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Review Article

Targeting of the Immune System - From Late-Stage Treatment to Upfront Neoadjuvant Therapy in Non-Small-Cell Lung Cancer

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Abstract

Lung cancer continues to be a significant global health challenge, characterized by high mortality rates and limited treatment options in its advanced stages. However, the advent of immunotherapy has begun to transform the therapeutic landscape, offering new hope for pa-tients. This paper aims to provide a detailed analysis of the current state and prospects of im-munotherapy in the management of lung cancer. Specifically, it will offer a comprehensive his-torically review of recent clinical trials, emerging immunotherapeutic agents, predictive bi-omarkers, and novel targets for non-small cell lung cancer from the development of immuno-therapy for metastatic lung cancer to advances in immunotherapy in the neoadjuvant and ad-juvant setttings. Moreover, the paper will explore the challenges and opportunities associated with immunotherapy, including resistance mechanisms and the potential of combination ther-apies. Through this analysis, the paper intends to underscore the revolutionary impact of im-munotherapy on lung cancer treatment, advocating for the advancement of more personalized and efficacious therapeutic strategies.

Keywords: Immunotherapy; Immune Checkpoint Inhibitor; Non-Small Cell Lung Cancer; Neoadjuvant; Adjuvant

Introduction

Lung cancer is the most common cause of cancer-related mortality globally, with an estimated 1.8 million deaths from the disease each year [1,2]. Even with improve-ments in early identification and traditional therapies like radiation, chemotherapy, and surgery, the prognosis for many lung cancer patients is still poor, especially for those with advanced stages of the disease. This has contributed to a search for cutting-edge treatment strategies that may improve patient outcomes.

Immunotherapy has significantly transformed the field of cancer treatment in recent years, providing an oppor-tunity of hope for individuals diagnosed with lung cancer. Immunotherapy utilizes the immune system to identify and eliminate cancer cells, as opposed to traditional treatments that target the cancer cells. The evolution in cancer treatment approach has resulted in significant clinical improvements in different types of cancer, such as lung can-cer [2]. Immunotherapy utilizes the immune system to trigger an immune response against tumor antigens, ena-bling the treatment and eradication of undetected micro-metastatic cancer cells.

Immune checkpoint inhibitors (ICIs) work by disrupting the co-inhibitory sig-naling pathway and promoting immune-mediated elimination of cancer cells through targets such as programmed cell death ligand 1 (PD-L1), programmed cell death protein 1 (PD-1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). The article provides an in-depth review of the most recent immunotherapy drugs approved for treating non-small cell

lung cancer (NSCLC). We analyze their use in different stages of the disease, including metastatic cases and early-stage presenta-tions where neoadjuvant and perioperative treatments have recently been approved by the FDA, with the expectation of additional uses in the future [2-4]. Immune check-points are crucial for regulating the activity of immune cells and maintaining a balance between anti-inflammatory and pro-inflammatory signals. Immune checkpoint inhibi-tors (ICIs) utilize these inhibitory proteins to benefit from anti-tumor immunity against malignancies. This review examines the sequential development of therapeutic ap-provals, starting with treatments for metastatic disease, advancing to locally advanced disease stages, and most recently including adjuvant and neoadjuvant therapies [1,2].

Checkpoint inhibitors approved for NSCLC

In the field of cancer immunotherapy, several checkpoint inhibitors have been studied. However, only inhibitors that target PD-1/PD-L1 and CTLA-4 have been approved by the FDA for treating lung cancer. Although ongoing research is being conducted on other checkpoints like TIGIT, TIM-3, and LAG-3, these are currently in the clinical trial phase and have demonstrated initial effectiveness data. However, they have not yet obtained regulatory approval for their use in treating lung cancer [1,5]. The list of the anti-PD1/PDl-1 and anti-CTL4 inhibitors can be found in Table 1.

Medication	Mechanism of Action	FDA Approvals*
Cemiplimab	PD-1 inhibitor	First-line monotherapy with PD-L1 ≥50% with no EGFR, ALK, ROS1 mutations,
		First-line treatment in locally advanced or metastatic disease† in combination with platinum-based chemotherapy with no EGFR, ALK, ROS1 mutations
Nivolumab	PD-1 inhibitor	Neoadjuvant therapy in combination with platinum-doublet chemotherapy,
		First-line therapy in metastatic disease in combination with ipilimumab and/or platinum doublet chemotherapy with no EGFR or ALK mutations
Pembrolizumab	PD-1 inhibitor	First-line monotherapy in stage III or metastatic disease† with PD-L1 ≥1% with no EGFR or ALK mutations,
		First-line treatment in metastatic nonsquamous in combination with chemotherapy with no EGFR or ALK mutations,
		Adjuvant monotherapy in stage IB, II, or IIIA disease following resection and platinum-based chemotherapy
Atezolizumab	PD-L1 inhibitor	Adjuvant monotherapy in stage II-IIIA disease with PD-L1 ≥1% following resection and platinum-based chemotherapy,
		First-line monotherapy in metastatic disease with PD-L1 ≥50% with no EGFR or ALK mutations,
		First-line treatment in metastatic, nonsquamous disease in combination with chemotherapy ± bevacizumab with no EGFR or ALK mutations
Durvalumab	PD-L1 inhibitor	Treatment in stage 3 unresectable disease following chemoradiation,
		Treatment in metastatic disease in combination with tremelimumab and platinum-based chemotherapy with no EGFR or ALK mutations
Ipilimumab	CTLA-4 inhibitor	First-line treatment in metastatic disease with PD-L1 ≥1% in combination with nivolumab with no EGFR or ALK mutations,
		First-line treatment in metastatic/recurrent disease in combination with nivolumab and platinum doublet chemotherapy with no EGFR or ALK mutations
Tremelimumab	CTLA-4 inhibitor	Treatment in metastatic disease in combination with durvalumab and platinum-based chemotherapy with no EGFR or ALK mutations
*within NSCLC; †patients not surgical or chemoradiation candidates		

Table 1: Immune Checkpoint Inhibitors.

The PD-1 and PD-L1 pathway

PD-1 is a cell surface receptor found on T cells and other types of immune cells, including B cells, natural killer cells, and myeloid suppressor cells. PD-L1 proteins are primarily found on tumor cells and stromal cells, including fibroblasts and macrophages. T lymphocytes and cells that line the inner surface of blood vessels, known as endothelial cells, express PD-1 proteins. On the other hand, antigen-presenting cells (APCs) express PD-2 proteins. When the PD-L1 and PD-L2 molecules bind to the PD-1 receptors, it interferes with the normal functioning and communication pathways of T cells. Tumor cells in malignancies like non-small-cell lung cancer (NSCLC) have the ability to increase the expression of PD-L1.

CTLA-4 Pathway

CTLA-4, also referred to as CD152, is a protein receptor predominantly found on T cells. T-cell activation takes place in the immune system when antigens on anti-gen-presenting cells (APCs) bind to the T-cell receptor, and co-stimulation is triggered by interactions between B7 and CD28. CTLA-4 facilitates a parallel and inhibitory pathway. It competes with CD28, a costimulatory homolog, to bind to the same ligands on APCs. This results in a reduction in the production of interleukin-2 and a slowed progression of the cell cycle. The downregulation of T-cell and immune response oc-curs earlier in the antigen presentation process compared to the PD-1/PD-L1 pathway [3,4].

PD-1 Inhibitors

Metastatic NSCLC has three FDA-approved PD-1 inhibitors: cemiplimab, nivolumab, and pembrolizumab. Cemiplimab is a type of antibody called a recombi-nant human immunoglobulin G4 monoclonal antibody. It can be used alone or in com-bination with other treatments for metastatic non-small cell lung cancer (NSCLC). EMPOWER-Lung 1 is a phase 3 trial that compared cemiplimab with chemotherapy to chemotherapy alone and found higher median overall survival (OS) in the combination group. This study conducted a comparison between cemiplimab and platinum-based chemotherapy in patients with metastatic NSCLC and PD-L1 levels of 50% or higher. The results indicated that patients who received cemiplimab monotherapy had a longer median overall survival. As a result, cemiplimab was authorized as the initial treatment for patients with metastatic NSCLC who have PD-L1 levels of 50% or higher and do not have any actionable driver mutations. Pembrolizumab, a PD-1 inhibitor, is rec-ommended for use in this specific group of patients [5,6].

Pembrolizumab is a type of antibody called a humanized immunoglobulin G4 monoclonal antibody. It is used to treat different conditions in non-small cell lung cancer (NSCLC). The National Comprehensive Cancer Network (NCCN) recommends using immunohistochemistry testing to assess PD-L1 expression as a companion diag-nostic biomarker test. This testing should also be done before initiating first-line thera-py for metastatic NSCLC [7-10]. KEYNOTE-024, KEYNOTE-042, and KEYNOTE-001 are clinical trials that provided evidence for the use of pembrolizumab as the initial treatment for patients with advanced non-small cell lung cancer (NSCLC) and a PD-L1 expression level of at least 1%. However most of the benefit seen was in patients with PDL1>50% and not in patients with PDL-1 between 1-49% for that reason the use of this agent for that population remains controversial despite FDA approval.

The clinical trials known as KEYNOTE-189, KEYNOTE-407, and KEYNOTE-021 have demonstrated that the combination of pembrolizumab and chemotherapy, as opposed to chemotherapy alone, enhances overall survival (OS) in patients with meta-static non-small cell lung cancer (NSCLC) and PD-L1 levels below 1%.

Nivolumab is a human immunoglobulin G4 monoclonal antibody and can be uti-lized with or without ipilimumab within NSCLC. CheckMate-057 is a phase 3 trial that compared nivolumab to docetaxel in patients with metastatic no squamous NSCLC that progressed on first-line therapy. Patients receiving nivolumab had a higher OS and duration of response leading to its indication as subsequent therapy within this patient population. This was the first indication for nivolumab in metastatic disease in the second line setting [11,12].

PD-L1 Inhibitors

Atezolizumab and durvalumab are two PD-L1 inhibitors approved by the FDA for use in non-small-cell lung cancer (NSCLC). In both first-line metastatic and adjuvant settings, atezolizumab-a humanized G1 monoclonal antibody-can be employed. With PD-L1 levels =50% and no detectable driver mutations, it is the only PD-L1 inhib-itor authorized for use as first-line treatment in patients with metastatic NSCLC. Clin-ical trials including IMpower 110, IMpower 150, and IMpower 130 have resulted in these indications for metastatic NSCLC [13-15].

A human immunoglobulin G1 monoclonal antibody called durvalumab has been demonstrated to improve overall survival (OS) in patients with stage III unresectable non-small cell lung cancer (NSCLC) when given in after concurrent chemoradio-therapy [16].

3.0 The integration of immune-checkpoint inhibitors and chemotherapy.The immune checkpoint inhibitors employ different mechanisms and pathways, such as the PD-1/PD-L1 and CTLA-4 pathways. The purpose of combining immune checkpoint inhibitors (ICIs) with different mechanisms was to overcome resistance patterns and enhance effectiveness. CheckMate-227

was a phase 3 trial led by Hellmann and his team. It was an open-label study that aimed to compare the effectiveness of nivolumab plus ipilimumab, nivolumab alone, and chemotherapy in patients with metastatic non-small cell lung cancer (NSCLC) who had a PD-L1 level of at least 1%. The overall survival (OS) of patients who received nivolumab and ipilimumab was enhanced, regardless of their PD-L1 levels, with a median OS of 17.1 months compared to 14.9 months in the control group (P=0.007) [17]. Although these studies showed that combination immunotherapy was able to increase survival and be indicated as first-line therapy in certain patients with NSCLC, not all combinations have been shown to have the same results. Riziv and colleagues conducted an open-label, randomized, phase 3 trial within 1,118 patients with treatment-naïve, metastatic NSCLC with no EGFR or ALK genetic alterations. Patients received either durvalumab, durvalumab plus tremelimumab, or platinum-based chemotherapy, and OS was 11.9 months in the durvalumab plus tremelimumab group, 16.3 months in the durvalumab group, and 12.9 months in the chemotherapy group. There was no statistically significant difference between durvalumab and durvalumab plus tremelimumab compared to chemotherapy [18]. Combination immune-checkpoint inhibitor therapy has shown great advances, but more clinical data and evidence of benefit is needed to establish its place in therapy. There continues to be evolving treatment options comparing immunotherapy in different stages in the last 8 years (Table 2).

Place in Therapy	Trial	Year	Immune Checkpoint Inhibitors	Number of patients
Stage IV	KEYNOTE-024	2016	Pembrolizumab vs CT	305
	CheckMate 026	2017	Nivolumab vs CT	423
	IMpower150	2018	Atezolizumab/CT vs bevacizumab/CT vs Atezolizumab/Bevacizumab/CT	356
	KEYNOTE-189	2018	Pembrolizumab/CT vs CT	616
	KEYNOTE-407	2018	Pembrolizumab/CT vs CT	559
	CheckMate 227	2019	Nivolumab/Ipilimumab vs Nivolumab vs CT	2876
	KEYNOTE-042	2019	Pembrolizumab vs CT	1274
	IMpower110	2020	Atezolizumab vs CT	572
	CheckMate 9LA	2021	Nivolumab + Ipilimumab +CT vs CT	719
Stage III	PACIFIC	2017	Durvalumab vs Placebo	713
Adjuvant	IMpower010	2021	Atezolizumab vs Observation	1280
	PEARLS	2022	Pembrolizumab vs Placebo	1955
Perioperative	CheckMate 77T	2020	Nivolumab vs Placebo	461
	KEYNOTE-671	2023	Pembrolizumab vs Placebo	397
	NADIM II	2023	Nivolumab vs Placebo	86
	AEGEAN	2023	Durvalumab vs Placebo	802
	NEOTORCH	2023	Toripalimab Placebo	404
CT: Chemotherapy.				

Table 2: Immune Checkpoint Inhibitor Trials within NSCLC.

Role of Checkpoint inhibitors in metastatic disease

In 2016, Reck and colleagues conducted a phase 3 trial called KEYNOTE-024. The trial compared pembrolizumab with platinum-based chemotherapy, which was cho-sen by the investigators. The study involved 305 patients who had not received any previous treatment for stage IV non-small cell lung cancer (NSCLS) and did not have EGFR and ALK mutations [6]. The median progression-free survival (PFS) was 10.3 months in the pembrolizumab group, compared to 6.0 months in the chemotherapy group (P<0.001). The overall survival (OS) rate at 6 months was 80.2% in the pem-brolizumab group compared to 72.4% in the chemotherapy group (P=0.005). The find-ings demonstrated the superior efficacy of immunotherapy compared to chemotherapy when used as the initial treatment for advanced non-small cell lung cancer (NSCLC) with a PD-L1 expression level of over 50%, and in the absence of sensitizing EGFR or ALK mutations. The incidence of severe treatment-related adverse events was equiva-lent with 21.4% in the pembrolizumab group, compared to 20.7% in the chemother-apy group. In the pembrolizumab group, the only immune-mediated events of grade 3 or 4 were severe skin reactions (3% of patients), pneumonitis (2% of patients), and coli-tis (1% of patients). No grade 5 immune mediated adverse events occurred.

After this investigation, Mok and his colleagues released a publication called KEYNOTE-042 in 2019. This study involved a comparable group of patients to the one mentioned earlier, but it also encompassed patients with PD-L1 by TPS as low as 1%. The study categorized the patients into three groups based on their Tumor Proportion Score (TPS): TPS =1%, TPS =20%, and TPS =50%. The overall survival (OS) was signifi-cantly longer in the pembrolizumab group compared to the chemotherapy group, re-gardless of the three-tumor proportion score (TPS) categories. The highest hazard ratio (HR) was 0.69, with a 95% confidence interval (CI) of 0.56-0.85, and a p-value of 0.0003 for TPS >50%. This study expanded the FDA authorization for pembrolizumab, con-sidering a TPS score greater than 1% [7]. The incidence of immune-mediated adverse events was like that observed in the KEYNOTE0-24 trial. There were 177 occurrences (28%) of adverse events in 636 patients (8% of which were grade =3) in the pembroli-zumab group. The only immune-mediated events of grade 3 or lower were pneumonit-is, skin reactions, and hepatitis.

In the following year of 2020, the Checkmate 026 study was published by Carbone and colleagues. This was a phase 3 trial of patients with untreated stage IV or recur-rent NSCLC and a PD-L1 TPS of =5% to receive nivolumab or platinum-based chemo-therapy [19]. There were 423 patients received treatment including patients ECOG 0-1 and central nervous system (CNS) disease. The median OS in the primary analysis was 14.4 months in the nivolumab group and 13.2 months in the chemotherapy group (HR for death, 1.02; 95% CI, 0.80 to 1.30). This trial showed nivolumab did not show a longer PFS compared to chemotherapy among patients with previously untreated stage IV or recurrent NSCLC with a PD-L1 >5%. Patients had lower grade 3 or 4 treat-ment-related adverse events with nivolumab than with chemotherapy (18% vs. 51%).

The IMpower 110 study conducted by Herbst and colleagues was a comparative study that examined the efficacy of atezolizumab in comparison to chemotherapy. The study enrolled 570 patients with tumors exhibiting high PD-L1 expression. The median overall survival in the immunotherapy group was 7.1 months longer than in the chemotherapy group (p=0.01). The number 13 is enclosed in square brackets. The inci-dence of grade 3 or 4 adverse events in the atezolizumab group was 30.1%, which was higher than that observed in the Checkmate 026 study. In 2021, Sezer and colleagues conducted a monotherapy trial of immunotherapy in advanced lung cancer called the EMPOWER-Lung 1 trial. The trial compared cemiplimab to platinum doublet chemo-therapy. The primary endpoints of the study were overall survival (OS) and progres-sion-free survival (PFS). The median overall survival (OS) was not determined with cemiplimab compared to 14.2 months with chemotherapy. The hazard ratio (HR) was 0.57, indicating a significant difference, with a p-value of 0.0002. The median progres-sion-free survival (PFS) was 8.2 months for patients treated with cemiplimab, com-pared to 5.7 months for those treated with chemotherapy. The hazard ratio (HR) was 0.54, indicating a significant difference between the two groups. The p-value was less than 0.0001. This information is based on reference [5]. The predominant grade 3-4 treatment-related adverse events observed with cemiplimab were anemia (4%), neu-tropenia (1%), and pneumonia (5%).

Various immunotherapy agents with distinct mechanisms were employed to de-velop combination immunotherapy regimens, hypothesizing that the targeting of different receptors (such as CTLA-4, PD-1, and PD-L1) could enhance survival out-comes without raising the risk of toxicities. This study, conducted by Paz-Ares and colleagues, involved the randomization of patients with stage IV NSCLC in the Checkmate 9LA trial. The patients were divided into two groups: one receiving nivolumab plus ipilimumab combined with platinum doublet, and the other receiving chemotherapy alone. The primary endpoint of overall survival (OS) was significantly longer in the immunotherapy group compared to the control group, with a median of 14.1 months versus 10.7 months. The hazard ratio (HR) was 0.69, indicating a lower risk of death in the immunotherapy group. The p-value was 0.00065, indicating a highly significant difference between the two groups. As a result, the FDA approved this treatment regardless of the PD-L1 status [20]. It is important to note that 30% of individuals in the

combination group experienced significant adverse events related to their treatment, regardless of the severity.

After the previously mentioned comparison of immunotherapy versus chemo-therapy trials, a trend appeared with studies comparing immunotherapy plus chemo-therapy versus chemotherapy to determine if the addition of immunotherapy showed benefit without increasing toxicities. The IMpower 150 trial by Socinski and colleagues compared atezolizumab plus carboplatin plus paclitaxel (ACP), bevacizumab plus carboplatin plus paclitaxel (BCP), and atezolizumab plus BCP (ABCP). The median PFS was longer in the ABCP group than the BCP group (8.3 months vs. 6.8 months; HR for disease progression or death, 0.62; P<0.001); The results showed the addition of ate-zolizumab to bevacizumab plus chemotherapy significantly improved PFS and OS among patients with metastatic non-squamous NSCLC, regardless of PD-L1 expres-sion and EGFR or ALK mutations [21]. Adverse events were high in all groups (>90%). The most common grade 3 or 4 treatment-related adverse events were neutropenia, fe-brile neutropenia, and hypertension.

Ghandi and colleagues published Keynote 189, a phase 3 trial comparing chemo-therapy plus immunotherapy versus chemotherapy. 616 patients with ECOG 0-1, stage IV non-squamous NSCLC without EGFR or ALK mutations who had received no pre-vious treatment were randomized to receive pemetrexed and a platinum-based drug pembrolizumab or placebo, followed by pembrolizumab or placebo plus pemetrexed maintenance therapy. One important exclusion criterion in this study was evidence of symptomatic CNS metastasis. The primary endpoints were OS and PFS, OS at 12 months was 69.2% in the pembrolizumab-combination group versus 49.4% in the pla-cebo combination group (HR for death, 0.49; P<0.001). All PD-L1 categories showed improved OS [22]. Adverse events occurred in 99% of the patients in the pembroli-zumab combination, of those Immune-mediated adverse events occurred in 22.7%.

Several trials did not distinguish between different histology groups, such as squamous and non-squamous types. Additionally, combination immunotherapy has not been effective in treating squamous cell carcinoma, despite immunotherapy be-coming the standard first-line treatment for advanced cases. In 2019, Hellman and colleagues conducted the Checkmate-227 trial, which revealed a significant overall survival (OS) advantage in patients with squamous cell histology [18].

This was a phase 3 trial, where patients with ECOG 0-1, stage IV or recurrent (30% of patients with squamous histology) NSCLC, and a PD-L1 expression level of 1% or more were randomized to receive a PD-1 and CTLA-4 inhibitor (nivolumab plus ipilimumab), nivolumab alone, or chemotherapy. Patients had no previous chemo-therapy exposure and were excluded if they had untreated or symptomatic CNS me-tastasis. The primary endpoint specifically looked at OS between patients who received nivolumab plus ipilimumab as compared with chemotherapy with a PD-L1 expression level of 1% or more. In this patient subgroup, the median duration of OS was 17.1 with nivolumab plus ipilimumab and 14.9 months with chemotherapy (P=0.007). OS at 1 year was 62% vs 56% and at 2 years, 40% vs 32% with nivolumab plus ipilimumab and chemotherapy respectively. Grade 3 or 4 adverse events was similar in nivolumab plus ipilimumab (32%) and in the chemotherapy group (36%).

Keynote-407 by Paz-Ares and colleagues compared pembrolizumab or placebo plus carboplatin and paclitaxel in patients with stage IV disease with squamous his-tology [10]. The authors reported a median OS of 15.9 months in the pembrolizumab group and 11.3 months in the placebo group (HR for death, 0.64; P<0.001). The OS benefit was seen across all PD-L1 expression categories. The median PFS was 6.4 months in the pembrolizumab combination group and 4.8 months in the place-bo-combination group (HR for disease progression or death, P<0.001). This showed a longer OS with immunotherapy in the squamous histology type. Rates of adverse events of grade 3 or higher were similar in the pembrolizumab group (69%) and in the placebo group (68%).

Checkpoint inhibitors in Locally Advanced (Stage IIIB disease)

Following the positive results of immunotherapy, with or without chemotherapy, in treating advanced NSCLC, Antonia and his colleagues published the PACIFIC trial in 2018 [23]. This study was a phase 3 clinical trial conducted on patients diagnosed with stage III unresectable non-small cell lung cancer (NSCLC) who did not experience any disease progression following concurrent chemoradiotherapy. The primary end-points of the study were progression-free survival (PFS) and overall survival (OS). The two-year overall survival (OS) rate was 66.3% in the durvalumab group, while it was 55.6% in the placebo group (P=0.005). Durvalumab significantly increased overall sur-vival (OS) compared to placebo (P=0.0025). The incidence of new lesions was 22.5% in the durvalumab group and 33.8% in the placebo group, indicating a lower occurrence of new brain metastasis. This trial not only showed the improved overall survival (OS) of durvalumab, but also its potential to effectively prevent the spread of cancer to other parts of the body after definitive chemoradiation. Nevertheless, it is important to high-light that the administration of durvalumab led to a comparable rise in adverse effects when compared to the administration of a placebo. The Durvalumab group had a 29% occurrence of severe grade 3 or 4 adverse events, whereas the placebo group had a 26.1% occurrence. Pneumonia was the most frequently documented severe adverse event of grade 3 or 4. The challenge in stage III disease is to precisely determine which patients are classified as “medical” candidates and which are

classified as "anatomical" surgical candidates. These discussions mainly take place on multidisciplinary tumor boards.

Moving immunotherapy to the adjuvant setting

The IMpower 010 trial involved the enrollment of patients with surgically re-moved stage IB to IIIA NSCLC in 2018, as stated by Felip and colleagues [7]. In this clinical trial, patients who had completed adjuvant platinum-doublet chemotherapy were randomly assigned to receive either atezolizumab for a maximum of 1 year or the best available supportive care. Postoperative radiotherapy was prohibited. A total of 1,005 patients were included in the study. Among them, 87.8% had stage II–IIIA disease, and out of these patients, 53% had PD-L1 levels equal to or greater than 1%. The primary outcome measure, disease-free survival (DFS), demonstrated a significant im-provement with atezolizumab compared to best supportive care, with a median DFS not yet reached versus 35.3 months (hazard ratio [HR] 0.66; p=0.004). The incidence of grade 3 or 4 adverse events was 22.0% in the atezolizumab group and 11.5% in the placebo group.

In October 2021, the FDA granted approval for the use of adjuvant atezolizumab in patients with resected stage II–IIIA PD-L1-positive NSCLC, based on the findings of this study [24].

The PEARLS trial [8] by Brien and colleagues was a triple-blinded, place-bo-controlled phase III trial enrolling patients with the same disease stages as in the previous trial but it did not mandate adjuvant platinum-doublet chemotherapy in pa-tients with stage II–IIIA disease, measuring same primary endpoint DFS. Patients were randomly assigned to receive pembrolizumab or placebo. After a median follow-up of 35.6 months, the primary endpoint favored pembrolizumab (median 53.6 months vs. 42.0 months with placebo; HR 0.76; P=0.0014) [25]. Serious adverse events occurred in 24% of participants in the pembrolizumab group and 15% in the placebo group. In contrast to the IMpower 010 trial, PD-L1 expression of =50% was not asso-ciated with DFS benefit. The results of these trials led to the FDA approval of pem-brolizumab for adjuvant treatment after platinum-based chemotherapy in patients with stage IB–IIIA NSCLC, irrespective of expression of PD-L1.

Going from Neoadjuvant to /Perioperative Trials

The improvement in OS in the advanced and adjuvant setting, has led to the ques-tion if immunotherapy in the neoadjuvant setting could be the next step for better out-comes. Provencio and colleagues from the NADIM II trial, report a phase II trial where 87 patients with resectable stage IIIA or IIIB NSCLC (8th edition AJCC Cancer Staging Manual) with ECOG 0-1 were randomized to receive neoadjuvant nivolumab plus platinum-based chemotherapy or chemotherapy alone, followed by surgery [26]. Pa-tients in the experimental group who had R0 resections received adjuvant treatment with nivolumab for 6 months. The primary endpoint was a pathological complete re-sponse (pCR), as a surrogate for OS. 57 patients were assigned to the experimental group and 29 were assigned to the control group. pCR occurred in 21 of 57 patients (37%) in the experimental group and in 2 of 29 patients (7%) in the control group (P=0.02). The percentage of patients with a major pCR was greater in the experimental group (53%) than in the control group (14%). The same was true for OS: a response was observed in 75% of the patients in the experimental group and in 48% in the control group (RR, 1.56). OS at 24 months was 85.0% in the experimental group and 63.6% in the control group (HR for death, 0.43). Neoadjuvant treatment with nivolumab plus chemotherapy resulted in a higher percentage of patients undergoing surgery than chemotherapy alone. A total of 53 patients (93%) in the experimental group and 20 pa-tients (69%) in the control group underwent surgery. R0 resection was achieved in 50 patients (94%) in the experimental group and in 17 (85%) in the control group. Grade 3 or 4 adverse events that occurred during the neoadjuvant phase were 19% and 10% respectively, in the two groups. We point out that this study adds information to the neoadjuvant landscape with the two important limitations of pCR not being validated as an OS surrogate as well as a study with a higher number of patients will be needed.

In the study conducted by Wakeee and colleagues, known as KEYNOTE-671, a larger cohort of patients was included in 2018 [17]. This study conducted a phase 3 tri-al to assess the effects of perioperative pembrolizumab in individuals diagnosed with early-stage non-small cell lung cancer (NSCLC). Individuals diagnosed with resectable stage II, IIIA, or IIIB (N2 stage) non-small cell lung cancer (NSCLC) were randomly as-signed to receive either neoadjuvant pembrolizumab or a placebo. Both groups also received cisplatin chemotherapy. Following this treatment, all participants underwent surgery and were then given either adjuvant pembrolizumab or a placebo. The main outcomes measured in the study were event-free survival (EFS) and overall survival (OS) [27]. The 24-month estimated freedom from progression or death rate was 62.4% in the pembrolizumab group and 40.6% in the placebo group. The hazard ratio was 0.58 with a 95% confidence interval, and the p-value was less than 0.001. The pem-brolizumab group had an estimated 24-month overall survival (OS) rate of 80.9%, while the placebo group had a rate of 77.6% (P=0.02). In the pembrolizumab group, a significant pathological complete response (pCR) was observed in 30% of the patients, compared to 11% in the placebo group (P<0.0001). There was a higher incidence of treatment-related adverse events of grade 3 or higher in the pembrolizumab group (44%) compared to the placebo group (37%).

Compared to NADIM II, we highlight that this trial not only had a higher number of patients but also included OS as a primary endpoint. This seems to be the trend go-ing forward in upcoming studies, where a "sandwich" approach will compose of neo-adjuvant and adjuvant therapy with immunotherapy ± chemotherapy.

The phase III checkmate 77T trial conducted by Cascone T et al from the MD An-derson group investigated perioperative strategies in patients with resectable stage IIA and IIIB NSCLC. The trial compared the efficacy of neoadjuvant nivolumab plus chemotherapy followed by surgery and adjuvant nivolumab, with neoadjuvant chem-otherapy followed by surgery [28]. After 25 months of follow-up, the perioperative regimen of continuing nivolumab reduced the risk of disease recurrence, progression, or death by 42% (p= 0.00025). The secondary endpoints of the study included the rate of pathological complete response, which was 35% in the treatment group compared to 12% in the control group. Surgical procedures were conducted in 78% of the patients in the nivolumab/chemotherapy group and 77% of the patients in the chemotherapy-only group. The 12-month EFS rate was 73% compared to 59%, while the 18-month event free survival rate was 70% compared to 50%. The enhanced functional status (EFS) advantage of the nivolumab treatment group was apparent in various subcategories. The effect was more noticeable in patients with squamous histology, stage III disease, and PD-L1 expression of 1% or higher. The incidence of grade 3 or 4 treatment-related adverse events was 32% in the perioperative group and 25% in the control group. The occurrence of surgery-related adverse events was 12% in both groups.

With a similar concept of perioperative immunotherapy strategy but this time with Durvalumab, Heymach et al published the results of the AEGEAN study, where 800 patients with stage II-IIIB where randomized to "sandwich approach" as the Checkmate 77T trial. At the 12-month landmark analysis, event-free survival was ob-served in 73.4% of the patients who received durvalumab vs 64.5% of the patients who received placebo. pCR was significantly greater with durvalumab than with placebo (17.2% vs. 4.3% 13.0; P<0.001. Adverse events of maximum grade 3 or 4 occurred in 42.4% of patients with durvalumab and in 43.2% with placebo [29].

As more immunotherapies are tested in this perioperative setting, more studies continue to show improvement when compared to perioperative chemotherapy alone as shown by the recently published Neotorch trial by Lu S et al, where 500 patients with stage II-III NSCLC got this same strategy tested but this time with toripalimab. The major pathological response rate was 48.5% (95% CI, 41.4%-55.6%) in the toripal-imab group vs 8.4% (95% CI, 5.0%-13.1%) in the placebo group (between-group differ-ence, 40.2% [95% CI, 32.2%-48.1%], P < .001).

Discussion

We performed a comprehensive analysis of immunotherapy in NSCLC. encom-passing its utilization first in advanced metastatic disease as well as in early-stage ne-oadjuvant immunotherapy recently [1,19]. Historically, scientific progress has pre-dominantly concentrated on addressing late-stage diseases before shifting attention to early-stage ailments. The pattern is clearly visible in the context of NSCLC, where treatments that focus on PD-1/PD-L1 and CTLA-4 are now being used for adjuvant and neoadjuvant purposes as well. This is important because a significant number of pa-tients experience the reappearance or return of their condition after surgery and be-come beyond recovery. The advancements in the development of immune checkpoint inhibitors have been a significant milestone. The effectiveness of these treatments has been proven in clinical trials, such as Keynote and Checkmate, both when used in combination with chemotherapy and as standalone treatments. This has led to a sig-nificant improvement in the overall survival rate of patients [20-22].

The progression of research on treating metastatic disease has established the founda-tion for these significant scientific advancements, progressively shifting the attention towards earlier stages of lung cancer, including stage III and now early stages I-IIIA. The adoption of earlier intervention has emerged as the prevailing norm in healthcare, presenting a hopeful prospect for patients [23-25]. The justification for this approach is founded on the assumption that by focusing on the tumor microenvironment prior to the development of metastasis, it is possible to achieve more efficient disease manage-ment. This has the potential to change a previously incurable diagnosis into a condi-tion that can be controlled. The significance of ongoing research and innovation in cancer treatment is highlighted by this fundamental change in approach [17, 26]. The objective is to enhance survival rates and enhance the quality of life for patients at every stage of non-small cell lung cancer (NSCLC). The incorporation of immunother-apy into early-stage lung cancer treatment regimens is a significant advancement that demonstrates our progressing knowledge of cancer biology and therapeutic approach-es [26-30].

A crucial factor in this process has been the simultaneous advancement of predic-tive biomarkers, such as PDL-1 expression and tumor mutational burden. These bi-omarkers aid in the customization of treatments by categorizing the disease and iden-tifying patients who would most likely benefit from the medication without an unnec-essary higher chance of experiencing adverse events. Nevertheless, these biomarkers are not ideal due to the presence of tumor heterogeneity in the case of PD1/PDL-1 and the absence of standardization in the technology used to calculate TMB. As a result, we are unable to accurately predict which patients will derive benefits. For instance, based on keynote 024

and 042, it is evident that PDL>50% serves as a strong indicator of re-sponse. However, the actual response rate (ORR) is only 40%, indicating that even with such high levels of PDL1, responses can fail in 60% of patients. Therefore, we are still far from achieving precision medicine in this context, as we do with targeted therapy. The incorporation of the ideal biomarker PDL1 expression has the potential to involve the analysis of self-released and tumor cell DNA through liquid biopsies, utilizing state-of-the-art technologies to offer unparalleled insights [15-19].

By analyzing data from previous studies and conducting trials with targeted in-quiries, we can strive to identify the most effective combination of oncology treat-ments, including modalities such as immunotherapy, in the context of radiation ther-apy, surgery, and interventional radiology procedures. Other challenges, like those en-countered with other therapeutic approaches, include the lack of effectiveness in cer-tain patients due to resistance mechanisms such as tumor immunization and altera-tions in the microenvironment leading to an increase in regulatory cells. However, these specific challenges are beyond the scope of this review. Some promising areas for future exploration include the development of agents that can specifically target al-ternative checkpoints like TIM-3, LAG-3, and TIGIT to overcome resistance. Potential synergistic approaches to counteract future occurrences of cancer include the utiliza-tion of oncolytic viruses, cancer vaccines, chimeric antigen receptor T cells, targeted antibodies, bone marrow transplantation, and Tyrosine kinase inhibitors [21-24].

It is crucial to recognize that although numerous studies have documented adverse events associated with checkpoint inhibitors, it is primarily adverse events of grades 3 and 4 that require therapy discontinuation. Regardless of the potential for severe com-plications including colitis, pneumonitis, and other adverse effects, checkpoint inhibi-tors are considered safer and more tolerable alternatives to palliative chemotherapy in the medical community [25-28]. However, despite being substantial, the overall sur-vival advantages provided by checkpoint inhibitors are limited. This highlights the critical significance of continuous investigation in the field of metastatic disease. On an ongoing basis, these types of research initiatives have shifted their attention towards the early phases of lung cancer, more precisely stages III and the preliminary stages I-IIIA. This development signifies a fundamental change in thinking, solidifying im-munotherapy as a very important modality for these initial phases [28-30]. The evo-lution signifies a more extensive pattern in oncological treatment approaches, which is to commence intervention during the early phases of the disease with the aim of en-hancing survival rates and the well-being of patients. This underscores the critical im-portance of ongoing research and development in the field of cancer therapy.

Conclusion

The introduction of anti-PD1/PDL1 and anti-CTL4 immunotherapy represents a transformative advancement in the management of lung cancer. Its use starting in metastatic disease and moving to an upfront neoadjuvant/perioperative therapy for NSCLC has been substantiated by a number of clinical trials and evidence. Immuno-therapy's presence in NSCLC continues to expand as new and ongoing data emerge. Despite these advances, the field faces significant challenges, such as identifying more effective biomarkers to predict therapeutic response and devising strategies to prevent or overcome resistance mechanisms. Addressing these hurdles is essential for broad-ening the applicability of immunotherapy, with the goal of treating and potentially curing a larger cohort of patients.

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