A randomized, placebo-controlled phase 2 study of ganitumab (AMG 479) or conatumumab (AMG 655) in combination with gemcitabine in patients with metastatic pancreatic cancer


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Received 15 December 2011; revised 5 March 2012; accepted 10 April 2012

Background: We evaluated the efficacy and safety of ganitumab (a mAb antagonist of insulin-like growth factor 1 receptor) or conatumumab (a mAb agonist of human death receptor 5) combined with gemcitabine in a randomized phase 2 trial in patients with metastatic pancreatic cancer.

Patients and methods: Patients with a previously untreated metastatic pancreatic adenocarcinoma and an Eastern Cooperative Oncology Group (ECOG) performance status ≤1 were randomized 1:1:1 to i.v. gemcitabine 1000 mg/m² (days 1, 8, and 15 of each 28-day cycle) combined with open-label ganitumab (12 mg/kg every 2 weeks [Q2W]), double-blind conatumumab (10 mg/kg Q2W), or double-blind placebo Q2W. The primary end point was 6-month survival rate.
**Results:** In total, 125 patients were randomized. The 6-month survival rates were 57% (95% CI 41–70) in the ganitumab arm, 59% (42–73) in the conatumumab arm, and 50% (33–64) in the placebo arm. The grade ≥3 adverse events in the ganitumab, conatumumab, and placebo arms, respectively, included neutropenia (18/22/13%), thrombocytopenia (15/17/8%), fatigue (13/12/5%), alanine aminotransferase increase (15/5/8%), and hyperglycemia (18/2/3%).

**Conclusions:** Ganitumab combined with gemcitabine had tolerable toxicity and showed trends toward an improved 6-month survival rate and overall survival. Additional investigation into this combination is warranted. Conatumumab combined with gemcitabine showed some evidence of activity as assessed by the 6-month survival rate.

**Key words:** AMG 479, conatumumab, ganitumab, gemcitabine, pancreatic cancer, phase 2 trial

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**introduction**

Pancreatic cancer is the fourth leading cause of cancer-related death in the United States [1] and the eighth leading cause of cancer-related death worldwide [2]. First-line treatments for patients with metastatic disease include single-agent gemcitabine or gemcitabine-based combinations [3]. Several clinical trials have been unsuccessful with cytotoxic or targeted agents combined with gemcitabine [4–9] in demonstrating significant improvements in overall survival (OS). Erlotinib combined with gemcitabine has been associated with a modest but statistically significant improvement in OS [10]. Recently, treatment with 5-fluourouracil/leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) was associated with longer OS than gemcitabine in patients with a good performance status [11]. Nevertheless, more effective treatments with novel agents are needed.

The insulin-like growth factor (IGF)-1 receptor (IGF1R) and its ligands, IGF-1 and IGF-2, are overexpressed in normal pancreatic cells and in tumors [12, 13]. Preclinical evidence has suggested a protumorigenic role for the IGF1R axis [14]. Pharmacological blockade of IGF1R inhibits the growth and viability of pancreatic cancer cells [14], and tumor cells with KRAS mutations remain sensitive to IGF1R inhibition [15, 16]. Ganitumab (AMG 479) is an investigational, fully human, mAb inhibitor of IGF1R that prevents binding of IGF-1 and IGF-2 to IGF1R [15]. In human pancreatic cancer xenograft models, ganitumab demonstrated single-agent activity that was enhanced in combination with gemcitabine [15]. In a phase 1b study, ganitumab in combination with gemcitabine had acceptable toxicity and was associated with a disease control rate (complete response + partial response + stable disease) of 80% in patients with advanced solid tumors [17].

Pancreatic tumors express higher levels of apoptosis ligand 2/tumor necrosis factor receptor-related apoptosis-inducing ligand (TRAIL), death receptor (DR) 4, and DR5 than does normal pancreatic tissue [18]. Mutations in codon 12 of KRAS are found in ~70%–90% of pancreatic adenocarcinomas [19, 20]; RAS transformation sensitizes some normal cells to TRAIL-induced apoptosis [21]. Conatumumab (AMG 655) is an investigational, fully human, mAb agonist of DR5 that induces apoptosis [22]. In a pancreatic cancer xenograft model, conatumumab demonstrated single-agent activity that was enhanced when it was combined with gemcitabine [22]. In a phase 1b study in patients with metastatic pancreatic cancer, conatumumab in combination with gemcitabine yielded a disease control rate of 69% and a 6-month survival of 76% with acceptable toxicity [23].

Given the results of phase 1b studies with ganitumab and conatumumab, the objective of this randomized phase 2 study was to evaluate the efficacy and safety of these agents when they are used in combination with gemcitabine in patients with metastatic pancreatic cancer.

**methods**

**patients**

The following were the patient (aged ≥18 years) eligibility criteria for this study: histologically or cytologically documented metastatic adenocarcinoma of the pancreas, no prior treatment with chemotherapy or radiotherapy for pancreatic cancer, and an Eastern Cooperative Oncology Group performance status (ECOG PS) of zero or one. The patients were required to have a hemoglobin level of ≥9 g/dl, an absolute neutrophil count (ANC) of ≥1.5 × 10⁹/l, a platelet count of ≥100 × 10⁹/l, a partial thromboplastin time of ≤1.3 × upper limit of normal (ULN), and an international normalized ratio of ≤1.5 (unless receiving anticoagulation therapy). Adequate renal and hepatic functions were required [serum creatinine ≤0.5 mg/dl or calculated creatinine clearance ≥40 ml/min; aspartate aminotransferase or alanine aminotransferase [ALT] ≤2.5 × ULN or ≤5.0 × ULN with liver metastasis; total bilirubin ≤2.0 × ULN; amylase ≤2.0 × ULN; and lipase ≤2.0 × ULN]. Patients with adequately controlled type 1 or 2 diabetes were allowed [fasting blood sugar (FBS) ≤160 mg/dl and hemoglobin A1c <8%, amended during the study to FBS <150 mg/dl only].

Patients with an external biliary drain or who had a myocardial infarction or unstable/uncontrolled cardiac disease in the previous 6 months or a major surgical procedure within 30 days of enrollment were excluded. Patients must have recovered from prior surgery. Institutional review board approval was obtained for all the study procedures. Each patient provided written informed consent before enrollment.

**randomization and masking**

This randomized, placebo-controlled, phase 2 study was conducted at 37 participating centers in the United States and was part 2 of a phase 1b/2 study. Patients were randomly allocated 1:1:1 to receive gemcitabine in combination with ganitumab, conatumumab, or placebo. Randomization was stratified according to whether the ECOG PS was zero or one. The treatment assignment in the conatumumab and placebo arms was blinded. The ganitumab arm was open label because of the requirement of dose reductions (for grade 4 neutropenia and grade 3/4 thrombocytopenia), which were not required for conatumumab or placebo.

**treatment**

Gemcitabine (1000 mg/m²) was administered iv. over 30 min on days 1, 8, and 15 of each 28-day cycle. The selected doses of ganitumab (12 mg/kg...
[17] and conatumumab (10 mg/kg [23]) (Amgen Inc., Thousand Oaks, CA, USA) appeared tolerable in phase 1b studies. Ganitumab, conatumumab, and placebo were administered by a 1-h infusion, which if well tolerated, could subsequently be reduced to 30 min. If 1-h infusions were poorly tolerated, subsequent infusions could be extended to 2 h. The treatment was continued until radiographic progression (per modified Response Evaluation Criteria in Solid Tumors [RECIST] version 1.0), clinical progression, unacceptable toxicity, or withdrawal of consent.

**dose adjustments**

Toxicity assessments were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE] version 3.0. Depending upon the timing and degree of toxicity, gemcitabine was to be withheld and/or reduced by 25%. Ganitumab, conatumumab, or placebo were withheld until grade ≥3 hepatic transaminase increases or amylase/lipase increases improved to grade ≤1. Ganitumab was to be discontinued permanently for grade ≥2 bleeding associated with grade 3 or 4 thrombocytopenia and was to be withheld and reduced by 50% for an ANC ≤0.5 × 10^9/l or for a platelet count of ≤50 × 10^9/l. Subsequent platelet counts of ≤50 × 10^9/l resulted in permanent discontinuation. There were no planned dose reductions for conatumumab. The patients were discontinued if ganitumab, conatumumab, or placebo were withheld for more than 28 days. If gemcitabine was withheld, then ganitumab, conatumumab, or placebo was also withheld until gemcitabine could be safely resumed.

**study evaluations**

**safety**

The assessments before each administration of the investigational product included adverse events (AEs; graded according to NCI-CTCAE version 3.0), concomitant medications, vital signs, and laboratory tests [comprehensive chemistry panel, including magnesium, fasting glucose (day 1 of cycles 2, 3, and 4, and every other cycle; ganitumab arm only), and amylase, lipase, and creatinine kinase (conatumumab and placebo arms only)]. Complete blood counts were required before gemcitabine administration. Urine, ECOG PS, and coagulation were assessed once per cycle.

**anti-conatumumab and anti-ganitumab antibodies**

Serum for the assessment of anti-ganitumab or anti-conatumumab antibodies was collected predose on days 1, 29, and 57; every 56 days thereafter; and at follow-up visits (30 and 60 days after the last dose). Anti-ganitumab and anti-conatumumab antibodies were assayed by an electrochemiluminescence bridging immunoassay [24, 25].

**antitumor activity**

Tumors were evaluated by computed tomography or magnetic resonance imaging according to modified RECIST (version 1.0) within 21 days before enrollment and once every 8 ± 1 weeks from study day 1. Tumor response was based on investigator assessment of imaging. Responses were confirmed by subsequent imaging no less than 4 weeks after the initial indication of response. An assessment of stable disease required follow-up measurements no earlier than 49 days after randomization.

**statistical design and analysis**

The primary end point was 6-month survival rate. Six-month survival rates and differences between the survival rates were estimated by using the Kaplan–Meier method and were stratified on the basis of ECOG PS. The variance of the proportions was estimated using Greenwood’s formula. The secondary end points included objective response rate (ORR; sum of complete and partial response rates), progression-free survival (PFS; time from randomization to disease progression or death, whichever occurred first), OS (time from randomization to death), incidence of AEs and laboratory abnormalities, incidence of anti-ganitumab and anti-conatumumab antibodies, and the dose intensity of gemcitabine when combined with the investigational products. The pharmacokinetics, biomarker, and health-related quality-of-life analyses will be reported elsewhere.

By design, this study estimated the effects of addition of ganitumab or conatumumab to gemcitabine. However, with a minimum of 6-month follow-up for 120 patients, the study had ~80% power to detect a difference in 6-month survival rates of 45% with placebo and 69% for the investigational product arms at a 20% two-sided level of significance.

The primary analysis was conducted 6 months after the 120th patient was randomized to obtain an estimate of the 6-month survival rate. The analysis reported here was conducted 5 months after the primary analysis to obtain a more mature dataset for estimation of the OS hazard ratio. The full analysis set included all the randomized patients. The safety analysis set included all the patients who received ≥1 dose of the investigational products.

PFS per to investigator assessment and OS were analyzed using Cox proportional hazards models stratified according to the randomization stratification factor of ECOG PS zero or one. The differences between the experimental arms and the placebo arm were estimated with hazard ratios (HR) and CIs; P values are for descriptive purposes. The effects of potential prognostic factors were assessed using Cox regression. Kaplan–Meier estimates and 95% CIs of the median OS and PFS times were calculated.

Confidence intervals for ORR were calculated using the Clopper Pearson method. Differences (95% CI) in the ORR were estimated using the Newcombe Wilson Method with continuity correction. SAS version 9.1 (SAS Institute Inc., Cary, NC) was used for all analyses.

**results**

**patient characteristics**

Between March 2008 and April 2009, 125 patients were randomized (ganitumab, n = 42; conatumumab, n = 41; placebo, n = 42); 40, 41, and 40 patients, respectively, received investigational products (Figure S1). Two patients in the ganitumab arm did not receive treatment as a result of ineligibility based on ECOG PS. Two patients in the placebo arm did not receive treatment as a result of withdrawn consent and disease progression. Patient demographics and baseline characteristics were similar between the treatment arms (Table 1). The percentage of patients with lesions in the head of the pancreas was similar across the treatment arms (ganitumab arm, 29%; conatumumab arm, 27%; placebo arm, 29%), but because the site of pancreatic lesion was not specified in approximately one third of the patients, the true percentages might have varied.

**exposure**

The median number of cycles in the ganitumab, conatumumab, and placebo arms was 4, 4, and 2, respectively. The median relative dose intensity of gemcitabine was similar between the ganitumab and placebo arms but was slightly lower in the conatumumab arm (Table S1). Second-line chemotherapy was reported to have been subsequently administered to 14, 20, and 14% of patients in the ganitumab, conatumumab, and placebo arms, respectively. The proportion of patients with ≥1 treatment delay in gemcitabine or investigational product was similar across the treatment arms (Table S2).
**Table 1.** Patient demographics and baseline characteristics<sup>a</sup>

<table>
<thead>
<tr>
<th></th>
<th>Ganitumab 12 mg/kg + gemcitabine (n = 42)</th>
<th>Conatumumab 10 mg/kg + gemcitabine (n = 41)</th>
<th>Placebo + gemcitabine (n = 42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, n (%)</td>
<td>Male 25 (60)</td>
<td>24 (59)</td>
<td>26 (62)</td>
</tr>
<tr>
<td></td>
<td>Female 17 (40)</td>
<td>17 (41)</td>
<td>16 (38)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td>White or Caucasian 35 (83)</td>
<td>32 (78)</td>
<td>37 (88)</td>
</tr>
<tr>
<td></td>
<td>Black or African American 4 (10)</td>
<td>3 (7)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>ECOG performance status, n (%)</td>
<td>0 19 (45)</td>
<td>17 (41)</td>
<td>16 (38)</td>
</tr>
<tr>
<td>Time since primary diagnosis (months)</td>
<td>Median 66</td>
<td>61</td>
<td>61</td>
</tr>
<tr>
<td>Prior surgery or procedure for pancreatic adenocarcinoma, n (%)</td>
<td>Resection 6 (14)</td>
<td>6 (15)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Tumor differentiation</td>
<td>Well 4 (10)</td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Unknown</td>
<td>19 (45)</td>
<td>20 (49)</td>
<td>19 (45)</td>
</tr>
<tr>
<td>Lesions in the pancreas, n (%)</td>
<td>Head 12 (29)</td>
<td>11 (27)</td>
<td>12 (29)</td>
</tr>
<tr>
<td>Lesions outside the pancreas, n (%)</td>
<td>Liver 29 (69)</td>
<td>27 (66)</td>
<td>33 (79)</td>
</tr>
</tbody>
</table>

ECOG, Eastern Cooperative Oncology Group.
<sup>a</sup>Full analysis set.
<sup>b</sup>Patients with lesions in both the head and the neck of the pancreas were counted in both categories.
<sup>c</sup>Includes both target and nontarget lesions.

**survival and response**

At the time of this analysis, 95 (76%) patients died (ganitumab, n = 29; conatumumab, n = 32; placebo, n = 34). The median time to OS censoring (n = 30) was 11.8 months. The 6-month survival rate was 57% (95% CI 41%–70%) in the ganitumab arm and 50% (95% CI 33%–64%) in the placebo arm (Table 2). The 12-month survival rate was 39% (95% CI 25%–54%) in the ganitumab arm and 23% (95% CI 12%–38%) in the placebo arm. For the ganitumab arm versus the placebo arm, the HR for OS was 0.65 (95% CI 0.41–1.04; P = 0.072) and the HR for OS was 0.67 (95% CI 0.41–1.12; P = 0.12) (Table 2, Figure 1). Cox proportional hazard models adjusted for baseline covariates gave similar estimated HRs for PFS and OS (Table 2).

The 6-month survival rate was 59% (95% CI 42%–73%) in the conatumumab arm and 50% (95% CI 33%–64%) in the placebo arm (Table 2). The 12-month survival rate was 20% (95% CI 9%–34%) in the conatumumab arm and 23% (95% CI 12%–38%) in the placebo arm. For the conatumumab arm versus the placebo arm, the HR for PFS was 0.65 (95% CI 0.41–1.05; P = 0.082), and the HR for OS was 0.87 (95% CI 0.53–1.43; P = 0.59) (Table 2, Figure 1). Cox proportional hazard models adjusted for baseline covariates gave similar estimated HRs for PFS and OS (Table 2).

In univariate analyses of baseline covariates, sex and presence of liver metastases were significant prognostic factors for OS, whereas presence of liver metastases and ECOG PS (0 or 1) were significant prognostic factors for PFS (Table S3).

The response rate was determined by the investigators from 117 (94%) patients with measurable disease at baseline. The responses were required to be confirmed after at least 4 weeks. All the responses were partial. The ORR in the ganitumab, conatumumab, and placebo arms was 10, 3, and 3%, respectively (Table 2). The disease control rate in the ganitumab, conatumumab, and placebo arms was 51, 6, and 7% respectively (Table 2). The 12-month survival rate was 39% (95% CI 25%–54%) in the ganitumab arm and 23% (95% CI 12%–38%) in the placebo arm. For the ganitumab arm versus the placebo arm, the HR for OS was 0.65 (95% CI 0.41–1.05; P = 0.082), and the HR for OS was 0.87 (95% CI 0.53–1.43; P = 0.59) (Table 2, Figure 1). Cox proportional hazard models adjusted for baseline covariates gave similar estimated HRs for PFS and OS (Table 2).

**safety**

The incidence of grade ≥3 AEs in the ganitumab, conatumumab, and placebo arms was 85, 88, and 68%, respectively. Grade 3 or 4 AEs occurring in ≥5% of patients are summarized in Table 3. Grade 3 or 4 increases in amylase and lipase occurred in 5 and 7% of patients, respectively, in the conatumumab arm but were not observed in the placebo arm. One patient in the ganitumab arm had grade 4 hyperglycemia. There were no severe infusion reactions. Serious (e.g. life-threatening or incapacitating) AEs of any grade occurred in 58, 59, and 43% of patients in the ganitumab, conatumumab, and placebo arms, respectively. There was one potentially treatment-related death: a patient in the ganitumab arm with a history of radiographic contrast-associated renal insufficiency died of acute renal failure during the first treatment cycle.
Pretreatment anti-ganitumab and anti-conatumumab antibodies were detected in two patients and one patient, respectively. No post-treatment antibodies were detected.

**discussion**

In this randomized phase 2 study, ganitumab combined with gemcitabine was associated with trends toward improved 6- and 12-month survival rates, PFS, OS, and disease control rate compared with placebo combined with gemcitabine. Although trends toward improved 6-month survival, PFS, and disease control rate were observed with the addition of conatumumab to gemcitabine, the 12-month survival rate, OS, and ORR were no better than in the placebo arm.

We observed evidence of improved antitumor activity across a number of efficacy end points among patients who received ganitumab combined with gemcitabine compared with those who received placebo combined with gemcitabine. The

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**Table 2. Efficacy analysis**

<table>
<thead>
<tr>
<th>Category</th>
<th>Ganitumab 12 mg/kg + gemcitabine (n = 42)</th>
<th>Conatumumab 10 mg/kg + gemcitabine (n = 41)</th>
<th>Placebo + gemcitabine (n = 42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OSb</td>
<td>OS events, n (%)</td>
<td>29 (69)</td>
<td>32 (78)</td>
</tr>
<tr>
<td>KM 6-month survival</td>
<td>KM 6-month survival [ % (95% CI)]</td>
<td>57 (41–70)</td>
<td>59 (42–73)</td>
</tr>
<tr>
<td>Stratified KM differencec [ % (95% CI)]</td>
<td>5.7 (–15.6 to 27.1)</td>
<td>9.5 (–12.3 to 31.4)</td>
<td></td>
</tr>
<tr>
<td>KM 12-month survival</td>
<td>KM 12-month survival [ % (95% CI)]</td>
<td>39 (25–54)</td>
<td>20 (9–34)</td>
</tr>
<tr>
<td>Stratified KM differencec [ % (95% CI)]</td>
<td>14.8 (–5.4 to 35.0)</td>
<td>–3.5 (–22.7 to 15.8)</td>
<td></td>
</tr>
<tr>
<td>Median KM OS time [months (95% CI)]</td>
<td>8.7 (5.3–12.2)</td>
<td>7.5 (4.8–10.0)</td>
<td>5.9 (4.1–9.7)</td>
</tr>
<tr>
<td>Stratified HR* (95% CI)</td>
<td>0.67 (0.41–1.12)</td>
<td>0.87 (0.53–1.43)</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.12</td>
<td>0.59</td>
<td></td>
</tr>
<tr>
<td>Adjusted HRd (95% CI)</td>
<td>0.64 (0.37–1.09)</td>
<td>0.88 (0.52–1.49)</td>
<td></td>
</tr>
<tr>
<td>PFSb</td>
<td>PFS events, n (%)</td>
<td>37 (88)</td>
<td>38 (93)</td>
</tr>
<tr>
<td>Median KM PFS time [months (95% CI)]</td>
<td>5.1 (2.8–5.8)</td>
<td>4.0 (3.3–5.0)</td>
<td>2.1 (1.9–3.3)</td>
</tr>
<tr>
<td>Stratified HR* (95% CI)</td>
<td>0.65 (0.41–1.04)</td>
<td>0.65 (0.41–1.05)</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.072</td>
<td>0.082</td>
<td></td>
</tr>
<tr>
<td>Adjusted HRd (95% CI)</td>
<td>0.60 (0.36–1.02)</td>
<td>0.65 (0.39–1.06)</td>
<td></td>
</tr>
<tr>
<td>Responsec</td>
<td>Patients with measurable disease, n (%)</td>
<td>39 (93)</td>
<td>38 (93)</td>
</tr>
<tr>
<td>ORR (CR or PR),g n (%)</td>
<td>4 (10)</td>
<td>1 (3)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>95% CIh</td>
<td>2.9–24.2</td>
<td>0.07–13.8</td>
<td>0.06–13.2</td>
</tr>
<tr>
<td>Best overall response assessment, n (%)</td>
<td>Confirmed CR</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>Confirmed PR</td>
<td>4 (10)</td>
<td>1 (3)</td>
</tr>
<tr>
<td></td>
<td>Stable diseasei</td>
<td>16 (41)</td>
<td>22 (58)</td>
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<tr>
<td></td>
<td>Progressive disease</td>
<td>13 (33)</td>
<td>12 (32)</td>
</tr>
<tr>
<td></td>
<td>Unknownj</td>
<td>6 (15)</td>
<td>3 (8)</td>
</tr>
</tbody>
</table>

CR, complete response; HR, hazard ratio; KM, Kaplan–Meier; OS, overall survival; ORR, objective response rate; PFS, progression-free survival; PR, partial response.

aFull analysis set.
bDefined as the time from randomization to death. The overall median time to censoring for OS was 11.8 months (n = 30).
cRelative to the placebo + gemcitabine arm. KM estimates and Cox proportional hazard models for OS and PFS were stratified on the basis of Eastern Cooperative Oncology Group performance status (ECOG PS) (0 or 1). P values per stratified log-rank test.
dCox proportional hazard models adjusted for covariates [sex, age, ECOG PS (0 or 1), presence of liver metastases, and baseline sum of the longest diameters].

eDefined as the time from randomization to disease progression (determined radiographically or clinically) or death, whichever occurred first. The overall median time to censoring for PFS was 4.1 months (n = 12).

fAssessment of tumor response was based on investigator evaluation of imaging.
gConfirmed partial or complete response among patients with measurable disease at baseline per modified RECIST version 1.0. Confirmation of response was required at least 28 days after the initial documentation of the response.
hCIs were calculated by the Clopper Pearson method.
iThe best overall response of stable disease required a radiologically determined response of stable disease or better no earlier than study day 49.
jNo postbaseline assessment or unevaluable.
12-month survival rate in the ganitumab arm (39%) was higher than in the placebo arm (23%) and higher than historical rates for gemcitabine monotherapy (23%) or gemcitabine-based combinations (22%–35%) described in other phase 2 studies in this disease [26–29]. In addition, the median OS time in the placebo arm (5.9 months) is consistent with that observed for gemcitabine monotherapy (5.6–5.9 months) [10, 29, 30], and the median OS time for the ganitumab arm (8.7 months) is within the range reported for other gemcitabine-based doublets (5.7–8.0 months) [26–28] in metastatic pancreatic cancer patients. Although the 6-month survival rate in the conatumumab arm was higher than in the placebo arm, other efficacy end points did not consistently suggest clinical benefit.

At the time of this analysis, the data were relatively mature, with deaths in 76% of patients. The consistency in the results across efficacy end points in the ganitumab arm and the relative maturity of the dataset suggest that the combination of ganitumab and gemcitabine may be a promising treatment of metastatic pancreatic cancer. However, evidence of activity must be confirmed in larger studies. Ganitumab in combination with gemcitabine is currently being investigated in a randomized phase 3 study of metastatic adenocarcinoma of the pancreas (Gemcitabine and AMG 479 in Metastatic Adenocarcinoma of the Pancreas; Clinicaltrials.gov, NCT01231347). Anti-IGF1R monoclonal antibodies other than ganitumab in combination with gemcitabine and erlotinib are also being evaluated in phase 2 trials in this disease [31, 32]. It should be noted that in a recent phase 3 trial for select good-performance-status patients, FOLFIRINOX has demonstrated efficacy over gemcitabine in the treatment of metastatic pancreatic cancer, but the toxicity profile was less favorable than with gemcitabine [11]. Additionally, an encouraging OS and a 12-month survival were observed in an open-label nonrandomized phase 1/2 study of nab-paclitaxel (Taxol, Bristol-Myers Squibb Company, Princeton, NJ, USA) combined with gemcitabine in patients with metastatic pancreatic cancer [33]. Given these results, consideration could be given to investigation into anti-IGF1R monoclonal antibodies in combination with chemotherapy regimens other than gemcitabine.

Ganitumab and conatumumab appeared tolerable when administered in combination with gemcitabine. The toxicity profiles were consistent with the expected additive effects of
each agent, and there was no evidence that the combinations exacerbated the single-agent toxic effects [17, 23–25, 34]. Thrombocytopenia and hyperglycemia have been observed with similar frequency and severity in patients with advanced solid tumors treated with ganitumab as monotherapy [25] or combined with gemcitabine [17]. The suspension of a recent phase 3 study of the IGF1R inhibitor figitumumab combined with paclitaxel and carboplatin in non-small-cell lung cancer due to increased toxicity (including serious hyperglycemia) [35] underscores the importance of vigilant monitoring of these AEs in future studies. Increased lipase was reported with similar frequency and severity in patients with advanced solid tumors who received conatumumab monotherapy [24, 34] and in patients with metastatic pancreatic cancer who received conatumumab combined with gemcitabine in the phase 1b study [23].

Numerous phase 3 studies of metastatic pancreatic cancer have failed to achieve their primary end point despite encouraging results in single-arm phase 2 studies [36]. A key strength of this study was its randomized design that included a common concurrent control arm. However, it should be noted that this study was designed to estimate the effect of the treatment with the combination of ganitumab and gemcitabine or conatumumab and gemcitabine versus placebo and gemcitabine. It was neither designed nor sized to assess definitively whether there were statistically significant differences in the efficacy outcomes among the treatment arms.

**Figure 2.** Maximum change from baseline in tumor measurements per modified RECIST and investigator assessment for patients who received gemcitabine combined with ganitumab 12 mg/kg Q2W (A), conatumumab 10 mg/kg Q2W (B), or placebo Q2W (C). Q2W, every 2 weeks.
In conclusion, these data suggest that ganitumab combined with gemcitabine had an acceptable toxicity profile and showed trends toward an improved 6-month survival rate and an improved OS; however, these results need to be confirmed in a larger population. The combination of conatumumab and gemcitabine was tolerable and showed some evidence of an improved 6-month survival rate. The ongoing phase 3 study is designed to provide additional information on the safety and efficacy of ganitumab combined with gemcitabine in metastatic adenocarcinoma of the pancreas.

acknowledgements

The authors thank the participating patients and their families, the investigators, Jennifer Gansert, MD, PhD (Amgen Inc.), for helpful comments, and Kathryn Boorer, PhD (Amgen Inc.), and Benjamin Scott, PhD (funded by Amgen Inc.), for assistance with writing the report.

funding

This work was supported by Amgen Inc.

disclosures

FG, JM, YH, EGF, and EL are employees of and shareholders in Amgen Inc. SLB is an employee of and a shareholder in Amgen Ltd. HLK received research funding and honoraria (for presentations at educational meetings) from and is an advisor for Amgen Inc. JJS received research funding from Amgen Inc. DAR is an advisor for Amgen Inc. CSF is an advisor for Amgen Inc., ImClone Systems, Genentech, Inc., Roche, and Infinity Pharmaceuticals. LEG, EBG, CMRL, HS, DC, and DMK have declared no conflicts of interest.

references