



Review

Comparative Efficacy of ALK Inhibitors for Treatment-Naïve ALK-Positive Advanced Non-Small Cell Lung Cancer with Central Nervous System Metastasis: A Network Meta-Analysis

Koichi Ando ^{1,2,*}, Ryo Manabe ¹, Yasunari Kishino ¹, Sojiro Kusumoto ¹, Toshimitsu Yamaoka ^{1,3}, Akihiko Tanaka ¹, Tohru Ohmori ^{1,4} and Hironori Sagara ¹

- ¹ Division of Respiratory and Allergology, Department of Medicine, Showa University School of Medicine, 1-5-8 Hatanodai, Shinagawa-ku, Tokyo 142-8666, Japan
- ² Division of Internal Medicine, Showa University Dental Hospital Medical Clinic, Senzoku Campus, Showa University, 2-1-1 Kita-senzoku, Ohta-ku, Tokyo 145-8515, Japan
- ³ Advanced Cancer Translational Research Institute, Hatanodai Campus, Showa University, 1-5-8 Hatanodai, Shinagawa-ku, Tokyo 142-8555, Japan
- ⁴ Department of Medicine, Division of Respiratory Medicine, Tokyo Metropolitan Health and Hospitals Corporation, Ebara Hospital, 4-5-10 Higashiyukigaya, Ohta-ku, Tokyo 145-0065, Japan
- * Correspondence: koichi-a@med.showa-u.ac.jp; Tel.: +81-3-3784-8532

Abstract: Central nervous system (CNS) metastases and acquired resistance complicate the treatment of anaplastic lymphoma kinase (ALK) rearrangement-positive (ALK-p) advanced non-small cell lung cancer (NSCLC). Thus, this review aimed to provide a comprehensive overview of brain metastasis, acquired resistance, and prospects for overcoming these challenges. A network meta-analysis of relevant phase III randomized controlled trials was performed to compare the efficacies of multiple ALK inhibitors by drug and generation in overall patients with ALK-p untreated advanced NSCLC and a subgroup of patients with CNS metastases. The primary endpoint was progression-free survival (PFS). Generation-specific comparison results showed that third-generation ALK inhibitors were significantly more effective than second-generation ALK inhibitors in prolonging the PFS of the subgroup of patients with CNS metastases. Drug-specific comparison results demonstrated that lorlatinib was the most effective in prolonging PFS, followed by brigatinib, alectinib, ensartinib, ceritinib, crizotinib, and chemotherapy. While lorlatinib was superior to brigatinib for PFS in the overall patient population, no significant difference between the two was found in the subgroup of patients with CNS metastases. These results can serve as a foundation for basic, clinical, and translational research and guide clinical oncologists in developing individualized treatment strategies for patients with ALK-p, ALK inhibitor-naïve advanced NSCLC.

Keywords: brain metastasis; ALK rearrangement; acquired resistance; network meta-analysis



Citation: Ando, K.; Manabe, R.; Kishino, Y.; Kusumoto, S.; Yamaoka, T.; Tanaka, A.; Ohmori, T.; Sagara, H. Comparative Efficacy of ALK Inhibitors for Treatment-Naïve ALK-Positive Advanced Non-Small Cell Lung Cancer with Central Nervous System Metastasis: A Network Meta-Analysis. *Int. J. Mol. Sci.* **2023**, *24*, 2242. <https://doi.org/10.3390/ijms24032242>

Academic Editor: Federico Cappuzzo

Received: 23 December 2022

Revised: 18 January 2023

Accepted: 20 January 2023

Published: 23 January 2023



Copyright: © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction

1.1. Overview

The tremendous advances in tumor molecular research over the past two decades have contributed enormously to our understanding of the etiology of non-small cell lung cancer (NSCLC), which constitutes 84% of all primary lung cancers [1–5]. As a result, therapeutic strategies for NSCLC have evolved remarkably and are still undergoing further development [1,3]. Despite these advances, lung carcinoma currently remains the primary cause of cancer-related mortality, representing 13% of all deaths related to cancer. Localized NSCLC has a reported 5-year survival rate of 63%. However, most NSCLC cases are diagnosed in an advanced stage. The 5-year survival rate of patients with progressive cancer is currently approximately 7%, even with current recommended therapeutic regimens [2,5,6]. Thus, further improvements and developments are needed to treat NSCLC. Along with the expansion of

cancer genome medicine, genetic diagnostic technologies, treatment options, cancer gene panel tests (cancer genome profiling tests) and liquid biopsy, which examines numerous genes in cancer tissue samples, is being standardized [3,7–11]. These technologies have contributed to a further paradigm shift toward personalized medicine for NSCLC. Three to five percent of NSCLC cases harbor anaplastic lymphoma kinase (ALK) gene fusions, the most common of which is echinoderm microtubule-associated protein-like 4-ALK (EML4-ALK) [12–16].

As shown in Figure 1, EML4-ALK activates downstream signals such as phosphatidylinositol 3-kinase-AKT (PI3K-AKT), Janus kinase/signal transduction and activation factor (JAK/STAT) signaling cascade, reticular activation system (RAS), and various kinase activity, which consequently promote the production of fusion proteins that inhibit apoptosis [12,17–19]. This phenomenon promotes tumor survival, growth, progression, and metastasis to other organs, including metastasis to the central nervous system (CNS), and in different cancer types, including NSCLC [1,2,8,15,18–23].

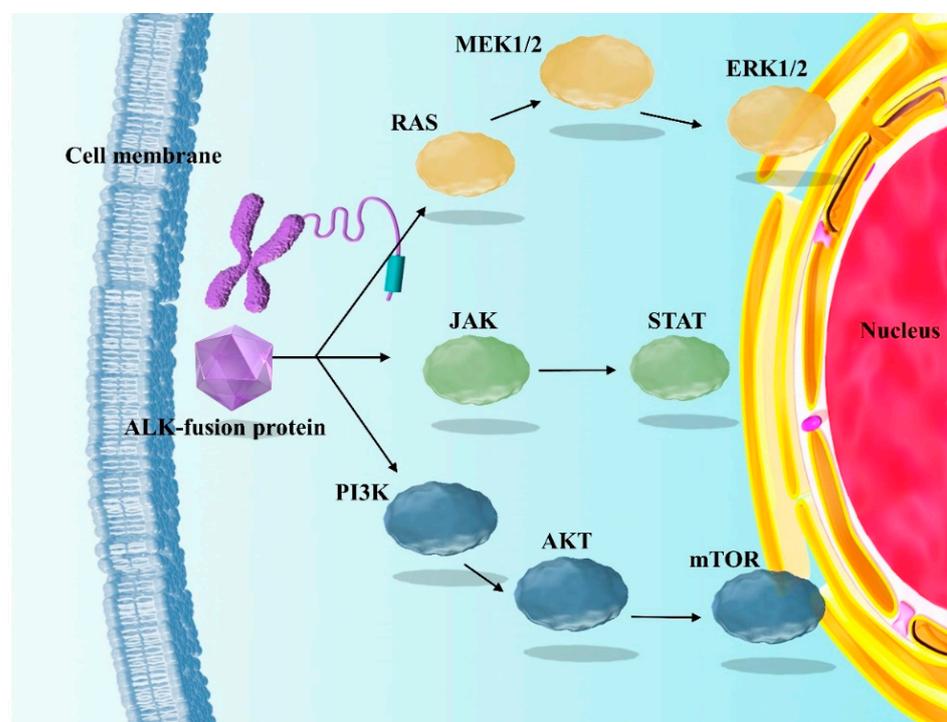


Figure 1. Mechanisms of ALK translocation cancer progression. EML4-ALK translation triggers the initiation of the PI3K-AKT, RAS, and JAK/STAT signaling cascades that influence tumor growth, proliferation, and viability. ERK, extracellular signal-regulated kinase EML4-ALK, echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase; PI3K, phosphatidylinositol-3 kinase; mTOR, mammalian target of rapamycin; STAT, signal transducer and activator of transcription. ALK, anaplastic lymphoma kinase; mammalian target of rapamycin; JAK, Janus kinase; MEK, mitogen-activated extracellular signal regulated kinase; RAS, reticular activating system.

Lung cancer has a high probability of metastasis to the CNS, and patients with advanced NSCLC involving driver gene alterations, such as EGFR mutations and ALK rearrangements, frequently have brain metastases (BM). The incidence of BM in such patients is 37–64% [14,24,25]. Hence, treatment strategies focusing on BM are essential to manage patients with advanced NSCLC, especially those with ALK rearrangements. Whole-brain radiotherapy (WBRT) is the primary treatment option for patients with BM from NSCLC. However, tyrosine kinase inhibitor (TKI)-targeted driver gene alteration has marked antitumor activity against BM in tumors with driver alterations [14,26]. Therefore, systemic pharmacotherapy with TKIs is a promising treatment option for BM from ALK rearrangement-positive (ALK-p) NSCLC. Multiple therapies have been introduced. In 2011,

the U.S. FDA first approved crizotinib as the leading ALK inhibitor. Subsequently, second- and third-generation ALK inhibitors have been approved and reported to have superior efficacy and antitumor activity to crizotinib in patients with CNS metastases.

Nevertheless, therapeutic strategies targeting ALK-p NSCLC with CNS metastases remain to be developed, and current strategies need to be improved [2,12,14].

Even patients who respond well to initial therapy with ALK inhibitors may experience tumor recurrence because of acquired resistance to these drugs via multiple mechanisms, including secondary ALK resistance mutations and tumor growth promoting molecular pathways. Therefore, the mechanisms underlying acquired resistance to ALK inhibitors must be elucidated to develop novel strategies to treat patients with ALK-p advanced NSCLC, especially those with CNS metastases [4,12].

In this meta-analysis report we first summarize the different ALK inhibitors (crizotinib, ceritinib, alectinib, brigatinib, entrectinib, and lorlatinib) used in patients with ALK-p advanced NSCLC. We then discussed the treatment of patients with CNS metastases and the prospects for overcoming acquired resistance mutations in these patients.

1.2. ALK Inhibitors

ALK inhibitors bind to the ATP-binding pocket of the intracellular tyrosine kinase domain, and regulate their downstream signals such as the RAS, PI3K-AKT, JAK/STAT signaling cascades which are involved in tumor progression; attenuation of these cascades produces an antitumor effect [8,20,27]. At present, several ALK inhibitors, including crizotinib, alectinib, ceritinib, brigatinib, entrectinib, and lorlatinib, have been approved as standard therapy for ALK-p NSCLC [1,3,17].

1.2.1. Crizotinib

Crizotinib is a first generation ALK inhibitor authorized for the potential therapeutic application in the treatment of ALK-p NSCLC. Two phase III trials (PROFILE1014 [28] and PROFILE1029 [29]) reported that progression-free survival (PFS) is longer in patients treated with crizotinib monotherapy than in those treated with platinum combination therapy (hazard ratio [HR] 0.45, 95% confidence interval [CI]: 0.35–0.60; HR 0.402, 95% CI: 0.286–0.565). Drug resistance usually develops within a year, and the disease metastasizes to the brain because crizotinib cannot penetrate the blood–brain barrier (BBB) [2,30–32]. The major toxicities of crizotinib monotherapy include liver dysfunction, visual disturbances, and gastrointestinal toxicities such as diarrhea and nausea. Although PFS is longer with crizotinib monotherapy than with platinum combination therapy, multiple phase III trials have shown that other ALK-TKI monotherapies (alectinib, brigatinib, and lorlatinib) are more effective than crizotinib in prolonging PFS [1,33–35]. Previous clinical trials and our previous NMA showed that a toxicity level of Grade 3 or higher is more frequent with crizotinib monotherapy than with alectinib monotherapy [35].

1.2.2. Ceritinib

Ceritinib is a second-generation ALK inhibitor developed to improve the low activity of first-generation ALK-TKIs against CNS diseases and overcome resistance. A phase III study (ASCEND-4) found that the PFS of patients with stage IV ALK-p NSCLC and PS 0–1 is longer with ceritinib monotherapy than with platinum combination therapy (HR 0.55, 95% CI: 0.42–0.73) [36]. However, Grade 3 or higher adverse events are more frequent with ceritinib monotherapy (65%) than with platinum combination therapy (49%). The main toxicities of ceritinib include liver dysfunction and gastrointestinal toxicities, including anorexia, diarrhea, nausea, and vomiting [1,36].

1.2.3. Alectinib

Three phase III trials (J-ALEX [37], ALEX [35], and ALESIA [38]) involving patients with ALK-p stage IV NSCLC and PS 0–1 found that PFS is significantly longer in patients treated with alectinib monotherapy than in those treated with crizotinib monotherapy

(HR 0.38, 95% CI: 0.26–0.55; HR 0.47, 95% CI: 0.34–0.65; HR 0.22, 95% CI: 0.13–0.38). Updated results of the ALEX trial reported that overall survival (OS) is longer with alectinib monotherapy than with crizotinib monotherapy (HR 0.67, 95% CI: 0.46–0.98) [35]. The J-ALEX study showed that like ceritinib, alectinib has a high response rate and excellent brain penetration and that Grade 3 or higher adverse events are less frequent with alectinib monotherapy (32%) than with crizotinib monotherapy (57%) [37]. Our previous NMA has shown that alectinib monotherapy has superior efficacy to other ALK inhibitors [39]. The main toxicities of alectinib monotherapy include dysgeusia, myalgia, and skin rash; as with other kinase inhibitors, interstitial pneumonitis should also be noted [1,35,37,38].

1.2.4. Brigatinib

A phase III trial (ALTA-1L [34]) that included patients with stage IV ALK-p NSCLC and PS 0–1 revealed that the PFS of these patients is longer with brigatinib monotherapy than with crizotinib monotherapy (HR 0.49, 95% CI: 0.33–0.74) [34]. Our NMA reported that brigatinib monotherapy has a relatively favorable efficacy in patients with BM. However, no significant difference was demonstrated when brigatinib monotherapy was compared with alectinib monotherapy [39,40]. Grade 3 or higher adverse events are more frequent with brigatinib monotherapy (61%) than with crizotinib monotherapy (55%) [34]. The major toxicities associated with brigatinib monotherapy include hypertension, interstitial pneumonia, elevated creatine kinase, skin rash, and gastrointestinal toxicities, such as nausea, vomiting, and diarrhea [1,34].

1.2.5. Ensartinib

A phase III eXalt3 trial demonstrated that ensartinib (X-396) monotherapy, as a first-line treatment for patients with ALK-p advanced NSCLC, is better than crizotinib monotherapy in prolonging PFS (HR 0.51, 95% CI: 0.35–0.72) [41]. In addition, the intracranial response efficiency of ensartinib monotherapy is higher (63.6%; $n = 7/11$ patients) than that of crizotinib monotherapy (21.1%; $n = 4/19$ patients). However, the incidence of treatment-related serious adverse events is higher with ensartinib monotherapy (7.7%) than with crizotinib monotherapy (6.1%), with no new safety signals [41].

1.2.6. Lorlatinib

A phase III trial (CROWN [33]) showed that the PFS of patients with stage IV ALK-p NSCLC and PS 0–1 is significantly longer with lorlatinib monotherapy than with crizotinib in the overall patient population and a subgroup of patients with CNS metastases (HR 0.28, 95% CI: 0.19–0.41). However, the incidence of Grade 3 or higher adverse events is higher (72%) with lorlatinib monotherapy than with crizotinib monotherapy (56%). The major toxicities of lorlatinib monotherapy include hypercholesterolemia, hypertriglyceridemia, weight gain, and hypertension, with cognitive dysfunction (2%) reported as the most common adverse event [1,33].

1.3. Current Insights and Future Prospects on Treatment Strategies for ALK-p NSCLC with BM

In this section we discuss the treatment options for asymptomatic and symptomatic BM cases and the future direction of drug therapy development.

For asymptomatic BM cases, single-drug therapy with TKIs is the preferred and recommended treatment option because the patients' tumors, including BM, are expected to have high responsiveness to these drugs [14,26].

However, BM progression can easily cause neurological symptoms and rapidly deteriorate the patient's condition. For example, BM lesions in the brain stem or close to the pyramidal tract can rapidly deteriorate, even if their size is small. Thus, intracranial radiotherapy is preferred for such patients, even those who are asymptomatic. Close monitoring of BM and the timing of radiotherapy intervention are critical in managing asymptomatic cases [1,12,14].

For symptomatic BM cases intracranial radiotherapy is the primary treatment option because robust local control of BM and neurological improvement are expected. The drugs selected by treating physicians are also essential in managing symptomatic BM cases. Several phase III clinical trials demonstrated that the intracranial antitumor activity of second- or further-generation ALK-TKIs is higher than that of crizotinib [42,43]. Lorlatinib, a third-generation ALK-TKI that can be delivered to the CNS, shows robust intracranial tumor response [33]. In a previous clinical trial the objective response rate (ORR) of lorlatinib (82%) in ALK-TKI-naïve patients with BM is higher than that of crizotinib [44]. However, hyperlipidemia and neurological adverse events such as cognitive impairment, anxiety, and depression are specific to lorlatinib [44]. Given the differences in adverse events induced by ALK-TKIs [33,42,43,45], patients' conditions and concomitant diseases should be considered when selecting ALK-TKIs.

Drug delivery into the CNS is generally prevented and primarily regulated by the BBB. WBRT can irreversibly disrupt the BBB and improve the delivery of ALK-TKIs [46,47]. WBRT is effective against BM and can enhance drug delivery to intracranial lesions. However, the incidence of cognitive impairment after WBRT is higher than that after stereotactic radiotherapy [48]. Assumption of the remaining neurological function after cranial radiotherapies and individualized treatment options should be discussed on a case-by-case basis by a multidisciplinary team.

Drug therapy combined with other agents and fourth-generation ALK-TKIs are future treatment options for ALK-p NSCLC with BM.

Glycogen synthase kinase 3 (GSK3) is a serine-threonine kinase that serves an essential role in many cellular processes; thus, it has been considered as a promising target in various malignant diseases including brain tumors [49]. A preclinical study demonstrated that a GSK3 inhibitor in combination with lorlatinib can overcome lorlatinib resistance [50]. In addition to its antitumor effects, GSK3 inhibition also exerts neuroprotective effects by promoting DNA repair. Thus, lorlatinib treatment combined with GSK3 inhibitors can be more potent and neurologically less toxic for patients with BM from ALK-p NSCLC. Fourth-generation ALK-TKIs, such as TPX-0131 and NUV-655, have been developed and are now under investigation. These drugs can penetrate the CNS and thus are more potent than conventional ALK-TKIs [51,52]. They are active against ALK-p NSCLC with L1196M and G1202R mutations, which are resistant to third-generation ALK-TKIs such as lorlatinib [51,52]. Thus, fourth-generation ALK-TKIs are a promising treatment option for BM from ALK-p NSCLC, especially for those cases where other ALK-TKIs failed.

Radiotherapy, drug therapy, and their combinations have markedly progressed and prolonged the survival of patients with BM from ALK-p NSCLC. However, individualized treatment selection is a critical component for managing such patients. Thus, a multidisciplinary team comprising thoracic and radiation oncologists should conduct individualized treatment discussions to prolong the survival of patients with BM from ALK-p NSCLC.

1.4. Mechanisms of Acquired Resistance to ALK Inhibitors and Prospects for Novel Strategies

Although crizotinib can significantly prolong the response rate and PFS of patients with ALK-p NSCLC, disease progression inevitably occurs after treatment because of the acquired resistance of 1–2 years [33]. The mechanisms underlying the acquired resistance to ALK inhibitors are classified into two categories: (1) ALK-dependent resistance mechanisms, such as secondary ALK resistance mutations and ALK amplification; and (2) ALK-independent resistance mechanisms, such as bypass signaling pathway activation and lineage changes [53].

Secondary ALK inhibitor resistance mutations were previously identified in 20–30% of tumor samples with crizotinib failure [54]. Among the crizotinib-resistant secondary mutations, L1196M and G1269A are the most frequently detected in clinical samples [55]. The L1196M and G1269A mutations are located in the ATP-binding pocket and hinder crizotinib binding. Other crizotinib-resistant mutations include I1151T, L1152P/R, C1156Y,

G1128A, I1171T/N/S, F1174V, E1201K, G1202R, S1206C/Y, and V11180L [56–58], which may enhance the ATP-binding affinity and enzymatic activity of the kinase.

Second-generation ALK inhibitors, such as ceritinib, alectinib, and brigatinib, have been developed and approved clinically to overcome crizotinib-resistant mutations. These inhibitors are potent against common crizotinib-resistant mutations, L1196M, and G1269A [32,59–61]. Patients whose ALK-p NSCLC conditions have been treated with second-generation ALK inhibitors inevitably develop acquired resistance, and secondary acquired resistance mutations have been determined in approximately 50–70% of these patients. Figure 2 shows the pharmacological activities of alectinib and lorlatinib against ALK fusion proteins with resistant mutations. The G1202R mutation occurs in the solvent-front ATP-binding site region of ALK and weakens the binding of all first- and second-generation ALK inhibitors because of steric hindrance [62,63].

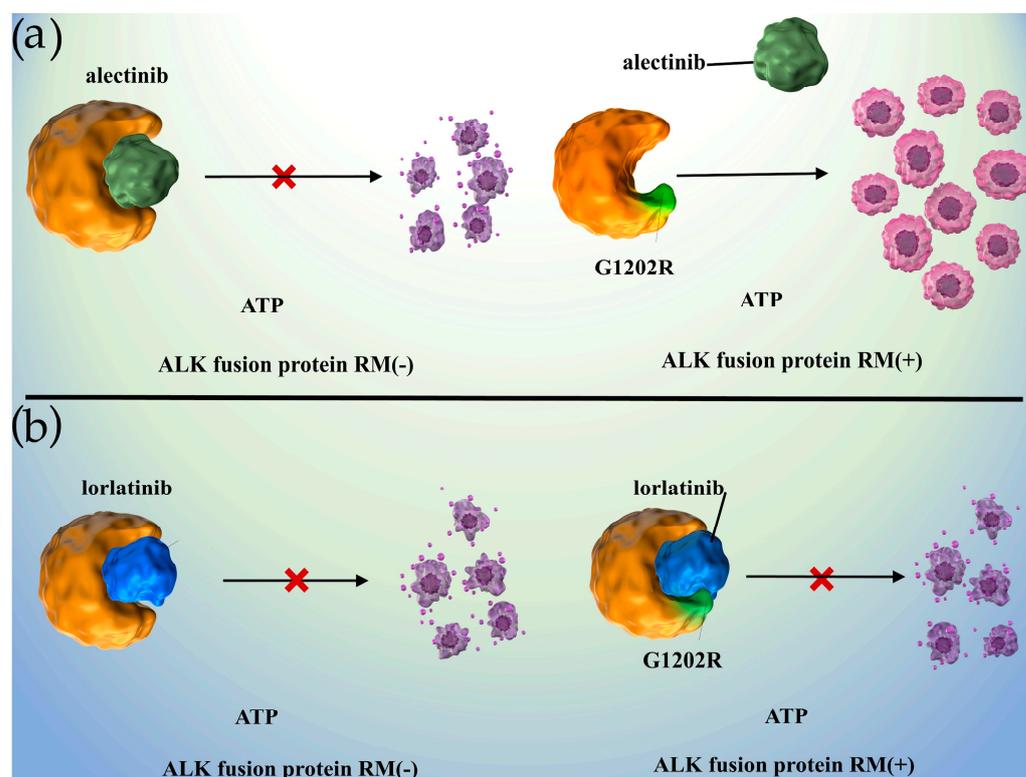


Figure 2. Different pharmacological activities of (a) alectinib and (b) lorlatinib toward ALK fusion proteins with resistance mutations. (a) Resistance mutations (e.g., G1202R) prevent alectinib from combining with the ATP-binding domain of the ALK fusion protein. (b) Lorlatinib successfully associated with the ALK fusion protein's ATP-binding pocket with resistance mutations, and downstream signals associated with tumor progression are downregulated; ATP, adenosine triphosphate; RM, resistance mutation; ALK, anaplastic lymphoma kinase.

Although the G1202R mutation is rarely detected in crizotinib-relapsed clinical samples (2%), it is the most frequent resistance mutation following the administration of second-generation ALK inhibitors, accounting for 40–65% of all acquired resistance mutations [31,64,65]. Second-generation ALK inhibitors have greater potency than crizotinib; thus, resistance mutation purification is suggested. Given its poor potency against ALK kinase activity, crizotinib may select less potent resistance mutations. Alectinib-resistant mutations include G1202R and I1171N. Interestingly, heterogeneous tumor evolution and high tumor mutation levels possibly contribute to the rapid acquisition of alectinib resistance [66]. Ceritinib resistance mutations include T1151K, T1151R, F1174V, and G1202R [58,67,68], whereas brigatinib resistance mutations include D1203N and E1210K [69,70].

In 2018 lorlatinib was approved by the U.S. FDA for the treatment of patients with ALK-p NSCLC. Lorlatinib displays activity against all potential ALK-TKI resistance mutations, including L1196M, G1269A, and G1202R [64]. Lorlatinib is considered to be one of ALK inhibitors that may hold promise for overcoming the high frequency of ALK inhibitor resistance mutations, particularly G1202R [64]. Next-generation sequencing results showed that ALK mutations in several lorlatinib-resistant individuals accumulate during consecutive dosing of an ALK inhibitor. ALK combined mutations reported to date include L1196M/D1203N, F1174L/G1202R, and C1156Y/G1269A [71]. ALK D1203N is more common during failure of lorlatinib than during failure of second-generation ALK inhibitors [69]. Interestingly, some ALK inhibitor-related compound mutations conferring lorlatinib resistance led to re-sensitization to first- or second-generation ALK inhibitors [13]. ALK amplification involves an ALK-dependent resistance mechanism. Crizotinib causes ALK gene amplification as a resistance mechanism; however, its occurrence is rarer than that of ALK resistance mutations. Moreover, second- and third-generation ALK inhibitors are not identified, suggesting that they may not be clinically relevant as highly potent ALK inhibitors [64].

Activating bypass signaling pathways is important in ALK-independent resistance mechanisms via gene alterations, autocrine signaling with ligand overexpression, and feedback signaling. Such pathways include epidermal growth factor receptor signaling [30,72], KIT amplification [31], MET amplification [73–75], IGF-1R activation [76], BRAF V600E mutation [74], and increased expression of the MET ligand of hepatocyte growth factor [77]. Different from the previous addicted ALK activation, the bypass signal activation leads to the activation of downstream factors such as the RAF/MEK/ERK and PI3K/AKT pathways, and provides survival signals. P-glycoproteins (P-gp) encoded by the multidrug resistance 1 (*MDR1*) gene can induce multidrug resistance through the ATP-dependent efflux of chemotherapeutic agents [78]. P-gp actively excludes the substrate from the blood at the BBB, thereby limiting CNS penetration [79]. In most patients with crizotinib failure the CNS is the primary metastatic site [80]. Brain accumulation of ceritinib is restricted by P-gp and BCRP [81]; otherwise, alectinib and lorlatinib are non P-gp substrates that can achieve higher concentrations in the CNS. As a potential resistance mechanism, P-gp overexpression was determined in patients with tumor tissues of crizotinib- and ceritinib-resistant ALK mutant NSCLC [82]. Phenotypic changes are also a mechanism of ALK inhibitor resistance in ALK-mutated NSCLC. Epithelial-to-mesenchymal transition (EMT) and small cell lung cancer (SCLC) or squamous cell carcinoma conversion have been reported after ALK inhibitor therapy for ALK-p adenocarcinoma [83–86]. Histological changes in tumors from adenocarcinoma to SCLC have been reported in 3–10% of patients with EGFR-TKI-resistant NSCLC [87]. The histological changes may be associated with retinoblastoma loss acquisition and genetic/epigenetic features of SCLC, such as EGFR-TKI resistance [88]. With regard EMT, molecular mechanisms such as inhibitor resistance are unknown. Moreover, histone deacetylase inhibitors can overcome this EMT-mediated ALK inhibitor resistance by reversing EMT pre-clinically.

1.5. Significance of the Present Meta-Analysis

Based on these prospects, we conducted a comprehensive literature search and network meta-analysis (NMA; UMIN 000049680). The results of this meta-analysis provide important information to guide clinical oncologists treating non-small cell lung cancer when considering treatment strategies for patients with ALK-p, ALK inhibitor-naive advanced NSCLC.

2. Results

2.1. Systematic Review

A systematic literature search identified 2724 studies (478 from PubMed [89], 834 from Cochrane Central Register of Controlled Trials [CENTRAL] [90], 356 from EMBASE [91], and 1056 from SCOPUS [92]), with 1907 that remained after removing duplicates. After

employing the Patients, Interventions, Comparisons, Outcomes, and Study Design (PICOS) approach, nine research studies were selected for inclusion in the NMA, of which two articles compared crizotinib with platinum based chemotherapy (PROFILE1014 [28] and PROFILE1029 [29]), three compared alectinib with crizotinib (ALEX [35], J-ALEX [37], and ALESIA [38]), and one each compared ceritinib with chemotherapy, brigatinib with crizotinib, lorlatinib with crizotinib, and ensartinib with crizotinib (ACEND-4 [36], ALTA-1L [34], CROWN [33], and eXalt3 [41], respectively). The study selection process is summarized in Figure 3. The primary inclusion criteria are summarized in Table S1, and the main characteristics of the included studies are summarized in Table S2. The data of 2484 patients from the nine studies (chemotherapy: 461, crizotinib: 1025, ceritinib: 189, alectinib: 380, brigatinib: 137, lorlatinib: 149, ensartinib 143) were used for the analysis. A network map of the present network meta-analysis is shown in Figure 4.

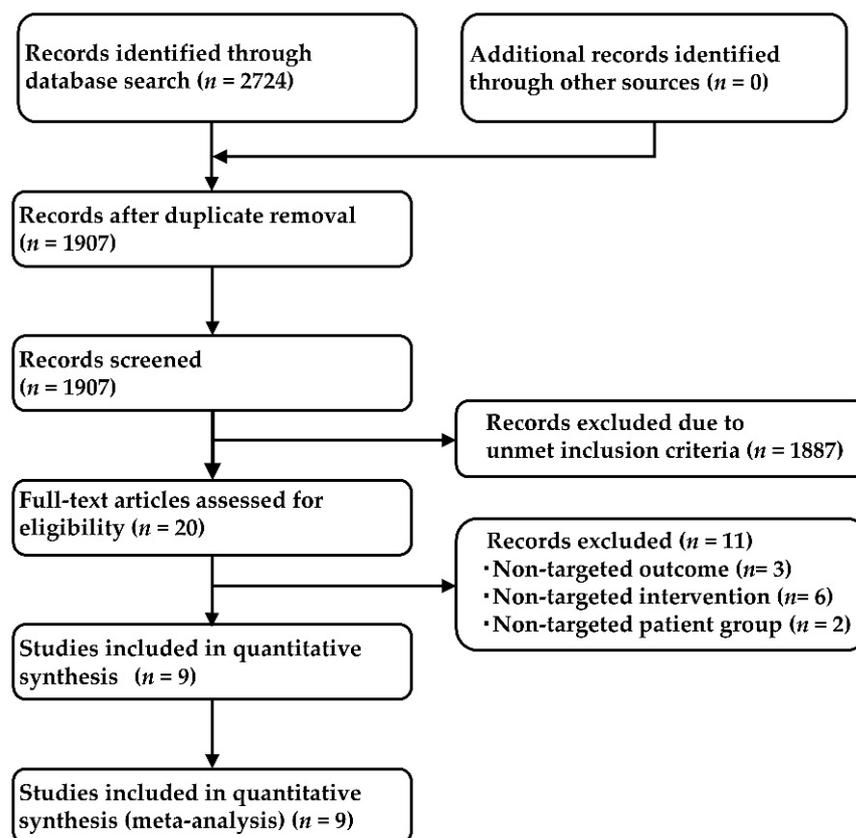


Figure 3. Process diagram of the research selection.

2.2. Comparison of ALK Inhibitors by Generation

2.2.1. PFS in Overall Patients

The efficacies of chemotherapy, first-generation ALK inhibitors (crizotinib), second-generation ALK inhibitors (ceritinib, alectinib, brigatinib, and ensartinib), and third-generation ALK inhibitors (lorlatinib) in prolonging PFS were compared between generations in the overall patient population of ALK-p, ALK inhibitor-naïve advanced NSCLC. Statistically significant differences were found among all generations compared (3rd vs. 2nd, 3rd vs. 1st, 2nd vs. 1st, 3rd vs. Chemo, 2nd vs. Chemo, and 1st vs. Chemo) (Figure 5a, Table S3). Ranking by generation showed that third-generation ALK inhibitors had the best PFS benefit, followed by second-generation ALK inhibitors, first-generation ALK inhibitors, and chemotherapy (Table S4).

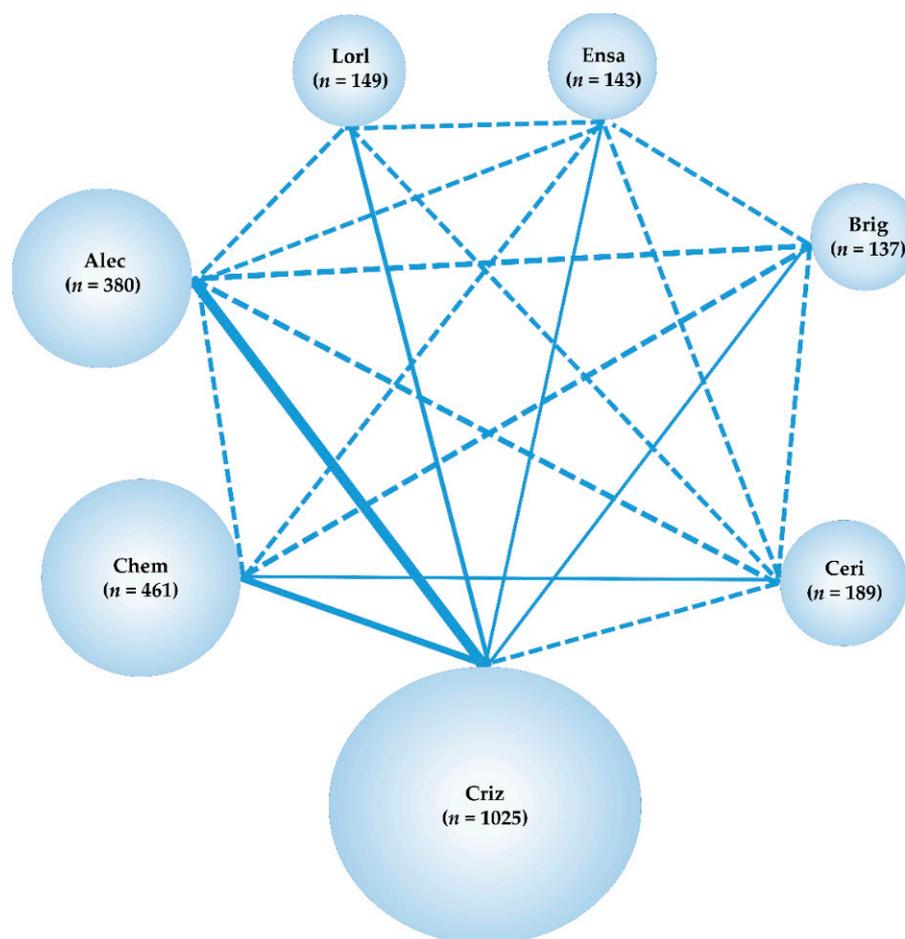


Figure 4. Network map of the seven therapeutic groups: ensartinib, lorlatinib, brigatinib, alectinib, ceritinib, crizotinib, and chemotherapy. In this network map randomized controlled trials (RCTs) were represented by a solid line, with the breadth of the solid line correlated with the numbers of studies included. Broken lines represent no head-to-head RCTs and trial to comparison of treatments. n is the total number of patients in each group; Ensa, ensartinib; Lorl, lorlatinib; Brig, brigatinib; Alec, alectinib; Criz, crizotinib; Ceri, ceritinib; Chem, chemotherapy.

2.2.2. PFS in a Subgroup of Patients with CNS Metastases

The efficacies of chemotherapy, first-generation ALK inhibitors (crizotinib), second-generation ALK inhibitors (ceritinib, alectinib, brigatinib, and ersatinib), and third-generation ALK inhibitor (lorlatinib) in prolonging the PFS in a subgroup of patients with CNS metastases were compared. Statistically significant differences were found between third- and second-generation ALK inhibitors, third- and first-generation ALK inhibitors, second- and first-generation ALK inhibitors, third-generation ALK inhibitors and chemotherapy, and second-generation ALK inhibitors and chemotherapy, but not between first-generation ALK inhibitors and chemotherapy (Figure 5b, Table S3). Ranking by generation showed that third-generation ALK inhibitors had the highest PFS efficacy, followed by second-generation ALK inhibitors, first-generation ALK inhibitors, and chemotherapy (Table S4).

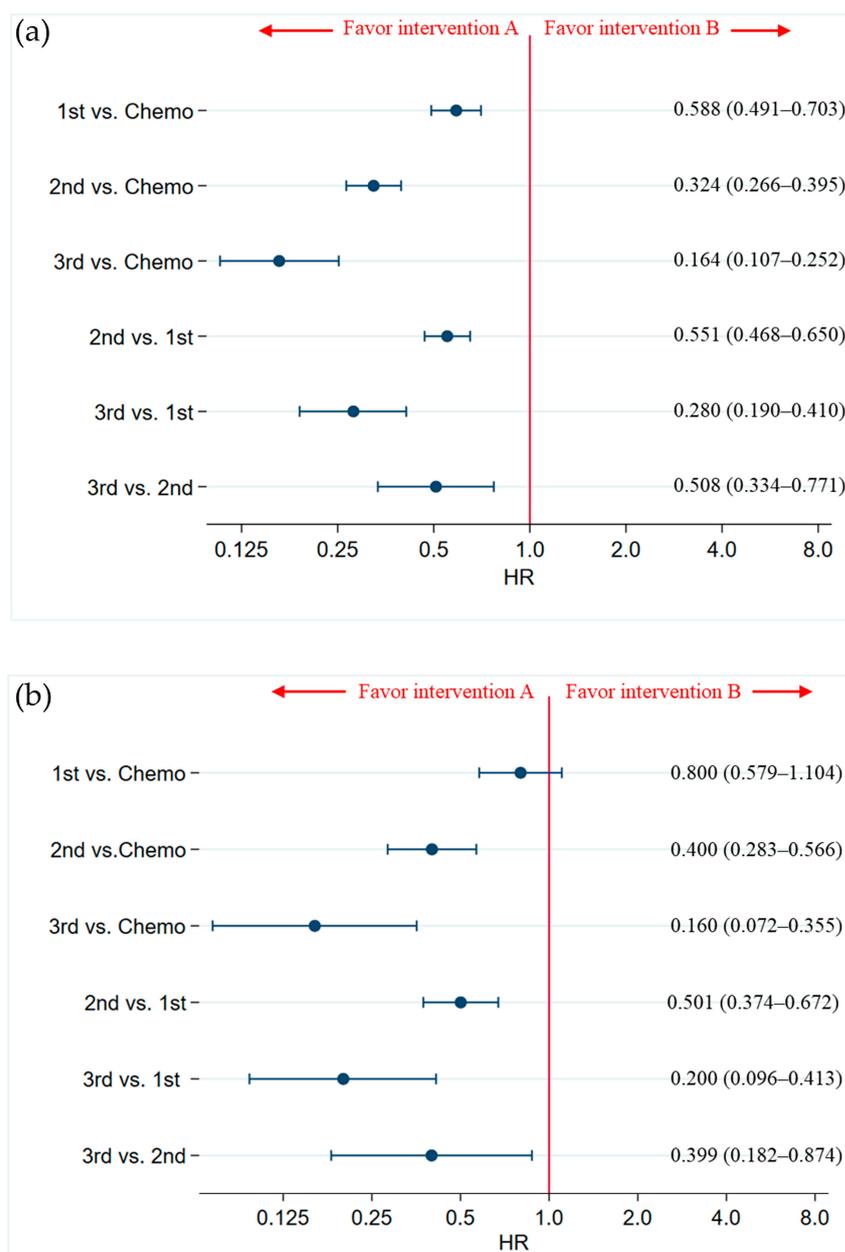


Figure 5. Comparison of the efficacies of chemotherapy, first-generation ALK inhibitors (crizotinib), second-generation ALK inhibitors (ceritinib, alectinib, brigatinib, and ensartinib), and third-generation ALK inhibitors (lorlatinib) in prolonging the PFS of (a) overall patients with ALK-p, ALK inhibitor-naive advanced NSCLC and (b) a subgroup of patients with CNS metastases. Data are expressed as hazard ratios (HRs) and 95% credible intervals (CrIs); ALK, anaplastic lymphoma kinase; ALK-p, anaplastic lymphoma kinase rearrangement positive; NSCLC, non-small cell lung cancer; CNS, central nervous system.

2.3. Comparison among ALK Inhibitors

2.3.1. PFS in Overall Patients

A paired comparison of the efficacies of ensartinib, lorlatinib, brigatinib, alectinib, ceritinib, crizotinib, and chemotherapy in prolonging the PFS of the overall patients is presented in Table S5. Ranking by drug showed that lorlatinib was the most effective in prolonging PFS, followed by alectinib, brigatinib, ensartinib, crizotinib, ceritinib, and chemotherapy (Table S6).

2.3.2. PFS in a Subgroup of Patients with CNS Metastases

A paired comparison of the efficacies of ensartinib, lorlatinib, brigatinib, alectinib, ceritinib, crizotinib, and chemotherapy in prolonging the PFS in the subgroup of patients with CNS metastases is presented in Table S5. Ranking by drug showed that lorlatinib was the most effective in prolonging PFS, followed by brigatinib, alectinib, ensartinib, crizotinib, ceritinib, and chemotherapy (Table S6).

2.3.3. PFS in Non-Asian Subgroup

A paired comparison of the efficacies of ensartinib, lorlatinib, brigatinib, alectinib, ceritinib, crizotinib, and chemotherapy in prolonging the PFS in non-Asian subgroup was presented in Table S7. Ranking by drug showed that lorlatinib was the most effective in prolonging PFS, followed by alectinib, brigatinib, ensartinib, ceritinib, crizotinib, and chemotherapy (Table S8).

2.3.4. PFS in Asian Subgroup

A paired comparison of the efficacies of ensartinib, lorlatinib, brigatinib, alectinib, ceritinib, crizotinib, and chemotherapy in prolonging the PFS in the subgroup of patients with CNS metastases is presented in Table S7. Ranking by drug showed that ensartinib was the most effective in prolonging PFS, followed by alectinib, brigatinib, lorlatinib, crizotinib, ceritinib, and chemotherapy (Table S8).

2.4. Evaluation of Bias

The qualities of the studies that were included were appraised on the basis of the Cochrane-recommended Risk of Bias tool 2 (RoB2) [93]. Nine studies that were included in the present systematic review and NMA were judged as “some concerns” in the overall assessment. Specifically, they were all open-label studies judged as some concerns in terms of bias due to deviations from intended interventions or bias in measurement of the outcome. PROFILE 1029 [29] was also judged as some concerns in terms of bias arising from randomization because this process was not sufficiently detailed. No domains were identified as high risk (Figure S1).

2.5. Sensitivity Analysis

Of the nine studies included in this analysis, three (ALTA-1L [34], J-ALEX [37] and eXalt3 [41]) included a group of patients who had received partial chemotherapy. To address this heterogeneity, a sensitivity analysis [94,95] was performed by eliminating patients with previous exposure to chemotherapy from these three trials. Consequently, the paired comparison results of the four treatment groups were sustained (Table S9). Further, comparable results were achieved for the ranking of the four treatment groups (Table S10). These results indicated that the inclusion or exclusion of the patients with previous chemotherapy did not impact the overall definitive conclusions.

2.6. Assessment of Study-to-Study Heterogeneity

In addition, ALEX [35], J-ALEX [37], ALESIA [38], ALTA-L1 [34], and eXalt3 [41] compared crizotinib with second-generation ALK inhibitors. Therefore, we also evaluated the inter-trial heterogeneity of PFS in these five trials [96]. Results showed that I^2 was 49.8% ($p = 0.093$), indicating mild between-trial heterogeneity (Figure S2).

3. Discussion

This review provides a comprehensive overview of future therapeutic strategies for ALK-p, ALK inhibitor-naïve advanced NSCLC with CNS metastases, mechanisms underlying acquired resistance, and strategies to overcome this challenge.

The efficacies of six ALK inhibitors (ensartinib, lorlatinib, brigatinib, alectinib, ceritinib, and crizotinib) were compared with that of chemotherapy in the overall patients with ALK-p, ALK inhibitor-naïve advanced NSCLC and in the subgroup of patients with CNS

metastases. The comparisons were conducted by ALK inhibitor generation and by drug. Generation-specific comparison results showed that third-generation ALK inhibitors had the best efficacy in prolonging the PFS of the overall patient population and in the subgroup of patients with CNS metastases. Statistically significant differences in efficacy were found between third-generation ALK inhibitors and second- and first-generation ALK inhibitors in the overall patients and in the subgroup of patients with CNS metastases. Significant differences in efficacy in prolonging PFS were also demonstrated between second- and first-generation ALK inhibitors. Drug-specific comparison results showed that lorlatinib had the best efficacy in prolonging PFS in the overall patients, followed by alectinib, brigatinib, ensartinib, ceritinib, crizotinib, and chemotherapy. The differences between lorlatinib and brigatinib, ensartinib, ceritinib, crizotinib, and chemotherapy were statistically significant. Analysis of the subgroup of patients with CNS metastases showed that lorlatinib exerted the most favorable effect, followed by brigatinib, ensartinib, ceritinib, crizotinib, and chemotherapy. The differences between lorlatinib and ensartinib, ceritinib, crizotinib, and chemotherapy were statistically significant.

Several previous meta-analyses have compared the efficacies of ALK inhibitors in patients with ALK-p, ALK inhibitor-naïve advanced NSCLC [39,40,97–104]. However, a generation-specific comparison of the efficacies of six ALK inhibitors (ensartinib, lorlatinib, alectinib, brigatinib, ceritinib, and crizotinib) in patients with CNS metastases remains lacking. For the first time, we compared the efficiencies of these six ALK inhibitors by generation in prolonging the PFS of the overall patient population and a subgroup of patients with CNS metastases. Results showed that the third-generation ALK inhibitors were better than the other generations in prolonging the PFS of the overall patients and the subgroup of patients with CNS metastases, respectively.

Notable findings were also obtained in drug-specific comparisons. For instance, lorlatinib was significantly better than brigatinib in prolonging the PFS of the overall patients, but their difference was not significant in the subgroup of patients with CNS metastases. In addition, evaluation results showed that brigatinib ranked third in the overall participant population but second, above alectinib, in the subgroup of patients with CNS metastases. These results support the theory that brigatinib, along with lorlatinib, is a potential first-line treatment option for ALK-p, ALK inhibitor-naïve advanced NSCLC with CNS metastases.

Our results also suggest that lorlatinib has potential as a novel first-line treatment for ALK-p, ALK inhibitor-naïve advanced NSCLC. However, lorlatinib should not be recommended for all patients with this disease because its tolerability is reportedly lower than that of alectinib, and its effect on OS was not evaluated. Furthermore, in our analysis of racial differences lorlatinib ranked highest in PFS among non-Asians, whereas ensartinib ranked highest among Asians. Further clinical studies are warranted to develop a detailed treatment strategy for first-line treatment of ALK-p ALK-untreated advanced NSCLC.

This NMA has several limitations. First, the study compared the efficacies of six ALK inhibitors in the overall patients and subgroup of patients with CNS metastases. However, OS and safety outcomes were not analyzed because of insufficient data reported for CNS metastases. Further validation is needed to determine whether the results of this comparative analysis of PFS in the subgroup with CNS metastases will be consistent with the results of the comparative analyses of OS and safety outcomes. Second, this analysis included patients who had received systemic anticancer chemotherapy and those who had not. Although the results of sensitivity analysis showed that the inclusion and exclusion of patients who had undergone systemic anti-cancer chemotherapy did not apparently influence the results, we cannot completely rule out the potential impact of this heterogeneity on the final conclusions. Third, mild heterogeneity, although not statistically significant, was demonstrated in the five studies comparing second-generation ALK inhibitors with crizotinib (ALEX [35], J-ALEX [37], ALESIA [38], ALTA-L1 [34], and eXalt3 [41]). Although the NMA used a Bayesian model that assumed potential heterogeneity among the included studies, we cannot completely rule out the possibility that individual potential heterogene-

ity may have influenced the final conclusions. Finally, the number of included studies is as few as nine references, and we cannot completely exclude the possibility that the insufficient number of included studies may affect the convergence status of the models in the Bayesian network meta-analysis. To address this issue, the convergence status of our model was visually assessed. The results confirmed the favorable convergence status of our analysis. These results suggest that the number of studies covered was sufficient, at least in terms of model convergence.

4. Materials and Methods

4.1. Comprehensive Literature Search

A comprehensive literature search was conducted to identify relevant reports published from 1946 to the present. On 3 December 2022, four databases (PubMed [89], CENTRAL [90], EMBASE [91], and SCOPUS [92]) were searched for studies on NSCLC and ALK inhibitors by using keywords such as “ensartinib”, “lorlatinib”, “brigatinib”, “alectinib”, “ceritinib”, “crizotinib”, and their Medical Subject Headings terms. Appendix A shows the keywords used in the search. The strategy was also used for searching the EMBASE, CENTRAL, and SCOPUS databases to ensure comprehensiveness, robustness, and certainty of the search. The strategy used for searching PubMed was also used for searching EMBASE, CENTRAL, and SCOPUS. If data necessary for the analysis were not available from the journals, the authors were consulted by e-mailing the corresponding authors. The main purpose of this systematic review was to verify all publicized phase III clinical trials in order to make comparisons and rank the efficacy of the seven therapeutic groups in terms of efficacy; namely, ensartinib, lorlatinib, brigatinib, alectinib, ceritinib, crizotinib, and chemotherapy in patients with ALK-p advanced NSCLC. The analyses in this review were based on the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines [105] and the PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions (PRISMA-NMA) [106]. Two investigators (KA and AA) independently conducted the literature search. Inclusion and exclusion criteria were adapted to the retrieved studies using the PICOS approach to ensure the currency of indirect comparative analyses by handling potential heterogeneity in clinical and methodological aspects between studies.

4.2. Quality Assessment

We assessed the quality of the RCTs included in the NMA using the RoB2 recommended by the Cochrane Collaboration [93]. The following parameters were rated as low risk, some concerns, or high risk: (1) bias arising from the randomization process; (2) bias due to deviations from the intended intervention; (3) bias due to missing outcome data; (4) bias in measurement of the outcome; and (5) bias in selection of the reported result. Evaluations were performed independently by two researchers (KA and SK), and any discrepancies were resolved by a third researcher (TY).

4.3. Inclusion Criteria (Pre-Defined PICOS)

4.3.1. Patients

The following inclusion criteria were used: (1) age 18 years or older; (2) histologically or cytologically confirmed progressive or metastatic ALK-p NSCLC; (3) performance status of 0 to 2 (on a 5-point scale, higher numbers indicating more severe disability); (4) at least one measurable lesion assessed according to RECIST version 1.1,25; and (5) no prior exposure to ALK-targeted therapy.

4.3.2. Intervention

In this analysis, patients treated with ensartinib (225 mg/day), lorlatinib (100 mg/day), brigatinib (180 mg/day), alectinib (300 or 600 mg/day), ceritinib (750 mg/day), crizotinib (250 mg/day), and platinum-based chemotherapy (all doses and dosage forms were approved, recommended, or specified in the Phase III study) were considered. Phase III

trials that included any of these agents were eligible for inclusion. Crizotinib was the first approved ALK inhibitor and the former first-line agent for initial therapy, and platinum-based chemotherapy was the first-line agent for ALK-p treatment-naïve NSCLC prior to the approval of crizotinib. Thus, crizotinib or platinum-based chemotherapy was assumed as the common comparator for each treatment.

4.3.3. Outcome

The primary efficacy endpoint was PFS in all participants and in the subgroup of patients with CNS metastases, with corresponding HRs and 95% credible intervals (CrIs). To rank the relative efficacy of each therapeutic approach, the surface under the cumulative rank under the curve (SUCRA) values were calculated for each endpoint, with higher SUCRA values corresponding to a more preferred therapeutic approach for the corresponding endpoints [107]. These analyses were performed on the overall participants and on each subgroup with CNMS. In addition, analyses were performed also by race (Asian and non-Asian) to account for demographics. To be eligible for this systematic review and NMA, the trial under analysis had to include at least one defined efficacy endpoint. These defined endpoints were analyzed only if data were available from the included trials. Two authors (KA and SK) independently extracted relevant data and resolved discrepancies in consultation with the third author (TY).

4.3.4. Study Design

The research for this systematic review and meta-analysis was a phase III trial of a parallel-group RCT.

4.4. Statistical Analysis

The Bayesian NMA was performed following robustly established methods developed at the National Institute of Medical Research [108,109]. We applied a non-informative prior distribution, employed the standard Bayesian model described by Dias et al. [108,109], and assumed inconsistency and heterogeneity among the included studies. Gibbs sampling on the basis of a Markov chain Monte Carlo method was utilized to evaluate the posterior distribution of the effect size [110,111]. The number of iterations was set to 50,000, with the first 10,000 being a burn-in sample to eliminate the influence of initial values. Effect sizes were expressed as HR and its 95% CrI, and the difference in effect size between treatment groups for each endpoint was considered significant if the 95% CrI did not include 1. SUCRA values ranged from 0% to 100%, with higher SUCRA values indicating better treatment outcomes [107]. The Brooks–Gelman–Rubin (BGR) diagnostic method was also used for the convergent diagnosis of all comparisons [112,113]. Both visual and BGR diagnostics confirmed the convergence of the model. OpenBUGS 1.4.0 (MRC Biostatistics Unit, Cambridge Public Health Research Institute, /jk, Cambridge, UK) was used for the Bayesian analysis, and STATA (ver. 14, StataCorp., College Station, TX, USA) was used to visualize the results (College Station, TX, USA).

4.5. Sensitivity Analysis

A sensitivity analysis [95] was conducted by including or excluding research that was deemed heterogeneous based on the existence of conceptual heterogeneity between the included studies. This analysis was performed to evaluate whether the inclusion or exclusion of conceptually heterogeneous studies impacts the overall final conclusions.

4.6. Assessment for between-Study Heterogeneity

We evaluated the statistical heterogeneity among the included studies to determine whether it impacts the final conclusions [96]. Statistical heterogeneity between studies was expressed as I² statistic (%). A heterogeneity between 30% and less than 50% was considered to indicate mild heterogeneity between studies, between 50% and 70% moderate

heterogeneity, and greater than 70% high heterogeneity. The I² statistic was calculated using pairwise meta-analysis with a random-effects model.

4.7. Ethical Aspects

Institutional Review Board approval and patient consent were waived because of the retrospective nature of this systematic review.

5. Conclusions

This review outlines future treatment strategies and future prospects for ALK-p, ALK inhibitor-naïve advanced NSCLC with CNS metastasis, with a focus on elucidating and overcoming acquired resistance mechanisms. In addition, the therapeutic efficacies of ALK inhibitors in prolonging the PFS of the overall patients with ALK-p, ALK inhibitor-naïve advanced NSCLC and a subgroup of patients with CNS metastases are compared by drug and by generation. Generation-specific comparison shows that third-generation ALK inhibitors are significantly more efficient than second-generation and first-generation ALK inhibitors in prolonging the PFS of the overall patients and subgroup of patients with CNS metastases. Drug-specific comparison demonstrates that lorlatinib is the most efficient in prolonging the PFS of the overall patients and subgroup of patients with CNS metastases. Notably, although a significant difference in efficacy of prolonging PFS was found between lorlatinib and brigatinib in the overall patient population, no such significant difference was found in the subgroup of patients with CNS metastases. These results indicate a trend toward brigatinib as a promising first-line treatment option along with lorlatinib in the subgroup of patients with CNS metastases. These results can serve as a foundation for basic, clinical, and translational research and guide clinical oncologists in developing individualized treatment strategies for ALK-p ALK inhibitor-naïve advanced NSCLC. This NMA includes direct and indirect comparisons, and additional studies are warranted to confirm the results. The results of this analyses can serve as a basis for further clinical studies formulating novel treatment strategies for ALK-p ALK inhibitor-naïve advanced NSCLC with CNS metastases or acquired resistance mutations.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/ijms24032242/s1>.

Author Contributions: Conceptualization, K.A., R.M., Y.K., S.K., T.Y., A.T., T.O. and H.S.; Data curation, K.A., R.M., S.K. and T.Y.; Formal analysis, K.A.; Funding acquisition, K.A., A.T. and H.S.; Investigation, K.A., R.M., S.K. and T.Y.; Methodology, K.A., R.M., S.K. and T.Y.; Project administration, K.A., R.M., S.K. and T.Y.; Resources, K.A., A.T. and H.S.; Software, K.A.; Supervision, K.A., Y.K., T.Y., A.T., T.O. and H.S.; Validation, K.A., R.M., Y.K., S.K., T.Y., A.T., T.O. and H.S.; Visualization, K.A.; Writing—original draft, K.A.; Writing—review and editing, K.A., R.M., Y.K., S.K., T.Y., A.T., T.O. and H.S. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Ethical review and approval were waived for this clinical study because it is a systematic review and meta-analysis, and only previously published de-identified patient data were used.

Informed Consent Statement: Patient consent was waived because of the retrospective nature of this systematic data review and meta-analysis.

Data Availability Statement: The authors affirm that the analyzed datasets in this present work are available from the corresponding author upon reasonable request.

Acknowledgments: We specially express our gratitude to Toshiro Tango of the Research Center for Medical Statistics, Hisashi Noma of the Institute of Statistical Mathematics for statistical analysis support, and Takashi Tsujino of Science Graphics Corporation for graphical presentation support. We would like to gratefully thank the members of the Department of Respiriology and Allergology, Showa University School of Medicine and the Showa University Research Administration Center for their insightful comments and valuable suggestions.

Conflicts of Interest: The authors declare no conflict of interest.

Appendix A. Search Strategies in PubMed

Table A1. Search Strategies in PubMed (Searched on 3 December 2022).

Search	Query	Results
#1	("Non-Small Cell Lung Cancer" OR "Non-Small Cell Lung Carcinoma" OR "Non Small Cell Lung Carcinoma" OR "Non-Small-Cell Lung Carcinoma" OR "Non small Cell Lung Cancer" OR "Non-Small-Cell Lung Carcinomas" OR "NSCLC")	95,433
#2	("crizotinib" [ALL] OR ("crizotinib" [Supplementary Concept] OR "PF-02341066" [ALL] OR "PF 02341066" [ALL] OR "PF02341066" [ALL] OR "xalkori" [ALL] OR "ceritinib" [ALL] OR "ceritinib" [Supplementary Concept] OR "LDK-378" [ALL] OR "LDK 378" [ALL] OR "LDK378" [ALL] OR "zykadia" [ALL]) OR "alectinib" [ALL] OR ("alectinib" [Supplementary Concept] OR "CH-5424802" [ALL] OR "CH 5424802" [ALL] OR "CH5424802" [ALL] OR "RO-5424802" [ALL] OR "RO 5424802" [ALL] OR "RO5424802" [ALL] OR "alecensa" [ALL] OR "brigatinib" [ALL] OR ("brigatinib" [Supplementary Concept] OR "AP-26113" [ALL] OR "AP 26113" [ALL] OR "AP26113" [ALL] OR "alunbrig" [ALL]) OR "lorlatinib" [ALL] OR ("lorlatinib" [Supplementary Concept] OR "PF-06463922" [ALL] OR "PF 06463922" [ALL] OR "PF06463922" [ALL] OR "lorbrena" [ALL]) OR "ensartinib" [ALL] OR ("ensartinib" [Supplementary Concept] OR "X-396" [ALL]) OR "cisplatin" [ALL] OR "cisplatin" [Supplementary Concept] OR "CDDP" [ALL] OR "carboplatin" [ALL] OR "carboplatin" [Supplementary Concept] OR "CBDCA" [ALL] OR "Platinum" [ALL])	141,836
#3	("anaplastic lymphoma kinase" OR "ALK inhibitor" OR "ALK" OR "ALKI")	14,355
#4	("Randomized Controlled trial" [Title/Abstract] OR "Controlled clinical trial" [Title/Abstract] OR "Randomized" [Title/Abstract] OR "Placebo" [Title/Abstract] OR "Randomly" [Title/Abstract] OR "Trial" [Title/Abstract] OR "Drug Therapy" [Title/Abstract] OR "Groups" [Title/Abstract])	3,510,441
#5	#1 AND #2 AND #3 AND #4	478

References

- The Japanese Lung Cancer Society Guideline. 2022. Available online: <https://www.haigan.gr.jp/guideline/2022/> (accessed on 3 December 2022).
- Cognigni, V.; Pecci, F.; Lupi, A.; Pinterpe, G.; De Filippis, C.; Felicetti, C.; Cantini, L.; Berardi, R. The landscape of ALK-rearranged non-small cell lung cancer: A comprehensive review of clinicopathologic, genomic characteristics, and therapeutic perspectives. *Cancers* **2022**, *14*, 4765. [[CrossRef](#)] [[PubMed](#)]
- Duma, N.; Santana-Davila, R.; Molina, J.R. Non-small cell lung cancer: Epidemiology, screening, diagnosis, and treatment. *Mayo Clin. Proc.* **2019**, *94*, 1623–1640. [[CrossRef](#)] [[PubMed](#)]
- Yamaoka, T.; Kusumoto, S.; Ando, K.; Ohba, M.; Ohmori, T. Receptor tyrosine kinase-targeted cancer therapy. *Int. J. Mol. Sci.* **2018**, *19*, 3491. [[CrossRef](#)] [[PubMed](#)]
- Siegel, R.L.; Miller, K.D.; Fuchs, H.E.; Jemal, A. Cancer statistics, 2021. *CA Cancer J. Clin.* **2021**, *71*, 7–33. [[CrossRef](#)]
- Sung, H.; Ferlay, J.; Siegel, R.L.; Laversanne, M.; Soerjomataram, I.; Jemal, A.; Bray, F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J. Clin.* **2021**, *71*, 209–249. [[CrossRef](#)]
- Villa, M.; Sharma, G.G.; Manfroni, C.; Cortinovis, D.; Mologni, L. New advances in liquid biopsy technologies for anaplastic lymphoma kinase (ALK)—Positive cancer. *Cancers* **2021**, *13*, 5149. [[CrossRef](#)]
- Frankel, D.; Nanni, I.; Ouafik, L.H.; Camilla, C.; Pellegrino, E.; Beaufils, N.; Greillier, L.; Dutau, H.; Astoul, P.; Kaspi, E.; et al. Comparison between immunocytochemistry, FISH and NGS for ALK and ROS1 rearrangement detection in cytological samples. *Int. J. Mol. Sci.* **2022**, *23*, 10556. [[CrossRef](#)]
- Montella, M.; Ciani, G.; Granata, V.; Fusco, R.; Grassi, F.; Ronchi, A.; Cozzolino, I.; Franco, R.; Zito Marino, F.; Urraro, F.; et al. Preliminary experience of liquid biopsy in lung cancer compared to conventional assessment: Light and shadows. *J. Pers. Med.* **2022**, *12*, 1896. [[CrossRef](#)]
- Jóri, B.; Falk, M.; Hövel, I.; Weist, P.; Tiemann, M.; Heukamp, L.C.; Griesinger, F. Acquired G2032R resistance mutation in ROS1 to lorlatinib therapy detected with liquid biopsy. *Curr. Oncol.* **2022**, *29*, 6628–6634. [[CrossRef](#)]
- Vanni, I.; Coco, S.; Truini, A.; Rusmini, M.; Dal Bello, M.G.; Alama, A.; Banelli, B.; Mora, M.; Rijavec, E.; Barletta, G.; et al. Next-generation sequencing workflow for NSCLC critical samples using a targeted sequencing approach by ion torrent PGM™ platform. *Int. J. Mol. Sci.* **2015**, *16*, 28765–28782. [[CrossRef](#)]

12. Lin, J.J.; Zhu, V.W.; Yoda, S.; Yeap, B.Y.; Schrock, A.B.; Dagogo-Jack, I.; Jessop, N.A.; Jiang, G.Y.; Le, L.P.; Gowen, K.; et al. Impact of EML4-ALK variant on resistance mechanisms and clinical outcomes in ALK-positive lung cancer. *J. Clin. Oncol.* **2018**, *36*, 1199–1206. [[CrossRef](#)] [[PubMed](#)]
13. Okada, K.; Araki, M.; Sakashita, T.; Ma, B.; Kanada, R.; Yanagitani, N.; Horiike, A.; Koike, S.; Oh-Hara, T.; Watanabe, K.; et al. Prediction of ALK mutations mediating ALK-TKIs resistance and drug re-purposing to overcome the resistance. *eBiomedicine* **2019**, *41*, 105–119. [[CrossRef](#)] [[PubMed](#)]
14. Balasubramanian, S.K.; Sharma, M.; Venur, V.A.; Schmitt, P.; Kotecha, R.; Chao, S.T.; Suh, J.H.; Angelov, L.; Mohammadi, A.M.; Vogelbaum, M.A.; et al. Impact of EGFR mutation and ALK rearrangement on the outcomes of non-small cell lung cancer patients with brain metastasis. *Neurol. Oncol.* **2020**, *22*, 267–277. [[CrossRef](#)] [[PubMed](#)]
15. Gristina, V.; La Mantia, M.; Iacono, F.; Galvano, A.; Russo, A.; Bazan, V. The emerging therapeutic landscape of ALK inhibitors in non-small cell lung cancer. *Pharmaceuticals* **2020**, *13*, 474. [[CrossRef](#)]
16. Elsayed, M.; Christopoulos, P. Therapeutic sequencing in ALK+ NSCLC. *Pharmaceuticals* **2021**, *14*, 80. [[CrossRef](#)]
17. Morán, T.; Quiroga, V.; Gil Mde, L.; Vilà, L.; Pardo, N.; Carcereny, E.; Capdevila, L.; Muñoz-Mármol, A.M.; Rosell, R. Targeting EML4-ALK driven non-small cell lung cancer (NSCLC). *Transl. Lung Cancer Res.* **2013**, *2*, 128–141.
18. Lei, Y.; Lei, Y.; Shi, X.; Wang, J. EML4-ALK fusion gene in non-small cell lung cancer. *Oncol. Lett.* **2022**, *24*, 277. [[CrossRef](#)]
19. Papageorgiou, S.; Pashley, S.L.; O'Regan, L.; Khan, S.; Bayliss, R.; Fry, A.M. Alternative treatment options to ALK inhibitor monotherapy for EML4-ALK-driven lung cancer. *Cancers* **2022**, *14*, 3452. [[CrossRef](#)]
20. Chioureas, D.; Beck, J.; Baltatzis, G.; Vardaki, I.; Fonseca, P.; Tsesmetzis, N.; Vega, F.; Leventaki, V.; Eliopoulos, A.G.; Drakos, E.; et al. ALK+ anaplastic large cell lymphoma (ALCL)-derived exosomes carry ALK signaling proteins and interact with tumor microenvironment. *Cancers* **2022**, *14*, 2939. [[CrossRef](#)]
21. Daugrois, C.; Bessiere, C.; Dejean, S.; Anton-Leberre, V.; Commes, T.; Pyronnet, S.; Brousset, P.; Espinos, E.; Brugiere, L.; Meggetto, F.; et al. Gene expression signature associated with clinical outcome in ALK-positive anaplastic large cell lymphoma. *Cancers* **2021**, *13*, 5523. [[CrossRef](#)]
22. Wulf, A.M.; Moreno, M.M.; Paka, C.; Rampasekova, A.; Liu, K.J. Defining pathological activities of ALK in neuroblastoma, a neural crest-derived cancer. *Int. J. Mol. Sci.* **2021**, *22*, 11718. [[CrossRef](#)] [[PubMed](#)]
23. Verdura, S.; Encinar, J.A.; Fernández-Arroyo, S.; Joven, J.; Cuyàs, E.; Bosch-Barrera, J.; Menendez, J.A. Silibinin suppresses the hyperlipidemic effects of the ALK-tyrosine kinase inhibitor lorlatinib in hepatic cells. *Int. J. Mol. Sci.* **2022**, *23*, 9986. [[CrossRef](#)] [[PubMed](#)]
24. Matsumoto, S.; Takahashi, K.; Iwakawa, R.; Matsuno, Y.; Nakanishi, Y.; Kohno, T.; Shimizu, E.; Yokota, J. Frequent EGFR mutations in brain metastases of lung adenocarcinoma. *Int. J. Cancer* **2006**, *119*, 1491–1494. [[CrossRef](#)] [[PubMed](#)]
25. Zou, Z.; Xing, P.; Hao, X.; Wang, Y.; Song, X.; Shan, L.; Zhang, C.; Liu, Z.; Ma, K.; Dong, G.; et al. Intracranial efficacy of alectinib in ALK-positive NSCLC patients with CNS metastases—a multicenter retrospective study. *BMC Med.* **2022**, *20*, 12. [[CrossRef](#)]
26. Petrelli, F.; Lazzari, C.; Ardito, R.; Borgonovo, K.; Bulotta, A.; Conti, B.; Cabiddu, M.; Capitanio, J.F.; Brighenti, M.; Ghilardi, M.; et al. Efficacy of ALK inhibitors on NSCLC brain metastases: A systematic review and pooled analysis of 21 studies. *PLoS ONE* **2018**, *13*, e0201425. [[CrossRef](#)]
27. Ducray, S.P.; Natarajan, K.; Garland, G.D.; Turner, S.D.; Egger, G. The transcriptional roles of ALK fusion proteins in tumorigenesis. *Cancers* **2019**, *11*, 1074. [[CrossRef](#)]
28. Solomon, B.J.; Mok, T.; Kim, D.W.; Wu, Y.L.; Nakagawa, K.; Mekhail, T.; Felip, E.; Cappuzzo, F.; Paolini, J.; Usari, T.; et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. *N. Engl. J. Med.* **2014**, *371*, 2167–2177. [[CrossRef](#)]
29. Wu, Y.L.; Lu, S.; Lu, Y.; Zhou, J.; Shi, Y.K.; Sriuranpong, V.; Ho, J.C.M.; Ong, C.K.; Tsai, C.M.; Chung, C.H.; et al. Results of PROFILE 1029, a Phase III Comparison of first-Line crizotinib versus Chemotherapy in East Asian Patients with ALK-Positive Advanced non-small Cell Lung Cancer. *J. Thorac. Oncol.* **2018**, *13*, 1539–1548. [[CrossRef](#)]
30. Sasaki, T.; Koivunen, J.; Ogino, A.; Yanagita, M.; Nikiforow, S.; Zheng, W.; Lathan, C.; Marcoux, J.P.; Du, J.; Okuda, K.; et al. A novel ALK secondary mutation and EGFR signaling cause resistance to ALK kinase inhibitors. *Cancer Res.* **2011**, *71*, 6051–6060. [[CrossRef](#)]
31. Katayama, R.; Shaw, A.T.; Khan, T.M.; Mino-Kenudson, M.; Solomon, B.J.; Halmos, B.; Jessop, N.A.; Wain, J.C.; Yeo, A.T.; Benes, C.; et al. Mechanisms of acquired crizotinib resistance in ALK-rearranged lung Cancers. *Sci. Transl. Med.* **2012**, *4*, 120ra17. [[CrossRef](#)]
32. Kodama, T.; Tsukaguchi, T.; Yoshida, M.; Kondoh, O.; Sakamoto, H. Selective ALK inhibitor alectinib with potent antitumor activity in models of crizotinib resistance. *Cancer Lett.* **2014**, *351*, 215–221. [[CrossRef](#)] [[PubMed](#)]
33. Shaw, A.T.; Bauer, T.M.; de Marinis, F.; Felip, E.; Goto, Y.; Liu, G.; Mazieres, J.; Kim, D.W.; Mok, T.; Polli, A.; et al. First-line lorlatinib or crizotinib in advanced ALK-positive lung cancer. *N. Engl. J. Med.* **2020**, *383*, 2018–2029. [[CrossRef](#)] [[PubMed](#)]
34. Camidge, D.R.; Kim, H.R.; Ahn, M.J.; Yang, J.C.-H.; Han, J.Y.; Lee, J.S.; Hochmair, M.J.; Li, J.Y.; Chang, G.C.; Lee, K.H.; et al. Brigatinib versus crizotinib in ALK-Positive non-small-Cell Lung Cancer. *N. Engl. J. Med.* **2018**, *379*, 2027–2039. [[CrossRef](#)] [[PubMed](#)]
35. Peters, S.; Camidge, D.R.; Shaw, A.T.; Gadgeel, S.; Ahn, J.S.; Kim, D.W.; Ou, S.I.; Pérol, M.; Dziadziuszko, R.; Rosell, R.; et al. Alectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer. *N. Engl. J. Med.* **2017**, *377*, 829–838. [[CrossRef](#)]

36. Soria, J.C.; Tan, D.S.W.; Chiari, R.; Wu, Y.L.; Paz-Ares, L.; Wolf, J.; Geater, S.L.; Orlov, S.; Cortinovis, D.; Yu, C.J.; et al. First-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged non-small-cell lung cancer (ASCEND-4): A randomised, open-label, phase 3 study. *Lancet* **2017**, *389*, 917–929. [[CrossRef](#)] [[PubMed](#)]
37. Hida, T.; Nokihara, H.; Kondo, M.; Kim, Y.H.; Azuma, K.; Seto, T.; Takiguchi, Y.; Nishio, M.; Yoshioka, H.; Imamura, F.; et al. Alectinib versus crizotinib in patients with ALK-positive non-small-cell lung cancer (J-ALEX): An open-label, randomised phase 3 trial. *Lancet* **2017**, *390*, 29–39. [[CrossRef](#)]
38. Zhou, C.; Kim, S.W.; Reungwetwattana, T.; Zhou, J.; Zhang, Y.; He, J.; Yang, J.J.; Cheng, Y.; Lee, S.H.; Bu, L.; et al. Alectinib versus crizotinib in untreated Asian patients with anaplastic lymphoma kinase-positive non-small-cell lung cancer (ALESIA): A randomised phase 3 study. *Lancet Respir. Med.* **2019**, *7*, 437–446. [[CrossRef](#)]
39. Ando, K.; Manabe, R.; Kishino, Y.; Kusumoto, S.; Yamaoka, T.; Tanaka, A.; Ohmori, T.; Sagara, H. Comparative efficacy and safety of lorlatinib and alectinib for ALK-rearrangement positive advanced non-small cell lung cancer in Asian and non-Asian patients: A systematic review and network meta-analysis. *Cancers* **2021**, *13*, 3704. [[CrossRef](#)]
40. Ando, K.; Akimoto, K.; Sato, H.; Manabe, R.; Kishino, Y.; Homma, T.; Kusumoto, S.; Yamaoka, T.; Tanaka, A.; Ohmori, T.; et al. Brigatinib and alectinib for ALK rearrangement-positive advanced non-small cell lung cancer with or without central nervous system metastasis: A systematic review and network meta-analysis. *Cancers* **2020**, *12*, 942. [[CrossRef](#)]
41. Horn, L.; Wang, Z.; Wu, G.; Poddubskaya, E.; Mok, T.; Reck, M.; Wakelee, H.; Chiappori, A.A.; Lee, D.H.; Breder, V.; 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*, 1617–1625. [[CrossRef](#)]
42. Gadgeel, S.; Peters, S.; Mok, T.; Shaw, A.T.; Kim, D.W.; Ou, S.I.; Pérol, M.; Wrona, A.; Novello, S.; Rosell, R.; et al. Alectinib versus crizotinib in treatment-naive anaplastic lymphoma kinase-positive (ALK+) non-small-cell lung cancer: CNS efficacy results from the ALEX study. *Ann. Oncol.* **2018**, *29*, 2214–2222. [[CrossRef](#)] [[PubMed](#)]
43. Nishio, M.; Nakagawa, K.; Mitsudomi, T.; Yamamoto, N.; Tanaka, T.; Kuriki, H.; Zeaiter, A.; Tamura, T. Analysis of central nervous system efficacy in the J-ALEX study of alectinib versus crizotinib in ALK-positive non-small-cell lung cancer. *Lung Cancer* **2018**, *121*, 37–40. [[CrossRef](#)] [[PubMed](#)]
44. Johnson, T.W.; Richardson, P.F.; Bailey, S.; Brooun, A.; Burke, B.J.; Collins, M.R.; Cui, J.J.; Deal, J.G.; Deng, Y.L.; Dinh, D.; et al. Discovery of (10R)-7-amino-12-fluoro-2,10,16-trimethyl-15-oxo-10,15,16,17-tetrahydro-2H-8,4-(metheno)pyrazolo[4,3-h][2,5,11]-benzoxadiazacyclotetradecine-3-carbonitrile (PF-06463922), a macrocyclic inhibitor of anaplastic lymphoma kinase (ALK) and c-ros oncogene 1 (ROS1) with preclinical brain exposure and broad-spectrum potency against ALK-resistant mutations. *J. Med. Chem.* **2014**, *57*, 4720–4744. [[PubMed](#)]
45. Gadgeel, S.M.; Shaw, A.T.; Govindan, R.; Gandhi, L.; Socinski, M.A.; Camidge, D.R.; De Petris, L.; Kim, D.W.; Chiappori, A.; Moro-Sibilot, D.L.; et al. Pooled analysis of CNS response to alectinib in two studies of pretreated patients with ALK-positive non-small-cell lung cancer. *J. Clin. Oncol.* **2016**, *34*, 4079–4085. [[CrossRef](#)]
46. Hart, E.; Odé, Z.; Derieppe, M.P.P.; Groenink, L.; Heymans, M.W.; Otten, R.; Lequin, M.H.; Janssens, G.O.R.; Hoving, E.W.; van Vuurden, D.G. Blood-brain barrier permeability following conventional photon radiotherapy—A systematic review and meta-analysis of clinical and preclinical studies. *Clin. Transl. Radiat. Oncol.* **2022**, *35*, 44–55. [[CrossRef](#)]
47. Okawa, S.; Shibayama, T.; Shimonishi, A.; Nishimura, J.; Ozeki, T.; Takada, K.; Kayatani, H.; Minami, D.; Sato, K.; Fujiwara, K.; et al. Success of crizotinib combined with whole-brain radiotherapy for brain metastases in a patient with anaplastic lymphoma kinase rearrangement-positive non-small-cell lung cancer. *Case Rep. Oncol.* **2018**, *11*, 777–783. [[CrossRef](#)]
48. Van Grinsven, E.E.; Nagtegaal, S.H.J.; Verhoeff, J.J.C.; van Zandvoort, M.J.E. The impact of stereotactic or whole brain radiotherapy on neurocognitive functioning in adult patients with brain metastases: A systematic review and meta-analysis. *Oncol. Res. Treat.* **2021**, *44*, 622–636. [[CrossRef](#)]
49. Mills, C.N.; Nowshheen, S.; Bonner, J.A.; Yang, E.S. Emerging roles of glycogen synthase kinase 3 in the treatment of brain tumors. *Front. Mol. Neurosci.* **2011**, *4*, 47. [[CrossRef](#)]
50. Shimizu, Y.; Okada, K.; Adachi, J.; Abe, Y.; Narumi, R.; Uchibori, K.; Yanagitani, N.; Koike, S.; Takagi, S.; Nishio, M.; et al. GSK3 inhibition circumvents and overcomes acquired lorlatinib resistance in ALK-rearranged non-small-cell lung cancer. *NPJ Precis. Oncol.* **2022**, *6*, 16. [[CrossRef](#)]
51. Murray, B.W.; Zhai, D.; Deng, W.; Zhang, X.; Ung, J.; Nguyen, V.; Zhang, H.; Barrera, M.; Parra, A.; Cowell, J.; et al. TPX-0131, a potent CNS-penetrant, next-generation inhibitor of wild-type ALK and ALK-resistant mutations. *Mol. Cancer Ther.* **2021**, *20*, 1499–1507. [[CrossRef](#)]
52. Ou, S.I.; Nagasaka, M.; Brazel, D.; Hou, Y.; Zhu, V.W. Will the clinical development of 4th-generation “double mutant active” ALK TKIs (TPX-0131 and NVL-655) change the future treatment paradigm of ALK+ NSCLC? *Transl. Oncol.* **2021**, *14*, 101191. [[CrossRef](#)] [[PubMed](#)]
53. Romanidou, O.; Landi, L.; Cappuzzo, F.; Califano, R. Overcoming resistance to first/second generation epidermal growth factor receptor tyrosine kinase inhibitors and ALK inhibitors in oncogene-addicted advanced non-small cell lung cancer. *Ther. Adv. Med. Oncol.* **2016**, *8*, 176–187. [[CrossRef](#)] [[PubMed](#)]
54. Awad, M.M.; Shaw, A.T. ALK inhibitors in non-small cell lung cancer: Crizotinib and beyond. *Clin. Adv. Hematol. Oncol.* **2014**, *12*, 429–439.
55. Lin, J.J.; Riely, G.J.; Shaw, A.T. Targeting ALK: Precision medicine takes on drug resistance. *Cancer Discov.* **2017**, *7*, 137–155. [[CrossRef](#)] [[PubMed](#)]

56. Ai, X.; Niu, X.; Chang, L.; Chen, R.; Ou, S.I.; Lu, S. Next generation sequencing reveals a novel ALK G1128A mutation resistant to crizotinib in an ALK-Rearranged NSCLC patient. *Lung Cancer* **2018**, *123*, 83–86. [[CrossRef](#)] [[PubMed](#)]
57. Kim, S.; Kim, T.M.; Kim, D.W.; Go, H.; Keam, B.; Lee, S.H.; Ku, J.L.; Chung, D.H.; Heo, D.S. Heterogeneity of genetic changes associated with acquired crizotinib resistance in ALK-rearranged lung cancer. *J. Thorac. Oncol.* **2013**, *8*, 415–422. [[CrossRef](#)] [[PubMed](#)]
58. Yanagitani, N.; Uchibori, K.; Koike, S.; Tsukahara, M.; Kitazono, S.; Yoshizawa, T.; Horiike, A.; Ohyanagi, F.; Tambo, Y.; Nishikawa, S.; et al. Drug resistance mechanisms in Japanese anaplastic lymphoma kinase-positive non-small cell lung cancer and the clinical responses based on the resistant mechanisms. *Cancer Sci.* **2020**, *111*, 932–939. [[CrossRef](#)] [[PubMed](#)]
59. Friboulet, L.; Li, N.; Katayama, R.; Lee, C.C.; Gainor, J.F.; Crystal, A.S.; Michellys, P.Y.; Awad, M.M.; Yanagitani, N.; Kim, S.; et al. The ALK inhibitor ceritinib overcomes crizotinib resistance in non-small cell lung cancer. *Cancer Discov.* **2014**, *4*, 662–673. [[CrossRef](#)]
60. Sakamoto, H.; Tsukaguchi, T.; Hiroshima, S.; Kodama, T.; Kobayashi, T.; Fukami, T.A.; Oikawa, N.; Tsukuda, T.; Ishii, N.; Aoki, Y. CH5424802, a selective ALK inhibitor capable of blocking the resistant gatekeeper mutant. *Cancer Cell* **2011**, *19*, 679–690. [[CrossRef](#)]
61. Zhang, S.; Anjum, R.; Squillace, R.; Nadworny, S.; Zhou, T.; Keats, J.; Ning, Y.; Wardwell, S.D.; Miller, D.; Song, Y.; et al. The potent ALK inhibitor brigatinib (AP26113) overcomes mechanisms of resistance to first- and second-generation ALK inhibitors in preclinical models. *Clin. Cancer Res.* **2016**, *22*, 5527–5538. [[CrossRef](#)]
62. Gainor, J.F.; Shaw, A.T. Emerging paradigms in the development of resistance to tyrosine kinase inhibitors in lung cancer. *J. Clin. Oncol.* **2013**, *31*, 3987–3996. [[CrossRef](#)] [[PubMed](#)]
63. Katayama, R.; Lovly, C.M.; Shaw, A.T. Therapeutic targeting of anaplastic lymphoma kinase in lung cancer: A paradigm for precision cancer medicine. *Clin. Cancer Res.* **2015**, *21*, 2227–2235. [[CrossRef](#)] [[PubMed](#)]
64. Gainor, J.F.; Dardaei, L.; Yoda, S.; Friboulet, L.; Leshchiner, I.; Katayama, R.; Dagogo-Jack, I.; Gadgeel, S.; Schultz, K.; Singh, M.; et al. Molecular mechanisms of resistance to first- and second-generation ALK inhibitors in ALK-rearranged lung cancer. *Cancer Discov.* **2016**, *6*, 1118–1133. [[CrossRef](#)] [[PubMed](#)]
65. Ignatius Ou, S.H.; Azada, M.; Hsiang, D.J.; Herman, J.M.; Kain, T.S.; Siwak-Tapp, C.; Casey, C.; He, J.; Ali, S.M.; Klempner, S.J.; et al. Next-generation sequencing reveals a Novel NSCLC ALK F1174V mutation and confirms ALK G1202R mutation confers high-level resistance to alectinib (CH5424802/RO5424802) in ALK-rearranged NSCLC patients who progressed on crizotinib. *J. Thorac. Oncol.* **2014**, *9*, 549–553. [[PubMed](#)]
66. Makimoto, G.; Ohashi, K.; Tomida, S.; Nishii, K.; Matsubara, T.; Kayatani, H.; Higo, H.; Ninomiya, K.; Sato, A.; Watanabe, H.; et al. Rapid acquisition of alectinib resistance in ALK-positive lung cancer with high tumor mutation burden. *J. Thorac. Oncol.* **2019**, *14*, 2009–2018. [[CrossRef](#)] [[PubMed](#)]
67. Mehlman, C.; Chaabane, N.; Lacave, R.; Kerrou, K.; Ruppert, A.M.; Cadranel, J.; Fallet, V. Ceritinib ALK T1151R resistance mutation in lung cancer with initial response to brigatinib. *J. Thorac. Oncol.* **2019**, *14*, e95–e96. [[CrossRef](#)]
68. Zhu, V.W.; Cui, J.J.; Fernandez-Rocha, M.; Schrock, A.B.; Ali, S.M.; Ou, S.I. Identification of a novel T1151K ALK mutation in a patient with ALK-rearranged NSCLC with prior exposure to crizotinib and ceritinib. *Lung Cancer* **2017**, *110*, 32–34. [[CrossRef](#)]
69. Dagogo-Jack, I.; Rooney, M.; Lin, J.J.; Nagy, R.J.; Yeap, B.Y.; Hubbeling, H.; Chin, E.; Ackil, J.; Fargo, A.F.; Hata, A.N.; et al. Treatment with next-generation ALK inhibitors fuels plasma ALK mutation diversity. *Clin. Cancer Res.* **2019**, *25*, 6662–6670. [[CrossRef](#)]
70. Sabari, J.K.; Santini, F.C.; Schram, A.M.; Bergagnini, I.; Chen, R.; Mrad, C.; Lai, W.V.; Arbour, K.C.; Drilon, A. The activity, safety, and evolving role of brigatinib in patients with ALK-rearranged non-small cell lung cancers. *Oncotargets Ther.* **2017**, *10*, 1983–1992. [[CrossRef](#)]
71. Recondo, G.; Mezquita, L.; Facchinetti, F.; Planchard, D.; Gazzah, A.; Bigot, L.; Rizvi, A.Z.; Frias, R.L.; Thiery, J.P.; Scoazec, J.Y.; et al. Diverse resistance mechanisms to the third-generation ALK inhibitor lorlatinib in ALK-rearranged lung cancer. *Clin. Cancer Res.* **2020**, *26*, 242–255. [[CrossRef](#)]
72. Miyawaki, M.; Yasuda, H.; Tani, T.; Hamamoto, J.; Arai, D.; Ishioka, K.; Ohgino, K.; Nukaga, S.; Hirano, T.; Kawada, I.; et al. Overcoming EGFR bypass signal-induced acquired resistance to ALK tyrosine kinase inhibitors in ALK-translocated lung cancer. *Mol. Cancer Res.* **2017**, *15*, 106–114. [[CrossRef](#)] [[PubMed](#)]
73. Gouji, T.; Takashi, S.; Mitsuhiro, T.; Yukito, I. Crizotinib can overcome acquired resistance to CH5424802: Is amplification of the MET gene a key factor? *J. Thorac. Oncol.* **2014**, *9*, e27–e28. [[CrossRef](#)]
74. Shi, R.; Filho, S.N.M.; Li, M.; Fares, A.; Weiss, J.; Pham, N.A.; Ludkovski, O.; Raghavan, V.; Li, Q.; Ravi, D.; et al. BRAF V600E mutation and MET amplification as resistance pathways of the second-generation anaplastic lymphoma kinase (ALK) inhibitor alectinib in lung cancer. *Lung Cancer* **2020**, *146*, 78–85. [[CrossRef](#)] [[PubMed](#)]
75. Tsuji, T.; Ozasa, H.; Aoki, W.; Aburaya, S.; Funazo, T.; Furugaki, K.; Yoshimura, Y.; Ajimizu, H.; Okutani, R.; Yasuda, Y.; et al. Alectinib resistance in ALK-rearranged lung cancer by dual salvage signaling in a clinically paired resistance model. *Mol. Cancer Res.* **2019**, *17*, 212–224. [[CrossRef](#)] [[PubMed](#)]
76. Lovly, C.M.; McDonald, N.T.; Chen, H.; Ortiz-Cuaran, S.; Heukamp, L.C.; Yan, Y.; Florin, A.; Ozretić, L.; Lim, D.; Wang, L.; et al. Rationale for co-targeting IGF-1R and ALK in ALK fusion-positive lung cancer. *Nat. Med.* **2014**, *20*, 1027–1034. [[CrossRef](#)]
77. Chen, H.; Lin, C.; Peng, T.; Hu, C.; Lu, C.; Li, L.; Wang, Y.; Han, R.; Feng, M.; Sun, F.; et al. Metformin reduces HGF-induced resistance to alectinib via the inhibition of Gab1. *Cell Death Dis.* **2020**, *11*, 111. [[CrossRef](#)]

78. Gottesman, M.M.; Fojo, T.; Bates, S.E. Multidrug resistance in cancer: Role of ATP-dependent transporters. *Nat. Rev. Cancer* **2002**, *2*, 48–58. [[CrossRef](#)]
79. Ohtsuki, S.; Terasaki, T. Contribution of carrier-mediated transport systems to the blood-brain barrier as a supporting and protecting interface for the brain; importance for CNS drug discovery and development. *Pharm. Res.* **2007**, *24*, 1745–1758. [[CrossRef](#)]
80. Zhang, L.; Zaorsky, N.G.; Palmer, J.D.; Mehra, R.; Lu, B. Targeting brain metastases in ALK-rearranged non-small-cell lung cancer. *Lancet Oncol.* **2015**, *16*, e510–e521. [[CrossRef](#)]
81. Kort, A.; Sparidans, R.W.; Wagenaar, E.; Beijnen, J.H.; Schinkel, A.H. Brain accumulation of the EML4-ALK inhibitor ceritinib is restricted by P-glycoprotein (P-GP/ABCB1) and breast cancer resistance protein (BCRP/ABCG2). *Pharmacol. Res.* **2015**, *102*, 200–207. [[CrossRef](#)]
82. Katayama, R.; Sakashita, T.; Yanagitani, N.; Ninomiya, H.; Horiike, A.; Friboulet, L.; Gainor, J.F.; Motoi, N.; Dobashi, A.; Sakata, S.; et al. P-glycoprotein mediates ceritinib resistance in anaplastic lymphoma kinase-rearranged non-small cell lung cancer. *eBiomedicine* **2016**, *3*, 54–66. [[CrossRef](#)] [[PubMed](#)]
83. Gong, J.; Gregg, J.P.; Ma, W.; Yoneda, K.; Moore, E.H.; Daly, M.E.; Zhang, Y.; Williams, M.J.; Li, T. Squamous cell transformation of primary lung adenocarcinoma in a patient with EML4-ALK fusion variant 5 refractory to ALK inhibitors. *J. Natl. Compr. Cancer Netw.* **2019**, *17*, 297–301. [[CrossRef](#)] [[PubMed](#)]
84. Oya, Y.; Yoshida, T.; Uemura, T.; Murakami, Y.; Inaba, Y.; Hida, T. Serum ProGRP and NSE levels predicting small cell lung cancer transformation in a patient with ALK rearrangement-positive non-small cell lung cancer: A case report. *Oncol. Lett.* **2018**, *16*, 4219–4222. [[CrossRef](#)] [[PubMed](#)]
85. Park, S.; Han, J.; Sun, J.M. Histologic transformation of ALK-rearranged adenocarcinoma to squamous cell carcinoma after treatment with ALK inhibitor. *Lung Cancer* **2019**, *127*, 66–68. [[CrossRef](#)]
86. Zhu, Y.C.; Liao, X.H.; Wang, W.X.; Xu, C.W.; Zhuang, W.; Zhong, L.H.; Du, K.Q.; Chen, Y.P.; Chen, G.; Fang, M.Y. Patients harboring ALK rearrangement adenocarcinoma after acquired resistance to crizotinib and transformation to small-cell lung cancer: A case report. *OncoTargets Ther.* **2017**, *10*, 3187–3192. [[CrossRef](#)]
87. Sequist, L.V.; Waltman, B.A.; Dias-Santagata, D.; Digumarthy, S.; Turke, A.B.; Fidias, P.; Bergethon, K.; Shaw, A.T.; Gettinger, S.; Cosper, A.K.; et al. Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors. *Sci. Transl. Med.* **2011**, *3*, 75ra26. [[CrossRef](#)]
88. Niederst, M.J.; Sequist, L.V.; Poirier, J.T.; Mermel, C.H.; Lockerman, E.L.; Garcia, A.R.; Katayama, R.; Costa, C.; Ross, K.N.; Moran, T.; et al. RB loss in resistant EGFR mutant lung adenocarcinomas that transform to small-cell lung cancer. *Nat. Commun.* **2015**, *6*, 6377. [[CrossRef](#)]
89. PubMed. Available online: <https://pubmed.ncbi.nlm.nih.gov/> (accessed on 3 December 2022).
90. Cochrane Central Register of Controlled Trials [CENTRAL]. Available online: <https://www.cochranelibrary.com/> (accessed on 3 December 2022).
91. Embase. Available online: <https://www.embase.com/login> (accessed on 3 December 2022).
92. Scopus. Available online: <https://www.scopus.com/home.uri> (accessed on 3 December 2022).
93. Higgins, J.P.; Thomas, J.; Chandler, J.; Cumpston, M.; Li, T.; Page, M.J.; Welch, V.A. *Cochrane Handbook for Systematic Reviews of Interventions*; John Wiley & Sons: Hoboken, NJ, USA, 2019.
94. Copas, J.; Shi, J.Q. Meta-analysis, funnel plots and sensitivity analysis. *Biostatistics* **2000**, *1*, 247–262. [[CrossRef](#)]
95. Chootrakool, H.; Shi, J.Q.; Yue, R. Meta-analysis and sensitivity analysis for multi-arm trials with selection bias. *Stat. Med.* **2011**, *30*, 1183–1198. [[CrossRef](#)]
96. Higgins, J.P.T.; Thompson, S.G. Quantifying heterogeneity in a meta-analysis. *Stat. Med.* **2002**, *21*, 1539–1558. [[CrossRef](#)]
97. Fan, J.; Fong, T.; Xia, Z.; Zhang, J.; Luo, P. The efficacy and safety of ALK inhibitors in the treatment of ALK-positive non-small cell lung cancer: A network meta-analysis. *Cancer Med.* **2018**, *7*, 4993–5005. [[CrossRef](#)]
98. Lee, Y.C.; Hsieh, C.C.; Lee, Y.L.; Li, C.Y. Which should be used first for ALK-positive non-small-cell lung cancer: Chemotherapy or targeted therapy? A meta-analysis of five randomized trials. *Medicina* **2019**, *55*, 29. [[CrossRef](#)] [[PubMed](#)]
99. Zhang, Z.; Guo, H.; Lu, Y.; Hao, W.; Han, L. Anaplastic lymphoma kinase inhibitors in non-small cell lung cancer patients with brain metastases: A meta-analysis. *J. Thorac. Dis.* **2019**, *11*, 1397–1409. [[CrossRef](#)] [[PubMed](#)]
100. Elliott, J.; Bai, Z.; Hsieh, S.C.; Kelly, S.E.; Chen, L.; Skidmore, B.; Yousef, S.; Zheng, C.; Stewart, D.J.; Wells, G.A. ALK inhibitors for non-small cell lung cancer: A systematic review and network meta-analysis. *PLoS ONE* **2020**, *15*, e0229179. [[CrossRef](#)] [[PubMed](#)]
101. Hoang, T.; Myung, S.K.; Pham, T.T.; Park, B. Efficacy of crizotinib, ceritinib, and alectinib in ALK-positive non-small cell lung cancer treatment: A meta-analysis of clinical trials. *Cancers* **2020**, *12*, 526. [[CrossRef](#)]
102. Chuang, C.H.; Chen, H.L.; Chang, H.M.; Tsai, Y.C.; Wu, K.L.; Chen, I.H.; Chen, K.C.; Lee, J.Y.; Chang, Y.C.; Chen, C.L.; et al. Systematic review and network meta-analysis of anaplastic lymphoma kinase (ALK) inhibitors for treatment-naïve ALK-positive lung cancer. *Cancers* **2021**, *13*, 1966. [[CrossRef](#)]
103. Wu, K.L.; Chen, H.L.; Tsai, Y.M.; Lee, T.H.; Chang, H.M.; Tsai, Y.C.; Chuang, C.H.; Chang, Y.C.; Tu, Y.K.; Yang, C.J.; et al. First-line anaplastic lymphoma kinase (ALK) inhibitors for ALK-positive lung cancer in Asian populations: Systematic review and network meta-analysis. *J. Clin. Med.* **2021**, *10*, 4376. [[CrossRef](#)]

104. Wang, L.; Sheng, Z.; Zhang, J.; Song, J.; Teng, L.; Liu, L.; Li, Q.; Wang, B.; Li, B. Comparison of lorlatinib, alectinib and brigatinib in ALK inhibitor-naïve/untreated ALK-positive advanced non-small-cell lung cancer: A systematic review and network meta-analysis. *J. Chemother.* **2022**, *34*, 87–96. [[CrossRef](#)]
105. Liberati, A.; Altman, D.G.; Tetzlaff, J.; Mulrow, C.; Gøtzsche, P.; Ioannidis, J. The PRISMA statement for reporting systematic and meta-analyses of studies that evaluate interventions: Explanation and elaboration. *PLoS Med.* **2009**, *6*, e1000100. [[CrossRef](#)]
106. Hutton, B.; Salanti, G.; Caldwell, D.M.; Chaimani, A.; Schmid, C.H.; Cameron, C.; Ioannidis, J.P.; Straus, S.; Thorlund, K.; Jansen, J.P.; et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: Checklist and explanations. *Ann. Intern. Med.* **2015**, *162*, 777–784. [[CrossRef](#)]
107. Salanti, G.; Ades, A.E.; Ioannidis, J.P. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: An overview and tutorial. *J. Clin. Epidemiol.* **2011**, *64*, 163–171. [[CrossRef](#)] [[PubMed](#)]
108. Hoaglin, D.C.; Hawkins, N.; Jansen, J.P.; Scott, D.A.; Itzler, R.; Cappelleri, J.C.; Boersma, C.; Thompson, D.; Larholt, K.M.; Diaz, M.; et al. Conducting indirect-treatment-comparison and network-meta-analysis studies: Report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: Part 2. *Value Health* **2011**, *14*, 429–437. [[CrossRef](#)] [[PubMed](#)]
109. Jansen, J.P.; Fleurence, R.; Devine, B.; Itzler, R.; Barrett, A.; Hawkins, N.; Lee, K.; Boersma, C.; Annemans, L.; Cappelleri, J.C. Interpreting indirect treatment comparisons and network meta-analysis for health-care decision making: Report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: Part 1. *Value Health* **2011**, *14*, 417–428. [[CrossRef](#)]
110. Ades, A.E.; Cliffe, S. Markov chain Monte Carlo estimation of a multiparameter decision model: Consistency of evidence and the accurate assessment of uncertainty. *Med. Decis. Mak.* **2002**, *22*, 359–371. [[CrossRef](#)]
111. Lu, G.; Ades, A.E. Combination of direct and indirect evidence in mixed treatment comparisons. *Stat. Med.* **2004**, *23*, 3105–3124. [[CrossRef](#)] [[PubMed](#)]
112. Brooks, S.P.; Gelman, A. General methods for monitoring convergence of iterative simulations. *J. Comp. Graph. Stat.* **1998**, *7*, 434–455.
113. Brooks, S.P.; Roberts, G.O. Convergence assessment techniques for Markov chain Monte Carlo. *Stat. Comput.* **1998**, *8*, 319–335. [[CrossRef](#)]

Disclaimer/Publisher’s Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.