INPLASY

# Efficacy and Safety of Treatment Beyond Progression with anti-PD-(L)1 Therapy in Patients with Advanced Non-Small Cell Lung Cancer: A Meta-analysis

INPLASY2025100067
doi: 10.37766/inplasy2025.10.0067
Received: 18 October 2025
Published: 18 October 2025

He, JJ; Chen, CY; Lin, AQ; Luo, P; Wei, T; Zhang J.

**Corresponding author:**
Jingjun He

823351077@qq.com

**Author Affiliation:**
Zhujiang Hospital of Southern Medical University.

**ADMINISTRATIVE INFORMATION**

**Support -** The authors received no financial support for this work.

**Review Stage at time of this submission -** Completed but not published.

**Conflicts of interest -** None declared.

**INPLASY registration number:** INPLASY2025100067

**Amendments -** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 18 October 2025 and was last updated on 18 October 2025.

## INTRODUCTION

**Review question / Objective** P (Population): Adult patients with advanced NSCLC who have experienced disease progression after first-line anti-PD-(L)1 (immunotherapy) treatment.
I (Intervention): Continuation of anti-PD-(L)1 therapy beyond progression (as monotherapy or in combination with other treatments, such as chemotherapy).
C (Comparison): Alternative treatments that do not involve continued anti-PD-(L)1 blockade (e.g., switching to chemotherapy alone).
O (Outcomes): Primary outcomes: Overall Survival (OS) and Progression-Free Survival (PFS). Secondary outcomes: Objective Response Rate (ORR) and incidence of grade ≥3 adverse events.
S (Study design): Both randomized controlled trials and single-arm observational studies were included for quantitative synthesis.

**Condition being studied** Advanced non-small cell lung cancer (NSCLC) is the most common subtype of lung cancer and a leading cause of cancer-related mortality worldwide. Most patients are diagnosed with inoperable, advanced disease. For those without targetable driver mutations, first-line immunotherapy—specifically inhibitors targeting the programmed death-1 (PD-1) pathway or its ligand (PD-L1)—has transformed the treatment landscape, offering more durable responses and improved overall survival compared to chemotherapy alone.

However, primary or acquired resistance is common, and a significant proportion of patients experience disease progression during or after first-line anti-PD-(L)1 therapy. This poses a critical and unresolved challenge in clinical practice: what is the optimal subsequent treatment? One key strategy under investigation is continuing anti-PD-(L)1 therapy beyond initial progression. The biological rationale is that a pre-primed immune system may still exert anti-tumor activity, and combining immunotherapy with a new cytotoxic or targeted agent upon progression could potentially

overcome resistance mechanisms. Nevertheless, continuing the same therapy after radiographic progression challenges conventional oncology practice.

The efficacy and safety of this "treatment beyond progression" strategy remain uncertain, with conflicting evidence and a lack of standardized guidelines. This meta-analysis systematically evaluates the clinical value of continuing PD-(L)1 inhibition after disease progression in advanced NSCLC, aiming to inform this specific therapeutic decision.

## METHODS

**Participant or population** This review will include adult patients diagnosed with advanced non-small cell lung cancer (NSCLC) who experienced disease progression during or after prior anti–PD-(L)1 inhibitor–based therapy.

**Intervention** The intervention of interest is the continuation of PD-(L)1 inhibitor therapy beyond initial radiological or clinical disease progression. This includes patients who either:
a) continue the same PD-(L)1 inhibitor as monotherapy, or
b) continue the same PD-(L)1 inhibitor in combination with a new systemic agent (such as chemotherapy or a targeted therapy) introduced at the time of progression.

**Comparator** The comparator is the discontinuation of PD-(L)1 inhibitor therapy upon initial disease progression. Patients in the comparator group typically receive alternative systemic treatment, which may include chemotherapy, targeted therapy, or a switch to a different therapeutic class, but do not continue the original PD-(L)1 inhibitor.

**Study designs to be included** The search was limited to studies published in English, and only randomized controlled trials, single-arm clinical trials and retrospective study on anti-PD-(L)1 were included.

**Eligibility criteria**
(1) Patients must have received anti-PD-(L)1 therapy before progression.
(2) The intervention under study must include inhibitors targeting the PD-1 or PD-L1 proteins.
(3) Studies must report on at least one of the outcomes: median overall survival (mOS), median progression-free survival (mPFS), objective response rate (ORR), or treatment-related adverse events (TRAEs).

**Information sources** Comprehensive literature searches were conducted in the following electronic bibliographic databases from their inception to the present: PubMed/MEDLINE, Embase, the Cochrane Library, and Web of Science Core Collection. No additional sources such as trial registries or conference proceedings were included.

**Main outcome(s)**
The primary outcomes of this meta-analysis are:
Overall Survival (OS): Defined as the time from treatment initiation (post-progression) to death from any cause. Effect measures will include hazard ratios (HR) with 95% confidence intervals.
Progression-Free Survival (PFS): Defined as the time from treatment initiation (post-progression) to disease progression or death from any cause. Effect measures will include hazard ratios (HR) with 95% confidence intervals.
Secondary outcomes include:
Objective Response Rate (ORR): Defined as the proportion of patients achieving complete or partial response according to RECIST criteria.
Treatment-Related Adverse Events (TRAEs): The incidence of grade ≥3 adverse events as assessed by CTCAE criteria.

**Quality assessment / Risk of bias analysis** The methodological quality and risk of bias of the included studies were assessed using two standardized tools according to study design. For randomized controlled trials (RCTs), the revised Cochrane Risk of Bias tool (RoB 2) was used to evaluate bias across five domains. For non-randomized studies, the Newcastle-Ottawa Scale (NOS) was applied to assess quality across three domains.

**Strategy of data synthesis** We utilized the onlinemeta v1.0 web tool11, a platform designed for meta-analysis. To calculate the standard deviation (SD) for the continuous variables mPFS and mOS in meta-analysis, we employed the method recommended by Cochrane for converting SDs from confidence intervals using their official 'data to standard deviation calculator'. The statistical heterogeneity of the combined effect sizes for each regimen was assessed using the Chi-square test for heterogeneity. If $p < 0.05$, there was a statistically significant difference in the therapeutic effects between regimens. When a particular treatment protocol was represented by only one study, the results were analyzed using a Welch's independent samples t-test for preliminary insights, though these findings were interpreted with caution due to limited data.

**Subgroup analysis** Subgroup analyses were performed to compare the efficacy and safety across different post-progression treatment regimens.

**Sensitivity analysis** Sensitivity analyses will be conducted to assess the robustness of the pooled results by:
Repeating the primary analysis using different statistical models: Comparing the results obtained from the fixed-effects model with those from the random-effects model.
Examining the influence of individual studies: Iteratively removing each included study one at a time to determine if any single study disproportionately influences the overall effect size.
Restricting analysis by study quality: Re-analyzing the data by including only studies with a low risk of bias (e.g., high-quality RCTs as per RoB 2, or single-arm studies with a NOS score above a specified threshold).

**Country(ies) involved** China.

**Keywords** Non-small cell lung cancer; PD-(L)1 inhibitor; immunotherapy; Treatment beyond progression.

**Contributions of each author**
Author 1 - Jingjun He - Author 1 performed data collection and analysis, created the data visualizations, and wrote the manuscript.
Email: 823351077@qq.com
Author 2 - Cui Chen - Author 1 performed data collection and analysis.
Email: 874812341@qq.com
Author 3 - AnQi Lin - Author 3 conceived and designed the analysis.
Email: smulinanqi0206@i.smu.edu.cn
Author 4 - Peng Luo - Author 4 conceived and designed the analysis. And The author read, provided feedback and approved the final manuscript.
Email: luopeng@smu.edu.cn
Author 5 - Ting Wei - The author read, provided feedback and approved the final manuscript.
Email: 258077534@qq.com
Author 6 - Jian Zhang - The author read, provided feedback and approved the final manuscript.
Email: blacktiger@139.com