HGF as a Circulating Biomarker of Onartuzumab Treatment in Patients with Advanced Solid Tumors

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Abstract

The objective of this study was to evaluate circulating hepatocyte growth factor (cHGF) as a pharmacodynamic biomarker of Met inhibition for onartuzumab (MetMAb, OA5D5v2) in a phase I trial in patients with advanced cancers and a phase II trial in non–small cell lung cancer (NSCLC). The phase I study was a dose escalation trial with onartuzumab administered i.v. once every three weeks. The phase II study was a randomized two-arm trial in which onartuzumab or placebo was administered in combination with erlotinib in 137 patients with second and third line (2/3L) NSCLC. cHGF levels were evaluated by ELISA at multiple time points over the treatment period. Onartuzumab administration resulted in an acute and sustained rise in cHGF in both the phase I and phase II studies. Elevation in cHGF was independent of dose or drug exposure and was restricted to onartuzumab treatment. Neither higher baseline nor elevated change in cHGF levels upon treatment could simply be attributed to tumor burden or number of liver metastasis. We have shown that elevated cHGF can consistently and reproducibly be measured as a pharmacodynamic biomarker of onartuzumab activity. The elevation in cHGF is independent of tumor type, dose administered, or dose duration. Although these studies were not powered to directly address the contribution of cHGF as a predictive, on-treatment, circulating biomarker, these data suggest that measurement of cHGF in future expanded studies is warranted.

Mol Cancer Ther; 12(6); 1122–30. ©2013 AACR.

Introduction

Activation of the Met pathway in both epithelial and endothelial cells by its only known ligand, hepatocyte growth factor (HGF, also known as scatter factor), results in a wide array of biological responses ranging from cell proliferation and cell invasiveness to more complex morphological changes, such as branching morphogenesis (1–4). These diverse roles in response to Met signaling contribute to tumor growth and metastasis. As a consequence, aberrant Met activation because of overexpression of HGF and/or Met is poorly prognostic in multiple cancer types, including non–small cell lung cancer (NSCLC), breast, and colorectal cancers (5–9). Recent phase I and phase II clinical studies have substantiated the clinical potential for Met inhibitors with preliminary evidence of antitumor activity using the anti-Met antibody, onartuzumab (MetMAb, OA5D5v2: Genentech Inc.), or Met tyrosine kinase inhibitors (TKI; refs. 9–11).

Onartuzumab is a recombinant, humanized, monoclonal antibody that binds to the SEMA domain of Met thereby blocking HGF binding and subsequent Met activation (12, 13). In preclinical studies, inhibition of Met signaling with onartuzumab results in pathway suppression and blockade of ligand-induced cell proliferation, migration, invasion, and cell survival (13, 14). Onartuzumab has preclinical antitumor activity in multiple tumor models when used as a single agent as well as in combination with various targeted and standard of care therapeutics (13, 14). Onartuzumab is currently being evaluated in phase II and phase III clinical studies for the treatment of multiple cancer types in combination with erlotinib, bevacizumab, and chemotherapy.

In addition, dual inhibition of Met and EGFR signaling by coadministration of onartuzumab with erlotinib in a phase II trial showed both progression free survival (PFS) and overall survival (OS) benefit compared with treatment with erlotinib alone in second line NSCLC patients with overexpression of tumor Met (11).

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Biomarkers are increasingly being evaluated in early phase I trials to show proof of target engagement, pathway inhibition, and for confirmation of mechanism of action, thereby increasing the probability of success of novel molecular entities in phase II studies (15, 16). The circulation (serum, plasma, whole blood) provides a non-invasive medium to evaluate dose-response and biological activity of therapeutic agents. Circulating HGF is...
associated with poor outcome in multiple disease indications including NSCLC, colorectal cancer (CRC), and head and neck cancers (17–19). Moreover, high levels of circulating HGF in plasma are also associated with resistance to receptor tyrosine kinase and BRAF inhibition (20–23). Given that onartuzumab blocks HGF binding to Met (13), we hypothesized that target engagement might result in elevated levels of cHGF as a consequence of ligand displacement from the receptor or by compensatory upregulation. Thus, we evaluated circulating levels of HGF as a potential pharmacodynamic biomarker in phase I and phase II clinical trials of onartuzumab administered as a single agent or in combination with the EGFR inhibitor erlotinib (10, 11, 24). In addition to assessing pharmacodynamic effects, we looked for correlations between HGF levels and liver metastasis, tumor burden and, clinical benefit from onartuzumab.

### Materials and Methods

#### Reagents

Affinity-purified goat polyclonal antibodies to human HGF were generated at Genentech Inc. Recombinant human HGF was also generated at Genentech Inc.

#### Study design

The phase Ia, OAM4224g study, was an open-label, dose escalation study of the safety and pharmacology of onartuzumab in 34 patients with locally advanced or metastatic solid tumors. The trial consisted of a dose escalation of single-agent onartuzumab (stage 1) administered i.v. at 1, 4, 10, 15, 20, and 30 mg/kg once every 3 weeks and a single-agent expansion at the recommended phase II dose (stage II). The phase II study (ClinicalTrials.gov identifier NCT00854308, OAM4558g) was a randomized, double-blind, placebo-controlled study in 137 patients with locally advanced or metastatic (stage IIIb/IV) NSCLC comparing erlotinib (150 mg oral, daily dose) plus placebo or onartuzumab (15 mg/kg i.v. q3 weeks). Procured plasma (K2-EDTA anticoagulant) from mBC, CRC, and NSCLC patients, as well as healthy individuals, was obtained from Conversant Healthcare Systems, Inc. Patient serum samples were obtained from 32 patients in the phase I OAM4224g study (ClinicalTrials.gov Identifier NCT01068977) at predose cycle 1 (C1D1), cycle 1 day 2 (C1D2), predose cycle 2 (C2D1), and predose cycle 3 (C3D1). Optional, exploratory serum and plasma (K2-EDTA anticoagulant) samples were also obtained from 82 patients in the phase II OAM4558g study, at screening (−14 to Day 1), predose cycle 1 (C1D1), 2.5 hours postdose cycle 1, cycle 1 day 10 to 14 (C1D10-14), predose cycles 2 to 4 (C2D1, C3D1, C4D1) and then at the study drug discontinuation visit (SDDV) that occurred ~30 days after the last dose. All patients on the trials and vendor collections provided written informed consent for use of bio-fluids for exploratory analysis of biomarkers.

#### Serum and plasma samples

Circulating HGF as a Pharmacodynamic Biomarker

HGF quantification by ELISA

Plasma HGF levels were measured by ELISA. Briefly, wells of NUNC MaxiSorp microtiter plates were coated with 0.5 μg/mL of affinity purified goat anti-human (hu) HGF polyclonal antibody overnight at 4°C and then blocked with assay diluent (PBS pH 7.4 with 0.5% bovine albumin, 0.05% Tween 20, 0.25% CHAPS, 0.35M NaCl, 5 mmol/L EDTA and, 10 ppm Proclin 300). Standards, controls, and plasma samples were diluted with assay diluent, loaded in duplicate, and incubated for 2 hours at room temperature. Affinity-purified goat anti-huHGF-biotin was diluted to 150 ng/mL in assay diluent and added to plates and incubated for 1 hour at room temperature. Following incubation of avidin-conjugated horseradish peroxidase (diluted to 40 ng/mL in PBS, pH 7.4, containing 0.5% BS, 0.05% Tween 20, and 10 ppm Proclin 300) for 1 hour, the reaction was visualized by the addition of a chromogenic substrate (3,3',5,5'-tetramethylbenzidine) for 15 minutes. The reaction was stopped with 1M phosphoric acid, and absorbance was measured at 450 nm using an ELISA plate reader: the 630 nm reference wavelength was subtracted from the recorded spectra in accordance with the manufacturer’s instructions. Wash buffer with PBS containing 0.05% Tween 20 was used, plates were washed 3 times for the first 2 wash steps and 4 times for the remainder of the procedure. As a reference for quantification, a standard curve was established by the serial dilution of recombinant huHGF (2000−15.625 pg/mL). Lower limit of quantification (LLOQ) for the assay was 210 pg/mL.

#### Statistical analysis

Pearson and Spearman correlations and Mann-Whitney tests were done on cHGF from plasma versus serum, plasma from healthy donors versus cancer patients, and plasma from patients pretreatment versus posttreatment using GraphPad Prism version 5 (GraphPad Software).

#### Results

Circulating HGF is elevated in cancer patients

The prevalence of cHGF at baseline (predose) was evaluated in procurred, nonstudy associated plasma samples from healthy donors and metastatic breast (mBC), CRC, and NSCLC indications. cHGF in plasma from healthy donors was detected above the LLOQ in only 10/45 samples. The levels in these samples ranged from 215 to 692 pg/mL with a median of 261 pg/mL. cHGF was significantly elevated in cancer plasma from all 3 indications relative to healthy donors. Moreover, the levels measured in CRC and NSCLC (median values of 730 and 663 pg/mL, respectively) were approximately 2-fold higher than those in mBC (median value 326 pg/mL; Fig. 1A). To examine this dynamic in the clinic, cHGF was measured in serum from patients on the dose-escalating phase I study of onartuzumab that enrolled patients with locally advanced or metastatic tumors. In this study, a wide range of baseline cHGF in serum across all indications...
from 250 to 8058 pg/mL (median value of 1,104 pg/mL) was observed (Fig. 1B). As compared with age-matched serum from healthy donors (median value 460 pg/mL), we observed a median 2.5-fold elevation in cHGF in these patients. Similarly, baseline cHGF was also measured in plasma from the phase II study of onartuzumab conducted in second/third line NSCLC. Baseline cHGF levels in the phase II study were in the range of 210 to 11,375 pg/mL (median value of 466 pg/mL). There was no significant difference between baseline cHGF in the placebo versus the onartuzumab arm (Fig. 1C) and similar to the phase I study, median baseline levels in the phase II population were on average ~2-fold higher than plasma from healthy donors, and were similar to levels in the acquired NSCLC plasma samples. Previous observations by Sakon and colleagues (25) have showed increased levels of HGF in serum when compared to plasma. To compare results from the phase I and phase II studies, cHGF was measured in a subset of patients in both serum and plasma from healthy donors. Mann–Whitney analysis was done to evaluate the difference between the 2 populations. C, predose (baseline) plasma was collected from patients in the phase II study. cHGF levels from the placebo/erlotinib arm are plotted compared with the onartuzumab/erlotinib arm. D, correlation of serum and plasma cHGF measurements. A correlation analysis was done between cHGF values from 48 paired, baseline serum, and plasma patient samples. E, correlation analysis done for cHGF levels from 124 serum and plasma parallel measurements across multiple time points.
measurements in serum and plasma across all time points, a very strong correlation was observed ($r = 0.974$; Fig. 1E) thus allowing for comparison between the 2 trials.

**Serum HGF is a biomarker of Met target engagement**

We hypothesized that onartuzumab binding to the Met receptor may lead to ligand displacement resulting in elevated levels of ligand and hence evaluated cHGF as a biomarker of target engagement in the single-agent phase Ia trial (10). Serum samples at various pre- and posttreatment time points from 29 patients (of 34 patients enrolled in the phase Ia study) were evaluated for HGF levels using ELISA assays. Administration of onartuzumab was associated with an acute rise in serum HGF at day 2 in 40% of the patients, showing at least a 1.5-fold increase in cHGF (Fig. 2A). As a measure of the PK/PD relationship, cHGF levels were monitored over the dose escalation. The rise in cHGF was sustained through the dosing cycle and appeared to be independent of dose administered (Fig. 2B) or disease indication. Three of the 29 patients evaluated showed an acute 3- to 8-fold decrease in serum HGF at day 2. Coincidentally, these 3 patients had the highest levels of HGF at baseline in the phase I study ranging from 4,000 to 8,000 pg/mL (Fig. 2C). Of these, a single gastric cancer patient showed an immediate and sustained decrease in cHGF from a baseline of $3441 \pm 301.8$ pg/mL to near physiologic levels of $526.8 \pm 91.98$ pg/mL for the duration of the treatment cycle. This was the only patient to achieve an RECIST complete response to single-agent onartuzumab (Fig. 2B). Catenacci characterizes this patient as having evidence for an autocrine production of HGF (24).

A shed protein that constitutes the extracellular domain (ECD) of Met can be found in circulation and shows a dose-dependent elevation upon onartuzumab treatment in the phase Ia study (26). This rise in shed Met is likely because of drug binding to the shed protein resulting in altered clearance of the receptor (26). We did not observe a

![Figure 2](https://www.aacrjournals.org/mct/aacrbf.png)

Figure 2. cHGF is elevated upon onartuzumab administration in phase I patients. A, cHGF was measured at predose, 24 hours after onartuzumab infusion (C1D2) and at the end of the first cycle, C2D1 (day 21), for patients in the phase Ia study. Data represent ratios of cHGF to predose levels for each individual patient. B, phase I dose escalation cHGF measurements. The ratio of predose cHGF and the levels upon dose escalation of single-agent onartuzumab administered i.v. at 1, 4, 10, 15, 20, and 30 mg/kg once every 3 weeks. C, cHGF levels for all patients measured at predose; C1D2 and C2D1 were plotted in ascending order of baseline levels and compared with percentage change in tumor response as assessed by measurement of sum of the longest unidimensional diameter for lesions of interest using computed tomography scans.
correlation between levels of shed Met and cHGF upon onartuzumab administration in the phase I study (Supplementary Fig. S1).

**cHGF elevation upon onartuzumab treatment in a phase II study in NSCLC**

Observations from the phase I clinical trial prompted further evaluation of cHGF as a biomarker of onartuzumab in the OAM4558g phase II study in advanced NSCLC. OAM4558g is a randomized, double-blind, placebo-controlled study with 137 patients treated with onartuzumab or placebo, in combination with erlotinib. In this study, serial analysis of cHGF was conducted in 44 patients in the placebo plus erlotinib arm and 38 patients in the onartuzumab plus erlotinib arm. Baseline cHGF levels remained relatively stable as assessed by parallel measurements at screening and at the predose time point (Supplementary Fig. S2). In the placebo group, cHGF levels generally remained unchanged for the duration of the first cycle of drug administration (Fig. 3A). In contrast, cHGF levels in the onartuzumab-treated patients changed from a median baseline value of 515 to 1167 pg/mL before the second cycle. Although baseline values in the placebo and onartuzumab-containing arms were comparable, a consistent increase and broader distribution of cHGF with an average increase of 2.6-fold was observed in the onartuzumab/erlotinib arm (Fig. 3B). cHGF levels increased significantly at days 10 to 14 postdose and plateaued through multiple cycles of therapy (Fig. 3C). Additional evidence for cHGF as a pharmacodynamic biomarker of onartuzumab target engagement was found in patients in the placebo arm who crossed over to the onartuzumab/erlotinib arm at disease progression. Baseline, C2D1, crossover predose and, C2D1 post crossover measurements of cHGF were available in 10/24 patients. In all but 2 cases, cHGF increased upon crossover (Fig. 3D) with an average 3.7-fold increase over predose values.

**Figure 3.** cHGF from phase II plasma samples is elevated upon onartuzumab administration. A, cHGF was measured at predose and at the end of the first cycle, C2D1 (day 21) after onartuzumab infusion for patients in the phase II study. cHGF values (pg/mL) are plotted as pre- and postdose for both the placebo/erlotinib and onartuzumab/erlotinib arms. Mann-Whitney analysis was done comparing predose versus postdose populations. B, a frequency distribution analysis was done comparing predose versus postdose populations. C, a frequency distribution analysis was done for cHGF from both arms of the phase II study. Measurements are ratios of cHGF to predose levels. C, cHGF was measured in plasma samples at predose, 2.5 hours after the first infusion (C1D2.5h), at day 10 to 14 after the first infusion (C1D10-14), at the end of the first infusion cycle (C2D1), and again at the end of the second infusion cycle (C3D1) in both placebo/erlotinib and onartuzumab/erlotinib treatment arms. Data represent ratios of cHGF measurements relative to predose levels for each individual patient. D, plasma was collected from 10 placebo/erlotinib treated patients that crossed over to the onartuzumab/erlotinib regimen. Plasma was obtained at predose and at 21 days after infusion with placebo/erlotinib (C2D1), then at predose before crossover onto the onartuzumab/erlotinib regimen (XO-predose), and again at 21 days after infusion on the onartuzumab/erlotinib regimen (XO-C2D1). Data represent a time course of cHGF levels for each patient.
Relationship between cHGF and tumor expression of Met receptor by IHC

Evaluation of efficacy in patients with high tumor Met receptor expression defined by an IHC score of 2+ or 3+ (Met positive) was a coprimary endpoint of the OAM4558g phase II trial (11). The addition of onartuzumab to erlotinib improved both PFS and OS in Met positive patients compared with erlotinib alone, resulting in a near 3-fold reduction in the risk of death (11). We evaluated the relationship between cHGF and Met expression as defined by IHC scores of 0, 1+, 2+, or 3+. Baseline cHGF levels were comparable in all four subgroups of Met expressing patients (Fig. 4A). Consistent with this observation, no statistically significant association between OS and HGF levels was observed (Yauch and colleagues, submitted) showing that Met IHC is still the best predictive diagnostic assay for onartuzumab.

Next, we examined if magnitude of pharmacodynamic modulation of cHGF correlated with tumor Met expression. Consistent with data shown in Fig. 3, there was little change in cHGF levels in the placebo-treated patients regardless of tumor Met status. In the onartuzumab-containing arm differences in cHGF, modulation were detected in the tumor Met expressing groups but no statistically significant trend was observed (Fig. 4B).

cHGF modulation and response to onartuzumab

The diverse roles of HGF as a cellular growth, motility, and morphogenic factor led us to evaluate potential associations between cHGF levels and liver metastasis, tumor stage, tumor burden, or tumor response. Neither the presence of liver metastasis (Fig. 5A) or stage of the tumor (Fig. 5B), at diagnosis, correlated with levels of cHGF. Comparisons of baseline cHGF did not correlate with either initial tumor burden (Fig. 5B) or tumor response (Fig. 5B). Similarly, there was no relationship between changes in cHGF levels and tumor response. More statistically rigorous analysis was done to evaluate a relationship between changes in cHGF levels and PFS and/or OS in the Met-positive group but these were inconclusive because of the small sample size.

Discussion

A number of agents targeting Met signaling are currently in clinical trials including small molecule inhibitors to Met such as tivantinib (ARQ197) and antibodies targeting HGF such as rilotumumab (AMG 102; 27). Clinical studies that have evaluated HGF as a biomarker of Met pathway inhibition for tivantinib and rilotumumab suggest that different modes of Met inhibition can yield different results on levels of cHGF. For example, rilotumumab administration led to a dose-dependent elevation in cHGF in a phase I study, likely because of stabilization of drug-bound protein resulting in increased half-life of cHGF (28). In phase I clinical studies evaluating the small molecule inhibitor tivantinib, no obvious changes in cHGF were observed upon drug treatment (29).

In this study, we identified cHGF as a robust, pharmacodynamic biomarker of onartuzumab treatment in cancer patients receiving this agent. The effect is specific to onartuzumab treatment as unequivocally showed in the phase II study where the placebo/erlotinib-containing regimen had little effect on cHGF as compared with the onartuzumab-containing arm. It is unlikely that feedback mechanisms, such as differential expression of HGF in tumor cells, explain this phenomenon as evidence for autocrine activation in NSCLC tumors from the phase II study was infrequent (unpublished observation). However, upregulation of HGF derived from the stroma cannot be excluded. No correlation was observed between drug exposure and cHGF levels upon onartuzumab administration in both the phase I and phase II studies, suggesting that PK alone does not drive the magnitude of biomarker modulation (data not shown). One possible explanation of the elevation in cHGF may be that...
onartuzumab displaces HGF binding to Met, resulting in increased circulating levels.

HGF was discovered as a complex mitogen produced by liver Kupffer cells and sinusoidal endothelial cells, capable of promoting liver regeneration via stimulation of hepatocytes (3, 30–32). cHGF is frequently associated with liver dysfunction or damage (31) and is elevated in liver diseases including cirrhosis and hepatitis independent of Met receptor expression (33). cHGF is also elevated in many cancers and is associated with increased incidence of tumor cell invasion, distant metastasis, and poor prognosis (18, 34, 35). Within tumors, HGF expression is generally restricted to the stromal compartment with fibroblasts being the predominant source of HGF production (36). In addition, tumor resident vascular endothelial cells, smooth muscle cells, macrophages, and neutrophils are also cellular sources of HGF (37). In tumors that are driven by autocrine production of HGF, the contribution of tumor-cell derived HGF to total plasma levels may be significant. Consistent with this hypothesis, the one patient with HGF-driven autocrine disease (24) with a complete response in the phase I study presented with supraphysiologic levels of baseline cHGF that decreased to near physiologic levels upon onartuzumab administration. Evaluation of cHGF as an on-treatment predictive marker of response (sustained decrease in cHGF upon onartuzumab administration) in autocrine-driven disease warrants further investigation. However, it is unlikely that supraphysiologic levels of baseline cHGF alone reflect autocrine-driven disease. Although we observed patients in the NSCLC phase II study with similar high levels of baseline chHGF, tumor HGF mRNA expression in archival tumors from patients in this study was low. Furthermore, tumor HGF mRNA expression did not correlate with levels of cHGF (unpublished observation).

Recent studies have suggested an important role for stromal-derived HGF as a mechanism for drug resistance, highlighting the importance of tumor microenvironment derived growth factors on tumor growth and response to therapy (22, 23). Wilson and colleagues showed that high baseline chHGF in patients with melanoma was associated with worse outcome (PFS and
OS) in a trial testing the BRAF inhibitor vemurafenib (22). These studies primarily assessed associations of pretreatment levels of HGF with response to therapies. However changes in HGF levels, potentially as an on-treatment circulating biomarker of response to treatment, was not evaluated. The relationship between chGF levels, on-treatment, and PFS and OS in the Met-positive group in the phase II onartuzumab study was inconclusive because of small sample size but will be evaluated in future studies with onartuzumab. The relative ease of collecting samples for blood-based biomarker analysis would undeniably allow for easier implementation of the biomarker strategy in global clinical trials.

We have shown that elevated circulating HGF can consistently and reproducibly be measured as an on-target pharmacodynamic biomarker of onartuzumab activity. Although the phase II was not powered to directly address the contribution of chGF as a predictive on-treatment biomarker, these data suggest that measurement of chGF in additional phase II or expanded phase III studies is warranted.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors’ Contributions

Conception and design: E. Penuel, R.L. Yauch, A. Peterson, P.S. Hegde

Development of methodology: E. Penuel, C. Li, V. Parab, L. Burton, K.J. Cowan

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): V. Parab, L. Burton, K.J. Cowan, M. Merchant, P. Patel, A. Peterson, P.S. Hegde

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): V. Parab, L. Burton, K.J. Cowan, M. Merchant, R.L. Yauch, P. Patel, M.R. Lacker, P.S. Hegde

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Study supervision: A. Peterson

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Received January 8, 2013; revised March 15, 2013; accepted March 15, 2013; published OnlineFirst March 27, 2013.

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