Introduction to the peripheral T-cell lymphoma review series: advances in molecular characterization, classification refinement and treatment optimization

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Peripheral T-cell lymphomas (PTCL), also known as mature T- and NK-cell lymphomas, are a diverse group of diseases with variable clinical presentations, including predominantly nodal or extranodal involvement, as well as rare leukemic forms. In Western populations PTCL represent 10% of all non-Hodgkin lymphomas; however, 20% of all non-Hodgkin lymphomas in Asia have a T/NK-cell phenotype with a higher proportion of Epstein-Barr virus (EBV)- or human T-lymphoma virus 1 (HTV1)-associated entities also seen. In the present review series, four papers cover our current understanding of PTCL disease biology, as well as optimal therapeutics in 2023 based on best available evidence, with a focus on nodal and selected extranodal entities.

Eleven distinct or provisional PTCL entities were described in the Revised European American Lymphoma classification in 1994, and the subsequent World Health Organization (WHO) updates evolved to describe over 30 different PTCL subtypes today. In 2022, two separate classifications were developed. The 5th edition of the WHO classification (WHO-HAEM5), led by experts designated by the International Agency for Research on Cancer (IARC), was published as a review[1] and a beta version of the blue book is available online pending publication in a definitive form. A separate International Consensus Classification (ICC) was proposed by the Clinical Advisory Committee, a group which had directed the WHO classifications in the past, and is led by international lymphoma experts encompassing clinical, pathology and basic science expertise.[2] Both classifications are referred to here for completeness, and differences from, as well as comparisons to, the 2017 4th revised WHO classification (WHO-HAEM4R) are highlighted in Table 1. While the ICC maintains the distinction between provisional and definitive disease entities, all diseases are established along the same rank in the WHO-HAEM5. Several entities introduced in the WHO-HAEM4R as provisional have been confirmed in both classifications.

From the first identification of a T-cell receptor rearrangement to establish monoclonality in T-cell lymphomas,[3] genetics has always been integral to the diagnosis of PTCL. However, apart from the fusion of *NPM::ALK* as a result of t(2;5)(p23;q35) in anaplastic lymphoma kinase (ALK)-positive (ALK$^+$) anaplastic large cell lymphoma (ALCL),[4] and the more recently discovered *DUSP22* and *TP63* rearrangements in ALK-negative (ALK$^-$) ALCL,[5,6] very few structural disease-defining aberrations have been described. Comprehensive studies evaluating the molecular profiles and mutational landscapes of PTCL have markedly enriched the characterization and defining criteria of several disease entities and enhanced our understanding of their pathobiology and pathogenesis, translating into significant classification changes. In some cases, genomic analysis has also provided prognostic information and helped to identify key oncogenic drivers which have informed therapeutics. Importantly, the ICC published a companion paper describing the current role as well as the promise of genomics and molecular testing across all lymphomas, including PTCL.[7]

Although there are a daunting number of PTCL entities and the projection is further expansion, being disease 'splitters' (*vs.* 'lumpers') has the advantage of highlighting the peculiar biology and natural history of each entity with parallel optimization of treatment approaches. The so-called 'nodal' PTCL include PTCL not otherwise specified (NOS), ALCL and follicular helper T-cell lymphoma (TFHL), this last being referred to as nodal T-follicular helper (TFH) cell lymphomas in the WHO-HAEM5. A new entity has also been added to nodal PTCL: '(primary) nodal EBV-positive T/NK-cell lymphoma' and is deemed a provisional entity in the ICC (Table 1). In addition to EBV positivity, tumor cells are positive for cytotoxic markers and limited studies have suggested a very poor outcome, not unlike that of advanced stage extranodal NK/T-cell lymphoma.[8] Although the term 'nodal' is something of a misnomer as extranodal sites of involvement are

Table 1. Mature T- and NK-cell neoplasms in the International Consensus Classification (ICC) and World Health Organization (WHO)-HAEM5 classification (2022) in reference to the WHO-HAEM4R classification (2017) (adapted from Alaggio *et al.*[1] and Campo *et al.*[2]).

WHO-HAEM4R 2017	ICC 2022	WHO-HAEM5 2022
T-prolymphocytic leukemia	T-cell prolymphocytic leukemia	T-prolymphocytic leukemia
T-cell large granular lymphocytic leukemia	T-cell large granular lymphocytic leukemia	T-large granular lymphocytic leukemia
Chronic lymphoproliferative disorder of NK cells	*Chronic lymphoproliferative disorder of NK cells*	NK-large granular lymphocytic leukemia
Adult T-cell leukemia/lymphoma	Adult T-cell leukemia/lymphoma	Adult T-cell leukemia/lymphoma
EBV-positive T-cell/NK-cell lymphoproliferative disorders of childhood	EBV-positive T-cell/NK-cell lymphoproliferative disorders of childhood	EBV-positive T- and NK-cell lymphoid proliferations and lymphomas of childhood
Hydroa vacciniforme-like lymphoproliferative disorder	Hydroa vacciniforme lymphoproliferative disorder, classic type and systemic type	Hydroa vacciniforme lymphoproliferative disorder
Severe mosquito bite allergy	Severe mosquito bite allergy	Severe mosquito bite allergy
Chronic active EBV infection of T- and NK-cell type, systemic form	Chronic active EBV disease, systemic (T-cell and NK-cell phenotype)	Systemic chronic active EBV disease
Systemic EBV-positive T-cell lymphoma of childhood	Systemic EBV-positive T-cell lymphoma of childhood	Systemic EBV-positive T-cell lymphoma of childhood
Extranodal NK/T-cell lymphoma, nasal type	Extranodal NK/T-cell lymphoma, nasal type	Extranodal NK/T-cell lymphoma
Aggressive NK-cell leukemia	Aggressive NK-cell leukemia	Aggressive NK-cell leukemia
Not listed as an entity, subtype of peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS)	*Primary nodal EBV⁺ T-cell/NK-cell lymphoma*	EBV⁺ nodal T- and NK-cell lymphoma
Enteropathy-associated T-cell lymphoma	Enteropathy-associated T-cell lymphoma	Enteropathy-associated T-cell lymphoma
Not listed as an entity	Type II refractory celiac disease	Not listed as an entity
Monomorphic epitheliotropic intestinal T-cell lymphoma	Monomorphic epitheliotropic intestinal T-cell lymphoma	Monomorphic epitheliotropic intestinal T-cell lymphoma
Intestinal T-cell lymphoma, NOS	Intestinal T-cell lymphoma, NOS	Intestinal T-cell lymphoma, NOS
Indolent T-cell lymphoproliferative disorder of the gastrointestinal tract	Indolent clonal T-cell lymphoproliferative disorder of the gastrointestinal tract	Indolent T-cell lymphoma of the gastrointestinal tract
Not listed	Indolent NK-cell lymphoproliferative disorder of the gastrointestinal tract	Indolent NK-cell lymphoproliferative disorder of the gastrointestinal tract
Hepatosplenic T-cell lymphoma	Hepatosplenic T-cell lymphoma	Hepatosplenic T-cell lymphoma
Mycosis fungoides	Mycosis fungoides	Mycosis fungoides
Sézary syndrome	Sézary syndrome	Sézary syndrome
Primary cutaneous CD30⁺ T-cell lymphoproliferative disorders	Primary cutaneous CD30⁺ T-cell lymphoproliferative disorders	Primary cutaneous CD30⁺ T-cell lymphoproliferative disorder: Lymphomatoid papulosis
Lymphomatoid papulosis	Lymphomatoid papulosis	Primary cutaneous CD30+ T-cell lymphoproliferative disorder
Primary cutaneous anaplastic large cell lymphoma	Primary cutaneous anaplastic large cell lymphoma	Primary cutaneous anaplastic large cell lymphoma
Primary cutaneous CD4⁺ small/medium T-cell lymphoproliferative disorder	Primary cutaneous CD4⁺ small/medium T-cell lymphoproliferative disorder	Primary cutaneous small/medium CD4⁺ T-cell lymphoproliferative disorder
Subcutaneous panniculitis-like T-cell lymphoma	Subcutaneous panniculitis-like T-cell lymphoma	Subcutaneous panniculitis-like T-cell lymphoma

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WHO-HAEM4R 2017	ICC 2022	WHO-HAEM5 2022
Primary cutaneous gamma-delta T-cell lymphoma	Primary cutaneous gamma-delta T-cell lymphoma	Primary cutaneous gamma-delta T-cell lymphoma
Primary cutaneous acral CD8⁺ T-cell lymphoma	Primary cutaneous acral CD8⁺ T-cell lymphoproliferative disorder	Primary cutaneous acral CD8⁺ T-cell lymphoproliferative disorder
Primary cutaneous CD8⁺ aggressive epidermotropic cytotoxic T-cell lymphoma	Primary cutaneous CD8⁺ aggressive epidermotropic cytotoxic T-cell lymphoma	Primary cutaneous CD8⁺ aggressive epidermotropic cytotoxic T-cell lymphoma
Not listed	Not listed	Primary cutaneous peripheral T-cell lymphoma, NOS
Peripheral T-cell lymphoma, NOS	Peripheral T-cell lymphoma, NOS	Peripheral T-cell lymphoma, NOS
Nodal lymphomas of T follicular helper origin	Follicular helper T-cell lymphoma	Nodal T-follicular helper (TFH) cell lymphoma
Angioimmunoblastic T-cell lymphoma	Follicular helper T-cell lymphoma, angioimmunoblastic type (angioimmunoblastic T-cell lymphoma)	Follicular helper T-cell lymphoma, angioimmunoblastic type (angioimmunoblastic T-cell lymphoma)
Follicular T-cell lymphoma	Follicular helper T-cell lymphoma, follicular type	Follicular helper T-cell lymphoma, follicular type
Nodal peripheral T-cell lymphoma with T follicular helper phenotype	Follicular helper T-cell lymphoma, NOS	Follicular helper T-cell lymphoma, NOS
Anaplastic large cell lymphoma, ALK-positive	Anaplastic large cell lymphoma, ALK-positive	ALK-positive anaplastic large cell lymphoma
Anaplastic large cell lymphoma, ALK-negative	Anaplastic large cell lymphoma, ALK-negative	ALK-negative anaplastic large cell lymphoma
Breast implant-associated anaplastic large cell lymphoma	Breast implant-associated anaplastic large cell lymphoma	Breast implant-associated anaplastic large cell lymphoma

The entities are listed according to the order in which they appear in the ICC 2022. Shading/no shading denotes groups of entities. Provisional entities in WHO-HAEM4R and the ICC are shown in italics. EBV: Epstein-Barr virus; NOS: not otherwise specified; ALCL: anaplastic large cell lymphoma.

not uncommon across all subtypes, this terminology is useful to distinguish these subtypes of lymphoma from those arising primarily in extranodal sites or skin as well as leukemic PTCL subtypes.

PTCL-NOS has long been recognized as the 'wastebasket' diagnosis since it captures entities that do not meet the criteria for a defined PTCL subtype. As such, PTCL-NOS is a heterogenous group that still has not been fully delineated. Bisig and de Leval[9] describe the proposed subtypes, GATA3 and TBX21, which were first identified through Affymetrix molecular profiling.[10] This distinction is reproduced using an immunohistochemistry algorithm[11] and it is hoped that in the future, a molecular Nanostring assay[12] utilizing RNA derived from formalin-fixed, paraffin-embedded tissue can be applied. The GATA3 subtype with a signature of TH2 cells, including GATA3 and targets as well as components of the PI3K pathway, has an inferior prognosis compared to the TB2X1 subtype which has higher expression of TBX21 (T-bet) and EOMES and their targets (e.g., CCL3, IFNγ).[10] However, the story has emerged as being more complicated, because a subset of TBX21 associated with the presence of *DNMT3A* mutations and cytotoxic gene expression signature has also an inferior prognosis.[13] Furthermore, several cases remain 'unclassified'. Although not yet incorporated in current classifications, correlative studies integrating molecular classification of PTCL-NOS in clinical trials may elucidate whether the GATA3 and TBX21 subtypes have a differential response to novel therapies.

In the WHO-HAEM4R 2017 classification, a new category for TFHL was created to expand beyond the prototype, angioimmunoblastic T-cell lymphoma (AITL), to encompass cases previously classified as PTCL-NOS that have a TFH phenotype, currently defined as the presence of two or more of BCL6, CD10, CXCL13, PD1 and ICOS by immunohistochemistry, but lacking the morphological criteria for AITL. In addition, the TFHL category includes the less common morphological variant, follicular T-cell lymphoma. Minor nomenclature differences can be noted when comparing the ICC and WHO-HAEM5 (Table 1). The genomic landscape of TFHL has been well characterized with recurrent mutations in *TET2, DNMT3A, IDH2* and *RHOA*. Although not mandatory, mutational profiling is now routinely performed at many centers and is helpful for the diagnosis of TFHL,[7,14] especially for borderline cases, and can guide therapeutics.[15]

ALCL is broadly divided into ALK⁺ ALCL, identified by the presence of the ALK protein detected by immunohistochemistry, and the morphologically similar ALK⁻ ALCL. ALK⁻ ALCL was once proposed to be combined with PTCL-NOS because of its poor outcome,[16] but later studies confirmed a more favorable prognosis.[17] Almost 10 years ago, further

genetic heterogeneity was discovered with the identification of a *DUSP22* rearrangement in 20-30% cases.[18] As described by Bisig and de Leval, *DUSP22*-rearranged cases have distinct morphological, immunohistochemical and molecular features, establishing them as a genetic subtype in the ICC, but not in the WHO-HAEM5 classification, due to disparate prognoses in studies which collectively suggest that they are likely more intermediate between ALK$^+$ ALCL and 'triple negative' ALCL which lack any rearrangement of *ALK, DUSP22* or *TP63*.[19-21] Approximately 2-8% of cases of ALK$^-$ ALCL harbor a *TP63* rearrangement which is associated with a dismal outcome.[18] These cases are not yet a distinct genetic subtype as further studies are needed to fully characterize them.

Extranodal entities, as detailed by Lewis, Zhou and Dogan,[22] with a clinical lens provided by Stuver, Epstein-Peterson and Horwitz,[23] are identified by their primary location. They constitute a diverse and rare group of diseases with a limited number of dedicated clinical trials, making therapeutic advancement very challenging. Subcutaneous panniculitis-like T-cell lymphoma was first recognized in the 2001 WHO classification which was later refined to exclude cases with a γδ phenotype that are lumped into primary cutaneous γδ T-cell lymphoma because of a similar poor prognosis.[24] Approximately 20% are associated with hemophagocytic lymphohistiocytosis, which can be particularly severe in those

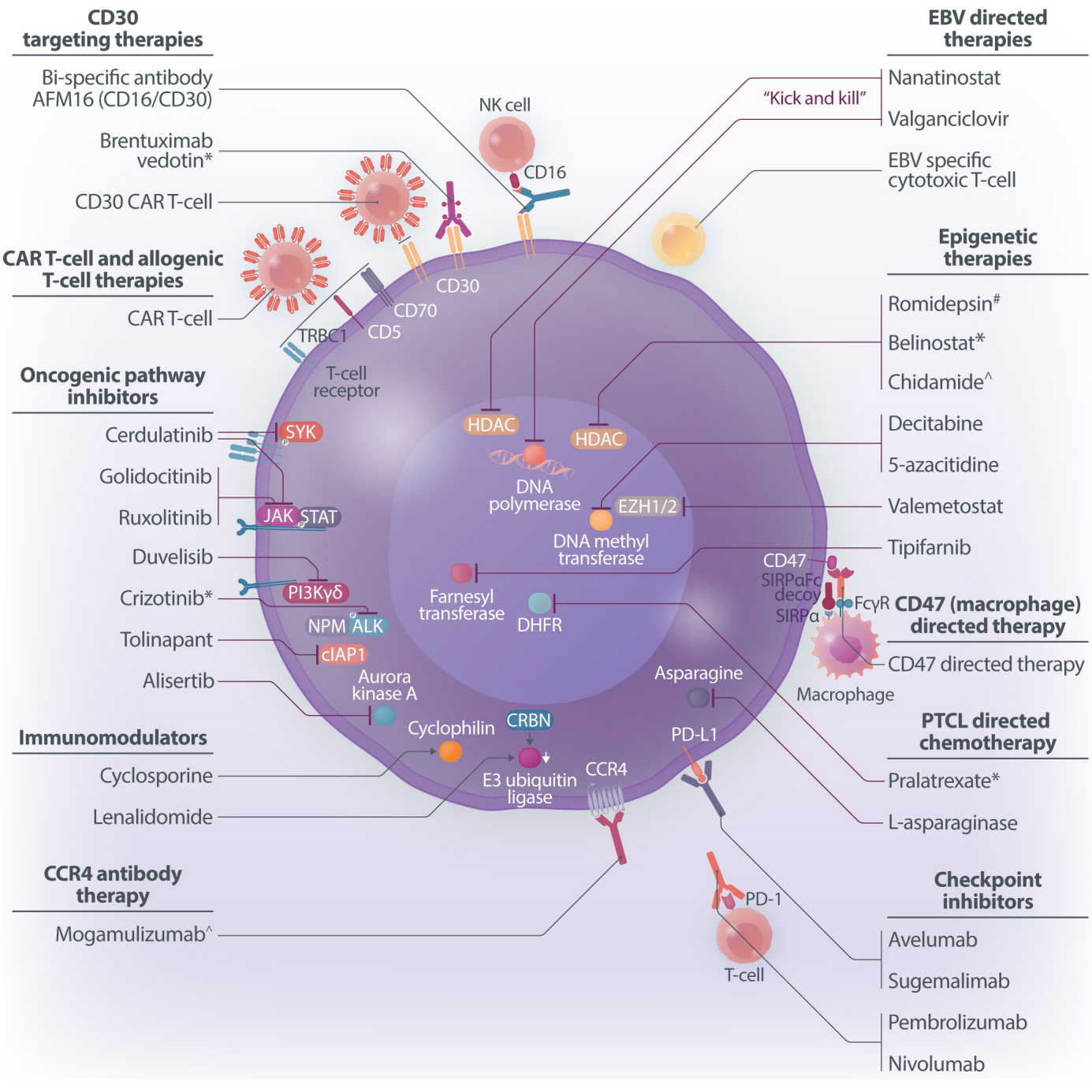

Figure 1. Systemic agents approved, previously studied, or under investigation in peripheral T-cell lymphomas/mature T/NK-lymphomas. *Approved in the USA; brentuximab vedotin (BV) is globally approved in relapsed/refractory (R/R) anaplastic large cell lymphoma (ALCL) and for front-line treatment in CD30$^+$ PTCL; BV-CHP (BV, cyclophosphamide, doxorubicin, prednisolone) in Europe approved in ALCL only. #Romidepsin was previously approved in the USA/Canada but withdrawn following report of the negative findings of the phase III, RO-CHOP (romidepsin, cyclophosphamide, doxorubicin, vincristine, predisone) *versus* CHOP study; pralatrexate is not approved in Europe. ^Approved outside the USA, mogamulizumab is approved in Japan only for CCR4$^+$ R/R PTCL (and adult T-cell leukemia/lymphoma [positive for human T-lymphotropic virus 1]); chidamide is approved in China only for R/R PTCL. Please also see Table 2 and the reviews by Ngu and Savage[15] and Stuver, Epstein and Horwitz[25] for drug approvals and disease rationale. ALK: anaplastic lymphoma kinase; CAR: chimeric antigen receptor; cIAP1: cytoplasmic inhibitor of apoptosis 1; CRBN: cereblon; DHFR: dihydrofolate reductase; EBV: Epstein-Barr virus; EZH: enhancer of zest

Table 2. Selected drugs, their targets and disease rationale under study in peripheral T-cell lymphoma/mature NK/T-cell neoplasms.

Drug class, type and/or target	Regulatory approval/indication as of July 2023	Disease rationale
Anti-CD30 targeting agents		
Antibody-drug conjugate: brentuximab vedotin BV-CHP	R/R ALCL (Global) Front-line CD30+ PTCL (FDA) Front-line ALCL and CD30+ PTCL-NOS/AITL (Health Canada) Front-line ALCL (EMA)	ALCL > EATL > other CD30+ PTCL
Anti-CD30 CAR T-cell therapy	None	ALCL > other CD30+ PTCL
Bi-specific antibody e.g., AFM 16 (CD30/CD16 [NK cell])	None	ALCL > other CD30+ PTCL
CAR T-cell and allogeneic T-cell therapy targets beyond CD30		
CD70	None	CD70+ PTCL
CD5	None	CD5+ PTCL
TRBC1 positive	None	TRBC1+ PTCL
PD1 inhibitor: pembrolizumab, nivolumab PDL inhibitor: sugemalimab,[a] avelumab	None[a]	Extranodal NK/TCL, ? primary nodal EBV+ T/NK-cell lymphoma
Anti-CD47 antibody and CD47 decoy	None	CTCL>PTCL(nodal)
EBV-directed therapies		
EBV-specific cytotoxic T cells	None	Extranodal NK/TCL, ? primary nodal EBV+ T/NK-cell lymphoma
Nanostinostat and valganiclovir	None	NK/TCL > EBV+ nodal PTCL
Epigenetic therapies		
HDAC inhibitors	Romidepsin[b] (FDA, Health Canada) Belinostat (FDA) Chidamide (NMDA China)	TFHL > other PTCL (nodal)
Hypomethylating agents: 5-azacitidine, decitabine	None	TFHL > other PTCL (nodal)
EZH2 inhibitors: valemetostat	None	TFHL > other PTCL (nodal)
Farnesyltransferase inhibitor: tipifarnib	None	AITL and CXCL12 wild type?
Oncogenic pathway inhibition		
PI3γ kinase inhibitor: duvelisib	None	TFHL > other PTCL (nodal)
JAK/STAT inhibitor: ruxolitinib	None	JAK2 mutation, pSTAT3+ > unselected Hemophagocytic lymphohistiocytosis
ALK inhibitor: crizotinib	R/R ALK+ ALCL 1-21 years (FDA)	R/R ALK+ ALCL
Aurora kinase inhibitor: alisertib	None	Unknown
Inhibitor of apoptosis: tolinapant	None	Unknown
Immunomodulators		
Lenalidomide	None	?TFHL
Cyclosporine	None	SCPTCL (some TFHL)
PTCL-specific chemotherapy		
Dihydrofolate reductase inhibitor	Pralatrexate (USA, Canada)	PTCL-NOS/ALCL > AITL
Asparagine depletion: pegylated asparaginase	None	Extranodal NKTCL, speculation primary nodal EBV+ T/NKCL

[a]Sugemalimab: Food and Drug Administration (FDA) breakthrough therapy and orphan drug designation and breakthrough designation by the National Medical Products Administration (NMPA) in China. [b]De-listed by the FDA and Health Canada after the negative CHOP *versus* Ro-CHOP study. BV-CHP: brentuximab vedotin-cyclophosphamide, doxorubicin and prednisone; R/R: relapsed/refractory; ALCL: anaplastic large cell lymphoma; PTCL: peripheral T-cell lymphoma; NOS: not otherwise specified; AITL: angioimmunoblastic T-cell lymphoma; EMA: European Medicines Agency; EATL: enteropathy-associated T-cell lymphoma; CAR: chimeric antigen receptor; PD1: programmed cell death 1; PDL: programmed cell death ligand; TCL: T-cell lymphoma; EBV: Epstein-Barr virus; HDAC: histone deacetylase; TFHL: follicular helper T-cell lymphomas; SCPTCL: subcutaneous panniculitis like T-cell lymphoma; T/NKCL: T/NK-cell lymphoma.

harboring a germline mutation in *HAVCR2*.[25] Hepatosplenic T-cell lymphoma often occurs in the setting of chronic immunosuppression, especially in patients receiving combination therapy with tumor necrosis-α inhibitor therapy and thiopurines (e.g., azathioprine). Intestinal T/NK cell lymphoma includes the familiar enteropathy-associated T-cell lymphoma (previously referred to as type 1 EATL) linked to celiac disease, which was importantly distinguished from monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL) (previously referred to as 'type 2' EATL) in the WHO-HAEM4R classification, each having a distinct genetic landscape, with highly recurrent *SETD2* mutations observed in the latter. Intestinal T-cell lymphoma NOS was introduced in the WHO-HAEM4R classification to capture cases that would have previously been included with PTCL-NOS and is retained in the 2022 proposals. Indolent T- and NK-cell lymphoproliferative disorders of the gastrointestinal tract (with the term lymphoma used in the WHO-HAEM5 for T-cell cases) are critical to recognize in order to avoid use of chemotherapy which does not appear to impact the natural history. Historically, treatment paradigms in mature T- and NK-cell neoplasms have been largely modelled on those for aggressive B-cell lymphomas, leading to default use of CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) or CHOP-like chemotherapy,[26] which remains the standard comparison arm in clinical trials today. With a still high risk of relapse, etoposide is often added to CHOP chemotherapy (CHOEP) coupled with consolidative autologous stem cell transplant; however, in the absence of a randomized trial, practices vary. With improved understanding of the molecular basis of disease and exciting expansion of novel therapies under investigation in relapsed/refractory PTCL (Figure 1, Table 2), as outlined by Ngu and Savage,[15] more recent studies have integrated these agents in the front-line setting, including chemotherapy-free approaches, with a particular interest in TFHL.

CHOP (and CHOEP) has the best track record in ALCL, especially ALK$^+$ ALCL. The practice-changing ECHELON-2 study in CD30$^+$ PTCL evaluated the addition of the anti-CD30 antibody drug conjugate brentuximab vedotin (BV) to CHP (CHOP with the omission of vincristine because of the overlapping peripheral neuropathy), and demonstrated improved progression-free and overall survival compared to CHOP chemotherapy, leading to a new treatment paradigm with particular relevance in ALCL.[27] Uncertainties remaining around the efficacy of CHP-BV in non-ALCL CD30$^+$ PTCL subtypes have led to differences in regulatory approval, with use of this regimen in Europe restricted to ALCL alone[15] (Table 2).

With a growing realization that a 'one size fits all' approach is suboptimal in PTCL, entity-specific studies have evolved, leading to the complete abandonment of CHOP in some entities, even in the absence of a randomized controlled trial. This is best exemplified in the extranodal subtypes.[23] Extranodal NK/T-cell lymphoma is typified by overexpression of P-glycoprotein which imparts a multi-drug resistance phenotype, including resistance to anthracyclines. As outlined by Stuver and colleagues,[23] this led to the exploration of non-CHOP chemotherapy, with clear improvement in outcomes with asparaginase-based regimens as well as cisplatin-based combinations in early-stage disease along with early integration of radiotherapy for disease that could be encompassed in a radiation field. Since extranodal NK/T-cell lymphoma is an EBV-driven disease, programmed death ligand (PDL) and PD1 inhibitors show clear therapeutic promise and are under investigation in a variety of settings (Figure 1, Table 2).[23] Non-CHOP regimens (e.g., ICE - ifosfamide, carboplatin, etoposide) are also preferred in the primary therapy of hepatosplenic T-cell lymphoma followed typically by an allogeneic stem cell transplant. At the other end of the spectrum, immunomodulator therapy, such as cyclosporine, has evolved to be the treatment of choice in subcutaneous panniculitis like T-cell lymphoma with a recent small series also indicating that the JAK1/2 inhibitor ruxolitinib is highly effective in those with refractory hemophagocytic lymphohistiocytosis.[23,28]

With an increased understanding of the genetic and molecular basis of PTCL, more rational, biologically driven and subtype-specific research is underway. As highlighted by Ngu and Savage,[15] TFHL represent the 'poster child' for more personalized therapies as studies emerge showing sensitivity to epigenetic modifiers, with some long-term remissions being achieved[29] (Figure 1, Table 2). This has led to studies of combinations of novel agents, most often integrating epigenetic therapies and even including cohorts of treatment-naïve patients; however, the curative potential of these combinations is still unknown.

Overall, although progress in mature NK/T-cell neoplasms has lagged behind that in B-cell lymphomas, a renewed focus has led to important advances in understanding the molecular basis of these diseases as well as success in shifting the therapeutic bar in many subtypes; despite this, there is still work to be done. Modern clinical trials have evolved in some cases to focus on specific entities or pathways, often integrating rich correlative studies to elucidate markers of response and resistance. Ultimately, for our community of disease splitters, this 'divide and conquer' approach will lead to more customized treatment approaches and improved outcomes across the whole spectrum of PTCL.

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Contributions

KJS and LdL wrote the manuscript.

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