Application of Lazertinib in Brain Metastases of Non-Small Cell Lung Cancer

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ABSTRACT

Lazertinib is an oral, brain-penetrating, irreversible third-generation epidermal growth factor receptor tyrosine kinase inhibitor that selectively targets EGFR T790M resistance mutations and common activation mutations (Ex19del, L858R), while exhibiting weaker inhibitory effects on wild-type EGFR. It provides a novel therapeutic option for brain metastases in EGFR-mutated non-small cell lung cancer. This article systematically reviews the pharmacological characteristics, preclinical studies, clinical evidence, safety profile, and resistance mechanisms of lazertinib. Preclinical studies demonstrated that lazertinib exhibits significant intracranial distribution advantage and antitumor activity in brain metastasis mouse models, with higher tumor exposure levels in the brain compared to plasma and superior efficacy over control drugs. In clinical trials, whether as first-line or second-line treatment, lazertinib monotherapy showed a high objective remission rate in intracranial tumors, and brought lasting benefits to patients with brain metastasis, and a clear effect was also observed in patients with meningeal metastasis. In the combination therapy, lazertinib combined with amivantamab can further improve the prognosis of patients with brain metastasis and significantly prolong the progression-free survival time in the brain. In terms of safety, the adverse reactions of lazertinib monotherapy are mainly mild to moderate, and the adverse reactions of combined therapy are generally controllable. Venous thromboembolism can be effectively managed by preventive anticoagulation. The mechanism of drug resistance mainly includes EGFR C797S mutation and MET amplification. In a word, Lazertinib showed significant and lasting intracranial anti-tumor activity in patients with brain metastases from EGFR mutation NSCLC, which provided a new effective treatment choice for this high-risk group.

Keywords: Lazertinib, Non-Small Cell Lung Cancer, Brain Metastasis, Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor, Blood-Brain Barrier Penetration.

1. INTRODUCTION

Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, accounting for about 85% of all lung cancer cases. Brain metastasis is a common distant metastasis site in NSCLC patients, and about 30%-50% patients will have brain metastasis during the disease progression. In patients with advanced NSCLC with epidermal growth factor receptor (EGFR) mutation, the proportion may even be as high as 60%. Brain metastasis will not only cause a series of clinical symptoms such as headache, epilepsy and neurological dysfunction, but also seriously affect the quality of life of patients, and it is also a key prognostic factor. Although systemic therapy has made progress in recent years, it is difficult for many drugs to reach effective therapeutic concentration in cerebrospinal fluid and brain parenchyma because of the existence of blood-brain barrier, which brings challenges to the treatment of brain metastasis. Traditional radiotherapy can control local lesions, but it will bring long-term side effects such as cognitive decline, and the effect on multiple or progressive lesions is limited [1]. Therefore, it is an urgent need to develop targeted drugs that can effectively cross the blood-brain barrier and have systemic and central nervous system activities to improve the prognosis of patients with brain metastases from non-small cell lung cancer (NSCLC).

EGFR mutation is one of the most important driving gene changes in NSCLC, especially in Asian population. The development of EGFR tyrosine kinase inhibitors (TKIs) has profoundly changed the therapeutic pattern of EGFR mutant NSCLC. The first generation of EGFR-TKIs (gefitinib, erlotinib) and the second generation of EGFR-TKIs (afatinib, dacomitinib) are effective for sensitive mutations, but their ability to cross the blood-brain barrier is limited, which leads to unsatisfactory curative effect on brain metastasis. In addition, most patients will eventually develop disease due to acquired drug resistance (especially T790M mutation) [2]. The third generation EGFR-TKI osimertinib can firmly bind to

the site of C797, and can also effectively inhibit T790M mutation. Clinical research shows that TKIs is more effective than the first generation TKIS in the whole body and brain, so it has become an important first choice for treatment. However, osimertinib will still encounter the problems of drug resistance and side effects, which indicates that we may need more optimized drugs [3,4].

Lazertinib is a new generation of EGFR-TKI, and its molecular structure is optimized on the basis of osimertinib: hydrophilic amino group and hydrophobic benzene ring are added, which greatly enhances its ability to cross the blood-brain barrier. Preclinical experiments show that it is more effective than osimertinib in inhibiting brain metastasis [4,5]. The research and development of Lazertinib is a great progress of EGFR-TKI in dealing with brain metastasis and drug resistance. This article wants to systematically talk about its pharmacological characteristics, clinical evidence and safety in the treatment of brain metastases from NSCLC, hoping to provide reference for clinical work.

2. PHARMACOLOGICAL CHARACTERISTICS OF LAZERTINIB

2.1 Chemical Structure and Mechanism of Action

Lazertinib, its chemical name is n-[5-[[4-[(Dimethyl Amino) methyl]-3-phenyl-1h-pyrazol-1-yl) pyrimidine-2-yl] amino]-4-methoxy-2-(Mor. The substituents (benzene ring and dimethylamino methyl group) on that pyrazole ring enable it to bind with T790M mutant more selectively, and at the same time reduce the inhibition on wild-type EGFR [5]. Its morpholine group replaces the diamine chain in osimertinib, which improves the solubility and lipophilicity of the drug and enables it to cross the blood-brain barrier more effectively. This feature is very important for the treatment of brain metastases in NSCLC.

From the mechanism of action (Figure 1), Lazertinib reversibly binds to the hinge region of EGFR kinase through its aminopyrimidine structure, and then its acrylamide warhead will undergo Michael addition reaction with Cys797 in the catalytic region to form irreversible covalent bonds, thus inhibiting the activity of EGFR kinase for a long time [5]. This covalent binding will block the autophosphorylation and dimer activation of EGFR, thus effectively inhibiting two key signal pathways of tumor cell survival and proliferation: MAPK(RAS-RAF-MEK-ERK) pathway and PI3K/AKT/mTOR pathway [8]. This drug has high selectivity for EGFR with sensitive mutations such as T790M, L858R and Ex19del, but its inhibitory effect on wild-type EGFR is weak [7], which is the structural basis of its high efficiency and low toxicity as a therapeutic drug.

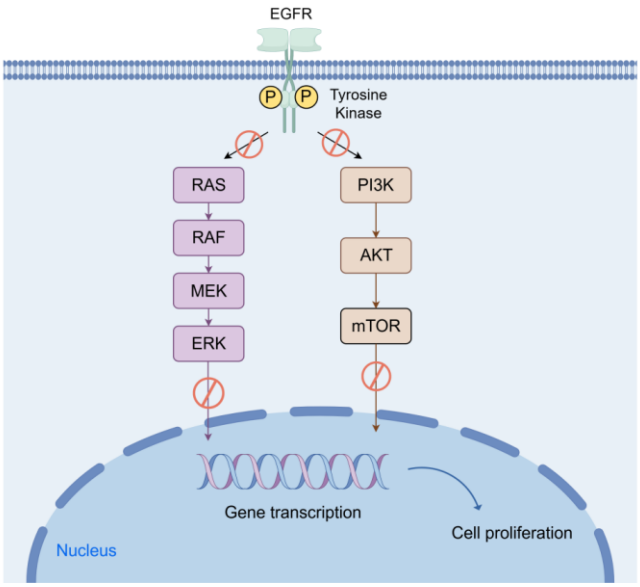

Figure 1. Schematic diagram of the mechanism of action of Lazertinib.

Lazertinib covalently binds to Cys797 of the mutant EGFR kinase domain, competitively occupying the ATP-binding site and inhibiting EGFR autophosphorylation. The figure demonstrates the interruption of the phosphorylation (P) signal, blockade of downstream MAPK pathways (RAS-RAF-MEK-ERK) and PI3K/AKT/mTOR pathways, ultimately leading

to suppressed tumor cell proliferation.

2.2 Pharmacokinetics

Lazertinib exhibits high selectivity for EGFR single mutations (Ex19del, L858R, T790M) and double mutations (Ex19del/T790M, L858R/T790M) (IC50 range:1.7-20.6 nmol/L). More importantly, lazertinib has low inhibitory activity on wild-type EGFR, which is the core reason for its good safety in clinical application [7].

At the cellular level, Lazertinib inhibits EGFR phosphorylation through irreversible binding, effectively blocking the transmission of downstream signal pathways. This drug can induce apoptosis of tumor cells with EGFR mutation, which shows that apoptosis-related proteins are activated and the cell survival rate is significantly reduced [4,9].

In addition, Lazertinib shows pharmacodynamic advantages by virtue of its excellent central nervous system penetration ability. Lazertinib can effectively cross the blood-brain barrier and reach the therapeutic concentration in brain tissue and cerebrospinal fluid [10], which provides a key pharmacodynamic basis for the treatment of brain metastases because of its extremely low affinity for P-glycoproteins and breast cancer resistance proteins [8].

2.3 Pharmacokinetics

Lazertinib is absorbed quickly by oral administration, and the median time to reach the highest concentration is 2-4 hours, showing linear pharmacokinetic characteristics in the dose range of 20-320 mg. After continuous administration for about 15 days, it reached a stable state, and the cumulative ratio was 2-3 times. A high-fat diet has no clinically relevant effect on its absorption, allowing for co-administration with food or administration on an empty stomach, which provides convenience. The drug has a large apparent volume of distribution (approximately 4264 L), indicating extensive tissue distribution; plasma protein binding rates range from 99.1% to 99.7%. Lazertinib is primarily cleared via a glutathione S-transferase M1-mediated metabolic pathway, with CYP3A4 metabolism as a secondary route. The terminal half-life is approximately 64.7 hours, supporting once-daily dosing. The drug is mainly excreted via feces (approximately 84%) and less than 5% is excreted in urine. Age, sex, body weight, and mild hepatic or renal impairment have no significant impact on pharmacokinetic characteristics [6,7,8].

3. PRECLINICAL RESEARCH

Preclinical studies of larazertinib have provided direct evidence for its application in the treatment of brain metastases in non-small cell lung cancer.

In a mouse model of brain metastasis with intracranial implantation of H1975 (L858R/T790M) cells, the median survival duration in the lazertinib-treated group reached 124 days, compared to only 65 days in the osimertinib-treated group (dose:10 mg/kg), indicating that lazertinib nearly doubled the median survival period[4,10].In an EGFR-mutant mouse brain metastasis model, lazertinib demonstrated superior efficacy in inducing tumor regression compared to osimertinib at equivalent molar concentrations ($p<0.05$). After 49 days of treatment, the lazertinib group exhibited significantly better inhibition of intracranial tumor growth than the osimertinib group [10].

Pharmacokinetic studies have demonstrated that Lazertinib exhibits favorable distribution characteristics in intracranial lesions. Following a single administration, the uptake of Lazertinib by intracranial tumor tissues was significantly higher than that in plasma or brain tissue, with a relative exposure ratio (AUC ratio) of 7.0 for intracranial tumors/plasma and 7.9 for intracranial tumors/brain tissue, confirming that Lazertinib can achieve therapeutic concentrations in intracranial tumors [4,10].

In subcutaneous xenograft models, lazertinib also demonstrated potent antitumor activity. In the H1975 tumor mouse model, a 3 mg/kg dose of lazertinib achieved 86.85% tumor regression after 13 days of treatment, whereas the equivalent dose of osimertinib only achieved 7.24% tumor regression [4,10]. When the dose was increased to 10 mg/kg (clinically equivalent to 240 mg once daily), lazertinib achieved near-complete tumor regression with a tumor regression rate as high as 90%. In patient-derived xenograft models (PDX), lazertinib (25 mg/kg) treatment for 20 days resulted in an tumor suppression rate of 87.5% [10].

4. CLINICAL TRIAL

4.1 Monotherapy

4.1.1 LASER201 Study

LASER201 (NCT03046992) was a multicenter, open-label, first-in-human Phase I/II clinical trial designed to evaluate the efficacy and safety of razitinib in patients with advanced EGFR-mutated (L858R,19del, G719X, and L861Q) NSCLC who had progressed after prior treatment with first-or second-generation EGFR-TKI [11,12]. A total of 181 patients participated in the trial, and the recommended dose of razitinib was 240 mg once a day. In the second-line treatment group of 76 T790M positive patients, the objective remission rate reached 55.3%, and the median progression-free survival time was 11.1 months [13]. This study pays special attention to the curative effect of razitinib on patients with brain metastasis. In 7 patients with measurable intracranial lesions, the objective remission rate of brain was as high as 85.7% (6/7), and the control rate of intracranial diseases reached 100% (7/7). The duration of median intracranial remission was 15.1 months, and the median intracranial progression-free survival time was 26.0 months [11,13]. In 22 patients with measurable brain metastasis, the objective remission rate of brain was 54.5%, and the control rate of intracranial diseases was 90.9% [14]. In addition, among all the 181 patients treated with razitinib, only 7.2% took brain metastasis as the main site of disease progression, indicating that it has a lasting control effect on intracranial lesions [7].

4.1.2 LASER301 Study

LASER301 (NCT04248829) is a global, multicenter, randomized, double-blind, Phase III clinical trial designed to evaluate the efficacy and safety of razitinib versus gefitinib as first-line treatment in patients with locally advanced or metastatic EGFR-mutated (ex19del/L858R) NSCLC [15]. A total of 393 previously untreated EGFR-mutated advanced NSCLC patients were enrolled and randomly assigned to either the razitinib group (240 mg once daily) or the gefitinib group (250 mg once daily). The results demonstrated that the median progression-free survival in the razitinib group was significantly superior to that in the gefitinib group (20.6 months vs. 9.7 months), with a hazard ratio of 0.45 (95% CI: 0.34–0.58, P <0.001) [15]. In a subgroup analysis of patients with brain metastases, razitinib also showed a significant advantage. Among patients with confirmed central nervous system metastases on baseline brain scans, the median progression-free survival in the razitinib group was significantly longer than that in the gefitinib group (16.4 months vs. 9.5 months), with a hazard ratio of 0.42 (95% CI: 0.26-0.68) [15,16]. Further analysis revealed that the median intracranial progression-free survival in the razitinib group was 28.2 months, significantly superior to the 8.4 months in the gefitinib group; the intracranial objective response rate in the razitinib group was 94%, higher than the 73% in the gefitinib group [16].

4.1.3 Phase II study: Intracranial activity independent of T790M status

A recently published phase II non-randomized controlled trial (NCT05326425) evaluated the intracranial activity of larazertinib in EGFR-mutated NSCLC patients who had progressed to central nervous system involvement after prior first- or second-generation EGFR-TKI therapy [17]. This study recruited 40 patients, 38 of whom could evaluate the curative effect, including 12 with soft tissue metastasis. The results showed that the objective intracranial remission rate was 55% (21/38, 95 95% CI: 38.3-71.4), including 3 cases of complete intracranial remission and 18 cases of partial intracranial remission. The control rate of intracranial diseases reached 97% (37/38). In T790M positive subgroup, the objective remission rate was 80% (4/5). T790M negative subgroup was 43% (9/21); The unknown subgroup of T790M status was 67% (8/12). The median intracranial progression-free survival time was 15.8 months (95% CI: 15.2-not achieved), and the median intracranial remission duration was 14.5 months (95% CI: 13.8-not achieved). It is worth noting that in 12 patients with soft tissue metastasis, the objective remission rate was 63.6%, and the median intracranial progression-free survival time was 15.2 months. Pharmacokinetic analysis showed that the median blood-brain barrier penetration rate of lazertinib was 46.2% (95% CI: 26.1-58.6) in 6 matched cerebrospinal fluid and plasma samples, which provided direct pharmacological evidence for its intracranial efficacy [17].

4.1.4 Summary Analysis of LASER201 and LASER301

In order to further evaluate the effect of razitinib on patients with brain metastases, the researchers conducted a summary analysis of patients who participated in the LASER201 and LASER301 studies and used razitinib [18]. The analysis included 64 patients with central nervous system metastasis before treatment. among whom 24 had at least one measurable intracranial lesion. At a median follow-up of 26.1 months, the median intracranial progression-free survival (IPFS) was 27.7 months (95% CI: 15.7-32.8) in the full intracranial analysis set. For patients who had not previously received brain radiotherapy, the median intracranial IPFS was 28.2 months (95% CI: 14.8-33.2); for those who had previously received

brain radiotherapy, the median intracranial IPFS was 20.5 months (95% CI: 8.4-not reached). Among the 24 patients with at least one measurable intracranial lesion, the objective intracranial response rate was 92% (22/24), including complete response in 6 cases (25%) and partial response in 16 cases (67%). The intracranial disease control rate was 96% (23/24). The median duration of intracranial response was 26.5 months (95% CI:8.3-30.1), with a median time to intracranial response of 5.4 weeks (95% CI:5.3-11.9). Cumulative incidence analysis revealed that the cumulative incidence of central nervous system progression (excluding death and non-central nervous system progression events) at 24 months was 15.3%, further confirming the sustained control efficacy of razitinib over intracranial lesions [18].

4.1.5 Ongoing Phase II Trial

An ongoing single-center, open-label, single-arm Phase II trial (KCT0006951) aims to further evaluate the efficacy of razitinib alone or in combination with local therapy as first-line treatment in patients with EGFR mutation-positive NSCLC and brain metastases. The study plans to enroll 75 patients, with the decision to combine local therapy (surgery, stereotactic radiotherapy, or whole-brain radiotherapy) based on the severity of neurological symptoms, tumor size, number, and location. The primary endpoints are progression-free survival and intracranial progression-free survival [19].

4.2 Combination Therapy

4.2.1 CHRYRALIS Study

CHRYSALIS (NCT02609776) was an open-label, Phase I clinical trial whose Cohort E evaluated the efficacy and safety of amivantamab combined with razitinib in patients with advanced EGFR-mutated (exon 19del or L858R) NSCLC who had progressed after osimertinib treatment but had not received chemotherapy [22]. As of April 19,2021, a total of 45 patients were enrolled, 42% of whom were Asian, and 69% carried the ex19del mutation. All patients had previously received third-generation EGFR-TKI therapy, with 73% receiving it as second-line treatment. At a median follow-up of 11.1 months, the investigator assessed an objective response rate of 36% (95% CI, 22-51), including 1 complete response and 15 partial responses. The median duration of response was 9.6 months (95% CI, 5.3-not reached), and the median progression-free survival was 4.9 months (95% CI, 3.7-9.5). Among the 13 patients with a history of brain metastases at baseline, 3 experienced central nervous system progression during treatment (2 with new lesions and 1 with progression of existing lesions) [22].

4.2.2 CHRYRALIS-2 Study

CHRYSALIS-2 (NCT04077463) was an I/IIb phase clinical trial that evaluated the efficacy and safety of amivantamab combined with lazertinib in patients with advanced NSCLC harboring non-classical EGFR mutations (e.g., G719X, S768I, L861Q, etc.). The cohort included 105 patients, comprising 49 first-line patients and 56 patients who had previously received first-line or second-line therapy, with 31% of patients having baseline brain metastases. At a median follow-up of 16.1 months, the objective response rate in the overall population was 52% (95% CI, 42-62), the median duration of response was 14.1 months (95% CI, 9.5-26.2), the median progression-free survival was 11.1 months (95% CI, 7.8-17.8), and the median overall survival was not reached (95% CI, 22.8-not reached) [23,24].

4.2.3 MARIPOSA Study

MARIPOSA (NCT04487080) was a global, multicenter, randomized, phase III clinical trial designed to evaluate the efficacy and safety of amivantamab combined with lazertinib versus osimertinib monotherapy as first-line treatment for advanced EGFR-mutated (exon 19del or L858R) NSCLC [25,26]. A total of 1,074 patients were enrolled and randomly assigned in a 2:2:1 ratio to the amivantamab plus lazertinib group, osimertinib monotherapy group, or lazertinib monotherapy group. At a median follow-up of 22.0 months, the median progression-free survival (PFS) in the combination therapy group was significantly superior to that in the osimertinib monotherapy group (23.7 months vs. 16.6 months), with a hazard ratio (HR) of 0.70 (95% CI, 0.58-0.85, P <0.001). The objective response rates were 78% and 73%, respectively, with median response durations of 25.8 months and 16.8 months. In the subgroup of patients with brain metastases, the median PFS was 18.3 months, superior to the 14.7 months observed in the osimertinib group (HR 0.69,95% CI, 0.53-0.92)[25].Extended follow-up (median follow-up 31.1 months) demonstrated a 3-year intracranial progression-free survival rate of 38% in the combination therapy group, significantly higher than the 18% observed in the osimertinib group[27].Subgroup analysis in Asian patients also confirmed the superiority of combination therapy in patients with brain metastases. Among patients with a history of brain metastases at baseline, the median progression-free survival in the combination therapy group was 18.3 months, superior to the 14.7 months observed in the osimertinib group (HR 0.72,95% CI 0.51-1.02) [28].

4.2.4 LAZARUS Study

LAZARUS (KCT0005919) was a multicenter, single-arm, phase II clinical trial designed to evaluate the efficacy of razitinib combined with pemetrexed in patients with EGFR-mutated NSCLC and soft tissue brain metastases. A total of 36 patients with cytologically confirmed soft tissue brain metastases were enrolled, among whom 94.4% had received prior systemic therapy. Among the 29 patients who met the efficacy criteria, the objective response rate was 24.1% (95% CI, 10.3-43.5%), and the disease control rate was 96.6% (95% CI, 82.2-99.9%). In 8 patients with measurable brain metastases, the objective intracranial response rate was 25.0% (2/8), and the intracranial disease control rate was 100% (8/8). The median progression-free survival was 9.3 months (95% CI, 5.0-10.3), and the median overall survival was 9.9 months (95% CI, 5.5-13.6). The cerebrospinal fluid cytology negativity rates were 9.4% in cycle 2 and 11.5% in cycle 3. Pharmacokinetic analysis revealed median cerebrospinal fluid/plasma concentration ratios of razitinib in cycles 2 and 3 to be 0.5 and 0.53, respectively, providing direct pharmacological evidence for its intracranial efficacy in patients with soft tissue brain metastases [29].

4.2.5 MSKCC Phase II Study

A Phase II study conducted by Memorial Sloan Kettering Cancer Center (MSK) (NCT04965090) specifically evaluated the efficacy of amivantamab combined with larazertinib in previously treated patients with EGFR-mutated lung cancer accompanied by new or progressive central nervous system metastases, including brain parenchymal metastases (BrM) and leptomeningeal metastases (LMD)[30].A total of 41 patients were enrolled, comprising 20 in the brain metastasis cohort and 21 in the leptomeningeal metastasis cohort. The median number of prior treatment lines was 2 (range:1-7), with 41% harboring EGFR del19,37% L858R,12% ex20ins, and 10% rare mutations. After almost 15.5 months' follow-up, the overall effective rate (combined with RECIST and RANO-BM evaluation) for patients with brain metastases reached 50% (95% CI:27-73%). Among them, the objective effective rate of the whole body is 30%, and the objective effective rate of the brain is 40%. Their median progression-free survival was 5.8 months (95% CI:3.6-not achieved) and their median overall survival was 17.4 months (95% CI:15.4-not achieved).

In patients with meningeal metastasis, the overall effective rate (combined with RECIST and RANO-LM evaluation) was 33% (95% CI:15-57%), and the overall objective effective rate was 33%. Their median progression-free survival was 7.8 months (95 95% CI:4.2-12.2), and their median overall survival was 14.4 months (95% CI:8.9-not achieved).

Among those patients with soft tissue meningioma who can be evaluated, 67% (14/21) have reduced the number of circulating tumor cells in cerebrospinal fluid. However, it is worth noting that the objective intracranial effective rate evaluated according to RANO-LM criteria is 0%, which indicates that we may need more comprehensive evaluation criteria to better see the clinical benefits of these patients with soft tissue meningiomas. This study provides evidence supporting the efficacy of amivantamab combined with lazertinib for the treatment of brain metastases [30].

4.2.6 MARIPOSA-2 Study

MARIPOSA-2 (NCT04988295) is a global, multicenter, randomized, Phase III clinical trial designed to evaluate the efficacy of amivantamab combined with chemotherapy (± razitinib) versus chemotherapy alone in patients with advanced EGFR-mutated NSCLC who had progressed after osimertinib treatment. A total of 657 patients were enrolled and randomly assigned to the amivantamab-razitinib-chemotherapy group, amivantamab-chemotherapy group, or chemotherapy-only group. In terms of intracranial efficacy, the median intracranial progression-free survival was 12.8 months in the amivantamab-razitinib-chemotherapy group and 12.5 months in the amivantamab-chemotherapy group, both superior to the 8.3 months observed in the chemotherapy-only group (HRs both 0.55) [31].

4.3 Safety

Lazertinib monotherapy demonstrated favorable safety profiles. In the LASER201 study, the most common adverse reactions included rash (34.6%), pruritus (33.3%), and paresthesia (32.1%), predominantly grade 1-2, with a serious adverse event rate of 28.2% [13,20]. In the LASER301 study, paresthesia occurred in 39% of patients. Regarding hepatotoxicity, the proportion of ALT/AST elevation was lower than that observed in the gefitinib group, and the incidence of interstitial lung disease was low (3%) [15]. In terms of cardiac safety, lazertinib has little effect on cardiac function, and no clinically significant QT interval prolongation or left ventricular ejection fraction decrease has been observed [21]. The safety of combination therapy is consistent with the results of each single drug treatment scheme reported before, and no new safety signals have been found. In MARIPOSA study, the most common adverse reactions in amivantamab plus lazertinib group were rash (75%), paronychia (67%), hypoalbuminemia (59%) and infusion-related reactions (56%), and the incidence of adverse events ≥3 was 70%. The incidence of venous thromboembolism was 30%, which mainly occurred

in the first 4 months of treatment, but no thrombotic events were observed in patients receiving preventive anticoagulation treatment [25]. In MSKCC study, 50% patients need to stop taking drugs, 17% need to reduce the dosage, and 7% stop treatment because of toxicity, which shows that preventive anticoagulation can effectively reduce the risk of thrombosis [30]. In LAZARUS study, the incidence of peripheral neuropathy and rash was 33.3% respectively, and the incidence of adverse events ≥ grade 3 was 13.9% [29].

Generally speaking, whether razitinib is used alone or together with other drugs, it has a good effect on NSCLC patients with EGFR mutation and brain metastasis. When razitinib is used alone, no matter the first treatment or the follow-up treatment, the tumor in the brain can be controlled, and the patient cannot get worse for a longer time, especially for patients with T790M negative and meningeal metastasis. Combined with other drugs, the effect will be better. Like MARIPOSA's research, amivantamab plus razitinib can prolong the progression-free survival of patients and control the time of tumors in the brain more than osimertinib alone, which provides a stronger first-line treatment for patients with brain metastasis. Table 1 summarizes the main results of each experiment.

Table 1. summarizes the major clinical trials of lazertinib.

Experiment name	registration mark	Trial Details
LASER201[11]	NCT03046992	Stage I/II; advanced EGFR T790M-positive NSCLC with progression after prior EGFR-TKI therapy
LASER301[15]	NCT04248829	Stage III; first-line treatment for advanced NSCLC with EGFR mutation (ex19del/L858R)
- [17]	NCT05326425	Stage II; NSCLC with EGFR mutations showing central nervous system progression after first/second-generation EGFR-TKI therapy
LAZARUS [29]	KCT0005919	Stage II; EGFR-mutated NSCLC with soft meningeal metastases
CHRYSALIS（Cohort E）[22]	NCT02609776	Stage I; Advanced NSCLC with EGFR mutations that progressed after osimertinib treatment (unreated by chemotherapy)
CHRYSALIS-2 (C cohort [23]	NCT04077463	Stage I/IIb; advanced NSCLC with non-classical EGFR mutations (untreated or previously treated)
MARIPOSA [25]	NCT04487080	Stage III; first-line treatment for advanced NSCLC with EGFR mutation (ex19del/L858R)
- [30]	NCT04965090	Stage II; EGFR-mutated lung cancer with newly developed or progressive brain metastases/soft tissue metastases after prior treatment
MARIPOSA-2[31]	NCT04988295	Stage III; advanced EGFR-mutated NSCLC with progression after osimertinib treatment

5. DRUG RESISTANCE MECHANISMS

Although Lazertinib has demonstrated significant efficacy in the treatment of EGFR-mutated NSCLC, long-term use inevitably faces the challenge of acquired resistance. The resistance mechanisms of Lazertinib can be classified into two major categories: EGFR-dependent (on-target) and non-EGFR-dependent (off-target) [32].

The EGFR C797S mutation is the most common mechanism of acquired resistance to third-generation EGFR-TKIs [33]. Park et al. first reported a clinical case of EGFR C797S cis mutation occurring after treatment with razitinib. The patient experienced disease progression after 6.2 months of razitinib therapy, and subsequent testing revealed a newly acquired EGFR C797S cis mutation (located on the same allele as T790M), while both T790M and exon 19del mutations remained present. The patient-derived cell line exhibited complete resistance to both razitinib and osimertinib[34].Other secondary EGFR mutations, including L792X, G796X, and L718Q, have also been reported[35]. In addition, the loss of T790M is also one of the reasons why some patients are resistant to razitinib [36].

MET gene amplification is the most important pathway activation mechanism [32] In MARIPOSA study, the incidence of MET amplification in lenvatinib combined with amivantamab was 4.4%, which was significantly lower than that in osimertinib alone (13.6%, P=0.017) [37]. Other pathway activation mechanisms include HER2 amplification, KRAS mutation, PIK3CA amplification and FGFR3-TACC3 fusion. Histological transformation is also one of the mechanisms of drug resistance, including small cell lung cancer transformation and epithelial-mesenchymal transformation (EMT) [32].

6. CONCLUSION

As a new generation of third-generation EGFR-TKI that can enter the brain, Lazertinib has a great molecular structure and can well cross the blood-brain barrier, so it shows a very special clinical value in the treatment of NSCLC patients with brain metastasis with EGFR mutation. Clinical research has proved that Lazertinib alone can effectively control the lesions in the brain, and if it is used together with a new drug like amivantamab, the treatment effect for patients with brain metastasis will be better. However, drug resistance mechanisms such as EGFR C797S mutation and MET amplification are still the main problems that limit the long-term efficacy. Future strategies should include dynamically monitoring drug resistance signals through liquid biopsy and exploring combination therapy to delay or overcome drug resistance, so that Lazertinib can play a more critical role in the comprehensive treatment of brain metastases from NSCLC with EGFR mutation.

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