Erlotinib versus docetaxel as second-line treatment of patients with advanced non-small-cell lung cancer and wild-type *EGFR* tumours (TAILOR): a randomised controlled trial

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Summary

Background **Erlotinib is registered for treatment of all patients with advanced non-small-cell lung cancer (NSCLC). However, its efficacy for treatment of patients whose tumours are *EGFR* wild-type—which includes most patients—is still contentious. We assessed the efficacy of erlotinib compared with a standard second-line chemotherapy in such patients.**

Methods **We did this randomised controlled trial in 52 Italian hospitals. We enrolled patients who had metastatic NSCLC, had had platinum-based chemotherapy, and had wild-type *EGFR* as assessed by direct sequencing. Patients were randomly assigned centrally (1:1) to receive either erlotinib orally 150 mg/day or docetaxel intravenously 75 mg/m² every 21 days or 35 mg/m² on days 1, 8, and 15, every 28 days. Randomisation was stratified by centre, stage, type of first-line chemotherapy, and performance status. Patients and investigators who gave treatments or assessed outcomes were not masked to treatment allocation, investigators who analysed results were. The primary endpoint was overall survival in the intention-to-treat population. The study is registered at ClinicalTrials.gov, number NCT00637910.**

Findings **We screened 702 patients, of whom we genotyped 540. 222 patients were enrolled (110 assigned to docetaxel *vs* 112 assigned to erlotinib). Median overall survival was 8·2 months (95% CI 5·8–10·9) with docetaxel versus 5·4 months (4·5–6·8) with erlotinib (adjusted hazard ratio [HR] 0·73, 95% CI 0·53–1·00; p=0·05). Progression-free survival was significantly better with docetaxel than with erlotinib: median progression-free survival was 2·9 months (95% CI 2·4–3·8) with docetaxel versus 2·4 months (2·1–2·6) with erlotinib (adjusted HR 0·71, 95% CI 0·53–0·95; p=0·02). The most common grade 3–4 toxic effects were: low absolute neutrophil count (21 [20%] of 104 in the docetaxel group *vs* none of 107 in the erlotinib group), skin toxic effects (none *vs* 15 [14%]), and asthenia (ten [10%] *vs* six [6%]).**

Interpretation **Our results show that chemotherapy is more effective than erlotinib for second-line treatment for previously treated patients with NSCLC who have wild-type *EGFR* tumours.**

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Introduction

By the time most patients are diagnosed with non-small-cell lung cancer (NSCLC), the disease is already advanced.[1] Platinum doublets are the first-line treatment for unselected advanced NSCLC and three drugs have been approved for second-line treatment: docetaxel, pemetrexed, and erlotinib. Docetaxel is effective for second-line treatment of metastatic NSCLC, prolonging progression-free survival and overall survival.[2,3] Pemetrexed has been shown to have a similar efficacy to docetaxel in the same setting.[4] In 2005, a landmark trial[5,6] showed that erlotinib—a small molecule inhibitor of EGFR tyrosine kinase—improved overall survival, progression-free survival, and quality of life, compared with placebo in previously treated patients deemed unfit for further chemotherapy. Three studies have described activating mutations in advanced NSCLC that made tumours more sensitive to the EGFR tyrosine kinase inhibitors gefitinib and erlotinib.[7–9] At present, EGFR tyrosine kinase inhibitors are the treatment of choice for patients with *EGFR*-mutated tumours as both first and further lines of treatments.[10] However, most patients have *EGFR* wild-type and the role of EGFR tyrosine kinase inhibitors in the treatment of these patients is still contentious. Nevertheless, erlotinib is approved for second-line and third-line treatment of unselected patients.[11,12]

At least six randomised trials have compared EGFR tyrosine kinase inhibitors with second-line chemotherapy in patients with NSCLC.[13–18] Although all trials showed much the same survival with both approaches, no trial was properly designed to investigate the treatment benefit according to *EGFR* genotype. Retrospective analyses by genotype were also restricted by the high percentage patients with unknown EGFR status, in most cases reaching 80% or more.[10]

At present, two EGFR tyrosine kinase inhibitors are commercially available for patients with *EGFR* mutations: gefitinib and erlotinib.[10,19] Only erlotinib is approved for patients with wild-type *EGFR* tumours.[11]

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Because the benefit of EGFR tyrosine kinase inhibitors varies widely between patients with *EGFR* mutations and those with wild-type *EGFR*, it is crucial to establish which second-line treatment is preferable. Thus, we did the TArceva Italian Lung Optimization tRial (TAILOR), to compare erlotinib with docetaxel in patients who failed first-line platinum-based chemotherapy and who had the wild-type *EGFR* gene.[20,21]

Methods

Study design and patients

This multicentre, randomised trial was done in 52 Italian hospitals. Patients with advanced NSCLC were registered and genotyped for *EGFR* and *KRAS* mutations. We enrolled patients with wild-type *EGFR* (appendix),[21] who had recurrence or progression after failing platinum-based chemotherapy. Tumour samples were centrally reclassified on the basis of the 2004 WHO classification.[22] Suitable samples were genotyped in parallel by investigators in two independent laboratories using two different techniques. *EGFR* mutational status of exons 19–21 was assessed by Sanger sequencing and by RFLP. *KRAS* genotyping was done by Sanger sequencing and high-resolution melting analysis. The Scorpion/ARMS technique[23,24] was used for samples with little material. In cases of disagreement, the analysis was repeated, starting from biopsies. Results were uploaded to the study database within 7 days and automatically communicated to investigators. Patients with mutated *EGFR* tumours were treated with EGFR tyrosine kinase inhibitors and excluded from the study.

See Online for appendix

Other eligibility criteria were: no previous treatment with taxanes or anti-EGFR drugs, an Eastern Cooperative Oncology Group performance status of 2 or less, and adequate vital functions.

The trial was initially designed to assess the different effects of docetaxel and erlotinib according to selected biomarkers (*EGFR* amplification and protein expression, and *KRAS* mutations).[20,21] At the first planned interim analysis, the independent data and safety monitoring committee did a pre-planned masked efficacy analysis, which suggested—in conjunction with other data[25]—that these biomarkers had no effect. As a result, the committee recommended changing the primary objective to a comparison of efficacy between the two groups. Therefore, the protocol was amended accordingly in May, 2011 and the primary objective was changed. The sample size was recalculated by two independent statisticians (appendix). The study still had the desired power to detect a difference in survival between treatment groups and only lost the power to test the interaction between treatments and biomarkers.[26]

For the **QLQ-C30 questionnaire** see http://groups.eortc.be/qol/eortc-qlq-c30]

The ethics committees and relevant health authorities of each participating institution approved the study protocol and amendments. All patients provided written informed consent. The study complied with the declaration of Helsinki and was done in accordance with good clinical practice guidelines.

Randomisation and masking

A customised, web-based database was set up for registration, randomisation, monitoring, local data entry, and central data management. We used electronic clinical research forms. Treatment was randomly allocated in a 1:1 ratio with a minimisation algorithm, which stratified treatment allocation by centre, stage, type of first-line platinum-based chemotherapy (pemetrexed *vs* vinorelbine *vs* gemcitabine), and Eastern Cooperative Oncology Group performance status (0–1 *vs* 2). Investigators who did tumour genotyping were masked to treatment allocation. Because of the nature of the interventions, patients were not masked to assigned treatment. Investigators who gave treatment and assessed outcomes were not masked to treatment allocation, but investigators who analysed results were.

Procedures

Erlotinib 150 mg was given orally every day. In cases of grade 3–4 toxic effects, treatment was withheld for up to 15 days or the dose was reduced to 100 mg, or both. Patients discontinued the study if severe toxic effects recurred after doses of 150 mg were resumed. Docetaxel was given intravenously, at either 75 mg/m² every 21 days, or 35 mg/m² on days 1, 8, and 15, every 28 days. In cases of severe toxic effects, doses were reduced by a maximum of 50% for those on the 75 mg/m² dose or down to 30 mg/m² for those on the 35 mg/m² dose. The two docetaxel regimens have similar efficacy and are both approved in Italy.[27] Further treatment, but not crossover, was permitted. Tumour response was assessed at baseline and every 9 weeks according to RECIST 1.1 criteria. Toxic effects were graded according to the National Cancer Institute common toxicity terminology criteria for adverse events (version 3.0).[28] Quality of life was assessed with QLQ-C30 questionnaire and QLQ-LC13 questionnaire[29] given at baseline and before each treatment cycle.

A certified academic research organisation was in charge of study monitoring, data management, and data analysis. All participating centres were audited at least once. Data completeness, consistency, and accuracy were checked with a predefined data validation plan. The independent data and safety monitoring committee assessed the results of interim analyses during the trial. Two independent radiologists, masked to treatment assignment, did post-hoc reviews of all the scans of responding patients.

The primary endpoint was overall survival. Secondary endpoints were progression-free survival, the proportion of patients who had a response, and quality of life.

Statistical analysis

To achieve 80% power at a 0·05 two-sided significance level to detect a 33% fall in mortality, we calculated that 199 events were required and 220 patients had to be followed up for at least 1 year. We assumed that 5% of

patients would be lost to follow-up. We expected a similar reduction in progression-free survival. We assessed all efficacy outcomes in the intention-to-treat population, which included all enrolled patients who did not violate the eligibility criteria. Only patients who had received at least one treatment cycle were included in the safety analysis. Overall survival and progression-free survival were assessed from the time of treatment allocation to death from any cause or disease progression. Patients who had not died or had disease progression at the date of study cutoff were censored at the last available information on status.

Time-to-event data were analysed by the Kaplan-Meier method. Cox proportional hazards model was used to adjust the treatment effect for histology, smoking habit, Eastern Cooperative Oncology Group performance status, sex, best response to first-line chemotherapy, and *KRAS* mutational status. Proportional hazards assumptions for Cox models were verified through graphical plots of Schoenfeld residuals over time, by adding time-dependent variables in the model and testing their statistical significance (appendix). A further analysis was done to assess possible treatment effects by factor interactions using a χ^2 test for heterogeneity and described with forest plots.

A subgroup analysis of differences according to pre-specified baseline variables is ongoing and results will be presented elsewhere. Responses were compared with the χ^2 test and adverse events were compared by the χ^2 for trends. All χ^2 tests were calculated for one degree of freedom (unless specified), the associated p values were two-sided. The analyses were done with SAS (version 9.2). The trial is registered with ClinicalTrials.gov, number NCT00637910.

	Docetaxel group (n=110)	Erlotinib group (n=109)
Age (years)	67 (35–83)	66 (40–81)
Sex		
Men	73 (66%)	77 (71%)
Women	37 (34%)	32 (29%)
Eastern Cooperative Oncology Group performance status		
0	53 (48%)	52 (48%)
1	50 (45%)	48 (44%)
2	7 (6%)	9 (8%)
Histology		
Squamous	23 (21%)	31 (28%)
Adenocarcinoma	83 (75%)	69 (63%)
Large-cell carcinoma	1 (1%)	1 (1%)
Bronchoalveolar	0 (0%)	3 (3%)
Others	3 (3%)	5 (5%)
Smoking habits		
Current and former smokers	80 (73%)	90 (83%)
Never smokers	30 (27%)	19 (17%)
Ethnic origin		
White	109 (99%)	108 (99%)
Asian	1 (1%)	1 (1%)
Previous chemotherapy		
First line	102 (93%)	100 (92%)
Adjuvant	7 (6%)	9 (8%)
Unknown	1 (1%)	0 (0%)
Previous best response to first-line treatment	n=102	n=100
Complete response	0 (0%)	1 (1%)
Partial response	36 (35%)	44 (44%)
Stable disease	36 (35%)	24 (24%)
Progressive disease	30 (29%)	31 (31%)

Data are median (IQR), n, or n (%).

Table 1: **Baseline demographics**

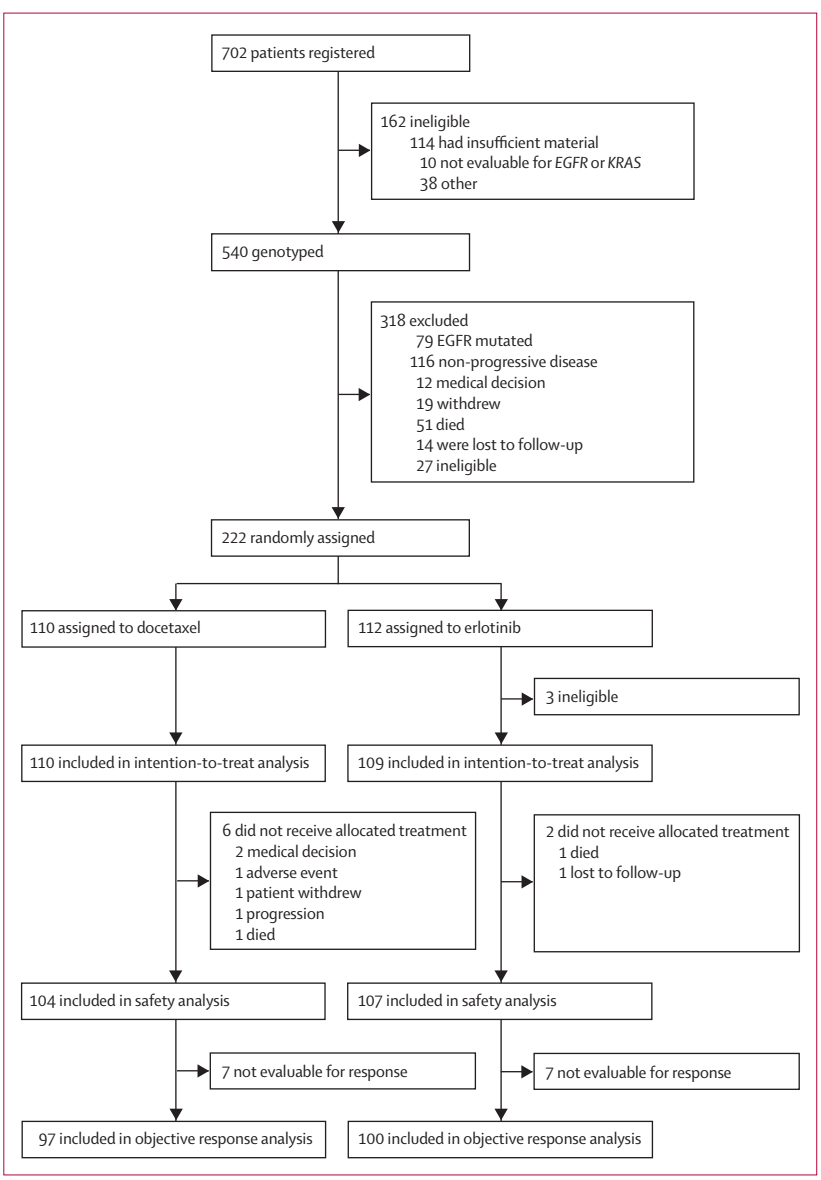

Figure 1: **Trial profile**

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

	Docetaxel group (n=51)	Erlotinib group (n=53)
Pemetrexed	18 (35%)	22 (42%)
Gemcitabine	11 (22%)	9 (17%)
Vinorelbine	18 (35%)	14 (26%)
Docetaxel	0 (0%)	8 (15%)
Erlotinib	4 (8%)	0 (0%)

Table 2: **Post-progression treatment**

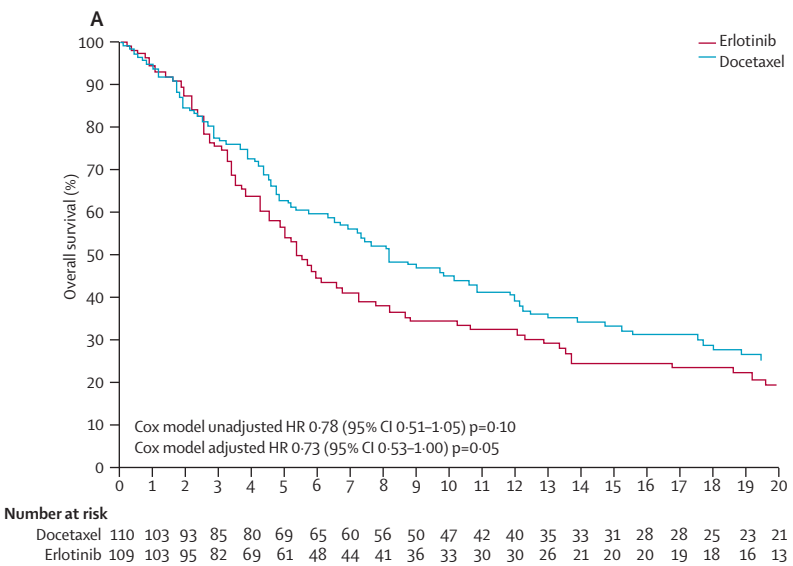

Figure 2: **Kaplan-Meier survival curves**
Overall survival (A) and progression-free survival (B).

Results

From Oct 12, 2007, to March 13, 2012, 702 patients were registered; of whom, 540 were genotyped and 222 were enrolled. 110 patients were randomly assigned to receive docetaxel and 112 to receive erlotinib. Table 1 shows baseline characteristics. The cutoff date for analysis was Jan 31, 2013.

Figure 1 shows the trial profile. The main reason for exclusion from genotyping was lack of sufficient tissue. The main reasons for exclusion from the intention-to-treat population were the presence of *EGFR* mutation, early death, or no apparent progression after first-line chemotherapy.

Treatment was primarily discontinued because of disease progression and death (73/104 [70%] in the docetaxel group *vs* 94/107 [88%] in the erlotinib group). Other reasons for discontinuation—patient or doctor decision, treatment-unrelated serious adverse events, toxic effects—were similar between treatment groups. Roughly half of patients in each group received a third-line treatment with vinorelbine, gemcitabine, or pemetrexed (table 2). In violation of the trial protocol, seven patients in the erlotinib group crossed to docetaxel treatment and four in the docetaxel group crossed to erlotinib treatment after progression.

Patients treated with docetaxel received a median of three cycles, with a median dose per cycle of 91 mg/m² for the weekly schedule and 75 mg/m² for the 3-weekly schedule. Patients treated with erlotinib received a median of two cycles, with a median dose of 137 mg/day.

After a median follow-up of 33 months (IQR 21–33), 196 patients had disease progression and 187 died. 16 of those that died (eight in each group) progressed clinically and died without radiological confirmation of progression. Figure 2 shows the survival curves. Median overall survival was 8·2 months (95% CI 5·8–10·9) in the docetaxel group and 5·4 (4·5–6·8) in the erlotinib group (adjusted hazard ratio [HR] 0·73, 95% CI 0·53–1·00; p=0·05; unadjusted HR 0·78, 95% CI 0·51–1·05; p=0·10). Survival after 1 year was 39·6% (95% CI 36·1–43·4) versus 31·8% (95% CI 29·1–34·7).

Median progression-free survival was 2·9 months (95% CI 2·4–3·8) in the docetaxel group and 2·4 months (2·1–2·6) in the erlotinib group (adjusted HR 0·71, 95% CI 0·53–0·95; p=0·02; unadjusted HR 0·72, 95% CI 0·55–0·94; p=0·01). Progression-free survival at 6 months was 27·3% (95% CI 25·1–29·7) in the docetaxel group and 16·5% (15·4–17·7) in the erlotinib group. Median survival after progression was 3·2 months (95% CI 2·1–4·9) for docetaxel and 2·5 months (1·6–3·7) for erlotinib. Median times to evaluation were much the same in each group up to the last evaluation (appendix).

	Docetaxel group (n=97)	Erlotinib group (n=100)	p value*
CR	5 (5·2%; 1·7–11·6)	0 (0·0; 0·0–0·0)	0·001
PR	10 (10·3%; 5·1–18·1)	3 (3·0%; 0·6-8·5)	..
SD	28 (28·9%; 20·1–39·0)	23 (23·0%; 15·2-32·5)	..
PD	54 (55·7%; 45·2–65·8)	74 (74·0%; 64·3-82·3)	..

Data are n (%; 95% CI) unless stated otherwise. CR=complete response. PR=partial response. SD=stable disease. PD=progressive disease. *χ^2 test for trend.

Table 3: **Best response to treatment**

Significantly more patients had a response or achieved disease control with docetaxel than did those treated with erlotinib: 15 (15·5%, 95% CI 8·9–24·2) patients in the docetaxel group had an objective response to treatment, compared with three (3·0%, 0·6–8·5) in the erlotinib group (p=0·003); 43 (44·3%, 31·4–52·1) in the docetaxel group achieved disease control versus 26 (26·0%, 17·7–35·7) in the erlotinib group (p=0·007; table 3). Investigator assessments of response were confirmed by post-hoc independent review in 94·4% of cases (three in the erlotinib group and 14 in the docetaxel group). Tumour samples from the three patients in the erlotinib group who had responses were re-sequenced from the original biopsies in a posthoc assessment, confirming the absence of mutations in *EGFR* exons 18–21.

Outcomes across all subgroups seemed better with docetaxel than with erlotinib, both in terms of overall survival and progression-free survival, although many of these differences were not significant (figure 3). No interaction was detected between any of the considered factors, including *KRAS* mutational status, which had no prognostic effect (figure 3). In the multivariable analysis, only treatment and performance status were significantly associated with overall and progression-free survival (appendix).

18 (17%) of 104 patients in the docetaxel group and 19 (18%) of 107 in the erlotinib group had a treatment delay related to toxic effects. Treatment-related adverse events led to dose modifications in 23 (22%) of 104 patients in the docetaxel group and 23 (21%) of 107 in the erlotinib group (table 4). Neutropenia, neurological toxic effects, alopecia, asthenia, and nausea were more common in the docetaxel group than in the erlotinib group; most patients in the erlotinib group had skin toxic effects (table 5, appendix). One patient in each group died from treatment-related sequelae (grade 4 diarrhoea in the erlotinib group and febrile neutropenia in the docetaxel group).

In the erlotinib group grade 3–4 skin toxic effects were not associated with overall survival (HR 0·70, 95% CI 0·39–1·27; p=0·24), progression-free survival

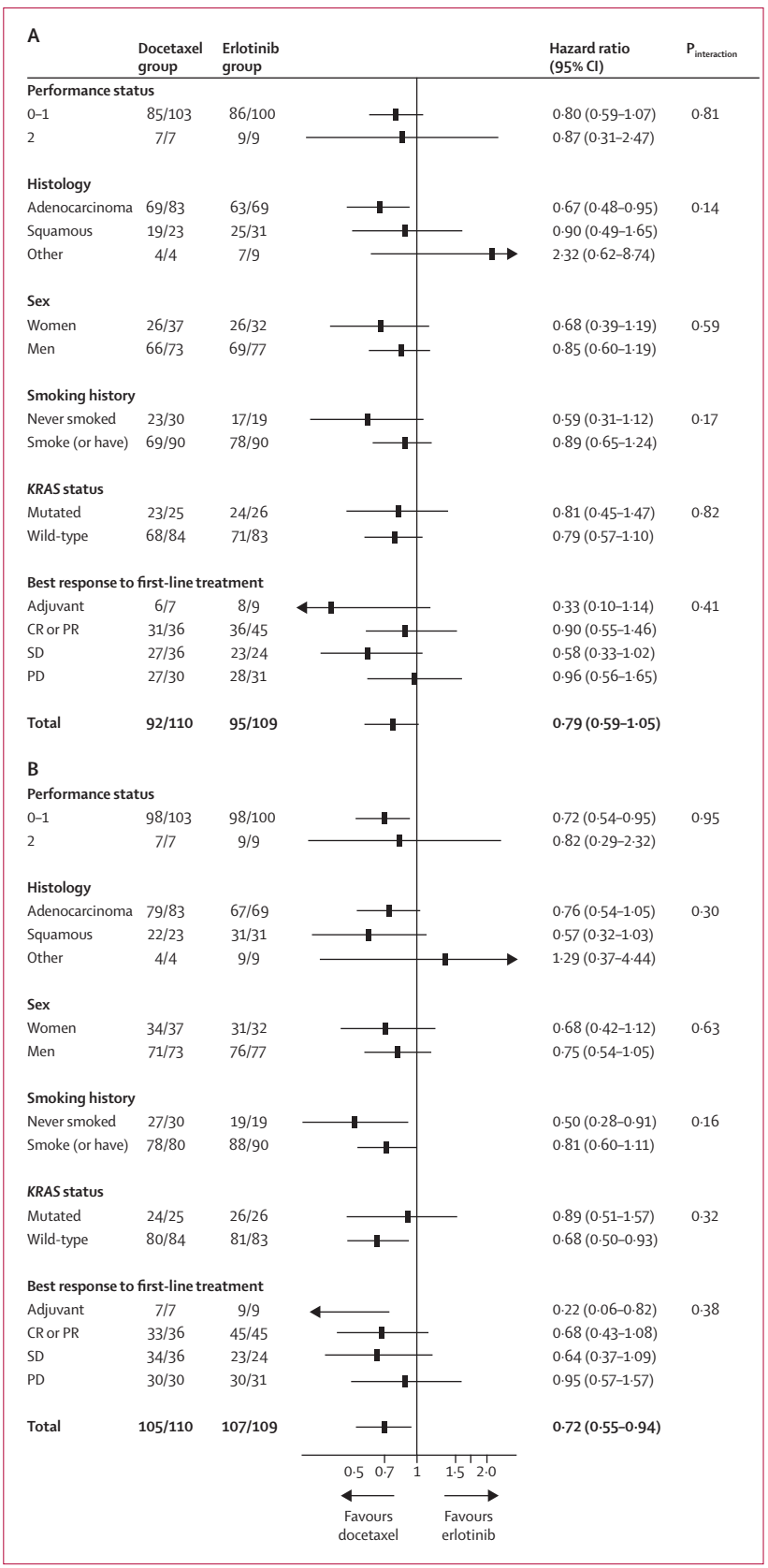

Figure 3: **Effect of treatment on survival in subgroups**
Data are events/patients. Overall survival (A) and progression-free survival (B). CR=complete response. PR=partial response. SD=stable disease. PD=progressive disease.

	Docetaxel group (n=104)		Erlotinib group (n=107)
	Weekly regimen (n=41)	3-weekly regimen (n=63)	
Patients with serious adverse events	7 (17%)	8 (13%)	15 (14%)
Treatment-related serious adverse events	2 (5%)	2 (3%)	2 (2%)
Treatment-related deaths	0 (0%)	1 (2%)	1 (1%)
Treatment-related adverse events leading to withdrawal	2 (5%)	2 (3%)	3 (3%)
Treatment-related adverse events leading to dose modification	11 (27%)	12 (19%)	23 (21%)

Table 4: **Safety analysis**

	Docetaxel group (n=104)			Erlotinib group (n=107)		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Febrile neutropenia	5 (5%)	1 (1%)	3 (3%)	0 (0%)	0 (0%)	0 (0%)
Neutropenia	31 (30%)	9 (9%)	12 (12%)	3 (3%)	0 (0%)	0 (0%)
Diarrhoea	22 (21%)	2 (2%)	0 (0%)	32 (30%)	3 (3%)	0 (0%)
Alopecia	34 (33%)	12 (12%)	3 (3%)	2 (2%)	0 (0%)	0 (0%)
Asthenia	51 (49%)	10 (10%)	0 (0%)	40 (37%)	4 (4%)	2 (2%)
Neurological	17 (16%)	10 (10%)*	1 (1%)	5 (5%)	1 (1%)*	1 (1%)
Nausea or vomiting	24 (23%)	3 (3%)	0 (0%)	11 (10%)	1 (1%)	0 (0%)
Dermatological†	4 (4%)	0 (0%)	0 (0%)	62 (58%)	10 (9%)	5 (5%)

*Includes grade 2 events. †Includes rash, nail disorders, dry skin, and pruritus.

Table 5: **Drug-related adverse events**

(HR 0·68, 95% CI 0·39–1·18; p=0·17), or response rate (χ^2 0·80; p=0·37), although these analyses are based on only 13 deaths and 15 disease progressions. Data about quality of life have not yet been analysed, and will be reported separately.

Discussion

Our results show that chemotherapy should remain the second-line treatment of choice in patients with NSCLC with wild-type *EGFR* status. Docetaxel was better than erlotinib for all clinical outcomes. Our multivariable analysis adjusted for possible confounding factors, some of which were unbalanced at baseline, was consistent with these results. The baseline differences were simply the result of chance, as confirmed by the results of the interaction analysis. Progression was assessed in a similar proportion of patients in each group, excluding potential major biases in the analyses.[30] Erlotinib was not better than docetaxel in any of the subgroup analyses, including those of non-smokers and wild-type *KRAS* carriers, even though other studies[31] suggest higher activity of EGFR tyrosine kinase inhibitors in these patients.

Six other trials have compared chemotherapy with an EGFR tyrosine kinase inhibitor. Two[13,14] compared erlotinib with chemotherapy, while the remaining four[14–18] compared gefitinib with chemotherapy. None were specifically designed to address the role of *EGFR* as a predictive marker. Subgroup analyses by genotype are open to potential bias: *EGFR* was genotyped in five trials and only in a proportion of enrolled patients (range 12–52%) in each trial.[21] In all these trials, the results in the wild-type *EGFR* population were statistically inconclusive and clinically contradictory. In addition, a meta-analysis[10] concluded that progression-free survival is longer in patients with wild-type *EGFR* when treated with chemotherapy compared with tyrosine kinase inhibitors (HR 1·23, 95% CI 1·05–1·46), but overall survival does not differ significantly (HR 0·93, 95% CI 0·79–1·10). TAILOR was included in the meta-analysis of progression-free survival, but not that of overall survival.

In trials of first-line treatment, tyrosine kinase inhibitors have also fared worse than chemotherapy when either added to or compared with platinum-based regimens in patients with wild-type *EGFR*.[10] Furthermore, in a subgroup analysis involving less than 50% of the SATURN trial population,[32] the effect of erlotinib on progression-free survival was much lower in the subgroup of patients with wild-type *EGFR* (HR 0·78, 95% CI 0·63–0·96; p=0·01), than that in patients with an *EGFR* mutation (HR 0·1, 95% CI 0·04–0·25; p=0·0001). In the INFORM trial,[33] which investigated maintenance with gefitinib, a subgroup analysis of 27% of the genotyped population showed a significant benefit of treatment in patients with mutant (HR 0·17, 95% CI 0·07–0·42) but not in those with wild-type *EGFR* (HR 0·86, 95% CI 0·48–1·51). The small benefit of tyrosine kinase inhibitors in patients with the wild-type *EGFR* in the SATURN trial, coupled with the sporadic objective responses in TAILOR and other trials[34,35]—suggests two possibilities. Either unknown genetic damage caused a positive response to erlotinib[36] even in the absence of a mutated *EGFR*, or *EGFR* mutations were not detected because of tumour heterogeneity. To investigate these possibilities, we are planning to do exome sequencing on samples from the erlotinib responders in the TAILOR population.

When TAILOR was designed, oncogene addiction had been shown for only a handful of cancers.[37] Now, genotyping is used to personalise treatment for 10–20% of patients with NSCLC carrying mutated *EGFR* or the *EML4–ALK* translocation. Many new candidate genomic features for personalisation of treatment have been identified and some encode targetable kinases (eg, ROS1, RET), although these alterations are rare.[38] Most of these mutations seem to be mutually exclusive, thus defining

clinically distinct entities for which safe corresponding target drugs are already available. Thus, the ineffectiveness of erlotinib for wild-type *EGFR* tumours is not surprising.[36]

However, genotyping is not always feasible in patients with NSCLC; in TAILOR, around 20% of tissue samples from registered patients were inadequate for genetic testing. Clinical criteria are less discriminating than is mutational analysis for identification of tumours that are sensitive to EGFR tyrosine kinase inhibitors, therefore improvements in tissue acquisition and handling are needed. However, for the rare cases in which tissue samples are unattainable, erlotinib treatment should be considered if the patient is thought to have characteristics (eg, female, adenocarcinoma histology, non-smoker, Asian ethnic origin) suggestive of having an *EGFR*-mutated tumour. Furthermore, skin toxic effects after initial treatment might be used as an indicator of response in patients with unknown *EGFR* genotype or in patients with wild-type *EGFR*, as suggested by the results of TOPICAL.[39] Skin toxic effects were not a significant predictor of responsiveness in TAILOR and we cannot explain this discrepancy. Possibly, misclassification of intensity could have reduced the size of the association—in TAILOR the incidence of grade 3–4 toxic effects was higher than that usually reported, whereas the incidence of all grades of skin toxic effects accords with previous findings. The low number of events might also have reduced the size of the association.

Our study has some limitations. First, TAILOR was originally designed to also test the effect of *EGFR* expression, *EGFR* amplification, and *KRAS* mutation on treatment outcomes.[20] Because the immunohistochemistry and fluorescent in-situ hybridisation assays were unreliable for *EGFR* expression and amplification, we changed to a straightforward superiority design. However, the amendment of the trial design was done totally independently, and did not affect eligibility, the randomisation procedure, or outcome measurement. As a result of these changes, we could not properly assess the predictive role of *KRAS* mutation because of lack of power for the interaction test. Second, although patients were enrolled consecutively, the proportion who had adenocarcinoma was higher than expected. Until 2011, the test for the *EGFR* mutation was not routinely done in Italy. Clinicians might have therefore favoured the registration of patients with adenocarcinoma because the incidence of *EGFR* mutations is expected to be higher in this subgroup. Indeed, the percentage of genotyped patients with mutated *EGFR* was higher than expected for a white population. However, this fact does not impinge on the internal validity or the results of the trial.

TAILOR drew patients from daily clinical practice of small and large general hospitals throughout Italy; therefore, the results are likely to be widely generalisable. Furthermore, we were able to use robust logistics and centralised, quality-controlled genotyping.

Panel: Research in context

Systematic review

The study question was formulated based on a previous systematic review.[40] Since then, evidence has been published about the role of biological and clinical features in prediction of efficacy of EGFR tyrosine kinase inhibitors.[22]

Interpretation

EGFR tyrosine kinase inhibitors are the treatment of choice for patients with non-small-cell lung cancer who have *EGFR* mutations, but their role in the treatment of patients with wild-type *EGFR* tumours is still contentious. 22 studies have indirectly addressed this issue in subgroup analyses of non-genotyped populations, both in first-line and second-line treatment, or as maintenance. TAILOR is, to the best of our knowledge, the only study to investigate this issue in a direct comparison of docetaxel and erlotinib for second-line treatment after platinum-based chemotherapy. Our results show that docetaxel is more effective than erlotinib in this population. Thus, in the absence of a target oncogene, the one-size-fits-all cytotoxic approach to second-line treatment of advanced non-small-cell lung cancer remains the best option.

In conclusion, our results unequivocally show that—although neither docetaxel nor erlotinib are magic bullets for second-line treatment of NSCLC—a cytotoxic approach to treatment of patients with NSCLC is still the best option in the absence of a clear therapeutic target (panel).

Contributors

AS was the principal investigator. MCG, MB, and VT had the idea for the study. The steering committee designed the study. IF and ER collected data. ER, IF, and VT did the statistical analysis. GF, AB, FL, LM, MT, and RL were the principal investigators at the centres with the highest recruitment. MB, SV, FB, MM, MG, and CL did the molecular and pathological examinations. GG chaired the independent data monitoring and safety committee. MCG, VT, MB, and SM wrote the first draft. All the investigators reviewed and approved the final version. A full list of the TAILOR trialists can be found in the appendix.

Conflicts of interest

MCG, OM, and VT have been consultants for Eli-Lilly. MCG has been a consultant for Boehringer Ingelheim. VT and RL have been consultants for Roche. OM and VT have been consultants for Amgen. The other authors declare that they have no conflicts of interest.

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