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ORIGINAL REPORT

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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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%] *v* 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.

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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

ASSOCIATED CONTENT

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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 tumorigenesis.[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 erlotinib[17] 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 were stratified by MET immunohistochemistry (IHC) clinical score (2+ *v* 3+), number of prior lines of therapy (one *v* two), histology (nonsquamous *v* squamous), and *EGFR* mutation status (activating mutation *v* wild type [by cobas *EGFR* assay; Roche Molecular Diagnostics, Pleasanton, CA]). Patients received treatment until disease progression (PD), unacceptable toxicity, patient or physician decision, or death. The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice. All patients provided written informed consent before any study-related procedures.

Patients

Patients with stage IIIB to IV locally advanced or metastatic NSCLC 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 GI 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-Total 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.[5,18,19] 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 $P \leq .006$) for superior efficacy and HR of 0.94 or greater (one-sided $P \geq .32$) 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 randomly assigned patients who received at least one dose of study treatment, grouped according to whether any full or partial dose of onartuzumab or placebo was received.

Median PFS and median OS were estimated using Kaplan-Meier analysis. Estimated HRs and 95% CIs of PFS and OS were determined using a stratified Cox regression model. Estimates of ORRs and 95% CIs were calculated using the Blyth-Still-Casella method. ORRs in the treatment groups were compared using the stratified Mantel-Haenszel test, and 95% CIs were determined using the normal approximation to the binomial distributions. Biomarker subgroup analyses for OS, PFS, and ORR were performed using formalin-fixed paraffin-embedded tumor samples obtained from patients at enrollment.

RESULTS

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 (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 *EGFR* mutation.

Table 1. Baseline Characteristics of the ITT Population

Characteristic	No. (%)	
	Onartuzumab + Erlotinib (n = 250)	Placebo + Erlotinib (n = 249)
Median age, years	62	63
Sex		
Male	139 (56)	139 (56)
Female	111 (44)	110 (44)
ECOG PS		
0	93 (37)	78 (31)
1	153 (61)	169 (68)
2	4 (2)	1 (0.5)
Missing	0 (0)	1 (0.5)
Asian race	35 (14)	37 (15)
Histology*		
Nonsquamous	210 (84)	218 (88)
Squamous	40 (16)	31 (12)
Prior lines of therapy*		
Two	161 (64)	157 (63)
Three	89 (36)	92 (37)
EGFR mutation positive*	28 (11.2)	29 (11.6)
MET IHC*		
2+	198 (79)	195 (78)
3+	52 (21)	54 (22)

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

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%], 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% 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%]; Fig 3A). Median PFS was similar between arms (2.7 *v* 2.6 months in the onartuzumab *v* placebo arm, respectively), and the stratified HR was 0.99 (95% 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

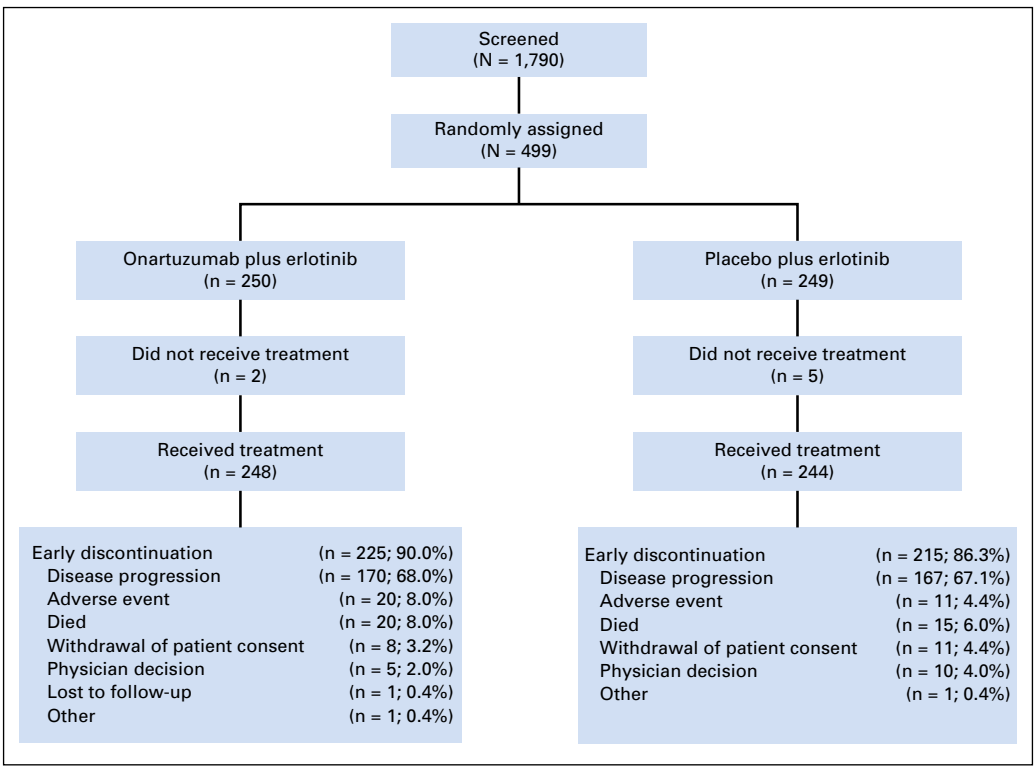
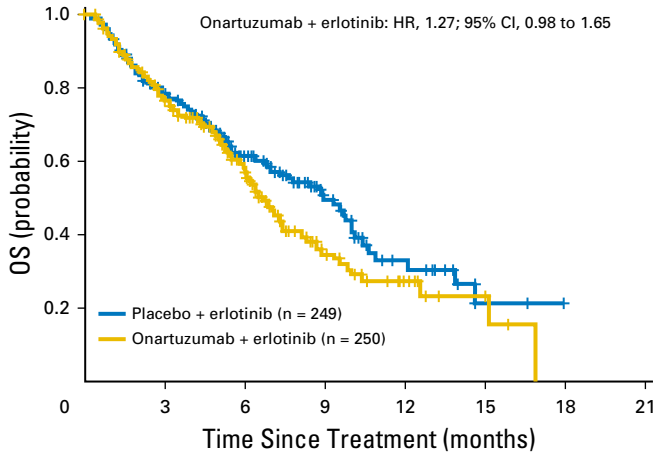


Fig 1. CONSORT diagram of patient flow through the study. Primary efficacy analysis cutoff: October 26, 2013.

A



No. of patients at risk

Placebo + erlotinib	249	183	110	43	14	3	1
Onartuzumab + erlotinib	250	177	100	29	12	4	

B

Baseline Risk Factors	Placebo + Erlotinib (n = 249) Total No.	No.	Events	Median (months)	Onartuzumab + Erlotinib (n = 250) No.	Events	Median (months)	HR	95% CI
All patients	499	249	114	9.1	250	130	6.8	1.27	0.98 to 1.63
Sex									
Male	278	139	71	7.0	139	79	6.4	1.17	0.85 to 1.62
Female	221	110	43	9.9	111	51	8.8	1.36	0.90 to 2.05
Age group, years									
< 65	295	143	72	9.1	152	84	6.5	1.25	0.91 to 1.71
65–75	167	90	36	9.4	77	37	7.5	1.17	0.74 to 1.86
> 75	37	16	6	14.7	21	9	7.6	3.83	1.06 to 13.84
Race									
Asian	72	37	13	10.2	35	9	NE	0.71	0.30 to 1.67
Black or African American	12	8	3	NE	4	2	5.0	2.26	0.32 to 16.23
Native Hawaiian or other Pacific Islander	1				1	0	NE	NE	NE to NE
White	362	180	85	9.0	182	103	6.4	1.30	0.98 to 1.74
Multiple	34	16	9	9.6	18	8	6.5	1.41	0.53 to 3.71
Other race	4	1	0	NE	3	2	4.2	> 999.99	0.00 to NE
Unknown	14	7	4	7.4	7	6	4.9	0.86	0.26 to 3.62
ECOG PS									
0	171	78	27	10.2	93	34	9.0	1.21	0.73 to 2.01
1 or 2	327	170	87	7.0	157	96	5.9	1.32	0.99 to 1.77
MET IHC score									
2+	393	195	86	9.4	198	105	6.8	1.35	1.02 to 1.80
3+	106	54	28	9.1	52	25	6.4	1.02	0.59 to 1.75
Prior lines of therapy									
1	318	157	72	9.0	161	79	7.1	1.13	0.82 to 1.55
2	181	92	42	9.4	89	51	6.3	1.62	1.07 to 2.45
Histology									
Nonsquamous	428	218	95	9.8	210	109	6.5	1.34	1.02 to 1.77
Squamous	71	31	19	6.4	40	21	7.2	0.88	0.47 to 1.64
EGFR mutation									
Yes	57	29	2	NE	28	7	12.6	4.68	0.97 to 22.63
No	442	220	112	7.8	222	123	6.4	1.19	0.92 to 1.54

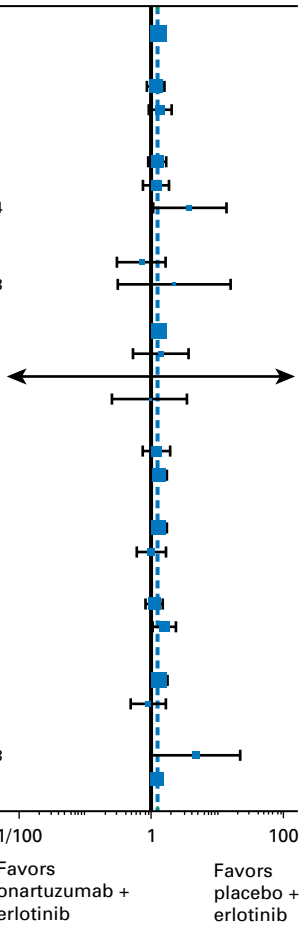


Fig 2. (A) Kaplan-Meier curves of overall survival (OS) in the intent-to-treat population. Crosses indicate censored patients. (B) Subanalysis of OS in key clinical subgroups. ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; IHC, immunohistochemistry; NE, not evaluable.

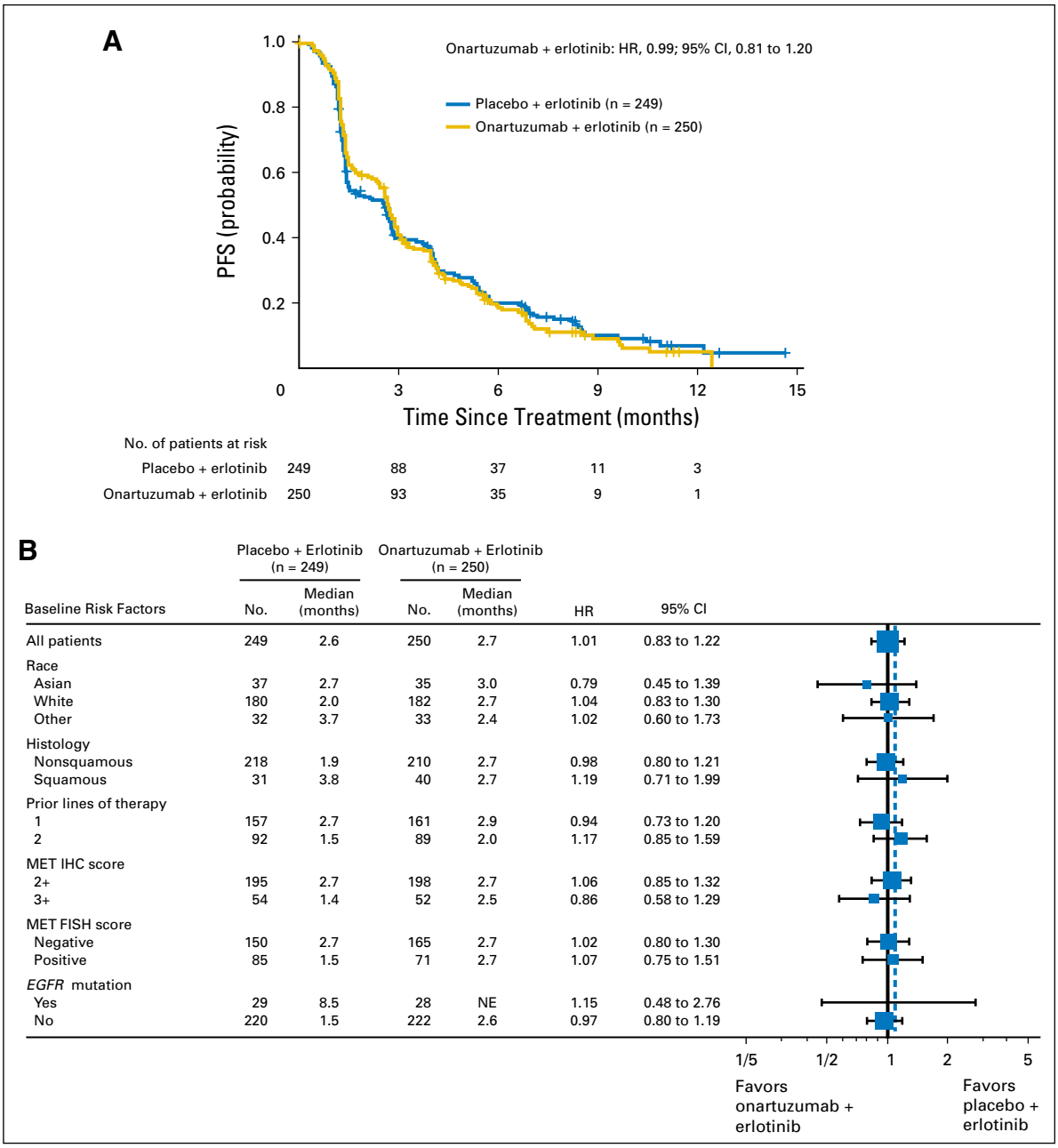


Fig 3. (A) Kaplan-Meier curves of progression-free survival (PFS) in the intent-to-treat population. Crosses indicate censored patients. (B) Subanalysis of PFS in key clinical subgroups. FISH, fluorescence in situ hybridization; HR, hazard ratio; IHC, immunohistochemistry.

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

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 (63 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 acneiform (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 acneiform (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.

DISCUSSION

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.

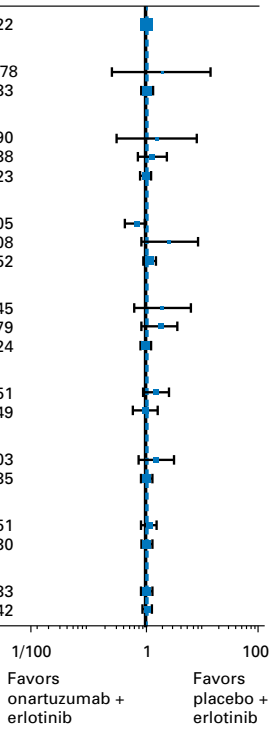
As for the size of the phase II versus III study, statistical modeling showed that the phase II results were robust. A larger phase II study would have been required (assuming that the phase III results revealed the risk–benefit ratio of onartuzumab accurately) to mitigate the treatment effect observed 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 chemotherapy 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	Total No.	Placebo + Erlotinib (n = 249) No.	Events	Median (months)	Onartuzumab + Erlotinib (n = 250) No.	Events	Median (months)	HR	95% CI
All patients	499	249	204	2.6	250	210	2.7	1.01	0.83 to 1.22
BRAF mutation									
Detected	5	3	3	1.3	2	2	2.4	1.73	0.23 to 12.78
Not detected	311	149	120	2.0	162	137	2.7	1.04	0.81 to 1.33
EGFR mutation									
Detected	20	12	3	NE	8	3	NE	1.57	0.31 to 7.90
No call	50	20	16	2.7	30	25	1.7	1.25	0.66 to 2.38
Not detected	246	120	104	1.4	126	111	2.7	0.94	0.72 to 1.23
KRAS mutation									
Detected	88	42	38	1.4	46	41	3.1	0.67	0.43 to 1.05
No call	15	7	6	1.9	8	8	1.3	2.58	0.82 to 8.08
Not detected	213	103	79	2.8	110	90	2.7	1.13	0.83 to 1.52
PIK3CA mutation									
Detected	15	7	4	4.1	8	7	3.4	1.88	0.55 to 6.45
No call	36	17	13	3.7	19	16	1.6	1.75	0.81 to 3.79
Not detected	265	128	106	1.4	137	116	2.7	0.96	0.73 to 1.24
MET gene amplification									
Amplified	65	39	36	1.4	26	23	1.3	1.47	0.86 to 2.51
Other	91	46	36	2.8	45	35	2.8	0.94	0.59 to 1.49
EGFR gene amplification									
Amplified	41	23	20	2.8	18	14	1.6	1.46	0.70 to 3.03
Other	242	116	90	2.7	126	103	2.8	1.01	0.76 to 1.35
MET FISH									
Positive	156	85	72	1.5	71	58	2.7	1.07	0.75 to 1.51
Negative	315	150	118	2.7	165	141	2.7	1.02	0.80 to 1.30
EGFR FISH									
Positive	280	137	109	2.7	143	116	2.8	1.02	0.79 to 1.33
Negative	191	98	81	2.2	93	83	2.6	1.04	0.77 to 1.42



B

Baseline Risk Factors	Total No.	Placebo + Erlotinib (n = 249) No.	Events	Median (months)	Onartuzumab + Erlotinib (n = 250) No.	Events	Median (months)	HR	95% CI
All patients	499	249	114	9.1	250	130	6.8	1.27	0.98 to 1.63
BRAF mutation									
Detected	5	3	1	NE	2	1	NE	> 999.99	0.0 to NE
Not detected	331	149	68	9.1	162	92	6.5	1.39	1.01 to 1.90
EGFR mutation									
Detected	20	12	1	NE	8	2	12.6	2.92	0.26 to 32.93
No call	50	20	10	6.5	30	18	5.6	1.42	0.64 to 3.19
Not detected	246	120	58	7.8	126	73	6.4	1.34	0.95 to 1.89
KRAS mutation									
Detected	88	42	19	NE	46	26	8.8	0.95	0.52 to 1.74
No call	15	7	4	5.1	8	6	4.6	2.08	0.51 to 8.49
Not detected	213	103	46	9.1	110	61	6.3	1.63	1.11 to 2.39
PIK3CA mutation									
Detected	15	7	1	NE	8	4	5.0	3.73	0.39 to 36.02
No call	36	17	7	7.4	19	12	3.3	2.25	0.84 to 6.03
Not detected	265	128	61	9.1	137	77	6.5	1.33	0.95 to 1.86
MET gene amplification									
Amplified	65	39	24	9.6	26	16	6.0	1.66	0.86 to 3.21
Other	91	46	21	9.4	45	20	8.4	1.13	0.60 to 2.11
EGFR gene amplification									
Amplified	41	23	11	10.1	18	10	6.0	2.01	0.83 to 4.87
Other	242	116	50	9.4	126	65	7.1	1.35	0.93 to 1.96
MET FISH									
Positive	156	85	45	9.4	71	36	6.4	1.28	0.82 to 2.01
Negative	315	150	62	9.9	165	87	6.9	1.36	0.98 to 1.89
EGFR FISH									
Positive	280	137	61	9.8	143	74	7.0	1.42	1.01 to 1.99
Negative	191	98	46	7.8	93	49	6.8	1.13	0.76 to 1.70

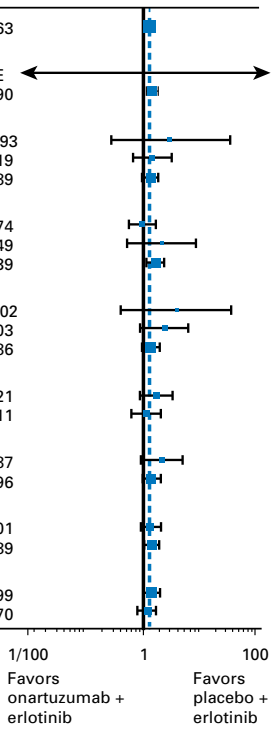


Fig 4. Subanalyses of (A) progression-free and (B) overall survival in biomarker subgroups. EGFR, epidermal growth factor receptor; FISH, fluorescence in situ hybridization; HR, hazard ratio; NE, not evaluable.

Table 2. Summary of AEs Occurring in > 10% of Patients (safety population)

AE	Onartuzumab + Erlotinib (n = 248)				Placebo + Erlotinib (n = 244)			
	All Grades (%)	Grade 1 (%)	Grade 2 (%)	Grade 3 to 5 (%)	All Grades (%)	Grade 1 (%)	Grade 2 (%)	Grade 3 to 5 (%)
Total No. (%) of patients with one or more AEs	245 (98.8)				234 (95.9)			
Total No. (%) of patients with one or more serious AEs	84 (33.9)				75 (30.7)			
Overall skin and subcutaneous tissue disorders	80.2	31.9	31.0	17.3	75.8	36.9	28.3	10.7
Rash	38.7	17.7	13.3	7.7	37.3	19.7	12.3	5.3
Diarrhea	39.1	27.8	8.5	2.8	47.1	31.6	11.9	3.7
Dermatitis acneiform	31.9	14.1	13.3	4.4	26.2	13.1	9.8	3.3
Decreased appetite	29.0	16.1	12.1	0.8	32.0	13.5	15.2	3.3
Nausea	27.8	19.0	7.3	1.6	25.8	15.6	7.8	2.5
Fatigue	27.0	12.5	10.1	4.4	30.3	12.7	12.7	4.9
Peripheral edema	21.8	13.7	7.3	0.4	7.8	6.6	1.2	0
Dyspnea	21.8	6.5	10.1	5.2	19.3	9.0	5.7	4.5
Dry skin	20.2	14.9	4.8	0.4	22.1	18.9	3.3	0
Hypoalbuminemia	17.3	4.4	8.9	4.0	3.7	1.2	2.5	0
Vomiting	14.9	12.5	2.0	0.4	15.2	13.5	1.6	0
Cough	14.1	8.9	5.2	0	22.1	14.8	7.4	0
Venous thrombotic events	6.5	0	2.8	3.6	3.3	0.4	1.2	0.8
Arterial thrombotic events	2.4	0	0	2.4	0.8	0	0	0.8
GI perforation	0.4	0	0	0.4	0.4	0	0	0.4
Neutropenia	0.4	0.4	0	0	1.2	0	0	1.2

Abbreviation: AE, adverse event.

(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% *v* 49.7%) and ORR (30% *v* 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 *v* 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 carcinoma[32] 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.

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Appendix

Table A1. Central Laboratory Pathologist Percentage Agreement

Agreement Rate	No. (%)
Laboratory one	
Overall percentage agreement	191 of 207 (92.3)
Average positive agreement	88 of 103 (85.4)
Average negative agreement	103 of 104 (99.0)
Laboratory two	
Overall percentage agreement	135 of 153 (88.2)
Average positive agreement	57 of 75 (76.0)
Average negative agreement	78 of 78 (100.0)

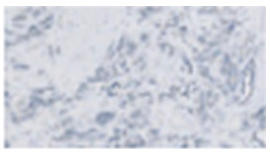
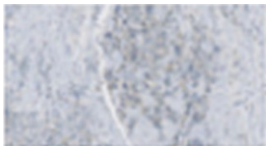
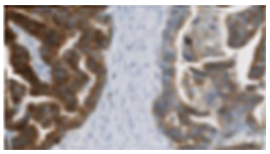
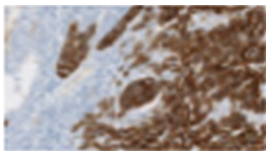
Clinical Diagnosis	IHC Score	Staining Criteria	Representative IHC Images
Negative	**0**	No or equivocal staining in tumor cells or < 50% tumor cells with membrane and/or cytoplasmic staining	
Negative	**1+**	≥ 50% tumor cells with weak or higher membrane and/or cytoplasmic staining but < 50% tumor cells with moderate or higher staining intensity	
Positive	**2+**	≥ 50% tumor cells with moderate or higher membrane and/or cytoplasmic staining but < 50% tumor cells with strong staining intensity	
Positive	**3+**	≥ 50% tumor cells with strong or higher membrane and/or cytoplasmic staining intensity	

Fig A1. MET immunohistochemistry (IHC) scoring criteria.