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ORIGINAL REPORT

Randomized Phase II Trial of Onartuzumab in Combination With Erlotinib in Patients With Advanced Non–Small-Cell Lung Cancer

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ABSTRACT

Purpose
Increased hepatocyte growth factor/MET signaling is associated with poor prognosis and acquired resistance to epidermal growth factor receptor (EGFR) –targeted drugs in patients with non–small-cell lung cancer (NSCLC). We investigated whether dual inhibition of MET/EGFR results in clinical benefit in patients with NSCLC.

Patients and Methods
Patients with recurrent NSCLC were randomly assigned at a ratio of one to one to receive onartuzumab plus erlotinib or placebo plus erlotinib; crossover was allowed at progression. Tumor tissue was required to assess MET status by immunohistochemistry (IHC). Coprimary end points were progression-free survival (PFS) in the intent-to-treat (ITT) and MET-positive (MET IHC diagnostic positive) populations; additional end points included overall survival (OS), objective response rate, and safety.

Results
There was no improvement in PFS or OS in the ITT population (n = 137; PFS hazard ratio [HR], 1.09; $P = .69$; OS HR, 0.80; $P = .34$). MET-positive patients (n = 66) treated with erlotinib plus onartuzumab showed improvement in both PFS (HR, .53; $P = .04$) and OS (HR, .37; $P = .002$). Conversely, clinical outcomes were worse in MET-negative patients treated with onartuzumab plus erlotinib (n = 62; PFS HR, 1.82; $P = .05$; OS HR, 1.78; $P = .16$). MET-positive control patients had worse outcomes versus MET-negative control patients (n = 62; PFS HR, 1.71; $P = .06$; OS HR, 2.61; $P = .004$). Incidence of peripheral edema was increased in onartuzumab-treated patients.

Conclusion
Onartuzumab plus erlotinib was associated with improved PFS and OS in the MET-positive population. These results combined with the worse outcomes observed in MET-negative patients treated with onartuzumab highlight the importance of diagnostic testing in drug development.

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INTRODUCTION

Non–small-cell lung cancer (NSCLC) represents 85% of all lung cancer cases; once metastatic, median survival is 10 to 12 months.[1] Treatment with erlotinib, a small-molecule inhibitor of the epidermal growth factor receptor (EGFR), improves survival in patients with recurrent NSCLC and progression-free survival (PFS) in patients with untreated NSCLC with EGFR-activating mutations.[2-4] Unfortunately, resistance eventually occurs; thus, understanding mechanisms of resistance has been the focus of much research.

MET, a transmembrane tyrosine kinase receptor, is involved in cell proliferation, survival, motility, and invasion in normal and tumor cells.[5] MET is frequently dysregulated in tumor cells via multiple mechanisms, particularly elevated expression, with or without gene amplification.[5,6] Elevated MET expression, observed commonly in NSCLC tumor tissues (61%),[7] has been associated with worse prognosis.[5,8,9]

MET activation increases the expression of some EGFR ligands,[10] and coactivation of EGFR and MET is described in a distinct subset of NSCLCs.[11] Genetic amplification/overexpression of

MET has been implicated as a mechanism of erlotinib resistance in tumors with EGFR-activating mutations,[12] and resistance to erlotinib has been observed in an NSCLC wild-type cell line (H596) on MET activation.[13] Thus, EGFR and MET may cooperate in driving tumorigenesis.

MET is activated on binding by hepatocyte growth factor (HGF; also known as scatter factor), the only known ligand for the MET receptor.[5] Onartuzumab (MetMAb; Genentech, South San Francisco, CA) is a humanized monovalent (one-armed) monoclonal antibody that binds the extracellular domain of MET to block HGF binding and activation.[14,15] The unique one-armed design of onartuzumab circumvents agonist activity observed with bivalent anti-MET antibodies.[16] We conducted a global, randomized, placebo-controlled, phase II study in patients with recurrent NSCLC evaluating onartuzumab plus erlotinib versus placebo plus erlotinib.

PATIENTS AND METHODS

Patients

Eligible patients had to be age ≥ 18 years; have received one or two systemic regimens (including platinum-based chemotherapy) for advanced (stage IIIB/IV) NSCLC; have an Eastern Cooperative Oncology Group performance status (ECOG PS) ≤ 2; have measurable disease; consent to providing sufficient representative tumor tissue; and have adequate hematologic, renal, and liver function. Key exclusion criteria included ≥ 30 days of exposure to an EGFR-targeted therapy, untreated CNS metastasis, or any major medical condition that could interfere with participation.

Study Design

The study was sponsored and study drugs provided by Genentech. The protocol was approved by the institutional review board of each participating center and conducted according to the Declaration of Helsinki. All patients provided written informed consent. The clinical investigators collected the data, which were stored by the sponsor.

OAM4558g was a phase II, double-blind, placebo-controlled, randomized (ratio of one to one) global trial designed to evaluate the activity and safety of onartuzumab plus erlotinib versus placebo plus erlotinib in patients with recurrent NSCLC. Dynamic hierarchic random assignment was performed through an interactive voice response system and stratified according to smoking status (never or < 100 cigarettes lifetime *v* current smoker or ≥ 100 cigarettes), ECOG PS (0/1 *v* 2), and histology (squamous cell carcinoma [SCC] *v* non-SCC). After disease progression, patients randomly assigned to placebo plus erlotinib could receive onartuzumab added to erlotinib, provided they met specific eligibility criteria (ECOG PS ≤ 2, no new CNS metastasis).

Study Treatments

Onartuzumab (15 mg/kg diluted in 0.9% normal saline solution to total volume of 250 cm^3) or placebo (250 cm^3 0.9% normal saline solution provided by investigative site) was administered by intravenous infusion every 3 weeks. Erlotinib was administered orally at 150 mg daily; dose reductions (to no less than 50 mg daily) or interruptions (≤ 7 consecutive days) for related toxicities were permitted. No dose reductions of onartuzumab were allowed. Blinded treatment continued until disease progression, unacceptable toxicity, or death.

Assessments

During the study, tumor measurement and survival status were collected for evaluation of PFS, overall survival (OS), and objective response rate (ORR). Computed tomography (CT) scans were obtained at baseline and every two cycles (6 weeks) for the first six cycles and then every three cycles thereafter. Disease status per RECIST was assessed by the investigator. Patients were also monitored for adverse events (AEs), changes in laboratory values, and physical examination findings.

Tumor Tissue Assessments

Tumor tissue, archival permitted, was collected for confirmation of NSCLC and evaluation of MET expression by immunohistochemistry (IHC)

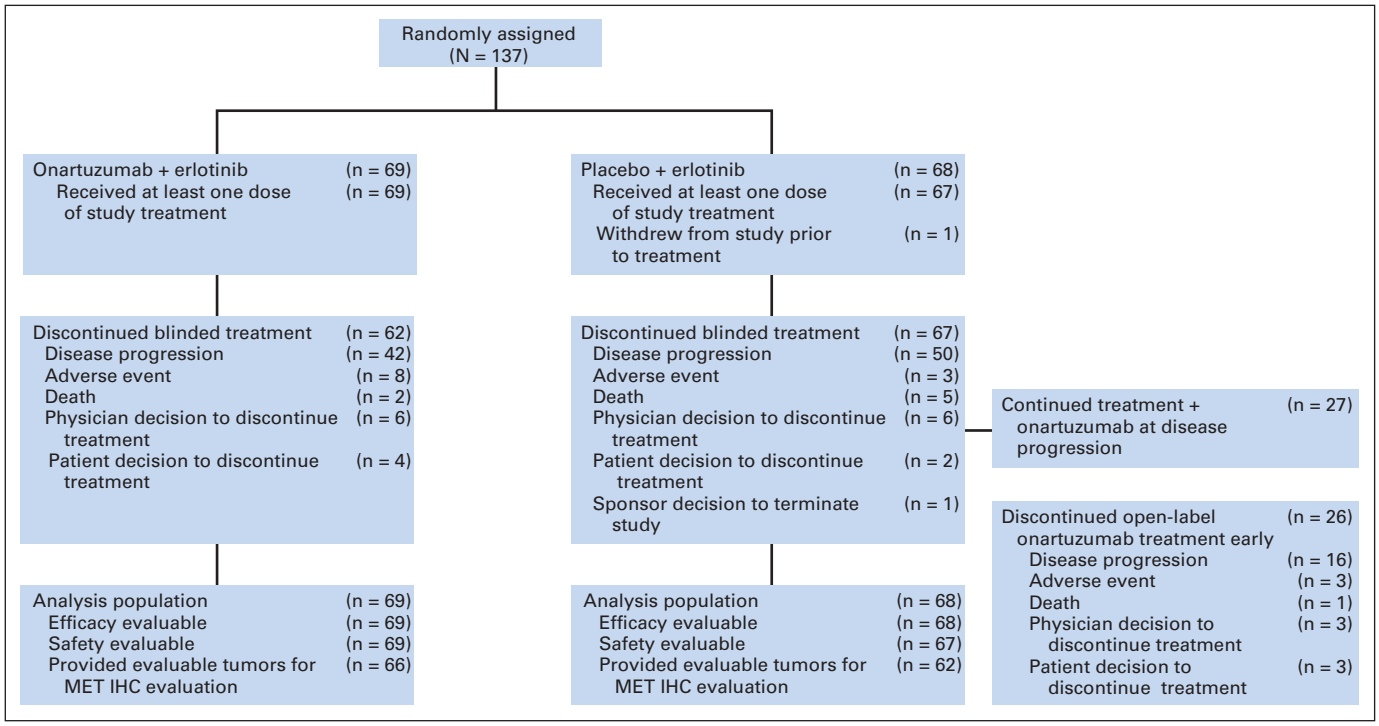

Fig 1. CONSORT diagram. IHC, immunohistochemistry.

using the CONFIRM SP44 anti-MET monoclonal antibody (Ventana Medical Systems, Tucson, AZ; cat No. 790-4430). A MET IHC scoring system was used to evaluate both staining intensity (negative, weak, moderate, or strong) and prevalence of these intensities in tumor cells.[17] The four MET diagnostic subgroups were defined as: 3+ (≥ 50% of tumor cells staining with strong intensity); 2+ (≥ 50% of tumor cells with moderate or higher staining but < 50% with strong intensity); 1+ (≥ 50% of tumor cells with weak or higher staining but < 50% with moderate or higher intensity); or 0 (no staining or < 50% of tumor cells with any intensity). MET positivity was defined as a score of 2+ or 3+. MET status was determined centrally after random assignment and before unblinding.

Statistical Analysis

The coprimary end points were PFS in the intent-to-treat (ITT) and MET-positive populations, defined as the time from random assignment to the first occurrence of disease progression (according to RECIST 1.0) or death resulting from any cause within 30 days of the last treatment or the latest CT assessment (censored). It was anticipated that 50% of enrolled patients would have MET-positive tumors. The study was to accrue 120 patients to provide 84 PFS events overall, with 42 in the MET-positive population. For patients with MET-positive tumors, the median PFS in the control arm was expected to be 3.3 months, and the desired median PFS in the onartuzumab plus erlotinib arm was 5.5

Table 1. Patient Demographic and Clinical Characteristics

	ITT				MET Negative				MET Positive			
	Placebo Plus Erlotinib (n = 68)		Onartuzumab Plus Erlotinib (n = 69)		Placebo Plus Erlotinib (n = 31)		Onartuzumab Plus Erlotinib (n = 31)		Placebo Plus Erlotinib (n = 31)		Onartuzumab Plus Erlotinib (n = 35)	
Characteristic	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Age, years												
Median	63		64		61		63		64		66	
Range	42-83		30-83		42-83		45-82		44-82		30-83	
Sex*												
Male	42	62	40	58	17	55	20	65	20	65	18	51
Female	26	38	29	42	14	45	11	35	11	35	17	49
Race*												
White	61	90	61	88	28	90	27	87	28	90	32	91
Black or African American	5	7	4	6	3	10	3	10	1	3	1	3
Asian	1	1	2	3	0	0	0	0	1	3	1	3
Other	0	0	1	1	0	0	0	0	0	0	1	3
Not available	1	1	1	1	0	0	1	3	1	3	0	0
ECOG PS*												
0	21	31	22	32	9	29	8	26	10	32	13	37
1	45	66	43	62	22	71	20	65	19	61	21	60
2	2	3	4	6	0	0	3	10	2	6	1	3
Histology*												
Adenocarcinoma	41	60	40	58	17	55	12	39	21	68	26	74
Squamous cell	20	29	20	29	12	39	14	45	5	16	5	14
Large cell	3	4	6	9	1	3	4	13	2	6	2	6
Bronchioloalveolar	1	1	0	0	0	0	0	0	1	3	0	0
Other	3	4	3	4	1	3	1	3	2	6	2	6
Smoking history*												
Current/former	60	88	59	86	30	97	29	93	25	81	28	80
Never-smoker†	8	12	10	14	1	3	2	7	6	19	7	20
Line of therapy*												
Second	46	68	46	67	20	65	21	68	22	71	22	63
Third	22	32	23	33	11	35	10	32	9	29	13	37
MET IHC status*												
Positive	31	46	35	51	0	0	0	0	31	100	35	100
Negative	31	46	31	45	31	100	31	100	0	0	0	0
Unknown	6	9	3	4	0	0	0	0	0	0	0	0
KRAS mutation*												
Wild type	43	63	43	62	21	68	19	61	20	65	24	69
Mutant	13	19	13	19	7	23	6	19	6	19	7	20
Unknown	12	18	13	19	3	10	6	19	5	16	4	11
EGFR mutation*												
Wild type	50	74	49	71	24	77	25	81	24	77	24	69
Mutant	6	9	7	10	4	13	0	0	2	7	7	20
Unknown	12	18	13	19	3	10	6	19	5	16	4	11

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; IHC, immunohistochemistry; ITT, intent to treat.
*Because of rounding, some percentages do not sum to 100.
†Never-smokers defined as those who had never smoked or smoked < 100 cigarettes in lifetime.

months, corresponding to a hazard ratio (HR) of 0.6. The type I (two-sided) and II error rates were set as 10% and 50%, respectively. Additional objectives included assessment of OS, ORR, safety, and tolerability. All outcomes were assessed in the ITT and MET diagnostic groups. Median PFS and OS were estimated from Kaplan-Meier curves. Stratified log-rank test was used to test the difference in PFS and OS between treatment arms. Estimated HRs and 95% CIs were determined using a stratified Cox regression model. All authors reviewed the data and manuscript and vouch for the accuracy, completeness, and fidelity of this report to the study protocol.

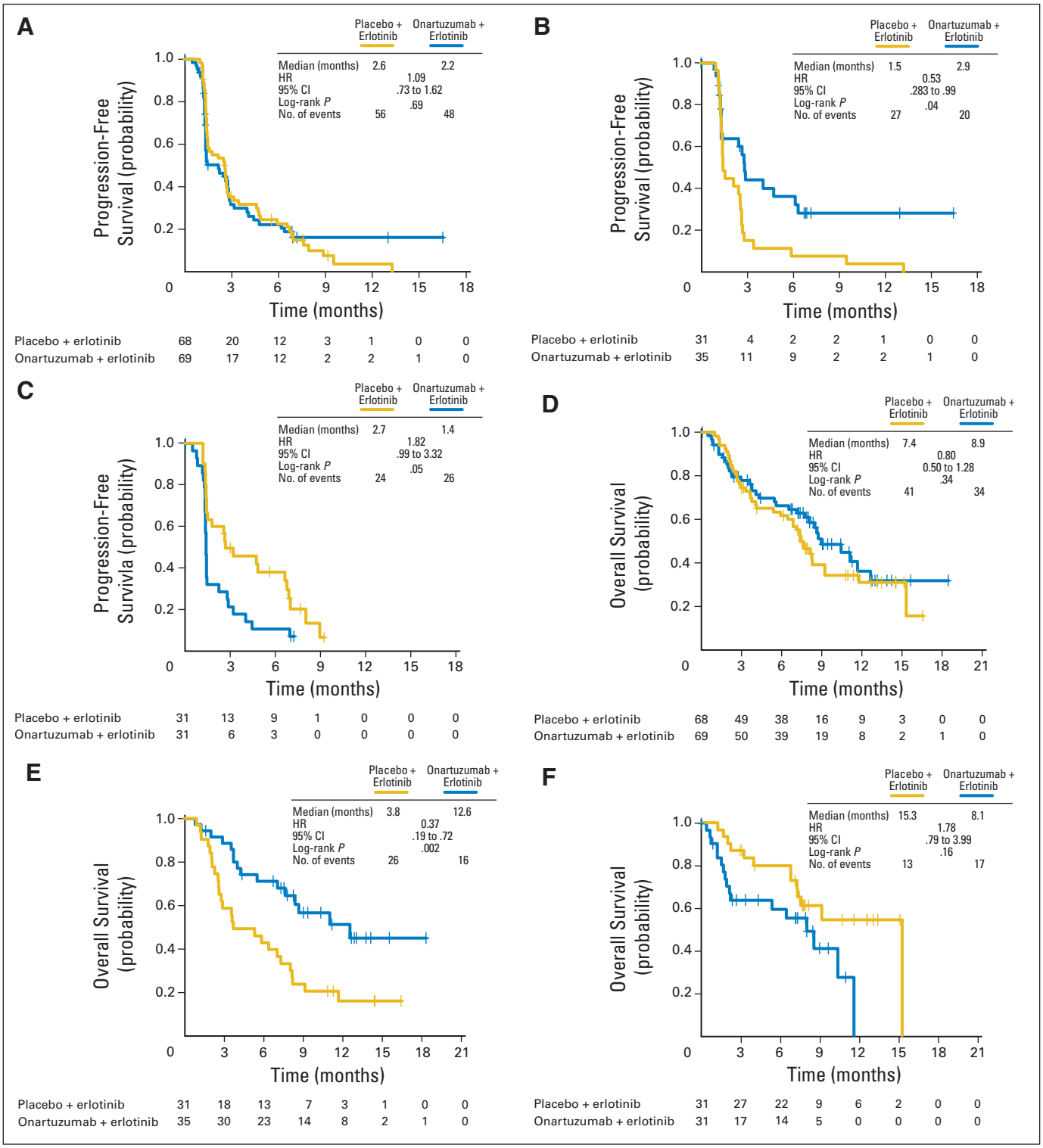

Fig 2. Kaplan-Meier estimates of (A, B, C) progression-free and (D, E, F) overall survival outcomes in (A, D) intent-to-treat, (B, E) MET-positive, and (C, F) MET-negative populations. HR, hazard ratio.

RESULTS

Patients

From March 2009 to August 2010, 137 patients were randomly assigned, 69 to onartuzumab plus erlotinib and 68 to placebo plus erlotinib. One hundred thirty-six patients received at least one dose of study treatment (one patient assigned to placebo was removed for pain before receiving any study drug; Fig 1). Median patient follow-up was 10.4 months (range, .1 to 18.4 months).

Baseline characteristics were well balanced between the treatment groups in the ITT population and within the MET diagnostic subgroups, with the exception of *EGFR* mutation status (Table 1). Of note, SCC was more prevalent in MET-negative versus MET-positive patients (42% *v* 15%, respectively), whereas never-smokers were less

A

Baseline Risk Factor	Placebo + Erlotinib n	Placebo + Erlotinib Median (months)	Onartuzumab + Erlotinib n	Onartuzumab + Erlotinib Median (months)	Hazard Ratio
All patients	31	3.8	35	12.6	0.382
MET Dx IHC scores					
2+	25	6.5	26		0.401
3+	6	2.9	9	11.1	0.046
Histology category					
Nonsquamous cell	26	3.7	30	11.1	0.470
Squamous cell	5	6.5	5		0.000
Tobacco history					
< 100 cigarettes	6	6.5	7		0.763
≥ 100 cigarettes	25	3.7	28	12.6	0.298
ECOG performance status					
0/1	29	3.8	34	11.1	0.411
≥ 2	2	3.9	1		0.000
EGFR mutation					
Wild type	24	4.8	24	8.7	0.462
Mutant	2		7		4.81E7
KRAS mutation					
Wild type	20	6.8	24		0.344
Mutant	6	2.8	7	8.1	1.217
Sex					
Female	11	9.2	17	11.1	0.969
Male	20	2.8	18		0.174
Line of therapy					
Second	22	4.8	22	12.6	0.395
Third	9	3.7	13	8.7	0.327
Age, years					
< 65	16	3.7	17	8.7	0.440
≥ 65	15	5.9	18	12.6	0.333

B

Baseline risk factor	Placebo + Erlotinib n	Placebo + Erlotinib Median (months)	Onartuzumab + Erlotinib n	Onartuzumab + Erlotinib Median (months)	Hazard Ratio
All subjects	68	7.4	69	8.9	0.802
Histology category					
Nonsquamous cell	48	7.6	49	10.4	0.795
Squamous cell	20	7.1	20	8.6	0.814
Tobacco history					
< 100 cigarettes	8	8.3	10		0.759
≥ 100 cigarettes	60	7.4	59	8.9	0.792
ECOG performance status					
0/1	66	7.6	65	8.9	0.785
≥ 2	2	3.9	4	3.4	0.852
EGFR mutation					
Wild type	50	7.4	49	8.5	0.922
Mutant	6		7		2.194
KRAS mutation					
Wild type	43	7.7	43	10.4	0.783
Mutant	13		13	8.5	1.633
Sex					
Female	26	15.3	29	11.1	1.631
Male	42	6.5	40	8.6	0.548
Line of therapy					
2nd	46	7.6	46	10.4	0.880
3rd	22	7.4	23	8.6	0.673
Age, years					
< 65	36	8.2	35	8.7	0.974
≥ 65	32	7.4	34	11.1	0.635

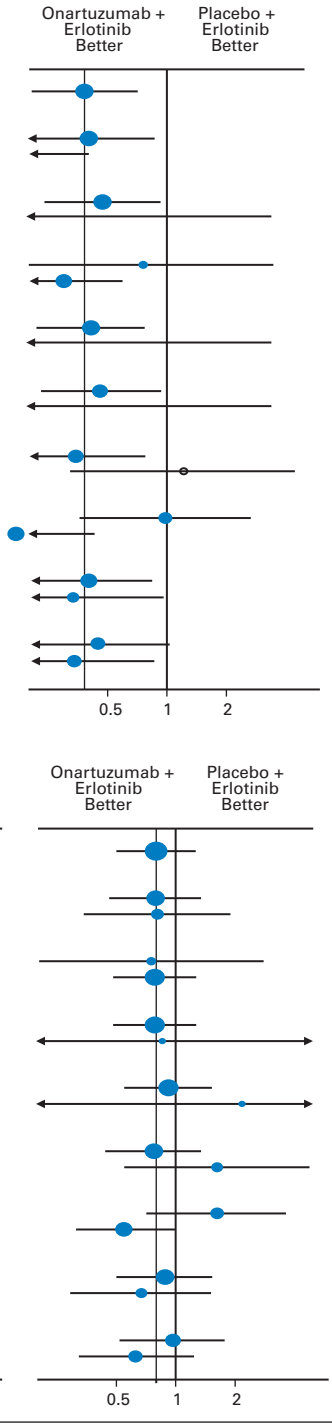

Fig 3. Forest plots of overall survival outcomes in (A) MET-positive and (B) intent-to-treat populations. Dx, diagnosis; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; IHC, immunohistochemistry.

prevalent in MET-negative versus MET-positive patients (5% *v* 20%, respectively).

All patients enrolled had tissue submitted for analysis. MET status was determined in 128 patients (93%; Fig 1); 66 (52%) were MET positive. Mutation testing was performed in 112 patients (88%): 26 (23%) harbored a *KRAS* mutation, and 13 (12%) had a nonoverlapping *EGFR* mutation.

Twenty-seven patients (12 MET positive, 13 MET negative, and two MET with status unevaluable) randomly assigned to placebo had onartuzumab added to continued treatment with erlotinib at the time of disease progression (Fig 1).

Efficacy

PFS. PFS did not differ between treatment arms (median, 2.6 months for placebo plus erlotinib *v* 2.2 months for onartuzumab plus erlotinib; HR, 1.09; $P = .69$; Fig 2A) in the ITT population. However, the addition of onartuzumab treatment resulted in a 47% reduction in the risk of disease progression in the MET-positive subgroup, which was statistically significant (median, 1.5 *v* 2.9 months; HR: 0.53; $P = .04$; Fig 2B). MET-negative patients experienced progression earlier with onartuzumab versus placebo (median, 2.7 *v* 1.4 months; HR, 1.82; $P = .05$; Fig 2C).

OS. OS did not differ significantly between treatment arms (median, 7.4 months for placebo plus erlotinib *v* 8.9 months for onartuzumab plus erlotinib; HR, 0.80; $P = .34$; Fig 2D) in the ITT population. However, the addition of onartuzumab nearly tripled survival compared with placebo in the MET-positive population (median, 3.8 *v* 12.6 months, HR, 0.37; $P = .002$; Fig 2E). In the MET-negative population, those randomly assigned to onartuzumab had shorter survival versus those receiving placebo (median, 15.3 *v* 8.1 months; HR, 1.78; $P = .16$; Fig 2F).

ORRs. The ORRs were not significantly different between the two treatment arms in all three specified populations (ITT: 4.4% for placebo plus erlotinib *v* 5.8% for onartuzumab plus erlotinib; MET positive: 3.2% *v* 8.6%; MET negative: 6.5% *v* 3.2%; Appendix Table A1, online only).

Exploratory and sensitivity analyses. The impact of demographic and baseline characteristics, including histology, smoking history, sex, baseline ECOG PS, line of therapy, age, MET IHC score (0, 1+, 2+, or 3+), *EGFR* mutation status, and *KRAS* mutation status, on PFS and OS was examined using exploratory analyses. Analysis of the MET-positive subgroup for both PFS (data not shown) and OS (Fig 3A) showed that the treatment effect of onartuzumab plus erlotinib was similar across most of the

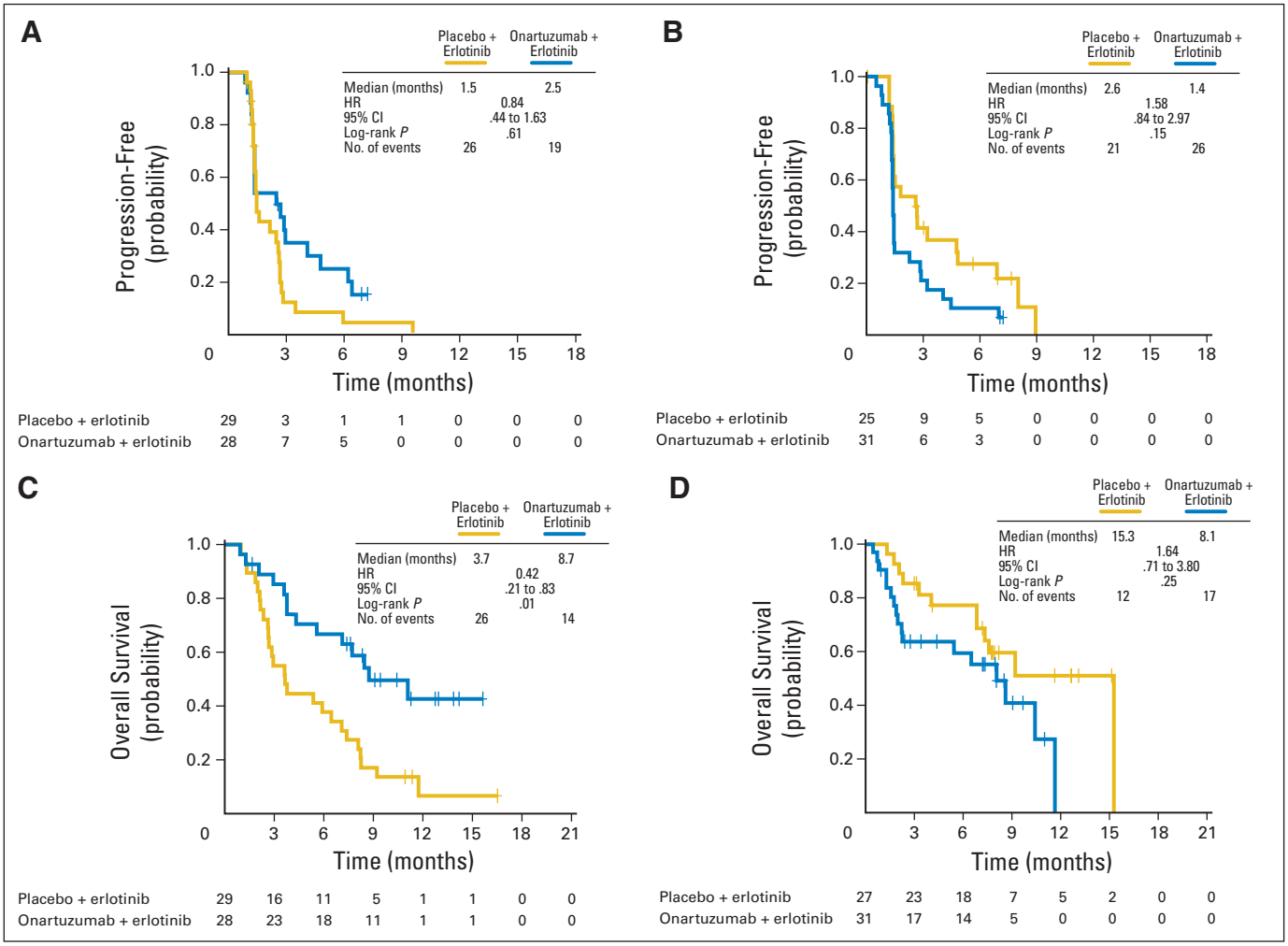

Fig 4. Kaplan-Meier estimates of (A, B) progression-free and (C, D) overall survival in (A, C) MET-positive and (B, D) MET-negative populations, excluding known *EGFR* mutation–positive patients. HR, hazard ratio.

Table 2. Most Commonly Reported AEs

	ITT				MET Negative				MET Positive			
	Placebo Plus Erlotinib (n = 67)		Onartuzumab Plus Erlotinib (n = 69)		Placebo Plus Erlotinib (n = 31)		Onartuzumab Plus Erlotinib (n = 31)		Placebo Plus Erlotinib (n = 31)		Onartuzumab Plus Erlotinib (n = 35)	
AE	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Rash												
All grades	41	61.2	42	60.9	18	58.1	18	58.1	19	61.3	22	62.9
Grade 3	2	3.0	6	8.7	1	3.2	2	6.5	1	3.2	4	11.4
Grade 4	0	0.0	1	1.4	0	0.0	0	0.0	0	0.0	1	2.9
Diarrhea												
All grades	35	52.2	28	40.6	17	54.8	8	25.8	13	41.9	18	51.4
Grade 3	3	4.5	4	5.8	1	3.2	1	3.2	2	6.5	3	8.6
Grade 4	0	0.0	1	1.4	0	0.0	0	0.0	0	0.0	1	2.9
Fatigue*												
All grades	24	35.8	22	31.9	11	35.5	6	19.4	12	38.7	16	45.7
Grade 3	2	3.0	6	8.7	1	3.2	2	6.5	1	3.2	4	11.4
Nausea*												
All grades	21	31.3	22	31.9	10	32.3	9	29.0	9	29.0	13	37.1
Grade 3	2	3.0	0	0.0	1	3.2	0	0.0	1	3.2	0	0.0
Decreased appetite*												
All grades	16	23.9	14	20.3	5	16.1	4	12.9	10	32.3	10	28.6
Grade 3	1	1.5	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Dyspnea*												
All grades	16	23.9	13	18.8	6	19.4	4	12.9	8	25.8	8	22.9
Grade 3	3	4.5	3	4.3	1	3.2	1	3.2	2	6.5	1	2.9
Cough†												
All grades	13	19.4	13	18.8	7	22.6	4	12.9	6	19.4	7	20.0
Vomiting†												
All grades	13	19.4	4	5.8	7	22.6	2	6.5	5	16.1	2	5.7
Anemia*												
All grades	10	14.9	10	14.5	3	9.7	4	12.9	6	19.4	6	17.1
Grade 3	1	1.5	0	0.0	1	3.2	0	0.0	0	0.0	0	0.0
Dermatitis acneiform†												
All grades	10	14.9	10	14.5	6	19.4	5	16.1	3	9.7	5	14.3
Dry skin†												
All grades	10	14.9	8	11.6	5	16.1	2	6.5	5	16.1	5	14.3
Pain*												
All grades	8	11.9	4	5.8	6	19.4	0	0.0	1	3.2	4	11.4
Grade 3	3	4.5	1	1.4	3	9.7	0	0.0	0	0.0	1	2.9
Pruritus†												
All grades	8	11.9	4	5.8	3	9.7	3	9.7	5	16.1	0	0.0
Anxiety												
All grades	7	10.4	6	8.7	2	6.5	2	6.5	4	12.9	3	8.6
Back pain*												
All grades	7	10.4	7	10.1	2	6.5	5	16.1	5	16.1	2	5.7
Grade 3	2	3.0	1	1.4	1	3.2	1	3.2	1	3.2	0	0.0
Chest pain†												
All grades	7	10.4	2	2.9	5	16.1	1	3.2	2	6.5	1	2.9
Pyrexia*												
All grades	6	9.0	10	14.5	2	6.5	5	16.1	3	9.7	5	14.3
Grade 3	0	0.0	1	1.4	0	0.0	0	0.0	0	0.0	1	2.9
Asthenia*												
All grades	6	9.0	9	13.0	3	9.7	4	12.9	2	6.5	5	14.3
Grade 3	0	0.0	3	4.3	0	0.0	0	0.0	0	0.0	3	8.6
Urinary tract infection†												
All grades	6	9.0	4	5.8	4	12.9	2	6.5	2	6.5	2	5.7
Insomnia*												
All grades	5	7.5	8	11.6	2	6.5	3	9.7	3	9.7	5	14.3
Grade 3	0	0.0	1	1.4	0	0.0	0	0.0	0	0.0	1	2.9

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Table 2. Most Commonly Reported AEs (continued)

AE	ITT				MET Negative				MET Positive			
	Placebo Plus Erlotinib (n = 67)		Onartuzumab Plus Erlotinib (n = 69)		Placebo Plus Erlotinib (n = 31)		Onartuzumab Plus Erlotinib (n = 31)		Placebo Plus Erlotinib (n = 31)		Onartuzumab Plus Erlotinib (n = 35)	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Peripheral edema*												
All grades	5	7.5	16	23.2	3	9.7	7	22.6	2	6.5	8	22.9
Grade 3	0	0.0	2	2.9	0	0.0	0	0.0	0	0.0	2	5.7
Pneumonia‡												
All grades	3	4.5	5	7.2	2	6.5	4	12.9	1	3.2	1	2.9
Grade 3	2	3.0	4	5.8	1	3.2	3	9.7	1	3.2	1	2.9
Grade 5	0	0.0	1	1.4	0	0.0	1	3.2	0	0.0	0	0.0

NOTE. Table shows AEs occurring at frequency of ≥ 10%, ordered by frequency in placebo plus erlotinib (ITT) group.
Abbreviations: AE, adverse event; ITT, intent to treat.
*No grade 4 or 5 AEs.
†No grade 3 to 5 AEs.
‡No grade 4 AEs.

subgroups. The statistical significance of the treatment effect on OS was maintained in the MET-positive subgroup after adjusting for sex in the Cox regression model (OS: HR, 0.35; $P = .0013$). Similarly, results for most subgroups of the ITT population were consistent with the OS primary analysis (Fig 3B).

PFS and OS analyses, removing known *EGFR* mutation–positive patients, were performed to address the imbalance in both MET-positive and MET-negative populations. The overall interpretation of the results was unchanged (Fig 4).

Prognosis, assessed in patients assigned to placebo plus erlotinib, was worse in MET-positive versus MET-negative patients for both PFS (HR, 1.71; $P = .06$) and OS (HR, 2.61; $P = .004$; Appendix Fig A1, online only).

For patients originally randomly assigned to receive placebo who chose to receive onartuzumab added to continued erlotinib treatment, the majority experienced events at or before the next subsequent tumor assessment. There was no difference in PFS for these patients based on their tumor MET status (median, 1.3 months for MET positive *v* 1.5 months for MET negative).

IHC evaluation. To determine the appropriateness of the IHC cut point of ≥ 50% of tumor cells staining moderately or strongly, outcome analyses were performed in populations with ≥ 10% or ≥ 90% of tumor cells staining at moderate to strong intensity. Compared with the 50% cutoff, treatment benefit in both PFS and OS was diminished using the less stringent cutoff of ≥ 10% (PFS: HR, 0.78; $P = .317$; OS: HR, 0.52; $P = .023$) and was similar using the more stringent cutoff of ≥ 90% (PFS: HR, 0.47; $P = .028$; OS: HR, 0.3; $P = .001$). To assess the adequacy of the intensity cut point, PFS and OS were assessed by each of the four MET IHC scores (3+, 2+, 1+, 0). The benefit of adding onartuzumab was maintained in both 2+ and 3+, and the detriment was observed in both 0 and 1+ (Appendix Fig A2, online only).

Safety

During the blinded stage, 129 patients (94.2%) discontinued onartuzumab/placebo treatment: 62 patients (89.9%) in the onartuzumab plus erlotinib arm and 67 patients (98.5%) in the placebo plus erlotinib arm. The rate of discontinuation because of AEs was slightly higher in the onartuzumab plus erlotinib arm (11.6%) compared with the placebo plus erlotinib arm (4.4%). Within the onartuzumab plus erlotinib arm, this rate was higher in MET-positive patients (22.9%) than in MET-negative patients (6.5%). The most common reason for treatment discontinuation was disease progression (onartuzumab plus erlotinib, 42 patients [60.9%]; placebo plus erlotinib, 50 patients [73.5%]; Fig 1).

The most common AEs (all grades) in the safety-evaluable population (n = 136) were rash (60.9% *v* 61.2%), diarrhea (40.6% *v* 52.2%), fatigue (31.9% *v* 35.8%), and nausea (31.9% *v* 31.3%) for erlotinib plus onartuzumab versus erlotinib plus placebo, respectively (Table 2). AEs more frequently observed with onartuzumab were peripheral edema, pyrexia, asthenia, insomnia, and pneumonia. Most were grade 1 or 2 in severity. For patients originally randomly assigned to receive placebo who chose to receive onartuzumab added to continued erlotinib, the subsequent AE profile was similar.

Grade ≥ 3 AEs were more frequent in patients receiving onartuzumab, regardless of MET status; however, no specific pattern was identified (Table 2). In the ITT population, serious AEs were reported in 42.0% of patients randomly assigned to onartuzumab and in 32.8% of patients randomly assigned to placebo. A majority of serious AEs were grade 3 in severity and indistinguishable from the underlying disease (pneumonia, dyspnea, hemoptysis, pulmonary embolism, respiratory distress) or from a potential erlotinib effect (interstitial lung disease and rash). There were four AEs, primarily NSCLC associated, that resulted in death in each treatment arm (Appendix Table A2, online only).

DISCUSSION

Patients with MET-positive NSCLC seemed to benefit from the combination of onartuzumab and erlotinib. Patients randomly assigned to placebo plus erlotinib performed similarly to historic controls.[18,19] Consistent with previous reports, MET expression was associated with worse prognosis. The addition of onartuzumab in MET-positive patients resulted in median PFS and median OS results similar to those observed in MET-negative patients receiving erlotinib alone. This

suggests that the addition of onartuzumab to erlotinib in MET-positive patients abrogated the negative prognostic effect of MET expression. Clinical benefit from the addition of onartuzumab to erlotinib was observed in nearly all analyzed MET-positive subgroups. Furthermore, the degree of benefit seemed to be proportional to the relative intensity of MET expression, supporting the criteria used to define MET-positive disease.

In the MET-positive population, the ORRs were low (confined mostly to those harboring *EGFR* mutations), and there was no difference between treatment groups. Interestingly, the magnitude of gain in median OS in the onartuzumab versus placebo treatment arms was much greater than that in median PFS (median OS gain of 8.8 months *v* 1.4 months for mPFS).

Low response rates, coupled with a disproportionate PFS to OS improvement, suggest that blockade of MET signaling in MET-positive disease may be acting through a mechanism distinctly different from other receptor tyrosine kinase inhibitors. MET has been implicated in the spread of metastases, and therefore, the therapeutic benefit of onartuzumab may derive from inhibition of cancer-cell migration and invasion rather than direct inhibition of existing tumor growth.

Analyses of pharmacokinetics, safety, AEs, patterns of disease progression, and cause of death did not explain the worse outcome observed in the MET-negative population treated with onartuzumab plus erlotinib. The pharmacokinetics of both agents was not altered (data not shown), nor were there obvious safety signals to explain the findings. MET, like other proteins, has been postulated to possess both tumor-suppressor and oncogenic properties.[20] If such were the case in NSCLC, MET might be acting as a tumor suppressor in MET-negative disease and as an oncogene in MET-positive disease. Alternatively, dual inhibition of EGFR and MET may have different consequences in tumors with lower versus higher MET expression, suggesting this phenomenon may only be seen against a background of EGFR inhibition. The worse outcomes observed in the onartuzumab-treated MET-negative NSCLC population may be an effect unique to patients with NSCLC. Other cancers for which MET has been described as a negative prognostic factor, such as gastric cancer,[21] exhibit lower levels of MET expression as measured by IHC using the SP44 antibody (unpublished data). The definition of MET positivity used to predict for benefit from onartuzumab may differ for cancers other than NSCLC. Future studies evaluating outcomes in patients with MET-negative tumors treated with onartuzumab will require close observation for similar results.

Despite the supporting sensitivity analyses regarding the efficacy outcomes and diagnostic cut points, there are limitations to this study, including small sample size, which could have been affected by both known and unknown confounders, and no prospective stratification on MET status (definition of MET positivity was determined before unblinding but after random assignment). Nonetheless, the results are encouraging given the magnitude of benefit observed in more than one half of the study patients with NSCLC. Without a diagnostic hypothesis, the results observed in the ITT population would have likely led to a decision to discontinue onartuzumab development. Combined with the observations in the MET-negative subgroup, these results highlight the importance of diagnostic development in clinical oncology studies. The activity observed in this study, combined with the prevalence of MET and its association with poor prognosis in other indications, provides a rationale for further clinical evaluation in NSCLC and other indications. A randomized phase III study evaluating erlotinib with or without onartuzumab in patients with MET-positive NSCLC is under way.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Table A1. ORRs in Randomly Assigned Patients

	ITT (n = 137)				MET Positive (n = 66)				MET Negative (n = 62)			
	Placebo Plus Erlotinib (n = 68)		Onartuzumab Plus Erlotinib (n = 69)		Placebo Plus Erlotinib (n = 31)		Onartuzumab Plus Erlotinib (n =35)		Placebo Plus Erlotinib (n = 31)		Onartuzumab Plus Erlotinib (n = 31)	
ORR	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
No. of patients experiencing OR	3	4.4*	4	5.8*	1	3.2	3	8.6	2	6.5	1	3.2
95% CI	1.2 to 11.7		2.0 to 13.9		0.2 to 16.1		2.4 to 21.5		1.2 to 20.0		0.2 to 16.1	
Difference in ORR	1.4				5.3				−3.2			
95% CI	−6.0 to 8.7				−5.8 to 16.5				−13.9 to 7.4			
Stratified *P*	.7101				.3671				.6726			

Abbreviations: ITT, intent to treat; OR, objective response; ORR, objective response rate.
*Six of these patients had known *EGFR* mutation–positive tumors.

Table A2. Summary of Safety Data

AE	All Patients				MET Negative				MET Positive			
	Placebo Plus Erlotinib (n = 67)		Onartuzumab Plus Erlotinib (n = 69)		Placebo Plus Erlotinib (n = 31)		Onartuzumab Plus Erlotinib (n = 31)		Placebo Plus Erlotinib (n = 31)		Onartuzumab Plus Erlotinib (n = 35)	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Any adverse event	67	100.0	68	98.6	31	100.0	31	100.0	31	100.0	35	100.0
Grade ≥ 3	32	47.8	38	55.1	13	41.9	17	54.8	17	54.8	20	57.1
Grade 3	25	37.3	26	37.7	12	38.7	10	32.3	11	35.5	15	42.9
Grade 4	4	4.5	8	11.6	1	3.2	4	12.9	2	6.5	4	11.4
Serious AE	22	32.8	29	42.0	9	29.0	13	41.9	11	35.5	15	42.9
AE leading to onartuzumab/ placebo discontinuation	2	3.0	10	14.5	0	0.0	2	6.5	2	6.5	8	22.9
AE leading to death	4	6.0	4	5.8	0	0.0	3*	9.7	4†	12.9	1‡	2.9

Abbreviation: AE, adverse event.
*AEs reported: hemoptysis, pulmonary embolism, and pneumonia.
†AEs reported: interstitial lung disease, respiratory distress (n = 2), and unspecified cause (n = 1).
‡AE reported: aspiration pneumonia.

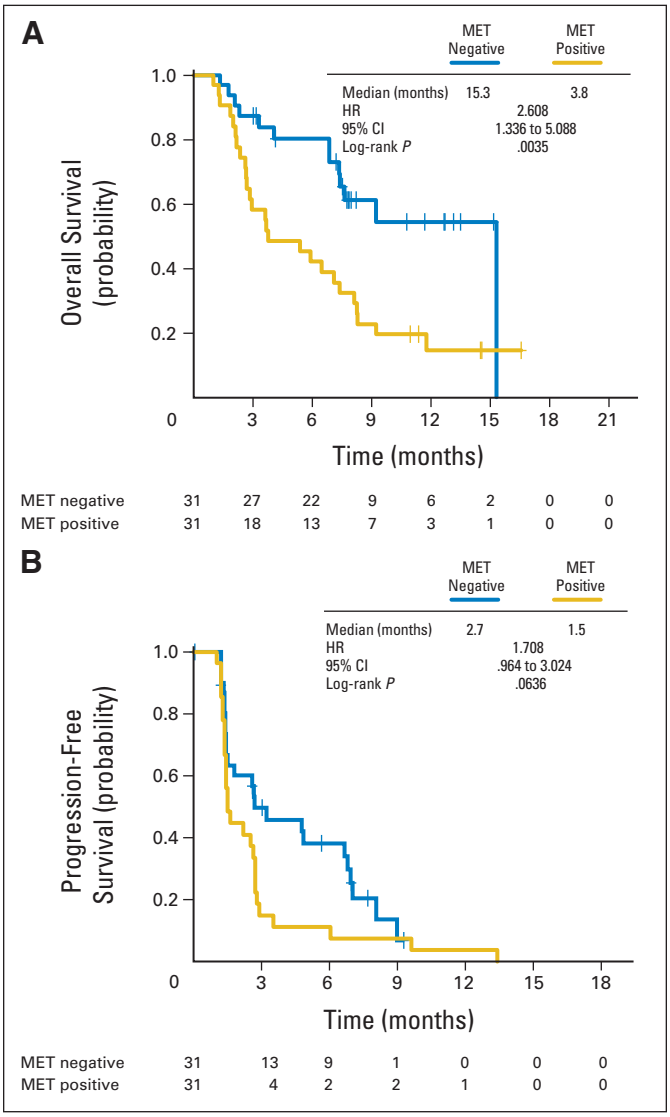

Fig A1. (A) Overall and (B) progression-free survival by MET status in patients receiving erlotinib plus placebo. HR, hazard ratio.

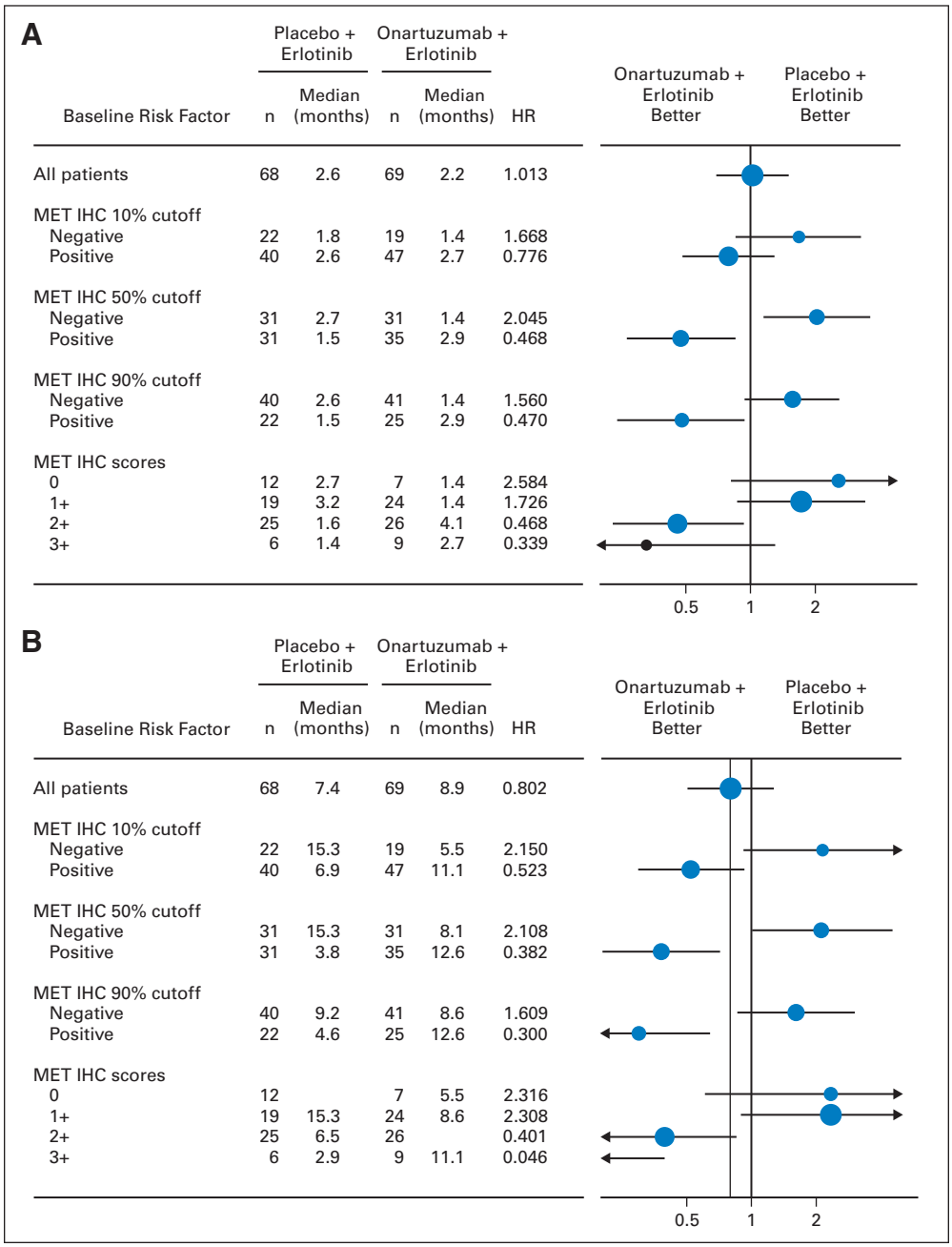

Fig A2. Forest plots of (A) progression-free and (B) overall survival by MET immunohistochemistry (IHC) cutoff (≥ 10%, ≥ 50%, and ≥ 90%) and MET IHC score (0, 1+, 2+, and 3+). HR, hazard ratio.