INPLASY

Efficacy and safety of Neoadjuvant Chemoimmunotherapy Plus Chemoradiotherapy (NCRT) versus Chemoradiotherapy (CRT) Subsequent immune consolidation for Unresectable Stage III NSCLC: A Meta-Analysis

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Corresponding author:
duan jiayi

djy199808192813@163.com

Author Affiliation:
Taizhou Hospital of Zhejiang Province, Shaoxing University, Zhejiang Province, 317000, China.

Duan, JY; Zheng, JX; Zhou, YT; Chen, M; Zhou, C; Gu, PJ; Zhu, J; Zhou, SN; Yang, HH.

ADMINISTRATIVE INFORMATION

Support - Personal source.

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

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202680002

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 1 August 2026 and was last updated on 1 August 2026.

INTRODUCTION

Review question / Objective Review question: Is neoadjuvant chemo-immunotherapy followed by definitive chemoradiotherapy and consolidation immunotherapy (NCRT) superior to chemoradiotherapy followed by consolidation immunotherapy (CRT, PACIFIC-like regimen) in terms of survival outcomes and safety for patients with unresectable stage III NSCLC.
Objective: This systematic review and meta-analysis aimed to evaluate the comparative efficacy and safety of the NCRT sequence versus the CRT sequence in the treatment of unresectable stage III NSCLC, based on published phase II and III interventional studies.

Condition being studied Unresectable stage III non-small cell lung cancer (NSCLC) in patients receiving curative-intent concurrent chemoradiotherapy.

METHODS

Participant or population Patients with histologically confirmed, unresectable stage III (IIIA, IIIB, or IIIC) non-small cell lung cancer (NSCLC), aged 18 years or older, receiving curative-intent concurrent chemoradiotherapy. Studies including patients with EGFR, ALK, or ROS1 alterations were not excluded unless specified by the original study criteria.

Intervention Neoadjuvant chemoimmunotherapy (PD-1/PD-L1 inhibitors ± platinum-based chemotherapy) followed by definitive concurrent chemoradiotherapy and consolidation immunotherapy.

Comparator Concurrent chemoradiotherapy followed by consolidation immunotherapy (PD-1/PD-L1 inhibitors) without prior neoadjuvant/induction immunotherapy.

Study designs to be included Interventional studies, including phase II single-arm trials and phase III randomized controlled trials, evaluating

neoadjuvant chemoimmunotherapy followed by chemoradiotherapy and consolidation immunotherapy (NCRT) or the standard PACIFIC-like consolidation regimen (CRT) in unresectable stage III NSCLC.

Eligibility criteria We included phase II single-arm trials and phase III randomized controlled trials evaluating neoadjuvant chemoimmunotherapy followed by chemoradiotherapy and consolidation immunotherapy (NCRT) versus the standard PACIFIC-like consolidation regimen (CRT) in adult patients with unresectable stage III NSCLC. Studies were required to report at least one of the following: PFS, OS, ORR, or safety data. Retrospective studies, case reports, and studies with concurrent immunotherapy during radiotherapy were excluded.

Information sources We searched MEDLINE (via PubMed), Cochrane Central Register of Controlled Trials (via Cochrane Library), EMBASE (via Ovid), and Web of Science from inception to March 1, 2026. Conference abstracts from AACR, ASCO, ASTRO, ELCC, ESMO, ESMO Asia, ESMO-IO, ESMO-TAT, and WCLC (2010–2026) were hand-searched. Grey literature was searched via OpenGrey and Google Scholar. Reference lists of included studies and relevant reviews were screened. ClinicalTrials.gov was searched for ongoing trials. No language restrictions were applied. The full search strategies are provided in the supplementary materials.

Main outcome(s) Progression-free survival (PFS), defined as time from randomization/treatment initiation to disease progression or death. Secondary outcome(s): Overall survival (OS), objective response rate (ORR), grade ≥3 pneumonitis.

Quality assessment / Risk of bias analysis Risk of bias will be assessed independently by two reviewers using the RoBANS tool for non-randomized studies and the Cochrane RoB 2.0 tool for randomized controlled trials. Discrepancies will be resolved by consensus or by consulting a third reviewer. The following domains will be assessed: selection of participants, intervention measurement, blinding of outcome assessment, incomplete outcome data, selective reporting, and confounding variables (RoBANS); and randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result (RoB 2.0). Each domain will be rated as low, moderate/high, or unclear risk. The results will be presented in summary tables and figures. Studies with high risk of bias will not be automatically excluded but will be considered in sensitivity analyses.

Strategy of data synthesis Pooled proportions with 95% confidence intervals will be calculated using random-effects models (DerSimonian-Laird method) with logit transformation. Subgroup analyses will compare NCRT vs. CRT groups. Heterogeneity will be assessed using Cochran's Q test and I^2 statistic. Leave-one-out sensitivity analyses will be performed. For survival endpoints, individual-level data will be reconstructed from Kaplan-Meier plots using validated algorithms and pooled to generate summary survival curves. Publication bias will be assessed using funnel plots if ≥10 studies are included. Certainty of evidence will be assessed using GRADE. All analyses will be performed using R and Review Manager 5.3.

Subgroup analysis Subgroup analyses will compare outcomes between the NCRT group (neoadjuvant chemoimmunotherapy followed by cCRT and consolidation) and the CRT group (cCRT followed by consolidation only). Exploratory subgroup analyses may be performed based on radiotherapy fractionation, induction regimen type, PD-L1 expression, or study design, if sufficient data are available. Subgroup differences will be assessed using χ^2 tests and I^2 statistics.

Sensitivity analysis Leave-one-out sensitivity analyses will be performed by sequentially excluding each study and recalculating the pooled estimates to assess robustness. Sensitivity analyses will also be conducted excluding studies with substantial heterogeneity (e.g., EA5181 Arm B) and studies with moderate or high risk of bias. Results will be considered robust if point estimates remain within the 95% CI of the primary pooled estimate.

Country(ies) involved China.

Keywords non-small cell lung cancer; neoadjuvant chemoimmunotherapy; chemoradiotherapy; immunotherapy sequencing; meta-analysis.

Contributions of each author

Author 1 - jiayi duan.
Author 2 - jiaxi zheng.
Author 3 - yiting zhou.
Author 4 - meng chen.
Author 5 - chao zhou.
Author 6 - pinjun gu.
Author 7 - jian zhu.
Author 8 - suna zhou.
Author 9 - haihua yang.