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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

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ABSTRACT

Introduction Targeted therapy is now the standard treatment for patients with epidermal growth factor receptor (EGFR) mutations, yet resistance continues to be a significant challenge. Enhancing the efficacy of targeted therapies and prolonging patient survival remain critical clinical priorities. Although combining third-generation EGFR tyrosine kinase inhibitors (TKIs) with intravenous chemotherapy has demonstrated promising results, it is unclear if oral chemotherapy regimens combined with EGFR TKIs could also improve survival outcomes.

Methods and analysis EVOLUTION is a multicentre, phase II clinical trial conducted across three tertiary hospitals in China: Shanghai Pulmonary Hospital (lead centre), Zhongshan Hospital Affiliated to Fudan University and Shanghai Fifth People's Hospital Affiliated to Fudan University. The study will enrol 60 patients with locally advanced or metastatic lung cancer harbouring EGFR-sensitive mutations who have not previously undergone systemic therapy. Participants will be administered a combination regimen of aumolertinib (110 mg orally, once a day in a 28-day cycle, continuously) and Lastet (25 mg orally, administered in a 28-day cycle, with 2 weeks on followed by 2 weeks off). The primary endpoint is progression-free survival, and the secondary endpoints are overall survival, objective response rate, disease control rate and duration of response. Tumour response will be assessed by the investigators according to the Response Evaluation Criteria in Solid Tumors 1.1. Patient enrolment is currently underway.

Ethics and dissemination Ethical approval for this study was granted by the Ethics Committee of Shanghai Pulmonary Hospital in April 2024 (approval number: L23-334). Patients will participate after providing informed consent. The results of the study will be disseminated through peer-reviewed journals and presentations at academic conferences.

Trial registration number NCT06463171.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is a prospective, multicentre study designed to test the efficacy of combining aumolertinib and oral chemotherapy.
⇒ The primary endpoint is progression-free survival, with a long follow-up period and regular assessments to ensure comprehensive monitoring.
⇒ The sample size is limited to 60 patients, and the need to recruit a larger cohort in future studies may prolong study duration and delay clinical translation.
⇒ The single-arm study design lacks a control group, potentially introducing selection and observation biases.

INTRODUCTION

The rapid advancement of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) has markedly improved the survival of patients with non-small cell lung cancer (NSCLC). Aumolertinib, a third-generation EGFR TKI, is now a widely recommended first-line therapy for patients with advanced NSCLC that exhibit EGFR-sensitive mutations.[1] However, the issue of drug resistance persists, with its mechanisms still largely unexplored. Addressing the urgent need to prolong survival and enhance life quality for patients with EGFR-mutant NSCLC is a significant clinical challenge. The FLAURA2 study showed that combining osimertinib with intravenous chemotherapy could lengthen the median progression-free survival (PFS) compared with monotherapy.

Exploring whether the combination of third-generation EGFR TKIs with other chemotherapy agents could further improve survival outcomes is also crucial. Etoposide (VP-16), used in conjunction with platinum-based agents, is a recognised treatment for both small cell and non-small cell lung cancer.[2] Recent research suggests that etoposide may help delay the development of resistance to osimertinib by inducing DNA

Figure 1. Study design

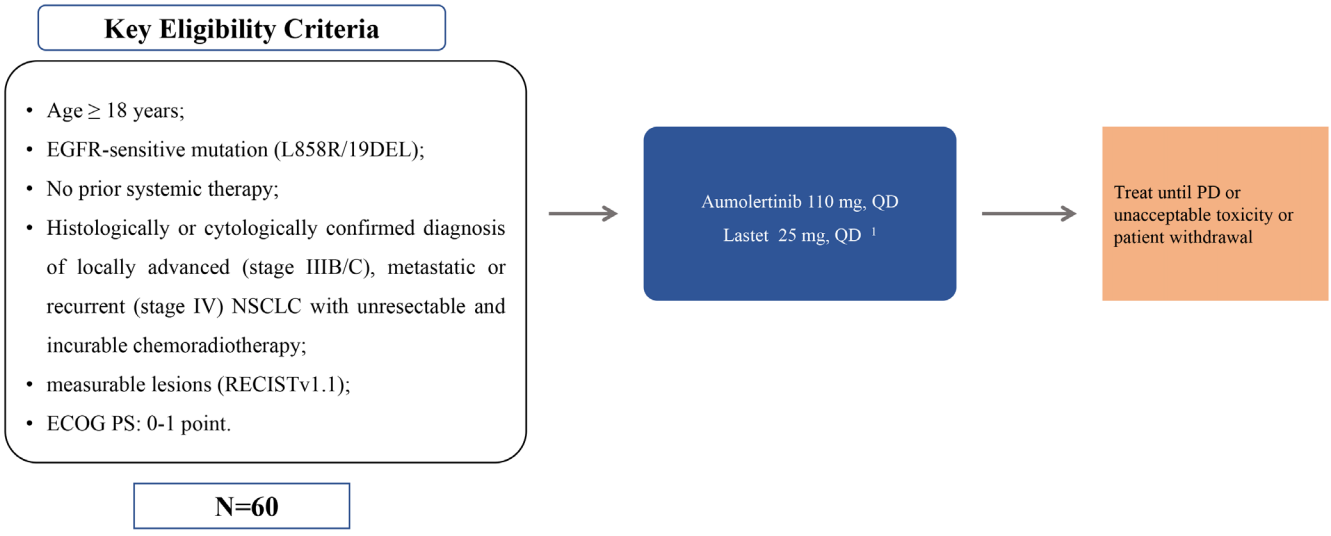

Figure 1 Study design. [1]Lastet at a daily dose of 25 mg is taken continuously for 2 weeks followed by a 2-week break. EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; PD, progressive disease; ECOG,Eastern Cooperative Oncology Group; PS,Performance Status; QD, once per day; RECIST, Response Evaluation Criteria in Solid Tumors.

damage and apoptosis in resistant cells.[3] Lastet, an orally administered capsule form of etoposide, allows for outpatient treatment, which is more convenient than intravenous methods.

Given the encouraging findings from preclinical cell experiments and patient-derived xenograft (PDX) models, the synergy between third-generation EGFR TKIs and VP-16 appears promising for enhanced tumour suppression. Consequently, we have launched a phase II clinical study (NCT06463171) to assess the effectiveness of combining aumolertinib with Lastet as a first-line treatment for EGFR-mutated, locally advanced or metastatic NSCLC. This study aims to further explore the therapeutic advantages of integrating targeted therapy with oral VP-16 in patients with advanced EGFR-mutant NSCLC.

METHODS AND ANALYSIS

Study design

This multicentre, single-arm clinical study, initiated by Shanghai Pulmonary Hospital and led by Professor Chunxia Su, aims to evaluate the efficacy and safety of aumolertinib combined with Lastet in patients with locally advanced or metastatic NSCLC harbouring EGFR-sensitive mutations. Participants will receive a combination regimen of aumolertinib (110 mg daily) and Lastet (25 mg orally daily) (figure 1). Treatment will continue until disease progression, intolerable toxicity, initiation of a new antitumour therapy, withdrawal of informed consent, loss to follow-up, death or other conditions deemed by the investigator as reasons to discontinue treatment, whichever occurs first, with a maximum treatment duration of 24 months. The primary endpoint is the median PFS as assessed by the investigator based on the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. The secondary study endpoints are objective response rate (ORR), disease control rate (DCR), duration of response (DOR) and overall survival (OS). All adverse events (AEs) and unintended effects will be systematically collected, assessed and reported following regulatory requirements. AEs will be documented through regular patient assessments and spontaneous reporting. The severity and causality of AEs will be evaluated by the study investigators, and serious adverse events (SAEs) will be reported to the appropriate regulatory authorities and ethics committees. Appropriate management strategies will be implemented to ensure participant safety. Additionally, the hospital has purchased commercial insurance to cover compensation for participants in the event of adverse reactions.

Research data will be stored in an Electronic Data capure (EDC) system, with access limited to authorised personnel only, ensuring data security and confidentiality. Data will be de-identified, and any shared information will be anonymised to protect participant confidentiality before, during and after the trial, in accordance

with ethical and regulatory guidelines. Audits will be conducted every 6 months by an independent third-party auditing agency to ensure compliance with the study protocol, data integrity, participant safety and adherence to Good Clinical Practice guidelines.

Statistical methods

Efficacy will be assessed according to RECIST 1.1. The evaluation will include PFS, ORR, DOR, DCR and OS. Safety assessments will include the incidence, severity and relationship of all AEs, treatment-related adverse events (TRAEs) and SAEs. The number of participants who discontinue the study due to AEs will be recorded. Additionally, changes in vital signs, physical examination findings and laboratory test results will be monitored before, during and after treatment. For efficacy analysis, the median PFS and OS, along with their 95% CIs, will be estimated using the Kaplan-Meier method, and survival curves will be generated. ORR and DCR will be calculated based on tumour response assessments at each treatment cycle, including their corresponding 95% CIs. For DOR, the Kaplan-Meier method will be used to determine the median duration and generate a survival curve. For safety analysis, treatment exposure, the number of completed treatment cycles, dose modifications and the cumulative number of dose adjustments will be summarised.

Inclusion criteria

Patients eligible for enrolment in the study must meet all the following criteria:

1. Written informed consent obtained prior to the implementation of any trial-related procedures.
2. Age ≥18 years.
3. Patients with locally advanced (stage IIIB/IIIC), metastatic or recurrent (stage IV) NSCLC, confirmed histologically or cytologically, who are ineligible for surgical intervention and cannot undergo curative radiochemotherapy, as per the ninth edition of the tumor node metastasis (TNM) staging classification of the International Association for the Study of Lung Cancer and the American Joint Committee on Cancer.
4. Provision of archived tumour tissue or tissue obtained from a biopsy at screening for biomarker testing, including EGFR mutation status.
5. Presence of an EGFR-sensitive mutation (19DEL/L858R).
6. At least one measurable lesion confirmed by the investigator according to RECIST 1.1 criteria.
7. Patients who have previously received platinum-containing adjuvant chemotherapy/radiotherapy, neoadjuvant chemotherapy/radiotherapy or radical radiochemotherapy for advanced disease, with disease progression occurring >6 months after the last treatment, are eligible.
8. Expected life expectancy of ≥3 months.
9. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0–1.
10. Adequate haematological function, defined as an absolute neutrophil count $\geq 1.5\times10^9$/L, platelet count $\geq 100\times10^9$/L and haemoglobin ≥90 g/L (without blood transfusion in the past 7 days).
11. Adequate liver function, defined as total bilirubin level ≤1.5 times the upper limit of normal (ULN) and aspartate aminotransferase and alanine aminotransferase levels ≤2.5 times the ULN or ≤5 times the ULN in patients with liver metastasis.
12. Adequate renal function, defined as serum creatinine ≤1.5 times the ULN or creatinine clearance ≥50 mL/min (calculated according to the Cockcroft-Gault formula).
13. Adequate coagulation function, defined as an international normalised ratio (INR) or prothrombin time (PT) ≤1.5 times the ULN; if on anticoagulant therapy, INR/PT should be within the therapeutic range.
14. Women of childbearing potential must have a negative pregnancy test within 7 days prior to the start of treatment and use reliable contraception methods (such as intrauterine devices, oral contraceptives or condoms) during the trial and for 30 days afterwards. Men of childbearing potential should use condoms during the trial and for 30 days after its completion.
15. Willingness to comply with regular follow-up visits and adhere to trial requirements.

Exclusion criteria

1. Currently participating in another interventional clinical study.
2. Underwent surgical treatment (major surgery related to cancer), chemotherapy, molecular targeted therapy, immunotherapy, cell therapy or radiotherapy within 4 weeks prior to the first dose (except for palliative radiotherapy, which must be within 2 weeks before the first dose); received endocrine therapy within 2 weeks before the first dose; and underwent traditional Chinese medicine treatment after signing informed consent.
3. Previously received anti-EGFR therapy.
4. Used traditional Chinese medicine with antitumour indications or immunomodulatory drugs (eg, thymosin, interferon and interleukin) within 2 weeks before the first dose.
5. History of allergic reactions to any components of the study drugs.
6. Active haemoptysis (more than half a teaspoon per episode), active diverticulitis, abdominal abscess, gastrointestinal obstruction or peritoneal metastasis.
7. Tumour compression of the surrounding vital organs (such as the oesophagus) with related symptoms, compression of the superior vena cava or invasion of major mediastinal vessels or the heart.
8. Presence of clinically uncontrollable pleural effusion/peritoneal effusion/pericardial effusion; patients who do not need to drain the effusion or stop

draining for 3 days without a significant increase in effusion can be enrolled.
9. Known brain metastases; patients with asymptomatic, mildly symptomatic or stable brain metastases as judged by the investigator can be enrolled.
10. Known mental illness or substance abuse that may affect compliance with trial requirements.
11. Recently treated with a full dose of oral or non-oral anticoagulants or thrombolytics; prophylactic use of anticoagulants is permitted.
12. Medical history, disease, treatment or laboratory abnormality that may interfere with the trial results or prevent the subject from participating fully in the study, or if the investigator considers participation not to be in the best interest of the subject.

Endpoints

The primary endpoint is PFS, defined as the period from the start of treatment until disease progression or death from any cause, whichever occurs first, assessed up to 24 months.

The following are the secondary endpoints:

1. ORR: defined as the proportion of patients in the study or treatment group who achieve an objective response, either a complete response or a partial response.
2. DCR: described as the proportion of patients who have achieved a response to treatment, encompassing not only complete and partial responses but also stable disease.
3. DOR: a clinical measure used to determine the length of time during which a tumour continues to respond to treatment without the cancer worsening.
4. OS: measured from the date of initiation of treatment to the date of death from any cause, assessed up to 24 months.

Treatment and follow-up

Participants in this study will receive a combination of aumolertinib and Lastet. Aumolertinib will be administered orally at a dose of 110 mg once a day in a continuous 28-day cycle. Lastet will be administered orally at a dose of 25 mg daily in a 28-day cycle, consisting of 2 weeks of continuous administration followed by a 2-week break.

The clinical research coordinator (CRC) is responsible for coordinating participant follow-up and collecting clinical outcome data. The CRC will conduct a safety follow-up 30 days after the last dose and survival follow-up every 90 days.

Treatment will continue until disease progression, intolerable toxicity, initiation of new antitumour therapy, withdrawal of informed consent, loss to follow-up, death or other conditions determined by the investigator to necessitate discontinuation of treatment, whichever occurs first. The maximum duration of treatment is 24 months. Tumour responses (complete or partial) must be confirmed at least 4 weeks after the initial response or at the next scheduled evaluation time point. Tumour imaging assessments will be conducted every 6 weeks (±7 days) from enrolment, every 9 weeks (±7 days) after 24 weeks and every 12 weeks (±7 days) after 48 weeks.

Sample size calculation

Based on historical data, aumolertinib monotherapy has shown a median PFS of 19.3 months. Given etoposide's established efficacy in treating small cell lung cancer (SCLC), its combination with aumolertinib is designed to prevent or mitigate this transformation, which we hypothesise may lead to prolonged PFS and a more favourable HR. Therefore, we estimate an HR of approximately 0.7 for this combination therapy. The enrolment period is set for 12 months, with a follow-up duration of 36 months. To achieve a statistical power of 80.1% at a significance level of 0.2, a total of 54 patients is required. Considering a projected dropout rate of 10%, the final sample size is adjusted to 60 patients.

Recruitment will primarily occur through the oncology clinic at Shanghai Pulmonary Hospital. We will also collaborate with other cancer centres and patient advocacy groups to expand the pool of eligible participants. Methods to raise awareness and attract participants will include advertising through hospital websites, social media platforms and cancer-related forums.

Study status

Patient enrolment commenced on 12 June 2024, and the first patient was enrolled on 1 July 2024. We expect to complete patient enrolment by December 2025. Data analysis is scheduled to begin in March 2026, and we plan to complete the study by June 2026.

Patient and public involvement

None.

ETHICS AND DISSEMINATION

This study received approval from the Ethics Committee of Shanghai Pulmonary Hospital in April 2024 (approval number: L23-334). The protocol has undergone two revisions, with the latest version being the third edition (approval number: L24-334-2). Patients will be enrolled following the provision of informed consent (online supplemental file 1). The results will be presented at academic conferences and published in peer-reviewed journals.

Protocol revisions

First revision

The indication for aumolertinib is as a first-line treatment for adult patients with locally advanced or metastatic NSCLC who are positive for EGFR exon 19 deletions or exon 21 (L858R) substitution mutations. Consequently, we limited the inclusion criteria to patients with lung cancer carrying EGFR-sensitive mutations (19DEL/L858R). This change was reflected in the revised inclusion criteria. Ethical approval for this modification was reviewed and approved by the ethics committee (approval number: L24-334-1).

Second revision

The second revision was made to further clarify the inclusion and exclusion criteria. The changes include the following:

1. Addition of renal function and creatinine clearance criteria (inclusion criteria).
2. Definition of treatments not allowed within specific time frames before enrolment (exclusion criteria).
3. Clarification of requirements regarding haemoptysis and pleural/peritoneal/pericardial effusion (exclusion criteria).
4. Inclusion of patients with mild symptoms of brain metastases to broaden the potential beneficiary population (exclusion criteria).
5. Removal of exclusion criteria for active systemic infections, including tuberculosis, hepatitis B, hepatitis C and HIV.

Ethical approval for this revision was also reviewed and approved by the ethics committee (approval number: L24-334-2).

DISCUSSION

As the efficacy of targeted therapy approaches a plateau, an increasing number of studies are exploring combination strategies to overcome drug resistance. The integration of targeted therapy with antiangiogenic agents has shown promising efficacy. The NEJ026,[4] ARTEMIS[5] and BEVERLY[6] studies have demonstrated that combining erlotinib with bevacizumab significantly improves median PFS.

The NEJ009 study was the first to demonstrate that combining gefitinib with chemotherapy could extend the PFS by 9 months[7]; however, it did not improve the OS.[8] Additionally, the incidence of grade ≥3 TRAEs was significantly higher in the combination group compared with the single-agent group (65.3% vs 31.0%).

The FLAURA2 study, the first to evaluate a third-generation EGFR TKI in combination with chemotherapy, reported a median PFS of 25.5 months with osimertinib plus chemotherapy, compared with 16.7 months with osimertinib monotherapy.[9] Based on the FLAURA2 study design, we selected PFS as the primary endpoint because it is a standard and robust measure in EGFR TKI trials, reduces bias from censoring and facilitates direct comparison with historical data such as AENEAS. While 12-month PFS could offer earlier insights, it may be less reliable, which is why PFS was chosen as the primary endpoint in our study.

Although the OS data from the FLAURA2 study remain immature, a trend towards improved survival has been observed (HR 0.75, 95% CI 0.57 to 0.97).[10] However, the incidence of grade ≥3 AEs was substantially higher in the combination therapy group (64% vs 27%), highlighting the increased toxicity associated with this approach. Additionally, the requirement for regular hospitalisation for intravenous chemotherapy may limit its widespread adoption.

VP-16, a DNA topoisomerase II (Topo II) inhibitor, induces apoptosis by stabilising the Topo II–DNA complex, thereby preventing DNA replication and transcription. This interaction leads to DNA single-strand and double-strand breaks, ultimately triggering apoptosis.[11 12] Recent studies have shown that VP-16 synergistically enhances DNA damage and promotes apoptosis, effectively reducing the viability of osimertinib-resistant cell lines. Moreover, combination therapy with VP-16 significantly delayed the onset of resistance in PDX models, highlighting its potential in overcoming acquired resistance to osimertinib.[3]

Although combination therapy is associated with a higher incidence of adverse effects in clinical settings, preclinical studies have found no statistically significant differences in body weight between mice receiving combination treatment and those treated with a single agent. Histological examination of major organs, including the heart, liver, lungs, kidneys and spleen, showed no significant pathological changes between the two groups. Additionally, serum protein levels and enzyme activity remained comparable across all test groups. These findings suggest that the combination therapy exhibits a favourable safety profile in immunocompetent mice. In addition, etoposide is primarily used in the treatment of SCLC, and SCLC transformation is one of the mechanisms of resistance to third-generation EGFR TKIs, although such transformation occurs in less than 10% of cases.[13]

Despite the strengths of this study, it is important to acknowledge its limitations. The single-arm study design lacks a control group, which may introduce selection and observation biases, potentially limiting the reliability of efficacy and safety assessments. To address this limitation, we acknowledge the potential value of comparing our findings with real-world data. While we do not incorporate a synthetic control arm within our study design, future analyses could leverage historical data from real-world studies to contextualise our results. Such comparisons, using methods like propensity score matching, may help assess the robustness of our findings. However, this approach would be exploratory and subject to inherent limitations, such as data heterogeneity and potential confounding factors. Further studies incorporating predefined methodologies and ethical approvals would be required to formally integrate a synthetic control arm into clinical research. Additionally, the sample size of our study is limited to 60 patients; the need to recruit a larger cohort in future studies may prolong study duration and delay clinical translation.

Contributors CS: conception and design, administrative support. JC, LL, JZ, YW, XY: provision of study materials or patients. LL, JZ, YW, XY: collection and assembly of data. JC, LW: data analysis and interpretation. All authors: manuscript writing. CS: guarantor. All authors: final approval of the manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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