A Phase II Study of First-line Afatinib For Patients Aged ≥ 75 Years With EGFR Mutation-positive Advanced Non-small Cell Lung Cancer: North East Japan Study Group Trial NEJ027

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Abstract

Background: We investigated afatinib in elderly patients with epidermal growth factor receptor (*EGFR)* mutation-positive advanced non-small cell lung cancer (NSCLC).

Patients and Methods: This was a single-arm, open-label, phase II study, performed in multiple centres in Japan. Previously untreated patients, aged ≥ 75 years, with *EGFR* mutation-positive (Del19 or L858R) advanced NSCLC were treated with afatinib 40 mg until disease progression or unacceptable toxicity. Adverse events (AEs) were managed with protocol defined dose adjustments. The primary endpoint was objective response rate (ORR) by central review.

Results: In total, 38 patients received at least one dose of afatinib, and 37 were evaluable for response. Median age was 77.5 years (range 75–91), all patients had an Eastern Cooperative Oncology group performance status of 0 or 1, and 60.5% had Del19-positive disease. ORR was 75.7% (2 complete responses and 26 partial responses). Median progression-free survival was 14.2 months (95% confidence interval [CI], 9.5–19.0). Median overall survival (OS) was 35.2 months (95% CI, 35.2–not reached); the 2-year OS rate was 78.3%. The most common grade III/IV treatment-related AEs (TRAEs) were diarrhoea (28.9%), paronychia (23.7%), and rash/acne (15.8%). Dose reductions due to TRAEs were reported in 78.9% of patients, and 8 (21.1%) patients discontinued afatinib due to TRAEs. No treatment-related deaths were reported.

Conclusion: First-line afatinib administered at a starting dose of 40 mg was well tolerated with dose adjustments and was associated with encouraging activity in Japanese patients aged ≥ 75 years with *EGFR* mutation-positive NSCLC.

Trial Registration: The trial is registered with Japan Registry of Clinical Trials (JRCT) as trial number 031180136 (date of initial registration: 19 February 2019), and the University Hospital Network (UMIN) as trial number 000017877 (date of initial registration: 11 June 2015).

Introduction

Lung cancer is the leading cause of cancer-related death worldwide, and among men in Japan.[1] Epidermal growth factor receptor (EGFR) activation through tumour *EGFR* gene mutations drives malignancy in a proportion of patients with non-small cell lung cancer (NSCLC). Activating *EGFR* mutations are found in up to 50% of NSCLC tumours from Asian populations, including in 30–40% of Japanese patients.[2,3] Patients whose tumours harbour *EGFR* mutations may be sensitive to EGFR tyrosine kinase inhibitors (TKIs), which are recommended treatment options in this setting.[1,4,5]

Afatinib is a second-generation, irreversible ErbB-family blocker[6] that is approved in many countries, including Japan,[7] for the first-line treatment of patients with *EGFR* mutation-positive NSCLC. In the global, phase III LUX-Lung 3 study,[8] and the phase III LUX-Lung 6 study in Asian patients,[9] first-line afatinib significantly prolonged progression-free survival (PFS) compared with standard platinum-based

chemotherapy in patients with *EGFR* mutation-positive NSCLC. In both of these studies, afatinib also improved overall survival (OS) versus platinum-based chemotherapy in patients with tumours harbouring *EGFR* exon 19 deletions (Del19).[10] In the global, phase IIb LUX-Lung 7 study, first-line afatinib significantly improved PFS compared with the first-generation EGFR TKI gefitinib in patients with *EGFR* mutation-positive (Del19/L858R) NSCLC.[11,12] Afatinib was generally well tolerated in these studies; treatment-related adverse events (TRAEs) were mainly EGFR TKI class-related toxicities, and were managed with tolerability-guided dose reductions. Few treatment discontinuations were reported.[8,9] Among Japanese patients in LUX-Lung 3, prolonged PFS and improved OS in patients with *EGFR* Del19-positive tumours was confirmed for afatinib versus platinum-based chemotherapy.[13] The safety profile of afatinib in Japanese patients was as to be expected from EGFR-TKI exposure, but a higher rate of afatinib dose reductions was observed compared with the overall LUX-Lung 3 population (76% vs. 52%).[8,13]

Lung cancer is most frequently diagnosed between the ages of 65 and 74 years.[14] In 2018, of approximately 2 million cases worldwide, 76% were in patients aged > 60 years and 44% were in those aged > 70 years.[15] With the population of older patients diagnosed with NSCLC increasing, the choice of first-line treatment for these patients is an important decision, which may be complicated by age-related factors such as comorbidities and polypharmacy.[16] Current Pan-Asian clinical practice guidelines advise that immunotherapy should be considered for elderly patients with NSCLC without a druggable oncogene driver.[1] Carboplatin-based doublet chemotherapy is recommended for eligible patients aged ≥ 70 years with Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–2 and adequate organ function, while single-agent chemotherapy remains the standard of care for patients not eligible for doublet chemotherapy.[1] Asian treatment guidelines also recommend EGFR TKI monotherapy as first-line treatment for the general population of patients with *EGFR* mutation-positive NSCLC,[1,17] and there is evidence that EGFR TKIs may be effective for some elderly patients with *EGFR* mutation-positive NSCLC.[18] Indeed, in a subgroup analysis of the LUX-Lung 3, 6, and 7 studies, afatinib was effective and tolerable in patients with *EGFR* mutation-positive NSCLC, independent of age at diagnosis.[16]

In addition to evidence from the LUX-Lung studies, a phase I trial including treatment at the approved dose of 40 mg, and a phase II trial employing afatinib 30 mg support the feasibility of first-line afatinib as a treatment option in elderly Japanese patients with *EGFR* mutation-positive NSCLC.[19,20] The aim of the current study was to further investigate the antitumour activity and safety profile of daily afatinib (40 mg) in previously untreated Japanese patients aged ≥ 75 years, with *EGFR* mutation-positive NSCLC.

Patients And Methods

Study Design

NEJ027 was a single-arm, multicentre, open-label, phase II study of first-line afatinib in patients aged ≥ 75 years, with *EGFR* mutation-positive NSCLC. The primary endpoint was objective response rate (ORR).

Secondary endpoints were PFS, PFS in patients with *EGFR* Del19- versus L858R-positive disease, time to treatment failure (TTF), OS, disease control rate (DCR), 1- and 2-year survival rates, and frequency of adverse events (AEs).

The study was approved by the Institutional Review Boards of all participating institutions and was performed in accordance with the Declaration of Helsinki, the International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, Good Clinical Practice, and local laws. All patients provided written informed consent.

The trial is registered with the Japan Registry of Clinical Trials (JRCT) as trial number 031180136, and the University Hospital Network (UMIN) as trial number 000017877.

Patients and Treatment

Patients were aged ≥ 75 years, with histologically or cytologically confirmed stage III/IV disease (according to the General Rule for Clinical and Pathological Record of Lung Cancer, 7th edition)[21] or recurrent NSCLC, ≥ 1 measurable lesion (per Response Evaluation Criteria in Solid Tumours [RECIST] version 1.1), and *EGFR* Del19- or L858R-positive disease (see Supplementary Methods). An ECOG PS of 0–1, and a life expectancy of > 3 months was required. Previous treatment with chemotherapy or EGFR-targeting therapy was not allowed, and patients with active lung disease, and hypersensitivity to the study drug were excluded.

Patients received afatinib at a starting dose of 40 mg/day until disease progression or unacceptable toxicity. Continuation of afatinib treatment after disease progression was permitted. Appropriate prevention and management of designated AEs (diarrhoea and skin disorders) was provided through treatment interruptions and dose reductions. Dose adjustments were implemented for Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 grade ≥ 3 AEs or prolonged selected grade 2 AEs (including diarrhoea, stomatitis, rash, nausea, vomiting) despite best supportive care. During treatment interruptions, afatinib was suspended until severity recovered to grade ≤ 1 or baseline severity. If recovery was achieved within 14 days, afatinib was resumed at a lower dose by 10-mg decrements to a minimum of 20 mg/day; otherwise, dosing was permanently discontinued. If 20 mg/day was intolerable, afatinib was permanently discontinued.

Outcomes and Assessments

Radiographic evaluation was performed every 8 weeks, and then every 12 weeks after 1 year. Response was assessed by extramural central review, including by the executive secretariat, according to RECIST version 1.1. Tumour response was defined as the proportion of patients with a complete response (CR) or partial response (PR). Tumour responses were confirmed by reassessment after 4 weeks.

Definitions of secondary endpoints, including PFS, OS, DCR, and TTF, are included in the Supplementary Methods. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Japanese

version 13.1 and graded by the CTCAE version 4.0. AEs were monitored throughout the study period, and worst grade was reported.

EGFR mutation analysis is described in the Supplementary Methods

Statistical Considerations

A sample size of 35 patients was required based on the assumption that an expected ORR of > 70% would be clinically acceptable efficacy, and < 45% would be unacceptable (Supplementary Methods).

The safety analysis set (SAS) included all enrolled patients who received at least one dose of afatinib. The full analysis set (FAS) comprised all patients in the SAS, excluding those who had not been evaluated after starting treatment, and those who did not have an adequately evaluated lesion. Tumour response was evaluated in the FAS. Time-to-event data are descriptive and were estimated using Kaplan–Meier methodology (Supplementary Methods). The last date of confirmation of survival was 18th October 2019.

The collection, management, and statistical analysis of patient data was outsourced to an independent organisation without involvement of the researchers or sponsor.

Role of the Funding Source

The study was funded by Nippon Boehringer Ingelheim Co. Ltd. The sponsor had no involvement in the study design, collection, analysis or interpretation of data, or in the decision to submit the article for publication.

Results

Patients

Between January 28, 2016, and September 14, 2017, 38 patients were enrolled and treated in the SAS. One patient was excluded with no appropriate measurable lesion; thus, the FAS comprised 37 patients (Supplementary Figure 1).

In the SAS population, the median age was 77.5 years (range 75–91), 15 (39.5%) patients were male, and all patients had an ECOG PS of 0–1 (Table 1). The most frequent baseline comorbidities were hypertension in 19 (50%) patients and hyperlipidaemia in 15 (39%) patients. Other complications included diabetes mellitus, thyroid disease, and chronic obstructive pulmonary disease, in 2 patients each. More than one third of patients (34.2%) had brain metastases. *EGFR* Del19 was more common than L858R mutation. There were no marked differences in baseline characteristics between the SAS and FAS populations (Table 1).

Antitumour Activity

Tumour response is summarised in Table 2 (individual patient responses are detailed in Supplementary Figure 2). The ORR was 75.7% (95% confidence interval [CI], 58.8–88.2) overall and was not markedly different in patients with *EGFR* Del19- versus L858R-positive tumours (72.7% vs. 80.0%). The DCR was also similar between these subgroups (86.4% vs. 93.3%).

The median follow-up period was 834 days (range 73–1156). Median PFS was 14.2 months (95% CI, 9.5–19.0). Median OS was 35.2 months (95% CI, 35.2–not reached), and 1- and 2-year OS rates were 83.8% and 78.3%, respectively. Median TTF was 18.7 months (95% CI, 10.6–22.5; Figure 1).

In patients with *EGFR* Del19- or L858R-positive tumours, median PFS was 18.2 months and 12.9 months, respectively (Supplementary Figure 3). Median OS was not reached in patients with Del19-positive tumours and was 35.2 months in those with L858R-positive disease; 2-year OS rates were 77.0% and 80.0%, respectively. The median TTF was 18.6 months in patients with Del19-positive tumours and 19.2 months in those with L858R-positive disease.

Treatment Exposure and Safety

In the SAS, median duration of treatment was 494 days (range 8–950). Thirty (78.9%) patients required at least one dose reduction of afatinib (Table 3). Treatment duration and afatinib dosage in individual patients is summarised in Figure 2. Twenty-eight patients discontinued afatinib treatment, mainly due to disease progression (15 patients). At data cut-off, 9 patients remained on treatment without disease progression, including the 1 patient excluded from the FAS, and 1 patient treated at < 20 mg (Supplementary Figure 1).

TRAEs are summarised in Table 4. Grade 3/4 TRAEs were reported in 28 (73.7%) patients; the most common were diarrhoea (11 [28.9%]), paronychia (9 [23.7%]), and rash/acne (6 [15.8%]). Thirty (78.9%) patients had TRAEs leading to afatinib dose reductions, and 28 (73.7%) had TRAEs leading to afatinib treatment interruptions; the most common reasons for dose reductions or interruptions were diarrhoea (26 events) and rash/acne (20 events; Figure 2). Eight (21.1%) patients discontinued treatment due to TRAEs; 4 had pneumonitis, 2 had paronychia, 1 had rash, and 1 had appetite loss and oedema. There were 14 recorded deaths, none of which was treatment related. Thirteen patients died due to lung cancer progression and one from debility due to dementia progression.

Treatment after Disease Progression

Twelve patients with disease progression continued afatinib beyond progression for > 30 days, and 1 was still receiving afatinib at data cut-off. Of the 28 patients who discontinued afatinib, 8 did not receive any further treatment, while 20 received second-line treatments (osimertinib n = 5, other EGFR-TKIs n = 7, cytotoxic agents alone n = 5, platinum-doublet chemotherapy n = 2, pembrolizumab n = 1). In total, 8 patients received osimertinib during the observation period (3 in third or later lines).

Discussion

In this study, we examined elderly patients aged ≥ 75 years (median [range] 77.5 [75–91] years); this has been identified previously as a relevant cut-off when considering the age at which more effective and tolerable therapies compared with chemotherapy are needed.[16,22] Baseline patient and disease characteristics were largely similar to those reported in two previous investigations of afatinib in Japanese patients aged ≥ 75 years (median [range] 79 [75–87] years)[19] and > 70 years (median [range] 77 [70–85] years),[20] and in a subgroup analysis of older patients in the LUX-Lung 7 study (median [range] 79 [75–86] years).[16] However, the frequency of patients with Del19-positive disease (61%) was slightly higher than reported in elderly patients in the other two Japanese studies (20% to 55%), [19,20] and in the LUX-Lung 7 subanalysis (37%).[16] Most patients (84%) in the current study had comorbidities, the most common being hypertension, and more than one third (34%) had baseline brain metastases.

The ORR was 75.7%, and the primary endpoint of the study was met. Clinical activity of afatinib with respect to response and other efficacy outcomes (PFS and OS) was encouraging, consistent with other studies in elderly Japanese patients treated with afatinib in the same setting.[19,20] Efficacy outcomes were also similar in patients with *EGFR* Del19- and L858R-postive tumours, as reported previously.[20]

The safety profile of afatinib was as expected from EGFR TKI treatment in elderly Japanese patients,[13,20,23] and was manageable with dose reductions. Previous data suggest that Japanese patients are more likely to develop pneumonitis than patients of other nationalities when treated with EGFR TKIs.[24] In the current study, 5 (13.2%) patients had treatment-related pneumonitis (1 grade 3 and 1 grade 4), 4 of whom discontinued treatment. Similarly, in a previous phase II study of elderly Japanese patients treated with afatinib, pneumonitis was reported in 4 (10%) patients, 1 of whom had grade 3 pneumonitis and 2 of whom died whilst on treatment, suggesting that elderly patients treated with an EGFR TKI should be monitored for pneumonitis.[20]

The starting dose of afatinib in the current study was 40 mg; however, a previous phase II study in elderly Japanese patients reported acceptable tolerability and encouraging antitumour activity with a starting dose of 30 mg afatinib.[20] This raises discussion on whether the afatinib starting dose should be lower than 40 mg in older Japanese patients, and as low as 20 mg in some instances.[20] Nevertheless, while dose reductions due to AEs were more frequent in the current study compared with the previous phase II study (79% vs. 48%), rates of treatment discontinuation were comparable (21% vs. 20%). Further, post-hoc analyses of LUX-Lung 3, 6, and 7 showed that reductions from the afatinib 40 mg starting dose had no effect on therapeutic efficacy.[25-27] Therefore, our findings of promising efficacy and manageable toxicity with afatinib 40 mg may argue against using a reduced starting dose in elderly Japanese patients with good performance status. Instead, starting at 40 mg and employing dose reductions may mitigate the effects of potential interpatient differences in drug pharmacokinetics/pharmacodynamics, while reducing the possibility of under treatment at lower afatinib doses.

There is accumulating evidence that TKIs may be more effective in elderly than in younger patients with *EGFR* mutation-positive NSCLC.[18,26] Moreover, given that kinase inhibitors usually show milder toxicity

than cytotoxic chemotherapy, the current Japanese Lung Cancer Society guideline for stage IV NSCLC recommends (level 1C) the use of any EGFR TKI for the first-line treatment of elderly patients with a driver oncogene.[17] In this regard, afatinib may be a suitable choice for elderly patients with *EGFR* mutation-positive NSCLC who are receiving multiple concomitant medications, due to its reported low potential for drug–drug interactions, and low exposure to hepatic metabolism and excretion.[28]

The interpretation of this analysis should be treated with caution due to limitations, including the single-arm design of the study, and the small numbers of patients investigated overall and in *EGFR* mutation subgroups.

Conclusion

Afatinib at a starting dose of 40 mg was well tolerated with dose adjustments, and was associated with encouraging antitumour activity in Japanese patients aged ≥ 75 years, with *EGFR* mutation-positive NSCLC.

Abbreviations

EGFR: epidermal growth factor receptor; TKI: tyrosine kinase inhibitors; NSCLC: non-small cell lung cancer; AE: adverse event; ORR: objective response rate; DCR: disease control rate; PFS: progression-free survival; OS: overall survival; TTF: time to treatment failure; TRAE: treatment-related AE; del19: *EGFR* exon 19 deletions; ECOG: Eastern Cooperative Oncology Group; PS: performance status; RECIST: Response Evaluation Criteria in Solid Tumours; CTCAE: common Terminology Criteria for Adverse Events; CR: complete response; PR: partial response; CR, complete response; DCR, disease control rate; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.; CI, confidence interval; MedDRA :Medical Dictionary for Regulatory Activities; SAS: The safety analysis set; FAS: the full analysis set; BMI: body mass index; RT, radiotherapy; SRS, stereotactic radiosurgery; QOD, every other day; ALT, alanine aminotransferase; AST, aspartate aminotransferase; NR, not reached.

Declarations

Ethics approval and consent to participate

The study was approved by the Institutional Review Boards of all participating institutions and was performed in accordance with the Declaration of Helsinki, the International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, Good Clinical Practice, and local laws. All patients provided written informed consent. The trial is registered with the Japan Registry of Clinical Trials (JRCT) as trial number 031180136, and the University Hospital Network (UMIN) as trial number 000017877.

Consent for publication

Not applicable.

Availability of data and materials

Data available upon reasonable request from the corresponding author.

Competing interests

O.Y. reports honoraria from Ono Pharmaceutical Co., Ltd., Bristol-Myers Squibb, Taiho Pharmaceutical Co., Ltd., MSD, Chugai Pharmaceutical Co., Ltd., and AstraZeneca. S.S. reports honoraria from Nippon Boehringer Ingelheim Co., Ltd., AstraZeneca, Chugai Pharmaceutical Co., Ltd., MSD, Bristol-Myers Squibb, Ono Pharmaceutical Co., Ltd., Eli Lilly and Company, Pfizer, Novartis, Taiho Pharmaceutical Co., Ltd., and Kyowa Hakko Kirin Co., Ltd. S.W. reports honoraria from Eli Lilly and Company, Pfizer, Novartis, AstraZeneca, Chugai Pharmaceutical Co., Ltd., Bristol-Myers Squibb, Boehringer Ingelheim, MSD, Ono Pharmaceutical Co., Ltd., Daiichi Sankyo and Taiho Pharmaceutical Co., Ltd. M.M. reports honoraria from AstraZeneca, Boehringer Ingelheim, Chugai Pharmaceutical Co., Ltd., Eli Lilly and Company, MSD, Novartis Pharma, Ono Pharmaceutical Co., Ltd. and Taiho Pharmaceutical Co., Ltd. O.H. reports honoraria from AstraZeneca, Boehringer Ingelheim and Novartis, and grants or funds from GlaxoSmithKline, AstraZeneca, Novartis, Bayer Health Care, Boehringer Ingelheim and Daiichi Sankyo. S.M. reports honoraria from AstraZeneca K.K., Bristol-Myers Squibb, Chugai Pharmaceutical Co. Ltd., Eisai Co., Ltd., Eli Lilly Japan K.K., MSD K.K., Nippon Boehringer Ingelheim Co., Ltd., Ono Pharmaceutical Co., Ltd., Pfizer Japan Inc., and Taiho Pharmaceutical Co. Ltd., and research funding to their institution from Nippon Boehringer Ingelheim Co., Ltd. K.K. reports honoraria (speech fees) from AstraZeneca, Boehringer Ingelheim, Bristrol-Myers Squibb, Pfizer, Eli Lilly and Company, Taiho Pharmaceutical Co., Ltd., Chugai Pharmaceutical Co. and Ono Pharmaceutical Co., Ltd. A.G. reports honoraria from Boehringer Ingelheim. Y.M., S.K. K.U. and T.N. declare no conflict of interest.

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Authors' contributions

Y.M. contributed to study design, data acquisition, data analysis and interpretation, and manuscript preparation and review. O.Y., S.S., S.K., S.W., K.U., M.M. and O.H. contributed to data acquisition and manuscript review. T.N. contributed to study design and manuscript review. S.M. contributed to study design, statistical analysis and manuscript review. K.K. contributed to data acquisition, quality control of data and algorithms, and manuscript review. A.G. contributed to study concept and design, and manuscript editing and review. All authors approved the final version of the manuscript, and agree to be accountable for all aspects of the work.

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Tables

Table 1 Patient and Disease Characteristics at Baseline in the Safety Analysis Set and Full Analysis Set

Characteristic	Safety analysis set N = 38	Full analysis set N = 37
Sex,		
Male	15 (39.5)	15 (40.5)
Female	23 (60.5)	22 (59.5)
Age, years		
Median (range)	77.5 (75–91)	77.0 (75–91)
Weight, kg		
Median (range)	50.2 (30.8–72.2)	50.5 (30.8–72.2)
BMI, kg/m^2		
Median (range)	21.0 (16.5–26.0)	21.2 (16.5–26.0)
Smoking status		
Never	26 (68.4)	25 (67.6)
Former/current	12 (31.6)	12 (32.4)
ECOG PS		
0	21 (55.3)	20 (54.1)
1	17 (44.7)	17 (45.9)
Histological classification		
Adenocarcinoma	38 (100)	37 (100)
Clinical stage at study entry		
IIIB	1 (2.6)	1 (2.7)
IV	28 (73.7)	28 (75.7)
Postoperative recurrence	9 (23.7)	8 (21.6)
Comorbidities		
Yes	32 (84.2)	31 (83.8)
No	6 (15.8)	6 (16.2)
Metastases at study entry		
No distant metastases	4 (10.5)	4 (10.8)
Lung	10 (26.3)	10 (27.0)

Bone	13 (34.2)	13 (35.1)
Post-palliative RT	1 (2.6)	1 (2.7)
Brain	13 (34.2)	13 (35.1)
Post palliative SRS	3 (7.9)	3 (8.1)
Liver	4 (10.5)	4 (10.8)
Pleural	11 (28.9)	11 (29.7)
EGFR mutation categories		
Del19	23 (60.5)	22 (59.5)
L858R	15 (39.5)	15 (40.5)

Data are n (%) unless otherwise stated.

Abbreviations: BMI = body mass index; ECOG PS = Eastern Cooperative Oncology Group performance status; *EGFR* = epidermal growth factor receptor; RT = radiotherapy; SRS = stereotactic radiosurgery.

Table 2 Tumour Response

Parameter	**Full analysis set**	***EGFR* mutation**	
	N = 37	**Del19**	**L858R**
		n = 22	**n = 15**
Best response, n (%)			
CR	2 (5.4)	2 (9.1)	0
PR	26 (70.3)	14 (63.6)	12 (80.0)
SD	5 (13.5)	3 (13.6)	2 (13.3)
PD	2 (5.4)	1 (4.5)	1 (6.7)
NE	2 (5.4)	2 (9.1)	0
ORR, n (%)	28 (75.7)	16 (72.7)	12 (80.0)
(95% CI)	(58.8–88.2)	(49.8–89.3)	(51.9–95.7)
DCR, n (%)	33 (89.2)	19 (86.4)	14 (93.3)
(95% CI)	(74.6–97.0)	(65.1–97.1)	(68.1–99.8)

Abbreviations: CI = confidence interval; CR = complete response; DCR = disease control rate; *EGFR* = epidermal growth factor receptor; NE = not evaluable; ORR = objective response rate; PD = progressive disease; PR = partial response; SD = stable disease.

Table 3 Afatinib Exposure and Treatment Adjustment Due to Treatment-Related Adverse Events

Category	Safety analysis set N = 38
Afatinib exposure	
Median treatment duration[a], days (range)	494 (8–950)
Median treatment days[b], n (range)	492 (8–932)
Mean afatinib dose[c], mg	29.7 (10.6–40.0)
Median relative dose intensity[d], % (range)	74.2 (26.4–100)
Treatment adjustments, n (%)	
Initial treatment dose 40 mg	38 (100)
Dose reduction	30 (78.9)
Final treatment dose	
40 mg	8 (21.1)
30 mg	12 (31.6)
20 mg	14 (36.8)
30 mg QOD	1 (2.6)
20 mg QOD	3 (7.9)
Treatment interruption	28 (73.7)
Treatment discontinuation	8 (21.1)

QOD, every other day; TRAEs, treatment-related adverse events.

Data are n (%) unless otherwise stated. In addition to afatinib exposure, data for dose reductions, treatment interruption and discontinuation due to TRAEs are shown.

[a] From start of treatment to discontinuation or censoring, including days of treatment interruption.

[b] Not including treatment interruption days.

[c] Total afatinib dose/treatment duration.

[d] (mean afatinib dose/40) x 100.

Table 4 Treatment-related Adverse Events

Adverse event	Any grades	Grade I or II	Grade III or IV
Any	38 (100)	10 (26.3)	28 (73.7)
Diarrhoea	36 (94.7)	25 (65.8)	11 (28.9)
Rash/acne[a]	30 (78.9)	24 (63.2)	6 (15.8)
Paronychia	26 (68.4)	17 (44.7)	9 (23.7)
Stomatitis	26 (68.4)	21 (55.3)	5 (13.2)
Appetite loss	13 (34.2)	8 (21.1)	5 (13.2)
Vomiting	6 (15.8)	5 (13.2)	1 (2.6)
Pneumonitis	5 (13.2)	3 (7.9)	2 (5.3)[b]
Fatigue	5 (13.2)	5 (13.2)	0
Nausea	4 (10.5)	4 (10.5)	0
Oedema	4 (10.5)	4 (10.5)	0
Infection	4 (10.5)	3 (7.9)	1 (2.6)
ALT/AST increased	9 (23.7)	8 (21.1)	1 (2.6)
Creatinine increased	8 (21.1)	8 (21.1)	0
Anaemia	8 (21.1)	7 (18.4)	1 (2.6)
Hypoalbuminemia	8 (21.1)	8 (21.1)	0
Thrombocytopenia	6 (15.8)	6 (15.8)	0
Hypokalaemia	6 (15.8)	5 (13.2)	1 (2.6)
Leukocytopenia	4 (10.5)	4 (10.5)	0

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; TRAE = treatment-related adverse event.

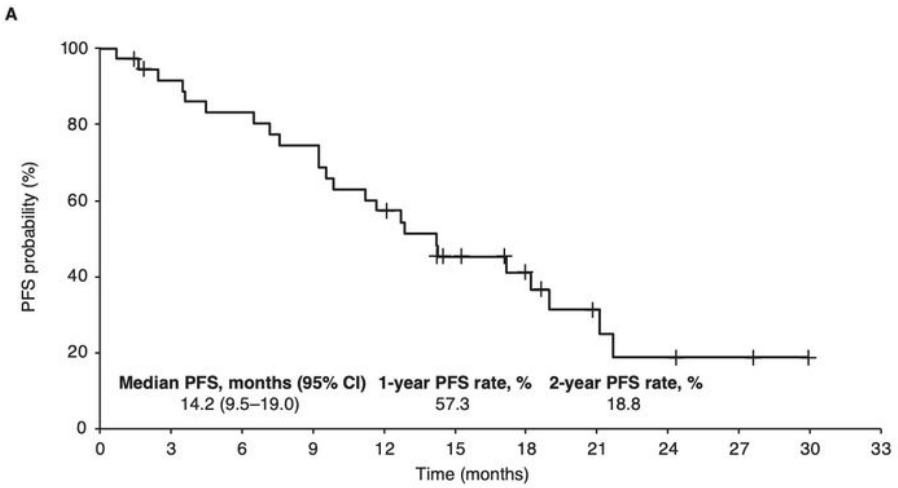
Data are n (%) TRAEs in > 10% of patients in the safety analysis set (n = 38) listed by Medical Dictionary for Regulatory Activities (MedDRA) preferred terms and grade by Common Terminology Criteria for

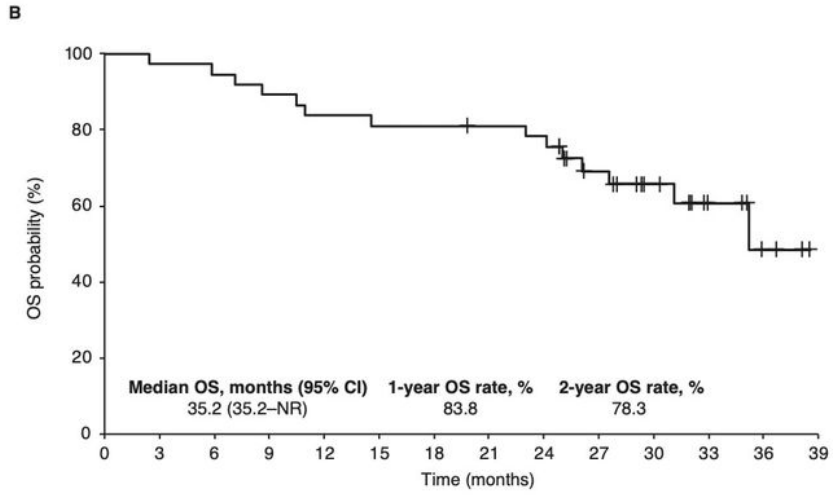
Adverse Events (CTCAE), version 4.0.

[a] Includes papulopustular rash, rash pustular, and rash acneiform.

[b] Includes one patient with grade IV pneumonitis.

Figures





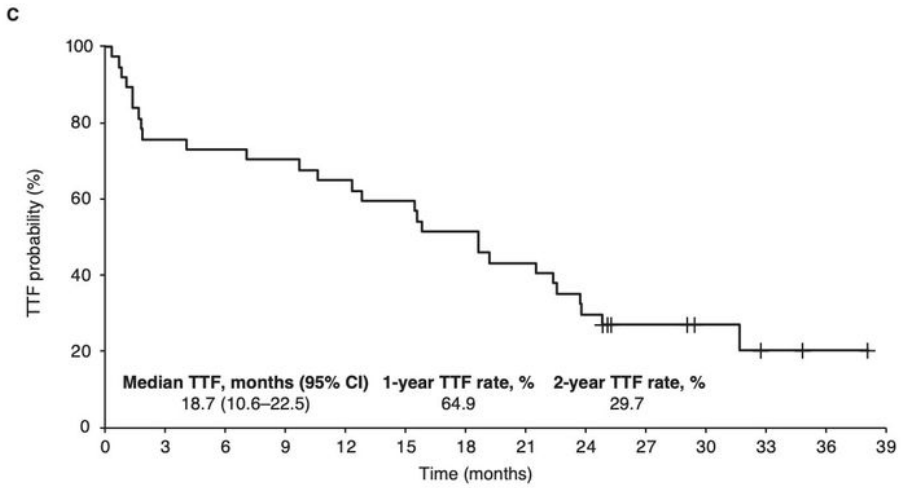


Figure 1

Kaplan–Meier Survival Analysis In The Full Analysis Set (n = 37). (A) Progression-free Survival (PFS)a. (B) Overall Survival (OS). (C) Time to Treatment Failure (TTF). Abbreviations: CI = confidence interval; NR = not reached; QOD = every other day. aPFS was Censored for 4 Patients Receiving Afatinib < 20 mg/day. These Patients Were Treated as Censored When They Fell below the 20 mg/day Minimum Dose Specified in the Protocol.

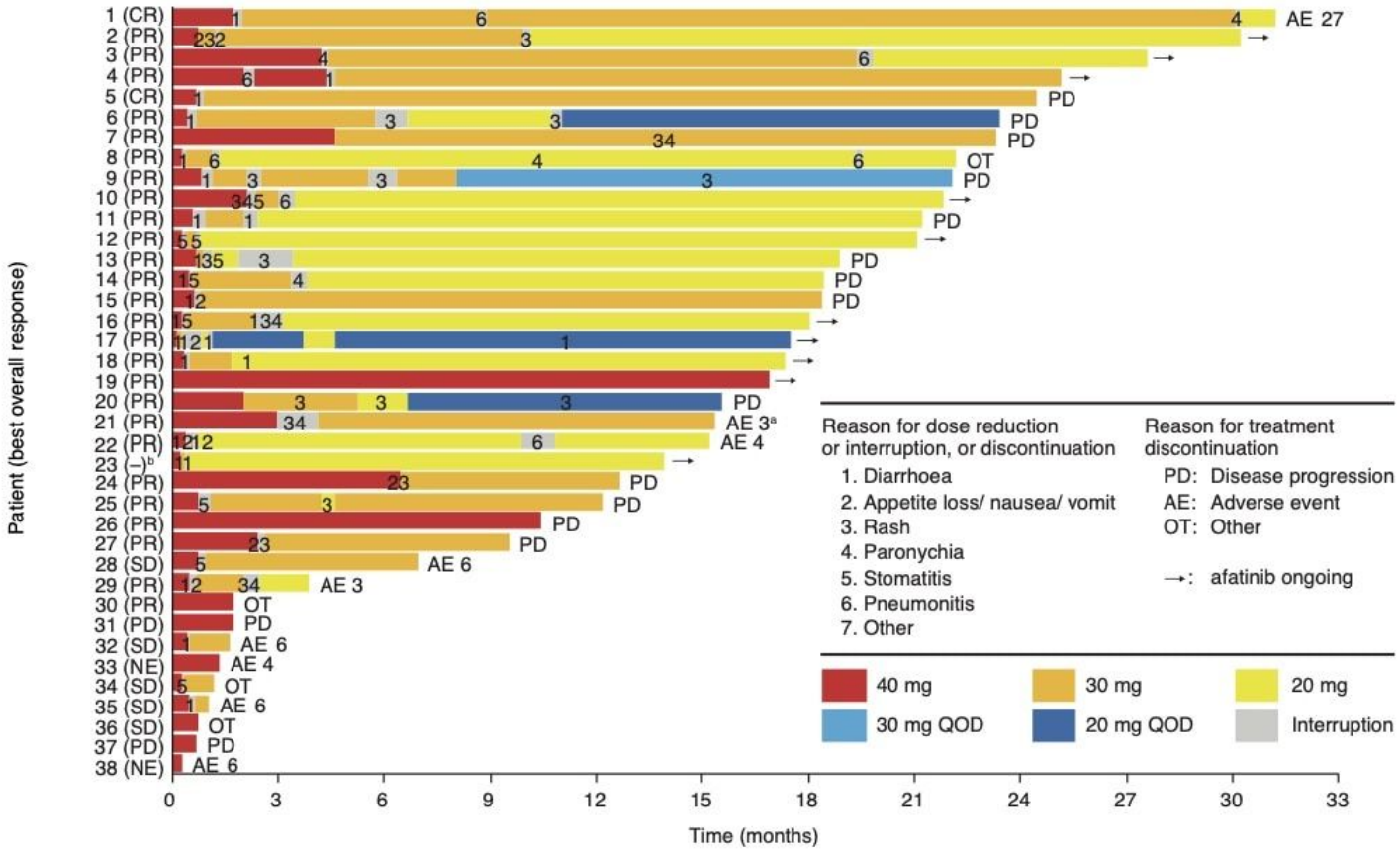


Figure 2

Treatment Duration and Afatinib Dose in the Safety Analysis Set (n = 38). Abbreviations: AE = adverse event; CR = complete response; NE = not evaluable; OT = other; PD = progressive disease; PR = partial response; QOD = every other day; SD = stable disease. aFor Patient 21, Protocol Treatment was Discontinued Due to Disease Progression; Thereafter, Afatinib Treatment Beyond PD was Discontinued Due to Skin Disorders. bOne Patient Had No Appropriate Measurable Lesion and was not Included in the Full Analysis Set.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- NEJ027SupplementarymaterialFINAL.docx