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Cetuximab plus carboplatin and paclitaxel with or without bevacizumab versus carboplatin and paclitaxel with or without bevacizumab in advanced NSCLC (SWOG S0819): a randomised, phase 3 study

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Summary

Background EGFR antibodies have shown promise in patients with advanced non-small-cell lung cancer (NSCLC), particularly with squamous cell histology. We hypothesised that *EGFR* copy number by fluorescence in-situ hybridisation (FISH) can identify patients most likely to benefit from these drugs combined with chemotherapy and we aimed to explore the activity of cetuximab with chemotherapy in patients with advanced NSCLC who are *EGFR* FISH-positive.

Methods We did this open-label, phase 3 study (SWOG S0819) at 277 sites in the USA and Mexico. We randomly assigned (1:1) eligible patients with treatment-naive stage IV NSCLC to receive paclitaxel (200 mg/m²; every 21 days) plus carboplatin (area under the curve of 6 by modified Calvert formula; every 21 days) or carboplatin plus paclitaxel and bevacizumab (15 mg/kg; every 21 days), either with cetuximab (250 mg/m² weekly after loading dose; cetuximab group) or without (control group), stratified by bevacizumab treatment, smoking status, and M-substage using a dynamic-balancing algorithm. Co-primary endpoints were progression-free survival in patients with *EGFR* FISH-positive cancer and overall survival in the entire study population. We analysed clinical outcomes with the intention-to-treat principle and analysis of safety outcomes included patients who received at least one dose of study drug. This study is registered with ClinicalTrials.gov (number NCT00946712).

Findings Between Aug 13, 2009, and May 30, 2014, we randomly assigned 1313 patients to the control group (n=657; 277 with bevacizumab and 380 without bevacizumab in the intention-to-treat population) or the cetuximab group (n=656; 283 with bevacizumab and 373 without bevacizumab in the intention-to-treat population). *EGFR* FISH was assessable in 976 patients and 400 patients (41%) were *EGFR* FISH-positive. The median follow-up for patients last known to be alive was 35·2 months (IQR 22·9–39·9). After 194 progression-free survival events in the cetuximab group and 198 in the control group in the *EGFR* FISH-positive subpopulation, progression-free survival did not differ between treatment groups (hazard ratio [HR] 0·92, 95% CI 0·75–1·12; p=0·40; median 5·4 months [95% CI 4·5–5·7] *vs* 4·8 months [3·9–5·5]). After 570 deaths in the cetuximab group and 593 in the control group, overall survival did not differ between the treatment groups in the entire study population (HR 0·93, 95% CI 0·83–1·04; p=0·22; median 10·9 months [95% CI 9·5–12·0] *vs* 9·2 months [8·7–10·3]). In the prespecified analysis of EGFR FISH-positive subpopulation with squamous cell histology, overall survival was significantly longer in the cetuximab group than in the control group (HR 0·58, 95% CI 0·36–0·86; p=0·0071), although progression-free survival did not differ between treatment groups in this subgroup (0·68, 0·46–1·01; p=0·055). Overall survival and progression-free survival did not differ among patients who were EGFR FISH non-positive with squamous cell histology (HR 1·04, 95% CI 0·78–1·40; p=0·77; and 1·02, 0·77–1·36; p=0·88 respectively) or patients with non-squamous histology regardless of EGFR FISH status (for EGFR FISH-positive 0·88, 0·68–1·14; p=0·34; and 0·99, 0·78–1·27; p=0·96; respectively; and for EGFR FISH non-positive 1·00, 0·85–1·17; p=0·97; and 1·03, 0·88–1·20; p=0·69; respectively). The most common grade 3–4 adverse events were decreased neutrophil count (210 [37%] in the cetuximab group *vs* 158 [25%] in the control group), decreased leucocyte count (103 [16%] *vs* 74 [20%]), fatigue (81 [13%] *vs* 74 [20%]), and acne or rash (52 [8%] *vs* one [<1%]). 59 (9%) patients in the cetuximab group and 31 (5%) patients in the control group had severe adverse events. Deaths related to treatment occurred in 32 (6%) patients in the cetuximab group and 13 (2%) patients in the control group.

Interpretation Although this study did not meet its primary endpoints, prespecified subgroup analyses of patients with EGFR FISH-positive squamous-cell carcinoma cancers are encouraging and support continued evaluation of anti-EGFR antibodies in this subpopulation.

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Research in Context

Evidence before this study

The treatment of non-small-cell lung cancer (NSCLC) has changed substantially in recent years. While many patients benefit from targeted therapy or immunotherapy, many still receive chemotherapy in the front-line setting. Improving upon this is crucial and targeting EGFR is one such approach. We searched PubMed for clinical trials published in English from Jan 1, 2007, to July 30, 2017, with the terms "lung cancer and EGFR"; 515 results were retrieved. Of these, several published after the beginning of our trial accrual were of particular relevance. Results of the phase 2 lung cancer cetuximab study and the phase 3 FLEX study showed the benefit of treatment with EGFR antibodies plus chemotherapy over chemotherapy alone in patients with EGFR-positive advanced NSCLC. Subsequent analyses of FLEX showed the use of EGFR expression analysis as a biomarker for survival benefit with cetuximab. A similar biomarker, *EGFR* FISH-positivity, has shown predictive potential in several clinical trials, thus warranting further analysis in larger patient populations. Most recently, these findings have been reinforced by the results of the SQUIRE trial, which investigated the anti-EGFR antibody necitumumab plus chemotherapy in patients with tumours expressing EGFR. However, analyses from other studies of cetuximab plus chemotherapy had conflicting results, finding no correlation between EGFR expression and outcome. We aimed to determine whether *EGFR* FISH-positivity could predict the efficacy of anti-EGFR antibody therapy with cetuximab in combination with chemotherapy.

Added value of this study

To our knowledge, our phase 3 trial is the largest biomarker validation study designed to assess the ability of *EGFR* FISH-positivity to predict outcomes to first-line cetuximab treatment in combination with platinum-based doublet chemotherapy, with or without bevacizumab. The co-primary objectives, comparison of progression-free survival in patients who were *EGFR* FISH-positive and overall survival in the entire study population, did not differ between cetuximab and non-cetuximab treatment groups. Among the secondary objectives, overall survival and progression-free survival did not differ between cetuximab and non-cetuximab treatment groups with or without bevacizumab treatment or when stratified by *EGFR* FISH-positivity. Although *EGFR* FISH-positivity was not predictive in the overall NSCLC patient population, patients with squamous cell histology who were *EGFR* FISH-positive had longer overall survival with cetuximab treatment than those patients who did not receive cetuximab; this association was not seen for patients with squamous cell histology who were *EGFR* FISH non-positive or in patients without squamous cell histology regardless of *EGFR* FISH status.

Implications of all the available evidence

Although, cetuximab added to carboplatin and paclitaxel, with or without bevacizumab, did not extend overall survival in the overall study population or progression-free survival in the patients with *EGFR* FISH-positive cancers, our findings, in addition to recent data from the SQUIRE trial, suggest that the biology of squamous cell NSCLC might be fundamentally different from that of non-squamous NSCLC in its responsiveness to EGFR inhibition.

Introduction

Although the incidence and mortality rates associated with lung cancer have steadily declined in the past decade, lung cancer continues to be the leading cause of death from cancer in the USA, with more than 158 000 associated deaths estimated for 2016.[1] Non-small-cell lung cancer (NSCLC) constitutes around 80% of lung cancers. The standard of care for advanced NSCLC has evolved from best supportive care to the use of multiple regimens, including platinum-based chemotherapy, molecularly targeted drugs, and immunotherapy.[2] The targeted drugs that inhibit EGFR have had multiple generations of development.[3–6] The tyrosine kinase inhibitors (TKIs) erlotinib, gefitinib, and afatinib confer dramatic clinical responses in the subset of patients who harbour *EGFR* tyrosine-kinase domain mutations, but have shown only modest efficacy in unselected previously treated patients,[3] and have been less effective as first-line drugs in combination with chemotherapy in *EGFR*-unmutated patients with advanced NSCLC.[7]

Cetuximab, a highly specific, chimerised, monoclonal antibody targeting EGFR, has been investigated in combination with platinum-based chemotherapies for the treatment of chemotherapy-naive patients with advanced NSCLC on the basis of biological evidence showing that the EGFR pathway plays a part in lung cancer development and progression.[8,9] Furthermore, the poor efficacy of oral EGFR TKIs in combination with chemotherapy suggested that an alternative EGFR-directed approach was needed and preclinical models showed synergy with chemotherapy and cetuximab.[5,10,11] In patients with *EGFR* mutations using varied dosing schedules, there were indications of activity for EGFR TKIs and chemotherapy. The Southwest Oncology Group (SWOG) did two phase 2 clinical trials, S0342 and S0536,[12–14] to evaluate the efficacy and safety of adding cetuximab to first-line treatment of advanced NSCLC. The S0342 trial evaluated whether activity of cetuximab concurrently with or sequentially after chemotherapy was sufficient in treatment-naive advanced NSCLC to select one of these regimens for further study.[12] A secondary analysis of this trial[13] indicated that *EGFR* copy number, as assessed by fluorescence in-situ hybridisation (*EGFR* FISH), might be associated with improved survival in this patient population. The S0536 trial[14] was designed to assess the safety and feasibility of a chemotherapy doublet (carboplatin and paclitaxel) given concurrently with a biologic doublet consisting of the anti-VEGF monoclonal antibody bevacizumab and cetuximab as

first-line therapy in advanced NSCLC. This trial also assessed *EGFR* FISH as a biomarker of response. The primary safety endpoint, evaluation of grade 4–5 haemorrhage-related toxicities, was met with only 2% (n=2) of the study population with death due to pulmonary haemorrhage, with all other toxicities similar to previous cetuximab combinations.[12,14,15] The overall proportion of patients who achieved an objective response was 52 (55%) of 95 patients and overall disease control was achieved in 77%; moreover, the median progression-free survival was 7 months and overall survival was 15 months.[14] The results supported a potential association between *EGFR* FISH-positivity and enhanced clinical outcome.[14]

Given the overall safety, efficacy, and biomarker results from the S0342 and S0536 studies, we aimed to investigate the safety and effectiveness of first-line therapy with cetuximab plus carboplatin and paclitaxel chemotherapy with or without bevacizumab in patients with advanced NSCLC and designed this study to validate *EGFR* FISH as a predictive biomarker for cetuximab in this population.[16] We hypothesised that *EGFR* FISH-positivity would be associated with increased progression-free survival or overall survival, or both.

Methods

Study design and participants

We did this randomised, open-label, phase 3 study at 277 sites in the USA and Mexico (appendix pp 1–5). Patients had histologically or cytologically proven stage IV primary NSCLC that was newly diagnosed or recurrent after previous surgery or irradiation. We excluded patients if they had received previous chemotherapy for NSCLC, platinum-based chemotherapy for any purpose, any drug targeting the EGFR or VEGF pathways, any chimerised or mouse monoclonal antibody therapies, or had documented presence of human anti-mouse antibodies. Patients were required to have CT or MRI scans to document the extent of their disease; measurable disease was assessed within 28 days before registration and non-measurable disease was assessed within 42 days of registration. CT or MRI scans were required within 42 days before registration to determine the extent of CNS disease; patients with adequately treated, controlled brain metastases could be included if the patient had no residual neurological dysfunction when off corticosteroid treatment for 1 day or longer. At least 28 days must have passed since the patient had major surgery. Laboratory and clinical tests were done within 14 days before registration and had to meet certain requirements: absolute neutrophil count of 1500 cells per µL or more; platelet count of 100 000 platelets per µL or more; haemoglobin of 9 g/dL or more; serum creatinine less than or equal to the institutional upper limit of normal (IULN) and a calculated or measured creatinine clearance of 50 creatinine clearance per min or more; adequate hepatic function (serum bilirubin ≤2×IULN and either aspartate aminotransferase or alanine aminotransferase ≤2×IULN; for patients with liver metastases, bilirubin and either aspartate aminotransferase or alanine aminotransferase must be ≤5×IULN); Zubrod performance status of 0 (fully active, able to carry on all predisease performance without restriction) to 1 (restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature); less than grade 2 symptomatic neuropathy-sensory; no evidence of active infection or acute hepatitis; no history (within the past 6 months) of cerebrovascular accident, myocardial infarction, or unstable angina, and no evidence of uncontrolled hypertension, New York Heart Association grade 2 or worse congestive heart failure, serious cardiac arrhythmia requiring medication, or clinically significant vascular disease. No other previous malignancy was allowed except adequately treated basal cell or squamous cell skin cancer, in-situ cervical cancers, adequately treated stage I or II cancer from which the patient is in complete remission, or any other cancer from which the patient has been disease-free for 5 years. Patients provided smoking history and we discouraged patients from becoming pregnant or nursing because of the increased risk of fetal harm from the chemotherapeutic drugs.

Patients were not suitable for bevacizumab if they had a squamous cell tumour component of 50% or more; history of haemoptysis (≥0·5 teaspoon of red blood per event within the past year); cavitary pulmonary lesion; history of documented haemorrhagic diathesis or coagulopathy; non-healing wound or bone fracture, abdominal fistula, gastro-intestinal perforation, or intra-abdominal abscess; or were receiving anticoagulation. Patients were placed in the no bevacizumab stratum if they did not receive bevacizumab; reasons could include being unsuitable for bevacizumab or if the patient or physician decided to not treat the patient with bevacizumab. Patients with CNS metastases were defined as suitable for bevacizumab until a protocol amendment on June 1, 2013. For patients receiving bevacizumab, if the urine protein-creatinine ratio was more than 0·5, 24-h urine protein was required to be lower than 1000 mg for enrolment. This trial was approved by the institutional review boards of the participating institutions and all patients provided written informed consent. The protocol is available in the appendix.

See Online for appendix

Randomisation

We randomly allocated patients with equal probability (1:1) and stratified by bevacizumab-treatment status (treatment *vs* no treatment), smoking status (current or former *vs* never), and stage (M1a *vs* M1b) with a dynamic-balancing algorithm.[17] We enrolled patients via a web-based application and simultaneous randomisation was by a computer programme. Sites were automatically notified of the patient's randomisation group at the time of enrolment. Patients and investigators were not masked to treatment.

Procedures

Patients received chemotherapy with paclitaxel (200 mg/m²; 3 h intravenous infusion; every 21 days) and carboplatin (area under the curve of 6 by modified Calvert formula; 30 min intravenous infusion immediately following paclitaxel; every 21 days) for a maximum of six cycles or until one of the criteria for removal from treatment was met, which included disease progression based on the investigator's assessment or symptomatic deterioration, unacceptable toxicity, or treatment delay of longer than 4 weeks. We chose carboplatin and paclitaxel as the chemotherapy regimen for this trial because it is acceptable for all histologies that were eligible for the trial and because of previous SWOG data with this regimen in combination in the phase 2 S0342 trial.[12,13]

For the patients receiving bevacizumab the dose schedule was 15 mg/kg in a 30–90 min intravenous infusion 1 h after carboplatin every 21 days. The patients randomly assigned to receive cetuximab were given a 400 mg/m² loading dose as a 2 h intravenous infusion on week 1 of cycle 1, followed by 250 mg/m² weekly dosing starting on week 2, 1 h before paclitaxel. These patients were premedicated with 50 mg intravenous diphenhydramine hydrochloride before the first dose of

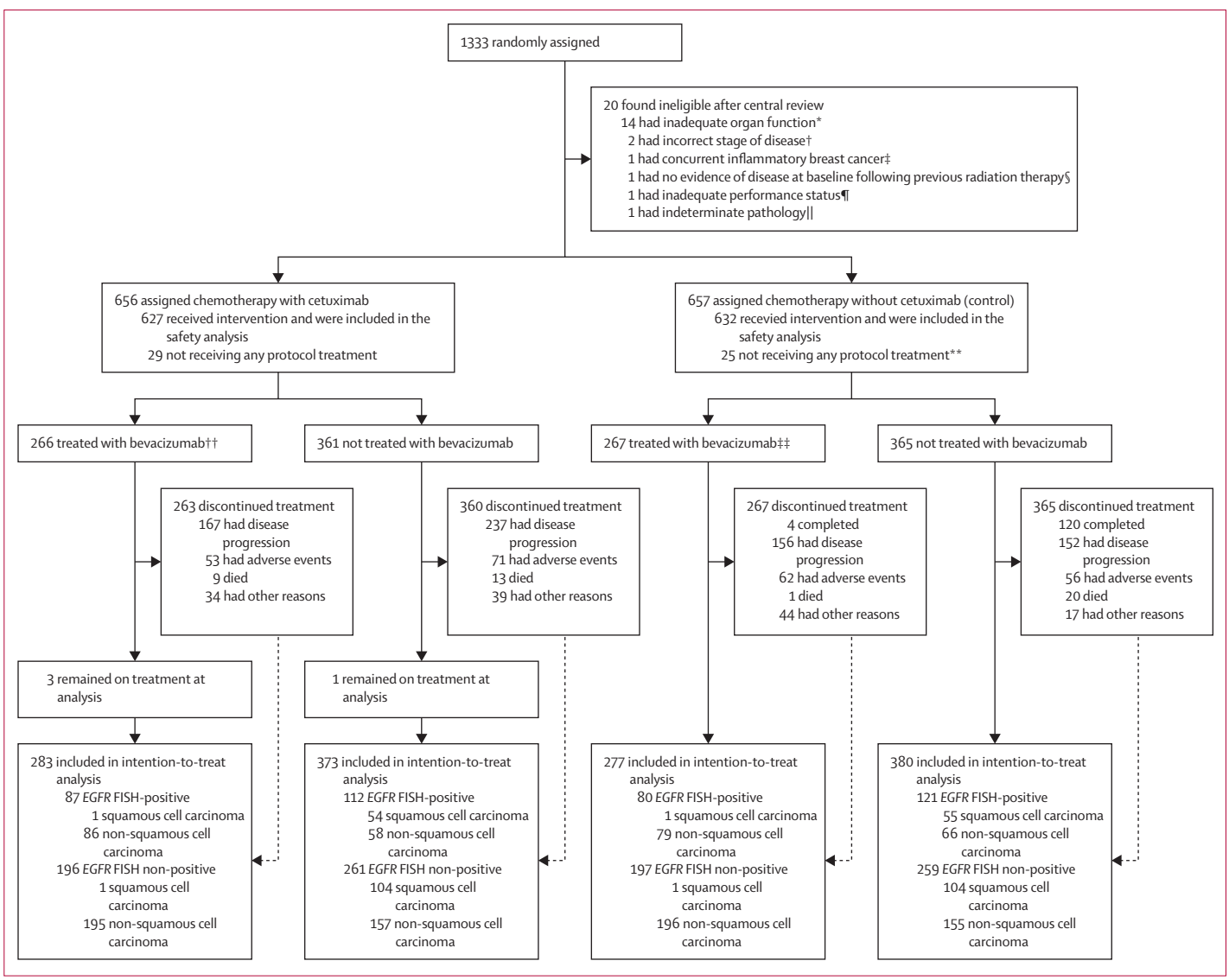


Figure 1: **Trial profile**

EGFR FISH non-positive includes *EGFR* FISH-negative and *EGFR* FISH status unknown. FISH=fluorescence in-situ hybridisation. *Ten in the control group (three treated with bevacizumab and seven not treated with bevacizumab) and four in the cetuximab group (one treated with bevacizumab and three not treated with bevacizumab). †One in the control group (not treated with bevacizumab) and one in the cetuximab group (treated with bevacizumab). ‡One in the cetuximab group (not treated with bevacizumab). §One in the control group (not treated with bevacizumab). ¶One in the control group (not treated with bevacizumab). ||One in the control group (treated with bevacizumab). **Includes the one patient who withdrew consent. ††In the cetuximab group, 26 were treated with bevacizumab when medically contraindicated, nine had a carboplatin dosing error, and eight were considered to have protocol deviations for miscellaneous reasons. ‡‡In the control group, 25 were treated with bevacizumab when medically contraindicated, 14 had a carboplatin dosing error, and eight were considered to have protocol deviations for miscellaneous reasons.

cetuximab to prevent hypersensitivity reaction. Dose reductions were allowed in the event of toxicity and all dose reductions were permanent.

Laboratory monitoring occurred every cycle of treatment starting at cycle 2 and included complete blood counts, serum creatinine, calculated or measured creatinine clearance, urine protein-creatinine ratio, total bilirubin, serum glutamic oxaloacetic transaminase or serum glutamic aspartate aminotransferase, alkaline phosphatase, international normalised ratio, albumin, lactate dehydrogenase serum sodium, calcium, and magnesium. Assessment of toxicity was done by Common Terminology Criteria for Adverse Events (CTCAE) 4.0 and was done at every cycle of treatment starting at cycle 2.

We followed up patients for 3 years after registration or until death. CT or MRI scans were assessed by the investigator using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 every 6 weeks for the first 9 months and every 3 months thereafter, until disease progression.

Paraffin-embedded, formalin-fixed tumour specimens or fine-needle aspirate slides for *EGFR* FISH analysis were submitted before the start of therapy. We evaluated *EGFR* FISH and *KRAS* mutational status at each interim analysis. We did *EGFR* FISH analysis with the Colorado EGFR Scoring System, as reported previously.[13] Tumours were considered to be *EGFR* FISH-positive if they harboured four or more copies of *EGFR* in 40% or more of cells or if they showed *EGFR* amplification (defined as gene-to-chromosome ratio ≥2, presence of gene cluster, or ≥15 gene copies in ≥10% of cells). We classified tumours that were successfully tested and did not meet these criteria as *EGFR* FISH-negative. *EGFR*-mutational testing was not a required test for this trial.

Outcomes

The co-primary endpoints were progression-free survival (defined as the duration from randomisation to progression, symptomatic deterioration, or death from any cause, whichever comes first, by RECIST 1.1 as assessed by the treating investigator) in patients who are *EGFR* FISH-positive and overall survival (defined as the duration from randomisation to death from any cause) in the entire study population. Central review of progression-free survival was specified in the protocol; these data will be presented in a separate manuscript. Secondary endpoints included overall survival in patients who were *EGFR* FISH-positive; progression-free survival in the entire study population; response (confirmed plus unconfirmed complete and partial responses) by in the subset of patients with measurable disease at baseline in the entire study population and the *EGFR* FISH-positive subset; assessment of the toxicity by bevacizumab treatment subgroup; prospective testing of *EGFR* FISH as a predictive marker; overall survival and progression-free survival within the bevacizumab treatment subgroups; an evaluation of the role of *KRAS* mutations in terms of cetuximab efficacy; and comparison of results of *EGFR* FISH with *KRAS* mutations, *EGFR* mutations, EGFR immunohistochemistry, and other potential EGFR-related biomarkers. The analysis of *KRAS*, EGFR immunohistochemistry, and other EGFR-related biomarkers will be presented in a separate manuscript.

Before data analysis, we amended the protocol on May 1, 2015, to add a prespecified analysis of overall survival and progression-free survival among patients with squamous cell histology, both overall and stratified by *EGFR* FISH status, based on results from the SQUIRE trial.[18]

Statistical analysis

The basis for the statistical design of the study has been previously described.[16] Although the study had co-primary endpoints, the sample size was based on the primary endpoint within the *EGFR* FISH-positive population. The

	EGFR FISH-positive		All patients	
	Control group (n=201)	Cetuximab group (n=199)	Control group (n=657)	Cetuximab group (n=656)
Age (years)	64 (34–84)	62 (37–80)	63 (30–86)	63 (19–84)
>65 years	94 (47%)	78 (39%)	278 (42%)	275 (42%)
Sex				
Male	115 (57%)	125 (63%)	359 (55%)	385 (59%)
Female	86 (43%)	74 (37%)	298 (45%)	271 (41%)
M-stage				
M1a	54 (27%)	43 (22%)	297 (45%)	292 (45%)
M1b	147 (73%)	156 (78%)	303 (46%)	305 (46%)
Bevacizumab treatment				
Yes	80 (40%)	87 (44%)	277 (42%)	283 (43%)
No	121 (60%)	112 (56%)	380 (58%)	373 (57%)
Smoking history				
Current	89 (44%)	94 (47%)	297 (45%)	292 (45%)
Former	94 (47%)	87 (44%)	303 (46%)	305 (46%)
Never	18 (9%)	18 (9%)	57 (9%)	59 (9%)
Histology				
Squamous cell carcinoma	56 (28%)	55 (28%)	161 (25%)	160 (24%)
Adenocarcinoma	120 (60%)	130 (65%)	408 (62%)	411 (63%)
Other*	25 (12%)	14 (7%)	88 (13%)	85 (13%)
Performance status†				
0	64 (32%)	81 (41%)	229 (35%)	256 (39%)
1	137 (68%)	118 (59%)	427 (65%)	400 (61%)
EGFR FISH status‡				
Positive	201 (100%)	199 (100%)	201 (31%)	199 (30%)
Negative	NA	NA	293 (45%)	283 (43%)
Unknown	NA	NA	163 (25%)	174 (27%)

Data are median (range) or n (%). FISH=fluorescence in-situ hybridisation. NA=not applicable. *Includes large-cell carcinoma, bronchioloalveolar carcinoma, mixed, other, and not reported. †One patient in the control group was missing documentation. ‡In the control and cetuximab groups for all patients, *EGFR* FISH analysis failed in 23 (4%) and 35 (5%) patients, 82 (12%) and 74 (11%) cases had inadequate specimens, and there were no data in 58 (9%) and 65 (10%) cases, respectively.

Table 1: **Baseline demographics and characteristics**

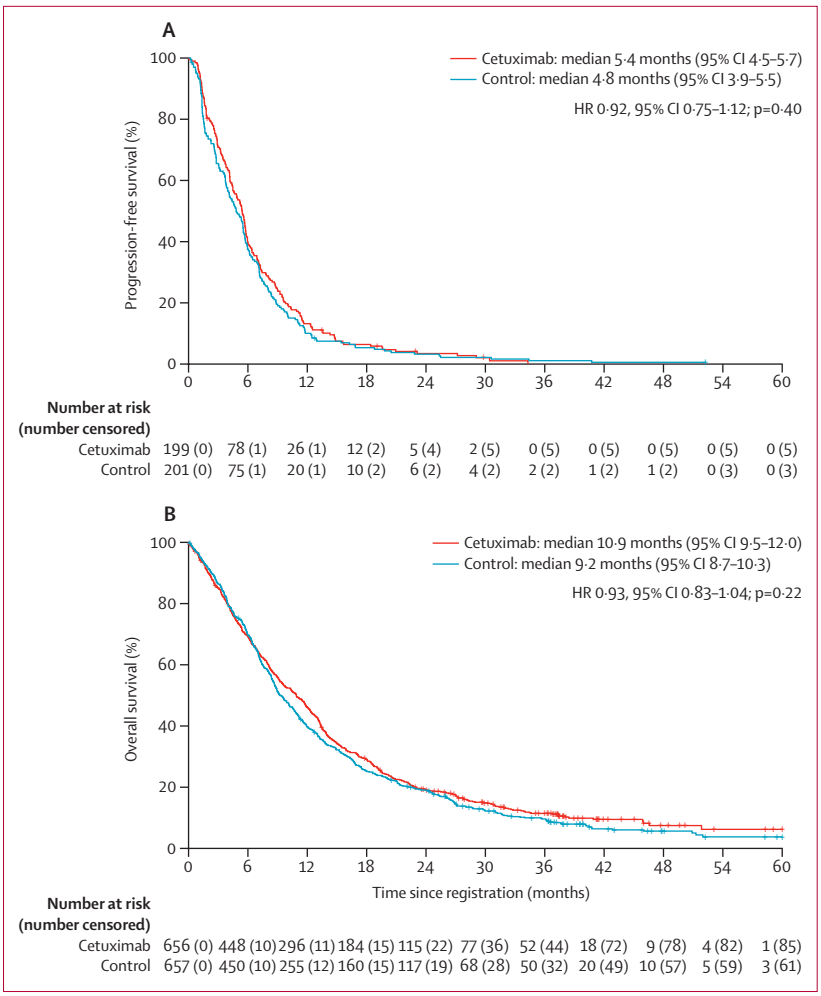


Figure 2: **Progression-free survival in patients with *EGFR* fluorescence in-situ hybridisation-positive cancers (A) and overall survival in the entire study population (B)**

study-wide type I error is 2·5%, with 2% allocated to the *EGFR* FISH-positive objective. The original design for the *EGFR* FISH-positive objective was based on a design with 92% power to detect a hazard ratio (HR) of 0·75 at the one-sided 2% level, which requires 297 progression-free survival events. 618 patients who were *EGFR* FISH-positive were needed assuming exponential survival, 50% of patients treated with bevacizumab, a median progression-free survival of 4 months in patients not treated with bevacizumab, a median progression-free survival of 6 months in patients treated with bevacizumab, uniform accrual over 4 years, and 1 year of follow-up.

The total target sample size was 1546 patients, which was based on the assumption that 80% of patients would be evaluable for *EGFR* FISH status, and of them, 50% would be *EGFR* FISH-positive. The level of testing within the entire study population was set to be 0·015, accounting for the correlation between the two co-primary endpoints. Under the design assumptions above, and assuming a median overall survival of 10 months for patients not treated with bevacizumab and 12 months for patients treated with bevacizumab, the study had 86% power to detect an HR of 0·83 for overall survival with a one-sided 0·015 level log-rank test within the entire study population. As the sample size for the study was determined by the number of patients accrued who were *EGFR* FISH-positive, the study protocol included specification that the study might be modified on the basis of the observed prevalence of *EGFR* FISH-positivity.

On June 1, 2014, the study design was amended to account for the lower than estimated percentage of accrued patients known to be *EGFR* FISH-positive. Accrual to the study was also lower than anticipated. The amended accrual goal was 400 patients who were *EGFR* FISH-positive; on the basis of a design with 80% power; all other design parameters remained unchanged.

The interim-analysis plan has been fully described.[16] Interim analyses were to take place when 30%, 67%, and 85% of the expected progression-free survival events within the *EGFR* FISH-positive population had been observed. Interim analyses evaluated early stopping for either efficacy or futility both in the overall population and by FISH grouping.

We analysed overall survival and progression-free survival with a two-sided log-rank test stratified according to the factors mentioned before. We estimated HRs and corresponding 95% CIs with a stratified Cox proportional-hazards model, with randomised group as a single covariate. We did not evaluate the proportional hazards assumption. Survival curves for each treatment group were estimated by the Kaplan-Meier method and survival was derived from the Kaplan-Meier estimates. For overall survival, patients last known to be alive were censored at the date of last contact; for progression-free survival, patients last known to be alive and progression free were censored at the date of last contact.

We compared the proportion of patients who achieved an objective response with a two-sided, stratified Cochran–Mantel-Haenszel test, with exact 95% CIs calculated with the use of the Clopper–Pearson method. Secondary analyses used a significance level of 5%. We used the intention-to-treat principle for analysis of clinical outcomes, including all patients randomly assigned but excluding those patients found ineligible centrally after randomisation. Analysis of toxicity included patients who received at least one dose of protocol treatment.

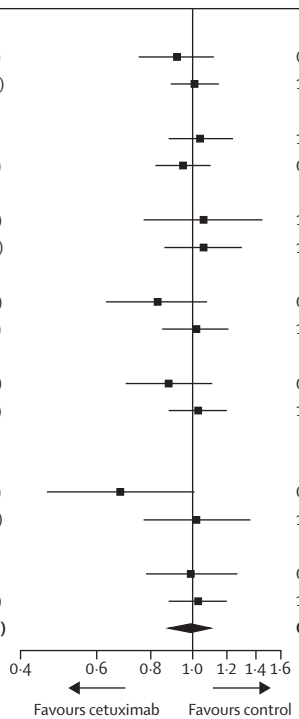
The study was overseen by the SWOG Data Safety Monitoring Committee on a twice a year basis. We used SAS (version 9.4) for all statistical analyses. This trial is registered with ClinicalTrials.gov (number NCT00946712).

Role of the funding source

This trial was sponsored by SWOG and National Cancer Institute cooperative group of which the authors are members. The funder contributed to study design, data collection, data analysis, data interpretation, and writing of the report. The corresponding author had full access

A

	Control (n/N)	Median (95% CI)	Cetuximab (n/N)	Median (95% CI)	HR (95% CI)	p value
EGFR–FISH						
Positive	198/201	4·8 (3·9–5·5)	194/199	5·4 (4·5–5·7)	0·92 (0·75–1·12)	0·40
Non-positive	440/456	4·3 (4·1–4·9)	443/457	4·4 (4·0–4·8)	1·01 (0·89–1·15)	0·50
Treated with bevacizumab						
Yes	266/277	5·9 (5·5–6·7)	270/283	5·7 (5·3–6·1)	1·04 (0·88–1·24)	0·62
No	372/380	3·8 (3·1–4·2)	367/373	4·1 (3·5–4·4)	0·95 (0·82–1·10)	0·49
Bevacizumab by FISH						
Positive	78/80	6·7 (5·7–8·0)	84/87	6·2 (5·7–8·0)	1·06 (0·77–1·45)	0·74
Non-positive	188/197	5·6 (5·3–6·4)	186/196	5·4 (4·6–5·8)	1·06 (0·86–1·30)	0·57
No bevacizumab by FISH						
Positive	120/121	3·7 (2·8–4·6)	110/112	4·4 (3·8–5·2)	0·83 (0·63–1·08)	0·16
Non-positive	252/259	4·0 (3·0–4·2)	257/261	4·0 (3·1–4·3)	1·02 (0·85–1·21)	0·85
Histology						
SCCA	158/161	3·7 (2·8–4·3)	158/160	4·2 (3·7–4·6)	0·88 (0·70–1·11)	0·29
Non-squamous	480/496	4·9 (4·3–5·5)	479/496	5·1 (4·4–5·4)	1·03 (0·88–1·20)	0·69
Histology by FISH						
SCCA						
Positive	55/56	2·8 (2·6–4·1)	54/55	4·5 (3·8–5·2)	0·68 (0·46–1·01)	0·055
Non-positive	103/105	4·1 (3·0–4·8)	104/105	4·0 (2·9–4·5)	1·02 (0·77–1·36)	0·88
Non-squamous						
Positive	143/145	5·5 (4·6–6·1)	140/144	5·7 (5·2–6·5)	0·99 (0·78–1·27)	0·96
Non-positive	337/351	4·5 (4·1–5·3)	339/352	4·6 (4·1–5·3)	1·03 (0·88–1·20)	0·69
Total population	**638/657**	**4·5 (4·2–5·1)**	**637/656**	**4·6 (4·2–5·2)**	**0·99 (0·88–1·10)**	**0·83**



B

	Control (n/N)	Median (95% CI)	Cetuximab (n/N)	Median (95% CI)	HR (95% CI)	p value
EGFR–FISH						
Positive	184/201	9·8 (8·7–12·1)	170/199	13·4 (11·5–14·8)	0·81 (0·66–1·00)	0·054
Non-positive	409/456	8·9 (8·4–10·2)	400/457	9·5 (8·2–10·9)	0·95 (0·83–1·09)	0·85
Treated with bevacizumab						
Yes	244/277	11·6 (10·5–13·6)	236/283	12·7 (10·9–13·4)	0·97 (0·81–1·16)	0·72
No	349/380	8·1 (7·2–8·7)	334/373	9·2 (8·1–10·9)	0·90 (0·78–1·05)	0·19
Bevacizumab by FISH						
Positive	72/80	13·2 (11·2–19·9)	71/87	15·9 (13·4–19·1)	0·87 (0·63–1·22)	0·43
Non-positive	172/197	11·2 (9·9–13·0)	165/196	10·9 (9·1–12·5)	1·04 (0·84–1·29)	0·70
No bevacizumab by FISH						
Positive	112/121	8·7 (5·9–10·2)	99/112	11·2 (8·6–12·9)	0·77 (0·58–1·02)	0·066
Non-positive	237/259	8·1 (7·2–8·6)	235/261	8·4 (7·2–10·3)	0·97 (0·81–1·17)	0·76
Histology						
SCCA	150/161	8·0 (7·1–8·8)	148/160	9·6 (8·2–11·5)	0·85 (0·67–1·07)	0·17
Non-squamous	443/496	10·2 (9·0–11·2)	422/496	11·2 (9·6–12·5)	1·00 (0·85–1·17)	0·97
Histology by FISH						
SCCA						
Positive	53/56	6·1 (4·2–8·7)	52/55	11·8 (8·6–13·5)	0·58 (0·39–0·86)	0·0071
Non-positive	97/105	8·4 (7·2–9·9)	96/105	8·5 (6·4–10·4)	1·04 (0·78–1·40)	0·77
Non-squamous						
Positive	131/145	12·1 (9·7–13·8)	118/144	14·3 (11·4–17·7)	0·88 (0·68–1·14)	0·34
Non-positive	312/351	9·2 (8·5–10·8)	304/352	10·0 (8·4–11·7)	1·00 (0·85–1·17)	0·97
Total population	**593/657**	**9·2 (8·7–10·3)**	**570/656**	**10·9 (9·5–12·0)**	**0·93 (0·83–1·04)**	**0·22**

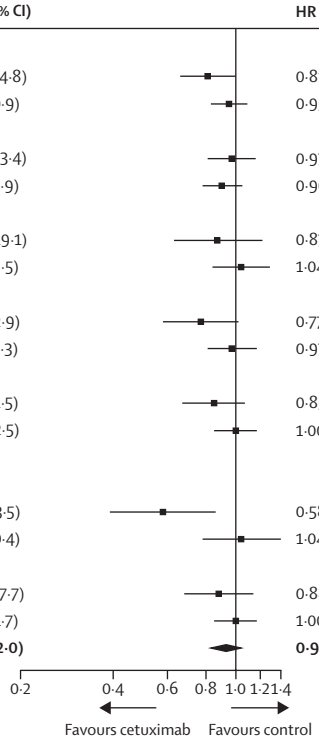


Figure 3: **Forest plots for progression-free survival (A) and overall survival (B)**
EGFR FISH non-positive includes *EGFR* FISH-negative and *EGFR* FISH status unknown. HR=hazard ratio. FISH=fluorescence in-situ hybridisation. SCCA=squamous cell carcinoma.

	All patients	*EGFR* FISH-positive	*EGFR* FISH-non-positive*
All patients			
Cetuximab group	257/617 (42%, 38–46)	87/187 (47%, 39–54)	170/430 (40%, 35–44)
Control group	227/623 (36%, 33–40)	82/191 (43%, 36–50)	145/432 (34%, 29–38)
p value	0·060	0·48	0·069
Bevacizumab			
Cetuximab group	126/266 (47%, 41–53)	44/83 (53%, 42–64)	82/183 (45%, 38–52)
Control group	118/255 (46%, 40–52)	46/75 (61%, 50–72)	72/180 (40%, 33–47)
p value	0·80	0·29	0·35
No bevacizumab			
Cetuximab group	131/351 (37%, 32–42)	43/104 (41%, 32–51)	88/247 (36%, 30–42)
Control group	109/368 (30%, 25–34)	36/116 (31%, 23–39)	73/252 (29%, 23–35)
p value	0·029	0·11	0·11
Squamous cell histology			
Cetuximab group	59/150 (39%, 32–47)	23/50 (46%, 32–60)	36/100 (36%, 27–45)
Control group	54/155 (35%, 27–42)	21/54 (39%, 26–52)	33/101 (33%, 24–42)
p value	0·42	0·46	0·62
Non-squamous histology			
Cetuximab group	198/467 (42%, 38–47)	64/137 (47%, 38–55)	134/330 (41%, 35–46)
Control group	173/468 (37%, 33–41)	61/137 (45%, 36–53)	112/331 (34%, 29–39)
p value	0·090	0·72	0·072

Data are n/N (objective response, 95% CI). FISH=fluorescence in-situ hybridisation. RECIST=Response Evaluation Criteria in Solid Tumors. *Includes *EGFR* FISH-negative and *EGFR* FISH status unknown.

Table 2: **Objective response in subsets of patients with measurable disease (per RECIST) at baseline**

to all of the data in the study and had final responsibility for the decision to submit for publication.

Results

From Aug 13, 2009, to May 30, 2014, we randomly assigned 1333 patients; after central review 20 patients were found ineligible, thus 1313 patients were assigned to receive either cetuximab plus chemotherapy (cetuximab group; n=656) or chemotherapy only (control group; n=657; figure 1). The median follow-up for patients last known to be alive was 35·2 months (IQR 22·9–39·9). Patient demographics and characteristics were similar between treatment groups (table 1). We evaluated specimens for *EGFR* FISH in 1190 (91%) patients and specimens from 1034 (87%) patients were adequate for testing. The FISH assay failed in specimens from 58 patients leaving 976 (94%) of 1034 patients with assessable specimens. Of these 976 specimens, 400 (41%) were *EGFR* FISH-positive (table 1). We classified the remaining 913 eligible patients as FISH non-positive (combination of *EGFR* FISH-negative and *EGFR* FISH status unknown).

Of 1313 patients eligible for treatment, 53 (4%) did not receive any protocol treatment and one patient (<1%) withdrew consent before being evaluated for toxicity; the resulting 1259 patients (96%; 627 in the cetuximab group and 632 in the control group) were evaluated for safety (figure 1). Major protocol deviations occurred in 135 patients (some had more than one deviation; 64 in the control group and 71 in the cetuximab group): in addition to the 53 patients who did not receive treatment, 51 were treated with bevacizumab when medically contraindicated, 23 had a carboplatin dosing error, and 16 others were considered to have protocol deviations for miscellaneous reasons (figure 1).

In patients with *EGFR* FISH-positive cancers, after 194 progression-free survival events in the cetuximab group and 198 in the control group progression-free survival did not differ between the treatment groups (HR 0·92, 95% CI 0·75–1·12; p=0·40; figure 2). The median progression-free survival was 5·4 months (95% CI 4·5–5·7) in the cetuximab group and 4·8 months (3·9–5·5) in the control group.

After 570 deaths in the cetuximab group and 593 in the control group, overall survival did not differ between the treatment groups in the entire study population (HR 0·93, 95% CI 0·83–1·04; p=0·22; figure 2). Median overall survival was 10·9 months (95% CI 9·5–12·0) in the cetuximab group versus 9·2 months (8·7–10·3) in the control group (figure 3). Additionally, progression-free survival did not differ between the treatment groups, nor did the objective response (figure 3, table 2). Overall survival in patients with *EGFR* FISH-positive cancers was significantly different between the treatment groups (figure 3). Objective response in patients with *EGFR* FISH-positive cancers did not differ between the treatment groups (table 2).

Bevacizumab treatment was not associated with overall survival, progression-free survival, or objective response in either the whole population or when patients were stratified by *EGFR* FISH status (figure 3, table 2).

254 (43%) of 594 patients who progressed in the control group and 257 (44%) of 590 in the cetuximab group reported receiving therapy after progression on this study. Postprogression therapy appears to be balanced between the treatment groups (data not shown).

In the subpopulation of patients with squamous cell histology, overall survival, progression-free survival, and objective response did not differ between the treatment groups (figure 3, table 2). In the prespecified analysis of *EGFR* FISH-positive subpopulation with squamous cell histology, overall survival was significantly longer in the cetuximab group than in the control group, although progression-free survival and objective response did not differ between treatment groups in this subgroup (figure 3, table 2). Among patients who were *EGFR* FISH non-positive with squamous cell histology, there were no differences in progression-free survival, overall survival, or objective response between treatment groups (figure 3, table 2). Additionally, overall survival, progression-free survival, and objective response were not different between treatment groups for patients with non-squamous histology regardless of *EGFR* FISH status (figure 3, table 2).

632 patients received protocol treatment in the control group, with 262 (41%) having at least one dose reduction of one of the drugs during the entire course of their protocol

	Cetuximab group with no bevacizumab (n=361)				Cetuximab group with bevacizumab (n=266)				Control group with no bevacizumab (n=365)				Control group with bevacizumab (n=267)			
	1–2	3	4	5	1–2	3	4	5	1–2	3	4	5	1–2	3	4	5
Haematological																
Haemoglobin*	180 (50%)	32 (9%)	5 (1%)	0	131 (49%)	10 (4%)	1 (<1%)	0	203 (56%)	30 (8%)	5 (1%)	0	144 (54%)	21 (8%)	4 (1%)	0
Neutrophils*	38 (11%)	62 (17%)	59 (16%)	0	47 (18%)	32 (12%)	57 (21%)	0	48 (13%)	38 (10%)	47 (13%)	0	41 (15%)	29 (11%)	44 (16%)	0
Platelets*	105 (29%)	12 (3%)	10 (3%)	0	76 (29%)	16 (6%)	5 (2%)	0	113 (31%)	22 (6%)	8 (2%)	0	100 (37%)	17 (6%)	4 (1%)	0
Leucocytes*	94 (26%)	57 (16%)	11 (3%)	0	76 (29%)	28 (11%)	7 (3%)	0	104 (28%)	31 (8%)	10 (3%)	0	73 (27%)	25 (9%)	8 (3%)	0
Lymphopenia	52 (14%)	30 (8%)	5 (1%)	0	39 (15%)	20 (8%)	5 (2%)	0	50 (14%)	21 (6%)	3 (<1%)	0	39 (15%)	12 (4%)	3 (1%)	0
Febrile neutropenia	0	14 (4%)	4 (1%)	0	0	9 (3%)	2 (<1%)	0	0	6 (2%)	3 (<1%)	2 (<1%)	0	13 (5%)	3 (1%)	0
Non-haematological																
Acne or rash	243 (67%)	19 (5%)	0	0	180 (68%)	33 (12%)	0	0	24 (7%)	1 (<1%)	0	0	31 (12%)	0	0	0
Fatigue	216 (60%)	36 (10%)	4 (1%)	0	152 (57%)	39 (15%)	2 (<1%)	0	209 (57%)	41 (11%)	1 (<1%)	0	181 (68%)	30 (11%)	2 (<1%)	0
Neuropathy sensory	178 (49%)	21 (6%)	0	0	134 (50%)	14 (5%)	0	0	152 (42%)	32 (9%)	2 (<1%)	0	157 (59%)	22 (8%)	1 (<1%)	0
Dermatology other†	199 (55%)	5 (1%)	0	0	163 (61%)	9 (3%)	0	0	173 (47%)	0	0	0	153 (57%)	0	0	0
Hypomagnesaemia	157 (43%)	13 (4%)	6 (2%)	0	143 (54%)	8 (3%)	1 (<1%)	0	93 (25%)	2 (<1%)	0	0	69 (26%)	1 (<1%)	3 (1%)	0
Nausea or vomiting	153 (42%)	19 (5%)	0	0	123 (46%)	13 (5%)	0	0	150 (41%)	11 (3%)	0	0	126 (47%)	17 (6%)	0	0
Myalgias	120 (33%)	13 (4%)	0	0	95 (36%)	17 (6%)	1 (<1%)	0	112 (31%)	23 (6%)	0	0	99 (37%)	21 (8%)	0	0
Anorexia	109 (30%)	15 (4%)	1 (<1%)	0	77 (29%)	9 (3%)	0	0	100 (27%)	13 (4%)	0	0	98 (37%)	9 (3%)	0	0
Mucositis	103 (29%)	4 (1%)	0	0	91 (34%)	6 (2%)	0	0	33 (9%)	2 (<1%)	0	0	59 (22%)	0	0	0
Diarrhoea	95 (26%)	13 (4%)	0	0	89 (33%)	5 (2%)	1 (<1%)	0	78 (21%)	7 (2%)	0	0	71 (27%)	8 (3%)	0	0
Constipation	121 (34%)	1 (<1%)	0	0	92 (35%)	3 (1%)	0	0	91 (25%)	3 (<1%)	0	0	88 (33%)	1 (<1%)	0	0
Lung haemorrhage	22 (6%)	1 (<1%)	0	1 (<1%)	74 (28%)	1 (<1%)	0	1 (<1%)	10 (3%)	1 (<1%)	0	1 (<1%)	63 (24%)	2 (<1%)	0	1 (<1%)
Hypertension	10 (3%)	1 (<1%)	1 (<1%)	0	35 (13%)	15 (6%)	0	0	10 (3%)	4 (1%)	0	0	51 (19%)	23 (9%)	1 (<1%)	0
Weight loss	79 (22%)	3 (<1%)	0	0	70 (26%)	1 (<1%)	0	0	61 (17%)	3 (<1%)	0	0	68 (25%)	5 (2%)	0	0
Hypokalaemia	72 (20%)	16 (4%)	4 (1%)	0	39 (15%)	14 (5%)	1 (<1%)	0	30 (8%)	12 (3%)	2 (<1%)	0	36 (13%)	6 (2%)	2 (<1%)	0
Pulmonary other†	55 (15%)	12 (3%)	4 (1%)	3 (<1%)	50 (19%)	13 (5%)	3 (1%)	1 (<1%)	51 (14%)	6 (2%)	2 (<1%)	4 (1%)	47 (18%)	9 (3%)	1 (<1%)	1 (<1%)
Taste alteration	76 (21%)	0	0	0	67 (25%)	0	0	0	58 (16%)	0	0	0	67 (25%)	0	0	0
Hypoalbuminaemia	87 (24%)	3 (<1%)	0	0	59 (22%)	4 (2%)	0	0	54 (15%)	7 (2%)	0	0	51 (19%)	1 (<1%)	0	0
Infection	43 (12%)	12 (3%)	8 (2%)	3 (<1%)	44 (17%)	16 (6%)	3 (1%)	2 (<1%)	19 (5%)	27 (7%)	2 (<1%)	3 (<1%)	24 (9%)	16 (6%)	1 (<1%)	0
Hyperglycaemia	61 (17%)	8 (2%)	1 (<1%)	0	56 (21%)	4 (2%)	0	0	60 (16%)	10 (3%)	1 (<1%)	0	56 (21%)	6 (2%)	3 (1%)	0
Alanine aminotransferase	51 (14%)	2 (<1%)	1 (<1%)	0	56 (21%)	4 (2%)	1 (<1%)	0	25 (7%)	3 (<1%)	0	0	23 (9%)	2 (<1%)	0	0
Hypocalcaemia	73 (20%)	7 (2%)	0	0	45 (17%)	1 (<1%)	0	0	34 (9%)	1 (<1%)	0	0	31 (12%)	0	0	0
Hyponatraemia	53 (15%)	12 (3%)	1 (<1%)	0	43 (16%)	12 (5%)	2 (<1%)	0	41 (11%)	12 (3%)	1 (<1%)	0	32 (12%)	14 (5%)	2 (<1%)	0
Aspartate aminotransferase	50 (14%)	2 (<1%)	1 (<1%)	0	51 (19%)	4 (2%)	1 (<1%)	0	24 (7%)	3 (<1%)	0	0	24 (9%)	3 (1%)	0	0
Pruritus	58 (16%)	3 (<1%)	0	0	47 (18%)	4 (2%)	0	0	14 (4%)	0	0	0	21 (8%)	0	0	0
Dizziness	52 (14%)	4 (1%)	0	0	47 (18%)	3 (1%)	0	0	42 (12%)	4 (1%)	1 (<1%)	0	31 (12%)	5 (2%)	0	0
Muscle weakness	34 (9%)	17 (5%)	2 (<1%)	0	35 (13%)	14 (5%)	0	0	35 (10%)	10 (3%)	1 (<1%)	0	32 (12%)	9 (3%)	1 (<1%)	0
Alkaline phosphatase	64 (18%)	0	0	0	46 (17%)	1 (<1%)	0	0	46 (13%)	2 (<1%)	0	0	32 (12%)	0	0	0
Cough	36 (10%)	2 (<1%)	0	0	43 (16%)	0	0	0	36 (10%)	1 (<1%)	0	0	30 (11%)	0	0	0
Allergic reaction	20 (6%)	16 (4%)	8 (2%)	0	24 (9%)	12 (5%)	5 (2%)	0	8 (2%)	6 (2%)	0	0	8 (3%)	2 (<1%)	1 (<1%)	0
Heartburn	40 (11%)	0	0	0	40 (15%)	1 (<1%)	0	0	19 (5%)	0	0	0	33 (12%)	0	0	0
Dehydration	34 (9%)	20 (6%)	0	0	28 (11%)	9 (3%)	2 (<1%)	0	34 (9%)	14 (4%)	1 (<1%)	0	27 (10%)	11 (4%)	1 (<1%)	0

(Table 3 continues on next page)

	Cetuximab group with no bevacizumab (n=361)				Cetuximab group with bevacizumab (n=266)				Control group with no bevacizumab (n=365)				Control group with bevacizumab (n=267)			
	1–2	3	4	5	1–2	3	4	5	1–2	3	4	5	1–2	3	4	5
(Continued from previous page)																
Thrombosis or embolism	3 (<1%)	4 (1%)	3 (<1%)	0	4 (2%)	16 (6%)	14 (5%)	2 (<1%)	1 (<1%)	4 (1%)	1 (<1%)	0	2 (<1%)	16 (6%)	5 (2%)	0
Proteinuria	6 (2%)	0	0	0	26 (10%)	5 (2%)	1 (<1%)	0	2 (<1%)	0	0	0	19 (7%)	4 (1%)	0	0
Neuropathy motor	34 (9%)	5 (1%)	0	0	18 (7%)	4 (2%)	0	0	18 (5%)	9 (2%)	0	0	19 (7%)	9 (3%)	0	0
Nail changes	36 (10%)	2 (<1%)	0	0	25 (9%)	2 (<1%)	0	0	10 (3%)	0	0	0	26 (10%)		0	0
Gastrointestinal pain	17 (5%)	5 (1%)	0	0	20 (8%)	6 (2%)	0	0	12 (3%)	2 (<1%)	0	0	14 (5%)	4 (1%)	0	0
Muscle weakness: low. extrem.	18 (5%)	6 (2%)	1 (<1%)	0	18 (7%)	2 (<1%)	0	0	18 (5%)	3 (<1%)	0	0	21 (8%)	3 (1%)	0	0
Cardiac other†	24 (7%)	5 (1%)	1 (<1%)	1 (<1%)	17 (6%)	1 (<1%)	4 (2%)	1 (<1%)	15 (4%)	3 (<1%)	1 (<1%)	1 (<1%)	10 (4%)	1 (<1%)	1 (<1%)	0
Gastrointestinal haemorrhage	3 (<1%)	2 (<1%)	0	0	10 (4%)	2 (<1%)	0	1 (<1%)	1 (<1%)	0	0	0	11 (4%)	4 (1%)	2 (<1%)	0
Cytokine-release syndrome	12 (3%)	3 (<1%)	3 (<1%)	0	12 (5%)	3 (1%)	0	1 (<1%)	8 (2%)	0	0	0	5 (2%)	0	0	0
Pneumonitis	0	3 (<1%)	0	0	4 (2%)	4 (2%)	1 (<1%)	0	0	1 (<1%)	0	0	1 (<1%)	1 (<1%)	0	0
Cardiac arrhythmia	6 (2%)	2 (<1%)	0	0	7 (3%)	0	1 (<1%)	0	6 (2%)	1 (<1%)	1 (<1%)	1 (<1%)	2 (<1%)	1 (<1%)	2 (<1%)	0
Hyperkalaemia	5 (1%)	0	2 (<1%)	0	6 (2%)	2 (<1%)	0	0	8 (2%)	1 (<1%)	0	0	7 (3%)	0	0	0
Confusion	2 (<1%)	2 (<1%)	1 (<1%)	0	7 (3%)	1 (<1%)	0	0	2 (<1%)	0	0	0	0	1 (<1%)	0	0
Ocular other†	2 (<1%)	0	0	0	7 (3%)	0	1 (<1%)	0	1 (<1%)	0	0	0	1 (<1%)	1 (<1%)	0	0
Hypoxia	4 (1%)	5 (1%)	1 (<1%)	0	2 (<1%)	0	0	0	1 (<1%)	2 (<1%)	0	0	0	0	0	0
Nasal or paranasal reactions	2 (<1%)	0	0	0	4 (2%)	0	1 (<1%)	0	1 (<1%)	0	0	0	6 (2%)	0	0	0
Death (not otherwise specified)	0	0	0	6 (2%)	0	0	0	5 (2%)	0	0	0	0	0	0	0	1 (<1%)
Gastrointestinal perforation	0	0	0	1 (<1%)	0	2 (<1%)	2 (<1%)	1 (<1%)	0	0	0	0	0	0	2 (<1%)	0
Gastrointestinal other†	4 (1%)	0	1 (<1%)	0	3 (1%)	0	1 (<1%)	1 (<1%)	4 (1%)	0	0	0	0	1 (<1%)	0	0
CNS ischaemia	0	1 (<1%)	0	0	1 (<1%)	0	2 (<1%)	1 (<1%)	0	0	0	0	0	1 (<1%)	0	1 (<1%)
Bronchospasm	3 (<1%)	0	0	0	2 (<1%)	0	2 (<1%)	0	1 (<1%)	0	0	0	3 (1%)	0	0	0
Hypoglycaemia	2 (<1%)	1 (<1%)	1 (<1%)	0	4 (2%)	0	0	0	1 (<1%)	2 (<1%)	0	0	3 (1%)	0	0	0
Neurology other†	3 (<1%)	1 (<1%)	0	1 (<1%)	2 (<1%)	0	0	0	3 (<1%)	0	0	0	2 (<1%)	0	0	0
Syndromes other†	2 (<1%)	0	2 (<1%)	0	0	0	0	0	1 (<1%)	0	0	0	0	0	0	0
Allergy other†	0	0	2 (<1%)	0	1 (<1%)	0	0	0	0	0	0	0	2 (<1%)	0	0	0
Gastrointestinal ulcer	0	1 (<1%)	1 (<1%)	0	1 (<1%)	0	0	0	0	0	0	0	1 (<1%)	0	1 (<1%)	0

(Table 3 continues on next page)

treatment, which included 142 (53%) of 267 patients receiving bevacizumab, and 120 (33%) of 365 patients not receiving bevacizumab. Of the 627 patients who received protocol treatment in the cetuximab group, 365 (58%) had at least one dose reduction of one of the drugs during the entire course of their protocol treatment, which included 188 (71%) of 266 patients receiving bevacizumab, and 177 (49%) of 361 patients not receiving bevacizumab. Patients who discontinued treatment for drug-related toxicity are summarised in figure 1, with detailed causes in the appendix (pp 8–9).

The most common grade 3–4 adverse events were decreased neutrophil count (210 [37%] of 627 patients in the cetuximab group *vs* 158 [25%] of 632 patients in the control group), decreased leucocyte count (103 [16%] *vs* 74 [20%]), fatigue (81 [13%] *vs* 74 [20%]), and acne or rash (52 [8%] *vs* one [<1%]; table 3). As expected, 76% of patients treated with cetuximab had some type of skin rash.

13 (2%) of 593 deaths in the control group were related to treatment: four due to infection or febrile neutropenia, two due to lung haemorrhage, one due to dyspnoea, one due to decreased carbon monoxide diffusing capacity (DLCO), one due to DLCO and respiratory failure, one due to respiratory failure, one due to dyspnoea, asystole, and cardiac arrest, one due to CNS ischaemia, and one for whom the exact cause of death could not be determined (table 3). An additional ten patients died due to adverse events unrelated to treatment. These included pneumonitis (n=1), pulmonary disease (n=3), cardiac disease (n=2), infection (n=1), perforation of the stomach (n=1), DLCO (n=1), aorta injury (n=1), and thrombosis or embolism with cardiac disease (n=1; one death attributed to two adverse events; appendix). The remaining 570 deaths in this treatment group were due to disease progression.

32 (6%) of 570 deaths in the cetuximab group were related to treatment: five due to infection, three due to haemorrhage, two due to perforation of the colon, two due to multiorgan failure, two due to DLCO, one due to respiratory failure, one due to cardiac arrest, one due to seizure, one due to a pneumoperitoneum, one due to thrombosis or embolism, one due to thrombosis or embolism in combination with other unidentifiable causes, one due to hypotension, one due to dyspnoea, one due to cytokine-release syndrome, one due to CNS ischaemia, and eight for whom the exact cause of death could not be determined (table 3). An additional 13 patients died due to adverse events unrelated to treatment. These included CNS ischaemia with cardiac ischaemia or infarction (n=1), DLCO (n=2), thrombosis or embolism (n=1), thrombotic microangiopathy (n=1), dyspnoea (n=2), cardiac disease (n=1), pleural effusion (n=2), lung haemorrhage (n=1), pulmonary disease (n=1), and aspiration (n=1; appendix). The remaining 525 deaths were due to disease progression.

Severe adverse events were defined as all deaths due to adverse events and any unexpected grade 4 adverse events related to treatment. 59 (9%) patients in the cetuximab group had severe adverse events, with allergic reaction

	Cetuximab group with no bevacizumab (n=361)				Cetuximab group with bevacizumab (n=266)				Control group with no bevacizumab (n=365)				Control group with bevacizumab (n=267)			
	1–2	3	4	5	1–2	3	4	5	1–2	3	4	5	1–2	3	4	5
(Continued from previous page)																
Hyperuricaemia	2 (<1%)	0	0	0	0	0	0	0	1 (<1%)	0	0	0	1 (<1%)	0	1 (<1%)	0
Aspiration	0	1 (<1%)	1 (<1%)	0	0	0	0	0	0	0	0	0	0	0	0	0
Pericardial effusion	1 (<1%)	0	1 (<1%)	0	0	0	0	0	0	0	0	0	0	0	0	0
Airway obstruction (bronchus)		0	0	0	0	0	0	0	1 (<1%)	0	1 (<1%)	0	0	0	0	0
Cardiopulmonary arrest	0	0	1 (<1%)	0	0	0	1 (<1%)	0	0	0	0	0	0	0	1 (<1%)	0
Adrenal insufficiency	0	0	1 (<1%)	0	1 (<1%)	0	0	0	0	0	0	0	0	0	0	0
Colitis	0	0	1 (<1%)	0	0	1 (<1%)	0	0	0	0	0	0	0	0	0	0
Cardiac ischaemia or infarction		0	1 (<1%)	0	0	0	0	0	0	0	0	0	0	0	1 (<1%)	0
Visceral arterial ischaemia	0	0	1 (<1%)	0	0	0	0	0	0	0	0	0	0	0	0	0
Maximum grade for any adverse event	96 (27%)	143 (40%)	97 (27%)	16 (4%)	43 (16%)	119 (45%)	84 (32%)	16 (6%)	133 (36%)	137 (38%)	66 (18%)	9 (2%)	79 (30%)	110 (41%)	70 (26%)	4 (1%)

Treatment-related adverse events, excluding events with maximum grade of 3 or lower and occurring in less than 10% of patients. One patient receiving cetuximab, bevacizumab, and chemotherapy had syncope of unknown grade. *Decreased count. †Adverse event for which there is no matching Common Terminology Criteria for Adverse Events term.

Table 3: **Treatment-related adverse events by grade**

(n=8) and death (n=11) being the most common and 31 (5%) patients in the control group had severe adverse events with pulmonary (n=6) and febrile neutropenia (n=5) being the most common (appendix pp 6–7).

Discussion

In this randomised, multicentre, open-label, phase 3 trial investigating the addition of cetuximab to standard chemotherapy in patients with advanced NSCLC did not meet its co-primary objectives of increasing progression-free survival in patients with *EGFR* FISH-positive cancers or overall survival in the entire population. The scientific premise of this study the hypothesis, based on previous preclinical and clinical data, that EGFR antibodies (as opposed to EGFR TKIs) synergise with chemotherapy, and that this synergy is enhanced in patients with *EGFR* FISH-positive cancers.[5,10,11]

The EGFR pathway plays a part in *EGFR* non-mutated NSCLC, as evidenced by the small benefit of erlotinib versus placebo in the second-line and third-line treatment settings.[3] However, when EGFR TKIs were evaluated concurrently with chemotherapy in previously untreated patients, no clinical benefit was seen.[7,19] EGFR monoclonal antibodies represent alternatives for EGFR inhibition in EGFR non-mutated NSCLC due to additional effects on receptor internalisation and antibody-dependent cellular toxicity not seen with EGFR TKIs.[20,21] Cetuximab has produced favourable efficacy in combination with platinum-based chemotherapy in studies of early lung cancer and is well recognised for its activity in combination with chemotherapy or radiotherapy in other tumour types, such as colorectal cancer and head and neck cancer.[22] It also has favourable efficacy in combination with platinum-based chemotherapy in several early-phase trials in NSCLC.[20] Two NSCLC phase 3 trials investigating chemotherapy plus cetuximab showed contradictory results: the FLEX trial[9] met its primary overall survival endpoint (ie, survival for combination was longer than chemotherapy alone), while the BMS-099 trial[8] did not meet its primary progression-free survival endpoint (ie, survival for combination was not longer than chemotherapy alone). A meta-analysis[23] of cetuximab trials in NSCLC concluded that the addition of cetuximab to a platinum doublet significantly improved the objective response, progression-free survival, and overall survival compared with the platinum doublet alone with a manageable toxicity profile. Of additional interest, in the FLEX trial[24] the greatest benefit in overall survival was achieved in those patients with tumours with squamous cell histology, especially those patients with high EGFR protein expression. Although squamous cell NSCLC rarely harbours *EGFR* mutation, it is known to have a high incidence of EGFR overexpression. Following this observation, a recently completed phase 3 trial (SQUIRE)[18] in advanced stage squamous cell lung cancer of gemcitabine-cisplatin with or without the newer EGFR monoclonal antibody necitumumab also showed improved overall survival in the necitumumab group versus the chemotherapy alone group, resulting in approval of this regimen in the USA and Europe.

To our knowledge, the current trial, S0819, is the largest study to definitively evaluate the role of cetuximab in patients with *EGFR* FISH-positive NSCLC and in unselected patients with advanced NSCLC. In the unselected patient population, overall survival was similar between the treatment groups. The median overall survival and progression-free survival were similar to those in the BMS-099 trial. These results might have been predictable given that no so-called all-comer front-line, randomised, phase 3 trial of chemotherapy plus a targeted drug has shown a survival advantage with the exception of the modest survival benefit with bevacizumab plus paclitaxel and carboplatin shown in the E4599 trial.[15] Building on this triplet therapy, the S0536 trial sought to evaluate whether the addition of cetuximab to this regimen would be safe and enhance efficacy.[14] S0536 did show a non-overlapping and manageable toxicity profile coupled with a higher objective response, progression-free survival, and overall survival with the quadruple regimen compared with the triplet therapy garnering further support for cetuximab as an active drug in the treatment of lung cancer. However, our study did not show a survival benefit of the four-drug regimen compared with chemotherapy (with or without bevacizumab) alone. The highly selected patient population enrolled in S0536 might have accounted for the positive findings, which were not confirmed in this larger randomised trial. In our study, a total of 560 (43%) patients received chemotherapy and bevacizumab with or without cetuximab.

Success with targeted therapies in lung cancer is largely attributable to identifying a predictive biomarker; therefore, incorporating a biomarker-driven co-primary endpoint was essential to this study. As such, and to the best of our knowledge, S0819 is the first cooperative group, phase 3 trial to use this strategy. *EGFR* FISH-positivity was selected as a promising predictive biomarker of outcome for the treatment of advanced NSCLC with EGFR inhibitors based on several trials.[16,25,26] In the Canadian phase 3 BR.21 study,[26] which compared erlotinib with placebo in patients whose disease progressed despite chemotherapy, the authors found significant associations between objective response and polysomy or amplification of *EGFR*. A similar result was ascertained from the phase 3 FLEX study,[25] which showed a significant benefit of cetuximab in addition to cisplatin and vinorelbine chemotherapy in extending survival in patients whose cancers exhibited high levels of EGFR. As mentioned earlier, *EGFR* FISH-positivity was associated with significantly longer median overall survival and progression-free survival in patients treated with cetuximab, carboplatin, and paclitaxel in S0342.[13,26–30]

Tissue acquisition was critical for our study and efforts aimed at improving its quality were central to this

protocol. Of all tissue specimens received, 91% were determined to be in usable condition, 87% were analysable for *EGFR* FISH, and the assay was successful in 94% of specimens. Specific efforts were made to improve the attainment of usable and analysable tissue over the course of study. A separate manuscript is in development to describe these efforts and their impact.

Although *EGFR* FISH was not a predictive marker for the overall patient population in our study, we identified a subpopulation of patients with squamous cell histology in which *EGFR* FISH-positivity predicted a beneficial response to treatment with cetuximab. As previously stated, squamous cell histology is known to have a high incidence of EGFR expression.[28] In this select group of patients, the addition of cetuximab to chemotherapy improved overall survival compared with chemotherapy alone (HR 0·58, 95% CI 0·39–0·86; p=0·0071). These results are very similar to the results observed in the *EGFR* FISH-positive cohort in the SQUIRE trial[18] comparing necitumumab plus gemcitabine and cisplatin with gemcitabine and cisplatin alone (HR 0·79, 95% CI 0·69–0·92; p=0·002 for overall survival; and HR 0·84, 95% CI 0·72–0·97; p=0·018 for progression-free survival) in which *EGFR* FISH was assessed by the same method in the same laboratory as our study. These findings indicate a different predictive mechanism for EGFR monoclonal antibodies compared with EGFR TKIs that could be beneficial in distinct biological subsets.

Cetuximab treatment was associated with an increase in grade 3 or worse adverse events for acne or rash and allergic reaction. However, the safety profile was similar to that reported in other phase 3 trials[8,9] of cetuximab treatment. With respect to the quadruple drug combination, the addition of bevacizumab did increase cetuximab toxicity with regard to some events, including fatigue, acne or rash, thrombosis or embolism, hypertension, and myalgias. Future clinical trials that investigate combinations with immune checkpoint inhibitors would be an important next step for these drugs. Potential limitations of this study are that it was designed and done with cetuximab before data for the fully humanised antibody necitumumab were available that recognised EGFR monoclonal antibodies as likely to be best directed against squamous cell lung cancer.

In summary, the addition of cetuximab to platinum-based chemotherapy with or without bevacizumab had no clinically significant benefit in patients with *EGFR* FISH-positive cancers or in the intention-to-treat patient population. The observation in the subset of patients with *EGFR* FISH-positive squamous cell carcinoma highlights the need to further characterise subpopulations of patients who might benefit from EGFR-inhibitor therapies in the chemotherapy-naive advanced NSCLC setting.

Contributors

RSH, MWR, JM, PCM, KO, DRG, TJS, ESK, and FRH contributed to study design. RSH, MWR, JM, KK, PG, PCM, DRG, LB, AK, ESK, and CDB contributed to writing the Article. MWR and JM prepared figures, RSH, MWR, JM, PCM, SMA, CR, DRG, LB, ESK, and MV-G contributed to data collection. RSH, MWR, JM, PCM, SMA, CR, DRG, AK, TJS, GM, ESK, FRH, CDB, MV-G, and KK contributed to data analysis. RSH, MWR, JM, PG, PCM, KO, SMA, CR, DRG, LB, AK, TJS, ESK, FRH, CDB, MV-G, and KK contributed to data interpretation. FRH was responsible for analysing the biomarkers. RSH, PG, KO, SMA, CR, DRG, LB, GM, ESK, KK, and TJS contributed to provision of study materials and patients. All authors contributed to critical review, editing and revision of manuscript draft, and approval of the final version.

Declaration of interests

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