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Lazertinib and amivantamab in the treatment of lung cancer with EGFR mutation

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ABSTRACT

Worldwide, the leading cause of mortality is lung cancer. There are two most common types of this cancer: non-small cell lung cancer (NSCLC), which is in first place in prevalence, and small cell lung cancer (SCLC). Lack of health screening and nonspecific symptoms are the leading causes of diagnosis in advanced or metastatic states. Late detection and resistance to therapy are the reasons why the prognosis remains poor. Lifestyle, environmental factors, and genetic mutations contribute to the development of lung cancer. The most common proto-oncogene in non-small cell lung cancer is EGFR. Upon mutation, it becomes an oncogene, which is a potential therapeutic target. This study aims to review the innovative guidelines for locally advanced or metastatic NSCLC with EGFR mutations. One of the well-known third-generation EGFR tyrosine kinase inhibitors (TKIs) is Osimertinib. Unfortunately, it quickly developed resistance. There is a significant need to overcome resistance by combining lazertinib with amivantamab in both first- and second-line treatments. These drugs work through a different mechanism, allowing them to attack cancer cells from multiple angles. Studies like Mariposa, Mariposa-2, Papillon, Chrysalis, and Chrysalis-2 show new therapeutic options for patients with Locally Advanced or Metastatic NSCLC with EGFR Mutation (Ex20ins, ex19del, p.L858R). Furthermore, some studies show that reducing amivantamab's side effects and improving patient comfort can be achieved. There are two opinions: one is additional dexamethasone premedication, and the second is switching its administration from intravenous to subcutaneous.

Keywords: lazertinib, amivantamab, lung cancer

1. INTRODUCTION

Annually, approximately 1.8 million people die from lung cancer. It makes this the leading cause of mortality among all cancers. The risk factors for developing this malignancy include smoking, e-cigarettes, passive smoking, environmental factors

such as air pollution, genetic predisposition, and lifestyle factors, including alcohol consumption (Chen et al., 2014; Soo et al., 2017; Li et al., 2022; Bade and Dela Cruz, 2020). The two most common types of lung cancer are non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), which occur with frequencies of approximately 85% and 15%, respectively.

Histopathologically, types of NSCLC are adenocarcinoma and squamous cell carcinoma, which occur with similar frequencies, as well as the less common large cell carcinoma.

Less than 16% of patients with NSCLC survive five years, which makes a very weak prognosis. The reason is the late detection of the disease and resistance to treatment. Therefore, there is a need for additional research into diagnosis and treatment. The enormous scale of the problem makes it crucial for both individual patients and the worldwide healthcare system (Chen et al., 2014; Soo et al., 2017; Li et al., 2022; Guo et al., 2022; Nooreldeen and Bach, 2021).

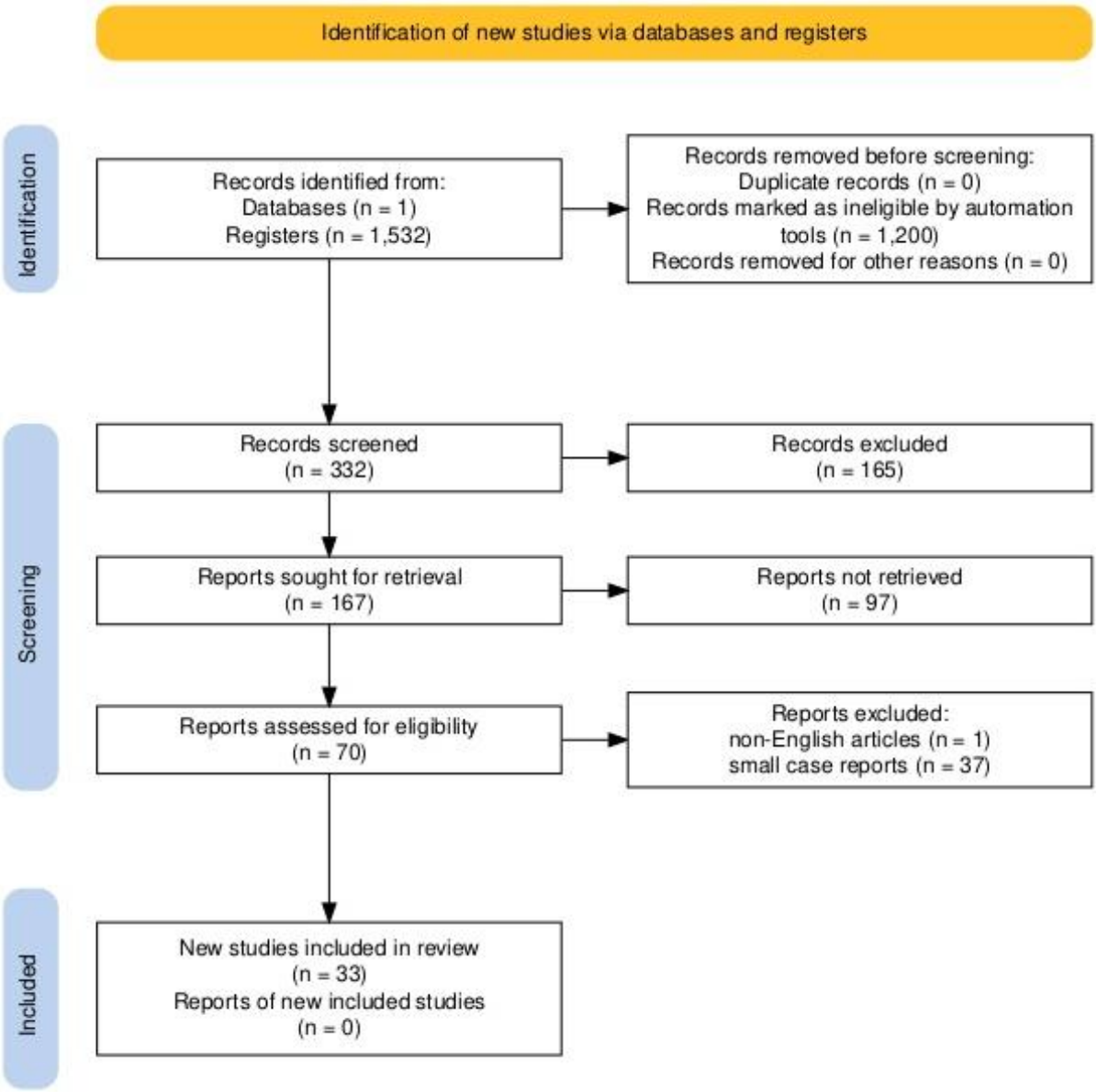

Fig 1. PRISMA flow diagram

2. REVIEW METHODS

We analysed materials from the PubMed database. The keywords that we were looking for were: "Lazertinib", "amivantamab", "non-small cell lung cancer", "EGFR mutation", and "Premedication". The process of selecting articles is shown in Figure 1. The review

analyzes articles published between January 2014 and May 2025. During the analysis of the articles, we used inclusion and exclusion criteria to select the most relevant for our review.

Inclusion criteria: randomized, double-masked studies published in the last decade, and high quality studies written in English.

Exclusion criteria: small case reports, non-English articles.

3. RESULTS AND DISCUSSION

Mutations

New techniques, such as next-generation sequencing (NGS), enable the identification of mutations in non-small cell lung cancer cells. Many of these mutations represent potential therapeutic targets, which is why they are significant. The most common mutations occur in the genes EGFR, ALK, ROS1, KRAS, HER2, BRAF, MET, and NTRK1. Therapeutic targets, in addition to genetic mutations, also include metabolic and resistance-related targets.

Mutations in the EGFR gene occur in approximately 10% of NSCLC patients, depending on the population. It is detected almost threefold more often among Asians than Europeans. Non-smokers and women are also more exposed to this mutation. Deletions in exon 19 and the L858R substitution mutation in exon 21 are the most common mutations, which account for up to 85% of mutations within the EGFR gene. Next in terms of frequency is the exon 20 insertion mutation (Ex20ins), which accounts for 4-10% of mutations within the EGFR gene. Other examples include G719X, S768I, and L861Q.

Increased expression or secondary mutations within the EGFR gene itself are the primary causes of most acquired resistance to TKI inhibitors (first- and second-generation), which contribute to drug resistance and pose a significant clinical challenge. The most typical additional mutation, which accounts for approximately half of these, is the T790M. Other known additional mutations include, for example, G724S, L718X, and C797S (Chen et al., 2014; Soo et al., 2017; Guo et al., 2022; Yang et al., 2022; Burnett et al., 2021).

Treatment

Surgical treatment, involving resection of the affected lobe or entire lung, along with lymph nodes, is the primary treatment for NSCLC in stages I-IIIA. Additionally, patients with tumors in stages II and IIIA receive adjuvant chemotherapy with cisplatin. Chemotherapy is also a standard of care for patients with locally advanced or metastatic NSCLC who are not candidates for targeted therapy or immunotherapy (Niu et al., 2024; Liu et al., 2025; Bertolaccini et al., 2024). In this study, we will discuss the latest scientific findings regarding the modern treatment of locally advanced or metastatic NSCLC with EGFR mutations.

Osimertinib is a third-generation EGFR tyrosine kinase inhibitor (TKI). Patients with NSCLC who have EGFR mutations receive it as a first-line treatment. In 2017, a randomized, double-masked phase III trial (Flaura) was conducted in China. According to the study, osimertinib demonstrated superior efficacy in treating advanced NSCLC with EGFR mutations compared to earlier generations of EGFR TKIs. Osimertinib improved both survival and safety. However, despite being designed to overcome resistance, osimertinib also becomes ineffective over time (Guo et al., 2022; Cheng et al., 2021; Jonna and Subramaniam, 2019; Soria et al., 2018; Arter and Nagasaka, 2024; Garassino et al., 2025; Hasan and Nagasaka, 2025; Patil et al., 2024).

The emergence of resistance led to investigations into combining lazertinib with amivantamab. Lazertinib is a third-generation TKI active against EGFR mutations, including common resistance mutations such as T790M. What is essential is that lazertinib penetrates the blood-brain barrier. It is crucial because patients with NSCLC often have metastasis in the central nervous system (Brazel and Nagasaka, 2024; Oh et al., 2025; Xu et al., 2024; Kadyrbayeva et al., 2024).

Amivantamab is a bispecific antibody and an IgG1 immunoglobulin. It was created by combining parts of the antigen-binding (Fab) arms of MET and EGFR antibodies. Amivantamab's action is multifaceted. One mechanism of action is the blockade of EGFR and MET ligands. It binds to the extracellular domains of both proteins. In that treatment works independently of intracellular mutations, such as those acquired from previous treatments. In this way, it inhibits receptor phosphorylation and downstream signaling, ultimately leading to the apoptosis of the cancer cell (Cho et al., 2023).

Blocking both ligands is significant because both pathways are interconnected. Inhibiting only one could lead to compensation through the other tracks, which is a bidirectional correlation. This is why amivantamab acts on both pathways. Interestingly, its effect is even stronger than if two separate drugs, each blocking one of these ligands, were used simultaneously. Another mechanism of action, occurring after amivantamab binds to ligands on the surface of the cancer cell, is receptor degradation. The antibody-receptor complex is endocytosed and degraded by the cancer cell's lysosomes. Furthermore, amivantamab directs the immune system. It can activate NK cells, macrophages, and monocytes.

The combination of amivantamab and lazertinib attackes the cancer cell from both the outside and the inside, which is why this combination is so effective. Notable studies include Mariposa, Mariposa-2, Papillon, Chrysalis, and Chrysalis-2. Studies such as Papillon, Chrysalis, and Chrysalis-2 provide information on the efficacy of amivantamab in treating NSCLC with EGFR Ex20ins mutations (table 1).

In contrast, the Mariposa and Mariposa-2 studies demonstrate the benefits of using amivantamab in treating NSCLC with EGFR ex19del or p.L858R mutations. The Papillon and Mariposa studies describe first-line treatment, while the Chrysalis, Chrysalis-2, and Mariposa-2 studies address second-line treatment (Hasan and Nagasaka, 2025; Brazel and Nagasaka, 2024; Oh et al., 2025; Cho et al., 2023; Felip et al., 2024; Cho et al., 2022; Park et al., 2021; Zhou et al., 2023; Kaakour and Nagasaka, 2024; Passaro et al., 2024; Chouaïd et al., 2025).

Table 1. Data from pivotal studies involving amivantamab

	Chrysalis	**Papillon**	***Mariposa***	***Mariposa-2***
	Phase I Study	Phase III Study	Phase III Study	Phase III Study
Mutation	*EGFR* Ex20ins	*EGFR* Ex20ins	*EGFR* ex19del lub p.L858R	*EGFR* ex19del lub p.L858R
Patient group	progression after platinum-based chemotherapy	previously untreated	previously untreated	progression during or after osimertinib monotherapy
Number of patients	362	308	1074	657
Comparative treatments	ami in monotherapy	ami-chemo (carboplatin and pemetrexed) vs chemo (carboplatin and pemetrexed)	ami+laz vs osi	ami-chemo (with or without lazertinib) vs chemo
Progression-Free Survival (PFS)	PFS ami: 8.3 months (95% CI: 6.5–10.9)	PFS ami+chemo: 11.4 months (95% CI: 9.8–13.7) Chemo: 6.7 months (95% CI: 5.6–7.3)	PFS Ami+laz: 23.7 months (95% CI: 19.1–27.7) Osi: 16.6 months (HR = 0.70; 95% CI: 0.58–0.85; p < 0.001)	PFS ami+laz+chemo: 8.3 months (95% CI: 6.8–9.1) ami+chemo: 6.3 months (95% CI: 5.6–8.4) Chemo: 4.2 months (95% CI: 4.0–4.4)
Intracranial PFS	no data provided	no data provided	Ami+laz: 8.3 months (95% CI: 16.6–23.7) Osi: 13.0 months (95% CI: 12.2–16.4)	Ami-chemo: 12.5 months (95% CI: 10.8 – not estimable) Ami-laz-chemo: 12.8 months (95% CI: 11.1–14.3) Chemo: 8.3 months (95% CI: 7.3–11.3)
ORR	ORR: 40% (95% CI: 29–51)	ORR ami-chemo: 73% (95% CI: 65–80) Chemo: 47% (95%	ORR Ami+laz: 86% (95% CI: 83–89) Osi: 85% (95% CI:	ORR (ami-chemo): 64% (95% CI: 55%–72%) (ami-laz-chemo):

		CI: 39–56)	81–88)	63% (95% CI: 57%–69%) Chemo: 36% (95% CI: 30%–42%)
Temporary OS	22.8 months (95% CI: 14.6, not evaluable)	ami-chemo compared to chemo alone	not statistically significant	no data provided
Adverse events	Rash, infusion-related reactions, paronychia, stomatitis, pruritus, diarrhea, hypoalbuminemia, peripheral edema	Neutropenia, hypoalbuminemia, infusion-related reactions, rash, anemia	Thrombotic events (VTE) increased with ami+laz, mainly grade 1–2, occurred early	Hematologic: less without laz

ami: Amivantamab; chemo: chemotherapy; Osi: Osimertinib; Laz: Lazertinib; vs: versus; CI: Confidence Interval; mo: months; HR: Hazard Ratio; p: p-value; ORR: Overall Response Rate; OS: Overall Survival; DoR: Duration of Response; NE: Not Estimable

Patients with EGFR Exon20ins mutations have particularly poor prognoses. The Chrysalis and Papillon studies demonstrate that amivantamab showed clinically significant efficacy in both first-line and second-line treatments (with disease progression after platinum-based chemotherapy). In previously untreated patients, adding amivantamab to chemotherapy extends progression-free survival. This antibody has therapeutic potential in monotherapy and in combination with other drugs.

The results of the Mariposa and Mariposa-2 studies were positive for patients with EGFR ex19 deletions or p.L858R mutations. The combination of these drugs was also more effective in patients with co-occurring TP53 mutations, brain or liver metastases at the onset of therapy, detectable ctDNA at the start and during treatment. In untreated patients, the combination of amivantamab + lazertinib was more effective than osimertinib. The median progression-free survival was more than half a year longer with amivantamab + lazertinib than with osimertinib. The overall survival and median duration of response were also higher for amivantamab + Lazertinib (table 1).

The Mariposa-2 study offers new options for patients who have progressed on osimertinib. Both the amivantamab -chemo and amivantamab –lazertinib - chemo regimens improve progression-free survival, overall response rate, interim overall survival, and intracranial progression-free survival compared to chemotherapy alone.

The safety profile of amivantamab + lazertinib was consistent with previous reports. Despite numerous adverse effects, most were grade 1 or 2 side effects. What is more, patients received effective treatment with anticoagulants. Before Amivantamab infusion patients get premedication with antihistamines and antipyretics. Premedication is crucial because, for most intravenously administered anti-cancer drugs, the incidence of Infusion-Related Reactions (IRRs) is very high. For Amivantamab, the rate is approximately 67%. Therefore, the Phase 2 SKIPPirr study investigated what additional premedication could reduce the occurrence of infusion-related adverse events.

The study included 68 participants with advanced NSCLC and an EGFR mutation (exon 19 deletion or exon 21 L858R). There were four cohorts. The first two received dexamethasone. The first cohort received a total of 2 doses, each 4 mg, and the second cohort received a total of 5 doses, each 8 mg. The third cohort received a total of 5 doses of 10 mg of montelukast, while the fourth received a single dose of 25 mg of methotrexate. The cohorts receiving 4 mg of dexamethasone and 25 mg of methotrexate did not pass the first stage, and the one receiving 10 mg of montelukast did not pass the second stage. Only the cohort with extended dexamethasone administration (8 mg per dose) achieved success. IRRs decreased approximately threefold (from 67.4% to 22.5%), representing a significant success that can have a substantial impact on patient treatment. Moreover, premedication with an additional 8 mg of dexamethasone reduced the average infusion time from approximately 5 hours to about 4.4 hours. In all the above-mentioned studies, patients got Amivantamab intravenously, and Lazertinib orally (Spira et al., 2025).

In search of further ways to improve patient comfort associated with treatment, interesting and promising studies on Paloma, Paloma-2, and Paloma-3 were conducted, focusing on changing the administration of Amivantamab from intravenous to subcutaneous. In all Paloma studies, Amivantamab was in combination with lazertinib. The randomized, international Phase III Paloma-3 study

evaluated whether subcutaneous administration improves patient convenience, increases tolerability, and reduces adverse events, predominantly venous thromboembolic disease, compared to intravenous administration, while maintaining treatment efficacy.

The study involved a group of 418 patients, who were randomized 1:1, with 209 individuals in the intravenous administration group and 209 in the subcutaneous administration group (table 2).

Table 2. Subcutaneous versus intravenous administration

	Subcutaneous Administration	**Intravenous Administration**
ORR	30%	33%
PFS	6.1 months	4.3 months
OS	Significantly higher	Lower
IRRs	13%	66%
VTE (Venous Thromboembolism)	9%	14%
Administration Time	Approx. 5 min	Approx. 5 h

Subcutaneous administration was associated with shorter administration time, resulting in greater convenience for the patient (Table 2). Furthermore, the subcutaneous form of Amivantamab demonstrated better tolerability and fewer adverse events, including venous thromboembolic disease. Furthermore, subcutaneous administration had non-inferior efficacy compared to intravenous administration (Leighl et al., 2024).

Another circumstance, beyond the adverse effects, is the high cost of therapy with lazertinib, or its combination with amivantamab, when compared to osimertinib. These drugs are costly, and therefore their use in treatment is not cost-effective from an economic standpoint. There is a need for cost optimization to enable the widespread introduction of these drugs (Cao et al., 2024).

4. CONCLUSION

Amivantamab plus lazertinib is a promising combination for both first- and second-line treatment of NSCLC with EGFR gene mutations. The outcomes of the presented studies suggest that it prolongs both Overall Survival and Progression-Free Survival in patients without risk factors and those who already have them at the beginning of therapy. Amivantamab plus lazertinib is an unusual combination, in which lazertinib performs inside the tumor cell and amivantamab outside. Moreover, amivantamab acts not only on the EGFR and MET receptors, but can also result in phagocytosis of the antibody-receptor combination and activate cells of the host's immune system. The most current studies focus on reducing the side effects of this therapy by predetermining and modifying the route of administration. The combination of these two drugs is complementary and highly effective, while also being safe and comfortable for the patient.

Abbreviations:
ami: Amivantamab
chemo: chemotherapy
Osi: Osimertinib
Laz: Lazertinib
vs: versus
CI: Confidence Interval
mo: months
HR: Hazard Ratio
p: p-value
ORR: Overall Response Rate
OS: Overall Survival
DoR: Duration of Response
NE: Not Estimable

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Informed consent

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Conflict of interest

The authors declare that there is no conflict of interest.

Data and materials availability

All data associated with this work are present in the paper.

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