In this study, large clusters were specifically observed in cancer cell-implanted blood, and an approach for finding these clusters in the blood has possibility for the development of a new cancer metastasis diagnostic method. Results in this study were obtained using hemolyzed blood samples *in vitro*; therefore, the large cluster formations should also be confirmed for blood *in vivo* as a next step to achieve such a new diagnostic method. One possibility for the mechanism of large cluster formation is an aggregation of implanted cancer cells by immune reaction of the rat with antibody formation. In this study, blood samples were picked up from the rat 2 weeks after implantation; therefore, time-course measurements of cluster formations after implantation might be one useful way to confirm the above possibility, and our developed system can also be used to confirm this.

Conclusion

In this study, an on-chip multi-imaging flow cytometry system was developed to find cell clusters in blood samples. The system can take both BF and FL pictures simultaneously, and can obtain imaging biomarkers; cell area, nucleus area, number of nuclei, and perimeter ratio (S, S_n, N_n, and R), in real time. By using the developed system, sample blood of rats in which cancer cells had been pre-implanted was measured and compared with that of healthy rats. In terms of the results, clustered cells having (1) S larger than 200 μm^2 and (2) S_n larger than 90 μm^2 were specifically observed in cancer cell-implanted blood, but were not observed in healthy rats. In addition, (3) N_n higher than 3 was specific for cancer-implanted blood and (4) R smaller than 0.90 was specific for all clusters having N_n higher than 3, which were specific for cancer-implanted blood. Finally, quantitative gene copy number assay was performed for the large clusters, and they were shown to be CTCs. These results indicate the usefulness of the imaging biomarkers for characterizing clusters, and that the developed system is useful to identify clustered CTCs in blood.

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Author Contributions

Conceived and designed the experiments: HK TA KN YM KY. Performed the experiments: HK HT YN KS AH MO MG TA. Analyzed the data: HK KS AH MO MG TA KN YM KY. Contributed reagents/materials/analysis tools: HK HT YN KS AH MO MG TA KN YM KY. Wrote the paper: HK KY.

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ORIGINAL ARTICLE

First-Line Crizotinib versus Chemotherapy in *ALK*-Positive Lung Cancer

Benjamin J. Solomon, M.B., B.S., Ph.D., Tony Mok, M.D., Dong-Wan Kim, M.D., Ph.D., Yi-Long Wu, M.D., Kazuhiko Nakagawa, M.D., Ph.D., Tarek Mekhail, M.D., Enriqueta Felip, M.D., Ph.D., Federico Cappuzzo, M.D., Jolanda Paolini, B.Sc., Tiziana Usari, B.Sc., Shrividya Iyer, Ph.D., Arlene Reisman, M.P.H., Keith D. Wilner, Ph.D., Jennifer Tursi, M.Sc., and Fiona Blackhall, M.D., Ph.D., for the PROFILE 1014 Investigators*

ABSTRACT

BACKGROUND

The efficacy of the ALK inhibitor crizotinib as compared with standard chemotherapy as first-line treatment for advanced *ALK*-positive non–small-cell lung cancer (NSCLC) is unknown.

METHODS

We conducted an open-label, phase 3 trial comparing crizotinib with chemotherapy in 343 patients with advanced *ALK*-positive nonsquamous NSCLC who had received no previous systemic treatment for advanced disease. Patients were randomly assigned to receive oral crizotinib at a dose of 250 mg twice daily or to receive intravenous chemotherapy (pemetrexed, 500 mg per square meter of body-surface area, plus either cisplatin, 75 mg per square meter, or carboplatin, target area under the curve of 5 to 6 mg per milliliter per minute) every 3 weeks for up to six cycles. Crossover to crizotinib treatment after disease progression was permitted for patients receiving chemotherapy. The primary end point was progression-free survival as assessed by independent radiologic review.

RESULTS

Progression-free survival was significantly longer with crizotinib than with chemotherapy (median, 10.9 months vs. 7.0 months; hazard ratio for progression or death with crizotinib, 0.45; 95% confidence interval [CI], 0.35 to 0.60; P<0.001). Objective response rates were 74% and 45%, respectively (P<0.001). Median overall survival was not reached in either group (hazard ratio for death with crizotinib, 0.82; 95% CI, 0.54 to 1.26; P=0.36); the probability of 1-year survival was 84% with crizotinib and 79% with chemotherapy. The most common adverse events with crizotinib were vision disorders, diarrhea, nausea, and edema, and the most common events with chemotherapy were nausea, fatigue, vomiting, and decreased appetite. As compared with chemotherapy, crizotinib was associated with greater reduction in lung cancer symptoms and greater improvement in quality of life.

CONCLUSIONS

Crizotinib was superior to standard first-line pemetrexed-plus-platinum chemotherapy in patients with previously untreated advanced *ALK*-positive NSCLC. (Funded by Pfizer; PROFILE 1014 ClinicalTrials.gov number, NCT01154140.)

From Peter MacCallum Cancer Centre, Melbourne, VIC, Australia (B.J.S.); State Key Laboratory of South China, Hong Kong Cancer Institute, Department of Clinical Oncology, Chinese University of Hong Kong, Shatin (T. Mok), and Guangdong Lung Cancer Institute, Guangzhou (Y.-L.W.) — both in China; Seoul National University Hospital, Seoul, South Korea (D.-W.K.); Kinki University, Osaka, Japan (K.N.); Florida Hospital Cancer Institute, Orlando (T. Mekhail); Vall d'Hebron Institute of Oncology, Vall d'Hebron University Hospital, Barcelona (E.F.); Istituto Toscano Tumori, Livorno (F.C.), and Pfizer Oncology, Milan (J.P., T.U., J.T.) — both in Italy; Pfizer Oncology (S.I.) and Pfizer Global Innovative Pharma Business (A.R.) — both in New York; Pfizer Oncology, La Jolla, CA (K.D.W.); and the Christie Hospital and Institute of Cancer Sciences, Manchester University, Manchester, United Kingdom (F.B.). Address reprint requests to Dr. Solomon at the Department of Medical Oncology, Peter MacCallum Cancer Centre, St. Andrew's Pl., East Melbourne, VIC 3002, Australia; or at ben.solomon@petermac.org.

*A complete list of the investigators in the PROFILE 1014 trial is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Solomon and Mok contributed equally to this article.

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Rearrangements of the anaplastic lymphoma kinase (*ALK*) gene are present in 3 to 5% of non–small-cell lung cancers (NSCLCs).[1,2] They define a distinct subgroup of NSCLC that typically occurs in younger patients who have never smoked or have a history of light smoking and that has adenocarcinoma histologic characteristics.[3-5]

Crizotinib is an oral small-molecule tyrosine kinase inhibitor of ALK, MET, and ROS1 kinases.[6] In phase 1 and 2 studies, crizotinib treatment resulted in objective tumor responses in approximately 60% of patients with *ALK*-positive NSCLC and in progression-free survival of 7 to 10 months.[7-9] In a randomized phase 3 trial involving patients with advanced *ALK*-positive NSCLC who had received previous platinum-based chemotherapy, crizotinib showed efficacy superior to that of single-agent second-line chemotherapy with either pemetrexed or docetaxel.[10] However, the efficacy of crizotinib as initial treatment for patients with newly diagnosed advanced *ALK*-positive NSCLC as compared with the existing standard-of-care, platinum-based double-agent chemotherapy,[11,12] is unknown.

We report the results of an ongoing international, multicenter, randomized, open-label, phase 3 study (PROFILE 1014) that compares crizotinib treatment with pemetrexed-plus-platinum chemotherapy with respect to efficacy, safety, and patient-reported outcomes in patients with previously untreated advanced *ALK*-positive NSCLC.

METHODS

PATIENTS

Patients were eligible for enrollment if they had histologically or cytologically confirmed locally advanced, recurrent, or metastatic nonsquamous NSCLC that was positive for an *ALK* rearrangement (as determined centrally with the use of a Vysis ALK Break Apart FISH Probe Kit [Abbott Molecular])[7,13] and if they had received no previous systemic treatment for advanced disease. Other eligibility criteria included an age of 18 years or older; measurable disease as assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1[14] (summarized in Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org); an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2 (on a scale of 0 to 5, with 0 indicating that the patient is asymptomatic and higher numbers indicating increasing disability)[15]; and adequate hepatic, renal, and bone marrow function (as defined in the study protocol). Patients with treated brain metastases were eligible if the metastases were neurologically stable for at least 2 weeks before enrollment and the patient had no ongoing requirement for glucocorticoids. All patients provided written informed consent before enrollment.

STUDY OVERSIGHT

The protocol was approved by the institutional review board or independent ethics committee at each participating center and complied with the International Ethical Guidelines for Biomedical Research Involving Human Subjects, Good Clinical Practice guidelines, the Declaration of Helsinki, and local laws. The study was designed by the sponsor (Pfizer) and by members of the PROFILE 1014 steering committee (see the Supplementary Appendix). The sponsor collected and analyzed the data in conjunction with the authors, all of whom had full access to the data. The manuscript was written by the first two authors, with medical writing support from ACUMED (Tytherington, United Kingdom, and New York) funded by the sponsor. All the authors vouch for the accuracy and completeness of the data and for the fidelity of this report to the study protocol. The protocol and statistical analysis plan are available at NEJM.org.

STUDY DESIGN AND TREATMENT

Patients were randomly assigned, in a 1:1 ratio, to receive oral crizotinib, at a dose of 250 mg twice daily, or intravenous chemotherapy (pemetrexed, at a dose of 500 mg per square meter of body-surface area, plus either cisplatin, at a dose of 75 mg per square meter, or carboplatin, target area under the curve of 5 to 6 mg per milliliter per minute) administered every 3 weeks for a maximum of six cycles. The choice of platinum chemotherapy was made by the investigator. Randomization was stratified according to ECOG performance status (0 or 1 vs. 2), Asian or non-Asian race, and presence or absence of brain metastases. Treatment was continued until RECIST-defined disease progression, development of unacceptable toxic effects, death, or withdrawal of consent. Continuation of crizotinib beyond disease progression was allowed for patients who had been randomly assigned to crizotinib if the patient was perceived by the investigator to be having clinical benefit.

Patients in the chemotherapy group who had disease progression as confirmed by independent radiologic review could cross over to crizotinib treatment if safety screening criteria were met.

The primary end point was progression-free survival (the time from randomization to RECIST-defined progression, as assessed by independent radiologic review, or death). Secondary end points included the objective response rate, overall survival, safety, and patient-reported outcomes.

ASSESSMENTS

Tumor assessment was performed during screening (within 28 days before randomization), every 6 weeks during treatment, and at the post-treatment follow-up visits (which were scheduled every 6 weeks) until RECIST-defined progression. For patients who crossed over to crizotinib treatment or continued crizotinib treatment beyond progression, assessments continued to be performed every 12 weeks. Brain or bone lesions that were detected at the time of screening were evaluated in all subsequent tumor assessments (i.e., every 6 weeks). In all patients, brain and bone scanning was repeated every 12 weeks to monitor for new lesions. All scans were submitted for central independent radiologic review by radiologists who were unaware of the group assignments.

Adverse events were classified and graded according to Common Terminology Criteria for Adverse Events, version 4.0. Patient-reported outcomes were assessed with the use of the European Organisation for Research and Treatment of Cancer (EORTC) quality-of-life core questionnaire (QLQ-C30),[16,17] the corresponding lung cancer module (QLQ-LC13),[18] and the EuroQol Group 5-Dimension Self-Report Questionnaire (EQ-5D).[19]

STATISTICAL ANALYSIS

We estimated that with 229 events of progression or death, the study would have 85% power to detect a 50% improvement in progression-free survival with crizotinib versus chemotherapy (from 6 months to 9 months), at a one-sided alpha level of 0.025. The prespecified number of events for the primary end point was reached in November 2013; the data cutoff date was November 30, 2013. Efficacy end points were measured in the intention-to-treat population, which included all patients who underwent randomization. The Kaplan–Meier method was used to estimate time-to-event end points. Two-sided log-rank tests stratified according to baseline stratification factors were used for between-group comparisons of progression-free survival and overall survival; stratified Cox regression models were applied to estimate hazard ratios. As prespecified in the protocol, overall survival was also analyzed with the rank-preserving structural failure time model[20-22] to explore the effect of crossover to crizotinib in the chemotherapy group. All analyses in the chemotherapy group, with the exception of the analysis of overall survival, included only data collected before crossover to crizotinib. We used a two-sided stratified Cochran–Mantel–Haenszel test to compare the objective response rate between treatment groups. Safety evaluations were performed in the as-treated population, which included all patients who received at least one dose of study medication. Safety results were not adjusted for the shorter duration of treatment in the chemotherapy group. Patient-reported outcomes were evaluated in patients in the intention-to-treat population who also had a baseline assessment and at least one post-baseline assessment. Additional details of the statistical methods are provided in the Supplementary Appendix.

RESULTS

PATIENTS

Between January 2011 and July 2013, a total of 343 patients underwent randomization — 172 to crizotinib and 171 to chemotherapy (intention-to-treat population) (Fig. S1 in the Supplementary Appendix). Three patients underwent randomization but received no study treatment, leaving 340 patients in the as-treated population — 171 patients in the crizotinib group and 169 in the chemotherapy group (with 91 patients receiving pemetrexed–cisplatin and 78 receiving pemetrexed–carboplatin). At the time of data cutoff, the median duration of follow-up for overall survival was 17.4 months for patients assigned to crizotinib and 16.7 months for those assigned to chemotherapy. The baseline characteristics in the intention-to-treat population were well balanced between the groups (Table 1).

EFFICACY

The median progression-free survival was 10.9 months (95% confidence interval [CI], 8.3 to 13.9) among patients in the crizotinib group, as compared with 7.0 months (95% CI, 6.8 to 8.2) among patients in the chemotherapy group (hazard ratio

Table 1. Baseline Characteristics in the Intention-to-Treat Population.*

Characteristic	Crizotinib (N=172)	Chemotherapy (N=171)
Age — yr		
Median	52	54
Range	22–76	19–78
Male sex — no. (%)	68 (40)	63 (37)
Race — no. (%)†		
White	91 (53)	85 (50)
Asian	77 (45)	80 (47)
Other	4 (2)	6 (4)
Smoking status — no. (%)		
Never smoked	106 (62)	112 (65)
Former smoker	56 (33)	54 (32)
Current smoker	10 (6)	5 (3)
Histologic characteristic of tumor — no. (%)		
Adenocarcinoma	161 (94)	161 (94)
Nonadenocarcinoma	11 (6)	10 (6)
ECOG performance status — no. (%)‡		
0 or 1	161 (94)	163 (95)
2	10 (6)	8 (5)
Extent of disease — no. (%)		
Locally advanced	4 (2)	3 (2)
Metastatic	168 (98)	168 (98)
Time since first diagnosis — mo		
Median	1.2	1.2
Range	0–114.0	0–93.6
Brain metastases present — no. (%)	45 (26)	47 (27)

* There were no significant differences between the groups in any of the characteristics listed in this table.
† Race was self-reported.
‡ The Eastern Cooperative Oncology Group (ECOG) performance status was assessed at the time of screening; the score was not reported for one patient in the crizotinib group. Scores range from 0 to 5, with higher scores indicating increasing disability; an ECOG performance status of 0 indicates that the patient is fully active, 1 that the patient is ambulatory but restricted in strenuous activity, and 2 that the patient is ambulatory and capable of self-care but is unable to work.

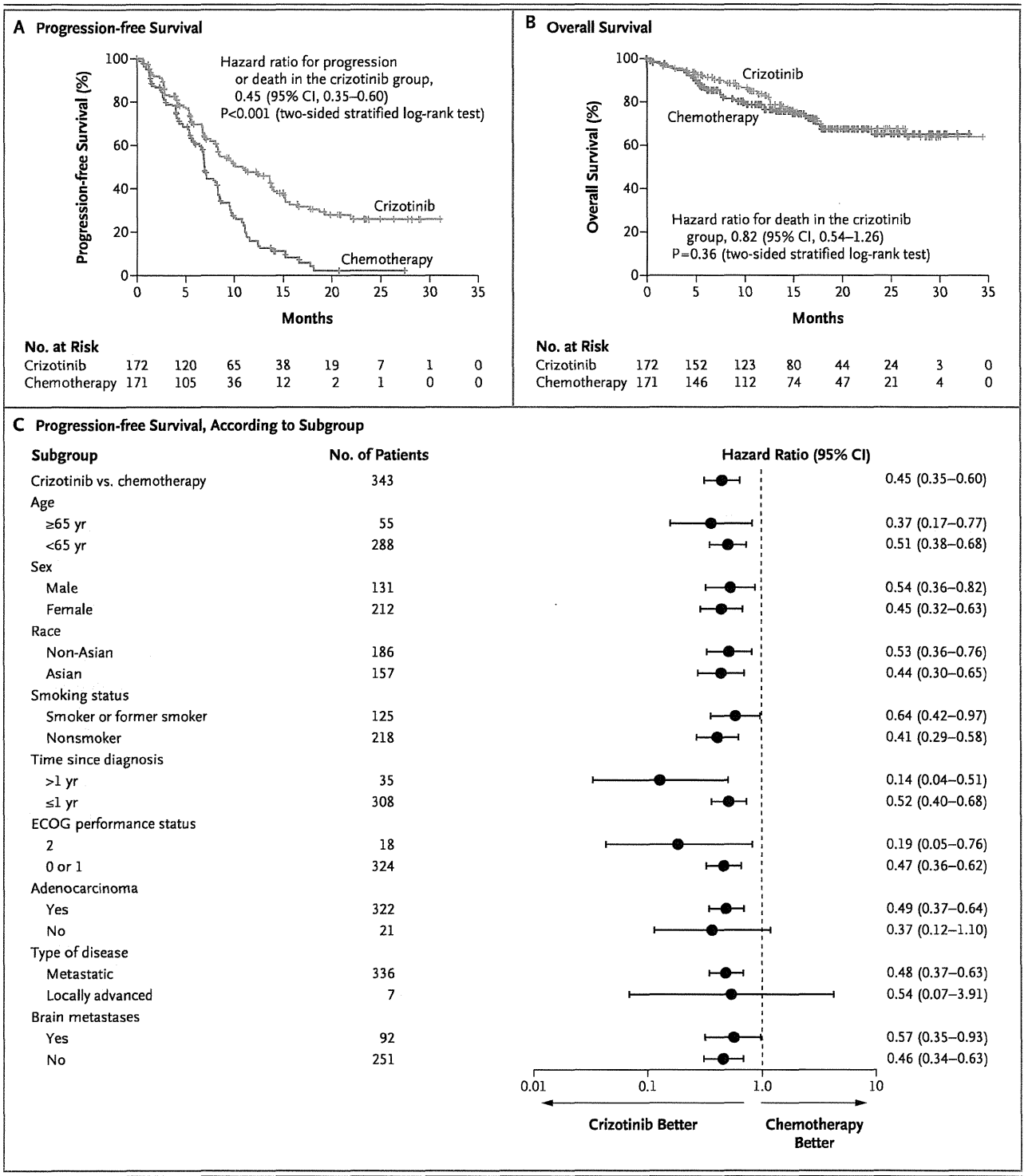
Figure 1 (facing page). Progression-free and Overall Survival.

Panel A shows Kaplan–Meier estimates of progression-free survival in the intention-to-treat population. There were 100 events of progression or death with crizotinib (89 progression events as assessed by independent radiologic review and 11 deaths without documented progression) and 137 events with chemotherapy (132 progression events as assessed by independent radiologic review and 5 deaths without documented progression). The median progression-free survival was 10.9 months with crizotinib as compared with 7.0 months with chemotherapy. The rate of progression-free survival at 18 months was 31% (95% CI, 23 to 39) in the crizotinib group and 5% (95% CI, 2 to 10) in the chemotherapy group. Panel B shows Kaplan–Meier estimates of overall survival in the intention-to-treat population. Because the rate of death from any cause at the time of data cutoff was relatively low (26%; 90 of the 343 patients who underwent randomization), the median overall survival was not reached in either group. Of the 171 patients randomly assigned to chemotherapy, 120 (70%) subsequently received crizotinib treatment. Of the 172 patients assigned to crizotinib, 21 (12%) subsequently received platinum-based chemotherapy. This analysis was not adjusted for crossover. Tick marks on the curves in Panels A and B indicate censoring of data. Panel C shows hazard ratios and 95% confidence intervals for the treatment effect on progression-free survival in subgroups of the intention-to-treat population defined according to prespecified stratification factors and baseline characteristics. Race was self-reported. Eastern Cooperative Oncology Group (ECOG) performance status scores range from 0 to 5, with higher scores indicating increasing disability; an ECOG performance status of 0 indicates that the patient is fully active, 1 that the patient is ambulatory but restricted in strenuous activity, and 2 that the patient is ambulatory and capable of self-care but is unable to work. Data for ECOG performance status were missing for 1 patient.

for progression or death with crizotinib, 0.45; 95% CI, 0.35 to 0.60; P<0.001) (Fig. 1A). The hazard ratio favored crizotinib across most subgroups defined according to stratification factors and other baseline characteristics (Fig. 1C).

The objective response rate was significantly higher with crizotinib than with chemotherapy (74% [95% CI, 67 to 81] vs. 45% [95% CI, 37 to 53], P<0.001) (Table 2). The median duration of response was 11.3 months and 5.3 months, respectively. The best percentage change from baseline in target lesions and the best overall response in individual patients are shown in Figure S2 in the Supplementary Appendix. Intracranial lesions progressed or new intracranial lesions developed in 25 patients in the crizotinib group and in 26 patients in the chemotherapy group (15% each).

There was no significant difference in overall survival between patients in the crizotinib group and those in the chemotherapy group at the time of the progression-free survival analysis (hazard ratio for death with crizotinib, 0.82; 95% CI, 0.54 to 1.26; P=0.36) (Fig. 1B) — probably owing to the relatively low rate of death from any cause



(26%; 90 of the 343 patients who underwent randomization) and the fact that 70% of the patients in the chemotherapy group crossed over to crizotinib treatment. The probability of 1-year survival was 84% (95% CI, 77 to 89) in the crizotinib group and 79% (95% CI, 71 to 84) in the chemotherapy group. After adjustment for crossover with the rank-preserving structural failure time model, the hazard ratio for death with crizotinib was 0.60 (95% CI, 0.27 to 1.42) as calcu-

Table 2. Response to Treatment in the Intention-to-Treat Population.*

Response	Crizotinib (N=172)	Chemotherapy (N=171)
Type of response — no. (%)		
Complete response	3 (2)	2 (1)
Partial response	125 (73)	75 (44)
Stable disease	29 (17)	63 (37)
Progressive disease	8 (5)	21 (12)
Could not be evaluated†	7 (4)	10 (6)
Objective response rate — % (95% CI)‡	74 (67–81)	45 (37–53)
Time to response — mo§		
Median	1.4	2.8
Range	0.6–9.5	1.2–8.5
Duration of response — mo¶		
Median	11.3	5.3
95% CI	8.1–13.8	4.1–5.8

* Tumor responses were assessed with the use of Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, and were confirmed by independent radiologic review.

† Responses could not be evaluated in 4 patients in each group because of early death.

‡ P<0.001 for the comparison between the two groups. The 95% confidence interval was calculated with the use of the exact method based on the F distribution.

§ The time to tumor response was calculated from the date of randomization to the date of the first documentation of a partial or complete response as determined by independent radiologic review.

¶ The duration of response was calculated from the date of the first documentation of a partial or complete response to the date of RECIST-defined progression or death, with the use of the Kaplan–Meier method.

lated with the Wilcoxon test (Fig. S3A in the Supplementary Appendix) and 0.67 (95% CI, 0.28 to 1.48) as calculated with the log-rank test (Fig. S3B in the Supplementary Appendix), indicating that crossover may have confounded the results of the primary overall survival analysis.

Among patients randomly assigned to crizotinib, 74 of 89 patients with progressive disease (83%) continued to receive crizotinib beyond disease progression for a median of 3.0 months (range, 0.7 to 22.6). A total of 21 patients assigned to crizotinib (12%) subsequently received platinum-based chemotherapy. At data cutoff, 79 patients who had been randomly assigned to crizotinib (46%) and 62 patients assigned to chemotherapy who had crossed over to crizotinib (36%) were still receiving crizotinib therapy. Eighteen patients in the chemotherapy group who had progressive disease did not receive follow-up therapy with crizotinib; additional details are provided in the Supplementary Appendix. Other systemic therapies received during follow-up are listed in Table S2 in the Supplementary Appendix. The baseline characteristics of the patients and the efficacy outcomes in subgroup analyses of crizotinib versus individual chemotherapy regimens were similar to those in the analysis of the overall population (Table S3 and Fig. S4 in the Supplementary Appendix).

SAFETY AND ADVERSE EVENTS

The median duration of treatment was 10.9 months (range, 0.4 to 34.3) in the crizotinib group (a median of 16 cycles started [range, 1 to 50]) and 4.1 months (range, 0.7 to 6.2) in the chemotherapy group (a median of 6 cycles of chemotherapy started [range, 1 to 6]). The most common adverse events of any cause for which the incidence was at least 5 percentage points higher in the crizotinib group than in the chemotherapy group were vision disorder (occurring in 71% of the patients), diarrhea (in 61%), and edema (in 49%); and the events for which the incidence was at least 5 percentage points higher in the chemotherapy group than in the crizotinib group were fatigue (occurring in 38% of the patients), anemia (in 32%), and neutropenia (in 30%) (Table 3). Most adverse events in the two treatment groups were grade 1 or 2 in severity. Grade 3 or 4 elevations of aminotransferase levels occurred in 24 patients in the crizotinib group (14%) and in 4 patients in the chemotherapy group (2%), but these elevations were managed primarily with dose interruptions or dose reductions. Four hepatic events resulted in permanent discontinuation of treatment in the crizotinib group: three events involved elevated aminotransferase levels only (one event of grade 3 elevation of both alanine and aspartate aminotransferase levels and one event each of grade 2 and grade 3 elevation of the alanine aminotransferase level), and one event involved a grade 2 drug-induced liver injury that met the criteria for Hy's law[23] (elevated aminotransferase and total bilirubin levels without evidence of cholestasis [i.e., no elevated serum alkaline phosphatase level]) (see the Supplementary Appendix). An additional case that met the criteria for Hy's law occurred in a patient in the chemotherapy group after crossover to crizotinib. No deaths from hepatic dysfunction occurred. Grade 3 or 4 neutropenia occurred in 11% of patients in the

Table 3. Adverse Events from Any Cause in the As-Treated Population.*

Adverse Event	Crizotinib (N=171)		Chemotherapy (N=169)†	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
Higher frequency in crizotinib group				
Vision disorder‡	122 (71)	1 (1)	16 (9)	0
Diarrhea	105 (61)	4 (2)	22 (13)	1 (1)
Edema§	83 (49)	1 (1)	21 (12)	1 (1)
Vomiting	78 (46)	3 (2)	60 (36)	5 (3)
Constipation	74 (43)	3 (2)	51 (30)	0
Elevated aminotransferases§	61 (36)	24 (14)	22 (13)	4 (2)
Upper respiratory infection§	55 (32)	0	21 (12)	1 (1)
Abdominal pain§	45 (26)	0	20 (12)	0
Dysgeusia	45 (26)	0	9 (5)	0
Headache	37 (22)	2 (1)	25 (15)	0
Pyrexia	32 (19)	0	18 (11)	1 (1)
Dizziness§	31 (18)	0	17 (10)	2 (1)
Pain in extremity	27 (16)	0	12 (7)	0
Higher frequency in chemotherapy group				
Fatigue	49 (29)	5 (3)	65 (38)	4 (2)
Neutropenia§	36 (21)	19 (11)	51 (30)	26 (15)
Stomatitis§	24 (14)	1 (1)	34 (20)	2 (1)
Asthenia	22 (13)	0	41 (24)	2 (1)
Anemia§	15 (9)	0	54 (32)	15 (9)
Leukopenia§	12 (7)	3 (2)	26 (15)	9 (5)
Thrombocytopenia§	2 (1)	0	31 (18)	11 (7)
Similar frequency in the two treatment groups				
Nausea	95 (56)	2 (1)	99 (59)	3 (2)
Decreased appetite	51 (30)	4 (2)	57 (34)	1 (1)
Cough§	39 (23)	0	33 (20)	0
Neuropathy§	35 (20)	2 (1)	38 (22)	0
Dyspnea§	30 (18)	5 (3)	26 (15)	4 (2)

* Adverse events are listed here if they were reported in 15% or more of patients in either treatment group; rates were not adjusted for differences in treatment duration. Higher frequency indicates a difference of 5 percentage points or more between groups; similar frequency indicates a difference of less than 5 percentage points between groups.

† Only events that occurred before crossover to crizotinib are included.

‡ The category of vision disorder comprised a cluster of adverse events including (in descending order of frequency in the crizotinib group) visual impairment, photopsia, blurred vision, vitreous floaters, reduced visual acuity, diplopia, and photophobia.

§ This item comprised a cluster of adverse events that may represent similar clinical symptoms or syndromes.

crizotinib group and in 15% in the chemotherapy group, with no cases of febrile neutropenia reported with crizotinib and two with chemotherapy. Other grade 3 or 4 adverse events from any cause are shown in Table S4 in the Supplementary Appendix. Two patients (1%) in the crizotinib group had interstitial lung disease, resulting in permanent discontinuation of crizotinib treatment.

Adverse events from any cause that were associated with permanent discontinuation of treatment occurred in 12% of the patients in the

crizotinib group and in 14% of those in the chemotherapy group (before crossover); the corresponding rates of adverse events deemed by the investigator to be related to treatment that were associated with permanent discontinuation were 5% and 8%. One case of fatal pneumonitis, considered to be related to crizotinib treatment, occurred in a patient who had crossed over from chemotherapy. Grade 5 adverse events of any cause are shown in Table S5 in the Supplementary Appendix. With the exception of the fatal pneumonitis, described above, that occurred after crossover to crizotinib, no deaths were reported that were deemed by the investigators to be related to treatment.

PATIENT-REPORTED OUTCOMES

Baseline scores on the QLQ-C30, QLQ-LC13, and EQ-5D are summarized in Table S6 in the Supplementary Appendix. There was a significantly greater overall improvement from baseline in global quality of life among patients who received crizotinib than among those who received chemotherapy ($P<0.001$) (Fig. 2A, and see the Results section in the Supplementary Appendix for additional details). Crizotinib was also associated with a significantly greater overall improvement from baseline in physical, social, emotional, and role functioning domains ($P<0.001$) (Fig. 2A).

There was a significantly greater overall reduction from baseline with crizotinib than with chemotherapy in the symptoms of pain, dyspnea, and insomnia as assessed with the use of the QLQ-C30 (Fig. 2B) and in the symptoms of dyspnea, cough, chest pain, arm or shoulder pain, and pain in other parts of the body as assessed with the use of the QLQ-LC13 (Fig. 2C) ($P<0.001$ for all comparisons) (see the Results section in the Supplementary Appendix for additional details). Patients treated with crizotinib also had a significantly greater delay in the worsening of lung-cancer symptoms (a composite of cough, dyspnea, or pain in the chest) than did patients treated with chemotherapy (hazard ratio for worsening of symptoms with crizotinib, 0.62; 95% CI, 0.47 to 0.80; $P=0.002$; estimated probability of being event-free at 6 months, 38% vs. 22%) (Fig. S5 in the Supplementary Appendix). A significantly greater improvement from baseline was observed in EQ-5D general health status scores (as assessed with the use of a visual-analogue scale) with crizotinib than with chemotherapy ($P=0.002$).

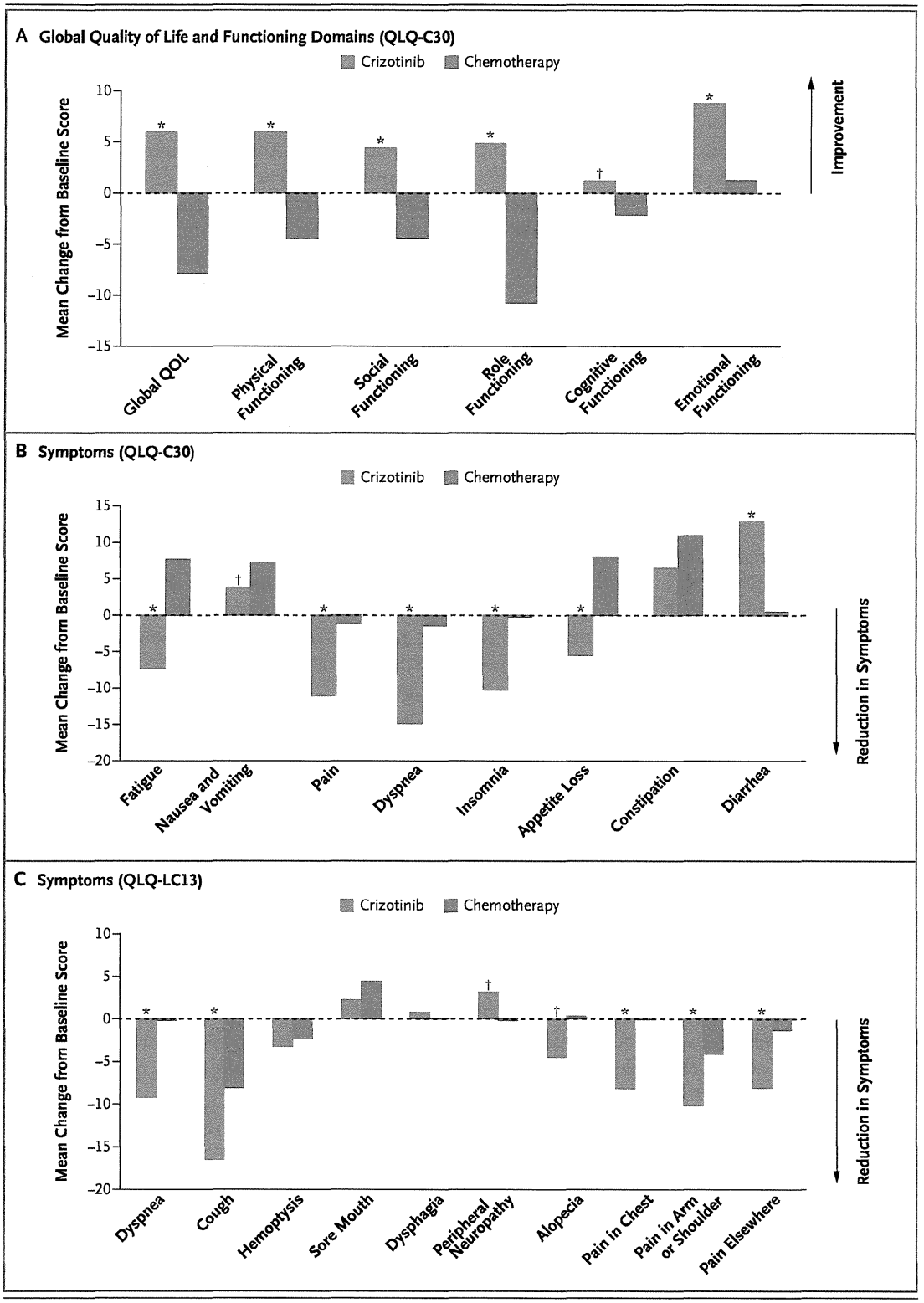
Figure 2 (facing page). Overall Change from Baseline in Global Quality of Life, Functioning Domains, and Symptoms.

Panel A shows the overall change from baseline in global quality of life (QOL) and functioning domains as assessed with the use of the European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire (QLQ-C30). Panels B and C show the overall change from baseline in symptoms as assessed with the QLQ-C30 and the corresponding module for lung cancer (QLQ-LC13), respectively. Patient-reported outcomes were assessed at baseline, on days 7 and 15 of cycle 1, on day 1 of every subsequent cycle, and at the end of treatment. Scores on each scale ranged from 0 to 100. For global quality of life and functioning domains, higher scores indicate better global quality of life or functioning, and hence positive changes (upward bars) indicate improvement from baseline; for symptoms, higher scores indicate greater severity of symptoms, and hence negative changes (downward bars) indicate improvement from baseline. A change of 10 points or more is considered to be a clinically meaningful change. An asterisk indicates $P<0.001$, and a dagger $P<0.05$ for the comparison between treatment groups. In Panel C, the mean changes from the baseline score in dysphagia and in pain in the chest with chemotherapy were 0.10 and −0.05, respectively.

DISCUSSION

This study showed the superiority of first-line therapy with crizotinib over pemetrexed-plus-platinum chemotherapy in patients with previously untreated advanced *ALK*-positive NSCLC. Initial treatment with crizotinib significantly prolonged progression-free survival as compared with chemotherapy consisting of pemetrexed plus cisplatin or carboplatin. These results were independent of the type of platinum treatment administered, the performance status of the patient, the patient's race, and the presence or absence of brain metastases. Crizotinib treatment was also associated with a significantly higher response rate and significantly greater improvements in patient-reported measures of physical functioning, key lung-cancer symptoms (cough, dyspnea, chest pain, and fatigue), and global quality of life.

The standard of care for newly diagnosed NSCLC has generally been platinum-based double-agent chemotherapy,[11] except in the case of NSCLC that is positive for an epidermal growth



factor receptor (*EGFR*) mutation, for which randomized trials have shown superior efficacy of EGFR tyrosine kinase inhibitors over chemotherapy.[24-28] For tumors with nonsquamous histologic characteristics, cisplatin–pemetrexed has been shown to be superior to cisplatin–gemcitabine.[12]

Given that most advanced *ALK*-positive NSCLCs have nonsquamous histologic characteristics, pemetrexed in combination with cisplatin or carboplatin was selected as the standard chemotherapy for this trial. The efficacy of pemetrexed-based first-line chemotherapy has since been documented in *ALK*-positive NSCLC,[29,30] a finding that supports this selection. A potential limitation of our study was that pemetrexed was not continued beyond the planned six cycles of pemetrexed-plus-platinum chemotherapy, since this was not considered to be a standard approach when the study was initiated. However, in a study of patients without disease progression after four cycles of cisplatin–pemetrexed, maintenance pemetrexed therapy improved median progression-free survival over placebo by only 1.3 months (4.1 months vs. 2.8 months) from the start of maintenance therapy.[31] The way in which the use of maintenance pemetrexed therapy or other chemotherapy regimens would have affected the results in the control group of the current study is unclear.

The magnitude of the improvement in progression-free survival observed in the current study is similar to that observed in studies of *EGFR*-mutation–positive tumors treated with first-line EGFR tyrosine kinase inhibitors.[24-26] Although formal comparison across studies cannot be made, the efficacy of crizotinib in the first-line setting (median progression-free survival, 10.9 months; objective response rate, 74%) appeared to be greater than that seen with crizotinib in an otherwise similar patient population that had received previous treatment with platinum-based chemotherapy (median progression-free survival, 7.7 months; response rate, 65%).[10] Initiating crizotinib as first-line therapy in patients whose tumors test positive for *ALK* rearrangements maximizes the probability that these patients will benefit from ALK-directed therapy.

Overall survival did not differ significantly between the treatment groups at the time of this analysis, with a relatively small number of deaths reported (26%; 90 of the 343 patients who underwent randomization). As seen in randomized phase 3 studies of first-line EGFR tyrosine kinase inhibitors versus chemotherapy in *EGFR*-mutation–positive NSCLC, this finding is most likely attributable to the confounding effects of crossover treatment.[32] Of the 171 patients randomly assigned to chemotherapy, 120 received crizotinib treatment during follow-up for survival. It should be noted that the median survival had not been reached in either group, with a median follow-up of 17 months.

The safety profile of crizotinib was consistent with that reported earlier in patients with previously treated advanced *ALK*-positive NSCLC[10] and differed from that observed with chemotherapy. The incidence of adverse effects in the two treatment groups was probably affected by the fact that the duration of therapy with crizotinib was longer than that with chemotherapy and that crizotinib continued to be used in some patients beyond progression.[33] Discontinuations of therapy occurred in 5% of patients with crizotinib-related adverse events and in 8% of patients with chemotherapy-related adverse events. More serious potential adverse events previously reported with crizotinib were hepatotoxic and pulmonary toxic effects.[10] In the current study, grade 3 or 4 elevations of aminotransferase levels occurred in 14% of the patients in the crizotinib group and could be managed with dose interruptions or dose reductions. Two patients discontinued crizotinib therapy because of interstitial lung disease, and one case of fatal pneumonitis was reported in a patient who had crossed over from chemotherapy to crizotinib.

In conclusion, in patients with previously untreated *ALK*-positive NSCLC, crizotinib treatment was superior to pemetrexed-plus-platinum chemotherapy with respect to progression-free survival, objective response rate, reduction of lung-cancer symptoms, and improvement in quality of life.

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Tolerability of Nintedanib (BIBF 1120) in Combination with Docetaxel: A Phase 1 Study in Japanese Patients with Previously Treated Non–Small-Cell Lung Cancer

Isamu Okamoto, MD, PhD,† Masaki Miyazaki, MD, PhD,*‡ Masayuki Takeda, MD, PhD,* Masaaki Terashima, MD, PhD,*§ Koichi Azuma, MD, PhD,*‖ Hidetoshi Hayashi, MD, PhD,*¶ Hiroyasu Kaneda, MD, PhD,* Takayasu Kurata, MD, PhD,*# Junji Tsurutani, MD, PhD,* Takashi Seto, MD, PhD,** Fumihiko Hirai, MD, PhD,** Koichi Konishi, BPharm,†† Akiko Sarashina, MSc,‡‡ Nobutaka Yagi, MSc,†† Rolf Kaiser, MD,§§ and Kazuhiko Nakagawa, MD, PhD**

Background: This phase I, open-label study evaluated the safety/tolerability and maximum tolerated dose of second-line nintedanib combined with docetaxel in Japanese patients with advanced non–small-cell lung cancer.

Methods: Eligible patients received docetaxel 60 or 75 mg/m^2 (day 1) plus nintedanib 100, 150, or 200 mg twice daily (bid; days 2–21) in 21-day cycles. Standard 3 + 3 dose escalations were performed separately in patient cohorts with a body surface area (BSA) of less than 1.5 m^2 (BSA <1.5) and BSA greater than or equal to 1.5, respectively.

Results: Forty-two patients (17 BSA <1.5, 25 BSA ≥1.5) were treated. The maximum tolerated dose of nintedanib was 150 and 200 mg bid in patients with BSA less than 1.5 and BSA greater than or equal to 1.5 (BSA ≥1.5), respectively, in combination with 75 mg/m^2 of docetaxel. Dose-limiting toxicities (all grade 3 hepatic enzyme elevations) occurred in 12 patients (six per cohort). Drug-related adverse events included neutropenia (95%), leukopenia (83%), fatigue (76%), alopecia (71%), decreased appetite (67%), and elevations in alanine aminotransferase (64%) and aspartate aminotransferase (64%). All hepatic enzyme elevations were reversible and manageable with dose reduction or discontinuation. Among 38 evaluable patients, 10 (26%) had a partial response and 18 (47%) had stable disease.

Conclusion: Continuous treatment with second-line nintedanib combined with docetaxel was manageable and showed promising signs of efficacy in Japanese patients with advanced non–small-cell lung cancer.

Key Words: Clinical trials, Phase I, Docetaxel, Japanese, Nintedanib, Non–small-cell lung cancer, Pharmacokinetics.

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Few treatment options are available for patients with advanced non–small-cell lung cancer (NSCLC) who fail first-line chemotherapy. Currently, the only licensed second-line therapies for individuals with NSCLC, who do not harbor identifiable driver oncogenes, such as sensitizing epidermal growth factor receptor (*EGFR*) gene mutations or anaplastic lymphoma kinase (*ALK*) gene translocations, are docetaxel, gemcitabine, pemetrexed (for nonsquamous NSCLC), and erlotinib.[1] Although these treatments are efficacious, survival benefits are modest. Hence, there is an urgent need for effective and well-tolerated second-line options.

Angiogenesis plays an important role in the development and differentiation of NSCLC.[2] Targeting vascular endothelial growth factor (VEGF) signaling appears to be particularly important in advanced NSCLC, given the proven efficacy of the VEGF-targeted monoclonal antibody bevacizumab as first-line therapy in large-scale trials.[3,4] However, to date no oral tyrosine kinase inhibitors of VEGF receptors have been approved for the treatment of advanced NSCLC. Mechanisms that support solid tumor angiogenesis include VEGF, fibroblast growth factor, and platelet-derived growth factor signaling pathways.[5–8] Nintedanib (BIBF 1120) is a potent, oral, small-molecule triple angiokinase inhibitor that targets VEGF receptors 1 to 3, platelet-derived growth factor

*Department of Medical Oncology, Kinki University Faculty of Medicine, Osaka, Japan; †Center for Clinical and Translational Research, Faculty of Medicine, Kyusyu University Hospital, Fukuoka, Japan; ‡Department of Internal Medicine, Suita Municipal Hospital, Osaka, Japan; §Department of Medical Oncology, Nara Hospital, Kinki University Faculty of Medicine, Nara, Japan; ‖Department of Medicine, Division of Respirology, Neurology, and Rheumatology, Kurume University Hospital, Fukuoka, Japan; ¶Department of Medical Oncology, Kishiwada Municipal Hospital, Osaka, Japan; #Department of Thoracic Oncology, Kansai Medical University, Hirakata Hospital, Osaka, Japan; **Department of Medical Oncology, National Kyushu Cancer Centre, Fukuoka, Japan; ††Department of Medical Oncology, National Kyushu Cancer Centre, Fukuoka, Japan; ‡‡Nippon Boehringer Ingelheim Co. Ltd., Medical Development Division, Hyogo, Japan; and §§Clinical Pharmacokinetics/Pharmacodynamics Department, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany.

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Address for correspondence: Isamu Okamoto, MD, PhD, Center for Clinical and Translational Research, Kyushu University Hospital, 3-1-1 Maidashi, Higashiku, Fukuoka 812-8582, Japan. E-mail: okamotoi@kokyu.med.kyushu-u.ac.jp

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receptors alpha and beta, and fibroblast growth factor receptors 1 to 3, besides RET and Flt3.[9] Preclinical experiments have shown that nintedanib can delay tumor growth and inhibit angiogenesis in various xenograft models of human cancer, including NSCLC.[9] More recently, the global LUME-Lung 1 phase III trial (Study 1199.13; NCT00805194) for previously treated advanced NSCLC demonstrated that treatment with a combination of nintedanib and docetaxel produced a significant and clinically meaningful improvement in overall survival compared with docetaxel and placebo in predefined patients with adenocarcinoma tumor histology.[10]

In a recent Japanese phase I study, the maximum tolerated dose (MTD) of nintedanib monotherapy was 200 mg bid, which is lower than the MTD of 250 mg bid for Caucasian patients.[11,12] Although the reason for this difference remains unclear, analogous differences in the tolerability of chemotherapy for advanced NSCLC between Japanese and US patients have been reported previously, and have been related to differences in genotypic variants between the two populations.[13] In addition, the standard dose of docetaxel 60 mg/m^2 commonly employed for Japanese patients with advanced NSCLC[14] is lower than the 75 mg/m^2 dose used for Western populations.[10,15] This phase I dose-escalation study (Study 1199.29; NCT00876460) was conducted to define the MTD of nintedanib combined with docetaxel, and to confirm the safety/tolerability profile of the combination in Japanese patients with advanced NSCLC following failure of first-line platinum-based chemotherapy.

PATIENTS AND METHODS

Study Population

Patients aged 20 to 74 years with histologically or cytologically confirmed, advanced stages IIIB to IV or recurrent NSCLC (any histology) who had received one platinum-based chemotherapy regimen (not containing docetaxel) were enrolled. Patients had an Eastern Cooperative Oncology Group performance status of 0 to 1, a life expectancy exceeding 3 months, and adequate organ function. Exclusion criteria included: active brain metastases; gastrointestinal disorders that could interfere with the absorption of the study drug; history of major thrombotic or clinically relevant major bleeding event in the past 6 months; clinically significant hemoptysis in the past 3 months; active multiple primary neoplasms; or significant cardiovascular disease.

Study Design

This open-label trial utilized a standard 3 + 3 dose-escalation design. Eligible patients received intravenous docetaxel at a dose of 60 mg/m^2 or 75 mg/m^2 on day 1, followed by continuous, oral nintedanib bid on days 2 to 21 in 21-day cycles. Nintedanib was started at a dose of 100 mg bid and escalated up to 200 mg bid in 50 mg bid intervals. Continuous nintedanib monotherapy was permitted in cases where docetaxel had to be permanently discontinued for reasons other than progression, and the patient had already received at least four treatment cycles of combination therapy.

Dose-limiting toxicity (DLT) was defined as nonhematologic toxicity greater than Common Terminology Criteria for Adverse Events (CTCAE) grade 3, excluding electrolyte abnormalities or isolated elevations of γ-glutamyl transpeptidase (γ-GT); grade 3 or higher gastrointestinal toxicity or hypertension despite optimal supportive care/intervention; grade 4 neutropenia for more than 7 days despite optimal supportive care; grade 4 febrile neutropenia of any duration; grade 2 or higher alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) elevations combined with grade 2 or higher bilirubin elevations; inability to resume nintedanib dosing within 14 days of stopping treatment due to treatment-related toxicity. DLTs observed in the first 21 days of treatment were used to determine MTD, defined as the highest dose at which incidence of DLTs in cycle 1 was less than or equal to 33.3%.

After testing nintedanib 100 mg bid plus docetaxel 60 mg/m^2 (N100/D60), nintedanib 150 mg bid plus docetaxel 60 mg/m^2 (N150/D60), and nintedanib 200 mg bid plus docetaxel 60 mg/m^2 (N200/D60) without considering body surface area (BSA), dose escalations were performed separately in two patient cohorts with a BSA of less than 1.5 m^2 (BSA <1.5) and greater than or equal to 1.5 m^2 (BSA ≥1.5), respectively. This protocol amendment was recommended by the external Efficacy and Safety Review Committee following early observation of a high incidence of DLTs in patients with a BSA of less than 1.5 m^2.

The institutional review board reviewed and approved the protocol and its amendments. The trial was conducted in compliance with the study protocol, the Declaration of Helsinki, and Good Clinical Practice guidelines. All patients provided written informed consent.

Assessments

Adverse events (AEs) were assessed according to CTCAE version 3.0 throughout the trial and for 28 days after treatment cessation. All safety analyses were undertaken in patients who had received 1 dose or more of nintedanib. Objective tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST 1.0). Tumor assessment was performed at screening and every 6 weeks on day 1 (within 7 days) of each odd-numbered treatment cycle (cycles 3, 5, etc.). Hematology and biochemistry assessments were undertaken at screening and at predefined intervals during the trial.

To investigate the possible effect of nintedanib on the pharmacokinetics (PK) of docetaxel, blood samples were taken predose and 1, 1.5, 2, 3, 4, 7, 24, and 48 hours postdose on days 1 to 3 of cycles 1 and 2. Sampling for PK characterization of nintedanib was carried out on days 2 to 3 of cycle 1, with samples taken predose, 1, 2, 3, 4, 6, 7, 10, and 24 hours after the morning dose. Samples for evaluation of trough concentrations of nintedanib were taken on days 8 and 15 of the first two cycles, and on days 1 to 3 during cycle 2, before the morning dose. All PK analyses were carried out using WinNonlin software, applying a noncompartmental approach.

Statistical Analysis

The primary end points were the determination of the MTD of nintedanib in combination with docetaxel at doses

of 60 or 75 mg/m^2, and the assessment of the frequency and severity of AEs. Secondary end points included PKs of nintedanib and docetaxel, best tumor response and progression-free survival (PFS). Descriptive statistics are presented.

RESULTS

Patients

A total of 43 patients with advanced NSCLC were enrolled into this study from March 2009 to August 2012. One patient discontinued due to a non-DLT adverse event before the first dose of nintedanib was administered and was excluded from the study. Baseline characteristics, except for gender and clinical stage, were similar between the two BSA cohorts (Table 1).

At the time of the database lock (June 11, 2013), all 42 patients had discontinued combination treatment. Reasons for discontinuation included progressive disease (n = 22), AEs (n = 14), and withdrawal of consent (n = 3). Three patients continued to be treated with nintedanib monotherapy after discontinuation of docetaxel due to drug-related AEs (grade 1 and 2 peripheral neuropathy in two patients, and grade 2 pleural effusion in one patient). Median (range) number of days of treatment administered was 126.5 (7–1339).

Maximum Tolerated Dose and Dose-Limiting Toxicities

The allocation of patients to treatment during the study is summarized in Figure 1. Of the 42 patients who received nintedanib treatment, three patients were excluded from the DLT assessment due to low compliance with study treatment: one excluded patient had a non-DLT adverse event,

TABLE 1. Patient Characteristics at Baseline and Treatment Allocation

	Patients with BSA <1.5 m^2 (n = 17)	Patients with BSA ≥1.5 m^2 (n = 25)	All Patients (n = 42)
Age, years			
Median (range)	65 (45–72)	62 (47–73)	64 (45–73)
Gender, n (%)			
Male	6 (35)	23 (92)	29 (69)
Female	11 (65)	2 (8)	13 (31)
ECOG performance score, n (%)			
0	6 (35)	8 (32)	14 (33)
1	11 (65)	17 (68)	28 (67)
Clinical stage, n (%)			
IIIB	1 (6)	6 (24)	7 (17)
IV	16 (94)	19 (76)	35 (83)
Histology, n (%)			
Adenocarcinoma	14 (82)	19 (76)	33 (79)
Squamous cell carcinoma	3 (18)	5 (20)	8 (19)
Large-cell carcinoma	0	1 (4)	1 (2)

bid, twice daily; BSA, body surface area; D, docetaxel; DLT, dose-limiting toxicity; ECOG, Eastern Cooperative Oncology Group; N, nintedanib.

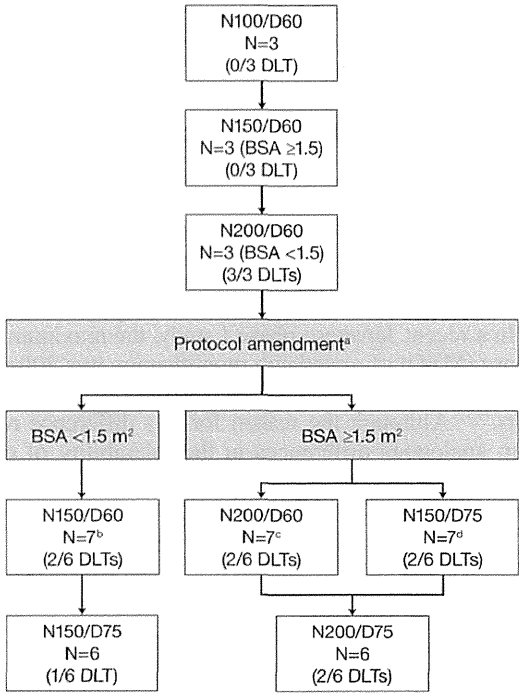

FIGURE 1. Patient flow. N100/D60, nintedanib 100 mg bid plus docetaxel 60 mg/m^2; N150/D60, nintedanib 150 mg bid plus docetaxel 60 mg/m^2; N150/D75, nintedanib 150 mg bid plus docetaxel 75 mg/m^2; N200/D60, nintedanib 200 mg bid plus docetaxel 60 mg/m^2; N200/D75, nintedanib 200 mg bid plus docetaxel 75 mg/m^2. [a]Protocol amendment by the Efficacy and Safety Review Committee, which recommended separate assessments of dose levels for patients with a body surface area (BSA) <1.5 m^2 and ≥1.5 m^2. [b]One patient was replaced due to low compliance with study drugs administration with a non-dose-limiting toxicity adverse event (pneumonia). [c]One patient was replaced due to insufficient data to evaluate the duration of grade 4 neutropenia as a dose-limiting toxicity. [d]One patient was replaced due to early withdrawal of consent.

the second patient withdrew consent before the completion of cycle 1, and there were insufficient data to confirm a DLT occurrence in the third patient. Three patients were enrolled in the N100/D60 cohort, three patients in the N150/D60 cohort, and three patients in the N200/D60 cohort, without consideration of their BSA. No DLT was observed for the first and second cohorts (N100/D60 and N150/D60). At 200 mg bid (N200/D60), all three patients experienced DLTs (ALT, AST, and γ-glutamytranferase increases in two patients, and ALT and AST increase in one patient) that were fully reversible (Table 2). All three patients who experienced DLTs at N200/D60 had BSA less than 1.5, whereas the three patients treated with N150/D60 who did not experience DLTs had BSA greater than or equal to 1.5. In a previous investigation of nintedanib monotherapy in Japanese patients,[11] all DLTs at 200 mg bid were observed in patients whose BSAs were smaller than those of patients without observed DLTs. The external Efficacy and Safety Review Committee recommended the protocol amendments for reassessment of

TABLE 2. Observed Dose-Limiting Toxicities in Treatment Cycle 1 at Each Nintedanib Dose Level Among Evaluable Patients with BSA <1.5 m^2 or BSA ≥1.5 m^2

Cohort	Nintedanib Dose (mg bid)	Docetaxel Dose (mg/m^2)	No. of DLTs/Patients[a]	Nature of DLT
—	100	60	0/3[b]	—
BSA <1.5m^2	150	60	2/6	(1) ALT and AST elevation; (2) ALT elevation
		75	1/6	(1) ALT and AST elevation
	200	60	3/3	(1) ALT, AST, and γ-GT elevation; (2) ALT, AST, and γ-GT elevation; (3) ALT and AST elevation
BSA ≥1.5m^2	150	60	0/3	—
		75	2/6	(1) ALT and γ-GT elevation; (2) ALT elevation
	200	60	2/6	(1) ALT, AST and γ-GT elevation; (2) ALT and γ-GT elevation
		75	2/6	(1) ALT, AST, and γ-GT elevation; (2) ALT elevation

[a]Patients eligible for evaluation of dose-limiting toxicity.
[b]BSA in 100 mg bid group: <1.5 m^2, $n = 1$; ≥1.5 m^2, $n = 2$.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; bid, twice daily; BSA, body surface area; DLT, dose-limiting toxicity; γ-GT, gamma glutamyltransferase.

the N150/D60 dose in patients with BSA less than 1.5, and for subsequent dose escalations to be performed separately for cohorts with BSA less than 1.5 and BSA greater than or equal to 1.5, respectively.

As shown in Table 2, of 12 patients with BSA less than 1.5 treated in the N150/D60 or the nintedanib 150 mg bid plus docetaxel 75 mg/m^2 (N150/D75) cohorts, three patients experienced DLTs (liver enzyme elevations that were reversible with dose reduction or discontinuation); two in the N150/D60 cohort and one in the N150/D75 cohort. Of 12 patients with BSA greater than or equal to 1.5 treated in the N200/D60 and the nintedanib 200 mg bid plus docetaxel 75 mg/m^2 (N200/D75) cohorts, respectively, two of six patients in each cohort experienced DLTs (reversible liver enzyme elevations). In eight of 12 patients who developed DLTs, nintedanib was reintroduced with dose reduction following rapid recovery of liver enzyme levels; one patient required a second dose reduction (Fig. 2). The MTD of nintedanib was thus 150 and 200 mg bid combined with 75 mg/m^2 of docetaxel in the BSA less than 1.5 and BSA greater than or equal to 1.5 cohorts, respectively.

Safety Profile of Nintedanib

Of the 42 patients who received combination treatment, the most frequent drug-related AEs (all CTCAE grades) were neutropenia, leukopenia, fatigue, alopecia, decreased appetite, ALT/AST elevations, diarrhea, and γ-GT elevations (Table 3). The only grade 4 AEs were neutropenia ($n = 37$) and leukopenia ($n = 9$). Liver enzyme elevations were asymptomatic, and manageable with dose reduction or discontinuation. Among drug-related AEs commonly observed with other VEGF-targeted tyrosine kinase inhibitors, grade 1 or 2 rash was observed in 17 patients, grade 2 proteinuria in one patient, and grade 1 bleeding in seven patients; hypertension, perforation, and thromboembolism were not observed in this study.

Two patients died during the study period. One of these deaths occurred in a male patient (53 years of age; BSA = 1.92 m^2), who was previously treated concurrently with radiation to the mediastinum and systemic chemotherapy (vinorelbine plus cisplatin) until 19 months before beginning the present study treatment (N200/D60) for metastatic disease in mediastinal lymph nodes and an abdominal para-aortic lymph node. He responded to the study treatment

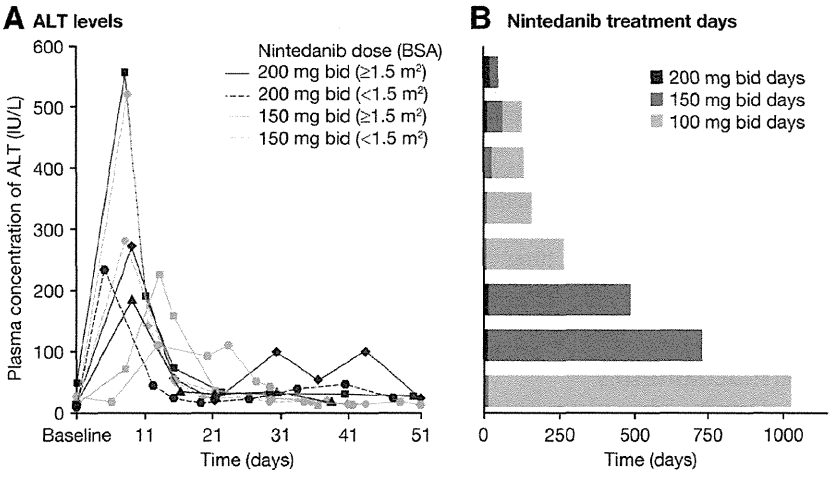

FIGURE 2. Change in alanine aminotransferase (ALT) values in all eight patients with dose reduction on nintedanib by dose-limiting toxicity (DLT) during first treatment course and nintedanib treatment days. BSA, body surface area.

ALT, alanine aminotransferase; bid, twice daily; DLT, dose-limiting toxicity

TABLE 3. Frequency of Patients with Drug-Related AEs (≥20% Incidence) Across all Dose Groups in all Treatment Courses by Body Surface Area

	Patients with BSA <1.5 m² (*n* = 17)		Patients with BSA ≥1.5 m² (*n* = 25)		All patients (*n* = 42)	
n (%)	CTCAE grade 3–4	All CTCAE grades	CTCAE grade 3–4	All CTCAE grades	CTCAE grade 3–4	All CTCAE grades
Hematologic						
Neutropenia	17 (100)	17 (100)	23 (92)	23 (92)	40 (95)	40 (95)
Leukopenia	10 (59)	14 (82)	17 (68)	21 (84)	27 (64)	35 (83)
Anemia	0	4 (24)	0	6 (24)	0	10 (24)
Nonhematologic						
Fatigue	0	15 (88)	0	17 (68)	0	32 (76)
Alopecia	0	12 (71)	0	18 (72)	0	30 (71)
Decreased appetite	1 (6)	13 (76)	0	15 (60)	1 (2)	28 (67)
Diarrhea	0	6 (35)	1 (4)	16 (64)	1 (2)	22 (52)
Dysgeusia	0	6 (35)	0	11 (44)	0	17 (40)
Rash	0	8 (47)	0	9 (36)	0	17 (40)
Nausea	0	7 (41)	0	8 (32)	0	15 (36)
Vomiting	0	9 (53)	0	5 (20)	0	14 (33)
Stomatitis	0	4 (23)	0	8 (32)	0	12 (29)
Peripheral sensory neuropathy	1 (6)	3 (18)	0	7 (28)	1 (2)	10 (24)
Edema	0	5 (29)	0	4 (16)	0	9 (21)
Laboratory abnormalities						
ALT increased	6 (35)	13 (76)	6 (24)	14 (56)	12 (29)	27 (64)
AST increased	5 (29)	13 (76)	2 (8)	14 (56)	7 (17)	27 (64)
γ-GT increased	3 (18)	10 (59)	4 (16)	12 (48)	7 (17)	22 (52)
ALP increased	1 (6)	9 (53)	0	9 (36)	1 (2)	18 (43)

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BSA, body surface area; CTCAE, Common Terminology Criteria for Adverse Events; γ-GT, gamma glutamyltransferase.

(partial response), and the combination treatment was continued until cycle 27. Notable on-treatment AEs were grade 3 to 4 neutropenia and grade 1 fatigue, with no AEs of bleeding observed before the fatal event. On day 12 of cycle 27, the patient died with bleeding suggestive of hemoptysis. The second death occurred in a woman (69 years; BSA = 1.29 m²) who had progressed after first-line platinum-based chemotherapy, and received a total of three cycles of N150/D75 in the present study. On the planned day 1 of cycle 4, a grade 1 AST elevation was observed, docetaxel administration was postponed, and nintedanib treatment was interrupted. Eight days after nintedanib interruption, the study treatment was postponed again because of a grade 1 AST elevation despite no abnormalities in any other vital signs. Fourteen days after nintedanib interruption, the patient died. Based on the details available, the most probable reason for death for both patients was underlying advanced progressive lung cancer. However, the information was not sufficient to clarify the reasons for their events.

Pharmacokinetics

Despite interpatient variability, nintedanib AUC and C_{max} increased in an almost dose-proportional manner following single-dose administration (Supplemental Table S1, SDC 1, http://links.lww.com/JTO/A737). Plasma concentrations of nintedanib reached maximum levels 2 to 3 hours postadministration and then declined, with a half-life of 8 to 9 hours.

PK analysis revealed no apparent interactions between nintedanib and docetaxel. The AUC and C_{max} for nintedanib (non-dose-normalized) in this study were similar to those observed in a previous Japanese phase I study of single-agent nintedanib.[11] Similarly, coadministration of nintedanib did not affect docetaxel PKs (Supplemental Table S2, SDC 1, http://links.lww.com/JTO/A737; Supplemental Figure S1, SDC 2, http://links.lww.com/JTO/A738).

Dose-normalized PK parameters ($C_{max,norm}$, $AUC_{0-12,norm}$, and $AUC_{0-\infty,norm}$) were compared among patients with BSA less than 1.5 and BSA greater than or equal to 1.5 patients. Although geometric mean values of nintedanib $C_{max,norm}$, $AUC_{0-12,norm}$, and $AUC_{0-\infty,norm}$ were slightly higher in patients with BSA less than 1.5 than in patients with BSA greater than or equal to 1.5, the wide overlap of individual patient values indicated no significant differences in nintedanib exposure between the two patient cohorts (Figure 3).

Efficacy

Four of 42 patients were excluded from the efficacy evaluation for objective response according to RECIST because they had no post-treated tumor measurement due to treatment discontinuation during cycle 1; discontinuation

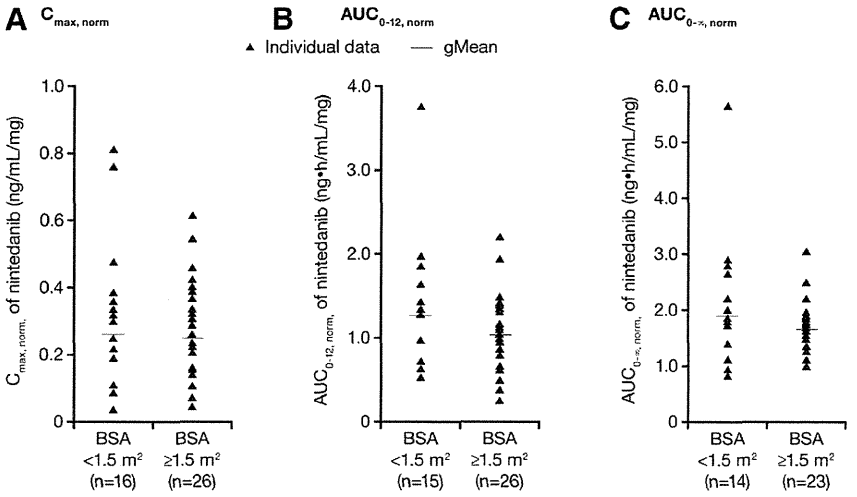

FIGURE 3. $C_{max, norm}$ (*A*), $AUC_{0-12, norm}$ (*B*), and $AUC_{0-\infty, norm}$ (*C*) of nintedanib following single oral administration of nintedanib 100, 150, or 200 mg in patients with a body surface area <1.5 m² or ≥1.5 m². $AUC_{0-\infty, norm}$, dose-normalized area under the concentration–time curve (0–∞ hours); $AUC_{0-12, norm}$, dose-normalized area under the concentration–time curve (0–12 hours); $C_{max, norm}$, dose-normalized peak concentration; gMean, geometric mean; BSA, body surface area.

was related to DLTs in three patients and early withdrawal of consent in one patient. Among 38 assessable patients, 10 had a partial response (two patients in the N150/D60 cohort, five in the N150/D75 cohort, two in the N200/D60 cohort, and one in the N200/D75 cohort), yielding an overall response rate of 26.3% (95% confidence interval [CI]: 13.4–43.1%) (Supplemental Table S3, SDC 1, http://links.lww.com/JTO/A737). All 10 responders had nonsquamous histology: nine with adenocarcinoma and one with large-cell carcinoma. A further 18 patients (47.4%) had stable disease, yielding a disease control rate of 73.7%. Median PFS was 5.7 months [95% CI: 4.3–8.3 months].

DISCUSSION

This phase I trial was conducted to determine the MTD of nintedanib in combination with docetaxel in Japanese patients with advanced NSCLC who had previously received platinum-based chemotherapy. The MTD of nintedanib was 150 and 200 mg bid in patients with BSA less than 1.5 and BSA greater than or equal to 1.5 in combination with 75 mg/m² of docetaxel, respectively. The protocol was amended so that patients were divided according to BSA (<1.5 m² and ≥1.5 m²) due to the occurrence of an unexpectedly high number of DLTs in patients with a lower BSA (i.e., <1.5 m²). All DLTs were grade 3 liver enzyme elevations (ALT, AST, or γ-GT), and were completely reversible with dose reduction or discontinuation. A reduced dose of nintedanib was successfully reintroduced following rapid recovery of enzyme levels for eight of 12 patients who had developed liver enzyme level-related DLTs.

All three patients with BSA less than 1.5 treated with nintedanib 200 mg experienced DLTs, whereas only four of 12 patients with BSA greater than or equal to 1.5 treated at the same dose developed DLTs. This is consistent with our previous phase I study of nintedanib monotherapy, in which three of four patients with BSA less than 1.5 in the 200 mg bid cohort developed DLTs (grade 3 hepatic enzyme elevations), whereas DLTs were not reported in eight patients with BSA greater than or equal to 1.5 treated at the same dose.[11]

Studies with other small-molecule tyrosine kinase inhibitors also suggest that dosing according to BSA might be meaningful. For example, a low BSA has been associated with a high incidence of severe toxicities and DLTs in patients treated with sunitinib.[16,17] Furthermore, a reduced dose of 300 mg/day imatinib in low-BSA patients with chronic myeloid leukemia showed equivalent efficacy to the standard dose.[18,19] A large-scale PK analysis of imatinib identified a weak inverse correlation between trough concentration of imatinib and BSA.[20] Based on these observations, larger-scale investigations are warranted to identify optimal initial dosing of nintedanib, especially in low-BSA patients.

In addition to liver enzyme elevations, common drug-related AEs included hematologic toxicities, alopecia, and gastrointestinal AEs. Many of these toxicities are commonly observed during docetaxel administration.[15] These AEs were reversible and could usually be managed effectively with supportive therapies (except for alopecia). The mild-to-moderate gastrointestinal AEs and asymptomatic, reversible liver enzyme increases are consistent with the established safety/tolerability profile of nintedanib in NSCLC and other tumor types.[10,11,21–25] AEs associated with many other VEGF-targeted tyrosine kinase inhibitors, such as grade 3–4 skin toxicities, hypertension, bleeding, perforation, thromboembolism, and proteinuria,[26] were either absent or infrequent in this study.

The PK profile of nintedanib following docetaxel administration was very similar to that seen in our phase I nintedanib monotherapy study.[11] This suggests that docetaxel has no clinically relevant effect on the PK of nintedanib. Analyses of blood samples taken on day 1 of cycle 1 with docetaxel alone, and day 1 of cycle 2 of docetaxel/nintedanib showed that coadministration of nintedanib did not affect the PK of docetaxel. This is consistent with findings from a phase I study of nintedanib/docetaxel in patients with prostate cancer.[25] In the present study, we found no clear differences in PK data from patients with BSA less than 1.5 and BSA greater than or equal to 1.5. This could be due to the small sample size, so population-based PK analyses of nintedanib are needed.

Our study showed that 26% of patients achieved an objective response to nintedanib/docetaxel, with a median PFS of 5.7 months. This high level of antitumor activity is

consistent with data from the global LUME-Lung 1 trial of nintedanib/docetaxel in NSCLC, where a statistically significant improvement in PFS was observed in all patients, and a significant extension in overall survival was seen in patients with adenocarcinoma.[10]

In conclusion, the MTD for continuous daily treatment with nintedanib plus docetaxel (75 mg/m^2) was 150 and 200 mg bid in patients with BSA less than 1.5 and BSA greater than or equal to 1.5, respectively. There were no clinically relevant PK interactions between nintedanib and docetaxel. DLTs were observed in one-third of enrolled patients, and there were two fatal events including hemoptysis; therefore, careful observation of patients receiving nintedanib in combination with docetaxel is required in future investigations.

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JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Randomized Phase III Trial Comparing Weekly Docetaxel Plus Cisplatin Versus Docetaxel Monotherapy Every 3 Weeks in Elderly Patients With Advanced Non–Small-Cell Lung Cancer: The Intergroup Trial JCOG0803/WJOG4307L

Tetsuya Abe, Koji Takeda, Yuichiro Ohe, Shinzoh Kudoh, Yukito Ichinose, Hiroaki Okamoto, Nobuyuki Yamamoto, Hiroshige Yoshioka, Koichi Minato, Toshiyuki Sawa, Yasuo Iwamoto, Hideo Saka, Junki Mizusawa, Taro Shibata, Shinichiro Nakamura, Masahiko Ando, Akira Yokoyama, Kazuhiko Nakagawa, Nagahiro Saijo, and Tomohide Tamura

Tetsuya Abe and Akira Yokoyama, Niigata Cancer Center Hospital, Niigata; Koji Takeda, Osaka City General Hospital; Shinzoh Kudoh, Osaka City University; Shinichiro Nakamura, West Japan Oncology Group Data Center; Kazuhiko Nakagawa, Kinki University, Osaka; Yuichiro Ohe, National Cancer Center Hospital East, Chiba; Yukito Ichinose, National Kyushu Cancer Center, Fukuoka; Hiroaki Okamoto, Yokohama Municipal Citizens Hospital, Kanagawa; Nobuyuki Yamamoto, Wakayama Medical University School of Medicine, Wakayama; Hiroshige Yoshioka, Kurashiki Central Hospital, Kurashiki; Koichi Minato, Gunma Cancer Center, Gunma; Toshiyuki Sawa, Gifu Municipal Hospital, Gifu; Yasuo Iwamoto, Hiroshima City Hospital, Hiroshima; Hideo Saka, Nagoya Medical Center; Masahiko Ando, Nagoya University Hospital, Aichi; Junki Mizusawa and Taro Shibata, Japan Clincal Oncology Group Data Center, National Cancer Center; Nagahiro Saijo, Japanese Society of Medical Oncology; and Tomohide Tamura, National Cancer Center Hospital, Tokyo, Japan.

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Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: Tetsuya Abe, MD, PhD, Niigata Cancer Center Hospital, 2-15-3 Kawagishi-cho, Chuo-ku, Niigata 951-8566, Japan; e-mail: t-abe@niigata-cc.jp.

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ABSTRACT

Purpose
This phase III trial aimed to confirm the superiority of weekly docetaxel and cisplatin over docetaxel monotherapy in elderly patients with advanced non–small-cell lung cancer (NSCLC).

Patients and Methods
Chemotherapy-naïve patients with stage III, stage IV, or recurrent NSCLC age ≥ 70 years with a performance status of 0 or 1 who were considered unsuitable for bolus cisplatin administration were randomly assigned to receive docetaxel 60 mg/m^2 on day 1, every 3 weeks, or docetaxel 20 mg/m^2 plus cisplatin 25 mg/m^2 on days 1, 8, and 15, every 4 weeks. The primary end point was overall survival (OS).

Results
In the first interim analysis, OS of the doublet arm was inferior to that of the monotherapy arm (hazard ratio [HR], 1.56; 95% CI, 0.98 to 2.49), and the predictive probability that the doublet arm would be statistically superior to the monotherapy arm on final analysis was 0.996%, which led to early study termination. In total, 276 patients with a median age of 76 years (range, 70 to 87 years) were enrolled. At the updated analysis, the median survival time was 14.8 months for the monotherapy arm and 13.3 months for the doublet arm (HR, 1.18; 95% CI, 0.83 to 1.69). The rates of grade ≥ 3 neutropenia and febrile neutropenia were higher in the monotherapy arm, and those of anorexia and hyponatremia were higher in the doublet arm.

Conclusion
This study failed to demonstrate any survival advantage of weekly docetaxel plus cisplatin over docetaxel monotherapy as first-line chemotherapy for advanced NSCLC in elderly patients.

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INTRODUCTION

Lung cancer is the leading cause of cancer-related death in most developed countries. Non–small-cell lung cancer (NSCLC) accounts for 85% of all lung cancers, and more than 50% of patients with NSCLC already have advanced disease at diagnosis.[1] The number of elderly patients with lung cancer has also increased, and the median age at diagnosis is 70 years.[2]

The Elderly Lung Cancer Vinorelbine Italian Study, in which single-agent vinorelbine was compared with the best supportive care, first demonstrated the benefits of chemotherapy in elderly patients with advanced NSCLC.[3] In the Multicenter Italian Lung Cancer in the Elderly Study, a combination of vinorelbine plus gemcitabine did not improve survival over vinorelbine or gemcitabine alone and only increased the toxicity frequency.[4] Therefore, single-agent vinorelbine or gemcitabine was established as the standard treatment for elderly patients with NSCLC. We compared docetaxel (every 3 weeks) with vinorelbine in the West Japan Thoracic Oncology Group (the former name of the West Japan Oncology Group [WJOG]) 9904 study, which revealed significantly superior responses and better survival in the docetaxel arm.[5]