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2 **Title:** Factors influencing the efficacy of programmed cell death protein 1/programmed
3 death-ligand 1 inhibitors in non-small cell lung cancer

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27 Clinical Question Box

28 What factors affect the efficacy of immune checkpoint inhibitors, especially PD-(L)1
29 inhibitors, in patients with non-small cell lung cancer?

30 The efficacy of PD-(L)1 inhibitors in non-small cell lung cancer reflects interactions
31 among tumor biology, the tumor microenvironment, treatment context, and host factors.
32 Higher tumor-cell PD-L1 expression and an inflamed immune contexture are the most
33 clinically established favorable features. Tumor mutational burden, T-cell states,
34 tertiary lymphoid structures, oncogenic drivers and co-mutations, body composition,
35 microbiota, and concomitant medications may provide additional information, but most
36 remain context dependent or investigational. Actionable oncogenic drivers, poor
37 performance status, cachexia, and baseline corticosteroid use for cancer-related
38 symptoms are generally associated with reduced benefit, particularly from immune
39 checkpoint inhibitors monotherapy. No single variable is sufficiently accurate for
40 universal treatment selection; integrated and dynamic assessment is therefore required.

41

Abstract

Immune checkpoint inhibitors (ICIs), particularly programmed cell death protein 1/programmed death-ligand 1 (PD-1/PD-L1) inhibitors, are central to the treatment of non-small cell lung cancer (NSCLC), and a subset of patients achieves durable benefit. In historical studies of broadly selected patients receiving ICI monotherapy, objective responses occurred in approximately 20%, although response rates vary substantially according to treatment line, PD-L1 expression, molecular subtype, patient selection, and the use of combination regimens. This narrative review used targeted searches of PubMed/MEDLINE, ClinicalTrials.gov, and reference lists of key publications to identify English-language evidence available through May 2026, prioritizing pivotal randomized trials, prospective translational studies, consensus statements, guidelines, and recent high-quality reviews. We critically examine tumor-microenvironmental features, PD-L1 expression, tumor mutational burden (TMB), oncogenic driver alterations, combination strategies, and patient-related factors that may influence PD-(L)1 inhibitor efficacy. Although other immune checkpoints, including cytotoxic T-lymphocyte-associated protein 4 and lymphocyte-activation gene 3, are discussed when directly relevant to combination therapy, the principal focus is PD-1/PD-L1-directed treatment. Current evidence supports PD-L1 as the most widely implemented biomarker, but no single factor adequately captures the biological and temporal heterogeneity of treatment response. Integrated, dynamic, and context-specific biomarker models, supported by prospective validation, are therefore required to

63 improve precision immuno-oncology.

64 **Keywords:** non-small cell lung cancer; programmed cell death protein 1; immune

65 checkpoint inhibitors; tumor microenvironment; tumor mutational burden; combination

66 therapy

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1. Background

The programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) axis is a major mechanism of tumor immune escape that attenuates antitumor T-cell activity. ICIs targeting PD-1, including nivolumab and pembrolizumab, and PD-L1, including atezolizumab and durvalumab, have improved survival across multiple stages and treatment settings of NSCLC.¹

Immune checkpoint inhibition also encompasses targets such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and lymphocyte-activation gene 3 (LAG-3). However, PD-(L)1 blockade remains the principal immunotherapeutic backbone in NSCLC, whereas CTLA-4, LAG-3, and other checkpoint-directed agents are generally used or investigated in combination with PD-(L)1 inhibitors. Accordingly, this review focuses on factors that influence the efficacy of PD-1/PD-L1-directed therapy; broader immunotherapy concepts are included only when they directly inform this scope.²

The magnitude of benefit from PD-(L)1 blockade is highly context dependent. Historical ICI monotherapy studies in broadly selected advanced NSCLC populations reported objective response rates of approximately 20%, whereas substantially higher rates are observed in selected patients with high PD-L1 expression and with chemoimmunotherapy or other combination regimens.³ Response also varies by treatment line, histologic and molecular subtype, disease burden, and host condition. Primary and acquired resistance therefore remain common and create an urgent need

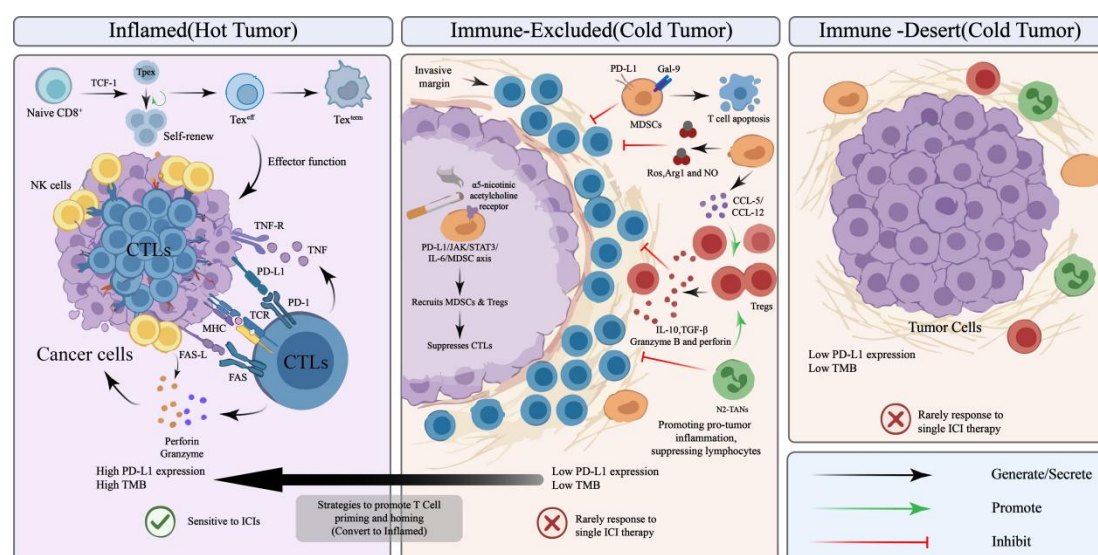
for clinically reproducible predictive strategies. This review critically evaluates tumor-microenvironmental factors, PD-L1, tumor mutational burden (TMB), oncogenic driver alterations, treatment combinations, and patient characteristics, with particular attention to evidentiary limitations and clinical actionability.

Relevant English-language publications were identified through targeted searches of PubMed/MEDLINE and ClinicalTrials.gov and through review of the reference lists of pivotal articles, with coverage through May 2026. Priority was given to randomized trials, prospective clinical and translational studies, major retrospective cohorts, consensus statements, guidelines, and recent high-quality reviews. Because the objective was an interpretive narrative synthesis rather than an exhaustive systematic review, no PRISMA-based study-selection process or formal risk-of-bias assessment was performed.

2. Tumor microenvironment (TME) factors

The TME comprises tumor and immune cells, vascular and stromal compartments, signaling molecules, and extracellular matrix. A commonly used spatial framework classifies tumors as immune-inflamed, immune-excluded, or immune-desert. Immune-inflamed tumors contain intratumoral T cells and interferon-related signaling and are generally more responsive to PD-(L)1 blockade.⁴ In immune-excluded tumors, CD8⁺ T cells accumulate at the invasive margin or within stroma without effective tumor penetration, whereas immune-desert tumors contain few tumor-reactive T cells. These phenotypes are biologically useful but are neither discrete nor stable, and their assessment is not standardized; individual tumors may contain mixed regions and may change over time or during treatment.⁵⁻⁷

Clinical response reflects the balance between antitumor immunity and suppressive cellular and stromal programs. CD8⁺ T-cell recruitment and activation can favor response, whereas MDSCs, Tregs, suppressive myeloid states, N2-like TANs, fibroblast barriers, and abnormal vasculature may limit immune-cell trafficking or function (Figure 1). Many of these relationships are supported by translational or observational evidence and have not yet yielded standardized tests for routine treatment selection.



2.1. CD8⁺ T cell infiltration and immune activation

CD8⁺ T cells, or cytotoxic T lymphocytes, eliminate tumor cells after antigen recognition, and greater intratumoral CD8⁺ density has been associated with improved outcomes after ICI therapy in NSCLC.⁸ Functional state is at least as important as cell number. CD28 co-expression may identify a population with preserved proliferative capacity, whereas high expression of inhibitory receptors such as TIM-3 can mark dysfunctional or terminally exhausted states and potential resistance mechanisms.⁹

Progenitor-exhausted T (Tpex) cells, commonly characterized by TCF1 and PD-1 expression, retain stem-like properties and can self-renew and generate more differentiated effector-exhausted cells after PD-1 blockade.^{10,11} Higher Tpex-related signatures or TCF1+PD-1+ tumor-infiltrating lymphocytes have been associated with response and survival in NSCLC. However, Tpex identification is not standardized. It may require multiparameter immunohistochemistry, flow cytometry, or high-dimensional single-cell assays; marker definitions, spatial compartments, sampling

time, and analytic thresholds differ across studies. Tpex measurement therefore remains investigational and is not currently a routine clinical biomarker.¹²

2.2.Tertiary lymphoid structures and high-resolution TME profiling

Tertiary lymphoid structures (TLSs) are organized aggregates of B cells, T cells, dendritic cells, and specialized stromal or vascular elements that can support local antigen presentation and lymphocyte activation. Mature, germinal-center-containing TLSs and greater TLS abundance have been associated with pathological response and improved outcomes after immunotherapy or chemioimmunotherapy in NSCLC.^{13,14} Nevertheless, TLS presence alone is not uniformly predictive; maturation state, location, stromal context, specimen size, and scoring method can alter interpretation.

Single-cell RNA sequencing and spatial transcriptomic or multiplex-imaging approaches can resolve immune-cell states, clonotypes, spatial neighborhoods, and cell-cell communication networks that are obscured by bulk assays. These methods have identified potentially informative interactions among Tpex cells, dendritic cells, B-cell-rich TLSs, macrophages, fibroblasts, endothelial cells, and tumor cells.^{10,15} Their clinical translation remains limited by tissue requirements, cost, technical variability, computational dependence, and the absence of prospectively validated decision thresholds.

Despite strong biological rationale, most TME biomarkers remain investigational because reproducibility is affected by intratumoral and temporal heterogeneity, biopsy

site and size, pre-analytical handling, assay platform, cell-state definitions, spatial scoring, and treatment exposure. Prospective studies using analytically validated assays and predefined thresholds are needed before these measurements can reliably guide therapy.

2.3.Immunosuppressive network

Myeloid-derived suppressor cells (MDSCs): MDSCs comprise heterogeneous immature myeloid populations that suppress T-cell activity through checkpoint-ligand expression, oxidative and nitrosative stress, amino-acid depletion, and immunosuppressive cytokines. Elevated circulating or intratumoral MDSC levels have been associated with inferior outcomes and primary resistance to ICIs in NSCLC, but they are not validated treatment-selection biomarkers.^{16,17}

Under hypoxic or STAT3-active conditions, monocytic MDSCs may differentiate toward tumor-associated macrophage states. Preclinical depletion or reprogramming of MDSCs can enhance checkpoint blockade, but clinical feasibility remains uncertain. Tumor-intrinsic PD-L1 signaling through the JAK/STAT3/IL-6 axis has also been linked to MDSC-mediated immunosuppression in PD-L1-high NSCLC, providing a mechanistic rationale rather than a validated clinical strategy.¹⁸⁻²⁰

Regulatory T cells (Tregs): Tregs suppress activities of CD8⁺ T and natural killer cells by secreting inhibitory cytokines (e.g., IL-10, TGF- β), granzyme B, and perforin. Spatial analysis revealed that a shortened mean nearest neighbor distance between

Tregs and CD4⁺ T cells/tumor cells is predictive of a poor prognosis of NSCLC, whereas proximity to CD8⁺ T cells may indicate local immune activation.¹⁵ PD-L1-positive lung cancer stem-like cells may also contribute to an immunosuppressive lymph-node microenvironment.²¹

Smoking-related nicotinic receptor signaling may stabilize tumor-cell PD-L1 through STAT3/Jab1 signaling; however, the cited evidence does not establish a direct clinical relationship among smoking, Treg function, and ICI efficacy.²² Experimental strategies that reduce Treg-mediated suppression, including epigenetic modulation, can enhance antitumor immunity in preclinical models, but remain investigational.²³

Tumor-associated neutrophils and systemic inflammatory indices: The N1/N2 framework is a useful simplification, but neutrophil states are plastic and cannot be reliably assigned by routine clinical assays. Elevated baseline or early on-treatment neutrophil-to-lymphocyte ratio and platelet-related inflammatory indices are consistently associated with poorer outcomes during ICI-based therapy.²⁴⁻²⁶ These markers are inexpensive and accessible, but cutoff values vary and confounding by infection, corticosteroid exposure, tumor burden, and comorbidity limits their use as treatment-specific predictive biomarkers. The reported association between a higher neutrophil-to-lymphocyte ratio and ICI-related myocarditis requires external validation and should not be used for clinical risk stratification at present.²⁷

3. Cancer cell-related factors

3.1. PD-L1 expression

PD-L1 immunohistochemistry remains the most widely implemented biomarker for selecting PD-(L)1-directed therapy in NSCLC, despite substantial limitations.^{1,28}

Higher tumor-cell PD-L1 expression enriches for response to pembrolizumab monotherapy in oncogene driver-negative advanced NSCLC, but PD-L1 is neither necessary nor sufficient for benefit, particularly when ICIs are combined with chemotherapy.

PD-L1 is spatially and temporally heterogeneous and can be altered by prior therapy, inflammation, specimen type, and sampling site. Patients with low or undetectable expression may respond, whereas some tumors with high expression exhibit primary resistance.^{28,29} Small biopsies and cytology specimens may not represent the entire tumor, and interobserver variation near clinical cutoffs can change treatment classification.

Assay selection and scoring method also affect interpretation. The 22C3, 28-8, and SP263 assays generally show comparable tumor-cell staining, whereas SP142 tends to label fewer tumor cells and may classify some specimens at a lower expression category.³⁰ The Tumor Proportion Score (TPS) is the percentage of viable tumor cells with membranous PD-L1 staining and is the principal scoring system used for most NSCLC treatment decisions. The Combined Positive Score (CPS) includes PD-L1-

positive tumor cells, lymphocytes, and macrophages relative to the number of viable tumor cells; it is established in several other tumor types but is not the dominant scoring system for NSCLC. Assays, antibodies, platforms, specimen requirements, and clinically validated cutoffs should therefore be matched to the treatment indication rather than assumed to be universally interchangeable. The cellular source of PD-L1 may add biological information, but immune-cell and spatial scoring remain less standardized than tumor-cell TPS.³¹

3.2.Tumor mutational burden(TMB)

The TMB is generally defined as the number of somatic mutations detected per megabase of interrogated genomic sequence. Higher TMB may increase the probability of generating immunogenic neoantigens, but only a subset of nonsynonymous mutations is processed, presented by major histocompatibility complex molecules, and recognized by T cells. TMB should therefore be regarded as an indirect measure of potential tumor immunogenicity rather than a direct measure of neoantigen quality.³²

3.2.1. Feasibility of Predicting Efficacy in NSCLC

A higher TMB can increase the probability of neoantigen generation and has been associated with response to PD-(L)1 inhibitors in several NSCLC cohorts.³³⁻³⁶ However, the randomized evidence is not uniformly positive. CheckMate 026 did not meet its primary progression-free survival endpoint in the prespecified PD-L1-selected population; an exploratory whole-exome analysis suggested improved response and

233 progression-free survival with nivolumab in tumors with high TMB, but not a clear
234 overall-survival advantage.³⁷ CheckMate 227 subsequently demonstrated a
235 progression-free survival benefit from nivolumab plus ipilimumab in a TMB-high
236 subgroup, whereas longer-term overall-survival benefit was not restricted to that
237 subgroup.³⁸ These findings reduced enthusiasm for using TMB as an isolated treatment-
238 selection biomarker in NSCLC.

239 TMB is influenced by smoking-related mutagenesis, DNA-repair defects, tumor purity,
240 sequencing depth, and specific genomic contexts. dMMR/MSI-H tumors can
241 accumulate mutations and respond to checkpoint blockade, but MSI-H is uncommon in
242 NSCLC and does not account for most TMB-high cases.³⁸⁻⁴⁰ A high TMB may therefore
243 reflect several biologically distinct processes, and its predictive value varies according
244 to tumor type, treatment regimen, and the accompanying immune context.

245 3.2.2. Challenges in TMB Standardization

246 Whole-exome sequencing is a research reference method for TMB quantification but is
247 costly, data intensive, and difficult to implement routinely. Clinical testing generally
248 relies on targeted next-generation sequencing panels. Panel size, genomic territory,
249 tumor purity, germline filtering, inclusion of synonymous variants, driver-variant
250 handling, and bioinformatic pipelines can each shift the reported TMB value.
251 Consequently, the same numerical cutoff cannot be assumed to have identical meaning
252 across assays.

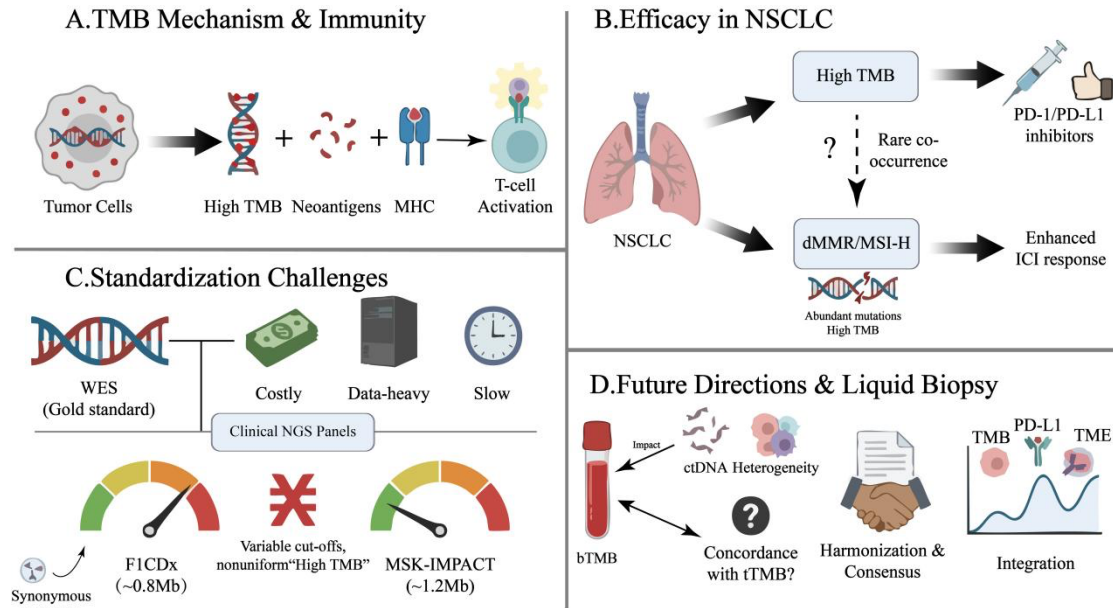
FDA-authorized assays such as FoundationOne CDx and MSK-IMPACT cover different genes and genomic territories and apply different analytic procedures. A designation of 10 mutations/Mb on one panel is therefore not necessarily equivalent to 10 mutations/Mb on another. Pre-analytical variables further affect tissue TMB. Blood TMB is attractive because it is minimally invasive, but low circulating tumor DNA shedding, clonal hematopoiesis, disease burden, and tumor-site heterogeneity can impair accuracy, and tissue-blood concordance has not been consistently validated for treatment selection in phase III NSCLC trials.⁴¹

Harmonization initiatives have improved cross-platform understanding, but clinically important disagreement persists near cutoff values and can lead to patient misclassification.^{42,43} Regulatory and clinical adoption has therefore remained limited relative to early expectations. Negative or equivocal randomized findings, assay dependence, uncertain optimal thresholds, limited reproducibility of blood-based measurements, and incomplete evidence that TMB adds independent information beyond PD-L1 and immune contexture all contribute to this caution.

Future use of TMB should emphasize assay-specific validation, cancer- and treatment-context-specific calibration, and analysis as a continuous or probabilistic variable rather than a universal binary threshold. TMB is most plausibly informative as one component of a composite model incorporating PD-L1, immune-cell or gene-expression signatures, spatial immune architecture, relevant driver and co-mutations, and dynamic blood-based markers.^{44,45} Such models require prospective validation and demonstration that

their use improves clinical outcomes.

Accordingly, future standards should define assay-, tumor-, and treatment-specific interpretation and specify the clinical settings in which tissue- or blood-based TMB measurements are appropriate (Figure 2).



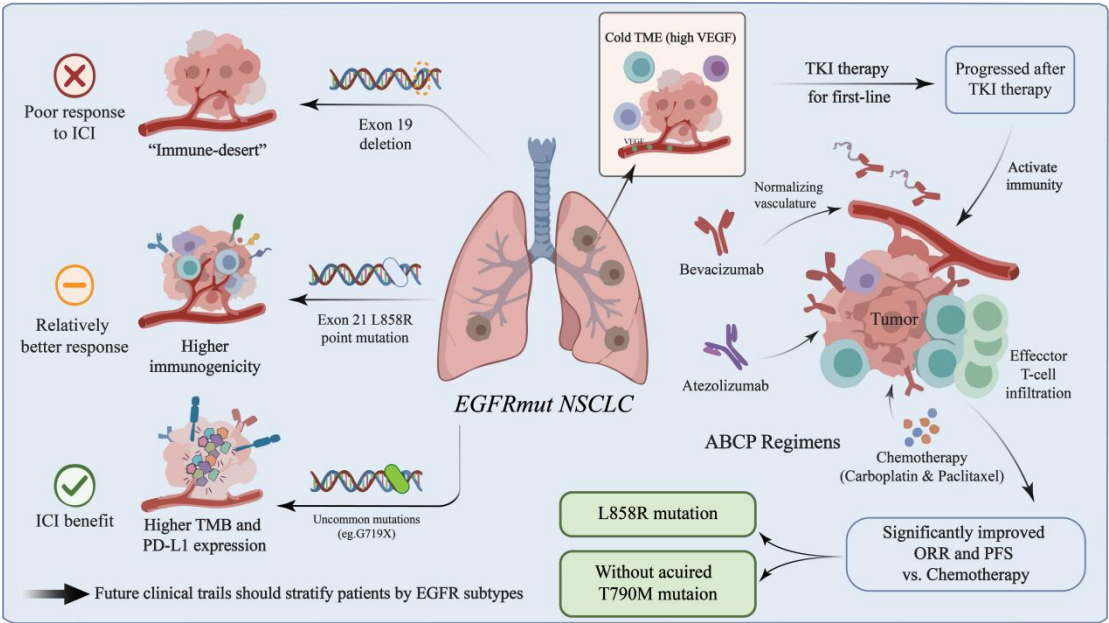
3.3. Driver alterations

Somatic alterations influence both oncogenic signaling and the immune phenotype of NSCLC. However, an association with outcome after ICI therapy does not necessarily establish a treatment-specific predictive biomarker, because many alterations also carry independent prognostic effects. For patients with an actionable oncogenic driver, matched targeted therapy remains the preferred initial strategy in the relevant clinical setting. ICI efficacy after targeted-therapy failure is heterogeneous and should be interpreted according to the specific driver, co-mutations, smoking history, PD-L1 expression, treatment regimen, and available alternatives.^{13,46}

3.3.1. EGFR-mutant disease and combination strategies

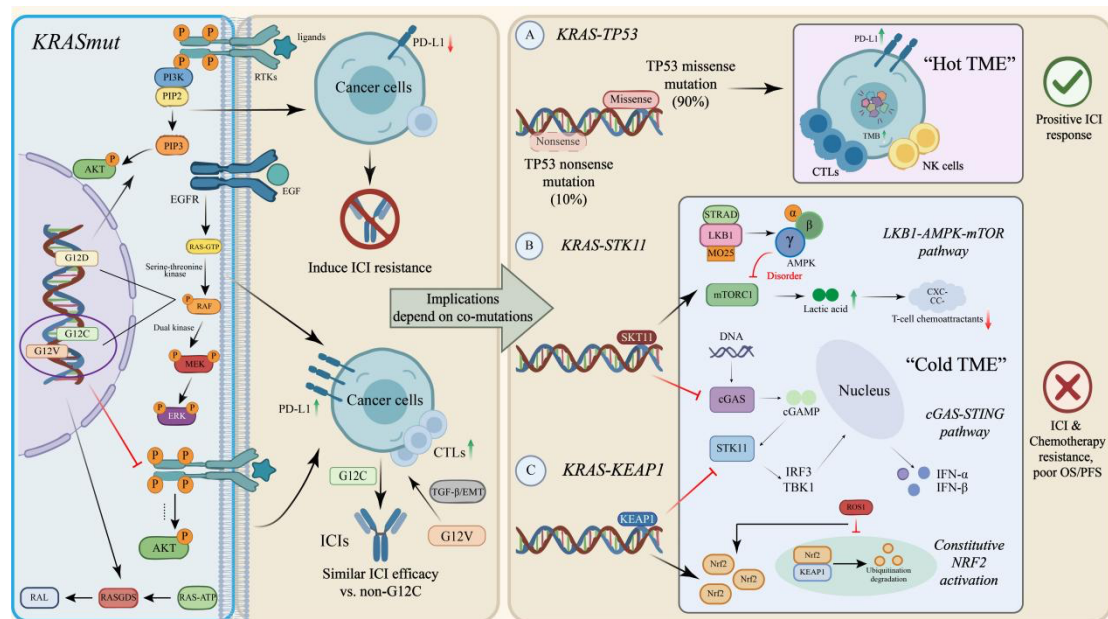
Epidermal growth factor receptor (*EGFR*) mutations are enriched in never-smokers, adenocarcinoma, Asian populations, and women. As a group, *EGFR*-mutant tumors often have lower TMB, less effective CD8+ T-cell infiltration, and limited benefit from ICI monotherapy compared with smoking-associated, driver-negative NSCLC.⁴⁷ Nevertheless, *EGFR*-mutant disease is heterogeneous. Some retrospective studies suggest that exon 21 L858R tumors may be more immunogenic or more responsive than exon 19 deletion tumors, whereas other analyses have not confirmed a clinically meaningful difference.⁴⁸ Co-mutations, smoking exposure, uncommon *EGFR* variants, prior therapies, and selection bias may account for part of the observed variation. Uncommon mutations such as G719X may occur in tumors with higher PD-L1 or TMB, but current evidence is insufficient to use mutation subtype alone to select ICI therapy.⁴⁹ ICI monotherapy generally has limited activity after failure of *EGFR* tyrosine kinase inhibitors, but regimens that combine PD-L1 blockade, chemotherapy, and antiangiogenic therapy may partially overcome immune exclusion in selected patients. Exploratory subgroup analyses from IMpower150 suggested activity of atezolizumab, bevacizumab, carboplatin, and paclitaxel after targeted-therapy failure, and ORIENT-31 demonstrated a progression-free survival benefit from sintilimab, a bevacizumab biosimilar, and chemotherapy in *EGFR*-mutant disease.^{50,51} These findings support treatment-context-specific combination strategies rather than a general conclusion that *EGFR*-mutant tumors are ICI sensitive. Antiangiogenic effects on vascular

normalization, myeloid suppression, and T-cell trafficking are biologically plausible, but the relative contribution of each component remains uncertain (Figure 3).



3.3.2. KRAS mutations and co-mutations

Common KRAS substitutions include G12C, G12D, G12V, and G12A. KRAS-mutant NSCLC is frequently smoking-associated and may have higher TMB and an inflamed TME, but response cannot be inferred from KRAS status alone.^{52,53} Some studies report higher PD-L1 expression and TMB in G12C than in non-G12C tumors without a consistent difference in ICI efficacy, whereas preclinical and translational data suggest that G12D may be associated with lower PD-L1 expression and reduced CD8+ T-cell infiltration.^{52,54} Clinical interpretation should therefore incorporate co-mutations and treatment context because the immune phenotype of KRAS-mutant tumors is strongly influenced by the co-mutation landscape (Figure 4).



The interaction of KRAS with serine/threonine kinase 11 (STK11, also known as LKB1) or kelch-like ECH-associated protein 1 (KEAP1) is supported by mechanistic and clinical observations. In experimental models, STK11 loss can impair AMP-activated protein kinase (AMPK)-related metabolic control and suppress cGAS-STING/type I interferon signaling, reducing T-cell-recruiting chemokines and promoting an immune-excluded or immune-desert phenotype.⁵⁵⁻⁵⁷ These mechanistic data are biologically compelling, but they should not be equated with a prospectively validated clinical test. Retrospective cohorts associate STK11 alterations with poorer outcomes after immunotherapy and chemotherapy, indicating that at least part of the effect may be prognostic rather than uniquely predictive of PD-(L)1 resistance.⁵⁸⁻⁶¹

KEAP1 loss activates NRF2-dependent antioxidant and metabolic programs and may reduce interferon signaling and immune-cell recruitment in preclinical systems.^{62,63} Clinical series consistently associate *KEAP1*, particularly with concurrent *STK11* and

KRAS alterations, with adverse prognosis. However, assay definitions, variant functional status, co-mutation structure, and treatment selection differ across cohorts. *STK11* and *KEAP1* should therefore be regarded as important risk stratifiers and investigational predictive markers, not as standalone validated reasons to withhold an otherwise indicated ICI regimen.

TP53 alterations are similarly heterogeneous. Some missense alterations and *KRAS*-*TP53* co-mutations are associated with greater genomic instability, inflammatory signaling, and improved ICI outcomes in retrospective analyses, whereas truncating or functionally distinct variants may not confer the same phenotype.^{64,65} Mutation class, clonality, co-mutations, and tumor context should be considered, and *TP53* status alone is not a validated treatment-selection biomarker.

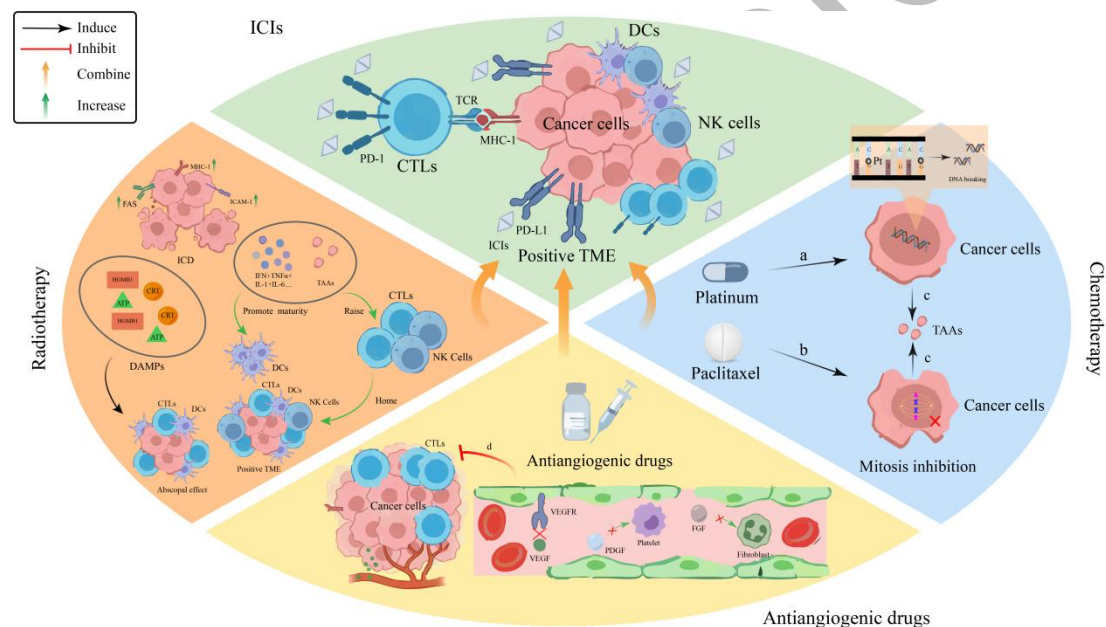
3.3.2. Other actionable oncogenic drivers

ICI outcomes also vary across tumors harboring alterations in anaplastic lymphoma kinase (ALK), ROS proto-oncogene 1, receptor tyrosine kinase (ROS1), RET proto-oncogene (RET), MET proto-oncogene, receptor tyrosine kinase (MET) exon 14 skipping, erb-b2 receptor tyrosine kinase 2 (ERBB2/HER2), and B-Raf proto-oncogene, serine/threonine kinase (BRAF). Rearrangement-driven tumors such as ALK-, ROS1-, and many RET-positive cancers commonly arise in never-smokers, have relatively low TMB, and show low response rates to ICI monotherapy despite occasional high PD-L1 expression. Outcomes in MET exon 14-skipping, ERBB2/HER2-mutant, and BRAF-

altered NSCLC are more variable and may depend on smoking history, mutation subtype, and co-mutations.^{13,46} Matched targeted therapies should be prioritized when available; subsequent immunotherapy decisions should be individualized rather than based on a single driver category.

4. Combination therapy and treatment modalities

PD-L1 expression, oncogenic-driver status, histology, disease burden, and patient fitness guide the selection of monotherapy or combination treatment in NSCLC. Chemotherapy, radiotherapy, antiangiogenic agents, dual checkpoint blockade, and other immunomodulatory strategies can broaden benefit, but efficacy must be balanced against toxicity, treatment discontinuation, quality of life, financial burden, and the possibility of exposing patients to unnecessary therapy (Figure 5).



4.1. Combination with chemotherapeutic agents

Chemoimmunotherapy improves response and survival in multiple first-line NSCLC settings and can benefit patients across PD-L1 categories.⁶⁶ Reported ORRs of approximately 33%-47% with combination regimens versus approximately 20%-25% with historical monotherapy illustrate broader activity, but these figures are not directly comparable across trials.^{67,68} Chemoimmunotherapy does not eliminate immune-related

adverse events (irAEs) and adds chemotherapy-related hematologic and nonhematologic toxicity.⁶⁹ Associations between irAEs and longer progression-free or overall survival have been reported, but these analyses are vulnerable to guarantee-time and immortal-time bias and should not be interpreted as evidence that irAEs are beneficial.^{70,71} Randomized patient-reported outcome data from KEYNOTE-189 showed maintenance of global health status and delayed symptom deterioration in the trial population, although individual quality-of-life effects depend on baseline symptoms, comorbidity, cumulative chemotherapy, and toxicity.⁷² Financial burden and access may also influence the real-world value of prolonged combination treatment. Clinical selection is therefore essential, particularly for frail patients, those with cachexia, and those with high PD-L1 expression who may be candidates for monotherapy.⁷³

Perioperative chemoimmunotherapy has improved pathological response and event-free survival in resectable NSCLC, including PD-L1-negative subgroups in pooled analyses.⁷⁴ However, pathological response does not fully capture long-term benefit, and perioperative treatment can delay surgery or produce immune-related and chemotherapy-related toxicity. Future studies should define which patients require neoadjuvant plus adjuvant therapy, identify optimal chemotherapy backbones and treatment duration, and incorporate molecular residual disease and patient-reported outcomes.

4.2. Combination with radiotherapy

Radiotherapy can induce immunogenic cell death, antigen release, and local immune remodeling, providing a rationale for combination with PD-(L)1 blockade.⁷⁵ Combining stereotactic body radiotherapy (SBRT) with PD-(L)1 blockade can enhance local immune activation and has produced signals of increased out-of-field response in selected studies; however, a reproducible increase in the clinical abscopal effect has not been established.⁷⁶⁻⁷⁹ Proposed mechanisms include antigen release, altered tumor PD-L1 expression, increased CD8⁺ T-cell recruitment, and modulation of MDSCs and Tregs. Important unresolved variables include total dose, fraction size, irradiated site and volume, number of lesions, sequencing relative to ICI, treatment interval, baseline immune phenotype, and patient selection. High-dose SBRT may enhance antigen release but can also deplete radiosensitive lymphocytes, whereas low-dose radiation may alter stromal and myeloid compartments without reliably controlling tumor. Pulmonary toxicity is particularly relevant in NSCLC, and the interaction between radiation pneumonitis and immune-mediated pneumonitis requires careful prospective evaluation.^{80,81}

4.3. Combination with antiangiogenic drugs

Antiangiogenic therapy may improve perfusion, reduce VEGF-mediated immune suppression, and facilitate lymphocyte trafficking, providing a rationale for combination with PD-(L)1 blockade. IMpower150 and ORIENT-31 support selected chemotherapy-antiangiogenic-immunotherapy regimens after targeted-therapy failure in EGFR-mutant NSCLC.^{50,51} In previously untreated, driver-negative, PD-L1-positive

advanced NSCLC, the phase III HARMONi-2 study conducted in China showed longer progression-free survival with the PD-1/VEGF bispecific antibody ivonescimab than with pembrolizumab; however, overall-survival maturity, external generalizability, regulatory status, and VEGF-related toxicity require consideration.⁸²⁻⁸⁴ Bleeding, hypertension, proteinuria, thromboembolic risk, regimen complexity, and cost must also be considered. Evidence from single-arm phase II studies, including endostatin-containing regimens, should not be interpreted as equivalent to randomized phase III confirmation.⁸⁵

4.4. Combination with other immunotherapeutic agents

Dual PD-(L)1 and CTLA-4 blockade can produce durable survival benefit and offers a chemotherapy-sparing option for selected patients, but it increases immune-mediated toxicity and requires careful patient selection.^{86,87} Neoadjuvant nivolumab plus relatlimab and pembrolizumab followed by delayed administration of the selective JAK1 inhibitor itacitinib have shown early clinical activity, but these approaches remain investigational in NSCLC.^{88,89} T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domains (TIGIT) and other co-inhibitory receptors are biologically attractive targets; however, early-phase signals have not established a consistent new standard, and randomized confirmation is required.⁹⁰

4.5. Antibody-drug conjugate combinations

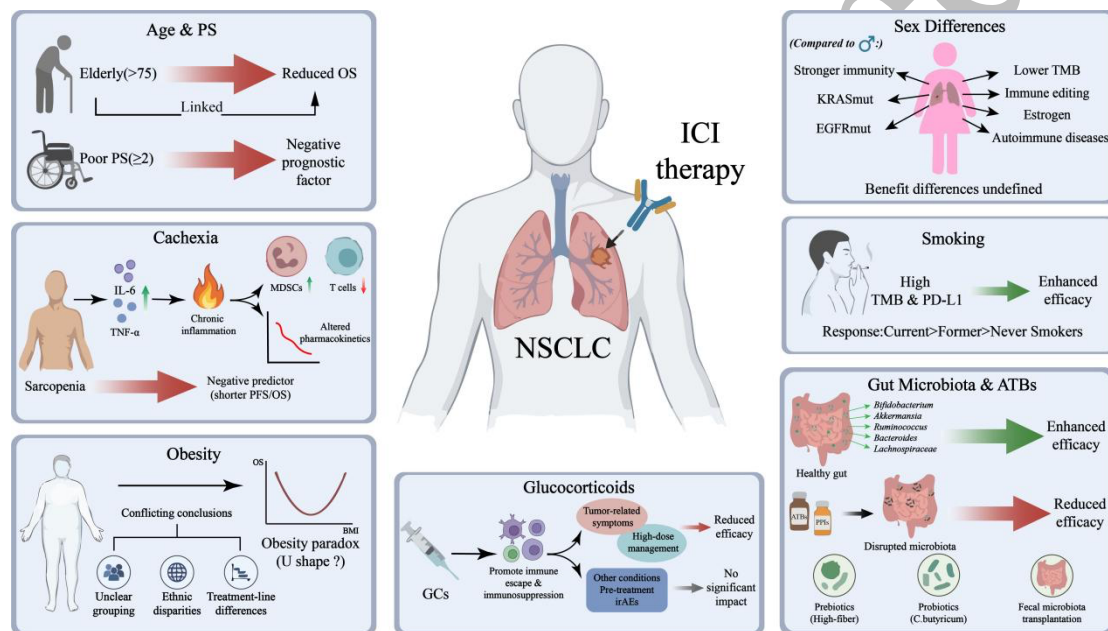
Antibody-drug conjugates (ADCs) deliver cytotoxic payloads to antigen-expressing tumor cells and may complement PD-(L)1 blockade through tumor-cell killing, antigen release, immunogenic cell death, and potential Fc-mediated immune effects. In the phase Ib TROPION-Lung02 study, datopotamab deruxtecan plus pembrolizumab, with or without platinum-based chemotherapy, demonstrated encouraging antitumor activity in previously untreated advanced NSCLC without actionable genomic alterations.⁹¹ The regimen remains investigational; the contribution of immune remodeling to clinical efficacy is incompletely established, and target expression, payload toxicity, stomatitis, hematologic toxicity, and interstitial lung disease/pneumonitis require careful evaluation. ADC-ICI combinations should therefore be described as promising but not uniformly proven across targets or settings.

4.6. Selected phase III studies and unresolved questions

At the May 2026 literature cutoff, TROPION-Lung08 (NCT05215340) was evaluating first-line datopotamab deruxtecan plus pembrolizumab versus pembrolizumab alone in advanced nonsquamous NSCLC with PD-L1 TPS $\geq 50\%$.⁹² PACIFIC-4/RTOG-3515 (NCT03833154) was evaluating durvalumab versus placebo after SBRT in unresected, node-negative early-stage NSCLC. Neither trial had reported definitive phase III efficacy results. These studies are designed to clarify incremental survival benefit, toxicity, quality of life, and the biomarker-defined populations most likely to benefit.

5. Individual patient characteristics

Host characteristics and concomitant medications can modify ICI outcomes through immune competence, systemic inflammation, pharmacokinetics, comorbidity, and treatment tolerance. Most supporting data are observational and are vulnerable to confounding; these variables should usually be interpreted as prognostic or hypothesis-generating rather than as independent treatment-selection biomarkers (Figure 6).



5.1. Age and performance status

The effect of chronological age on ICI efficacy remains uncertain. Large observational cohorts and meta-analyses suggest that the magnitude of benefit may be attenuated in some patients aged 75 years or older, but older adults are underrepresented in randomized trials and differ substantially in frailty, comorbidity, organ function, performance status, and competing mortality.^{93,94} Ageing can increase mutation burden while simultaneously altering immune function; chronological age alone therefore

provides an incomplete estimate of likely benefit.

Poorer performance status is one plausible explanation for less favorable outcomes in some older cohorts, but this is a potential confounding pathway rather than an established age-specific mechanism. ECOG performance status is a strong prognostic factor in advanced NSCLC, and patients with ECOG PS ≥ 2 generally have poorer outcomes than those with PS 0-1.⁹⁵ Because poor PS may result from reversible tumor burden, chronic comorbidity, frailty, or terminal decline, its meaning should be assessed clinically rather than used as an isolated contraindication.

5.2. Cancer Cachexia

Cancer cachexia is a multifactorial syndrome characterized by progressive skeletal-muscle loss, with or without adipose-tissue loss, and is commonly accompanied by systemic inflammation. Cachexia and sarcopenia are consistently associated with shorter progression-free and overall survival during ICI-based treatment, although the extent to which they are predictive rather than prognostic remains uncertain.⁹⁶⁻⁹⁹ IL-6, TNF- α , myeloid-cell expansion, impaired T-cell function, altered drug clearance, reduced physiologic reserve, and treatment intolerance may contribute. Baseline nutritional and body-composition assessment is therefore clinically relevant, but interventional evidence showing that reversal of cachexia improves ICI efficacy is limited.

5.3. Obesity

Retrospective studies have reported an “obesity paradox,” in which overweight patients appear to have improved outcomes with ICIs, but results are inconsistent after adjustment for confounding.¹⁰⁰⁻¹⁰⁴ BMI cannot distinguish skeletal muscle from adipose tissue or characterize visceral versus subcutaneous adiposity. Sarcopenia, low muscle attenuation, visceral adiposity, and combined phenotypes such as sarcopenic obesity may be more biologically and prognostically informative than BMI alone.⁹⁹ Future studies should use standardized CT-based body-composition measures, prespecified sex- and population-specific thresholds, and adjustment for performance status, smoking, disease burden, cachexia, and treatment line. BMI alone should not guide the selection of PD-(L)1 therapy.

5.4. Sex differences

Sex-related differences in immunity, hormones, tobacco exposure, tumor genomics, and adverse-event risk provide a biological rationale for differential ICI outcomes.¹⁰⁵⁻¹⁰⁸ However, clinical studies and meta-analyses have produced inconsistent estimates, and observed differences may reflect histology, smoking history, *EGFR/KRAS* distribution, treatment regimen, or other confounders.¹⁰⁹⁻¹¹² Some analyses suggest greater relative benefit from chemoimmunotherapy than monotherapy in women, whereas others show no significant sex interaction. Current evidence does not support selecting or withholding PD-(L)1 therapy solely on the basis of sex; sex should instead be incorporated as a prespecified variable in adequately powered trials and multiparameter prediction models.

5.5. Smoking history

A history of tobacco exposure is associated with higher mutation burden and may enrich for response to ICI monotherapy in NSCLC, particularly in driver-negative disease.^{113,114} This association reflects smoking-related mutagenesis and correlated tumor biology; it does not imply that smoking is clinically desirable or should be continued. Tobacco use causes cancer, cardiovascular and pulmonary disease, treatment complications, and mortality. Smoking cessation should be recommended at every stage of care, and smoking history should be interpreted with PD-L1, oncogenic drivers, TMB, and other clinical factors rather than as an independent therapeutic target.

5.6. Gut microbiota and antibiotics

The gut microbiome can influence systemic immunity through microbial metabolites, epithelial-barrier function, and the gut-lung axis. In NSCLC cohorts, microbial diversity and taxa including *Akkermansia*, *Bifidobacterium*, *Alistipes*, and selected Firmicutes have been associated with ICI outcomes.¹¹⁵⁻¹²¹ These findings are associations rather than proof of causation. Reported taxa are not fully consistent across cohorts, and abundance may reflect geography, diet, ethnicity, comorbidity, medication exposure, stool-collection procedures, sequencing platform, reference database, and bioinformatic pipeline.

Antibiotic or proton-pump inhibitor exposure has been associated with poorer outcomes in several observational studies and meta-analyses, particularly when exposure occurs

near ICI initiation.¹²²⁻¹²⁶ Nevertheless, confounding by infection, frailty, hospitalization, disease severity, indication, and cumulative exposure is difficult to eliminate, and other analyses have not demonstrated a causal detrimental effect.¹²⁷ Clinically indicated antibiotics should not be withheld, but unnecessary exposure and prolonged broad-spectrum treatment should be avoided according to antimicrobial-stewardship principles. Microbiome studies should prespecify exposure windows and dose, account for indication, and use standardized sampling and analytic methods.

Dietary modification, probiotics, and fecal microbiota transplantation are being investigated as microbiome-directed strategies.^{128,129} Evidence in NSCLC remains preliminary: probiotic data are largely retrospective or small, and fecal microbiota transplantation has not become standard practice. Candidate biomarkers such as plasma citrulline and blood or stool bacterial measurements require independent validation.¹³⁰ Intervention trials should include rigorous donor and product characterization, infection surveillance, dietary control, longitudinal sampling, and harmonized sequencing and bioinformatic workflows before clinical implementation.

5.7. Glucocorticoids

Glucocorticoids can suppress T-cell receptor signaling, alter lymphocyte and myeloid-cell states, promote Treg or M2-like programs, and potentially disrupt TLSs or the microbiome.¹³¹⁻¹³³ These mechanisms support biological concern, but dose, duration, timing, and indication are critical. Short courses used for chemotherapy premedication

or appropriate treatment of immune-related adverse events should not be interpreted in the same manner as persistent baseline steroids for cancer-related symptoms.

Retrospective studies associate baseline systemic glucocorticoid use, commonly defined as ≥ 10 mg/day prednisone equivalent, and early high-dose exposure with poorer response and survival during ICI therapy.¹³⁴⁻¹³⁹ However, indication bias is substantial: patients receiving glucocorticoids for dyspnea, brain metastases, cancer pain, or other palliative indications often have greater disease burden, poorer performance status, and worse prognosis independent of the drug itself. Analyses separating palliative from nonpalliative indications suggest that part of the observed association is attributable to this clinical context.¹³⁵ Glucocorticoids should therefore be used at the lowest effective dose for the shortest appropriate duration, without delaying clinically necessary treatment of immune-related toxicity or other serious conditions.

6. Summary and Future Prospects

The efficacy of PD-(L)1 inhibitors in NSCLC is governed by interactions among tumor genomics, immune contexture, host condition, treatment exposure, and time. PD-L1 is clinically implemented, whereas most other proposed markers are incompletely standardized or are primarily prognostic. The central clinical implication is therefore not to replace one imperfect biomarker with another, but to integrate complementary variables while recognizing the quality and context of the supporting evidence.

6.1. Key Determinants of Therapeutic Response

An integrated framework should combine analytically validated baseline variables with early on-treatment measurements. Baseline components may include PD-L1 TPS, actionable driver and co-mutation profiles, calibrated TMB, tumor burden and metastatic sites, immune-cell and gene-expression features, body composition, performance status, and relevant medication exposure. Spatial transcriptomics and single-cell sequencing can refine the interpretation of T-cell states, TLSs, myeloid programs, stromal barriers, and cell-cell interactions, but these technologies require simplification and standardization before routine use.¹²⁻¹⁴

Dynamic biomarkers may be more informative than a static pretreatment specimen. Early reductions in circulating tumor DNA, particularly when integrated with circulating immune-cell features or imaging response, have been associated with durable clinical benefit in NSCLC.^{45,140} Serial ctDNA may also help distinguish

molecular response from radiographic ambiguity, but low-shedding tumors and isolated intracranial disease remain important limitations. Additional dynamic measures may include peripheral immune-cell states, inflammatory indices, radiomic changes, and repeated tissue sampling when clinically feasible.

Artificial-intelligence-assisted models may integrate clinical, genomic, pathology, radiology, and longitudinal data at a scale that is difficult to interpret manually. Radiomic approaches have shown that imaging features can approximate CD8+ infiltration and associate with response to PD-(L)1 blockade.¹⁴¹ However, AI models are vulnerable to overfitting, dataset shift, missing data, and hidden confounding. External validation, calibration, transparent reporting, and demonstration of clinical utility are required before deployment.

6.2. Controversies and Directions

Major unresolved issues include cross-platform TMB calibration; assay and cutoff harmonization for spatial immune biomarkers; the predictive versus prognostic roles of *STK11*, *KEAP1*, cachexia, and concomitant medications; optimal sequencing of targeted therapy and ICI-based combinations in oncogene-driven disease; and reproducible microbiome measurement. Future studies should avoid simplistic positive/negative labels and should prespecify treatment setting, specimen type, timing, analytic method, and clinically meaningful decision thresholds.

Two trial concepts may accelerate progress. First, a biomarker-adaptive platform trial

could assign or reassign patients using an integrated baseline profile comprising tumor genomics, PD-L1, spatial immune architecture, ctDNA, and host factors, with treatment arms added or discontinued according to prospectively defined Bayesian decision rules. Second, a longitudinal co-clinical trial could obtain serial ctDNA, peripheral immune profiling, imaging, and paired tissue or spatial analyses to identify early resistance states and trigger protocol-defined treatment adaptation. These designs should include patient-reported outcomes, toxicity, cost-effectiveness, and equitable access. Ultimately, precision immuno-oncology will require prospectively validated, dynamic multiparameter models that improve patient outcomes beyond current clinical and PD-L1-based selection.

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Figure Legends

Figure 1. Tumor Immune Microenvironment Phenotypes

Immune-inflamed, immune-excluded, and immune-desert tumors differ in the abundance and localization of effector lymphocytes and may differ in responsiveness to immune checkpoint blockade; these phenotypes are dynamic and overlapping.

Figure 2. Tumor Mutational Burden as a Biomarker in NSCLC

Higher tumor mutational burden may increase neoantigen availability and enrich for immune checkpoint inhibitor response, although its predictive performance is assay- and context-dependent.

Figure 3. Heterogeneity of EGFR-Mutant NSCLC and Combination Strategies

Immune checkpoint inhibitor monotherapy generally has limited activity after EGFR tyrosine kinase inhibitor failure, although immune phenotypes vary across molecular and clinical subgroups.

Figure 4. KRAS Co-Mutations and Immune Heterogeneity in NSCLC

KRAS-TP53 tumors may exhibit a more inflamed phenotype, whereas STK11/LKB1 and KEAP1 alterations are associated with immune exclusion and poorer outcomes.

Figure 5. Rationale for Combining PD-(L)1 Blockade With Other Therapies

Cytotoxic therapies may enhance antigen release and immunogenic cell death, whereas VEGF inhibition may normalize tumor vasculature and reduce immune suppression.

1085 Figure 6. Host and Treatment-Related Factors Influencing ICI Outcomes

1086 Performance status, cachexia, sarcopenia, corticosteroid use, smoking, obesity,
1087 microbiota, antibiotics, and proton-pump inhibitors have been associated with immune
1088 checkpoint inhibitor outcomes, although many relationships are context-dependent.