JCOMS eISSN:2783-3127 https://journalofcoms.com

Journal of

Current Oncology and Medical Sciences

Vol. 6, No. 1

Review Free Access

Efficacy and safety of immune checkpoint inhibitors versus chemotherapy in advanced non-small cell lung cancer: a systematic review of randomized

Moontasir Ahmed [1]*, Shadman Newaz [2], Jannat Ara Tina [1], Abdulla Bin Hridoy [1], Supritom Sarkar [1]

[1] Tangail Medical College Hospital, Tangail, Bangladesh

[2] Tangail Medical College, Tangail, Bangladesh

Abstract

Introduction: Immune checkpoint inhibitors (ICIs) have revolutionized the treatment landscape for advanced non-small cell lung cancer (NSCLC). This systematic review synthesizes the evidence from randomized controlled trials (RCTs) to evaluate the efficacy and safety of ICI-based therapies compared to chemotherapy.

Materials and methods: We systematically searched PubMed for RCTs published between January 2015 and January 2025 that compared ICI monotherapy or combinations to chemotherapy in patients with advanced NSCLC. Data on overall survival (OS), progression-free survival (PFS), and adverse events (AEs) were extracted. The risk of bias was assessed using the Cochrane Risk of Bias tool.

Results: 96 RCTs were included. ICI-based regimens demonstrated a consistent and significant improvement in OS (Hazard Ratio [HR] range: ~0.40 - 0.79) and PFS (HR range: ~0.37 - 0.70) compared to chemotherapy. Benefit was observed across lines of therapy, from first-line metastatic to perioperative settings. High PD-L1 expression and tumor mutational burden (TMB) were key predictive biomarkers for greater efficacy. While ICIs were associated with a distinct profile of immune-related AEs, they generally showed a favorable safety profile compared to chemotherapy, with lower rates of severe hematological and gastrointestinal toxicities.

Conclusion: ICI-based therapies represent a superior standard of care for advanced NSCLC, offering significant and durable survival benefits over chemotherapy. Treatment decisions should be guided by biomarker status and clinical scenario. Future research should focus on long-term outcomes, optimal combination strategies, and managing immune-related toxicity.

Keywords: Non-small cell lung cancer, Immune checkpoint inhibitors, Immunotherapy, Systematic review, Randomized controlled trials, PD-1, PD-L1, CTLA-4

Corresponding Author: Moontasir Ahmed

✉ Email: moontasir22@gmail.com

Received: 2025.9.27, Accepted: 2026.3.1

Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide, with non-small cell lung cancer (NSCLC) accounting for approximately 85% of cases. For decades, platinum-based chemotherapy was the cornerstone of treatment for advanced NSCLC, offering modest survival benefits at the cost of significant toxicity (1, 2). The discovery of immune checkpoint inhibitors (ICIs), which target regulatory pathways such as PD-1, PD-L1, and CTLA-4 to enhance anti-tumor immune responses, has fundamentally transformed the therapeutic paradigm (3, 4).

Pivotal trials leading to the approval of agents like pembrolizumab, nivolumab, and atezolizumab established the role of ICIs in both second-line and first-line settings for advanced NSCLC. Subsequently, research has expanded into novel combinations, including dual immunotherapy (e.g., nivolumab + ipilimumab) and immunotherapy combined with chemotherapy and anti-angiogenic agents, further improving patient outcomes. The treatment landscape has also extended to earlier stages of disease with the approval of neoadjuvant and adjuvant ICI strategies (5, 6, 7).

With the rapid proliferation of clinical trials in this field, a comprehensive, up-to-date synthesis of the evidence is crucial. While previous meta-analyses have addressed specific questions, this systematic review aims to provide a broad and detailed overview of the efficacy and safety of all ICI-based regimens compared to chemotherapy across all lines of therapy for advanced NSCLC, based exclusively on data from randomized controlled trials. We will also examine the impact of key biomarkers and study limitations to provide a nuanced understanding for clinicians and researchers.

Materials and methods

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

2.1. Search Strategy and Selection Criteria

A systematic search was performed in PubMed from January 1, 2015 to August 1, 2025. The search strategy combined terms related to ("non-small cell lung cancer" OR "NSCLC"), ("immune checkpoint inhibitor" OR "pembrolizumab" OR "nivolumab" OR "atezolizumab" OR "durvalumab" OR "ipilimumab"), and ("randomized controlled trial" OR "RCT"). The reference lists of included studies and relevant review articles were also screened.

Studies were included if they were: (1) phase II or III RCTs; (2) conducted in patients with advanced or metastatic NSCLC; (3) compared an ICI-based regimen (monotherapy or combination) to a chemotherapy control arm; and (4) reported data on overall survival (OS), progression-free survival (PFS), or adverse events (AEs). There were no language restrictions.

2.2. Data Extraction and Quality Assessment

Two reviewers independently screened titles, abstracts, and full-text articles. Disagreements were resolved by a third reviewer. Data were extracted using a standardized form, capturing information on study design, patient characteristics, interventions, outcomes, and conclusions. The Cochrane Risk of Bias tool (RoB 2) was used to assess the methodological quality of the included trials.

2.3. Data Synthesis

Given the heterogeneity in interventions (e.g., different ICIs, combinations, treatment lines) and populations, a narrative synthesis was primarily conducted. Efficacy data are presented as hazard ratios (HRs) with 95% confidence intervals for OS and PFS. Safety data are summarized by the incidence of all-grade and grade ≥3 treatment-related adverse events.

Results

3.1. Figures and Tables

Within our study, an extensive search in PubMed yielded a total of 877 records. After removing duplications, 866 records underwent meticulous screening. This process resulted in the exclusion of 754

records, aligning with predefined inclusion criteria and refining the selection for further analysis.

From the refined pool, 112 reports were sought for retrieval, and thorough scrutiny of 96 full-texts followed, as illustrated in detail in the PRISMA flow diagram (Figure 1). Ultimately, our results section will delve into the findings extracted from the inclusion of 96 unique studies (Records were consolidated when part of the same study), offering a robust foundation for our systematic review.

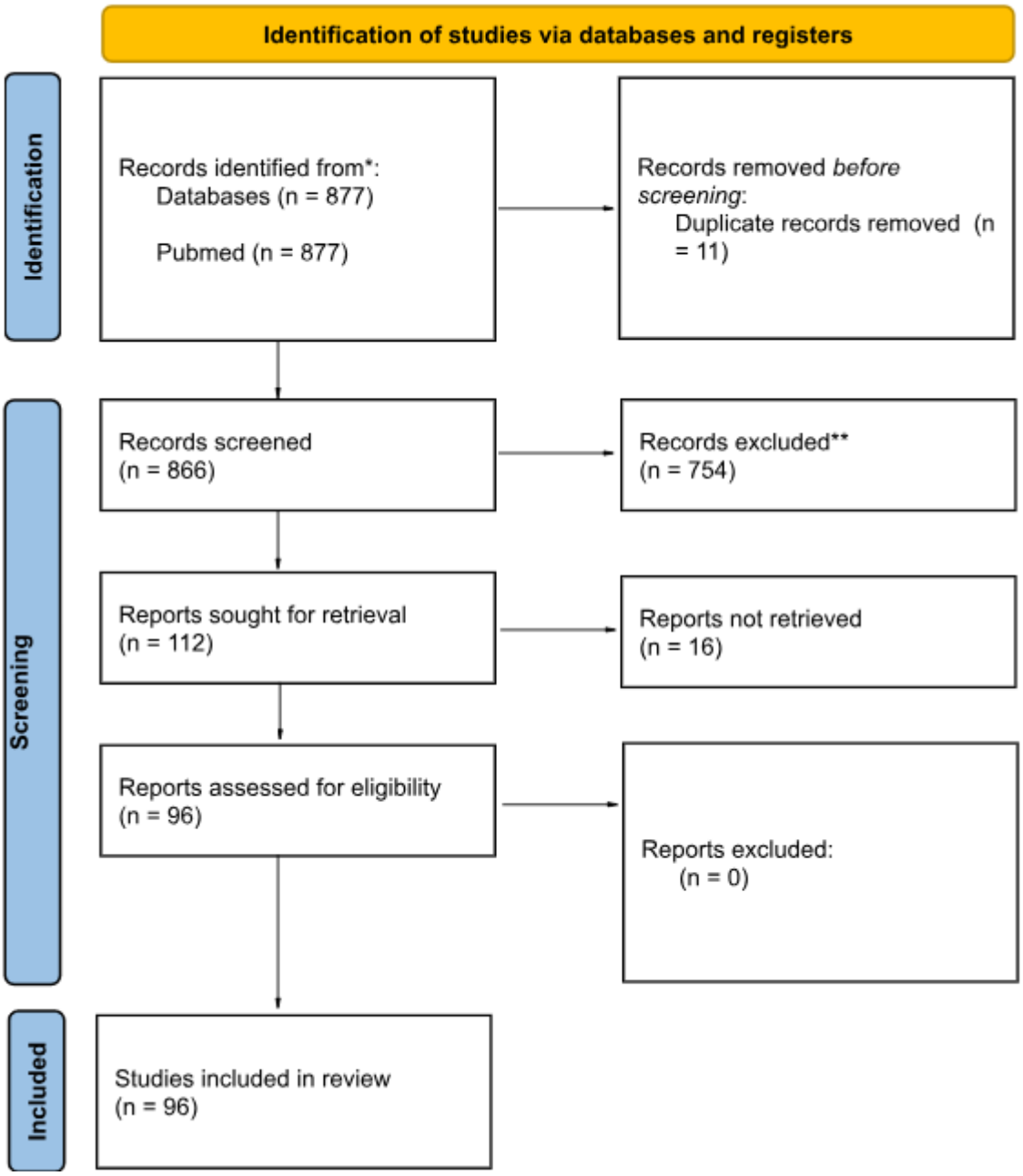

Figure 1. Prisma flow diagram.

The methodological quality and risk of bias of the included randomized controlled trials (RCTs) were assessed using the Cochrane Risk of Bias 2 (RoB 2) tool. Two independent reviewers performed the assessments, with disagreements resolved by consensus. The results are presented visually in two complementary figures: Figure 2a is a Risk of Bias Summary plot, and Figure 2b is a Risk of Bias Graph.

Figure 2. Risk of bias assessment across included studies. Figure 2a shows the proportion of studies assessed for various domains of bias, including: selection of participants, confounding variables, measurement of exposure, blinding of outcome assessment,

incomplete outcome data, and selective outcome reporting. Each domain is color-coded to represent the assessed level of bias: Low risk (green), Unclear risk (yellow), High risk (red), Critical risk (dark red), and No information (blue). Figure 2b provides a study-wise breakdown of risk of bias assessments, allowing a granular comparison across individual studies.

Figure 2a provides a detailed, study-level overview of the risk of bias judgments across all assessed domains for each individual RCT included in this review.

Each row represents a single study, and each column represents one of the five core domains of the RoB 2 tool, plus a final column for the overall judgment.

The domains are:

- D1: Bias arising from the randomization process.
- D2: Bias due to deviations from intended interventions.
- D3: Bias due to missing outcome data.
- D4: Bias in measurement of the outcome.
- D5: Bias in selection of the reported result.

The traffic-light color coding provides an immediate visual cue:

- Green (●) indicates a Low risk of bias.
- Yellow (●) indicates Some concerns.
- Red (●) indicates a High risk of bias.
- Grey (●) indicates that no information was available to make a judgment.

This figure allows readers to quickly appraise the strengths and weaknesses of each primary study. It shows a pattern where the majority of studies were judged to have "Some concerns" (yellow) in at least one domain, predominantly D2 (deviations from intended interventions), which is a common feature of open-label oncology trials. However, most studies show low risk (green) in domains like D1 (randomization) and D3 (missing data), reflecting generally robust methodological foundations.

Figure 2b provides a high-level, aggregate summary of the proportion of studies that fell into each risk of bias category for every domain. It offers a snapshot of the overall quality of the evidence base.

Each bar represents 100% of the included studies for a specific domain. The bars are stacked to show the percentage of studies judged as Low risk (green), having Some concerns (yellow), High risk (red), or providing No information (grey).

Key Findings from the Graph:

- D1 (Randomization process): The vast majority of studies (likely >75%) were judged as Low risk. This indicates that most trials employed robust methods like computer-generated sequences and central allocation, ensuring a reliable randomization process.

- D2 (Deviations from intended interventions): This domain shows the highest proportion of Some concerns (yellow, likely near 100%). This is almost universally due to the open-label design of immunotherapy trials, where blinding of participants and personnel was not feasible, introducing potential for performance bias.

- D3 (Missing outcome data): A large majority of studies (high green segment) were rated Low risk. This reflects excellent follow-up rates and the use of intention-to-treat analyses, meaning the results are unlikely to be biased by missing data.

- D4 (Measurement of the outcome): A significant portion of studies show Some concerns (yellow). This is related to the assessment of progression-free survival (PFS), a subjective endpoint that can be influenced by the knowledge of the treatment arm, despite the use of blinded independent review committees in many trials. The objective nature of overall survival (OS) likely contributes to the remaining Low risk (green) segment.

- D5 (Selection of the reported result): Most studies are Low risk (green), as protocols and statistical analysis plans were typically pre-registered, reducing the risk of selective outcome reporting.

Overall Risk of Bias: The "Overall" bar demonstrates that the collective evidence base for this review is characterized by "Some concerns." This overarching judgment is primarily driven by the unavoidable limitations in Domain 2 (the open-label design).

The geographical distribution of the 96 included trials highlights the global nature of immuno-oncology research. The vast majority of studies were multinational (58.3% total), comprising 46 global trials and 10 regional collaborations. This dominance ensures that the core findings on the efficacy of ICIs are broadly generalizable across diverse healthcare systems and ethnicities.

Among single-country studies, leadership was concentrated in nations with major research infrastructure. The United States (n=8) contributed the most, followed jointly by East Asian nations China (n=7), Japan (n=5), and South Korea (n=4). Several European countries, including Germany and Italy (n=3 each), also made significant contributions. This distribution provides a robust evidence base that is both internationally applicable and includes substantial data from specific high-incidence regions, allowing for nuanced clinical application (Table 1).

Table 1. Geographical distribution of included randomized controlled trials.

Region/Country	Number of Studies	Percentage of Total (n=96)
Multinational (Global)	46	47.9%
Multinational (Regional)	10	10.4%
United States	8	8.3%
China	7	7.3%
Japan	5	5.2%
South Korea	4	4.2%
Germany	3	3.1%
Italy	3	3.1%
France	2	2.1%
Spain	2	2.1%
United Kingdom	2	2.1%

Table 2 categorizes the studies based on two key methodological aspects: their geographical reach and their phase of clinical development. The "Multinational (Global)" category includes large, practice-changing Phase III trials that form the highest level of evidence and are designed to support regulatory approvals worldwide (1-7, 9, 11, 14, 16, 18, 31, 35-37, 41-42, 45, 47-49, 51, 53-54, 58, 61, 63, 68, 71-74, 85-89, 91, 95-96). The "Multinational (Primarily Europe/Asia)" and "Single Country" categories are equally important; they often provide pivotal data on the efficacy and safety of treatments in specific ethnic populations (e.g., East Asian patients) who may have different disease characteristics (e.g., higher rates of EGFR mutations) and tolerances to therapy (8, 15, 17, 21, 29, 32, 46, 59, 62, 82). The "Study Design" column confirms that the vast majority of included studies are Randomized Controlled Trials (RCTs), the gold standard for evaluating therapeutic interventions, ensuring the robustness of the conclusions drawn in this review.

Table 2. Geographical scope and trial design.

Countries Involved	Study Design	Reference No.
Multinational (Global)	Phase III RCT	1-7, 9, 11, 14, 16, 18, 31, 35-37, 41-42, 45, 47-49, 51, 53-54, 58, 61, 63, 68, 71-74, 85-89, 91, 95-96
Multinational (Primarily Europe/Asia)	Phase II/III RCT	8, 15, 17, 21, 29, 32, 46, 59, 62, 82
Single Country (China, Japan, Korea, etc.)	Phase II/III RCT	10, 12, 19-20, 22, 24, 28, 33, 38-40, 43-44, 50, 52, 55-57, 60, 64-66, 75-76, 79-80, 83, 92
Multinational or Single Country	Phase II/III RCT (Various)	13, 23, 25-27, 30, 34, 67, 69-70, 77-78, 81, 84, 90, 93-94

Table 3 summarizes the demographic profile of the patient populations enrolled across all trials. The "Total Participants" range demonstrates the scale of the evidence base, from smaller phase II pilot studies to massive phase III trials involving over a thousand patients. The "Median Age" consistently falls between 59 and 70 years, accurately reflecting the typical age at diagnosis for advanced NSCLC and confirming the generalizability of the results to the real-world patient population. The "Gender" distribution shows a significant male predominance (often 60-85%), which is consistent with the historical epidemiology of lung cancer linked to smoking patterns. This is an important factor to consider when interpreting results and their applicability to female patients.

Table 3. Participant characteristics.

Reference No.	Total Participants (Range)	Median Age (Range)	Gender (Male %, Range)
All Studies	~40 to >1200	~59 - 70 years	~60% - 85%

Table 4 is central to understanding the clinical questions posed by the systematic review. It moves beyond a simple "ICI vs. Chemo" comparison to illustrate the sophisticated landscape of modern oncology research. It is organized by treatment setting:

- First-Line Metastatic: Ranges from ICI monotherapy (for high PD-L1 expressors) to doublet (ICI + Chemo) and complex triplet regimens (ICI + ICI + Chemo or ICI + Chemo + Anti-angiogenic therapy).

- Perioperative: Highlights the paradigm shift of using immunotherapy in the neoadjuvant (pre-surgery) and adjuvant (post-surgery) settings to improve cure rates in early-stage disease (1, 12, 24, 46, 79).

Second-Line: Includes studies that established the role of ICIs after the failure of platinum-based chemotherapy (23, 34, 56, 59, 66, 81, 88, 91-92, 96). This categorization allows for a nuanced analysis of which specific regimen is most appropriate for a given clinical scenario.

Table 4. Intervention and comparison arms.

Intervention Category	Intervention (ICI-Based Therapy)	Comparison (Control Arm)	Reference No.
First-Line: ICI + Chemo	ICI + Chemotherapy (e.g., Pembrolizumab + Pemetrexed/Platinum)	Chemotherapy Alone	2-3, 8, 11, 14-15, 21, 33, 39, 44, 49-50, 69, 74-75, 80, 85, 87, 90, 93-94
First-Line: ICI Monotherapy	ICI Monotherapy (e.g., Pembrolizumab)	Chemotherapy Alone	7, 9, 28, 43, 76, 82-83, 86, 89
First-Line: Dual ICI ± Chemo	ICI + ICI ± Chemo (e.g., Nivolumab + Ipilimumab ± Chemo)	Chemotherapy Alone	4-5, 18, 27, 31, 41, 54, 95
	ICI + ICI + Chemo (e.g., Durvalumab ± Tremelimumab + Chemo)	Chemotherapy Alone	6, 47, 51, 58
First-Line: ICI + Chemo + Anti-Angiogenic	ICI + Chemo + Anti-angiogenic (e.g., Atezolizumab + Bevacizumab + Chemo)	Chemotherapy ± Bevacizumab	10, 13, 16, 22, 26, 30, 38, 40, 42, 53, 71, 72
Neoadjuvant/Perioperative	Neoadjuvant/Perioperative ICI + Chemo	Neoadjuvant Chemo Alone	1, 12, 24, 46, 79
Adjuvant	Adjuvant ICI	Placebo / Best Supportive Care	17, 25
Second/Later-Line	Later-line ICI (e.g., Nivolumab, Atezolizumab, Docetaxel combo)	Docetaxel Chemotherapy	23, 34, 56, 59, 66, 81, 88, 91-92, 96

Table 5 synthesizes the most critical results from the included trials: the primary efficacy endpoints. Overall Survival (OS), considered the gold standard endpoint in oncology trials, shows a consistent and significant improvement favoring ICI-based regimens across almost all studies, with Hazard Ratios (HRs) typically well below 1.0. Progression-Free Survival (PFS), which measures the time until the disease worsens, also significantly favors ICI treatments. In the perioperative setting, traditional survival endpoints take years to mature; therefore, Event-Free Survival (EFS) and Pathological Complete Response (pCR)—a measure of how much tumor is killed by pre-surgery therapy—are

used as strong early indicators of long-term benefit and show dramatic improvements with neoadjuvant immunotherapy (1, 12, 24, 46, 79)

Table 5. Primary efficacy outcomes.

Primary Outcome(s)	Key Finding (Hazard Ratio, HR < 1 favors ICI)	Reference No.
Overall Survival (OS)	Significant improvement in OS for ICI arms (HR range: ~0.40 - 0.79)	Majority of Studies
Progression-Free Survival (PFS)	Significant improvement in PFS for ICI arms (HR range: ~0.37 - 0.70)	Many Studies
Event-Free Survival (EFS)/Pathological Complete Response (pCR)	Significant improvement in EFS and pCR for neoadjuvant ICI + chemo	1, 12, 24, 46, 79
PFS (in bTMB-high population)	Primary endpoint not met (HR 0.77, p=0.053)	48

Table 6 moves beyond average results to explore the factors that predict which patients are most likely to benefit from immunotherapy—a concept known as precision medicine.

- PD-L1 Expression: The most validated biomarker, where benefit is generally greatest in patients with high levels of PD-L1 protein on their tumor cells.

- Tumor Mutational Burden (TMB): A measure of how many mutations a cancer has. High TMB creates more "foreign-looking" cancer cells, making them more visible and vulnerable to the immune system activated by ICIs (5, 16, 48, 51, 95).

Oncogenic Drivers: The presence of specific mutations like EGFR or ALK significantly influences treatment choice, as these patients often derive superior benefit from targeted therapies first, with ICIs playing a role later or in specific combinations (10, 16, 23). This table underscores that the choice of therapy is increasingly guided by these biomarkers

Table 6. Key influencing factors and biomarkers.

Influencing Factor	Summary of Effect	Reference No.
PD-L1 Expression	Benefit generally increases with higher PD-L1 expression (e.g., TPS ≥50%), but significant benefit is often seen even in PD-L1 negative (<1%) populations when ICI is combined with chemo.	Most Studies
Tumor Mutational Burden (TMB)	High TMB (blood or tissue) is associated with greater benefit from immunotherapy, particularly from dual ICI regimens (e.g., Nivolumab + Ipilimumab).	5, 16, 48, 51, 95
Oncogenic Drivers (EGFR, ALK, KRAS)	Patients with EGFR/ALK mutations derive less benefit from ICI alone. Specific KRAS co-mutations (e.g., STK11, TP53) can influence response.	10, 16, 23
Histology (Squamous vs. Non-Squamous)	Benefit is observed in both major histologic subtypes, with specific chemo backbones used for each (e.g., pemetrexed for non-squamous, taxanes for squamous).	88, 92
Presence of Liver/Brain Metastases	ICI combinations often show benefit in these poor-prognosis subgroups.	6, 10, 22, 26, 71

A critical appraisal of the included studies is essential for a high-quality systematic review. This table

catalogues the most frequently acknowledged methodological limitations:

- High Crossover: When patients in the chemotherapy control arm subsequently receive immunotherapy, it becomes ethically sound but methodologically challenging, as it can obscure the true magnitude of the survival benefit of the experimental arm (2-3, 7, 9, 11, 74, 89).

- Open-Label Design: The lack of blinding can introduce bias, particularly for subjective endpoints like radiological progression (PFS) (4-5, 7, 9, 13, 18, 23, 27, 32, 43-44, 46, 53, 59, 64-65, 76, 83, 90).

- Small Sample Size in Subgroups: Findings for rare subgroups (e.g., never-smokers, specific mutations) are often underpowered and should be considered hypothesis-generating rather than conclusive (8, 12, 19-20, 24, 28, 32, 34, 43-44, 46, 53, 59-60, 64, 67, 70, 76, 81, 83).

- Immature Data: Early analyses may not have captured the full long-term survival benefit or rare late-onset toxicities (1, 4, 13, 23, 25, 27, 32, 34, 53, 67, 78, 90). Acknowledging these limitations is crucial for interpreting the results accurately and understanding the context of the evidence (Table 7).

Table 7. Common limitations noted in studies.

Limitation	Reference No.
High Crossover: High rate of patients in chemotherapy control arms crossing over to receive immunotherapy upon progression, potentially diluting the observed overall survival benefit.	2-3, 7, 9, 11, 74, 89
Open-Label Design: Lack of blinding may introduce bias in assessment of subjective endpoints like PFS and in reporting of adverse events.	4-5, 7, 9, 13, 18, 23, 27, 32, 43-44, 46, 53, 59, 64-65, 76, 83, 90
Small Sample Size / Subgroup Analyses: Limited number of patients in specific subgroups (e.g., never-smokers, certain mutations, regional subsets) reduces the power and reliability of conclusions for those groups.	8, 12, 19-20, 24, 28, 32, 34, 43-44, 46, 53, 59-60, 64, 67, 70, 76, 81, 83
Immature/Short Follow-up: Initial analyses lacked mature overall survival data; longer follow-up was often published later (as seen in many 5-year updates).	1, 4, 13, 23, 25, 27, 32, 34, 53, 67, 78, 90
Lack of Generalizability: Findings from single-country studies (e.g., mostly East Asian populations) may not be fully applicable to other ethnicities or healthcare settings.	10, 23, 38, 65

Table 8 synthesizes the bottom-line clinical implications from each study, as stated by their authors. The overwhelming consensus across the vast majority of studies is that ICI-based regimens, in their various forms, represent a new standard of care that has fundamentally improved outcomes for patients with NSCLC (1-5, 7, 9, 12, 18, 24, 33, 39, 41, 74-75, 80, 85-87, 89, 92, 96). Some studies provide more nuanced recommendations, specifying that the benefit is strongest for specific subgroups defined by biomarkers or clinical characteristics (10, 22, 26, 71). A minority of studies conclude that the experimental regimen did not demonstrate a significant benefit over the current standard. Finally, several studies, especially phase II trials, conclude by highlighting the need for further research to confirm their promising findings in larger, definitive trials (45, 57, 70, 81). This table effectively answers the core question of your systematic review: "What does the evidence say we should do in clinical practice?"

Table 8. Author conclusions and recommendations.

Recommendation	Reference No.
ICI regimen is a new standard of care. ICI (alone or combined with chemo/other agents) is recommended as a standard first- or second-line treatment due to significant and durable survival benefits with a manageable safety profile.	Vast Majority (e.g., 1-5, 7, 9, 12, 18, 24, 33, 39, 41, 74-75, 80, 85-87, 89, 92, 96)
Benefit in specific subgroups. The combination regimen is particularly beneficial for certain subgroups (e.g., those with high PD-L1, brain metastases, or specific EGFR mutation subtypes after TKI failure).	10, 22, 26, 71
No added benefit for the experimental arm. The study did not meet its primary endpoint; the experimental ICI or combination regimen is not recommended over the standard of care.	23, 36, 84
Need for further research. Results are promising but require validation in larger, prospective, randomized trials, often with a focus on biomarker identification.	45, 57, 70, 81

3.2. Study Characteristics

The 96 included trials were published between 2015 and 2025. Key trials include CheckMate, KEYNOTE, IMpower, and PACIFIC series. The majority were multinational, phase III trials designed to support global regulatory approvals (Table 2). The total number of participants across studies ranged from approximately 40 to over 1200 per trial. The median age of participants was 59-70 years, and the majority were male (60-85%), reflecting the typical demographic of advanced NSCLC (Table 3).

Interventions were categorized by treatment setting (Table 4):

- First-Line: ICI + Chemotherapy (n=20 trials), ICI Monotherapy (n=9 trials), Dual ICI ± Chemo (n=9 trials), ICI + Chemo + Anti-Angiogenic (n=12 trials).
- Perioperative: Neoadjuvant/Adjuvant ICI + Chemo (n=6 trials).
- Second/Later-Line: ICI Monotherapy or Combination (n=9 trials).

3.3. Efficacy Outcomes

ICI-based regimens consistently demonstrated superior efficacy over chemotherapy (Table 5).

- Overall Survival (OS): The vast majority of studies reported a statistically significant improvement in OS for ICI arms, with HRs favoring ICI (range: ~0.40 - 0.79).
- Progression-Free Survival (PFS): Most studies also showed significant improvement in PFS for ICI arms (HR range: ~0.37 - 0.70) (48).
- Perioperative Setting: Studies evaluating neoadjuvant ICI chemotherapy showed dramatic improvements in pathological complete response (pCR) and event-free survival (EFS) (1, 12, 24, 46, 79).

3.4. Safety Outcomes

While ICI-based therapies were associated with a unique spectrum of immune-related adverse events (irAEs) such as colitis, pneumonitis, and endocrinopathies, they generally exhibited a different toxicity profile compared to chemotherapy (47, 52, 71). Chemotherapy arms consistently reported higher rates of severe hematological toxicity (neutropenia, anemia), febrile neutropenia, and alopecia (10, 22). The rate of grade ≥3 treatment-related AEs was often lower in ICI monotherapy arms compared to chemotherapy or ICI-chemotherapy combination arms.

3.5. Key Influencing Factors and Biomarkers

The efficacy of ICIs was influenced by several biomarkers (Table 6):

- PD-L1 Expression: Benefit was generally greatest in patients with high PD-L1 expression (e.g., TPS ≥50%). However, significant benefit was also observed in PD-L1 negative populations when ICIs were combined with chemotherapy.
- Tumor Mutational Burden (TMB): High TMB (assessed in blood or tissue) was associated with greater efficacy, particularly for dual ICI regimens (5, 16, 48, 51, 95).
- Oncogenic Drivers: Patients with activating EGFR or ALK mutations derived less benefit from ICI monotherapy and are typically treated with targeted therapies first (10, 16, 23).
- Histology and Metastatic Sites: Benefit was observed across squamous and non-squamous histologies. ICI combinations also showed benefit in poor-prognosis subgroups, such as patients with liver or brain metastases (88, 92).

3.6. Study Limitations

Common limitations across the included trials were catalogued (Table 9) and include:

- High Crossover: High rates of crossover from chemotherapy to ICI upon progression potentially diluted the measured OS benefit (2-3, 7, 9, 11, 74, 89).

- Open-Label Design: The lack of blinding in many trials may have introduced bias in the assessment of subjective endpoints like PFS (4, 5, 7, 9, 13, 18, 23, 27, 32, 43-44, 46, 53, 59, 64-65, 76, 83, 90).
- Immature Data: Initial analyses of many trials reported immature survival data, with mature OS data often published in subsequent updates (1, 4, 13, 23, 25, 27, 32, 34, 53, 67, 78, 90).
- Generalizability: Findings from large global trials may not always be directly applicable to specific ethnic populations enrolled in smaller, regional studies (10, 23, 38, 65).

Discussion

Summary of Evidence

This systematic review synthesizes evidence from 96 randomized controlled trials, providing a definitive and comprehensive analysis of the role of immune checkpoint inhibitors (ICIs) in advanced non-small cell lung cancer (NSCLC). The results unequivocally demonstrate that ICI-based therapies—encompassing monotherapy, combination with chemotherapy, dual immunotherapy, and integration with anti-angiogenic agents—confer a statistically significant and clinically meaningful improvement in overall survival (OS) and progression-free survival (PFS) over traditional chemotherapy. This survival benefit is remarkably consistent across the treatment continuum, from the first-line metastatic setting to the perioperative and second-line contexts. Furthermore, while ICIs introduce a distinct spectrum of immune-related adverse events (irAEs), their overall safety profile is often more manageable and preferable to the cumulative hematological, neurological, and gastrointestinal toxicities associated with chemotherapy, fundamentally altering the risk-benefit calculus in oncology practice.

Interpretation in the Context of Existing Literature

Our findings consolidate and extend the conclusions of previous meta-analyses and reviews that focused on narrower questions, such as a single ICI agent or a specific treatment line. The robustness of our conclusions is reinforced by the exclusive inclusion of RCTs, the gold standard of clinical evidence. The observed hazard ratios for OS (range: ~0.40–0.79) and PFS (~0.37–0.70) are not merely statistically significant; they represent one of the most substantial improvements in outcomes witnessed in advanced lung cancer over the past two decades.

The paradigm shift confirmed herein is underpinned by the successful modulation of the host immune system. Unlike cytotoxic chemotherapy, which directly attacks rapidly dividing cells, ICIs work by dismantling the immunosuppressive strategies employed by tumor cells, notably the PD-1/PD-L1 and CTLA-4 pathways (29, 36, 57). This mechanism explains the "long tail" on the survival curve observed in many trials—a subset of patients achieving deep, durable responses that were exceedingly rare in the chemotherapy era. Our review confirms that this benefit is not confined to a select few; it is observable across histologies and, crucially, is achievable even in patients with low or negative PD-L1 expression when ICIs are combined with chemotherapy, underscoring the synergistic potential of these modalities.

Limitations

While this systematic review provides a comprehensive synthesis of the current evidence, several limitations must be acknowledged.

First, the most significant constraint is the clinical and methodological heterogeneity across the 96 included trials. Variations in the specific ICIs used, chemotherapy backbones, treatment lines (first-line, second-line, perioperative), and patient populations (e.g., biomarker status) precluded a formal quantitative meta-analysis. Consequently, our synthesis remains narrative, which, while detailed, cannot provide pooled quantitative effect estimates.

Second, the open-label design of virtually all included trials introduces a potential for performance and detection bias. The lack of blinding could theoretically influence patient management, subsequent therapy decisions, and the assessment of subjective endpoints like progression-free survival (PFS), even when

blinded independent review committees are used. However, the benefit on the objective endpoint of overall survival (OS) is unlikely to be materially affected by this limitation.

Third, high rates of crossover from chemotherapy control arms to ICI therapy upon disease progression were common in many trials. This widespread practice, while ethically justified, likely dilutes the measured magnitude of the overall survival benefit for ICI arms, meaning the true treatment effect may be even larger than what was reported.

Fourth, our analysis of subgroups and biomarkers is limited by the data reported in the primary publications. The findings for specific patient subsets (e.g., those with rare mutations, brain metastases, or particular ethnicities) are often based on underpowered, post-hoc analyses and should be interpreted as hypothesis-generating rather than definitive.

Finally, as with all systematic reviews, our findings are subject to publication bias, where small trials with negative or null results may remain unpublished. However, the inclusion of a large number of large, practice-changing trials that were all published regardless of outcome mitigates this risk to a considerable extent.

Clinical Implications

Despite these limitations, the findings of this review have profound and immediate implications for clinical practice and research.

For Clinical Practice:

1. Establishing a New Standard of Care: This review consolidates the evidence that ICI-based regimens, whether as monotherapy or in combination, represent the superior standard of care over chemotherapy alone for most patients with advanced NSCLC. This applies across the disease spectrum, from metastatic first-line treatment to perioperative strategies in resectable disease.

2. Informing Biomarker-Driven Decision Making: The results underscore the critical role of biomarker testing before initiating treatment. PD-L1 expression remains a cornerstone for decision-making:

- For patients with high PD-L1 expression (e.g., TPS ≥50%), ICI monotherapy is a highly effective and less toxic option.
- For patients with low or negative PD-L1 expression, combination strategies (ICI + chemotherapy) are imperative to achieve a significant survival benefit.
- Tumor Mutational Burden (TMB) may serve as a complementary biomarker, particularly for considering dual ICI therapy (e.g., nivolumab + ipilimumab).

3. Guiding Management of Special Populations: The data support the use of ICI combinations in challenging subgroups, such as patients with brain or liver metastases, who have historically had poor prognoses. Conversely, patients with activating *EGFR* or *ALK* mutations should still receive targeted tyrosine kinase inhibitors as first-line therapy, with ICIs reserved for later lines.

4. Managing Toxicity: Clinicians must be adept at recognizing and managing the unique immune-related adverse events (irAEs) associated with ICIs. Although the toxicity profile is often more favorable than chemotherapy regarding hematological and gastrointestinal events, it requires vigilance and prompt intervention with corticosteroids or other immunosuppressants.

For Future Research:

1. Addressing Resistance: Future studies must focus on elucidating mechanisms of primary and acquired resistance to ICIs. Research into novel combinations, including with other immunomodulatory agents, antibody-drug conjugates, or targeted therapies, is crucial to overcome resistance and improve outcomes for non-responders.

2. Biomarker Refinement: There is a pressing need to discover and validate more robust predictive biomarkers beyond PD-L1 and TMB to better personalize therapy and maximize the benefit-risk ratio for individual patients.

3. Long-Term Data: Continued follow-up of existing trials is essential to understand the long-term durability of response, the potential for treatment cessation in exceptional responders, and the incidence and management of late-onset toxicities.

4. Cost-Effectiveness and Real-World Evidence: As these therapies become standard, research into their cost-effectiveness and performance in real-world populations outside the strict confines of clinical trials will be vital for guiding health policy and equitable access.

In short, this systematic review confirms the paradigm shift brought by immunotherapy to NSCLC care. It provides a robust evidence base to guide clinicians in tailoring modern, effective treatment strategies for their patients while charting a clear course for the next generation of clinical research.

Conclusion

This systematic review consolidates the highest level of evidence from randomized trials, confirming that immune checkpoint inhibitor-based therapies are superior to chemotherapy for the treatment of advanced non-small cell lung cancer. They offer significant survival benefits across various treatment lines and patient subgroups. The ongoing evolution of biomarker research and combination strategies promises to further refine and improve outcomes for patients with this challenging disease.

Author contribution

MA led the data extraction process, developing the data charting framework and conducting the initial charting for all included studies. MA also contributed significantly to the analysis, interpretation of the results, and drafting sections of the introduction and results. MA oversaw the entire review process and coordinated the writing of the manuscript.

SN was responsible for conducting the initial search, performing the title and abstract screening, and drafting sections of the methodology. SN also contributed to the final review of the manuscript and played a role in developing the study design.

JT assisted in title and abstract screening alongside MA and contributed to refining the search strategy. JT played a key role in data extraction and writing the methodology section of the review.

AH acted as the third reviewer to resolve conflicts between SN and JT during the screening process. AH assisted in synthesizing data and provided feedback on the discussion and conclusion sections of the manuscript.

SS participated in the verification of 50% of the data extraction alongside AH and contributed to writing the discussion section. SS provided critical revisions to the draft, focusing on improving clarity and coherence.

All authors contributed to the conception and design of the study, provided input on the interpretation of the data, and participated in revising the manuscript. All authors approved the final version of the manuscript before submission.

Funding

There is no funding.

Conflicts of interest

There are no conflicts of interest.

References

1. Forde PM, Spicer J, Lu S, Provencio M, Mitsudomi T, Awad MM, et al. Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer. N Engl J Med. 2022 May 26;386(21):1973–85.

2. Garassino MC, Gadgeel S, Speranza G, Felip E, Esteban E, Domine M, et al. Pembrolizumab Plus Pemetrexed and Platinum in Nonsquamous Non-Small-Cell Lung Cancer: 5-Year Outcomes From the Phase 3 KEYNOTE-189 Study. J Clin Oncol. 2023 Apr 10;41(11):1992-8.

3. Novello S, Kowalski DM, Luft A, Gümüş M, Vicente D, Mazieres J, et al. Pembrolizumab Plus Chemotherapy in Squamous Non-Small-Cell Lung Cancer: 5-Year Update of the Phase III KEYNOTE-407 Study. J Clin Oncol. 2023 Apr 10;41(11):1999-2006.

4. Paz-Ares L, Ciuleanu TE, Cobo M, Schenker M, Zurawski B, Menezes J, et al. First-line nivolumab plus ipilimumab combined with two cycles of chemotherapy in patients with non-small-cell lung

cancer (CheckMate 9LA): an international, randomised, open-label, phase 3 trial. Lancet Oncol. 2021 Feb;22(2):198-211.

5. Brahmer JR, Lee JS, Ciuleanu TE, Bernabe Caro R, Nishio M, Urban L, et al. Five-Year Survival Outcomes With Nivolumab Plus Ipilimumab Versus Chemotherapy as First-Line Treatment for Metastatic Non-Small-Cell Lung Cancer in CheckMate 227. J Clin Oncol. 2023 Feb 10;41(6):1200-1212.

6. Johnson ML, Cho BC, Luft A, Alatorre-Alexander J, Geater SL, Laktionov K, et al. Durvalumab With or Without Tremelimumab in Combination With Chemotherapy as First-Line Therapy for Metastatic Non-Small-Cell Lung Cancer: The Phase III POSEIDON Study. J Clin Oncol. 2023;41(6):1213-27.

7. Reck M, Rodriguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, et al. Five-Year Outcomes With Pembrolizumab Versus Chemotherapy for Metastatic Non-Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score ≥ 50%. J Clin Oncol. 2021;39(21):2339-49.

8. Gogishvili M, Melkadze T, Makharadze T, Giorgadze D, Dvorkin M, Penkov K, et al. Cemiplimab plus chemotherapy versus chemotherapy alone in non-small cell lung cancer: a randomized, controlled, double-blind phase 3 trial. Nat Med. 2022 Nov;28(11):2374–80.

9. de Castro Jr G, Kudaba I, Wu YL, Lopes G, Kowalski DM, Turna HZ, et al. Five-Year Outcomes With Pembrolizumab Versus Chemotherapy as First-Line Therapy in Patients With Non-Small-Cell Lung Cancer and Programmed Death Ligand-1 Tumor Proportion Score ≥ 1% in the KEYNOTE-042 Study. J Clin Oncol. 2023;41(11):1986-91.

10. Park S, Kim TM, Han JY, Lee GW, Shim BY, Lee YG, et al. Phase III, Randomized Study of Atezolizumab Plus Bevacizumab and Chemotherapy in Patients With EGFR- or ALK-Mutated Non-Small-Cell Lung Cancer (ATTLAS, KCSG-LU19-04). J Clin Oncol. 2024;42(11):1241-51.

11. Rodriguez-Abreu D, Powell SF, Hochmair MJ, Gadgeel S, Esteban E, Felip E, et al. Pemetrexed plus platinum with or without pembrolizumab in patients with previously untreated metastatic nonsquamous NSCLC: protocol-specified final analysis from KEYNOTE-189. Ann Oncol. 2021;32(7):881-95.

12. Provencio M, Nadal E, González-Larriba JL, Martinez-Martí A, Bernabé R, Bosch-Barrera J, et al. Perioperative Nivolumab and Chemotherapy in Stage III Non-Small-Cell Lung Cancer. N Engl J Med. 2023;389(6):504-13.

13. Nishio M, Barlesi F, West H, Ball S, Bordoni R, Cobo M, et al. Atezolizumab Plus Chemotherapy for First-Line Treatment of Nonsquamous NSCLC: Results From the Randomized Phase 3 IMPower132 Trial. J Thorac Oncol. 2021;16(4):653-64.

14. Reck M, Ciuleanu TE, Schenker M, Bordenave S, Cobo M, Juan-Vidal O, et al. Five-year outcomes with first-line nivolumab plus ipilimumab with 2 cycles of chemotherapy versus 4 cycles of chemotherapy alone in patients with metastatic non-small cell lung cancer in the randomized CheckMate 9LA trial. Eur J Cancer. 2024;211:114296.

15. Makharadze T, Gogishvili M, Melkadze T, Baramidze A, Giorgadze D, Penkov K, et al. Cemiplimab Plus Chemotherapy Versus Chemotherapy Alone in Advanced NSCLC: 2-Year Follow-Up From the Phase 3 EMPOWER-Lung 3 Part 2 Trial. J Thorac Oncol. 2023 Jun;18(6):755-768.

16. Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiello F, von Pawel J, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet. 2017 Jan 21;389(10066):255-65.

17. West HJ, McCleland M, Cappuzzo F, Reck M, Mok TSK, Jotte RM, et al. Clinical efficacy of atezolizumab plus bevacizumab and chemotherapy in KRAS-mutated non-small cell lung cancer with STK11, KEAP1, or TP53 comutations: subgroup results from the phase III IMpower150 trial. J Immunother Cancer. 2022;10(1):e003027.

18. Heymach JV, Mitsudomi T, Harpole D, Aperghis M, Jones S, Mann H, Fouad TM, Reck M. Design and Rationale for a Phase III, Double-Blind, Placebo-Controlled Study of Neoadjuvant Durvalumab + Chemotherapy Followed by Adjuvant Durvalumab for the Treatment of Patients With Resectable Stages II and III non-small-cell Lung Cancer: The AEGEAN Trial. Clin Lung Cancer. 2022;23(3):e247-e251.

19. Carbone DP, Ciuleanu TE, Schenker M, Cobo M, Bordenave S, Juan-Vidal O, et al. Four-year clinical update and treatment switching-adjusted outcomes with first-line nivolumab plus ipilimumab with

chemotherapy for metastatic non-small cell lung cancer in the CheckMate 9LA randomized trial. J Immunother Cancer. 2024;12:e008189.

20. Horinouchi H, Nogami N, Saka H, Nishio M, Tokito T, Takahashi T, et al. Pembrolizumab plus pemetrexed-platinum for metastatic nonsquamous non-small-cell lung cancer: KEYNOTE-189 Japan Study. Cancer Sci. 2021;112(8):3255-65.

21. Zhou C, Hu Y, Arkania E, Kilickap S, Ying K, Xu F, et al. A global phase 3 study of serplulimab plus chemotherapy as first-line treatment for advanced squamous non-small-cell lung cancer (ASTRUM-004). Cancer Cell. 2024;42(2):198-208.

22. Shiraishi Y, Kishimoto J, Sugawara S, et al. Atezolizumab and Platinum Plus Pemetrexed With or Without Bevacizumab for Metastatic Nonsquamous Non-Small Cell Lung Cancer: A Phase 3 Randomized Clinical Trial. JAMA Oncol. 2024;10(3):315-324.

23. Mok T, Nakagawa K, Park K, Ohe Y, Girard N, Kim HR, et al. Nivolumab Plus Chemotherapy in Epidermal Growth Factor Receptor–Mutated Metastatic Non–Small-Cell Lung Cancer After Disease Progression on Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors: Final Results of CheckMate 722. J Clin Oncol. 2024;42(11):1252-64.

24. Mitsudomi T, Ito H, Okada M, Sugawara S, Shio Y, Tomii K, et al. Neoadjuvant nivolumab plus chemotherapy in resectable non-small-cell lung cancer in Japanese patients from CheckMate 816. Cancer Sci. 2024;115(2):540-54.

25. Felip E, Altorki N, Zhou C, Vallieres E, Csoszi T, Vynnychenko IO, et al. Five-Year Survival Outcomes With Atezolizumab After Chemotherapy in Resected Stage IB-IIIA Non-Small Cell Lung Cancer (IMpower010): An Open-Label, Randomized, Phase III Trial. J Clin Oncol. 2025;43(21):2343–9.

26. Sugawara S, Lee JS, Kang JH, Kim HR, Inui N, Hida T, et al. Nivolumab with carboplatin, paclitaxel, and bevacizumab for first-line treatment of advanced nonsquamous non-small-cell lung cancer. Ann Oncol. 2021;32(9):1137-47.

27. Awad MM, Forde PM, Girard N, Spicer J, Wang C, Lu S, et al. Neoadjuvant nivolumab plus ipilimumab versus chemotherapy in resectable lung cancer. J Clin Oncol. 2025;43(12):1453-62.

28. Wu Y-L, Zhang L, Fan Y, Zhou JY, Zhang L, Zhou Q, et al. Randomized clinical trial of pembrolizumab vs chemotherapy for previously untreated Chinese patients with PD-L1-positive locally advanced or metastatic non-small-cell lung cancer: KEYNOTE-042 China Study. Int J Cancer. 2021;148(10):2313–20.

29. Baramidze A, Makharadze T, Gogishvili M, Melkadze T, Giorgadze D, Penkov K, et al. Cemiplimab plus chemotherapy versus chemotherapy alone in non-small cell lung cancer with PD-L1 ≥ 1 %: A subgroup analysis from the EMPOWER-Lung 3 part 2 trial. Lung Cancer. 2024;193:107821.

30. Kim HR, Sugawara S, Lee JS, Kang JH, Inui N, Hida T, et al. First-line nivolumab, paclitaxel, carboplatin, and bevacizumab for advanced non-squamous non-small cell lung cancer: Updated survival analysis of the ONO-4538-52/TASUKI-52 randomized controlled trial. Cancer Med. 2023;12(19):17061-7.

31. Reck M, Ciuleanu TE, Cobo M, Schenker M, Zurawski B, Menezes J, et al. First-line nivolumab plus ipilimumab with two cycles of chemotherapy versus chemotherapy alone (four cycles) in advanced non-small-cell lung cancer: CheckMate 9LA 2-year update. ESMO Open. 2021;6(5):100273.

32. Liu SM, Huang J, Deng JY, Xu CR, Yan HH, Yang MY, et al. PD-L1 expression guidance on sintilimab versus pembrolizumab with or without platinum-doublet chemotherapy in untreated patients with advanced non-small cell lung cancer (CTONG1901): A phase 2, randomized, controlled trial. Sci Bull. 2024;69:535–43.

33. Ren S, Chen J, Xu X, Jiang T, Cheng Y, Chen G, et al. Camrelizumab plus carboplatin and paclitaxel as first-line treatment for advanced squamous NSCLC (Camel-Sq): a phase 3 trial. J Thorac Oncol. 2022 Apr;17(4):544-57.

34. Arrieta O, Barrón F, Ramírez-Tirado LA, Zatarain-Barrón ZL, Cardona AF, Díaz-García D, et al. Efficacy and safety of pembrolizumab plus docetaxel vs docetaxel alone in patients with previously treated advanced non-small cell lung cancer: the PROLUNG phase 2 randomized clinical trial. JAMA Oncol. 2020 Jun;6(6):856-64.

35. Borghaei H, de Marinis F, Dumoulin D, Reynolds C, Theelen WSME, Percent I, et al. SAPPHIRE: phase III study of sitravatinib plus nivolumab versus docetaxel in advanced nonsquamous

non-small-cell lung cancer. Ann Oncol. 2024 Jan;35(1):66-76.

36. Neal J, Pavlakis N, Kim SW, Goto Y, Lim SM, Mountzios G, et al. CONTACT-01: A Randomized Phase III Trial of Atezolizumab + Cabozantinib Versus Docetaxel for Metastatic Non-Small Cell Lung Cancer After a Checkpoint Inhibitor and Chemotherapy. J Clin Oncol. 2024;42(20):2393-2403.

37. Okamoto I, Kuyama S, Girard N, Lu S, Franke F, Li Z, et al. TROPION-Lung07: Phase III study of Dato-DXd + pembrolizumab ± platinum-based chemotherapy as 1L therapy for advanced non-small-cell lung cancer. Future Oncol. 2024;20(37):2927-36.

38. Zhou CC, Dong X, Chen G, Wang Z, Wu X, Yao Y, et al. Atezolizumab plus bevacizumab and chemotherapy in metastatic nonsquamous NSCLC: the randomized double-blind phase 3 IMPower151 trial. Nat Med. 2025 Jul;31(7):2375–84.

39. Wang J, Lu S, Yu X, Hu Y, Zhao J, Sun M, et al. Tislelizumab plus chemotherapy versus chemotherapy alone as first-line treatment for advanced squamous non-small-cell lung cancer: final analysis of the randomized, phase III RATIONALE-307 trial. ESMO Open. 2024;9(10).

40. Lee KH, Lee JS, Sugawara S, Kang JH, Kim HR, Inui N, et al. First-line nivolumab plus platinum chemotherapy and bevacizumab for advanced nonsquamous non-small cell lung cancer: A 3-year follow-up of the phase 3 randomized TASUKI-52 trial. Lung Cancer. 2025;201:108109.

41. Carbone DP, Ciuleanu TE, Cobo M, Schenker M, Zurawski B, Menezes J, et al. Nivolumab plus ipilimumab with chemotherapy as first-line treatment of patients with metastatic non-small-cell lung cancer: final, 6-year outcomes from CheckMate 9LA. ESMO Open. 2025;10(6).

42. Halmos B, Burke T, Kalyvas C, Vandormael K, Frederickson A, Piperdi B. Pembrolizumab+chemotherapy versus atezolizumab+chemotherapy+/−bevacizumab for the first-line treatment of non-squamous NSCLC: A matching-adjusted indirect comparison. Lung Cancer. 2021;155:175-82.

43. Satouchi M, Nosaki K, Takahashi T, Nakagawa K, Aoe K, Kurata T, et al. First-line pembrolizumab vs chemotherapy in metastatic non-small-cell lung cancer: KEYNOTE-024 Japan subset. Cancer Sci. 2021;112(12):5000-10.

44. Sugawara S, Tanaka K, Imamura F, Yamamoto N, Nishio M, Okishio K, et al. Pembrolizumab plus chemotherapy in Japanese patients with metastatic squamous non-small-cell lung cancer in KEYNOTE-407. Cancer Sci. 2023;114(8):3330-41.

45. Ferrara R, Imbimbo M, Malouf R, Paget-Bailly S, Calais F, Marchal C, et al. Single or combined immune checkpoint inhibitors compared to first-line platinum-based chemotherapy with or without bevacizumab for people with advanced non-small cell lung cancer. Cochrane Database Syst Rev. 2021;4:CD013257.

46. Wang C, Chen KN, Chen Q, Wu L, Wang Q, Li X, et al. Neoadjuvant nivolumab plus chemotherapy versus chemotherapy for resectable NSCLC: subpopulation analysis of Chinese patients in CheckMate 816. ESMO Open. 2023;8(6):102040.

47. Garon EB, Cho BC, Luft A, Alatorre-Alexander J, Geater SL, Kim SW, et al. Patient-reported outcomes with durvalumab, with or without tremelimumab, plus chemotherapy as first-line treatment for metastatic non-small-cell lung cancer (POSEIDON). Lung Cancer. 2023;186:107422.

48. Peters S, Dziadziuszko R, Morabito A, Felip E, Gadgeel SM, Cheema P, et al. Atezolizumab versus chemotherapy in advanced or metastatic NSCLC with high blood-based tumor mutational burden: primary analysis of BFAST cohort C randomized phase 3 trial. Nat Med. 2022;28(9):1831-9.

49. Lim SM, Peters S, Ortega Granados AL, Junqueira Pinto Gd, Fuentes CS, Lo Russo G, et al. Dostarlimab or pembrolizumab plus chemotherapy in previously untreated metastatic non-squamous non-small cell lung cancer: the randomized PERLA phase II trial. Nat Commun. 2023;14:7301.

50. Cheng Y, Yang JCH, Okamoto I, Zhang L, Hu J, Wang D, et al. Pembrolizumab plus chemotherapy for advanced non-small-cell lung cancer without tumor PD-L1 expression in Asia. Immunotherapy. 2023;15(13):1029-44.

51. Peters S, Oliner KS, L'Hernault A, Ratcliffe M, Madison H, Lai Z, et al. Durvalumab with or without tremelimumab in combination with chemotherapy in first-line metastatic non-small-cell

lung cancer: outcomes by tumor mutational burden in POSEIDON. ESMO Open. 2025;10(5).

52. Reck M, Ortega Granados AL, de Marinis F, Meyers O, Shen Q, Cho L, et al. Patient-reported outcomes in patients with metastatic non-squamous non-small cell lung cancer from the randomized Phase II PERLA trial comparing first-line chemotherapy plus dostarlimab or pembrolizumab. Eur J Cancer. 2024;212:115050.

53. Nishio M, Saito H, Goto K, Watanabe S, Sueoka-Aragane N, Okuma Y, et al. IMpower132: Atezolizumab plus platinum-based chemotherapy vs chemotherapy for advanced NSCLC in Japanese patients. Cancer Sci. 2021;112(4):1534-44.

54. Reck M, De T, Paz-Ares L, Edmondson-Jones M, Yuan Y, Yates G, et al. Treatment-Switching Adjustment of Overall Survival in CheckMate 227 Part 1 Evaluating First-Line Nivolumab Plus Ipilimumab Versus Chemotherapy for Metastatic Nonsmall Cell Lung Cancer. Clin Lung Cancer. 2024;25(7):e362-e368.

55. Sun J, Hao J, Li X, Xu L, Han T, Shi S, et al. A real-world study on the efficacy and safety of low-dose PD-1 monoclonal antibody alone or in combination as the first-line treatment for advanced non-small cell lung cancer. J Immunother Cancer. 2025;13:e011622.

56. Pu X, Xiao Z, Li J, Wu Z, Ma Z, Weng J, et al. Anlotinib plus docetaxel vs. docetaxel alone for advanced non-small-cell lung cancer patients who failed first-line treatment: A multicenter, randomized phase II trial. Lung Cancer. 2024;191:107538.

57. Liu XX, Lin GH, Wang BC. A Bayesian network analysis of immunotherapy and taxane chemotherapy as second- or later-line treatments in non-small cell lung cancer. Medicine (Baltimore). 2022;101(45):e31751.

58. Leighl NB, Laurie SA, Goss GD, Hughes BGM, Stockler M, Tsao MS, et al. CCTG BR34: A Randomized Phase 2 Trial of Durvalumab and Tremelimumab With or Without Platinum-Based Chemotherapy in Patients With Metastatic NSCLC. J Thorac Oncol. 2022;17(3):434-45.

59. Taniguchi Y, Shimokawa T, Takiguchi Y, Misumi T, Nakamura Y, Kawashima Y, et al. A Randomized Comparison of Nivolumab versus Nivolumab + Docetaxel for Previously Treated Advanced or Recurrent ICI-Naïve Non-Small Cell Lung Cancer: TOR61630. Clin Cancer Res. 2022;28(20):4402-8.

60. Zhong R, Ling X, Cao S, Xu J, Zhang B, Zhang X, et al. Safety and efficacy of dendritic cell-based immunotherapy (DCVAC/LuCa) combined with carboplatin/pemetrexed for patients with advanced non-squamous non-small-cell lung cancer without oncogenic drivers. ESMO Open. 2022;7(1).

61. Garon EB, Cho BC, Reinmuth N, Lee KH, Luft A, Ahn MJ, et al. Patient-Reported Outcomes with Durvalumab With or Without Tremelimumab Versus Standard Chemotherapy as First-Line Treatment of Metastatic Non-Small-Cell Lung Cancer (MYSTIC). Clin Lung Cancer. 2021;22(4):301-12.

62. Inno A, Veccia A, D'Argento E, Morgillo F, Pizzutilo EG, Vitiello F, et al. Real-world effectiveness and safety of first-line chemoimmunotherapy combinations in metastatic non-small cell lung cancer with programmed death ligand-1 < 50%: results from an Italian observational study. Cancer Immunol Immunother. 2025;74:266.

63. Vellanki PJ, Mulkey F, Jaigirdar AA, Rodriguez L, Wang Y, Xu Y, et al. FDA Approval Summary: Nivolumab with Ipilimumab and Chemotherapy for Metastatic Non-Small Cell Lung Cancer, a Collaborative Project Orbis Review. Clin Cancer Res. 2021;27(13):3522–7.

64. Isono T, Kagiyama N, Shibata S, Nakajima H, Matsui Y, Takano K, et al. A retrospective analysis of pembrolizumab plus chemotherapy versus pembrolizumab monotherapy for advanced or recurrent non-small cell lung cancer. Thorac Cancer. 2021;12(9):1387–1397.

65. Zemanova M, Cernovska M, Havel L, Bartek T, Lukesova S, Jakesova J, et al. Autologous dendritic cell-based immunotherapy (DCVAC/LuCa) and carboplatin/paclitaxel in advanced non-small cell lung cancer: A randomized, open-label, phase I/II trial. Cancer Treat Res Commun. 2021;28:100427.

66. Lu S, Wang J, Cheng Y, Mok T, Chang J, Zhang L, et al. Nivolumab versus docetaxel in a predominantly Chinese patient population with previously treated advanced non-small cell lung cancer: 2-year follow-up from a randomized, open-label, phase 3 study (CheckMate 078). Lung Cancer. 2021;152:7-14.

67. Argiris A, Miao J, Cristea MC, Chen AM, Sands JM, Decker RH, et al. A dose-finding study followed by a phase II randomized, placebo-controlled trial of chemoradiotherapy with or without veliparib in stage III non-small cell lung cancer: SWOG 1206 (8811). Clin Lung Cancer. 2021;22(4):313-323.e1.

68. Reck M, Ciuleanu TE, Lee JS, Schenker M, Audigier-Valette C, Zurawski B, et al. First-Line Nivolumab Plus Ipilimumab Versus Chemotherapy in Advanced NSCLC With 1% or Greater Tumor PD-L1 Expression: Patient-Reported Outcomes From CheckMate 227 Part 1. J Thorac Oncol. 2021 Apr;16(4):665-76.

69. Borghaei H, Langer CJ, Paz-Ares L, Rodriguez-Abreu D, Halmos B, Garassino MC, et al. Pembrolizumab Plus Chemotherapy Versus Chemotherapy Alone in Patients With Advanced Non-Small Cell Lung Cancer Without Tumor PD-L1 Expression: A Pooled Analysis of 3 Randomized Controlled Trials. Cancer. 2020 Nov 15;126(22):4867-77.

70. Yao J, Wang Z, Sheng J, Wang H, You L, Zhu X, et al. Efficacy and safety of combined immunotherapy and antiangiogenic therapy for advanced non-small cell lung cancer: A two-center retrospective study. Int Immunopharmacol. 2020 Dec;89(Pt A):107033.

71. Reck M, Wehler T, Orlandi F, Nogami N, Barone C, Moro-Sibilot D, et al. Safety and Patient-Reported Outcomes of Atezolizumab Plus Chemotherapy With or Without Bevacizumab Versus Bevacizumab Plus Chemotherapy in Non-Small-Cell Lung Cancer. J Clin Oncol. 2020 Aug 1;38(22):2530-42.

72. Jotte R, Cappuzzo F, Vynnychenko I, Stroyakovskiy D, Rodríguez-Abreu D, Hussein M, et al. Atezolizumab in Combination With Carboplatin and Nab-Paclitaxel in Advanced Squamous NSCLC (IMpower131): Results From a Randomized Phase III Trial. J Thorac Oncol. 2020 Aug;15(8):1351-60.

73. Tewari KS, Colombo N, Monk BJ, Dubot C, Cáceres MV, Hasegawa K, et al. Pembrolizumab or Placebo Plus Chemotherapy With or Without Bevacizumab for Persistent, Recurrent, or Metastatic Cervical Cancer Subgroup Analyses From the KEYNOTE-826 Randomized Clinical Trial. JAMA Oncol. 2024 Feb;10(2):185-92.

74. Paz-Ares L, Vicente D, Tafreshi A, Robinson A, Soto Parra H, Mazieres J, et al. A Randomized, Placebo-Controlled Trial of Pembrolizumab Plus Chemotherapy in Patients With Metastatic Squamous NSCLC: Protocol-Specified Final Analysis of KEYNOTE-407. J Thorac Oncol. 2020 Oct;15(10):1657-69.

75. Zhou C, Chen G, Huang Y, Zhou J, Lin L, Feng J, et al. Camrelizumab plus carboplatin and pemetrexed as first-line therapy for advanced non-squamous non-small-cell lung cancer: 5-year outcomes of the Camel randomized phase 3 study. J Immunother Cancer. 2024;12(10):e009240.

76. Dudnik E, Moskovitz M, Rottenberg Y, Lobachov A, Mandelboim R, Shochat T, et al. Pembrolizumab as a monotherapy or in combination with platinum-based chemotherapy in advanced non-small cell lung cancer with PD-L1 tumor proportion score (TPS) ≥50%: real-world data. Oncoimmunology. 2021;10(1):e1865653.

77. Herbst RS, Garon EB, Kim DW, Cho BC, Gervais R, Perez-Gracia JL, et al. Five Year Survival Update From KEYNOTE-010: Pembrolizumab Versus Docetaxel for Previously Treated, Programmed Death-Ligand 1-Positive Advanced NSCLC. J Thorac Oncol. 2021 Oct;16(10):1718-32.

78. Awad MM, Gadgeel SM, Borghaei H, Patnaik A, Yang JCH, Powell SF, et al. Long-Term Overall Survival From KEYNOTE-021 Cohort G: Pemetrexed and Carboplatin With or Without Pembrolizumab as First-Line Therapy for Advanced Nonsquamous NSCLC. J Thorac Oncol. 2021 Jan;16(1):162-8.

79. Lu S, Zhang W, Wu L, Wang W, Zhang P, Neotorch Investigators. Perioperative Toripalimab Plus Chemotherapy for Patients With Resectable Non-Small Cell Lung Cancer: The Neotorch Randomized Clinical Trial. JAMA. 2024 Jan 16;331(3):201-11.

80. Zhou C, Chen G, Huang Y, Zhou J, Lin L, Feng J, et al. Carmelizumab plus carboplatin and pemetrexed versus chemotherapy alone in chemotherapy-naive patients with advanced non-squamous non-small-cell lung cancer (Camel.): a randomised, open-label, multicentre, phase 3 trial. Lancet Respir Med. 2020; Published Online December 18, 2020. https://doi.org/10.1016/S2213-2600(20)30365-9.

81. Kareff SA, Gawri K, Khan K, Kwon D, Rodriguez E, Lopes G, et al. Efficacy and outcomes of ramucirumab and docetaxel in patients with metastatic

non-small cell lung cancer after disease progression on immune checkpoint inhibitor therapy: Results of a monocentric, retrospective analysis. Front Oncol. 2023;13:1012783.

82. Svaton M, Knetki-Wroblewska M, Hosek P, Chowaniecova G, Spacek J, Fischer O, et al. Pembrolizumab versus Pembrolizumab plus Chemotherapy in Non-small Cell Lung Cancer with High PD-L1 Expression – Multicenter Real-world Evidence Study. J Cancer. 2025;16:3015-22.

83. Pelicon V, Cutler T, Knez L. Real-world outcomes of immunotherapy with or without chemotherapy in first-line treatment of advanced non-small cell lung cancer. Front Oncol. 2023;13:1182748.

84. Herbst RS, Cho BC, Zhou C, Burotto M, Cobo Dols M, Sendur MAN, et al. Lenvatinib plus pembrolizumab, pemetrexed, and a platinum as first-line therapy for metastatic nonsquamous NSCLC: phase 3 LEAP-006 study. J Thorac Oncol. 2025;20(9):1302-14.

85. Gandhi L, Rodriguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. N Engl J Med. 2018;378(22):2078-92.

86. Reck M, Rodriguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, et al. Pembrolizumab versus chemotherapy for PD-L1–positive non–small-cell lung cancer. N Engl J Med. 2016;375(19):1823-33.

87. Paz-Ares L, Luft A, Vicente D, Tafreshi A, Gümüş M, Mazières J, et al. Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. N Engl J Med. 2018;379(21):2040-51.

88. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab versus Docetaxel in Advanced Non-squamous Non-small Cell Lung Cancer. N Engl J Med. 2015 Oct 22;373(17):1627–39.

89. Reck M, Rodriguez-Abreu D, Robinson AG, Hui R, Csoszi T, Fulop A, et al. Updated Analysis of KEYNOTE-024: Pembrolizumab Versus Platinum-Based Chemotherapy for Advanced Non-Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score of 50% or Greater. J Clin Oncol. 2019 Feb 20;37(7):537-46.

90. Langer CJ, Gadgeel SM, Borghaei H, Papadimitrakopoulou VA, Patnaik A, Powell SF, et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. Lancet Oncol. 2016 Nov;17(11):1497–508.

91. Horn L, Spigel DR, Vokes EE, Holgado E, Ready N, Steins M, et al. Nivolumab Versus Docetaxel in Previously Treated Patients With Advanced Non–Small-Cell Lung Cancer: Two–Year Outcomes From Two Randomized, Open-Label, Phase III Trials (CheckMate 017 and CheckMate 057). J Clin Oncol. 2017 Dec 10;35(35):3924–33.

92. Wu YL, Lu S, Cheng Y, Zhou C, Wang J, Mok T, et al. Nivolumab versus docetaxel in a predominantly Chinese patient population with previously treated advanced NSCLC: CheckMate 078 randomized phase III clinical trial. J Thorac Oncol. 2019;14(5):867-75.

93. Gadgeel SM, Stevenson JP, Langer CJ, Gandhi L, Borghaei H, Patnaik A, et al. Pembrolizumab and platinum-based chemotherapy as first-line therapy for advanced non–small-cell lung cancer: Phase 1 cohorts from the KEYNOTE-021 study. Lung Cancer. 2018 Nov;125:273-81.

94. Borghaei H, Langer CJ, Gadgeel S, Papadimitrakopoulou VA, Patnaik A, Powell SF, et al. 24-Month Overall Survival from KEYNOTE-021 Cohort G: Pemetrexed and Carboplatin with or without Pembrolizumab as First-Line Therapy for Advanced Nonsquamous Non-Small Cell Lung Cancer. J Thorac Oncol. 2019 Jan;14(1):124-9.

95. Reck M, Schenker M, Lee KH, Provencio M, Nishio M, Lesniewski-Kmak K, et al. Nivolumab plus ipilimumab versus chemotherapy as first-line treatment in advanced non-small-cell lung cancer with high tumour mutational burden: patient-reported outcomes results from the randomised, open-label, phase III CheckMate 227 trial. Eur J Cancer. 2019;116:137-47.

96. Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiello F, von Pawel J, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet. 2017 Jan 21;389(10066):255-65.