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Overcoming Tumor-Induced Immune Suppression: From Relieving Inhibition to Providing Costimulation with T Cell Agonists

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Abstract

Recent advancements in T-cell biology and antibody engineering have opened doors to significant improvements in cancer immunotherapy. Initial success with monoclonal antibodies targeting key receptors that inhibit T-cell function such as cytotoxic T lymphocyte antigen 4 (CTLA-4) and programmed death-ligand 1 (PD-1) have demonstrated the potency of this new class of therapy, highlighted by long-term complete responses for metastatic cancers once thought incurable. However, only a subset of patients responds to checkpoint blockade because of a multitude of factors, including an immunosuppressive tumor microenvironment and the mutational burden of the cancer. Novel antibodies, as well as ligand-immunoglobulin fusion proteins that target costimulatory immune receptors, are being developed and tested in clinical trials to further enhance the anti-tumor immune response. Many of these costimulatory receptors are in the tumor necrosis factor receptor superfamily (TNFRSF) and are expressed on multiple immune cell types, including inhibitory cells. While TNFRSFs signal through common pathways, the outcome of targeting different receptors depends on the functional status of the cell types expressing the relevant receptors. In this review, we discuss the current state of targeted costimulatory immunotherapy.

1 Introduction

The generation of potent T-cell-mediated anti-tumor immunity relies on the provision of several critical signals, including T-cell receptor (TCR)-mediated recognition of peptide-major histocompatibility complex (MHC) molecules on antigen-presenting cells (APCs) along with appropriate costimulatory signals [1, 2]. Even in the presence of these optimal conditions, tumors utilize a myriad of mechanisms to evade and suppress the immune

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response. For example, tumors suppress recognition and visibility to the immune system by changing their microenvironment (TME) and reducing MHC class I presentation of tumor-associated antigens (TAAs). Changes to the TME can occur through secretion of immunosuppressive cytokines such as interleukin (IL)-10 and transforming growth factor (TGF)-β, which inhibit effector T-cell responses and promote regulatory FoxP3$^+$ cluster of differentiation (CD)-4 T-cell regulatory (Treg) function [3] or through upregulation of programmed death-ligand 1 (PD-L1), which inhibits the TCR signaling pathway. PD-L1 binds to programmed cell death protein 1 (PD-1) expressed by activated or exhausted T cells, resulting in phosphatase activity that inhibits TCR kinase signaling [4, 5]. Importantly, tumors that are immunologically "silent," which refers to low MHC I and high PD-L1 expression, often have little or no response to immunotherapy [6–9].

Thus, there is an urgent need to develop therapies that enhance tumor antigen presentation along with T-cell priming, activation, and differentiation to counteract tumor-induced immune evasion and suppression. One such approach is to enhance T-cell recognition of TAAs presented on MHC molecules through the provision of exogenous tumor-specific vaccines, known as therapeutic vaccination [10, 11]. However, therapeutic vaccines have achieved limited clinical success thus far. Another approach is the provision of monoclonal antibodies (mAb) that block inhibitory checkpoint molecules such as cytotoxic T lymphocyte antigen 4 (CTLA-4), PD-1, and PD-L1. In contrast to therapeutic vaccines, checkpoint blockade immunotherapy has demonstrated significant therapeutic benefit for patients with metastatic cancer, which has led to US FDA approval for a variety of tumor types [6, 7]. A third approach is the use of agonist mAbs that boost T-cell function by engaging costimulatory molecules such as OX40, 4–1BB, and CD40. In this review, we review checkpoint inhibitors and their impact on the current landscape of cancer immunotherapy, followed by a discussion of the current state of therapies that target T-cell costimulatory receptors with a focus on OX40, 4–1BB, glucocorticoid-induced tumor necrosis factor receptor (TNFR)-related protein (GITR), CD40, and inducible T-cell costimulator (ICOS) and their use in combination with checkpoint inhibitors.

2 Checkpoint Inhibitors (Anti-CTLA-4, Anti-PD-1) and the First Bispecific Antibody

The first T-cell-targeted immunotherapies came after the discovery of immune checkpoints that regulate activation and inhibition following TCR stimulation. One of the first inhibitory regulators of T-cell function to be cloned was CTLA-4 in 1987 [12]. CTLA-4 and the homologous receptor CD28 both bind to B7–1 and B7–2 ligands expressed on APCs [13–15]. When CD28 engages B7 ligands, it enhances the TCR signaling pathway through enhanced phosphoinositide 3 kinase (PI3K) activity. However, activated T cells downregulate expression of CD28 and upregulate CTLA-4, which inhibits T-cell signaling by engaging B7 ligands with 20-fold higher affinity than CD28, thereby blocking CD28-mediated costimulation. Additionally, CTLA-4 is constitutively expressed on Tregs. In mouse models of cancer, CTLA-4 blockade was shown to boost anti-tumor immunity by inhibiting Tregs and enhancing T-cell effector function [16, 17].

These data led to the clinical development of two blocking antibodies targeting human CTLA-4 (aCTLA-4): ipilimumab [18] and tremelimumab [19–21]. Clinical trials of ipilimumab for the treatment of metastatic melanoma showed promising results, which led to a successful phase III trial in 2009 for patients with high-grade unresectable melanoma. This trial showed a 10.1-month overall median survival when receiving ipilimumab alone compared with 6.4 months' survival for patients receiving a gp100 vaccine alone. The addition of the gp100 vaccine to ipilimumab therapy had no additional impact on overall survival in these patients [22]. Tremelimumab was not as successful, perhaps because of its staggered treatment schedule of infusions every 3 months compared with every 3 weeks for ipilimumab. Ipilimumab was subsequently approved for metastatic melanoma in 2011. Tremelimumab is still being investigated for several other indications but has not seen clinical success for melanoma, small cell lung cancer, or mesothelioma [20].

The success of immunotherapies such as ipilimumab in 2011 and the vaccine-based therapy sipuleucel-T for hormone-refractory prostate cancer in 2010 led to the development of multiple T-cell-targeted immunotherapy agents (Table 1). Leading candidates to be targeted by the next wave of immunotherapies were T-cell checkpoints PD-1 and PD-L1, molecules that inhibit T-cell activity and function when engaged [23]. The PD-1/PD-L1 pathway is upregulated in many cancers and is an important mechanism of inhibiting activated tumor-reactive T cells [24]. Two PD-1-blocking antibodies (aPD-1), pembrolizumab and nivolumab, demonstrated clinical success and received FDA approval. Pembrolizumab was approved in 2014 following a successful phase III trial investigating its use following failed ipilimumab therapy for advanced metastatic melanoma [25]. Pembrolizumab was approved for metastatic non-small-cell lung cancer in 2015 [26], metastatic head and neck squamous cell carcinoma in 2016 [27], and DNA mismatch repair-deficient solid tumors in 2017. Nivolumab is currently FDA approved for metastatic melanoma, renal cell carcinoma, lung cancer, bladder cancer, and Hodgkin's lymphoma [28]. Additionally, three antibodies targeting PD-L1 (aPD-L1) have also seen success in clinical trials, including FDA approval of atezolizumab for the treatment of metastatic non-small-cell lung cancer [29], durvalumab for the treatment of metastatic urothelial cancer [30], and avelumab for the treatment of non-small-cell lung cancer [31].

Among this next wave of agents was an alternate class of immunotherapeutic antibodies that simultaneously target two different receptors, known as Bispecific T-cell Engagers (BiTE) [32]. BiTEs are engineered antibodies that contain Fab (Fragment, antigen-binding) regions against different targets to link two different surface proteins together. If the targeted surface proteins are expressed on different cells, then the BiTE will link the two cells together. This rationale was used to develop one of the first BiTEs, blinatumomab [33]. This BiTE targets CD19 overexpressed on B-cell malignancies and CD3 expressed by T cells in order to bring the cancer cell and the T cell together, with the goal of simultaneously enhancing T-cell activity through CD3 binding [33]. Blinatumomab was FDA approved for acute lymphoblastic leukemia in 2014.

While these various immunotherapeutic agents have demonstrated marked success, particularly in a subset of cancers (melanoma, lung), several important issues remain. One of the primary challenges is that immunotherapy typically only benefits a subset of patients.

Other issues include the onset of potentially severe adverse events (SAEs) associated with therapy that can be enhanced when these agents are given in combination, such as in the case of aCTLA-4/aPD-1 therapy [34]. Additional questions remain about treatment timing, dosage, administration route, and identification of patients who are most likely to respond to therapy. While ipilimumab, pembrolizumab, and nivolumab have proven that immune checkpoint blockade can lead to long-term responses in metastatic disease, immunotherapy agents in development are aimed at engaging T-cell costimulatory receptors to activate and enhance the T-cell-mediated anti-tumor response.

3 Targeting the TNFRSF, ICOS, and Combination Immunotherapy

Recent studies have increasingly focused on therapies targeting costimulatory receptors expressed on activated T cells and APCs (Fig. 1). TNFR superfamily (TNFRSF) members are a promising class of immune-modulating molecules that are under rapid development for cancer immunotherapy. TNFRSF members are typically homotrimeric transmembrane proteins with a cysteine-rich extracellular domain [35]. Intracellular signaling domains of TNFRSFs can induce pro-apoptotic or pro-survival and pro-inflammatory programs depending on the cell type and signaling domains expressed. TNFRSFs signal through TNFR-associated factor (TRAF) adaptor proteins. Activating TRAF proteins (TRAF1, TRAF2, and TRAF5) signal to activate the canonical nuclear factor (NF)-κB and c-Jun N-terminal kinase (JNK) pathway and activate the inhibitor of apoptosis (IAP) [36]. These signaling pathways enhance T-cell function and survival following TNFRSF engagement. However, some TNFRSFs, such as TNF-related apoptosis-inducing ligand (TRAIL) receptor and apoptosis antigen 1 (FAS) receptor, signal through death domains to initiate a caspase-mediated apoptosis program [37]. Multiple pro-survival and pro-inflammatory TNFRSFs are expressed on T cells following TCR activation, making them promising targets both as monotherapies and as complementary targets to the established checkpoint inhibitor immunotherapy agents. Thus, targeting TNFRSFs with agonistic antibodies and ligand-Fc fusion proteins has the potential to potently activate and enhance the anti-tumor T-cell response.

Antibodies that target receptors can either be inhibitory (antagonist) or activating (agonist) and must be designed and engineered specifically to accomplish those signals. The most commonly used antibody isotype for immunotherapy is immunoglobulin G (IgG), but several subtypes of IgG influence its immune function depending on how they engage Fc γ receptors or activate the complement system cascade [38]. IgG1 strongly induces antibody-dependent cellular cytotoxicity (ADCC) by engaging Fc γ receptors, which lends itself well to targeting tumor-specific antigens (e.g., herceptin, which targets the Her2 receptor on breast cancer) or potentially depleting inhibitory immune cells, such as Tregs. However, nivolumab and pembrolizumab are IgG4 isotype antibodies, which only weakly engage Fc γ receptors and makes them amenable for receptor blockade without inducing ADCC.

Antibodies used for clinical applications are typically produced in three forms: murine, humanized, and fully human. Murine antibodies produced by mouse hybridomas are seen as foreign and can thus only be dosed for a short time before the human immune system mounts an adaptive immune response to clear the foreign (murine) antibody. Humanized

antibodies are modified murine antibodies engineered such that the Fc regions of the Fab domain are comprised of the human antibody sequence [39]. Humanized antibodies can be dosed without inducing an adaptive immune response [40]. An alternative to antibody targeting is to generate ligand-Fc fusion proteins, which express the natural ligand bound to the Fc region of the antibody rather than engineering a human antibody with different binding kinetics and regions of interaction compared with the natural ligand [41]. This may provide an advantage over conventional antibodies for targeting TNFRSFs, which are homotrimeric and bind homotrimeric ligands. The natural homotrimeric TNFRSF ligand binds the TNFRSF molecules in a way that may be different than the complementary-binding region of an antibody to produce superior engagement.

3.1 OX40

OX40 (CD134; TNFRSF4) is expressed by CD4 and CD8 T cells following TCR ligation [42, 43]. Murine Tregs also express OX40, although high OX40 expression on human Tregs is only seen following activation [44–46]. OX40 is transiently expressed 24–72 h after T-cell activation, which creates a critical window for engagement with its ligand, OX40 ligand (OX40L; CD252). OX40L is also transiently expressed on APCs, with particularly high expression on CD40-licensed dendritic cells (DC), which are important for priming CD8 T-cell responses [47]. The costimulatory activity of OX40 was initially discovered in 1987, when it was shown that agonistic antibody targeting of OX40-enhanced CD4 T-cell proliferation in vitro [48]. Following this, the ligand for OX40 was discovered to be a previously known glycoprotein expressed in human T-cell lymphoma/leukemia virus-1 infected cells, formerly known as gp34 [49].

Early studies on the role of OX40-OX40L interaction in experimental autoimmune encephalomyelitis (EAE) and murine models of arthritis demonstrated that blocking antibodies against either OX40 or OX40L effectively decreased autoimmunity [50]. Building upon these data, it was shown that T cells isolated from the TME expressed OX40 and subsequently hypothesized that these were tumor-reactive T cells. Additional studies revealed that treatment with an agonist aOX40 mAb or OX40L-IgG fusion protein significantly enhanced tumor-free survival across four different murine tumor models [51]. Depletion of CD4 or CD8 T cells demonstrated that the efficacy of aOX40 therapy was T cell-dependent. To investigate whether OX40 expression on CD8 T cells was necessary for treatment efficacy, OT-I TCR transgenic mice, which express a TCR specific for the SIINFEKL peptide of ovalbumin protein, were crossed with OX40-deficient mice, to create $OX40^{-/-}$ OT-Is. In this antigen-specific model, $OX40^{-/-}$ OT-I T cells exhibited reduced CD8 T-cell expansion and survival as compared with wild-type OT-I T cells, highlighting the critical role that OX40 signaling plays in regulating CD8 T-cell activation and survival [52]. Moreover, direct ligation of an OX40 agonist to antigen-specific CD8 T cells significantly enhanced expression of the effector molecule, granzyme B, leading to enhanced tumor regression and long-term survival of tumor-bearing mice [53].

These preclinical studies showed the efficacy of agonist aOX40 therapy and formed a rationale for further evaluation in clinical trials. An initial phase I clinical trial used a murine IgG anti-human OX40 mAb for the treatment of patients with metastatic carcinoma,

lymphoma, or sarcoma (NCT01644968). After three doses of aOX40, 12 of 30 patients saw a reduction in at least one metastatic lesion [54]. However, the study was limited to three sequential doses given within 5 days because a murine antibody was used. Despite this use of a murine antibody, the trial still demonstrated that aOX40 therapy led to immunological effects (T-cell proliferation) and supported further clinical development. Currently, several phase I and II clinical trials are ongoing to evaluate aOX40 therapy across multiple cancer types, including head and neck (MEDI6469; NCT02274155), colorectal neoplasia (MEDI6469; NCT02559024), metastatic prostate (MEDI6469; NCT01303705), renal cell carcinoma (PF-04518600; NCT03092856), and solid tumors (INCAGN01949; NCT02923349) [Table 2]. Additionally, multiple phase I clinical trials are exploring aOX40 in combination with other immunotherapies, including tremelimumab (aCTLA-4) and durvalumab (aPD-L1) for the treatment of advanced solid tumors (MEDI0562; NCT02705482, and NCT02205333), in combination with pembrolizumab alone (GSK3174998; NCT02528357), or the combination of pembrolizumab and nivolumab for advanced cancers (BMS-986178; NCT02737475), and in combination with a Toll-like receptor 9 (TLR9) agonist for lymphomas (BMS-986178; NCT03410901). Results from these clinical trials are pending, but results from a phase I dose-escalation trial for the treatment of advanced solid malignancies using a combination of aOX40 and aPD-L1 (MOXR0916; NCT02410512) showed no high-grade adverse effects at the higher dosage, indicating that this combination was well tolerated. Agonist aOX40 therapy is a promising and exciting treatment that may lend itself well to combinations with checkpoint inhibitors such as aPD-1 and aCTLA-4.

3.2 CD40

CD40L (CD154; TNFSF5) is expressed primarily on activated CD4 T cells, along with B cells, monocytes, natural killer (NK) cells, basophils, and mast cells [55]. This ligand plays an important role in binding CD40 (TNFRSF5) expressed on APCs and B cells and acting as an important signal to induce activation [56]. The interaction between CD40 and CD40L is critical for developing an adaptive immune response that is highly context dependent on the cell types and cytokines involved. Activated CD4 T-cell CD40L engagement of CD40 on B cells results in TRAF adaptor protein induction of NF-κB, mitogen-activated protein kinase (MAPK), PI3K, and phospholipase γ pathways that activate B cells [57, 58]. Activated B cells form germinal centers, undergo antibody isotype switching, and differentiate into plasma cells to produce antibodies [59]. Signaling through CD40 on DCs is a critical step for DC “licensing,” which enables DCs to prime CD8 T-cell responses effectively through cross-presentation [60–63]. Enhancing APC activation and DC licensing is the main rationale behind agonist aCD40 therapy and the rationale behind its use in combination therapy [64]. Studies of agonistic aCD40 antibodies in murine models of cancer have shown significant therapeutic efficacy. In a mesothelioma model, aCD40 was effective in inhibiting tumor growth in a dose-dependent manner [65]. Interestingly, one group discovered that aCD40 therapy was more effective at clearing tumors in a lymphoma model when treatment was delayed [66]. It was speculated that the larger tumor burden of delayed treatment may increase the available tumor antigens that can be taken up and cross-presented by DCs.

An initial clinical trial using recombinant human CD40L for non-Hodgkin's lymphoma showed some promise when one of 32 patients had a complete response and another had a partial response in the absence of major toxicity [67]. Several CD40 agonists have moved forward into clinical trials, including the humanized aCD40 CP-870,893, which led to a partial response in 14% of patients with melanoma (NCT01103635) [68]. Studies investigating SGN-40 have not induced any clinical responses to date, but SGN-40 is being used in a clinical trial for lymphomas (NCT00435916) and in combination with rituximab (NCT00655837). Other agents in clinical trials include HCD122 (lucatumumab) for lymphomas (NCT01275209, NCT00670592) [69], CDX-1140 for solid cancers (NCT03329950), and APX005 M for solid tumors (NCT02482168), central nervous system tumors (NCT03389802), and esophageal cancer (NCT03165994). Additional monotherapy trials include ADC-1013 for solid tumors (NCT02379741) and Chi Lob 4/7 for advanced malignancies (NCT01561911). Combination therapy trials include APX005 M in combination with pembrolizumab for metastatic melanoma (NCT02706353) and in combination with nivolumab for metastatic lung cancer, melanoma, and pancreatic cancer (NCT03123783, NCT03214250).

While initial clinical trial data suggest that agonistic CD40 agents may not be effective as monotherapies, CD40 agonists may be effective agents in combination with other immunotherapies. Agonistic CD40 agents may also synergize well with chemotherapies and radiation, which release tumor antigens to aid in the antigen-presentation process. Different antibodies have seen varying levels of SAEs, which suggests that a clear understanding of the optimal timing and dosage for these drugs will be critical to their development and future success.

3.3 4–1BB

4–1BB (CD137; TNFRSF9) is a glycosylated costimulatory molecule expressed transiently on activated T cells, NK cells, and DCs, as well as expressed constitutively on Tregs [70]. Engagement of 4–1BB by its ligand 4–1BBL (CD137L; TNFSF9) induces strong T-cell activation and survival, particularly in activated CD8 T cells [71, 72]. The role of 4–1BB in cancer immunology has been evaluated in 4–1BBL-deficient mice, which develop spontaneous B-cell lymphomas, and in 4–1BB$^{-/-}$ mice, which develop systemic lupus erythematosus likely due to tumor-suppressive activity of 4–1BBL for B cells [73, 74]. Initial studies of 4–1BB agonists in cancer models of sarcoma and mastocytoma showed enhanced numbers of tumor-specific CD8 T cells and improved T-cell memory against tumor re-challenge [75]. 4–1BB agonists have since been shown to have efficacy across multiple tumor models by inducing a population of tumor-specific cytotoxic CD8 T cells that produce potent pro-inflammatory cytokines and effector molecules, such as granzymes [76–79].

4–1BB also plays an important role in activating and enhancing NK cell function through Fc γ receptors [80]. Based on this finding, it was hypothesized that 4–1BB stimulation of NK cells aids in NK-mediated antibody-dependent cell-mediated cytotoxicity (ADCC). This would make agonistic 4–1BB therapy a candidate for use in combination with tumor antigen-targeted antibodies such as rituximab, which targets CD20 for the treatment of non-

Hodgkin's lymphoma and chronic lymphocytic leukemia. In murine models of lymphoma, an agonist a4–1BB showed strong efficacy when given after rituximab treatment [81].

A phase I clinical trial of utomilumab (a4–1BB) in combination with rituximab for patients with B-cell lymphomas resulted in two complete responses in follicular lymphoma that lasted beyond 2 years (NCT01307267). An increase in memory T cells and activated NK cells was also observed. No significant SAEs were reported, with no patients stopping treatment due to toxicity in the utomilumab study [82]. Utomilumab is also being tested in multiple clinical trials with other agents such as avelumab (aPD-L1; NCT02554812), aOX40 (NCT02315066), mogamulizumab (an aCCR4 antibody; NCT02444793), and pembrolizumab (NCT02179918). Another phase I/II study of an a4–1BB agonist (urelumab; NCT02253992) resulted in dose-dependent adverse effects and a 50% objective response rate in patients with advanced metastatic melanoma when given with aPD-1 (nivolumab); it is also being tested in combination with nivolumab for bladder cancer and other malignant tumors (NCT02845323, NCT02534506). Clearly, 4–1BB agonists are an agent of great interest both as a monotherapy and in combination with other immunotherapies.

3.4 GITR

GITR (CD357; TNFRSF18) is expressed on activated T cells, constitutively expressed on Tregs, and moderately expressed on memory T cells [83, 84]. Once activated, T cells transiently express GITR 24 h after stimulation. GITR expression is regulated by the FoxP3 transcription factor in Tregs and by canonical NF-κB signaling in activated T cells [85]. GITR signaling in activated T cells lowers the threshold for CD28 co-stimulation and results in NF-κB, MAPK, and JNK signal pathway activation through TRAF adaptor proteins [86, 87]. However, the rationale for targeting GITR with mAbs relies on its high constitutive expression on Tregs and costimulatory signaling in CD4 and CD8 T cells. GITR was originally thought to be a unique marker of Tregs before later being found on other cell types [88]. Anti-GITR antibodies seem to be well tolerated without inducing significant autoimmunity. Targeting GITR with IgG1 antibodies has been effective at depleting tumor-infiltrating Tregs from the TME, but not in the periphery in a B16 mouse model of melanoma [89]. Using a FoxP3-GFP transgenic mouse, it was discovered that aGITR was effective in depleting Tregs in B16 tumor-bearing mice, resulting in tumor clearance [90]. On activated CD4 and CD8 T cells, GITR is upregulated following TCR stimulation and signals through activating TRAF molecules to enhance proliferation, pro-inflammatory cytokine production, and resistance to Treg-mediated suppression [91–93].

Based on the high expression of GITR on tumor-infiltrating Tregs, aGITR therapy is expected to be more effective in cancers with high levels of infiltrating Tregs such as cervical, renal cell, hepatocellular, lung, and melanoma [94, 95]. Therefore, it is hypothesized that aGITR therapy would synergize well with other immunotherapies; however, the potential for more severe SAEs resulting from Treg depletion will need to be taken into consideration. Multiple clinical trials are underway testing both aGITR mAbs and GITRL-Fc fusion proteins, including trials as monotherapy (INCAGN0187; NCT02697591), (GWN323; NCT02740270), (TRX518; NCT01239134), and (OMP-336B11; NCT03295942). Anti-GITR mAbs are also being tested in combination with pembrolizumab

(MK-4166; NCT02132754, NCT02553499), (INCAGN0187; NCT03277352, NCT03126110) and nivolumab (BMS-986156; NCT02598960, NCT03335540). MEDI1873 is a novel hexameric GITRL-Fc fusion protein aimed at enhancing activated T-cell function, rather than depleting Tregs, and has shown superior activity compared with aGITR mAbs in vivo (NCT02583165) [96].

3.5 ICOS

ICOS (CD278) is an immunoglobulin superfamily receptor expressed on activated T cells [97]. Its ligand, ICOSL (CD275; B7-H2) is expressed on both B cells and DCs [98]. ICOS, CD28, and CTLA-4 all share a homologous proline-rich motif that facilitates their binding to B7 ligands. While CD28 and CTLA-4 can bind B7–1, B7–2, and B7-H2, ICOS is only known to bind B7-H2, although in a different position from CD28 and CTLA-4 and at much higher affinity [99, 100]. ICOS stimulation by ICOSL induces PI3K and AKT pathway signaling, which aides in CD4 T-cell differentiation into follicular T helper cells (T_{FH}), Th_1, and Th_2 T cells [101]. The effect of ICOS signaling on activated CD4 T cells appears to be context dependent, although signaling likely drives IL-4 and IL-10 production for Th_2 differentiation in the absence of additional stimulation [102].

Interestingly, ICOS is upregulated on CD4 T cells following aCTLA-4 therapy, suggesting that ICOS expression is linked to CTLA-4 and may play a compensatory role to CTLA-4 when CTLA-4 is blocked therapeutically [103]. Additionally, therapeutic synergy was observed when both pathways were targeted [103–105]. In the B16 melanoma model, CTLA-4 blockade and an agonist aICOS mAb synergized to provide protection that the monotherapies did not [103]. Clinical trials for aICOS include MEDI-570 for various lymphomas (NCT02520791), GSK3359609 in combination with pembrolizumab for solid tumors (NCT02723955), and JTX-2001 in combination with nivolumab for solid tumors (NCT02904226). Future clinical trials may focus on aICOS in combination with aCTLA-4 agents to determine whether this combination induces additional therapeutic benefit over either therapy alone.

4 Conclusions

Immunotherapy has shown great promise in recent years, leading to durable responses and even cures for a subset of patients with metastatic cancer. While targeting immune checkpoints such as CTLA-4 and PD-1 has proven to be a viable therapy, it has not been a universal success. Targeting inhibitory receptors with a single agent may not be enough to augment the anti-cancer response and overcome cancer-mediated immune suppression. New antibodies and ligand-Fc fusion proteins targeting costimulatory receptors such as OX40, 4–1BB, GITR, and ICOS might provide T cells with a stimulus that is otherwise lacking in the TME. Other costimulatory therapies are targeting alternative (non-T cell) cell types such as DCs (aCD40 therapy) and NK cells (a4–1BB). Moving forward, there is a critical need to understand how to rationally combine these agents, including balancing increased efficacy with the potential for increased toxicity. As the field moves into combination therapies of inhibitory and activating antibodies, sequencing of these agents will also be critical for eliciting potent anti-cancer responses. However, synergistic combination therapy may have

the added benefit of working effectively at lower doses, leading to less severe adverse events. A great deal of effort is also focusing on identifying predictive biomarkers of response. For example, tumor-specific PD-L1 expression has already proven to be a predictive marker for aPD-1 therapy in some instances; however, additional immunological analysis may be critical for deciding which immunotherapies to use in combination. In conclusion, immunotherapy targeting of costimulatory receptors, particularly of the TNFRSF, are a promising addition to the growing list of immunotherapy agents being tested in clinical trials.

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Key Points

Immune checkpoint blockade releases the brakes on effector T cells and can induce clinical responses in a subset of patients with metastatic cancer.

Antibodies capable of activating costimulatory receptors on T cells are a promising new class of immunotherapy drugs being evaluated alone or in combination with other immunotherapeutics for patients with advanced cancer.

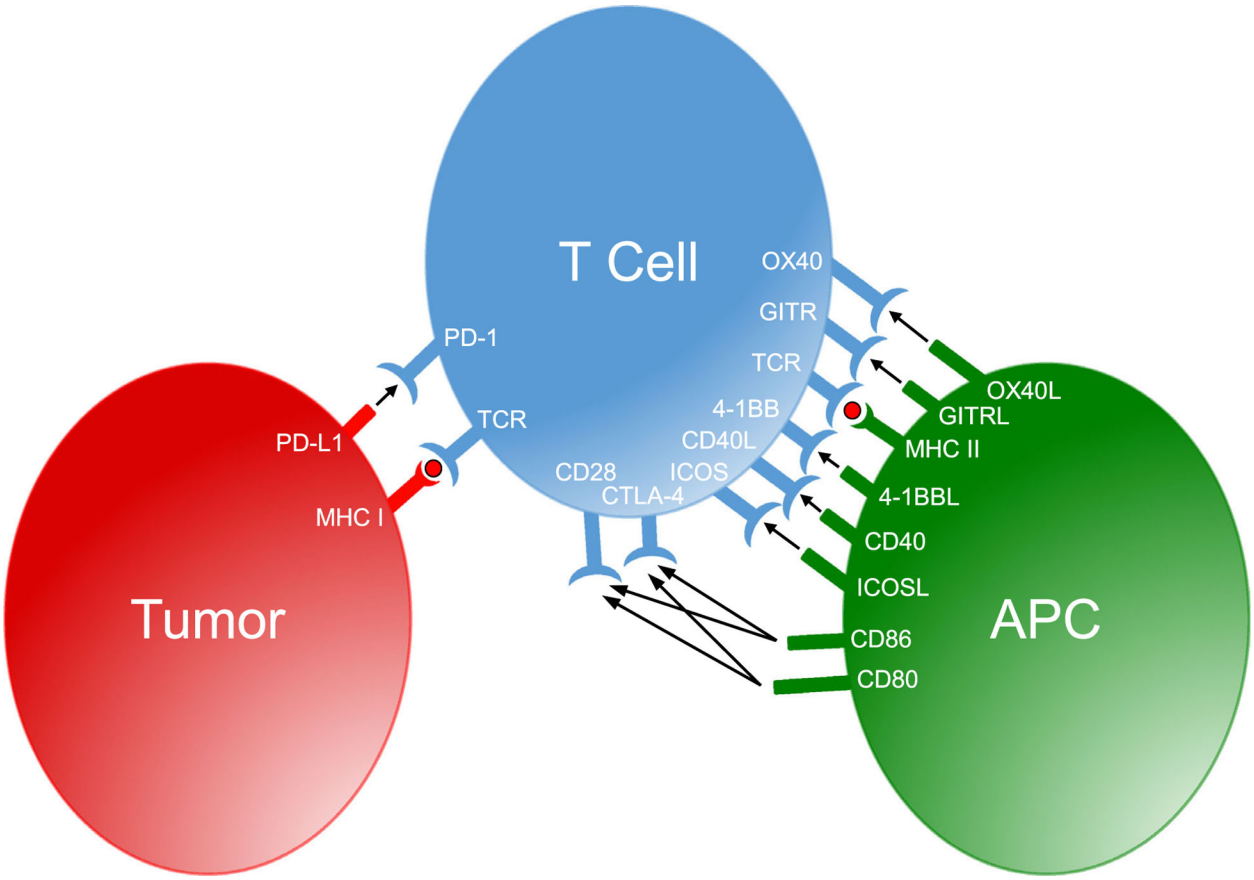

Fig. 1.

Inhibitory checkpoint and costimulatory receptors with their respective ligands expressed by antigen-presenting cells, T cells, and tumor cells. *APC* antigen-presenting cells, *CD* cluster of differentiation, *CTLA* cytotoxic T lymphocyte antigen, *GITR* glucocorticoid- induced tumor necrosis factor receptor -related protein, *ICOS* inducible T-cell costimulator, *MHC* major histocompatibility complex, *PD* programmed cell death protein, *TCR* T-cell receptor

Table 1

US FDA-approved T-cell targeted immunotherapies

Target	Mechanism	Name	Company
CTLA-4	Treg depletion, enhanced CD28 costimulation	Ipilimumab	BMS
PD-1	Block PD-1:PD-L1 interaction by targeting PD-1 on T cells, enhanced TCR signaling	Pembrolizumab	Merck
		Nivolumab	BMS
PD-L1	Block PD-1:PD-L1 interaction by blocking PD-L1 on tumor cells, enhanced TCR signaling	Durvalumab	AstraZeneca
		Avelumab	Merck
		Atezolizumab	Genentech
CD19 and CD3	Link T cells to cancerous B cells, enhanced TCR signaling by activating CD3	Blinatumomab	Amgen

BMS Bristol-Myers Squibb, *CD* cluster of differentiation, *CTLA* cytotoxic T lymphocyte antigen, *PD-1* programmed cell death protein 1, *PD-L1* programmed death ligand 1, *TCR* T-cell receptor, *Treg* regulatory T cells

Table 2

Agonist antibody and Fc-ligands in clinical trials as mono and combination immunotherapies

Target	Mechanism	Name	Company	Clinical Trial
0X40	Enhanced T cell NF-κB signaling	MEDI6469	MedImmune	NCT02274155
				NCT02559024
				NCT01303705
		PF-04518600	Pfizer	NCT03092856
		INCAGN01949	Incyte	NCT02923349
		MEDI0562	MedImmune	NCT02705482
		BMS-986178	BMS	NCT02205333
		GSK3174998	GlaxoSmithKline	NCT02737475
		MOXR0916	Genentech	NCT03410901
				NCT02528357
				NCT02410512
CD40	Enhanced DC cross-presentation to CD8 T cells	CP-870,893	Pfizer	NCT01103635
		CDX-1140	Celldex Therapeutics	NCT03329950
		SGN-40	Seattle Genetics	NCT00435916
		HCD122	Novartis	NCT01275209
				NCT00670592
		APX005 M	Apexigen	NCT02482168
				NCT02706353
				NCT03123783
				NCT03389802
				NCT03165994
				NCT03214250
		ADC1013	Alligator Bioscience	NCT02379741
		Chi Lob 4/7	University of Southampton	NCT01561911
4–1BB	Enhanced NK cell ADCC	Utomilumab	Pfizer	NCT02554812
		Urelumab	BMS	NCT02315066
				NCT02444793
				NCT02179918

Target	Mechanism	Name	Company	Clinical Trial
				NCT02845323
				NCT02253992
				NCT02534506
GITR	Intratumoral Treg depletion	MK-4166	Merck	NCT02132754
				NCT02553499
		BMS-986156	BMS	NCT02598960
				NCT03335540
		MEDI1873	MedImmune	NCT02583165
		INCAGN01876	Incyte	NCT03277352
		GWN323	Novartis	NCT03126110
		TRX518	Leap Therapeutics	NCT02697591
		OMP-336B11	OncoMed Pharmaceuticals	NCT02740270
				NCT01239134
				NCT03295942
ICOS	Enhanced downstream TCR signaling following aCTLA-4 therapy	MEDI570	MedImmune	NCT02520791
		GSK3359609	GlaxoSmithKline	NCT02723955
		JTX-2011	Jounce Therapeutics	NCT02904226

aCTLA-4 antibodies targeting cytotoxic T lymphocyte antigen 4, *ADCC* antibody-dependent cell-mediated cytotoxicity, *BMS* Bristol-Myers Squibb, *CD* cluster of differentiation, *DC* dendritic cell, *GITR* glucocorticoid-induced tumor necrosis factor receptor-related protein, *ICOS* inducible T-cell costimulator, *NF* nuclear factor, *NK* natural killer, *TCR* T-cell receptor, *Treg* regulatory T cell