Peer Review File
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REVIEWER A

Comment 1: Analyzing brain metastases it is essential to have a MRT done. However, nothing could be found in the whole manuscript. When MRT were not consistently performed data cannot be evaluated. Furthermore, the number and size of brain metastases should be included in the prognosis. Nothing was described in this manuscript.

Reply 1: As the study reviewed patient electronic records, some aspects of patient details may not be available. This is stated in the limitations of the study in the Discussion (Line 438) "Importantly, because brain imaging data were not analyzed further in this study, there is a possibility that brain metastases were missed in patients classified as being without baseline brain metastases". Although MRT was not followed up regularly, additional MRT was taken in most cases when the disease progressed in the evaluation of treatment response.

Changes in the text: Information about the type and number of brain metastases and leptomeningeal metastases has been added to Table 1.

Comment 2: In addition it is essential to know whether brain metastases were treated with radiotherapy, either as whole brain irradiation or SBRT. Nothing can be found about local treatment in this manuscript.

Reply 2: The need for local treatment in the presence of initial brain metastasis in patients with EGFR-mutant NSCLC is controversial. In one study, afatinib was associated with a CNS response rate of 67% and a CNS PFS of 24.7 months without local treatment, even in the presence of initial brain metastases (dx.doi.org/10.21037/tlcr-22-79). However, local treatment is considered essential for CNS failure after first-line afatinib therapy. This study was a retrospective review of patient records, so although we had data on the type of brain metastases, we did not investigate the type of local treatment. Although this is a limitation of our study, the combination of afatinib and local treatment for initial brain metastases is still controversial and is based on the judgement of medical staff. And if a patient without brain metastases develops brain metastases after using afatinib, we assume that the best local treatment would have been chosen based on the patient's brain lesion status.

Changes in the text: The Limitations part of the Discussion has been updated to include the following (Page 18/Lines 442-447):

Additionally, although we collected data on the type of brain metastases, we did not investigate the type of local treatment. Although this is a limitation of our study, the combination of afatinib and local treatment for initial brain metastases is still controversial and is based on the judgement of medical staff. And if a patient without brain metastases develops brain metastases after using afatinib, we assume that the best local treatment would have been chosen based on the patient's brain lesion status.

Comment 3: There were clinical prognostic factors described in combination with

brain metastases, e.g. performance status, stage or other metastatic sites. However, these findings are not discussed. Therefore, the reader does not know what is the information of these findings. Should patients with these confounding factors treated in another way, e.g. chemotherapy? Should these patients evaluated for brain metastases more often than other patients? Are there data in the literature whether there are associations between special metastatic sites?

Reply 3: The existing discussion provides an overview of prognostic factors for brain metastasis. Line 355 (Discussion) "CNS failure was associated with ECOG status, uncommon *EGFR* mutations, and pleural metastasis status". Independent risk factors for brain metastasis from other retrospective studies and commonality of risk factors for *EGFR* mutation-positive advanced NSCLC with those for brain metastasis in NSCLC are then reviewed.

Changes in the text: An additional sentence and new reference have been added (Line 354-355): In NSCLC, brain is the third most common single metastatic site after bone and lung; and for two metastases, the most common sites are bone plus lung followed by bone plus brain (55).

Comment 4: In the discussion part the findings of the results are not described but just mentioned again what is somehow boring for the reader. In addition, there are quite confusing data about other substances, e.g. erlotinib. Furthermore, quite a long part of the discussion are trials with sequence therapies. However, as there are no data of the data analyzed by Kim et al. on further therapies this part is futile.

Reply 4: The sentence beginning "Kim et al. found that sequential first-line afatinib followed by second-line Osimertinib" (originally Line 343) was deleted. Paragraph from Line 351 (beginning "In global real-world clinical practice studies of EGFR mutation-positive NSCLC") about sequential afatinib and osimertinib was deleted.

Changes in the text: Sentence originally beginning on Line 343, paragraph from Lines 351 to 357 and references originally numbered 58-62 were all deleted.

Comment 5: There are ethnical differences between Asian and Caucasian patients in incidence, prognosis and outcome towards EGFR mutated tumors. However, studies described in the discussion do not differentiate or separate these trials.

Reply 5: The ethnicity of participants in the LUX-Lung 3, 6 and 7 trials has been added (Line 294 onwards).

Changes in the text: "In the multinational LUX-Lung 3 trial which included both Asian and non-Asian patients, median PFS in afatinib-treated patients with *versus* without brain metastases was 11.1 *versus* 13.8 months; in the LUX-Lung 6 study of Asian patients was 8.2 *versus* 11.1 months; and in the multinational LUX-Lung 7 study was …".

Comment 6: Some relevant prospective data on afatinib 1st line in EGFR mutated NSCLC patients, e.g. GIDEON trial, are missing in the discussion.

Reply 6: Results from the GIDEON trial of first-line afatinib in mutation-positive EGFR NSCLC [Brückl et al. 2021] are summarized in the Discussion.

Changes in the text: Line 313 sentence added "Results from a recent prospective non-interventional study in Germany …".

Minor points Comment 1. The reader is bored by to many numbers and percentages given in the results part and by repeating those facts in the discussion. Those facts should be summarized in one or two tables and just mentioned in the text.
Minor points Reply 1: Results and discussion edited.
Changes in the text: Multiple revisions have been made in the Results and Discussion sections.

Minor points Comment 2. Table design is quite confusing and has no clear structure. In addition, tables 3-5 should be presented as supplement only.
Minor points Reply 2: Headers for *P* values in Tables 1, 4 and 5 have been changed for clarity. Tables 4 and 5 are presented as Supplementary Tables 2 and 3, respectively. Table 3 is retained as Reviewer B considers that the absence of pleural effusion as a risk factor for the development of brain metastases is a novel finding (Comment 2) and we consider that these results need to be presented in the manuscript.
Changes in the text: Tables 4 and 5 are presented as Supplementary Tables 2 and 3, respectively.

Minor points Comment 3. Comparing data with the literature always makes it more clear to give these information in a table instead of getting out of hand in the text.
Minor points Reply 3: This would detract from the data in the current tables which have been rearranged (see above) to include two Supplementary Tables.
Changes in the text: None.

Minor points Comment 4. Afatinib is not anymore the preferred treatment but osimertinib, which has an even better CNS penetrance. This fact should be discussed.
Minor points Reply 4: Preclinical studies of Osimertinib and other TKIs are reviewed briefly.
Changes in the text: The Discussion has been expanded (beginning Line 288) to include the following: Preclinical studies show osimertinib has greater penetration of the rodent blood-brain barrier than other EGFR TKIs (41,42), which may explain these results. However, there are no studies which directly compare the incidence of CNS failure in patients with metastatic NSCLC treated with osimertinib or afatinib.

REVIEWER B

Comment 1: Please add the actual number of patients in Table 2 to present the results more clearly.
Reply 1: Data added to Table 2.
Changes in the text: Column 1 in Table 2 has been updated to include the number of patients in each category.

Comment 2: Authors newly identified the absence of pleural effusion as a risk factor for the development of brain metastases (Table 3). This is a novel finding and the underlying mechanism should be mentioned in the Discussion section.

Reply 2: In our study, Table 1 shows that pleural metastases were present in 26% of cases with initial brain metastases and 43% of cases without initial brain metastases, which differs from the high incidence of metastases to other organs (liver, bone) in the presence of initial brain metastases. And the absence of pleural metastases was a risk factor for the development of brain metastases. There may be differences in the organs that metastasise depending on the characteristics of the patient's lung cancer, so patients with pleural metastases may have characteristics that make them less likely to develop brain metastases.

Similarly, Qing Li et al (Brain parenchymal and leptomeningeal metastasis in non-small cell lung cancer; doi.org/10.1038/s41598-022-26131-z) found that patients with brain metastases from NSCLC had more liver, lymph node, and adrenal metastases, but fewer pleural metastases, compared with patients without brain metastases. And in both univariate and multivariate analyses, the absence of pleural metastases was a risk factor for brain or leptomeningeal metastases (brain pleural metastases, OR: 0.495, 95% CI: 0.325-0.756; leptomeningeal metastases, OR(0.307, 95% CI: 0.172-0.547).

In contrast, Wen Ouyang et al (Risk factors of metachronous brain metastasis in patients with EGFR-mutated advanced non-small cell lung cancer; doi.org/10.1186/s12885-020-07202-8) found that in CNS failure in patients without brain metastases, pleural metastasis was a risk factor in univariate and multivariate analysis (OR: 5.283, 95% CI 1.851-15.053). An alternative hypothesis is that afatinib is so effective against pleural metastases that it prevents deterioration that could lead to brain metastases.

Changes in the text: The above points have been included in new text added to the Discussion section (beginning Line 368).

Comment 3: The redundancy of the discussion section seems to make it difficult to understand the main points of this study. Please revise it more concise, by omitting discussions that are less relevant to this study.

Reply 3: The Discussion was edited with sections on sequential therapy deleted and the section on real-world studies of Asian patients moved to after discussion of LUX-Lung clinical trials

Changes in the text:

- Sentences discussing sequence therapies (originally beginning Line 343) were deleted.
- To improve the flow, the section discussing real-world studies of Asian patients has been moved to after discussion of LUX-Lung clinical trials.

REVIEWER C

Comment 1: Rewrite the discussion section since there are some redundant and non-relevant descriptions. Please refer to the following with a view of points in the discussion section. I usually evaluate the discussion section in accordance with the

following (but they are not mandatory):
a. What is the conclusion? (based on major findings and related study's purpose or hypothesis)
b. Interpretation of your findings-what further explanation should you give to help readers understand and appreciate the importance of your research?
c. How findings fit in with existing literature. Study that agrees and Study that disagrees, with possible explanations for differences.
d. Clarify the novelty/strength of study.
e. Clarify limitations of study and other valid criticisms.
f. Clarify generalizations to other populations.
g. Clarify why finding the knowledge gap is important
h. Clarify implications of findings/speculation
i. Clarify avenues for further study

Reply 1: As noted elsewhere (in response to other Reviewer comments), changes were made to the discussion. Conclusions remain in a separate section at the end of the Discussion (as per TLCR author guidelines).

Changes in the text:

- At the beginning of the Discussion (Line 247) now reads "This retrospective real-world study investigated the CNS failure rate of first-line afatinib in patients with *EGFR*-mutant NSCLC with or without brain metastasis.
- Sentences discussing sequence therapies (originally beginning Line 343) were deleted.
- The section discussing real-world studies of Asian patients has been moved to after discussion of LUX-Lung clinical trials.

Comment 2: I recommend the authors clarify the details and results in the patients having uncommon EGFR mts including frequency of baseline brain

Reply 2: Details about uncommon *EGFR* mutations have been added in a new Supplementary Table (Supplementary Table 1 – see below).

Changes in the text: An additional sentence has been added to Lines 200-202: Uncommon EGFR mutations in patients with or without baseline brain metastases are summarized in Supplementary Table 1.

Supplementary Table 1. Uncommon EGFR mutation status in patients

Parameter	No baseline brain metastases		Baseline brain metastases (n = 262)	Total (n =703)
	New brain metastases (n = 92)	No brain metastases (n = 349)		
Major uncommon mutation				
G719X	4 (30.8)	12 (38.7)	5 (22.7)	21 (31.8)
L816Q	2 (15.4)	7 (22.6)	5 (22.7)	14 (21.2)
Compound				

G719X+S768I	3 (23.1)	4 (12.9)	4 (18.2)	11 (16.7)
T790M+sensitive mutations*	0 (0.0)	2 (6.5)	2 (9.1)	4 (6.1)
G719X+L861Q	0 (0.0)	2 (6.5)	1 (4.5)	3 (4.5)
19deletion+20insertion	1 (7.7)	1 (3.2)	0 (0.0)	2 (3.0)
T790M+G719X	1 (7.7)	0 (0.0)	0 (0.0)	1 (1.5)
19deletion+L861Q	0 (0.0)	0 (0.0)	1 (4.5)	1 (1.5)
Exon 20 insertion	2 (15.4)	2 (6.5)	1 (4.5)	5 (7.6)
S768I	0 (0.0)	1 (3.2)	2 (9.1)	3 (4.5)
T790M	0 (0.0)	0 (0.0)	1 (4.5)	1 (1.5)

*Sensitive mutations included EGFR 19 deletion and L858R mutation.

Comment 3: How many patients were treated with osimertinib or IO after afatinib? Clarify the details after afatinib if the authors collected data
Reply 3: Osimertinib was used in 145 patients, 20.6% of the total 703 patients. IO was not used. As this study evaluated the efficacy of afatinib in patients with and without CNS metastases, it did not include treatment after afatinib.
Changes in the text: No changes required.

Comment 4: Clarify the pts at risk in figure 1.
Reply 4: We do not believe that anything needs to be clarified regarding Figure 1.
Changes in the text: No changes required.

REVIEWER D

Comment 1: 194 - yes, patients with baseline brain metastases consisted of fewer males, but new brain metastases were more common in men during treatment (tabele 1). Relevant text is: “patients with baseline brain metastases (n=262) consisted of fewer males (45.4% vs 54.9%, P=0.015), and had involvement of more metastatic sites (3–6 sites: 42.4% vs 12.5%, P<0.001)”
Reply 1: Comment only – no changes required.
Changes in the text: No changes.

Comment 2: Whether the disease of women and men was the same advanced in baseline?
Reply 2: In our study, baseline brain metastasis was more prevalent in women, which may reflect the bias of patients enrolled in a real-world study. However, among women without baseline brain metastasis, 21.1% developed new brain metastases and, among men, a similar rate of new brain metastases was observed (20.6%). CNS progression was similar in both men and women.
Changes in the text: No change necessary.

Comment 3: Female achieved better OS and TOT -in baseline brain metastases and in new brain metastases. Based on the study LUX-lung 3 and 6, we know that women respond better to treatment and the presented data confirms this.
Reply 3: In both univariate and multivariate analyses, there was no significant difference in CNS failure between males and females (Table 2). In LUX-lung 3 and 6, there were no significant differences in PFS in males *versus* females.
Changes in the text: None.

Comment 4: 208 -more often men, but it is statistically insignificant (gender is a factor of poorer response to EGFR TKI). Relevant text (line 203) "Compared with 349 (79.1%) patients without CNS failure, patients who developed CNS failure during treatment were younger (mean age: 60.9 vs 64.2 years, P=0.012), had a higher ECOG performance status (PS) (≥ 2: 18.6% vs 3.7%, P<0.001), more metastatic site involvement (3–6 sites: 32.6% vs 7.2%, P<0.001), advanced stage disease (Stage IVB: 51.1% vs 26.4%, P<0.001), and baseline liver metastasis (15.2% vs 6.6%, P=0.008) and/or bone metastasis (52.2% vs 32.1%, P<0.001(Table 1)."
Reply 4: Not statistically significant – no further comment required.
Changes in the text: None.

Comment 5: 314 - yes, osimertinib binds irreversibly to mutant EGFR at the C797 residue [312: The T790M mutation in the EGFR gene is the most common cause of resistance after first- or second-generation TKI therapy (44,45) and is localized within the ATP-binding pocket of EGFR]
Reply 5: Comment only - no changes required.
Changes in the text: None.

Comment 6: 606 - table 1- maybe it's worth adding a female gender
Reply 6: We analyzed by gender (female/male comparison) using the chi-square test.
Changes in the text: Table 1 has been modified to include details for males and females.

Comment 7: 615 - 3 years : cumulative incidence of central nervous system in male-28,5%, female-32%, how many were women and how many were men? [Table 2. Cumulative incidence (%) of central nervous system (CNS) failure1 in patients without brain metastases at baseline]
Reply 7: Data added to Column 1 in Table 2.
Changes in the text: Column 1 in Table 2 has been updated to include the number of patients in each category.

REVIEWER E
Comment 1: We would like to know the differences of efficacy and impact of the prognostic factors between afatinib and other TKIs.
Reply 1: The comparison between first- and second-generation EGFR-TKIs is always an interesting topic. However, we did not specifically include it in our discussion

because our study is based on a cohort of patients on first-line treatment with afatinib; consequently, we believe that discussion of this interesting topic is generally beyond the scope of the current study. However, as noted elsewhere (in response to other Reviewer comments), some changes have been made to the Discussion section, some of which we believe briefly address the Reviewer's comment (see the section on real-world studies of Asian patients, some of which discuss comparisons between TKIs).
Changes in the text: Various changes made to the Discussion – in particular, the section discussing real-world studies of Asian patients (beginning Line 319) has been moved to after discussion of the LUX-Lung clinical trials.