Peer Review File

Article information: https://dx.doi.org/10.21037/tlcr-23-383

Reviewer A

This is the update survival data regarding afatinib monotherapy for chemo-naïve patients with EGFR common/uncommon mutations.
The analysis was conducted on 421 cases and is considered to be important data.

PFS and OS was reported as 20.2 and 48.6 months.
The OS is relatively reasonable for Asians considering the previously reported data. On the other hand, the PFS for Afatinib is typically around 12 months in previously reported prospective studies, which may be influenced by the testing interval or some other factor. Please add this consideration.
Answer:
Thank you for the feedback. We acknowledge that the PFS of Afatinib is typically 12 months and recent meta-analyses reported PFS of 11 months. However, recent prospective trials and real-world studies conducted in Japan and Korea reported a longer PFS of 16-18 months. Thus, the longer PFS may be attributed to the East Asian demographic. In addition, the 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. We have added both points to the discussion.

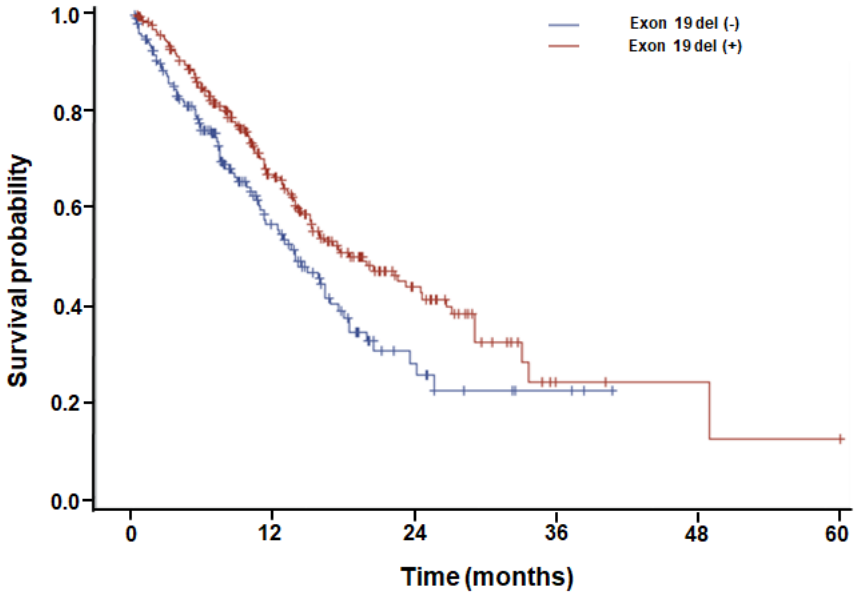
Changes:
Added to the discussion (line 155-159): The median PFS observed in this study was almost twice longer than that reported in pooled analyses of patients with uncommon EGFR mutations (11 months) (17) and in EGFR-TKI-naïve patients (13 months) (18). However, recent prospective trials and real-world studies conducted in Japan and Korea reported similar PFS of 16-20 months (7, 19, 20).

Added to discussion (line 214-216): 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.

Please add data and discussion on whether there was any difference in PFS and OS for EGFR status, especially Exon19deletion and L858R.
Answer: As suggested, we have conducted additional analysis for the PFS and OS sub-

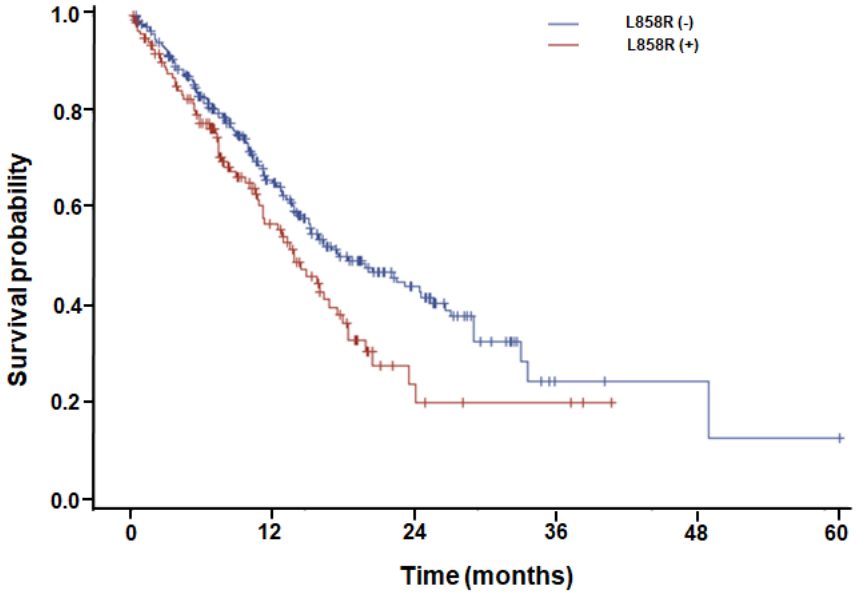
grouped by the presence or absence of Exon19 deletion (Del19) and L858R. As shown, the presence of Del19 is associated with longer PFS while L858R with shorter PFS. Individually, neither mutation was associated with increased OS.

1. PFS based on the presence or absence of Exon 19 deletion.



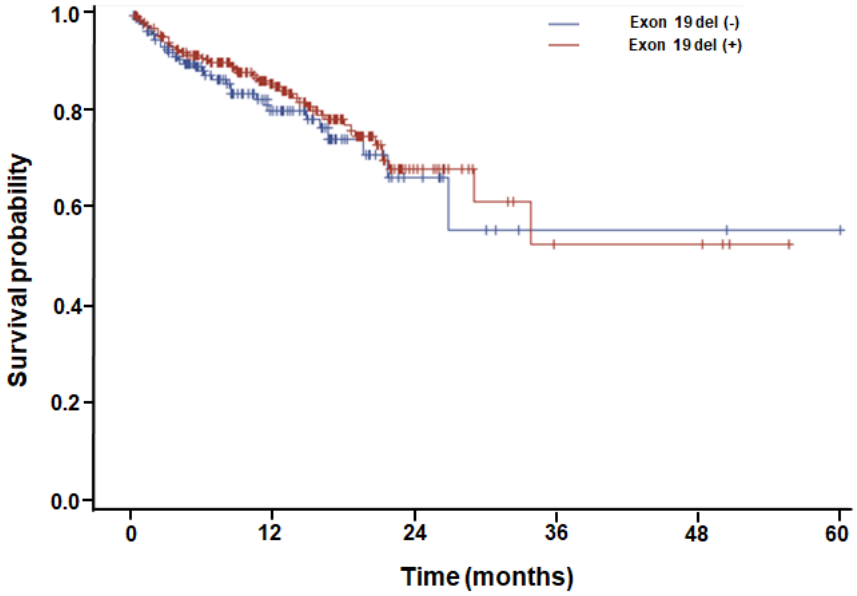
	No. of patients	Median OS (95% CI), months	36-mo OS rate	60-mo OS rate	p-value
Del19	252	20.8 (17.1– 27.8)	32.1%	12.0%	0.009
Others	163	15.6 (12.6– 19.0)	22.2%	22.2%	

2. PFS based on the presence or absence of L858R



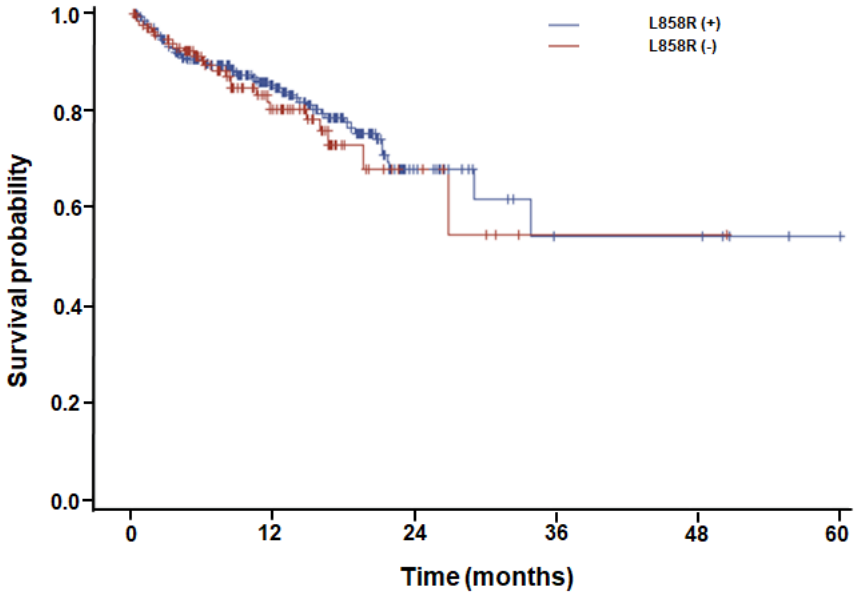
	No. of patients	Median OS (95% CI), months	36-mo OS rate	60-mo OS rate	p-value
L858R	129	15.6 (12.6–19.0)	19.4%	19.4%	0.017
Others	286	19.9 (17.1–27.7)	32.0%	12.0%	

3. OS based on the presence or absence of Exon 19



	No. of patients	Median OS (95% CI), months	36-mo OS rate	60-mo OS rate	p-value
Del19	256	NR (40.9–NR)	68.1%	52.5%	0.432
Others	161	NR (37.7–NR)	66.4%	55.4%	

4. OS based on the presence or absence of L858R



	No. of patients	Median OS (95% CI), months	36-mo OS rate	60-mo OS rate	p-value
L858R	137	NR (37.7–NR)	68.0%	54.4%	0.553
Others	280	NR (40.9–NR)	67.7%	53.9%	

Changes:
Added to results (line 123-127):
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). However, no statistical differences in OS were seen when comparing the presence vs absence of Del19 (p=0.432) and L858R (p=0.553).

These 4 figures are added as supplementary figures 3, 4, 5, and 6 respectively.

Please add subgroup analysis regarding PS as well.
Thank you for the comment. While we capture data for our patients' baseline performance status, it is not part of the outcome measures of the current study. We will take this comment into account in future analyses.

Change: No change made.

Reviewer B

I've reviewed your manuscript titled "Real-world first-line afatinib for advanced EGFR mutation-positive non-small cell lung cancer in Korea: updated survival data", which presents examining the effectiveness of first-line afatinib treatment in the EGFR mutation-positive NSCLC cohort. Your study offers novel insights into the prognostic factors associated with this patient population, notably the significant role of baseline brain metastases and common EGFR mutations on patient survival. It provides valuable real-world data and a unique perspective that adds in this area. However, some revisions would significantly enhance the clarity and impact of your manuscript.

Major comments
1. Details on Brain Metastases: You clearly identified the presence of brain metastases as a poor prognostic factor in this cohort. However, more information is needed to fully understand this association. It would be beneficial to provide more detailed information on the presence or absence of brain metastases in the patients included in your study, as well as the specific treatment modalities used to address these metastases. This information could have significant implications for the prognosis and therefore would strengthen the validity of your results.

Answer:
Thank you for the comment. Indeed, brain metastasis is an important prognostic factor

in this study. We have added a breakdown of treatments received for brain metastasis at the time of lung cancer diagnosis and the duration of Afatinib treatment received as a supplementary table.

Changes:
Added Supplementary Table 2. Treatment of patients with brain metastasis at the time of initial lung cancer diagnosis and their Afatinib treatment duration.

Brain metastasis Treatment	n	%	Afatinib Treatment Duration (start to end of administration)				
			mean	SD	median	Q1	Q3
No treatment	60	41.4 %	324.6	247.4	308	125	464
Surgery	7	4.8%	452.1	300.4	430	261	752
GKRS	21	14.5 %	457.9	292.2	435	231	614
CyberKife	4	2.8%	259.8	136.1	209.5	168	351.5
WBRT	51	35.1 %	290.1	188.1	258	167	376
SRS	2	1.4%	178.0	8.5	178	172	184

If possible, please send the afatinib response rate (CR, PR, SD, PD), PFT, and OS data of patients with brain metastases at the time of diagnosis but not treated (0: no).
Answer:
The Afatinib response rates, PFS, and OS for the group that received only Afatinib without any specific treatment at the time of brain metastasis diagnosis are as follow:

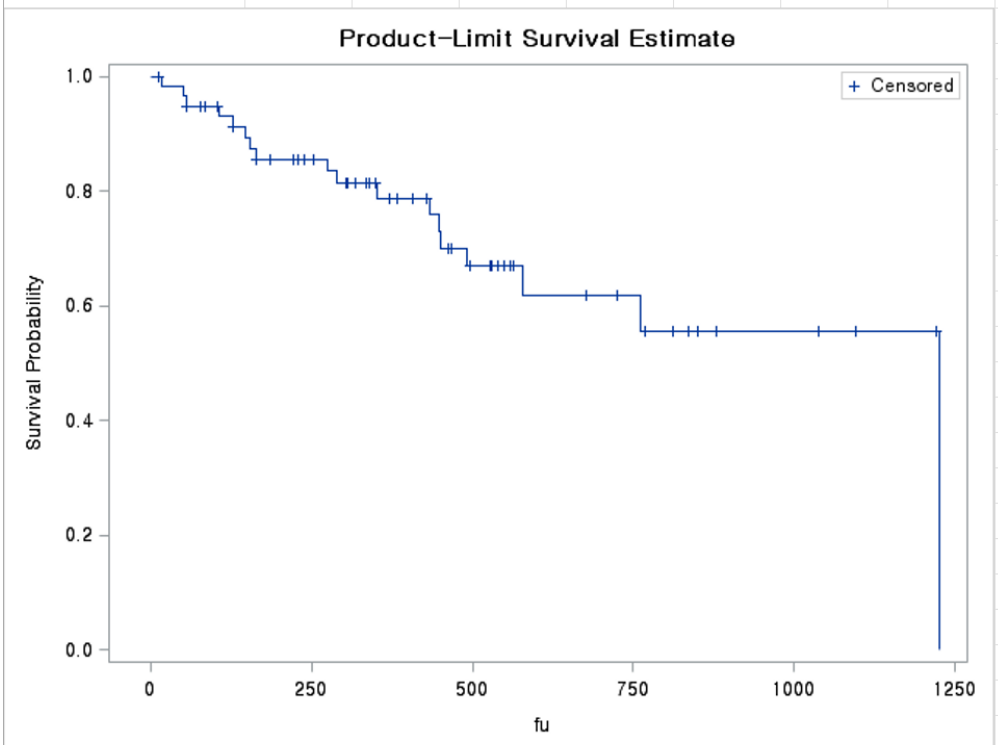
(1) Objective response rate (ORR): 0.712

[1] CR	0 (0.0%)
[2] PR	37 (71.15%)
[3] SD	9 (17.31%)
[4] PD	6 (11.54%)

* There are 8 patients with data loss.

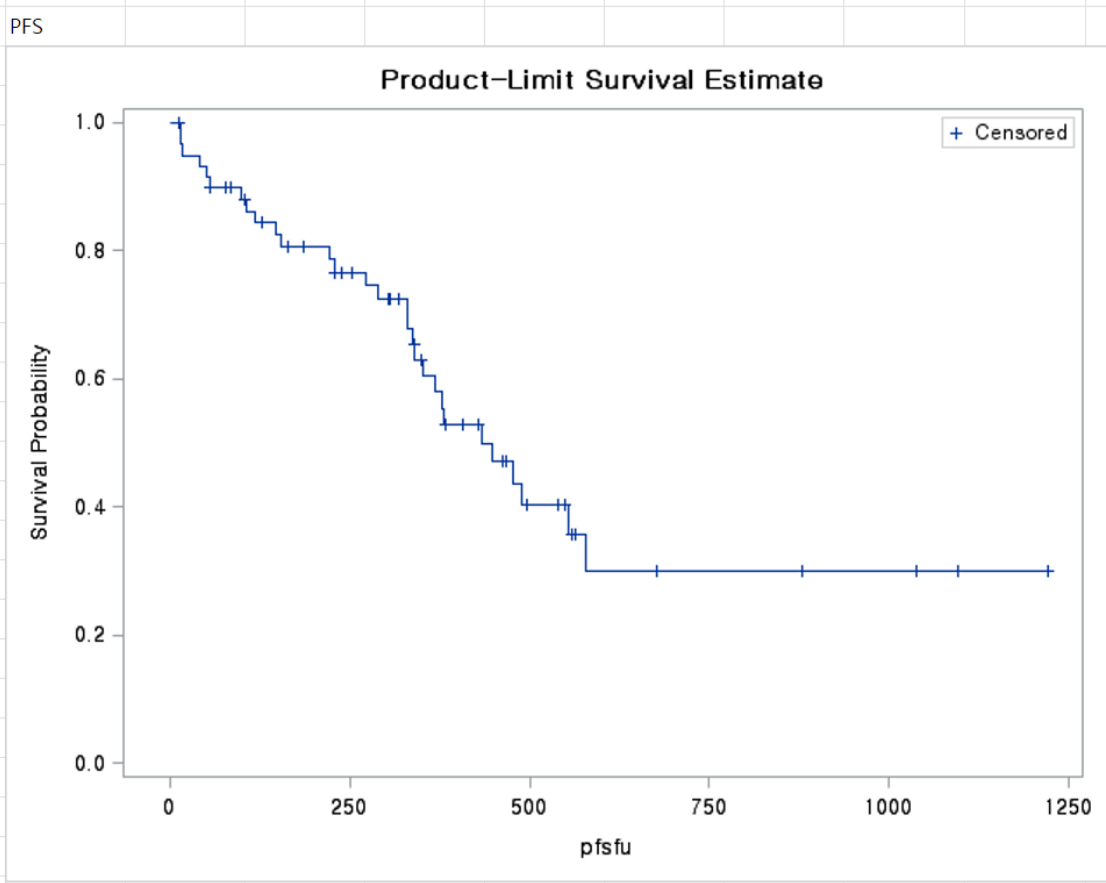
(2) OS

OS



Total	Failed	Censored	Percent Censored	Median	95% CI		3yr	5yr
60	18	42	70	1227	577	1227	0.5558	0

(3) PFS



Total	Failed	Censored	Percent Censored	Median	95% CI		3yr	5yr
60	29	31	51.67	433	341	577	0.2986	0.2986

Changes:

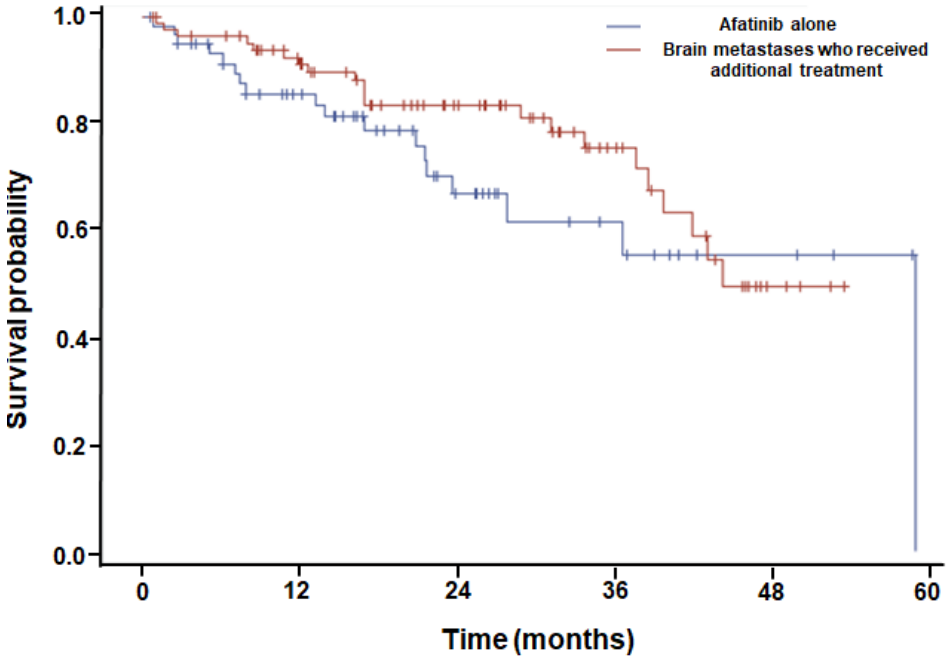
Results (line 112-118): Among patients with brain metastasis, 41.4% were not receiving treatment during initial lung cancer diagnosis (Supplementary Table 2). Among patients who were not receiving treatment, the objective response rate of 0.712 (0% complete response, 71.2% partial response, 17.3% stable 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).

2. Comparison of people who received treatment for brain metastases at the time of diagnosis and those who did not.

Answer: We have performed additional analysis on the 145 patients who had brain metastasis at diagnosis, comparing those who received afatanib alone vs those who received additional treatment for brain metastasis. We did not observe any statistically

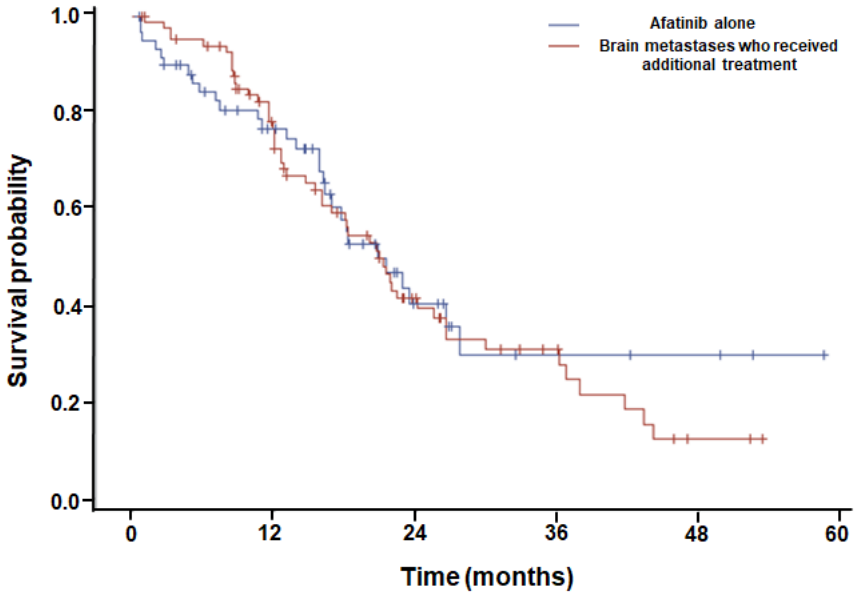
significant differences in PFS and OS between the two subgroups.

(1) OS



	No. of patients	Median OS (95% CI), months	36-mo OS rate	60-mo OS rate	p-value
Treated	85	30.6 (27.5–NR)	49.6%	49.6%	0.220
Not treated	60	40.9 (19.2–40.9)	55.6%	0%	

(2) PFS



	No of patients	Median OS (95% CI), months	36-mo OS rate	60-mo OS rate	p-value
Treated	85	14.5 (11.2–17.8)	12.4%	12.4%	0.683
Not treated	60	14.4 (11.4–19.2))	29.9%	29.9%	

Changes:

In addition to the additions in the results section specified above, we have added both charts as supplementary figures 1 and 2.

We have also added to the discussion (line 176-178):

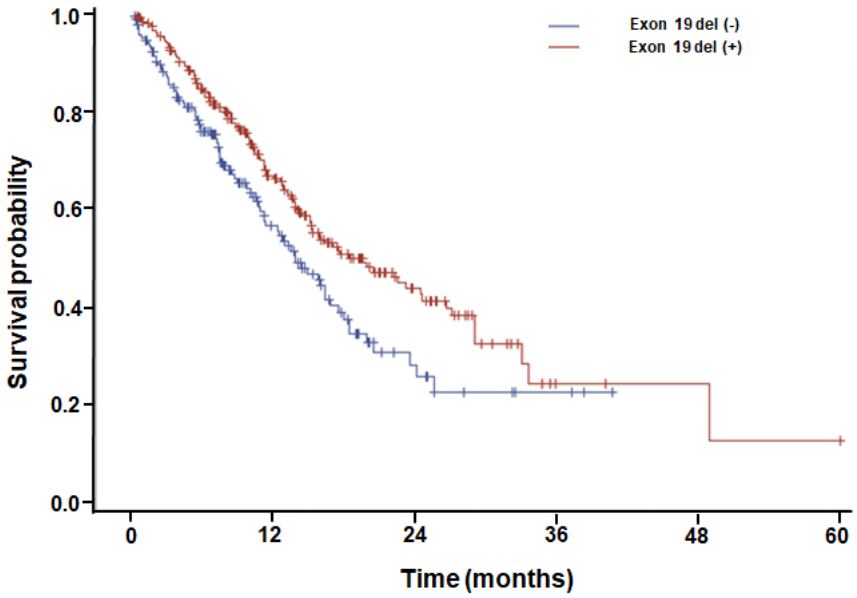
However, there was no statistically significant difference in PFS and OS between patients who received additional treatment for their brain metastasis compared with those who did not.

2. Differences in Therapeutic Efficacy between E19del and L858R Mutations: Prior research has suggested that there may be differences in the therapeutic efficacy of treatments depending on whether patients harbor E19del or L858R mutations, particularly in East Asian populations. Including an analysis comparing the effects of these two common EGFR mutations in your paper could provide additional insights and enhance the interest and relevance of your study to readers.

Answer: As suggested, we have conducted additional analysis for the PFS and OS sub-grouped by the presence or absence of Exon19 deletion (Del19) and L858R. As shown, the presence of Del19 is associated with longer PFS while L858R with shorter PFS.

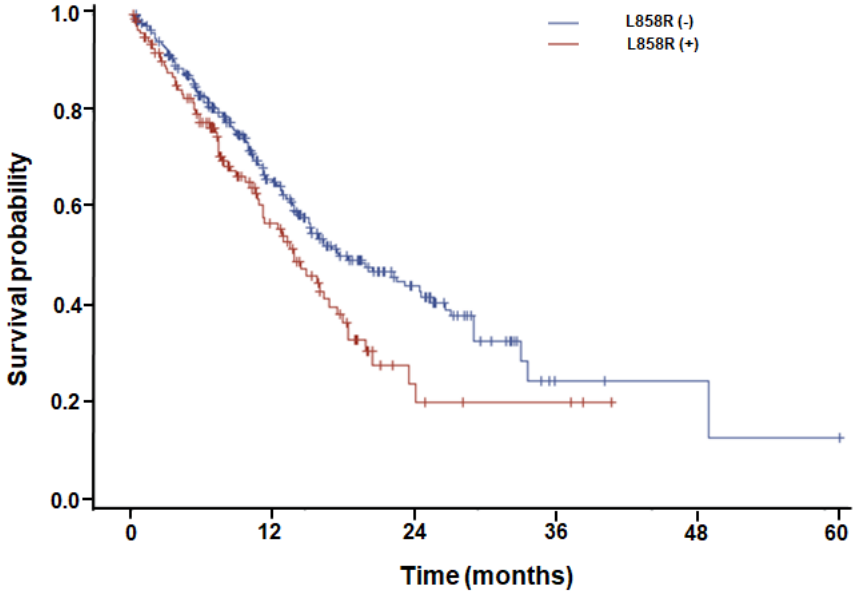
Individually, neither mutation was associated with increased OS.

1. PFS based on the presence or absence of Exon 19 deletion.



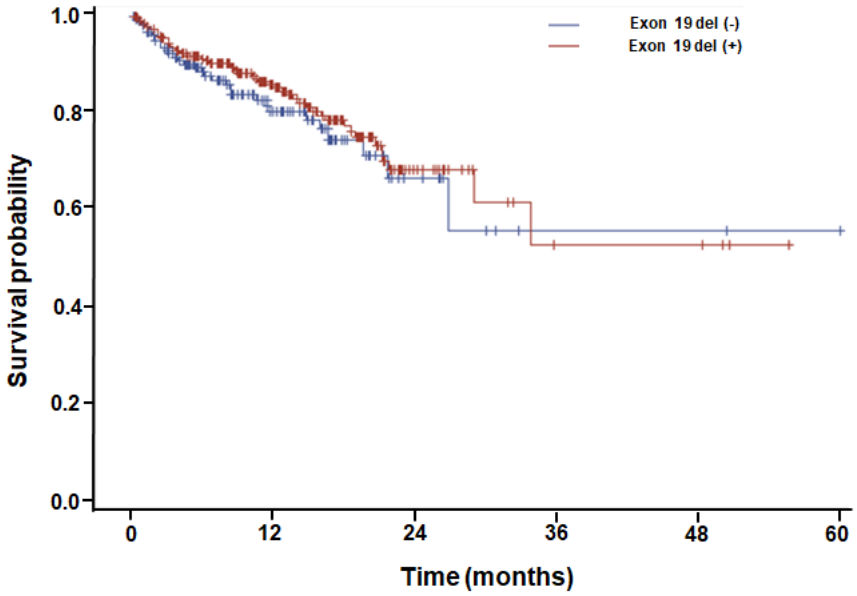
	No. of patients	Median OS (95% CI), months	36-mo OS rate	60-mo OS rate	p-value
Del19	252	20.8 (17.1– 27.8)	32.1%	12.0%	0.009
Others	163	15.6 (12.6– 19.0)	22.2%	22.2%	

2. PFS based on the presence or absence of L858R



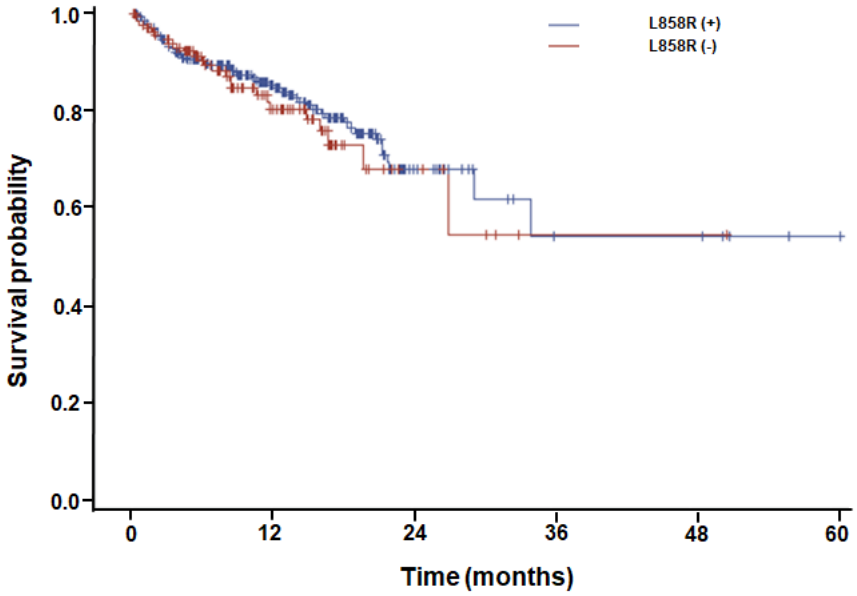
	No. of patients	Median OS (95% CI), months	36-mo OS rate	60-mo OS rate	p-value
L858R	129	15.6 (12.6–19.0)	19.4%	19.4%	0.017
Others	286	19.9 (17.1–27.7)	32.0%	12.0%	

3. OS based on the presence or absence of Exon 19



	No. of patients	Median OS (95% CI), months	36-mo OS rate	60-mo OS rate	p-value
Del19	256	NR (40.9–NR)	68.1%	52.5%	0.432
Others	161	NR (37.7–NR)	66.4%	55.4%	

4. OS based on the presence or absence of L858R



	No. of patients	Median OS (95% CI), months	36-mo OS rate	60-mo OS rate	p-value
L858R	137	NR (37.7–NR)	68.0%	54.4%	0.553
Others	280	NR (40.9–NR)	67.7%	53.9%	

Changes:
Added to results (line 123-127):
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). However, no statistical differences in OS were seen when comparing the presence vs absence of Del19 (p=0.432) and L858R (p=0.553).

These 4 figures are added as supplementary figures 3, 4, 5, and 6 respectively.

3. Comparison of First-line Therapies in the Discussion: In the Discussion section, it would be beneficial to position your findings within the broader context of first-line therapy options for NSCLC patients with EGFR mutations. For example, a comparison of the effectiveness and side effect profiles of afatinib, osimertinib, or erlotinib plus ramucirumab could be included. This would highlight the strengths of afatinib as a first-line therapy and provide a more comprehensive view of the therapeutic landscape.
Answer:
In general, other studies tend to report first-line afatinib to have shorter Progression-Free Survival (PFS) compared to osimertinib. However, this cohort study has demonstrated a longer PFS of first-line afatinib, comparable to first-line osimertinib. Given the potential opportunity for second-line osimertinib therapy after first-line afatinib, there may be a specific subset of patients who, if prone to developing T790M as a resistance mechanism, could indicate that a first-line afatinib plus subsequent osimertinib treatment strategy might be superior to first-line osimertinib treatment alone. Furthermore, the PFS observed in this study was comparable to that of the combination treatment of erlotinib and ramucirumab, an anti-VEGF-R2 antibody. However, the rate of grade ≥3 adverse events were higher than observed in afatinib in our previous publication. A large real-world study has also demonstrated afatinib to have statistically higher PFS and one-year OS, supporting the real-world effectiveness and safety of afatinib. We have added these points in the discussion.

Changes:
Added to discussion (Line 155-161):
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 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.

Added to discussion (Line 166-172):
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 ≥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 one-year OS of afatinib compared with erlotinib and gefitinib (23). These results support the real-world effectiveness and safety of afatinib.

Reviewer C

The authors retrospectively analyzed the medical record of patients with EGFR-mutated NSCLC who had been treated with 1st-line afatinib. They found the presence of brain metastases and common EGFR-mutations significantly affected survival time. Although this study included a lot of patients treated with first-line afatinib and the results of this study are solid, but lack novelty. As the authors mentioned, these findings have been reported elsewhere. In addition, first line osimertinib has been used for patients with EGFR-mutated NSCLC in worldwide. Thie study does not move the field forward.
Answer: We appreciate the valuable input. However, in a well-controlled population, the 1st line afatinib plus subsequent osimertinib treatment strategy may demonstrate superior outcomes over 1st line osimertinib. Therefore, it is crucial to identify subgroups of chemo-naive EGFR m(+) patients where subsequent treatment provides better efficacy. To achieve this, the search for clinical characteristics or biomarkers that can identify such subgroups should be considered necessary.' In this study, we have also demonstrated that first-line afatinib has comparable PFS to first-line Osimertinib. Our result suggests that 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.

Change:
Added to discussion (Line 155-161):
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 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.

Reviewer D

This study has already reported OS results in this journal, but since the OS results were immature in the previous report, it is assumed that this report is an investigation of OS with a further extended observation period.
Usually in prospective clinical trials, after the initial report, a report on mature survival data may be reported in another paper. Updating OS data in a retrospective trial does not seem to be as valuable as reporting it in a separate paper. At least, it is a report that has a much lower impact than the previous report.

The difference in survival with and without brain metastases is also to be expected.
Answer: We appreciate the feedback. We believe this article is important as it provides a follow-up to previously immature OS data. This study also investigated the different subgroups of patients based on baseline EGFR mutations to identify patients who may be more likely to benefit from first-line afatinib treatment. In addition, in response to comments from other reviewers, we have added further insight into the outcome among patients with brain metastasis, adding to the novelty of the paper. We have highlighted the additional insight provided by the current study in the discussion.

Changes:
Added to discussion (line 143-146):
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 EGRF mutations.

Reviewer E

Choi et al. present a manuscript about afatinib treatment in EGFR mutation positive NSCLC patients in Korea. The same group already published data about this cohort earlier. Now, the focus lies on updated survival data.

The manuscript is written clearly and in acceptable English. The data are relevant, especially as 3rd generation EGFR TKI are not approved for 1st line therapy in Korea.

Major points:

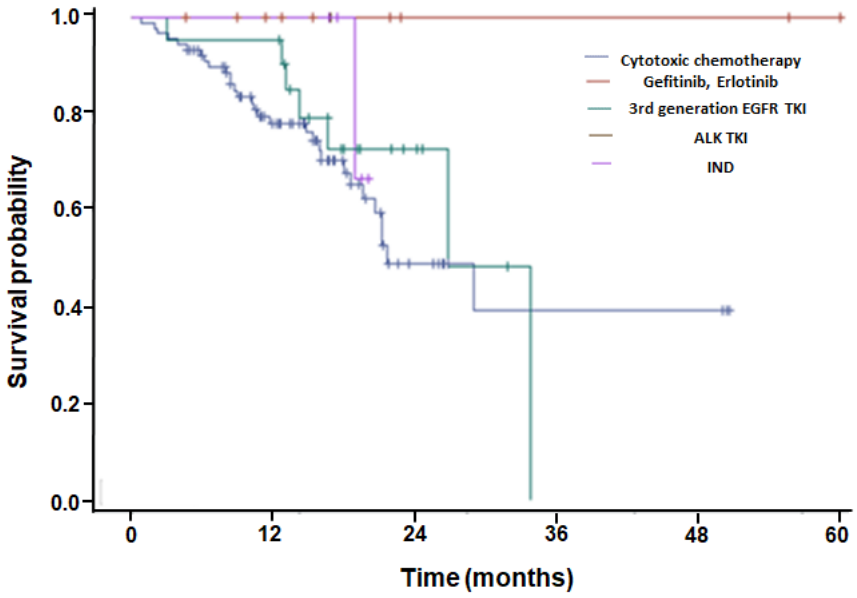
1. data are missing about further therapies after progression to afatinib. Here, it should be clearly described, how many patients have received osimertinib or other TKI or chemotherapy. PFS2 or at least OS data should be presented for those groups (e.g., no further treatment, osimertinib 2nd line, chemotherapy 2nd line). In addition, survival data should be given for patients with uncommon EGFR mutations.

Answer:
Thank you for the feedback. We have provided the treatment patients received following PD as supplementary table 1.

	n	%
Cytotoxic chemotherpy	90	71.43
Gefitinib, Erlotinib	9	7.14
3rd EGFR TKI	21	16.67
ALK TKI	1	0.79
IND	5	3.97

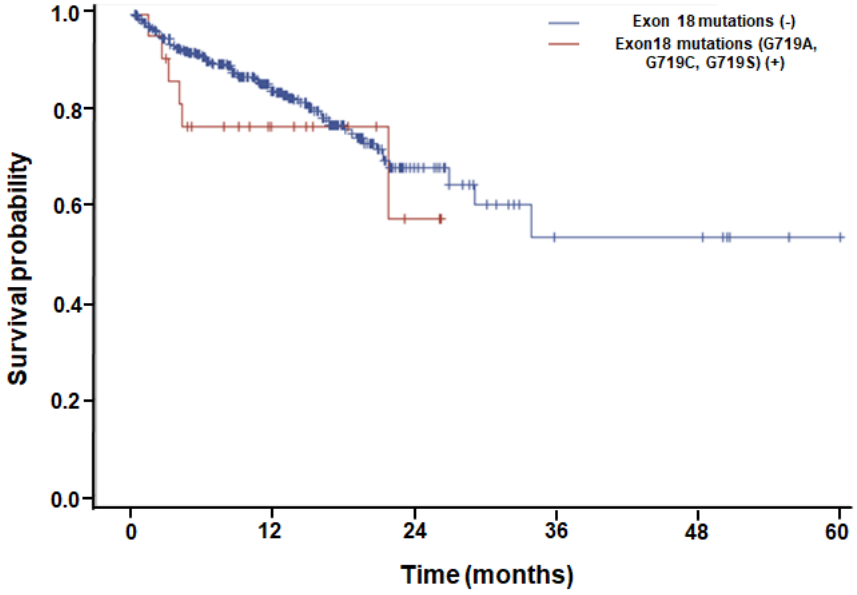
We have also provided additional data on the OS of patients by the treatment received and by the presence of uncommon EGFR mutations. Unfortunately, we do not have PFS2 data for these subgroup analyses.

Supplementary Figure 9. Kaplan-Meier overall survival curves in patients according to treatment received after PD.



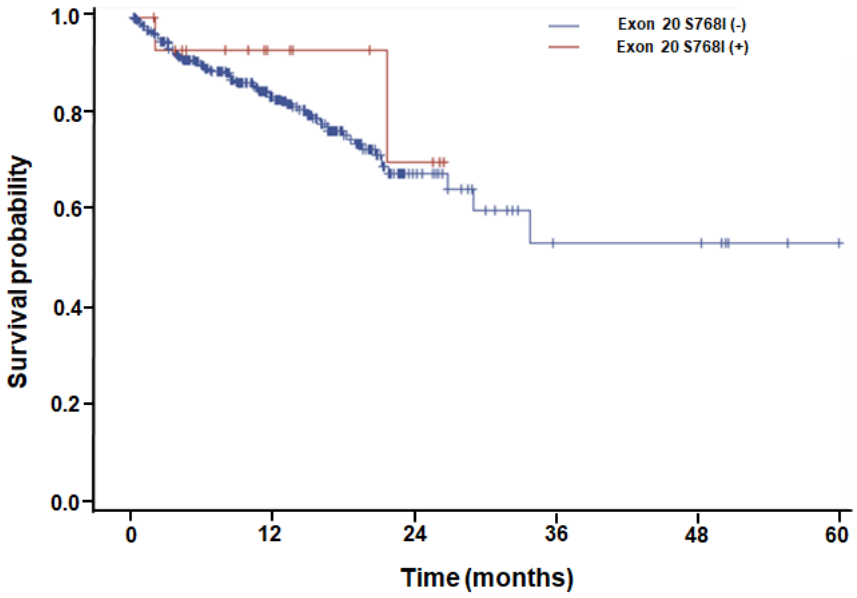
	No. of patients	Median OS (95% CI), months	36-mo OS rate	60-mo OS rate	p-value
Cytotoxic chemotherapy	90	20.5 (27.5–NR)	49.1%	39.3%	0.239
Gefitinib, Erlotinib	9	NR (NR–NR)	100%	100%	
3rd generation EGFR TKI	21	37.7 (23.4–47.6)	72.7%		
ALK TKI	1	NR (NR–NR)	100%	100%	
IND	5	NR (NR–NR)	66.7%	66.7%	

Supplementary Figure 7. Kaplan-Meier overall survival curves in patients according to the presence or absence of Exon18 mutations (G719A, G719C, G719S)



	No. of patients	Median OS (95% CI), months	36-mo OS rate	60-mo OS rate	p-value
Exon 18 mutations (G719A, G719C, G719S)	22	NR (30.5–NR)	57.4%	57.4%	0.315
others	395	NR (40.9–NR)	68.1%	53.7%	

Supplementary Figure 8. Kaplan-Meier overall survival curves in patients according to the presence or absence of Exon 20 S768I



	No. of patients	Median OS (95% CI), months	36-mo OS rate	60-mo OS rate	p-value
Exon 20 (S768I)	16	NR (30.5–NR)	70.0%	70.0%	0.503
others	401	NR (40.9–NR)	67.6%	53.3%	

Changes:
Added Supplementary Table 1, Supplementary Figures 7, 8, and 9.

Result (line 130-133): There were no significant differences in OS based on the presence or absence of Exon 18 mutations (G719A, G719C, G719S) (p=0.3149); Supplementary Figure 7) or Exon 20 mutation S768I (p=0.5032; Supplementary Figure 8).”

Result (line 135-137): Lastly, there was no significant difference in OS based on treatment received after progression to afatinib (p=0.239; Supplementary Figure 9).

Discussion (line 191-193): 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).

2. There are other real world evidence data in the literature. A comparable study with comparable results was performed in Germany (GIDEON trial) with similar data regarding important subgroups, e.g., older patients, dose reductions and brain metastases (Brueckl et al., Therap Adv in Med Oncology 2021 and Brueckl et al., J Geriat Oncology 2022). These data should be included in the discussion as those data confirm the data from Korea.

Answer: Thank you for the wonderful suggestion. We have added these publications to support the findings of this study in the discussion.

Changes:

Added in discussion:

Line (201-203): ", and results from the GIDEON perspective non-interventional study demonstrating higher median PFS in patients ≥70 years (26)."

Line (206-209): "The GIDEON study also reported comparable effectiveness of starting dose of <40 mg and 40 mg (28). These results suggest first-line afatinib to be an effective treatment option in elderly patients with an option for dose adjustment."

3. Data presented in the results part should not be repeated in the discussion part (e.g., lines 157-165).

Answer: Thank you for the suggestion. We have removed redundant data that does not add to the discussion. However, we decided to keep the results which are needed for ease of comparison with previous studies as well as results from previous studies.

Changes:

Removed:

Line 174-176: "Median OS in the absence of baseline brain metastases was 65.6 months, compared with 32.2 months in their presence, an increase of more than 33 months"

Line 179: "from 30.1 to 49.6 months"