A Phase I Pharmacokinetic and Pharmacodynamic Study of Dalotuzumab (MK-0646), an Anti-Insulin-like Growth Factor-1 Receptor Monoclonal Antibody, in Patients with Advanced Solid Tumors

Francesco Atzori1, Josep Tabernero1, Andrés Cervantes3, Ludmila Prudkin1, Jordi Andreu1, Edith Rodríguez-Braun1, Amparo Domingo3, Jorge Guijarro1, Cristina Gamez2, Jordi Rodon1, Serena Di Cosimo1, Holly Brown4, Jason Clark4, James S. Hardwick4, Robert A. Beckman4, William D. Hanley4, Karl Hsu4, Emiliano Calvo5, Susana Roselló3, Ronald B. Langdon4, and José Baselga1,5

Abstract

Purpose: Insulin-like growth factor-1 receptor (IGF-1R) mediates cellular processes in cancer and has been proposed as a therapeutic target. Dalotuzumab (MK-0646) is a humanized IgG1 monoclonal antibody that binds to IGF-1R preventing receptor activation. This study was designed to evaluate the safety and tolerability of dalotuzumab, determine the pharmacokinetic (PK) and pharmacodynamic (PD) profiles, and identify a recommended phase II dose.

Experimental Design: Patients with tumors expressing IGF-1R protein were allocated to dose-escalating cohorts of three or more patients each and received intravenous dalotuzumab weekly, every 2 or 3 weeks. Plasma was collected for PK analysis. Paired baseline and on-treatment skin and tumor biopsy samples were collected for PD analyses.

Results: Eighty patients with chemotherapy-refractory solid tumors were enrolled. One dose-limiting toxicity was noted, but a maximum-tolerated dose was not identified. Grade 1 to 3 hyperglycemia, responsive to metformin, occurred in 15 (19%) patients. At dose levels or more than 5 mg/kg, dalotuzumab mean terminal half-life was 95 hours or more, mean \( C_{\text{min}} \) was more than 25 \( \mu \)g/mL, clearance was constant, and serum exposures were approximately dose proportional. Decreases in tumor IGF-1R, downstream receptor signaling, and Ki67 expression were observed. \(^{18}\)F-Fluorodeoxyglucose positron emission tomography metabolic responses occurred in three patients. One patient with Ewing's sarcoma showed a mixed radiologic response. The recommended phase II doses were 10, 20, and 30 mg/kg for the weekly, every other week, and every third week schedules, respectively.

Conclusions: Dalotuzumab was generally well-tolerated, exhibited dose-proportional PK, inhibited IGF-1R pathway signaling and cell proliferation in treated tumors, and showed clinical activity. The low clearance rate and long terminal half-life support more extended dosing intervals. Clin Cancer Res; 17(19): 1–9. ©2011 AACR.

Introduction

Signaling by the insulin-like growth factor (IGF) receptor plays a key role in regulating cellular metabolism, growth, and cell fate in response to changes in nutrient availability (1–3). The IGF receptor 1 (IGF-1R) is a tetrameric receptor tyrosine kinase that is widely expressed by normal and neoplastic cells. There are several lines of evidence that suggest that this receptor may play a role in the survival and proliferation of human tumors. Epidemiologic studies indicate an association between plasma IGF-1 ligand levels and increased risk for breast, prostate, and colon cancers (1, 4–6). In colorectal cancer, IGF-1R overexpression correlates with...
tumor cell proliferation, tumor stage, and decreased overall survival (7, 8). In preclinical models, IGF-1R activation is required to establish and maintain transformed phenotypes induced by several known oncogenes and confers protection from a number of anticancer therapies by promoting cell survival through antiapoptotic mechanisms (1, 9–11). In addition, in experimental models, there is ample evidence that inhibition of IGF-1R activation results in antitumor activity (1). Taking these considerations together, IGF-1R was proposed as a target for cancer therapy and several compounds targeting IGF-1R are in various stages of clinical development (11–21).

Dalotuzumab (MK-0646) is a humanized IgG1 monoclonal antibody (mAb) against IGF-1R selected on the basis of specificity for IGF-1R over the insulin receptor, and in vitro/in vivo antiproliferative activity against cells that over-express IGF-1R (22). Dalotuzumab binds to IGF-1R with a $K_d$ of approximately 1 nmol/L, induces receptor internalization and degradation, and inhibits IGF-1- and IGF-2-mediated cell proliferation, IGF-1R autophosphorylation, and AKT phosphorylation (23, 24).

This phase I study was aimed to determine the safety, tolerability, and pharmacokinetic (PK) parameters of dalotuzumab when administered to patients with advanced solid tumors. On the basis of preclinical data obtained in xenograft models, a trough concentration of 25 µg/mL was targeted in this study. Key secondary objectives included determination of the dose at which receptor binding by dalotuzumab is saturated in tumor tissue and exploration of the pharmacodynamic (PD) effects of dalotuzumab on IGF-1R–dependent pathways through sequential tumor and skin biopsies. These objectives were pursued to support characterization of the recommended phase II dose for further development. Antitumor efficacy was also assessed.

The results from this clinical study of single-agent dalotuzumab show that the humanized monoclonal antibody is well tolerated in patients with advanced cancer. Extensive pharmacodynamic and pharmacokinetic analyses identified a minimal biologically effective dose, even though a maximum-tolerated dose was not determined. The favorable safety and toxicity profile of dalotuzumab, combined with its demonstrated inhibition of IGF-1R signaling and high rate of disease stabilization, make it a good candidate for combination therapy with chemotherapy and other signal transduction inhibitors. One particular combination supported by preclinical evidence, dalotuzumab in combination with an mTOR inhibitor, may be beneficial because it prevents the paradoxical activation of the IGF-1R signaling pathway by mTOR inhibitors.

Methods

Study design

This was a multicenter, open-label, single-arm, nonrandomized phase I clinical trial. Its primary objectives were to establish the PK profile of intravenous dalotuzumab and to define the maximum tolerated dose (MTD) of dalotuzumab, should this be encountered before the maximum planned dose was reached (20 mg/kg/wk). Beginning with a weekly dose of 1.25 mg/kg, cohorts of 3 to 6 patients each were treated sequentially with escalating doses of 2.5, 5.0, 10, 15, and 20 mg/kg dalotuzumab (Supplementary Table S1). The first 4 weeks of dosing were used as the toxicity evaluation period for the purposes of dose escalation. A conventional "3 + 3" dose escalation scheme was used with no intrapatient dose escalation. Once the maximum planned weekly dose (20 mg/kg) was achieved, every other week (Q2W) and every third week (Q3W) schedules were explored with dalotuzumab doses of 20 and 30 mg/kg, respectively. Patients were to continue on treatment with dalotuzumab until they experienced progressive disease or unacceptable toxicity, withdrew consent, or were withdrawn at the investigator's discretion.

Adverse responses to treatment were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE version 3.0). Dose-limiting toxicity (DLT) was defined as toxicity of grade 3 or 4. A maximum of one DLT was counted per patient. Any patient who required more than 2 dose reductions because of DLT was discontinued from the study. If none of the first 3 patients experienced a DLT at a given dose level, then testing proceeded to the next dose level. If one of the first 3 patients experienced a DLT, then 3 additional patients were entered to expand the cohort to 6. If 2 patients in a cohort (of 3 or 6) experienced a DLT, then the MTD was determined as the preceding dose level. Patients with a DLT were withdrawn from the study (except for infusion reactions and hypersensitivity reactions) unless they had resolution of their DLT to baseline or grade 1 within 2 weeks of their next scheduled dose (at which time, at the discretion of the investigator, they could continue receiving treatment at the next lower dose level for the remainder of the study). The safety analysis included all adverse events reported while patients were receiving treatments and within 30 days following final administrations of study drug.

Additional study objectives included evaluation of the PD effects of dalotuzumab on the IGF-1R–dependent signaling pathways in skin and tumor and assessment of antitumor efficacy.

Patients

Main inclusion criteria were presence of a histologically or cytologically confirmed metastatic or locally advanced tumor that expressed IGF-1R protein and was unresponsive to standard therapy, patient 18 years or older, life expectancy 12 weeks or more, presence of disease accessible to repeated biopsy, Eastern Cooperative Oncology Group
(ECOG) performance status of 2 or better, and adequate bone marrow, hepatic, and renal functions. Patients were required to have a tumor specimen available for analysis (fresh or recently paraffin-embedded). Expression of IGF-1R protein was evaluated by immunohistochemistry and considered positive if staining (of membrane and/or cytoplasm) was present above background in 10% or more of tumor cells in a tissue section. Additional inclusion criteria are in the Supplemental Information. Patients with plasma fasting glucose levels of more than 150 mg/dL or glycated hemoglobin (HbA1c) of 8% or more were excluded. All patients gave informed consent, and approval was obtained from the ethics committees at each participating institution. The study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki and registered with ClinicalTrials.gov (NCT00701103).

Assessments

Vital signs, body weight, ECOG performance status, complete blood cell count, and adverse events were assessed immediately prior to each dalotuzumab dose. A 12-lead ECG was recorded when the first dose was given, in the 4th or 5th week of treatment, the 9th or 10th week, and once every 8 to 9 weeks thereafter for the remainder of the trial.

Serum was collected prior to every dalotuzumab infusion for PK analysis; PD endpoints in serum were analyzed after 4 to 5 weeks of treatment and at later time points. Skin and tumor specimens were obtained at baseline (within 5 days prior to initiation of dalotuzumab) and within 72 hours predose in either the third or fourth week of treatment. Response of solid tumors to treatment was evaluated radiologically (computed tomographic scan or MRI) using Response Evaluation Criteria in Solid Tumors (RECIST) 1.0.

These evaluations were carried out predose, 9 to 10 weeks after initiating treatments with dalotuzumab, and every 6 to 8 weeks thereafter for the remainder of the trial. Tumor metabolic rate was assessed by 18F-fluorodeoxy-glucose positron emission tomography (18FDG-PET) scan within 120 hours prior to initial dose of dalotuzumab, within 72 hours predose in the 3rd or 4th week, the 9th or 10th week, and every 16 to 18 weeks thereafter.

Pharmacokinetics

Blood samples were obtained for measurement of serum dalotuzumab levels at the following times: immediately prior to infusion of the first dose, immediately before the end of this first infusion, and 0.5, 5, 10, 24, 30, 48, and 96 hours following the start of this first infusion, and immediately prior to each subsequent infusion. Serum concentrations of dalotuzumab were analyzed by an ELISA that used the extracellular domain of recombinant human IGF-1R to capture dalotuzumab. Captured dalotuzumab was detected by mouse anti-human IgGFC antibodies conjugated to horseradish peroxidase. The lower limit of dalotuzumab quantitation in serum was 20 ng/mL. Additional ELISA methodology is provided in the Supplemental Information.

Pharmacodynamics

The PD effects of dalotuzumab in tumor and skin were assessed in all patients from whom paired pretherapy and on-therapy specimens were available. Processing of the samples, immunohistochemistry, and statistical analysis were conducted as described previously (25, 26) and in the Supplementary Information. Briefly, immunohistochemical analysis of total IGF-1R, total and phosphorylated (p) EGF (pEGF), total IRS-1, pAKT (Ser473), pAKT (Thr308), pMAPK (T202/Y204), pS6 (Ser240/4), p4EBP1 (Thr70), total eIF4E, pS6 kinase (Ser1108), and Ki67 were done in formalin-fixed, paraffin-embedded sections from tumor and skin samples according to standard methods (see Supplementary Table S2 for antibody sourcing). Qualitative changes in the expression of markers were assessed in a blinded fashion. For quantitative analysis, histochemical scores (H-scores) were calculated by light microscopic examination of complete tumor sections and epidermal tissue in skin samples, as previously described (25, 26).

Paired pretherapy and on-therapy samples were analyzed using the Wilcoxon rank test by SPSS Data Analysis Program version 10.0 (SPSS Inc.). Statistical tests were conducted at the 2-sided 0.05 level of significance. Serum levels of IGF-1 and IGF-2 and IGF-binding protein (IGFBP)-1, -2, and -3 were measured by ELISA before and after 4 weeks on treatment.

Results

Patients

Between January 2006 and June 2008, a total of 80 patients were enrolled. All data were analyzed and all patients receiving at least 1 dose of dalotuzumab were included in the safety, PK, and PD analyses. Patients receiving at least 2 dalotuzumab doses were evaluated for efficacy.

Baseline characteristics for enrolled patients are presented in Table 1. Median patient age was 57 years (range: 19–81), the median number of prior therapies was 3, and the most frequent malignancies were colorectal (24%) and breast cancer (21%). The median length of dalotuzumab treatment was 44 days (range: 1–324). Five patients discontinued treatment because of treatment-related adverse events, 2 withdrew consent, and 1 discontinued for an unspecified medical reason following the recommendation of the investigator. Seventy-one patients were removed from the study because of disease progression. All patients received at least 1 infusion of dalotuzumab and were considered evaluable for safety.

Patients assigned to the weekly regimens of dalotuzumab received an average of 7.4 infusions (range: 1–37). Patients assigned to the 20 mg/kg Q2W regimen received an average of 3.4 infusions (range: 1–5). Patients assigned to the 30 mg/kg Q3W regimen received an average of 5.1 infusions (range: 2–16).

Tolerability

Of 80 patients enrolled, 67 (83.8%) experienced clinical adverse events, the majority of which were mild to
moderate in severity (grades 1–2). Five patients (6.3%) experienced clinical adverse events of grade 3 or more. The most common clinical adverse events were asthenia, hyperglycemia, back pain, and aspartate aminotransferase elevation, experienced by 21.3%, 18.8%, 13.8%, and 10.0% of patients, respectively. Twenty-two patients (27.5%) experienced a clinical adverse event considered by the investigators to be possibly, probably, or definitely related to dalotuzumab therapy (Table 2). Five patients experienced serious adverse events, one of which was considered to be possibly related to the treatment. This single drug-related serious adverse event was experienced by a patient in dose cohort 3 (5 mg/kg) who had grade 3 purpura on the lower extremities (diagnosed as leukocytoclastic vasculitis as per skin biopsy) and resolved in 21 days. Because the drug-related serious adverse event was experienced during the initial 4-week evaluation period, it was considered a DLT and dose cohort 3 was expanded to 6 patients. No other DLTs were observed. Treatment was completed at all 8 of the prespecified dose levels without an MTD being reached. No patients experienced adverse events that required a dose reduction of dalotuzumab.

### Table 1. Patient and disease characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N = 80</th>
</tr>
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<tbody>
<tr>
<td>Age, median (range), y</td>
<td>57 (19–81)</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>40 (50.0)</td>
</tr>
<tr>
<td>Female</td>
<td>40 (50.0)</td>
</tr>
<tr>
<td>ECOG performance status, n (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>33 (41.3)</td>
</tr>
<tr>
<td>1</td>
<td>45 (56.2)</td>
</tr>
<tr>
<td>2</td>
<td>2 (2.5)</td>
</tr>
<tr>
<td>Prior therapies, n (%)</td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>8 (10.0)</td>
</tr>
<tr>
<td>2</td>
<td>11 (13.8)</td>
</tr>
<tr>
<td>≥3</td>
<td>61 (76.3)</td>
</tr>
<tr>
<td>Tumor types, n (%)</td>
<td></td>
</tr>
<tr>
<td>Colorectal</td>
<td>19 (23.8)</td>
</tr>
<tr>
<td>Breast</td>
<td>17 (21.3)</td>
</tr>
<tr>
<td>Ewing’s sarcoma</td>
<td>6 (7.5)</td>
</tr>
<tr>
<td>Ovarian</td>
<td>5 (6.3)</td>
</tr>
<tr>
<td>Malignant melanoma</td>
<td>5 (6.3)</td>
</tr>
<tr>
<td>Bone sarcoma</td>
<td>3 (3.8)</td>
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<tr>
<td>Others</td>
<td>25 (31.3)</td>
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### Table 2. Summary of treatment-related clinical adverse events

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Total patients (N = 80)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1–2</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>14</td>
</tr>
<tr>
<td>Asthenia</td>
<td>6</td>
</tr>
<tr>
<td>Chills</td>
<td>2</td>
</tr>
<tr>
<td>Leukocytoclastic vasculitis</td>
<td>0</td>
</tr>
<tr>
<td>Tumor pain</td>
<td>0</td>
</tr>
<tr>
<td>Bone pain</td>
<td>1</td>
</tr>
<tr>
<td>Pelvic pain</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td>1</td>
</tr>
<tr>
<td>Infected neoplasm</td>
<td>1</td>
</tr>
<tr>
<td>Infusion-related reaction</td>
<td>1</td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td>1</td>
</tr>
<tr>
<td>Rash</td>
<td>1</td>
</tr>
<tr>
<td>Palmar-plantar erythrodysesthesia</td>
<td>1</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>1</td>
</tr>
<tr>
<td>Myopathy</td>
<td>1</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>1</td>
</tr>
</tbody>
</table>

NOTE: Each patient was counted only once within a category. When an adverse event was reported more than once in the same patient with different intensity grades, only the highest grade was counted.

<sup>a</sup>Adverse events considered by investigators to be possibly, probably, or definitely treatment related.

<sup>b</sup>Includes 14 patients with clinical adverse events of hyperglycemia (including one adverse event of grade 3 intensity) and one with a laboratory adverse event of increased blood glucose level.

<sup>c</sup>In 4 additional patients, adverse events of hyperglycemia (n = 3, one each with grades 1, 2, and 3) or blood glucose increased (n = 1, grade 1) were reported as not treatment related because of preexisting or concomitant conditions (including acute pancreatitis and corticosteroid treatment).

### Pharmacokinetics

After the first intravenous dose, mean dalotuzumab plasma concentrations declined biexponentially from peak concentration (C<sub>max</sub>) through 168 hours (Fig. 1A). The mean terminal half-life (t<sub>1/2</sub>) generally increased as doses were increased. It was 95 hours or more at all weekly doses of more than 5 mg/kg (Table 3). The mean serum clearance was 0.007 mL/min/kg in the 20 mg/kg weekly cohort and had comparable values in the 5, 10, and 15 mg/kg weekly cohorts (Fig. 1B). The area under the concentration–time curves from time of the first dose (AUC<sub>0–</sub>∞), estimated from the first dose, increased proportionally with increasing doses (Fig. 1C).

Mean trough concentrations exceeded 25 μg/mL for all weekly doses of 10 mg/kg or more, for 20 mg/kg Q2W, and for 30 mg/kg Q3W (Fig. 1A). Each individual patient in the weekly 10 mg/kg cohort (n = 6) met this targeted trough concentration at the end of the first week of treatment and continued to meet it in subsequent weeks. There was moderately high interpatient PK variability (coefficients of variation generally 25%–50%) in the observed values for AUC, trough serum concentration, and terminal half-life (Table 3).
Pharmacodynamics

We obtained 33 matched pairs of baseline and on-treatment tumor specimens (2, 5, 6, 7, and 7 pairs from the 1.25, 5, 10, 15, and 20 mg/kg weekly dose level cohorts, respectively, and 3 pairs each from the 20 mg/kg Q2W and 30 mg/kg Q3W cohorts). We also obtained a total of 69 matched pairs of baseline and on-treatment skin biopsies (3, 3, 6, 13, 12, and 15 from the 1.25, 2.5, 5, 10, 15, and 20 mg/kg dose level cohorts, respectively), and 7 and 10 pairs from the 20 mg/kg Q2W and 30 mg/kg Q3W cohorts, respectively). It was found that 3 weeks of dalotuzumab treatment significantly reduced mean H-scores (averaged across all doses) for IGF-1R in both tumor (Fig. 2A; \( P = 0.02 \)) and skin (Fig. 2B; \( P = 0.04 \)).

![Figure 1. PK behavior of dalotuzumab following administration of weekly intravenous infusions. A, mean serum concentration–time profiles. B, mean serum clearance following first infusion versus dose (error bars, 95% CI). C, exposure (AUC\(_{0-\infty}\)) versus dose (error bars, 95% CI). For first dose: \( n = 5, 1.25 \) mg/kg; \( n = 3, 2.5 \) mg/kg; \( n = 8, 5.0 \) mg/kg; \( n = 6, 10 \) mg/kg; \( n = 6, 15 \) mg/kg; \( n = 7, 20 \) mg/kg; \( n = 11, 20 \) mg/kg Q2W; \( n = 11, 30 \) mg/kg Q3W.](image)

<table>
<thead>
<tr>
<th>Dose, mg/kg</th>
<th>Schedule</th>
<th>Doses before testing</th>
<th>( n )</th>
<th>( {\text{AUC}}_{0-\infty}, ) mg/mL h</th>
<th>( C_{eoi}, ) ( \mu )g/mL</th>
<th>( C_{\text{trough}}^{a} ) ( \mu )g/mL</th>
<th>Clearance, mL/min/kg</th>
<th>( V_{ss}, ) L/kg</th>
<th>Apparent ( t_{1/2}^{b} ), h</th>
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<tbody>
<tr>
<td>1.25 Weekly</td>
<td>1</td>
<td>5</td>
<td>1.6 (0.4)c</td>
<td>19.4 (1.6)</td>
<td>2.4 (2.2)</td>
<td>0.013 (0.004)</td>
<td>0.072 (0.020)</td>
<td>67 (46–121)d</td>
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<tr>
<td>2.5 Weekly</td>
<td>1</td>
<td>3</td>
<td>3.7 (1.1)</td>
<td>25.1 (10.1)</td>
<td>7.2 (3.0)</td>
<td>0.012 (0.003)</td>
<td>0.088 (0.020)</td>
<td>79 (53–113)</td>
<td></td>
</tr>
<tr>
<td>5 Weekly</td>
<td>1</td>
<td>8</td>
<td>12.9 (4.4)</td>
<td>89.1 (16.5)</td>
<td>21.2 (8.3)</td>
<td>0.007 (0.003)</td>
<td>0.061 (0.020)</td>
<td>83 (41–240)</td>
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<tr>
<td>10 Weekly</td>
<td>1</td>
<td>6</td>
<td>28.9 (10.4)</td>
<td>139.4 (22.5)</td>
<td>54.8 (13.3)</td>
<td>0.006 (0.002)</td>
<td>0.091 (0.012)</td>
<td>169 (134–265)</td>
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<tr>
<td>15 Weekly</td>
<td>1</td>
<td>6</td>
<td>39.4 (14.5)</td>
<td>281.0 (54.3)</td>
<td>81.2 (38.6)</td>
<td>0.007 (0.004)</td>
<td>0.068 (0.014)</td>
<td>95 (43–165)</td>
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<tr>
<td>20 Weekly</td>
<td>1</td>
<td>7</td>
<td>52.7 (19.2)</td>
<td>345.4 (61.4)</td>
<td>110.5 (46.0)</td>
<td>0.007 (0.003)</td>
<td>0.082 (0.026)</td>
<td>129 (74–240)</td>
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<tr>
<td>20 Q2W</td>
<td>1</td>
<td>11</td>
<td>45.9 (14.4)</td>
<td>278.5 (115.7)</td>
<td>57.0 (22.7)</td>
<td>0.008 (0.003)</td>
<td>0.079 (0.014)</td>
<td>106 (44–134)</td>
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<tr>
<td>30 Q3W</td>
<td>1</td>
<td>11</td>
<td>92.6 (29.8)</td>
<td>500.0 (138.2)</td>
<td>70.4 (34.1)</td>
<td>0.006 (0.003)</td>
<td>0.080 (0.019)</td>
<td>142 (73–187)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: \( C_{eoi} \), concentration at the end of infusion; \( V_{ss} \), volume of distribution at steady state.

\(^{a}\)Concentration at the end of first dosing interval (168 hours for Q1W, 336 hours for Q2W, and 504 hours for Q3W).

\(^{b}\)Harmonic mean (range).

\(^{c}\)Concentration at the end of first dosing interval (168 hours for Q1W, 336 hours for Q2W, and 504 hours for Q3W).

\(^{d}\)As indicated otherwise, values are reported as mean (SD).

\(^{e}\)Harmonic mean (range).

\(^{f}\)Except as indicated otherwise, values are reported as mean (SD).

\(^{g}\)\( N = 4 \) where indicated for 1.25 mg/kg cohort.
accompanied by significant reductions in the H-scores for several proteins for which expression levels are known to be modulated by IGF-1R pathway signaling. These included pS6 (\(P = 0.031\)), pEIF4G (\(P = 0.046\)), pMAPK (\(P = 0.035\)), and Ki67 (Fig. 2A; \(P = 0.03\)). The mean H-score for epidermal growth factor receptor (EGFR) was also significantly decreased (\(P = 0.016\)). In Figure 3A and B, representative images are shown for changes in biomarker expression observed in tumor and skin specimens obtained prior to treatment and on day 14. These are from a patient treated weekly with 15 mg/kg dalotuzumab.

These decreases in tumor and skin expression of IGF-1R were accompanied by altered serum levels of markers of IGF-1R pathway activation (Supplementary Fig. S1). Pooling outcomes across all dose cohorts, mean serum IGF-1 and IGF-BP3 levels were increased by 153% and 41%, respectively, after 5 weeks of therapy. No other markers showed any consistent pattern of change (Supplementary Fig. S1).

**Efficacy**

Of 80 patients enrolled, 76 had tumors evaluable for efficacy by RECIST. Per these criteria, stable disease was observed in 6 of these patients. Four (with cholangiocarcinoma, adenocarcinoma of unknown origin, metastatic bladder cancer, and melanoma) had stable disease per se, 1 (with Ewing’s sarcoma) had a mixed response (Supplementary Fig. S2), and 1 (with a neuroendocrine tumor) had a minor response. These responses ranged in duration from 13 to 43 weeks (Supplementary Table S3). In addition, \(^{18}\)FDG-PET metabolic responses were observed in 3 patients. One patient in the 15 mg/kg dose level cohort, diagnosed with melanoma, achieved disease stabilization for 13 weeks and a decrease in \(^{18}\)FDG uptake from 38 to 25 g/mL (ratio = 0.66, assessed after 8 weeks of dalotuzumab treatment; Supplementary Fig. S3a). The observed decrease in \(^{18}\)FDG uptake correlated with decreased tumor Ki67 expression as assessed by immunohistochemical staining (Supplementary Fig. S3b).

**Discussion**

In this first in-human study of dalotuzumab, this humanized anti-IGF-1R mAb was generally well tolerated throughout the range of doses tested, including 1.25 to 20 mg/kg administered weekly, 20 mg/kg Q2W, and 30 mg/kg Q3W. The most common adverse event was hyperglycemia,
which was considered to be treatment related in 15 (19%) of the 80 patients treated with dalotuzumab. In addition, there were 4 cases of hyperglycemia that investigators considered to be not treatment related. Hyperglycemia is recognized as a potential adverse effect of treatment with anti-IGF-1R antibodies (27). In prior studies of AMG-479 and figitumumab, it was reported in 7 of 53 (13%) and 5 of 29 (17%) treated patients, respectively (16, 17). When it occurred in the present study, it was adequately controlled by oral antihyperglycemic agents and did not interfere with dalotuzumab dosing. Thrombocytopenia has also been reported (as a DLT) in a prior study of dalotuzumab (28) and also in a study of the anti-IGF-1R antibody AMG-479 (16). None was observed in the present study. The maximum planned dose (20 mg/kg) was reached in this dose-escalation study and thus the MTD was not determined.

As with other mAbs targeted at cell-surface receptors, binding of dalotuzumab to its target (IGF-1R) triggers receptor-mediated endocytosis (23). The PK behavior of dalotuzumab is thus expected to conform to a pattern of target-mediated disposition such that low doses insufficient to saturate the target will produce clearance kinetics dominated by high-affinity binding of dalotuzumab to its target (followed by its irreversible internalization into target cells) and high doses will produce kinetics associated with FcRn-mediated protection of dalotuzumab from intracellular degradation (followed by its release into the plasma and/or interstitial space; ref. 29). When examined over a range of doses, generally linear PK behavior is not expected until saturation of the target has been achieved. Using this model as the basis for interpreting the present PK findings, it seems that target saturation was achieved by weekly doses of 5.0 mg/kg or more. The interpatient variability in AUC, trough serum concentration, and terminal half-life observed in this study was comparable with that observed previously with other IGF-1R mAbs (16, 17). The physiologic basis for this PK variability is unclear, although contributing factors may include individual differences in tumor burden, tumor type, and tumor expression levels of IGF-1R.

On the basis of PD data from preclinical models, 25 μg/mL was prespecified as the targeted minimum serum trough concentration in this study. This target was achieved in all patients who received 10 mg/kg of dalotuzumab weekly, 20 mg/kg Q2W, or 30 mg/kg Q3W, and it seems (as discussed earlier) that such doses achieved target saturation. Consequently, all of these doses and schedules are recommended phase II doses for use in future evaluations of dalotuzumab. We have chosen a dose of 10 mg/kg weekly for a number of follow-up studies in breast cancer.

Dalotuzumab treatment induced a series of mechanistically based PD effects. Most notably, we observed significant reductions in IGF-1R protein expression in tumor and skin, consistent with the known induction of IGF-1R internalization and degradation that follows dalotuzumab binding to IGF-1R (23, 24). Decreased IGF-1R signaling was also achieved, as indicated by significant on-therapy decreases in tumor pS6, pEIF4G, and Ki67 expression. Significant increases in serum IGF-1 and IGF-BP3 levels were observed, and such increases are expected as a compensatory reaction to disruption of IGF-1R function. Among the 80 patients enrolled in the present study, 72 (90%) received doses of dalotuzumab likely to have saturated IGF-1R. Hence, this study did not have a design suited for the observation and characterization of dose dependency in either PD or antitumor effects.
The efficacy data currently available from clinical studies of IGF-1R–targeted mAbs are limited, and phase I clinical trials such as the present study are not primarily designed to test efficacy. Thus, the available data must be interpreted with caution. The data do seem to show, however, that some advanced, solid tumors respond to monotherapy with these agents, although most do not. In the present study, there was RECIST-defined disease stabilization (including 1 partial and 1 mixed response) in 6 of the 76 patients (7.9%) who received dalotuzumab monotherapy and had tumors evaluable by RECIST. In a phase I trial of the agent AMG-479, there was antitumor activity in 4 of 53 patients treated (7.5%), with one of these being a complete response that was maintained for at least 28 months (16). In a trial of the anti-IGF-1R antibody IMC-A12 in patients with metastatic colorectal cancer that was refractory to cetuximab or panitumumab, no antitumor activity was observed among the 23 patients who received IMC-A12 monotherapy and a single partial response was observed among the 41 patients who received IMC-A12 plus cetuximab (20). On the other hand, in a prior study of the IGF-1R–targeted antibody figitumumab in which inclusion was restricted to patients with sarcomas, there was disease stabilization or an objective response in 10 of 28 patients assessed (17).

The higher rate of responses in patients with sarcomas suggests that other specific populations or factors may be identified that predict who will benefit from IGF-1R–targeted monotherapy or combinations of IGF-1R–targeted mAbs with other agents. In this regard, a recent trial with figitumumab has reported significant correlation between pretreatment levels of free IGF-1 and objective responses to anti-IGF-1R therapy in patients with advanced non–small-cell lung cancer treated with figitumumab plus paclitaxel or carboplatin (21). In the present trial, most tumors did not respond to treatment despite selection for patients with tumors that expressed IGF-1R. Because all patients in the present study had IGF-1R–expressing tumors, it remains unknown whether or not the presence of such expression was a necessary condition for clinical benefit. It is possible that tumor IGF-1R expression has little or no predictive value about response to dalotuzumab treatment, just as tumor expression of the EGFR in metastatic colorectal cancer is not correlated with tumor response to mAbs targeting the EGFR (30). When tumor target expression is found to lack predictive value, there may be underlying technical reasons, such as sampling bias, variability in sample handling, limited assay sensitivity or specificity, or evolution of tumors between when biopsies were obtained and treatments applied (31). Given, however, the presence of multiple redundant signaling pathways within tumor cells, intervention by monotherapy to perturb a single signaling pathway alone may simply be inadequate for clinical benefit in the majority of patients. This may explain why we observed significant PD activity in the present study, but with limited efficacy.

On the basis of the favorable safety profile, efficacy data, and inhibition of IGF-1R and its downstream signal transduction pathway, dalotuzumab is currently being evaluated in combination with chemotherapy and with other signal transduction inhibitors. For example, mTOR inhibition results in activation of upstream AKT that could result in decreased therapeutic efficacy (26). mTOR inhibitor–mediated activation of AKT is due to a paradoxical activation of the IGF-1R signaling pathway (25, 32). Coadministration of dalotuzumab prevents mTOR inhibitor–mediated activation of AKT, providing a strong rationale for clinical investigation of dalotuzumab and mTOR inhibitor combinations. An ongoing phase I clinical study is exploring this approach with a combination of dalotuzumab with the mTOR inhibitor ridaforolimus (NCT00730379) and recently reported encouraging clinical activity, especially in patients with estrogen receptor–positive, highly proliferative tumors (33). Preclinical models suggest a synergistic effect on tumor growth inhibition when dalotuzumab is combined with cetuximab, an anti-EGFR mAb (22). The activity of dalotuzumab combined with irinotecan/cetuximab is being evaluated in patients with refractory, metastatic colorectal cancer with wild-type KRAS (NCT00925015).

In summary, dalotuzumab is generally well tolerated and, at the recommended dose and schedule, achieves desired serum exposures and decreases tumor IGF-1R protein levels, downstream IGF-1R signaling, and Ki67 expression.

Disclosure of Potential Conflicts of Interest

H. Brown, J. Clark, J.S. Hardwick, R.A. Beckman, W.D. Hanley, K. Hsu, and R.B. Langdon are current employees of Merck & Co., Inc., or were at the time the study was conducted. J. Tabernero, J. Baselga, and E. Calvo have served as compensated scientific advisors to Merck & Co., Inc. J. Baselga is a consultant/advisory board member of Merck & Co., Inc. F. Atzori, A. Cervantes, L. Prudkin, J. Andreu, E. Rodriguez-Braun, A. Domingo, J. Guijarro, C. Gamez, J. Rodon, S. Di Cosimo, and S. Rosello have no conflicts of interest to disclose. The corresponding author had final responsibility for the decision to submit the manuscript for publication.

Authors’ Contributions


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Francesco Atzori, Josep Tabernero, Andrés Cervantes, et al.

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