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(REVIEW ARTICLE)

A systematic assessment on emerging drug in the treatment of non-small cell lung cancer -pembrolizumab

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Abstract

Non-small cell lung cancer (NSCLC) is a leading cause of cancer-related death. While surgery can cure many patients, a significant number may still succumb to the disease over time, even with additional chemotherapy or radiation therapy. Immunotherapies including T-cell therapy, cytokine therapy, and oncolytic viruses, have shown promise in cancer treatment. Checkpoint inhibitors, in particular, have demonstrated encouraging response rates (RRs). Pembrolizumab, a human-derived anti-PD-1 antibody, is one such emerging therapy. This analysis aims to determine the effectiveness of the emerging drug pembrolizumab in treating NSCLC. A systematic assessment was performed by conducting a literature search of previously conducted studies using various search databases and the relevant studies and articles were included in the final assessment of the review. Immune checkpoint inhibitors (ICIs) have emerged as a viable therapeutic option for NSCLC, including in the front-line setting. Pembrolizumab should be considered a standard first-line treatment for NSCLC patients. Additionally, patients with advanced NSCLC have benefited from immunotherapy advancements, particularly checkpoint inhibitors targeting PD-1/PD-L pathways.

Keywords: Non-small cell lung cancer; Pembrolizumab; Emerging drug; Chemotherapy; PD-1/PD-L antibody

1. Introduction

The root cause of tumor-related mortalities in the US is lung cancer. People with non-small cell lung cancer (NSCLC) who were first identified with early-stage disease had lobectomy as their primary treatment choice(1,2). After local control, radiation or surgery was frequently effective. Stereotactic body radiation therapy (SBRT) is a promising novel non-conventional treatment option for patients with initial-stage, negative-node cancer(3). Three years later, the localized restriction has increased to approximately 90%. Furthermore, 92% and 73% of patients with T1 and T2 disease had local control five years after undergoing SBRT even for operable patients(1). Conventionally fractionated radiotherapy (RT) is one of the treatments available for individuals with operable node-positive or locally advanced cancer (RT)(4). Primary surgery is performed before or after platinum-based chemotherapy in suitable locally advanced patients(5). These patients are frequently staged as IIIA (AJCC v7), and post-operative RT is advised in the event of persistent N2 lymph nodes(6). Chemo-radiotherapy before surgery is another approach to treat resectable N2 disease. Chemotherapy and radiation are used to treat patients with locally advanced, unresectable NSCLC(7). These treatments can be done simultaneously or sequentially. NSCLC is leading cancer-related cause of death. Surgery cures many patients, but many will still die, even with or without additional chemo and radiation, especially in the long run. At diagnosis, more than half of patients are informed that they have a fatal disease. Immunotherapies include T-cell therapy, cytokine therapy, and viruses that kill cancer cells. Checkpoint inhibitors are being extensively studied because of promising response rates (RRs). There is substantial evidence that they work against NSCLC(8). Pembrolizumab is also available as an anti-PD-1 antibody derived from human cells. After getting FDA approval in 2015, it became the

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only checkpoint inhibitor that could be used as first-line therapy for metastatic NSCLC resistant to platinum(4). According to the findings of the KEYNOTE-001 and KEYNOTE-010 trials, pembrolizumab was approved for second-line therapy by the FDA. Initially, it was only recommended for people with a high level of PD-L1 expression(9). In 2017, pembrolizumab and chemotherapy drugs like carboplatin were approved as the front-line therapy for metastatic non-squamous NSCLC(10).

Significant immune modulation activity is observed in NSCLC following immunotherapy and radiation treatment (RT). Through radio sensitization and a prolonged systemic immune response, the innate and adaptive immune systems may help control the systemic disease(10). This systematic review aims to determine the effectiveness of pembrolizumab in treating NSCLC.

2. Materials and methodology

A comprehensive literature search was conducted using PubMed, Embase, Web of Science, clinicaltrials.gov, and Cochrane Library databases up to October 2022 to identify studies on NSCLC. The reference lists of the included articles and the relevant literature were also manually searched. The following primary search terms were used: NSCLC, Pembrolizumab as Monotherapy, Pembrolizumab with RT, pembrolizumab as a neoadjuvant therapy, pembrolizumab as 1st line therapy, pembrolizumab as 2nd line therapy, pembrolizumab safety and efficacy, and pembrolizumab trials. Relevant studies and articles were included in the initial assessment of the review, and duplicate records were removed. The included studies were screened based on titles and abstracts, with some studies being excluded. Subsequently, a full-text assessment was conducted to include the most relevant studies and articles (Figure. 1)

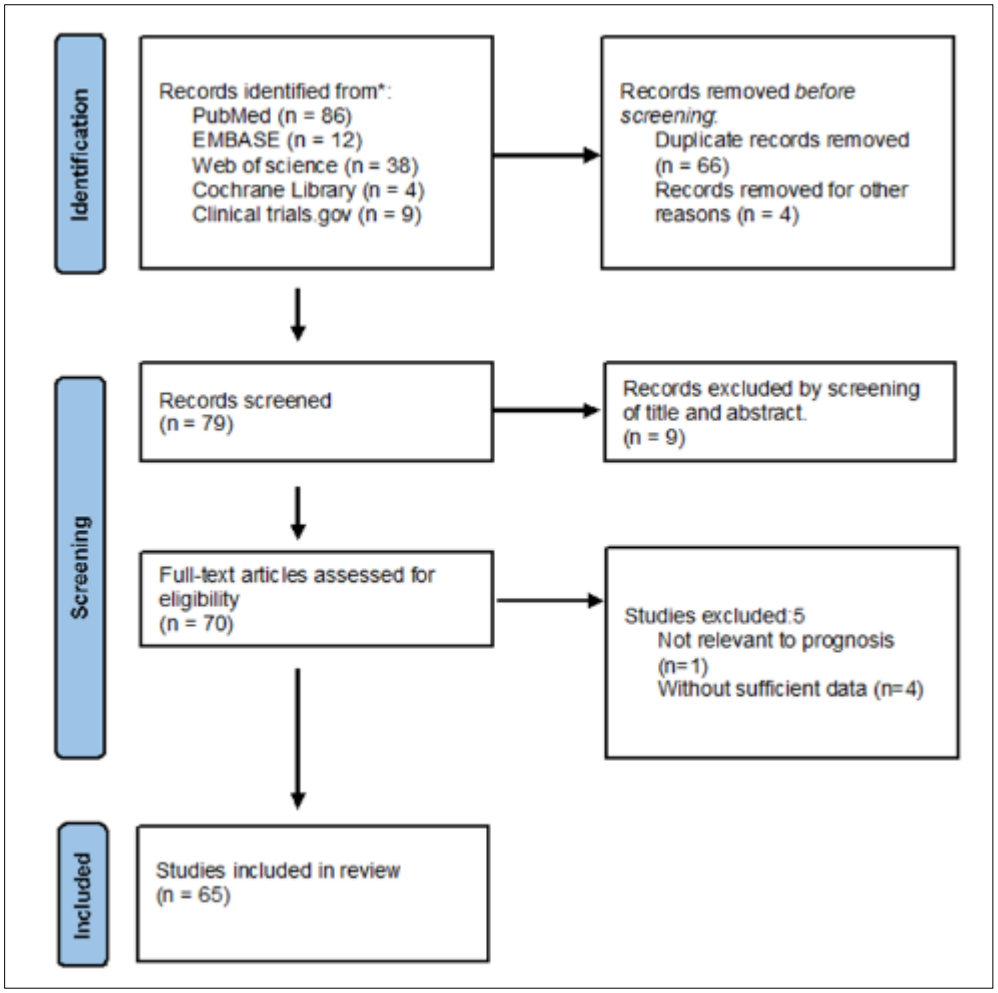

Figure 1 Flowchart of the study screening and selection process of this systematic review

3. Pembrolizumab as Monotherapy

The approved immunotherapy medication for first-line therapy for advanced NSCLC is pembrolizumab alone, which targets the PD-1 receptor(11). Patients who received immunotherapy had a long-term advantage as 37% of squamous cell carcinomas and 34% of non-squamous cell carcinomas maintained their efficacy two years after treatment(12,13). In the non-randomized Phase I Keynote 001 study, pembrolizumab as monotherapy demonstrated a remarkable advantage in the treatment of NSCLC patients, achieving a RR **of** 58.3%(14). Due to the importance of these findings, the PD-L1 TPS ≥50% threshold was chosen as the cutoff to determine which patients would receive pembrolizumab as monotherapy in first-line therapy(15). Furthermore, promising results for second-line pembrolizumab in patients with PD-L1-positive tumors were reported(16). For use as first-line treatment for advanced NSCLC with high PD-L1 expression and without EGFR or ALK mutations, pembrolizumab received approval from the FDA and the EMA in October 2016 and December 2016, respectively(17). Currently, pembrolizumab is only available as a first-line treatment for patients with PD-L1 TPS ≥50%, who represent just over 30% of all individuals with metastatic NSCLC(18).

Pembrolizumab was recently compared to chemotherapy in the open-label Phase III Keynote 042 study for NSCLC patients with PD-L1 TPS ≥1%, excluding those with sensitizing EGFR mutations or ALK rearrangements (19)**.** This study aimed to expand access to immunotherapy. Patients were randomly assigned to receive either intravenous pembrolizumab 200 mg every three weeks for up to 35 cycles or carboplatin in combination with either paclitaxel or pemetrexed, depending on tumor histology, for up to six cycles. The primary endpoint, OS, was evaluated in sequential subgroups with PD-L1 TPS of ≥50%, ≥20%, and ≥1%. Secondary endpoints included safety (in the TPS ≥1% group), PFS, and RR. However, further investigation is still ongoing.Comparing first-line pembrolizumab to platinum-based chemotherapy**,** the improvement in survival was notable(20). Pembrolizumab's safety profile was consistent with previous findings (G. Lopes et al., 2018). Despite longer treatment exposure, it demonstrated a lower incidence of grade 3 to 4 therapy-related adverse events compared to chemotherapy(21). This was the first study to confirm the superiority of immunotherapy over chemotherapy in terms of OS as the primary endpoint. Due to pembrolizumab's favorable toxicity profile, it may **be** more widely used in NSCLC patients who are PD-L1 positive. However, for now, clinical practice is unlikely to change significantly, as the true benefit is observed mainly in the PD-L1 ≥50% subgroup(22).

According to investigations by Checkmate057, Keynote010, POPLAR, and OAK47, pembrolizumab, nivolumab, and atezolizumab are effective treatment options for patients with metastatic NSCLC who have progressed following chemotherapy(4,23,24). Higher PD-L1 expression levels are associated with greater benefit**.** In addition to Keynote024's evidence(25) demonstrating that pembrolizumab is beneficial for patients with PD-L1 expression ≥50% **in** first-line NSCLC therapy, Gilberto Lopes' presentation of Keynote042 at the 2018 ASCO annual meeting showed that pembrolizumab can also benefit patients with PD-L1 expression ≥1%(26). This treatment is currently restricted to patients with high tumor mutational burden (TMB-H), with those exhibiting strong PD-L1 expression deriving the greatest benefit(27).

4. Combination of pembrolizumab with chemotherapy

Immunotherapy and chemotherapy are combined because cytotoxic chemotherapeutic drugs may a) trigger immunological activity(28), b) increase tumor antigen (Ag) presentation(29), c) reduce regulatory T cells(30) and myeloid-derived suppressor cells(31), and d) produce PD-L1 expression in tumor cells(29). Pembrolizumab with pemetrexed and carboplatin became front-line therapy for progressed non-squamous NSCLC, regardless of PD-L1 status(32). Patients receiving pembrolizumab had significantly longer OS than those receiving chemotherapy. However, pembrolizumab also increased treatment-related toxicity in the PD-L1 TPS group(33).

Immunotherapy and chemotherapy have been the subjects of several studies for those with metastatic malignancies who have never undergone treatment. These trials showed beneficial outcomes despite PDL-1 status, making them a better choice for people with lower PDL-1 levels. Pemetrexed with platinum-based chemotherapy plus pembrolizumab was examined in patients with NSCLC in Keynote189(34,35). Patients had four rounds of pembrolizumab maintenance treatment after receiving pemetrexed, platinum-based chemotherapy, and pembrolizumab. Pembrolizumab plus chemotherapy improved OS in previously untreated individuals with advanced NSCLC, with benefits observed across all PD-L1-positive groups. OS was 69.2% in the pembrolizumab group compared to 49.4% in the placebo group, with hazard ratios (HRs) for disease progression or mortality of 0.49(33) and 0.59 in patients with PD-L1 expression of 1% and 1–49%, respectively(2). It was randomized between carboplatin plus paclitaxel, nab-paclitaxel plus pembrolizumab, and placebo groups. Following four cycles of combination therapy, patients received 35 cycles of pembrolizumab or placebo. Regardless of PD-L1 expression, pembrolizumab demonstrated a significant improvement in OS compared to placebo(36,37). Overall survival (OS) increased by 36% (HR 0.64), which was attributed to

pembrolizumab(38). The addition of pembrolizumab to the treatment regimen also resulted in a 44% improvement in progression-free survival (PFS) (HR 0.56)(37). These benefits were observed in patients with metastatic squamous disease, regardless of PD-L1 status(39).

5. Pembrolizumab with Radiotherapy

T-cell checkpoint drugs have substantial and lasting efficacy in some advanced lung tumor patients(23,24,34,40). Anti-PD-L1 drugs demonstrate a response in 20% of previously treated lung cancer patients. The therapy is durable and well-tolerated. T-cell checkpoint drugs have shown an improvement in PFS in melanoma patients compared to a placebo(35). T-cell checkpoint inhibitors should be considered for use in initial-stage lung tumor patients. Since only a minority of patients benefit from anti-PD-L1 drugs, effective combination strategies are needed to enhance the effectiveness of immunotherapy(41,42). Combining immunotherapy with RT is promising approach for treating lung cancer patients(43). Immunotherapy enhances the engagement of cytotoxic lymphocytes with tumor cells during radiation therapy**.** RT is well-suited for synergistic effects with PD-1/PD-L1 blockades. Stereotactic ablative radiotherapy (SABR) and PD-1 inhibitors have demonstrated the potential to eliminate cancer. This approach has also shown effectiveness in eradicating lymph node involvement and metastases. The "abscopal effect" explains their potential application in brain metastases (44). In NSCLC, clinical trials are assessing the potential of radiation to enhance immunotherapy efficacy. The combination of immunotherapy and radiation has been shown to improve overall response rate (ORR), PFS, and OS compared to immune checkpoint inhibitors (ICIs) alone. However, this combination therapy may also increase pulmonary toxicity(4).

Combining RT with chemotherapy has proven to be more effective than either treatment alone, leading to improved local and systemic disease control. Beyond merely radiosensitizing cancer cells, combined modality therapy may enhance treatment outcomes by modifying tumor-host interactions. Immunotherapy includes adoptive T-cell transfer, oncolytic viruses, and cytokine therapy. Immunotherapy using ICIs has demonstrated high RRs and is gaining increasing attention. This review focuses on ICIs and RT in operable NSCLC. However, chemo-RT, immunotherapy, and surgery carry potential risks that remain underexplored. Preoperative RT can cause lung fibrosis or edema, which may complicate surgery or impair wound healing(44). Similarly, postoperative RT may lead to pneumonitis or long-term lung fibrosis, impacting lung function(44).

6. Effect of pembrolizumab as a neoadjuvant therapy

Adoptive cell transfer, vaccinations, and tumor necrosis factor (TNF)-based treatments are among the emerging neoadjuvant immunotherapies under clinical investigation(45). In a clinical trial, patients with Stage IIB-IIIB NSCLC received cisplatin and gemcitabine as part of a neoadjuvant chemo-immunotherapy regimen, followed by random assignment to either a placebo or recombinant TNF coupled with thymosin-alpha. The RR for chemo-immunotherapy was 71%, compared to 50% for neoadjuvant chemotherapy alone(46). In a more recent study, NK cell counts declined in the chemotherapy group but remained stable in the chemo-immunotherapy group. A meta-analysis of randomized trials involving 472 participants found that adjuvant adoptive immunotherapy significantly reduced the relative mortality hazard by 39%(47).

7. Pembrolizumab as second-line therapy:

Pembrolizumab is the most widely used checkpoint inhibitor and has received FDA approval in the US for NSCLC treatment as a second-line therapy. The KEYNOTE-010 trial confirmed its efficacy. In this randomized, placebo-controlled, Phase III study, pembrolizumab was compared to docetaxel, the current gold standard chemotherapy. OS was significantly improved with pembrolizumab at both dosages compared to chemotherapy: at 2 mg/kg, the HR was 0.71, and at 10 mg/kg, the HR was 0.61. Both doses were well-tolerated, with fewer Grade 3-5 adverse effects than docetaxel(38). Patients with a PD-L1 expression positivity rate above 1% demonstrated the greatest OS benefits with pembrolizumab(38).

8. Pembrolizumab as first-line therapy:

When there are no contraindications to immunotherapy, pembrolizumab is recommended for patients with advanced-stage PS 0-1 NSCLC who do not have driver mutations and whose tumors express PD-L1 at levels of 50% or higher(15). For all Stage IV PS 0-1 NSCLC patients without driver mutations, platinum-based doublet chemotherapy is recommended, even if PD-L1 expression is low (TPS <50%) or unknown(5). Compared to supportive care, cisplatin monotherapy improves OS and provides better quality of life (QoL**)**(49). Meta-analyses have shown that cisplatin-based

combination therapies achieve higher RRs and slightly longer OS compared to carboplatin-based regimens(50). If a patient has a known sensitivity to cisplatin, carboplatin may be considered as an alternative chemotherapy option(51). Non-platinum regimens have demonstrated lower efficacy compared to platinum-based regimens(52). Recent Phase III trials have shown that adding immunotherapy to platinum-based chemotherapy significantly improves efficacy, regardless of PD-L1 status(33,36,53).

8.1. Squamous cell lung cancer (SCC)

For PS 0-1 SCC patients without significant multiple morbidities, third-generation cytotoxic drugs are recommended as an addition to platinum-based doublet chemotherapy(8). 4 cycles are advised, with up to 6 cycles considered in certain circumstances(8,54).

The chemotherapy regimen should be selected based on the anticipated adverse effect profile. A Phase III trial reported that a combination of nab-paclitaxel and carboplatin had greater RRs than paclitaxel/carboplatin while reduced neurotoxicity(55). In recent times, two randomized phases III studies have demonstrated that, in SCC, the addition of pembrolizumab to the recommended front-line chemotherapy regimen results in significantly longer OS and PFS(9) than chemotherapy alone(56).

8.2. Non-squamous cell lung cancer (Non-SCC)

People suffering from non-SCC who have low (TPS <50%) or unidentified PD-L1 levels can receive any platinum-based doublet with a third-generation drug(53). Pemetrexed-based combination chemotherapy is a potential treatment option. According to findings from a meta-analysis and a planned subgroup analysis of a randomized Phase III study, this regimen had a marginal but statistically significant survival advantage over gemcitabine- or docetaxel-based combinations(53,57). Two randomized clinical trials have demonstrated that bevacizumab/paclitaxel/carboplatin combination chemotherapy, followed by maintenance bevacizumab, improves OS. Thus, patients with metastatic PS 0-1 non-SCC who have no contraindications to antiangiogenic therapy may receive it(9,50). Patients with PS 0-1 who have at least a stable disease and have recovered from front-line chemotherapy's residual toxicity may consider maintenance therapy. After four cycles of platinum-based chemotherapy without pemetrexed, pemetrexed switch maintenance may be considered(58). Patients with controlled disease after four cycles of pemetrexed platinum-based chemotherapy should be evaluated for continuous pemetrexed maintenance(20,58). In recent years, three randomized Phase III trials have demonstrated that, regardless of PD-L1 expression, the addition of pembrolizumab to front-line chemotherapy in non-SCC significantly prolonged OS and PFS(59). Among the combinations, pembrolizumab with pemetrexed and platinum-based chemotherapy is the only regimen approved by the European Medicines Agency(20).

9. Safety and efficacy/Toxicity

The RRs, PFS, and OS of patients treated with anti-PD-L1 therapies are all higher than those treated with conventional **chemotherapy**. The degree to which tumor cells express PD-L1 can help guide clinical decision-making. Notable examples include medications that block the PD-1/PD-L1 pathway, which numerous cancers use to evade immune surveillance and editing. To explain further, while PD-L1 is expressed on the surface of tumor cells, PD-1 is strongly expressed on the surface of activated T cells in response to infection. The immune response is suppressed when PD-1 binds to its ligand, PD-L1, forming a complex that dampens the cytotoxic T-cell response. By exploiting this pathway, tumor cells evade antitumor activity by suppressing the immune system**.** Inhibitors of PD-1 or PD-L1 restore the anti-cancer activity of cytotoxic T cells by blocking this immune-suppressive signaling(9-11). Cancer biomarkers, which are measurable biochemical indicators of tumor pathology or treatment response, are also crucial **for** immunotherapy, as they aid in screening, diagnosis, and prognosis(60).

9.1. Toxicity

Most cancer patients receiving PD-1/PD-L1 blockade therapy do not experience significant improvements, and only a small proportion benefit from single-agent immune checkpoint inhibitors. This has driven research towards developing more powerful combination therapies. Additionally, a major limitation of tumor-targeting therapies is that the effectiveness of targeted drugs is usually restricted to cancers with specific mutation sites, whereas cancer cells often harbor multiple mutation sites(2,4). Immune-related adverse events (AEs) are common during anti-PD-1/L1 blockade therapy**,** including pneumonitis, skin toxicity, arthralgia, hepatitis, colitis, and endocrinopathy. Corticosteroids are frequently used to manage immune-related AEs, and their use does not compromise the efficacy of anti-PD-1/L1 therapies(60).

10. Pembrolizumab trials

- Study of Pemetrexed+Platinum Chemotherapy with or Without Pembrolizumab in Participants with First-Line Metastatic Non-squamous NSCLC -Japan Extension Study.
  This study aims to evaluate pembrolizumab's safety in combination with pemetrexed/platinum chemotherapy versus pemetrexed/platinum chemotherapy alone in adult Japanese participants with malignant non-squamous NSCLC who had not received prior treatment for advanced disease. Participants were randomly allocated **to receive** pembrolizumab in combination with pemetrexed/platinum. This interventional, randomized, double-blind Phase III trial began on February 22, 2016. A total of 40 participants were selected based on inclusion criteria, which required stage IV non-squamous NSCLC, sufficient organ function, and a minimum survival expectancy of three months**.** It is an ongoing study, estimated to end on February 8, 2023(61).

- Study of Pembrolizumab Versus Platinum-Based Chemotherapy for Participants with Programmed Cell Death-Ligand 1-Positive Advanced or Metastatic NSCLC.
  In this interventional, randomized, open-label Phase III trial, participants with PD-L1-positive NSCLC were randomly **allocated** to receive pembrolizumab as monotherapy for up to 35 cycles or standard-of-care platinum-based chemotherapy. The trial commenced on October 30, 2014, and concluded on February 26, 2018. A total of 1274 participants were selected, with inclusion criteria **requiring** no prior treatment for advanced NSCLC, **a** minimum survival expectancy of three months, and sufficient organ function. The study was completed as planned(62).

- Study of Pembrolizumab Compared to Platinum-Based Chemotherapies in Participants with Metastatic NSCLC.
  This interventional, randomized, open-label Phase III trial aimed to evaluate the efficacy and safety of pembrolizumab compared with platinum-based chemotherapy in previously untreated participants with stage IV, PD-L1 strongly expressing NSCLC**.** The study began on August 25, 2014, and was completed on May 9, 2016. A total of 305 participants were enrolled, meeting the inclusion criteria of stage IV NSCLC, no prior therapy for advanced NSCLC, and a minimum survival expectancy of three months with sufficient organ function**.** The study was completed as planned(63).

- Study of Two Doses of Pembrolizumab Versus Docetaxel in Previously Treated Participants with NSCLC.
  In this trial, two doses of pembrolizumab were compared with docetaxel in participants whose disease had progressed after platinum-containing systemic therapy**.** Participants were randomly allocated **to** receive either pembrolizumab 2 mg/kg once every three weeks, pembrolizumab 10 mg/kg, or docetaxel 75 mg/m^2. This interventional Phase II/III randomized trial enrolled 1354 participants**,** with inclusion criteria requiring NSCLC and a minimum survival expectancy of three months**.** The trial began on August 9, 2013, and concluded on September 30, 2020**.** The research was completed as planned(64).

- Study of Pembrolizumab in Participants with Progressive Locally Advanced or Metastatic Carcinoma, Melanoma, or NSCLC.
  The key hypotheses of this study were that pembrolizumab would demonstrate tolerable safety, exhibit a clinically significant disease control rate in participants with melanoma and NSCLC, and show a more substantial RR in participants whose tumors expressed PD-L1**.** This interventional Phase I study enrolled 1260 participants and was conducted from March 4, 2011, to December 11, 2018**.** The inclusion criteria required a histological or cytological diagnosis of melanoma (MEL) or any type of carcinoma**, with intolerance to** established standard medical anti-cancer therapies for the respective tumor type. The study was completed as planned(65).

11. Future Recommendations

We must first determine **the** optimal dosage, frequency, and treatment sequence for combination therapies. We must also be careful to avoid ineffective combinations that may increase toxicity. Secondly, new and more accurate immunological biomarkers are expected to be developed for patient selection, in addition to the biomarkers previously mentioned. Third, an extensive study of NSCLC stages, patient age, tumor microenvironment (TME), and metastatic cancer types is required to improve the accuracy of combination therapy(10).

12. Conclusion

ICIs have become a viable therapy option, even as a front-line treatment for NSCLC**.** Pembrolizumab should **be** considered a conventional front-line therapy for NSCLC patients with a satisfactory performance status whose tumors express PD-L1 at levels above 50%. ICIs can restore and maintain antitumor immunity by inhibiting the mechanisms that suppress the immune response to cancer. There are four PD-1/PD-L1 blocking drugs in clinical use**,** and immunotherapy-based regimens are recommended either alone or in combination with chemotherapy. Currently, active combination trials are evaluating ICIs alongside chemotherapy, targeted therapy, and other immunotherapies. While initial treatment recommendations for ICIs have remained consistent, their use in oncogene-driven subpopulations remains controversial. **For** many patients without targetable oncogenic drivers, choosing between therapy option**s is challenging** due to the limited number of direct cross-comparison studies. The search for predictive **biomarkers** to identify patients who would benefit most from ICIs is ongoing**.** Most treatment studies agree that PD-L1 protein expression, assessed by immunohistochemistry, and tumor mutational burden (TMB) are the most reliable predictors of response. However, further research is needed **t**o refine patient selection and determine the most effective combination therapies for NSCLC in different clinical settings. Patients with advanced NSCLC have also benefited from the development of immunotherapy, particularly checkpoint inhibitors targeting PD-1/PD-L1.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare no conflict of interest.

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