Published in: The Lancet Oncology (2015), vol. 16, pp. 328-337
Status : Postprint (Author's version)

Necitumumab plus pemetrexed and cisplatin as first-line therapy in patients with stage IV non-squamous non-small-cell lung cancer (INSPIRE): an open-label, randomised, controlled phase 3 study

Luis Paz-Ares, Jörg Mezger, Tudor E Ciuleanu, Jürgen R Fischer, Joachim von Pawel, Mariano Provencio, Andrzej Kazarnowicz, György Losonczy, Gilberto de Castro jr, Aleksandra Szczesna, Lucio Crino, Martin Reck, Rodryg Ramlau, Ernst Ulsperger, Christian Schumann, Jose Elias A Miziara, Álvaro E Lessa, Mircea Dediu, Beatrix Bálint, Henrik Depenbrock, Victoria Soldatenkova, Raffael Kurek, Fred R Hirsch, Nick Thatcher, Mark A Socinski, for the INSPIRE Investigators[1]

Instituto de Biomedicina de Sevilla-IBIS(HospitalVirgendel Rocîo/Universidad de Sevilla/ CSIC), Sevilla, Spain, and Hospital Universitario Doce de Octubre and CNIO Lung Cancer Unit, Madrid, Spain (L Paz-Ares MD);
St Vincentius Kliniken, Karlsruhe, Germany (Prof J Mezger MD);
Institute of Oncology and University of Medicine and Pharmacy, Cluj-Napoca, Romania (Prof TE Ciuleanu MD);
Klinik Lowenstein GmbH, Lowenstein, Germany (J R Fischer MD);
Asklepios-Fachkliniken Munchen-Gauting, Gauting, Germany (J von Pawel MD);
Hospital Puerta de Hierro, Madrid, Spain (Prof M Provencio MD);
Samodzielny Publiczny Zespol Gruzlicy i Chorob Pluc w Olsztynie, Olsztyn, Poland (A Kazarnowicz M D);
Semmelweis Egyetem, Budapest, Hungary (Prof G Losonczy MD);
Instituto do Cancer do Estado de Sao Paulo (ICESP), Sao Paulo, Brazil (GdeCastroJrMD);
Mazowieckie Centrum Leczenia Chorob Ptuc i Gruzlicy, Otwock, Poland (A Szczesna MD);
Ospedale Santa Maria della Misericordia, Perugia, Italy (L Crino MD);
LungenClinic Grosshansdorf, Airway Research Center North (ARCN), Member of the German Center for Lung Research (DZL),Grosshansdorf, Germany (M Reck MD);
Poznan University of Medical Sciences, Wielkopolskie Centrum Pulmonologii iTorakochirurgii, Poznan, Poland (Prof R Ramlau MD);
Landesklinikum Horn, NO, Austria (E Ulsperger MD);
Department of Internal Medicine II, University Clinic Ulm, Ulm, Germany, and Klinik fur Pneumologie, Thoraxonkologie, Schlaf-und Beatmungsmedizin, Kempten-Oberallgäu, Germany (C Schumann MD);
Hospital de Cancer de Barretos, Sao Paulo, Brazil (J E A Miziara MD);
Hospital Santa Izabel-Santa Casa de Misericordia da Bahia, Nazare, Nazare, Brazil (Á E Lessa MD);
Institute of Oncology Bucharest, Bucharest, Romania (M Dediu MD);
Csongrád Megye Mellkasi Betegségek Szakkórhâza, Deszk, Hungary (B Bálint PhD);
Lilly Deutschland GmbH, Bad Homburg, Germany (H Depenbrock MD, V Soldatenkova MSc, R Kurek MD);
University of Colorado, Division of Medical Oncology, Aurora, CO, USA (Prof F R Hirsch MD);
The Christie Hospital, National Health Services Trust, Manchester, UK (N Thatcher FRCP);
University of Pittsburgh Cancer Institute, University of Pittsburgh, Pittsburgh, PA, USA (Prof M A Socinski MD)

[1] See appendix for full list of study investigators

Published in: The Lancet Oncology (2015), vol. 16, pp. 328-337
Status : Postprint (Author's version)

SUMMARY

Background. Necitumumab is a second-generation recombinant human immunoglobulin G1 EGFR monoclonal antibody that competitively inhibits ligand binding. We aimed to compare necitumumab plus pemetrexed and cisplatin with pemetrexed and cisplatin alone in patients with previously untreated, stage IV, non-squamous non-small-cell lung cancer (NSCLC).

Methods. We did this randomised, open-label, controlled phase 3 study at 103 sites in 20 countries. Patients aged 18 years or older, with an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 and adequate organ function, were randomly assigned 1:1 to treatment with a block randomisation scheme (block size of four) via a telephone-based interactive voice-response system or interactive web-response system. Patients received either cisplatin 75 mg/m^2 and pemetrexed 500 mg/m^2 on day 1 of a 3-week cycle for a maximum of six cycles alone, or with necitumumab 800 mg on days 1 and 8. Necitumumab was continued after the end of chemotherapy until disease progression or unacceptable toxic effects. Randomisation was stratified by smoking history, ECOG performance status, disease histology, and geographical region. Patients and study investigators were not masked to group assignment. The primary endpoint was overall survival. Efficacy analyses were by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00982111.

Findings. Between Nov 11, 2009, and Feb 2, 2011, we randomly assigned 633 patients to receive either necitumumab plus pemetrexed and cisplatin (n=315) or pemetrexed and cisplatin alone (n=318). Enrolment was stopped on Feb 2, 2011, after a recommendation from the independent data monitoring committee. There was no significant difference in overall survival between treatment groups, with a median overall survival of 11·3 months (95% CI 9·5-13·4) in the necitumumab plus pemetrexed and cisplatin group versus 11·5 months (10·1-13·1) in the pemetrexed and cisplatin group (hazard ratio 1·01 [95% CI 0·84-1·21]; p=0·96). The incidence of grade 3 or worse adverse events, including deaths, was higher in the necitumumab plus pemetrexed and cisplatin group than in the pemetrexed and cisplatin group; in particular, deaths regarded as related to study drug were reported in 15 (5%) of 304 patients in the necitumumab group versus nine (3%) of 312 patients in the pemetrexed and cisplatin group. Serious adverse events were likewise more frequent in the necitumumab plus pemetrexed and cisplatin group than in the pemetrexed and cisplatin group (155 [51%] of 304 vs 127 [41%] of 312 patients). Patients in the necitumumab plus pemetrexed and cisplatin group had more grade 3-4 rash (45 [15%] of 304 vs one [<1%] of 312 patients in the pemetrexed and cisplatin alone group), hypomagnesaemia (23 [8%] vs seven [2%] patients), and grade 3 or higher venous thromboembolic events (23 [8%] vs 11 [4%] patients) than did those in the pemetrexed and cisplatin alone group.

Interpretation. Our findings show no evidence to suggest that the addition of necitumumab to pemetrexed and cisplatin increases survival of previously untreated patients with stage IV non-squamous NSCLC. Unless future studies identify potentially useful predictive biomarkers, necitumumab is unlikely to provide benefit in this patient population when combined with pemetrexed and cisplatin.

Funding. Eli Lilly and Company.

Published in: The Lancet Oncology (2015), vol. 16, pp. 328-337
Status : Postprint (Author's version)

INTRODUCTION

Non-small-cell lung cancer (NSCLC) is a heterogeneous disease with respect to tumour histology and molecular profile.[1-2] Patients with *EGFR* wild-type, ALK translocation-negative non-squamous NSCLC (adenocarcinoma, large-cell carcinoma, and other non-squamous histology), and a good performance status, might be offered a wide choice of first-line regimens consisting of a platinum-based doublet of cisplatin or carboplatin combined with pemetrexed, a taxane, gemcitabine, or vinorelbine, with or without bevacizumab.[3] The presence in tumours of sensitising mutations of *EGFR* or *ALK* translocations—driver lesions predictive of outcome for particular targeted drugs—offers the possibility of specific, pathway-directed systemic therapy for some patients with adenocarcinoma.[4-6] However, tumour *EGFR* mutation status does not seem to be associated with efficacy of EGFR antibody therapy.[7] In the past few years, expansion of first-line treatment options for patients with non-squamous NSCLC has been reflected in improvements in overall survival.

Most advanced NSCLCs express EGFR, and aberrant function of the EGFR pathway seems to be a key factor in the development of some NSCLCs.[8] The randomised phase 3 FLEX study showed that addition of the EGFR antibody cetuximab to cisplatin plus vinorelbine significantly improved overall survival (hazard ratio [HR] 0·871 [95% CI 0·762-0·996]; p=0·044), but not progression-free survival (0·943 [0·825-1·077]; p=0·39) in the first-line treatment of patients with EGFR-expressing advanced NSCLC.[8] This improvement in overall survival was accompanied by significant adverse effects in the cetuximab group, in particular an increased incidence of febrile neutropenia, an adverse event that was prevalent in the chemotherapy group. Nevertheless, the FLEX study provided a rationale for the testing of other EGFR antibodies in this setting.

Necitumumab is a second-generation recombinant human immunoglobulin G1 (IgG1) EGFR monoclonal antibody that binds EGFR with high affinity, competing with the natural ligands and thereby preventing receptor activation by all known ligands and thus inhibiting downstream signalling.[9] For first-line treatment of patients with advanced non-squamous NSCLC, pemetrexed and cisplatin is an established chemotherapy regimen.[10,11] In murine NSCLC xenograft models, addition of necitumumab to pemetrexed and cisplatin resulted in a substantial increase in anti-tumour activity (unpublished data), suggesting that this regimen was appropriate for use in our present study.

We did the INSPIRE study to investigate whether addition of necitumumab to pemetrexed and cisplatin would improve survival in the first-line treatment of patients with advanced non-squamous NSCLC. We postulated that the choice of pemetrexed and cisplatin as the chemotherapy regimen when combined with an EGFR antibody would result in a lower incidence of febrile neutropenia than did the cisplatin and vinorelbine regimen used in the FLEX study. We also expected to minimise the rate of hypersensitivity reactions on the basis of the human constitution of necitumumab. In parallel, the phase 3 SQUIRE study[12] assessed the efficacy and safety of necitumumab plus gemcitabine and cisplatin as first-line treatment for patients with advanced squamous NSCLC.

METHODS

Study design and patients

We did this open-label, randomised, controlled phase 3 study at 103 sites in 20 countries (appendix). Full inclusion and exclusion criteria are in the appendix. Briefly, eligible patients were aged 18 years or older with histologically or cytologically confirmed stage IV (according to the American Joint Committee on Cancer staging system[13]) non-squamous

NSCLC who had not received chemotherapy for the treatment of advanced disease. Other key inclusion criteria included measurable disease as defined by RECIST 1.0 criteria,[14] an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2, and adequate organ function (white blood cell count of ≥3000 cells per μL, with an absolute neutrophil cell count of ≥1500 cells per μL, a platelet count of ≥100000 cells per μL, and a haemoglobin concentration of ≥9·5 g/dL; total bilirubin of ≤1·5xfhe upper limit of normal [ULN] and aspartate aminotransferase and alanine aminotransferase of ≤5·0x the ULN in the presence of liver metastases, or of ≤2·5x the ULN in the absence of liver metastases; and serum creatinine of ≤1·2xthe ULN or a calculated creatinine clearance of >50 mL/min). The availability of archived tumour tissue for biomarker analysis was also an inclusion criterion.

Key exclusion criteria included symptomatic brain metastases, clinically significant third-space fluid retention requiring repeated drainage, peripheral neuropathy of grade 2 or worse and major surgery or investigational therapy in the 4 weeks before randomisation. Patients were also excluded if they had superior vena cava syndrome contraindicating hydration; clinically relevant coronary artery disease or uncontrolled congestive heart failure (New York Heart Association class III or IV[15]); myocardial infarction within 6 months before randomisation; an ongoing or active infection (needing antibiotics), including active tuberculosis or known infection with HIV; a history of clinically significant neurological or psychiatric disorders, including dementia, seizures, or bipolar disorder, potentially precluding protocol compliance; any other serious uncontrolled medical disorders or psychological disorder that would, in the opinion of the investigator, restrict the patient's ability to complete the study or sign an informed consent document; a known allergy or history of hypersensitivity reaction to any of the treatment components, including any ingredient used in the formulation of necitumumab, or any other contraindication to one of the given treatments; a concurrent active malignancy other than adequately treated basal-cell carcinoma of the skin or preinvasive carcinoma of the cervix (a patient with previous history of malignancy other than NSCLC was eligible, provided that they had been free of disease for ≥3 years); a known history of drug abuse; or if the patient was pregnant or breastfeeding.

All patients provided written informed consent. This study was done in accordance with the International Conference on Harmonization and good clinical practice guidelines and was approved by the local ethics committees at each study centre.

Randomisation and masking

Patients were randomly assigned (1:1), with a block randomisation scheme (block size of four) via a telephone-based interactive voice-response system or interactive web-response system, to receive necitumumab plus pemetrexed and cisplatin or pemetrexed and cisplatin alone. Randomisation was stratified by smoking history (non-smoker vs ex-light smoker vs smoker), ECOG performance status (0-1 vs 2), disease histology (adenocarcinoma or large-cell carcinoma vs other), and geographical region (North America, Europe, Australia vs South America, South Africa, Asia [India]). Patients received the first dose of study drug within 7 days of randomisation.

After the first treatment session, we expected that the likely occurrence of acneiform rash in patients in the necitumumab plus pemetrexed and cisplatin group would unmask most patients and investigators to treatment assignment. For this reason, we did the study open-label. However, the aggregate clinical data provided to the sponsor during the study were masked to treatment assignment to preserve the integrity of the trial. The sponsor of the study had unmasked access only to serious adverse event data.

Procedures

Chemotherapy comprised intravenous cisplatin 75 mg/m^2 and pemetrexed 500 mg/m^2 on day 1 of a 3-week cycle, for a maximum of six cycles. Necitumumab at an absolute dose of 800 mg was given intravenously on days 1 and 8. Before administration of pemetrexed, patients received oral corticosteroid, folic acid (350-1000 µg orally, once daily), and vitamin B12 supplementation, according to the pemetrexed label. We allowed dose modifications of all study drugs according to protocol-defined criteria (appendix). In particular, necitumumab dose modification was allowed after occurrence of a reversible grade 3 or 4 necitumumab-related adverse event (ie, an event that resolved to grade 2 or lower—eg, fatigue, anorexia, fever) that needed a delay of treatment for up to 6 weeks after day 1 of the most recent treatment cycle. In this setting, necitumumab could be re-administered at a reduced dose of 600 mg if necessary. We allowed a second dose reduction to 400 mg for this level of event (grade 3 or 4). Events that needed more than two dose reductions warranted automatic discontinuation of necitumumab. Patients were withdrawn from treatment if they developed a grade 3 or 4 infusion reaction.

After six cycles of study therapy, patients without progressive disease in the necitumumab group continued with necitumumab on the same treatment schedule until radiographically documented progressive disease or the occurrence of unacceptable toxic effects. Patients in the chemotherapy alone group were observed until radiographically documented progressive disease. Study therapy was discontinued on occurrence of progressive disease or unacceptable toxic effects.

We assessed tumour response, according to RECIST 1.0, by CT or MRI at baseline (within 21 days before randomisation) and then every 6 weeks after the first dose of study therapy until radiographically documented progressive disease. Complete blood counts and serum chemistry were obtained at baseline and on days 1 and 8 of each cycle until discontinuation of chemotherapy, and before treatment on day 1 of each cycle thereafter for patients in the necitumumab group. Coagulation profile and urinalysis assessments were done at baseline, on day 1 of cycle 1, and every 6 weeks thereafter. For female patients, a pregnancy test was done at baseline and every 6 weeks thereafter.

Treatment-emergent adverse events were reported according to the Medical Dictionary for Regulatory Activities (version 12.0)[16] and were graded with the National Cancer Institute-Common Terminology Criteria for Adverse Events (version 3.0).[17] An independent data monitoring committee monitored safety on a regular basis. We assessed patient health status with the patient Lung Cancer Symptom Scale[18] and EuroQol-5D.[19] At each scheduled timepoint, assessment of the Lung Cancer Symptom Scale was done before EuroQol-5D. We assessed expression of tumour EGFR protein by immuno-histochemistry with the EGFR PharmDx Kit (Dako, Carpinteria, CA). We classified the level of expression by immunohistochemistry score on a continuous scale of 0-300 (H-score), as previously described.[20,21] Other exploratory biomarker analyses are ongoing and will be reported elsewhere.

Outcomes

The primary endpoint was overall survival, defined as the time from randomisation to death from any cause. Secondary endpoints were: progression-free survival, defined as time from randomisation to radiographic progression or death from any cause; objective response, defined as the proportion of patients who had a best response of complete response or partial response; time to treatment failure, defined as time from the date of randomisation until the

date of the first radiographical documentation of progressive disease, death by any cause, discontinuation of treatment for any reason, or initiation of new anticancer therapy; safety; self-reported health status (EuroQol-5D index score, Visual Analog Scale score, and Lung Cancer Symptom Scale index score); immunogenicity of necitumumab; and EGFR protein expression.

Statistical analysis

Using a two-sided log-rank test at the 5% significance level, the original planned sample size of 947 patients would have given a power of 85% for detection of a significant improvement in overall survival, from 11·0 months for pemetrexed and cisplatin[11] to 13·75 months for necitumumab plus pemetrexed and cisplatin, as denoted by an HR for necitumumab plus pemetrexed and cisplatin versus pemetrexed and cisplatin of 0·80. After inclusion of 633 patients, enrolment was stopped after a recommendation from the independent data monitoring committee. The amended final analysis was planned when at least 474 deaths were recorded and gave a power of 68% according to the assumptions that governed the original power calculation.

We assessed efficacy in the intention-to-treat population, which included all randomised patients. Safety was assessed in patients who received any dose of study drug and was analysed according to actual therapy received. We estimated overall and progression-free survival with the Kaplan-Meier method and compared both between treatment groups with the log-rank test, stratified by the randomisation strata. We estimated HRs and 95% CIs from stratified Cox proportional hazards models. We compared the proportion of patients achieving an objective response in each treatment group with the Cochran-Mantel-Haenszel test, with adjustment for the stratification variables. The overall significance level was set at 0·05; no adjustment was done for multiple testing for the secondary endpoints.

Findings from an immunohistochemistry analysis of the FLEX study suggested that a tumour EGFR H-score of 200 or more was predictive for cetuximab benefit; this finding was apparent both in the overall trial population and in adenocarcinoma and squamous-cell-carcinoma subgroups.[20] In an exploratory analysis of our study, we investigated whether an EGFR H-score of 200 or more was predictive for necitumumab benefit by comparing treatment outcome in high (H-score ≥200) versus low (H-score <200) EGFR expression groups with Cox regression analysis. This analysis was done in the translational research population, comprising patients in the safety population who had a valid (ie, calculable for that patient from available data) non-missing result for EGFR H-score, and who were enrolled for more than two cycles before the decision was made to terminate enrolment.

We analysed data with SAS (version 9.1.3). This study is registered with ClinicalTrials.gov, number NCT00982111.

Role of the funding source

The funder of the study was responsible for data management, commissioning of laboratory investigations, and statistical analyses, and designed the study in conjunction with LP-A, NT, FRH, and MAS (steering committee investigators). The funder interpreted data in collaboration with the authors and commissioned drafting of the manuscript. The steering committee had full access to all the data in the study and had the final responsibility for the decision to submit for publication.

Published in: The Lancet Oncology (2015), vol. 16, pp. 328-337
Status : Postprint (Author's version)

RESULTS

Study enrolment began on Nov 11, 2009. After a series of meetings between June 14, 2010, and Jan 31, 2011, the independent data monitoring committee recommended that study enrolment be stopped, and necitumumab treatment discontinued in patients who had not completed two cycles of treatment. This recommendation was made based on data of non-fatal and fatal thromboembolic events from the sponsor's serious adverse event database and on the overall number of deaths from all causes shown in the clinical database, which were unbalanced against the experimental group. These findings led the independent data monitoring committee to conclude that the investigational treatment was disadvantageous to patients. A statistical time-to-event analysis done on Jan 31, 2011, showed that most fatal thromboembolic events had happened within the first two cycles of therapy, and, based on these results, patients who had completed two cycles of treatment (defined as completion of cycle 2, day 8) were allowed to continue study treatment with necitumumab. Patients who continued receiving necitumumab were asked to provide informed consent to continue.

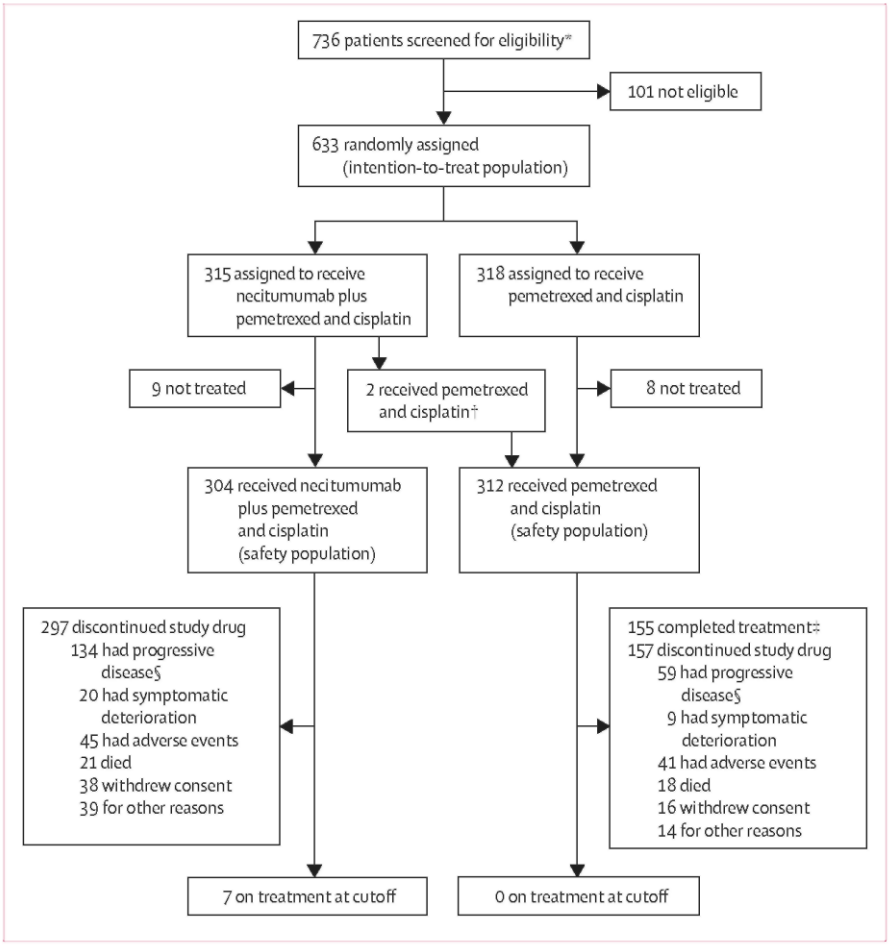
After the recommendation of the data monitoring committee, the sponsor, in conjunction with the steering committee, halted enrolment on Feb 2, 2011. Figure 1 shows the resulting study profile. We randomly assigned 633 patients to receive necitumumab plus pemetrexed and cisplatin (n=315) or pemetrexed and cisplatin alone (n=318); these patients constituted the intention-to-treat population. Baseline characteristics were balanced between the treatment groups (table 1). The safety population comprised 616 patients who received any dose of study drug.

Exposure to chemotherapy was similar between treatment groups (appendix). The median relative dose intensity of necitumumab was 93% (IQR79·7-100·0). Of the 301 patients who received necitumumab plus pemetrexed and cisplatin, and whose serum was analysed for the presence of anti-necitumumab antibodies, 37 (12%) patients had positive samples at any time during the study and 13 (6%) of 229 patients had positive samples after treatment; nine (3%) patients had treatment-emergent positive samples. Of the 13 patients with positive samples after treatment, all had transient positive samples (defined as either one positive sample or two or more non-consecutive positive samples) and none had persistent positive samples (defined as at least two consecutive, positive samples). The overall frequency of treatment-emergent antibody positive samples was considered too low to allow any further analysis.

The data cutoff was Nov 14, 2012, at which time 482 (76%) patients had died (censoring rate 24%). The median duration of follow-up was 24·5 months (IQR 22·3-27·5) for the necitumumab plus pemetrexed and cisplatin group and 25·6 months (IQR 22·5-27·4) for the pemetrexed and cisplatin group. There was no significant difference in overall survival between treatment groups (table 2, figure 2). No clear differences in overall survival were noted across subgroups (appendix). There was no significant difference between treatment groups for progression-free survival (figure 2), objective response, or disease control (table 2). Time to treatment failure was shorter in patients in the necitumumab plus pemetrexed and cisplatin group than in those in the pemetrexed and cisplatin group (table 2); however, this finding might be confounded by the decision to stop treatment early in some patients in the necitumumab group. Systemic post-study anticancer therapy was moderately balanced between the treatment groups; the most frequently used drugs in both groups were docetaxel and erlotinib (appendix).

Published in: The Lancet Oncology (2015), vol. 16, pp. 328-337
Status : Postprint (Author's version)

Figure 1. *Trial profile*



*Two patients were counted twice in error in the total number of screened patients. †Two patients were randomly assigned to the necitumumab plus pemetrexed and cisplatin group, but incorrectly received treatment with pemetrexed and cisplatin alone. These patients were therefore considered as part of the necitumumab plus pemetrexed and cisplatin group of the intention-to-treat population, but of the pemetrexed and cisplatin group for analyses of safety. ‡Patients who completed all planned cycles of chemotherapy. §Radiographically documented.

We investigated the effect of level of EGFR protein expression on outcome in the translational research population, comprising 490 patients who were assessable for EGFR H-score and who were enrolled for more than two cycles before enrolment was stopped (appendix). This later restriction avoided possible confounding of the analysis after the recommendation to stop enrolment and the early withdrawal of therapy for some patients in the experimental group. However, there were no relevant differences in baseline characteristics and outcomes between the subset of patients included in the translational research population and those of the safety population, or between the treatment groups of this subpopulation (data not shown). H-score was high (≥200) in 200 (41%) of 490 assessable patients, and low (<200) in 290 (59%) patients (appendix). In both the high and low EGFR protein-expression groups, there were no significant differences between treatment groups for overall survival (figure 2), progression-free survival (figure 2), or response, and no significant interaction between treatment and EGFR-expression groups (appendix). In the investigation of the predictive value of H-score as a continuous covariate, there were no statistically significant differences between groups (estimated at different levels of H-score) in terms of overall or progression-free survival or objective response, and no significant interaction

between treatment and H-score as a continuous variable (appendix). However, we noted that patients with high tumour EGFR expression had a significantly lower risk of death versus those with low EGFR expression in both the necitumumab group and the control group (appendix). Correspondingly, we recorded better outcomes in both treatment groups for high EGFR expression compared with low expression for progression-free survival and response (appendix).

Table 1 . *Baseline characteristics*

	Necitumumab plus Pemetrexed and cisplatin (n=315)	**Pemetrexed and cisplatin alone (n=318)**
Sex		
Male	214 (68%)	210 (66%)
Female	101 (32%)	108 (34%)
1 Age (years)	61(55-67)	60 (53-67)
Age group (years)		
<65	200 (63%)	216 (68%)
≥65	115 (37%)	102 (32%)
<70	263 (83%)	267 (84%)
≥70	52(17%)	51 (16%)
Ethnic origin		
White	292 (93%)	298 (94%)
Asian	2 (<1%)	0
Other	21 (7%)	20 (6%)
ECOG performance status		
0	115 (37%)	132 (42%)
1	183 (58%)	166 (52%)
2	16(5%)	20 (6%)
Missing	1 (<1%)	0
Smoking history		
Non-smoker	51 (16%)	53 (17%)
Ex-light smoker	26 (8%)	27(8%)
Smoker	238 (76%)	238 (75%)
Disease histology		
Adenocarcinoma	281 (89%)	286 (90%)
Large-cell carcinoma	26 (8%)	25 (8%)
Other	7(2%)	7(2%)
Missing	1 (<1%)	0
Previous anticancer therapy		
Surgery	83 (26%)	91 (29%)
Radiotherapy	33 (10%)	41 (13%)
Systemic (adjuvant or	9 (3%)	11 (3%)
neoadjuvant)		

Data are n (%) or median (IQR). ECOG=Eastern Cooperative Oncology Group.

220 (72%) of 304 patients in the necitumumab plus pemetrexed and cisplatin group and 185 (59%) of 312 patients in the pemetrexed and cisplatin group had one or more grade 3 or higher treatment-emergent adverse events (appendix). The most common events according to

system organ class were blood and lymphatic system disorders and gastrointestinal disorders (appendix). Grade 3 or worse adverse events, according to preferred terms, that were more common in the necitumumab plus pemetrexed and cisplatin group than the pemetrexed and cisplatin group included rash, hypomagnesaemia, and asthenia (appendix).

We recorded adverse events leading to delay or modification of at least one study drug in 144 (47%) of 304 patients in the necitumumab plus pemetrexed and cisplatin group and 98 (31%) of 312 patients in the pemetrexed and cisplatin group. The most frequent of these events in the necitumumab plus pemetrexed and cisplatin group were skin and subcutaneous disorders and gastrointestinal disorders. Adverse events leading to discontinuation of at least one study drug were reported for 77 (25%) of 304 patients in the necitumumab plus pemetrexed and cisplatin group (most commonly, skin, and subcutaneous tissue disorders) and 51 (16%) of 312 patients in the pemetrexed and cisplatin group (most commonly, investigations [a system organ class that includes laboratory tests and vital signs]).

Including those events related to progressive disease, 49 (16%) of 304 patients in the necitumumab plus pemetrexed and cisplatin group and 32 (10%) of 312 patients in the pemetrexed and cisplatin group died from an adverse event (appendix). These events were regarded as related to study treatment in 15 (5%) of 304 patients in the necitumumab plus pemetrexed and cisplatin group and nine (3%) of 312 patients in the control group. Serious adverse events were reported more frequently in the necitumumab plus pemetrexed and cisplatin group than in the pemetrexed and cisplatin group (155 [51%] of 304 vs 127 [41%] of 312 patients).

To further explore safety, we defined composite categories on the basis of the known safety profiles of other EGFR antibodies or clinical experience with necitumumab (table 3). The incidence of grade 3 or worse venous thromboembolic events was higher in the necitumumab plus pemetrexed and cisplatin group than in the pemetrexed and cisplatin group (table 3). Review of all available data did not identify any baseline risk factor that might have been predictive of such events for patients in the necitumumab plus pemetrexed and cisplatin group. Other adverse events of interest that were more frequent in the necitumumab plus pemetrexed and cisplatin group than in the pemetrexed and cisplatin group included skin reactions—a class effect of EGFR-targeting drugs (table 3).

Health status was similar in both treatment groups (data not shown). In particular, the responses to the nine individual items of the Lung Cancer Symptom Scale, the average symptom burden index, the quality-of-life item, and total score were generally similar between treatment groups at baseline and from cycles 1 to 6 (data not shown). Similarly, the EuroQol-5D index and visual analogue scores by assessment visit were also generally consistent and similar between treatment groups at baseline and from cycles 1 to 6 (data not shown).

Published in: The Lancet Oncology (2015), vol. 16, pp. 328-337
Status : Postprint (Author's version)

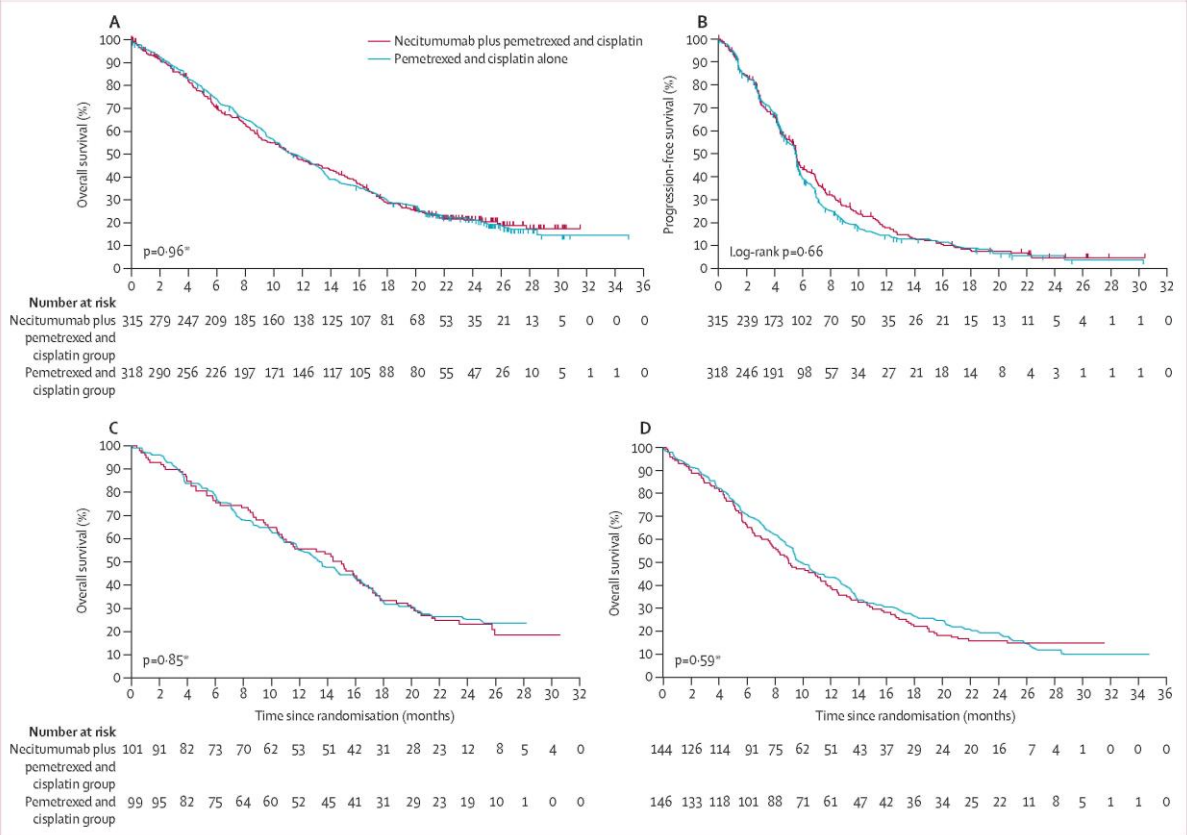
***Table2**: Efficacy endpoints*

	Necitumumab plus pemetrexed and cisplatin (n=315)	**Pemetrexed and cisplatin alone (n=3l8)**
Overall survival		
Deaths	236(75%)	246 (77%)
Median (95% CI; months)	11·3 (9-5-13-4)	11·5 (10-1-13-1)
Hazard ratio (95% CI)*	1·01 (0-84-1-21)	
Log-rank p value*	0-96	
Rate (95% CI)		
6 month	70% (65-75)	74% (69-79)
1 year	47% (42-53)	49% (43-54)
Progression-free survival		
Deaths or disease progression	231 (73%)	239 (75%)
Median (95% CI; months)	5-6(5-1-6-0)	5-6(4-8-5-7)
Hazard ratio (95% CI)*	0-96(0-80-1-16)	
Log-rank p value*	0-66	
Rate (95% CI)		
6 month	44% (38-50)	40% (34-45)
Time to treatment failure †		
Events	305(97%)	305 (96%)
Median (95% CI; months)	3-5(3-2-3-9)	4-3(3-3-4-8)
Hazard ratio (95% CI)*	1-18 (1-00-1-39)	
Log-rank p value*	0-046	..
Rate (95% CI)		
3 month	59% (53-64)	58% (53-63)
6 month	22% (18-27)	31% (26-37)
Response		
Best overall		
Complete response	0	4(1%)
Partial response	98 (31%)	98 (31%)
Stable disease	133 (42%)	133 (42%)
Progressive disease	32 (10%)	44 (14%)
Not assessable	11 (4%)	12 (4%)
Missing	41 (13%)	27(9%)
Proportion of patients achieving an objective response (%; 95% CI)	98 (31%; 26-36)	102 (32%; 27-37)
Odds ratio (95% CI)*	0-96(0-68-1-34)	..
Cochran-Mantel-Haenszel p value*	0-79	..
Proportion of patients achieving disease control† (%; 95% CI)	231 (73%; 68-78)	235 (74%; 69-78)

Data are n (%), unless otherwise indicated. *Stratified by randomisation strata (smoking history, Eastern Cooperative Oncology Group performance status, disease histology, and geographical region), † Defined as the proportion of patients who had a best response of complete response, partial response, or stable disease (prespecified analysis).

Published in: The Lancet Oncology (2015), vol. 16, pp. 328-337
Status : Postprint (Author's version)

Figure 2. *Kaplan-Meier estimates of overall (A) and progression-free survival (B) in the intention-to-treat population, and of overall survival in the high (C) and low (D) EGFR expression subgroups of thetranslational research population*



Vertical lines in figure parts A and B show censored patients. Proportions censored were 79 (25%) of 315 patients in the necitumumab pluspemetrexed and cisplatin group and 72 (23%) of 318 patients in the pemetrexed and cisplatin group for overall survival (A), and 84 (27%) and 79 (25%), respectively, for progression-free survival (B). Proportions censored were 26 (26%) of 101 patients in the necitumumab pluspemetrexed and cisplatin group and 27 (27%) of 99 patients in the pemetrexed and cisplatin group for patients with an EGFR H-score >200 (C), and 29 (20%) of 144 patients and 24 (16%) of 146 patients, respectively, for patients with an EGFR H-score <200 (D). *Likelihood ratio test.

DISCUSSION

Our findings provide no evidence to show that the addition of necitumumab to pemetrexed and cisplatin as first-line therapy improves overall survival in patients with stage IV non-squamous NSCLC. The statistical power of the study was reduced by its early curtailment. Nevertheless, the HR for death in the final analysis and the consistent absence of benefit in other efficacy endpoints, including progression-free survival and response, suggest that addition of necitumumab to pemetrexed and cisplatin is unlikely to improve the outcome in this setting (panel). The reason for this absence of necitumumab benefit is not clear. Notably, findings from the randomised phase 3 SELECT trial[23] showed no benefit of addition of cetuximab to pemetrexed in patients with NSCLC who had had progressive disease during or after one previous platinum-based chemotherapy regimen.

Although termination of enrolment and the conditions for continuation somewhat complicate interpretation of the safety data, the overall incidence of grade 3 or worse adverse events was higher in the necitumumab plus pemetrexed and cisplatin group than in the pemetrexed and

cisplatin group. This finding is in line with those from other randomized studies[24] investigating the addition of an EGFR antibody to first-line chemotherapy regimens. This increased incidence was most apparent for hypomagnesaemia-associated events and skin reactions, side-effects that are typically associated with EGFR antibodies.[25,26] Grade 3 or worse fatigue-related events were likewise reported more frequently in the necitumumab plus pemetrexed and cisplatin group than in the pemetrexed and cisplatin group, as were grade 3 or worse venous thromboembolic events. Use of necitumumab was not associated with an increase in the incidence of hypersensitivity or infusion-related reactions, as would be expected in view of the human constitution of this IgG1 antibody.

A meta-analysis[27] showed that use of cisplatin is associated with an increased risk of venous thromboembolic events compared with non-cisplatin-based chemotherapy. In patients with advanced solid tumours, another meta-analysis[28] showed that use of cetuximab or panitumumab with platinum-based chemotherapy is associated with an increased risk of venous thromboembolic events compared with the same chemotherapy alone. The level of thromboembolic events noted in the necitumumab group in our study is therefore likely to be due to an additive effect from the administration of platinum doublet chemotherapy in conjunction with an EGFR antibody. Similarly, the relative increase in the incidence of venous thrombosis was similar between patients given necitumumab plus gemcitabine and cisplatin and those given gemcitabine and cisplatin alone in a parallel phase 3 trial that included only patients with squamous NSCLC.[12] We identified no clinical variable, including age, ECOG performance status, smoking history, or relevant medical history that predicted for the development of venous thromboembolic events. However, we could not formally assess the relevance of previous central catheter insertion or treatment with low-molecular-weight heparin. We would also note that there are no clear data suggesting that prophylactic use of anticoagulants is effective in reducing the incidence of thromboembolic events in patients receiving an EGFR antibody in combination with platinum-based chemotherapy.

Other EGFR monoclonal antibodies that have been investigated in clinical trials of patients with NSCLC include cetuximab,[8,23,29-31] matuzumab,[32,33] and panitumumab.[34,35] A meta-analysis[24] of individual patient data from four randomised studies, in which chemotherapy plus cetuximab was compared with chemotherapy alone for the first-line treatment of patients with advanced NSCLC, reported that the cetuximab survival benefit might be greater for patients with squamous-cell carcinoma (HR 0·77 [95% CI 0·64-0·93]) than for those with adenocarcinoma (HR 0-94 [0·82-1·09]). Notably, the SQUIRE trial[12] showed an overall and progression-free survival advantage for necitumumab plus gemcitabine and cisplatin compared with gemcitabine and cisplatin alone in patients with squamous NSCLC.

Analysis of findings from the FLEX study[20] suggested that a tumour EGFR immunohistochemistry score of 200 or more was predictive of cetuximab survival benefit. In an exploratory analysis of immunohistochemistry-assessable patients in this study, no evidence showed that a score of 200 or more was predictive of survival or other efficacy outcomes. Similarly, a clear differential effect of necitumumab on overall or progression-free survival according to an H-score cutoff of 200 was not reported in the SQUIRE trial.[12] However, outcomes in each treatment group in the present study were better for patients with high levels of tumour EGFR expression than for those with low levels, consistent with the prognostic value of the H-score threshold for patients in this study. In view of the overall absence of compelling evidence that tumour EGFR expression is a strong favourable prognostic indicator in patients with NSCLC,[36,38] one possible explanation for these findings might be that high tumour EGFR expression is of predictive value in patients receiving

pemetrexed and cisplatin chemotherapy. However, overall, these data do not provide any additional evidence to support the predictive value of EGFR H-score in relation to EGFR-targeted treatments. Exploratory analyses of the predictive and or prognostic value of other biomarkers (*EGFR* copy number, *EGFR* and *KRAS* mutation status, and *ALK* status) are ongoing and will be reported elsewhere.

Table 3. *Adverse events of interest*

	Necitumumab plus pemetrexed and cisplatin (n=304)				**Pemetrexed and cisplatin (n=312)**			
	Any grade	Grade 3	Grade 4	Grade 5	Any grade	Grade 3	Grade 4	Grade 5
Neutropenia	97 (32%)	40 (13%)	15 (5%)	0	101 (32%)	51 (16%)	6 (2%)	0
Anaemia	79 (26%)	22 (7%)	1 (<1%)	0	98 (31%)	23 (7%)	1 (<1%)	0
Fatigue	169 (56%)	33 (11%)	1 (<1%)	0	159 (51%)	18 (6%)	1 (<1%)	0
Hypomagnesaemia	81 (27%)	14 (5%)	9 (3%)	0	40 (13%)	4 (1%)	3 (1%)	0
Skin reactions	237 (78%)	48 (16%)	1 (<1%)	0	59 (19%)	2 (<1%)	0	0
Rash	230 (76%)	44 (15%)	1 (<1%)	0	49 (16%)	1 (<1%)	0	0
Hypersensitivity or infusion-related reaction	6 (2%)	0	0	0	4 (1%)	0	0	0
Eye disorders	49 (16%)	0	0	0	36 (12%)	1 (<1%)	0	0
Interstitial lung disease	4 (1%)	0	0	0	3 (1%)	0	1 (<1%)	1 (<1%)
Arterial thromboembolic events*	13 (4%)	4 (1%)	1 (<1%)	3 (1%) †	18 (6%)	6 (2%)	0	5 (2%)‡
Venousthromboembolic events*	40 (13%)	18 (6%)	2 (<1%)	3 (1%)§	26 (8%)	6 (2%)	1 (<1%)	4 (1%) ¶
Unexplained death*				11 (4%)				5(2%)

Data are n (%). Table shows data for adverse events according to composite categories of preferred terms grouped by medical concept. Adverse events of grade 1-2 in ≥10% of patients in either treatment group, or at grades 3-5 in one or more patients in either treatment group, are presented in the appendix. *Identified on the basis of medical review of all adverse events with an outcome of death; mainly representative of cases with no definitive diagnosis or with limited information aboutthe cause of death. †One cerebral ischaemia, one peripheral ischaemia, one myocardial infarction. ‡Three cerebrovascular accidents, one embolism, one myocardial infarction. §Three pulmonary embolisms. ¶Four pulmonary embolisms.

Published in: The Lancet Oncology (2015), vol. 16, pp. 328-337
Status : Postprint (Author's version)

Panel: Research in context

Systematic review

We searched PubMed,with notime restriction; abstracts from the USA and international meetings; and trial websites including ClinicalTrials.gov, for English-language preclinical reports and clinical trials assessing chemotherapy in patients with lung cancer, EGFR therapies in these patients, and the combination of these methods. Studies about this topic were scarce atthetime of ourtrial design. Search terms included "lung cancer", "EGFR", and "targeted therapy". Supportive clinical data included a phase 1 pharmacological study[22] of necitumumab in patients with advanced solid tumours, which showed that necitumumab was well tolerated, associated with preliminary evidence of antitumour activity, and achieved biologically relevant concentrations throughoutthe dosing period. The conclusion from this systematic review was that combining chemotherapy and anti-EGFR therapies might improve efficacy in patients with advanced lung cancer.The decision to study treatment-naive patients was based on the above literature review, and identified asan area of unmet need, because approved treatments in the first-line setting are associated with only modest survival and quality-of-life improvements at best. After discussion from clinicians, researchers, and regulatory bodies, we decided that efficacy endpoints such as overall survival and progression-free survival were the best outcomes for a clinical trial of this population.

Interpretation

Ourfindings show that addition of necitumumab to pemetrexed ancisplatin did not improve efficacy or safety outcomes in this unselected population of patients receiving first-line therapy for advanced non-squamous non-small-cell lung cancer. Moreover, no evidence suggested a predictive association between an EGFR H-score of 200 or more and survival for necitumumab plus pemetrexed and cisplatin in this setting. Additional analyses of exploratory biomarkers are ongoing.

CONTRIBUTORS

LP-A was a member of the steering committee for the study, contributed to the literature search, study design, data collection, data interpretation writing and review of the report, and overall trial coordination. JM contributed to data collection, data analysis, data interpretation, and writing of the manuscript. JRF and JvP contributed to patient recruitment, data collection, and review of the manuscript. MP contributed to data collection, data interpretation, and review of the manuscript. TEC, AK, GL, GdC, AS, JEAM, AEL, and BB contributed to data collection and review of the manuscript. LC contributed to the trial recruitment, review of the manuscript scientific contents, and approved the study conclusions. MR contributed to collection and interpretation of data, and writing and reviewing of the manuscript. RR contributed to data collection and interpretation, data analysis, assembly of data, provision of patients, and review of the manuscript. EU contributed to data collection, discussion of data, and manuscript approval. CS contributed to data collection, data interpretation, and revision of the manuscript. MD contributed to data collection, writing and review of the report, and data interpretation. HD contributed to data collection, data interpretation and discussion, and review of the manuscript. VS contributed to the data collection, data analysis, data interpretation, and writing and review of the report. RK was a member of the steering committee for the study, contributed to the study design, data analysis, data interpretation, review of the study report, and writing of the manuscript. FRH was a member of the steering committee for the study, did biomarker studies related to the clinical trial, and commented on and approved the manuscript. NT contributed to the data interpretation, and writing and

review of the report. MAS was a member of the steering committee for the study and contributed to the study design, discussion of data and results, and manuscript writing and review.

DECLARATION OF INTERESTS

LP-A and TEC have received personal fees from Eli Lilly and Company outside the submitted work. JvP reports participating in advisory boards for Pfizer, Novartis, Vertex, AbbVie, Clovis, and Teva during the conduct of study. GdC received personal fees from Eli Lilly and Company during the conduct of the study. MR has received personal fees from Eli Lilly and Company, and fees from F Hoffmann-La Roche, Bristol-Myers Squibb, Pfizer, Boehringer Ingelheim, AstraZeneca, Novartis, and Daiichi-Sankyo outside the submitted work. RR has received personal fees from Eli Lilly and Company and Boehringer Ingelheim, grants from Roche, and personal fees from MSD outside the submitted work. CS has received personal fees for speaking outside the submitted work. MD has received personal fees from Eli Lilly and Company, Amgen, Novartis, Pfizer, Boehringer Ingelheim, Roche, and AstraZeneca outside the submitted work. HD, VS, and RK are employees of Eli Lilly and Company. FRH's laboratory has received a grant from Lilly-Imclone for doing biomarker studies related to this clinical trial, and has participated in advisory boards for Eli Lilly and Company. FRH has also received grants from the University of Colorado during the conduct of the study, and from Lilly-Imclone for consultancy and service on advisory boards outside the submitted work. NT has received personal fees from Eli Lilly and Company during the conduct of the study and personal fees from other companies, including but not limited to Eli Lilly and Company, Roche, Boehringer Ingelheim, Teva, Novartis, and AstraZeneca, outside the submitted work. All other authors declare no competing interests.

ACKNOWLEDGMENTS

This study was funded by Eli Lilly and Company. We thank the patients, their families, and the study personnel at all sites for participating in this study. LP-A is funded by Fondo de Investigación Sanitaria (grant number PI1102688) and Red Temática de Investigación Cooperativa en Cancer (R12/0036/0028). We thank Jim Heighway (Cancer Communications and Consultancy, Knutsford, UK) and Jody Arsenault (inVentiv Health Clinical, Princeton, NJ, USA) for providing writing assistance, and Noëlle Gasco (inVentiv Health Clinical) for providing editorial assistance. Work by inVentiv was funded by Eli Lilly and company.

REFERENCES

1 Travis WD, Brambilla E, Riely GJ. New pathologic classification of lung cancer: relevance for clinical practice and clinical trials. *J Clin Oncol* 2013; 31: 992-1001.

2 Thomas A, Rajan A, Lopez-Chavez A, Wang Y, Giaccone G. From targets to targeted therapies and molecular profiling in non-small cell lung carcinoma. *Ann Oncol* 2013; 24: 577-85.

3 Reck M, Popat S, Reinmuth N, et al. Metastatic non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2014; 25 (suppl 3): iii27-39.

4 Cooper WA, Lam DC, O'Toole SA, Minna JD. Molecular biology of lung cancer. *J Thome Dis* 2013; 5 (suppl 5): S479-90.

5 Gerber DE, Gandhi L, Costa DB. Management and future directions in non-small cell lung cancer with known activating mutations. *Am Soc Clin Oncol Educ Book* 2014: e353-65.

6 Kerr KM, Bubendorf L, Edelman MJ, et al. Second ESMO consensus conference on lung cancer: pathology and molecular biomarkers for non-small-cell lung cancer. *Ann Oncol* 2014; 25:1682-90.

7 Douillard JY, Pirker R, O'Byrne KJ, et al. Relationship between EGFR expression, EGFR mutation status, and the efficacy of chemotherapy plus ceruximab in FLEX study patients with advanced non-small-cell lung cancer. *J Thome Oncol* 2014; 9: 717-24.

8 Pirker R, Pereira JR, Szczesna A, et al. Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open-label randomised phase III trial. *Lancet* 2009; 373:1525-31.

9 Dienstmann R, Felip E. Necitumumab in the treatment of advanced non-small cell lung cancer: translation from preclinical to clinical development. *Expert Opin Biol Ther 2011;* 11:1223-31.

10 Cohen MH, Justice R, Pazdur R. Approval summary: pemetrexed in the initial treatment of advanced/metastatic non-small cell lung cancer. *Oncologist* 2009; 14: 930-35.

11 Scagliotti GV, Parikh P, von Pawel J, et al. 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* 2008; 26: 3543-51.

12 Thatcher N, Hirsch FR, Szczesna A, et al. A randomized, multicenter, open-label, phase III study of gemcitabine-cisplatin (GC) chemotherapy plus necitumumab (IMC-11F8/LY3012211) versus GC alone in the first-line treatment of patients (pts) with stage IV squamous non-small cell lung cancer (sq-NSCLC). *J Clin Oncol* 2014; 32: 8008.

13 Edge S, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A. AJCC Cancer Staging Manual, 7th edn. New York: Springer, 2010.

14 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.

15 The Criteria Committee of the New York Heart Association. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels, 9th edn. Boston, MA: Little, Brown and Company, 1994.

16 International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) MedDRA the Medical Dictionary for Regulatory Activities. A registered trademark of the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA). Chantilly, VA: Northrop Grumman MSSO, 2009.

17 National Cancer Institute, National Institutes of Health, US Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. May 28, 2009. http://ctep.cancer.gov/protocolDevelopment/electronic_ applications/docs/ctcaev3.pdf (accessed Feb 8, 2015).

18 Hollen PJ, Gralla RJ, Kris MG, et al. Measurement of quality of life in patients with lung cancer in multicenter trials of new therapies. Psychometric assessment of the Lung Cancer Symptom Scale. *Cancer 1994;* 73: 2087-98.

19 Nord E. EuroQol: health-related quality of life measurement. Valuations of health states

by the general public in Norway. *Health Policy* 1991; 18: 25-36.

20 Pirker R, Pereira JR, von Pawel J, et al. EGFR expression as a predictor of survival for first-line chemotherapy plus cetuximab in patients with advanced non-small-cell lung cancer: analysis of data from the phase 3 FLEX study. *Lancet Oncol* 2012; 13: 33-42.

21 Hirsch FR, Varella-Garcia M, Bunn PA Jr, et al. Epidermal growth factor receptor in non-small-cell lung carcinomas: correlation between gene copy number and protein expression and impact on prognosis. *J Clin Oncol* 2003; 21: 3798-807

22 Kuenen Bl, Witteveen PO, Ruijter R, et al. A phase I pharmacologic study of necitumumab (IMC-11F8), a fully human IgGl monoclonal antibody directed against EGFR in patients with advanced solid malignancies. *Clin Cancer Res* 2010; 16:1915-23.

23 Kim ES, Neubauer M, Cohn A, et al. Docetaxel or pemetrexed with or without cetuximab in recurrent or progressive non-small-cell lung cancer after platinum-based therapy: a phase 3, open-label, randomised trial. *Lancet Oncol* 2013; 14:1326-36.

24 Pujol JL, Pirker R, Lynch TJ, et al. Meta-analysis of individual patient data from randomized trials of chemotherapy plus cetuximab as first-line treatment for advanced non-small cell lung cancer. *Lung Cancer* 2014; 83: 211-18.

25 Petrelli F, Borgonovo K, Cabiddu M, Ghilardi M, Barni S. Risk of anti-EGFR monoclonal antibody-related hypomagnesemia: systematic review and pooled analysis of randomized studies. *Expert Opin Drug Saf 2012;* 11 (suppl 1): S 9-19.

26 Segaert S, Van Cutsem E. Clinical signs, pathophysiology and management of skin toxicity during therapy with epidermal growth factor receptor inhibitors. *Ann Oncol* 2005; 16:1425-33.

27 Seng S, Liu Z, Chiu SK, et al. Risk of venous thromboembolism in patients with cancer treated with cisplatin: a systematic review and meta-analysis. J *Clin Oncol* 2012; 30: 4416-26.

28 Petrelli F, Cabiddu M, Borgonovo K, Barni S. Risk of venous and arterial thromboembolic events associated with anti-EGFR agents: a meta-analysis of randomized clinical trials. *Ann Oncol* 2012; 23:1672-79.

29 Butts CA, Bodkin D, Middleman EL, et al. Randomized phase II study of gemcitabine plus cisplatin or carboplatin, with or without cetuximab, as first-line therapy for patients with advanced or metastatic non small-cell lung cancer. J *Clin Oncol* 2007; 25: 5777-84.

30 Lynch TJ, Patel T, Dreisbach L, et al. Cetuximab and first-line taxa ne/ carboplatin chemotherapy in advanced non-small-cell lung cancer: results of the randomized multicenter phase III trial BMS099.J *Clin Oncol2010;* 28: 911-17

31 Rosell R, Robinet G, Szczesna A, et al. Randomized phase II study of cetuximab plus cisplatin/vinorelbine compared with cisplatin/ vinorelbine alone as first-line therapy in EGFR-expressing advanced non-small-cell lung cancer. *Ann Oncol* 2008; 19: 362-69.

32 Hartmann JT, Kollmannsberger C, Cascorbi I, et al. A phase I pharmacokinetic study of matuzumab in combination with paclitaxel in patients with EGFR-expressing advanced non-small cell lung cancer. *Invest New Drugs* 2013; 31: 661-68.

33 Schiller JH, von Pawel J, Schutt P, et al. Pemetrexed with or without matuzumab as second-line treatment for patients with stage IIIB/ IV non-small cell lung cancer. J *Thorac Oncol* 2010; 5:1977-85.

34 Blumenschein GR Jr, Reckamp K, Stephenson GJ, et al. Phase lb study of motesanib, an oral angiogenesis inhibitor, in combination with carboplatin/paclitaxel and/or panitumumab

for the treatment of advanced non-small cell lung cancer. *Clin Cancer Res* 2010; 16: 279-90.

35 Crawford J, Swanson P, Schwarzenberger P, et al. A phase 2 randomized trial of paclitaxel and carboplatin with or without panitumumab for first-line treatment of advanced non-small-cell lung cancer. *J Thorac Oncol* 2013; 8:1510-18.

36 Meert AP, Martin B, Delmotte P, etal. The role of EGF-R expression on patient survival in lung cancer: a systematic review with meta-analysis. *Eur Respir J* 2002; 20: 975-81.

37 Nakamura H, Kawasaki N, Taguchi M, Kabasawa K. Survival impact of epidermal growth factor receptor overexpression in patients with non-small cell lung cancer: a meta-analysis. *Thorax* 2006; 61:140-45.

38 Nicholson RI, Gee JM, Harper ME. EGFR and cancer prognosis. *Eur J Cancer* 2001; 37 (suppl 4): S9-15.