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Review

Peripheral T-Cell Lymphoma NOS: Current Management and Emerging Therapeutic Strategies

Steven A. Kessler [1], Milan Khealani [2], Aditi Singh [3] and Juan Jose Chango Azanza [3,*]

[1] Department of Medicine, University of Minnesota, Minneapolis, MN 55455, USA; kessl334@umn.edu
[2] Department of Hematology and Medical Oncology, University of Minnesota, Minneapolis, MN 55455, USA; kheal001@umn.edu
[3] Department of Hematology and Medical Oncology, Minneapolis VA Medical Center, Minneapolis, MN 55417, USA; aditi.singh2@va.gov
* Correspondence: juanjose.changoazanza@va.gov

Abstract

Peripheral T-cell lymphomas (PTCLs) are a heterogeneous group of lymphoproliferative disorders arising from mature T-cells and account for approximately 10% of all non-Hodgkin lymphomas. PTCL not otherwise specified (PTCL-NOS) is the most common subtype and is considered a diagnosis of exclusion after other PTCL subtypes have been ruled out. Therefore, PTCL-NOS exhibits extreme heterogeneity in its morphologic features, molecular characteristics, and clinical manifestations. Prognosis in PTCL is dismal with a 5-year overall survival (OS) of 20–30%. Diagnosis can be challenging, and efforts to improve risk stratification and optimize therapeutic management continue to evolve. This review systematically summarizes recent advances in the understanding of the epidemiology, classification, histopathology, diagnosis, and management of PTCL-NOS. We discuss emerging therapeutic options and future directions aimed at improving outcomes for this aggressive disease.

Keywords: peripheral T-cell lymphoma; PTCL-NOS; non-Hodgkin lymphoma; T-cell lymphoma; recent advances

1. Introduction

Mature T-cell and Natural Killer (NK)-cell neoplasms constitute a broad group of lymphoproliferative disorders arising from post-thymic T-cells or NK-cells, accounting for over 10–12% of all lymphoid malignancies [1]. The term "peripheral T-cell lymphoma (PTCL)" is commonly used in clinical practice to describe all mature T-cell and NK-cell neoplasms. However, the most common subtype of mature T-cell and NK-cell lymphoproliferative disorders is peripheral T-cell lymphoma not otherwise specified (PTCL-NOS), accounting for approximately 25% of cases [2]. The 5th Edition of the World Health Organization Classification of Hematolymphoid Tumors (WHO-5) and the International Consensus Classification (ICC) define a broad category of mature T-cell and Natural Killer (NK)-cell neoplasms of which PTCL-NOS is the most common subtype [3,4]. PTCL-NOS is considered a diagnosis of exclusion of all PTCLs that do not meet criteria for any other entities defined in both major classifications. As a diagnosis of exclusion, PTCL-NOS can have heterogeneity in its morphologic features and clinical presentation, making it more challenging to diagnose, risk-stratify, and manage.

The clinical management of PTCL-NOS remains one of the most challenging areas in malignant hematology, with a 5-year OS of only 20–30% [5]. Recent discoveries have

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revealed molecular heterogeneity encompassing distinct oncogenic subtypes, divergent pathways, and diverse clinical outcomes [6]. Two major molecular subtypes have been identified. First, PTCL-TBX21 reflects derivation from T helper 1 (Th1)-like cells and exhibits epigenetic mutations such as TET2 and DNMT3a (cytotoxic phenotype) with a more favorable prognosis [7]. Second, PTCL-GATA3 has high genomic complexity associated with TP53 and CDKN2A deletions, PI3K pathway activation, and significantly worse overall survival [8]. Importantly, an algorithm based on immunohistochemistry has been developed with high sensitivity and reproducibility to subclassify PTCL-NOS into these two relevant molecular subtypes which allows risk stratification for clinical practice and clinical trials [9].

The optimal frontline therapy for PTCL-NOS remains controversial [10]. The role of consolidative stem cell transplantation is generally important in first remission. However, there may be a role in risk stratification of patients with the PTCL-GATA3 who may potentially benefit from early transplantation [11]. The ECHELON-2 trial showed benefit with the addition of brentuximab vedotin to cyclophosphamide, doxorubicin, and prednisone (CHP) for CD30-positive PTCL and represents an important advance although it is unclear if the benefit is significant for the PTCL-NOS subtype [12]. Novel therapies targeting epigenetic dysregulation include EZH1/2 inhibitors, HiDAC inhibitors, oncogenic signaling pathways (PI3K, JAK2/STAT), immunotherapy, and possible combination therapies based on the molecular subtype [13].

This review provides a comprehensive overview of PTCL-NOS describing its classification, histopathology, clinical features, risk stratification, molecular and genetic target options, current therapeutic approaches, and emerging strategies. We aim to provide clinicians with tools for an evidence-based approach to the management of this challenging condition with an emphasis on the understanding and application of risk stratification and targeted therapies.

2. Classification of PTCL

The WHO-5 classification of mature lymphoid neoplasms reflects ongoing advances in molecular biology, immunophenotyping, and gene expression profiling. The most prevalent major subgroups of PTCL include PTCL-NOS (26–37% of cases), angioimmunoblastic T-cell lymphoma (AITL) (20%), NK/T-cell lymphoma (17%), and anaplastic large cell lymphoma (10–15%) [14]. Together, these subtypes represent up to 89% of all PTCL cases.

One of the most significant changes has been the formal consolidation of T-follicular helper (TFH) cell lymphomas into a single definitive umbrella entity under the WHO-5 classification [15]. Under the revised 4th WHO (WHO-4R) classification, AITL was a distinct entity while follicular T-cell lymphoma and nodal PTCL with TFH phenotype were only provisional categories. As a result, many cases showing TFH features that did not meet full criteria for AITL were classified as PTCL-NOS. However, in the WHO-5 classification, these three categories are unified under the nodal TFH lymphoma umbrella including angioimmunoblastic-type, follicular-type, and NOS-type. Thus, cases with partial TFH features that were previously classified as PTCL-NOS are now termed nodal TFH cell lymphoma, NOS. The modification substantially reduces the size and heterogeneity of the PTCL-NOS subgroup [15]. The diagnostic criteria for nodal TFH cell lymphoma require expression of at least two TFH markers (PD-1, CXCL13, CXCR5, ICOS, BCL6, and CD10). If only one marker is present, the case is classified as PTCL-NOS.

Another consideration is the additional changes in the classification of EBV-positive nodal T- and NK-cell lymphoma absent in the WHO-4R review, now a definitive entity in WHO-5. EBV-positive nodal T- and NK-cell lymphoma is an aggressive and rare condition with a strong association with immunodeficiency or immune dysregulation, presenting

predominantly in the lymph nodes and Waldeyer's ring but affecting extranodal sites [16]. EBV-positive nodal T/NK-cell lymphomas have significantly worse outcomes compared to PTCL-NOS due to its lower genomic instability, upregulation of immune pathways including interferon α/γ response and IL6/JAK/STAT3 signaling, and downregulation of EBV mRNA compared to extranodal NK/T-cell lymphoma [17]. EBER tissue testing must show positivity in T and NK-cells rather than the surrounding B-cells to distinguish it from PTCL-NOS [17].

Other provisional entities now classified as definitive by the WHO-5 classification include the monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL), indolent T-cell lymphoma of the gastrointestinal tract, breast implant-associated anaplastic large cell lymphoma (ALCL), NK-large granular lymphocytic leukemia, and indolent NK-cell lymphoproliferative disorder of the gastrointestinal tract [3].

Despite these modifications, PTCL-NOS remains a diagnosis of exclusion by both WHO-4R and WHO-5 definitions. Although the molecular subtypes of PTCL-TBX21 and PTCL-GATA3 are recognized as biologically and prognostically distinct, they are not considered separate entities currently [14]. The 2023 Society of Hematopathology/European Association for Hematopathology (SH/EA4HP) Workshop emphasized the clinical importance of subclassifying PTCL-NOS into these molecular subtypes in routine practice, and emerging subgroups such as nodal gamma-delta PTCL-NOS and cytotoxic PTCL-NOS (EBV-negative) are under active characterization, though these remain under the PTCL-NOS umbrella at present [18].

3. Epidemiology

PTCL-NOS is the most common subtype of the mature T/NK-cell neoplasms in Western populations [5]. Its relative frequency varies significantly by geographic region and has declined over time with the evolving classification systems that have better defined other entities as described in Section 2 [14,19,20]. The landmark International T-Cell Lymphoma Project (ITCLP) enrolled 1314 patients across 22 centers worldwide and showed that PTCL-NOS accounted for 25.9% of all cases, making it the single most prevalent subtype [21]. The T-Cell Project 1.0 reported a frequency of 35–36% globally, with consistent predominance across North America (33%), Europe (37%), and South America (40%) [5]. The COMPLETE study in the United States showed that PTCL-NOS represented 51.3% of nodal PTCLs, while the LEO-MER Prospective Cohort Study reported a frequency of 35.1% [21]. The largest Latin American cohort study to date (n = 1979) similarly identified PTCL-NOS as the most common subtype at 35%, followed by adult T-cell leukemia/lymphoma (17%) and extranodal NK/T-cell lymphoma (15%) [5].

Geographic variation in PTCL subtype distribution is surprisingly broad and reflects the influence of genetic ancestry, viral epidemiology, and environmental factors [5,22,23]. In East Asia, extranodal NK/T-cell lymphoma (ENKL) is the most prevalent subtype, accounting for 28.6% of cases in the International Cooperative non-Hodgkin T-cell Lymphoma (ICT) prospective study, with PTCL-NOS representing only 20.8% [5]. A Beijing-based registry study reported PTCL-NOS as the most prevalent subtype [20]. In sub-Saharan Africa, PTCL-NOS remains the most common subtype (41%), with a notably younger median age at diagnosis (45 years) compared to Western cohorts [24].

In the Beijing registry, the proportional representation of PTCL-NOS among all PTCLs declined from 45.55% in 2007–2010 to 27.24% in 2015–2018, reflecting the rising recognition of other subtypes such as ENKL and AITL rather than a true decline in incidence [20]. A Finnish nationwide registry study reported a mean annual incidence of PTCL-NOS of 0.62 per 100,000 (range 0.45–0.87), with incidence peaking in men aged 80–84 years [25].

In Japan, the incidence of PTCL-NOS has gradually increased, particularly among elderly individuals [26].

The demographic profile of PTCL-NOS is consistent across registries with a median age at diagnosis from 57 to 63 years and a male predominance (male-to-female ratio of approximately 1.5–2:1) [5,20,25]. Most patients present with advanced-stage disease (Ann Arbor stage III–IV in 60–76%), B symptoms (44–51%), elevated serum lactate dehydrogenase (42–53%), and extranodal involvement (54%). Bone marrow involvement is found in approximately 28% of patients [5].

Racial and ethnic disparities in PTCL-NOS are well established [22,27,28]. Black Americans have higher incidence and significantly shorter median OS (33 vs. 61 months for Caucasians; HR 1.143, $p < 0.001$) [28], with socioeconomic status further stratifying outcomes (median OS 45 months for income below $50,000 vs. 78 months above $75,000; $p < 0.001$) [28].

Table 1 below outlines the racial, socioeconomic, and diagnostic disparities in PTCL-NOS.

Table 1. *Racial, Socioeconomic, and Access Disparities in PTCL-NOS.*

Domain	Key Data	Clinical Significance	Source
Racial Disparities			
Trial Enrollment & Eligibility	• 1L trial enrollment: 7.1% (NHB) vs. 16% (NHW); $p = 0.02$ • NHB less likely to enroll on multivariate analysis: OR 0.32; $p = 0.01$ • Trial eligibility (ECHELON-2 criteria): 35% (NHB) vs. 63% (NHW); $p < 0.001$ • Eligibility gap driven by ECOG, ANC, and creatinine differences	• NHB enrolled at <half the rate of NHW patients • Eligibility barriers precede enrollment barriers, disproportionately excluding NHB and Hispanic patients at trial screening	*Sanjurjo* et al., *2025* [27]
Treatment & Response	• Novel agent receipt: 19% (NHB) vs. 33% (NHW); $p < 0.01$ • 1L CR rate: 39% (NHB) vs. 62% (NHW); $p = 0.001$ • Median OS: 33 mo (Black) vs. 61 mo (Caucasian); HR 1.143; $p < 0.001$	• Lower CR rates in NHB likely reflect reduced access to novel agents rather than intrinsic biologic differences • Race is an independent predictor of OS	*Adams* et al., *2016* *Sanjurjo* et al., *2025* [27]
Socioeconomic Disparities			
SES, Survival & Trial Access	• Median OS: 45 mo (<$50 K) vs. 78 mo (>$75 K); $p < 0.001$ • High SDI independently associated with worse OS; $p = 0.002$ • Trial enrollment associated with improved OS even in high-SDI patients: HR 0.62; $p = 0.08$ • 1L trial enrollment: median OS 121 mo vs. 61 mo (not enrolled); $p = 0.03$; HR 0.66; $p = 0.04$	• 33-month OS gap by income, comparable in magnitude to the difference between effective and ineffective therapy • Trial enrollment partially mitigates SES-driven disparities and represents the highest-yield intervention	*Rehman* et al., *2025* *Sanjurjo* et al., *2025* [27]
Diagnostic Access Disparities			
NGS Subtyping Access	• NGS-based PTCL-GATA3/TBX21 subtyping unavailable in most LMICs • IHC-based algorithm is a pragmatic surrogate; not universally accessible	• Biomarker-driven strategies (e.g., GUIDANCE-03) inaccessible in most LMICs • Subtype-guided risk stratification remains aspirational outside resource-rich settings	*Amador* et al., *2025*

Abbreviations: 1L, first-line; ANC, absolute neutrophil count; CR, complete response; ECOG, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; IHC, immunohistochemistry; LMIC, low- and middle-income country; mo, months; NHB, non-Hispanic Black; NHW, non-Hispanic White; NGS, next-generation sequencing; OR, odds ratio; OS, overall survival; PTCL-NOS, peripheral T-cell lymphoma not otherwise specified; SDI, Social Deprivation Index; SES, socioeconomic status.

Outcomes and Prognosis

Survival outcomes for PTCL-NOS remain dismal and have shown no meaningful improvement over the past two decades despite evolving treatment strategies. The 10-year follow-up of the ITCLP reported a 5-year overall survival of 31% (95% CI 26–36) and 10-year overall survival of 23% (95% CI 18–28) in PTCL-NOS, the lowest among all major subtypes [5]. The Beijing registry showed a 5-year age-standardized relative survival of 29.18% (95% CI 23.03–35.67%), with no meaningful improvement observed between the 2011–2014 and 2015–2018 periods [20]. Similarly, a Finnish nationwide study found no improvement in overall survival between the periods 2007–2013 and 2014–2019 in either younger (37.5 vs. 49.0 months; $p = 0.219$) or older (8.8 vs. 6.3 months; $p = 0.488$) age groups [25]. Age at diagnosis profoundly impacts prognosis: median overall survival for patients aged less than 70 years was 28.7 months (95% CI 14.2–46.9), whereas patients aged 70 years or older had a median overall survival of only 4.9 months (95% CI 2.7–7.1) [25]. Importantly, when patients with PTCL-NOS achieve disease control and remain alive at 5 years, the probability of surviving to 10 years is 78% (95% CI 43–113), suggesting that durable early disease control identifies a small subset capable of long-term survival [5].

When compared to other PTCL subtypes, PTCL-NOS consistently demonstrates inferior outcomes. The COMPLETE study showed superior overall survival in ALCL compared to PTCL-NOS (HR 0.46; 95% CI 0.25–0.84; $p = 0.01$), while AITL did not differ significantly (HR 0.93; $p = 0.73$) [21]. In the Finnish registry study, both AITL and ALCL carried a significantly more favorable prognosis than PTCL-NOS, with hazard ratios of 0.71 ($p < 0.001$) and 0.58 ($p < 0.001$), respectively [25].

4. Clinical Manifestations

Patients with PTCL-NOS typically present with constitutional symptoms and generalized lymphadenopathy; approximately 87% have nodal disease and 62% extranodal involvement at diagnosis [29]. Most patients (69%) present with advanced-stage disease (Ann Arbor stage III–IV), and B symptoms (fever, night sweats, weight loss) which are observed in 44–67% of cases [2,30]. An elevated serum lactate dehydrogenase (LDH) can be used as a marker of tumor burden and aggressive biology since it is present in 42–78% of patients at diagnosis [5,29].

Extranodal involvement is common in PTCL-NOS and contributes to its clinical heterogeneity. Common sites of extranodal involvement include the bone marrow (present in 20–28% of cases), liver, skin, spleen, and gastrointestinal tract [2,29,30]. Hepatosplenomegaly is frequently observed, particularly in patients with bone marrow involvement or complications such as hemophagocytic lymphohistiocytosis (HLH) [31]. Paraneoplastic syndromes are uncommon but can be seen in patients with PTCL-NOS and include eosinophilia, HLH, polymyositis, subacute demyelinating polyradiculoneuropathy, cutaneous vasculitis, and gluten-sensitive enteropathy [32].

Cutaneous manifestations in PTCL-NOS may occur as either primary cutaneous disease or secondary involvement from systemic disease. The distinction has important prognostic implications [33]. Primary cutaneous PTCL-NOS (pcPTCL-NOS) is a rare and aggressive entity, accounting for less than 2% of cutaneous T-cell lymphomas and is recognized as a distinct entity in the WHO5 classification [19,34]. Clinically, pcPTCL-NOS manifests with solitary or disseminated rapidly growing nodules, tumors, papules, or less commonly ulcers, typically involving the head, trunk, and limbs [33,35]. Epidermotropism is rarely present and only mild and focal, distinguishing it from mycosis fungoides [33]. It is important to note, however, that cutaneous T-cell lymphomas such as plaque-stage mycosis fungoides that has lost its epidermotropism can be particularly challenging to distinguish from PTCL-NOS, and in some cases this distinction may not be possible with certainty even

after thorough clinicopathological correlation. Unusual immunophenotypes are frequent, including CD4−/CD8− and aberrant expression of the B-cell marker CD20 in up to 18% of cases [33,35]. The prognosis of pcPTCL-NOS is generally poor, with 5-year overall survival rates of 54–61% [33,36]. Secondary cutaneous involvement from systemic PTCL-NOS is present in 10–18% of patients and represents a poor prognostic marker. Clinically, it may manifest as erythroderma, plaques, nodules, or tumors [36].

The clinical presentation of PTCL-NOS may also vary by molecular subtype. PTCL-GATA3 carries significantly worse overall survival ($p = 0.01$) and serves as an independent adverse predictor of outcomes ($p = 0.0015$) [6,9]. However, within the PTCL-TBX21 subtype, a cytotoxic subset (cytotoxic PTCL-NOS) has been identified with significantly worse outcomes compared to non-cytotoxic PTCL-TBX21 cases ($p = 0.05$) [6]. In a dedicated study of 54 Western patients with nodal cytotoxic PTCL-NOS, 95% were subclassified as PTCL-TBX21, and these patients frequently presented with a background of impaired immunity (10 with prior B-cell malignancies, 4 with underlying immune disorders), demonstrating aggressive behavior with a median overall survival of only 12.7 months [30]. Thus, while PTCL-TBX21 overall carries a more favorable prognosis than PTCL-GATA3, the cytotoxic subset within PTCL-TBX21 partially offsets this advantage [30,37].

5. Diagnosis

PTCL-NOS is a diagnosis of exclusion and requires an extensive evaluation of clinical features, morphology, immunophenotype, and molecular data to confirm a T-cell neoplasm and exclude all the other defined entities under the PTCL umbrella [3,5]. Importantly, adequate tissue sampling requires an excisional or incisional biopsy. Fine-needle aspirations do not provide enough tissue to evaluate and exclude all the subtypes of PTCL adequately [16].

5.1. Histomorphology

PTCL-NOS has a broad variety of cytological and morphological features, with partial or complete effacement of the nodal architecture by paracortical or diffuse infiltrates [2]. The neoplastic cells are often usually medium to large-sized with irregular, pleomorphic, hyperchromatic or vesicular nuclei, conspicuous nucleoli, and frequent mitotic activity [9], although cases can show cells that are difficult to distinguish from normal small T-cells, making morphological assessment alone insufficient for diagnosis. A polymorphous inflammatory background is common and may include small lymphocytes, eosinophils, plasma cells, histiocytes, and scattered large B-cells [2]. An inflammatory background is significantly more frequent in the PTCL-TBX21 molecular subtype than in PTCL-GATA3 [9]. Hodgkin/Reed–Sternberg (HRS)-like cells may occasionally be present, posing a diagnostic challenge with classic Hodgkin lymphoma [9].

In cutaneous involvement, the neoplastic infiltrate typically forms dermal and subcutaneous nodules, with or without necrosis. Epidermotropism and angiocentricity are occasionally observed [33]. Splenic involvement is variable and may range from focal nodules to diffuse white pulp involvement [9].

5.2. Immunophenotype

PTCL-NOS is positive for pan-T-cell antigens (CD2, CD3, CD5, CD7), with variably decreased or absent expression of CD5 and CD7, noting that these antigens are retained in a subset of cases [2]. Most PTCL-NOS are more frequently CD4-positive than CD8-positive, though finding double-positive (CD4+/CD8+) or double-negative (CD4−/CD8−) expression can occur [30]. TCR$\alpha\beta$ expression is present in most cases, but rare cases are positive for TCR$\gamma\delta$ or are T-cell receptor-negative [2,30]. Expression of one or more cytotoxic

markers (TIA-1, granzyme B, perforin) is seen in 20–35% of cases and is predominantly associated with the PTCL-TBX21 molecular subtype. Furthermore, the more aggressive cytotoxic subset (cytotoxic PTCL-NOS) can show expression of the three markers [30]. CD30 expression can occur in more than 25% of PTCL-NOS cases and it is typically variable and not uniformly or strongly positive, distinguishing it from anaplastic large cell lymphoma. CD30 positivity, even when weak, may have therapeutic utility where brentuximab vedotin is available [9]. CD56 is positive in a subset of cases, and aberrant B-cell marker expression (typically CD20) can rarely be seen [2,9]. Scattered EBER-positive B-cells may be present within the tumor microenvironment. However, EBER positivity in T or NK-cells should prompt reclassification to EBV-positive nodal T- and NK-cell lymphoma [3,9].

Recognition of T-follicular helper (TFH) markers is crucial as this condition has been recognized in the WHO-5 classification as a separate entity [3]. Expression of a single TFH marker (PD-1, CXCL13, CXCR5, ICOS, BCL6, CD10) remains acceptable for a diagnosis of PTCL-NOS, but cases with diffuse positivity for two or more TFH markers should be reclassified as nodal TFH cell lymphoma [3,4].

5.3. Molecular Subtyping by Immunohistochemistry

An IHC algorithm using GATA3, TBX21, CCR4, and CXCR3 antibodies subclassifies PTCL-NOS with 85% sensitivity and high interobserver reproducibility [9]. Validated in 124 patients, IHC-defined subtypes showed significantly different OS (p = 0.003), with PTCL-GATA3 as an independent adverse predictor on multivariate analysis (p = 0.0015) [9]. The 2023 SH/EA4HP Workshop endorsed routine subclassification to facilitate risk stratification and trial enrollment [18]. An important limitation of the current classification framework warrants acknowledgment: the WHO classification was conceived as a globally applicable system, yet the molecular aspects of PTCL-NOS subclassification—particularly those dependent on next-generation sequencing (NGS) panels—are realistically only accessible in resource-rich settings. NGS-based subtyping is not widely available in low- and middle-income countries, where the majority of the world's lymphoma burden is managed. The IHC-based algorithm represents a pragmatic surrogate, though even standardized IHC panels may not be universally available. Clinicians and classification committees should bear this disparity in mind when applying or implementing molecular subtyping in routine practice.

5.4. Molecular and Genetic Features

PTCL-NOS generally shows complex karyotypes with multiple recurrent chromosomal abnormalities including gains in chromosomes 7q and 7p, encompassing the oncogenes CDK6 (7q21.2) and CARD11 (7p22.2) [16]. Alterations at T-cell receptor gene loci, most commonly the TRA locus at 14q11.2, can be seen less frequently [16]. Next-generation sequencing can show frequent abnormalities in tumor suppressor genes, including rearrangements of TP63 and mutations/deletions of CDKN2A, PTEN, and TP53 (associated with poor clinical outcomes) [9,16]. Co-deletion of CDKN2A and PTEN is highly specific for PTCL-NOS and is rarely observed in other mature T-cell neoplasms [16]. Recurrent mutations found in epigenetic regulators are common, including TET2 (61%), DNMT3A (39%), KMT2C, SETD1B, and YTHDF2 [9,18].

The PTCL-GATA3 exhibits greater genomic complexity with frequent loss or mutation of tumor suppressor genes targeting the TP53-CDKN2A axis and PI3K pathways, along with co-occurring gains/amplifications of STAT3 and STAT5B [9,16,18]. PTCL-TBX21 has fewer copy number abnormalities, primarily targeting cytotoxic effector genes, with frequent mutations in DNA methylation (TET2, DNMT3A) [9,16]. Most cases demonstrate

monoclonal rearrangement of the TR genes [16]. RHOA p.G17V and IDH2 p.R172 mutations are absent in PTCL-NOS, helping to differentiate it from nodal TFH cell lymphomas [23].

Comparisons of the PTCL-GATA3 and PTCL-TBX21 molecular subtypes are outlined below in Table 2.

Table 2. *Comparison of PTCL-GATA3 and PTCL-TBX21 Molecular Subtypes.*

Feature	PTCL-GATA3 *Higher-Risk Subtype*	PTCL-TBX21 *Lower-Risk Subtype*
Biology and IHC Subclassification		
Cell of origin	Th2-like effector T cells	Th1-like effector T cells
IHC markers	• GATA3+ • CCR4+	• TBX21+ • CXCR3+
Molecular and Genetic Features		
Genomic complexity	High; frequent copy number alterations	Lower; predominantly epigenetic mutations
Key mutations	• TP53 loss/mutation • CDKN2A deletion • PTEN loss • Co-deletion CDKN2A + PTEN (highly specific for PTCL-NOS) • STAT3/STAT5B gains	• TET2 (61%) • DNMT3A (39%) • KMT2C, SETD1B, YTHDF2 mutations • Cytotoxic effector gene alterations
Signaling pathway	PI3K–AKT–mTOR activation	DNA methylation dysregulation
RHOA/IDH2	Absent—distinguishes from nodal TFH lymphoma	Absent—distinguishes from nodal TFH lymphoma
Histopathology and Immunophenotype		
Tumor microenvironment	• Less inflammatory background • Lower PD-L1, LAG3, IDO1 expression	• Inflammatory background more frequent • Higher PD-L1, LAG3, IDO1 expression
Cytotoxic markers	• Less common overall	• More frequent (TIA-1, granzyme B, perforin) • Cytotoxic subset: all 3 co-expressed; 95% classified as PTCL-TBX21
Clinical and Prognostic Features		
Overall survival	• Significantly worse OS • Independent adverse predictor on MVA; $p = 0.0015$ • HR 2.34 for PFS (Japanese cohort; $p = 0.032$)	• Comparatively more favorable OS • Cytotoxic subset: median OS 12.7 mo—partially offsets advantage
Risk stratification	• High IPI + PTCL-GATA3 = independent adverse predictors • Consider early intensification/ASCT in CR1	• Standard risk profile • Cytotoxic subset warrants higher risk designation
Therapeutic Implications		
Frontline approach	• CHOP/CHOEP/DA-EPOCH; prioritize clinical trial enrollment • ASCT consolidation in CR1—particularly important given worse OS • PI3Kγ/δ inhibitors: preclinical survival benefit	• CHOP/CHOEP/DA-EPOCH • Epigenetic-targeted therapy rational (TET2/DNMT3A mutations) • CC-486 + CHOP: TET2 mutation may predict benefit
Emerging targets	• PI3K inhibitors • JAK/STAT inhibitors • EZH1/2 inhibitors	• Hypomethylating agents • EZH1/2 inhibitors • Mutation-directed therapy (GUIDANCE-03 framework)

Abbreviations: ASCT, autologous stem cell transplantation; CDKN2A, cyclin-dependent kinase inhibitor 2A; CR1, first complete remission; DNMT3A, DNA methyltransferase 3A; EZH1/2, enhancer of zeste homolog 1/2; HR, hazard ratio; IDO1, indoleamine 2,3-dioxygenase 1; IHC, immunohistochemistry; IPI, International Prognostic Index; JAK, Janus kinase; LAG3, lymphocyte-activation gene 3; mo, months; MVA, multivariate analysis; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PI3K, phosphoinositide 3-kinase; PTCL-NOS, peripheral T-cell lymphoma not otherwise specified; STAT, signal transducer and activator of transcription; TET2, ten-eleven translocation 2; TFH, T-follicular helper; Th1/Th2, T helper 1/2; TIA-1, T-cell intracellular antigen 1; TP53, tumor protein 53.

5.5. Diagnostic Criteria

Essential diagnostic criteria for PTCL-NOS according to the WHO-5 include (1) an abnormal T-cell infiltrate that is morphologically or immunophenotypically aberrant and/or monoclonal by ancillary studies; (2) tumor cells negative or expressing only one TFH marker; (3) EBER positivity restricted to scattered B-cells only; and (4) exclusion of all other mature nodal or extranodal T- and NK-cell lymphomas, including ALK+ ALCL, ALK− ALCL, adult T-cell leukemia/lymphoma, and extranodal NK/T-cell lymphoma [3,15,19]. Desirable criteria include clonal TR gene rearrangements and subclassification into PTCL-TBX21 or PTCL-GATA3 [3,9,16,19].

The essential IHC panel should include CD20, CD3, CD10, BCL6, Ki-67, CD5, CD30, CD2, CD4, CD8, CD7, CD56, TCR beta, TCR delta, PD1/CD279, ALK, and TP63, with a minimum of two to three TFH markers if nodal TFH lymphoma is suspected [9]. EBER in situ hybridization is essential. Molecular analysis to detect clonal TRB and TRG rearrangements is useful but not sufficient alone for diagnosis, as clonal T-cell expansions can be identified in non-malignant conditions [9]. Of note, anti-TCRβ1/2 (TRBC1/2) antibodies that function on formalin-fixed paraffin-embedded (FFPE) material as well as in flow cytometry are now available and are likely to become an increasingly important component of IHC and flow-cytometric workup for T-cell lymphomas [38,39].

5.6. Differential Diagnosis

As a diagnosis of exclusion, PTCL-NOS requires exclusion of all other PTCL subtypes. In cases with Hodgkin/Reed–Sternberg-like cells (HRS-like) or scattered large B-cells, the differential includes classic Hodgkin lymphoma and T-cell/histiocyte-rich large B-cell lymphoma [23,30]. Classic Hodgkin lymphoma is identified by HRS cells that are characteristically strongly CD30-positive, MUM1-positive, weakly Pax5-positive, and CD15-positive in the majority of cases. T-cell/histiocyte-rich large B-cell lymphoma is recognized by strong CD20 and Pax5 expression on the scattered large neoplastic B-cells. These diagnoses cannot be established on T-cell marker profiles alone, and appropriate B-cell and accessory marker staining is essential. STAT6, pSTAT6, and PD-L1 immunohistochemistry can aid in distinguishing HRS cells of classic Hodgkin lymphoma (STAT6+, pSTAT6+, PD-L1+ in 70–85%) from HRS-like cells in PTCL, which are positive in only approximately 10% of cases [30]. Other differentials include reactive conditions with paracortical lymph node hyperplasia including viral infections such as infectious mononucleosis or drug reactions, immune lymphoproliferative syndrome (ALPS), and Kikuchi–Fujimoto disease [16].

5.7. Staging and Imaging

Staging is performed according to the Lugano modification of the Ann Arbor staging system [1,40]. FDG-PET/CT is the preferred imaging modality for staging and response assessment, as patients with T-cell lymphomas have frequent extranodal disease that may be missed by CT alone [40]. PET/CT shows FDG-avid disease at baseline in 98% of patients with PTCL-NOS. Furthermore, additional extranodal sites are recognized by PET/CT scan in 25% of patients when compared to contrast-enhanced CT [16,40,41]. At end of treatment, a negative PET/CT is associated with superior 2-year progression-free survival (55% vs. 29%; HR 0.45; $p = 0.021$) and remains an independently prognostic, supporting incorporation of PET/CT as a standard of care in PTCL management [40]. Essential workup includes bone marrow biopsy, CBC with a differential, comprehensive metabolic panel, LDH, and calculation of the International Prognostic Index.

Summarizing all of this, Figure 1 below shows the overall diagnostic algorithm for PTCL-NOS along with initial staging, workup, and treatment planning.

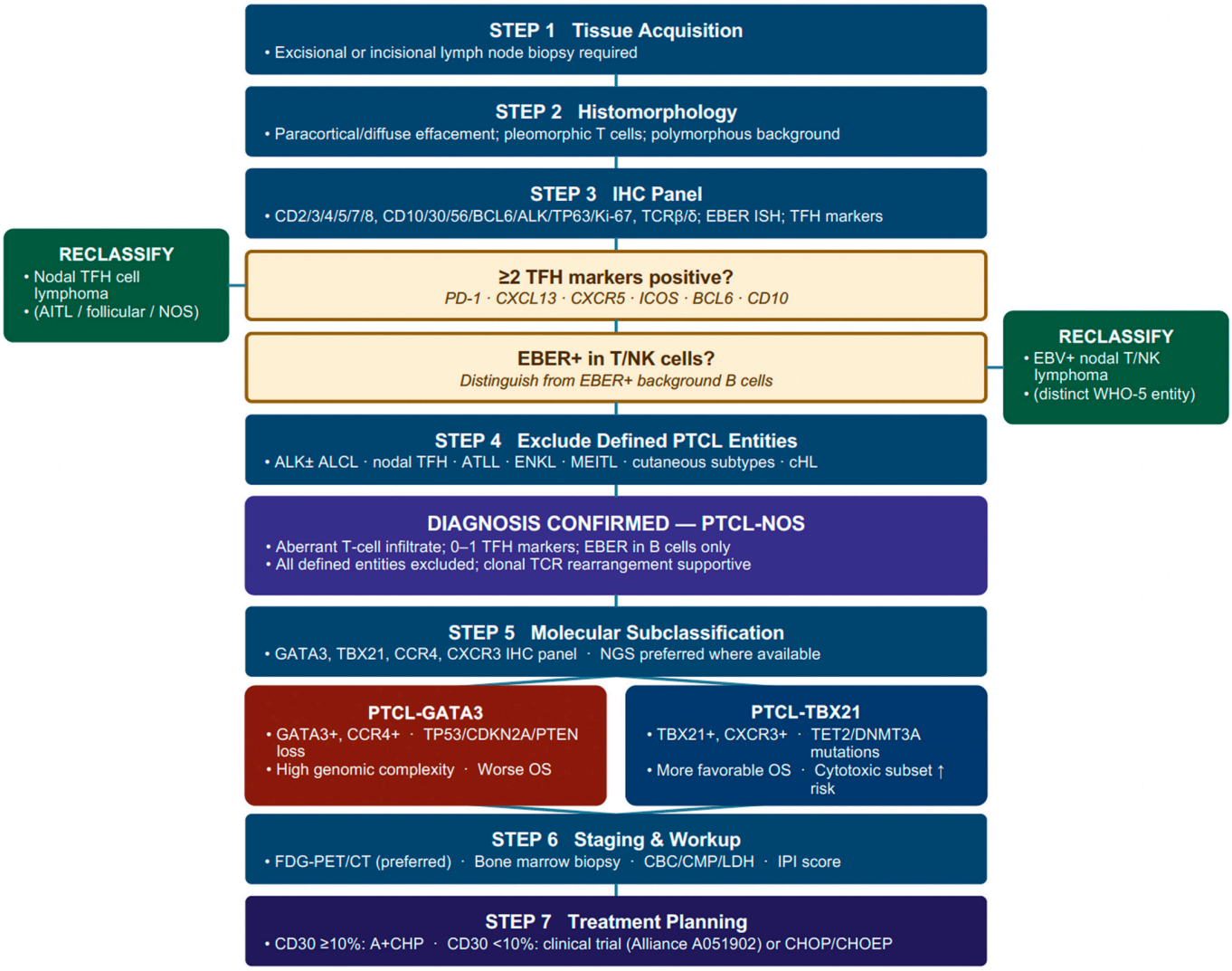


Figure 1. Diagnostic algorithm for peripheral T-cell lymphoma not otherwise specified. Abbreviations: A + CHP, brentuximab vedotin + cyclophosphamide, doxorubicin, prednisone; AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large cell lymphoma; ASCT, autologous stem cell transplantation; ATLL, adult T-cell leukemia/lymphoma; CBC, complete blood count; cHL, classic Hodgkin lymphoma; CMP, comprehensive metabolic panel; CR1, first complete remission; EBER, Epstein–Barr virus-encoded RNA; ENKL, extranodal NK/T-cell lymphoma, nasal type; FDG-PET/CT, fluorodeoxyglucose positron emission tomography/computed tomography; HTLV-1, human T-cell lymphotropic virus type 1; IHC, immunohistochemistry; IPI, International Prognostic Index; ISH, in situ hybridization; LDH, lactate dehydrogenase; MEITL, monomorphic epitheliotropic intestinal T-cell lymphoma; NGS, next-generation sequencing; NK, Natural Killer; NOS, not otherwise specified; OS, overall survival; PTCL-NOS, peripheral T-cell lymphoma not otherwise specified; TCR, T-cell receptor; TFH, T-follicular helper; WHO 5, 5th edition World Health Organization classification.

6. Current Management and Emerging Therapies

The optimal frontline therapy for PTCL-NOS remains controversial, and the NCCN guidelines explicitly state that while anthracycline-based regimens confer a favorable prognosis in ALCL and ALK-positive lymphoproliferative disorders, these regimens have not provided the same favorable results for other PTCL histologies, and therefore clinical trial enrollment is preferred for the management of PTCL-NOS [10,40].

6.1. Anthracycline-Based Chemotherapy: CHOP and CHOEP

CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) has remained the de facto standard first-line regimen for PTCL-NOS for decades, even though the pivotal studies establishing CHOP in non-Hodgkin lymphoma included only B-cell patients, with no prospective evidence supporting its use in PTCL [42,43]. The LEO-MER prospective cohort study (720 patients) confirmed that 70% of patients receive CHOP-based induction, and non-ALCL subtypes including PTCL-NOS had significantly inferior outcomes compared to ALCL, with a hazard ratio for event-free survival of 2.97 and for overall survival of 3.71 [44].

The addition of etoposide to CHOP (CHOEP) has been explored as a strategy to intensify induction. A Dutch nationwide population-based study of 1427 patients less than 65 years with stage II–IV PTCL (44% PTCL-NOS) found that 5-year OS was 64% with CHOEP versus 44% with CHOP ($p < 0.01$). However, after adjusting for subtype, IPI, and ASCT, the survival benefit of etoposide was significant only for ALK+ ALCL, not independently for PTCL-NOS or AITL [45]. A Czech population-based study of 906 patients similarly showed improved 5-year PFS (32.9% vs. 25.0%, $p = 0.001$) and OS (65.6% vs. 47.6%, $p = 0.008$) with CHOEP versus CHOP in patients less than 60 years, though subtype-specific analyses were not reported [46]. A large Latin American cohort study confirmed that patients receiving CHOEP or EPOCH had similar outcomes to those receiving CHOP in PTCL-NOS specifically, in contrast to ALK-negative ALCL where etoposide-containing regimens were associated with superior 3-year OS (67% vs. 41%, $p = 0.018$) [5]. Taken together, the evidence suggests that the benefit of etoposide addition is most robust in ALCL and remains uncertain for PTCL-NOS specifically.

6.2. Dose-Adjusted EPOCH

Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) is listed as a preferred first-line option for PTCL-NOS by the NCCN [40]. A multicenter phase II trial (West-JHOG PTCL0707) evaluated DA-EPOCH in 41 untreated PTCL patients (21 PTCL-NOS, 17 AITL). The overall response rate was 78% with a CR rate of 61%. At a median follow-up of 24 months, 2-year PFS was 53.3% and 2-year OS was 73.2%. Younger patients (60 years or younger) had particularly favorable outcomes (ORR 94.1%, CR 70.6%, 2-year PFS 62.5%, 2-year OS 82.4%). The regimen was tolerable, with grade 3 or higher neutropenia in 74.5% and febrile neutropenia in only 9% [47]. The single-arm design, absence of a CHOP comparator, and mixed PTCL population limit conclusions specific to PTCL-NOS.

6.3. Brentuximab Vedotin + CHP: The ECHELON-2 Trial

The ECHELON-2 trial represents the most significant advance in frontline PTCL therapy to date. This landmark phase 3, double-blind, randomized trial enrolled 452 patients with previously untreated CD30-positive PTCL (10% or greater CD30 expression) and compared A + CHP (brentuximab vedotin + cyclophosphamide, doxorubicin, prednisone) to CHOP. A + CHP demonstrated a 29% reduction in PFS events (median PFS 48.2 vs. 20.8 months; HR 0.71, $p = 0.011$) and a 34% reduction in risk of death (HR 0.66, $p = 0.024$), with a 77% probability of survival at 36 months, without increased toxicity [48]. At the 5-year update, PFS rates were 51.4% versus 43.0% (HR 0.70) and OS rates were 70.1% versus 61.0% (HR 0.72), with benefits generally consistent across key subgroups [12].

The applicability of ECHELON-2 to PTCL-NOS specifically requires careful interpretation. Critically, 75% of enrolled patients had systemic ALCL, and the trial was not powered for individual subtype comparisons. In the PTCL-NOS subgroup, the hazard ratios for both PFS and OS were numerically less than 1 favoring A + CHP, but the confidence intervals

were wide and overlapped 1 [48]. It remains unclear whether the benefit observed in the overall population is driven primarily by the ALCL subgroup or extends meaningfully to PTCL-NOS. A comprehensive 2026 review in *Blood Advances* critically examined the CHOP-plus strategy and concluded that outside of ALCL, where brentuximab vedotin has improved survival, this approach has generally failed, with most 5-drug regimens adding toxicity without clear benefit in non-ALCL subtypes [42].

The ongoing SGN35-032 phase 2 study is evaluating A + CHP in non-ALCL PTCL with less than 10% CD30 expression. Among 66 efficacy-evaluable patients, the ORR was 77% (95% CI: 65.3–86.7%) with a CR rate of 65%, suggesting activity even in low-CD30-expressing disease, though subtype-specific breakdowns were not provided [49].

6.4. Failed CHOP-Plus Strategies

Multiple attempts to improve upon CHOP by adding novel agents have been largely unsuccessful in PTCL-NOS.

Romidepsin + CHOP (Ro-CHOP): The phase 3 Ro-CHOP trial (LYSA, 421 patients) randomized patients to romidepsin + CHOP versus CHOP alone. The addition of romidepsin did not improve PFS (median 12.0 vs. 10.2 months; HR 0.81, $p = 0.096$), response rates (ORR 63% vs. 60%), or OS (51.8 vs. 42.9 months), while significantly increasing grade 3 or higher adverse events including thrombocytopenia (50% vs. 10%), anemia (47% vs. 17%), and neutropenia (49% vs. 33%) [50]. The final analysis at 6 years of follow-up confirmed these findings (PFS HR 0.79, $p = 0.054$; OS HR 0.88, $p = 0.324$). Notably, in an exploratory analysis, the TFH subgroup showed a significant PFS benefit with Ro-CHOP (median 19.5 vs. 10.6 months; HR 0.703, $p = 0.039$), but no benefit was observed in non-TFH PTCL, which includes most PTCL-NOS [51]. A separate Italian phase Ib/II study (PTCL13) of romidepsin-CHOEP followed by high-dose therapy and autologous stem cell transplantation in 86 untreated PTCL patients similarly failed to meet its primary endpoint, with an 18-month PFS of only 46.2% against a target of 70% [52].

Alemtuzumab + CHOP: The randomized phase 3 DSHNHL ACT-2 trial (116 elderly PTCL patients, age 61–80) compared alemtuzumab-CHOP to CHOP. While CR/CRu rates were numerically higher with A-CHOP (60% vs. 43%), 3-year OS was worse with A-CHOP (37% vs. 56%), driven by increased grade 3 or higher infections (40% vs. 21%) and 4 versus 1 infection-related deaths. Alemtuzumab added to CHOP increased response rates but did not improve survival due to treatment-related toxicity [53]. Earlier phase II studies of alemtuzumab-CHOP showed high CR rates (71%) but substantial infectious complications including CMV reactivation, invasive aspergillosis, and JC virus encephalitis [54].

6.5. Consolidative Autologous Stem Cell Transplantation

The role of consolidative autologous stem cell transplantation (ASCT) in first remission is generally considered important for transplant-eligible patients with PTCL-NOS, though definitive randomized evidence is lacking. The NCCN recommends consideration of consolidation with autologous HCT after first-line therapy [40]. A Bayesian network meta-analysis of 45 studies presented at ASCO 2025 found that in the PTCL-NOS subgroup specifically, HCT showed the best OS probability (77%; 95% CI: 0.75–0.95), while CHOP ranked highest for PFS (47.6%). Paradoxically, HCT had the lowest PFS probability (16.6%) in PTCL-NOS, suggesting that while HCT may rescue patients who relapse, it may not prevent relapse in this subtype [55]. The EBMT 2025 recommendations state that for transplant-eligible patients with non-ALK+ ALCL (including PTCL-NOS) in complete metabolic response, autologous HCT consolidation should be considered, though the committee noted that pivotal studies supporting autoHCT were conducted before the PET era, and whether all PET-negative CR patients benefit remains unknown [55]. Prospec-

tive randomized studies (TRANSCRIPT, TRANSFER) are ongoing to definitively address this question [56].

Patients with PTCL-GATA3 may particularly benefit from early transplantation or intensified consolidation given its worse OS, high genomic complexity, and PI3K-AKT-mTOR activation [9,57,58]. In multivariate analysis, a high IPI score (3–5) and the PTCL-GATA3 subtype identified by immunohistochemistry were independent adverse predictors of OS (p = 0.0015) [9]. A Japanese cohort study of 100 PTCL-NOS patients confirmed that PTCL-GATA3 was an independent prognostic factor for PFS on multivariate analysis (HR 2.34, p = 0.032) and showed lower expression of tumor immunity-related genes (PD-L1, LAG3, IDO1) compared to PTCL-TBX21 [59]. Preclinical assessment of mouse models recapitulating the PTCL-GATA3 transcriptome showed that PI3Kγ/δ inhibitors significantly improved survival, supporting a potential therapeutic approach for this high-risk subgroup [57].

6.6. Emerging Biomarker-Driven Frontline Strategies

The recognition of molecular heterogeneity within PTCL-NOS has prompted the development of biomarker-driven frontline strategies that move beyond the uniform CHOP approach.

GUIDANCE-03 trial: This open-label, multicenter phase 2 study evaluated mutation-directed targeted agents added to CHOP (CHOPX) versus CHOP alone in 96 newly diagnosed PTCL patients. Targeted agents were selected based on mutational profiling: decitabine for TP53 mutations, azacitidine for TET2/KMT2D mutations, tucidinostat for CREBBP/EP300 mutations, and lenalidomide for patients without the above mutations. The study met its primary endpoint, with a CR rate of 64.6% with CHOPX versus 33.3% with CHOP (OR 0.27, p = 0.004), and median PFS of 25.5 versus 9.0 months (HR 0.57, p = 0.041). Median OS trended favorably but did not reach significance (not reached vs. 30.9 months; HR 0.55, p = 0.088) [60].

Oral azacitidine + CHOP: A multicenter phase 2 study evaluated oral azacitidine (CC-486) priming plus CHOP as initial treatment for PTCL. In 20 evaluable patients, the CR rate was 75%, including 88.2% for PTCL-TFH (n = 17). Two-year PFS was 65.8% for all patients and 69.2% for PTCL-TFH, while 2-year OS was 68.4% and 76.1%, respectively. TET2 mutations were significantly associated with CR (p = 0.007), favorable PFS (p = 0.004), and OS (p = 0.015), while DNMT3A mutations were associated with adverse PFS (p = 0.016) [58]. Most patients in this study had TFH-phenotype disease, and the applicability to PTCL-NOS, which typically lacks TFH-associated epigenetic mutations, remains uncertain.

Alliance A051902 (NCT04803201): This ongoing randomized phase 2 US intergroup study is comparing CHO(E)P alone versus CHO(E)P + oral azacitidine versus CHO(E)P + duvelisib in previously untreated CD30-negative PTCL (CD30 less than 10%). The study is stratified by age (greater than 60 vs. 60 or younger) and TFH phenotype and is powered to detect a 25% improvement in CR rate (45% to 70%). Key eligible histologies include PTCL-NOS, AITL, and TFH lymphomas. This trial is specifically designed for the CD30-negative population that was underrepresented in ECHELON-2 and represents the most important ongoing frontline study for PTCL-NOS [43].

In summary, the treatment landscape for PTCL-NOS remains defined by the inadequacy of current CHOP-based approaches. The ECHELON-2 trial represents an important advance for CD30-positive PTCL, but its benefit for PTCL-NOS specifically remains uncertain given the predominance of ALCL in the trial population. Multiple CHOP-plus strategies including romidepsin and alemtuzumab have failed to improve outcomes in non-TFH, non-ALCL subtypes [10].

Table 3 below describes and compares the overall key clinical trials in the frontline management of PCTL-NOS.

Table 3. *Key Clinical Trials in the Frontline Management of PTCL-NOS.*

Trial	Regimen	Population	Key Outcomes	Key Caveat
Phase 3 Randomized Controlled Trials				
ECHELON-2	A + CHP vs. CHOP	• N = 452 untreated CD30+ PTCL • 75% systemic ALCL	• PFS: 48.2 vs. 20.8 mo (HR 0.71; $p = 0.011$) • OS: HR 0.66 ($p = 0.024$) • 5-yr PFS: 51.4% vs. 43.0% • 5-yr OS: 70.1% vs. 61.0%	• 75% of patients had ALCL—trial not powered for PTCL-NOS • HR for PFS and OS in PTCL-NOS numerically < 1 but CIs crossed 1
Ro-CHOP	Romidepsin + CHOP vs. CHOP	• N = 421 untreated PTCL • Majority non-ALCL	• PFS: 12.0 vs. 10.2 mo (HR 0.81; $p = 0.096$)—primary endpoint not met • OS: 51.8 vs. 42.9 mo (HR 0.88; $p = 0.324$) • 6-yr follow-up confirmed no benefit (PFS HR 0.79; $p = 0.054$)	• Significant added toxicity without survival benefit • Exploratory TFH subgroup showed PFS benefit (HR 0.703)—not applicable to PTCL-NOS
DSHNHL ACT-2	Alemtuzumab-CHOP vs. CHOP	• N = 116 • Age 61–80 years	• CR/CRu: 60% vs. 43% • 3-yr OS: 37% vs. 56%—worse with A-CHOP • Higher CR did not translate to survival benefit	• Increased infectious deaths offset higher CR rates • Alemtuzumab added toxicity without improving OS
Phase 2 Trials				
DA-EPOCH	Dose-Adjusted EPOCH	• N = 41 (21 PTCL-NOS, 17 AITL) • Median follow-up 24 mo	• ORR: 78%; CR: 61% • 2-yr PFS: 53.3%; 2-yr OS: 73.2% • Age $\leq$ 60: CR 70.6%, 2-yr OS 82.4%	• Single-arm; no CHOP comparator • Mixed PTCL-NOS + AITL population—PTCL-NOS outcomes not reported separately
GUIDANCE-03	Mutation-directed agent + CHOP vs. CHOP	• N = 96 newly diagnosed PTCL • Subtype breakdown not specified	• CR: 64.6% vs. 33.3% (OR 0.27; $p = 0.004$) • Median PFS: 25.5 vs. 9.0 mo (HR 0.57; $p = 0.041$) • OS trend only: NR vs. 30.9 mo (HR 0.55; $p = 0.088$)	• Requires NGS profiling for treatment assignment • PTCL-NOS subtype-specific outcomes not reported separately
SGN35-032 *(Ongoing)*	A + CHP	• N = 66 efficacy-evaluable • CD30 < 10% non-ALCL PTCL	• ORR: 77% (95% CI: 65.3–86.7%) • CR: 65% *PFS/OS not yet reported*	• Preliminary data; subtype-specific outcomes not yet available
Key Ongoing Randomized Trial				
Alliance A051902 *NCT04803201*	CHO(E)P vs. CHO(E)P + oral azacitidine vs. CHO(E)P + duvelisib	• Untreated CD30 < 10% PTCL • PTCL-NOS, AITL, TFH lymphomas eligible	• Primary endpoint: CR rate • Powered to detect 25% improvement in CR (45% $\rightarrow$ 70%) *Results pending—most important active frontline study for PTCL-NOS*	• Designed specifically for CD30-negative population underrepresented in ECHELON-2

Abbreviations: A + CHP, brentuximab vedotin + cyclophosphamide, doxorubicin, prednisone; AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large cell lymphoma; CHO(E)P, CHOP ± etoposide; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CR, complete response; CRu, complete response unconfirmed; DA-EPOCH, dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin; HR, hazard ratio; mo, months; NGS, next-generation sequencing; NR, not reached; OR, odds ratio; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PTCL-NOS, peripheral T-cell lymphoma not otherwise specified; TFH, T-follicular helper.

7. Conclusions

PTCL-NOS remains one of the most diagnostically and therapeutically challenging entities in malignant hematology. As a diagnosis of exclusion, it encompasses a biologically heterogeneous group of mature T-cell neoplasms whose boundaries continue to narrow with each iteration of the WHO and ICC classifications, most notably through the formal recognition of nodal TFH cell lymphomas and EBV-positive nodal T- and NK-cell lymphoma as distinct entities.

The identification of two biologically distinct molecular subtypes, PTCL-GATA3 and PTCL-TBX21, has substantially refined our understanding of this disease. PTCL-GATA3 is characterized by high genomic complexity, PI3K-AKT-mTOR pathway activation, and frequent tumor suppressor loss, and is associated with a significantly worse prognosis, whereas PTCL-TBX21 is more often associated with epigenetic dysregulation and a comparatively more favorable outcome. An immunohistochemistry-based algorithm now permits reasonably reliable subtype assignment in routine practice. Where available, this approach can support risk stratification and clinical trial enrollment.

Despite this biological progress, CHOP-based therapy remains the de facto standard without a clear evidence base specific to PTCL-NOS. Multiple CHOP-plus strategies have failed to improve outcomes in this subtype, and the benefit of brentuximab vedotin plus CHP from ECHELON-2 remains uncertain for PTCL-NOS given the predominance of systemic ALCL in that trial. The field is now moving in a more promising direction toward biomarker-driven, subtype-specific therapy. The GUIDANCE-03 trial demonstrated that mutation-directed treatment selection can meaningfully improve response rates over CHOP, and the ongoing Alliance A051902 trial represents one of the most important active frontline studies for CD30-negative PTCL. Looking ahead, EZH1/2 inhibitors, JAK/STAT pathway inhibitors, PI3K-targeted agents, and immunotherapy combinations represent promising emerging strategies, particularly in the context of molecular subtypes. Meaningful progress will likely require prospective molecular subtyping embedded within clinical trial design and sustained international collaboration.

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Abbreviations

The following abbreviations are used in this manuscript:

ALCL	Anaplastic Large Cell Lymphoma
ALK	Anaplastic Lymphoma Kinase
ALPS	Autoimmune Lymphoproliferative Syndrome
AITL	Angioimmunoblastic T-Cell Lymphoma
ASCT	Autologous Stem Cell Transplantation
ASCO	American Society of Clinical Oncology
CBC	Complete Blood Count

CHP	Cyclophosphamide, Doxorubicin, Prednisone
CHOP	Cyclophosphamide, Doxorubicin, Vincristine, Prednisone
CHOEP	Cyclophosphamide, Doxorubicin, Vincristine, Etoposide, Prednisone
CMV	Cytomegalovirus
CR	Complete Response
CRu	Complete Response Unconfirmed
DA-EPOCH	Dose-Adjusted Etoposide, Prednisone, Vincristine, Cyclophosphamide Doxorubicin
DNMT3A	DNA Methyltransferase 3 Alpha
EBMT	European Bone Marrow Transplantation
EBV	Epstein–Barr Virus
EBER	EBV-Encoded Small RNA
ENKL	Extranodal NK/T-Cell Lymphoma
EPOCH	Etoposide, Prednisone, Vincristine, Cyclophosphamide, Doxorubicin
EZH1/2	Enhancer of Zeste Homolog 1/2
FDG-PET/CT	Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography
GATA3	GATA Binding Protein 3
HCT	Hematopoietic Cell Transplantation
HiDAC	Histone Deacetylase Inhibitor
HLH	Hemophagocytic Lymphohistiocytosis
HR	Hazard Ratio
HRS	Hodgkin/Reed–Sternberg
ICC	International Consensus Classification
ICT	International Cooperative Non-Hodgkin T-Cell Lymphoma
IHC	Immunohistochemistry
IPI	International Prognostic Index
ITCLP	International T-Cell Lymphoma Project
JAK	Janus Kinase
LDH	Lactate Dehydrogenase
LEO-MER	Lymphoma Epidemiology of Outcomes and Molecular Epidemiology Resource
LYSA	Lymphoma Study Association
MEITL	Monomorphic Epitheliotropic Intestinal T-Cell Lymphoma
NCCN	National Comprehensive Cancer Network
NK	Natural Killer
NOS	Not Otherwise Specified
OR	Odds Ratio
ORR	Overall Response Rate
OS	Overall Survival
pcPTCL-NOS	Primary Cutaneous Peripheral T-Cell Lymphoma Not Otherwise Specified
PD-1	Programmed Cell Death Protein 1
PD-L1	Programmed Death-Ligand 1
PET	Positron Emission Tomography
PFS	Progression-Free Survival
PI3K	Phosphoinositide 3-Kinase
PTCL	Peripheral T-Cell Lymphoma
PTCL-GATA3	Peripheral T-Cell Lymphoma, GATA3 Molecular Subtype
PTCL-NOS	Peripheral T-Cell Lymphoma, Not Otherwise Specified
PTCL-TBX21	Peripheral T-Cell Lymphoma, TBX21 Molecular Subtype
SH/EA4HP	Society of Hematopathology/European Association for Hematopathology
STAT	Signal Transducer and Activator of Transcription
TBX21	T-Box Transcription Factor 21
TCR	T-Cell Receptor
TET2	Ten-Eleven Translocation 2
TFH	T-Follicular Helper

Th1	T Helper 1
TIA-1	T-Cell Intracellular Antigen 1
TP53	Tumor Protein 53
TR	T-Cell Receptor Gene
WHO	World Health Organization
WHO-4R	World Health Organization Classification, Revised Fourth Edition
WHO-5	World Health Organization Classification, Fifth Edition

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