Afatinib is an irreversible ErbB family blocker, the preclinical activity of which includes *EGFR*-mutant cell lines that have common mutations, including T790M.[10,11] Results from phase I/II trials have complemented these two preclinical studies, demonstrating the efficacy of afatinib in patients with NSCLC who harbor EGFR-activating mutations.[12] These trials also included a phase I study in Japan that suggested modest clinical activity of afatinib in such patients following progression on erlotinib, gefitinib, or both and identified the maximum-tolerated dose of afatinib as 50 mg.[13]

This phase II trial was conducted in Japan to evaluate the efficacy of 50-mg afatinib monotherapy in third- and fourth-line patients with NSCLC who had progressed while receiving erlotinib and/or gefitinib treatment.

PATIENTS AND METHODS

Study Design

This was a multicenter, single-arm, open-label phase II trial of afatinib monotherapy in patients with NSCLC who had progressed on currently available EGFR TKIs. The primary end point was objective response rate (ORR) by independent review according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.0.[14] Secondary end points were time to ORR, duration of ORR, frequency and duration of clinical benefit (complete response [CR], partial response [PR], and stable disease [SD]), PFS, overall survival (OS), and disease control rate (DCR).

The study was conducted in line with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines and with the approval of each institutional review board. All patients provided written informed consent before study participation.

Study Population

Patients were required to have had at least 12 weeks of prior EGFR TKIs, which served as an enrichment strategy for patients with EGFR-activating mutations and subsequent acquired resistance mutations. Although *EGFR* mutation status at screening, including T790M status, was not required, mutation analysis was performed if adequate tumor tissue was available from existing specimens or by rebiopsy.

Patients were at least age 20 years, had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1, and a life expectancy of at least 3 months. Patients had to have either pathologically or cytologically confirmed stage IIIB to IV adenocarcinoma, with at least one tumor lesion measurable by computed tomography or magnetic resonance imaging. Patients who were incurable with radiotherapy and had received at least one, but not more than two, lines of chemotherapy (including at least one platinum-based regimen) were eligible. Following initial clinical benefit from chemotherapy, eligible patients should have had radiographically confirmed progression according to RECIST 1.0 following at least 12 weeks of erlotinib and/or gefitinib treatment. However, they should not have received either of these drugs within 2 weeks of starting afatinib nor should they have received any other investigational drug within 4 weeks before enrollment. Thoracic radiotherapy was not permitted nor was any radiotherapy permitted within 4 weeks before enrollment.

Patients were excluded if they had gastrointestinal disorders with diarrhea as a major symptom, significant cardiovascular disease, serious drug hypersensitivity, coelomic fluid retention, uncontrolled concomitant diseases, inadequate baseline organ function, additional significant malignancies diagnosed within the past 5 years, and brain tumors and/or brain metastases (symptomatic or requiring treatment).

Treatment

Patients received a single daily oral dose of afatinib at a starting dose of 50 mg 1 hour before food until progressive disease (PD), withdrawal of consent, or withdrawal due to adverse events (AEs). If patients experienced any grade $\geq$ 3 drug-related AE, as assessed by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0 or grade 2 diarrhea, nausea, or vomiting for $\geq$ 7 consecutive days despite appropriate supportive care, afatinib was stopped for up to 14 days. Following this and recovery to a grade $\leq$ 1 AE or baseline (whichever was higher), afatinib could be restarted with the dose reduced by 10 mg; this dose reduction could be repeated a second time. However, after a third occurrence, afatinib was discontinued. Treatment of tumor-related symptoms and AEs by medications such as antidiarrheals, antibiotics, analgesics, and antiemetics was allowed.

Efficacy Assessments

Baseline tumor assessments used computed tomography or magnetic resonance imaging scans of one to 10 target lesions at the initial screening. Patients who received at least one dose of afatinib and who had baseline disease measurable by RECIST were included in the efficacy analysis. ORR was measured by monitoring the same target lesions at 4, 8, and 12 weeks following the initial treatment and then every 8 weeks thereafter until study end. Patients were assigned by best response to one of the following RECIST categories: CR, PR, SD, or PD. Patients experiencing a CR or PR lasting for more than 4 weeks were defined as those with an ORR, whereas clinical benefit also included patients experiencing SD, which must have been observed after at least 6 weeks on the study. All imaging data were independently reviewed by a separate central evaluation committee, which consisted of two independent radiologists and a specialist for chest diseases, none of whom were involved in the study.

Safety and Tolerability Assessments

AEs defined by NCI-CTCAE version 3.0 were assessed during and after afatinib treatment.

Mutation Analyses

Molecular marker studies were performed on the majority of baseline primary tumors (by using tissue or serum samples or pleural effusion specimens). Only two tumor samples (pleural effusion specimen and tumor tissue) underwent rebiopsy at the time of disease progression with prior EGFR TKIs. At the central laboratory, tumor and serum samples were analyzed by the Scorpion amplification refractory mutation system method. By using tumor samples, K-ras codon 12/13 and exons 18 to 21 in the tyrosine kinase domain of the EGFR were analyzed by the direct sequencing method if there was a sufficient volume of DNA.

Acquired Resistance Criteria

Acquired resistance to erlotinib and/or gefitinib was defined by using the Jackman criteria: (1) being *EGFR* mutation positive, (2) having CR/PR to erlotinib and/or gefitinib or SD for at least 6 months with erlotinib and/or gefitinib, (3) receiving no erlotinib and/or gefitinib for less than 4 weeks, and (4) receiving no intervening chemotherapy.[15]

Statistical Analyses

A planned analysis (September 15, 2010) was performed 36 weeks after the initiation of afatinib treatment in the last entered patient, and a second planned analysis was done (February 14, 2011) to include mature efficacy data based on the independent review. A sample size of 60 patients was required to provide 94% power to detect statistically significant evidence of afatinib activity based on the assumption that the true response rate was $\geq$ 10%. The null hypothesis was a $\leq$ 1% ORR using an exact binomial test with a one-sided significance level of 0.025. Patients documented as having taken at least one dose of afatinib who had at least one response assessment were included in the primary analysis. Median PFS and OS calculations used Kaplan-Meier methods, and 95% CIs were calculated by using Greenwood's SE estimates.

RESULTS

Patient Population

Between June 16, 2009, and February 14, 2011, at 20 sites across Japan, 62 patients were entered onto the trial and received at least one dose of afatinib. At the second planned analysis, 58 patients (93.5%) had discontinued treatment because of PD (64.5%), AEs (25.8%), and

Table 1. Patient Demographics and Baseline Characteristics

Characteristic	Afatinib No.	Afatinib %
No. of patients	62	100
Sex		
Male	14	22.6
Female	48	77.4
Age, years		
Median	65.0	
Range	33-84	
Baseline ECOG PS		
0	29	46.8
1	33	53.2
Smoking history		
Never-smokers	43	69.4
< 15 pack-years and stopped > 1 year before diagnosis	7	11.3
Current or other ex-smoker	12	19.4
Clinical stage at screening		
IIIB	5	8.1
IV	57	91.9
EGFR mutation test[a]	56	90.3
Positive	45	72.6
Exon 19 deletion	22	35.5
Exon 19 deletion + L858R	1	1.6
Exon 19 deletion + T790M	1	1.6
Exon 19 deletion + other	1	1.6
L858R	15	24.2
L858R + T790M	1	1.6
L858R + other	3	4.8
L861Q	1	1.6
Negative	11	17.7
EGFR mutation unknown	6	9.7
No. of previous chemotherapy regimens		
1	52	83.9
2	10	16.1
Other previous anticancer therapies		
Surgery	15	24.2
Radiotherapy	21	33.9
Other	1	1.6
Best response to previous EGFR TKI		
CR	2	3.2
PR	38	61.3
SD	22	35.5
Previous EGFR TKIs		
Erlotinib only	7	11.3
Gefitinib only	49	79.0
Both erlotinib and gefitinib	6	9.7
Duration of previous EGFR TKI, weeks		
12 to < 24	3	4.8
24 to < 36	10	16.1
36 to < 48	13	21.0
≥ 48	36	58.1
Interval from discontinuation of EGFR TKI to start of afatinib, weeks		
< 4	52	83.9
4 to < 8	7	11.3
8 to < 12	2	3.2
≥ 12	1	1.6
Patients fulfilling Jackman et al[15] criteria of acquired resistance to prior EGFR TKI	51	82.3

Abbreviations: CR, complete response; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; PR, partial response; PS, performance status; SD, stable disease; TKI, tyrosine kinase inhibitor.
[a]Tumor tissue, pleural effusion specimens, or serum samples tested locally and/or by central laboratory.

refusal to continue treatment (3.2%). Four patients (6.5%) were continuing treatment and, as of February 8, 2012, one patient was still receiving afatinib. Mean total treatment time was 4.59 months (maximum treatment time, 16.3 months) for all 62 patients.

Patient demographics and baseline characteristics are provided in Table 1. The majority of patients were female (77.4%), 46.8% had an ECOG PS of 0, and 69.4% were never-smokers. Mutation testing was performed on 56 patients (90.3%), and 45 (72.6%) were determined to be *EGFR* mutation positive in their primary tumor according to local and/or central laboratory analyses (Appendix Table A1, online only). Acquired T790M was reported as a mutation sequence code in two patients (3.2%). No *KRAS* mutations were found among 12 patients with tissue sample test results.

The majority of patients (79.0%) had previously received gefitinib, 11.3% had received erlotinib, and 9.7% had received both. Patients had been on previous EGFR TKIs for a median of 57.5 weeks, and 95.2% had been on previous EGFR TKIs for at least 24 weeks. Approximately two thirds of patients (64.5%) had a response (PR/CR) to prior EGFR TKI therapy. The median interval from EGFR TKI discontinuation to afatinib treatment initiation was 3 weeks (range, 2 to 13 weeks). Fifty-one patients (82.3%) met the Jackman definition of having acquired resistance to erlotinib and/or gefitinib.

Antitumor Activity

Sixty-one patients were evaluable for tumor response (Table 2); one was excluded because of lack of evaluable tumor imaging data. Of 61 evaluable patients, five (8.2%; 95% CI, 2.7% to 18.1%) achieved a confirmed response, all of which were PRs, and 35 (57.4%) had SD for at least 6 weeks, with a DCR of 65.6% by independent review. Most responses were seen within 8 weeks of afatinib initiation. The mean duration of response was 24.4 weeks. Afatinib reduced the size of target lesions in 79% of all patients during the treatment period (Fig 1), with nine patients (16%) having at least a 30% reduction in tumor size. However, tumor size reduction did not last for more than 4 weeks in four of nine patients.

Median PFS was 4.4 months (95% CI, 2.8 to 4.6 months) by independent review (Fig 2A). The PFS data were mature, with 72.1% of patients having a PFS event at the time of the second planned analysis. Median OS was 19.0 months (95% CI, 14.9 months to not

Table 2. Overview of Response Rate by Independent Review

Response	Response Rate No.	Response Rate %	95% CI
Total No. of patients	61	100[a]	
DCR (CR, PR, or SD)	40	65.6	52.3 to 77.3
ORR (CR or PR)	5	8.2	2.7 to 18.1
CR	0	0.0	—
PR	5	8.2	—
SD	35	57.4	—
PD	17	27.9	—
Not evaluable	4	6.6	—

Abbreviations: CR, complete response; DCR, disease control rate; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.
[a]One patient with exon 19 deletion was excluded from the efficacy evaluation because of lack of evaluable tumor imaging data after the start of afatinib treatment.

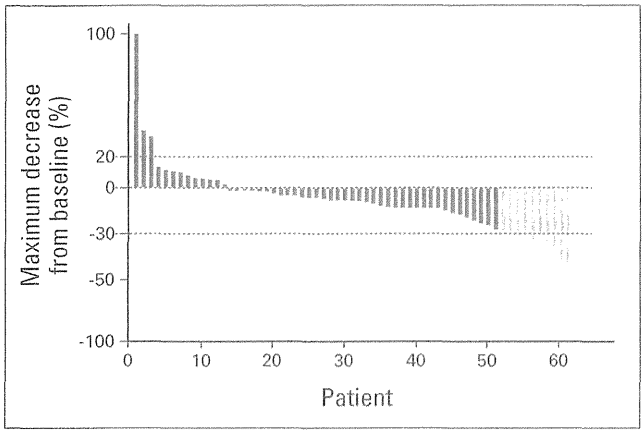

Fig 1. Waterfall plot of percent change from baseline in measurable tumor at the time of best response (by independent review). Data for patients with a decrease from baseline of 30% or more are shown in gold; data for patients with an increase from baseline of more than 100% to a decrease from baseline of less than 30% are shown in blue.

achieved; Fig 2B), with the probability of survival at 12 months estimated to be 73.0%; in addition, 34.4% of patients had an OS event. As of February 9, 2012, median OS was 18.4 months, and 63.9% of patients had an OS event.

Subgroup analysis of the efficacy data based on sex (women *v* men), ECOG PS (0 *v* 1), type of prior EGFR TKI (erlotinib *v* gefitinib), and the number of previous chemotherapy regimens (one *v* two) showed little variation in ORRs and DCRs (Appendix Table A2, online only). Efficacy data by mutation type were also similar among deletions in exon 19 (del19), L858R, and others (Table 3).

Patients meeting the Jackman criteria for acquired resistance had a median PFS of 4.4 months, PR of 5.9%, and DCR of 68.6%. Of the two patients with T790M mutations who underwent rebiopsy at the time of disease progression with prior EGFR TKI therapy, one patient harboring an L858R + T790M mutation had durable SD for 9 months, and the other patient with a del19 + T790M mutation had SD for 1 month. In *EGFR* mutation–negative patients, the ORR was 27% (three of 11), which was higher than in *EGFR* mutation–positive (4.5%; two of 44) or mutation-unknown (0%; zero of six) patients.

Safety and Tolerability

All 62 patients experienced an AE, with diarrhea and skin events being the most frequently reported (Table 4). Diarrhea occurred in all 62 patients, rash/acne in 57 patients (91.9%), and stomatitis in 53 patients (85.5%). Grade 3 diarrhea occurred in 37.1% of patients, and rash/acne occurred in 27.4% of patients. Loperamide use was capped at 8 mg per day for treatment of diarrhea (90.3% of patients received loperamide), and less than 10% of patients received systemic antibiotics for rash.

All patients received a starting dose of afatinib 50 mg per day, with 69.4% of patients requiring dose reduction to 40 mg per day, and 35.5% requiring further dose reduction to 30 mg per day. The most common AE leading to dose reduction was diarrhea, affecting 41.9% of patients. Treatment-related AEs leading to discontinuation of afatinib were experienced by 18 patients (29.0%) and were due to rash/acne (n = 7); decreased appetite (n = 3); diarrhea, interstitial lung disease, and stomatitis in two patients each; and dehydration, fatigue, nail effects, and pyrexia in one patient each. Four of these patients (three with rash, one with paronychia) had PD confirmed by tumor assessments at the same time as afatinib discontinuation due to AEs. Drug-related serious AEs occurred in 11.3% of patients, with diarrhea (6.5%) being the most common. Two interstitial lung disease-like AEs (grade 3 and grade 1) were considered to be related to study drug; in each case, the patient fully recovered after stopping afatinib. One on-treatment death as a result of hypoxia occurred after disease progression, which was not considered by the investigator to be drug related.

DISCUSSION

There is an increasing need to develop new molecular targeted agents that address the issue of resistance to erlotinib and/or gefitinib in patients with NSCLC who initially respond to treatment and then subsequently progress.[16] Previous phase II studies with criteria similar

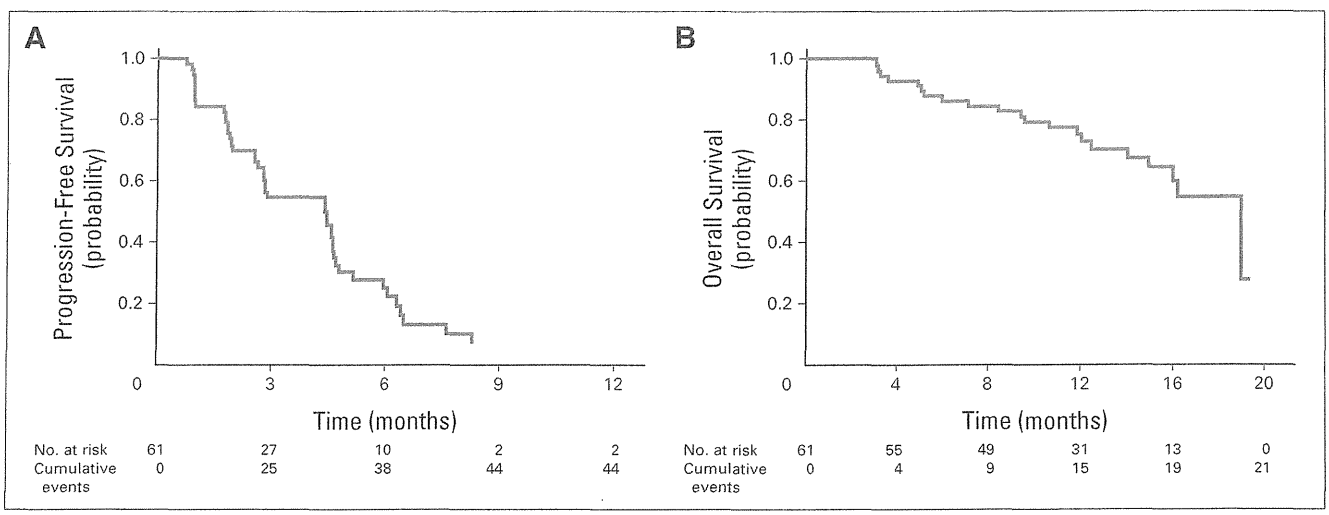

Fig 2. Kaplan-Meier plot of (A) progression-free survival by independent review and (B) median overall survival.

Table 3. Overview of DCR, ORR, and PFS by Mutation Type

	EGFR Mutation Type											
	Exon 19 Deletion				L858R				Other			
Response	No.	%	95% CI	Percentile	No.	%	95% CI	Percentile	No.	%	95% CI	Percentile
Total No. of patients	21	100*			15	100			8	100.0		
DCR (CR, PR, or SD)	14	66.7	43.0 to 85.4		10	66.7	38.4 to 88.2		5	62.5	24.5 to 91.5	
ORR (CR or PR)	1	4.8	0.1 to 23.8		1	6.7	0.2 to 31.9		0	0.0	0	
Median PFS, months	1.9			25th	1.9			25th	1.3			25th
	4.6				3.6				3.7			
	5.2			75th	5.3			75th	8.3			75th

Abbreviations: CR, complete response; DCR, disease control rate; EGFR, epidermal growth factor receptor; ORR, objective response rate; PFS, progression-free survival; PR, partial response; SD, stable disease.
*One patient who had an exon 19 deletion was excluded from the efficacy evaluation because of lack of evaluable tumor imaging data after the start of afatinib treatment.

to that of the current LUX-Lung 4 trial with prior failure of erlotinib and/or gefitinib and an enrichment strategy for patients with *EGFR* mutations by using XL-647, dasatinib, neratinib, and the combination of cetuximab plus erlotinib showed low ORR ranging from 0% to 3%.[17-20] The results of our trial demonstrated modest but noteworthy activity of afatinib in this difficult-to-treat population, with a median PFS of 4.4 months and an ORR of 8.2% (independent review).

As might be expected for a group of patients with NSCLC who derived significant benefit from prior erlotinib and/or gefitinib therapy, the study population was highly enriched (85%) for patients with *EGFR* mutations. This was further reflected in the patient demographics, with a large percentage of women and never-smokers. The trial was also highly enriched (82%) for patients meeting the Jackman criteria of acquired resistance, and the efficacy findings were similar in that subpopulation compared with the overall study population, with similar PFS results for the Jackman group of patients shown in LUX-Lung 1.[21] In the LUX-Lung 1 double-blind, placebo-controlled phase IIB/III study of afatinib plus best supportive care in patients with NSCLC who had progressed after prior chemotherapy and erlotinib and/or gefitinib treatment, a median PFS of 4.5 months was reported in those patients fulfilling the Jackman criteria for acquired resistance, which is consistent with the median PFS of 4.4 months reported in this trial.[21]

The estimated median OS of 19 months observed in this trial is of interest. However, nearly half the patients entering this trial were symptom-free with an ECOG PS of 0, and 72.6% had an EGFR-mutant tumor, suggesting the selection of a relatively good prognostic cohort despite their extensive pretreatment.

The Jackman criteria of acquired resistance to EGFR TKIs were fulfilled by 82% of the patients in this trial. The efficacy of afatinib in this subgroup of patients suggests that the clinical effect of afatinib is not merely due to re-exposure to another EGFR TKI, a phenomenon that was previously reported.[22] Although the literature reports that approximately 50% of the patients who develop acquired resistance to EGFR TKIs show secondary T790M mutation,[23] a relatively low incidence of T790M mutations was observed in this study. This may be due to the fact that tissue sampling was obtained before erlotinib and/or gefitinib exposure, and very few patients underwent rebiopsy.

The AEs observed in this phase II trial were consistent with the known safety profile reported for inhibitors of EGFR.[6] All patients experienced an AE considered to be drug related, with diarrhea, rash/acne, and stomatitis being the most common AEs. AEs were mostly managed by dose reduction and/or medical treatment. The rates of grade 3 diarrhea and rash/acne reported in this trial were similar to those of the LUX-Lung 2 phase II trial, in which a large proportion of patients (87%) were Asian.[24] In LUX-Lung 2 (afatinib 50 mg per day in first- and second-line patients whose tumors harbored *EGFR* mutations), diarrhea and rash/acne occurred in 94% of patients, with grade 3 diarrhea reported in 22% of patients and grade 3 rash/acne in 28% of patients.[24] The frequency and severity of AEs and treatment discontinuation due to AEs appears to be higher with afatinib compared with the historical data reported with erlotinib and gefitinib.[2-7,25] However, the early and proactive management of AEs, including dose

Table 4. All AEs for All Grades and NCI-CTCAE Grade 3 in ≥ 10% of Patients

	All Grades		Grade 3	
Preferred Term	No.	%	No.	%
No. of patients	62	100.0	62	100.0
Total with AEs	62	100.0	49	79.0
Diarrhea	62	100.0	23	37.1
Rash/acne	57	91.9	17	27.4
Stomatitis	53	85.5	6	9.7
Nail effect	43	69.4	7	11.3
Decreased appetite	38	61.3	3	4.8
Fatigue	25	40.3	5	8.1
Nausea	23	37.1	1	1.6
Vomiting	17	27.4	1	1.6
Weight decreased	17	27.4	0	0.0
Epistaxis	16	25.8	0	0.0
Lip effect	16	25.8	0	0.0
Ocular event	15	24.2	1	1.6
Dry skin	14	22.6	0	0.0
Dysgeusia	11	17.7	0	0.0
Dehydration	9	14.5	5	8.1
Nasal inflammation	8	12.9	0	0.0
Nasopharyngitis	7	11.3	0	0.0

NOTE. For all adverse events (AEs) listed, no grade 4 or grade 5 events occurred.
Abbreviations: AE, adverse event; NCI-CTCAE, National Cancer Institute–Common Terminology Criteria for Adverse Events.

reduction and the use of additional symptomatic therapies, could have been effective in our study, allowing patients who benefited from afatinib to continue on treatment as observed in the LUX-Lung 1 trial (afatinib 50 mg was the starting dose).[21] Proactive supportive management also has the potential to maintain quality of life by reducing the impact of AEs.

On the basis of the modest but noteworthy activity of afatinib observed in this trial in patients with NSCLC who have acquired resistance to erlotinib and/or gefitinib, additional studies to improve on the activity of afatinib in this setting are ongoing. In preclinical T790M tumor models, combined EGFR targeting with afatinib and cetuximab induced near CRs that were not seen with either agent alone or with a cetuximab plus erlotinib combination.[26] On the basis of these early observations, a phase IB trial is currently testing the combination of afatinib and cetuximab in a patient population similar to that of LUX-Lung 4. Preliminary results have shown that more than 90% of patients thus far have derived clinical benefit, including approximately 40% ORR in both T790M-positive and T790M-negative settings.[27,28]

To extend the investigation of afatinib in advanced NSCLC, the ongoing LUX-Lung 3 and LUX-Lung 6 randomized phase III studies are comparing the efficacy of first-line afatinib monotherapy with cisplatin and either pemetrexed or gemcitabine in white and Asian patients with NSCLC who are harboring *EGFR* mutations. Initial results from LUX-Lung 3 demonstrated a significant improvement in PFS of 11.1 months with afatinib compared with 6.9 months for chemotherapy.[29]

In conclusion, this phase II study conducted in Japan in a study population with NSCLC enriched for *EGFR* mutations showed modest but noteworthy efficacy of oral afatinib, an irreversible ErbB family blocker, in third- and fourth-line patients with NSCLC with acquired resistance to erlotinib and/or gefitinib. Further evaluation of the potential of afatinib in patients with advanced NSCLC will be addressed by the LUX-Lung phase III clinical trial program and the ongoing study of the afatinib plus cetuximab combination in the resistance setting.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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Appendix

Table A1. Results of *EGFR* Mutation Testing Performed in Either a Local or Central Laboratory

	EGFR Mutation Test							
	Central Laboratory Using Tissue and Pleural Effusion Specimens		Central Laboratory Using Serum Samples		Local Laboratory*		Central or Local Laboratory†	
Mutation	No.	%	No.	%	No.	%	No.	%
No. of patients treated	62		62		62		62	
No. of patients with *EGFR* mutation test results	27	43.5	45	72.6	37	59.7	56	90.3
Positive	23	85.2	3	6.7	37	100.0	45	72.6
Exon 19 deletion	10	37.0	2	4.4	18‡	48.6	22‡	35.5
Exon 19 deletion + L858R	0	0.0	0	0.0	1	2.7	1	1.6
Exon 19 deletion + T790M	1	3.7	0	0.0	0	0.0	1	1.6
Exon 19 deletion + other	1	3.7	0	0.0	0	0.0	1	1.6
L858R	8	29.6	1	2.2	16	43.2	15	24.2
L858R + T790M	0	0.0	0	0.0	1	2.7	1	1.6
L858R + other	3	11.1	0	0.0	0	0.0	3	4.8
L861Q	0	0.0	0	0.0	1	2.7	1	1.6
Negative	4	14.8	42	93.3	0	0.0	11	17.7

Abbreviation: EGFR, epidermal growth factor receptor.
*Information on sample/specimen type unavailable.
†Results using tissue, pleural effusion specimens, or serum samples. If multiple data were available for a patient, positive data and/or more detailed data were selected.
‡Included one patient who was excluded from the efficacy analysis because the patient had no evaluable tumor imaging data after the start of afatinib treatment.

Table A2. Summary of DCR and ORR by Sex, ECOG PS, Previous Chemotherapy Regimens, and Type of Prior EGFR TKI

	DCR			ORR		
Variable	No.	%	95% CI	No.	%	95% CI
Sex						
Male (n = 14)	10	71.4	41.9 to 91.6	1	7.1	0.2 to 33.9
Female (n = 47)	30	63.8	48.5 to 77.3	4	8.5	2.4 to 20.4
Baseline ECOG PS						
0 (n = 29)	20	69.0	49.2 to 84.7	2	6.9	0.8 to 22.8
1 (n = 32)	20	62.5	43.7 to 78.9	3	9.4	2.0 to 25.0
No. of previous chemotherapy regimens						
1 (n = 51)	31	60.8	46.1 to 74.2	4	7.8	2.2 to 18.9
2 (n = 10)	9	90.0	55.5 to 99.7	1	10.0	0.3 to 44.5
Prior use of EGFR TKI						
Erlotinib (n = 7)	4	57.1	18.4 to 90.1	1	14.3	0.4 to 57.9
Gefitinib (n = 48)	32	66.7	51.6 to 79.6	4	8.3	2.3 to 20.0
Erlotinib and gefitinib (n = 6)	4	66.7	22.3 to 95.7	0		0

Abbreviations: DCR, disease control rate; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; ORR, objective response rate; PS, performance status; TKI, tyrosine kinase inhibitor.

CH5424802 (RO5424802) for patients with *ALK*-rearranged advanced non-small-cell lung cancer (AF-001JP study): a single-arm, open-label, phase 1–2 study

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Summary

Background Currently, crizotinib is the only drug that has been approved for treatment of *ALK*-rearranged non-small-cell lung cancer (NSCLC). We aimed to study the activity and safety of CH5424802, a potent, selective, and orally available ALK inhibitor.

Methods In this multicentre, single-arm, open-label, phase 1–2 study of CH5424802, we recruited ALK inhibitor-naive patients with *ALK*-rearranged advanced NSCLC from 13 hospitals in Japan. In the phase 1 portion of the study, patients received CH5424802 orally twice daily by dose escalation. The primary endpoints of the phase 1 were dose limiting toxicity (DLT), maximum tolerated dose (MTD), and pharmacokinetic parameters. In the phase 2 portion of the study, patients received CH5424802 at the recommended dose identified in the phase 1 portion of the study orally twice a day. The primary endpoint of the phase 2 was the proportion of patients who had an objective response. Treatment was continued in 21-day cycles until disease progression, intolerable adverse events, or withdrawal of consent. The analysis was done by intent to treat. This study is registered with the Japan Pharmaceutical Information Center, number JapicCTI-101264.

Findings Patients were enrolled between Sept 10, 2010, and April 18, 2012. The data cutoff date was July 31, 2012. In the phase 1 portion, 24 patients were treated at doses of 20–300 mg twice daily. No DLTs or adverse events of grade 4 were noted up to the highest dose; thus 300 mg twice daily was the recommended phase 2 dose. In the phase 2 portion of the study, 46 patients were treated with the recommended dose, of whom 43 achieved an objective response (93·5%, 95% CI 82·1–98·6) including two complete responses (4·3%, 0·5–14·8) and 41 partial responses (89·1%, 76·4–96·4). Treatment-related adverse events of grade 3 were recorded in 12 (26%) of 46 patients, including two patients each experiencing decreased neutrophil count and increased blood creatine phosphokinase. Serious adverse events occurred in five patients (11%). No grade 4 adverse events or deaths were reported. The study is still ongoing, since 40 of the 46 patients in the phase 2 portion remain on treatment.

Interpretation CH5424802 is well tolerated and highly active in patients with advanced *ALK*-rearranged NSCLC.

Funding Chugai Pharmaceutical Co, Ltd.

Introduction

A fusion tyrosine kinase gene comprising the *EML4* gene and the *ALK* gene has been identified in non-small-cell lung cancer (NSCLC) with inversion of chromosome 2p. Mouse 3T3 fibroblasts expressing *EML4-ALK* had increased transforming activity and tumorigenicity.[1] Transgenic mice expressing *EML4-ALK* fusion gene in lung alveolar epithelial cells were generated and exhibited development of adenocarcinoma in lungs shortly after birth,[2] suggesting that the *EML4-ALK* fusion gene could be a driver mutation for NSCLC and serve as a promising candidate for a therapeutic target.[1,3] Therefore, the introduction of new ALK inhibitors is expected to improve the treatment of patients with *ALK*-rearranged NSCLC.[3]

So far, crizotinib, a multi-targeted receptor tyrosine kinase inhibitor of *ALK*, *MET*, and *ROS1* oncogene,[4,5] is the only agent that has been approved for *ALK*-rearranged NSCLC in the USA, European Union, Japan, and other countries. In the phase 1 trial of crizotinib in patients with *ALK*-rearranged NSCLC, 87 of 143 evaluable patients had an objective response (60·8%, 95% CI 52·3–68·9). Median progression-free survival (PFS) was 9·7 months.[6] In a retrospective study[7] comparing survival outcomes in crizotinib-treated patients enrolled in the phase 1 trial and crizotinib-naive controls screened during the same period, crizotinib therapy was associated with better survival. However, resistance to crizotinib occurs by a number of mechanisms, including *ALK* gene alterations, such as *ALK* point mutations and copy number gain, and activation of bypass signalling through activation of other oncogenes.[8,9] Additionally, poor penetration of crizotinib across the blood–brain barrier is thought to be associated with a higher incidence of brain involvement if relapse occurs.[10] In the crizotinib phase 2 trial, the most common site for single organ disease progression was the brain.[11]

CH5424802 (RO5424802; Chugai Pharmaceutical Co, Ltd, Tokyo, Japan) is a novel, highly selective oral ALK inhibitor. In-vitro kinase assays showed that this compound selectively inhibits ALK. CH5424802 also shows high anti-tumour activity both in vitro and in vivo against tumour cell lines with some type of *ALK* gene alteration, such as NSCLC and anaplastic large-cell lymphoma lines harbouring an *ALK* fusion gene and a neuroblastoma line harbouring amplified *ALK* gene. More importantly, CH5424802 yielded potential anti-tumour activity against the gatekeeper Leu1196Met mutation in *EML4-ALK*,[12] which has been identified in tumour cells refractory to crizotinib.[13]

We report the results of a phase 1–2 study of CH5424802 (AF-001JP study) that was designed to identify the maximum tolerated dose (MTD) and pharmacokinetic parameters of the drug, and subsequently to assess its activity and safety in ALK inhibitor-naive patients with *ALK*-rearranged NSCLC.

Methods

Study design and patients

This study was a multicentre, single-arm, open-label, phase 1–2 trial (AF-001JP). Patients were eligible if they were aged 20 years or older; had histologically or cytologically confirmed advanced or metastatic *ALK*-rearranged stage IIIB, IV, or recurrent NSCLC; had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1; had measurable lesions as defined by Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1) (for the phase 2 portion only); received two or more (phase 1 portion) or one or more (phase 2 portion) previous chemotherapy regimens; and had adequate haematological, hepatic, and renal function. We excluded patients who had received previous treatment with any ALK inhibitor. Other exclusion criteria included symptomatic brain metastases or brain metastases requiring treatment, history of serious cardiac dysfunction, clinically significant gastrointestinal abnormality that would affect the absorption of the study drug, and pregnant or lactating women.

To identify whether patients were positive for *ALK* fusion gene expression, formalin-fixed paraffin-embedded sections from previous diagnostic or surgical procedures were sent to the laboratory in the Cancer Institute, Japanese Foundation for Cancer Research, Tokyo, Japan, and screened using anti-ALK immunohistochemistry with iAEP method (ALK Detection Kit, Nichirei Bioscience, Tokyo, Japan).[14–16] In patients who were positive by immunohistochemistry, the fluorescence in-situ hybridisation (FISH) test was subsequently done for confirmation. An experienced pathologist (KT) judged these tests. Additionally, we did a multiplex RT-PCR method (SRL, Tokyo, Japan) on samples of cells or frozen cancer tissue sections. We deemed patients to be positive for *ALK* fusion gene expression when either FISH or RT-PCR showed positive results.

In this study, patients gave written informed consent for *ALK* assessment by a central laboratory. If tumours were confirmed to be *ALK* positive, patients signed another informed consent form for enrolment into this trial. Patients participating in the study were treated at 13 hospitals in Japan. The study was approved by the institutional review board at each participating institution, and done in accordance with the Declaration of Helsinki and Good Clinical Practices.

Procedures

In the phase 1 portion of this study, patients received CH5424802 orally twice daily (once in the morning and once in the evening) in an open-label, sequential-cohort, dose-escalation study. We did the dose escalation with an accelerated titration design[17] under fasting conditions from 20 mg to 300 mg twice daily. We determined a dose of 300 mg twice daily as the highest planned dose on the basis of the available safety information about the additive formulation in Japan. Patients fasted for 2 h before administration and 1 h after administration. We predefined dose-limiting toxicities (DLTs) as a treatment-related adverse event that occurs during the DLT assessment period (from day 1 to day 3 in cycle 0 and from day 1 to day 21 in cycle 1) and met any of the following criteria: grade 4 thrombocytopenia, grade 4 neutropenia continuing for 4 days or more, non-haematological toxic effects of grade 3 or worse (excluding transient electrolyte abnormalities and diarrhoea, nausea, or vomiting that recovers to grade 2 or lower with appropriate treatment), and events that required suspension of treatment for at least 7 days. The recommended dose was to be determined after taking into consideration tumour response in addition to the MTD, safety, and pharmacokinetic parameters under fasting conditions. While this fasting part was ongoing with DLT assessment in the cohort of patients given 300 mg twice daily, we amended the study to conduct a non-fasting part at doses of 240 mg and 300 mg twice daily by a traditional 3+3 design. We assessed the effect of food by comparing results under fasting and non-fasting conditions at both doses in the two groups of patients.

In the phase 2 portion of this study, patients received CH5424802 at the recommended dose identified in the phase 1 portion of the study orally twice a day (once in the morning and once in the evening). The patients fasted for 2 h before administration and 1 h after administration. Treatment was continued in 21-day cycles until disease progression, intolerable adverse events, or withdrawal of consent.

Tumours were assessed every cycle until four cycles and every two cycles thereafter, with RECIST version 1.1. In the phase 2 portion, tumour assessment from brain to pelvis at baseline was mandatory. Tumour assessment in this trial was done with CT scans for chest and abdomen; with CT or MRI for head, neck, and pelvis; and with bone scintigraphy, PET, x-ray, CT, or MRI for bone. Adverse

events were monitored up to the 28th day after the final dose, and assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE version 4.0). When vision disorders occurred during this trial, an ophthalmological examination was done.

If a patient had thrombocytopenia or neutropenia of grade 4 or a non-haematological toxic effect of grade 3 or higher occurred, treatment with CH5424802 would be suspended until the toxic effects improved to grade 1 or lower, or the baseline grade. If the period of suspension was 14 days or less, treatment with CH5424802 could be resumed at the same dose level. If the period of suspension was longer than 14 days, treatment with CH5424802 would be resumed at a reduced dose. Treatment with CH5424802 would be discontinued permanently if treatment could not be resumed within 21 days of suspension. Additionally to these criteria, at the initiation of every cycle, treatment with CH5424802 would commence after it had been confirmed that all the following criteria were met (neutrophil count ≥1500 cells per μL [this criterion was amended so that patients with a neutrophil count ≥1000 cells per μL could receive the next cycle of treatment], platelet count ≥$7·5\times10^4$ cells per μL; non-haematological toxic effects of grade ≤1 or grade at baseline with exception of investigator's judgment).

	Phase 1 (n=24)	Phase 2 (n=46)
Age, years	42·5 (28–67, 39·0–60·0)	48·0 (26–75, 37·5–54·5)
Sex		
Female	13 (54%)	24 (52%)
Male	11 (46%)	22 (48%)
Smoking status		
Never	14 (58%)	27 (59%)
Former	10 (42%)	18 (39%)
Present	0	1 (2%)
Histological findings*		
Adenocarcinoma	22 (92%)	46 (100%)
Squamous-cell carcinoma	1 (4%)	0
Large-cell carcinoma	1 (4%)	0
Clinical stage (at screening)		
IIIB	0	2 (4%)
IV	14 (58%)	31 (67%)
Postoperative recurrence	10 (42%)	13 (28%)
ECOG performance status		
0	9 (38%)	20 (43%)
1	15 (63%)	26 (57%)
ALK diagnosis†		
Immunohistochemistry and FISH	22 (92%)	39 (85%)
RT-PCR	2 (8%)	7 (15%)
EGFR status*		
Wild-type	22 (92%)	41 (89%)
Mutation	0	0
Unknown	2 (8%)	5 (11%)
Previous chemotherapy regimens for metastatic disease		
0	0	1 (2%)‡
1	1 (4%)‡	21 (46%)
2	10 (42%)	9 (20%)
≥3	13 (54%)	15 (33%)

Data are median (range, IQR) or number of patients (%). ECOG=Eastern Cooperative Oncology Group. FISH=fluorescence in-situ hybridisation. *Histological findings and EGFR status were reported by the investigator site. †ALK diagnosis was performed in two central reference laboratories (one for immunohistochemistry and FISH, and the other for RT-PCR). ‡Regarded as eligible for inclusion because relapse occurred within 6 months of completion of adjuvant chemotherapy.

Table 1: **Demographics and baseline characteristics**

Pharmacokinetics

In the phase 1 portion of the study, we obtained 2 mL blood samples at pre-dose, 0·5 h, 1 h, 2 h, 4 h, 6 h, 8 h, 10 h, 24 h, 32 h, 48 h, and 72 h after single oral administration of CH5424802, and at pre-dose, 0·5 h, 1 h, 2 h, 4 h, 6 h, 8 h, and 10 h at steady state under fasting and non-fasting conditions. The blood samples were centrifuged at 1500–2000×g for 10 min at 4°C. The plasma samples were then stored at –70°C or less. We measured drug concentrations in plasma by the liquid chromatography-mass spectrometry and liquid chromatography-tandem mass spectrometry with limit of quantitation of 0·1 ng/mL.

Statistical analysis

The primary endpoint of the phase 1 portion was DLT, MTD, safety, and pharmacokinetic parameters. The primary endpoint of the phase 2 portion was the proportion of patients who had an objective response, as determined by an independent review committee, which was to be confirmed by a subsequent scan. Secondary endpoints included safety, the proportion of patients who achieved disease control, progression-free survival, overall survival, and pharmacokinetic parameters.

In the phase 1 portion of the study, we did all statistical analyses in a descriptive manner; and we thus did no formal hypothesis testing. We analysed plasma CH5424802 concentrations with Phoenix WinNonlin Version 6.2 (Pharsight Corporation, Mountain View, CA, USA). We directly obtained the maximum plasma concentrations (C_{max}) from the plasma-concentration curves for every participant. We calculated the area under the plasma concentration-time curve (AUC) for every individual using the linear log trapezoidal method as implemented in Phoenix WinNonlin.

In the phase 2 portion of this study, initially, we used a threshold response rate of 25% for reference based on the response rate of a platinum doublet regimen that is a standard treatment for NSCLC,[18] and an expected response rate of 70% based on the response rate of the patients to crizotinib.[19] Since 12 individuals are necessary to yield a statistical power of 80% with a two-sided significance of 5%, we calculated a target sample size of

15 patients to allow for dropouts. Subsequently, the response rate of crizotinib for patients with *ALK*-rearranged NSCLC was published.[20] We amended this study to test the null hypothesis of a threshold response rate of 45% for the study drug, based on the reported response rate of crizotinib.[21] We kept the expected response rate at 70%. Consequently, 41 patients were required to yield a statistical power of 90% with a two-sided significance of 5%. Allowing for dropouts, we identified the target sample size in this study as 45 patients. Considering the multiplicity of the analysis, we determined that the null hypothesis assessing 45 patients with the threshold response rate of 45% should be tested only when the null hypothesis assessing 15 patients with a threshold response rate of 25% was rejected.

We did the analysis by intent to treat. The decision as to whether to reject the null hypothesis that the response rate of 45% or less was based on whether the lower limit of the 95% CI estimated using the Clopper-Pearson method exceeded 45%. We estimated the proportion of patients who achieved disease control together with an estimate of the CI with the Clopper-Pearson method. Additionally, we did a pot-hoc subgroup analysis of response rate with regard to the age, sex, ECOG PS, body-mass index (BMI), number of previous chemotherapy regimens for metastatic disease, history of treatment with pemetrexed, types of ALK diagnostic method, and status of brain metastasis. All analyses were done with SAS version 9.2. This study is registered with the Japan Pharmaceutical Information Center, number JapicCTI-101264.

Role of the funding source

This study was designed and funded by the study sponsor (Chugai Pharmaceutical Co, Ltd) and monitored by a clinical research organisation (EPS Corporation). The clinical research organisation collected all data and the study sponsor did all data analysis and interpretation, with input from the authors and investigators. The initial draft of the report was reviewed and commented on by all authors, and by employees of Chugai Pharmaceutical Co, Ltd. 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

The first patient identified with *ALK*-positive NSCLC was enrolled on Sept 10, 2010, and received their first dose on Sept 14, 2010. The last patient was enrolled on April 18, 2012, and received their first dose on April 18, 2012. Data cutoff for this report was July 31, 2012.

For both the phase 1 and phase 2 parts of this study, 436 patients were screened for ALK and 135 (31%) patients were identified as *ALK*-positive. 70 patients were enrolled and treated in either the phase 1 (24 patients) or the phase 2 portions (46 patients). The major reason for

	Patients	Dose-limiting toxicities
Fasting		
20 mg (twice daily)	1	None
40 mg (twice daily)	1	None
80 mg (twice daily)	1	None
160 mg (twice daily)	3	None
240 mg (twice daily)	3	None
300 mg (twice daily)	6	None
Non-fasting		
240 mg (twice daily)	3	None
300 mg (twice daily)	6	None

Table 2: Dose escalation and dose-limiting toxicities in phase 1 (n=24)

	Patients	T_{max} (h)	C_{max} (ng/mL)	C_{trough} (ng/mL)	AUC_{0-10} (ng·h/mL)
Fasting					
20 mg (twice daily)	1	4·00	25·5	19·6	220
40 mg (twice daily)	1	3·83	63·9	34·9	479
80 mg (twice daily)	1	2·00	150	105	1310
160 mg (twice daily)	3	4·61 (1·15)	300 (104)	214 (34)	2310 (598)
240 mg (twice daily)	3	3·33 (1·15)	385 (100)	262 (115)	2970 (937)
300 mg (twice daily)	6	3·99 (2·17)	575 (322)	463 (369)	4970 (3260)
Non-fasting					
240 mg (twice daily)	3	5·24 (1·13)	380 (83)	332 (79)	3300 (838)
300 mg (twice daily)	6	5·32 (1·58)	528 (138)	425 (150)	4220 (1190)

Data are individual values or mean (SD), unless otherwise stated. T_{max}=time to reach maximum concentration. C_{max}=maximum plasma concentration. C_{trough}=plasma concentration at trough. AUC_{0-10}=area under plasma-concentration time curve from 0-10 h.

Table 3: Pharmacokinetic parameters of CH5424802 at steady state in the patients under fasting and non-fasting conditions (n=24)

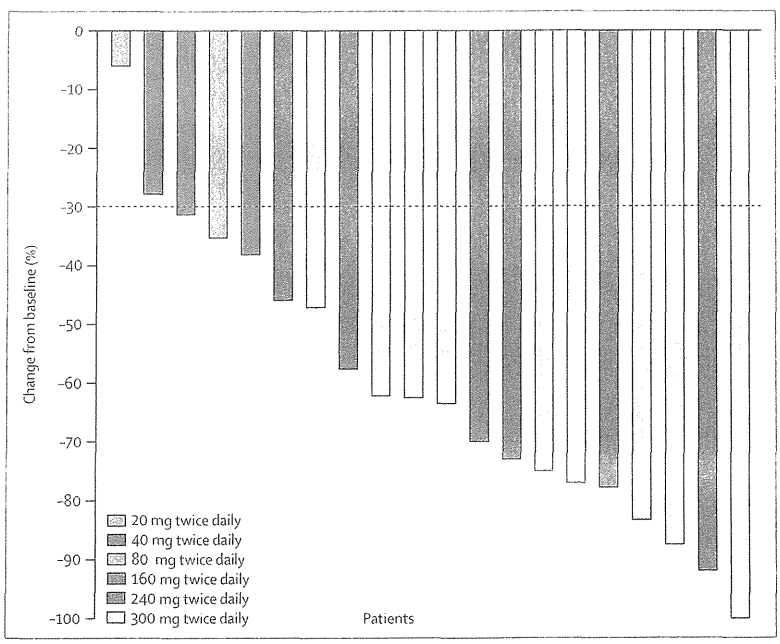

Figure 1: Waterfall plot of best percentage change in target lesions from baseline on investigator assessment (20 patients with measurable lesions in phase 1)

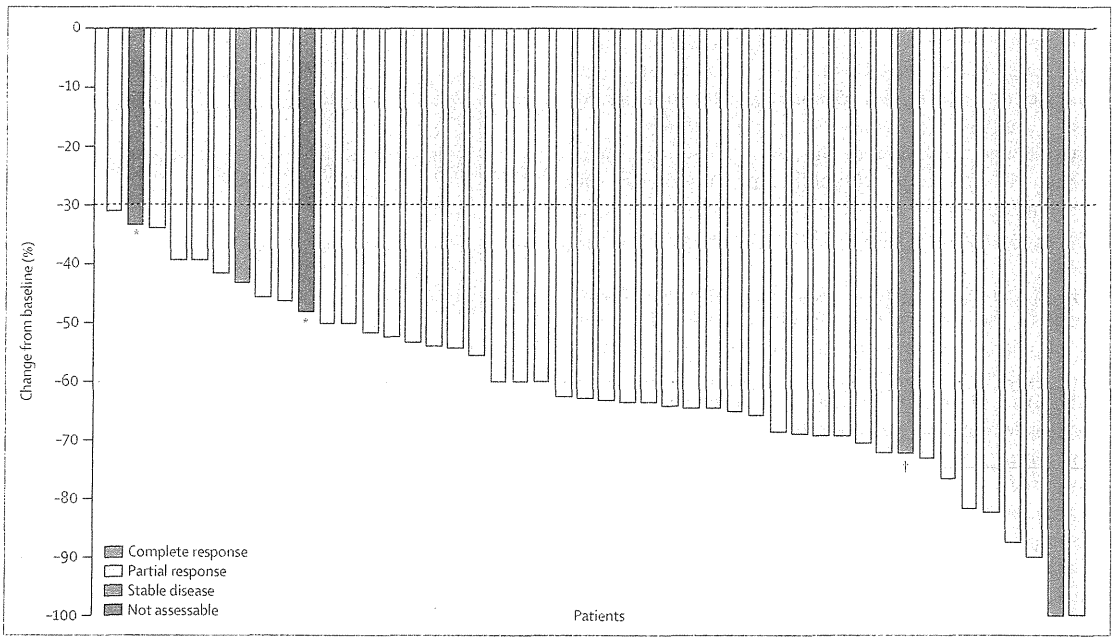

Figure 2: **Waterfall plot of best percentage change in target lesions from baseline based on independent review committee assessment (46 patients in phase 2)** *Indeterminate response by early stopping because of safety reasons. †Classified as complete response according to the definition of Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 for patients for whom lymph nodes were identified as target lesions and which were reduced to less than 10 mm. These responses (complete response and partial response) were confirmed by subsequent scan.

exclusion of the other 65 ALK-positive patients was because of other eligibility criteria, or a reason not specified by investigators.

Table 1 summarises the baseline characteristics of patients enrolled in this study. In the phase 1 portion of the study, 15 patients were treated with CH5424802 under fasting conditions in six cohorts (20–300 mg twice a day), and nine were treated under non-fasting conditions in two cohorts (240 mg and 300 mg twice a day).

All 24 patients in the phase 1 part of the study completed at least two cycles, and had at least one adverse event while on study. Eight (33%) of 24 patients had grade 3 adverse events. Four patients had six adverse events that were deemed to be related to the study treatment—neutropenia (three patients, 13%), blood bilirubin increased (one patient, 4%), hypophosphataemia (one patient, 4%), and leucopenia (one patient, 4%). We noted no grade 4 adverse events or deaths at any dose level. We noted no DLTs up to the highest dose (300 mg twice a day; table 2). One patient had a dose reduction due to rash at a dose of 300 mg twice a day in the phase 1 portion, but no patient needed drug discontinuation because of adverse events. Thus, we did not identify the MTD in this study.

Blood samples were taken from all 24 patients. Table 3 shows the pharmacokinetics parameters at steady state after multiple dosing (day 21 in cycle 1). T_{max} was between 2·00 h and 4·61 h constantly throughout the dose range (20–300 mg twice daily), and the AUC_{0-10} increased in an approximately linear way within the dose range under the fasting condition. We compared the absorption of CH5424802 under fasting and non-fasting conditions at 240 mg and 300 mg twice daily. The plasma exposures at steady state were similar under fasting and non-fasting conditions, although it took longer to reach T_{max} under non-fasting conditions.

Of the 24 patients, all 20 (83%) patients with measureable lesions based on RECIST criteria and treated with CH5424802 showed tumour shrinkage and 17 (85%) of 20 patients had a partial response by investigator's assessment (figure 1). All 15 patients with measurable lesions treated at doses higher than 160 mg twice a day achieved a partial response (240 mg [six patients], and 300 mg [nine patients]). One patient (4%) with non-measurable lesions met the criteria of RECIST version 1.1 for a complete response. The mean duration of treatment was 11·8 months (range 3–18) with a median follow-up of 12·05 months (range 4·7–20·8). 16 (67%) patients enrolled during the phase 1 portion of this trial remained on study treatment as of July 31, 2012.

On the basis of these results, the planned highest dose (300 mg twice daily) was judged as acceptable to be the recommended dose in the phase 2 portion.

Of the 46 patients enrolled in the phase 2 portion of the trial (all of whom had measureable lesions), two patients (4·3%, 95% CI 0·5–14·8) achieved a complete response, 41 patients (89·1%, 76·4–96·4) had a partial response, and one patient (2·2%, 0·1–11·5) had stable disease by independent review committee assessment (figure 2). No

patient had progressive disease; two patients (4·3%) had an unknown response because of early withdrawal. Thus 43 patients (93·5%, 95% CI 82·1–98·6) had an objective response, and 44 (95·7%, 95% CI 85·2–99·5) achieved disease control. We noted no apparent differences in response when analysed by age, sex, ECOG PS, BMI, number of previous chemotherapy regimens for metastatic disease, history of treatment with pemetrexed, types of *ALK* test, and status of brain metastasis (data not shown).

Figure 2 shows a waterfall plot of the best percentage change in the size of target lesions from baseline. All patients had a reduction in tumour size of more than 30%. Response to treatment was noted early, and 30 (65%) of 46 patients reached the criteria for partial response within 3 weeks (cycle 1) and 40 (87%) patients did so within 6 weeks (cycle 2; figure 3).

The study is still ongoing; 40 (87%) of 46 patients remained on treatment as of data cutoff and more follow-up is needed for precise estimation of treatment duration and progression-free survival in the phase 2 portion. The median treatment duration as of data cutoff had already passed 7·1 months (range 1–11) with a median follow-up period of 7·6 months (3·4–11·3).

Of the 46 patients in the phase 2 portion, 15 (33%) patients had known brain metastases, of whom 12 (26%) had previous radiation for CNS metastases and three (7%) were clinically stable without symptoms at baseline. Seven patients had prolonged periods of disease control for more than 6 months on CH5424802 treatment (average 6·5 months, range 0·8–11·3). No progression of CNS lesions in any of the patients was noted by the time of data cutoff, although radiotherapy before treatment might have affected the natural history of brain disease. Of the patients with CNS lesions, 12 were on treatment at data cutoff, and three patients had discontinued treatment because of brain oedema, tumour haemorrhage, and progression of non-CNS tumour lesions. Two of the three patients who had baseline CNS lesion but no radiation continued the study medication for more than 300 days without progression of brain metastases.

Adverse events were recorded in all 46 patients included in the safety analysis. Grade 3 adverse events were reported in 17 (37%) patients, but no grade 4 adverse events or deaths were reported. Serious adverse events occurred in five (11%) patients (brain oedema, radius fracture, tumour haemorrhage, cholangitis sclerosing, and alveolitis allergic). Four (9%) patients discontinued treatment because of adverse events (brain oedema, tumour haemorrhage, interstitial lung disease, and sclerosing cholangitis), which were considered related to CH5424802 with the exception of brain oedema. 22 (48%) patients suspended treatment whithin the 21-day limit because of adverse events. No patients required dose reduction.

Table 4 shows treatment-related adverse events reported in 10% of patients or more. Treatment-related adverse events were noted in 43 (93%) of 46 patients. 12 (26%) patients had treatment-related grade 3 adverse events, including two patients each having decreased neutrophil count and increased blood creatine phosphokinase. Other treatment-related grade 3 adverse events were noted in one patient each only.

The most frequently reported treatment-related adverse events were dysgeusia, followed by increased aspartate aminotransferase (AST), increased blood bilirubin, increased blood creatinine, rash, constipation, and increased alanine aminotransferase (ALT; table 4). Almost all events were grade 1 or 2 (118 of 125 events, 94%).

All cases of dysgeusia were of grade 1 in nature and were not accompanied by loss of appetite. Increased blood bilirubin of grade 3 was noted in one patient, and other changes in laboratory values were limited to transient increases in AST and ALT and an increase in

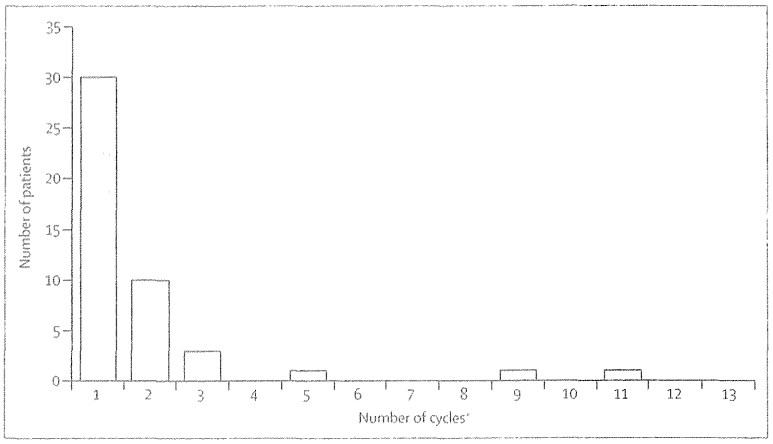

Figure 3: Number of patients who had tumour size reduction of 30% or more by treatment cycle in phase 2
*One cycle lasted 3 weeks.

	All grades	Grade 3
Dysgeusia	14 (30%)	0
Increased AST	13 (28%)	0
Increased blood bilirubin	13 (28%)	1 (2%)
Increased blood creatinine	12 (26%)	0
Rash	12 (26%)	1 (2%)
Constipation	11 (24%)	0
Increased ALT	10 (22%)	1 (2%)
Decreased neutrophil count	8 (17%)	2 (4%)
Increased blood CPK	7 (15%)	2 (4%)
Stomatitis	7 (15%)	0
Increased blood ALP	6 (13%)	0
Myalgia	6 (13%)	0
Nausea	6 (13%)	0

AST=aspartate aminotransferase. ALT=alanine aminotransferase. CPK=creatine phosphokinase. ALP=alkaline phosphatase.

Table 4: Treatment-related adverse events reported in 10% or more of patients enrolled in phase 2 (n=46)

Panel: Research in context

Systematic review

We searched PubMed for articles published in English until January, 2013 (no restriction for the starting date), with the search terms "ALK", "crizotinib", and "NSCLC". Although identified studies had small sample sizes, the effects of standard chemotherapy on *ALK*-rearranged non-small-cell lung cancer have been reported to be insufficient.[18] Crizotinib, a first-in-class ALK inhibitor, has been shown to be effective in patients with *ALK*-rearranged non-small-cell lung cancer.[6,23–25] While our study was underway, crizotinib was granted approval in the USA (on Aug 26, 2011), and subsequently in the EU and Japan. However, resistance to crizotinib-based treatment often develops within the first year after the start of treatment.[9]

Interpretation

Our phase 1–2 study suggests that CH5424802 is active and tolerable for treatment of patients with advanced *ALK*-rearranged non-small-cell lung cancer. ALK expression in normal tissue is very low[26] and might not be activated generally. CH5424802 is a selective ALK inhibitor and, therefore, allows a high exposure while limiting side-effects. The high proportion of patients achieving an objective response and the favourable effects on brain metastases suggest that CH5424802 is a promising ALK inhibitor. Investigation of CH5424802 in patients who are resistant to crizotinib is ongoing (NCT01588028).[27]

blood bilirubin of grade 1 or 2, and no case met Hy's law criteria[22] to suggest liver injury. The rash reported was clinically different from that caused by EGFR tyrosine kinase inhibitors, and limited to grade 1 or 2 in almost all patients. All increases in blood creatinine were grade 1 or 2. Visual disorders were rare with only visual impairment in one patient (2%), and blurred vision in another patient (2%), both of which were grade 1. Gastrointestinal toxic effects were mild, including nausea (six patients, 13%), diarrhoea (two patients, 4%), and vomiting (one patient, 2%). No cases of grade 3 nausea, diarrhoea, or vomiting were reported. All other adverse events were mild in severity.

Discussion

The results of this phase 1–2 study showed that CH5424802, given at a dose of 300 mg twice daily, is safe and active in patients with *ALK*-rearranged NSCLC. Almost 94% of patients achieved an objective response, and early reductions in tumour size of at least 30% were noted in most patients within the first 6 weeks. The proportion of patients who achieved an objective response noted here for CH5424802 is substantially higher than that of crizotinib (60·8% and 53%) in two separate early phase trials (panel).[6,23] Although median progression-free survival has not yet been reached, the median treatment duration at the time of data cutoff had already passed 7·1 months, and 40 of 46 patients remained on treatment.

The activity of CH5424802 could be explained by its potency and highly selective inhibitory effect on ALK. Whereas crizotinib is a multitargeted receptor tyrosine kinase inhibitor of *ALK*, *MET*, and *ROS1*, CH5424802 is highly selective for ALK without activity against MET and ROS1. In preclinical studies using Ba/F3 cells expressing the EML4-ALK fusion protein, CH5424802 showed more than two-fold higher potency than did crizotinib.[8,12] Moreover, the trough concentration of crizotinib given at the clinically recommended dose (250 mg twice daily) is reported to be 292 ng/mL,[28] whereas that of CH5424802 (at 300 mg twice daily) is 463 ng/mL, suggesting that sustained high blood concentrations can be achieved. Thus, sufficiently high exposure of CH5424802 was achieved in the clinical setting. Since ALK expression in normal adult tissues is extremely low,[26] the high selectivity for ALK might contribute to the better activity and safety profile of CH5424802 than crizotinib. On the other hand, there may be ethnic differences in pharmacokinetics of CH5424802 between Asian and non-Asian populations, as noted with crizotinib, which will be assessed in an ongoing phase 1–2 study in the USA (NCT01588028).[27]

Although most *ALK*-rearranged NSCLCs respond to treatment with ALK tyrosine kinase inhibitors, resistance to treatment with crizotinib often develops within the first year. This resistance is thought to be attributed to point mutations and amplification of the *ALK* fusion gene in a third of cases or activation of bypass signalling in other cases.[8,9] Most notably, the Leu1196Met aminoacid substitution has been shown to confer resistance to crizotinib, which corresponds to the gatekeeper mutations of *EGFR* (Thr790Met) and *BCR-ABL* (Thr315Ile), a mechanism of resistance to gefitinib and imatinib, respectively.[8,9] The fact that CH5424802 inhibits *EML4-ALK* Leu1196Met-driven cell growth[12] is another reason that CH5424802 could be more active than crizotinib. Currently, a clinical study assessing the activity of CH5424802 in patients who failed to respond to crizotinib-based treatment is ongoing (NCT01588028).[27]

Although limited by the small number of patients, and potential confounding by previous treatment with radiotherapy, CH5424802 seems to have activity in patients with CNS disease. In the three patients with CNS metastases but who did not receive brain irradiation, CNS lesions showed responses to treatment, which is encouraging considering almost half of patients treated with crizotinib have CNS relapse.[11]

In the present study, we did immunohistochemistry and FISH tests, and we deemed patients with double-positive results, or those confirmed by RT-PCR, as being positive for *ALK* fusion gene expression. By contrast, the crizotinib phase 1 trial[6,24] included patients who were positive by FISH test only, and later it was reported[29] that a higher response rate was noted in patients with double-positive

results, suggesting that there might have been patients with false-positive results by FISH test. Therefore, the difference in the diagnostic methods might contribute to the observed difference in the activity between the two drugs, and this should be explored in future studies.

CH5424802 was generally well tolerated with manageable adverse events. Although four patients discontinued treatment because of adverse events in this study, all 42 patients continued treatment with CH5424802 without any dose modification at the time of data cutoff. No adverse events specific to CH5424802 leading to discontinuation were identified either. Among 43 events in 22 patients with drug suspension, 24 events (56%) were due to the strict cycle initiation criteria. Since this is a first-in-human trial and safety profile of ALK inhibitors were not well known at the initiation of this study, strict cycle initiation criteria were defined, in addition to treatment suspension and dose reduction criteria. Patients with grade 2 non-haematological toxic effects or decreased neutrophil count suspended CH5424802 until they resolved to grade equal to or lower than 1 or grade at baseline at the initiation of each following cycle. Symptoms such as visual and gastrointestinal disorders (diarrhoea, vomiting, and nausea) that were frequently reported with crizotinib occurred at a low rate in this study. This could be related to the high selectivity of this compound to ALK kinase. The inhibitory activity against other kinases, such as MET and ROS1 by crizotinib, might be a reason for these side-effects of crizotinib.

Almost a third of the patients screened for ALK assessment were identified as *ALK* positive. This *ALK*-positive ratio is higher than that previously reported,[1] which might be due to bias by selecting patients with negative EGFR mutations, younger age, or non-smoking status. Limitations of this study can include a lack of any *EML4-ALK* mutational data. The study was also limited by a rather small enrolment and short follow-up period, and by its non-randomised nature.

Based on the results of the present study, CH5424802 could be an effective and safe option for the treatment of *ALK*-rearranged NSCLC. Further studies to confirm the efficacy of the drug and to assess its activity in patients resistant to crizotinib are ongoing.

Contributors

All authors contributed to data analysis, data interpretation, and writing of the report.

Conflicts of interest

TSe has received lecture fees and research funding from Chugai, Pfizer, and Novartis. KK has received lecture fees from Chugai, Pfizer, Novartis, and Astellas, and research funding from Chugai and Pfizer. MN has received lecture fees from Chugai and Pfizer, and research funding from Chugai, Pfizer, and Novartis. KN has received lecture fees and research funding from Chugai, Pfizer, Novartis, and Astellas. MM has received lecture fees from Chugai and Novartis, and research funding from Novartis. AI has received lecture fees and research funding from Chugai. TH has received lecture fees and research funding from Chugai, Pfizer, and Novartis. NY has received lecture fees from Chugai and Pfizer; research funding from Chugai, Pfizer, and Novartis; and advisory fee from Novartis. HY has received lecture fees from Chugai and Pfizer, and research funding from Chugai and Novartis. MH has received lecture fees from Chugai and Pfizer, and research funding from Chugai. YO has received lecture fees, research funding, and travel grants from Chugai, Pfizer, and Novartis. NN has received lecture fees and research funding from Chugai and Pfizer. KT has received lecture fees and research funding from Chugai and Nichirei, and advisory fee from Chugai and Nichirei. TSh and TTan are employees of Chugai Pharmaceutical Co, Ltd. TTam has received lecture fees from Chugai, Pfizer, and Novartis, and research funding from Chugai.

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Randomized phase II trial of uracil/tegafur and cisplatin versus vinorelbine and cisplatin with concurrent thoracic radiotherapy for locally advanced unresectable stage III non-small-cell lung cancer: NJLCG 0601

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ABSTRACT

Introduction: The optimal chemotherapy with thoracic radiotherapy (TRT) for locally advanced non-small-cell lung cancer (NSCLC) remains to be established. This randomized phase II study of concurrent chemoradiotherapy was conducted to compare uracil/tegafur (UFT) and cisplatin with vinorelbine and cisplatin for stage III NSCLC.

Patients and methods: Patients with unresectable stage III NSCLC were randomized to receive UP (400 mg/m^2 UFT on days 1–14 and 29–42 and 80 mg/m^2 cisplatin on days 8 and 36) or NP (20 mg/m^2 vinorelbine on days 1, 8, 29, and 36 and 80 mg/m^2 cisplatin on days 1 and 29). TRT began on day 1 (total 60 Gy in 30 fractions).

Results: Of 70 enrolled patients, 66 were evaluable for efficacy and safety. The overall response rates were 80% (95% CI: 67–93%) and 71% (95% CI: 55–87%) for the UP arm and the NP arm. With a median follow-up of 20.2 months, the progression-free survival and median survival time were 8.8 and 26.9 months in the UP arm, and 6.8 and 21.7 months in the NP arm. The 2-/3-year survival rates were 51.0/34.3% and 46.9/33.4% for the UP arm and the NP arm, respectively. Grade 3/4 neutropenia occurred in 20% and 58% of patients in the UP and NP arms, respectively.

Conclusion: Combined with concurrent TRT, the UP arm achieved better efficacy and safety compared with the NP arm, suggesting it to be a promising candidate as a standard regimen for locally advanced NSCLC. Further evaluation of the UP arm is warranted.

1. Introduction

Lung cancer remains the leading cause of death related to cancer worldwide [1]. Non-small-cell lung cancer (NSCLC) accounts for 80% of lung cancer cases, and approximately 30% of NSCLC patients present with locally advanced disease [2].

In the 1980s, US cooperative groups showed that cisplatin-based, second-generation chemotherapy followed by thoracic radiotherapy (TRT) for stage III NSCLC improved median survival time (MST) and 5-year survival compared with TRT alone [3,4]. In the 1990s, two randomized studies that compared concurrent versus sequential cisplatin-based, second-generation chemoradiotherapy demonstrated that the concurrent approach provided superior survival outcome, although it was also associated with greater toxicity [5,6]. However, even in a meta-analysis, the superiority of concurrent chemoradiotherapy to sequential one was reported [7]. Thus, concurrent chemoradiotherapy is regarded as the standard treatment for locally advanced NSCLC.

During the last decade, platinum-based third-generation chemotherapies, such as paclitaxel, vinorelbine, gemcitabine,

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and docetaxel, have been proven to improve the survival of patients with metastatic NSCLC compared with second-generation chemotherapies [8–10]. In addition, several phase I and II studies of third-generation chemotherapy with concurrent TRT for locally advanced NSCLC provided promising survival outcomes [11–17]. However, it seems to be difficult to deliver full doses of the above-described regimens because of dose-limiting toxicities.

Concurrent chemoradiotherapy with vinorelbine and cisplatin (NP) is one of the commonly used regimens for locally advanced NSCLC in Japan, yielding a reasonable response rate, median survival time (MST), and 3-year survival rate in a phase I trial and retrospective analysis [17,18]. Subsequently, in a recent phase III study comparing second- and third-generation regimens with concurrent TRT for unresectable stage III NSCLC, weekly paclitaxel, carboplatin, and TRT followed by 2 courses of triweekly consolidation provided good results in terms of both efficacy and toxicity [19]. And also weekly docetaxel, cisplatin and TRT provided better efficacy and hematological toxicities [20]. It has therefore been suggested that these regimens should be regarded as standard treatments for locally advanced NSCLC.

Although UFT, an oral preparation of uracil and tegafur, is seldom used for metastatic NSCLC, two phase II studies of UFT plus cisplatin (UP) in advanced NSCLC have exhibited efficacy almost equivalent to other potent regimens [21,22]. Moreover, a full dose regimen of UP chemotherapy with concurrent TRT for locally advanced NSCLC in a multi-institutional phase II trial has shown a promising outcome with low hematological toxicity [23].

The optimal combination chemotherapy with TRT for locally advanced NSCLC remains to be established. Thus, to select a proper candidate for a phase III study of chemoradiotherapy, we conducted a randomized phase II study comparing the UP arm with the NP arm.

2. Patients and methods

2.1. Patient eligibility

The study population consisted of patients between 20 and 75 years of age inclusive, with cytologically or histologically confirmed NSCLC with unresectable stage IIIA or IIIB disease. Mediastinoscopies were not performed and lymph node metastases were clinically diagnosed based on the results of computed tomography (CT) scan and/or positron emission tomography (PET) scan. Unresectable stage IIIA disease was defined by the presence of multiple/bulky N2 mediastinal lymph nodes on CT such that, in the judgment of the treating investigator, the patients were unsuitable as candidates for surgical resection. Patients were required to have lesions measurable with the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0.

Other eligibility criteria included an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, no prior systemic chemotherapy, TRT or thoracic surgery. Laboratory requirements included a white blood cell count of 4000 mm^{-3} or more, a neutrophil count of 2000 mm^{-3} or more, a platelet count of 100,000 mm^{-3} or more, a hemoglobin level of 10 g/dL or more, a total bilirubin level of 1.5 mg/dL or less, an AST/ALT value of twice the upper normal limit or less, a creatinine level of 1.5 mg/dL or less, a creatinine clearance of 60 mL/min or more, and partial pressure of arterial oxygen of 60 torr or more.

Patients were ineligible if they had concomitant malignancies, active infectious diseases, serious complications such as ileus, uncontrolled diabetes mellitus, heart failure, renal failure, or hepatic failure, malignant pleural or pericardial effusion, interstitial pneumonitis or pulmonary fibrosis apparent on chest X-ray, and other medical problems regarded as making them ineligible for this study by physicians. Lactating, pregnant or possibly pregnant women, or those willing to become pregnant were also excluded. The study protocol was approved by the institutional review board of each hospital concerned and written informed consent was obtained from each patient.

Prestudy radiographic assessment to document tumor staging for eligibility included CT of the thorax including the upper abdomen, brain CT or magnetic resonance imaging and radioisotopic bone scan. PET scan was allowed to be substituted for radioisotopic bone scan.

2.2. Treatment schedules

Patients were randomly assigned to one of two treatment arms (UP arm and VP arm) as shown in Fig. 1 (CONSORT diagram), stratified by gender (male *v* female), age (59 or younger *v* 60–64 *v* 65–69 *v* 70–75), histology (adenocarcinoma *v* squamous cell carcinoma *v* large cell carcinoma *v* other), and clinical stage (IIIA *v* IIIB).

In the UP arm, oral UFT (400 mg/m^2/day) twice daily before meals from days 1 to 14 and from days 29 to 42 and cisplatin (80 mg/m^2) via intravenous infusion on days 8 and 36 were administered. According to body surface area (BSA), the actual dose of UFT was modified as follows: BSA less than 1.25 m^2, 500 mg/day (300 mg in the morning and 200 mg in the evening); BSA 1.25 m^2 or more, 600 mg/day (300 mg b.i.d.). Concurrent TRT was given in daily fractions of 2 Gy from day 1 up to a total of 60 Gy in 30 fractions over a 6-week period. In the NP arm, vinorelbine (20 mg/m^2) on days 1, 8, 29, and 36 and cisplatin (80 mg/m^2) on days 1 and 29 were administered intravenously. The schedule of TRT was the same as that of the UP arm.

Two cycles of additional treatment with the same dosage were optionally permitted in both arms as consolidation chemotherapy. There was no evidence that consolidation chemotherapy prolonged overall survival for locally advanced NSCLC. Therefore, consolidation chemotherapy was considered at the investigator's discretion.

2.3. Radiotherapy

Radiotherapy began on day 1 of chemotherapy in both arms with a linear accelerator photon beam of 4 MV or more.

In this study, both 2D and 3D treatment planning systems were allowed. Radiation doses were specified at the center of the target volume. 3D dose constraints for both planning target volume and normal-risk organs were not determined in the protocol. The doses were calculated assuming tissue homogeneity with correction for lung tissues in 3D treatment planning. As it turned out, 3D treatment planning was performed for all 66 patients who received radiotherapy.

The initial 40 Gy was delivered to the large field target volume, which included the primary tumor, ipsilateral hilum, and mediastinum. No prophylactic irradiation of the supraclavicular fossa area was given. The other 20 Gy was delivered to a pair of oblique fields to avoid excess irradiation of the spinal cord.

2.4. Treatment modifications

The administration of cisplatin was withheld on either arm if there was a decrease in the leukocyte count to below 3000 mm^{-3}, or the neutrophil count to under 1500 mm^{-3}, or the platelet count to less than 100,000 mm^{-3}, or if grade 2 or more nonhematological toxicities were observed, except for alopecia, anorexia, and malaise, until resolution of toxicity to grade 0 or 1. In the UP arm, UFT was stopped and then reduced in subsequent cycles from 600 mg or 500 mg to 400 mg or 300 mg, respectively if any grade 4 hematological toxicities, or grade 3 or worse nonhematological toxicities, except for alopecia, anorexia, or malaise, were observed. Whenever grade 2 diarrhea or stomatitis occurred, UFT was reduced. In the NP

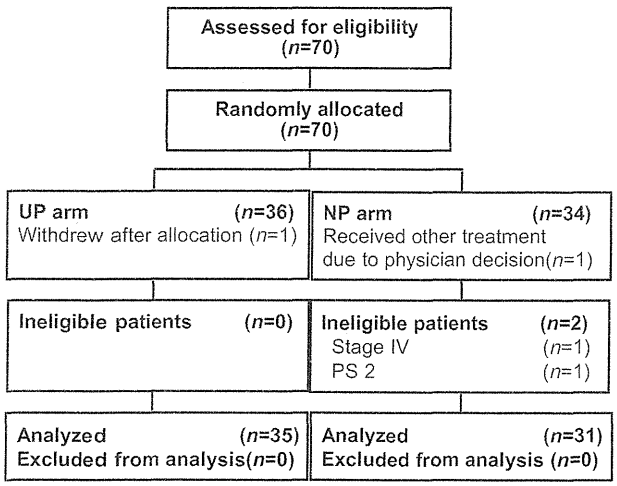

Fig. 1. CONSORT diagram. UP, uracil/tegafur and cisplatin; NP, vinorelbine and cisplatin.

arm, the administration of vinorelbine on days 8, 29, or 36 was omitted and a delay of up to 7 days was permitted if any grade 2 or worse hematological or nonhematological toxicities were observed. TRT was withheld on either arm in cases of any grade 4 hematological toxicities, grade 3 or worse esophagitis or dermatitis, grade 1 or worse fever, or any sign of pneumonitis. Any patient unable to receive a subsequent cycle within 7 days was removed from the protocol treatment, but was included in the study analysis.

2.5. Evaluation of efficacy and safety

All eligible patients who received any protocol treatment were regarded as evaluable for efficacy and safety. Complete blood cell counts and biochemistry tests were performed once a week during the treatment period. Thoracic CT was performed every 4 weeks during and after the treatment period until progressive disease was recognized.

The response was evaluated according to RECIST version 1.0 in the extramural review. Progression-free survival (PFS) was defined as the period from the date of randomization to the date when disease progression was first observed or death occurred. Overall survival (OS) was defined as the period between randomization and death from any cause. Toxicities were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

2.6. Statistical analysis

The primary endpoint was overall response rate (ORR), and secondary endpoints included PFS, OS, and the level of toxicity. Assuming that an ORR of 80% in eligible patients would indicate potential usefulness, while an ORR of 60% would be the lower limit of interest, with alpha = 0.05 and beta = 0.20, the estimated required accrual was 33 patients in each arm. Allowing for dropouts, the accrual goal was determined to be 35 patients in each arm.

Fisher's exact test was used to estimate the correlation among different variables between arms. Survival estimation was performed according to the Kaplan–Meier method.

3. Results

3.1. Patient characteristics

Between February 2006 and May 2009, 70 patients were enrolled from 5 institutions and were allocated to the UP arm ($n = 36$) and NP arm ($n = 34$). Of the 70 patients enrolled, 4 patients were excluded from final analysis, including one patient due to withdrawal of the informed consent before the allocated treatment, 2 patients due to ineligibility (stage IV and PS 2), and 1 patient who received a different regimen based on the physician's judgment instead of the protocol treatment. Eventually 66 patients (UP arm, $n = 35$ and NP arm, $n = 31$) were evaluable for efficacy and safety (CONSORT diagram, Fig. 1). No remarkable differences in demographic characteristics were found between the two treatment arms (Table 1).

Table 1
Characteristics of patients in each treatment arm.

Characteristic	UP arm ($n = 35$)		NP arm ($n = 31$)		P
	No.	%	No.	%	
Gender					0.6841
Male	28	80.0	26	83.9	
Female	7	20.0	5	16.1	
Age (years)					0.8326
Median	62		61		
59≥	12	34.3	14	45.2	
60–64	10	28.6	8	25.8	
65–69	7	20.0	5	16.1	
70–75	6	17.1	4	12.9	
PS (ECOG)					0.8281
0	16	45.7	15	48.4	
1	19	54.3	16	51.6	
Histology					0.4765
Adenocarcinoma	17	48.6	19	61.3	
Squamous cell carcinoma	15	42.9	11	35.5	
Large cell carcinoma	2	5.7	0	0	
Other	1	2.9	1	3.2	
Stage					0.8888
IIIA	13	37.1	11	35.5	
IIIB	22	62.9	20	64.5	

3.2. Treatment administered

As shown in Table 2, the median number of treatment cycles was 3 (range 1–4) in both arms. 94.3% of patients in the UP arm and 93.5% of patients in the NP arm underwent the projected two cycles of chemotherapy and concurrent TRT. As consolidation chemotherapy, 60% of patients in the UP arm and 58.1% of patients in the NP arm received the additional treatment with the same regimen as allowed by the protocol. Main reason for quitting chemotherapy after two cycles of the protocol treatment was investigator's discretion. Most of patients who received consolidation chemotherapy completed 4 cycle of treatment altogether as long as the progression was not observed.

In all except 1 patient in each arm, 60 Gy concurrent TRT was completed.

Table 2
Treatment delivery.

	UP arm ($n = 35$)		NP arm ($n = 31$)	
	No.	%	No.	%
Cycle number				
1	2	5.7	2	6.5
2	12	34.3	11	35.5
3	5	14.3	7	22.6
4	16	45.7	11	35.5
Median	3.0		3.0	
TRT (Gy)				
60	34	97.1	30	96.8
50–59	0	0	1	3.2
40–49	1	2.9	0	0
Median	60.0		60.0	

Table 3
Objective response rates.

	UP arm (n = 35)		NP arm (n = 31)	
	No.	%	No.	%
Complete response	2	5.7	1	3.2
Partial response	26	74.3	21	67.7
Stable disease	7	20.0	7	22.6
Progressive disease	0	0.0	2	6.5
Response rate (CR + PR[a])	28	80.0	22	71.0

[a] P = 0.5659.

3.3. Efficacy

In the UP arm, the ORR was 80% (95% CI, 67–93%), including 2 patients (6%) with a complete response (CR), 26 (74%) with a partial response (PR), and no patient with progressive disease (PD). In the NP arm, the ORR was 71% (95% CI, 55–87%), including 1 patient (3%) with CR, 21 (68%) with PR, and 2 (6%) with PD (Table 3). Although the response rate in the UP arm was superior to that in the NP arm, this difference between two arms was not statistically significant (P = .566).

The PFS and OS data are shown in Fig. 2. With a median follow-up of 20.2 months, 40 patients had died. The median PFS were 8.8 months (95%CI, 6.7–11.1 months) in the UP arm, and 6.8 months (95%CI, 5.2–9.6 months) in the NP arm, respectively. The MST in the UP arm was 26.9 months (95% CI, 16.3–52.9 months) compared with 21.7 months (95% CI, 14.5–45.3 months) in the NP arm. The 2-/3-year survival rates were marginally higher in the UP arm (51.0/34.3%) than that in the NP arm (46.9/33.4%).

The sites of first failure among 31 recurrent cases in the UP arm, 12 (38.7%) were local and 19 (61.3%) were distant including 11 patients with brain metastasis, whereas among 26 recurrent cases in the NP arm, 14 (53.8%) were local, 12 (46.2%) were distant, including 6 with brain metastasis (data not shown).

3.4. Safety

Grade 3 or worse toxicities in each arm are shown in Table 4. Grades 3 and 4 neutropenia and febrile neutropenia were significantly more frequent in the NP arm than in the UP arm (P = .002 and .044, respectively). Although anorexia, nausea/vomiting, and diarrhea over grade 3 tended to be more frequent in UP arm, there were no statistically significant differences between the two arms in these categories. No one had grade 3 or worse esophagitis in either arm. Two patients in the NP arm died of radiation pneumonitis approximately five months after the completion of 60 Gy of TRT.

4. Discussion

We set out to compare oral fluoropyrimidine with third-generation anticancer agent in platinum-based chemoradiotherapy for locally advanced stage III NSCLC. The combined modality strategy with chemotherapy and concurrent TRT is considered as a standard treatment for locally advanced unresectable NSCLC. However, the optimal chemotherapy regimen remains to be determined. Two randomized phase III studies comparing third-generation regimen with second-generation regimen combined with concurrent TRT showed superior survival outcomes in third-generation regimen [19,20]. Moreover, based on recent randomized phase II and III studies, weekly carboplatin and paclitaxel with TRT has become a commonly used regimen, and is regarded as the reference arm for future phase III studies [16,19].

In this trial, we adopted the response rate as a primary endpoint because it is not influenced by post trial treatment. On the other hand, most of recent chemoradiotherapy phase II trials choose 2-year survival rate or PFS as primary endpoint. Thus, we also carefully followed-up for PFS and OS. Both the UP arm and NP arm showed a reasonably good response rate and survival outcomes in the present study. These data were comparable to those of third-generation regimens in other previous phase II and III trials. As to the primary endpoint, the ORR of the UP arm was better, but not with statistical significance, than that of the NP arm. In addition, the median PFS, the median OS, and the 2-year survival rate in the UP arm were better than those in the NP arm. There was a non-significant trend toward more favorable survival data in the UP arm than the NP arm although the small sample size in this study prevented reaching a definite conclusion.

It cannot be denied that epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) such as gefitinib and erlotinib could contribute to long-term survival. EGFR mutation screening was not routinely performed in this study, because this examination was not available at the start of this study. Among 36 patients (UP arm, n = 20 and NP arm, n = 16) who subsequently underwent EGFR mutation screening, 5 patients in the UP arm and 3 patients in the NP arm harbored mutated EGFR (data not shown). Only 2 of them, both in the UP arm achieved PR and long-term survival. Hence, it is difficult to evaluate whether the use of EGFR-TKIs would have resulted in better survival outcomes.

It is noteworthy in the present study that hematological toxicities were very mild in the UP arm. In particular, the incidence of grade 3 or worse neutropenia in the UP arm was remarkably lower than not only in the NP arm of this study but also in the other regimens referred to above. Moreover, no febrile neutropenia was observed in the UP arm. Although grade 3 gastrointestinal toxicities which are common in fluoropyrimidines were more frequent in the UP arm than in the NP arm, they were all reversible and manageable thus this does not seem to be a critical impact. Therefore, UP

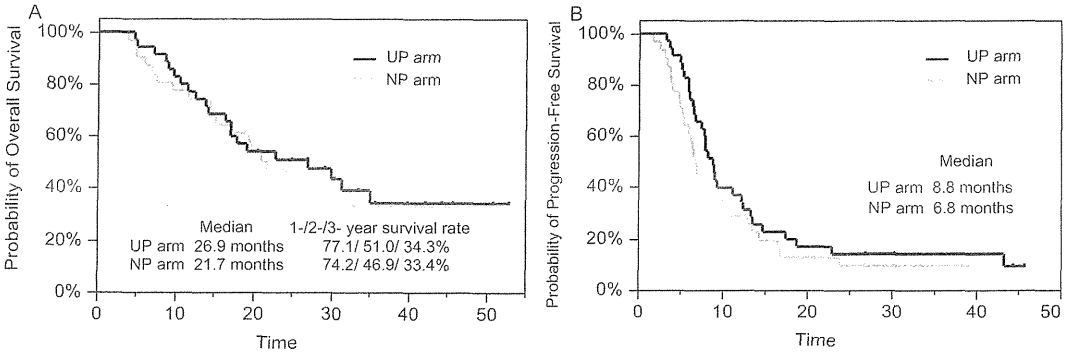

Fig. 2. (A) Overall survival and (B) progression free survival in each arm.