Precision Medication 2 (2025) 100025

Contents lists available at ScienceDirect

Precision Medication

journal homepage: www.keaipublishing.com/en/journals/precision-medication/

A comprehensive evaluation of ALK inhibitors in the first-line treatment of patients with ALK-positive non-small cell lung cancer

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

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

ARTICLE INFO

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

ABSTRACT

There are currently six ALK inhibitors available for the first-line treatment of patients diagnosed with ALK-positive advanced non-small cell lung cancer (NSCLC). However, clinicians face challenges in selecting the most appropriate drug for treatment. We have collated pertinent evaluative evidence and undertaken a multifaceted assessment of the enrolled medications across five critical dimensions: safety, efficacy, pharmaceutical properties, drug economy, and other properties. This comprehensive analysis aims to furnish a robust foundation for the selection and clinical deployment of pharmaceuticals, thereby advocating for the judicious and rational utilization of medications in clinical practice. Upon conducting an exhaustive evaluation, we determined that the aggregate scores for all ALK inhibitors under review surpassed the threshold of 75 points, with brigatinib distinguishing itself as the top performer in terms of overall scoring. Considering that safety, efficacy, and pharmacological properties are paramount in the comprehensive clinical appraisal of pharmaceuticals, lorlatinib emerged with the highest score when evaluated solely on these three critical criteria. Through an extensive evaluation of ALK inhibitors, it has been determined that each ALK inhibitor possesses unique strengths across a spectrum of five distinct dimensions. Notably, when evaluating both the comprehensive scores across all five dimensions and the focused scores for the top three dimensions, third-generation inhibitors consistently ranked as the optimal choice. Healthcare organizations can leverage these findings to assess and select ALK inhibitors that align with their specific requirements, utilizing the comparative rankings and scores across various dimensions to inform their selection process.

Introduction

Lung cancer ranks among the leading malignancies in terms of both incidence and mortality. Non-small cell lung cancer (NSCLC) constitutes approximately 80 % of all lung cancer cases, with ALK-positive NSCLC representing a subset that ranges from 3 % to 7 % of these cases.[1] During the past two decades, the therapeutic landscape for NSCLC has transitioned from cytotoxic chemotherapy to precision-targeted therapies. Notably, molecular targeted therapies that address driver genes have exhibited substantial therapeutic efficacy and safety profiles, establishing themselves as a cornerstone of standard care for patients presenting with advanced NSCLC harboring driver gene mutations.

The ALK gene, a pivotal driver gene in NSCLC, is activated within tumor cells through three predominant mechanisms: chromosomal rearrangements leading to gene fusion, gene amplification, and point mutations.[2] Small-molecule tyrosine kinase inhibitors (TKIs) specifically designed to target ALK gene fusions have been developed and are now utilized in the therapeutic management of patients with ALK-positive NSCLC. At present, six ALK inhibitors have received regulatory approval for the first-line treatment of patients with advanced ALK-positive NSCLC. These include crizotinib, alectinib, ceritinib, brigatinib, ensartinib, and lorlatinib.[3] However, in the context of advanced ALK-positive NSCLC, all six ALK inhibitors are categorized as first-line treatment options, which presents complexities in clinical decision-making.

Previous study had provided comprehensive evaluations of the six ALK inhibitors for first-line treatment of advanced ALK-positive NSCLC, contributing valuable insights to the field.[4] However, these evaluations predominantly relied on pairwise meta-analyses and descriptive comparisons—methods that, despite their utility, were susceptible to inherent biases. Moreover, the lack of direct comparative evidence

* Corresponding author.
E-mail address: raoyf@zju.edu.cn (Y. Rao).

https://doi.org/10.1016/j.prmedi.2025.100025
Received 9 January 2025; Received in revised form 20 March 2025; Accepted 23 March 2025
Available online 19 May 2025
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Table 1
ALK inhibitors included in the evaluation.

Drugs	Specifications and Packaging	Research & Development companies	Purchase prices	Therapeutic indications
Crizotinib	200 mg* 60, 250 mg* 60	Pfizer	200 mg: ¥11574; 250 mg: ¥13728	1. ALK-positive locally advanced or metastatic NSCLC; 2.ROS1-positive advanced NSCLC
Ceritinib	150 mg* 150	Novartis	¥20400	ALK-positive locally advanced or metastatic NSCLC
Alectinib	150 mg* 224	Roche	¥15232	ALK-positive locally advanced or metastatic NSCLC
Ensartinib	25 mg* 7, 100 mg* 14	Betta	25 mg: ¥411.74; 100 mg: ¥2380	ALK-positive locally advanced or metastatic NSCLC
Brigatinib	30 mg* 28, 90 mg* 28, 180 mg* 28	Takeda	30 mg: ¥2408; 90 mg: ¥5583.48; 180 mg: ¥9492	ALK-positive locally advanced or metastatic NSCLC
Lorlatinib	25 mg* 90, 100 mg* 30	Pfizer	25 mg: 16405.2; 100 mg: 15804	ALK-positive locally advanced or metastatic NSCLC

Table 2
Guideline endorsements of six ALK inhibitors.

Guidelines	Recommendations	Crizotinib	Ceritinib	Alectinib	Brigatinib	Ensartinib	Lorlatinib
NCCN	First-line treatment of ALK-positive advanced NSCLC	2 A	2 A	2 A	2 A	/	2 A
CSCO		I	I	I	I	I	I
ESMO		I, B	I, B	I, A	I, A	/	I, A

Note: NCCN: National Comprehensive Cancer Network, CSCO: Chinese Society of Clinical Oncology, ESMO: European Society for Medical Oncology.

undermines their practical applicability, posing significant challenges for clinicians when making informed treatment decisions among these agents. Therefore, this study undertaken a thorough evaluation of these ALK inhibitors for their utility in the first-line management of advanced ALK-positive NSCLC patients. The evaluation framework was informed by the 'A Quick Guideline for Drug Evaluation and Selection in Chinese Medical Institutions (the Second Edition)',[5] and rigorously validated through a structured Delphi process, with the objective of furnishing medical institutions with evidence-based decision support for pharmaceutical selection and clinical medication choices.

Materials and methods

Evaluation methods

The development of our evaluation criteria and scoring system was grounded in "A Quick Guideline for Drug Evaluation and Selection in Chinese Medical Institutions (Second Edition)",[5] which outlines specific evaluation rules and scoring benchmarks. For items lacking predefined scores, we employed the Delphi method to establish appropriate scoring values. For instance, although the guideline designates a maximum score of 6 points for primary outcome measures, it does not provide guidance on scoring intervals for individual drugs. In these instances, we applied the Delphi method, conducting structured discussions with expert panels to derive the final scores for each drug.

Expert consultation approach

Below we provide additional clarification about our Delphi-based scoring system:

Two-Stage Delphi Process:

Stage 1 (Item Identification): Experts reached consensus on 5 core evaluation dimensions through iterative discussions.

Stage 2 (Score Allocation): A structured 3-round scoring procedure was implemented:

Round 1: Anonymous baseline scoring with justification requirements;

Round 2: Controlled group discussions to resolve discrepancies;

Round 3: Final consensus scoring with > 80 % agreement threshold.

Scoring Rationale (such as progression-free survival [PFS]):

The differential scoring (6.0–5.0 in 0.2 increments) reflects both clinical evidence and expert judgment:

Evidence Basis: Pooled analysis of 3 RCTs (n = 772) showed median PFS differences ≤ 1.8 months between middle-ranked agents (ensartinib = 25.8 months, brigatinib = 24 months), justifying smaller intervals;

Expert Consensus: While some advocated for wider intervals to emphasize PFS importance, 73 % of panelists maintained that clinically meaningful differentiation exists only between extreme performers (lorlatinib vs. crizotinib/ceritinib).

Drugs for evaluation

In China, six ALK inhibitors have received regulatory approval for the first-line treatment of patients with advanced ALK-positive NSCLC, comprising crizotinib, ceritinib, alectinib, brigatinib, ensartinib, and lorlatinib (Table 1). Except for crizotinib, these medications are distinctive, lacking any corresponding generic alternatives or drugs available through centralized procurement. Given that clinical trials were focused on the innovator drugs, the evaluation of these medications was anchored in the data derived from the original research products.

Data collection

The data sources comprise pharmaceutical package inserts, the latest editions of authoritative clinical practice guidelines (including the NCCN Guidelines, CSCO Guidelines, and ESMO Guidelines), phase III clinical trials, network meta-analyses, economic studies, the Zhejiang Province Healthcare Security Bureau Information Database (https://med.ybj.zj.gov.cn), the National Healthcare Security Administration Information Database (https://code.nhsa.gov.cn), and the National Medical Products Administration Drug Evaluation Center (https://www.cde.org.cn), as well as other reputable databases.

Comprehensive evaluation

Initially, a panel of experts was convened to deliberate and established the evaluation criteria. Following this, the enrolled medications were subjected to a scoring and assessment process across various dimensions, based on the aggregated data. The evaluation was conducted

Table 3
Clinical efficacy and safety of six ALK inhibitors.

References	Study type	Sample size	Efficacy	Safety
Solomon BJ 2014[6]	RCT	Crizotinib: n = 172; Chemotherapy: n = 171	Crizotinib vs chemotherapy: OS: NR vs 47.5 months PFS: 10.9 vs 7.0 months ORR: 74 % vs 45 %	The most frequently reported ADRs associated with crizotinib are blurred vision, diarrhea, nausea, and edema. In contrast, the common ADRs observed with chemotherapy regimens include nausea, fatigue, vomiting, and anorexia.
Soria JC 2017[7]	RCT	Ceritinib: n = 189; Chemotherapy: n = 187	Ceritinib vs chemotherapy: OS: NR vs 26.2 months PFS: 16.6 vs 8.1 months ORR: 72.5 % vs 26.7 %	The predominant ADRs associated with ceritinib are diarrhea, nausea, vomiting, and increased levels of ALT. For chemotherapy, the frequently observed ADRs include nausea, vomiting, and anemia.
Hida T 2017[8]	RCT	Alectinib: n = 103; Crizotinib: n = 104	Alectinib vs crizotinib: OS: NR vs 57.4 months; PFS: 34.8 vs 10.9 months; ORR: 82.9 % vs 75.5 %	Crizotinib exhibits a higher prevalence of Grade 3 or 4 ADRs in comparison to alectinib, with incidence rates of 52 % and 26 %, respectively. Additionally, dose interruptions attributed to ADRs are more frequently observed with crizotinib.
Horn L 2021[9]	RCT	Ensartinib: n = 143; Crizotinib: n = 147	Ensartinib vs crizotinib: OS: NR vs NR PFS: 25.8 vs 12.7 months ORR: 75 % vs 67 %	The occurrence of serious ADRs that emerge during treatment, as well as the need for dose reductions or treatment discontinuations, is comparable between the two drugs.
Camidge DR 2020[10]	RCT	Brigatinib: n = 137; Crizotinib: n = 138	Brigatinib vs crizotinib: OS: NR vs NR PFS: 24 vs 11 months ORR: 74 % vs 62 %	The ADRs of the two drugs are similar.
Shaw AT 2020[11]	RCT	Lorlatinib: n = 149; Crizotinib: n = 147	Lorlatinib vs crizotinib: OS: NR vs NR PFS: NR vs 9.8 months ORR: 76 % vs 58 %	Lorlatinib exhibits a higher prevalence of serious ADRs relative to crizotinib, predominantly attributed to lipid level alterations. The rate of treatment discontinuation due to ADRs is comparable between the two medications.
Ma HC 2021[12]	Network meta-analysis	9 RCTs were included in this network meta-analysis	Based on PFS ranking: Lorlatinib > alectinib > ensartinib > brigatinib > crizotinib > ceritinib; Based on ORR ranking: Alectinib > lorlatinib > brigatinib > ensartinib > ceritinib > crizotinib.	The ranking of drugs based on the incidence of moderate ADRs, from the lowest to the highest, is as follows: Crizotinib < brigatinib = lorlatinib < ceritinib = ensartinib < alectinib. Conversely, the ranking based on the incidence of serious ADRs, from the lowest to the highest, is: Alectinib < crizotinib < brigatinib < ensartinib < lorlatinib < ceritinib.

Note: RCT: randomized-controlled trial, OS: overall survival, PFS: progression-free survival, ORR: objective response rate, ADRs: adverse drug reactions, ALT: alanine aminotransferase,

independently by two researchers. In instances where there were substantial divergences in their assessments, a third party was consulted to mediate and determine the final outcome through consensus.

Results

Efficacy

The evaluation of drug efficacy was comprised of three critical dimensions: therapeutic indications, guideline endorsements, and clinical efficacy, with a cumulative scoring system totaling 27 points.

Therapeutic indications

All six ALK inhibitors have received approval for the treatment of ALK-positive locally advanced or metastatic NSCLC as detailed in Table 1; however, there exists a variance in their recommendation tiers within various clinical guidelines, as outlined in Table 2. The NCCN Guidelines endorse five ALK inhibitors for the first-line treatment of advanced ALK-positive NSCLC, with ensartinib not included, primarily due to its absence from the U.S. market. In alignment, the ESMO Guidelines advocate for five ALK inhibitors that have international market availability, highlighting alectinib, brigatinib, and lorlatinib as preferred options. The CSCO Guidelines extend their recommendation to encompass all six ALK inhibitors, with alectinib identified as the optimal choice. Consequently, in the domain of therapeutic indications, alectinib, brigatinib, and lorlatinib each garner a score of 5, whereas the other ALK inhibitors are allocated a score of 3.

Guideline endorsements

All six ALK inhibitors are highly endorsed within the guidelines, with both Chinese and international authoritative guidelines unanimously advocating for their use in the first-line treatment of patients with advanced ALK-positive NSCLC, albeit with some variance in the degree of recommendation. Given that the CSCO guidelines classify all six drugs as level I recommendations, each of the ALK inhibitors was allocated a score of 12 points, as delineated in Table 2.

Clinical efficacy

In the context of advanced cancer, the principal efficacy endpoints for oncological drugs are overall survival (OS) and PFS, with objective response rate (ORR) serving as the secondary efficacy endpoint. A comprehensive analysis was conducted, incorporating six phase III clinical trials and a single network meta-analysis, as specified in Table 3. With the exception of trials involving ceritinib and crizotinib, where the control arm was treated with chemotherapy, the control arm in the remaining trials consisted of crizotinib. Given the limited comparability across the various clinical trials, the findings from the network meta-analysis were predominantly utilized to assess the efficacy of the six ALK inhibitors. As the median OS has not been reached in many studies to date, PFS emerges as the primary efficacy endpoint of reference. According to the network meta-analysis, the PFS ranking was as follows: lorlatinib > alectinib > ensartinib > brigatinib > crizotinib > ceritinib. Consequently, scores of 6, 5.8, 5.6, 5.4, 5.2, and 5 were assigned to the primary endpoint for these six ALK inhibitors, respectively. For the secondary efficacy endpoint of ORR, the ranking based on the network meta-analysis was alectinib > lorlatinib > brigatinib > ensartinib > ceritinib > crizotinib. Accordingly, scores of 4, 3.8, 3.6, 3.4, 3.2, and 3 were assigned to the secondary endpoint for these six ALK inhibitors, respectively.

In conclusion, the stratification and scoring of the six ALK inhibitors in terms of pharmaceutical efficacy were delineated as follows: alectinib and lorlatinib each garnered a score of 26.8 points, succeeded by

Table 4
ADRs scores of six ALK inhibitors.

Drugs	Moderate ADRs scores	Severe ADRs scores	Composite ADRs scores
Crizotinib	3.0	4.8	7.8
Ceritinib	2.6	4.0	6.6
Alectinib	2.4	5.0	7.4
Ensartinib	2.6	4.4	7.0
Brigatinib	2.8	4.6	7.4
Lorlatinib	2.8	4.2	7.0

Note: ADRs: adverse drug reactions.

brigatinib with 26 points, ensartinib with 24 points, and rounding out the list, ceritinib and crizotinib both secured 23.2 points.

Safety

The drug safety assessment was comprised of four key dimensions: ADRs, considerations for special populations, drug-drug interactions that result in ADRs, and additional relevant factors, all contributing to a cumulative score of 25 points.

ADRs

Variations in ADRs existed among different ALK inhibitors, making it inappropriate to isolate and compare the incidence of specific ADRs. Given that clinical trials were conducted as pairwise comparisons, our primary reference relied on the outcomes of network meta-analyses.[12] The data analysis from the referenced literature indicated the ranking of the six ALK inhibitors from lowest to highest in terms of the incidence of moderate ADRs (Grades 1–2) as follows: crizotinib < brigatinib = lorlatinib < ceritinib = ensartinib < alectinib. Conversely, the ranking for the incidence of severe ADRs (Grades 3–4) from lowest to highest diverges somewhat from that of moderate ADRs, with the order being: alectinib < crizotinib < brigatinib < ensartinib < lorlatinib < ceritinib (Table 3). Furthermore, corresponding scores of 3, 2.8, 2.6, and 2.4 points are assigned based on the ranking from lowest to highest incidence of moderate ADRs. Similarly, scores of 5, 4.8, 4.6, 4.4, 4.2, and 4 points are assigned based on the ranking from lowest to highest incidence of severe ADRs. The final safety scores are presented in Table 4.

Special populations

The six ALK inhibitors, as per their respective drug labeling, were not indicated for pediatric use, nor for women who are pregnant or lactating; however, they were deemed appropriate for utilization in the elderly population. In individuals with compromised hepatic or renal function, all six ALK inhibitors were administered without the necessity for dosage adjustments. Regarding ADRs stemming from drug interactions, alectinib and ensartinib were administered without the need for dosage adjustments, whereas brigatinib necessitates such adjustments. Conversely, lorlatinib, ceritinib, and crizotinib were contraindicated in combination with drugs that might interact adversely. The ADRs associated with these six ALK inhibitors were irreversible and were characterized as both teratogenic and carcinogenic. While lorlatinib, brigatinib, and ensartinib were not accompanied by black box warnings, crizotinib, ceritinib, and alectinib were equipped with such warnings to highlight their potential risks. The detailed scoring for special populations was delineated in Table 5.

To sum up, the safety scores among the six ALK inhibitors were quite comparable. Ensartinib leaded the pack with a safety score of 18, largely attributed to its lower frequency of ADRs. It is closely followed by alectinib and brigatinib, both garnering 17.4 points each, lorlatinib with 16 points, crizotinib with 15.8 points, and ceritinib with 14.6 points.

Pharmaceutical properties

The assessment of pharmaceutical properties was anchored in five key dimensions: pharmacological activity, in vivo pharmacokinetics, pharmaceutics and administration method, storage condition, and expire date, all contributing to a cumulative score of 28 points.

Pharmacological activity

The six ALK inhibitors demonstrated established efficacy and possessed a clearly understood mechanism of action, effectively countering ALK-positive NSCLC by suppressing the mutant activity of ALK kinase in both *in vitro* and *in vivo* models. Regarding pharmaceutical innovation, crizotinib stood as a first-generation ALK inhibitor, with ceritinib, alectinib, ensartinib, and brigatinib classified as second-generation inhibitors, and lorlatinib representing the third-generation class. Consequently, in the domain of pharmacological activity, we awarded scores as follows: 4.6 points for crizotinib, 4.8 points for ceritinib, alectinib, ensartinib, and brigatinib, and 5 points for lorlatinib, acknowledging its status as the most advanced generation of ALK inhibitors.

In vivo pharmacokinetics

Consulting both Chinese and international package inserts, the detailed pharmacokinetic parameters for the six ALK inhibitors were delineated in Table 6. Crizotinib, alectinib, and lorlatinib were characterized by well-defined *in vivo* profiles and comprehensive pharmacokinetic data, earning them a score of 5. In contrast, ceritinib, ensartinib, and brigatinib had incomplete pharmacokinetic data, resulting in an assigned score of 3 points.

Pharmaceutics and administration method

Upon reviewing the main components and auxiliary materials of package leaflets from both Chinese and international sources,

Table 5
Special populations scores of six ALK inhibitors.

Drugs	Pediatric patients	Elderly patients	Pregnant and lactating patients	Hepatic insufficiency	Renal insufficiency	Drug-drug interactions	Others*	Special populations scores
Crizotinib	0	1	0	3	3	0	0	7
Ceritinib	0	1	0	3	3	0	0	7
Alectinib	0	1	0	3	3	0	0	7
Ensartinib	0	1	0	3	3	0	1	8
Brigatinib	0	1	0	3	3	0	1	8
Lorlatinib	0	1	0	3	3	0	1	8

Note : *: others encompass the reversibility of ADRs, the potential for teratogenic and carcinogenic effects, and the issuance of special drug alerts.

Table 6
Pharmacokinetic parameters of six ALK inhibitors.

Drugs	Administration route	F/%	T_{max}/h	Cmax/ng.mL^{-1}	AUC/ng.hr.mL^{-1}	Vd/L	PPBR/%	$T_{1/2}$/h	CL/(L.h^{-1})	Key metabolic enzymes	Renal clearance/%
Crizotinib	orally	43	4–6	621	6530	1772	91	42.0	60.0	CYP3A	22.0
Ceritinib	orally	/	4–6	/	/	4230	97	41.0	33.2	CYP3A	1.3
Alectinib	orally	37	4	665	7430	4016	> 99	33.0	81.9	CYP3A4	< 0.5
Ensartinib	orally	/	3	206	5230	1700	> 90	28.8	32.4	CYP3A4	10.21
Brigatinib	orally	/	1–4	552	8165	153	66	25.0	12.7	CYP2C8、CYP3A4	25.0
Lorlatinib	orally	81	1.2	577	5650	305	66	24.0	11.0	CYP3A4、UGT1A4	48.0

Note: F: relative bioavailability, T_{max}: peak time, C_{max}: peak concentration, AUC: area under curve, V_d: volume of distribution, PPBR: binding rate of plasma protein, $T_{1/2}$: half-life, CL: clearance.

ensartinib was the only ALK inhibitor that did not list its auxiliary materials, earning it 1 point, whereas the other ALK inhibitors each scored 2 points. All six ALK inhibitors adhered to the criteria for clinical application and dosage adjustment regarding their specifications and packaging, thus each was granted 2 points. In the category of dosage form, all six ALK inhibitors were oral, and accordingly, each was awarded 2 points. Regarding administration frequency, crizotinib and alectinib, which were dosed twice daily, received 1.5 points, while the other four medications dosed once daily each received 2 points. Self-administration was possible for all six ALK inhibitors, each scoring 2 points. Concerning storage conditions, all six ALK inhibitors were designed for storage at room temperature, and each was allocated 3 points. When it came to expiry date, ceritinib and ensartinib, with a relatively brief duration of 24 months, each received 1 point, whereas the remaining ALK inhibitors, with a expiry date of 36 months, each garnered 1.5 points. As a result, the scores and rankings for the six ALK inhibitors across pharmaceutical formulation and administration, storage conditions, and expiry date were as follows: lorlatinib with 17.5 points, crizotinib, brigatinib, and ceritinib each with 17 points, alectinib with 16 points, and ensartinib with 15 points (Table 7).

To sum up, the six ALK inhibitors had been ranked and scored in the domain of pharmaceutical properties with the following results: lorlatinib led at 27.5 points, followed by brigatinib at 26.8 points, alectinib at 25.8 points, ceritinib and ensartinib tied at 24.8 points each, and crizotinib at 24.6 points.

Drug economy

The six ALK inhibitors were classified as innovative drugs without any generic drugs, resulting in no points being allocated for this criterion. In evaluating potential substitutable drugs for the main indication, the daily treatment cost of each ALK inhibitor served as our principal references. Based on the formulaic calculations, brigatinib received a score of 10 points, ensartinib 8.5 points, ceritinib 8.3 points, crizotinib 7.4 points, lorlatinib 6.4 points, and alectinib 6.2 points. As previously highlighted, the absence of generic alternatives for these six ALK inhibitors meant that the drug economy scores were predominantly informed by the evaluations of substitutable drugs for the main indication, as detailed in Table 8.

Other properties

An assessment of other properties for the six ALK inhibitors was shown in Table 9. The distribution of rankings and scores for other properties was as follows: Crizotinib, ceritinib, alectinib and lorlatinib took the top positions with 5.5 points each, followed by brigatinib with 5.3 points and ensartinib with 3.5 points. Ensartinib's lower score was mainly due to the low ranking of its research & development company and the drug was not already on the international market.

Comprehensive evaluation

Drawing from the assessments spanning the aforementioned criteria, the six ALK inhibitors under consideration had all achieved scores surpassing 75 points, as detailed in Table 10. Brigatinib emerged with the highest composite score of 85.5 points. Considering the pivotal dimensions of drug evaluation—safety, efficacy, and pharmaceutical properties—lorlatinib attained the top score of 70.3 points when these criteria were exclusively assessed.

When evaluating ALK inhibitors by generation, we identified both consistent trends and notable exceptions across key dimensions: (1) Efficacy: With the exceptions of alectinib and ceritinib, efficacy generally followed a clear hierarchy: third-generation > second-generation > first-generation. (2) Safety: Excluding ceritinib, safety profiles exhibited the trend: second-generation > third-generation > first-generation. (3) Pharmaceutical Properties: A consistent ranking was

Table 7
Pharmaceutics and administration, storage conditions, and expiry date of six ALK inhibitors.

Drugs	Main components and auxiliary materials	Specifications and packaging suitable for dose adjustment	Dosage form	Dosage	Administration frequency	Self-administration	Storage conditions	Expiry date	Total score
Crizotinib	Complete (2)	Yes (2)	Oral (2)	Fixed (2)	Bid (1.5)	Yes (2)	Room temperature, not light-protected (4)	36 months (1.5)	17
Ceritinib	Complete (2)	Yes (2)	Oral (2)	Fixed (2)	Qd (2)	Yes (2)	Room temperature, not light-protected (4)	24 months (1)	17
Alectinib	Complete (2)	Yes (2)	Oral (2)	Fixed (2)	Bid (1.5)	Yes (2)	Room temperature, light-protected (3)	36 months (1.5)	16
Ensartinib	Does not list its auxiliary materials (1)	Yes (2)	Oral (2)	Fixed (2)	Qd (2)	Yes (2)	Room temperature, light-protected (3)	24 months (1)	15
Brigatinib	Complete (2)	Yes (2)	Oral (2)	Require adjustment (1.5)	Qd (2)	Yes (2)	Room temperature, not light-protected (4)	36 months (1.5)	17
Lorlatinib	Complete (2)	Yes (2)	Oral (2)	Fixed (2)	Qd (2)	Yes (2)	Room temperature, not light-protected (4)	36 months (1.5)	17.5

Note: Bid: twice daily, Qd: once daily.

observed: third-generation > second-generation > first-generation. (4) Drug economy: Except for alectinib, cost-effectiveness aligned with: second-generation > first-generation > third-generation. (5) Other properties: Apart from ensartinib, the evaluation results showed minimal variation across generations. Regarding total scores, the overall trend (excluding brigatinib) was: third-generation > second-generation > first-generation. Similarly, for the top three domain scores (excluding ceritinib), the pattern remained consistent: third-generation > second-generation > first-generation.

Discussion

ALK inhibitors constitute the first-line therapy for patients afflicted with ALK-positive advanced NSCLC. At present, six ALK inhibitors have obtained regulatory approval in China for this specific indication and have been endorsed by the NCCN, ESMO, and CSCO guidelines, with recommendations largely grounded in their efficacy and safety profiles. Despite these endorsements, healthcare institutions frequently encounter uncertainties when it comes to drug selection or treatment recommendations, often pondering which ALK inhibitors to incorporate or prioritize within clinical settings. In response to these challenges, this article presented a comprehensive evaluation of the six ALK inhibitors. Brigatinib distinguished itself as the most advantageous ALK inhibitor, as determined by a composite scoring assessment across five critical dimensions: safety, efficacy, pharmaceutical properties, drug economy, and other properties. Considering the pivotal dimensions of drug evaluation—safety, efficacy, and pharmaceutical properties—lorlatinib attained the top score. Our analysis by ALK inhibitor generation revealed distinct patterns of performance across key dimensions: third-generation agents consistently outperformed in efficacy, pharmaceutical properties, and other properties, whereas second-generation inhibitors were superior in safety and drug economy. Notably, when evaluating both the comprehensive scores across all five dimensions and the focused scores for the top three dimensions, third-generation inhibitors consistently ranked as the optimal choice. These findings provide a robust, evidence-based complement to current clinical guidelines, offering clinicians a nuanced framework to tailor first-line treatment selection for advanced ALK-positive NSCLC based on individual patient needs and prioritized therapeutic dimensions.

While we acknowledge that another study had explored ALK inhibitor evaluation,[4] our work was distinct in both methodology and

Table 8
Drug economy evaluation of six ALK inhibitors.

Drugs	Daily treatment costs	Scores of generic drugs score	Scores of substitutable drugs for the main indication*	Drug Economy scores
Crizotinib	¥228.8 (250 mg/tablet)* 2 = ¥457.6	/	7.4	7.4
Ceritinib	¥136 (150 mg/tablet)* 3 = ¥408	/	8.3	8.3
Alectinib	¥68 (150 mg/tablet)* 8 = ¥544	/	6.2	6.2
Ensartinib	¥170 (100 mg/tablet)* 2 + ¥58.82 (25 mg/tablet) = ¥398.82	/	8.5	8.5
Brigatinib	¥339 (180 mg/tablet)	/	10.0	10.0
Lorlatinib	¥526.8 (100 mg/tablet)	/	6.4	6.4

Note: *The drug featuring the lowest daily treatment cost was assigned a maximum score of 10 points. The score calculation for the drug under evaluation was determined by the formula: 10 × (Lowest daily treatment cost / Daily treatment cost of the drug being evaluated).

Table 9
Other properties scores of six ALK inhibitors.

Drugs	Research & Development companies	Medical insurance	Essential medicines	Centralized procurement of drugs	Innovative drugs/ generic drugs	Company ranking	Listed in multiple countries	Scores
Crizotinib	Pfizer	Class B has payment terms (1.5)	No (1)	No (0)	Innovative drug (1)	Ranked 6th in the 2024 Pharm Exec Top 50 Companies (1)	Yes (1)	5.5
Ceritinib	Novartis	Class B has payment terms (1.5)	No (1)	No (0)	Innovative drug (1)	Ranked 3rd in the 2024 Pharm Exec Top 50 Companies (1)	Yes (1)	5.5
Alectinib	Roche	Class B has payment terms (1.5)	No (1)	No (0)	Innovative drug (1)	Ranked 5th in the 2024 Pharm Exec Top 50 Companies (1)	Yes (1)	5.5
Ensartinib	Betta	Class B has payment terms (1.5)	No (1)	No (0)	Innovative drug (1)	Not in the 2024 Pharm Exec Top 50 Companies (0)	No (0)	3.5
Brigatinib	Takeda	Class B has payment terms (1.5)	No (1)	No (0)	Innovative drug (1)	Ranked 13th in the 2024 Pharm Exec Top 50 Companies (0.8)	Yes (1)	5.3
Lorlatinib	Pfizer	Class B has payment terms (1.5)	No (1)	No (0)	Innovative drug (1)	Ranked 6th in the 2024 Pharm Exec Top 50 Companies (1)	Yes (1)	5.5

focus: 1) Our assessment system was meticulously developed in alignment with the "A Quick Guideline for Drug Evaluation and Selection in Chinese Medical Institutions (Second Edition)"[5] and rigorously validated through a structured Delphi process. This process engaged a multidisciplinary panel of experts in multiple iterative rounds of discussion, ensuring both methodological robustness and clinical relevance. Consequently, the resulting scoring system is not only authoritative but also highly practical for real-world application. Unlike previous study, our framework integrates multiple dimensions (safety, efficacy, pharmaceutical properties, drug economy, and other properties) tailored to first-line advanced ALK-positive NSCLC, which has not been systematically addressed in prior work. In addition, our scoring system was rigorously developed and validated through a Delphi process, ensuring its relevance and applicability to local clinical settings.

While our evaluation system provides a comprehensive framework for assessing ALK inhibitors, we acknowledge that frequent fluctuations in drug indications and pricing may raise valid concerns about the long-term applicability of our findings in real-world clinical and policy settings. For the 6 ALK inhibitors evaluated in our study, the core indications for first-line treatment of advanced ALK-positive NSCLC have remained stable. Since their initial approvals, the primary indications for these agents in first-line settings have not undergone significant changes. Updates to drug labels typically involve safety information or secondary indications, which do not affect our evaluation framework. By concentrating on first-line treatment, our study avoids the variability associated with later-line or off-label use, ensuring the stability of our conclusions.

While drug pricing is indeed dynamic, our analysis accounts for the current landscape of ALK inhibitors in China, six evaluated drugs are all listed in the National Reimbursement Drug List (NRDL), have already undergone price negotiation, and its cost is relatively fixed. To ensure the continued relevance of our findings, we have implemented several safeguards: 1) The evaluation framework is designed to allow updates to individual components (e.g., price adjustments, new safety data) without requiring a complete overhaul; 2) We commit to monitoring regulatory and policy changes and will provide updated assessments as needed in future work.

By apportioning scores based on assessment outcomes, medications could be ranked across various dimensions, facilitating drug selection and decision-making processes.[13] ALK inhibitors garnered distinct scores under disparate evaluative criteria. Safety, efficacy, and pharmaceutical properties represented the pivotal dimensions in the comprehensive clinical assessment of pharmaceuticals; lorlatinib secured the highest score when these three dimensions were exclusively considered. Alectinib and lorlatinib achieved the highest scores when the efficacy dimension was isolated for assessment. Lorlatinib exhibited the most significant advantage in the pharmaceutical properties dimension. Ensartinib ranked highest in the drug safety dimension, whereas brigatinib outperformed in the drug economy dimension. In the dimension of other properties, crizotinib, ceritinib, alectinib, and lorlatinib were at the forefront. Consequently, healthcare institutions could tailor their evaluations, either singularly or in combination across different dimensions, aligned with the objectives of drug selection to derive the quantified assessment outcomes necessary for informed decision-making.

Admittedly, this evaluation carries certain inherent limitations. First, our scoring system was developed through expert discussions, and we have taken every possible measure to reduce potential bias. Nevertheless, given the inherently subjective nature of such discussions, complete objectivity cannot be guaranteed. As a result, it is essential to interpret our findings with appropriate caution. Principally, within the domain of efficacy, our reliance on network meta-analysis results stems from the absence of direct clinical trial data for a head-to-head comparison of these six ALK inhibitors, which may engender some degree of bias. Additionally, while PFS serves as the primary endpoint in ongoing clinical trials, the gold standard for efficacy, OS, remains immature and may not align with the ultimate clinical treatment outcomes. In the realm of safety, the incidence of ADRs is informed by network meta-analysis results, which, despite partially fulfilling the criteria for a

Table 10
Composite scores of six ALK inhibitors.

Drugs	Efficacy	Safety	Pharmaceutical properties	Drug economy	Other properties	Total scores	Total scores of the first three items
Crizotinib	23.2	15.8	24.6	7.4	5.5	76.5	63.6
Ceritinib	23.2	14.6	24.8	8.3	5.5	76.4	62.6
Alectinib	26.8	17.4	25.8	6.2	5.5	81.7	70.0
Ensartinib	24.0	18.0	24.8	8.5	3.5	78.8	66.8
Brigatinib	26.0	17.4	26.8	10.0	5.3	85.5	70.2
Lorlatinib	26.8	16.0	27.5	6.4	5.5	82.2	70.3

comprehensive assessment, are not exempt from potential bias. Lastly, as clinical evidence is in a state of flux, with package inserts and guidelines undergoing revisions and drug pricing being subject to change, the comprehensive assessment outcomes for these six ALK inhibitors are contingent upon the current evidence base. Consequently, it is imperative that the findings of this study be dynamically recalibrated in response to emerging evidence.

Declarations

Not applicable.

Authors' contributions

Y. Zhang: Software, investigation, formal analysis, and data curation. Y. Hong: Validation and investigation. Y. Rao: Writing – review and editing, validation, supervision, project administration, methodology, and conceptualization. Z. Ye: Writing – original draft, investigation, funding acquisition, data curation, and conceptualization. Y. Zhou: Investigation, formal analysis, and data curation. L. Liu: Investigation, formal analysis, and data curation.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Funding

This research was supported by the Fund of Zhejiang Pharmaceutical Association (2022ZYYL01).

Declaration of Competing Interest

The authors declare that they have no competing interests.

Acknowledgements

Not applicable.

Authors' other information

Not applicable.

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