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REVIEW ARTICLE

An update on the role of immune checkpoint inhibitors in lung cancer: A narrative systematic review

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Abstract

Introduction: Lung cancer (LC) remains the leading cause of cancer-related mortality worldwide, and its aggressive nature necessitates the development of alternative therapeutic strategies. Immune checkpoint inhibitors (ICIs) have shown remarkable success in LC treatment. Despite advances with programmed cell death protein-1/programmed cell death ligand-1 inhibitors, many patients experience limited or short-lived responses, prompting interest in novel ICIs such as T-cell immunoreceptor with immunoglobulin and tyrosine-based inhibitory motif domain (TIGIT), lymphocyte-activation gene 3 (LAG-3), and indoleamine 2,3-dioxygenase 1 (IDO-1).

Objectives: This narrative systematic review aimed to assess the clinical efficacy and safety of these novel ICIs compared to standard ICI therapy in LC.

Methods: A systematic literature search was conducted across PubMed, Web of Science, and ClinicalTrials.gov. The search covered studies published from January 2020 to January 2025, to identify randomized controlled trials (RCTs) evaluating novel ICIs in LC. Due to substantial heterogeneity in study design, intervention targets, and outcome reporting, findings were synthesized narratively in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Risk of bias was assessed using RoB 2.

Results: Five RCTs involving a total of 825 patients were included. TIGIT inhibition demonstrated benefit in progression-free survival and response rate. LAG-3 inhibitors showed mixed efficacy, with potential dose-related differences. IDO-1 inhibitors failed to improve outcomes compared with standard ICI. Reporting quality varied, with concerns regarding incomplete outcome data in some trials.

Conclusion: These findings suggest promise for novel ICIs but are limited by small study numbers, methodological bias, and clinical heterogeneity. Larger, well-designed Phase III trials are required to validate these results.

Keywords: Lung cancer; Immune checkpoint inhibitors; Immunotherapy; Narrative systematic review

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1. Introduction

Lung cancer (LC) continues to represent the leading cause of cancer-related mortality worldwide, accounting for more than 1.8 million deaths in 2022.[1] Histologically, the disease is dominated by non-small cell LC (NSCLC), which constitutes 75–80% of all cases, and small cell LC (SCLC), which accounts for 10–15%.[2] This classification determines the treatment approach.[3]

Current strategies include surgery, radiotherapy, and systemic treatments such as chemotherapy.[3] Because LC is genetically complex and characterized by a high mutational burden that promotes rapid treatment resistance,[4] alternative therapeutic options are needed. Targeted therapies have improved outcomes for subsets of NSCLC patients harboring mutations in epidermal growth factor receptor and anaplastic lymphoma kinase.[3] Yet, most patients without these alterations—as well as nearly all SCLC patients—still face limited overall survival (OS) and rely on chemotherapy as first-line treatment. The advent of immune checkpoint inhibitors (ICIs) has transformed the therapeutic landscape of LC, particularly for NSCLC, where they now constitute an integral part of standard care (SOC). In SCLC, ICIs are combined with chemotherapy as first-line treatment.[3] ICIs block inhibitory pathways that suppress T-cell activity, preventing the tumor cells from evading immune surveillance.[5,6]

Key inhibitory axes used in SOC include the programmed cell death protein-1/programmed cell death ligand-1 (PD-1/PD-L1) and cytotoxic T lymphocyte antigen-4 (CTLA-4) pathways. Their blockade allows effective T-cell activation previously suppressed by the expression of PD-L1 on tumor cells and by B7-1/2 on antigen-presenting cells.[5,6] Approved ICIs used in LC treatment include PD-1 inhibitors, such as nivolumab and pembrolizumab; PD-L1 inhibitors, such as atezolizumab, cemiplimab, and durvalumab; and CTLA-4 inhibitors, such as ipilimumab.[3]

Biomarker testing is crucial for identifying patients more likely to benefit from regimens incorporating targeted therapies or immunotherapies. In patients with NSCLC, PD-L1 expression, microsatellite instability, and tumor mutational burden have been validated as predictors of improved outcomes after ICI treatment. Therefore, the indication for ICIs depends on PD-L1 expression levels above specific thresholds.[3,7] For SCLC, however, PD-L1 expression has not proven predictive, and ICI-based regimens are currently indicated mainly for extensive-stage disease, generally alongside chemotherapy during both induction and maintenance phases. For both types of LC, enrollment in clinical trials is encouraged whenever feasible.[3]

Despite these advances, durable benefits are achieved in only about 30% of advanced NSCLC and 20% of SCLC patients. This is due to complex resistance mechanisms such as T-cell exhaustion and altered tumor metabolism.[7-9] Moreover, PD-L1 expression alone provides incomplete predictive value due to inter- and intratumor heterogeneity, as well as variability in testing methods.[5,9,10] Emerging research has identified additional immune targets that may overcome resistance and broaden response rates. These include lymphocyte-activation gene 3 (LAG-3), T-cell immunoglobulin and mucin-domain containing-3, T-cell immunoreceptor with immunoglobulin and tyrosine-based inhibitory motif domain (TIGIT), V-domain immunoglobulin suppressor of T-cell activation, indoleamine 2,3-dioxygenase (IDO-1) pathway, cluster of differentiation (CD) 47, CD73, and natural killer (NK) group 2 member A. All these immune checkpoints remain under clinical evaluation and could serve as both biomarkers and therapeutic targets.[5,6,11-15]

Although early trials indicate that ICIs carry a higher incidence of immune-related adverse events (AEs) than chemotherapy, toxicity appears comparable between single- and dual-ICI regimens.[16] Continued investigation is therefore essential to refine efficacy-safety profiles and clarify mechanisms underlying resistance and toxicity.[17,18]

This narrative systematic review compiles and interprets current evidence on novel ICIs in LC treatment. It aims to emphasize agents designed to overcome resistance to SOC PD-1, PD-L1, and CTLA-4 therapies and to extend clinical benefit to a broader population of LC patients. Given the limited and heterogeneous clinical evidence, this review employs a narrative synthesis rather than a quantitative meta-analysis.

2. Methods

2.1. Eligibility criteria

The eligibility of retrieved studies was determined according to the following criteria: (i) LC patients were treated with novel ICIs alone or in combination with SOC ICIs, with the option to include additional therapies; (ii) there was a comparator arm with SOC ICIs as monotherapy or combination; and (iii) the study evaluated clinical and safety outcomes associated with novel ICI treatment. When multiple publications originated from the same clinical trial, the latest or most complete publication was selected. Case reports, reviews, systematic reviews, meta-analyses, conference abstracts, articles irrelevant to this study, and articles not written in English were excluded. Studies enrolling various cancer types, including LC, were included only when survival and safety outcomes for the LC subgroup were reported; otherwise, they were

excluded. Studies without reported results were excluded, as this review aimed to assess the therapeutic value of novel ICIs through outcome evaluation. To ensure a robust narrative systematic review and minimize risk of bias, non-randomized clinical trials (NRCTs) were excluded. Full eligibility criteria are detailed in the review protocol (available online—10.37766/inplasy2025.7.0056)).

2.2. Search strategy

This narrative systematic review complied with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2020 guidelines.[19] A systematic search of PubMed, Web of Science, and ClinicalTrials.gov was performed between May 10 and June 12, 2025, and included studies published from January 2020 to January 2025. Medical Subject Headings and keyword terms related to "lung cancer," "immune checkpoint inhibitors," and "drug resistance" were used. The full search strategies for each database are provided in Appendix A1.

2.3. Selection process

All identified records were uploaded to PICO Portal (https://picoportal.org/), an online systematic review management platform. The platform facilitated the title and abstract screening by structuring the review process and retrieving abstracts for each reference. Two independent authors screened titles and abstracts against the inclusion criteria, using PICO Portal to facilitate abstract retrieval and workflow management. As the platform did not support full-text review or data extraction at the time, these steps were performed manually using shared documents. Disagreements were resolved through consensus or consultation with a third reviewer. The study selection process is depicted in the PRISMA flow diagram in Figure 1.

Most full-text exclusions were related to study design or intervention criteria. Non-randomized, retrospective, or observational studies were excluded to maintain methodological consistency across trials. Studies investigating only established ICIs (PD-1, PD-L1, or CTLA-4) or lacking a novel ICIs component were considered ineligible. Additional exclusions included absence of relevant outcomes (e.g., OS, progression-free survival [PFS], objective response rate [ORR], AE), unavailable full text, incomplete reporting preventing eligibility assessment, duplicate or redundant publications, and protocols or trial registrations without results. Detailed reasons for exclusion are provided in Appendix A2.

2.4. Data extraction and outcomes

Two reviewers independently performed data extraction using a standardized data collection table. Extracted variables included authors, title, study design, population, intervention, comparator, sample size, median follow-up duration, and assessed outcomes. Any discrepancies were resolved through discussion or adjudicated by a third reviewer.

The selected outcomes were OS, PFS, event-free survival (EFS), disease-free survival (DFS), ORR, partial response rate (PRR), complete response rate (CRR), and AE.

2.5. Risk of bias assessment

We used the Cochrane Risk of Bias 2 tool assessment to evaluate potential sources of bias in the included randomized clinical trials across five domains: (i) Bias arising from the randomization process, (ii) bias due to deviations from intended interventions, (iii) bias due to missing outcome data, (iv) bias in measurement of the outcome, and (v) bias in selection of the reported result.[20] This assessment was performed for each measure of treatment effect listed at the end of Section 2.4. Data extraction and outcomes. Each domain was rated as "low risk," "some concerns," or "high risk" according to pre-specified criteria. "Some concerns" typically reflected incomplete reporting of allocation methods, unclear blinding, or lack of pre-registered analysis plans. "High risk" ratings were applied when deviations from intended interventions were evident, selective reporting was likely, or outcome data were incomplete or inconsistently presented. Risk of bias was evaluated for each relevant reported outcome. Two independent authors performed the quality assessment, and disagreements were resolved through discussion or by a third reviewer.

2.6. Effect measures

Effect measures were extracted for outcomes of interest as defined by the eligibility criteria: OS, PFS, DFS, EFS, ORR, PRR, CRR, and AEs.

Effect measures were recorded as reported in each study without transformation. OS, PFS, DFS, and EFS were presented as median time in months, with 95% confidence intervals (CIs) and/or hazard ratios (HRs) when available. ORR, PRR, and CRR were reported as the percentage of participants achieving each response category based on Response Evaluation Criteria in Solid Tumors or other pre-specified definitions. AE was presented as the frequency and percentage of participants experiencing treatment-emergent or serious AE, often stratified by grade.

2.7. Synthesis methods

Due to substantial heterogeneity among the included studies, primarily resulting from the evaluation of different novel ICIs across varied therapeutic settings, a meta-analysis was not conducted. Instead, a qualitative narrative

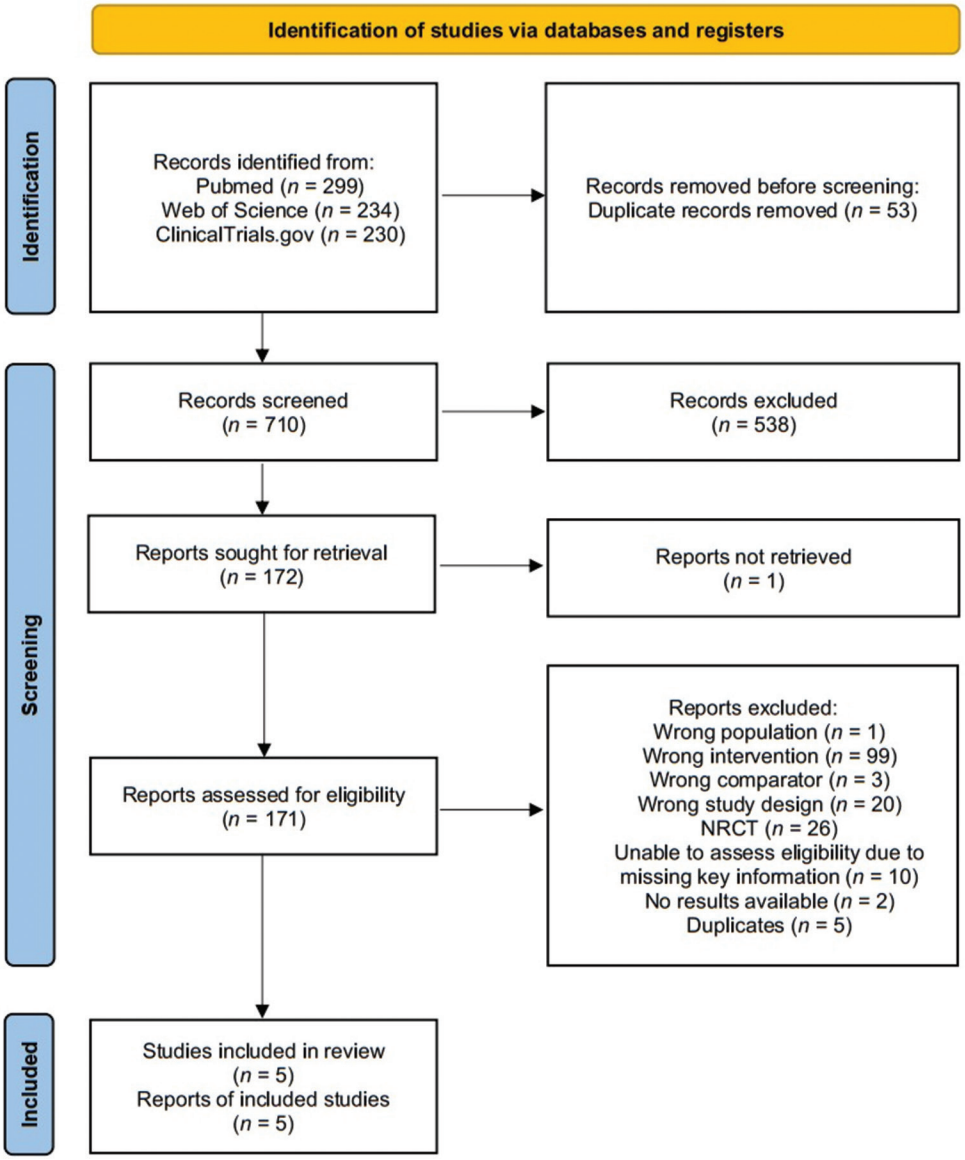

Figure 1. Preferred reporting items for systematic reviews and meta-analyses 2020 flow diagram showing the identification, screening, eligibility assessment, and inclusion of studies
Abbreviation: NRCT: Non-randomized clinical trials

synthesis was performed to group and compare findings descriptively. This methodological approach allowed the identification of patterns and differences across studies by grouping them according to intervention and outcomes based on eligibility criteria, despite the limited availability of directly comparable interventions and/or homogeneous populations.

All effect measures were extracted directly from the original study publications without statistical transformation and were presented in structured summary tables. No sensitivity or subgroup analyses were performed. The interpretation of results considered the risk of bias and the methodological characteristics of each study.

2.8. Certainty assessment

The certainty of the evidence was evaluated qualitatively following the principles of the grading of recommendations assessment, development, and evaluation (GRADE) framework. Because the number of included studies was small and clinical heterogeneity was substantial, a formal quantitative GRADE rating was not feasible. Instead, we appraised each key outcome across the standard GRADE domains—risk of bias, consistency, precision, and directness of evidence—and summarized these assessments narratively in Section 3.6. Certainty of evidence. These qualitative ratings guided the interpretation of findings rather than producing numerical scores.

3. Results

3.1. Study selection

As illustrated in Figure 1, the comprehensive literature search yielded 763 articles. After removing 53 duplicates and excluding 538 records based on titles and abstracts screening for failing to meet the inclusion criteria, 172 full-text articles were assessed for eligibility, mainly due to incomplete information available in abstracts. Of these, one study was excluded because the full text was unavailable, making it impossible to retrieve the report, and 165 were excluded for the following reasons: wrong population (n = 1), wrong intervention (n = 99), wrong comparator (n = 3), wrong study design (n = 20), NRCT (n = 26), ICI treatment unknown or eligibility not assessable due to missing key information (n = 11), and duplicates (n = 5). Ultimately, five studies met the inclusion criteria and were included in this narrative systematic review.[21-25]

Among the excluded records, 26 studies were NRCTs that would otherwise have met the inclusion criteria but were excluded based on study design. In addition, two studies lacked available results despite completion. One was completed with only one participant, leaving no outcome data for analysis.[26] The other had a comparator arm excluded from certain groups during the trial and provided insufficient data for risk of bias assessment, with no evaluable protocol or full report.[27]

3.2. Study characteristics

The main design and demographic features of the five included studies are summarized in Table 1. All were randomized controlled trials (RCTs) investigating ICIs in LC. All enrolled patients had NSCLC. One study (NCT04205552) focused on resectable NSCLC (stage IB-IIIa) in the neoadjuvant setting,[25] while the remaining four studies enrolled patients with advanced or metastatic

Table 1. Characteristics of included studies

NCT	Study (author)	Study design	Population (LC type)	Intervention (novel ICI)	Comparator (SOC ICI)	Sample size	Follow-up duration
NCT03322540	Tokito.[21]	Phase II RCT	Metastatic NSCLC (PD-L1 ≥50%)	Pembrolizumab+ epacadostat (anti-IDO-1)	Pembrolizumab+ placebo	154 (77/77)	Median=6.8 months experimental, 7.0 months control
NCT04205552	Schuler *et al.*[25]	Phase II RCT	Resectable NSCLC (stage I–III)	Nivolumab+ relatlimab (anti-LAG3)	Nivolumab alone	60 (30/30)	Median 12 months
NCT03516981	Gutierrez *et al.*[23]	Phase II RCT	Treatment-naive advanced NSCLC (stage IV)	Pembrolizumab+ lenvatinib (TKI) or favezelimab (anti-LAG3) (200 mg/800 mg)	Pembrolizumab+ quavonlimab	243 (lenvatinib *n*=80/favezelimab 200mg *n*=30/ favezelimab 800mg *n*=51/quavonlimab *n*=82)	Median 14.1 months
NCT03563716	Cho *et al.*[24]	Phase II RCT	Chemo-naive PD-L1 selected advanced NSCLC	Tiragolumab (anti-TIGIT) + atezolizumab	Placebo+ atezolizumab	135 (experimental: 67, control: 68)	Median 30.4 months
NCT03322566	Boyer *et al.*[22]	Phase II RCT	Treatment-naive metastatic NSCLC	E+P+C	Pembrolizumab+ placebo+ chemotherapy	233 (experimental E+P + C: *n*=91; E+P: *n*=55; control; *n*=87)	Median 5.1 months (E+P + C), 7.2 months (control)
NCT	**Study (author)**	**Study design**	**OS**	**PFS**	**DFS**	**ORR**	**PRR**
NCT03322540	Tokito.[21]	Phase II RCT	Median=NR (both arms), HR 0.74 (95% CI: 0.36–1.52); *P*=0.205	Median=6.7 months experimental, 6.2 months control; HR 1.10 (95% CI: 0.69–1.76); *P*=0.659	-	Experimental: 32.5% (22.2–44.1); control: 39.0% (28.0–50.8), difference: −6.5% (95% CI−21.5 to 8.7), *P*=0.8000	-

(Cont'd...)

Table 1. ***(Continued)***

NCT	Study (author)	Study design	Population (LC type)	Intervention (novel ICI)	Comparator (SOC ICI)	Sample size	Follow-up duration
NCT04205552	Schuler *et al.*[25]	Phase II RCT	Experimental: 100%, control: 93%	-	Experimental: 93%, control: 89%	Experimental: 27%, control: 10%	Experimental: 27%, control: 10%
NCT03516981	Gutierrez *et al.*[23]	Phase II RCT	Median=experimental - levantinib: 19.4 months (15.9–22.7), favezelimab 200 mg: 14.8 months (7.6–25.4), favezelimab 800 mg: 15.8 months (11.7–NR); control: 20.2 months (14.1–25.7)	Median=experimental levantinib: 8.5 months (6.0–12.5), favezelimab 200 mg: 2.1 months (2.0–6.5), favezelimab 800 mg: 6.1 months (3.5–8.3); control: 6.1 months (3.5–10.3)	-	Experimental levantinib: 35.0% (24.7–46.5), favezelimab 200 mg: 23.3% (9.9–42.3) and favelimab 800 mg: 29.4% (17.5–43.8); control: 25.6% (16.6–36.4)	-
NCT03563716	Cho *et al.*[24]	Phase II RCT	Median=23.2 months experimental, 14.5 months control; HR 0.69 95% CI: 0.44–1.07; *P*=0.093	Median=experimental: 5.4 months (4.2–not estimable), control: 3.6 months (2.7–4.4); HR 0.62 (95% CI: 0.42–0.91); *P*=0.013	-	Experimental: 38.8% (26.4–51.2); control: 20.6% (10.2–30.9); *P*=0.013	-
NCT03322566	Boyer *et al.*[22]	Phase II RCT	Median=NR (both arms), HR 1.90 (95% CI: 0.93–3.90); *P*=0.96	Median=experimental (E+P+C): 8.0 months, control: 8.2 months; HR: 1.47 (95% CI: 0.91–2.36); *P*=0.94	-	Experimental (E+P+C): 26.4% (17.7–36.7); control: 44.8% (34.1–55.9); difference: –18.5% (95% CI: –32.0 to –4.3); *P*=0.9948	-

Notes: Summary of the five included randomized clinical trials by population, intervention, comparator arms, sample size, and median follow-up. Outcomes, such as overall survival, progression-free survival, disease-free survival, objective response rate, and partial response rate, are reported when available.

Abbreviations: CI: Confidence interval, CRR: Complete response rate; DFS: Disease-free survival; EFS: Event-free survival; E+P: Pembrolizumab+epacadostat; E+P+C: Pembrolizumab+epacadostat+chemotherapy; HR: Hazard ratio; ICI: Immune checkpoint inhibitor; IDO-1: Indoleamine 2,3-dioxygenase; LAG-3: Lymphocyte-activation gene 3; LC: Lung cancer; NR: Not reached; NSCLC: Non-small cell lung cancer; ORR: Objective response rate; OS: Overall survival, PD-L1: Programmed cell death ligand-1; PFS: Progress-free survival, PRR: Partial response rate; RCT: Randomized controlled trial; SOC: Standard of care, TIGIT: T-cell immunoreceptor with immunoglobulin and tyrosine-based inhibitory motif domain; TKI: Tyrosine kinase inhibitor.

NSCLC (stage IV), either treatment-naive or previously treated.

Sample sizes ranged from 60 to 233 participants. The investigated interventions involved novel ICIs targeting IDO-1 (epacadostat),[21,22] TIGIT (tiragolumab),[24] and LAG-3 (relatlimab[25] and favezelimab[23]), each administered in combination with SOC PD-1/PD-L1 inhibitors, such as pembrolizumab, atezolizumab, or nivolumab.

Comparators in most trials consisted of the same PD-1/PD-L1 inhibitor used in the experimental arm, either as monotherapy or with a placebo. In one trial, the experimental arm included triple therapy combining a novel ICI, pembrolizumab, and chemotherapy, compared with pembrolizumab plus placebo and chemotherapy.[22] Another trial tested a dual-ICI combination (a novel ICI plus an SOC ICI) with a tyrosine kinase inhibitor (lenvatinib) versus a dual SOC ICI regimen.[23]

The studies assessed outcomes, including OS, PFS, ORR (e.g., PRR and CRR), DFS, and AEs (including grade ≥3 treatment-emergent AEs). Other outcomes, such as the duration of response, biomarker analyses (e.g., kynurenine levels, PD-L1 tumor proportion score, and exploratory subgroup analyses were reported in some studies but were not part of our predefined eligibility criteria. Details of outcome comparisons across studies are summarized in Tables 1 and 2.

3.3. Risk of bias

Risk of bias was assessed separately for each outcome across all five studies, as shown in Figure 2. No single outcome was designated as primary, and all were weighed equally.

Across the five included RCTs, risk-of-bias judgments varied by outcome. Two studies had mostly low risk of bias, with some concerns for a single outcome. One study had some concerns across all outcomes, primarily in Domain 1

Table 2. Adverse events reported in the included studies

NCT	Study (author)	AE
NCT03322540	Tokito *et al.*[21]	Grade ≥3 TRAE=experimental: 21.3%, control: 24.7%; any AE=experimental: 92.0%, control: 93.5%. Most common SAE (≥2%) were: Experimental - pneumonia (4.0%), anemia (2.7%), atelectasis (2.7%), and pneumonitis (2.7%); control - pneumonia (3.9%), pneumonitis (2.6%), and hypotension (2.6%)
NCT04205552	Schuler *et al.*[25]	Grade ≥3 TRAE=experimental: 13%, control: 10%. Most common TRAE with incidence ≥10% at least in one arm were: experimental – hyperthyroidism (27%) and hypothyroidism (17%); control – fatigue (27%) and hyperthyroidism (23%)
NCT03516981	Gutierrez *et al.*[23]	Grade 3–5 TRAE ≥6.7% of patients in all treatment arms; any AE ≥90.0% of patients in all treatment arms. Most common any-grade TRAE were: Pembrolizumab+lenvatinib - hypertension (50.0%) and hypothyroidism (30.0%); pembrolizumab+favezelimab 200 mg – pruritus (20.0%) and hypothyroidism (13.3%); pembrolizumab+favezelimab 800 mg – pruritus (15.7%) and diarrhea, fatigue, and hypothyroidism (13.7% each); pembrolizumab+quavonlimab – pruritus (20.7%) and fatigue (13.4%)
NCT03563716	Cho *et al.*[24]	Serious TRAE=experimental: 21%, control: 12%. The most common grade ≥3 TRAE: Lipase increase (experimental: 9%, control: 3%)
NCT03322566	Boyer *et al.*[22]	Any AE, TRAE, grade 3–5 AE, grade 3–5 TRAE, SAE, and TRSAE: Experimental (E+P + C) were slightly higher (<10% difference) compared to controls. The most frequent (>2%) drug-TRSAE: experimental (E+P+C) – febrile neutropenia (4.4%), diarrhea (2.2%), lower respiratory tract infection (2.2%), and neutropenia (2.2%); control - pneumonia (3.5%) and diarrhea (2.3%)

Note: Safety outcomes from the five included randomized trials, including rates of any adverse events, grade ≥3 adverse events, treatment-related events, and serious adverse events, when available. Abbreviations: AE: Adverse event; E+P+C: Pembrolizumab+epacadostat+chemotherapy; SAE: Serious adverse event; TRAE: Treatment-related adverse events; TRSAE: Treatment-related serious adverse event.

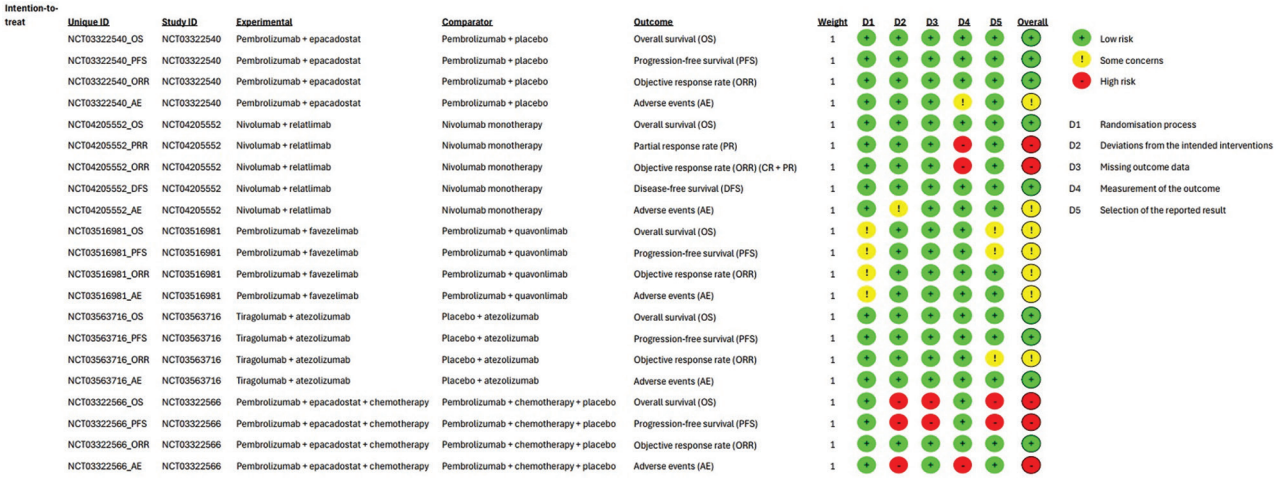

Figure 2. Risk-of-bias assessment of included randomized trials using the Cochrane RoB 2 tool across five domains and evaluated outcomes (overall survival, progression-free survival, disease-free survival, objective response rate, partial response rate, and adverse events), when available
Abbreviations: CR: Complete response rate; PR: Partial response

(bias arising from the randomization process) and Domain 5 (bias in selection of the reported result). Two studies had at least two outcomes with a high risk of bias, primarily due to issues in Domain 2 (bias due to deviations from intended interventions).

The most frequently flagged domain was Domain 5 (bias in selection of the reported result), largely due to the absence of pre-specified analysis plans. Domain 4 (bias in measurement of the outcome) also raised frequent concerns, particularly for outcomes like AEs and ORR, which may rely on subjective or unblinded assessments.

Detailed justifications for each domain-specific risk-of-bias judgment, derived from the RoB 2 Excel tool, are available upon request and were used to generate the traffic-light plot presented in Figure 2, which depicts the distribution of risk-of-bias judgments per outcome and domain.

3.4. Trial outcomes by immune target

Five clinical trials were included in this synthesis, all evaluating novel ICIs in patients with LC. Interventions targeted distinct pathways, including IDO-1, LAG-3, and

TIGIT. Due to substantial clinical and methodological heterogeneity, particularly in dosing regimens, disease stages, therapeutic combinations, and outcome metrics, a meta-analysis was not conducted. Key efficacy data for each trial are summarized in Table 1, and AE profiles in Table 2.

3.4.1. IDO-1 inhibitors

Two Phase II RCTs (NCT03322540 and NCT03322566) evaluated combinations involving the IDO-1 inhibitor epacadostat with SOC therapies in patients with advanced LC. Comparators included PD-L1 monotherapy[21] or chemoimmunotherapy.[22] Neither trial demonstrated a statistically or clinically meaningful benefit of the novel ICI in OS, PFS, or ORR compared with control arms. For example, in one study,[22] survival outcomes numerically favored the control arm (HR: 1.90, 95% CI: 0.93–3.90), and the intervention arm had a lower ORR (26.4% vs. 44.8%).[21,22] Both trials had methodological limitations, including incomplete reporting and unclear randomization procedures, which reduced confidence and reliability in their findings.

3.4.2. LAG-3 inhibitors

Two RCTs evaluated combinations involving LAG-3 and PD-1/PD-L1 inhibitors. NCT03516981 paired favezelimab with pembrolizumab, assessing 200 mg and 800 mg doses, while NCT04205552 paired relatlimab with nivolumab in patients with resectable[25] or metastatic cancers.[23] As shown in Tables 1 and 2, in the favezelimab trial, both dosing arms showed inferior OS (14.8–15.8 months vs. 20.2 months for control). PFS was lower at 200 mg (2.1 vs. 6.1 months) but matched the control at 800 mg. ORR improved slightly at 800 mg (29.4% vs. 25.6%) and decreased at 200 mg (23.3%). Grade ≥3 AEs were fewer, particularly at 200 mg (6.7% vs. 23.2%).[23] On the other hand, the relatlimab study (NCT04205552), combining anti-LAG-3 with nivolumab, showed higher OS (100% vs. 93%) and DFS (93% vs. 89%), as well as higher ORR and PRR (both 27% vs. 10%), compared with nivolumab alone. AEs were slightly higher (13% vs. 10%).[25]

Overall, favezelimab demonstrated modest improvements in response at higher doses but was associated with inferior survival outcomes. In contrast, relatlimab showed numerically superior survival and higher response rates in a neoadjuvant setting. However, direct comparisons between trials are limited due to differences in disease stage, therapeutic context, comparator arms, and the absence of reported statistical significance across these LAG-3-targeting strategies.[23,25]

3.4.3. TIGIT inhibitor

A single Phase II RCT (NCT03563716)[24] evaluated tiragolumab plus atezolizumab compared with placebo plus atezolizumab in PD-L1-positive metastatic NSCLC patients. As presented in Table 1, TIGIT inhibition demonstrated statistically significant improvements in PFS (HR: 0.62; p=0.013) and ORR (38.8% vs. 20.6%; p=0.013). OS also favored the intervention (23.2 vs. 14.5 months; HR: 0.69; p=0.093), although this difference did not reach statistical significance. Grade ≥3 AEs were higher in the intervention arm,[24] as shown in Table 2.

3.5. Comparative synthesis and methodological interpretation

Across all included trials, the direction of effect varied by molecular target. TIGIT blockade showed the most favorable efficacy outcomes in terms of PFS and ORR; however, this evidence was derived from a single Phase II trial and should therefore be considered preliminary until confirmed by ongoing Phase III studies. LAG-3 inhibition produced mixed outcomes with potential dose-dependent effects. High-dose favezelimab (800 mg) yielded modest gains in ORR without a survival advantage, whereas relatlimab showed improved survival metrics in the neoadjuvant setting. In contrast, IDO-1 inhibition failed to confer measurable clinical benefit, with one study favoring the control arm in both survival and response outcomes. A comparative overview of efficacy and safety across all molecular targets is provided in Tables 1 and 2, highlighting variability in response patterns and AE frequencies.

Overall, studies were rated as having a moderate risk of bias. IDO-1 inhibitor trials showed concerns due to incomplete reporting and unclear allocation methods. The favezelimab trial had risks associated with its open-label design and early-phase limitations, while the relatlimab and TIGIT studies provided more complete outcome data and better blinding.

Results were synthesized narratively through qualitative sensitivity assessments grouped by molecular target (IDO-1, LAG-3, and TIGIT). The direction of effect was evaluated based on reported HRs, response rates, and survival metrics. Interpretations remained consistent when considering only trials with complete outcome reporting (e.g., HR and CIs). Excluding studies with inconclusive or negative results, such as those involving IDO-1 inhibitors, did not alter the conclusions for other agents—for example, TIGIT blockade maintained the strongest efficacy signal. Similarly, focusing solely on the higher dose favezelimab arm (800 mg) reinforced a modest yet favorable trend in ORR. These observations support the robustness of the synthesized conclusions despite variations in dose, outcome reporting, and trial design.

This narrative synthesis revealed meaningful variation in efficacy across drug classes. Several factors contributed

to the heterogeneity observed across study outcomes. Notably, dose variation played a critical role, particularly within LAG-3 trials, where the 800 mg dose demonstrated better efficacy than the 200 mg dose. The nature of combination therapies also influenced results; for example, IDO-1 inhibitors were administered alongside anti-PD-1 agents or chemotherapy, potentially modifying their effect. In addition, inconsistencies in outcome reporting, such as missing HRs for OS, limit interpretability. Variations in clinical populations, including tumor stages and treatment lines, further constrained comparisons. These discrepancies highlight the need for more standardized trial designs and reporting practices in future research involving novel ICIs.

3.6. Certainty of evidence

Although the GRADE approach was not formally applied, the certainty of the evidence was assessed qualitatively using GRADE-informed criteria, considering study design, risk of bias, consistency, precision, and completeness of reporting. The relative strength and consistency of outcomes summarized in Table 1 (efficacy) and Table 2 (safety) informed these GRADE-based judgments.

Among the evaluated outcomes, certainty was highest for PFS, supported by consistent findings in the TIGIT and LAG-3 (relatlimab) studies with complete reporting of effect estimates. However, confidence was reduced by inconsistency and imprecision in the favezelimab 200 mg arm and in the IDO-1 inhibitor trials.

Certainty in OS was judged as low to moderate. While TIGIT inhibition showed a favorable trend, results were frequently reported without HRs or CIs, particularly in IDO-1 studies, limiting interpretability and statistical strength.

For ORR, the certainty of the evidence was low. Several studies lacked detailed reporting of response categories or omitted CIs entirely. High risk of selective reporting, especially in the relatlimab and TIGIT trials, and variation in effects across interventions and doses further reduced confidence.

Grade ≥3 AEs were consistently reported across all included studies, with standardized use of the Common Terminology Criteria for AEs grading and clear stratification by treatment attribution and seriousness. Most trials provided detailed tabulations of event types, incidence thresholds (e.g., ≥10%), and associated discontinuations or deaths. However, some variability existed in the granularity of immune-related AE reporting and in the categorization of drug-attributable versus general toxicities. While overall reporting quality was strong, concerns remained regarding selective AE domain reporting in some trials, particularly early-phase or open-label designs. Based on this, the certainty of evidence for safety outcomes was judged as moderate, reflecting solid but variably detailed AE characterization.

DFS and PRR were each reported in only one study (NCT04205552), limiting comparative synthesis and generalizability. While relatlimab demonstrated favorable DFS and PRR compared with control, the certainty of these findings is very low due to reliance on a single dataset, high risk of bias in outcome reporting, and absence of supporting evidence from other trials.

In summary, the evidence base provides moderate certainty that TIGIT inhibition improves PFS, low to moderate certainty for OS and AE outcomes, low certainty for ORR, and very low certainty for DFS and PRR due to single-study reporting and unclear reliability.

4. Discussion

Although we initially aimed to assess a broad range of novel ICIs, only a small number of immune targets were represented in the studies that met the inclusion criteria. Among these, TIGIT, LAG-3, and IDO-1 emerged as the primary molecular pathways investigated in the context of LC.

The CITYSCAPE Phase II randomized trial (NCT03563716)[24] evaluated tiragolumab plus atezolizumab in PD-L1-positive NSCLC and reported a 38% reduction in the risk of progression or death (HR: 0.62, 95% CI: 0.42–0.91) and an increased ORR (38.8% vs. 20.6%), with a favorable safety profile. These findings generated substantial early interest in TIGIT as a novel immune checkpoint target. TIGIT is an inhibitory receptor expressed on T cells and NK cells, where it competes with the costimulatory receptor CD226 for binding to ligands, such as CD155 on tumor or antigen-presenting cells. Its blockade has been shown to restore effector function and enhance antitumor immunity, potentially explaining the initial clinical benefit observed in this clinical trial (NCT03563716).[28] However, CITYSCAPE was an early-phase study with a limited sample size and was rated as having a moderate risk of bias due to an open-label design and lack of confirmatory endpoints.

Subsequent Phase III SKYSCRAPER trials tempered early optimism. In SKYSCRAPER 01, tiragolumab plus atezolizumab failed to significantly improve OS or PFS in PD-L1-high NSCLC (OS HR: ~0.81; not statistically significant).[29] Meanwhile, SKYSCRAPER 06, which combined tiragolumab, atezolizumab, and chemotherapy, was halted early due to inferior PFS (HR: 1.27) and markedly worse OS (HR: 1.33) compared with control.[30] This trajectory, from promising Phase II results to negative Phase III outcomes, illustrates the risk of

overinterpreting early-phase efficacy and underscores the need for replication in large, well-powered Phase III studies. Therefore, although TIGIT inhibition remains mechanistically appealing, current clinical evidence does not yet support its efficacy in NSCLC. According to GRADE criteria, the certainty of evidence remains low to moderate due to concerns regarding imprecision, risk of bias, and lack of consistency across trial phases.

In contrast, trials of LAG-3 inhibitors yielded mixed results. LAG-3, another T-cell inhibitory receptor, was traditionally thought to bind major histocompatibility complex (MHC) class II molecules; however, recent evidence has identified fibrinogen-like protein 1 (FGL-1) as a major ligand in tumors with low MHC-II expression. FGL-1 is frequently overexpressed in NSCLC, where it suppresses T-cell activation through LAG-3 binding, promoting immune escape. This may help explain the varied efficacy of LAG-3 targeting agents, which may be influenced by factors such as FGL-1 expression levels, the tumor microenvironment, and the degree of pathway inhibition achieved at different doses.[31] For example, the favezelimab trial demonstrated slight improvements in response rate at higher doses (800 mg vs. 200 mg), suggesting a dose-response relationship that could influence clinical benefit.[23] In the relatlimab trial (NCT04205552),[25] OS and DFS were improved compared with the control arm. These results align with external Phase III data from RELATIVITY-047 in melanoma, where relatlimab combined with nivolumab improved PFS, supporting LAG-3 as a promising co-target.[32]

The two IDO-1 inhibitor trials (NCT03322540 and NCT03322566) failed to demonstrate clinical benefit and often favored the control arm in survival and response outcomes.[21,22] In contrast to other immune targets, IDO-1 mediates metabolic immunosuppression by degrading tryptophan into kynurenine. Low tryptophan levels impair effector T-cell proliferation and antitumor activity, while high kynurenine levels promote immunosuppression through the development of regulatory T cells. Despite its strong theoretical rationale, IDO-1 inhibition failed to produce clinical benefit in the included trials. This may reflect compensatory mechanisms through other tryptophan-catabolizing enzymes (such as tryptophan 2, 3-dioxygenase or IDO-2) or insufficient pharmacodynamic activity of the inhibitors at the tumor site, limiting their impact on the immunosuppressive microenvironment.[33] This finding is consistent with the broader setbacks in IDO-1-targeted therapies across cancer immunotherapy, particularly following the failure of multiple late-phase programs.[34]

These outcome trends align closely with the efficacy estimates reported in Table 1 and the safety profiles detailed in Table 2. The underlying mechanisms for each immune target are illustrated in Figure 3, which provides

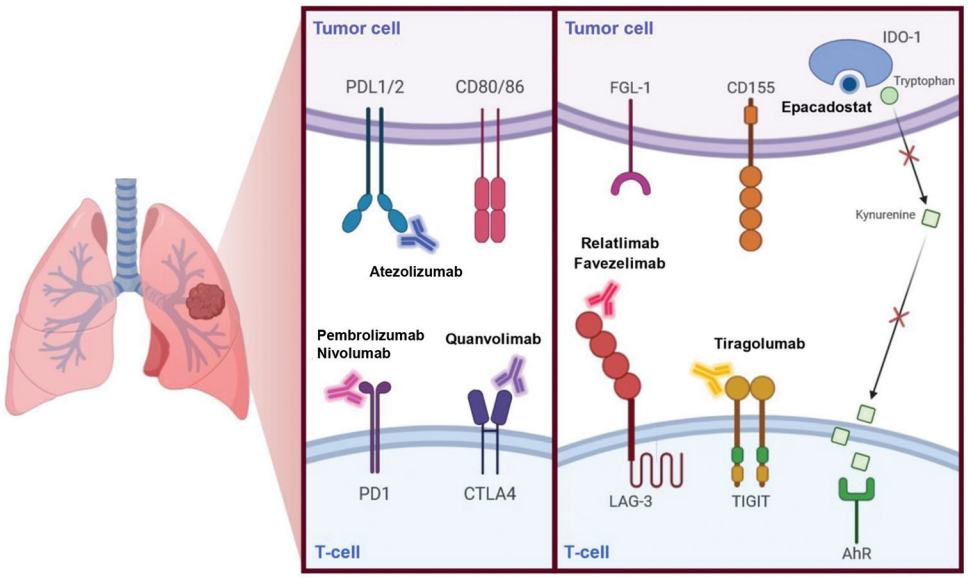

Figure 3. Mechanistic pathways. Schematic representation of immune checkpoint pathways targeted by standard-of-care inhibitors (PD-1, PD-L1, and CTLA-4) and novel inhibitors (LAG-3, TIGIT, and IDO-1) evaluated in this review. Image(s) provided by Servier Medical Art (https://smart.servier.com), licensed under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/)

Abbreviations: AhR: Aryl hydrocarbon receptor; CD80/86: Cluster of differentiation 80/86 (B7-1/B72); CD155: Cluster of differentiation 155 (poliovirus receptor); CTLA-4: Cytotoxic T-lymphocyte antigen 4; FGL-1: Fibrinogen-like protein 1; IDO-1: Indoleamine 2,3-dioxygenase 1; LAG-3: Lymphocyte-activation gene 3; PD-1: Programmed cell death protein 1; PD-L1/2: Programmed death-ligand 1/2; TIGIT: T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domains

an overview of the cellular pathways modulated by the ICIs evaluated in the included studies.

Together, the findings from this synthesis highlight three key insights. First, although TIGIT inhibition initially showed encouraging results, its efficacy signal remains inconclusive due to the lack of confirmation in Phase III trials. Second, LAG-3 emerges as a context-dependent but biologically promising target, particularly at higher doses or in specific tumor settings. Third, IDO-1 has not yet demonstrated clinical utility to date despite a strong mechanistic appeal. Variability across agents and outcomes reinforces the need for larger, biomarker-stratified trials to define optimal settings for deploying novel ICIs.

Quantitative synthesis was not feasible due to heterogeneity between studies, emphasizing the need for harmonization in ICI trial design and reporting. Future research should prioritize large-scale, randomized studies stratified by molecular and immunological biomarkers, standardized outcome reporting (including ORR, PFS, and AE profiles), and head-to-head comparisons of emerging checkpoint inhibitors to establish therapeutic hierarchies.

Finally, the overall certainty of evidence, as qualitatively assessed using GRADE, ranged from low to moderate across outcomes. This was driven primarily by the early-phase designs, small sample sizes, heterogeneity, and reporting limitations. These factors must be addressed in future research to clarify the clinical role of novel ICIs in cancer immunotherapy and ensure durable, meaningful clinical benefit for a broader patient population.

This narrative systematic review is limited by the small number of included studies and the substantial heterogeneity among them in design, interventions, and outcome reporting. Most trials were Phase II with modest sample sizes and incomplete data, which restricted the ability to perform quantitative synthesis and may have introduced reporting bias. Nonetheless, the qualitative synthesis and risk of bias assessment provide a transparent overview of the current evidence landscape.

5. Conclusion

Among novel immune checkpoint targets, TIGIT inhibition demonstrated relatively consistent clinical benefit, but results remain preliminary and unconfirmed in Phase III trials. LAG-3 inhibitors showed mixed results depending on dose and tumor context, while IDO-1 inhibitors failed to improve efficacy across studies. The current evidence is limited by small, heterogeneous, mostly Phase II trials. Larger, biomarker-driven studies are needed to define the clinical value of these emerging targets and determine their potential to extend immunotherapy benefit to broader patient populations.

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Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Data curation: Diana Martins, Fernando Mendes
Writing – original draft: All authors
Writing–review & editing: Diana Martins, Fernando Mendes

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

All data and materials used in this review are available from the corresponding author upon request.

Further disclosure

The review protocol was submitted for registration on the INPLASY platform and is published under the registration number INPLASY202570056 with DOI 10.37766/inplasy2025.7.0056; therefore, the protocol is publicly available.

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Appendices

A1. Research strategy per database

(i) PubMed (via the National Center for Biotechnology Information) - Last searched: May 10, 2025

(Lung neoplasms) AND (immune checkpoint inhibitors) AND (Biomarkers) NOT (B7-H1 antigen) NOT (programmed cell death-1 receptor) NOT (CTLA-4 antigen)

Filters: Published from January 1, 2020, to January 1, 2025.

(Lung neoplasm) AND (immune checkpoint inhibitors) AND (immunotherapy AND drug resistance)

Filters: Clinical trial; clinical trial, phase I; clinical trial, phase II; Clinical trial, phase III; Clinical trial, phase IV; Randomized controlled trial; published from January 1, 2020, to January 1, 2025.

(Lung neoplasms) AND (immune checkpoint inhibitors) AND (immunotherapy NOT drug resistance)

Filters: Clinical trial; clinical trial, phase I; clinical trial, phase II; clinical trial, phase III; clinical trial, phase IV; randomized controlled trial; published from January 1, 2020, to January 1, 2025.

(ii) Web of Science (via Clarivate) - Last searched: May 11, 2025

(ALL=[lung neoplasm]) AND (ALL=[immune checkpoint inhibitors]) NOT (ALL=[PD-1]) NOT (ALL=[PD-L1]) NOT (ALL=[CTLA-4])

Filters: Published from January 1, 2020, to January 1, 2025.

(ALL=[lung neoplasm]) AND (ALL=[immune checkpointinhibitors])AND(ALL=[immunotherapy]) AND (ALL=[drug resistance])

Filters: Published from January 1, 2020, to January 1, 2025.

(ALL=[lung neoplasm]) AND (ALL=[immune checkpointinhibitors])AND(ALL=[immunotherapy]) NOT (ALL=[drug resistance])

Filters: Published from January 1, 2020, to January 1, 2025.

(iii) ClinicalTrials.gov - Last searched: June 12, 2025

Condition: Lung cancer
Other terms: Lung neoplasms
Intervention: Immune checkpoint inhibitors
Sex: All
Age: Adult (18–64); older adult (65+)
Study phase: Phase 1; Phase 2; Phase 3; Phase 4
Study type: Interventional
Study results: With results
Last update posted: From January 1, 2020, to January 1, 2025.

A2. List of reasons for exclusion during article screening

- Wrong population: Any condition other than lung cancer (non-small cell lung cancer or small cell lung cancer)
- Wrong intervention: Did not include a novel immune checkpoint inhibitor (ICI)
- Wrong comparator: Comparator arm did not include a standard of care ICI (monotherapy or combination)
- Wrong outcome: Did not assess at least one of the following: Overall survival, progression-free survival, disease-free survival, event-free survival, objective response rate, partial response rate, complete response rate, adverse event
- Wrong study design: Not a randomized controlled trial (e.g., systematic reviews, meta-analysis, and case reports)
- Not a randomized controlled trial
- Full text not available
- Unable to assess eligibility due to missing key information - insufficient detail to determine if inclusion criteria were met (e.g., unclear population, intervention, comparator, or outcomes)
- No results available: Protocol-only entries, trial registrations without outcomes, abstracts without data, or unpublished studies
- Duplicate or redundant publication: multiple publications from the same clinical trial; the most recent or most complete record was selected.