Boosting Cancer Immunotherapy with Anti-CD137 Antibody Therapy

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Abstract

In the past 5 years, immunomodulatory antibodies have revolutionized cancer immunotherapy. CD137, a member of the tumor necrosis factor receptor superfamily, represents a promising target for enhancing antitumor immune responses. CD137 helps regulate the activation of many immune cells, including CD4+ T cells, CD8+ T cells, dendritic cells, and natural killer cells. Recent studies indicate that the antitumor efficacy of therapeutic tumor-targeting antibodies can be augmented by the addition of agonistic antibodies targeting CD137. As ligation of CD137 provides a costimulatory signal in multiple immune cell subsets, combination therapy of CD137 antibody with therapeutic antibodies and/or vaccination has the potential to improve cancer treatment. Recently, clinical trials of combination therapies with agonistic anti-CD137 mAbs have been launched. In this review, we discuss the recent advances and clinical promise of agonistic anti-CD137 monoclonal antibody therapy.

Introduction

Antibody-based strategies for cancer treatment have dramatically advanced in the past 20 years (1). Since rituximab was approved as the first monoclonal antibody (mAb) for the treatment of cancer in 1997 (2, 3), several mAbs have become standard of care for the treatment of both solid tumors and hematologic malignancies (Table 1). Most of the approved mAbs (e.g., rituximab, trastuzumab, and cetuximab) target tumor-associated antigens on the surface of cancer cells and inhibit cell growth. Although several effective antibodies have emerged, long-term, durable responses remain elusive, and resistance and relapse remain major problems (4–6). Immunomodulatory antibodies have revolutionized cancer immunotherapy and helped garner the breakthrough distinction (7–11). In 2011, the FDA approved the cytotoxic T-lymphocyte–associated protein 4 (CTLA-4)–specific mAb, ipilimumab, for the treatment of metastatic melanoma, representing a major milestone in cancer immunotherapy (12). The second FDA-approved immunomodulatory agent, pembrolizumab, is anti–programmed cell death 1 (PD-1, PDCD1 or CD279) mAb, which was approved in 2014 (13). In the same year, blinatumomab, a novel bispecific T-cell engager (BiTE) antibody specific to CD19 and CD3, was approved for patients with acute lymphoblastic leukemia (14). Most cancer immunotherapy strategies stimulate the patient’s immune system to overcome immunosuppression induced by tumor cells and generate an antitumor immune response. The clinical data and recent FDA approvals validate mAb-mediated cancer immunotherapy as a valuable therapeutic strategy.

In addition to checkpoint blockade agents such as ipilimumab and pembrolizumab, agents targeting the tumor necrosis factor (TNF) superfamily of costimulatory receptors have entered development (8). CD137 is one of the TNF receptor family targets that have advanced into clinical trials. CD137 regulates many immune cells, including CD4+ and CD8+ T cells, regulatory T cells (Treg), dendritic cells (DC), and natural killer (NK) cells (15, 16). Recent studies indicate that the addition of anti-CD137 mAbs can augment the antitumor efficacy of immunomodulatory antibodies.

CD137

CD137 (4-1BB) or TNF receptor superfamily member 9 (TNFRSF9) is a costimulatory receptor that belongs to the TNF receptor superfamily (9, 16, 17). The cDNA of CD137 was cloned in 1989 as an inducible gene from stimulated T cells (18). Follow-up studies showed that CD137 is also detectable on Tregs, DCs, and NK cells. The functional role of CD137 in enhancing cytotoxic T-cell responses was established in 1997, and soon anti-CD137 mAbs were being explored as cancer therapies (19). Melero and colleagues (20) first reported that the administration of anti-CD137 mAbs could eradicate established large tumors in mice, including the poorly immunogenic Ag104A sarcoma and the highly tumorigenic P815 mastocytoma. The immune response induced by anti-CD137 mAbs was shown to be mediated by CD8+ cells and accompanied by a marked augmentation of tumor-selective cytolytic T-cell activity. CD137 signaling also promotes some CD4+ helper T-cell functions that facilitate a CD8+ CTL response. Interestingly, the efficacy of anti-CD137 mAbs was long lasting and generated memory responses as mice survived rechallenge with the same tumor. The role of CD137 in antitumor responses was also demonstrated in CD137−/− mice in the B16F10 melanoma model (21). The knockout mice displayed...
increased metastasis in the lungs and shorter survival time compared with wild-type mice. Anti-CD137 mAbs elicit several immune responses on different types of immune cells. The mechanism of anticancer effects mediated by these cells is described below (Fig. 1). In addition, the role of CD137 signaling has been studied in several autoimmune processes (16), including rheumatoid arthritis, experimental autoimmune encephalomyelitis, and systemic lupus erythematosus. These studies showed significant protection against the autoimmune disorders. This dual immunoregulatory activity of CD137 offers the possibility to enhance antitumor activity without autoimmune side effects associated with immunotherapy approaches.

Costimulation through CD137

T cells. The immune response induced by anti-CD137 mAbs is mediated by both CD8\(^+\) and CD4\(^+\) T cells and is accompanied by a significant increase in tumor-selective cytolytic T-cell activity, including increased T-cell proliferation, resistance to apoptosis,
T-cell activation (7, 8). One of the best-characterized costimulatory activities in T cells is mediated by CD137. In vivo studies showed that CD137 agonistic antibody can costimulate both CD4+ and CD8+ T cells and induce IL2 and IL8 secretion by DCs and macrophages, leading to enhanced T-cell proliferation and cytokine secretion (22). Anti-CD137 therapy was ineffective in B6 mouse embryo C3 tumors, TC-1 lung carcinoma, and B16.F10 melanoma models, when CTLs were depleted (23). In melanoma tumor models, anti-CD137 antibodies not only prevented activation-induced cell death but also augmented CD8+ T-cell proliferative potential and enhanced cytolytic activity against tumor cells (24). In addition, costimulation through CD137 and OX40 activates Akt to promote cell cycling through regulation of cyclins and cyclin-dependent kinases (25).

Regulatory T cells. Regulatory T cells (forkhead box P3 (FOXP3)+ or CD4+CD25+) downregulate the functions of T cells to prevent autoimmunity. They also suppress the cytotoxic response of T cells, which leads to immune tolerance to cancer. Recently, we have demonstrated that surface expression of both OX40 and CTLA-4 is limited to the tumor-specific Treg subset (26). Local immunomodulation by the injection of anti-OX40 and anti–CTLA-4 mAbs into one tumor elicited a potent antitumor immune response that led to eradication of distant tumors. Thus, Tregs may control local tumor immunomodulation and also mediate systemic tumor eradication. CD137 is also expressed on Tregs (15). Curran and colleagues (27) and Guo and colleagues (28) reported that anti-CD137 mAb reduced Treg infiltration in tumors. Guo and colleagues (28) asserted that anti-CD137 mAb directly reduced Tregs. Curran and colleagues (27) claimed that Tregs were reduced as a percentage of the tumor T-cell pool that did not necessarily involve any change to the Tregs themselves. It was also reported that only CD137-negative Tregs infiltrated tumor sites and provided protection, while the population of CD137-positive Tregs consisted primarily of activated Tregs (29). Houot and colleagues (30) demonstrated that depletion of Tregs dramatically enhanced anti-CD137 therapy in mice. Based on these reports, suppression or elimination of Tregs may be a valuable component of future therapeutic strategies.

Dendritic cells. DCs represent unique antigen-presenting cells capable of sensitizing T cells to both new and recall antigens. DCs have been shown to play an important role in CD137-mediated antitumor immunity (31); their removal eliminated the efficacy of anti-CD137 in tumor in vivo (32). Anti-CD137 mAbs, when combined with vaccination with tumor cell lysate-pulsed DCs (TP-DC), accelerated tumor regression and enhanced the survival of tumor-bearing mice (33), suggesting a role for vaccinated DCs with upregulated CD137 in enhancing CTL antitumor activity. In the presence of human CD137L extracellular domain (scCD137L), antigen-loaded human DCs markedly increased the functions of antitumor CTL as measured by T-lymphocyte proliferation, IL2 and IFNγ secretion, cell viability, and cytotoxicity (34). Recently, DCs were shown to be negatively regulated by immunosuppressive invariant natural killer T cells (iNKT) in 4T1 mouse mammary tumors, and the selective elimination of DCs by iNKT immunosuppressive cells was shown (35). Here, priming of T cells to a tumor-specific CD8+ T-cell epitope in mice treated with radiotherapy and anti–CTLA-4 or anti-CD137 mAbs was markedly enhanced in INKt-−− compared with wild-type mice. These data suggest DCs play a critical role in the regulation of CD137-mediated CTL activation by enhancing costimulation.

NK cells. NK cells (CD3-CD56− cells) initiate innate immune responses toward tumor and virus-infected cells (36, 37). One of the primary mechanisms of antitumor activity of mAbs is antibody-dependent cell-mediated cytotoxicity (ADCC), whereby NK cells bearing an Fc receptor (CD16) bind to the antibody-targeted tumor cell and mediate tumor cell lysis. CD137 was also detected on NK cells. It was reported that selective depletion of NK cells in mice by the anti-AsialoGM1 or anti-NK1.1 antibodies completely abrogated the antitumor effect of anti-CD137 mAb, implying an immunoregulatory function of CD137 on NK cells (30, 38). Expression of CD137 on NK cells increases significantly when NK cells encounter mAbs bound to tumor cells (39–41). Anti-CD137 mAbs potenti ated the antitumor activity of anti-CD20 and anti-HER2 (also known as ERBB2) mAbs in the mouse models of lymphoma and breast cancer, respectively. We reasoned that the addition of an agonistic mAb against CD137 would further stimulate activated NK cells and result in enhanced ADCC toward a mAb bound to tumor cells (17). Therefore, combination therapy of anti-CD137 mAb with mAbs targeting tumor-associated antigens is an appealing strategy.

Preclinical Studies of CD137 Antibody

Antitumor efficacy was also observed in several tumor models, such as MCA205 sarcoma, MC38 colon carcinoma, GL261 glioma, TC1 carcinoma, J558 myeloma, and A549 human alveolar adenocarcinoma cell lines (16). However, anti-CD137 mAb monotherapy did not eradicate some poorly immunogenic tumors, namely C3 tumor and B16/D5 melanoma (23, 42). To improve the therapeutic efficacy of anti-CD137 mAbs, several combination therapies were investigated.

Combination with other immunomodulators

Overcoming regulatory mechanisms of T cells can enhance antitumor responses. For example, PD-1, CTLA-4, T-cell immunoglobulin mucin-3 (TIM-3; also known as HAVCR2) and lymphocyte activation gene 3 (LAG-3; also known as CD223) negatively regulate T-cell function, whereas CD137, OX40, and CD40 provide costimulation (7). Combination therapies can potenti ate T cell–based cancer immunotherapy (Table 2). Agonistic CD137 mAbs with anti–CTLA-4 or anti-CD40 mAbs increased the survival of mice injected with MC38 murine colon cancer cells (43, 44). Uno and colleagues (45) reported that an agonistic mAb to death receptor 5 (DR5; also known as TNFRSF10B), the apoptosis-inducing receptor for TNF-related apoptosis-inducing ligand, combined with agonistic mAbs to the costimulatory molecules CD40 and CD137, rapidly stimulated tumor-specific effector CD8+ T cells that led to eradication of preestablished tumors. This combination was named “trimAb.” In addition to trimAb, the effects of anti–CTLA-4 mAb, anti–glucocorticoid-induced TNF-receptor mAb, or anti–PD-1 mAb were examined (46). Blockade of CTLA-4-mediated signals by an antagonistic mAb substantially further stimulated tumor regression.
increased the tumor rejection rate of trimAb therapy, although the immune responses of draining lymph node cells were not augmented. Anti-DR5 and anti-CD1d mAb with anti-CD137 mAb (1DMab therapy) were also reported to show enhanced effectiveness (47). Interestingly, 1DMab therapy was more effective than trimAb therapy with anti-CTLA-4 mAb (45). Remarkably, combination of anti-DR5 and anti-CD1d mAb with anti-CD137 increased the tumor rejection rate of trimAb therapy, although Tregs were critical. Simultaneous dual costimulation after surgical resection of subcutaneous tumors. Similarly, immunizations in combination with the costimulatory agonistic anti-CD137 mAb significantly enhanced the immune responses in Her-2/neu mice, resulting in complete tumor rejection (53). Using vaccines that stimulate a broad immune responses induced by tumor lysate–pulsed DC (TP-DC) vaccinations. Combined therapy with TP-DC plus anti-CD137 mAb resulted in lower local recurrence rates and improved survival after surgical resection of subcutaneous tumors. Similarly, immunizations in combination with the costimulatory agonistic anti-CD137 mAb significantly enhanced the immune responses in Her-2/neu mice, resulting in complete tumor rejection (53). Using vaccines that stimulate a broad immune response in combination with costimulatory molecules could significantly improve the antitumor immune response in tolerant hosts. CpG vaccination and oncolytic viruses, as well as adoptive transfer of tumor-specific CTLs, were also potentiated by agonistic anti-CD137 mAb (54–57). Thus, agonistic anti-CD137 mAb can modulate immune responses to several vaccinations and enhance antitumor efficacy.

**Combination with vaccination**

DCs can be pulsed with tumor-associated antigens by a variety of methods that result in the ability of DCs to prime naive T cells, and DCs can mediate regression of established tumor when given as a vaccine in animal models (Table 2). Ito and colleagues (33) and Lee and colleagues (52) examined the role of anti-CD137 administration in modulating the immune responses induced by tumor lysate–pulsed DC (TP-DC) vaccinations. Combined therapy with TP-DC plus anti-CD137 mAb resulted in lower local recurrence rates and improved survival after surgical resection of subcutaneous tumors. Similarly, immunizations in combination with the costimulatory agonistic anti-CD137 mAb significantly enhanced the immune responses in Her-2/neu mice, resulting in complete tumor rejection (53). Using vaccines that stimulate a broad immune response in combination with costimulatory molecules could significantly improve the antitumor immune response in tolerant hosts. CpG vaccination and oncolytic viruses, as well as adoptive transfer of tumor-specific CTLs, were also potentiated by agonistic anti-CD137 mAb (54–57). Thus, agonistic anti-CD137 mAb can modulate immune responses to several vaccinations and enhance antitumor efficacy.

**Combination with mAb therapy targeting tumor antigens**

One of the primary mechanisms of antitumor activity of mAbs is ADCC (58). Kohrt and colleagues (39) demonstrated that an anti-CD137 agonistic mAb enhances the antitumor
activity of therapeutic mAbs rituximab, trastuzumab, and cetuximab by enhancing ADCC (Table 2). In addition, human NK cells upregulate CD137 after encountering mAbs and tumor cells in vitro and in patients, and subsequent stimulation of these NK cells with anti-CD137 mAb enhances mAb-dependent cytotoxicity against tumor cells (41). Therefore, sequential administration of therapeutic antibodies and CD137 mAb with a 24-hour gap would be better than concurrent administration. Stagg and colleagues (59) also reported interesting results showing that not only anti-CD137 mAb but also anti–PD-1 mAb enhanced the antitumor activity of a Her2-targeting mAb in mice. In a clinical trial, a combination therapy of anti–PD-1 mAb with rituximab achieved a 66% objective response rate in patients with relapsed follicular lymphoma who were previously treated with rituximab (60). This strongly suggests that combination of immunomodulators, including anti-CD137 mAbs, with tumor targeting mAbs can enhance the clinical efficacy of therapeutic antibodies (61).

**Clinical Trials of CD137**

Two fully humanized mAbs of CD137, urelumab (BMS-663513) and PF-05082566, have been developed for clinical use. Urelumab is a fully human IgG4 mAb developed by Bristol-Myers Squibb, and PF-05082566 is a fully human IgG2 mAb developed by Pfizer. They are agonistic mAbs, which bind to the extracellular domain of human CD137. Clinical trials of anti-CD137 mAbs are summarized in Table 3.

**Urelumab (BMS-663513)**

The NCT00309023 study was a first-in-human open-label, ascending, multidose phase I–II trial conducted in patients with locally advanced or metastatic solid tumors (62). In the dose-escalation phase of the study, patients were sequentially assigned to one of six dose cohorts (0.3–15 mg/kg) to receive urelumab once every 3 weeks. Eighty-three patients (54 melanoma, 15 renal cell carcinoma, 13 ovarian, and 1 prostate) have been treated. Dose-limiting toxicities were reported in the 0.3-mg/kg (grade 3 neutropenia) and 15-mg/kg (grade 4 neutropenia) cohorts. Overall, fatigue (all, 26%; grade 3–4, 3%), reversible grade 3–4 transaminitis (11%), and grade 3–4 neutropenia (5%) were the most common agent-related adverse events. Three partial response and 4 stable disease cases occurred at all three doses tested in expansion cohorts. Preliminary biomarker analysis demonstrated increased expression of IFN-inducible genes in peripheral blood, serum neopterin levels, and percentage of circulating activated CD8+ and CD4+ T cells following a single treatment. These data suggest that urelumab was tolerable across a wide dose range (0.3–15 mg/kg). Based on the phase I study, a randomized, multidose, open-label, phase II study of urelumab as a second-line monotherapy was designed in the patient with metastatic melanoma. However, the study was terminated in May 2009 due to fatal hepatotoxicity. The mechanism of anti-CD137 mAb-induced hepatotoxicity remains unclear, although the relationship between the CD137 pathway and hepatotoxicity was suspected (50, 63, 64). Therefore, careful dosing of anti-CD137 mAb is needed to avoid the risk for severe hepatotoxicity.

Following the first clinical trial, several combination therapies with chemotherapy (NCT00351325), chemoradiation (NCT00461110), ipilimumab (NCT00803374), rituximab (NCT01775631; ref. 65), cetuximab (NCT02110082), and elotuzumab (NCT02252263) have been launched as phase I or I/II studies. We have initiated a biomarker study (NCT01471210) using the novel technology of mass cytometry time of flight (66, 67). Preliminary findings from 4 patients showed an increase in CD8+ T cells and NK cells with a decrease in CD4+ T cells and regulatory CD4+ T cells. These preliminary data are consistent with anti-CD137 agonist. Although the studies (NCT00351325, NCT00461110, and NCT00803374) were terminated or withdrawn, low-dose therapies (<0.1 mg/kg) of urelumab in combination with approved mAbs are worthy of attention.

**PF-05082566**

Clinical trials of PF-05082566 are also ongoing. NCT01307267 is an open-label, dose-escalation study that was conducted in patients with advanced malignancies, and the preliminary data were reported (68). Cohorts of 3 to 6 patients were enrolled initially using a 3+3 design (0.006–0.3 mg/kg), then a time-to-event continual reassessment method design for higher doses (0.6–5 mg/kg). Patients received PF-05082566 via i.v. infusion every 4 weeks (1 cycle) with an 8-week period for assessment of

**Table 3. Clinical trials of anti-CD137 agonistic mAbs**

<table>
<thead>
<tr>
<th>NCT number</th>
<th>Phase</th>
<th>Condition</th>
<th>Combination</th>
<th>Start year</th>
<th>Status (May 2015)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT00309023</td>
<td>I/II</td>
<td>Metastatic or locally advanced solid tumors</td>
<td>—</td>
<td>2005</td>
<td>Terminated</td>
</tr>
<tr>
<td>NCT00351325</td>
<td>I</td>
<td>Advanced solid malignancies</td>
<td>Chemotherapy</td>
<td>2007</td>
<td>Terminated</td>
</tr>
<tr>
<td>NCT00461110</td>
<td>I</td>
<td>Non-small cell lung cancer</td>
<td>Chemoradiation</td>
<td>2008</td>
<td>Terminated</td>
</tr>
<tr>
<td>NCT0062664</td>
<td>II</td>
<td>Melanoma</td>
<td>—</td>
<td>2008</td>
<td>Completed</td>
</tr>
<tr>
<td>NCT00803374</td>
<td>I</td>
<td>Advanced malignant melanoma</td>
<td>Ipilimumab (anti–CTLA-4 mAb)</td>
<td>2010</td>
<td>Withdrawn</td>
</tr>
<tr>
<td>NCT01471210</td>
<td>I</td>
<td>Advanced and/or metastatic solid tumors</td>
<td>—</td>
<td>2012</td>
<td>Recruiting</td>
</tr>
<tr>
<td>NCT01775631</td>
<td>I</td>
<td>Relapsed/refractory B-cell NHL</td>
<td>Rituximab (anti–CD20 mAb)</td>
<td>2013</td>
<td>Recruiting</td>
</tr>
<tr>
<td>NCT02010082</td>
<td>I</td>
<td>Colorectal cancer, head and neck cancer</td>
<td>Cetuximab (anti–EGFR mAb)</td>
<td>2014</td>
<td>Recruiting</td>
</tr>
<tr>
<td>NCT02252263</td>
<td>I</td>
<td>Multiple myeloma</td>
<td>Elotuzumab (anti–CS1 mAb)</td>
<td>2014</td>
<td>Recruiting</td>
</tr>
<tr>
<td>NCT02253992</td>
<td>I</td>
<td>Advanced solid tumors, advanced B-cell NHL</td>
<td>Nivolumab (anti–PD-1 mAb)</td>
<td>2014</td>
<td>Recruiting</td>
</tr>
<tr>
<td>NCT02420938</td>
<td>II</td>
<td>Relapsed/refractory/high-risk untreated chronic lymphocytic leukemia</td>
<td>Rituximab (anti–CD20 mAb)</td>
<td>2015</td>
<td>Not yet recruiting</td>
</tr>
<tr>
<td>NCT00351325</td>
<td>I</td>
<td>CD20-positive NHL</td>
<td>Rituximab (anti–CD20 mAb)</td>
<td>2011</td>
<td>Recruiting</td>
</tr>
<tr>
<td>NCT02179998</td>
<td>I</td>
<td>Advanced solid tumors</td>
<td>MK-3475 (anti–PD-1 mAb)</td>
<td>2014</td>
<td>Recruiting</td>
</tr>
</tbody>
</table>

**Abbreviation:** NHL, non-Hodgkin lymphoma.
dose-limiting toxicity (DLT). Twenty-seven patients have been treated with PF-05082566 up to the 0.3-mg/kg dose level, including 11 with colorectal cancer, 6 with Merkel cell carcinoma, and 2 with pancreatic adenocarcinoma. Twenty-five patients completed the DLT assessment period and 7 patients remain on therapy. All discontinuations from treatment were due to disease progression. One patient treated at 0.06 mg/kg had grade 3 elevation in alkaline phosphatase. No additional significant elevations in liver enzymes and no DLTs have occurred to date. The best overall response of stable disease was observed in 22% (6 of 27) patients. These results suggest that PF-05082566 was well tolerated, with evidence of disease stabilization in multiple patients.

Combination with anti–PD-1 mAbs

In 2014, one of the most interesting combination therapies with anti–CD137 mAbs is with nivolumab or MK-3475 (anti–PD-1 mAbs) for patients with advanced solid tumors or advanced B-cell non-Hodgkin lymphoma. The safety and tolerability of urelumab administered in combination with nivolumab is being assessed in a phase I/II dose-escalation and cohort expansion study (NCT02253992). Nivolumab and urelumab were administered every 3 weeks and every 2 weeks up to 12 cycles and every 4 weeks up to 3 cycles, respectively. NCT02179918 is a phase Ib study of PF-05082566 in combination with MK-3475. Both agents are administered every 3 weeks. A preclinical study indicated that combination of anti–CD137 and anti–PD-1 mAbs enhanced hepatic toxicity, compared with one of the agents alone (50). Although this combination has potential for good efficacy, its toxicity should be evaluated in humans.

Conclusions

More than 20 years have passed since the identification of CD137 as an immune modulator (18). One of the most promising findings is the anticancer efficacy of agonistic anti–CD137 mAb (20). The strong preclinical successes underscore the importance of CD137 in cancer therapy, especially in combination therapy. Several clinical trials of urelumab (BMS-663513) had been terminated or withdrawn, because of hepatitis. However, clinical trials of combination therapies using low-dose urelumab with rituximab, cetuximab, and anti–PD-1 mAbs have been launched. In addition, another anti–CD137 mAb, PF-05082566, has been developed. We believe anti–CD137 mAbs hold great clinical promise. Their clinical potential should be tested in conjunction with other FDA-approved immunomodulators and antibody therapeutics. It is anticipated that combination cancer immunotherapy with CD137 will make significant contributions to the field of cancer immunotherapy.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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