Lung Cancer 134 (2019) 46–51

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

A phase Ib study of the combination of afatinib and ruxolitinib in *EGFR* mutant NSCLC with progression on EGFR-TKIs

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ARTICLE INFO

Keywords:
Afatinib
Ruxolitinib
EGFR
T790M
Non-Small cell lung cancer (NSCLC)

ABSTRACT

Objectives: We evaluated the safety and efficacy of the combination therapy of afatinib, an irreversible epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), and ruxolitinib, a *JAK1/2* selective inhibitor, in patients with *EGFR* mutant NSCLC progressing on at least one kind of EGFR-TKI.

Materials and Methods: In this phase Ib open-label study, we used a 3 + 3 dose-escalation design. Patients with histologically diagnosed *EGFR*-mutant stage IV NSCLC and documented disease progression on EGFR-TKI therapies were enrolled. Afatinib only was administered on day 1 through day 8 (run-in period), then ruxolitinib was administered concurrently with afatinib until disease progression. The primary endpoints were to determine the dose-limiting toxicity (DLT) and a recommended phase II dose of the combination regimen. We also included a dose confirmation cohort for the highest dose, and an expansion cohort for T790 M mutation.

Results: As of October 2017, 30 patients participated in the study, of which 20 had T790 M mutations. Because no DLT was observed in nine patients at the highest dose level (50 mg afatinib once daily plus 25 mg ruxolitinib twice daily), nine patients with T790 M mutations were enrolled in a dose-expansion cohort. Frequent adverse events included diarrhea (G3 in 3 of 22 cases), anemia (G3 in 1 of 26 cases), paronychia (G1/2 in 14 cases), acneiform rash (G1 in 13 cases), and oral mucositis (G1/2 in 12 cases). Objective response rate was 23.3% (no complete response [CR] and 7 partial responses [PR]) and disease control rate was 93.3% (no CR, 7 PR and 21 stable diseases). The median progression-free survival was 4.9 months (95% CI, 2.4–7.5).

Conclusion: The combination of afatinib and ruxolitinib was tolerated by patients, with modest clinical activity observed in NSCLC with acquired resistance to EGFR-TKIs (NCT02145637).

1. Introduction

The epidermal growth factor receptor (*EGFR*) mutation is a major therapeutic target of non-small cell lung cancer (NSCLC). Although *EGFR*-mutant NSCLC accounts for only 5–15% of NSCLC patients in the United States and Europe, approximately 40–60% of NSCLC patients in East Asia harbor the *EGFR* mutation [1,2]. Gefitinib and erlotinib, two first-generation EGFR tyrosine kinase inhibitors (TKIs), had a dramatic response on NSCLC with activating *EGFR* mutations [3–5]; however, acquired resistance occurred in most of the patients [6]. Second-generation irreversible EGFR-TKIs were expected to overcome the observed resistance to first-generation EGFR-TKIs. However, contrary to promising preclinical findings [7,8], a large-scale clinical study revealed that the second-generation irreversible EGFR-TKI afatinib did not improve overall survival in patients with disease progression on gefitinib or erlotinib [9].

The most common mechanism of resistance to first-generation EGFR-TKIs is the T790 M gatekeeper mutation, which is found in 50–60% of resistant tumors [10]. In a previous preclinical study, we demonstrated that a NSCLC cell line harboring the *EGFR* T790 M mutation exhibited *de novo* resistance through the activation of the Janus Kinase 1/ Signal Transducer and Activator of Transcription 3 (JAK1/STAT3) signaling pathway by the autocrine production of interleukin-6 (IL-6) in response to irreversible EGFR-TKIs [11]. In addition, we reported that knocking out STAT3 using siRNA or a JAK inhibitor increased the anti-tumor efficacy of afatinib in a NSCLC xenograft model with *EGFR* T790 M [11].

Based on this proof of principle, we conducted a phase Ib study to

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https://doi.org/10.1016/j.lungcan.2019.05.030
Received 11 February 2019; Received in revised form 3 May 2019; Accepted 27 May 2019

evaluate the safety and efficacy of the combination of afatinib and ruxolitinib, a selective JAK1 and JAK2 inhibitor, in *EGFR*-mutant NSCLC patients with disease progression on EGFR-TKIs.

2. Material and methods

2.1. Study overview

The study was a prospective, single center, open-label phase Ib study of *EGFR*-mutant NSCLC patients with acquired resistance to previous EGFR-TKI therapies (ClinicalTrial.gov identifier: NCT02145637). The study complied with the Severance Hospital Institutional Review Board and the Korean Ministry of Food and Drug Safety regulations and was conducted in accordance with the Declaration of Helsinki. All patients signed written informed consent prior to participation.

The primary objective of the study was to establish a recommended phase II dose (RP2D) by examining the dose-limiting toxicity (DLT) and the maximum tolerated dose (MTD) of afatinib and ruxolitinib combination therapy in patients with *EGFR*-mutant NSCLC with disease progression on previous EGFR-TKI regimens. The secondary objectives included assessment of safety, tolerability, and efficacy (objective response rate [ORR], disease control rate [DCR], progression-free survival [PFS], and overall survival [OS]) of the combination therapy.

2.2. Patients

A total of 30 patients were enrolled in the study as of October 2017. The criteria for inclusion in the study were: male or female aged 20 years or older; histologically diagnosed *EGFR*-mutant stage IV NSCLC (per AJCC cancer staging guidelines, 7th edition); evidence of disease progression on at least one EGFR-TKI except afatinib; a performance status score of 0 or 1 according to the Eastern Cooperative Oncology Group (ECOG) Scale; a measurable or non-measurable lesion under the RECIST 1.1 criteria; improved drug-related toxicity at CTCAE 4.03 $\leq$ Grade 1; and clinically normal hematological, renal, and hepatic functions. Patients with significant gastrointestinal disease, digestive disorders, major organ failure, interstitial lung disease, symptomatic central nervous system metastases, pregnant and/or lactating, previously treated with ruxolitinib, or that were HIV positive or with active hepatitis were excluded.

2.3. Study design

This phase Ib study followed a conventional 3 + 3 design for a dose-escalation cohort. If MTD was not reached within the prescribed cohort dose levels, an additional six subjects were recruited to the highest dose level cohort to confirm the safety and efficacy of the highest combination dose (dose confirmation cohort). DLT was assessed during cycle 1 of the subject treatment in each dose level. We established the RP2D as the dose that elicited the proper clinical response as well as similar safety and tolerability to the MTD or that did not exceed the MTD.

The initial dose was 30 mg afatinib once daily and 15 mg ruxolitinib twice daily. We planned five dose levels: 1) 30 mg afatinib and 15 mg ruxolitinib (level I); 2) 40 mg afatinib and 15 mg ruxolitinib (level II); 3) 50 mg afatinib and 15 mg ruxolitinib (level III); 4) 50 mg afatinib and 20 mg ruxolitinib (level IV); and 5) 50 mg afatinib and 25 mg ruxolitinib (level V). In addition, we included six expansion levels (level Ia, IIa, IIb, IIIa, IIIb, and IVa). If the DLT was observed in a dose-escalation cohort, we tried the expansion level, which included the same dose of afatinib and the increased dose of ruxolitinib administered at the previous level without DLT (detailed information and the dose-escalation scheme is provided in the Supplementary Material). Once the recruitment of a dose-escalation cohort was completed and the RP2D was determined, we recruited additional subjects with the *EGFR* T790 M mutation for a dose-expansion cohort.

Each dosing cycle was 28 days. Only in the first cycle, we set an 8-day run-in period at the beginning of a cycle, during which only afatinib was administered. Starting on day 9, ruxolitinib was administered with afatinib for 28 days. This schedule assumed that prior treatment with afatinib had stimulated the tumor JAK/STAT3 pathway and that drug resistance would be obtained. For all subsequent cycles, afatinib and ruxolitinib were simultaneously administered from day 1 to day 28 of each cycle and administration continued without an off-dose period (Supplementary Material).

2.4. Drug administration

Patients were treated orally with the level-specific afatinib dose once daily and the level-specific ruxolitinib dose twice daily. The combination of drugs was administered with a cup of water at the same time ($\pm$ 2 h) each day, at least 1 h before or 3 h after food consumption.

2.5. Statistical analysis

All safety and efficacy profiles were evaluated by the investigators. Safety profiles were analyzed and described for all patients who received at least one cycle of the combination therapy. The ORR was defined as the proportion of the sum of the PR plus complete response (CR), and the DCR was defined as the proportion of the sum of PR plus CR plus stable disease (SD) for $\geq$ 8 weeks among all patients per the Response Evaluation Criteria in Solid Tumors (RECIST) version1.1. ORR and DCR were calculated using binomial proportions and described with 95% confidence intervals (CIs).

PFS was defined as the time from randomization to the objective progression of the tumor(s) or to death, whichever occurred first. Overall survival (OS) was defined as the time from randomization to the time of death, irrespective of cause [12]. The Kaplan-Meier method was used for the survival analysis, and the survival curves were compared using a log-rank test. All statistical analyses were performed using SPSS version 23.0 (IBM, Armonk, NY).

3. Results

3.1. Patient enrollment

Between May 2015 and October 2017, 35 patients were screened and 30 patients were enrolled in the study. Among the patients, 21 were enrolled in the dose-escalation cohort and 9 were enrolled in the dose-expansion cohort. The median age of the patients was 57.5 years (range, 33–80 years), and 19 (63.3%) were women. Baseline characteristics are shown in Table 1. The median duration of follow-up was 8.5 months (range, 1.4–39.7 months). At the time of the initial NSCLC diagnosis, 16 patients had the *EGFR* exon 19 deletion, 13 patients had the *EGFR* exon 21 L858R mutation, and 1 patient had the *EGFR* exon 18 G719X mutation, who met the Jackman criteria [13]. Regarding previous EGFR-TKI treatment, 19 patients were treated with gefitinib, seven patients were treated with erlotinib, two patients were treated with gefitinib and erlotinib, one patient was treated with erlotinib and osimertinib, and one patient was treated with erlotinib, osimertinib, and gefitinib. Prior to initiating the study treatment, the *EGFR* T790 M mutation was identified in 11 of the 21 patients (52.4%) in the dose-escalation cohort as well as in all nine of the patients (100%) in the dose-expansion cohort.

3.2. Dose-escalation status and treatment-related adverse events

Because DLT was not observed in any of the five major dose levels in the dose-escalation cohorts, an additional six patients were enrolled in a dose confirmation cohort and administered the highest dose level (50 mg afatinib once daily plus 25 mg ruxolitinib twice daily). We did not detect DLT among the nine patients at the highest dose level. Taking

Table 1
Baseline characteristics of Study patients (N = 30).

Characteristics		No. of patients (%)
Age (year)		
	Mean (standard deviation)	57.7 (10.12)
	Median (range)	57.5 (33–80)
Sex		
	Male	11 (36.7%)
	Female	19 (63.3%)
Smoking status		
	Never	21 (70%)
	Former	5 (16.7%)
	Current	4 (13.3%)
ECOG performance status		
	0	16 (53.3%)
	1	14 (46.7%)
Histology		
	Adenocarcinoma	28 (93.4%)
	Squamous cell carcinoma	1 (3.3%)
	Poorly differentiated carcinoma	1 (3.3%)
EGFR sensitizing mutations status		
	Exon19 del	16 (53.3%)
	L858R	13 (43.4%)
	G719X	1 (3.3%)[a]
EGFR T790M		
	Yes	20 (66.7%)
	No	10 (33.3%)
Prior EGFR TKI treatment		
	Gefitinib	19 (63.4%)
	Erlotinib	7 (23.3%)
	Gefitinib, erlotinib	2 (6.7%)
	Erlotinib, osimertinib	1 (3.3%)
	Erlotinib, osimertinib, gefitinib	1 (3.3%)
Prior line of treatment		
	1	15 (50%)
	2	5 (16.7%)
	≥3	10 (33.3%)

[a] This patient met the Jackman criteria.

the safety, tolerability, and efficacy of the five dose levels into consideration, we determined the RP2D was 50 mg afatinib once daily plus 25 mg ruxolitinib twice daily.

Nine patients with the *EGFR* T790 M mutation were enrolled in the dose-expansion cohort at the established RP2D (Table 2). The most frequent drug-related adverse events (AEs) were anemia and diarrhea. Although anemia was found in 26 of 30 patients (86.7%) and diarrhea was found in 22 of 30 patients (73.3%), G3 anemia and G3 diarrhea were reported in only one (3.3%) and three (10%) of the patients, respectively. Other frequent AEs included paronychia (G1 in 11 cases, G2 in three cases), acneiform rash (G1 in 13 cases), and oral mucositis (G1 in nine cases, G2 in three cases). Treatment-related AEs are listed in Table 3. Serious AEs (SAEs) not related to the combination therapy were reported in nine patients: lung infection (G3 in one patient, G4 in one patient, and G5 in two patients), anemia (G3 in two patients), bone pain (G2 in two patients), and dyspnea (G3 in one patient).

Table 2
Patients enrollment and dose escalation status.

Dose level	Afatinib (mg)	Ruxolitinib (mg)	N enrolled	N of DLTs	N of DR
1	30	15	3	0	
2	40	15	3	0	
3	50	15	3	0	
4	50	20	3	0	1
5	50	25	3	0	
$5^{\text{dose confirmation}}$	50	25	6	0	1
$5^{\text{expansion}}$	50	25	9	0	1

Abbreviations: DLT dose limiting toxicity; DR dose reduction; N number.

3.3. Response assessment

Efficacy was evaluated in all 30 patients. The resulting ORR and DCR were 23.3% (95% CI, 8.2–38.5) and 93.3% (95% CI, 84.2–100), respectively (SD in 21 patients), across all dose levels. PR was observed in three patients at dose level II, two patients at dose level III, and two patients at dose level V. One of the two patients who confirmed to have small-cell carcinoma transformation of tumors that were re-biopsied before enrollment in the study showed a significant increase in the number and size of total target lesions according to RECIST criteria version 1.1 (+270%). Among the 20 patients with the *EGFR* T790 M mutation (T790M+), five (25%) had PR, and 15 had SD as the best response. The ORR in the T790M + patients was 25% (95% CI, 6.0–44.0), versus 20% (95% CI, 0–44.8) in the patients without the *EGFR* T790 M mutation (T790M-; $P = 0.760$). The DCR was 100% in T790M+ patients and 80% in T790M- patients ($P = 0.038$). Twenty-one of the 30 patients (70%) (15 of 20 T790M+ patients) experienced a decrease in total target lesions. The best responses of the target lesions at each level-specific dose are shown in Fig. 1.

3.4. Survival outcomes

As of December 2018, all 30 patients completed the study treatment. We confirmed that there were 16 deaths not related to the combination therapy and eight patients that stopped the study treatment due to causes other than disease progression. Two patients could not continue the treatment due to bacterial pneumonia and subsequently died of respiratory failure and septic shock. Two patients suspended the combination therapy due to the use of antibiotics for pneumonia that exceeded 2 weeks. Because the study protocol prohibited the discontinuation of the study drugs for a period greater than 2 weeks, the patients were excluded from the study. Three patients withdrew from this study because of G2-3 diarrhea. One patient could not continue the cancer treatment for personal reasons.

The median PFS of all patients was 4.9 months (95% CI, 2.4–7.5) (Fig. 2). Among them, the 20 T790M + patients exhibited a median PFS of 4.9 months (95% CI, 2.5–7.3) and the 10 T790M- patients exhibited a median PFS of 3.1 months (95% CI, 0–8.8) ($P = 0.212$). The median OS of all patients was 9.6 months (95% CI, 0–23.7), whereas the median OSs of the T790M+ and the T790M- patients were 9.6 months (95% CI, 0–27.4) and 9.1 months (95% CI, 1.8–16.4), respectively ($P = 0.555$). Twenty-two patients received other cancer treatment regimens following this study—11 patients were treated with a third-generation EGFR-TKI targeting T790M, and five patients received immune checkpoint inhibitors, including nivolumab and pembrolizumab.

4. Discussion

In this study, we investigated the efficacy and safety of the combination therapy of afatinib and ruxolitinib for *EGFR*-mutant NSCLC patients on EGFR-TKI with disease progression. STAT3 plays a critical role as a transducer of interferon-α (IFNα)-, interferon-γ (IFNγ)-, and IL-6-mediated signaling pathways, and in the expression of transcription factor-regulating genes related to tumor progression [14]. In recent studies, the JAK/STAT pathway has been shown to function as an escape pathway of irreversible EGFR-TKIs in tumors with the EGFR T790 M mutation [11], both as a feedback activation mechanism following MEK inhibition in oncogene-addicted tumors [15], and as a potent immune checkpoint modulator [14,16,17] in NSCLC.

Although the mechanisms underlying acquired resistance are

Table 3
Summary of treatment-related adverse events according to CTCAE[a].

Adverse event[b]		All grade N (%)	G1 N (%)	G2 N (%)	G3 N (%)	G4 N (%)
Non-hematologic						
	Diarrhea	22 (73.3)	14 (46.7)	5 (16.7)	3 (10)	0
	Paronychia	14 (46.7)	11 (36.7)	3 (10)	0	0
	Rash acneiform	13 (43.3)	13 (43.3)	0	0	0
	Mucositis oral	12 (40)	9 (30)	3 (10)	0	0
	Aspartate aminotransferase increased	5 (16.7)	4 (13.3)	1 (3.3)	0	0
	Anorexia	4 (13.3)	2 (6.7)	2 (6.7)	0	0
	Abdominal pain	4 (13.3)	2 (6.7)	2 (6.7)	0	0
	Pruritus	3 (10)	3 (10)		0	0
	Creatinine increased	2 (6.7)	1 (3.3)	1 (3.3)	0	0
	Dry skin	2 (6.7)	2 (6.7)	0	0	0
	Fatigue	2 (6.7)	0	2 (6.7)	0	0
	Insomnia	1 (3.3)	1 (3.3)	0	0	0
	Dry mouth	1 (3.3)	1 (3.3)	0	0	0
Hematologic						
	Anemia	26 (86.7)	9 (30)	16 (53.3)	1 (3.3)	0
	White blood cell decreased	2 (6.7)	2 (6.7)	0	0	0

[a] CTCAE, common terminology criteria for adverse events, version 4.03.
[b] Adverse events were reported during or within 30 days of study treatment (90 days for serious adverse events and events of clinical interest).

diverse, approximately 60% of the tumors with EGFR mutations acquire resistance after progression on a first-line EGFR-TKI through target modification following the substitution of threonine for methionine at amino acid 790 in the EGFR sequence [2]. To target the resistance mechanisms, researchers have tried target-specific inhibitors or blocking other relevant pathways in a resistance model. In our preclinical study, we demonstrated that afatinib activated the IL-6 receptor/JAK1/STAT3 signaling pathway in NSCLC cell lines harboring the T790 M mutation, and that the inhibition of JAK improved the efficacy of the irreversible EGFR-TKI [11]. Therefore, we embarked on evaluating the safety and efficacy of the combination of JAK inhibitor and irreversible EGFR-TKI in *EGFR*-mutant NSCLC patients. In this study, we did not observe any DLT up to the highest dose level and established the RP2D as 50 mg afatinib once daily combined with 25 mg ruxolitinib twice daily, taking efficacy and safety into consideration. The most frequent and significant toxicities were anemia and diarrhea. However, G3 toxicities were observed in four patients (three patients with G3 diarrhea and one patient with G3 anemia). Because diarrhea was caused by afatinib, the dose of afatinib was reduced in three patients during this study. Although anemia was thought to be caused by ruxolitinib, we did not reduce the ruxolitinib dose. Further, the anemia was asymptomatic and spontaneously improved.

Recently, Yu et al. conducted a phase I/II clinical trial that evaluated the combination therapy of ruxolitinib and erlotinib in patients

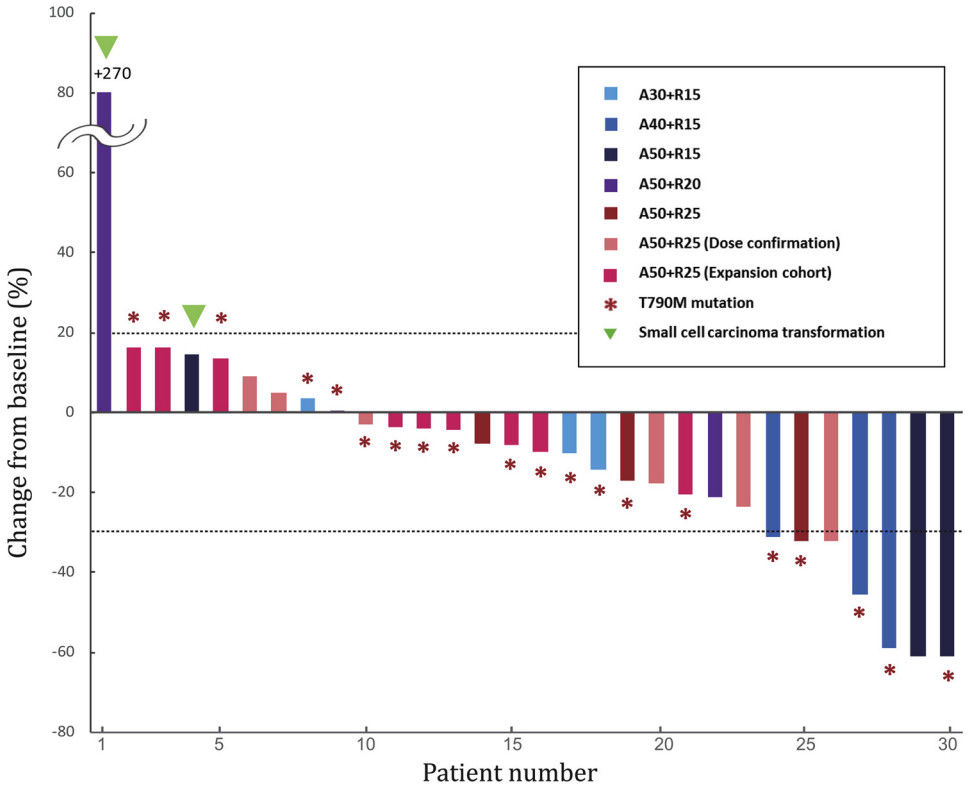

Fig. 1. Best response of target lesions in all patients (n = 30) according to RECIST version 1.1 (A, afatinib; R, ruxolitinib).

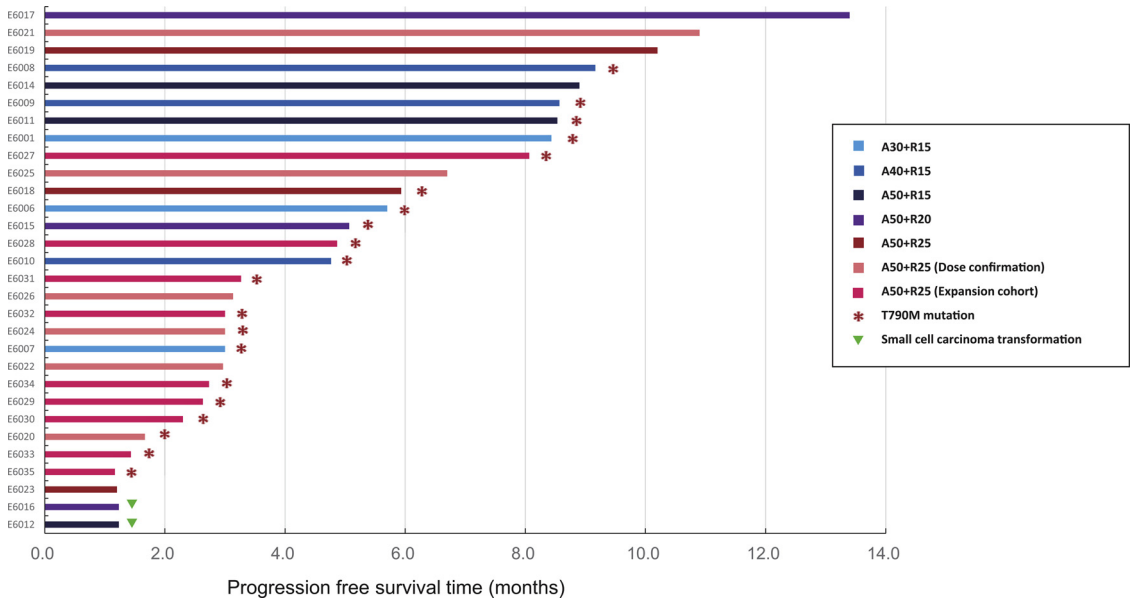

Fig. 2. Duration of progression free survival for individual patients with dose level and T790 M status. (A, afatinib; R, ruxolitinib).

with *EGFR*-mutant lung adenocarcinomas resistant to erlotinib [18]. They observed one patient with PR among 22 patients (including four patients with T790 M), and the median PFS was 2.2 months (95% CI, 1.4–4.1) [18]. In the current study, the median PFS of all patients was 4.9 months (95% CI, 2.4–7.5) and the ORR was 23.3%. Among the 30 patients, including 20 patients with T790 M mutations, we observed PR in seven patients, SD in 21, and PD in two patients. The seven patients with PR maintained the afatinib and ruxolitinib combination treatment for a median of 8.5 months (95% CI, 3.9–13.1). Among the seven patients with PR, five harbored the T790 M mutation.

The higher clinical efficacy observed in our study could be related to afatinib, which has also been shown to have modest activity against the T790 M mutation in a few cases [19,20]. In the LUX-Lung 1 trial, the ORR was 7% (all cases exhibited PR), the DCR was 58%, and the median PFS was 3.3 months (95% CI, 2.79–4.40) in the afatinib group [9]. Additionally, in the LUX-Lung 4 trial, afatinib monotherapy yielded an ORR of 8.2%, a DCR of 65.6%, and a median PFS of 4.4 months in patients with NSCLC who progressed on erlotinib and/or gefitinib [19]. In the study, two patients with T790 M mutations had SD for 1 month and 9 months, respectively [19]. Because the LUX-Lung 1 and LUX-Lung 4 trials demonstrated the modest efficacy of afatinib in *EGFR*-mutant NSCLC patients previously treated with erlotinib and/or gefitinib [9,19], we believe substituting erlotinib with afatinib could be potentially responsible for the higher clinical efficacy observed in this study.

In the current study, we hypothesized that a treatment that targeted JAK/STAT3 could improve the clinical efficacy of afatinib in NSCLC patients with the T790 M mutation, for which osimertinib has become the standard of care [21,22]. Actually, the clinical efficacy achieved by the combination of irreversible EGFR TKI and JAK1/2 inhibitor seems to be lower than those of osimertinib. In this study, 20 patients with T790 M mutation showed a median PFS of 4.9 months (95% CI, 2.5–7.3), which was inferior to those of osimertinib in AURA study (9.6 months) [23], in AURA study phase II extension component (12.3 months) [24], and in AURA3 study (10.1 months) [21]. In addition, among 20 T790M + patients in our study, 7 patients were treated with osimertinib after failure of this study, and their median PFS to osimertinib was 6.5 months (95% CI, 0–13.7). Given these evidences, the combination of afatinib and ruxolitinib might fail to achieve sufficient suppression on *EGFR* T790 M mutation of the NSCLC patients, compared to osimertinib. Although JAK/STAT3 activation is one of the important resistance mechanisms to irreversible EGFR TKI in T790 M mutant NSCLC, which is not enough to solely inhibit the proliferation of T790 M mutant NSCLC. Therefore, we are trying to find the role of JAK/STAT3 signaling inhibition in combination with osimertinib or in patients with resistance to osimertinib. To this end, AZD4205, a novel JAK1 inhibitor, is being investigated to determine if JAK inhibition improves the efficacy of osimertinib in preclinical and clinical settings [25,26]. In our study, two patients were previously treated with osimertinib. A patient with the exon 19 deletion and small-cell carcinoma transformation in a re-biopsied tumor prior to study enrollment showed rapid progression on the afatinib and ruxolitinib combination. Although the other patient with a T790 M mutation who was treated with osimertinib exhibited a modest decrease in tumor burden (shrinkage of 8.0% of target lesions), the patient withdrew from the study due to G2 diarrhea and general weakness.

Based on proof-of-concept gained form our previous preclinical study [11], the patients with T790 M mutation possibly responded to the combination of afatinib and ruxolitinib better than the patients without T790 M mutations. However, the clinical efficacy was not different according to the existence of T790 M mutation in this study. Although there were possible predictive biomarkers of this combination including JAK/STAT3 activation [27], MEK inhibition [15], or immune checkpoint modulation [14,16,17], we could not perform the biomarker study due to the lack of tumor tissue collected by the patients. This is an important limitation of this study, and we plan to analyze predictive biomarkers in the prospective studies using JAK inhibitors.

5. Conclusions

In conclusion, the combination of afatinib with ruxolitinib was well tolerated and yielded modest clinical benefit in NSCLC patients with acquired resistance to EGFR-TKIs. The findings suggest that targeting the JAK1/STAT3 pathway may be a potential therapeutic strategy for *EGFR*-mutant NSCLC patients that exhibit disease progression on EGFR-TKIs.

Funding

This work was supported by grants from the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT & Future Planning (grant number

2016R1A2B3016282 to B.C. Cho; grant number 2017M3A9E9072669 to H. R. Kim).

Conflict of interest statement

Cho BC reports research grants from Novartis, Bayer, AstraZeneca, the MOGAM Biotechnology Research Institute, Dong-A ST, Champions Oncology, Janssen, Yuhan, Ono, Dizal Pharma, and MSD, a consulting role with Novartis, AstraZeneca, Boehringer-Ingelheim, Roche, BMS, Ono, Yuhan, Pfizer, Eli Lilly, Janssen, Takeda, and MSD, and stock ownership in TheraCanVac Inc. Kim HR reports research grants from Ono, BMS, and AstraZeneca.

Acknowledgements

We would like to acknowledge Boehringer Ingelheim and Novartis Pharmaceuticals for providing the investigational drugs afatinib and ruxolitinib, respectively. Some of the results of this study were presented as a mini oral presentation at the 2017 International Association for the Study of Lung Cancer (IASLC) 18th World Conference on lung cancer held October 15-18, 2017, in Yokohama, Japan. This manuscript includes the abstract presented at the IASLC 18th World Conference.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.lungcan.2019.05.030.

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