Peer Review File

Article information: https://dx.doi.org/10.21037/tlcr-24-881

Reviewer A

Comment 1

This study is a retrospective multicenter study involving 15 centers across multiple countries, providing a relatively large real-world sample of patients with EGFR-mutant NSCLC. The analysis of various endpoints like PFSglob, PFS1, and OS, along with subgroup analyses, offers in-depth insights. The main findings are as follows: A total of 300 patients were enrolled, with 161 in the osimertinib group and 139 in the sequence group. The osimertinib group had a longer median PFS1 (19.0 months vs. 16.8 months, p = 0.03), while the sequence group had a better PFSglob initially (32.4 months vs 26.5 months, p = 0.04), but this difference was not significant in multivariate Cox analysis or after propensity score matching. Osimertinib upfront was associated with better PFSglob in poor-prognosis groups such as those with high-TB, CNS or liver involvement, and poor PS. Response rates (ORR and DCR) were comparable between the two groups. However, the retrospective design may introduce selection and recall biases since patients in the sequence group had to undergo two lines of treatment while those in the osimertinib group did not. Although a propensity score was used for correction, the potential for residual bias remains. Additionally, the lack of data on certain aspects like the long-term outcomes of combination therapies and detailed information on patient quality of life could limit the comprehensiveness of the study's conclusions.

Response: We thank the reviewer for these comments.

Changes in the text: All limitations raised by the reviewer are addressed in the discussion section (last paragraph).

Comment 2

In the title, I suggest to indicate the retrospective cohort study design.

Response: Thank you for this comment.

Changes in the text: We modified the title accordingly: "*UPFRONT OSIMERTINIB AND AS SEQUENTIAL THERAPY IN PATIENTS WITH EGFR-MUTANT NON-SMALL CELL LUNG CANCER (NSCLC): BENEFIT ACROSS PATIENTS GROUPS IN A REAL-WORLD RETROSPECTIVE COHORT- THE SMILE STUDY*".

Comment 3

In the abstract, the introduction did not describe the clinical needs for this comparative study of two cohorts, the methods did not describe the inclusion of subjects, follow up procedures, treatments, and efficacy and safety outcomes, and the conclusion did not have comments on the clinical implications of the findings.

Response: We thank the reviewer for this remark.

Changes in the text: We modified the abstract in order to clarify the point raised by the reviewer. We added the following sentences:

- Introduction :" *Intensification of L1 with chemotherapy or amivantamab has shown improved outcomes at the cost of increased toxicity, raising questions about the optimal patients selection*."
- Methods: "*Retrospective multicenter study including consecutive patients with mEGFR (ex19/ex21) aNSCLC treated with either osimertinib or the sequence of 1G followed by osimertinib ("sequence group"). Central nervous system metastases were permitted.*" And "*Secondary endpoints were overall survival, PFS of the L1 treatment, and tumor response according to each center daily practice (ORR and DCR)."*
- Conclusion:" *This study raises the question of patients selection and treatment tailoring for the first line management of metastatic mEGFR NSCLC."*

Comment 4

In the introduction of the main text, the authors need to explain the clinical needs for the real-world evidence for comparing osimertinib with the sequence of 1G followed by osimertinib, and have more detailed hypotheses on the efficacy and safety of both treatments. In the real-world clinical practice, patients have different indications for osimertinib alone or the sequence of 1G followed by osimertinib. The authors need to explain whether such comparisons are feasible and the generalizability of the comparative results because of the selection bias in PSM analysis.

Response: We thank the reviewer for asking to clarify this point.

Changes in the text: We already addressed this matter in the introduction section : line 16 to 23 and also line 24 to 31.

For more clarity, we added the following sentence: "*Exploring subgroups potentially benefiting of sequential anti-EGFR treatment is clinically interesting as it allows patients to stay on oral and well tolerated drugs as long as possible.*"

Comment 5

In the methodology, please describe the clinical research design of this study, follow

up procedures, assessment baseline clinical characteristics, and safety outcomes. In statistics, details of the handling of missing data are needed and ensure P<0.05 is two-sided.

Response: We thank the reviewer for these comments.

Changes in the text: The design of the study is already described in the Patients and Methods section, Study design and population sub-section.

We added the following informations in the Patients and Methods section:

- « *Patients' follow-up was conducted in according to each centers' daily practice until data collection*»
- "*Data were registered in an electronic Case Report Form (CRF) from each patients' medical record.*"

Regarding safety outcomes, we did not collected this information as the objective of this study was focused on the efficacy of both treatments strategies.

Finaly, missing data handling is already described in the manuscript with this sentence :" Regarding missing data, no imputation was made, and variables with more than 20% of missing data were discarded.".

p- values were two-sided, but we did not add it to the manuscript in order to limit the confusion for the reader as it is not a prospective trial. If the Editor wishes we can add this to the method section.

Comment 6

Please consider to cite several related papers: 1. Li J, Wang Y, Zhao Z, Wang S, Yan W, Chen X, Chen T, Li P, Wang S, Fang Q, Peng L, Han Y, Tang J, Leng X. Osimertinib as a neoadjuvant therapy in resectable EGFR-mutant non-small cell lung cancer: a real-world, multicenter retrospective study. Transl Lung Cancer Res 2024;13(12):3344-3351. doi: 10.21037/tlcr-24-541. 2. Luo FX, Arter ZL, Ou SI, Nagasaka M. FLAURA in the real world: osimertinib in potentially trial-eligible and ineligible patients with EGFR-mutated advanced non-small cell lung cancer. AME Clin Trials Rev 2024;2:101. 3. Wu F, Zeng Y, Neal JW. Consolidation osimertinib for unresectable stage III epidermal growth factor receptor (EGFR)-mutated non-small cell lung cancer: redefining standard care. Transl Lung Cancer Res 2024;13(10):2853-2855. doi: 10.21037/tlcr-24-540. 4. Weng CD, Liu KJ, Jin S, Su JW, Yao YH, Zhou CZ, Li YF, Chen ZX, Chen HJ, Li YY, Tang KJ, Yang JJ. Triple-targeted therapy of dabrafenib, trametinib, and osimertinib for the treatment of the acquired BRAF V600E mutation after progression on EGFR-tyrosine kinase

inhibitors in advanced EGFR-mutated non-small cell lung cancer patients. Transl Lung Cancer Res 2024;13(10):2538-2548. doi: 10.21037/tlcr-24-358.

Response: Thank you for these interesting studies.
Changes in the text: The most relevant one was added in our references and discussion :
14. Luo FX, Arter ZL, Ou SI, Nagasaka M. FLAURA in the real world: osimertinib in potentially trial-eligible and ineligible patients with EGFR-mutated advanced non-small cell lung cancer. AME Clin Trials Rev 2024;2:101. 3.

Reviewer B

1. Abstract: please introduce the abbreviations in their first use.
We explained the abbreviations in their first use.

2. For research involving human experiments, the article must include a statement that ethical approval was obtained (**or a statement that it was not required and why**), including the name of the ethics committee(s) or institutional review board(s), **the number/ID of the approval(s)**, and a statement that the participants gave informed consent before taking part (**or a statement that it was not required and why**).

Authors should also state that the study conformed to the provisions of the Declaration of Helsinki (as revised in 2013), available at: https://www.wma.net/wp-content/uploads/2016/11/DoH-Oct2013-JAMA.pdf

Describe this information in **both the "Method" section of Main Text and the "Ethical Statement" section of Footnote**.
- Suggested wording*: "The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional/regional/national ethics/committee/ethics board of ******* (**No.: the registration number of ethics board**) and informed consent was taken from all the patients."*
For Retrospective Human Studies, consent is not a must.
- Suggested wording*: "The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional/regional/national ethics/committee/ethics board of ******* (**NO.: the**

registration number of ethics board*) and individual consent for this retrospective analysis was waived.*

As advised we added the above statement in the manuscript.

3. Only one of the ethics committees has granted ethical approval for this multicenter study, while the others have not. Could you please explain the reason for this discrepancy?

The study was approved by a central ethic committee, as necessary for retrospective studies. Then each center validated the participation to the study in their own ethic committee as per the local rules.

We added the following sentence to the manuscript: "This study was approved by the internal ethics committee at Gustave Roussy (IRB number 2021-01) and in each center according to the local rules."

4. Figures & Tables

1) Supplementary figure 2 is a flowchart, not supplementary figure 1. Please verify the supplementary figure citation in the study population.

We modified the reference to the flowchart to the following: "Supplementary Flowchart".

2) Please cite supplementary figure 1 into the main body of the text.

We cited this supplementary Figure in the Patients and Methods section/Endpoints paragraph.

3) Table 1: please add a heading to the top left cell.

We added the precision in Table 1.

4) Table 1: the number may not sum to group total, for instance, 96+168+12≠300. Please check it.

We added the missing modality "Current smoker" to the Table and now the numbers are adding properly.

5) Table 2: a table is not allowed to divided as two parts according to journal's format requirement. If authors would like to split the table, it should be split into independent ones, naming the splitting tables with the word 'Table' and following an appropriate numbers (e.g., 'Table 2' and 'Table 3'). Alternatively, if authors insist on merging them into one table, please add general headings in the top cells.

Here is some format example for your reference:

1) https://tlcr.amegroups.org/article/view/94727/html tables 1 and 2

2) https://tlcr.amegroups.org/article/view/84554/html table 1

As advised we split the Table 2 into Table 2 and Table 3.

6) Table 2: are these values the same?

Sequence (n=139)
32.4 (29.4-38.4)
65.9% (58.4-74.3)
65.9% (58.4-74.3)

Thank you for having spotted this error. We corrected it with the right numbers.

7) Table 2: the p value is inconsistent with the main text, please check it.

PFS1				
- Median, months (95%CI)	18.0 (95%CI:16.0-20.4)	19.0 (16.1-26.5)	16.8 (14.1-19.8)	0.03
- 18 months rate (95%CI)	50.0% (44.4-56.3)	53.3% (45.5-62.4)	47.1% (39.4-56.3)	
ORR, %	83.7%	80.9%	87.0%	0.15
DCR, %	96.9%	95.5%	98.6%	0.18

16 Two hundred and five patients were evaluable for response. In this population, ORR was
17 83.7%, and DCR was 96.9% (**Table 2A**). No differences were observed in terms of ORR
18 between the osimertinib and the sequence groups (80.9% vs. 87.0%, respectively; *p*=0.16).
19 DCR was also comparable (95.5% in osimertinib group vs. 98.6% in sequence group,
20 *p*=0.18).

Thank you for this remark, we modified the p value in the text to be consistent with the table.

8) Please cite supplementary table 1 and supplementary table 3 consecutively in the main body of the text.

We cited the supplementary table 1 in the Patients' characteristics section, and the supplementary table 3 in the subgroups analysis section.

9) Please provide supplementary table 3 in an editable format; do not insert it as an image in a Word document.

We provided the table in an editable format in the Supplementary material file.

10) Any abbreviations used in figures and tables, as well as their captions, should be defined in a footnote beneath each corresponding table/figure. Even if they were explained in the main text, full terms must be defined again for clarity, so that figures and tables can be read on their own.

We defined the abbreviations used in figures and tables.

5. Author's name does not match with the mentioned name, please check it.

group. To address this bias, a propensity score was generated for correction. Despite the limitation, this study represents the largest real world study in a European population exploring the potential advantages of upfront Osimertinib or as sequential therapy in advanced m*EGFR* NSCLC. Our results corroborate the one from Okuma et al in an Asian population (18).

18. Castañón E, Rolfo C, Viñal D, López I, Fusco JP, Santisteban M, et al. Impact of epidermal growth factor receptor (EGFR) activating mutations and their targeted treatment in the prognosis of stage IV non-small cell lung cancer (NSCLC) patients harboring liver metastasis. J Transl Med. 2015 Aug 7;13:257.

Thank you for this comment. We corrected this inconsistency.

6. When reporting P values, authors should follow our guidelines as listed below. P values reported on main text should be consistent as those on tables and figures.

Reporting of P values:

- The description of the P value should be in the uppercase format, i.e., "P".
- If P value <0.001, report "P<0.001" to avoid reporting unnecessarily excessive precision (except hypothesis tests that include correlations or studies with exponentially small P values, such as genetic association studies, which can be reported exponentially, e.g., P=1×10-5).
- If 0.001≤ P value <0.01, report the specific P value to 3 decimal places, e.g., "P=0.001" or "P=0.009".
- **If P value≥0.01, report the specific P value to 2 decimal places, e.g., "P=0.01" "P=0.06" "P=0.10" "P=0.90". When the P value is near 0.05, report the specific P value to 3 decimal places, e.g., "P=0.046" or "P=0.052".**
- If the P value is >0.99, report "P>0.99".
- Do not report "not significant" simply because the data is greater than an arbitrary value, and do not report only vague bounds such as P<0.05, as described above, but report the exact P value.

We modified the p-values accordingly.