



# Real-world first-line afatinib for advanced *EGFR* mutation-positive non-small cell lung cancer in Korea: updated survival data

Juwhan Choi<sup>1</sup>, Chang Min Choi<sup>2</sup>, Yoon Soo Chang<sup>3</sup>, Kye Young Lee<sup>4</sup>, Seung Joon Kim<sup>5</sup>, Sei Hoon Yang<sup>6</sup>, Jeong Seon Ryu<sup>7</sup>, Jeong Eun Lee<sup>8</sup>, Shin Yup Lee<sup>9</sup>, Ji Young Park<sup>10</sup>, Young-Chul Kim<sup>11</sup>, In-Jae Oh<sup>11</sup>, Chi Young Jung<sup>12</sup>, Sang Hoon Lee<sup>13</sup>, Seong Hoon Yoon<sup>14</sup>, Sung Yong Lee<sup>1</sup>, Tae Won Jang<sup>15</sup>

<sup>1</sup>Division of Pulmonary, Department of Internal Medicine, Korea University Guro Hospital, Seoul, South Korea; <sup>2</sup>Department of Pulmonary and Critical Care Medicine, Ulsan University Asan Medical Center, Seoul, South Korea; <sup>3</sup>Division of Pulmonary, Department of Internal Medicine, Yonsei University Gangnam Severance Hospital, Seoul, South Korea; <sup>4</sup>Precision Medicine Lung Cancer Center, Konkuk University Medical Center, Seoul, South Korea; <sup>5</sup>Division of Pulmonary, Department of Internal Medicine, Catholic University Seoul St. Mary's Hospital, Seoul, South Korea; <sup>6</sup>Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Wonkwang University Hospital, Iksan, South Korea; <sup>7</sup>Division of Pulmonary, Department of Internal Medicine, Inha University Hospital, Incheon, South Korea; <sup>8</sup>Division of Pulmonary, Department of Internal Medicine, Chungnam National University Hospital, Daejeon, South Korea; <sup>9</sup>Division of Pulmonary, Department of Internal Medicine, Kyungpook National University, Daegu, South Korea; <sup>10</sup>Division of Pulmonary, Allergy and Critical Medicine, Department of Internal Medicine, Hallym University Sacred Heart Hospital, Anyang, South Korea; <sup>11</sup>Department of Internal Medicine, Chonnam National University Medical School and Hwasun Hospital, Hwasun, South Korea; <sup>12</sup>Division of Pulmonary, Department of Internal Medicine, Daegu Catholic University Medical Center, Daegu, South Korea; <sup>13</sup>Division of Pulmonary, Department of Internal Medicine, Yonsei University Severance Hospital, Seoul, South Korea; <sup>14</sup>Division of Pulmonary, Department of Internal Medicine, Pusan National University Yangsan Hospital, Yangsan, South Korea; <sup>15</sup>Division of Pulmonary, Department of Internal Medicine, Kosin University Gospel Hospital, Busan, South Korea

**Contributions:** (I) Conception and design: YS Chang, JS Ryu, Shin Yup Lee, Sung Yong Lee, JY Park, CY Jung, SH Lee, SH Yoon, J Choi, TW Jang; (II) Administrative support: CM Choi, KY Lee, J Choi, TW Jang; (III) Provision of study materials or patients: CM Choi, YS Chang, KY Lee, YC Kim, CY Jung, SH Yoon, TW Jang; (IV) Collection and assembly of data: CM Choi, KY Lee, JS Ryu, JY Park, J Choi, TW Jang; (V) Data analysis and interpretation: Shin Yup Lee, CM Choi, KY Lee, SJ Kim, SH Yang, JS Ryu, JE Lee, Sung Yong Lee, JY Park, IJ Oh, CY Jung, SH Lee, SH Yoon, J Choi, TW Jang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

**Correspondence to:** Tae Won Jang, MD. Division of Pulmonary, Department of Internal Medicine, Kosin University Gospel Hospital, 262 Gamchenro, Suh Gu, Busan 49267, South Korea. Email: jangtw22@hanmail.net.

**Background:** Data from clinical trials and real-world studies show that afatinib is effective in treating non-small cell lung cancer (NSCLC) harboring activating mutations in the epidermal growth factor receptor (*EGFR*) gene. A previous analysis of patients enrolled in the Korean Academy of Tuberculosis and Respiratory Disease (KATRD) *EGFR* cohort showed that first-line afatinib was well tolerated and effectiveness results were encouraging. At the time of the previous analysis, survival data were not mature. Here we briefly present updated survival data from the cohort.

**Methods:** The study was a retrospective, multicenter (15 sites) review of electronic records of Korean adult patients (aged >20 years) with advanced *EGFR* mutation-positive NSCLC who initiated first-line afatinib (N=421). Progression-free survival (PFS) and overall survival (OS) were evaluated using Kaplan-Meier survival curves.

**Results:** Overall, median PFS was 20.2 months and median OS was 48.6 months. OS rates at 36 and 60 months were 60.1% and 42.3%, respectively. Presence *vs.* absence of baseline brain metastases was associated with significantly reduced median PFS (14.9 *vs.* 28.0 months; P<0.001) and median OS (32.2 *vs.* 65.6 months; P<0.001). The presence of common baseline *EGFR* mutations (Del19, L858R) was associated with significantly prolonged median OS (49.6 *vs.* 30.1 months; P=0.017). In patients stratified by the presence/absence of T790M *EGFR* mutation, the T790M mutation was associated with significantly reduced median PFS (P=0.0005) but there was no significant difference between groups in survival (P=0.263). There were no significant differences in PFS or OS for patients stratified by afatinib dose reduction or by age group (<70 *vs.* ≥70 years).

**Conclusions:** Afatinib was effective in Korean patients with *EGFR* mutation-positive NSCLC with median OS over 4 years. The presence of baseline brain metastases and/or uncommon *EGFR* mutations were associated with reduced survival. In the absence of baseline brain metastases, median OS was more than 5 years.

**Keywords:** Afatinib; epidermal growth factor receptor (EGFR); first-line; non-small cell lung cancer (NSCLC); real-world

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## Introduction

Targeted therapy with epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are effective for treating non-small cell lung cancer (NSCLC) harboring activating mutations in the *EGFR* gene (1). The frequency of *EGFR* mutations varies according to ethnicity and is higher in Asians than in Western populations. In Asian patients with advanced NSCLC and adenocarcinoma histology, *EGFR* mutations are found in around half of all

tumors. The most common *EGFR* mutations detected in NSCLC are exon 19 deletion (Del19) and a point mutation (L858R) in exon 21 (2,3).

Approved TKIs include first- (gefitinib, erlotinib), second- (afatinib, dacomitinib) and third- (osimertinib) generation agents. Although treatment with first-line gefitinib, erlotinib and afatinib is the standard of care for *EGFR* mutation-positive NSCLC, resistance inevitably develops, commonly due to secondary acquisition of the T790M *EGFR* mutation. The third-generation *EGFR* TKI, osimertinib is effective against *EGFR* T790M-positive NSCLC (1). In Korea, osimertinib is not reimbursable currently for first-line treatment and is used as second-line therapy.

In clinical trials, first-line afatinib has consistently shown efficacy with good tolerability in patients with *EGFR* mutation-positive NSCLC (4-8). Real-world studies have also demonstrated the effectiveness and tolerability of first-line afatinib in these patients (9-11). A single-center retrospective analysis of Korean patients reported that first-line afatinib had superior progression-free survival (PFS) compared to gefitinib or erlotinib (10). In a multicenter real-world study of Korean patients with *EGFR* mutation-positive NSCLC, initial analysis showed that first-line afatinib was well tolerated with no new safety signals and effectiveness results were encouraging including in patients with baseline brain metastases and/or uncommon *EGFR* mutations (11). At the time of the previous analysis (data cut-off 4 April 2019), survival data were not mature. Here, we briefly present updated effectiveness results including PFS and overall survival (OS). We present this article in accordance with the STROBE reporting checklist (available at <https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-383/rc>).

### Highlight box

#### Key findings

- First-line afatinib was an effective treatment in patients with advanced epidermal growth factor receptor (*EGFR*) mutation positive non-small cell lung cancer (NSCLC). The median progression-free survival (PFS) was 20.2 months and overall survival (OS) was 48.6 months.

#### What is known and what is new?

- Afatinib has been shown to be efficacious with good tolerability in clinical trials. Previously, interim analysis of the current retrospective multicenter reported encouraging effectiveness data and a favorable safety profile.
- The current report provided an updated result with the mature OS data. In addition, presence of baseline brain metastases was identified to reduce median PFS, while OS was found to be longer in patients with common *EGFR* mutations. Afatinib was also observed to be similarly effective regardless of patient age.

#### What is the implication, and what should change now?

- First-line afatinib is an effective treatment strategy for Korean patients with *EGFR* mutation-positive NSCLC, especially in the subset harboring common *EGFR* mutations. Favorable OS is observed with afatinib alone without any specific brain treatment in patients with brain metastasis, indicates the utility of afatinib in the treatment of brain metastasis patients.

## Methods

### Patient population

Details of the study have been published previously (11). Briefly, this was a retrospective, multicenter (15 sites across South Korea) review of electronic records of adult patients (aged >20 years) with advanced *EGFR* mutation-positive NSCLC enrolled in the Korean Academy of Tuberculosis and Respiratory Disease (KATRD) *EGFR* cohort who had initiated first-line afatinib between April 2007 and December 2018 (11). Patient subgroups included the presence or absence of baseline brain metastases, afatinib dose reduction, baseline *EGFR* mutation type, age group, and treatments received.

### Statistical analysis

Outcomes were PFS and OS evaluated using Kaplan-Meier survival curves. PFS was defined as the time from initiation of afatinib to objective tumor progression or all-cause death according to RECIST 1.1 criteria. OS was defined as the time from the first dose of afatinib until death. PFS and OS were censored using a data cut-off date of 31 August 2021. A log-rank test and Cox proportional hazards model were used to compare patient subgroups. Statistical analyses were performed using SAS version 9.4. A P value of <0.05 was considered statistically significant.

### Ethical statement

The study was conducted in accordance with the guidelines of the Helsinki Declaration (as revised in 2013). The study was approved by the institutional ethics review boards of: Korea University Guro Hospital (No. 2018GR0013), Asan Medical Center (No. 2018-0012), Yonsei University Gangnam Severance Hospital (No. 3-2020-0003), Konkuk University Medical Center (No. KUH1010909), Catholic University Seoul St. Mary's Hospital (No. KC20RCDI0129), Wonkwang University Hospital (No. WKUH-201606-HR-058), Inha University Hospital Institutional Review Board (No. 2020-01-016), Chungnam National University Institutional Review Board (No. CNUH 2020-02-022-006), Kyungpook National University Chilgok Hospital Institutional Review Board (No. KNUCH 2020-01-010), Hallym University Sacred Heart Hospital Institutional Review Board (No. HALLYM 2020-07-041), Chonnam National University Hwasun Hospital Institutional Review Board (No. CNUHH-2017-179),

Daegu Catholic University Medical Center Institutional Review Board (No. CR-18-097), Institutional Review Board of Severance Hospital (No. 4-2019-1214), Pusan National University Yangsan Hospital Institutional Review Board (No. 05-2020-006), and Kosin University Gospel Hospital Institutional Review Board (No. KUGH 2017-11-030). Individual consent for this retrospective analysis was waived.

## Results

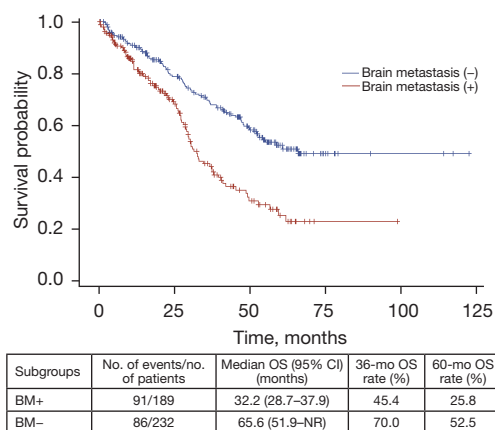
As reported previously (11), most patients in the KATRD *EGFR* cohort treated with first-line afatinib (N=422) were male (54.3%), never smokers (52.1%), with stage IVA/B disease (91.9%), adenocarcinoma (95.3%), Eastern Cooperative Oncology Group (ECOG) performance status <2 (72.5%), and received the approved afatinib starting dose (40 mg, once daily; 82.9%). The most received treatment following progression to afatinib was cytotoxic chemotherapy (71.6%) followed by 3<sup>rd</sup> generation TKIs (16.7%) (Table S1). Overall, 39.8% had baseline brain metastases, and common baseline *EGFR* mutations detected were Del19 (59.0%) and L858R (25.1%) (11).

Kaplan-Meier analyses of the cohort (n=421) showed that median PFS was 20.2 months [95% confidence interval (CI): 17.5–24.5] and median OS was 48.6 months (95% CI: 40.8–56.4). OS rates at 36 and 60 months were 60.1% and 42.3%, respectively.

Subgroup analyses showed that the presence *vs.* absence of baseline brain metastases was associated with significantly reduced median PFS (14.9 *vs.* 28.0 months; P<0.001) and median OS (32.2 *vs.* 65.6 months; P<0.001). Figure 1 shows Kaplan-Meier survival curves for OS in patients with/without brain metastases. Comparative OS rates at 36 and 60 months in patients with or without brain metastases were 45.4% *vs.* 70.0% and 25.8% *vs.* 52.5%, respectively.

Among patients with brain metastasis, 41.4% were not receiving treatment during initial lung cancer diagnosis (Table S2). Among patients who were not receiving treatment, the objective response rate of 0.712 (0% complete response, 71.2% partial response, 17.3% stable disease, and 11.5% progressive disease). There was no statistically significant difference between patients with brain metastasis who received *vs.* did not receive brain metastasis treatment in terms of PFS (14.5 *vs.* 14.4 months; P=0.683) and OS (30.6 *vs.* 40.9 months; P=0.220) (Figures S1,S2).

The presence of common baseline *EGFR* mutations (Del19, L858R) was associated with significantly prolonged



**Figure 1** Kaplan-Meier overall survival curves in patients with (BM+) or without (BM-) baseline brain metastases. BM, brain metastasis; CI, confidence interval; OS, overall survival; NR, not reached.

OS (49.6 vs. 30.1 months;  $P=0.017$ ). Comparative OS rates at 36 and 60 months in patients with or without common *EGFR* mutations were 61.3% vs. 43.4% and 44.0% vs. 20.6%, respectively. Individually, a statistically significant increase in PFS was seen in patients with Del19 (20.8 vs. 15.6 months;  $P=0.009$ ) while statistically significant lower PFS was seen in patients with L858R (15.6 vs. 19.9 months;  $P=0.017$ ) (Figures S3,S4). However, no statistical differences in OS were seen when comparing the presence vs. absence of Del19 ( $P=0.432$ ) and L858R ( $P=0.553$ ) (Figures S5,S6).

The presence of acquired *EGFR* T790M mutation was associated with significantly reduced median PFS (18.6 vs. 21.9 months;  $P=0.0005$ ), but there were no significant differences in median OS between T790M+ and T790M- groups (52.5 vs. 48.6 months;  $P=0.263$ ). There were no significant differences in OS based on the presence or absence of exon 18 mutations (G719A, G719C, G719S) ( $P=0.315$ ; Figure S7) or exon 20 mutation S768I ( $P=0.503$ ; Figure S8).

There were no significant differences in PFS or OS for patients stratified by afatinib dose reduction or by age group ( $<70/\geq 70$  years) (Table 1). Lastly, there was also no significant difference in OS based on treatment received after progression to afatinib ( $P=0.239$ ; Figure S9).

## Discussion

A previous publication on the effectiveness of first-line afatinib in the KATRD *EGFR* cohort of patients with

advanced *EGFR* mutation-positive NSCLC (data cut-off 4 April 2019) reported median time-to-treatment discontinuation (TTD) of 17.8 months and an overall response rate of 62.6%. Afatinib was well-tolerated and treatment-related adverse events (mainly diarrhea and rash) were managed effectively with dose reductions (11). Here, we provide an update on the previous analysis and provide additional insight into the effectiveness of first-line afatinib on subgroups of patients based on brain metastasis and baseline *EGFR* mutations.

In this brief updated analysis, median PFS was 20.2 months and median OS was 48.6 months. Median OS was superior to that reported in other real-world clinical studies of *EGFR* mutation-positive NSCLC patients. Two global studies of patients treated with sequential afatinib and osimertinib reported median OS of 37.6 months (12) and 36.5 months (13) and median OS was longer in Asian patient subgroups in both studies (44.8 and 42.3 months, respectively). Chart review of Japanese patients treated with afatinib reported a median OS of 38.6 months (14). In two retrospective Taiwanese studies, median OS was 39.1 months in patients treated with afatinib (15) and 37.0 months in patients who received first-line gefitinib, afatinib or erlotinib (16). The median PFS observed in this study was almost twice longer than that reported in pooled analyses of patients with uncommon *EGFR* mutations (11 months) (17) and in *EGFR*-TKI-naïve patients (13 months) (18). However, recent prospective trials and real-world studies conducted in Japan and Korea reported similar PFS of 16–20 months (7,19,20). Thus, first-line Afatinib followed by a second-line osimertinib may present a new treatment strategy for a specific subset of patients who are prone to developing T790M as a resistance mechanism. This is supported by a recently published data from the retrospective “Totality outcome of afatinib sequential treatment in patients with *EGFR* mutation-positive non-small cell lung cancer in South Korea (TOAST)” study showed that first-line afatinib treatment with various second-line treatments, including osimertinib, is an effective therapeutic strategy for *EGFR* mutation-positive NSCLC patients (21). The median PFS observed in this study was also comparable to the PFS of the combination therapy of erlotinib with ramucirumab, an anti-VEGF-R2 antibody, among patients with *EGFR*-mutated advanced NSCLC (22). However, the trial reported higher incidence rates of grade  $\geq 3$  adverse events than reported for afatinib in our previous publication (11). Further, a large real-world comparison study of TKIs in Europe reported statistically significant PFS and 1-year OS of afatinib

**Table 1** PFS and OS in the cohort and subgroups

Subgroups	PFS		OS	
	Median (95% CI) (months)	P value	Median (95% CI) (months)	P value
Overall (N=421)	20.2 (17.5–24.5)	–	48.6 (40.7–56.4)	–
BM status		<0.001		<0.001
BM+ (n=189)	14.9 (13.0–17.4)		32.2 (28.7–37.9)	
BM– (n=232)	28.0 (21.9–36.7)		65.6 (51.9–NR)	
EGFR mutation type		0.546		0.017
Common* (n=392)	20.6 (18.1–25.1)		49.6 (41.1–60.6)	
Uncommon (n=29)	13.8 (5.5–48.6)		30.1 (9.5–59.3)	
Dose reduction		0.513		0.189
Yes (n=253)	20.9 (17.6–26.5)		52.8 (41.1–65.6)	
No (n=168)	18.7 (14.6–25.8)		41.8 (31.2–51.9)	
Age group		0.1099		0.725
<70 years (n=273)	19.1 (16.4–23.9)		49.1 (40.4–58.6)	
≥70 years (n=148)	23.2 (17.2–36.4)		47.8 (34.0–NR)	
EGFR mutation <sup>†</sup>		0.0005		0.263
T790M+ (n=100)	18.6 (15.1–21.4)		52.5 (42.4–65.6)	
T790M– (n=321)	21.9 (17.4–29.0)		48.6 (36.6–NR)	

P values were calculated by log-rank tests. \*, common *EGFR* mutations were Del19 and L858R and present in 59.0% and 25.1% of patients, respectively (11); †, treated with sequential afatinib and osimertinib (n=21) or afatinib and chemotherapy (n=89) (11). PFS, progression-free survival; OS, overall survival; CI, confidence interval; BM, brain metastases; NR, not reached; EGFR, epidermal growth factor receptor.

compared with erlotinib and gefitinib (23). These results support the real-world effectiveness and safety of afatinib.

Baseline brain metastases, which were present in nearly 40% of patients, were associated with significantly reduced PFS and OS. However, there was no statistically significant difference in PFS and OS between patients who received additional treatment for their brain metastasis compared with those who did not. Common baseline *EGFR* mutations (Del19, L858R) were also associated with significantly prolonged median OS. When analyzed separately, Del19 mutation was associated with increased PFS but L858R mutation was associated with lower PFS. Association of the presence of the Del19 mutation at baseline (but not the L858R mutation) with prolonged OS was previously reported in patients treated with sequential afatinib and osimertinib with increases in median OS by 4 months (12) and 1.5 months (13). Thus, it is likely that first-line Afatinib to be beneficial in patients with baseline Del19 mutation.

A retrospective South Korean study which categorized uncommon *EGFR* mutations (n=64) according to their incidence showed that first-line afatinib was effective in patients with NSCLC harboring “major uncommon” (G719X and L861Q), and compound *EGFR* mutations. Median OS was 30.6 and 29.1 months, respectively. However, survival in patients with “minor uncommon” mutations (exon 20 insertion, S768I, and *de novo* T790M) was reduced: median OS was 8.5 months (24). We did not observe statistically significant differences in OS based on the presence of uncommon mutations in Exon 18 (G719A, G719C, G719S) or exon 20 (S768I).

No significant differences in survival were found between patients stratified by the presence/ absence of T790M *EGFR* mutation treated with afatinib and subsequent therapy with osimertinib/chemotherapy. Sequential afatinib and osimertinib is known to be superior to sequential afatinib and chemotherapy for NSCLC harboring a T790M

mutation (25).

Afatinib was effective in elderly patients  $\geq 70$  years of age and supports results from the Japanese phase 2 trial of *EGFR* mutation-positive patients aged  $\geq 75$  years with advanced NSCLC who achieved a median OS of 35.2 months (26), subgroup analyses of older patients ( $\geq 65$  and  $\geq 75$  years) in the LUX-Lung 3, 6 and 7 clinical trials (27), and results from the GIDEON prospective non-interventional study demonstrating higher median PFS in patients  $\geq 70$  years (28). Effectiveness of afatinib was also shown in patients who had the dose reduced to 20 or 30 mg. Systematic review of six studies which compared 30 mg with 40 mg doses of afatinib concluded that effectiveness, as evaluated by PFS, appeared to be similar in patients who had no brain metastasis (29). The GIDEON study also reported comparable effectiveness of starting dose of  $< 40$  and 40 mg (30). These results suggest first-line afatinib to be an effective treatment option in elderly patients with an option for dose adjustment.

As noted in the previous publication which reported primary analyses from the KATRD cohort (11), study limitations mainly relate to the retrospective study design. Nevertheless, our study represents real-world clinical practice and provides useful insights regarding the use of first-line afatinib for the treatment of advanced *EGFR* mutation-positive NSCLC in Korea. Assessment of PFS in this study was conducted by the investigators rather than by blinded independent central reviewers, which may contribute to the slightly longer PFS observed in this study.

## Conclusions

In conclusion, afatinib was effective in Korean patients with *EGFR* mutation-positive NSCLC with a median OS of over 4 years. The presence of baseline brain metastases and/or uncommon *EGFR* mutations were associated with reduced survival. In the absence of baseline brain metastases, median OS was more than 5 years.

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## Footnote

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*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the guidelines of the Helsinki Declaration (as revised in 2013). The study was approved by the institutional ethics review boards of Korea University Guro Hospital (No. 2018GR0013), Asan Medical Center (No. 2018-0012), Yonsei University Gangnam Severance Hospital (No. 3-2020-0003), Konkuk University Medical Center (No. KUH1010909), Catholic University Seoul St. Mary's Hospital (No. KC20RCDI0129), Wonkwang University Hospital (No. WKUH-201606-HR-058), and Inha University Hospital Institutional Review Board (No. 2020-01-016), Chungnam National University Institutional Review Board (No. CNUH 2020-02-022-006), Kyungpook National University Chilgok Hospital Institutional Review Board (No. KNUCH 2020-01-010), Hallym University Sacred Heart Hospital Institutional Review Board (No. HALLYM 2020-07-041), Chonnam National University

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