Icotinib versus gefitinib in previously treated advanced non-small-cell lung cancer (ICOGEN): a randomised, double-blind phase 3 non-inferiority trial

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Summary

Background **Icotinib, an oral EGFR tyrosine kinase inhibitor, had shown antitumour activity and favourable toxicity in early-phase clinical trials. We aimed to investigate whether icotinib is non-inferior to gefitinib in patients with non-small-cell lung cancer.**

Methods **In this randomised, double-blind, phase 3 non-inferiority trial we enrolled patients with advanced non-small-cell lung cancer from 27 sites in China. Eligible patients were those aged 18–75 years who had not responded to one or more platinum-based chemotherapy regimen. Patients were randomly assigned (1:1), using minimisation methods, to receive icotinib (125 mg, three times per day) or gefitinib (250 mg, once per day) until disease progression or unacceptable toxicity. The primary endpoint was progression-free survival, analysed in the full analysis set. We analysed EGFR status if tissue samples were available. All investigators, clinicians, and participants were masked to patient distribution. The non-inferiority margin was 1·14; non-inferiority would be established if the upper limit of the 95% CI for the hazard ratio (HR) of gefitinib versus icotinib was less than this margin. This study is registered with ClinicalTrials.gov, number NCT01040780, and the Chinese Clinical Trial Registry, number ChiCTR-TRC-09000506.**

Findings **400 eligible patients were enrolled between Feb 26, 2009, and Nov 13, 2009; one patient was enrolled by mistake and removed from the study, 200 were assigned to icotinib and 199 to gefitinib. 395 patients were included in the full analysis set (icotinib, n=199; gefitinib, n=196). Icotinib was non-inferior to gefitinib in terms of progression-free survival (HR 0·84, 95% CI 0·67–1·05; median progression-free survival 4·6 months [95% CI 3·5–6·3] *vs* 3·4 months [2·3–3·8]; p=0·13). The most common adverse events were rash (81 [41%] of 200 patients in the icotinib group *vs* 98 [49%] of 199 patients in the gefitinib group) and diarrhoea (43 [22%] *vs* 58 [29%]). Patients given icotinib had less drug-related adverse events than did those given gefitinib (121 [61%] *vs* 140 [70%]; p=0·046), especially drug-related diarrhoea (37 [19%] *vs* 55 [28%]; p=0·033).**

Interpretation **Icotinib could be a new treatment option for pretreated patients with advanced non-small-cell lung cancer.**

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Introduction

Lung cancer is the leading cause of cancer-related death worldwide.[1] Chemotherapy has been the cornerstone of treatment for non-small-cell lung cancer for many years. However, the development of EGFR tyrosine kinase inhibitors (TKIs) has led to substantial clinical improvements in treatment outcomes. Gefitinib and erlotinib are EGFR TKIs that were shown to greatly improve clinical outcomes and safety when compared with chemotherapy or placebo in second-line or further-line treatment, resulting in a recommendation for EGFR TKI monotherapy in unselected populations.[2,3] EGFR mutations can increase tumour sensitivity to EGFR TKIs[4,5] and are more common in Asian people (40–50%) than in white people (10%);[6–9] therefore, EGFR TKIs might be particularly beneficial in Asian populations.

Icotinib, an orally administered EGFR TKI, has potent antitumour activity in vitro and in vivo.[10] Moreover, icotinib showed high specificity and selectivity to its target EGFR in a preclinical kinase profiling study: only EGFR and its mutants were inhibited among 88 kinases profiled.[10] A favourable safety profile was noted in phase 1 and 2 trials; the most common adverse events included rash and diarrhoea, and no cases of interstitial lung disease were reported.[11,12] The clinical benefit of icotinib was further shown in a phase 2 study[13] in which 103 patients were enrolled at ten dose levels. Objective responses were noted in 29·2% of patients, disease control was achieved in 78·1%; three complete responses were reported.[13]

One of the major differences between icotinib and other TKIs such as gefitinib is the half-life in the body. According to previous findings,[14] icotinib has a shorter half-life than

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gefitinib, owing to the different profiles of the P450 metabolism enzymes that metabolise these drugs. The half-life is about 40 h for gefitinib and about 6–8 h for icotinib;[11,15] therefore, gefitinib is taken once per day, whereas icotinib is taken three times per day (maximum tolerated dose 625 mg). The therapeutic window for icotinib—defined as the tolerable and effective dose range—was 100–625 mg three times per day.[13]

On the basis of the promising results with icotinib, we did a phase 3 randomised head-to-head trial (ICOGEN) at several sites across China to test the hypothesis that icotinib has similar clinical benefits and tolerability to gefitinib in patients with non-small-cell lung cancer.

Methods

Study design and patients

ICOGEN was a randomised, double-blind, head-to-head, phase 3 trial designed to assess whether icotinib is non-inferior to gefitinib in patients with locally advanced or metastatic non-small-cell lung cancer after failure of at least one platinum-based chemotherapy regimen. We recruited patients from 27 hospitals in China.

Eligible patients had histologically or cytologically confirmed, locally advanced (stage IIIB) or metastatic (stage IV) non-small-cell lung cancer with progression after at least one platinum-based chemotherapy regimen. Stages of cancer were classified according to the American Joint Committee on Cancer (AJCC) sixth edition of the tumour-node-metastasis staging system. Other eligibility criteria included: age 18–75 years, Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, at least one measurable lesion by Response Evaluation Criteria in Solid Tumors version 1.0 (RECIST), and adequate haematological and biochemical values. We excluded patients from the study if they had symptomatic brain metastases, malignant tumour within the previous 5 years, severe infection, congestive heart failure, previous treatment with drugs targeting EGFR, and a history of interstitial lung disease.

The study protocol was approved by independent ethics committees at every participating centre. All patients provided written informed consent before participation in the study. The study was undertaken in full accordance with International Conference of Harmonisation Good Clinical Practice guidelines, the Declaration of Helsinki, and other bioethical principles.

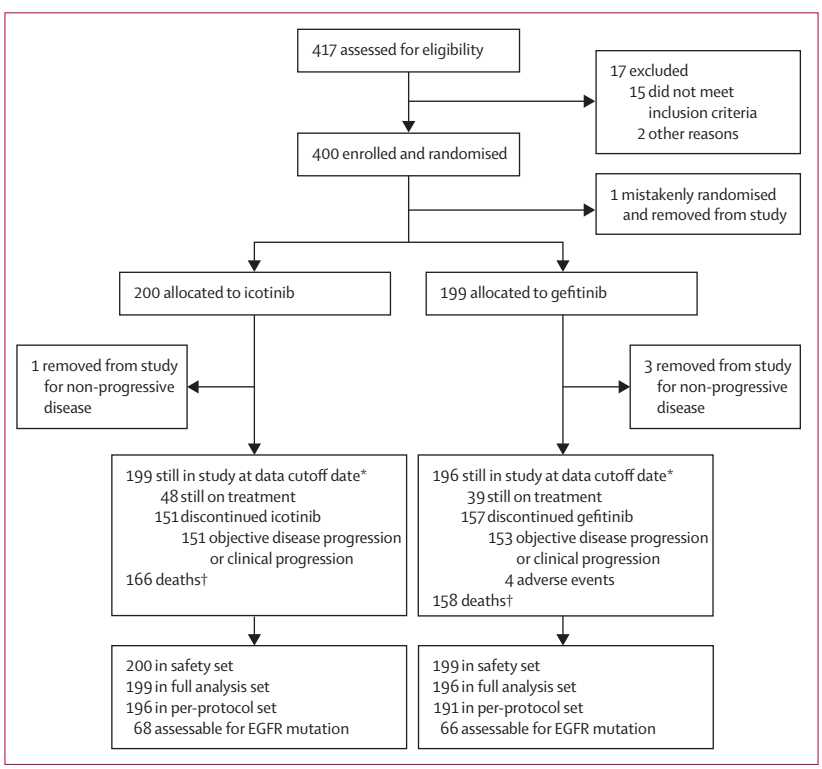

Figure 1: **Trial profile**
*Data cutoff date was June 13, 2010. †Overall survival data obtained in December, 2011.

Randomisation and masking

Randomisation was done by study staff logging into the central interactive randomisation network system. Minimisation methods were used. Patients were randomly assigned (1:1) to receive oral icotinib or gefitinib with a computer-generated sequence, stratified by pathological type (adenocarcinoma *vs* non-adenocarcinoma), smoking status, and ECOG performance status (0–1 *vs* 2). All investigators, clinicians, and participants were masked to patient distribution.

Procedures

Patients received 125 mg oral icotinib in tablet form three times per day and gefitinib-matching placebo tablets once daily, or 250 mg gefitinib in tablet form once daily and icotinib-matching placebo tablets three times daily, until disease progression, or unacceptable toxicity. The icotinib and gefitinib placebo tablets were identical in appearance to the actual drug tablets. No post-progression crossover was permitted.

Administration of study drug was designed to start within 2 days after randomisation. For patients who had grade 3 or 4 adverse events, dose reductions of icotinib or gefitinib were not recommended, but treatment was allowed to be interrupted for up to 14 days. If the adverse events did not resolve after 2 weeks of interruption, patients were withdrawn and excluded from the final primary endpoint analysis.

The primary endpoint was progression-free survival. The primary analysis was to assess non-inferiority of icotinib to gefinitib in the full analysis set (all randomly assigned patients that received at least one dose of study drug and did not seriously violate the protocol in any way). We also assessed efficacy in the per-protocol population, which was defined as patients who did not substantially deviate from the inclusion or exclusion criteria upon entry into the study, or from the protocol.

Secondary endpoints included overall survival, time to progression, the proportion of patients who achieved an objective response, toxic effects, and quality of life. Progression-free survival was defined as the duration between the date of randomisation and the date of the earliest occurrence of disease progression or death. Time to progression was defined as the duration between the date of randomisation and the date of the earliest occurrence of disease progression. Overall survival was defined as the time between the date of randomisation and the date of death due to any cause. We required all response assessments to be reviewed by an independent response evaluation committee (IREC), which was established at the start of the trial. However, two patients were not able to be assessed by the IREC because of uncompleted imaging data, but they were still included in the final analysis of the response rates. Tumour response assessment was done according to RECIST initially at 4 weeks after the first dose of study drug was received and then subsequently at 6 week intervals. We assessed quality of life with the use of the fourth edition of the Functional Assessment of Cancer Therapy–Lung (FACT-L) questionnaire and the Lung Cancer Symptoms Scale (LCSS).[16] Toxic effects were monitored and graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events, version 3.0.[17]

Gene mutations were investigated retrospectively (before unblinding of this study) with an EGFR PCR kit (Scorpions amplification refractory mutation system, Qiagen, Germany) to analyse exons 18–21 when paraffin-embedded tissues were available.

Statistical analysis

Median progression-free survival for Asian patients with non-small-cell lung cancer receiving gefitnib as second-line or third-line treatment is about 4·2 months.[18] The non-inferiority margin was predefined at 87·5% with the effect retention method.[19] The non-inferiority margin in terms of hazard ratio (HR) would be 1·14. Thus, non-inferiority would be established if the upper limit of the 95% CI for the HR of icotinib versus gefitinib was less than 1·14 in the full analysis set.

We calculated a sample size of 156 patients per group, assuming a type I error of 0·05 (one-sided), an 80% power of test, an assumed median progression-free survival of 4·2 months for gefitinib,[18] a non-inferiority margin of 87·5% (HR 1·14), a 0·5 coefficient of variability, and a 1:1 ratio of the sample sizes of the two groups. Since the anticipated dropout rate was 10%, and the actual value of coefficient of variability was likely to surpass our estimation of 0·5, we calculated that optimum sample size would be 200 patients per group in this study.

Based on the Cox proportional hazards model and considering the effect of smoking status (smoker *vs* non-smoker), ECOG performance status score (0–1 *vs* 2), and pathological type (adenocarcinoma *vs* non-adenocarcinoma), we estimated HR and 95% CI in the full analysis population and the per-protocol population with 80% power and a two-sided type I error of 0·05. Kaplan-Meier analyses were used to estimate median progression-free survival and overall survival, and the log-rank test was used to assess the difference between the two groups. We compared the differences in objective responses and disease control with the multivariate logistic regression model with the same covariates and odds ratios; we calculated 95% CIs as well. We analysed total LCSS and FACT-L scores with

	Icotinib (n=199)	Gefitinib (n=196)
Age (years)	57 (50–62)	57 (50–64)
Sex		
Men	117 (59%)	111 (57%)
Women	82 (41%)	85 (43%)
Smoking status		
Smokers	98 (49%)	94 (48%)
Non-smokers	101 (51%)	102 (52%)
ECOG performance status		
0–1	173 (87%)	175 (89%)
2	26 (13%)	21 (11%)
Tumour histology		
Adenocarcinoma	149 (75%)	150 (77%)
Squamous-cell carcinoma	34 (17%)	36 (18%)
Other*	16 (8%)	10 (5%)
Tumour metastases		
Liver	28 (14%)	21 (11%)
Lymph nodes	142 (71%)	132 (67%)
Adrenal glands	12 (6%)	28 (14%)
Brain	24 (12%)	26 (13%)
Bone	81 (41%)	77 (39%)
Other	97 (49%)	105 (54%)
Disease stage		
IIIB	37 (19%)	34 (17%)
IV	162 (81%)	162 (83%)
Previous chemotherapy		
1 regimen	126 (63%)	107 (55%)
2 regimens	72 (36%)	89 (45%)
3 regimens	1 (<1%)	0
EGFR status	n=68	n=66
Mutant	29 (43%)	39 (59%)
19del	16 (55%)	25 (64%)
Leu858Arg	10 (34%)	10 (26%)
Other†	3 (10%)	4 (10%)
Wild type	39 (57%)	27 (41%)

Data are median (IQR) or number (%). ECOG=Eastern Cooperative Oncology Group. *Including large-cell (two patients in the icotinib group *vs* two patients in the gefitinib group), mixed (six *vs* one), and other histology (eight *vs* seven). †Including Gly719X/Ser768Ile, Thr790Met, and Leu861Gln.

Table 1: **Baseline characteristics of patients in the full analysis set**

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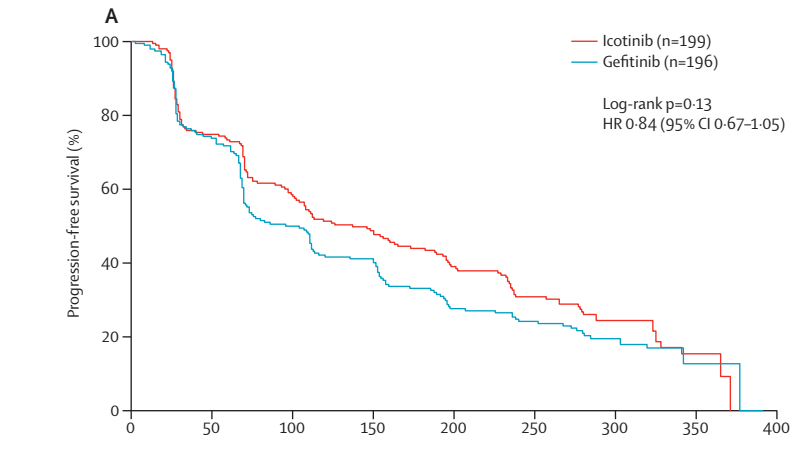

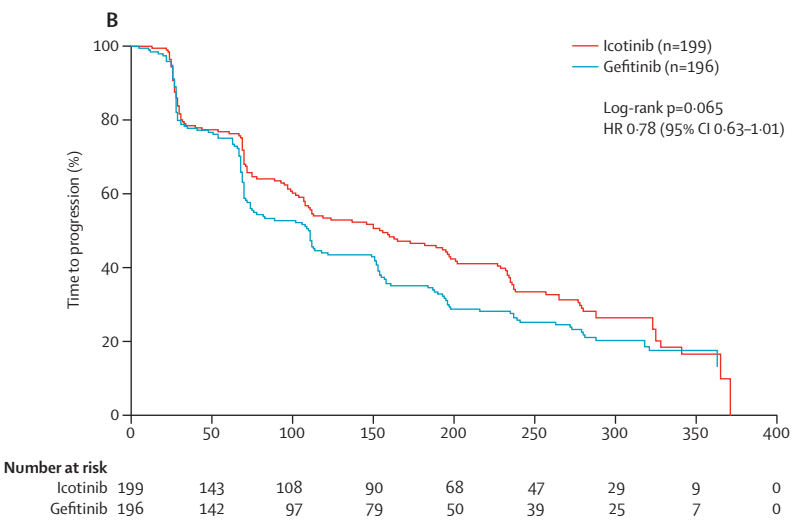

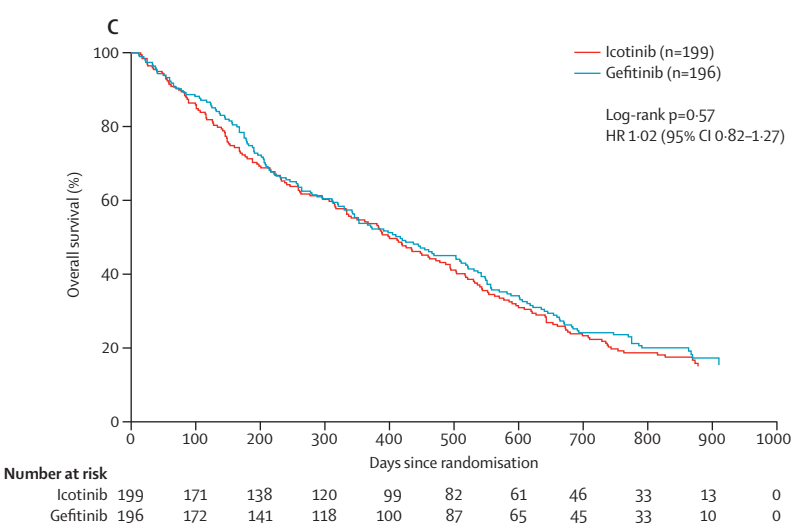

non-parametric tests, and did subgroup analysis and EGFR mutation type analysis.

We analysed safety and toxicity with a descriptive statistical method in the safety set (all randomly assigned patients that received at least one dose of the study drug). We used Fisher's exact test to compare the incidence of total and major adverse events between groups.

This study is registered with ClinicalTrials.gov, number NCT01040780, and the Chinese Clinical Trial Registry, number ChiCTR-TRC-09000506.

Role of the funding source

The coprincipal investigators (YSu and LZ[1]) and members of the study steering committee designed the trial in collaboration with the study sponsor, and the study was supervised by the steering committee and the sponsor. The sponsor provided funding and organisational support and collected the data. This report was written by YSu, who had full access to all the study data, and had final responsibility for the decision to submit for publication.

Results

417 patients were recruited for the eligibility assessment and 400 (96%) were enrolled between Feb 26, 2009, and Nov 13, 2009 (figure 1). One patient was excluded because of incorrect randomisation, and 399 were randomly assigned to receive icotinib (200 patients) or gefitinib (199 patients; figure 1). The study groups were similar at baseline (table 1). All 399 patients were included in the safety set, whereas 395 patients were included in the full analysis set (199 assigned to icotinib and 196 assigned to gefitinib); one patient in the icotinib group and three in the gefitinib group were excluded from the full analysis set because they had non-progressive disease at enrolment.

308 patients had progressed or died by the data cutoff date of June 13, 2010: 151 (76%) patients in the icotinib group had an event (137 [69%] progressions and 14 [7%] deaths) as did 157 (80%) of those in the gefitinib group (148 [76%] progressions and nine [5%] deaths). Icotinib was non-inferior to gefitinib in terms of progression-free survival in the full analysis set (HR [icotinib *vs* gefitinib] 0·84, 95% CI 0·67–1·05; p=0·13), with the upper confidence limit less than the predefined non-inferiority margin of 1·14 (figure 2A). Median progression-free survival was 4·6 months (95% CI 3·5–6·3) in the icotinib group and 3·4 months (2·3–3·8) in the gefitnib group; however, this difference was not significant. Findings were much the same when progression was assessed by investigators rather than confirmed by central review (appendix).

We noted similar results when considering time to progression (figure 2B). There was no significant difference in median time to progression between the

Figure 2: **Kaplan-Meier analysis of primary and secondary endpoints**
Kaplan-Meier curves for progression-free survival (A), time to progression (B), and overall survival (C) in the full analysis set. HR=hazard ratio.

two treatments in the full analysis set (5·2 months [95% CI 3·6–6·6] in the icotinib group *vs* 3·7 months [2·5–5·0] in the gefitinib group; figure 2B). However, the difference in time to progression in the per-protocol population was marginally significant (5·1 months [3·6–6·6] in the icotinib group *vs* 3·6 months [2·4–4·1] in the gefitinib group; HR 0·78 [95% CI 0·62–0·99]; p=0·042). The per-protocol analysis for progression-free survival and time to progression were much the same as those in the full analysis set (appendix).

We obtained overall survival data in December, 2011. By that time 324 patients had died, and 56 (28%) in the icotinib group and 70 (36%) in the gefitinib group with progression had received subsequent therapies (appendix). Overall survival in the full analysis population was similar for icotinib and gefitinib (166 [83·4%] patients died in the icotinib group *vs* 158 [80·6%] patients in the gefitinib group; figure 2C). Median overall survival was 13·3 months (95% CI 11·1–16·2) in the icotinib group versus 13·9 months (11·4–17·3) in the gefitinib group.

Objective responses were noted in much the same proportion of patients in each group (table 2); disease control was also similar in both groups (table 2).

Progression-free survival was consistent across clinical subgroups such as disease stage, sex, ECOG performance status, smoking status, and previous chemotherapy (figure 3). We noted progression-free survival was significantly longer with icotinib than with gefitinib in the subgroup of patients without adenocarcinoma (HR 0·61, 95% CI 0·39–0·97; p=0·035); however, this benefit was not significantly different from that noted in patients with adenocarcinoma who received icotinib (HR 0·88, 0·68–1·14; $p_{interaction}$=0·27; figure 3). A higher proportion of patients with squamous-cell carcinoma had an objective response in the icotinib group (5 [15%] of 34) than those in the gefitinib group (2 [6%] of 36; appendix).

Tissue samples were available for 152 (38%) of 395 patients; 134 (34%) samples were assessable for EGFR mutations (18 failed to pass the quality assessment). Of the 134 samples, 68 (51%) were positive for mutation, and 66 (49%) were wild type (table 1). The main EGFR mutation type was 19del, followed by Leu858Arg (table 1). We noted no significant difference in the distribution of EGFR mutants between the icotinib and gefitinib groups (p=0·72; table 1).

According to the Kaplan-Meier analysis, progression-free survival was significantly longer in patients who had an EGFR mutation than in those with wild-type EGFR (median 6·3 months [95% CI 5·0–8·0] *vs* 2·3 months [1·1–2·5]; figure 4). When patients with EGFR mutations and those with wild-type EGFR were assessed separately, progression-free and overall survival did not significantly differ between treatment groups (figure 4). Median progression-free survival in patients with mutated EGFR in the icotinib group was 7·8 months (95% CI 3·7–12·2) and in the gefitinib group was 5·3 months (3·7–9·3), and overall survival in patients with mutated EGFR was 20·9 months (95% CI 16·2–27·2) in the icotinib group and 20·2 months (17·9–28·9) in the gefitinib group (figure 4).

The most common adverse events were rash, diarrhoea, pain, and raised concentrations of aminotransferases (table 3). Icotinib was associated with a lower number of treatment-related adverse events than was gefitinib with respect to overall incidence (121 [61%] of 200 patients *vs* 140 [70%] of 199 patients; p=0·046) and diarrhoea (37 [19%] *vs* 55 [28%]; p=0·033). Four patients in the gefitinib group were withdrawn because they had more than 2 weeks of treatment interruption because of intolerable

See Online for appendix

	Icotinib group (n=199)	Gefitinib group (n=196)	Odds ratio (95% CI)	p value
Complete response	1 (0·05%)	0	..	..
Partial response	54 (27·1%)	53 (27·2%)	..	..
Stable disease	95 (47·7%)	93 (47·7%)	..	..
Progressive disease	42 (21·1%)	40 (20·5%)	..	..
Objective response	55 (27·6%)	53 (27·2%)	1·02 (0·66–1·59)	0·91
Disease control	150 (75·4%)	146 (74·9%)	1·03 (0·65–1·62)	0·90
Objective response (EGFR-mutant population*)	18 (62·1%)	21 (53·8%)	1·40 (0·53–3·80)	0·49
Disease control (EGFR-mutant population*)	25 (86·2%)	37 (94·9%)	0·34 (0·04–1·87)	0·22

Data are number (%) unless otherwise indicated. RECIST=Response Evaluation Criteria in Solid Tumors version 1.0.
*n=29 in icotonib group; n=39 in the gefitinib group.

Table 2: **Best response by RECIST**

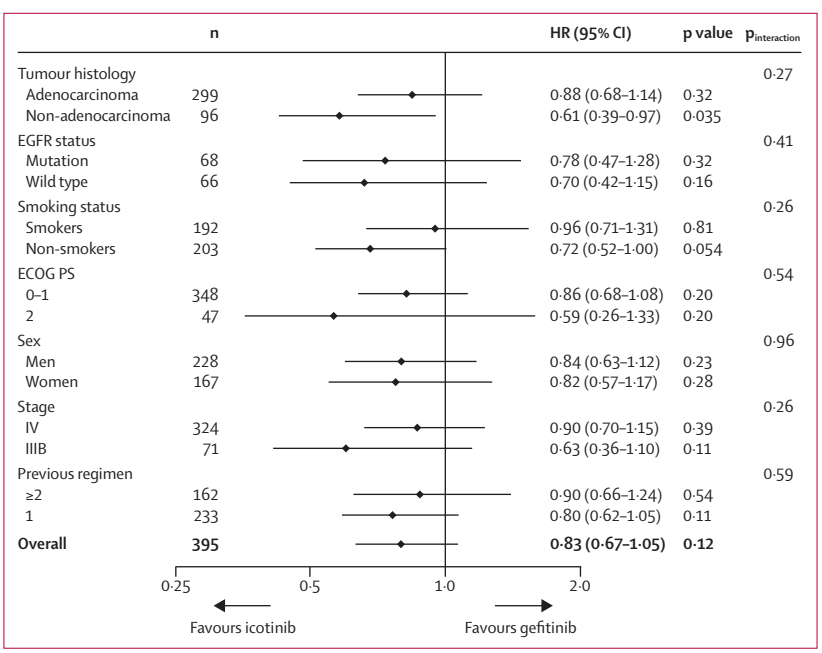

Figure 3: **Progression-free survival by subgroup in the full analysis set**
ECOG PS=Eastern Cooperative Oncology Group performance status. HR=hazard ratio.

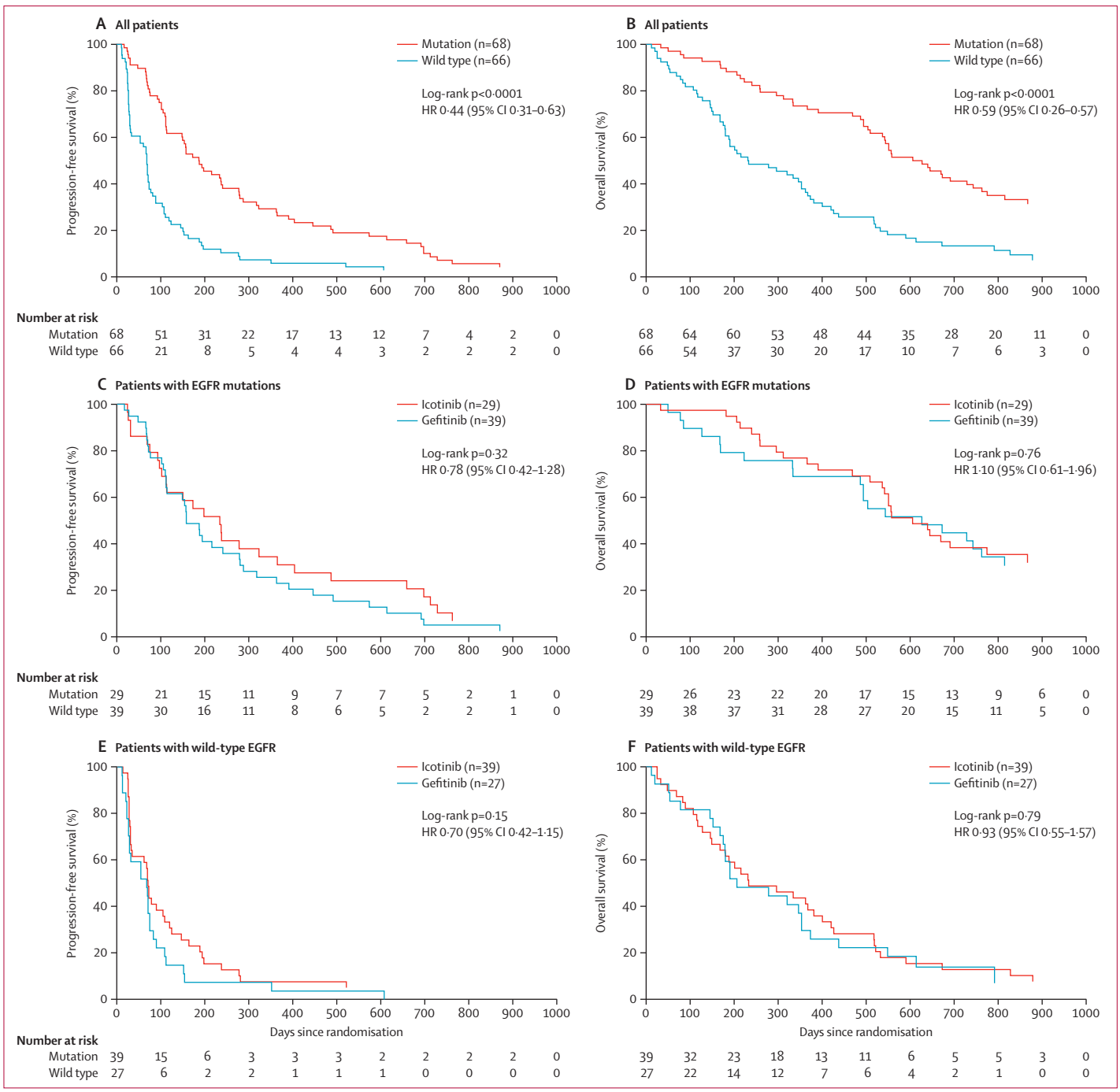

Figure 4: **Kaplan-Meier analysis of progression-free and overall survival according to EGFR mutation status**
Kaplan-Meier curves for progression-free survival (A) and overall survival (B) in all patients stratified by EGFR mutation status (mutated or wild-type EGFR); progression-free survival (C) and overall survival (D) in patients with positive EGFR mutations stratified by treatment group; and progression-free survival (E) and overall survival (F) in patients with wild-type EGFR stratified by treatment group. HR=hazard ratio.

adverse events. However, no patients in the icotinib group had their treatment interrupted because of adverse events. No cases of interstitial lung disease were reported and no deaths were deemed to be treatment-related in either group.

Patients who had responded to the quality-of-life questionnaire at baseline and had at least one follow-up assessment were included in the quality-of-life analysis (199 patients in the icotinib group and 196 patients in the gefitinib group). We noted improvements in both groups

at weeks 4, 10, 16, and 22, but these improvements did not differ between groups (appendix).

Discussion

Our results show that icotinib is non-inferior to gefitinib in terms of progression-free survival; overall survival and tumour responses were also much the same with the two drugs. Although a retrospective analysis and a phase 2 study recently compared the effect of gefitinib and erlotinib in pretreated patients with non-small-cell lung cancer,[20,21] to our knowledge, this study is the first to prospectively compare two molecularly targeted agents head to head in pretreated patients with non-small-cell lung cancer in a phase 3 study.

Gefitinib is now widely used as a second-line or third-line treatment for non-small-cell lung cancer, and is associated with a median progression-free survival of 2·2 months in an unselected population and more than 3 months in Asian populations.[3,18] Our results are similar, showing a median progression-free survival of 3·4 months for gefitinib.

Results of our efficacy analysis showed that icotinib was clinically equivalent to gefitinib in previously treated patients with non-small-cell lung cancer. Median progression-free survival with icotinib was 4·6 months. Overall survival was much the same with both agents. These data further confirm the antitumour activity of icotinib that had been shown in previous clinical trials. In a phase 1 study of 40 pretreated patients with non-small-cell lung cancer receiving icotinib, overall median progression-free survival was 4·6 months.[22] In our study, the proportion of patients who received subsequent therapies was higher in the gefitinib group than in the icotinib group. We believe that the subsequent therapies might have affected patients' overall survival.

Our results are consistent with those of other randomised studies in patients with non-small-cell lung cancer taking TKIs in a similar clinical setting (panel). In the INTEREST study,[3] patients randomly assigned to take docetaxel or gefitinib as second-line or third-line treatments showed similar progression-free survival (2·2 months in the gefitinib group *vs* 2·7 months in the docetaxel group; p=0·47), resulting in a recommendation for gefitinib monotherapy in this setting by the study investigators.[3] Furthermore, Lee and colleagues[24] reported a median progression-free survival of 3·3 months for patients with non-small-cell lung cancer in the gefitinib group versus 3·4 months in the docetaxel group when both agents were used as second-line therapies.[24]

With respect to safety, icotinib was associated with a lower number of treatment-related adverse events when compared with gefitinib for both overall incidence and diarrhoea, suggesting that icotinib might have the better safety profile. Icotinib also seems to have a better safety profile than gefitinib for other major adverse events, such as rash and raised concentrations of amino-transferases, although none of these differences was statistically significant. Moreover, across both groups, seven grade 3 or 4 treatment-related adverse events occurred (three skin-related and four diarrhoea), and four patients were withdrawn from the study because of intolerable toxicity in the gefitinib group, whereas in the icotinib group we observed only one grade 3 skin adverse event and no patients were withdrawn from the study because of toxicity (table 3). Results of our recently finished phase 4 study of 6087 patients has confirmed this favourable safety profile of icotinib.[23] We believe that the better safety profile of icotinib could be attributed to its much broader therapeutic window as mentioned

	All adverse events		Grade 3–4 adverse events		Drug-related adverse events		
	Icotinib (n=200)	Gefitinib (n=199)	Icotinib (n=200)	Gefitinib (n=199)	Icotinib (n=200)	Gefitinib (n=199)	p value
Rash	81 (41%)	98 (49%)	1 (<1%)	2 (1%)	80 (40%)	98 (49%)	0·070
Diarrhoea	43 (22%)	58 (29%)	0	4 (2%)	37 (19%)	55 (28%)	0·033
Pain	36 (18%)	22 (11%)	4 (2%)	3 (2%)	4 (2%)	3 (2%)	0·84
Raised aminotransferase	21 (11%)	26 (13%)	2 (1%)	1 (<1%)	16 (8%)	25 (13%)	0·14
Haemoptysis	12 (6%)	16 (8%)	0	1 (<1%)	1 (<1%)	1 (<1%)	1·00
Loss of appetite	11 (6%)	14 (7%)	0	0	6 (3%)	7 (4%)	0·46
Vomiting	10 (5%)	9 (5%)	0	0	5 (3%)	4 (2%)	0·89
Oral ulcer	9 (5%)	12 (6%)	0	0	7 (4%)	10 (5%)	0·51
Leucopenia	9 (5%)	12 (6%)	0	0	6 (3%)	10 (5%)	0·38
Nausea	8 (4%)	13 (6%)	1 (<1%)	0	6 (3%)	10 (5%)	1·00
Total patients*	166 (83%)	165 (83%)	14 (7%)	20 (10%)	121 (61%)	140 (70%)	0·046

Data are number (%) of patients, unless otherwise stated. Adverse events and drug-related adverse events with an incidence of 5% or greater in either group are listed in this table. All adverse events were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0) *Total number of patients who had at least one adverse event in each group; some patients had more than one adverse event.

Table 3: **Adverse events and drug-related adverse events**

Panel: Research in context

Systematic review

We did a systematic review of the scientific literature with the search keywords "gefitinib", "erlotinib", and "head-to-head trial" before starting this trial. We found no prospective head-to-head phase 3 trial for EGFR tyrosine kinase inhibitors (TKIs). We selected gefitinib as a control for the following reasons: a meta-analysis[18] had been done into the use of gefitinib as a second-line or third-line therapy in Asian patients with non-small-cell lung cancer, but no such report for erlotinib was available at the time; and gefitinib was indicated for both second-line and third-line use in China, whereas erlotinib was only indicated for third-line therapy.

Interpretation

To our knowledge, ICOGEN represents the first head-to-head phase 3 trial comparing two EGFR TKIs. Our study shows that icotinib has a similar efficacy but better safety profile than gefitinib when given to pretreated, unselected patients with stage IIIB or IV non-small-cell lung cancer. A recently finished phase 4 study that enrolled 6087 patients with non-small-cell lung cancer in a routine clinical setting further validated this finding.[23] As a novel EGFR TKI, icotinib provides a new therapeutic option for non-small-cell lung cancer patients.

previously, and could also be due to its high selectivity toward kinases. Additionally, icotinib is metabolised by several enzymes, such as CYP2C19, CYP3A4, and CYP2E1,[14] which decreases the accumulation of the drug and the possibility of drug–drug interactions, compared with drugs metabolised mainly by one enzyme.

In our study, non-smokers, patients with adenocarcinoma histology, stage IIIB disease, or ECOG performance status score of 0–1 had an observed progression-free survival benefit, occurring both in patients given icotinib and those given gefitinib. In the subgroup analysis, we reported that icotinib was associated with longer progression-free survival than was gefitinib in patients without adenocarcinoma, but not in patients with adenocarcinoma. However, the $p_{interaction}$ value was non-significant. The EGFR mutation status was not clear in the subgroup without adenocarcinoma since it was analysed retrospectively, but previous reports showed patients without adenocarcinoma have a lower proportion of EGFR mutations than do those with adenocarcinoma.[25] Additionally, the proportion of patients with squamous-cell carcinoma who had an objective response was non-significantly higher in the icotinib group than in the gefitinib group. Thus, further studies are warranted to investigate the benefit of icotinib in patients without adenocarcinoma according to EGFR status.

Several studies[4,5,26] have shown that positive EGFR mutations are associated with better survival and a better clinical response with EGFR TKIs than are wild-type mutations. In the ISEL trial,[27] the proportion of patients who had an objective response with gefitinib was higher in patients with an EGFR mutation (six [37·5%] of 16 patients) than in patients without an EGFR mutation (three [2·6%] of 116 patients). In our study, we observed a greater proportion of objective responses in patients with mutated EGFR than in those with wild-type EGFR in both the gefitinib group and the icotinib group. Our study also showed that patients with EGFR mutations seem to have longer survival than patients with wild-type EGFR when receiving second-line EGFR TKI treatments. This finding was supported by a retrospective study assessing the efficacy of icotinib in patients with an EGFR mutation.[28] In that study, the progression-free survival was 8·5 months for patients receiving icotinib as second-line or further-line treatment.

Our study has several limitations. First, we used one-sided type I error of 0·05 designed as a non-inferiority trial. However, insufficient sample size had little effect on type I error because median progression-free survival was 4·6 months for icotinib, which was longer than that for gefitinib (3·4 months). Second, we included non-selected patients with non-small-cell lung cancer because identification of EGFR status before second-line treatment was not clinically recommended at the time the trial began. In the retrospective study into the EGFR status of our participants, we noted that the gefitinib group contained a higher proportion of patients with mutated EGFR (59%) than did the icotinib group (43%). Since patients with EGFR mutations might receive more of benefit from EGFR TKIs, we should have seen better efficacy in the gefitinib group. Therefore, our findings are unlikely to be due to the imbalance in patients with EGFR mutations between the two groups. Third, other potential selection biases should be considered. For example, the icotinib group had more patients who received just one regimen of chemotherapy than did the gefitinib group (63% *vs* 55%; p=0·07). However, this limitation does not seem to have distorted our findings.

In summary, the ICOGEN study established the non-inferiority of icotinib when compared with gefitinib, showing that icotinib is a valid therapeutic option for patients with non-small-cell lung cancer as a second-line or third-line treatment, although patients might find taking icotinib three times a day an inconvenience. Furthermore, patients with EGFR mutations are more likely to benefit from icotinib than those without.

Contributors

Principal investigator (YSu), coprincipal investigator (LZ[1]), and members of the study steering committee designed the trial with the sponsor. YSu wrote the report. YSu, LZ(1), YSh, XL, CZ, LZ(2), SZ, DW, QL, SQ, CH, YZ, JC, YC, JF, HZ, YSo, Y-LW, NX, JZ, RL, CB, YJ, WL, HD, SJ, JW, LL, and WZ were centre investigators and recruited and treated patients. FT, YW, and LD were involved in the study conduct and supervision. ZW did the data analysis and interpretation. All authors reviewed and approved the final report.

Conflicts of interest

FT, YW, and LD are employees of Zhejiang Beta Pharma. ZW is an employee of Hangzhou Tigermed Consulting, a Chinese contract research organisation. All other authors declare that they have no conflicts of interest.

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