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CP-751871

Human Anti-IGF-1R Monoclonal Antibody
Oncolytic

Fully human IgG_2 antibody to insulin-like growth factor type 1 receptor (IGF-1R)

CAS: 943453-46-1

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Abstract

CP-751871, generated using the former Abgenix's (now Amgen) XenoMouse® technology, is a fully human IgG_2 antibody with high binding affinity for the human insulin-like growth factor 1 receptor (IGF-1R). Combination of CP-751871 with doxorubicin, 5-fluorouracil or tamoxifen produced greater antitumor effects in xenograft models than any of the agents alone. CP-751871 (0.05-20 mg/kg) alone or combined with docetaxel or carboplatin and paclitaxel proved to be well tolerated in phase I studies. An interim analysis of a phase II study conducted in patients with non-small cell lung cancer (NSCLC) indicated that CP-751871 was safe and well tolerated alone or in combination with paclitaxel and carboplatin, with a greater percentage of patients treated with CP-751871 combined with paclitaxel and carboplatin obtaining an objective response compared to those treated with paclitaxel and carboplatin.

Background

Insulin-like growth factor 1 (IGF-1) and 2 (IGF-2) play important roles in the regulation of cell growth, differentiation and survival. The IGF-1 receptor (IGF-1R) is a tyrosine kinase receptor expressed on many tumor cells and is involved in mitogenesis, angiogenesis and tumor cell survival. Upon activation, IGF-1R activates the phosphatidylinositol 3-kinase (PI3K) pathway and protein kinase B (PKA/Akt), among other signaling pathways, and high serum levels of IGFs have been associated with an increased risk for cancer. Multiple independent approaches have demonstrated that inhibition of IGF-1R signals may be an effective approach to cancer therapy (1-5). Several strategies have been used to inhibit IGF-1R function, including antisense oligonucleotides (6-10), peptide analogues of IGF-1 (11), specific kinase inhibitors (12, 13) and monoclonal antibodies (14-16). However, no therapies targeting the IGF-1R are currently clinically available for the treatment of cancer.

CP-751871 is a fully human IgG_2 antibody generated using the former Abgenix's (now Amgen) XenoMouse® technology. The antibody potently inhibits IGF-1R and has demonstrated antitumor activity. Phase I, II and III clinical studies of CP-751871 alone and in combination with chemotherapeutic agents are currently under way.

Preclinical Pharmacology

CP-751871 exhibited high binding affinity for the extracellular domain of human IGF-1R, with a K_d of 1.5 nM, and it bound to the IGF-1R expressed on human, cynomolgus monkey and rhesus monkey cells with K_d values of 0.6, 0.5 and 0.6 nM, respectively. However, no binding to rat, dog, rabbit or marmoset receptors was observed. In NIH/3T3 cells overexpressing the IGF-1R, CP-751871 blocked the binding of IGF-1 to IGF-1R with an IC_{50} of 1.8 nM. *In vitro*, CP-751871 inhibited IGF-1-induced autophosphorylation of IGF-1R with an IC_{50} of 0.42 nM. Downregulation of IGR-1R by CP-751871 was observed in several cell lines, including NIH/3T3/IGF-1R and MCF7 human breast cancer cells, RPMI 8226 human multiple myeloma cells and human primary peripheral blood mononuclear cells (PBMCs). *In vivo*, IGF-1R downregulation was proportional to serum concentrations of CP-751871 (125 μg i.p.) in athymic mice bearing NIH/3T3/1GF-1R tumors. CP-751871 led to > 90% downregulation of IGF-1R at 24 h after administration, followed by an increase to 70% of control levels 48-72 h after administration, maintained for 7 days. CP-751871 given alone (31.25-125 μg i.p.) inhibited the growth of NIH/3T3/IGF-1R, MCF7, COLO 205 human colon adenocarcinoma and NCI-H460 human lung cancer xenografts in athymic mice, and combination with doxorubicin (7.5 mg/kg i.v.), 5-fluorouracil (100 mg/kg i.v.) or tamoxifen (3 mg/kg) resulted in enhanced antitumor activity compared to the agents alone (1, 17).

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CP-751871 (0.03 μg/ml) downregulated IGF-1R expression by more than 50% in both multiple myeloma cells and granulocytes isolated from patients (18).

Pharmacokinetics and Metabolism

Pharmacokinetic parameters of CP-751871 were first analyzed in cynomolgus monkeys, a species in which it shows similar affinity for IGF-IR as in humans. The C_{max} of CP-751871 ranged from 0.1 to 2.0 mg/ml after i.v. administration of 3-100 mg/kg and antibody concentrations increased almost linearly with dose. The systemic clearance was low (0.0065-0.0116 ml/min/kg), with an elimination $t_{1/2}$ of approximately 6 days (1, 17). In athymic mice bearing NIH/3T3/IGF-1R tumors administered a single dose of CP-751871 (125 μg i.p.), serum levels were 40 μg/ml at 24 h, decreasing to 20 μg/ml at 48-72 h after administration, with a $t_{1/2}$ of 4-6 days (1).

In the first-in-human phase I dose-escalation study, the pharmacokinetics of CP-751871 were evaluated in patients with multiple myeloma. Patients received CP-751871 at doses of 0.025-20 mg/kg by i.v. infusion, alone or in combination with oral dexamethasone and/or rapamycin, on day 1 of a 4-week cycle for up to 14 cycles. Plasma exposure of CP-751871 increased with dose and the pharmacokinetics were consistent with target-mediated disposition (19, 20). Similar findings were obtained in a trial in patients with advanced solid tumors treated with CP-751871 (0.05-10 mg/kg) plus tamoxifen (200 mg/m^2) and carboplatin (AUC6) every 3 weeks (21).

The pharmacokinetic parameters of CP-751871 (3, 6, 10 or 20 mg/kg) in patients with advanced solid tumors were analyzed in another dose-escalation study. Patients received CP-751871 on day 1 of each 21-day cycle, and the pharmacokinetic parameters were evaluated during cycles 1 and 4. Plasma concentrations and exposure increased dose-dependently. Following repeated administration, moderate accumulation was observed in most patients (22).

Using blood samples collected from patients treated with CP-751871 alone or in combination with chemotherapy in phase I trials, it was shown that exposure of CP-751871 increased with dose over the 800-fold dose range evaluated and the pharmacokinetic profile was consistent with target-mediated disposition (23).

Safety

In the initial phase I clinical trial of CP-751871 (0.025-20 mg/kg) conducted in patients with multiple myeloma, no dose-limiting toxicity (DLT) was observed. Grade 3 toxicity of hyperglycemia, anemia, aspartate aminotransferase (AST) increase and muscle weakness (1 case each) was seen on the highest dose (19, 20).

The safety and tolerability, in addition to the pharmacokinetics, of CP-751871 were further evaluated in the study in patients with advanced solid tumors administered CP-751871 (3, 6, 10 or 20 mg/kg i.v. on day 1 of each 21-day cycle). No DLT was observed and grade 3 toxicities at the highest dose were 1 case each of fatigue and arthralgia; the most common adverse events were hyperglycemia, anorexia, nausea, elevated AST, elevated γ-glutamyltransferase, diarrhea, hyperuricemia and fatigue (22, 24).

In another phase I study of CP-751871 (0.1-10 mg/kg) combined with docetaxel (75 mg/m^2) conducted in patients with advanced cancer, no CP-751871-related grade 3 or 4 adverse events were observed; docetaxel-related grade 3/4 neutropenia, neutropenic fever and diarrhea were reported. One patient experienced grade 2 hyperglycemia, which was considered possibly related to CP-751871 (25, 26).

Safety was also examined in an open-label phase Ib/II study in patients with advanced solid tumors. The phase Ib portion involved 30 patients, 23 with non-small lung cancer (NSCLC), who were treated with paclitaxel (200 mg/m^2), carboplatin (AUC6) and CP-751871 (0.05-10 mg/kg) every 3 weeks for up to 6 cycles, and the phase II study enrolled 73 patients with NSCLC to receive the triple combination or paclitaxel and carboplatin without CP-751871. No DLT was seen in the phase Ib study, although there was 1 case of grade 3 γ-glutamyltransferase elevation attributable to CP-751871, and grade 2 events included muscle pain, diarrhea, anemia, asthenia and orthostatic hypertension (21, 27, 28). In the phase II portion, grade 3/4 toxicities included hyperglycemia (20% on triple combination and 10% on paclitaxel + carboplatin), fatigue (15% and 8%, respectively), neutropenia (13% and 20%, respectively) and neuropathy (10% and 4%, respectively) (27-29).

Clinical Studies

In the first-in-human study in a total of 34 patients with multiple myeloma who had relapsed or were refractory to previous treatment, 2 remissions and 4 partial remissions were reported on therapy with CP-751871 (0.025-20 mg/kg by i.v. infusion on days 1 of 4-week cycles for up to 14 cycles) plus dexamethasone. Downregulation of IGF-1R and increase in circulating IGF-1 levels were seen at doses of CP-751871 of 1.5 mg/kg and above (19, 20).

Although no objective responses were seen in the phase I trial in 24 patients with advanced solid tumors treated with CP-751871 3-20 mg/kg by i.v. infusion on day 1 of 3-week cycles, 10 of 15 patients treated with the highest dose had disease stabilization (22, 24).

The efficacy of CP-751871 was also assessed in the phase I trial in combination with docetaxel in 27 patients with advanced cancer and in the phase II trial in 73 patients with NSCLC. In the phase I study, 7 of 21 castration-resistant prostate cancer patients had a confirmed partial response and 1 had an unconfirmed partial response, and there were 6 cases of disease stabilization for over 6 months. IGF-1R expression in circulating tumor cells was undetectable at CP-751871 doses > 3 mg/kg (25, 26). In the phase II study, an objective response was achieved by 22 of 48 patients (46%) on CP-751871 + paclitaxel + carboplatin and 8 of 32 (32%) on paclitaxel +

carboplatin; 1 of 4 patients treated with CP-751871 after progression on paclitaxel + carboplatin had a partial response (27-29).

Five phase I trials of CP-751871 alone and in combination with other agents are under way in patients with advanced NSCLC, breast cancer and solid tumors (30-34), as are 4 phase II trials of the antibody alone or in combination in patients with Ewing's sarcoma, refractory, metastatic colorectal cancer, hormone-refractory prostate cancer and advanced breast cancer (35-38), and a phase III study in combination with carboplatin and paclitaxel in patients with advanced NSCLC (39).

Source

Pfizer, Inc. (US).

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