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Galiximab

Rec INN; USAN

Primatized Anti-CD80 Monoclonal Antibody Treatment of Non-Hodgkin's Lymphoma

Anti-B7.1 MAb
IDEC-114

Immunoglobulin G_1, anti-(human CD80 [antigen]) (human-*Macaca irus* monoclonal IDEC-114 heavy chain), disulfide with human-*Macaca irus* monoclonal IDEC-114 λ-chain, dimer

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Abstract

CD80 (B7-1) is an important co-stimulatory molecule expressed on a variety of lymphoma cells. Galiximab, a primatized anti-CD80 monoclonal antibody, exerts antitumor activity *in vitro* via antibody-dependent cell-mediated cytotoxicity. Originally evaluated for use in the treatment of psoriasis, galiximab was subsequently tested in patients with lymphoma and showed a favorable safety profile and promising biological activity. Combination of galiximab and rituximab produced enhanced antitumor activity *in vivo* and in the clinic. Phase III trials are being conducted in combination with rituximab in non-Hodgkin's lymphoma (NHL).

Background

According to the National Cancer Institute (NCI), the incidence of non-Hodgkin's lymphoma (NHL) has nearly doubled over the past 30 years. It is estimated that nearly 360,000 Americans are currently living with NHL and approximately 63,190 new cases of NHL are expected to occur in the United States alone in 2007. Despite advances in cancer research and drug development, the treatment of lymphoma remains challenging because of the relatively high relapse and refractory rates associated with the disease (1, 2).

CD80 (B7-1) is a co-stimulatory molecule that plays key roles in regulating T-cells, as well as normal and malignant B-cell activity. CD80 and CD86 (B7-2) activate T-cells by binding to their receptor CD28, expressed constitutively on unstimulated T-cells and T-cells in psoriatic lesions. Following T-cell activation, CD152 (CTLA-4, or cytotoxic T-lymphocyte-associated antigen), a high-affinity CD80/CD86 counter-receptor, is expressed and CD80 or CD86 binding to CD152 leads to downregulation of T-cell activation, thereby counteracting the co-stimulation mediated by CD28. As persistent T-cell activation has been suggested to be involved in the pathophysiology of psoriasis, the co-stimulatory pathway, particularly CD80, was proposed as a promising therapeutic target for psoriasis. Due to the fact that it is expressed transiently on activated B-cells and constitutively on a variety of B-cell lymphomas, including follicular lymphoma, CD80 is also an attractive target for B-cell lymphoma therapy (3-13).

Galiximab (IDEC-114) is a primatized anti-CD80 IgG_1 monoclonal antibody with primate (cynomolgus monkey) variable regions and human IgG_1 constant regions. The agent was developed at Biogen Idec using its PRIMATIZED® antibody technology to decrease immunogenicity. Galiximab is currently in phase III clinical development for the treatment of relapsed or refractory follicular NHL. The agent was previously evaluated for its potential in the treatment of psoriasis, but its development for this indication was not further pursued based on phase II efficacy data.

Preclinical Pharmacology

The antitumor activity of galiximab alone or in combination with rituximab was evaluated *in vitro* and *in vivo*. *In vitro*, galiximab killed the CD80- and CD20-positive B-cell lymphoma cell lines SB and SKW via antibody-dependent cell-mediated cytotoxicity (ADCC), and combination of galiximab and rituximab was associated with enhanced cytotoxicity. The antitumor activity of galiximab at 100, 200 and 400 μg per injection was further evaluated *in vivo* using severe combined immunodeficient (SCID) mice implanted with human B-cell lymphoma xenografts. Galiximab demonstrated comparable antitumor activity to rituximab. Combination of galiximab and rituximab again demonstrated synergistic antitumor activity. Mice injected with 200 μg galiximab together with 200 μg rituximab had

Y. Wang. IBC, 8106 Runnymeade Dr., Frederick, MD 21702, USA. N. Mealy. Prous Science, P.O. Box 540, 08080 Barcelona, Spain.

a significantly greater disease-free survival than mice administered either agent alone (200 or 400 μg each) (14-16).

The *in vivo* efficacy of galiximab alone or in combination with other agents, such as fludarabine or doxorubicin, was further evaluated using murine s.c. Raji and disseminated SKW lymphoma xenograft models. Similar studies were performed with rituximab. Both galiximab and rituximab at a dose of 3 mg/kg/week exhibited significant inhibition of tumor growth in the Raji model. Galiximab (3 mg/kg/week) combined with fludarabine (50 or 100 mg/kg/day for 5 days) showed significantly enhanced activity compared to either agent alone. Similar results were observed in animals treated with rituximab. Compared with controls or doxorubicin (2.5 mg/kg/day x 3), treatment with galiximab (5 mg/kg/week x 6) significantly enhanced survival in the SKW model (17).

Lenalidomide, a thalidomide analogue with immunomodulatory effects, also enhanced the antitumor effect of galiximab both *in vitro* and *in vivo*. *In vivo*, combination treatment with galiximab and lenalidomide led to prolonged survival (44 days) in SCID mice compared to either agent alone (18).

Pharmacokinetics and Metabolism

The preclinical pharmacokinetics/pharmacodynamics of galiximab were evaluated in chimpanzees. Eight chimpanzees received 5 weekly i.v. infusions of either formulation buffer or galiximab (3, 10 or 30 mg/kg). Pharmacokinetic analysis indicated that the peak plasma levels (C_{max}) and area under the curve (AUC) for galiximab increased in a dose-proportional manner. The serum half-life ($t_{1/2}$) of galiximab ranged from 247 to 431 h. Galiximab did not affect the absolute numbers or relative percentages of $CD4^-$, $CD8^-$ or $CD20^+$ lymphocytes (19).

The pharmacokinetics of galiximab in patients with moderate to severe psoriasis were examined in a phase I/II clinical trial. The serum $t_{1/2}$ of galiximab was approximately 13 days in patients treated with single i.v. infusions (5-15 mg/kg). Mean C_{max} and AUC were both dose-proportional. No significant differences were observed in either clearance rate or volume of distribution among dose groups (20, 21). A multiple-dose (2.5-15.0 mg/kg once weekly or every 2 weeks x 4) phase I/II study in 35 patients with moderate to severe psoriasis also assessed the pharmacokinetics of galiximab. The C_{max} and AUC were proportional to dose and the half-life was 14-19 days; clearance was 0.11-0.12 ml/h/kg and the volume of distribution was 56-66 ml/kg (22).

Two multiple-dose phase II trials in a total of 228 patients with moderate to severe psoriasis treated with galiximab 1-5 mg/kg weekly x 8, 10 mg/kg every other week x 8, 15 mg/kg monthly x 4 or placebo also included pharmacokinetic analysis. The mean C_{max} and AUC were, again, dose-proportional. The median serum $t_{1/2}$ was approximately 15 days (23).

The clinical pharmacokinetics of galiximab in patients with relapsed or refractory follicular lymphoma were assessed in a multicenter, dose-escalating phase I/II study. Results indicated dose-proportional increases in C_{max} and AUC, with mean values for C_{max} of 149.8, 302.1, 501.2 and 709.1 μg/ml, respectively, following doses of 125, 250, 375 and 500 mg/m^2 by weekly i.v. infusion x 4, and mean AUC values of 4086, 7499, 20,851 and 26,613 μg.day/ml, respectively. Peak plasma levels were reached (t_{max}) in a mean of 18.7-21.0 days and the mean serum $t_{1/2}$ was 13-24 days (24-27). Similar results emerged from a phase I/II study evaluating galiximab (125-500 mg/m^2/week x 4) combined with rituximab (375 mg/m^2/week x 4) in patients with relapsed or refractory follicular NHL. Again, C_{max} and AUC for galiximab were dose-proportional and the mean half-life was 25.7 days. Combination therapy did not appear to alter the pharmacokinetics of galiximab (28-31). Pharmacokinetic parameters were found to be affected by body surface area and gender (32).

Safety

Single i.v. infusions of galiximab of 0.05-15 mg/kg were well tolerated in patients with moderate to severe psoriasis. Treatment-related adverse events (AEs) were generally mild and transient, and nearly one-third of treatment-related AEs occurred on infusion days. The most common AEs included asthenia (29%), chills (25%), headache (25%), dizziness (17%), fever (13%) and infection (13%). No serious AEs were reported (20, 21).

Multiple-dose galiximab was also well tolerated in patients with moderate to severe psoriasis. Overall, 26 (74%) of the 35 evaluable patients experienced AEs, the most common including infection (29%), pruritus (17%) and chills (11%). Other AEs included asthenia, fever, pain, dizziness and rhinitis. The majority of the reported AEs (77%) were grade 1. Anti-galiximab antibodies were not observed. Mean peripheral blood $CD3^+$, $CD4^+$ and $CD19^+$ lymphocyte counts fluctuated within the normal range and blood chemistry values also remained within the normal range for most patients (22).

The safety of galiximab was also explored in the phase I/II study in patients with relapsed or refractory follicular lymphoma (24-27). Twenty-two (60%) of 37 patients experienced drug-related AEs, most of which were grade 1 or 2, the most common being fatigue, nausea and headache. One patient experienced anemia and febrile neutropenia, which were not related to galiximab and resolved after treatment. No patient developed anti-galiximab antibodies.

When combined with rituximab, galiximab at doses of 125-500 mg/m^2 also proved to be safe and well tolerated in patients with relapsed or refractory lymphoma. The majority of AEs were grade 1 or 2, and most were mainly observed on infusion days. In the phase I part of the study, all 12 patients completed the treatment without any serious AEs and no patient experienced dose-limiting toxicity. The most common AEs included rigors, nausea and fatigue (28). In the phase II part of the study, 61 (95%) patients experienced treatment-related AEs, with the

most common events including lymphopenia (44%), leukopenia (38%), fatigue (38%), neutropenia (23%) and chills (23%). Toxicity was similar to that reported for rituximab alone (30, 31).

Clinical Studies

The activity of galiximab in the treatment of psoriasis was first evaluated in an open-label, single-escalating-dose study. Twenty-four patients received a single i.v. infusion of galiximab (0.05-15 mg/kg). Patients in the 10 mg/kg dose group achieved the greatest improvement in terms of Psoriasis Area and Severity Index (PASI) scores, with the mean total PASI score improving 25% from baseline. Patients in the 0.05, 0.25, 1 and 15 mg/kg galiximab groups experienced 7%, 4%, 4% and 6% improvements in mean PASI scores, respectively, and no improvement was reported in patients receiving 5 mg/kg galiximab. Overall Physician's Global Psoriasis Assessment (PGA) ratings were also improved in the two higher dose groups: 80% of patients on 10 mg/kg had fair or better ratings by day 29 and 60% of patients on 15 mg/kg had fair or better ratings at either day 15 or day 29. Mean total Psoriasis Severity Scores (PSSs) also improved in all but the lowest dose groups. The greatest improvement (32%) in PSS occurred on 10 mg/kg. In addition, the average thickness of plaque biopsy specimens was reduced and intralesional T-lymphocytes decreased after treatment with galiximab (20, 21).

To further evaluate the potential clinical activity of galiximab in the treatment of psoriasis, a multicenter, open-label phase I/II study was conducted evaluating multiple doses and different schedules (22). A total of 35 patients with moderate to severe plaque psoriasis were divided into 7 cohorts (5 patients in each cohort) and received i.v. galiximab as an outpatient treatment. Fourteen (40%) of the 35 patients achieved a clinical endpoint of a 50% or greater reduction in PASI during the study period. Twenty (57%) of 35 patients achieved a PGA rating of good or above and 7 (20%) patients achieved a PGA rating of excellent. A decrease in the mean total PSS was observed in all dose groups by day 15, and the mean total PSS decreased from 7.6 at baseline to 5.0 on day 127. Patients continued to benefit from the treatment after the last dose. On day 127, 10 (29%) of the 35 patients achieved a reduction of 50% or greater in PASI, which was associated with a decrease in the $CD3^+$ cell count.

The potential use of galiximab in the treatment of psoriasis was further assessed in two randomized, double-blind, placebo-controlled phase II studies. A total of 228 patients with moderate to severe plaque psoriasis were randomized to receive i.v. infusions of galiximab (1, 2.5 or 5 mg/kg weekly for 8 weeks, 10 mg/kg every other week for 8 weeks or 15 mg/kg monthly for 4 months) or placebo. In these studies, patients on higher doses of galiximab experienced a greater response than those treated with lower doses of galiximab or placebo. However, the differences among the treatment groups were not statistically significant (23).

The efficacy of galiximab monotherapy in the treatment of lymphoma was examined in the multicenter, dose-escalating phase I/II trial in patients with relapsed or refractory follicular lymphoma (24-27). A total of 35 patients, the majority of whom had stage III or IV disease, received 4 weekly 1-h i.v. infusions of galiximab at a dose of 125-500 mg/m^2 in an outpatient setting. The overall response rate was 11% (4 responders), with 2 complete responses and 1 partial response. Three of the responders were in the 375 mg/m^2 dose group and 1 in the 500 mg/m^2 dose group. Time to best response occurred at 3, 6, 9 and 12 months, when serum concentrations of galiximab were near or below the limit of detection. Twelve patients (34%) had stable disease and about 50% of the patients showed a decrease in indicator lesions after galiximab treatment. The median time to progression for assessable patients was 1.7 months, but 2 patients remained on study without progression at 22 and 24.4 months.

A multicenter phase I/II clinical trial is evaluating the efficacy of galiximab combined with rituximab in patients with relapsed or refractory follicular lymphoma (33). In the phase I part of the study, all 12 patients completed the study treatment and reached their initial efficacy evaluation on day 50. Three patients achieved a complete response or an unconfirmed complete response, and 4 patients experienced a partial response (28). In the phase II part of the study, 64 patients received 500 mg/m^2 galiximab and 375 mg/m^2 rituximab once a week for 4 weeks. At 20.4 months' median follow-up, the overall response rate was 64%, including 17% complete responses, 16% unconfirmed complete responses and 31% partial responses. The median progression-free survival (PFS) was 12.1 months, which is higher than that achieved in patients on rituximab alone (9.4 months); median PFS was 15.4 months in rituximab-naïve patients. Univariate analysis indicated no correlation between response and baseline characteristics, although there were fewer responses in patients with elevated lactate dehydrogenase (LDH), a poor Follicular Lymphoma International Prognostic Index (FLIPI) score and grade 3 follicular histology (29-31).

Phase II and III studies of galiximab in combination with rituximab in patients with follicular NHL are in progress (34-36).

Source

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