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Review Article

# The role of immunotherapy in lung cancer: Actual scenery

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**ABSTRACT**

More than half of those who succumb to cancer each year also lose their battle with the disease, making cancer a leading cause of death worldwide. After surgery, hormonal therapy, radiotherapy and chemotherapy, which are preferred in cancer management, immunotherapy has revolutionized. In this mini-review, we cover the various immunotherapeutic approaches used in contemporary cancer immunotherapies. These are immune checkpoint blockade, an attemp planned to 'unleash' robust T cell responses, and adaptive cellular therapies connected on the infusion of tumor-struggling immune cells into the body. One of these attemps, Nivolumab, became the first ICI to be approved to treat lung cancer in 2014. To date, different ICIs, such as pembrolizumab, atezolizumab, and durvalumab, have been in a row introduced into clinical medicine and have shown significant effect. Therefore, in this mini-review, we present some emerging goals and attemps in cancer immunotherapy.

**Keywords:** Lung cancer, Checkpoint inhibitor, Chimeric antigen receptor T cells, Cytotoxic T-lymphocyte antigen 4, Programmed cell death protein 1

## 1. INTRODUCTION

In the world, lung cancer (LC), one of the deadliest malignancies, causes more than 25% of all cancer-related fatalities each year [1]. According to estimates, there are 1.8 million new cases of lung cancer each year, and 1.6 million people die from the disease [2-4]. The depressing survival results in patients with LC are currently is directing great try to develop new treatments for this high-risk group. Most statistics of patients with LC include both small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). SCLC sources from badly differentiated neuro endocrine cells, results in rapid metastasis, and has a weak prognosis with weak response to therapy. The incidence of small cell cancers is higher, especially among men, and is associated with a history of smoking. Generally, approximately 10% to 15% of all lung cancers are SCLC, and about 80% to 85% are NSCLC [5-8]. The current conventional treatments currently used for NSCLC are surgery, chemotherapy, radiation therapy, immunotherapy and targeted therapies [9]. Among the targeted therapies, epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), ROS1 and BRAF have provided significant improvements especially in patients with advanced course [10]. In recent years, immunotherapies such as programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte associated protein 4 (CTLA-4) inhibitors have replaced chemotherapy and gained therapeutic support against these mutations [11]. Nevertheless, chemotherapy is the first choice for patients who are not suitable for unidirectional and/or combined forms of immunotherapy. These patients may have immunotherapy contraindications or conditions of concern associated with combination immunotherapy, such as efficiency or risk of toxicity

[12]. Radiation therapy, on the other hand, uses high-energy radiation such as gamma rays, X-rays, protons, or electron rays to completely destroy the tumor site. Surgical interventions are recommended as a therapy choice in early-degree NSCLC [13].

Advanced lung cancer has a poor prognosis and standard therapies with cytotoxic anticancer drugs have restricted therapeutic impacts [14,15]. Various forms of immunotherapy have been developed after the years, like immunostimulating cytokines, oncolytic viruses, and tumor-targeting antibodies, that work by enhancing the anti-neoplastic effect of the existing immune system [16]. For cancer immunotherapy, agents are used to enable or increase the activation of the immune system to offensive cancer cells [17-19]. Cancer immunotherapy has altered the paradigm for cancer treatment [20,21]. At the same time, this method purpose to enhance antitumor immune responses with less off-target effects than chemotherapies and another agents that directly destroy cancer cells [22]. In last years, the dealling of the detailed mechanism of cancer immunotherapy and the positive results of anti PD-1 antibodies, one of the immune checkpoint inhibitors (ICIs), in clinical studies have marked a new era in the therapy of lung cancer [23]. Significant research in advanced NSCLC has informed developed survival with anti-PD-1/PD-L1 antibody therapy, both single and in combination with chemotherapy. For this reason, immunotherapy is considered a encouraging approach to treat certain types of cancer and furthermore to cure the disease [24,25]. Effective results have been obtained by stimulating the immune system instead of directly destroying cancer cells, which is why immunotherapy has now become the fifth sought-after step in cancer treatment after radiotherapy, surgery, medical oncology and interventional oncology.

This mini-review will review (ICPIs) and (CAR-) T cells, the two main agents behind recent immunotherapeutic agents in NSCLC and SCLC [26,27].

### 1.1. Immune Checkpoint Inhibitors (ICI)

The adaptive immune system, which arises with the production of many antigens, can distinguish cancers from normal cells [28-31]. These exceptional cancer antigens are recognized by T-cell receptors (TCR) thanks to major histocompatibility complexes (MHC) on antigen-presenting cells (APCs). According to these methods, which include T cell activation, clonal proliferation of antigen-specific cells, immune effector cell aggregation, cytokine release, and ultimately cytotoxic T cell-mediated tumor cell killing, tumor growth will eventually stop. The balance of costimulatory and inhibitory molecular interactions between T cells and APCs governs all of these scenarios. However, tumor cells can evade an immune attack by increasing inhibitory signaling and decreasing costimulatory signaling. [32,33]. Given its success in treating cancer, the first approved ICPI was an antibody against CTLA-4 and PD-1 or PD-L1 [34,35].

#### *1.1.1. CTLA4*

The family of immunoglobulins includes CTLA4. Furthermore, together with the T cell co-stimulatory protein CD28, is co-expressed by activated T cells. Humans produce three isoforms as a result of gene splicing. They are the exon 1 and exon 4 versions, the soluble form of CTLA-4, and the full-length CTLA-4, respectively [36]. During T cell receptor (TCR)-mediated and CD28-mediated T cell activation, CTLA4 expression on effector T cells is increased to enable downstream regulation of immunity. The discovery of CTLA 4 as a negative regulator of T cell activation has helped to explain how it might activate the T cells' therapeutic response against cancer. CTLA 4-mediated tumor withdrawing mechanisms are pleiotropic but associated with T lymphocyte activity. T cell replies are required for the therapeutic effects of CTLA 4 directed agents. In animal models, consumed T cell abolished tumoricidal activity [37,38]. Studies have indicated the antitumor effect and clinical avails of antibodies such as ipilimumab, which block CTLA-4 interplays through ligands [39,40].

#### *1.1.2. PD1*

PD-1 and PD-L1 are members of the type I transmembrane protein class [41]. Immunity is severely inhibited by programmed cell death protein 1 (PD1). Natural killer T cell, T cell, B cell and activated monocytes all mean the PD1 protein. PDL1

and PDL2 are the two ligands for PD1, which are both related in cell death. In a research, it was shown that regenerated T cells in the peripheral blood of lung cancer patients after PD1 suppression express CD28 [42,43]. Anti-PD1/PD-L1 immunotherapy methods, blocks PD1, an inhibitory lymphocyte receptor, while releasing anti-tumor immune cytotoxicity [44,45].

#### *1.1.3. PDL1*

PDL1 causes PD1-mediated immune suppression because it is structurally expressed on T cells, B cells, macrophages, non-lymphoid organs like the heart and lungs, in parenchymal cells, and on the surface of tumor cells. PDL1 expression, but not PDL2, has also been found in the placenta, pancreatic islets, and cardiac endothelium at low levels, suggesting a function for PDL1 in immunological tolerance. In addition, PDL1 blockade is effective in the treatment of malignancies of the bladder, lung and other organs [43-46].

Biochemical experiments confirmed that [italic] in silico[/italic] nominees are true inhibitors of the PD-1/PD-L1 interplay. These results were also verified [italic]in vitro[/italic]. Additionally, the study demonstrated the capability of small molecule inhibitors to reduce tumor masses and mediate antitumor immune reactions using the PD-1/PD-L1 mouse model [47].

#### *1.1.4. PDL2*

PDL2, such as PDL1, is an immune checkpoint inhibitor. Although the activity of PDL2 is less well understood than PDL1, its clinical value is still under investigation [48]. The activation of PD1 by PDL2 significantly reduces CD4+ T cell increment and cytokine formation that is mediated by the TCR123. At the same time, novel studies revealed that PDL2 can reduce PDL1 and/or PD1 connecting and increase the expression of CD3 and excitable T-cell co-stimulator (ICOS) on T cells, perchance through conjectural second receptor. Former searches have demonstrated that PDL2 could develop T cell activity through a PD1 free method [49,50].

The promotion of ICI has certainly been the first of all oncologic accomplishment of the last ten years.

**Table 1.** FDA Immune Checkpoint Inhibitors Approved for NSCLC

| Agent | Molecular Target |
|---|---|
| Ipilimumab | CTLA-4 |
| Nivolumab | PD-1 |
| Pembrolizumab | PD-1 |
| Cemiplimab | PD-1 |
| Atezolizumab | PD-L1 |
| Durvalumab | PD-L1 |

FDA confirmations started with ipilimumab for melanoma in 2011 [51]. At present confirmed ICIs for NSCLC as of October 2022 are shown in Table 1 [52,53].

### 1.2. Chimeric Antigen Receptors (CARs)

CARs are at the tender spot of this grand revision of adoptive T cell treatments and concretize a pass from classic immunology to synthetic cell therapy. CARs are synthetic fusion proteins made up of a transmembrane domain, an extracellular domain that can precisely bind to a target molecule expressed on the surface of tumor cells, and an intracellular domain that sends a warning to activate T cells when the extracellular domain interacts with its target. The extracellular domain of an antibody is typically composed of the antigen-recognition regions as a single-chain unstable fragment [54,55]. CAR-T cells detect particular tumor antigens in an MHC-independent way, activating and carrying out their anticancer function [56]. Clinical application of CAR T-cell therapies against LC remnants is constrained by physical and immunological barriers, antigen escape and heterogeneity, on-target off-tumor toxicity, and a number of additional reasons [57]. With CAR T-cell therapy, the patient's own genetically altered T cells are used to find and eradicate the malignancy [58]. The complete range of activity of checkpoint blocking medications used one or in combination is now the focus of significant research due to the intricate biology of immune checkpoint pathways, which still holds plenty mysteries [58-60]. Since rerouted T cell therapy was first introduced by CAR, it has become recognized as a viable cancer treatment method. Contrary to TCRs, CARs are synthetic receptors having cytoplasmic signaling domains, transmembrane domains, and extracellular

antigen identification domains. As a result, CARs are skilled of shifting the specificity of T and NK cells to tumor-associated antigens (TAAs) produced on tumor cells by identifying the targeted antigen in an MHC-independent manner [59]. Some patients have responded highly to immunotherapy, while others do not have the same positive response. No one can predict how your body will respond to any one treatment. A doctor should definitely determine what to expect when using an immunotherapy drug and what the right treatment is for you [61].

## 2. CONCLUSION

The outlook for treating hematological malignancies has changed as a result of cancer immunotherapies such ICIs and CAR-T. Even if there are more individuals who have long-term survival after receiving ICI therapy than with other treatments, these examples are rare. The choice of new therapeutics and efficacy-enhancing methods, like combination therapy, remains a difficult problem to tackle. To ensure that immunotherapy is successful in the future, predictive criteria must be improved. Although PD-L1 and CARs are both useful in case selection, it is now known that resistance can arise through multiple mechanisms. Despite the fact that immuno chemotherapy has made significant progress in the treatment of LC, it is anticipated that it will continue to advance when targeted medicines or new combinations of therapies are developed. Clinical investigations are evaluating the advancement of novel therapeutic options, such as the combination of PD-1/PD-L1 inhibitors with other ICIs and DNA repair targeted medicines.

### Author contribution

Concept: İE, GAÇ; Design: İE, GAÇ; Supervision: GAÇ; Data Collection and/or Processing: İE, AH, SNE, GAÇ; Literature Search: İE, AH, SNE, GAÇ; Writing: İE, GAÇ; Critical Reviews: İE, GAÇ.

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