Review Article

Immune Checkpoints and Their Inhibition in T-Cell Lymphomas

(T-cell lymphoma / T-cell-derived malignancies / immune checkpoints / immune checkpoint inhibitors / PD-1 / PD-L1 / CTLA-4 / LAG-3 / TIM-3 / TIGIT / OX40/OX40L / anti-PD-1 / anti-PD-L1 / anti-CTLA-4 / nivolumab / pembrolizumab / toripalimab / sintilimab / geptanolimab / atezolizumab / avelumab / durvalumab / ipilimumab / ALCL / anaplastic large cell lymphoma / ENKTL / extranodal NK/T-cell lymphoma / MF / mycosis fungoides / SS / Sézary syndrome / PTCL / peripheral T-cell lymphoma)

JANA SEŇAVOVÁ[1,2], ANEŽKA RAJMONOVÁ[1], VÁCLAV HEŘMAN[1,2], FILIP JURA[1], ADRIANA VEĽASOVÁ[1], IVA HAMOVÁ[1,2], ANTON TKACHENKO[1], KRISTÝNA KUPCOVÁ[1,2], ONDŘEJ HAVRÁNEK[1,2]

[1] BIOCEV, First Faculty of Medicine, Charles University, Prague, Czech Republic
[2] 1st Department of Medicine – Department of Haematology, First Faculty of Medicine, Charles University and General University Hospital in Prague, Prague, Czech Republic

Received March 7, 2024. Accepted October 7, 2024.

This study was supported by Charles University in Prague (Cooperatio), project National Institute for Cancer Research (reg. No. LX22NPO5102) – funded by the European Union – Next Generation EU, Programme EXCELES. JS, AR, VH, AV and IO acknowledge support by the project "Grant Schemes at CU" (reg. No. CZ.02.2.69/0.0/0.0/19_073/0016935) START/MED/085. AT received support from EHA Ukraine Bridge Funding awarded by the European Hematology Association.

Corresponding author: Ondřej Havránek, BIOCEV, First Faculty of Medicine, Charles University, Prumyslova 595, 25250 Vestec, Czech Republic; Phone and Fax: (+420) 325 873 029; e-mail: ondrej.havranek@lf1.cuni.cz

Abbreviations: ADCP – antibody-dependent cellular phagocytosis, AITL – angioimmunoblastic T-cell lymphoma, AKT – protein kinase B, ALCL – anaplastic large cell lymphoma, ALK +/− – anaplastic lymphoma kinase positive/negative, AP1 – activator protein 1, APC – antigen-presenting cell, ASCT – autologous stem cell transplantation, ATLL – adult T-cell leukemia/lymphoma, BV – brentuximab vedotin, C-ALCL – primary cutaneous anaplastic large cell lymphoma, CAR – chimeric antigen receptor, CD – cluster of differentiation, CHOEP – cyclophosphamide, doxorubicin, vincristine, etoposide, prednisolone, CHOP – cyclophosphamide, doxorubicin, vincristine, prednisolone, CITN-10 – cancer immunotherapy trials network, CR – complete remission, CTCL – primary cutaneous T-cell lymphoma, CTLA-4 – cytotoxic T-lymphocyte-associated protein 4, CTLs – cytotoxic T lymphocytes, DA-EPOCH – dose-adjusted etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin, DLBCL – diffuse large B-cell lymphoma, DNMTi – DNA methyltransferase inhibitors, EATL – enteropathy-associated T-cell lymphoma, EBV – Epstein-Barr virus, ENKTL – extranodal NK/T-cell lymphoma, ENKTL-NT – extranodal NK/T-cell lymphoma-nasal type, ERK – extracellular signal-regulated kinase, FAERS – FDA Adverse Event Reporting System, FDA – U.S. Food and Drug Administration, GATA3 – GATA binding protein 3, HDACi – histone deacetylase inhibitors, HL – Hodgkin lymphoma, HTLV-1 – human T-cell leukemia virus 1, ICIs – immune checkpoint inhibitors, ICOS – inducible co-stimulator, IDO1i – indoleamine 2,3-dioxygenase 1 inhibitors, IL – interleukin, INF-α – interferon alpha, INF-γ – interferon gamma, IPI – international prognostic index, ITIM – immunoreceptor tyrosine-based inhibitory motif, ITK-SYK – gene fusion of interleukin-2-inducible T-cell kinase and spleen tyrosine kinase, ITSM – immunoreceptor tyrosine-based switch motif, JAK/STAT – Janus kinase/signal transducers and activators of transcription, LAG-3 – lymphocyte-activation gene 3, LMPs – latent membrane proteins, LyP – lymphomatoid papulosis, MAPK – mitogen-activated protein kinase, MEITL – monomorphic epitheliotropic intestinal T-cell lymphoma, MF – mycosis fungoides, MHC I/II – major histocompatibility complex I/II, NF-κB – nuclear factor kappa-light-chain-enhancer of activated B-cells, NHL – non-Hodgkin lymphoma, NK – natural killer, NMP1-ALK – gene fusion of nucleophosmin 1 with anaplastic lymphoma kinase, ORR – overall response rate, OS – overall survival, PBMCs – peripheral blood mononuclear cells, PD – progressive disease, PD-1 – programmed cell death protein 1, *PDCD1* – programmed cell death 1 gene, PD-L1 – programmed death ligand 1, PD-L2 – programmed death ligand 2, PFS – progression-free survival, P-GEMOX – pegaspargase, gemcitabine, oxaliplatin, PI3K – phosphoinositide 3-kinase, PMBL – primary mediastinal B-cell lymphoma, PR – partial response, PTCL – peripheral T-cell lymphoma, PTCL-NOS – peripheral T-cell lymphoma, not otherwise specified, PTEN – phosphatase and tensin homolog, R/R – relapsed/refractory, RT – radiotherapy, SD – stable disease, SHIP2 – SH2-containing 5'-inositol phosphatase 2, SHP2 – Src homology 2 domain-containing protein tyrosine phosphatase, sPD-L1 – soluble programmed death ligand 1, SS – Sézary syndrome, T-ALL – T-cell acute lymphoblastic leukemia, TAM – tumor-associated macrophage, TCL – T-cell lymphoma, TCR – T-cell receptor, TFH – T follicular helper, TGF-β – transforming growth factor beta, Th – T helper, TIGIT – T-cell immunoreceptor with Ig and ITIM domains, TILs – tumor-infiltrating

lymphocytes, TIM – tumor-infiltrating macrophage, TIM-3 – T-cell immunoglobulin and mucin domain-containing protein 3, T-LGLL – T-large granular lymphocytic leukemia, TMB – tumor mutational burden, TME – tumor microenvironment, TNF – tumor necrosis factor, T-PLL – T-cell prolymphocytic leukemia, TRAE – treatment-related adverse event, TRAFs – tumor necrosis factor receptor-associated factors, Tregs – regulatory T cells, VEGF – vascular endothelium growth factor, ZAP-70 – zeta-chain-associated protein kinase 70.

Abstract. T-cell lymphomas (TCLs) are a rare and heterogeneous subgroup of non-Hodgkin lymphomas (NHLs), forming only 10 % of all NHL cases in Western countries. Resulting from their low incidence and heterogeneity, the current treatment outcome is generally unfavorable, with limited availability of novel therapeutic approaches. Therefore, the recent success of immune checkpoint inhibitors (ICIs) in cancer treatment motivated their clinical investigation in TCLs as well. Multiple studies showed promising results; however, cases of TCL hyperprogression following ICI treatment and secondary T-cell-derived malignancies associated with ICI treatment of other cancer types were also reported. In our review, we first briefly summarize classification of T-cell-derived malignancies, general anti-tumor immune response, immune evasion, and immune checkpoint signaling. Next, we provide an overview of immune checkpoint molecule deregulation in TCLs, summarize available studies of ICIs in TCLs, and review the above-mentioned safety concerns associated with ICI treatment and T-cell-derived malignancies. Despite initial promising results, further studies are necessary to define the most suitable clinical applications and ICI therapeutic combinations with other novel treatment approaches within TCL treatment. ICIs, and their combinations, might hopefully bring the long awaited improvement for the treatment of T-cell-derived malignancies.

Introduction

T-cell lymphomas (TCLs) are relatively rare and highly heterogeneous malignant tumors. They represent one of many subgroups of non-Hodgkin lymphomas (NHLs), accounting only for 10–20 % of all NHL cases (10–15 % in Western countries and 15–20 % in Asian countries) (Vose et al., 2008; Al-Hamadani et al., 2015; Zhang and Dalal, 2019; Liu et al., 2022). Given their low incidence, population-based studies are limited. The TCL incidence rate keeps increasing over the last 20 years, being 1 to 2 cases per 100,000 inhabitants per year (Marchi and O'Connor, 2020). Recent studies reported the incidence of mature T/NK-cell lymphomas between 3 and 4 cases per 100,000 inhabitants per year in Germany (Assaf et al., 2023) and the incidence of TCLs between 1 and 2 cases per 100,000 inhabitants per year in 31 European Medicines Agency member states (Zhang and Dalal, 2019). TCLs most frequently develop at the age of 40–50 and their incidence is affected by ethnicity. For example, peripheral T-cell lymphomas (PTCLs) occur more frequently in Alaskan and Native Americans, while extranodal NK/T-cell lymphomas (ENKTLs) are very common in Asia and at Pacific islands. The highest relative incidence of TCLs is within the African American population (Anderson et al., 1998; Al-Hamadani et al., 2015; Adams et al., 2016; Shah et al., 2019; Zain and Hanona, 2021). In contrast, TCL mortality is stable or even showing a slightly decreasing trend due to generally improved NHL treatment strategies (Abouyabis et al., 2008; Thandra et al., 2021).

TCLs comprise a relatively wide group of very heterogeneous malignant tumors derived from T cells. Malignant T-cell transformation is frequently associated with defects in their maturation and lineage commitment. TCLs could be generally classified based on their clinical behavior (indolent vs. aggressive) or based on underlying biological characteristics, similarity to normal T-cell counterparts, and stage of differentiation block. Another clinically-based TCL classification reflects tumor localization and divides TCLs into cutaneous, peripheral, and extranodal lymphomas from natural killer cells (Ghione et al., 2018). TCLs are much less studied in comparison to B-cell-derived malignancies and are subjects of substantially lower number of basic, translational, as well as clinical studies and trials. This could be at least partially attributed to the above-mentioned low incidence rate and related generally lower interest to study rare diseases. On the other hand, search for better treatment options also continues in TCLs. Several immunotherapy-based approaches showed success in hematological malignancies as well as in solid oncology. Particularly, immune checkpoint inhibitors caused a paradigm shift in the treatment of solid tumors. Therefore, we aimed to summarize the role of checkpoint molecules in TCLs and to outline options of immune checkpoint inhibition for TCL treatment. Introductory sections on T-cell malignancies, standard TCL treatment approaches, and general mechanisms of tumor-immune system interaction are followed by sections summarizing the functional role of immune checkpoint molecules in TCLs and the status and expectations of checkpoint inhibitor use in the treatment of these tumors.

T-Cell-Derived Malignancies

As mentioned above, T-cell-derived malignancies are a very heterogeneous group of neoplasms. The specifics and differences of individual tumor types primarily reflect the naturally wide heterogeneity of T-cell populations. This heterogeneity is further affected by a large range of different routes of malignant transformation (and associated somatic DNA alterations) and by clinical appearance. Therefore, the classification of T-cell and NK-cell malignancies includes over 30 subtypes of TCLs (Alaggio et al., 2022).

T-cell-derived malignancies can be grouped into two major categories: precursor T-cell leukemias/lympho-

mas and mature T-cell neoplasms. These categories are then further divided based on different criteria such as the cell of origin, morphology, or disease presentation. Precursor T-cell neoplasms, represented mainly by T-lymphoblastic leukemias/lymphomas, are aggressive malignancies characterized by rapid onset with often life-threatening symptoms. They mostly affect children and young adults (Bardelli et al., 2021).

Mature T-cell-derived malignancies, which are the focus of our review, encompass many different entities with a broad spectrum of clinical manifestations ranging from indolent chronic diseases (e.g., selected primary cutaneous TCLs) to aggressive systemic lymphomas with a poor prognosis (Iżykowska et al., 2020). Most mature T-cell-derived neoplasms originate from different types of $CD4^+$ helper T cells, although certain types also arise from $CD8^+$ cytotoxic T cells or other T-cell subtypes.

Individual TCL subtypes have distinct clinicopathological features corresponding to their genetic and molecular background. The most important and recurrent alterations involve deregulation of T-cell receptor and cytokine signaling, mutations in epigenetic regulators, and alterations enabling immune evasion. All these alterations have a direct effect on the tumor cells-microenvironment interaction, as recently reviewed (Van Arnam et al., 2018). Given the outlined biological complexity, low frequency, and often significantly underexplored characteristics (in comparison to B-cell lymphomas), the correct TCL diagnosis is challenging and in many cases requires modern molecular and genomic methods on top of classical morphological evaluation (Alaggio et al., 2022). The major categories of mature T-cell-derived tumors according to the WHO classification are briefly described below and summarized in Fig. 1, keeping in mind certain differences in comparison to an alternative International Consensus Classification of lymphoid malignancies (Campo et al., 2022).

Mature T-cell leukemias

Mature T-cell leukemias form a group of rare diseases with primary manifestation in the blood/bone marrow compartment (Herling et al., 2004). T-cell prolymphocytic leukemia (T-PLL) is an aggressive neoplasm often presenting itself with high lymphocytosis and hepatosplenomegaly. Hallmark alterations in T-PLL are gene rearrangements involving the T-cell leukemia/lymphoma 1 (TCL1) family of proteins and defects in DNA damage response pathways (Schrader et al., 2018).

In contrast, adult T-cell leukemia (ATLL, 10 % of TCL, < 1 % of all lymphomas) develops from human T-cell leukemia virus 1 (HTLV-1)-infected cells after a long latency period needed for accumulation of additional genetic events. It is the only retroviral-induced cancer in humans. TCR signaling activation and immune evasion are critical events within ATLL pathogenesis (having also prognostic implications) (Vose et al., 2008; Kataoka et al., 2018).

Chronic antigenic stimulation and defective Fas-mediated apoptosis appear to be drivers of T-large granular lymphocytic leukemia (T-LGLL) (Yang et al., 2008). Common activating mutations of *STAT3* and associated reactive cytopenias often cause symptoms requiring treatment (Barilà et al., 2020), but the overall clinical course is usually indolent.

Sézary syndrome (SS), a leukemic form of cutaneous T-cell lymphoma, could be usually distinguished from other T-cell leukemias by association with erythroderma. SS is closely related to other subtypes of cutaneous TCLs (e.g., mycosis fungoides), but it is a distinct entity that may originate from a specific population of central memory T cells (Campbell et al., 2010).

Primary cutaneous T-cell lymphomas

Primary cutaneous T-cell lymphomas (CTCLs) are much more frequent than their B-cell counterparts, representing about 80 % of primary cutaneous lymphoma cases (Dobos et al., 2020). Most CTCLs are indolent but progressive diseases with no available cure, except for allogeneic stem cell transplantation (Willemze et al., 2019; Kempf and Mitteldorf, 2021).

The most prevalent CTCL subtype (two thirds of CTCL cases, < 5 % of all lymphomas) worldwide is mycosis fungoides (MF) (Dobos et al., 2020; Hristov et al., 2023), a chronic clonal proliferation of skin-resident effector memory T cells with characteristic immunophenotype (Campbell et al., 2010). MF has also a very typical clinical evolution (from formation of patches, through plaques, to tumors and extracutaneous spread). MF treatment reflects the clinical stage and is stage-adapted (Willemze et al., 2018). Molecular genetic studies of MF and SS showed high genomic instability that results in a complex karyotype with frequent focal deletions (Choi et al., 2015). It suggests a critical role of UV radiation in the pathogenesis of these two lymphomas (Jones et al., 2021).

Primary cutaneous $CD30^+$ T-cell lymphoproliferative disorders include lymphomatoid papulosis (LyP) and primary cutaneous anaplastic large cell lymphoma (C-ALCL). These are very close entities with an overlapping spectrum of cases. Prognosis of LyP as well as C-ALCL is excellent despite their morphological resemblance to their systemic counterparts (Bekkenk et al., 2000). Other CTCL subtypes are generally very rare entities.

Nodal T-follicular helper cell lymphomas

The family of nodal T-follicular helper cell lymphomas includes tumors with immunophenotypic and transcriptional profiles resembling normal follicular helper T cells (de Leval et al., 2007; Huang et al., 2009). All three histological subtypes, angioimmunoblastic (formerly angioimmunoblastic T-cell lymphoma – AITL, 19 % of PTCL, 4 % of all lymphomas), follicular, and not otherwise specified, have unfavorable outcome (Vose et al., 2008). These lymphomas frequently develop on the background of clonal hematopoiesis and, aside from other lymphoma recurrent DNA alterations, share mutations in DNA and histone methylation regulators and

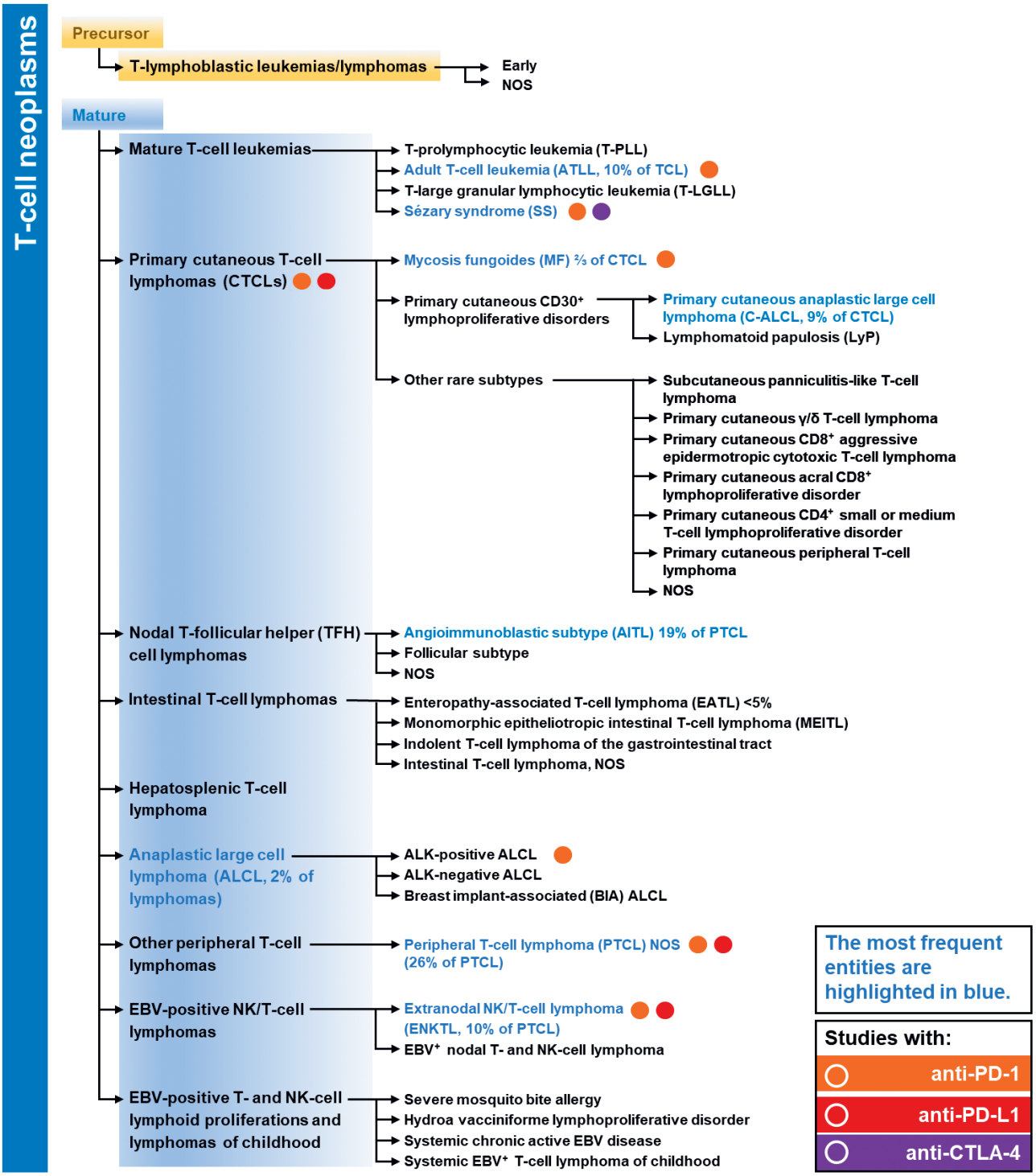

Fig. 1. The WHO classification of T-cell-derived malignancies (adapted from Alaggio et al., 2022). The most frequent entities are highlighted in blue. Entities where studies with checkpoint inhibitors were reported are marked.
Abbreviations: ALCL – anaplastic large cell lymphoma, ALK – anaplastic lymphoma kinase, ATLL – adult T-cell leukemia, EATL – enteropathy-associated T-cell lymphoma, EBV – Epstein-Barr virus, ENKTL – extranodal NK/T-cell lymphoma, LyP – lymphomatoid papulosis, MEITL – monomorphic epitheliotropic intestinal T-cell lymphoma, MF – mycosis fungoides, NK – natural killer, NOS – not otherwise specified, PTCL – peripheral T-cell lymphoma, SS – Sézary syndrome, TCL – T-cell lymphoma, T-LGLL – T-large granular lymphocytic leukemia, T-PLL – T-prolymphocytic leukemia, TFH – T follicular helper.

members of the TCR signaling pathway (Vallois et al., 2016; Maria Pamela et al., 2017; Lewis et al., 2020).

Intestinal T-cell lymphomas

Enteropathy-associated T-cell lymphoma (EATL) and monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL) are both rare and aggressive intestinal T-cell lymphomas with poor prognosis, high chemoresistance, and short overall survival. EATL is associated with refractory celiac disease and differs from MEITL at the level of immunophenotype and spectrum of genomic alterations (Mutzbauer et al., 2018; Veloza et al., 2022). In contrast, indolent T-cell lymphoma of the gastrointestinal tract has a protracted clinical course (Margolskee et al., 2013).

Hepatosplenic T-cell lymphomas

Patients with rare hepatosplenic T-cell lymphomas have a very bad prognosis with inevitable disease progression and lethal outcome. No standard of care is available to date. Typical symptoms include weakness, fever, and organomegaly and are frequently accompanied by cytogenetic abnormalities and associated cytopenias. Malignant cells usually harbor γδ TCR (Yabe et al., 2016).

Anaplastic large cell lymphomas

Systemic anaplastic large cell lymphomas (ALCLs, approximately 2 % of all lymphomas) can be divided into two subgroups based on the rearrangement and consequent expression of anaplastic lymphoma kinase (ALK). ALK is most frequently overexpressed due to translocation t(2;5)(p23;q35), leading to *NPM1-ALK* gene fusion (Pittaluga et al., 1997). ALK-positive ALCL usually affects young individuals and has favorable prognosis. ALK-negative ALCL is a more heterogeneous disease with emerging prognostically relevant genetic subtypes (Parrilla Castellar et al., 2014; Onaindia et al., 2019). ALK^+ as well as ALK^- ALCLs are morphologically variable; however, the so-called "hallmark cells" are usually present (Benharroch et al., 1998). By definition, all cases also express CD30 (Tsuyama et al., 2017; Iżykowska et al., 2020; Alaggio et al., 2022). A specific entity is breast implant-associated ALCL – usually a non-invasive neoplasm arising around breast implants (Di Napoli et al., 2019).

Peripheral T-cell lymphomas, not otherwise specified

The group of peripheral T-cell lymphoma, not otherwise specified (PTCL, NOS, 26 % of all PTCLs) has a significant molecular heterogeneity and is characterized by aggressive clinical behavior that is associated with poor prognosis. It remains a diagnosis *per exclusionem* despite multiple new molecular subtypes of T-cell-derived malignancies (Vose et al., 2008; Heavican et al., 2019).

Epstein-Barr virus-positive NK/T-cell lymphomas

Most cases of EBV^+ NK/T-cell lymphomas occur in Asia and Latin America, forming approximately 10 % of PTCLs (Vose et al., 2008; Haverkos et al., 2016). Extranodal NK/T-cell lymphoma (ENKTL) predominantly involves the upper aerodigestive tract and adjacent sites. The role of Epstein-Barr virus (EBV) infection in the pathogenesis of ENKTL is not completely understood (Haverkos et al., 2017). However, the serum viral DNA load is predictive of the patients' outcome – a detectable level of EBV-DNA reflects worse clinical stage, performance status, and survival (Suzuki et al., 2011). Nodal EBV^+ NK/T cell lymphoma is a novel and rare entity with a unique genetic background and dismal prognosis (Wai et al., 2022).

EBV^+ T- and NK-cell lymphoid proliferations and lymphomas of childhood

EBV^+ T- and NK-cell lymphoid proliferations and lymphomas of childhood include various (localized or systemic) forms of chronic active EBV disease and, e.g., EBV^+ T-cell lymphoma of childhood, all recently reviewed (Cohen et al., 2020).

Standard T-Cell Lymphoma Treatment Approaches

General T-cell lymphoma treatment approaches are overviewed in Fig. 2. There are multiple therapeutic approaches used in TCL treatment. Chemotherapy regimens are generally analogous to those commonly used in B-cell-derived lymphomas (e.g., CHOP, CHOEP, DA-EPOCH). Interestingly, it was reported that the cyclophosphamide, doxorubicin, and oxaliplatin combination could promote immunogenic cell death and (along with vincristine) increase MHC I expression and antigen presentation. This results in enhanced anti-tumor immunity (Chen and Emens, 2013; Neuwelt et al., 2020; Chen et al., 2022). Apart from standard chemotherapy, specific treatment adjustment is necessary in certain situations. For example, use of non-anthracycline regimens is required in ENKTL because of poor anthracycline tissue bioavailability (Yamaguchi et al., 1995, 2018; Yong et al., 2003; Lee et al., 2006; Jeong, 2020; Zain and Hanona, 2021). The use of autologous stem cell transplantation is being continuously discussed and could be recommended in disseminated chemo-sensitive TCLs (Nawa et al., 1999; Sasaki et al., 2000; Kouzaki et al., 2004; Fox et al., 2015; Yhim et al., 2015; Jeong, 2020). Allogeneic hematopoietic stem cell transplantation is the only potentially curative method for relapsed/refractory (R/R) TCLs. However, it is frequently difficult to achieve pre-transplantation complete remission (Murashige et al., 2005; Yamaguchi et al., 2018; Zain and Hanona, 2021). Radiotherapy (RT) is mainly used within the treatment of localized TCL forms,

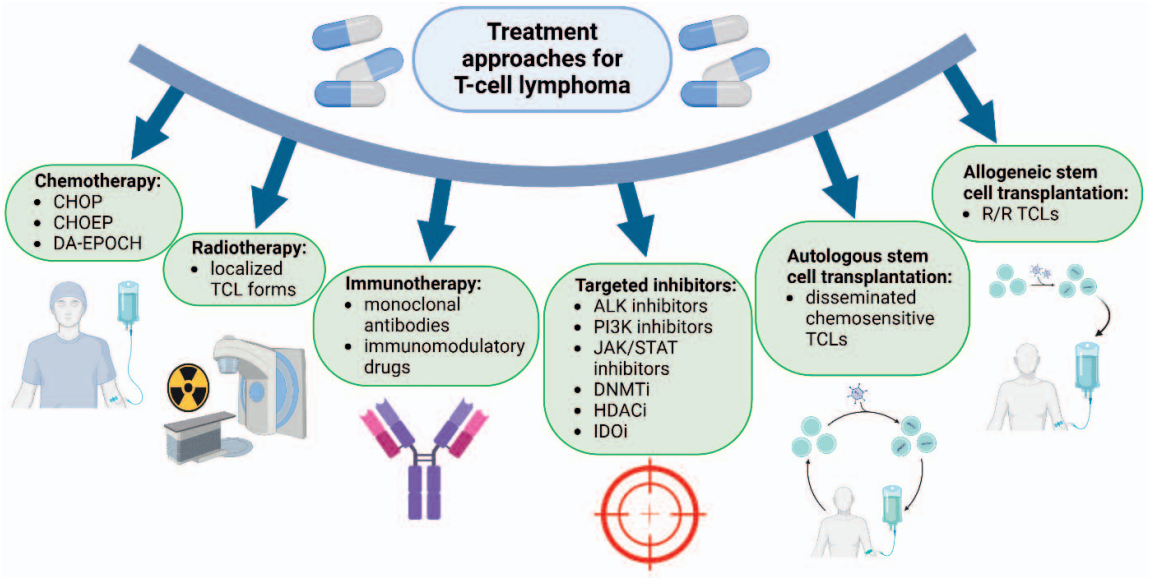

Fig. 2. Overview of T-cell lymphoma treatment approaches.
Abbreviations: ALK – anaplastic lymphoma kinase, CHOP – cyclophosphamide, doxorubicin, vincristine, prednisolone, CHOEP – cyclophosphamide, doxorubicin, vincristine, etoposide, prednisolone, DA-EPOCH – dose-adjusted etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin, DNMTi – DNA methyltransferase inhibitors, IDO1i – indoleamine 2,3- dioxygenase 1 inhibitors, HDACi – histone deacetylase inhibitors, JAK/STAT – Janus kinase/signal transducers and activators of transcription, PI3K – phosphoinositide 3-kinase, R/R – relapsed/refractory, TCL – T-cell lymphoma.

e.g., local forms of ENKTL nasal type (along with chemotherapy within a first-line treatment). However, RT use in TCL treatment is still being discussed (Kim et al., 2000; You et al., 2004; Jiang et al., 2012; Wang et al., 2013; Yamaguchi et al., 2018; Jeong, 2020). Standard TCL treatment strategies (including targeted inhibitors) were recently summarized in detail by Ghione et al. (2018).

Importantly, multiple additional targeted inhibitors are used or currently evaluated within clinical trials, specifically, ALK inhibitors (e.g., crizotinib, effective in ALK$^+$ ALCL), phosphoinositide 3-kinase (PI3K) inhibitors, JAK/STAT pathway inhibitors, DNA methyltransferase inhibitors (DNMTi), histone deacetylase inhibitors (HDACi), or indoleamine 2,3-dioxygenase 1 (IDO1) inhibitors (Fantin et al., 2008; Mossé et al., 2013, 2017; Prokoph et al., 2018; Torossian et al., 2019; Iżykowska et al., 2020; Zain and Hanona, 2021). Examples of currently evaluated inhibitors include HDACi vorinostat (effective in *STAT3*-mutated cases), belinostat, or romidepsin (more selective HDACi), and JAK kinase inhibitor ruxolitinib (Karube et al., 2013; Coiffier et al., 2014; O'Connor et al., 2015; McEachron et al., 2016; Yamaguchi et al., 2018; Iyer et al., 2019; Jeong, 2020; Zain and Hanona, 2021).

Immunotherapy of TCLs is mostly used within clinical trials and is mainly limited to monoclonal antibodies and immunomodulatory drugs (including checkpoint inhibitors that will be discussed in a separate section later). Alemtuzumab is an anti-CD52 monoclonal antibody that blocks T-cell activation and proliferation. It is used as a first-line therapy of T-PLL. Brentuximab vedotin (BV), an anti-CD30 monoclonal antibody covalently linked with microtubule toxin monomethyl auristatin E (widely used in Hodgkin lymphoma), is effective in several types of PTCL (ALCL, CTCL CD30$^+$) and used in combination with chemotherapy (Horwitz et al., 2014, 2019; Iżykowska et al., 2020; Neuwelt et al., 2020; Zain and Hanona, 2021; Chen et al., 2022). Mogamulizumab, an anti-CCR4 antibody, which activates cellular cytotoxicity, is used in relapsed ATLL and CTCL (Kim et al., 2018; Iżykowska et al., 2020; Zain and Hanona, 2021). Alemtuzumab, BV, and mogamulizumab were already approved for TCL treatment (Ghione et al., 2018; Iżykowska et al., 2020). Daratumumab, anti-CD38 antibody, showed a therapeutic effect in (R/R) ENKTL (Wang et al., 2015). Anti-CD25 and anti-CD47 antibodies are in clinical trials in PTCL and CTCL (Prince et al., 2010; Folkes et al., 2018; Ghione et al., 2018; Zain and Hanona, 2021). Other immunotherapy-based approaches include the use of interferon alpha (INF-α) in CTCL and ATLL (Hodson et al., 2011; Ghione et al., 2018; Zain and Hanona, 2021). Autologous cytotoxic T-lymphocytes (CTLs) targeted against latent membrane proteins (LMPs) were very effective in a clinical trial involving EBV-positive lymphomas. Almost all patients achieved long-term complete remission (Bollard et al., 2014; Jeong, 2020). CTLs were also used as a consolidation treatment following chemoradiotherapy in relapsed EBV$^+$ lymphomas, and additional clinical trials are ongoing (Ghione et al., 2018; Prockop et al., 2020; Wai et al., 2022).

Anti-Tumor Immune Response

The immune system has generally been accepted as a critical component of the anti-tumor defense system (Calì et al., 2017). Therefore, the idea of exploiting the host immune system for cancer treatment has been considered for a long time. However, only recent advances in our understanding of complex and dynamic interactions between the host immune system and tumor cells have permitted the development of successful immunotherapies that have revolutionized anti-cancer treatment. Identification of new druggable targets has allowed modulation and/or activation of the anti-tumor immune response (Waldman et al., 2020). Before proceeding to overview immunotherapeutic approaches in T-cell lymphomas (focusing on immune checkpoint inhibitors), we would like to briefly summarize the key aspects of anti-tumor immunity. We will focus specifically on the role of T cells (as the key players and regulators of the anti-tumor immune response), with a particular emphasis on immune checkpoints and tumor cell characteristics allowing them to evade the host immune response (Fig. 3).

For an effective anti-tumor immune response, tumor-released antigens need to be processed by antigen-presenting cells (APCs), with consequent priming and activation of T cells. Subsequently, the anti-tumor T cells must infiltrate the tumor and be locally activated. Antigen-specific effector T cells are then capable of eliminating the tumor cells. To be antigenic, tumor cells need to aberrantly express neoantigens (e.g., mutated proteins), proteins expressed only in immune privileged sites, or highly tissue-specific antigens. A critical step of the anti-tumor immune response occurs with the activation of naïve T lymphocytes via interaction of their T-cell receptor (TCR) with a specific major histocompatibility complex (MHC) on APCs (macrophages, dendritic cells, and B cells) (Toes et al., 1999; Lee et al., 2020). This interaction is accompanied by interaction of additional co-stimulatory receptors and ligands on the surface of APCs and T cells (Muenst et al., 2016).

TCR-tumor peptide/MHC interactions-mediated activation of naïve T cells promotes their differentiation into specific types of T cells, mainly $CD8^+$ cytotoxic T lymphocytes (CTLs) or $CD4^+$ T helper cells (Th cells).

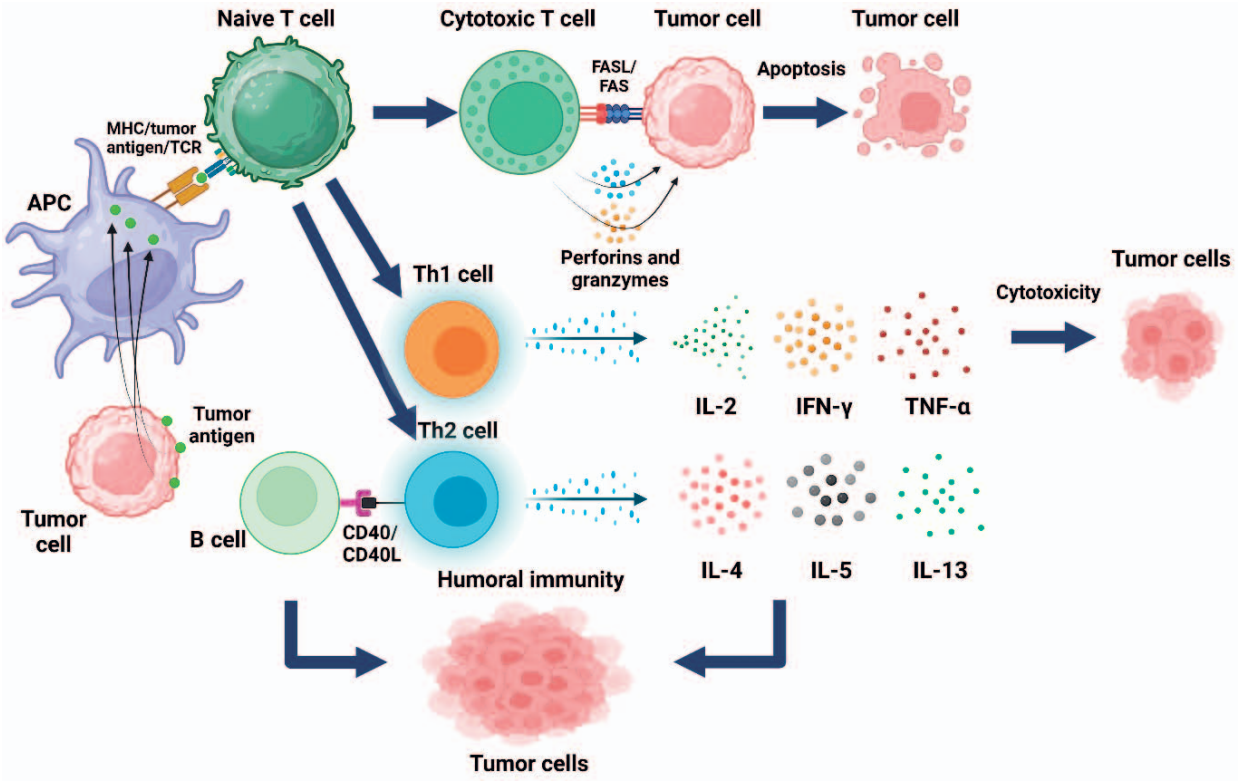

Fig. 3. T-cell-mediated anti-tumor immune response. Naïve T cells recognize antigens presented by an APC through the MHC in a TCR-dependent manner. This results in differentiation of T cells into cytotoxic T cells, Th1, or Th2 cells. Cytotoxic cells trigger tumor cell death via secretion of perforins and granzymes or by promoting Fas-mediated apoptosis. Th1 cells secrete cytokines that mediate destruction of tumor cells. Th2 cells recruit B cells and secrete cytokines that mediate humoral anti-tumor immunity.

Abbreviations: APC – antigen-presenting cell, INF-γ – interferon gamma, IL – interleukin, MHC – major histocompatibility complex, TCR – T-cell receptor, TNF-α – tumor necrosis factor alpha, Th1 cell – type 1 helper cell, Th2 cell – type 2 helper cell.

Importantly, CTLs could directly elicit their anti-tumor activity through granzyme/perforin pathway-associated cytotoxicity or Fas protein/Fas ligand (Fas/FasL)-mediated apoptosis (Zhang and Bevan, 2011; Hay and Slansky, 2022; Zöphel et al., 2022). Since CTLs are considered among the most effective mediators of anti-tumor immunity, they are well suited for immunotherapeutic intervention (Farhood et al., 2019; Raskov et al., 2021).

In addition to CTLs, $CD4^+$ T cells also contribute to anti-tumor immunity (Kravtsov et al., 2022). Th cells can further differentiate into multiple subsets (including Th1, Th2, Th17, Th9, Treg, and Tfh). This differentiation is tightly regulated and controlled by the diverse landscape of cytokines, available co-stimulatory molecules, and antigen presentation (Basu et al., 2021). Additionally, individual subsets of Th cells can shape the anti-tumor immunity in different ways (Silva et al., 2023).

Th1 and Th2 classes of $CD4^+$ T cells are the best-characterized and predominant Th subgroups with distinct functions. Th1 cells contribute to the anti-tumor immunity in a complex manner. By producing interleukin 2 (IL-2), interferon gamma (INF-γ), and tumor necrosis factor alpha (TNF-α), Th1 cells reinforce the tumor-suppressing activity of CTLs and NK cells and contribute to upregulation of MHC expression on APCs (Zhang et al., 2014; Lee et al., 2021).

In contrast, the role of Th2 cells within anti-tumor immunity is less straightforward. Th2 cells secrete cytokines such as IL-4, IL-5, and IL-13, which modulate the humoral immune response (Junttila, 2018; Kokubo et al., 2022; Silva et al., 2023). Importantly, Th2 cells promote the anti-tumor activity of macrophages and eosinophils (Jacenik et al., 2023). Th2 cells also express the CD40 ligand (CD40L). CD40L can consequently bind to CD40 expressed on the cell surface of B cells, promoting B-cell activation and supporting the complex anti-tumor immune response (Chatzigeorgiou et al., 2009). On the other hand, Th2 cell-produced cytokines (such as IL-17) might promote tumorigenesis by their proangiogenic effects and negative regulation of cell-mediated anti-tumor response (Basu et al., 2021).

Immune Checkpoint Signaling and Its Deregulation in T-Cell-Derived Malignancies

During the tumor development and progression, the above-described powerful anti-tumor immune response is counteracted by the "immune evasion" process. Constant anti-tumor selection pressure leads to evolution of various mechanisms and/or tumor cell characteristics to evade the host immune system detection and reaction. These might include loss of antigenicity, immunosuppressive tumor microenvironment (TME), or overexpression of immune checkpoint molecules (Beatty and Gladney, 2015; Kim and Cho, 2022). Immunosuppressive TME, which is frequently mediated by regulatory T cells (Tregs) and tumor-associated macrophages (TAMs), is associated with T-cell anergy, suppression of T- and B-cell activation, impairment of antigen presentation process, or microenvironment matrix remodeling (Fig. 4) (Battaglia et al., 2006; Kondelkova et al., 2010; Muenst et al., 2016; Bennani and Ansell, 2019; Ohue and Nishikawa, 2019).

Upregulation of immune checkpoint molecules is a very important mechanism of immune evasion (Drake et al., 2006). These ligand-receptor pairs are powerful inhibitors of immune response (Jutz et al., 2017; Zhang and Zheng, 2020). Programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) are the two most well-known and characterized immune checkpoint molecules expressed on multiple types of immune cells. Their widespread expression determines their strong capability of immune response regulation (Buchbinder and Desai, 2016). The overview of immune checkpoint signaling is provided in Fig. 5. Multiple studies have also identified deregulation of immune checkpoint molecules in T-cell-derived malignancies, which might be an integral part of TCL development.

PD-1 – PD-L1/PD-L2 signaling

The PD-1 receptor is expressed by almost all types of immune cells including activated T and B cells. It binds programmed death ligand 1 (PD-L1) and programmed death ligand 2 (PD-L2). PD-L1 is mainly expressed by B and T lymphocytes, dendritic cells, macrophages, as well as by certain non-immune system tissues (e.g., pulmonary, hepatic, or splenic cells). PD-L2 expression is limited to a few distinct subtypes of dendritic cells and macrophages (Keir et al., 2008; Jiang et al., 2019).

PD-1/PD-L1 or PD-L2 interaction triggers phosphorylation of intracellular PD-1 immunoreceptor tyrosine-based switch motif (ITSM) and immunoreceptor tyrosine-based inhibitory motif (ITIM) and leads to recruitment of phosphatases such as Src homology region 2 domain-containing phosphatase-2 (SHP2), opposing the effect of TCR and CD28 activation signals (Menter and Tzankov, 2018; Sharpe and Pauken, 2018). Downstream signaling consequences include inhibition of phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) and Ras/ERK signaling pathways, inhibition of TCR-mediated signal, inactivation of nuclear factor kappa-light-chain-enhancer of activated B-cells (NF-κB) and activator protein 1 (AP1) signaling pathways, and reduction of CD28 signaling (Sheppard et al., 2004; Sharpe and Pauken, 2018; Antonangeli et al., 2020). Generally, PD-1 activation leads to decreased T-cell activation and reduction of immune cell survival, proliferation, and production of cytokines (Sharpe and Pauken, 2018).

Physiologically, PD-1/PD-L1 or PD-L2 interactions help to maintain the equilibrium between activated and deactivated T cells (Shi et al., 2013). On the other hand, as mentioned above, PD-L1/2 overexpression in tumor cells supports T-cell exhaustion and immunosuppression (Querfeld et al., 2018). Moreover, it has been reported that the PD-L1 overexpression also suppresses

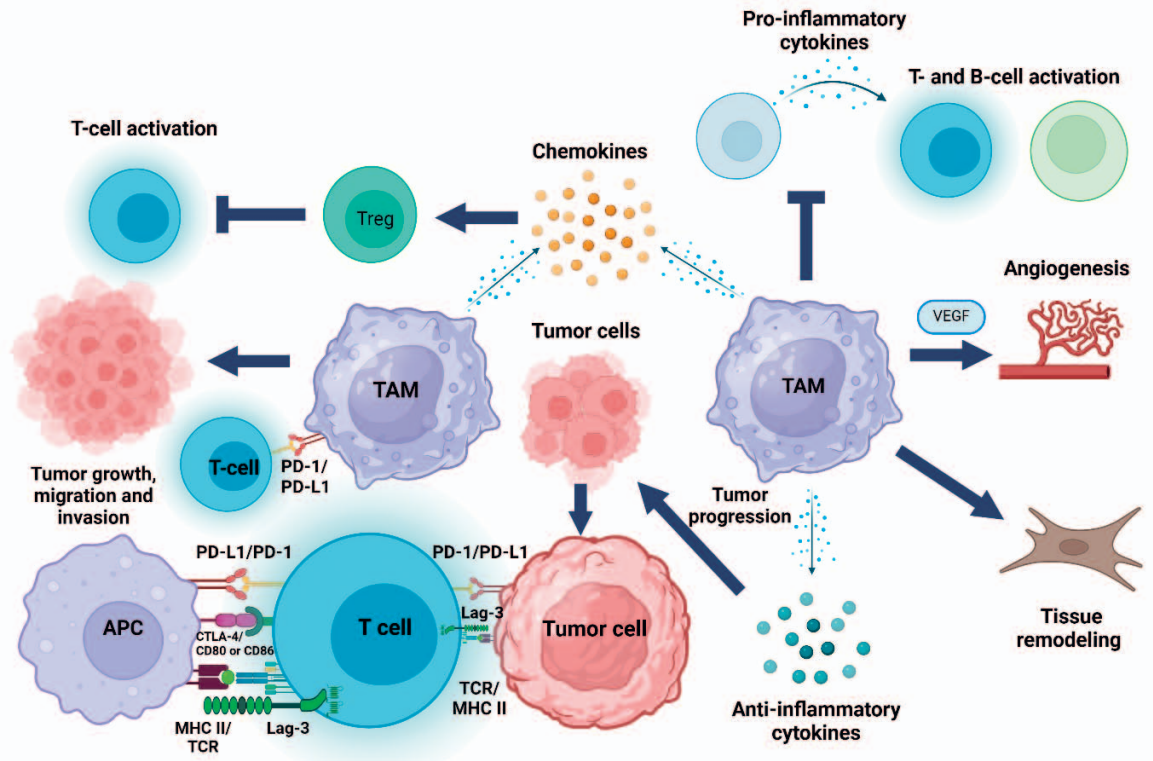

Fig. 4. Immunosuppressive tumor microenvironment and immune checkpoints. Immunosuppressive effects of tumor-associated macrophages (TAMs) are mediated by promoting angiogenesis, triggering tissue remodeling, preventing release of pro-inflammatory cytokines that activate B and T cells, secreting anti-inflammatory cytokines, and via chemokine-mediated activation of Treg cells. Additionally, immunosuppression is mediated by immune checkpoints, including PD-1/PD-L1, CTLA-4 and LAG-3 pathways.
Abbreviations: APC – antigen-presenting cell, CTLA-4 – cytotoxic T-lymphocyte-associated protein 4, Lag-3 – lymphocyte-activation gene 3, MHC II – major histocompatibility complex class II, PD-1 – programmed cell death protein 1, PD-L1 – programmed death ligand 1, TAM – tumor-associated macrophage, TCR – T-cell receptor, VEGF – vascular endothelium growth factor.

anti-tumor immunity by blocking antibody-dependent cellular phagocytosis (ADCP) executed by macrophages (Su et al., 2018). Studies of PD1 and PD-L1/PD-L2 deregulation in T-cell-derived malignancies are summarized below and overviewed in Table 1.

PD-1 in T-cell lymphoma

PD-1, a membrane receptor expressed on activated T cells, inhibits the immune response in peripheral tissues and promotes self-tolerance. It could be detected in the majority of T-follicular helper cell lymphomas, but also in PTCL-NOS, ALCL, diffuse large B-cell lymphoma (DLBCL), Hodgkin lymphoma, or follicular lymphoma (Krishnan et al., 2010; Neuwelt et al., 2020; Chen et al., 2022).

T-cell lymphomas frequently harbor deletions involving the genomic locus of PD-1-encoding gene *PDCD1*. In consequence, this deletion supports proliferation of malignant T cells. Notably, the highest frequency of *PDCD1* deletions was detected in advanced stages of CTCL (Wartewig et al., 2017). Interestingly, it was shown that EBV-positive lymphomas have higher PD-1 surface expression, leading to evasion from the immune response (Neuwelt et al., 2020; Hatic et al., 2021; Chen et al., 2022). In ENKTL, tumor cell expression of PD-1 is very low but relatively frequent in TME cells (up to 36 % of cases) (Jo et al., 2017; Nagato et al., 2017). In ATLL tumor cells, PD-1 is expressed in about 20 % of cases (Kozako et al., 2009). In SS, malignant cells express PD-1 in over ¾ of cases (Decroos et al., 2021). This confirms the findings of Saulite et al. (2020) reporting that PD-1 expression is much stronger in tumor cells in comparison to non-tumor $CD4^+$ T cells.

PD-1 could have diagnostic significance, e.g., tumor cell-associated PD-1 expression is higher in SS than MF (Cetinözman et al., 2012). PD-1 was also evaluated as an important biomarker. PD-1-positive peripheral blood mononuclear cells (PBMCs) in PTCL were characterized by abnormal expression of innate immunity genes, overexpression of CTLA-4, downregulation of INF-γ, and cytotoxicity defects (Zhang et al., 2019; Chen et al., 2022). In CTCL, skin lesion-derived tumor-infiltrating

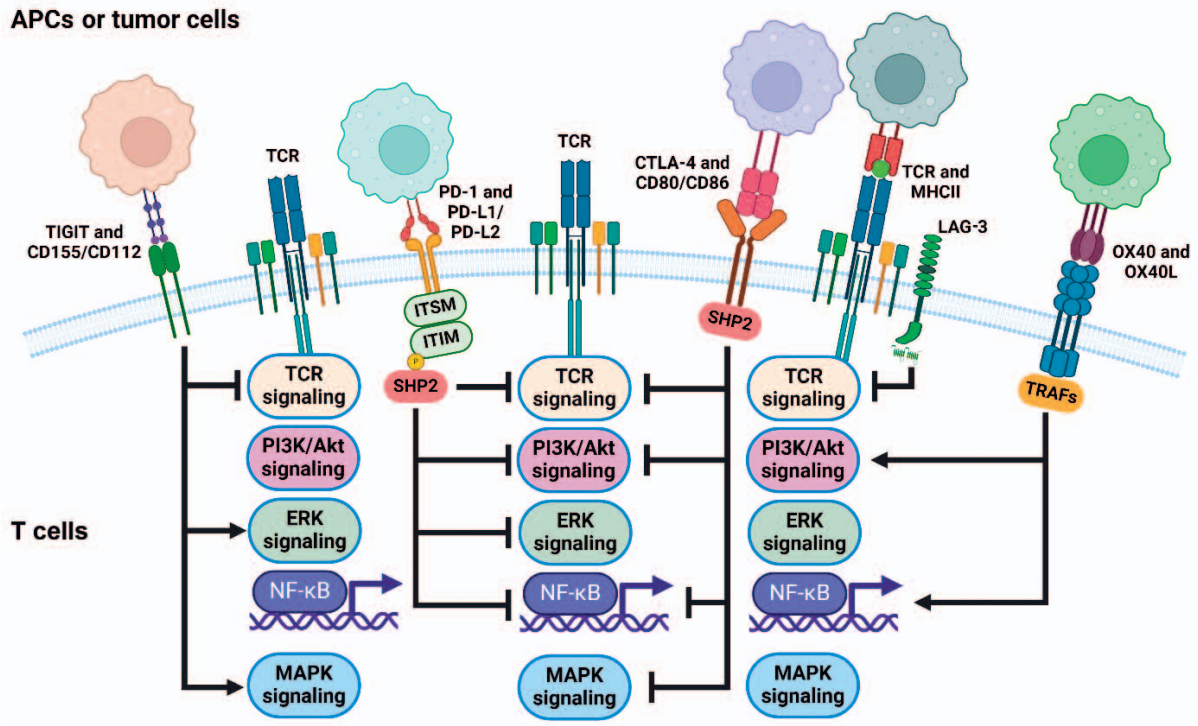

Fig. 5. Overview of T-cell intracellular signaling related to immune checkpoint molecules. PD-1/PD-L1(PD-L2), CTLA-4/CD86(CD80), TIGIT/CD155(CD112) and LAG-3 intracellular signaling transduction inhibits TCR signaling. Furthermore, PD-1/PD-L1(PD-L2), CTLA-4/CD86(CD80), TIGIT/CD155(CD112), LAG-3, and OX40/OX40L signaling modulates downstream survival- and activation-regulating PI3K/AKT, MAPK, ERK, and NF-κB pathways maintaining the balance between activated and non-activated T cells. Inhibitory (PD-1/PD-L1(PD-L2), CTLA-4/CD86(CD80), TIGIT/CD155(CD112) and LAG-3 pathways) and stimulatory (OX40/OX40L pathway) immune checkpoint molecules fine-tune the immune response, which makes them a promising target for pharmacological interventions in cancer.
Abbreviations: AKT – protein kinase B, APC – antigen-presenting cell, CTLA-4 – cytotoxic T-lymphocyte-associated protein 4, ERK – extracellular signal-regulated kinase, ITIM – immunoreceptor tyrosine-based inhibitory motif, ITSM – immunoreceptor tyrosine-based switch motif, LAG-3 – lymphocyte-activation gene 3, MAPK – mitogen-activated protein kinase, MHC II – major histocompatibility complex class II, NF-κB – nuclear factor kappa-light-chain-enhancer of activated B-cells, PD-1 – programmed cell death protein 1, PD-L1 – programmed death ligand 1, PI3K – phosphoinositide 3-kinase, SHP2 – Src homology 2 domain-containing protein tyrosine phosphatase, TCR – T-cell receptor, TIGIT – T-cell immunoreceptor with Ig and ITIM domains, TRAFs – tumor necrosis factor receptor-associated factors.

T cells have higher expression of PD-1 (and other immune checkpoint molecules) in comparison to controls. This difference was further enhanced in advanced stage disease and associated with activated T-cell exhaustion (Querfeld et al., 2018; Neuwelt et al., 2020).

Taken together, PD-1 expression on tumor cells and tumor-infiltrating immune cells is highly variable and depends on the type of T-cell malignancy. More studies are needed to exactly define its role in tumor development or its usability as a biomarker.

PD-L1 in T-cell lymphoma

PD-L1 interacts with PD-1 to downregulate the adaptive anti-tumor immunity (Doroshow et al., 2021). PD-L1 can be upregulated by INF-γ (Kataoka et al., 2015; Takeuchi et al., 2021) and JAK/STAT signaling (Tabanelli et al., 2019; Chen et al., 2022), and its expression, along with PD-L2, can be increased by viral infection (Cao et al., 2019; Neuwelt et al., 2020). In tumor cells, overexpression of PD-L1 is one of the frequent mechanisms of immune evasion. Similarly to PD-1, PD-L1 expression and its levels are extremely variable in T-cell-derived tumors. Chen et al. (2013) showed that two thirds of ENKTL cases were associated with significant expression of PD-L1 in tumor cells. These data are supported by Panjwani et al. (2018), who demonstrated PD-L1 expression in 39 % of ENKTL-NT cases in malignant cells, as well as in the TME (19 %). In other ENKTL studies, PD-L1 expression was observed even more frequently (in approximately 80 %) in both malignant and tumor-infiltrating cells (Jo et al., 2017). In ENKTL, the serum levels of PD-L1 and its expression in tumor tissues are generally considered a marker of shorter progression-free survival (PFS), overall sur-

Table 1. Deregulation of PD-1 and PD-L1/PD-L2 in T-cell-derived malignancies

Tumor type	Finding	Reference
T-lymphoblastic lymphoma/leukemia	No expression of PD-L1 and PD-L2 in tumor or TME cells	(Panjwani et al., 2018)
ATLL	PD-L1 expression in TME stromal cells is a prognostic marker (good prognosis) PD-L1 expression in tumor cells is a marker of poor prognosis	(Miyoshi et al., 2016)
ATLL	PD-1 is expressed in tumor cells in 20 % of cases	(Kozako et al., 2009)
CTCL	Frequent mutations of *PDCD1* in tumor cells	(Wartewig et al., 2017)
MF and SS	Higher PD-1 expression in malignant T cells in SS than MF	(Cetinözman et al., 2012)
SS	High PD-1 expression in blood $CD4^+$ T cells Lower PD-L1 expression in blood $CD4^+$ T cells compared with healthy individuals Low PD-L2 expression in blood $CD4^+$ T cells; T lymphocytes in the affected skin express PD-1 excessively, PD-L1 slightly, and do not express PD-L2	(Saulite et al., 2020)
SS	PD-1 expression in tumor tissue in 76 % of cases PD-L1 expression is observed in all cases both in tumor and TME cells	(Decroos et al., 2021)
AITL	PD-L1 and PD-L2 are expressed in malignant and TME cells in the same proportion of cases (80 % and 5 %, respectively)	(Panjwani et al., 2018)
PTCL	High PD-L1 expression in tumor tissue, suggested as a prognostic marker	(Zhao et al., 2019)
PTCL-NOS	PD-L1 is expressed in tumor and TME cells (26 % and 9 %, respectively) PD-L2 expression in malignant cells is not frequent (2 %) No PD-L2 expression in the TME	(Panjwani et al., 2018)
ENKTL	PD-L1 expression in tumor cells in 67 % of cases	(Chen et al., 2013)
ENKTL	Elevated sPD-L1 is a marker of early relapse and poor prognosis	(Wang et al., 2016)
ENKTL	PD-L1 expression in tumor and TME cells in about 80 % of cases PD-1 expression in malignant and TME cells in 1.2 % and 11.4 % of cases, respectively	(Jo et al., 2017)
ENKTL	PD-L1 expression in tumor cells and TIMs PD-1 expression in mononuclear cells in 36 % of cases, high sPD-L1 serum levels	(Nagato et al., 2017)
ENKTL	PD-L1 is expressed in tumor and TME cells in 39 % and 19 % of cases, respectively PD-L2 is not expressed in malignant or TME cells	(Panjwani et al., 2018)

Abbreviations: AITL – angioimmunoblastic T-cell lymphoma, ATLL – adult T-cell leukemia, CTCL – cutaneous T-cell lymphoma, ENKTL – extranodal NK/T-cell lymphoma, nasal type, MF – mycosis fungoides, PD-1– programmed cell death protein 1, PD-L1 – programmed death ligand 1, PTCL – peripheral T-cell lymphoma, PTCL-NOS – peripheral T-cell lymphoma, not otherwise specified, sPD-L1 – soluble programmed death ligand 1, SS – Sézary syndrome, TIM – tumor-infiltrating macrophage, TME – tumor microenvironment.

vival (OS), and disease progression or early relapse (Yamaguchi et al., 2018; He et al., 2021). Elevated circulating concentrations of sPD-L1 observed in ENKTL are considered predictive biomarkers of early relapse and unfavorable outcome (Wang et al., 2016; Nagato et al., 2017). On the other hand, PD-L1 expression in both malignant and non-malignant cells in ENKTL was linked to better prognosis (Kim et al., 2016). Links between the level of PD-L1 expression in ENKTL and the favorable clinical outcomes have been confirmed in a recently published meta-analysis (Li et al., 2023).

Furthermore, in PTCL-NOS, PD-L1 is expressed in tumor cells in 26 % of cases, while its expression in TME is detectable only in 9 % of cases (Panjwani et al., 2018). Similar expression of PD-L1 was found in tumor and TME cells (in 80 % of cases for both) in AITL (Panjwani et al., 2018). At the same time, neither malignant nor TME cells express this protein in T-lymphoblastic lymphoma/leukemia (Panjwani et al., 2018). In contrast to T-lymphoblastic lymphoma/leukemia, PD-L1 expression is omnipresent in malignant and TME cells in SS (Decroos et al., 2021). Conversely, lower PD-L1 expression in blood $CD4^+$ T cells is detected in SS patients in comparison to healthy individuals (Saulite et al., 2020). PD-L1 was highly expressed in ALCL cell lines in comparison to its low expression in T-ALL cell lines. Furthermore, no PD-L1 expression was found in SS cell lines (Andorsky et al., 2011). PD-L1 and PD-1 expression was also reported in both types of ALCL (ALK^+ and ALK^-) and was linked to STAT3 activation. Frequent PD-L1 overexpression and its copy number variants were detected in breast-implant-associated ALCL (Tabanelli et al., 2019).

Additionally, PD-L1 is expressed in PTCL and CTCL mainly on cellular components of the TME. PD-L1 expression in tumor and TME cells was suggested as a prognostic marker in PTCL and ATLL. PD-L1 expression on tumor cells was a poor prognostic marker. In contrast, PD-L1 positivity of tumor-infiltrating cells was a positive prognostic marker (Miyoshi et al., 2016; Zhao et al., 2019). Expression of PD-L1 on stromal cells in ATLL is associated with better prognosis. However, its expression on malignant ATLL cells is linked with unfavorable outcome (Miyoshi et al., 2016).

PD-L2 in T-cell lymphoma

PD-L2 has higher affinity to PD-1 than PD-L1 but has lower and largely unpredictable expression in T-cell-derived malignancies. Its expression is more frequently reported in B-cell lymphomas (Gu et al., 2021). Moreover, PD-L2 was much less studied in T-cell malignancies compared to PD-1/PD-L1. No PD-L2 expression was reported for T-lymphoblastic lymphoma/leukemia (Panjwani et al., 2018) or malignant and TME cells in ENKTL-NT (Panjwani et al., 2018). Low frequency of PD-L2 expression was found in PTCL-NOS tumor cells (2 % of cases) as well as in malignant and TME cells in AITL (5 % of cases) (Panjwani et al., 2018). Likewise, only very low expression of PD-L2 was reported in circulating $CD4^+$ T cells and skin lesion-associated T lymphocytes in SS (Saulite et al., 2020).

CTLA-4

Another inhibitory receptor expressed on the surface of T cells is CTLA-4. It is a CD28 homolog that binds CD80 and CD86 ligands with even higher affinity than CD28 (Chen and Flies, 2013). CTLA-4 binding to CD80/CD86 (located on the surface of APCs) inhibits TCR signaling in an SH2-containing 5'-inositol phosphatase 2 (SHIP2)-dependent manner and downregulates PI3K/AKT signaling cascade activation (Hossen et al., 2023). Furthermore, CTLA-4 activation is capable to inhibit NF-κB and MAPK pathways (Harlin et al., 2002; Chikuma, 2017). Following T-cell activation, CD28 is usually downregulated and replaced by CTLA-4 or inducible co-stimulator (ICOS). CTLA-4 and ICOS have functionally distinct and opposite effects on the T-cell response – negative regulation by CTLA-4 and positive regulation by ICOS (Rudd and Schneider, 2003). Within the normal immune response, CTLA-4 activation protects T cells from indefinite activation and exhaustion (Rowshanravan et al., 2018). The CTLA-4 pathway maintains the balance between survival, proliferation, and apoptosis of T cells. It helps to suppress the activity of effector T cells and, at the same time, to enhance the immunomodulatory function of Tregs, both reducing the immune response (Kim and Cho, 2022; Hossen et al., 2023). Studies of CTLA-4 deregulation in T-cell-derived malignancies are summarized below and overviewed in Table 2.

CTLA-4 in T-cell lymphoma

The highest constitutive CTLA-4 expression can be detected in Tregs, but its expression can also be found at conventional T cells (Walker and Sansom, 2015).

Multiple studies have demonstrated excessive expression of CTLA-4 in various types of lymphoma (Oyewole-Said et al., 2020; Chen et al., 2021). In ATLL, tumor cell overexpression of CTLA-4 was found in 15 % of cases (Shimauchi et al., 2008). In T-large granular lymphocytic leukemia (T-LGLL), CTLA-4 expression in $CD8^+$ cells is linked to their reduced inducibility (Wlodarski et al., 2004). Overexpression and the highest expression of CTLA-4 in tumor cells was shown for MF and SS (Wong et al., 2006). Additionally, transcriptomic analysis revealed CTLA-4 overexpression in CD30-positive transformed MF (Lai et al., 2023), and the CTLA-4 expression level positively correlated with the disease stage (Wong et al., 2006; Menter and Tzankov, 2018; Neuwelt et al., 2020). Notably, CTLA-4 upregulation in SS malignant T cells was associated with impaired proteasome function and consequent GATA binding protein 3 (GATA3) activation (Gibson et al., 2013). In ALCL, the *CTLA4* gene is frequently hypermethylated and hence downregulated (Hassler et al., 2016).

Yoo et al. (2016) reported recurrent *CTLA4*:*CD28* translocations in TCLs with the highest frequency in T-follicular helper cell lymphomas, including AITL. The resulting CTLA-4:CD28 fusion protein triggers T-cell activation, proliferation, and consequently higher levels of IL-2. The oncogenic effect of C-terminal do-

Table 2. Deregulation of CTLA-4 in T-cell-derived malignancies

Tumor type	Finding	Reference
ATLL	CTLA-4 is expressed in tumor cells and has negative prognostic significance	(Onishi et al., 2022)
ATLL	CTLA-4 is overexpressed in tumor cells in 15 % of cases	(Shimauchi et al., 2008)
SS	CTLA-4 is upregulated in tumor cells	(Gibson et al., 2013)
MF	CTLA-4 is overexpressed in tumor cells	(Wong et al., 2006)
CD30-positive transformed MF	CTLA-4 is upregulated in tumor cells	(Lai et al., 2023)
ALCL	*CTLA4* gene hypermethylation and repression	(Hassler et al., 2016)

Abbreviations: AITL – angioimmunoblastic T-cell lymphoma, ALCL – anaplastic large cell lymphoma, ATLL – adult T-cell leukemia/lymphoma, CTLA-4 – cytotoxic T-lymphocyte-associated protein 4, MF – mycosis fungoides, SS – Sézary syndrome.

main of CD28 fusion with the N-terminal domain of CTLA-4 was documented in many T-cell lymphomas (Takeuchi et al., 2021).

CTLA-4 expression seems to be an adverse prognostic factor in ATLL (Onishi et al., 2022), the same as in SS. On the other hand, it opens options for its therapeutic utilization (Sadeghi et al., 2022). CTLA-4 could potentially diagnostically discriminate cutaneous ALCL from CD30-positive transformed MF and MF in general (Wong et al., 2006; Lai et al., 2023).

The CTLA-4 expression pattern in malignant T cells and TME of T-cell lymphomas is still poorly understood; however, there are strong indications for its potential diagnostic, prognostic, and therapeutic utilization.

Other immune checkpoint molecules

Other immune checkpoint molecules, including lymphocyte-activation gene 3 (LAG-3), T-cell immunoglobulin and mucin domain-containing protein 3 (TIM-3), T-cell immunoreceptor with Ig and ITIM domains (TIGIT), or OX40/OX40L, are much less studied.

LAG-3 is expressed mainly by T cells, NK cells, B cells, and dendritic cells. It co-localizes with CD3, CD4 and CD8 and is recognized as an inhibitor of T-cell function (including $CD4^+$ Tregs and anergic $CD8^+$ T cells) (Huo et al., 2022). Its high expression levels are associated with T-cell exhaustion (He et al., 2016). Activated LAG-3 signaling shows functional synergy with the PD-1/PD-L1 signaling pathway. It enhances expression of PD-1 receptor, which further reduces activation of T cells (Long et al., 2018).

TIM-3 has been suggested as another immune checkpoint molecule that decreases T-cell activity. It is expressed on T lymphocytes (both $CD4^+$ and $CD8^+$), macrophages, and dendritic cells (Sakuishi et al., 2010; Sauer et al., 2023). Interaction of TIM-3 with galectin-9 on the surface of tumor cells triggers cell death of effector T cells; therefore, it reduces the anti-tumor immune response (Takeuchi et al., 2021).

TIGIT is mostly expressed on effector T cells and NK cells. Its immunosuppressive effect is triggered by CD155 and CD112 ligands (Yu et al., 2009). TIGIT and its co-stimulatory analog CD226 share a similar structure, which makes their relationship comparable to the relationship between CTLA-4 and CD28 (Jutz et al., 2017; Manieri et al., 2017). The TIGIT interaction with CD155, which is expressed on dendritic cells, induces ERK phosphorylation and MAPK signaling pathway activation, with consequent modulation of IL-10 and IL-12 production (Yu et al., 2009). TIGIT can directly inhibit TCR-driven activation of T cells, restrain Th1 and Th17 cells, and potentiate Th2 cells (Joller et al., 2011, 2014).

OX40/OX40L belongs to the TNFR/TNF superfamily. OX40 is expressed on activated $CD4^+$ and $CD8^+$ T cells, as well as NK cells and Tregs (Fu et al., 2020). Following T-cell activation (by TCR-antigen stimulation), OX40 is expressed within 12–24 hours in resting T cells and as soon as in 4 hours in memory T cells. This enables memory T cells to perform much faster secondary immune response (Fu et al., 2020). Consequently, the OX40-OX40L interaction stimulates T-cell expansion, survival, and cytokine production. This process is further amplified by OX40-mediated inhibition of Tregs (Webb et al., 2016). Given their function, OX40/OX40L agonists could be potentially used to enhance the anti-tumor immune response. Studies of LAG-3, TIM-3, TIGIT, and OX40/OX40L immune checkpoint molecule deregulation in T-cell-derived malignancies are summarized below and overviewed in Table 3.

Other immune checkpoint molecules in T-cell lymphoma

LAG-3, TIM-3, TIGIT, or OX40/OX40L are much less studied in T-cell malignancies. However, determination of their expression levels or their deregulation might provide novel therapeutic avenues for the therapy of T-cell lymphomas.

Similarly to previously discussed immune checkpoint molecules, the expression of LAG-3 is highly variable. LAG-3 is expressed in tumor tissue in 95 % of ENKTL cases (Feng et al., 2018). On the other hand, reduced expression was found in clonal and non-clonal $CD4^+$ T cells in SS (Anzengruber et al., 2019). In PTCL, TME- and tumor cell-associated expression of LAG-3 is uncommon (Murga-Zamalloa et al., 2020). However, LAG-3 overexpression was detected in T cells in CTCL (Querfeld et al., 2018). Importantly, overexpression of LAG-3 can be associated with anti-PD-1 treatment resistance (Michot et al., 2021).

TIM-3 expression could be found in tumor tissue of over 90 % of ENKTLs. This high expression was even suggested as a negative prognostic factor (Feng et al., 2018). In ATLL, TIM-3 is expressed in over 40 % of cases, potentiates chemoresistance, and negatively affects anti-tumor immunity (Horlad et al., 2016). Moreover, TIM-3 expression was demonstrated in TME stromal cells in ATLL (Takeuchi et al., 2021). At the same time, it is not frequently detectable in PTCL (Murga-Zamalloa et al., 2020).

Scarce data are available on TIGIT expression and its contribution to the pathophysiology of T-cell malignancies. Huuhtanen et al. (2022) showed that the TIGIT overexpression was associated with T-cell exhaustion in T-LGLL. Other than that, TIGIT expression was assessed mainly in CTCL, particularly in SS, where it seems to be overexpressed in $CD4^+$ T cells (Jariwala et al., 2017) and tumor T cells (Anzengruber et al., 2019). Its upregulation was associated with tumor progression on treatment (Borcherding et al., 2023).

The OX40/OX40L pathway was implicated in pathogenesis of CTCL, namely MF and SS. In MF and SS, tumor cells frequently co-express OX40 and OX40L, which was suggested to support tumor cell proliferation (Kawana et al., 2021). Additionally, OX40 expression could also be found in malignant cells of ATLL. OX40 expression in ATLL was associated with excessive ad-

Table 3. Deregulation of less studied immune checkpoint molecules in T-cell-derived malignancies

Immune checkpoint molecule	Tumor type	Finding	Reference
LAG-3	CTCL	$CD4^+$ CTCL populations in the skin contain more LAG-3-positive T cells compared to healthy individuals	(Querfeld et al., 2018)
	SS	Reduced expression of LAG-3 in blood $CD4^+$ T cells and in clonal and non-clonal $CD4^+$ T cells	(Anzengruber et al., 2019)
	PTCL	LAG-3 is rarely detected in tumor cells and TME	(Murga-Zamalloa et al., 2020)
	ENKTL	LAG-3 is expressed in over 90 % of cases in tumor tissues	(Feng et al., 2018)
TIM-3	ATLL	TIM-3 is expressed in lymphoma cells in over 40 % of cases	(Horlad et al., 2016)
	ATLL	TIM-3 is expressed in stromal cells in TME	(Takeuchi et al., 2021)
	PTCL	TIM-3 is rarely detected in tumor cells and TME	(Murga-Zamalloa et al., 2020)
	ENKTL	TIM-3 is expressed in over 90 % of cases in tumor tissues	(Feng et al., 2018)
TIGIT	T-LGLL	TIGIT overexpression in tumor cells is associated with T-cell exhaustion	(Huuhtanen et al., 2022)
	SS	Higher percentage of TIGIT-expressing $CD4^+$ T cells in the skin	(Jariwala et al., 2017)
	SS	High TIGIT expression in clonal and non-clonal $CD4^+$ T cells	(Anzengruber et al., 2019)
	Treated SS	TIGIT upregulation in malignant T cells following treatment	(Borcherding et al., 2023)
OX40/OX40L	ATLL	OX40 expression in PBMCs and lymph node cells (among them, over 60 % of cells are tumor cells)	(Imura et al., 1997)
	MF and SS	Excessive expression of OX40 in lesional skin and tumor cells	(Kawana et al., 2021)
	LyP	OX40 strong expression in tumor tissues in 38 % of patients	(Gniadecki and Rossen, 2003)
	PTCL	OX40 expression in tumor tissues in 94 % of angioimmunoblastic lymphomas, 100 % of angiocentric lymphomas, and 48 % of large-cell lymphomas	(Jones et al., 1999)

Abbreviations: ATLL – adult T-cell leukemia/lymphoma, CTCL – primary cutaneous T-cell lymphoma, ENKTL – extranodal NK/T-cell lymphoma, LAG-3 – lymphocyte activation gene 3, LyP – lymphomatoid papulosis, MF – mycosis fungoides, PBMCs – peripheral blood mononuclear cells, PTCL – peripheral T-cell lymphoma, SS – Sézary syndrome, TIGIT – T-cell immunoreceptor with Ig and ITIM domains, TIM-3 – T-cell immunoglobulin and mucin domain-containing protein 3, T-LGLL – T-large granular lymphocytic leukemia, TME – tumor microenvironment.

hesion to endothelial cells, which suggests that OX40 might improve the capacity of malignant cells to infiltrate tissue (Imura et al., 1997). Furthermore, OX40 expression in tumor tissues has been reported in over one third of patients with LyP (Gniadecki and Rossen, 2003). Tumor tissue-associated OX40 expression could also be detected in most cases of PTCL (Jones et al., 1999).

Taken together, the expression of the majority of immune checkpoint molecules in TCL is highly variable. It is necessary to carefully define these expression patterns in tumor cells as well as in TME and to establish the role of immune checkpoint molecules within the pathogenesis of TCL. All this could help to identify biomarkers for appropriate therapeutic use of immune checkpoint inhibitors.

Immune Checkpoint Inhibitors in the Treatment of T-Cell Lymphomas

Immune checkpoint inhibitors (ICIs) are primarily monoclonal antibodies aimed to enhance the anti-tumor immune response by T-cell reactivation (Hatic et al., 2021). The most widely studied and commonly used ICIs are anti-PD-1 monoclonal antibodies (nivolumab, pembrolizumab, cemiplimab), anti-PD-L1 monoclonal antibodies (durvalumab, atezolizumab, avelumab), and anti-CTLA-4 monoclonal antibodies (ipilimumab) (Basudan, 2022). A schematic overview of the main checkpoint inhibitors is provided in Fig. 6.

The first cancer type where ICIs were tested successfully (and showed a good efficacy and response rates) was melanoma (Board et al., 2021; Pathak and Zito, 2024). It was for the first time that metastatic melanoma could have been cured by a non-surgical approach, which caused a paradigm shift in the treatment of melanoma. Based on that, ICIs are now well established within the metastatic melanoma first line of treatment (Michielin et al., 2019; Swetter et al., 2019; Pathak and Zito, 2024). Later, the efficacy of ICIs was documented in multiple other solid cancers within first-line therapy as well as after treatment failure, including renal, lung, ovarian, colorectal, gastroesophageal, urothelial, breast, and cervical cancers and selected hematological tumors (Hodgkin lymphoma and primary mediastinal B-cell

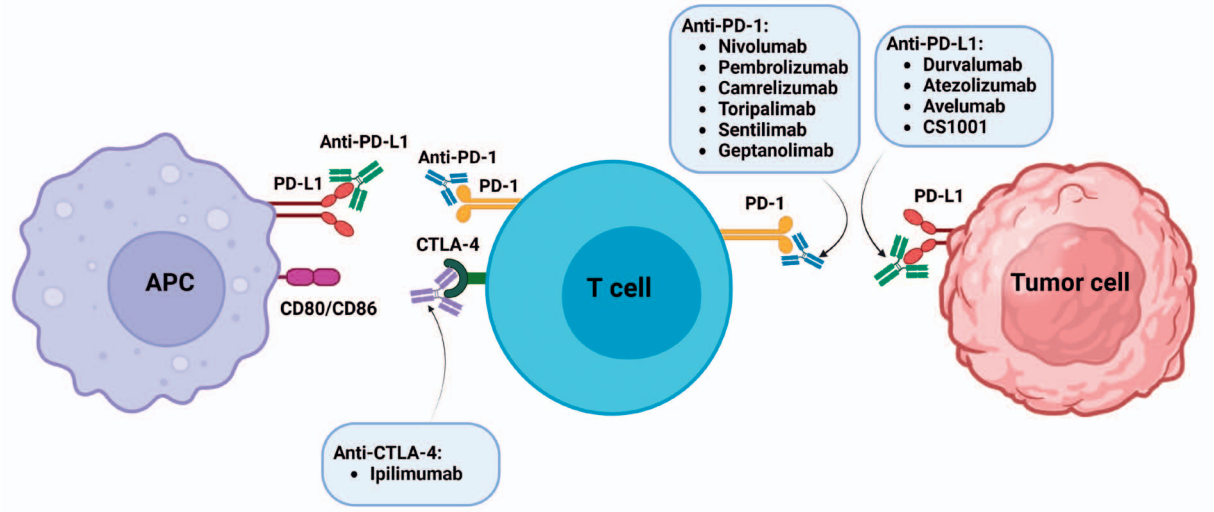

Fig. 6. The main immune checkpoint inhibitors. Several groups of immune checkpoint inhibitors, including anti-PD-1, anti-PD-L1, and anti-CTLA-4 antibodies, have been tested in T-cell malignancies.
Abbreviations: APC – antigen-presenting cell, CTLA-4 – cytotoxic T-lymphocyte-associated protein 4, PD-1 – programmed cell death protein 1, PD-L1 – programmed death ligand 1.

lymphoma) (Garon et al., 2015; Nanda et al., 2016; Garassino et al., 2018; Xu et al., 2018b; Chung et al., 2019; von Tresckow et al., 2019; Zinzani et al., 2019; Ferrara et al., 2020; Bajorin et al., 2021; Hatic et al., 2021; Basudan, 2022; Forde et al., 2022; Kaushik et al., 2022; Shitara et al., 2022). As a next step to further improve the treatment outcome, various ICI combinations and/or their combinations with chemotherapy are extensively studied in clinical trials. For example, the combination of anti-PD-1 with anti-CTLA-4 or anti-TIM-3 showed encouraging results in several solid cancers (including melanoma) and hematological tumors (Ribas and Wolchok, 2018; Sun et al., 2018; Curigliano et al., 2021). Clinical utilization of ICIs in solid cancers was recently extensively reviewed by Twomey and Zhang (2021).

On the other hand, a high proportion of patients do not respond to ICI treatment. Therefore, prediction of the treatment response is of utmost importance. It was shown that high tumor mutational burden (TMB, a total number of nonsynonymous mutations per tumor) is associated with a better chance of substantial treatment response. High TMB tumors produce a higher number of cancer-associated neo-antigens – the basis of immune cell-mediated tumor cell recognition. Clinical data support this hypothesis. ICIs showed very good treatment results in melanoma (a tumor type having generally one of the highest TMB) but low efficacy in acute lymphoblastic or chronic myeloid leukemias (both having generally very low TMB) (Knaus et al., 2017; Klempner et al., 2020; Matsushita, 2021). TMB is highly variable in TCLs. It largely depends on the subtype. The highest TMB could be detected in PTCL-NOS and TCLs with mutated *TP53* (Heavican et al., 2019).

Nivolumab (anti-PD-1) was the first checkpoint inhibitor approved for any hematological malignancy (Ghione et al., 2018). It is approved for relapsed Hodgkin lymphoma after autologous stem cell transplantation (Younes et al., 2016; Armand et al., 2018). Pembrolizumab, another humanized anti-PD-1 antibody, is approved for primary mediastinal B-cell lymphoma (Armand et al., 2019; Zinzani et al., 2019). Furthermore, its efficacy is evaluated in clinical trials for DLBCL (Smith et al., 2020). ICIs showed promising results also in other B-cell-derived tumors (including relapsed primary central nervous system lymphomas, chronic lymphocytic leukemia in Richter's transformation, or mantle cell lymphoma). However, their use might not be as straightforward as in solid cancers due to the immunological features of B-cell tumors. The use of ICIs in B-cell-derived malignancies was recently reviewed (Armengol et al., 2021). We will further focus only on ICI studies in TCLs.

Clinical trials with ICIs in the treatment of T-cell lymphomas are summarized for each immune checkpoint molecule below and overviewed in Table 4.

Anti-PD-1

Nivolumab, an anti-PD-1 antibody, was evaluated in different types of TCLs (for example, MF, CTCL, non-CTCL, and PTCL) in monotherapy or in combination with ipilimumab or chemotherapy. Various results were reported in MF and PTCL (Lesokhin et al., 2016; Bennani et al., 2019). However, a few accelerated progressions were observed, for example, in indolent ATLL (Ratner et al., 2018).

Pembrolizumab is another humanized anti-PD-1 antibody widely and successfully used in various cancers (Garon et al., 2015; Ribas et al., 2015). In CTCL, CITN-10

Table 4. Overview of clinical trials with checkpoint inhibitors in T-cell-derived malignancies

Immune checkpoint inhibitor	Tumor type	Finding	Reference
anti-PD-1			
Nivolumab	ATLL (indolent)	Low effectiveness, risk of progression	(Ratner et al., 2018)
	MF/PTCL	Moderate effectiveness: • 17 % PR • 43 % SD	(Lesokhin et al., 2016)
	PTCL (R/R)	Moderate effectiveness: • ORR 33 % (4/12, 2 × CR, 2 × PR) • PFS < 3 months • OS < 7 months	(Bennani et al., 2022)
Pembrolizumab	MF/SS (R/R)	High effectiveness and durable response: • ORR 38 % (9/24) • 2 × CR • 7 × PR • at 1 year: PFS 65 %, OS 95 %	(Khodadoust et al., 2020)
	PTCL	Consolidation after ASCT, promising effectivity: • at 18 months after ASCT • 13 of 21 treated patients were alive and achieved PFS	(Kwong et al., 2017; Merrill et al., 2023)
	PTCL (R/R)	Combination with romidepsin: • ORR 44 % • 3 × CR (PFS > 10 month) • 2 × PR	(Iyer et al., 2019)
	ENKTL	High effectiveness: • ORR 100 % (7/7)	(Kwong et al., 2017; Khodadoust et al., 2020)
	ENKTL	High effectiveness in combination with radiotherapy: • ORR 57.1 % • 2 × CR • 2 × PR • response duration, PFS, OS > 4 months	(Li et al., 2018)
Toripalimab	ENKTL (R/R)	High effectiveness in combination with chemotherapy: • ORR 3/3 • 2 × CR • 1 × PR	(Du et al., 2020)
Sintilimab	ENKTL (R/R)	High effectiveness and safety: • ORR 75 % (21/28) • CR 21.4 % • PR 53.6 % • 2-year OS 78.6 %	(Tao et al., 2019)
	ENKTL	Combination with P-GEMOX, in 9 patients: • 88.9 % ORR • 66.7 % of patients in CR at 10.6 months	(Cai et al., 2020a)
Geptanolimab	PTCL (R/R)	Good effectiveness: • ORR 40.4 % (36/89) • 13 × CR • 23 × PR multiple side effects – TRAE > 3 in 25.5 %, mostly hematological	(Shi et al., 2021)

trial for R/R MF and SS reported a good response rate (44 % overall response rate, ORR), although 50 % of patients reported transitionally exacerbated skin symptoms (Khodadoust et al., 2020). Another trial with pembrolizumab in combination therapy with romidepsin in R/R PTCL showed a response rate of 44 %, with three patients achieving complete remission lasting for more than 10 months (Iyer et al., 2019). Another currently evaluated combination includes pembrolizumab, pralatrexate (dihydrofolate reductase inhibitor), and decitabine (epigenetic modifier) in NCT03240211 clinical trial. Pembrolizumab combined with radiotherapy in older patients with ENKTL had a promising effect in case reports; some of them even achieved complete remission lasting for over two years (Klee et al., 2020). Pembrolizumab was also highly effective in a study on NK/T-cell lymphomas after L-asparaginase failure (Kwong et al., 2017) and showed a promising effect in PTCL after

Immune checkpoint inhibitor	Tumor type	Finding	Reference
anti-PD-L1			
Atezolizumab	relapsed CTCL	Moderate effectiveness: • ORR 15.4 % (4/26) • SD 38.5 % (N = 10) • PD 23.1 % (N = 6) • not evaluable 11.5 % • early death 11.5 %	(Stadler et al., 2021)
Avelumab	PTCL (R/R)	Low effectiveness: • 53 % (18/34) non-suitable for first restaging • 17.6 % PR • 20.6 % PD • 8.8 % SD	(Ahearne et al., 2020)
	ENKTL	PD-L1 expression-dependent treatment efficacy: • ORR 38 % (8/21) • CR 24 % (5/21) • treatment response correlated with blood EBV DNA decrease	(Kim et al., 2020)
Durvalumab	CTCL (R/R)	Effective in combination with lenalidomide: • 9/13 PR • 2/13 PD • 2/13 PD	(Querfeld et al., 2019)
CS1001	ENKTL (R/R)	Complete remission in 36 % of cases, ORR 44 %	(Huang et al., 2019)
anti-CTLA-4			
Ipilimumab	SS	Case reports, good clinical response	(Bar-Sela and Bergman, 2015; Sekulic et al., 2015)

Abbreviations: ASCT – autologous stem cell transplantation, ATLL – adult T-cell leukemia/lymphoma, CR – complete remission, CTCL – primary cutaneous T-cell lymphoma, CTLA-4 – cytotoxic T-lymphocyte-associated protein 4, EBV – Epstein-Barr virus, ENKTL – extranodal NK/T-cell lymphoma, MF – mycosis fungoides, ORR – overall response rate, OS – overall survival, PD – progressive disease, PD-1 – programmed cell death protein 1, PD-L1 – programmed death ligand 1, PFS – progression-free survival, P-GEMOX – pegaspargase, gemcitabine, oxaliplatin, PR – partial response, PTCL – peripheral T-cell lymphoma, R/R – relapsed/refractory, SD – stable disease, SS – Sézary syndrome, TRAE – treatment-related adverse event.

autologous stem cell transplantation (ASCT) (Merrill et al., 2023).

Several authors reported single cases of pembrolizumab or nivolumab treatment in R/R ALK$^+$ ALCL with high PD-1 expression (Hebart et al., 2016; Prokoph et al., 2018; Rigaud et al., 2018), which had a good effect with manageable adverse symptoms. All three patients were young adults with relapsed ALCL achieving a good response to PD-1 blockade.

Camrelizumab (humanized anti-PD-1 antibody) was already approved for Hodgkin lymphoma (Markham and Keam, 2019; Nie et al., 2019) and is currently under extensive evaluation in T-cell malignancies as monotherapy and in combination with apatinib – a selective vascular endothelial growth factor receptor 2 inhibitor (Liu et al., 2023). Moreover, camrelizumab, apatinib, pegaspargase, and radiotherapy combination is tested in stage IE/IIE of ENKTL treatment (NCT04366128) (Sun et al., 2022), and camrelizumab in combination with anti-CD30$^+$ CAR (chimeric antigen receptor) T cells is evaluated within phase II clinical trial in CD30$^+$ lymphomas (NCT05320081).

Toripalimab (humanized anti-PD-1 monoclonal antibody) was evaluated in combination with chemotherapy (chidamide, etoposide, thalidomide) in clinical trial in three R/R ENKTL patients (Du et al., 2020). All three patients responded, two of them were in durable complete remission, while one achieved partial remission. Several other studies for ENKTL with or without asparaginase are underway (e.g., NCT04365036).

Sintilimab (also a humanized anti-PD-1 antibody with a stronger affinity to PD-1 than nivolumab or pembrolizumab) has shown efficacy and safety in R/R ENKTL in the ORIENT-4 study (Tao et al., 2019). One case report of relapsed ENKTL described complete remission with the sintilimab and chidamide combination (Yan et al., 2020). Importantly, sintilimab was already approved for the treatment of R/R Hodgkin lymphoma in China (Shi et al., 2019). However, a related study reported a higher incidence of peri-engraftment respiratory distress syndrome in patients undergoing autologous stem cell transplantation with prior treatment by sintilimab than with other PD-1 inhibitors (Bai et al., 2021). In another prospective study of nine ENKTL patients, sintilimab showed promising results in combination with P-GEMOX (pegaspargase, gemcitabine, oxaliplatin); 88.9 % ORR with 66.7 % of patients in complete remission at 10.6 months (Cai et al., 2020a). These promising results led

to initiation of the follow-up NCT04127227 study for newly diagnosed ENKTL (Cai et al., 2020b).

Shi et al. (2021) showed in an open-label, phase II clinical trial that R/R PTCL patients with high expression of PD-L1 have a good response to geptanolimab (another humanized anti-PD-1 antibody) with 40.4 % ORR. Despite quite frequent adverse effects (mostly hematological), it could be considered safe and promising.

Anti-PD-1 therapy was also tested in combination with CAR T-cell therapy, but only in a mouse experimental model (Nguyen et al., 2023). It was documented that ICIs potentiate CAR T-cell expansion and have a synergistic effect (John et al., 2013a, b). There is a potential for synergic combinations of these immunotherapeutic approaches. For example, anti-CD5 CAR T cells showed promising therapeutic results in T-cell lymphomas (Hill et al., 2019, 2020).

Anti-PD-L1

Multiple anti-PD-L1 antibodies have been developed and are currently tested in clinical trials, including TCL studies (e.g., atezolizumab, avelumab, durvalumab, and CS1001).

Atezolizumab showed excellent effects in solid tumors (Herbst et al., 2020) and was evaluated in relapsed CTCL. However, it showed only moderate effectivity with 15.4 % ORR (Stadler et al., 2021).

Avelumab was evaluated in a phase II clinical trial in ENKTL and demonstrated PD-L1 expression-dependent treatment efficacy with 38 % ORR (Kim et al., 2020). The second study (AVAIL-T) reported a minimal effect of avelumab on the tumor size in R/R PTCL with more than 50 % of patients not reaching the first evaluation point (progression, death, withdrawal of consent); however, no hyperprogression was reported (Ahearne et al., 2020).

The safety of durvalumab in combination with lenalidomide was tested in advanced CTCL in a phase I study with promising results – 70 % of patients reached partial remission (Querfeld et al., 2019). Durvalumab is also being evaluated in PTCL and CTCL in the open-label, multi-arm DURABILITY trial with different combinations of epigenetic modifiers (pralatrexate, romidepsin, and 5-azacytidine).

CS1001 was tested in R/R ENKTL with 36 % of patients achieving durable complete remission (Huang et al., 2019).

Anti-CTLA-4 and other checkpoint inhibitors

Ipilimumab showed very promising responses in personalized treatment of TCL cases with oncogenic CTLA-4:CD28 fusion (Sekulic et al., 2015; Yoo et al., 2016). A case report of one patient with relapsed melanoma on ipilimumab treatment was published after he achieved complete remission of MF (Bar-Sela and Bergman, 2015). Other checkpoint inhibitors have not been evaluated in T-cell lymphomas so far. Ieramilimab (anti-LAG-3 antibody) in combination with spartalizumab (anti-PD-1) showed promising results and combined anti-tumor effect in advanced solid tumors (Schöffski et al., 2022). Vibostolimab, ASP8374, COM902, tiragolumab, etigilimab, and other anti-TIGIT antibodies were tested mainly in combination with anti-PD-1 or anti-PD-L1, and these combinations also improved treatment results in various advanced cancers (Hansen et al., 2021; Shirasuna et al., 2021; Mettu et al., 2022; Niu et al., 2022).

Generally, multiple studies showed a great promise that ICIs could potentially improve the treatment outcomes of patients with T-cell-derived malignancies. On the other hand, targeting these powerful immune-modulating molecules could be associated with severe adverse effects including secondary malignancy development. Further studies are needed to establish a biomarker-based treatment approach to pair the most promising ICIs with the appropriate clinical situation.

Safety Concerns Associated with Immune Checkpoint Inhibitors

Given the critical role of checkpoint molecules within the immune system and the potency of checkpoint inhibitors, many adverse effects are associated with their use, potentially limiting the treatment efficacy (overviewed in Fig. 7). These frequently include immediate infusion-related symptoms, non-specific off-target symptoms, and (most importantly) risk of autoimmune inflammation of practically any organ (e.g., heart, skin, thyroid gland, kidneys, etc.) (Voskens et al., 2013; Osorio et al., 2017; Xu et al., 2018a; Teufel et al., 2019; Zhang et al., 2023). Fatigue is a very common symptom, which could be potentially related to hypophysitis or thyroid malfunction (frequently associated with anti-PD-1 therapy). On the other hand, adrenal insufficiency or diabetes mellitus are rare (Akturk et al., 2019; Elia et al., 2020). Skin-related adverse events are usually low-grade. Hepatic impairment is mostly dominated by isolated liver test elevation. Nevertheless, cases of severe hepatitis have been observed. Quite common is colitis (Palmieri and Carlino, 2018). Cardiac toxicity (myocarditis, acute hearth failure, arrhythmia, fibrosis, etc.) (Läubli et al., 2015; Heinzerling et al., 2016; Johnson et al., 2016; Tadokoro et al., 2016; Varricchi et al., 2018) and pulmonal complications are rare but serious adverse events (e.g., pneumonia, pneumonitis, or sarcoidosis) (Palmieri and Carlino, 2018). Severe neurological complications are also rare, but ICI treatment could be associated with autoimmune encephalitis, meningitis, encephalopathy, autoimmune disease such as myasthenia gravis, or Guillain-Barré syndrome (Kao et al., 2018; Anderson et al., 2019; Safa et al., 2019; Janssen et al., 2021; Salim et al., 2021; Vogrig et al., 2022). Peripheral neuropathy is not as common as with chemotherapy, but its incidence and grade are higher in chemotherapy-ICI combinations (Palmieri and Carlino, 2018; Tian et al., 2020). Acute kidney failure or acute interstitial nephritis were also reported, more frequently with anti-CTLA-4 inhibitors than with anti-PD-L1 nivolumab (Fadel et al.,

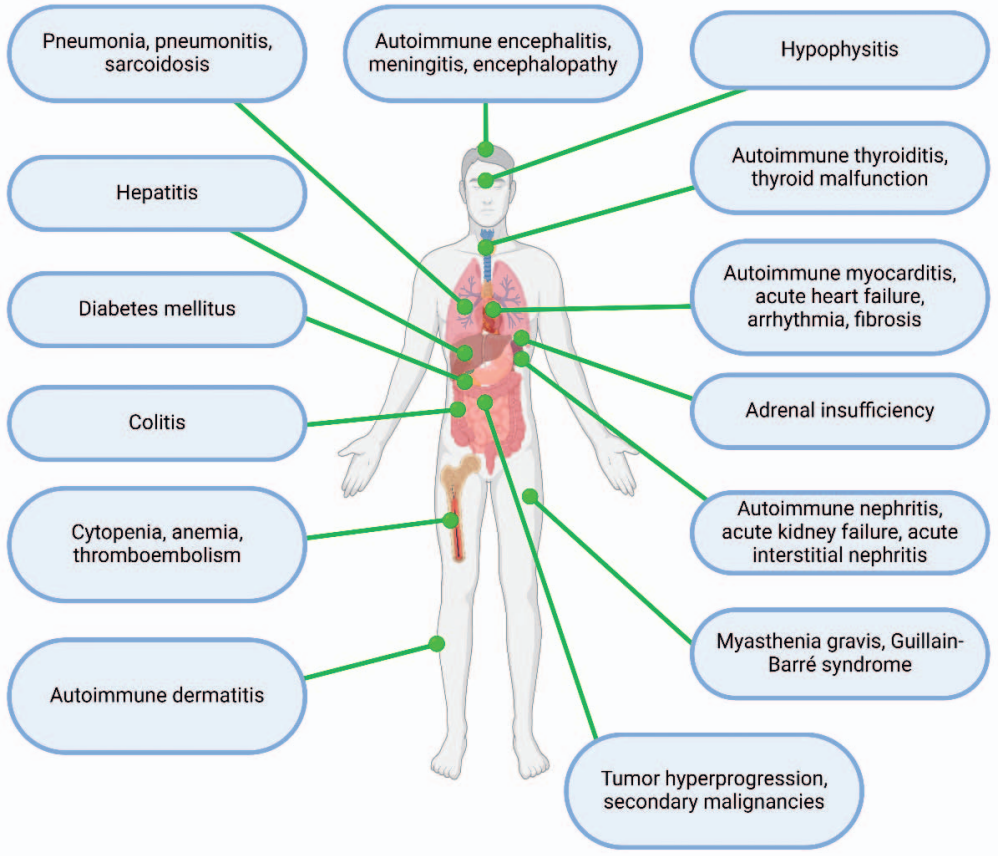

Fig. 7. Overview of immune checkpoint inhibitors-associated adverse effects

2009; Voskens et al., 2013; Izzedine et al., 2014). Hematological adverse effects include reactive cytopenias, infrequent but potentially lethal aplastic anemia, hemophilia, cryoglobulinemia, or thromboembolic events (Akhtari et al., 2009; Delyon et al., 2011; Pellegrino et al., 2017; Ni et al., 2019; Anand et al., 2020; Moik et al., 2021; Yun et al., 2021; Kroll et al., 2022).

Importantly, many checkpoint molecules are expressed by malignant T cells; therefore, there are specific concerns regarding the effect of ICIs directly on T-cell-derived tumors such as post ICI treatment tumor hyperprogression (Ohmoto and Fuji, 2023). ICIs might also activate specific T-cell clonal expansion (and T-cell-derived malignancy) as a secondary malignancy related to ICI treatment for another cancer type (Stuver and Moskowitz, 2023). As mentioned above, nivolumab treatment was associated with cases of accelerated tumor progression in ATLL (Ratner et al., 2018; Rauch et al., 2019). Cases of tumor hyperprogression were also reported in R/R PTCL treated with nivolumab (Bennani et al., 2022) and pembrolizumab in combination with romidepsin (Iyer et al., 2020). Secondary T-cell malignancies were unfortunately linked to multiple anti-PD-1 antibodies (nivolumab, ipilimumab), and they were classified as adverse effects of treatment by the FDA Adverse Event Reporting System (FAERS) in 0.02 % of patients (Wang et al., 2018; Anand et al., 2020). Moreover, case reports of newly developed PTCL-NOS and AITL were also reported after pembrolizumab treatment because of another cancer type (Duke et al., 2020; Avelino et al., 2022; van Eijs et al., 2023).

Taken together, the use of ICIs has its drawbacks and limitations. Their use in TCLs still needs to be further evaluated with the aim to predict and/or avoid cases of hyperprogression and improve treatment efficacy. This could be achieved using appropriate biomarkers at the level of tumor cells/tumor microenvironment analysis or additional up-to-date techniques (e.g., liquid biopsy) (Lu et al., 2022; Pfeiferova et al., 2022).

Conclusion

T-cell lymphomas present a challenge to successful treatment due to their low frequency, heterogeneity, prevalent insensitivity to standard chemotherapy regimens, and frequent relapses. Moreover, their rare incidence limits the research interest and negatively affects the feasible design of clinical trials. Generally, the therapeutic goal is to find appropriate cancer cell-targeted treatment (or immunotherapy) and/or their combinations to specifically inhibit the tumor cell growth without affecting non-malignant cells.

Allogenic stem cell transplantation had partial success; however, targeted treatment, including immunotherapy, would have much greater and wider utilization. Development of effective combinations of targeted

drugs and chemotherapy could bring even greater benefits. One of the most recent and very promising therapeutic strategies includes ICIs in combination with CAR T-cell therapy.

On the other hand, there are certain risks associated with the use of ICIs, including T-cell lymphoma hyperprogression, secondary T-cell-derived malignancy development following ICI treatment, general adverse effects associated with ICIs, or primary and secondary resistance. Variable expression of immune checkpoints and multiple microenvironmental factors might also affect the efficacy of ICIs, with the need to find appropriate biomarkers to identify the most suitable clinical situation. Nevertheless, ongoing studies should define soon and more clearly the efficacy and safety of ICIs in the T-cell lymphoma treatment. Confirmation of initial promising results might, therefore, add another treatment modality towards the long awaited improvement of the T-cell-derived malignancy treatment outcome.

Figure production statement

Figures were created by biorender.com.

References

Abouyabis, A. N., Shenoy, P. J., Lechowicz, M. J. et al. (2008) Incidence and outcomes of the peripheral T-cell lymphoma subtypes in the United States. *Leuk. Lymphoma* **49**, 2099-2107.

Adams, S. V., Newcomb, P. A., Shustov, A. R. (2016) Racial patterns of peripheral T-cell lymphoma incidence and survival in the United States. *J. Clin. Oncol.* **34**, 963-971.

Ahearne, M. J., Gaskell, C., Jackson, A. E. et al. (2020) AVAIL-T: A phase 2a trial of avelumab, and anti-PD-L1 antibody, in relapsed and refractory peripheral T-cell lymphoma (PTCL). *Blood* **136**, 18-19.

Akhtari, M., Waller, E. K., Jaye, D. L. et al. (2009) Neutropenia in a patient treated with ipilimumab (anti-CTLA-4 antibody). *J. Immunother.* **32**, 322-324.

Akturk, H. K., Kahramangil, D., Sarwal, A. et al. (2019) Immune checkpoint inhibitor-induced Type 1 diabetes: a systematic review and meta-analysis. *Diabet. Med.* **36**, 1075-1081.

Al-Hamadani, M., Habermann, T. M., Cerhan, J. R. et al. (2015) Non-Hodgkin lymphoma subtype distribution, geodemographic patterns, and survival in the US: a longitudinal analysis of the National Cancer Data Base from 1998 to 2011. *Am. J. Hematol.* **90**, 790-795.

Alaggio, R., Amador, C., Anagnostopoulos, I. et al. (2022) The 5th edition of the World Health Organization classification of haematolymphoid tumors: lymphoid neoplasms. *Leukemia* **36**, 1720-1748.

Anand, K., Ensor, J., Pingali, S. R. et al. (2020) T-cell lymphoma secondary to checkpoint inhibitor therapy. *J. Immunother. Cancer* **8**, e000104.

Anderson, D., Beecher, G., Nathoo, N. et al. (2019) Proposed diagnostic and treatment paradigm for high-grade neurological complications of immune checkpoint inhibitors. *Neurooncol. Pract.* **6**, 340-345.

Anderson, J. R., Armitage, J. O., Weisenburger, D. D. (1998) Epidemiology of the non-Hodgkin's lymphomas: distributions of the major subtypes differ by geographic locations. Non-Hodgkin's lymphoma classification project. *Ann. Oncol.* **9**, 717-720.

Andorsky, D. J., Yamada, R. E., Said, J. et al. (2011) Programmed death ligand 1 is expressed by non-Hodgkin lymphomas and inhibits the activity of tumor-associated T cells. *Clin. Cancer Res.* **17**, 4232-4344.

Antonangeli, F., Natalini, A., Garassino, M. C. et al. (2020) Regulation of PD-L1 expression by NF-κB in cancer. *Front. Immunol.* **11**, 584626.

Anzengruber, F., Ignatova, D., Schlaepfer, T. et al. (2019) Divergent LAG-3 versus BTLA, TIGIT, and FCRL3 expression in Sézary syndrome. *Leuk. Lymphoma* **60**, 1899-1907.

Armand, P., Engert, A., Younes, A. et al. (2018) Nivolumab for relapsed/refractory classic Hodgkin lymphoma after failure of autologous hematopoietic cell transplantation: extended follow-up of the multicohort single-arm phase II checkmate 205 trial. *J. Clin. Oncol.* **36**, 1428-1439.

Armand, P., Rodig, S., Melnichenko, V. et al. (2019) Pembrolizumab in relapsed or refractory primary mediastinal large B-cell lymphoma. *J. Clin. Oncol.* **37**, 3291-3299.

Armengol, M., Santos, J. C., Fernández-Serrano, M. et al. (2021) Immune-checkpoint inhibitors in B-cell lymphoma. *Cancers (Basel)* **13**, 214.

Assaf, C., Dobos, G., Zech, I. M. et al. (2023) Epidemiology of mature T/NK-cell lymphomas in Germany – a representative cross-sectional study based on SHI claims data. *J. Dtsch. Dermatol. Ges.* **21**, 1320-1327.

Avelino, A. R., Elmanaseer, O., Wrzesinski, S. et al. (2022) T-cell prolymphocytic leukaemia associated with immune checkpoint inhibitor (pembrolizumab). *BMJ Case Rep.* **15**, e245603.

Bai, B., Wang, X. X., Gao, Y. et al. (2021) Prior anti-PD-1 therapy as a risk factor for life-threatening peri-engraftment respiratory distress syndrome in patients undergoing autologous stem cell transplantation. *Bone Marrow Transplant.* **56**, 1151-1158.

Bajorin, D. F., Witjes, J. A., Gschwend, J. E. et al. (2021) Adjuvant nivolumab versus placebo in muscle-invasive urothelial carcinoma. *N. Engl. J. Med.* **384**, 2102-2114.

Bar-Sela, G., Bergman, R. (2015) Complete regression of mycosis fungoides after ipilimumab therapy for advanced melanoma. *JAAD Case Rep.* **1**, 99-100.

Bardelli, V., Arniani, S., Pierini, V. et al. (2021) T-cell acute lymphoblastic leukemia: biomarkers and their clinical usefulness. *Genes (Basel)* **12**, 1118.

Barilà, G., Teramo, A., Calabretto, G. et al. (2020) Stat3 mutations impact on overall survival in large granular lymphocyte leukemia: a single-center experience of 205 patients. *Leukemia* **34**, 1116-1124.

Basu, A., Ramamoorthi, G., Albert, G. et al. (2021) Differentiation and regulation of T_H cells: a balancing act for cancer immunotherapy. *Front. Immunol.* **12**, 669474.

Basudan, A. M. (2022) The role of immune checkpoint inhibitors in cancer therapy. *Clin. Pract.* **13**, 22-40.

Battaglia, M., Gregori, S., Bacchetta, R. et al. (2006) Tr1 cells: from discovery to their clinical application. *Semin. Immunol.* **18**, 120-127.

Beatty, G. L., Gladney, W. L. (2015) Immune escape mechanisms as a guide for cancer immunotherapy. *Clin. Cancer Res.* **21**, 687-692.

Bekkenk, M. W., Geelen, F. A. M. J., van Voorst Vader, P. C. et al. (2000) Primary and secondary cutaneous CD30$^+$ lymphoproliferative disorders: a report from the Dutch Cutaneous Lymphoma Group on the long-term follow-up data of 219 patients and guidelines for diagnosis and treatment. *Blood* **95**, 3653-3661.

Benharroch, D., Meguerian-Bedoyan, Z., Lamant, L. et al. (1998) ALK-positive lymphoma: a single disease with a broad spectrum of morphology. *Blood* **91**, 2076-2084.

Bennani, N. N., Ansell, S. M. (2019) Tumor microenvironment in T-cell lymphomas. *Cancer Treat. Res.* **176**, 69-82.

Bennani, N. N., Kim, H. J., Pederson, L. D. et al. (2022) Nivolumab in patients with relapsed or refractory peripheral T-cell lymphoma: modest activity and cases of hyperprogression. *J. Immunother. Cancer* **10**, e004984.

Bennani, N. N., Pederson, L. D., Atherton, P. et al. (2019) A phase II study of nivolumab in patients with relapsed or refractory peripheral T-cell lymphoma. *Blood* **134**, 467.

Board, R., Smittenaar, R., Lawton, S. et al. (2021) Metastatic melanoma patient outcomes since introduction of immune checkpoint inhibitors in England between 2014 and 2018. *Int. J. Cancer* **148**, 868-875.

Bollard, C. M., Gottschalk, S., Torrano, V. et al. (2014) Sustained complete responses in patients with lymphoma receiving autologous cytotoxic T lymphocytes targeting Epstein-Barr virus latent membrane proteins. *J. Clin. Oncol.* **32**, 798-808.

Borcherding, N., Severson, K. J., Henderson, N. et al. (2023) Single-cell analysis of Sézary syndrome reveals novel markers and shifting gene profiles associated with treatment. *Blood Adv.* **7**, 321-335.

Buchbinder, E. I., Desai, A. (2016) CTLA-4 and PD-1 pathways: similarities, differences, and implications of their inhibition. *Am. J. Clin. Oncol.* **39**, 98-106.

Cai, J., Liu, P., Huang, H. et al. (2020a) Combination of anti-PD-1 antibody with P-GEMOX as a potentially effective immunochemotherapy for advanced natural killer/T cell lymphoma. *Signal Transduct.Target. Ther.* **5**, 289.

Cai, Q., Huang, H., Liu, P. et al. (2020b) Safety and preliminary efficacy of sintilimab plus P-gemox (pegaspargase, gemcitabine and oxaliplatin) regimen as first-line treatment for patients with advanced extranodal natural killer/T cell lymphoma, nasal type: an open-label, multicenter, phase 2 study. *Blood* **136**, 26-27.

Calì, B., Molon, B., Viola, A. (2017) Tuning cancer fate: the unremitting role of host immunity. *Open Biol.* **7**, 170006.

Campbell, J. J., Clark, R. A., Watanabe, R. et al. (2010) Sezary syndrome and mycosis fungoides arise from distinct T-cell subsets: a biologic rationale for their distinct clinical behaviors. *Blood* **116**, 767-771.

Campo, E., Jaffe, E. S., Cook, J. R. et al. (2022) The international consensus classification of mature lymphoid neoplasms: a report from the Clinical Advisory Committee. *Blood* **140**, 1229-1253.

Cao, S., Wylie, K. M., Wyczalkowski, M. A. et al. (2019) Dynamic host immune response in virus-associated cancers. *Commun. Biol.* **2**, 109.

Cetinözman, F., Jansen, P. M., Vermeer, M. H. et al. (2012) Differential expression of programmed death-1 (PD-1) in Sézary syndrome and mycosis fungoides. *Arch. Dermatol.* **148**, 1379-1385.

Chatzigeorgiou, A., Lyberi, M., Chatzilymperis, G. et al. (2009) CD40/CD40L signaling and its implication in health and disease. *Biofactors* **35**, 474-483.

Chen, B. J., Chapuy, B., Ouyang, J. et al. (2013) PD-L1 expression is characteristic of a subset of aggressive B-cell lymphomas and virus-associated malignancies. *Clin. Cancer Res.* **19**, 3462-3473.

Chen, G., Emens, L. A. (2013) Chemoimmunotherapy: reengineering tumor immunity. *Cancer Immunol. Immunother.* **62**, 203-216.

Chen, L., Flies, D. B. (2013) Molecular mechanisms of T cell co-stimulation and co-inhibition. *Nat. Rev. Immunol.* **13**, 227-242.

Chen, X., Wu, W., Wei, W. et al. (2022) Immune checkpoint inhibitors in peripheral T-cell lymphoma. *Front. Pharmacol.* **13**, 869488.

Chen, Y., Li, M., Cao, J. et al. (2021) CTLA-4 promotes lymphoma progression through tumor stem cell enrichment and immunosuppression. *Open Life Sci.* **16**, 909-919.

Chikuma, S. (2017) CTLA-4, an essential immune-checkpoint for T-cell activation. *Curr. Top. Microbiol. Immunol.* **410**, 99-126.

Choi, J., Goh, G., Walradt, T. et al. (2015) Genomic landscape of cutaneous T cell lymphoma. *Nat. Genet.* **47**, 1011-1019.

Chung, H. C., Ros, W., Delord, J. P. et al. (2019) Efficacy and safety of pembrolizumab in previously treated advanced cervical cancer: results from the phase II KEYNOTE-158 study. *J. Clin. Oncol.* **37**, 1470-1478.

Cohen, J. I., Iwatsuki, K., Ko, Y. H. e al. (2020) Epstein-Barr virus NK and T cell lymphoproliferative disease: report of a 2018 international meeting. *Leuk. Lymphoma* **61**, 808-819.

Coiffier, B., Pro, B., Prince, H. M. et al. (2014) Romidepsin for the treatment of relapsed/refractory peripheral T-cell lymphoma: pivotal study update demonstrates durable responses. *J. Hematol. Oncol.* **7**, 11.

Curigliano, G., Gelderblom, H., Mach, N. et al. (2021) Phase I/Ib clinical trial of sabatolimab, an anti-TIM-3 antibody, alone and in combination with spartalizumab, an anti-PD-1 antibody, in advanced solid tumors. *Clin. Cancer Res.* **27**, 3620-3629.

de Leval, L., Rickman, D. S., Thielen, C. et al. (2007) The gene expression profile of nodal peripheral T-cell lymphoma demonstrates a molecular link between angioimmunoblastic T-cell lymphoma (AITL) and follicular helper T (TFH) cells. *Blood* **109**, 4952-4963.

Decroos, A., Giustiniani, J., Pelletier, L. et al. (2021) PD1 in Sézary syndrome: a repressor of cell survival sometimes lost during progression, but a new target using depleting antibodies? *Eur. J. Cancer* **156**, S14-S15.

Delyon, J., Mateus, C., Lambert, T. (2011) Hemophilia A induced by ipilimumab. *N. Engl. J. Med.* **365**, 1747-1748.

Di Napoli, A., De Cecco, L., Piccaluga, P. P. et al. (2019) Transcriptional analysis distinguishes breast implant-associated anaplastic large cell lymphoma from other peripheral T-cell lymphomas. *Mod. Pathol.* **32**, 216-230.

Dobos, G., Pohrt, A., Ram-Wolff, C. et al. (2020) Epidemiology of cutaneous T-cell lymphomas: a systematic review and meta-analysis of 16,953 patients. *Cancers (Basel)* **12**, 2921.

Doroshow, D. B., Bhalla, S., Beasley, M. B. et al. (2021) PD-L1 as a biomarker of response to immune-checkpoint inhibitors. *Nat. Rev. Clin. Oncol.* **18**, 345-362.

Drake, C. G., Jaffee, E., Pardoll, D. M. (2006) Mechanisms of immune evasion by tumors. *Adv. Immunol.* **90**, 51-81.

Du, L., Zhang, L., Li, L. et al. (2020) Effective treatment with PD-1 antibody, chidamide, etoposide, and thalidomide (PCET) for relapsed/refractory natural killer/T-cell lymphoma: a report of three cases. *Onco Targets Ther.* **13**, 7189-7197.

Duke, T. C., Nair, R., Torres-Cabala, C. et al. (2020) Angioimmunoblastic T-cell lymphoma associated with immune checkpoint inhibitor treatment. *JAAD Case Rep.* **6**, 1264-1267.

Elia, G., Ferrari, S. M., Galdiero, M. R. et al. (2020) New insight in endocrine-related adverse events associated to immune checkpoint blockade. *Best Pract. Res. Clin. Endocrinol. Metab.* **34**, 101370.

Fadel, F., El Karoui, K., Knebelmann, B. (2009) Anti-CTLA4 antibody-induced lupus nephritis. *N. Engl. J. Med.* **361**, 211-212.

Fantin, V. R., Loboda, A., Paweletz, C. P. et al. (2008) Constitutive activation of signal transducers and activators of transcription predicts vorinostat resistance in cutaneous T-cell lymphoma. *Cancer Res.* **68**, 3785-3794.

Farhood, B., Najafi, M., Mortezaee, K. (2019) $CD8^+$ cytotoxic T lymphocytes in cancer immunotherapy: a review. *J. Cell. Physiol.* **234**, 8509-8521.

Feng, Y., Zhong, M., Liu, Y. et al. (2018) Expression of TIM-3 and LAG-3 in extranodal NK/T cell lymphoma, nasal type. *Histol. Histopathol.* **33**, 307-315.

Ferrara, R., Imbimbo, M., Malouf, R. et al. (2020) Single or combined immune checkpoint inhibitors compared to first-line platinum-based chemotherapy with or without bevacizumab for people with advanced non-small cell lung cancer. *Cochrane Database Syst. Rev.* **12**, Cd013257.

Folkes, A. S., Feng, M., Zain, J. M. et al. (2018) Targeting CD47 as a cancer therapeutic strategy: the cutaneous T-cell lymphoma experience. *Curr. Opin. Oncol.* **30**, 332-337.

Forde, P. M., Spicer, J., Lu, S. et al. (2022) Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer. *N. Engl. J. Med.* **386**, 1973-1985.

Fox, C. P., Boumendil, A., Schmitz, N. et al. (2015) High-dose therapy and autologous stem cell transplantation for extranodal NK/T lymphoma in patients from the Western hemisphere: a study from the European Society for Blood and Marrow Transplantation. *Leuk. Lymphoma* **56**, 3295-3300.

Fu, Y., Lin, Q., Zhang, Z. et al. (2020) Therapeutic strategies for the costimulatory molecule OX40 in T-cell-mediated immunity. *Acta Pharm. Sin. B* **10**, 414-433.

Garassino, M. C., Cho, B. C., Kim, J. H. et al. (2018) Durvalumab as third-line or later treatment for advanced non-small-cell lung cancer (ATLANTIC): an open-label, single-arm, phase 2 study. *Lancet Oncol.* **19**, 521-536.

Garon, E. B., Rizvi, N. A., Hui, R. et al. (2015) Pembrolizumab for the treatment of non-small-cell lung cancer. *N. Engl. J. Med.* **372**, 2018-2028.

Ghione, P., Moskowitz, A. J., De Paola, N. E. K. et al. (2018) Novel immunotherapies for T cell lymphoma and leukemia. *Curr. Hematol. Malig. Rep.* **13**, 494-506.

Gibson, H. M., Mishra, A., Chan, D. V. et al. (2013) Impaired proteasome function activates GATA3 in T cells and upregulates CTLA-4: relevance for Sézary syndrome. *J. Invest. Dermatol.* **133**, 249-257.

Gniadecki, R., Rossen, K. (2003) Expression of T-cell activation marker CD134 (OX40) in lymphomatoid papulosis. *Br. J. Dermatol.* **148**, 885-891.

Gu, Q., Li, J., Chen, Z. et al. (2021) Expression and prognostic significance of PD-L2 in diffuse large B-cell lymphoma. *Front. Oncol.* **11**, 664032.

Hansen, K., Kumar, S., Logronio, K. et al. (2021) COM902, a novel therapeutic antibody targeting TIGIT augments anti-tumor T cell function in combination with PVRIG or PD-1 pathway blockade. *Cancer Immunol. Immunother.* **70**, 3525-3540.

Harlin, H., Hwang, K. W., Palucki, D. A. et al. (2002) CTLA-4 engagement regulates NF-κB activation in vivo. *Eur. J. Immunol.* **32**, 2095-2104.

Hassler, M. R., Pulverer, W. et al. (2016) Insights into the pathogenesis of anaplastic large-cell lymphoma through genome-wide DNA methylation profiling. *Cell Rep.* **17**, 596-608.

Hatic, H., Sampat, D., Goyal, G. (2021) Immune checkpoint inhibitors in lymphoma: challenges and opportunities. *Ann. Transl. Med.* **9**, 1037.

Haverkos, B. M., Coleman, C., Gru, A. A. et al. (2017) Emerging insights on the pathogenesis and treatment of extranodal NK/T cell lymphomas (ENKTL). *Discov. Med.* **23**, 189-199.

Haverkos, B. M., Pan, Z., Gru, A. A. et al. (2016) Extranodal NK/T cell lymphoma, nasal type (ENKTL-NT): an update on epidemiology, clinical presentation, and natural history in North American and European cases. *Curr. Hematol. Malig. Rep.* **11**, 514-527.

Hay, Z. L. Z., Slansky, J. E. (2022) Granzymes: the molecular executors of immune-mediated cytotoxicity. *Int. J. Mol. Sci.* **23**, 1833.

He, H.-X., Gao, Y., Fu, J.-C. et al. (2021) VISTA and PD-L1 synergistically predict poor prognosis in patients with extranodal natural killer/T-cell lymphoma. *Oncoimmunology* **10**, 1907059.

He, Y., Rivard, C. J., Rozeboom, L. et al. (2016) Lymphocyte-activation gene-3, an important immune checkpoint in cancer. *Cancer Sci.* **107**, 1193-1197.

Heavican, T. B., Bouska, A., Yu, J. et al. (2019) Genetic drivers of oncogenic pathways in molecular subgroups of peripheral T-cell lymphoma. *Blood* **133**, 1664-1676.

Hebart, H., Lang, P., Woessmann, W. (2016) Nivolumab for refractory anaplastic large cell lymphoma: a case report. *Ann. Intern. Med.* **165**, 607-608.

Heinzerling, L., Ott, P. A., Hodi, F. S. et al. (2016) Cardiotoxicity associated with CTLA4 and PD1 blocking immunotherapy. *J. Immunother. Cancer* **4**, 50.

Herbst, R. S., Giaccone, G., de Marinis, F. et al. (2020) Atezolizumab for first-line treatment of PD-L1-selected patients with NSCLC. *N. Engl. J. Med.* **383**, 1328-1339.

Herling, M., Khoury, J. D., Washington, L. T. et al. (2004) A systematic approach to diagnosis of mature T-cell leukemias reveals heterogeneity among WHO categories. *Blood* **104**, 328-335.

Hill, L., Rouce, R. H., Smith, T. S. et al. (2020) CD5 CAR T-cells for treatment of patients with relapsed/refractory CD5 expressing T-cell lymphoma demonstrates safety and anti-tumor activity. *Biol. Blood Marrow Transplant.* **26**, S237.

Hill, L. C., Rouce, R. H., Smith, T. S. et al. (2019) Safety and anti-tumor activity of CD5 CAR T-cells in patients with relapsed/refractory T-cell malignancies. *Blood* **134**, 199.

Hodson, A., Crichton, S., Montoto, S. et al. (2011) Use of zidovudine and interferon alfa with chemotherapy improves survival in both acute and lymphoma subtypes of adult T-cell leukemia/lymphoma. *J. Clin. Oncol.* **29**, 4696-4701.

Horlad, H., Ohnishi, K., Ma, C. et al. (2016) TIM-3 expression in lymphoma cells predicts chemoresistance in patients with adult T-cell leukemia/lymphoma. *Oncol. Lett.* **12**, 1519-1524.

Horwitz, S., O'Connor, O. A., Pro, B. et al. (2019) Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): a global, double-blind, randomised, phase 3 trial. *Lancet* **393**, 229-240.

Horwitz, S. M., Advani, R. H., Bartlett, N. L. et al. (2014) Objective responses in relapsed T-cell lymphomas with single-agent brentuximab vedotin. *Blood* **123**, 3095-3100.

Hossen, M. M., Ma, Y., Yin, Z. et al. (2023) Current understanding of CTLA-4: from mechanism to autoimmune diseases. *Front. Immunol.* **14**, 1198365.

Hristov, A. C., Tejasvi, T., Wilcox, R. A. (2023) Cutaneous T-cell lymphomas: 2023 update on diagnosis, risk-stratification, and management. *Am. J. Hematol.* **98**, 193-209.

Huang, H.-Q., Tao, R., Zou, L. et al. (2019) Preliminary results from a multicenter, single-arm, phase 2 study of CS1001, an anti-programmed death-ligand 1 (PD-L1) human monoclonal antibody (mAb), in patients (pts) with relapsed or refractory extranodal natural killer/T cell lymphoma (rr-ENKTL). *Blood* **134**, 2833.

Huang, Y., Moreau, A., Dupuis, J. et al. (2009) Peripheral T-cell lymphomas with a follicular growth pattern are derived from follicular helper T cells (TFH) and may show overlapping features with angioimmunoblastic T-cell lymphomas. *Am. J. Surg. Pathol.* **33**, 682-690.

Huo, J.-L., Wang, Y.-T., Fu, W.-J. et al. (2022) The promising immune checkpoint LAG-3 in cancer immunotherapy: from basic research to clinical application. *Front. Immunol.* **13**, 956090.

Huuhtanen, J., Bhattacharya, D., Lönnberg, T. et al. (2022) Single-cell characterization of leukemic and non-leukemic immune repertoires in $CD8^+$ T-cell large granular lymphocytic leukemia. *Nat. Commun.* **13**, 1981.

Imura, A., Hori, T., Imada, K. et al. (1997) OX40 expressed on fresh leukemic cells from adult T-cell leukemia patients mediates cell adhesion to vascular endothelial cells: implication for the possible involvement of OX40 in leukemic cell infiltration. *Blood* **89**, 2951-2958.

Iyer, S. P., Neelapu, S. S., Burns, E. et al. (2019) A phase I/II study to examine the safety and efficacy of pembrolizumab 200 mg fixed dose administered every 3 weeks (Q3W) in combination with romidepsin in relapsed or refractory peripheral T-cell lymphoma (PTCL). *Blood* **134**, 1546.

Iyer, S. P., Xu, J., Becnel, M. R. et al. (2020) A phase II study of pembrolizumab in combination with romidepsin demonstrates durable responses in relapsed or refractory T-cell lymphoma (TCL). *Blood* **136**, 40-41.

Iżykowska, K., Rassek, K., Korsak, D. et al. (2020) Novel targeted therapies of T cell lymphomas. *J. Hematol. Oncol.* **13**, 176.

Izzedine, H., Gueutin, V., Gharbi, C. et al. (2014) Kidney injuries related to ipilimumab. *Invest. New Drugs* **32**, 769-773.

Jacenik, D., Karagiannidis, I., Beswick, E. J. (2023) Th2 cells inhibit growth of colon and pancreas cancers by promoting anti-tumorigenic responses from macrophages and eosinophils. *Br. J. Cancer* **128**, 387-397.

Janssen, J. B. E., Leow, T. Y. S., Herbschleb, K. H. et al. (2021) Immune checkpoint inhibitor-related Guillain-Barré syndrome: a case series and review of the literature. *J. Immunother.* **44**, 276-282.

Jariwala, N., Benoit, B., Kossenkov, A. V. et al. (2017) TIGIT and Helios are highly expressed on $CD4^+$ T cells in Sézary syndrome patients. *J. Invest. Dermatol.* **137**, 257-260.

Jeong, S. H. (2020) Extranodal NK/T cell lymphoma. *Blood Res.* **55**, S63-S71.

Jiang, M., Zhang, H., Jiang, Y. et al. (2012) Phase 2 trial of "sandwich" L-asparaginase, vincristine, and prednisone chemotherapy with radiotherapy in newly diagnosed, stage IE to IIE, nasal type, extranodal natural killer/T-cell lymphoma. *Cancer* **118**, 3294-3301.

Jiang, Y., Chen, M., Nie, H. et al. (2019) PD-1 and PD-L1 in cancer immunotherapy: clinical implications and future considerations. *Hum. Vaccin. Immunother.* **15**, 1111-1122.

Jo, J. C., Kim, M., Choi, Y. et al. (2017) Expression of programmed cell death 1 and programmed cell death ligand 1 in extranodal NK/T-cell lymphoma, nasal type. *Ann. Hematol.* **96**, 25-31.

John, L. B., Devaud, C., Duong, C. P. et al. (2013a) Anti-PD-1 antibody therapy potently enhances the eradication of established tumors by gene-modified T cells. *Clin. Cancer Res.* **19**, 5636-5646.

John, L. B., Kershaw, M. H., Darcy, P. K. (2013b) Blockade of PD-1 immunosuppression boosts CAR T-cell therapy. *Oncoimmunology* **2**, e26286.

Johnson, D. B., Balko, J. M., Compton, M. L. et al. (2016) Fulminant myocarditis with combination immune checkpoint blockade. *N. Engl. J .Med.* **375**, 1749-1755.

Joller, N., Hafler, J. P., Brynedal, B. et al. (2011) Cutting edge: TIGIT has T cell-intrinsic inhibitory functions. *J. Immunol.* **186**, 1338-1342.

Joller, N., Lozano, E., Burkett, P. R. et al. (2014) Treg cells expressing the coinhibitory molecule TIGIT selectively inhibit proinflammatory Th1 and Th17 cell responses. *Immunity* **40**, 569-581.

Jones, C. L., Degasperi, A., Grandi, V. et al. (2021) Spectrum of mutational signatures in T-cell lymphoma reveals a key role for UV radiation in cutaneous T-cell lymphoma. *Sci. Rep.* **11**, 3962.

Jones, D., Fletcher, C. D. M., Pulford, K. et al. (1999) The T-cell activation markers CD30 and OX40/CD134 are expressed in nonoverlapping subsets of peripheral T-cell lymphoma. *Blood* **93**, 3487-3493.

Junttila, I. S. (2018) Tuning the cytokine responses: an update on interleukin (IL)-4 and IL-13 receptor complexes. *Front. Immunol.* **9**, 888.

Jutz, S., Hennig, A., Paster, W. et al. (2017) A cellular platform for the evaluation of immune checkpoint molecules. *Oncotarget* **8**, 64892-64906.

Kao, J. C., Brickshawana, A., Liewluck, T. (2018) Neuromuscular complications of programmed cell death-1 (PD-1) inhibitors. *Curr. Neurol. Neurosci. Rep.* **18**, 63.

Karube, K., Tsuzuki, S., Yoshida, N. et al. (2013) Comprehensive gene expression profiles of NK cell neoplasms identify vorinostat as an effective drug candidate. *Cancer Lett.* **333**, 47-55.

Kataoka, K., Iwanaga, M., Yasunaga, J.-I. et al.(2018) Prognostic relevance of integrated genetic profiling in adult T-cell leukemia/lymphoma. *Blood* **131**, 215-225.

Kataoka, K., Nagata, Y., Kitanaka, A. et al. (2015) Integrated molecular analysis of adult T cell leukemia/lymphoma. *Nat. Genet.* **47**, 1304-1315.

Kaushik, I., Ramachandran, S., Zabel, C. et al. (2022) The evolutionary legacy of immune checkpoint inhibitors. *Semin. Cancer Biol.* **86**, 491-498.

Kawana, Y., Suga, H., Kamijo, H. et al. (2021) Roles of OX40 and OX40 ligand in mycosis fungoides and Sézary syndrome. *Int. J. Mol. Sci.* **22**, 12576.

Keir, M. E., Butte, M. J., Freeman, G. J. et al. (2008) PD-1 and its ligands in tolerance and immunity. *Annu. Rev. Immunol.* **26**, 677-704.

Kempf, W., Mitteldorf, C. (2021) Cutaneous T-cell lymphomas – an update 2021. *Hematol. Oncol.* **39**, 46-51.

Khodadoust, M. S., Rook, A. H., Porcu, P. et al. (2020) Pembrolizumab in relapsed and refractory mycosis fungoides and Sézary syndrome: a multicenter phase II study. *J. Clin. Oncol.* **38**, 20-28.

Kim, G. E., Cho, J. H., Yang, W. I. et al. (2000) Angiocentric lymphoma of the head and neck: patterns of systemic failure after radiation treatment. *J. Clin. Oncol.* **18**, 54-63.

Kim, S. J., Lim, J. Q., Laurensia, Y. et al. (2020) Avelumab for the treatment of relapsed or refractory extranodal NK/T-cell lymphoma: an open-label phase 2 study. *Blood* **136**, 2754-2763.

Kim, S. K., Cho, S. W. (2022) The evasion mechanisms of cancer immunity and drug intervention in the tumor microenvironment. *Front. Pharmacol.* **13**, 868695.

Kim, W. Y., Jung, H. Y., Nam, S. J. et al. (2016) Expression of programmed cell death ligand 1 (PD-L1) in advanced stage EBV-associated extranodal NK/T cell lymphoma is associated with better prognosis. *Virchows Arch.* **469**, 581-590.

Kim, Y. H., Bagot, M., Pinter-Brown, L. et al. (2018) Mogamulizumab versus vorinostat in previously treated cutaneous T-cell lymphoma (MAVORIC): an international, open-label, randomised, controlled phase 3 trial. *Lancet Oncol.* **19**, 1192-1204.

Klee, G., von Dücker, L., Terheyden, P. (2020) Sustained complete remission of extranodal NK/T-cell lymphoma, nasal type, following pembrolizumab and radiation therapy. *J. Dtsch. Dermatol. Ges.* **18**, 1019-1021.

Klempner, S. J., Fabrizio, D., Bane, S. et al. (2020) Tumor mutational burden as a predictive biomarker for response to immune checkpoint inhibitors: a review of current evidence. *Oncologist* **25**, e147-e159.

Knaus, H. A., Kanakry, C. G., Luznik, L. et al. (2017) Immunomodulatory drugs: immune checkpoint agents in acute leukemia. *Curr. Drug Targets* **18**, 315-331.

Kokubo, K., Onodera, A., Kiuchi, M. et al. (2022) Conventional and pathogenic Th2 cells in inflammation, tissue repair, and fibrosis. *Front. Immunol.* **13**, 945063.

Kondelkova, K., Vokurkova, D., Krejsek, J. et al. (2010) Regulatory T cells (TREG) and their roles in immune system with respect to immunopathological disorders. *Acta Medica (Hradec Kralove)* **53**, 73-77.

Kouzaki, H., Kitanishi, T., Kitano, H. et al. (2004) Successful treatment of disseminated nasal T-cell lymphoma using high-dose chemotherapy and autologus peripheral blood stem cell transplantation: a case report. *Auris Nasus Larynx* **31**, 79-83.

Kozako, T., Yoshimitsu, M., Fujiwara, H. et al. (2009) PD-1/PD-L1 expression in human T-cell leukemia virus type 1 carriers and adult T-cell leukemia/lymphoma patients. *Leukemia* **23**, 375-382.

Kravtsov, D. S., Erbe, A. K., Sondel, P. M. et al. (2022) Roles of CD4+ T cells as mediators of antitumor immunity. *Front. Immunol.* **13**, 972021.

Krishnan, C., Warnke, R. A., Arber, D. A. et al. (2010) PD-1 expression in T-cell lymphomas and reactive lymphoid entities: potential overlap in staining patterns between lymphoma and viral lymphadenitis. *Am. J. Surg. Pathol.* **34**, 178-189.

Kroll, M. H., Rojas-Hernandez, C., Yee, C. (2022) Hematologic complications of immune checkpoint inhibitors. *Blood* **139**, 3594-3604.

Kwong, Y. L., Chan, T. S. Y., Tan, D. et al. (2017) PD1 blockade with pembrolizumab is highly effective in relapsed or refractory NK/T-cell lymphoma failing L-asparaginase. *Blood* **129**, 2437-2442.

Lai, P., Liu, F., Liu, X. et al. (2023) Differential molecular programs of cutaneous anaplastic large cell lymphoma and CD30-positive transformed mycosis fungoides. *Front. Immunol.* **14**, 1270365.

Läubli, H., Balmelli, C., Bossard, M. et al. (2015) Acute heart failure due to autoimmune myocarditis under pembrolizumab treatment for metastatic melanoma. *J. Immunother. Cancer* **3**, 11.

Lee, J., Lozano-Ruiz, B., Yang, F. M. et al. (2021) The multifaceted role of Th1, Th9, and Th17 cells in immune checkpoint inhibition therapy. *Front. Immunol.* **12**, 625667.

Lee, M. Y., Jeon, J. W., Sievers, C. et al. (2020) Antigen processing and presentation in cancer immunotherapy. *J. Immunother. Cancer* **8**, e001111.

Lee, S. H., Ahn, Y. C., Kim, W. S. et al. (2006) The effect of pre-irradiation dose intense CHOP on anthracyline resistance in localized nasal NK/T-cell lymphoma. *Haematologica* **91**, 427-428.

Lesokhin, A. M., Ansell, S. M., Armand, P. et al. (2016) Nivolumab in patients with relapsed or refractory hemato-

logic malignancy: preliminary results of a phase Ib study. *J. Clin. Oncol.* **34**, 2698-2704.

Lewis, N. E., Petrova-Drus, K., Huet, S. et al. (2020) Clonal hematopoiesis in angioimmunoblastic T-cell lymphoma with divergent evolution to myeloid neoplasms. *Blood Adv.* **4**, 2261-2271.

Li, W., Zheng, Q., Luo, X. et al. (2023) The predictive implication of programmed cell death ligand 1 expression in extranodal natural killer/T-cell lymphoma and its correlation with clinicopathological features: a systematic review and meta-analysis. *Transl. Cancer Res.* **12**, 2115-2127.

Li, X., Cheng, Y., Zhang, M. et al. (2018) Activity of pembrolizumab in relapsed/refractory NK/T-cell lymphoma. *J. Hematol. Oncol.* **11**, 15.

Liu, S., Liu, W., Li, H. et al. (2022) Epidemiological characteristics of peripheral T-cell lymphoma: a population-based study. *Front. Oncol.* **12**, 863269.

Liu, Y., Song, Y., Zuo, S. et al. (2023) Antitumor activity and safety of camrelizumab combined with apatinib in patients with relapsed or refractory peripheral T-cell lymphoma: an open-label, multicenter, phase II study. *Front. Immunol.* **14**, 1128172.

Long, L., Zhang, X., Chen, F. et al. (2018) The promising immune checkpoint LAG-3: from tumor microenvironment to cancer immunotherapy. *Genes Cancer* **9**, 176-189.

Lu, C., Zhang, Y. C., Chen, Z. H. et al. (2022) Applications of circulating tumor DNA in immune checkpoint inhibition: emerging roles and future perspectives. *Front. Oncol.* **12**, 836891.

Manieri, N. A., Chiang, E. Y., Grogan, J. L. (2017) TIGIT: a key inhibitor of the cancer immunity cycle. *Trends Immunol.* **38**, 20-28.

Marchi, E., O'Connor, O. A. (2020) The rapidly changing landscape in mature T-cell lymphoma (MTCL) biology and management. *CA Cancer J. Clin.* **70**, 47-70.

Margolskee, E., Jobanputra, V., Lewis, S. K. et al. (2013) Indolent small intestinal CD4+ T-cell lymphoma is a distinct entity with unique biologic and clinical features. *PLoS One* **8**, e68343.

Maria Pamela, D., Francois, L., Edoardo, M. et al. (2017) Integrative clinicopathological and molecular analyses of angioimmunoblastic T-cell lymphoma and other nodal lymphomas of follicular helper T-cell origin. *Haematologica* **102**, e148-e151.

Markham, A., Keam, S. J. (2019) Camrelizumab: first global approval. *Drugs* **79**, 1355-1361.

Matsushita, M. (2021) Novel treatment strategies utilizing immune reactions against chronic myelogenous leukemia stem cells. *Cancers (Basel)* **13**, 5435.

McEachron, T. A., Kirov, I., Wungwattana, M. et al. (2016) Successful treatment of genetically profiled pediatric extranodal NK/T-cell lymphoma targeting oncogenic STAT3 mutation. *Pediatr. Blood Cancer* **63**, 727-730.

Menter, T., Tzankov, A. (2018) Mechanisms of immune evasion and immune modulation by lymphoma cells. *Front. Oncol.* **8**, 54.

Merrill, M. H., Dahi, P. B., Redd, R. A. et al. (2023) A phase 2 study of pembrolizumab after autologous stem cell transplantation in patients with T-cell non-Hodgkin lymphoma. *Blood* **142**, 621-628.

Mettu, N. B., Ulahannan, S. V., Bendell, J. C. et al. (2022) A phase 1a/b open-label, dose-escalation study of etigilimab alone or in combination with nivolumab in patients with locally advanced or metastatic solid tumors. *Clin. Cancer Res.* **28**, 882-892.

Michielin, O., van Akkooi, A. C. J., Ascierto, P. A. et al. (2019) Cutaneous melanoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up†. *Ann. Oncol.* **30**, 1884-1901.

Michot, J. M., Mouraud, S., Adam, J. et al. (2021) CD8+ T lymphocytes immune depletion and LAG-3 overexpression in Hodgkin lymphoma tumor microenvironment exposed to anti-PD-1 immunotherapy. *Cancers (Basel)* **13**, 5487.

Miyoshi, H., Kiyasu, J., Kato, T. et al. (2016) PD-L1 expression on neoplastic or stromal cells is respectively a poor or good prognostic factor for adult T-cell leukemia/lymphoma. *Blood* **128**, 1374-1381.

Moik, F., Chan, W. E., Wiedemann, S. et al. (2021) Incidence, risk factors, and outcomes of venous and arterial thromboembolism in immune checkpoint inhibitor therapy. *Blood* **137**, 1669-1678.

Mossé, Y. P., Lim, M. S., Voss, S. D. et al. (2013) Safety and activity of crizotinib for paediatric patients with refractory solid tumors or anaplastic large-cell lymphoma: a Children's Oncology Group phase 1 consortium study. *Lancet Oncol.* **14**, 472-480.

Mossé, Y. P., Voss, S. D., Lim, M. S. et al. (2017) Targeting ALK with crizotinib in pediatric anaplastic large cell lymphoma and inflammatory myofibroblastic tumor: a Children's Oncology Group study. *J. Clin. Oncol.* **35**, 3215-3221.

Muenst, S., Laubli, H., Soysal, S. D. et al. (2016) The immune system and cancer evasion strategies: therapeutic concepts. *J. Intern. Med.* **279**, 541-562.

Murashige, N., Kami, M., Kishi, Y. et al. (2005) Allogeneic haematopoietic stem cell transplantation as a promising treatment for natural killer-cell neoplasms. *Br. J. Haematol.* **130**, 561-567.

Murga-Zamalloa, C. A., Brown, N. A., Wilcox, R. A. (2020) Expression of the checkpoint receptors LAG-3, TIM-3 and VISTA in peripheral T cell lymphomas. *J. Clin. Pathol.* **73**, 197-203.

Mutzbauer, G., Maurus, K., Buszello, C. et al. (2018) SYK expression in monomorphic epitheliotropic intestinal T-cell lymphoma. *Mod. Pathol.* **31**, 505-516.

Nagato, T., Ohkuri, T., Ohara, K. et al. (2017) Programmed death-ligand 1 and its soluble form are highly expressed in nasal natural killer/T-cell lymphoma: a potential rationale for immunotherapy. *Cancer Immunol. Immunother.* **66**, 877-890.

Nanda, R., Chow, L. Q., Dees, E. C. et al. (2016) Pembrolizumab in patients with advanced triple-negative breast cancer: phase Ib KEYNOTE-012 study. *J. Clin. Oncol.* **34**, 2460-2467.

Nawa, Y., Takenaka, K., Shinagawa, K. et al. (1999) Successful treatment of advanced natural killer cell lymphoma with high-dose chemotherapy and syngeneic peripheral blood stem cell transplantation. *Bone Marrow Transplant.* **23**, 1321-1322.

Neuwelt, A., Al-Juhaishi, T., Davila, E. et al. (2020) Enhancing antitumor immunity through checkpoint blockade as a therapeutic strategy in T-cell lymphomas. *Blood Adv.* **4**, 4256-4266.

Nguyen, H. H., Bui, K. C., Nguyen, T. M. L. et al. (2023) The safety of CAR-T cells and PD-1 antibody combination on an experimental model. *Biochem. Biophys. Res. Commun.* **649**, 25-31.

Ni, D., AlZahrani, F., Smylie, M. (2019) AIHA and pancytopenia as complications of pembrolizumab therapy for metastatic melanoma: a case report. *Case Rep. Oncol.* **12**, 456-465.

Nie, J., Wang, C., Liu, Y. et al. (2019) Addition of low-dose decitabine to anti–PD-1 antibody camrelizumab in relapsed/refractory classical Hodgkin lymphoma. *J. Clin. Oncol.* **37**, 1479-1489.

Niu, J., Maurice-Dror, C., Lee, D. H. et al. (2022) First-in-human phase 1 study of the anti-TIGIT antibody vibostolimab as monotherapy or with pembrolizumab for advanced solid tumors, including non-small-cell lung cancer(☆). *Ann. Oncol.* **33**, 169-180.

O'Connor, O. A., Horwitz, S., Masszi, T. et al. (2015) Belinostat in patients with relapsed or refractory peripheral T-cell lymphoma: results of the pivotal phase II BELIEF (CLN-19) study. *J. Clin. Oncol.* **33**, 2492-2499.

Ohmoto, A., Fuji, S. (2023) Rapid T-cell lymphoma progression associated with immune checkpoint inhibitors. *Expert Rev. Hematol.* **16**, 535-541.

Ohue, Y., Nishikawa, H. (2019) Regulatory T (Treg) cells in cancer: Can Treg cells be a new therapeutic target? *Cancer Sci.* **110**, 2080-2089.

Onaindia, A., de Villambrosía, S. G., Prieto-Torres, L. et al. (2019) DUSP22-rearranged anaplastic lymphomas are characterized by specific morphological features and a lack of cytotoxic and JAK/STAT surrogate markers. *Haematologica* **104**, e158-e162.

Onishi, A., Fuji, S., Kitano, S. et al. (2022) Prognostic implication of CTLA-4, PD-1, and PD-L1 expression in aggressive adult T-cell leukemia-lymphoma. *Ann. Hematol.* **101**, 799-810.

Osorio, J. C., Ni, A., Chaft, J. E. et al. (2017) Antibody-mediated thyroid dysfunction during T-cell checkpoint blockade in patients with non-small-cell lung cancer. *Ann. Oncol.* **28**, 583-589.

Oyewole-Said, D., Konduri, V., Vazquez-Perez, J. et al. (2020) Beyond T-cells: functional characterization of CTLA-4 expression in immune and non-immune cell types. *Front. Immunol.* **11**, 608024.

Palmieri, D. J., Carlino, M. S. (2018) Immune checkpoint inhibitor toxicity. *Curr. Oncol. Rep.* **20**, 72.

Panjwani, P. K., Charu, V., DeLisser, M. et al. (2018) Programmed death-1 ligands PD-L1 and PD-L2 show distinctive and restricted patterns of expression in lymphoma subtypes. *Hum. Pathol.* **71**, 91-99.

Parrilla Castellar, E. R., Jaffe, E. S., Said, J. W. et al. (2014) ALK-negative anaplastic large cell lymphoma is a genetically heterogeneous disease with widely disparate clinical outcomes. *Blood* **124**, 1473-1480.

Pathak, S., Zito, P. M. (2024) *Clinical Guidelines for the Staging, Diagnosis, and Management of Cutaneous Malignant Melanoma.* StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing.

Pellegrino, B., Musolino, A., Tiseo, M. (2017) Anti-PD-1-related cryoglobulinemia during treatment with nivolumab in NSCLC patient. *Ann. Oncol.* **28**, 1405-1406.

Pfeiferova, L., Safarikova, M., Ulrych, J. et al. (2022) Circulating cell-free DNA extraction from liquid biopsy for cancer research. *Folia Biol. (Praha)* **68**, 153-157.

Pittaluga, S., Wlodarska, I., Pulford, K. et al. (1997) The monoclonal antibody ALK1 identifies a distinct morphological subtype of anaplastic large cell lymphoma associated with 2p23/ALK rearrangements. *Am. J. Pathol.* **151**, 343-351.

Prince, H. M., Duvic, M., Martin, A. et al. (2010) Phase III placebo-controlled trial of denileukin diftitox for patients with cutaneous T-cell lymphoma. *J. Clin. Oncol.* **28**, 1870-1877.

Prockop, S., Doubrovina, E., Suser, S. et al. (2020) Off-the-shelf EBV-specific T cell immunotherapy for rituximab-refractory EBV-associated lymphoma following transplantation. *J. Clin. Invest.* **130**, 733-747.

Prokoph, N., Larose, H., Lim, M. S. et al. (2018) Treatment options for paediatric anaplastic large cell lymphoma (ALCL): current standard and beyond. *Cancers (Basel)* **10**, 99.

Querfeld, C., Leung, S., Myskowski, P. L. et al. (2018) Primary T cells from cutaneous T-cell lymphoma skin explants display an exhausted immune checkpoint profile. *Cancer Immunol. Res.* **6**, 900-909.

Querfeld, C., Wu, X., Stiller, T. et al. (2019) Phase 1 results of anti-PD-ligand 1 (durvalumab) and lenalidomide in patients with cutaneous T cell lymphoma and correlation with programmed death ligand 1 expression and gene expression profile. *Blood* **134**, 4024.

Raskov, H., Orhan, A., Christensen, J. P. et al. (2021) Cytotoxic $CD8^+$ T cells in cancer and cancer immunotherapy. *Br. J. Cancer* **124**, 359-367.

Ratner, L., Waldmann, T. A., Janakiram, M. et al. (2018) Rapid progression of adult T-cell leukemia-lymphoma after PD-1 inhibitor therapy. *N. Engl. J. Med.* **378**, 1947-1948.

Rauch, D. A., Conlon, K. C., Janakiram, M. et al. (2019) Rapid progression of adult T-cell leukemia/lymphoma as tumor-infiltrating Tregs after PD-1 blockade. *Blood* **134**, 1406-1414.

Ribas, A., Puzanov, I., Dummer, R. et al. (2015) Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial. *Lancet Oncol.* **16**, 908-918.

Ribas, A., Wolchok, J. D. (2018) Cancer immunotherapy using checkpoint blockade. *Science* **359**, 1350-1355.

Rigaud, C., Abbou, S., Minard-Colin, V. et al. (2018) Efficacy of nivolumab in a patient with systemic refractory ALK+ anaplastic large cell lymphoma. *Pediatr. Blood Cancer* **65**, https://doi.org/10.1002/pbc.26902

Rowshanravan, B., Halliday, N., Sansom, D. M. (2018) CTLA-4: a moving target in immunotherapy. *Blood* **131**, 58-67.

Rudd, C. E., Schneider, H. (2003) Unifying concepts in CD28, ICOS and CTLA4 co-receptor signalling. *Nat. Rev. Immunol.* **3**, 544-556.

Sadeghi, M., Khodakarami, A., Ahmadi, A. et al. (2022) The prognostic and therapeutic potentials of CTLA-4 in hematological malignancies. *Expert Opin. Ther. Targets* **26**, 1057-1071.

Safa, H., Johnson, D. H., Trinh, V. A. et al. (2019) Immune checkpoint inhibitor related myasthenia gravis: single center experience and systematic review of the literature. *J. Immunother. Cancer* **7**, 319.

Sakuishi, K., Apetoh, L., Sullivan, J. M. et al. (2010) Targeting Tim-3 and PD-1 pathways to reverse T cell exhaustion and restore anti-tumor immunity. *J. Exp. Med.* **207**, 2187-2194.

Salim, A., Tapia Rico, G., Shaikh, A. et al. (2021) A systematic review of immune checkpoint inhibitor-related neurological adverse events and association with anti-neuronal autoantibodies. *Expert Opin. Biol. Ther.* **21**, 1237-1251.

Sasaki, M., Matsue, K., Takeuchi, M. et al. (2000) Successful treatment of disseminated nasal NK/T-cell lymphoma using double autologous peripheral blood stem cell transplantation. *Int. J. Hematol.* **71**, 75-78.

Sauer, N., Janicka, N., Szlasa, W. et al. (2023) TIM-3 as a promising target for cancer immunotherapy in a wide range of tumors. *Cancer Immunol. Immunother.* **72**, 3405-3425.

Saulite, I., Ignatova, D., Chang, Y. T. et al. (2020) Blockade of programmed cell death protein 1 (PD-1) in Sézary syndrome reduces Th2 phenotype of non-tumoral T lymphocytes but may enhance tumor proliferation. *Oncoimmunology* **9**, 1738797.

Schöffski, P., Tan, D. S. W., Martín, M. et al. (2022) Phase I/II study of the LAG-3 inhibitor ieramilimab (LAG525) ± anti-PD-1 spartalizumab (PDR001) in patients with advanced malignancies. *J. Immunother. Cancer* **10**, e003776.

Schrader, A., Crispatzu, G., Oberbeck, S. et al. (2018) Actionable perturbations of damage responses by TCL1/ATM and epigenetic lesions form the basis of T-PLL. *Nat. Commun.* **9**, 697.

Sekulic, A., Liang, W. S., Tembe, W. et al. (2015) Personalized treatment of Sézary syndrome by targeting a novel CTLA4:CD28 fusion. *Mol. Genet. Genomic Med.* **3**, 130-136.

Shah, N., Adrianzen Herrera, D., Shah, U. et al. (2019) Unique racial patterns in rare T-cell lymphomas: a national cancer registry analysis from 2001 to 2015. *J. Clin. Oncol.* **37 (Suppl.15)**, https://doi.org/10.1200/JCO.2019.37.15_suppl.e190

Sharpe, A. H., Pauken, K. E. (2018) The diverse functions of the PD1 inhibitory pathway. *Nat. Rev. Immunol.* **18**, 153-167.

Sheppard, K. A., Fitz, L. J., Lee, J. M. et al. (2004) PD-1 inhibits T-cell receptor induced phosphorylation of the ZAP70/CD3ζ signalosome and downstream signaling to PKCθ. *FEBS Lett.* **574**, 37-41.

Shi, L., Chen, S., Yang, L. et al. (2013) The role of PD-1 and PD-L1 in T-cell immune suppression in patients with hematological malignancies. *J. Hematol. Oncol.* **6**, 74.

Shi, Y., Su, H., Song, Y. et al. (2019) Safety and activity of sintilimab in patients with relapsed or refractory classical Hodgkin lymphoma (ORIENT-1): a multicentre, single-arm, phase 2 trial. *Lancet Haematol.* **6**, e12-e19.

Shi, Y., Wu, J., Wang, Z. et al. (2021) Efficacy and safety of geptanolimab (GB226) for relapsed or refractory peripheral T cell lymphoma: an open-label phase 2 study (Gxplore-002). *J. Hematol. Oncol.* **14**, 12.

Shimauchi, T., Kabashima, K., Tokura, Y. (2008) Adult T-cell leukemia/lymphoma cells from blood and skin tumors express cytotoxic T lymphocyte-associated antigen-4 and Foxp3 but lack suppressor activity toward autologous $CD8^+$ T cells. *Cancer Sci.* **99**, 98-106.

Shirasuna, K., Koelsch, G., Seidel-Dugan, C. et al. (2021) Characterization of ASP8374, a fully-human, antagonistic anti-TIGIT monoclonal antibody. *Cancer Treat. Res. Commun.* **28**, 100433.

Shitara, K., Ajani, J. A., Moehler, M. et al. (2022) Nivolumab plus chemotherapy or ipilimumab in gastro-oesophageal cancer. *Nature* **603**, 942-948.

Silva, R. C. M. C., Lopes, M. F., Travassos, L. H. (2023) Distinct T helper cell-mediated antitumor immunity: T helper 2 cells in focus. *Cancer Pathog. Ther.* **1**, 76-86.

Smith, S. D., Till, B. G., Shadman, M. S. et al. (2020) Pembrolizumab with R-CHOP in previously untreated diffuse large B-cell lymphoma: potential for biomarker driven therapy. *Br. J. Haematol.* **189**, 1119-1126.

Stadler, R., Romero, P. O., Bagot, M. et al. (2021) Phase II trial of atezolizumab (anti-PD-L1) in the treatment of stage IIB–IVB mycosis fungoides/Sézary syndrome patients relapsed/refractory after a previous systemic treatment (PARCT). *Eur. J. Cancer* **156**, S22-S23.

Stuver, R., Moskowitz, A. J. (2023) Therapeutic advances in relapsed and refractory peripheral T-cell lymphoma. *Cancers (Basel)* **15**, 589.

Su, S., Zhao, J., Xing, Y. et al. (2018) Immune checkpoint inhibition overcomes ADCP-induced immunosuppression by macrophages. *Cell* **175**, 442-457 e23.

Sun, C., Mezzadra, R., Schumacher, T. N. (2018) Regulation and function of the PD-L1 checkpoint. *Immunity* **48**, 434-452.

Sun, P., Wang, Y., Yang, H. et al. (2022) Combination of anti-PD-1 antibody, anlotinib and pegaspargase "sandwich" with radiotherapy in localized natural killer/T cell lymphoma. *Front. Immunol.* **13**, 766200.

Suzuki, R., Yamaguchi, M., Izutsu, K. et al. (2011) Prospective measurement of Epstein-Barr virus-DNA in plasma and peripheral blood mononuclear cells of extranodal NK/T-cell lymphoma, nasal type. *Blood* **118**, 6018-6022.

Swetter, S. M., Tsao, H., Bichakjian, C. K. et al. (2019) Guidelines of care for the management of primary cutaneous melanoma. *J. Am. Acad. Dermatol.* **80**, 208-250.

Tabanelli, V., Corsini, C., Fiori, S. et al. (2019) Recurrent PDL1 expression and PDL1 (CD274) copy number alterations in breast implant-associated anaplastic large cell lymphomas. *Hum. Pathol.* **90**, 60-69.

Tadokoro, T., Keshino, E., Makiyama, A. et al. (2016) Acute lymphocytic myocarditis with anti-PD-1 antibody nivolumab. *Circ. Heart Fail.* **9**, e003514.

Takeuchi, M., Miyoshi, H., Ohshima, K. (2021) Tumor microenvironment of adult T-cell leukemia/lymphoma. *J. Clin. Exp. Hematop.* **61**, 202-209.

Tao, R., Fan, L., Song, Y. et al. (2019) Sintilimab for relapsed/refractory (r/r) extranodal NK/T-cell lymphoma (ENKTL):

a multicenter, single-arm, phase 2 trial (ORIENT-4). *J. Clin. Oncol.* **37**, 7504.

Teufel, A., Zhan, T., Härtel, N. et al. (2019) Management of immune related adverse events induced by immune checkpoint inhibition. *Cancer Lett.* **456**, 80-87.

Thandra, K. C., Barsouk, A., Saginala, K. et al. (2021) Epidemiology of non-Hodgkin's lymphoma. *Med. Sci. (Basel)* **9**, 5.

Tian, Y., Gao, A., Wen, Q. et al. (2020) Immune-related neurological toxicities of PD-1/PD-L1 inhibitors in cancer patients: a systematic review and meta-analysis. *Front. Immunol.* **11**, 595655.

Toes, R. E., Ossendorp, F., Offringa, R. et al. (1999) CD4 T cells and their role in antitumor immune responses. *J. Exp. Med.* **189**, 753-756.

Torossian, A., Broin, N., Frentzel, J. et al. (2019) Blockade of crizotinib-induced BCL2 elevation in ALK-positive anaplastic large cell lymphoma triggers autophagy associated with cell death. *Haematologica* **104**, 1428-1439.

Tsuyama, N., Sakamoto, K., Sakata, S. et al. (2017) Anaplastic large cell lymphoma: pathology, genetics, and clinical aspects. *J. Clin. Exp. Hematop.* **57**, 120-142.

Twomey, J. D., Zhang, B. (2021) Cancer immunotherapy update: FDA-approved checkpoint inhibitors and companion diagnostics. *AAPS J.* **23**, 39.

Vallois, D., Dobay, M. P. D., Morin, R. D. et al. (2016) Activating mutations in genes related to TCR signaling in angioimmunoblastic and other follicular helper T-cell-derived lymphomas. *Blood* **128**, 1490-1502.

Van Arnam, J. S., Lim, M. S., Elenitoba-Johnson, K. S. J. (2018) Novel insights into the pathogenesis of T-cell lymphomas. *Blood* **131**, 2320-2330.

van Eijs, M. J. M., van der Wagen, L. E., Mous, R. et al. (2023) Hematologic malignancies following immune checkpoint inhibition for solid tumors. *Cancer Immunol. Immunother.* **72**, 249-255.

Varricchi, G., Marone, G., Mercurio, V. et al. (2018) Immune checkpoint inhibitors and cardiac toxicity: an emerging issue. *Curr. Med. Chem.* **25**, 1327-1339.

Veloza, L., Cavalieri, D., Missiaglia, E. et al. (2022) Monomorphic epitheliotropic intestinal T-cell lymphoma comprises morphologic and genomic heterogeneity impacting outcome. *Haematologica* **108**, 181-195.

Vogrig, A., Muñiz-Castrillo, S., Farina, A. et al. (2022) How to diagnose and manage neurological toxicities of immune checkpoint inhibitors: an update. *J. Neurol.* **269**, 1701-1714.

von Tresckow, B., Fanale, M., Ardeshna, K. M. et al. (2019) Patient-reported outcomes in KEYNOTE-087, a phase 2 study of pembrolizumab in patients with classical Hodgkin lymphoma. *Leuk. Lymphoma* **60**, 2705-2711.

Vose, J., Armitage, J., Weisenburger, D. (2008) International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. *J. Clin. Oncol.* **26**, 4124-4130.

Voskens, C. J., Goldinger, S. M., Loquai, C. et al. (2013) The price of tumor control: an analysis of rare side effects of anti-CTLA-4 therapy in metastatic melanoma from the ipilimumab network. *PLoS One* **8**, e53745.

Wai, C. M. M., Chen, S., Phyu, T. et al. (2022) Immune pathway upregulation and lower genomic instability distinguish EBV-positive nodal T/NK-cell lymphoma from ENKTL and PTCL-NOS. *Haematologica* **107**, 1864-1879.

Waldman, A. D., Fritz, J. M., Lenardo, M. J. (2020) A guide to cancer immunotherapy: from T cell basic science to clinical practice. *Nat. Rev. Immunol.* **20**, 651-668.

Walker, L. S., Sansom, D. M. (2015) Confusing signals: recent progress in CTLA-4 biology. *Trends Immunol.* **36**, 63-70.

Wang, D. Y., Salem, J. E., Cohen, J. V. et al. (2018) Fatal toxic effects associated with immune checkpoint inhibitors: a systematic review and meta-analysis. *JAMA Oncol.* **4**, 1721-1728.

Wang, H., Wang, L., Liu, W. J. et al. (2016) High post-treatment serum levels of soluble programmed cell death ligand 1 predict early relapse and poor prognosis in extranodal NK/T cell lymphoma patients. *Oncotarget* **7**, 33035-33045.

Wang, L., Wang, H., Li, P. F. et al. (2015) CD38 expression predicts poor prognosis and might be a potential therapy target in extranodal NK/T cell lymphoma, nasal type. *Ann. Hematol.* **94**, 1381-1388.

Wang, L., Wang, Z. H., Chen, X. Q. et al. (2013) First-line combination of gemcitabine, oxaliplatin, and L-asparaginase (GELOX) followed by involved-field radiation therapy for patients with stage IE/IIE extranodal natural killer/T-cell lymphoma. *Cancer* **119**, 348-355.

Wartewig, T., Kurgyis, Z., Keppler, S. et al. (2017) PD-1 is a haploinsufficient suppressor of T cell lymphomagenesis. *Nature* **552**, 121-125.

Webb, G. J., Hirschfield, G. M., Lane, P. J. (2016) OX40, OX40L and autoimmunity: a comprehensive review. *Clin. Rev. Allergy Immunol.* **50**, 312-332.

Willemze, R., Cerroni, L., Kempf, W. et al. (2019) The 2018 update of the WHO-EORTC classification for primary cutaneous lymphomas. *Blood* **133**, 1703-1714.

Willemze, R., Hodak, E., Zinzani, P. L. et al. (2018) Primary cutaneous lymphomas: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Approved by the ESMO Guidelines Committee: December 2006, last update January 2018. This publication supersedes the previously published version – Ann. Oncol. 2013; 24 (Suppl. 6): vi149–vi154. *Ann. Oncol.* **29**, iv30-iv40.

Wlodarski, M. W., Quimper, M., Gondek, L. et al. (2004) Study of CTLA-4 regulation in large granular lymphocyte leukemia cells and their normal counterparts. *Blood* **104**, 3871.

Wong, H. K., Wilson, A. J., Gibson, H. M. et al. (2006) Increased expression of CTLA-4 in malignant T cells from patients with mycosis fungoides – cutaneous T-cell lymphoma. *J. Invest. Dermatol.* **126**, 212-219.

Xu, C., Chen, Y. P., Du, X. J. et al. (2018a) Comparative safety of immune checkpoint inhibitors in cancer: systematic review and network meta-analysis. *BMJ* **363**, k4226.

Xu, X., Huang, Z., Zheng, L. et al. (2018b) The efficacy and safety of anti-PD-1/PD-L1 antibodies combined with chemotherapy or CTLA4 antibody as a first-line treatment for advanced lung cancer. *Int. J. Cancer* **142**, 2344-2354.

Yabe, M., Medeiros, L. J., Tang, G. (2016) Prognostic factors of hepatosplenic T-cell lymphoma: clinicopathologic study of 28 cases. *Am. J. Surg. Pathol.* **40**, 676-688.

Yamaguchi, M., Kita, K., Miwa, H. et al. (1995) Frequent expression of P-glycoprotein/MDR1 by nasal T-cell lymphoma cells. *Cancer* **76**, 2351-2356.

Yamaguchi, M., Suzuki, R., Oguchi, M. (2018) Advances in the treatment of extranodal NK/T-cell lymphoma, nasal type. *Blood* **131**, 2528-2540.

Yan, Z., Yao, S., Liu, Y. et al. (2020) Durable response to sintilimab and chidamide in a patient with pegaspargase- and immunotherapy-resistant NK/T-cell lymphoma: case report and literature review. *Front. Oncol.* **10**, 608304.

Yang, J., Epling-Burnette, P. K., Painter, J. S. et al. (2008) Antigen activation and impaired Fas-induced death-inducing signaling complex formation in T-large-granular lymphocyte leukemia. *Blood* **111**, 1610-1616.

Yhim, H. Y., Kim, J. S., Mun, Y. C. et al. (2015) Clinical outcomes and prognostic factors of up-front autologous stem cell transplantation in patients with extranodal natural killer/T cell lymphoma. *Biol. Blood Marrow Transplant.* **21**, 1597-1604.

Yong, W., Zheng, W., Zhang, Y. et al. (2003) L-asparaginase-based regimen in the treatment of refractory midline nasal/nasal-type T/NK-cell lymphoma. *Int. J. Hematol.* **78**, 163-167.

Yoo, H. Y., Kim, P., Kim, W. S. et al. (2016) Frequent CTLA4-CD28 gene fusion in diverse types of T-cell lymphoma. *Haematologica* **101**, 757-763.

You, J. Y., Chi, K. H., Yang, M. H. et al. (2004) Radiation therapy versus chemotherapy as initial treatment for localized nasal natural killer (NK)/T-cell lymphoma: a single institute survey in Taiwan. *Ann. Oncol.* **15**, 618-625.

Younes, A., Santoro, A., Shipp, M. et al. (2016) Nivolumab for classical Hodgkin's lymphoma after failure of both autologous stem-cell transplantation and brentuximab vedotin: a multicentre, multicohort, single-arm phase 2 trial. *Lancet Oncol.* **17**, 1283-1294.

Yu, X., Harden, K., Gonzalez, L. C. et al. (2009) The surface protein TIGIT suppresses T cell activation by promoting the generation of mature immunoregulatory dendritic cells. *Nat. Immunol.* **10**, 48-57.

Yun, N. K., Alrifai, T., Miller, I. J. et al. (2021) Pembrolizumab-induced autoimmune haemolytic anemia in a patient with chronic lymphocytic leukaemia successfully treated with ibrutinib. *BMJ Case Rep.* **14**, e245350.

Zain, J. M., Hanona, P. (2021) Aggressive T-cell lymphomas: 2021 updates on diagnosis, risk stratification and management. *Am. J. Hematol.* **96**, 1027-1046.

Zhang, N., Bevan, M. J. (2011) $CD8^+$ T cells: foot soldiers of the immune system. *Immunity* **35**, 161-168.

Zhang, N., Dalal, M. R. (2019) PRO66 incidence and prevalence of T-cell lymphoma in the EMA member states: methodology for estimation in rare malignancies of CTCL and PTCL. *Value Health* **22**, S853.

Zhang, W., Shen, H., Zhang, Y. et al. (2019) Circulating PD-1 (+) cells may participate in immune evasion in peripheral T-cell lymphoma and chidamide enhance antitumor activity of PD-1 (+) cells. *Cancer Med.* **8**, 2104-2113.

Zhang, Y., Cui, Y., Li, Y. et al. (2023) Immune checkpoint inhibitor-induced primary hyperparathyroidism in a small-cell lung cancer patient: a case report. *Medicina (Kaunas)* **59**, 215.

Zhang, Y., Zhang, Y., Gu, W. et al. (2014) TH1/TH2 cell differentiation and molecular signals. *Adv. Exp. Med. Biol.* **841**, 15-44.

Zhang, Y., Zheng, J. (2020) Functions of immune checkpoint molecules beyond immune evasion. *Adv. Exp. Med. Biol.* **1248**, 201-226.

Zhao, S., Sun, M., Meng, H. et al. (2019) TLR4 expression correlated with PD-L1 expression indicates a poor prognosis in patients with peripheral T-cell lymphomas. *Cancer Manag. Res.* **11**, 4743-4756.

Zinzani, P. L., Santoro, A., Gritti, G. et al. (2019) Nivolumab combined with brentuximab vedotin for relapsed/refractory primary mediastinal large B-cell lymphoma: efficacy and safety from the phase II CheckMate 436 study. *J. Clin. Oncol.* **37**, 3081-3089.

Zöphel, D., Angenendt, A., Kaschek, L. et al. (2022) Faster cytotoxicity with age: increased perforin and granzyme levels in cytotoxic $CD8^+$ T cells boost cancer cell elimination. *Aging Cell* **21**, e13668.