INPLASY

INPLASY2025120080

doi: 10.37766/inplasy2025.12.0080

Received: 22 December 2025

Published: 22 December 2025

Corresponding author:
Yang Liu

2110122429@stu.pku.edu.cn

Author Affiliation:
Department of Urology, Peking University People's Hospital.

Evaluation of Surrogate Endpoints for Overall Survival and Quality of Life: Analysis based on the past ten years' Randomized Controlled Trials of Adjuvant Immunotherapy

Liu, Y; Li, JC; Song, YX; Du, YQ; Qin, CP; Xu, T.

ADMINISTRATIVE INFORMATION

Support - This study was supported by Noncommunicable Chronic Diseases-National Science and Technology Major Project (2024ZD0525700), The National Key Research and Development Program of China (2023YFC2507000), Innovation Fund for Outstanding Doctoral Candidates of Peking University Health Science Center (BMU2024BSS001), National Natural Science Foundation of China (82471866, 82271877, 82472912), Natural science foundation of Beijing, China (7242150, QY25150), Beijing Municipal Science & Technology Commission (Z221100007422097), Capital's Funds for Health Improvement and Research of China (2022-4-4087), Peking University People's Hospital Scientific Research Development Funds (RDGS2022-02, RDX2024-01).

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

Conflicts of interest - None declared.

INPLASY registration number: INPLASY2025120080

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 22 December 2025 and was last updated on 22 December 2025.

INTRODUCTION

Review question / Objective Participants (P): Patients with completely resected solid tumors. Intervention (I): Adjuvant immunotherapy. Comparator (C): Placebo, observation, or standard of care (chemotherapy/ interferon). Outcome (O): Primary: Correlation (R^2) between treatment effects on recurrence-based endpoints (DFS/RFS/EFS) and Overall Survival (OS) at both arm- and trial-levels. Secondary: Correlation between Quality of Life (QoL) outcomes and survival endpoints.

Condition being studied Resectable solid tumors treated with adjuvant immunotherapy.

METHODS

Search strategy

Embase
#1 'adjuvant therapy'/exp OR adjuvant.ab.ti OR postoperative.ab.ti
#2 'immune checkpoint inhibitor' OR immunotherapy.ab.ti OR pembrolizumab.ab.ti OR nivolumab.ab.ti OR ipilimumab.ab.ti OR atezolizumab.ab.ti OR durvalumab.ab.ti

#3 'neoplasm'/exp OR cancer.ab.ti OR neoplasm*.ab.ti OR tumor.ab.ti OR tumour.ab.ti OR malignant.ab.ti OR malignancy.ab.ti OR carcinoma.ab.ti
#4 'randomized controlled trial'/exp OR randomized.ab.ti OR randomised.ab.ti OR placebo.ab.ti OR rct.ab.ti
#5 #1 AND #2 AND #3 AND #4
#6 #5 AND (2016:py OR 2017:py OR 2018:py 2019:py OR 2020:py OR 2021:py OR 2022:py OR 2023:py OR 2024:py OR 2025:py)

PubMed
#1 adjuvant[tiab] OR "adjuvant setting"[tiab] OR postoperative[tiab] OR post-operative[tiab] OR resected[tiab] OR resection[tiab] OR "early stage"[tiab] OR "early-stage"[tiab] OR "curative intent"[tiab] OR "Chemotherapy, Adjuvant"[Mesh] OR "Radiotherapy, Adjuvant"[Mesh] OR "Immunotherapy, Adjuvant"[Mesh]
#2 "Immunotherapy"[Mesh] OR "Immune Checkpoint Inhibitors"[Mesh:noexp] OR "Programmed Cell Death 1 Receptor/antagonists and inhibitors"[Mesh] OR "CTLA-4 Antigen/ antagonists and inhibitors"[Mesh] OR immunotherapy[tiab] OR "immune checkpoint"[tiab] OR "checkpoint blockade"[tiab] OR pembrolizumab[tiab] OR "Pembrolizumab"[Mesh] OR nivolumab[tiab] OR "Nivolumab"[Mesh] OR atezolizumab[tiab] OR "Atezolizumab"[Mesh] OR durvalumab[tiab] OR "Durvalumab"[Mesh] OR avelumab[tiab] OR "Avelumab"[Mesh] OR ipilimumab[tiab] OR "Ipilimumab"[Mesh] OR cemiplimab[tiab] OR "Cemiplimab"[Mesh] OR PD-1[tiab] OR PD-L1[tiab] OR CTLA-4[tiab] OR "anti-PD-1"[tiab] OR "anti-PD-L1"[tiab] OR "anti-CTLA-4"[tiab] OR "PD 1 inhibitor*"[tiab] OR "PD L1 inhibitor*"[tiab] OR "CTLA 4 inhibitor*"[tiab]
#3 "Neoplasms"[Mesh] OR cancer[tiab] OR neoplasm*[tiab] OR tumor[tiab] OR tumour[tiab] OR oncology[tiab] OR malignant[tiab] OR malignancy[tiab] OR carcinoma[tiab] OR sarcoma[tiab]
#4 "Randomized Controlled Trial"[Publication Type] OR "Randomized Controlled Trials as Topic"[Mesh] OR randomi?ed[tiab] OR randomly[tiab] OR placebo[tiab] OR RCT[tiab] OR trial[tiab] OR "phase 2"[tiab] OR "phase II"[tiab] OR "phase 3"[tiab] OR "phase III"[tiab]
#5 #1 AND #2 AND #3 AND #4 AND ("2016/01/01"[Date - Publication] : "2025/12/31"[Date - Publication]) NOT (metastatic[tiab] OR "advanced cancer"[tiab] OR "advanced disease"[tiab] OR "first line"[tiab] OR "first-line"[tiab] OR "1st line"[tiab] OR neoadjuvant[tiab] OR perioperative[tiab] OR "unresectable"[tiab] OR letter[pt] OR editorial[pt] OR comment[pt]).

Participant or population Patients with completely resected solid tumors (including but not limited to melanoma, lung cancer, urothelial carcinoma, renal cell carcinoma, etc.) who are eligible for adjuvant therapy.

Intervention Adjuvant immune checkpoint inhibitors (ICIs), specifically anti-PD-1, anti-PD-L1, or anti-CTLA-4 antibodies, administered either as monotherapy or in combination with other therapeutic agents.

Comparator Placebo, observation, or active control (non-ICI standard of care, such as chemotherapy or interferon).

Study designs to be included Randomized Controlled Trials (RCTs); specifically Phase II and Phase III trials.

Eligibility criteria Inclusion criteria: Randomized controlled trials (RCTs) evaluating adjuvant immunotherapy in patients with resectable solid tumors. Studies reporting quantitative data for both Overall Survival (OS) and at least one surrogate endpoint (DFS, EFS, RFS, DMFS, or PFS) or Quality of Life (QoL). Sample size of at least 50 patients.
Exclusion criteria: Phase I studies or non-randomized trials. Studies conducted in neoadjuvant or metastatic settings.Reviews, conference abstracts, study protocols, and basic research. Studies with sample sizes less than 50.

Information sources A systematic search will be conducted in electronic databases including PubMed and Embase. The search will cover the period from January 1, 2016, to November 30, 2025.

Main outcome(s) The primary outcome is the strength of the association (surrogacy) between treatment effects on the composite recurrence-free endpoint (DFS/EFS/RFS) and Overall Survival (OS). The relationship between treatment effects on survival endpoints and Quality of Life (QoL), specifically measuring the mean difference in EORTC QLQ-C30 global health status scores.

Additional outcome(s) Individual correlations of PFS, DFS, EFS, RFS, and DMFS with Overall Survival (OS).

Data management Two investigators will independently screen titles and abstracts, followed

by full-text review. Disagreements will be resolved by a third author. Data will be extracted using a standardized form.
Survival Data: Survival rates at specific time points will be extracted using Engauge Digitizer (V.12.1).
IPD Reconstruction: Individual patient data will be reconstructed from Kaplan-Meier curves using the IPDfromKM package in R software to calculate restricted Hazard Ratios.

Quality assessment / Risk of bias analysis The methodological quality of the included RCTs will be assessed independently by two reviewers using the Cochrane Risk of Bias tool (version 2.0). Domains assessed will include randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result.

Strategy of data synthesis We will use unweighted linear regression models to estimate the correlation between log-transformed surrogate endpoints and log-transformed OS outcomes.
Trial-level surrogacy: Quantified by the coefficient of determination (R^2).
Interpretation criteria: $R^2 < 0.50$ (weak), $0.50 \leq R^2 \leq 0.69$ (moderate), $R^2 \geq 0.70$ (strong).
QoL Analysis: The mean difference in QoL scores will be modelled as a function of the log HR for survival endpoints.

Subgroup analysis Subgroup analyses will be conducted to explore potential heterogeneity. Stratification factors will include:Study phase (Phase II vs. Phase III), Cancer type (e.g., Melanoma, NSCLC, Urothelial Carcinoma, etc.), Treatment regimen (PD-1, PD-L1, CTLA-4, or combinations), Median follow-up duration (60 months).

Sensitivity analysis Sensitivity analyses will be performed to assess the robustness of the findings, potentially by excluding trials with high risk of bias or small sample sizes, if applicable.

Language restriction English.

Country(ies) involved China.

Keywords Adjuvant immunotherapy; Surrogate endpoint; Overall survival; Quality of life.

Contributions of each author
Author 1 - Yang Liu - Conceptualization, Methodology, Software, Formal analysis, Writing - Original Draft.
Email: 2110122429@stu.pku.edu.cn
Author 2 - Jincong Li - Conceptualization, Methodology, Software, Validation.
Email: 2110122419@stu.pku.edu.cn
Author 3 - Yuxuan Song - Methodology, Software, Validation, Investigation, Resources, Writing - Review & Editing.
Email: yuxuan_song2013@163.com
Author 4 - Yiqing Du - Data Curation, Visualization.
Email: duyiqing@bjmu.edu.cn
Author 5 - Caipeng Qin - Data Curation, Visualization.
Email: fances_wind@yeah.net
Author 6 - Tao Xu - Supervision, Project administration, Funding acquisition.
Email: xutao@pkuph.edu.cn