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

Rafael Rosell, Enric Carcereny, Radj Gervais, Alain Vergnenegre, Bartomeu Massuti, Enriqueta Felip, Ramon Palmero, Ramon Garcia-Gomez, Cinta Pallares, Jose Miguel Sanchez, Rut Porta, Manuel Cobo, Pilar Garrido, Flavia Longo, Teresa Moran, Amelia Insa, Filippo De Marinis, Romain Corre, Isabel Bover, Alfonso Illiano, Eric Dansin, Javier de Castro, Michele Milella, Noemi Reguart, Giuseppe Altavilla, Ulpiano Jimenez, Mariano Provencio, Miguel Angel Moreno, Josefa Terrasa, Jose Muñoz-Langa, Javier Valdivia, Dolores Isla, Manuel Domine, Olivier Molinier, Julien Mazieres, Nathalie Baize, Rosario Garcia-Campelo, Gilles Robinet, Delvys Rodriguez-Abreu, Guillermo Lopez-Vivanco, Vittorio Gebbia, Lioba Ferrera-Delgado, Pierre Bombaron, Reyes Bernabe, Alessandra Bearz, Angel Artal, Enrico Cortesi, Christian Rolfo, Maria Sanchez-Ronco, Ana Drozdowskyj, Cristina Queralt, Itziar de Aguirre, Jose Luis Ramirez, Jose Javier Sanchez, Miguel Angel Molina, Miquel Taron, Luis Paz-Ares, on behalf of the Spanish Lung Cancer Group in collaboration with the Groupe Français de Pneumo-Cancérologie and the Associazione Italiana Oncologia Toracica

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 (4·5–5·8) 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.

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See Comment page 216

Catalan Institute of Oncology, Badalona, Spain (R Rosell MD, E Carcereny MD, T Moran MD, C Queralt PhD, I de Aguirre PhD, J L Ramirez PhD, M Taron PhD); **Pangaea Biotech, USP Dexeus University Institute, Barcelona, Spain** (R Rosell, M A Molina PhD, M Taron); **Centre François Baclesse, Caen, France** (R Gervais MD); **Hopital du Cluzeau, Limoges, France** (Prof A Vergnenegre MD); **Hospital General de Alicante, Alicante, Spain** (B Massuti MD); **Hospital Vall d'Hebron, Barcelona, Spain** (E Felip MD); **Catalan Institute of Oncology, Bellvitge, Spain** (R Palmero MD); **Hospital Gregorio Marañon, Madrid, Spain** (R Garcia-Gomez MD); **Hospital Sant Pau, Barcelona, Spain** (C Pallares MD); **Hospital 12 de Octubre, Madrid, Spain** (J M Sanchez MD); **MD Anderson, Madrid, Spain** (J M Sanchez); **Catalan Institute of Oncology, Girona, Spain** (R Porta MD); **Hospital Carlos Haya, Malaga, Spain** (M Cobo MD); **Hospital Ramon y Cajal, Madrid, Spain** (P Garrido MD); **Azienda Policlinico Umberto I, Rome, Italy** (F Longo MD); **Hospital Clinico, Valencia, Spain** (A Insa MD); **Azienda Ospedaliera Camillo Forlanini, Rome, Italy** (F De Marinis MD); **CHU Rennes Hopital**

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[1] and are associated with response to gefitinib and erlotinib.[2–4] 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.[3,5,6]

Ponchaillou, Rennes, France (R Corre MD); Hospital Son Llatzer, Mallorca, Spain (I Bover MD); Ospedale dei Colli, Naples, Italy (A Illiano MD); Centre Oscar Lambret, Lille, France (E Dansin MD); Hospital La Paz, Madrid, Spain (J de Castro MD); Hospital Regina Elena, Rome, Italy (M Milella MD); Hospital Clinic, Barcelona, Spain (N Reguart MD); Azienda Ospedaliera Policlinico G Martino, Messina, Italy (G Altavilla MD); Hospital de la Princesa, Madrid, Spain (U Jimenez MD); Hospital Puerta de Hierro, Madrid, Spain (M Provencio MD); Complejo Hospitalario de Jaen, Jaen, Spain (M A Moreno MD); Hospital Son Dureta, Mallorca, Spain (J Terrasa MD); Hospital Dr Peset, Valencia, Spain (J Muñoz-Langa MD); Hospital Virgen de las Nieves, Granada, Spain (J Valdivia MD); Hospital Lozano Blesa, Zaragoza, Spain (D Isla MD); Fundacion Jimenez-Diaz, Madrid, Spain (M Domine MD); Hospital Le Mans, Le Mans, France (O Molinier MD); Hospital Larrey, Toulouse, France (Prof J Mazieres MD); CHU Angers, Angers, France (N Baize MD); Hospital Teresa Herrera, La Coruña, Spain (R Garcia-Campelo MD); Centre

Four prospective randomised clinical trials, all of which were undertaken in Asian patients, showed that gefitinib[7–9] and erlotinib[10] 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<0·0001).[8] 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 (10·8 months *vs* 5·4 months; HR 0·30, 95% CI 0·22–0·41; p<0·001) and a higher response rate (73·7% *vs* 30·7%; p<0·001) than did patients who received carboplatin plus paclitaxel. Results from the OPTIMAL study,[10] comparing erlotinib with carboplatin plus gemcitabine in Chinese patients with NSCLC and EGFR mutations, showed an HR for PFS of 0·16 (95% CI 0·10–0·26) in favour of erlotinib (median 13·1 months for erlotinib *vs* 4·6 months for standard chemotherapy).

In a phase 2 trial,[11] Asian and non-Asian patients with advanced NSCLC who were positive for EGFR protein expression or who had a high EGFR gene copy number were randomly allocated to receive erlotinib or erlotinib plus chemotherapy; in a subgroup of nine patients with EGFR mutations who were treated with erlotinib alone, median PFS was 18·2 months.[11] In non-Asian patients, two prospective studies have tested the feasibility of screening for EGFR mutations. In a phase 2 study[12] of 31 patients with confirmed EGFR mutations from the USA, median PFS for patients treated with gefitinib was 9·2 months. We screened 2105 Spanish patients with advanced NSCLC and identified EGFR mutations in 350 (17%) patients.[13] Median PFS in 217 patients treated with erlotinib was 14 months. On the basis of these results, we undertook the European Tarceva versus Chemotherapy (EURTAC) study, in which we aimed to compare erlotinib with platinum-based chemotherapy as first-line treatment for patients with advanced NSCLC. Our trial is the first randomised trial targeting a non-Asian population of patients whose tumours have EGFR mutations.

Methods

Study design and participants

In our open-label, multicentre, randomised phase 3 trial we enrolled eligible participants attending hospitals in France, Italy, and Spain. Eligibility criteria included histological diagnosis of stage IIIB (with pleural effusion) or stage IV NSCLC (based on the sixth TNM staging system), measurable or evaluable disease, presence of

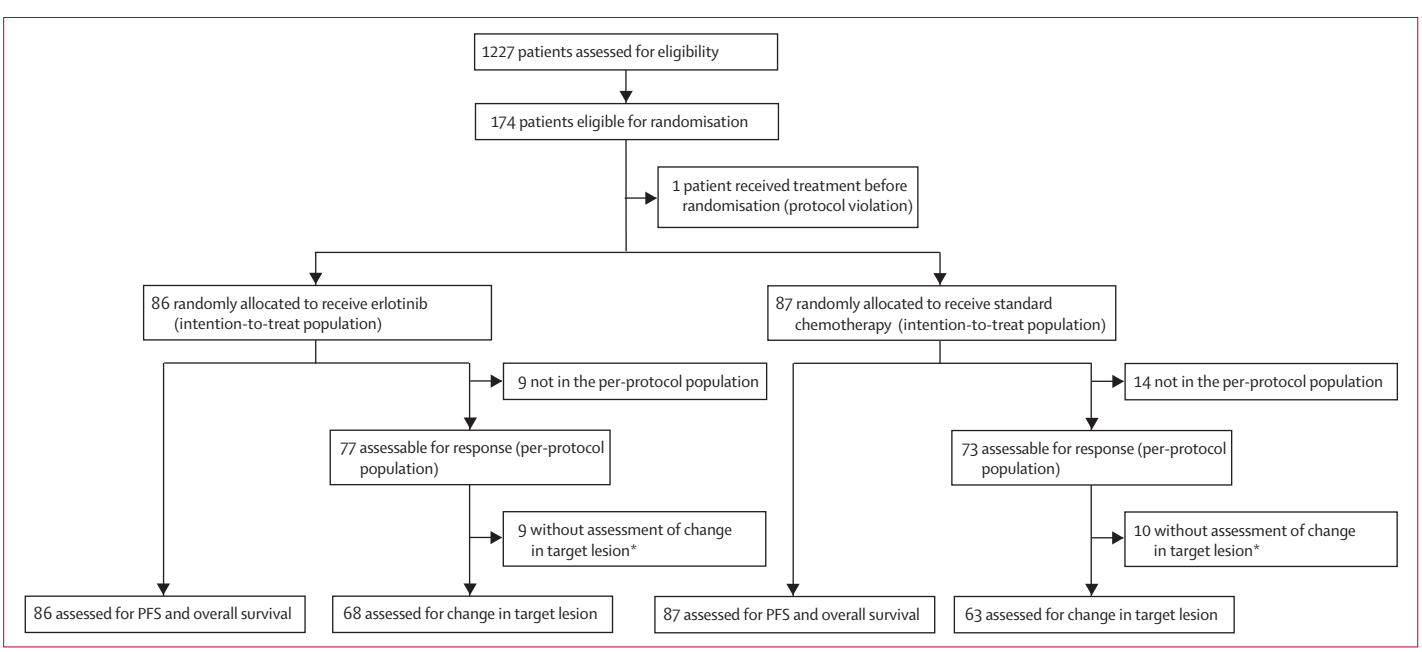

Figure 1: **Trial profile**
Criteria for inclusion in the per-protocol population included receipt of at least one dose of the study drug and at least one post-baseline assessment (or death before the first post-baseline assessment) and no major protocol violations. PFS=progression-free survival. *Non-measurable disease at baseline or time of response assessment.

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 drugs with different administration routes and schedules. To avoid bias, centralised randomisation was used, and PFS and treatment responses were confirmed by an external review of CT scans by a central review board (Synarc, San Francisco, CA, USA).

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 docetaxel on day 1, or AUC 5 on day 1 with 1000 mg/m² gemcitabine on days 1 and 8). Pemetrexed had not been approved for first-line treatment when the study was designed and was therefore not a treatment option. The choice of chemotherapy regimen was left to the investigator's discretion. Chemotherapy was scheduled for four cycles unless development of intolerable toxic effects or disease progression occurred. Erlotinib was continued until disease progression, development of intolerable toxic effects, or withdrawal of consent. Crossover was part of the study design 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 QIAmp 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′ nuclease PCR assay (TaqMan assay, Applied Biosystems) with a FAM MGB-labelled probe for the wild-type and a VIC MGB-labelled

	Erlotinib (n=86)	Standard chemotherapy (n=87)
Sex, female	58 (67%)	68 (78%)
Age, years		
Mean (SD)	63·44 (10·95)	64·15 (9·23)
Median (range, IQR)	65 (24–82, 56–72)	65 (29–82, 60–71)
Smoking status		
Never smoked	57 (66%)	63 (72%)
Previous smoker	22 (26%)	12 (14%)
Current smoker	7 (8%)	12 (14%)
ECOG performance status		
0	27 (31%)	30 (34%)
1	47 (55%)	45 (52%)
2	12 (14%)	12 (14%)
Histological diagnosis		
Adenocarcinoma	82 (95%)	78 (90%)
Bronchoalveolar adenocarcinoma	0	2 (2%)
Large-cell carcinoma	3 (3%)	1 (1%)
Squamous-cell carcinoma	1 (1%)	0
Other*	0	6 (7%)
Clinical stage		
N3 (not candidate for thoracic radiotherapy)	1 (1%)	0
IIIA	1 (1%)	0
IIIB (malignant pleural effusion)	6 (7%)	5 (6%)
IV	78 (91%)	82 (94%)
Bone metastasis		
Yes	28 (33%)	29 (33%)
No	58 (67%)	58 (67%)
Brain metastasis		
Yes	9 (10%)	11 (13%)
No	77 (90%)	76 (87%)
Type of *EGFR* mutation		
Deletion of exon 19	57 (66%)	58 (67%)
L858R mutation in exon 21	29 (34%)	29 (33%)

Data are n (%) unless otherwise stated. ECOG=Eastern Cooperative Oncology Group. *Four undifferentiated carcinomas, one pleomorphic carcinoma, and one adenosquamous carcinoma.

Table 1: **Baseline demographic and clinical characteristics of the intention-to-treat population**

Hospitalier Universitaire Morvan, Brest, France (G Robinet MD); **Hospital Insular de Gran Canaria, Las Palmas, Spain** (D Rodriguez-Abreu MD); **Hospital Cruces, Bilbao, Spain** (G Lopez-Vivanco MD); **Casa di Cura La Maddalena, Palermo, Italy** (V Gebbia MD); **Hospital La Candelaria, Tenerife, Spain** (L Ferrera-Delgado MD); **Centre Hospitalier Emile Muller, Mulhouse, France** (P Bombaron MD); **Hospital Nuestra Señora de Valme, Sevilla, Spain** (R Bernabe MD); **Centro di Riferimento Oncologico, Aviano Pordenone, Italy** (A Bearz MD); **Hospital Miguel Servet, Zaragoza, Spain** (A Artal MD); **La Sapienza University, Rome, Italy** (E Cortesi MD); **Clinica Rotger, Palma de Mallorca, Spain** (C Rolfo MD); **University of Alcala de Henares, Madrid, Spain** (M Sanchez-Ronco PhD); **Pivotal, Madrid, Spain** (A Drozdowskyj PhD); **Autonomous University of Madrid, Madrid, Spain** (Prof J J Sanchez MD); **and Hospital Virgen del Rocio, Sevilla, Spain** (L Paz-Ares MD)

Correspondence to: Dr Rafael Rosell, Catalan Institute of Oncology, Hospital Germans Trias i Pujol, Medical Oncology Service, Ctra Canyet, 08916 Badalona, Barcelona, Spain **rrosell@iconcologia.net**

For the **trial protocol** see http://www.gecp.org/trials/eurtrac/GECP_06_%2001_Protocol_Version_f_eng_%2026-jun-09.pdf

See **Online** for appendix

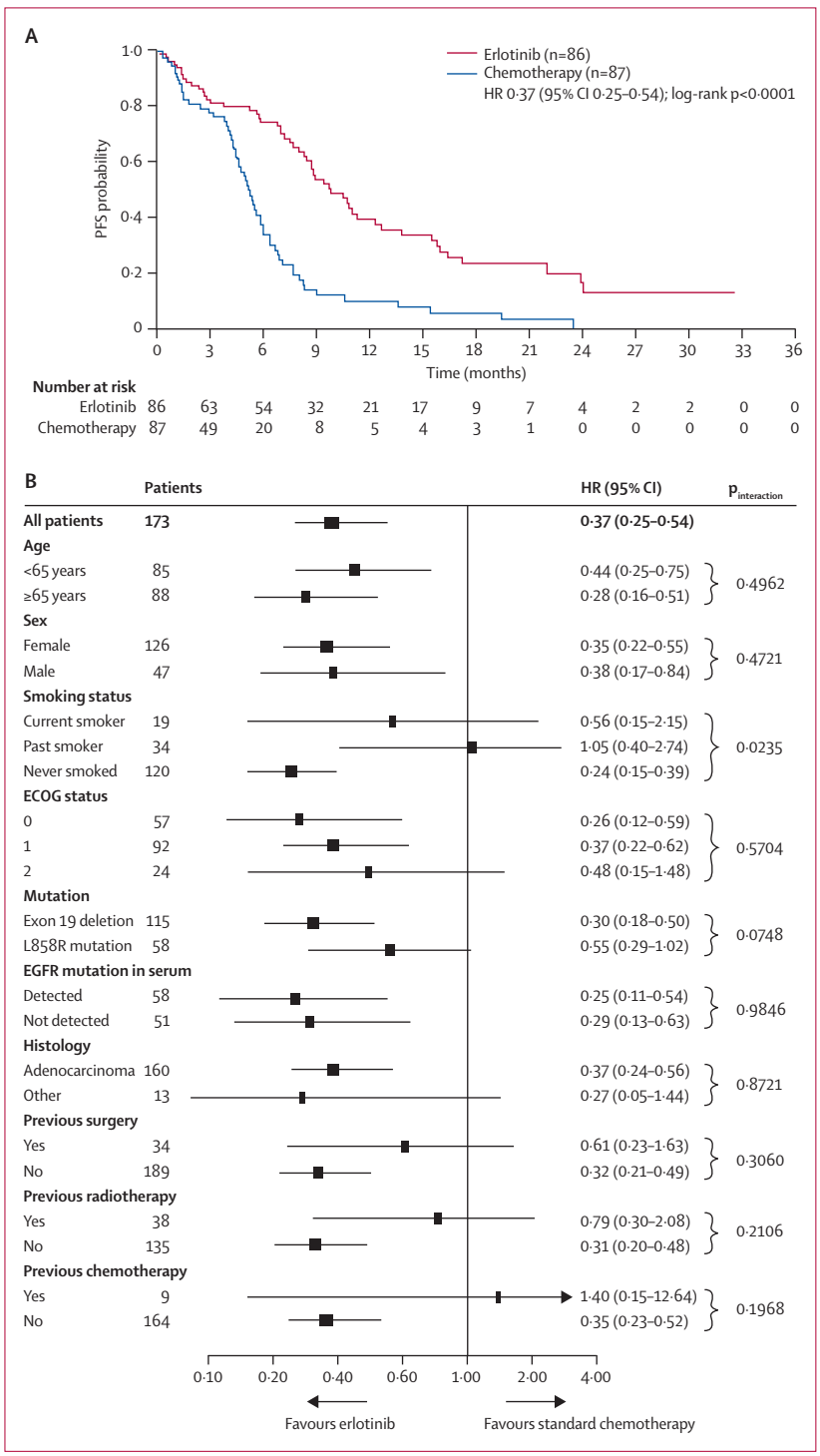

Figure 2: **Progression-free survival by treatment group**
(A) Kaplan-Meier estimates of progression-free survival according to radiographic evidence in the intention-to-treat population. (B) Subgroup analyses of progression-free survival in the intention-to-treat population.

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.[14] 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.[15]

Statistical analyses

We postulated that PFS would be 10 months with erlotinib and 6 months with chemotherapy.[16] 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[17] 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 χ^2 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 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 0·37, 95% CI 0·25–0·54; p<0·0001; figure 2). 1 year PFS was 40% (95% CI 28–52) in the erlotinib group and 10% (4–20) in the chemotherapy group; 2 year PFS was 11% (5–26) in the erlotinib group and 0% (not assessable) in the standard chemotherapy group.

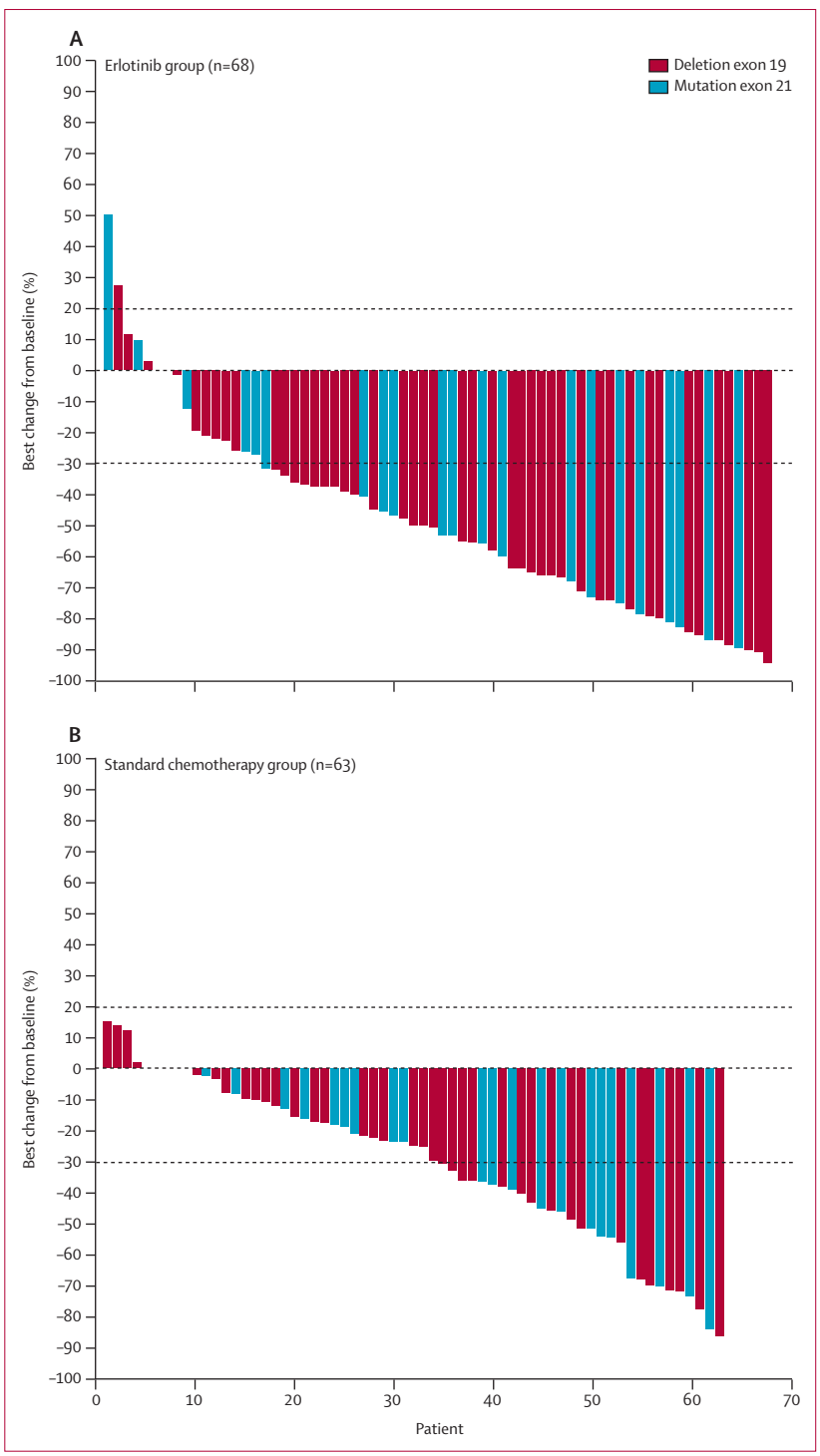

Figure 3: **Waterfall plots of best percentage change from baseline in tumour size for individual patients in the erlotinib group (A) and the standard chemotherapy group (B)**
Data are shown for the subpopulation of patients with measurable disease at baseline and at the time of response assessment (figure 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.[14]

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).

	Erlotinib (n=84)			Standard chemotherapy (n=82)			p value for grade 3–4
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4	
Fatigue	43 (51%)	5 (6%)	0	43 (52%)	16 (20%)	0	0·0086
Rash	56 (67%)	11 (13%)	0	4 (5%)	0	0	0·0007
Diarrhoea	44 (52%)	4 (5%)	0	15 (18%)	0	0	0·1206
Appetite loss	26 (31%)	0	0	26 (32%)	2 (2%)	0	0·2425
Anaemia	9 (11%)	0	1 (1%)	37 (45%)	3 (4%)	0	0·3644
Neutropenia	0	0	0	15 (18%)	12 (15%)	6 (7%)	<0·0001
Alopecia	12 (14%)	0	0	13 (16%)	2 (2%)	0	0·2425
Neuropathy	7 (8%)	0	1 (1%)	11 (13%)	1 (1%)	0	1·0000
Arthralgia	8 (10%)	1 (1%)	0	4 (5%)	1 (1%)	0	1·0000
Thrombocytopenia	1 (1%)	0	0	1 (1%)	6 (7%)	6 (7%)	0·0003
Aminotransferase rise	3 (4%)	2 (2%)	0	5 (6%)	0	0	0·4970
Febrile neutropenia	0	0	0	1 (1%)	1 (1%)	2 (2%)	0·1183
Pneumonitis	0	1 (1%)	0	0	1 (1%)	0	1·0000

Adverse events were assessed according to the National Cancer Institute Common Terminology Criteria version 3.0.[35]

Table 2: **Common adverse events in the safety population**

	Erlotinib group (n=84)	Standard chemotherapy group (n=82)
Any adverse event (all grades)	82 (98%)	81 (99%)
Treatment-related adverse event (all grades)	78 (93%)	78 (95%)
Grade 3 or 4 adverse event	38 (45%)	55 (67%)
Dose reduction due to adverse event	18 (21%)	23 (28%)
Dose reduction due to drug-related adverse event	18 (21%)	21 (26%)
Discontinuation due to an adverse event	11 (13%)	19 (23%)
Discontinuation due to drug-related adverse event	5 (6%)	16 (20%)
Any severe adverse event	27 (32%)	25 (30%)
Treatment-related severe adverse event	5 (6%)	16 (20%)
Treatment-related death*	1 (1%)	2 (2%)
Interstitial lung disease-like events	1 (1%)	1 (1%)

The safety analysis included all patients who were randomly allocated to treatment groups and received at least one dose of study drug. We prospectively defined adverse events and used the Medical Dictionary for Regulatory Activities (MedDRA) version 13.0 for the reporting of adverse events,[18] and prespecified a list of events in the protocol. *One patient in erlotinib group had hepatotoxicity, two patients in the chemotherapy group had cerebrovascular accidents (one after related grade 5 infection).

Table 3: **Safety data**

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 8·8–16·4) in the erlotinib group compared with 4·6 months (95% CI 4·1–5·6) for those in the standard chemotherapy group (appendix). By contrast, the HR for patients with the L858R mutation was 0·55 (95% CI 0·29–1·02; p=0·0539), with a median PFS of 8·4 months (95% CI 5·2–10·8) 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 13 (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 aminotransferase 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[7–10] (appendix). 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,[10] 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.[13] 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[19] (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,[20] 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).[21] 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%).[7–10] 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%.[22]

In EURTAC, we noted no major differences in overall survival between the two groups. Recent reports[23,24] 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

Panel: Research in context

Systematic review

We systematically reviewed PubMed and the Cochrane Library before starting this trial. We searched for reports published in English before Dec 31, 2006, with the search terms "lung neoplasm", "TKI", "EGFR mutation", and "first-line therapy", before assessing the quality of the evidence according to evidence-based medicine and giving greatest weight to data from prospective multicentre phase 2 or 3 clinical trials. At the time the EURTAC started, IPASS,[7] the WJTOG3405 study,[8] and the NEJ002 study[9] were in progress. These three studies showed that gefitinib was better than standard chemotherapy as first-line therapy in Asian patients with non-small-cell lung cancer (NSCLC) who had EGFR mutations. Results from the OPTIMAL trial,[10] reported in 2011, noted equivalent effects for erlotinib in Asian patients.

Interpretation

To our knowledge, the EURTAC is the first phase 3 study to show that erlotinib can improve median progression-free survival in European patients (who were predominantly white) with EGFR mutation-positive NSCLC compared with standard chemotherapy. Our results are consistent with previous studies in Asian patients and our own experience in European patients and suggest that EGFR tyrosine-kinase inhibitors have greater first-line efficacy than does standard chemotherapy in this group of patients in this setting. Our results also clearly show the clinical usefulness of testing for EGFR mutations at baseline in patients with NSCLC to guide treatment and improve outcomes. Despite progress in recent years, lung cancer remains the leading cause of cancer death, and increased understanding of the potential of biomarkers will hopefully lead to improved outcomes. We recommend that tissue-based screening for EGFR mutations be part of routine clinical practice and that EGFR tyrosine-kinase inhibitors be the standard first-line treatment for patients with NSCLC and EGFR mutations. Clinicians now know that they need to screen their patients for EGFR mutations, and if mutations are detected, patients should be started with a tyrosine-kinase inhibitor—either erlotinib or gefitinib, dependent on the standard of care at each institution.

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,[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.

Contributors

RR and LP-A were the principal investigators. RR, BM, TM, MS-R, JJS, and LP-A contributed to protocol design, recruitment of patients, and data interpretation. AD and JJS did the statistical analyses. CQ, IdA, JLR, and MAM did the molecular analyses. MT supervised the molecular analyses. RR wrote the manuscript. All other authors helped recruit patients. All authors reviewed and approved the final version of the manuscript.

Conflicts of interest

LP-A has given scientific advice and lectures with compensation from Hoffmann-La Roche. RC has received travel grants and consulted for Hoffmann-La Roche at an advisory board meeting for bevacizumab. All other authors declared no conflicts of interest.

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