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PD-1 Inhibitors in Non-Small Cell Lung Cancer: Advances in Immunotherapy and Future Prospects

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Abstract

PD-1 inhibitors, such as pembrolizumab and nivolumab, have transformed the treatment landscape for advanced non-small cell lung cancer (NSCLC), offering substantial improvements in survival. Pembrolizumab, particularly effective in tumors with high PD-L1 expression (≥50%), has demonstrated significant overall survival (OS) and progression-free survival (PFS) benefits as monotherapy, and when combined with chemotherapy for patients with lower PD-L1 expression or EGFR/ALK-negative mutations. Clinical trials like KEYNOTE-024, KEYNOTE-189, and KEYNOTE-407 have reinforced the efficacy of pembrolizumab, showcasing its impact in both non-squamous and squamous NSCLC subtypes. Nivolumab, combined with ipilimumab, has also shown promise, especially in patients with PD-L1 expression ≥1%, as evidenced by the CheckMate-227 and CheckMate-9LA trials. As second-line therapy, both pembrolizumab and nivolumab have demonstrated efficacy in patients progressing after platinum-based chemotherapy, further solidifying their role in NSCLC management. Biomarkers such as PD-L1 expression and tumor mutational burden (TMB) play a crucial role in guiding immunotherapy choices, ensuring a more personalized treatment approach. Despite the benefits, PD-1 inhibitors are associated with immune-related adverse events (irAEs) that require careful management. The future of NSCLC treatment lies in optimizing biomarker-driven strategies, improving combination therapies, and addressing challenges such as resistance to immunotherapy. PD-1 inhibitors represent a major advancement, significantly improving outcomes for patients with advanced NSCLC.

Keywords: Immunotherapy; Non-Small Cell Lung Cancer (NSCLC); PD-1 Inhibitors

Abbreviation: AVMs: Arteriovenous Malformations; NSCLC: Non-Small Cell Lung Cancer; PD-L1: Programmed Death-Ligand 1; EGFR: Epidermal Growth Factor Receptor; ALK: Anaplastic Lymphoma Kinase; ORR: Overall Response Rate; PFS - Progression-Free Survival; OS: Overall Survival; TPS: Tumor Proportion Score; TMB: Tumor Mutational Burden; irAEs: Immune-Related Adverse Events; CTLA-4: Cytotoxic T-Lymphocyte Antigen 4; HR: Hazard Ratio; CI: Confidence Interval; AE: Adverse Event

Introduction

Lung cancer is the leading cause of cancer incidence and mortality worldwide [1]. Non-small cell lung cancer (NSCLC), the most common epithelial lung cancer, accounts for ~85% of all lung cancer types [2]. The most common types of NSCLC are squamous cell carcinoma, large cell carcinoma and

adenocarcinoma, but there are several other types that occur less frequently, and all types can occur in unusual histological variants. Although NSCLCs are generally known to be associated with cigarette smoke, adenocarcinomas may be found in non-smoker patients [3]. If identified at an early stage (stage I), NSCLC has a favorable prognosis (5 year survival rate of 70-90%). However, advanced disease (stage III and IV) is associated with a poorer prognosis [4]. Recently, research into tumor immunity has opened avenues for targeted molecular therapy and immunotherapies against programmed cell death protein 1 (PD-1) receptors, in the treatment of NSCLC [5,6]. Notably, the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have approved 2 drugs against the PD-1 receptor, Pembrolizumab and Nivolumab, to treat advanced disease [6,7].

Pembrolizumab (formerly lambrolizumab) is a selective humanized IgG4 kappa monoclonal antibody currently approved by the FDA for treatment of metastatic NSLSC and advanced melanoma [8]. It was first approved in the United States by the Food Drug Administration (FDA) in September of 2014 and in Europe by the EMA in July of 2015 [8]. The EMA has approved Pembrolizumab for the treatment of NSCLC, melanoma, classical Hogkin's lymphoma, urothelial cancer, head and neck squamous cell carcinoma, renal cell carcinoma, oesophageal cancer, gastroesophageal junction cancer, gastric cancer, triple-negative breast cancer, endometrial carcinoma, cervical cancer, biliary tract cancer, and colorectal cancer (when microsatellite instability-high or mismatch repair deficient) [9].

Nivolumab is a fully human IgG4 monoclonal antibody PD-1 receptor blocker [10,11]. It was first approved in the United States by the FDA in December of 2014 [11] and by the EMA in June of 2015 [12]. It is currently approved for use for the treatment of resectable and metastatic NSCLC, metastatic melanoma, malignant pleural mesothelioma, advanced renal cell carcinoma, classical Hodgkin's lymphoma, squamous cell carcinoma of head and neck, urothelial carcinoma, colorectal carcinoma, hepatocellular carcinoma, esophageal cancer, gastroesophageal junction cancer and gastric cancer [13].

Mechanism of Action of PD-1 Inhibitors

The Programmed cell death protein 1 (PD-1) is a transmembrane protein belonging to CD2/CTLA-4 superfamily. The Programmed cell death ligand 1 (PD-L1) belongs to B7 family of T cell co-inhibitory molecules [14]. PDL1 expressed by cancer cells binds to PD-1 on the surface of T-cells, thereby inhibiting T cell activation and leading to cancer immune escape [15]. The interaction between PD-1 and PD-L1 can transmit inhibitory signals within cells, suppressing lymphocyte proliferation and activation, thereby diminishing immune capacity [16]. When tumor- infiltrating lymphocytes (TILs) recognize tumor antigens, they initiate 'adaptive resistance' mediated by PD-1/PD-L1 pathway to assist tumor immune evasion and distant metastasis [17]. Specifically, this is manifested as follows, (I) PD1/PD-L1 interaction suppresses the activation and proliferation of T cells, promoting T cell dysfunction and apoptosis. (II) PD-1/PD-L1 interaction enhances the function of regulatory T cells (Tregs) and induces immune tolerance. (III) PD-1/PD-L1 interaction promotes the polarization of TAM and other immune cells into tumor-promoting phenotypes, facilitating immune escape and cancer progression. (III) Signaling of PD-L1 within cancer cells may prevent the apoptosis of tumor cells themselves, and the interaction of PD-L1 with CD80 can suppress the immune response [18].

Pembrolizumab is a humanized monoclonal IgG4 kappa antibody directed against human cell surface PD-1 on lymphocytes. When PD-L1 engages with PD-1, the T-cell function becomes inhibited; pembrolizumab blocks the PD-1: PD-L1 complex formation allowing improved T- cell mediated killing [19,20]. Nivolumab is also a humanized monoclonal IgG4 antibody that binds to PD-1 receptors with high specificity and affinity. In cancer, aberrant PD-L1 expression by tumor cells or immune cells in the tumor microenvironment deactivates PD-1 expressing tumor-infiltrating lymphocytes, allowing tumor cells to escape immune recognition and elimination [21,22]. By inhibiting PD-1 function, nivolumab releases immune cells from pathological immune suppression, allowing them to recognize and counter tumor cells.

Clinical Trials and Efficacy in NSCLC

The efficacy of PD-1 inhibitors in treatment of NSCLC has been investigated in several notable studies. KEYNOTE-024 was an open-label, phase 3 study that was published in 2016 which investigated the role of monotherapy Pembrolizumab in NSCLC. The study randomly assigned 305 untreated patients to receive either Pembrolizumab (at fixed dose of 200 mg q3wks) or platinum-based chemotherapy. Inclusion criteria included PD-L1 expression on ≥ 50% tumor cells and exclusion criteria required that patients have no mutation of EGFR (epidermal growth factor receptor) or ALK (anaplastic lymphoma kinase) gene translocation [23]. In the intention-to-treat population, median progression-free survival was 10.3 months in the pembrolizumab group (95% CI, 6.7 to not reached) vs 6.0 months in the control platinum chemotherapy group (95% CI, 4.2 to 6.2) (hazard ratio for disease progression or death 0.50, 95% CI, 0.37 to 0.68, P< 0.001). Furthermore, the estimated rate of overall survival at 6 months was 80.2% in the Pembrolizumab group versus 72.4% in the chemotherapy group (hazard ratio for death 0.60, 95% CI, 0.41 to 0.89; P=0.005) [24]. Response rate in Pembrolizumab group was 44.8% compared to 27.8% in chemotherapy group, as well as treatment-related adverse effects of all grades were less frequent in pembrolizumab group, 73.4%, compared to chemotherapy group, 90.0% [23]. This resulted in FDA approval of pembrolizumab as first line therapy for metastatic NSCLC with PD-L1 expression of ≥ 50% and without EGFR/ALK mutations in October 2016. As of July 2017, median follow up was 25.2 months during which, median overall survival (OS) of the pembrolizumab

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group was 30.0 months versus 14.2 months in chemotherapy group, indicating that pembrolizumab therapy alone reduced risk of desk by 37% compared to platinum-based chemotherapy [23].

Although KEYNOTE-024 was the first clinical study to show improved overall survival (OS) in NSCLC with pembrolizumab monotherapy compared to chemotherapy, this was only demonstrated in patients with PD-L1 expression of ≥ 50% with no EGFR/ALK mutation which only represents 30% of patients receiving PD-L1 inhibitor therapy. KEYNOTE-042 sought to address this by investigating whether the population of patients with PD-L1 expression between 1-49% benefitted from pembrolizumab. KEYNOTE-042 was a randomized, controlled, open-label, phase III trial study which studied the OS of NSCLC patients with PD-L1 express ≥ 1% with pembrolizumab monotherapy (200 mg q3wks) vs chemotherapy [25]. Patients in both groups were subdivided into PD-L1 levels of 1-19%, 20-49% and ≥50% [24]. Once median follow-up reached 12.8 months, the OS of pembrolizumab group was significantly greater in all three subgroups compared to chemotherapy alone (16.7 vs 12.1, 17.7 vs 13.0, 20.0 vs 12.2). The rate of treatment-related adverse effects in the pembrolizumab group was 63% compared to 90% in the chemotherapy group [25]. KEYNOTE-042 was able to confirm that pembrolizumab was beneficial as first-line monotherapy in NSCLC regardless of PD-L1 expression in tumor cells. Based on these results, FDA expanded indications of pembrolizumab to include NSCLC patients with PD-L1 ≥1% and without EGFR/ALK gene mutations.

The synergistic relationship between PD-L1 inhibitor immunotherapy and chemotherapy together has also been explored and shown improved efficacy compared to that of chemotherapy alone. KEYNOTE-021G was an open-label, randomized, Phase 2, multi-cohort study which enrolled 123 patients that were chemotherapy naive, stage 3B or 4, with non-squamous NSCLC with EGFR/ALK negative mutations [26]. Patients were randomly assigned into pembrolizumab plus chemotherapy (carboplatin, pemetrexed) and chemotherapy alone group. At a median follow-up time of 23.9 months, the overall response rate (ORR) was 56.7% in the PD-L1 inhibitor plus chemotherapy group compared to 30.2% in the chemotherapy alone group. 37% of the experimental group had died at the time of analysis versus 56% in the chemotherapy alone group. Median progression free survival (PFS) in the pembrolizumab and chemotherapy group was 24.0 months compared to 9.3 months in the chemotherapy group [3]. At the two year follow-up mark, KEYNOTE-021G demonstrated that pembrolizumab combined with traditional chemotherapy was able to reduce disease progression by 47% and risk of death by 44% in advanced non-squamous NSCLC patients [24]. Furthermore, these findings are reinstated in KEYNOTE-189 which is a randomized, placebo-controlled phase III clinical trial, which enrolled 616 patients with untreated metastatic non-squamous NSCLC without EGFR/ALK mutations [27]. It's important to note that about one-third of patients in this study had negative PD-L1 expression of tumor. The data cut-off date was presented at the American Society of Clinical Oncology's Annual Meeting and results showed that median OS was 22 months in pembrolizumab combined with chemotherapy compared to 10.6 months in the placebo combination group, which is more than double. The two-year survival rate was 45.7% in the pembrolizumab combination group versus 27.3% in the placebo chemotherapy combination group [27]. KEYNOTE-189 and KEYNOTE-021G were able to demonstrate the synergistic effect of pembrolizumab combined with traditional chemotherapy compared to chemotherapy alone in non-squamous advanced NSCLC with negative EGFR/ALK mutations.

In like manner, compared to non-squamous NSCLC, the squamous subtype only makes up 15% of NSCLC and survival rate is about 5% even with comprehensive surgery, radiotherapy and chemotherapy. KEYNOTE-407 is a double-blind, Phase III study enrolled 559 patients with metastatic squamous NSCLC and assigned subjects to pembrolizumab and chemotherapy combination group or placebo-chemotherapy combination group in a 1:1 ratio [24]. At the median follow-up of 7.8 months, the median OS in the experimental group was 15.9 months compared to 11.3 months in the placebo combination group, regardless of PD-L1 expression. Median PFS was 6.4 months in the pembrolizumab-combination group versus 4.8 months in the placebo-combination group [24]. Thus, KEYNOTE-407 exemplified similar efficacy of pembrolizumab combination therapy in metastatic squamous NSCLC with PD-L1 ≥1% similar to that in the more popularly studied non-squamous NSCLC.

Both pembrolizumab and nivolumab are anti-PD1 monoclonal antibodies that are within the IgG4 subtype, however they differ in epitope-paratope binding which may explain differences in clinical efficacy between the two. CheckMate-026 is a Phase 3, open label, randomized which compared the efficacy of monotherapy nivolumab versus platinum chemotherapy in stage 4/recurrent PD-L1 positive NSCLC [28]. 541 patients were enrolled in this study and median progression free survival was 4.2 months in the nivolumab group compared to 5.9 months in the chemotherapy group. In addition, in patients with PD-L1 expression ≥5% nivolumab did not improve progression free survival (HR, 1.15; 95% CI 0.91 to 1.45; P = 0.25) [28]. It is notable that compared to chemotherapy nivolumab displayed a favorable safety profile with rate of treatment related AE of 71% in any stage NSCLC compared to 92% in the chemotherapy group [28]. More recently, CheckMate-227 published in 2022 studied the combined efficacy of nivolumab and ipilimumab (anti-CTLA-4 monoclonal antibody) compared to chemotherapy alone [29]. This randomized, open-label, Phase 3 trial found that four-year overall survival was 29% vs 18% in PD-L1≥1% and 24% vs 10% in PD-L1<1%, in immunotherapy combination and chemotherapy alone group respectively [29]. At four-year follow-up, even with patients oss nivolumab and ipilimumab for two years, the immunotherapy combination demonstrated long-term increase in survival in NSCLC.

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First-Line Therapy for Advanced or Metastatic NSCLC

Pembrolizumab (Keytruda), a PD-1 immune checkpoint inhibitor, is widely used as a first-line treatment for advanced or metastatic non-small cell lung cancer (NSCLC), with treatment decisions guided primarily based on PD-L1 expression levels on tumor cells [30]. For patients whose tumors express PD-L1 ≥50%, pembrolizumab is approved for use as monotherapy, provided the tumors do not harbor EGFR (endothelial growth factor receptor) or ALK (anaplastic lymphoma kinase) mutations [31,32]. This recommendation is supported by the results of the KEYNOTE-024 trial, which demonstrated significantly improved overall survival (OS) and progression-free survival (PFS) compared to standard platinum-based chemotherapy, with a median OS of 30 months versus 14.2 months, respectively [31].

For patients with PD-L1 expression between 1-49% or PD-L1-negative tumors, pembrolizumab is typically used in combination with chemotherapy [33,34]. Two pivotal studies, KEYNOTE-189 and KEYNOTE-407, support this combination therapy approach. In KEYNOTE-189, pembrolizumab was combined with pemetrexed and platinum chemotherapy in patients with nonsquamous NSCLC, demonstrating significant improvements in both OS and PFS, irrespective of PD-L1 expression [33]. Similarly, KEYNOTE-407 evaluated pembrolizumab with carboplatin and either paclitaxel or nab-paclitaxel in patients with squamous NSCLC, also showing a marked survival benefit compared to chemotherapy alone [34].

PD-L1 expression is assessed using the Tumor Proportion Score (TPS), where a score of ≥50% qualifies patients for pembrolizumab monotherapy, while lower scores often indicate the need for combination therapy [35]. For nonsquamous NSCLC, pembrolizumab is typically paired with pemetrexed and a platinum-based agent, while for squamous NSCLC, it is combined with carboplatin and paclitaxel/nab-paclitaxel. Importantly, pembrolizumab is not indicated for patients with EGFR or ALK mutations, as targeted therapies are more effective in those cases [30-35]. The introduction of pembrolizumab has shifted the paradigm of NSCLC treatment, offering personalized therapy with improved survival outcomes based on PD-L1 expression.

Nivolumab (Opdivo) in combination with ipilimumab (Yervoy), a CTLA-4 inhibitor, has emerged as an important option in the first-line treatment of advanced or metastatic non-small cell lung cancer (NSCLC), particularly for patients whose tumors express PD-L1 ≥1% [36,37]. This combination leverages dual immune checkpoint inhibition, with nivolumab targeting the PD-1/PD-L1 pathway and ipilimumab enhancing T-cell activation via CTLA-4 blockade. The CheckMate-227 trial demonstrated significant benefits for this combination, showing improved overall survival (OS) compared to chemotherapy, particularly in patients with PD-L1 expression ≥1%. Even in those with PD-L1-negative tumors, the combination showed efficacy, offering an immunotherapy-based alternative to chemotherapy [38]. Further evidence from the CheckMate-9LA trial supported the addition of two cycles of platinum-based chemotherapy to nivolumab and ipilimumab in patients regardless of PD-L1 status. This combination also demonstrated survival advantages, particularly for those who might not have otherwise been ideal candidates for immunotherapy alone [39].

The nivolumab and ipilimumab regimen is especially advantageous for patients who may not tolerate long-term chemotherapy due to its more favorable toxicity profile compared to traditional chemotherapy. As a result, it offers a valuable first-line treatment option, particularly for patients who wish to avoid chemotherapy, with clinical trials confirming its efficacy in improving long-term outcomes [36-39]. This dual immunotherapy combination represents an innovative approach, focusing on boosting the patient's immune response to effectively target and eliminate cancer cells in NSCLC. PD-1 inhibitors, such as pembrolizumab and nivolumab have significantly transformed the treatment of advanced or metastatic NSCLC particularly as first-line therapies. These therapies are associated with fewer and less severe side effects compared to chemotherapy, with common immune-related adverse events (irAEs) being mild, such as fatigue and rash, although serious irAEs like pneumonitis or colitis can occur. Additionally, PD-1 inhibitors offer a chemotherapy-free treatment option for patients with high PD-L1 expression, providing an effective alternative with a more favorable toxicity profile [40]. For those with lower PD-L1 expression (1-49%) or no PD-L1 expression, combination approaches with chemotherapy or other immunotherapies, such as nivolumab with ipilimumab, have shown efficacy across a broader patient population [39].

However, PD-1 inhibitors come with certain limitations. Their efficacy is often lower in patients with PD-L1-negative or low-expressing tumors, limiting the use of monotherapy in these populations [33,34]. Additionally, PD-1 inhibitors can take weeks or months to show a clinical response, making them less suitable for patients with rapidly progressing disease who need immediate tumor reduction [40]. Despite their generally favorable side effect profile, PD-1 inhibitors can cause irAEs, which may require immunosuppressive treatments and can pose serious risks [41]. Moreover, not all patients respond to PD-1 inhibitors, and some may develop acquired resistance over time, though the mechanisms behind this are not fully understood [41]. PD-L1 expression, the primary biomarker used to guide therapy, is not always predictive of response, as some patients with high expression may not respond, and others with low expression may benefit, complicating treatment decisions. Finally, cost and accessibility remain significant challenges, as PD-1 inhibitors are expensive and may not be readily accessible to all patients or healthcare systems [40]. Overall, PD-1 inhibitors have revolutionized NSCLC treatment by offering a personalized, mechanism-based therapy that significantly improves outcomes for many patients, particularly when used in combination approaches. However, the variability in response rates, potential for immune-related toxicity, and limitations tied to biomarker expression require careful patient selection and management.

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Second-Line and Later Therapy for NSCLC

Pembrolizumab and nivolumab have shown significant efficacy as second-line and later therapies for non-small cell lung cancer (NSCLC) in patients who have progressed after platinum-based chemotherapy. Both agents target the programmed death-1 (PD-1) pathway, which tumors often exploit to evade immune detection. In clinical trials, nivolumab demonstrated improved overall survival compared to docetaxel, a standard second-line chemotherapy, for previously treated patients with NSCLC, irrespective of PD-L1 expression levels. Similarly, pembrolizumab showed efficacy in this setting, particularly in patients whose tumors expressed PD-L1, with higher expression levels correlating with better responses. Notably, patients with PD-L1 tumor proportion scores (TPS) of 50% or more have derived greater benefits from pembrolizumab compared to standard chemotherapy. These findings underscore the importance of PD-L1 status as a biomarker for selecting patients likely to benefit from pembrolizumab, while nivolumab may be considered more broadly across PD-L1 expression levels therapies [42-45].

Combination Therapies

The use of PD-1 inhibitors in combination with other therapeutic modalities has emerged as a key strategy to enhance the efficacy of immunotherapy in NSCLC. Combining PD-1 inhibitors such as pembrolizumab or nivolumab with chemotherapy has demonstrated superior outcomes in clinical trials, particularly in first-line treatment settings. For example, pembrolizumab combined with platinum-based chemotherapy has shown significantly improved overall survival and progression-free survival compared to chemotherapy alone in patients with metastatic NSCLC. This combination appears to stimulate the immune system while simultaneously targeting the cancer cells directly, creating a more favorable environment for immunotherapy. Additionally, combination strategies involving PD-1 inhibitors and other immunotherapies, such as CTLA-4 inhibitors (e.g., ipilimumab), are being explored. Nivolumab combined with ipilimumab has shown promising results, particularly in tumors with high tumor mutational burden (TMB). Targeted therapies, including those directed at oncogenic drivers like EGFR or ALK mutations, are also being investigated alongside PD-1 inhibitors, although these combinations present more complexity and challenges in patient selection [42-45].

Biomarkers and Personalized Medicine

The role of biomarkers in selecting patients for PD-1 inhibitor therapy in non-small cell lung cancer (NSCLC) is pivotal for the success of immunotherapy. Two key biomarkers, PD-L1 expression and tumor mutational burden (TMB), have been instrumental in identifying patients likely to benefit from treatment with PD-1 inhibitors like pembrolizumab and nivolumab [46]. PD-L1 expression, as assessed by immunohistochemistry, is widely used as a predictive marker. The degree of PD-L1 expression on tumor cells is positively correlated with the likelihood of response to PD-1 inhibitors. Studies have demonstrated that patients with higher PD-L1 expression, particularly those with over 50% tumor cell staining, tend to have better outcomes from immunotherapy, leading to its adoption as a selection criterion for these treatments. However, PD-L1 expression alone is not a perfect predictor, as some patients with low or no PD-L1 expression still respond to PD-1 inhibitors. This has prompted ongoing research into additional biomarkers to complement PD-L1 in refining patient selection [47]. Another crucial biomarker, tumor mutational burden (TMB), has emerged as a complementary indicator of response to PD-1 inhibitors. TMB refers to the number of somatic mutations present in a tumor genome, with a high TMB reflecting an increased likelihood of generating neoantigens that can be recognized by the immune system. Several studies, including analyses from the CheckMate 227 trial, have shown that patients with a high TMB are more likely to benefit from PD-1/PD-L1 inhibitor therapy, independent of PD-L1 expression. As a result, TMB is being incorporated into clinical practice to guide treatment decisions, although it is not yet universally applied [48].

In addition to PD-L1 and TMB, other emerging biomarkers are being investigated to enhance the precision of immunotherapy. For instance, the expression of immune-related genes and the presence of specific immune cell populations in the tumor microenvironment are being explored as potential predictors of response. The identification of tumor-infiltrating lymphocytes (TILs), which indicate an active immune response within the tumor, has been linked to better outcomes in immunotherapy. Similarly, genetic mutations in DNA repair pathways, such as deficiencies in mismatch repair (MMR), have been associated with heightened sensitivity to PD-1 inhibitors. Moreover, circulating biomarkers, such as blood-based TMB and liquid biopsy techniques, offer less invasive options for predicting response and monitoring treatment efficacy in real-time [49].

As the field of personalized medicine continues to evolve, the integration of multiple biomarkers will likely lead to more precise and individualized approaches to PD-1 inhibitor therapy. This strategy promises to maximize therapeutic benefit while minimizing unnecessary toxicity in patients with NSCLC. While PD-L1 expression and TMB currently form the backbone of biomarker-driven immunotherapy, emerging biomarkers are set to refine and improve patient selection further, ultimately advancing the effectiveness of treatment strategies [50].

Adverse Events and Immune-Related Toxicities

PD-1 inhibitors are associated with a distinct profile of immune-related adverse events (irAEs), which result from their mechanism of action—enhancing immune activity against cancer cells. Common irAEs include dermatologic issues such as rash and pruritus, gastrointestinal symptoms like diarrhea and

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colitis, and endocrine disorders such as hypothyroidism and adrenal insufficiency. In rare cases, more severe toxicities like pneumonitis, hepatitis, and myocarditis can occur. Management of irAEs typically involves immunosuppressive therapy, such as corticosteroids, particularly for moderate to severe toxicities. For mild irAEs, treatment interruption may suffice. Monitoring patients for irAEs is crucial, especially during long-term use, as some toxicities may develop late into treatment or even after discontinuation. Early recognition and intervention are key to minimizing complications and maintaining patients on therapy [51,52].

Conclusion

PD-1 inhibitors, particularly pembrolizumab and nivolumab, have redefined the therapeutic landscape of advanced non-small cell lung cancer (NSCLC), offering improved survival outcomes, especially when used in biomarker-driven approaches. Their success as first-line therapies, either as monotherapy or in combination with chemotherapy, has been well-documented in key clinical trials such as KEYNOTE-021G, KEYNOTE-189, and CheckMate-227. Furthermore, their use in second-line settings has provided new treatment avenues for patients who have progressed after traditional chemotherapy. The identification of biomarkers, including PD-L1 expression and tumor mutational burden (TMB), has allowed for a more targeted and personalized approach to therapy, optimizing patient selection and enhancing therapeutic efficacy.

Despite their benefits, PD-1 inhibitors are not without limitations. Immune-related adverse events (irAEs), while generally manageable, require careful monitoring and intervention to prevent serious complications. Additionally, the response rates vary, with some patients experiencing resistance or suboptimal outcomes, particularly those with low PD-L1 expression or rapidly progressing disease. Future directions in NSCLC treatment will likely involve refining biomarker strategies, enhancing combination therapies, and addressing the challenges of resistance to maximize patient benefit. Overall, PD-1 inhibitors represent a critical advancement in NSCLC management, significantly improving the prognosis for many patients while paving the way for continued innovation in immunotherapy.

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