Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open-label randomised phase III trial

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Summary

Background Use of cetuximab, a monoclonal antibody targeting the epidermal growth factor receptor (EGFR), has the potential to increase survival in patients with advanced non-small-cell lung cancer. We therefore compared chemotherapy plus cetuximab with chemotherapy alone in patients with advanced EGFR-positive non-small-cell lung cancer.

Methods In a multinational, multicentre, open-label, phase III trial, chemotherapy-naive patients (≥18 years) with advanced EGFR-expressing histologically or cytologically proven stage wet IIIB or stage IV non-small-cell lung cancer were randomly assigned in a 1:1 ratio to chemotherapy plus cetuximab or just chemotherapy. Chemotherapy was cisplatin 80 mg/m² intravenous infusion on day 1, and vinorelbine 25 mg/m² intravenous infusion on days 1 and 8 of every 3-week cycle) for up to six cycles. Cetuximab—at a starting dose of 400 mg/m² intravenous infusion over 2 h on day 1, and from day 8 onwards at 250 mg/m² over 1 h per week—was continued after the end of chemotherapy until disease progression or unacceptable toxicity had occurred. The primary endpoint was overall survival. Analysis was by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00148798.

Findings Between October, 2004, and January, 2006, 1125 patients were randomly assigned to chemotherapy plus cetuximab (n=557) or chemotherapy alone (n=568). Patients given chemotherapy plus cetuximab survived longer than those in the chemotherapy-alone group (median 11·3 months *vs* 10·1 months; hazard ratio for death 0·871 [95% CI 0·762–0·996]; p=0·044). The main cetuximab-related adverse event was acne-like rash (57 [10%] of 548, grade 3).

Interpretation Addition of cetuximab to platinum-based chemotherapy represents a new treatment option for patients with advanced non-small-cell lung cancer.

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Introduction

Patients with advanced non-small-cell lung cancer are treated with a combination of a platinum drug (cisplatin or carboplatin) and a non-platinum drug (eg, vinorelbine), which results in a slight increase in survival and relief of cancer-related symptoms.[1] Cisplatin-based two-drug combinations are slightly better than carboplatin-based combinations in patients with good performance status and adequate organ function.[2] Strategies to further improve survival of patients with advanced non-small-cell lung cancer include the addition of targeted drugs to cytotoxic chemotherapy,[3] and chemotherapy that is customised according to biomarkers.[4]

Epidermal growth factor receptor (EGFR) is a promising therapeutic target in non-small-cell lung cancer.[5] The EGFR-directed tyrosine kinase inhibitors erlotinib and gefitinib are established treatment options for patients with advanced disease who have been pretreated with platinum-based combinations[6,7] but their addition to first-line chemotherapy does not improve outcome.[8–11] Cetuximab (Erbitux, developed by Merck KGaA, Darmstadt, Germany, under licence from Imclone Systems, Branchburg, NJ, USA), an anti-EGFR immunoglobulin G1 monoclonal antibody, has shown activity when given in combination with cisplatin in preclinical studies.[12,13] The results of a randomised phase II trial in 86 patients with advanced EGFR-expressing non-small-cell lung cancer suggested an increased response rate and improved survival in patients given cisplatin and vinorelbine plus cetuximab compared with those given the same chemotherapy alone.[14] We therefore did the phase III FLEX (First-Line ErbituX in lung cancer) trial with the aim of showing a prolonged overall survival time with chemotherapy plus cetuximab compared with chemotherapy alone as first-line treatment in patients with EGFR-expressing advanced non-small-cell lung cancer.

Methods

Study design

We randomly assigned chemotherapy-naive patients with EGFR-expressing advanced non-small-cell lung cancer centrally using an interactive voice response system (IVRS) in a ratio of 1:1 to chemotherapy plus cetuximab or chemotherapy alone in a multinational, open-label, phase III trial done in 155 centres. The clinical research

organisation generated the random allocation schedule using a computer; physicians and study monitors did not have access to the code. Randomisation was stratified by the Eastern Cooperative Oncology Group (ECOG) performance status (0–1 *vs* 2) and tumour stage (IIIB with malignant pleural effusion [wet IIIB] *vs* IV). Permutated blocks were assigned to each of four randomisation strata.

Patients

Chemotherapy-naive patients with histologically or cytologically proven stage wet IIIB or stage IV non-small-cell lung cancer and immunohistochemical evidence of EGFR expression in at least one positively stained tumour cell (DakoCytomation pharmDxTM immunohistochemistry kit, Dako, Glostrup, Denmark) were eligible for the study. Other inclusion criteria included age 18 years or older, ECOG performance status 0–2, adequate organ (bone marrow, kidney, liver, heart) function, and the presence of at least one bidimensionally measurable tumour lesion. Exclusion criteria were known brain metastases, previous treatment with EGFR-targeted drugs or monoclonal antibodies, major surgery within 4 weeks or chest irradiation within 12 weeks before study entry, active infection, pregnancy, and symptomatic peripheral neuropathy (National Cancer Institute's common toxicity criteria, version 2, grade ≥2).

Patients provided written informed consent before entry into the study so that tumour samples could be obtained and EGFR status assessed. Patients with EGFR-expressing tumours who met the inclusion criteria and had signed another written informed consent were randomly assigned to treatment. The study was approved by the independent ethics committees for each trial centre and the relevant authorities of the various countries, and was done in accordance with the International Conference on Harmonisation and Good Clinical Practice, the Declaration of Helsinki, and the legal requirements of the various countries.

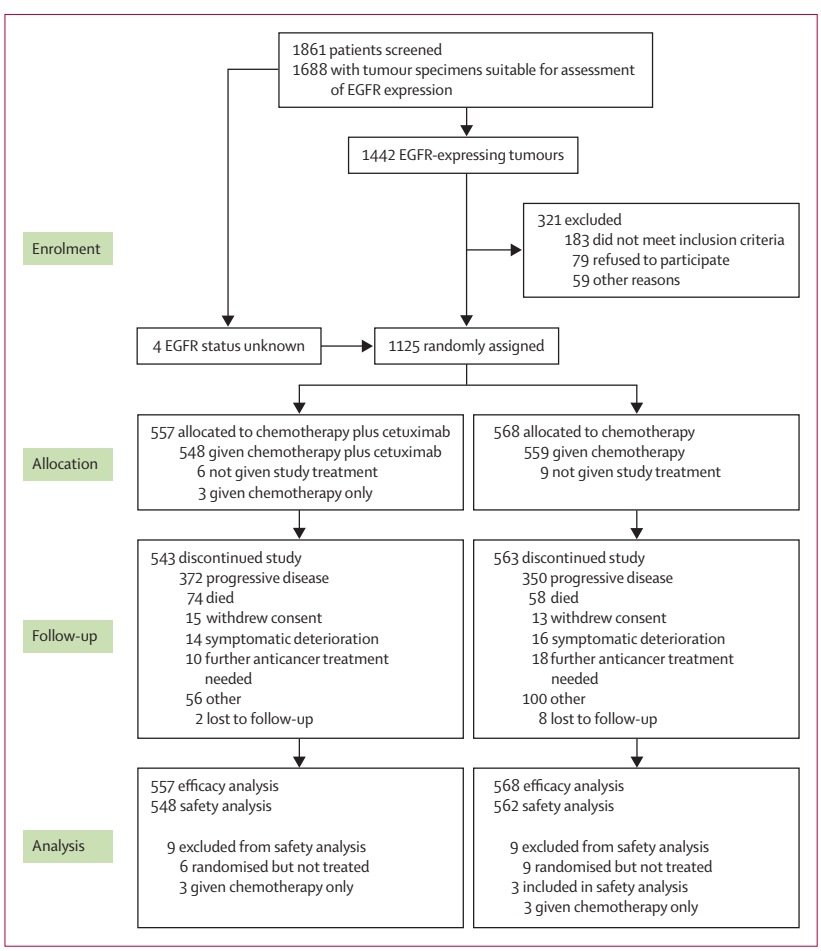

Figure 1: **Trial profile**
EGFR=epidermal growth factor receptor.

Treatment

Chemotherapy consisted of cisplatin 80 mg/m² intravenous infusion on day 1, and vinorelbine 25 mg/m² intravenous infusion on days 1 and 8 of every 3-week cycle for up to six cycles. The vinorelbine dose was reduced from 30 mg/m² to 25 mg/m² by protocol amendment because grade 3 and 4 neutropenia occurred more frequently than expected in both groups early during the study. Prophylactic antiemetic drugs and hydration were administered according to local practice. Cetuximab was intravenously infused at a starting dose of 400 mg/m² over 2 h on day 1, and from day 8 onwards at a dose of 250 mg/m² over 1 h per week. Premedication with an antihistamine drug was mandatory before the first infusion and was recommended for all further infusions. Cetuximab was infused before chemotherapy on days when both treatments were given. It was continued after the end of chemotherapy until disease progression or unacceptable toxicity occurred.

Assessments

Tumour response was assessed by imaging methods (eg, CT) according to the modified WHO criteria at intervals of 6 weeks after randomisation until disease progression in both groups. Follow-up visits every 8 weeks were used to record any further anticancer treatment and survival status after disease progression.

Overall survival time was calculated in months from time of randomisation to the date of death. Progression-free survival was measured as time from randomisation until radiologically confirmed disease progression was first noted or death from any cause occurred (when death occurred within 60 days of the last tumour response assessment or randomisation). Time-to-treatment failure was a posthoc analysis and included the following events: progressive disease (radiologically confirmed or not), study discontinuation due to toxicity, start of another anticancer treatment without documented progressive disease, withdrawal of consent, and death.

Quality of life was assessed with the European Organisation for Research and Treatment of Cancer

	Cisplatin and vinorelbine plus cetuximab (N=557)	Cisplatin and vinorelbine (N=568)
Age (years)		
Median (range)	59 (18–78)	60 (20–83)
≥65	172 (31%)	179 (32%)
Sex		
Men	385 (69%)	405 (71%)
Women	172 (31%)	163 (29%)
Ethnic origin		
White	466 (84%)	480 (85%)
Asian	62 (11%)	59 (10%)
Other	29 (5%)	29 (5%)
ECOG performance status		
0	132 (24%)	121 (21%)
1	333 (60%)	343 (60%)
2	92 (17%)	104 (18%)
Tumour stage		
IIIB	35 (6%)	33 (6%)
IV	522 (94%)	535 (94%)
Histology		
Adenocarcinoma	255 (46%)	277 (49%)
Squamous cell carcinoma	190 (34%)	187 (33%)
Other*	112 (20%)	104 (18%)
Never smoked	121 (22%)	123 (22%)

Data are number (%), unless otherwise indicated. ECOG=Eastern Cooperative Oncology Group. *Includes large cell, adenosquamous, and undifferentiated carcinomas.

Table 1: **Baseline characteristics**

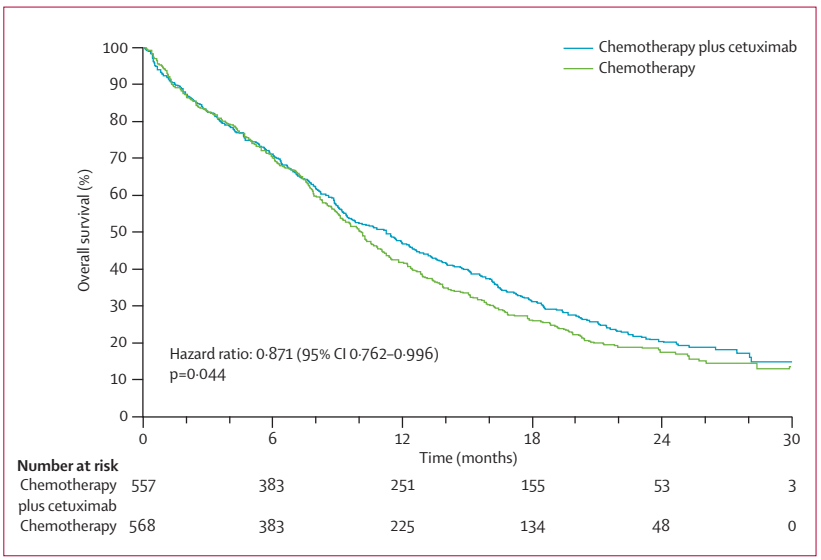

Figure 2: **Kaplan-Meier estimates of overall survival time in the intention-to-treat population**

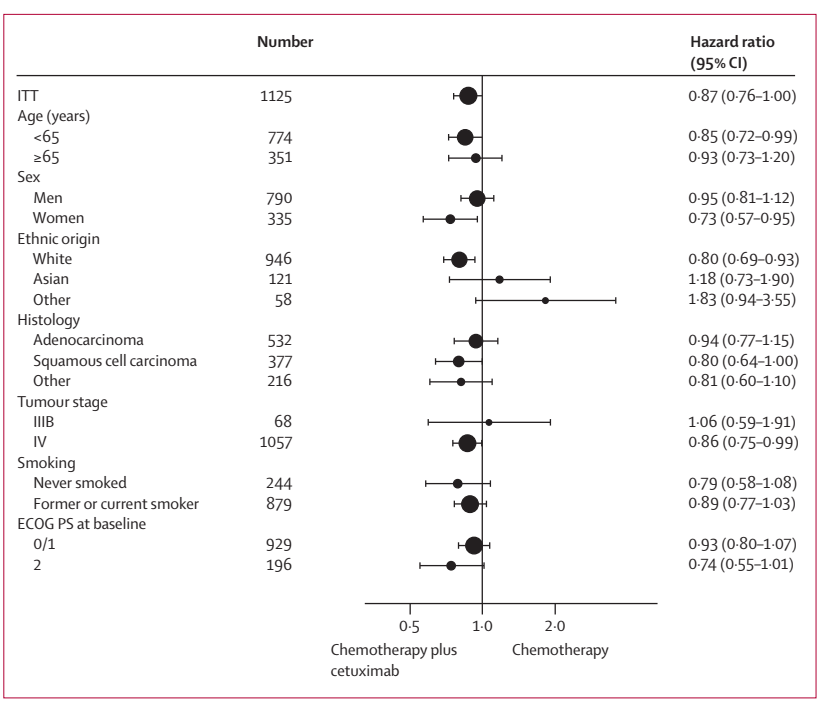

Figure 3: **Hazard ratios for death on the basis of prespecified subgroup analysis of intention-to-treat (ITT) population**

Only the interaction between the treatment and the ethnic origin was significant (p=0·011). Almost all Asian patients were accrued in the southeast Asian countries (Hong Kong, Singapore, South Korea, Taiwan). Sizes of the circles are proportional to the number of patients. ECOG PS=Eastern Cooperative Oncology Group performance status.

quality of life questionnaire C30 (EORTC QLQ-C30, version 3.0), EORTC lung cancer specific QLQ-LC13, and EuroQoL (EQ-5D) questionnaires. Complete blood counts were done at baseline and every week during the treatment phase, and serum chemistry was done at baseline and before every cycle. Clinical adverse events and changes in the laboratory parameters were assessed according to the National Cancer Institute's common toxicity criteria (version 2).

Statistical analysis

The primary endpoint was overall survival. Secondary endpoints included progression-free survival, best overall response, quality of life, and safety. Time-to-treatment failure was assessed in a posthoc analysis. Calculation of the sample size of 1100 patients (845 deaths) was made on the assumption of a hazard ratio (HR) of 0·8 (or an increase in overall survival time from 8 months in the chemotherapy-alone group to 10 months in the chemotherapy-plus-cetuximab group), a power of 90%, a two-sided significance level of 5%, a recruitment period of 17 months, and an additional follow-up period of 14 months. Analysis of the study was planned after 845 deaths had been reported. Efficacy analysis was by intention to treat. All statistical tests for comparison of treatment groups were two-sided with a significance level α of 5%. Subgroup analyses of overall survival time, which had been prespecified in the statistical analysis plan, were done for the prognostic factors and for ethnic origin.

Differences in survival times were assessed with stratified log-rank tests (stratified by randomisation strata). HRs were calculated with Cox regression stratified for randomisation strata. A Cox regression model with

	Cisplatin and vinorelbine plus cetuximab (N=548)		Cisplatin and vinorelbine alone (N=562)		p value*
	Grade 3	Grade 4	Grade 3	Grade 4	
Any event†	157 (29%)	342 (62%)	191 (34%)	294 (52%)	0·01
Haematological adverse events					
Neutropenia	79 (14%)	210 (38%)	77 (14%)	212 (38%)	0·67
Leukopenia	82 (15%)	57 (10%)	81 (14%)	28 (5%)	0·02
Febrile neutropenia	85 (16%)	34 (6%)	62 (11%)	25 (4%)	0·0086
Anaemia	68 (12%)	8 (1%)	89 (16%)	5 (<1%)	0·21
Non-haematological adverse events					
Dyspnoea	34 (6%)	13 (2%)	43 (8%)	8 (1%)	0·83
Fatigue	35 (6%)	5 (<1%)	34 (6%)	3 (<1%)	0·72
Vomiting	33 (6%)	1 (<1%)	37 (7%)	1 (<1%)	0·72
Pulmonary embolism	0	23 (4%)	5 (<1%)	11 (2%)	0·26
Respiratory failure	4 (<1%)	11 (2%)	0	8 (1%)	0·14
Sepsis	0	10 (2%)	2 (<1%)	1 (<1%)	0·053
Adverse events of special interest					
Acne-like rash‡	57 (10%)	0	1 (<1%)	0	0·0001
Hypokalaemia	32 (6%)	2 (<1%)	17 (3%)	3 (<1%)	0·050
Cardiac events§	9 (2%)	22 (4%)	15 (3%)	13 (2%)	0·69
Diarrhoea	23 (4%)	2 (<1%)	12 (2%)	1 (<1%)	0·047
Infusion-related reactions¶	14 (3%)	5 (<1%)	7 (1%)	0	0·017
Bleeding events‖	6 (1%)	4 (<1%)	6 (1%)	9 (2%)	0·42

Data are number (%), unless otherwise indicated. Table shows adverse events that were reported in ≥5% of patients (grade 3 or 4) or >1% of patients (grade 4), or adverse events of special interest in either group. *For differences between treatment groups for grades 3 or 4 combined. †Includes all grade 3 or 4 events. ‡Defined in Medical Dictionary for Regulatory Activity (MedDRA) as acne, acne pustular, dermatitis acneiform, dry skin, erythema, folliculitis, pruritus, rash, rash erythematous, rash follicular, rash generalised, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, skin exfoliation, skin hyperpigmentation, telangiectasia, xerosis. Any grade acne-like rash was noted in 382 patients given chemotherapy plus cetuximab and in 42 patients given chemotherapy alone. §Cardiac events was a special adverse event category consisting of five medical concepts: arrest, arrhythmia, congestive heart failure, ischaemia or infarction, and sudden death. Main grade 3 or 4 cardiac events in patients given chemotherapy plus cetuximab and chemotherapy alone were arrhythmia (12 *vs* 17, respectively), congestive heart failure (9 *vs* 9, respectively), infarction or ischaemia (8 *vs* 4, respectively), and sudden death (2 *vs* 0, respectively). ¶Allergy or anaphylaxis, dyspnoea, fever, and other events (cardiac failure, hypotension, syncope, and shock). Main grade 3 or 4 infusion-related reactions in patients given chemotherapy plus cetuximab and chemotherapy alone were allergy and anaphylaxis (14 *vs* 1, respectively). ‖All terms defined in MedDRA ; recorded grade 3 or 4 adverse events were cerebral haemorrhage, gastrointestinal haemorrhage, haematemesis, haemoptysis, melaena, pulmonary haemorrhage, purpura, and respiratory tract haemorrhage. Main grade 3 or 4 bleeding events in patients given chemotherapy plus cetuximab and chemotherapy alone were cerebral haemorrhage (1 *vs* 2, respectively), haematemesis (3 *vs* 0, respectively), haemoptysis (3 *vs* 7, respectively), and pulmonary haemorrhage (1 *vs* 2, respectively).

Table 2: **Adverse events in the safety population**

stepwise selection was done to identify variables of potential prognostic value. Thereafter, the treatment effect adjusted for these selected variables was calculated. The Cox model was also used to examine the interaction of treatment effect with subgroup status in an exploratory analysis. Differences in the best overall response rates between the treatment groups were analysed with the Cochran-Mantel-Haenszel test.

All patients who received at least one infusion of study treatment were included in the safety analysis. Differences in frequencies of adverse events between treatment groups were analysed with Fisher's exact test. The p values (two-sided) presented are purely exploratory because of the high number of tests done. No adjustment for multiplicity of testing was made. An independent data safety monitoring board reviewed the safety data twice.

This study is registered with ClinicalTrials.gov, number NCT00148798.

Role of the funding source

The Global Clinical Development Unit Oncology and the Department of Biostatistics at Merck KGaA, Darmstadt, Germany, in collaboration with RP, KO'B, TG, and UG, designed the study. Merck KGaA provided cetuximab, sponsored the trial, and did the statistical analyses. RP had full access to all the study data and, in accordance with the other authors and the sponsor, decided where to submit for publication.

Results

Figure 1 shows the trial profile. Between October, 2004, and January, 2006, 1125 patients (intention-to-treat population) were assigned to chemotherapy plus cetuximab or just chemotherapy. Table 1 shows that the baseline characteristics of the randomly assigned patients were well balanced between the groups.

Median number of chemotherapy cycles given to patients was four (range 0–6 for chemotherapy plus cetuximab, and 1–7 for chemotherapy alone) and median duration of chemotherapy was 14 weeks (0–25 for chemotherapy plus cetuximab, and 3–26 for chemotherapy alone). Median dose of cisplatin was 25 mg/m² per week (IQR 22–27) in the chemotherapy-plus-cetuximab group versus 24 mg/m² per week (22–26) in the chemotherapy-alone group; and median dose of vinorelbine was 17 mg/m² per week (15–19) in both groups. Cetuximab was given for a median duration of 18 weeks (range 1–135) at a median dose of 236 mg/m² per week (excluding the initial dose of 400 mg/m² per week; IQR 212–249). Patients in the chemotherapy-plus-cetuximab group were given EGFR-directed tyrosine kinase inhibitors less frequently than those in the chemotherapy-alone group (93 [17%] of 557 *vs* 152 [27%] of 568) in the poststudy treatment period. Similar proportions of patients were given chemotherapy (240 [43%] of 557 *vs* 226 [40%] of 568) and radiotherapy (117 [21%] of 557 *vs* 131 [23%] of 568) in both groups in the poststudy treatment period.

Median follow-up time was 23·8 months (95% CI 22·1–24·9 for chemotherapy plus cetuximab, and 22·4–24·8 for chemotherapy alone) in both groups. In the intention-to-treat population, overall survival was significantly prolonged in the chemotherapy-plus-cetuximab group compared with the chemotherapy-alone group (HR 0·871, 0·762–0·996; p=0·044). The median overall survival was 11·3 months (9·4–12·4) in the chemotherapy-plus-cetuximab group and 10·1 months (9·1–10·9) in the chemotherapy alone group, and 47% and 42% of patients were alive at 1 year, respectively (figure 2).

In the subgroup analyses, cetuximab was associated with an increase in survival for most subgroups (figure 3). In white patients (n=946), HR was 0·803 (95% CI

0·694–0·928; p=0·003), and median survival times were 10·5 months (9·2–12·0) with chemotherapy plus cetuximab versus 9·1 months (8·2–10·1) with just chemotherapy. A survival benefit was seen in all histological subgroups of non-small-cell lung cancer, with median survival times of 12·0 months (9·6–14·8) versus 10·3 months (8·3–12·1), respectively, for patients with adenocarcinomas (n=413), 10·2 months (8·2–12·0) versus 8·9 months (7·8–9·8), respectively, for those with squamous cell carcinomas (n=347), and 9·0 months (6·5–11·5) versus 8·2 months (6·9–10·2), respectively, for patients with other histological subtypes (n=185) in the chemotherapy-plus-cetuximab group versus chemotherapy-alone group.

The combination of chemotherapy and cetuximab was better than chemotherapy alone in terms of response rates (overall 203 [36%] of 557 *vs* 166 [29%] of 568, p=0·010; complete 9 [2%] of 557 *vs* 6 [1%] of 568; partial 194 [35%] of 557 *vs* 160 [28%] of 568). Progression-free survival time was not different (HR 0·943, 95% CI 0·825–1·077; p=0·39), median 4·8 months in both groups (4·2–5·3 for chemotherapy plus cetuximab, 4·4–5·4 for chemotherapy alone) but more patients in the chemotherapy-alone group were censored (137 [24%] of 568 *vs* 100 [18%] of 557). Thus time-to-treatment failure was calculated as a posthoc sensitivity analysis and was prolonged by the addition of cetuximab to chemotherapy (0·860, 0·761–0·971; p=0·015, median 4·2 months [3·9–4·4] *vs* 3·7 months [3·1–4·2]). More patients in the chemotherapy-alone group started another anticancer treatment without documented disease progression or toxicity (40 [7%] of 568 and 14 [3%] of 557, respectively) and as a result fewer patients discontinued treatment with documented disease progression (349 [61%] and 366 [66%] patients, respectively).

Use of the stepwise Cox regression model confirmed the prognostic significance of sex (women better than men), performance status, histology (adenocarcinomas better than squamous cell carcinomas), region (Australasia [113 of 154 patients were Asian] better than Europe), and smoking status (never-smokers better than former smokers better than current smokers). The treatment effect seen in the multivariate model (HR 0·863, 95% CI 0·751–0·993; p=0·039) confirmed the effect seen in the primary analysis. Of note, women (56 [46%] of 121 *vs* 258 [27%] of 946), ECOG performance status 0 or 1 (114 [94%] of 121 *vs* 767 [81%] of 946), adenocarcinomas (87 [72%] of 121 *vs* 413 [44%] of 946), and never-smokers (63 [52%] of 121 *vs* 161 [17%] of 946) were more common in Asian patients than in white patients. These differences and the frequent use of EGFR tyrosine kinase inhibitors in Asian patients (74 [61%] of 121 *vs* 160 [17%] of 946) in subsequent lines of treatment might partly explain the better prognosis in Asian patients than in white patients (median survival 19·5 months [16·4–23·3] *vs* 9·6 months [9·0–10·4]).

No significant differences were noted in the quality of life between the two groups but these results might have been affected by the low return rate of the questionnaires, which decreased from about 70% at baseline to less than 15% at the end of study (data not shown).

No safety concerns were identified at the two meetings of an independent data safety monitoring board. Table 2 summarises the adverse events. The safety profiles of the study treatment combinations were consistent with the known pattern of side-effects of the individual agents used. As expected with an anti-EGFR antibody, acne-like skin rash grade 3 (10% *vs* <1%), diarrhoea grades 3 and 4 (5% *vs* 2%), and infusion-related reactions grades 3 and 4 (4% *vs* <1%) were more common in patients given chemotherapy plus cetuximab. Similar proportions of patients had neutropenia and febrile neutropenia grade 4 in the two groups (table 2). Grade 3 and 4 sepsis was more common in the chemotherapy-plus-cetuximab group. However, treatment-related deaths were similar in both groups (15 [3%] of 548 *vs* 10 [2%] of 562).

Discussion

The FLEX trial showed that overall survival is prolonged with the EGFR targeted antibody cetuximab added to chemotherapy in patients with advanced non-small-cell lung cancer across all histological subtypes. Results of this study are consistent with those from other randomised phase II trials[14,15,16] and the BMS-099 phase III trial.[17,18] The BMS-099 trial[17,18] was not powered to detect a significant difference in overall survival. However, a reduction in the risk of death of the same magnitude as that in FLEX was noted when cetuximab was added to carboplatin plus a taxane in the treatment of patients with advanced non-small-cell lung cancer who were not selected according to the EGFR status of their tumours.[18] Cetuximab has also shown efficacy in combination with chemotherapy in patients with metastatic colorectal cancer, and in combination with radiotherapy or chemotherapy in patients with squamous cell cancer of the head and neck.[19–21]

Prespecified subgroup analyses in the FLEX trial showed a benefit associated with cetuximab that was independent of sex, performance status, tumour histology, and smoking status. The efficacy of cetuximab was clear for white patients representing 84% of the intention-to-treat population. Survival for Asian patients (11% of population) enrolled into the FLEX trial was much better than that of white patients, regardless of treatment arm, suggesting differences related to ethnic origin in non-small-cell lung cancer and potential differences in patient selection.

The findings of the FLEX trial confirm that the addition of cetuximab to a platinum-based two-drug combination increases tumour response rates. Increased response rates have been reported in several phase II trials [14,15,16,22–24] and the BMS-099 phase III trial.[17] Thus the benefit of cetuximab seems to be independent of the platinum-based drug combinations used.

Progression-free survival did not improve much. We noted different censoring patterns in the two treatment

groups in the analysis of progression-free survival. This difference might be due to more patients in the chemotherapy-alone group starting another anticancer treatment before progressive disease was radiologically documented. Analysis of time-to-treatment failure as a posthoc sensitivity analysis for progression-free survival showed a significant benefit with chemotherapy plus cetuximab.

Prolongation of survival was achieved with an acceptable safety profile. Cetuximab-related adverse events included acne-like rash, occasional diarrhoea, and rare infusion reactions. The recorded rates of febrile neutropenia, including sepsis, did not affect the administration of chemotherapy and, most importantly, did not result in an increase in treatment-related deaths. On the basis of the results of the FLEX study, we recommend for clinical practice vinorelbine 25 mg/m² per day on days 1 and 8, and cisplatin 80 mg/m² on day 1 of every 3-week cycle when used in combination with cetuximab in patients with advanced non-small-cell lung cancer.

Chemotherapy plus cetuximab was superior to chemotherapy alone for advanced non-small-cell lung cancer in our study, whereas EGFR-directed tyrosine kinase inhibitors in combination with chemotherapy were not in four previous randomised trials.[8–11] These findings might be related to differences in mechanism of action and patient selection criteria. First, cetuximab binding to the EGFR induces internalisation of the antibody-receptor complex and downregulation of the receptor, which does not usually happen when tyrosine kinase inhibitors are used. Second, cetuximab has immunological effects, such as antibody-dependent cell-mediated cytotoxicity and complement-dependent cytotoxicity.[25] Third, patients in the FLEX study, unlike those in trials with EGFR-directed tyrosine kinase inhibitors, were selected on the basis of immunohistochemical EGFR expression but the clinical relevance of this selection criterion is uncertain.

Future research might clarify questions such as the optimum duration of cetuximab treatment and the selection of patients with biomarkers. KRAS mutation status, EGFR mutations, gene copy number assessed with fluorescent in-situ hybridisation, and EGFR expression did not seem to be predictive markers of benefit from cetuximab in non-small-cell lung cancer in the BMS-099 trial.[26] Retrospective translational research with tumour specimens obtained from patients in the FLEX study is in progress. However, such analyses of biomarkers should be standardised and prospectively validated before widespread clinical use.[27] Although the patients in this trial were eligible if they had tumours with immunohistochemically detectable EGFR expression, the most appropriate biomarker for the selection of patients with non-small-lung cancer for treatment with cetuximab remains to be determined. However, a prespecified analysis of the data from our study shows that the development of acne-like rash is associated with an improved outcome for patients given cetuximab in combination with chemotherapy.[28]

In conclusion, cetuximab added to platinum-based chemotherapy can be regarded as a new standard first-line treatment option for patients with EGFR-expressing advanced non-small-cell lung cancer. Cetuximab also provides new opportunities for clinical research into the treatment of non-small-cell lung cancer at earlier stages.

Contributors

RP, KO'B, TG, and UG were involved in the design of the trial. RP, JRP, AS, JvP, MK, RR, IV, KP, CTY, VG, JKR, EB, KO'B, FdM, WE, and UG recruited patients and gathered data at their centres. RP, MK, RR, KP, KO'B, FdM, WE, TG, ME, and UG were involved in data analysis and interpretation. RP, KO'B, TG, and ME wrote the report. All authors have approved the final version of the report to be published.

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Conflicts of interest

RP has received speaker's fee and honoraria for advisory boards and consulting from Eli Lilly, Merck KGaA, Pierre Fabre, and Roche. KP has received honoraria from AstraZenecea, Eli Lilly, Roche, Merck KGaA, Merck Sharp and Dohme, and Pfizer. JvP, FdM, and WE have received honoraria for advisory boards and consulting from Merck KGaA. KO'B received research funding, speaker's fee, and honoraria for advisory board from Merck KGaA. TG and ME are full-time employees of Merck KGaA. UG received research funding or honoraria for consulting and advisory boards from AstraZeneca, Eli Lilly, Merck KGaA, Novartis, Pierre Fabre, Roche, Bayer, GlaxoSmithKline, and Alpha Cell. JRP, AS, MK, RR, IV, CTY, VG, JKR, and EB declare that they have no conflicts of interest.

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