INPLASY PROTOCOL

To cite: Tao et al. Efficacy and safety of first-line treatments for patients with advanced anaplastic lymphoma kinase gene rearrangements in non-small cell lung cancer: a systematic review and network meta-analysis. Inplasy protocol 202170079. doi: 10.37766/inplasy2021.7.0079

Received: 24 July 2021

Published: 24 July 2021

Corresponding author:
Linzhu Zhai

linzhuzhai@163.com

Author Affiliation:
1 Cancer Center, the First Affiliated Hospital of Guangzhou University of Chinese Medicine 2 Sun Yat-sen University Cancer Center; State Key Laboratory of Oncology in South China; Collaborative Innovation Center for Cancer Medicine.

Support: **National Natural Science Found.**

Review Stage at time of this submission: **Data analysis.**

Conflicts of interest:
None declared.

Efficacy and safety of first-line treatments for patients with advanced anaplastic lymphoma kinase gene rearrangements in non-small cell lung cancer: a systematic review and network meta-analysis

Tao, J[1]; Zhang, C[2]; Zhou, L[3]; Liu, Z[4]; Zhou, Y[5]; Zheng, C[6]; Lin, L[7]; Zhao, Y[8]; Zhai, L[9].

Review question / Objective: **Population; patients had histologically confirmed non-small cell lung cancer with ALK gene rearrangement. Intervention: anaplastic lymphoma kinase inhibitors. Comparison: anaplastic lymphoma kinase inhibitors or chemotherapy. Outcome: objective response rate (ORR), progression-free survival (PFS), overall survival (OS), and grade ≥ 3 adverse events (AEs). Study design: network meta-analysis.**
Condition being studied: **Advanced anaplastic lymphoma kinase gene rearrangements in non-small cell lung cancer. We searched the PubMed, Embase, and ClinicalTrials.gov databases up to March 1, 2021 with the keywords "crizotinib," "alectinib," "ceritinib," "brigatinib," "lorlatinib," "ensartinib," "non-small cell lung cancer," and the category was limited to "clinical trial." Specific retrieval strategies are presented in Table S2. To improve the credibility of this article, we updated outcomes of these included studies from important international conferences (i.e., the World Conference on Lung Cancer, the American Society of Clinical Oncology, the European Society for Medical Oncology, and the Chinese Society of Clinical Oncology) by inspecting relevant conference abstracts.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 24 July 2021 and was last updated on 24 July 2021 (registration number INPLASY202170079).

INTRODUCTION

Review question / Objective: **Population; patients had histologically confirmed non-small cell lung cancer with ALK gene rearrangement. Intervention: anaplastic lymphoma kinase inhibitors. Comparison: anaplastic lymphoma kinase inhibitors or**

chemotherapy. Outcome: objective response rate (ORR), progression-free survival (PFS), overall survival (OS), and grade ≥ 3 adverse events (AEs). Study design: network meta-analysis.

Condition being studied: Advanced anaplastic lymphoma kinase gene rearrangements in non-small cell lung cancer. We searched the PubMed, Embase, and ClinicalTrials.gov databases up to March 1, 2021 with the keywords "crizotinib," "alectinib," "ceritinib," "brigatinib," "lorlatinib," "ensartinib," "non-small cell lung cancer," and the category was limited to "clinical trial." Specific retrieval strategies are presented in Table S2. To improve the credibility of this article, we updated outcomes of these included studies from important international conferences (i.e., the World Conference on Lung Cancer, the American Society of Clinical Oncology, the European Society for Medical Oncology, and the Chinese Society of Clinical Oncology) by inspecting relevant conference abstracts.

METHODS

Participant or population: Patients had histologically confirmed non-small cell lung cancer with ALK gene rearrangement.

Intervention: Anaplastic lymphoma kinase inhibitors.

Comparator: Anaplastic lymphoma kinase inhibitors or chemotherapy.

Study designs to be included: The study compared the clinical efficacy and toxic of anaplastic lymphoma kinase inhibitors.Study compared clinical efficancy and toxic about anaplastic lymphoma kinase inhibitorsalk

Eligibility criteria: All of the included trials had to meet the following certification. First, we only included phase II/III randomized controlled trials. Second, patients had histologically confirmed non-small cell lung cancer with ALK gene rearrangement. Finally, all of the included trials had to compare any two or more different arms and report at least one of the following clinical outcomes: objective response rate (ORR), progression-free survival (PFS), overall survival (OS), and grade ≥ 3 adverse events (AEs).

Information sources: We searched the PubMed, Embase, and ClinicalTrials.gov databases up to March 1, 2021 with the keywords "crizotinib," "alectinib," "ceritinib," "brigatinib," "lorlatinib," "ensartinib," "non-small cell lung cancer," and the category was limited to "clinical trial." Specific retrieval strategies are presented in Table S2. To improve the credibility of this article, we updated outcomes of these included studies from important international conferences (i.e., the World Conference on Lung Cancer, the American Society of Clinical Oncology, the European Society for Medical Oncology, and the Chinese Society of Clinical Oncology) by inspecting relevant conference abstracts.

Main outcome(s): Lorlatinib was associated with the best PFS and was suitable for patients with or without brain metastases. Brigatinib led to the best PFS in Asian patients. We also found that alectinib induced the least toxicity and ceritinib (750 mg, fasted) was the drug with the most severe side effects. These findings provide evidence for selecting appropriate ALK inhibitors in ALK gene rearrangement advanced NSCLC but need to be validated in large randomized controlled studies.

Quality assessment / Risk of bias analysis: Titles and abstracts were screened, and the full texts of potentially eligible articles were sequentially assessed for final inclusion. We assessed the risk of bias of individual studies using the Cochrane risk-of-bias tool. Items were scored as low, high, or unclear risk of bias.

Strategy of data synthesis: Two independent readers analyzed the included trials with the direction of a predefined protocol. Discrepancies were resolved by discussion with a third reader. The information extracted from the selected articles was as follows: study ID,

intervention arm, control arm, median PFS, and median OS. We preferred the data from ITT populations and evaluated them by BICR to include more objective data. After long-term follow-up and inclusion of data from important international conferences, the updated results were used to replace the data from the original study paper. As for grade ≥ 3 AEs, we preferred the data recorded as treatment-related AEs, but if AEs were not specified as treatment-related in a study, we included all AEs.

Subgroup analysis: The subgroup analysis was performed in patients with baseline brain metastases and without brain metastases. We further analyzed the drugs that yielded the best benefit in Asian patients.

Sensitivity analysis: To assess the robustness and reliability of results, we planned three sensitivity analyses as the dosage of alectinib was 300 mg in the J-ALEX study. However, it was 600 mg in other clinical studies. Therefore, we excluded the J-ALEX study in pooled PFS analysis and further subgroup analysis in PFS to make the research more persuasive.

Country(ies) involved: China.

Keywords: non-small cell lung cancer; first-line treatment; target therapy; anaplastic lymphoma kinase; network meta-analysis.

Contributions of each author:
Author 1 - Jiahao Tao.
Author 2 - Cuifen Zhang.
Author 3 - Ling Zhou.
Author 4 - Zeyu Liu.
Author 5 - Yanqun Zhou.
Author 6 - Chuangjie Zheng.
Author 7 - Lizhu Lin.
Author 8 - Yuanyuan Zhao.
Author 9 - Linzhu Zhai.