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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STATEMENT OF TRANSLATIONAL RELEVANCE

Aberrant up-regulation of the MET pathway is frequent in human malignancies, and leads to branching morphogenesis and invasion. MET activation may also occur during states of hypoxia, which may enable migration/invasion towards regions of normoxia. This Phase Ia and Ib study shows onartuzumab- a humanized, monovalent (one-armed) monoclonal antibody that blocks HGF binding- is well tolerated as single-agent and in combination with bevacizumab. In this setting of good safety, we show how PK-PD modeling may be used to derive a recommended Phase II dose. One patient with clinically relevant exposure and with autocrine MET gastric cancer achieved a complete response.
Abstract (Word count: 247; max. 250)

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

Experimental design: This 3+3 dose-escalation study comprised three stages: (1) phase Ia dose-escalation of onartuzumab at doses of 1, 4, 10, 20, and 30 mg/kg intravenously every 3 weeks; (2) phase Ia cohort expansion at the recommended phase II dose (RP2D) of 15 mg/kg; and (3) phase Ib dose-escalation of onartuzumab at 10 and 15 mg/kg in combination with bevacizumab (15 mg/kg intravenously Q3W). Serum samples were collected for evaluation of pharmacokinetics, potential pharmacodynamic markers, and anti-therapeutic antibodies.

Results: Thirty-four patients with solid tumors were treated in phase Ia and nine 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 ~8–12 days. There were no apparent pharmacokinetic interactions between onartuzumab and bevacizumab, and anti-therapeutic antibodies did not appear 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.
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, 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 towards regions of normoxia (12). Enhanced antitumor activity has been observed when combining onartuzumab with an anti-VEGF antibody in preclinical models (10). These 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 (IV) infusion every 3 weeks (Q3W), either alone or in combination with bevacizumab (15 mg/kg IV 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 US sites (The University of Chicago and Cancer Institute of New Jersey). 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 defined by Response Evaluation Criteria in Solid Tumors (RECIST) (13); Eastern Cooperative Oncology Group (ECOG) performance status 0–2; adequate renal (creatinine ≤1.5 mg/dL or creatinine clearance ≥50 mL/min), hematologic (granulocytes ≥1500/μL, platelets ≥100,000/μL, hemoglobin ≥10 g/dL), and hepatic function (AST, ALT 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 anti-tumor 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 prior to enrollment, or major surgery within 28 days prior to 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., South San Francisco, CA) at dose levels of 1, 4, 10, 20, and 30 mg/kg administered by IV Q3W, and to identify the RP2D; (2) in the phase Ia 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] or 15 mg/kg IV Q3W [RP2D]) with bevacizumab (15 mg/kg IV Q3W; supplied by Genentech, Inc., South San Francisco, CA). 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, non-compliance, change in eligibility, or if the investigator felt it was in their best interest. Patients in phase Ib who experienced bevacizumab-related adverse events (AEs) discontinued bevacizumab, but could continue with onartuzumab treatment.
Phase I dose-escalation study of onartuzumab

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 non-hepatic major organ toxicity, or grade ≥3 hepatic toxicity considered to be related to the study drug. Patients were assessed for AEs on Day 1, 8 and 15 of Cycles 1 and 2, and on Day 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 enzyme-linked immunosorbent assays
(ELISA) with a limit of quantification of 200 ng/mL and 78 ng/mL, respectively
(Supplemental material). Shed MET levels were measured by
electrochemiluminescence assay (Supplemental material) at baseline, 24 hours post
first dose and at the end of the first cycle.

The onartuzumab pharmacokinetic data collected in Cycle 1 were analyzed by
non-compartmental analysis with WinNonlin (version 5.2; Pharsight Corporation,
Mountain View, CA) 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
Phase I dose-escalation study of onartuzumab pharmacokinetics model) (14) to explore the potential impact of onartuzumab administration on bevacizumab exposure.

Pharmacokinetic/pharmacodynamic modeling and simulation was used to estimate the onartuzumab tumoristatic concentration (TSC), where 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 anti-tumor 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 anti-tumor 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.
Anti-therapeutic antibody assessments

Serum samples for evaluating anti-therapeutic antibodies (ATAs) 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 anti-onartuzumab 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 IL-8. Methods for serum HGF and IL-8 are reported elsewhere (16). Serum shed MET levels were evaluated 24 hours post 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 (pre-dose), Cycle 1 Day 2; and at Cycle 2 and Cycle 3 Day 1 (pre-dose). 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 NSCLC patients 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 I 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 21–36 patients in the phase Ia dose-escalation cohort, 6–12 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 to 10). In phase Ib, the median number of onartuzumab and bevacizumab doses received by the 9 patients was 4 (range, 1 to 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, seven 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 material, Table S1).

During phase Ib, three of the nine 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; CT of chest scan 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 material, Table S2). For nine 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 material, 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 non-compartmental analysis. Onartuzumab appeared 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 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 (~3–5 mL/day/kg) (17). The other pharmacokinetic parameters increased proportionally with dose. The mean terminal half-life was 8–12 days. Based on population PK simulated concentrations at the end of cycles 1 and cycle 3 (steady-state), C_{trough} concentrations increased slightly from 29.4 to 40.4 µg/mL, and the percent of patients with C_{trough} above the TSC of 15 µg/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 µg/mL, suggesting that concentrations above 15 µg/mL could result in net tumor shrinkage (15). Therefore, 15 µg/mL was selected as the C_{trough} 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 μg/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 (non-small cell lung cancer) 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 Ia) and combination therapy with bevacizumab (phase Ib; 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 C_min and C_max data points in other treatment cycles (data not shown). These results suggest that co-administration of onartuzumab and bevacizumab does not appear to impact the exposure to either drug.

Anti-therapeutic antibodies

ATAs were evaluated in 42 patients. Six patients tested positive for ATAs to onartuzumab; for all six patients, the response was minimal, with a titer range of 1.5–1.9 (minimum reportable titer, 1.4). For one of these patients, an ATA response was also observed in the pre-treatment sample, which fell within the assay’s validated false-positive rate. All ATA responses were determined to be primarily towards the non-engineered framework of onartuzumab; the pharmacokinetic profiles of the ATA-positive patients did not appear to be affected by the immunogenicity. None of the ATA responses appeared 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 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 rise in shed MET levels in all patients. A ~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 rise over pre-dose levels, suggesting saturation of the peripheral receptors at these dose levels.

Tumor assessments

Fig. 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 pre-treatment 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 one 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
Phase I dose-escalation study of onartuzumab (AMG102) (20) and ficlatuzumab (AV-299) (21), two anti-HGF antibodies, suggesting that this toxicity may be an on target finding.

The MET/HGF axis is involved in many biological 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 vascular endothelial growth factor, including during states of hypoxia (11, 12). The ability for 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). While onartuzumab has a slightly faster clearance compared to 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 co-administration does not appear to impact 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 appear to
impact pharmacokinetics, were not associated with AEs, and were found to be primarily towards the non-engineered 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, since 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 rise 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. Since shed MET levels can rise 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 (20mg/kg) during phase Ia. The activity observed supports the presumed biology and suggests there may be certain disease states where 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; NCT01496742) and phase III studies (ClinicalTrials.gov: NCT01662869; NCT01456325) are ongoing to evaluate the efficacy and safety of onartuzumab in patients with a variety of advanced solid tumors.

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References


Table legends

**Table 1.** Patient demographics and baseline characteristics

**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 3.** Pharmacokinetic parameters estimated using non-compartmental analysis for Cycle 1 data
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<th>Phase Ib escalation</th>
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<td>–</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>2 (6)</td>
<td>–</td>
</tr>
<tr>
<td>Other</td>
<td>6 (18)</td>
<td>1 (11)</td>
</tr>
<tr>
<td>ECOG PS, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>19 (56)</td>
<td>3 (33)</td>
</tr>
<tr>
<td>1</td>
<td>14 (41)</td>
<td>5 (56)</td>
</tr>
<tr>
<td>2</td>
<td>1 (3)</td>
<td>1 (11)</td>
</tr>
</tbody>
</table>

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status.
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></th>
<th>Phase Ia escalation and expansion (n = 34)</th>
<th>Phase Ib escalation (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1 or 2</td>
<td>Grade 3&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Any adverse event, n (%)</td>
<td>15 (44)</td>
<td>7 (21)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>13 (38)</td>
<td>0</td>
</tr>
<tr>
<td>Edema, peripheral</td>
<td>6 (18)</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>4 (12)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (12)</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (9)</td>
<td>0</td>
</tr>
<tr>
<td>Weight increased</td>
<td>1 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Anorexia</td>
<td>3 (9)</td>
<td>0</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>3 (9)</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>0</td>
<td>1 (3)</td>
</tr>
<tr>
<td>AST increased</td>
<td>0</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>0</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>0</td>
<td>1 (3)</td>
</tr>
</tbody>
</table>

Abbreviation: AST, aspartate aminotransferase.

<sup>a</sup>There were no grade 4 events.
Table 3. Pharmacokinetic parameters estimated using non-compartmental analysis for Cycle 1 data

<table>
<thead>
<tr>
<th>Parameter (mean ± SD)</th>
<th>Phase Ia escalation and expansion (single-agent onartuzumab)</th>
<th>Phase Ib (onartuzumab + bevacizumab)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>No. of patients</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>C(_{\text{max}}) (μg/mL)</td>
<td>27.1 ± 2.64</td>
<td>95.5 ± 17.2</td>
</tr>
<tr>
<td>C(_{\text{min}}) (μg/mL)</td>
<td>LTR</td>
<td>8.26 ± 2.74</td>
</tr>
<tr>
<td>AUC(_{0-21}) (d·μg/mL)</td>
<td>67.3 ± 10.8</td>
<td>460 ± 99.5</td>
</tr>
<tr>
<td>CL (mL/d/kg)</td>
<td>15.0 ± 2.38</td>
<td>7.07 ± 1.88</td>
</tr>
<tr>
<td>V(_{\text{ss}}) (mL/kg)</td>
<td>64.0 ± 11.9</td>
<td>77.6 ± 9.56</td>
</tr>
<tr>
<td>t(_{1/2}) (d)</td>
<td>2.74 ± 0.404</td>
<td>8.55 ± 2.23</td>
</tr>
</tbody>
</table>

Note: The data were grouped on the basis of the dose level and study stage.
Phase I dose-escalation study of onartuzumab

Abbreviations: AUC_{0-21}, area under the concentration–time curve from 0 to 21 days; CL, systemic clearance; C_{max}, peak concentration; C_{min}, trough concentration; LTR, less than reportable; SD, standard deviation; t_{1/2}, elimination half-life; V_{ss}, steady-state volume of distribution.
Figure legends

**Figure 1.** Serum concentration–time profiles for (a) onartuzumab in Cycle 1 \((n = 43)\); (b) Model of onartuzumab dose projected to achieve minimum tumoristatic concentration (MTC) and (c) bevacizumab for nine patients in phase Ib treated with onartuzumab (10 and 15 mg/kg) and bevacizumab (15 mg/kg).

Concentrations presented as mean \((\pm\) standard deviation) in Fig. 1a. Figure 1b represents percent of patients with onartuzumab steady-state trough concentration projected to have a greater than the minimum tumoristatic concentration versus Q3W doses of onartuzumab. The solid line in Fig. 1c indicates median and dashed lines indicate 2.5th and 97.5th percentiles of bevacizumab predicted concentrations based on population pharmacokinetics model. Pharmacokinetics measurements were completed at Cycle 1, immediately prior to onartuzumab dosing, and post-dose at the following time intervals: 30 minutes, 2 hours, 4 hours, 7 hours, 24 hours, 48 hours, 72 hours, Day 8, and Day 11.

**Figure 2.** Evaluation of shed MET through Cycle 1 of onartuzumab therapy. Serum shed MET levels were evaluated 24 hours post first dose and at the end of Cycle 1 (Day 21) using an ELISA based assay. Data are represented as a ratio to pre-dose levels at each dose group.

**Figure 3.** Waterfall plot showing the best response (as assessed by Response Evaluation Criteria in Solid Tumors) to onartuzumab administered by intravenous infusion once every 3 weeks as a single agent (1 to 30 mg/kg) or in combination (10 and 15 mg/kg) with bevacizumab (15 mg/kg).
SLD, sum of longest diameters.

Highlighted patient (red dotted line) had a complete response.

*Patient discontinued study treatment early – subject's/legal guardian's decision to withdraw. **Patient discontinued study treatment early – disease progression.

**Figure 4.** IHC staining for intratumoral (a) MET and (b) HGF protein expression in the patient with a complete response.

HGF, hepatocyte growth factor; IHC, immunohistochemistry.
Concentrations presented as mean (±standard deviation).

Patients with SS trough conc ≥ MTC (%)

Q3W onartuzumab dose (mg/kg)

Observed bevacicizumab serum concentrations (open circles) from 9 patients in Phase I is treated with onartuzumab and bevacicizumab and solid line shows the 97.5% percentile of bevacizumab predicted concentrations based on population PK.
Figure 4

A

c-MET IHC

B

HGF IHC