Tumor microenvironment-mediated resistance to immune checkpoint inhibitors in non-small cell lung cancer: Mechanisms, combination strategies and clinical perspectives (Review)

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Abstract. Non-small cell lung cancer (NSCLC) is one of the leading causes of cancer-associated mortality worldwide. Immune checkpoint inhibitors targeting programmed cell death protein 1, programmed death-ligand 1 (PD-L1) and cytotoxic T lymphocyte-associated protein 4 have transformed the treatment landscape of NSCLC. However, primary and acquired resistance limit durable clinical benefit. The current review article aimed to summarize tumor microenvironment-mediated resistance as an interconnected biological process rather than a collection of isolated factors. Immunosuppressive myeloid populations, regulatory lymphocytes, cancer-associated fibroblasts, extracellular matrix remodeling, vascular endothelial growth factor-driven vascular dysfunction, hypoxia, transforming growth factor-β signaling and metabolic reprogramming cooperate with defects in antigen presentation, dysregulation of serine/threonine kinase 11/Kelch-like ECH-associated protein 1/nuclear factor erythroid 2-related factor 2/stimulator of interferon genes and oncogenic driver signaling to generate immune-desert (minimal immune cell infiltration), immune-excluded (immune cells retained outside tumors) or exhausted immune-inflamed (immune-cell infiltration with functional exhaustion) phenotypes. The present review also critically evaluated combination therapeutic strategies, distinguishing phase III-supported standards from early-phase clinical or preclinical approaches, while highlighting considerations associated with patient selection, toxicity and the evolving regulatory context. Finally, an operational biomarker framework integrating PD-L1 expression, tumor mutational burden, interferon γ-associated signatures, spatial profiling, circulating tumor DNA, exosomal biomarkers and microbiome features was proposed to guide precision immunotherapy in NSCLC.

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Abbreviations: ALK, anaplastic lymphoma kinase; ARG1, arginase 1; CTLA-4, cytotoxic T lymphocyte-associated protein 4; ECM, extracellular matrix; EGFR, epidermal growth factor receptor; ICI, immune checkpoint inhibitor; LAG-3, lymphocyte activation gene 3; MDSC, myeloid-derived suppressor cell; MHC, major histocompatibility complex; NSCLC, non-small cell lung cancer; PD-L1, programmed death-ligand 1; TAM, tumor-associated macrophage; TGF-β, transforming growth factor-β; TIGIT, T cell immunoreceptor with Ig and ITIM domains; TIM-3, T cell immunoglobulin and mucin-domain containing protein 3; TKI, tyrosine kinase inhibitor; TMB, tumor mutational burden; TME, tumor microenvironment; Treg, regulatory T cell; VEGF, vascular endothelial growth factor

Key words: non-small cell lung cancer, tumor microenvironment, immune checkpoint inhibitor, immunotherapy resistance, combination therapy, biomarker, patient stratification

Contents

1. Introduction

Non-small cell lung cancer (NSCLC) is a global health challenge; in 2022, lung cancer accounted for ~2.48 million new cases and 1.82 million deaths worldwide (1-3). Global burden statistics, including incidence and mortality estimates, describe the worldwide disease burden, whereas stage-specific survival statistics, including the poor prognosis associated with metastatic disease, are commonly derived from population-based registries such as the Surveillance, Epidemiology, and End Results (SEER) Program (4). Therefore, these metrics are

complementary indicators rather than as estimates originating from a single dataset.

Platinum-based chemotherapy and targeted therapy against oncogenic drivers, including epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK) and ROS proto-oncogene 1 receptor tyrosine kinase (ROS1), have improved the management of NSCLC (5). Although these therapeutic modalities primarily inhibit tumor cell proliferation and survival, emerging evidence has suggested that they also regulate antitumor immunity. For example, activation of EGFR signaling and the development of resistance to EGFR-tyrosine kinase inhibitors (TKIs) affects programmed death-ligand 1 (PD-L1) expression and facilitates immune escape. Therefore, tumor-cell-directed treatment and tumor-host immune interactions should be considered to be biologically interconnected rather than mutually exclusive (5-7).

Programmed cell death protein 1, PD-L1 and cytotoxic T lymphocyte-associated protein 4 (CTLA-4) are well-established immune checkpoint targets (8-14). In metastatic NSCLC, objective response and clinical benefit from immune checkpoint inhibitors (ICIs) vary significantly based on PD-L1 tumor proportion score, oncogenic driver status, disease stage, treatment regimen and patient population. These broad response ranges should be interpreted within their clinical context. For example, ICI monotherapy is used for selected patients with high PD-L1 expression; chemo-immunotherapy is used for metastatic NSCLC without actionable drivers; durvalumab following concurrent chemoradiotherapy is used for unresectable stage III NSCLC; and neoadjuvant nivolumab plus chemotherapy is used for selected patients with resectable NSCLC (8-14).

The present review aimed to summarize tumor microenvironment (TME)-mediated ICI resistance in NSCLC, including the effects of immunosuppressive cells, stromal-triggered immune exclusion, abnormal angiogenesis, hypoxia, metabolic stress, impaired antigen-presentation and oncogenic alterations in the context of immune-inflamed (immune cell infiltration with functional exhaustion), immune-excluded (immune cells retained largely outside tumor nests) and immune-desert (minimal immune-cell infiltration) tumor phenotypes. The present study aimed to distinguish clinically established and investigational combination therapeutic approaches and identify biomarkers that could help guide patient selection.

The present narrative review prioritized English-language publications indexed in PubMed (https://pubmed.ncbi.nlm.nih.gov/), major oncology guidelines, pivotal phase II/III clinical trials, meta-analyses and mechanistic studies published from January 1946 to June 2026. Search terms included 'NSCLC', 'immune checkpoint inhibitor', 'tumor microenvironment', 'resistance', 'TAM', 'MDSC', 'Treg', 'CAF', 'VEGF', 'TGF-β', 'hypoxia', 'STK11', 'KEAP1', 'antigen presentation', 'biomarker', 'ctDNA', 'spatial omics', 'microbiome' and 'combination therapy'. Clinical evidence was weighted according to trial phase, population relevance, maturity of clinical endpoints and regulatory or guideline significance, whereas preclinical and hypothesis-generating studies were primarily used to support mechanistic concepts rather than as established clinical standards.

2. Composition of the TME and immunosuppressive mechanisms

The TME is a complex system composed of tumor, immune and stromal cells, including fibroblasts, the extracellular matrix (ECM) and various soluble factors. Interactions among the aforementioned components serve an essential role in regulating tumor initiation, progression and immune evasion (13). Overall, the interaction between these components through intercellular molecular pathways facilitates the establishment of an immunosuppressive microenvironment that directly influences the efficacy of immunotherapy (14).

Cell components and immunosuppressive functions. Single-cell and spatial studies (15-19) have shown that the cell TME is highly heterogeneous in NSCLC. Therefore, tumor-associated macrophages (TAMs) should not be interpreted solely within a rigid M1/M2 binary model. Historically, although M1-like macrophages have been associated with pro-inflammatory and antitumor activity and M2-like macrophages have been generally linked to tissue repair, angiogenesis, immune suppression and tumor progression, accumulating evidence (16-20) has indicated the presence of a continuum of macrophage activation states rather than two distinct subtypes. Within the TME, hypoxia, tumor-derived cytokines and stromal-derived signals, activate TAM programs that produce vascular endothelial growth factor (VEGF), matrix metalloproteinases, IL-10 and several chemokines that recruit regulatory T cells (Tregs), while suppressing effector T cell activity (15-20). Collectively, these factors can determine macrophage phenotype.

Consistently, myeloid-derived suppressor cells (MDSCs) warrant subtype-specific interpretation. Monocytic MDSCs predominantly suppress immunity through the expression of arginase 1 (ARG1), inducible nitric oxide synthase (iNOS), IL-10 and TGF-β, whereas polymorphonuclear MDSCs are more closely associated with reactive oxygen species (ROS) production and oxidative stress. These mechanisms deplete L-arginine, impair T cell receptor signaling, inhibit natural killer and $CD8^+$ T cell function and promote the expansion of Tregs (21,22). This suppresses antitumor immunity through several mechanisms, including the secretion of IL-10 and TGF-β, CD25 expression-mediated IL-2 consumption and CTLA-4-mediated competition for CD80/CD86 on antigen-presenting cells (23-25). Cancer-associated fibroblasts and ECM remodeling promote immune evasion by increasing stromal stiffness and secreting TGF-β, thus attenuating lymphocyte infiltration and promoting the development of immune-excluded tumors (26-30).

Key molecular pathways and immune checkpoints. Within the TME, lymphocyte activation gene 3 (LAG-3) serves as an inhibitor of T cell activation and proliferation while enhancing the immunosuppressive activity of Tregs through high-affinity binding to major histocompatibility complex (MHC) class II molecules (31). T cell immunoglobulin and mucin-domain-containing protein 3 (TIM-3) is another inhibitory immune checkpoint receptor that restrains T-cell activation and effector function and is predominantly expressed on T helper (Th)1 and type 1 cytotoxic (Tc1) cells.

After binding ligands such as galectin-9, TIM-3 suppresses Th1/Tc1-mediated responses and promotes T cell exhaustion (32). T cell immunoreceptor with Ig and ITIM domains (TIGIT), which is predominantly expressed on the surface of $CD8^+$ T cells, mediates immunosuppression in the TME by binding to receptors on antigen-presenting cells, including CD155 (33). TIGIT is also present on Tregs, where it enhances suppressive capacity and inhibits the activation, proliferation and effector activity of immune cells (34).

Metabolic and physical inhibitory factors. The TME is typically characterized by hypoxia, which activates hypoxia-inducible factor-1α, induces VEGF expression and directly or indirectly upregulates PD-L1 (35). Hypoxia also serves a key role in promoting lactate accumulation, nutrient competition and acidic stress through distinct but interconnected mechanisms. Lactic acid preferentially supports the metabolism of Tregs (36). By contrast, extracellular acidosis and glucose deprivation impair $CD8^+$ effector T cell function by inhibiting cytokine production, proliferation and cytotoxic activity (37). In parallel, hypoxia, impaired perfusion, high interstitial pressure and metabolic restriction attenuate immune infiltration and activity, eventually resulting in a non-inflamed or dysfunctional immune phenotype.

The TME represents a dynamic and highly heterogeneous ecosystem in which cell factors, molecular pathways and physicochemical characteristics can collectively determine the efficacy of immunotherapy. Consequently, targeting key regulatory mechanisms within the TME and reshaping the immune milieu through focused intervention represent promising strategies for improving clinical responses to immunotherapy in NSCLC.

3. Mechanisms through which the TME contributes to ICI resistance

The TME serves a key role in mediating resistance to ICIs, thereby severely limiting the clinical benefits of immunotherapy. The mechanisms underlying TME-mediated resistance are complex and can be categorized into three primary domains: Tumor-intrinsic, tumor-extrinsic and systemic factors.

Tumor-intrinsic mechanisms. Tumor-intrinsic resistance is primarily characterized by the loss or impairment of antigen presentation. Mutations or deletions in β2 microglobulin disrupt the assembly and transport of MHC class I, while human leukocyte antigen class I downregulation decreases recognition by $CD8^+$ T cells (38,39). Alterations in serine/threonine kinase 11 (STK11), also known as liver kinase B1 (LKB1) and KEAP1 define a clinically important immune-resistant state. Loss of STK11 suppresses stimulator of interferon genes-dependent type I interferon signaling, thereby attenuating innate immune activation and dendritic cell priming. These alterations are commonly associated with low PD-L1 expression and decreased $CD8^+$ T cell infiltration. Concurrent loss of KEAP1 results in activation of nuclear factor erythroid 2-related factor 2-dependent antioxidant and metabolic programs, promoting immune evasion and resistance to ICIs (40,41). EGFR- and ALK-driven NSCLC is commonly characterized by lower tumor mutational burden (TMB), decreased neoantigenicity and a less inflamed immune contexture (the composition, density, functional state and spatial distribution of immune cells within the tumor) (6). In EGFR-mutant NSCLC, resistance to EGFR-TKIs promotes immune escape through increased PD-L1 expression (7), whereas Ras homolog family member B (RHOB)-dependent AKT signaling represents a distinct tumor-intrinsic mechanism of EGFR-TKI resistance (42).

Tumor-extrinsic mechanisms. The marked expansion of immunosuppressive cell populations within the TME, including Tregs, MDSCs and TAMs, substantially contributes to immune evasion and tumor progression through several mechanisms. For example, Tregs display greater infiltration, abundance and suppressive capacity in tumor tissue than in peripheral blood and non-tumor tissue, thus impairing effector T cell function by secreting inhibitory cytokines such as IL-10 and TGF-β and by expressing CTLA-4, which competes for co-stimulatory signals for T cell activation (43). MDSCs accumulate in the peripheral blood and tumor tissue of patients with NSCLC and suppress T-cell proliferation and function through ARG1, iNOS, ROS and TGF-β (21). TAMs, including M2-like macrophages, promote angiogenesis and recruit Tregs by secreting VEGF, IL-10 and CCL17/22, while also driving T cell exhaustion through the production of tryptophan metabolites (17).

Systemic factors. Systemic factors affect the response to ICIs but require disease-specific interpretation. In NSCLC, exposure to antibiotics and specific features of the gut microbiome are associated with ICI efficacy, while taxa such as *Akkermansia muciniphila*, *Bifidobacterium* spp. and *Ruminococcus* have been involved in promoting a favorable immune milieu in certain NSCLC cohorts (44-48). Associations involving *Fusobacterium* are stronger in colorectal cancer compared with NSCLC and should be considered extrapolative unless supported by NSCLC-specific datasets. Host nutrition, sarcopenia, hypoalbuminemia, elevated C-reactive protein levels and a high neutrophil-to-lymphocyte ratio reflect systemic inflammation and impaired immune competence (49).

Collectively, the TME-mediated resistance to ICIs in patients with NSCLC arises from the interplay between tumor genotype, antigen presentation, the local immunosuppressive cell ecosystem, stromal architecture, metabolic stress and the host systemic state. Fig. 1 summarizes the aforementioned integrated framework, including immune-desert and -excluded and exhausted inflamed phenotypes, and links each resistance domain to its corresponding therapeutic rationale.

4. TME-oriented combination treatment strategies

To overcome the limitations imposed by the immunosuppressive TME, combination therapies tailored to its characteristics have become a central strategy in tumor immunotherapy (50). These approaches aim to reverse TME-mediated immunosuppression, promote immune cell infiltration and activation and achieve durable antitumor responses by targeting multiple mechanisms, thereby improving clinical outcomes.

Immune-immune combination therapy. Combination therapies should be evaluated according to the evidence level, patient selection and toxicity profile rather than biological plausibility

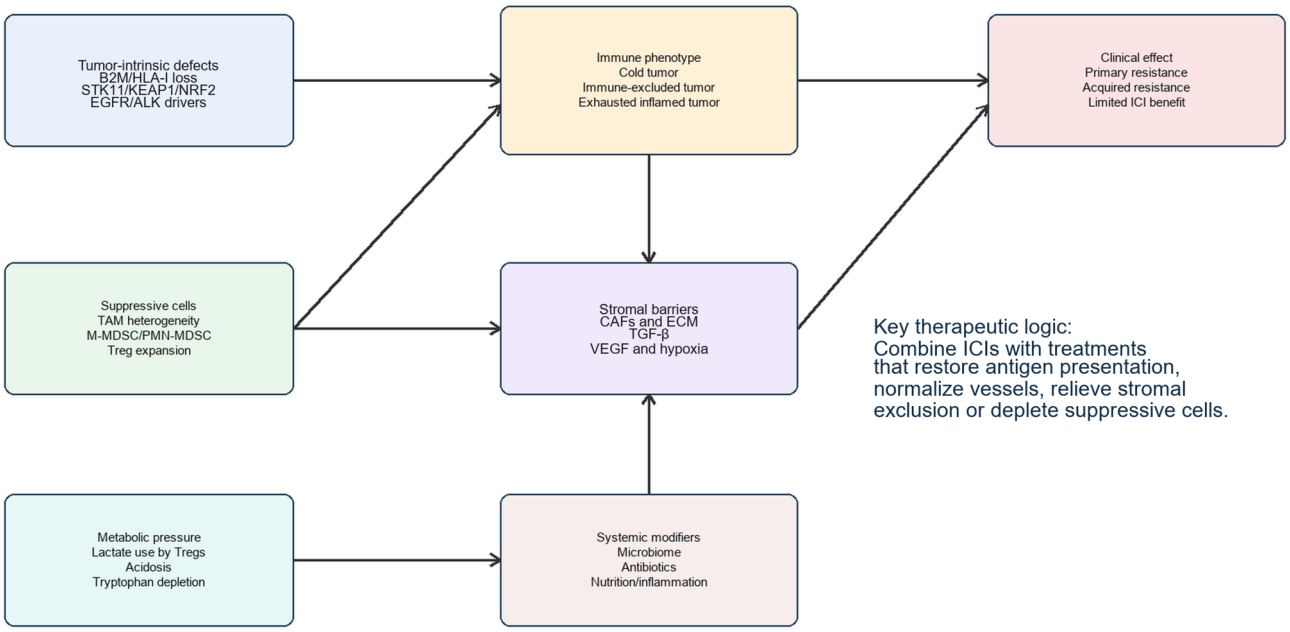

Figure 1. Integrated model of tumor microenvironment-mediated resistance to ICIs in non-small cell lung cancer, including immune-desert, immune-excluded and exhausted immune-inflamed phenotypes. An immune-desert, or cold, tumor has minimal immune-cell infiltration. B2M, β2 microglobulin; HLA-I, human leukocyte antigen class I; STK11, serine/threonine kinase 11; TAM, tumor-associated macrophage; M-MDSC, monocytic myeloid-derived suppressor cell; PMN-MDSC, polymorphonuclear myeloid-derived suppressor cell; Treg, regulatory T cell; CAF, cancer-associated fibroblast; ECM, extracellular matrix; ICI, immune checkpoint inhibitor.

alone. Dual immune checkpoint blockade with nivolumab + ipilimumab has shown notable efficacy in phase III clinical trials in selected patients with advanced NSCLC, including the CheckMate 227 trial. However, the interpretation of these results depends on PD-L1 expression, TMB-defined analyses, study endpoints and the comparator arm (50-52). By contrast, emerging immune checkpoint combinations require caution (53). Although the CITYSCAPE trial suggested clinical efficacy of tiragolumab + atezolizumab in patients with PD-L1-positive NSCLC, the subsequent phase III SKYSCRAPER-01 trial failed to meet the overall survival endpoint (54,55). Similarly, although LAG-3 and TIM-3 remain biologically promising, their clinical adoption in NSCLC requires confirmation through mature clinical trials (56-59).

Immune-anti-vascular combination therapy. Anti-angiogenic therapy has a strong mechanistic rationale because VEGF promotes abnormal vasculature, hypoxia, Treg/MDSC accumulation and impaired lymphocyte trafficking. The IMpower150 trial supported the use of atezolizumab + bevacizumab, carboplatin and paclitaxel in patients with metastatic non-squamous NSCLC and is clinically notable for demonstrating efficacy in subgroups such as patients with baseline liver metastases and those with EGFR-mutant disease after TKI failure (60-66). This regimen is therefore more clinically actionable compared with investigational combinations such as ICIs with anti-angiogenic TKIs, TGF-β-targeted agents or myeloid-cell-targeted agents, although its use is affected by regional approvals, histology, prior therapy and the risk of bleeding or vascular complications.

Immunotherapy combined with radiotherapy or chemotherapy. The combination of ICIs with chemotherapy or radiotherapy is currently considered a standard treatment approach in unresectable stage III NSCLC after concurrent chemoradiotherapy and metastatic driver-negative NSCLC treated with chemo-immunotherapy. Chemotherapy induces immunogenic cell death, decreases suppressive myeloid cell populations and increases antigen release, whereas radiotherapy predominantly serves as an *in situ* vaccine by releasing tumor antigens, increasing antigen presentation and promoting interferon-mediated immune activation (67-70). The PACIFIC regimen (durvalumab after concurrent chemoradiotherapy [CRT]) is an established treatment strategy following concurrent chemoradiotherapy for patients with unresectable stage III NSCLC and chemo-immunotherapy regimens such as KEYNOTE-189 represent the standard first-line option for patients with metastatic non-squamous NSCLC without actionable drivers (67-70). However, these clinical benefits should be balanced against treatment-related adverse events, including pneumonitis and bone marrow toxicity; baseline comorbidities should be assessed separately because they may increase treatment risk.

Immunotherapy-targeted therapy combinations. In EGFR- or ALK-driven NSCLC, ICI monotherapy typically shows limited efficacy, and combinations with TKIs can result in notable toxicity, including pneumonitis and hepatotoxicity (71,72). The KEYNOTE-789 trial did not demonstrate a clear clinical advantage of pembrolizumab + chemotherapy after EGFR-TKI failure (73). In the post-osimertinib setting, CHRYSALIS-2 evaluated amivantamab + lazertinib without the addition of an ICI. Therefore, this regimen should be interpreted as a targeted therapy regimen rather than an ICI-based combination therapy (74,75). In patients with oncogene-driven NSCLC, clinical decision-making should prioritize targeted

Table I. Tumor microenvironment-oriented combination therapeutic strategies for NSCLC.

Strategy	Rationale	Evidence level	Limitations	(Refs.)
Dual PD-1/CTLA-4 blockade	CTLA-4 blockade primes naive T cells; PD-1 blockade restores exhausted T-cell proliferation, cytokine production and cytotoxicity	Phase III support in advanced NSCLC	More irAEs than with single-agent ICI; benefit varies by subgroup	(51,52, 54,55)
Anti-VEGF + ICI + chemotherapy	Vascular normalization and decreased suppressive myeloid/Treg tone	Supported by the IMpower150 trial in metastatic non-squamous NSCLC	Approval and clinical use vary by region, histology and risk	(60-66)
ICI + chemotherapy/ radiotherapy	Antigen release, immunogenic cell death and immune priming	Standard of care in defined metastatic or stage III settings	Pneumonitis and marrow toxicity require monitoring	(67-70)
ICI + targeted therapy	Potential immune remodeling following driver inhibition	Mixed/limited evidence in EGFR/ALK-positive NSCLC	TKI-ICI toxicity and limited efficacy of ICI monotherapy	(71-75)
Microbiome/metabolic intervention	Modulation of systemic immunity and metabolic suppression	Early clinical/preclinical evidence	Warrants prospective validation and standardization	(46-48, 76-78)

NSCLC, non-small cell lung cancer; irAE, immune-related adverse event; ICI, immune checkpoint inhibitor; TKI, tyrosine kinase inhibitor.

therapy, chemotherapy-based treatment options and carefully selected anti-VEGF/ICI/chemotherapy combinations rather than the indiscriminate use of TKI-ICI combinations.

Immunotherapy combined with microbiome and metabolic regulation. Microbiome- and metabolism-associated interventions remain promising but are largely investigational. Fecal microbiota transplantation, probiotics, dietary fiber manipulation, indoleamine 2,3-dioxygenase (IDO) inhibition, lactate metabolism targeting and related approaches have a strong mechanistic appeal but require prospective clinical validation, standardized assessment approaches and safety monitoring before their clinical implementation in patients with NSCLC (46-48,76-78).

The main therapeutic categories of combination treatment strategies, their biological rationale, level of clinical evidence and their key limitations are summarized in Table I, and an evidence-stratified overview is shown in Fig. 2.

5. Biomarkers and patient stratification

Biomarker-guided patient stratification should be operational rather than descriptive. Although PD-L1 is a clinically useful biomarker, its limitations include spatial heterogeneity, temporal changes following therapy, assay-specific PD-L1 tumor proportion score cutoffs used to select patients for ICI-containing regimens and imperfect predictive value. PD-L1 assay comparability has been evaluated by the Blueprint PD-L1 IHC Comparability Project, which indicated substantial concordance among several validated, regulatory-approved antibody-platform combinations, although assay interchangeability remains incomplete and the Ventana PD-L1 SP142 immunohistochemistry assay may show lower tumor cell staining in the same lung cancer specimens compared with the 22C3, 28-8 and SP263 assays (79). In selected NSCLC cohorts, high TMB has been associated with increased immune infiltration and improved outcomes with PD-1/PD-L1 blockade, but its predictive potential is affected by the sequencing platform, cutoff value and tumor purity and type, and high TMB is not universally predictive across cancer types (80,81). IFN-γ-related signatures and $CD8^+$ T cell infiltration reflect immune activation, while spatial transcriptomics distinguishes inflamed, excluded and desert phenotypes (82-84). Microbiome features are also being investigated as response markers (47). Liquid biopsy, circulating tumor DNA dynamics and exosomal markers represent promising approaches for monitoring tumor burden and treatment resistance, although prospectively validated thresholds are needed to inform treatment decisions (85,86). These biomarkers and assessment approaches are summarized in Table II (87). Recent studies using multi-omics, network analysis, artificial intelligence and immune microenvironment modeling further illustrate how biomarker discovery is evolving beyond single markers (88-92).

6. Safety and toxicity management of combination therapy

Toxicity management is a key component of combination therapy. Immune-related adverse events arise not only from enhanced T cell activation and autoantibody production but also from molecular mimicry, bystander T cell activation, epitope spreading, cytokine dysregulation and disruption of peripheral immune tolerance (93,94). Dual immune checkpoint blockade and ICI-based combination therapies increase

Table II. Biomarkers and assessment approaches for patient stratification in non-small cell lung cancer.

Marker/assessment approach	Strengths	Limitations	Clinical interpretation
PD-L1 immunohistochemistry	Widely available; helps identify approved ICI-containing regimens for which PD-L1 expression is a selection criterion	Heterogeneity, variable thresholds, assay differences	Interpretation depends on clinical stage, histology, assay platform and oncogenic driver status
Tumor mutational burden	Reflects neoantigen potential	Platform/cutoff variability; imperfect predictor	Interpretation depends on PD-L1 status, sequencing platform and immune context
IFN-γ/CD8 signatures	Captures immune activation	Requires a validated assay and high-quality tissue	Identification of inflamed tumors
Spatial omics	Distinguishes inflamed, excluded and desert phenotypes	Cost, access, lack of prospective validation	Guide tumor micro-environment-targeted combination therapy
Circulating tumor DNA/ exosomes	Dynamic monitoring of tumor burden and resistance	Thresholds and timing are not standardized	Track early response and acquired resistance to therapy
Microbiome	Potential systemic immune modifier	Sampling, diet and antibiotic use as confounding factors	Investigational method for patient stratification

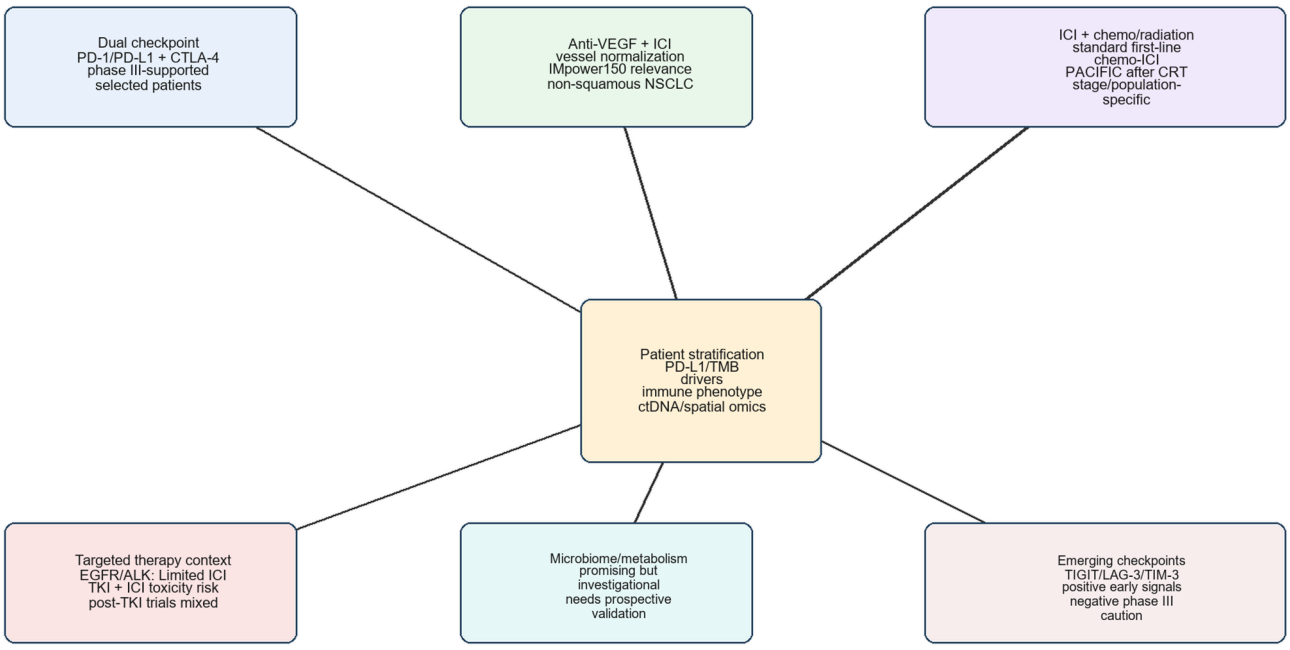

Figure 2. Evidence-stratified tumor microenvironment-oriented therapeutic strategies. ICI, immune checkpoint inhibitor; NSCLC, non-small cell lung cancer; chemo, chemotherapy; PACIFIC, phase III trial of durvalumab after concurrent chemoradiotherapy in unresectable stage III NSCLC; CRT, chemoradiotherapy; TMB, tumor mutational burden; ctDNA, circulating tumor DNA; TKI, tyrosine kinase inhibitor; TIGIT, T cell immunoreceptor with Ig and ITIM domains; LAG-3, lymphocyte activation gene 3; TIM-3, T cell immunoglobulin and mucin-domain containing protein 3.

the incidence and severity of immune-mediated toxicity compared with single-agent therapy, although the risks vary according to the treatment regimen and patient population (95,96). Management should follow guideline-based toxicity grading and include the prompt exclusion of infection or disease progression, temporary interruption of ICI therapy for clinically notable toxicities, therapy with corticosteroids or organ-specific immunosuppressive agents when indicated and consideration of treatment rechallenge after recovery (97-99). For patients with EGFR/ALK-driven NSCLC and those treated with thoracic radiotherapy, vigilance is warranted due to the increased risk of pneumonitis.

7. Conclusion and future perspectives

One of the principal challenges to immunotherapy in NSCLC is immune resistance, with the TME serving as a notable mediator of this process. Resistance generally reflects an integrated phenotype rather than a single molecular alteration. Defects in antigen-presentation, STK11/KEAP1 biology, suppressive myeloid and regulatory immune cell networks, stromal exclusion, abnormal vasculature, hypoxia and metabolic stress collectively contribute to the development of immune-desert, immune-excluded and exhausted immune-inflamed tumor phenotypes.

Several significant issues remain unresolved. Establishing which TME features are causal drivers of ICI failure rather than associated findings remains a priority. Practical treatment algorithms must define how to integrate spatial immune phenotypes, ctDNA dynamics and conventional biomarkers. Prospective studies are needed to identify patients who benefit from intensified immune checkpoint blockade or anti-VEGF-based combinations and those who are primarily exposed to additional toxicity. Oncogene-driven NSCLC also requires validated stratification after targeted therapy failure. Finally, microbiome- and metabolism-based interventions require standardized methods and prospective validation.

Future research should focus on prospective biomarker-defined clinical trials, harmonized PD-L1, TMB and spatial omics assays, longitudinal liquid biopsy monitoring, and mechanism-based studies including patients with STK11/KEAP1- and EGFR/ALK-altered NSCLC, as well as clinical trials with toxicity-conscious designs. In this context, recent methodological advances in immune microenvironment analysis, network toxicology, artificial intelligence-based multimodal modeling and integrative translational frameworks may provide useful analytical directions (88-92). However, disease-specific validation in NSCLC immunotherapy remains essential.

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Authors' contributions

JM conceived and designed the study, performed the literature review and wrote and edited the manuscript. QX edited the manuscript. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, artificial intelligence tools were used to improve the readability and language of the manuscript, and subsequently, the authors revised and edited the content produced by the artificial intelligence tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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