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ORIGINAL REPORT

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ABSTRACT

Purpose
Tivantinib, a MET receptor tyrosine kinase inhibitor, demonstrated increased anticancer activity in preclinical and early clinical studies when combined with erlotinib. Our study aimed to confirm efficacy and safety of the combination in previously treated patients with non–small-cell lung cancer (NSCLC).

Patients and Methods
Patients with advanced nonsquamous NSCLC previously treated with one to two systemic regimens, including a platinum doublet, were randomly assigned at a 1:1 ratio to receive erlotinib 150 mg daily plus oral tivantinib 360 mg twice daily (E + T) or erlotinib plus placebo (E + P) until disease progression. Tumor specimens were evaluated for *EGFR* and *KRAS* mutations, MET expression, and *MET* gene amplification. The primary end point was overall survival (OS). Secondary and exploratory objectives included progression-free survival (PFS), OS in molecular subgroups, and safety.

Results
The study enrolled 1,048 patients and was discontinued for futility at the interim analysis. OS did not improve with E + T versus E + P (median OS, 8.5 *v* 7.8 months, respectively; hazard ratio [HR], 0.98; 95% CI, 0.84 to 1.15; $P = .81$), even though PFS increased (median PFS, 3.6 *v* 1.9 months; HR, 0.74; 95% CI, 0.62 to 0.89; $P < .001$). Exploratory subgroup analyses suggested OS improvement in patients with high MET expression (HR, 0.70; 95% CI, 0.49 to 1.01). Most common adverse events occurring with E + T versus E + P were rash (33.1% *v* 37.3%, respectively), diarrhea (34.6% *v* 41.0%), asthenia or fatigue (43.5% *v* 38.1%), and neutropenia (grade 3 to 4; 8.5% *v* 0.8%).

Conclusion
E + T was well tolerated and increased PFS but did not improve OS in the overall nonsquamous NSCLC population.

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INTRODUCTION

Lung cancer is a leading cause of cancer-related death, with approximately 1,825,000 new patient cases and 1,590,000 deaths worldwide in 2012.[1] Non–small-cell lung cancer (NSCLC) represents 85% of all lung cancers.[2] For patients with locally advanced or metastatic disease, systemic chemotherapy provides a modest but statistically significant improvement in survival.[3] In the last 15 years, clinical research efforts with targeted agents have endeavored to improve survival beyond cytotoxic chemotherapy.

Overexpression of the N-methyl-N′-nitrosoguanidine human osteosarcoma transforming gene (*MET*) or aberrant signaling of MET receptor tyrosine kinase occurs in lung cancer and other solid tumors. The involvement of MET in multiple signal transduction pathways affecting tumor-cell proliferation, mobilization, and angiogenesis

makes it an interesting potential target for cancer therapy.[4-6] Tivantinib (ARQ 197; ArQule, Woburn, MA; Daiichi-Sankyo, Tokyo, Japan) is an orally available selective small molecule that inhibits MET receptor tyrosine kinase with a novel ATP-independent binding mechanism, leading to inhibition of cell proliferation and induction of apoptosis in MET-expressing cancer cells.[7,8] Although epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors have shown higher therapeutic activity when *EGFR*-sensitizing mutations are detected,[9] the EGFR inhibitor erlotinib (Tarceva; Genentech, San Francisco, CA) has demonstrated efficacy in previously treated patients with advanced NSCLC.[10,11] Consequently, dual inhibition of MET and EGFR with the combination of tivantinib plus erlotinib was a rational approach to be explored in advanced NSCLC. A randomized phase II study of tivantinib plus erlotinib versus erlotinib alone in 167 patients with chemotherapy-pretreated, EGFR inhibitor–naive advanced NSCLC showed trends toward improved progression-free (PFS) and overall survival (OS) in the nonsquamous NSCLC subpopulation and improved PFS in the *EGFR* wild-type (WT) and *KRAS*-mutant subpopulations.[12] The objective of this phase III randomized, double-blind, placebo-controlled study (MARQUEE [ARQ 197 Plus Erlotinib Versus Placebo Plus Erlotinib for the Treatment of Non-Squamous, Non-Small-Cell Lung Cancer]) was to confirm the efficacy and safety of tivantinib plus erlotinib versus erlotinib plus placebo in previously treated patients with locally advanced or metastatic nonsquamous NSCLC.[13]

PATIENTS AND METHODS

Patients

Eligible patients were adults age ≥ 18 years with histologically or cytologically confirmed, locally advanced or metastatic (stage IIIb to IV) nonsquamous NSCLC with measurable disease according to RECIST (version 1.1),[14] Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, and adequate bone marrow, liver, and kidney functions. Patients had to have received one or two prior systemic anticancer regimens, including prior platinum-based chemotherapy, without prior exposure to EGFR inhibitors, tivantinib, or any other MET inhibitor. Archival or fresh tissue samples for biomarker analyses and *EGFR* mutation status were mandatory for all patients. Patients with clinically unstable brain metastases or history of cardiac disease, uncontrolled hypertension, or other active malignancies were excluded.

Study Design, Treatment, and Study Objectives

The study was conducted according to the Declaration of Helsinki and approved by appropriate independent ethics committees or institutional review boards at all sites. Patients provided written informed consent before study participation and consent for tissue collection for biomarker assessment. An independent data monitoring committee periodically reviewed safety data and the interim analysis results.

After screening, patients were randomly assigned at a ratio of 1:1 to receive oral erlotinib 150 mg once daily plus oral tivantinib 360 mg twice daily (E + T) or oral erlotinib 150 mg once daily plus matching placebo (E + P). Patients were stratified by number of prior therapies (one *v* two), sex (male *v* female), smoking history (never *v* ever), and *EGFR* and *KRAS* mutation status (mutant *v* WT or unknown). Treatment continued until unacceptable toxicity, disease progression, or another discontinuation criterion was met. Tivantinib or erlotinib dose delays of ≤ 14 days were permitted for grade ≥ 3 nonhematologic toxicities until resolution to grade 1 or baseline, and treatment was reintroduced at a reduced dosage of one or both drugs depending on the toxicity. For hematologic toxicities of grade ≥ 3 or platelet counts $< 50 \times 10^9$/L, tivantinib was withheld until absolute neutrophil and platelet counts returned to baseline ($\geq 1.5 \times 10^9$/L and $\geq 100 \times 10^9$/L, respectively).

The primary objective was OS in the intent-to-treat (ITT) population. Secondary objectives included OS in the *EGFR* WT subgroup, PFS in the ITT population, and safety. Exploratory analyses were performed for other predefined subgroups and efficacy parameters. Tumor response was assessed by investigators according to RECIST (version 1.1).[14]

Statistical Analysis

The study hypothesis was that E + T would improve OS relative to E + P in the ITT population. For 90% power to detect a hazard ratio (HR) of 0.75 at a two-sided significance level of 0.01, 735 events were required. Assuming 18 months of enrollment, 12 additional months of follow-up, and a 9% rate of loss to follow-up, the target enrollment was 988 patients.

An interim analysis was planned after approximately 50% of planned events had occurred to allow early stopping for efficacy or futility. Stopping boundaries were determined using the Lan-DeMets family with O'Brien-Fleming parameters,[15] while specifying nonbinding futility stopping boundaries. At the first interim efficacy analysis with 485 events, the one-sided *P* value stopping boundaries were .00055 for efficacy stopping and .0743 for futility stopping.

OS and PFS were compared using stratified log-rank tests adjusting for number of prior therapies, sex, and smoking history. Kaplan-Meier estimates of the medians and corresponding 95% CIs were determined. An unstratified Cox proportional hazards regression model was performed to obtain the point estimate of the HR and 95% CI. Secondary efficacy end points were similarly analyzed. Safety was assessed by the investigator based on the incidence and severity of treatment-emergent adverse events (TEAEs) and their relationship to either treatment arm.

Molecular Analyses

Biomarkers in archival or fresh tumor samples were analyzed in the following order of priority: *EGFR* mutation, MET expression (determined by immunohistochemistry), *KRAS* mutation, and *MET* gene amplification when sufficient tumor tissue was available. Mutations in *EGFR* and *KRAS* were determined by polymerase chain reaction analysis using the Qiagen Rotor-Gene (Qiagen, Hilden, Germany) at central laboratories (Covance, Indianapolis, IN; Geneva, Switzerland); existing mutation results were used if they were from accredited local laboratories. MET expression was analyzed at a central laboratory (LabCorp, Research Triangle Park, NC) using the SP44 rabbit monoclonal antibody (Ventana Medical Systems, Tucson, AZ). MET expression was defined as high if membranous staining intensity was ≥ 2 in ≥ 50% of tumor cells. On the basis of limited MET epitope stability, MET analyses by immunohistochemistry must have been performed within 90 days of sectioning to be considered valid. *MET* gene copy number and chromosome 7 copy number were determined by fluorescence in situ hybridization using probes (LSI D7S486) for *MET* (7q31) and *CEP7* (Abbott Molecular, Des Plaines, IL).

RESULTS

Patient Population and Disposition

Between January 2011 and July 2012 in Europe and Russia, the United States, Latin America, Canada, and Australia, 1,624 patients were screened, 576 failed to meet inclusion or exclusion criteria, and 1,048 were randomly assigned (E + T, n = 526; E + P, n = 522; Fig 1). Of these patients, 976 (93%) subsequently discontinued study treatment, and two were lost to follow-up. The most common reason for treatment discontinuation was progressive disease (E + T, n = 295; E + P, n = 350). Patients received study treatments for a mean of 16.2 weeks (range, 0.1 to 84.0) in the E + T group and 13.9 weeks (range, 0.1 to 92.0) in the E + P group.

The preplanned interim OS analysis was performed after 485 deaths, and the result crossed the protocol-defined stopping boundary for futility. Consequently, the independent data monitoring committee recommended study discontinuation, even though there were no

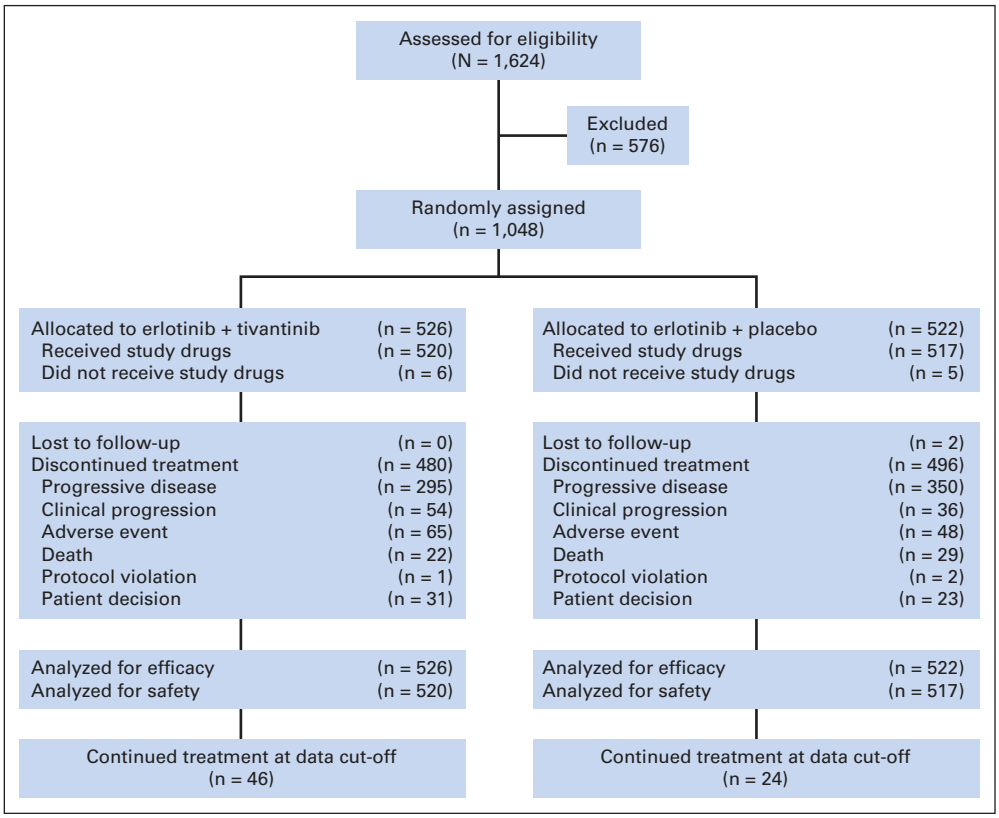

Fig 1. CONSORT diagram.

safety concerns, and PFS had improved. Blinding of treatment assignment was maintained, and patients receiving treatment were allowed to continue. A data cutoff was applied on December 15, 2012, at which time 614 survival events (58.6%) had occurred (E + T, n = 300 [57.0%]; E + P, n = 314 [60.2%]). Results for the *EGFR*-mutant subpopulation were immature, and the study was continued for these patients and those receiving study treatment with clinical benefit.

Patient Characteristics

Among the 1,048 randomly assigned patients, treatment groups were well balanced for baseline demographics and clinical characteristics (Table 1). Median age was 62.0 years (range, 24 to 89 years); 59.1% of patients were men, 81.0% were either current or former smokers, 93.0% had adenocarcinoma, and approximately two thirds had received only one prior systemic therapy.

Nearly all patients had *EGFR* mutation status determined, with 89.4% having *EGFR* WT tumors (Table 2). Among 986 patients with known tumor *KRAS* mutation status, 28.8% were *KRAS* mutant. Of 1,048 randomly assigned patients, 445 tumor samples were investigated for MET expression by immunohistochemistry, and 47.4% of these had high expression. A total of 476 patients had samples evaluable for *MET* amplification assessment: 54 (11.3%) had *MET* copy number > 4, and four patients (two in each arm) had *MET* amplification with *MET*:*CEP7* ratio > 2. No patient had a *MET*:*CEP7* ratio > 5.

Efficacy

OS did not differ significantly between treatment groups in the ITT population (HR, 0.98; 95% CI, 0.84 to 1.14; $P = .81$; Fig 2A). Median OS was 8.5 versus 7.8 months for the E + T and E + P arms, respectively. Similarly, OS was not significantly different (median OS: E + T, 7.2 months; E + P, 7.1 months; HR, 1.00; 95% CI, 0.85 to 1.18; $P = .94$) within the *EGFR* WT subgroup, which comprised approximately 89.4% of the ITT population. In contrast to OS, tivantinib significantly increased median PFS in the ITT population (HR, 0.74; 95% CI, 0.64 to 0.85; $P < .001$) from 1.9 to 3.6 months (Fig 2B). In the *EGFR* WT subgroup, PFS was also significantly longer (HR, 0.72; 95% CI, 0.62 to 0.83; $P < .001$) with E + T than with E + P (median PFS, 2.7 *v* 1.9 months).

Subgroup Analyses

In the preplanned exploratory analysis of the subgroup of 211 patients with high MET tumor expression, a trend for OS benefit favoring E + T was observed (median OS, 9.3 *v* 5.9 months; HR, 0.70; 95% CI, 0.49 to 1.01; Fig 3A). PFS also improved in the subgroup of patients with high MET expression (median, 3.7 *v* 1.9 months; HR, 0.72; 95% CI, 0.52 to 0.99; Fig 3B). No association was observed between tivantinib treatment and other biomarker and demographic subgroups (Fig 4). Longer OS was observed in tumors with *MET* gene copy number > 4 (HR, 0.83; 95% CI, 0.43 to 1.61), but the limited sample size precluded any meaningful conclusion. For the *EGFR*-mutant subgroup (n = 109), OS and PFS data at the cutoff time are still immature, with only 30 deaths.

EGFR and *KRAS* mutations were almost completely exclusive of each other, whereas MET expression was independent of *EGFR* and *KRAS* genotypes. Among fully defined molecular subgroups, the largest was *EGFR* WT, *KRAS* WT, and MET low (n = 143), where OS did not improve (median OS: E + T, 7.5 months; E + P, 6.4 months; HR,

Table 1. Patient Baseline Demographic and Clinical Characteristics (ITT population)

Characteristic	Erlotinib Plus Tivantinib (n = 526) No. (%)	Erlotinib Plus Placebo (n = 522) No. (%)
Age, years		
Mean	61.2	61.1
SD	10.1	9.8
Median	62.0	61.0
Range	26-89	24-87
Sex		
Female	216 (41.1)	213 (40.8)
Male	310 (58.9)	309 (59.2)
Race		
White	430 (81.7)	446 (85.4)
Black	16 (3.0)	12 (2.3)
Asian	8 (1.5)	5 (1.0)
Other or not reported	71 (13.5)	59 (11.3)
Smoker		
Never	101 (19.2)	98 (18.8)
Ever	425 (80.8)	424 (81.2)
Current	98 (18.6)	97 (18.6)
Former	327 (62.2)	327 (62.6)
ECOG PS		
0	168 (31.9)	168 (32.2)
1	357 (67.9)	353 (67.6)
2	1 (0.2)	1 (0.2)
Tumor stage at study entry		
IIIb	22 (4.2)	14 (2.7)
IV	499 (94.9)	501 (96.0)
Not reported	5 (1.0)	7 (1.3)
NSCLC histologic type		
Adenocarcinoma	480 (91.3)	495 (94.8)
Large-cell carcinoma	31 (5.9)	20 (3.8)
Other nonadenocarcinoma	15 (2.8)	7 (1.4)
Unclassified nonadenocarcinoma	7 (1.3)	3 (0.6)
Prior NSCLC radiotherapy		
Yes	232 (44.1)	219 (42.0)
No	294 (55.9)	303 (58.0)
Prior NSCLC surgery		
Yes	238 (45.2)	253 (48.5)
No	288 (54.8)	269 (51.5)
No. of prior NSCLC systemic therapies		
1	346 (65.8)	348 (66.7)
2	180 (34.2)	174 (33.3)
Brain metastases	66 (12.5)	80 (15.3)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; ITT, intent to treat; NSCLC, non–small-cell lung cancer; SD, standard deviation.

Table 2. Tumor Biomarkers Status (ITT population)

Characteristic	Erlotinib Plus Tivantinib (n = 526) No. (%)	Erlotinib Plus Placebo (n = 522) No. (%)
EGFR mutation status		
Mutant	56 (10.6)	53 (10.2)
Wild type	469 (89.2)	468 (89.7)
Unknown	1 (0.2)	1 (0.2)
KRAS mutation status		
Mutant	136 (25.9)	148 (28.4)
Wild type	356 (67.7)	346 (66.3)
Unknown	34 (6.5)	28 (5.4)
MET expression status		
High	104 (19.8)	107 (20.5)
Low	107 (20.3)	127 (24.3)
Unknown	315 (59.9)	288 (55.2)
MET FISH status		
Positive*	27 (5.1)	27 (5.2)
Negative	195 (37.1)	227 (43.5)
Unknown	304 (57.8)	268 (51.3)

Abbreviations: FISH, fluorescent in situ hybridization; ITT, intent to treat; MET, mesenchymal-epithelial transition.
**MET* gene copy number ≥ 4.

1.09; 95% CI, 0.72 to 1.65). In the *EGFR* WT, *KRAS* WT, and MET high subgroup (n = 119), OS was prolonged for E + T (median OS: E + T, 8.8 months; E + P, 5.0 months; HR, 0.56; 95% CI, 0.35 to 0.89).

Response to Treatment

The overall objective response rate (ORR) was 10.3% (95% CI, 8.0 to 13.2) with E + T and 6.5% (95% CI, 4.7 to 9.0) with E + P. The disease control rate (objective response plus stable disease) was 45.8% in patients receiving E + T (95% CI, 41.6 to 50.1) and 32.0% in those receiving E + P (95% CI, 28.1 to 36.1). Median duration of objective response was 40.4 weeks with E + T and 47.9 weeks with E + P.

Postdiscontinuation Therapy

After study treatments were discontinued, 192 (36.5%) of 526 patients in the E + T group and 231 (44.3%) of 522 in the E + P group received subsequent therapy, primarily chemotherapy (E + T, 29.5%; E + P, 38.8%).

Exploratory Multivariable Cox Regression

A stepwise forward and backward model selection approach was taken in an exploratory multivariable Cox regression analysis with treatment retained in the model. Potential prognostic factors, including *EGFR* genotype, *KRAS* genotype, MET expression, age, baseline ECOG PS, sex, number of prior lines of therapy for NSCLC, smoking history, best response to prior therapy, and region, were fit into the Cox regression model along with the interaction with treatment. In the stepwise multivariable analysis, the final model for OS selected the following factors: *EGFR* genotype, best response to prior therapy, ECOG PS (and interaction), line of prior therapy, MET expression (and interaction), region, and smoking history. Notable interactions with treatment were observed, prompting closer examination of the subgroups (Fig 4).

Safety

In the safety population of 1,037 patients who received any dose of study drug, 1,016 (98.0%) experienced at least one TEAE: 513 (98.7%) in the E + T group and 503 (97.3%) in the E + P group. The most common TEAEs in the E + T versus E + P group were fatigue or asthenia (43.5% *v* 38.1%, respectively), diarrhea (34.6% *v* 41.0%), rash (33.1% *v* 37.3%), and decreased appetite (29.0% *v* 28.8%; Table 3). Myelosuppression, a known toxicity of tivantinib, was observed in this study. TEAEs related to myelosuppression for E + T versus E + P included anemia (16.0% *v* 9.9%), neutropenia (11.9% *v* 1.9%), leukopenia (5.8% *v* 1.0%), and febrile neutropenia (3.3% *v* 0.4%). Grade ≥ 3 TEAEs were 8.5% *v* 0.8% for neutropenia and 6.3% *v* 2.9% for anemia, respectively. Eight patients developed interstitial lung disease (ILD; E + T, n = 3; E + P, n = 5). Bradycardia was reported in 14

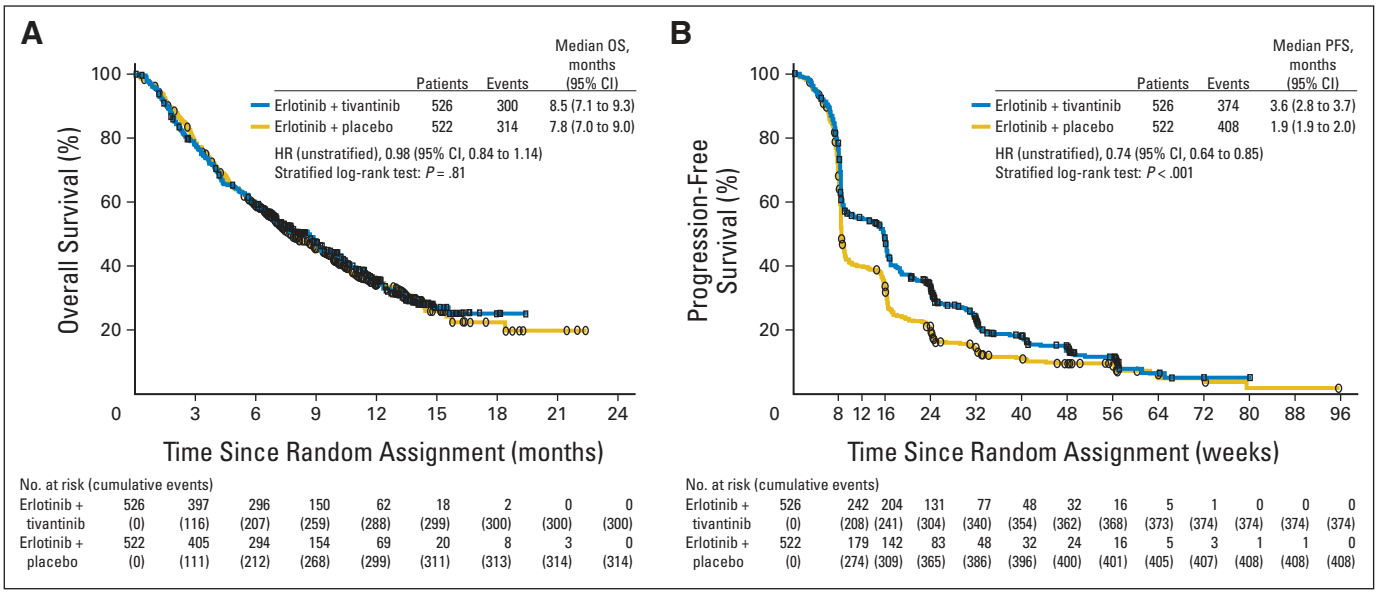

Fig 2. (A) Overall survival (OS) and (B) progression-free survival (PFS) for patients receiving erlotinib plus tivantinib versus erlotinib plus placebo (intent-to-treat population). HR, hazard ratio.

patients (2.7%) receiving E + T and none of the patients receiving E + P; two cases in the E + T group were grade ≥ 3.

During the study, 614 patients (59.2%) died, mainly as a result of disease progression (E + T, 46.0%; E + P, 48.4%). Of all deaths, 142 (13.7% of safety population) were classified as TEAEs (E + T, 14.8%; E + P, 12.6%), most related to underlying disease, leaving 66 deaths related to a TEAE other than disease progression (E + T, 6.2%; E + P, 6.6%). The most common reasons for death in these patients receiving E + T versus E + P were respiratory failure (1.0% *v* 1.2%, respectively), sepsis or septic shock (1.0% *v* 0.2%), and pneumonia or bronchopneumonia (0.6% *v* 1.0%). Five deaths (1.0%) with E + T and three deaths (0.6%) with E + P were considered associated with tivantinib or placebo. At least one serious adverse event (SAE) occurred in 410 patients (E + T, 42.1%; E + P, 36.9%), the most common being respiratory events, as expected. Differences in SAE incidence between E + T and E + P treatment groups, respectively, were generally related to myelosuppression: anemia (3.1% *v* 1.2%), febrile neutropenia (2.9% *v* 0.4%), and neutropenia (2.1% *v* 0.2%). There was also a higher incidence of the following SAEs with E + T versus E + P, respectively: pneumonia (3.8% *v* 2.1%) and sepsis (1.0% *v* 0.4%).

DISCUSSION

This phase III study did not meet its primary end point of improved OS in previously treated patients with locally advanced or metastatic

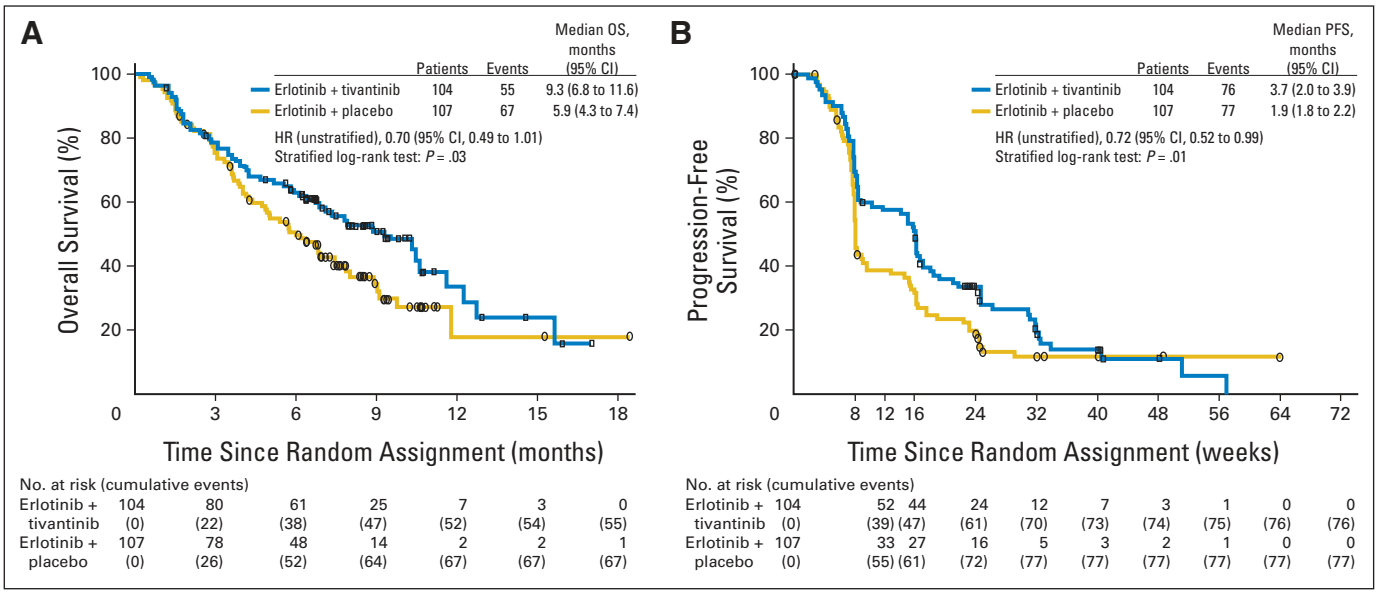

Fig 3. (A) Overall (OS) and (B) progression-free survival (PFS) for MET-high subgroup. HR, hazard ratio.

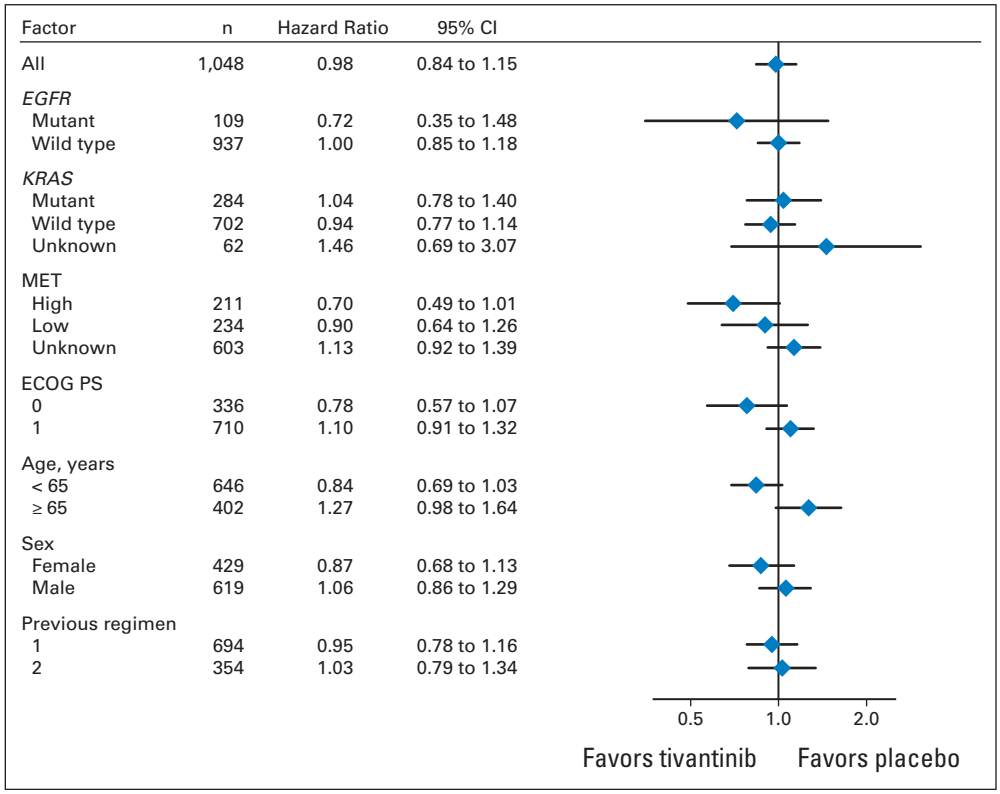

Fig 4. Forest plot of overall survival hazard ratio by predefined subgroups. ECOG PS, Eastern Cooperative Group performance status; MET, mesenchymal-epithelial transition expression.

nonsquamous NSCLC, although significant improvement in PFS and increased ORR were observed. In addition, an exploratory analysis indicated OS and PFS benefit with tivantinib in the subgroup of patients with MET-high status by immunohistochemistry. In the subgroup of patients with tumor *MET* gene copy number > 4, there was no difference in OS between treatment groups, but only four patients had selective *MET* amplification with a *MET*:*CEP7* ratio > 2. Although the drugs were well tolerated, the survival benefit may have been diminished by the associated adverse events (AEs), such as asthenia or fatigue and neutropenia.

Table 3. Treatment-Emergent AEs in ≥ 15% of Patients in Either Treatment Group

	Erlotinib Plus Tivantinib (n = 520) No. (%)		Erlotinib Plus Placebo (n = 517) No. (%)	
AE	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
Fatigue or asthenia	226 (43.5)	47 (9.0)	197 (38.1)	41 (7.9)
Diarrhea	180 (34.6)	13 (2.5)	212 (41.0)	19 (3.7)
Rash	172 (33.1)	10 (1.9)	193 (37.3)	20 (3.9)
Decreased appetite	151 (29.0)	15 (2.9)	149 (28.8)	15 (2.9)
Dyspnea	136 (26.2)	46 (8.8)	117 (22.6)	38 (7.4)
Nausea	121 (23.3)	4 (0.8)	123 (23.8)	9 (1.7)
Cough	110 (21.2)	6 (1.2)	91 (17.6)	4 (0.8)
Dermatitis acneiform	90 (17.3)	7 (1.3)	98 (19.0)	11 (2.1)
Vomiting	73 (14.0)	5 (1.0)	81 (15.7)	6 (1.2)
Anemia	83 (16.0)	33 (6.3)	51 (9.9)	15 (2.9)

Abbreviation: AE, adverse event.

In another recent phase III trial of tivantinib plus erlotinib compared with tivantinib plus placebo in previously treated Asian patients with nonsquamous NSCLC and *EGFR* WT, OS and PFS were also numerically prolonged in patients receiving tivantinib. However, the study was discontinued early because of toxicity concerns related to the incidence of ILD—a known AE observed in Japanese patients treated with EGFR inhibitors—in the tivantinib plus erlotinib group.[16] In our study, which did not include Asian patients, the combination of tivantinib plus erlotinib was generally well tolerated. AE profiles were similar between treatment groups, with the exception of more frequent neutropenia and anemia with tivantinib. The combination of tivantinib with erlotinib did not increase the known risk of ILD associated with erlotinib.[17]

Aberrant activation of the hepatocyte growth factor/MET signaling pathway through *MET* gene amplification and/or high MET protein expression is known to occur in many solid tumors.[6,18] Phase I and II studies of tivantinib as monotherapy or in combination with other agents in patients with different tumor types, including NSCLC, have indicated a potential benefit for tivantinib and possible roles of MET protein expression, *MET* amplification, and *KRAS* mutation as predictive markers of efficacy.[12,19-24] Although our phase III study did not meet its primary end point, the data suggest a potential benefit in patients with high MET expression, consistent with the hypothesis that MET expression could be a potential biomarker for activity in this setting. Recent in vitro studies have reported that tivantinib has activity against cells that harbor little or undetectable levels of MET, suggesting additional mechanisms of action, including tubulin inhibition[25-27] or the possible involvement of cellular mechanisms[28] and signaling pathways activated by MET.[29] Although it is unclear the

effect that such activity may have in the clinical setting, data from this and other randomized phase II trials demonstrate that tivantinib has greater survival benefit in patients with high MET expression.[19,23]

Several other agents have shown efficacy in patients with specific molecular aberrations in NSCLC. Crizotinib, an oral tyrosine kinase inhibitor of MET, is indicated for the treatment of anaplastic lymphoma kinase–positive metastatic NSCLC.[30-32] It has also demonstrated antitumor activity in a small group of patients with *MET*-amplified advanced NSCLC, defined as selective gene amplification with *MET*:*CEP7* ratio ≥ 1.8 to ≤ 2.2 (low), > 2.2 to < 5 (intermediate), and ≥ 5 (high).[33,34] In comparison, only four patients in our study had selective *MET* gene amplification with a *MET*:*CEP7* ratio ≥ 2.0, and only one had a ratio > 3.0.

Onartuzumab—a monovalent monoclonal antibody targeting the MET receptor—in combination with erlotinib in a phase II study of patients with advanced NSCLC with high MET expression by immunohistochemistry improved OS and PFS.[35] However, a subsequent randomized phase III trial performed in patients with advanced NSCLC with high MET expression was stopped early for futility.[36] The determination of high MET expression in both onartuzumab studies seemed to be generally similar (immunohistochemistry staining intensity ≥ 2 in $\geq 50\%$ of tumor cells using SP44 antibody), but some methodologic details are unavailable.[35,36] As additional investigations of targeted agents are conducted in patients with MET-high NSCLC, an appropriate definition of MET-high status will be critical to identify those patients who will benefit most from MET-targeted therapies.

In summary, the addition of tivantinib to erlotinib was well tolerated but did not improve survival in the overall population of patients with nonsquamous NSCLC, although PFS and ORR were improved. Further investigation of tivantinib in patients with nonsquamous NSCLC with high MET expression is warranted, as is exploration of the most relevant tumor biomarkers to select patients for combined MET and EGFR inhibition therapy.

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Disclosures provided by the authors are available with this article at www.jco.org.

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