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T-cell lymphoma following chimeric antigen receptor-T therapy: a cause for concern?

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F.S and M.R. conceptualized the project, interpreted and discussed the literature, and wrote the manuscript. J.A.F and S.J.S. reviewed, provided conceptual feedback and edited the manuscript. M.R.. supervised the project. All authors reviewed, provided critical textual additions and approved the final manuscript.

Abstract

Chimeric antigen receptor (CAR) T-cell therapy has revolutionized the treatment of relapsed or refractory B-cell malignancies and multiple myeloma, with tens of thousands of patients treated worldwide. As survival improves, long-term safety has come into focus, and rare reports of T-cell lymphomas occurring after CAR T-cell infusion have prompted regulatory scrutiny and heightened clinical attention.

Drawing on pivotal trials, real-world registries, meta-analyses, pharmacovigilance data, and detailed molecular case reports, we review the incidence, biological plausibility, and clinical relevance of lymphomas arising after CAR T-cell therapy. Registry data and large institutional series consistently show that secondary T-cell malignancies are exceedingly rare, with reported incidences of approximately 0.03-0.3% depending on the cohort, and far less common than therapy-related myeloid neoplasms, solid tumors, and non-melanoma skin cancers in heavily pretreated populations. Most molecularly characterized post-CAR T-cell lymphomas lack evidence of CAR vector-driven transformation and appear to reflect pre-existing or therapy-selected clonal T-cell populations in the context of clonal hematopoiesis, immune dysregulation, and, in some cases, viral reactivation. Nevertheless, rare CAR-positive cases with informative integration-site data confirm that vector-related transformation is biologically possible, although exceptional and probably dependent on cooperating host or clonal events.

We also discuss pathogenetic mechanisms, diagnostic pitfalls, and practical recommendations for surveillance and patient counseling.

In conclusion, secondary T-cell lymphomas represent a concerning but extremely uncommon complication of CAR T-cell therapy. Vigilance through standardized long-term follow-up and rigorous molecular investigation of suspected cases is warranted, but current evidence does not undermine the overwhelmingly favorable benefit-risk profile of CAR T-cell therapy.

Main text

1) Introduction

Chimeric antigen receptor (CAR) T-cell therapy has transformed the management of relapsed or refractory B-cell lymphoma, acute lymphoblastic leukemia, and multiple myeloma. With multiple commercially approved products and tens of thousands of patients treated worldwide, CAR T cells are now firmly established as a standard of care for diseases that historically carried dismal prognoses[1–9]. As durable remissions and long-term survival have become increasingly common in a subset of CAR T-treated patients, attention has progressively shifted from early toxicities, such as cytokine release syndrome and immune effector cell-associated neurotoxicity, to long-term safety. Beginning in late 2023[10] and continuing through 2024[11] the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC)[12] highlighted rare reports of T-cell malignancies occurring after CAR T-cell therapy, prompting class-wide label updates and recommendations for lifelong surveillance[13]. These communications were appropriately triggered by post marketing reports, emerging case reports, and pharmacovigilance signals that raised the possibility of CAR-associated T-cell lymphomagenesis. Given the well-established historical precedent of insertional mutagenesis in early gene therapy trials[14], such reports understandably generated concern among clinicians, regulators, and patients. However, interpreting these events requires careful contextualization.

CAR T-cell recipients represent a uniquely vulnerable population, typically exposed to multiple lines of cytotoxic and immunosuppressive therapies, frequently harboring clonal hematopoiesis, and experiencing profound immune perturbation[15–19]. Disentangling events causally attributable to CAR T-cell products from those reflecting background or therapy-related risk, therefore, remains challenging. This review aims to critically examine the current evidence on lymphomas arising after CAR T-cell therapy, with a specific focus on T-cell malignancies. We integrate data from national and international registries, pivotal and large clinical trials, real-world cohorts, and molecularly characterized case reports to define the best available incidence, explore pathogenetic mechanisms, and outline clinical and regulatory implications of post-CAR T-cell lymphoid malignancies. Our goal is to provide a balanced perspective grounded in denominators rather than anecdotes, emphasizing vigilance without alarm in the interpretation of these rare events.

2) Global exposure to CAR T-cell therapy and secondary malignancies: defining the denominator and contextualizing T-cell lymphomas

Any assessment of late safety signals following CAR T-cell therapy critically depends on an accurate definition of the population at risk. While exact denominators vary according to region and reporting system, available estimates indicate that more than 40,000 patients worldwide have been treated with autologous CAR T-cell products across hematologic indications, including large B-cell lymphoma, mantle cell lymphoma, follicular lymphoma, acute lymphoblastic leukemia, chronic lymphocytic leukemia, and multiple myeloma[20–23]. As CAR T-cell therapy moves into earlier treatment lines and additional diseases, the rapidly growing use of this therapy makes reliable denominators essential for interpreting rare adverse events.

The first signal assessments relied heavily on spontaneous reporting systems, most notably the US FDA Adverse Event Reporting System (FAERS)[24]. While indispensable for signal detection, such systems are inherently limited by underreporting, reporting bias, lack of standardized adjudication, and, most importantly, the absence of a true denominator. Consequently, pharmacovigilance databases cannot provide population-based incidence estimates and may either inflate perceived causality or miss unreported events. Registry-based data offer a more robust framework for contextualizing late events. National and multicenter registries are better positioned to capture consecutive patients, apply standardized definitions, and enable longitudinal follow-up (**Table 1**).

At an international level, the *Center for International Blood and Marrow Transplant Research* (CIBMTR) captured 11,345 recipients of commercial CAR T-cell therapies through December 2023, including 8,060 patients enrolled in formal post-authorization safety studies with a median follow-up of 13 months[25]. Within this cohort, 565 secondary or subsequent malignant neoplasms were reported, predominantly non-melanoma skin cancers and therapy-related myeloid neoplasms, whereas three T-cell malignancies were identified, none showing aberrant CAR expression by routine clinical immunophenotyping, although this is not equivalent to vector-specific molecular exclusion[25]. The *French DESCAR-T* registry reported a single T-cell malignancy among 3,066 patients treated with commercial CAR T-cell products since 2018, corresponding to an incidence of approximately 0.03%[26]. Prospective real-world data further support this interpretation. In the *Italian CART-SIE* database, secondary primary malignancies (SPM) were observed in 4% of 651 CAR T-cell-treated patients, a frequency consistent with expectations for heavily pretreated lymphoma populations[27]. As in other studies, the burden of secondary malignancies was driven largely by myeloid neoplasms and solid tumors, while T-cell malignancies represented an exceptionally rare subset, accounting for only 2 of 651 patients (0.3%)[27]. Large registry studies and meta-analyses provide the necessary denominators to contextualize the risk of secondary primary malignancies after CAR T-cell therapy. A systematic review and meta-analysis including more than 5,500 patients treated with approved CD19- and BCMA-directed CAR T cells reported an overall SPM incidence of approximately 6%, with hematologic malignancies representing the most frequent category and T-cell malignancies accounting for 1.5% of all SPM events[28]. Importantly, randomized trials comparing CAR T-cell therapy with standard-of-care strategies have not demonstrated an excess risk of SPMs in the CAR T-cell arms within currently available follow-up[29–33]; however, trial follow-up remains too short to exclude very late or very rare events. Similar conclusions emerged from large single-institution and national registry experiences, in which the cumulative incidence of second malignancies was driven predominantly by myelodysplastic syndromes, acute myeloid leukemia, and solid tumors[34,35].

Taken together, these data indicate that SPMs following CAR T-cell therapy are more readily explained by background risk and cumulative treatment exposure than by a broad CAR-specific oncogenic effect. Within this broader landscape, T-cell lymphomas occupy a numerically marginal but biologically distinctive position. Their rarity contrasts with the attention they have received, driven by the theoretical concern that genetically modified T cells might undergo malignant transformation. This biological specificity, rather than numerical impact, provides the rationale for

examining T-cell lymphomas separately from the more common and better-characterized spectrum of secondary malignancies.

3) T-cell lymphomas after CAR T-cell therapy: case-based evidence

Reports of T-cell lymphomas arising after CAR T-cell therapy encompass a biologically heterogeneous group of entities that can be broadly categorized into three non-mutually exclusive scenarios (**Figure 1**): 1) CAR-negative T-cell lymphomas arising in the post-CAR T-cell setting (**Table 2**) 2) CAR-positive T-cell malignancies with demonstrable involvement of the CAR transgene (**Table 3**), and 3) clonal T-cell proliferations or "mimickers" that may simulate lymphoma but follow a benign or self-limited course (**Table 2**). This classification requires molecular caution: detection of low-level CAR sequences in a biopsy may reflect admixed CAR T cells rather than a malignant CAR-transduced clone.

3.1) CAR-negative T-cell lymphomas after CAR T-cell therapy. Most molecularly adjudicated T-cell lymphomas reported after CAR T-cell therapy do not show evidence of CAR transgene expression or integration. In the wake of the FDA safety communication, *Ghilardi et al.* provided one of the first detailed biological analyses of this concern, reporting a peripheral T-cell lymphoma that developed three months after commercial axi-cel CD19 CAR T-cell therapy. In this case, low CAR transgene levels were attributable to infiltrating CAR T cells rather than malignant transformation. Deep clonotypic and genomic analyses demonstrated that the neoplastic T-cell clone was already detectable at very low frequency before CAR T-cell infusion, supporting a pre-existing clonal origin rather than CAR-driven oncogenesis[36]. *Hamilton et al.* later described a lethal Epstein-Barr virus (EBV)-positive T-cell lymphoma arising after axicabtagene ciloleucel infusion, in which extensive molecular profiling excluded oncogenic vector integration and instead revealed shared DNMT3A and TET2 mutations consistent with clonal hematopoiesis[34]. Additional CAR-negative events have been reported beyond single-case mechanistic studies, including a PTCL-NOS after liso-cel with no detectable CAR transgene[37].

These observations are most consistent with indirect pathogenetic mechanisms, whereby profound immune perturbation following lymphodepletion and CAR T-cell expansion associated with an inflammatory milieu may permit the outgrowth of pre-existing malignant or premalignant T-cell clones. In this scenario, CAR T-cell therapy might function as a permissive or accelerating factor rather than a direct oncogenic driver[38].

3.2) CAR-positive T-cell malignancies – Molecularly definitive evidence that CAR-modified T cells can become a malignant clone has been provided by a small number of molecularly characterized cases. *Ozdemirli* et al. reported an indolent $CD4^+$ cytotoxic T-cell lymphoma involving the gastrointestinal tract in a patient treated with ciltacabtagene autoleucel for multiple myeloma, in which CAR gene expression was detected in tumor cells and whole-genome sequencing identified a single lentiviral integration site within the SSU72 gene[39]. Although the clinical course was relatively indolent, this case established biological plausibility without proving that integration alone was sufficient for transformation. More aggressive phenotypes have also been described. *Kobbe et al.* reported a rapidly progressive peripheral T-cell lymphoma occurring approximately one month after tisagenlecleucel infusion, in which the malignant clone expressed

the CAR transgene and harbored multiple lentiviral integration sites[40]. Notably, the same T-cell clone was retrospectively detectable at low frequency prior to CAR T-cell manufacturing, suggesting expansion of a pre-existing population rather than de novo transformation.
Perica et al. later reported an indolent $CD4^+$ T-cell lymphoma of the gastrointestinal tract arising after BCMA-directed CAR T-cell therapy, in which high-resolution integration site analysis demonstrated lentiviral CAR insertion within the TP53 tumor suppressor gene, providing one of the clearest examples in which insertional mutagenesis may have contributed to malignant transformation[41]. Finally, *Braun et al*. described a leukemic peripheral T-cell lymphoma developing after sequential exposure to BCMA-directed CAR T cells and a GPRC5D-directed bispecific antibody, in which longitudinal single-cell multiomic profiling revealed clonal expansion of CAR-expressing T cells originating from a TET2-mutated precursor, highlighting the role of pre-existing clonal vulnerability combined with chronic antigenic stimulation[42].

At the population level, CAR-positive T-cell malignancies remain exceptional. Collectively, these observations indicate that insertional mutagenesis or CAR-driven transformation is possible but occurs in an exceedingly small minority of patients. Notably, the level of mechanistic resolution varies substantially across reports; the most informative cases combine sensitive CAR detection with integration-site mapping and longitudinal clonotypic analyses, thereby allowing a clearer distinction between CAR-derived transformation and the expansion of pre-existing clones.

3.3) Mimickers and diagnostic pitfalls. Adding further complexity, not all clonal T-cell proliferations observed after CAR T-cell therapy represent autonomous malignant lymphomas. For example, *Maurer et al.* reported a clonally expanded nodal T-cell population with histologic features suggestive of T-cell lymphoma that arose during acute infection and subsequently regressed spontaneously, with no detectable CAR transgene by whole-genome sequencing[43]. Along the same spectrum of diagnostic mimickers, *Capes et al.* described severe post-CAR T-cell cytopenias driven by an oligoclonal expansion of large granular lymphocyte–like $CD8^+$ T cells in the bone marrow, lacking CAR expression and responsive to immunosuppressive therapy, underscoring how reactive clonal T-cell proliferations may masquerade as malignant processes in the post-CAR T-cell setting[44].
Further supporting this diagnostic caution, *Ho et al*. recently described a case of massive CD4-skewed cilta-cel expansion associated with immune-related adverse events, in which extensive TCR repertoire and vector integration analyses showed polyclonal CAR T-cell expansion without evidence of clonal dominance or malignant transformation[45].

Such cases highlight the risk of overdiagnosis and overtreatment if clinical, pathological, and molecular data are not integrated longitudinally and reconciled with the clinical tempo[38]. Together, case-based evidence underscores that T-cell lymphomas after CAR T-cell therapy represent a spectrum of entities with distinct biological underpinnings, ranging from rare CAR-derived malignancies to indirect, therapy-associated lymphomas and benign mimickers.

4) Pathogenetic mechanisms: disentangling causality
Understanding the biological basis of T-cell lymphomas arising after CAR T-cell therapy requires disentangling causality from coincidence in a profoundly perturbed immunologic landscape.

Available evidence supports a multifactorial model in which direct CAR-related mechanisms appear to account for only a minority of cases, while indirect processes predominate.

4.1) Expansion of pre-existing clonal T-cell populations. A recurring theme across molecularly characterized cases is the presence of pre-existing clonal T-cell or hematopoietic populations detectable before infusion or in the manufactured product. Retrospective analyses have demonstrated that the malignant clone was present at low frequency in the apheresis product or even months to years earlier, prior to CAR T-cell manufacturing[40]. In such cases, CAR transduction, manufacturing, and subsequent in vivo expansion may select for or amplify an already abnormal clone rather than initiate transformation de novo. This concept is further supported by reports of oligoclonal or monoclonal T-cell expansions following CAR T-cell therapy that do not invariably progress to overt lymphoma[43]. These expansions highlight the potent selective pressures imposed by lymphodepleting chemotherapy, homeostatic cytokine signaling, and antigen-driven proliferation in the post-infusion period.

4.2) Clonal hematopoiesis and shared mutational landscapes – Clonal hematopoiesis of indeterminate potential (CHIP), particularly involving epigenetic regulators such as DNMT3A and TET2, has emerged as a key predisposing factor. Recent studies have shown that CHIP is detectable in approximately 25% to 50% of patients undergoing CAR T-cell therapy[15–19], reflecting the heavy pretreatment and advanced age typical of this population. Several post-CAR T-cell T-cell lymphomas share CHIP-associated mutations between malignant T cells and non-malignant hematopoietic compartments, indicating a common ancestral clone[34,42]. Beyond its role as a reservoir of premalignant clones, CHIP is increasingly recognized as a pro-inflammatory state. Loss-of-function alterations in TET2 and DNMT3A can enhance myeloid-cell inflammatory output, including activation of inflammasome-related pathways and increased production of IL-1β, IL-6, and other inflammatory mediators. Mechanistically, TET2-deficient macrophages have been shown to up-regulate IL-1β through both transcriptional derepression and enhanced NLRP3 inflammasome-dependent processing, whereas DNMT3A or TET2 loss can also trigger mitochondrial DNA release, cGAS activation, and type I interferon signaling in human macrophages. These observations provide a biological basis for linking CHIP-associated epigenetic lesions to exaggerated innate immune activation rather than viewing CHIP solely as a passive marker of prior therapy or aging[46–48]. This is particularly relevant in the CAR T-cell setting, where lymphodepletion, immune reconstitution, CAR T-cell expansion, CRS, infections, and prolonged cytopenias generate a highly inflammatory post-treatment milieu. Such inflammation may provide both a proliferative advantage and a selective pressure for pre-existing CHIP-derived hematopoietic clones, including rare clones with lymphoid or multilineage potential, although this remains incompletely proven in individual cases. These mutations may therefore confer increased fitness, genomic instability, or altered differentiation potential, lowering the threshold for malignant progression under immune stress. In this framework, CAR T-cell therapy acts as a biological stress test that unmasks latent clonal vulnerabilities rather than serving as the primary oncogenic insult.

4.3) Immune dysregulation and viral reactivation. Profound immune perturbation is a defining feature of CAR T-cell therapy. Lymphodepleting chemotherapy, followed by rapid immune

reconstitution that can be shaped by CAR-modified cells creates a permissive environment for dysregulated immune responses. B-cell aplasia, hypogammaglobulinemia, and prolonged cytopenias further impair immune surveillance. This spectrum of hematologic toxicity is now recognized as immune effector cell-associated hematotoxicity (ICAHT), a distinct and frequent complication of CAR T-cell therapy that differs qualitatively from conventional chemotherapy-induced myelosuppression. ICAHT may occur early or late after infusion and reflects the combined effects of lymphodepletion, baseline hematopoietic reserve, systemic inflammation, bone marrow microenvironment injury, and CAR T-cell-driven immune activation. Severe or prolonged ICAHT is clinically relevant because it predisposes patients to bacterial, fungal, and viral infections, contributes to non-relapse mortality, and may mark a sustained state of impaired immune surveillance rather than a transient cytopenic phase. *Rejeski et al.* specifically emphasize that hematologic toxicity after CAR T-cell therapy is common, can predispose to clinically relevant infections, and has now been formalized through EHA/EBMT grading into early and late ICAHT[18]. Emerging data also suggest that delayed immune reconstitution may have consequences beyond infection. Exploratory abstract-level data from a single-center retrospective analysis at the University of Pennsylvania further support a possible link between prolonged immune dysfunction and secondary malignancy risk after CAR T-cell therapy. In this cohort of 284 patients with B-cell lymphoma, *Chong and colleagues* reported non-melanoma skin cancers in 21 patients (7%) after CAR T-cell therapy. Failure to recover an absolute lymphocyte count ≥1 × 10^3 cells/μL, as well as longer time to lymphocyte recovery, was associated with a higher risk of non-melanoma skin cancer. Although these findings remain preliminary and require confirmation in full peer-reviewed datasets, they suggest that delayed lymphocyte recovery may represent a clinically informative marker of persistent immune dysfunction after CAR T-cell therapy[49].

Several reported T-cell lymphomas after CAR T-cell therapy have also been associated with Epstein–Barr virus positivity, supporting a role for viral reactivation in lymphomagenesis under conditions of immune suppression[34]. In such cases, the temporal association with CAR T-cell infusion likely reflects a broader state of post-treatment immune dysregulation rather than a direct vector-mediated effect.

4.4) Insertional mutagenesis: rare but biologically plausible. Genetic modification of T cells using integrating vectors inherently carries a theoretical risk of insertional mutagenesis. This concern is grounded in historical experience from early gene therapy trials, in which retroviral integration near proto-oncogenes led to malignant transformation[14]. In the CAR T-cell setting, however, extensive clinical experience with lentiviral and gammaretroviral vectors has demonstrated a reassuring long-term safety profile in large clinical cohorts, although the available data do not eliminate rare, patient-specific events[38,50]. This conclusion is further supported by a large long-term follow-up study of 783 patients treated across 38 trials with lentiviral or gammaretroviral gene-modified T-cell therapies, encompassing more than 2,200 patient-years of observation. In that analysis, 18 patients developed secondary malignancies, but tumor vector-copy-number testing and integration-site analyses did not support vector-mediated insertional mutagenesis; one T-cell lymphoma was observed, but the malignant T cells were not marked by

vector integration[51]. Nevertheless, rare cases provide proof of principle. CAR-positive T-cell malignancies with demonstrable vector integration into host genomic loci have been reported, including insertion within genes implicated in transcriptional regulation or cell-cycle control[21,34–36]. Importantly, several reported cases of CAR-associated T-cell malignancies show multiple vector integration sites without clear enrichment near canonical oncogenes, suggesting that vector insertion alone is unlikely to be sufficient to drive malignant transformation[38]. This observation is consistent with the integration profile of modern self-inactivating lentiviral vectors and contemporary gamma-retroviral systems, which generally have lower enhancer-promoter activity than early gene-therapy vectors.
Non-viral systems illustrate a related but distinct risk. Transformation events have also been reported with piggyBac transposon-engineered CAR T cells, in which CAR-expressing T-cell lymphomas showed high transgene copy numbers and complex genomic alterations[52], highlighting that transgene copy number, genomic instability, and clonal selection may matter at least as much as the identity of the integration platform. These include the two product-derived CAR T-cell lymphomas reported in the Australian CARTELL trial of donor-derived piggyBac-modified CD19 CAR T cells, one presenting as a retroperitoneal CD4-positive CAR T-cell lymphoma and the second detected as an asymptomatic thoracic para-aortic/mediastinal CAR T-cell tumor during post-trial screening[53].

Taken together, these observations argue against a simple linear model of CAR-driven oncogenesis and instead support a multistep process requiring cooperating events, including pre-existing clonal hematopoiesis, oncogenic mutations, possible chronic antigenic stimulation, and selective pressures imposed during CAR T-cell manufacturing and in vivo expansion.

4.5) An integrated multistep model. Taken together, available data support a multistep model in which T-cell lymphomas after CAR T-cell therapy arise from the convergence of predisposing host factors and therapy-induced selective pressures (**Figure 1**). Pre-existing clonal abnormalities, clonal hematopoiesis, or latent viral infection provide the substrate, while lymphodepletion, inflammatory cytokine milieus, and CAR-driven expansion may act as accelerants. Rarely, CAR vector integration may contribute as an additional cooperating event, rather than as a sole driver. This integrated model reconciles the biological plausibility of CAR-related oncogenesis with the exceptionally low incidence observed in large registries and provides a rational framework for diagnostic evaluation, risk communication, and surveillance.

5) Clinical implications: diagnosis, monitoring, and patient counseling
Although T-cell lymphomas reported after CAR T-cell therapy are extremely rare and biologically heterogeneous, they have important practical implications for clinical management. The principal challenge is to ensure timely recognition of true malignant events while avoiding overdiagnosis and overtreatment of transient or reactive T-cell proliferations.

5.1) Diagnostic approach. Any new or progressive lymphadenopathy, extranodal lesion, or unexplained systemic symptoms arising after CAR T-cell therapy should prompt tissue diagnosis whenever feasible. Excisional biopsy or multiple core biopsies are preferred over fine-needle aspiration to enable comprehensive histologic, immunophenotypic, and molecular assessment.

A minimal diagnostic work-up should include: (i) full histopathologic evaluation with extended immunohistochemistry, (ii) assessment of T-cell receptor clonality, and (iii) Epstein–Barr virus testing. Given the central question of causality, evaluation for CAR transgene presence should be pursued in suspected cases, and whenever feasible the original product lot, vector map, apheresis/manufacturing material, and pre-infusion samples should be retrieved, ideally using sensitive molecular approaches rather than immunophenotyping alone, which may lack sensitivity or fail to detect truncated or transcriptionally silent constructs[54].
Recommended methods include quantitative PCR (qPCR) or digital droplet PCR (ddPCR) targeting vector-specific sequences (such as the CAR transgene, WPRE element, or lentiviral LTR), next-generation sequencing-based assays for vector detection, and RNA-based approaches to identify CAR transcripts when transcriptionally active constructs are present. In addition, flow cytometry using anti-idiotype antibodies or CAR-specific detection reagents may provide supportive evidence but should not be considered definitive in isolation. A major practical limitation is the lack of standardized reagents, assay platforms, and reporting thresholds for CAR detection across centers. This is particularly relevant because sensitivity and specificity may vary substantially depending on the target sequence, primer/probe design, antibody reagent, and the availability of product-specific reference material. When CAR positivity is detected or strongly suspected, further molecular characterization, including vector copy number quantification and integration site analysis using techniques such as linear amplification–mediated PCR (LAM-PCR)[55], ligation-mediated PCR, or targeted next-generation sequencing, may provide critical mechanistic insight by determining whether the malignant clone derives from CAR-modified T cells and by identifying potential integration events near cancer-related genes. However, these analyses currently remain restricted to specialized research or reference laboratories, and results should be interpreted with hematopathology, treating-center, manufacturer, and regulatory input. Importantly, detection of T-cell clonality alone should not be equated with malignancy. Clonal T-cell expansions may occur in reactive or inflammatory settings, particularly in the context of immune reconstitution, infection, or cytokine-driven proliferation following CAR T-cell therapy.

5.2) Diagnostic pitfalls and dynamic assessment. Several reported cases highlight that clonal T-cell proliferations after CAR T-cell therapy may follow a self-limited course, including spontaneous regression without lymphoma-directed treatment. In clinically stable patients with atypical or borderline findings, short-interval reassessment with repeat imaging or biopsy may be appropriate before initiating aggressive therapy. This dynamic approach is particularly relevant when clinical presentation coincides with intercurrent infection or inflammatory triggers. Conversely, rapidly progressive disease, organ compromise, or unequivocal histologic features of aggressive T-cell lymphoma warrant prompt treatment according to standard T-cell lymphoma guidelines, independent of CAR transgene status.

5.3) Monitoring and follow-up. Given the absence of a validated screening strategy and the exceedingly low incidence of T-cell malignancies, routine surveillance specifically targeting these events is not justified beyond product-label and guideline-recommended long-term follow-up after CAR T-cell therapy. Lifelong clinical monitoring should focus on new symptoms, unexplained cytopenias, and persistent lymphadenopathy, integrated within existing survivorship programs. At present, there is insufficient evidence to support systematic pre-infusion screening for clonal T-

cell populations or clonal hematopoiesis solely to mitigate this rare risk of post-CAR T-cell lymphomas. This does not exclude a potential role for CHIP assessment in other contexts, including risk stratification for therapy-related myeloid neoplasms, prolonged cytopenias, inflammatory toxicity, or other CAR T-cell outcomes; however, its use specifically to prevent or predict post-CAR T-cell lymphomas remains unsupported by current evidence. Such approaches remain investigational.

5.4) Patient counseling – Patient communication should emphasize that T-cell lymphomas after CAR T-cell therapy are exceptionally rare and that the overall benefit-risk profile of CAR T-cell therapy remains overwhelmingly favorable for approved indications. Transparent discussion of long-term follow-up requirements and prompt reporting of new symptoms should be encouraged, while avoiding alarmist framing that could undermine confidence in a highly effective therapy.

6) Conclusions

Research in the field of chimeric antigen receptor (CAR) T-cell therapy is currently evolving along two complementary directions. On one hand, substantial efforts aim to improve efficacy and expand clinical indications, including the exploration of novel target antigens[56,57], optimization of CAR design[58], and advances in cell manufacturing strategies[59]. On the other hand, increasing attention is being devoted to improving safety[60], both by mitigating acute toxicities and by understanding and preventing potential long-term complications. Within this broader context, lymphomas arising after CAR T-cell therapy represent a rare but biologically informative phenomenon that has prompted substantial clinical and scientific attention, despite their very low observed incidence. When evaluated against robust denominators from national and international registries, T-cell malignancies following CAR T-cell therapy occur at an exceedingly low frequency, well below 1% in available registry datasets, with important caveats related to follow-up duration, product mix, and ascertainment in heavily pretreated oncohematologic populations[61].

Accumulating molecular evidence indicates that most reported cases are not primarily driven by CAR vector integration. Instead, they reflect the convergence of pre-existing clonal vulnerabilities, clonal hematopoiesis, viral reactivation, and profound immune perturbation in heavily pretreated patients. Rare CAR-positive T-cell malignancies with demonstrable transgene integration confirm biological plausibility but appear to require additional cooperating events and remain exceptional. From a clinical perspective, these observations underscore the importance of careful diagnostic evaluation rather than routine surveillance for an exceedingly rare complication. Integration of histopathology, molecular clonality, viral studies, and sensitive assays for CAR detection is essential to distinguish true malignant transformation from reactive or self-limited T-cell proliferations. Avoiding overtreatment of benign mimickers is as critical as recognizing aggressive disease when it occurs. Regulatory and pharmacovigilance efforts have appropriately emphasized systematic reporting and long-term follow-up, enabling continued refinement of risk estimates without restricting access to highly effective therapies. Importantly, the available body of evidence does not support a reassessment of the overall benefit–risk balance of CAR T-cell therapy, which remains overwhelmingly favorable.

In conclusion, T-cell lymphomas following CAR T-cell therapy should prompt vigilance, standardized investigation, transparent reporting, and continued data collection, but not alarm. As CAR T-cell therapy expands to earlier lines of treatment and new indications, ongoing collaborative surveillance will further clarify rare late effects while preserving the transformative impact of this therapeutic modality.

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Tables

Table 1. T-cell malignancies reported after CAR T-cell: Registry-based denominators and incidence estimates.

Study	Patients	CAR T-cell product(s)	Follow-up	Secondary malignancies	T-cell malignancies	CAR integration
DESCAR-T Registry, France (Dulery et al., Nat Med 2025)	3,066	Commercial anti-CD19 & anti-BCMA	Median 12.7–17.7 months	-	1 case (0.03%)	Yes Integration in PLAAT4
CIBMTR (Levine et al, Nat Med 2024)	11,345	Commercial	13 months	565 SPM (4.9%)	3 cases (0.03%)	No
CART-SIE Database, Italy (Barone et al., BJH 2024)	651	Commercial anti-CD19	12.2 months	28 SPMs (4.3%)	2 cases (0.3%)	No

Table 2. CAR-negative T-cell lymphomas and mimickers.

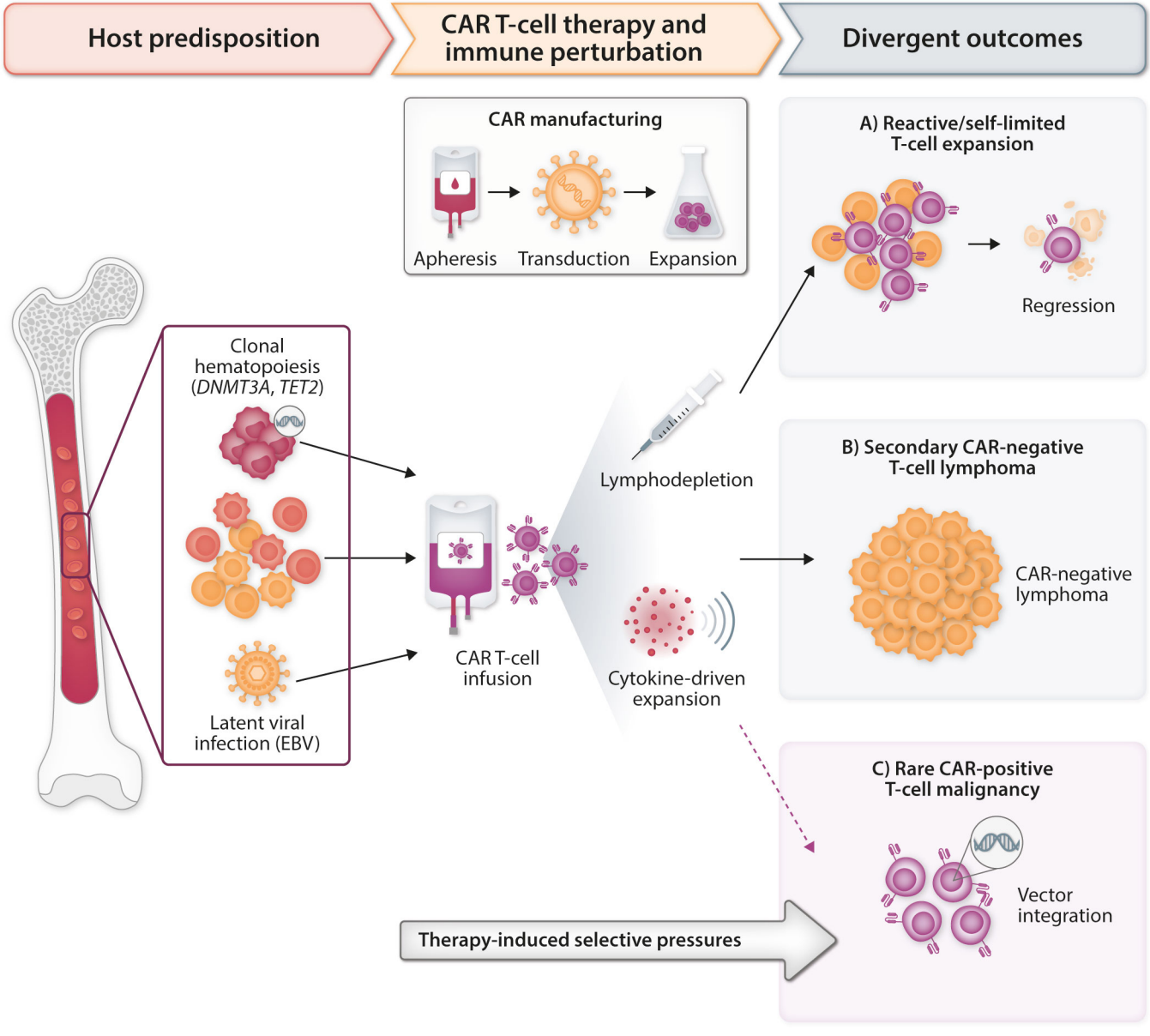
Reference	Product	Time	Key biology	Interpretation
Ghilardi et al., Nat Med 2024	axi-cel	~3 months	Dominant TCR clone detectable pre-infusion	Pre-existing clonal TCL unmasked post-CAR T; not CAR-driven
Hamilton et al., NEJM 2024	axi-cel	54 days	EBV+, DNMT3A/TET2 CHIP	Indirect mechanism
Tatetsu et al., IJH 2025	liso-cel	8 months	PTCL-NOS, CAR not detected	Therapy-associated TCL
Maurer et al., Nat Commun 2025	axi-cel	During infection	Clonal TFH-like expansion, regression	Diagnostic mimicker
Capes et al., BJH 2025	axi-cel	Variable (post-infusion cytopenia phase)	Oligoclonal CD8+ LGL–like marrow T-cell expansion; CAR-negative; immune-mediated cytopenias; response to immunosuppression	Reactive LGL-like clonal expansion; diagnostic mimicker, not lymphoma
Ho et al., Nat Med 2026	cilta-cel	Day 13 peak expansion; CirAEs from day 31 onward	Extreme CD4-skewed CAR T-cell hyperexpansion; diverse TCR Vβ repertoire; no clonal dominance by vector integration analysis; IL-15–CCL5–CCR5 axis implicated	Polyclonal, non-malignant CAR T-cell hyperexpansion causing immune-related toxicity; diagnostic mimicker, not lymphoma

Table 3. Case report CAR-positive T-cell malignancies.

Reference	Indication/ Product	Time to onset	Histology phenotype	Molecular findings	Interpretation
Ozdemirli et al., NEJM 2024	MM / cilta-cel	~4–8 months	Indolent CD4+ cytotoxic GI TCL	CAR+, insertion in SSU72	CAR-derived lymphoma; integration not necessarily sole driver
Kobbe et al., NEJM 2024	LBCL / tisa-cel	~1 month	Aggressive PTCL	CAR+, multiple integration sites	Expansion of pre-existing clone
Perica et al., NEJM 2025	MM / cilta-cel	~2 months	Indolent CD4+ GI T-cell lymphoma / LPD	Lentiviral integration in TP53 and TANGO2.	Strong insertional mutagenesis signal involving TP53 with cooperating events
Braun et al., Nat Med 2025	MM / cilta-cel; then talquetamab	9 months	Leukemic PTCL with cutaneous and intestinal involvement; T-LGLL-like features	Two CAR+ clones; multiple integration sites; clonal evolution from TET2-mutated precursor	Multistep model: pre-existing clonal vulnerability plus therapy-driven selection
Dulery et al., Nat Med 2025	DLBCL / tisa-cel	3 years	Primary cutaneous CD30+ TCL	Integration in PLAAT4	Exceptional CAR-positive event; causality plausible

Figure 1 – Proposed pathogenetic model of T-cell lymphomagenesis after CAR T-cell therapy

Host predisposition, including clonal hematopoiesis, pre-existing T-cell clones, and latent viral infection, may interact with CAR T-cell manufacturing, lymphodepletion, cytokine-driven immune activation, and therapy-induced selective pressures. These events may lead to reactive/self-limited T-cell expansions, secondary CAR-negative T-cell lymphomas, or, rarely, CAR-positive T-cell malignancies driven by vector integration.


Host predisposition
CAR T-cell therapy and immune perturbation
Divergent outcomes
CAR manufacturing
Apheresis
Transduction
Expansion
A) Reactive/self-limited T-cell expansion
Regression
Clonal hematopoiesis (DNMT3A, TET2)
Latent viral infection (EBV)
CAR T-cell infusion
Lymphodepletion
Cytokine-driven expansion
B) Secondary CAR-negative T-cell lymphoma
CAR-negative lymphoma
C) Rare CAR-positive T-cell malignancy
Vector integration
Therapy-induced selective pressures