

## USE OF IMMUNOTHERAPY FOR TREATMENT OF LUNG ADENOCARCINOMA: PROGRESS AND FUTURE PERSPECTIVES

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**Abstract:** Lung adenocarcinoma is a subtype of non-small cell lung cancer with rapid progression and poor prognosis. In the last two decades, immunotherapy has shown promise in the treatment of this type of neoplasia. A bibliographic review was used, in which scientific articles in English and Portuguese published between 2020 and 2023 in the databases: Scielo, Lilacs and Pubmed were searched, with the descriptors Lung adenocarcinoma, Immunotherapy and Treatment. 102 articles were found, 32 abstracts were read, and 5 articles were selected for the preparation of the work. Immunotherapy aims to stimulate the immune system itself to generate a response against cancer cells and provide an antitumor environment. Checkpoint inhibitors have been used exclusively or combined with other therapeutic forms for the treatment of lung adenocarcinoma. The most studied and in clinical use are T lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1) or its ligand (PD-L1). The use of anti-PD-1 and anti-PD-L1 antibodies in lung cancer has shown a 10 to 30% response and an improvement in progression-free survival. There are two PD-1 inhibitors to be used for the treatment of adenocarcinoma, nivolumab and pembrolizumab, and two PD-L1 inhibitors: durvalumab and atezolizumab. The latter was approved by ANVISA in 2019 and proved to be effective for the treatment of patients with metastatic non-small cell non-squamous cell lung adenocarcinoma. Combination therapy with atezolizumab increased survival by approximately seven months. Thus, it becomes evident that the use of immunotherapy for the treatment of lung adenocarcinoma, especially in metastatic cases, is a promising therapeutic option. In addition to having fewer side effects and weakening the patient's immune system to a lesser extent.

**Keywords:** Lung adenocarcinoma, Immunotherapy, Treatment

## INTRODUCTION

According to 2023 estimates, lung cancer is the third most common in men (18,020 new cases) and the fourth in women in Brazil (14,540 new cases). The incidence, over the last 20 years, has been decreasing, however, it is still relevant, as shown by the aforementioned data.

Smoking is the main risk factor associated with lung cancer, the smoke produced by it contains more than 7,000 compounds and chemical substances, at least 50 of which are carcinogenic, and some such as nitrosamine, directly linked to nicotine.

It is also associated with the angiogenic capacity of nicotine, further contributing to the proliferation of neoplastic cells. In about 85% of diagnosed cases, tobacco is in the patient's personal history.

The clinical features of lung cancer can be vague, with symptoms such as cough, dyspnea and hemoptysis, evolving to constitutional symptoms, such as fever, weight loss and asthenia, only in more advanced stages. Therefore, the importance of knowing the natural history of the disease and its risk factors, especially tobacco, to raise the hypothesis of lung cancer and earlier investigation.

Treatment is guided by the histological type of neoplasm, varying in severity and prognosis. It is divided into small cell lung cancer (SCLC), which is less prevalent, and non-small cell lung cancer (NSCLC), corresponding to 80% to 85%. The main subtypes of NSCLC are: adenocarcinoma, currently more prevalent, squamous cell carcinoma (or squamous cell) and large cell carcinoma (undifferentiated).

Pulmonary adenocarcinoma is a subtype of non-small cell lung cancer that progresses rapidly and usually has a poor prognosis. For many years, the standard treatment for this

type of cancer has been surgical resection with or without exclusive chemotherapy and/or radiotherapy, which only prove to be effective in the early stages of the disease.

However, in the last two decades, immunotherapy has shown great promise in the treatment of lung adenocarcinoma, managing to reduce the size of the tumor or slow its growth and offer a much longer-lasting response, as well as a better quality of life for the patient.

## OBJECTIVES

The aim of this work is to carry out a systematic bibliographical review, to study the advances in the use of immunotherapy for the treatment of lung adenocarcinoma and to indicate the future perspective.

## METHODS

A literary review was used, in which scientific articles in English and Portuguese published between the years 2020 and 2023 in the databases: Scielo, Lilacs and Pubmed were searched. Descriptors combined with the term "AND" and "OR" were used: Lung adenocarcinoma, Immunotherapy and Treatment. 102 articles were found and 32 abstracts were read, of which 5 articles were selected for the preparation of the work and discarded those in which there was no correlation with immunotherapy and lung adenocarcinoma. Duplicate articles, abstracts that did not address the topic and those that did not meet the inclusion criteria were excluded.

## DISCUSSION

### IMMUNOTHERAPY

An important function of the immune system is its ability to attack normal and abnormal cells in the body. To do this, he uses a checkpoint - molecules on immune cells that need to be turned on (or turned off) to initiate an immune response. Cancer cells use these checkpoints to avoid being attacked by the immune system.

In view of this, newer drugs target these control points. Currently, drugs are used to stimulate the patient's own immune system to generate an immune response against cancer cells and provide an antitumor environment. These are known as checkpoint inhibitors and have been used exclusively or combined with other therapeutic forms for the treatment of lung adenocarcinoma.

### CTLA4 E PD-L1

Of these, the most studied and in clinical use are T lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1) or its ligand (PD-L1). CTLA-4 regulates the function and activity of T lymphocytes, being a protein receptor being expressed when the T cell is active. PD-1, on the other hand, is an immune cell checkpoint protein, preventing T cell proliferation when present.

Examples of CTLA-4 inhibitors are ipilimumab and tremelimumab. These drugs are used together with a PD-1 inhibitor (ipilimumab with nivolumab and tremelimumab with durvalumab), and can be used together with chemotherapy as the first treatment for the disease advanced, obtaining good results.

### ATEZOLIZUMAB AND DURVALUMAB

The use of anti-PD-1 and anti-PD-L1 antibodies in lung cancer has shown a 10 to 30% response and an improvement in progression-free survival. Currently, there are already two PD-1 inhibitors to be used for the treatment of adenocarcinoma Nivolumab and Pembrolizumab, and two PD-L1 inhibitors: Durvalumab and Atezolizumab.

The PACIFIC study, which compared the use of durvalumab with placebo in patients with non-small cell lung cancer in stage III, unresectable and without disease progression after chemoradiotherapy, corroborated the beneficial use of the drug. About 33.1% of the patients who used Durvalumab remained alive and without progression. In addition to promising clinical efficacy and acceptable safety profile.

Furthermore, Durvalumab is also shown to be effective in those patients who have not experienced disease progression after two or more cycles of platinum-based chemoradiotherapy as consolidation therapy. Leading a disease-free life time and no distant metastasis, about 23 months.

Atezolizumab, on the other hand, was approved by ANVISA in 2019 and has shown to be very promising for the treatment of patients with metastatic non-small cell non-squamous cell lung adenocarcinoma. Its approval was based on the IMpower 110 phase study.

IMpower110 is a global, randomized, open-label, phase 3 trial to examine the efficacy and safety of atezolizumab compared to platinum-based chemotherapy in PD-L1-positive and metastatic patients who have not previously received chemotherapy.

The study demonstrated that atezolizumab combination therapy can reduce tumor size in addition to slowing its growth, and also increase survival compared with

chemotherapy alone, greater at 7.1 months in the atezolizumab group than in the platinum-based chemotherapy.

## CONCLUSION

Thus, it becomes evident that the use of immunotherapy for the treatment of lung adenocarcinoma, especially in metastatic

cases, is a very promising therapeutic option. A new direction of treatment is foreseen in which immunotherapy for this type of cancer is being used more and more, in preference to chemotherapy, since it has fewer side effects and does not weaken the patient's immune system so much.

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