

Limertinib: The third-generation EGFR-TKI developed in China for the treatment of EGFR-Mutated non-small cell lung cancer

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Non-small cell lung cancer (NSCLC) remains the dominant form of lung cancer and one of the most serious threats to global cancer health. For patients whose tumors harbor epidermal growth factor receptor (EGFR) mutations, targeted therapy has transformed clinical care from a chemotherapy-dominated model into a molecularly guided treatment era. Yet resistance, brain metastases, and long-term disease control continue to challenge both patients and clinicians.

Limertinib, also known as ASK120067 and marketed in China as Aoyixin®, is a third-generation EGFR tyrosine kinase inhibitor (EGFR-TKI) independently developed in China (Figure 1). Its approval for both EGFR T790M-positive NSCLC after prior EGFR-TKI therapy and first-line treatment of EGFR-sensitive mutation-positive advanced NSCLC marks an important milestone for China's innovative oncology drug development.

MECHANISM OF ACTION AND PRECLINICAL DEVELOPMENT

Limertinib is an orally administered, irreversible, third-generation EGFR-TKI designed to inhibit both classical EGFR-sensitive mutations and the EGFR T790M resistance mutation. EGFR exon 19 deletion and exon 21 L858R mutation are common driver alterations in NSCLC. These mutations act like a jammed accelerator pedal, continuously stimulating tumor-cell growth and survival. Earlier-generation EGFR inhibitors can initially slow this signal, but resistance frequently emerges.¹

One of the most important resistance mechanisms is the T790M mutation. This mutation changes the structure of the EGFR kinase domain and weakens the binding of first- or second-generation EGFR-TKIs. Limertinib was designed to overcome this molecular barrier by targeting mutant EGFR more effectively while reducing unnecessary inhibition of wild-type EGFR. This selectivity is clinically important because wild-type EGFR inhibition in normal tissues is associated with adverse effects such as rash and diarrhea.

Preclinical development showed that limertinib had potent antitumor activity in EGFR-mutant models, including models carrying resistant mutations. Its central nervous system penetration also attracted attention because brain metastases are a frequent and difficult complication in EGFR-mutated NSCLC. These mechanistic features provided the rationale for clinical testing in both acquired T790M-positive disease and first-line EGFR-sensitive mutation-positive disease.

CLINICAL EFFICACY: PIVOTAL PHASE IIB AND PHASE III FINDINGS

Although the public clinical development story of limertinib is mainly supported by a pivotal Phase IIB study and a later Phase III first-line trial rather than a conventional Phase IIa/IIb sequence, its clinical evidence can still be understood in two stages: proof of activity in resistant disease and expansion into first-line therapy.

In the pivotal Phase IIB study, limertinib was evaluated in patients with locally advanced or metastatic EGFR T790M-mutated NSCLC who had progressed after previous EGFR-TKI therapy. This was a population with clear unmet clinical need because T790M-positive resistance often limits the benefit of earlier EGFR-targeted drugs. In 301 patients, limertinib achieved an objective response rate of 68.8% and a disease control rate of 92.4% by independent review. The median progression-free survival reached 11.0 months, and the median duration of response was 11.1 months.

Importantly, limertinib also showed intracranial activity. Among 99 patients with CNS metastases, the ORR was 64.6%; among the 41 patients with assessable CNS lesions, the confirmed CNS-ORR was 56.1%, supporting the

intracranial activity of limertinib. This matters because the brain can act like a protected "sanctuary site," where many anticancer drugs have difficulty reaching effective concentrations.²

The first-line Phase III trial further expanded the clinical value of limertinib. In treatment-naïve patients with locally advanced or metastatic NSCLC carrying EGFR-sensitive mutations, limertinib was compared with gefitinib. Median progression-free survival was 20.7 months with limertinib versus 9.7 months with gefitinib, corresponding to a 56% reduction in the risk of disease progression or death. Among patients with baseline CNS lesions, median CNS progression-free survival was 20.7 months with limertinib compared with 7.1 months with gefitinib.³

Updated overall survival data reported at ELCC 2026 further strengthened the survival narrative. Limertinib achieved a median overall survival of 43.3 months compared with 34.5 months for gefitinib, extending survival by nearly nine months and reducing the risk of death by 22%. In patients with brain metastases, the updated data suggested a 30% reduction in the risk of death, highlighting the drug's potential role in long-term disease control for this high-risk population.⁴

LIMITATIONS AND KNOWLEDGE GAPS

Despite these encouraging findings, several questions remain. First, the first-line Phase III trial used gefitinib, a first-generation EGFR-TKI, as the comparator. While this clearly demonstrates superiority over an earlier standard, it does not directly answer how limertinib compares with other third-generation EGFR-TKIs such as osimertinib, aumolertinib, or furmonertinib.

Second, resistance to third-generation EGFR-TKIs remains inevitable for many patients. The mechanisms of resistance after limertinib require further clarification, including MET amplification, EGFR C797S mutation, histologic transformation, and activation of bypass signaling pathways. Understanding these mechanisms will be essential for designing rational combination therapies.

Third, although updated survival and CNS data are promising, longer follow-up and real-world studies are still needed. Outcomes such as quality of life, duration of intracranial control, optimal treatment sequencing, and post-progression strategies will determine how limertinib is positioned in daily practice.

COMPARATIVE CONSIDERATIONS AND SAFETY PROFILE

Limertinib enters an increasingly competitive third-generation EGFR-TKI landscape. In China, the directly relevant options for common EGFR-sensitizing mutations and/or acquired T790M include osimertinib, aumolertinib, furmonertinib, befotertinib, rezivertinib, rilertinib, zorifertinib, and limertinib. Across pivotal first-line trials, these agents have generally achieved a median progression-free survival of approximately 20 months, compared with 9-14 months for first-generation comparators. Osimertinib has the broadest global evidence base, whereas aumolertinib and furmonertinib are established China-developed first-line alternatives. Befotertinib, rezivertinib, and rilertinib further expand the domestically available T790M-directed options, while zorifertinib has a specific first-line indication for patients with CNS metastases. Limertinib is supported by evidence spanning post-EGFR-TKI T790M-positive disease and randomized first-line therapy, together with intracranial activity and updated overall survival data.⁵

Safety is another key consideration. In the pivotal Phase IIB study, grade ≥3 treatment-related adverse events occurred in 34.6% of patients, with diarrhea



Figure 1. Limertinib approved as an innovative drug for the treatment of NSCLC in China

treatment of adults with locally advanced or metastatic NSCLC whose disease progressed during or after prior EGFR-TKI therapy and in whom an EGFR T790M mutation has been confirmed. This inclusion may improve patient access and reduce the financial burden associated with long-term targeted therapy.

Future development may focus on three directions. The first is global expansion, including international registration strategies and broader clinical collaboration. The second is combination therapy, especially with MET inhibitors, anti-angiogenic drugs, chemotherapy, or next-generation agents designed to overcome EGFR-TKI resistance. The third is precision sequencing, in which molecular testing at baseline and progression guides when and how limertinib should be used.

For patients with EGFR-mutated NSCLC, limertinib provides a new source of hope. Its

(13.0%), hypokalemia (4.3%), anemia (4.0%), and rash (3.3%) being the most common. One patient developed grade 2 treatment-related interstitial lung disease (1/301; 0.3%). Treatment-related adverse events led to dose interruption in 24.6% of patients and permanent discontinuation in 2.0%, with no treatment-related deaths reported.² In the first-line Phase III study, grade ≥ 3 treatment-related adverse events and treatment-related serious adverse events occurred in 25% and 5% of patients receiving limertinib, respectively. No interstitial lung disease was reported, and approximately 1.8% of patients permanently discontinued treatment because of adverse events.³ Depending on the severity and persistence of toxicity, management may involve temporary treatment interruption, dose reduction after recovery, or permanent discontinuation. The recommended reduced dose is 80 mg once daily in the first-line setting and 80 mg twice daily in the post-resistance setting. Treatment should be interrupted when interstitial lung disease is suspected and permanently discontinued if the diagnosis is confirmed.

Nevertheless, direct head-to-head comparisons among third-generation EGFR-TKIs are almost absent. An updated network meta-analysis found no statistically significant differences in progression-free survival among the evaluated third-generation agents. Therefore, cross-trial observations should not be interpreted as evidence that limertinib is uniformly superior. Instead, it should be positioned as an additional evidence-based option, with treatment selection guided by mutation subtype, CNS involvement, agent-specific toxicity, maturity of overall survival evidence, accessibility, and reimbursement.

GLOBAL FUTURE

Limertinib represents more than a single new drug. It reflects the growing strength of China's innovative drug development, from molecular design and preclinical discovery to pivotal clinical trials and regulatory approval. Effective January 1, 2026, limertinib was included as a negotiated Category B drug in China's 2025 National Reimbursement Drug List. Reimbursement is limited to (1) first-line treatment of adults with locally advanced or metastatic NSCLC harboring an EGFR exon 19 deletion or exon 21 L858R substitution, and (2)

efficacy in systemic disease, encouraging CNS activity, and favorable safety profile make it a meaningful addition to the targeted therapy toolbox. As longer-term data accumulate, limertinib may help reshape the treatment landscape for EGFR-mutated NSCLC in China and potentially beyond.

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AUTHOR CONTRIBUTIONS

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DECLARATION OF INTERESTS

The authors declare no competing interests.