INPLASY PROTOCOL

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Conflicts of interest:
None.

Efficacy and safety of therapies for ALK-positive non-small cell lung cancer with brain metastasis: a Bayesian network meta-analysis

Zhao, BH[1]; Han, Y[2].

Review question / Objective: **What is the best treatment for ALK-positive non-small cell lung cancer and what the rankings of these treatments based on their efficacy? Safety of these treatments should also be ordered when administrated in clinical practice.**
Condition being studied: **ALK-positive non-small cell lung cancer with brain metastasis.**
Information sources: **Relating published trials were identified after a rigorous literature search on PubMed, EMBASE, Cochrane Library and ClinicalTrials.gov from inception to Dec 2020. The key items used were: ALK positive¡±, ¡°non-small cell lung cancer¡±, ¡°NSCLC¡±, ¡°randomized controlled trials¡±. No restrictions were applied on language. Reference lists were searched manually for additional records.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 16 January 2021 and was last updated on 16 January 2021 (registration number INPLASY202110056).

INTRODUCTION

Review question / Objective: **What is the best treatment for ALK-positive non-small cell lung cancer and what the rankings of these treatments based on their efficacy? Safety of these treatments should also be ordered when administrated in clinical practice.**

Rationale: **(ALK) gene define a subset of nonšCsmall cell lung cancers (NSCLCs) that are highly sensitive to small-molecule ALK tyrosine kinase inhibitors. Previous clinical trials showed that the second generation ALK-inhibitors including alectinib, brigatinib, and ensartinib were superior to crizotinib as first-line therapy. Despite improved efficacy of second**

generation inhibitors, drug resistance and recurrent disease (including CNS progression) is often the cause of death.

Condition being studied: ALK-positive non-small cell lung cancer with brain metastasis.

METHODS

Participant or population: All the published RCTs of adult patients (šR 18 year) whose ECOG status was 0 or 1 that compared any systematic interventions (pharmaceutical, surgical, radiological, combinations etc.) for advanced ALK mutation positive NSCLC were identified. The included patients within selected trials must have positive and clear advanced ALK mutant cancer diagnoses.

Intervention: Experimental and control arm considered reasonable treatments to ALK positive NSCLC patients.

Comparator: Experimental and control arm considered reasonable treatments to ALK positive NSCLC patients.

Study designs to be included: Rigorous randomized controlled trials.

Eligibility criteria: (1) Populations: Adult (¡Ý 18 y) histologically or cytologically confirmed NSCLC patients with sensitizing ALK mutation positive and asymptomatic or neurologically stable brain metastases. Eligible participants had an Eastern Cooperative Oncology Group (ECOG) performance score of 0 or 1, a life expectancy of at least 3 months and certain levels of organ function (bone marrow, liver, kidney function etc.). There were no restrictions regarding other characteristics. (2) Interventions and comparisons: Reasonable regimens (including surgery, pharmaceutical intervention, and RT). (3) Outcome: At least PFS or overall survival (OS) had to be reported. Adverse effects might also be reported. (4) Study design: phase II/III RCTs or randomized trial lasting at least one year. Only ASCO, ESMO, IASLC, SNO conference abstracts were considered. Studies involving patients with confirmed metastases in the spinal cord or leptomeningeal, who had less than 3 months life expectancy were excluded30. Case reports, basic research, reviews, and meta-analyses were also excluded.

Information sources: Relating published trials were identified after a rigorous literature search on PubMed, EMBASE, Cochrane Library and ClinicalTrials.gov from inception to Dec 2020. The key items used were: ALK positive¡±, ¡°non-small cell lung cancer¡±, ¡°NSCLC¡±, ¡°randomized controlled trials¡±. No restrictions were applied on language. Reference lists were searched manually for additional records.

Main outcome(s): We mainly analyzed overall survival (OS) and progression free survival (PFS) of the included trials, safety profiles may also be analyzed in there is abundant evidence.

Additional outcome(s): We mainly analyzed overall survival (OS) and progression free survival (PFS) of the included trials, safety profiles may also be analyzed in there is abundant evidence.

Data management: Data and eligible clincial trials were entered into standard tables, search history was stored in Endnote X9.

Quality assessment / Risk of bias analysis: The quality of each trial was assessed with the modified version of the Cochrane Risk of Bias tool.

Strategy of data synthesis: The Bayesian network meta-analysis (NMA) was performed with a random effects model to estimate the HR and 95% credible interval (95% CrI) for PFS and OS between trial arms. In studies with directly unavailable HR, we extracted and estimated the HR and corresponding standard errors from the KaplanšCMeier curves, if available, with the methods described by Tierney et al. In the case of multi-arm trials (trials with three or more interventions), adjustments were made to preserve randomization and correlation within multi-arm trials by

converting log-HRs to log-hazards. Markov Chain Monte Carlo (MCMC) methods were used to obtain the data, and we evaluated the inconsistency of the model by the edge-splitting method based on all direct and indirect evidence. Relative treatment rankings were displayed graphically with rankograms.

Subgroup analysis: Subgroup and sensitivity analyses were performed by eliminating very old trials and by eliminating biased trials.

Sensibility analysis: Subgroup and sensitivity analyses were performed by eliminating very old trials and by eliminating biased trials.

Language: English.

Country(ies) involved: China.

Keywords: ALK-positive, NSCLC, brain metastasis, Bayesian network meta-analysis.

Dissemination plans: The review would be updated timely.

Contributions of each author:
Author 1 - Binghao Zhao - The author drafted the manuscript.
Author 2 - Yan Han - The author provided statistical expertise, and check the manuscript.