

Treatment of peripheral T-cell lymphomas

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Abstract

Peripheral T-cell lymphomas (PTCLs) are rare neoplasms that recently have been the subject of much research into their complex pathophysiology. PTCLs are a heterogeneous group of tumors consisting of nodal and extranodal leukemic and cutaneous neoplasms. PTCLs are associated with complex biology and arduous pathology which is currently being studied. According to this research, the pathophysiology of PTCLs can be divided into intrinsic and extrinsic mechanisms. Among the intrinsic mechanisms, scientists have described JAK-STAT pathway deregulation, as well as different somatic mutations including *RB1*, *PTEN*, *TP53* and structural changes to the receptors. Also, there are scientific papers that correlate Epstein-Bárr virus or human T-cell lymphotropic virus type 1 infections with the occurrence of the neoplasm. PTCLs are most likely to develop in Asian and African populations. Due to poor clinical outcomes, PTCL treatment is the subject of intense clinical research. As a result of that, new drugs have been approved by the Food and Drug Administration for use among patients with refractory PTCL: pralatrexate, an antifolate drug; romidepsin, belinostat, an inhibitor for histone deacetylase, and brentuximab vedotin, a CD30 antibody. Also, clinical trials with mogamulizumab are being carried out for PTCL treatment. In addition to this, lenalidomide, as a substance that regulates the immune system and has shown antineoplastic effect in several hematological studies, could possibly be considered as treatment.

Key words: T-cell lymphoma, peripheral T-cell lymphoma, brentuximab vedotin, mogamulizumab

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Introduction

Peripheral T-cell lymphomas (PTCLs) are rare neoplasms that develop from mature-stage T-cells and natural killer cells (NK), presenting diverse clinical symptoms. A subtype of non-Hodgkin lymphoma, the heterogeneous group of PTCLs accounts for c.10–15% of tumors. The World Health Organization (WHO) categorizes PTCL into four, depending on localization: nodal, extranodal, leukemic, and cutaneous neoplasms. There are approximately 30 subtypes of PTCL, where the most prevalent nodal T-cell lymphomas are: peripheral T cell lymphoma not otherwise specified (PTCL-NOS) [1]; nodal T cell lymphoma with T follicular helper (TFH) phenotype which includes angioimmunoblastic

T cell lymphoma (AITL); and systemic anaplastic large cell lymphoma (sALCL).

PTCLs are associated with complex biology and arduous pathology which is being studied. Among the causes of tumor pathogenesis are the abovementioned deregulation of the signaling pathways controlling T-cell development, differentiation and maturation; remodeling of the peritumor environment, and virus-mediated rewiring of T-cell biology [2]. Some studies have related Epstein-Bárr virus (EBV) or (HTLV-1, human T-cell lymphotropic virus type 1) infections with the occurrence of the neoplasm [3–5]. PTCLs are more likely to develop in Asian and African populations, and most frequently in people aged 60 and above, although a few cases of PTCL in childhood

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have been reported. They appear more often among males than females.

Pathogenesis

Many PTCLs remain unclassified and are known as peripheral T cell lymphoma not otherwise specified (PTCL-NOS). Even so, two subpopulations have been identified. One displays high expression of the GATA3 [6] transcription factor (described as master regulator for T-helper-2 cells). The other group features TBX21 exposition (master regulator for T-helper-1 cells and cytokine T cells) together with EOMES [7], and this results in a better prognosis of the clinical process. All of the above supports the assumption that these two subpopulations present unique cells of origin. Considering the very complex molecular genesis of PTCL, researchers have distinguished between intrinsic and extrinsic mechanisms that control T-cell transformation.

Intrinsic mechanisms

The first described intrinsic molecular event is JAK-STAT deregulation (performing a crucial role in cytokine signaling) that activates mutation which results in enhancing cell growth and main resistance to targeted therapy [8, 9]. Activation of the STAT precedes a unique transcriptional pattern which is characterized by the expression of genes that are responsible for growing, immune response, angiogenesis, and many metabolic pathways [10]. Moreover, alternations of the structure and somatic mutations are reported among intrinsic mechanisms. Studies have shown that loss of *PRDM1*, *CDKN2A*, *CDKN2B*, *RB1*, *PTEN*, *TP53* genes is observed in the GATA1-PTCL-NOS group of neoplasms, whereas mutations occurring in *VAV1*, *ITK*, *SYK* are present in PTCL-NOS and TFH-PTCL [11]. The next observable molecular mechanism that leads to the permanent activation or dysregulation of respective signaling pathways in PTCL are uncontrolled T-cell receptor (TCR) signaling trend [12, 13]. The loss of negative regulators of TCR, structural diversions as well as somatic mutations, constitute activation of the TCR signaling pathway leading to progression of the neoplasms [14]. Metabolic changes contributing to the expression of the PTCL-NOS often refer to the overexpression of the proteins linked to the lipid metabolism [15]. In addition to this, dysregulation of the choline metabolism has also been described in the pathophysiology of PTCLs, maintaining AKT and ERK phosphorylation, RAS activity and MYC oncoprotein expression [16]. Also, the phosphoinositide 3-kinase (PI3K) (maintaining the metabolism of glucose, glutamine, lipids and nucleotides) pathway deregulation affects the phenotype and the metabolism of T-cells neoplasms [17, 18]. Studies show that levels of AKT phosphorylation can correlate with an inferior outcome of PTCL [19] (Table I).

Table I. Intrinsic and extrinsic mechanisms of PTCL pathogenesis

Intrinsic mechanism	Extrinsic mechanism
JAK-STAT deregulation	Decreased immunogenicity of host
Enhanced cell growth and resistance to targeted therapy	Immunosuppression by Treg cells
Loss of <i>PRDM1</i> [*] , <i>CDKN2A</i> [#] , <i>CDKN2B</i> [#] , <i>RB1</i> ^{&} , <i>PTEN</i> [#] , <i>TP53</i> [‡]	Mutations in T- and NK-cells
Dysfunction of immune response, angiogenesis and enhanced cell growth	
Uncontrolled TCR ⁺⁺ signaling trend	EBV infection
Permanent activation and dysregulation of signaling pathways	
Lipid metabolism	
Overexpression of proteins linking to expression of PTCL-NOS	HTLV-1 infection
Choline metabolism	Environment
AKT/ERK phosphorylation, RAS activity, MYC oncoprotein expression	More neoplasms in Asia
PI3K [‡] deregulation	Production of VEGF
Glucose, glutamine, lipids and nucleotides metabolism	Level of VEGF correlates with progression of lymphoma

^{*}Denotes protein BLIMP-1 that is crucial for most terminal effector cell differentiation in CD4 and CD8 T cells; [#]CDKN2A and PTEN deletions have emerged as most frequent aberration associated with poor outcomes in patients with peripheral T-cell lymphoma not otherwise specified (PTCL-NOS). PTEN acts as tumor suppressor gene through action of its phosphatase protein product; [&]RB1 retinoblastoma protein 1, a tumor suppressor protein; [‡]together with damage to *TP53* gene, tumor suppression is severely compromised; ⁺⁺TCR is a protein complex found on surface of T cells, or T lymphocytes, that is responsible for recognizing fragments of antigen as peptides bound to major histocompatibility complex (MHC); it is responsible for developing uncontrolled signaling pathways; [‡]PI3K as a phosphoinositide; 3-kinases are involved in cellular functions such as cell growth, proliferation, differentiation, motility, survival and intracellular trafficking, which in turn are involved in cancer; TCR – T-cell receptor; EBV – Epstein-Barr virus; HTLV-1 – human T-cell lymphotropic virus type 1; PI3K – phosphoinositide 3-kinase; VEGF – vascular endothelial growth factor

Extrinsic mechanisms

Taking into account the extrinsic mechanisms, the tumor cells in PTCLs are remarkably dependent on the environment. As already mentioned, the activation of TCR combined with the cytokine signals are essential factors in PTCL occurrence [20]. Protumorigenic pathways, combined with decreased immunogenicity of the host, are major agents responsible for the successful growth and survival of neoplastic cells. Furthermore, mutations in T- and NK-cells diverge the microenvironment of cells and are responsible for the systemic symptoms that frequently

Table II. New medical agents in treatment of peripheral T-cell lymphoma

Substance	Receptor	Dosage	Survival
Brentuximab vedotin	CD30	1.8 mg/kg every 21 days	PFS 16.7 months
Ruxolitinib	JAK1, JAK2	20 mg (orally) twice daily	Not reported
Lenalidomide	Cereblon	Lenalidomide (25 mg per day for 14 days every 21 days) +CHOP (standard, every 21 days)	PFS 2 yrs 42%
Mogamulizumab	CCR4	Once a week for eight weeks by intravenous infusion at 1.0 mg/kg	PFS 3 months
Pembrolizumab	PD1, PD-L1	200 mg fixed dose every three weeks in combination with romidepsin	Overall response rate 44%

PFS – progression-free survival; CHOP – cyclophosphamide, doxorubicin, vincristine, and prednisone

occur with PTCLs. Immunosuppression by Treg cells as well as different models of immunoevasion in PTCL have also been noted. Among PTCL-NOS, there is loss of MHC class I proteins and CIITA, that is responsible for the MHC class II transactivator and *TP53* with *CDKN2A* alternations [21, 22]. Moreover, both tumor and endothelial cells can produce vascular endothelial growth factor (VEGF), the levels of which can correspond to the progression of lymphoma [23]. Moreover, PD1+ PTCL cells inhibit the immune response throughout the transmembrane protein, resulting in downmodulation on CD8+ T-cells [24]. Additionally, high levels of flice-like inhibitory protein (flip) can develop PTCL evasion [25].

As for the overexpression of CD47, this can inhibit antitumor macrophage activity and recently has been used in a targeted therapy using CD47 antibodies or CD47 receptor molecules [26]. As a prevention of the expansion of PTCL, a mechanism of host-suppression is being looked into as possible therapy maintenance. In accordance with the studies, PDL1 is highly expressed in ENKTCL176, ALK+ ALCL and among the subpopulation of PTCLs [27, 28]. Soluble factor (PDL1) plays a role as a main biomarker rather than predicting the clinical outcomes among patients with PTCL. There are reports regarding EBV correlation with PTCL occurrence: recent data shows that EBV may affect precursor lymphoid cells that can develop into T, B or NK cells. Recently, EBV-associated lymphoproliferative diseases have been described, in a broad range from highly aggressive PTCL to chronic active EBV infection without any presence of neoplasms.

There is a higher incidence of PTCL lymphomas in Asia, supposedly due to the clonal expansion of premalignant EBV-infected normal T-cells and NK cells. Therefore, insufficiency of the immune system to eliminate the EBV infections plays a crucial role in the development of these neoplasms. Another viral factor associated mainly with ATLL is HTLV-1, at which the risk of developing lymphoma is low (7% in males and 2% in females) [29]. Many reports show that HTLV-1 is clonally integrated with tumor cell genetic content [30].

Treatment

For most subtypes of PTCLs, initial treatment is a combination of a chemotherapy regimen based on either CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), or CHOEP (etoposide, vincristine, doxorubicin, cyclophosphamide, and prednisone), or another multidrug plan [31]. Considering the high risk of PTCL relapse, researchers recommend the implementation of high-dose chemotherapy followed by autologous stem cell transplantation. The Food and Drug Administration (FDA) has approved four substances for use in patients with refractory PTCL: pralatrexate, an antifolate drug; romidepsin, belinostat, an inhibitor for histone deacetylase (HDAC), and brentuximab vedotin, a CD30 antibody (Table II). For CD30-expressing PTCLs, brentuximab vedotin (BV), an antibody that can combine cytotoxic monomethylauristatin E (MMAE), a potent microtubule-disrupting substance, into anti-CD30+ lymphoma cells, is now approved for use in combination with cyclophosphamide, doxorubicin, and prednisone as an initial treatment [32, 33].

Considering the complex biology, the diversity in describing CD30 expression, and the differing mechanisms of management, the level of CD30 antibodies expression is not a predictive factor of the response to BV [34]. A study found that single-agent BV given at 1.8 mg/kg intravenously every three weeks for up to 16 cycles in 58 patients with relapsed or refractory (R/R) sALCL showed an overall response rate (ORR) of 86%, with a 57% complete response (CR) in a pivotal phase II study leading to approval in the USA, EU, and Japan for R/R sALCL. Responses in sALCL appear to be durable: 5-year overall survival (OS) and progression-free survival (PFS) were 79% and 57%, respectively, in patients who achieved a CR. In patients who did not achieve CR, 5-year OS was 25% [35].

Moreover, for many PTCLs, the JAK-STAT pathway is described as a potential target for the new therapies. Studies are currently testing monotherapy using the JAK inhibitor ruxolitinib in treatment-naive as well as relapsed PTCL [36]. Following the pathogenesis of SYK signaling trend, cerdulatinib, described as a dual SYK-JAK inhibitor, has shown

significant efficacy in a phase IIa clinical trial (43% of refractory PTCL with a partial or complete response, and 50% responses in patients with AITL) [37]. Among different immunotherapies, lenalidomide as an immunoregulator has shown antineoplastic effect in several hematological studies [38]. Maintaining binding to cereblon, suppressing the cell cycle by the degradation of cyclin-dependent kinases, lenalidomide presents an antiproliferative activity [39]. It also has immunomodulatory effects based on the increased levels of IL-2 present among T-cell and NK-cell activity. Lenalidomide has been studied as a single agent in recurrent PTCL, showing a response rate of 33%, and currently is being studied in combination with CHOP as first-line treatment among patients with AITL [40].

The next immunotherapy drug, mogamulizumab, a monoclonal antibody CCR4 that stimulates antibody-dependent cellular cytotoxicity has shown potential antitumor effect against PTCL cell lines and ATLL mouse models in research trials [41]. Mogamulizumab was approved by the Japan FDA in 2012 for the treatment of ATLL, based on a multicenter phase II study conducted in 28 relapsed patients. In 2018, it was approved for the treatment of recurrent mycosis fungoides and Sézary syndrome (~40% positive for CCR4) [42].

Studies show that many PTCLs constitutively express PD1 or PDL1, the blockage of which has been shown to be therapeutic in a variety of host intratumoral cells in non-Hodgkin and Hodgkin lymphoma. Pembrolizumab is described as efficient in relapsed NK-cell/T-cell lymphomas and also shows moderate activity in PTCL [43]. Moreover, rapid progression after a single infusion of nivolumab, a PD1 humanized antibody, was observed among patients with ATLL. The gene expression profile of tumor-associated Treg cells and ATLL cells after PD1 blockade was remarkably similar, suggesting a suppressive role of PD1 in indolent ATLL [44]. This is combined with the findings that PD1 suppresses oncogenic T cell signaling in a mouse model via PTEN and attenuates signaling by AKT and protein kinase C (PKC) in premalignant cells [45]. Additionally, the role of CAR (chimeric antigen receptor) T cell therapy is limited to those patients with relapsed PTCL. Research shows that CD30+ CAR-T cells present some effects in mouse models, but the reactivity against alloreactive T cells or Treg cells that express very high levels of CD30 remains unknown. CD30 CAR-T cells clinical trials have demonstrated either a stable disease or partial response [46]. Only one patient with ALCL in any of these clinical trials presented a complete remission that lasted nine months. Recently, CD4 CAR-T cells have shown cytotoxic efficacy both in PTCL cell lines and in mouse models, with some degree of antineoplastic effect and on-target/off-tumor effect leading to CD4+ T cell lymphopenia. Also, expressions of CD37 and CCR4 were recently shown to be targets for CAR-T cell therapy [47].

PTCL as a rare, very heterogeneous group of neoplasms, show advanced mechanisms of molecular biology, as well as distinct subgroups with defined clinical outcomes and responses to therapies. Improvements will be needed to achieve early detection and to anticipate recurrences. With the creation of research networks, the future will feature genomic studies as well as clinical trials testing new agents that could be used to tackle this rare neoplasm. Collecting more data should broaden the understanding of the molecular mechanisms that may lead to new rationally-based strategies of treatment.

The recent FDA approval of novel agents and their promising results, together with new drugs and immune-based therapies, are expected to improve clinical outcomes, although therapies using multiple targets might also be necessary to maintain therapeutic success.

Author's contributions

JK – preparatory work, collection of literature; GM – work concept, preparatory work, critical reviewing, data collection and interpretation, acceptance of final version for publication.

Conflict of interest

None.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform requirements for manuscripts submitted to biomedical journals.

References

1. Vose J, Armitage J, Weisenburger D, et al. International T-Cell Lymphoma Project. International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. *J Clin Oncol.* 2008; 26(25): 4124–4130, doi: [10.1200/JCO.2008.16.4558](https://doi.org/10.1200/JCO.2008.16.4558), indexed in Pubmed: [18626005](https://pubmed.ncbi.nlm.nih.gov/18626005/).
2. Anderson JR, Armitage JO, Weisenburger DD. Epidemiology of the non-Hodgkin's lymphomas: distributions of the major subtypes differ by geographic locations. Non-Hodgkin's Lymphoma Classification Project. *Ann Oncol.* 1998; 9(7): 717–720, doi: [10.1023/a:1008265532487](https://doi.org/10.1023/a:1008265532487), indexed in Pubmed: [9739436](https://pubmed.ncbi.nlm.nih.gov/9739436/).
3. Tremat P, Tabiasco J, Andre P, et al. Evidence for early infection of nonneoplastic natural killer cells by Epstein-Barr virus. *J Virol.* 2002; 76(21): 11139–11142, doi: [10.1128/jvi.76.21.11139-11142.2002](https://doi.org/10.1128/jvi.76.21.11139-11142.2002), indexed in Pubmed: [12368357](https://pubmed.ncbi.nlm.nih.gov/12368357/).
4. Inghirami G, Chan WC, Pileri S, et al. AIRC 5xMille consortium 'Genetics-driven targeted management of lymphoid malignancies'. Peripheral T-cell and NK cell lymphoproliferative disorders: cell of origin, clinical and pathological implications. *Immunol Rev.* 2015; 263(1): 124–159, doi: [10.1111/imr.12248](https://doi.org/10.1111/imr.12248), indexed in Pubmed: [25510275](https://pubmed.ncbi.nlm.nih.gov/25510275/).

5. Weiss LM, Jaffe ES, Liu XF, et al. Detection and localization of Epstein-Barr viral genomes in angioimmunoblastic lymphadenopathy and angioimmunoblastic lymphadenopathy-like lymphoma. *Blood*. 1992; 79(7): 1789–1795, indexed in Pubmed: [1373088](#).
6. Wang T, Feldman AL, Wada DA, et al. GATA-3 expression identifies a high-risk subset of PTCL, NOS with distinct molecular and clinical features. *Blood*. 2014; 123(19): 3007–3015, doi: [10.1182/blood-2013-12-544809](#), indexed in Pubmed: [24497534](#).
7. Iqbal J, Wright G, Wang C, et al. Lymphoma Leukemia Molecular Profiling Project and the International Peripheral T-cell Lymphoma Project. Gene expression signatures delineate biological and prognostic subgroups in peripheral T-cell lymphoma. *Blood*. 2014; 123(19): 2915–2923, doi: [10.1182/blood-2013-11-536359](#), indexed in Pubmed: [24632715](#).
8. Shouse G, Nikolaenko L. Targeting the JAK/STAT pathway in T cell lymphoproliferative disorders. *Curr Hematol Malig Rep*. 2019; 14(6): 570–576, doi: [10.1007/s11899-019-00545-5](#), indexed in Pubmed: [31741284](#).
9. Gupta M, Maurer M, Stenson M, et al. In-vivo activation of STAT3 in angioimmunoblastic T cell lymphoma, PTCL not otherwise specified, and ALK negative anaplastic large cell lymphoma: implications for therapy. *Blood*. 2013; 122(21): 844–844, doi: [10.1182/blood.v122.21.844.844](#).
10. Dufva O, Kankainen M, Kelkka T, et al. Aggressive natural killer-cell leukemia mutational landscape and drug profiling highlight JAK-STAT signaling as therapeutic target. *Nat Commun*. 2018; 9(1): 1567, doi: [10.1038/s41467-018-03987-2](#), indexed in Pubmed: [29674644](#).
11. Fujiwara SI, Yamashita Y, Nakamura N, et al. High-resolution analysis of chromosome copy number alterations in angioimmunoblastic T-cell lymphoma and peripheral T-cell lymphoma, unspecified, with single nucleotide polymorphism-typing microarrays. *Leukemia*. 2008; 22(10): 1891–1898, doi: [10.1038/leu.2008.191](#), indexed in Pubmed: [18633432](#).
12. Palomero T, Couronné L, Khlambanian H, et al. Recurrent mutations in epigenetic regulators, RHOA and FYN kinase in peripheral T cell lymphomas. *Nat Genet*. 2014; 46(2): 166–170, doi: [10.1038/ng.2873](#), indexed in Pubmed: [24413734](#).
13. Feldman AL, Sun DX, Law ME, et al. Overexpression of Syk tyrosine kinase in peripheral T-cell lymphomas. *Leukemia*. 2008; 22(6): 1139–1143, doi: [10.1038/leu.2008.77](#), indexed in Pubmed: [18401419](#).
14. Wilcox RA, Sun DX, Novak A, et al. Inhibition of Syk protein tyrosine kinase induces apoptosis and blocks proliferation in T-cell non-Hodgkin's lymphoma cell lines. *Leukemia*. 2010; 24(1): 229–232, doi: [10.1038/leu.2009.198](#), indexed in Pubmed: [19776763](#).
15. Mahadevan D, Spier C, Della Croce K, et al. Transcript profiling in peripheral T-cell lymphoma, not otherwise specified, and diffuse large B-cell lymphoma identifies distinct tumor profile signatures. *Mol Cancer Ther*. 2005; 4(12): 1867–1879, doi: [10.1158/1535-7163.MCT-05-0146](#), indexed in Pubmed: [16373702](#).
16. Xiong J, Bian J, Wang L, et al. Dysregulated choline metabolism in T-cell lymphoma: role of choline kinase- α and therapeutic targeting. *Blood Cancer J*. 2015; 5: 287, doi: [10.1038/bcj.2015.10](#), indexed in Pubmed: [25768400](#).
17. Rohr J, Guo S, Huo J, et al. Recurrent activating mutations of CD28 in peripheral T-cell lymphomas. *Leukemia*. 2016; 30(5): 1062–1070, doi: [10.1038/leu.2015.357](#), indexed in Pubmed: [26719098](#).
18. Kittipongdaja W, Wu X, Garner J, et al. Rapamycin suppresses tumor growth and alters the metabolic phenotype in T-cell lymphoma. *J Invest Dermatol*. 2015; 135(9): 2301–2308, doi: [10.1038/jid.2015.153](#), indexed in Pubmed: [25897830](#).
19. Pechloff K, Holch J, Ferch U, et al. The fusion kinase ITK-SYK mimics a T cell receptor signal and drives oncogenesis in conditional mouse models of peripheral T cell lymphoma. *J Exp Med*. 2010; 207(5): 1031–1044, doi: [10.1084/jem.20092042](#), indexed in Pubmed: [20439541](#).
20. Lin ZX, Bai B, Cai QC, et al. High numbers of tumor-associated macrophages correlate with poor prognosis in patients with mature T- and natural killer cell lymphomas. *Med Oncol*. 2012; 29(5): 3522–3528, doi: [10.1007/s12032-012-0244-6](#), indexed in Pubmed: [22562823](#).
21. Watatani Y, Sato Y, Miyoshi H, et al. Molecular heterogeneity in peripheral T-cell lymphoma, not otherwise specified revealed by comprehensive genetic profiling. *Leukemia*. 2019; 33(12): 2867–2883, doi: [10.1038/s41375-019-0473-1](#).
22. Fujiwara SI, Yamashita Y, Nakamura N, et al. High-resolution analysis of chromosome copy number alterations in angioimmunoblastic T-cell lymphoma and peripheral T-cell lymphoma, unspecified, with single nucleotide polymorphism-typing microarrays. *Leukemia*. 2008; 22(10): 1891–1898, doi: [10.1038/leu.2008.191](#), indexed in Pubmed: [18633432](#).
23. Zhao WL, Mourah S, Mounier N, et al. Vascular endothelial growth factor-A is expressed both on lymphoma cells and endothelial cells in angioimmunoblastic T-cell lymphoma and related to lymphoma progression. *Lab Invest*. 2004; 84(11): 1512–1519, doi: [10.1038/labinvest.3700145](#), indexed in Pubmed: [15311211](#).
24. Karwacz K, Bricogne C, MacDonald D, et al. PD-L1 co-stimulation contributes to ligand-induced T cell receptor down-modulation on CD8+ T cells. *EMBO Mol Med*. 2011; 3(10): 581–592, doi: [10.1002/emmm.201100165](#), indexed in Pubmed: [21739608](#).
25. de Charette M, Houot R. Hide or defend, the two strategies of lymphoma immune evasion: potential implications for immunotherapy. *Haematologica*. 2018; 103(8): 1256–1268, doi: [10.3324/haematol.2017.184192](#), indexed in Pubmed: [30006449](#).
26. Jain S, Van Scoyk A, Morgan EA, et al. Targeted inhibition of CD47-SIRP α requires Fc-Fc γ R interactions to maximize activity in T-cell lymphomas. *Blood*. 2019; 134(17): 1430–1440, doi: [10.1182/blood.2019001744](#), indexed in Pubmed: [31383641](#).
27. Marzec M, Zhang Q, Goradia A, et al. Oncogenic kinase NPM/ALK induces through STAT3 expression of immunosuppressive protein CD274 (PD-L1, B7-H1). *Proc Natl Acad Sci USA*. 2008; 105(52): 20852–20857, doi: [10.1073/pnas.0810958105](#), indexed in Pubmed: [19088198](#).
28. Wilcox RA, Feldman AL, Wada DA, et al. B7-H1 (PD-L1, CD274) suppresses host immunity in T-cell lymphoproliferative disorders. *Blood*. 2009; 114(10): 2149–2158, doi: [10.1182/blood-2009-04-216671](#), indexed in Pubmed: [19597183](#).
29. Inghirami G, Chan WC, Pileri S, et al. AIRC 5xMille consortium 'Genetics-driven targeted management of lymphoid malignancies'. Peripheral T-cell and NK cell lymphoproliferative disorders: cell of origin, clinical and pathological implications. *Immunol Rev*. 2015; 263(1): 124–159, doi: [10.1111/imr.12248](#), indexed in Pubmed: [25510275](#).
30. Cheng J, Kydd AR, Nakase K, et al. Negative regulation of the SH2-homology containing protein-tyrosine phosphatase-1 (SHP-1) P2 promoter by the HTLV-1 Tax oncoprotein. *Blood*. 2007; 110(6): 2110–2120, doi: [10.1182/blood-2006-11-058388](#), indexed in Pubmed: [17540846](#).
31. d'Amore F, Gaulard P, Trümper L, et al. ESMO Guidelines Committee. Peripheral T-cell lymphomas: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2015; 26(Suppl 5): v108–v115, doi: [10.1093/annonc/mdv201](#), indexed in Pubmed: [26314772](#).

32. Foss F, Horwitz SM, Coiffier B, et al. Pralatrexate in patients with relapsed or refractory peripheral T-cell lymphoma: results from the pivotal PROPEL study. *J Clin Oncol.* 2011; 29(9): 1182–1189, doi: [10.1200/JCO.2010.29.9024](https://doi.org/10.1200/JCO.2010.29.9024), indexed in Pubmed: [21245435](https://pubmed.ncbi.nlm.nih.gov/21245435/).
33. Pro B, Advani R, Brice P, et al. National Comprehensive Cancer Network. Hodgkin lymphoma, version 2.2012 featured updates to the NCCN guidelines. *J Natl Compr Canc Netw.* 2012; 10(5): 589–597, doi: [10.6004/jnccn.2012.0061](https://doi.org/10.6004/jnccn.2012.0061), indexed in Pubmed: [22570290](https://pubmed.ncbi.nlm.nih.gov/22570290/).
34. Barta SK, Gong JZ, Porcu P. Brentuximab vedotin in the treatment of CD30+ PTCL. *Blood.* 2019; 134(26): 2339–2345, doi: [10.1182/blood.2019001821](https://doi.org/10.1182/blood.2019001821), indexed in Pubmed: [31697814](https://pubmed.ncbi.nlm.nih.gov/31697814/).
35. Domingo-Domènech E, Boumendil A, Climent F, et al. Lymphoma Working Party of the European Society for Blood and Marrow Transplantation, Lymphoma Working Party of the European Society for Blood and Marrow Transplantation. SGN-30: a basis for the effective treatment of CD30 positive hematopoietic malignancies. *Expert Opin Investig Drugs.* 2008; 17(12): 1883–1887, doi: [10.1517/13543780802493440](https://doi.org/10.1517/13543780802493440), indexed in Pubmed: [19012503](https://pubmed.ncbi.nlm.nih.gov/19012503/).
36. Moskowitz AJ, Ghione P, Jacobsen E, et al. Final results of a phase II biomarker-driven study of ruxolitinib in relapsed and refractory T-cell lymphoma. *Blood.* 2019; 134(Suppl 1): 4019–4019, doi: [10.1182/blood-2019-125017](https://doi.org/10.1182/blood-2019-125017).
37. Horwitz S, Feldman T, Hess B, et al. A phase 2 study of the dual SYK/JAK inhibitor cerdulatinib demonstrates good tolerability and clinical response in relapsed/refractory peripheral T-cell lymphoma and cutaneous T-cell lymphoma. *Blood.* 2019; 134(Suppl 1): 466–466, doi: [10.1182/blood-2019-123986](https://doi.org/10.1182/blood-2019-123986).
38. Hopfinger G, Nösslinger T, Lang A, et al. Lenalidomide in combination with vorinostat and dexamethasone for the treatment of relapsed/refractory peripheral T cell lymphoma (PTCL): report of a phase I/II trial. *Ann Hematol.* 2014; 93(3): 459–462, doi: [10.1007/s00277-014-2009-0](https://doi.org/10.1007/s00277-014-2009-0), indexed in Pubmed: [24441915](https://pubmed.ncbi.nlm.nih.gov/24441915/).
39. Lopez-Girona A, Mendy D, Ito T, et al. Cereblon is a direct protein target for immunomodulatory and antiproliferative activities of lenalidomide and pomalidomide. *Leukemia.* 2012; 26(11): 2326–2335, doi: [10.1038/leu.2012.119](https://doi.org/10.1038/leu.2012.119), indexed in Pubmed: [22552008](https://pubmed.ncbi.nlm.nih.gov/22552008/).
40. Lemonnier F, Safar V, Beldi-Ferchiou A, et al. Integrative analysis of a phase 2 trial combining lenalidomide with CHOP in angioimmunoblastic T-cell lymphoma. *Blood Adv.* 2021; 5(2): 539–548, doi: [10.1182/bloodadvances.2020003081](https://doi.org/10.1182/bloodadvances.2020003081), indexed in Pubmed: [33496747](https://pubmed.ncbi.nlm.nih.gov/33496747/).
41. Fujita Y, Nakaya A, Fujita S, et al. Mogamulizumab treatment of refractory peripheral T-cell lymphoma following autologous stem cell transplantation: A case report. *Mol Clin Oncol.* 2016; 4(2): 151–153, doi: [10.3892/mco.2015.695](https://doi.org/10.3892/mco.2015.695), indexed in Pubmed: [26893851](https://pubmed.ncbi.nlm.nih.gov/26893851/).
42. Ollila TA, Sahin I, Olszewski AJ. Mogamulizumab: a new tool for management of cutaneous T-cell lymphoma. *Onco Targets Ther.* 2019; 12: 1085–1094, doi: [10.2147/OTT.S165615](https://doi.org/10.2147/OTT.S165615), indexed in Pubmed: [30799938](https://pubmed.ncbi.nlm.nih.gov/30799938/).
43. Li X, Cheng Y, Zhang M, et al. Activity of pembrolizumab in relapsed/refractory NK/T-cell lymphoma. *J Hematol Oncol.* 2018; 11(1): 15, doi: [10.1186/s13045-018-0559-7](https://doi.org/10.1186/s13045-018-0559-7), indexed in Pubmed: [29386072](https://pubmed.ncbi.nlm.nih.gov/29386072/).
44. Han Y, Liu D, Li L. PD-1/PD-L1 pathway: current researches in cancer. *Am J Cancer Res.* 2020; 10(3): 727–742, indexed in Pubmed: [32266087](https://pubmed.ncbi.nlm.nih.gov/32266087/).
45. Fiore D, Cappelli LV, Broccoli A, et al. Peripheral T cell lymphomas: from the bench to the clinic. *Nat Rev Cancer.* 2020; 20(6): 323–342, doi: [10.1038/s41568-020-0247-0](https://doi.org/10.1038/s41568-020-0247-0), indexed in Pubmed: [32249838](https://pubmed.ncbi.nlm.nih.gov/32249838/).
46. Grover NS, Savoldo B. Challenges of driving CD30-directed CAR-T cells to the clinic. *BMC Cancer.* 2019; 19(1): 203, doi: [10.1186/s12885-019-5415-9](https://doi.org/10.1186/s12885-019-5415-9), indexed in Pubmed: [30841880](https://pubmed.ncbi.nlm.nih.gov/30841880/).
47. Pinz K, Liu H, Golightly M, et al. Preclinical targeting of human T-cell malignancies using CD4-specific chimeric antigen receptor (CAR)-engineered T cells. *Leukemia.* 2016; 30(3): 701–707, doi: [10.1038/leu.2015.311](https://doi.org/10.1038/leu.2015.311), indexed in Pubmed: [26526988](https://pubmed.ncbi.nlm.nih.gov/26526988/).