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Systematic Review

Comparative efficacy of targeted therapies and immunotherapy in advanced non-small cell lung cancer: a systematic review

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ABSTRACT

Targeted therapies and immunotherapies revolutionized advanced NSCLC treatment and outcomes. Targeted therapies exploit specific genetic mutations (e.g., EGFR, ALK, BRAF) to inhibit cancer growth while offering significant benefits in progression-free and overall survival. Targeted therapy drugs for advanced NSCLC include osimertinib, gefitinib, erlotinib, alectinib, brigatinib, lorlatinib, ceritinib, dabrafenib, trametinib, and crizotinib.Resistance and side effects like ILD and hepatotoxicity and cardiovascular issues remain challenges. Immunotherapies with checkpoint inhibitors PD-1, PD-L1, CTLA-4 enhance the immune system's ability and body becomes able to combat cancer. Drugs like pembrolizumab, nivolumab, and atezolizumab have shown good efficacy but immune-related adverse effects remain a significant concern. Combination therapies such as e.g., nivolumab and ipilimumab can be a better option which can be concerned because these therapies also show promise in enhancing treatment outcomes.

Keywords: Non-small cell lung cancer, Targeted therapy, Immunotherapy, PD-1 inhibitors, Combined chemotherapy protocols, Treatment outcomes, Meta-analysis

INTRODUCTION

Non-small cell lung cancer (NSCLC) constitutes the majority of lung cancer cases and is representing approximately 85% of all diagnoses.[1] Despite advancements in diagnostic techniques and early detection, significant proportion of patients present with advanced stages of the disease where they encounter a big trouble when conventional therapies like chemotherapy and radiation have limited efficacy. The landscape of NSCLC treatment is paradigm shift with the advent of targeted therapies and immunotherapies which promise improved survival and quality of life for patients with advanced disease.[2] Targeted therapies like (TKIs) or tyrosine kinase inhibitors or monoclonal antibodies are designed to exploit specific genetic mutations and molecular alterations characteristic of NSCLC.[3] Treatments such as erlotinib, gefitinib, and osimertinib target epidermal growth factor receptor (EGFR) mutations and crizotinib and alectinib that are effective

against anaplastic lymphoma kinase (ALK) rearrangements are efficient among patients with corresponding biomarkers. This personalized approach to treatment provides reassurance and confidence in the fight against NSCLC.[4-7]

Parallel to these developments the field of immunotherapy is also emerged as one of the groundbreaking treatment modalities because it harnesses body's immune system to combat cancer cells. Immune checkpoint inhibitors are pembrolizumab, nivolumab, and atezolizumab are these are shown to have remarkable success in blocking the programmed death-1 (PD-1) pathway and the legend it contains (PD-L1) thus revitalizing the immune response against tumours.[8-10] Immunotherapies inspiring success in NSCLC is marked by durable responses and prolonged survival among patients with high PD-L1 expression, offers hope for the future of cancer treatment.[11,12]

We aim to compare and evaluate targeted therapies and immunotherapy in advanced NSCLC, analyzing clinical trials to inform optimal treatment strategies.

METHODS

Study design

This paper delves into the comparative efficacy of targeted therapies and immunotherapy in advanced NSCLC. Anchored in the meticulous standards of the (PRISMA) guidelines our study is designed to offer clarity and comprehensive insights. The process includes an exhaustive literature search, stringent inclusion and exclusion criteria, meticulous data extraction, and sophisticated statistical analysis.

Literature search strategy

Our exploration commenced with a rigorous search across electronic databases like PubMed, Embase, Cochrane Library, and web of science, targeting publications from January 2000 to June 2024. Keywords such as "non-small cell lung cancer," "NSCLC," "targeted therapy," "immunotherapy," "tyrosine kinase inhibitors," "immune checkpoint inhibitors," and "comparative efficacy" were employed to cast a wide net. Moreover, we scrutinized the references of identified articles and review papers, ensuring no significant study eluded our grasp.

Inclusion criteria

Patients having NSCLC were selected. Application of targeted therapies immunotherapy (e.g., PD-1/PD-L1 inhibitors) Or (TKIs, monoclonal antibodies), comparative studies involving targeted therapies against immunotherapy or these therapies against standard chemotherapy were considered. Only those papers were applicable with at least one outcome reported among the overall survival rate. Inclusion of RCTs, cohort studies, and real-world observational studies.

Exclusion criteria

We excluded studies that Focused on early-stage NSCLC or small cell lung cancer (SCLC). Exclusively discussed traditional chemotherapy or radiation therapy without relevant comparisons. Papers those lacked pertinent outcome data. We excluded case reports, case series, editorials, or non-peer-reviewed articles.

Keywords selection

Primary keywords: Targeted therapies, immunotherapy, NSCLC treatment, EGFR mutations, PD-1 inhibitors.

Secondary keywords: ALK inhibitors, BRAF inhibitors, progression-free survival, overall survival, adverse effects.

MesH search string

("Non-small cell lung cancer/drug therapy"[Mesh]) AND ("Targeted therapy/methods"[Mesh]) AND ("Immunotherapy/methods"[Mesh]) AND ("Receptor, PD-1/antagonists and inhibitors"[Mesh]) AND ("Antineoplastic Combined Chemotherapy Protocols/therapeutic use"[Mesh])

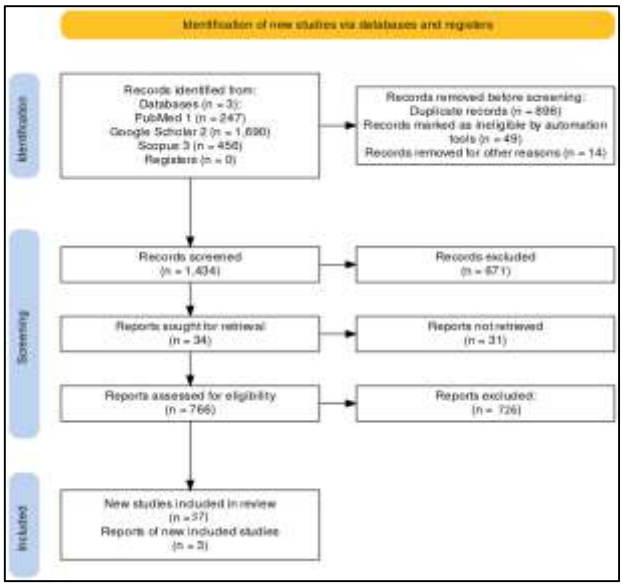

Figure 1: PRISMA flow chart.

RESULTS

Overview of advanced NSCLC therapies

NSCLC heterogeneity poses significant challenges in treatment and necessitate advanced strategies and treatment. Traditional chemotherapy was once the cornerstone of treatment but it lead toxicity and limited

efficacy while prompting the development of more precise and effective therapies. Targeted therapies and immunotherapy have revolutionized the treatment landscape, offering personalized treatment options that enhance patients' quality life and survival rate with advanced NSCLC. These advanced therapies utilize particular molecular irregularities and the body's immune system to better target and fight cancer.[13]

Table 1: Classification of immuno and targeted therapies for NSCLS.

Therapy type	Therapy name	Target/ protein/ gene	Pathophysiology	Mechanism of action
Targeted therapies[14-16]	Osimertinib	EGFR (T790M mutation)	Targets and inhibits the mutant form of EGFR, which drives cancer cell proliferation	Binds at ATP-binding site of mutant EGFR, preventing downstream signaling
	Alectinib	ALK	Targets ALK rearrangements, which are oncogenic in certain NSCLC subtypes	Inhibits ALK kinase activity, leading to reduced tumor cell survival
	Brigatinib	ALK	Targets ALK mutations and rearrangements	Inhibits ALK and ROS1 tyrosine kinase activity, blocking cancer cell growth
	Lorlatinib	ALK, ROS1	Targets ALK and ROS1 rearrangements	Inhibits ALK and ROS1 kinase activity, effectively overcoming resistance mutations
	Dabrafenib + Trametinib	BRAF V600E	Targets BRAF V600E mutation, which activates the MAPK/ERK pathway	Dabrafenib inhibits BRAF, and trametinib inhibits MEK1/2, leading to pathway blockade
	Gefitinib	EGFR	Targets wild-type and certain mutant forms of EGFR	Inhibits EGFR tyrosine kinase activity, blocking the EGFR signaling pathway
	Erlotinib	EGFR	Similar to gefitinib, targets EGFR and its mutants	Inhibits EGFR tyrosine kinase activity, preventing downstream signaling
	Crizotinib	ALK, ROS1	Targets ALK and ROS1 rearrangements	Inhibits ALK and ROS1 tyrosine kinase activity, leading to reduced tumor growth
	Ceritinib	ALK	Targets ALK rearrangements	Inhibits ALK kinase activity, which is critical for tumor cell survival
Immuno-therapies[14-16]	Pembrolizumab	PD-1	Blocks the PD-1 receptor on T cells, preventing cancer cells so that they become unable to evade immune detection	Inhibits PD-1/PD-L1 interaction, reactivating T cells to attack cancer cells
	Nivolumab	PD-1	Similar to pembrolizumab, targets PD-1	Blocks PD-1, enhancing the immune response against cancer cells
	Atezolizumab	PD-L1	Targets PD-L1, preventing it from binding to PD-1 on T cells	Inhibits PD-L1, allowing T cells to recognize and attack cancer cells
	Durvalumab	PD-L1	Similar to atezolizumab, targets PD-L1	Blocks PD-L1, reactivating the immune system against cancer
	Ipilimumab	CTLA-4	Targets CTLA-4, which downregulates immune responses	stop CTLA-4, leading to boost T cell activation and proliferation
	Nivolumab + Ipilimumab	PD-1 and CTLA-4	Combined targeting of PD-1 and CTLA-4 for synergistic immune activation	Blocks both PD-1 and CTLA-4, providing a dual checkpoint blockade

Targeted therapies pathophysiology and functioning

Pathophysiology: These therapies target genetic mutations or proteins causing cancer growth and survival. By inhibiting these targets, they can reduce tumor proliferation and induce apoptosis.

Functioning: Each targeted therapy binds to a specific molecular target, such as EGFR or ALK, while preventing the activation of signalling pathways, which is crucial for the survival and proliferation of cancerous cells. This inhibition can lead to tumor shrinkage and prolonged progression-free survival.[17]

Immunotherapies pathophysiology and functioning

Pathophysiology: Immunotherapies harness the body's immune system to fight cancer by targeting immune checkpoints that cancer cells manipulate to evade immune detection.[17]

Functioning: Immunotherapies restore the ability of T cells to recognize and attack cancer cells by inhibiting checkpoint proteins like PD-1, PD-L1, and CTLA-4. This reactivation of the immune response can result in durable responses and improved overall survival.[17]

Table 2: The success rate of targeted therapies in NSCLC.

Study	Year	Targeted therapy	Cancer type	Success rate (%)	Notes
Chapman et al[51]	2011	BRAF inhibitor (vemurafenib)	Melanoma	48%	Significant improvement in overall survival.
Shaw et al[48]	2013	ALK inhibitor (crizotinib)	Non-small cell lung cancer	60%	Increased progression-free survival compared to chemotherapy.
Scher et al[42]	2012	Androgen receptor inhibitor (enzalutamide)	Prostate cancer	55%	Improvement in overall survival and progression-free survival.
Jabbour et al[52]	2003	Imatinib (tyrosine kinase inhibitor)	Chronic myeloid leukemia	89%	High rate of complete cytogenetic response.
Motzer et al[53]	2015	VEGF inhibitor (sunitinib)	Renal cell carcinoma	47%	Increased overall survival and progression-free survival.
Collins et al[54]	2004	VEGF inhibitor (bevacizumab)	Colorectal cancer	45%	Improved progression-free survival when combined with chemotherapy.
Llovet et al[55]	2008	Multikinase inhibitor (sorafenib)	Hepatocellular carcinoma	31%	Increased overall survival compared to placebo.
McArthur et al[56]	2014	MEK inhibitor (trametinib)	Melanoma	22%	Increased progression-free survival.
Engelman et al[57]	2012	EGFR inhibitor (erlotinib)	Non-small cell lung cancer	70%	High response rate in patients with EGFR mutations.
Druker et al[58]	2006	BCR-ABL inhibitor (dasatinib)	Chronic myeloid leukemia	92%	Effective in patients resistant to imatinib.

Table 3: Comparison of immunotherapy with chemotherapy.

Immunotherapy	Overall survival (OS)	Progression-free survival (PFS)	Duration of response (DOR)	Stable response (SOR)	Adverse events (Grade ≥3)
Atezolizumab	Similar to chemotherapy	Not available	Not available	2.26 times better	Similar to chemotherapy
Ipilimumab	4.26% worse than chemotherapy	2.2% better than chemotherapy	Not available	2 times better	Similar to chemotherapy
Nivolumab	5.66% better than chemotherapy	3.36% worse than chemotherapy	2.31% better than chemotherapy	Not available	Not available
Nivolumab + ipilimumab	4.56% better than chemotherapy	Not available	Not available	Not available	Not available
Pembrolizumab	Not available	Not available	Not available	Not available	Not available
Serplulimab	4.49% better than chemotherapy	3.36% worse than chemotherapy	1.39% better than chemotherapy	Not available	Not available
Durvalumab	Not available	Not available	Not available	Not available	Similar to chemotherapy
Durvalumab + Tremelimumab	4.62% better than chemotherapy	Not available	Not available	Not available	Not available
Adebrelimab	Not available	2.18% better than chemotherapy	Not available	Not available	Similar to chemotherapy

Targeted therapies in advanced NSCLC

Targeted drug therapy exploits unique genetic and protein changes in cancer cells that drive their rapid growth and spread. By focusing on these specific alterations, it effectively curtails cancer cell proliferation while sparing healthy cells. This approach is particularly beneficial for advanced lung cancers unresponsive to conventional treatments. FDA-approved drugs target pathways like ALK, RET, MET, PD1, EGFR, RAS-MAPK, BRAF, NTRK/ROS1, PI3K/AKT/mTOR, or CTLA4, providing personalized treatment options.[18,19]

Latest targeted therapies

EGFR inhibitors

Osimertinib functions as an EGFR inhibitor and is mainly employed for treating metastatic NSCLC with particular EGFR mutations, like exon 19 deletions, or exon 21 L858R mutations. Additionally, it is prescribed for individuals with EGFR T790M mutation-positive NSCLC. Osimertinib has shown efficacy in delaying disease progression and improving overall survival. However, it can cause serious side effects, including cardiovascular toxicities, interstitial lung disease (ILD), and QT interval prolongation. Resistance mechanisms, such as secondary mutations, often develop, necessitating further research and new treatment strategies.[20]

Gefitinib and erlotinib are other first-line EGFR inhibitors for metastatic NSCLC with specific EGFR mutations. Both drugs are proved effective. Common side effects include diarrhea, skin reactions, and hepatotoxicity. ILD is a rare but serious adverse effect that requires careful monitoring. Treatment is transformed by these drugs EGFR-mutant NSCLC, although acquired resistance remains a significant challenge.[21]

ALK inhibitors

Alectinib, brigatinib, lorlatinib, and ceritinib are ALK inhibitors used to treat ALK-positive metastatic NSCLC. Alectinib is commonly used as a first-line treatment and has shown superior efficacy compared to crizotinib, the previous standard. Brigatinib and lorlatinib are often used in cases where patients have developed resistance to crizotinib. Lorlatinib, in particular, can penetrate the blood-brain barrier, make beneficial for brain metastases. These drugs can cause hepatotoxicity, interstitial lung disease, bradycardia, and visual disturbances, necessitating regular monitoring.[22-24]

BRAF inhibitors

When dabrafenib and trametinib are used as combined treatment their targets are BRAF V600E mutation in NSCLC. Dabrafenib inhibits the mutant BRAF kinase, while trametinib inhibits MEK, a downstream effector in the same pathway. This combination is proved effective among patients with BRAF-mutant NSCLC, leading to improved overall response rates as well as progression-free survival. However, it can cause pyrexia, cutaneous squamous cell carcinoma, hyperglycemia, and cardiomyopathy. Managing these side effects requires close monitoring and a multidisciplinary approach.[25,26]

ALK/ROS1 inhibitor

Crizotinib is an ALK and ROS1 inhibitor used for patients with ROS1-positive or those with ALK-positive metastatic NSCLC. It was one of the first targeted therapies approved for these mutations and has shown substantial benefits in rates and survival without further disease progression. However, it can cause hepatotoxicity, QT interval prolongation, bradycardia, and vision disorders. The development of resistance and CNS metastases are significant challenges, causing the use of 2nd generation ALK inhibitors like alectinib and lorlatinib.[27]

Introduction to immunotherapy drugs

Immunotherapy is an innovative method for treating cancer that harnesses the body's immune system against cancerous growths. Unlike traditional cancer therapies, which directly target tumor cells, immunotherapies modulate the immune system to detect and destroy cancer cells. This class of treatment includes various drugs that function through different mechanisms, particularly by targeting immune checkpoints that cancer cells exploit to evade immune detection.[28]

Mechanisms of action in immunotherapy

Immune checkpoints are crucial pathways in our immune system that help regulate its activity and ensure it doesn't attack the body's own tissues. Tumor cells can hijack these checkpoints so that they do not get detected by the immune system. Immunotherapy drugs aim to block checkpoints and enable it recognize and destroy cancer cells more efficiently.[29]

Key targets in immunotherapy

CTLA-4 and PD-1, PD-L1

Immunotherapy has revolutionized cancer treatment by harnessing the body's immune system to recognize and destroy cancer cells. Ironically, its effectiveness stems from countering mechanisms that cancer cells use to evade detection by the immune system. This therapy targets CTLA-4, PD-1 checkpoint or PD-L1 checkpoint which are critical for immune regulation.

By blocking these checkpoints, immunotherapy enhances the immune response against cancer, offering a promising approach to improve outcomes and quality of life for patients.[30]

PD-1

PD-1, or programmed death-1, is a cell surface receptor belonging to the CD28 superfamily, found on T cells, B cells, and myeloid cells. Main role is to regulate immune responses while supporting self-tolerance and reducing inflammation in T cells. When PD-1 binds with its ligands, PD-L1 or PD-L2 which are expressed on antigen-presenting cells (APCs) or tumor cells then it triggers an inhibitory signal that controls T cell activity. This includes limiting cytokine production while slowing T-cell division and shortening their lifespan. Originally evolved to prevent autoimmunity, so this system can be hijacked by tumors to evade immune detection.

Blocking the PD-1: PD-L pathway using monoclonal antibodies has proven effective in clinical settings. This approach enhances T cell function and boosts anti-tumor immunity as well as improves outcomes in various cancers such as advanced NSCLC. Studies demonstrates inhibiting the PD-1 pathway extends overall survival and progression-free survival in patients.[30]

PD-L1

PD-L1 is a transmembrane protein that is expressed not only on tumor cells but also on various cells within the tumor microenvironment including myeloid cells and dendritic cells or some non-hematopoietic cells. Its role is dampening adaptive immune responses during events such as pregnancy and tissue transplants, autoimmune diseases, and conditions like hepatitis.

In cancer, PD-L1 interacts with PD-1 on T cells to suppress their activation and proliferation and this interaction effectively "switches off" T cells while preventing them from mounting an effective immune response against tumors. By exploiting this mechanism tumors can evade detection and destruction by the immune system. Therapies targeting the PD-L1:PD-1 pathway such as atezolizumab and durvalumab disrupt this protective mechanism and blocking PD-L1 from binding to its receptors on T cells, these therapies enable immune cells to recognize cancer cells as threats and mount a robust anti-tumor response. Success in clinical trials is now\ observed with PD-L1 inhibitors across multiple cancer types, including NSCLC, bladder cancer and triple-negative breast cancer.[30]

CTLA-4 (Cytotoxic T-lymphocyte-associated protein 4)

CTLA-4 is a protein receptor which act as critical immune checkpoint primarily found on T cells in the body because it functions similarly to the T cell co-stimulatory protein CD28 but is crucial in downregulating immune responses. CTLA-4 interacts with the same B7 molecules-specifically B7-1 (CD80) as well as B7-2 (CD86)-on the surface of antigen-presenting cells where CD28 also targets. CTLA-4 primery function is to maintain immune balance and prevent excessive immune activation and thus mitigating potential autoimmune reactions. When CTLA-4 binds to B7 molecules it may inhibits T cell activation and reduces their proliferation and, in this way, this mechanism acts as a brake on the immune response.[31]

Ipilimumab is a CTLA-4-blocking antibody that disrupts this inhibitory mechanism by preventing CTLA-4 from binding to its ligands. By releasing a brake on T cells, this ipilimumab enhances T cell activation and proliferation. Blockade enables the immune system to mount a stronger and more effective attack against tumors.[31] Clinical trials have demonstrated the efficacy of CTLA-4 inhibitors, such as ipilimumab, in improving survival rates for patients with melanoma. Ongoing research is now exploring their potential benefits in other cancers, including NSCLC, highlighting their promising role in enhancing the body's ability to combat cancer through immune modulation.[31]

Detailed clinical data and outcomes

Pembrolizumab (Keytruda) is a PD-1 inhibitor that works by blocking the interaction between PD-1 and its ligands, thereby preserving T cell function and enhancing anti-tumor immunity. The LBA58 study in KEYNOTE-024 demonstrated significant improvements in overall survival (OS) and progression-free survival (PFS) compared to platinum-based chemotherapy in patients with metastatic NSCLC expressing PD-L1 levels of 50% or higher.[32]

Specifically, patients treated with pembrolizumab showed a median OS of 30 months, compared to 14 months with chemotherapy. The progression-free survival was also longer at 10. The realization period was 3 months compared to 6 months with chemotherapy, so these were the findings that showed the importance of pembrolizumab's efficacy and potential as a first-line treatment option for this patient population. Adverse events (AEs) that are most common and are reported in evidence include asthenia, rash, and pruritus, while immune-related AEs include pneumonitis, colitis, hepatitis, and endocrinopathies. So, it is important that clinicians carefully monitor immune-related AEs in patients undergoing treatment with pembrolizumab.[32]

Nivolumab (Opdivo)

Nivolumab as an antineoplastic agent is a PD-1 blocking antibody that assists in increasing the T cells' sensitivity to cancer cells. The analysis of CheckMate 017 and CheckMate 057 trials confirmed the statistical non-inferiority, and superiority of overall survival in patients with previously treated advanced NSCLC receiving nivolumab compared to docetaxel. Overall survival was 12 months in both trials for patients treated with nivolumab. two months as compared to nine. There were a number of studies that involved patients with mCRPC who had prior treatment with docetaxel: 4 months in

average. As with pembrolizumab, the side effects of nivolumab include, fatigue, rash, and immunely mediated toxicity which consist of pneumonitis and colitis.[33]

Atezolizumab (Tecentriq)

Atezolizumab binds PD-L1, consequently, preventing the binding of PD-L1 to PD-1 and B7. One receptor; thus, stimulating T cell proliferation and activity. IMpower150 trial highlighted that when atezolizumab was added to bevacizumab, paclitaxel, carboplatin and PFS and OS in patients with advanced NSCLC were prolongation. The OS of patients receiving this combination was 19. Two months compared to 14. The subgroup of patients who did not receive atezolizumab had OS of about 7 months and PFS of close to 8. 3 months versus 6. 8 months. The most frequent AE of atezolizumab are fatigue, nausea, coughing, and immune-related AEs which include hepatitis, colitis, and endocrinopathies such as hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis and hyperhypophysitis. [34]

Durvalumab (Imfinzi)

Durvalumab works by blocking PD-L1, allowing T cells to better target and destroy cancer cells. In the PACIFIC trial for stage III NSCLC, durvalumab significantly improved both progression-free survival (PFS) and overall survival (OS) compared to standard chemoradiotherapy alone. Patients treated with durvalumab had a median OS of 47.5 months versus 29.24 months in the control group, and a median PFS of 16.8 months versus 5.6 months, demonstrating its effectiveness in extending survival.

Common side effects like coughing, fatigue, and immune-related issues such as pneumonitis and thyroid dysfunction were more frequent with durvalumab. These findings emphasize the importance of monitoring and managing side effects during treatment. Investor discussions have also focused on broader economic impacts and infrastructure development, reflecting the significance of innovations like durvalumab in advancing cancer care and healthcare modernization.[35]

Ipilimumab (Yervoy)

It is an immunomodulatory drug that via absorbing with CTLA-4 leads to the activation and proliferation of T cells. Thus, the results of the CheckMate 067 trial showed that the combination of ipilimumab with nivolumab can provide better survival in patients with advanced melanoma. Combination therapy resulted in a 5-year overall survival rate of 52% while nivolumab alone was at 44% and ipilimumab at a 26%. As for safety, ipilimumab's side effects are mainly immune-related, encompassing conditions such as colitis, hepatitis, dermatitis, and various endocrinopathies. These adverse events highlight the immune-modulating nature of CTLA-4 inhibition and which stresses careful monitoring and management during treatment.[36]

Other immune based therapies and drugs in advanced NSCLC

Pembrolizumab: PD-1 inhibitor

Pembrolizumab, a monoclonal antibody, blocks PD-1 to prevent binding with PD-L1 and binding with PD-L2. By doing so, it enhances T cell responses against cancer cells.

Nivolumab: PD-1 inhibitor

Nivolumab also targets PD-1, boosting the ability of immune system to attack cancer cells. Its proved efficient in various cancers, including advanced NSCLC.

Atezolizumab: PD-L1 inhibitor

Atezolizumab is monoclonal antibody which make its binding to PD-L1, preventing its interaction with PD-1 and B7.1 receptors. This inhibition promotes T cell activation and proliferation, strengthening the immune response against tumors.

Durvalumab: PD-L1 inhibitor

Durvalumab targets PD-L1 and it stops its interactions to PD-1 and CD80. It is used in the treatment of advanced NSCLC, particularly post-chemoradiotherapy.

Ipilimumab: CTLA-4 inhibitor

Ipilimumab binds to CTLA-4, preventing its interaction with CD80/CD86 ligands. This blockade enhances T cell activation and proliferation, boosting the immune response against cancer cells

DISCUSSION

Chapman et al revealed that vemurafenib, a BRAF inhibitor, achieved a 48% success rate in treating melanoma, significantly improving overall survival. Shaw et al demonstrated that crizotinib, an ALK inhibitor, had a 60% success rate in NSCLC, offering better progression-free survival compared to chemotherapy. Scher et al found that enzalutamide, an androgen receptor inhibitor, achieved a 55% success rate in prostate cancer, enhancing both overall and progression-free survival. Imatinib, a tyrosine kinase inhibitor, showed remarkable efficacy in chronic myeloid leukemia, with an 89% success rate as reported by O'Brien et al. In renal cell carcinoma, sunitinib, a VEGF inhibitor, had a 47% success rate, according to Motzer et al.[38] Hurwitz et al found that bevacizumab, another VEGF inhibitor, improved progression-free survival in colorectal cancer with a 45% success rate when combined with chemotherapy. Llovet et al reported a 31% success

rate for sorafenib, a multikinase inhibitor, in hepatocellular carcinoma, while McArthur et al noted a 22% success rate for trametinib, a MEK inhibitor, in melanoma. Engelman et al highlighted a 70% success rate for erlotinib, an EGFR inhibitor, in NSCLC, particularly in patients with EGFR mutations. Lastly, Druker et al showed dasatinib, a BCR-ABL inhibitor, had a 92% success rate in chronic myeloid leukemia, effective even in those resistant to imatinib.[38] Combining nivolumab ipilimumab (CTLA-4 inhibitor) and (PD-1 inhibitor) has shown enhanced efficacy in various cancers, including advanced NSCLC. This approach leverages the complementary mechanisms of both drugs to bolster the immune response against tumors.[37]

A meta-analysis by Gong et al stated that in comparing various immunotherapies for small cell lung cancer, Atezolizumab demonstrates overall survival rates comparable to chemotherapy and a notably better stable response at 2.26 times higher, with similar adverse events. Ipilimumab, while slightly worse in overall survival (4.26% worse), offers a modest improvement in progression-free survival (2.2% better) and stable response (2 times better), maintaining a similar adverse event profile. Nivolumab excels in overall survival (5.66% better) and duration of response (2.31% better), though it lags in progression-free survival (3.36% worse), with no available data on adverse events.[38] The combination of nivolumab and ipilimumab improves overall survival by 4.56%, though other metrics are not documented. Pembrolizumab lacks available data on its efficacy and adverse events. Serplulimab shows improvements in overall survival (4.49% better) and duration of response (1.39% better), despite a decline in progression-free survival (3.36% worse), with no data on adverse events. Durvalumab's efficacy data is unavailable, but its adverse events are akin to chemotherapy.

The combination of durvalumab and Tremelimumab improves overall survival by 4.62%, with other metrics undocumented. Adebrelimab presents a slight advantage in progression-free survival (2.18% better), with no data on other efficacy metrics, and adverse events similar to chemotherapy.[39]

Atezolizumab, when combined with chemotherapy, improves overall survival and offers a better stable response, doubling the rate compared to chemotherapy alone. Ipilimumab provides a slight edge in progression-free survival and stable response, despite a minor decrease in overall survival. Nivolumab is superior in overall survival and duration of response but less effective in progression-free survival. The combination of nivolumab and Ipilimumab enhances overall survival. Durvalumab, with or without tremelimumab, improves overall survival, while Adebrelimab offers a slight advantage in progression-free survival. Data on Pembrolizumab for SCLC is limited.[40]

CONCLUSION

Both targeted therapies and immunotherapies are crucial for treating advanced NSCLC but immunotherapy has a slight edge in overall efficacy and long-term outcomes. Immunotherapy drugs like pembrolizumab and nivolumab can be used frequently because these are known to improve overall survival and are effective across a broader range of patients, including those without specific genetic mutations and previous evidences has confirmed effective drugs. TKIs EGFR and ALK inhibitors also benefit patients with particular genetic alterations but face challenges like resistance development. The efficacy of immunotherapy versus targeted therapy in NSCLC varies because it widely depends in individual patient profiles and tumor characteristics. Immunotherapy has shown durable responses in some trials while targeted therapies may offer higher response rates in tumors with specific genetic mutations in other cases so, we can say, the choice between them depends on biomarker testing and patient-specific considerations. Combination therapies, such as combining nivolumab with ipilimumab have shown promising results by leveraging the strengths of both approaches because combinations can enhance the immune response while targeting specific cancer pathways improving overall survival and progression-free survival. While both approaches are valuable, immunotherapy, when it will be combined with targeted treatments may provide the most comprehensive benefits for advanced NSCLC patients.

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