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Kei Morikawa, Saori Takata, Hisashi Tanaka, Hidetoshi Itani, Masashi Ishihara, Kazuya Horiuchi, Yasuhiro Kato, Shinnosuke Ikemura, Hideyuki Nakagawa, Yoshiro Nakahara, Yoshitaka Seki, Akihiro Bessho, Nobumasa Takahashi, Kentaro Hayashi, Takeo Endoh, Kiyoshi Takeyama, Toshiya Maekura, Nagio Takigawa, Akikazu Kawase, Makoto Endoh, Kenji Nemoto, Kazuma Kishi, Kenzo Soejima, Yusuke Okuma, Kenichi Yoshimura, Daisuke Saigusa, Yae Kanai, Koji Ueda, Akira Togashi, Noriyuki Matsutani & Nobuhiko Seki

Efficacy and Safety Findings of the EXTRA Study in Older Adult EGFR-Mutant Lung Cancer Patients Receiving Afatinib as First-Line Treatment

Kei Morikawa[1], Saori Takata[2], Hisashi Tanaka[3], Hidetoshi Itani[4], Masashi Ishihara[5], Kazuya Horiuchi[6], Yasuhiro Kato[7], Shinnosuke Ikemura[8], Hideyuki Nakagawa[9], Yoshiro Nakahara[10], Yoshitaka Seki[11], Akihiro Bessho[12], Nobumasa Takahashi[13], Kentaro Hayashi[14], Takeo Endoh[15], Kiyoshi Takeyama[16], Toshiya Maekura[17], Nagio Takigawa[18], Akikazu Kawase[19], Makoto Endoh[20], Kenji Nemoto[21], Kazuma Kishi[22], Kenzo Soejima[23], Yusuke Okuma[24], Kenichi Yoshimura[25], Daisuke Saigusa[26], Yae Kanai[27], Koji Ueda[28], Akira Togashi[29], Noriyuki Matsutani[30], Nobuhiko Seki[31]*

[1]Department of Internal Medicine, St. Marianna University School of Medicine, Kanagawa, Japan; mokke@marianna-u.ac.jp

[2]Department of Respiratory Medicine, Kyorin University School of Medicine, Tokyo, Japan; s-takata@ks.kyorin-u.ac.jp

[3]Department of Respiratory Medicine Hirosaki University Graduate, Aomori, Japan; xyghx335@gmail.com

[4]Department of Respiratory Medicine, Japanese Red Cross Ise Hospital, Mie, Japan; ittann0630@gmail.com

[5]Division of Medical Oncology, Department of Internal Medicine, Teikyo University School of Medicine, Tokyo, Japan; mt.medical1224@gmail.com

[6]Respiratory Disease Center, Showa University Northern Yokohama Hospital, Kanagawa, Japan; kazuya.horiuchi.0921@gmail.com

[7]Departments of Thoracic Oncology and Respiratory Medicine, Tokyo Metropolitan Cancer and Infectious Diseases Center, Tokyo, Japan; y-kato@nms.ac.jp

[8]Division of Pulmonary Medicine, Keio University Hospital, Tokyo, Japan; ike_shinnosuke.a5@keio.jp

[9]Department of Respiratory Medicine, National Hospital Organization, Hirosaki Hospital, Aomori, Japan; nakahide@hirosaki-hosp.jp

[10]Department of Respiratory Medicine, Kitasato University School of Medicine, Kanagawa, Japan; md100062@kitasato-u.ac.jp

[11]Department of Internal Medicine, The Jikei University Daisan Hospital, Tokyo, Japan; sekiyoshi@gmail.com

[12]Department of Respiratory Medicine, Japanese Red Cross Okayama Hospital, Okayama, Japan; abessho@okayama-med.jrc.or.jp

[13]Department of General Thoracic Surgery, Saitama Cardiovascular and Respiratory Center, Saitama, Japan; takahashi.nobumasa@pref.saitama.lg.jp

[14]Division of Respiratory Medicine, Department of Internal Medicine, Nihon University School of Medicine, Tokyo, Japan; hayashi.kentaro@nihon-u.ac.jp

[15]National Hospital Organization Mito Medical Center, Ibaraki, Japan; endo.takeo.sb@mail.hosp.go.jp

[16]Department of Respiratory Medicine, Tokyo Women's Medical University School of Medicine, Tokyo, Japan; takeyama.kiyoshi@twmu.ac.jp

[17]Department of Respiratory Medicine, Hoshigaoka Medical Center, Osaka, Japan; toshiya1027@gmail.com

[18]Department of General Internal Medicine 4, Kawasaki Medical School, Okayama, Japan; ntakigaw@gmail.com

[19]First Department of Surgery, Hamamatsu University School of Medicine, Shizuoka, Japan; akawase@hama-med.ac.jp

[20]Department of Thoracic Surgery, Yamagata Prefectural Central Hospital, Yamagata, Japan; m-endoh@ypch.gr.jp

[21]Department of Respiratory Medicine, National Hospital Organization, Ibarakihigashi National Hospital, Ibaraki, Japan; nemoken1124@yahoo.co.jp

[22]Department of Respiratory Medicine, Respiratory Center, Toranomon Hospital, Tokyo, Japan; kazuma.kishi@med.toho-u.ac.jp

[23]Clinical and Translational Research Center, Keio University Hospital, Tokyo, Japan; ksoejima@yamanashi.ac.jp

[24]Departments of Thoracic Oncology and Respiratory Medicine, Tokyo Metropolitan Cancer and Infectious diseases Center Komagome Hospital, Tokyo, Japan; yokuma@ncc.go.jp

[25]Medical Center for Translational and Clinical Research, Hiroshima University Hospital, Hiroshima, Japan; keyoshim@hiroshima-u.ac.jp

[26]Laboratory of Biomedical and Analytical Sciences, Faculty of Pharma-Science, Teikyo University, Tokyo, Japan; saigusa.daisuke.vf@teikyo-u.ac.jp

[27]Department of Pathology, Keio University School of Medicine Tokyo, Japan; ykanai@keio.jp

[28]Project for Realization of Personalized Cancer Medicine, Cancer Precision Medicine Center, Japanese Foundation for Cancer Research, Tokyo, Japan; koji.ueda@jfcr.or.jp

[29]Nippon Boehringer Ingelheim Co., Ltd., Tokyo, Japan; akira.togashi@boehringer-ingelheim.com

[30]Department of Surgery, Teikyo University Mizonokuchi Hospital, Kanagawa, Japan; matsutan@med.teikyo-u.ac.jp

[31]Division of Medical Oncology, Department of Internal Medicine, Teikyo University School of Medicine, Tokyo, Japan; nseki@med.teikyo-u.ac.jp

***Corresponding author**: Nobuhiko Seki

Division of Medical Oncology, Department of Internal Medicine, Teikyo University School of Medicine

2-11-1 Kaga, Itabashi-ku, Tokyo 173-8605, Japan

Tel.: +81 3 3964 1211

Fax: +81 3 3964 9177

E-mail: nseki@med.teikyo-u.ac.jp

Abstract

The EXTRA trial was the first to identify predictive biomarkers for afatinib efficacy in *epidermal growth factor receptor (EGFR)*-mutant NSCLC. We analyzed the clinical data of older adult patients before translational analysis. This prospective study involved untreated patients with EGFR-mutant NSCLC who received afatinib at an initial dose of 40 mg/day, followed by stepwise dose reductions, ultimately reaching 20 mg administered every other day. Treatment efficacy and adverse events (AEs) were compared between non-older and older adult patients. Among the 103 patients, 71 were aged <75 years, and 32 were aged ≥75 years. Despite increased dose reductions in the older adults, progression-free survival was comparable: 21.5 vs. 18.6 months for non-older and older adults, respectively. The median overall survival (OS) was not reached in either group; the 2-year OS rates were 82% and 75% in non-older and older adults, respectively. Median post-progression survival in patients administered second-line drug therapy was 14.3 and 11.2 months in non-older (*n*=42) and older adults (*n*=20), respectively. Among older adults, 31 (97%) patients experienced AEs of all grades, and only six patients had grade ≥3 AEs with no grade 5 AEs. Afatinib demonstrated comparable therapeutic efficacy and safety in older and non-older adult patients with advanced *EGFR*-mutant NSCLC.

Trial registration: UMIN-CTR identifier (UMIN000024935)

Keywords: Afatinib; EGFR-TKI; elderly patient; non-small-cell lung cancer (NSCLC)

Introduction

The use of molecular targeted drugs has dramatically improved treatment outcomes for non-small cell lung cancer (NSCLC) harboring genetic alterations.[1-3] In particular, the treatment landscape for EGFR-mutated NSCLC is characterized by diverse therapeutic strategies, including chemotherapy or an anti-angiogenic agent, and was the first to be treated with gefitinib (an *EGFR*-tyrosine kinase inhibitor [TKI]) in Japan in 2002. Since then, many clinical trials have been conducted on *EGFR*-mutant NSCLC patients, including Eastern Asians, women, and non-smokers.[4,5] Past clinical trials and real-world data (RWD) suggest that *EGFR*-mutant NSCLC includes many older adult patients.[6] Therefore, the clinical implementation focused on older adult patients in the aged society is important for oncologists outside of clinical trials [6-8] since the treatment improves the prognosis even in older adult people aged ≥85 years.[9] In Japan, several EGFR TKIs are available for first-line treatment, and clinical guidelines recommend treatment based on different therapeutic efficacy and adverse event (AE) profiles for specific populations, including age or frailty.[10,11]

Osimertinib shows a clinically significant therapeutic effect compared with first-generation EGFR-TKIs (standard of care [SOC] group) and establishes a solid position as a first-line treatment for advanced *EGFR*-mutant NSCLC.[12] However, the point estimate of the hazard ratio (HR) for the osimertinib group versus the SOC group was >1 (HR: 1.39; 95% CI: 0.83–2.34), and the median overall survival (OS) for the osimertinib group was 39.3 months (not reached in the SOC group); notably, this subgroup analysis was statistically underpowered,[13] and the follow-up period was shorter than that of previous clinical trials.[14,15] Moreover, RWD suggests that osimertinib frequently causes drug-induced pneumonia, especially in the older adults.[16,17]

Hence, there is a persistent clinical question regarding whether osimertinib is the best EGFR-TKI as a first-line treatment in the Japanese population. In addition, age-specific subgroup analyses in Japanese patients have not been reported in the FLAURA trial. Consequently, the most appropriate treatment strategy for EGFR-mutant lung cancer in older adults in Japan remains unclear. Notably, only a limited number of prospective single-arm phase II studies evaluating afatinib have been conducted.[18,19]

We have been conducting exosome-focused translational research for afatinib (EXTRA) study to elucidate the therapeutic effects of afatinib as a first-line treatment and to decipher mechanisms of drug resistance using omics analyses of plasma.[20,21] Prior to the omics analysis, which constitutes the core of this study, we performed an analysis of the clinical data with a particular focus on elderly patients, given the limited available evidence and the substantial unmet clinical needs in this population.

Methods

Study design

The EXTRA study was designed as a prospective, single-arm, observational study to identify novel predictive biomarkers for longer OS after first-line treatment with afatinib via a comprehensive association employing multiomics (genomics, proteomics, epigenomics, and metabolomics) analysis of serial peripheral blood samples (free molecules in sera/plasma and exosome-packaged molecules).[20]

Patient eligibility

The main inclusion criteria for registration were age ≥ 20 years, histologically or cytologically confirmed metastatic or locally advanced NSCLC, an *EGFR* mutation (common

or uncommon), Eastern Cooperative Oncology Group performance status (PS) of 0 or 1, and adequate bone marrow, renal, and liver function.

The main exclusion criteria were interstitial pneumonia or pulmonary fibrosis, active infection, uncontrolled disease, and other active malignant diseases.

Study treatment

Enrolled patients were initially treated with afatinib at a dose of 40 mg/day, which was adjusted according to the toxicities observed by the investigators. Patients who developed drug-related AEs (grade ≥ 2) temporarily refrained from receiving afatinib until recovery to grade 1, and the treatment was resumed with a 10 mg dose reduction of afatinib. For patients who developed drug-related AEs (grade ≥ 2) after decreasing the afatinib dose, the dose was further decreased by 10 mg. Dose reductions were allowed up to three times, and the minimum afatinib dose was set at 20 mg every alternate day. Once the dose was reduced, dose re-escalation was not permitted. Adverse events were prospectively monitored during treatment through scheduled clinical visits and laboratory evaluations, and severity was assessed using CTCAE version 4.0.

Treatment was discontinued in patients who developed afatinib-induced interstitial lung disease (grade ≥ 1) or in those requiring a fourth dose reduction. Treatment was continued until disease progression, unacceptable toxicity, or withdrawal of patient consent.

Assessment

Thoracoabdominal CT and head CT or MRI were used to evaluate tumor response. Tumor assessment was performed every 8 weeks for the first 24 weeks of treatment and every 12 weeks thereafter until progressive disease (PD), treatment discontinuation, withdrawal of consent, or death. The date of treatment initiation was defined as the reference date. Tumor

response was evaluated according to the Response Evaluation Criteria in Solid Tumors, version 1.1.

AEs were classified using the Medical Dictionary for Regulatory Activities, and their severity was assessed according to the Common Terminology Criteria for Adverse Events version 4.0.

Statistical analysis

The primary endpoint was the identification of novel predictive biomarkers of afatinib for a longer OS. The secondary endpoints were the following clinical indicators matched with the generated omics data: objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), OS, and AEs. ORR was defined as the percentage of patients with complete (CR) or partial (PR) radiological response. DCR was defined as the percentage of patients with CR, PR, or stable disease (SD). PFS was defined as the time from registration to confirmation of PD or death due to any cause. OS was defined as the time from registration to death from any cause.

The 95% CI for the ORR and DCR proportions was calculated using the Clopper–Pearson method. The median PFS and OS and their 95% CIs were estimated using the Kaplan–Meier method. Between-group comparisons were performed using the log-rank test. Statistical analyses were performed using the SAS ver. 9.4 (SAS Institute Inc., Cary, NC, USA). Fisher's exact test, chi-square test, and Mann–Whitney *U* test were used as appropriate to test the proportions between the two groups.

Ethics

This study complied with all principles of the Declaration of Helsinki (as revised in 2013) and was approved by the Ethical Review Board for Medical and Health Research Involving

Human Subjects at Teikyo University (Approval No. 16-066, November 10, 2016). Written informed consent was obtained from all the enrolled patients. This trial was registered with the University Hospital Medical Information Network Clinical Trial Registry (UMIN000024935).

Results

Among the 103 patients prospectively enrolled, 71 were aged < 75 years (non-older adult group), and 32 were aged ≥ 75 years (older adult group). The median age was 66.0 and 79.5 years for the non-older adult and older adult groups, respectively. No significant deviations in other clinical parameters were noted between the two groups (Table 1).

Based on cut-off data after a median observation period of 35 months, in the non-older adult group, first-line afatinib was discontinued in 51 (72%) patients (due to PD and AEs in 45 (88%) and 6 (12%) patients, respectively). In the older adult group, the treatment was discontinued in 30 (94%) patients (due to PD, AEs, and physicians' decisions in 25 (83%), 3 (10%), and 2 (7%) patients, respectively) (Figure 1).

The ORR in patients with evaluable lesions was 61.3% in the non-older adult group (*n*=62) and 77.4% in the older adult group (*n*=31) (chi-square test, *P*=0.185).

Median PFS was 21.5 months (95% CI, 13.6–25.7 months) in the non-older adult group (*n*=71) and 18.6 months (95% CI, 13.8–24.4) in the older adult group (*n*=32). The 1-year PFS rate was 70% in the non-older adult group, and 75% in the older adult group, and the 2-year PFS rate was 42% in the non-older adult group and 31% in the older adult group, indicating no significant difference in PFS between the two groups (log-rank test, *P*=0.3) (Figure 2A). In multivariate analysis, age was not a predictive factor for PFS (Table 2).

The median OS was not reached in either the non-older adult (*n*=71) or the older adult (*n*=32) groups. The 1-year OS rates were 92% and 88% in the non-older adult and older adult

groups, respectively, and the 2-year OS rates were 82% and 75% in the non-older adult and older adult groups, respectively, indicating no significant difference in the OS between the two groups (log-rank test, *P*=0.6) (Figure 2B). The multivariate analysis also showed that age was not a prognostic factor for OS (Table 2).

For the non-older adult group, the median afatinib treatment durations in patients with final reduced doses of 40 (*n*=23), 30 (*n*=18), and 20 (*n*=23) mg/day, and 20 mg every other day (*n*=7) were 16.3, 16.7, 16.4, and 26.9 months, respectively (Figure 3A).

In the older adult group, the median afatinib treatment durations in patients with final reduced doses of 40 (*n*=4), 30 (*n*=5), and 20 (*n*=12) mg/day, and 20 mg every other day (*n*=11) were 1.4, 15.4, 19.4, and 18.3 months, respectively (Figure 3B).

The median number of afatinib dose reductions was 2 (range, 0–3) in both the non-older adult and older adult groups, but the number of reductions was significantly greater in the older adult group than in the non-older adult group (Mann–Whitney *U* Test, *P*=0.001).

The non-older adult group had 70 (99%) cases of all grades of AEs, 18 (25%) cases of grade 3 or higher AEs, and 1 (1%) case of grade 5 pneumonitis. The older adult group had 31 cases (97%) of all grades of AEs, 6 (19%) cases of grade 3 or higher AEs, and no cases of grade 5 AEs (Table S1). Thus, no differences in the frequency of AEs were noted between the two groups (Mann–Whitney *U* test, *P*=0.874).

Notable adverse events included grade 3 or higher diarrhea in 10 (14%) patients in the non-older adult group and 1 (3%) patient in the older adult group (Fisher's exact test, *P*=0.166).

Among patients who discontinued afatinib as first-line treatment, 42 (82%) of 51 patients in the non-older adult group and 20 (67%) of 30 in the older adult group transitioned to second-line treatment (chi-square test, *P*=0.180). Among the patients who transitioned to

drug treatment, osimertinib was used in 11 (26.2%) patients in the non-older adult group and 14 (70%) patients in the older adult group (chi-square test, $P<0.001$).

Median post-progression survival (PPS) in patients administered second-line drug therapy was 14.3 months (95% CI, 20.7–NA) in the non-older adult group ($n=42$) and 11.2 months (95% CI, NA–NA) in the older adult group ($n=20$). The 1-year PPS rate was 75% in the non-older adult group and 66% in the older adult group, and the 2-year PPS rate was 46% in the non-older adult group and 51% in the older adult group, indicating a significant difference in PPS between the two groups (log-rank test, $P=0.1$) (Figure 4).

Discussion

In this subgroup analysis of the EXTRA study, we prospectively examined and compared the therapeutic efficacy and safety of afatinib for advanced/recurrent *EGFR*-mutant lung adenocarcinoma between the older adult and non-older adult groups. Although the cut-off data were based on a median observation period of 35 months, 28% of patients in the non-older adult group continued to receive afatinib, and the median PFS for this group was 21.5 months compared to 18.6 months for the older adult group. These results are considered potentially superior compared with those of similar previous studies, [18,19,22] and drug administration records suggest that dose reduction is significant in older adult patients to ensure tolerability and achieve sequential therapy.

It is pertinent to discuss two representative prospective studies evaluating EGFR-TKIs in older adult patients. One such study is the multicenter, single-arm, phase II NEJ027 trial (n=38), which investigated the antitumor activity and safety of first-line afatinib in treatment-naïve patients aged 75 years or older with advanced EGFR-mutant NSCLC harboring exon 19 deletions or exon 21 L858R mutations.[18] Afatinib was initiated at a dose of 40 mg/day.

The median patient age was 77.5 years; all patients had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–1, and 60.5% harbored exon 19 deletions. The median follow-up duration was 838 days. The primary endpoint, objective response rate (ORR), was achieved in 75.7% of the 37 patients evaluable for efficacy, including two complete responses and 26 partial responses. Patients with uncommon EGFR mutations were excluded, and the study population included 34% of patients with brain metastases and 34% with postoperative recurrence. The median progression-free survival (PFS) was 14.2 months, the median overall survival (OS) was 35.2 months, and the 2-year survival rate was 78.3%. Dose reductions due to treatment-related adverse events (TRAEs) were required in 78.9% of patients, and treatment discontinuation due to TRAEs occurred in 21.1% (8 patients); notably, no treatment-related deaths were reported.

In the multicenter, single-arm, phase II SPIRAL-0 study (n=38), the median patient age was 80 years, and 97% of patients had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–1; 42.1% harbored exon 19 deletions, and the median follow-up duration was 27.6 months.[23] Patients with uncommon EGFR mutations were excluded, whereas those with brain metastases (26%) and postoperative recurrence (29%) were included. The primary endpoint, the 1-year progression-free survival (PFS) rate, was 59.4% among the 38 patients evaluable for efficacy, which did not meet the predefined hypothesis of 70%. The 2-year survival rate was 75.1%, and the treatment discontinuation rate due to treatment-related adverse events (TRAEs) was 17.5%, which was comparable to that observed in the NEJ027 study.[18] The objective response rate (ORR) was 78.9%, the median PFS was 15.9 months (95% confidence interval [CI], 9.8–20.3), and the median overall survival (OS) was not reached (95% CI, 29.9–not reached).

In this EXTRA study, 32 patients aged ≥ 75 years were included among 103 prospectively enrolled patients. The median age was 79.5 years (range, 75–88 years); 14

(44%) patients had exon19 deletion, 13 (40%) had Ex21L858R, 8 (25%) had brain metastasis, and 7 (22%) had postoperative recurrence. The clinical background was considered similar to that in the previous clinical trials.[18,19,23] With regard to the treatment effect, the PFS of 18.6 months in the older adult group was longer than that in previous clinical trials and was identical to the PFS of 21.5 months in the non-older adult group. As evident from the Kaplan–Meier curves (Figure 3A), the curves for both groups roughly overlapped until 20 months, suggesting that initial treatment with EGFR-TKIs can be expected to be effective regardless of age.

As is clear from the swimmer plot for dose reduction, afatinib dose reduction to ≤ 20 mg/day was required in 72% of older adult patients, compared with that in 42% of non-older adult patients. Statistically, in the older adult group, cases in which 40 mg/day was continued (P=0.034) were significantly fewer, and there were more cases in which 20 mg was administered every other day (P=0.002) than in the non-older adult group. In previous clinical trials also, the treatment effect was not decreased with dose reduction.[22] Therefore, a prospective clinical trial was conducted in which afatinib was initiated at 30 or 20 mg/day.[19,24] In particular, trials starting with low-dose afatinib showed favorable results, with a PFS of 15.2 months.[24] Based on the results of this study, maintaining a general condition sufficient to tolerate oral treatment may be important, even in older adults. The key factors in realizing this strategy are “appropriate dose reduction” and “continuation of an appropriate dose” of EGFR-TKIs in the first-line treatment. Although afatinib at a dose of 20 mg administered every other day is not recommended in the prescribing information and therefore represents a methodological limitation of this study, this dosing approach is likely to be acceptable in routine clinical practice.

The Kaplan–Meier curve for OS (Figure 2B) showed a divergence between the two groups from approximately 2 years and at a median observation period of 35 months. This

divergence could be due to the fact that the older adults have fewer treatment options after second-line treatment, and there are differences in the rate of transition to second-line treatment. However, there was no significant difference in the Kaplan–Meier curve of PPS for the population that transitioned to post-treatment, suggesting that it is important to continue post-treatment to the extent possible.

In recent years, clinical trials that do not use osimertinib as first-line therapy have reported an OS that is more than one year longer than that in the FLAURA trial. [25] Phase 3 trials for direct comparison with osimertinib have also been conducted, and the primary endpoint is expected to be reported soon.[26] RWD suggests that osimertinib frequently causes drug-induced pneumonia, especially in older adults.[16,17] In OSI-FACT-EP, the largest retrospective analysis of RWD in an older adult Japanese subset, treatment was discontinued owing to AEs in 28.6% of 203 older adult patients, with interstitial pneumonia of all grades in 20.7% and grades 3–5 (G3–5) in 6.9% older adult patients.[16] In another retrospective study on RWD in Japan, 17% of 132 older adult patients had interstitial pneumonia of all grades, and 9.1% had G3–5.[17] At present, there is no evidence to support an association between limited dose-adjustment flexibility of osimertinib and the incidence of drug-induced interstitial lung disease; nevertheless, this possibility remains speculative and cannot be excluded. Therefore, it is necessary to reconsider osimertinib as the best drug for first-line treatment, at least in the Japanese population.

This was a subgroup analysis of the clinical part of the EXTRA study. Although this was a prospective study, it was limited by the small number of patients. A prospective head-to-head comparison study of osimertinib and afatinib is underway, and the results are expected to be published soon.[27]

Conclusions

The therapeutic efficacy and safety of afatinib were comparable between the older adult and non-older adult patients with advanced EGFR-mutant NSCLC, although dose reductions were more common in older adults.

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Author Contributions

Kei Morikawa, Original draft writing, Resources, review & editing, Saori Takata, Resources, Writing , Writing – review & editing, Hisashi Tanaka, Resources, Writing – review & editing, Hidetoshi Itani, Resources, Writing – review & editing, Masashi Ishihara, Resources, Writing – review & editing, Kazuya Horiuchi, Resources, Writing – review & editing, Yasuhiro Kato, Resources, Writing – review & editing, Shinnosuke Ikemura, Resources, Writing – review & editing, Hideyuki Nakagawa, Resources, Writing – review & editing, Yoshiro Nakahara, Resources, Writing – review & editing, Yoshitaka Seki, Resources, Writing – original draft, Writing – review & editing, Akihiro Bessho, Resources, Writing – review & editing, Nobumasa Takahashi, Resources, Writing – review & editing, Kentaro Hayashi, Resources, Writing – review & editing, Takeo Endo, Resources, Writing – review & editing, Kiyoshi Takeyama, Resources, Writing – review & editing, Toshiya Maekura, Resources, Writing – review & editing, Nagio Takigawa, Resources, Writing – original draft, Writing – review & editing, Akikazu Kawase, Resources, Writing – review & editing, Makoto Endoh, Resources, Writing – review & editing, Kenji Nemoto, Resources, Writing – review & editing, Kazuma Kishi, Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Validation, Writing – original draft, Writing – review & editing, Kenzo Soejima, Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Validation, Writing – original draft, Writing – review & editing, Yusuke Okuma, Conceptualization, Data curation, Formal analysis, Investigation,

Methodology, Project administration, Validation, Writing – original draft, Writing – review & editing, Kenichi Yoshimura, Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing, Daisuke Saigusa, Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Validation, Writing – original draft, Writing – review & editing, Yae Kanai, Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Validation, Writing – original draft, Writing – review & editing, Koji Ueda, Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Validation, Writing – original draft, Writing – review & editing, Akira Togashi, Conceptualization, Methodology, Project administration, Writing – review & editing, Noriyuki Matsutani, Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Validation, Writing – original draft, Writing – review & editing, and Nobuhiko Seki, Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Validation, Writing – original draft, Writing – review & editing.

Data availability

All data generated or analysed during this study are included in this published article and its Supplementary Information file.

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Competing interests

Kei Morikawa: personal fees as honoraria from AstraZeneca, Boehringer Ingelheim, Chugai Pharmaceutical, Eli Lilly, Takeda Pharmaceutical; Hisashi Tanaka: personal fees as honoraria from Ono Pharmaceutical, Bristol Myers Squibb, AstraZeneca, Chugai Pharmaceutical, Boehringer Ingelheim, and Pfizer; Yoshitaka Seki: personal fees as honoraria from AstraZeneca, Eli Lilly, MSD, Ono Pharmaceutical, Novartis, Taiho Pharmaceutical, Chugai Pharmaceutical, Boehringer Ingelheim, Shionogi, Sanofi, Kyowa Kirin, Kyorin Pharmaceutical, and GSK; Nagio Takigawa: personal fees as honoraria from Boehringer-Ingelheim Japan, Chugai Pharmaceutical, Eli Lilly Japan, Ono Pharmaceutical, AstraZeneca, Bristol-Myers Squibb Company Japan, Daiichi-Sankyo Pharmaceutical, Taiho Pharmaceutical, Pfizer Inc. Japan, Nippon Kayaku Co. Ltd., Takeda Pharmaceutical Co. Ltd., MSD, and Kyowa Hakko Kirin. Kazuma Kishi: research funding and personal fees as honoraria from Boehringer Ingelheim; Yusuke Okuma: research funding, advisory fee, and personal fees as honoraria from AstraZeneca; research funding from AbbVie and Merck Sharp & Dohme; and personal fees as honoraria from and Chugai Pharmaceutical, Eisai, Eli Lilly, MSD, Ono Pharmaceutical, Takeda Pharmaceutical, and Taiho Pharmaceutical; Akira Togashi: employee of Boehringer Ingelheim; Nobuhiko Seki: research funding and personal fees as honoraria from Eli Lilly, Ono Pharmaceutical, Boehringer Ingelheim, Taiho Pharmaceutical, Chugai Pharmaceutical, Takeda Pharmaceutical, Nippon Kayaku, Pfizer, and Daiichi Sankyo; research funding from Eisai and Shionogi; and personal fees as honoraria from AstraZeneca, MSD, Bristol Myers Squibb, Novartis, and Kyowa Kirin. No potential conflicts of interest were disclosed by the other authors.

Ethics declarations:

This study complied with all principles of the Declaration of Helsinki (as revised in 2013) and was approved by the Ethical Review Board for Medical and Health Research Involving Human Subjects at Teikyo University (Approval No. 16-066, November 10, 2016). Written informed consent was obtained from all the enrolled patients. This trial was registered with the University Hospital Medical Information Network Clinical Trial Registry (UMIN000024935).

Figure Captions

Figure 1. Patient flow diagram. y/o: year old

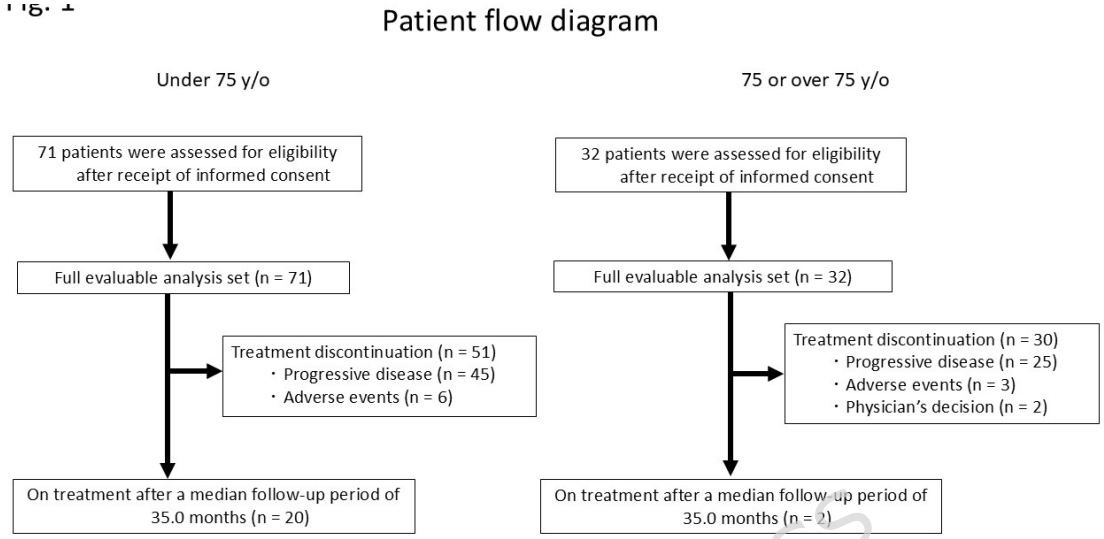


Figure 2. Kaplan–Meier curves for progression-free survival and overall survival in elderly and non-elderly people. OS: overall survival; PFS: progression-free survival

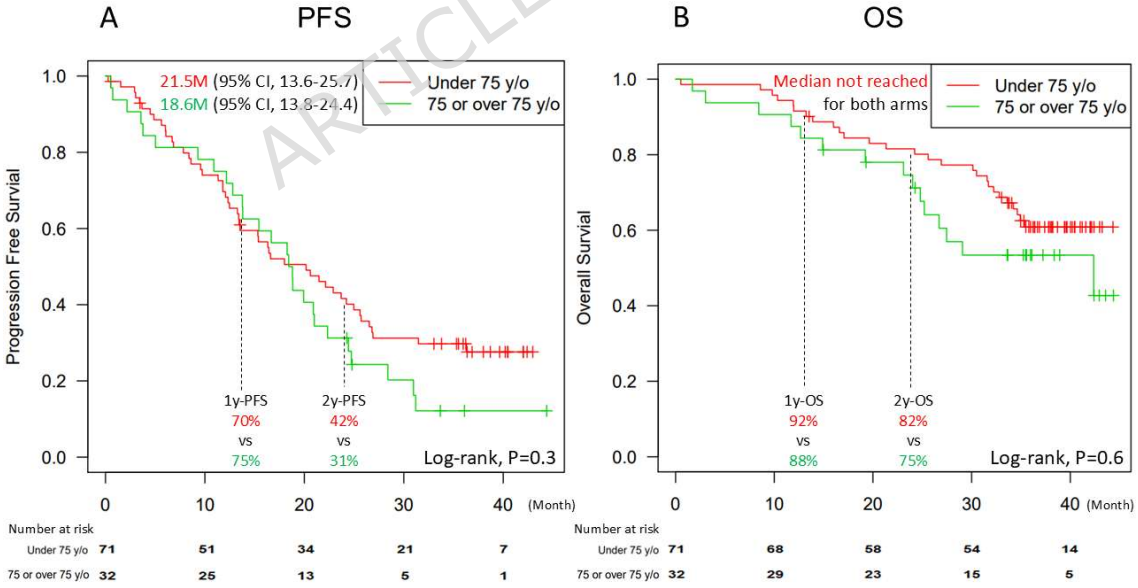


Figure 3. Swimmer's plot of time to treatment failure according to dose reduction in elderly (A) and non-elderly people (B).

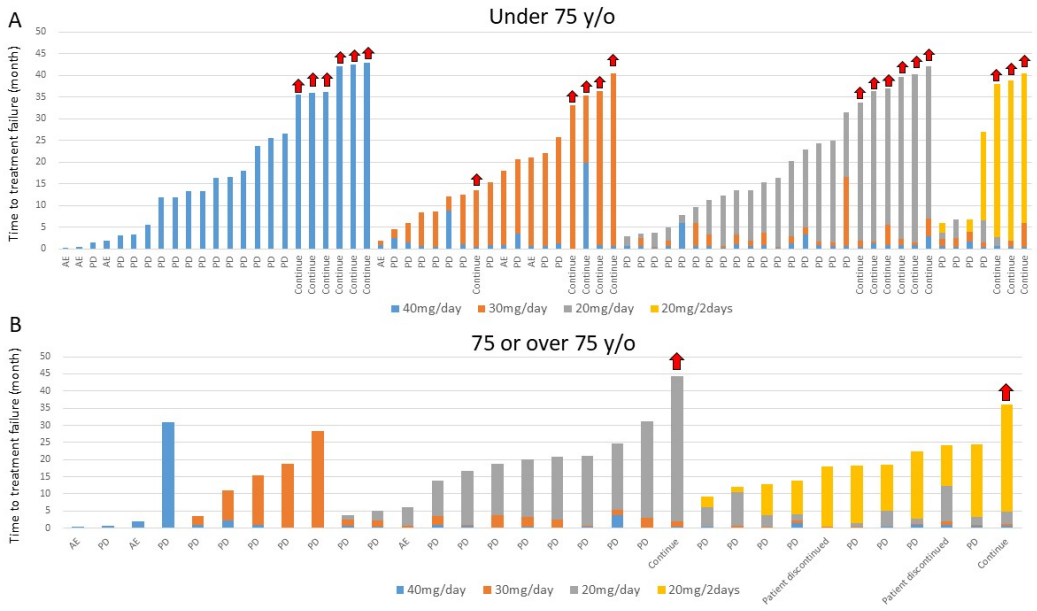
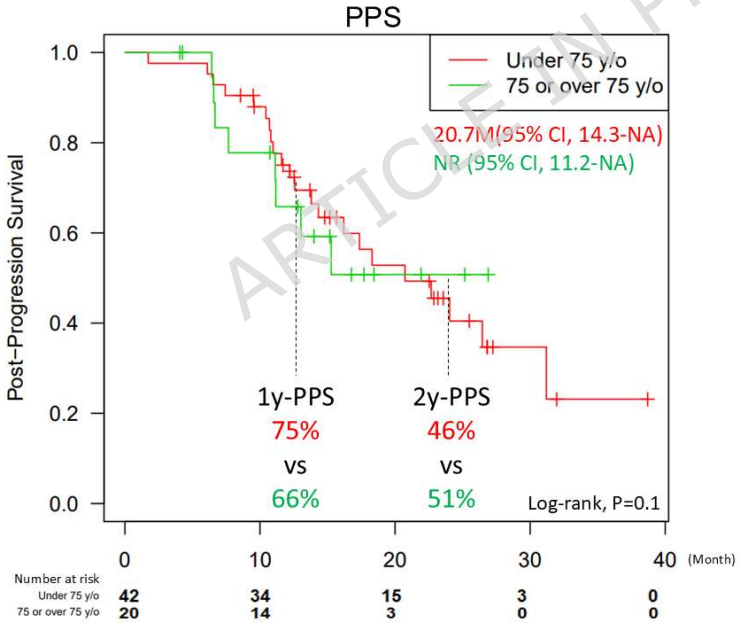


Figure 4. Kaplan–Meier curves for post-progression survival and overall survival in elderly and non-elderly people. PPS: post-progression survival



Tables

Table 1. Patient characteristics

	< 75 y/o	**≥ 75 y/o**
	No. of patients (%)	No. of patients (%)
Total	71 (100)	32 (100)
Age (years)		
Median (range)	66 (42–74)	79.5 (75–88)
<70	50 (70)	
70–74	21 (30)	
75–79		16 (50)
≥ 80		16 (50)
Sex		
Male	19 (27)	8 (25)
Female	52 (73)	24 (75)
PS		
0	38 (54)	14 (44)
1	33 (46)	18 (56)
Stage		
IIIB	50 (70)	25 (78)
IV		
Post-surgery recurrence	21 (30)	7 (22)
Brain metastasis		
Present	15 (21)	8 (25)
Absent	56 (79)	24 (75)
Histology		

Adenocarcinoma	71 (100)	32 (100)
EGFR mutation		
Exon 18	2 (3)	1 (3)
Exon 19 deletion	38 (54)	14 (44)
Exon 20 insertion	1 (1)	2 (6)
Exon 20 T790M	0 (0)	1 (3)
Exon 21 L858R	28 (39)	13 (41)
Exon 21 L861Q	1 (1)	0 (0)
Exon 20 S768I + Exon 18 G719X	1 (1)	1 (3)

PS, performance status; *EGFR*, *epidermal growth factor receptor*.

Table 2. Multivariate analysis of PFS and OS

	COX proportional hazard model for PFS and OS					
	PFS			OS		
Independent variable	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Gender: Male vs. Female	1.02	0.56–1.75	0.94	1.17	0.53–2.38	0.66
Age: <75 vs. ≥75	0.97	0.56–1.71	0.92	0.83	0.43–1.69	0.6
Stage: post-surgery vs. III/IV	0.46	0.23–0.85	0.01	0.41	0.13–1.03	0.059
EGFR mt: Uncommon						
vs. Ex19	0.81	0.35–2.04	0.2	0.68	0.27–1.96	0.47
vs. Ex21	1.29	0.58–3.20		1.01	0.40–2.89	
PS: 0 vs. 1	0.57	0.34–0.96	0.03	0.34	0.15–0.68	0.002
Brain metastasis: present vs. absent	1.35	0.74–2.36	0.31	1.37	0.66–2.67	0.37

CI, confidence interval; *EGFR*, *epidermal growth factor receptor*; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.