Erlotinib plus bevacizumab versus erlotinib alone in patients with *EGFR*-positive advanced non-squamous non-small-cell lung cancer (NEJ026): interim analysis of an open-label, randomised, multicentre, phase 3 trial

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Summary

Background Resistance to first-generation or second-generation EGFR tyrosine kinase inhibitor (TKI) monotherapy develops in almost half of patients with *EGFR*-positive non-small-cell lung cancer (NSCLC) after 1 year of treatment. The JO25567 phase 2 trial comparing erlotinib plus bevacizumab combination therapy with erlotinib monotherapy established the activity and manageable toxicity of erlotinib plus bevacizumab in patients with NSCLC. We did a phase 3 trial to validate the results of the JO25567 study and report here the results from the preplanned interim analysis.

Methods In this prespecified interim analysis of the randomised, open-label, phase 3 NEJ026 trial, we recruited patients with stage IIIB–IV disease or recurrent, cytologically or histologically confirmed non-squamous NSCLC with activating *EGFR* genomic aberrations from 69 centres across Japan. Eligible patients were at least 20 years old, and had an Eastern Cooperative Oncology Group performance status of 2 or lower, no previous chemotherapy for advanced disease, and one or more measurable lesions based on Response Evaluation Criteria in Solid Tumours (1.1). Patients were randomly assigned (1:1) to receive oral erlotinib 150 mg per day plus intravenous bevacizumab 15 mg/kg once every 21 days, or erlotinib 150 mg per day monotherapy. Randomisation was done by minimisation, stratified by sex, smoking status, clinical stage, and *EGFR* mutation subtype. The primary endpoint was progression-free survival. This study is ongoing; the data cutoff for this prespecified interim analysis was Sept 21, 2017. Efficacy was analysed in the modified intention-to-treat population, which included all randomly assigned patients who received at least one dose of treatment and had at least one response evaluation. Safety was analysed in all patients who received at least one dose of study drug. The trial is registered with the University Hospital Medical Information Network Clinical Trials Registry, number UMIN000017069.

Findings Between June 3, 2015, and Aug 31, 2016, 228 patients were randomly assigned to receive erlotinib plus bevacizumab (n=114) or erlotinib alone (n=114). 112 patients in each group were evaluable for efficacy, and safety was evaluated in 112 patients in the combination therapy group and 114 in the monotherapy group. Median follow-up was 12·4 months (IQR 7·0–15·7). At the time of interim analysis, median progression-free survival for patients in the erlotinib plus bevacizumab group was 16·9 months (95% CI 14·2–21·0) compared with 13·3 months (11·1–15·3) for patients in the erlotinib group (hazard ratio 0·605, 95% CI 0·417–0·877; p=0·016). 98 (88%) of 112 patients in the erlotinib plus bevacizumab group and 53 (46%) of 114 patients in the erlotinib alone group had grade 3 or worse adverse events. The most common grade 3–4 adverse event was rash (23 [21%] of 112 patients in the erlotinib plus bevacizumab group *vs* 24 [21%] of 114 patients in the erlotinib alone group). Nine (8%) of 112 patients in the erlotinib plus bevacizumab group and five (4%) of 114 patients in the erlotinib alone group had serious adverse events. The most common serious adverse events were grade 4 neutropenia (two [2%] of 112 patients in the erlotinib plus bevacizumab group) and grade 4 hepatic dysfunction (one [1%] of 112 patients in the erlotinib plus bevacizumab group and one [1%] of 114 patients in the erlotinib alone group). No treatment-related deaths occurred.

Interpretation The results of this interim analysis showed that bevacizumab plus erlotinib combination therapy improves progression-free survival compared with erlotinib alone in patients with *EGFR*-positive NSCLC. Future studies with longer follow-up, and overall survival and quality-of-life data will be required to further assess the efficacy of this combination in this setting.

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Research in context

Evidence before this study

EGFR tyrosine kinase inhibitor (TKI) monotherapy has been established as the standard treatment for patients with *EGFR*-positive non-small-cell lung cancer (NSCLC). However, the median progression-free survival for patients treated with EGFR TKI monotherapy is approximately 10–12 months. We searched PubMed from database inception to Oct 1, 2018, for clinical trials published in English using the search terms "erlotinib", "bevacizumab", "NSCLC", and "EGFR". We identified two phase 2 trials that assessed the activity of erlotinib plus bevacizumab as first-line treatment for *EGFR*-positive NSCLC: BELIEF and JO25567. The BELIEF study showed that combined therapy with bevacizumab and erlotinib had higher efficacy in tumours with the Thr790Met mutation than those without. In the JO25567 study, median progression-free survival with the bevacizumab and erlotinib combination was 16 months (95% CI 13·9–18·1). The results of the FLAURA study showed the activity of first-line osimertinib treatment, a third-generation TKI, in patients with locally advanced or metastatic NSCLC: median progression-free survival was 18·9 months (95% CI 15·2–21·4). Although these results were superior to those obtained with first-generation EGFR TKI monotherapy, appropriate treatment after osimertinib resistance was not established. Our search identified no phase 3 trials of combined treatment with erlotinib and bevacizumab as a first-line treatment in this setting.

Added value of this study

To our knowledge, this is the first phase 3 study to compare the efficacy of erlotinib plus bevacizumab with erlotinib alone in patients with *EGFR*-positive NSCLC. The results from this interim analysis suggest that patients given bevacizumab and erlotinib had improved progression-free survival compared with patients given erlotinib monotherapy. Although further follow-up is needed, these preliminary data suggest that the combination of bevacizumab and erlotinib has the potential to become one of the standard treatment strategies for patients with *EGFR*-positive NSCLC.

Implications of all the available evidence

Two other phase 3 clinical trials in patients with *EGFR*-positive NSCLC—BEVERLY (NCT02633189) and Artemis (NCT02759614)—which are testing the addition of bevacizumab to erlotinib, are ongoing. The results of these studies are awaited to confirm the preliminary data of this trial on the efficacy and safety of bevacizumab plus erlotinib in this setting.

Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide. Most patients with lung cancer are diagnosed at an advanced stage and prognosis remains poor despite the development of novel therapeutic strategies.[1,2] In 2004, pivotal trials established EGFR tyrosine kinase inhibitor (TKI) therapy as standard of care for patients with *EGFR*-positive lung cancer.[3–6] Until 2018, only three first-line EGFR TKIs were clinically available: gefitinib, erlotinib, and afatinib.[7,8] Although 60–80% of patients with *EGFR*-positive tumours had responses following treatment with these drugs, median progression-free survival remains poor (around 1 year) as a result of acquired therapeutic resistance.[3–8]

To improve progression-free survival, combination treatments with first-generation or second-generation TKIs have been evaluated in multiple clinical trials.[9,10] Bevacizumab is a VEGF monoclonal antibody, which inhibits angiogenesis to suppress tumour growth by restricting oxygen and nutrient supply to tumours. In the BeTa lung phase 3 study,[11–14] the combination of bevacizumab and erlotinib was compared with erlotinib monotherapy to evaluate activity in patients with non-small-cell lung cancer (NSCLC) who were not stratified by *EGFR* mutation status. Although no substantial differences in overall survival were identified between the groups, subgroups analyses suggested that patients with *EGFR*-positive NSCLC responded better to combination therapy than did patients with *EGFR*-negative disease. On the basis of the results of the BeTa lung study, the JO25567 phase 2 trial was done.[11,15,16] Chemotherapy-naive patients with non-squamous NSCLC harbouring common *EGFR* mutations were randomly assigned to receive erlotinib plus bevacizumab or erlotinib monotherapy. Median progression-free survival was significantly improved in the erlotinib plus bevacizumab group compared with the erlotinib monotherapy group (16·0 months [95% CI 13·9–18·1] *vs* 9·7 months [5·7–11·1], hazard ratio [HR] 0·54 [95% CI 0·36–0·79]) and had an acceptable toxicity profile. However, the results of the phase 2 JO25567 study cannot be considered entirely conclusive since the study was inadequately powered to assess overall survival. We therefore did this phase 3 trial to compare erlotinib plus bevacizumab combination therapy with erlotinib monotherapy for the treatment of patients with *EGFR*-positive non-squamous NSCLC.

Methods

Study design and participants

NEJ026 was a randomised, open-label, multicentre, phase 3 study done in 69 centres across Japan (appendix pp 6–8).

Eligible patients were at least 20 years old and had histologically or cytologically confirmed non-squamous NSCLC, *EGFR*-positive status (exon 19 deletion or exon 21 Leu858Arg point mutation), stage IIIB–IV disease (defined according to the 7th edition of the *General Rule for Clinical and Pathological Record of Lung Cancer* [2010][17])

See Online for appendix

or recurrent disease, one or more measurable lesions based on Response Evaluation Criteria in Solid Tmours (RECIST 1.1), an Eastern Cooperative Oncology Group performance status of 2 or lower, and a life expectancy of at least 3 months. Patients with the coexistent *EGFR*-Thr790Met mutations, known to confer resistance to EGFR TKIs, and those who received previous chemotherapy were excluded. Eligibility criteria regarding pretreatments and washout periods before entry included: 6 months or more must have elapsed since the day of final administration of preoperative or postoperative adjuvant chemotherapy, 4 weeks or more must have elapsed since surgery, 2 weeks or more must have elapsed since the last pleurodesis that did not use anticancer drugs, 2 weeks or more must have elapsed since the last biopsy involving an incision, 2 weeks or more must have elapsed since the last treatment for trauma, 2 weeks or more must have elapsed since the systemic administration of steroids for any period of time exceeding 4 weeks, and 4 weeks or more must have elapsed since the administration of other investigational drugs. Criteria on physiological parameters and organ function requirements are in the appendix (p 10). Patients with asymptomatic brain metastasis were considered eligible to enrol in the study. A full list of inclusion and exclusion criteria are in the appendix (pp 9–13).

The study was done in accordance with the Helsinki Declaration and Good Clinical Practice Guidelines. The study protocol was reviewed and approved by the ethical committee of the Non-Profit Organization MINS Institutional Review Board and by the local institutional review boards of the participating institutions. Written informed consent was obtained from all enrolled patients.

Randomisation and masking

Patients were randomly assigned (1:1) to receive erlotinib plus bevacizumab or erlotinib alone. Randomisation was done by minimisation, stratified by sex (women *vs* men), smoking status (non-smoker or former light smoker *vs* other smoker), clinical stage (stage IIIB *vs* stage IV *vs* postoperative recurrence), and *EGFR* mutation subtype (exon 19 deletion *vs* Leu858Arg point mutation). Former light smokers were defined as individuals who had smoked less than 10 pack-years (pack-years defined as duration [years]×quantity [sticks per day] divided by 20) in their lifetime and had stopped smoking more than 15 years before the study. Other smokers were defined as individuals who had smoked more than former light smokers (ie, those who had smoked more than 10 pack-years in their lifetime, including current smokers). Central randomisation was done at a data centre (AC Medical, Tokyo, Japan) using patient enrolment sheets provided by the investigators. The data centre notified investigators of treatment allocation for each patient. All patients and investigators were unmasked to treatment allocation.

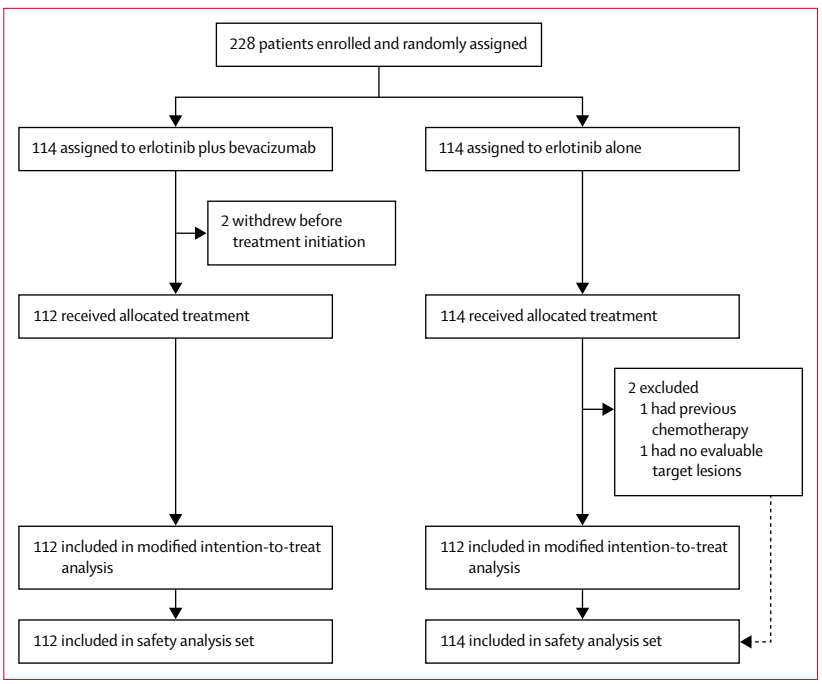

Figure 1: **Trial profile**

Procedures

We defined the study period as the period between patient enrolment and progressive disease after first-line treatment. The observation period lasted from progressive disease after first-line treatment to progressive disease during second-line treatment (appendix p 16).

Patients assigned to the erlotinib plus bevacizumab group received oral erlotinib 150 mg once daily and intravenous bevacizumab 15 mg/kg once every 21 days. Patients assigned to the erlotinib alone group received oral erlotinib 150 mg once daily. For both groups, one treatment cycle was defined as 21 days. Complete blood cell counts, serum chemistry, urinalysis, blood coagulation-fibrinolysis testing, and arterial blood oxygen saturation tests were done every 21 days. Patients remained on treatment until disease progression or intolerable toxicity. Two steps of dose reduction of erlotinib were permitted (to 100 mg per day and 50 mg per day) in the event that a dose reduction criterion was fulfilled (appendix pp 25–27). Dose reductions of bevacizumab were not permitted, thus treatment was discontinued in patients who had intolerable toxicity.

Radiological evaluation of tumours was done every 6 weeks until 18 months after treatment initiation, and every 12 weeks thereafter until disease progression according to RECIST 1.1. For evaluating the primary endpoint, an independent review committee de-identified all tumour images and evaluated tumour response according to the rules published in RECIST 1.1.

Adverse events were monitored throughout the study period and graded according to the National Cancer

	Erlotinib plus bevacizumab group (n=112)	Erlotinib alone group (n=112)
Age (years)		
Median	67 (61–73)	68 (62–73)
<75	92 (82%)	89 (79%)
≥75	20 (18%)	23 (21%)
Sex		
Men	41 (37%)	39 (35%)
Women	71 (63%)	73 (65%)
Smoking status		
Never smoked	65 (58%)	64 (57%)
Former light smoker	6 (5%)	7 (6%)
Other smoker	41 (37%)	41 (37%)
ECOG performance status		
0	64 (57%)	68 (61%)
1	48 (43%)	42 (38%)
2	0	2 (2%)
Histopathological classification		
Adenocarcinoma	110 (98%)	112 (100%)
Large cell carcinoma	1 (1%)	0
Other	1 (1%)	0
***EGFR* genomic aberration**		
Exon 19 deletion	56 (50%)	55 (49%)
Exon 21 Leu858Arg mutation	56 (50%)	57 (51%)
Clinical stage at screening		
IIIB	8 (7%)	8 (7%)
IV	82 (73%)	84 (75%)
Postoperative recurrence	22 (20%)	20 (18%)
CNS metastases		
Yes	36 (32%)	36 (32%)
No	76 (68%)	76 (68%)

Data are median (IQR) or n (%). ECOG=Eastern Cooperative Oncology Group.

Table 1: **Patient characteristics**

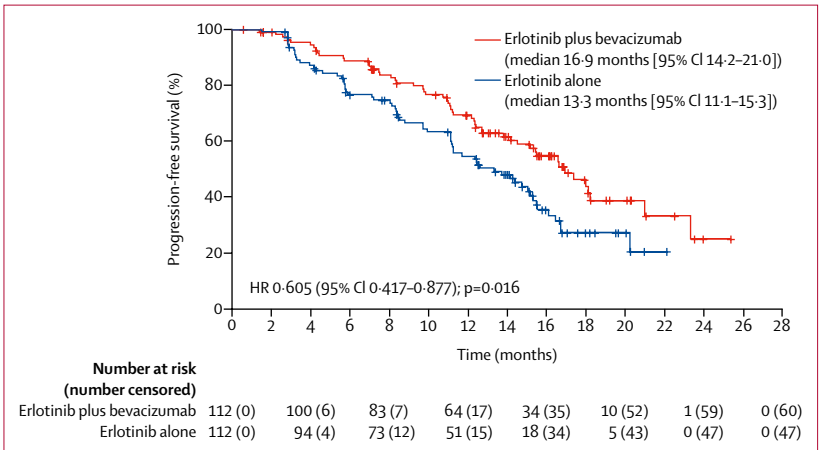

Figure 2: **Progression-free survival in the modified intention-to-treat population**
HR=hazard ratio.

Institute Common Terminology Criteria for Adverse Events, version 4.0.

Patient-reported quality of life was assessed every 12 weeks using the European Organization for Research and Treatment of Cancer quality of life questionnaire (EORTC-QLQ)-C30 or EORTC-QLQ-LC13 scoring manual.

During the observation period, which started when patients had disease progression, patients received protocol-recommended second-line treatment (a combination of platinum and pemetrexed in the erlotinib plus bevacizumab group and bevacizumab in combination with platinum plus pemetrexed in the erlotinib alone group) or the most appropriate next treatment as judged by the investigators.

To evaluate EGFR TKI resistance, tissue and plasma samples were collected. Plasma samples were collected during pretreatment, 6 weeks after initiation of study treatment, at the time of disease progression with first-line treatment, 6 weeks after initiation of second-line treatment, and at the time of disease progression with second-line treatment. Tissue samples were collected during pretreatment, at the time of disease progression with first-line treatment, and at the time of disease progression with second-line treatment. Plasma and tumour samples were screened for *EGFR* mutations using the peptide nucleic acid-locked nucleic acid PCR clamp method.[18]

Outcomes

The primary endpoint was progression-free survival, defined as the time from randomisation until disease progression with first-line treatment or death. Secondary endpoints were overall survival (defined as time from randomisation until death), tumour response, including the proportion of patients with an objective response (defined as complete or partial response) and disease control (defined as complete response, partial response, or stable disease), duration of response (defined as time from confirmation of complete or partial response to disease progression), safety, and quality of life. These secondary endpoints will be reported once follow-up is completed.

Exploratory endpoints were biomarker analyses of tissue and plasma samples to study the association between changes in *EGFR* mutation status and therapeutic effect, time from enrolment to progressive disease after second-line treatment, and a pooled analysis of overall survival combining data from the present study and the phase 2, JO25567 study. These exploratory endpoints will be reported separately.

Statistical analysis

Based on the progression-free survival results observed in the JO25567 study, we expected a median progression-free survival of 10 months in the erlotinib alone group and 16 months in the erlotinib plus bevacizumab group. With this assumption, the number of progression-free survival events required to detect an HR of 0·63 with a

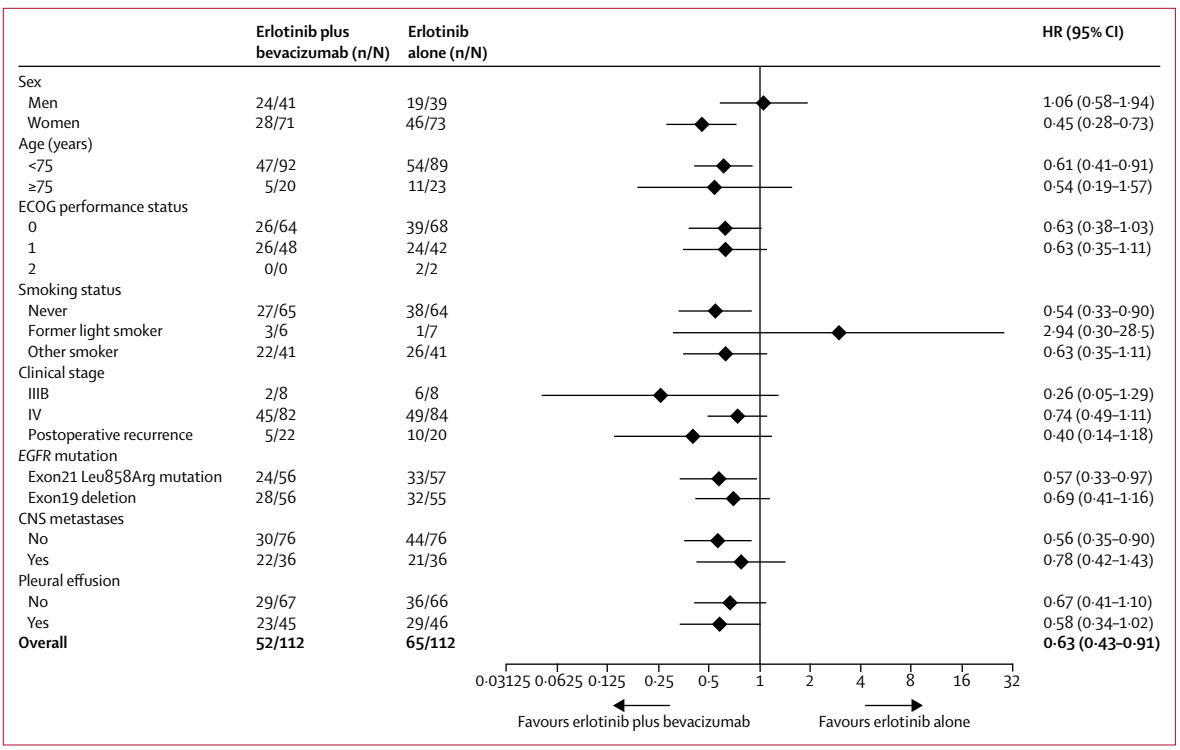

Figure 3: **Subgroup analysis of progression-free survival by baseline characteristics**
HR=hazard ratio. ECOG=Eastern Cooperative Oncology Group.

significance level of 5% (two-sided) and a detection power of 80% was 147. Assuming an enrolment period of 18 months (and assuming patient enrolment remained constant) and an observation period of 18 months, the required number of patients was 214 (107 in each group).

The aim of the interim analysis reported here was to analyse the difference in the primary endpoint between treatment groups when 67% of the required progression-free survival events (100 cases) were observed. At the data cutoff date (Sept 21, 2017), 117 progression-free survival events had occurred; thus, the nominal significance level for the interim analysis was calculated to be 0·024 for 117 progression-free survival events using the O'Brien-Fleming α spending function adjusted for multiple comparisons. The information fraction at the planned interim analysis was 0·796. An independent data monitoring committee oversaw the study. The protocol specified that if at the interim analysis, the difference in the primary endpoint between the groups was determined to be statistically significant, early discontinuation of the study would be considered. However, the decision of whether or not to discontinue the study was to be considered with comprehensive clinical judgment based on analysis results concerning futility and not based solely on the results of the statistical tests.

Efficacy endpoints were analysed in the modified intention-to-treat population, which included all randomly assigned patients who received at least one dose of the study drug and had response evaluations. All randomly assigned patients who received at least one dose of the study drug were included in the safety analysis set.

Kaplan-Meier survival curves were constructed for progression-free survival and compared using a stratified log-rank test. HR and associated 95% CIs were calculated by Cox proportional hazard analysis. 95% CIs for median progression-free survival were calculated using the method of Brookmeyer and Crowley.[19] Multivariate Cox-regression models were used for the adjusted comparison of progression-free survival between treatment groups, using the same stratification factors used at randomisation (appendix p 14). Tumour responses were compared between the erlotinib plus bevacizumab and erlotinib alone groups using the χ^2 test.

Post-hoc subgroup analyses of progression-free survival were done, by *EGFR* mutation status and by prespecified patient characteristics (including CNS metastasis and pleural effusion) using the same statistical methods as used for the primary outcome. Fisher's exact test was used to compare toxicity betw een the two treatment groups. All reported p values are two-sided. No imputation methods were used for missing data in the statistical analyses.

Statistical analyses were done using SAS (version 9.4). This trial is registered with the University Hospital Medical Information Network Clinical Trials Registry, number UMIN000017069.

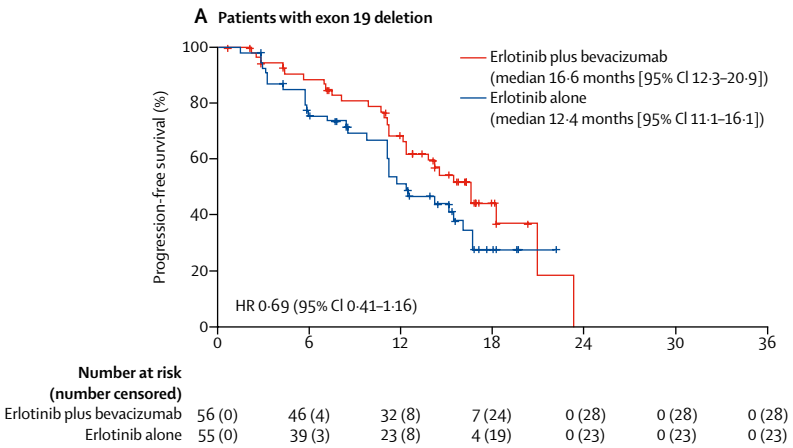

Figure 4: **Progression-free survival by *EGFR* mutation status**
HR=hazard ratio.

	Erlotinib plus bevacizumab group (n=112)	Erlotinib alone group (n=112)	p value*
Complete response	8 (7%)	4 (4%)	..
Partial response	73 (65%)	70 (63%)	..
Stable disease	25 (22%)	34 (30%)	..
Progressive disease	4 (4%)	2 (2%)	..
Not evaluable	2 (2%)	2 (2%)	..
Objective response	81 (72%; 63·1–80·4)	74 (66%; 56·5–74·7)	0·31
Disease control	106 (95%; 88·7–98·0)	108 (96%; (91·1–99·0)	0·52

Data are n (%). *p value for χ^2 test.

Table 2: **Response as per independent review committee's assessment**

Role of the funding source

The funder of the study approved the study design, and was involved in the provision of information, but had no role in the 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.

Results

Between June 3, 2015, and Aug 31, 2016, 228 patients were enrolled and randomly assigned to receive erlotinib plus bevacizumab (n=114) or erlotinib alone (n=114). Two patients in the erlotinib plus bevacizumab group withdrew from the study before treatment initiation (one withdrew consent and one withdrew at the physician's discretion) and were excluded from all analyses. Two patients in the erlotinib monotherapy group were randomised in error; one patient had received adjuvant uracil-tegafur treatment less than 6 months before enrolment and one patient was unable to receive radiological evaluation because they had no evaluable target lesions. Thus, 112 patients in each treatment group were included in the modified intention-to-treat population (figure 1).

The baseline characteristics of all randomly assigned patients were well balanced (table 1). Of the 224 patients who received treatment, 222 (99%) had adenocarcinoma, and one (1%) patient in the erlotinib and bevacizumab group had large cell carcinoma, and one (1%) patient in the erlotinib and bevacizumab group had non-small-cell carcinoma. The tested *EGFR* genomic aberrations were well balanced across the treatment groups and the proportion of patients with CNS metastases was the same in both groups (32%; table 1).

At data cutoff for the preplanned interim progression-free survival analysis (Sept 21, 2017), 117 patients had a progression-free survival event (52 [46%] of 112 patients in the erlotinib plus bevacizumab group and 65 [58%] of 112 patients in the erlotinib alone group), which represented 79·6% of the final number of events required. Median follow-up was 12·4 months (IQR 7·0–15·7). Median progression-free survival was 16·9 months (95% CI 14·2–21·0) in the erlotinib plus bevacizumab group versus 13·3 months (11·1–15·3) in the erlotinib alone group (HR 0·605, 95% CI 0·417–0·877; p=0·016; figure 2).

The independent data monitoring committee held a meeting on Jan 23, 2018, and recommended early termination of the study based on the results of the interim analysis. However, we considered that the study should be continued to obtain data for our other endpoints in addition to progression-free survival.

A post-hoc subgroup analysis based on patient characteristics suggested that progression-free survival HRs favoured the erlotinib plus bevacizumab group over the erlotinib alone group in most subgroups, although these differences were not statistically significant (figure 3). The subgroup analyses by *EGFR* genomic aberration type suggested that median progression-free survival was longer in patients with Leu858Arg mutations in the erlotinib and bevacizumab group than in the erlotinib group (17·4 months [95% CI 12·6–not estimable] *vs* 13·7 months [8·8–15·5]; figure 4). No differences were found between treatment groups in patients with EGFR exon 19 deletions (figure 4). Median

progression-free survival of patients stratified by pleural effusion and CNS metastases status are shown in the appendix (pp 17, 18).

81 (72%) of 112 patients (95% CI 63·1–80·4) in the erlotinib plus bevacizumab group and 74 (66%) of 112 patients (56·5–74·7) in the erlotinib alone group had an objective response (p=0·31). 106 (95%) of 112 patients (88·7–98·0) in the erlotinib plus bevacizumab group and 108 (96%) of 112 patients (91·1–99·0) in the erlotinib alone group achieved disease control (p=0·52; table 2). Figure 5 shows the change in tumour size from baseline for all patients with measurable disease at baseline. Patients in the erlotinib plus bevacizumab group seemed to have a better response in terms of reductions in target lesion sizes than did patients in the erlotinib alone group. No patients in the erlotinib plus bevacizumab group had an increase in tumour size, which would have represented intrinsic resistance. 38 (68%) of 56 patients with Leu858Arg mutations and 43 (77%) of 56 patients with exon 19 deletions in the erlotinib plus bevacizumab group achieved an objective response compared with 37 (65%) of 57 patients with Leu858Arg mutations and 37 (67%) of 55 patients with exon 19 deletions in the erlotinib alone group (appendix pp 2, 19).

The median duration of erlotinib treatment was 405 days (range 5–807) in the erlotinib plus bevacizumab group versus 364 days (range 43–736) in the erlotinib alone group. Mean dose intensity was 121·7 mg per day in the erlotinib plus bevacizumab group versus 127·3 mg per day in the erlotinib alone group (table 3). The median duration of bevacizumab treatment in the erlotinib plus bevacizumab group was 350 days (range 21–736).

The duration of progression-free survival and treatment dosages are shown in the appendix (p 20). Erlotinib dose reduction was not associated with shorter progression-free survival.

98 (88%) of 112 patients in the erlotinib plus bevacizumab group and 53 (46%) of 114 patients in the erlotinib alone group had grade 3 or worse adverse events (table 4). The most common grade 3–4 adverse event was rash (23 [21%] of 112 patients in the erlotinib plus bevacizumab group *vs* 24 [21%] of 114 patients in the erlotinib alone group). Nine (8%) of 112 patients in the erlotinib plus bevacizumab group and five (4%) of 114 patients in the erlotinib alone group had serious adverse events (appendix p 15). The most common serious adverse events were grade 4 neutropenia (two [2%] of 112 patients in the erlotinib plus bevacizumab group) and grade 4 hepatic dysfunction (one [1%] of 112 patients in the erlotinib plus bevacizumab group and one [1%] of 114 patients in the erlotinib alone group). No treatment-related deaths occurred in either treatment group. The proportion of patients with hypertension (46% *vs* 10%), proteinuria (32% *vs* 5%), and non-pulmonary haemorrhage (26% *vs* 3%) was higher in the erlotinib plus bevacizumab group than the erlotinib alone group (table 4), and these events were associated

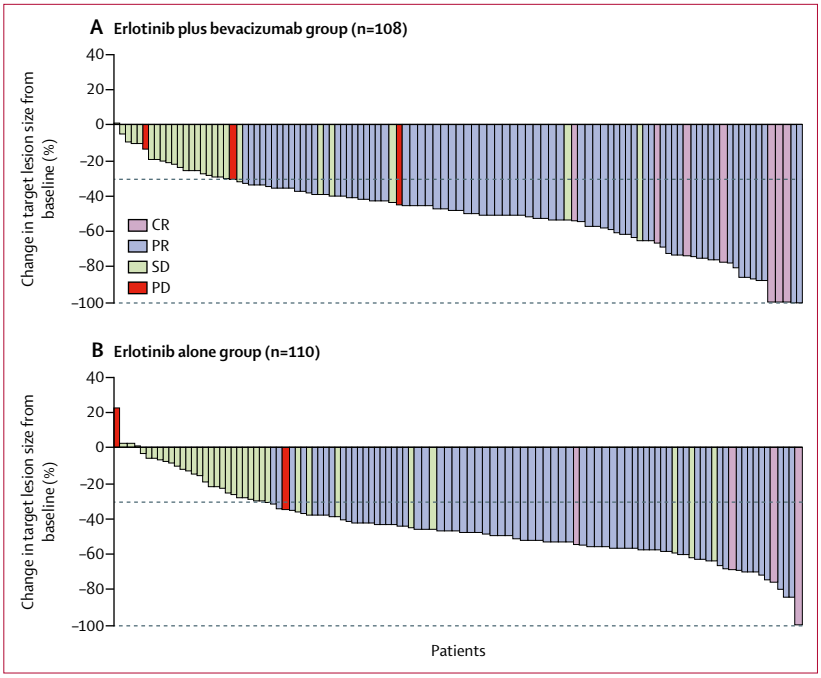

Figure 5: **Best percentage change from baseline in target lesion size**
Responders were confirmed by Response Evaluation Criteria in Solid Tumors guidelines. CR=complete response. PR=partial response. SD=stable disease. PD=progressive disease.

	Erlotinib plus bevacizumab group (n=112)	Erlotinib alone group (n=112)
Erlotinib		
Median treatment duration (days)	405 (5–807)	364 (43–736)
Dose intensity (mg per day)	121·7	127·3
Discontinued due to adverse events	21 (19%)	17 (15%)
Bevacizumab		
Median treatment duration	350 (21–736)	..
Discontinued due to adverse events	33 (29%)	..

Data are median (range), mean, or n (%).

Table 3: **Dose intensity by treatment group**

with bevacizumab treatment. 23 (21%) of 112 patients in the erlotinib plus bevacizumab group had grade 1 non-pulmonary haemorrhage, four (4%) had grade 2 non-pulmonary haemorrhage, and two (2%) had grade 3 non-pulmonary haemorrhage. Interstitial lung disease was only observed in the erlotinib alone group (five [4%] of 114 patients). 33 (29%) of 112 patients discontinued bevacizumab due to adverse events. The most common adverse events resulting in bevacizumab discontinuation were proteinuria (11 [33%] patients), haemorrhage (excluding pulmonary haemorrhage; three [9%] patients), and hepatic dysfunction (three [9%] patients; appendix p 3). 48 (43%) of 112 patients in the erlotinib and bevacizumab group and 47 (41%) of 114 patients in the erlotinib alone group required dose reductions of erlotinib (data not shown). The most common adverse

	Erlotinib plus bevacizumab group (n=112)				Erlotinib alone group (n=114)			
	All	Grade 1–2	Grade 3	Grade 4	All	Grade 1–2	Grade 3	Grade 4
Rash	98 (88%)	75 (67%)	23 (21%)	0	99 (87%)	75 (66%)	24 (21%)	0
Diarrhoea	53 (47%)	47 (42%)	6 (5%)	0	47 (41%)	45 (39%)	2 (2%)	0
Proteinuria	36 (32%)	28 (25%)	8 (7%)	0	6 (5%)	5 (4%)	1 (1%)	0
Pulmonary haemorrhage	2 (2%)	2 (2%)	0	0	0	0	0	0
Non-pulmonary haemorrhage	29 (26%)	27 (24%)	2 (2%)	0	3 (3%)	2 (2%)	1 (1%)	0
Hypertension	52 (46%)	26 (23%)	26 (23%)	0	11 (10%)	10 (9%)	1 (1%)	0
Increased aminotransferase	30 (27%)	21 (20%)	6 (5%)	3 (3%)	34 (30%)	28 (25%)	5 (4%)	1 (1%)
Stomatitis	23 (21%)	22 (20%)	1 (1%)	0	12 (11%)	11 (10%)	1 (1%)	0
Paronychia	17 (15%)	15 (13%)	2 (2%)	0	18 (16%)	15 (13%)	3 (3%)	0
Decreased appetite	13 (12%)	11 (10%)	2 (2%)	0	6 (5%)	5 (4%)	1 (1%)	0
Anaemia	6 (5%)	2 (2%)	4 (4%)	0	2 (2%)	2 (2%)	0	0
Gastrointestinal perforation	1 (1%)	0	0	1 (1%)	0	0	0	0
Increased amylase	1 (1%)	0	0	1 (1%)	1 (1%)	0	0	1 (1%)
Hypernatremia	1 (1%)	0	0	1 (1%)	1 (1%)	1 (1%)	0	0
Neutropenia	1 (1%)	0	0	1 (1%)	2 (2%)	1 (1%)	1 (1%)	0
Febrile neutropenia	1 (1%)	0	0	1 (1%)	0	0	0	0
Sepsis	1 (1%)	0	0	1 (1%)	0	0	0	0
Strangulation ileus	1 (1%)	0	0	1 (1%)	0	0	0	0
Lower limb oedema	2 (2%)	1 (1%)	1 (1%)	0	1 (1%)	0	1 (1%)	0
Acute renal failure	1 (1%)	0	1 (1%)	0	1 (1%)	0	1 (1%)	0
Skin infection	1 (1%)	0	1 (1%)	0	1 (1%)	0	1 (1%)	0
Headache	1 (1%)	0	1 (1%)	0	2 (2%)	2 (2%)	0	0
Increased alkaline phosphatase	3 (3%)	3 (3%)	0	0	4 (4%)	2 (2%)	2 (2%)	0
Increased bilirubin	3 (3%)	3 (3%)	0	0	4 (4%)	4 (4%)	0	0
Thrombosis	2 (2%)	1 (1%)	1 (1%)	0	6 (5%)	5 (4%)	1 (1%)	0
Decreased performace status	1 (1%)	0	1 (1%)	0	0	0	0	0
Pharyngalgia	1 (1%)	0	1 (1%)	0	0	0	0	0
Dacryocystitis	1 (1%)	0	1 (1%)	0	0	0	0	0
Peripheral sensory neuropathy	0	0	0	0	1 (1%)	0	1 (1%)	0
Hearing impaired	0	0	0	0	1 (1%)	0	1 (1%)	0
Hypokalaemia	0	0	0	0	4 (4%)	3 (3%)	1 (1%)	0
Hypophosphatemia	0	0	0	0	1 (1%)	0	1 (1%)	0
Urinary retention	0	0	0	0	1 (1%)	0	1 (1%)	0
Interstitial lung disease	0	0	0	0	5 (4%)	5 (4%)	0	0

Data are n (%). Grade 1-2 events occurring in more than 10% of patients and all grade 3-4 events are shown. No grade 5 events were recorded.

Table 4: **Adverse events in the safety population**

events resulting in erlotinib discontinuation were rash (eight [7%] of 112 patients in the erlotinib plus bevacizumab group and eight [7%] of 114 patients in the erlotinib alone group; appendix p 5).

Discussion

To the best of our knowledge, this is the first report of a multicentre phase 3 study to compare the efficacy of bevacizumab and erlotinib combination treatment with that of erlotinib monotherapy in patients with NSCLC. Our preplanned interim analysis showed that the median progression-free survival of patients in the erlotinib plus bevacizumab group was significantly improved compared with that of patients in the erlotinib alone group. The addition of bevacizumab to erlotinib therefore seems to be a promising strategy to improve progression-free survival in patients with *EGFR*-positive NSCLC. Multivariate analyses of progression-free survival indicated that erlotinib and bevacizumab combination therapy was broadly effective. A number of toxicities associated with bevacizumab, such as hypertension, proteinuria, and haemorrhage, were more common in the erlotinib plus bevacizumab group than the erlotinib alone group, but these were deemed to be manageable. The proportion of patients with adverse events in each treatment group was acceptable and were consistent with the level of toxicity observed in the JO25567 phase 2 trial. Notably, non-pulmonary haemorrhage was more

common in the erlotinib plus bevacizumab group than the erlotinib alone group. In the JO25567 study, 54 (72%) of 75 patients in the erlotinib plus bevacizumab group had non-pulmonary haemorrhage of any grade, and two patients (3%) had grade 3 non-pulmonary haemorrhage. These data indicate that the safety profiles of erlotinib plus bevacizumab in this study and the JO25567 study are comparable.

In patients with NSCLC, combination chemotherapy treatment with bevacizumab is known to be effective against CNS metastases and pleural effusion.[20–24] In this study, our subgroup analysis suggests that the addition of bevacizumab had no progression-free survival benefit for patients with asymptomatic CNS metastases. Another subgroup analysis suggested that erlotinib and bevacizumab combination treatment improves progression-free survival in patients with tumours driven by the Leu858Arg mutation, which usually have an inferior response to EGFR TKIs when compared with tumours driven by the exon 19 deletion.[7,25]

The mechanism by which bevacizumab and erlotinib combination treatment has improved efficacy in terms of progression-free survival compared with erlotinib remains unknown. In addition to a possible anti-angiogenic contribution, we hypothesise that bevacizumab might normalise blood flow in tumour blood vessels, thus improving drug delivery,[26,27] or autocrine or paracrine signalling by the VEGF receptor might induce cancer cell proliferation and anti-apoptosis. Bevacizumab might inhibit this effect, which would help to restore apoptosis. An animal study[28,29] showed that the addition of bevacizumab to erlotinib treatment restored resistance to the VEGF-mediated pathway, although a clear mechanism has not been elucidated.

Although the primary endpoint was met and the independent data monitoring committee recommended that the study was stopped, we continue investigation on secondary and exploratory endpoints. To elucidate the role of bevacizumab in combination with EGFR TKIs, data on overall survival, post-treatment prognosis, and quality of life, and data from liquid biopsy studies are necessary. These analyses were planned to be done sequentially. Liquid biopsy to detect activating mutations and Thr790Met resistance mutations is one of the analyses prespecified in our study. The BELIEF study[14] showed that the combination of bevacizumab and erlotinib had better activity in tumours with Thr790Met mutations than in tumours without Thr790Met mutations. More than 30% of pretreatment Thr790Met mutations were detected using highly sensitive methods. A review[30] reported that the frequency of pretreatment Thr790Met mutations varies substantially in the literature (0–79%) and is dependent on the detection method used. The peptide nucleic acid-locked nucleic acid clamp method used in our study is used clinically and has moderate sensitivity. The results of the BELIEF study cannot be compared with our study since different methods were used to detect *EGFR* mutations. In the current study, we assumed that Thr790Met mutations represented acquired resistance mechanism rather than intrinsic resistance.

In the JO25567 study,[31] median overall survival in the erlotinib plus bevacizumab group did not differ from that in the erlotinib alone group (47·0 months *vs* 47·4 months; HR 0·81, 95% CI 0·53–1·23). However, the study was not designed to detect overall survival-related benefits and the overall survival analysis was done for only half of patients who provided consent. Therefore, a combined analysis of overall survival data from the NEJ026 and JO25567 studies has been prespecified. To resolve any ethical issues associated with our approach, this study was continued after all investigators were notified of the results of our interim analysis and permission was obtained from patients in the erlotinib monotherapy group for the addition of bevacizumab to the treatment regimen.

Some candidate EGFR TKIs for first-line treatment of *EGFR*-positive NSCLC have been studied with the expectation that they would improve progression-free survival and overall survival compared with first-generation EGFR TKI monotherapy. The third generation EGFR TKI, osimertinib, is one such candidate. 40–60% of EGFR TKI monotherapy-resistant tumours harbour the *EGFR* exon 20 Thr790Met mutation.[32,33] Osimertinib was designed to overcome Thr790Met resistance. The FLAURA study[34] comparing osimertinib monotherapy with gefitinib or erlotinib monotherapy in untreated patients harbouring *EGFR* activating mutations showed that patients given osimertinib achieved longer progression-free survival than did patients given first-generation EGFR TKIs. In 2018, first-line osimertinib treatment was approved in the USA and Japan for the treatment of *EGFR*-positive NSCLC.[34,35] In the FLAURA study,[34] the median progression-free survival for patients administered osimertinib monotherapy was 18·9 months. However, data for follow-up treatment after disease progression was not established and overall survival data are immature at present. In 2018, we demonstrated the efficacy of carboplatin and pemetrexed plus gefitinib treatment relative to gefitinib monotherapy.[10] The median progression-free survival for patients in the carboplatin and pemetrexed with gefitinib group was 20·9 months and median overall survival was 52·2 months, which was longer than the median progression-free survival (11·2 months) and overall survival (38·3 months) for patients in the monotherapy group. Although haematological toxicities were higher than expected in the carboplatin and pemetrexed group, their frequency was similar to that observed in patients treated with a standard regimen of carboplatin plus pemetrexed. Since toxicity profiles and baseline parameters for patients vary widely, the optimum regimen (erlotinib and bevacizumab combination

therapy, osimertinib treatment, or a combination of TKI and chemotherapy) should be considered on a case-by-case basis.

Our study has several limitations. First, the sample size was small. The study was not powered for subgroup analysis of the primary endpoint. Thus, the results of the subgroup analysis should be interpreted with caution. Second, osimertinib treatment might affect overall survival, the data for which are immature at present. Because patients with *EGFR* mutations are expected to have improved overall survival compared with patients without *EGFR* mutations, we plan to evaluate progressive disease after second-line treatment as an exploratory analysis. Although we defined second-line treatment as chemotherapy with or without bevacizumab, osimertinib treatment was allowed in patients with Thr790Met mutations appearing at disease progression during first-line treatment. The prevalence of Thr790Met mutations might have varied between both groups after study treatment, which would influence overall survival.

In conclusion, NEJ026 met the primary endpoint at the preplanned interim analysis, showing that patients with *EGFR*-positive NSCLC treated with a combination of bevacizumab and erlotinib had longer progression-free survival than patients treated with erlotinib alone. These results suggest that combination therapy with bevacizumab and erlotinib has the potential to become a standard treatment for patients with *EGFR*-positive NSCLC if the overall survival data and quality of life analyses are favourable.

Contributors

MMa was the principal investigator. TF, KH, TN, SM, and KK contributed to the study design, data analysis, and data interpretation. HS, NF, KW, SS, SI, YoT, OY, MO, KY, IN, AG, KA, FK, YuT, YF, HN, GA, SW, and MMi contributed to patient recruitment and data collection. HS, TF, and MMa prepared the initial draft of the report with input from other authors. All authors approved the final version of the report.

Declaration of interests

HS reports grants from Chugai Pharmaceutical, AstraZeneca, and MSD; and personal fees from Ono Pharmaceutical, Nippon Boehringer Ingelheim, and Novartis Pharma, outside the submitted work. TF reports personal fees from AstraZeneca and Boehringer Ingelheim, outside the submitted work. SS reports personal fees from Chugai Pharmaceutical, AstraZeneca, Nippon Boehringer Ingelheim, MSD, Taiho Pharmaceutical, Pfizer, Eli Lilly and Company, Novartis, Kyowa Hakko Kirin, Bristol-Myers Squibb, and Ono Pharmaceutical, outside the submitted work. SI reports grants and personal fees from Ono Pharmaceutical, Chugai Pharmaceutical, AstraZeneca, MSD, Bristol-Myers Squibb, Eli Lilly Japan, Taiho Pharmaceutical, and Daiichi Sankyo, outside the submitted work. MO reports grants and clinical trial fees from Chugai Pharmaceutical paid to their institution. AG reports personal fees from Chugai Pharmaceutical. KA has received honoraria from Ono Pharmaceutical, Bristol-Myers Squibb, AstraZeneca, and Chugai Pharmaceutical. YF reports personal fees from Chugai Pharmaceutical and AstraZeneca, outside the submitted work. SW reports personal fees from AstraZeneca, Chugai Pharmaceutical, Bristol-Myers Squibb, Boehringer Ingelheim, Ono Pharmaceutical, and Taiho Pharmaceutical, outside the submitted work. KH reports personal fees from Chugai Pharmaceutical, during the conduct of the study; and has a patent for an *EGFR* mutation detection method, with royalties paid to LSI Medience. TN reports grants from Chugai Pharmaceutical, during the conduct of the study. SM reports grants from North East Japan Study Group, during the conduct of the study; and personal fees from Chugai Pharmaceutical, outside the submitted work. KK reports grants from Chugai Pharmaceutical, during the conduct of the study. MMa reports personal fees from Chugai Pharmaceutical, during the conduct of the study; grants and personal fees from Boehringer Ingelheim, and AstraZeneca; and personal fees from Eli Lilly. NF, KW, YoT, OY, KY, IN, FK, YuT, HN, GA, and MMi declare no competing interests.

Data sharing

Deidentified participant data will be made available when analyses of all primary and secondary endpoints have been published, following the completion of a data transfer agreement.

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