INPLASY PROTOCOL

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None declared.

Biomarkers of resistance mechanisms in innovative lung cancer treatments - A systematic Review

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Review question / Objective: **This systematic review aims to provide an overview of the immunotherapy resistance mechanisms and identify potential biomarkers associated with immunotherapy response in NSCLC, as well as examine new treatment options to overcome this hurdle.**
Condition being studied: **Lung Cancer (LC) remains one of the leading cancers worldwide. In 2020, were globally estimated 2 206 771 new cases and 1 796 144 deaths, representing the uttermost frequent cause of cancer death. LC is classified histologically into small cell lung cancer (SCLC) or non-small cell lung cancer (NSCLC), being the last one the most common, representing 80 to 85% of all LC. The three predominantly subtypes of NSCLC are lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC) and large cell carcinoma (LCLC). NSCLC is usually diagnosed in advanced-staged disease due to ambiguous and delayed severe symptoms.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 03 September 2022 and was last updated on 03 September 2022 (registration number INPLASY202290011).

INTRODUCTION

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METHODS

Search strategy: This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We conducted an extensive search on the PubMed database undertaking literature from randomised clinical trials (RCT), review articles (RA), clinical trials (CT), meta-analysis and systematic reviews, using the following MeSH Terms "Non-Small Cell Lung Carcinoma", "Immunotherapy", "Resistance", "Immune Checkpoint Inhibitors", "Tumour Microenvironment", "Biomarkers", "Liquid Biopsy". All the selected articles were initially undergoing inclusive and exclusion criteria and sorted afterwards by title and abstract.

Participant or population: Only Non-Small Cell Lung Cancer patients will be addressed in this review.

Intervention: Non-Small Cell Lung Cancer patients submitted to immunotherapy presenting specific biomarkers profiles (PD-L1, Tumour mutational burden, mutation status, cytokines expression, etc).

Comparator: Overall Survival, Progression Free Survival and objective response rate in NSCLC patients also submitted to immunotherapy but presenting differences in biomarkers expression, described in intervention.

Study designs to be included: Clinical Trials and Meta-analysis.

Eligibility criteria: English language, Free-full text articles and clinical trials in humans were initially imposed and all manuscripts out of the main context were excluded. Additionally, it was only taken into consideration, papers between 2017 and 2022.

Information sources: We conducted an extensive search on the PubMed database.

Main outcome(s): Better responses were shown in patients with high PD-L1 expression than in low expression. Patients with high tumor mutational burden showed longer median overall survival (OS) and progression-free survival. Harboring certain types of mutations displayed worse ICI outcomes. The high presence of TILs and high expression of cytokines were related to better Overall Survival outcomes.

Quality assessment / Risk of bias analysis: The quality of evidence was assessed with the ROBVIS risk of bias tool.

Strategy of data synthesis: The data was firstly analyzed by considering different patient groups with different expressions of certain biomarker(s) undergoing immunotherapy. Then, we analyzed the method used and, finally, we considered overall survival, progression-free survival and objective response rate results between the groups.

Subgroup analysis: The suitable enrolled participants undertaking immunotherapy were split into different groups according to different biomarker expressions. (PD-L1 score, TMB, mutation profile, Blood-based immune cells count, metabolites expression, microbiome)

Sensitivity analysis: ROBVIS tool.

Language restriction: Only English manuscripts were accepted.

Country(ies) involved: Portugal.

Keywords: NSCLC; Immunotherapy; Resistance; Immune Checkpoint Inhibitors;

Tumor Microenvironment; Biomarkers; Liquid Biopsy.

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