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MONOGRAPH

GANITUMAB

Rec INN; USAN

Human Anti-CD221 (IGF-IR) Monoclonal Antibody

AMG-479

Immunoglobulin G, anti-(human insulin-like growth factor I receptor) (human monoclonal heavy chain), disulfide with human monoclonal light chain, dimer

Immunoglobulin G_1, anti-(human insulin-like growth factor 1 receptor (IGF-I receptor, EC 2.7.10.1, CD221)); human monoclonal γ1 heavy chain (222-219')-disulfide with human monoclonal κ light chain, dimer (228-228'':231-231'')-bisdisulfide

CAS: 905703-97-1

EN: 425140

SUMMARY

Ganitumab (AMG-479) is a fully human monoclonal IgG_1 antibody that binds insulin-like growth factor 1 receptor (IGF-I receptor) and is being evaluated in clinical studies as monotherapy and in combination with other agents. The IGF system ganitumab targets has been implicated in the risk of cancer in recent years, including evidence from epidemiological data, research in cancer models and knowledge of the downstream signaling pathways Ras/Raf/extracellular signal-regulated kinase (ERK)/mitogen-activated protein kinase (MAPK) and lipid kinase phosphatidylinositol 3-kinase (PI3K)/AKT, networks which are involved in cell proliferation and survival. As a result, various means of targeting the IGF-I receptor are being explored. Inhibition of IGF-I receptor activation by ganitumab has demonstrated oncolytic potential in vitro and in vivo, and the antibody has reached phase I clinical assessment in non-Hodgkin's lymphoma, phase I/II development for solid tumors, metastatic pancreatic cancer and small cell lung cancer, and phase II evaluation for soft tissue sarcoma, Ewing's sarcoma, neuroendocrine, ovarian, metastatic colorectal and breast cancer. A phase III study of the combination of ganitumab and gemcitabine in metastatic adenocarcinoma of the pancreas is under way, and numerous other trials of ganitumab alone or in combination with other therapies are presently ongoing.

PREPARATION*

A human Fab library (Target Quest Q Fab library), containing 3.7 x 10^{10} clones, is constructed using peripheral blood lymphocytes from four healthy donors and splenic lymphocytes from one patient with gastric carcinoma. The library is screened for anti-IGF-I receptor antibodies and the phagemid DNA mixtures of the selected phages are amplified. Then, the DNA is digested with AscI and EcoRI, obtaining a 2.1-kb fragment containing the heavy chains and a 3.9-kb fragment containing the light chains and a pCES1 vector portion. Both fragments are then ligated in a 3:1 ratio (2.1-kb fragment:3.9-kb fragment), precipitated and used to transform *Escherichia coli* TG1 cells by electroporation. The new library is then screened for IGF-I receptor binding affinity and the Fab selected corresponds to the L16H16 combination. After that, the DNA of the heavy variable region is amplified (PCR) and ligated into a plasmid encoding for the human IgG_1 constant region domain and the DNA of the light chain is cloned into an expression vector. Finally, both vectors are cotransfected in order to obtain stable lines expressing ganitumab (1).

BACKGROUND

Evidence has accumulated over many years implicating the insulin-like growth factor 1 receptor (IGF-I receptor) in oncological processes, but only recently have efforts been made to exploit the target for cancer therapies. In the intervening years, antibodies have come to be used therapeutically and tyrosine kinase receptors have come into focus as targets for treatment. The result is that several laboratories are currently testing strategies for interfering with the function or expression of the IGF-I receptor using antibodies directed against the extracellular portion of the receptor, small-molecule tyrosine kinase inhibitors specific for the receptor, molecules which interfere with ligand binding to the IGF-I receptor, antisense or small interfering RNA (siRNA) approaches to reduce receptor expression, dominant-negative IGF-I receptor affecting receptor activity, or agents that target downstream signaling pathways. It is also hoped that targeting the IGF-I receptor can increase the therapeutic efficacy of existing treatments, as experimental evidence indicates that the receptor may be involved in blocking the efficacy of other apoptosis-inducing agents and in the development of resistance to some therapies. Synergistic induction of apoptosis has been seen with IGF-I receptor inhibitors and compounds acting on other kinases (2).

The IGF system is involved in regulating growth and is part of a larger insulin-related signaling network involving three ligands (IGF-I, IGF-II and insulin) and at least four receptors (IGF-I receptor, IGF-II receptor, insulin receptor [IR] and hybrid receptors). The IGF-I receptor is a transmembrane tyrosine kinase receptor found in normal tissues, which mediates IGF biological effects; the IGF-II receptor lacks

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intrinsic signaling activity and acts as a negative regulator of IGF activity through sequestration, endocytosis and degradation of IGF-II. The IGF-I receptor is activated by IGF-I and IGF-II, and the activation of the IGF-I receptor by IGF-I is associated with proliferation and inhibition of apoptosis. Various other lines of evidence implicate the IGF system in malignancy. Epidemiological studies have revealed links between insulin resistance and the risk for carcinomas affecting the breast, lung, prostate, colon and kidney. Genetic polymorphisms in genes encoding IGF-I and insulin-like growth factor-binding protein 3 (IGFBP-3) modulate cancer risk. Lifestyle factors such as obesity, physical activity and diet have been linked to cancer risk, and hyperinsulinemia, and decreased IGFBP-1 can result from excess energy balance. Hyperinsulinemia and low IGFBP-1 levels have also been associated with an increased risk of cancer occurrence, relapse and death. Growth rate during adolescence, mediated by increased IGF-I production, has also been associated with cancer risk. High circulating levels of IGF-I have been associated with an increased risk of various cancers, including breast, lung, head and neck, colorectal, pancreas, synovial sarcoma and prostate cancer. Over 20 years ago, the IGF-I receptor was detected in surgically resected tumor specimens, and an antibody targeting the receptor inhibited human breast cancer xenograft proliferation in vivo. Anti-IGF-I receptor treatments have shown antineoplastic activity in many in vitro and in vivo models of human cancers. There is also evidence that functional IGF-I receptors are necessary for transformation induced by oncogene activation, chemical carcinogens and other means (2-5).

IGF-I receptor ligand binding leads to stimulation of two important signaling pathways involved in cellular proliferation and survival: the Ras/Raf/extracellular signal-regulated kinase (ERK)/mitogen-activated protein kinase (MAPK) pathway and the lipid kinase phosphatidylinositol 3-kinase (PI3K)/Akt pathway (Fig. 1). Ligand binding to the IGF-I receptor leads to a conformational change and phosphorylation of the tyrosine kinase domain and subsequent activation of the binding sites of a series of docking proteins, including SHC-transforming protein and the IR substrates IRS-1 to IRS-4. These substrates initiate the PI3K/Akt and Ras/Raf/ERK/MAPK downstream signaling cascades. SHC-transforming protein binding to the juxtamembrane region of the IGF-I receptor activates ERK and 14-3-3 proteins binding to the *C*-terminus of the IGF-I receptor. Depending on the cellular context, downstream activation of the Ras/Raf/ERK/MAPK pathway affects cell growth, survival and differentiation. Phosphorylation of PI3K leads to increased phosphatidylinositol 3,4,5-trisphosphate (PIP_3), an effect inhibited by the tumor suppressor phosphatase and tensin homolog (PTEN) by conversion of PIP_3 to phosphatidylinositol 4,5-bisphosphate (PIP_2). Increased PIP_3 activates downstream 3-phosphoinositide-dependent protein kinase PDK1 and protein kinase B (c-Akt), resulting in effects on cellular survival, growth, metabolism and cell cycle progression. Both pathways also have effects on mammalian target of rapamycin (mTOR), which can affect cell growth (4, 5).

Furthermore, interactions between the IGF-I receptor and other signaling pathways have been documented, including pathways mediated by epidermal growth factor receptor (EGFR), receptor tyrosine-protein kinase erbB-2 (HER2/neu), vascular endothelial growth factor (VEGF) and estrogen and androgen receptors. These interactions have implications for cancer prevention, treatment efficacy and resistance, and tumor angiogenesis (2, 4, 5).

The result of this accumulation of knowledge concerning the IGF-I receptor is that over 30 compounds targeting the receptor are being investigated. One that has reached clinical development is ganitumab (AMG-479), a fully human monoclonal IgG_1 anti-IGF-I receptor antibody. Ganitumab has been shown to inhibit IGF-I receptor activation in vitro, inhibit the proliferation of cancer cells in vitro and inhibit tumor growth in xenograft models of pancreatic cancer and sarcoma. Inhibition of the growth of xenografts with relevant genetic mutations (*RAS/RAF*, *PIK3/PTEN* and *P53*) has also been demonstrated with the agent. Preclinical efficacy is enhanced by combination of ganitumab with other oncolytic agents. In clinical studies, ganitumab has been administered to patients with a variety of cancers, including phase II trials in patients with pancreatic and breast cancer. Fifteen clinical trials are currently evaluating the agent alone or in combination with other therapies in patients with advanced solid tumors and colorectal, pancreatic, small cell lung, ovarian, neuroendocrine and breast cancer, and Ewing's sarcoma (4).

PRECLINICAL PHARMACOLOGY

Ganitumab has been studied preclinically in a variety of cancer cells and models. The effects of ganitumab were evaluated in the IGF-I receptor-expressing pancreatic cell lines BxPC-3 and MIA PaCa-2, which also differentially express the IR. Ganitumab bound to the IGF-I receptor with an apparent K_D of 0.33 nmol/L, without cross-reacting with the IR. The compound inhibited the binding of IGF-I and IGF-II to the IGF-I receptor, with IC_{50} values of 0.53 and 0.59 nmol/L, respectively, but did not inhibit the binding of insulin to the IR. Ganitumab inhibited IGF-I- and IGF-II-induced IGF-I receptor autophosphorylation in BxPC-3 and MIA PaCa-2 cells and inhibited IGF-I-induced IR phosphorylation in MIA PaCa-2 cells. The compound also inhibited IGF-I- and IGF-II-induced Akt phosphorylation in both cell lines, as well as insulin-induced Akt phosphorylation in BxPC-3 cells. Ganitumab was able to capture IGF-I receptor/IR hybrids in MIA PaCa-2 cells. Basal IGF-I receptor activity was inhibited by over 80% in BxPC-3 and MIA PaCa-2 xenografts, and inhibition of BxPC-3 and MIA PaCa-2 xenograft growth was dose-dependent, significant and reached 80% and 78%, respectively, with ganitumab 300 μg given twice weekly. Ganitumab appeared to be proapoptotic in BxPC-3 cells and antimitogenic in MIA PaCa-2 cells. In these models, efficacy was significantly better with the combination of ganitumab and gemcitabine than with either agent alone: tumor growth inhibition was enhanced by 30% in the BxPC-3 model and by 22% in the MIA PaCa-2 model (6).

Additive efficacy against BxPC-3 xenografts was also seen when ganitumab was combined with the EGFR inhibitors panitumumab, erlotinib and gefitinib. Triple combination of optimal doses of ganitumab, panitumumab and gemcitabine was associated with tumor regression, while the combination of panitumumab and gemcitabine produced only tumor stasis. The combination regimens were not associated with adverse effects or changes in body weight (7).

Activation of the IGF-I receptor leads to activation of the PI3K/Akt and MAPK pathways, and disruption of these interactions may have therapeutic benefit in endometrial cancer. Experiments using ganitumab and the type I endometrial cancer cell lines ECC-1/P72 and RL-95-2 appeared to support this hypothesis. While ganitumab alone did not greatly inhibit the proliferation of either cell

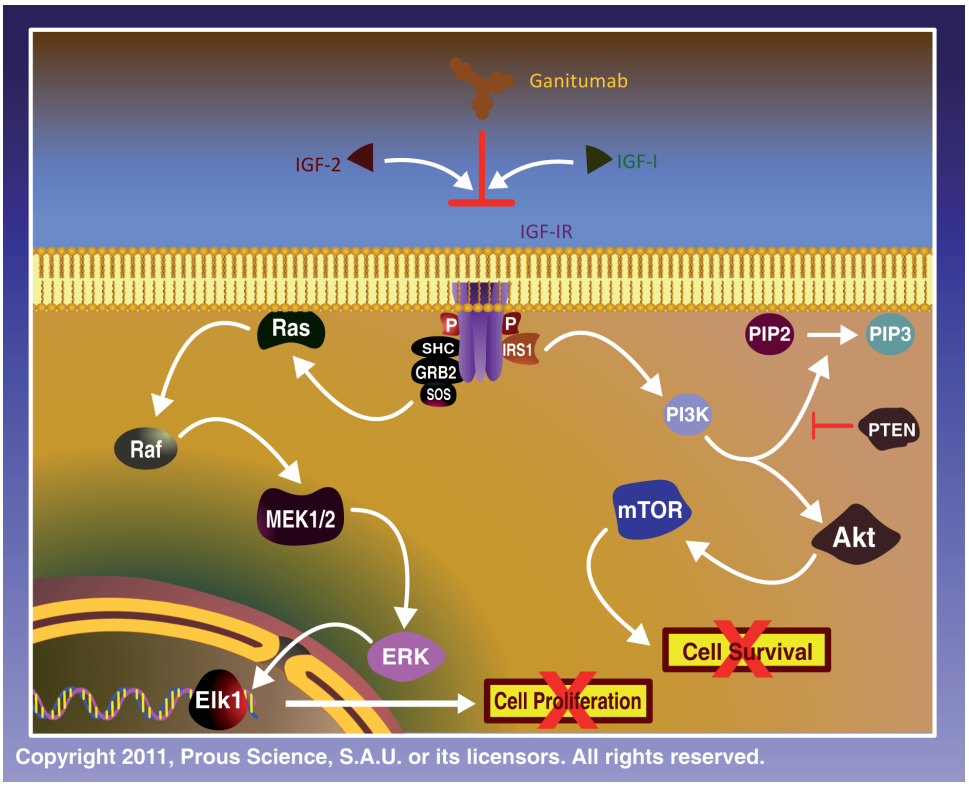

Figure 1. Mechanism of action of ganitumab. Ganitumab is a fully human monoclonal antibody that targets insulin-like growth factor 1 receptor (IGF-I receptor), which is strongly implicated in both tumorigenesis and metastasis. Ganitumab disrupts the Ras/Raf/ERK/MAPK pathway and PI3K/Akt signaling cascades downstream of the IGF-I receptor, thereby suppressing tumor cell proliferation and promoting tumor cell apoptosis.

line, significant inhibition (mean of 29% and 36%, respectively, in ECC-1/P72 and RL-95-2 cells) was seen when the antibody was given in the presence of IGF-I. The effect of ganitumab appeared to be independent of dose. In the presence of IGF-I, ganitumab decreased the phosphorylation of the IGF-I receptor, Akt and p42/p44 MAPK (8).

mTOR inhibitors such as rapamycin induce Akt activation, an effect which may be IGF-I-dependent. The possibility that ganitumab can block this process and thereby act synergistically with mTOR inhibitors was investigated in vitro and in vivo. In three human sarcoma cell lines, rapamycin treatment was associated with a twofold increase in phospho-Akt and over 80% inhibition of phospho-p70S6K. With combination treatment with rapamycin and ganitumab, rapamycin-induced phospho-Akt was inhibited by over 90%, while the level of inhibition of phospho-p70S6K seen with rapamycin alone was not affected. Ganitumab inhibited rapamycin-induced Akt activation in nude mice with sarcoma xenografts. In mice with human sarcoma SK-ES-1 xenografts, significantly enhanced tumor responses were seen with the combination of rapamycin 0.5 mg/kg and ganitumab 300 μg given i.p. twice weekly for 2 weeks compared to the individual compounds. Efficacy was also enhanced compared to rapamycin alone, but not compared to ganitumab alone, in mice with SJSA-1 sarcoma xenografts treated with both agents, while efficacy was not improved over the individual agents in mice bearing A673 sarcoma xenografts (9).

Ganitumab inhibited Akt and p70S6K phosphorylation induced by IGF-I in SK-ES-1, SJSA-1 and A673 cells in vitro and in xenografts created from these cell lines. Basal phospho-Akt activity was also inhibited in SJSA-1 xenografts. Significant tumor growth inhibition was observed in mice bearing SK-ES-1 and SJSA-1 xenografts after treatment with ganitumab (300 μg twice weekly) alone. The growth of A673 xenografts was not inhibited by ganitumab alone, but tumor growth inhibition with the combination of ganitumab and cyclophosphamide (25 mg/kg three times per week) was significant compared to either agent alone (10).

The activity of ganitumab was evaluated in xenograft models with genetic alterations in Ras/Raf, PI3K/PTEN and p53 pathways. Significantly, 40-70% tumor growth inhibition was observed in colorectal cancer COLO 205 (*BRAF*), pancreatic cancer MIA PaCa-2 (*KRAS*) and colon cancer HCT 116 (*KRAS*) models. Inhibition of > 70% was noted in the *P53* mutant models BxPC-3 (pancreatic cancer) and SK-NEP-1 (Ewing's sarcoma), and inhibition went beyond 80% in

the *MDM2*-amplified SJSA-1 (osteosarcoma) model. Mixed responses were seen in models with PI3K-activating mutations. Resistance was seen, however, in four *PTEN*-null/mutated tumor models. The possible relationship between loss of *PTEN* function and ganitumab efficacy was also noted in a study of biomarkers of ganitumab response using clinical data (see below) (11).

SAFETY

In a first-in-human safety and pharmacokinetic study of ganitumab, patients with solid tumors refractory to standard therapy or for which there was no standard therapy received i.v. infusions of ganitumab every 2 weeks. One patient with non-Hodgkin's lymphoma was also enrolled. Doses were initiated at 1 mg/kg and escalated to 3, 10 and 20 mg/kg, with administration on days 1, 15 and 29 followed by a 28-day period without treatment. A dose-expansion phase evaluated treatment at 20 mg/kg (the highest tolerable dose) and 12 mg/kg. The 53 patients studied received a median of 3 treatments, with the only dose-limiting toxicity (DLT; grade 3 thrombocytopenia leading to dose reduction) occurring in the group receiving 20 mg/kg. The maximum tolerated dose was not determined and the dose of 20 mg/kg was considered tolerable. Hematological toxicities in the study were primarily mild anemia and early-onset, transient and reversible thrombocytopenia. Grade 3 thrombocytopenia occurred in eight patients treated at 12 or 20 mg/kg. Most nonhematological toxicities were mild, and the most commonly related to ganitumab were fatigue, thrombocytopenia, fever, rash, chills and anorexia. Laboratory evidence of hyperparathyroidism was seen in 3 patients treated at 12 or 20 mg/kg, and hyperglycemia developed in 3 of 50 patients without preexisting diabetes treated at those doses. Two of three patients with preexisting diabetes had significant worsening of glucose control (12).

Five of the patients included in the study had metastatic gastrointestinal carcinoid tumors, and all experienced ganitumab-related grade 1/2 adverse events and one also had grade 3 diarrhea. Three patients had serious adverse events that were considered most likely related to underlying disease. There were no DLTs among these patients (13).

An open phase Ib study evaluated ganitumab (6 or 12 mg/kg i.v. every 2 weeks) in combination with either panitumumab (6 mg/kg i.v. every 2 weeks) or gemcitabine (1000 mg/m^2 i.v. on days 1, 8 and 15 every 4 weeks). Study subjects had advanced solid tumors. Data from 18 patients reported while the trial was ongoing, 10 in the panitumumab group and 8 in the gemcitabine group, indicated that the drug combinations appeared tolerable. There was one DLT of grade 3 hyperglycemia in the panitumumab arm and one DLT of grade 4 neutropenia in the gemcitabine arm. Treatment-related grade 3/4 hyperglycemia also occurred in the panitumumab arm (10%), while treatment-related grade 3/4 AST/ALT elevation was noted in the gemcitabine arm (13%). Other adverse events of any grade seen in the panitumumab cohort were anemia, thrombocytopenia, rash/stomatitis, hypomagnesemia, fatigue, nausea/vomiting/anorexia, diarrhea and dizziness. Except for diarrhea and dizziness, these were also observed in the gemcitabine group (14).

Another phase Ib trial compared ganitumab and rilotumumab (AMG-102), a fully human MAb targeting hepatocyte growth factor, in 27 patients with extensive-stage small cell lung cancer. Study subjects were given ganitumab 18 mg/kg or rilotumumab 15 mg/kg on day 2 of cycle 1 and on day 1 of subsequent cycles, with etoposide (100 mg/m^2 on days 1-3) plus either carboplatin (AUC = 5 mg/mL.min) or cisplatin (75 mg/m^2) on day 1 every 3 weeks for four to six cycles. Neutropenia and thrombocytopenia were the most common grade 3 or higher adverse events across cohorts, but four patients given rilotumumab had a venous thrombotic event: three of eight given cisplatin and one of six given carboplatin (15).

Gemcitabine was combined with either conatumumab or ganitumab in a randomized, placebo-controlled phase II study in patients with metastatic pancreatic cancer. Conatumumab is a fully human MAb that binds to the extracellular domain of human tumor necrosis factor receptor superfamily member 10B (death receptor 5, TRAIL-R2). Study subjects (N = 125) received double-blind treatment with conatumumab 10 mg/kg i.v. on days 1 and 15 plus gemcitabine 1000 mg/m^2 i.v. on days 1, 8 and 15 every 28 days, open-label treatment with ganitumab 12 mg/kg i.v. on days 1 and 15 plus gemcitabine or double-blind treatment with placebo plus gemcitabine. The ganitumab arm was open due to expected thrombocytopenia and hyperglycemia. Grade 3 or higher adverse events in the conatumumab, ganitumab and placebo arms were neutropenia (22%, 18% and 13%, respectively), thrombocytopenia (17%, 15% and 8%, respectively), abdominal pain (17%, 8% and 13%, respectively), fatigue (12%, 13% and 5%, respectively) and hyperglycemia (2%, 18% and 13%, respectively). Combining conatumumab or ganitumab with gemcitabine was well tolerated overall (16).

A randomized, double-blind, placebo-controlled phase II study enrolled 156 individuals with hormone receptor-positive metastatic or locally advanced breast cancer. The participants received ganitumab or placebo and additional exemestane or fulvestrant treatment, determined by the investigator. Ganitumab 12 mg/kg i.v. or placebo was administered every 2 weeks with either once-daily exemestane 25 mg p.o. or fulvestrant 500 mg i.m. on day 1 and 250 mg i.m. on days 15 and 29, and every 4 weeks thereafter. Safety findings were as expected. Adverse events of grade 3 or more occurred in 42% of ganitumab-treated patients and serious adverse events affected 25% of these individuals. The most common adverse events of grade 3 or more in ganitumab-treated subjects were hyperglycemia, neutropenia, thrombocytopenia, asthenia and elevated aspartate aminotransferase. In this group, 8% of participants discontinued treatment due to adverse events (17).

CLINICAL STUDIES

In the first-in-human study in 53 patients with solid tumors cited above, ganitumab appeared to bind to the IGF-I receptor on neutrophils in an exposure-dependent manner, and the dose of 20 mg/kg was associated with increased circulating levels of IGF-I. Exposure to ganitumab increased dose-proportionally, with mean systemic clearance values of 8.6-15.3 mL/kg/day and mean elimination half-life values of 7-11 days. Accumulation was minimal. Dosing with at least 12 mg/kg every 2 weeks or 18 mg/kg every 3 weeks appeared to be sufficient to maintain drug concentrations at effective levels observed in xenograft studies. A confirmed complete response was seen in one patient with chemotherapy-refractory Ewing's/primitive neuroectodermal tumor (PNET) and the response was sustained at 30 months after the beginning of treatment. A par-

tial response was seen in another patient with Ewing's/PNET, but therapy was discontinued due to myelodysplasia syndrome. No response was seen in another 10 patients with histological Ewing's/PNET entered into the expansion phase of the study (12).

Of the five patients enrolled in this study who had metastatic gastrointestinal carcinoid tumors, one treated at 3 mg/kg experienced a confirmed partial response, while four treated at 20 mg/kg had stable disease (13). A phase II study in patients with gastrointestinal carcinoid tumors is ongoing.

In the phase Ib study evaluating ganitumab in combination with either panitumumab or gemcitabine, a partial response occurred in a patient with colon cancer who received treatment with ganitumab 12 mg/kg and panitumumab. The patient had previously progressed when treated with cetuximab. A best response of stable disease was noted in five of six evaluable patients in the panitumumab group and in four of five patients in the gemcitabine group (14).

In the second part of a phase I/II clinical trial, patients with wild-type *KRAS* metastatic colorectal cancer are being treated with panitumumab plus rilotumumab, ganitumab or placebo. Enrollment was completed and 142 patients had received at least one dose of study drug, according to a recent report (18).

In the phase I and phase Ib studies above, serum levels of IGF-I and IGFBP-3 increased in a dose-dependent manner with ganitumab doses of 1-12 mg/kg, reaching a plateau at higher doses. Baseline levels and changes in IGF-I and IGFBP-3 levels did not differ greatly between patients with and without a tumor response. A partial response to treatment occurred in a patient with an activating *KRAS* mutation, and no responses were observed in tumors lacking expression of *PTEN*. Further study may confirm the value of the expression and mutations of regulators of the IGF-I receptor pathway as biomarkers of response to ganitumab treatment (19).

When ganitumab was compared to rilotumumab in patients with extensive-stage small cell lung cancer also treated with etoposide plus either cisplatin or carboplatin, exposure to the individual agents did not appear to be affected by combination therapy. Of 21 evaluable patients, 2 had a complete response, 16 had a partial response (8 confirmed and 8 unconfirmed) and 2 had stable disease. A randomized, placebo-controlled phase of the phase II study was initiated (20).

In the phase II study in 125 patients with metastatic pancreatic cancer, gemcitabine was combined with conatumumab, ganitumab or placebo and 6-month overall survival rates in these groups were 59%, 57% and 50%, respectively, 12-month overall survival rates were 20%, 39% and 23%, respectively, median overall survival was 7.5, 8.7 and 5.9 months, respectively, and median progression-free survival was 4.0, 5.1 and 2.1 months, respectively. Objective responses were noted in one patient, four patients and one patient in the conatumumab, ganitumab and placebo groups, respectively, while stable disease was achieved by 58%, 41% and 38% of these groups, respectively (16). The ganitumab/gemcitabine combination is being studied in a phase III trial in metastatic pancreatic cancer.

Lastly, no improvement in the primary endpoint of progression-free survival measured by modified RECIST criteria was seen with ganitumab 12 mg/kg i.v. in the randomized, double-blind, placebo-controlled phase II study in 156 patients with hormone receptor-positive metastatic or locally advanced breast cancer (17).

A check of trials registered at ClinicalTrials.gov reveals 15 other currently active studies in a variety of cancers (Table I).

SOURCE

Amgen, Inc. (US).

Table I. *Ongoing clinical trials of ganitumab alone or in combination with other treatments (February 9, 2011).*

Phase	Cancer type	ClinicalTrials.gov Identifier	Ref.
I	Advanced solid tumors	NCT00974896	21
I	Advanced solid tumors	NCT01061788	22
I	Advanced solid tumors and colorectal cancer	NCT01122199	23
I/II	Advanced, refractory solid tumors	NCT00819169	24
I/II	Metastatic pancreatic cancer	NCT00630552	25
I/II	Metastatic colorectal tumors with wild-type *KRAS* status	NCT00788957	26
I/II	Extensive-stage small cell lung cancer	NCT00791154	27
II	Metastatic colorectal carcinoma expressing wild-type *KRAS*	NCT00891930	28
II	Recurrent platinum-sensitive ovarian cancer	NCT00719212	29
II	Hormone receptor-positive locally advanced or metastatic breast cancer	NCT00626106	30
II	Optimally debulked epithelial ovarian cancer	NCT00718523	31
II	Relapsed or refractory Ewing's sarcoma and desmoplastic small round cell tumors	NCT00563680	32
II	*KRAS*-mutant metastatic colorectal carcinoma	NCT00813605	33
II	Carcinoid and pancreatic neuroendocrine tumors	NCT01024387	34
III	Metastatic adenocarcinoma of the pancreas	NCT01231347	35

AUC, area under the concentration–time curve; C_{max}, peak plasma concentration; t_{max}, time to peak plasma levels (values are geometric means); n, number of subjects.

DISCLOSURES

The author states no conflicts of interest.

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