Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial

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Summary

Background Erlotinib has been shown to improve progression-free survival compared with chemotherapy when given as first-line treatment for Asian patients with non-small-cell lung cancer (NSCLC) with activating EGFR mutations. We aimed to assess the safety and efficacy of erlotinib compared with standard chemotherapy for first-line treatment of European patients with advanced EGFR-mutation positive NSCLC.

Methods We undertook the open-label, randomised phase 3 EURTAC trial at 42 hospitals in France, Italy, and Spain. Eligible participants were adults (>18 years) with NSCLC and EGFR mutations (exon 19 deletion or L858R mutation in exon 21) with no history of chemotherapy for metastatic disease (neoadjuvant or adjuvant chemotherapy ending ≥6 months before study entry was allowed). We randomly allocated participants (1:1) according to a computer-generated allocation schedule to receive oral erlotinib 150 mg per day or 3 week cycles of standard intravenous chemotherapy of cisplatin 75 mg/m² on day 1 plus docetaxel (75 mg/m² on day 1) or gemcitabine (1250 mg/m² on days 1 and 8). Carboplatin (AUC 6 with docetaxel 75 mg/m² or AUC 5 with gemcitabine 1000 mg/m²) was allowed in patients unable to have cisplatin. Patients were stratified by EGFR mutation type and Eastern Cooperative Oncology Group performance status (0 vs 1 vs 2). The primary endpoint was progression-free survival (PFS) in the intention-to-treat population. We assessed safety in all patients who received study drug (±1 dose). This study is registered with ClinicalTrials.gov, number NCT00446225.

Findings Between Feb 15, 2007, and Jan 4, 2011, 174 patients with EGFR mutations were enrolled. One patient received treatment before randomisation and was thus withdrawn from the study; of the remaining patients, 86 were randomly assigned to receive erlotinib and 87 to receive standard chemotherapy. The preplanned interim analysis showed that the study met its primary endpoint; enrolment was halted, and full evaluation of the results was recommended. At data cutoff (Jan 26, 2011), median PFS was 9.7 months (95% CI 8.4–12.3) in the erlotinib group, compared with 5.2 months (1.8–7.9) in the standard chemotherapy group (hazard ratio 0.37, 95% CI 0.25–0.54; p<0.0001). Main grade 3 or 4 toxicities were rash (11 [13%] of 84 patients given erlotinib vs none of 82 patients in the chemotherapy group), neutropenia (none vs 18 [22%]), anaemia (one [1%] vs three [4%]), and increased aminotransferase concentrations (two [2%] vs 0). Five (6%) patients on erlotinib had treatment-related severe adverse events compared with 16 patients (20%) on chemotherapy. One patient in the erlotinib group and two in the standard chemotherapy group died from treatment-related causes.

Interpretation Our findings strengthen the rationale for routine baseline tissue-based assessment of EGFR mutations in patients with NSCLC and for treatment of mutation-positive patients with EGFR tyrosine-kinase inhibitors.

Funding Spanish Lung Cancer Group, Roche Farma, Hoffmann-La Roche, and Red Tematica de Investigacion Cooperativa en Cancer.

Introduction Mutations in EGFR—either small in-frame deletions in exon 19 or aminoacid substitution [leucine to arginine at codon 858 (L858R)] clustered around the ATP-binding pocket of the tyrosine kinase domain—are present in 10–26% of non-small-cell lung cancer (NSCLC) tumours and are associated with response to gefitinib and erlotinib.1-3 Studies of lung cancer cell lines and transgenic mice with EGFR mutations have shown the oncogenic transformation potential of these mutations, with enhanced response to EGFR inhibitors.1,5,6
Four prospective randomised clinical trials, all of which were undertaken in Asian patients, showed that gefitinib\(^7\) and erlotinib\(^8\) as initial treatment for EGFR-mutant NSCLC improved outcomes compared with chemotherapy. The Iressa Pan-Asia Study (IPASS)\(^7\) enrolled patients with lung adenocarcinoma who had never smoked or who were previously light smokers, independent from their EGFR mutation status; patients were randomly allocated to receive carboplatin plus paclitaxel or gefitinib. In a subgroup analysis of 261 patients with EGFR mutations, median progression-free survival (PFS) was 9·5 months for patients receiving gefitinib compared with 6·3 months for those receiving chemotherapy (hazard ratio [HR] for progression 0·48, 95% CI 0·36–0·64; p<0·001). By contrast, gefitinib was ineffective in 176 patients with wild-type EGFR (2·85, 2·05–3·98; p<0·001).\(^7\) The WJTOG3405 study\(^8\) enrolled only individuals with EGFR mutations and randomly allocated participants to receive gefitinib or docetaxel plus cisplatin. Participants in the gefitinib group had a longer median PFS (9·2 months) than did those in the standard chemotherapy group (6·3 months; HR 0·49, 95% CI 0·34–0·71; p<0·001).\(^7\) The NEJ002 study\(^9\) also enrolled only patients with EGFR mutations, who were randomly allocated to receive gefitinib or carboplatin plus paclitaxel. Participants in the gefitinib group had a longer median PFS (9·2 months) than did those in the standard chemotherapy group (6·3 months; HR 0·49, 95% CI 0·34–0·71; p<0·001).\(^7\)

Methods

Study design and participants

In our open-label, multicentre, randomised phase 3 trial, we enrolled eligible patients attending hospitals in France, Italy, and Spain. Eligibility criteria included histological diagnosis of stage IIB (with pleural effusion) or stage IV NSCLC (based on the sixth TNM staging system), measurable or evaluable disease, presence of
activating EGFR mutations (exon 19 deletion or L858R mutation in exon 21), age older than 18 years, and no history of chemotherapy for metastatic disease (neoadjuvant or adjuvant chemotherapy was allowed if it ended ≥6 months before entry to study). Patients with asymptomatic, stable brain metastases were eligible for inclusion.

The protocol was approved by the institutional review board of every participating centre, and all patients provided written informed consent. An independent data monitoring committee reviewed safety and interim efficacy data (members listed in the appendix).

Randomisation and masking
A clinical research organisation (PIVOTAL, Madrid, Spain) did central randomisation with a computer-generated system. Patients were registered via fax after provision of informed consent. The system combined stratification factors and treatments assigned to the previous patients and then generated the next allocation assignment. Stratification factors were type of EGFR mutations (exon 19 deletion vs L858R) and Eastern Cooperative Oncology Group (ECOG) performance status (0 vs 1 vs 2). Participants were randomly allocated in 1:1 ratio to receive erlotinib or standard chemotherapy. Throughout the study, doctors and study participants were not masked to the identity of the study treatment, because patients were treated with standard chemotherapy. Throughout the study, doctors and all patients were randomly allocated in 1:1 ratio to receive erlotinib or standard chemotherapy (randomisation and masking).

Procedures
Eligible participants received oral erlotinib (150 mg per day) or 3 week cycles of standard intravenous chemotherapy (75 mg/m² cisplatin plus 75 mg/m² docetaxel on day 1 or 75 mg/m² cisplatin on day 1 plus 1250 mg/m² gemcitabine on days 1 and 8). Patients who were ineligible for cisplatin treatment received intravenous carboplatin chemotherapy instead (3 week cycles of AUC 6 on day 1 with 75 mg/m² cisplatin plus 1250 mg/m² gemcitabine on days 1 and 8). Pemetrexed had not been approved for first-line treatment when the study was designed and recommended at the time of documented progression unless contraindicated or refused by the patients.

We obtained all tumour specimens from the original biopsy sampling before any treatment was given and before randomisation. We derived genomic DNA from tumour tissue obtained by laser capture microdissection (Palm, Oberlensheim, Germany) and isolated DNA from serum or plasma (or both) with the QIAamp DNA blood mini kit (Qiagen, Hilden, Germany), starting from 0·4 mL of material. All tissue samples were analysed with Sanger sequencing (exons 19 and 21). Additionally, we confirmed all participants had EGFR mutations with an independent technique: deletions in exon 19 were established by length analysis after PCR amplification with a FAM-labelled primer in an ABI prism 3130 DNA analyser (Applied Biosystems, Foster City, CA, USA); L858R mutations in exon 21 were detected with a 5´ nucleotide PCR assay (TaqMan assay, Applied Biosystems) with a FAM MGB-labelled probe for the wild-type and a VIC MGB-labelled labelling primer for the L858R mutant.
probe for the mutant sequence. For serum samples, both length analysis after PCR amplification for exon 19 deletions and TaqMan assay for L858R mutations were done in the presence of a protein nucleic acid (PNA) clamp, which was designed to inhibit the amplification of the wild-type allele (see appendix for more details).

We did radiological assessments with CT at baseline and every 6 weeks thereafter according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0. Use of PET was available at the discretion of the investigator. The primary endpoint, PFS, was defined as the time from the date of randomisation to the date when disease progression was first observed or death occurred. We calculated overall survival from the date of randomisation to the date of death. The primary analysis was based on investigator assessment; however, treatment response and PFS were confirmed by external review. We assessed adverse events according to the National Cancer Institute Common Terminology Criteria version 3.0.

Statistical analyses
We postulated that PFS would be 10 months with erlotinib and 6 months with chemotherapy. We estimated that 135 events would be needed for the study to have a power of 80% to confirm superiority of erlotinib compared with standard chemotherapy, with the use of a log-rank test and a two-sided significance level of 5%. We planned an interim analysis when 65% of PFS events (88 events) had occurred. A Lan-DeMets alpha-spending function with a Pocock stopping boundary was used to maintain the significance level at 5% with a 0.037 significance level at interim and 0.025 for the final analysis based on 135 events. Assuming a 5% yearly dropout rate, we planned to enrol 174 patients. All patients were censored at crossover for the analysis of PFS. We drew Kaplan-Meier curves and made comparisons with the log-rank test. We calculated HRs (95% CI) with a Cox proportional-hazards analysis. Prespecified adjustment factors included Eastern Cooperative Oncology Group (ECOG) performance status and type of mutation (exon 19 deletion vs L858R).

Secondary endpoints were response rate, overall survival, and EGFR mutation analysis in serum. For the overall survival analysis, patients were not censored at crossover, and we used Kaplan-Meier curves and the log-rank test for comparisons. Response rates were compared between the two groups with the χ² test. According to the statistical analysis plan, all randomly allocated patients would be included in the intention-to-treat analysis, apart from those patients starting a study drug before randomisation. Additionally, we also calculated response in the per-protocol population.

All analyses were two-sided with a 5% significance level and were done with SAS version 8.2, SPSS version 17.0, or S-PLUS version 6.1. This study is registered with ClinicalTrials.gov, number NCT00446225.

Role of the funding source
The study was designed and sponsored by the Spanish Lung Cancer Group, which coordinated the trial, managed the database, and did the primary analyses. None of the funding organisations had any input into the design of the study.
study or the collection of data. Roche Farma and Hoffmann-La Roche provided input to the analysis and interpretation of results. The corresponding author had full access to all the study data and final responsibility for the decision to submit for publication. All authors attest to the fidelity of the article, the full protocol, and the statistical analysis.

**Results**

Between Feb 15, 2007, and Jan 4, 2011, we screened 1227 patients from 42 institutions in Spain, France, and Italy for EGFR mutations. Results were available in less than 7 days from receipt of the tumour sample. We randomly assigned 173 patients with EGFR mutations to receive erlotinib or standard chemotherapy (figure 1). 33 patients were not candidates for cisplatin treatment and received carboplatin. Baseline characteristics were well balanced between the two groups (table 1). All but two patients were white; 78 (91%) patients in the erlotinib group and 82 (94%) patients in the standard chemotherapy group had stage IV disease, and most of the remaining patients had stage III disease with malignant pleural effusion (now classified as stage IV disease in the seventh TNM staging system). One patient in the erlotinib group had bulky N3 disease that was not suitable for radiotherapy. The predominant histology was adenocarcinoma in both groups (table 1).

At final data cutoff (Jan 26, 2011), the median follow-up was 18·9 months (IQR 10·7–29·0) for the erlotinib group and 14·4 months (7·1–24·8) for the chemotherapy group. The median duration of erlotinib treatment was 8·2 months (range 0·3–32·9, IQR 3·1–12·0); the median duration of chemotherapy treatment was 2·8 months (0·7–5·1, 1·0–2·6); the median number of chemotherapy cycles administered was four (one to six, two to four). Although the planned number of chemotherapy cycles was four, nine patients continued chemotherapy after the fourth cycle due to clinical benefit. The appendix shows reasons for withdrawal from the study in both groups and information about treatment after discontinuation of the assigned study drug.

At the preplanned interim analysis (data cutoff Aug 2, 2010), median PFS was 9·4 months (95% CI 7·9–12·3) in the erlotinib group and 5·2 months (4·4–5·8) in the standard chemotherapy group (HR 0·42, 95% CI 0·27–0·64; p<0·0001; appendix). After review of the interim analysis data, the independent data monitoring committee recommended halting of enrolment, full assessment of study data, and publication of study results. In the final analysis (data cutoff Jan 26, 2011), median PFS was 9·7 months (95% CI 8·4–12·3) for patients treated with erlotinib compared with 5·2 months (95% CI 4·5–5·8) for those treated with chemotherapy (HR 0·42, 95% CI 0·27–0·64; p<0·0001; appendix). At the final data cutoff (Jan 26, 2011), median PFS was 9·7 months (95% CI 8·4–12·3) for patients treated with erlotinib compared with 5·2 months (95% CI 4·5–5·8) for those treated with chemotherapy (HR 0·42, 95% CI 0·27–0·64; p<0·0001; appendix). After review of the interim analysis data, the independent data monitoring committee recommended halting of enrolment, full assessment of study data, and publication of study results. In the final analysis (data cutoff Jan 26, 2011), median PFS was 9·7 months (95% CI 8·4–12·3) for patients treated with erlotinib compared with 5·2 months (95% CI 4·5–5·8) for those treated with chemotherapy (HR 0·42, 95% CI 0·27–0·64; p<0·0001; appendix).

**Figure 3:** Waterfall plots of best percentage change from baseline in tumour size for individual patients in the erlotinib group (A) and the standard chemotherapy group (B). Data are shown for the subpopulation of patients with measurable disease at baseline and at the time of response assessment (figure 1). Nine patients in the erlotinib group and ten patients in the standard chemotherapy group who were included in the per-protocol population assessable patient set are not shown because they had non-measurable disease at baseline or at the time of response assessment. Bars show data from individual patients. Negative values suggest tumour shrinkage and positive values suggest progressive disease; the dashed lines show the thresholds for a partial response (ie, shrinkage by 30%) or for progressive disease (growth by 20%) according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria.²⁰
Figure 2 shows the HRs for the risk of progression by subgroup. For participants with ECOG performance status 0, the estimated median PFS was 23.9 months (95% CI 9.7–not assessable) for patients in the erlotinib group compared with 6 months (4.3–8.0) for those in the standard chemotherapy group (p=0.0006; appendix). For patients with ECOG performance status 1, estimated median PFS was 8.8 months (95% CI 7.5–10.8) in the erlotinib group and 5.0 months (4.1–5.5) in the standard chemotherapy group (p<0.0001; appendix). For patients with performance status 2, estimated median PFS was 8.3 months (95% CI 1.0–16.4) in the erlotinib group and 4.4 months (95% CI 0.3–6.0) in the standard chemotherapy group (p=0.191; appendix).

We noted a favourable HR for never smokers treated with erlotinib compared with those treated with standard chemotherapy (0.24, 95% CI 0.15–0.39; p<0.0001), but not for current or previous smokers. Median PFS for never smokers was 9.7 (95% CI 8.3–15.5) in the erlotinib group and 5.1 (4.4–5.6) in the standard chemotherapy group. For current smokers it was 8.7 (5.7–15.8) in the erlotinib group and 4.2 (1.0–15.4) in the standard chemotherapy group and for previous smokers it was 10.7 (2.7–13.8) in the erlotinib group and 8.0 (1.2–not assessable) in the standard chemotherapy group. The HR for patients harbouring the exon 19 deletion was 0.30 (95% CI 0.18–0.50; p<0.0001), with a median PFS of 11.0 months (95% CI 8.3–16.4) in the erlotinib group compared with 6.0 months (95% CI 4.9–6.8) in the standard chemotherapy group (appendix).

In the multivariable analysis of PFS, including age, sex, smoking status, type of mutation, number of metastatic sites, and site of metastases, only treatment group and performance status were significant factors for PFS (appendix).

In the intention-to-treat population, two (2%) of 86 patients in the erlotinib group had a complete response, whereas 48 (56%) of 86 in the erlotinib group and 13 (15%) of 87 in the standard chemotherapy group attained a partial response (appendix). 77 (90%) patients in the erlotinib group and 73 (84%) in the standard chemotherapy group satisfied the criteria for inclusion in the per-protocol population (figure 1). Two (3%) of 77 patients in the erlotinib group had a complete response. 47 (61%) of 77 patients in the erlotinib group and 11 (18%) of 73 patients in the standard chemotherapy group had partial response (odds ratio 7.5, 95% CI 3.6–15.6; p<0.0001; appendix).

Figure 3 shows the best percentage change from baseline in tumour size for every patient with measurable disease at baseline and at the time of response assessment.

By the final data cutoff, 38 (44%) of 86 patients in the erlotinib group and 31 (36%) of 87 patients in the standard chemotherapy group had died. 66 (76%) of 87 patients in the standard chemotherapy group crossed over to receive EGFR tyrosine kinase inhibitors, primarily erlotinib (appendix). Overall survival did not differ significantly between treatment groups: median overall survival was 19.3 months (95% CI 14.7–26.8) in the erlotinib group compared with 19.5 months (16.1–not assessable) in the standard chemotherapy group (HR 1.04, 95% CI 0.65–1.68; p=0.87; appendix).

We included all patients who had received at least one dose of a study drug in the safety analysis. The most common adverse events in the erlotinib group were rash (11 [13%] of 84 patients at grade 3) and increased amino-transferase concentrations (two [2%] of 82 patients at...
grade 3; table 2). The most common adverse events in the standard chemotherapy group were anaemia (three [4%] grade 3) and neutropenia (18 [22%] grade 3–4; table 2). No increased incidence of pneumonitis was noted in the erlotinib group (table 2). 11 (13%) patients in the erlotinib group and 19 (23%) in the standard chemotherapy group were withdrawn from the trial treatment because of adverse events. One patient in the erlotinib group and two patients in the standard chemotherapy group died from treatment-related causes. Table 3 shows a summary of safety data.

Baseline blood samples were available from 109 patients (57 in the erlotinib group and 52 in the chemotherapy group). EGFR mutations were detected in the baseline blood samples of 58 patients (appendix). PFS for patients with mutations detected in serum was 10.7 months (95% CI 6.8–15.5) in the erlotinib group compared with 4.2 months (3.2–6.0) in the standard chemotherapy group (HR 0.25, 95% CI 0.12–0.54; p=0.0002; figure 2, appendix). PFS for patients in whom mutations were not detected was 12.6 months (95% CI 8.3–not assessable) in the erlotinib group compared with 6.0 months (4.9–9.0) in the standard chemotherapy group (HR 0.29, 95% CI 0.13–0.63; p=0.0010; figure 2, appendix).

**Discussion**

To our knowledge, EURTAC is the first prospective head-to-head phase 3 study comparing efficacy and safety of first-line erlotinib with platinum-based chemotherapy in non-Asian patients with advanced NSCLC and EGFR mutations (panel). Patients treated with erlotinib had longer PFS, a higher response rate, and milder side-effects than did those treated with standard chemotherapy.

The HR for progression in our study was 0.37, which is akin to the pooled HR for progression of 0.23 (95% CI 0.19–0.27) from the four studies in Asian patients (panel). Together, these findings show benefit for EGFR tyrosine-kinase inhibitors in Asian and our European populations. In EURTAC, benefit was seen in most subgroups of patients included in the analyses, apart from a notable exception in former smokers. Current smokers seemed to benefit more from erlotinib than did former smokers, but the subgroups were too small to draw definite conclusions. This finding was unexpected and not in line with previous studies. In the OPTIMAL trial, both present and former smokers showed a benefit from erlotinib and former smokers seemed to have a longer PFS compared with never smokers in our previous study.

About 30% of the patients in the present study were performance status 0, and the HR for progression in this group of patients was 0.26. The HR for progression for patients with exon 19 deletions was 0.30, compared with 0.55 for those with L858R mutations. These rates are broadly similar to the updated analysis of IPASS (HR of 0.38 for exon 19 deletions and 0.55 for L858R). Moreover, in the present study, the HR for patients with EGFR mutations detected in serum was 0.25 in favour of erlotinib, which is also in line with findings from IPASS, in which the HR for patients with EGFR mutations in serum was 0.29 in favour of gefitinib. However, the subgroup analyses must be interpreted with caution because of the small number of patients in each group; nonetheless these findings might be useful for future studies.

In our previous study in patients with NSCLC with EGFR mutations, the response rate to erlotinib was 71% (139 of 197 assessable patients). In the present study, 49 (64%) of 77 assessable patients treated with erlotinib met the criteria for a confirmed response. The confirmed response rate in the standard chemotherapy group in this study was 18% (13 of 73 patients), which is lower than was that reported in the phase 3 trials in Asian patients (31–47%). However, in several phase 3 trials in non-Asian patients comparing different platinum-based regimens in advanced NSCLC, response rates ranged from 15% to 30–6%.

In EURTAC, we noted no major differences in overall survival between the two groups. Recent reports suggest that patients with EGFR mutations who are treated with erlotinib could respond to chemotherapy at the time of clinical progression. Furthermore, at the time of clinical progression, most patients in the standard chemotherapy group crossed over to receive erlotinib as second-line treatment, producing a potential carryover effect in these patients.

Although the protocol called for completion of the lung cancer symptom scale by all patients to measure quality
of life, the compliance rate was very low. At baseline, 63\% of questionnaires in the standard chemotherapy group and 70\% in the erlotinib group were recorded, but at the first visit, this rate dropped to 21\% in the standard chemotherapy group and 27\% in the erlotinib group. Few patients completed the questionnaire after the four cycles of chemotherapy, leading to an imbalance in the completion rate between the two groups. Because of the low compliance rate and the imbalance between the groups, the analysis of time to symptomatic progression was regarded as inconclusive.

The EURTAC results reinforce the feasibility of upfront genotyping of patients and the improved outcomes attained with therapy directed against a known target. Taken together with the findings of the OPTIMAL study,\textsuperscript{10} our results suggest a benefit in PFS with first-line erlotinib in a European population and confirm those improvements attained with EGFR-targeted agents in Asian patients, thus strengthening the rationale for routine baseline tissue-based assessment of EGFR mutations in patients with NSCLC.

References