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An Update Regarding the Role of Immune Checkpoint Inhibitors in LungCancer – A Systematic Review

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 13 July 2025 and was last updated on 13 July 2025.

INTRODUCTION

Review question / Objective According to PRISMA's recommendation, we selected a specific framework of population (P), intervention (I), comparison (C), outcome (O), and study design (S). (PICOS) to define study eligibility: Population (P): Patients diagnosed with lung cancer; Intervention (I): new immune checkpoint inhibitors ; Comparison (C): standard-of-care ICI (e.g., PD-L1, PD-1, CTLA-4) ; Outcome (O): overall survival, progression-free survival, event-free survival, disease-free survival, objective response rate, complete response rate, partial response rate, and adverse events; Research Design (S): Randomised controlled trials on humans.

Condition being studied Lung cancer (LC) remains the leading cause of cancer-related death worldwide, accounting for over 1.8 million deaths in 2022. The two main types are non-small cell lung cancer (NSCLC), comprising 75–80% of cases, and small cell lung cancer (SCLC), accounting for 10–15%. This classification guides treatment strategies.

LC treatment includes surgery, radiation, and systemic therapies such as chemotherapy. Due to the aggressive nature of LC and its high mutational burden, factors that drive immunogenicity and resistance to conventional treatments, alternative therapies are needed. Recently, targeted therapies became standard care for NSCLC patients with specific mutations in epidermal growth factor (EGFR) and anaplastic lymphoma kinase (ALK) genes, improving survival for this subgroup. However, NSCLC patients without these mutations and most SCLC patients still rely primarily on chemotherapy, with limited overall survival.

Immunotherapy with immune checkpoint inhibitors (ICI) has transformed LC treatment, especially in NSCLC. ICI restore T-cell function by blocking immune-suppressive pathways, enabling immune recognition of tumor cells. Key targets include the PD-1/PD-L1 and CTLA-4 pathways. Approved ICI for LC include PD-1 inhibitors (e.g. nivolumab, pembrolizumab), PD-L1 inhibitors (e.g.

atezolizumab, cemiplimab, durvalumab), and the CTLA-4 inhibitors (e.g. ipilimumab).

Biomarker testing is essential to identify patients who may benefit from targeted or immunotherapies. In NSCLC, validated biomarkers for predicting response to ICI include PD-L1 expression, microsatellite instability (MSI), and tumor mutational burden (TMB). The indication for ICI therapy depends on PD-L1 expression thresholds. However, in SCLC, PD-L1 is not a reliable predictor. Still, ICI is part of first-line treatment in extensive-stage SCLC for eligible patients, often combined with chemotherapy during induction and maintenance phases.

Despite ICI success, most advanced NSCLC (~70%) and SCLC (~80%) patients do not achieve lasting benefit due to resistance mechanisms such as T-cell exhaustion and altered tumor metabolism. Moreover, PD-L1 predictive value is limited by tumor heterogeneity and inconsistent testing. Novel immune targets under investigation include Lymphocyte-activation gene 3 (LAG-3), T cell immunoglobulin and mucin-domain containing-3 (TIM- 3), T cell immunoreceptor with immunoglobulin and tyrosine-based inhibitory motif (ITIM) domain (TIGIT), V-domain immunoglobulin suppressor of T cell activation (VISTA), the Indoleamine 2,3-dioxygenase (IDO-1) pathway, CD47, CD73 and Natural Killer Group 2 Member A (NKG2A), though none are yet approved.

Studies show ICI therapies, whether used in monotherapy or in combination, are associated with more immune-related adverse events (AE) than chemotherapy. However, AE rates do not differ significantly between monotherapy and dual ICI therapy. Ongoing research is essential to explore these new targets, improve treatment efficacy, and address safety concerns, as some AE can severely affect quality of life, raise costs, and, in more severe cases, lead to serious health complications or death cause serious complications.

This systematic review aims to identify and synthesize current evidence on emerging ICIs in LC treatment, targeting resistance to standard ICIs (PD-1, PD-L1, CTLA-4) and aiming to expand the benefits of immunotherapy to more patients.

METHODS

Search strategy We selected relevant studies published between between January 2020 and January 2025, written in English, in PubMed and Web of Sciences databases, and on ClinicalTrials.gov registry, on May 10 and 11, 2025 and on June 10, 2025, respectively.

The following keywords (Medical Subject Headings terms) were used to search all databases: "Lung Neoplasms" (D008175), "Immune Checkpoint Inhibitors" (D000082082), "Biomarkers" (D015415), "Immunotherapy" (D007167), "Drug Resistance" (D004351), "Programmed Cell Death 1 Receptor" (D061026), "B7-H1 Antigen" (D060890) and "CTLA-4 Antigen" (D060908)"Gastrointestinal Microbiome" (D000069196), "Colorectal Neoplasms" (D015179), "Host Microbial Interactions" (D000076662), "Drug Therapy" (D004358), "Immunotherapy" (D007167) and "Radiotherapy" (D011878). Searches were performed with AND or NOT. The obtained literature was imported into "PICO Portal literature review" platform, which enhances the efficiency of the review process by consolidating all articles and their corresponding assessments in a centralised platform.

Participant or population Patients diagnosed with lung cancer.

Intervention New immune checkpoint inhibitors.

Comparator Standart of care immune checkpoint inhibitors (e.g. PD-L1, PD-1, CTLA-4).

Study designs to be included Randomised controlled trials on humans.

Eligibility criteria The articles to be analysed in this review will be studied and selected by submitting them to the following inclusion and exclusion criteria. The articles to be included must be written in English, randomized clinical trials on humans, and published from January 2020 until January 2025. The exclusion criteria correspond to any articles that are reviews, metanalysis, systematic reviews, clinical cases, non-randomized clinical trials, conference abstracts, and articles whose titles, abstracts and content are irrelevant to this study and not written in English. When there were multiple publications for the same clinical trial, we selected the latest or most complete publication. If recruiting various cancers including lung cancer (LC), the study was included only when survival outcomes and safety outcomes of LC subgroup were reported, otherwise, it was discarded. Furthermore, studies were excluded if they were considered to have limitations such as a high risk of bias, incomplete data reporting, or an unclear study objective.

Information sources PubMed, Web of Science and ClinicalTrials.gov.

Main outcome(s) Overall Survival, Progression-free survival, Event-free survival, Disease-free survival, Objective response rate, Complete response rate, Partial response rate, Adverse events.

Quality assessment / Risk of bias analysis The risk of bias assessment for the studies included in this systematic review was conducted using the Risk-Of-Bias VISualization (Robvis) tool, a comprehensive and widely used tool to assess the quality and risk of bias in research studies. The RoB 2 tool offers a structured framework for evaluating risk of bias in randomised trials, encompassing five domains where bias may be introduced: arising from the randomisation, deviations from intended intervention, missing outcome data, and selection of the reported result.

Strategy of data synthesis Given the study design, interventions, and outcome measures among the included studies, a narrative synthesis approach was employed for data analysis.

Subgroup analysis The articles will be subgrouped .
Although no formal subgroup analysis was conducted, the review organised findings by intervention type, more specifically by novel immune checkpoint inhibitors being targeted, as an informal subgroup approach. This grouping allowed the review to identify patterns unique to each therapeutic approach and observe differences in microbiome composition, diversity, and associated clinical outcomes.

Sensitivity analysis A formal sensitivity analysis was not conducted, primarily due to the small number of included studies and the absence of standardised effect sizes or quantitative outcomes, being preferred a qualitative interpretation of the results.Given the anticipated clinical and methodological heterogeneity among included studies, the scope for formal sensitivity analyses may be limited. However, where feasible, we will explore the impact of excluding studies at high risk of bias, or those with extreme results, to assess the robustness of findings. The results of these analyses will be interpreted with caution due to expected variability.

Language restriction English.

Country(ies) involved Portugal.

Keywords Lung Neoplasms, Immune Checkpoint Inhibitors, Immunotherapy, Drug Resistance.

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