PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

Title (Provisional)

Aumolertinib in combination with Lastet in the first-line treatment of EGFR-mutated locally advanced or metastatic non-small cell lung cancer (EVOLUTION): protocol for a single-arm phase II clinical trial

Authors

Chen, Jianing; Wang, Li; Liu, Li; Zhao, Jing; Wu, Yan; Yu, Xin; Su, Chunxia

VERSION 1 - REVIEW

Reviewer	**1**
Name	**Frost, Nikolaj**
Affiliation	**Charite Universitatsmedizin Berlin**
Date	**10-Jan-2025**
COI	**None**

In the dynamic field of first-line treatment options for patients with common EGFR mutations, the addition of an oral chemotherapeutic agent appears to be a logical and promising approach. Chen and colleagues present the protocol for a prospective, multi-center, single-arm trial evaluating the combination of aumolertinib with oral etoposide. The protocol provides a thorough description of the inclusion and exclusion criteria, statistical methodology, and follow-up procedures.

I have the following minor comments for consideration:

Exclusion Criterion No. 9 (Brain Metastases): This criterion requires clarification. Which patients with brain metastases are eligible for inclusion in the trial, and which are not? Please provide a more detailed description of eligibility criteria for patients with brain metastases.

Statistics: Further elaboration on the assumed hazard ratio (HR) of 0.7 for progression-free survival (PFS) is needed. While the FLAURA2 study is mentioned, it is unclear how this assumption was derived or justified. Please provide additional context or rationale supporting the estimated HR.

Reviewer	**2**
Name	**Chouaïd, Christos**
Affiliation	**Centre Hospitalier Intercommunal de Creteil**
Date	**16-Mar-2025**
COI	**None**

Thanks for the opportunity to evaluate this protocol.

No major comments, but I suggested in the discussion section to add a smal paragraph on the choice of the primary endpoint, particularly why the median PFS was used and not the 12-month PFS, which would have provided faster results.

Furthermore, did the authors plan an indirect comparison or a comparison with a synthetic arm?

VERSION 1 - AUTHOR RESPONSE

Reviewer: 1
Dr. Nikolaj Frost, Charite Universitatsmedizin Berlin
Comments to the Author:
In the dynamic field of first-line treatment options for patients with common EGFR mutations, the addition of an oral chemotherapeutic agent appears to be a logical and promising approach. Chen and colleagues present the protocol for a prospective, multi-center, single-arm trial evaluating the combination of aumolertinib with oral etoposide. The protocol provides a thorough description of the inclusion and exclusion criteria, statistical methodology, and follow-up procedures.

I have the following minor comments for consideration:
Exclusion Criterion No. 9 (Brain Metastases): This criterion requires clarification. Which patients with brain metastases are eligible for inclusion in the trial, and which are not? Please provide a more detailed description of eligibility criteria for patients with brain metastases.
Response: Thank you for your comment. We have clarified Exclusion Criterion No. 9 as follows:
1.Karnofsky Performance Status (KPS) Score < 60, indicating poor functional status.
2.Severe Neurological Symptoms, including severe headache, vomiting, neck stiffness, seizures, sensory or motor deficits, or visual disturbances, which may impact patient safety and the accurate assessment of trial endpoints.

Statistics: Further elaboration on the assumed hazard ratio (HR) of 0.7 for progression-free survival (PFS) is needed. While the FLAURA2 study is mentioned, it is unclear how this assumption was derived or justified. Please provide additional context or rationale supporting the estimated HR.
Response: Thank you for your comment. The FLAURA2 study, which investigated the combination of Osimertinib with chemotherapy (including platinum-based doublet chemotherapy), demonstrated a hazard ratio (HR) of 0.62 for PFS, favoring the Osimertinib-chemotherapy combination. This provided strong evidence for the potential benefit of combining the third generation EGFR-TKI therapy with chemotherapy, leading to a better progression-free survival compared to osimertinib alone.
In contrast to the FLAURA2 design, our study is an open-label, single-arm study investigating the combination of Aumolertinib with etoposide. Based on the existing literature, we estimate the HR to be 0.7 for our combination therapy. The key points supporting this assumption include:
Etoposide in Combination: A recently published study (PMID: 38451729, DOI: 10.1172/JCI172716) highlighted that early combination therapy with VP16 can delay or prevent the development of

acquired resistance to third-generation EGFR-TKIs. This finding is critical, as VP16 may offer a mechanistic advantage in combination with EGFR-TKI therapy by reducing the likelihood of resistance.
Mechanism of Resistance in Third-Generation EGFR-TKIs: One of the primary mechanisms of acquired resistance to third-generation EGFR-TKIs is the transformation of non-small cell lung cancer (NSCLC) into small cell lung cancer (SCLC) (PMID:39353908). Since etoposide is a well-established treatment for SCLC, the combination strategy aims to prevent or mitigate this transformation, which we hypothesize will contribute to a better PFS and a more favorable HR.

Reviewer: 2
Prof. Christos Chouaïd, Centre Hospitalier Intercommunal de Creteil
Comments to the Author:
Thanks for the opportunity to evaluate this protocol.
No major comments, but I suggested in the discussion section to add a small paragraph on the choice of the primary endpoint, particularly why the median PFS was used and not the 12-month PFS, which would have provided faster results.
Response: Thank you for your insightful question. We chose median PFS as the primary endpoint because it is a standard, robust measure in EGFR-TKI trials, minimizes bias from censoring, and allows direct comparison with historical data like AENEAS. While 12-month PFS could provide earlier insights, it may be less stable.

Furthermore, did the authors plan an indirect comparison or a comparison with a synthetic arm?
Response: Thank you for your valuable suggestion. To address the limitation of a single-arm study, we plan to use a synthetic control arm based on historical data from real-world studies. We will match baseline characteristics using methods like propensity score matching and compare key outcomes such as PFS and OS to contextualize our results. This approach will help strengthen our study's findings.