INPLASY PROTOCOL

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Support: **None.**

Review Stage at time of this submission: **Formal screening of search results against eligibility criteria.**

Conflicts of interest:
There is no conflicts of interest of this meta-analysis.

The Role of EGFR-TKIs as Adjuvant Therapy in EGFR Mutation-Positive Early-Stage NSCLC: a meta-analysis

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Review question / Objective: **We conducted a meta-analysis of the randomized controlled trials to compare the efficacy and adverse events rates between adjuvant EGFR-TKIs and placebo/chemotherapy in EGFR mutation-positive NSCLC patients, potential influencing factors were also evaluated.**
Condition being studied: **Lung cancer is one of the most common malignant tumors. As the cornerstone and standard therapy of adjuvant therapy, research of adjuvant chemotherapy has encountered a bottleneck for limited therapeutic effect as well as many side effects. As a result, people are eager to find better adjuvant treatments. In the past ten years, epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) have become the first-line treatment for EGFR mutation-positive advanced non-small cell lung cancer (NSCLC) patients because of their good curative effect and few side effects. However, the role of adjuvant targeted therapy as well as the timing of adjuvant targeted therapy, the duration of medication, the preferred drugs and preferred gene mutation types are not completely clear, and there is much heterogeneity among studies. Recently, ADJUVANT study has updated its overall survival data and the preliminary data of ADAURA has also been published, which are quite important high quality randomized controlled trials of limited studies on this field. This meta-analysis will include these latest study results.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 26 October 2020 and was last updated on 26 October 2020 (registration number INPLASY2020100098).

INTRODUCTION

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METHODS

Search strategy: We searched Pubmed, Embase, and Cochrane Central Library from January 1, 2000 to September 20, 2020, using the keywords "Carcinoma, Non-Small-Cell Lung" and its synonyms, epidermal growth factor receptor, resectable, operable, adjuvant, post-operative, and survival. The search was limited to clinical trials. Abstracts of academic conference including American Society of Clinical Oncology Annual meeting, World Conference on Lung Cancer, European Society for Medical Oncology and registered clinical trials were also included to identify relevant studies.

Participant or population: NSCLC patients with EGFR-mutant, stage IB-IIIA disease that underwent radically resection.

Intervention: Random assignment of participants to treatment with post-operative epidermal growth factor receptor tyrosine kinase inhibitor.

Comparator: Random assignment of participants to treatment with postoperative chemotherapy/placebo.

Study designs to be included: Randomized controlled trials.

Eligibility criteria: Clinical trials that met the following criteria were included: (a) randomized controlled trials in NSCLC patients with EGFR-mutant, stage IB-IIIA disease that underwent radically resection; (b) random assignment of participants to treatment with postoperative epidermal growth factor receptor tyrosine kinase inhibitor or chemotherapy/placebo; and (c) reporting of disease-free survival and overall survival. Exclusion criteria were (a) studies that adjuvant immunotherapy was evaluated; and (b) studies with a sample size less than 50. Duplicate records and republished studies, reviews, meta-analysis, case reports, non-English reports were also excluded from the analysis.

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Main outcome(s): Disease free survival and overall survival.

Additional outcome(s): Rate of severe adverse events.

Quality assessment / Risk of bias analysis: Two authors independently evaluated the quality of the included studies based on the Cochrane Collaboration's Tool for assessing risk of bias in Cochrane Handbook for Systematic Reviews of Interventions, which includes selection bias, implementation bias, measurement bias, loss to follow-up bias, publication

bias, and other biases. Differences and disagreements were resolved by discussion with introduction of a third author.

Strategy of data synthesis: The data analysis of this study was done using R, version 3.6.2 (R Core Team, Vienna, Austria). Log-transformed HR and standard error values combined with the generic inverse variance method were used to evaluate HR in DFS and OS with a significance level $\alpha=0.05$. We applied I^2 test and Q test for heterogeneity estimation22. $I^2>50\%$ or Q test $P<0.1$ is considered significant heterogeneity and the random effects model will be used. Otherwise, the fixed-effects model will be used. The Begg's test and Egger's test were used to quantitatively measure the publication bias.

Subgroup analysis: Subgroup analysis will be done according to disease stage, mutation type, median treatment duration, generation of drugs, previous adjuvant chemotherapy. Subgroup analysis without 2 or more eligible studies will be abandoned. The median medication duration of the studies will be extracted and the weighted average will be calculated as the cut off value for dividing the studies into two different subgroups.

Sensibility analysis: In the sensitivity analysis, we will deletion of any research one by one and calculate the results. Next we will compare these results with the initial results to estimate the sensibility of the concol.

Language: English.

Country(ies) involved: China.

Keywords: epidermal growth factor receptor tyrosine kinase inhibitors, adjuvant treatment, non-small cell lung cancer, targeted therapy, survival.

Dissemination plans: We are going to publish our results in SCI journals.

Contributions of each author:

Author 1 - Chutong Lin - The author drafted the manuscript.
Author 2 - Fengling Hu - Study selection and data extraction was done independently by two authors separately.
Author 3 - Hongling Chu - The author is responsible for the methodology of this meta-analysis.
Author 4 - Peng Ren - The author read, provided feedback and approved the final manuscript.
Author 5 - Shanwu Ma - The author read, provided feedback and approved the final manuscript.
Author 6 - Jingdi Wang - The author read, provided feedback and approved the final manuscript.
Author 7 - Jie Bai - The author read, provided feedback and approved the final manuscript.
Author 8 - Xuan Han - The author read, provided feedback and approved the final manuscript.
Author 9 - Shaohua Ma - The author is the corresponding author of this work. Discrepancies of author 1 and author 2 were resolved by consensus that included author 9.