum-resistant ovarian, fallopian, or peritoneal cancer	Aduro Biotech, Inc.
			Anti-PD-1 Azacitidine	NCT03182894	1/2	Chemo-refractory metastatic colorectal cancer	James J Lee
			Anti-PD-1	NCT03196232	2	Metastatic or unresectable gastroesophageal junction and gastric adenocarcinoma	Pamela L Kunz

Target	Agent(s)	Mechanism of Action	Other agents	Identifier	Phase	Disease(s)	Sponsor
			-	NCT02764151	1	Malignant gliomas	Pfizer
	Pf-06840003	Small-molecule inhibitor of IDO-1	-	NCT02048709	1	Recurrent advanced solid tumors	Genentech, Inc.
	GDC-0919	Small-molecule inhibitor of IDO-1	-	NCT03164603	1	Recurrent advanced solid tumors	NewLink Genetics Corporation
	NLG802	Small-molecule inhibitor of IDO-1	-	NCT01222286	2	Multiple Myeloma	Innate Pharma, National Institute of Health
KIR family	IPH2101	Monoclonal anti-KIR2D antibody	lenalidomide	NCT01217203	1	Multiple Myeloma	Innate Pharma, National Institute of Health National Institute of Health
			-	NCT01248455	2	Multiple Myeloma	
			Anti-CTLA-4	NCT01750580,	1	Advanced solid tumors	Bristol-Myers Squibb
	Lirilumab	Monoclonal anti-KIR2DL1,2,3 antibody	Anti-PD-1 alone or with Anti-CTLA-4	NCT01714739	1/2	Advanced solid tumors	Bristol-Myers Squibb Innate Pharma
			Anti-CD20	NCT02481297	2	Hematologic malignancies	
			Anti-SLAMF7	NCT02252263	1	Multiple myeloma	
			Chemotherapy: 5-azacytidine	NCT02399917	2	Acute Myeloid Leukemia	
			Anti-PD-1	NCT01592370	1	Hematologic Malignancies	
			Chemotherapy: 5-azacytidine	NCT02599649	2	Hematologic malignancies	
			-	NCT01687387	2	Acute Myeloid Leukemia	
			-	NCT02593045	1	Hematologic malignancies	
	IPH4102	Monoclonal anti-KIR3DL2 antibody	-	NCT02921685	1/2	Hematologic Malignancies	Institut Paoli-Calmettes; Innate Pharma
CD94/ NKG2A	IPH2201	Monoclonal anti-NKG2A antibody	-	NCT02557516	1/2	Chronic Lymphocytic Leukemia	Institut Paoli-Calmettes; Innate Pharma Innate pharma
			Anti-EGFR	NCT02643550	1	Advanced Head and Neck malignancies	
			-	NCT02459301	1	Advanced Gynecologic malignancies	Canadian Cancer Trials Group; Innate Pharma
			Anti-PD-L1	NCT02671435	1	Advanced solid malignancies	MedImmune
			-	NCT03088059	2	Advanced Head and Neck malignancies with PD-L1 therapy naïve or PD-L1 resistant	European Organisation for Research and Treatment of Cancer

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