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Exploratory analysis of front-line therapies in REVEL: a randomised phase 3 study of ramucirumab plus docetaxel versus docetaxel for the treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy

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ABSTRACT

Introduction Non-small-cell lung cancer (NSCLC) is a heterogeneous disease. Front-line therapy may affect responses to subsequent treatment regimens, thus influencing second-line therapy decision making. In the randomised phase 3 REVEL study, second-line ramucirumab plus docetaxel (ram+doc) versus docetaxel (doc) improved survival of patients with metastatic NSCLC. We explore efficacy, safety and quality-of-life (QoL) in REVEL based on front-line therapy.

Methods Patients were grouped by specific front-line therapy received. Overall survival (OS), progression-free survival (PFS), objective response rate, safety and QoL were assessed descriptively. Kaplan-Meier estimation and Cox proportional hazards modelling were used; frequencies reported in percentages.

Results Baseline characteristics of 1253 patients were generally well balanced between treatment arms within each front-line therapy subgroup. For patients with non-squamous disease (n=912), induction therapies included platinum-based chemotherapy plus a taxane (n=227; 25%) or pemetrexed (n=449; 49%), with (n=172; 19%) or without bevacizumab. For patients with squamous disease (n=328), induction therapies included platinum-based chemotherapy plus gemcitabine (n=176; 54%) or a taxane (n=69; 21%). A highly selected subgroup (n=127; 14%) received pemetrexed continuation maintenance therapy. Ram+doc improved median OS and PFS versus doc across front-line therapy subgroups, as reflected by HRs ranging from 0.78 to 0.91 and 0.66 to 0.92, respectively, similar to results in the overall intention-to-treat cohort (HRs: 0.86 and 0.76, respectively). High-grade treatment-emergent adverse events of special interest (including neutropenia, febrile neutropenia, leucopenia and hypertension) were generally higher in ram+doc-treated patients relative to doc-treated patients regardless of front-line therapy. No clear differences in safety or QoL were seen across front-line therapy subgroups; outcomes were consistent with those reported in the overall intention-to-treat cohort.

Conclusions Results of this exploratory analysis suggest that second-line ram+doc may be effective regardless

Key questions

What is already known about this subject?

- Second-line ramucirumab, a vascular endothelial growth factor receptor-targeted antibody, plus docetaxel improved efficacy compared with placebo plus docetaxel in patients with advanced non-small-cell lung cancer (NSCLC) in REVEL, a large phase 3 trial.
- Little is known regarding what role, if any, front-line therapy and maintenance therapy have on the efficacy, safety and quality-of-life outcomes of patients treated with second-line therapy.

What does this study add?

- Overall, second-line ramucirumab plus docetaxel appeared clinically beneficial across a wide range of patients with non-squamous or squamous metastatic NSCLC who progressed during or after front-line treatment with platinum-based chemotherapy in combination with a taxane, pemetrexed, gemcitabine or bevacizumab.

How might this impact on clinical practice?

- In light of the rapidly evolving treatment landscape for advanced NSCLC, this analysis provides additional data for clinicians on appropriate treatment sequencing strategies in this difficult-to-treat NSCLC population.

of prior treatment with platinum-based chemotherapy plus a taxane, pemetrexed, gemcitabine or bevacizumab. Overall, ram+doc is clinically beneficial across a wide range of patients with metastatic NSCLC who have progressed after various front-line therapies.
Trial registration number NCT01168973.

INTRODUCTION

Non-small-cell lung cancer (NSCLC) accounts for nearly 85% of all lung cancers and includes predominately adenocarcinomas, squamous carcinoma and large cell carcinoma.[1] Unfortunately, nearly 70% of patients with NSCLC will present with advanced-stage disease, at which time, treatments with curative intent (surgery or radiotherapy) are no longer feasible. Depending on the country or region, the estimated 5-year survival rate of metastatic (stage IV) NSCLC is between 2% and 13%.[2]

In the first-line setting for stage IV NSCLC lacking targetable mutations, standard of care has frequently consisted of platinum-based combination chemotherapy including a taxane, pemetrexed, gemcitabine or bevacizumab, depending on histological subtype.[3] A recent therapeutic advancement in first-line treatment options is the use of an immune-checkpoint inhibitor as a single agent or in addition to platinum-based combination chemotherapy. Single-agent pembrolizumab has been approved in the European Union (EU)[4] as a first-line treatment option for patients with metastatic NSCLC whose tumours have high PD-L1 expression (tumour proportion score (TPS) ≥50%) based on the results of the phase 3 Study Keynote 024.[5] Results of a subsequent phase 3 study, Study Keynote 042,[6] further demonstrated the efficacy of single-agent pembrolizumab versus platinum-based chemotherapy in the first-line setting in patients with metastatic NSCLC and a PD-L1 TPS ≥1%, and thus lead to the approval of first-line pembrolizumab monotherapy in this patient population in both Japan[7] and the USA.[8] Pembrolizumab has also been approved in the EU,[4] Japan[7] and the USA[8] as first-line therapy in combination with pemetrexed and platinum chemotherapy for patients with metastatic non-squamous NSCLC based on the phase 2 Study Keynote 021G[9 10] and the phase 3 Study Keynote 189,[11] and is approved in combination with chemotherapy in the EU,[4] Japan[7] and the USA,[8] for patients with metastatic squamous NSCLC based on the phase 3 Study Keynote 407.[12] Other immuno-oncology and chemotherapy combinations, such as the IMpower 150 regimen, which has been approved in the EU[13] and USA[14] and includes atezolizumab and chemotherapy in combination with bevacizumab, have also demonstrated efficacy in patients with metastatic non-squamous NSCLC.[15 16]

Given the changing treatment landscape and the emergence of immune-checkpoint inhibitors and chemotherapy combinations in the first-line setting, docetaxel in combination with an antiangiogenic agent may be an appropriate second-line treatment option following progression on a platinum containing regimen.[17] The randomised phase 3 REVEL trial (NCT01168973),[18] which included patients with non-squamous and squamous stage IV NSCLC, demonstrated that the addition of ramucirumab, an antibody targeted to the vascular endothelial growth factor receptor 2, to docetaxel improved survival compared with docetaxel alone (increase of 1.4 months for overall survival (OS); HR 0.86; 95% CI 0.75 to 0.98; p=0.023) after disease progression on platinum-based chemotherapy. Although the REVEL study was not powered for subgroup analysis, most preplanned subgroup analyses in the original report showed numerically longer survival in the ramucirumab plus docetaxel arm, including patients with squamous and non-squamous histology.[18] The REVEL trial also demonstrated an acceptable safety profile and no detriment to quality of life (QoL) as reported by the patients when ramucirumab was added to docetaxel.[18 19] The results of this study led to the approval of ramucirumab plus docetaxel for second-line treatment of patients with metastatic NSCLC in the EU[20] and USA,[21] and this combination was also approved in Japan based on both the REVEL study[18] and a phase 2 study[22] with a similar study design conducted in Japanese patients. In addition, nintedanib, a triple angiokinase inhibitor, in combination with docetaxel was approved in the EU only for patients with advanced non-squamous NSCLC.[23]

In general, additional data are needed to assess the potential effects of prior treatments on subsequent second-line therapy considering the use of different chemotherapy regimens in the first line. Little is known regarding what role, if any, front-line therapy and maintenance therapy have on the efficacy, safety and QoL outcomes of patients treated with second-line therapy. Here, we present results of a retrospective, exploratory analysis of the data from the REVEL trial investigating the potential impact of prior chemotherapy (a taxane, gemcitabine or pemetrexed as part of platinum-based front-line therapy) on efficacy, safety and QoL. Additional efficacy, safety and QoL data are presented for a subset of patients who received pemetrexed induction, followed by pemetrexed maintenance therapy and for those whose front-line therapy included bevacizumab.

MATERIALS AND METHODS

Study design and patients

The REVEL study design has been previously reported.[18] Briefly, REVEL was a randomised, double-blind, placebo-controlled phase 3 trial evaluating the clinical benefits of ramucirumab in combination with docetaxel for adult patients (aged 18 years or older) with pathologically confirmed stage IV NSCLC that had progressed on or after a platinum-containing chemotherapy, with or without bevacizumab or maintenance therapy. Patients were randomised 1:1 to receive intravenous docetaxel 75 mg/m^2 plus intravenous ramucirumab 10 mg/kg or placebo on day 1 of a 21 day cycle. Patients received treatment until disease progression or unacceptable toxicity. Those who discontinued combination therapy because of adverse events related to ramucirumab or docetaxel were

allowed to continue monotherapy with either agent until disease progression or unacceptable toxicity.

Study assessments and clinical endpoints

Tumour response was assessed by investigators according to Response Evaluation Criteria in Solid Tumors V.1.1 at baseline and every 6 weeks (±3 business days) thereafter until radiographic documentation of disease progression. Adverse events were coded according to the Medical Dictionary for Regulatory Activities, V.16.1, and graded with the National Cancer Institute Common Terminology Criteria for Adverse Events, V.4.0. Patient-reported outcomes were assessed with the Lung Cancer Symptom Scale (LCSS) questionnaire.

The primary endpoint was OS, defined as the time from randomisation to death from any cause. Secondary endpoints included progression-free survival (PFS), defined as the time from randomisation until progression or death from any cause, and objective response rate (ORR), defined as the proportion of patients with a best overall response of complete or partial response.

Statistical analyses

The statistical analysis plan for the REVEL intention-to-treat (ITT) population has been previously reported.[18] In this post hoc analysis of front-line therapies administered prior to enrolment in REVEL, patients were grouped according to the specific agent received as part of the first-line regimen (a taxane, pemetrexed (with or without pemetrexed continuation maintenance), gemcitabine or bevacizumab). For each first-line therapy subgroup, a corresponding subgroup that did not receive prior treatment with the specified agent was also generated. Endpoints evaluated were OS, PFS, ORR, safety and patient-reported QoL outcomes. For efficacy analysis, OS and PFS were estimated using the Kaplan-Meier method and a Cox proportional hazards model with treatment as the only variable. Summaries for baseline characteristics, ORR and treatment-emergent adverse events (TEAEs) were given in percentages. A TEAE is defined as any untoward medical occurrence that either occurs or worsens at any time after treatment baseline and which does not necessarily have to have a causal relationship with study treatment. The primary QoL analysis was time to deterioration using a prespecified ≥15 mm increase from baseline of the LCSS and was evaluated using the Cox proportional hazards model, stratified by Eastern Cooperative Oncology Group performance status, sex, country group and prior maintenance therapy. Total LCSS and average symptom burden index were calculated as described.[19] Analyses were carried out using SAS V.9.1.2 or higher.

RESULTS

Patients and demographics

The ITT population of REVEL (n=1253) consisted of 912 (73%) patients with non-squamous, 328 (26%) patients with squamous and 13 (1%) patients with unknown histology.[18] Of the 912 patients with non-squamous NSCLC randomised in REVEL, 908 patients received prior first-line therapy and were included in the current exploratory analysis. All patients with squamous histology were included, while the 13 patients with unknown histology were excluded from analysis.

In the ITT population of REVEL, patient demographics, baseline disease characteristics and prior therapies were generally balanced between treatment arms and were consistent with the overall population of patients with advanced NSCLC enrolled in other clinical trials.[18] Almost all patients in REVEL (99.4%) had received prior platinum-based chemotherapy (eight patients did not receive prior platinum-based chemotherapy), 22% had received prior maintenance therapy, 24% had received a prior taxane (paclitaxel only) and 14% had received prior bevacizumab as first-line treatment.

In the current analysis, modest differences in some baseline characteristics between prior therapy subgroups (irrespective of treatment arm) were observed (table 1 and online supplementary table S1). For example, compared with the other prior therapy subgroups, a slightly higher proportion of patients who received prior treatment with gemcitabine were male. However, baseline demographics and clinical characteristics were well balanced between treatment arms within prior therapy subgroups. Among REVEL patients who had received a taxane, pemetrexed or gemcitabine in platinum-based front-line therapy (table 1), the median ages ranged from 60 to 64 years with 53%–71% of patients ages 18 to <65 years. Additionally, 65% of these patients were male, predominately white, and 52%–70% had less than 9 months since prior therapy before enrolling in REVEL (table 1). Similar baseline characteristics were observed in patients who received bevacizumab as part of front-line therapy (see online supplementary table S1).

For patients with non-squamous disease, the most frequent induction therapies were platinum based that included a taxane (n=227; 25%) or pemetrexed (n=449; 49%), with (n=172; 19%) or without bevacizumab (see online supplementary table S2). For patients with squamous disease, the most frequent induction therapies included gemcitabine (n=176; 54%) or a taxane (n=69; 21%) (see online supplementary table S2). The frequency of patients who received poststudy therapy and the type of poststudy therapy received were also reasonably balanced (see online supplementary table S3).

Efficacy in REVEL by front-line therapy

Taxane

Approximately 24% of patients in REVEL received front-line taxane chemotherapy (n=227 for non-squamous and n=69 for squamous) (table 2 and online supplementary table S2). For taxane-treated patients, numerically longer medians for OS (10.8 vs 10.4 months; HR 0.85; 95% CI 0.64 to 1.13) and PFS (4.4 vs 3.6 months; HR 0.92; 95% CI 0.72 to 1.19) and a higher ORR (18% vs 13%) were observed in the

Table 1 Baseline characteristics of REVEL patients, all histologies, by main prior therapy subgroups

	Taxane*				Pemetrexed†				Gemcitabine‡			
	Yes		No		Yes		No		Yes		No	
	Ram (n=153)	Pl (n=149)	Ram (n=475)	Pl (n=476)	Ram (n=220)	Pl (n=229)	Ram (n=242)	Pl (n=217)	Ram (n=89)	Pl (n=87)	Ram (n=68)	Pl (n=84)
Median age, years	63	63	62	61	61	60	62	61	64	64	64	62
Age group, years												
18 to <65	91 (59)	90 (60)	300 (63)	317 (67)	142 (65)	163 (71)	152 (63)	140 (64)	49 (55)	46 (53)	43 (63)	54 (64)
≥65	62 (40)	59 (40)	175 (37)	159 (33)	78 (35)	66 (29)	90 (37)	77 (35)	40 (45)	41 (47)	25 (37)	30 (36)
Median weight, kg	72	70	74	71	73	72	72	68	76	73	77	71
Male	99 (65)	87 (58)	320 (67)	328 (69)	131 (59)	148 (65)	161 (66)	129 (59)	69 (77)	73 (84)	51 (75)	61 (73)
Race (self-reported)§												
White	128 (84)	117 (78)	398 (84)	386 (81)	191 (87)	178 (78)	196 (81)	174 (80)	73 (82)	74 (85)	59 (87)	69 (82)
Asian	11 (7)	11 (7)	63 (13)	75 (16)	22 (10)	42 (18)	29 (12)	22 (10)	15 (17)	12 (14)	7 (10)	10 (12)
Black or African American	6 (4)	9 (6)	11 (2)	7 (1)	7 (3)	8 (3)	7 (3)	7 (3)	1 (1)	0	1 (1)	1 (1)
Other	8 (5)	12 (8)	3 (<1)	8 (2)	–	1 (<1)	10 (4)	14 (6)	0	1 (1)	1 (1)	4 (5)
ECOG PS¶												
0	51 (33)	50 (34)	156 (33)	149 (31)	79 (36)	77 (34)	82 (34)	62 (29)	25 (28)	27 (31)	20 (29)	28 (33)
1	102 (67)	99 (66)	318 (67)	326 (68)	141 (64)	151 (66)	160 (66)	155 (71)	64 (72)	60 (69)	48 (71)	56 (67)
Time since prior therapy												
<9 months	85 (56)	77 (52)	315 (66)	297 (62)	137 (62)	134 (58)	156 (64)	133 (61)	62 (70)	60 (69)	41 (60)	45 (54)
≥9 months	68 (44)	72 (48)	158 (33)	179 (38)	83 (38)	95 (41)	86 (35)	84 (39)	27 (30)	27 (31)	27 (40)	39 (46)
Smoking group**												
Ever	121 (79)	105 (70)	397 (84)	378 (79)	182 (83)	177 (77)	190 (78)	155 (71)	79 (89)	75 (86)	59 (87)	71 (85)
Never	32 (21)	44 (29)	77 (16)	97 (20)	38 (17)	52 (23)	52 (21)	61 (28)	10 (11)	12 (14)	9 (13)	13 (15)
Best response to platinum-based chemotherapy												
CR, PR, or SD	106 (69)	110 (74)	314 (66)	307 (64)	162 (74)	166 (72)	151 (62)	129 (59)	65 (73)	61 (70)	38 (56)	55 (65)
PD	40 (26)	35 (23)	138 (29)	147 (31)	49 (22)	56 (24)	80 (33)	74 (34)	22 (25)	23 (26)	24 (35)	27 (32)
Missing	7 (5)	4 (3)	23 (5)	22 (5)	9 (4)	7 (3)	11 (4)	14 (6)	2 (2)	3 (3)	6 (9)	2 (2)
Front-line therapy included												
Bevacizumab	41 (27)	36 (24)	47 (10)	56 (12)	44 (20)	53 (23)	41 (17)	33 (15)	0	1 (1)	3 (4)	3 (4)
Taxane	–	–	–	–	9 (4)	8 (3)	107 (44)	102 (47)	5 (6)	1 (1)	29 (43)	33 (39)
Maintenance therapy	35 (23)	36 (24)	100 (21)	107 (22)	81 (37)	89 (39)	33 (14)	30 (14)	13 (15)	14 (16)	7 (10)	7 (8)

Data are presented as n (%) unless otherwise stated.
*ITT population; the top three reported prior therapy combinations with taxane were: carboplatin (12% Ram arm vs 14% Pl arm), bevacizumab plus carboplatin (5% vs 5%), and cisplatin (2% vs 3%).
†Non-squamous population; the top three reported prior therapy combinations with pemetrexed were: cisplatin (16% Ram arm vs 16% Pl arm), carboplatin (11% vs 11%) and bevacizumab plus carboplatin (3% vs 4%).
‡Squamous population; the top three reported prior therapy combinations with gemcitabine were: cisplatin (11% Ram arm vs 11% Pl arm), carboplatin (10% vs 9%) and cisplatin plus necitumumab (1% vs 1%).
§Data not available for a patient in pemetrexed induction (no; ramucirumab arm).
¶Data not available for a patient in pemetrexed induction (yes; placebo arm).
**Data not available for a patient in pemetrexed (no; ramucirumab arm).
CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; ITT, intention-to-treat; PD, progressive disease; Pl, placebo plus docetaxel arm; PR, partial response; Ram, ramucirumab plus docetaxel arm; SD, stable disease.

Table 2 Efficacy endpoints in the overall trial population and in selected prior therapy subgroups in REVEL

Prior therapy subgroup (population)	N		OS (months)			PFS (months)			ORR (%)	
	Ram	Pl	Ram	Pl	HR* (95% CI)	Ram	Pl	HR* (95% CI)	Ram	Pl
REVEL (ITT)	628	625	10.5	9.1	0.86 (0.75 to 0.98)	4.5	3.0	0.76 (0.68 to 0.86)	23	14
Taxane (ITT)										
Yes	153	149	10.8	10.4	0.85 (0.64 to 1.13)	4.4	3.6	0.92 (0.72 to 1.19)	18	13
No	475	476	10.3	9.0	0.87 (0.75 to 1.01)	4.5	2.9	0.73 (0.63 to 0.83)	24	14
Pemetrexed (non-squamous)										
Yes	220	229	11.8	9.0	0.78 (0.62 to 0.98)	5.1	3.7	0.69 (0.56 to 0.85)	20	15
Front-line+maintenance†‡	64	63	16.3	11.4	0.80 (0.48 to 1.33)	5.8	3.9	0.66 (0.43 to 1.01)	23	14
No	242	217	11.0	9.9	0.86 (0.68 to 1.07)	4.5	3.5	0.77 (0.63 to 0.94)	24	14
Gemcitabine (squamous)										
Yes	89	87	10.2	7.4	0.91 (0.64 to 1.29)	4.2	2.8	0.73 (0.51 to 1.04)	24	13
No	68	84	9.3	8.5	0.87 (0.59 to 1.27)	4.2	2.7	0.75 (0.52 to 1.06)	31	8
Bevacizumab (non-squamous)										
Yes	85	86	11.1	7.7	0.78 (0.53 to 1.15)	4.5	2.8	0.70 (0.49 to 0.98)	12	14
No	380	361	11.1	9.9	0.84 (0.70 to 1.00)	4.7	3.9	0.74 (0.63 to 0.86)	24	15

*Stratified HR.
†Patients received front-line pemetrexed, followed by pemetrexed maintenance therapy.
‡OS from start of pemetrexed induction was 24.9 months (range: 17.7–32.9) for the Ram arm versus 17.5 months (range: 13.8–25.6) for the Pl arm.
ITT, intention-to-treat; N, number of patients; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Pl, placebo plus docetaxel arm; Ram, ramucirumab plus docetaxel arm.

ramucirumab plus docetaxel arm compared with the placebo plus docetaxel arm (figures 1A and 2A and table 2). Similarly, patients who had not previously received a taxane experienced numerically longer medians for OS (10.3 vs 9.0 months; HR 0.87; 95% CI 0.75 to 1.01) and PFS (4.5 vs 2.9 months; HR 0.73; 95% CI 0.63 to 0.83) and a higher ORR (24% vs 14%) in the ramucirumab plus docetaxel arm than in the placebo plus docetaxel arm (figures 1A and 2A and table 2).

Pemetrexed

Of the 449 patients with non-squamous carcinoma who received prior pemetrexed-based induction chemotherapy, 220 (49%) were randomised to the ramucirumab plus docetaxel arm and 229 (51%) to the placebo plus

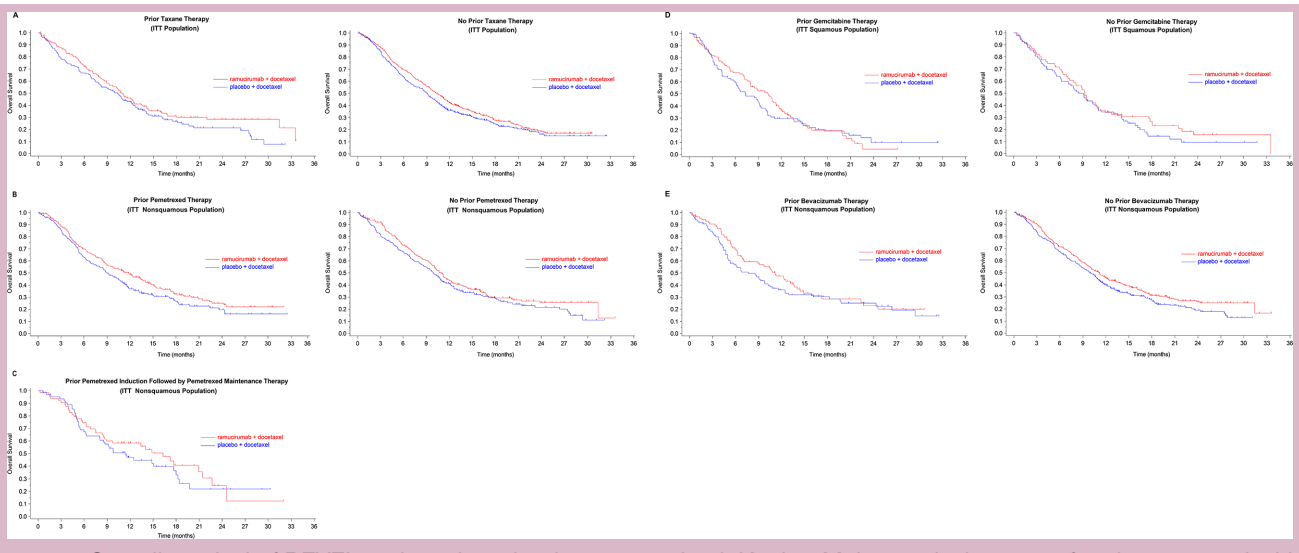

Figure 1 Overall survival of REVEL patients by prior therapy received. Kaplan-Meier survival curves of patients treated with ramucirumab plus docetaxel or placebo plus docetaxel by front-line therapy that included (A) a taxane versus no taxane, (B) pemetrexed induction versus no pemetrexed induction, (C) pemetrexed induction followed by pemetrexed maintenance, (D) gemcitabine versus no gemcitabine and (E) bevacizumab versus no bevacizumab.

docetaxel arm (table 1). Ramucirumab plus docetaxel treatment of patients with prior pemetrexed resulted in longer medians for OS (11.8 vs 9.0 months; HR 0.78; 95% CI 0.62 to 0.98) and PFS (5.1 vs 3.7 months; HR 0.69; 95% CI 0.56 to 0.85) and a higher ORR (20% vs 15%) as compared with placebo plus docetaxel treatment (figures 1B and 2B and table 2). In patients who had not previously received pemetrexed, patients treated with ramucirumab plus docetaxel also had longer medians for OS (11.0 vs 9.9 months; HR 0.86; 95% CI 0.68 to 1.07) and PFS (4.5 vs 3.5 months; HR 0.77; 95% CI 0.63 to 0.94) and a higher ORR (24% vs 14%) than patients treated with placebo plus docetaxel (figures 1B and 2B and table 2).

Pemetrexed induction followed by pemetrexed maintenance

The rate of prior maintenance therapy was higher in patients treated with pemetrexed (n=170; 38%) than in those who had not received pemetrexed as part of front-line therapy (n=63; 14%) (table 1). In the highly selected subgroup of patients who did not progress on pemetrexed induction therapy and subsequently received pemetrexed maintenance therapy (n=127; 14% of non-squamous patients), median OS was 16.3 months in the ramucirumab plus docetaxel arm (n=64) compared with 11.4 months in the placebo plus docetaxel arm (n=63) (HR 0.80; 95% CI 0.48 to 1.33), with median PFS (5.8 vs 3.9 months; HR 0.66; 95% CI 0.43 to 1.01) and ORR (23% vs 14%) showing similar trends (figures 1C and 2C and table 2).

Gemcitabine

In patients with squamous carcinoma who received front-line gemcitabine (n=176; 54%) (see online supplementary table S2), those treated with ramucirumab in combination with docetaxel (n=89) had longer medians for OS (10.2 vs 7.4 months; HR 0.91; 95% CI 0.64 to 1.29) and PFS (4.2 vs 2.8 months; HR 0.73; 95% CI 0.51 to 1.04) and a higher ORR (24% vs 13%) compared with those who received placebo plus docetaxel (n=87) (figures 1D and 2D and table 2). Likewise, patients who had not received prior gemcitabine had longer medians for OS (9.3 vs 8.5 months; HR 0.87; 95% CI 0.59 to 1.27) and PFS (4.2 vs 2.7; HR 0.75; 95% CI 0.52 to 1.06) and a higher ORR (31% vs 8%) in the ramucirumab plus docetaxel arm than in the placebo plus docetaxel arm (figures 1D and 2D and table 2).

Bevacizumab

A total of 19% (n=171) of non-squamous patients in REVEL received prior treatment with bevacizumab as part of front-line therapy (table 2 and online supplementary table S2). Prior bevacizumab-treated patients in the ramucirumab plus docetaxel arm (n=85) compared with those in the placebo plus docetaxel arm (n=86) had longer medians for OS (11.1 vs 7.7 months; HR 0.78; 95% CI 0.53 to 1.15) and PFS (4.5 vs 2.8 months; HR 0.70; 95% CI 0.49 to 0.98) but a numerically lower ORR (12% vs 14%) (figures 1E and 2E and table 2). In patients who had not previously received bevacizumab, patients treated with ramucirumab plus docetaxel had longer medians for OS (11.1 vs 9.9 months; HR 0.84; 95% CI 0.70 to 1.00) and PFS (4.7 vs 3.9 months; HR 0.74; 95% CI 0.63 to 0.86) and a higher ORR (24% vs 15%) than similar patients who received placebo plus docetaxel (figures 1E and 2E and table 2). Although the ORR in patients who had received prior bevacizumab was numerically lower in the ramucirumab plus docetaxel arm compared with the placebo plus docetaxel arm, the addition of ramucirumab to docetaxel generally improved efficacy relative to placebo plus docetaxel with respect to OS and PFS, regardless of whether or not patients received prior bevacizumab treatment.

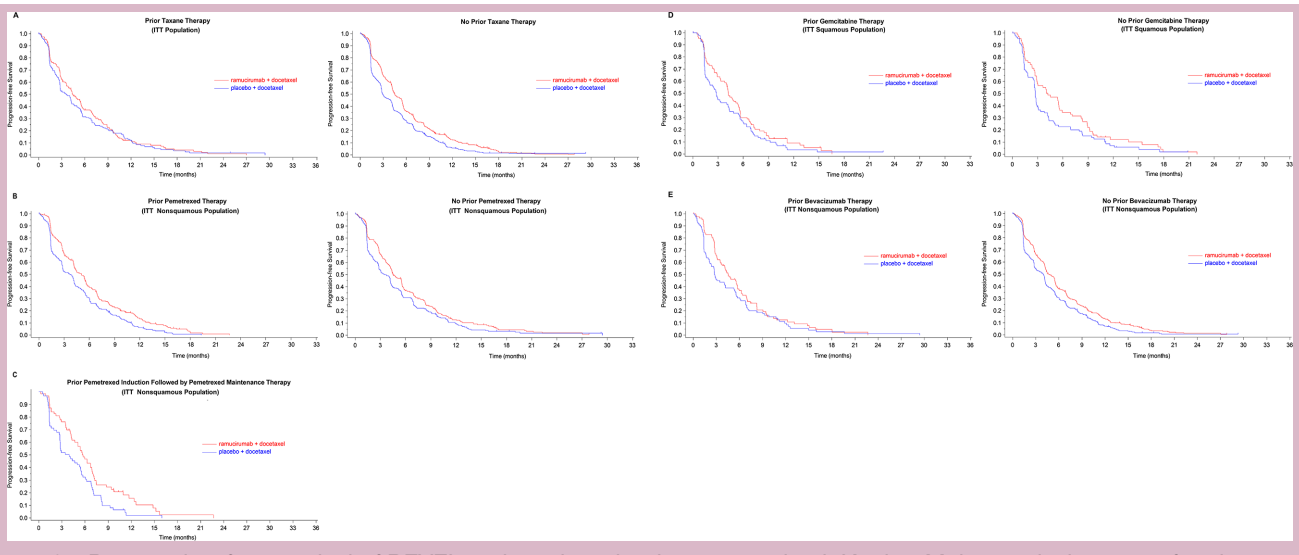

Figure 2 Progression-free survival of REVEL patients by prior therapy received. Kaplan-Meier survival curves of patients treated with ramucirumab plus docetaxel or placebo plus docetaxel by front-line therapy that included (A) a taxane versus no taxane, (B) pemetrexed induction versus no pemetrexed induction, (C) pemetrexed induction followed by pemetrexed maintenance, (D) gemcitabine versus no gemcitabine and (E) bevacizumab versus no bevacizumab.

Safety in REVEL by frontline therapy

A safety overview for prior therapy subgroups is shown in table 3 and online supplementary table S4. The incidence of TEAEs and of serious TEAEs was similar between the ramucirumab plus docetaxel and placebo plus docetaxel treatment arms, irrespective of front-line therapy. In general, the incidence of grade ≥3 TEAEs was slightly higher in the ramucirumab plus docetaxel arm than in the placebo plus docetaxel arm for most prior therapy subgroups. The dose adjustments of any study drug due to TEAEs were also higher in the ramucirumab plus docetaxel arm for each subgroup. Although numbers were small, the incidence of TEAEs leading to discontinuation of any REVEL study drug was consistently higher in the ramucirumab plus docetaxel arm compared with the placebo plus docetaxel arm, regardless of type of prior therapy. The TEAEs that resulted in death were relatively few across prior therapy subgroups. To further explore safety, TEAEs of special interest were defined based on the known safety profiles and prior clinical experience with ramucirumab or docetaxel. Consistent with the ITT population of REVEL, events of grade ≥3 hypertension, neutropenia, febrile neutropenia and leucopenia (in squamous histology only) were each reported more frequently in the ramucirumab plus docetaxel arm than in the placebo plus docetaxel arm in all prior therapy subgroups.

QoL in REVEL by front-line therapy

The LCSS completion rate was 75%. Overall, no apparent differences were observed for time to deterioration of LCSS items between the ramucirumab plus docetaxel and placebo plus docetaxel arms, as indicated by HRs and 95% CIs (including 1.0) in the patients treated with and without a prior taxane, pemetrexed, gemcitabine or bevacizumab, or in the patients who received or did not receive pemetrexed continuation maintenance therapy (see online supplementary figure S1A–E).

DISCUSSION

In the ITT population of REVEL, which included patients with non-squamous and squamous histology, ramucirumab plus docetaxel had statistically significant and clinically meaningful OS, PFS and ORR benefits relative to the control arm.[18] The changing landscape in the treatment of metastatic NSCLC and the emergence of immuno-oncology and chemotherapy combinations in the first-line setting[8 11 12 14–16] have renewed an interest in the combination of ramucirumab and docetaxel as a treatment option in the postplatinum setting. The current exploratory analysis, in which baseline characteristics were generally balanced between treatment arms within prior therapy subgroups, indicated that ramucirumab plus docetaxel improved median OS and median PFS compared with placebo plus docetaxel regardless of the type of first-line treatment given, as reflected by HRs ranging from 0.78 to 0.91 and 0.66 to 0.92, respectively, similar to median OS and median PFS in the overall ITT cohort (HRs 0.86 and 0.76, respectively).[18] Prior induction therapy choice also did not have an apparent impact on ORR observed in patients treated with ramucirumab plus docetaxel relative to patients treated with placebo plus docetaxel. It should be noted that these subgroup analyses were not prespecified and were unadjusted for multiple comparisons. Thus, uncertainty exists in the data such that results are primarily useful for generating hypotheses.

Given the use of a taxane in the first-line setting, whether it is appropriate to use docetaxel following a taxane-containing regimen is a clinically relevant question. It is of specific interest that for patients treated with a prior taxane, numerically longer median OS was observed in the ramucirumab plus docetaxel arm compared with the placebo plus docetaxel arm, with a similar HR observed in patients who did not receive prior treatment with a taxane. These results suggest that the clinical benefits of the addition of ramucirumab to docetaxel are not diminished by prior treatment with a taxane in the first-line setting.

Although treatment-free intervals are suggested to be important factors when assessing treatment options for advanced lung cancer,[24] the current findings indicate a ramucirumab-associated survival benefit for patients with good performance status who progressed on pemetrexed maintenance following pemetrexed induction therapy. While not directly comparable to the REVEL study due to mixed patient characteristics, in a recent real-world evidence study, median OS from the beginning of first-line chemotherapy was 21.6 months for patients who received maintenance and second-line, single-agent therapy (pemetrexed, docetaxel or erlotinib).[25] In the subgroup of patients reported herein who did not progress on pemetrexed induction therapy and received pemetrexed maintenance (n=64), treatment with ramucirumab plus docetaxel was associated with a median OS of over 16 months from the start of second-line therapy and over 2 years from the start of pemetrexed-based induction therapy (table 2, footnote). Based on this finding, one could hypothesise that, like patients with better performance status, perhaps patients in this highly selected subgroup may be able to receive pemetrexed as part of induction/maintenance treatment, followed by subsequent treatment with ramucirumab in combination with docetaxel.

Given the utilisation of bevacizumab treatment in the first-line setting, whether it is appropriate to use ramucirumab following a bevacizumab-containing regimen is another clinically relevant question. Notably, for patients who had prior treatment with bevacizumab, ORR was numerically lower for patients in the ramucirumab plus docetaxel arm compared with the placebo plus docetaxel arm. However, in assessing the totality of the data for OS, PFS and ORR, ramucirumab plus docetaxel generally improved efficacy relative to placebo plus docetaxel, regardless of whether or not patients received prior treatment with bevacizumab.

Table 3 Selected treatment-emergent adverse events by main prior therapy subgroups in REVEL

	Taxane*				Pemetrexed†				Gemcitabine‡			
	Yes		No		Yes		No		Yes		No	
	Ram (n=154)	Pl (n=147)	Ram (n=473)	Pl (n=471)	Ram (n=220)	Pl (n=225)	Ram (n=245)	Pl (n=216)	Ram (n=89)	Pl (n=86)	Ram (n=68)	Pl (n=84)
TEAE overview												
Any grade	150 (97)	143 (97)	463 (98)	451 (96)	219 (99)	221 (98)	238 (97)	204 (94)	87 (98)	83 (96)	64 (94)	79 (94)
Grade ≥3	127 (82)	108 (73)	368 (78)	336 (71)	174 (79)	159 (71)	192 (78)	151 (70)	68 (76)	64 (74)	56 (82)	63 (75)
Serious	66 (43)	66 (45)	203 (43)	196 (42)	91 (41)	93 (41)	102 (42)	86 (40)	39 (44)	43 (50)	34 (50)	36 (43)
Leading to discontinuation of any study drug	9 (6)	7 (5)	49 (10)	25 (5)	30 (14)	19 (8)	14 (6)	5 (2)	8 (9)	1 (1)	6 (9)	5 (6)
Leading to dose adjustment of any study drug	64 (42)	56 (38)	235 (50)	169 (36)	117 (53)	84 (37)	108 (44)	83 (38)	44 (49)	29 (34)	29 (43)	25 (30)
With outcome of death	11 (7)	13 (9)	23 (5)	22 (5)	6 (3)	9 (4)	12 (5)	16 (7)	6 (7)	4 (5)	10 (15)	5 (6)
TEAE ≥G3 of SI												
Bleeding/haemorrhage§	4 (3)	4 (3)	11 (2)	10 (2)	3 (1)	3 (1)	8 (3)	5 (2)	1 (1)	2 (2)	3 (4)	3 (4)
Epistaxis	0	1 (<1)	2 (<1)	0	0	0	2 (<1)	0	0	0	0	0
GI haemorrhage§	1 (<1)	1 (<1)	3 (<1)	1 (<1)	1 (<1)	0	2 (<1)	1 (<1)	0	0	1 (1)	1 (1)
Pulmonary haemorrhage§	2 (1)	1 (<1)	6 (1)	7 (1)	2 (<1)	1 (<1)	3 (1)	3 (1)	1 (1)	2 (2)	2 (3)	2 (2)
Haemoptysis	1 (<1)	0	3 (<1)	4 (<1)	1 (<1)	1 (<1)	2 (<1)	1 (<1)	1 (1)	1 (1)	0	1 (1)
Hypertension§	9 (6)	5 (3)	26 (5)	8 (2)	17 (8)	5 (2)	10 (4)	8 (4)	4 (4)	0	4 (6)	0
Infusion-related reaction§	1 (<1)	0	4 (<1)	4 (<1)	2 (<1)	2 (<1)	2 (<1)	1 (<1)	0	0	1 (1)	1 (1)
Proteinuria	1 (<1)	0	0	0	0	0	1 (<1)	0	0	0	0	0
Venous thromboembolic§	2 (1)	4 (3)	9 (2)	14 (3)	3 (1)	11 (5)	4 (2)	4 (2)	1 (1)	1 (1)	3 (4)	2 (2)
Renal failure§	1 (<1)	0	2 (<1)	2 (<1)	0	1 (<1)	2 (<1)	0	0	1 (1)	1 (1)	0
Arterial thromboembolic§	2 (1)	1 (<1)	4 (<1)	7 (1)	0	5 (2)	3 (1)	2 (<1)	1 (1)	0	2 (3)	0
Haematological TEAE ≥G3												
Neutropenia§	79 (51)	59 (40)	227 (48)	187 (40)	110 (50)	90 (40)	114 (46)	81 (37)	41 (46)	31 (36)	37 (54)	39 (46)
Leucopenia§	18 (12)	11 (7)	68 (14)	66 (14)	25 (11)	29 (13)	31 (13)	23 (11)	15 (17)	10 (12)	14 (21)	13 (15)
Anaemia§	7 (4)	7 (5)	11 (2)	28 (6)	4 (2)	14 (6)	10 (4)	11 (5)	2 (2)	7 (8)	2 (3)	2 (2)
Febrile neutropenia	21 (14)	19 (13)	79 (17)	43 (9)	37 (17)	20 (9)	38 (15)	22 (10)	15 (17)	13 (15)	10 (15)	7 (8)
Thrombocytopenia§	3 (2)	2 (1)	15 (3)	2 (<1)	4 (2)	1 (<1)	8 (3)	2 (<1)	4 (4)	0	2 (3)	1 (1)

This table shows selected TEAEs reported irrespective of cause and according to either preferred term or consolidated category. Data are presented as n (%).
*Intention-to-treat population.
†Non-squamous population.
‡Squamous population.
§Consolidated category.
G, grade; GI, gastrointestinal; Pl, placebo plus docetaxel arm; Ram, ramucirumab plus docetaxel arm; SI, special interest; TEAE, treatment-emergent adverse event.

Although limitations of the small sample size should be taken into consideration, these results suggest that the clinical benefits of the addition of ramucirumab to docetaxel are not diminished by prior treatment with bevacizumab in the first-line setting.

As the main goal of therapy for patients with advanced NSCLC is prolongation of patient survival without experiencing intolerable side effects or having a negative impact on QoL,[26] the choice of lung cancer therapy also considers, in part, whether or not a treatment reduces symptoms and/or improves or maintains QoL.[27 28] Importantly, the clinical benefit of ramucirumab plus docetaxel in REVEL was not at significant expense of safety or QoL.[18 19] Rates of TEAEs and of common grade 3 or worse TEAEs of special interest (including neutropenia, febrile neutropenia, leucopenia and hypertension) were generally higher in ramucirumab plus docetaxel-treated patients relative to the placebo plus docetaxel-treated patients, regardless of prior therapy. Despite the greater frequency of higher-grade adverse events in the ramucirumab plus docetaxel arm and the relatively low LCSS completion rate, which was similar between treatment arms, the addition of ramucirumab to docetaxel was not a detriment to patient-reported QoL when compared with the placebo plus docetaxel arm.[18 19] The QoL results in this exploratory subgroup analysis are consistent with results in the ITT population, suggesting prior therapy does not have an impact on QoL at the time of subsequent therapy.

The analyses presented here provide additional clinical data to inform the use of ramucirumab plus docetaxel as a second-line treatment option following chemotherapy regimens including a taxane, pemetrexed, gemcitabine or bevacizumab. In contrast to other antiangiogenic agents such as bevacizumab[29] or nintedanib[23] that are active only in non-squamous metastatic NSCLC, ramucirumab is approved for use in both non-squamous and squamous metastatic NSCLC.[18 21] Previous exploratory subgroup analyses of the REVEL study have also demonstrated that efficacy and safety outcomes were consistent between the ITT population and patients who were refractory to front-line therapy,[30] as well as patients who had rapid disease progression within 12 weeks of starting initial platinum-based therapy.[31] These results indicate that ramucirumab added to docetaxel could provide a clinical benefit even in these hard to treat patient populations. The efficacy, safety and QoL data from the additional subgroup analyses presented here provide further evidence that ramucirumab plus docetaxel is clinically beneficial across a wide range of patients in the second-line postplatinum setting, including patients who continue to have good performance status but who have progressed on the front-line therapies evaluated herein.

As immuno-oncology and chemotherapy combinations, which have recently emerged as treatment options in the first-line setting,[7 11 12 15 16] were not available as treatment options when the REVEL study was conducted, there are currently no available efficacy and safety data for ramucirumab plus docetaxel following treatment with both immunotherapy and chemotherapy in the first line. However, based on what is known regarding mechanism of action, the efficacy and safety profile for ramucirumab plus docetaxel following both immunotherapy and chemotherapy in the first line is expected to be consistent with what was observed in REVEL. There are ongoing efforts to use real-world evidence to evaluate outcomes for ramucirumab plus docetaxel in the postimmunotherapy setting,[32 33] and additional studies are needed to specifically evaluate outcomes for ramucirumab plus docetaxel following immuno-oncology and chemotherapy combinations in the first line.

In summary, the results of this exploratory analysis suggest that second-line ramucirumab plus docetaxel therapy may be effective regardless of type of front-line therapy. Although we do not have data on patients treated with chemotherapy plus an immune-checkpoint inhibitor as frontline therapy, in that clinical scenario, subsequent treatment with ramucirumab plus docetaxel could be considered.

Conclusion

The overall findings from these analyses suggest that the combination of ramucirumab and docetaxel may be effective regardless of the type of front-line therapy received. For patients who have received prior treatment with a taxane, pemetrexed, gemcitabine or bevacizumab as part of their first-line treatment regimen, ramucirumab in combination with docetaxel may be considered as a subsequent second-line treatment option. Given that the current work from REVEL was a retrospective, exploratory analysis, the results should be viewed with caution and robust prospective studies are warranted.

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