Comprehensive Clinical Evaluation of ALK Inhibitors for First-Line Treatment of Patients with ALK-Positive Advanced Non-Small Cell Lung Cancer: Postprint

Authors: Ye Ziqi, Zhou Yujun, Liu Liu, Zhang Yanfang, Hong Yun, Rao Yuefeng, Yuefeng Rao

Date: 2025-09-01T00:16:37+00:00

Abstract

Background Currently, six ALK inhibitors (including crizotinib, alectinib, ceritinib, brigatinib, ensartinib, and lorlatinib) have been approved for first-line treatment of ALK-positive advanced non-small cell lung cancer, yet clinical decision-making remains challenging.

Objective To comprehensively evaluate these six ALK inhibitors across five dimensions—safety, efficacy, pharmaceutical characteristics, economy, and other attributes—to provide an evidence-based foundation for clinical medication decisions.

Methods Data required for evaluation regarding drug efficacy, safety, pricing, etc., were collected from database inception to December 2024, sourced from drug package inserts, National Comprehensive Cancer Network (NCCN), Chinese Society of Clinical Oncology (CSCO) and European Society for Medical Oncology (ESMO) guidelines, network meta-analyses, as well as authoritative platforms including the Zhejiang Province Two-Designated Institutions Medical Security Information Platform, National Medical Insurance Information Database, and Center for Drug Evaluation of the National Medical Products Administration. Based on the *Quick Guide for Drug Evaluation and Selection in Chinese Medical Institutions (2nd Edition)*, a comprehensive evaluation system comprising five dimensions (safety, efficacy, pharmaceutical characteristics, economy, and other attributes) was constructed using the Delphi method to conduct a thorough assessment of the six ALK inhibitors: crizotinib, alectinib, ceritinib, brigatinib, ensartinib, and lorlatinib. An expert panel of nine members with senior professional titles and over five years of experience in relevant fields underwent six rounds of discussion to finalize evaluation criteria

(three rounds to determine evaluation items and another three rounds to determine score allocation for each item). Final results were independently evaluated and statistically analyzed by a two-person group according to the established evaluation standards for the six ALK inhibitors.

Results The comprehensive evaluation ranking of the six ALK inhibitors was: brigatinib (85.5 points) > alectinib (82.7 points) > lorlatinib (82.2 points) > ensartinib (78.8 points) > ceritinib (77.4 points) > crizotinib (76.5 points). The optimal agent for core dimensions (safety/efficacy/pharmaceutical characteristics) was alectinib (71.0 points). Generational trend evaluation results showed: second generation > third generation > first generation (except for ceritinib/ensartinib); core dimension generational trend evaluation results showed: third generation > second generation > first generation (except for alectinib/ceritinib).

Conclusion This study confirms that different ALK inhibitors each possess distinct advantages across the five dimensions of efficacy, safety, pharmaceutical characteristics, economy, and other attributes. Brigatinib demonstrated higher comprehensive evaluation scores than other ALK inhibitors, while alectinib showed higher core dimension scores than other ALK inhibitors. Second- and third-generation agents demonstrated superior overall performance. These evaluation results can provide important reference for medical institutions to select individualized treatment regimens according to clinical needs.

Full Text

Comprehensive Evaluation of ALK Inhibitors in The First-Line Treatment of Patients with ALK-Positive Non-Small Cell Lung Cancer

YE Ziqi, ZHOU Yujun, LIU Liu, ZHANG Yanfang, HONG Yun, RAO Yuefeng*

Department of Clinical Pharmacy, the First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310003, China

*Corresponding author: RAO Yuefeng, Chief pharmacist/Doctoral supervisor; E-mail: raoyf@zju.edu.cn

Abstract

Background: Currently, six ALK inhibitors (including crizotinib, alectinib, ceritinib, brigatinib, ensartinib, and lorlatinib) have been approved for first-line treatment of ALK-positive advanced non-small cell lung cancer (NSCLC), yet clinical decision-making remains challenging. **Objective:** This study aimed to comprehensively evaluate these six ALK inhibitors across five dimensions (safety, efficacy, pharmaceutical properties, drug economy, and other properties) to provide evidence-based support for clinical drug selection. **Methods:** Data collected from database inception through December 2024 were sourced from drug labels, guidelines by the National Comprehensive Cancer Network

(NCCN), Chinese Society of Clinical Oncology (CSCO), and European Society for Medical Oncology (ESMO), network meta-analyses, as well as authoritative platforms including Zhejiang Provincial Two-Designated Healthcare Security Information Database, the National Healthcare Security Administration Information Database, and the National Medical Products Administration Drug Evaluation Center, covering information essential for evaluating drug efficacy, safety, and pricing. Based on the "Rapid Guideline for Drug Evaluation and Selection in Chinese Medical Institutions (2nd Edition)," a comprehensive evaluation system comprising five dimensions (safety, efficacy, pharmaceutical properties, drug economy, and other properties) was developed using the Delphi method to assess six ALK inhibitors (crizotinib, alectinib, ceritinib, brigatinib, ensartinib, and lorlatinib).

A nine-member expert panel with senior titles and over five years of relevant experience conducted six discussion rounds to finalize evaluation criteria (three rounds to define items and three to assign weights). Final scoring and statistical analysis were performed independently by a two-author team according to the established standards. **Results:** The overall ranking of the six ALK inhibitors was: brigatinib (85.5 points) > alectinib (82.7 points) > lorlatinib (82.2 points) > ensartinib (78.8 points) > ceritinib (77.4 points) > crizotinib (76.5 points). Alectinib scored highest in the core dimensions (safety, efficacy, and pharmaceutical properties) (71.0 points). Generational trend analysis revealed that second-generation inhibitors outperformed third-generation and first-generation drugs (except for ceritinib/ensartinib), while in core dimensions, third-generation inhibitors scored higher than second-generation and first-generation drugs (except for alectinib/ceritinib). **Conclusion:** This study demonstrates that different ALK inhibitors exhibit distinct advantages across the five evaluated dimensions. Brigatinib achieved the highest overall score, while alectinib ranked highest in core dimensions. Second- and third-generation drugs generally performed better, providing valuable evidence for individualized treatment selection based on clinical needs.

Keywords: ALK inhibitors; Non-small cell lung cancer; Comprehensive evaluation; Clinical rational drug use; Individualized treatment

1 Materials and Methods

1.1 Data Collection

Data were collected from database inception through December 2024 from drug labels (crizotinib: Pfizer Investment Co., Ltd.; alectinib: Shanghai Roche Pharmaceuticals Co., Ltd.; ceritinib: Beijing Novartis Pharmaceutical Co., Ltd.; brigatinib: Takeda [China] International Trading Co., Ltd.; ensartinib: Betta Pharmaceuticals Co., Ltd.; lorlatinib: Pfizer Investment Co., Ltd.), the *NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer (2024.V4)* [6], *CSCO Guidelines for Diagnosis and Treatment of Non-Small Cell Lung Cancer (2024 Edition)* [7], *ESMO Clinical Practice Guidelines for*

Diagnosis and Treatment of Non-Small Cell Lung Cancer (2023 Edition) [8], network meta-analysis by Ma et al. [9], and authoritative platforms including Zhejiang Provincial Two-Designated Healthcare Security Information Platform (https://med.ybj.zj.gov.cn), National Healthcare Security Information Database (https://code.nhsa.gov.cn), and National Medical Products Administration Drug Evaluation Center (https://www.cde.org.cn) regarding drug efficacy, safety, and pricing data. Clinical study inclusion criteria were: (1) reporting at least one primary endpoint including overall survival (OS) or objective response rate (ORR); (2) randomized controlled trials in Chinese or English; (3) excluding case reports, studies with sample size <50, and studies without control groups. Two researchers independently extracted required data.

1.2 Included Drugs

Currently, six ALK inhibitors are approved for first-line treatment of advanced ALK-positive NSCLC in China: crizotinib, ceritinib, alectinib, brigatinib, ensartinib, and lorlatinib. Except for crizotinib, none have generic or centralized procurement alternatives available. Given that clinical trials were all conducted with original drugs, this evaluation included six original drugs for comprehensive assessment.

1.3 Evaluation Method

Based on the *Rapid Guideline for Drug Evaluation and Selection in Chinese Medical Institutions (2nd Edition)* [5], which employs Mini Health Technology Assessments (Mini-HTA) combined with System of Objectified Judgement Analysis (SOJA), we established an evaluation system comprising five major dimensions: pharmaceutical properties, efficacy, safety, drug economy, and other properties, with pharmaceutical properties, efficacy, and safety as the three core dimensions. Dimension weights were determined jointly by the steering group and expert panel through the Delphi method. For specific scoring details and items not explicitly defined in the guideline (such as specific drug scoring for primary outcome indicators), this study organized a nine-member expert assessment team with senior titles and over five years of relevant experience, including three oncology experts, three pharmaceutical experts, two health economics experts, and one evidence-based medicine expert, to conduct systematic Delphi evaluation.

The process consisted of two phases: **Phase 1: Item Determination (3 rounds)**—(1) first round to determine core dimensions; (2) second round to define specific items under core dimensions; (3) third round to confirm the evaluation indicator list. **Phase 2: Score Allocation (3 rounds)**—(1) first round: experts completed anonymous scoring independently; (2) second round: consensus meeting held to discuss controversial scoring criteria; (3) third round: rescoring based on revision suggestions until approval rate >80% for each scoring standard. This study conducted multi-dimensional evaluation of included drugs

based on the evaluation criteria confirmed by multidisciplinary experts. The evaluation was completed independently by two researchers; significant scoring discrepancies were arbitrated by a third expert, with final results determined through discussion.

1.4 Evaluation Indicators

This study constructed an evaluation system from five dimensions: efficacy, safety, pharmaceutical properties, drug economy, and other properties.

1.4.1 Efficacy: Total Score 27 points, including:

(1) **Indication (5 points):** First choice in NCCN, ESMO, or CSCO guidelines = 5 points; second choice = 3 points; optional = 1 point.
(2) **Guideline recommendation (12 points):** Level I recommendation (Class A evidence = 12 points, Class B = 11 points, Class C and others = 10 points), Level II recommendation (Class A = 9 points, Class B = 8 points, Class C and others = 7 points), expert consensus recommendation (society-organized based on systematic review = 6 points, society-organized = 5 points, others = 4 points), systematic review/Meta-analysis (large sample/high quality = 3 points, small sample/low quality = 2 points, non-RCT systematic review = 1 point).
(3) **Clinical efficacy (10 points):** Based on network meta-analysis results from Ma et al. [9], using PFS as primary endpoint for ranking: optimal PFS = 6 points, other drugs scored with 0.2-point decremental intervals; using ORR as secondary endpoint: optimal ORR = 4 points, other drugs scored with 0.2-point decremental intervals.

1.4.2 Safety: Total Score 25 points, including:

(1) **Adverse drug reactions (ADRs) (8 points):** Moderate ADRs (CTCAE grades 1-2): Based on Ma et al. [9] network meta-analysis, ranking by incidence rate: lowest incidence = 3 points, others with 0.2-point decremental intervals; Severe ADRs (CTCAE grades 3-4): Based on comparative results, lowest incidence = 5 points, others with 0.2-point decremental intervals.
(2) **Special populations (11 points):** Pediatric use: 2 points (all approved = 2 points, >3 months = 1.9 points, >6 months = 1.8 points, >9 months = 1.7 points, >1 year = 1.6 points); Geriatric use: 1 point (approved = 1 point, caution = 0.5 points); Pregnancy: 1 point (first trimester approved = 1 point, second trimester = 0.8 points, third trimester = 0.5 points); Lactation: 1 point (approved = 1 point, caution = 0.5 points); Hepatic impairment: 3 points (severe = 3 points, moderate = 2 points, mild = 1 point); Renal impairment: 3 points (severe = 3 points, moderate = 2 points, mild = 1 point).
(3) **ADRs from drug interactions (3 points):** No dose adjustment needed = 3 points, dose adjustment required = 2 points, concurrent use prohibited

= 1 point.

(4) **Other factors (3 points):** Reversible ADRs = 1 point, no teratogenicity or carcinogenicity = 1 point, no special medication warnings = 1 point.

1.4.3 Pharmaceutical Properties: Total Score 28 points, including:

(1) **Pharmacological action (5 points):** Definite clinical efficacy, clear mechanism, innovative mechanism or target = 5 points; definite efficacy, clear mechanism = 4 points; moderate efficacy, unclear mechanism = 2 points; general efficacy, unclear mechanism = 1 point.

(2) **Pharmacokinetics (5 points):** Clear pharmacokinetics with complete parameters = 5 points; clear pharmacokinetics with incomplete parameters = 3 points; unclear pharmacokinetics or no related studies = 1 point.

(3) **Pharmaceutics and administration (12 points):** Active ingredients and excipients: 2 points (both clear = 2 points, one clear = 1 point); Specifications and packaging: 2 points (both suitable for clinical use and dose adjustment = 2 points, one suitable = 1 point); Dosage form: 2 points (oral/inhalation/topical = 2 points, subcutaneous/intramuscular injection = 1.5 points, intravenous infusion/injection = 1 point); Dosing: 2 points (fixed dose = 2 points, dose adjustment during treatment = 1.5 points, weight/BSA-based calculation = 1 point); Dosing frequency: 2 points ($ $1 time/day = 2 points, 2 times/day = 1.5 points, $ $3 times/day = 1 point); Convenience: 2 points (self-administration without assistance = 2 points, self-administration after training or with help = 1.5 points, healthcare professional administration = 1 point).

(4) **Storage conditions (4 points):** Storage: 3 points (room temperature = 3 points, cool storage = 2 points, refrigeration/freezing = 1 point); Light protection: 1 point (no light protection needed = 1 point).

(5) **Shelf life (2 points):** $ $60 months = 2 points, $ $36 to <60 months = 1.5 points, $ $24 to <36 months = 1 point, $ $12 to <24 months = 0.5 points, <12 months = 0.25 points.

1.4.4 Drug Economy: Total Score 10 points. Based on average daily treatment cost assessment, comparing differences in average daily treatment costs between evaluated drugs and alternative drugs for main indications. The drug with lowest daily treatment cost receives 10 points; other drugs' scores = (lowest daily treatment cost / evaluated drug's daily treatment cost) × 7.

1.4.5 Other Properties: Total Score 10 points, including:

(1) **Inclusion in National Reimbursement Drug List (2024)** [10]: Class A without payment conditions = 3 points, Class A with conditions = 2.5 points, Class B without conditions = 2 points, Class B with conditions = 1.5 points, not included = 1 point.

(2) **Inclusion in National Essential Medicines List (2018 Edition)** [11]: Essential medicine without special requirements = 3 points, essential medicine with special requirements = 2 points, not essential = 1 point.
(3) **National centralized procurement winner**: 1 point if included, 0 points if not.
(4) **Consistency evaluation**: Original/reference drug = 1 point, generic passing consistency evaluation = 0.5 points.
(5) **Manufacturer status**: Top 50 global pharmaceutical companies in 2024 = 1 point, not top 50 = 0 points.
(6) **Global availability**: Marketed both internationally and domestically = 1 point, domestic only = 0 points.

2 Results

2.1 Efficacy Evaluation

Indications: All six ALK inhibitors are approved for ALK-positive advanced NSCLC, but guideline recommendations differ. The *NCCN Guidelines for NSCLC (2024.V4)* [6] recommends five ALK inhibitors (crizotinib, ceritinib, alectinib, brigatinib, and lorlatinib). The *ESMO Guidelines for NSCLC (2023 Edition)* [8] also recommends five ALK inhibitors (same as NCCN), with alectinib, brigatinib, and lorlatinib as preferred options. The *CSCO Guidelines for NSCLC (2024 Edition)* [7] recommends all six ALK inhibitors, with alectinib as the optimal recommendation. Therefore, alectinib, brigatinib, and lorlatinib each received 5 points, while crizotinib, ceritinib, and ensartinib received 3 points.

Guideline recommendations: All six ALK inhibitors received Level I recommendation (Class 1A evidence) in the *CSCO Guidelines for NSCLC (2024 Edition)* [7], thus each received 12 points.

Clinical efficacy: Based on Ma et al. [9] network meta-analysis using PFS as primary endpoint and ORR as secondary endpoint: PFS scores were lorlatinib (6 points) > alectinib (5.8 points) > ensartinib (5.6 points) > brigatinib (5.4 points) > crizotinib (5.2 points) > ceritinib (5 points). ORR scores were alectinib (4 points) > lorlatinib (3.8 points) > brigatinib (3.6 points) > ensartinib (3.4 points) > ceritinib (3.2 points) > crizotinib (3 points). Comprehensive efficacy scores: alectinib and lorlatinib (both 26.8 points) > brigatinib (26 points) > ensartinib (24 points) > ceritinib and crizotinib (both 23.2 points).

2.2 Safety Evaluation

ADRs: Based on Ma et al. [9] network meta-analysis: moderate ADR scores were crizotinib (3 points) > brigatinib and lorlatinib (both 2.8 points) > ceritinib and ensartinib (both 2.6 points) > alectinib (2.4 points). Severe ADR scores were alectinib (5 points) > crizotinib (4.8 points) > brigatinib (4.6 points) > ensartinib (4.4 points) > lorlatinib (4.2 points) > ceritinib (4 points). Combined

ADR scores: crizotinib (7.8 points) > alectinib and brigatinib (both 7.4 points) > lorlatinib and ensartinib (both 7 points) > ceritinib (6.6 points).

Special populations: None of the six ALK inhibitors are approved for pediatric, pregnant, or lactating women. All six can be used in elderly patients, and none require dose adjustment for hepatic or renal impairment. Therefore, all six drugs received 7 points in this category, with specific scores shown in Table 1 .

Drug interaction ADRs: When ADRs from drug interactions occur, alectinib and ensartinib require no dose adjustment (3 points), brigatinib requires dose adjustment (2 points), while lorlatinib, ceritinib, and crizotinib prohibit concurrent use with drugs having adverse interactions (1 point).

Other factors: All six ALK inhibitors have reversible ADRs and no teratogenicity or carcinogenicity. Crizotinib has medication warnings (risk of heart failure and visual loss in pediatric patients) and received 0 points, while alectinib, ceritinib, lorlatinib, brigatinib, and ensartinib have no warnings (1 point each).

Comprehensive safety scores: alectinib (18.4 points) > ensartinib (18 points) > brigatinib (17.4 points) > lorlatinib (16 points) > crizotinib (15.8 points) > ceritinib (15.6 points).

2.3 Pharmaceutical Properties Evaluation

Pharmacological action: All six ALK inhibitors have definite efficacy and clear mechanisms. Regarding innovation: crizotinib as first-generation ALK inhibitor received 4.6 points; ceritinib, alectinib, ensartinib, and brigatinib as second-generation inhibitors each received 4.8 points; lorlatinib as third-generation drug received 5 points.

Pharmacokinetics: Crizotinib, alectinib, and lorlatinib have complete pharmacokinetic parameters in their labels (5 points each). Ceritinib (lacking relative bioavailability, peak concentration, and AUC), ensartinib (lacking relative bioavailability), and brigatinib (lacking relative bioavailability) received 3 points each due to incomplete parameters, as shown in Table 2 .

Pharmaceutics and administration: Ensartinib did not list excipients (1 point), while the other five ALK inhibitors had complete ingredient information (2 points each). All six had suitable specifications and packaging for clinical use and dose adjustment (2 points each). All were oral formulations (2 points each). For dosing frequency: crizotinib and alectinib require twice-daily dosing (1.5 points each), while ceritinib, ensartinib, brigatinib, and lorlatinib require once-daily dosing (2 points each). All six ALK inhibitors can be self-administered (2 points each), as detailed in Table 3 .

Storage conditions: All six ALK inhibitors can be stored at room temperature (3 points each), as shown in Table 3.

Shelf life: Ceritinib and ensartinib have 24-month shelf lives (1 point each), while the other four drugs have 36-month shelf lives (1.5 points each), as shown in Table 3.

Comprehensive pharmaceutical properties scores: lorlatinib (27.5 points) > brigatinib (26.8 points) > alectinib (25.8 points) > ceritinib and ensartinib (both 24.8 points) > crizotinib (24.6 points).

2.4 Drug Economy Evaluation

Based on average daily treatment cost calculations: brigatinib (10 points) > ensartinib (8.5 points) > ceritinib (8.3 points) > crizotinib (7.4 points) > lorlatinib (6.4 points) > alectinib (6.2 points), as shown in Table 4 .

2.5 Other Properties Evaluation

Other properties evaluation included whether drugs are reimbursed by medical insurance, essential medicines, centrally procured, original drugs, internationally marketed, and manufacturer ranking. Comprehensive results: crizotinib, ceritinib, alectinib, and lorlatinib (all 5.5 points) > brigatinib (5.3 points) > ensartinib (3.5 points), as shown in Table 5 .

3 Discussion

The overall ranking of six ALK inhibitors was: brigatinib (85.5 points) > alectinib (82.7 points) > lorlatinib (82.2 points) > ensartinib (78.8 points) > ceritinib (77.4 points) > crizotinib (76.5 points). Alectinib ranked highest in core dimensions (safety/efficacy/pharmaceutical properties) (71.0 points), as shown in Table 6 .

Among the six ALK inhibitors, crizotinib is first-generation; ceritinib, alectinib, ensartinib, and brigatinib are second-generation; and lorlatinib is third-generation. Generational evaluation showed: (1) **Efficacy:** Third-generation (lorlatinib 26.8 points) > second-generation (ensartinib 24.0 points, brigatinib 26.0 points) > first-generation (crizotinib 23.2 points) (except alectinib/ceritinib); (2) **Safety:** Second-generation (alectinib 18.4 points, ensartinib 18.0 points, brigatinib 17.4 points) > third-generation (lorlatinib 16.0 points) > first-generation (crizotinib 15.8 points) (except ceritinib); (3) **Pharmaceutical properties:** Third-generation (lorlatinib 27.5 points) > second-generation (ceritinib 24.8 points, alectinib 25.8 points, ensartinib 24.8 points, brigatinib 26.8 points) > first-generation (crizotinib 24.6 points); (4) **Drug economy:** Second-generation (ceritinib 8.3 points, ensartinib 8.5 points, brigatinib 10.0 points) > first-generation (crizotinib 7.4 points) > third-generation (lorlatinib 6.4 points) (except alectinib); (5) **Other properties:** Minimal generational differences (except ensartinib).

Overall generational trends: second-generation (alectinib 82.7 points, brigatinib 85.5 points) > third-generation (lorlatinib 82.2 points) > first-generation (crizo-

tinib 76.5 points) (except ceritinib/ensartinib). Core dimension evaluation: third-generation (lorlatinib 70.3 points) > second-generation (ensartinib 66.8 points, brigatinib 70.2 points) > first-generation (crizotinib 63.6 points) (except alectinib/ceritinib), as shown in Table 6 .

Significant progress has been made in first-line targeted therapy for ALK-positive advanced NSCLC. Currently, six original ALK inhibitors are approved in China and recommended by NCCN, ESMO, and CSCO guidelines. However, selecting optimal drugs remains challenging, particularly regarding differences between generations in efficacy, safety, and drug economy. This study established a five-dimensional evaluation system integrating safety, efficacy, pharmaceutical properties, drug economy, and other properties to provide evidence for clinical decision-making. Results showed brigatinib performed best in overall scoring (85.5 points), while alectinib ranked highest when focusing on the three core dimensions of drug evaluation (safety, efficacy, and pharmaceutical properties) (71.0 points), providing important reference for individualized treatment.

This scoring system enables quantitative ranking of six ALK inhibitors across multiple dimensions, providing objective basis for clinical decision-making. Specifically: alectinib scored higher than other ALK inhibitors in the three core dimensions; alectinib and lorlatinib scored higher than others in efficacy alone; lorlatinib scored higher in pharmaceutical properties; alectinib scored higher in safety; brigatinib scored higher in drug economy; and crizotinib, ceritinib, alectinib, and lorlatinib scored higher in other properties. In generational analysis, third-generation drugs scored higher than first- and second-generation drugs in efficacy, pharmaceutical properties, and other properties, with advantages in brain metastasis and resistance mutations (e.g., G1202R). Second-generation drugs scored higher in safety and drug economy. Notably, considering the high incidence of brain metastasis (35-50%) in ALK-positive NSCLC, second- and third-generation drugs significantly improved central nervous system lesion control through excellent blood-brain barrier penetration, with lorlatinib showing better efficacy for leptomeningeal metastasis than other ALK inhibitors.

While previous studies have evaluated ALK inhibitors, this study demonstrates methodological innovation: (1) strictly following the *Rapid Guideline for Drug Evaluation and Selection in Chinese Medical Institutions (2nd Edition)* [5] and employing structured Delphi method with multidisciplinary expert panel for multi-round validation, ensuring methodological rigor and clinical applicability; (2) constructing a systematic evaluation framework integrating multi-dimensional indicators tailored for first-line treatment of advanced ALK-positive NSCLC; (3) the Delphi-validated scoring system better meets clinical practice needs, providing methodological reference for similar studies.

This study's results apply to first-line treatment decision-making for ALK-positive advanced NSCLC, particularly for: (1) high brain metastasis burden patients: prioritize third-generation drugs (lorlatinib) with stronger blood-brain barrier penetration; (2) economically constrained patients: prioritize

second-generation drugs (e.g., brigatinib); (3) resistance mutation patients: third-generation drugs effective against G1202R and other mutations. The six evaluated ALK inhibitors maintain stable core indications for first-line treatment of advanced ALK-positive NSCLC without major changes since approval. By strictly limiting to first-line treatment scenarios, this study avoided interference from later-line or off-label use, ensuring reliability and timeliness. Although drug pricing has some volatility, this study's drug economy evaluation reflects current market reality under China's medical insurance policy: all six ALK inhibitors have been included in the *National Basic Medical Insurance, Work Injury Insurance, and Maternity Insurance Drug Catalog (2024)* [10] through national reimbursement negotiations, establishing relatively stable pricing systems.

To ensure long-term validity of conclusions, our team designed a dynamic update mechanism: (1) modular evaluation system design allows independent updates for single variables such as price adjustments or new safety data without reconstructing the entire framework; (2) establishing regular monitoring mechanisms to continuously track drug policy changes and update relevant data in subsequent studies. This design ensures both reliability of current results and 预留 s adequate space for future adjustments.

This study has limitations: (1) the expert discussion-based scoring system, though rigorously validated, carries subjective risk requiring cautious interpretation. Specifically: efficacy evaluation relies on network meta-analysis data, which may introduce bias due to lack of head-to-head trials; safety data also 来源于 network meta-analysis, with potential bias in ADR incidence assessment; (2) using PFS as primary efficacy indicator requires caution as immature OS data may affect final efficacy assessment; (3) evaluation results only reflect current evidence levels and require dynamic updates with changes in drug labels, guideline revisions, and price adjustments; (4) this study did not cover later-line treatment or special populations (e.g., hepatic impairment), requiring individualized assessment. These factors suggest clinical decisions should adjust conclusions based on latest evidence.

In summary, this study innovatively integrated multi-dimensional evidence and expert consensus to establish an ALK inhibitor evaluation system providing important reference for clinical practice. These results not only provide evidence-based basis for individualized treatment decisions but also offer methodological reference for medical insurance policy adjustment and similar studies.

Author Contributions: YE Ziqi conducted literature search, guideline review, and drafted the manuscript. ZHOU Yujun, LIU Liu, ZHANG Yanfang, and HONG Yun collected and organized relevant data. RAO Yuefeng was responsible for quality control, review, supervision of the entire research process, and manuscript revision.

Conflict of Interest: None declared.

References: [1] ADDEO A, TABBO F, ROBINSON T, et al. Precision

Medicine in ALK Rearranged NSCLC: A Rapidly Evolving Scenario [J]. Crit Rev Oncol Hematol, 2018, 122:150-156. DOI:10.1016/j.critrevonc.2017.12.015. [2] BAYLISS R, CHOI J, FENNELL D A, et al. Molecular mechanisms that underpin EML4-ALK driven cancers and their response to targeted drugs [J]. Cell Mol Life Sci, 2016, 73(6):1209-1224. DOI:10.1007/s00018-015-2117-6. [3] PENG L, ZHU L P, SUN Y L, et al. Targeting ALK rearrangements in NSCLC: current state of the art [J]. Front Oncol, 2022, 12:863461. DOI:10.3389/fonc.2022.863461. [4] WANG W Q, XU T, ZHANG J J, et al. A comprehensive clinical evaluation of first-line drugs for ALK-positive advanced non-small cell lung cancer [J]. J Thorac Dis, 2023, 15(4):1935-1947. DOI:10.21037/jtd-23-380. [5] ZHAO Z G, DONG Z J, LIU J P. Rapid Guideline for Drug Evaluation and Selection in Chinese Medical Institutions (2nd Edition) [J]. Herald of Medicine, 2023, 42(4):447-456. DOI:10.3870/j.issn.1004-0781.2023.04.001. [6] RIELY G J, WOOD D E, ETTLINGER D S, et al. Non-small cell lung cancer, version 4.2024, NCCN clinical practice guidelines in oncology [J]. J Natl Compr Canc Netw, 2024, 22(4):249-274. DOI:10.6004/jnccn.2204.0023. [7] Chinese Society of Clinical Oncology Guidelines Working Committee. CSCO Guidelines for Diagnosis and Treatment of Non-Small Cell Lung Cancer (2024 Edition) [M]. Beijing: People's Medical Publishing House, 2024:1-112. [8] HENDRIKS L E, KERR K M, MENIS J, et al. Oncogene-addicted metastatic non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up [J]. Ann Oncol, 2023, 34(4):339-357. DOI:10.1016/j.annonc.2022.12.009. [9] MA H C, LIU Y H, DING K L, et al. Comparative efficacy and safety of first-line treatments for advanced non-small cell lung cancer with ALK-rearranged: a meta-analysis of clinical trials [J]. BMC Cancer, 2021, 21(1):1278. DOI:10.1186/s12885-021-08895-8. [10] National Healthcare Security Administration, Ministry of Human Resources and Social Security. Notice on Issuing the National Reimbursement Drug List (2024 Edition) [A/OL]. (2024-11-27) [2025-04-01]. https://www.gov.cn/zhengce/zhengceku/202411/content_{6989859}.htm. [11] Notice on Issuing the National Essential Medicines List (2018 Edition) [A/OL]. (2018-09-30) [2025-04-01]. https://www.gov.cn/zhengce/zhengceku/2018-12/31/content_{5435470}.htm. [12] SETO T, HAYASHI H, SATOUCHI M, et al. Lorlatinib in previously treated anaplastic lymphoma kinase-rearranged non-small cell lung cancer: Japanese subgroup analysis of a global study [J]. Cancer Sci, 2020, 111(10):3726-3738. DOI:10.1111/cas.14576. [13] WEICKHARDT A J, SCHEIER B, BURKE J M, et al. Local ablative therapy of oligoprogressive disease prolongs disease control by tyrosine kinase inhibitors in oncogene-addicted non-small-cell lung cancer [J]. J Thorac Oncol, 2012, 7(12):1807-1814. DOI:10.1097/JTO.0b013e3182745948. [14] CACCESE M, FERRARA R, PILOTTO S, et al. Current and developing therapies for the treatment of non-small cell lung cancer with ALK abnormalities: update and perspectives for clinical practice [J]. Expert Opin Pharmacother, 2016, 17(17):2253-2266. DOI:10.1080/14656566.2016.1242578. [15] GEZELIUS E, PLANCK M, HAZEM B, et al. Intrathecal pemetrexed for leptomeningeal metastases in a patient with ALK-rearranged lung adenocarcinoma: a case report [J]. Cancer

Chemother Pharmacol, 2024, 95(1):6. DOI:10.1007/s00280-024-04735-8.
(Received: 2025-04-01; Revised: 2025-07-17) (Editor: LI Weixia)