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Ticilimumab

Prop INN

Anti-CTLA-4 Antibody
Oncolytic

Tremelimumab (USAN)
CP-675206

Immunoglobulin G_2, anti-(human CTLA-4 [antigen]) (human monoclonal CP-675206 clone 11.2.1 heavy chain) disulfide with human monoclonal CP-675206 clone 11.2.1 light chain, dimer

Immunoglobulin G_2, anti-(human cytotoxic T-lymphocyte protein 4 [CD152 antigen]) (human monoclonal CP-675206 clone 11.2.1 heavy chain) disulfide with human monoclonal CP-675206 clone 11.2.1 light chain, dimer

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Abstract

Ticilimumab (tremelimumab, CP-675206), a fully human IgG_2 monoclonal antibody targeting CTLA-4, has been developed to boost the body's immune system to target tumor cells. Ticilimumab showed antitumor activity and an acceptable safety profile in preclinical studies. Phase I clinical trials demonstrated that it can be safely administered to patients with advanced melanoma at up to 15 mg/kg i.v. Dose-limiting toxicities and autoimmune phenomena included diarrhea, dermatitis and hypothyroidism. Antitumor responses in patients with melanoma who received ticilimumab were attributed to improved T-cell immunity. Clinical trials are ongoing in melanoma, renal cell carcinoma, colorectal adenocarcinoma and non-small cell lung cancer (NSCLC).

Background

CTLA-4 (CD152) is a type I transmembrane protein expressed by activated T-lymphocytes and monocytes, which is crucial for the maintenance of immunological tolerance. Following T-cell activation through the T-cell receptor (TCR), a second co-stimulatory signal involves an interaction between B7 (CD80/CD86) molecules on antigen-presenting cells (APCs) and CD28 on T-cells. Once activated, the T-cells express another receptor, CTLA-4, that competes with CD28 for binding to B7 molecules, thereby inhibiting T-cell responses and the immune response. Preclinical studies have demonstrated that CTLA-4 knockout mice develop fatal lymphoproliferative disease, and blockade of CTLA-4 led to enhanced T-cell responses, autoimmunity and tumor rejection (1-15).

Clinical study results with the human anti-CTLA-4 antibody MDX-010 (ipilimumab; Medarex, Bristol-Myers Squibb) demonstrated antitumor activity and the development of autoimmune toxicity when given in combination with tumor vaccines in patients with melanoma (16-18). Ticilimumab (tremelimumab, CP-675206) is another fully human IgG_2 monoclonal antibody specifically targeting CTLA-4, developed using the former Abgenix's (now Amgen) XenoMouse® antibody generation technology, that enhances T-cell activation *in vitro* (19). Ticilimumab is currently in phase III clinical development for the treatment of advanced melanoma; phase I trials for the treatment of renal cancer and phase II trials for the treatment of non-small cell lung cancer (NSCLC) and colorectal cancer are also under way.

Preclinical Pharmacology

In vitro experiments demonstrated that ticilimumab potently and selectively binds to human and monkey CTLA-4-Ig, with over 500-fold less affinity for human CD28-Ig, B7.2-Ig and IgG_1, and no affinity for human Fc receptors. It also inhibited the binding of human CTLA-4-Ig to B7 molecules with IC_{50} values of 0.50-0.65 nM. Although by itself it had no effect on cytokine release, it induced IL-2 and interferon gamma production in stimulated human T-cell blasts (19). Ticilimumab was also shown to concentration-dependently enhance superantigen-stimulated IL-2 production in human and monkey whole blood and peripheral blood mononuclear cells (PBMCs). This effect was similar in samples from normal subjects and cancer patients and independent of cancer type or stage (19-21).

Pharmacokinetics

The pharmacokinetics of ticilimumab were examined in a phase I trial in 39 patients with solid tumors, including 34 with melanoma. Following a single i.v. infusion at doses of 0.01-15 mg/kg, ticilimumab demonstrated a biphasic pharmacokinetic profile. The plasma concentrations and AUC increased dose-proportionally. The antibody displayed a long terminal half-life (22.1 days), low

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clearance (0.132 ml/h/kg) and a small volume of distribution (81.2 ml/kg). Efficacy (see below) was strongly associated with systemic exposure to the agent. Most patients responding to ticilimumab showed plasma levels at 4 weeks above 30 μg/ml, the target concentration according to preclinical studies (22).

Safety

In the above study, dose-limiting toxicity of diarrhea and dermatitis occurred in 3 of 6 patients at the highest dose, and the maximum tolerated dose (MTD) was therefore considered to be 10 mg/kg. Vitiligo, autoimmune thyroiditis, hypothyroidism and panhypopituitarism were also reported (22).

The safety profile of ticilimumab was further evaluated in another dose-finding phase I trial in patients with advanced melanoma. Fourteen patients received the antibody at a dose of 3 (n=3), 6 (n=3) or 10 mg/kg (n=8) monthly. Grade 2 treatment-related adverse events included dermatitis, pruritus, diarrhea, hypothyroidism, urticaria and myalgia. Three patients experienced grade 3 diarrhea (2 on 10 mg/kg and 1 on 3 mg/kg), but no grade 4 adverse events were reported. One patient on the highest dose showed a response which was associated with intratumoral cytotoxic T-lymphocyte (CTL) infiltration and this dose was recommended for phase II testing (23, 24).

Clinical Studies

The phase I trial in 39 patients with solid tumors also examined the antitumor activity of ticilimumab. At the time of reporting, 2 patients with melanoma had achieved a complete response and 2 others had partial responses; 4 patients had stable disease and 5 patients experienced extended progression-free survival after local treatment of progressive metastases. No relapses were noted, and although 10 mg/kg was defined as the MTD, higher doses/plasma levels were associated with greater antitumor activity (22).

Data from a phase I trial of single doses of 0.01, 0.1, 1, 3, 6, 10 and 15 mg/kg (22) and a phase I/II study of multiple doses of 3, 6 and 10 mg/kg monthly (phase I) (23, 24) and 10 mg/kg once monthly or 15 mg/kg every 3 months (phase II) were used to select the dose/schedule of ticilimumab for patients with metastatic melanoma. Although the dose of 10 mg/kg was considered to be the MTD in the former trial, the higher dose was also associated with significant clinical activity and toxicity resolved within 3 months, which led to the inclusion of this dose in the phase II trial. As the dose of 10 mg/kg once monthly proved to be safe in the phase I portion of the phase I/II trial, it was also included in the phase II part of the study. Preliminary results from the phase II study in 18 patients showed a similar response rate for both doses, but 15 mg/kg every 3 months was better tolerated (25).

The safety, pharmacokinetics, immunostimulatory and clinical activity of ticilimumab were also evaluated in two phase I trials (22-24) in 53 patients with solid malignancies. Ticilimumab proved safe and was well tolerated overall. Of the 43 patients with measurable melanoma, 18 achieved long-term survival and 5 had an objective response. Among the patients who did not achieve an objective response, 5 had surgical resection of metastatic lesions and remained relapse-free at the time of reporting (26).

To elucidate the antitumor mechanisms of ticilimumab in patients with malignant melanoma, biological and immunomodulatory events after CTLA-4 blockade with ticilimumab were examined in patients who participated in multiple-dose phase I/II clinical trials. Thirty patients who received ticilimumab at a dose of 10 mg/kg every month (n=20) or 15 mg/kg every 3 months (n=10) were evaluated at study entry and at 14-day intervals thereafter. Lymphocyte immunophenotypes and IL-2 and IL-10 production were evaluated, and the expression of T-regulatory-related genes in PBMCs was studied. Four of 12 patients with immune-related adverse events achieved objective antitumor responses, while only 1 of 18 patients without immune-related adverse events achieved an objective antitumor response. Antitumor responses were found to be associated with reductions in T-regulatory cells and constitutive IL-10 production, an increase in IL-2 production and a positive correlation between transcripts of CTLA-4 and glucocorticoid-induced tumor necrosis factor receptor (TNFR) (27, 28).

Data from the first clinical study of ticilimumab in patients with melanoma were used to examine potential determinants of clinical activity. Results suggested that prior treatment with a MART-1 peptide vaccine appeared to enhance the activity of the antibody (29).

Phase II trials of ticilimumab in patients with refractory metastatic colorectal adenocarcinoma and NSCLC are in progress (30, 31). Pfizer is also sponsoring a multinational, open-label, randomized phase III study to compare the efficacy in terms of overall survival of ticilimumab with dacarbazine or temozolomide in patients with surgically incurable melanoma who have not received prior chemotherapy or biochemotherapy. The study is currently recruiting patients (32). Furthermore, a phase I dose-escalation trial is evaluating the safety and efficacy of ticilimumab combined with sunitinib in patients with treatment-naïve metastatic renal cell carcinoma (33), and another open-label phase I study is evaluating the safety and immune effects of ticilimumab in combination with MART-1 peptide-pulsed dendritic cells in patients with advanced melanoma (34).

Source

Pfizer, Inc. (US).

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