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Original Article

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East Asian Subgroup Analysis of a Randomized, Double-Blind, Phase 3 Study of Docetaxel and Ramucirumab Versus Docetaxel and Placebo in the Treatment of Stage IV Non-small Cell Lung Cancer Following Disease Progression after One Prior Platinum-Based Therapy (REVEL)

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Purpose

REVEL demonstrated improved overall survival (OS), progression-free survival (PFS), and objective response rate (ORR) with docetaxel+ramucirumab versus docetaxel+placebo in 1,253 intent-to-treat (ITT) stage IV non-small cell lung cancer patients with disease progression following platinum-based chemotherapy. Results from the East Asian subgroup analysis are reported.

Materials and Methods

Subgroup analyses were performed in the East Asian ITT population (n=89). Kaplan-Meier analysis and Cox proportional hazards regression were performed for OS and PFS, and the Cochran-Mantel-Haenszel test was performed for response rate.

Results

In docetaxel+ramucirumab (n=43) versus docetaxel+placebo (n=46), median OS was 15.44 months versus 10.17 months (hazard ratio [HR], 0.762; 95% confidence interval [CI], 0.444 to 1.307), median PFS was 4.88 months versus 2.79 months (HR, 0.658; 95% CI, 0.408 to 1.060), and ORR was 25.6% (95% CI, 13.5 to 41.2) versus 8.7% (95% CI, 2.4 to 20.8). Due to increased incidence of neutropenia and febrile neutropenia in East Asian patients, starting dose of docetaxel was reduced for newly enrolled East Asian patients (75 to 60 mg/m^2, n=24). In docetaxel+ramucirumab versus docetaxel+placebo, incidence of neutropenia was 84.4% versus 72.7% (75 mg/m^2) and 54.5% versus 38.5% (60 mg/m^2). Incidence of febrile neutropenia was 43.8% versus 12.1% (75 mg/m^2) and 0% versus 7.7% (60 mg/m^2).

Conclusion

Results of this subgroup analysis showed a trend favoring ramucirumab+docetaxel for median OS, PFS, and improved ORR in East Asian patients, consistent with ITT population results. Reduction of starting dose of docetaxel in East Asian patients was associated with improved safety.

Key words
Ramucirumab, Docetaxel, Non-small-cell lung carcinoma, East Asia

Introduction

Lung cancer is the leading cause of cancer-related death in both men and women in East Asia [1]. Lung cancer is classified as either small cell or non-small cell lung cancer (NSCLC) [2], and the latter group is histologically subdivided into squamous-cell carcinomas (25%) and non-squamous cell carcinomas (adenocarcinomas [55%] and large-cell carcinomas [5%]). The remaining NSCLC tumors are classified as "other" (5%) and "not otherwise specified" (10%) [2]. Initial therapy for NSCLC generally consists of four to six cycles of platinum-based chemotherapy [3], and some patients subsequently receive maintenance therapy [4]. Current clinically approved second-line therapies for non-squamous NSCLC include docetaxel, erlotinib, pemetrexed [5-7], and, very recently in some countries, nintedanib and nivolumab.

Treatment with docetaxel has resulted in improved overall survival (OS) compared with best supportive care [5]. Treatment with erlotinib has been shown to result in improved OS [6] over placebo. Pemetrexed provided overall efficacy similar to that of docetaxel [6] but had a greatly improved safety profile and is only approved and recommended for non-squamous NSCLC [7].

Vascular endothelial growth factors (VEGFs) have emerged as key regulators of angiogenesis, and the expression of VEGFs has been correlated with poor prognosis in several solid tumor types, including NSCLC [8]. Both VEGF and VEGF receptor-2 (VEGFR-2)–mediated signaling have an important role in angiogenesis and tumor growth [9]. Blockade of VEGFR-2 signaling inhibits formation, proliferation, and migration of new blood vessels [10].

The addition of bevacizumab, a recombinant humanized monoclonal antibody against VEGF, to carboplatin-paclitaxel first-line chemotherapy resulted in a significant improvement in OS in eligible patients with non-squamous NSCLC [11]. However, the addition of bevacizumab to first-line cisplatin-gemcitabine did not improve OS, albeit an improvement in progression-free survival (PFS) was observed [12].

Ramucirumab (IMC-1121B, ImClone Systems, Bridgewater, NJ) is a human recombinant IgG1 monoclonal antibody that specifically binds to the extracellular domain of VEGFR-2 with high affinity, preventing binding of VEGF ligands and receptor activation [13]. Two positive phase 3 studies investigating second-line treatment of advanced gastric cancer [14,15] showed that ramucirumab significantly improved survival as a single agent and in combination with paclitaxel. In addition, a positive phase 3 study investigating second-line treatment of metastatic colorectal carcinoma [16] showed that ramucirumab significantly improved survival in combination with folinic acid, 5-fluorouracil, and irinotecan (FOLFIRI).

It is important to note that studies from East Asia have reported higher rates of epidermal growth factor receptor (*EGFR*) mutations in NSCLC patients [17]. The superior response of *EGFR*-mutated NSCLC patients to therapy may impact the analysis of various treatment types, indicating the need to include screening for *EGFR* mutations in routine diagnostics and to analyze the response of East Asian NSCLC patients to therapy as a separate subgroup of the intent-to-treat (ITT) population.

Recognition of differences in OS and toxicity between East Asian and Caucasian patients with NSCLC, with longer survival [18], higher response rates, and greater toxicity to chemotherapy and targeted therapy reported in East Asian patients is increasing [19]. Therefore, subanalyses are now often conducted in East Asian NSCLC patients to establish the dosage in this ethnic group of NSCLC patients.

The REVEL study was a global, randomized, placebo-controlled, double-blind, multi-center phase 3 study comparing docetaxel+ramucirumab combination treatment with docetaxel treatment (docetaxel+placebo) in patients with stage IV NSCLC who showed disease progression after platinum-based therapy. This study showed that docetaxel+ramucirumab combination treatment improves survival as second-line treatment of patients with stage IV NSCLC. The aim of our analysis was to assess the efficacy and safety of docetaxel+ramucirumab combination treatment versus docetaxel treatment in the East Asian versus the non–East Asian subgroups from the REVEL study.

Materials and Methods

1. Study design and patients

The study design and patient eligibility for REVEL has been previously published [20]. Each center's institutional review board or independent ethics committee approved this study. The study followed the guiding principles of the Declaration of Helsinki and the Good Clinical Practice Guidelines of the International Conference on Harmonisation. All patients provided written informed consent before enrollment. The key endpoints evaluated in the East Asian subgroup included OS, PFS, objective response rate (ORR), and safety.

2. Randomization

Randomization and procedures have also been published previously [20]. Patients were randomly assigned on a 1:1

Table 1. Baseline characteristics

Variable	Docetaxel+ramucirumab combination treatment		Docetaxel (docetaxel+placebo)	
	East Asian (n=43)	Non–East Asian (n=585)	East Asian (n=46)	Non–East Asian (n=579)
Age (yr)				
Median (range)	62 (35-81)	62 (21-85)	57.5 (25-78)	61 (26-86)
< 65	27 (62.8)	364 (62.2)	33 (71.7)	374 (64.6)
≥ 65	16 (37.2)	221 (37.8)	13 (28.3)	205 (35.4)
Sex				
Male	36 (83.7)	383 (65.5)	37 (80.4)	378 (65.3)
Female	7 (16.3)	202 (34.5)	9 (19.6)	201 (34.7)
Race[a),b)]				
White	0	526 (89.9)	0	503 (86.9)
Asian	43 (100)	31 (5.3)	46 (100)	40 (6.9)
Black	0	17 (2.9)	0	16 (2.8)
Other	0	11 (1.9)	0	20 (3.5)
Geographic region of origin	43 (100)	585 (100)	46 (100)	579 (100)
ECOG performance status[c),d)]				
0	12 (27.9)	195 (33.3)	11 (23.9)	188 (32.5)
1	31 (72.1)	389 (66.5)	35 (76.1)	390 (67.4)
Missing	0	1 (0.2)	0	1 (0.2)
Disease				
Measurable	42 (97.7)	564 (96.4)	45 (97.8)	558 (96.4)
Non-measurable	1 (2.3)	21 (3.6)	1 (2.2)	21 (3.6)
Smoking history				
Ever	34 (79.1)	484 (82.7)	32 (69.6)	451 (77.9)
Never	9 (20.9)	100 (17.1)	14 (30.4)	127 (21.9)
Unknown	0	1 (0.2)	0	1 (0.2)
Histological subtype				
Non-squamous	28 (65.1)	437 (74.7)	30 (65.2)	417 (72.0)
Squamous	15 (34.9)	142 (24.3)	16 (34.8)	155 (26.8)
Unknown	0	6 (1.0)	0	7 (1.2)
EGFR status				
Wild type	18 (41.9)	189 (32.3)	22 (47.8)	175 (30.2)
Mutant	3 (7.0)	12 (2.1)	1 (2.2)	17 (2.9)
Unknown	22 (51.2)	380 (65.0)	23 (50.0)	383 (66.1)
Missing	0	4 (0.7)	0	4 (0.7)
Best response to platinum based chemotherapy				
CR, PR, or SD	32 (74.4)	388 (66.3)	38 (82.6)	379 (65.5)
PD	8 (18.6)	170 (29.1)	5 (10.9)	177 (30.6)
Missing	3 (7.0)	27 (4.6)	3 (6.5)	23 (4.0)
Previous maintenance treatment				
No	38 (88.4)	455 (77.8)	34 (73.9)	448 (77.4)
Yes	5 (11.6)	130 (22.2)	12 (26.1)	131 (22.6)
Previous taxane				
No	37 (86.0)	438 (74.9)	42 (91.3)	434 (75.0)
Yes	6 (14.0)	147 (25.1)	4 (8.7)	145 (25.0)
Previous bevacizumab				
No	41 (95.3)	499 (85.3)	44 (95.7)	489 (84.5)
Yes	2 (4.7)	86 (14.7)	2 (4.3)	90 (15.5)

Table 1. Continued

Variable	Docetaxel+ramucirumab combination treatment		Docetaxel (docetaxel+placebo)	
	East Asian (n=43)	Non–East Asian (n=585)	East Asian (n=46)	Non–East Asian (n=579)
Time since previous therapy (mo)				
< 9	28 (65.1)	372 (63.6)	31 (67.4)	343 (59.2)
≥ 9	14 (32.6)	212 (36.2)	15 (32.6)	236 (40.8)
Missing	1 (2.3)	1 (0.2)	0	0

Values are presented as median interquartile range or number (%). ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease. [a]As established by self-report, [b]Data not available for one patient in the ramucirumab group, [c]Assessed according to ECOG guidelines, with 0 as asymptomatic, 1 as restricted in strenuous activity but ambulatory and able to do light work, or 2 as ambulatory and capable of all self-care but unable to work, [d]Data not available for one patient in each group.

basis to receive either docetaxel (75 mg/m^2, 60-minute intravenous infusion)+ramucirumab (10 mg/kg, 60-minute intravenous infusion) combination treatment administered on day 1 of a 21-day (3-week) cycle or docetaxel (75 mg/m^2, 60-minute intravenous infusion)+placebo (60-minute intravenous infusion) administered on day 1 of a 3-week cycle.

Randomization was stratified according to Eastern Cooperative Oncology Group performance status (0 vs. 1), sex (female vs. male), prior maintenance therapy (yes vs. no), and geographic region (East Asia vs. non-East Asia). Randomization was performed separately within each of the 16 strata (or cells) defined by all combinations of these four variables.

In May 2012, based on a higher rate of neutropenia and febrile neutropenia in East Asian patients compared to non-East Asian patients, the independent data monitoring committee recommended amending the protocol to reduce the starting dose of docetaxel for newly enrolled patients in East Asia from 75 to 60 mg/m^2. All East Asian patients enrolled at an earlier stage of the study and receiving treatment at the time of this decision remained at the original dose of docetaxel and continued to receive a docetaxel dose of 75 mg/m^2 for the remainder of the study.

3. Statistical analysis

Detailed statistical methods have been previously published [20]. The East Asian population (Korea and Taiwan) used for the subgroup analyses was defined as patients enrolled at study sites in Korea and Taiwan; patients of Korean and Taiwanese ethnicity enrolled at sites in countries other than Korea or Taiwan were not included in the East Asian subgroup.

The non–East Asian population used in the subgroup analyses was defined as patients enrolled at study sites throughout the world outside of Korea and Taiwan.

The primary and secondary endpoints evaluated were OS, PFS, ORR, and safety. Kaplan-Meier analysis and Cox proportional hazards regression were performed for OS and PFS and the Cochran-Mantel-Haenszel test was performed for ORR. This study is registered with http://www.ClinicalTrials.gov (No. NCT01168973).

Results

1. Patients

Baseline demographics, disease characteristics, NSCLC histology, and prior therapy were balanced between treatment arms and the two populations of patients (Table 1).

2. Efficacy

In the 89 East Asian patients, median OS was 15.4 months (95% confidence interval [CI], 10.09 to 21.52) for the docetaxel+ramucirumab combination treatment arm (n=43) and 10.2 months (95% CI, 5.26 to 17.58) for the docetaxel treatment arm (n=46) (stratified hazard ratio [HR], 0.762; 95% CI, 0.444 to 1.307) (Fig. 1A).

In the 1,164 non–East Asian patients, median OS was 10.3 months (95% CI, 9.30 to 11.07) for the docetaxel+ramucirumab combination treatment arm (n=585) and 9.1 months (95% CI, 8.18 to 9.92) for the docetaxel treatment arm (n=579) (stratified HR, 0.864; 95% CI, 0.753 to 0.991) (Fig. 1B).

In East Asian patients, median PFS was 4.9 months (95%

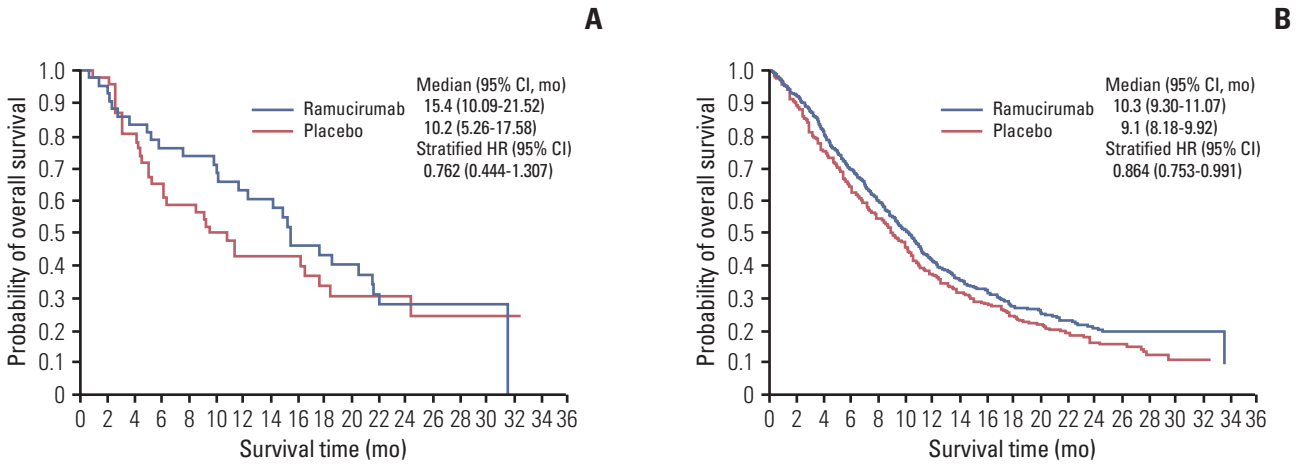

Fig. 1. Kaplan-Meier estimates of overall survival for East Asian patients (A) and non–East Asian patients (B). CI, confidence interval; HR, hazard ratio.

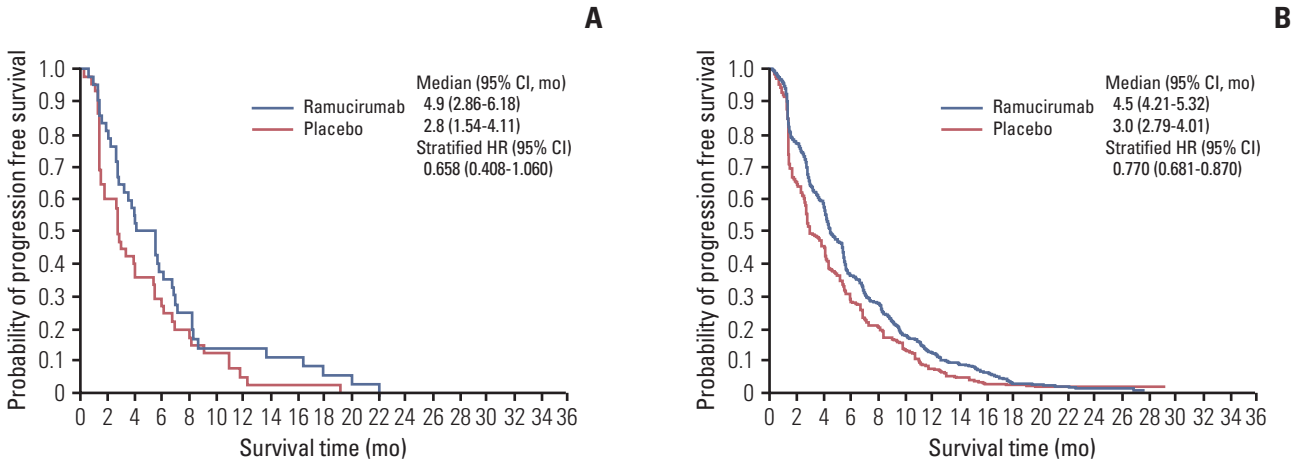

Fig. 2. Kaplan-Meier estimates of progression-free survival for East Asian patients (A) and non–East Asian patients (B). CI, confidence interval; HR, hazard ratio.

CI, 2.86 to 6.18) for the docetaxel+ramucirumab combination treatment arm and 2.8 months (95% CI, 1.54 to 4.11) for the docetaxel treatment arm (stratified HR, 0.658; 95% CI, 0.408 to 1.060) (Fig. 2A). The ORR was 25.6% (95% CI, 13.5 to 41.2) in the docetaxel+ramucirumab combination treatment arm and 8.7% (95% CI, 2.4 to 20.8) in the docetaxel treatment arm (Table 2).

In non–East Asian patients, median PFS was 4.5 months (95% CI, 4.21 to 5.32) for the docetaxel+ramucirumab combination treatment arm and 3.0 months (95% CI, 2.79 to 4.01) for the docetaxel treatment arm (stratified HR, 0.770; 95% CI, 0.681 to 0.870) (Fig. 2B). The ORR was 22.7% (95% CI, 19.4 to 26.3) in the docetaxel+ramucirumab combination treatment arm and 14% (95% CI, 11.3 to 17.1) in the docetaxel treatment arm (Table 2).

3. Safety

A summary of the safety evaluation at the 75 mg/m^2 dose of docetaxel in East Asian and non–East Asian patients is shown in Table 3. A summary of the safety evaluation for newly enrolled East Asian patients (n=24) who received the reduced starting dose of docetaxel (60 mg/m^2) in both the docetaxel+ramucirumab combination and the docetaxel

Table 2. Objective tumor response

Best overall response	East Asian		Non–East Asian	
	Docetaxel+ramucirumab combination treatment (n=43)	Docetaxel (docetaxel+placebo) (n=46)	Docetaxel+ramucirumab combination treatment (n=585)	Docetaxel (docetaxel+placebo) (n=579)
Complete response	0	0	3 (0.5)	2 (0.3)
Partial response	11 (25.6)	4 (8.7)	130 (22.2)	79 (13.6)
Stable disease	19 (44.2)	19 (41.3)	239 (40.9)	225 (38.9)
Objective response	11 (25.6)	4 (8.7)	133 (22.7)	81 (14.0)
95% CI	13.5-41.2	2.4-20.8	19.4-26.3	11.3-17.1
Disease control rate[a]	30 (69.8)	23 (50.0)	372 (63.6)	306 (52.8)
95% CI	53.9-82.8	34.9-65.1	59.5-67.5	48.7-57.0

Values are presented as number (%) unless otherwise indicated. CI, confidence interval. [a]Denotes best response for complete response, partial response, or stable disease.

treatment arms is shown in Table 4.

At the 75 mg/m^2 dose of docetaxel, the number of East Asian patients with at least 1 grade ≥ 3 treatment-emergent adverse event (TEAE) was 31 (96.9%) for the docetaxel+ramucirumab combination treatment arm versus 26 (78.8%) for the docetaxel treatment arm (Table 3). The number of non–East Asian patients with at least 1 grade ≥ 3 TEAE, regardless of causality, was 458 for the docetaxel+ramucirumab combination treatment arm (78.4%) versus 411 for the docetaxel treatment arm (71.9%).

At the reduced starting dose of docetaxel (60 mg/m^2), the number of East Asian patients with at least 1 grade ≥ 3 TEAE was six in the docetaxel+ramucirumab combination treatment arm (54.5%) versus seven in the docetaxel treatment arm (53.8%) (Table 4).

At the 75 mg/m^2 dose of docetaxel, the number of East Asian patients with grade ≥ 3 neutropenia was 26 (81.3%) in the docetaxel+ramucirumab combination treatment arm versus 24 (72.7%) in the docetaxel treatment arm. The number of non–East Asian patients with grade ≥ 3 neutropenia was 274 (46.9%) in the docetaxel+ramucirumab combination treatment arm versus 217 (37.9%) in the docetaxel treatment arm (Table 3).

At the reduced starting dose of 60 mg/m^2 of docetaxel, the number of East Asian patients with grade ≥ 3 neutropenia was six in the docetaxel+ramucirumab combination treatment arm (54.5%) and five in the docetaxel treatment arm (38.5%) (Table 4).

At the 75 mg/m^2 dose, the number of East Asian patients with febrile neutropenia was 14 in the docetaxel+ramucirumab combination treatment arm (43.8%) versus four in the docetaxel treatment arm (12.1%). The number of non–East Asian patients with febrile neutropenia was 86 in the docetaxel+ramucirumab combination treatment arm (14.7%) versus 57 in the docetaxel treatment arm (10.0%).

At the reduced starting dose of 60 mg/m^2 of docetaxel, the number of East Asian patients with febrile neutropenia was 0 in the docetaxel+ramucirumab combination treatment arm and one (7.7%) in the docetaxel+treatment arm.

In East Asian patients, at the 75 mg/m^2 dose of docetaxel, the categories of adverse events of special-interest (AESIs), regardless of grade, and potentially associated with the VEGF pathway, that occurred more frequently in the docetaxel+ramucirumab combination treatment arm versus the docetaxel treatment arm were bleeding/hemorrhage events (11 patients [34.4%] vs. 4 patients [12.1%]), pulmonary hemorrhage events (5 patients [15.6%] vs. 3 patients [9.1%]), gastrointestinal hemorrhage events (2 patients [6.3%] vs. 0 patient), gastrointestinal perforation (2 patients [6.3%] vs. 0 patient), and proteinuria (1 patient [3.1%] vs. 0 patient). In non–East Asian patients, at the 75 mg/m^2 dose of docetaxel, any grade AESIs that occurred more frequently in the docetaxel+ramucirumab combination treatment arm versus the docetaxel treatment arm were bleeding/hemorrhage events (167 patients [28.6%] vs. 88 patients [15.4%]), gastrointestinal hemorrhage events (15 patients [2.6%] vs. 10 patients [1.7%]), gastrointestinal perforation (4 patients [0.7%] versus 2 patients [0.3%]), and proteinuria (18 patients [3.1%] vs. 5 patients [0.9%]) (Table 3).

In East Asian patients, at the reduced starting dose of 60 mg/m^2 of docetaxel, any grade AESIs potentially associated with the VEGF pathway and that occurred more frequently in the docetaxel+ramucirumab combination treatment arm vs. the docetaxel treatment arm were bleeding/hemorrhage events (3 patients [27.3%] vs. 2 patients [15.4%]), pulmonary hemorrhage events (2 patients [18.2%] vs. 1 patient [7.7%]), proteinuria (2 patients [18.2%] vs. 0 patient), and hypertension (3 patients [27.3%] vs. 0 patient) (Table 4).

Table 3. Summary of treatment-emergent adverse events at 75 mg/m^2 docetaxel in ≥ 20% East Asian and non–East Asian patients in the docetaxel+ramucirumab combination treatment arm

Variable	Docetaxel+ramucirumab combination treatment (75 mg/m^2)				Docetaxel (docetaxel+placebo) (75 mg/m^2)			
	East Asian (n=32)		Non–East Asian (n=584)		East Asian (n=33)		Non–East Asian (n=572)	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Adverse event								
Decreased appetite	21 (65.6)	0	158 (27.1)	14 (2.4)	12 (36.4)	0	136 (23.8)	8 (1.4)
Stomatitis	16 (50.0)	1 (3.1)	124 (21.2)	26 (4.5)	12 (36.4)	0	66 (11.5)	10 (1.7)
Dyspnea	14 (43.8)	0	122 (20.9)	23 (3.9)	8 (24.2)	1 (3.0)	140 (24.5)	50 (8.7)
Fatigue[a)]	15 (46.9)	1 (3.1)	324 (55.5)	87 (14.9)	13 (9.4)	0	291 (50.9)	65 (11.4)
Diarrhea	12 (37.5)	1 (3.1)	186 (31.8)	28 (4.8)	8 (24.2)	0	160 (28.0)	19 (3.3)
Myalgia	12 (37.5)	0	64 (11.0)	4 (0.7)	12 (36.4)	0	52 (9.1)	4 (0.7)
Productive cough	12 (37.5)	0	26 (4.5)	1 (0.2)	4 (12.1)	0	25 (4.4)	2 (0.3)
Pyrexia	12 (37.5)	0	92 (15.8)	3 (0.5)	5 (15.2)	0	72 (12.6)	2 (0.3)
Alopecia	11 (34.4)	0	146 (25.0)	0	15 (45.5)	0	138 (24.1)	0
Anemia[a)]	10 (31.3)	3 (9.4)	118 (20.2)	15 (2.6)	9 (27.3)	2 (6.1)	163 (28.5)	33 (5.8)
Insomnia	10 (31.3)	0	57 (9.8)	3 (0.5)	4 (12.1)	0	42 (7.3)	1 (0.2)
Cough	9 (28.1)	0	121 (20.7)	3 (0.5)	7 (21.2)	0	116 (20.3)	5 (0.9)
Nausea	9 (28.1)	0	159 (27.2)	7 (1.2)	4 (12.1)	0	164 (28.7)	9 (1.6)
Oropharyngeal pain	8 (25.0)	0	38 (6.5)	0	5 (15.2)	0	26 (4.5)	0
Peripheral sensory neuropathy[a)]	8 (25.0)	0	63 (10.8)	13 (2.2)	8 (24.2)	0	50 (8.7)	4 (0.7)
Hematologic adverse events								
Neutropenia[a)]	27 (84.4)	26 (81.3)	312 (53.4)	274 (46.9)	24 (72.7)	24 (72.7)	255 (44.6)	217 (37.9)
Febrile neutropenia	14 (43.8)	14 (43.8)	86 (14.7)	86 (14.7)	4 (12.1)	4 (12.1)	57 (10.0)	57 (10.0)
Anemia	10 (31.3)	3 (9.4)	118 (20.2)	15 (2.6)	9 (27.3)	2 (6.1)	160 (20.8)	32 (5.6)
Thrombocytopenia[a)]	3 (9.4)	2 (6.3)	79 (13.5)	15 (2.6)	0	0	32 (5.6)	4 (0.7)
AESIs (categories)								
Bleeding/Hemorrhage	11 (34.4)	0	167 (28.6)	15 (2.6)	4 (12.1)	0	88 (15.4)	14 (2.4)
Pulmonary/Hemorrhage	5 (15.6)	0	42 (7.2)	8 (1.4)	3 (9.1)	0	42 (7.3)	8 (1.4)
GI hemorrhage	2 (6.3)	0	15 (2.6)	4 (0.7)	0	0	10 (1.7)	2 (0.3)
GI perforation	2 (6.3)	2 (6.3)	4 (0.7)	3 (0.5)	0	0	2 (0.3)	2 (0.3)
Infusion-related reaction	1 (3.1)	0	22 (3.8)	5 (0.9)	3 (9.1)	0	22 (3.8)	3 (0.5)
Proteinuria	1 (3.1)	0	18 (3.1)	1 (0.2)	0	0	5 (0.9)	0

Values are presented as number (%). AESIs, adverse events of special interest; GI, gastrointestinal. [a)]Consolidated adverse event category comprising synonymous MedDRA ver. 16.1 preferred terms.

Discussion

Although this subgroup analysis of the East Asian population vs. the non–East Asian population is not powered to demonstrate significant improvement, in the East Asian subgroup that received docetaxel+ramucirumab combination treatment, compared with the East Asian subgroup treated with docetaxel+placebo, the trend of prolonged OS (15.4 months vs. 10.2 months, respectively) (Fig. 1A), PFS (4.9 months vs. 2.8 months, respectively) (Fig. 2A), and ORR (25.6% vs. 8.7%, respectively) (Table 2) is consistent with the treatment effect observed in the overall ITT population in the REVEL trial.

Pharmacological studies of docetaxel have indicated a slower plasma clearance of docetaxel in Asian patients compared with Caucasian patients [21]. In addition, according to several studies, adverse events (AEs), predominantly hematological AEs, are higher in Asians than in Caucasians receiving docetaxel [21,22], with neutropenia being the predominant toxicity [22]. Studies in East Asian patients with NSCLC have indicated the need to decrease the dose of docetaxel or use the prophylactic support of growth factors in this ethnic group [22]. In a Japanese study, a reduction in

Table 4. Summary of treatment-emergent adverse events at reduced (60 mg/m²) dose of docetaxel in ≥ 20% East Asian patients in the docetaxel+ramucirumab combination treatment arm

Variable	Docetaxel+ramucirumab combination (60 mg/m²) (n=11)		Docetaxel (docetaxel+placebo) (60 mg/m²) (n=13)	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Adverse event				
Decreased appetite	3 (27.3)	0	6 (46.2)	0
Stomatitis	6 (54.5)	0	2 (15.4)	0
Fatigue[a)]	4 (36.4)	0	5 (38.5)	0
Alopecia	5 (45.5)	0	3 (23.1)	0
Anemia[a)]	3 (27.3)	0	2 (15.4)	0
Cough	3 (27.3)	0	5 (38.5)	0
Pneumonia	3 (27.3)	3 (27.3)	1 (7.7)	1 (7.7)
Hypertension	3 (27.3)	1 (9.1)	0	0
Hematologic adverse events				
Neutropenia[a)]	6 (54.5)	6 (54.5)	5 (38.5)	5 (38.5)
Febrile neutropenia	0	0	1 (7.7)	1 (7.7)
Anemia	3 (27.3)	0	2 (15.4)	0
Thrombocytopenia	2 (18.2)	1 (9.1)	0	0
AESIs (categories)[b)]				
Bleeding/Hemorrhage	3 (27.3)	0	2 (15.4)	0
Pulmonary/Hemorrhage	2 (18.2)	0	1 (7.7)	0
Proteinuria	2 (18.2)	0	0	0
Hypertension	3 (27.3)	1 (9.1)	0	0

Values are presented number (%). AESIs, adverse events of special interest. [a)]Consolidated adverse event category comprising synonymous MedDRA ver. 16.1 preferred terms, [b)]Not subjected to the ≥ 20% criterion.

the starting dose of docetaxel from 75 to 60 mg/m² was associated with an improved safety profile and a reduction in the incidence of neutropenia and febrile neutropenia in Japanese patients [23].

In the current study, a decrease in the dosage of docetaxel resulted in decreased incidence of neutropenia in East Asian patients to a rate similar to that observed in non–East Asian patients (54.5% in East Asian patients in the 60 mg/m² docetaxel group vs. 53.4% in non–East Asian patients). In addition, the incidence of febrile neutropenia in East Asian patients showed a similar decrease with the lowering of the starting docetaxel dose (0 in East Asian patients in the 60 mg/m² docetaxel group vs. 14.7% in non–East Asian patients).

This analysis did not show an increased risk of sepsis, and there was no significant increase in thromboembolic events in the docetaxel+ramucirumab combination treatment group in both the East Asia and non–East Asia subgroups. Hypertension was mild and bleeding events in patients who received docetaxel+ramucirumab combination treatment were mainly due to grade 1-2 epistaxis in both the East Asia and non–East Asia subgroups.

Ramucirumab binds specifically to the extracellular domain of VEGFR-2, rather than the VEGF ligand; therefore, the effects of ramucirumab may be localized to abnormal vasculature [24]. Several studies of small-molecule VEGF inhibitors have not resulted in improved OS; however, some have been associated with benefits in PFS, particularly in the setting of NSCLC [25]. In the current study, ramucirumab showed an advantage in OS in previously treated NSCLC patients, while bevacizumab has been shown to prolong survival as first-line therapy for non-squamous NSCLC [12].

The current analysis of the REVEL trial had some limitations. First, the REVEL trial was not powered to show a significant improvement in East Asian patients. Second, as mentioned earlier, due to the higher incidence of *EGFR* mutations in East Asian NSCLC patients [13,14], a *post hoc* analysis would have been beneficial in factoring in the number of patients with *EGFR* mutations; however, *EGFR* mutation testing was not required for study entry, and the number of patients with known *EGFR*-positive mutation status in the overall REVEL population was very small (33 patients) and even smaller in the East Asia subgroup (n=3) (Table 1) [20].

Conclusion

In the REVEL trial, docetaxel (75 mg/m^2)+ramucirumab combination treatment was well tolerated in the non-East Asia subgroup and at the reduced starting dose of 60 mg/m^2 in the East Asia subgroup. The reduced dose of docetaxel in the East Asia subgroup had a positive effect on safety with a decrease in the incidence of neutropenia and febrile neutropenia and a decrease in the overall frequency of grade ≥ 3 TEAEs. REVEL demonstrated a favorable benefit-risk profile in East Asian patients with stage IV NSCLC who showed disease progression after platinum-based chemotherapy. Consistent with the ITT population results, this subgroup analysis showed a trend in the prolongation of median OS and PFS and improved ORR in the East Asia patient population treated with docetaxel+ramucirumab combination treatment, in conjunction with favorable tolerability based on manageable AEs.

The results of the REVEL trial indicate a significant new second-line therapeutic option for East Asian patients with advanced NSCLC after platinum-based chemotherapy.

Conflicts of Interest

Jin-Hyoung Kang and Jin-Yuan Shih received honoraria from Eli Lilly and Company. Annamaria Hayden Zimmermann, Pablo Lee, Ekaterine Alexandris, Tarun Puri, and Mauro Orlando are employees of Eli Lilly & Company. Tarun Puri and Mauro Orlando hold stock with Eli Lilly and Company. All remaining authors have declared no conflicts of interest.

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