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

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Summary

Background Available preclinical and phase 2 clinical data suggest that the addition of cetuximab, a monoclonal antibody directed against the epidermal growth factor receptor (EGFR), to chemotherapy might improve outcome in patients with advanced non-small-cell lung cancer (NSCLC). We aimed to assess whether the addition of cetuximab to chemotherapy improved progression-free survival in patients with recurrent or progressive NSCLC after platinum-based therapy.

Methods In this unmasked, open-label randomised phase 3 trial we enrolled patients with metastatic, unresectable, or locally advanced NSCLC from 121 sites in Canada and the USA. Eligible patients were those aged 18 years or older who had experienced progressive disease during or after one previous platinum-based regimen. Initially, patients were randomly assigned to receive either pemetrexed (500 mg/m²) or docetaxel (75 mg/m²) and then randomly assigned within each group to receive their chemotherapy with or without cetuximab (400 mg/m² at first dose and 250 mg/m² weekly thereafter) until disease progression or unacceptable toxicity. However, after a change in the standard of care, investigators chose whether to treat with pemetrexed or docetaxel on a patient-by-patient basis. The primary analysis was changed to compare progression-free survival with cetuximab plus pemetrexed versus pemetrexed, on an intention-to-treat basis. This study is registered with ClinicalTrials.gov, number NCT00095199.

Findings Between Jan 10, 2005, and Feb 10, 2010, we enrolled 939 patients; data for one patient was accidentally discarded. Of the remaining 938 patients, 605 received pemetrexed (301 patients with cetuximab and 304 alone) and 333 received docetaxel (167 in combination with cetuximab and 166 alone). Median progression-free survival with cetuximab plus pemetrexed was 2·9 months (95% CI 2·7–3·2) versus 2·8 months (2·5–3·3) with pemetrexed (HR 1·03, 95% CI 0·87–1·21; p=0·76). The most common grade 3–4 adverse events with cetuximab plus pemetrexed were fatigue (33 [11%] of 292 patients), acneiform rash (31 [11%]), dyspnoea (29 [10%]), and decreased neutrophil count (28 [10%]), and with pemetrexed alone were dyspnoea (35 [12%] of 289 patients), decreased neutrophil count (26 [9%]), and fatigue (23 [8%]). A significantly higher proportion of patients in the cetuximab plus pemetrexed group (119 [41%] of 292 patients) experienced at least one serious adverse event than those patients in the pemetrexed group (85 [29%] of 289 patients; p=0·0054). Nine (3%) of 292 treated patients in the cetuximab and pemetrexed group died of adverse events compared with five (2%) of 289 treated patients in the pemetrexed alone group.

Interpretation The use of cetuximab is not recommended in combination with chemotherapy in patients previously treated with platinum-based therapy.

Funding Eli Lilly and Company and ImClone Systems LLC, a wholly owned subsidiary of Eli Lilly and Company.

Introduction

Most patients receiving front-line cytotoxic therapy for advanced non-small-cell lung cancer (NSCLC) experience progressive disease.[1] Due to limited life expectancy, goals of second-line treatment are prolonged survival with symptom palliation, and enhanced quality of life. A review of phase 3 clinical trials[2] done between 1991 and 2006 involving second-line and beyond systemic chemotherapy in this patient population identified that the median proportion of patients achieving an objective response across trials was 6·8%, and median overall survival was 6·6 months. It is clear that improvements are needed in this setting.

Several single agents are approved for use in advanced, second-line NSCLC, including pemetrexed, docetaxel, and erlotinib.[3–6] In a phase 3 trial comparing pemetrexed with docetaxel in patients with recurrent stage III or IV NSCLC treated with one previous chemotherapy regimen pemetrexed resulted in clinically equivalent efficacy outcomes, with significantly fewer side-effects.[5] Pemetrexed has since been shown to be more efficacious in patients with non-squamous histology.[7]

Cetuximab is a monoclonal antibody directed against epidermal growth factor receptor (EGFR), and is approved by the US Food and Drug Administration (FDA) for use in colorectal and head and neck cancers.

Preclinical studies in lung cancer cell lines and xenografts have assessed the effect of cetuximab, and shown tumour growth inhibition in EGFR-positive lung cancer cell lines when combined with taxanes and platinum.[8] At the time of protocol development, some phase 2 clinical data were available. A single-arm phase 2 study of cetuximab plus docetaxel in second-line NSCLC showed that the combination had promising safety and efficacy (20% of patients achieved an objective response, median time to progression was 104 days, and median overall survival was 7·5 months).[9] A randomised phase 2 study of cetuximab with cisplatin plus vinorelbine compared with cisplatin plus vinorelbine as first-line therapy for patients with advanced NSCLC showed a greater proportion of patients achieving objective responses when treated with cetuximab (35% [15 of 43] *vs* 28% [12 of 43]).[10] In patients who become refractory to front-line chemotherapy, no new treatment has shown significant survival benefit in unselected patient populations for the past decade outside of single-agent therapy. Therefore, our objective was to test the addition of cetuximab to standard chemotherapy in a randomised phase 3 trial.

Methods

Participants

This open-label, parallel-group, randomised phase 3 study was done at 121 sites in the USA and Canada (appendix). Patients aged 18 years or older with metastatic, unresectable, or locally advanced NSCLC who experienced progressive disease during or after one previous platinum-based regimen were eligible. Key eligibility criteria included baseline Karnofsky performance status of 60–100 at entry, measurable disease, and tissue availability for EGFR determination by immunohistochemistry. Exclusion criteria included symptomatic or uncontrolled brain metastases, uncontrolled pleural effusion or ascites, peripheral neuropathy greater than grade 2 (as defined by National Cancer Institute Common Terminology Criteria for Adverse Events [CTCAE] version 3.0),[11] or previous treatment with any EGFR inhibitor, docetaxel, or pemetrexed. Patients were also excluded if they were unable to interrupt aspirin or other non-steroidal anti-inflammatory drugs or were unable or unwilling to take folic acid and vitamin B_{12} supplementation.

All patients gave written informed consent. This study was done in accordance with the Declaration of Helsinki, good clinical practice guidelines, and approved by local ethics committees in accordance with an assurance filed with and approved by the US Department of Health and Human Services.

Randomisation and masking

In the original study design, patients were first randomly assigned to receive a chemotherapy agent (docetaxel or pemetrexed), and then randomly assigned to treatment with cetuximab or chemotherapy alone. The initial primary analysis was a comparison of the proportion of patients achieving an objective response when treated with weekly cetuximab in combination with docetaxel or pemetrexed chemotherapy versus chemotherapy alone. During the trial, external data[5] became available showing that pemetrexed had equivalent activity to docetaxel in the second-line setting, but with fewer side-effects. This resulted in a shift in the standard of care. After consultation with FDA, the trial was amended in May, 2007, so that the investigator would choose whether to give docetaxel or pemetrexed as the chemotherapy agent on a patient-by-patient basis.

As chemotherapy was no longer a randomised comparison, the primary analysis population was changed from all patients to patients treated with pemetrexed. The outcomes of the docetaxel-treated group and the overall chemotherapy group (patients treated with either docetaxel and pemetrexed) became exploratory analyses. The statistical analysis plan was proactively amended at that time to account for these changes.

Randomisation was done with a centralised interactive voice response system (IVRS), developed and implemented by Almac Clinical Technologies (San Francisco, CA, USA). Within each chemotherapy group, patients were then randomly assigned (1:1) to receive cetuximab plus chemotherapy, or chemotherapy alone. Stratification factors were: investigative centre, Karnofsky performance status (80–100 *vs* 60–70), time from last platinum dose to progression or recurrence (90 days or fewer *vs* more than 90 days), and previous first-line paclitaxel therapy (yes *vs* no). The randomisation was done with the Pocock and Simon dynamic balancing procedure,[12] which minimises the imbalance between treatments arms within the levels of the stratification factors.

See Online for appendix

Once a patient completed the screening assessment and was deemed eligible for the study, the investigator or designee called into the IVRS system (available 24 h) to obtain the treatment assignment for that patient. Upon completion of randomisation, the first dose of study therapy was to be given within 7 days. This was an open-label study, hence allocations were not masked from the patient or investigator. During study conduct, treatment assignment was masked from the sponsor through a data and treatment scrambling process, which was in place until the database was locked and ready for statistical analyses.

Procedures

The initial dose of cetuximab (ImClone LLC, Branchburg, NJ, USA) was 400 mg/m² intravenously over 120 min. Subsequently, the cetuximab dose was 250 mg/m² intravenously over 60 min weekly. 1 h after receiving cetuximab, patients received either docetaxel 75 mg/m² intravenously over 60 min or pemetrexed 500 mg/m² over 10 min. The chemotherapy agent was given on day 1 of each 3 week cycle. Patients received chemotherapy for a maximum of six cycles unless there was earlier evidence

of progressive disease or unacceptable toxic effects. Patients received cetuximab until progressive disease or unacceptable toxic effects.

Patients treated with pemetrexed were given folic acid, vitamin B_{12}, and dexamethasone, as described in the pemetrexed prescribing information. Patients given cetuximab were pretreated with diphenhydramine hydrochloride, and those given docetaxel were pretreated with oral corticosteroids. Prophylactic growth factors were not allowed, but growth factors could be used if indicated. The protocol did not permit any crossover during the treatment period. Once patients were off protocol treatment, physicians were allowed to treat patients as per best clinical practice.

For pemetrexed, dose adjustments at the start of a cycle of therapy were based on platelet and neutrophil nadir counts from the preceding cycle of therapy. The absolute neutrophil count (ANC) had to be $1{\cdot}5\times10^9$ cells per L or greater, and the platelet count had to be 100×10^9 platelets per L or greater before the start of the next cycle. Treatment was delayed to allow time for recovery. Upon recovery, treatment was resumed at 50%, 75%, or 100% of the dose, depending on the ANC and platelet counts. For patients who developed neutropenic fever, treatment was delayed for up to 2 weeks until recovery of the ANC to greater than $1{\cdot}5\times10^9$ cells per L, resolution of fever, and treatment of recorded infections was complete; treatment was resumed at 75% of the previous pemetrexed dose. For diarrhoea leading to the need for hospital admission (or of at least grade 3), treatment was delayed until resolution and then resumed at 75% of the previous pemetrexed dose. For other non-haematological toxic effects greater than or equal to grade 3 (with the exception of alopecia, grade 3 aminotransferase elevations, nausea, or vomiting), treatment was delayed until resolution to less than or equal to the patient's original baseline grade; treatment resumed at 75% of the previous dose if deemed appropriate by the investigator.

For docetaxel, patients who were dosed initially at 75 mg/m² and who experienced either febrile neutropenia, neutrophils of less than 500 cells per µL for more than 1 week, severe or cumulative cutaneous reactions, or other grade 3/4 non-haematological toxic effects during docetaxel treatment had treatment withheld until resolution of the toxic effects; treatment was then resumed at 55 mg/m² for the remainder of the study. Patients who developed greater than grade 3 peripheral neuropathy had docetaxel treatment discontinued entirely. Patients who needed a delay of longer than 14 days in starting a new cycle of chemotherapy (>35 day interval between consecutive cycles) were removed from the study.

Cetuximab was not omitted with chemotherapy delays, nor were chemotherapy doses omitted during cetuximab delays. If a patient receiving cetuximab discontinued any agent because of drug-specific toxic effects, the other agent could be continued. Radiographic tumour assessments of the chest and abdomen were repeated every 6 weeks until progressive disease. CT, MRI of the brain, and bone scans were repeated as clinically indicated. Safety was assessed with the CTCAE.[11] The Medical Dictionary for Regulatory Activities (version 14·0) preferred terms for adverse events known to be associated with cetuximab were pooled into composite terms (all grades). The safety population consisted of patients who entered randomisation and received at least one dose of therapy. Patients completed quality-of-life questionnaires (Lung Cancer Subscale [LCS] of the Functional Assessment of Cancer Therapy for Patients with Lung Cancer [FACT-L]) before the start of therapy, before each cycle, and at therapy end.

EGFR expression in tumour tissue was not required for study eligibility; however, tissue was collected and analysed for EGFR expression by immunohistochemistry (EGFR pharmDx Kit for Dako Autostainer [K1494]; Glostrup, Denmark). Furthermore, histoscore (H-score) assessment was done by trained central pathologists, and correlated with clinical outcome using a predefined cutoff for low (below 200) and high (200 or greater), as reported.[13] For biomarker analyses, treatment assignment and clinical outcome was masked from the pathologists.

Statistical analysis

When the study began the primary endpoint was objective response. For this analysis we planned to enrol 800 patients (200 patients in each of the four groups), with 85% power and 5% two-sided α for response, and 80% power and 5% two-sided α for overall survival. At the time of the amendment, 515 patients had been enrolled (the intention-to-treat population), but accruing study data were not reviewed.

After amendment, the primary efficacy endpoint was progression-free survival as assessed by the independent review committee in the pemetrexed intention-to-treat population. Progression-free survival of living patients with no evidence of progression was censored on the date of the last tumour assessment. Assuming a median progression-free survival of roughly 2·9 months with pemetrexed alone, and 3·9 months with the combination, 605 patients in the pemetrexed treatment groups provided greater than 90% power to detect a statistically significant difference in progression-free survival, using a two-sided log-rank test at the 5% significance level. Final analysis would be done when 506 progression-free survival events had occurred in the combined pemetrexed groups. Enrolment in the docetaxel group remained open until 605 patients had been enrolled in the pemetrexed groups. Thus, the planned total enrolment was about 900 patients. There was no target number of progression-free survival events in the docetaxel groups. Follow-up for progression-free survival for all patients continued until roughly 506 patients in the pemetrexed groups experienced progressive disease or death. After the amendment, the power to detect a statistically

significant difference in overall survival was 85% (with a two-sided α of 5%).

Secondary objectives included comparisons of overall survival (defined as the time from randomisation to the date of death; in a living patient, survival was censored on the last date the patient was known to be alive), objective response measurements, disease control rate (proportion of patients who achieved best response of complete response, partial response, or stable disease), symptom response rates (two or more point increases from baseline in the seven-item LCS score that was maintained for two consecutive assessments at least 3 weeks, and no more that 5 weeks, apart), time to symptomatic progression (as symptom response, but with a decrease from baseline), response duration, and safety. All tests of treatment effects between with and without cetuximab were done at a two-sided significance level of 0·05.

Tumour response and disease progression were assessed both by the investigator and by the independent review committee with modified WHO criteria.[14] The safety population consisted of patients who entered randomisation and received at least one dose of therapy. Symptom response rate and time to symptomatic progression were assessed for all patients who entered randomisation with the seven-item LCS of the FACT-L.

Time-to-event endpoints were analysed with unstratified Kaplan-Meier methods, and Cox regression was used to estimate the hazard ratio (HR) and 95% CI. For categorical endpoints, such as response, the unstratified Mantel Haenszel test was used. Fisher's exact test was used to compare grades 3 to 5 adverse events.

Each endpoint had three sets of analyses: pemetrexed versus cetuximab plus pemetrexed, docetaxel versus cetuximab plus docetaxel, and combined chemotherapy versus cetuximab plus chemotherapy. The primary comparisons were for pemetrexed, so only these results are reported here; selected results for the docetaxel and combined chemotherapy groups are reported in the appendix.

Preplanned subgroup analyses were done on histology and EGFR status. The methods for these subgroup analyses mirrored the primary analyses of each of the endpoints. Data were analysed with SAS version 9.1.3. This study is registered with Clinicaltrials.gov, number NCT00095199.

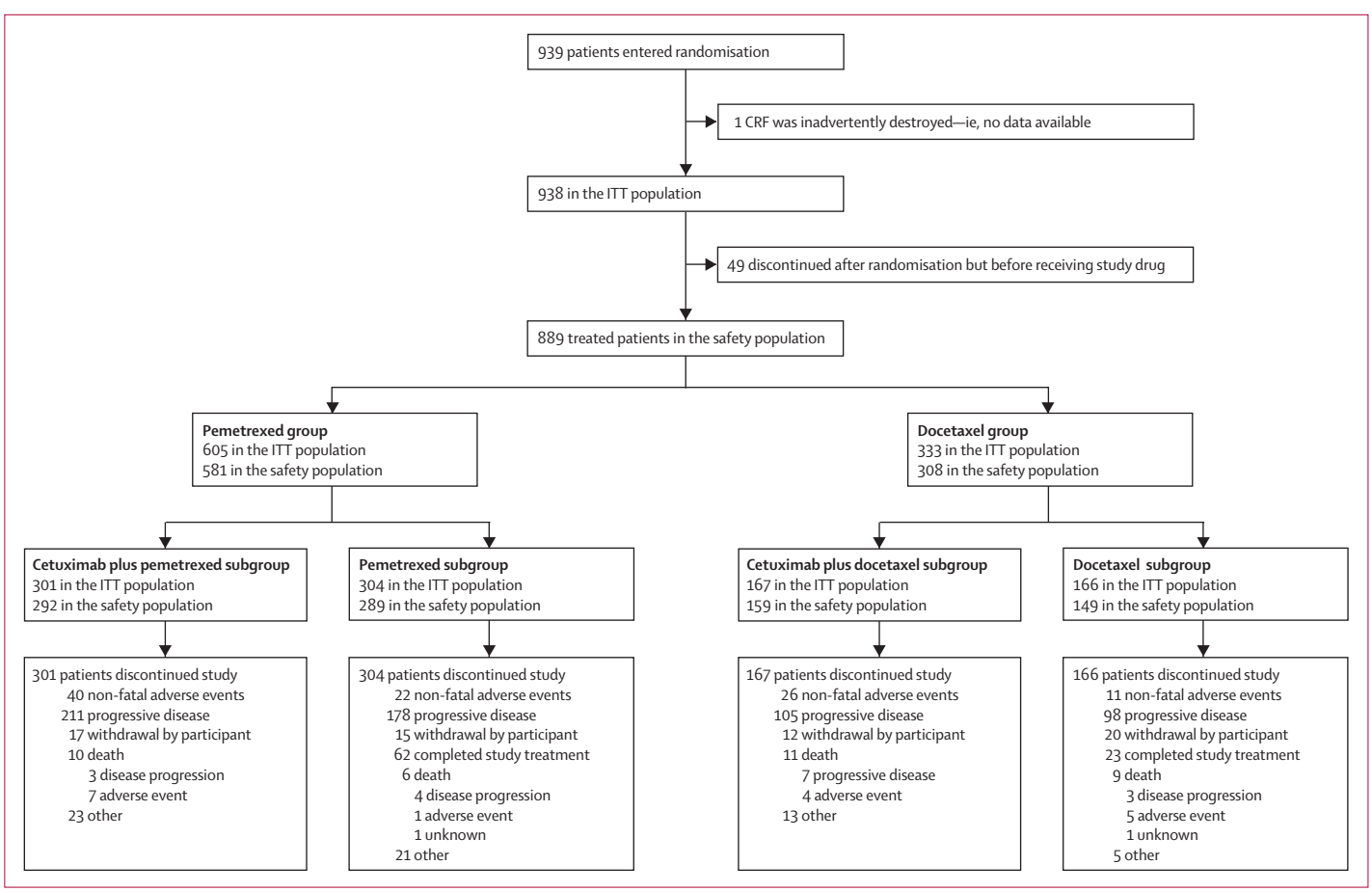

Figure 1: **Trial profile**
CRF=case report form. ITT=intention-to-treat.

Role of funding source

The sponsors provided the study drug; were responsible for the design of the study; the collection, analysis, and interpretation of data; and coordination of report preparation. The corresponding author had full access to all data and final responsibility to submit for publication.

	Cetuximab plus pemetrexed (N=301)	Pemetrexed (N=304)
Age, years	64·0 (37–84)	65·0 (38–89)
Sex		
Male	173 (57%)	188 (62%)
Female	128 (43%)	116 (38%)
Ethnic origin		
White	268 (89%)	265 (87%)
Black	25 (8%)	24 (8%)
Asian	3 (1%)	6 (2%)
Hispanic	4 (1%)	8 (3%)
Other	1 (<1%)	1 (<1%)
Country		
Canada	36 (12%)	34 (11%)
USA	265 (88%)	270 (89%)
Karnofsky performance status		
60–70	47 (16%)	49 (16%)
80–100	252 (84%)	254 (84%)
Missing or unknown	2 (<1%)	1 (<1%)
EGFR results		
Undetectable	21 (7%)	32 (11%)
1+	36 (12%)	35 (12%)
2+	46 (15%)	53 (17%)
3+	118 (39%)	108 (36%)
Missing	80 (27%)	76 (25%)
Pathological diagnosis		
Non-squamous	225 (75%)	233 (77%)
Adenocarcinoma	161 (53%)	185 (61%)
Large-cell carcinoma	19 (6%)	7 (2%)
All other diagnoses	45 (15%)	41 (13%)
Squamous	76 (25%)	71 (23%)
Distant metastases at study entry		
None reported	97 (32%)	109 (36%)
Distant metastases reported	204 (68%)	195 (64%)
Time from last platinum dose to progression or recurrence		
≤90 days	165 (55%)	165 (54%)
>90 days	136 (45%)	138 (45%)
Missing	0	1 (<1%)
Previous paclitaxel therapy		
Yes	223 (74%)	224 (74%)
No	78 (26%)	80 (26%)
Investigator-reported response rate to previous platinum	101 (34%)	98 (32%)*

Data median (range) or n (%). EGFR=epidermal growth factor receptor. *n=303 (data from one patient was missing).

Table 1: **Baseline characteristics for pemetrexed group**

Results

Figure 1 shows the trial profile and the appendix lists the study sites. The number of discontinued patients is analysed from the intention-to-treat population. All data for one patient were accidently discarded at the research site. Hence, the intention-to-treat population contained 938 patients (515 before the amendment of May, 2007), of whom 605 were in the pemetrexed group. Table 1 shows baseline characteristics of the pemetrexed group. The characteristics of the docetaxel and combined chemotherapy groups are shown in the appendix. 292 patients in the cetuximab plus pemetrexed subgroup and 289 patients in the pemetrexed subgroup received one or more doses of any study drug, and so constituted the safety population.

Of patients receiving cetuximab plus pemetrexed, 60 (21%) continued to receive cetuximab after the completion of chemotherapy. Table 2 shows a summary of drug exposure.

291 (97%) of 301 patients experienced disease progression or death in the cetuximab plus pemetrexed group, as did 279 (92%) of 304 patients in the pemetrexed subgroup. Median progression-free survival was 2·9 months (95% CI 2·7–3·2) in the cetuximab plus pemetrexed group, versus 2·8 months (2·5–3·3) in the pemetrexed alone group (HR 1·03, 95% CI 0·87–1·21; p=0·76; figure 2). The investigator-reviewed median PFS was 2·9 months (95% CI 2·7–3·1) with cetuximab plus pemetrexed and 2·7 months (1·9–3·0) with pemetrexed (HR 0·94, 95% CI 0·80–1·11; p=0·47). There were no differences between the two groups' progression-free survival when analysed by histology (figure 3 and data not shown).

277 (92%) of 301 patients died in the cetuximab plus pemetrexed group, as did 261 (86%) of 304 patients in the pemetrexed group. Median overall survival was 6·9 months (95% CI 6·3–7·9) in the cetuximab plus pemetrexed group, and 7·8 months (6·8–8·4) in the pemetrexed alone group (HR 1·01, 95% CI 0·86–1·20; p=0·86; figure 2). When analysed by histology, there were no differences in overall survival between the two treatment groups (figure 3).

The proportions of patients achieving an objective response were not significantly different between the two treatment groups. In the cetuximab plus pemetrexed group 20 (7%) of 301 patients (95% CI 3·8–9·5) achieved a partial response as did 13 (4%) of 304 patients (95% CI 2·0–6·6) in the pemetrexed alone group (odds ratio [OR] 1·59, 95% CI 0·78–3·26; p=0·20); no patients achieved a complete response. The proportions of patients achieving disease control (were similar in both groups: 157 patients (52%, 95% CI 46·5–57·8) in the cetuximab plus pemetrexed group achieved disease control as compared with 146 patients (48%, 95% CI 42·4–53·6) in the pemetrexed group (OR 1·18, 95% CI 0·86–1·62; p=0·31). Median response duration with cetuximab plus pemetrexed was 4·2 months (95% CI 2·9–5·5) versus 6·9 months

(4·0–16·4) with pemetrexed (HR 1·58, 95% CI 0·74–3·36; p=0·24).

For patients randomly assigned to receive cetuximab plus docetaxel, median progression-free survival was 2·4 months (95% CI 1·6–2·9) versus 1·5 months (1·5–2·5) with docetaxel (HR 0·91, 95% CI 0·73–1·13; p=0·39; appendix). Median overall survival was 5·8 months (95% CI 4·7–8·3) with cetuximab plus docetaxel, and 8·2 months (6·1–9·2) with docetaxel (HR 1·13, 95% CI 0·90–1·41; p=0·31). The proportion of patients achieving an objective response (complete response plus partial response) was 13 of 167 (8%, 95% CI 3·7–11.8) in the cetuximab plus docetaxel group versus 11 of 166 (7%, 95% CI 2·8–10·4) in the docetaxel group (HR 1·19, 95% CI 0·52–2·74; p=0·68). The appendix shows the complete efficacy outcomes for the combined chemotherapy and docetaxel groups, which are reported as supportive analyses.

Data and conclusions from prespecified efficacy subgroup analyses by EGFR and histology were not different to the overall findings of the study (figure 3).

Of 292 patients, 15 (5%) in the cetuximab plus pemetrexed group needed dose reductions for cetuximab and ten (3%) needed dose reductions for pemetrexed. 12 (4%) of 289 patients in the pemetrexed group needed dose reductions. 130 patients (45%) in the cetuximab plus pemetrexed group had dose delays for cetuximab and 79 (27%) had dose delays for pemetrexed; 74 patients (26%) in the pemetrexed group needed a dose delay. 96 patients (33%) in the cetuximab plus pemetrexed group had dose omissions for cetuximab and 41 (14%) had dose omissions for pemetrexed; 30 patients (10%) in the pemetrexed group needed dose omissions.

All 292 patients receiving cetuximab plus pemetrexed had one or more grade 1–5 CTCAE adverse event; of these, 278 (95%) patients had one or more grade 1–5 cetuximab-related adverse event. In the pemetrexed group, 282 (98%) of 289 patients had one or more grade 1–5 adverse event. A significantly greater proportion of patients in the cetuximab plus pemetrexed group (203 [70%] of 292) had one or more adverse events of grade 3–5 than those patients in the pemetrexed group (153 [53%] of 289; p<0·0001); significantly more patients in the cetuximab plus pemetrexed group also had at least one serious adverse event than pemetrexed alone 119 [41%] of 292 *vs* 85 [29%] of 289; p=0·0054). Table 3 shows a summary of adverse events occurring in greater than 10% of patients in either group (any grade) or 2% or more patients in either group (for grade 3 or higher) in the pemetrexed groups. The appendix shows grade 3–5 adverse events in 5% or greater of the patients in either docetaxel group.

Preferred terms for adverse events known to be associated with cetuximab were pooled into composite terms. Of the 13 composite terms, seven (all grades) occurred at a significantly higher incidence in the cetuximab plus pemetrexed group relative to the pemetrexed group: acneiform rash, hypomagnesaemia, infection excluding sepsis, infusion reaction, mucositis or stomatitis, sepsis, and thromboembolic events (table 4 and not shown). Significantly more common composite grade 3–4 adverse events in the cetuximab plus

	Pemetrexed group safety population,combination therapy phase (N=581)			Cetuximab monotherapy phase (N=60)
	Cetuximab plus pemetrexed (n=292)		Pemetrexed (n=289)	
	Cetuximab	Pemetrexed		
Duration of therapy, weeks	9·9 (1·0–23·1)	12·0 (3·0–23·1)	9·6 (3·0–33·0)	7·0 (1·0–91·0)
Number of cycles received	3·0 (1·0–6·0)	4·0 (1·0–6·0)	3·0 (1·0–10·0)	2·0 (1·0–30·0)
Dose intensity	94% (33·3–105·0)	100% (42·9–106·7)	100% (42·9–107·7)	98% (26·7–105·0)

Data median (range).

Table 2: **Summary of drug exposure**

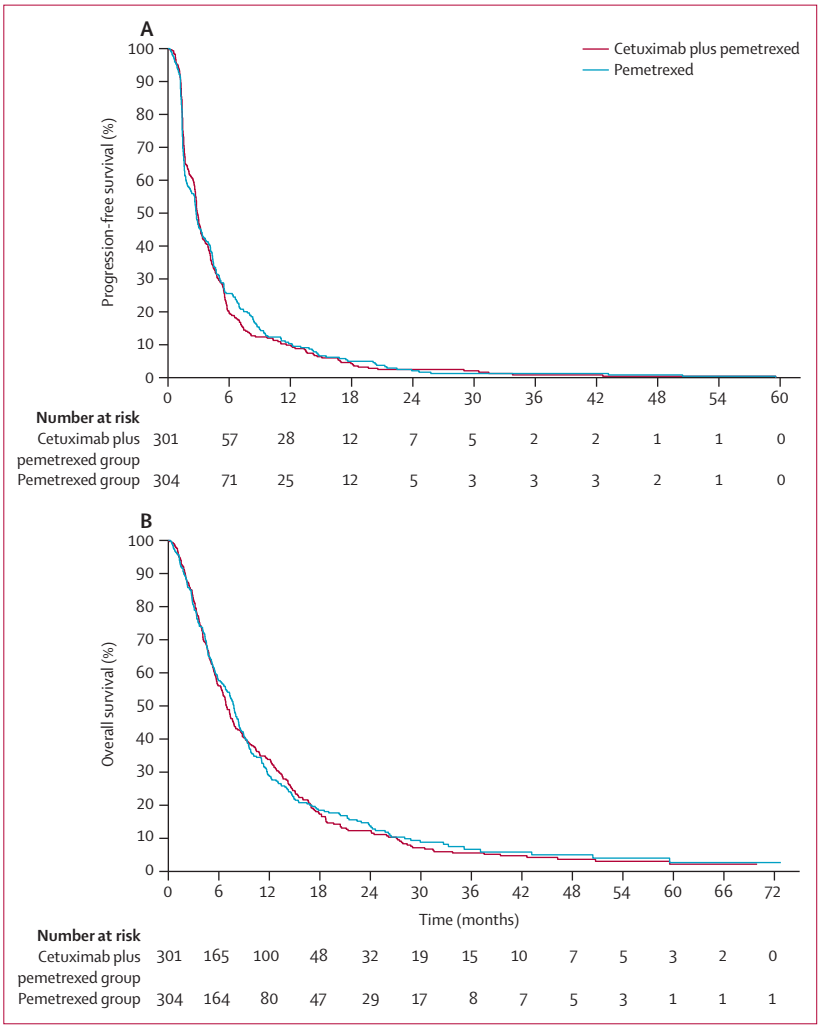

Figure 2: **Kaplan-Meier analysis for progression-free survival, and overall survival**
Kaplan-Meier curves for progression-free survival (A), and overall survival (B).

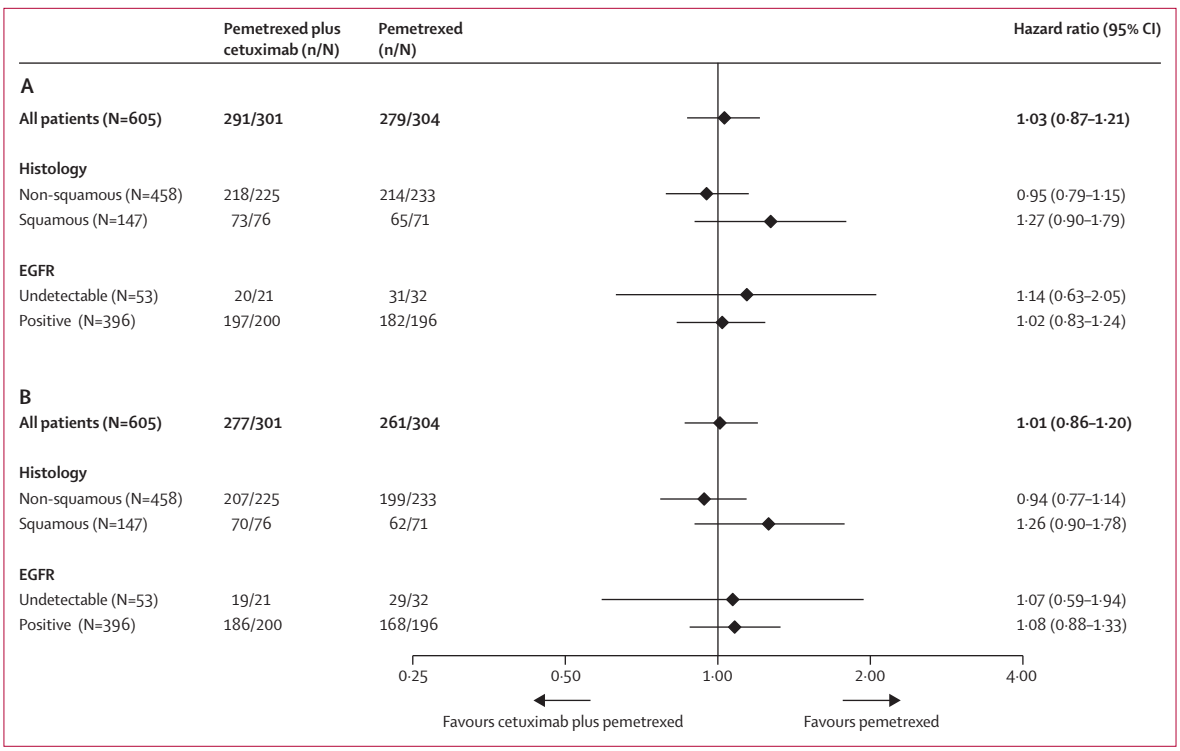

Figure 3: **Survival in the EGFR and histology subgroups**
Progression-free survival (A) and overall survival (B) for pemetrexed-treated patients. n=number of events. N=population size. EGFR=epidermal growth factor receptor.

pemetrexed group than with the pemetrexed group included acneiform rash, hypomagnaesaemia, infusion reactions, and sepsis (table 4). Although there was no significant between-group difference recorded in all grade cardiac events—five (2%) deaths due to cardiac events were reported in the cetuximab plus pemetrexed subgroup (three patients died from cardiac arrest, one from myocardial infarction, and one from heart palpitations; one cardiac arrest was assessed as possibly related to cetuximab treatment). No cardiac-related deaths were reported in the pemetrexed subgroup.

In the cetuximab plus pemetrexed group intention-to-treat population, 40 (13%) of 301 patients discontinued the study because of non-fatal (at the time of discontinuation) adverse events of all causes, as did the 22 (7%) of 304 patients in the pemetrexed group. Nine deaths (3%) in 292 treated patients during therapy or within 30 days from last treatment dose were due to adverse events in the cetuximab plus pemetrexed group: cerebral infarction; respiratory failure; septic shock; cardiopulmonary arrest (n=2); cardiac arrest; urosepsis; pneumonia, sepsis, and myocardial infarction; and pneumonia. Five deaths (2%) in 289 treated patients during therapy or within 30 days from last treatment dose were due to adverse events in the pemetrexed group: hypoxia; respiratory failure and pneumonia; pneumonia and acute renal failure; respiratory arrest; and symptomatic deterioration.

At baseline and at the cycle six visit, quality-of-life questionnaire completion compliance for all assessments was greater than 90% in the cetuximab plus pemetrexed and pemetrexed alone groups. At the follow-up visit, 126 (42%) of 301 patients in the cetuximab plus pemetrexed group, and 126 (41%) of 304 patients had completed the assessments. No significant differences were recorded between the two groups the in FACT-L total, Trial Outcome Index, or subscale scores (physical, social or family, emotional, functional).

Symptom response rate was not significantly different between the 48 (16%) of 301 patients in the cetuximab plus pemetrexed group and 64 (21%) of 304 patients in the pemetrexed group who completed the LCS of the FACT-L questionnaire at the beginning of the study (17·1%, 95% CI 12·7–21·6 *vs* 22·9%, 17·9–27·8; p=0·09). There was also no significant difference between symptomatic progression rate at any time in the 52 (17%) patients assessed in the cetuximab plus pemetrexed group (18·0%, 95% CI 13·6–22·4) as compared with the 43 (14%) patients in the pemetrexed group (15·0%, 10·9–19·1; p=0·33).

Demographics for patients having tissue available for EGFR analysis were similar to those of the intention-to-treat population. 449 tissue samples were available, of which 221 (49%) were taken from patients in the cetuximab plus pemetrexed group and 228 (51%) were from patients in the pemetrexed group. Treatment effect

	Cetuximab plus pemetrexed (N=292)				Pemetrexed (N=289)			
	Grades 1–2	Grade 3	Grade 4	Grade 5	Grades 1–2	Grade 3	Grade 4	Grade 5
Patients with ≥1 CTCAE	89 (30%)	138 (47%)	41 (14%)	24 (8%)	129 (45%)	107 (37%)	36 (12%)	10 (3%)
Abdominal pain	29 (10%)	8 (3%)	0	0	23 (8%)	8 (3%)	0	0
Allergic reaction	7 (2%)	5 (2%)	3 (1%)	0	4 (1%)	1 (<1%)	0	0
Anaemia	55 (19%)	16 (5%)	3 (1%)	1 (<1%)	57 (20%)	11 (4%)	4 (1%)	0
Anorexia	82 (28%)	6 (2%)	0	0	56 (19%)	5 (2%)	0	0
Atrial fibrillation	6 (2%)	6 (2%)	2 (1%)	0	4 (1%)	2 (1%)	1 (<1%)	0
Back pain	27 (9%)	15 (5%)	0	0	14 (5%)	5 (2%)	0	0
Confusion	12 (4%)	10 (3%)	0	0	14 (5%)	3 (1%)	1 (<1%)	0
Constipation	71 (24%)	8 (3%)	0	0	57 (20%)	4 (1%)	0	0
Cough	46 (16%)	3 (1%)	0	0	42 (15%)	4 (1%)	0	0
Dehydration	21 (7%)	14 (5%)	1 (<1%)	0	15 (5%)	6 (2%)	1 (<1%)	0
Diarrhoea	79 (27%)	2 (1%)	0	0	36 (12%)	2 (1%)	0	0
Dizziness	40 (14%)	5 (2%)	0	0	15 (5%)	0	0	0
Dry skin	62 (21%)	1 (<1%)	0	0	9 (3%)	0	0	0
Dyspnoea	53 (18%)	25 (9%)	4 (1%)	3 (1%)	43 (15%)	31 (11%)	4 (1%)	0
Oedema limbs	55 (19%)	5 (2%)	0	0	33 (11%)	2 (1%)	0	0
Epistaxis	32 (11%)	1 (<1%)	0	0	11 (4%)	0	0	0
Fatigue	128 (44%)	29 (10%)	4 (1%)	0	112 (39%)	22 (8%)	1 (<1%)	0
Fever	45 (15%)	5 (2%)	0	0	42 (15%)	1 (<1%)	0	0
Generalised muscle weakness	25 (9%)	15 (5%)	1 (<1%)	0	21 (7%)	15 (5%)	0	0
Hyperglycaemia	7 (2%)	5 (2%)	0	0	10 (3%)	11 (4%)	1 (<1%)	0
Hypokalaemia	23 (8%)	8 (3%)	0	0	9 (3%)	2 (1%)	0	0
Hypomagnesaemia	55 (19%)	3 (1%)	2 (1%)	0	16 (6%)	1 (<1%)	0	0
Hypotension	25 (9%)	11 (4%)	2 (1%)	0	8 (3%)	2 (1%)	0	0
Hypoxia	8 (3%)	4 (1%)	1 (<1%)	0	4 (1%)	6 (2%)	0	1 (<1%)
Infections and infestations—other	30 (10%)	4 (1%)	0	0	19 (7%)	2 (1%)	0	0
Infusion related reaction	9 (3%)	5 (2%)	5 (2%)	0	0	0	0	0
Lung infection	8 (3%)	16 (5%)	1 (<1%)	3 (1%)	9 (3%)	16 (6%)	3 (1%)	1 (<1%)
Mucositis oral	52 (18%)	4 (1%)	0	0	21 (7%)	0	0	0
Nausea	114 (39%)	5 (2%)	0	0	87 (30%)	5 (2%)	0	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0	0	0	9 (3%)	0	0	0	3 (1%)
Neutrophil count decreased	8 (3%)	22 (8%)	6 (2%)	0	14 (5%)	14 (5%)	12 (4%)	0
Non-cardiac chest pain	20 (7%)	2 (1%)	0	0	22 (8%)	6 (2%)	0	0
Pain	22 (8%)	10 (3%)	2 (1%)	0	18 (6%)	12 (4%)	1 (<1%)	0
Platelet count decreased	9 (3%)	5 (2%)	5 (2%)	0	12 (4%)	4 (1%)	9 (3%)	0
Pleural effusion	2 (1%)	10 (3%)	2 (1%)	0	7 (2%)	5 (2%)	0	0
Pruritus	31 (11%)	0	0	0	6 (2%)	0	0	0
Rash acneiform	193 (66%)	31 (11%)	0	0	6 (2%)	0	0	0
Rash maculopapular	43 (15%)	2 (1%)	0	0	39 (13%)	0	0	0
Respiratory failure	0	2 (1%)	2 (1%)	5 (2%)	0	1 (<1%)	1 (<1%)	2 (1%)
Respiratory, thoracic and mediastinal disorders	26 (9%)	4 (1%)	1 (<1%)	1 (<1%)	25 (9%)	3 (1%)	1 (<1%)	0
Sepsis	0	4 (1%)	3 (1%)	4 (1%)	0	0	0	1 (<1%)
Skin and subcutaneous tissue disorders	60 (21%)	3 (1%)	0	0	12 (4%)	0	0	0
Thromboembolic event	5 (2%)	15 (5%)	2 (1%)	0	4 (1%)	7 (2%)	1 (<1%)	0
Vomiting	58 (20%)	6 (2%)	0	0	41 (14%)	4 (1%)	0	0
White blood cell decreased	7 (2%)	5 (2%)	1 (<1%)	0	7 (2%)	6 (2%)	3 (1%)	0

Data are number of patients (%). Events are maximum grade per CTCAE (version 3·0). CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events.

Table 3: **Summary of adverse events occurring in more than 10% of patients in either group (any grade) or 2% or more of patients in either group (for grade 3 or higher)**

	Cetuximab plus pemetrexed (N=292)			Pemetrexed (N=289)		
	All	Grade 3–4	Grade 5†	All	Grade 3–4	Grade 5†
Acneiform rash	243 (83·2%)‡	34 (11·6%)§	0	53 (18·3%)‡	0§	0
Cardiac events	44 (15·1%)	14 (4·8%)	5 (1·7%)	37 (12·8%)	12 (4·2%)	0
Febrile neutropenia	4 (1·4%)	4 (1·4%)	0	5 (1·7%)	5 (1·7%)	0
Hypomagnesaemia	136 (46·6%)‡	12 (4·1%)§	0	60 (20·8%)‡	1 (0·3%)§	0
Infusion-related reaction	43 (14·7%)‡	19 (6·5%)§	0	8 (2·8%)‡	0§	0
Sepsis	14 (4·8%)‡	9 (3·1%)§	4 (1·4%)	3 (1·0%)‡	1 (0·3%)§	2 (0·7%)
Thromboembolic events	23 (7·9%)‡	18 (6·2%)	0	12 (4·2%)‡	8 (2·8%)	0

Data are n (%). N=population size. n=number of patients with at least one CTCAE. CTCAE=Common Terminology Criteria for Adverse Events. *Graded using CTCAE version 3·0. †p values not calculated. ‡p≤0·05 using ordinal-based χ^2 test comparing treatment arms. §p≤0·05 using Fisher's exact test comparing treatment arms.

Table 4: **Selected all grades and grade 3–5 composite term adverse events***

Panel: Research in context

Systematic review

In an attempt to improve therapeutic outcome for patients with NSCLC, we combined chemotherapy with cetuximab in patients with NSCLC who had disease progression after platinum-based therapy. We reviewed preclinical reports and clinical trials assessing chemotherapy in lung cancer, EGFR therapies in lung cancer, and the combination of these agents, which were limited at the time of protocol origination. This included searching PubMed, abstracts from US and international meetings, and trial websites such as ClinicalTrials.gov. Search terms included "lung cancer", "EGFR", and "targeted therapy". Supportive clinical phase 2 data included: a single-arm phase 2 study of cetuximab plus docetaxel in second-line NSCLC (done by the principal investigator of our trial), which showed that the combination had promising safety and efficacy,[9] and a randomised phase 2 study, which showed a greater number of patients achieved an objective response when treated with cetuximab plus cisplatin plus vinorelbine as compared with cisplatin plus vinorelbine in first-line advanced NSCLC.[10] The conclusion from this systematic review was that combining chemotherapy and anti-EGFR therapies might have activity in patients with advanced lung cancer, and we thus began our trial. The decision to study patients in the previously treated setting was based on the above literature review, and identified as an area of unmet need, because only docetaxel, and subsequently pemetrexed, were approved as single agents in a second-line setting. After much discussion from clinicians, researchers, and regulatory bodies, efficacy endpoints such as improvements in response rate and progression-free survival were a realistic goal for a clinical trial in this population.

Interpretation

Our findings show that adding cetuximab to pemetrexed does not improve efficacy or saftey outcomes in this unselected population of patients receiving second-line therapy for advanced NSCLC. There is no predictive association between EGFR status, as assessed by immunohistochemistry staining or histoscore, and survival for cetuximab. Further work is needed to better define biomarkers that can identify patients who could most benefit from anti-EGFR antibody treatment in lung cancer.

by EGFR staining intensity was assessed for positive (EGFR 1+, 2+, 3+), and negative (EGFR undetectable) status. There were no significant differences between the two treatment groups in median progression-free survival, or in overall survival, when assessed by positive and negative EGFR staining intensity (figure 3).

An analysis for treatment effect analysed by H-score was also done in 406 patients with low H-score (below 200) or high H-score (200 or greater) as previously described.[13] For patients with low H-score, median progression-free survival was 2·7 months (95% CI 1·8–3·2) with cetuximab plus pemetrexed, and 3·1 (2·6–4·1) with pemetrexed alone (HR 1·11, 95% CI 0·84–1·46; p=0·48); among patients with high H-scores, the median progression-free survival was 3·2 months (2·7–4·6) with cetuximab plus pemetrexed, and 3·7 (1·7–4·5) with pemetrexed alone (HR 1·02, 0·77–1·37; p=0·86; appendix). For patients with low H-score, median overall survival was 6·7 months (5·3–8·6) with cetuximab plus pemetrexed, and 6·6 months (4·7–9·2) with pemetrexed alone (HR 0·96, 0·72–1·27; p=0·76); for patients with high H-score, median overall survival was 7·7 months (6·5–10·9) with cetuximab plus pemetrexed and 8·0 months (7·0–9·1) with pemetrexed alone (HR 1·17, 0·86–1·57; p=0·32; appendix). No treatment by H-score interaction was recorded for either progression-free survival (p=0·71), or overall survival (p=0·35 using 200 cutpoint).

Discussion

Our findings show that the addition of cetuximab to pemetrexed did not improve progression-free survival, nor were there improvements in any of the other assessed efficacy or quality-of-life measures, including overall survival. More and worse adverse events were recorded with cetuximab plus pemetrexed, mainly due to skin-related toxic effects, gastrointestinal symptoms (diarrhoea or stomatitis), and hypomagnesaemia. Likewise, there was no improvement in outcome when patients were assessed by subgroup analysis for histological type or EGFR status.

Targeting EGFR and HER pathways has been important in many cancers, including colon, breast, head and neck, and lung cancer. Both tyrosine kinase inhibitors and monoclonal antibodies have shown activity in these cancers (cetuximab, panitumumab, erlotinib, gefitinib, lapatinib, afatinib).[6,10,15–26] Nonetheless, identifying the appropriate population of patients for these therapies has been challenging. Driver mutations have been identified in small groups of patients, but for most patients targets for corresponding drugs are either unavailable or have yet to be identified.

Cetuximab has been assessed in other studies of patients with NSCLC. In the open-label phase 3 FLEX trial,[22] chemotherapy-naive patients with stage IIIB wet or stage IV NSCLC were randomly assigned to receive cisplatin plus vinorelbine with and without cetuximab. This study met its primary endpoint, with patients receiving cetuximab experiencing improved overall survival compared with those without cetuximab (11·3 months *vs* 10·1 months; HR 0·871 [95% CI 0·762–0·996]; p=0·044). In BMS099, the addition of cetuximab to taxane plus carboplatin did not improve the primary endpoint of progression-free survival, but a significantly greater proportion of patients achieved an objective response than did those not treated with

cetuximab.[20] BMS099 was not powered to detect a difference in overall survival, but the hazard ratio for death was similar to FLEX (BMS099 HR 0·890 *vs* FLEX HR 0·871), but dissimilar to our findings (HR 1·01).[20,22] In BMS099 and our trial, patients were not selected on the basis of EGFR expression, whereas in FLEX, only patients with EGFR-positive tumours were enrolled.[20,22] Another notable difference is that patients enrolled in FLEX and BMS099 were chemotherapy naive,[20,22] whereas patients enrolled in our trial had received a prior platinum-containing regimen.

There have been substantial challenges in improving survival in previously treated patients with NSCLC.[1] A current challenge is selection of patients most likely to benefit from a given therapy. For patients with colon cancer, *KRAS* mutational status is an important biomarker that can be used to establish which patients might benefit most with cetuximab therapy.[27] We postulated that relevant EGFR markers might predict benefit with cetuximab therapy. Previous studies have produced mixed results. In BMS099, several possible predictive biomarkers (*KRAS* and *EGFR* mutations, and EGFR positivity by fluorescence in-situ hybridisation and immunohistochemistry) were assessed, and no significant associations were identified between tested biomarkers and outcome.[28] A retrospective analysis of FLEX showed no difference in outcomes by biomarker status (*KRAS* and *EGFR* mutations, *EGFR* copy number, PTEN expression).[29]

A subsequent analysis of FLEX showed a significant association between EGFR expression by immunohistochemistry and improved outcomes, with high EGFR expression (H-score of 200 or higher) being associated with improved overall survival, time-to-treatment failure, and a greater proportion of patients achieving objective responses when treated with cetuximab than when treated with cisplatin plus vinorelbine alone.[13] There was no improvement in outcomes in the low H-score group (H-score lower than 200).[13] However, an H-score analysis of patients treated with cetuximab in the BMS099 trial only showed a significant association between high EGFR expression and the proportion of patients achieving an objective response.[30] Our trial did not show any benefit in patients when using H-scores, either at the predefined cutoff of 200, or as a continuous variable. The tissue collected in our study was assumed to be mostly baseline diagnostic tissue and might not fully represent the tumour-marker status when second-line treatment was started. Despite a vigorous attempt to collect tissue samples during the study, about 25% of patients' tissue samples were not available, not submitted by the site, or in some cases were not suitable for EGFR or H-score biomarker analyses. The EGFR and H-score analyses were done in all patients for whom there was sufficient tissue for assessment. The demographics for patients who had sufficient tissue were similar to those of the intention-to-treat population, suggesting that the group of patients for whom there was sufficient tissue was fairly representative of the entire patient population in the study.

Quality-of-life questionnaires were administered, but the rate of response from study participants decreased during the course of the study, similar to other reported studies in lung cancer. Various reasons for the drop in response rates could include disease progression or the patient not feeling well, the site not being as diligent in the collection of the quality-of-life data, or death due to cancer. This information was not specifically collected.

Present studies might help delineate which patients might benefit from treatment with cetuximab. An ongoing study (SWOG S0819) is designed to directly test the effect of combined EGFR and VEGF blockade together with chemotherapy, incorporating EGFR FISH as a coprimary endpoint.[31]

In conclusion, adding cetuximab to pemetrexed did not improve outcomes, and worsened toxic effects, including skin, diarrhoea or stomatitis, and hypomagnesaemia, in this unselected population of patients receiving second-line treatment for advanced NSCLC. Biomarkers, including EGFR staining intensity and H-score, were not predictive in defining patients who might benefit from cetuximab in this setting and should not be used for clinical decision making. The identification of NSCLC patients most likely to benefit from cetuximab remains a challenge.

Contributors

ESK, CR, TK, and LSi participated in the conception and design of the study. ESK, MN, AC, LSc, LG, JC, FR, CR, TK, SC, LSi, and SS participated in the collection and assembly of data. ESK, AC, CR, TK, LSc, LSi, and SS participated in data analysis and interpretation. ESK, AC, LSc, and FR provided study materials and patients. CR provided administrative support. All authors participated in the writing and critical revision of this report and approved the final version.

Conflicts of interest

ESK and CR received research funding and honoraria from Eli Lilly and Company and served as consultants for Eli Lilly. MN served as medical director at McKesson Specialty Health and currently serves as medical director for McKesson Specialty Health-US Oncology. LSc and FR received research funding from Eli Lilly and Company. TK was employed by ImClone Systems (a subsidiary wholly owned by Eli Lilly and Company) during this trial. SS and LSi are employed by Eli Lilly and Company and own stock. The other authors declare that they have no conflicts of interest.

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