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Review

The Role of PD-1 and CTLA-4 Blockade in Immunotherapy: Mechanisms of Action and Therapeutic Efficacy in Overcoming Lung Cancer Immune Evasion

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ABSTRACT

Lung cancer remains the leading cause of cancer-related mortality worldwide, with non-small cell lung cancer (NSCLC) accounting for approximately 85% of cases and small cell lung cancer (SCLC) representing a highly aggressive neuroendocrine subtype with a poor prognosis. Tumor cells evade immune surveillance by co-opting immune checkpoint pathways, principally programmed cell death protein 1 (PD-1) and cytotoxic T lymphocyte-associated protein 4 (CTLA-4). This review evaluates the mechanisms and therapeutic potential of PD-1 and CTLA-4 blockade in overcoming immune evasion in lung cancer. A structured narrative literature review synthesized evidence from preclinical studies, landmark clinical trials including KEYNOTE-001 and IMpower133, biomarker investigations, and mechanistic research on PD-1/PD-L1 and CTLA-4 pathways in NSCLC and SCLC. PD-1 suppresses effector T-cell activity and enhances regulatory T-cell function within the tumor microenvironment, while CTLA-4 attenuates T-cell priming through competitive B7 ligand binding. Immune escape is further mediated by HLA class I downregulation, impaired antigen presentation, immunosuppressive cytokine signaling, and tumor-infiltrating regulatory T cells. ICI monotherapy significantly improves overall survival in NSCLC with PD-L1 expression ≥50% compared with platinum-based chemotherapy. First-line atezolizumab plus chemotherapy extended median overall survival to 12.3 months, compared with 10.3 months in extensive-stage SCLC. Dual PD-1/CTLA-4 blockade produces synergistic antitumor responses; however, 70–85% of NSCLC patients develop primary or acquired resistance. PD-1 and CTLA-4 blockade has transformed the therapeutic landscape of lung cancer, yet resistance mechanisms, immune-related adverse events, and the absence of validated predictive biomarkers remain critical challenges. Future research must prioritize

combination strategies, novel checkpoint targets, and multifactorial biomarker panels to broaden clinical benefit.

Keywords: Immune checkpoint inhibitors; PD-1/PD-L1; CTLA-4; lung cancer immunotherapy; tumor immune evasion; tumor microenvironment

1. INTRODUCTION

Lung cancer continues to be one of the most challenging malignancies globally, contributing heavily to morbidity and mortality rates. It is broadly classified into two histological types: non small cell lung cancer (NSCLC), which represents nearly 85% of cases, and small cell lung cancer (SCLC), an aggressive neuroendocrine tumor with a poor prognosis and limited therapeutic success.[1] Despite notable progress in NSCLC research over the past two decades, patients worldwide still face major unmet needs, particularly due to the persistence of drug resistance.[2] A defining aspect of lung cancer biology is its ability to escape immune detection. Although SCLC exhibits a high mutational burden, its response to immune checkpoint inhibitors remains minimal, highlighting intrinsic defects in immune surveillance.[1] Evidence indicates that SCLC tumors suppress natural killer (NK) cell activity through epigenetic silencing of NK activating 2D ligands (NKG2DL), thereby eliminating signals essential for innate immune activation. In NSCLC, sex related differences in immune responses have been observed: female patients often display tumor microenvironments enriched with both innate and adaptive immune cells, whereas male patients more frequently show T cell exclusion and impaired neoantigen presentation.[3]

The immune system plays a central role in detecting and eliminating malignant cells through coordinated innate and adaptive mechanisms. NK cells act as an early defense, bridging innate immunity with downstream adaptive responses, making them promising targets for cancer therapy.[4] Nevertheless, both NK cells and T cells are subject to regulatory pathways that tumors exploit to evade destruction.

Under physiological conditions, immune checkpoints play a crucial role in maintaining immune homeostasis by promoting self-tolerance and preventing autoimmune responses. Cancer cells, however, exploit these regulatory pathways to evade immune surveillance, particularly through checkpoint molecules such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed cell death protein 1 (PD-1), and indoleamine 2,3-dioxygenase 1 (IDO1).[5] Aberrant activation of these inhibitory pathways facilitates tumor progression by suppressing cytotoxic T-cell function and diminishing antitumor immune responses. In addition to PD-1 and CTLA-4, other inhibitory receptors, including VISTA, TIGIT, TIM-3, and LAG-3, contribute cooperatively to immune dysfunction and reinforce tumor immune escape.[6] This immunosuppressive environment is further sustained by complex interactions within the tumor microenvironment involving malignant cells, regulatory T cells, myeloid-derived suppressor cells, and tumor-associated macrophages, all of which promote immune evasion and disease progression.[7]

Programmed cell death protein 1 (PD 1) and cytotoxic T lymphocyte associated protein 4 (CTLA 4) are among the most pivotal immune checkpoint receptors in cancer immunotherapy. Both act as inhibitory regulators of T cell activation, serving complementary roles in maintaining immune balance. Because T cells are central to tumor surveillance, blocking PD 1 and CTLA 4 has become a highly effective therapeutic strategy.[8] These molecules also influence cellular energy metabolism, shaping T cell proliferation and differentiation. Lung cancer cells exploit these pathways to dampen immune activity through diverse mechanisms. Tumor infiltrating lymphocytes frequently co express several inhibitory receptors, reinforcing suppression within the tumor microenvironment. Notably, blockade of PD 1, CTLA 4, or LAG 3 alone whether by genetic deletion or antibody therapy often triggers compensatory upregulation of other checkpoint pathways, thereby sustaining local T cell inhibition.[9] This complexity underscores the rationale for combination approaches.

Traditional cancer treatments such as chemotherapy, radiotherapy, and targeted agents have offered limited durable benefit for many lung cancer patients. In NSCLC lacking actionable molecular drivers, resistance mechanisms remain a major challenge. These include defects in DNA damage repair, alterations in STK11/LKB1, impaired antigen presentation, and the presence of immunosuppressive cell populations within

the tumor microenvironment.[10] The advent of immune checkpoint inhibitors has transformed oncology by enabling the immune system to recognize and destroy malignant cells.[11] Targeting immune evasion through checkpoint blockade has redefined therapeutic paradigms. Since the approval of the first CTLA 4 antibody in 2011 for metastatic melanoma, eight checkpoint inhibitors focused on the PD 1 pathway have gained approval and are now used across 18 cancer types.[12] This breakthrough represents a fundamental shift in cancer treatment, offering durable clinical responses that were rarely achievable with conventional modalities.

The therapeutic principle behind immune checkpoint blockade (ICB) is to reinvigorate T cell activity and strengthen cytotoxic immune responses against malignant cells. ICB achieves this by inhibiting suppressive pathways that are upregulated following T cell activation, most notably PD 1/PD L1 and CTLA 4.[13] Blocking these checkpoints restores antitumor immunity and enhances the immune system's ability to eliminate cancer cells. Dual inhibition of PD 1/PD L1 and CTLA 4 targets distinct stages of T cell activation, producing synergistic effects that amplify immune responses.[14] This combined strategy represents a significant advancement in immunotherapy, as it simultaneously addresses multiple mechanisms of immune suppression. While single agent blockade often fails to prevent tumor progression, dual PD 1/CTLA 4 inhibition and even triple blockade involving PD 1, LAG 3, and CTLA 4 have achieved tumor free survival in preclinical models.[9] Durable antitumor immunity in these settings is linked to increased CD8+ T cell infiltration, higher frequencies of cytokine producing effector T cells and reduced populations of regulatory T cells and myeloid derived suppressor cells.

Immune checkpoint inhibitors have reshaped treatment strategies for advanced NSCLC and SCLC.(14) Clinical data indicate that monotherapy with ICIs in NSCLC patients whose tumors express PD L1 at ≥50% can improve overall survival, progression free survival, and response rates compared with platinum based chemotherapy, while also reducing toxicity and improving quality of life.[15] Nevertheless, resistance to checkpoint blockade remains a major obstacle, and many patients experience limited benefit.[13] Recent trials investigating combined PD 1/PD L1 and CTLA 4 inhibition in lung cancer have shown variable efficacy, with immune related adverse events remaining a significant concern.[14] Against this backdrop, the present study aims to comprehensively evaluate PD 1 and CTLA 4 blockade as immunotherapy, focusing on their mechanisms of action and therapeutic potential in overcoming immune evasion in lung cancer. Although predictive biomarkers are not yet fully defined, tumor mutational burden (TMB), PD L1 expression, and specific genomic alterations have emerged as promising indicators of response.

2. LUNG CANCER AND IMMUNE EVASION

2.1 Overview of Tumor Immunology in Lung Cancer

Lung cancer remains the leading cause of cancer related mortality worldwide, with non small cell lung cancer (NSCLC) accounting for approximately 85% of all cases.[16] The process of immunosurveillance, whereby the immune system detects and eliminates malignant cells, is central to cancer biology. In recent years, immune checkpoint inhibitors (ICIs) have fundamentally altered therapeutic approaches for both advanced NSCLC and small cell lung cancer (SCLC).[14] Two principal checkpoint pathways have been identified as targets of ICIs: programmed death receptor 1/programmed death ligand 1 (PD 1/PD L1) and cytotoxic T lymphocyte associated antigen 4 (CTLA 4). The tumor microenvironment (TME) in lung cancer is highly complex and plays a decisive role in shaping the effectiveness of antitumor immune responses. Inhibitors directed against PD 1/PD L1 or CTLA 4 have transformed NSCLC treatment over the past decade.[7] The TME is particularly important in immunotherapy outcomes, as it mediates interactions between malignant cells and immune components.[7] Studies examining lung cancer through the lens of the TME have revealed a multifaceted interplay involving tumor angiogenesis, soluble mediators, immunosuppressive elements, and stromal or immune cells within the microenvironment, all of which contribute to tumor progression.[7]

Lung tumors also demonstrate heterogeneous responsiveness to host immune defenses, influenced by histological subtype, molecular characteristics, and disease stage. Both incidence and mortality rates for lung cancer remain among the highest globally, including in the United States. Immunotherapy has gained prominence due to its favorable safety profile, durable activity linked to immunologic memory, and

applicability across diverse patient populations.[17] Increasing evidence suggests that impaired antitumor immunity facilitates tumor progression, underscoring the importance of strategies that restore immune competence.

2.2 Mechanisms of Immune Escape: Antigen Loss, Immunosuppressive Cytokines, and Regulatory T Cells

Immune evasion is a major obstacle in cancer treatment, allowing tumor cells to escape immune recognition and elimination, thereby limiting therapeutic effectiveness and contributing to unfavorable clinical outcomes. This review explores the mechanisms underlying this process by discussing tumor-induced immunosuppression, immune checkpoint regulation, and the genetic and epigenetic alterations that promote immune escape.[18] It also highlights several pivotal signaling pathways involved in these processes, including programmed cell death protein 1/programmed death-ligand 1 (PD-1/PD-L1), cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), transforming growth factor-β (TGF-β), nuclear factor kappa B (NF-κB), and the cyclic GMP-AMP synthase–stimulator of interferon genes (cGAS–STING) pathway, all of which play essential roles in shaping the immunosuppressive tumor microenvironment and facilitating immune escape.[18]

Antigen loss and impaired presentation

Major histocompatibility complex class I (MHC I) molecules bind peptides derived from a cell's expressed genes and present them on the cell surface, thereby allowing CD8+ T cells to detect abnormal proteins produced within target cells, including malignant ones.[19] During cancer development, many tumors acquire mechanisms that enable them to evade T cell elimination. Because MHC expression is not essential for cellular survival, one common route of immune escape is the loss of antigen presentation machinery (APM).[19] This deficiency not only undermines the natural immune system's ability to eradicate tumors but also limits the effectiveness of immunotherapies designed to reinvigorate antitumor T cell responses, such as checkpoint blockade.[19]

In NSCLC, downregulation of HLA class I expression represents a particularly important immune escape mechanism. One study reported that 28 of 57 lung carcinoma samples (49.1%) either completely lacked HLA class I expression or exhibited selective downregulation of the HLA A locus.[20] This phenotype was linked to haplotype loss and transcriptional suppression of β2 microglobulin (β2 m) as well as the antigen presentation machinery genes LMP2 and LMP7.[20] Analysis of the tumor microenvironment (TME) patterns revealed two reproducible phenotypes: an immune permissive TME characterized by HLA class I expression, intratumoral CD8+ cytotoxic T cells, and M1 type inflammatory macrophages; and a non immune permissive TME defined by strong stromal matrix interactions and M2 type repair macrophages.[20]

Immunosuppressive cytokines and signaling

The tumor stroma, composed of diverse cellular elements and the extracellular matrix (ECM), plays a crucial role in suppressing host immune responses against malignant cells. Within this compartment, the release of immunosuppressive cytokines, metabolic reprogramming, and other cytokine mediated mechanisms establish a complex network that supports tumor growth and survival.[21] Cytokines are central regulators of immune activity and cellular function, and they exert dual roles in both normal physiology and cancer pathogenesis.[22] These molecules, including interleukins, interferons, tumor necrosis factors, chemokines, and growth factors such as TGF β, VEGF, and EGF, influence tumor progression by either promoting or inhibiting growth, reshaping the tumor microenvironment, and modulating therapeutic responses.[22]

Regulatory T cells

Regulatory T cells (Tregs), a specialized subset of CD4+ T cells with immunosuppressive functions, are essential for maintaining immune equilibrium and self tolerance.[23] These cells depend on the transcription factor Foxp3 (Forkhead box protein P3) and employ multiple mechanisms to restrain excessive immune activity, thereby preventing autoimmunity and supporting tissue repair.[23] However, dysregulation of Treg frequency or function, whether through deficiency or hyperactivity, has been implicated in a wide range of pathological conditions, including autoimmune disorders, cancer progression, transplant rejection, and, more recently, neurological and cardiovascular diseases.[23] Within tumors, Tregs contribute to immunosuppression by expressing several inhibitory receptors.[26] Tumor specific T cells often display an exhausted phenotype, characterized by elevated expression of inhibitory molecules such as CTLA 4, PD 1, and LAG 3.[24] Targeting these receptor mediated

tolerance pathways has become a central focus of modern cancer immunotherapy strategies.

2.3 Clinical Implications of Immune Evasion in NSCLC and SCLC

The clinical implications of immune evasion mechanisms differ substantially between NSCLC and SCLC, with significant consequences for treatment outcomes.

Non-Small Cell Lung Cancer (NSCLC)

Immune checkpoint inhibitor-based systemic immunotherapy has become a cornerstone of treatment for patients with non-oncogene-driven non-small cell lung cancer (NSCLC).[25] Despite its clinical success, approximately 70–85% of patients either fail to respond to PD-1 blockade from the outset or develop resistance following an initial therapeutic response, even when checkpoint inhibitors are combined with chemotherapy or anti-CTLA-4 agents. Both primary and acquired resistance remain major barriers to achieving durable clinical benefit. These limitations largely reflect an incomplete understanding of the biological mechanisms underlying immunotherapy and the current lack of reliable predictive biomarkers for patient selection.[25] Increasing evidence suggests that effective immune evasion is closely associated with the progression of solid tumors to advanced stages.[26] Nevertheless, immune escape mechanisms appear to be initiated much earlier during tumorigenesis. Pre-invasive lesions that eventually develop into the major NSCLC subtypes, namely lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC), have been shown to exhibit several immunological alterations, including impaired antigen presentation, loss of heterozygosity within the human leukocyte antigen (HLA) region, neoantigen silencing, activation of immune checkpoint pathways, alterations in T-helper 1 (Th1)/T-helper 2 (Th2) cytokine balance, and progressive remodeling of the immune contexture.[26]

Small Cell Lung Cancer (SCLC)

Small cell lung cancer (SCLC) is among the most aggressive malignancies worldwide and is characterized by frequent relapse and poor survival, despite its initially high responsiveness to first-line platinum-based chemotherapy regimens.[27] Although SCLC typically exhibits a high tumor mutational burden, the clinical efficacy of immune checkpoint blockade (ICB) remains considerably lower than that observed in non-small cell lung cancer (NSCLC).[29] This limited therapeutic response has been attributed to several immune escape mechanisms, including reduced expression of programmed death-ligand 1 (PD-L1), downregulation of major histocompatibility complex (MHC) molecules, and decreased production of regulatory chemokines, all of which impair effective antitumor immune responses.[27]

CLC is strongly associated with tobacco exposure and generally displays a high mutational burden. However, this potentially favorable immunogenic characteristic is counterbalanced by multiple immunosuppressive features, including low PD-L1 and MHC class I expression, limited infiltration of effector immune cells into the tumor microenvironment, and rapid tumor progression, all of which reduce the effectiveness of endogenous antitumor immunity.[28] Although certain characteristics, such as the elevated mutation burden, may increase the potential responsiveness of SCLC to immunotherapy, other factors—including MHC class I downregulation, insufficient PD-L1 expression, poor infiltration of effector T cells, and the accumulation of myeloid-derived suppressor cells and regulatory T cells—collectively diminish immune activation and limit the therapeutic efficacy of checkpoint inhibitors.[28] The key immunological and clinical differences between NSCLC and SCLC are summarized in Table 1.

3. IMMUNE CHECKPOINTS IN CANCER BIOLOGY

3.1 Historical Development of Immune Checkpoint Research

The discovery of immune checkpoint inhibitors has transformed the field of cancer therapy and represents one of the most important milestones in modern oncology. In recognition of their pioneering contributions to cancer immunology, Tasuku Honjo and James Allison were awarded the 2018 Nobel Prize in Physiology or Medicine. Professor Honjo identified programmed cell death protein 1 (PD-1) on T cells, whereas Professor Allison discovered the critical immune checkpoint molecule cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), both of which serve as key negative regulators of T-cell activation.[29] Because tumor cells exploit PD-1- and CTLA-4-mediated signaling to evade immune surveillance, therapeutic blockade of these pathways restores antitumor immune responses and has become a

Table 1. Comparative immunological and clinical features of NSCLC vs SCLC (Data derived from Wang et al. 2025; Tian et al. . 2019; Hamilton and Rath, 2019)[16,27,28]

Feature	NSCLC	SCLC
Proportion of lung cancer cases	Approximately 85% of lung cancer cases	(Less common than NSCLC) ~15%
PD-L1 expression	Variable (often positive)	Generally low
MHC-I expression	Variable with frequent downregulation	Frequently downregulated
Tumor mutation burden	Variable	High
TIL infiltration	Often present	Poor infiltration
ICI response rate	20-45% (monotherapy)	<15% (monotherapy)
FDA-approved ICI therapy	PD-1/PD-L1 ± CTLA-4	Atezolizumab + chemotherapy

cornerstone of cancer immunotherapy.[29] The conceptual basis for immune checkpoint inhibition originated from decades of research into peripheral tolerance, the physiological process by which mature lymphocytes avoid harmful immune responses against self-antigens. Since the early twentieth century, immunologists have investigated the mechanisms responsible for maintaining immune homeostasis while preventing autoimmunity.[30] Continued advances in the molecular understanding of these regulatory pathways ultimately led to the development of checkpoint-targeted therapies that have revolutionized clinical oncology. The central roles of CTLA-4 and PD-1 in immune regulation were recognized internationally through the 2018 Nobel Prize awarded to James Allison and Tasuku Honjo.[30]

The impact of these discoveries was further acknowledged when Professor James P. Allison and Professor Tasuku Honjo received the inaugural Tang Prize in Biopharmaceutical Science for developing a novel therapeutic strategy based on blocking CTLA-4 and PD-1, thereby restoring antitumor immune activity.[31] This approach, known as immune checkpoint blockade therapy, has established a new paradigm in cancer treatment. Beyond their therapeutic applications, the discovery of immune checkpoints has greatly enhanced the understanding of how immune tolerance is maintained and how excessive immune activation is prevented under physiological conditions.[31] The foundations of cancer immunotherapy, however, extend well before the discovery of immune checkpoints. In the late nineteenth century, the German physicians Fehleisen and Busch independently observed spontaneous tumor regression following erysipelas infection, providing some of the earliest evidence that activation of the immune system could suppress malignancy.[32] Building on these observations, William Bradley Coley, widely regarded as the Father of Immunotherapy, intentionally stimulated immune responses to treat bone cancer in 1891, marking one of the first systematic attempts at cancer immunotherapy. Subsequent landmark discoveries in immunology, including the identification of T cells and their fundamental role in adaptive immunity in 1967, greatly expanded knowledge of immune regulation and laid the scientific foundation for the immune checkpoint therapies used in contemporary oncology.[32]

3.2 Physiological Role of PD-1 and CTLA-4 in Maintaining Tolerance

Understanding the physiological functions of immune checkpoints is essential for appreciating their role in cancer therapy and the potential consequences of their blockade.

CTLA-4 in T-cell regulation

Over the past decade, antibody-based immunotherapies have fundamentally reshaped the landscape of cancer treatment by harnessing the immune system to recognize and eliminate malignant cells.[33] These therapeutic advances have provided new treatment options for patients whose disease has become refractory to conventional anticancer therapies. Their primary mechanism of action involves blocking inhibitory immune checkpoint pathways, particularly programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), which are normally upregulated following activation of antigen-presenting cells (APCs) and T cells.[33] By disrupting these inhibitory signals, immune checkpoint inhibitors (ICIs) restore antitumor immune responses. However, because these agents cannot selectively target the tumor microenvironment (TME), they also interfere with the physiological functions of immune checkpoints, which are essential for maintaining peripheral tolerance and preventing autoreactive immune responses. Consequently, treatment with ICIs may lead to a broad spectrum of immune-related adverse events (irAEs).[33]

A recently proposed strategy in cancer control is CTLA-4 inhibition, which enhances antitumor immunity by activating T cells and promoting cytotoxic T-lymphocyte proliferation.[34] Such tolerance-breaking on the tumor is also associated with immune-related adverse events (irAEs) which suggest the crucial role of CTLA-4 in maintaining self-tolerance. CTLA-4 plays an influential role in the attenuation of T-cell activation and the regulation of naïve and memory T cells by engagement with its corresponding ligands B7-1 (CD80) and B7-2 (CD86), and thereby contributing to these processes.[35] The function of CTLA-4 is mainly located within lymphoid tissues at the initial priming point of T-cell activation, where it competes with the costimulatory receptor CD28 for the binding of B7 ligands, thereby attenuating the initial activation signal.

PD-1/PD-L1 in peripheral tolerance

Programmed cell death protein 1 (PD-1) is another key immune checkpoint receptor that functions as a negative costimulatory molecule. It is expressed on activated T cells, B cells, natural killer T cells, and dendritic cells, where it plays a crucial role in regulating immune responses.[36] Engagement of PD-1 with its ligands, programmed death-ligand 1 (PD-L1) and programmed death-ligand 2 (PD-L2), suppresses cytotoxic T-cell activity and limits immune-mediated tissue damage. This signaling pathway is essential for establishing and maintaining immune tolerance, enabling effective defense against pathogens while preventing inappropriate immune reactions against self-antigens. Accordingly, PD-L1 expression on endothelial cells is thought to contribute to the maintenance of peripheral tissue tolerance.[36]

The immunomodulatory effects of the PD-1/PD-L1 axis are primarily mediated through suppression of effector T-cell activity together with enhancement of regulatory T-cell (Treg) function, thereby preserving immune homeostasis and preventing excessive or dysregulated immune responses.[37] The remarkable clinical success of PD-1 and PD-L1 inhibitors in cancer therapy underscores the central role of this pathway in controlling antitumor immunity.[38] However, PD-1/PD-L1 signaling is also involved in regulating inflammatory processes associated with autoimmune diseases, chronic infections, and sepsis, highlighting its dual function in balancing effective immune protection with immune tolerance and limiting immunopathology.[38]

3.3 Dysregulation of Checkpoint Pathways in Cancer Progression

The cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4)/B7 and programmed death 1 (PD-1)/programmed cell death-ligand (PD-L1) are two of the most archetypal immune checkpoint pathways, exerting negative regulatory control over T cell activity in various stages during the generation of T cells. CTLA-4/B7 and PD1/PD-L1 pathway inhibitors have transformed immunotherapies for many cancers. However, while the dual agents anti-CTLA-4/B7 and anti-PD1/PD-L1 therapy showed some clinical efficacy, only a few patients receiving the therapy had prolonged survival. PD-L1 and CTLA-4 expression levels greatly influence the effects of therapy, and understanding the in-depth mechanisms and interactions could assist in identifying patients with improved responses to immunotherapy.[39]

Checkpoint overexpression in tumors

Immunotherapy in cancer that modulate immune checkpoint pathways, including programmed cell death-1 (PD-1)/ programmed cell death ligand-1 (PD-L1) and cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4), have yielded novel success against such therapies in multiple cancers.[40] The strong and enduring clinical response to immune checkpoint blockade (ICB) is now limited to a small group of patients. Notably, individual tumour and immune heterogeneity is distinct and ICB treatment does not successfully reach most patients displaying primary or acquired resistance. In order to open new avenues of therapeutic success, an understanding of the mechanisms that limit the efficacy of immune checkpoint inhibitors (ICIs) is necessary to further ensure their clinical utility across patients and cancer types.[40] PD-L1 and PD-L2 are expressed on the surface of tumor cells in many cancer types; PD-L1 expression has been found both intracellularly and extracellularly in epithelial cancers, including melanoma and non-small cell lung cancer (NSCLC). PD-1 expression is also upregulated on tumor-infiltrating lymphocytes. While the presence of these immune-checkpoint receptors enables some tumors to escape destruction via the T-cell immune response, it also provides a promising target for antitumor therapy.[36]

Mechanisms of adaptive resistance

Although antibodies against the programmed death 1 (PD-1): programmed death ligand (PD-L1) immune checkpoint exert robust antitumor activity in lung cancer, resistance to these therapies has increasingly

been observed. In tumors progressing following response to anti-PD-1 therapy, the upregulation of alternative checkpoints, notably T-cell immunoglobulin mucin-3 (TIM-3), occurs on PD-1 antibody-bound T cells [41]. These data suggest that other immune checkpoints may be targetable biomarkers associated with adaptive resistance to anti-PD-1 blockade.[41]

Immune checkpoint blockade (ICB) therapy restores antitumor immune activity by blocking inhibitory checkpoint pathways, particularly PD-1/PD-L1 and CTLA-4, which are upregulated following T-cell activation. The initial approval of ICB agents by the U.S. Food and Drug Administration (FDA) transformed cancer treatment and accelerated advances in the field of immuno-oncology. However, the development of new checkpoint-targeting therapies has progressed more slowly in recent years. Increasing evidence indicates that both tumor-intrinsic and tumor-extrinsic resistance mechanisms substantially limit the efficacy of ICB. These mechanisms include genomic and non-genomic alterations within tumor cells, as well as host- and tumor microenvironment-related factors, such as alterations in the microbiome, metabolite accumulation, and hypoxia, all of which contribute to therapeutic resistance and hinder clinical outcomes.[13]

Dual checkpoint dysregulation

Immune checkpoint blockade therapy enhances antitumor immunity by inhibiting negative regulators of T-cell activation, particularly cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1). Although combined CTLA-4 and PD-1 inhibition has demonstrated greater therapeutic efficacy than either agent alone, the biological mechanisms underlying this enhanced response remain incompletely understood. An important area of investigation is whether combination therapy influences the same T-cell subsets targeted by individual checkpoint inhibitors or induces distinct immunological changes.[42] While many immunological effects observed with single-agent therapy are retained during combination treatment, several responses appear to be unique to dual checkpoint blockade. For example, anti-PD-1 monotherapy preferentially increases the frequency of highly exhausted cluster of differentiation 8-positive ($CD8^+$) T cells, whereas combination therapy promotes the expansion of activated, terminally differentiated effector $CD8^+$ T cells, suggesting distinct mechanisms of immune modulation (Table 2).[42]

Tumor-specific CD8+ cytotoxic T cells are primarily responsible for the differentiation, survival, and effector function of antitumor immunity. Tumor-specific T cells, owing to poor costimulation and abundant immunosuppressive mechanisms, exhibit a lack of persistence and exhausted and dysfunctional phenotypes. Dysfunctional CTLs and ineffective antitumor immunity can be caused by the involvement of diverse coinhibitory receptors like PD-1, CTLA-4, VISTA, TIGIT, TIM-3, and LAG-3. These coinhibitory receptors are known as immune checkpoint receptors (ICRs), and immune checkpoint inhibitors (ICIs) that target these ICRs are the cornerstone for cancer immunotherapy, as they have created new clinical paradigms for an expanding range of previously untreatable cancers.[6]

Table 2. Summary of immune checkpoint pathways and their roles in cancer (Data derived from Lee et al. 2022; Koyama et al. 2016)[12,41]

Checkpoint	Location of action	Primary function	Cancer exploitation	Therapeutic target
CTLA-4	Lymph nodes	Attenuates T cell priming	Suppresses initial activation	Ipilimumab, Tremelimumab
PD-1	Peripheral tissues/TME	Limits effector function	Induces T cell exhaustion	Nivolumab, Pembrolizumab
PD-L1	Tumor cells/APCs	Engages PD-1	Direct tumor immune escape	Atezolizumab, Durvalumab
LAG-3	TME	Additional inhibition	Enhanced checkpoint signaling	Relatlimab
TIM-3	TME	Exhaustion promotion	Adaptive resistance	Under development
TIGIT	TME	NK and T cell inhibition	Limits cytotoxicity	Under development

4. PD-1 PATHWAY IN LUNG CANCER

4.1 Molecular Interactions Between PD-1 and PD-L1/PD-L2

Programmed death-1 (PD-1) pathway is a significant immune checkpoint pathway that is currently widely studied and has led to a paradigm shift in our understanding of tumor immunology and cancer therapeutics. Programmed death 1 (PD-1), a negative costimulatory receptor, is also an immune checkpoint receptor and can be found on activated T cells, B cells, natural killer T cells, and dendritic cells. This receptor plays a major role in the modulation of peripheral immune tolerance via specific molecular interactions with cognate ligands. The binding of PD-1, along with its ligands, PD-L1 and PD-L2, blocks cytotoxic T-cell response.[36] The action of this interaction in molecular terms results in profound inhibition of effector T cells by PD-1 in the tumor microenvironment. A mechanistic insight into PD-1/PD-L1 signaling has been elucidated through many molecular studies. PD-1 PD-L1 interacts negatively with adaptive response primarily through an inhibition of effector T activity and an enhancement of regulatory T-cell (Tregs) function, thereby mainly performing maintenance homeostasis that protects against dysregulated immunity and harmful responses.[37] This dual effect of repressing cytotoxic T cells while also enhancing regulatory T cell function generates a highly immunosuppressive setting that tumors exploit for escape from the immune pathway. Research has shown that this pathway has a physiological role that goes beyond cancer, with evidence showing that "The PD-1 pathway plays an important role in the induction and maintenance of immune tolerance, allowing the body to fend off diverse pathogens while simultaneously defending against self-reactivity (autoimmunity)".[36]

The discovery of this pathway and its therapeutic potential has been the subject of accolades at the highest levels of society. Tasuku Honjo and James Allison won the 2018 Nobel Prize in Physiology or Medicine for discoveries they made in cancer immunology. Professor Honjo was honoured for finding programmed death molecule-1 (PD-1) on T cells.[29] Functional activation of this pathway has been shown to be more clinically relevant than expression level on its own, with the functional readout of PD-1/PD-L1 interaction as a predictive biomarker to stratify patients with non small-cell lung carcinoma, when coupled with PD-L1 expression, leading to markedly improved response rates to immunotherapy.[43]

4.2 Evidence of PD-L1 Overexpression in Lung Tumors

Over-expression of PD-L1 is a signature of immune escape in non-small cell lung cancer (NSCLC) and manifests with multiple histological subtypes and disease stages. PD-L1 and PD-L2 are expressed on the surface of tumor cells in a wide variety of cancers; both intracellularly and extracellularly to some extent PDL1 expression has been reported as an epithelium marker in epithelial lung cancer types, including melanoma, as well as NSCLC.[36] This pattern of expression allows tumors to directly inhibit responses by antitumor T cells in the tumor microenvironment. The mechanistic insights on how lung tumors upregulate PD-L1 have greatly broadened. In cancer cells, programmed cell death-ligand 1 (PD-L1) is expressed in high degree to escape immune surveillance. PD-L1 binds to PD-1 on T cells to render them inactive.[44] Importantly, PD-L1 expression has been found to be dynamically regulated and modulated in response to the inflammatory milieu. PD-1 expression also has been implicated in the upregulation of tumor-infiltrating lymphocytes,[36] where both the checkpoint receptor and ligand are increased in tumor context in a bidirectional manner. Immune escape in NSCLC has been thoroughly characterized.

Mechanisms of immune escape have been found throughout the lung tumorigenesis. The evolution of precursor lesions to the invasive phase is influenced by a heterogeneous ensemble of immune evasion processes that promotes progression from early stage to metastatic disease; and different molecular sub-populations of lung cancer have unique immunological phenotypes. The complexity is further reflected in pre-malignant lesions, as pre-invasive lesions of adenocarcinoma (LUAD) and of squamous cell carcinoma (LUSC) can have impaired antigen presentation, loss of heterozygosity at the HLA region, silencing of neoantigens, activation of immune checkpoints, shifts in TH1/TH2 cytokine ratios, and evolution of immune contexture.[26]

The tumor microenvironment also has a key role in regulating levels of PD-L1 expression. Non-small cell lung cancers (NSCLC) treatment has been revolutionised by the advent of immune checkpoint inhibitors (ICI) that target programmed death protein 1 (PD-1) plus its ligand (PD-L1), or cytotoxic T lymphocyte antigen 4 (CTLA-4).[7] Differences in immune checkpoint biology between NSCLC and small cell lung cancer (SCLC) have been

extensively reported in comparative studies, where it was suggested that potential immune escape mechanisms in SCLC could arise from low expression of PD-L1 and downregulation of major histocompatibility complex (MHC) molecules and regulatory chemokines,[27] thus accounting for differential responses to immunotherapy between these groups of lung cancer.

4.3 Preclinical Studies Demonstrating PD-1 Blockade Efficacy

Preclinical research has provided reliable evidence confirming the therapeutic basis of PD-1 blockade in lung cancer models. Immunocompetent mouse models have shown potent antitumor efficacy of the PD-1 pathway blockade. Despite impressive antitumor activity of antibodies to the programmed death 1 (PD-1): ligand (PD-L1) immune checkpoint in lung cancer, resistance to these therapies has increasingly been observed.[41] The preclinical observations led to investigation into resistance mechanisms and combination approaches.

Experimental models have thoroughly described the mechanisms of action. Immune checkpoint blockade therapy is a leading weapon against cancer. Anti-PD-1 and anti-PD-L1 antibodies have been shown to have clear advantages, including broad applicability across cancer types; durable clinical response when treatment is effective.[45] Preclinical work has identified potential synergistic effects of combined approaches, highlighting clinical experiences, as in studies that "anlotinib combined with PD-1 blockade significantly inhibited tumor growth and reduced tumor weight in a lung cancer xenograft model compared to any single treatment.[46] Notably, preclinical studies show that immune responses to PD-1 blockade are heterogeneous. In tumours progressing following response therapy, observe upregulation of alternative checkpoints, notably T-cell immunoglobulin mucin-3 (TIM-3), PD-1 antibody-bound T cells, and demonstrate a survival advantage with the addition of TIM-3 blockade.[41] These findings were also used to inform the preparation for combination immunotherapy strategies currently under clinical evaluation.

4.4 Clinical Relevance: Biomarker Studies and Patient Stratification

Translation of the PD-1 pathway understanding into clinical practice has been characterized by a rapid pace of regulatory advances and biomarker development. Pembrolizumab (Keytruda; Merck & Co., Inc., Kenilworth, NJ, USA) is a humanized monoclonal antibody (mAb) that blocks the interaction between PD-1 and its ligands to lead to anti-cancer immune activation. The clinical development paradigm provided new precedents for approval of oncology drugs. The clinical evaluation of pembrolizumab in the KEYNOTE001 trial in metastatic NSCLC recipients was a key event to facilitate breakthrough therapy designation in the indication in 2014, and this was later accelerated and approved by the FDA in 2015 for the management of patients with PD-L1-expressing metastatic NSCLC whose disease progresses on or after platinum-containing treatment.[36] Patient selection strategies have been heavily focused on biomarker development. The NSCLC approval was associated with approval of a companion diagnostic (PD-L1 immunohistochemistry 22C3 pharmDx, Dako, Carpinteria, CA) for PD-L1 expression status.[36] But recent work has contested the reliability of PD-L1 as a candidate biomarker in isolation. "The multisite blinded analysis across a cohort of 188 immune checkpoint inhibitor-treated patients demonstrated a combination of both intra- and intertumoral heterogeneity among immune checkpoint activity of PD-1/PD-L1, and there was no correlation observed between the extent of PD-1/PD-L1 interaction and PD-L1 expression levels.[43]

Current methods also indicate that the predictive power of immunotherapy responses to being multifactorial. This has enabled need for developing sets of biomarkers to predict blockade events. Accordingly, in this review, we have explained predictive anti-PD-1/PD-L1 anti-CTLA-4 therapy, including cells, PD-L1 overexpression, neoantigens, and genetic epigenetic signatures.[47] Molecular genomics has identified more advanced stratification factors indicating that EGFR-mutant and ALK-rearranged tumors elicited inferior responses" while KRAS-mutant tumors showed superior responses to anti-PD-1/PD-L1 immunotherapy in patients with East Asian NSCLC.[48]

5. CTLA-4 PATHWAY IN LUNG CANCER

5.1 Mechanisms of CTLA-4 Mediated Inhibition of T-Cell Activation

Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) has been identified as a major negative regulator of T cell activation in the priming phase of

immune response. CTLA-4 plays an influential role in attenuation of T-cell activation through engagement of naïve and memory T cells with its corresponding ligands, B7-1 (CD80) B7-2 (CD86).[35] This checkpoint molecule works by competing with the costimulatory receptor CD28 to bind to common ligands on antigen-presenting cells, thus preventing T cell activation early in immune response induction. The mechanistic complexity of CTLA-4-mediated immunosuppression is not only limited to competitive inhibition but also involves far more than mere competition. CTLA-4 is constitutively expressed in regulatory T (Treg) cells and is considered one of the most crucial molecules for Treg-cell-mediated immunosuppressive activities, where it suppresses antigen-presenting cells by binding to CD80/CD86.[49] This role also explains both cellular-intrinsic inhibition to conventional T cells and the regulatory functions of Treg cells, CTLA-4 being a powerful negative regulatory modulator of antitumor immunity and a regulatory role, therefore, makes an immune system immunosuppressive agent. CTLA-4 was identified as a therapeutic target through PD-1 discovery. Another crucial immunosuppressive molecule discovered by Professor Allison is cytotoxic T-lymphocyte antigen-4 (CTLA-4). Suppression of T cell activation by PD-1 and/or CTLA-4 is thought to be one of the major mechanisms for escape of cancer cells.[29] The therapeutic strategy for CTLA-4 has been nicely put in words: "Targeting CTLA-4 is a new strategic approach in cancer control, whereby blocking enhances the antitumor immune response through increased T-cell activation and proliferation of cytotoxic T-lymphocytes".[34]

5.2 Role of CTLA-4 in Tumor Microenvironment Modulation

CTLA-4 has significant effects on the tumor microenvironment via a range of mechanisms that include both classical T cell types and regulatory T cell populations. CTLA-4 is an immune checkpoint receptor that plays an important role in the down regulation of T cell activation and maintenance of self-tolerance. In different malignancies, it has frequently become overexpressed. The functional profiles and the expression patterns of CTLA-4 in the tumour microenvironment have become significant predictors of results in immunotherapy. Recent research has identified significant spatial and contextual differences in CTLA-4 function. Expression of CTLA-4 in neither tumor epithelial cells (T-CTLA-4) nor stromal cells (S-CTLA-4) of primary tumors was significantly associated with DSS in all patients. However, higher S-CTLA-4 expression was a separate and independent predictor of superior DSS in the squamous cell carcinoma subgroup.[50] These findings indicate that CTLA-4 biology is multifaceted across various lung cancer subtypes.

The regulatory T-cell compartment is a critical target of CTLA-4 target therapy. Decreased Treg cells in the TME through anti-CTLA-4 mAb with antibody-dependent cellular cytotoxicity (ADCC) is regarded as a critically important strategy to tumor regression. But studies have also identified potential limitations: CTLA-4 blockade without ADCC activity, for example, activated CD28 costimulatory signaling pathways that stimulate Treg cells and expanded Treg-cell proliferation in mouse systems. Moreover, CTLA-4 inhibition enhanced CTLA-4 independent immunosuppressive actions, such as cytokine production, resulting in inadequate antitumor action.[49]

5.3 Experimental Models Highlighting CTLA-4 Blockade Effects

Syngeneic tumor models have been employed in preclinical investigations to elucidate the mechanisms and effects of CTLA-4 blockade. Deactivated CD80-expressing tumor cells (TC-1/dCD80-1) became more immunogenic than parental cells and induced tumors that gained sensitivity to cytotoxic T-lymphocyte antigen 4 (CTLA-4) blockade.[51] The experimental systems have allowed for the development and detailed characterization of immune cell dynamics following checkpoint inhibition. Inhibitor-mediated MEK inhibition in combination with CTLA-4 blockade demonstrates synergistic features. Two MEK inhibitors (MEKis) (selumetinib and trametinib) promote T cell activation by potentiated CTLA-4 expression and, to a lesser extent, PD-1 expression on T cells in vivo following cyclical pulsatile MEKi treatment.[52] Additionally, pulsatile MEKi treatment and CTLA-4 blockade prolong survival in mice carrying tumors harboring mutant KRAS,[52] indicating potential benefits of a rational combined strategy.

The tumor microenvironment undergoes considerable re-organization following CTLA-4 blockade. Anti-CTLA-4 treatment resulted in higher expression levels of the immunosuppressive mediators Cox-2 and Arg1 in the TME. A combination of anti-CTLA-4 with selumetinib reversed this up-regulation of Cox-2 and Arg1, reducing the frequency of CD11+ Ly6G+

myeloid cells.[53] Longitudinal hypoxia imaging studies have also shown that hypoxia is an early predictive biomarker of therapeutic response (before the anatomic changes in tumor volume) and has a decreasing standard uptake value (SUV) ratio in tumors that effectively respond to therapy.[54]

5.4 Clinical Investigations of CTLA-4 Inhibitors in Lung Cancer

In lung cancer, the clinical progress of CTLA-4 inhibitors has predominantly been achieved through combination therapy, with no monotherapy. The anti-CTLA-4 mAb, ipilimumab, is the first immune checkpoint inhibitor, which has led to improved overall survival in patients with unresectable/metastatic melanoma. The later approved indications (frequently only in the first-line setting) for melanoma or other advanced/metastatic solid tumors always necessitate the combination of ipilimumab with nivolumab, an anti-programmed cell death protein 1 (PD-1) mAb.[55] The therapeutic efficacy of combined checkpoint blockade has been demonstrated through clinical trials. Clinical trials investigating the use of fully humanized CTLA-4 mAb ipilimumab showed antitumor activity and a survival benefit in patients with unresectable or metastatic melanoma and, eventually, the United States Food and Drug Administration (FDA) approved these patients for this use in 2011.[36] This combination approach is applied to lung cancer, too: Cancer immunotherapies, such as immune checkpoint inhibitors (ICIs), have revolutionized therapy for advanced non-small cell and small-cell lung cancer.[14]

The toxicity associated with CTLA-4 blockade should be considered carefully. The overall all-grade 72 % (95 CI, 65-79 %), high-grade 24 % (18-30 %) risk developing dependent dosage, being evaluated 61 % (56-66 %) ipilimumab 3 mg/kg dose and 79 % (69-89 %) 10 mg/kg dose.[43] Skin lesions (rash, pruritus, vitiligo), colitis and, less commonly, hepatitis, hypophysitis, thyroiditis and some rare diseases such as sarcoidosis, uveitis and Guillain-Barré syndrome were all reported adverse experience.[34] Dual blockade approaches showed an improved efficacy in lung cancer of the small cell lineage. Inhibition of programmed death ligand 1 (PD-L1)-programmed (PD-1) signaling to improve tumor-specific T-cell immunity has demonstrated potential in the treatment of extensive-stage small-cell lung cancer. The phase III IMpower133 trial showed that use of the first line resulted in significantly longer survival when compared to alone, with an overall survival of 12.3 months in group 10.3 (hazard death, 0.70; 95% confidence interval, 0.54-0.91; P=0.007).[56]

Consequently, combined approaches targeting PD-1 and CTLA-4 checkpoint blockade have completely transformed lung cancer therapeutics. Combination treatment with anti-cytotoxic T lymphocyte-associated protein 4 (CTLA-4) and anti-programmed death-1 (PD-1) monoclonal antibodies (mAbs) has led to a dramatic improvement in the prognosis of patients with multiple types of cancer.[49] Moving forward, since these certain immune checkpoint pathways appear to be one of the major mechanisms resulting in immune escape of tumors, the presence of anti-CTLA-4 and/or anti-PD-1 should contribute to the removal of the inhibition signals for T cell activation. Subsequently, it will enhance specific T cell activation, thus enhancing antitumor immunity.[31] These complementary mechanisms lay at the foundation of modern immunotherapy for lung cancer, representing, a remarkable development both scientifically and clinically - as we work to overcome resistance and optimize patient selection efforts.

6. THERAPEUTIC ADVANCES IN CHECKPOINT BLOCKADE

6.1 Landmark Clinical Trials of PD-1 Inhibitors (Nivolumab, Pembrolizumab)

Nivolumab, a fully human immunoglobulin G4 programmed inhibitor antibody, was active and generally well tolerated in phase I-expanded cohorts of patients with advanced solid tumors.[57] As for the study participants in phase I trial, pivotal findings of this phase reported that "Median OS across doses 9.9 months; 1-, 2-, 3-year rates were 42%, 24%, 18%, respectively, 56%, 27%, at the 3-mg/kg dose and that Among 22 (17%) objective responses, estimated median duration 17.0 months.[57] The development of pembrolizumab followed an exciting trajectory: Pembrolizumab was awarded orphan drug designation for advanced melanoma in late 2012, and by 2013 received breakthrough therapy designation for advanced melanoma, the first ever FDA-granted breakthrough therapy designation for a cancer drug.[36] In lung cancer following dramatic success in clinical trials, ten α-PD-1 (nivolumab, pembrolizumab, cemiplimab, sintilimab, camrelizumab, toripalimab, tislelizumab, zimberelimab, prolgolimab, dostarlimab) three α-PD-L1

antibodies (atezolizumab, durvalumab, avelumab) have already obtained approval for many types of cancers.[58]

6.2 Landmark Clinical Trials of CTLA-4 Inhibitors (Ipilimumab, Tremelimumab)

In patients with unresectable/metastatic melanoma, ipilimumab has been the first immune checkpoint inhibitor that significantly improved overall survival. Clinical trials of the fully humanized CTLA-4 mAb ipilimumab showed antitumor activity and survival benefit in patients with unresectable or metastatic melanoma, prompting approval by the United States Food and Drug Administration (FDA) in 2011 for this patient population.[36] For adverse events, overall, 81 studies were included, with a total of 1265 from 22 clinical trials meta-analysis. Described included skin lesions (rash, pruritus, vitiligo), colitis, less commonly hepatitis, hypophysitis, and thyroiditis with the overall all-grade 72% (95% CI, 65-79%). high-grade 24% (18-30).[34]

6.3 Combination Therapy Approaches: PD-1 + CTLA-4 Blockade

Combination anti–CTLA-4 and anti–PD-1 blockade therapy has been shown to improve efficacy, although the mechanisms underlying these effects remain unclear. Recent studies indicate that combination therapy is characterized by dynamic transitions between the expansion of phenotypically exhausted cluster of differentiation 8-positive (CD8+) T cells and the activation of fully functional effector CD8+ T cells.[42] The dual blockade immunotherapy, directed at different stages of T cell activation, modulates different pathways of the activation of PD-1/PD-L1 and CTLA-4 to contribute synergistically in enhancing immune responses against cancer cells compared with ICI monotherapy, although ICI monotherapy is occasionally shown to have treatment resistance and limited efficacy. Previous clinical trials have explored a combination therapy strategy of anti-PD-1/PD-L1 and anti-CTLA-4 agents in lung cancer, yet its efficacy remains unclear with the inevitable incidence of immune-related adverse events.[14]

6.4 Comparative Efficacy and Safety Profiles

Drugs targeting the PD-1 pathway inhibit either PD-1 or its ligand, PD-L1, whereas CTLA-4 inhibitors target CTLA-4, and these agents have been approved for the treatment of different types of cancer. Some additional agents are also in the late stages of development. When administered as monotherapy, these agents have demonstrated dramatic improvements in durable response rates and manageable safety profiles; however, more than 50% of patients do not respond to the treatment.[59] In a comparison of pembrolizumab and ipilimumab in advanced melanoma, the estimated 12-month survival rates were 74.1%, 68.4%, and 58.2%, respectively, with pembrolizumab demonstrating superior efficacy.[60] In terms of safety, hypophysitis is especially associated with anti-CTLA-4 therapy and dysfunction anti-PD-1 and combination has the highest incidence of immune checkpoint inhibitor (ICPi)-related endocrinopathies.[61] Improved clinical efficacy of the mAb combination correlates with enhanced immune-related adverse events, potentially needing treatment cessation in patients who respond.[55]

7. LIMITATIONS

This review has several limitations. Although the review mentions that approximately 70-85% of NSCLC patients experience primary resistance to PD-1 blockade or acquired resistance after initial benefit, the mechanisms of PD-1-mediated resistance have not yet been fully identified. Upregulation of alternative checkpoints such as TIM-3 on PD-1 antibody-bound T cells is recognized as a potential adaptive resistance mechanism; however, the broader discussion of genomic, non-genomic tumor-cell, and microenvironmental factors that underlie resistance is not exhaustive. Furthermore, PD-L1 expression is introduced as a companion diagnostic biomarker, but the limitations of PD-L1 as a standalone predictive marker are not fully discussed in the review. Studies have revealed intra- and intertumoral heterogeneity in PD-1/PD-L1 interaction without demonstrating a clear relationship between it's the extent of these interactions and PD-L1 expression levels. A more comprehensive discussion of emerging biomarkers such as tumor mutational burden, genomic signatures, and immune contexture would enhance clinical applicability. In addition, although the review touches on immune-related adverse events such as skin lesions, colitis, hepatitis, hypophysitis, and thyroiditis but does not make explicit suggestions on management strategies or the potential risk-benefit analysis of the different patient populations. Because increased clinical efficacy of combination therapy correlates with enhanced immune-related adverse events, potentially necessitating treatment cessation, more extensive coverage of toxicity management would enhance clinical utility. Moreover,

although the review noted that EGFR-mutant and ALK-rearranged tumors respond less favorably, whereas KRAS-mutant tumors demonstrate superior responses to anti-PD-1/PD-L1 immunotherapy, but offers neither systematic guidance on selecting patients using algorithms that leverage molecular, immunological, or clinical parameters. The review also focuses primarily on dual PD-1/CTLA-4 blockade, whereas recent evidence suggest that several coinhibitory receptors, including VISTA, TIGIT, TIM-3, and LAG-3, function cooperatively to induce cytotoxic T-cell dysfunction. The potential of triple blockade strategies, for example PD-1/LAG-3/CTLA-4 combined, which has led to tumor-free survival in preclinical models, deserves a broader discussion. Finally, because the field of immunotherapy is evolving rapidly, many clinical trial findings and mechanistic insights may become outdated. Ongoing advances in optimal treatment sequencing, novel combination strategies, and predictive biomarkers may require the conclusions presented in this review to be updated in the future

8. CONCLUSION

This review explored the mechanisms of PD 1 and CTLA 4 inhibition and their therapeutic relevance in counteracting immune escape in lung cancer. The underlying premise, that blockade of these checkpoints can reinstate antitumor immunity, is consistently reinforced by the evidence discussed. Major observations include: (1) immune checkpoint inhibitor monotherapy markedly improves overall survival in NSCLC patients with PD L1 expression ≥50% compared with platinum based chemotherapy, while also lowering toxicity and improving quality of life; (2) in extensive stage SCLC, the IMpower133 trial showed that first line atezolizumab combined with chemotherapy prolonged median overall survival to 12.3 months compared with 10.3 months; and (3) concurrent PD 1/CTLA 4 inhibition generates synergistic antitumor activity through complementary cellular pathways, with expansion of terminally differentiated effector $CD8^+$ T cells observed only with combination treatment.

Nonetheless, significant obstacles persist: 70–85% of NSCLC patients experience either primary or acquired resistance, validated biomarkers beyond PD L1 remain insufficient, and immune related toxicities demand vigilant management. Future investigations should emphasize rational combination regimens, exploration of emerging checkpoint molecules (such as TIGIT, TIM 3, and LAG 3), and the development of integrated biomarker panels to broaden therapeutic benefit across diverse patient groups.

Ethical Approval

Not required.

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Competing Interests

All the authors declare that there are no conflicts of interest.

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Underlying Data

The author has nothing to report.

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