Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study

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Summary

Background First-line chemotherapy for advanced non-small-cell lung cancer (NSCLC) is usually limited to four to six cycles. Maintenance therapy can delay progression and prolong survival. The oral epidermal growth factor receptor (EGFR) tyrosine-kinase inhibitor erlotinib has proven efficacy and tolerability in second-line NSCLC. We designed the phase 3, placebo-controlled Sequential Tarceva in Unresectable NSCLC (SATURN; BO18192) study to assess use of erlotinib as maintenance therapy in patients with non-progressive disease following first-line platinum-doublet chemotherapy.

Methods Between December, 2005, and May, 2008, 1949 patients were included in the run-in phase (four cycles of platinum-based chemotherapy). At the end of the run-in phase, 889 patients who did not have progressive disease were entered into the main study, and were randomly allocated using a 1:1 adaptive randomisation method through a third-party interactive voice response system to receive erlotinib (150 mg/day; n=438) or placebo (n=451) until progression or unacceptable toxicity. Patients were stratified by EGFR immunohistochemistry status, stage, Eastern Cooperative Oncology Group performance status, chemotherapy regimen, smoking history, and region. Co-primary endpoints were progression-free survival (PFS) in all analysable patients irrespective of EGFR status, and PFS in patients whose tumours had EGFR protein overexpression, as determined by immunohistochemistry. This study is registered with www.ClinicalTrials.gov, number NCT00556712.

Findings 884 patients were analysable for PFS; 437 in the erlotinib group and 447 in the placebo group. After a median follow-up of 11·4 months for the erlotinib group and 11·5 months for the placebo group, median PFS was significantly longer with erlotinib than with placebo: 12·3 weeks for patients in the erlotinib group versus 11·1 weeks for those in the placebo group (HR 0·71, 95% CI 0·62–0·82; p<0·0001). PFS was also significantly longer in patients with EGFR-positive immunohistochemistry who were treated with erlotinib (n=307) compared with EGFR-positive patients given placebo (n=311; median PFS 12·3 weeks in the erlotinib group *vs* 11·1 weeks in the placebo group; HR 0·69, 0·58–0·82; p<0·0001). The most common grade 3 or higher adverse events were rash (37 [9%] of 443 patients in the erlotinib group *vs* none of 445 in the placebo group) and diarrhoea (seven [2%] of 443 patients *vs* none of 445). Serious adverse events were reported in 47 patients (11%) on erlotinib compared with 34 patients (8%) on placebo. The most common serious adverse event was pneumonia (seven cases [2%] with erlotinib and four [<1%] with placebo).

Interpretation Maintenance therapy with erlotinib for patients with NSCLC is well tolerated and significantly prolongs PFS compared with placebo. First-line maintenance with erlotinib could be considered in patients who do not progress after four cycles of chemotherapy.

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Introduction

Non-small-cell lung cancer (NSCLC) accounts for most cases of lung cancer, and is often diagnosed at an advanced stage when treatment options are limited. First-line treatment of advanced NSCLC is based on the backbone of platinum-doublet chemotherapy, with a median overall survival of 8–11 months.[1]

Although around 70 to 80% of patients who receive first-line chemotherapy will experience clinical benefit in terms of response or stable disease,[2–5] subsequent disease progression is often rapid, with most patients experiencing progressive disease within 2–3 months of their final chemotherapy cycle.[3,6,7] Several trials have investigated prolonged-duration platinum-based chemotherapy in the first-line setting, but longer treatment periods had modest or no incremental overall survival benefit and increased toxicity.[8–13]

Second-line treatments are indicated after disease progression, but studies suggest that around 30–50% of patients do not receive second-line therapy.[3,6–11,14–17] Rapid progression, declining performance status, and increased symptom burden can render patients unsuitable to receive further treatment.[7] This means that a large proportion of patients might lose the opportunity to receive effective therapy after first-line treatment. The effect of active maintenance therapy on disease

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progression when introduced immediately after first-line platinum-doublet chemotherapy has therefore been investigated for patients with advanced NSCLC.[17] A precedent already exists for this approach, with first-line biological agents such as bevacizumab and cetuximab being continued until disease progression.[2,15,18] Recent trials of maintenance chemotherapy given immediately after first-line treatment regimens have shown improvements in progression-free survival (PFS)[6,7] and overall survival.[6]

The oral epidermal growth factor receptor (EGFR) tyrosine-kinase inhibitor (TKI) erlotinib is an established second-line treatment for advanced NSCLC.[19,20] Significant improvements in overall survival, time to symptom deterioration, and quality of life (QoL) were noted with erlotinib versus placebo in patients who had received at least one previous line of therapy,[21,22] with similar efficacy to second-line chemotherapy.[23] Erlotinib has shown efficacy in a broad patient population, regardless of age, sex, ethnic origin, or histology, with benefits in both adenocarcinoma and squamous-cell carcinoma.[21] A first-line trial of erlotinib with concurrent chemotherapy showed a significantly increased ($p=0\cdot045$) duration of response among patients receiving erlotinib in combination with chemotherapy followed by maintenance erlotinib (compared with placebo in combination and maintenance).[24] This proven efficacy, combined with oral administration and acceptable tolerability, make erlotinib a strong candidate for investigation in the maintenance setting.

See Online for webappendix

We designed the phase 3, placebo-controlled Sequential Tarceva in Unresectable NSCLC (SATURN; BO18192) study to investigate the effect of erlotinib as maintenance therapy on PFS in patients with non-progressive disease following first-line platinum-doublet chemotherapy. We assessed PFS in the overall population and in patients with tumours that over-express EGFR.

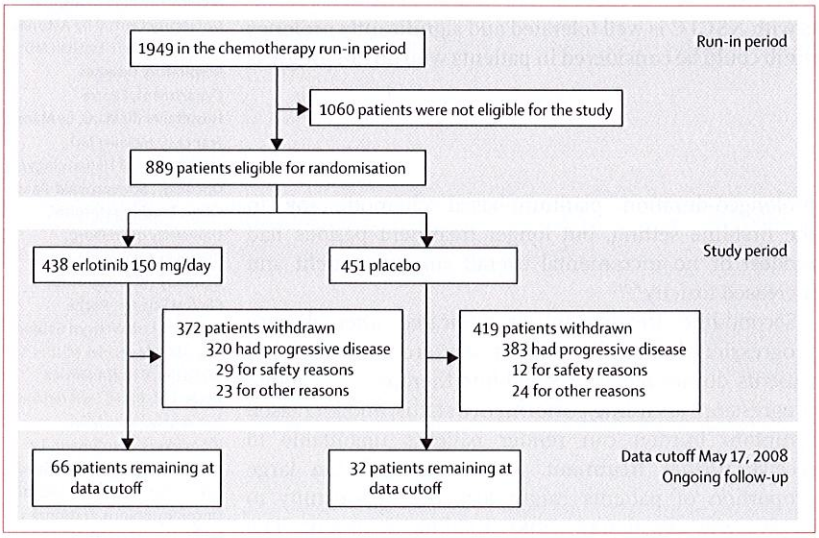

Figure 1: Trial design and profile

Methods

Patients

The SATURN study was done at 110 sites in 26 countries. Patients entering the chemotherapy run-in phase of the study had to be aged 18 years or over, with histologically documented, measurable (according to Response Evaluation Criteria In Solid Tumours [RECIST] 1.0[25]), unresectable or metastatic NSCLC. The main exclusion criteria were previous exposure to anti-EGFR agents; uncontrolled, symptomatic brain metastases; and any other malignancies within the previous 5 years (excluding carcinoma in situ; for full inclusion and exclusion experience see webappendix).

Following initial screening and enrolment, patients received four cycles of platinum-doublet chemotherapy (the investigator could select one of seven standard chemotherapy regimens). In the absence of unacceptable toxicity, patients who met the following criteria—completion of four cycles of standard platinum-doublet chemotherapy without disease progression (ie, complete response, partial response, or stable disease); Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; adequate renal, hepatic, and haematological function; a negative pregnancy test for females of child-bearing age—were randomly allocated to receive oral erlotinib 150 mg/day or placebo until disease progression, unacceptable toxicity, or death.

The study was done in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The protocol was approved by local ethics committees at each investigating centre. All enrolled patients gave informed written consent, both for study participation and the provision of tumour samples.

Randomisation and masking

Randomisation was done using a 1:1 adaptive randomisation method (using minimisation as proposed by Pocock and Simon[26]) via a third-party interactive voice response system. Patients were stratified by EGFR immunohistochemistry status (positive; negative; indeterminate), disease stage (IIIB; IV), ECOG performance status (0; 1), chemotherapy regimen (cisplatin and gemcitabine; carboplatin and docetaxel; other), smoking history (current; former; never smokers) and region (North America, South America, western Europe, eastern Europe, southeast Asia, and Africa). The randomisation list was not made available to the study centres, trial monitors, statisticians, or study sponsor.

Procedures

Collection of tumour tissue for biomarker assessment was mandatory at screening. EGFR immunohistochemistry status was determined using the Dako EGFR pharmDx kit (DakoCytomation, Glostrup, Denmark); tumours were considered EGFR immunohistochemistry-positive if 10% or more of tumour cells showed membranous staining of any intensity. *EGFR* mutation

analyses were done using DNA lysates from macrodissected or microdissected tissue samples with a minimum tumour-cell content of 60%. Exons 18–21 of the *EGFR* gene were amplified by PCR using nested primers, and multiple independent products were sequenced on both strands. Mutations had to be confirmed on both strands of at least two PCR products.

Baseline characteristics were collected at the time of randomisation (ie, following completion of the initial chemotherapy phase). Asian ethnic origin included patients from both the east Asian and southeast Asian region, and the Indian subcontinent. Smoking status was analysed as follows: patients who had smoked less than 100 cigarettes in their lifetime were designated never smokers; those who had smoked 100 or more cigarettes but had not smoked within the last year were classed as former smokers; the remaining patients were classed as current smokers.

Tumour assessments were done by CT scan, spiral CT scan, or MRI at initial screening, after completion of chemotherapy (study baseline), then at 6-week intervals until week 48, and every 12 weeks thereafter; assessments ceased after confirmation of disease progression. Tumour response was classified by RECIST 1.0.

Adverse events and serious adverse events were classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0. QoL was assessed using the Functional Assessment of Cancer Therapy–Lung (FACT–L) questionnaire at 6-week intervals until week 48, and every 12 weeks thereafter. In case of adverse events, dose reductions (in decrements of 50 mg) and interruptions (for ≤2 weeks) were permitted, at the investigator's discretion. On disease progression, the choice of further therapy was at the investigator's discretion, and unblinding was permitted only if the investigator judged that an EGFR TKI was the only possible second-line treatment option. The sponsor remained blinded to this information.

Statistical analysis

The co-primary endpoints were PFS in all analysable patients irrespective of EGFR status, and PFS in patients with EGFR immunohistochemistry-positive tumours. Assessment of PFS considered both objective progression and clinical progression, and a two-sided log-rank test was used for a basic comparison of the two treatment groups (erlotinib versus placebo). Median PFS was estimated by the Kaplan-Meier method. Hazard ratios (HRs) and 95% CI were estimated using Cox regression analysis. Statistical analyses were done using SAS (version 8.2).

The alpha level of 5% was split between the two co-primary endpoints: 3% for all patients and 2% for patients with EGFR immunohistochemistry-positive tumours. A total of 731 events were required to detect a HR of 0·8 for erlotinib versus placebo, with 80% power at a two-sided 3% significance level. Assuming an 18-month accrual period, 6-month follow-up, and a 5% dropout rate, this required 427 patients per group in the maintenance phase of the study. A dropout rate of 50% was assumed between the start of chemotherapy and randomisation, meaning that 854 patients needed to be screened per group. The trial was controlled for alpha-spend due to interim analysis (for efficacy at approximately 54% of required

	Erlotinib (N=438)	Placebo (N=451)
Median age (range; years)	60·0 (33–83)	60·0 (30–81)
Sex		
Male	321 (73)	338 (75)
Female	117 (27)	113 (25)
Stage		
IIIB	116 (26)	109 (24)
IV	322 (74)	342 (76)
Ethnic origin		
Caucasian	370 (84)	376 (83)
Asian	62 (14)	69 (15)
Other	6 (1)	6 (1)
ECOG performance status		
0	135 (31)	145 (32)
1	303 (69)	306 (68)
Smoking status		
Current smoker	239 (55)	254 (56)
Former smoker	122 (28)	122 (27)
Never smoker	77 (18)	75 (17)
Histology		
Adenocarcinoma/bronchoalveolar carcinoma	205 (47)	198 (44)
Squamous-cell carcinoma	166 (38)	194 (43)
Other	67 (15)	59 (13)
Response to previous chemotherapy		
Complete response	1 (<1)	1 (<1)
Partial response	183 (42)	209 (47)
Stable disease	252 (58)	235 (52)
Other/unknown	2 (<1)	6 (1)
EGFR IHC status		
Positive	308 (70)	313 (69)
Negative	62 (14)	59 (13)
Indeterminate	16 (4)	24 (5)
Missing	52 (12)	55 (12)
EGFR mutation status		
Activating mutation	22 (5)	27 (6)
Other mutation (including resistance mutations)	7 (2)	2 (<1)
Wild-type	199 (45)	189 (42)
Indeterminate	33 (8)	39 (9)
Missing	177 (40)	194 (43)

Data are n (%) unless stated otherwise. ECOG=Eastern Cooperative Oncology Group. IHC=immunohistochemistry.

Table 1: **Baseline characteristics of the overall population (maintenance phase)**

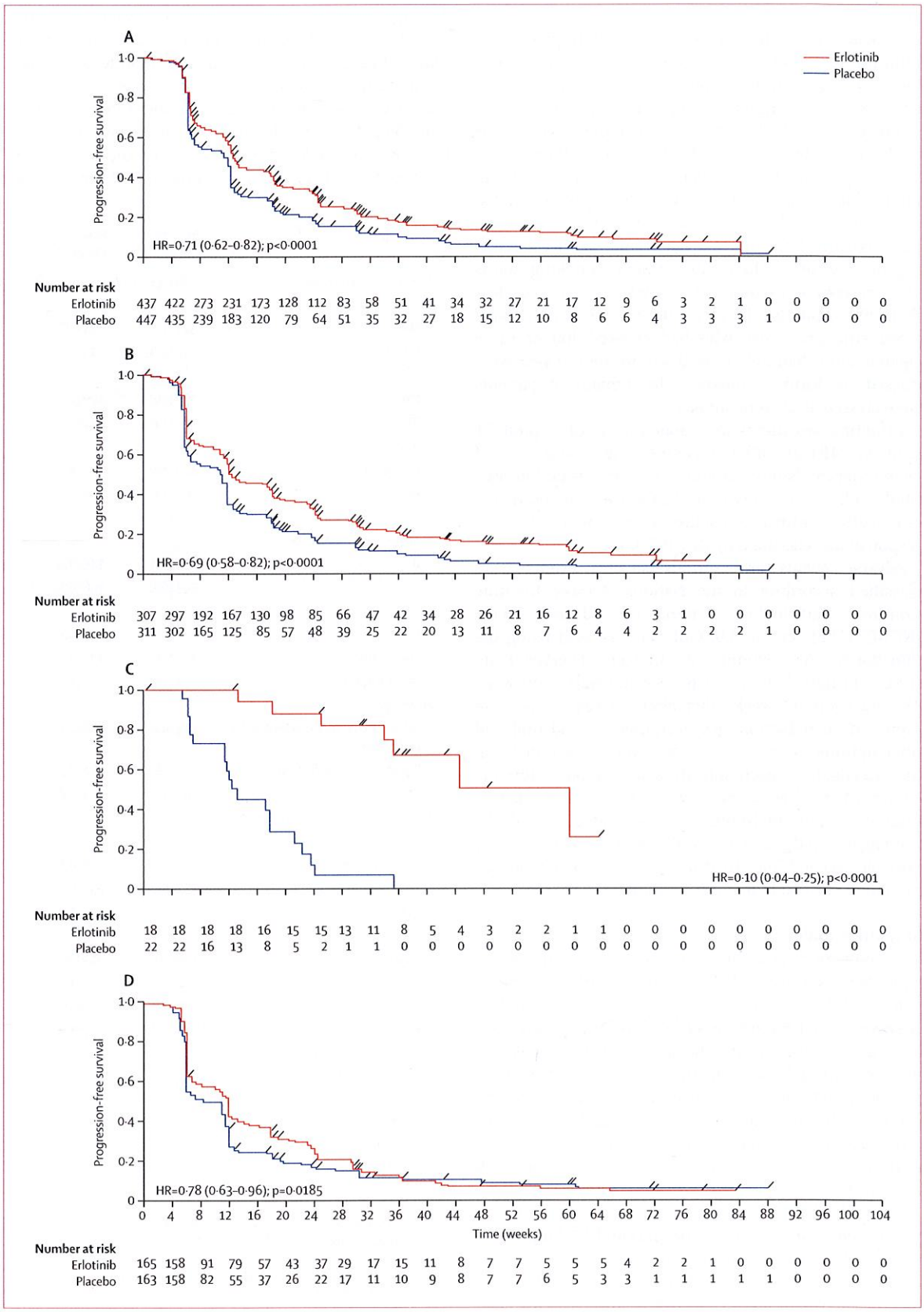

Figure 2: Kaplan-Meier estimates of progression-free survival in the intention-to-treat population (A), progression-free survival in patients with EGFR immunohistochemistry-positive tumours (B), progression-free survival in patients with *EGFR* mutation-positive tumours (C), and progression-free survival in patients with *EGFR* wild-type tumours (D)

PFS events in the intention-to-treat population) by the Lan–DeMets alpha-spending function with an O'Brien–Fleming boundary. An independent data safety monitoring board reviewed safety data every 3 months, and reviewed interim efficacy and safety analyses. The sponsor remained blinded to the treatment groups until the primary PFS analysis was complete. At the interim analysis, the data safety monitoring board recommended to continue the trial.

Secondary endpoints were overall survival in the intention-to-treat population and in patients with EGFR immunohistochemistry-positive tumours; PFS in patients with EGFR-negative tumours; time to progression (TTP); tumour response; time to deterioration of symptoms, and QoL. All time-to-event endpoints were measured from randomisation. For overall survival, TTP, time to symptom deterioration, QoL, and PFS in the EGFR-negative subgroup, two-sided log-rank tests were used to compare the treatment groups. Estimates of the treatment effect were expressed as HRs including 95% CI, which were estimated by the Kaplan-Meier method. Best response in each treatment group was summarised by presenting the rate and 95% CI according to Pearson–Clopper for each response category.

Pre-planned analyses of PFS according to predefined clinical subgroups and candidate biomarkers were also carried out.

This study is registered with the ClinicalTrials.gov, number NCT00556712.

Role of the funding source

This trial was designed and funded by the study sponsor and monitored by a clinical research organisation (Covance, Basel, Switzerland). Data were collected by the clinical research organisation and all data analysis and interpretation was done by the trial sponsor, with input from the authors and investigators. The initial draft of the manuscript was reviewed and commented on by all authors, and by employees of F Hoffmann-La Roche. The corresponding author had full access to the study data and took full responsibility for the final decision to submit the paper.

Results

The study design and trial profile are shown in figure 1. Between December, 2005, and May, 2008, 1949 patients were screened and received first-line platinum doublet chemotherapy. The specific regimen used was at the discretion of individual investigators and reflective of normal clinical practice, with the exception that bevacizumab and pemetrexed were not permitted. Details of regimens were not recorded for the pre-randomisation population; however, the most common regimens recorded among the 878 patients in the safety analysis population were carboplatin plus gemcitabine (252 patients; 29%), cisplatin plus gemcitabine (235 patients; 27%) and carboplatin plus paclitaxel (165 patients; 19%). Following

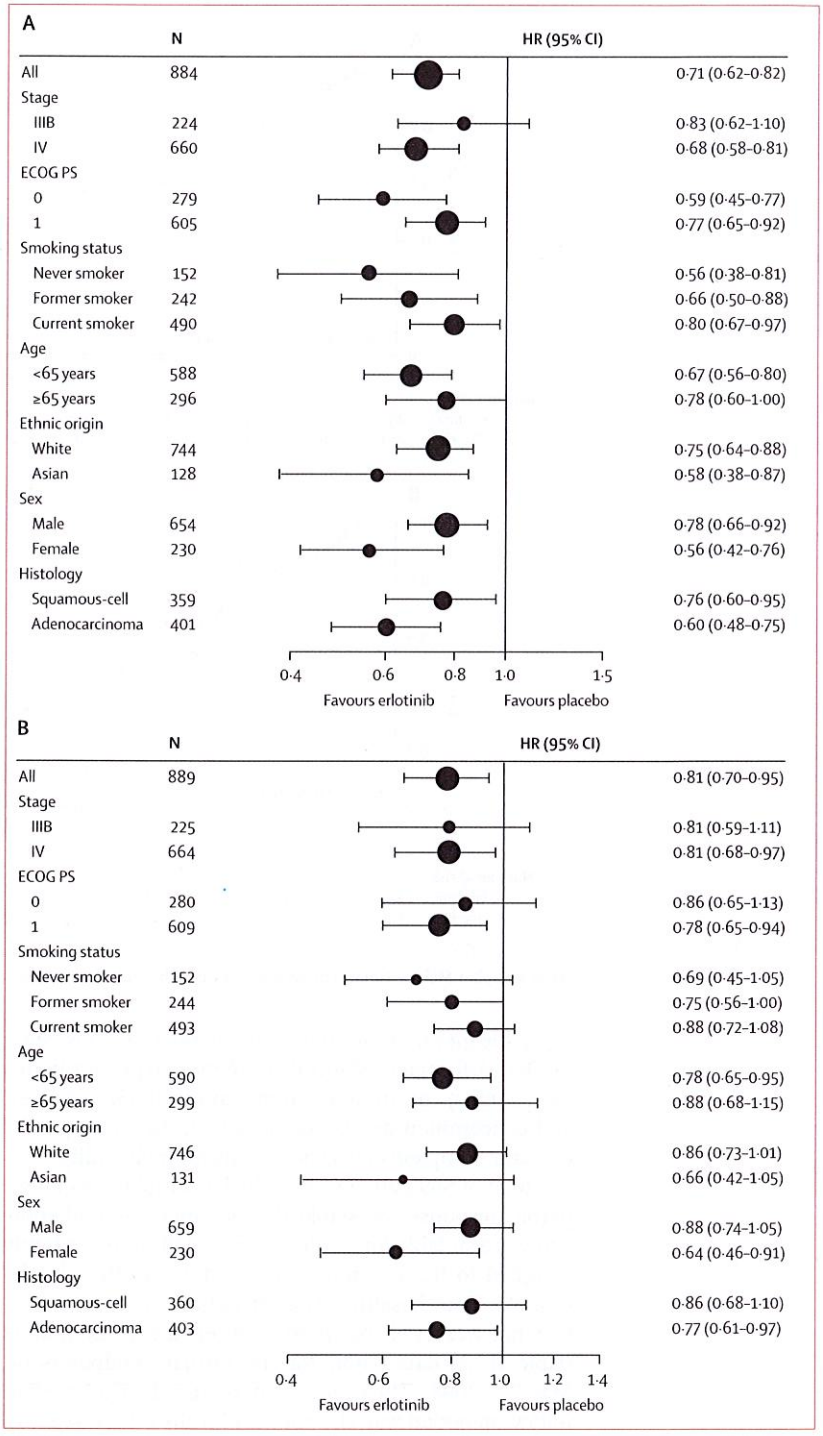

Figure 3: **Subgroup analyses of progression-free survival (A) and overall survival (B)**
For progression-free survival, only the interactions between treatment effect and ethnic origin (p=0·01) and treatment effect and sex (p=0·04) were significant. For overall survival, only the interaction between treatment effect and ethnic origin (p=0·03) was significant. The size of the circles are proportional to the number of patients in each group. HR=hazard ratio. ECOG=Eastern Cooperative Oncology Group.

first-line chemotherapy, 428 patients (22%) had progressive disease, 162 (8%) had died and 89 (5%) withdrew consent to participate in the study. 381 patients (20%) were

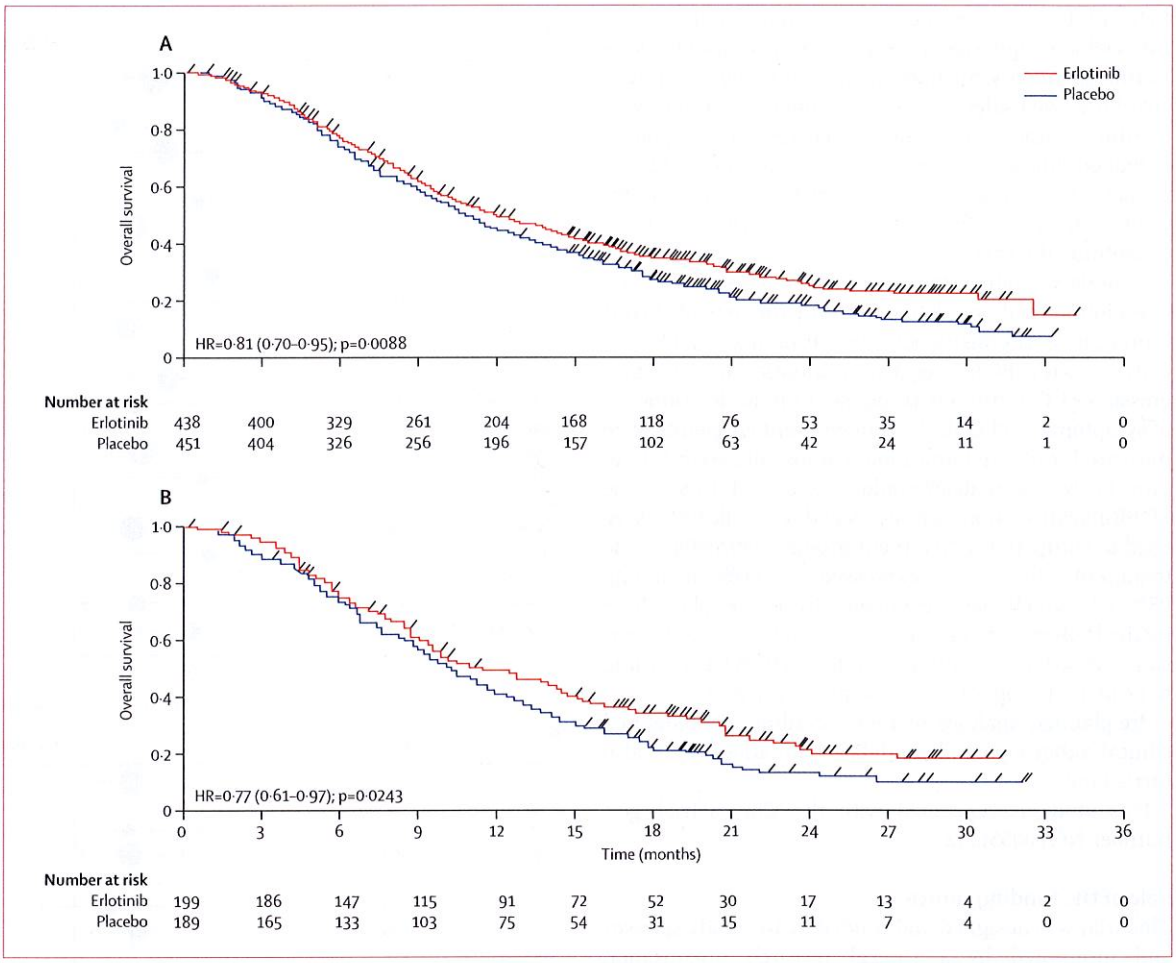

Figure 4: Kaplan-Meier estimates of overall survival in the intention-to-treat population (A) and in patients with EGFR wild-type tumours (B)

ineligible for randomisation, with the main reasons being ECOG performance status deterioration to greater than 1 (90 patients), no tumour sample available (37 patients), and concomitant disease (26 patients); the webappendix contains complete details of reasons for ineligibility.

A total of 889 patients (45%) had a complete response, partial response, or stable disease after chemotherapy and were suitable for randomisation; 438 were randomly assigned to the erlotinib group and 451 to the placebo group). The baseline characteristics of randomised patients were well balanced between the study groups (table 1). At data cutoff for the primary endpoints on May 17, 2008, 749 events had occurred. The median follow-up period was 11·4 months for the erlotinib group and 11·5 months for the placebo group.

Five patients progressed before randomisation, and were not included in the PFS analysis. Overall, 884 patients were analysable for PFS; 437 in the erlotinib group and 447 in the placebo group. PFS was significantly prolonged with erlotinib versus placebo in all analysable patients, irrespective of EFGR status (median PFS 12·3 *vs* 11·1 weeks; HR 0·71, 95% CI 0·62–0·82; p<0·0001; figure 2A), and in patients with EGFR immunohistochemistry-positive tumours (median PFS 12·3 *vs* 11·1 weeks; HR 0·69, 0·58–0·82; p<0·0001; figure 2B). At 6 months, 83 patients receiving erlotinib versus 53 patients receiving placebo were still at risk for progression (ie, were still ongoing in the trial and had not yet experienced progressive disease or death). The proportion of patients with PFS at 6 months was 25% (95% CI 21%–29%) in patients receiving erlotinib, versus 15% (95% CI 12%–19%) in those receiving placebo. Biomarker analysis for *EGFR* mutation status showed that erlotinib was active in patients with *EGFR*-activating mutations (HR 0·10, 0·04–0·25; p<0·0001; figure 2C) and in those with wild-type *EGFR* (HR 0·78, 0·63–0·96; p=0·0185; figure 2D).[27] Subgroup analyses of PFS by clinical characteristics also suggested improved PFS with erlotinib compared with placebo across subgroups; of note, this benefit was seen irrespective of histology (figure 3).

Best tumour response rate (ie, complete response plus partial response) was 11·9% (52 patients) with erlotinib versus 5·4% (24 patients) with placebo (p=0·0006). Additionally, the 12-week disease control rate (complete response, partial response, or stable disease maintained

for more than 12 weeks) was 40·8% (178 patients) with erlotinib compared with 27·4% (122 patients) with placebo (p<0·0001).

Overall survival was significantly prolonged with erlotinib versus placebo in the intention-to-treat population (median 12·0 *vs* 11·0 months; HR 0·81, 95% CI 0·70–0·95; p=0·0088; figure 4A) and the EGFR immunohistochemistry-positive population (HR 0·77, 0·64–0·93; p=0·0063), as well as in patients whose tumours did not harbour activating *EGFR* mutations (HR 0·77, 0·61–0·97; p=0·0243; figure 4B). Overall survival data for the *EGFR* mutation-positive population are highly censored (ie, most patients have not yet experienced an event), and there was extensive cross-over of placebo patients with *EGFR* mutation-positive status, most of whom (16 of 24 patients; 67%) went on to receive an EGFR TKI in second-line therapy; median overall survival has not yet been reached for this subgroup receiving erlotinib (HR 0·83, 0·34–2·02; p=0·6810). Patients who had stable disease after first-line chemotherapy seemed to have a more pronounced overall survival benefit with maintenance erlotinib (median 11·9 *vs* 9·6 months with placebo; HR 0·72, 0·59–0·89; p=0·0019) than those who had a previous complete response or partial response (median 12·5 *vs* 12·0 months with placebo; HR 0·94, 0·74–1·20; p=0·618).

Erlotinib was well tolerated in the maintenance setting, with a tolerability profile similar to that seen in the phase 3 BR.21 study.[22] Safety data were available for 878 patients (four patients in the placebo group and three in the erlotinib group received no trial treatment; two patients in each group had no safety follow-up, and one patient in the placebo group unblinded himself). No unexpected toxicities were noted. Treatment-related adverse events reported in more than 5% of patients are shown in table 2. The most commonly reported adverse events with erlotinib were rash and diarrhoea (predominantly grade 1 or 2 in severity); no grade 4 rash or diarrhoea was reported. Serious adverse events were reported in 47 patients (11%) on erlotinib, compared with 34 patients (8%) on placebo. 61 serious adverse events were reported with erlotinib, compared with 39 in the placebo group. The most frequently reported serious adverse event was pneumonia: seven cases (2%) were reported with erlotinib, compared with four (<1%) with placebo.

Most patients did not require dose reductions or interruptions. 70 patients (16%) receiving erlotinib required a dose reduction or interruption due to an adverse event, compared with 15 patients (3%) receiving placebo. Withdrawal due to adverse events occurred in 20 patients (5%) in the erlotinib group versus seven patients (2%) in the placebo group. Documented post-study treatments were similar across both treatment groups (table 3) with the exception of EGFR TKI therapy, which was reported in 95 (21%) patients in the placebo group compared with 50 (11%) patients in the erlotinib group.

	Erlotinib (N=433)		Placebo (N=445)	
	All grades	Grade ≥3	All grades	Grade ≥3
Patients with one or more treatment-related adverse events	281 (65)	54 (12)	89 (20)	4 (1)
Skin and subcutaneous tissue disorders	267 (62)	39 (9)	45 (10)	0 (0)
Rash	258 (60)	37 (9)	34 (8)	..
Pruritus	27 (6)	1 (<1)	9 (2)	..
Gastrointestinal disorders	101 (23)	9 (2)	37 (8)	1 (<1)
Diarrhoea	79 (18)	7 (2)	14 (3)	0 (0)
General disorders and administration site conditions	38 (9)	3 (1)	13 (3)	1 (<1)
Metabolism and nutrition disorders	23 (5)	1 (<1)	10 (2)	1 (<1)
Anorexia	22 (5)	1 (<1)	10 (2)	1 (<1)
Infections and infestations	23 (5)	4 (1)	1 (<1)	0 (0)

Data are n (%).

Table 2: **Treatment-related adverse events (any grade and grade ≥3) by body system reported in more than 5% of patients**

	Erlotinib (N=438)	Placebo (N=451)
All classes*	309 (71)	325 (72)
Taxanes (including docetaxel)	132 (30)	142 (31)
Antimetabolites (including pemetrexed)	105 (24)	103 (23)
Antineoplastic agents	72 (16)	80 (18)
EGFR TKIs	50 (11)	95 (21)
Platinum compounds	40 (9)	53 (12)

Data are n (%). *Number of cases with at least one treatment. TKI=tyrosine kinase inhibitor.

Table 3: **Documented post-study treatments received**

There was no statistically significant difference in QoL (assessed using the FACT–L QoL instrument) for patients receiving erlotinib compared with those receiving placebo (HR 0·96, 95% CI 0·79–1·16 for time to deterioration in QoL). A post-hoc analysis showed that time to pain (HR 0·61, 0·42–0·88; p=0·008) and time to analgesic use (HR 0·66, 0·46–0·94; p=0·02) were both significantly improved with erlotinib versus placebo, although time to cough (HR 0·77, 0·49–1·21; p=0·2546) and time to dyspnoea (HR 0·75, 0·48–1·17; p=0·2054) were not significantly affected.

Discussion

The SATURN trial is, to our knowledge, the first study to show that a targeted therapy, given as maintenance immediately after a standard first-line platinum-based chemotherapy regimen, can significantly improve the outcome of metastatic NSCLC. PFS was significantly improved with erlotinib in the overall population, irrespective of EGFR status, and in patients with EGFR immunohistochemistry-positive tumours; an improvement in PFS with erlotinib versus placebo was noted in all patient subgroups, irrespective of sex, ethnic origin, histology or smoking status. Furthermore, a PFS benefit

with erlotinib was noted in both *EGFR* mutation-positive and *EGFR* wild-type subgroups, with those with *EGFR* mutation-positive tumours obtaining the greatest benefit from erlotinib. Overall survival was also significantly longer with erlotinib than with placebo in the intention-to-treat population. The PFS benefit seen for patients with *EGFR* mutation-positive tumours did not translate into an equally impressive overall survival benefit, probably due to the high degree of censoring and the 67% cross-over rate to second-line EGFR TKI therapy in the placebo group for this population.

As expected, skin rash and diarrhoea were more often seen with erlotinib, although most cases were mild to moderate, and there were no unexpected toxicities. Overall, the incidence and severity of adverse events in SATURN were slightly lower than those observed in the BR.21 study of second-line and third-line erlotinib.[21] This might be due to the better performance status of patients in the SATURN study, or perhaps improved awareness and management of erlotinib-related adverse events among investigators. Patients receiving erlotinib had similar QoL to those receiving placebo. Interestingly, both time to pain and time to analgesic use were longer with erlotinib than with placebo. The acceptable tolerability profile of erlotinib, together with proven efficacy in all patient subgroups and oral dosing, distinguishes erlotinib from other agents in this setting, and could provide greater treatment choice for clinicians.

Experience from clinical practice suggests that less than half of patients with advanced NSCLC receive a second-line therapy. Theoretically, maintenance therapy should improve survival not because these agents are more effective when given earlier, but simply because this approach enables us to give patients access to more lines of effective treatment and treat a greater number of patients, including those who might otherwise be unsuitable for additional lines of therapy. In the study of Fidias and colleagues,[7] patients who received delayed docetaxel had the same survival as those who received immediate docetaxel; however, 37% of patients in the delayed group never received docetaxel, compared with only 5% of patients in the immediate group. A similar trend was seen in a trial of maintenance pemetrexed versus placebo, where about a third of patients in the placebo group received only a single line of treatment, while in the experimental group over half of all patients received at least three lines of anticancer therapy.[6] This imbalance in treatment intensity might be the driving element in the improved PFS and survival seen in these maintenance trials.

However, the question of whether using an agent as first-line maintenance is better than using the same agent at progression remains unanswered. Overall, the data suggest that patients are likely to obtain a similar benefit from standard second-line options whether they are used immediately after first-line chemotherapy or delayed until disease progression. However, based on the results of SATURN and other studies, we need to consider the risk of rapid progression after first-line chemotherapy more carefully and offer maintenance therapy to patients, since there is no way to predict which patients will have the opportunity to receive second-line therapy.

In conclusion, the SATURN study is, to our knowledge, the first trial to show that maintenance therapy with a targeted agent following conventional chemotherapy can significantly prolong PFS and overall survival in advanced NSCLC. These findings suggest that by offering treatment immediately after first-line chemotherapy, we can ensure that more patients have the opportunity to benefit from active therapy, delaying disease progression and prolonging survival times.

Contributors

All authors contributed to data analysis, data interpretation, and writing.

Conflicts of interest

FC has received honoraria from Roche, Eli-Lilly, AstraZeneca, and Boehringer, and payment for development of educational presentations including service on speakers' bureaus from Roche, Eli-Lilly, AstraZeneca, and Boehringer. TC has received payment for development of educational presentations including service on speakers' bureaus from Roche, Eli-Lilly, Pfizer, and Amgen. EJ has received honoraria and travel and accommodation expenses from Roche, and has patents planned, pending, or issued. WB has received support for travel to meetings for the study from F Hoffmann-La Roche and his institution received a supply of the study drug and support with clinical report form entries. WB has also received payment for local ad boards and oral presentations at meetings, and honoraria from Roche, Lilly, and AstraZeneca, and travel and accommodation expenses from Roche and Lilly. IM and GK are employees of F Hoffmann-La Roche. BK is an employee of F Hoffmann-La Roche and has stock options with F Hoffmann-La Roche. LS, SC, AS, EE, OM, and GG have no conflicts to declare.

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