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Reviewer A

Authors confirmed the results of previous phase 3 study by analyzing their own real-world big data. I understand that this is the largest real world study comparing osimertinib with first-generation EGFR-TKIs as a first-line treatment. Although authors described the difference of follow-up duration and limitation of NMPA on timing of osimertinib usage (line 332-336), I thought they were critical. I would like to know new findings they stressed in this manuscript, different from previous studies.

Reply: Thank you very much for your advice. To date, multiple studies have demonstrated the PFS benefits associated with first-line osimertinib compared with first-generation EGFR-TKIs. However, whether first-line osimertinib produces an OS benefit has yielded varying results in different studies. In the FLAURA trial, first-line osimertinib significantly prolonged OS (38.8 vs. 31.8 months, P=0.046). In the FLAURA China subgroup analysis, the osimertinib group exhibited a trend towards prolonged OS, although it did not reach statistical significance (33.1 vs. 25.7 months, P=0.442). Conversely, in the Japanese subgroup, an opposite trend was observed, with the osimertinib group and the comparator group having OS of 39.9 months vs. "not reached" (P=0.215). Furthermore, OS data from other studies exploring the efficacy of first-line osimertinib remained immature. To the best of our knowledge, our study standed as the first real-world research to support the significant OS extension achieved by osimertinib as observed in the FLAURA trial, further substantiating the superiority of first-line osimertinib over first-generation EGFR-TKIs. We have modified the text as advised (see Page3, line79-81; Page10, line319-332).

Changes in the text: Page3, line79-81and Page10, line319-332, which were marked in yellow.

Reviewer B

Comment 1: The authors compare real world efficacy of osimerinib to first generation EGFR TKI. While the paper is well written and the survival data quite complete, I have a few questions.

-is the database only including certain participating hospitals in China or is it meant to have a patient population that is representative of all lung cancer patients in China?

Reply 1: Thank you for your comment. In January 2018, the CAPTRA-Lung study was launched with the collaboration of 16 medical centers from various regions of China. As of October 31, 2022, with its growing influence, the CAPTRA-Lung study has grown to encompass the participation of 36 research centers and has gathered data from a cohort of 10,156 patients diagnosed with advanced or metastatic NSCLC, aiming to provide insights into real-world therapeutic regimens for all Chinese patients with advanced or metastatic NSCLC. The text has been modified according to your advice (see Page3, line93-95).

Changes in the text: Page3, line93-95, which was marked in yellow.

Comment 2: -after the availability of osimertinib, were all patients treated with this drug or did some receive first generation EGFR TKI? If the later is true, this needs to be explained in the manuscript.

Reply 2: Thank you for your advice. Osimertinib was approved by the National Medical Products Administration for first-line treatment in 2019. However, due to economic considerations, some patients with advanced NSCLC carrying EGFR mutations continued to receive first-generation EGFR-TKIs as their initial treatment. After PSM, 274 NSCLC patients diagnosed in 2019 and later were included, 92 patients (33.6%) among whom continued first-line treatment with first-generation EGFR-TKIs. This information has been clarified in the article (see Page6, line182-189).

Changes in the text: Page6, line182-189, which was marked in yellow.

Comment 3: -the proportion of patients with high grade adverse events is much lower than expected. In particular rates of severe pneumonia is are lower than previous publications. Please explain.

Reply 3: Thank you for your advice. The occurrence of AEs of high grade in our study was lower than that in clinical trials, as adverse event reporting primarily relied on medical records from various medical centers due to the retrospective nature of this multicenter real-world study, which could potentially result in underreporting or underestimation of adverse events. Additionally, patients experiencing severe adverse events might seek medical attention at nearby hospitals and subsequently be lost to follow-up. These factors could contribute to a lower incidence of high-grade adverse events and severe pneumonia in this study compared to previous researches. Although the occurrence of high-grade adverse reactions is notably low in this study, it remains crucial to maintain careful monitoring during the course of treatment. We have added explanations based on your advice (see Page12, line385-395).

Changes in the text: Page12, line385-395, which was marked in yellow.

Comment 4: -in order to compare rates of adverse events between the groups, was there an attempt to control for immortal time bias?

Reply 4: Thank you for your comment. To minimize immortal time bias, only patients receiving osimertinib or first-generation EGFR-TKIs for the first time were included in this study and the observation period started from the initiation of EGFR-TKI treatment. Besides, propensity score matching was performed to ensures comparability of two groups. We have added relevant explanations in the manuscript (see Page5, line132-134 and 140-143).

Changes in the text: Page5, line132-134 and 140-143, which were marked in yellow.

Reviewer C

Comment 1: China is a multi-ethnic country. Is it correct to understand that all the patients included in this study were Asian? If this is true, I would appreciate it if you could specify that all the patients are Asian population.

Reply 1: Thank you very much for your reminding. All participants included in the study were

Asian population. We have added relevant explanations in the manuscript (see Page5, line157-158).
Changes in the text: Page5, line157-158, which was marked in yellow.

Comment 2: PD-L1 expression levels may affect the effectiveness of EGFR-TKIs in patients with EGFR-mutated NSCLC. Have you analyzed the association between PD-L1 expression levels and the effectiveness of EGFR-TKIs in patients with EGFR-mutated NSCLC who are receiving osimertinib or first-generation TKIs?
Reply 2: Thank you for your suggestion. We did not analyze the relationship between PDL1 expression levels and the efficacy of EGFR-TKIs for the following reason. Among the 606 patients included after propensity score matching, 422 patients (70.0%) were diagnosed with NSCLC in 2019 or earlier. At that time, first-line immunotherapy had not been widely used in China as pembrolizumab was approved by the National Medical Products Administration in 2019 for first-line treatment of advanced NCSLC patients, and PDL1 testing was not a routine clinical procedure. Therefore, data on PDL1 expression in the CAPTRA-Lung database were severely lacking, and as a result, we did not further analyze the relationship between PDL1 expression levels and the efficacy of EGFR-TKIs. We are planning to conduct relevant research in the future. We have made explanations in the limitations section of our manuscript (see Page12-13, line402-404).
Changes in the text: Page12-13, line402-404, which was marked in yellow.

Comment 3: In the FLAURA trial, patients with unstable symptomatic CNS metastasis were excluded. Did the data you used distinguish between unstable symptomatic CNS metastasis and stable CNS metastasis? If they were distinguished, what was the effect of osimertinib on patients with unstable CNS symptomatic metastasis? Since it's a study using real-world data, this is a point I definitely want to know.
Reply 3: Thank you for your comment. Among 202 patients in the osimertinib group, 64 individuals (31.7%) presented with baseline CNS metastases, including 29 (14.4%) with stable CNS metastases, 9 (4.5%) with unstable symptomatic CNS metastases, and 26 (12.9%) with an undisclosed status. Among 404 patients in the first-generation EGFR-TKI group, 114 (28.2%) had baseline brain metastases, including 80 (19.8%) with stable CNS metastases, 17 (4.2%) with unstable symptomatic CNS metastases, and 17 (4.2%) with an unknown status.
For patients with baseline stable CNS metastases, the osimertinib group showed significantly extended PFS compared to the comparator group, with median values of 25.5 months (95% CI: 3.1-47.9) vs. 8.4 months (95% CI: 6.3-10.5), respectively (HR 0.26 [95% CI: 0.13-0.53]; P < 0.001). OS was also significantly improved in the osimertinib group, with a median OS that was "not reached" vs. 25.8 months (95% CI: 22.3-29.3) in the comparator group (HR 0.03 [95% CI: 0-0.39]; P <0.001). For patients with baseline unstable symptomatic brain metastases, the median PFS ("not reached" vs. 14.1 months, P=0.190) and OS (33.5 vs. 23.4 months, P=0.320) were longer in the osimertinib group than that in the first-generation EGFR-TKI group, although without statistical significance. However, it's important to exercise caution in interpreting the results for these subgroups due to the relatively small number of patients in each subgroup. We have added explanations in the text (see Page6, line176-182; Page7-8, line220-238; Figure S1; Figure S2).

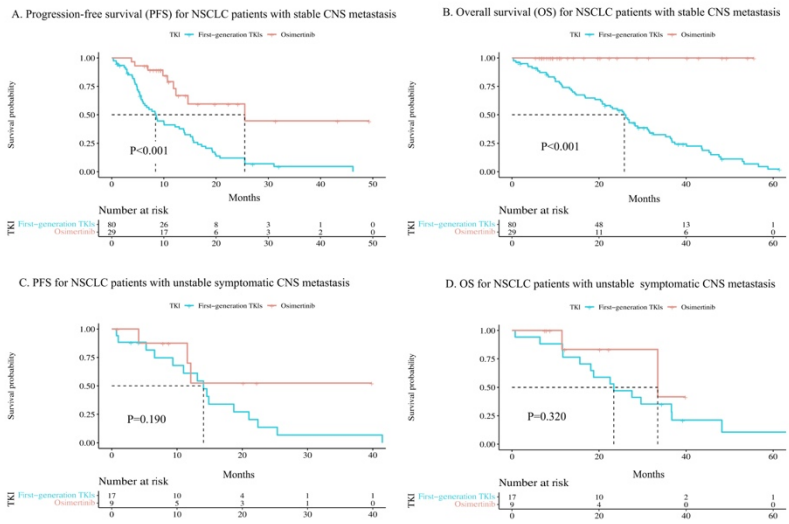

Figure S2 Progression-free survival curves and overall survival curves for NSCLC patients in subset stratified according to the status of baseline CNS metastases.
Changes in the text: Page6, line176-182; Page7-8, line220-238; Figure S1; Figure S2

Comment 4: This study provides real-world data from China, primarily focusing on the Asian population, which I believe is crucial for understanding Osimertinib. In relation to the FLAURA trial, several subset analyses have been reported. While Osimertinib demonstrated significant efficacy in non-Asian populations, it appeared to have a less pronounced effect in Asians. Therefore, I consider the contrasting results of this study, which utilized real-world data, to be important insights.
Reply 4: Thank you for your comment.
Changes in the text: No changes.

Reviewer D

Comment 1: This is a manuscript of retrospective analyses of patients of non-small cell lung cancer with EGFR mutation comparing first-generation and third-generation EGFR tyrosine kinase inhibitors. Their results consisted of real-world data support the efficacy and safety of the third-generation EGFR-TKI Osimertinib. The manuscript is well-written, and the results are well organized. The reviewer believes that the current study would give important information to readers in the area.
Reply 1: Thank you for your comment.
Changes in the text: No changes.

Comment 2: The period of first or third generation TKI might be different. The patients were registered between 2010 and 2022. The first generation TKIs might have delivered in first half of the period, and osimertinib must have delivered the second half. These

should be described in the manuscript (the distribution of patients in each era, for example 2010-2014, 2014-2018, and 2018-2022).

Reply 2: Thank you for your valuable suggestions. Following propensity score matching, the distribution of 202 patients in the osimertinib group across the years 2010-2013, 2014-2018, and 2019-2022 was 0 (n=0), 10.0% (n=20), and 90.1% (n=182), respectively. In the first-generation EGFR-TKI group, the distribution of 404 patients was 7.7% (n=31), 69.6% (n=281), and 22.8% (n=92), respectively. We have modified this article accordingly (see Page6, line182-186).

Changes in the text: Page6, line182-186, which was marked in yellow.

Comment 3: Detail of the family history of cancer should be determined. First-degree or more degrees, and how are this information collected? And what kind of evidence about family history to be included in propensity scores?

Reply 3: We would like to express our gratitude for the valuable recommendation provided. A family history of cancer was defined as a self-reported history of cancer in first-degree or second-degree relatives. First-degree relatives included parents, siblings, or children, while second-degree relatives included nieces, nephews, aunts, uncles, or grandparents. Variables that could influence the outcomes of treatment were used to generate a propensity score, including gender, age, ECOG, smoking history, pathology, EGFR mutations, and CNS metastases. Given that many studies have indicated a connection between a family history of malignancies and the prognosis of lung cancer patients, we also integrated "family history of tumor" into our propensity model. We have modified our text as advised and cited relevant references (see Page4, line117-120; Page5, line134-139; Reference 27-29).

Changes in the text: Page4, line117-120; Page5, line134-139; Reference 27-29.