Dacomitinib compared with placebo in pretreated patients with advanced or metastatic non-small-cell lung cancer (NCIC CTG BR.26): a double-blind, randomised, phase 3 trial

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Summary

Background Dacomitinib is an irreversible pan-HER tyrosine-kinase inhibitor with preclinical and clinical evidence of activity in non-small-cell lung cancer. We designed BR.26 to assess whether dacomitinib improved overall survival in heavily pretreated patients with this disease.

Methods In this double-blind, randomised, placebo-controlled, phase 3 trial, we enrolled adults (aged ≥18 years) with advanced or metastatic non-small-cell lung cancer from 75 centres in 12 countries. Eligible patients had received up to three previous lines of chemotherapy and either gefitinib or erlotinib, and had assessable disease (RECIST 1.1) and tumour tissue samples for translational studies. Patients were stratified according to centre, performance status, tobacco use, best response to previous EGFR tyrosine-kinase inhibitor, weight loss within the previous 3 months, and ethnicity, and were then randomly allocated 2:1 to oral dacomitinib 45 mg once-daily or matched placebo centrally via a web-based system. Treatment continued until disease progression or unacceptable toxicity. The primary outcome was overall survival in the intention-to-treat population; secondary outcomes included overall survival in predefined molecular subgroups, progression-free survival, the proportion of patients who achieved an objective response, safety, and quality of life. This study is completed, although follow-up is ongoing for patients on treatment. This study is registered with ClinicalTrials.gov, number NCT01000025.

Findings Between Dec 23, 2009, and June 11, 2013, we randomly assigned 480 patients to dacomitinib and 240 patients to placebo. At the final analysis (January, 2014), median follow-up was 23·4 months (IQR 15·6–29·6) for patients in the dacomitinib group and 24·4 months (11·5–38·9) for those in the placebo group. Dacomitinib did not improve overall survival compared with placebo (median 6·83 months [95% CI 6·08–7·49] for dacomitinib *vs* 6·31 months [5·32–7·52] for placebo; hazard ratio [HR] 1·00 [95% CI 0·83–1·21]; p=0·506). However, patients in the dacomitinib group had longer progression-free survival than those in the placebo group (median 2·66 months [1·91–3·32] *vs* 1·38 months [0·99–1·74], respectively; HR 0·66 [95% CI 0·55–0·79]; p<0·0001), and a significantly greater proportion of patients in the dacomitinb group achieved an objective response than in the placebo group (34 [7%] of 480 patients *vs* three [1%] of 240 patients, respectively; p=0·001). Compared with placebo, the effect of dacomitinib on overall survival seemed similar in patients with *EGFR*-mutation-positive tumours (HR 0·98, 95% CI 0·67–1·44) and *EGFR* wild-type tumours (0·93, 0·71–1·21; $p_{interaction}$=0·69). However, we noted qualitative differences in the effect of dacomitinib on overall survival for patients with *KRAS*-mutation-positive tumours (2·10, 1·05–4·22) and patients with *KRAS* wild-type tumours (0·79, 0·61–1·03; $p_{interaction}$=0·08). Compared with placebo, patients allocated dacomitinib had significantly longer time to deterioration of cough (p<0·0001), dyspnoea (p=0·049), and pain (p=0·041). 185 (39%) of 477 patients who received dacomitinib and 86 (36%) of 239 patients who received placebo had serious adverse events. The most common grade 3–4 adverse events were diarrhoea (59 [12%] patients on dacomitinib *vs* no controls), acneiform rash (48 [10%] *vs* one [<1%]), oral mucositis (16 [3%] *vs* none), and fatigue (13 [3%] *vs* four [2%]).

Interpretation Dacomitinib did not increase overall survival and cannot be recommended for treatment of patients with advanced non-small-cell lung cancer previously treated with chemotherapy and an EGFR tyrosine-kinase inhibitor.

Funding Canadian Cancer Society Research Institute and Pfizer.

Introduction

Most patients with non-small-cell lung cancer present with advanced or metastatic disease.[1] Treatment options include platinum-based chemotherapy,[2,3] bevacizumab,[4] maintenance therapy,[5–7] second-line chemotherapy,[8,9] and EGFR inhibitors.[10] An activating *EGFR* mutation predicts benefit from EGFR tyrosine-kinase inhibitors,[11] but the NCIC CTG BR.21 trial of erlotinib versus best supportive care showed unselected patients with non-small-cell lung cancer also had increased survival from second-line or third-line erlotinib.[12]

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See **Comment** page 1289

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See Online for appendix

For the **protocol** see http://www.ctg.queensu.ca/public/publications/BR26_public/br26-Protocol-Amend3-2014MAY26_Public_Secured.pdf

To date, no drugs have shown increased overall survival after treatment with chemotherapy and an EGFR tyrosine-kinase inhibitor. In the ZEPHYR trial,[13] patients were randomly allocated to vandetanib, a dual inhibitor of EGFR and VEGF-R, or best supportive care. Patients treated with vandetanib had longer progression-free survival than did those with best supportive care, but there was no difference in overall survival between treatment groups. The LUX-Lung 1 trial assessed afatinib, an irreversible dual EGFR/HER2 inhibitor, versus best supportive care in patients with adenocarcinoma who had received at least 12 weeks of an EGFR tyrosine-kinase inhibitor.[14] Although progression-free survival was significantly longer in the afatinib group, overall survival was not significantly increased compared to best supportive care in this selected population.

Dacomitinib (PF-00299804; Pfizer, NY, USA) is an irreversible inhibitor of the HER family of tyrosine kinases, with broader activity than erlotinib or gefitinib, which selectively target EGFR. Xenograft studies showed tumour regression from dacomitinib in non-small-cell lung cancer murine models derived from cell lines including Thr790Met (T790M) mutation.[15] Phase 1 and 2 trials of dacomitinib showed evidence of activity in non-small-cell lung cancer. Tumour response or stabilisation was noted in nearly half of patients with non-small-cell lung cancer who had received previous chemotherapy and EGFR tyrosine-kinase inhibitor therapy;[16–18] a greater proportion of patients treated with dacomitinib achieved a tumour response, and had a longer progression-free survival time than those treated with erlotinib in a phase 2 study.[19] Activity was reported in patients with *EGFR* and *KRAS* wild-type tumours. Therefore, dacomitinib showed promise as a therapy for advanced non-small-cell lung cancer, including in patients without *EGFR* mutations. On this basis, we aimed to assess dacomitinib versus best supportive care in a phase 3 setting of an unselected population of heavily pretreated patients with non-small-cell lung cancer.

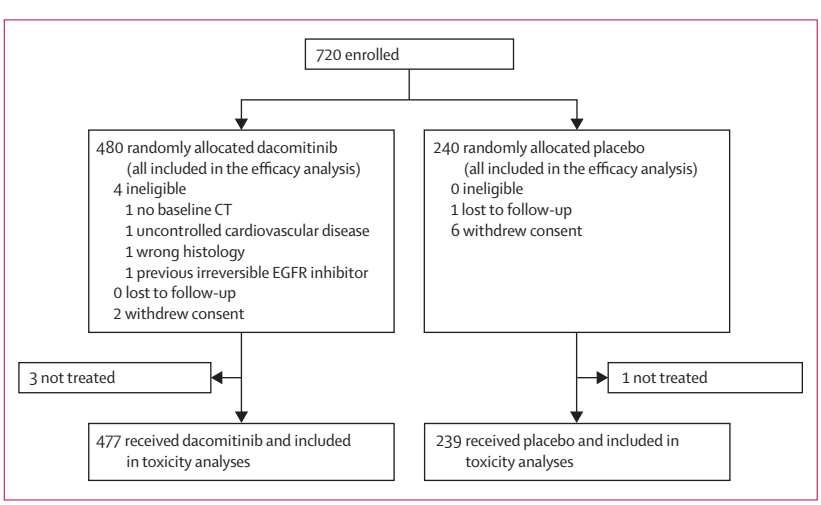

Figure 1: **Trial profile**

Methods

Study design and participants

NCIC CTG BR.26 was a randomised, placebo-controlled, phase 3 trial that enrolled patients from 75 centres in 12 countries (appendix). Eligible patients were aged 18 years or older and had histologically or cytologically confirmed non-small-cell lung cancer, tumour tissue available for translational studies, assessable disease by RECIST 1.1[20] (but measurable disease was not required), Eastern Cooperative Oncology Group (ECOG) performance status 0–3 (patients with performance status of 3 were only eligible if they were believed to have a life expectancy of 6 weeks or more), creatinine less than 1·5 times the upper limit of normal (ULN), bilirubin less than 1·5 times the ULN, alanine aminotransferase less than 2·5 times the ULN (unless liver metastases were present, in which case <5 times the ULN), and at least 21 days since previous therapy. Patients needed to have received the following previous standard systemic therapies for advanced or metastatic non-small-cell lung cancer: one or two previous chemotherapy lines (this requirement was increased to a maximum of three after a protocol amendment [July 21, 2011] to account for variation in the standard of care in different jurisdictions); a previous platinum agent and at least one chemotherapy combination regimen (apart from patients aged 70 years or older for whom single agent and non-platinum chemotherapy was permissible); and previous erlotinib or gefitinib, but no previous therapy with an irreversible EGFR tyrosine-kinase inhibitor—previous EGFR tyrosine-kinase inhibitor therapy had to have failed.

Patients were ineligible if: they were undergoing any concurrent treatment with any other experimental drug or other anti-cancer therapy, or with any other drugs highly dependent on CYP2D6 metabolism; they had had uncontrolled cardiovascular diseases, prolonged QT interval from any cause, untreated CNS metastases, uncontrolled infections, or if they were pregnant, or using inadequate contraception.

Research ethics board approval was obtained by all institutions, and all patients provided written informed consent before entering the trial.

Randomisation and masking

Randomisation was done by the NCIC CTG centrally through a web-based system, after confirmation of eligibility. Patients were stratified according to centre, ECOG performance status (0–1 *vs* 2–3), tobacco use (never *vs* former or current), best response to previous EGFR tyrosine-kinase inhibitor (progressive disease [PD] *vs* other), weight loss within the previous 3 months (<5% *vs* ≥5% or unknown), and ethnicity (East Asian *vs* other), then randomly assigned 2:1 to either dacomitinib or placebo using the dynamic minimisation method. The

	Dacomitinib (n=480)	Placebo (n=240)
Age, years	63·5 (32–86)	65·5 (34–90)
<65 years	259 (54%)	114 (48%)
≥65 years	221 (46%)	126 (53%)
ECOG performance status		
0	74 (15%)	34 (14%)
1	287 (60%)	148 (62%)
2	102 (21%)	42 (18%)
3	17 (4%)	16 (7%)
Sex		
Male	244 (51%)	120 (50%)
Female	236 (49%)	120 (50%)
Smoking status		
Never*	174 (36%)	85 (35%)
Former	262 (55%)	133 (55%)
Current	44 (9%)	22 (9%)
Histology		
Adenocarcinoma	360 (75%)	168 (70%)
Squamous	63 (13%)	44 (18%)
Mixed NSCLC	3 (1%)	2 (1%)
NSCLC (NOS)	34 (7%)	21 (9%)
Other	20 (4%)	5 (2%)
Ethnic origin		
White	288 (60%)	144 (60%)
East Asian†	141 (29%)	70 (29%)
Other Asian	31 (6%)	17 (7%)
Other	20 (4%)	9 (4%)
Number of sites of disease		
1	36 (8%)	28 (12%)
2	106 (22%)	46 (19%)
3	121 (25%)	64 (27%)
4	96 (20%)	51 (21%)
≥5	120 (25%)	51 (21%)
(Table 1 continues in next column)		

	Dacomitinib (n=480)	Placebo (n=240)
(Continued from previous column)		
Number of previous chemotherapy regimens		
0	1 (<1%)	0
1	132 (28%)	64 (27%)
2	290 (60%)	148 (62%)
≥3	57 (12%)	28 (12%)
Best response to previous EGFR tyrosine-kinase inhibitor		
Complete or partial response	62 (13%)	31 (13%)
Stable disease	199 (41%)	107 (45%)
Progressive disease	142 (30%)	66 (28%)
Unknown	77 (16%)	36 (15%)
Previous pemetrexed for advanced disease		
No	198 (41%)	112 (47%)
Yes	282 (59%)	128 (53%)
Previous radiation		
No	230 (48%)	108 (45%)
Yes	250 (52%)	132 (55%)
Measurable disease		
No	28 (6%)	13 (5%)
Yes	452 (94%)	227 (95%)
EGFR mutation status‡		
Mutant	114 (24%)	68 (28%)
Wild-type	235 (49%)	114 (48%)
Unknown	131 (27%)	58 (24%)
KRAS mutation status‡		
Mutant	57 (12%)	21 (9%)
Wild-type	220 (46%)	120 (50%)
Unknown	203 (42%)	99 (41%)

Data are number (%) or median (range). ECOG=Eastern Cooperative Oncology Group. NCSLC=non-small-cell lung cancer. NOS=not otherwise stated. *Fewer than 100 cigarettes in lifetime. †China, Indonesia, Japan, Malaysia, Singapore, South Korea, Taiwan, Thailand, and Vietnam. ‡Analysis from NSCLC samples collected as part of the clinical trial; if a sample was unavailable or insufficient for analyses, results from applicable local testing were included if available.

Table 1: **Baseline characteristics**

randomisation schedule was generated by the NCIC CTG statistician (KD). Patients, investigators, response assessors, and the study statistician were all masked to treatment allocation.

Procedures

Oral dacomitinib (45 mg daily) or matched placebo was administered in a double-blind fashion and continued until disease progression or unacceptable toxicity occurred. A maximum of two dose reductions (to 30 mg or 15 mg) were permitted. Study drug was held for up to 21 days for related adverse events. Permanent drug discontinuation for grade 4 toxicities or pneumonitis (see protocol for additional details) was required. Baseline and on-treatment assessments included history, physical examination, complete blood count, biochemistry, CT scan of chest and upper abdomen plus other sites of known disease, urinalysis (baseline), electrocardiogram (baseline and as indicated), adverse events (baseline and on-treatment) with National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4, quality of life with the European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ)-30 and LC-13.[21] Routine imaging of the brain was not done. Resource utilisation and health utilities index (EQ-5D) were collected at Canadian and Australian sites only. History, physical examination, blood work, and assessment of adverse events were done at the end of every cycle (every 4 weeks) during treatment. We did repeat imaging at 4 weeks and 8 weeks, then every 8 weeks until documentation of disease progression, or once every 12 weeks for patients who discontinued treatment for reasons other than disease progression. Patients in the placebo group were not allowed crossover to dacomitinib at the time of progression.

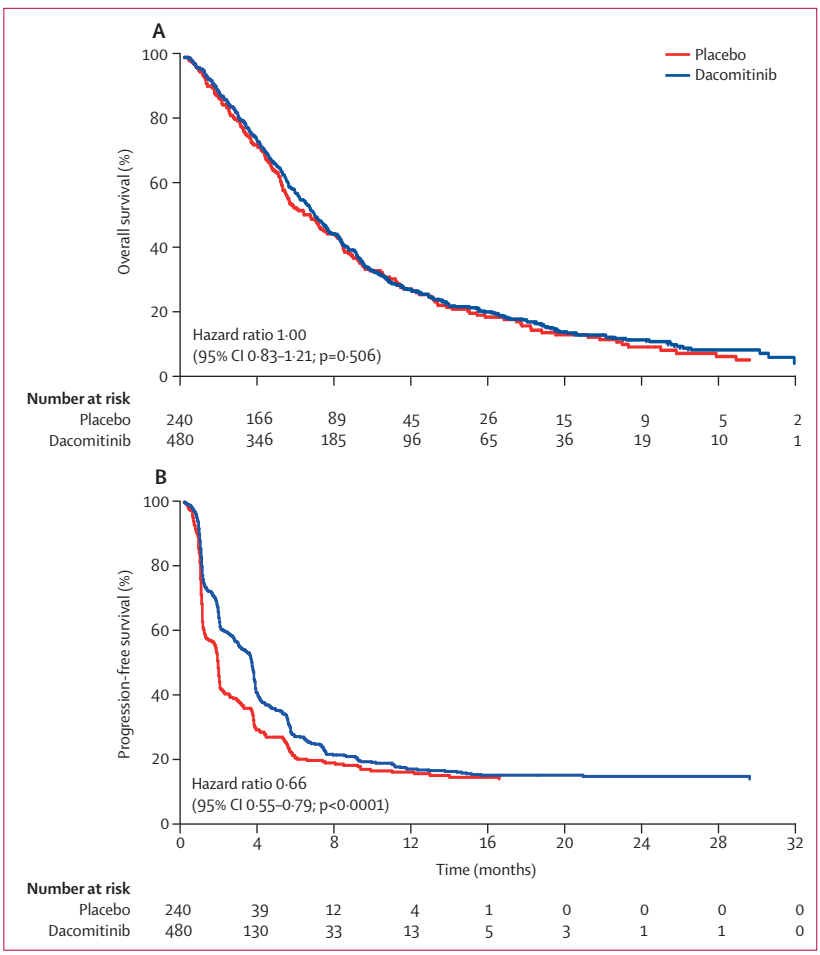

Figure 2: **Kaplan-Meier curves for overall survival (A) and progression-free survival (B) for dacomitinib versus placebo**

EGFR and *KRAS* mutation analysis were done centrally using PCR based on Scorpion ARMS technology (Qiagen, Valencia, CA, USA). Analysis was done by Clarient Diagnostic Services (Aliso Viejo, CA, USA). There was insufficient material for testing in some patients; in these cases local *EGFR* and *KRAS* results were used if available; this strategy was decided post hoc to increase the number of patients with available results.

Outcomes

The primary study outcome was overall survival, measured from the date of randomisation until the date of death from any cause. Secondary outcomes included overall survival in the *KRAS* wild-type and *EGFR* mutation subsets, progression-free survival, defined as time from randomisation to progression or death from any cause, the proportion of patients achieving an objective response, assessed according to RECIST 1.1,[20] time to response and response duration, toxicity, quality-of-life, defined as time from randomisation to symptom deterioration, health economic assessment (incremental cost-effectiveness and cost–utility analysis from the perspective of a government payer; results not reported here), and translational outcomes with tissue and blood markers.

Statistical analysis

We calculated our sample size to detect a 33% increase in overall survival with 90% power and a one-sided significance level of 2·5%. We needed 581 deaths for the final analysis. Assuming a median survival of 4 months in the control group from the control arm of BR.21,[10] and enrolling 28 patients per month, we needed 720 patients over 26 months, with a minimum of 6 months follow-up after accrual had completed. We did not plan any interim analysis for efficacy. One interim analysis for futility was planned when 300 events had taken place. Before the planned interim analysis, recruitment to Asian centres had proceeded more rapidly than at the other centres and we were concerned that the high proportion of Asian patients in the interim analysis population was not representative of the overall study population (ie, because of a high proportion of patients carrying *EGFR* mutations). With the approval of the data and safety monitoring committee, the interim analysis plan was amended on April 23, 2012, to change the outcome of interest from overall survival to progression-free survival. If the hazard ratio (HR) for progression-free survival was greater than 0·67 the trial would close for futility, otherwise it would continue to full accrual.

The primary analysis for overall survival was done in the intention-to-treat population (all patients randomly allocated to treatment). We estimated survival distributions with the Kaplan-Meier method. The statistical analysis plan specified a one-sided statistical test for overall survival and progression-free survival based on the planned interim analysis for futility. All other p values were two sided. We used a stratified logrank test, incorporating stratification factors at randomisation (excluding centre) and *KRAS* status (unknown *vs* mutation *vs* wild-type), to compare overall survival and progression-free survival between the two groups. We did secondary analyses for overall survival in patients with *KRAS* wild-type and *EGFR*-mutated tumours with stratified logrank tests. For progression-free survival, patients not progressing at the time of the datalock were censored as of the date of their last assessment. Patients commencing new anticancer therapy in the absence of progression were censored on the date the new therapy began. Patients with incomplete baseline assessment, or no reassessment of disease (unless death occurred before day 28) were censored as of the date of randomisation. We used Cox regression model with interaction terms included to test the differential effect (comparison of hazard ratios) of dacomitinib versus placebo in different subgroups. We assessed overall response in patients with at least one measurable lesion and one disease assessment after baseline with RECIST 1.1. We calculated the proportion of patients achieving an overall response in the intention-to-treat population and

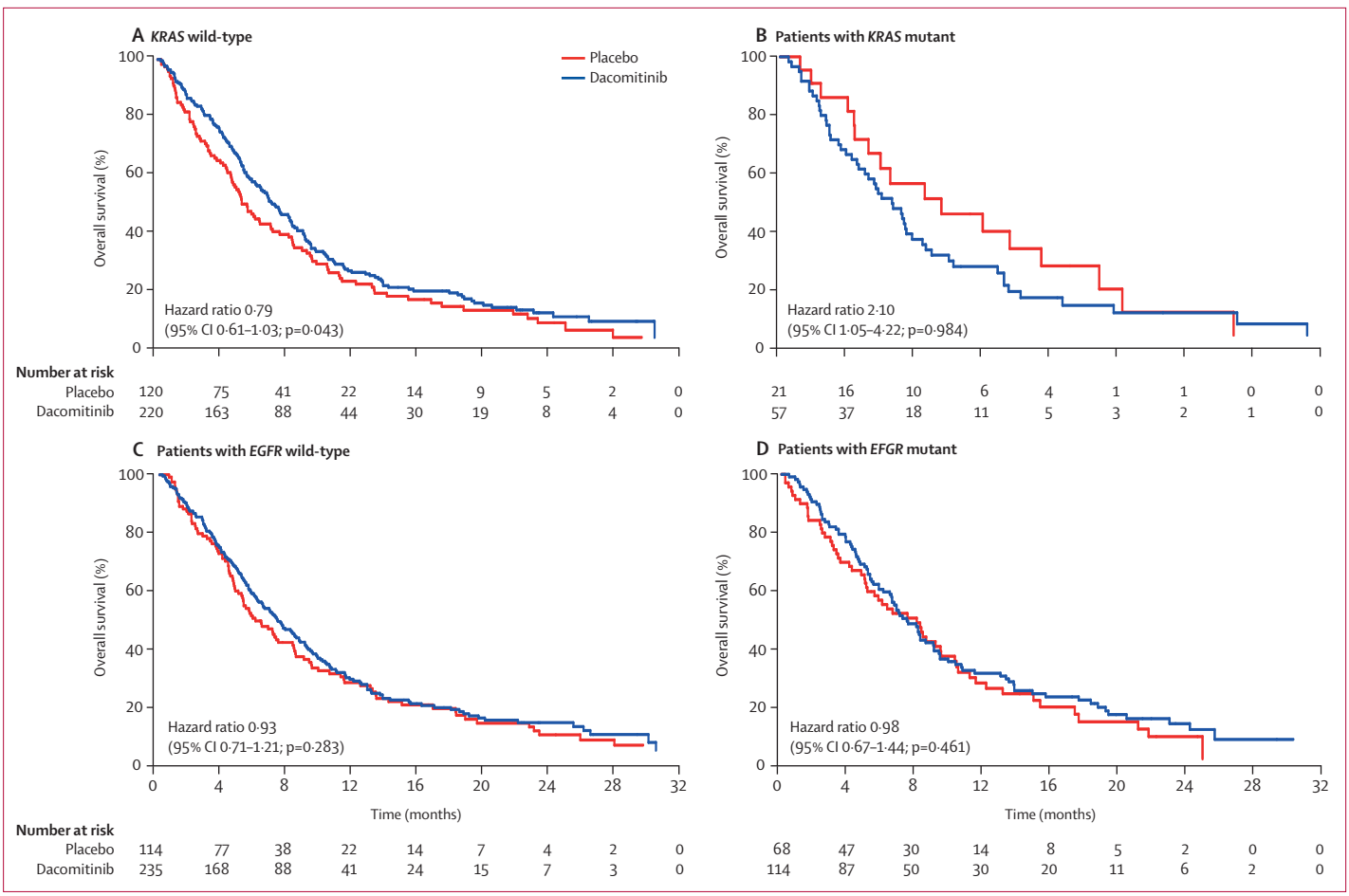

Figure 3: **Kaplan-Meier curves for overall survival for patients with *KRAS* wild-type (A), *KRAS*-mutation-positive (B), *EGFR* wild-type (C), and *EGFR*-mutation-positive (D) non-small-cell lung cancer**

in patients with at least one measurable lesion; comparison of overall response between groups was done with the Cochrane Mantel-Haenszel test adjusting for stratification factors and *KRAS* status.

All patients who received at least one dose of study drug were included in safety analyses. Safety monitoring was done every 6 months by the NCIC CTG data safety and monitoring committee. We report frequency of adverse events, although we did not make statistical comparisons because of concerns about multiple testing. We defined compliance with completion of quality-of-life questionnaires as the number of forms completed divided by the number of forms expected at the assessment point. The primary quality-of-life analyses were defined as time from randomisation to symptom deterioration (decrease of ≥10 points from baseline) for pain, cough, or dyspnoea and were compared with the logrank test adjusted by the Hockberg method for multiple endpoints. As additional analyses, we analysed change in scores from baseline at each assessment point for the individual items and domains of the EORTC QLQ-30 and EORTC LC-13. All analyses were done with SAS version 9.2.

This study is registered with ClinicalTrials.gov, number NCT01000025.

Role of the funding source

NCIC CTG BR.26 was designed by a trial committee that included members of the NCIC CTG, Australasian Lung cancer Trials Group (ALTG), and National Cancer Institute (NCI) Naples. The NCIC CTG collected, managed, analysed the data, and maintains the database. Support for the trial was provided by the NCIC CTG and Pfizer Oncology. The report was written by members of the NCIC CTG. All authors and Pfizer personnel reviewed the manuscript and provided comments. The senior investigator (PAB), senior biostatistician (KD), and study chair (PME) reviewed and confirmed the completeness and accuracy of the data. The corresponding author had full access to all of the data, and the final responsibility to submit for publication.

Results

Between Dec 23, 2009, and June 11, 2013, 720 patients were randomly allocated to treatment; 480 (67%) to dacomitinib

	Dacomitinib		Placebo		HR (95% CI)	$p_{interaction}$
	n	Median survival, months (95% CI)	n	Median survival, months (95% CI)		
Overall survival						
ECOG performance status						0·253
0 or 1	361 (75%)	8·21 (7·23–9·03)	182 (76%)	7·33 (5·65–8·64)	0·90 (0·74–1·10)	
2 or 3	119 (25%)	4·01 (3·15–5·00)	58 (24%)	4·27 (2·92–5·78)	1·12 (0·80–1·56)	
Smoking						0·017
Never	178 (37%)	7·56 (6·08–9·03)	86 (36%)	5·44 (4·30–8·41)	0·74 (0·56–0·98)	
Former or current	302 (63%)	6·64 (5·82–7·29)	154 (64%)	6·97 (5·45–8·28)	1·13 (0·91–1·40)	
Best response to previous EGFR TKI						0·003
Progressive disease	157 (33%)	5·49 (4·73–6·28)	66 (28%)	7·52 (5·16–9·13)	1·36 (1·00–1·87)	
Other	323 67%)	7·56 (6·77–8·28)	174 (73%)	6·01 (5·13–7·33)	0·79 (0·65–0·97)	
Weight loss						0·951
<5%	394 (87%)	7·56 (6·93–8·34)	193 (80%)	7·20 (5·55–8·38)	0·96 (0·79–1·16)	
≥5%	86 (18%)	4·19 (3·42–5·09)	47 (20%)	4·67 (2·23–5·78)	0·95 (0·66–1·37)	
Ethnic origin						0·105
East Asian	141 (29%)	7·89 (5·98–9·03)	70 (29%)	5·91 (4·99–8·41)	0·78 (0·57–1·06)	
Other	339 (71%)	6·60 (5·91–7·29)	170 (71%)	6·31 (5·19–8·08)	1·04 (0·85–1·27)	
KRAS						0·08*
Mutation	57 (12%)	5·82 (4·11–7·23)	21 (9%)	8·28 (4·27–14·90)	2·10 (1·05–4·22)	
Wild-type	220 (50%)	7·00 (6·01–8·21)	120 (50%)	5·19 (4·53–7·00)	0·79 (0·61–1·03)	
Unknown	203 (42%)	6·67 (5·98–8·08)	99 (41%)	7·20 (5·45–8·44)	1·02 (0·78–1·33)	
EGFR						0·69*
Mutation	114 (24%)	7·23 (6·08–8·61)	68 (28%)	7·52 (4·99–9·49)	0·98 (0·67–1·44)	
Wild-type	235 (49%)	6·93 (5·82–8·08)	114 (48%)	5·55 (4·60–7·20)	0·93 (0·71–1·21)	
Unknown	131 (27%)	6·37 (5·42–7·46)	58 (24%)	7·06 (5·29–8·77)	1·12 (0·79–1·58)	
Progression-free survival						
ECOG performance status						0·274
0 or 1	361 (75%)	3·32 (2·60–3·55)	182 (76%)	1·66 (0·99–1·77)	0·64 (0·54–0·77)	
2 or 3	119 (25%)	1·54 (0·95–1·81)	58 (24%)	1·05 (0·89–1·71)	0·82 (0·59–1·14)	
Smoking status						0·004
Never	178 (37%)	3·32 (2·43–3·61)	86 (36%)	0·95 (0·89–1·71)	0·51 (0·39–0·67)	
Former or current	302 (63%)	2·20 (1·84–2·89)	154 (64%)	1·68 (1·05–1·84)	0·80 (0·66–0·98)	
Best response to previous EGFR TKI						0·001
Progressive disease	157 (33%)	1·71 (1·12–1·84)	66 (28%)	1·74 (0·92–2·04)	1·05 (0·78–1·41)	
Other	323 67%)	3·52 (2·83–3·61)	174 (73%)	1·12 (0·95–1·71)	0·56 (0·46–0·68)	
Weight loss						0·724
<5%	394 (82%)	2·96 (2·30–3·48)	193 (80%)	1·64 (0·95–1·77)	0·67 (0·56–0·80)	
≥5%	86 (18%)	1·64 (0·95–1·87)	47 (20%)	1·12 (0·92–1·68)	0·77 (0·53–1·13)	
Ethnic origin						0·002
East Asian	141 (29%)	3·06 (1·87–3·55)	70 (29%)	0·92 (0·85–0·95)	0·46 (0·34–0·62)	
Other	339 (71%)	2·53 (1·84–3·32)	170 (71%)	1·74 (1·12–1·84)	0·79 (0·65–0·95)	
KRAS						0·005*
Mutation	57 (12%)	1·61 (0·92–1·87)	21 (9%)	1·86 (0·95–2·33)	1·34 (0·78–2·29)	
Wild-type	220 (46%)	3·06 (1·91–3·55)	120 (50%)	1·05 (0·92–1·71)	0·58 (0·46–0·73)	
Unknown	203 (42%)	2·83 (1·87–3·55)	99 (41%)	1·64 (0·95–1·81)	0·69 (0·54–0·89)	
EGFR						0·029*
Mutation	114 (24%)	3·52 (2·53–3·68)	68 (28%)	0·95 (0·89–1·64)	0·48 (0·35–0·66)	
Wild-type	235 (49%)	1·91 (1·77–2·79)	114 (48%)	1·63 (0·99–1·81)	0·75 (0·59–0·95)	
Unknown	131 (27%)	2·89 (1·84–3·58)	58 (24%)	1·74 (0·95–1·84)	0·74 (0·54–1·02)	

TKI=tyrosine-kinase inhibitor. *Excluded patients with unknown marker status.

***Table 2*: Subgroup analysis of overall survival and progression-free survival for dacomitinib *vs* placebo (logrank comparison)**

and 240 (33%) to placebo (figure 1; table 1). The final analysis was done in January, 2014, after a median follow-up of 23·4 months (IQR 15·6–29·6) for patients assigned to dacomitinib and 24·4 months (11·5–38·9) for those assigned to placebo. Three patients allocated to dacomitinib and one patient allocated to placebo did not receive allocated study therapy. Tumour samples were insufficient for *EGFR* testing in 189 (26%) patients and *KRAS* testing in 302 (42%) patients. Results for *EGFR* testing were obtained from local pathology reports rather than the central laboratory in 80 (11%) patients and *KRAS* testing in 30 (4%) patients (table 1). After the final analysis patients were unmasked to treatment allocation. Patients on dacomitinib were allowed to continue therapy if they were benefiting from it.

All 720 patients were included in the efficacy analyses. At the final analysis, 602 (84%) of 720 patients had died (403 [84%] of 480 patients in the dacomitinib group and 199 [83%] of 240 in the placebo group), primarily from non-small-cell lung cancer. Dacomitinib did not increase overall survival compared with placebo (median 6·83 months [95% CI 6·08–7·49] *vs* 6·31 months [5·32–7·52], respectively; hazard ratio [HR] 1·00 [95% CI 0·83–1·21]; figure 2). However, we noted that qualitative differences seem to exist in the effect of dacomitinib on overall survival according to *KRAS* status, although this difference was not significant ($p_{interaction}$=0·08; figure 3). We noted no evidence of a treatment interaction by *EGFR* mutation status for overall survival. The effect of dacomitinib was similar in patients with *EGFR* mutation positive tumours and *EGFR* wild-type ($p_{interaction}$=0·69). Prespecified subgroup analyses for overall survival are shown in table 2.

Dacomitinib increased progression-free survival compared with placebo (median 2·66 months [95% CI 1·91–3·32] *vs* 1·38 months [0·99–1·74], respectively; HR 0·66 [95% CI 0·55–0·79]; figure 2). Pre-specified subgroup analyses for progression-free survival are shown in table 2.

No patient had a complete response (table 3). In the intention-to-treat population, 34 (7%) patients in the dacomitinib group and three (1%) patients in the placebo group had a partial response (p=0·001). 242 (50%) of patients in the dacomitinib group and 101 (42%) of controls had stable disease. We noted a similar proportion of patient achieving an overall response in the 452 patients with at least one measurable lesion (table 3). Among patients allocated to dacomitinib, we noted an increased proportion of patients achieving an overall response in never smokers, patients with *KRAS* wild-type, and those with a previous response to EGFR tyrosine-kinase inhibitor (appendix). Overall response was not different among patients with a good performance status (0–1) and poor performance status (2–3), those with weight loss, and East Asians versus patients of other ethnicity (appendix).

	Dacomitinib (n=480)	Placebo (n=240)
Proportion with measurable disease by RECIST	452 (94%)	227 (95%)
Total still on treatment at time of data cutoff	10 (2%)	2 (1%)
Complete response	0	0
Partial response	34 (7%)	3 (1%)
Time to response, months	3·7 (0·79–3·87)	0·99 (0·82–1·87)
Duration of response, months	3·3 (2·07–4·53)	0·56 (0·36–12·8)
Partial response in patients with at least one measurable lesion	34/452 (8%)	3/227 (1%)
Stable disease*	242 (5%)	101 (42%)
Progressive disease	125 (26%)	101 (42%)
Not assessable	41 (9%)	20 (8%)

Data are n (%), n/N (%), or median (IQR). RECIST=Response Evaluation Criteria in Solid Tumors. *Defined as having stable disease for 2 months or longer after randomisation to treatment.

Table 3: **Treatment responses**

Safety analyses were done in the 716 patients (477 in the dacomitinib group and 239 in the placebo group) who had received at least one dose of study drug. 165 (35%) of 477 patients in the dacomitinib group and six (3%) of 239 patients in the placebo group had at least one dose reduction. The mean relative dose intensity was 0·81 (95% CI 0·79–0·82) for dacomitinib and 0·94 (0·93–0·96) for placebo. 43 (9%) patients in the dacomitinib group discontinued treatment because of unacceptable toxicity, as did two (1%) patients in the placebo group. The side-effect profile of dacomitinib is consistent with other irreversible EGFR inhibitors (table 4). The most common side-effects attributable to dacomitinib were diarrhoea, acneiform rash, maculo-papular rash, mucositis, dry skin, paronychia, anorexia, and fatigue. The incidence of grade 3 or worse toxicities was low, with only diarrhoea and rash reported by more than 10% of participants.

185 (39%) patients in the dacomitinib group had serious adverse events, as did 86 (36%) in the placebo group. The numbers of serious adverse events leading to death (all-cause fatal events within 30 days, or those regarded as related to study medication within 30 days after last dose of study medication) were similar between the two treatment groups (90 [19%] patients *vs* 47 [20%] controls). These events were mainly related to non-small-cell lung cancer. Three deaths were judged by the investigators to be related to dacomitinib (two respiratory failures and one death not otherwise specified).

Overall compliance with completion of quality-of-life questionnaires was about 90% across all cycles. Time to deterioration in three prespecified symptoms was longer for patients treated with dacomitinb than those treated with placebo: cough (median 12·0 months [95% CI 9·2–not reached] *vs* 4·6 months [2·1–7·9]; p<0·0001), dyspnoea (median 5·6 months [4·0–11·3] *vs* 4·6 months [3·7–6·5]; p=0·049), and pain (median 3·0 months [2·3–3·8] *vs* 1·9 months [1·9–3·1]; p=0·041). We noted no systematic difference between the treatment

	Dacomitinib (n=477)				Placebo (n=239)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Diarrhoea	312 (65%)	58 (12%)	1 (<1%)	0	36 (15%)	0	0	0
Acneiform rash	227 (48%)	47 (10%)	1 (<1%)	0	17 (7%)	1 (<1%)	0	0
Maculopapular rash	63 (13%)	11 (2%)	0	0	11 (5%)	0	0	0
Oral mucositis	180 (38%)	15 (3%)	1 (<1%)	0	4 (2%)	0	0	0
Dry skin	140 (29%)	3 (<1%)	0	0	16 (7%)	0	0	0
Paronychia	124 (26%)	10 (2%)	0	0	0	0	0	0
Fatigue	91 (19%)	13 (3%)	0	0	24 (10%)	4 (2%)	0	0
Nausea	93 (19%)	2 (<1%)	0	0	20 (8%)	1 (<1%)	0	0
Vomiting	90 (19%)	5 (1%)	0	0	4 (2%)	0	0	0
Anorexia	90 (19%)	12 (3%)	0	0	17 (7%)	1 (<1%)	0	0
Pruritus	71 (15%)	5(1%)	0	0	18 (8%)	0	1 (<1%)	0
PPE	47 (10%)	7 (1%)	0	0	2 (1%)	0	0	0
Epistaxis	43 (9%)	0	0	0	0	0	0	0
Conjunctivitis	39 (8%)	4 (<1%)	0	0	0	0	0	0
Dry mouth	39 (8%)	1 (<1%)	0	0	4 (2%)	0	1 (<1%)	0
Dry eye	30 (6%)	0	0	0	1 (1%)	0	0	0
Dysgeusia	31 (6%)	0	0	0	2 (1%)	0	0	0
Weight loss	25 (5%)	2 (<1%)	0	0	4 (2%)	0	0	0
Dehydration	4 (1%)	10 (2%)	1 (<1%)	0	0	0	0	0
Acute kidney injury	0	2 (<1%)	2 (<1%)	0	0	0	0	0
Erythema multiform	10 (2%)	2 (<1%)	0	0	0	0	0	0
Hypokalaemia	1 (<1%)	0	1 (<1%)	0	0	0	0	0
Lung infection	0	1 (<1%)	1 (<1%)	0	0	0	0	0
Pneumonitis	3 (<1%)	1 (<1%)	0	0	0	0	0	0
Death NOS	0	0	0	1 (<1%)	0	0	0	0
Respiratory failure	0	1 (<1%)	1 (<1%)	2 (<1%)	0	0	0	0

Data are n (%). Adverse events were coded by the Common Terminology Criteria for Adverse Events version 4.0. The table includes related adverse events of any grade (as judged by the investigator) that occurred in 5% or more of patients in either treatment group, as well as any grade 3–5 adverse events. PPE=palmar plantar erythrodysesthesia. NOS=not otherwise stated.

Table 4: **Treatment-related adverse events**

groups for the five functional domains (data not shown). Patients on dacomitinib had consistently better quality-of-life scores for constipation than did those on placebo, but worse scores for diarrhoea. Quality of life was better for haemoptysis in the dacomitinib group than the placebo group, but worse for appetite loss, sore mouth, and trouble swallowing; no consistent results were noted in other symptoms (data not shown). Health economic assessment and some translational outcomes are not reported here.

143 (37%) of 384 patients in the dacomitinib group and 83 (41%) of 203 patients in the placebo group received further therapy at the time of progression. Use of afatinib, another irreversible EGFR tyrosine-kinase inhibitor, was low (22 [6%] in the dacomitinib group *vs* 14 [7%] in the control group). Slightly more patients in the dacomitinib group received pemetrexed at progression (35 [9%] *vs* 13 [6%]). At the time of the final analysis, crossover was offered to patients, although no patients in the placebo group chose to receive dacomitinib.

Discussion

The results of the BR.26 trial show that dacomitinib did not improve overall survival for patients with non-small-cell lung cancer compared to placebo, although it did increase progression-free survival and improve key lung cancer symptoms (cough, dyspnoea, and pain). No differences were noted between treatment groups in global quality-of-life measures, although the safety profile of dacomitinib was generally tolerable.

Despite advances in the management of non-small-cell lung cancer in the past two decades, additional treatment options are needed for patients with advanced disease after progression with standard therapy (panel). Data from early phase clinical trials of dacomitinib showed activity in patients with *KRAS* wild-type tumours[15–17] and a randomised phase 2 trial[19] comparing erlotinib with dacomitinib suggested that the activity of dacomitinib was not restricted to patients with tumours containing *EGFR* mutations. Therefore, BR.26 assessed dacomitinib in a broad population of patients with non-small-cell lung cancer and was not restricted by molecular characteristics.

The results of BR.26 provide similar findings to other trials in pretreated patients with non-small-cell lung cancer. Both vandetanib[13] and afatinib[14] showed improvements in tumour response and progression-free survival compared with best supportive care, but without improvement in overall survival. Why the anti-tumour activity of these drugs did not translate into increases in overall survival is unclear. The patients in BR.26 and in the previous studies[13,14] had already received multiple therapies and had a short life expectancy, so might not have lived long enough to benefit from any treatment. Frequently, comparisons of overall survival are confounded by the use of subsequent therapies.[14] In the LUX-Lung 1 trial of afatinib versus best supportive care, more than two-thirds of patients received additional therapy at the time of disease progression. A post-hoc analysis of LUX-Lung 1 for overall survival, censoring patients at the time that they began additional therapy, suggested longer overall survival for patients randomised to afatinib (HR 0·64, 95% CI 0·43–0·95). However, the lack of evidence that fourth and subsequent lines of therapy improve survival in heavily pretreated patients does not support this point of view. Another plausible hypothesis is that the use of a further line of EGFR-directed therapy might result in upregulation of the expression of the receptor or its ligand, which would alter the post-progression tumour biology.

One of the strengths of our trial was the preplanned collection of tumour samples for biomarker correlative studies. We observed a higher proportion of patients with *EGFR* mutations and lower proportion with *KRAS* mutations than is expected in the literature. This finding probably is due to the longer overall survival of patients with *EGFR* mutations and greater likelihood of reaching third-line or fourth-line therapies. Thus, the survival estimates for patients on both treatment groups was longer than expected. Although BR.26 did not meet its primary outcome of improved overall survival, we noted some evidence of heterogeneity of treatment effect in prespecified subgroups. Clinical characteristics such as Asian ethnicity and never smoking are well documented predictors of response to an EGFR tyrosine-kinase inhibitor, although they are probably are surrogates for the presence of an *EGFR* mutation.[22] These findings were also observed in BR.26. However, we noted no differential effect of dacomitinib on overall survival according to *EGFR* status. Similarly, analysis of the RADIANT trial[23] of adjuvant erlotinib or placebo in patients with resected non-small-cell lung cancer did not show any differential effect on survival in patients with *EGFR*-mutated tumours. Patients with tumours containing *KRAS* mutations who were randomly allocated to dacomitinib had worse survival than did those allocated placebo. These findings lend support to the view that *KRAS* status could predict patients who should not receive an EGFR tyrosine-kinase inhibitor. This notion is further supported by similar findings reported in the BR.21 trial, in which no evidence was noted of a treatment interaction on overall survival for *EGFR* mutation status, and there were some non-significant evidence of worsened overall survival in patients with *KRAS*-mutated tumours.[10,12] The availability of plasma samples from our study might enable additional correlative studies.

Some limitations exist in our data. Despite the eligibility requirement for tumour samples, samples were not available or were inadequate for translational studies in 25–40% of patients; the timeframe of the study predates uniform testing for *EGFR* mutations for many patients. This problem was mitigated, in part, by obtaining local institutional results for *EGFR* and *KRAS* testing. However, these samples were mainly archival, and do not provide information about resistance mechanisms. Another potential limitation was the use of post-progression therapy. The trial was designed for patients who did not have additional standard treatment options and who would normally be managed by best supportive care. Therefore, the fact that some patients received additional therapy might confound the interpretation of overall survival in this situation. However, the switch to alternate systemic therapy was similar between the two groups, minimising the effect this treatment might have had on the primary survival outcome, and was substantially lower than that observed in the LUX-Lung 1 trial.[14]

Panel: Research in Context

Systematic review

We did not undertake a systematic review when planning this trial. We were aware of a number of guidelines or systematic reviews already undertaken on the use of EGFR tyrosine-kinase inhibitors after first-line therapy for advanced or metastatic non-small-cell lung cancer, including a systematic review and guideline on second-line or subsequent lines of therapy for non-small-cell lung cancer from Cancer Care Ontario. The senior investigators within the Lung Executive for the National Cancer Institute of Canada (NCIC) Clinical Trials Group (CTG) were familiar with other ongoing trials of oral tyrosine-kinase inhibitorsin heavily pretreated patients with non-small-cell lung cancer. At the time of study design, the ZEPHYR and Lux-Lung 1 trials[13,14] were not completed. The standard of care at that time for patients who were previously treated with chemotherapy and an EGFR tyrosine-kinase inhibitor was best supportive care. In view of the absence of any approved therapy for this group of patients we designed BR.26 to compare dacomitinib with the existing standard of care.

Interpetation

Our trial is the second study to assess an irreversible EGFR tyrosine-kinase inhibitor in patients with non-small-cell lung cancer who have already received prior chemotherapy, plus gefitinib or erlotinib. The findings of NCIC CTG BR.26 are similar to those of the Lux-Lung 1 trial,[14] although the trials were done in somewhat different populations of patients with non-small-cell lung cancer. BR.26 did not show any improvement in overall survival for patients randomly allocated dacomitinib. However, we noted an improvement in progression-free survival, as well as key lung cancer symptoms (cough, dyspnoea, and pain). However, at present, dacomitinib cannot be recommended as a treatment for patients with non-small-cell lung cancer. No therapies have been shown to improve survival after chemotherapy and an EGFR tyrosine-kinase inhibitor in this population. An unmet need therefore exists for additional treatment options.

For more on **non-small-cell lung cancer guidelines** see https://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=34349

The results of the phase 3 ARCHER 1009 trial of erlotinib versus dacomitinib were recently presented.[24] The results did not confirm the findings of the similarly designed randomised phase 2 trial. No differences were reported in overall survival or progression-free survival for dacomitinib compared with erlotinib and no advantage was reported in the *KRAS* wild-type population. An ongoing randomised phase 3 trial (ARCHER 1050) in patients with non-small-cell lung cancer and *EGFR*-mutated tumours is comparing dacomitinib with gefitinib in the first-line setting, which might help determine if dacomitinib has a therapeutic role in the treatment of non-small-cell lung cancer.

Contributors

PME, PAB, FAS, MM, FP, LS, NBL, MRS, CWL, M-ST, KD, and GDG were involved in the design of the trial and protocol development, data interpretation, and writing of the manuscript. PME, PAB, and KD reviewed and confirmed the completeness of the data and were involved in data analysis. All authors contributed to data collection and reviewed, commented, and approved the final report. ZG provided input from Pfizer to the conduct of the trial, reviewed the data, and provided commentary on the manuscript.

Declaration of interests

PME declares honoraria from Pfizer (from 2010), Roche, and Boehringer-Ingelheim. FAS declares honoraria from Roche. GL declares honoraria from Pfizer and Novartis. AM declares honoraria from Pfizer, AstraZeneca, and Roche. NB declares honoraria from Pfizer. RSS declares honoraria from AsreaZeneca, Boehringer-Ingelheim, Pfizer, and Roche. M-ST declares honoraria from Pfizer, AstraZeneca, Boehringer-Ingelheim, Roche, and Novartis. ZG is a Pfizer employee. GDG reports honoraria from Roche. PAB is funded by a Cancer Care Ontario Research Chair in Experimental Therapeutics. MM, FP, LS, SS, BCC, NBL, MRS, CWL, RW, VC, AGF, JHK, CFW, and KD declare no competing interests.

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