Biomarker Analyses from a Placebo-Controlled Phase II Study Evaluating Erlotinib ± Onartuzumab in Advanced Non-Small-Cell Lung Cancer: MET Expression Levels Are Predictive of Patient Benefit

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Statement of Translational Relevance

A hallmark of the successful clinical development of targeted therapies is the identification of the patient subgroups most likely to benefit from these agents. Recent clinical studies evaluating molecules targeting the MET signaling pathway, including onartuzumab and rilotumumab, have demonstrated benefit in patients whose tumors express high levels of MET protein. We describe the development, performance, and scoring criteria of a MET IHC test that differentiated patient outcomes for onartuzumab plus erlotinib versus erlotinib alone in a recent Phase II study in NSCLC. In a retrospective analysis of this study, multiple biomarkers related to MET and/or EGFR signaling were additionally examined. It was determined that the IHC test to detect tumor MET levels represented the best predictor of benefit. These results have guided the Phase III clinical development strategy for onartuzumab and provided further support for development of the MET IHC test as a potential companion diagnostic.
Abstract

Purpose: In a recent Phase II study of onartuzumab (MetMAb), patients whose non-small-cell lung cancer (NSCLC) tissue scored as positive for MET protein by immunohistochemistry (IHC) experienced a significant benefit with onartuzumab plus erlotinib (O+E) versus erlotinib. We describe development and validation of a standardized MET IHC assay and retrospectively evaluate multiple biomarkers as predictors of patient benefit.

Experimental Design: Biomarkers related to MET and/or epidermal growth factor receptor (EGFR) signaling were measured by IHC, FISH, quantitative reverse transcription PCR, mutation detection techniques and ELISA.

Results: A positive correlation between IHC, Western blotting, and MET mRNA expression was observed in NSCLC cell lines/tissues. An IHC scoring system of MET expression taking proportional and intensity-based thresholds into consideration was applied in an analysis of the Phase II study and resulted in the best differentiation of outcomes. Further analyses revealed a non-significant overall survival (OS) improvement with O+E in patients with high MET copy number (mean ≥5 copies/cell by FISH), however benefit was maintained in “MET IHC-positive”/MET FISH-negative patients (HR 0.37; P = 0.01). MET, EGFR, amphiregulin, epiregulin, or HGF mRNA expression did not predict a significant benefit with onartuzumab; a non-significant OS improvement was observed in patients with high tumor MET mRNA levels (HR 0.59; P = 0.23). Patients with low baseline plasma hepatocyte growth factor (HGF) exhibited a HR for OS of 0.519 (P = 0.09) in favor of onartuzumab treatment.

Conclusions: MET IHC remains the most robust predictor of OS and PFS benefit from O+E relative to all examined exploratory markers.
Introduction

MET, a receptor tyrosine kinase that binds hepatocyte growth factor (HGF) is frequently overexpressed in a variety of human malignancies. MET activation has been implicated in tumorigenesis, and MET signaling can be dysregulated through a variety of genetic or epigenetic mechanisms in cancer (1, 2). In non-small cell lung cancer (NSCLC), tumor MET receptor protein expression, HGF protein expression, and high MET gene copy number are indicative of poor prognosis (3–6). Although focal amplification of the MET gene is rare in primary lung tumors (~1% to 7%) (4), it is associated with oncogenic addiction, and with sensitivity, in preclinical models, to small molecule inhibitors (SMIs) targeting MET (7, 8). No activating mutations have been identified in the kinase domain of MET in NSCLC; however, somatic variants causing exon 14 skipping, can result in an alternatively spliced MET receptor lacking the juxtamembrane domain that sustains enhanced ligand-dependent MET signaling (9). Finally, genetic polymorphisms have been linked to enhanced MET signaling (R970C, T990I) (10), as well as to lower HGF binding affinity (N375S) (11).

A growing body of evidence has emerged to support a link between the MET and epidermal growth factor receptor (EGFR) signaling pathways. These receptor tyrosine kinases are often co-expressed in tumors, and evidence exists for functional transactivation that may amplify downstream signals (12). For example, activation of EGFR may occur through MET amplification or HGF-mediated induction of EGFR ligands (13). MET activation has been associated with resistance to EGFR inhibitors both preclinically and clinically (14–16). Collectively, these findings support the rationale for dual inhibition of MET and EGFR signaling.
Onartuzumab (MetMAb) is a recombinant, humanized, monovalent monoclonal antibody targeting MET (17). A Phase II study (OAM4558g) evaluated onartuzumab plus erlotinib (O+E) versus placebo plus erlotinib (p+E) in patients with second-/third-line NSCLC therapy (18). Patient tumor samples were evaluated for MET expression by immunohistochemistry (IHC) and were classified as MET-positive or MET-negative, after randomization, but prior to unblinding the treatment assignment. There was neither a progression-free survival (PFS) (HR 1.09; \( P = 0.69 \)), nor overall survival (OS) benefit (HR 0.80; \( P = 0.34 \)), in the intent-to-treat (ITT) population. However, the combination of O+E in MET-positive disease resulted in improved PFS and OS (HR 0.53, \( P = 0.04 \); HR 0.37, \( P = 0.002 \), respectively) (18).

In this article we describe the development and validation of the specific IHC assay and the corresponding scoring system that was used to assess MET protein expression in the OAM4558g clinical trial. In addition, we carry out retrospective analyses to further assess the diagnostic cut-point and evaluate additional biomarkers related to the MET and/or EGFR pathways, as predictors of benefit from onartuzumab plus erlotinib.

**Materials and Methods**

**Patients**

Patients aged \( \geq 18 \) years with measurable and previously treated (up to two prior regimens) stage IIIB/IV NSCLC were eligible. Submission of tumor tissue (archival permitted), as either a tissue block or unstained serial slides, was required. Written informed consent was obtained prior to any study-specific screening procedures. A total of 137 patients were randomized; 68 to p+E and 69 to O+E. Demographic and baseline
characteristics were generally well balanced across the treatment arms in the ITT and MET diagnostic subgroups, with few exceptions noted. A similar pattern in these characteristics was also observed across the treatment arms in the subgroups of FISH evaluable patients and quantitative reverse transcription polymerase chain reaction (qRT-PCR) evaluable patients (data not shown). Prioritization of specific biomarker analyses and number of tissues examined for the given analysis was as follows: MET IHC ($n = 128$), $EGFR/KRAS$ mutation analysis ($n = 112$), $MET/EGFR$ FISH ($n = 96$), $MET$ exon14 ($n = 87$) and N375S genotyping ($n = 113$) and finally, qRT-PCR ($n = 67$).

Plasma HGF levels were evaluated from 96 patients. The overlap in biomarker analyses is shown in Supplementary Table S1.

**Study design**

This was a Phase II double-blinded, multicenter, international randomized clinical trial (OAM4558g). Patients were randomly assigned in a 1:1 ratio to receive either onartuzumab (15 mg/kg) or placebo (both administered by intravenous infusion every 3 weeks), plus erlotinib (oral 150 mg daily). The co-primary endpoints were PFS in the ITT and MET-positive populations. Approximately 120 patients would be needed to estimate the PFS benefit in both these populations. Further details of the study design have been published previously (18).

**MET expression by IHC**

MET expression levels were evaluated using CONFIRM anti-total MET (SP44) rabbit monoclonal primary antibody (Ventana Medical Systems, Inc.; cat no. 790-4430), and a composite scoring system was devised to determine the status of MET. The IHC cut-point for positivity was prospectively defined in OAM4558g. The scoring of OAM4558g specimens was independently reviewed by a second pathologist, with an 88.3% concordance in calling MET-positive between pathologists. We did not observe a
difference in outcome based upon pathologist #2’s interpretation of the data. Further
details are included in the Supplementary Methods section.

**Western blot analysis**

Cell lines used for Western blotting were obtained from American Type Culture
Collection (Manassas, Virginia), National Cancer Institute Division of Cancer Treatment
and Diagnosis Tumor Repository, Bethesda, Maryland; or Japan Health Sciences
Foundation, Tokyo, Japan and were authenticated. For authentication, STR profiles
were determined for each line using the Promega PowerPlex 16 System. This was
performed once and compared to external STR profiles of cell lines (when available) to
determine cell line ancestry. Sixteen loci (fifteen STR loci and Amelogenin for gender
identification) were analyzed including, D3S1358, TH01, D21S11, D18S51, Penta E,
D5S818, D13S317, D7S820, D16S539, CSF1PO, Penta D, AMEL, vWA, D8S1179, and
TPOX. NSCLC cell lines were lysed in T-PER tissue extraction reagent (Thermo
Scientific, Rockford, Illinois) supplemented with protease and phosphatase inhibitors.
Proteins resolved by SDS-PAGE were electrophoretically transferred to polyvinylidene
difluoride membrane and Western blots were carried out using standard techniques. The
primary antibodies used in this study were: MET clone SP44 (Ventana Medical
Systems), MET clone L41G3 (Cell Signaling Technology, Danvers, Massachusetts),
MET clone 5D5 (HB-11895, American Type Culture Collection), and actin (catalog No.
sc-8432; Santa Cruz Biotechnology, Santa Cruz, California). A polyclonal antibody raised
against MST1R was a kind gift from Dr Amitabha Chaudhuri (Genentech, Inc.).

**Molecular assessments**

*MET* and *EGFR* gene copy numbers were evaluated by FISH; a CEP7 centromere
probe (Abbott Molecular) was used as a control. High-level *MET* amplification was
defined as tight gene clusters of ≥15 copies in ≥10% of tumor cells, or a *MET*:CEP7 ratio
of ≥2. A cut-off of ≥5 copies of MET/cell was predefined as the criterion for FISH-positive status (FISH+), based on prior prognostic data supporting this cut-off in NSCLC (4). Tumors were considered EGFR FISH+ based on a scoring system utilized in multiple clinical studies (19). Further details are included in the Supplementary Methods section.

DNA and RNA were isolated from macro-dissected tissue to enrich for tumor content. EGFR and KRAS mutations were evaluated using the DxS Genotyping kit. MET exon 14 variants were evaluated by Surveyor® nuclease digestion and detection by WAVE® analysis (Transgenomics, Inc.). A polymorphism at position N375S of MET was evaluated by pyrosequencing on the Pyromark Q24 (11). Expression of MET, HGF, EGFR, amphiregulin (AREG), and epieregulin (EREG) mRNA transcripts was evaluated by qRT-PCR on the Biomark platform (Fluidigm). The primer/probes utilized for profiling are shown in Supplementary Table S2 and further details are included in the Supplementary Methods section.

HGF quantification by ELISA

Plasma HGF levels were measured by ELISA, as described previously (20).

Statistical analysis

PFS was defined as the time from randomization to the first occurrence of disease progression or death on study from any cause, or to the last tumor assessment date if patients were progression free. OS was determined from randomization to the date of death, or the last known patient contact. For each treatment arm, the median PFS and OS were estimated from Kaplan-Meier curves. The PFS and OS treatment comparisons were based on a log-rank test at the 0.05 level of significance (2-sided). Estimated treatment effects for O+E relative to p+E were expressed as HRs with 95% confidence intervals (CIs), derived from an
unstratified Cox model. Survival analyses were performed in biomarker subgroups for PFS and OS.

Results

Development of the SP44 IHC test

To identify antibodies that would be suitable for detecting MET protein expression levels in formalin-fixed paraffin-embedded tissue specimens, we initially tested 16 commercially or internally available antibodies for their specificity and staining intensity on control tissues and cell lines (data not shown). The CONFIRM anti-total cMET (SP44) rabbit monoclonal antibody, generated against an intracellular epitope of MET, was chosen for further analysis based upon its initial reactivity pattern in NSCLC cell lines engineered to knockdown or ectopically express the MET gene (Supplementary Fig. S1). Furthermore, SP44 did not cross-react with the Ron receptor (MST1R), the closest homolog of MET (Supplementary Fig. S1C). IHC staining of NSCLC tissues (Fig. 1A) and cell lines (Supplementary Fig. S2A) revealed a range of staining intensities characterized as no staining (negative), weak, moderate, or strong; with a pattern that was primarily membranous with a variably strong cytoplasmic component. In NSCLC cell lines, the SP44 staining intensities associated with the degree of MET protein expression, as determined by Western blot analysis using both SP44, as well as an alternative anti-MET antibody (L41G3) (Fig. 1B). SP44 staining intensities also corresponded with the levels of MET detected on the surface of NSCLC cell lines using flow cytometry when probed with the bivalent form of the parent monoclonal antibody to onartuzumab (5D5) and no IHC staining was observed with SP44 in cell lines in
which 5D5 did not bind (Supplementary Fig. S2B and S2C). Finally, a statistically
significant association was observed between the intensity of IHC staining with SP44
and MET mRNA levels across a larger panel of NSCLC cell lines (Supplementary
Fig. S3) further supporting the specificity of this reagent.

In NSCLC tissues, heterogeneity in the intensity was frequently observed within
individual NSCLC tumors (Supplementary Fig. S4). To account for this heterogeneity, a
comprehensive clinical scoring system was developed that evaluated both membranous
and cytoplasmic staining intensity and percent of cells staining at a given intensity level
(Supplementary Table S3). A proportional cut-off of ≥50% was selected to ensure that a
majority of the cells within a given specimen expressed MET at either a weak (clinical
score = 1+), moderate (clinical score = 2+), or strong (clinical score = 3+) intensity level.
Specimens with no or equivocal staining in tumor cells or <50% of tumor cells staining at
any given intensity were considered negative (clinical score = 0). Using these IHC
scoring criteria we continued to observe a statistically significant (Jonckheere–Terpstra
P < 0.0001) relationship with MET mRNA expression in tumor specimens (Fig. 1C).
NSCLC tumors expressing moderate or strong levels of MET in ≥50% of cells (clinical
IHC score 2+ or 3+) were classified as MET-positive (MET IHC diagnostic positive). To
understand how intratumoral heterogeneity may impact this clinical diagnostic score, we
evaluated MET expression in ten patients for whom more than one paraffin block had
been submitted for analysis (Supplementary Table S4). Although variation was observed
in the proportion of cells staining at a given intensity, there was complete concordance in
the final IHC score for the multiple tissue specimens in these patients. Finally, using
these scoring criteria, we determined that 58% (±6%) of non-squamous and 26% (±11%)
of squamous cell tumor specimens were MET-positive across three separate series of
NSCLC tumor specimens (Table 1).
Evaluation of alternative scoring systems

We also evaluated the H-score method of semi-quantitatively assessing MET expression as an alternative to take into account the intensity and heterogeneity of MET staining (21). Both membranous and cytoplasmic staining were combined into a single intensity score. We observed a range of H-scores from 0 to 300, with a median H-score of 160 in the set of tissue samples collected from patients in OAM4558g. Most specimens within each clinical score category (0, 1+, 2+, and 3+) were distributed around the H-scores of 0, 100, 200, and 300, respectively (Supplementary Figs. S5 and S6), as would be expected if staining was completely homogeneous. When heterogeneity in staining intensity was present ($n = 64$ specimens exhibiting tumor cell populations with multiple staining intensity levels), positivity was primarily distributed between two different staining intensity levels ($n = 48$). Only 13% of specimens ($n = 16$) exhibited a significant degree of heterogeneity in which staining intensities were noted across 3 different levels. There were four specimens below the median H-score that were considered MET-positive when applying the clinical scoring algorithm; conversely, there was one specimen at the median H-score that was MET-negative by the clinical scoring system.

Defining the best cut-off for the MET IHC assay

The IHC cut-point for positivity was prospectively defined in OAM4558g. An analysis evaluating the appropriateness of this cut-point revealed that alternative proportional cut-points to define MET-positivity of ≥10% or ≥90% of tumor cells staining moderately or strongly did not result in a better differentiation of patient outcomes (18). To evaluate alternative cut-points in more detail, we examined PFS (Fig. 2A) and OS (Fig. 2B) based upon individual staining intensities using a 10%, 50%, or 90% proportional cut-off. Consistent with prior results, the best differentiation of patient outcomes was observed at the 50% cut-off and the differentiation was not greatly altered.
by applying different cut-offs to different staining intensities. More importantly, PFS was also analyzed in two subsets of patients whose IHC scores bordered the diagnostic cut-off: (1) group 1: patients categorized as MET-positive using a 10% cut-off but as MET-negative using 50% cut-off (patients whose tumors exhibited moderate to strong staining in 10–49% of tumor cells, Fig. 2C); and (2) group 2: patients categorized as MET-positive using 50% cut-off, but as MET-negative using a 90% cut-off (patients whose tumors exhibited moderate to strong staining in 50–89% of tumor cells, Fig. 2D). In group 1 (n = 21), patients treated with O+E had shorter PFS than patients treated with p+E (HR 3.065; P = 0.04), suggesting that using a 10% cut-off may incorporate patients who may not benefit from the study drug. Outcomes in group 2 patients were not statistically different between treatment arms, however there was a trend toward benefit in those who received O+E (n = 19; HR 0.47; P = 0.23). Similar findings were observed for OS (data not shown).

**Evaluation of alternative predictive markers of onartuzumab + erlotinib activity**

**Pathway mutations**

*EGFR* and *KRAS* genotyping data were obtained from 112 patients, mutations were identified in 13 (12%) and 26 (23%) samples, respectively, and were mutually exclusive. Nine of 13 *EGFR*\textsuperscript{mut} cases and 13 of the 26 *KRAS*\textsuperscript{mut} cases were MET-positive. *EGFR* mutations were identified in six of the seven patients with objective responses (Supplementary Tables S5 and S6); there were no responses in patients with *KRAS*\textsuperscript{mut} tumors. Exon 14, encoding the juxtamembrane domain of *MET*, was genotyped in 87 patients. A splice site deletion was detected in only one individual and alternative splicing was confirmed at the mRNA level (data not shown). Two additional patients (both on p+E) had tumors harboring exon 14 polymorphisms R970C and T990I. Polymorphisms
in MET N375S were found in 12 of 113 (11%) tumors tested; due to an imbalance between treatment subgroups, no further analysis was carried out.

**MET/EGFR copy number**

MET and EGFR copy number were evaluated by FISH for 96 patients. The median MET copy number was 3.44 copies/cell (range 1.6 to 25.0), with 19 (20%) evaluable tumors being MET FISH+, including eight (8%) harboring high-level MET amplification. The relationship between MET copy number and MET IHC clinical score is shown in Supplementary Fig. S7, with a statistically significant association of FISH positivity with IHC 3+ cases observed (Chi-square, \( P < 0.0001 \)). No high-level MET gene amplifications were identified in patients who had objective responses to therapy (Supplementary Table S6); however, a high-level MET amplification was identified in an EGFR\(^{mut} \) patient who did not respond to O+E.

The estimated HR for OS for patients who were MET FISH+ was 0.60 (\( P = 0.35 \)) in favor of O+E (Fig. 3A). No improvement in OS was observed using lower cut-offs for MET copy number (HR 0.89; \( P = 0.79 \)) for \( \geq 4 \) copies and HR 0.75; \( P = 0.37 \)) for \( \geq 3 \) copies: Supplementary Figs. S8A and S8B). To evaluate the impact of EGFR mutations on patient outcomes, we examined outcomes in the known EGFR\(^{wt} \) population: OS HR for patients with MET FISH+ tumors receiving O+E was 0.30 (\( P = 0.06 \)); PFS HR was 0.58 (\( P = 0.38 \)) (Fig. 3B). As observed in the ITT population, no improvement in OS was seen in the EGFR\(^{wt} \) populations further defined by \( \geq 4 \) (HR 0.76; \( P = 0.55 \)) or \( \geq 3 \) (HR 0.75; \( P = 0.40 \)) copies of MET/cell (Supplementary Figs. S8C and S8D, respectively).

To determine if the MET FISH+ patients influenced the benefit observed in the MET-positive subgroup, OS and PFS analyses were performed in both the MET IHC+/FISH− subgroups of the ITT and EGFR\(^{wt} \) populations. An OS HR of 0.37 (\( P = 0.01 \))
and a PFS HR of 0.24 ($P = 0.003$) was observed in the MET IHC+/FISH− ITT population (Fig. 3C). An OS HR of 0.51 ($P = 0.13$) and a PFS HR of 0.44 ($P = 0.10$) was observed in the MET IHC+/FISH− and $EGFR^{wt}$ patients (Fig. 3D).

Due to chromosome 7 polyploidy, gains in MET gene copy number have been shown to associate with high EGFR copy number gains (4). To ensure an unbiased analysis, EGFR and MET copy number variations were evaluated using identical criteria, as previously adopted for use in EGFR FISH testing (19). A significant association between EGFR and MET copy number was observed (Fisher exact, $P = 2.2 \times 10^{-5}$), with 24% ($n = 23$) of evaluable cases being positive for gains in both EGFR and MET copy number (data not shown). However, no clinical benefit was observed in this subpopulation (Supplementary Fig. S8E): OS HR 1.36 ($P = 0.54$); PFS HR 1.0 ($P = 1.0$).

**MET/EGFR pathway transcript expression**

Expression of mRNA transcripts for MET, HGF, EGFR, and the EGFR ligands, AREG and EREG, was evaluated by qRT-PCR in tumor biopsies from 67 patients. In this biomarker subpopulation, a non-significant improvement in OS (HR 0.49, $P = 0.11$) and PFS (HR 0.57; $P = 0.22$) was observed in IHC MET-positive patients. In patients with high tumor MET mRNA levels (median $\geq 3.16$), an OS HR of 0.59 ($P = 0.23$), and a PFS HR of 0.76 ($P = 0.51$) was observed (Fig. 4, Supplementary Table S7). No similar improvements in outcome were seen in any other mRNA subgroups for patients receiving O+E.

**Plasma HGF**

Pretreatment plasma protein levels of HGF were evaluated in 96 patients. The median level of HGF was 480.2 pg/mL (range 203 pg/mL to 11,375 pg/mL), with no significant difference in distribution between MET IHC diagnostic subgroups.
(Supplementary Fig. S9). No correlation of plasma HGF with tumor HGF mRNA levels was observed (data not shown). In this subpopulation of patients with evaluable plasma HGF data, both OS and PFS were consistent with what was observed in the general population: HR 0.39 ($P = 0.006$) in OS and HR 0.52 ($P = 0.06$) in PFS, respectively, in MET-positive patients. In patients who had baseline HGF protein below the median, the OS HR was 0.52 ($P = 0.09$) and PFS HR was 0.56 ($P = 0.10$) favoring O+E (Fig. 5A). In patients with baseline HGF protein $\geq$ median, the OS HR was 1.23 ($P = 0.56$) (Fig. 5B). In addition, a Cox proportional hazard regression model revealed no statistically significant association between OS and HGF level (HR 0.81; 95% CI, 0.52–1.25; $P = 0.339$) or between OS and HGF level and treatment (HR 1.68; 95% CI, 0.91–3.10; $P = 0.096$).

**Discussion**

In the OAM4558g study, the addition of onartuzumab to erlotinib resulted in improvements in both PFS and OS in patients whose tumor specimens were determined to be MET-positive by IHC (18). This benefit was not seen in the overall population, and patients with MET-negative tumors who received O+E had a worse outcome versus those treated with erlotinib alone. Therefore, the data indicate that the MET IHC assay may be a reliable diagnostic test for identifying NSCLC patients most likely to benefit from O+E; and as such, this test is currently being developed as a companion diagnostic for onartuzumab in combination with erlotinib (clinicaltrials.gov identifier: NCT01456325) (22). In this report, we describe the development and performance of this IHC test and compare its performance relative to alternative biomarkers.

Our investigation has identified that the SP44 monoclonal antibody binds MET with high specificity and generates a range of staining intensities that correlate well
with MET mRNA levels and MET protein levels determined by alternative means. As with many histologic tests, we observed intratumoral heterogeneity in MET protein expression levels in NSCLC tissues. To account for such heterogeneity, we examined various scoring systems that incorporate both staining intensity and percent malignant cell positivity. We reasoned that a cut-off that captures the MET expression signal in the majority of the malignant cell population in a specimen (i.e., ≥50%) would likely produce more reproducible findings. When using a cut-off of 50% of malignant cells in a biopsy sample with moderate and/or strong staining intensity, we observed that our call for positivity did not change when evaluating intratumoral heterogeneity in a small set of cases for which sections representing more than one area of the same resection specimen were available for analysis (Supplementary Table S4). More importantly, we demonstrated that this 50% cut-off was the criterion that best differentiated patient outcomes in the Phase II OAM4558g trial. A less stringent cut-off of 10% of malignant cells staining at moderate and/or strong intensity resulted in the inclusion of a subset of patients who did not benefit from O+E therapy in this trial, as shown by worse outcomes (PFS HR 3.065; \( P = 0.04 \)). Conversely, implementation of a more stringent cut-off of 90% of malignant cells staining at moderate and/or strong intensity would result in the loss of a subset of patients who trended toward improved outcomes with O+E, although this did not achieve statistical significance (PFS HR 0.464; \( P = 0.23 \)). Additional evaluations of outcome based on different staining intensities supported these proposed criteria. Overall, these data strongly suggest that the diagnostic cut-off that was prospectively defined represents a suitable scoring system for future clinical studies evaluating O+E in NSCLC. Other scoring criteria, such as H-score, were considered. However, exploratory analysis did not show that H-score could alter the interpretation of the outcomes from previous analyses (data not shown).
To determine whether MET IHC represented the best predictor of patient benefit in this study, additional biomarkers related to the MET and/or EGFR signaling pathways were measured. EGFR-activating mutations represent the strongest predictor of response to EGFR-targeted therapies in NSCLC. As expected in a primarily Caucasian population, ~12% of patients harbored EGFR mutations in this study. Of the seven patients who reported an objective response, all but one had an EGFR\textsuperscript{mut} tumor. One EGFR\textsuperscript{wt} patient had an objective response on O+E; however, it was not possible to associate this response to any other biomarker examined, including EGFR or MET gene amplification, MET mutation or high tumor/serum HGF levels. Most importantly, EGFR mutations did not drive the benefit observed in the MET-positive population, as the magnitude of the treatment benefit was maintained in MET-positive, EGFR\textsuperscript{wt} patients (OS HR 0.46; \( P = 0.03 \)) (18).

KRAS is a downstream effector of both EGFR and MET signaling and mutations in this gene provide a critical predictive marker for efficacy of EGFR-targeted antibodies in colorectal cancer. Although KRAS mutations predict for a lack of radiologic response to EGFR-targeted SMIs in NSCLC, any similar impact on PFS and OS remains unresolved (23, 24). In this study, the incidence of KRAS mutations was mutually exclusive from EGFR mutations, and did not significantly impact outcomes in patients receiving O+E in the ITT, MET-positive or MET-negative populations. However, given limitation in sample size, it remains to be determined whether this subgroup would indeed benefit from a MET inhibitor.

The role of high-level MET gene amplification has gained considerable attention, as it predicts for enhanced sensitivity to MET-targeted SMIs in preclinical models (7, 8), has recently been linked to anecdotal responses on MET-targeted agents in the clinic (25), and importantly, represents a mechanism of acquired
resistance to EGFR SMIs in $EGFR^{mut}$ NSCLC patients (14–16). Additionally, general increases in $MET$ copy number have been reported in many, but not all studies, to represent a negative prognostic factor in patients with NSCLC and may be relevant in the context of EGFR-targeted combination therapy, given that $EGFR$ and $MET$ copy number gains can be associated due to chromosome 7 ploidy. In this study, the frequency of high-level $MET$ gene amplification and high $MET$ copy number was 8% and 20%, respectively, which was in accordance (albeit at the high end) with previous studies. The association of $MET$ FISH positivity with the MET IHC 3+ subgroup suggests that high $MET$ gene copy number leads to high protein expression in this subgroup. Although the MET IHC 2+ score is also represented within the MET-positive subgroup, there was no corresponding association with high copy number gains. Non-significant improvements in PFS and OS were observed in the $MET$ FISH+ ITT and $EGFR^{wt}$ populations. However, this benefit was not maintained when lower copy number cut-offs were evaluated. This cut-off for $MET$ FISH positivity ($\geq5$ copies of $MET$/cell) has been linked with shortened OS and advanced-stage disease (4), and hence may identify a poor-prognostic population who could benefit from O+E. However, a statistically significant benefit was also observed in the MET-positive/FISH-negative population. These results would suggest that MET IHC status, rather than MET FISH status, performs better for predicting benefit, and that FISH status alone would miss a large population who may benefit from O+E. No improvement in outcome was observed in patients harboring gains in both $MET$ and $EGFR$ copy number, further suggesting that the benefit to this MET and EGFR-targeted combination therapy was not driven by the cases of general chromosome 7 ploidy.
Tumor mRNA expression of key MET and EGFR pathway genes was additionally evaluated as alternative predictive biomarkers. This not only included expression of MET/HGF, but expression levels of two EGFR ligands that can be transcriptionally regulated by MET activation, AREG and EREG. MET was the only mRNA biomarker examined that showed a trend toward improvement in OS and PFS, albeit this did not achieve statistical significance. This could likely be attributed to the small sample size, as only ~1/2 of the patients (n = 67) had material remaining following the prioritization of other biomarker assessments for transcriptional analysis. Regardless, evaluation of MET mRNA levels as an alternative predictive biomarker may warrant further investigation in future studies.

High serum or plasma HGF levels have been associated with poor prognosis in several cancers, including NSCLC (26–28). In a study of patients with NSCLC treated with EGFR SMIs, high serum HGF was associated with worse outcome (tumor response, PFS, and OS) (26). Despite our expectations that the addition of onartuzumab to erlotinib could improve outcomes versus erlotinib alone in patients with high plasma HGF at baseline, we did not observe a statistically significant association. In fact, a non-significant trend toward benefit was observed in patients with low baseline HGF. The study cited from Kasahara et al., evaluated serum HGF, whereas our study evaluated plasma HGF. However, this would unlikely explain the difference, as strong correlations between plasma and serum HGF levels have been observed (data not shown). High plasma HGF also failed to show a prognostic link in the p+E arm in our study (OS HR 0.75; P = 0.41), suggesting that the prognostic significance of circulating HGF may be influenced by differences in the population tested. It remains to be elucidated how HGF levels in circulation relate to intratumoral levels of HGF. Although elevated circulating HGF levels have been
observed in subsets of cancer patients, elevated circulating HGF levels have additionally been described in other settings, including certain viral or bacterial infections, graft versus host disease and surgical procedures (29–31).

In conclusion, MET IHC was a reliable and accurate assay for identifying NSCLC patients most likely to benefit from O+E, and outperformed the other examined exploratory markers. The retrospective, exploratory nature of these analyses, combined with small sample size, limit the scope of definitive conclusions to be drawn from these alternative biomarkers. Further investigations of these biomarkers using larger sample sizes are necessary to determine whether any would be useful in conjunction with MET IHC to better define subpopulations most likely to benefit from onartuzumab plus erlotinib. In addition, it will be imperative to determine whether such biomarkers will be useful in determining benefit to other onartuzumab-based therapies and/or other antagonists of the MET signaling pathway. The anti-HGF antibody, rilotumumab, in combination with standard-of-care chemotherapy exhibited a benefit in both PFS and OS compared with chemotherapy alone (OS HR 0.29; \( P = 0.012 \)) in gastric or gastroesophageal cancer patients with MET\textsuperscript{HIGH} tumors by IHC (32). Interestingly, similar to the OAM4558g NSCLC trial with onartuzumab, patients with MET\textsuperscript{LOW} tumors receiving HGF-targeted therapy seemed to do worse compared to patients receiving chemotherapy only (HR 1.84; \( P \) value not reported).

However, tumor MET expression did not predict for benefit on rilotumumab in a Phase II study in castration-resistant prostate cancer (33). Hence, the role of MET IHC in predicting benefit to onartuzumab and/or other MET-targeting therapies will likely need to be carefully evaluated within a given indication. Currently, the test reported here is being developed as a companion diagnostic for onartuzumab and is being used to screen and enroll only MET-positive patients in the Phase III study.
comparing onartuzumab in combination with erlotinib versus placebo plus erlotinib
(clinicaltrials.gov identifier: NCT01456325) (22).

Acknowledgments

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Grant Support

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References


Increased hepatocyte growth factor in serum in acute graft-versus-host


### Tables

**Table 1.** Prevalence of MET expression by SP44 IHC assay in NSCLC tumor specimens

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Abbreviations: Dx, diagnostic; IASLC, International Association for the Study of Lung Cancer; SCC, squamous cell carcinoma; TMA, tissue microarray.
Figure Legends

**Figure 1.** Characterization of SP44. (A) Representative images depicting the range of SP44 staining intensities (negative, weak, moderate, and strong staining) in malignant NSCLC tissues. (B) Relationship of SP44 immunohistochemistry staining intensity and MET protein levels by Western blotting in NSCLC cell lines using two anti-MET antibodies; four representative cell lines and staining intensity are shown. (C) Correlation of IHC score with MET mRNA levels in NSCLC tissues determined by quantitative reverse transcriptase PCR.

**Figure 2.** Evaluation of patient outcomes with onartuzumab plus erlotinib treatment based upon alternative IHC cut-offs. (A) Forest plot for PFS from OAM4558g according to different IHC intensities and different proportional cut-offs (10%, 50%, and 90%); (B) forest plot for OS in OAM4558g according to different IHC intensities and different proportional cut-offs (10%, 50%, and 90%). Kaplan–Meier estimates for progression-free survival in patients with IHC scores bordering the diagnostic cut-off: (C) patients defined as MET-positive using a 10% cut-off and MET-negative using a 50% cut-off; (D) patients defined as MET-positive using a 50% cut-off and MET-negative using a 90% cut-off.

**Figure 3.** Evaluation of patient outcomes with onartuzumab plus erlotinib based upon MET gene copy number. Kaplan–Meier estimates of OS according to MET FISH positivity (≥5 copies of MET/cell) in the ITT (A; n = 19) and EGFR$^{wt}$ (B; n = 15) populations. Kaplan–Meier estimates of OS in patients with MET-positive and MET FISH-negative (<5 copies of MET/cell) tumors in the ITT (C) and EGFR$^{wt}$ (D) populations.

**Figure 4.** Evaluation of patient outcomes with onartuzumab plus erlotinib based upon tumor mRNA expression. Forest plot showing association of MET, AREG,
EREG, EGFR, and HGF mRNA expression as determined by quantitative PCR with OS. High denotes mRNA levels ≥median; low denotes mRNA levels <median.

**Figure 5.** Evaluation of patient outcomes with onartuzumab plus erlotinib based upon plasma HGF levels. Kaplan–Meier estimates of OS in patients with (A) low (<median) baseline HGF levels and (B) with high (≥median) baseline HGF levels.
Figure 1

A

SP44 staining intensity: Negative

Weak

Moderate

Strong

B

SP44 staining intensity: Negative | Weak | Moderate | Strong

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C

MET mRNA ($2^{-\Delta\Delta C_{t}}$) vs. MET IHC score

Downloaded from clincancerres.aacR
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<th>Baseline risk factor</th>
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<th>O+E</th>
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<th>Median (months)</th>
<th>Hazard ratio (95% CI)</th>
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<td>2.013</td>
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**MET IHC 10% cut-off score**

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**MET IHC 50% cut-off score**

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**MET IHC 90% cut-off score**

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<td>4.1</td>
<td>0.447</td>
<td>(0.236–0.926)</td>
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<td>6</td>
<td>1.4</td>
<td>0.500</td>
<td>(0.011–2.255)</td>
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**Progression-free survival probability**

- **A**
  - Median time (months): 7.4
  - Hazard ratio: 8.9
  - 95% CI: (0.509–1.265)
  - P value: 0.343

- **B**
  - Median time (months): 7.4
  - Hazard ratio: 8.9
  - 95% CI: (0.509–1.265)
  - P value: 0.343

- **C**
  - Median time (months): 6.9
  - Hazard ratio: 1.4
  - 95% CI: (1.01–9.31)
  - Log-rank P value: 0.04

- **D**
  - Median time (months): 4.9
  - Hazard ratio: 3.4
  - 95% CI: (0.14–1.66)
  - Log-rank P value: 0.23
Figure 3

**A**

**MET FISH+ / ITT**

- **p+E** \((n=8; \text{patients with an event} = 7)\)
- **O+E** \((n=11; \text{patients with an event} = 7)\)

HR 0.60 (95% CI, 0.21–1.75), \(P = 0.35\)

**B**

**MET FISH+ / EGFR^{WT}**

- **p+E** \((n=6; \text{patients with an event} = 6)\)
- **O+E** \((n=9; \text{patients with an event} = 5)\)

HR 0.30 (95% CI, 0.08–1.11), \(P = 0.06\)

**C**

**MET IHC+ / MET FISH– / ITT**

- **p+E** \((n=17; \text{patients with an event} = 15)\)
- **O+E** \((n=20; \text{patients with an event} = 9)\)

HR 0.37 (95% CI, 0.16–0.85), \(P = 0.01\)

**D**

**MET IHC+ / MET FISH– / EGFR^{WT}**

- **p+E** \((n=16; \text{patients with an event} = 14)\)
- **O+E** \((n=14; \text{patients with an event} = 8)\)

HR 0.51 (95% CI, 0.21–1.23), \(P = 0.13\)
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Figure 5

**Plasma HGF low**

- **A**
  - \( p + E (n = 27; \text{patients with an event} = 18) \)
  - \( O + E (n = 21; \text{patients with an event} = 11) \)
  - HR 0.52 (95% CI, 0.24–1.12), \( P = 0.09 \)

**Plasma HGF high**

- **B**
  - \( p + E (n = 22; \text{patients with an event} = 15) \)
  - \( O + E (n = 26; \text{patients with an event} = 16) \)
  - HR 1.23 (95% CI, 0.60–2.52), \( P = 0.56 \)
Biomarker Analyses from a Placebo-Controlled Phase II Study Evaluating Erlotinib ± Onartuzumab in Advanced Non-Small-Cell Lung Cancer: MET Expression Levels Are Predictive of Patient Benefit

Hartmut Koeppen, Wei Yu, Jiping Zha, et al.

Clin Cancer Res Published OnlineFirst March 31, 2014.

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