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CD4+ T-Cell Program Dynamics Under PD-1/PD-L1 Blockade in NSCLC

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Abstract:

Immune checkpoint blockade (ICB) targeting PD-1/PD-L1 has transformed non-small cell lung cancer (NSCLC) therapy, yet durable benefit remains limited to a subset of patients. While most mechanistic and biomarker frameworks emphasize CD8+ T cells, accumulating single-cell, TCR, and spatial evidence indicates that CD4+ T cells can act as system-level organizers of anti-tumor immunity and resistance. This paper synthesizes NSCLC studies from 2018-2025 and weighs conclusions using an evidence-tier framework that prioritizes intra-patient longitudinal sampling (paired tumor biopsies and/or serial blood) and spatially resolved profiling. Findings are integrated across five recurring CD4 programs: TLS-associated CXCL13+ Tfh-like states, Th1-oriented helper/effector states, Th17-linked inflammatory states, FOXP3+ regulatory T cells (Tregs), and proliferative/activation-to-exhaustion trajectories. Across the strongest longitudinal tumor evidence, response most consistently aligns with coordinated on-therapy remodeling that strengthens TLS/Tfh organization and Th1-oriented output, whereas non-response is repeatedly linked to persistence or accumulation of activated intratumoral Treg states. Th17-associated signals show more variable directionality and remain lower-confidence under PD-1/PD-L1 blockade in NSCLC. Clonal tracking further connects benefit to productive proliferative bursts and blood-tumor clonal exchange within tumor-relevant T-cell pools. Together, these data support biomarker and treatment strategies that move beyond single markers toward composite, time-aware readouts capturing baseline immune infrastructure, suppressive balance, and on-therapy state transitions, and motivate rational combinations that relieve suppressive constraints while preserving productive CD4 help.

Keywords: NSCLC; Immunotherapy; PD-1/PD-L1 blockade; CD4 T cells; Biomarkers

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1. Introduction

Immune checkpoint blockade (ICB) targeting the PD-1/PD-L1 axis is a foundational therapy in non-small cell lung cancer (NSCLC), yet most patients fail to respond or eventually relapse, underscoring the need for better biomarkers and rational combinations. While PD-1/PD-L1 biology has been framed largely through CD8+ cytotoxic T cells, high-dimensional profiling increasingly supports a central role for CD4+ T cells in shaping whether anti-tumor immunity becomes productively organized within the tumor tissue [1]. CD4 programs can amplify immunity by supporting antigen presentation and sustaining effector responses, or suppress it through FOXP3+ regulatory T cells (Tregs), and PD-1 blockade is therefore expected to remodel multiple CD4 programs in clinically meaningful ways.

Since 2018, longitudinal single-cell and spatial approaches have made it possible to track CD4 state transitions under therapy. scRNA-seq with paired TCR profiling enables inference of clonal expansion, differentiation trajectories, and blood-tumor exchange, while spatial transcriptomic/proteomic methods add microanatomical context. Because CD4 states often represent continua of activation and tissue adaptation, within-patient longitudinal sampling (paired tumor biopsies and/or serial blood) is particularly informative for distinguishing baseline predictors from treatment-induced change.

Across NSCLC studies, three modules recur most consistently: (i) a TLS-associated Tfh-like program, frequently marked by CXCL13, which is associated with favorable outcomes and can mature or expand on therapy in responders; (ii) Th1-oriented CD4 immunity, linked to inflamed microenvironments and strengthened in responders during treatment; and (iii) an immunosuppressive Treg module, where activated tumor-resident states are enriched in non-responders and may blunt effective effectorization even under checkpoint release. Other CD4-linked signals are more context-dependent: Th17/IL-17-associated inflammation shows mixed evidence with limited high-confidence longitudinal tumor data, and proliferative/activation-to-dysfunction trajectories are most interpretable when anchored by clonal tracking and state-transition logic. These patterns motivate biomarker strategies that incorporate tissue context and on-therapy remodeling, while interpreting blood readouts cautiously given compartmental discordance.

This review synthesizes NSCLC evidence from 2018-2025 on five CD4 functional programs under PD-1/PD-L1 blockade: TLS/Tfh-like, Th1-oriented helper/effector, inflammatory Th17, FOXP3+ Treg, and proliferative/activation-to-dysfunction trajectories. Baseline predictors are separated from therapy-induced changes and weight conclusions by evidence strength, prioritizing longitudinal and spatial data when available, to clarify reproducible CD4 remodeling patterns associated with benefit versus resistance and their biomarker and combination-therapy implications.

2. Tfh-Like CD4 Responses and Tertiary Lymphoid Structures

Tertiary lymphoid structures (TLS) in pretreatment NSCLC tumors are among the strongest baseline correlates of favorable response to PD-1/PD-L1 blockade [2]. These Tfh-like CD4 cells typically express CXCR5, high PD-1 and ICOS, and produce B-cell-recruiting factors such as CXCL13 and IL-21 [2]. For instance, in a cohort of 53 advanced NSCLC tumors, TLS-positive cases showed better overall and progression-free survival and an immune-"hot" microenvironment enriched for both CD4 and CD8 T cells [2].

Longitudinal and spatial evidence further supports that PD-1 blockade can amplify this TLS/Tfh program in responders. In paired tumor biopsy analyses, responders commonly show on-therapy increases in CXCL13-expressing CD4+ T cells, alongside clonal proliferation that is less evident in non-responders [1]. Spatial profiling places these CXCL13+ CD4 cells near B-cell zones within TLS, consistent with TLS maturation or expansion during effective therapy [3]. In some settings, TLS has been reported as absent at baseline but detectable on treatment, suggesting therapy-associated lymphoid neogenesis; one neoadjuvant analysis noted that roughly a quarter of patients acquired newly detectable TLS after anti-PD-1 [4]. By contrast, non-responders often fail to induce the CXCL13+ CD4/TLS axis and may show persistently TLS-low contexts [4]. These patterns track clinical endpoints: stronger TLS/Tfh enrichment aligns with deeper tumor regression and prolonged progression-free survival ([2]), and in a cohort of 234 resected NSCLC cases after neoadjuvant chemo-immunotherapy, nearly half of non-responders (non-MPR) were characterized by a "TLS-low, Treg-high" microenvironment, while responders more often exhibited TLS-rich profiles [4].

Mechanistically and clinically, the TLS-associated CD4 program plausibly provides local scaffolding for sustained antigen presentation, coordinated T-B interactions, and durable effector organization under checkpoint release. The post-therapy clonal expansion of Tfh-like CD4 cells is consistent with tumor-antigen engagement that becomes productive when PD-1 brakes are lifted [5]. Clinically, on-treatment TLS growth has been linked to deeper re-

sponses [6], motivating combination strategies that promote lymphoid organization in TLS-negative tumors. A recent report also suggested sex-associated differences in the CXCL13-linked response signature, with stronger associations in female patients than in males [7], highlighting potential heterogeneity in how this program can be therapeutically leveraged.Th1-Oriented CD4 Immunity in NSCLC

3. Th1-Oriented CD4 Immunity in NSCLC

Th1-polarized CD4+ T cells, classically marked by TBET (TBX21) and production of IFN-γ, TNF, and IL-2, are a central helper axis supporting cellular immunity. In NSCLC, baseline tumors with a strong Th1/IFN-γ gene signature tend to be immunologically inflamed and are more likely to respond to PD-1 blockade [1, 8]. One illustrative example is the immunosuppressive context described by [9], where high TGF-β and low IFN-γ were associated with a Th17/Treg-skewed ecology and worse ICI outcomes. Broader evidence that IFN-γ-dominant "type 1" immune contextures, sometimes captured by compact effector signatures, predict checkpoint responsiveness [10].

Longitudinal tumor profiling indicates that effective therapy is commonly accompanied by strengthening of Th1-oriented CD4 immunity within the tumor. In paired analyses, responder tumors show post-treatment enrichment of CD4 states expressing Th1 genes (e.g., TBX21, IFNG) alongside chemokine programs that overlap with CXCL13+ peripheral helper/Tfh-like features, consistent with a hybrid Th1/Tfh phenotype that may couple type 1 effector help with local immune organization. Importantly, these Th1-oriented CD4 populations display clonal expansion preferentially in responders, consistent with antigen-driven proliferation being released under PD-1 blockade. Mechanistic work supports a causal role for CD4 help (often delivered through IFN-γ/IL-2-producing Th1-like cells) in licensing antigen-presenting cells and sustaining functional cytotoxic CD8 responses [1]. By contrast, non-responders frequently fail to mount a Th1 boost and can remain Th1-deficient even on therapy, particularly in microenvironments dominated by inhibitory cues such as TGF-β [9].

These dynamics associate with clinical outcomes: responders more often exhibit on-therapy induction of intratumoral IFN-γ and Th1-linked chemokines after treatment [1], whereas muted Th1 induction is enriched in non-responders in neoadjuvant settings [9]. Overall confidence in this module is high because within-patient tumor data support treatment-linked Th1 reinforcement in responders and because the helper logic is consistent with established immunological mechanisms [1]. The main caveat is context dependence-some tumor niches with persistent TGF-β-rich suppression (for example, certain metastatic sites) may blunt Th1 differentiation even under PD-1 blockade [9].

Clinically, early on-treatment assessment of Th1-associated markers (e.g., IFNG and downstream chemokines such as CXCL9/10) could serve as practical indicators of whether therapy is routing CD4 activation into productive type 1 help, while a failure to shift may flag patients at risk of non-response. These observations also motivate combination strategies that remove barriers to Th1 polarization. In NSCLC contexts where TGF-β antagonizes type 1 programs, targeting TGF-β has been proposed as a way to permit Th1 differentiation and improve response [11]. Similarly, CTLA-4 blockade can enhance costimulation and shift the CD4 balance toward Th1 while counteracting Treg dominance, providing a rationale for dual-checkpoint strategies in Th1-low settings [9].

4. Inflammatory Th17 Responses

Th17-polarized CD4+ T cells, classically marked by RORγt, CCR6, and IL-17A/F production, represent an inflammatory lineage with pleiotropic roles in cancer. In NSCLC, Th17 cells are typically a minor baseline subset but are detectable in some patients [12, 13]. Consistent with this coupling, NSCLC tumors with a Th17/Treg-high and Th1-low ecology (linked to TGF-β-rich contexts) have been associated with poor PD-1 outcomes [9]. More broadly, correlative analyses have reported that higher IL-17/Th17-associated signatures can track with unfavorable outcomes and reduced type-1 immunity in NSCLC [14, 15]. underscoring that Th17 markers may sometimes reflect bystander inflammation rather than a dominant driver of response [16].

Compared with Th1 and TLS/Tfh modules, treatment-induced Th17 dynamics under PD-1/PD-L1 blockade remain less well consolidated. Longitudinal paired-tumor data directly tracking Th17 state transitions are relatively sparse, in part because Th17 populations are small and difficult to resolve consistently across assays, and available evidence does not support a uniform expansion of Th17 cells under PD-1 monotherapy [9]. Instead, responder trajectories are more consistently characterized by CD4 remodeling toward Th1/Tfh-like programs, whereas non-responders may retain a Th17/Treg-skewed ecology when the underlying suppressive milieu is not altered [9]. A nuance is lineage plasticity: in some immunomonitoring contexts, combination strategies can be associated with Th17 cells acquiring more Th1-like features (e.g.,

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increased T-bet), consistent with Th17-to-Th1 reprogramming under type-1-favoring cytokine cues [17]. Across studies, the key biological tension is that IL-17 pathways can couple to pro-tumor circuits such as stromal remodeling, angiogenesis, and myeloid/neutrophil skewing, yet may also participate in immune recruitment or lymphoid organization depending on the broader context [16, 18].

Overall confidence is low to moderate. The weight of NSCLC evidence currently leans toward Th17/IL-17 readouts acting as a risk context marker, often overlapping with TGF-β-linked suppression/exclusion or ineffective inflammatory ecologies, rather than a reproducible favorable biomarker of PD-1/PD-L1 benefit [9, 15]. However, most supporting data are correlative and cross-sectional, and definitive within-patient longitudinal evidence is limited, making it difficult to distinguish whether Th17 is causal, compensatory, or merely correlated with a particular microenvironmental state. Practically, if on-treatment tumor-proximal readouts show Th17/IL-17 activity without a coordinated rise in type-1 effector programs, the most defensible interpretation is caution: this pattern may align with resistance-associated microenvironments and suggest that PD-1/PD-L1 monotherapy is unlikely to be sufficient [15]. This logic motivates combination approaches that attempt to address the broader suppressive circuit, including TGF-β-linked programs, although translating that rationale into clinical benefit has proven challenging-for example, the PD-L1/TGF-β trap bintrafusp alfa did not outperform pembrolizumab in a head-to-head setting in PD-L1-high advanced NSCLC [19].

5. Regulatory T-Cell Dynamics

Intratumoral FOXP3+ regulatory T cells (Tregs) are a central suppressive axis in NSCLC, but baseline risk is more consistently captured by suppressive balance and activated tumor-infiltrating Treg (tiTreg) states than by FOXP3 abundance alone. In anti-PD-1-treated NSCLC, a lower FOXP3/CD8 ratio in pretreatment tumors has been associated with better therapeutic response, supporting the idea that relative suppressive pressure versus effector capacity is clinically meaningful. Consistently, across PD-1-treated cohorts including lung cancer, the intratumoral balance of PD-1+ effector T cells to PD-1+ Tregs can outperform single biomarkers such as PD-L1 expression in predicting benefit. High-resolution tumor profiling reinforces that Treg quality matters: in serial tumor biopsies with scRNA/TCR sequencing, non-responders were enriched for activated/suppressive tiTreg programs (including IL1R2/TNFRSF9/LAYN-associated states), whereas responders generally did not show comparable enrichment [1]. Complementing this, computational analyses of NSCLC immunotherapy datasets found that activated tiTreg features (e.g., TNFRSF9 normalized to FOXP3) correlate with inferior anti-PD-1 response, while Treg abundance alone may be insufficient as a predictor [19]. A key caveat is compartment specificity: peripheral blood Treg dynamics do not necessarily mirror tumor-resident Tregs, and blood–tumor discordance exists, underscoring the danger of extrapolating blood-Treg directionality to the tumor microenvironment [20].

Longitudinally, responders and non-responders diverge in suppressive-effector trajectories, with timing and compartment shaping what is observed. In Tier-1 serial-biopsy NSCLC data, non-responders showed persistence and/or accumulation of suppressive tiTreg programs under therapy, whereas responders did not exhibit comparable increases in these suppressive states [1]. In larger neoadjuvant single-cell atlases, post-treatment tumors can be stratified into tumor immune microenvironment (TIME) subtypes, including a Treg-dominant subtype enriched among non-responders [4]. Mechanistically, several studies caution that PD-1 blockade can, in some contexts, preferentially expand highly suppressive PD-1+ effector Tregs, offering a plausible explanation for why suppressive axes may persist or even intensify during treatment in a subset of patients [21, 22].

Across these lines of evidence, a Treg-dominant or activated tiTreg-enriched tumor state correlates with poor response or resistance, particularly when effector reinvigoration is inadequate. This is supported by ratio-based baseline pathology (FOXP3/CD8) [23], effector-to-Treg balance predictors across PD-1-treated cohorts [24], and serial-biopsy single-cell evidence of suppressive tiTreg enrichment in non-responders [1]. Spatial context may further refine prognosis, as it was proposed that the niche localization of Tregs carries information, including reports that TLS-associated Tregs can link to inferior survival in NSCLC [25].

Overall confidence is moderate. Tumor-based studies consistently implicate activated tiTreg programs and suppressive balance in resistance [1, 19, 24], but directional claims about absolute Treg frequency shifts under PD-1 therapy are not uniform, and blood-based signals can show the opposite association [20]. Clinically, these patterns motivate combination strategies tailored to a resistance-prone, Treg-dominant ecology and emphasize the need to target tumor-infiltrating Treg subsets rather than globally depleting systemic Tregs. Candidate approaches include selectively targeting lung-relevant Treg subsets such as CCR8+ Tregs, which can suppress cytotoxic T-cell function and are therapeutically tractable in preclinical lung cancer models, and leveraging tumor-restricted markers such as IL1R2 proposed for selective tiTreg depletion

strategies [26, 27].

6. Proliferative and Exhausted CD4 T Cells

Even before treatment, many NSCLC tumors contain chronically stimulated CD4+ tumor-infiltrating lymphocytes that occupy an activation-to-dysfunction continuum, making "proliferative/exhausted" CD4 states a marker of an engaged but constrained compartment [28]. Clonally and spatially resolved data further support this framing: in a multi-regional lung cancer dataset generated during ICB, tumor-enriched CD4 clones overexpressed chronic-stimulation/tumor-reactivity genes (e.g., TIGIT, TOX, CTLA4, ENTPD1, CXCL13), mirroring patterns seen in tumor-enriched CD8 clones and indicating that exhaustion-linked markers can capture antigen-experienced, tumor-relevant repertoires [29].

Under PD-1 blockade, the most consistent longitudinal signal is selective amplification and redistribution of tumor-relevant clonotypes. First, blood-tumor clonal exchange emerges as a measurable correlate of response in resectable disease: in neoadjuvant PD-1-treated NSCLC with serial blood and tumor TCR sequencing, tumors achieving major pathologic response (MPR) showed higher intratumoral clonality and greater sharing of tumor clonotypes with peripheral blood, and the post-treatment tumor bed was enriched for clones that had expanded in blood around weeks 2-4 after therapy initiation; the intratumoral space occupied by these clonotypes inversely correlated with residual tumor [28]. Second, clonal tracking indicates state diversification within tumor-relevant clones. By identifying mutation-associated neoantigen (MANA)-specific T-cell clones and mapping them in scRNA/TCR space during neoadjuvant anti-PD-1. It was observed that many neoantigen-specific cells mapped to tissue-resident memory-like programs early after initiation, followed by broader diversification into effector-like states later in the treatment course [29]. Third, response-linked reinvigoration appears biased toward precursor-like exhausted trajectories that can renew downstream effector output, consistent with models in which PD-1 blockade preferentially boosts less-differentiated, expandable pools rather than only rescuing terminally dysfunctional cells [1].

A key 2018-2025 refinement is that the proliferative burst may be fueled by anatomically distributed progenitors rather than being exclusively intratumoral. In [30], multi-regional tumor sampling with tumor-draining lymph node and longitudinal blood suggested that tumor-specific exhausted populations and Tfh-like CD4 programs were clonally linked to TCF7+ SELL+ progenitor-like cells in draining lymph nodes, consistent with a reservoir that can seed and sustain intratumoral responses. The same study reported long-term persistence of tumor-specific CD4 and CD8 clones in peripheral blood for years after ICB, reinforcing that clinically meaningful antitumor dynamics can be systemic and durable when therapy succeeds [30]. Clinically, large post-neoadjuvant single-cell atlases further connect these concepts to endpoints: in 234 NSCLC tumors, tumor immune microenvironment subtypes stratified MPR rates, and precursor exhausted signatures correlated with recurrence-free survival, identifying a lower-recurrence subgroup even among patients without MPR [4].

Overall confidence is moderate to high. Across multiple longitudinal and TCR-tracking studies in resectable NSCLC, productive ICI response is accompanied by time-anchored proliferative expansion and redistribution of tumor-relevant clonotypes, while finer-grained exhaustion state shifts can be context-dependent and are best interpreted through clonal lineage and renewability logic.

7. Integrated synthesis across CD4 programs under PD-1/PD-L1 blockade

Across CD4 programs, baseline NSCLC immune states can be organized into two coupled dimensions: an immunogenic infrastructure axis (pre-existing TLS/Tfh organization and Th1-oriented effector readiness) and a suppressive constraint axis (activated intratumoral Treg states and chronically stimulated inhibitory-receptor-high CD4 compartments). The proliferative/exhausted CD4 compartment sits at the intersection of these axes: it indicates antigen engagement and checkpoint pressure at baseline, but its clinical meaning depends on whether the surrounding tissue context supports productive differentiation rather than constrained cycling or terminal dysfunction [4].

Longitudinal profiling under PD-1/PD-L1 blockade supports two broad remodeling trajectories that cut across individual program labels. In responders, on-therapy change is coordinated rather than isolated: tumor-relevant clones show a transient proliferative burst accompanied by diversification into functionally productive outputs, most consistently strengthening Th1-like effector signatures and/or amplifying TLS/Tfh-linked organization [4, 11, 29]. In non-responders, remodeling often appears stalled or diverted: Th1/Tfh strengthening is blunted, proliferative signals do not translate into durable effector output, and suppressive modules (activated tiTregs) remain prominent [19].

These trajectories highlight that the five programs are

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mechanistically interdependent rather than independent biomarkers. When these conditions hold, Th1-like programs rise and associate with the response [9, 11]. Tregs act as a counter-module that can suppress antigen-presenting cell function and constrain effector differentiation, with multiple datasets emphasizing that state (activated/suppressive tiTregs) is a key discriminator beyond abundance alone [19, 24]. Finally, proliferative/exhausted CD4 states are best interpreted as a kinetic readout of antigen engagement and checkpoint pressure; they become clinically informative mainly when paired with evidence that the proliferative burst is clonally linked to tumor-relevant exchange and productive downstream diversification [4, 29].

Clinically, this argues against single-marker interpretation and toward composite readouts that explicitly encode context and time. The most actionable interpretation likely requires jointly capturing: (i) TLS/Tfh presence and maturation, (ii) Th1 readiness and on-therapy strengthening, (iii) suppressive balance dominated by activated tiTreg states, and (iv) whether on-therapy proliferation connects to tumor-relevant clonal exchange and functional diversification [2-4, 19, 29]. Therefore, the most defensible biomarkers and mechanistic conclusions remain those anchored in baseline-to-on-therapy transitions measured directly in tumor tissue (Tier 1-2), ideally integrated with clonal and spatial evidence.

Confidence is highest for the integrated role of TLS/Tfh and Th1-oriented programs as favorable baseline features and on-therapy correlates of response, supported across multiple NSCLC tumor studies [2, 3, 9, 11]. Confidence is moderate for activated tiTreg programs as a resistance axis and for proliferative/exhausted remodeling as a component of successful response, because clonally resolved longitudinal tumor evidence remains limited and exhaustion definitions vary across studies [4, 19, 24, 29]. Confidence is lowest for Th17 directionality under PD-1 blockade in NSCLC due to mixed, often indirect evidence and limited paired-tumor validation [13, 14, 16]. Across modules, the central remaining gap is causal coupling: establishing whether and how TLS/Tfh maturation drives Th1 output and how tiTreg suppression reshapes these transitions will require more paired biopsies with integrated clonal tracking and spatially resolved measurements within the same patients.

8. Conclusion

The most reproducible CD4 remodeling signal under PD-1/PD-L1 blockade is a coordinated shift in immune organization and output. Tumors that benefit from therapy exhibit tissue-level immune infrastructure (TLS/Tfh-linked organization) together with type-1 helper/effector readiness, and convert on-therapy activation into durable Th1/Tfh-associated programs supported by tumor-relevant clonal expansion and exchange. In contrast, resistance frequently reflects a failure to route activation into productive differentiation: Th1/Tfh reinforcement is blunted, proliferative signals may remain kinetically "trapped," and suppressive balance persists through activated intratumoral Treg states. Th17/IL-17 signals remain the least consolidated module; current evidence more often supports Th17 as a context marker of alternative inflammatory or TGF-β-linked ecologies than as a favorable biomarker, but longitudinal validation is limited.

Clinically, these findings argue for composite, time-aware biomarker strategies that jointly measure baseline infrastructure (TLS/Tfh), effector output (Th1), suppressive constraint (activated tiTregs), and whether on-therapy proliferation connects to tumor-relevant clonal diversification. The key evidence gap is causal coupling: future studies integrating paired biopsies with clonal and spatial resolution are needed to test whether TLS/Tfh maturation drives Th1 output and how tiTreg programs divert these trajectories.

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