Safety, Tolerability, Pharmacokinetics and Antitumor Activity of Ganitumab, an Investigational Fully Human Monoclonal Antibody to Insulin-like Growth Factor Type 1 Receptor, Combined with Gemcitabine as First-line Therapy in Patients with Metastatic Pancreatic Cancer: A Phase 1b Study

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Received November 7, 2013; accepted March 10, 2014

Objective: Previous Phase 1 studies have shown the acceptable safety profile of ganitumab—a fully human monoclonal antibody to insulin-like growth factor Type 1 receptor—in patients with advanced solid tumors. However, ganitumab 20 mg/kg in combination with gemcitabine had not been administered to patients with metastatic pancreatic cancer. To evaluate the safety, tolerability, pharmacokinetics and antitumor activity of ganitumab 20 mg/kg combined with gemcitabine 1000 mg/m² as first-line therapy in patients with metastatic pancreatic cancer, we conducted a Phase 1b study.

Methods: Eligible patients were adults with previously untreated metastatic adenocarcinoma of the pancreas. Patients received gemcitabine 1000 mg/m² on Days 1, 8 and 15 plus ganitumab 20 mg/kg on Days 1 and 15 of each 28-day cycle. Gemcitabine was administered intravenously over 30–60 min. Ganitumab was administered intravenously over 60 min after completing gemcitabine infusion.

Results: Six patients were enrolled and received the study treatment. All patients had thrombocytopenia and leukopenia. Other most common adverse events were neutropenia and nausea. One patient had a dose-limiting toxicity defined as Grade 3 neutropenia with fever. Exposure to ganitumab 20 mg/kg was not affected by the administration of gemcitabine. No apparent pharmacokinetic drug–drug interaction was observed. No anti-ganitumab antibodies were detected. Five patients had a measurable tumor region at baseline. Of these, four patients had a best response of stable disease.

Conclusions: Ganitumab 20 mg/kg combined with gemcitabine 1000 mg/m² was tolerable and showed an acceptable safety profile in patients with untreated metastatic pancreatic cancer.

Key words: clinical trial Phase 1 – ganitumab – gemcitabine – pancreatic neoplasms – receptor, insulin-like growth factor type 1
**INTRODUCTION**

The insulin-like growth factor (IGF) system—the circulating ligands (insulin, IGF-1 and IGF-2), multiple receptors and binding proteins—plays a major role in cancer cell proliferation (1–3). In this system, IGF-1 acts as the primary regulator of growth, whereas IGF-2 has metabolic and mitogenic effects (4). Furthermore, a recent review has shown that the IGF Type 1 receptor (IGF-1R) plays a role in maintaining the malignant phenotype and disruption of IGF-1R activation leads to inhibited growth and motility of cancer cells (3). Thus, this family of growth factors, especially the IGF-1R, may present an excellent target for new therapeutic agents for anticancer treatment (5,6).

Ganitumab (previously known as AMG 479) is a fully human monoclonal antibody directed to IGF-1R. As a single agent, it inhibited the interaction of IGF-1R with IGF-1 and IGF-2 without cross-reacting to insulin receptor in IGF-1R-expressing pancreatic carcinoma cell lines (7). In addition, the combination of ganitumab with gemcitabine resulted in additive inhibitory activity both in vitro and in vivo (7). These results indicate that ganitumab is a clinical candidate for the treatment of patients with pancreatic cancer (PC).

Previous Phase 1 studies have shown that ganitumab can be administered safely to patients with advanced solid tumors at doses up to 20 mg/kg intravenously every 2 weeks (8,9). In a randomized Phase 2 study, ganitumab 12 mg/kg combined with gemcitabine 1000 mg/m² has shown evidence of activity with improved 6-month overall survival rates compared with gemcitabine alone in patients with metastatic PC (mPC) (10).

However, it is uncertain whether a higher dose level of ganitumab is needed to treat patients with mPC. A recent analysis using the data of the randomized Phase 2 study assessed the effect of ganitumab exposure on survival, and its results revealed that the progression-free survival and overall survival were longer in the high-exposure group than in the low-exposure group (11). According to this finding, a pharmacokinetic (PK) analysis was performed to determine a sufficient dose level, and the results showed that >90% of patients with mPC would reach high exposures when administered ganitumab 20 mg/kg (11).

Considering that ganitumab 20 mg/kg in combination with gemcitabine has not been administered in patients with mPC, we conducted a Phase 1b study to evaluate the safety, tolerability, PKs and antitumor activity of ganitumab 20 mg/kg combined with gemcitabine 1000 mg/m² as first-line therapy in this population.

**PATIENTS AND METHODS**

**STUDY DESIGN AND ETHICAL CONSIDERATIONS**

This Phase 1b, open-label study was conducted from August 2010 to February 2011 at three institutions in Japan. This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. Its protocol was reviewed and approved by the institutional review board of the participating institutions. All patients provided their written informed consent.

**PATIENT POPULATION**

Patients aged at least 20 years were eligible for the study if they had histologically or cytologically confirmed metastatic adenocarcinoma of the pancreas; Eastern Cooperative Oncology Group (ECOG) performance status of 0–1; and adequate hematologic, renal and hepatic functions. Adequate functions were defined as follows: hemoglobin ≥9 g/dl; absolute neutrophil count ≥1.5 × 10⁹/l; platelet count ≥100 × 10⁹/l; activated partial thromboplastin time ≤1.3 × the upper limit of normal (ULN) and international normalized ratio (INR) ≤1.5 (for patients who did not receive anticoagulation therapy); creatinine clearance >60 ml/min; aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 × ULN (≤5 × ULN for patients with liver metastases); total bilirubin ≤1.5 × ULN; and fasting blood glucose level ≤160 mg/dl.

Patients were excluded if they had received or were receiving any treatment for PC. Other exclusion criteria included the following: islet cell carcinoma, acinar cell carcinoma, nonadenocarcinoma, or adenocarcinoma originated from biliary tree or cystadenocarcinoma; a history of central nervous system metastases; internal or external biliary drain; a history of other malignancies; and myocardial infarction or uncontrolled cardiovascular disease including acute coronary syndrome or congestive heart failure within 6 months before enrollment. Pregnant women, breastfeeding women or patients who did not use adequate contraceptive precautions despite having a partner were also excluded.

**STUDY TREATMENT**

Initially, six patients received the study treatment (i.e. gemcitabine plus ganitumab), and three additional patients were to be enrolled if additional data for the safety or PK analysis were needed. Patients received gemcitabine 1000 mg/m² on Days 1, 8 and 15 as well as ganitumab 20 mg/kg on Days 1 and 15 of each 28-day cycle. Gemcitabine was administered intravenously over 30–60 min. Ganitumab was administered intravenously over 60 (±10) min after the completion of gemcitabine infusion. The infusion rate of ganitumab was slowed down (up to 120 min infusion) if patients could not tolerate the first infusion.

The dose of gemcitabine was reduced to Level 1 (750 mg/m²) or Level 2 (563 mg/m²) if patients had treatment-related neutropenia, thrombocytopenia or Grade 3 or greater non-hematologic toxicities that required dose reduction. The dose of ganitumab was reduced by 50% if patients had treatment-related Grade 3 or greater thrombocytopenia without Grade 2 or greater bleeding; febrile neutropenia; Grade 4 neutropenia; or Grade 3 neutropenia lasting 8 days or more. Antiemetic premedication for prophylaxis of nausea/vomiting associated with gemcitabine was allowed if necessary. Premedication with antihistamines,
corticosteroids or both was also allowed if patients had an infusion reaction. Patients continued the study treatment until the disease progression if they wished to receive it and had no unacceptable toxicities.

**Outcome Measures**

Medical history was collected within 14 days before enrollment. Patients were hospitalized at least 5 days from Day 1 of treatment. Adverse events were monitored throughout the study and were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.

Dose-limiting toxicity (DLT) was defined as any Grade 3 or greater toxicity that related to ganitumab during the first 28 days. DLTs did not include lymphopenia and infusion reaction. Fatigue, nausea, diarrhea, vomiting, leukopenia, neutropenia, febrile neutropenia, thrombocytopenia, hemoglobin decrease, increased AST or ALT, hyperglycemia and pulmonary embolism were included in DLTs if they met any of the following criteria: Grade 3 or greater neutropenia with fever (body temperature >38.5°C); Grade 4 leukopenia or neutropenia lasting 8 days or more; Grade 4 thrombocytopenia lasting 8 days or more; Grade 3 or greater thrombocytopenia (for patients who were receiving anticoagulation therapy); Grade 3 or greater thrombocytopenia accompanied by Grade 2 or greater bleeding; Grade 3 or greater thrombocytopenia requiring platelet transfusion; Grade 4 hemoglobin decrease; Grade 3 or greater thrombocytopenia lasting 8 days or more; Grade 4 fatigue; Grade 3 or greater nausea, diarrhea or vomiting despite maximum supportive care; AST or ALT >8 × ULN; AST or ALT >5 × ULN and ≤8 × ULN lasting 15 days or more (for patients with baseline values ≤2.5 × ULN); AST or ALT >2 × baseline value and ≤8 × ULN lasting 15 days or more (for patients with baseline values >2.5 × ULN and ≤4 × ULN); AST or ALT >3 × ULN accompanied by total bilirubin >2 × ULN or INR >1.5; any pulmonary embolism that required full-dose anticoagulation therapy (except for deep vein thrombosis); or Grade 4 hyperglycemia with ketoacidosis or hyperosmolar non-ketotic coma.

Blood pressure, pulse rate, body temperature and body weight were measured on Days 1, 8 and 15 of each treatment cycle. ECOG performance status was assessed on Day 1 of each cycle. Electrocardiograms were recorded before starting gemcitabine infusion and after completing ganitumab infusion on Days 1 and 15 of Cycle 1, Day 15 of Cycle 2 and Day 15 of every 3 cycles thereafter. Laboratory tests were performed periodically throughout the study.

Serum samples for PK analysis of ganitumab were collected before starting gemcitabine infusion, within 5 min before completing gemcitabine infusion, and 3 and 24 h after completing ganitumab infusion on Day 1 of Cycle 1; and before starting gemcitabine infusion on Days 8 and 15 of Cycle 1. Serum concentration of ganitumab was determined by using a validated double anti-idiotypic antibody sandwich immunoassay (8).

Plasma samples for PK analysis of gemcitabine were collected before starting gemcitabine infusion, within 5 min before completing gemcitabine infusion, and at 15, 30 and 90 min as well as 24 h (Day 1 only) after completing gemcitabine infusion on Days 1 and 8 of Cycle 1. Plasma concentration of gemcitabine was determined by using a validated method developed by Covance Bioanalytical Services, LLC. (Indianapolis, IN, USA).

Furthermore, serum samples for assessment of anti-ganitumab antibodies were collected pre-dose of gemcitabine on Day 1 of Cycles 1, 2 and 3, and every 2 cycles thereafter. Anti-ganitumab binding antibodies were detected by using a validated bridging immunoassay. Samples positive for anti-ganitumab binding antibodies were to be evaluated additionally for potential neutralizing capabilities in a cell-based assay.

Tumor response was evaluated at screening and every 8 weeks after starting the treatment by using computed tomography or magnetic resonance imaging and was classified according to the response evaluation criteria in solid tumors (12).

**Statistical Considerations**

All data were summarized descriptively. The PK parameters of ganitumab and gemcitabine were estimated by using non-compartmental methods with Phoenix WinNonlin software Version 6.1 (Pharsight Corporation, Mountain View, CA, USA). Categorical variables are expressed as frequencies and percentages. Continuous variables are expressed as the mean or the median combined with the standard deviation (SD) or the range. All data were analyzed by using SAS® System Version 9.1.3 (SAS Institute, Cary, NC, USA).

**RESULTS**

**Patient Disposition, Demographics and Baseline Characteristics**

A total of six patients were enrolled into the study. All patients received at least one dose of ganitumab and gemcitabine and were included in the safety and PK analyses. Of these, one patient had no measurable tumor region at baseline. This patient was excluded from the efficacy analysis. At the time of data analysis, all patients discontinued the study treatment: three patients because of disease progression, two because of adverse events (Grade 2 sudden hearing loss and Grade 1 interstitial pneumonia) and one according to the protocol (Grade 4 neutropenia that did not resolve within the prespecified period). The mean number of treatment cycles was 3 (range, 2–5). The mean relative dose intensity (=[total dose received/total dose expected per initial dose] × 100) was 91% (range, 57–100%) for ganitumab and 90% (range, 68–100%) for gemcitabine.

Table 1 shows the demographic and baseline characteristics of the study patients. The median age was 62 (range, 43–69) years. Three patients (50%) had ECOG performance status of zero. All patients had Stage IV PC. No patients received prior radiotherapy or other medication for PC.
Table 2. Adverse events occurring in at least two patients or categorized into Grade 3 or 4

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>Number of patients by adverse event grade ( (n = 6) )</th>
<th>Percentage of Grade 3/4 events</th>
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<tr>
<td>Hematologic</td>
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<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
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<td>Leukopenia</td>
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<td>Lymphopenia</td>
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</tr>
<tr>
<td>Non-hematologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>3 1 1 0</td>
<td>17</td>
</tr>
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<td>Constipation</td>
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<tr>
<td>Decreased appetite</td>
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</tr>
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<tr>
<td>Hemoglobin decreased</td>
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<td>0</td>
</tr>
<tr>
<td>Blood sodium decreased</td>
<td>0 0 1 0</td>
<td>17</td>
</tr>
</tbody>
</table>

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

PHARMACOKINETICS

Figure 1 shows the individual values of area under the serum concentration–time curve (AUC) of ganitumab in this study and previous studies. The distribution of AUC values after the first infusion of ganitumab 20 mg/kg in this study was similar to that in the Phase 1 study in Japanese patients with advanced solid tumors (9). Furthermore, individual AUC values in this study were higher than any value after the first infusion of ganitumab 12 mg/kg in the Phase 2 study in patients with mPC (10).

Figure 2 shows the individual values of dose-normalized AUC and maximum observed concentration \( (C_{\text{max}}) \) of gemcitabine on Days 1 and 8. Both of the individual AUC and \( C_{\text{max}} \) fluctuated and did not show meaningful changes between before (i.e. Day 1) and after (i.e. Day 8) administration of ganitumab. The mean \( (SD) \) \( C_{\text{max}} \) of gemcitabine was 12 990 (3727) ng/ml on Day 1 and 13 380 (6239) ng/ml on Day 8. The mean (SD) AUC\( _{\text{0–last}} \) of gemcitabine was 7740 (2173) and 6957 (3260) h-ng/ml, respectively.
ANTITUMOR ACTIVITY

In the analysis of tumor response, four patients (80%) had a best response of stable disease and one had progressive disease. The mean percent change of maximum tumor reduction from baseline was 6.6% (SD, 28.9%). The median time to progression was 58.0 (range, 37–113) days. Three patients had a time to progression longer than 100 days (113, 113 and 106 days).

DISCUSSION

This is the first study which evaluated the tolerability of ganitumab 20 mg/kg combined with gemcitabine 1000 mg/m², and the results show that this regimen was tolerable for patients with previously untreated mPC. Although three of six patients discontinued the study treatment owing to adverse events, these adverse events were generally manageable with treatment discontinuation and standard therapy. One event, interstitial pneumonia, did not resolve during the study, but its severity was mild.

The safety profile of this regimen was consistent with those in the previous studies. In our study, the most common adverse events were thrombocytopenia, leukopenia, neutropenia and nausea. These events were frequently reported in the previous single-agent studies of ganitumab (8,9). In these studies, patients with advanced solid tumors refractory to standard treatment received up to 20 mg/kg of ganitumab every 2 weeks, and the most common toxicities included fatigue and thrombocytopenia (8), as well as neutropenia and leukopenia (9). Neutropenia and thrombocytopenia were also frequently reported in the patients who received ganitumab 12 mg/kg in combination with gemcitabine 1000 mg/m² (10). Furthermore, leukopenia and neutropenia are the most common severe toxicities of gemcitabine (13). These results suggest that the safety profile of ganitumab does not differ whether it is administered as monotherapy or in combination with gemcitabine, even though its dose is increased to 20 mg/kg. They also suggest that ganitumab and gemcitabine may be combined without synergistic increase of toxicity.

In our study, Grade 2 hyperglycemia was reported in one patient. Although this patient had a history of diabetes, hyperglycemia was noted in 5 of 50 patients without diabetes in the previous single-agent study (8). Ganitumab did not bind to the insulin receptor in non-clinical experiments (7), but hyperglycemia is one of the major toxicities of IGF-1R inhibitors and mild increases in blood glucose levels occur in ≏25% of patients treated with anti-IGF-1R antibodies (14). Thus, careful monitoring for hyperglycemia is considered to be necessary. It should also be noted that sudden hearing loss occurred in one patient. A previous study in patients with
Turner’s syndrome has shown that sensorineural hearing loss was negatively correlated with the serum concentration of IGF-1 (15), which suggests that hearing loss may be associated with the use of IGF-1R inhibitors.

In the PK analysis, no apparent drug–drug interaction between ganitumab and gemcitabine was observed. Similar AUC values of ganitumab between our study and a Japanese Phase 1 study in patients with advanced solid tumors (9) indicated that exposure to ganitumab 20 mg/kg would not be affected by the administration of gemcitabine. The mean $C_{\text{max}}$ and AUC of gemcitabine in our study did not show any meaningful change between before and after administration of ganitumab. Gemcitabine is a small-molecule drug that is mainly eliminated by cytidine deaminase, whereas ganitumab is an immunoglobulin G1 monoclonal antibody considered to be mainly eliminated via catabolism. Therefore, a mechanism-based drug–drug interaction is not expected. The results on PK parameters in our study supported this expectation.

According to the exposure–response analysis, increased exposure to ganitumab was associated with prolonged progression-free survival and overall survival in patients with mPC (11). Since the ganitumab exposure at 20 mg/kg in our study appeared to be increased in a dose-dependent manner, when compared with that at 12 mg/kg in the Phase 2 study (10), further evaluation on the efficacy outcome at a ganitumab 20 mg/kg dose in patients with mPC is warranted.

No anti-ganitumab binding antibodies were detected in our study. In the previous single-agent study, anti-ganitumab binding antibodies were detected in one patient at Week 9, but no neutralizing antibodies were detected (8). In addition, the AUC values of ganitumab in this patient were similar after the first and third doses. Thus, we consider that the anti-ganitumab binding antibodies had no apparent effect on serum ganitumab concentrations.

Although assessment of efficacy was not a primary objective of our study, the combination of ganitumab and gemcitabine showed potential activity. Four patients (80%) achieved a best response of stable disease, and three (60%) had a time to progression longer than 100 days.

In conclusion, ganitumab 20 mg/kg combined with gemcitabine 1000 mg/m² was tolerable and showed an acceptable progression longer than 100 days. best response of stable disease, and three (60%) had a time to serum ganitumab concentrations. The anti-ganitumab binding antibodies had no apparent effect on the AUC values of ganitumab in this patient were similar after the first and third doses. Thus, we consider that the anti-ganitumab binding antibodies had no apparent effect on serum ganitumab concentrations.

Acknowledgements

We thank the study coordinators, nurses and patients involved in the study; and Kenichi Hayashi (Alamedic Co., Ltd., Tokyo, Japan) for writing assistance.

Funding

This work was supported by Takeda Bio Development Center Limited (Tokyo, Japan). T.O. and A.F. received research funding from TBDC.

Conflict of interest statement

Y.K., K.S. and T.T. are employees of Takeda Bio Development Center Ltd. J.G. is employed in a leadership position and owns stock of Amgen Inc. M.I. has no conflict of interest to disclose.

References