Results From the Phase III Randomized Trial of Onartuzumab Plus Erlotinib Versus Erlotinib in Previously Treated Stage IIIB or IV Non–Small-Cell Lung Cancer: METLung

David R. Spigel, Martin J. Edelman, Kenneth O’Byrne, Luis Paz-Ares, Simonetta Mocci, See Phan, David S. Shames, Dustin Smith, Wei Yu, Virginia E. Paton, and Tony Mok

ABSTRACT

Purpose
The phase III OAM4971g study (METLung) examined the efficacy and safety of onartuzumab plus erlotinib in patients with locally advanced or metastatic non–small-cell lung cancer selected by MET immunohistochemistry whose disease had progressed after treatment with a platinum-based chemotherapy regimen.

Patients and Methods
Patients were randomly assigned at a one-to-one ratio to receive onartuzumab (15 mg/kg intravenously on day 1 of each 21-day cycle) plus daily oral erlotinib 150 mg or intravenous placebo plus daily oral erlotinib 150 mg. The primary end point was overall survival (OS) in the intent-to-treat population. Secondary end points included median progression-free survival, overall response rate, biomarker analysis, and safety.

Results
A total of 499 patients were enrolled (onartuzumab, n = 250; placebo, n = 249). Median OS was 6.8 versus 9.1 months for onartuzumab versus placebo (stratified hazard ratio [HR], 1.27; 95% CI, 0.98 to 1.65; \( P = .067 \)), with a greater number of deaths in the onartuzumab arm (130 [52%] vs 114 [46%]). Median progression-free survival was 2.7 versus 2.6 months (stratified HR, 0.99; 95% CI, 0.81 to 1.20; \( P = .92 \)), and overall response rate was 8.4% and 9.6% for onartuzumab versus placebo, respectively. Exploratory analyses using MET fluorescence in situ hybridization status and gene expression showed no benefit for onartuzumab; patients with \( EGFR \) mutations showed a trend toward shorter OS with onartuzumab treatment (HR, 4.68; 95% CI, 0.97 to 22.63). Grade 3 to 5 adverse events were reported by 56.0% and 51.2% of patients, with serious AEs in 33.9% and 30.7%, for experimental versus control arms, respectively.

Conclusion
Onartuzumab plus erlotinib did not improve clinical outcomes, with shorter OS in the onartuzumab arm, compared with erlotinib in patients with MET-positive non–small-cell lung cancer.

J Clin Oncol 35:412-420. © 2016 by American Society of Clinical Oncology

INTRODUCTION

MET is a transmembrane receptor tyrosine kinase activated by hepatocyte growth factor (HGF) and plays a role in embryonic development and wound healing.\(^1,2\) Aberrant MET signaling can be driven by autocrine production of HGF, overexpression of MET, and amplification of the MET gene and may be an oncogenic factor in several human malignancies.\(^3-6\) Overexpression of MET is associated with poor prognosis in non–small-cell lung cancer (NSCLC); high MET gene copy number is linked with reduced overall survival (OS; hazard ratio [HR], 1.877; \( P = .0414 \)) and an increased risk of death after resection (HR, 1.618; \( P = .024 \)).\(^7,8\) Unselected patients with recurrent NSCLC are often treated with the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) erlotinib, which improves patient outcomes in second-line therapy\(^9\) and in first-line treatment for EGFR mutation–positive NSCLC.\(^10-13\) However, resistance to EGFR inhibitors frequently develops. MET and EGFR are often coexpressed, and MET can upregulate EGFR ligand expression, possibly providing a mechanism for the development of erlotinib resistance. Furthermore, amplification of
the MET gene occurs in lung cancers with acquired resistance to EGFR TKIs, demonstrating the synergy between MET and EGFR signaling.14,15

Onartuzumab is a recombinant, fully humanized, monovalent monoclonal antibody that binds the extracellular domain of MET, blocking interaction with HGF. This prevents activation of the MET signaling pathway, inhibiting the downstream events that lead to tumorogenesis.16 Onartuzumab was designed as a monovalent antibody because bivalent antibodies mimic HGF, stimulating MET signaling, whereas monovalent antibodies act as antagonists.16 Results from a phase II study of onartuzumab plus erlotinib in patients with NSCLC suggested that in patients with MET-positive disease, progression-free survival (PFS) and OS were improved compared with placebo plus erlotinib17 and that these results warranted further investigation. Here we report the efficacy and safety results of the phase III METLung trial (OAM4971g) comparing onartuzumab plus erlotinib with placebo plus erlotinib for patients with MET-positive NSCLC after platinum-based chemotherapy.

**PATIENTS AND METHODS**

**Study Design**

OAM4971g (METLung) was a randomized, multicenter, double-blind, placebo-controlled phase III trial evaluating the efficacy and safety of onartuzumab plus erlotinib in patients with locally advanced or metastatic NSCLC whose disease had progressed after prior chemotherapy. Patients were randomly assigned at a one-to-one ratio to receive either onartuzumab (15 mg/kg intravenously [IV] on day 1 of each 21-day cycle) plus daily oral erlotinib 150 mg or IV placebo plus daily oral erlotinib 150 mg. Patients were randomly assigned using a permuted-block method to ensure approximately equal numbers in the two treatment arms and stratified by MET immunohistochemistry (IHC) score, wild type or MET amplified (by FISH or CEP7 centromere probe [Abbott Molecular, Abbott Park, IL]) and histology (nonsquamous or squamous), number of prior lines of therapy (one or two), and Eastern Cooperative Oncology Group performance status of 0 or 1.

**Patients**

Patients with stage IIIB to IV locally advanced or metastatic NSCLC whose disease had progressed after prior chemotherapy and MET and EGFR mutation status were determined to be MET positive (≥ 50% of tumor cells with IHC scores of 2+ [moderate] or 3+ [strong] levels of MET)5 were enrolled. Patients had developed PD after one previous line of platinum-based chemotherapy but had not received more than two prior lines of treatment and had Eastern Cooperative Oncology Group performance status of 0 or 1.

Key exclusion criteria included prior treatment with an EGFR inhibitor, untreated brain metastases, interstitial lung disease, pleural effusion, pericardial fluid or ascites, serious active infection, uncontrolled G1 inflammatory disease, uncontrolled diabetes mellitus, major surgery 2 weeks before random assignment, and history of other invasive malignancy or cardiac disease.

**Study End Points**

The primary end point was OS in the intent-to-treat (ITT) population. Secondary end points included PFS and overall response rate (ORR) in the ITT population, biomarker analysis, and safety in the safety population.

**Assessments**

Tumor response was evaluated every 6 weeks until PD or death using RECIST (version 1.1). OS was calculated from the date of random assignment until death resulting from any cause. Repeat chest and abdominal computed tomography or magnetic resonance imaging scans were performed by the investigator every 6 weeks (± 7 days; before the start of every odd-numbered cycle) for the first 12 months and then every 12 weeks (± 14 days) thereafter. PFS was calculated from the date of random assignment until the date of first PD or death, whichever occurred first. ORR was defined as the percentage of patients with measurable disease at baseline whose tumors had a complete (CR) or partial response. Adverse events (AEs) were recorded and graded according to the National Cancer Institute Common Terminology Criteria for AEs (version 4.0) and classified according to the Medical Dictionary for Regulatory Activities. Patients were observed until death or discontinuation of trial participation.

**MET and EGFR Status**

The provision of tumor samples (archival tissue block or 15 serial cut unstained slides) was mandatory. Tumor samples were tested centrally (LabCorp, Burlington, NC; Histogenix, Antwerp, Belgium) to determine MET expression status (using the Ventana [Tucson, AZ] anti-Tot al c-MET [SP44] rabbit monoclonal antibody IHC assay) and EGFR status (cobas EGFR assay, Roche Molecular Diagnostics). A patient’s disease was considered positive if his or her tumor sample demonstrated at least 50% of cells stained positive with an intensity of 2+ or greater per Ventana investigational-use-only assay system guidelines.

Exploratory biomarkers were assessed in formalin-fixed paraffin-embedded tumor samples obtained from patients at enrollment. Samples were used for fluorescence in situ hybridization (FISH) analysis using a CEP7 centromere probe (Abbott Molecular, Abbott Park, IL), and a cutoff of five or more copies of MET per cell was predefined as the criterion for FISH-positive status.18,19,20 The link between MET amplification and MET-positive status by IHC was assessed, as was the impact of FISH status on OS, PFS, and ORR. The influence of EGFR mutation status on OS and PFS was investigated, and OS, PFS, and ORR were assessed in patients with amplified gene expression. Further mutation analysis was performed using a multiplex fluidigm platform.20

**Statistical Analysis**

The trial was designed to enroll approximately 490 patients. Final analysis was planned at 364 OS events, with one interim analysis planned after 67% of OS events. The interim analysis rejection boundaries were calculated to be HR of 0.73 or less (one-sided P ≤ .006) for superior efficacy and HR of 0.94 or greater (one-sided P ≥ .32) for futility.

The ITT population included all randomly assigned patients, grouped according to treatment assigned at random allocation regardless of whether they received any study treatment. The safety population included all patients who received at least one dose of study treatment. The primary end point was OS in the ITT population, biomarker analysis, and safety in the safety population.

**Patients**

Between January 2012 and August 2013, 499 patients were randomly assigned to receive onartuzumab plus erlotinib (n = 250)
or placebo plus erlotinib \((n = 249)\). Of the 499 patients enrolled, seven (two \([0.8\%]\) in the onartuzumab arm and five \([2.0\%]\) in the placebo arm) did not receive any treatment (Fig 1). At primary data cutoff (October 26, 2013) for the planned interim analysis, 23 patients \((9.2\%)\) in the onartuzumab arm and 29 \((11.6\%)\) in the placebo arm were still receiving onartuzumab or placebo. Patient characteristics were generally well balanced between the two treatment arms (Table 1). Median patient age was 61.5 years \((\text{range, 24 to 84 years})\), and 55.7% were men. Most patients \((78.8\%)\) had an MET IHC score of 2+, and 88.6% had no activating \(\text{EGFR}\) mutation.

**Efficacy**

After the required number of OS events \((244)\), the interim analysis was performed. Median duration of follow-up was 7.6 months in the onartuzumab arm and 8.0 months in the placebo arm. Analysis of the primary end point showed the number of deaths was greater in the onartuzumab arm than in the placebo arm \((130 \, 52\% \, v \, 114 \, 46\%, \, \text{respectively; \, Fig 2A})\). Median OS was 6.8 months in the onartuzumab arm versus 9.1 months in the placebo arm. The stratified HR was 1.27 \((95\% \, \text{CI, 0.98 to 1.65; \, log-rank \, \(P = .067\)})\). Analysis of OS in key clinical subgroups of the ITT population showed that results were consistent with the overall ITT population (Fig 2B).

PFS analysis in the ITT population showed that there were more events in the onartuzumab arm \((210 \, 84\%)\) than in the placebo arm \((204 \, 82\%; \, \text{Fig 3A})\). Median PFS was similar between arms \((2.7 \, v \, 2.6 \, \text{months \, in \, the \, onartuzumab \, v \, placebo \, arm, \, respectively})\), and the stratified HR was 0.99 \((95\% \, \text{CI, 0.81 to 1.20; \, log-rank \, \(P = .92\)})\). Findings from an analysis of PFS in key clinical subgroups were consistent with the overall ITT population results (Fig 3B).

The ORR was similar between the two arms: 8.4% in the onartuzumab arm compared with 9.6% in the placebo arm. One

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Onartuzumab + Erlotinib (n = 250)</th>
<th>Placebo + Erlotinib (n = 249)</th>
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<tr>
<td>Sex</td>
<td>Male 139 (56)</td>
<td>139 (56)</td>
</tr>
<tr>
<td></td>
<td>Female 111 (44)</td>
<td>110 (44)</td>
</tr>
<tr>
<td>ECOG PS</td>
<td>0 93 (37)</td>
<td>78 (31)</td>
</tr>
<tr>
<td></td>
<td>1 153 (61)</td>
<td>169 (68)</td>
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<tr>
<td></td>
<td>2 4 (2)</td>
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<td>Histology*</td>
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<tr>
<td></td>
<td>Nonsquamous 40 (16)</td>
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</tr>
<tr>
<td>Prior lines of therapy*</td>
<td>Two 161 (64)</td>
<td>157 (63)</td>
</tr>
<tr>
<td></td>
<td>Three 89 (36)</td>
<td>92 (37)</td>
</tr>
<tr>
<td>(\text{EGFR}) mutation positive*</td>
<td>28 (11.2)</td>
<td>29 (11.6)</td>
</tr>
<tr>
<td>MET IHC*</td>
<td>2+ 198 (79)</td>
<td>195 (78)</td>
</tr>
<tr>
<td></td>
<td>3+ 52 (21)</td>
<td>54 (22)</td>
</tr>
</tbody>
</table>

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; IHC, immunohistochemistry; ITT, intent to treat.

*Stratification factor

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![Fig 1. CONSORT diagram of patient flow through the study. Primary efficacy analysis cutoff: October 26, 2013.](image-url)
Fig 2. (A) Kaplan-Meier curves of overall survival (OS) in the intent-to-treat population. Crosses indicate censored patients. (B) Subanalysis of OS in key clinical subgroups. ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; IHC, immunohistochemistry; NE, not evaluable.
patient (0.4%) in the placebo arm had a CR, whereas no patient treated with onartuzumab had a CR.

**Biomarkers**

MET IHC was performed centrally and comprised both staining intensity and percentage of MET-expressing tumor cells (Appendix Fig A1, online only). By IHC, MET-positive tumors were defined as those with 50% or more of tumor cells showing moderate and/or strong staining intensity (MET 2+ or 3+). Overall agreement between central laboratory pathologists was greater than 88% (Appendix Table A1, online only).

A greater proportion of patients with MET IHC 2+ status were FISH negative (85.1%) than FISH positive (65.4%), whereas more patients with MET IHC 3+ status were FISH positive (34.6%) than FISH negative (14.9%). The PFS HR in patients with MET IHC 3+ status (n = 54) was 0.86 (95% CI, 0.58 to 1.29) compared with 1.06 (95% CI, 0.85 to 1.32) in patients (n = 195) with MET IHC 2+ status (Fig 3B). There were no statistically significant differences in OS, PFS, or ORR between the onartuzumab and placebo arms when analyzed by MET FISH status. The OS HR in patients with FISH-negative disease was 1.36 (95% CI, 0.98 to 1.89) compared with 1.28 (95% CI, 0.82 to 2.01) in patients with FISH-positive disease. The PFS HR in the FISH-negative group was 1.02 (95% CI, 0.80 to 1.30) compared...

![Fig 3.](A) Kaplan-Meier curves of progression-free survival (PFS) in the intent-to-treat population. Crosses indicate censored patients. (B) Subanalysis of PFS in key clinical subgroups. FISH, fluorescence in situ hybridization; HR, hazard ratio; IHC, immunohistochemistry.)
Phase III Study of Onartuzumab Plus Erlotinib in NSCLC

with 1.07 (95% CI, 0.75 to 1.51) for the FISH-positive group (Fig 3B). Patients with FISH-negative disease had an ORR of 9.7% and 8.7% and patients with FISH-positive disease had an ORR of 11.8% and 4.2% in the onartuzumab and placebo arms, respectively.

Although there was no significant association between EGFR mutation status and treatment outcomes, there was a trend toward shorter OS in patients with activating mutations who received onartuzumab and erlotinib, albeit with a small number of events in each arm (two for placebo and seven for onartuzumab; HR, 4.68; 95% CI, 0.97 to 22.63; Figs 2B and 3B). Similarly, there was no significant difference observed in OS or PFS between treatments in patients with amplification of MET (OS: HR, 1.66; 95% CI, 0.86 to 3.21; PFS: HR, 1.47; 95% CI, 0.86 to 2.51) or EGFR amplification (OS: HR, 2.01; 95% CI, 0.83 to 4.87; PFS: HR, 1.46; 95% CI, 0.7 to 3.03). On the basis of an unstratified analysis of the biomarker subgroups, there was no significant difference in PFS or OS for any other subgroup; however, patients who had a KRAS mutation showed a borderline association of benefit in the onartuzumab arm (PFS: HR, 0.67; 95% CI, 0.43 to 1.05; OS: HR, 0.95; 95% CI, 0.52 to 1.74; Figs 4A and 4B).

Safety

Median dose intensity of both onartuzumab and placebo was 100%. The median duration of treatment was longer for patients who received onartuzumab plus erlotinib (60.9 days [four doses]) than for those who received placebo plus erlotinib (40.6 days [2.5 doses]). Erlotinib was administered for a median of 66.5 days (65 doses) to patients in the onartuzumab arm and 49 days (47.5 doses) in the placebo arm.

A majority of patients reported at least one AE, mostly grade 1 or 2 in severity. There was a similar number in each arm: 245 (98.8%) in the onartuzumab arm and 234 (95.9%) in the placebo arm. The most common AEs (all grades) in the onartuzumab arm were rash (39%), diarrhea (39%), and dermatitis aciform (32%). In the placebo arm, the most common AEs (all grades) were diarrhea (47%), rash (37%), decreased appetite (32%), and fatigue (30% [Table 2]). AEs occurring in at least 5% more patients in the onartuzumab arm than in the placebo arm were peripheral edema (22% v 8%, respectively), hypoalbuminemia (17% v 4%, respectively), and dermatitis aciform (32% v 26%, respectively; Table 2). Grade 3 to 5 AEs were reported in 139 patients (56.0%) in the onartuzumab arm and 125 (51.2%) in the placebo arm. Grade 5 AEs occurred in 6.9% and 4.1% of patients in the onartuzumab and placebo arms, respectively. Serious AEs (SAEs) were reported in 84 patients (33.9%) in the onartuzumab arm and 75 (30.7%) in the placebo arm. Most SAEs were grade 3 in severity, with similar rates between arms. Grade 4 and 5 SAEs were more frequent in the onartuzumab arm (5.2% and 6.9%, respectively) than in the placebo arm (2.9% and 4.1%, respectively). The most frequently reported SAEs were respiratory, thoracic, and mediastinal disorders. The rate of AEs leading to onartuzumab or placebo discontinuation was 7.7% in the onartuzumab arm and 4.5% in the placebo arm.

The phase III METLung trial did not meet its primary end point, and the results did not confirm the findings of the earlier phase II study. Multiple exploratory biomarkers were also assessed, and these results were consistently negative across all biomarker subgroups.

The combination of onartuzumab and erlotinib demonstrated a tolerable safety profile, supporting the findings of the phase II study.17 The peripheral edema and hypoalbuminemia observed were likely to be a class effect of MET inhibition, because these AEs were also observed in the phase II study.17 the onartuzumab program as a whole,21 and a study of rilotumumab, another inhibitor of MET signaling.22

The results are in stark contrast to those of the phase II study,17 and a large number of comparisons have been performed between the studies in an effort to identify variables that might account for the different outcomes. With respect to patient selection, MET IHC for the phase II study was performed at Genentech (San Francisco, CA).5 The cutoff for MET positivity was defined before unblinding of the phase II trial. The pathologist who developed the assay at Genentech worked closely with Ventana to ensure consistency in how the assay was performed in the phase II study. The pathologist directly trained the central laboratories that performed the IHC for the phase III trial. Additionally, a three-way concordance analysis was performed before unblinding of the phase III trial to ensure consistency in assay and pathologist performance. All clinical and demographic variables were similar between the phase II and III studies. Taken together, it is unlikely that patient selection had an impact on the outcome of the phase III study. However, this study was based on IHC analysis, and emerging data suggest that splice-site mutations, which are drivers of MET activity, may be a better way to select patients for MET small-molecule inhibitors.23-25 In this context, it is important to note that it is presently unclear whether onartuzumab or rilotumumab would be efficacious in patients whose tumors harbor splice-site mutations, and none of the onartuzumab studies were designed to evaluate this question.

In the phase II trial, both PFS and OS favored the combination treatment, whereas the opposite was true in the phase III trial. Thus, it is unclear how the prioritization of end points would have affected the outcome.

As for the size of the phase II versus III study, statistical modeling showed that the phase II results were robust. A larger phase II study would have been required (assuming that the phase III results were robust) to mitigate the treatment effect observed in the phase II.

Additionally, patients with EGFR mutation–positive disease, included in this study, showed a detrimental trend when treated with a combination of onartuzumab and erlotinib. Although the number of patients for this analysis was limited, this result suggests that this population of patients does not benefit from the addition of onartuzumab to erlotinib, despite compelling preclinical data to the contrary. The treatment of EGFR wild-type NSCLC has changed, with studies comparing EGFR TKIs and chemotheraphy in a second-line setting showing that chemotherapy may be better than erlotinib, in the absence of a confirmed mutation.26,27

Results from other phase III studies using different inhibitors of MET signaling have also been negative. A phase II trial of the HGF inhibitor rilotumumab in gastric cancer demonstrated positive results.28 However, similarly to METLung, the RILOMET-1
### A

**Baseline Risk Factors**

<table>
<thead>
<tr>
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<th>Placebo + Erlotinib (n = 249)</th>
<th>Onartuzumab + Erlotinib (n = 250)</th>
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<tr>
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<td><strong>Events</strong></td>
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<tr>
<td><strong>95% CI</strong></td>
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<td>0.81 to 1.33</td>
</tr>
</tbody>
</table>

- **BRAF mutation**
  - Detected: 5 / 2 / 2.4 / 1.73 / 0.23 to 12.78
  - Not detected: 311 / 149 / 120 / 2.0 / 1.04 / 0.81 to 1.33

- **EGFR mutation**
  - Detected: 20 / 12 / 3 / NE / 1.57 / 0.21 to 7.90
  - No call: 50 / 20 / 16 / 2.7 / 1.25 / 0.66 to 2.38
  - Not detected: 246 / 120 / 104 / 1.4 / 0.94 / 0.72 to 1.23

- **KRAS mutation**
  - Detected: 88 / 42 / 38 / 1.4 / 0.67 / 0.43 to 1.05
  - No call: 15 / 7 / 6 / 1.9 / 2.58 / 0.82 to 8.08
  - Not detected: 213 / 103 / 79 / 2.8 / 1.13 / 0.83 to 1.52

- **MET gene amplification**
  - Amplified: 65 / 39 / 36 / 1.4 / 1.47 / 0.86 to 2.51
  - Other: 91 / 46 / 36 / 2.8 / 0.94 / 0.59 to 1.49

- **EGFR gene amplification**
  - Amplified: 41 / 23 / 20 / 2.8 / 1.46 / 0.70 to 3.03
  - Other: 242 / 116 / 90 / 2.7 / 1.01 / 0.76 to 1.35

- **MET FISH**
  - Positive: 156 / 85 / 72 / 1.5 / 1.07 / 0.75 to 1.51
  - Negative: 315 / 150 / 118 / 2.7 / 1.02 / 0.80 to 1.30

- **EGFR FISH**
  - Positive: 280 / 137 / 109 / 2.7 / 1.02 / 0.79 to 1.33
  - Negative: 191 / 98 / 81 / 2.2 / 1.04 / 0.77 to 1.42

### B

**Baseline Risk Factors**

<table>
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<tr>
<th></th>
<th>Placebo + Erlotinib (n = 249)</th>
<th>Onartuzumab + Erlotinib (n = 250)</th>
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<tbody>
<tr>
<td><strong>Total</strong></td>
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<td>250</td>
</tr>
<tr>
<td><strong>No.</strong></td>
<td>249</td>
<td>210</td>
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<tr>
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<td><strong>Median (months)</strong></td>
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<tr>
<td><strong>HR</strong></td>
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<td>1.09</td>
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<tr>
<td><strong>95% CI</strong></td>
<td>0.98 to 1.63</td>
<td>1.01 to 1.90</td>
</tr>
</tbody>
</table>

- **BRAF mutation**
  - Detected: 5 / 3 / 1 / NE / > 999.99 / 0.0 to NE
  - Not detected: 331 / 149 / 68 / 9.1 / 1.39 / 1.01 to 1.90

- **EGFR mutation**
  - Detected: 20 / 12 / 1 / NE / 2.92 / 0.26 to 32.93
  - No call: 50 / 20 / 10 / 6.5 / 1.42 / 0.64 to 3.19
  - Not detected: 246 / 120 / 58 / 7.8 / 1.34 / 0.95 to 1.89

- **KRAS mutation**
  - Detected: 88 / 42 / 19 / NE / 0.95 / 0.52 to 1.74
  - No call: 15 / 7 / 4 / 5.1 / 2.08 / 0.51 to 8.49
  - Not detected: 213 / 103 / 46 / 9.1 / 1.63 / 1.11 to 2.39

- **PIK3CA mutation**
  - Detected: 15 / 7 / 1 / NE / 3.73 / 0.39 to 36.02
  - No call: 36 / 17 / 7 / 7.4 / 2.25 / 0.84 to 6.03
  - Not detected: 265 / 128 / 61 / 9.1 / 1.33 / 0.95 to 1.86

- **MET gene amplification**
  - Amplified: 65 / 39 / 24 / 9.6 / 1.66 / 0.86 to 3.21
  - Other: 91 / 46 / 21 / 9.4 / 1.13 / 0.60 to 2.11

- **EGFR gene amplification**
  - Amplified: 41 / 23 / 11 / 10.1 / 2.01 / 0.83 to 4.87
  - Other: 242 / 116 / 50 / 9.4 / 1.35 / 0.93 to 1.96

- **MET FISH**
  - Positive: 156 / 85 / 45 / 9.4 / 1.28 / 0.92 to 2.01
  - Negative: 315 / 150 / 62 / 9.9 / 1.36 / 0.98 to 1.89

- **EGFR FISH**
  - Positive: 280 / 137 / 61 / 9.8 / 1.42 / 1.01 to 1.99
  - Negative: 191 / 98 / 46 / 7.8 / 1.13 / 0.76 to 1.70

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**Fig 4.** Subanalyses of (A) progression-free and (B) overall survival in biomarker subgroups. EGFR, epidermal growth factor receptor; FISH, fluorescence in situ hybridization; HR, hazard ratio; NE, not evaluable.
(Rilotumumab With ECX As First-Line Therapy in Advanced MET-Positive Gastric or Gastroesophageal Junction Adenocarcinoma) phase III trial in gastric cancer failed to meet its primary end point; the median OS of 9.6 months with rilotumumab was significantly lower than 11.5 months in the placebo arm (stratified HR, 1.37; 95% CI, 1.06 to 1.78; log-rank \( P = .016 \)). Additionally, the 12-month survival rate (38.4% vs 49.7%) and ORR (30% vs 39.2%) were lower in the rilotumumab arm than in the placebo arm. This trial was closed prematurely because of lack of activity and the observation of an imbalance of deaths between the two arms (128 vs 107).22

The collective experience with onartuzumab plus standard of care in multiple phase II and III trials of gastroesophageal adenocarcinoma,29 triple-negative breast cancer,30 recurrent glioblastoma,31 and colorectal carcinoma32 has also included disappointing efficacy results. These findings, together with the results from the METlung trial, suggest that MET inhibition via ligand-blocking antibodies may not be an effective therapeutic strategy.

### AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at ascopubs.org/journal/jco.

### AUTHOR CONTRIBUTIONS

Conception and design: David R. Spigel, Martin J. Edelman, Kenneth O’Byrne, Luis Paz-Ares, See Phan, Tony Mok

Provision of study materials or patients: David R. Spigel, Martin J. Edelman

Collection and assembly of data: David R. Spigel, Kenneth O’Byrne, Luis Paz-Ares, See Phan, David S. Shames, Dustin Smith, Virginia E. Paton, Tony Mok

Data analysis and interpretation: All authors

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

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Affiliations

David R. Spigel, Sarah Cannon Research Institute, Nashville, TN; Martin J. Edelman, University of Maryland Greenebaum Cancer Center, Baltimore, MD; Kenneth O’Byrne, Queensland University of Technology, Brisbane, Queensland, Australia; Luis Paz-Ares, Hospital Universitari i Politecnic de Valencia and Centro Nacional de Investigaciones Oncologicas, Madrid; University of Seville, Seville, Spain; Simonetta Mocci, See Phan, David S. Shames, Dustin Smith, Wei Yu, and Virginia E. Paton, Genentech, South San Francisco, CA; and Tony Mok, Chinese University of Hong Kong, Hong Kong, Special Administrative Region, People’s Republic of China.

Support

Supported by F. Hoffmann-La Roche, which also provided third-party medical writing assistance.
Phase III Study of Onartuzumab Plus Erlotinib in NSCLC

RESULTS FROM THE Phase III RANDOMIZED TRIAL OF ONARTUZUMAB PLUS ERLOTINIB VERSUS ERLOTINIB IN PREVIOUSLY TREATED STAGE IIIB OR IV NON–SMALL-CELL LUNG CANCER: METLung

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David R. Spigel
Consulting or Advisory Role: Genentech, Novartis, Celgene, Bristol-Myers Squibb, Eli Lilly, AstraZeneca, Pfizer, Boehringer Ingelheim
Speakers’ Bureau: Novartis
Research Funding: Genentech (Inst), Novartis (Inst), Celgene (Inst), Bristol-Myers Squibb (Inst), Eli Lilly (Inst), AstraZeneca (Inst), Pfizer (Inst), Clovis Oncology (Inst), Boehringer Ingelheim (Inst), Peregrine Pharmaceuticals (Inst), Oncogenex (Inst), OncoMed (Inst), Amgen (Inst), Astex Pharmaceuticals (Inst), Verastem (Inst), BIND Biosciences (Inst), Daiichi Sankyo (Inst), Immunogen (Inst), ImClone Systems (Inst), EMD Serono (Inst), University of Texas Southwestern Medical Center–Simmons Cancer Center (Inst), CytrRx (Inst)
Travel, Accommodations, Expenses: Genentech, Novartis, Celgene, Bristol-Myers Squibb, Eli Lilly, AstraZeneca, Pfizer, Clovis Oncology, Boehringer Ingelheim

Martin J. Edelman
Stock or Other Ownership: Biomarker Strategies
Consulting or Advisory Role: Eli Lilly, Bristol-Myers Squibb, Novartis, Genentech, Boehringer Ingelheim, ARIAD Pharmaceuticals
Research Funding: Eli Lilly (Inst), Bristol-Myers Squibb (Inst), Genentech (Inst), Endocyte (Inst)
Travel, Accommodations, Expenses: Eli Lilly, ARIAD Pharmaceuticals, Genentech
Other Relationship: AstraZeneca, Synta, Eli Lilly, Boehringer Ingelheim

Kenneth O’Byrne
Consulting or Advisory Role: Merck Sharp & Dohme, Boehringer Ingelheim, AstraZeneca, Genentech, Novartis, Bristol-Myers Squibb, Eli Lilly, Pfizer
Speakers’ Bureau: AstraZeneca, Genentech, Pfizer, Boehringer Ingelheim, Merck Sharp & Dohme, Bristol-Myers Squibb
Patents, Royalties, Other Intellectual Property: Australian provisional patents (Inst)
Travel, Accommodations, Expenses: AstraZeneca, Boehringer Ingelheim, Merck Sharp & Dohme, Bristol-Myers Squibb, Genentech

Luis Paz-Ares
Honoraria: Roche, Pfizer, Clovis Oncology, Bristol-Myers Squibb, Merck Sharp & Dohme, AstraZeneca, Eli Lilly, PharmaMar, Boehringer Ingelheim

Simonetta Mocci
Employment: Genentech

See Phan
Employment: Genentech
Stock or Other Ownership: Roche
Patents, Royalties, Other Intellectual Property: Genentech
Travel, Accommodations, Expenses: Genentech

David S. Shames
Employment: Genentech
Patents, Royalties, Other Intellectual Property: Roche
Stock or Other Ownership: Roche
Travel, Accommodations, Expenses: Genentech

Wei Yu
Employment: Genentech

Virginia E. Paton
Employment: Chinese University of Hong Kong
Leadership: Sanomics
Stock or Other Ownership: Sanomics
Honoraria: AstraZeneca, Genentech, Eli Lilly, Merck Serono, Bristol-Myers Squibb, Boehringer Ingelheim, Novartis, Clovis Oncology, Amgen, Janssen Pharmaceuticals, AVEO Pharmaceuticals, Biodexis, Prime Oncology, ACEA Biosciences, Vertex, SFJ Pharmaceuticals Group, Merck Sharp & Dohme, GlaxoSmithKline, Biomarin, Pfizer, Oncogenex, PeerVoice, Celgene
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Speakers’ Bureau: AstraZeneca, Eli Lilly, Boehringer Ingelheim, Pfizer, Amgen, Genentech, Merck Sharp & Dohme, Clovis Oncology, Bristol-Myers Squibb, Prime Oncology
Research Funding: AstraZeneca (Inst), Boehringer Ingelheim (Inst), Pfizer (Inst), Novartis (Inst), SFJ Pharmaceuticals Group (Inst), Roche (Inst), Merck Sharp & Dohme (Inst), Clovis Oncology (Inst), Bristol-Myers Squibb (Inst)
Travel, Accommodations, Expenses: AstraZeneca, Roche, Eli Lilly, Boehringer Ingelheim, Merck Serono, Pfizer, Amgen, Novartis,
Acknowledgment

We thank the investigators, the patients, and their families for their contribution to this clinical study. We also thank Alison Cardenas for her contribution to the safety analysis of this study. Louise Clarke (Gardiner-Caldwell Communications, an Ashfield Company, part of UDG Healthcare) provided third-party medical writing assistance, under the direction of the authors, funded by F. Hoffmann-La Roche.

Appendix

### Table A1. Central Laboratory Pathologist Percentage Agreement

<table>
<thead>
<tr>
<th>Agreement Rate</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory one</td>
<td></td>
</tr>
<tr>
<td>Overall percentage agreement</td>
<td>191 of 207 (92.3)</td>
</tr>
<tr>
<td>Average positive agreement</td>
<td>88 of 103 (85.4)</td>
</tr>
<tr>
<td>Average negative agreement</td>
<td>103 of 104 (99.0)</td>
</tr>
<tr>
<td>Laboratory two</td>
<td></td>
</tr>
<tr>
<td>Overall percentage agreement</td>
<td>135 of 153 (88.2)</td>
</tr>
<tr>
<td>Average positive agreement</td>
<td>57 of 75 (76.0)</td>
</tr>
<tr>
<td>Average negative agreement</td>
<td>78 of 78 (100.0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical Diagnosis</th>
<th>IHC Score</th>
<th>Staining Criteria</th>
<th>Representative IHC Images</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>0</td>
<td>No or equivocal staining in tumor cells or &lt; 50% tumor cells with membrane and/or cytoplasmic staining</td>
<td><img src="negative_0.png" alt="Image" /></td>
</tr>
<tr>
<td>Negative</td>
<td>1+</td>
<td>≥ 50% tumor cells with weak or higher membrane and/or cytoplasmic staining but &lt; 50% tumor cells with moderate or higher staining intensity</td>
<td><img src="negative_1+_png" alt="Image" /></td>
</tr>
<tr>
<td>Positive</td>
<td>2+</td>
<td>≥ 50% tumor cells with moderate or higher membrane and/or cytoplasmic staining but &lt; 50% tumor cells with strong staining intensity</td>
<td><img src="positive_2+_png" alt="Image" /></td>
</tr>
<tr>
<td>Positive</td>
<td>3+</td>
<td>≥ 50% tumor cells with strong or higher membrane and/or cytoplasmic staining intensity</td>
<td><img src="positive_3+_png" alt="Image" /></td>
</tr>
</tbody>
</table>

Fig A1. MET immunohistochemistry (IHC) scoring criteria.