Immunotherapy for Non-Small Cell Lung Cancer: Integrating Safety, Clinical Results, and Efficacy Data

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ABSTRACT

With non-small cell lung cancer accounting for almost 85% of occurrences, lung cancer continues to be a significant global health concern. Due to non-specific toxicity, poor medication absorption, and frequent resistance development, conventional treatments such as surgery, chemotherapy, radiation therapy, and targeted therapy offer little long-term control. Tumour growth and immune evasion are facilitated by key driver mutations, such as EGFR and KRAS, as well as changes in receptor tyrosine kinases and regulators like KLF5. Tumours utilise the PD-1/PD-L1 pathway, a key mechanism of immune suppression, to inhibit T-cell activation. Immune checkpoint drugs have been developed as a result, most notably pembrolizumab, a monoclonal antibody that selectively blocks the PD-1 receptor.

With its improved survival advantages in patients lacking actionable driver mutations, pembrolizumab has revolutionised the treatment of non-small cell lung cancer. Pembrolizumab monotherapy or in combination with chemotherapy has been shown to increase progression-free and overall survival in major trials (024, 042, 189, and others), particularly in patients with high PD-L1 expression. Five-year findings establish pembrolizumab as the first-line standard of therapy by confirming long-lasting survival benefits. Immune-related side effects, including pneumonitis, dermatitis, and thyroid dysfunction, need close observation even though they are usually well tolerated. This study highlights pembrolizumab's increasing significance in contemporary NSCLC treatment by summarising the aetiology of NSCLC, immune suppression mechanisms, and pembrolizumab's clinical efficacy and safety.

Keywords- NSCLC, PD-1, Pembrolizumab, PD-L1, Immunotherapy, Keynote trials, Progression-free survival, overall survival, Immune checkpoint inhibitors, T-cell activation, combination therapy, monotherapy, side effects, safety, progressive disease

1. Introduction

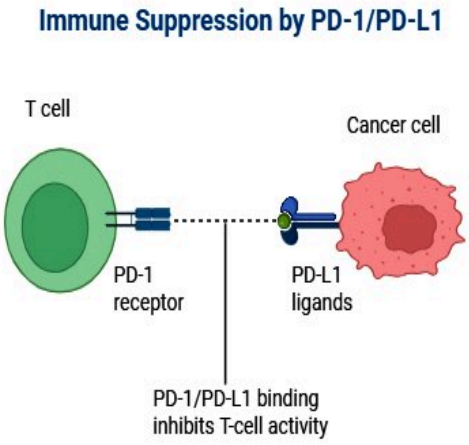
Lung cancer continues to be a serious hazard to public health worldwide. Small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) are the two types of lung cancer; about 85% of newly diagnosed instances of lung cancer are NSCLC. The fact that over two million people are diagnosed with this illness each year highlights how pervasive it is. Currently available treatments include targeted therapy, radiation therapy, chemotherapy, and surgery [1]. Surgical tumour removal along with adjuvant therapy is the treatment for stage I or II non-small cell lung cancer. On the other hand, chemotherapy or radiation therapy are used when the illness reaches stages III or IV. However, non-specific targeting, limited absorption, and the emergence of drug resistance restrict the effectiveness of nearly all standard chemotherapeutic medications in treating cancer. PD-1/PD-L1 inhibitors can significantly increase tumour response rates and extend survival in patients with NSCLC. However, not all patients react to treatment (initial resistance), and the development of treatment resistance (acquired resistance) is nearly certain [2]. Patients' outcomes have significantly improved when lung cancer is treated with immunotherapies like pembrolizumab, an anti-PD-1 receptor antibody. The effectiveness of pembrolizumab treatment and known correlations with PDL-1 expression on tumour cells have been thoroughly documented in earlier investigations [3]. In patients with non-small cell lung cancer (NSCLC) who received either pembrolizumab monotherapy (mono-pembro) or combined pembrolizumab plus chemotherapy (chemo-pembro), this investigation sought to assess survival outcomes and their correlates [4].

1.1. Causes of NSCLC

KLF5 is intimately associated with blood vessel development, tumour growth, and proliferation [5]. In the US, 15% of patients with NSCLC have epidermal growth factor receptor (EGFR) mutations; this percentage is higher among Asian patients [6]. Activating mutations in receptor tyrosine kinases (RTKs), such as those in the Epidermal Growth Factor Receptor gene, are commonly found driver mutations in NSCLC, which accounts for over 80% of cases of lung cancer [7].

Cause of Immunity Suppression

The negative costimulatory receptor known as programmed cell death 1 (PD-1) is mostly expressed on the surface of activated T lymphocytes. Tumour cells can express the PD-1 ligands PD-L1 and PD-L2. A key mechanism that tumours use to impede immune control is the binding of PD-1 and its ligands [8].

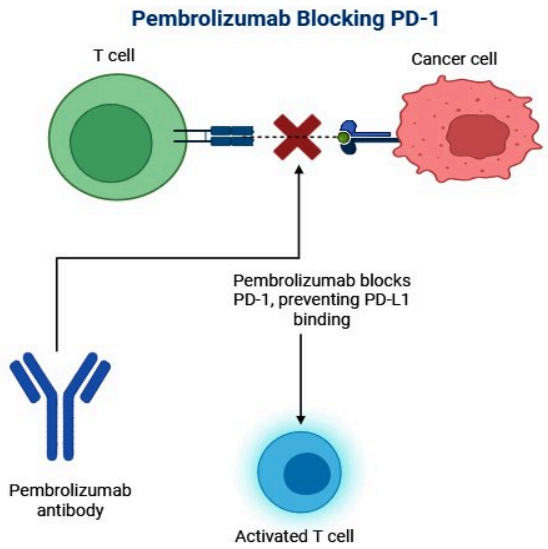


2. About Pembrolizumab

Patients with NSCLC who relapse or are resistant to first-line therapy can now be treated with immunotherapies like pembrolizumab [10]. Activated B and T cells carry the PD-1 receptor, an immunological checkpoint protein that typically suppresses overreaction. Through a negative feedback loop, PD-1 binding to its ligands (PD-L1 and PD-L2) on tumour cells suppresses T cells, resulting in immune system evasion. A humanised IgG4 monoclonal antibody that is extremely selective against PD-1 is called pembrolizumab. For patients with advanced NSCLC who have a programmed death-ligand 1 (PD-L1) tumour percentage score (TPS) of at least 50%, pembrolizumab is a typical first-line treatment. Overall survival (OS) was significantly higher in the pembrolizumab-alone arm of the KEYNOTE 024 study compared to the platinum combination therapy arm in patients with NSCLC who had a PD-L1 tumour percentage score (TPS) ≥ 50% and were receiving first-line treatment [9].

3. Mechanism of Action

Pembrolizumab is a humanised immunoglobulin G, subclass 4 (IgG4) monoclonal antibody (mAb) that activates T-cell-mediated immune responses against tumour cells by binding to the programmed cell death protein 1 (PD-1) receptor and preventing its interaction with programmed death-ligand 1 (PD-L1) and PD-L2. It has been demonstrated that PD-L1 is expressed in 20% to 60% of NSCLC tumours with both squamous and non-squamous histology. Patients with metastatic non-small cell lung cancer whose tumours express PD-L1 ≥ 1% and whose illness progresses during or after platinum-containing chemotherapy may be treated with pembrolizumab alone. Additionally, pembrolizumab is authorised in combination with platinum doublet chemotherapy for both squamous and nonsquamous NSCLC, as well as monotherapy in the first-line treatment of patients with NSCLC expressing PD-L1 ≥ 1% [10]. Since immune checkpoint inhibitors (ICIs) have shown a survival advantage over platinum-based chemotherapy, they are now the standard of care for patients with non-small cell lung cancer whose tumours do not contain targetable gene alterations [11]. Patients with NSCLC now have a higher chance of survival due to immunotherapy that uses programmed death-ligand 1 (PD-L1) or programmed death 1 (PD-1) receptor antibody therapies [12].



4. Uses

For non-small cell lung cancer, pembrolizumab with chemotherapy is safe and controllable [13]. When patients with advanced (NSCLC) have a PD-L1 tumour proportion score (TPS) of 50% or greater, pembrolizumab monotherapy has demonstrated exceptional efficacy. Pembrolizumab monotherapy considerably increased progression-free survival and overall survival when compared to chemotherapy alone, according to the KEYNOTE-024 and KEYNOTE-042 trials [14]. For metastatic non-small cell lung cancer without actionable driver mutations, immune checkpoint inhibitors (ICIs) that target the programmed-death-1/ programmed-death ligand 1 (PD-1/PD-L1) axis have established themselves as a first-line treatment. Four practice-changing first-line phase III randomised controlled studies have demonstrated that pembrolizumab, an ICI targeting PD-1, improves overall survival either by itself or in conjunction with chemotherapy as compared to chemotherapy alone in patients with advanced non-small cell lung cancer [15].

5. Efficacy of Pembrolizumab:

Inhibitors of programmed death 1 (PD-1) and its ligand PD-L1 are effective therapy for metastatic non-small-cell lung cancer (NSCLC). [16].

Five-Year Outcomes of Pembrolizumab

Despite using platinum-based chemotherapy, patients with advanced non-small-cell lung cancer (NSCLC) have historically had a dismal prognosis. The 5-year relative survival rate for patients with distant metastases is low worldwide; in the US, it was just 6.9% between 2010 and 2016. For NSCLC patients without oncogenic driver mutations, immunotherapy has changed the course of treatment. When given as monotherapy (in patients with programmed death ligand-1 [PD-L1] positive NSCLC) or in combination with chemotherapy (regardless of tumor PD-L1 expression), pembrolizumab, a monoclonal antibody against programmed death (PD-1), has been demonstrated in randomized controlled trials to improve overall survival (OS) versus platinum-based chemotherapy for patients with advanced or metastatic NSCLC without sensitizing EGFR or ALK alterations). A phase III randomised, open-label study called KEYNOTE-024 compares platinum with pembrolizumab monotherapy-based chemotherapy in patients with untreated non-small cell lung cancer (NSCLC) who had a PD-L1 tumour percentage score (TPS) of at least 50%. This was, as far as we are aware, the first

phase III study to demonstrate the superiority of immunotherapy over platinum-based chemotherapy in the first-line scenario. At the second interim analysis, the trial showed that pembrolizumab significantly improved OS and progression-free survival (PFS) when compared to chemotherapy. In later studies, OS remained enhanced for pembrolizumab compared to chemotherapy. Although five-year survival is a crucial milestone in cancer treatment, there hasn't been much data on patients with metastases for this period of follow-up until recently [17]. The estimated 5-year PFS rates were 3.5% versus 10.8%.

Pembrolizumab with chemotherapy was preferred by HRs for OS and PFS in all PD-L1 tumour proportion score (TPS) subgroups [18].

6. Safety of Pembrolizumab

The incidence of treatment-related adverse events (AEs) in the treated population (PD-L1 TPS ≥ 1%) was 90.2% in the chemotherapy group and 63.8% in the pembrolizumab group (Data Supplement). Neither treatment group experienced any new, lethal adverse events (AEs); all had already been reported. One patient in the chemotherapy and pembrolizumab groups experienced infusion reactions in 7.6% of cases and immune-mediated adverse events in 27.5% of cases, respectively. Immune-mediated adverse events and infusion reaction rates and exposure-adjusted treatment-related adverse events generally declined over time in both treatment groups [19]. The overall response, disease control rates, median progression-free survival (PFS), and overall survival (OS) of patients treated with first-line pembrolizumab monotherapy were 53.1%, 74.4%, 7.0 months, and not attained, respectively. Anorexia, exhaustion, skin rash, and hypothyroidism were frequent side effects. Pneumonitis and infection were the causes of two treatment-related deaths. Better PFS was linked to first-line pembrolizumab monotherapy for non-progressive disease (PD). Better OS was also associated with pembrolizumab monotherapy in non-PD patients with satisfactory performance status. For NSCLC with high PDL1 expression, first-line pembrolizumab monotherapy proved both safe and effective [20].

7. Conclusion:

In major KEYNOTE trials and real-world PK-guided investigations, pembrolizumab has consistently improved progression-free survival, overall survival, and tumour response, making it a very effective and well-tolerated therapeutic option for advanced non-small cell

lung cancer (NSCLC). In patients with high PD-L1 expression, its effectiveness is particularly noteworthy, and customised dosing strategies further improve clinical benefit.

Even though pembrolizumab is generally safe, immune-related side effects such as skin rashes, thyroid dysfunction, and pneumonitis are still significant issues that need to be identified and treated as soon as possible. All things considered, the data strongly support pembrolizumab as a key element of NSCLC treatment, providing long-lasting therapeutic advantages while highlighting the necessity of biomarker-guided patient selection and careful safety monitoring to maximise results.

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