Outcomes of Clinical Trials on the Roles of Immune Checkpoint Inhibitors in the Management of Lung Cancers: A Comprehensive Review

Saheed E. Sanyaolu[1], Maryam O. Adebayo[2], Oluwaseun O. Adekoya [3], Halimah O. Alao[4] and Fadilulahi A. Usman[5]

[1]Faculty of Pharmacy, Olabisi Onabanjo University, Ago-Iwoye, Ogun State, Nigeria
[2]University of Ibadan, Oyo State, Nigeria
[3]University of Saskatchewan, Canada
[4]Department of Pharmacognosy, University of Ilorin, Kwara State, Nigeria
[5]Department of Molecular Biology and Biotechnology, Nigerian Institute of Medical Research, Nigeria

Correspondence to: Saheed E. Sanyaolu, saheed.e.sanyaolu@gmail.com

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ABSTRACT

Lung cancer is a deadly clinical condition that necessitates critical clinical intervention for its management. This comprehensive review summarizes findings from clinical trials that assessed the efficacy and safety of immune checkpoint inhibitors (ICIs) for the management of lung cancer. Scientific databases were explored for reports from clinical trials on ICI roles in lung cancer management. Small cell lung cancer mostly develops from chronic smoking, and it is refractory to treatment, resulting in complications and death. On the other hand, many treatment modalities are available for non-small-cell lung cancer, including surgery, radiotherapy, and systemic therapy. ICIs, classified into programmed death-1, programmed death ligand 1 (PD-L1), and cytotoxic T-lymphocyte antigen 4 inhibitors, are used either alone or in combination with other targeted therapies or chemotherapy perioperatively to improve surgical outcomes for resectable lung cancer. Additionally, ICIs are also used in advanced unresectable metastatic lung cancer to reduce tumor growth or as palliative treatment to prolong survival and improve patients' quality of life. ICI monotherapy, compared to placebo and platinum-based chemotherapy, elicited positive clinical outcomes in patients with lung cancer, resulting in longer overall survival and progression-free survival with tolerable side effect profiles. Similarly, combination therapy comprising ICIs alongside tyrosine kinase inhibitors, platinum-based chemotherapy, or radiotherapy resulted in superior efficacy compared to drug combinations without ICIs but with higher incidences of adverse events. Notably, higher tumor expression of PD-L1 improved clinical response to ICIs.

Keywords: Immune checkpoint inhibitors, Non-small cell lung cancer, PD-L1 expression, Programmed death-1 inhibitor, Cytotoxic T-lymphocyte antigen 4 inhibitor

Highlights

- Immune checkpoint inhibitors (ICIs) were most investigated for the management of unresectable and advanced non-small-cell lung cancer
- Both ICI monotherapies and drug combinations containing ICIs showed superior efficacy compared to placebo and platinum-based chemotherapy.
- Patients with PD-L1 expression ≥50% experienced superior clinical benefits with ICIs

Introduction

Lung cancer is a group of neoplasms that originate from lung tissues, resulting in a substantial public health challenge. Lung cancer is a frequently diagnosed cancer globally and the most common cause of cancer deaths, with about 1.8 million deaths in 2022; additionally, new cases of lung cancer were reported to be close to 2.5 million worldwide in 2022.[1] The prognosis for lung cancer relies on multiple factors, including type, stage, and treatment modalities; the treatment outcomes and long-term survival rates associated with lung cancer are poor. Furthermore, lung cancer can result in complications such as pneumonia, heart failure, and metastasis to other organs, all of which are associated with high mortality risks.

Tobacco smoking is a widely known risk factor for lung cancer, and studies have shown that initiating smoking at a young age and chronic smoking substantially increase the risk of developing lung cancer.[1,2] Other notable risk factors include carcinogens such as asbestos, radon, arsenic, and biomass, genetic predisposition, and family history.[3] Therefore, measures targeted at controlling tobacco intake and air pollution, as well as early screening, particularly for those at high risk of this condition, are important for reducing its incidence. Common screening measures include chest radiographs, low-dose chest computed tomography, sputum cytology, fluorodeoxyglucose-positron emission tomography, magnetic resonance imaging, and biomarker testing.

Histology of Lung Cancer

Lung cancer is commonly classified, based on the type of cell affected, into small cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC), with diagnosis rates of <15% and 85–90%, respectively.[4] SCLC is predominantly caused by smoking; it is relatively more aggressive, has a poorer prognosis, and has limited treatment modalities than NSCLC. On the other hand, NSCLC is a more common type of lung cancer, and it has many subtypes—adenocarcinomas, squamous cell carcinomas, and large cell carcinomas.[5] United States Cancer Statistics[4] estimations of the respective prevalences of the types and subtypes of lung cancer in the US are indicated in Figure 1.

Similar to many other cancers, lung cancer, particularly NSCLC, is staged based on the American Joint Committee on Cancer TNM system, which comprises tumor, nodal involvement, and metastasis.[6] For lung cancer, the stages include 0, I, II, III, and IV.[7] The earliest stage, carcinoma in situ (stage 0), is characterized by a tumor in the lining of the lung or bronchi but no metastasis. In stage IV, the most advanced stage, cancer has metastasized to other parts of the body. Overall, the severity of cancer increases with increasing stages, and some stages are divided into sub-stages depending on the tumor size, location, or metastasis. Cancer

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staging is important for cancer prognostication and the design of clinical interventions.

Management of Lung Cancer

Treatment of lung cancer depends on the stage of the disease, and it may include surgery, radiotherapy, and systemic therapy.[8] These treatment modalities may be combined sequentially or simultaneously, depending on the treatment goal. Surgery is the gold standard treatment approach for resectable early-stage NSCLC.[9] This was traditionally undertaken through open thoracotomy; however, with technological advancements, video-assisted thoracoscopic surgery and robotic-assisted thoracic surgery have become common approaches for lung cancer resection, yielding better treatment outcomes.[10] Radiotherapy may be administered following surgical resection to reduce the risk of recurrence; however, its effectiveness as a postoperative therapy has been controversial.[10] Hence, routine administration of postoperative radiotherapy is uncommon. Contrastingly, radiotherapy alone may be recommended for patients with unresectable tumors, and it is also used as a palliative therapy.[2]

Systemic therapy, including chemotherapy, targeted therapy, and immunotherapy, may be combined with radiotherapy or used alone as an adjuvant treatment for advanced stages of lung cancer when surgical resection is not feasible or is declined by the patient.[11] For lung cancer, systemic therapy was historically limited to platinum-based agents and other chemotherapeutic agents. In recent years, systemic therapy has expanded to include targeted therapy and immunotherapy. These drug classes may be used as a neoadjuvant therapy to shrink tumors prior to resection, adjuvant therapy to reduce the postoperative risk of recurrence, or standalone treatment.[12] A notable class of immunotherapy drugs is the Immune checkpoint inhibitor (ICI) drug class, and it is discussed in detail in the subsequent sections of this review.

ICIs

ICIs, comprising programmed death-1 (PD-1), PD-L1, and cytotoxic T-lymphocyte antigen 4 (CTLA-4) inhibitors, are a class of monoclonal antibodies used as immunotherapy in the management of lung cancer.[13] This class of drugs targets the immune evasion and immunosuppressive mechanisms of tumor cells.

The process of immune evasion is complex, and it involves the PD-1/PD-L1 and CTLA-4 pathways. PD-1 is typically expressed at low levels in immune cells such as T cells and B cells.[14] The binding of PD-1 to its ligand (PD-L1) acts as a checkpoint in the immune system, inducing an inhibitory effect on the T cells and preventing the cytotoxic effects of T cells on tumor cells. Therefore, high expression of PD-1/PD-L1 on tumor cells facilitates their escape from immune cells and promotes their proliferation. Similarly, CTLA-4 is another protein receptor expressed by T cells, and it acts to downregulate T cell activation.[15] CTLA-4 binds to B7 molecules (CD80/CD86) to exert its inhibitory effects on T cells. Hence, inhibitors of PD-1/PD-L1 and CTLA-4, collectively known as ICIs, prevent the inhibition of immune cells, thus facilitating T cell activation and its attack on cancer cells.[16] Examples of ICIs are highlighted in Figure 2.

CTLA-4 inhibitors are not used alone; they are used in combination with PD-1 inhibitors. Overall, ICIs may be used alone or alongside other systemic agents such

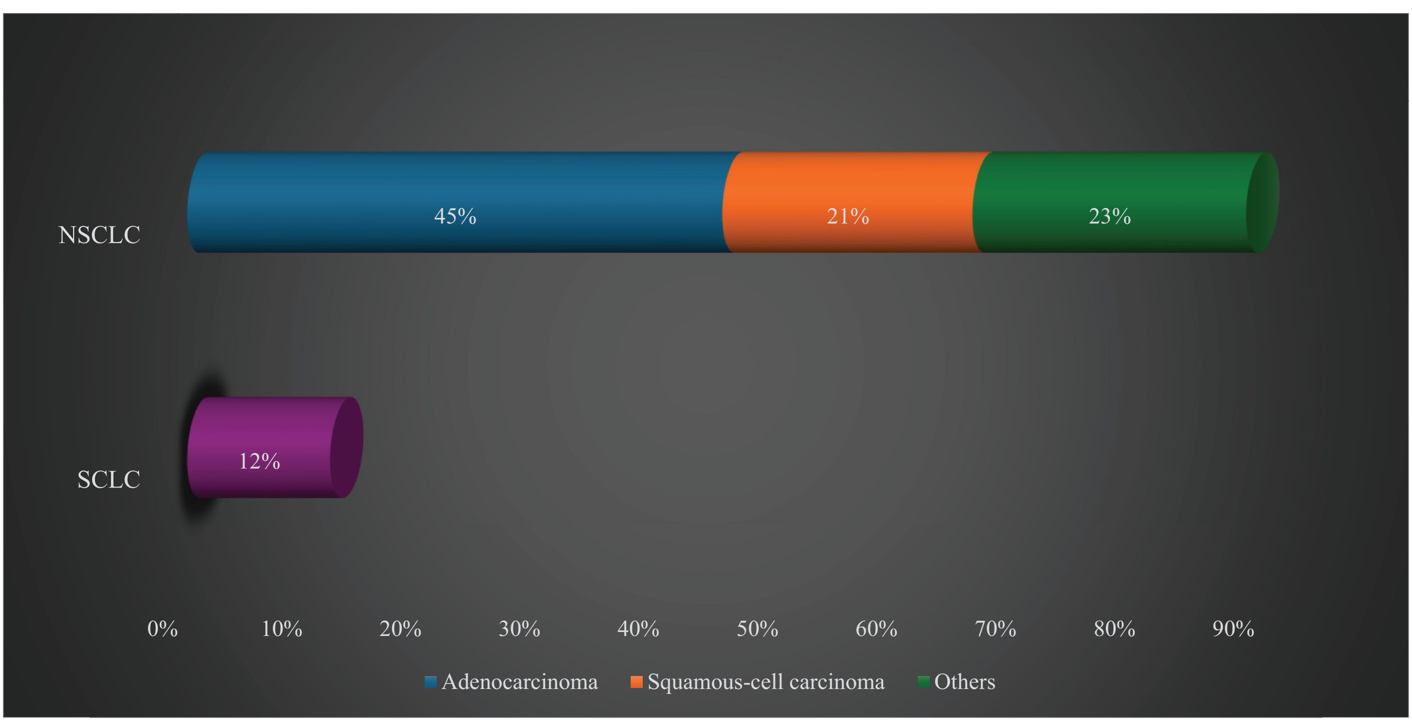

Fig 1 | Prevalences of types and subtypes of lung cancers. SCLC, small-cell lung cancer; NSCLC, non-small-cell lung cancer

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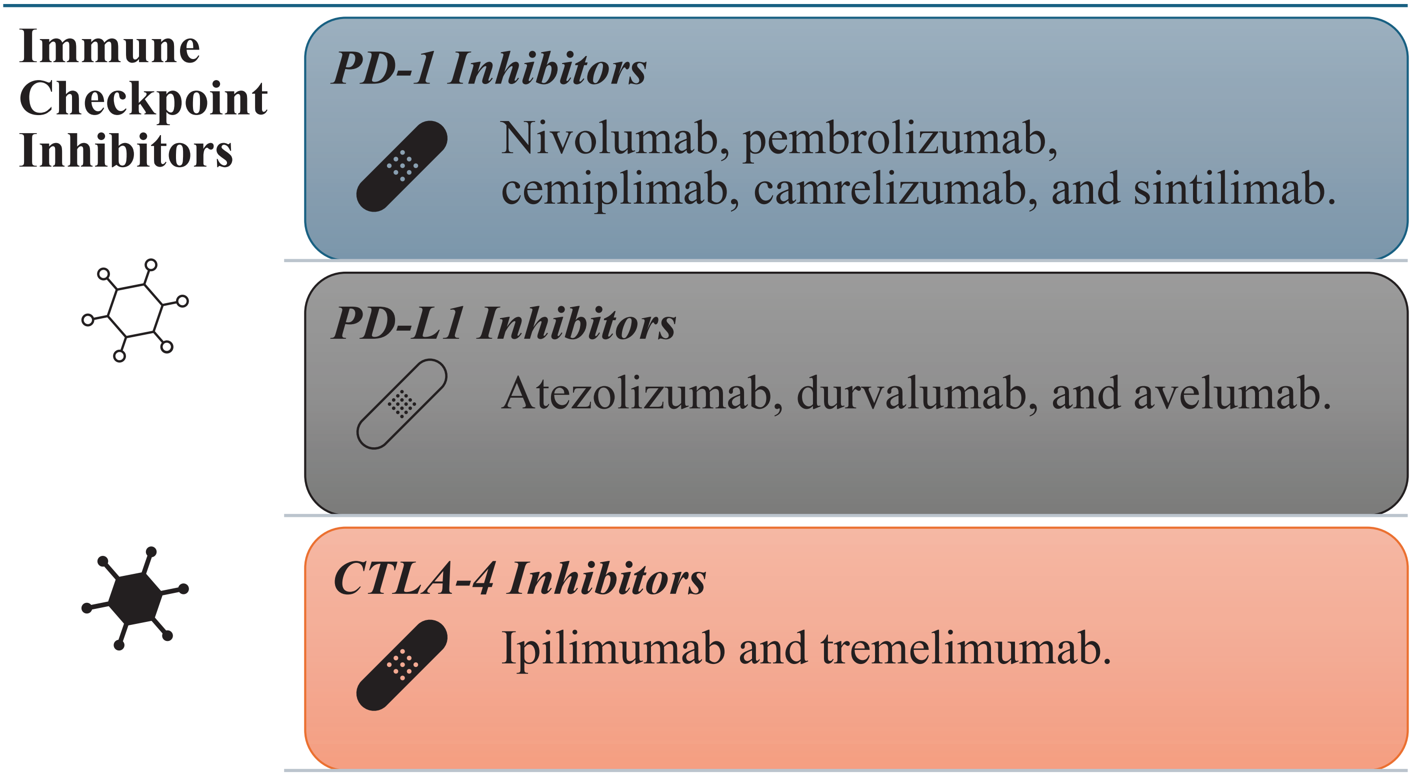

Fig 2 | Examples of immune checkpoint inhibitors. PD-1, programmed death-1; PD-L1, programmed death ligand 1; CTLA-4, cytotoxic T-lymphocyte antigen 4

as chemotherapeutic drugs, as adjuvant/neoadjuvant therapy, or for the management of advanced lung cancer. The use of ICIs is based on evidence from multiple clinical trials aimed at assessing their effectiveness and safety in patients with lung cancer. Outcomes from specific trials on different ICIs are explained below. A list of the clinical trials is provided in Figure 3.

Outcomes of Trials on ICI Monotherapy

PD-L1 Inhibitors

Atezolizumab

ICI monotherapies are used as adjuvant or neoadjuvant treatments perioperatively in resectable tumors; however, as a standalone treatment, they are typically reserved for advanced lung cancers, particularly NSCLC, which was conventionally managed with chemotherapy. In the IMpower110 randomized phase 3 trial,[17] the effectiveness and safety profiles of atezolizumab were compared with those of platinum-based chemotherapy (combinations involving cisplatin, carboplatin, pemetrexed, and gemcitabine) in patients with advanced squamous or nonsquamous NSCLC who had not received chemotherapy. With a median follow-up of 15.7 months, the median overall survival (OS) in the atezolizumab and chemotherapy groups was 20.2 and 13.1 months (hazard ratio [HR]: 0.59; P = 0.01), respectively. In terms of safety, grade 3 or 4 adverse events (AEs) occurred less frequently in the atezolizumab group (30.1% vs. 52.5%). These outcomes were associated with high PD-L1 expression in the patients, and the findings provided strengthened evidence for the use of ICIs in the treatment of lung cancers.

Similarly, in the POPLAR trial, which involved patients who had received platinum-based chemotherapy but experienced disease progression,[18] atezolizumab increased OS (12.6 months vs. 9.7 months; minimum follow-up: 13 months; HR: 0.73; P = 0.04) compared to docetaxel; treatment outcomes also correlated with increasing PD-L1 expression. These findings were corroborated by the OAK phase 3 randomized trial, which reported a median OS of 13.8 months vs. 9.6 months (HR: 0.73; P = 0.0003) for atezolizumab.[19]

Avelumab

Given its success in the management of Merkel cell carcinoma and advanced urothelial carcinoma, avelumab was assessed for its effectiveness in the management of treatment-naive NSCLC in the JAVELIN Solid Tumor trial,[20] a preliminary assessment for the JAVELIN Lung 200 study.[21] The patients received intravenous avelumab every 2 weeks. The study had a median follow-up of 18.6 months and recorded a median progression-free survival (PFS) of 4 months. Overall, this phase 1b trial reported a 12-month OS rate of 56.6% (95% confidence interval [CI]: 48.2–64.1) with a tolerable safety profile.

In the phase 3 trial of the JAVELIN Lung 200 study,[21] in which patients with advanced NSCLC who had received platinum-based chemotherapy were enrolled, OS did not differ significantly between patients who received avelumab and those who received docetaxel (11.4 months vs. 10.3 months; HR: 0.90). This was thought to be due to the high frequency of use of

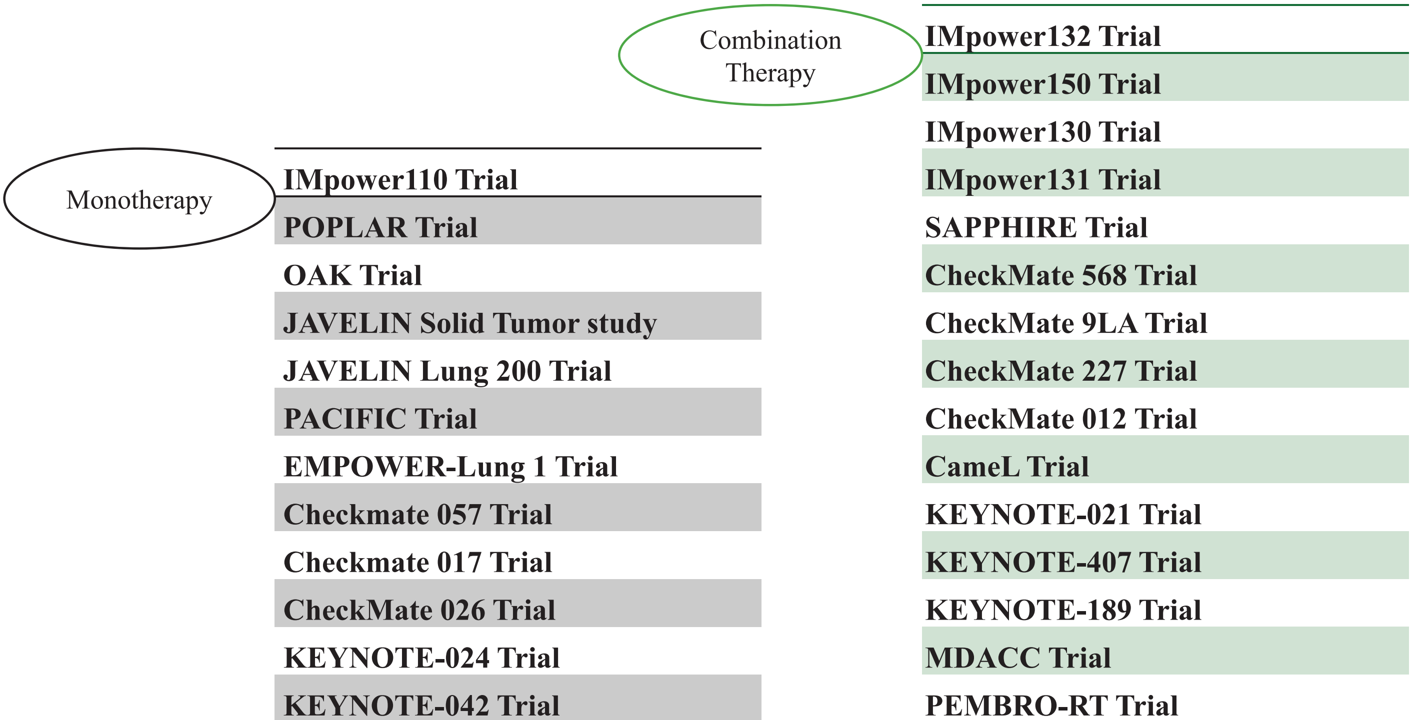

Fig 3 | Notable clinical trials on immune checkpoint inhibitor therapies

avelumab in the chemotherapy group after discontinuation of docetaxel due to reasons such as AEs and disease progression. However, in the 2-year follow-up analysis of the same study, the OS rate for patients who received avelumab compared to those who received docetaxel was 29.9% vs. 20.5% (HR: 0.87).[22] The rate increased further in subgroups of patients with high PD-L1 expression, resulting in approximately double OS rates in the avelumab arm compared to their respective docetaxel arms. These findings highlight the importance of avelumab in the long-term management of recurrent NSCLC in patients with PD-L1 expression.

Durvalumab

Contrary to the previously described trials, the PACIFIC trial assessed a PD-L1 inhibitor in comparison with a placebo.[23,24] In this phase 3 study, patients with advanced NSCLC were enrolled, and they received either durvalumab or placebo every 2 weeks as consolidation therapy. The median PFS was 16.8 months vs. 5.6 months (HR: 0.52; 95% CI: 0.42–0.65; $P < 0.001$) for durvalumab (compared to placebo), while the 12-month PFS rate was 55.9% vs. 35.3%.[23] In a second analysis of the study, with a median follow-up greater than 2 years, the 12-month OS rate was 66.3% vs. 55.6% (HR: 0.68; $P = 0.0025$). Likewise, durvalumab increased the time to death or distant metastasis (28.3 months vs. 16.2 months).[24]

In the 4-year survival analysis of the PACIFIC trial, Faivre-Finn et al.[25] reported that both the OS and PFS remained consistently higher in patients who received durvalumab. For the durvalumab and placebo arms, the OS rates were 49.6% and 36.3%, respectively, while the PFS rates were 35.3% and 19.5%, respectively. Reports from these analyses demonstrated both short-term and long-term importance of durvalumab as consolidative therapy for unresectable NSCLC.

PD-1 Inhibitors

Cemiplimab

Similar to the PD-L1 inhibitors, PD-1 inhibitors are also used as a monotherapy for managing advanced NSCLC based on evidence from multiple clinical trials. The OS and PFS associated with cemiplimab for advanced NSCLC were evaluated in the EMPOWER-Lung 1 study, which was undertaken in treatment centers across 24 countries globally.[26] The patients in the treatment and control groups received cemiplimab and the investigator's choice of platinum-doublet chemotherapy, respectively. The study recorded a high crossover rate from chemotherapy to cemiplimab, which impacted the credibility of the reported findings. Notwithstanding, cemiplimab resulted in a median PFS of 8.2 months vs. 5.7 months (HR: 0.54; $P < 0.0001$). Additionally, although the OS was not reached, the probability of 2-year survival was estimated to be 50% for cemiplimab vs. 27% for chemotherapy.

Nivolumab

CheckMate 017[27] and CheckMate 057[28] evaluated nivolumab in patients with squamous advanced NSCLC and nonsquamous advanced NSCLC, respectively. The 1-year OS rate for nivolumab (compared to docetaxel) was 42% vs. 24% in patients with squamous NSCLC and 51% vs. 39% in patients with nonsquamous NSCLC. Furthermore, the median PFS was 3.5 months

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vs. 2.8 months for squamous NSCLC but 2.3 months vs. 4.2 months for nonsquamous NSCLC. However, despite the unfavorable median PFS associated with nivolumab in patients with nonsquamous NSCLC, the PFS rate in this patient group was favorable (19% vs. 8% for nivolumab vs. docetaxel). The observed lower median PFS may be an indicator of delayed benefit in this patient group, a common phenomenon in immunotherapy.[29]

In the pooled analysis of CheckMate 017[27] and CheckMate 057[28], the effectiveness of nivolumab was found to be sustained after 5 years of follow-up.[30] The study reported a 5-year OS rate of 13.4% vs. 2.6% for nivolumab compared to docetaxel and a 5-year PFS rate of 8.0% vs. 0%. The analysis reported no new AEs relative to the preliminary studies.

Nivolumab has also been evaluated as a first-line therapy (CheckMate 026), compared to platinum-based chemotherapy, in patients with previously untreated advanced NSCLC.[31] However, nivolumab did not appear to significantly increase PFS (4.2 months vs. 5.9 months for nivolumab vs. chemotherapy) or OS (14.4 months vs. 13.2 months for nivolumab vs. chemotherapy) in this population. Nivolumab exhibited a better safety profile compared to chemotherapy. The low efficacy reported in this study could be due to many factors. The inclusion criteria in this study included a PD-L1 tumor expression level of ≥1%; higher PD-L1 expression levels have been attributed to better efficacy outcomes of ICIs in previous studies.[17,26] Hence, it is possible that the low expression level in this study affected patients' responses to nivolumab. Furthermore, more than half of the patients in the chemotherapy group received nivolumab as a subsequent therapy; this may have contributed to the improved response in the chemotherapy group.

Pembrolizumab

As a first-line therapy in patients with advanced or metastatic NSCLC in KEYNOTE-042,[32] pembrolizumab improved OS across three stratifications of PD-L1 tumor proportion scores: ≥1% (1,274 patients), ≥20% (818 patients), and ≥50% (599 patients). With a follow-up of more than 1 year, OS associated with pembrolizumab compared to platinum-based therapy was 20 months vs. 12.2 months, respectively, in the ≥1% group, 17.7 months vs. 13 months, respectively, in the ≥20% group, and 16.7 months vs. 12.1 months, respectively, in the ≥50% group. While the efficacy of pembrolizumab is expected to increase with increasing PD-L1 tumor proportion score, the higher number of patients in the low PD-L1 tumor proportion score subgroups could explain the higher OS in those subgroups.

Likewise, Reck et al.[33] in the KEYNOTE-024 study reported a median OS of 30 months vs. 14.2 months for pembrolizumab against platinum-based chemotherapy in patients with advanced NSCLC who had PD-L1 tumor proportion scores ≥50% after more than 2 years of follow-up. After about 5 years of follow-up, the median OS reduced (26.3 months) but was still approximately double that of the median OS in the platinum-based chemotherapy group (13.4 months), indicating sustained long-term effectiveness.[34]

The KEYNOTE-010 provided evidence for the use of pembrolizumab in the management of advanced disease for patients who experience disease progression after previous treatments.[35] The patients received 2 mg/kg of pembrolizumab, 10 mg/kg of pembrolizumab, or 75 mg/m^2 of docetaxel every 3 weeks. Median OS was higher in the two dose groups of pembrolizumab compared to docetaxel (2 mg/kg vs. 10 mg/kg vs. docetaxel: 10.4 months vs. 12.7 months vs. 8.5 months), with increasing dose resulting in longer OS. On the other hand, no significant difference was observed in PFS across the groups. In a subgroup of patients with at least 50% PD-L1 tumor expression, both the OS and PFS were significantly longer in those who received pembrolizumab compared to those who received docetaxel. However, higher incidences of grade 3–5 AEs were associated with the higher dose of pembrolizumab and the normal dose of docetaxel.

Outcomes of Trials on ICI Combination Therapies

PD-L1 Inhibitors

PD-L1 Inhibitor + Chemotherapy

The IMpower130,[36] IMpower131,[37] IMpower132,[38] and IMpower150,[39] phase 3 trials involved the assessment of the clinical efficacy of atezolizumab + chemotherapy combinations for the management of different types of advanced NSCLC as a first-line treatment. Findings from IMpower150[39] were published earlier and provided preliminary evidence for the improved clinical outcomes associated with atezolizumab + chemotherapy combination therapy for advanced NSCLC.

Only IMpower131[37] focused on squamous NSCLC, and the experimental group received atezolizumab with carboplatin + paclitaxel/nab-paclitaxel. The control group received only carboplatin + nab-paclitaxel. The treatments were administered every 3 weeks for 4–6 cycles, after which the treatment groups received atezolizumab maintenance therapy. The findings revealed improved median PFS in the treatment group (6.3 months vs. 5.6 months; HR: 0.71; $P = 0.0001$) and similar OS across the groups.

IMpower130[36] employed a similar regimen as IMpower131 in patients with advanced nonsquamous NSCLC: experimental group: atezolizumab and carboplatin + nab-paclitaxel; and control group: carboplatin + nab-paclitaxel. With a median follow-up of about 19 months, the study reported improvements in both median OS (18.6 months vs. 13.9 months; HR: 0.79; $P = 0.33$) and median PFS (7 months vs. 5.5 months; HR: 0.64; $P < 0.0001$) in the experimental group compared to the chemotherapy alone group. Contrastingly, IMpower132[38] replaced the chemotherapy regimen with carboplatin/cisplatin plus pemetrexed. Hence, the experimental group received atezolizumab and carboplatin/cisplatin plus pemetrexed, while the control group received carboplatin/cisplatin plus pemetrexed; the patients also received maintenance therapy. After a follow-up period of 14.8 months, the median PFS improved significantly in the experimental group, but the improvement in the median OS did not reach statistical significance.

PD-L1 Inhibitor + Radiotherapy

ICIs are also used in the early-stage and resectable NSCLC as adjuvant or neoadjuvant therapy to mitigate the risk of disease recurrence or shrink the tumor prior to resection. Altorki et al.[40] evaluated the use of neoadjuvant durvalumab monotherapy and dual therapy comprising durvalumab and stereotactic body radiotherapy in patients with potentially resectable NSCLC. Reports from this study suggested that the dual therapy resulted in synergistic outcomes, with a major pathological response (tumor shrinkage) observed only in two patients in the monotherapy group but in 16 patients in the dual therapy group (Odds ratio: 16.0; $P < 0.0001$). Additionally, half of the patients in the dual therapy group who had pathological responses experienced a complete pathological response. The treatment modalities exhibited comparable safety profiles, with a slightly higher incidence of grade 3–4 AEs in the dual therapy group.

PD-1 Inhibitors

PD-1 Inhibitors + Tyrosine Kinase Inhibitors

Tyrosine kinase inhibitors are another class of targeted therapy that inhibit cell division and angiogenesis and are used in the management of cancers. This class of drugs has also been investigated for the management of lung cancers. In a phase 1b study in China, Chu et al.[41] enrolled patients with advanced unresectable NSCLC and administered them with a dual drug therapy comprising sintilimab, a PD-1 inhibitor, and anlotinib, a tyrosine kinase inhibitor. Within approximately 16 months of follow-up, the median PFS was 15 months, and the 12-month PFS was 71.4%. This study was one of the first few studies to provide evidence for the use of chemotherapy-free drug combinations for treatment-naive patients with advanced NSCLC. Likewise, Zhou et al.[42] investigated a similar drug combination—camrelizumab (PD-1 inhibitor) and apatinib (tyrosine kinase inhibitor)—in patients with advanced nonsquamous NSCLC who were previously treated with chemotherapy. The study, also conducted in China, reported encouraging clinical efficacy and safety profiles for the combination, with median PFS and OS of 5.7 months and 15.5 months, respectively (approximately 19 months of follow-up).

In the recent SAPPHIRE phase 3 trial, treatment outcomes of sitravatinib plus nivolumab were compared with those of docetaxel in patients with advanced nonsquamous NSCLC.[43] The patients had received ICI and/or chemotherapy and had experienced disease progression; the new treatment was introduced to overcome the acquired resistance to ICIs. After receiving either sitravatinib plus nivolumab or docetaxel, neither the median OS nor the median PFS differed significantly between the two groups.

These reports indicate that while ICI plus tyrosine kinase inhibitor therapy may offer some benefits to treatment-naive and chemotherapy-pretreated patients with advanced NSCLC, these benefits may not be evident in patients who have already developed resistance to an ICI inhibitor.

PD-1 Inhibitor + CTLA-4 Inhibitor

CTLA-4 inhibitors are commonly combined with PD-1 inhibitors for the treatment of lung cancers. This is based on evidence from clinical studies such as CheckMate 012[44] and CheckMate 568[45] trials. These phase 1 and 2 trials, respectively, evaluated responses to nivolumab plus ipilimumab as a first-line therapy for patients with advanced NSCLC who had not received previous treatment. CheckMate 012[44] stratified patients to receive 3 mg/kg of nivolumab every 2 weeks plus either 1 mg/kg ipilimumab every 6 weeks or 1 mg/kg ipilimumab every 12 weeks. Contrarily, patients in CheckMate 568[45] received the same regimen of nivolumab plus only 1 mg/kg ipilimumab every 6 weeks. These two studies, conducted in North America, reported similar findings: objective response rates of 47% in the 12-week cohort and 38% in the 6-week cohort in CheckMate 012[44] and 30% overall in CheckMate 568.[45]

These reports prompted further assessment involving the comparison of nivolumab + ipilimumab with platinum-doublet chemotherapy in treatment-naive patients with advanced NSCLC.[46,47] CheckMate 227[46] and CheckMate 9LA[47] are phase 3 trials. In CheckMate 227,[46] although patients received nivolumab plus ipilimumab, chemotherapy, or nivolumab alone, the reported results were mostly for the first two cohorts. The median OS was 17.1 months vs. 13.9 months for nivolumab plus ipilimumab vs. chemotherapy cohorts, respectively. Fewer incidences of grade 3 or 4 AEs were reported for the nivolumab plus ipilimumab cohort. In the CheckMate 9LA,[47] patients received nivolumab plus ipilimumab plus chemotherapy or chemotherapy alone, and the median OS was 15.6 months vs. 10.9 months, respectively.

The NEOSTAR trial also revealed that neoadjuvant nivolumab plus ipilimumab induced pathologic response and tumor shrinkage prior to surgical resection in patients with operable tumors.[48]

PD-1 Inhibitors Plus Chemotherapy: Chemotherapy is historically the mainstay treatment for inoperable lung cancer; hence, even with the advent of ICIs and other targeted systemic therapies, many treatment guidelines still recommend the inclusion of chemotherapy in drug regimens for this patient population. Consequently, multiple studies have been undertaken to determine the benefits of drug combinations comprising ICIs and chemotherapy. The CameL study determined the efficacy of camrelizumab plus chemotherapy (carboplatin plus pemetrexed) for nonsquamous NSCLC in the Asian population, reporting significantly higher PFS with the combination (11.3 months) than with chemotherapy alone (8.3 months; HR: 0.60; $P = 0.0001$) after almost 1 year of follow-up.[49] Yang et al.[50] also evaluated a similar combination—sintilimab plus pemetrexed and cisplatin/carboplatin—in the Asian population and reported favorable PFS for the dual drug combination (8.9 months vs. 5.0 months; HR: 0.482; P < 0.00001) against chemotherapy alone. However, in both studies, higher incidences of AEs were reported in the experimental group.

Furthermore, pembrolizumab + chemotherapy was extensively investigated in the KEYNOTE 021,[51] KEYNOTE 189,[52] and KEYNOTE 407[53] trials. Despite utilizing different chemotherapy regimens (carboplatin + pemetrexed, cisplatin/carboplatin + pemetrexed, and carboplatin + paclitaxel/nab-paclitaxel, respectively), the trials reported favorable efficacy and safety profiles for the respective combinations. KEYNOTE 021,[51] a phase 2 trial, reported higher objective response in 33/60 patients in the experimental group compared to 18/63 patients in the chemotherapy alone group. The other two trials, which were phase three studies, reported higher OS, OS rates, and PFS in the experimental groups, with comparable safety profiles across the groups.

PD-1 Inhibitors plus Radiotherapy

Radiotherapy is known to potentiate the immune response to tumor cells, and its combination with immunotherapy is expected to result in excellent cancer treatment outcomes. Theelen et al.[54] undertook a pooled analysis of PEMBRO-RT[55] and MDACC[56] trials, which investigated the treatment benefits of immunoradiotherapy. In the PEMBRO-RT trial,[55] patients with advanced NSCLC underwent stereotactic body radiotherapy prior to commencing pembrolizumab therapy, while patients enrolled in the MDACC trial[56] received stereotactic body radiotherapy concurrently with pembrolizumab. With an overall median follow-up of 33 months, the pooled analysis resulted in a median PFS of 9 months vs. 4.4 months (HR: 0.67; P = 0.045) and OS of 19.2 months vs 8.7 months (HR: 0.67; P = 0.0004) for immunoradiotherapy vs. immunotherapy alone. Additionally, abscopal response, which is characteristic of radiotherapy, had a 41.7% (vs. 19.7%) rate in the immunoradiotherapy group with no new safety concerns compared with the individual therapies.

CTLA-4 Inhibitors

Based on the previous studies, which highlighted targeted radiotherapy as a potential immunomodulator in NSCLC treatment, Formenti et al.[57] evaluated the effectiveness of focal radiation therapy plus ipilimumab, a CTLA-4 inhibitor, in inducing abscopal responses. Abscopal responses occur when local radiation treatment of cancer results in systemic clinical responses at locations that are outside the treatment site; this is thought to be due to the activation of T cells, but the exact mechanism is not clearly understood. Although CTLA-4 inhibitors have little to no clinical effects on treatment outcomes of patients with metastatic NSCLC, in this study, ipilimumab alongside focal radiation therapy resulted in 18% of patients, with two and five of those patients exhibiting complete and partial responses, respectively. Furthermore, patients who completed the therapy in this study had a median OS (13 months) that was almost double that of the entire patient population (7.4 months; P < 0.001). Systemic clinical effects were accompanied by increased serum interferon-β and dynamic changes in T cells.

Predictors of Clinical Response to ICIs

Assessing potential biomarkers to determine the efficacy of ICIs can help identify patients who are more likely to benefit from lung cancer treatments. A review of the literature highlights key markers for predicting the effectiveness of ICIs, such as epidermal growth factor receptor (EGFR) mutations, PD-L1 expression levels, and T cell clones.

PD-L1 Expression Levels

PD-L1 has been widely recognized as a key predictive factor for the efficacy of ICIs and patient survival in multiple studies.[33,35] Higher tumor cell PD-L1 expression, as evaluated by immunohistochemistry in pretreatment tumor samples, is generally associated with improved treatment responses. Patients with a PD-L1 tumor proportion score of less than 1% tend to have a reduced likelihood of benefiting from single-agent anti-PD-1 therapy. However, notable survival benefits have been observed in these patients when undergoing ICI combination therapies, such as with radiotherapy or chemotherapy.[40] The greatest OS, PFS, and objective response rate benefits are typically seen in patients with a PD-L1 tumor proportion score of ≥50%.[58,59] Barlesi et al.[21] also indicated improved OS with higher PD-L1 cut-offs, such as 50% or 80% tumor cell expression.

Interestingly, ICIs may also demonstrate efficacy independent of PD-L1 expression. For instance, Formenti et al.[57] noted that CTLA-4 inhibition combined with radiotherapy did not correlate with PD-L1 expression in predicting abscopal responses. Similarly, Chu et al.[41] suggested that PD-L1 expression is not associated with the efficacy of anti-PD-1 therapy when combined with tyrosine kinase inhibitors.

EGFR Mutations

EGFR mutations have been linked to a lower total mutation burden and reduced responsiveness to anti-PD-1/PD-L1 therapies. Elevated EGFR levels are notably observed in patients with progressive NSCLC.[57] For patients without EGFR or ALK aberrations, ICIs such as anti-PD-1 therapies have demonstrated significant improvements in PFS and OS compared to platinum-based chemotherapy.[33] Conversely, in EGFR mutation-positive patients with NSCLC that progressed during or after platinum-based doublet chemotherapy, the mutation status may not significantly correlate with OS outcomes when treated with PD-1 therapies.

T Cell Clones

In patients with NSCLC treated with a combination of anti-CTLA-4 therapy and radiotherapy, it has been hypothesized that new tumor-specific T cell clones may emerge in those who respond most effectively to the treatment. Radiation therapy, when applied *in vivo*, might also enhance the expression of KPNA2, a protein linked to cancer progression, in NSCLC. Additionally, studies have shown that resected tumors from patients treated with PD-L1 and CTLA-4 combination therapies exhibit greater T cell receptor richness and clonality compared to adjacent, uninvolved lung tissues. These findings suggest that such combination therapies may promote a more diverse and targeted antitumor immune response.[57]

Following treatment with anti-PD-1 plus stereotactic radiotherapy, there was a significant increase in the number of mature and immature dendritic cells, M1 and M2 macrophages, and fibroblasts, enhancing antigen presentation and reshaping the tumor microenvironment.[40] This process aligns with the emergence of new tumor-specific T cell clones observed in patients with NSCLC who responded best to the combination of anti-CTLA-4 therapy and radiotherapy, highlighting the synergy between radiotherapy and immunotherapy in promoting robust antitumor immune responses.

Other Predictive Factors

Patients with high tumor burdens have been reported to show remarkable overall response rate (ORR) and minimal disease progression. This observation suggests that combining antiangiogenic tyrosine kinase inhibitors with anti-PD-1 immunotherapy could particularly benefit patients with greater genomic instability.[41]

Regarding interferon-β, in cases where anti-CTLA-4 antibodies failed to demonstrate significant efficacy—either alone or in combination with chemotherapy—Formenti et al.[57] found that focal radiation therapy significantly enhanced systemic immune responses. Elevated serum interferon-β levels postradiation, along with early dynamic changes in blood T cell clones, emerged as strong predictors of treatment response. This effect is linked to the activation of antitumor T cells through the cyclic GMP-AMP synthase/stimulator of interferon gene pathway, emphasizing the potential of combining focal radiation therapy with anti-CTLA-4 antibodies.

Discussions and Limitations of ICI-Based Therapies

Despite the significant progress made in recent years regarding systemic therapy for NSCLC, the development of drug resistance continues to make the management of lung cancer challenging.[60] Given that systemic therapy is typically reserved for advanced and inoperable tumors, treatment outcomes are poor.[61] This is attributed to the various interplay of gene mutations, angiogenesis, and other biological pathways of drug resistance.[62] Therefore, combination therapies targeting multiple pathologic pathways are recommended for the management of NSCLC, particularly as second-line or later therapy.[63] In a retrospective study, combinations of ICIs with other systemic agents were found to provide better treatment outcomes compared to ICI monotherapies.[64] Additionally, these combinations had comparable safety profiles with monotherapies. Other systemic therapies that are commonly combined with ICIs are chemotherapy and antiangiogenic treatments.[65]

Qin et al.[66] assessed the utility of ICI combinations with chemotherapy and targeted therapy in patients with NSCLC who had uncommon driver gene alterations. Uncommon driver gene alterations are mutations that play a significant role in the pathogenesis of a cancer type but are only found in small proportions of such cancer cases.[67] Examples of uncommon driver gene alterations are found in *ERBB2*, *BRAF*, *RET*, and *MET* for NSCLC.[68] Qin et al.[66] reported that the combinations were effective as both first-line and later-line treatments, with overall response rates of 51.5–60% and 14.3–30.8% for first-line treatments and second-/third-line treatments, respectively.

PD-1 plus chemotherapy treatments are significantly limited by all-cause AEs, which can lead to treatment discontinuation or even death. For instance, in a study by Gadgeel et al.,[59] two patients treated with first-line pembrolizumab combined with pemetrexed-platinum experienced severe adverse effects, including spinal fractures and a general decline in physical health. Acute kidney injury occurred more frequently in the anti-PD-1 combination group compared to the placebo-combination group. Additionally, immune-mediated AEs and infusion-related reactions (of any grade), such as hyper- and hypothyroidism and pneumonitis, were more prevalent in patients receiving pembrolizumab in combination with chemotherapy.

Combination therapies, such as anti-PD-1 combined with CTLA-4 inhibitors or tyrosine kinase inhibitors, have demonstrated meaningful pathologic response at surgery in patients with NSCLC. However, this aggressive approach is associated with serious adverse effects, including grade 3 diarrhea/colitis, grade 2 pneumonitis, hypoxia, and large nonmalignant pleural effusions requiring hospitalization. Grade 3–5 treatment-related AEs were reported, highlighting the challenges of tolerability in these therapies.[28]

By contrast, combining PD-1 inhibitors with radiotherapy has been found to be a more tolerable ICI adjuvant treatment. Common toxic effects primarily include fatigue, flu-like symptoms, and pruritus, with grade 3–5 pembrolizumab-related toxic effects occurring less frequently compared to other combination approaches. Additionally, although combination therapies generally demonstrate greater efficacy, single-agent therapies tend to have better safety profiles, making them a viable option for certain patient populations.

Moreover, identifying biomarkers to select patients most likely to benefit from these therapies remains challenging due to an incomplete understanding of the tumor microenvironment, ICI resistance mechanisms, and a lack of adequate animal models. This gap highlights the need for further research to discover predictive markers for the efficacy of ICIs in NSCLC. A review study that focused on immunotherapy-based combinations recommended biomarker-driven immunotherapy trials as the scope for future studies in this field.[69] This entails the use of specific biomarkers to identify and stratify patients as well as personalize treatment strategies in clinical trials.[70] This is expected to improve response to treatment and reduce the associated treatment toxicity.[71]

Conclusion

In this review, clinical trials conducted regarding the importance of ICI-targeted therapies were reviewed to generate concise evidence regarding clinical decision-making for lung cancer treatment. The majority of the research efforts on ICIs in the management of lung cancer gained traction in the past decade, and evidence from preliminary studies guided the design of subsequent research in this field. PD-1 and PD-L1 inhibitors are used as monotherapy treatment in patients with advanced cancer, while CTLA-4 inhibitors are primarily used in combination therapies. Clinical trials on ICI monotherapies such as IMpower110, POPLAR, OAK, JAVELIN Lung 200, and CheckMate (017, 024, 026, 042, and 057) trials proved, to various extents, that ICI monotherapies are effective for prolonging OS and PFS of patients; treatment outcomes were compared with those of chemotherapy and placebo effect, revealing superior outcomes with ICIs. However, patients experienced delayed effects in some of the trials. In terms of safety, ICI monotherapy resulted in comparable AEs with other targeted therapies and chemotherapies.

Likewise, ICI combinations with chemotherapy and radiotherapy also elicited favorable outcomes for patients in terms of efficacy and safety, as reported in trials such as IMpower (130, 131, 132, and 150), SAPPHIRE, CameL, and KEYNOTE (021, 189, and 407) trials. Abscopal response was reported for combinations that included radiotherapy, resulting in heightened immune response against cancer cells. Incidence and grades of AEs were commonly reflective of AEs associated with individual drugs in the combinations; therefore, combinations involving ICIs and chemotherapy resulted in higher incidences of AEs than chemotherapy alone. This review also found tumor expression of PD-L1 to be a common predictor of treatment outcomes; patients with ≥50% PD-L1 expression experienced more clinical benefits of ICIs than those with lower PD-L1 expression. Other predictors and indicators of clinical response included EGFR mutations, T cell clones, tumor burden, and serum interferon-β levels.

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