Safety and Pharmacokinetics of Ganitumab (AMG 479) Combined with Sorafenib, Panitumumab, Erlotinib, or Gemcitabine in Patients with Advanced Solid Tumors

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Abstract

Purpose: This phase 1b dose-escalation study assessed safety, tolerability, and pharmacokinetics of ganitumab, a fully human monoclonal antibody against the insulin-like growth factor 1 (IGF1) receptor, combined with targeted agents or cytotoxic chemotherapy in patients with advanced solid tumors.

Experimental Design: Patients with treatment-refractory advanced solid tumors were sequentially enrolled at 2 ganitumab dose levels (6 or 12 mg/kg i.v. every 2 weeks) combined with either sorafenib 400 mg twice daily, panitumumab 6 mg/kg every 2 weeks, erlotinib 150 mg once daily, or gemcitabine 1,000 mg/m² on days 1, 8, and 15 of each 4-week cycle. The primary end points were safety and pharmacokinetics of ganitumab.

Results: Ganitumab up to 12 mg/kg appeared well tolerated combined with sorafenib, panitumumab, erlotinib, or gemcitabine. Treatment-emergent adverse events were generally mild and included fatigue, nausea, vomiting, and chills. Three patients had dose-limiting toxicities: grade 3 hyperglycemia (ganitumab 6 mg/kg and panitumumab), grade 4 neutropenia (ganitumab 6 mg/kg and gemcitabine), and grade 4 thrombocytopenia (ganitumab 12 mg/kg and erlotinib). Ganitumab-binding and panitumumab-binding antibodies were detected in 5 and 2 patients, respectively; neutralizing antibodies were not detected. The pharmacokinetics of ganitumab and each cotherapy did not appear affected by coadministration. Circulating total IGF1 and IGF binding protein 3 increased from baseline following treatment. Four patients (9%) had partial responses.

Conclusions: Ganitumab up to 12 mg/kg was well tolerated, without adverse effects on pharmacokinetics in combination with either sorafenib, panitumumab, erlotinib, or gemcitabine. Ganitumab is currently under investigation in combination with some of these and other agents.

Introduction

The insulin-like growth factor 1 receptor (IGF1R) is a type 1 transmembrane tyrosine kinase receptor that, with its ligands insulin-like growth factor 1 (IGF1) and 2 (IGF2), regulates cell proliferation and apoptosis (1–4). The activity of IGFs is modulated by 6 IGF binding proteins (IGFBP), which may affect tumor growth and IGF function (5). There are several lines of evidence that implicate the IGF1R signaling axis in the development of human malignancies (6). Not only have constitutive IGF1R expression, IGF1R overexpression, and autocrine or paracrine signaling via IGF1R been proposed as mechanisms of transformation in several tumor types (7–11), but studies using gene knock-out mice have shown that IGF1R is required for transformation (12, 13).

In early-phase clinical trials, IGF1R inhibitors have shown acceptable toxicity profiles and evidence of antitumor activity (14). Several lines of evidence suggest that these agents might be combined with other anticancer agents in the treatment of solid tumors. Interactions between IGF1R and epidermal growth factor receptor (EGFR) have been reported in different cell types, and IGF1R may induce EGFR phosphorylation via autocrine or paracrine mechanisms involving EGF-like ligands (15–17). It was therefore postulated that combined inhibition of IGF1R and vascular endothelial growth factor (VEGF) or EGFR would be of therapeutic benefit. This rationale was further supported by...
patients with previously untreated metastatic pancreatic cancer. Combinations of IGF1R inhibitors and targeted or cytotoxic agents may improve treatment efficacy. We assessed the safety, pharmacokinetics, and antitumor activity of ganitumab combined with the multikinase inhibitor sorafenib, the fully human anti–epidermal growth factor receptor (EGFR) monoclonal antibody panitumumab, the EGFR small-molecule inhibitor erlotinib, or the nucleoside analogue gemcitabine. Ganitumab in combination with these agents was generally well tolerated, had favorable pharmacokinetics, and resulted in partial responses and tumor reductions in some patients. Ganitumab is currently under investigation in combination with targeted and cytotoxic agents for the treatment of several tumor types.

Translational Relevance
Ganitumab (AMG 479) is a fully human immunoglobulin G1 monoclonal antibody against the insulin-like growth factor 1 receptor (IGF1R). In early-stage trials, ganitumab had acceptable toxicity and evidence of activity in patients with advanced solid tumors and increased overall survival when combined with gemcitabine in patients with previously untreated metastatic pancreatic cancer. Preclinical studies reporting additive or synergistic inhibition of tumor cell growth, induction of apoptosis, and regression of tumor xenografts in several models when small-molecule tyrosine kinase inhibitors of IGF1R were combined with either of the EGFR inhibitors erlotinib or gefitinib (18–20). Similarly, combined treatment with an EGFR inhibitor and the multikinase inhibitor sorafenib was also associated with additive inhibition of cholangiocarcinoma cell growth (21). Furthermore, combination treatment with an IGF1R inhibitor and the cytotoxic chemotherapy gemcitabine was associated with additive inhibition of human pancreatic tumor xenograft growth (22).

Ganitumab (AMG 479) is a fully human immunoglobulin G1 monoclonal antibody against IGF1R that inhibits tumor cell proliferation, promotes tumor cell death, and causes regression of established tumor xenografts (23, 24). In a phase 1, first-in-human study, ganitumab as monotherapy had acceptable toxicity up to the maximum tested dose (20 mg/kg i.v. every 2 weeks) and showed antitumor activity in patients with solid tumors (25). The objectives of this study were to assess the safety, tolerability, and pharmacokinetics of ganitumab combined with the multikinase inhibitor sorafenib, the fully human anti-EGFR monoclonal antibody panitumumab, the EGFR tyrosine kinase inhibitor erlotinib, or the cytotoxic chemotherapy gemcitabine in patients with advanced solid tumors. In a phase 2 study, which used the data from this study to justify the dose of ganitumab combined with gemcitabine, the combination had acceptable toxicity and improved overall survival in patients with previously untreated metastatic pancreatic cancer (26).

Patients and Methods
Patients
Patients aged 18 years or more with pathologically or cytologically documented advanced solid tumors or renal cell carcinoma (sorafenib cohorts) refractory to at least 1 line of therapy or for which no standard or curative therapy was available; measurable or evaluable disease per World Health Organization (WHO) guidelines; an Eastern Cooperative Oncology Group performance status of 2 or less; life expectancy of 3 months or more; and adequate hematologic, renal, and hepatic function were eligible to enroll.

Exclusion criteria included unresolved toxicities from prior anticancer therapy; primary or metastatic central nervous system tumors (sorafenib cohorts only; controlled central nervous system tumors were allowed in other cohorts); uncontrolled hypertension; ascites or pleural effusion requiring treatment; abnormal pulmonary function, including impaired carbon monoxide diffusion capacity (gemcitabine cohorts); magnesium below the lower limit of normal (panitumumab cohorts); myocardial infarction, arterial thrombosis, or venous thrombosis within the previous 6 months; clinically significant hypoglycemia or hyperglycemia per investigator assessment; symptomatic congestive heart failure; unstable angina; unstable cardiac arrhythmia requiring treatment; peptic ulcer disease (sorafenib cohorts); major surgery within the previous 4 weeks (8 weeks for the sorafenib cohorts); anticoagulation therapy (except low-dose warfarin) within the previous week; active infection within the previous 2 weeks; and history of chronic hepatitis. Diabetes (type 1 or 2) and existence or risk for primary hepatic tumors were added as exclusion criteria after enrollment had begun.

Previous treatment with ganitumab or gemcitabine was not permitted. Prior treatment with cetuximab, panitumumab, sorafenib, bevacizumab, or erlotinib was allowed. Patients were excluded for anticancer therapy, radiation therapy, antibody therapy, retinoid therapy, hormonal therapy, or participation in clinical trials within the previous 4 weeks before enrollment (within the previous 6 weeks for nitrosoureas and mitomycin C). Concurrent hormone replacement therapy or gonadotropin-releasing hormone modulators were allowed for prostate cancer. Concomitant medications that interfered with cytochrome P450 3A metabolism were prohibited in the sorafenib and erlotinib cohorts. Institutional Review Board approval was obtained for all study procedures. All patients provided written informed consent before enrollment.

Study design
This phase 1b open-label, dose-escalation study used a 3 + 3 + 3 design to investigate the safety, tolerability, and pharmacokinetic profiles of ganitumab combined with sorafenib, panitumumab, erlotinib, or gemcitabine. The primary end points were safety [incidence of adverse events (AE), clinically significant changes in vital signs and laboratory tests] and pharmacokinetics of ganitumab. Secondary end points included the pharmacokinetics of each cotherapy, anti-ganitumab antibody formation, tumor...
response per WHO criteria, and volumetric tumor response by independent central assessment. Exploratory biomarker analyses were conducted, which included a pharmacodynamic analysis of serum IGF1 and IGFBP-3, immunohistochemical analysis of phosphatase and tensin homologue (PTEN) expression in archival tumors, and an analysis of somatic mutations in archival tumors.

Treatment and dose escalation

Fourteen dose cohorts of 3 to 9 patients each were initially planned, which included 10 cohorts to assess 2 dose levels of ganitumab (6 or 12 mg/kg every 2 weeks) combined with bevacizumab 10 mg/kg every 2 weeks, sorafenib 400 mg twice daily, panitumumab 6 mg/kg every 2 weeks, erlotinib 150 mg once daily, or gemcitabine 1,000 mg/m² on days 1, 8, and 15 of each 28-day cycle. Four optional ganitumab de-escalation cohorts were to be enrolled if intolerable toxicities occurred. Two planned bevacizumab cohorts were not enrolled after new evidence indicated that bevacizumab might have limited activity as a monotherapy in previously treated patients (27). The starting dose of 6 mg/kg and the target dose of 12 mg/kg for ganitumab were based on pharmacokinetic results from a preclinical tumor xenograft study and from the first-in-human study (25). Doses and schedules for sorafenib, panitumumab, erlotinib, and gemcitabine were based on product label information (28–31). Reduced doses of sorafenib and gemcitabine were allowed depending on the toxicities observed.

Initially, 3 patients were enrolled in each cohort at the first ganitumab dose level. Up to 9 patients could be enrolled in each cohort for additional safety and pharmacokinetic data. The decision to escalate to the second ganitumab dose level for each combination was made by the investigators and sponsor following review of available safety, laboratory, and pharmacokinetic data from a 21-day assessment period following the first dose. If 1 of 3 patients at the first dose level had a dose-limiting toxicity (DLT), then 3 additional patients were to be enrolled at the first dose level. If no further DLTs or serious ganitumab-related AEs were observed, enrollment in the second dose level could begin. If 2 of 6 patients at the first dose level had a DLT or serious ganitumab-related AE, then 3 additional patients were to be enrolled at the first dose level (for a total of 9 patients). A dose was considered toxic if 33% of patients or more experienced a DLT or serious ganitumab-related AE during the 21-day assessment period; the dose was to be stopped if 3 of 9 patients had a DLT.

Ganitumab was administered as a 1-hour intravenous infusion on day 2 of cycle 1 and on day 1 of each subsequent 2-week cycle. If 1-hour infusions were tolerated, subsequent infusions could be reduced to 30 minutes. If 1-hour infusions were poorly tolerated, subsequent infusions could be extended to 2 hours. Sorafenib was administered orally twice daily beginning on day 1. Panitumumab was administered as a 1-hour intravenous infusion on day 1 of each 2-week cycle. Erlotinib was administered orally once daily beginning on day 1. Gemcitabine was administered i.v. on days 1, 8, and 15 of each 4-week cycle. Study drugs were administered until disease progression or intolerable AE. Doses of study drugs could be withheld, reduced, or delayed per protocol-specified rules for the occurrence of toxicities; interruptions lasting more than 6 weeks resulted in study discontinuation. If ganitumab dosing was delayed, missed, or discontinued, cotherapies were also delayed, missed, or discontinued; however, ganitumab dosing was not altered as a result of altered dosing of cotherapies.

DLT and maximum tolerated dose

A DLT in all cohorts (except for the gemcitabine and sorafenib cohorts) was defined as any related grade of 3 or higher hematologic toxicity or nonhematologic toxicity occurring during the initial 21 days of treatment with ganitumab (except for alopecia or other well-described toxicity of the agents being investigated) according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0. A DLT in the gemcitabine cohorts was defined as any related grade of 3 or higher nonhematologic toxicity occurring during the initial 21 days of treatment with ganitumab (except for alopecia or other well-described toxicities). Grade 3 anemia, neutropenia, and thrombocytopenia were not considered DLTs unless the neutropenia was accompanied by fever higher than 38.5°C, the neutropenia lasted more than 7 days, or the thrombocytopenia was accompanied by bleeding. Grade 4 anemia, neutropenia, and thrombocytopenia were considered DLTs. The maximum tolerated dose of ganitumab was defined as the highest dose level at which fewer than 33% of treated patients in each arm had a DLT.

Study assessments

Safety and laboratory. All AEs occurring from enrollment until the last follow-up (30 days after the last dose) were recorded by investigators and graded per NCI-CTCAE version 3.0. Clinical chemistry, hematology, and urinalysis were assessed at screening, predose on days 1 and 8, before all subsequent ganitumab doses, and at the end-of-study visit.

Anti-ganitumab and anti-panitumumab antibodies. Blood samples for the assessment of anti-ganitumab antibodies were collected predose on days 1 (for panitumumab) or 2 (for ganitumab), days 29 and 57, every 12 weeks thereafter, and at the end-of-study visits (4 and 8 weeks after the last dose). Anti-ganitumab antibodies were assayed using an electrochemiluminescence bridging immunoassay as described previously (25). Anti-panitumumab antibodies were assayed using a bridging ELISA and a Biacore assay as described previously (32).

Pharmacokinetics. Blood samples for the measurement of pharmacokinetic profiles of ganitumab, sorafenib, panitumumab, erlotinib, and gemcitabine and its metabolite [2′-d difluorodeoxyuridine (dFdU)] were collected between weeks 5 (cycle 3, predose and postdose) and 7 (cycle 4, predose). Sparse samples were collected in weeks 1 (cycle 1, predose and postdose), 3 (cycle 2, predose and postdose), 11 (cycle 6, predose), and 15 (cycle 8, predose); predose every 12 weeks thereafter; and at the end-of-study visits (4...
and 8 weeks after the last dose). Serum concentrations of ganitumab and panitumumab were measured using a double-antibody sandwich immunoassay (25) and an electrochemiluminescence assay (33), respectively. Plasma concentrations of sorafenib, erlotinib, gemcitabine, and dFIL were measured by liquid chromatography with tandem mass spectrometry (see Supplementary Material). Pharmacokinetic parameters were estimated using non-compartmental methods with WinNonlin software (version 5.1.1; Pharsight Corp.).

Pharmacodynamic assessments. To assess the pharmacodynamic response of circulating IGF1 and IGFBP-3 to treatment with ganitumab, blood samples for the measurement of serum total IGF1 and IGFBP-3 were collected predose in cycles 1 (days 1, 2, and 8), 2 (day 15), 4 (day 43), and 6 (day 71), and at the end-of-study visit (4 weeks after the last dose of ganitumab). Serum IGF1 and IGFBP-3 were measured using competitive binding radioimmunoassays following alcohol/acid extraction. Briefly, extracts were incubated with rabbit polyclonal antisera specific for IGF1 or IGFBP-3 followed by radioiodinated purified recombinant human IGF1 or purified IGFBP-3. Concentrations of IGF1 and IGFBP-3 from control and test samples were determined from a dose–response curve generated in each assay using purified IGF1 or IGFBP-3. The sensitivities of the assays for IGF1 and IGFBP-3 were 15 and 0.3 ng/mL, respectively.

Analysis of tumor PTEN expression. Archival tumor samples were stained for nuclear and cytoplasmic expression of PTEN by immunohistochemistry and scored on a relative scale of 0 to 3 (0, no stain; 3, maximal stain). Tumor cells with a staining intensity of 1 or more in the nuclear or cytoplasmic compartments were considered PTEN positive. Detailed staining methods are described in the Supplementary Material.

Exploratory genetic analysis. DNA was extracted from archival formalin-fixed paraffin-embedded sections. To determine the somatic mutation status of HRAS, KRAS, NRAS, BRAF, PIK3CA, PTEN, and TP53, sequence libraries were generated and analyzed using the Roche 454 GS FLX Amplicon Sequencing platform. Detailed methods are available in the Supplementary Material.

Tumor assessment

Tumor assessment was carried out by computed tomography (CT) or magnetic resonance imaging and was evaluated by investigators within 4 weeks before enrollment and every 8 weeks (±1 week) thereafter. Volumetric CT analysis was performed by a central imaging laboratory (VirtualScopsics). Response was assessed by investigators per WHO criteria (34). A partial response was defined as a 50% or more decrease from baseline in the sum of the cross-products of the longest diameters (SPD) of index lesions for 4 or more weeks. Progressive disease was defined as at least a 25% increase in the SPD of index lesions taking as reference the nadir SPD recorded since the last treatment started or the presence of one or more new lesions. Stable disease was defined as neither sufficient shrinkage of index lesions to qualify for a partial response nor sufficient increase to qualify for progressive disease, taking as reference the nadir SPD since the treatment started. For duration of responses, responders who had not progressed or died during the study were censored at the last disease assessment.

Statistical analysis

Descriptive statistics were used to summarize demographic, safety, pharmacokinetic, biomarker, tumor assessment, and response data. The safety analysis set included all patients who received 1 or more doses of investigational product. All patients were included in efficacy analyses. Patients were categorized by the initial dose received.

Results

Patient demographics and disposition

Forty-six patients were enrolled at 3 centers in the United States between December 5, 2006, and September 2, 2009. All patients received at least 1 dose of ganitumab; 9 received at least 24 weeks of treatment. All patients received at least 1 dose of their respective cotherapies. Administration of the study drugs is summarized in Supplementary Table S1. Patients were enrolled sequentially, first completing treatment in the gemcitabine and panitumumab cohorts, followed by the sorafenib and erlotinib cohorts. Demographics and baseline characteristics are summarized in Table 1. The most common tumor types were colon (n = 11), ovarian (n = 6), breast (n = 4), and non–small cell lung (n = 3). The majority of patients (n = 31; 67%) had received 3 or more lines of prior cancer therapy and approximately one half had received radiotherapy (n = 24; 52%). Eleven patients (24%) discontinued the study early; reasons included consent withdrawn (n = 4), loss to follow-up (n = 2; after 4 and 6 doses, respectively), alternative therapy (n = 2), noncompliance (n = 1), AE (n = 1; see below, DLTs), and administrative decision (n = 1). Thirty-five patients (76%) completed the end-of-study visit.

Dose escalation, DLTs, and maximum tolerated dose

Overall 8 cohorts were enrolled in the study, comprising 20 patients in the ganitumab 6 mg/kg cohorts and 26 patients in the ganitumab 12 mg/kg cohorts. Initially, 3 patients were enrolled in cohorts to receive ganitumab 6 mg/kg combined with sorafenib 400 mg twice daily (cohort 1), panitumumab 6 mg/kg every 2 weeks (cohort 2), erlotinib 150 mg once daily (cohort 3), or gemcitabine 1,000 mg/m² (cohort 4). Two of these patients had DLTs: 1 in cohort 2 and 1 in cohort 4. In cohort 2, a patient with a thyroid tumor and history of diabetes had grade 3 hyperglycemia considered by investigators to be related to ganitumab. The patient’s baseline fasting glucose was 103 mg/dL; subsequent levels ranged from 189 to 350 mg/dL. The patient received treatment with insulin and the panitumumab dose was altered; the patient was eventually removed from the study owing to hyperglycemia. In cohort 4, a patient with a small cell lung tumor had grade...
### Table 1. Patient demographics and baseline characteristics

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<td>12 mg/kg ganitumab + 1,000 mg/m² gemcitabine (n = 3)</td>
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**Sex, n (%)**

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**ECOG performance status, n (%)**

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**Primary tumor type, n (%)**

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| 0 (0) | 0 (0)   | 0 (0)  | 0 (0)               | 0 (0)     | 0 (0)       | 0 (0)           | 0 (0)   | 0 (0)       | 0 (0)                    | 0 (0)     | 0 (0)                  | 0 (0)                       | (Continued on the following page)
<table>
<thead>
<tr>
<th>Cohort 1</th>
<th>Cohort 5</th>
<th>Cohort 2</th>
<th>Cohort 6</th>
<th>Cohort 3</th>
<th>Cohort 7</th>
<th>Cohort 4</th>
<th>Cohort 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 mg/kg ganitumab + 400 mg b.i.d sorafenib (n = 3)</td>
<td>12 mg/kg ganitumab + 6 mg/kg Q2W panitumumab (n = 6)</td>
<td>6 mg/kg ganitumab + 6 mg/kg Q2W panitumumab (n = 4)</td>
<td>12 mg/kg ganitumab + 150 mg qd erlotinib (n = 3)</td>
<td>6 mg/kg ganitumab + 1000 mg/m² gemcitabine (n = 8)</td>
<td>12 mg/kg ganitumab + 1000 mg/m² gemcitabine (n = 3)</td>
<td>Total (n = 46)</td>
<td></td>
</tr>
</tbody>
</table>

### Hepatocellular carcinoma
- Cohort 1: 1 (33)
- Cohort 5: 0 (0)
- Cohort 2: 0 (0)
- Cohort 6: 0 (0)
- Cohort 3: 0 (0)
- Cohort 7: 0 (0)
- Cohort 4: 0 (0)
- Cohort 8: 1 (2)

### Leiomyosarcoma
- Cohort 1: 0 (0)
- Cohort 5: 1 (10)
- Cohort 2: 0 (0)
- Cohort 6: 0 (0)
- Cohort 3: 0 (0)
- Cohort 7: 0 (0)
- Cohort 4: 0 (0)
- Cohort 8: 1 (2)

### Squamous cell carcinoma of the anus
- Cohort 1: 0 (0)
- Cohort 5: 1 (10)
- Cohort 2: 0 (0)
- Cohort 6: 0 (0)
- Cohort 3: 0 (0)
- Cohort 7: 0 (0)
- Cohort 4: 0 (0)
- Cohort 8: 1 (2)

### Neuroendocrine
- Cohort 1: 0 (0)
- Cohort 5: 1 (10)
- Cohort 2: 0 (0)
- Cohort 6: 0 (0)
- Cohort 3: 0 (0)
- Cohort 7: 0 (0)
- Cohort 4: 0 (0)
- Cohort 8: 1 (2)

### Pancreatic
- Cohort 1: 0 (0)
- Cohort 5: 0 (0)
- Cohort 2: 1 (17)
- Cohort 6: 0 (0)
- Cohort 3: 0 (0)
- Cohort 7: 0 (0)
- Cohort 4: 0 (0)
- Cohort 8: 1 (2)

### Prostate
- Cohort 1: 0 (0)
- Cohort 5: 0 (0)
- Cohort 2: 0 (0)
- Cohort 6: 0 (0)
- Cohort 3: 0 (0)
- Cohort 7: 0 (0)
- Cohort 4: 0 (0)
- Cohort 8: 1 (33)

### Rectal
- Cohort 1: 0 (0)
- Cohort 5: 0 (0)
- Cohort 2: 1 (25)
- Cohort 6: 0 (0)
- Cohort 3: 0 (0)
- Cohort 7: 0 (0)
- Cohort 4: 0 (0)
- Cohort 8: 1 (2)

### Sacrum chondroma
- Cohort 1: 0 (0)
- Cohort 5: 1 (10)
- Cohort 2: 0 (0)
- Cohort 6: 0 (0)
- Cohort 3: 0 (0)
- Cohort 7: 0 (0)
- Cohort 4: 0 (0)
- Cohort 8: 1 (2)

### Squamous cell head/neck
- Cohort 1: 0 (0)
- Cohort 5: 0 (0)
- Cohort 2: 0 (0)
- Cohort 6: 0 (0)
- Cohort 3: 0 (0)
- Cohort 7: 0 (0)
- Cohort 4: 0 (0)
- Cohort 8: 1 (2)

### Lines of prior therapy, n (%)

<table>
<thead>
<tr>
<th>Lines</th>
<th>Cohort 1</th>
<th>Cohort 5</th>
<th>Cohort 2</th>
<th>Cohort 3</th>
<th>Cohort 4</th>
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<td>1 (17)</td>
<td>1 (17)</td>
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<tr>
<td>2</td>
<td>2 (20)</td>
<td>3 (50)</td>
<td>3 (50)</td>
<td>0 (0)</td>
<td>3 (33)</td>
<td>2 (25)</td>
</tr>
<tr>
<td>≥3</td>
<td>3 (100)</td>
<td>7 (70)</td>
<td>2 (33)</td>
<td>4 (100)</td>
<td>3 (100)</td>
<td>5 (56)</td>
</tr>
</tbody>
</table>

### Lines of prior radiotherapy, n (%)

<table>
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<th>Cohort 5</th>
<th>Cohort 2</th>
<th>Cohort 3</th>
<th>Cohort 4</th>
<th>Cohort 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1 (33)</td>
<td>4 (40)</td>
<td>1 (17)</td>
<td>4 (100)</td>
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<td>1 (17)</td>
<td>0 (0)</td>
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<td>2 (25)</td>
</tr>
<tr>
<td>≥3</td>
<td>1 (33)</td>
<td>2 (20)</td>
<td>0 (0)</td>
<td>1 (33)</td>
<td>0 (0)</td>
<td>1 (13)</td>
</tr>
</tbody>
</table>

**NOTE:** Safety analysis set includes patients who received more than 1 dose of ganitumab.

*Abbreviations: b.i.d, twice daily; ECOG, Eastern Cooperative Oncology Group; Q2W, every 2 weeks; qd, once daily.*

*Patients were eligible if they had advanced solid tumors refractory to more than 1 line of therapy, if no standard or curative therapy was available, or if standard noncurative therapy was refused.*
### Table 2. Summary of AEs

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Patients, n (%)</th>
<th>Patients with ≥1 treatment-emergent AE</th>
<th>Patients with ≥1 serious AE</th>
<th>Patients with fatal AEs</th>
<th>Patients with ganitumab-related AEsa</th>
<th>Patients with grade ≥3 treatment-emergent AEsa</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6 mg/kg ganitumab + 400 mg b.i.d sorafenib</td>
<td>3 (100)</td>
<td>3 (100)</td>
<td>1 (33)</td>
<td>2 (67)</td>
<td>1 (11)</td>
</tr>
<tr>
<td>5</td>
<td>12 mg/kg ganitumab + 400 mg b.i.d sorafenib</td>
<td>10 (100)</td>
<td>10 (100)</td>
<td>6 (60)</td>
<td>1 (17)</td>
<td>1 (25)</td>
</tr>
<tr>
<td>2</td>
<td>6 mg/kg ganitumab + 6 mg/kg Q2W panitumumab</td>
<td>6 (100)</td>
<td>6 (100)</td>
<td>1 (10)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>6</td>
<td>12 mg/kg ganitumab + 6 mg/kg Q2W panitumumab</td>
<td>4 (100)</td>
<td>4 (100)</td>
<td>1 (10)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>3</td>
<td>6 mg/kg ganitumab</td>
<td>3 (100)</td>
<td>3 (100)</td>
<td>8 (80)</td>
<td>4 (67)</td>
<td>3 (75)</td>
</tr>
<tr>
<td>7</td>
<td>12 mg/kg ganitumab</td>
<td>9 (100)</td>
<td>9 (100)</td>
<td>6 (100)</td>
<td>3 (100)</td>
<td>1 (33)</td>
</tr>
<tr>
<td>4</td>
<td>6 mg/kg ganitumab + 6 mg/kg Q2W panitumumab</td>
<td>8 (100)</td>
<td>8 (100)</td>
<td>6 (100)</td>
<td>4 (100)</td>
<td>1 (33)</td>
</tr>
<tr>
<td>8</td>
<td>12 mg/kg ganitumab + 1,000 mg/m² gemcitabine</td>
<td>3 (100)</td>
<td>3 (100)</td>
<td>3 (100)</td>
<td>3 (100)</td>
<td>1 (33)</td>
</tr>
</tbody>
</table>

(Continued on the following page)
4 neutropenia. As a result of the DLTs, cohorts 2 and 4 were each expanded to 6 patients to collect additional safety and pharmacokinetic data. In addition, 2 patients were enrolled in cohort 4 as replacements for 2 patients who received ganitumab dosing errors (12 mg/kg instead of 6 mg/kg ganitumab) during the DLT assessment window.

Subsequently, 3 patients were enrolled in cohorts to receive ganitumab 12 mg/kg combined with sorafenib (cohort 5), panitumumab (cohort 6), erlotinib (cohort 7), or gemcitabine (cohort 8). One patient in cohort 7 with ovarian cancer had a DLT (grade 4 thrombocytopenia) after the first dose of ganitumab (day 5). The patient was removed from the study and did not receive subsequent treatment. Subsequently, cohorts 5 and 7 were expanded to 9 patients to collect additional safety and pharmacokinetic data. In addition, 1 patient each in cohorts 5 and 6 was replaced due to consent withdrawal and failure to complete DLT window, resulting in a total enrollment of 10 and 4 patients, respectively. Ganitumab at the highest tested dose of 12 mg/kg appeared to be well tolerated when combined with full doses of each cotherapy (as defined by a DLT rate <33%).

Safety and tolerability

Toxicity is summarized in Table 2. The most frequent ganitumab-related AEs were fatigue, nausea, vomiting, chills not associated with infusion, anorexia, and thrombocytopenia. The AEs considered related to treatment with the cotherapies were consistent with those previously reported for these agents (35–37). Grade 3 or higher treatment-emergent AEs occurred in 33 patients (72%). The most common (occurring in ≥4% of patients) grade 3 or higher treatment-emergent AEs were neutropenia, fatigue, anemia, palmar-plantar erythrodysesthesia syndrome, hypomagnesemia, rash, intestinal obstructions, and dehydration (see Table 2). Grade 3 or higher ganitumab-related AEs (each n = 1) were fatigue (cohort 5), thrombocytopenia (cohort 4), cataract (cohort 1), hyperglycemia (cohort 2), hyponatremia (cohort 5), and neutropenia (cohort 5). Serious AEs occurred in 15 patients (33%), none of which were considered by investigators to be related to ganitumab. The most frequent (occurring in ≥4% of patients) serious AEs were dehydration [cohort 5, n = 1 (10%); cohort 7, n = 1 (11%)], diarrhea [cohort 5, n = 1 (10%); cohort 7, n = 1 (11%)] and intestinal obstruction [cohort 3, n = 1 (13%); cohort 7, n = 1; (11%)]. Dehydration and diarrhea were the only serious AEs considered by investigators to be potentially related to treatment with a study drug (sorafenib; cohort 5).

Hyperglycemia was not reported in any patient aside from the occurrence considered a DLT. Two patients had hepatotoxicity events (grade 2 hepatic pain and grade 3 increased alanine aminotransferase), neither of which was considered by investigators to be related to ganitumab; however, the increased alanine aminotransferase was considered by investigators to be potentially related to treatment with sorafenib. Three patients (7%) had AEs identified as potential sensorineural hearing loss. However, only 1
patient (cohort 7) had sensorineural hearing loss (grade 2 hypoacusis) considered by investigators to be potentially related to ganitumab. The patient had prior exposure to loud noises and a 3- to 6-month history of diminished hearing before enrollment. No infusion reactions were reported during the study.

AEs considered potentially related to treatment with the cotherapies were consistent with those previously reported for these agents (35–37). Neutropenia events were reported in 7 patients (15%) overall and occurred predominantly in the gemcitabine cohorts (cohort 4, n = 4; cohort 5, n = 1; cohort 8, n = 2). In addition to the 1 case of grade 4 neutropenia in cohort 4 considered a DLT, grade 3 neutropenia occurred in 5 patients (cohort 4, n = 3; cohort 8, n = 2), grade 4 neutropenia occurred in 1 patient in cohort 5, and grade 1 leukopenia occurred in 1 patient in cohort 8. Of these events, only the grade 1 leukopenia and the grade 4 neutropenia were considered by the investigators to be potentially related to ganitumab. The grade 4 neutropenia was not considered a DLT because it occurred after the 21-day assessment period. Thrombocytopenia events occurred in the gemcitabine cohort (n = 7) and in the erlotinib cohort (n = 3).

Skin rash occurred in 33 patients (72%) overall and in 75%, 100%, 75%, and 36% of patients in the sorafenib, panitumumab, erlotinib, and gemcitabine cohorts, respectively. One patient who received sorafenib (cohort 5) had a grade 3 superior vena cava occlusion that was not considered related to ganitumab.

The only treatment discontinuations as a result of AEs are described above (cohort 2, hyperglycemia; cohort 7, thrombocytopenia). Delays in and reduced dosing of ganitumab occurred in 6 and 3 patients, respectively, as a result of AEs. One patient (cohort 5) died on study day 61 of respiratory failure not considered by investigators to be related to treatment with ganitumab. This patient, who had ovarian cancer for 10 years, had multiple surgeries and had been heavily pretreated with various chemotherapy agents before enrollment.

**Antibodies**

Ganitumab-binding antibodies were detected in 5 patients (11%) during the study, 2 of whom had detectable binding antibodies at or before baseline. Ganitumab-neutralizing antibodies were not detected in any patient before or during the study. Panitumumab-binding antibodies were detected in 2 patients (1 each in cohorts 2 and 6) with the Biacore assay but were not detected with the ELISA. In the patients with detectable binding antibodies with the Biacore assay, none were detected at or before baseline or within 90 days of the last dose. Panitumumab-neutralizing antibodies were not detected in any patient during the study.

**Pharmacokinetics**

The pharmacokinetic parameters of ganitumab and each cotherapy are shown in Tables 3 and 4, respectively. Estimates of mean ganitumab exposure (maximum observed serum concentration, minimum observed serum concentration, and area under the concentration versus time curve for a dosing interval) were approximately 2-fold greater among patients who received ganitumab 12 mg/kg versus 6 mg/kg in all cohorts, indicating that dose linearity was not affected by coadministration with sorafenib, panitumumab, erlotinib, or gemcitabine. Ganitumab clearance at both the 6 and 12 mg/kg doses in combination with sorafenib, panitumumab, erlotinib, and gemcitabine ranged from 8.94 to 17.0 mL/d/kg, which was within the expected range with monotherapy (25). Estimated pharmacokinetic parameters for sorafenib, panitumumab, erlotinib, and gemcitabine did not seem to be affected by coadministration with ganitumab (Table 4).

| Table 3. Pharmacokinetic parameter estimates of ganitumab after coadministration with sorafenib, panitumumab, erlotinib, or gemcitabinea |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Parameter, mean (SD) | Cohort 1 | Cohort 5 | Cohort 2 | Cohort 6 | Cohort 3 | Cohort 7 | Cohort 4 | Cohort 8 |
| Cmax, µg/mL | 106 (0) | 231 (54.1) | 129 (42.5) | 359 (84.6) | 133 (32.3) | 251 (64.1) | 114 (23.6) | 264 (28.0) |
| Cmin, µg/mL | 5.28 (NA) | 17.7 (13.5)b | 18.0 (6.46) | 34.6 (15.4) | 13.6 (3.29) | 33.9 (6.94) | 17.6 (9.80) | 31.7 (4.64) |
| AUCτ, h µg/mL | 388 (NA) | 879 (337)b | 643 (205) | 1,430 (234) | 529 (102) | 1,250 (186) | 592 (168) | 1,170 (266) |
| CL, mL/d/kg | 17.0 (NA) | 16.6 (7.49)b | 10.7 (5.02) | 8.94 (1.51) | 12.1 (1.85) | 10.1 (1.24) | 11.2 (3.46) | 10.6 (2.30) |

Abbreviations: AUCτ, area under the concentration versus time curve for a dosing interval; b.i.d, twice daily; CL, systemic clearance; Cmax, maximum observed serum concentration after dosing; Cmin, minimum observed serum concentration after dosing; NA, not assessable; Q2W, every 2 weeks; qd, once daily.

aData were available from only 1 patient.

bData available from only 8 patients.
Overall, 39 of 46 patients had evaluations of tumor response per WHO criteria (34) per investigator assessment. Of these, 35 had both baseline and posttreatment imaging; 4 had assessments based on new lesions or nonindex lesions (described in Fig. 1). The best result changes from baseline in SPD of index lesions of 35 patients are shown in Fig. 1. Four patients (9%) had partial responses as a best result. For these 4 patients, the duration of objective response was: 24 weeks for a patient with endometrial cancer in cohort 1 (sorafenib), 25.4 weeks for a patient with breast cancer in cohort 3 (erlotinib; censored at last assessment), 24.1 weeks for a

Table 4. Pharmacokinetic parameter estimates of sorafenib, panitumumab, erlotinib, and gemcitabine after coadministration with ganitumab

<table>
<thead>
<tr>
<th>Agent</th>
<th>Week</th>
<th>Dose</th>
<th>Regimen</th>
<th>n</th>
<th>Mean (SD) C_{max}, μg/mL</th>
<th>Mean (SD) AUC_{T}, h·μg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorafenib</td>
<td>5</td>
<td>400 mg</td>
<td>b.i.d.</td>
<td>2–4</td>
<td>5.36 (4.03)</td>
<td>37.0 (14.0)</td>
</tr>
<tr>
<td>Panitumumab</td>
<td>5</td>
<td>6 mg/kg</td>
<td>Q2W</td>
<td>8</td>
<td>197 (52.3)</td>
<td>35,280 (8,952)</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>5</td>
<td>150 mg</td>
<td>qd</td>
<td>6–9</td>
<td>1.59 (1.21)</td>
<td>33.5 (24.3)</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>1</td>
<td>1,000 mg/m²</td>
<td>QW</td>
<td>11</td>
<td>11.5 (3.51)</td>
<td>6.53 (0.967)</td>
</tr>
<tr>
<td>Gemcitabine^a</td>
<td>5</td>
<td>1,000 mg/m²</td>
<td>QW</td>
<td>11</td>
<td>11.0 (12.5)</td>
<td>6.38 (5.69)</td>
</tr>
<tr>
<td>dFdU^a</td>
<td>11</td>
<td>36.6 (5.66)</td>
<td></td>
<td>210 (29.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>dFdU^a</td>
<td>11</td>
<td>31.3 (7.58)</td>
<td></td>
<td>220 (48.1)</td>
<td></td>
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</tbody>
</table>

NOTE: Week 1 without ganitumab or week 5 with ganitumab.

Abbreviations: AUC_{T}, area under the concentration versus time curve for a dosing interval; b.i.d, twice daily; C_{max}, maximum observed serum concentration after dosing; Q2W, every 2 weeks; qd, once daily; QW, once weekly.

^a dFdU is a metabolite of gemcitabine.

Tumor response

Overall, 39 of 46 patients had evaluations of tumor response per WHO criteria (34) per investigator assessment. Of these, 35 had both baseline and posttreatment imaging; 4 had assessments based on new lesions or nonindex lesions (described in Fig. 1). The best result changes from baseline in SPD of index lesions of 35 patients are shown in Fig. 1. Four patients (9%) had partial responses as a best result. For these 4 patients, the duration of objective response was: 24 weeks for a patient with endometrial cancer in cohort 1 (sorafenib), 25.4 weeks for a patient with breast cancer in cohort 3 (erlotinib; censored at last assessment), 24.1 weeks for a

Figure 1. The best result changes from baseline in sum of the cross-products of the longest diameters of index lesions among evaluable patients with measurable disease (n = 35) per World Health Organization criteria and independent central review for patients who received ganitumab combined with sorafenib, panitumumab, erlotinib, or gemcitabine. Four patients are not included: 1 colon cancer patient (ganitumab 6 mg/kg + panitumumab) had progressive disease due to new lesions; 1 esophageal cancer patient (ganitumab 6 mg/kg + erlotinib) had progressive disease due to new lesions; 1 breast cancer patient (ganitumab 6 mg/kg + gemcitabine) with only nonindex lesions had stable disease; and 1 ovarian cancer patient (ganitumab 12 mg/kg + sorafenib) had progressive disease due to new lesions. CUO, carcinoma of unknown origin; GE, gastroesophageal; HC, hepatocellular carcinoma; HGSL, high-grade sarcoma, leiomyosarcoma; NSCLC, non–small cell lung cancer; SC, sacrum chordoma; SCCA, squamous cell carcinoma of the anus; SCHN, squamous cell head/neck; SCLC, small cell lung cancer.
patient with colon cancer in cohort 6 (panitumumab), and 16.9 weeks for a patient with prostate cancer in cohort 8 (gemcitabine). These 4 patients were heavily pretreated, having previously received multiple cytotoxic and targeted therapies. Twenty-three patients had best result of stable disease [sorafenib cohorts: cohorts 1 (n = 2), cohort 5 (n = 5); panitumumab cohorts: cohort 2 (n = 5), cohort 6 (n = 1); erlotinib cohorts: cohort 3 (n = 1), cohort 7 (n = 1); gemcitabine cohorts: cohort 4 (n = 7), cohort 8 (n = 1)]. Among these, 6 received treatment of 24 or more weeks, and the most frequent primary tumor types were colon (n = 5), thyroid, non–small cell lung, squamous cell, and ovarian (all n = 2). The remaining 12 evaluable patients had progressive disease as a best result [sorafenib cohorts: cohort 1 (n = 0), cohort 5 (n = 3); panitumumab cohorts: cohort 2 (n = 1), cohort 6 (n = 1); erlotinib cohorts: cohort 3 (n = 1), cohort 7 (n = 4); gemcitabine cohorts: cohort 4 (n = 1), cohort 8 (n = 1)]. There were no significant discordances in tumor response between the investigator and central assessments.

**Assessment of potential biomarkers**

At the 6 and 12 mg/kg doses of ganitumab, mean total serum levels of IGF1 increased from baseline to day 8 and remained relatively constant through week 11 or the end of study (Fig. 2A). At day 15 (collected at trough levels before the second dose), the IGF1 ratio to baseline was 1.31 at the 12 mg/kg dose of ganitumab and 1.20 at the 6 mg/kg dose, indicating the presence of a dose-dependent pharmacodynamic effect at both ganitumab dose levels. Mean total serum levels of IGFBP-3 increased from baseline to the end of study at both dose levels of ganitumab (Fig. 2B). No dose-dependent differences were observed. No associations were observed between the pharmacodynamic markers and change from baseline in SPD of target lesions.

We assessed potential associations between PTEN expression and response to treatment with ganitumab combined with sorafenib, panitumumab, erlotinib, and gemcitabine. Although immunohistochemical analysis of archival tumor samples confirmed cytoplasmic and nuclear expression of PTEN in the majority of available specimens, there was no observed association between the proportion of PTEN-positive cells and percentage change in SPD of target lesions (Supplementary Table S2).

An exploratory analysis of somatic mutations in genes with potential involvement in the IGF1R and EGFR signaling pathways (KRAS, BRAF, HRAS, NRAS, PIK3CA, PTEN,

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**Figure 2.** Mean (SD) change from baseline in serum total IGF1 (A) and IGFBP-3 (B).
antitumor activity of ganitumab in a variety of combinations versus single-agent treatment. Although anti-tumor activity was not a primary objective of this phase 1b study of heavily pretreated patients, 4 of 46 patients (9%) with the following tumor types had partial responses: endometrial (cohort 1), breast (cohort 3), colon (cohort 6), and prostate cancer (cohort 8). Twenty-three patients (59%) had stable disease, including 1 patient with neuroendocrine cancer and 1 patient with pancreatic cancer. One partial response occurred in each of the sorafenib, erlotinib, panitumumab, and gemcitabine cohorts with ganitumab at either dose level. Although these results suggest that there was some evidence of antitumor activity for each of the combinations, larger studies will be required to assess whether there were improvements in outcomes with these combinations versus single-agent treatment.

In the pharmacodynamic biomarker analysis, serum total IGF1 and IGFBP-3 increased from baseline following treatment with ganitumab at both dose levels. Similar increases in circulating IGF1 were observed following treatment with ganitumab 20 mg/kg in the first-in-human study (25).

In an exploratory analysis, we investigated whether there was an association between tumor expression of PTEN and tumor response. Preclinical evidence has suggested that the IGF1 signaling pathway promotes tumor cell proliferation and invasiveness through dephosphorylation of the tumor suppressor PTEN and activation of the PI3K/PTEN/Akt/NF-κB signaling pathway (44). Furthermore, loss of PTEN expression has been associated with poor outcomes among cancer patients (45, 46) and with lack of response to anti-EGFR therapy for metastatic colorectal cancer (47). Although the majority of tumor samples in this study was assessed as PTEN positive, there was no association between PTEN expression and change in tumor dimensions in the limited number of samples from a mixed patient population.

In conclusion, ganitumab at the target dose of 12 mg/kg combined with the approved doses of sorafenib, panitumumab, erlotinib, or gemcitabine had acceptable toxicity and showed evidence of antitumor activity, suggesting that further studies of ganitumab combinations for the treatment of solid tumors may be warranted at the doses established in this trial. Ganitumab combined with gemcitabine in metastatic pancreatic cancer is currently being investigated in a randomized phase 3 study (Gemcitabine and AMG 479 in Metastatic Adenocarcinoma of the Pancreas [GAMMA]; Clinicaltrials.gov, NCT01231347).

Disclosure of Potential Conflicts of Interest

G. Friberg, Y.C. Hwang, H. Deng, J. McCaffery, and M. Zhu are employees of and shareholders in Amgen Inc. L.S. Rosen has received research funding from Amgen Inc. E. Chan has served as a consultant/advisor for Amgen Inc., Genentech, ImClone, Celgene, Bristol-Myers Squibb, and Sanofi-Aventis. No potential conflicts of interest were disclosed by the other authors.

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34. Safety of Ganitumab Plus Targeted or Cytotoxic Agents
Safety and Pharmacokinetics of Ganitumab (AMG 479) Combined with Sorafenib, Panitumumab, Erlotinib, or Gemcitabine in Patients with Advanced Solid Tumors
