Immunotherapeutic Armamentarium In Non-Small Cell Lung Cancer Treatment And Unlocking The Potential: A Depth Review Study

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Abstract:

Lung cancer remains one of the most prevalent and lethal forms of cancer worldwide, with non-small cell lung cancer (NSCLC) comprising a significant majority of cases. Despite advancements in treatment modalities, including surgery, chemotherapy, and targeted therapy, the majority of patients are diagnosed at advanced stages, limiting the efficacy of conventional treatments. Immunotherapy has emerged as a promising therapeutic approach, leveraging the body's immune system to target and eliminate cancer cells. This review explores the pathophysiology of NSCLC, emphasizing key genetic mutations such as p16, KRAS, and EGFR, which play pivotal roles in tumor development and progression. Challenges in NSCLC treatment, including late-stage diagnosis and the heterogeneity of tumor subtypes, are discussed, highlighting the need for precise diagnostic techniques and personalized treatment strategies. Immunotherapeutic agents, particularly immune checkpoint inhibitors (ICIs), are examined in detail, including PD-1/PD-L1 inhibitors and CTLA-4 inhibitors. These agents have demonstrated significant

efficacy in clinical trials, leading to their approval by regulatory authorities such as the USFDA. Adoptive cell therapy (ACT), involving the manipulation and infusion of T cells, is also explored as a promising avenue for NSCLC treatment. The review encompasses completed and ongoing clinical trials investigating the efficacy and safety of ICIs and ACT, providing insights into the evolving landscape of immunotherapy for NSCLC. Combination approaches, such as the integration of immunotherapy with chemotherapy, radiation therapy, or targeted therapy, are highlighted for their synergistic effects and potential to improve clinical outcomes. In conclusion, immunotherapy represents a paradigm shift in the management of NSCLC, offering renewed hope for patients facing this formidable disease. The integration of immunotherapy with conventional treatments holds promise for enhancing immune responses, overcoming resistance mechanisms, and ultimately improving patient survival rates. However, challenges related to patient selection, treatment sequencing, and adverse event management necessitate ongoing research and clinical investigation. By refining combination approaches, establishing robust treatment guidelines, and optimizing patient care, the full potential of immunotherapy in synergy with other modalities can be realized, paving the way for improved clinical outcomes and prolonged survival for NSCLC patients worldwide**.**

Keywords: Non-small cell lung cancer, chemotherapy, immunotherapy, immune checkpoint inhibitors, cancer vaccines.

INTRODUCTION

Lung cancer is one of the most abundant type of cancer across the world. Lung cancer associated mortality is increasing throughout the world at a rapid rate.[1]. 80 percent of all patients with lung cancer are suffering from non-small cell lung cancer (NSCLC) while remaining 20 percent are diagnosed with Small cell lung cancer (SCLC). NSCLC is further having subtypes based on morphological variations as adenocarcinoma (ADC) comprising 40 -50 % of cases, squamous cell carcinoma (approximately 20-30% of all NSCLC cases) (SCC) and large cell carcinoma (LCC)[2]. Due to its relatively slow growth and low risk of metastasizing when compared to other lung cancer subtypes, lung adenocarcinoma has a favourable prognosis for discovery during screening. Squamous cell lung cancers

typically form within the bronchial tree, more specifically in the left or right bronchi, and smoking is widely acknowledged as the primary etiological factor linked with their development. Small cell carcinoma, SCC, and ADC all have characteristic cytologic and compositional properties, whereas LCC is made up of a heterogeneous assemblage of aggressive and poorly differentiated neoplasms[3]. In clinical settings only small number of patients get diagnosed with NSCLC and can be treated with surgical methods but 60 percent of patient get diagnosed at later stage (stage 3 and stage 4) which makes surgical treatment ineffective and need utilization of cytotoxic agent along with surgical methods. Newer advancements in treatment leads to development of targeted therapy. This has enhanced clinical outcomes but still the 5 years survival rate of lung cancer is less than 20 %. more recent development in immunotherapy has shown promising outcomes in lung cancer patients. these agents work by inhibiting specific immune checkpoints which leads to inhibition of cytotoxic immune response. for example, inhibition of PD1(Programmed death ligand -1) leads to inhibition of EGFRCD8 cells and resulting antitumour immune response. use of these agents requires identification of specific type of NSCLC which can be challenging. It is essential to correctly identify tumours according to their morphology in order to make efficient use of immunotherapy. However, the wide variety of tumours associated with lung cancer, particularly NSCLC, makes diagnosis challenging, particularly when working with scant biopsy samples. [4]. In patient with NSCLC, cytotoxic agents have very poor survival rate with high toxic effects, immunotherapy have generated several molecules which have shown significant positive difference in survival and reduced toxic effects to patients along with improved clinical outcome[5]. For the treatment of patients with advanced NSCLC, total of eight Immune checkpoint inhibitors (ICIs) in which three anti-PD-1 antibodies (nivolumab, pembrolizumab, cemiplimab), two CTLA-4 inhibitor (ipilimumab, tremelimumab) , and three anti-PD-L1 antibody (atezolizumab,Avelumab,Durvalumab), have been licenced by USFDA[1].

Pathophysiology of NSCLC

The mechanisms involved in the development of lung cancer is very complicated and poorly understood. It is postulated that recurrent encounters with carcinogenic substances, notably cigarette smoke, result in dysplasia within the lung epithelium.

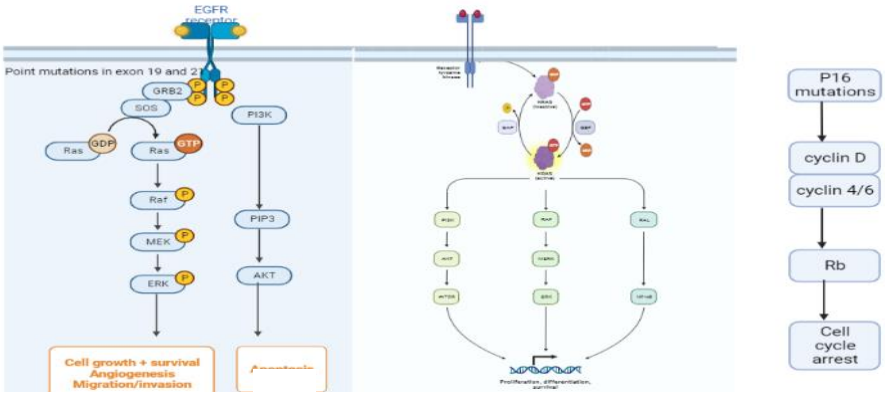
Prolonged exposure to these agents subsequently engenders genetic mutations, which exert an impact on the synthesis of proteins[6]. Thus, the cell cycle is thrown off, which encourages the development of cancer. The most frequent genetic changes linked to NSCLC lung cancer development include p16, KRAS, and EGFR[7].The pathophysiology has been depicted in Figure 1.

1. Epithelial growth factor receptor (EGFR):
   EGFR is a member of the erbB family of closely related receptor tyrosine kinases, which also includes erbB1 (also known as EGFR), erbB2 (HER2K), erbB3, and erbB4. It has a transmembrane section, an intracellular tyrosine kinase, and regulatory domains in addition to an extracellular ligand binding domain[8]. In NSCLC, a significant proportion of cases (43-89%) exhibit either overexpression of EGFR or mutations occurring within the intracellular region of EGFR. Another study indicates that approximately 25% of NSCLC cases harbor mutations specifically within the EGFR tyrosine kinase domain, and these mutations are correlated with elevated receptor expression in 75% of cases. Among the identified mutations within the EGFR tyrosine kinase domain, the majority (more than 90%) manifest as concise in-frame deletions in exon 19 or as point mutations in exon 21, specifically resulting in the substitution of leucine with arginine at codon 858 (L858R). These mutations possess the potential to trigger persistent activation of signal transduction pathways, leading to unrestrained cell proliferation and resistance to apoptosis, regardless of the presence of extracellular ligands. Two less prevalent mutations are detected in exons 18 and 21. Notably, it is observed that EGFR and KRAS mutations are mutually exclusive, indicating a mutually exclusive relationship between these two genetic alterations[9].

2. Kirsten rat sarcoma viral oncogene homolog (KRAS):
   Numerous tumours have been shown to have KRAS mutations. It is the most prevalent driving mutation in lung cancer. Almost 50% of KRAS mutations are codon 12 mutations (KRAS G12C mutations), which, in contrast to other mutations, are frequently found in people who have smoked in the past[10]. Subsequent to initial occurrences, there were genetic variations

observed, specifically substitutions in the glycine (Gly) amino acid, resulting in a valine (Val) G12V mutation at a frequency of 21%. Additionally, mutations were detected involving the substitution of the glycine (Gly) amino acid with aspartic acid (Asp), leading to a G12D mutation at a frequency of 17%. The prevalence of mutations and variations in the KRAS gene differs based on the smoking status of individuals. The presence of smoking-related KRASG12C mutations (found in 41% of former smokers) and KRASG12V mutations in current smokers (individuals who continue to smoke) is linked to transversion mutations in the DNA. These transversion mutations involve nucleotide alterations from guanine (G) to thymine (T) or guanine (Gua) to cytosine (Cyt). Conversely, CDK4G12D (56%), a transition mutation involving a nucleotide change from Gua to adenine (Ade), was the most prevalent KRAS mutation in patients with no smoking history[11].

3. p16 mutation:
   p16 is a gene that functions as a tumor suppressor and is situated on the 9th chromosome of humans. It comprises two introns and three exons. The p16 protein, which is produced by the p16 gene, competes with the cyclin D1 protein for binding to cyclin-dependent kinase 4 (CDK4). This competition leads to the inhibition of cyclin D1/CDK4 complex activity, DNA synthesis, and ultimately halts cell proliferation. When there is a low or absent expression of the p16 protein, uncontrolled cell growth and tumor formation occur. In patients with lung cancer, inactivation of the p16 gene is observed in approximately 25-70% of cases, indicating a strong association between alterations in the p16 gene and the development of tumors [12-13].



A **B** **C**

Figure 1: Pathophysiology involved in NSCLC, [A] represents point mutations in exon 19 and 21 on the EGFR receptors that have been associated with activation of cell signal pathways inducing cell growth, angiogenesis. [B] represents mutations in KRAS gene that activates various signal transduction pathways including mTOR, ERK leading to increased proliferation, differentiation and cell survival. [C] represents mutations in P16 pathways leading to cell cycle arrest

Challenges in NSCLC treatment

Over the past few years, there has been a notable shift in the approach to treating patients diagnosed with advanced NSCLC who have specific oncogene dependencies. The identification of various oncogene drivers has resulted in the creation of targeted therapies tailored to the molecular characteristics of the tumors. Like any remarkable breakthrough, targeted therapies come with their own set of distinct challenges. The major obstacles that hinders broader application of targeted therapies for potentially achieving a cure in advanced NSCLC include resistance in various forms, adverse effects, and the substantial cost of these agents, thereby restricting access for all NSCLC patients[14].

Resistance is the major problem for drugs being less effective not only in NSCLC but also in other types of cancers. This can have a partial response in some patients while a complete response in others. Primary resistance and Acquired resistance are the two main mechanism involved in drug resistance. Primary resistance, also known as intrinsic resistance, refers to the absence of an initial response to treatment despite the presence of a mutation that could be targeted[15]. When tumor progression occurs following an initial positive response to treatment, it is referred to as presumed resistance. A definition for acquired resistance to EGFR TKIs in NSCLC was offered by Jackman et al. in 2010. These fundamental ideas can serve as a broad framework for the clinical definition of acquired resistance with certain modifications[16].

Toxicities pose a significant hurdle in treating NSCLC, leading to therapy resistance. NSCLC offers diverse treatment choices like chemotherapy, targeted therapies, and immunotherapies. However, these treatments carry potential side effects in the form of organ-specific or systemic toxicities. Toxicities stem from chemotherapy's cytotoxic effects, off-target impacts of targeted therapies, or immune-related adverse events linked to immunotherapies[14].

Immunotherapy Basics:

Immunotherapy have modernised since its development and revolutionary outcome in patient with lung cancer as well as in other forms of carcinoma.

Principles of immunotherapy and mechanism of action:

Immunotherapy encompasses therapeutic strategies aimed at utilizing the intrinsic immune system to eliminate cancerous cells. It has gained significant attention in various systemic malignancies. The broad techniques employed in this therapeutic approach involve manipulating the immune system through immunomodulation, immunity checkpoint inhibition, active immunotherapy employing vaccines, and passive immunotherapy involving the use of antibodies and adoptive cell transfer[17].

ICIs enable T cells to initiate an immune response against tumors by bypassing the regular regulatory mechanisms involved in T cell activation. Tumor cells display specific antigens unique to the tumor on antigen-presenting cells (APCs), which allow T cells to recognize and target the tumor. Activation of T cells requires a secondary signal, wherein the CD28 receptor on T cells interacts with the B7 receptor (CD80/86) on APCs. However, T cell activation is a complex process that also triggers an inhibitory pathway, providing self-regulation by dampening or halting the T cell response. T cells express immune checkpoint molecules, including cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1), which become upregulated upon T cell activation[18]. CTLA-4 exerts its regulatory function by downregulating T cell activation through competitive inhibition of CD28 binding to B7 (CD80/86) and inducing cell cycle arrest in T cells. This leads to a reduction in T cell activation and subsequent immune response[19].

Immunotherapeutic agents:

Immunotherapy has emerged as a novel treatment approach for the treatment of metastatic NSCLC. It employs agents that manipulate and activate the patient's immune system to identify and eradicate cancerous cells. This strategy is based on the principle that the immune system has the inherent ability to recognize and target cancer cells by identifying unique molecular markers or antigens on their surface[20]. Immunotherapeutic agents, including ICIs, vaccines, and adoptive cell transfer, function by augmenting the immune response against cancer cells. This mechanism has the potential to impede tumor growth, induce tumor regression, and ultimately enhance patient outcomes[21]. This pioneering treatment approach has brought about a transformative impact in the field of oncology, presenting novel opportunities and renewed optimism for patients diagnosed with metastatic NSCLC.

Immune checkpoint inhibitors (ICIs):

Targeting immune checkpoint pathways to avoid or lessen tumor-mediated immune suppression has resulted in perhaps the most significant advancements in NSCLC immunotherapy. Clinical trials with NSCLC are focusing on a number of monoclonal antibodies that target immune checkpoint pathways, including those involving Programmed cell death protein 1 (PD-1), Programmed death ligand -

1 (PD-L1) and Cytotoxic T-lymphocyte associated protein 4 (CTLA-4) [22]. The mechanism ICIs in tumor cell destructions has been depicted in figure 2 and figure 3.

1. PD-1 and PD-L1

The PD-1 receptor can be found on various cell types such as CD4 and CD8 lymphocytes, B lymphocytes, natural killer (NK) cells, and T regulatory cells (Tregs). The PD-1 receptor interacts with specific ligands, namely PD-L1 (also known as CD274 or B7-H1) and PD-L2 (CD273 or B7-DC), forming crucial signalling pathways that regulate immune responses and maintain immune homeostasis[23]. PD-L1, which is found on T and B cells, dendritic cells, and macrophages, serves as an important checkpoint molecule in the immune system, playing a key role in regulating the balance between immune activation and tolerance. PD-L1 expression is typically raised in solid tumours, particularly in NSCLC, suggesting that it may be a suitable target for immune checkpoint blockade therapy intended to reactivate anti-tumor immune responses[24] [25]. PD-L1 can be found in the cell membrane and/or the cytoplasm, with expression observed in approximately 20-65% of NSCLC cases[26]. The increased presence of PD-L1 in surgically removed NSCLC tumors has been linked to a worse prognosis, although contrasting studies have indicated either improved outcomes or no significant association with survival[26] [27] [28] Numerous PD-1-targeting antibodies, including well-known ones like nivolumab, pembrolizumab, lambrolizumab, and pidilizumab, have been successfully created by the scientific community. These therapeutic antibodies have the potential to significantly advance cancer immunotherapy by utilising immune checkpoint inhibition to activate anti-tumor immune responses.

Nivolumab

Nivolumab is a fully human monoclonal antibody designed through genetic engineering, specifically targeting human PD-1. It is a second-line therapy fir advances NSCLC. It belongs to the IgG4 isotype, which was deliberately chosen to eliminate antibody-dependent cellular cytotoxicity (ADCC) effects. Unlike the prevalent IgG1 subtype commonly found in therapeutic oncology antibodies, which exhibit substantial ADCC activity, the IgG4 subtype possesses minimal ADCC capabilities[29]. A functional ADCC mechanism has the ability to reduce the population of activated T cells and tumor-infiltrating lymphocytes, thereby attenuating their activity, since PD-1 is expressed on T effector cells as well as other immune cells[30] [25].

In this Phase III trial (NCT01642004), 272 patients with advanced or metastatic squamous cell NSCLC who had previously been treated were enrolled and randomly assigned to two study arms. Arm A received Nivolumab (3 mg/kg solution intravenously every 2 weeks), while Arm B received Docetaxel (75 mg concentrate for solution for intravenous infusion every 3 weeks). The results showed that

Nivolumab had a median overall response rate of 20%, while Docetaxel had a median overall response rate of 9%. Moreover, Nivolumab exhibited a superior median overall survival rate of 9.2 months compared to Docetaxel's 6.0 months. It was also found that Nivolumab demonstrated a median progression-free survival of 3.5 months, surpassing docetaxel's 2.8 months. The presence of the PD-1 ligand (PD-L1) did not serve as a reliable indicator for either prognosis or treatment effectiveness. Notably, grade 3 or 4 treatment-related adverse events were significantly lower in the nivolumab group (7%) compared to the docetaxel group (55%). These findings indicate that regardless of PD-L1 expression level, Nivolumab showed better outcomes in terms of overall survival, response rate, and progression-free survival in patients with advanced squamous-cell NSCLC who had received prior treatment[31](Table 1).

The Phase IB/II clinical trial (NCT02523469) investigates the combination of ALT-803 and nivolumab in advanced NSCLC patients (Table 1). The study explores two arms: Arm A for ALT-803 + Nivolumab naive patients, and Arm B for ALT-803 + Nivolumab progressor patients. Different doses of ALT-803 (6mcg/kg, 10mcg/kg, 15mcg/kg, and 20mcg/kg) were administered along with a fixed dose of nivolumab (240mg). Median overall response rates were not reported, but ongoing treatment showed a median overall survival of 17.4 months. This safe outpatient approach provides promising evidence of the effectiveness of combining ALT-803 and nivolumab against NSCLC[32].

Pembrolizumab:

Pembrolizumab, a first-line immunotherapy drug designed to target the PD-1 protein, demonstrates significant effectiveness in combating advanced NSCLC. This humanized monoclonal antibody exhibits potent anti-tumor activity, particularly in cases where tumors exhibit high levels of the PD-L1 protein. By blocking the interaction between PD-1 and PD-L1, pembrolizumab enhances the body's immune response, leading to improved outcomes for patients with NSCLC. At present, the Food and Drug Administration (FDA) has granted approval for the use of this drug in treating advanced melanoma as well as metastatic squamous and non-squamous forms of NSCLC[33].

In a phase III clinical trial (NCT02142738), a randomized and open-label study, the efficacy of pembrolizumab was compared to platinum-based chemotherapy as a first-line treatment for patients with metastatic NSCLC who had strong PD-L1 protein expression (Table 1). The trial involved 305 participants and utilized pembrolizumab IV solution (200mg) along with other chemotherapy drugs such as paclitaxel, carboplatin, pemetrexed, cisplatin, and gemcitabine. The response rate was higher with pembrolizumab (44.8%) compared to chemotherapy (27.8%), and the mean duration of response was longer with pembrolizumab. Pembrolizumab also

demonstrated superior median progression-free survival (10.3 months) and overall survival (80.2%) compared to chemotherapy (6.0 months and 72.4% respectively). Moreover, pembrolizumab exhibited a lower incidence of adverse events[34].

Atezolimumab:

Atezolizumab (MPDL3280) is a type of monoclonal antibody known as IgG1, which has been specifically engineered with modifications in its Fc domain. These modifications aim to reduce the occurrence of antibody-mediated cellular cytotoxicity, a process that can lead to the depletion of T cells expressing PD-L. By implementing this design, atezolizumab helps prevent the loss of PD-L-expressing T cells, thereby preserving their function and enhancing the potential effectiveness of the treatment[35].The FDA has granted approval for the use of this drug as adjuvant therapy in patients with stage II and IIIA NSCLC, following surgical intervention and chemotherapy, for those individuals whose tumors meet the specified criteria[36].

In a phase III study (NCT02409342) (Table 1), researchers conducted an open-label, randomized trial to compare the effectiveness of atezolizumab, an anti-PD-L1 antibody, in combination with a platinum agent (cisplatin or carboplatin) and either pemetrexed or gemcitabine. The study involved chemotherapy-naive patients with stage IV non-squamous or squamous NSCLC who were selected based on their PD-L1 expression levels. Atezolizumab demonstrated a significant improvement in median overall survival (20.2 months) compared to platinum-based chemotherapy (13.1 months), regardless of the specific histologic type. This highlights the potential of atezolizumab in extending survival outcomes for NSCLC patients with high PD-L1 expression. Additionally, when considering the patients eligible for safety assessment, it was observed that adverse events were experienced by 90.2% of individuals in the atezolizumab group, whereas 94.7% of patients in the chemotherapy group encountered such events. Additionally, grade 3 or 4 adverse events were reported by 30.1% and 52.5% of patients in the respective treatment groups[36].

Durvalumab

Durvalumab (MEDI4736) is an immunotherapy drug that has received approval from the FDA. It functions by binding to the PD-L1 protein with exceptional affinity and specificity, effectively inhibiting its interactions with both PD-1 and CD80[37]. Notably, in 2018, the FDA approved durvalumab for patients diagnosed with unresectable stage III NSCLC whose disease has not progressed following concurrent platinum-based chemotherapy and radiotherapy. This approval was based on the positive outcomes observed in the PACIFIC trial, which demonstrated the efficacy of durvalumab in this patient population[38].

The global phase III MYSTIC trial (NCT02453282) investigated the effectiveness of durvalumab (MEDI4736) in combination with tremelimumab or durvalumab alone versus standard platinum-based chemotherapy as a first-line treatment for advanced or metastatic NSCLC. With 1,118 participants, the study focused on median overall survival as the primary endpoint. Results indicated that durvalumab monotherapy achieved a median overall survival of 16.3 months, surpassing chemotherapy's 12.9 months. However, combining durvalumab with tremelimumab lowered the median overall survival to 11.9 months. Although the trial fell short of demonstrating improved overall survival for durvalumab versus chemotherapy or durvalumab plus tremelimumab versus chemotherapy in PD-L1-expressing tumor patients, further exploratory analysis revealed that those with a blood tumor mutational burden (bTMB) threshold of 20 or more mutations per megabase experienced optimal overall survival benefits from the durvalumab and tremelimumab combination. In summary, the MYSTIC trial provided valuable insights into the potential of durvalumab monotherapy and identified a specific mutational burden subgroup that may benefit from the durvalumab and tremelimumab combination[39] (Table 1).

2. CTLA-4 inhibitors

CTLA-4, also known as CD152, serves as an immune checkpoint receptor involved in regulating T cell activation and maintaining self-tolerance. As a result, its presence within the tumor microenvironment holds promise as a significant prognostic and predictive biomarker for individuals with NSCLC[40]. The primary mechanism of action of CTLA-4 involves its competition with CD28 receptors for binding to B7 ligands, specifically B7-1/CD80 and B7-2/CD86, present on APCs. When T-cells are activated, the interaction between CD28 receptors on T-cells and B7 ligands on APCs plays a crucial role by providing the necessary second signal for T-cell activation[41].

A novel and entirely human IgG1 monoclonal antibody called ipilimumab, specifically targeting CTLA-4, has demonstrated promising antitumor effects and improved survival rates in patients with advanced melanoma. These encouraging outcomes suggest that ipilimumab holds promise as a potential treatment option for patients with advanced NSCLC[42].In 2020, the FDA made a significant announcement regarding the therapeutic advantages of combining nivolumab and ipilimumab for the treatment of unresectable malignant pleural mesothelioma (MPM) and NSCLC in adult patients. These immunotherapeutic drugs, administered intravenously, were found to be effective as a first-line treatment option for NSCLC patients with tumor PD-L1 expression of 1% or higher and no EGFR/ALK aberrations[43].

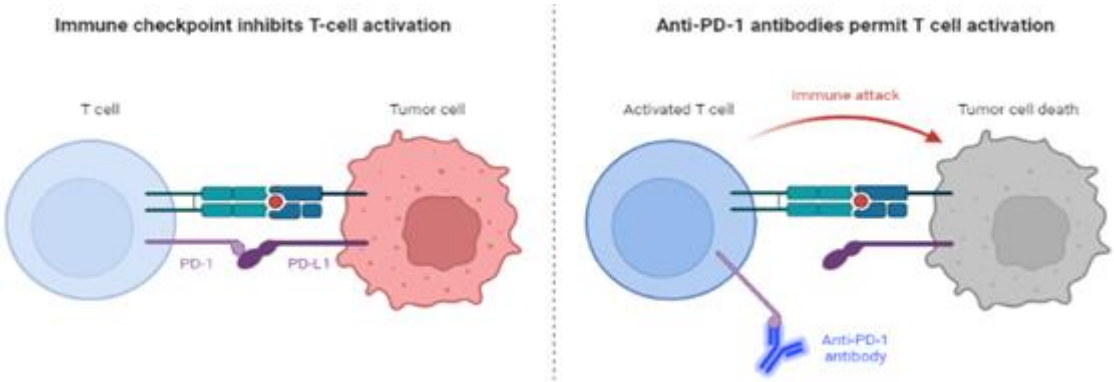


Figure 2: Mechanism of ICIs in the destruction on tumor cell.

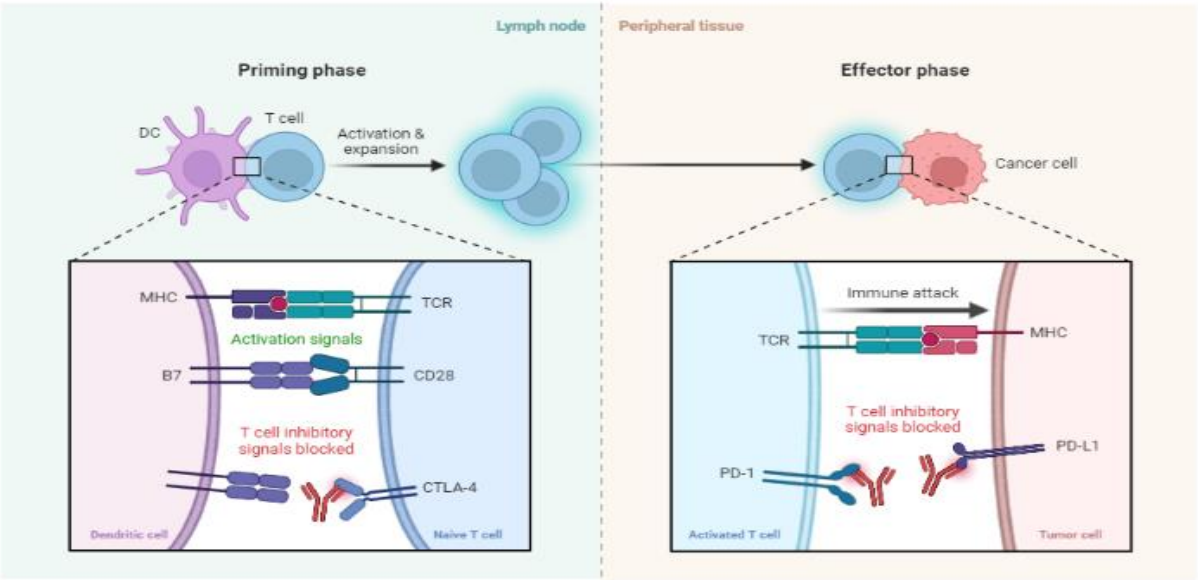


Figure 3: Inhibition of CTLA-4 or PD-1 signalling in tumor immunotherapy

Adoptive cell therapy (ACT):

Adoptive cell therapy (ACT) is an innovative immunotherapy technique that leverages the potency of the patient's immune system to combat specific diseases, with a primary focus on cancer. This individualized approach harnesses the patient's own immune cells to selectively identify and eliminate cancerous cells in the body[44].At present, ACT encompasses three distinct categories, each operating through its unique mechanism: ACT involving tumor-infiltrating lymphocytes (TIL), ACT employing T cell receptor (TCR) gene therapy, and ACT utilizing T cells modified with chimeric antigen receptors (CAR)[45].

In the realm of ACT, TIL therapy aims to overcome barriers

encountered by cancer patients' own T cells. Although these T cells possess the ability to target cancer cells, activation and longevity are crucial for an effective response. TIL therapy tackles this by extracting T cells that have infiltrated the tumor, activating and multiplying them in the lab, and subsequently reintroducing a substantial population back into the patient. Empowered with these activated T cells, the body gains a formidable force capable of seeking out and eliminating tumors with precision[46]. Although ACT utilizing TIL has demonstrated efficacy in melanoma, its effectiveness in treating metastatic NSCLC remains unexplored. In a notable development reported in 2020, a combination approach involving the use of PD-1 inhibitors alongside TIL therapy showcased promising early efficacy for the treatment of metastatic NSCLC. The phase one trial (NCT03215810) focused on patients with metastatic NSCLC who had experienced disease progression following nivolumab treatment. TILs were administered along with interleukin-2 (IL-2), followed by nivolumab to enhance the longevity of the TILs. Encouragingly, two out of thirteen evaluable patients achieved sustained complete responses, suggesting that the integration of TIL therapy with a PD-1 inhibitor holds substantial potential as a viable therapeutic avenue for individuals with metastatic NSCLC who have experienced progression following anti-PD-1 treatment[47].

Chimeric antigen receptors (CARs) are synthetic receptors designed to empower modified T cells with the ability to identify and eliminate tumor cells that exhibit specific antigens unique to the tumor[48].CAR-T cells consist of the patient's own T cells isolated from the blood and subjected to genetic engineering in the laboratory to integrate CARs onto their surface, enabling them to precisely target cancer cells with tumor-specific antigens. These engineered CAR-T cells are then expanded in a controlled environment outside the body before being reintroduced into the patient's system[49].As a result, CARs have the capability to selectively recognize and attach to particular antigens present on cancer cells, leading to the subsequent elimination and destruction of the cancerous cells[50]. CAR-T cell therapy has achieved significant success in treating various forms of blood cancers. However, the focus now lies in expanding the application of CAR-T cell therapy beyond hematologic tumors to encompass a wider range of solid tumors. Extensive research is currently underway to assess the safety and effectiveness of CAR-T cell therapy in treating solid cancers, with approximately one-third of ongoing CAR-T clinical trials dedicated to this exploration[51].Among these trials, a significant portion is dedicated to investigating CAR-T therapy for lung cancer treatment. While there has been remarkable progress in CAR-T therapy for lung cancer, numerous challenges and obstacles persist. As a result, the clinical implementation of CAR-T therapy for NSCLC and SCLC treatment continues to undergo rigorous investigation. Ongoing clinical trials investigating CAR-T therapy for NSCLC and SCLC are primarily centered around targeting specific antigens such as MSLN, MUC1, GPC3, PSCA, EGFR, CEA, HER2, PD-L1,

ROR1, and other promising markers. These trials aim to explore the potential of CAR-T therapy in effectively recognizing and eliminating lung cancer cells by leveraging the unique characteristics and expression patterns of these targeted antigens.

Cancer vaccines:

The objective of cancer vaccines is to activate the immune system by prompting it to identify and react to specific tumor antigens that are ideally found exclusively or abundantly on cancer cells[52].However, since many tumor antigens share similarities or are identical to normal self-antigens, making them less immunogenic, cancer vaccines typically incorporate potent adjuvants to enhance the effective presentation of these proteins by dendritic cells (DCs)[53]. The purpose of cancer vaccines is to carefully choose appropriate antigen targets that can initiate novel immune responses from T cells against cancer cells, enhance pre-existing responses, and broaden the range and diversity of the immune response specifically targeting the tumor[54].Various types of cancer vaccines have been developed for therapeutic purposes, and the following discussion highlights their relevance specifically to NSCLC.

Cell based vaccines:

Cell-based vaccines are created by utilizing either deceased or viable tumor cells that can elicit an immune response in the recipient, with the goal of safeguarding them against potential future diseases or infections. Approaches employing this method encompass the utilization of allogenic tumor cell lines, irradiated autologous tumor cells, or autologous tumor lysates[55].

The Studies evaluating cell-based vaccines in NSCLC have yielded discouraging outcomes. Among them, the GVAX vaccine, which entails genetically modifying whole tumor cells to secrete GM-CSF, employed a combination of autologous tumor cells with an allogenic cell line secreting GM-CSF. In a phase I/II trial examining safety and efficacy, no significant objective tumor responses were observed[56].

Belagenpumatucel-L is a cell-based vaccine comprising four NSCLC cell lines that have been transfected with a pCHEK/HBA2 vector carrying a human transforming growth factor (TGF)-β2-antisense sequence. Phase II trials initially confirmed the safety profile of this allogeneic whole tumor cell vaccine in NSCLC patients, while also demonstrating promising efficacy[57].

Peptide/Protein- specific vaccines:

Peptide-based vaccines imitate specific epitopes derived from antigens, which play a crucial role in initiating an immune response against cancer. These vaccines are designed to mimic the antigenic portions that are recognized by the immune system, effectively

triggering an immune response specifically targeted at combating cancer cells.

In the adjuvant setting, the MAGE-A3 cancer vaccine was investigated for its potential in patients with resected NSCLC. A phase III clinical trial (MAGRIT, NCT00480025) was conducted, involving patients with completely resected stage IB-IIIA MAGE-A3-positive NSCLC, who were randomly assigned to receive either the MAGE-A3 vaccine or a placebo. Unfortunately, the trial yielded unfavorable results, as there were no discernible disparities in disease-free survival between the groups[58].

Table 1: Completed Clinical trials of the approved immune check point inhibitors.

Agents/NCT Number	Study Title	Number of patients	Study Arms	Median response rates	Median survival rates	Study findings
PD-1 inhibitors						
Nivolumab (NCT01642004)	A Phase III trial, labelled as open-randomized, was conducted to compare the effectiveness of BMS-936558 (Nivolumab) with Docetaxel in treating individuals with advanced or metastatic squamous cell NSCLC who had received previous treatment.	272	Arm A: Nivolumab Nivolumab 3 mg/kg solution intravenously (IV) every 2 weeks Arm B: Docetaxel Docetaxel 75 mg concentrate for solution for intravenous infusion every 3 weeks	Median overall response rates: Nivolumab:20% Docetaxel: 9%	Median overall survival rates: Nivolumab: 9.2 months Docetaxel: 6.0 months	Irrespective of PD-L1 expression level, nivolumab demonstrated superior overall survival, response rate, and progression-free survival compared to docetaxel in patients with advanced squamous-cell NSCLC who had received prior treatment.
ALT-803 Plus Nivolumab (NCT02523469)	The study investigates the potential of combining nivolumab with ALT-803 in patients with previously treated, advanced, or metastatic NSCLC in a Phase IB/II clinical trial.	58	Arm A: ALT-803 + Nivolumab naive Arm B: ALT-803 + Nivolumab progressor ALT-803 doses: 6mcg/kg,10mcg/kg 15mcg/kg,20mcg/kg Nivolumab: 240mg	NA	Median overall survival rates: 17.4 month in patients receiving ongoing treatment	Administering ALT-803 in combination with nivolumab in an outpatient environment is deemed safe, paving the way for a potential breakthrough. The positive results of combining ALT-803 with PD-1 monoclonal

						antibody treatment provide strong evidence of its effectiveness against NSCLC.

Pembrolizumab (NCT02142738)	This phase III clinical trial is a randomized, open-label study comparing the efficacy of pembrolizumab versus platinum-based chemotherapy as a first-line treatment in patients with metastatic NSCLC who have strong expression of the PD-L1 protein.	305	Drug: Pembrolizumab IV solution (200mg) Drug: Paclitaxel IV solution (200mg) Drug: Carboplatin IV solution(500mg) Drug: Pemetrexed powder for infusion (500mg) Drug: Cisplatin IV solution (75mg) Drug: Gemcitabine Powder for infusion (1250mg)	Response rate: Pembrolizumab: 44.8 % Chemotherapy: 27.8% Mean duration of response: Was longer in prembrolizumab(not reached) range, [1.9+ to 14.5+ months] vs chemotherapy 6.3 months [range, 2.1+ to 12.6+])	Median progression free survival: Pembrolizumab: 10.3 months Chemotherapy: 6.0 months Overall survival: Pembrolizumab:80.2% Chemotherapy:72.4%	Among individuals diagnosed with advance NSCLC and having PD-L1 expression on a minimum of 50% of tumor cells, pembrolizumab demonstrated marked improvements in both progression-free survival and overall survival, accompanied by a lower incidence of adverse events compared to platinum-based chemotherapy.
Atezolimumab (NCT02409342)	This open-label, randomized phase III study compares the efficacy of atezolizumab, an anti-PD-L1 antibody, with a platinum agent (cisplatin or carboplatin) combined with either pemetrexed or gemcitabine in chemotherapy-naive patients with stage IV non-squamous or squamous NSCLC who have been selected based on PD-L1 expression.	572	Drug: Atezolizumab (1200mg) Drug: Carboplatin Drug: cisplatin (75mg/m^2) Drug: gemcitabine (1250 mg/m^2) Drug: Pemetrexed 500 mg/m^2)	NA	Median overall survival: Atezolimumab:20.2 months Chemotherapy:13.1 months	Regardless of the specific histologic type, atezolizumab treatment led to notably extended overall survival compared to platinum-based chemotherapy in patients with NSCLC exhibiting high PD-L1 expression.

Table 2: Ongoing clinical trials.

Durvalumab (NCT02453282)	The MYSTIC trial is a phase III, randomized, open-label, multi-center, global study that aims to investigate the effectiveness of MEDI4736 in combination with tremelimumab therapy or MEDI4736 monotherapy compared to standard of care platinum-based chemotherapy as a first-line treatment for patients diagnosed with advanced or metastatic NSCLC.	1118	Experimental: Monotherapy (Durvalumab) Experimental: Combination therapy (Durvalumab + tremelimumab) Active comparator: Standard of care Intervention: (Drug: Paclitaxel + Carboplatin Drug: Gemcitabine + Cisplatin Drug: Gemcitabine + Carboplatin Drug: Pemetrexed + Cisplatin Drug: Pemetrexed + Carboplatin)	NA	Median overall survival: Durvalumab: 16.3 months vs Chemotherapy: 12.9 months Median Overall survival: Durvalumab +Tremelimumab: 11.9 months	The phase 3 MYSTIC study did not achieve its primary objectives, which were to demonstrate improved overall survival (OS) with durvalumab compared to chemotherapy or improved OS or progression-free survival (PFS) with durvalumab in combination with tremelimumab compared to chemotherapy in patients whose tumors had at least 25% of tumor cells expressing PD-L1. However, further exploratory analyses revealed that there was an optimal OS benefit with durvalumab plus tremelimumab when the blood tumor mutational burden (bTMB) threshold was set at 20 or more mutations per megabase.

NCT04495153	86	This clinical trial aims to assess the impact of adding CAN-2409 and a prodrug to stage III/IV NSCLC patients receiving first-line IC) treatment with inadequate clinical response. CAN-2409 is a viral immunotherapy that enhances tumor-infiltrating T-cells and increases PD-L1 expression. Combining CAN-2409 with standard checkpoint inhibitors may enhance long-term outcomes in NSCLC patients with suboptimal ICI therapy response.	Stage III/IV NSCLC patients on first-line anti-PD-1/PD-L1 treatment +/- chemotherapy who fall into one of two cohorts: 1) those with stable disease after 18 weeks of ICI treatment, or 2) those with progressive disease after 18 weeks of ICI treatment.	Intervention: Aglatimagene besadenovec Cohort 1A and 1B - persistent but stable disease at least 18 weeks after starting ICI treatment. Cohort 2A and 2B - radiographic progressive disease at least 18 weeks after starting ICI treatment Cohort 3 - refractory disease defined as progressed by imaging at least 9 weeks after starting ICI treatment	Overall response rate (ORR), frequency of adverse events
NCT05805319	80	In this randomized trial conducted at a single center, patients diagnosed with NSCLC undergoing immune checkpoint inhibition will be assigned to receive either standard-of-care ICI therapy alone or in combination with a dietary intervention.	Confirmed histological diagnosis of NSCLC, Treatment with standard-of-care ICI Ability to eat solid foods	Control group: In the control group, patients will undergo dietary surveys and 24-hour recall surveys at baseline, 6 weeks, and 12 weeks after starting ICI treatment, without receiving dietary intervention or counselling from a dietician. Intervention group: In the intervention group, patients will receive dietary surveys, counseling to increase total fiber intake, and undergo dietary and 24-hour recall surveys at baseline, 6 weeks, and 12 weeks after starting ICI treatment.	Total fibre intake comparison between control and intervention arm, Improved panagiotakos MedDietScore comparison

NCT Number	No of Patients	Type of study	Eligibility criteria	Study Arms	Primary objectives
NCT04681131	240	This Phase 2 study is a multi-center, open-label trial that aims to assess the safety, tolerability, pharmacokinetics (PK), immunogenicity, and effectiveness against tumors of BA3011, a biologic ADC called CAB-AXL-ADC, which selectively targets the AXL protein. The study will evaluate both the standalone use of BA3011 and its combination with a PD-1 inhibitor in patients diagnosed with metastatic NSCLC.	Patients must not have had prior therapy with a conjugated or unconjugated auristatin derivative/vinca-binding site targeting payload, No recent major surgery (<4 weeks) prior to BA3011 treatment.	Experimental 1: Biological: CAB-AXL-ADC (BA3011) alone Experimental 2: CAB-AXL-ADC (BA3011) with PD-1 inhibitor	Confirmed objective response rate (ORR) and incidence of safety and efficacy
NCT03313804	57	This study aims to treat NSCLC and HNSCC patients initiating immune checkpoint inhibitors (e.g., Nivolumab, Atezolizumab, Pembrolizumab) as per FDA guidelines. A targeted radiation dose will be delivered to a non-CNS site within 14 days of starting immune checkpoint inhibitors. This approach enhances immune response by releasing tumor antigens from immune inaccessible areas,complementing the effects of checkpoint inhibitors.	Advanced or metastatic NSCLC with tumor size at least 1cm, Treatment for radiation therapy, life expectancy ≥ 3 months	Experimental: immune checkpoint inhibitor + radiation (Nivolumab or pembrolizumab or Atezolizumab) + Radiation therapy	six-month progression free survival (PFS) compared to historical control

Emerging immunotherapies:

Numerous strategies have been employed to optimize the efficacy of immune checkpoint inhibitors by identifying predictive biomarkers for patient selection. Phase III trials have demonstrated promising outcomes when combining PD-1/PD-L1 antibodies with chemotherapy or radiotherapy[59].However, resistance to these treatments remains a challenge as the tumor immune microenvironment is intricate and dynamic. Consequently, there is a growing demand to explore alternative immune checkpoints as potential targets for anti-cancer therapies.

Lymphocyte activation gene-3 (LAG-3):

Initially identified as a membrane protein found in activated NK cells and T lymphocytes, LAG-3 (CD223) is closely situated to the CD4 gene on chromosome 12. It is also expressed on dendritic cells (DCs), B cells, tumor-infiltrating lymphocytes (TILs), and regulatory T cells (Tregs). Early research indicates that LAG-3 acts as a negative regulator in the activation of CD4+ T lymphocytes and plays a critical role in the suppressive capabilities of Tregs[60].Research on LAG-3 in NSCLC patients has revealed contradictory findings. While one study linked LAG-3 protein expression to a negative prognosis and its correlation with PD-1/PD-L1 expression[61], Another study found LAG-3 expressed on TILs in tumor tissues, leading to improved survival[62].These contrasting outcomes underscore the need for additional investigation into the role of LAG-3 in cancer.

T-cell immunoglobulin- and mucin-domain-containing molecule (TIM-3):

TIM-3 serves as an inhibitory receptor, suppressing the activity of both effector T helper 1 (Th1) cells and cytotoxic T-lymphocytes (CTLs), and plays a crucial part in sustaining the tumor's immunosuppressive microenvironment[63].In NSCLC patients with lymph node metastasis and advanced tumor stages, elevated expression of TIM-3 has been observed primarily on CD4+ T cells, indicating its potential involvement in disease progression[64].

B7 Homolog 3 (B7-H3):

B7-H3, also known as CD276, belongs to the B7 family and was first identified in 2001 as a co-stimulator for both CD4+ and CD8+ T cells, promoting the proliferation of cytotoxic T cells and stimulating interferon gamma (IFN-γ) production in activated T cells. It is prevalent in 70% to 80% of NSCLC cases, and its high expression is associated with smoking history and reduced overall survival in patients. Moreover, soluble B7-H3 in malignant pleural effusions could serve as a potential biomarker for assessing the stage of NSCLC[65].

Human endogenous retrovirus- H long terminal repeat-associating protein -2 (HHLA2):

HHLA2, a member of the B7 family found in higher primates, has been detected in a significant percentage (65%) of NSCLC tumor tissues, particularly in cases with low PD-L1 expression[66]. However, its expression is limited in healthy lung tissue. HHLA2 shows promise as a potential therapeutic target for lung cancer and has been observed to impact angiogenesis through its interaction with TMIGD2 on endothelial cells[67]. Nonetheless, further research is needed to fully understand the precise mechanism of HHLA2-induced tumor immune suppression and the complex interplay between its co-inhibitory and

co-stimulatory effects with its ligand. More progress is necessary before HHLA2 immunotherapy can be applied clinically.

CD47 and signal regulatory protein α (SIRPα):

CD47 is a well-known cell surface protein recognized as the "don't eat me" signal, expressed on all human cells, while its receptor, SIRPα, is selectively found on myeloid and neuronal cells within the central nervous system. The binding of CD47 to SIRPα limits the phagocytic and cytotoxic functions of SIRPα-expressing cells, protecting CD47-positive healthy and cancerous cells from clearance[68]. Notably, NSCLC cell lines exhibit heightened CD47 expression, which correlates with tumor stages and distant lymph node metastases. Additionally, the downstream molecule CDC42 plays a pivotal role in promoting tumor invasion and metastasis[69].Consequently, the CD47/SIRPα axis presents a promising target for immunotherapy in both NSCLC and SCLC.

Ethical considerations and regulatory aspects:

Ethics are crucial in managing NSCLC, ensuring equal access to treatment regardless of socioeconomic factors. Addressing disparities and barriers in healthcare delivery is necessary for equitable care. Financial burdens impact access to appropriate NSCLC treatments, necessitating affordability, transparency, and fair allocation of resources. Healthcare providers and policymakers must consider these ethical considerations.

Regulatory agencies, such as the FDA and EMA, play a crucial role in managing NSCLC. They review and approve drugs based on rigorous clinical trial data evaluation for safety and efficacy. These agencies also monitor post-marketing safety and require ongoing surveillance of approved treatments. Pharmacovigilance systems are used to ensure the safety of NSCLC therapies, with healthcare providers, pharmaceutical companies, and patients encouraged to report any adverse events. This aids regulators in evaluating the ongoing safety of approved treatments.

Combination approaches and synergies:

Immunotherapeutic agent with chemotherapy:

The notable achievements of immunotherapy in treating NSCLC have prompted extensive investigations into combining therapies, with the goal of enhancing treatment outcomes and addressing resistance mechanisms. Among these combinations, the synergy between immunotherapy and chemotherapy has emerged as a promising approach, reshaping the treatment strategies for NSCLC patients.

Immunotherapy aims to stimulate the patient's immune system to target cancer cells, while chemotherapy employs cytotoxic drugs to

directly kill rapidly dividing cancer cells. Initially, these two treatment modalities may appear distinct in their mechanisms of action. However, recent research has elucidated the significant potential of integrating these approaches, uncovering a synergistic effect that can maximize the therapeutic impact and improve patient outcomes. Platinum-based combination chemotherapy has been well-established as the first-line treatment for advanced NSCLC and extensive-stage SCLC. These chemotherapeutic agents are commonly considered suitable candidates for combination therapy with ICIs. While the primary mechanism of action for many cytotoxic chemotherapeutic agents involves direct tumor cell killing through DNA damage, inhibition of DNA replication, and cell cycle arrest, they can also enhance the immune response against tumors. This is achieved through the induction of immunogenic cell death, characterized by the release of high mobility group box binding protein-1 (HMGB-1) or adenosine triphosphate (ATP) into the tumor microenvironment. Additionally, these chemotherapeutic agents disrupt immune evasion mechanisms employed by tumor cells, such as the downregulation of major histocompatibility complex class 1 (MHC-I) expression and reduced antigen presentation[70]. Upon the demise of cancer cells, there is a concurrent liberation of tumor antigens and danger-associated molecular patterns (DAMPs) within the tumor microenvironment. This phenomenon leads to an augmented exposure of neoantigens, subsequently intensifying both intratumoral and systemic immune responses. Consequently, the enhanced immune reactions bolster the efficacy of ICI therapy, resulting in heightened response rates[71]. A study published in 2016(Keynote-021) comparing Carboplatin in combination with pembrolizumab versus carboplatin monotherapy shows that patient who received combination has better clinical outcomes in advanced non squamous NSCLC than only monotherapy with Carboplatin [72].Clinical outcomes defined here in terms of multiple endpoints, including objective response rate, progression-free survival, duration of response, overall survival, safety, and the association between PD-L1 expression levels and antitumor activity. Use of ICIs as monotherapy is also limited to certain patients due to late diagnosis of disease and variations in expression of PD-1/PDL-1 expression. This may develop denovo resistance to ICI[73]. To prevent this ICIs are used along with chemotherapy drug as first line therapy in order to achieve desired clinical outcome from immunotherapy.

Radiation therapy and immunotherapy combination:

The combination of radiation therapy and immunotherapy in NSCLC holds tremendous potential, leveraging the local tumour control capabilities of radiation therapy with the systemic immune activation of immunotherapy. This synergistic approach aims to enhance treatment outcomes and improve survival rates in NSCLC patients. The mechanisms through which ionizing radiation induces cell death can be conceptually summarized as the 5R's of radiobiology: repair of

radiation-induced damage, accelerated re-proliferation following radiation exposure, redistribution of the cell cycle, reoxygenation of the tumor microenvironment, and modulation of radiosensitivity[74]. These processes collectively contribute to the complex response of cells to ionizing radiation and play significant roles in the effectiveness of radiation therapy in cancer treatment. Radiation therapy (RT) has the potential to induce a unique form of cellular self-destruction called immunogenic cell death (ICD), which can trigger specific immune responses by mechanisms that are currently not fully understood. ICD instigates subsequent immune reactions against tumors, characterized by the release of tumor-specific substances by irradiated tumor cells, the presentation of tumor-derived substances to T cells by APCs through a process called cross-presentation, and the movement of specialized T cells from lymph nodes to distant tumor locations[74-76].abscopal effect is a phenomenon in which radiation therapy helps immunotherapy to work synergistically. The mechanisms underlying the abscopal effect involve the interplay between RT-ICD and immunotherapy-mediated immune activation. RT induces ICD in tumor cells, leading to the release of danger signals, such as HMGB1, calreticulin exposure, and ATP release. These signals promote the recruitment and activation of APCs in the tumor microenvironment. Concurrently, immunotherapy, particularly ICIs targeting PD-1 or its ligand PD-L1, enhances T cell activation and counteracts immune suppression, facilitating the priming and infiltration of cytotoxic T cells into the tumor bed and distant metastatic sites[77]. Preclinical and clinical evidence has demonstrated the potential of combined RT and immunotherapy to induce abscopal responses in NSCLC. The synergy between RT and immunotherapy holds promise for enhancing local tumor control, reducing distant metastases, and improving overall survival. However, challenges such as optimal timing, radiation dosing, and patient selection need to be addressed to maximize the therapeutic benefits and minimize potential toxicities associated with this combination approach[78].

Target therapy along with Immunotherapy:

The possible use of targeted therapy along with immunotherapy in NSCLC involves leveraging their distinct mechanisms of action. Targeted therapy focuses on inhibiting specific molecular alterations in cancer cells, such as EGFR mutations or ALK rearrangements, thereby disrupting tumor growth signals. Immunotherapy, on the other hand, unleashes the body's immune system to recognize and attack cancer cells by blocking immune checkpoint proteins like PD-1 or PD-L1. By combining these approaches, targeted therapy can target specific molecular vulnerabilities in cancer cells, while immunotherapy enhances the immune response against the tumor, potentially leading to synergistic effects and improved treatment outcomes in NSCLC[79]. The utilization of molecular targeted drugs that hinder the activity of Vascular Endothelial Growth Factor (VEGF),

such as multi-kinase inhibitors that impede VEGF receptors, results in an augmentation of the process known as antigen presentation by dendritic cells. These drugs additionally enhance the activation of T cells during the initial stage, known as priming, and facilitate the movement of T cells from the lymph nodes to the location of the tumor by normalizing the vasculature within the tumor[80, 81]. Furthermore, scientific investigations have revealed that these drugs exert inhibitory effects on the development of regulatory T cells (Tregs), tumor-associated macrophages (TAMs), and myeloid-derived suppressor cells (MDSCs) within the tumor microenvironment. Additionally, they exhibit negative regulatory actions on the expression of immunosuppressive cytokines, including Transforming Growth Factor-beta (TGF-β) and Interleukin-10 (IL-10)[82]. Hence, the administration of VEGF inhibitors leads to the reprogramming of the immunosuppressive tumor microenvironment, transforming it into an environment that promotes immune stimulation.in this manner target therapy promotes response of immunotherapy in patients with advanced stage carcinoma.

Overcoming resistance and challenges:

Mechanism of immunotherapy resistance:

Immunotherapy resistance in NSCLC can arise from tumor-intrinsic factors like loss of antigen presentation, genetic alterations, altered antigen expression, and upregulation of alternative immune checkpoints. Factors within the tumor microenvironment, such as immunosuppressive cells, cytokines/chemokines, stromal components, and hypoxia, contribute to resistance. Immune cell dysfunction, including T cell exhaustion, impaired tumor-infiltrating lymphocytes, and immune cell exclusion, also plays a role. Genetic and epigenetic alterations impact immune-related pathways, and compensatory signaling pathways allow tumors to evade immune attack. Understanding these mechanisms helps develop strategies like combination therapies and personalized approaches to overcome immunotherapy resistance in NSCLC[83].

Strategies to overcome resistance:

Immunotherapies have transformed NSCLC treatment, but resistance remains a challenge. Strategies include combining therapies (e.g., PD-1/PD-L1 inhibitors with chemotherapy), targeting additional immune checkpoints (CTLA-4, LAG-3), modulating the tumor microenvironment (e.g., anti-PD-L1 with anti-VEGF), overcoming tumor heterogeneity with liquid biopsies, personalized medicine based on biomarkers (TMB, PD-L1), exploring novel immunotherapeutic targets (immune checkpoints, neoantigens), enhancing the immune response (vaccines, CAR-T cell therapy), using immunomodulatory agents (epigenetic modifiers), monitoring resistance through imaging or liquid biopsies, and early intervention.

These approaches are still being optimized through clinical trials and research[84].

ADR and safety of immunotherapy:

Immunotherapy in cancer patients has shown promising results and it has gained potential application and increased use has led to identification of new category of toxicity called immune related adverse event (iRAE). Skin, gastrointestinal (GI), endocrine, lung, and musculoskeletal iRAEs are commonly observed, while cardiovascular, hematologic, renal, neurologic, and ophthalmologic iRAEs are less frequent but well-recognized. Although most iRAEs are of mild to moderate severity, there are instances of serious and potentially life-threatening iRAEs reported in the literature, such as severe colitis, pneumonitis, encephalitis, toxic epidermal necrolysis, myocarditis, and autoimmune type I diabetes mellitus (T1DM) leading to diabetic ketoacidosis[73] .Pneumonitis is one of iRAE that can occur as a complication of checkpoint inhibitor therapy. It presents as inflammation in the lung tissue and can be challenging to diagnose and manage. Checkpoint inhibitor pneumonitis (CIP) is characterized by the presence of localized or widespread inflammation in the lung parenchyma. Symptoms often include cough, shortness of breath, and low levels of oxygen in the blood, although some cases may be asymptomatic. It is important to be vigilant for the development of CIP during checkpoint inhibitor therapy, as it has been associated with severe complications, including fatalities[85]. The incidence of any-grade iRAEs resulting from single-agent ICI therapy has been reported to be as high as 90% in certain studies[86], but according to one meta-analysis, the overall incidence of iRAEs with anti-CTLA-4 monotherapy (ipilimumab) is reported to be less than 75%[87]. The occurrence of iRAEs associated with ipilimumab and pembrolizumab has been found to depend on the dosage administered, with higher dose levels resulting in increased toxicity. Furthermore, the toxicity profile may also differ between the adjuvant and metastatic disease settings[87].

Mechanism of ADR:

The development of inflammatory toxicity, particularly driven by CD8 T cell activity, shares overlapping mechanisms with the therapeutic effects of the drugs. However, the precise pathogenesis of immune toxicity remains unclear, and other inflammatory cell types, including Th17 cells and others, have been implicated. The mechanism of toxicity may also differ among different ICIs and can influence the acuity, chronicity, and management of adverse events. Additionally, there have been instances where iRAEs have occurred in patients who have experienced sustained positive responses to treatment[88].

Management of ADR:

The successful management of iRAEs relies on timely identification and intervention, employing immune suppression and/or immunomodulatory approaches tailored to the specific organ

affected and the severity of the toxicity. Early involvement of specialized healthcare professionals, including physicians, nurses, and pharmacists with expertise in iRAEs, is crucial. Hospitalization may be required for severe iRAEs (grade ≥ 4) or grade 3 iRAEs that do not respond to treatment. Hospitalization can expedite diagnostic investigations and mitigate complications arising from potentially life-threatening iRAEs[89].

Ethical considerations and regulatory aspects:

Ethics are crucial in managing NSCLC, ensuring equal access to treatment regardless of socioeconomic factors. Addressing disparities and barriers in healthcare delivery is necessary for equitable care. Financial burdens impact access to appropriate NSCLC treatments, necessitating affordability, transparency, and fair allocation of resources. Healthcare providers and policymakers must consider these ethical considerations[90].

Regulatory agencies, such as the FDA and EMA, play a crucial role in managing NSCLC. They review and approve drugs based on rigorous clinical trial data evaluation for safety and efficacy. These agencies also monitor post-marketing safety and require ongoing surveillance of approved treatments. Pharmacovigilance systems are used to ensure the safety of NSCLC therapies, with healthcare providers, pharmaceutical companies, and patients encouraged to report any adverse events. This aids regulators in evaluating the ongoing safety of approved treatments[91].

Conclusion:

Immunotherapy, as an innovative treatment modality, has revolutionized the management of lung cancer, instilling a renewed sense of hope for patients worldwide. The integration of immunotherapy with chemotherapy, radiation therapy, or targeted therapy has yielded extraordinary synergistic effects, resulting in enhanced clinical outcomes. These concerted strategies hold immense promise in augmenting immune responses against tumors, overcoming resistance mechanisms, and ultimately elevating patient survival rates. Nonetheless, challenges pertaining to patient selection, treatment sequencing, and adverse event management necessitate further scientific exploration and rigorous clinical investigation. By meticulously refining these combination approaches, establishing robust treatment guidelines, and optimizing patient care, the full potential of immunotherapy in synergy with other modalities can be harnessed, leading to improved clinical outcomes and prolonged survival rates for patients grappling with this formidable disease.

Conflict of interests

The authors declare no conflict of interest for the present work

Ethics approval: Not applicable.

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