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Clinical Trial Results

Phase II Study of Low-Dose Afatinib Maintenance Treatment Among Patients with *EGFR*-Mutated Non-Small Cell Lung Cancer: North Japan Lung Cancer Study Group Trial 1601 (NJLCG1601)

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Trial Information

- **Trial Identifier:** UMIN 000020688
- **Sponsor**: North Japan Lung Cancer Study Group
- **Principal Investigator**: Shunichi Sugawara
- **IRB Approved**: Yes

Lessons Learned

- Low-dose afatinib maintenance treatment among patients with *EGFR*-mutated NSCLC achieved long-time to treatment failure with fewer treatment-related AEs without detracting from the therapeutic efficacy.
- This modified regimen represents a practical usage that balances effectiveness and safety.

Abstract

Background. Although afatinib is an effective therapy for patients with *EGFR*-mutated non-small cell lung cancer (NSCLC), drug-related adverse events (AEs) have often necessitated dose reductions. In a post hoc analysis of the LUX-Lung 3 and 6 trials, there was no difference in median progression-free survival (PFS) between patients who had the dose of afatinib reduced and those who did not. We thus evaluated the efficacy and tolerability of low-dose afatinib maintenance treatment among patients with NSCLC harboring *EGFR* mutations who had not been previously treated.

Methods. Eligible patients received afatinib 40 mg orally once daily. When prescribed grade ≥ 2 AEs, rash of grade ≥ 3, or unacceptable toxicity occurred, the afatinib dose was reduced from 40 to 30 mg and if needed from 30 to 20 mg. The primary endpoint was the 1-year PFS rate. Secondary endpoints were PFS, overall response rate (ORR), and toxicity.

Results. Among 30 patients, 93% had adenocarcinoma, 53% had exon 19 deletion, 37% had L858R, and 10% had minor mutations. The 1-year PFS rate was 50% (95% confidence interval [CI], 31.3–66.1) and the median PFS was 11.8 months (95% CI, 7.1–21.4). The incidence rate of grade ≥ 3 toxicities was 57%, including elevated aspartate aminotransferase/alanine aminotransferase level (13%), diarrhea (10%), and paronychia (10%).

Conclusion. Low-dose afatinib maintenance treatment reduced treatment-related AEs without detracting from the therapeutic efficacy. ***The Oncologist*** 2020;25:e1451–e1456

Discussion

This prospective study was designed to investigate the efficacy and tolerability of dose modification of afatinib according to AEs among patients with advanced NSCLC harboring *EGFR* mutations not previously treated with a tyrosine kinase

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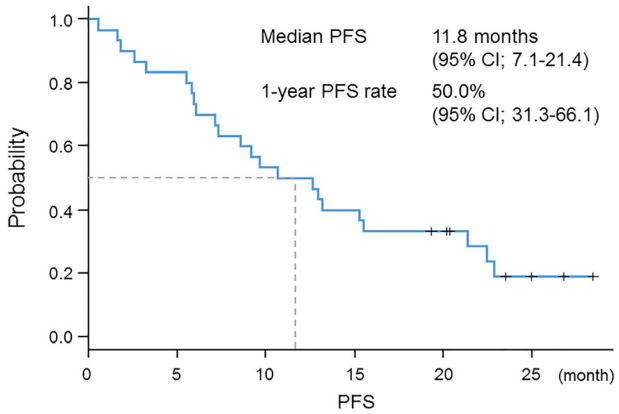

Figure 1. Kaplan-Meier curve of progression-free survival. Abbreviations: CI, confidence interval; PFS, progression-free survival.

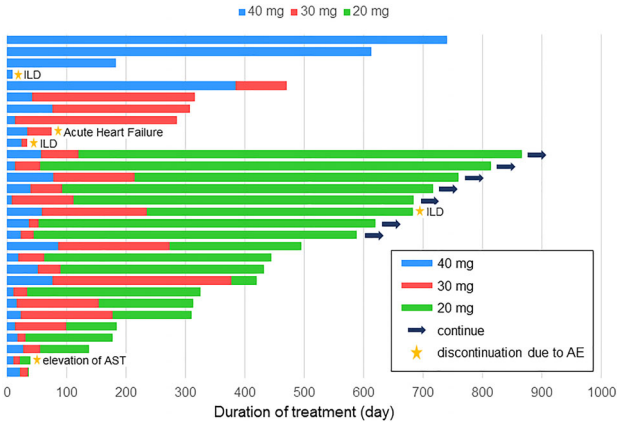

Figure 2. A swimmer plot of treatment duration in all patients. Stars represent discontinuation because of adverse events. Arrows represent the continuation at the time of data cutoff. Abbreviations: AE, adverse event; AST, aspartate aminotransferase; ILD, interstitial lung disease.

inhibitor (TKI) targeting the epidermal growth factor receptor (EGFR). In the LUX-Lung 3 trial, the median PFS with afatinib was 11.1 months, the 1-year PFS rate was approximately 45%, and the median overall survival (OS) was 28.2 months [1, 2]. The PFS of 11.8 months and the 1-year PFS rate of 50% in this study compare favorably with the results of the LUX-Lung 3 trial (Fig. 1). The swimmer plot of treatment duration among all patients showed a durable response with low-dose afatinib maintenance treatment (Fig. 2).

Although the subset analysis of Japanese patients in the LUX-Lung 3 trial showed a median PFS of 13.8 months and a median OS of 46.9 months, there was a higher rate of AEs peculiar to EGFR-TKI, such as diarrhea, rash/acne, and nail effects, and the incidence of AEs of grade ≥ 3 was approximately 70% in the Japanese subset [3]. Our study prescribed dose reduction among patients with treatment-related AEs of grade ≥ 2, rash of grade ≥ 3, or any grade of unacceptable toxicity. Most patients required dose reduction, and two-thirds of the patients required two dose reductions (Fig. 2). Regarding the toxicities of the modified dose, the incidence of all-cause treatment-related AEs of grade ≥ 3 decreased to 57%, which was tolerable compared with the incidence of AEs with afatinib in the LUX-Lung 3 trial. Moreover, only a few patients experienced severe AEs after dose reduction. The incidence of interstitial lung disease, a severe AE of concern among Japanese patients, was relatively high, but it seemed to have occurred by chance considering the small size of our study sample. The most frequent AEs, such as diarrhea, rash/acne, paronychia, and stomatitis, were acceptable because of early dose reduction and enabled treatment to be accomplished without discontinuation after such AEs. Thus, low-dose afatinib maintenance therapy reduced treatment-related AEs without detracting from the therapeutic efficacy. Our data support the feasibility of modified dose reduction of afatinib among patients with *EGFR*-mutated NSCLC. Low-dose afatinib maintenance treatment may be an acceptable treatment option for patients with *EGFR*-mutated NSCLC.

Trial Information	
Disease	Lung cancer – NSCLC
Stage of Disease/Treatment	Metastatic/advanced
Prior Therapy	None
Type of Study	Phase II, single arm
Primary Endpoint	1-year progression-free survival rate
Secondary Endpoints	
Progression-free survival, overall response rate, toxicity, incidence of grade ≥ 3 adverse events	
Additional Details of Endpoints or Study Design	
Study design: This study was a single-arm, phase II trial conducted at nine institutions in Japan.	
Inclusion criteria: Eligible patients were aged 20 years or older, with cytologically or histologically confirmed NSCLC that was classified as clinical stage IIIB–IV, or a postoperative recurrence harboring sensitive *EGFR* mutations except exon 20 insertion or T790M. The patients had not previously been treated with an EGFR-TKI, nor had they received more than two cycles of cytotoxic anticancer therapy except adjuvant chemotherapy after operation or immune checkpoint inhibitor, and they had at least one measurable lesion according to RECIST, an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, and an estimated life expectancy of ≥3 months. For radiation therapy, there was no history of radiation to the target lesion, ≥12 weeks had passed since the final dose of radiation had been administered to the chest, and ≥ 2 weeks had passed since the final dose of radiation had been administered to a body part other than the chest.	

Regarding surgery, ≥4 weeks had passed since the most recent day of operation. For patients with chest drainage or pleurodesis, ≥2 weeks had passed since the final treatment had been administered. Regarding anticancer agents, ≥3 weeks had passed since the last treatment had been administered. Laboratory criteria included a neutrophil count ≥1,500/mm^3, a platelet count ≥100,000/mm^3, a hemoglobin concentration ≥ 9 g/dL, total bilirubin level ≤ 1.5 mg/dL, aspartate transaminase and alanine transaminase levels ≤100 U/L, serum creatinine ≤1.5 mg/dL, and a partial pressure of arterial oxygen (PaO2) ≥60 mmHg. All enrolled patients provided written informed consent prior to enrolment in the present study.

Exclusion criteria: We excluded patients who had pulmonary disorders such as idiopathic pulmonary fibrosis or interstitial pneumonia; symptomatic brain metastasis; pleural effusion, ascites, or pericardial fluid requiring drainage; active infectious disorders; active double cancer; unstable cardiac disorders such as angina pectoris, acute myocardial infarction within 3 months or cardiac failure; uncontrollable diabetes mellitus or hypertension; gastrointestinal disorders with serious diarrhea requiring glucocorticoid therapy or immunosuppressive agents; and those regarded as unsuitable for this study by the investigators.

Treatment plan: The present study was conducted to evaluate the efficacy and tolerability of maintenance therapy with low-dose afatinib among patients with NSCLC harboring an *EGFR* mutation not previously treated with an EGFR-TKI. Patients initially received afatinib 40 mg orally once a day. The treatment was continued until disease progression, intolerable severe toxicity, or withdrawal of consent. Patients who experienced AEs of grade ≥ 2, rash of grade ≥ 3, or any grade of unacceptable toxicity could suspend treatment for up to 4 weeks. After suspension, treatment could be restarted based on the judgment of the investigators, and the dose of afatinib was decreased by 10 mg, initially to 30 mg/day and if needed down to 20 mg/day. After failure of afatinib, patients could receive any subsequent treatment, including continuation of afatinib, based on the judgment of the investigators.

Endpoints: The primary endpoint was the 1-year PFS rate. The secondary endpoints were PFS, ORR, toxicity profiles, and the incidence of AEs of grade ≥ 3. The follow-up period was 12 months after the last patient enrolment.

Statistical methods: For the primary endpoint, the minimum number of patients enrolled was 26, assuming a threshold 1-year PFS rate of 42% and an expected 1-year PFS rate of 63% with 90% power at a two-sided alpha of .05. Considering that 10% of patients could be ineligible, the sample size was set at 30 patients. The 1-year PFS rate and PFS were estimated using the Kaplan-Meier method. Safety analyses were used to summarize AEs by maximum Common Terminology Criteria for Adverse Events grade at each dose of afatinib during the entire treatment period.

Investigator's Analysis	Active and should be pursued further

Drug Information

Drug 1	
Generic/Working Name	Afatinib
Company Name	Boehringer-Ingelheim
Drug Type	Molecular targeting drug
Drug Class	EGFR
Dose	40 milligrams (mg) per flat dose
Route	Oral (p.o.)
Schedule of Administration	Afatinib 40 mg was administered orally once a day until either disease progression or the incidence of prescribed AEs.

Patient Characteristics

Number of Patients, Male	13
Number of Patients, Female	17
Stage	Stage IV (*n* = 19), postoperative recurrence (*n* = 11)
Age	Median (range): 69 (46–79)
Number of Prior Systemic Therapies	Median: 0
Performance Status: ECOG	0 — 22 1 — 7 2 — 1 3 — 0 Unknown — 0
Other	Exon 19 deletion (*n* = 16), L858R (*n* = 11), minor (*n* = 3: L861Q, *n* = 1; G719X, *n* = 2)
Cancer Types or Histologic Subtypes	Adenocarcinoma, 28; squamous cell carcinoma, 2

Primary Assessment Method	
Number of Patients Enrolled	30
Number of Patients Evaluable for Toxicity	30
Number of Patients Evaluated for Efficacy	30
Evaluation Method	RECIST 1.1
Response Assessment CR	*n* = 0 (0%)
Response Assessment PR	*n* = 23 (77%)
Response Assessment SD	*n* = 3 (10%)
Response Assessment PD	*n* = 1 (3%)
Response Assessment OTHER	*n* = 3 (10%)
(Median) Duration Assessments PFS	11.6 months, CI, 7.1–21.4

Kaplan-Meier Time Units, Months					
Time of scheduled assessment and/or time of event	**No. progressed (or deaths)**	**No. censored**	**Percent at start of evaluation period**	**Kaplan-Meier %**	**No. at next evaluation/No. at risk**
0			100.00	100.00	30
Outcome Notes			1-year PFS rate was 50% (95% CI, 31.3–66.1), which did not meet the statistical setting of this study.		

Adverse Events				
	All treatment (*n* = 30)		**Post-reduction (*n* = 26)**	
Adverse event, (≥10%)	**All grade, *n* (%)**	**Grade 3–4, *n* (%)**	**All grade, *n* (%)**	**Grade 3–4, *n* (%)**
Any cause	30 (100)	14 (47)	24 (92)	4 (15)
Diarrhea	29 (97)	3 (10)	7 (27)	0 (0)
Rash/acne	22 (73)	2 (4)	14 (54)	1 (4)
Paronychia	18 (60)	4 (13)	15 (58)	1 (4)
Stomatitis	18 (60)	2 (7)	5 (19)	0 (0)
Elevation of AST/ALT	11 (37)	3 (10)	6 (24)	2 (8)
Anorexia	8 (27)	2 (7)	0 (0)	0 (0)
Pruritus	6 (20)	0 (0)	2 (8)	0 (0)
Dry skin	4 (13)	1 (3)	3 (12)	0 (0)
Anemia	5 (17)	0 (0)	3 (12)	0 (0)
Interstitial lung disease	3 (10)	1 (3)	2 (8)	0 (0)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Adverse Events Legend

The rate of all-cause AEs grade ≥ 3 was 57% (17 of 30). Interstitial lung disease occurred in three patients, and one patient died. Two treatment-related deaths from interstitial lung disease, and acute cardiac failure were observed.

Assessment, Analysis, and Discussion	
Completion	Study completed
Investigator's Assessment	Active and should be pursued further

Lung cancer is the most common cause of cancer-related deaths worldwide. Unfortunately, at the time of their original diagnosis most patients present with metastatic disease, and their standard therapeutic option is chemotherapy. The identification of targetable oncogenic gene mutations, including *EGFR*, *ALK*, *ROS-1*, *BRAF*, and *NTRK*, have provided treatment options with molecular-targeted therapies developed for each specific genetic mutation [4]. Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) have proven to be more effective than platinum doublets without reducing the quality of life among patients with non-small cell lung cancer (NSCLC) harboring activating *EGFR* mutations [1, 5, 6].

Afatinib is a second-generation ErbB family blocker that downregulates ErbB signaling by irreversibly binding to EGFR (ErbB1), HER2/ErbB2, ErbB4, and all relevant ErbB family dimers. The broad spectrum of activity and irreversible inhibition might be more potent and prolonged than those of the reversible first-generation EGFR-TKIs [7, 8]. Among patients with previously untreated advanced *EGFR*-mutated NSCLC, first-line afatinib treatment has shown longer progression-free survival (PFS) and overall survival (OS) than platinum doublets [1, 9]. Moreover, in the LUX-Lung 7 trial, afatinib produced significant benefits in PFS and time to treatment failure compared with gefitinib in the first-line treatment of patients with previously untreated advanced *EGFR*-mutated NSCLC. However, more serious drug-related adverse events (AEs) were reported in the afatinib group than in the gefitinib group [10].

In the post hoc analyses of the LUX-Lung 3 and 6 trials, dose adjustment of afatinib because of patient intolerability led to a reduction in afatinib-related AEs. The median PFS for the patients with dose reduction in the first 6 months was not inferior to that of those without dose reduction in the first 6 months. Dose reduction was performed more commonly among Japanese patients, and most AEs caused by the administration of the EGFR-TKI occurred more frequently in the Japanese subset [1, 3, 11]. Therefore, we conducted this multicenter, phase II trial to evaluate the efficacy and tolerability of low-dose afatinib maintenance treatment with early dose reduction at grade ≥ 2 AEs among patients with NSCLC harboring *EGFR* mutations not previously treated with an EGFR-TKI. Our study showed a favorable PFS and tolerable AEs in comparison with those of the LUX-Lung 3 trial, although the 1-year PFS rate did not meet our primary endpoint.

Our study included not only common mutations (exon 19 deletion [Del-19] and L858R) but also uncommon mutations. Regarding the histological type, our study included not only patients with adenocarcinoma but also those with squamous cell carcinoma. The median PFS durations of patients with common and uncommon mutations were 12.8 and 7.4 months, respectively. Among patients with common mutations, the median PFS durations of Del-19 and L858R were 11.6 and 13.6 months, respectively, in this trial. Although the Japanese subset analysis of the LUX-Lung 3 trial showed more efficacy in the Del-19 subset than the L858R subset, a similar tendency was not shown in this study, likely because of the small sample size. Uncommon mutations identified in three patients were G719X (n = 2) and L861Q (n = 1). In a combined post hoc analysis of the LUX-Lung 2, 3, and 6 trials, the median PFS of afatinib in patients whose tumors harbored uncommon mutations was 10.7 months, which was shorter than that of patients with common mutations, and a similar tendency was shown in our study [12]. Regarding nonadenocarcinoma histology, there were a few reports about nonadenocarcinoma NSCLC harboring *EGFR* mutations but no data about treatment with afatinib. The median PFS of gefitinib was only 3.0 months among patients with nonadenocarcinoma NSCLC with *EGFR* mutation [13]. Our study included two patients with squamous cell carcinoma, and their PFS durations were only 6.1 and 8.7 months. The 1-year PFS rate did not meet our primary endpoint because of early discontinuation caused by AEs and the early progression of disease among patients with less frequently occurring mutations and squamous histology. Further studies are needed to determine the efficacy among these patients.

The present study had several limitations. First, this study used a small sample size comprising a heterogeneous patient population, including uncommon mutations and squamous histology. Second, the present study did not investigate the OS. Although the FLAURA study demonstrated a prolonged PFS and OS among patients with advanced NSCLC harboring *EGFR* mutations and osimertinib is recommended as first-line treatment, the median OS of the Asian subset in the FLAURA trial could not be proven to have statistical superiority [14]. The OS of afatinib is longer than that of gefitinib, and there has been no direct comparison between afatinib and osimertinib. It is possible that first-line afatinib treatment is longer than that with osimertinib. Although only in cases of receiving sequential afatinib and osimertinib, the overall time on treatment with afatinib followed by osimertinib was 46.7 months among Asian patients [15]. Concerning this limitation, the Gio-Tag Japan study, a prospective observational study of sequential treatment with afatinib followed by osimertinib for advanced *EGFR*-mutated NSCLC, is ongoing in Japan.

In conclusion, low-dose afatinib maintenance treatment for patients with NSCLC harboring *EGFR* mutations not previously treated with an EGFR-TKI showed favorable efficacy and less toxicity. Based on these results, a modified afatinib dosage should be used in practice. Further investigation will be needed to evaluate the utility of this study.

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Disclosures

Atsushi Nakamura: Merck Sharp & Dohme, Boehringer Ingelheim, Taiho Pharmaceutical, Kyowa Kirin (H); **Shunichi Sugawara:** Nippon Boehringer Ingelheim, AstraZeneca, Chugai Pharma, Pfizer, Eli Lilly and Company, Novartis, Bristol-Myers Squibb, MSD, Ono Pharmaceutical, Taiho Pharmaceutical, Kyowa Hakko Kirin (H). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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