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Quality of Life with Gefitinib in Patients with *EGFR*-Mutated Non-Small Cell Lung Cancer: Quality of Life Analysis of North East Japan Study Group 002 Trial

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Key Words. Lung carcinoma • Epidermal growth factor receptor • EGFR • Tyrosine kinase inhibitor • TKI • Gefitinib • Quality of life • QoL

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ABSTRACT

Background. For non-small cell lung cancer (NSCLC) patients with epidermal growth factor receptor (*EGFR*) mutations, first-line gefitinib produced a longer progression-free survival interval than first-line carboplatin plus paclitaxel but did not show any survival advantage in the North East Japan 002 study. This report describes the quality of life (QoL) analysis of that study.

Methods. Chemotherapy-naïve patients with sensitive *EGFR*-mutated, advanced NSCLC were randomized to receive gefitinib or chemotherapy (carboplatin and paclitaxel). Patient QoL was assessed weekly using the Care Notebook, and the primary endpoint of the QoL analysis

was time to deterioration from baseline on each of the physical, mental, and life well-being QoL scales. Kaplan-Meier probability curves and log-rank tests were employed to clarify differences.

Results. QoL data from 148 patients (72 in the gefitinib arm and 76 in the carboplatin plus paclitaxel arm) were analyzed. Time to defined deterioration in physical and life well-being significantly favored gefitinib over chemotherapy (hazard ratio [HR] of time to deterioration, 0.34; 95% confidence interval [CI], 0.23–0.50; $p < .0001$ and HR, 0.43; 95% CI, 0.28–0.65; $p < .0001$, respectively).

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Conclusion. QoL was maintained much longer in patients treated with gefitinib than in patients treated with standard chemotherapy, indicating that gefitinib should be

considered as the standard first-line therapy for advanced *EGFR*-mutated NSCLC in spite of no survival advantage. *The Oncologist* 2012;17:863–870

INTRODUCTION

Dysregulation of protein kinases is frequently observed in cancer cells. Therefore, protein kinases are attractive targets in the development of anticancer drugs such as small molecule inhibitors that block binding of ATP to the catalytic domain of the tyrosine kinase. In 2004, three groups of researchers reported that activating mutations of the epidermal growth factor receptor gene (*EGFR*) were present in a subset of non-small cell lung cancer (NSCLC) tumors, and that tumors with *EGFR* mutations were highly sensitive to *EGFR* tyrosine kinase inhibitors (TKIs) [1–3]. Since then, our multiple phase II studies confirmed a striking response to *EGFR* TKIs in this population [4–8].

In phase III NSCLC trials, *EGFR* TKIs such as gefitinib or erlotinib were compared with conventional chemotherapies initially in unselected patients [9–11], next on the basis of clinical characteristics [12], and subsequently using molecular selection [13–16]. Among them, the pivotal phase III study North East Japan (NEJ) 002 compared gefitinib with chemotherapy in first-line therapy for patients with NSCLC with mutated *EGFR* and confirmed, as the primary endpoint, that the progression-free survival (PFS) interval in the gefitinib group was significantly longer than that in the carboplatin plus paclitaxel group (10.8 months versus 5.4 months, hazard ratio [HR], 0.30; $p < .001$) [13]. A subgroup analysis of the Iressa® Pan-Asia Study (IPASS) [12] and similar phase III studies—the West Japan Thoracic Oncology Group 3405 trial [14], the OPTIMAL trial [15], and European Randomised Trial of Tarceva versus Chemotherapy [16]—also demonstrated a superior PFS outcome in patients treated with *EGFR* TKIs than in those treated with standard chemotherapies. However, the IPASS and NEJ 002 trials showed identical overall survival (OS) outcomes using gefitinib and chemotherapy in the first-line treatment of NSCLC patients harboring sensitive *EGFR* mutations [17, 18].

When the OS time is identical in the two arms, improvements in quality of life (QoL) and disease-related symptoms are among the key goals of treatment for NSCLC. However, there has been no prospective report describing QoL in NSCLC patients with sensitive *EGFR* mutations who were treated using an *EGFR* TKI. This QoL analysis was prospectively conducted as a secondary endpoint in the NEJ 002 study.

METHODS

This study was performed in accordance with the Helsinki Declaration (1964, amended in 2000) of the World Medical Association. The participating institutions received approval from their institutional ethics review boards. The details regarding patient eligibility and treatment were described previously [13]. Briefly, eligibility stipulated the presence of advanced NSCLC harboring a sensitive *EGFR* mutation, the absence of the resistant *EGFR* mutation T790M, no history of

chemotherapy, and age ≤ 75 years. *EGFR* mutation status was examined using the peptide nucleic acid-locked nucleic acid polymerase chain reaction (PNA-LNA PCR) clamp method [19]. Eligible patients were randomly assigned to receive either gefitinib (at a dose of 250 mg/day orally) or standard chemotherapy. Standard chemotherapy consisted of paclitaxel (at a dose of 200 mg/m² i.v.) and carboplatin (area under the concentration–time curve of 6), both administered on the first day of every 3-week cycle. Randomization was balanced by institution, sex, and stage. The primary endpoint was the PFS interval; secondary endpoints included the OS time, response rate, toxic effects, and QoL.

QoL Assessment

The Care Notebook (supplemental online Fig. 1) [20], which has been previously validated and reported [21, 22], was used to assess QoL. The Care Notebook is a self-administered, cancer-specific questionnaire that asks about cancer patients' conditions during 1 week regarding 24 items that are structured in multidimensional scales. The questionnaire consists of three major scales: physical well-being, mental well-being, and life well-being. These major scales are divided into several subscales. Physical well-being has three multi-item subscales, which are appetite loss (items P3, P4, P7), constipation (P6, P8), and fatigue (P9, P10), and three single-item measures, which are pain (item P1), shortness of breath (item P2), and sleeping trouble (P5). Mental well-being has three multi-item subscales, which are anxiety (M1, M2), irritation (M3, M5), and depression (M4, M6). Life well-being has three multi-item subscales, which are daily functioning (L1, L2), social functioning (L3, L4), and subjective QoL (L5–L8), which consists of peace of mind (L5), feeling of happiness (L6), QoL functioning (L7), and satisfaction with daily life (L8). Each item is asked using one word or a short phrase and employs an 11-point linear analog scale (0–10). A score of 10 in physical well-being and mental well-being indicates the heaviest burden. A score of 10 in life well-being indicates the best possible function or QoL; thus, the polarity of the data for life well-being was reversed before the analysis so that a greater score indicated a poorer QoL in all items of the questionnaire.

Seventy sheets of the Care Notebook were bundled as a booklet. Patients started answering the questionnaire before starting therapy and answered it once a week during first-line treatment. After completion of the questionnaire, the booklets were collected by the patients' doctors and sent to the QoL data center (Saitama Medical University).

Statistical Analyses

The primary endpoint in the QoL analysis, which was prospectively defined in the protocol of the clinical trial, was the time from random assignment of treatment to deterioration in the

following, which are clinically relevant and are frequently observed in patients with advanced NSCLC: (a) pain and shortness of breath (P1 and P2), (b) anxiety (M1 and M2), and (c) daily functioning (L1 and L2). From previous studies [23, 24], deterioration was recognized when the score changed from baseline by one of 11 points (9.1%) in a direction indicating a worse QoL at any timepoint. This primary analysis was performed for 20 weeks after the initiation of first-line therapy. All patients who had a baseline plus at least one follow-up QoL assessment were included in the time-to-deterioration analysis. Patients who had not deteriorated were censored at the time of the last QoL questionnaire completion. Kaplan–Meier curves and the log-rank test were used to compare the time to deterioration in each subscale between the two treatment arms. Also, more severe deterioration was defined as a score change of three of 11 points (27.3%) [23, 24].

In addition, we performed a secondary analysis using QoL data according to the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) standard method [25]. During the initial 20 weeks from the start of treatment, we first checked whether or not the scores showed an improvement at any time in a subscale by $\geq 9.1\%$ (one point or more) from baseline. In such cases, the response was judged to be “improved” even if the scores were initially or subsequently below the lower boundary, that is, -9.1% . If the response was not classified as improved, we next checked whether or not the scores showed a worsening in a subscale by $\geq -9.1\%$ from baseline, resulting in the response being classified as “worsened.” In cases that were classified as neither improved nor worsened, the response was classified as “stable.” A χ^2 test was used for comparisons between the two arms.

RESULTS

Summary of Clinical Outcomes

In the NEJ 002 study [13], 230 patients who had sensitive *EGFR* mutations were enrolled and were randomly assigned to either gefitinib ($n = 115$) or carboplatin plus paclitaxel ($n = 115$), and 114 and 110 patients, respectively, were included in the PFS analysis (Fig. 1). Patients in the gefitinib arm had a significantly longer PFS time (median PFS time, 10.8 months versus 5.4 months; HR, 0.30; 95% CI, 0.22–0.41; $p < .001$) and a higher response rate (73.7% versus 30.7%; $p < .001$) than patients in the chemotherapy arm. Second-line gefitinib was administered to 98.2% of patients in the carboplatin plus paclitaxel arm after disease progression. As a result, the median OS time was 27.7 months in the gefitinib arm and 26.6 months in the chemotherapy arm, with the difference in survival time not statistically significant ($p = .48$) [18]. The most common adverse events of any grade were rash (71.1%) and aspartate aminotransferase or alkaline phosphatase elevation (55.3%) in the gefitinib arm and neutropenia (77.0%), anemia (64.6%), appetite loss (56.6%), and sensory neuropathy (54.9%) in the chemotherapy arm [13].

Baseline QoL

Of the 224 patients, the QoL booklets of 163 patients (73%) were collected by their doctors and sent to the QoL data center.

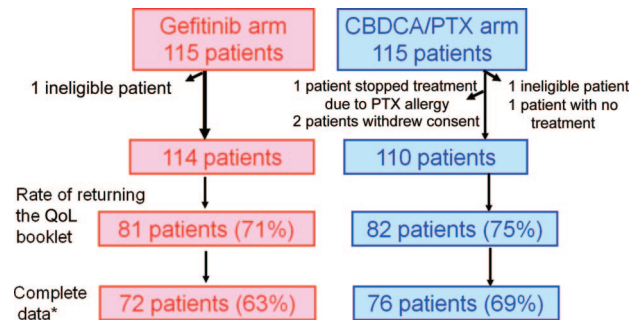


Figure 1. Patient disposition.

*The complete dataset was defined as having both a pretreatment measurement (baseline) and measurement(s) after starting the treatment during first-line therapy.

Abbreviations: CBDCA, carboplatin; PTX, paclitaxel; QoL, quality of life.

The rates of compliance among these 73% of patients were similar in the two arms. Of the 163 patients, 15 patients failed to provide complete information on their QoL prior to first-line therapy (nine patients in the gefitinib arm and six patients in the chemotherapy arm). Seventy-two patients (63%) in the gefitinib arm and 76 patients (69%) in the chemotherapy arm were investigated in this QoL analysis (Fig. 1). Demographics and disease characteristics were found to be well balanced in the two arms and were similar to those for the primary PFS analysis [13] (Table 1). Most patients had an Eastern Cooperative Oncology Group performance status (PS) score of 0 or 1 at the time of enrollment. Toxicity profiles for the patients in the QoL analysis were also similar to those for the patients in the PFS analysis [13].

Before the initiation of treatment, patients in both arms had similar baseline QoL scores on all subscales (Table 2). They had a low burden of physical well-being, but impairment was seen in the anxiety subscale (mean score, 40.5 and 40.8 in the gefitinib and carboplatin plus paclitaxel arms, respectively).

Time to Deterioration in QoL

In terms of the minimal clinically important difference in QoL, previous studies indicated that patients perceived a 5%–7% change in the scores on QoL questionnaires as clinically significant [23, 24]. The NCIC CTG recommends a 10% change as the value for clinical significance [25]. In the primary analysis of QoL in the NEJ 002 trial, deterioration was recognized when the score changed from baseline by one in 11 points (9.1%) or more in a direction indicating worse QoL at any timepoint. This criterion was chosen on the basis of our previous study, which estimated content validity by performing interviews with cancer patients (unpublished results). The times to 9.1% deterioration for pain and shortness of breath, anxiety, and daily functioning are summarized in Figure 2A. Significant differences between treatment arms were observed in deterioration of pain and shortness of breath (HR, 0.34; 95% CI, 0.23–0.50; $p < .0001$) and daily functioning (HR, 0.43; 95% CI, 0.28–0.65; $p < .0001$). There was no significant difference in anxiety between arms (HR, 0.72; 95% CI, 0.46–1.13; $p = .14$).

Characteristic	Gefitinib (n = 72), n (%)	CBDCA/PTX (n = 76), n (%)	p-value
Gender			
Male	24 (33%)	29 (38%)	.608 ^a
Female	48 (67%)	47 (62%)	
Mean age (range), yrs	63.0 (43–75)	62.2 (35–74)	.576 ^b
Smoking status			
Never	51 (71%)	46 (61%)	.227 ^a
Ever	21 (29%)	30 (39%)	
Performance status score, 0/1/2	40/32/0	43/32/1	.959 ^c
Histology, adenocarcinoma/other	67/5	74/2	.495 ^a
Stage, IIIB/IV/postoperative	10/52/10	15/52/9	.621 ^a
Type of mutation			
Deletion	37 (51%)	36 (47%)	.616 ^a
L858R	31 (43%)	36 (47%)	
Other	4 (6%)	4 (6%)	

Characteristics of patients investigated in the QoL analysis had no significant differences between arms.

^aFisher's exact test.
^bt-test.
^cWilcoxon test.

Abbreviations: CBDCA, carboplatin; PTX, paclitaxel; QoL, quality of life.

Measure	Gefitinib		CBDCA/PTX	
	Mean points	SD	Mean points	SD
Physical well-being	11.2	13.5	10.4	12.0
Appetite loss	6.8	13.0	5.9	11.5
Constipation	7.5	14.1	8.0	12.3
Pain and shortness of breath	13.5	23.2	10.5	18.5
Mental well-being	27.6	26.2	25.0	20.6
Anxiety	40.8	31.3	40.5	24.6
Irritation	18.3	25.2	14.3	20.4
Depression	23.5	27.9	20.0	24.3
Life well-being	26.4	19.3	22.9	17.1
Daily functioning	31.1	27.0	25.5	22.8
Social functioning	13.4	18.4	10.4	13.8
Subjective QoL	30.5	23.0	29.4	21.2

A 0–10 linear analog rating was changed to 0–100 points. For physical and mental well-being, a score of 100 represents the highest burden of symptoms. For life well-being, a score of 100 represents the worst possible function or QoL by changing the score polarity. There were no significant differences in scale and subscale scores between arms before starting first-line therapies. Abbreviations: CBDCA, carboplatin; PTX, paclitaxel; QoL, quality of life; SD, standard deviation.

From previous reports [23, 24], a change in QoL score >20%, indicating more severe QoL deterioration, was also investigated. Figure 2B summarizes the time to a 27.3% (three of 11 points) deterioration in pain and shortness of breath, anxiety, and daily functioning. Patients who received gefitinib had a significantly longer time to deterioration than patients who received carboplatin plus paclitaxel for pain and shortness of breath (HR, 0.28; 95% CI, 0.17–0.46; $p < .0001$) and daily functioning (HR, 0.32; 95% CI, 0.17–0.59; $p < .0001$) as well as anxiety (HR, 0.44; 95% CI, 0.22–0.87; $p = .01$), for which a significant difference was not observed in the analysis of a 9.1% deterioration (see above).

Proportion of Patients with Improved, Stable, or Worsened QoL

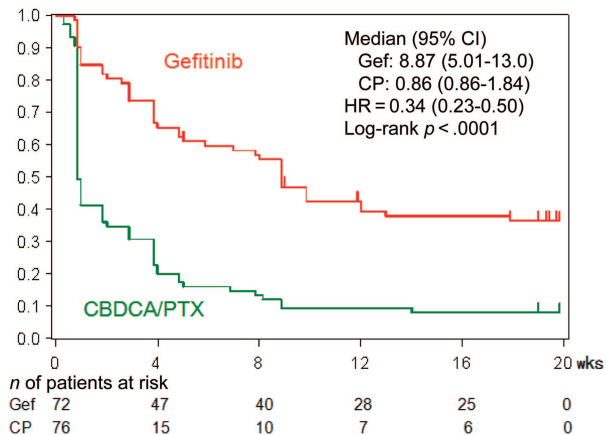
Table 3 details the QoL responses according to three categories (improved, stable, worse) defined in Methods. The χ^2 test indicated that the QoL subscales of appetite loss ($p = .014$), constipation ($p < .0001$), and pain and shortness of breath ($p < .0001$) favored gefitinib over standard chemotherapy, leading to superiority of the gefitinib group on the physical well-being scale ($p < .0001$). A similar trend was observed for the QoL subscales of daily functioning ($p = .007$), social functioning ($p = .035$), and subjective QoL ($p = .042$), leading to superiority of the gefitinib group on the life well-being scale ($p < .0001$). The subscale of the mental well-being scale did not show any significant difference between the treatment arms ($p = .458$).

DISCUSSION

This QoL analysis clearly demonstrated superior QoL in NSCLC patients with mutated *EGFR* receiving gefitinib, com-

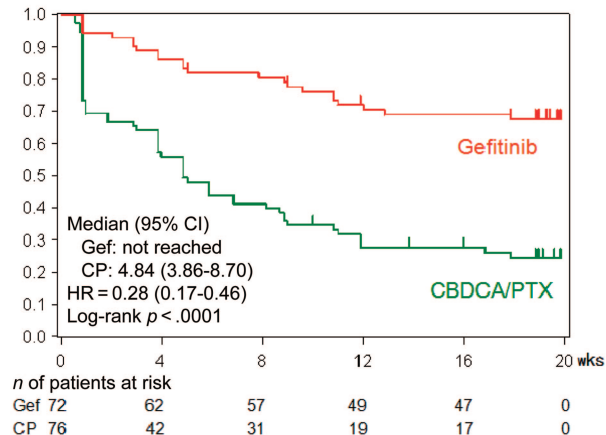
A. Time to 9.1% deterioration

A-1 Pain & Shortness of breath

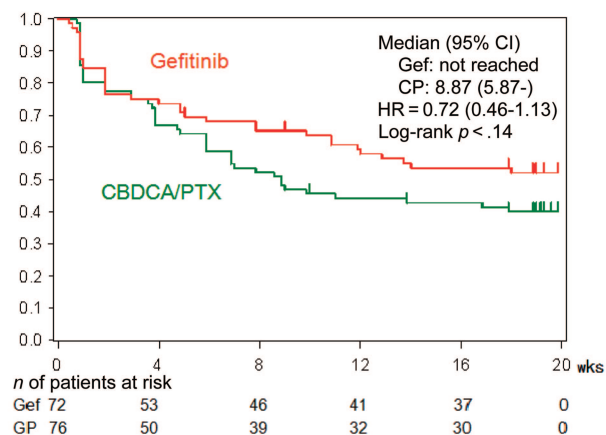


B. Time to 27.3% deterioration

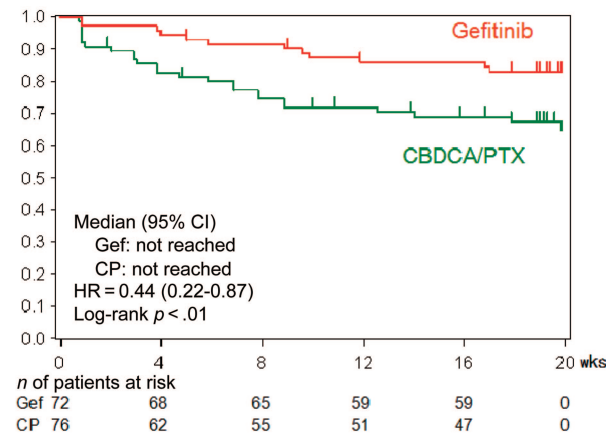
B-1 Pain & Shortness of breath



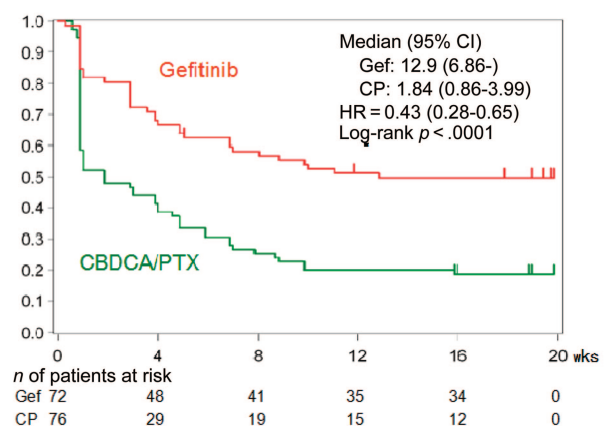
A-2 Anxiety



B-2 Anxiety



A-3 Daily functioning



B-3 Daily functioning

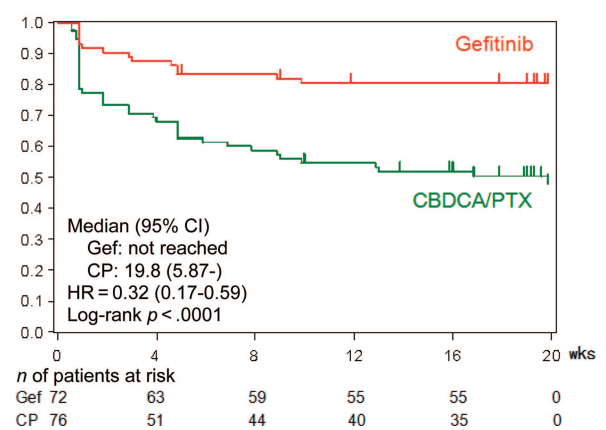


Figure 2. Time to deterioration of QoL. (A): Time to a 9.1% QoL deterioration for pain and shortness of breath (A-1), anxiety (A-2), and daily functioning (A-3) (B): Time to a 27.3% QoL deterioration for pain and shortness of breath (B-1), anxiety (B-2), and daily functioning (B-3).

Abbreviations: CBDCA, carboplatin; CI, confidence interval; CP, carboplatin plus paclitaxel; Gef, gefitinib; HR, hazard ratio; PTX, paclitaxel; QoL, quality of life.

Table 3. QoL response

Measure	Gefitinib, <i>n</i>			CBDCA/PTX, <i>n</i>			<i>p</i> -value
	Improved	Stable	Worse	Improved	Stable	Worse	
Physical well-being	18	28	26	16	10	50	<.0001
Appetite loss	13	21	38	14	8	54	.014
Constipation	16	24	32	23	6	47	<.0001
Pain and shortness of breath	21	18	33	16	3	57	<.0001
Mental well-being	33	16	23	40	11	25	.458
Anxiety	48	8	16	57	6	13	.535
Irritation	27	18	27	27	11	38	.181
Depression	35	15	22	36	10	30	.346
Life well-being	38	22	12	32	8	36	<.0001
Daily functioning	40	10	22	30	4	42	.007
Social functioning	23	28	21	16	22	38	.035
Subjective QoL	41	15	16	38	8	30	.042

In a secondary analysis of QoL responses, patients were classified as improved (>9.1%), stable (<9.1%, >−9.1%), or worsened (<−9.1%) for all scales and subscales according to the National Cancer Institute of Canada Clinical Trials Group standard QoL analysis framework. The χ^2 test was used to compare the distributions of these three categories between two treatment arms. Abbreviations: CBDCA, carboplatin; PTX, paclitaxel; QoL, quality of life.

pared with patients receiving chemotherapy. Better QoL in patients receiving gefitinib further endorses the preference of gefitinib as the first-line therapy for patients with NSCLC with mutated *EGFR* despite a lack of difference in OS outcomes. Accordingly, integration of QoL analyses into a clinical trial should be considered, because maintenance of a good QoL solidifies the clinical efficacy of the treatment being investigated. In addition, this analysis also highlights the importance of QoL endpoints in randomized trials analyzing PFS outcomes, because OS outcomes may be affected by subsequent therapies.

QoL recorded by patients in a self-reported form accurately demonstrated how the patients felt about their QoL during treatment. As soon as chemotherapy with carboplatin plus paclitaxel was started, a striking difference in QoL was observed (Fig. 2A). It seems reasonable that physical well-being deteriorated with chemotherapy in a high proportion of patients, considering that >95% of patients had a PS score of 0–1, a fact that is probably reflected by the low scoring in the baseline scores of physical well-being and daily functioning, with the majority of patients scoring <30. The NCIC CTG recommended matrix (Table 2) also showed that physical well-being was stable or improved in 60% of patients in the gefitinib group. In sharp contrast, scores for physical well-being deteriorated in 75% of patients in the chemotherapy group. This better QoL in the gefitinib group will help patients to maintain social activities, continue to work, and enjoy spending time with their families.

When patients were treated with gefitinib monotherapy in other trials, QoL and symptom improvement were rapid and were correlated with tumor response and survival [26, 27]. In the BR.21 study using unselected patients, another *EGFR* TKI, erlotinib, also improved tumor-related symptoms and impor-

tant aspects of QoL such as physical functioning [28]. Post hoc investigations in the IPASS study employing selection by background indicated that QoL was better in the gefitinib group than in the chemotherapy group for patients with *EGFR*-mutated NSCLC [29]. Taken together with our first prospective QoL analysis of patients with *EGFR*-mutated NSCLC, *EGFR* TKI therapy provides an advantage in terms of improving QoL and symptoms over conventional cytotoxic agents.

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) [30] and Functional Assessment of Cancer Therapy (FACT)–General [31] have been used in many clinical trials to assess the QoL of patients worldwide, and we have developed and validated Japanese versions of these tests for use mainly in clinical studies with the original developers [32, 33]. The Care Notebook [20–22] was originally developed in the 1990s for clinical practice and has a notebook-style format to collect valid and reliable QoL information repeatedly. The NEJ 002 study lacked sufficient support from clinical research coordinators, and doctors had to personally administer QoL questionnaires to patients and pick them up after the answers were completed. Therefore, we chose the Care Notebook, which has good results concerning concurrent validity with the EORTC QLQ-C30 and FACT–Spiritual Well-being [22], for QoL investigation on a weekly basis instead of the above gold standard questionnaires. More than 3,000 Care Notebooks were collected during the initial 20 weeks of treatment in this study, and this method might be the first success of a QoL investigation on a weekly basis for advanced cancer patients in a phase III trial.

This study has some limitations. First, compliance with the QoL survey was modest. Missing data in the QoL investigation

were found to be institution dependent. Namely, the doctors in some institutions did not give the Care Notebook to patients or did not pick it up after the answers were completed. However, randomization of the study treatments was stratified by institution, and therefore, the effects of selection bias might not be large. Both arms had similar patient characteristics (Table 1) and similar baseline QoL scores (Table 2). Although compliance was modest, this QoL difference between arms may represent that in the overall population. Secondly, because the primary endpoint of the NEJ 002 study focused on the PFS interval after first-line treatment, the QoL analysis also focused on patients treated during first-line treatment, and, therefore, the investigation period for the primary QoL analyses was relatively short (20 weeks) to reduce the effects of second-line treatment. Finally, the patients in this QoL analysis were a selected population—patients with a PS score of 0–1 whose tumor had *EGFR* mutation—which might potentially influence the QoL outcomes. However, in another study, namely the NEJ 001 study [7], which employed *EGFR* mutation-positive patients with an extremely poor PS, 68% of the patients improved from a PS score ≥ 3 at baseline to a PS score ≤ 1 with gefitinib therapy. Although no QoL investigation was conducted in the NEJ 001 study because of the patients being in extremely poor condition, the striking PS score improvement might have been related to improved QoL. This indicates that *EGFR* TKIs might universally ameliorate the QoL of patients with *EGFR*-mutated NSCLC, irrespective of their PS scores or symptomatic burdens.

SUMMARY

The QoL analysis of the NEJ 002 study clearly demonstrated that gefitinib maintained patient QoL longer than carboplatin plus paclitaxel during first-line treatment. A longer PFS interval with a better QoL during first-line treatment is valuable for advanced NSCLC patients with limited survival times. Although the OS time for patients first treated using gefitinib was not significantly different from that of patients treated using chemotherapy, the first-line use of gefitinib for advanced NSCLC harboring *EGFR* mutations is strongly recommended.

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This study is registered in University Hospital Medical Information (UMIN) Network Clinical Trial Registry (identification number, UMIN C000000376).

AUTHOR CONTRIBUTIONS

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