BRIEF REPORT

Tivantinib in Combination with Erlotinib versus Erlotinib Alone for *EGFR*-Mutant NSCLC: An Exploratory Analysis of the Phase 3 MARQUEE Study

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Received 2 October 2017; revised 13 December 2017; accepted 13 December 2017
Available online - 27 December 2017

ABSTRACT

Introduction: This exploratory subgroup analysis of the MARQUEE study evaluated the efficacy and safety of erlotinib plus tivantinib in patients with *EGFR*-mutant NSCLC.

Methods: Patients with advanced, nonsquamous, EGFR and mesenchymal-epithelial transition inhibitor–naive NSCLC previously treated with one or two lines of systemic therapy were randomized to oral erlotinib (150 mg once daily) plus tivantinib (360 mg twice daily) or to erlotinib plus placebo. The primary end point was overall survival.

Results: Among 1048 patients enrolled, 109 (10.4%) had *EGFR*-mutant disease. Erlotinib plus tivantinib improved progression-free survival in this subpopulation; median progression-free survival was 13.0 months for erlotinib plus tivantinib (n = 56) and 7.5 months for erlotinib plus placebo (n = 53) (hazard ratio = 0.49, 95% confidence interval: 0.31–0.77). Deaths occurred in 73 patients (67%), and median overall survival was 25.5 months in the erlotinib plus tivantinib arm versus 20.3 months in the erlotinib plus placebo arm (hazard ratio = 0.68, 95% confidence interval: 0.43–1.08). Common adverse events included diarrhea, rash, and asthenia. Neutropenia and febrile neutropenia were more common with erlotinib plus tivantinib.

Conclusions: Erlotinib plus tivantinib was tolerable and showed improved efficacy over erlotinib monotherapy in previously treated *EGFR*-mutant NSCLC.

Keywords: Lung cancer; nonsquamous; MET inhibitor; tivantinib; erlotinib; EGFR

Introduction

EGFR-targeted tyrosine kinase inhibitors (TKIs) are indicated as first-line therapy for NSCLC with activating *EGFR* mutations, including exon 19 deletions or exon 21 (L858R) substitutions.[1] The OPTIMAL, EURTAC, and ENSURE trials showed that erlotinib is highly effective in patients with previously untreated,

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Disclosure: Dr. Scagliotti is a consultant for Eli Lilly and has received honoraria from Eli Lilly, AstraZeneca, Pfizer, Roche, Merck, and Clovis Oncology. Dr. Shuster is an employee of and equity owner in Daiichi Sankyo, Inc. Dr. Ross provided diagnostic laboratory services as a central laboratory director for the MARQUEE trial. Dr. Wang is an employee of Daiichi Sankyo Pharma Development. Dr. Schwartz is an employee of and owns stock in ArQule, Inc. Dr. Akerley has received clinical research support from Astra Zeneca, Biodesix, Bristol Myers Squibb, and Daiichi Sankyo, Inc.

Trial Registration: Tivantinib plus Erlotinib versus Placebo plus Erlotinib for the Treatment of Nonsquamous, Non-Small Cell Lung Cancer. NCT01244191.

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ISSN: 1556-0864
https://doi.org/10.1016/j.jtho.2017.12.009

metastatic, *EGFR*-mutant NSCLC.[2–4] However, resistance to EGFR TKIs and relapse develop in most patients.[5]

Mesenchymal-epithelial transition (MET) receptor overexpression is common in nonsquamous NSCLC[5,6] and is associated with a poor prognosis.[7,8] Importantly, MNNG HOS Transforming gene (*MET*) amplification is associated with resistance to EGFR TKIs.[7,9] In vitro, inhibition of MET in tumor cells with acquired resistance to EGFR inhibitors restored sensitivity to EGFR inhibitors and reduced cell growth.[9] On the basis of preclinical models, disruption of MET signaling with small interfering RNA, TKIs, or antibodies inhibits the growth of NSCLC tumor cells and xenografts and can potentially overcome resistance.[10]

Tivantinib is a selective, oral, small-molecule MET inhibitor with an adenosine triphosphate–independent binding mechanism.[11,12] In the MARQUEE trial, in which approximately 90% of patients were *EGFR* wild type, erlotinib plus tivantinib significantly improved progression-free survival (PFS) (median PFS 3.6 versus 1.9 months; hazard ratio [HR] = 0.74, $p < 0.001$) but did not significantly improve overall survival (OS) versus that with erlotinib plus placebo.[6] A preplanned exploratory analysis of the subgroup of 211 patients with high tumor MET expression showed a potential OS benefit favoring erlotinib plus tivantinib (median OS 9.3 versus 5.9 months; HR = 0.70, 95% confidence interval [CI]: 0.49–1.01).[6]

Given that erlotinib monotherapy has activity in patients with an activating *EGFR* mutation, tivantinib plus erlotinib might have greater additive activity and may help to overcome or block acquired resistance to erlotinib. The objective of this exploratory analysis of MARQUEE was to evaluate the efficacy and safety of erlotinib plus tivantinib in the subgroup of 109 patients with *EGFR*-mutant NSCLC.

Patients and Methods

Patients

Patient characteristics have been described previously, as have biomarker analyses.[6] Patients were at least 18 years old with histologically or cytologically confirmed inoperable locally advanced or metastatic nonsquamous NSCLC.[6] They had received one or two prior chemotherapy regimens with a platinum-based doublet and no EGFR TKI or MET inhibitor therapy. All patients were tested by polymerase chain reaction assay for exon 19 deletion, T790M, L858R, L861Q, G719X, S768I, and exon 20 insertion *EGFR* mutations before randomization, and all had an *EGFR* mutation.

Study Design, Treatment, and Objectives

Patients were stratified on the basis of number of prior therapies, sex, smoking status, and *EGFR* and *KRAS* mutation status and were randomized 1:1 to oral erlotinib (150 mg once daily) plus tivantinib (360 mg twice daily) or erlotinib plus placebo. Exploratory end points included PFS, OS, association between *EGFR* mutation and PFS or OS, objective response rate, and safety. MARQUEE met the criteria for futility at the preplanned interim analysis, and the main study was discontinued. Results in the *EGFR*-mutant subgroup were not mature, and it was agreed to continue treatment and follow-up in that subgroup.[6]

Statistical Analysis

A data cut for this subgroup was prespecified to occur after approximately 70% of patients had died, which was projected to occur approximately 2.5 years after the last patient was randomized.

Results

Patient Population and Disposition

Among 1048 patients enrolled, 109 (10.4%) had an *EGFR* mutation and were included in the current analysis: 56 were randomized to erlotinib plus tivantinib and 53 to erlotinib plus placebo. The most common *EGFR* mutation was an exon 19 deletion (n = 55), followed by L858R (n = 39); five patients had an exon 20 insertion, and 10 patients had other *EGFR* mutations or the specific mutation was not reported (Table 1). Patient characteristics were generally similar between treatment groups.

At the time of the analysis, six patients (10.7%) in the erlotinib plus tivantinib group were still receiving study treatment 31 to 40 months from randomization, compared with none in the erlotinib plus placebo group. The *EGFR* mutations in the six patients with ongoing treatment included four with exon 19 deletions, one with L858R, and one exon 20 insertion. The most common reasons for discontinuation were disease progression and adverse events (AEs) (Table 2). More patients discontinued treatment because of disease progression in the erlotinib plus placebo group, whereas more discontinued because of AEs in the erlotinib plus tivantinib group.

Efficacy

Median PFS was longer in the erlotinib plus tivantinib group than in the erlotinib plus placebo group (13.0 versus 7.5 months, respectively; HR = 0.49, 95% CI: 0.31–0.77) (Fig. 1*A*). OS was similar in the erlotinib plus tivantinib group and in the erlotinib plus placebo group (median 25.5 versus 20.3 months, respectively; HR = 0.68, 95% CI: 0.43–1.08) (Fig. 1*B*). The objective response rate was 61% (95% CI: 48%–72%) in the erlotinib plus tivantinib group versus 43% (95% CI: 31%–57%) in the erlotinib plus placebo group (Table 3).

Table 1. Demographics of Patients with *EGFR* Mutations in the MARQUEE Trial

Characteristic	Tivantinib + Erlotinib (n = 56)	Placebo + Erlotinib (n = 53)
Median age, y (range)	59.5 (34-84)	65.0 (38-82)
Sex, n (%)		
Male	24 (42.9)	25 (47.2)
Female	32 (57.1)	28 (52.8)
ECOG performance status, n (%)		
0	21 (37.5)	17 (32.1)
1	35 (62.5)	36 (67.9)
Smoking history, n (%)		
Current	3 (5.4)	3 (5.7)
Former	26 (46.4)	18 (34.0)
Never	27 (48.2)	32 (60.4)
Race, n (%)		
White	46 (82.1)	44 (83.0)
Asian	2 (3.6)	2 (3.8)
Other/unknown	8 (14.3)	7 (13.2)
No. of prior regimens, n (%)		
1	39 (69.6)	40 (75.5)
2	17 (30.4)	13 (24.5)
Type of *EGFR* mutation, n (%)		
Exon 19 deletion	32 (57.1)	23 (43.4)
L858R	18 (32.1)	21 (39.6)
Exon 20 insertion	3 (5.4)	2 (3.8)
Other[a]	3 (5.4)	7 (13.2)
MET expression, n (%)[b]		
High	8 (14.3)	12 (22.6)
Low	16 (28.6)	10 (18.9)
Unknown	32 (57.1)	31 (58.5)
MET amplification, n (%)[c]		
High	2 (3.6)	3 (5.7)
Low	27 (48.2)	29 (54.7)
Unknown	27 (48.2)	21 (39.6)
KRAS, n (%)		
Positive	0	2 (3.8)
Negative	54 (96.4)	49 (92.5)
Unknown	2 (3.6)	2 (3.8)

[a]Other includes three patients with a G719X mutation, two patients with a S768I mutation, one patient with a G719X and S768I mutation; for four patients, a specific mutation was not reported.
[b]MET expression was defined as positive or high if membranous immunohistochemical staining intensity was 2 or higher in at least 50% of tumor cells.
[c]*MET* amplification by fluorescence in situ hybridization was defined as positive or high if the *MET* gene copy number was 4 or higher.
ECOG, Eastern Cooperative Oncology Group; MET, mesenchymal-epithelial transition; *MET*, MNNG HOS Transforming gene.

Among 55 patients with an *EGFR* exon 19 deletion, erlotinib plus tivantinib prolonged PFS (HR = 0.42, 95% CI: 0.23–0.77) with a numerical improvement in OS (HR = 0.68, 95% CI: 0.35–1.32). The improvements in PFS (HR = 0.80, 95% CI: 0.37–1.74) and OS (HR = 0.86, 95% CI: 0.39–1.92) were less pronounced in the 39 patients with the L858R *EGFR* mutation. The subgroup of 15 patients with exon 20 insertions or other *EGFR* mutations was too small and heterogeneous to allow for a meaningful analysis of PFS and OS outcomes.

Table 2. Patient Disposition

Reason for Treatment Discontinuation	Tivantinib + Erlotinib (n = 56)	Placebo + Erlotinib (n = 53)
Ongoing, n (%)	6 (10.7)	0
Reason for discontinuation, n (%)	50 (89.3)	53 (100.0)
Progressive disease	25 (44.6)	39 (73.6)
Clinical progression	4 (7.1)	4 (7.5)
Adverse event	10 (17.9)	2 (3.8)
Death	0	2 (3.8)
Lost to follow-up	0	0
Protocol violation	0	0
Withdrawal of consent	2 (3.6)	1 (1.9)
Other	1 (1.8)	2 (3.8)
Missing	8 (14.3)	3 (5.7)

Safety

The most common treatment-emergent AEs of any grade were diarrhea, rash, and asthenia, which occurred at similar rates in both treatment groups (Table 4). Both neutropenia and febrile neutropenia were more common in patients receiving erlotinib and tivantinib. The most common (>5%) treatment emergent AEs of grade 3 or higher were neutropenia (14.3%), asthenia or fatigue (5.4%), and anemia (5.4%) in patients receiving erlotinib plus tivantinib and anemia, neutropenia, asthenia or fatigue, dermatitis acneiform, and rash (5.7% each) in patients receiving erlotinib plus placebo. One death from pneumonia in a patient receiving erlotinib plus placebo was reported as treatment related. The safety profile of erlotinib plus tivantinib in this subgroup was similar to that observed in the overall study population despite the longer duration of therapy, which included patients treated with tivantinib for more than 3 years.[6]

Discussion

Studies have sought to determine whether MET inhibition can overcome or block emergence of resistance to EGFR inhibitors and prolong time to progression in NSCLC. This hypothesis is based on evidence that *MET* amplification is associated with resistance to EGFR inhibitors and inhibition of MET signaling can restore sensitivity to EGFR inhibitors.[7,9] Several clinical trials have suggested a potential clinical benefit of combining a MET inhibitor with an EGFR inhibitor in NSCLC.[6,13,14] These studies suggest that the benefit of this combination is greatest in patients with high MET expression or amplification, but the data are inconsistent. The current exploratory analysis was an attempt to clarify the benefit

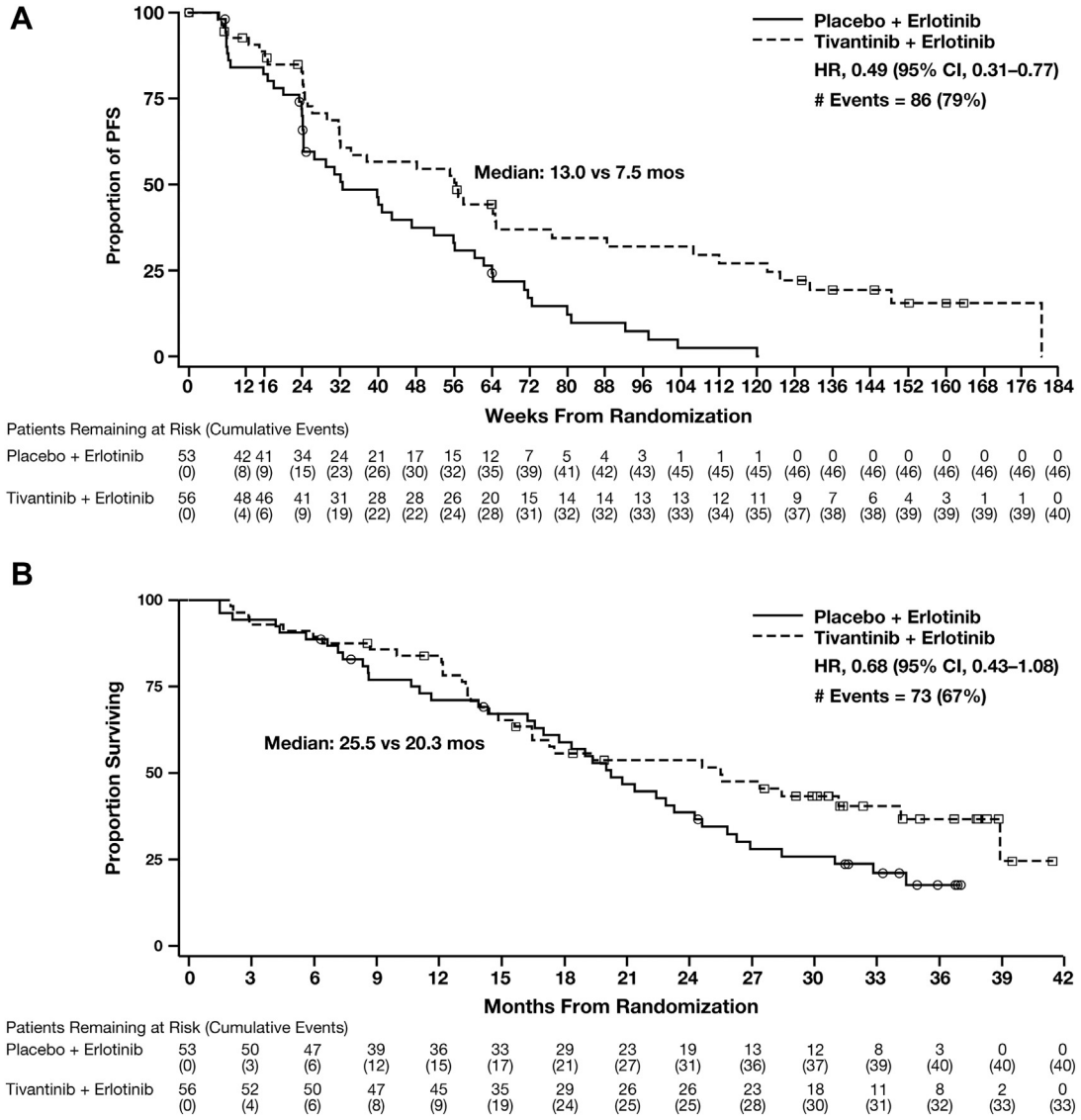

Figure 1. Progression-free survival (PFS) (*A*) and overall survival (*B*) in patients with *EGFR*-mutant disease enrolled in the MARQUEE study. CI, confidence interval; HR, hazard ratio.

of the combination of a MET inhibitor with an EGFR inhibitor in subsets of patients defined by *EGFR* mutation status regardless of MET expression.

The results suggest that tivantinib may augment the activity of erlotinib against tumors with an activating *EGFR* mutation, perhaps by overcoming intrinsic resistance to erlotinib mediated by MET expression or by preventing the emergence of MET expression. Treatment groups were fairly well balanced for MET expression, although more patients in the erlotinib plus placebo group had high MET expression (22.6%) than in the erlotinib plus tivantinib group (14.3%). In patients with *EGFR* mutations, erlotinib plus tivantinib was tolerable and improved PFS versus that in patients receiving erlotinib plus placebo, as in the overall study population, without improving OS. The benefit in patients receiving erlotinib plus tivantinib was most evident in patients with an exon 19 deletion; such patients were previously shown to have a greater

Table 3. Response Rate and Duration of Response

Response	Tivantinib + Erlotinib (n = 56)	Placebo + Erlotinib (n = 53)
Overall response rate (CR + PR)	60.7%	43.4%
Patients with subsequent PD	39.3%	39.6%
Median duration of response, weeks (min, max)	51.14 (3.4, 148.1)	39.43 (8.3, 112.0)

CR, complete response; PD, progressive disease; PR, partial response.

Table 4. Percentage of Patients with Treatment-Emergent Adverse Events with a Frequency of 20% or More or of Special Interest

MedDRA System, Organ, Class/Preferred Term	All Grades, %		Grades ≥3, %	
	Tivantinib + Erlotinib (n = 56)	Placebo + Erlotinib (n = 53)	Tivantinib + Erlotinib (n = 56)	Placebo + Erlotinib (n = 53)
Blood and Lymphatic				
Anemia	21.4	9.4	5.4	5.7
Febrile neutropenia	3.6	0	3.6	0
Neutropenia	26.8	9.4	14.3	5.7
Thrombocytopenia	0	1.9	0	1.9
Cardiac				
Bradycardia or sinus bradycardia	3.6	0	0	0
Gastrointestinal				
Diarrhea	39.3	43.4	3.6	3.8
Nausea	16.1	26.4	0	0
Stomatitis	8.9	11.3	0	0
Vomiting	12.5	18.9	1.8	1.9
General				
Asthenia or fatigue	30.4	26.4	5.4	5.7
Respiratory				
Cough	23.2	11.3	0	0
Skin				
Alopecia	14.3	1.9	–	–
Dermatitis acneiform	26.8	24.5	3.6	5.7
Dry skin	19.6	15.1	0	0
Rash	35.7	39.6	3.6	5.7

MedDRA, Medical Dictionary for Regulatory Activities.

response to TKIs than patients with the other common *EGFR* mutation, L858R.[15–17]

Limitations include the exploratory nature of the post hoc subgroup analysis and the limited number of patients with an *EGFR* mutation in MARQUEE. In addition, imbalances between treatment groups with respect to *KRAS* mutations and MET expression may have biased the results in favor of the erlotinib plus tivantinib group. Two patients (4%) in the erlotinib plus placebo group had tumors that also harbored a *KRAS* mutation compared with none in the erlotinib plus tivantinib group, and the presence of both *EGFR* and *KRAS* mutations is associated with a worse prognosis in lung cancer.[18] Likewise, MET expression and/or gene amplification is associated with shorter survival in lung cancer,[7,8] and both were observed in a slightly higher proportion of patients in the erlotinib plus placebo group. Furthermore, baseline characteristics were imbalanced with regard to *EGFR* mutation subtype, with a higher percentage of patients in the erlotinib plus tivantinib group harboring exon 19 deletions. Patients with this *EGFR* subtype may receive greater benefit from the combination regimen, thus potentially confounding the conclusion of an overall benefit in *EGFR*-driven NSCLC.

In conclusion, erlotinib plus tivantinib appears to enhance efficacy in patients with previously treated, *EGFR*-mutant, nonsquamous NSCLC compared with erlotinib alone, but confirmatory studies are needed. Taken together, the data from this exploratory analysis and from the previous subset analysis of MARQUEE support the hypothesis that the combination of an *EGFR* inhibitor and a MET inhibitor may be most effective in patients with tumors expressing high levels of *MET* and/or with activating *EGFR* mutations.

Acknowledgments

This work was supported by Daiichi Sankyo, Inc, which provided financial support for conduct of the research and preparation of the article. No grant number is applicable. The authors thank the patients and their families for their contribution to this study. Writing assistance was provided by Jeff Riegel, PhD, from ProEd Communications and funded by Daiichi Sankyo Inc.

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