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Lazertinib: on the Way to Its Throne

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Lazertinib is an oral, irreversible, third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) that forms an irreversible covalent bond to the Cys797 residue in the ATP-binding site of the EGFR kinase domain and exhibits a high selectivity for sensitizing and T790M EGFR mutations. In January 2021, it was first approved for the treatment of advanced or metastatic non-small cell lung cancer (NSCLC) patients with EGFR T790M who had previously received EGFR TKI therapy based on LASER201, a phase I/II trial. At a recommended dose of 240 mg, lazertinib achieved an encouraging anti-tumor activity in both extra- and intracranial lesions. With a high half-maximal inhibitory concentration for EGFR wildtype tumors, it is anticipated to pose a lower risk of skin and cardiac adverse events compared to osimertinib. Lazertinib is currently being investigated as a mono-therapy in first-line treatment and in combination with amivantamab under various settings. In this review, we systematically summarize the preclinical and clinical data of lazertinib and discuss future perspectives on the treatment of EGFR-mutant NSCLC.

Key Words: Lazertinib, non-small cell lung cancer, epidermal growth factor receptor, targeted therapy

INTRODUCTION

Treatment strategies for non-small cell lung cancer (NSCLC) haves transformed tremendously over the past decades. Surgical resection, radiation therapy, cytotoxic chemotherapies, immunotherapies, and targeted therapies have been adopted at different stages and according to the tumor biology. Among these advances, targeted therapy is the one which brought a paradigm shift in the treatment scheme for NSCLC patients with molecular alterations. It significantly improved response rates and survival outcomes for selected patients, compared to conventional cytotoxic chemotherapeutic agents.

Epidermal growth factor receptor (EGFR) is a transmembrane protein with cytoplasmic kinase activity that transduces signals leading to increased cell proliferation, angiogenesis, metastasis, and decreased apoptosis.[1] Mutations in the EGFR tyrosine kinase domain lead to constitutive activation of its kinase activity and activation of downstream signaling pathways, including PI3K/AKT/mTOR and Ras/Raf/MEK/ERK, which result in the apoptosis prevention or cell cycle progression.[1,2]

Despite the advent of EGFR tyrosine kinase inhibitors (TKI), early clinical trials without patient selection based on biomarkers have failed to demonstrate any superiority in survival outcomes over cytotoxic chemotherapy.[3] Their therapeutic capabilities were only visible after the identification of patients harboring activating EGFR mutations who demonstrate a unique susceptibility to EGFR TKIs.[4,5]

Resistance to first- [erlotinib, gefitinib, and icotinib (icotinib is approved only in China)] or second-generation (afatinib, dacomitinib) EGFR TKIs typically develops in 50%–80% of initially responding patients after a median progression-free survival (PFS) of 9–13 months.[6] Among the many resistance mechanisms involved, the emergence of a secondary mutation in the gatekeeper residue T790M is the most commonly encountered, accounting for 50%–60% of patients who are re-

sistant to first/second-generation EGFR-TKIs.[7,8] The T790M mutation leads to impaired binding of TKI via steric hindrance.[9,10] As such, targeted therapy in EGFR-mutant NSCLC patients has been dominated by the third-generation TKI osimertinib,[11-13] which irreversibly and selectively inhibits both EGFR-sensitizing and T790M mutations.[14] Nevertheless, the emergence of treatment resistance, a higher risk of cardiac toxicity, and the "financial burden" of osimertinib dictated a need for the development of novel third-generation EGFR TKI, which leads us to lazertinib.

INTRODUCTION TO LAZERTINIB

Lazertinib (YH-25448, JNJ-73841937, Leclaza™) is an oral, irreversible, third-generation EGFR-TKI developed for the treatment of EGFR-mutant NSCLC (Fig. 1). It irreversibly binds to the Cys797 residue in the ATP-binding site of the EGFR kinase domain via covalent bond formation and exhibits high selectivity for sensitizing and T790M EGFR mutations while sparing EGFR WT tumors.[15]

In January 2021, lazertinib was first approved in Korea for the treatment of advanced or metastatic NSCLC patients with EGFR T790M who had previously received EGFR TKI therapy at a recommended dose of 240 mg, taken orally once daily as tablets and without regard to food.[16]

PRECLINICAL STUDY

In its preclinical study, lazertinib significantly reduced the viability of Ba/F3 cells harboring Del19, L858R, Del19/T790M, and L858R/T790M mutations, with mean half-maximal inhibitory concentration (IC_{50}) values ranging from 3.3–5.7 nmol/L,[15] similar to those obtained from osimertinib (IC_{50} 3.5–4.3) but lower than those obtained from gefitinib (IC_{50} 10.2–7625.2). Additionally, lazertinib demonstrated a higher IC_{50} for EGFR

WT, compared to osimertinib (722.7 nmol/L vs. 519.1 nmol/L).

Compatibly, a cell-free in vitro kinase inhibition assay has demonstrated that lazertinib inhibits the kinase activities of mutant EGFRs, including Del19, L858R, and T790M, with IC_{50} values ranging between 1.7–20.6 nmol/L, and also uncommon EGFR mutants, such as G719X and L861Q. WT EGFR was less affected by lazertinib than osimertinib (IC_{50} 60 nmol/L vs. 20 nmol/L).[15]

The strong tumor inhibitory capability of lazertinib was robustly replicated in PDX models.[15] Lazertinib demonstrated a superior tumor regression percentage than osimertinib (86.85% vs. 7.24% using 3 mg/kg lazertinib and osimertinib, respectively) in H1975 tumor-bearing mice models without any compromise in body weight. At a higher dose of 10 mg/kg (clinically equivalent to 240 mg once daily), lazertinib achieved a near-complete tumor regression (90%).

Lazertinib suppressed EGFR downstream pathways, including phospho-EGFR, phospho-AKT, and phospho-ERK, with an inhibitory capacity comparable to or higher than that of osimertinib.[15] Once again, lazertinib did not inhibit EGFR signaling in a WT EGFR cell line.

Lastly, mouse models with intracranial implantation of H1975 cells were used to evaluate the efficacy of lazertinib in tumors with brain metastases.[15] Intracranial tumors demonstrated a higher uptake of lazertinib than plasma or brain tissue at a single dose of 10 mg/kg. The relative exposure ratios of brain-to-plasma, intracranial tumor-to-plasma, and intracranial tumor-to-brain were 0.9, 7.0, and 7.9, respectively. Lazertinib was determined not to be a BCRP substrate, but only a weak substrate of MDR1 and was less affected by efflux transporters and maintained higher drug concentrations in intracranial tumors. In in vivo models, lazertinib more effectively inhibited intratumor growth than osimertinib, with a significantly longer survival duration (the median survival duration of mice, 124 days vs. 65 days at 10 mg/kg).
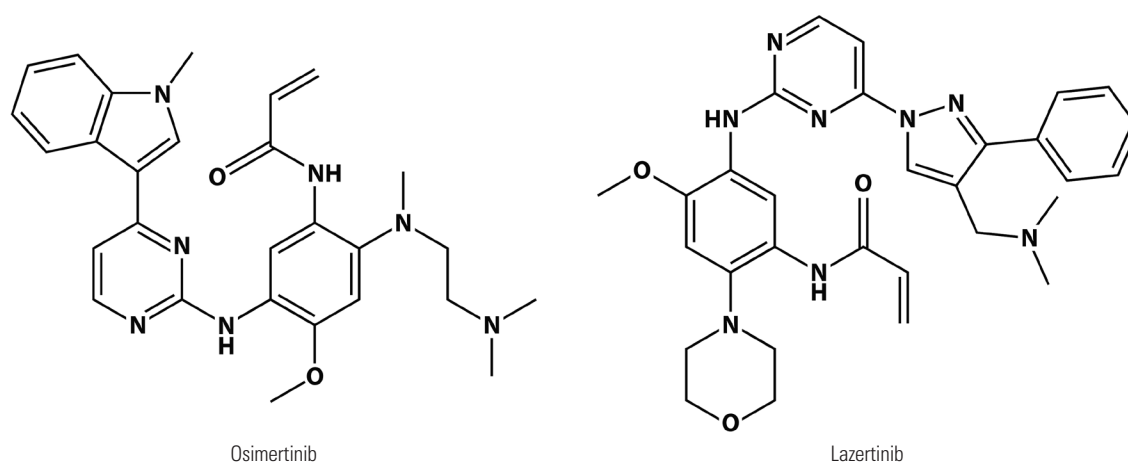

Osimertinib

Lazertinib

Fig. 1. Chemical structures of lazertinib and osimertinib.

CLINICAL STUDY

LASER201: a first-in-human phase I/II study

LASER201 (ClinicalTrials.gov Identifier: NCT03046992), a multicenter, open-label, phase I/II study, was conducted to evaluate the efficacy of lazertinib in advanced NSCLC patients with activating EGFR mutations (L858R, 19del, G719X, and L861Q) who had progressed on first- or second-generation EGFR TKI.[17,18] The study consisted of three parts: part A (dose-escalation), part B (dose-expansion), and part C (dose-extension in first- and second-line cohorts). It was conducted across 17 centers in South Korea (Part D is being conducted in countries other than Korea, including Caucasians).

No dose-limiting toxicity occurred in the dose-escalation part (doses of 20, 40, 80, 120, 160, 240, and 320 mg), and the dose-expansion cohorts were opened for five doses between 40 and 240 mg. Ultimately, a dose of 160 mg or higher was considered necessary to achieve sufficient and consistent target inhibition, and a dose of 240 mg once daily was selected for dose extension.[18]

In pooled analysis of 76 patients with T790M mutation in the second-line cohort, the median duration of lazertinib treatment was 13.3 months (range, 0.3–37.4).[17] The objective response rate (ORR) was 55.3% [95% confidence interval (CI), 44.1–66.4], including one complete response (1.3%) and 41 partial responses (53.9%), and the disease control rate (DCR) was 89.5% (95% CI, 82.6–96.4) with 26 patients achieving stable disease (Table 1). The median duration of response (DoR) was 17.7 months [95% CI, 9.9–not reached (NR)]. The median PFS and overall survival were 11.1 months (95% CI, 5.5–16.4) and NR, respectively, at a median follow-up of 22.0 months.

Additionally, although the patient numbers were limited, seven patients with measurable intracranial lesions demonstrated a confirmed intracranial ORR and DCR of 85.7% and 100.0%, respectively, with a median intracranial DoR of 15.1 months (95% CI, 2.8–NR) and intracranial PFS of 26.0 months (95% CI, 5.4–NR).[17]

The safety profiles were largely compatible with previous EGFR TKI studies.[11,19,20] The most common treatment-emergent adverse events of any grade were rash (37.2%), pruritus (34.6%), and paresthesia (33.3%),[17] mostly consistent with those reported from the AURA3 trial (Table 2).[21] The incidence of paresthesia was higher than that reported for osimertinib, although the underlying cause remains to be determined. A comparison of adverse events between lazertinib and osimertinib is discussed below.

Ongoing studies

LASER301 is a global, phase III trial aiming to compare the efficacy of lazertinib to gefitinib as a first-line treatment for locally advanced or metastatic EGFR-mutant NSCLC patients (NCT04248829).[22] The results are highly anticipated to uncover whether lazertinib can demonstrate superiority over first-generation TKI to secure its place in the first-line treatment (Table 3).

ABLATE (NCT05167851) is a two-arm, phase II trial which

Table 1. Clinical Efficacies of Lazertinib and Osimertinib

Drug (trial)	Lazertinib (LASER201) (n=76)	Osimertinib (AURA3) (n=279)
Phase	I/II	III
Best response, n (%)		
Complete response	1 (1.3)	4 (1.4)
Partial response	41 (53.9)	193 (69.2)
Stable disease	26 (34.2)	63 (22.6)
Progressive disease	6 (7.9)	33 (11.8)
Not evaluable	2 (2.6)	4 (1.4)
Objective response rate, n (%)	42 (55.3)	197 (70.6)
95% CI	44.1–66.4	65–76
Disease control rate, n (%)	68 (89.5)	260 (93.2)
95% CI	82.6–96.4	90–96
Duration of response, months	17.7	9.7
Median (95% CI)	9.9–NR	8.3–11.6
Progression-free survival, months	11.1	10.1
Median (95% CI)	5.5–16.4	8.3–12.3
Overall survival, months	NR*	26.8
Median (95% CI)		23.5–31.5
Intracranial response		
Total, n	7	30
Objective response rate, n (%)	6 (87.5)	21 (70.0)
Disease control rate, n (%)	7 (100.0)	28 (93.3)
Duration of response, months (95% CI)	15.1 (2.8–NR)	8.9 (4.3–NR)
Progression-free survival, months (95% CI)	26.0 (5.4–NR)	11.7 (10.0–NR)

CI, confidence interval; NR, not reached.
*The median overall survival was NR at a median follow-up of 22.2 months.

Table 2. Incidence of Treatment-Related Adverse Events

Drug (trial)	Lazertinib (LASER201) (n=78)		Osimertinib (AURA3, final analysis) (n=279)	
Grade	All grade	≥Grade 3	All grade	≥Grade 3
Treatment-related adverse events	69 (88.5)	11 (14.1)	237 (84.9)	24 (8.6)
Rash	29 (37.2)	1 (1.3)	88 (31.5)	1 (<1)
Pruritus	27 (34.6)	0	33 (11.8)	0
Diarrhea	21 (26.9)	1 (1.3)	89 (31.9)	3 (1.1)
Decreased appetite	20 (25.6)	0	23 (8.2)	1 (<1)
Paronychia	16 (20.5)	1 (1.3)	67 (24.0)	0
Constipation	15 (19.2)	0	7 (2.5)	0
Nausea	13 (16.7)	0	24 (8.6)	0
Fatigue	12 (15.4)	0	23 (8.2)	0
Stomatitis	9 (11.5)	0	40 (14.3)	0
Dry skin	8 (10.3)	0	54 (19.4)	0
Vomiting	8 (10.3)	1 (1.3)	12 (4.3)	0

Data are expressed as the number of patients (%).

Table 3. Ongoing Studies with Lazertinib as a Single Targeted Agent

Trial	Phase	Patients	Arms	Primary endpoint
LASER301 (NCT042488290)	III	Treatment-naïve mEGFR NSCLC	- Lazertinib - Gefitinib	PFS
ABLATE (NCT05167851)	II	Treatment-naïve mEGFR NSCLC	- Lazertinib+SBRT - Lazertinib	PFS
LU21-16 (NCT05277701)	II	Uncommon mEGFR NSCLC*	- Lazertinib	ORR
LU20-15	II	mEGFR NSCLC with BM, EGFR TKI-treated	- Lazertinib	Intracranial ORR
LU21-17	II	mEGFR NSCLC with BM, osimertinib-treated	- Lazertinib+pemetrexed/carboplatin	Intracranial ORR
LU21-01	II	mEGFR NSCLC with LM	- Lazertinib+pemetrexed	Post-LM OS

BM, brain metastases; EGFR, epidermal growth factor receptor; LM, leptomeningeal metastases; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; SBRT, Stereotactic Body Radiation Therapy.
*Patients with uncommon EGFR mutations (e.g., G719X, S768I, L861Q, G719X+S768I, G719X+L861Q, L861Q+S768I, L747S, S720A, E709A, exon 18 deletion) without common EGFR mutations, including exon 19 deletion, L858R, exon 20 insertion, or T790M.

evaluates the safety and efficacy of lazertinib with or without early local ablative radiation therapy in metastatic EGFR-mutant NSCLC patients with synchronous oligometastatic lesions.[23] LU21-16 (NCT05277701) is another phase II trial aimed to discover the efficacy of lazertinib in NSCLC patients with uncommon EGFR mutations.[24]

Several studies are ongoing to evaluate the intracranial efficacy of lazertinib based on its favorable blood-brain barrier (BBB) penetrating efficacy observed in preclinical and clinical studies. LU20-15 is recruiting EGFR-mutant NSCLC patients with brain metastases who had progressed on prior EGFR TKI treatments.[25] LU21-17 is assessing the efficacy of lazertinib combined with pemetrexed/carboplatin on EGFR-mutant NSCLC patients with asymptomatic brain metastases who had failed on osimertinib.[26] LU21-01 is designed to combine lazertinib with pemetrexed for EGFR-mutant NSCLC patients with leptomeningeal carcinomatosis.[27]

Combination approaches: amivantamab

Amivantamab (amivantamab-vmjw; Rybrevant™) is a bispecific monoclonal antibody targeting EGFR and mesenchymal-epithelial transition factor (MET).[28] By binding to extracellular domains of each receptor, amivantamab can inhibit ligand binding, promote receptor-antibody complex endocytosis and degradation, and induce Fc-dependent trogocytosis by macrophages and antibody-dependent cellular cytotoxicity by natural killer cells.[29] Synergistic inhibition of the EGFR by targeting the receptor's extracellular domains with amivantamab and the kinase domain with lazertinib hypothetically could elicit more potent inhibition of the EGFR pathway and could hold the potential to delay resistance.[30]

Based on this rationale, the efficacy of lazertinib in combination with amivantamab for EGFR-mutant NSCLC patients is being evaluated in several studies.

CHRYSALIS-1 (NCT02609776) has recruited patients with EGFR-mutant NSCLC who had progressed on available standard treatments. Part 1 dose-escalation determined the recommended phase 2 combination dose of 1050 mg amivantam-

ab (1400 mg if bodyweight ≥80 kg) and 240 mg lazertinib.[31] A distinct adverse event related to amivantamab was infusion-related reactions, mostly occurring on C1D1, which were managed by splitting the first dose (half dose on C1D1 and remainder on C1D2) and pre-medication with steroids, antihistamine, and antipyretics.[32] The combination therapy group reported higher incidences of rash (78%) and paronychia (42%), compared to the LASER201 group.[17,31] An interim analysis reported an improved outcome in the amivantamab+lazertinib combination group, compared to the amivantamab monotherapy group, for patients who had progressed on osimertinib but were chemotherapy-naïve: ORR of 36% (95% CI, 22–51) vs. 19% (95% CI, 12–27) and DoR of 9.6 months (95% CI, 5.3–NR) vs. 5.9 months (95% CI, 4.2–12.6), at a median follow-up duration of 11.1 and 6.9 months, respectively.[33] Patients with osimertinib-resistance mutations or amplifications in EGFR/MET identified by next-generation sequencing in either ctDNA or tumor biopsy or high immunohistochemistry staining for EGFR/MET were more likely to benefit from combination therapy.[34] However, further investigations are warranted on biomarker studies.

CHRYSALIS-2 (NCT04077463) is a phase I/Ib trial assessing the efficacy and safety of lazertinib alone (dose escalation) or in combination with amivantamab or combination with amivantamab and platinum doublet chemotherapy (dose expansion).[30] Interim results have been published for cohort A, EGFR-mutant NSCLC patients who had progressed on osimertinib and platinum-based chemotherapy.[35] Combination treatment with lazertinib plus amivantamab led to an ORR of 32% (95% CI, 16–52), and safety profiles were consistent with previous reports.[33]

MARIPOSA-1 (NCT04487080) is a multicenter, randomized, phase III trial comparing three experimental arms in treatment-naïve, EGFR-mutant NSCLC patients: amivantamab+lazertinib (arm A) vs. osimertinib (arm B) vs. lazertinib (arm C).[36,37] MARIPOSA-2 (NCT04988295) is combining platinum doublet chemotherapy to targeted agents in EGFR-mutant NSCLC patients who had progressed after osimertinib: amiva

ntamab+lazertinib+pemetrexed/carboplatin (arm A) vs. pemetrexed/carboplatin (arm B) vs. amivantamab+pemetrexed/carboplatin (arm C).[38,39] The primary endpoint is the PFS in both studies, with planned sample sizes of 1000 and 500 patients, respectively.

The combination of lazertinib and amivantamab has shown encouraging activity in EGFR-mutant NSCLC patients in various settings. Final analyses on the combination approach (CHRYSALIS-1,2 and MARIPOSA-1,2) are highly anticipated.

OSIMERTINIB–A FRIEND OR FOE?

EGFR is abundant in keratinocytes in the basal layer of the epidermis and undifferentiated keratinocytes proliferating in the external root sheath of hair follicles.[40] Hence, EGFR inhibition with TKI treatments can severely disrupt the skin homeostasis and ultimately lead to cutaneous toxicity, such as xerosis, pruritus, acneiform or papulopustular eruption, nail changes, and paronychia.[41] Such adverse events have been reported with EGFR TKI treatments, including osimertinib and lazertinib.

In a preclinical study, lazertinib demonstrated a high IC_{50} for EGFR WT cells, implying that it poses a lower likelihood of manifesting off-target toxicities, including rash and paronychia.[15] Lazertinib-treated mice showed minimal skin manifestation, while osimertinib-treated mice showed conspicuous skin changes, including keratosis on the face, neck, and abdomen.

Nonetheless, the actual incidence of skin-related adverse events, such as rash, pruritus, and paronychia, reported from patients did not differ between the two drugs (Table 2). Considering the interpretative challenges of cross-trial comparisons, further research on the incidence and management of adverse events related to lazertinib is warranted.

In addition, there are also concerns for cardiotoxicities, such as cardiac failure, atrial fibrillation, QT prolongation, myocardial infarction, and pericardial effusion, regarding osimertinib and other EGFR TKIs. Specifically, the risk of cardiac adverse events associated with osimertinib is a concern for clinicians.[42,43] The reported odds ratio for cardiac failure, atrial fibrillation, QT prolongation, myocardial infarction, and pericardial effusion when comparing osimertinib and other EGFR-TKIs were 2.2 (95% CI, 1.5–3.2), 2.1 (95% CI, 1.3–3.5), 6.6 (95% CI, 3.4–12.8), 1.2 (95% CI, 0.6–2.3), and 1.6 (95% CI, 0.8–3.3), respectively.[44]

Notwithstanding, the causal relationship between osimertinib and cardiac failure and the underlying mechanism thereof are not explicitly understood.[45] A proposed mechanism suggests that the inhibition of ERBB2 or HER2 and the AMPK pathway leads to reduced contractility, mitochondrial energy depletion, and cardiomyocyte apoptosis. Meanwhile, researchers have shown that lazertinib selectivity for HER2 over EGFR was 275-fold, compared to 6.7-fold for osimertinib, which implies that lazertinib has lower cardiotoxicity.[46]

Consistent with this background, lazertinib has been found to exert minimal effects on cardiac function in both preclinical and clinical studies.[46] No patients experienced clinically significant QT prolongation or decreased left ventricular ejection fraction. Considering that lazertinib demonstrated comparable anti-tumor efficacy to osimertinib, it may be considered a relatively safer option in terms of cardiotoxicity.[47]

Lastly, NSCLC patients with oncogenic-driven mutations such as EGFR are characterized by a high predilection for brain metastases, compared to unselected patients.[48,49] Brain metastasis is associated with deleterious effects on the patient's quality of life and survival,[50,51] highlighting a need for novel TKI with improved intracranial efficacy. Although osimertinib has an improved BBB penetration, compared to early-generation EGFR TKIs,[52] a significant proportion of patients (17%–20%) still experience disease progression in the brain after osimertinib treatment.[53,54] Lazertinib is not a substrate of BCRP and only a weak substrate of MDR1,[55] as opposed to osimertinib, which is a substrate of both BCRP and MDR1.[56] In LASER201, lazertinib demonstrated an encouraging intracranial activity with ORR of 87.5% and DCR of 100.0%, comparable to osimertinib from the AURA3 trial, which reported an intracranial ORR of 70.0% and DCR of 93.9%.[52] Nonetheless, the sample sizes in these studies were limited, and real-world data with a larger number of patients on lazertinib should be investigated.

CONCLUSIONS

Despite the remarkable advances in targeted therapies for NSCLC with oncogenic mutations, the area of unmet need still remains. Lazertinib, a novel third-generation EGFR TKI, effectively inhibited extracranial lesions and demonstrated encouraging intracranial penetration and favorable safety profiles, including reduced skin or cardiac adverse events compared to osimertinib. Accordingly, it could be considered a sound option for the treatment of EGFR-mutant NSCLC patients. However, confirmatory phase 3 data or direct head-to-head comparisons with other EGFR TKIs are needed to finalize its position in the treatment scheme of EGFR-mutant NSCLC patients. The results from ongoing studies on front-line settings and in combination with amivantamab or cytotoxic chemotherapies are highly anticipated.

AUTHOR CONTRIBUTIONS

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