Original research article

Outcomes in patients with aggressive or refractory disease from REVEL: A randomized phase III study of docetaxel with ramucirumab or placebo for second-line treatment of stage IV non-small-cell lung cancer☆

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ABSTRACT

Objectives: The REVEL study demonstrated improved efficacy for patients with advanced non-small cell lung cancer treated with ramucirumab plus docetaxel, independent of histology. This exploratory analysis characterized the treatment effect in REVEL patients who were refractory to prior first-line treatment.

Materials and methods: Refractory patients had a best response of progressive disease to first-line treatment. Endpoints included overall survival (OS), progression-free survival (PFS), objective response rate (ORR), quality of life (QoL), and safety. Kaplan-Meier and Cox proportional hazards regression were performed for OS and PFS, and Cochran-Mantel-Haenszel test was used for response. QoL was assessed with the Lung Cancer Symptom Scale. Sensitivity analyses were performed on subgroups of the intent-to-treat population with limited time on first-line therapy.

Results: Of 1253 randomized patients in REVEL, 360 (29%) were refractory to first-line treatment. Baseline characteristics were largely balanced between treatment arms. In the control arm, median OS for refractory patients was 6.3 versus 10.3 months for patients not meeting this criterion, demonstrating the poor prognosis of refractory patients. Median OS (8.3 vs. 6.3 months; HR, 0.86; 95% CI, 0.68–1.08), median PFS (4.0 vs. 2.5 months; HR, 0.71; 95% CI, 0.57–0.88), and ORR (22.5% vs. 12.6%) were improved in refractory patients treated with ramucirumab compared to placebo, without new safety concerns or further deteriorating patient QoL.

Conclusions: The effect of ramucirumab in refractory patients is similar to that in the intent-to-treat population.

The benefit/risk profile for refractory patients suggests that ramucirumab plus docetaxel is an appropriate treatment option even in this difficult-to-treat population.

1. Introduction

A majority of patients with non-small cell lung cancer (NSCLC) have advanced-stage disease at diagnosis [1,2]. First-line systemic treatment options for these patients are limited, providing a median overall survival (OS) of 8–13 months and a 5-year survival rate of only 4% [1,3–9]. Most NSCLC patients remain fit enough to receive second-line treatment after first-line platinum-based chemotherapy [11–13]. Although recent advances have improved clinical outcomes for patients with tumors harboring targetable driver mutations, most NSCLC tumors lack these mutations, highlighting the need for novel therapeutic interventions [10,13–15].

Vascular endothelial growth factor (VEGF) and VEGF receptor-2 (VEGFR-2)-mediated signaling play a major role in angiogenesis and tumor growth [16–18]. Several targeted therapies inhibiting VEGF-mediated angiogenesis have been developed as VEGF is both over-expressed and associated with poor clinical outcomes [19,20]. Bevacizumab added to standard treatments was shown to be beneficial to patients with NSCLC in the first- and second-line setting [21,22]. Nintedanib, a triple angiokinase inhibitor that inhibits signaling pathways activated by VEGF, fibroblast growth factor, and platelet-derived growth factor, in combination with docetaxel, improved survival in second-line NSCLC patients with adenocarcinoma histology when compared with docetaxel [23].

Ramucirumab is a human monoclonal antibody that specifically binds to the extracellular domain of VEGFR-2 with high affinity, inhibiting binding of VEGF ligands and receptor activation [24]. In REVEL, a large phase III trial, second-line ramucirumab plus docetaxel demonstrated improved OS, progression-free survival (PFS), and objective response rate (ORR) versus placebo plus docetaxel in patients with advanced NSCLC, independent of histology [25]. Accordingly, ramucirumab in combination with docetaxel has been approved for treatment of metastatic NSCLC with disease progression on or after platinum-based chemotherapy [26].

Patients with advanced NSCLC that is aggressive and rapidly progresses after first-line treatment have a poor prognosis and have been studied in several trials. The LUME-Lung 1 study identified time since start of first-line therapy (TSPT) < 9 months (defined as time from start of first-line therapy to start of second-line therapy) as a predictive marker of improved outcomes with nintedanib in combination with docetaxel in patients with advanced NSCLC with adenocarcinoma histology (median OS of 10.9 months vs. 7.9 months; hazard ratio [HR], 0.75; 95% confidence interval [CI], 0.60–0.92; log-rank $p = 0.0073$ for the nintedanib arm vs. placebo arm) [23,27]. In a prespecified analysis, the REVEL study also demonstrated a survival advantage for ramucirumab plus docetaxel-treated patients with advanced NSCLC and TSPT < 9 months, independent of histology [25]. Whereas results from the REVEL study represent a broader patient population, results from the LUME-Lung 1 study represent those with only adenocarcinoma histology. Taken together, these studies suggest that patients with advanced NSCLC and a poorer prognosis may potentially derive meaningful benefit from second-line therapy. This was the basis for our investigation into a more clinically meaningful and relevant way to describe advanced NSCLC patients who are high-risk and have aggressive disease. Refractory patients, those with a best response of progressive disease (PD) to first-line therapy, fit this description. The objective of this exploratory analysis was to characterize the treatment effect of ramucirumab plus docetaxel in patients from the REVEL study with advanced NSCLC who had aggressive disease and were refractory to first-line therapy. The relationship between these refractory patients

and other definitions of rapidly progressive disease will be discussed.

2. Materials and methods

2.1. Study design and patients

This exploratory subgroup analysis examined refractory patients from the REVEL study. REVEL was a randomized, double-blind, placebo-controlled phase III study in which patients were randomized 1:1 to receive intravenous (IV) docetaxel 75 mg/m^2 plus IV ramucirumab 10 mg/kg (ramucirumab arm) or placebo (control arm) on day 1 of a 21-day cycle [25]. Patients were refractory to first-line treatment if during that treatment they had a best overall response of PD according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

Patients were treated until radiographically confirmed disease progression, unacceptable toxicity, withdrawal, or death.

2.2. Outcomes and assessments

The primary endpoint was OS (time from randomization until death from any cause). Secondary endpoints included PFS (time from randomization until disease progression or death), ORR (percentage of patients with a complete or partial response), and disease control rate (DCR; percentage of patients with tumor response or stable disease), which were assessed according to RECIST v1.1 at baseline and every 6 weeks thereafter. Adverse events were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.0 [28]. Quality of life (QoL) was assessed at baseline, the end of each cycle, and at the 30-day follow-up using the Lung Cancer Symptom Scale (LCSS) [25,29,30].

2.3. Statistical analysis

The statistical analysis plan for the REVEL study [25], noted that REVEL was not powered for subgroup analyses. This exploratory analysis was conducted on the efficacy endpoints for the refractory population. Sensitivity analyses on other subgroups of patients with aggressive or rapidly progressing disease from the REVEL ITT population were explored. These included patients of all histologies or with only adenocarcinoma histology who remained on first-line therapy for short periods of time (≤4, ≤8, and ≤12 weeks) from the start of first-line therapy. We also included further characterization of patients with TSPT < 9 months with all histologies, nonsquamous, adenocarcinoma only, or squamous histologies. Kaplan-Meier estimates and Cox regression analyses of OS and PFS were performed for all subgroups. The log-rank test was used to compare survival outcomes. We compared ORRs and DCRs using the Cochran-Mantel-Haenszel test. In refractory patients, quality-of-life analysis used the Kaplan-Meier method and Cox regression to compare time to deterioration for each item of the LCSS as well as the total LCSS and the average symptom burden index (ASBI) between arms, with deterioration defined as a prespecified 15-mm or greater increase from baseline.

Treatment effects for OS and PFS were estimated using a multivariate Cox model by stepwise selection method. The stepwise selection used *p*-value < 0.05 as the criterion for including a variable and *p*-value ≥ 0.10 for excluding a variable. Potential covariates included best response to platinum-based chemotherapy (yes/no); geographic region; Eastern Cooperative Oncology Group performance status (ECOG PS); epidermal growth factor receptor status; prior maintenance therapy; prior bevacizumab treatment; prior taxane treatment; histology

(nonsquamous vs. squamous); race; gender; smoking history; age (< 65 vs. ≥65). Treatment was not used in the model building, but was forced into the final model. The HRs for treatment effect and the corresponding 95% CI were estimated from the final model. SAS version 9.1.2 or higher was used for all statistical analyses.

3. Results

3.1. Patients with TSPT < 9 months

Patients from the REVEL study with TSPT < 9 months had balanced baseline characteristics and post-discontinuation therapy (data on file, Eli Lilly and Company) across treatment arms (ramucirumab plus docetaxel versus placebo plus docetaxel). Patients treated with ramucirumab plus docetaxel (ramucirumab arm) had longer survival and better outcomes than those treated with placebo plus docetaxel (control arm) among patients with TSPT < 9 months (Supplemental Table 1) [25]. Results were trending in favor of ramucirumab plus docetaxel treatment across exploratory analyses by histology. In particular, nonsquamous patients with TSPT < 9 months had median OS of 9.7 months vs 6.9 months (HR 0.70 [95% CI 0.58, 0.85]), adenocarcinoma patients had median OS of 9.7 months vs 7.0 months (HR 0.71 [0.57, 0.89]), and squamous patients had median OS of 8.9 months vs 7.2 months (HR 0.84 [0.63, 1.14]) (Supplemental Table S1, Supplemental Fig. S1 and S2). These results prompted further investigation into patients with aggressive disease.

3.2. Refractory patients

In order to examine a subgroup of patients with a more clinically intuitive characterization of their aggressive disease based on a patient's response to therapy, we also examined patients who were refractory to first-line therapy. In the REVEL study, 28% of the ramucirumab arm and 29% of the control arm were refractory. Baseline disease and patient characteristics were largely balanced between treatment arms (Table 1) and were mostly similar to those observed for patients who responded to first-line therapy (Supplemental Table S2). Median age was similar between arms (ramucirumab, 63 years [range, 23–84] vs. control, 60 years [range, 29–87]). Most refractory patients had an ECOG PS of 1 (ramucirumab, 70% vs. control, 73%) and started second-line therapy within 9 months of initiating first-line treatment (ramucirumab, 88% vs. control, 85%). The refractory population included patients with nonsquamous (ramucirumab, 73% vs. control, 71%) or squamous (ramucirumab, 26% vs. control, 27%) histology; a subset of 213 REVEL refractory patients had adenocarcinoma histology.

3.3. Treatment administration in refractory patients

Treated refractory patients in the ramucirumab arm (n = 178) received a median of four cycles of ramucirumab (range, 1–23 cycles) and four cycles of docetaxel (range, 1–23 cycles); treated patients in the control arm (n = 180) received a median of three cycles of placebo (range, 1–32 cycles) and three cycles of docetaxel (range, 1–21 cycles; Supplemental Table S3). The median duration of ramucirumab or docetaxel treatment for patients in the ramucirumab arm was 12 weeks for both ramucirumab (range, 3–76 weeks) and docetaxel (range, 3–76 weeks). The median duration of placebo or docetaxel treatment for patients in the control arm was 9 weeks for both placebo (range, 3–103 weeks) and docetaxel (range, 3–66 weeks).

Treatment after study discontinuation was balanced between treatment arms (81 of 178 patients [46%] in the ramucirumab arm vs. 82 of 182 [45%] patients in the control arm; Supplemental Table S4).

3.4. Efficacy in refractory patients

For refractory patients, median OS for the ramucirumab arm was 8.3 months compared to 6.3 months for the control arm (HR, 0.86; 95% CI, 0.68–1.08; log-rank *p* = 0.197, Fig. 1A). A stepwise Cox proportional hazards model identified two significant prognostic factors for OS: ECOG PS (0 vs. 1) and time since prior therapy (< 9 months vs.

Table 1

Baseline patient and disease characteristics in REVEL refractory patients.

Parameter	RAM + DOC (N = 178)	PBO + DOC (N = 182)
Gender, *n* (%)		
Female	41 (23)	55 (30)
Male	137 (77)	127 (70)
Age, years		
Median age (range)	63 (23–84)	60 (29–87)
18– < 65, *n* (%)	116 (65)	138 (76)
≥65, *n* (%)	62 (35)	44 (24)
Race, *n* (%)		
White	149 (84)	149 (82)
Asian	24 (13)	30 (16)
African American	4 (2)	2 (1)
American Indian or Alaska native	0	1 (< 1)
Native Hawaiian or Other Pacific Islander	1 (< 1)	0
ECOG PS, *n* (%)		
0	53 (30)	50 (27)
1	125 (70)	132 (73)
Smoking history, *n* (%)		
Ever	152 (85)	142 (78)
Never	26 (15)	39 (21)
Missing	0 (0)	1 (< 1)
Pathological diagnosis at study entry, *n* (%)		
Nonsquamous	130 (73)	130 (71)
Adenocarcinoma	112 (63)	101 (55)
Squamous	46 (26)	50 (27)
Missing	2 (1)	2 (1)
Tumor baseline diameter, cm		
Mean (SD)	9 (5)	9 (6)
Median	7	7
Minimum	1	1
Maximum	24	38
Number of metastatic sites, *n* (%)		
1	29 (16)	21 (12)
2	46 (26)	48 (26)
≥3	102 (57)	112 (62)
Missing	1 (< 1)	1 (< 1)
***EGFR* at baseline, *n* (%)**		
Wild type	54 (30)	58 (32)
Mutant	2 (1)	2 (1)
Unknown/missing	122 (69)	122 (67)
Prior bevacizumab, *n* (%)		
No	159 (89)	168 (92)
Yes	19 (11)	14 (8)
Prior taxane (paclitaxel), *n* (%)		
No	138 (78)	147 (81)
Yes	40 (22)	35 (19)
Prior maintenance therapy, *n* (%)		
No	170 (96)	169 (93)
Yes[a]	8 (4)	13 (7)
Time since initiation of prior therapy[b], *n* (%)		
< 9 months	156 (88)	154 (85)
≥9 months	22 (12)	28 (15)

DOC, docetaxel; EGFR, epidermal growth factor receptor; ECOG PS, Eastern Cooperative Oncology Group performance status; *N*, number of patients in population; *n*, number of patients in a group; PBO, placebo; RAM, ramucirumab.

[a] These 21 patients were documented as having received prior therapy indicated for use as maintenance therapy at some point prior to receiving study drug.

[b] Time since initiation of prior therapy (< 9 months vs. ≥9 months) is describing a characteristic of the refractory patients included in this study. The majority of refractory patients had < 9 months since the start of prior therapy.
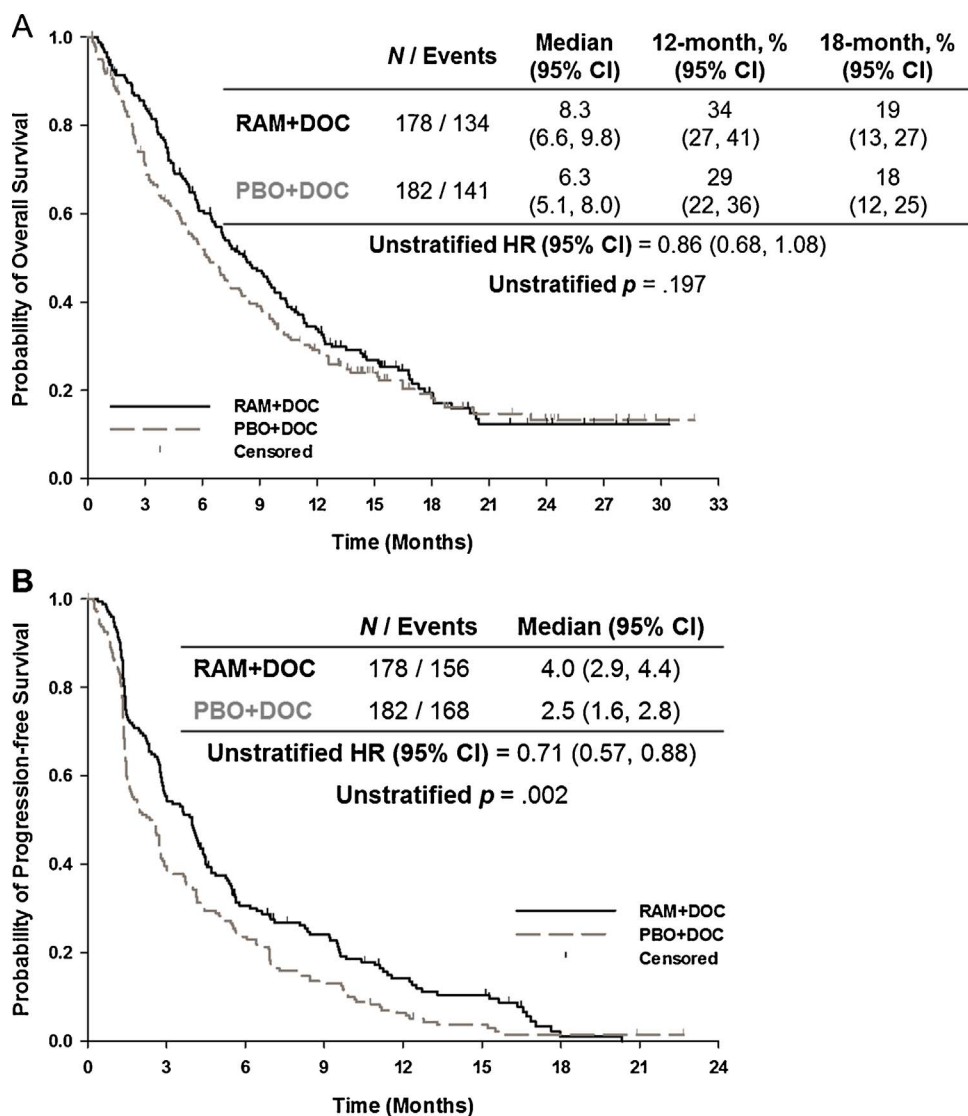
Fig. 1. Overall survival (A) and progression-free survival (B) in REVEL refractory patients (best response of progressive disease to first-line therapy) receiving ramucirumab and docetaxel compared with that in patients receiving placebo and docetaxel. CI, confidence interval; DOC, docetaxel; HR, hazard ratio; N, number of patients in treatment arm; PBO, placebo; RAM, ramucirumab.

≥9 months). The treatment effect was similar after adjusting for these factors (HR, 0.84; 95% CI, 0.66–1.06). Median PFS was longer for refractory patients in the ramucirumab versus control arm (4.0 months vs. 2.5 months; HR, 0.71; 95% CI, 0.57–0.88; log-rank) (Fig. 1B). The treatment effect of PFS was similar after adjusting for the significant baseline prognostic factor of ECOG PS 0 versus 1 (HR, 0.69; 95% CI, 0.56–0.86). The ORR (22.5% vs. 12.6%) and DCR (52.2% vs. 42.3%) for the refractory population were both higher in the ramucirumab arm (Table 2).

In the 213 refractory patients who also had adenocarcinoma histology, median OS was 8.5 months for the ramucirumab arm versus 6.2 months for the control arm (HR 0.78 [95% CI, 0.57–1.07]). The median PFS was 4.0 months in the ramucirumab arm versus 2.6 months in the control arm (HR 0.64 [95% CI, 0.48–0.85]) (Supplemental Fig. S3). The ORR was 20% versus 15% and the DCR was 51% versus 47% in the ramucirumab arm versus control arm, respectively.

3.5. Safety in refractory patients

A safety overview for refractory patients is shown in Table 3. A majority of the patients had treatment-emergent adverse events (TEAEs) in both treatment arms (97% vs. 95%). The number of patients with grade ≥3 toxicity was similar between the two arms (ramucirumab [74%] versus control [70%]). Dose adjustments required due to

TEAEs were higher in the ramucirumab arm (40% vs. 29%). However, discontinuations (5% vs. 4%) due to TEAEs and the incidence of serious TEAEs (45% vs. 47%) were similar between arms. The incidence of death from TEAEs was 6% in the ramucirumab arm and 9% in the control arm.

Table 2
Response in REVEL refractory patients.

Best Overall Response	RAM + DOC (N = 178)	PBO + DOC (N = 182)
CR, n (%)	1 (< 1)	1 (< 1)
PR, n (%)	39 (22)	22 (12)
SD, n (%)	53 (30)	54 (30)
ORR (CR + PR), % (95% CI)	22.5 (17, 29)	12.6 (8, 18)
p-value	0.014	
DCR (CR + PR + SD), % (95% CI)	52.2 (45, 60)	42.3 (35, 50)
p-value	0.049	

CI, confidence interval; CR, complete response; DCR, disease control rate; DOC, docetaxel; HR, hazard ratio; N, number of patients; n, number of patients in a group; ORR, objective response rate; PBO, placebo; PR, partial response; RAM, ramucirumab; SD, stable disease.

Table 3
Safety overview for REVEL refractory patients.

Parameter, n (%)	RAM + DOC (N = 178)	PBO + DOC (N = 180)
Any TEAE	173 (97)	171 (95)
Grade ≥3	131 (74)	126 (70)
TEAE leading to discontinuation	9 (5)	7 (4)
Ramucirumab/placebo	3 (2)	3 (2)
Docetaxel	6 (3)	4 (2)
TEAE leading to dose adjustment	71 (40)	52 (29)
Ramucirumab/placebo	53 (30)	33 (18)
Docetaxel	67 (38)	49 (27)
TEAE leading to death	11 (6)	17 (9)
TESAE	80 (45)	84 (47)

DOC, docetaxel; N, number of patients in population; n, number of patients in a group; PBO, placebo; RAM, ramucirumab; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event.

3.6. Quality of life in refractory patients

The QoL in refractory patients was similar between the ramucirumab and control arms (Fig. 2). Time to deterioration for each LCSS item was similar between arms; HRs ≤1 (favoring the ramucirumab arm) were observed for fatigue, dyspnea, hemoptysis, activity level, and global quality of life (Fig. 2).

3.7. Sensitivity analyses for patients with rapid progression

Exploratory analyses on other subgroups of patients from the REVEL ITT population with aggressive disease who had limited time on first-line therapy reflect similar outcomes to those seen in the population of refractory patients.

The results from patients in the REVEL ITT population who were on first-line therapy for ≤4, ≤8, and ≤12 weeks reflect a trend towards benefit from ramucirumab plus docetaxel in all subgroups, consistent with the overall ITT population and refractory subgroup (Table 4). Results from exploratory sensitivity analyses conducted for refractory patients with adenocarcinoma histology were similar (Supplemental Table S5).

4. Discussion

Patients from the REVEL study who were refractory to first-line therapy and treated with ramucirumab plus docetaxel, compared with those who received placebo plus docetaxel, had significantly improved

PFS, ORR, and DCR independent of histology. The median OS was also numerically improved, and overall treatment effects were consistent with those observed in the ITT population [25]. Similar rates of grade ≥3 TEAEs, serious adverse events, TEAEs leading to discontinuation, and fatal TEAEs were noted in the two arms in refractory patients, and were also similar to those previously seen in the ITT population (ITT ramucirumab vs. control: grade ≥3 TEAEs 79% vs. 72%, serious adverse events 43% vs. 42%, fatal TEAEs 5% vs. 6%) [25]. The demonstration of no added safety burden due to the addition of ramucirumab in this vulnerable population is strengthened by the observation that QoL outcomes are comparable to those from the REVEL ITT population (ITT total LCSS: HR, 0.99; 95% CI, 0.81–1.22 and ITT ASBI: HR, 0.93; 95% CI, 0.75–1.15) [30]. Moreover, post-discontinuation treatment for refractory patients was balanced between arms. This balance suggests that the observed benefit seen in refractory patients may be attributed to a treatment effect of ramucirumab in combination with docetaxel and is not at the further detriment to patient QoL.

It is difficult to uniquely define patients with rapidly progressing tumors. Having shorter time since start of prior therapy may be used in clinical trials as a marker for poorer prognosis. This was highlighted in the LUME-Lung 1 study that identified time since prior therapy of < 9 months as a prognostic marker for patients with advanced NSCLC and adenocarcinoma histology [27]. Ramucirumab plus docetaxel demonstrated improved efficacy in a population with TSPT < 9 months, independent of histology, as previously described and further characterized herein [25]. Similar results were seen in REVEL patients < 9 months TSPT with only adenocarcinoma histology (Supplemental Table S1). However, the clinical significance of a cutoff of 9 months is difficult to assess. In this study, we explored a more clinically meaningful description of patients with aggressive or rapidly progressing tumors. As anticipated, the population of refractory patients did overlap strongly with the population of patients who were less than 9 months from prior therapy (86% of refractory patients also had < 9 months from the start of prior therapy [Table 1]).

Patients who are refractory to treatment in the first-line setting likely have aggressive disease or tumors inherently resistant to treatments, thus representing an especially challenging and vulnerable population with a high unmet medical need. Prognosis for the refractory patients from the REVEL study was poor, considering the median OS in the control arm was only 6.3 months, versus 10.3 months for those who were not refractory [25]. Despite a poor prognosis, refractory patients were still fit enough for a chemotherapy-based regimen, as their baseline demographics and clinical characteristics were similar to those in the REVEL ITT population [25]. The median OS for refractory patients treated with ramucirumab plus docetaxel was 2 months longer than
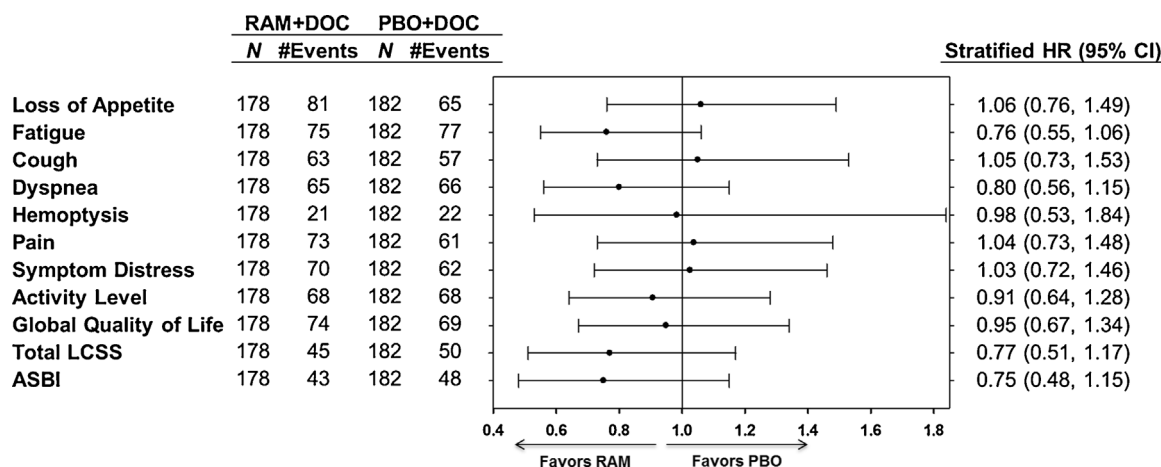

Fig. 2. Time to deterioration for Lung Cancer Symptom Scale in REVEL refractory patients. Summary of time to deterioration in each Lung Cancer Symptom Scale item and summary scores. ASBI, average symptom burden index; CI, confidence interval; DOC, docetaxel; HR, hazard ratio; LCSS, Lung Cancer Symptom Scale; N, number of patients in treatment arm; PBO, placebo; RAM, ramucirumab.

Table 4
Exploratory sensitivity analysis of efficacy in REVEL ITT patients.

ITT Population	Duration of First-line Therapy					
	≤ 4 Weeks		≤ 8 Weeks		≤ 12 Weeks	
	RAM + DOC (N = 33)	PBO + DOC (N = 24)	RAM + DOC (N = 112)	PBO + DOC (N = 88)	RAM + DOC (N = 244)	PBO + DOC (N = 204)
Median OS, months (95% CI)	8.8 (4.5, 15.3)	3.2 (2.4, 4.7)	8.6 (6.5, 10.4)	6.9 (5.0, 9.3)	9.2 (8.3, 10.3)	7.2 (6.0, 9.3)
Unstratified HR (95% CI)	0.40 (0.22, 0.73)		0.83 (0.61, 1.15)		0.85 (0.68, 1.05)	
12-month survival rate, % (95% CI)	34 (18, 51)	13 (3, 29)	33 (24, 42)	26 (17, 35)	34 (28, 40)	30 (24, 37)
18-month survival rate, % (95% CI)	27 (12, 44)	NE	19 (11, 27)	19 (11, 29)	21 (15, 27)	18 (13, 25)
Median PFS, months (95% CI)	2.9 (2.2, 5.3)	1.4 (1.1, 1.5)	3.3 (2.8, 4.2)	2.5 (1.5, 2.9)	4.1 (3.2, 4.4)	2.8 (1.8, 3.2)
Unstratified HR (95% CI)	0.44 (0.25, 0.78)		0.85 (0.64, 1.14)		0.75 (0.61, 0.91)	
ORR (CR + PR), % (95% CI)	24.2 (11.1, 42.3)	0.0 (0.0, 14.2)	23.2 (15.8, 32.1)	11.4 (5.6, 19.9)	26.2 (20.8, 32.2)	11.8 (7.7, 17.0)
DCR (CR + PR + SD), % (95% CI)	51.5 (33.5, 69.2)	20.8 (7.1, 42.2)	51.8 (42.1, 61.3)	45.5 (34.8, 56.4)	58.2 (51.7, 64.5)	46.6 (39.6, 53.7)

CI, confidence interval; CR, complete response; DCR, disease control rate; DOC, docetaxel; HR, hazard ratio; ITT, intent-to-treat; N, number of patients in population; n, number of patients in a group; NE, not estimated; ORR, objective response rate; OS, overall survival; PBO, placebo; PFS, progression-free survival; PR, partial response; RAM, ramucirumab; SD, stable disease.

those treated with placebo plus docetaxel and, although the results did not meet statistical significance, the HR was similar to that observed in the REVEL ITT population [25]. Interpretation of this observed survival benefit is difficult since this subgroup lacked power and the benefit of a pre-specified hypothesis. However, similar OS and PFS results to those seen in the REVEL refractory patients were also observed in sensitivity analyses of other subgroups of the REVEL ITT population defined by various durations of first-line treatment. These sensitivity analyses allowed us to categorize patients using more inclusive or restrictive definitions of "rapid progressors." While these subgroups were complementary to each other, they still included different populations of patients; for instance, of the 360 patients who met the "refractory" definition and the 200 patients whose time on first-line treatment was 8 weeks or less, 106 patients met both definitions. Thus, the definition of patients who might be considered "rapid progressors" or "hard-to-treat" is not unique.

In the LUME-Lung 1 study, an exploratory analysis examined the subset of adenocarcinoma patients with a best response of PD to first-line therapy. In these 117 patients, OS was longer in the docetaxel plus nintedanib arm compared with the docetaxel plus placebo arm (median OS 9.8 months [95% CI, 6.1–15.5] vs. 6.3 months [95% CI, 5.0–8.1]; HR 0.62 [95% CI, 0.41–0.94], $p = 0.0246$) [23]. In a comparable exploratory analysis, we identified a subset of 213 REVEL refractory patients who had adenocarcinoma histology and also found a trend towards improved median OS and PFS as well as improved response rates from the addition of ramucirumab to docetaxel. Taken together, these data suggest that this high-risk population of patients with rapidly progressing advanced NSCLC, regardless of histology, may see some benefit from second-line treatment with ramucirumab plus docetaxel, without additional safety or QoL concerns.

Recently, immunotherapy with nivolumab monotherapy was approved by the European Medicines Agency for patients with advanced nonsquamous NSCLC who progressed on prior chemotherapy. However, a post hoc exploratory multivariate analysis demonstrated that patients with poorer prognostic factors, including progression as best response to prior therapy, have a higher risk of death in the first 3 months of treatment with nivolumab when compared with docetaxel (20.2% vs. 15.2%) [31]. Considering this potential 2- to 3-month delay in effect with nivolumab treatment, the use of ramucirumab plus docetaxel may be considered for the high-risk population of advanced NSCLC patients refractory to first-line treatment.

Future research should consider that the efficacy of ramucirumab in patients with refractory disease may be related to its impact on the molecular pathways involved in angiogenesis-related tumor growth.

Considering that other antiangiogenic agents also have exhibited similar results in tumors resistant to first-line treatment [21,23,32], it is most likely that the response of these tumors is due to a dependency on angiogenic pathways for growth and survival. Ongoing analysis of biomarkers of angiogenic pathways for the REVEL study may help clarify the dependence of the efficacy of antiangiogenic agents on VEGF-dependent pathways in the second-line setting in refractory patients.

5. Conclusion

Weighing the potential benefits of treating refractory patients with ramucirumab against the potential risks, and considering the QoL and safety outcomes together, ramucirumab appears to be an appropriate treatment option for the difficult-to-treat population of NSCLC patients who are refractory to chemotherapy in the first-line setting.

Conflicts of interest

MR received compensation for consulting or advisory role and served on the speaker's bureau for Roche, Eli Lilly and Company, Bristol-Myers Squibb, MSD, AstraZeneca, Pfizer, Boehringer Ingelheim, and Celgene. LP-A has provided scientific advice to Eli Lilly and Company, Bristol-Myers Squibb, Pfizer, Boehringer Ingelheim, AstraZeneca, Roche, Clovis Oncology, MSD, Celgene, Bayer, and Merck. PB provided consulting or advisory role services for Eli Lilly and Company, Bristol-Myers Squibb, and Boehringer Ingelheim. DM-S reports personal fees from Eli Lilly and Company, Roche, Boehringer Ingelheim, Novartis, AstraZeneca, ARIAD, and Clovis Oncology. HB reports personal fees and other from Genentech, Eli Lilly and Company, Bristol-Myers Squibb, Celgene, and Clovis Oncology; personal fees from Pfizer, Merck, EMD Serono, Trovagene, and AstraZeneca; and other from Merck/Celgene and Millennium Pharmaceuticals. RJ reports honoraria and fees for speaker's bureau from Eli Lilly and Company and Bristol-Myers Squibb. NAP reports fees for consulting from Eli Lilly and Company, Boehringer Ingelheim, and AstraZeneca. FAS reports stock ownership in Eli Lilly and Company. AT declares receiving honoraria from Eli Lilly and Company. MT reports personal fees from Novartis, Roche, Pfizer, Eli Lilly and Company, Bristol-Myers Squibb, MSD, Celgene, Boehringer Ingelheim, and Pierre Fabre Laboratories. FC-D is

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.lungcan.2017.07.038.

References

[1] R.L. Siegel, K.D. Miller, A. Jemal, Cancer statistics, 2016, CA. Cancer J. Clin. 66 (2016) 7–30.
[2] A. Barzi, N. Pennell, Targeting angiogenesis in non-small cell lung cancer: Agents in practice and clinical development, Eur. J. Clin. Med. Oncol. 2 (2010) 31–42.
[3] M. Reck, S. Popat, N. Reinmuth, D. De Ruysscher, K.M. Kerr, S. Peters, Metastatic non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, Ann. Oncol. 25 (Suppl. 3) (2014) iii27–iii39.
[4] A. Sandler, R. Gray, M.C. Perry, J. Brahmer, J.H. Schiller, A. Dowlati, R. Lilenbaum, D.H. Johnson, Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer, N. Engl. J. Med. 355 (2006) 2542–2550.
[5] G. Scagliotti, S. Novello, J. von Pawel, M. Reck, J.R. Pereira, J. Thomas, J.E. Abrão Miziara, B. Balint, F. De Marinis, A. Keller, O. Arén, M. Csollak, I. Albert, C.H. Barrios, F. Grossi, M. Krzakowski, L. Cupit, F. Cihon, S. Dimatteo, N. Hanna, Phase III study of carboplatin and paclitaxel alone or with sorafenib in advanced non-small-cell lung cancer, J. Clin. Oncol. 28 (2010) 1835–1842.
[6] G.V. Scagliotti, P. Parikh, J. von Pawel, B. Biesma, J. Vansteenkiste, C. Manegold, P. Serwatowski, U. Gatzemeier, R. Digumarti, M. Zukin, J.S. Lee, A. Mellemgaard, K. Park, S. Patil, J. Rolski, T. Goksel, F. de Marinis, L. Simms, K.P. Sugarman, D. Gandara, Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer, J. Clin. Oncol. 26 (2008) 3543–3551.
[7] G.V. Scagliotti, I. Vynnychenko, K. Park, Y. Ichinose, K. Kubota, F. Blackhall, R. Pirker, R. Galiulin, T.E. Ciuleanu, O. Sydorenko, M. Dediu, Z. Papai-Szekely, N.M. Banaclocha, S. McCoy, B. Yao, Y.J. Hei, F. Galimi, D.R. Spigel, International, randomized, placebo-controlled, double-blind phase III study of motesanib plus carboplatin/paclitaxel in patients with advanced nonsquamous non-small-cell lung cancer: MONET1, J. Clin. Oncol. 30 (2012) 2829–2836.
[8] B. Besse, A. Adjei, P. Baas, P. Meldgaard, M. Nicolson, L. Paz-Ares, M. Reck, E.F. Smit, K. Syrigos, R. Stahel, E. Felip, S. Peters, 2nd ESMO Consensus Conference on Lung Cancer: non-small-cell lung cancer first-line/second and further lines of treatment in advanced disease, Ann. Oncol. 25 (2014) 1475–1484.
[9] N. Hanna, F.A. Shepherd, F.V. Fossella, J.R. Pereira, F. De Marinis, J. von Pawel, U. Gatzemeier, T.C. Tsao, M. Pless, T. Muller, H.L. Lim, C. Desch, K. Szondy, R. Gervais, Shaharyar, C. Manegold, S. Paul, P. Paoletti, L. Einhorn, P.A. Bunn Jr., Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy, J. Clin. Oncol. 22 (2004) 1589–1597.
[10] T. Li, H.J. Kung, P.C. Mack, D.R. Gandara, Genotyping and genomic profiling of non-small-cell lung cancer: implications for current and future therapies, J. Clin. Oncol. 31 (2013) 1039–1049.
[11] T.E. Stinchcombe, M.A. Socinski, Considerations for second-line therapy of non-small cell lung cancer, Oncologist 13 (Suppl. 1) (2008) 28–36.
[12] T.E. Stinchcombe, M.A. Socinski, Current treatments for advanced stage non-small cell lung cancer, Proc. Am. Thorac. Soc. 6 (2009) 233–241.
[13] F. de Marinis, A. Rossi, M. Di Maio, S. Ricciardi, C. Gridelli, Treatment of advanced non-small-cell lung cancer: Italian Association of Thoracic Oncology (AIOT) clinical practice guidelines, Lung Cancer 73 (2011) 1–10.
[14] F.A. Shepherd, J. Dancey, R. Ramlau, K. Mattson, R. Gralla, M. O'Rourke, N. Levitan, L. Gressot, M. Vincent, R. Burkes, S. Coughlin, Y. Kim, J. Berille, Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based

[15] F.V. Fossella, R. DeVore, R.N. Kerr, J. Crawford, R.R. Natale, F. Dunphy, L. Kalman, V. Miller, J.S. Lee, M. Moore, D. Gandara, D. Karp, E. Vokes, M. Kris, Y. Kim, F. Gamza, L. Hammershaimb, Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group, J. Clin. Oncol. 18 (2000) 2354–2362.
[16] P. Carmeliet, R.K. Jain, Angiogenesis in cancer and other diseases, Nature 407 (2000) 249–257.
[17] L.A. Sullivan, R.A. Brekken, The VEGF family in cancer and antibody-based strategies for their inhibition, MAbs 2 (2010) 165–175.
[18] Z. Zhu, P. Bohlen, L. Witte, Clinical development of angiogenesis inhibitors to vascular endothelial growth factor and its receptors as cancer therapeutics, Curr. Cancer Drug Targets 2 (2002) 135–156.
[19] S. Andersen, T. Donnem, S. Al-Saad, K. Al-Shibli, L.T. Busund, R.M. Bremnes, Angiogenic markers show high prognostic impact on survival in marginally operable non-small cell lung cancer patients treated with adjuvant radiotherapy, J. Thorac. Oncol. 4 (2009) 463–471.
[20] A. Yuan, C.J. Yu, W.J. Chen, F.Y. Lin, S.H. Kuo, K.T. Luh, P.C. Yang, Correlation of total VEGF mRNA and protein expression with histologic type, tumor angiogenesis, patient survival and timing of relapse in non-small-cell lung cancer, Int. J. Cancer 89 (2000) 475–483.
[21] A.B. Lima, L.T. Macedo, A.D. Sasse, Addition of bevacizumab to chemotherapy in advanced non-small cell lung cancer: a systematic review and meta-analysis, PLoS One 6 (2011) e22681.
[22] J. Cui, X. Cai, M. Zhu, T. Liu, N. Zhao, The efficacy of bevacizumab compared with other targeted drugs for patients with advanced NSCLC: a meta-analysis from 30 randomized controlled clinical trials, PLoS One 8 (2013) e62038.
[23] M. Reck, R. Kaiser, A. Mellemgaard, J.Y. Douillard, S. Orlov, M. Krzakowski, J. von Pawel, M. Gottfried, I. Bondarenko, M. Liao, C.N. Gann, J. Barrueco, B. Gaschler-Markefski, S. Novello, Docetaxel plus nintedanib versus docetaxel plus placebo in patients with previously treated non-small-cell lung cancer (LUME-Lung 1): a phase 3, double-blind, randomised controlled trial, Lancet Oncol. 15 (2014) 143–155.
[24] J.L. Spratlin, R.B. Cohen, M. Eadens, L. Gore, D.R. Camidge, S. Diab, S. Leong, C. O'Bryant, L.Q. Chow, N.J. Serkova, N.J. Meropol, N.L. Lewis, E.G. Chiorean, F. Fox, H. Youssoufian, E.K. Rowinsky, S.G. Eckhardt, Phase I pharmacologic and biologic study of ramucirumab (IMC-1121B), a fully human immunoglobulin G1 monoclonal antibody targeting the vascular endothelial growth factor receptor-2, J. Clin. Oncol. 28 (2010) 780–787.
[25] E.B. Garon, T.E. Ciuleanu, O. Arrieta, K. Prabhash, K.N. Syrigos, T. Goksel, K. Park, V. Gorbunova, R.D. Kowalyszyn, J. Pikiel, G. Czyzewicz, S.V. Orlov, C.R. Lewanski, M. Thomas, P. Bidoli, S. Dakhil, S. Gans, J.H. Kim, A. Grigorescu, N. Karaseva, M. Reck, F. Cappuzzo, E. Alexandris, A. Sashegyi, S. Yurasov, M. Pérol, Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial, Lancet 384 (2014) 665–673.
[26] E. Larkins, B. Scepura, G.M. Blumenthal, E. Bloomquist, S. Tang, M. Biable, P. Kluetz, P. Keegan, R. Pazdur, U.S. Food and Drug Administration approval summary: Ramucirumab for the treatment of metastatic non-small cell lung cancer following disease progression on or after platinum-based chemotherapy, Oncologist 20 (2015) 1320–1325.
[27] R. Kaiser, J.R. Barrueco, M. Reck, N. Hanna, C. Gann, P. Glomb, B. Gaschler-Markefski, Identification of a clinical biomarker for 2nd line combination with nintedanib in adenocarcinoma non-small cell lung cancer (NSCLC) patients in two phase III trials, Eur. J. Cancer 49 (Suppl. 2) (2013) abstr 3479.
[28] US Department of Health and Human Services, Common Terminology Criteria for Adverse Events v4.02 (CTCAE), 5/2009 update, (2015) http://evs.nci.nih.gov/ftp1/CTCAE/Archive/CTCAE_4.02_2009-09-15_QuickReference_8.5x11.pdf (Accessed 14 May 2017).
[29] P.J. Hollen, R.J. Gralla, M.G. Kris, C. Cox, Quality of life during clinical trials: conceptual model for the Lung Cancer Symptom Scale (LCSS), Support. Care Cancer 2 (1994) 213–222.
[30] M. Pérol, T.E. Ciuleanu, O. Arrieta, K. Prabhash, K.N. Syrigos, T. Goksel, K. Park, R.D. Kowalyszyn, J. Pikiel, C.R. Lewanski, M. Thomas, S. Dakhil, J.H. Kim, N. Karaseva, S. Yurasov, A. Zimmermann, P. Lee, G.C. Carter, M. Reck, F. Cappuzzo, E.B. Garon, Quality of life results from the phase 3 REVEL randomized clinical trial of ramucirumab-plus-docetaxel versus placebo-plus-docetaxel in advanced/metastatic non-small cell lung cancer patients with progression after platinum-based chemotherapy, Lung Cancer 93 (2016) 95–103.
[31] European Medicines Agency, Opdivo: EPAR – Product Information, (2017) http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003985/WC500189765.pdf (Accessed 07 July 2017).
[32] J.C. Soria, A. Mauguen, M. Reck, A.B. Sandler, N. Saijo, D.H. Johnson, D. Burcoveanu, M. Fukuoka, B. Besse, J.P. Pignon, Systematic review and meta-analysis of randomised, phase II/III trials adding bevacizumab to platinum-based chemotherapy as first-line treatment in patients with advanced non-small-cell lung cancer, Ann. Oncol. 24 (2013) 20–30.