International Platform of Registered Systematic Review and Meta-analysis Protocols

INPLASY

Treatment strategy for advanced or metastatic NSCLC patients with EGFR mutations after TKI-resistance: A scoping review

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ADMINISTRATIVE INFORMATION

Support - MSD China.

Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - Jiani Ding, Suijun Xiao, and Yan Yan were employed by MSD China. The other authors declared no conflicts of interest.

INPLASY registration number: INPLASY202550089

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 29 May 2025 and was last updated on 29 May 2025.

INTRODUCTION

Review question / Objective The purpose of this study is as follows: (1) To summarize all types of treatment regimens and outcomes, including efficacy and safety data, underway in NSCLC patients with EGFR mutations after TKI-resistance.
(2) To extract the specific TKI drugs previously received.
(3) To extract the different resistance mechanisms to explore promising directions for treatment strategies.

Background Non-small cell lung cancer (NSCLC) is the most common subtype of lung cancer. The epidermal growth factor receptor (EGFR) mutations are the most frequently encountered genomic alterations in NSCLC. Asia has a higher prevalence of EGFR mutations and a broader patient group for targeted therapy resistance studies compared to the West. Therefore, Chinese experts are in urgent need of research data in this area.

Despite the use of tyrosine kinase inhibitors (TKIs), all patients with EGFR mutations eventually develop resistance, typically after 9—12 months of treatment. Third-generation EGFR-TKIs, such as osimertinib, have improved outcomes for patients with EGFR-mutant NSCLC but resistance still develops. The development of fourth-generation EGFR-TKIs is still underway. Chemotherapy remains a therapeutic option for TKI-resistant NSCLC, although it offers modest clinical outcomes. Combination therapies, including the use of EGFR-TKIs with chemotherapy or anti-angiogenic agents, are being explored to increase antitumor efficacy. Lack of effective treatment strategies, such as Orient-31 and HARMONi-A approved in China, yet experts believe that this regimen provides limited efficacy improvement.
The diverse mechanisms of acquired resistance pose challenges in developing targeted therapies post-Osimertinib, highlighting a significant unmet medical need.

Rationale Patients with EGFR-mutant NSCLC inevitably develop resistance to tyrosine kinase inhibitors (TKIs) through mechanisms such as EGFR mutations that disrupt drug binding (e.g., C797S), activation of alternate pathways, and lineage plasticity leading to small cell transformation. Research gaps currently exist, with a need for a deeper understanding of the resistance mechanisms to TKIs and the identification of more effective treatments to target specific mechanisms of acquired resistance. While there has been considerable progress in understanding the resistance mechanisms to TKIs, there is a notable lack of systematic evidence synthesis.

Therefore, we need to systematically summarize all types of treatment regimens and acquired resistance mechanisms in NSCLC patients with EGFR mutations after TKI-resistance from high quality evidence, to offer clinical experts a clearer, more comprehensive understanding.

METHODS

Strategy of data synthesis PubMed

#1. "Carcinoma, Non-Small-Cell Lung"[Mesh] OR "Adenocarcinoma of Lung"[Mesh] OR Non-Small-Cell Lung Carcinoma*[tw] OR Nonsmall Cell Lung Cancer*[tw] OR NSCLC[tw] OR lung squamous carcinoma*[tw] OR squamous cell lung carcinoma*[tw] OR lung squamous cell carcinoma*[tw] OR Pulmonary squamous carcinoma*[tw] OR pulmonary squamous cell carcinoma*[tw] OR lung adenocarcinoma*[tw] OR pulmonary adenocarcinoma*[tw] OR large cell lung cancer*[tw]

#2. "epidermal growth factor receptor mutated"[tw] OR "epidermal growth factor receptor mutation"[tw] OR "EGFR-mutated"[tw] OR "EGFR-mutant*"[tw] OR "EGFR-mutation*"[tw] OR "EGFR Variant*"[tw] OR "EGFR-TKI"[tw] OR "EGFR-TKIs"[tw] OR "EGFR-tyrosine kinase inhibitor*"[tw]

#3. #1 and #2

#4. "Review Literature as Topic"[Mesh] OR "Review" [Publication Type] OR Review[ti] OR "Case Reports" [Publication Type] OR "Case Report"[ti] OR "A Case"[ti] OR "Meta-Analysis"[pt] OR "Meta-Analysis as Topic"[Mesh] OR "Systematic Review" [pt] OR "Systematic Reviews as Topic"[Mesh] OR "systematic"[Filter] OR "Meta-Analysis"[ti] OR Metaanalys*[ti] OR ("Animals"[Mesh] NOT ("Humans"[Mesh] AND "Animals"[Mesh]))

#5. #3 not #4

#6. "controlled clinical trial"[pt] OR "Controlled Clinical Trials as Topic"[MeSH] OR "Random Allocation"[MeSH] OR "Double-Blind Method"[MeSH] OR "single-blind method"[MeSH] OR "Control Groups"[MeSH] OR "cross-over studies"[MeSH] OR random*[tiab] OR placebo[tiab] OR trial[tiab] OR groups[tiab] OR crossover[tiab] OR cross-over[tiab] OR single blind*[tiab] OR double blind*[tiab] OR triple blind*[tiab] OR Factorial design*[tiab] OR "single arm"[tiab]

#5 and #6 and ("2009/01/01"[Date - Publication] : "3000"[Date - Publication])

Embase

#1. 'non small cell lung cancer'/exp OR (((lung OR pulmonary OR bronchial OR bronchus) NEAR/4 ("non small cell" OR "large cell" OR squamous OR epidermoid) NEAR/4 (cancer* OR carcinoma*)) OR NSCLC OR ((lung OR pulmonary OR bronchial OR bronchus) NEAR/3 (adenocarcinoma* OR adenocancer*))):ab,ti,kw

#2. ((("epidermal growth factor receptor*" OR EGFR) NEAR/5 (mutated OR mutant* OR mutation* OR Variant*)) OR "EGFR-TKI" OR "EGFR-TKIs" OR "EGFR-tyrosine kinase inhibitor*"):ab,ti,kw

#3. #1 and #2

#4. 'case report'/exp OR 'review'/exp OR [review]/lim OR (review OR "case report" OR "a case" OR 'Meta Analysis*' OR Metaanalys*):ti OR 'meta analysis'/exp OR 'meta analysis (topic)'/exp OR 'systematic review'/exp OR 'systematic review (topic)'/exp OR (('nonhuman'/exp OR 'animal'/exp) NOT 'human'/exp) OR [conference abstract]/lim

#5. #3 not #4

#6. 'controlled clinical trial'/exp OR 'Controlled Clinical Trial (Topic)'/exp OR 'double blind procedure'/de OR 'control group'/de OR 'crossover procedure'/de OR 'single blind procedure'/de OR 'triple blind procedure'/de OR 'placebo'/de OR 'randomization'/exp OR (random* OR trial OR groups OR placebo* OR crossover OR "cross-over" OR "Factorial design*" OR "single arm" OR ((Doubl* OR Singl* OR tripl*) NEAR/2 Blind*)):ab,ti,kw

#5 and #6 and [2009-2025]/py

Web of Science

#1. TS=(((lung OR pulmonary OR bronchial OR bronchus) NEAR/4 ("non small cell" OR "large cell" OR squamous OR epidermoid) NEAR/4 (cancer* OR carcinoma*)) OR NSCLC OR ((lung OR pulmonary OR bronchial OR bronchus) NEAR/3 (adenocarcinoma* OR adenocancer*)))

#2. TS=((("epidermal growth factor receptor*" OR EGFR) NEAR/5 (mutated OR mutant* OR mutation* OR Variant*)) OR "EGFR-TKI" OR "EGFR-TKIs" OR "EGFR-tyrosine kinase inhibitor*")

#3. #1 and #2

#4. TI=(veterinary OR rabbit* OR animal* OR mouse OR mice OR rodent* OR rat OR rats OR pig OR pigs OR porcine OR horse OR horses OR equine OR cow OR cows OR bovine OR goat OR goats OR sheep OR ovine OR canine OR dog OR dogs OR feline OR cat OR cats OR review OR

"case report" OR "a case") OR Review Article (Document Types) OR Meeting Abstract (Document Types)
#5. #3 not #4
#6. (TS=(((controlled OR Random*) NEAR/5 (Trial OR study)) OR "Random Allocation*" OR Randomization* OR "Double Blind" OR "single blind" OR "Control Group*" OR "Controlled Group*" OR "cross over" OR placebo* OR crossover OR random* OR "Factorial design*" OR "single arm" OR ((Doubl* OR Singl* OR tripl*) NEAR/2 Blind*)) OR TI=("trial" OR "RCT" OR "groups" OR "group"))
#5 and #6 and Timespan: 2009-01-01 to 2026-12-31 (Publication Date)
Cochrane
#1 MeSH descriptor: [Carcinoma, Non-Small-Cell Lung] explode all trees
#2 (((lung OR pulmonary OR bronchial OR bronchus) NEAR/4 ("non small cell" OR "large cell" OR squamous OR epidermoid) NEAR/4 (cancer* OR carcinoma*)) OR NSCLC OR ((lung OR pulmonary OR bronchial OR bronchus) NEAR/3 (adenocarcinoma* OR adenocancer*))):ti,ab,kw
#3 #1 or #2
#4 ((("epidermal growth factor receptor*" OR EGFR) NEAR/5 (mutated OR mutant* OR mutation* OR Variant*)) OR "EGFR-TKI" OR "EGFR-TKIs" OR "EGFR-tyrosine kinase inhibitor*"):ti,ab,kw
#5 #3 and #4 2856 ,trials.

Eligibility criteria Population: Patients with advanced or metastatic EGFR-mutated NSCLC who have developed resistance to TKIs.
Interventions: Subsequent treatments post the development of TKI resistance:
On-target inhibition (4th-gen TKI, 1st-gen TKI/mAb);
Bypass pathway inhibition (c-MET inhibitor);
Both on-target and bypass pathway inhibition (Bispecific antibody targeting EGFR and c-MET);
Targeting tumor-associated antigen (Trop2 ADC, HER3 ADC), etc; Chemotherapy, immunotherapy, anti-angiogenesis therapy and other treatment methods.
Comparisons: No limitation
Outcomes: Efficacy and safety outcomes, such as: overall survival rate (OS); progression-free survival (PFS); Intracranial Progression-Free Survival(iPFS); objective response rate(ORR); duration of response (DOR); Total adverse events (AE); Health-Related Quality of Life (HRQOL) etc.
Study design: Clinical trials, such as randomized controlled trials (RCTs), non-randomized controlled trials, single arm trials.
Only full manuscript will be considered.
Time: Define the study duration or treatment duration for studies to be included: No limitations. This study will include clinical trials published from 2009.
Other: English literature.

Source of evidence screening and selection After the search and automatic de-duplication, all identified citations will be uploaded into Rayyan (https://rayyan.ai/). Two reviewers will screen studies by reading titles and abstracts of the search results as 1st level screening. All potentially relevant citations will be requested and inspected in detail using the full-text version as 2nd level screening. Disagreements between reviewers will be resolved by discussion, with assistance from a third party if necessary. A PRISMA flow diagram will be constructed to show the full study-selection process. If important conference abstracts are found, those can be included as expert-supplemented literature.

Data management All data collected for the study should be recorded accurately, promptly, and legibly. Only data from published literature will be used for this scoping review. We will manage citations using EndNote. For study selection, all potential publications identified from the searches will be screened using Rayyan. The data from included studies will be accurately collected and recorded electronically, utilizing Microsoft Word and/or Excel file. The software package that will be used to conduct the analyses should also be documented.

Language restriction Only English literature will be searched.

Country(ies) involved China.

Keywords Non-small cell lung cancer; Treatment strategy; EGFR mutations; TKI-resistance; Scoping review.

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