Phase I Dose-Escalation Study of Onartuzumab as a Single Agent and in Combination with Bevacizumab in Patients with Advanced Solid Malignancies

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Abstract

Purpose: This first-in-human study evaluated the safety, immunogenicity, pharmacokinetics, and antitumor activity of onartuzumab, a monovalent antibody against the receptor tyrosine kinase MET.

Experimental Design: This 3+3 dose-escalation study comprised three stages: (i) phase Ia dose escalation of onartuzumab at doses of 1, 4, 10, 20, and 30 mg/kg intravenously every 3 weeks; (ii) phase Ia cohort expansion at the recommended phase II dose (RP2D) of 15 mg/kg; and (iii) phase Ib dose escalation of onartuzumab at 10 and 15 mg/kg in combination with bevacizumab (15 mg/kg intravenously every 3 weeks). Serum samples were collected for evaluation of pharmacokinetics, potential pharmacodynamic markers, and antitherapeutic antibodies.

Results: Thirty-four patients with solid tumors were treated in phase Ia and 9 in phase Ib. Onartuzumab was generally well tolerated at all dose levels evaluated; the maximum tolerated dose was not reached. The most frequent drug-related adverse events included fatigue, peripheral edema, nausea, and hypoalbuminemia. In the phase Ib cohort, onartuzumab at the RP2D was combined with bevacizumab and no dose-limiting toxicities were seen. Onartuzumab showed linear pharmacokinetics in the dose range from 4 to 30 mg/kg. The half-life was approximately 8 to 12 days. There were no apparent pharmacokinetic interactions between onartuzumab and bevacizumab, and antitherapeutic antibodies did not seem to affect the safety or pharmacokinetics of onartuzumab. A patient with gastric carcinoma in the 20-mg/kg dose cohort achieved a durable complete response for nearly 2 years.

Conclusions: Onartuzumab was generally well tolerated as a single agent and in combination with bevacizumab in patients with solid tumors. Clin Cancer Res; 20(6); 1666–75. ©2014 AACR.

Introduction

MET, a receptor tyrosine kinase, initiates branching morphogenesis in normal cells upon binding of its only known ligand, hepatocyte growth factor (HGF; also known as scatter factor). Branching morphogenesis involves cell proliferation, transformation, and migration (1, 2). Dysregulation of HGF and MET plays a key role in tumorigenesis (3, 4). Clinically, MET receptor expression is associated with poor prognosis in several cancers, including non–small cell lung cancer (NSCLC), breast cancer, gastric cancer, head and neck cancer, and glioblastoma (3). Components of the MET signaling pathway have emerged as attractive therapeutic targets (5–7).

Onartuzumab (formerly called MetMAb and PRO143966) is a humanized, monovalent (one-armed) monoclonal antibody that blocks HGF binding and prevents downstream cellular signaling (8). Onartuzumab was designed as a monovalent antibody to avoid the agonistic activity that may occur when a bivalent antibody binds two MET molecules (9). Onartuzumab demonstrated antitumor activity in various animal tumor models (6, 8, 10). MET and its downstream effectors interact with other tumorigenic pathways; MET activation functions as a potent regulator of the angiogenic switch by increasing expression of angiogenic molecules such as vascular endothelial growth factor (VEGF) (11). Hypoxia can induce expression of MET on tumor cells, which may enable improved tumor cell survival and/or migration toward regions of normoxia (12). Enhanced antitumor activity has been observed when combining onartuzumab with an anti-VEGF antibody in preclinical models (10). These
Patients with advanced solid malignancies. mab, alone and in combination with bevacizumab, in the safety, tolerability, and pharmacokinetics of onartuzumab—which is a humanized, monoclonal antibody that blocks hepatocyte growth factor binding—is well tolerated as a single agent and in combination with bevacizumab. In this setting of good safety, we show how pharmacokinetic/pharmacodynamic (PK-PD) modeling may be used to derive a recommended phase II dose. One patient with clinically relevant exposure and with autoimmune MET gastric cancer achieved a complete response.

Observations justify evaluation of combination therapies that target both angiogenesis and MET signaling.

We conducted a phase I dose-escalation study of onartuzumab to identify the maximum tolerated dose (MTD) and recommended phase II dose (RP2D), and to characterize the safety, tolerability, and pharmacokinetics of onartuzumab, alone and in combination with bevacizumab, in patients with advanced solid malignancies.

Materials and Methods

Onartuzumab was administered by intravenous (i.v.) infusion every 3 weeks (Q3W), either alone or in combination with bevacizumab (15 mg/kg i.v. Q3W) in patients with advanced solid malignancies refractory to standard of care therapy or for which standard of care therapy did not exist. This study was conducted at two U.S. sites (The University of Chicago, IL, and Cancer Institute of New Jersey, NJ). The protocol was approved by the Institutional Review Boards before patient recruitment and was conducted in accordance with the International Conference on Harmonisation E6 Guideline for Good Clinical Practice.

Eligibility criteria

Key inclusion criteria were adults with histologically confirmed solid malignancy that was incurable, locally advanced, or metastatic and that had failed to respond to at least one prior regimen or for which standard of care therapy did not exist; measurable or evaluable disease; at least 30 kg weight; life expectancy >3 months; adequate renal (creatinine <1.5 mg/dL or creatinine clearance >50 mL/min), hematologic (granulocytes >1,500/µL, platelets >100,000/µL, hemoglobin >10 g/dL), and hepatic function [aspartate aminotransferase, alanine aminotransferase, and total bilirubin within normal limits or National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) grade 1 or less if liver had tumor involvement].

Patients were generally excluded if they had received antitumor therapies or undergone a major surgical procedure within 4 weeks of the start of the study. Patients were excluded from the bevacizumab cohort in phase Ib if they had inadequately controlled hypertension as defined by systolic blood pressure >150 mmHg and/or diastolic blood pressure >100 mmHg, a history of cardiovascular disease or significant vascular disease within 6 months before enrollment, or major surgery within 28 days before start of dosing.

Study design and treatments

The study involved three stages: (1) the phase Ia dose-escalation phase was designed to determine the safety, tolerability, and pharmacokinetics of single-agent onartuzumab (supplied by Genentech, Inc.) at dose levels of 1, 4, 10, 20, and 30 mg/kg administered by i.v. Q3W, and to identify the RP2D; (2) in the phase I expansion, additional patients were enrolled to study safety and pharmacokinetics of single-agent onartuzumab at the RP2D; and (3) the phase Ib stage evaluated the combination of onartuzumab [10 mg/kg (one dose level below the RP2D)] with bevacizumab (15 mg/kg i.v. Q3W; supplied by Genentech, Inc.). Patients without progressive disease or significant toxicity could continue treatment with study drug(s) for a maximum of 16 cycles or 1 year.

Patients were discontinued from the study for any of the following reasons: dose-limiting toxicity (DLT), disease progression, noncompliance, change in eligibility, or if the investigator felt it was in their best interest. Patients in phase Ib who experienced bevacizumab-related adverse events (AE) discontinued bevacizumab, but could continue with onartuzumab treatment.

A standard 3+3 dose-escalation design applied for onartuzumab until the maximum administered dose of 30 mg/kg was reached in the phase Ia escalation and until the RP2D of 15 mg/kg was reached in phase Ib with bevacizumab. The dose of onartuzumab for each patient was dependent on dose level assignment and patient weight on or within 14 days of day 1 of cycle 1. Onartuzumab was administered over 90 ± 10 minutes for the first two doses. Subsequent doses were administered over 30 ± 10 minutes (for dose levels <10 mg/kg) or 60 ± 10 minutes (for dose levels ≥10 mg/kg). In phase Ib, onartuzumab was given before bevacizumab.

Safety, tolerability, and response assessments

The primary outcome measure was the safety and tolerability of onartuzumab alone or in combination with bevacizumab assessed based on the frequency and nature of DLTs, AEs (graded according to NCI CTCAE version 3.0), vital signs, and clinical laboratory parameters. Medical Dictionary for Regulatory Activities preferred terms were used. A DLT was defined as grade ≥3 hematologic toxicity, grade ≥3 nonhepatic major organ toxicity, or grade ≥3 hepatic toxicity considered to be related to the study drug. Patients were assessed for AEs on days 1, 8, and 15 of cycles 1 and 2, and on days 1 and 8 of each subsequent cycle. All AEs and serious AEs were summarized by term and grade.
Safety and tolerability were assessed through clinical and laboratory evaluations at weekly intervals for the first 6 weeks then at a minimum of every 3 weeks throughout the remainder of a patient’s study treatment.

Disease response and progression, based on investigator assessments and using RECIST 1.0 (13) were performed at baseline, and after cycles 2 and 4, then every third cycle thereafter until study termination. The same radiographic procedure used at baseline was used throughout the study. Bone and brain scans were performed as clinically indicated.

All patients who received any amount of onartuzumab alone or in combination with bevacizumab were included in the safety analysis. Patients who withdrew before day 2 of cycle 2 for reasons other than DLT were not evaluable for DLT and MTD assessments. The MTD was defined as the highest dose level at which less than one third of the group (comprising a minimum of 6 patients) experienced a DLT.

Pharmacokinetic assessments and analysis plan

Serum samples for establishing onartuzumab and bevacizumab concentrations were collected during cycle 1 before dosing, 0.5, 2, 4, and 7 hours, and 1, 2, 3, 7, 10, 14, and 21 days after dosing. Samples were collected before and 0.5 hours after dosing at every cycle thereafter and at treatment termination.

Diluted serum samples were assayed for onartuzumab and bevacizumab concentrations using validated sandwich ELISA with a limit of quantification of 200 and 78 ng/mL, respectively (Supplementary Material). Shed MET levels were measured by electrochemiluminescence assay (Supplementary Material) at baseline, 24 hours after first dose and at the end of the first cycle.

The onartuzumab pharmacokinetic data collected in cycle 1 were analyzed by noncompartmental analysis with WinNonlin (version 5.2; Pharsight Corporation) and were summarized by mean, standard deviation, and range. The data were compared across phase Ia escalation, phase Ia expansion, and phase Ib for onartuzumab. Measured bevacizumab data in phase Ib were compared with the predicted concentrations (based on published bevacizumab population pharmacokinetics model; ref. 14) to explore the potential impact of onartuzumab administration on bevacizumab exposure.

Pharmacokinetic/pharmacodynamic modeling and simulation was used to estimate the onartuzumab tumorstatic concentration (TSC), in which there is no net tumor growth. Estimated TSC was used as an efficacious target concentration to optimize the clinical dose and regimen.

This integrated analysis was based on the determined relationship between onartuzumab exposure in preclinical KP4 athymic xenograft mouse studies and the resulting antitumor activity in this model, and predicted human pharmacokinetics (15). The KP4 model was selected for this analysis, but other similar models, such as H596 and U87, had similar antitumor activity at comparable onartuzumab doses. Onartuzumab exposure and tumor response data were collected in KP4 athymic xenograft mice, and a tumor inhibition PK/PD model was developed. The PK driver of antitumor activity was directly determined from time–dose fractionation studies designed to identify concentration and time effects on tumor response. Human onartuzumab pharmacokinetics were predicted by allometric scaling based on PK data from cynomolgus monkey and used in the integrated PK/PD model. The theoretical onartuzumab treatment efficacy in humans was then predicted using drug-mediated antitumor activity derived from the tumor cell growth inhibition model and predicted clinical onartuzumab serum concentrations. Subsequently, 500 simulations based on the PK/PD modeling results were performed using an onartuzumab population pharmacokinetic model to determine the dose and regimen required to achieve steady-state trough concentrations above the TSC in >90% of patients.

Antitherapeutic antibody assessments

Serum samples for evaluating antitherapeutic antibodies (ATA) to onartuzumab were collected before each treatment cycle and at study termination. The samples were assayed in a validated bridging electrochemiluminescence assay. The relative sensitivity of the assay was estimated to be 143 ng/mL using affinity-purified polyclonal cynomolgus monkey antionartuzumab antibodies and the assay could detect 500 ng/mL of the antibodies in the presence of 50 μg/mL onartuzumab. Samples that screened positive were further evaluated by competitive binding experiments to understand whether the response was directed against the unique engineered part of the framework. The strength of positive responses was evaluated by titering (Supplementary Material).

Pharmacodynamic assessments

Blood was drawn at baseline and through cycle 3 of study treatment for measurements of serum HGF, shed MET, and interleukin (IL)-8. Methods for serum HGF and IL-8 are reported elsewhere (16). Serum-shed MET levels were evaluated 24 hours after first dose and at the end of cycle 1 (day 21) using an electrochemiluminescence assay (Supplementary Material). Serum levels of HGF and circulating shed MET were measured at baseline, cycle 1 day 1 (predose), cycle 1 day 2; and at cycle 2 and cycle 3 day 1 (predose). Levels of HGF and shed MET were compared among dose cohorts, and with concomitant serum concentrations of onartuzumab. To address potential variability due to platelet activation in serum, a comparison study was conducted in patients with NSCLC with matched collections of plasma and serum. An assessment of circulating HGF in this cohort showed a strong correlation of r = 0.974, thus justifying the use of serum in this phase 1 study (16).

Additional statistical analyses

Demographic and baseline characteristics were summarized using mean, standard deviation, median, and range for continuous variables, and proportion for categorical variables. Safety data were summarized by cohort.
The planned sample size was 21 to 36 patients in the phase Ia dose-escalation cohort, 6 to 12 patients in the phase Ia expansion cohort, and up to 9 patients in phase Ib, depending on the number of DLTs observed.

Results

Patient disposition and demographics

In total, 43 patients with solid malignancies (including colorectal, gastric, head and neck, liver/biliary, lung, melanoma, ovarian, pancreatic, and sarcoma tumors) were included in this study; 21 patients were enrolled in phase Ia dose escalation, 13 in phase Ia expansion, and 9 in phase Ib. Baseline demographic characteristics are summarized in Table 1.

Dose-limiting toxicity

In the phase Ia dose escalation, a single DLT of grade 3 pyrexia was observed in the 4 mg/kg cohort. There was no MTD identified, the maximum administered dose was 30 mg/kg, and the RP2D, based on preclinical pharmacokinetic/pharmacodynamic modeling (15), was determined to be 15 mg/kg; a total of 13 patients were treated at this dose level in the dose-expansion phase.

In phase Ib, a single DLT of grade 1 hemoptysis in a patient with a prior history of pulmonary hemorrhage was observed at the onartuzumab dose 15 mg/kg Q3W in combination with bevacizumab (see below). Based on this, the RP2D of onartuzumab in combination with bevacizumab was also determined to be 15 mg/kg.

Safety and tolerability

For the 34 patients treated with onartuzumab alone, the median number of doses received was 2 (range, 1–10). In phase Ib, the median number of onartuzumab and bevacizumab doses received by the 9 patients was 4 (range, 1–6).

Most AEs reported were of grade 1 or 2 severity and were reversible. Table 2 lists all onartuzumab-related grade 1 or 2 AEs experienced by >5% of patients, and all onartuzumab-related grade 3 AEs experienced in either phase Ia or Ib (there were no onartuzumab-related grade 4/5 events). During phase Ia, the most frequently reported onartuzumab-related AEs occurring in >10% of patients comprised fatigue (38%), peripheral edema (27%), nausea (12%), and hypoalbuminemia (12%). During phase Ia, 7 patients (21%) experienced grade 3 onartuzumab-related AEs. Two patients experienced serious AEs [fever (also a DLT) and peripheral edema] judged possibly related to study drug. With the exception of peripheral edema (severity reported as grade 1, n = 6; grade 2, n = 0; grade 3, n = 3), no other obvious dose relationship associated with AEs was demonstrated (Supplementary Table S1).

During phase Ib, 3 of the 9 treated patients (33%) experienced onartuzumab-related AEs (Table 2); no AEs ≥ grade 3 were observed. One serious AE of grade 1 hemoptysis (also a DLT) was reported as possibly related to bevacizumab. Pulmonary bleeding (any grade) was a protocol-defined DLT. This patient with gastric cancer and pulmonary metastases had a history of hemoptysis before entering the study; computed tomography scan of chest showed evidence of pulmonary lesions with central necrosis.

For the 34 patients treated in phase Ia, the most commonly reported AEs (>10% frequency) regardless of relationship to study drug were fatigue (56%), peripheral edema (35%), and decreased appetite (32%; Supplementary Table S2). For 9 patients in phase Ib, the most commonly (>10% frequency) reported AE regardless of relationship to study drug was fatigue (56%), followed by increased weight (33%; Supplementary Table S2).

In summary, an MTD for onartuzumab was not reached when administered alone and the RP2D of onartuzumab in combination with bevacizumab had no apparent impact on the severity or frequency of known bevacizumab-related AEs.

Pharmacokinetics/pharmacodynamics

Onartuzumab concentration–time data (Fig. 1a) were obtained from all 43 patients. Table 3 summarizes the main pharmacokinetic parameters estimated using noncompartmental analysis. Onartuzumab seemed to manifest linear pharmacokinetics in the dose range from 4 to 30 mg/kg, although clearance of the 1 mg/kg dose was faster than the

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### Table 1. Patient demographics and baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Phase Ia escalation and expansion (n = 34)</th>
<th>Phase Ib escalation (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>Median 63</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>Range 29–85</td>
<td>42–80</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td>Female 15 (44)</td>
<td>7 (78)</td>
</tr>
<tr>
<td></td>
<td>Male 19 (56)</td>
<td>2 (22)</td>
</tr>
<tr>
<td>Primary tumor, n (%)</td>
<td>Colorectal 6 (18)</td>
<td>4 (44)</td>
</tr>
<tr>
<td></td>
<td>Gastric 5 (15)</td>
<td>1 (11)</td>
</tr>
<tr>
<td></td>
<td>Head and neck 1 (3)</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Kidney —</td>
<td>1 (11)</td>
</tr>
<tr>
<td></td>
<td>Liver/biliary 1 (3)</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Lung 6 (18)</td>
<td>2 (22)</td>
</tr>
<tr>
<td></td>
<td>Melanoma 2 (6)</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Ovarian 2 (6)</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Pancreatic 3 (9)</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Sarcoma 2 (6)</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Other 6 (18)</td>
<td>1 (11)</td>
</tr>
<tr>
<td>ECOG PS, n (%)</td>
<td>0 19 (56)</td>
<td>3 (33)</td>
</tr>
<tr>
<td></td>
<td>1 14 (41)</td>
<td>5 (56)</td>
</tr>
<tr>
<td></td>
<td>2 1 (3)</td>
<td>1 (11)</td>
</tr>
</tbody>
</table>

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status.
other dose levels, suggesting target-mediated drug disposition at lower doses, which is commonly observed for antibodies. In the linear dose range, the group mean clearance values varied from 6.8 to 9.9 mL/d/kg, which may be slightly faster than typical bivalent antibodies (approximately 3–5 mL/day/kg; ref. 17). The other pharmacokinetic parameters increased proportionally with dose. The mean terminal half-life was 8 to 12 days. Based on population, PK simulated concentrations at the end of cycles 1 and 3 (steady-state), Ctrough concentrations increased slightly from 29.4 to 40.4 mg/mL, and the percentage of patients with Ctrough above the TSC of 15 mg/mL increased from 86% to 90%. Consistent with typical monoclonal antibodies, the volume of distribution was small across all dose groups, indicating limited tissue distribution.

Pharmacokinetic/pharmacodynamic modeling estimated the TSC for onartuzumab in KP4 pancreatic xenograft tumor–bearing mice to be 15 mg/mL, suggesting that concentrations above 15 mg/mL could result in net tumor shrinkage (15). Therefore, 15 mg/mL was selected as the Ctrough to achieve in the clinic. Population pharmacokinetic simulations based on data collected in this phase I trial indicated that a dose of 15 mg/kg Q3W would achieve steady-state trough concentrations of 15 mg/mL in ≥90% of patients (Fig. 1b). Therefore, 15 mg/kg on a Q3W dosing regimen was determined to be the RP2D. Other xenograft models representing diverse tumor-types, such as H596 (NSCLC) and U87 (glioblastoma multiforme), had similar antitumor activity at comparable onartuzumab doses.

Onartuzumab pharmacokinetic parameters at 15 mg/kg were similar for both monotherapy (phase la) and combination therapy with bevacizumab (phase lb; Table 3). The majority of observed bevacizumab concentration data points in the treatment cycle fell within the 90% confidence interval of predicted concentrations (Fig. 1c). Similar findings were observed using Cmin and Cmax data points in other treatment cycles (data not shown). These results suggest that coadministration of onartuzumab and bevacizumab does not seem to affect the exposure to either drug.

### Antitherapeutic antibodies

ATAs were evaluated in 42 patients. Six patients tested positive for ATAs to onartuzumab; for all 6 patients, the response was minimal, with a titer range of 1.5 to 1.9 (minimum reportable titer, 1.4). For 1 of these patients, an ATA response was also observed in the pretreatment sample, which fell within the assay’s validated false-positive rate. All ATA responses were determined to be primarily toward the nonengineered framework of onartuzumab; the pharmacokinetic profiles of the ATA-positive patients did not seem to be affected by the immunogenicity. None of the ATA responses seemed to correlate with any AEs.

### Evaluation of on-treatment shed MET levels in serum as a marker of target engagement

Other biomarkers thought to be modulated by MET signaling, such as HGF and IL-8, were evaluated at similar time points and are reported elsewhere (16). The extracellular domain of the MET receptor is proteolytically cleaved and shed into circulation (18) and was detected at baseline concentrations of 158 ± 62 ng/mL in the serum of the phase I patients. Serum was available from a total of 27 patients

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### Table 2. Treatment-related adverse events for onartuzumab administered by intravenous infusion once every 3 weeks, alone or in combination with bevacizumab, in Phase Ia escalation (onartuzumab 1 to 30 mg/kg) and expansion (onartuzumab 15 mg/kg), and phase Ib (bevacizumab 15 mg/kg plus onartuzumab 10 and 15 mg/kg)

<table>
<thead>
<tr>
<th>Phase Ia escalation and expansion (n = 34)</th>
<th>Phase Ib escalation (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 or 2</td>
<td>Grade 3*</td>
</tr>
<tr>
<td>Any adverse event, n (%)</td>
<td>Any adverse event, n (%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Fatigue</td>
</tr>
<tr>
<td>Edema, peripheral</td>
<td>Edema, peripheral</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>Hypoalbuminemia</td>
</tr>
<tr>
<td>Nausea</td>
<td>Nausea</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Vomiting</td>
</tr>
<tr>
<td>Weight increased</td>
<td>Weight increased</td>
</tr>
<tr>
<td>Anorexia</td>
<td>Anorexia</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>Muscle spasms</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>Abdominal pain</td>
</tr>
<tr>
<td>AST increased</td>
<td>AST increased</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>Pyrexia</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>Hyponatremia</td>
</tr>
</tbody>
</table>

Abbreviation: AST, aspartate aminotransferase.

*There were no grade 4 events.
receiving any dose of single-agent onartuzumab. Shed MET levels were evaluated to confirm target engagement in humans. As shown in Fig. 2, drug treatment resulted in an immediate increase in shed MET levels in all patients. An approximately 2-fold increase in shed MET was observed in all patients in all dose groups at the 24-hour time point. Evaluation of shed MET at the Cmin concentration of onartuzumab at the end of cycle 1 showed that patients in the 1 mg/kg group continued to maintain a 2-fold increase in shed MET. However, dose groups of 4 mg/kg and higher showed a 3- to 7-fold increase over predose levels, suggesting saturation of the peripheral receptors at these dose levels.

**Tumor assessments**

Figure 3 shows waterfall plots for best tumor response observed in individual patients during the study. There was one complete response (CR); no other RECIST responses were observed.

The CR was observed following 4 cycles of treatment with single-agent onartuzumab (20 mg/kg) in a 50-year-old patient with a solitary hepatic metastasis from gastric carcinoma (19) who had received prior chemotherapy and a prior investigative therapy. The CR was confirmed by magnetic resonance imaging and after the tenth cycle of onartuzumab the patient decided to stop study drug. Analysis of the pretreatment biopsy sample produced findings consistent with autocrine HGF/MET biology: Intratumoral MET and HGF expression were identified by immunohistochemistry (Fig. 4), chromosome 7 polyploidy (but no MET focal gene amplification) was identified by fluorescence in situ hybridization, and there was no evidence of MET gene mutation (19). This patient had elevated pretreatment serum HGF levels and was the only patient to show sustained decrease in HGF after onartuzumab treatment. This represents the sole patient in the trial with an objective response, and thus the only patient with tissue assessed for MET pathway markers.

**Discussion**

In this phase I dose-escalation study, onartuzumab was well tolerated when administered intravenously as a single agent at doses up to 30 mg/kg Q3W and in combination with bevacizumab at the RP2D of 15 mg/kg Q3W. The RP2D was selected based on the overall safety, as well as pharmacokinetic/pharmacodynamic modeling (15).

It is notable that no dose relationship with any AEs was evident, except for peripheral edema, which was observed as a treatment-related AE at doses exceeding 10 mg/kg. The majority of AEs were grade 1 or 2, with grade 3 events (three in total) reported during the phase Ia expansion (Table 2). One patient in phase Ia escalation (onartuzumab...
20 mg/kg, grade 1) and 1 patient in phase 1a expansion (onartuzumab 15 mg/kg, grade 3) discontinued treatment due to peripheral edema. Peripheral edema has also been reported in trials of other monoclonal antibodies targeting the MET signaling pathway, such as rilotumumab (AMG102; ref. 20) and ficlatuzumab (AV-299; ref. 21), two anti-HGF antibodies, suggesting that this toxicity may be an on-target finding.

The MET/HGF axis is involved in many biologic functions, including a central role in liver regeneration (22). No significant hepatotoxicity (manifested by changes in liver enzymes or total bilirubin) was observed with onartuzumab. It is important to note that small-molecule inhibitors against MET have been reported to lead to liver AEs, which may be related to off-target mechanisms (23). Additionally, MET activation also functions as a potent regulator of the angiogenic switch by increasing expression of angiogenic molecules such as VEGF, including during states of hypoxia (11, 12). The ability of onartuzumab and bevacizumab to be combined relatively safely allows broader testing of the combination in phase II programs.

Onartuzumab exhibits linear pharmacokinetics within the tested dose range of 4 to 30 mg/kg, indicating the saturation of target-mediated clearance. The clearance was slightly faster and the terminal half-life was slightly shorter compared with typical bivalent antibodies (17). Although onartuzumab has a slightly faster clearance compared with other antibodies, pharmacokinetic/pharmacodynamic modeling and simulation predicts the RP2D of 15 mg/kg Q3W will achieve steady-state trough concentrations above the TSC of 15 μg/mL in ≥90% of patients. Analyses of both onartuzumab and bevacizumab concentration data suggest that coadministration does not seem to affect drug exposure to either.

Because of the unique monovalent structure of onartuzumab, induction of ATAs was a concern. Although some onartuzumab-treated patients were ATA positive at one or more assessments, all ATA responses were low, did not seem to affect pharmacokinetics, were not associated with AEs,

Table 3. Pharmacokinetic parameters estimated using noncompartmental analysis for cycle 1 data

<table>
<thead>
<tr>
<th>Parameter (mean ± SD)</th>
<th>Phase 1a escalation (single-agent onartuzumab)</th>
<th>Phase Ib (onartuzumab + bevacizumab)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Cmax (μg/mL)</td>
<td>27.1 ± 6.4</td>
<td>9.5 ± 1.7</td>
</tr>
<tr>
<td>AUC0–21 (μg·h/mL)</td>
<td>47.3 ± 10.8</td>
<td>166 ± 27.0</td>
</tr>
<tr>
<td>Vss (mL/kg)</td>
<td>64.0 ± 11.6</td>
<td>135 ± 29.0</td>
</tr>
<tr>
<td>t1/2 (d)</td>
<td>2.04 ± 0.404</td>
<td>2.23 ± 3.18</td>
</tr>
</tbody>
</table>

NOTE: The data were grouped on the basis of the dose level and study stage. AUC0–21, area under the concentration–time curve from 0 to 21 days; CL, systemic clearance; Cmax, peak concentration; Cmin, trough concentration; t1/2, elimination half-life; Vss, steady-state volume of distribution.

Figure 2. Evaluation of shed MET through cycle 1 of onartuzumab therapy. Serum-shed MET levels were evaluated 24 hours after first dose and at the end of cycle 1 (day 21) using an ELISA-based assay. Data, ratio to predose levels at each dose group.

20 mg/kg, grade 1) and 1 patient in phase 1a expansion (onartuzumab 15 mg/kg, grade 3) discontinued treatment due to peripheral edema. Peripheral edema has also been reported in trials of other monoclonal antibodies targeting the MET signaling pathway, such as rilotumumab (AMG102; ref. 20) and ficlatuzumab (AV-299; ref. 21), two anti-HGF antibodies, suggesting that this toxicity may be an on-target finding.

The MET/HGF axis is involved in many biologic functions, including a central role in liver regeneration (22). No significant hepatotoxicity (manifested by changes in liver enzymes or total bilirubin) was observed with onartuzumab. It is important to note that small-molecule inhibitors against MET have been reported to lead to liver AEs, which may be related to off-target mechanisms (23). Additionally, MET activation also functions as a potent regulator of the angiogenic switch by increasing expression of angiogenic molecules such as VEGF, including during states of hypoxia (11, 12). The ability of onartuzumab and bevacizumab to be combined relatively safely allows broader testing of the combination in phase II programs.

Onartuzumab exhibits linear pharmacokinetics within the tested dose range of 4 to 30 mg/kg, indicating the saturation of target-mediated clearance. The clearance was slightly faster and the terminal half-life was slightly shorter compared with typical bivalent antibodies (17). Although onartuzumab has a slightly faster clearance compared with other antibodies, pharmacokinetic/pharmacodynamic modeling and simulation predicts the RP2D of 15 mg/kg Q3W will achieve steady-state trough concentrations above the TSC of 15 μg/mL in ≥90% of patients. Analyses of both onartuzumab and bevacizumab concentration data suggest that coadministration does not seem to affect drug exposure to either.

Because of the unique monovalent structure of onartuzumab, induction of ATAs was a concern. Although some onartuzumab-treated patients were ATA positive at one or more assessments, all ATA responses were low, did not seem to affect pharmacokinetics, were not associated with AEs,
and were found to be primarily toward the nonengineered framework of onartuzumab.

As this phase I study was the first examination of onartuzumab administration in humans, evidence of target engagement in humans was evaluated. On-treatment biopsies were unavailable to assess pharmacodynamic effects in the tumor directly. However, because the extracellular domain of the MET receptor is shed into circulation and serum was available at multiple time points, we evaluated soluble shed MET levels as a measure of target engagement and peripheral receptor occupancy (24). It is noteworthy that shed MET levels can increase in circulation as a result of complex formation with the drug, which has slower clearance than shed MET alone and could thereby result in an increase in serum-shed MET concentrations. Because shed MET levels can increase in circulation, levels may not necessarily reflect true peripheral receptor saturation; therefore, pharmacokinetic/pharmacodynamic modeling from preclinical xenograft models was used to support determination of the phase II dose. We also previously examined circulating HGF levels in phase I patients as a biomarker of MET inhibition for onartuzumab, and observed an increased level following onartuzumab treatment, which was independent of dose, but reflected the pharmacodynamic activity of the drug (16).

One patient with likely autocrine HGF/MET-driven gastric cancer had an objective CR to onartuzumab (20 mg/kg) during phase Ia. The activity observed supports the presumed biology and suggests there may be certain disease states in which single-agent onartuzumab could provide clinical benefit. Further studies will be required to better characterize the efficacy of onartuzumab in populations with autocrine MET, high MET, amplified MET, or even mutated MET disease (19), as well as to elucidate possible mechanisms of resistance to onartuzumab therapy, such as KRAS or RON amplification (25, 26).

In conclusion, this phase I study shows onartuzumab to be generally well tolerated when administered both alone and in combination with bevacizumab. The MTD was not reached with either single agent or combination dose escalations. Patients received the RP2D of 15 mg/kg Q3W without evidence of DLTs. A number of phase II studies (ClinicalTrials.gov: NCT01632228; NCT01590719; NCT01519804; NCT01418222; NCT01186991; and NCT01496742) and
phase III studies (ClinicalTrials.gov: NCT01662869 and NCT01456325) are ongoing to evaluate the efficacy and safety of onartuzumab in patients with a variety of advanced solid tumors.

Disclosure of Potential Conflicts of Interest

S. Eppler has ownership interest in a patent. P. Hege is employed as a Senior Scientist with Genentech. I. Nijem has ownership interest in company stock. D.V.T. Catenacci is a consultant/advisory board member and has received speakers bureau honoraria from Genentech. M.J. Ratain is a consultant/advisory board member for GLC and has received speakers bureau honoraria from Genentech. M.J. Ratain is a consultant/advisory board member for GLC and has received speakers bureau honoraria from Merck and has received stock. D.V.T. Catenacci is a consultant/advisory board member and has received research funding from Genetech Inc.

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References


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