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

Edward B Garon, Tudor-Eliade Ciuleanu, Oscar Arrieta, Kumar Prabhash, Konstantinos N Syrigos, Tuncay Goksel, Keunchil Park, Vera Gorbunova, Ruben Dario Kowalyszyn, Joanna Pikiel, Grzegorz Czyzewicz, Sergey V Orlov, Conrad R Lewanski, Michael Thomas, Paolo Bidoli, Shaker Dakhil, Steven Gans, Joo-Hang Kim, Alexandru Grigorescu, Nina Karaseva, Martin Reck, Federico Cappuzzo, Ekaterine Alexandris, Andreas Sashegyi, Sergey Yurasov, Maurice Pérol

Summary

Background Ramucirumab is a human IgG1 monoclonal antibody that targets the extracellular domain of VEGFR-2. We aimed to assess efficacy and safety of treatment with docetaxel plus ramucirumab or placebo as second-line treatment for patients with stage IV non-small-cell-lung cancer (NSCLC) after platinum-based therapy.

Methods In this multicentre, double-blind, randomised phase 3 trial (REVEL), we enrolled patients with squamous or non-squamous NSCLC who had progressed during or after a first-line platinum-based chemotherapy regimen. Patients were randomly allocated (1:1) with a centralised, interactive voice-response system (stratified by sex, region, performance status, and previous maintenance therapy [yes *vs* no]) to receive docetaxel 75 mg/m² and either ramucirumab (10 mg/kg) or placebo on day 1 of a 21 day cycle until disease progression, unacceptable toxicity, withdrawal, or death. The primary endpoint was overall survival in all patients allocated to treatment. We assessed adverse events according to treatment received. This study is registered with ClinicalTrials.gov, number NCT01168973.

Findings Between Dec 3, 2010, and Jan 24, 2013, we screened 1825 patients, of whom 1253 patients were randomly allocated to treatment. Median overall survival was 10·5 months (IQR 5·1–21·2) for 628 patients allocated ramucirumab plus docetaxel and 9·1 months (4·2–18·0) for 625 patients who received placebo plus docetaxel (hazard ratio 0·86, 95% CI 0·75–0·98; p=0·023). Median progression-free survival was 4·5 months (IQR 2·3–8·3) for the ramucirumab group compared with 3·0 months (1·4–6·9) for the control group (0·76, 0·68–0·86; p<0·0001). We noted treatment-emergent adverse events in 613 (98%) of 627 patients in the ramucirumab safety population and 594 (95%) of 618 patients in the control safety population. The most common grade 3 or worse adverse events were neutropenia (306 patients [49%] in the ramucirumab group *vs* 246 [40%] in the control group), febrile neutropenia (100 [16%] *vs* 62 [10%]), fatigue (88 [14%] *vs* 65 [10%]), leucopenia (86 [14%] *vs* 77 [12%]), and hypertension (35 [6%] *vs* 13 [2%]). The numbers of deaths from adverse events (31 [5%] *vs* 35 [6%]) and grade 3 or worse pulmonary haemorrhage (eight [1%] *vs* eight [1%]) did not differ between groups. Toxicities were manageable with appropriate dose reductions and supportive care.

Interpretation Ramucirumab plus docetaxel improves survival as second-line treatment of patients with stage IV NSCLC.

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David Geffen School of Medicine at UCLA/Translational Research in Oncology-US Network, Los Angeles, CA, USA (E B Garon MD); **Institute of Oncology Ion Chiricuta and University of Medicine and Pharmacy Iuliu Hatieganu, Cluj-Napoca, Romania** (Prof T-E Ciuleanu MD); **Instituto Nacional de Cancerologia (INCAN), Mexico City, Mexico** (O Arrieta MD); **Tata Memorial Centre, Mumbai, India** (Prof K Prabhash MD); **Oncology Unit GPP, Sotiria General Hospital, Athens School of Medicine, Athens, Greece** (Prof K N Syrigos MD); **Ege University School of Medicine, Izmir, Turkey** (Prof T Goksel MD); **Department of Medicine, Division of Hematology-Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea** (Prof K Park MD); **Department of Chemotherapy, N N Blokhin Cancer Research Center, Moscow, Russia** (V Gorbunova MD); **Centro de Investigaciones Clínicas, Clínica Viedma, Argentina** (R D Kowalyszyn MD); **Wojewódzkie Centrum Onkologii, Gdansk, Poland** (J Pikiel MD); **Chemotherapy Department, John Paul II Hospital, Krakow, Poland** (G Czyzewicz MD); **Pavlov State Medical University, St Petersburg, Russia** (Prof S V Orlov MD); **Charing Cross Hospital, London, UK** (C R Lewanski MD);

Introduction

Lung cancer is the leading cause of death from cancer in the world.[1] Advanced non-small-cell lung cancer (NSCLC) is responsible for most of these cases, and although therapy directed against driver mutations has led to impressive gains in many regions, most patients do not have mutations associated with approved targeted drugs.[2] Initial therapy usually entails four to six cycles of platinum-based chemotherapy,[3] and some patients subsequently receive maintenance therapy.[4] Although 30–40% of patients initially respond to cytotoxic therapy, all patients eventually have disease progression on or after treatment.[5]

Clinically approved second-line therapies for NSCLC include docetaxel, erlotinib, and pemetrexed.[3,6–8] Treatment with docetaxel led to improved overall survival compared with best supportive care[6] and erlotinib led to improved overall survival compared with placebo.[7] Pemetrexed did not differ in efficacy from docetaxel and is approved in non-squamous NSCLC.[8] Clinical outcomes in this second-line population are poor with objective response rates (ORR) of less than 10%, median progression-free survival (PFS) of less than 4 months, and median overall survival of 7–9 months.[9] Several phase 3 studies have assessed addition of a cytotoxic or targeted agents in previously treated patients, but outside of subset analyses, none of these studies showed an improvement in overall survival.[10] Treatment of patients with squamous tumour histology is especially challenging because of a lack of driver mutations

Internistische Onkologie der Thoraxtumoren, Thoraxklinik im Universitätsklinikum Heidelberg, Translational Lung Research Center Heidelberg (TLRC-H), German Center for Lung Research (DZL), Heidelberg, Germany (Prof M Thomas MD); **Medical Oncology, San Gerardo Hospital, Monza, Italy** (P Bidoli MD); **Cancer Center of Kansas, Wichita, KS, USA** (S Dakhil MD); **St Jansdal Hospital, Herderwijk, Netherlands** (S Gans MD); **Yonsei Cancer Center, Yonsei University Health System, Seoul, South Korea** (Prof J-H Kim MD); **Department of Medical Oncology, Institute of Oncology, Bucharest, Romania** (Prof A Grigorescu MD); **City Clinical Oncology Dispensary, St Petersburg, Russia** (N Karaseva MD); **LungenClinic Grosshansdorf, German Center for Lung Research (DZL), Grosshansdorf, Germany** (M Reck MD); **Istituto Toscano Tumori, Livorno, Italy** (F Cappuzzo MD); **ImClone Systems, Eli Lilly, Bridgewater, NJ, USA** (E Alexandris MS, S Yurasov MD); **Eli Lilly, Indianapolis, IN, USA** (A Sashegyi PhD); **Léon-Bérard Cancer Centre, Lyon, France** (M Pérol MD)

Correspondence to:
Dr Edward B Garon, Translational Oncology Research Laboratory, 2825 Santa Monica Blvd, Suite 200, Santa Monica, CA 90404, USA
egaron@mednet.ucla.edu

See Online for appendix

associated with response to approved agents, and the frequent central location of the tumour in proximity to large blood vessels and airways, haemoptysis, and worse overall prognosis.[2]

One hallmark of cancer is angiogenesis, the multistep formation of new capillaries and blood vessels.[11] Blockade of VEGFR-2 signalling inhibits formation, proliferation, and migration of new blood vessels.[12] Addition of bevacizumab, a recombinant humanised monoclonal antibody against VEGF, to carboplatin-paclitaxel first-line chemotherapy led to a significant improvement in overall survival in eligible patients with non-squamous NSCLC;[13] however, the addition of bevacizumab to first-line cisplatin plus gemcitabine did not improve overall survival.[14]

Ramucirumab (IMC-1121B, ImClone Systems, Bridgewater, NJ, USA) is a fully human IgG1 monoclonal antibody that specifically binds to the VEGFR-2 extracellular domain with high affinity, preventing binding of all VEGF ligands and receptor activation.[15] In second-line treatment of advanced gastric cancer, two positive phase 3 studies[16,17] showed ramucirumab significantly improved survival as a single agent and in combination with paclitaxel.

We aimed to assess efficacy and safety of ramucirumab plus docetaxel versus placebo plus docetaxel as second-line therapy in patients with stage IV NSCLC whose disease had progressed during or after first-line platinum-based chemotherapy with or without maintenance treatment.

Methods

Study design and patients

In this randomised, double-blind, placebo-controlled phase 3 REVEL study, we enrolled adults (aged ≥18 years) at academic medical centres and community clinics in 26 countries on six continents.[18] Eligible patients had pathologically confirmed, squamous or non-squamous stage IV NSCLC that had progressed during or after a single platinum-based chemotherapy regimen, with or without bevacizumab or maintenance therapy. We included patients with recurrent disease who had received adjuvant or neoadjuvant therapy or chemoradiotherapy for locally advanced disease if their disease had progressed up to 6 months after completion of adjuvant or neoadjuvant platinum-based therapy, or if their disease had progressed more than 6 months after therapy and during or after one subsequent platinum-based chemotherapy regimen. We excluded patients whose only previous therapy for advanced or metastatic disease was EGFR tyrosine kinase inhibitor monotherapy. Patients were eligible for inclusion if they had measurable or non-measurable disease (defined according to Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1)[19] with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Key exclusion criteria included major blood vessel involvement, intratumour cavitation, poorly controlled hypertension, gastrointestinal perforation or fistulae, arterial thromboembolic event within 6 months (before randomisation), gross haemoptysis within 2 months, or grade 3–4 gastrointestinal bleeding (defined by National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE], version 4.0)[20] within 3 months (see appendix for full details of exclusion criteria). The protocol was approved by site-specific ethics review boards. Study conduct was guided by principles of good clinical practice and the Declaration of Helsinki. Patients provided written informed consent before treatment initiation.

Randomisation and masking

We randomly assigned patients (1:1) to receive intravenous docetaxel 75 mg/m² plus intravenous ramucirumab 10 mg/kg (ramucirumab group) or intravenous docetaxel 75 mg/m² plus placebo (control group) on day 1 of a 21 day cycle. Randomisation was done via a centralised, interactive voice-response system and was stratified by performance status, sex, previous maintenance therapy (yes *vs* no), and geographical region (Taiwan and South Korea *vs* other). Patients, study staff, and the sponsor were masked to treatment assignment. Unmasking was to be done for individual patients in emergencies only.

Procedures

Patients received treatment cycles until radiographically confirmed disease progression, unacceptable toxicity, withdrawal, or death. An independent data monitoring committee performed periodic reviews of safety data and recommended on May 11, 2012, that new patients enrolled in east Asia should receive docetaxel 60 mg/m² rather than 75 mg/m². Use of colony-stimulating factors and erythroid-stimulating factors was permitted at investigator discretion. In case of treatment-related adverse events, up to two ramucirumab dose reductions were allowed (appendix). Docetaxel reductions followed label recommendations. Patients who discontinued combination therapy because of adverse events related to ramucirumab or docetaxel were allowed to continue monotherapy. Treatment after study discontinuation was done at the discretion of the investigators.

Outcomes

The primary endpoint was overall survival (time from randomisation until death). Secondary endpoints included PFS (time from randomisation until disease progression or death) and ORR as assessed by investigators according to RECIST 1.1 at baseline, and every 6 weeks thereafter. We reported adverse events according to NCI-CTCAE.[20]

We assessed patient-reported symptoms and quality-of-life at baseline, the end of each cycle, and at the end of therapy, using the Lung Cancer Symptom Scale (LCSS)[21]

and the EuroQoL Five Dimensions questionnaire.[22] The LCSS uses a 100 mm Visual Analog Scale (VAS) and includes six items focused on lung cancer symptoms (appetite loss, fatigue, cough, shortness of breath, blood in sputum, and pain) plus three global items (symptom distress, difficulties with daily activities, and global quality-of-life).[21] The global quality-of-life score portion of the LCSS will be mentioned in this report, with additional quality-of-life analysis published elsewhere.

Exploratory objectives included assessment of ramucirumab pharmacokinetics and immunogenicity in patient serum with a validated ELISA format,[16] and biomarker assessments with patient blood and plasma and archival tumour tissue, when available.

Statistical analysis

We planned to enrol 1242 patients, with an assumption of 869 overall survival events (30% censoring), and with 85% power to detect a hazard ratio (HR) for overall survival of 0·816 with a one-sided α level of less than 0·025, equating to a projected median overall survival of 7·5 months in the control group and 9·2 months in the ramucirumab group.

For the primary efficacy analysis, we did a stratified log-rank comparison of overall survival in the intention-to-treat population. An independent data monitoring committee interim efficacy analysis for futility was done after 150 overall survival events (details in appendix). Safety analyses included all patients who received at least one dose of study drug. We assessed sensitivity of the treatment effect from the primary analysis through adjustment for prespecified prognostic variables. This multivariate analysis aimed to determine whether treatment effect remained a significant predictor of outcome even when the effects of other variables shown to affect survival times were taken into account.

We used a gate-keeping strategy to control the overall type 1 error at 0·05 (two-sided) for analysis of the primary endpoint and secondary endpoints. Under this strategy, statistical testing to allow formal inferential statements proceeded sequentially: testing of PFS endpoint was permitted if overall survival test was significant, and testing of ORR endpoint was permitted if PFS was significant.

We created overall survival and PFS survival curves with the Kaplan-Meier method. We estimated HR with stratified Cox proportional hazards models. We used multivariable analysis with a stepwise Cox regression model of predefined baseline characteristics to examine the effect of treatment after adjustment for other significant prognostic factors (appendix). We compared ORRs (percentage of patients in the intention-to-treat population with a complete response or partial response) and disease control rates (percentage of patients in the intention-to-treat population with tumour response or stable disease) in each treatment group with the Cochran-Mantel-Haenszel test.

We scored LCSS data according to developer guidelines,[21] and calculated percentage compliance according to the number of completed assessments divided by the number of expected assessments (patients still on study) for the intention-to-treat population. The primary quality-of-life analysis used the Kaplan-Meier method and Cox regression to compare time to deterioration for each item of the LCSS between arms with a prespecified 15 mm or greater increase from baseline to define deterioration. We used SAS version 9.1.2 or higher for all statistical analyses.

This study was registered with ClinicalTrials.gov, number NCT01168973.

Role of the funding source

The study sponsor provided study drug and collaborated with investigators on study design, data collection, analysis, and interpretation, and preparation of this

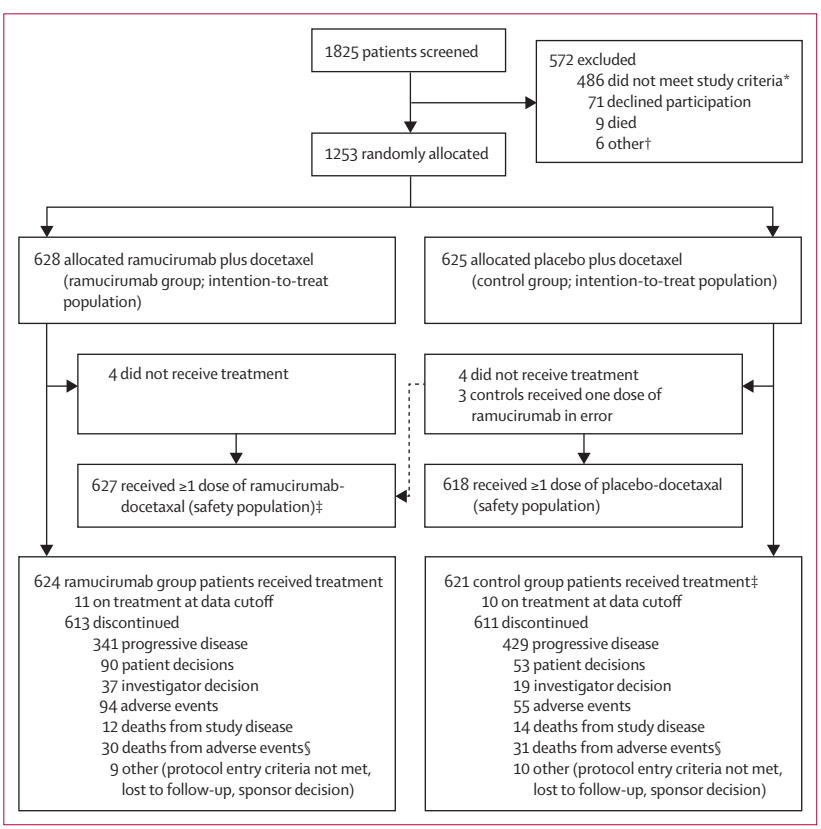

Figure 1: **Trial profile**

*Presence of untreated CNS metastases (143 patients [29%]), radiological evidence of major blood vessel involvement (63 patients [13%]), and inadequate organ function (48 patients [10%]). †Loss to follow-up (two patients), general health deterioration (one patient), tumour haemorrhage (one patient), ulcer (one patient), and unknown (one patient). ‡Includes three controls who received one dose of ramucirumab in error. §34 (5%) patients in the ramucirumb group and 35 (6%) controls had an adverse event that led to death either while on study or within 30 days after study discontinuation (among these patients, the deaths of 30 and 31 patients resulted in study discontinuation); 15 (2%) patients in the ramucirumb group and nine (1%) controls were possibly related to the study drugs, including haemorrhage events (five in the ramucirumab group and three in the control group), infection (four and two), cardiac events (two and two), respiratory arrest, distress, or inflammation (two and one), renal failure (one and none), pulmonary embolism (one and none), and ischaemic stroke (none and one).

	Ramucirumab plus docetaxel group (n=628)	Placebo plus docetaxel group (n=625)
Age, years		
Median (range)	62 (21–85)	61 (25–86)
<65 years	391 (62%)	407 (65%)
≥65 years	237 (38%)	218 (35%)
Sex		
Male	419 (67%)	415 (66%)
Female	209 (33%)	210 (34%)
Race (self-reported)*		
White	526 (84%)	503 (80%)
Asian	74 (12%)	86 (14%)
Black	17 (3%)	16 (3%)
Other	10 (2%)	20 (3%)
Region of origin		
East Asia (South Korea or Taiwan)	43 (7%)	46 (7%)
Other	585 (93%)	579 (93%)
ECOG performance status†		
0	207 (33%)	199 (32%)
1	420 (67%)	425 (68%)
Disease		
Measurable	606 (96%)	603 (96%)
Non-measurable	22 (4%)	22 (4%)
Smoking history		
Ever	518 (82%)	483 (77%)
Never	109 (17%)	141 (23%)
Unknown	1 (<1%)	1 (<1%)
Histological subtype		
Non-squamous	465 (74%)	447 (72%)
Squamous	157 (25%)	171 (27%)
Unknown	6 (1%)	7 (1%)
EGFR status		
Wild type	207 (33%)	197 (32%)
Mutant	15 (2%)	18 (3%)
Unknown or missing	406 (65%)	410 (66%)
Best response to platinum-based chemotherapy		
CR, PR, or SD	420 (67%)	417 (67%)
PD	178 (28%)	182 (29%)
Missing	30 (5%)	26 (4%)
Previous maintenance treatment		
No	493 (79%)	482 (77%)
Yes‡	135 (21%)	143 (23%)
Previous taxane		
No	475 (76%)	476 (76%)
Yes	153 (24%)	149 (24%)
Previous bevacizumab treatment		
No	540 (86%)	533 (85%)
Yes	88 (14%)	92 (15%)
Time since previous therapy		
<9 months	400 (64%)	374 (60%)
≥9 months	226 (36%)	251 (40%)
Missing	2 (<1%)	0

Data are n (%), unless otherwise stated. ECOG=Eastern Cooperative Oncology Group. CR=complete response. PR=partial response. SD=stable disease. PD=progressive disease. *Data not available for one patient in the ramucirumab group. †Data not available for one patient in each group. ‡Maintenance therapy in the ramucirumab group included pemetrexed (54 patients [9%]), bevacizumab (30 patients [5%]), EGFR tyrosine kinase inhibitor (16 patients [3%]), investigational drug (14 patients [2%]), and other (18 patients [3%]) and in the control group included pemetrexed (53 patients [9%]), bevacizumab (43 patients [7%]), EGFR tyrosine kinase inhibitor (14 patients [2%]), investigational drug (22 patients [4%]), and other (13 patients [2%]).

Table 1: **Baseline characteristics**

report. EBG wrote the first draft of the report with the sponsor and coauthors. The principal investigators had full access to all data, and all authors had final responsibility for the decision to submit for publication.

Results

We enrolled patients between Dec 3, 2010, and Jan 24, 2013 (figure 1, table 1). By data cutoff on of Dec 20, 2013, 884 patients had died (29% censoring rate). Four patients on each arm did not receive treatment, and three patients in the placebo group received one dose of ramucirumab inadvertently; thus for safety analyses, 627 patients were included in the ramucirumab group and 618 patients were included in the placebo group. Baseline characteristics were much the same for patients in the intention-to-treat population (table 1) and in squamous and non-squamous subgroups (data not shown).

At the time of primary analysis, 11 (2%) of 628 patients in the ramucirumab group and ten (2%) of 625 controls were still receiving treatment. 428 (68%) patients in the ramucirumab group had died (median follow-up 9·5 months [IQR 4·4–14·9]), as had 456 (73%) controls (8·8 months [3·7–13·7]).

Median overall survival was 10·5 months (IQR 5·1–21·2) in the ramucirumab group compared with 9·1 months (4·2–18·0) in the control group (stratified HR 0·86, 95% CI 0·75–0·98; p=0·023; figure 2). Treatment after study discontinuation was balanced between treatment arms (320 patients [51%] in the ramucirumab group *vs* 343 [55%] in the control group; appendix). This improvement in overall survival persisted on sensitivity analyses (appendix).

Although the study was not powered for subgroup analysis, most subgroups of patients had numerically longer survival on ramucirumab-docetaxel than placebo-docetaxel (appendix), including patients with non-squamous disease (11·1 months [IQR 5·3–24·3] in the ramucirumab group *vs* 9·7 months [4·4–19·6] in the control group; HR 0·83, 95% CI 0·71–0·97), patients with squamous disease (9·5 months [4·4–17·6] *vs* 8·2 months [3·6–14·9]; 0·88, 0·69–1·13), and responders to first-line

platinum treatment (11·2 months [5·6–24·5] *vs* 10·3 months [5·2–20·3]; 0·84, 0·71–0·99; appendix). Treatment response in non-responders to first-line platinum treatment was similar in both groups (8·3 months [4·2–16·3] *vs* 6·3 months [2·6–13·6]; 0·86, 0·68–1·08; appendix).

Median PFS was 4·5 months (IQR 2·3–8·3; 11·1% censoring) for the ramucirumab group compared with 3·0 months (1·4–6·9; 6·7% censoring) for the control group (HR 0·76, 95% CI 0·68–0·86; p<0·0001; figure 3). This effect was maintained after adjustment for other significant baseline prognostic factors (appendix). The effect of ramucirumab-docetaxel on PFS was consistent across most subgroups on the basis of baseline characteristics (appendix) including squamous and non-squamous histology.

144 (23%) of patients in the ramucirumab group had an investigator-assessed ORR compared with 85 (14%) controls (odds ratio [OR] 1·89, 95% CI 1·41–2·54; p<0·0001). We also noted this benefit in the disease control rate (402 [64%] patients in the ramucirumab group *vs* 329 [53%] controls; 1·60, 1·28–2·01; p<0·0001). Non-squamous and squamous subgroups had much the same response rate benefit (appendix).

Median treatment duration was 15·0 weeks (IQR 6·1–26·6) with ramucirumab (median 4·5 infusions [IQR 2·0–8·0]) and 12·0 weeks (6·0–21·0) with placebo (median 4·0 infusions [2·0–7·0]), and we noted a relative mean dose intensity of 94·6% (SD 11·0) for ramucirumab. Patients received a median of 4·0 docetaxel infusions (IQR 2·0–7·0 in the ramucirumab group, 2·0–6·0 in the placebo group) in both groups (appendix).

204 (33%) of 627 patients treated with ramucirumab-docetaxel had an adverse event resulting in at least one dose adjustment (ie, reduction, delay, or omission of any study drug during a cycle). 139 (23%) of 618 patients in the placebo-docetaxel group had at least one dose adjustment. The most common adverse events leading to dose adjustments for ramucirumab compared with placebo were neutropenia (77 [12%] patients in the ramucirumab group *vs* 55 [9%] controls), fatigue (54 [9%] patients *vs* 34 [6%] controls), and febrile neutropenia (44 [7%] patients *vs* 28 [5%] controls).

Grade 3 or worse haematological adverse events occurring in at least 10% of patients in the ramucirumab group included neutropenia, febrile neutropenia, and leucopenia (table 2). 75 patients in each group had grade 3 neutropenia. 231 (37%) of patients in the ramucirumab group and 171 (28%) controls had grade 4 neutropenia. Incidence of febrile neutropenia was higher in patients treated with ramucirumab than controls (grade 3: 61 [10%] patients *vs* 40 [6%] controls; grade 4: 39 [6%] patients *vs* 22 [4%] controls). Use of granulocyte colony-stimulating factors and granulocyte macrophage colony-stimulating factors did not differ between groups (262 [42%] patients *vs* 226 [37%] controls). 82 (13%) patients in the ramucirumab group and 50 (8%) controls were admitted to hospital for febrile neutropenia. Rates of sepsis did not differ between groups, with three deaths in each group. Incidence of anaemia was higher in the control group than the ramucirumab group, with 62 (10%) patients in the ramucirumab group and 76 (12%) controls receiving a transfusion.

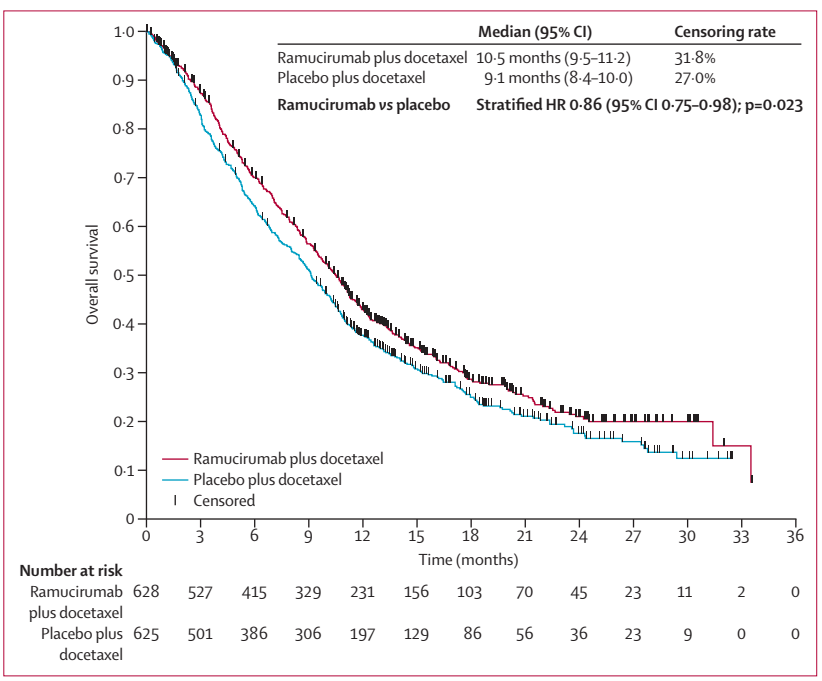

Figure 2: **Kaplan-Meier estimates of overall survival in the intention-to-treat population**
HR=hazard ratio.

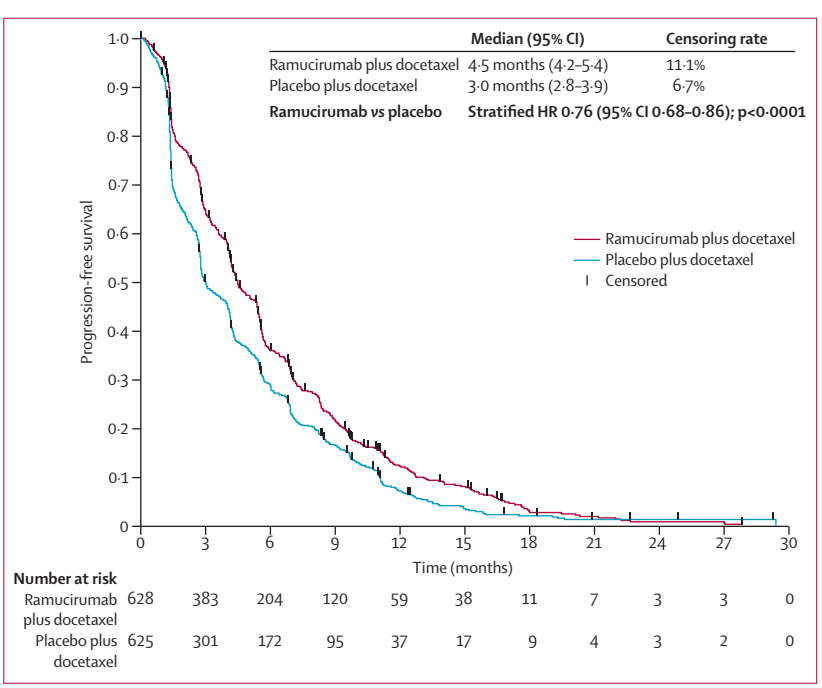

Figure 3: **Kaplan-Meier estimates of progression-free survival in the intention-to-treat population**
HR=hazard ratio.

Patients in the ramucirumab group had more bleeding or haemorrhage events of any grade (181 [29%] *vs* 94 [15%] controls), although rates of grade 3 or worse events were much the same (six grade 3 events in each group and one grade 4 event in the ramucirumab group [intracranial tumour haemorrhage]). Incidence of epistaxis of any grade was significantly higher in the ramucirumab group than in the control group, but few grade 3 or worse events occurred (table 2). Gastrointestinal and respiratory tract bleeding events, including haemoptysis and pulmonary haemorrhage, did not differ between groups (table 2) or according to histological disease type (appendix).

	Ramucirumab plus docetaxel group (n=627)		Placebo plus docetaxel group (n=618)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Treatment-emergent adverse events				
Any	613 (98%)	495 (79%)†	594 (95%)	444 (71%)
Fatigue	343 (55%)	88 (14%)	309 (49%)	65 (10%)
Decreased appetite	182 (29%)	14 (2%)	154 (25%)	8 (1%)
Diarrhoea	199 (32%)	29 (5%)	171 (27%)	19 (3%)
Nausea	169 (27%)	7 (1%)	170 (27%)	9 (1%)
Alopecia	162 (26%)	NA	156 (25%)	NA
Stomatitis	146 (23%)	27 (4%)	80 (13%)	10 (2%)
Neuropathy	145 (23%)	17 (3%)	126 (20%)	10 (2%)
Dyspnoea	138 (22%)	24 (4%)	149 (24%)	51 (8%)
Cough	133 (21%)	3 (<1%)	128 (20%)	5 (1%)
Pyrexia	104 (17%))	3 (<1%)	80 (13%)	2 (<1%)
Peripheral oedema	102 (16%)	0	53 (8%)	2 (<1%)
Constipation	101 (16%)	1 (<1%)	108 (17%)	6 (1%)
Mucosal inflammation	101 (16%)	18 (3%)	43 (7%)	3 (<1%)
Vomiting	87 (14%)	8 (1%)	88 (14%)	12 (2%)
Lacrimation increased	84 (13%)	1 (<1%)	28 (4%)	0
Myalgia	78 (12%)	4 (1%)	65 (10%)	4 (1%)
Arthralgia	72 (11%)	7 (1%)	49 (8%)	4 (1%)
Back pain	71 (11%)	7 (1%)	53 (8%)	2 (<1%)
Abdominal pain	68 (11%)	5 (1%)	61 (10%)	8 (1%)
Dysgeusia	67 (11%)	NA	46 (7%)	NA
Insomnia	67 (11%)	3 (<1%)	51 (8%)	1 (<1%)
Headache	66 (11%)	3 (<1%)	67 (11%)	6 (1%)
Haematological adverse events				
Neutropenia	345 (55%)	306 (49%)	284 (45%)	246 (39%)
Leucopenia	134 (21%)	86 (14%)	117 (19%)	77 (12%)
Anaemia	131 (21%)	18 (3%)	174 (28%)	35 (6%)
Febrile neutropenia	100 (16%)	100 (16%)	62 (10%)	62 (10%)
Thrombocytopenia	84 (13%)	18 (3%)	32 (5%)	4 (1%)
Adverse events of special interest				
Bleeding or haemorrhage	181 (29%)	15 (2%)	94 (15%)	14 (2%)
Epistaxis	116 (19%)	2 (<1%)	40 (6%)	1 (<1%)
Gastrointestinal haemorrhage	17 (3%)	4 (1%)	10 (2%)	2 (<1%)
Pulmonary haemorrhage	49 (8%)	8 (1%)	46 (7%)	8 (1%)
Haemoptysis	36 (6%)	4 (1%)	32 (5%)	4 (1%)
Hypertension	68 (11%)	35 (6%)	30 (5%)	13 (2%)
Infusion-related reaction	23 (4%)	5 (1%)	28 (4%)	4 (1%)
Proteinuria	21 (3%)	1 (<1%)	5 (1%)	0
Venous thromboembolic	16 (3%)	11 (2%)	36 (6%)	18 (3%)
Renal failure	14 (2%)	3 (<1%)	14 (2%)	2 (<1%)
Arterial thromboembolic	10 (2%)	6 (1%)	13 (2%)	8 (1%)
Congestive heart failure	6 (1%)	5 (1%)	4 (1%)	1 (<1%)
Gastrointestinal perforation	6 (1%)	5 (1%)	2 (<1%)	2 (<1%)

Adverse events reported according to MedDRA preferred terms , with some terms consolidated (full details in the appendix). NA=not applicable.

***Table 2*: Adverse events occurring in at least 10% of patients or of special interest irrespective of cause**

Hypertension occurred more frequently in the ramucirumab group than the control group (table 2), with one grade 4 hypertension event occurring in the ramucirumab group. The number of patients who had infusion-related reactions, venous or arterial thromboembolic events, or renal failure was low and much the same between groups. Most adverse events were manageable with dose adjustments or supportive care treatments.

Occurrence of serious adverse events was much the same in both treatment groups (269 [43%] in the ramucirumab group [263 hospital admissions] *vs* 262 [42%] in the control group [263 hospital admissions]). Increased incidence of neutropenia and febrile neutropenia in east Asia (Taiwan and South Korea) led to a docetaxel dosage change in this region: 65 (73%) patients received docetaxel 75 mg and 24 (27%) patients received docetaxel 60 mg. The lowered dose decreased the incidence of febrile neutropenia from 14 (44%) of 32 patients to none of 11 patients in the ramucirumab group and from four (12%) of 33 patients to one (8%) of 13 patients in the control group, and lowered the incidence of neutropenia to that reported in other regions. The mean duration of docetaxel treatment was much the same in the east Asian population and the rest of the world.

In the treated safety population, 53 patients in the ramucirumab group and 58 controls died on study or within 30 days of final study drug dose. The number of deaths due to adverse events was much the same between groups (figure 1).

At baseline, 484 (77%) patients in the ramucirumab group and 491 (79%) controls provided data on quality-of-life; at 30 day follow-up, 296 (47%) and 305 (49%) of patients provided data. The global quality-of-life analysis showed that time to deterioration did not differ between treatment groups (stratified HR 1·00, 95% CI 0·84–1·19; p=0·99), with 349 (56%) of patients in the ramucirumab group and 365 (58%) controls censored (appendix).

Discussion

To our knowledge, ramucirumab is the first new therapy for previously treated NSCLC to improve overall survival compared with an active comparator (panel). Other therapies have been approved on the basis of non-inferiority or comparisons with placebo and best supportive care. Our data analysis plan was straightforward and was maintained throughout the study.

Improvement of overall survival is regarded as the gold standard in NSCLC, especially for second-line therapy.[23] Other endpoints, including PFS, ORR, and disease control rate, also showed improvement with ramucirumab-docetaxel treatment. The duration of benefit in PFS (1·5 months) and overall survival (1·4 months) was much the same, suggesting that the delay in progression did not just extend time on drug but translated to a clinically meaningful additional duration of survival in this group of previously treated patients.

Our study population was representative of the general NSCLC population (table 1). Our large sample size makes an imbalance in the distribution of prognostic biomarkers unlikely, including molecular characteristics. Because pemetrexed is frequently used in first-line treatment of non-squamous carcinoma, docetaxel is the cornerstone of second-line treatment in advanced NSCLC, and has potential superiority over erlotinib in patients with wild-type EGFR.[24] Notably, the control group in our study had better outcomes than those that have been reported in other phase 3 studies with docetaxel,[8,25,26] despite our inclusion of patients who had received maintenance therapy after first-line platinum-based treatment. The reason for this disparity is unclear, although our exclusion of patients with performance status 2 or worse might have contributed. Such patients can be treated in second-line setting, but their outcome is poor with chemotherapy.[27] Exclusion of this group, in addition to other criteria that excluded patients at increased risk from anti-angiogenic therapy (major blood vessel encasement or invasion and intratumour cavitation) led to 572 (31%) of 1825 consented patients not being enrolled. Although the patient population was broad in comparison to currently approved anti-angiogenic agents,[13] the ineligibility of many patients who would be treated with docetaxel in this setting somewhat limits the generalisability of our results.

We noted benefits of ramucirumab in most subgroups analysed. However, questions about efficacy remain in elderly patients. A retrospective analysis of the E4599 study[28] suggested that patients aged 70 years or older had greater toxicity than did younger patients and no survival improvement when bevacizumab was added to chemotherapy. Of note, E4599 subset analysis also suggested lack of benefit in women,[13] whereas ramucirumab was much the same by sex. No interaction between age and treatment effect was noted in three other phase 3 studies (in other diseases) with ramucirumab.[16,17,29] With conflicting data in other studies and large confidence intervals, patient-based benefit-risk assessment will remain a key consideration in elderly patients.

Most toxicities were manageable with appropriate dose reductions and supportive care, without substantial reduction in the planned dose intensity of ramucirumab or docetaxel. Ramucirumab-docetaxel led to an increase in febrile neutropenia (16% *vs* 10%). At the 75 mg/m² dose, docetaxel was associated with a high rate of neutropenia in east Asian patients, but at 60 mg/m², the rate of neutropenia was much the same as in non-Asian patients. We did not note an increased risk of sepsis by group in our study, although the numbers were small. We noted no significant increase in thromboembolic events in the ramucirumab group, and hypertension was generally mild with only 35 (6%) patients experiencing grade 3 or worse hypertension. Bleeding events in the ramucirumab group were mainly due to grade 1–2 epistaxis.

In a randomised phase 2 study[30] of chemotherapy alone or in combination with bevacizumab, severe haemoptysis was noted in four (31%) of 13 patients with squamous cell carcinoma compared with two (4%) of 54 patients with adenocarcinoma. Subsequent bevacizumab studies excluded squamous cell disease.[31] The open-label, single-arm phase 2 BRIDGE study[32] attempted to reduce this risk in patients with squamous cell carcinoma through exclusion of patients with central tumours and delayed institution of bevacizumab until completion of two cycles

Panel: Research in context

Systematic review

We searched PubMed and the abstracts of major oncology congresses: American Society of Clinical Oncology (ASCO) Annual Meeting and European Society for Medical Oncology (ESMO); European Lung Cancer Conference (ELCC); Annual Meeting International Association for the Study of Lung Cancer (IASLC); World Conference Lung Cancer (WCLC); American Association for Cancer Research-National Cancer Institute-European Organisation for Research and Treatment of Cancer Congress (AACR-EORTC); and European Multidisciplinary Cancer Congress. We used MeSH and full-text search terms for lung and NSCLC and molecular targeted therapies, limiting our results to English language articles published between Jan 1, 2010, and March 25, 2014. For PubMed, we used the search terms ("molecular targeted therapy") OR ("molecular" AND "targeted") AND ("therapy" OR "therapies") AND ("lung neoplasms" OR "lung cancer") OR ("lung" AND "cancer") ("non small cell lung neoplasms" OR "non small cell lung cancer") AND ("2010/01/01":"2014/02/28"). For conferences, the search terms "metastatic lung cancer" or "advanced lung cancer" or "recurrent lung cancer" or "resistant lung cancer" were manually limited to abstracts on targeted therapies or phase 3 studies. We identified several potential targeted agents (either monoclonal antibodies, small-molecule tyrosine-kinase inhibitors, ALK inhibitors, Hsp90 inhibitors, COX-2 inhibitors, or mTOR inhibitors) that are under investigation either along with, or in place of, established treatments, including inhibitors of growth factors and their receptors (VEGF, EGFR, IGF, PD-1, PD-L1, C-MET), MEK inhibitors, and agents targeting the hedgehog pathway. We used information from the abstracts and ClinicalTrials.gov to identify the latest stage of clinical developments of these agents in lung cancer. We have restricted our discussion to agents we believe are most promising and relevant to patients with advanced non-small-cell lung cancer, on the basis of clinical study efficacy.

Interpretation

Various signalling processes including the VEGF pathway are involved in the development and progression of non-small-cell lung cancer. Experience with other monoclonal antibodies bevacizumab and cetuximab, the ALK inhibitor crizotinib, and the tyrosine kinase inhibitors erlotinib and gefitinib show that these pathways are valid targets for therapy. Our study shows that, in patients with advanced non-small-cell lung cancer with disease progression during or after first-line platinum-based therapy, ramucirumab plus docetaxel can significantly prolong survival compared with docetaxel, providing evidence for the role of a VEGFR-targeted therapy and offering patients with non-squamous and squamous recurrent disease a potential option for treatment.

of chemotherapy alone; however, the investigators ultimately determined that use of bevacizumab in squamous cell NSCLC was still investigational. Patients with squamous cell carcinoma seemed to derive similar benefit from ramucirumab plus docetaxel in our study without an increase in toxicity, particularly respiratory tract haemorrhage, when compared with the placebo group and non-squamous disease. As a result, ramucirumab-docetaxel could be an option for previously treated patients with squamous cell disease. Because ramucirumab specifically binds the extracellular domain of VEGFR-2 rather than the VEGF ligand, the effects might be localised to abnormal vasculature.[33]

Several studies of small molecule inhibitors of VEGFRs have not led to benefits in overall survival outside of subset analyses in NSCLC, although many have been associated with benefits in PFS.[34] One study of particular relevance is the LUME-Lung 1 study,[10] assessing nintedanib plus docetaxel. Unlike our study, LUME-Lung 1 assessed PFS as the primary endpoint. The study did meet its primary endpoint, but an overall survival benefit was not noted in the study population. A hierarchical statistical analysis showed an overall survival benefit in the adenocarcinoma subpopulation. By contrast with these small molecule VEGFR tyrosine kinase inhibitors, ramucirumab showed a survival advantage in previously treated NSCLC, and bevacizumab has prolonged survival as first-line therapy of non-squamous NSCLC. The reason for this disparity in efficacy between antibodies and small molecules is worthy of additional research, as it could affect design of future studies. We collected blood and tumour tissue from patients enrolled on study, and analysis of these specimens is ongoing.

Analysis of quality-of-life is important to assess the risk-benefit ratio with any new treatment, especially in the second-line setting in which the intent of treatment is palliative. In addition to the improvement of clinical outcomes, the analysis of quality-of-life suggests that no detriment was caused in patient-reported global quality-of-life through addition of ramucirumab to docetaxel in the second-line setting. The manageable safety profile and lack of detrimental effect on quality-of-life global score supports the consistent benefits seen in the efficacy endpoints.

Contributors

MP, EBG, and SY contributed to study design. EBG, T-EC, OA, KPr, KNS, TG, KPa, VG, RDK, JP, GC, SVO, CRL, MT, PB, SD, SG, J-HK, AG, NK, MR, FC, and MP contributed to data collection. EBG, MP, AS, EA, and SY contributed to data analysis and interpretation. All authors were involved in the drafting, review, and approval of the report.

Declaration of interests

T-EC reports Lilly Advisor board and symposia fees outside submitted work. EBG reports grants from Eli Lilly during the conduct of the study, personal fees from Boehringer Ingelheim, and grants from Novartis, Pfizer, AstraZeneca, Genentech, Puma Biotechnology, and Merck outside the submitted work. TG reports Eli Lilly personal or investigator fees. AG reports personal fees for lectures outside the submitted work. MP reports personal fees and non-financial support (medical writing support and invitations to medical congresses) from Eli Lilly and Hoffmann-La Roche, and personal fees from Pfizer, Genentech, Boehringer Ingelheim, and AstraZeneca, outside the submitted work. MR reports personal fees from Hoffmann-La Roche, Eli Lilly, Boehringer Ingelheim, AstraZeneca, Pfizer, Novartis, and BMS. MT reports personal fees from Eli Lilly, Novartis, Hoffmann-La Roche, and BMS. EA and SY are employees of ImClone Systems, a wholly owned subsidiary of Eli Lilly, Bridgewater, NJ, USA. AS is an employee of Eli Lilly, Indianapolis, IN, USA. All other authors declare no competing interests.

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References

1 Siegel R, Naishadham D, Jemal A. Cancer statistics 2012. *CA Cancer J Clin* 2012; **62:** 10–29.

2 Li T, Kung H-J, Mack PC, Gandara DR. Genotyping and genomic profiling of non-small cell-lung cancer: implications for current and future therapies. *J Clin Oncol* 2013; **31:** 1039–49.

3 Leighl NB. Treatment paradigms for patients with metastatic non-small-cell lung cancer: first-, second-, and third-line. *Curr Oncol* 2012; **19:** S52–58.

4 Gerber DE, Schiller JH. Maintenance chemotherapy for advanced non-small cell lung cancer: new life for an old idea. *J Clin Oncol* 2013; **31:** 1009–20.

5 Stinchcombe TE, Socinski MA. Current treatments for advanced stage non-small cell lung cancer. *Proc Am Thorac Soc* 2009; **6:** 233–41.

6 Shepherd FA, Dancey J, Ramlau R, et al. A prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. *J Clin Oncol* 2000; **18:** 2095–103.

7 Shepherd FA, Pereira JR, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med* 2005; **353:** 123–32.

8 Hanna N, Shepherd FA, Fossella FV, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. *J Clin Oncol* 2004; **22:** 1589–97.

9 Hotta K, Katsuyuki H, Yoshiro F, et al. Relationship between response and survival in more than 50,000 patients with advanced non-small cell lung cancer treated with systemic chemotherapy in 143 phase III trials. *J Thorac Oncol* 2007; **2:** 402–07.

10 Reck M, Kaiser R, Mellemgaard A, et al. 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 trial. *Lancet Oncol* 2014; **15:** 143–55.

11 Hanahan D, Weinberg RA. The hallmarks of cancer. *Cell* 2000; **100:** 57–70.

12 Skobe M, Rockwell P, Goldstein N, et al. Halting angiogenesis suppresses carcinoma cell invasion. *Nat Med* 1997; **3:** 1222–27.

13 Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med* 2006; **355:** 2542–50.

14 Reck M, von Pawel J, Zatloukal P, et al. Overall survival with cisplatin–gemcitabine and bevacizumab or placebo as first-line therapy for nonsquamous non-small-cell lung cancer: results from a randomised phase III trial (AVAiL). *Ann Oncol* 2010; **21:** 1804–09.

15 Spratlin JL, Cohen RB, Eadens M, et al. 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* 2010; **28:** 780–87.

16 Fuchs CS, Tomasek J, Yong CJ, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet* 2014; **383:** 31–39.

17 Wilke H, Van Cutsem E, Cheul S, et al. RAINBOW: a global, phase 3, randomized, double-blind study of ramucirumab plus paclitaxel versus placebo plus paclitaxel in the treatment of metastatic gastric adenocarcinoma following disease progression on first-line platinum- and fluoropyrimidine-containing combination therapy IMCL CP12–0922 (I4T-IE-JVBE). *J Clin Oncol* 2014; **32** (suppl 3)**:** abstr LBA7.

18 Garon EB, Cao D, Alexandris E, John WJ, Yurasov S. A randomized, double-blind, phase III study of docetaxel and ramucirumab versus docetaxel and placebo in the treatment of stage IV non-small-cell lung cancer after disease progression after 1 previous platinum-based therapy (REVEL): treatment rationale and study design. *Clin Lung Cancer* 2012; **13:** 505–09.

19 Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000; **92:** 205–16.

20 US Department of Health and Human Services. Common Terminology Criteria for Adverse Events v4.0 (CTCAE), 5/2009 update. http://evs.nci.nih.gov/ftp1/CTCAE/Archive/CTCAE_4.02_2009-09-15_QuickReference_8.5x11.pdf (accessed May 19, 2014).

21 Hollen PJ, Gralla RJ, Kris MG, Potanovich LM. Quality of life assessment in individuals with lung cancer: Testing the Lung Cancer Symptom Scale (LCSS). *Eur J Cancer* 1993; **29:** S51–58.

22 EuroQoL Group. EuroQol—a new facility for the measurement of health-related quality of life. *Health Policy* 1990; **16:** 199–208.

23 Booth CM, Eisenhauer EA. Progression-free survival: meaningful or simply measurable? *J Clin Oncol* 2012; **30:** 1030–33.

24 Garassino MC, Martelli O, Broggini M, et al. Erlotinib versus docetaxel as second-line treatment of patients with advanced non-small-cell lung cancer and wild-type EGFR tumours (TAILOR): a randomised controlled trial. *Lancet Oncol* 2013; **14:** 981–88.

25 Fossella FV, DeVore R, Kerr RN, et al. 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. *J Clin Oncol* 2000; **18:** 2354–62.

26 Kim ES, Hirsh V, Mok T, et al. Gefitinib versus docetaxel in previously treated non-small-cell lung cancer (INTEREST): a randomised phase III trial. *Lancet* 2008; **372:** 1809–18.

27 Di Maio M, Lama N, Morabito A, et al. Clinical assessment of patients with advanced non-small-cell lung cancer eligible for second-line chemotherapy: a prognostic score from individual data of nine randomised trials. *Eur J Cancer* 2010; **46:** 735–43.

28 Ramalingam SS, Dahlberg SE, Langer CJ, et al. Outcomes for elderly, advanced-stage non-small-cell lung cancer patients treated with bevacizumab in combination with carboplatin and paclitaxel: analysis of Eastern Cooperative Oncology Group Trial 4599. *J Clin Oncol* 2008; **26:** 60–65.

29 Mackey J, Ramos M, Lipatov O, et al. Primary results of ROSE/TRIO-12, a randomized placebo controlled phase III trial evaluating the addition of ramucirumab to first-line docetaxel chemotherapy in metastatic breast cancer. San Antonio Breast Cancer Symposium 36th Annual Meeting; San Antonio, TX, USA; Dec 10–14, 2013: abstr 238.

30 Johnson DH, Fehrenbacher L, Novotny WF, et al. Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. *J Clin Oncol* 2004; **22:** 2184–91.

31 Sandler AB, Schiller JH, Gray R, et al. Retrospective evaluation of the clinical and radiographic risk factors associated with severe pulmonary hemorrhage in first-line advanced, unresectable non-small-cell lung cancer treated with carboplatin and paclitaxel plus bevacizumab. *J Clin Oncol* 2009; **27:** 1405–12.

32 Hainsworth JD, Fang L, Huang JE et al. BRIDGE: an open-label phase II trial evaluating the safety of bevacizumab + carboplatin/paclitaxel as first-line treatment for patients with advanced, previously untreated, squamous non-small cell lung cancer. *J Thorac Oncol* 2011; **6:** 109–14.

33 Smith NR, Baker D, James NH, et al. Vascular endothelial growth factor receptors VEGFR-2 and VEGFR-3 are localized primarily to the vasculature in human primary solid cancers. *Clin Cancer Res* 2010; **16:** 3548–61

34 Crinò L, Metro G. Therapeutic options targeting angiogenesis in nonsmall cell lung cancer. *Eur Respir Rev* 2014; **23:** 79–91.