Putative Predictive Biomarkers of Survival in Patients with Metastatic Pancreatic Adenocarcinoma Treated with Gemcitabine and Ganitumab, an IGF1R Inhibitor

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Abstract

Purpose: This planned exploratory analysis assessed the predictive nature of baseline circulating factors of the insulin-like growth factor (IGF) axis on the treatment effect of ganitumab (monoclonal antibody inhibitor of IGF-1 receptor) plus gemcitabine in a randomized phase II study in metastatic pancreatic adenocarcinoma.

Experimental Design: Baseline levels of IGFs/IGF binding proteins (IGFBP) were analyzed in serum or plasma. Mutations and gene expression were analyzed in archival samples. Treatment effects between biomarker subgroups were compared for overall survival (OS). Associations of tumor markers with OS were evaluated.

Results: For patients with evaluable samples, ganitumab was associated with improved OS versus placebo (HR, 0.49; 95% CI: 0.28–0.87). The treatment effect on improved OS was strong in the patient subset with higher levels of IGF-1, IGF-2, or IGFBP-3, or lower levels of IGFBP-2, but not so on the other corresponding subset. Median OS of ganitumab versus placebo in patients with higher levels of IGF-1, IGF-2, and IGFBP-3 was 16 versus 6.8 months (HR, 0.25; 95% CI: 0.09–0.67), 16 versus 5.9 months (HR, 0.24; 95% CI: 0.09–0.68), and 16 versus 6.8 months (HR, 0.28; 95% CI: 0.11–0.73), and in patients with lower IGFBP-2 levels was 12.7 versus 6.6 months (HR, 0.19; 95% CI: 0.07–0.55). Interaction between treatment and IGFs/IGFBPs in multivariate analyses suggested predictive potential for IGF-2 ($P = 0.002$) and IGFBP-2 ($P = 0.02$). KRAS mutation status and PTEN expression were not associated with OS.

Conclusions: Baseline circulating factors of the IGF axis may predict OS benefit from ganitumab plus gemcitabine in metastatic pancreatic adenocarcinoma. *Clin Cancer Res; 19(15); 4282–9. ©2013 AACR.*

Introduction

Pancreatic cancer is the fourth-leading cause of cancer-related deaths in the United States, and most patients have advanced or metastatic disease at diagnosis (1, 2). Available treatments in this disease setting offer modest benefits. For example, the only approved targeted therapy for first-line treatment of metastatic disease is erlotinib combined with gemcitabine, which was approved in 2005 based on a statistically significant but modest improvement in overall survival (OS) (3, 4). Novel therapies and ways to identify patients who benefit from them are still needed.

The insulin-like growth factor (IGF)-1 receptor (IGF1R) is a rational drug target for pancreatic cancer given its role as a key regulator of proliferation, metabolism, and survival in tumor cells. IGF1R is activated by the binding of either of its 2 ligands, IGF-1 or IGF-2, which results in the activation of intracellular signaling pathways, including the Ras/MAP kinase and PI3K/Akt pathways (5–9). Several lines of evidence support a key role for IGF1R in transformed cells. For instance, *in vitro* studies showed that IGF1R overexpression in engineered cell lines resulted in cellular transformation (10). In animal models, IGF1R inhibition slowed the growth of pancreatic tumor xenografts and enhanced the effect of gemcitabine (11).

There are 6 IGF binding proteins (IGFBP-1 through IGFBP-6) that bind to the ligands in circulation and regulate their availability to engage IGF1R (12). IGFBP-3, the most abundant binding protein in circulation, accounts for the majority of ligand binding and is thought to sequester the ligands in an inactive form. In addition, the half-lives of the ligands are increased when in complex with IGFBP-3. For example, the half-life of unbound IGF-1 is 15 minutes and increases to 16 hours when bound to IGFBP-3 (13). These complexes are restricted to circulation as they are

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Translational Relevance

Identification of predictive markers for IGF1R inhibitors is an area of active research. Ganitumab, a fully human, monoclonal antibody inhibitor of IGF1R, plus gemcitabine showed longer survival than placebo plus gemcitabine as initial treatment for metastatic pancreatic adenocarcinoma in a randomized phase II trial. We hypothesized that baseline levels of circulating ligands of IGF1R and their associated binding proteins which regulate ligand availability would predict tumor dependence on IGF1R activity and therefore sensitivity to IGF1R inhibition. Consistent with this, analyses on assessing the predictive nature of the baseline circulating factors on the treatment effect of ganitumab suggested that some of the markers were potentially predictive for overall survival. Tumor somatic mutations in pathway-related genes and PTEN expression were analyzed but were not informative. The trends identified in this study inform investigation in future clinical studies in pancreatic cancer and other tumor types.

unable to cross the vascular endothelium, which is an important component in regulating IGF1R activity. Proteases are known to cleave IGFBP-3, and in tissues where these proteases are expressed, such as in neoplastic cells, the ligands are released and available to activate IGF1R (14). The functions of the remaining binding proteins are poorly understood but are thought to neutralize ligand activity (13). IGFBP-2, the second most abundant binding protein, is mostly found in an unsaturated form and has a lower affinity for the ligands than IGFBP-3. IGFBP-2 has been postulated to act as a sink for unbound ligands. In a physiologic context, IGF1R-dependent tumors would have high IGF1R ligand availability through high levels of circulating ligands and IGFBP-3 and low levels of neutralizing binding proteins, such as IGFBP-2.

A number of somatic mutations and genomic factors in tumor cells are known to activate pathways downstream of IGF1R, obviating the need for ligand-dependent activation. The KRAS gene is mutated in approximately 70% of pancreatic tumors (15). PTEN, a phosphatase that negatively regulates the PI3K/Akt pathway, is frequently inactivated through mutation, deletion, or downregulation of protein expression in carcinomas, leading to the constitutive activation of PI3K/Akt signaling (16–18). PTEN gene mutations or deletions are infrequent in pancreatic tumors (15), whereas PTEN expression is variable and potentially represents differential tumor dependence on IGF1R.

Ganitumab is an investigational, fully human, monoclonal antibody (IgG1) antagonist of IGF1R that blocks the binding of IGF-1 and IGF-2 to IGF1R. Ganitumab has been shown to inhibit proliferation and survival in pancreatic carcinoma cells (11). In a randomized phase II study in metastatic pancreatic adenocarcinoma, the addition of ganitumab to gemcitabine had manageable toxicities and

was associated with longer median OS than those treated with placebo and gemcitabine (8.7 versus 5.9 months; HR, 0.67; 95% CI: 0.41–1.12; $P = 0.12$); median progression-free survival was also longer with ganitumab treatment (5.1 versus 2.1 months; HR, 0.65; 95% CI, 0.41–1.04; $P = 0.072$; ref. 19).

In this report, the results of pre-planned, exploratory biomarker analyses from the phase II study are described. The objectives of the biomarker analyses were to (i) assess the predictive nature of the baseline circulating factors of the IGF axis on the treatment effect of ganitumab plus gemcitabine versus placebo plus gemcitabine on OS and (ii) identify associations between OS and mutations in genes of the Ras/MAP kinase and PI3K/Akt pathways and tumor expression levels of PTEN protein.

Materials and Methods

Patients

Eligible patients ($\geq$18 years) had metastatic adenocarcinoma of the pancreas, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and no prior chemo- or radiotherapy for pancreatic cancer. Complete eligibility criteria are reported elsewhere (19). Study procedures were approved by an Institutional review board. Patients provided written informed consent for the trial, including biomarker testing.

Study design

This was a multicenter, 3-arm, randomized phase II study. Patients were randomized 1:1:1 to receive gemcitabine with ganitumab (open label), placebo (blinded), or conatumumab (an investigational, fully human, monoclonal antibody agonist of human death receptor 5; blinded). Detailed treatment procedures were reported elsewhere (19). Briefly, ganitumab (12 mg/kg) and placebo were administered intravenously (IV) on days 1 and 15, and gemcitabine (1,000 mg/m^2) was administered intravenously on days 1, 8, and 15 of each 28-day cycle. Treatment with ganitumab continued until disease progression, unacceptable toxicity, or withdrawal of consent.

Sample collection

Serum and plasma samples were collected before treatment on day 1 (baseline). Samples were stored at $-80°$C until analysis. Archival formalin-fixed paraffin-embedded (FFPE) tumor samples from surgical resection or biopsy could be provided at any time during the study. Tissue blocks and paraffin-dipped slides were stored at $-20°$C.

Analysis of circulating biomarkers

Total IGF-1 and free IGF-1 (fIGF-1) were evaluated using specific immunoassays that distinguish between the total and free forms of the ligand. Baseline levels of total IGF-1 were measured in serum as described previously (20). Baseline levels of fIGF-1, IGF-2, IGFBP-1, IGFBP-2, IGFBP-3, and IGFBP-4 were measured in serum or plasma using immunoassays as described in the Supplementary Data.

Analysis of somatic mutations and PTEN protein expression in tumor tissues

DNA was extracted from archival FFPE tumor samples, and the mutational status of the following genes was analyzed by DNA sequencing: *KRAS*, *HRAS*, *NRAS*, *BRAF*, *PIK3CA*, *PTEN*, and *TP53*. Archival FFPE tumor samples were also stained for nuclear and cytoplasmic expression of PTEN by immunohistochemistry. Detailed methods are provided in the Supplementary Data.

Statistical analysis

Randomized patients who received at least 1 dose of ganitumab or placebo and who had an evaluable baseline sample for at least 1 circulating factor were included in the biomarker analysis set. For fIGF-1, values below the lower limit of quantitation (LLOQ), a value of half of the LLOQ was assigned. Values were log-transformed and then standardized (i.e., subtract mean and divide by SD) for easier interpretation of the estimates among biomarkers (21). High and low biomarker status was defined by the median value of each biomarker using data from both the ganitumab and placebo arms.

Kaplan–Meier plots of OS were generated for each circulating biomarker by treatment (ganitumab vs. placebo) and biomarker subgroup (high vs. low biomarker value). The median OS for each stratum was estimated. Treatment effects for OS by biomarker groups were evaluated using hazard ratios (HR) and confidence intervals (CI) estimated from Cox proportional hazards models. To evaluate the heterogeneity of the treatment effect on OS between the high and low subgroups, the interaction effect between treatment and biomarker subgroup was estimated using a Cox proportional hazards model, and the associated P values were calculated.

The above analyses were conducted for single biomarkers and selected ratios of biomarkers, including IGF1/IGFBP2, IGF1/IGFBP3, IGF2/IGFBP2, IGF2/IGFBP3, IGFBP2/IGFBP3, (IGF1+IGF2)/IGFBP2, and (IGF1+IGF2)/IGFBP3.

To evaluate the effect of potential confounding factors on OS, multivariate Cox proportional hazards modeling was conducted for each biomarker including potential confounding baseline factors as covariates in addition to treatment, biomarker of interest, and the interaction between treatment and biomarker (as a continuous variable). Standardization of the baseline factors was based on the evaluation of the distribution of the variable. The potential confounding factors considered included randomization factors (ECOG performance status and the presence or absence of liver metastasis); levels of serum albumin, alanine transaminase, aspartate transaminase, and alkaline phosphatase; and creatinine clearance.

To evaluate the predictive potential of single biomarkers and the ratio of biomarkers for OS, time-dependent receiver operating characteristic (ROC) curves (22) were evaluated for OS at 6 and 9 months. The discriminating potential of the single biomarker and the ratio of biomarkers on OS were determined by the area under the ROC curves (AUC). A larger AUC indicates better discriminating power.

Correlation between baseline ligand and binding protein values were evaluated with combined data from all treatment arms using Spearman rank correlation coefficient (R).

All analyses were considered exploratory. P values were not adjusted for multiple comparisons.

Results

Patients

Between March 2008 and April 2009, 84 patients were randomized in the ganitumab ($n = 42$) and placebo ($n = 42$) arms; 80 received treatment (ganitumab, $n = 40$; placebo, $n = 40$). Complete study results are reported separately (19).

Distribution of baseline levels of circulating factors in the IGF axis

Thirty-four and 33 patients in the ganitumab and placebo arms, respectively, had baseline blood samples that were evaluable for at least 1 baseline circulating biomarker. Baseline levels of total IGF-1, fIGF-1, IGF-2, and IGFBP-1, -2, -3, and -4 were similar across the ganitumab and placebo arms (Supplementary Fig. S1). Levels of fIGF-1 were below the assay's LLOQ in 64% of patients.

Effect of treatment on OS in circulating biomarker subgroups

As shown in Fig. 1, ganitumab was associated with improved OS compared with placebo (HR, 0.49; 95% CI: 0.28–0.87; $P = 0.02$) in the biomarker-evaluable patients. When the treatment effect was evaluated in the subgroups defined by the baseline levels of IGFs and IGFBPs, the treatment effect of ganitumab on improved OS was strong in the patient subset with higher levels of IGF-1, IGF-2, or IGFBP-3, or lower levels of IGFBP-2, but not so on the other corresponding subset. For example, for IGF-2, the ganitumab treatment effect was mainly attributed to patients with higher than median baseline levels of the biomarker: IGF-2 high group (HR, 0.24; 95% CI: 0.09–0.68; $P = 0.007$) versus IGF-2 low group (HR, 0.95; 95% CI: 0.44–2.08; $P = 0.91$) with P value testing for interaction between treatment and biomarker subgroups at 0.05. For IGFBP-2, the improved survival benefit from ganitumab was enhanced in the subgroup with lower than median baseline levels of the biomarker: IGFBP-2 high group (HR, 0.69, 95% CI: 0.30–1.59; $P = 0.38$) versus IGFBP-2 low group (HR, 0.19; 95%CI: 0.07–0.55, $P = 0.002$) with P value testing for interaction between treatment and biomarker subgroups at 0.38.

Kaplan–Meier plots of OS for each biomarker- and treatment-stratified subgroup are shown in Fig. 2. For total IGF-1, IGF-2, and IGFBP-3 each, the median OS in the high subgroups of the ganitumab arm was 16 months, which is approximately 3-times longer than the medians in the low subgroup of the same arm (4.7–5.6 months). In addition, for each of these biomarkers, the curves for the low subgroup of the ganitumab arm and both the low and high subgroups of the placebo arm were overlapping. For fIGF-1, the median OS in the high subgroup was longer in the
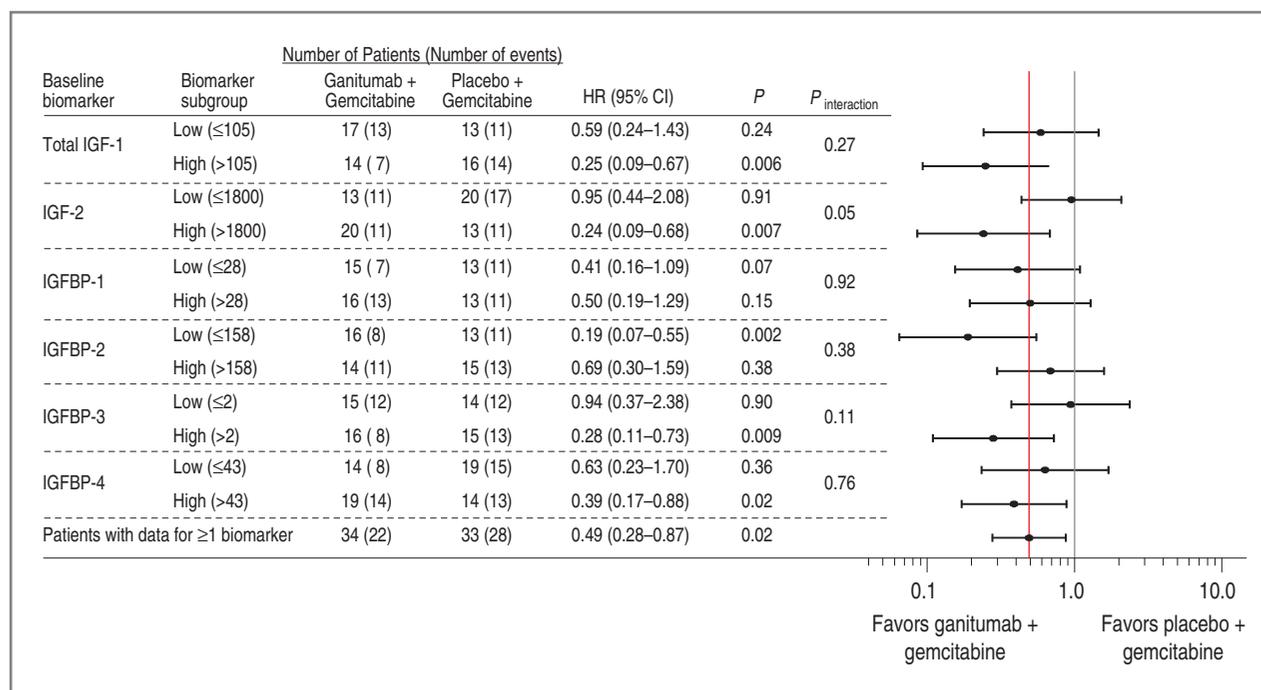
Figure 1. Forest plot for effect of treatment on OS in high and low biomarker subgroups. The red line denotes a HR of 0.49. All biomarker values are shown in ng/mL except for IGFBP-3 (mg/mL).

ganitumab versus placebo arm (11.1 vs. 3.6 months); however, it is worth noting that there were few patients ($n = 6$) in the placebo arm of the high subgroup, and approximately two-thirds of the patients overall had fIGF-1 levels below the LLOQ. For IGFBP-2, the low subgroup of the ganitumab arm showed a longer median OS than the low subgroup of the placebo arm (12.7 vs. 6.6 months), and the curves for the 2 high subgroups were overlapping.

Multivariate analysis adjusting for potential confounding factors treating biomarkers as continuous variables suggested that there was an interaction between treatment and baseline levels of IGF-2 ($P_{interaction} = 0.002$) and IGFBP-2 ($P_{interaction} = 0.02$), supporting the potential predictive value of these 2 markers (Supplementary Table S1).

Correlation between individual circulating factors in the IGF axis

Correlations between individual circulating factors were evaluated using data from both treatment arms combined (Fig. 3). Because of the high frequency of patients with undetectable fIGF-1, it was not included in the correlation analysis. As expected, positive correlations were observed between total IGF-1, IGF-2, and IGFBP-3, with the strongest positive correlation between IGF-2 and IGFBP-3 ($R = 0.781$, $P < 0.001$). Among the other binding proteins, baseline levels of IGFBP-1, IGFBP-2, and IGFBP-4 were positively correlated. IGFBP-2 did not strongly correlate with either IGF-2 or IGFBP-3, suggesting that these markers are independent and that use of a composite marker might have an even stronger predictive effect.

Evaluation of ratios as predictive markers

ROC curves for 9-month OS based on time-dependent ROC analysis of the ganitumab arm are shown in Supplementary Fig. S2. ROC curves for 6- and 9-month OS were similar (data not shown). The strongest predictive power was shown for the ratios IGF-2/IGFBP-2 and IGFBP-2/IGFBP-3 and is consistent with the finding that IGFBP-2 did not correlate with either IGF-2 or IGFBP-3.

Association between OS and tumor mutations or PTEN levels

IGF1R signaling is regulated by various oncogenes, including *PIK3CA*, *BRAF*, *H-*, *N-*, and *KRAS*, and tumor suppressors, such as *PTEN*. The frequency of *PI3KCA*, *BRAF*, *HRAS*, and *NRAS* mutations was too low to enable analysis of relationships with OS, however, *KRAS* mutation was observed in 50% of available samples from the ganitumab arm (based on 14 patients who received ganitumab and had evaluable samples; Supplementary Table S2). *KRAS* mutation data were not available for the placebo arm. Associations between *KRAS* mutational status and OS were evaluated in the ganitumab arm only. No clear associations were observed in the small number of patients evaluated (Supplementary Table S3).

Summary statistics for PTEN protein expression is provided in Supplementary Table S4. Associations between PTEN expression and OS were evaluated in the ganitumab arm only. No associations were observed (Supplementary Table S5).
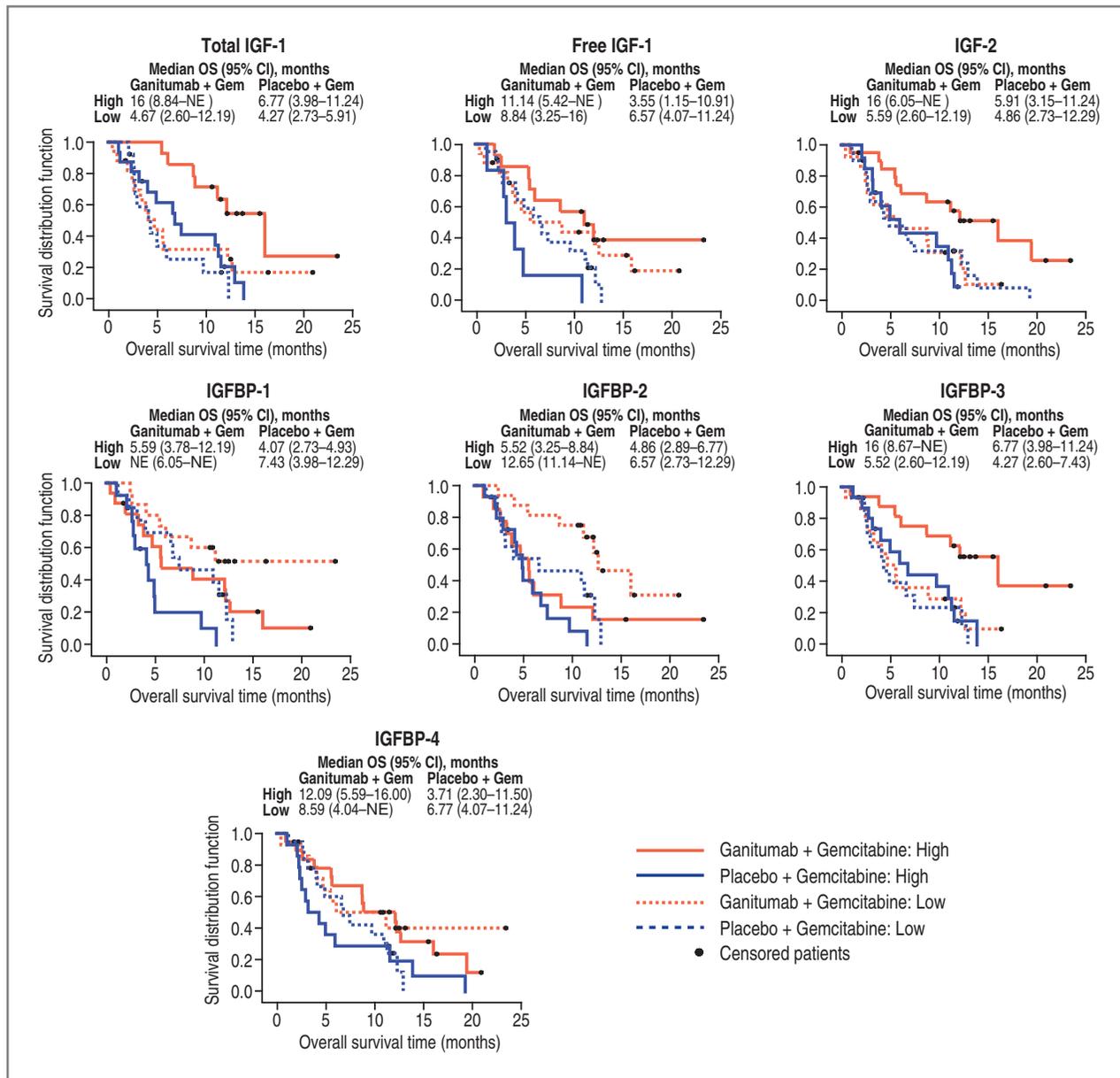
Figure 2. Kaplan–Meier plot of OS stratified by biomarker levels and treatment arms. Gem, gemcitabine; NE, not estimable.

Discussion

We hypothesized that tumors exposed to high levels of IGF1R ligands are dependent on IGF1R for growth and survival. This would manifest as enhanced sensitivity to tumor inhibition of IGF1R in patients with high levels of ligands or of IGFBP-3, a binding protein that stabilizes circulating ligands and is cleaved by local proteases to release ligands at the tissue level. The functions of the other binding proteins are not well characterized but may sequester ligands in circulation and away from tissues; therefore, low levels of these binding proteins would promote IGF1R ligand availability and thus tumor dependence on IGF1R.

In this phase II study of ganitumab and gemcitabine in metastatic pancreatic adenocarcinoma, baseline levels of circulating factors of the IGF axis were evaluated for potential associations with survival. The treatment effect of ganitumab was enhanced in patients with higher baseline levels of total IGF-1, IGF-2, and IGFBP-3 and lower baseline levels of IGFBP-2 as compared with unselected patients. Among the factors tested, an interaction effect between biomarker levels and treatment was observed for IGF-2 and IGFBP-2 in a multivariate analysis. Overall, this suggests that patients with high levels of IGF-2 and low levels of IGFBP-2 may be most sensitive to IGF1R inhibition.

Figure 3. Scatter plot of circulating biomarkers in the treatment arms combined.
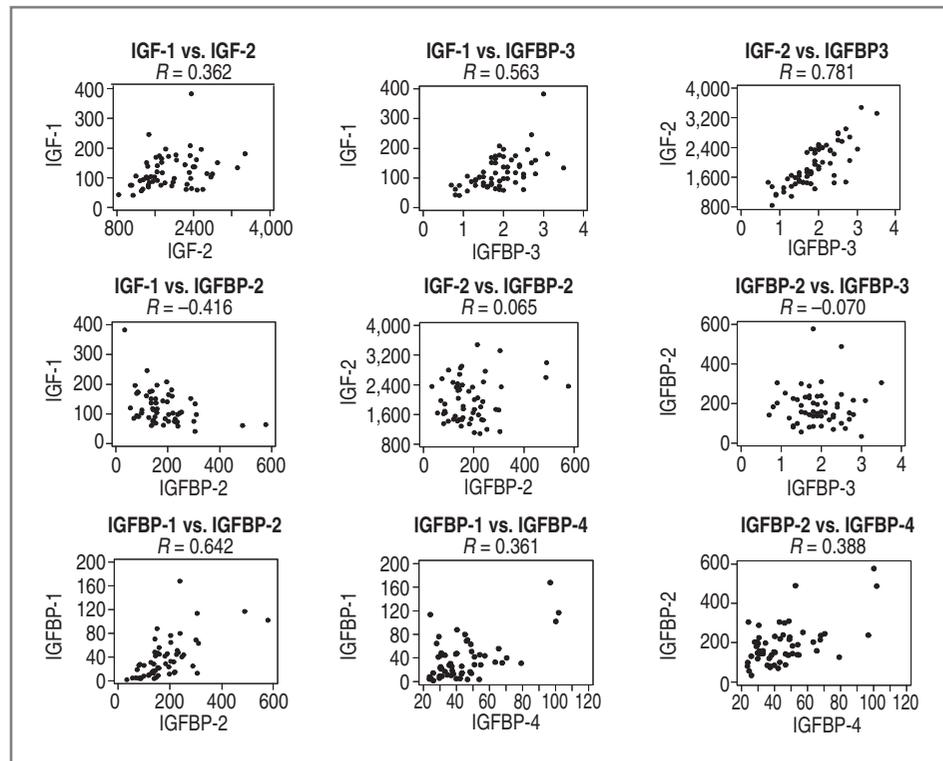
Positive correlations among the IGF1R-activating factors (IGF-1, IGF-2, and IGFBP-3) were seen. In addition, positive correlations among the IGF1R-inhibiting factors (IGFBP-1, -2, -4) were observed. Finally, the observation that there was a negative correlation between IGF-1 and IGFBP-2 but not between IGF-2 and IGFBP-2 suggests that IGFBP-2 may regulate the bioavailability of IGF-2 to a lesser extent than IGF-1.

The results from these analyses are concordant with the hypothesis that IGF1R signaling is an important driver of pancreatic cancer and are consistent with the results of the overall trial. IGF1R inhibitors may also be effective in other tumor types that are driven by high ligand levels, although to date clinical trials in unselected patients have not generally shown evidence of efficacy (23). Additional work to identify determinants indicative of tumor dependence on IGF1R is required.

Higher levels of serum total IGF-1 have been associated with increased risk of lung, breast, colon, and prostate cancer (24–27). Fewer studies, however, have examined the relationship between the IGF axis and pancreatic cancer. A recent meta-analysis suggests that levels of IGF-related markers are not predictive of pancreatic cancer risk (28), which is contrary to other reports of pancreatic cancer cases and matched controls (29, 30). Nonsignificant trends between high levels of IGF-1 and IGFBP-3 and risk of pancreatic cancer death have also been observed (31). In our study, levels of IGF-1 and IGFBP-3 did not seem to be prognostic but were associated with an improved treatment effect of ganitumab. No negative predictive marker has been identified as none of the biomarker-defined subgroups showed a worse outcome with ganitumab treatment.

Several limitations of our data should be noted. Results for fIGF-1 were not considered to be meaningful because levels were too low to be quantified in more than 50% of the patients. Using a different assay, levels of fIGF-1 were reported to be informative in non–small cell lung cancer with another IGF1R inhibitor, although assay limitations were also noted (32). Furthermore, our analyses were considered exploratory. *P* values were used descriptively, and nominal *P* values were generated with no adjustment for multiplicity. The sample size of this clinical trial was relatively small, and the ascertainment rate for baseline circulating biomarker samples was on average 91%. Potential ascertainment bias is possible as the treatment effect of ganitumab was more pronounced in the biomarker analysis set (HR, 0.49; 95% CI: 0.28–0.87) than the ITT analysis set (HR, 0.67; 95% CI: 0.41–1.12) (19). However, OS was not significantly different between patients with baseline circulating biomarker samples available and those without. The ascertainment rate for tumor tissue was lower than for serum (<50%), and the amount collected was insufficient for testing of IGF axis-specific markers after PTEN and *KRAS* analyses were conducted. Finally, the median value may not represent the optimal cutoff point for any or all of the markers tested. The development and testing of optimal thresholds will be evaluated in a larger clinical study.

Additional work is required to explore the ranges of these factors in patients with metastatic pancreatic adenocarcinoma compared with age-matched controls. It is noteworthy that the ranges of IGFBP-3 in this study

(0.70–3.5 mg/mL) were lower than those of healthy individuals for the assay employed (1.9–3.6 mg/mL for individuals 30–70 years old; ref. 33). The median level of IGFBP-3 (1.9 mg/mL), which was used as an arbitrary threshold, is at the lower end of this reference range. The significance of this observation is unclear and would require further testing to validate the median as the optimal threshold to predict efficacy. Finally, variables such as age, gender, ethnicity, nutritional status, obesity, and liver function may influence the levels of some factors that were explored in the multivariate analysis. Patients in the ganitumab arm were required to be fasting before blood draws; this was not required for patients in the placebo arm. Despite this difference, baseline levels of markers between the groups were relatively similar.

The low ascertainment rate of tumor tissues (<50% in the ganitumab arm) precluded a robust analysis of relationships between OS and PTEN expression, *KRAS* mutation, or tumor expression of IGF pathway signaling proteins. At the time of analysis, we prioritized the evaluation of PTEN and KRAS, and there was not sufficient tissue available to evaluate tumor markers specific to the IGF axis.

In summary, we have identified a number of potentially predictive biomarker candidates. Total IGF-2 and IGFBP-2 may serve as predictive markers that identify a subset of patients with an enriched treatment effect when ganitumab is added to gemcitabine. Further investigation of these and additional biomarkers are warranted.

Disclosure of Potential Conflicts of Interest

Y. Tudor, H. Deng, R. Tang, E. Loh, S.D. Patterson, L. Chen, and J.L. Gansert are employees of and shareholders in Amgen Inc. I. McCaffery, S. Suzuki, and S. Badola are former employees of and are shareholders in Amgen Inc. H.L. Kindler is an advisor for Amgen Inc. C.S. Fuchs is an advisor for Amgen Inc., ImClone Systems, Genentech, Inc., Roche, and Infinity Pharmaceuticals.

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Study supervision: S. Suzuki, C.S. Fuchs, J.L. Gansert

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Ian McCaffery, Yanyan Tudor, Hongjie Deng, et al.

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