

Original Article

Efficacy and Safety of Ensartinibin ALK-positive Non-Small Cell Lung Cancer Patients: A Systematic Review and Meta-analysis

Vinod Kumar Singh¹, Seema Awasthi¹, Jigar Haria ^{*1}, Prithpal Singh Matreja¹¹TMMC&RC, Teerthanker Mahaveer University, Moradabad, UP, India.Scan and read the
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Abstract

Background: NSCLC accounts for a significant proportion of global cancer mortality, with ALK-positive NSCLC constituting approximately 9% of cases. Ensartinib has demonstrated promising systemic and central CNS efficacy in clinical trials.**Methods:** A systematic review and meta-analysis were performed following PRISMA guidelines, using PubMed, Web of Science, Cochrane, and Scopus databases. RCTs and cohort studies reporting outcomes such as OS, PFS, RR, and adverse events in ALK-positive NSCLC patients treated with ensartinib were included. Data were synthesized using CMA software, and heterogeneity was assessed using chi-square tests and I^2 statistics.**Results:** Six studies encompassing 1,246 patients met the inclusion criteria. Pooled analysis revealed a RR of 56% (95% CI: 45–67%) and significant improvements in OS (Mean = 41.71 months, 95% CI: 31.64–51.77) and PFS (Mean = 8.88 months, 95% CI: 4.48–13.28). Common adverse events included rash (69%), nausea (19%), vomiting (15%), and transaminitis, with ALT (49%) and AST (42%) elevations.**Conclusions:** Ensartinib exhibits significant efficacy in improving OS and PFS in ALK-positive NSCLC, with manageable adverse effects. Its robust systemic and CNS activity supports its clinical utility as a second-generation ALK inhibitor. Further studies with bigger, diverse populations are warranted to validate these findings and explore long-term outcomes.

1. INTRODUCTION

Lung cancer is a leading cause of cancer-related deaths and illness globally (1), with non-small cell lung cancer (NSCLC) representing about 80–85% of lung cancer cases (2). A considerable number of patients are detected at advanced stages, marked by local progression and distant metastases. Currently, platinum-based chemotherapy remains the

standard therapy for advanced NSCLC. However, the treatment landscape has greatly advanced with improvements in genetic testing and the development of targeted therapies. The Anaplastic Lymphoma Kinase (ALK) gene has become a significant oncogenic driver in NSCLC, with ALK gene rearrangements found in around 9% of advanced NSCLC cases (3). As a result, medications that target ALK rearrangement could provide effective treatment

* Corresponding Author:

Jigar Haria

Affiliation: TMMC&RC, Teerthanker Mahaveer University, Moradabad, UP, India.

E-mail: jigarharhia332@gmail.com

for patients with this particular subtype of NSCLC. Crizotinib, the first ALK inhibitor to be approved, has demonstrated superior efficacy compared to conventional chemotherapy for NSCLC (4,5). However, most patients become resistant to crizotinib within a year via both ALK-dependent and ALK-independent mechanisms (6).

Additionally, almost 50% of patients on crizotinib experience progression in the central nervous system (CNS), due to either inadequate drug penetration or the development of acquired resistance (7,8). To overcome these challenges, several second and third-generation ALK tyrosine kinase inhibitors (TKIs) have been developed. The U.S. Food and Drug Administration (FDA) has approved ceritinib, alectinib, and brigatinib as second-generation inhibitors, while lorlatinib is approved as a third-generation inhibitor. Clinical trials have shown that second-generation ALK TKIs achieve objective response rates of approximately 40–50% and provide median progression-free survival (PFS) ranging from 6.9 to 15.6 months in patients who have developed resistance to crizotinib (9–11). Ensartinib (X-396), a second-generation ALK inhibitor, demonstrates promising activity in the central nervous system (CNS), remaining effective even in patients with prior ALK tyrosine kinase inhibitor treatments or existing CNS metastases (12). Unlike other second-generation ALK inhibitors, ensartinib is distinguished by its superior CNS penetration and broader resistance mutation coverage, making it a strong candidate for treating CNS-progressive disease. In phase 1 and 2 eXalt2 trials, ensartinib, administered at the recommended phase 2 dose of 225 mg once daily, demonstrated high response rates both systemically and in the CNS, in patients who were either ALK inhibitor-naïve or had previously been treated with crizotinib and/or a second-generation ALK inhibitor. Additionally, ensartinib exhibited a manageable safety profile, with rash (reported in ~30–40% of patients) and mild liver enzyme elevations (transaminitis) being the most common side effects—often less severe than those observed with ceritinib (12). Although individual clinical trials have shown promising results, a thorough synthesis of the available evidence is missing, creating uncertainty about ensartinib's comparative effectiveness and safety across different patient groups. This meta-analysis seeks to fill this knowledge gap by systematically reviewing and evaluating the efficacy and safety of ensartinib in treating ALK-positive NSCLC, offering clearer insights into its clinical value.

2. METHODS

In preparing this publication, we followed the checklist outlined in the Preferred Reporting Items for Systematic

Reviews and Meta-analyses (PRISMA) guideline (13). In addition, we tracked the guidelines provided in the Cochrane Handbook for Systematic Reviews and Meta-Analyses.

2.1. Search strategy and study selection

We searched PubMed, Cochrane, Web of Science, and Scopus databases from inception till December 2024, using the following query: ((ensartinib) OR (X-396)) AND ((Non-small Cell Lung Cancer) OR (NSCLC) OR (Lung Carcinoma) OR (lung Neoplasm)).

2.2. Selection criteria

We incorporated all studies that met the subsequent criteria: (1) Research designed as cohort studies or randomized controlled trials (RCTs), either single or double arm; (2) Research involving participants diagnosed with NSCLC; (3) Research in which the intervention group was administered ensartinib; (4) Research that reported at least one of the following outcomes: a) overall survival (OS), b) PFS, c) overall response rate (ORR), and d) adverse events. We omitted studies that were theses, reviews, conference abstracts, case reports, case series, in vitro investigations, and animal studies. Furthermore, research evaluating disparate outcomes was also omitted.

2.3. Selection of studies

Two reviewers independently assessed the studies in a two-phase process. First, they reviewed titles and abstracts based on the eligibility criteria. Then, they evaluated the full texts for eligibility in the systematic review. Any discrepancies were resolved by consulting a third reviewer.

2.4. Data extraction

Two reviewers extracted data from the relevant studies independently, recording the necessary information for analysis. If discrepancies in the extracted data were found, a third reviewer examined the original research to resolve the issue.

2.5. Quality assessment

NIH quality assessment tool was used to evaluate the quality of the included articles by two authors. This tool consists of fourteen items aimed at evaluating the methodology of both retrospective and prospective studies, covering aspects such as sample size calculation, exposure, and outcome assessment.

2.6. Data synthesis

All analyses were conducted using Comprehensive Meta-Analysis (CMA) statistical software (version 3). The data were analyzed using Event Rate (ER) with 95% confidence intervals for dichotomous outcomes. Heterogeneity was calculated using the chi-square test to determine significance and the I^2 statistic to measure its degree.

3. RESULTS

3.1. Literature search and characteristics of the included studies

Our comprehensive search identified 579 unique citations. Of these, 30 full-text articles were retrieved and assessed for eligibility. During the evaluation, 24 articles were excluded: 8 due to design inconsistencies with our study, and 16 because they did not meet either the primary or secondary outcomes. Ultimately, 6 studies (14-20), encompassing a total of 1,246 patients, were involved in this systematic review. The PRISMA flow diagram (Figure 1) outlined the study selection process, and a summary of the included studies, their populations, and key findings is provided in Table 1.

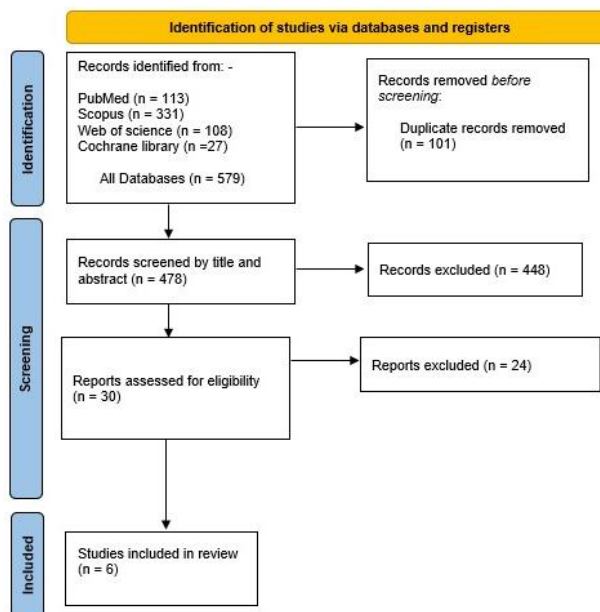


Figure 1. Flow chart of the selection of the included studies.

3.2. Risk of bias evaluation.

The included studies revealed fair quality with scores between 8.5 and 11. The details of the risk of bias evaluation for each study are revealed in **supplementary Table 1**.

3.3. Outcomes

3.3.1. Efficacy

3.3.1.1. Overall Response rate (ORR)

Five studies (15-19). have assessed the ORR. The overall analysis of the included studies showed an (ER) of 0.56 (95% CI: [0.45,0.67]), with moderate heterogeneity ($I^2 = 61.4\%$, $p = 0.0.32$). A random effects model was applied due to the presence of heterogeneity. There was no statistically significant difference between all pooled studies (p -value = 0.32) Fig 2.

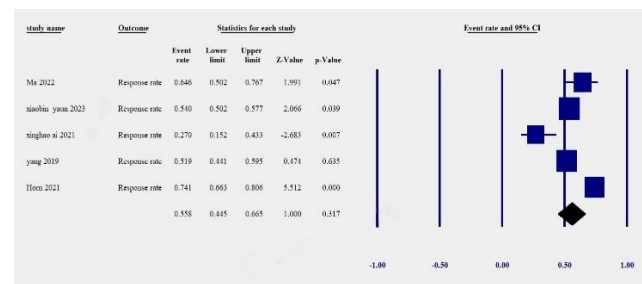


Figure 2. Forest plot of RR.

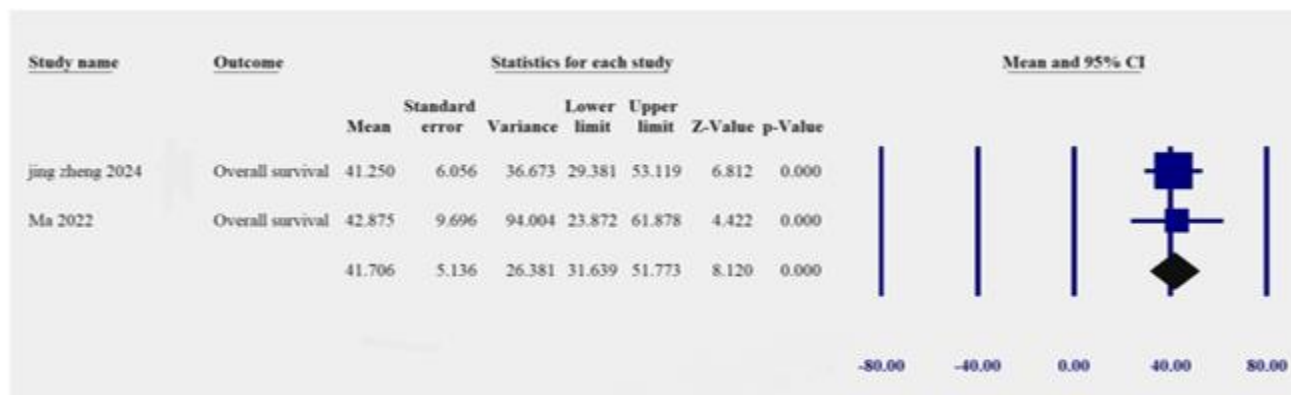
3.3.1.2. OS and PFS

Two studies (19,20). have evaluated the overall survival (OS) while three studies (16,17,19). evaluated the progression-free survival (PFS). For overall survival (OS), the pooled mean was 41.71 months (95% CI: [31.64, 51.77]), with low heterogeneity ($I^2 = 25.2\%$, $p = 0.18$); therefore, a fixed-effect model was used. For progression-free survival (PFS), the pooled mean was 8.88 months (95% CI: [4.48, 13.28]), with high heterogeneity ($I^2 = 72.8\%$, $p = 0.015$); hence, a random-effects model was applied. The results suggest that ensartinib leads to a significant improvement in OS in patients with ALK-positive NSCLC, as both the individual studies and the pooled analysis are statistically significant. In addition, the pooled results indicate that PFS is significantly improved, which supports the efficacy of the treatment in delaying disease progression in patients with ALK-positive NSCLC. Fig 3.

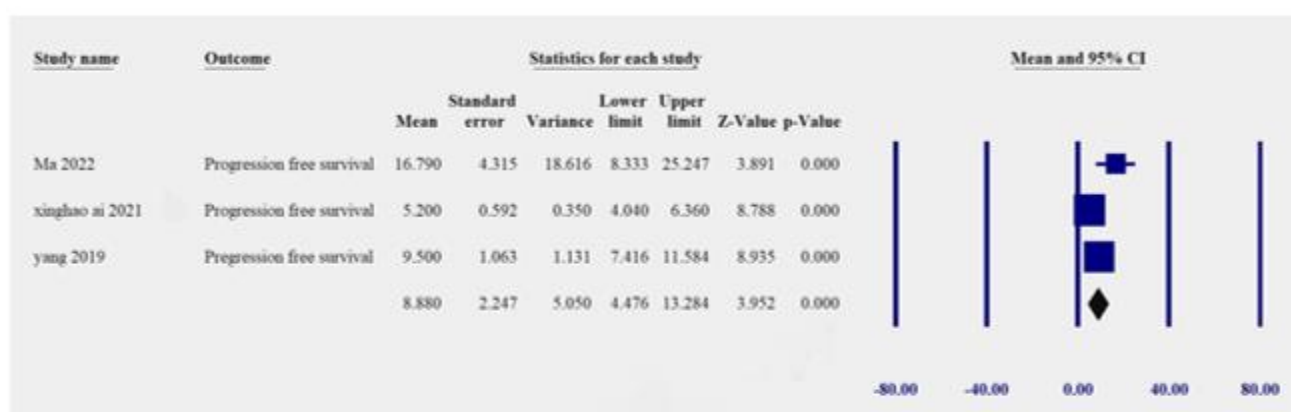
3.3.2. Safety

3.3.2.1. Nausea and vomiting

Four studies (16,17,19) have assessed the incidence of nausea while five studies (15-19) have measured the incidence of vomiting. The pooled analysis for nausea showed an event rate (ER) of 0.19 (95% CI: [0.12, 0.31]), with moderate heterogeneity ($I^2 = 58.6\%$, $p = 0.041$);



A) OS



B) PFS

Figure 3. Forest plot of OS and PFS.

therefore, a random-effects model was applied. For vomiting, the ER was 0.15 (95% CI: [0.08, 0.24]), with low heterogeneity ($I^2 = 27.3\%$, $p = 0.21$), and a fixed-effect model was used. The studies collectively provide strong evidence that nausea and vomiting are significant outcomes for ensartinib, and the significant p-values reinforce the reliability of these findings. Fig 4.

3.3.2.2. ALT and AST levels

Four studies (15-17,19) have evaluated the ALT and AST levels. The pooled analysis for ALT showed an ER of 0.49 (95% CI: [0.44, 0.55]), with low heterogeneity ($I^2 = 18.9\%$, $p = 0.27$), prompting use of a fixed-effect model. AST analysis yielded an ER of 0.42 (95% CI: [0.36, 0.48]), with moderate heterogeneity ($I^2 = 43.7\%$, $p = 0.11$), and a random-effects model was employed. The ALT levels across these studies do not show statistically significant

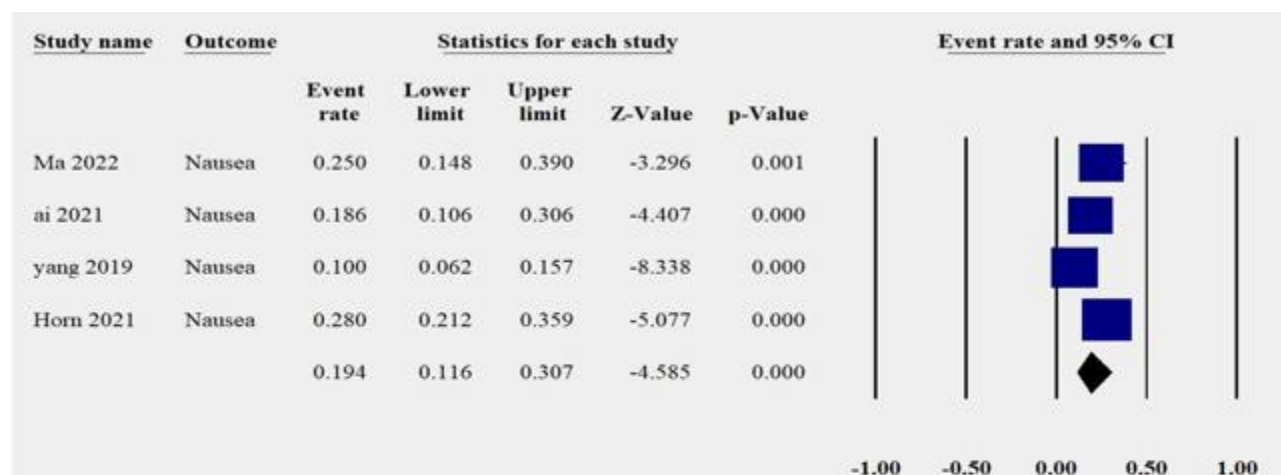
elevations, while there are statistically significant higher rates of AST levels among pooled studies. Fig 5.

3.3.2.3. Rash and pruritis

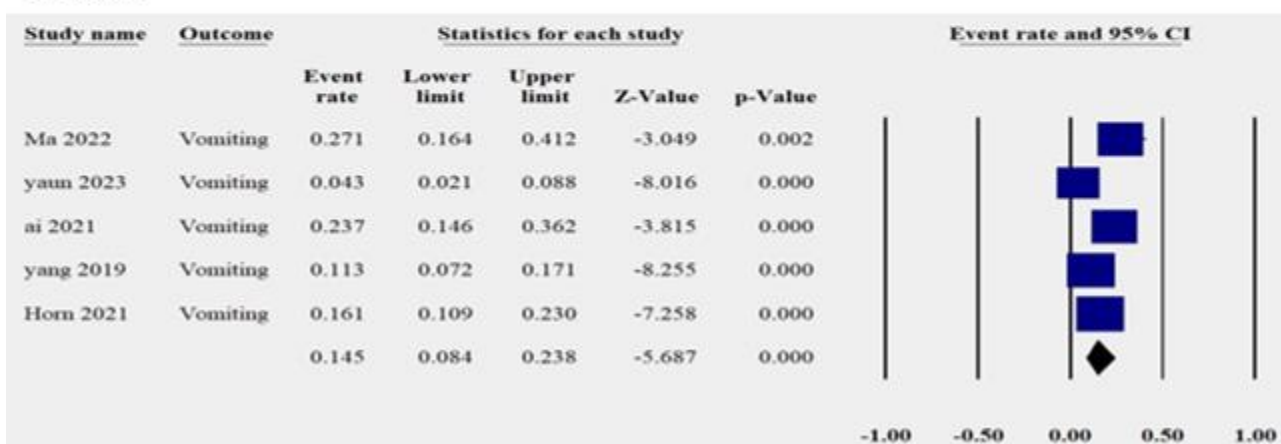
Five studies^{15–19} have evaluated the incidence of rash and pruritis. The pooled ER was 0.69 (95% CI: [0.66, 0.74]), with low heterogeneity ($I^2 = 22.4\%$, $p = 0.19$), and a fixed-effect model was used. Pruritis showed an ER of 0.21 (95% CI: [0.13, 0.34]), with moderate heterogeneity ($I^2 = 51.2\%$, $p = 0.078$), justifying a random-effects model. This provides strong evidence that rash and pruritis are significant outcomes for ensartinib. Fig 6.

3.3.2.4. Edema and constipation

Five studies (15-19) have assessed the incidence of edema and constipation. Edema showed an ER of 0.15 (95% CI: [0.09, 0.25]), with high heterogeneity ($I^2 = 67.9\%$, $p = 0.021$); hence, a random-effects model was used. Constipation showed an ER of 0.15 (95% CI: [0.09, 0.26]),



A) nausea



B) vomiting

Figure 4. Forest plot of nausea and vomiting.

with moderate heterogeneity ($I^2 = 49.5\%$, $p = 0.092$), and a random-effects model was also applied. This result revealed that edema and constipation are significant outcomes for ensartinib. Fig 7.

3.4. Publication Bias and Sensitivity Analysis

3.4.1. Publication Bias

Funnel plots were generated to assess potential publication bias for ORR and OS. For ORR, visual inspection of the funnel plot revealed no substantial asymmetry, suggesting low risk of publication bias. This was further supported by Egger's test ($p = 0.41$). Due to the small number of studies reporting OS ($k = 2$), funnel plot evaluation was inconclusive, and Egger's test was not conducted, consistent with methodological guidance.

3.4.2. Sensitivity Analysis

A leave-one-out sensitivity analysis was performed for ORR and OS. The pooled effect sizes remained stable across all iterations, indicating that the findings were not driven by any single study. This reinforces the reliability and robustness of the meta-analytic results.

4. DISCUSSION

In this systematic review and single-arm analysis, we thoroughly evaluated and summarized the efficacy and safety of ensartinib in ALK-positive NSCLC patients. Ensartinib exhibits a promising overall effect on OS and PFS, while there is no significant effect on response rate. On the other hand, ensartinib displays significantly adverse events such as nausea, vomiting, elevated AST levels, rash, pruritis, edema, and constipation.

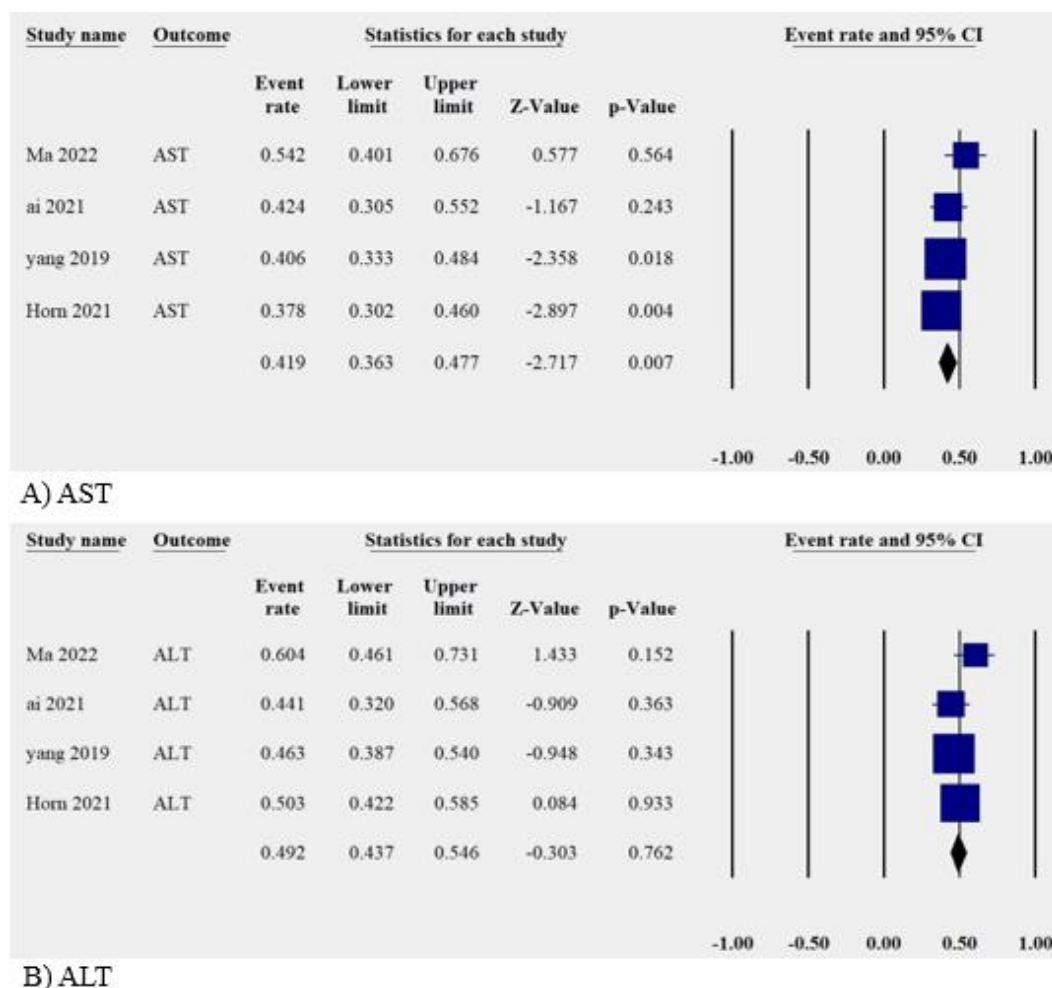


Figure 5. Forest plot of AST and ALT.

Multiple individual studies, including those by Horn (15) Xinghao Ai (17), Ma (19), and Yuan (18), have reported favorable response rates with ensartinib, reinforcing its consistent performance across diverse patient populations. Despite some variability, these results collectively support the clinical utility of ensartinib in improving response outcomes in ALK-positive NSCLC. OS and PFS were favorable with ensartinib administration in both Ma (2022) (19) and Zheng (2024) (20), with statistically significant P-values of 0.000 in both studies. These findings align with the results of our pooled analysis (P-value = 0.000), reinforcing the strength of the conclusion.

Ensartinib reveals a distinct safety profile compared to other ALK-TKIs. Its administration is associated with a higher rate of specific adverse events, such as rash, pruritus, edema, constipation, and gastrointestinal symptoms like nausea and vomiting. Our pooled analysis revealed a significant incidence of nausea and vomiting as adverse events

associated with ensartinib administration (P-value = 0.000). These findings are consistent with previous studies, including Ma (2022) (19) (P-value = 0.002), Yang (2019) (16) (P-value = 0.000), Xinghao Ai (2021) (17) (P-value = 0.000), and Yuan (2023) (18) (P-value = 0.000). This consistency highlights the need for careful monitoring and management of these adverse events during ensartinib treatment to improve patient tolerability and outcomes. Our pooled analysis also revealed a significant increase in rash and pruritus events associated with ensartinib administration. This finding aligns with the results of several previous studies, including Ma (2022) (19) (P-value = 0.000), Yuan (2023) (18) (P-value = 0.000), Xinghao Ai (2021) (17) (P-value = 0.015), and Horn (2021) (15) (P-value = 0.000). However, Yang (2019) (16) reported an insignificant association between ensartinib and the incidence of rash and pruritus (P-value = 0.156). These results underscore the importance of monitoring skin-related adverse events during

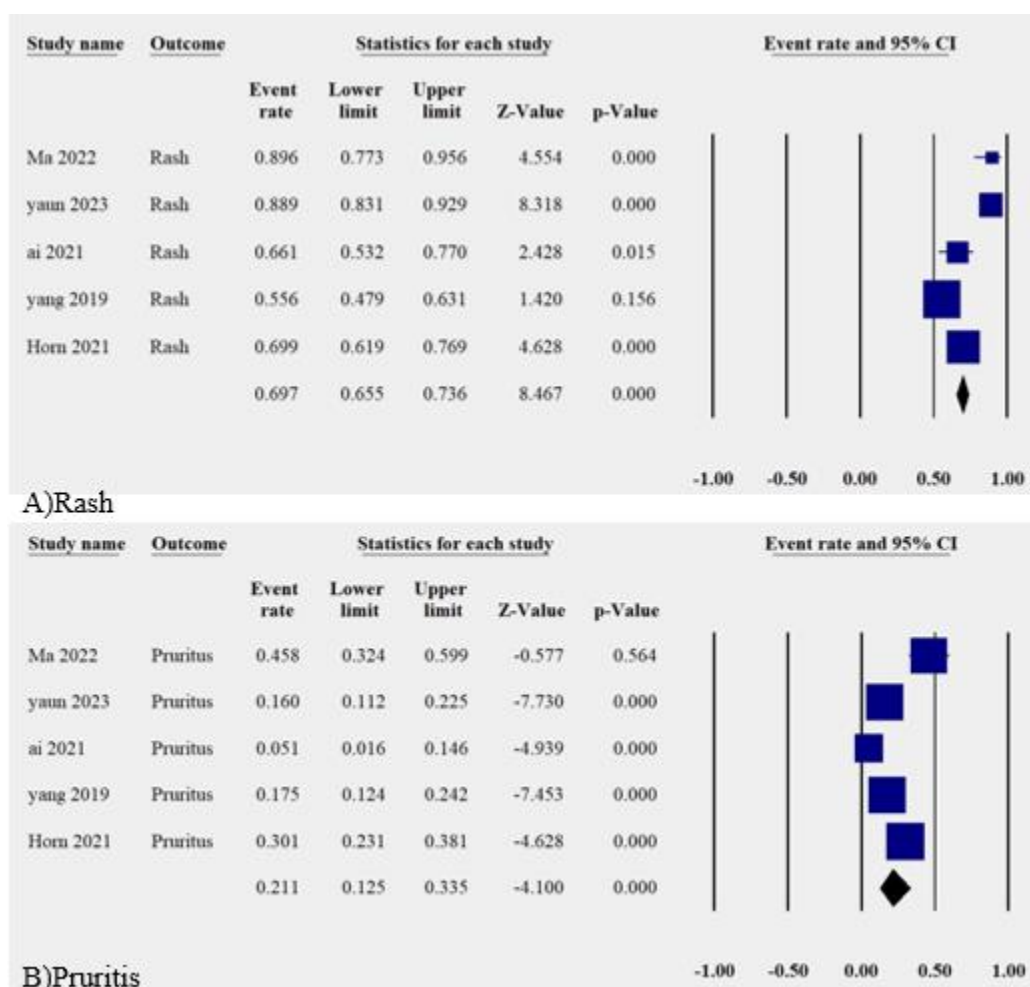


Figure 6. Forest plot of rash and pruritus.

treatment, as they may impact patient adherence and quality of life. A strong association has been identified between ensartinib administration and an increased incidence of edema and constipation. This has been consistently reported in previously published studies, including Ma (2022) (19), Yuan (2023) (18), Xinghao Ai (2021) (17), Yang (2019) (18), and Horn (2021) (15), all of which demonstrated a statistically significant relationship with P -value = 0.000. These findings are in line with the results of our pooled analysis, which also confirmed that ensartinib significantly elevates the incidence of both edema and constipation. These adverse events highlight the need for proactive management strategies to mitigate their impact on patient quality of life and ensure treatment adherence. The observed heterogeneity (as reflected in the I^2 statistics, e.g., 61.4% for ORR and 72.8% for PFS) may be attributed

to several clinical and methodological differences across studies. First, the included studies varied in design, with a mix of randomized controlled trials and single-arm phase II studies, which inherently differ in control of confounders and patient selection rigor. Second, there was variation in treatment setting—some studies included patients receiving ensartinib as a first-line therapy, while others evaluated second- or later-line use, which can significantly affect response rates and survival outcomes. Third, minor inconsistencies were noted in ensartinib dosing and treatment duration across trials, with some employing dose adjustments due to toxicity. These variations likely contributed to the inconsistency in effect estimates across studies. Future meta-analyses with subgroup and meta-regression analyses may further clarify the sources of heterogeneity.

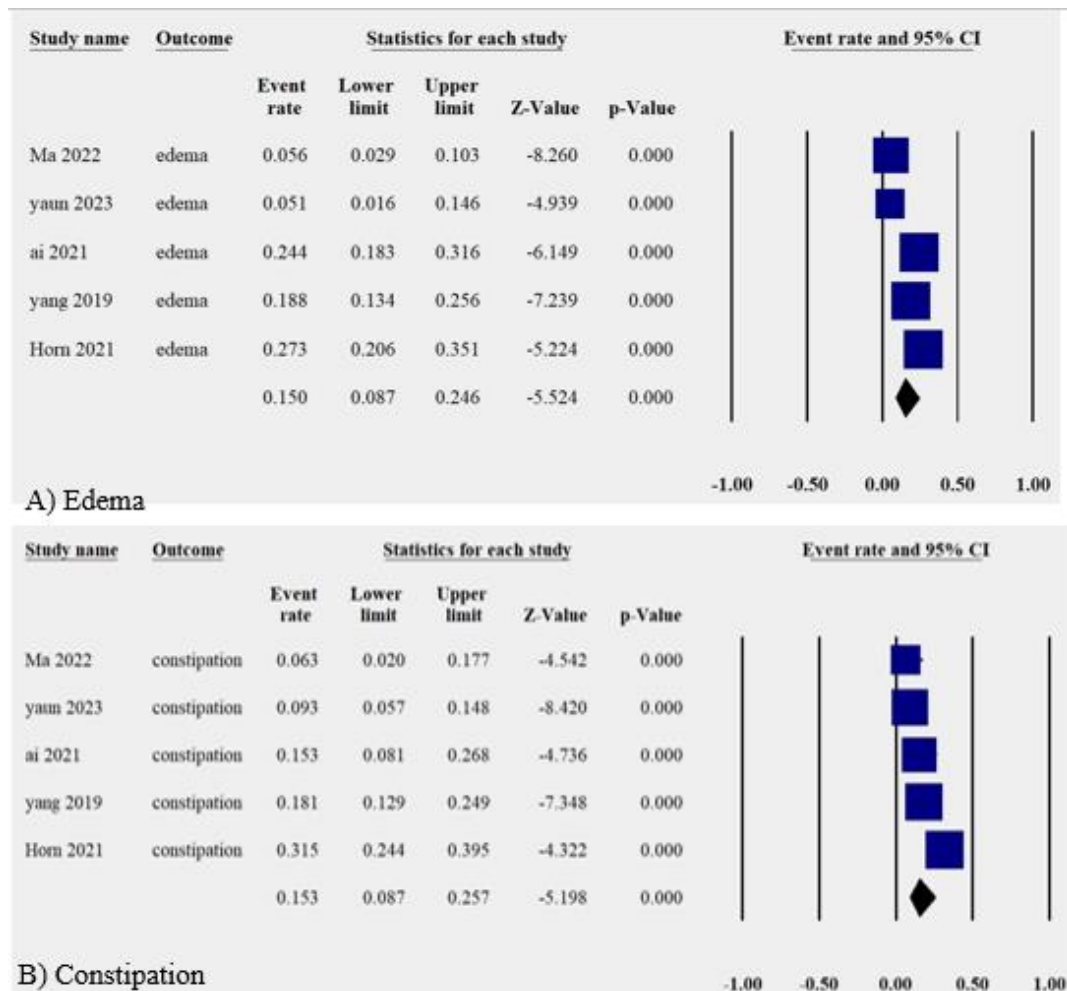


Figure 7. Forest plot of edema and constipation.

To better contextualize the clinical relevance of our findings, we compared the pooled estimates of OS and PFS with established regulatory benchmarks and MCID values. The U.S. FDA typically considers an OS improvement of at least **2–3 months** and a PFS improvement of 1–2 months to be clinically meaningful in advanced NSCLC settings. In our meta-analysis, the pooled OS of 41.71 months and PFS of 8.88 months substantially exceed these thresholds, underscoring the potential clinical utility of ensartinib in ALK-positive NSCLC. These findings not only demonstrate statistical significance but also meet and surpass clinically meaningful improvements recognized by regulatory agencies.

These findings underscore ensartinib's potential as a second-generation ALK inhibitor with notable systemic and CNS activity, especially in patients who have progressed on prior ALK-TKI therapy. The observed improvements in progression-free and overall survival, along with manageable

toxicity, suggest it could be a viable option in both first- and second-line settings. Clinicians should remain vigilant regarding skin-related and gastrointestinal side effects, which, while common, are typically manageable and should not preclude its use when benefits outweigh risks.

Ensartinib's strong CNS penetration also makes it an appealing choice in patients with brain metastases, a frequent site of progression in ALK-positive NSCLC.

5. LIMITATIONS

This meta-analysis has several limitations that warrant consideration. First, the number of included studies was limited ($n = 6$), and some outcomes such as overall survival (OS) were reported in only two studies, restricting the ability to conduct robust subgroup analyses or assess publication bias thoroughly. Second, the inclusion of both randomized controlled trials and single-arm studies may introduce

Table 1: main characteristics of the included studies

Study ID	Country	Patients (inclusion criteria)	Intervention		Sample size	Age, years; Median (range)	Sex, Male, n (%)	History of smoking, n (%)	Main findings
			Drug	Dose					
Ma 202219	China	Age 18–70 years. Pathologically confirmed NSCLC with ALK fusion. ECOG performance status 0–1. Sufficient bone marrow and organ function.	ensartinib	150, 200, 225, and 250 mg dose levels once daily in 28-day cycles	48	48 (23–77).	23 (47.9)	12 (25)	Ensartinib was well tolerated at a 225 mg dose and demonstrated strong anti-tumor activity in ALK+ NSCLC patients, including those with CNS metastases and prior TKI treatment.
Zheng 202420	China	Aged 18 or older. Diagnosed with locally advanced or metastatic ALK-positive NSCLC. ECOG performance status ≤ 2.	ensartinib	225 mg	180	NR	93 (51.67)	NR	Ensartinib enhanced overall survival (OS) in patients with advanced, crizotinib-resistant ALK-positive NSCLC.
Yuan 202318	China	Patients with unresectable stage IIIB–IV ALK-positive locally advanced or metastatic NSCLC. Aged 18 or older.	ensartinib	225 mg orally, once daily	682	57 (18–95)	306 (44.9)	34 (5.0%)	Ensartinib shows efficacy and tolerability in ALK-positive NSCLC patients in real-world clinical settings.
Ai 202117	China	Aged 18 or older. Histologically or cytologically confirmed locally advanced or metastatic NSCLC. ECOG performance status 0–1.	ensartinib 225 mg	225 mg orally once daily in continuous 28-day cycles	37	NR	NR	NR	Ensartinib showed moderate efficacy and a tolerable safety profile in ROS1-positive NSCLC patients.
Yang 201918	China	Aged 18 or older. Locally advanced or metastatic (stage IIIB or IV) ALK-positive NSCLC. No prior ALK inhibitor treatment other than crizotinib.	ensartinib	225 mg orally once daily	156	52 (44–60)	81 (52%)	47 (30%)	Ensartinib is effective and well tolerated in crizotinib-resistant ALK-positive NSCLC patients, including those with brain metastases.
Horn 202115	China	Aged 18 or older. Advanced or recurrent stage IIIB NSCLC (unsuitable for multimodality treatment) or metastatic stage IV NSCLC. ALK-positive status confirmed by local testing.	ensartinib	225 mg once daily	143	54 (25–86)	72 (50.3)	58 (40.6)	Ensartinib showed superior efficacy to crizotinib in treating both systemic and intracranial disease, positioning it as a new first-line treatment for ALK-positive NSCLC patients.

ALK; Anaplastic Lymphoma Kinase, NSCLC; non-small cell lung cancer, CNS; Central Nervous System, ECOG; Eastern Cooperative Oncology Group, TKI; Tyrosine Kinase Inhibitor.

heterogeneity due to methodological differences. Third, important clinical variables—such as patient comorbidities, performance status, prior treatments, and genetic mutation profiles—were not uniformly reported across studies, limiting our ability to perform more granular analyses. Lastly, although Egger's test was used for ORR, the assessment of publication bias for OS was not feasible due to the small number of studies. These limitations highlight the need for more standardized and comprehensive reporting in future trials evaluating ensartinib.

6. FUTURE PERSPECTIVES

The results of this systematic review and pooled analysis offer a thorough assessment of the efficacy and safety profile of ensartinib in ALK-positive NSCLC patients. However, several areas warrant further exploration to refine its clinical application. Future research should focus on large-scale, randomized controlled trials comparing ensartinib directly with other ALK-TKIs (e.g., alectinib, brigatinib, lorlatinib) to confirm its unique efficacy, especially in CNS-involved or TKI-pretreated populations. Additionally, understanding the underlying mechanisms driving the variability in response rates and adverse events, such as elevated AST levels and skin-related toxicities, can help identify predictive biomarkers for better patient selection and tailored therapy. Moreover, the management of adverse events remains a critical area of focus. Standardized clinical guidelines should be developed to manage commonly observed events such as rash, pruritus, gastrointestinal symptoms, and edema, which impact quality of life and treatment adherence. Optimizing dosing regimens could enhance patient adherence and quality of life. Finally, future research could explore the combination of ensartinib with other therapies, such as immunotherapy, to evaluate synergistic effects and expand its therapeutic potential.

7. CLINICAL RECOMMENDATIONS AND PRACTICE IMPLICATIONS

Based on current evidence, ensartinib demonstrates robust systemic and CNS activity and may be considered for both first- and second-line treatment settings. In particular, for treatment-naïve patients with brain metastases or at high risk of CNS progression, ensartinib may be a suitable first-line option due to its superior CNS penetration compared to other ALK inhibitors. In patients who have progressed on crizotinib or other ALK-TKIs, ensartinib provides a clinically meaningful second-line choice, particularly when CNS disease is the dominant progression site. Its manageable toxicity profile also makes it appealing for

patients with comorbidities or those requiring prolonged therapy. Ultimately, treatment selection should be individualized, taking into account prior ALK-TKI exposure, CNS status, tolerability, and molecular resistance mechanisms.

Finally, future directions should explore combination therapies, such as ensartinib with immune checkpoint inhibitors or CNS-penetrant agents, to overcome resistance and further improve outcomes. These approaches may also broaden ensartinib's utility beyond its current role in targeted monotherapy.

7. CONCLUSION

Ensartinib demonstrates promising efficacy in improving OS and PFS in ALK-positive NSCLC patients, as highlighted by our pooled analysis and supported by previous studies. Ensartinib also exhibits a distinct safety profile compared to other ALK-TKIs, with a significant association with adverse events such as rash, pruritus, edema, constipation, nausea, and vomiting. Ensartinib's unique safety and efficacy profile positions it as a valuable treatment option for ALK-positive NSCLC, but future research is required to optimize its use, mitigate adverse events, and identify patient populations that would benefit most.

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Conflict of interest

The authors declared no conflict of interest.

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Ethical statement

This research did not involve ethical considerations.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68(6):394-424. doi:10.3322/caac.21492
2. Gridelli C, Peters S, Sgambato A, Casaluze F, Adjei AA, Ciardiello F. ALK inhibitors in the treatment of advanced NSCLC. *Cancer Treat Rev*. 2014;40(2):300-306. doi:10.1016/j.ctrv.2013.07.002
3. Lee JK, Park HS, Kim D-W, et al. Comparative analyses of overall survival in patients with anaplastic lymphoma kinase-positive and matched wild-type advanced nonsmall cell lung cancer. *Cancer*. 2012;118(14):3579-3586. doi:10.1002/cncr.26668

4. Yoshida T, Oya Y, Tanaka K, et al. Clinical impact of crizotinib on central nervous system progression in ALK-positive non-small lung cancer. *Lung Cancer*. 2016;97:43-47. doi:10.1016/j.lungcan.2016.04.006
5. Shaw AT, Kim D-W, Nakagawa K, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. *N Engl J Med*. 2013;368(25):2385-2394. doi:10.1056/NEJMoa1214886
6. Lin JJ, Riely GJ, Shaw AT. Targeting ALK: precision medicine takes on drug resistance. *Cancer Discov*. 2017;7(2):137-155. doi:10.1158/2159-8290.CD-16-1123
7. Costa DB, Kobayashi S, Pandya SS, et al. CSF concentration of the anaplastic lymphoma kinase inhibitor crizotinib. *J Clin Oncol*. 2011;29(15):e443-5. doi:10.1200/JCO.2010.34.1313
8. Castellanos EH, Horn L. Re-Evaluating Progression in an Era of Progress: A Review of First- and Second-Line Treatment Options in Anaplastic Lymphoma Kinase-Positive Non-Small Cell Lung Cancer. *Oncologist*. 2016;21(6):755-761. doi:10.1634/theoncologist.2015-0396
9. Shaw AT, Kim D-W, Mehra R, et al. Ceritinib in ALK-rearranged non-small-cell lung cancer. *N Engl J Med*. 2014;370(13):1189-1197. doi:10.1056/NEJMoa1311107
10. Kim D-W, Tiseo M, Ahn M-J, et al. Brigatinib in Patients With Crizotinib-Refractory Anaplastic Lymphoma Kinase-Positive Non-Small-Cell Lung Cancer: A Randomized, Multicenter Phase II Trial. *J Clin Oncol*. 2017;35(22):2490-2498. doi:10.1200/JCO.2016.71.5904
11. Ou S-HI, Ahn JS, De Petris L, et al. Alectinib in Crizotinib-Refractory ALK-Rearranged Non-Small-Cell Lung Cancer: A Phase II Global Study. *J Clin Oncol*. 2016;34(7):661-668. doi:10.1200/jco.2015.63.9443
12. Horn L, Infante JR, Reckamp KL, et al. Ensartinib (X-396) in ALK-Positive Non-Small Cell Lung Cancer: Results from a First-in-Human Phase I/II, Multicenter Study. *Clin Cancer Res*. 2018;24(12):2771-2779. doi:10.1158/1078-0432.CCR-17-2398
13. Page M, McKenzie J, Bossuyt P, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. doi:10.1136/bmj.n71
14. Study Quality Assessment Tools | NHLBI, NIH. Accessed August 7, 2022. <https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools>
15. Horn L, Wang Z, Wu G, et al. Ensartinib vs Crizotinib for Patients With Anaplastic Lymphoma Kinase-Positive Non-Small Cell Lung Cancer: A Randomized Clinical Trial. *JAMA Oncol*. 2021;7(11):1617-1625. doi:10.1001/jamaoncol.2021.3523
16. Yang Y, Zhou J, Zhou J, et al. Efficacy, safety, and biomarker analysis of ensartinib in crizotinib-resistant, ALK-positive non-small-cell lung cancer: a multicentre, phase 2 trial. *Lancet Respir Med*. 2020;8(1):45-53. doi:10.1016/S2213-2600(19)30252-8
17. Ai X, Wang Q, Cheng Y, et al. Safety but Limited Efficacy of Ensartinib in ROS1-Positive NSCLC: A Single-Arm, Multicenter Phase 2 Study. *J Thorac Oncol*. 2021;16(11):1959-1963. doi:10.1016/j.jtho.2021.06.023
18. Yuan X, Wang Y, Yang M, et al. A retrospective study of ensartinib-treated ALK-positive locally advanced or metastatic NSCLC patients in China. *Lung Cancer Manag*. 2023;12(4):LMT61. doi:10.2217/lmt-2023-0005
19. Ma Y, Pan H, Liu Y, et al. Ensartinib in advanced ALK-positive non-small cell lung cancer: a multicenter, open-label, two-staged, phase 1 trial. *J Thorac Dis*. 2022;14(12):4751-4762. doi:10.21037/jtd-22-1606
20. Zheng J, Wang T, Yang Y, et al. Updated overall survival and circulating tumor DNA analysis of ensartinib for crizotinib-refractory ALK-positive NSCLC from a phase II study. *Cancer Commun (Lond)*. 2024;44(4):455-468. doi:10.1002/cac2.12524