Received: 30 November 2023 | Revised: 9 June 2024 | Accepted: 25 June 2024

DOI: 10.1002/cac2.12587

CANCER COMMUNICATIONS Open Access

REVIEW

Advances and clinical applications of immune checkpoint inhibitors in hematological malignancies

Wenyue Sun[1] | **Shunfeng Hu**[2] | **Xin Wang**[1,2,3,4,5]

[1]Department of Hematology, Shandong Provincial Hospital, Shandong University, Jinan, Shandong, P. R. China

[2]Department of Hematology, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, Shandong, P. R. China

[3]Taishan Scholars Program of Shandong Province, Jinan, Shandong, P. R. China

[4]Branch of National Clinical Research Center for Hematologic Diseases, Jinan, Shandong, P. R. China

[5]National Clinical Research Center for Hematologic Diseases, the First Affiliated Hospital of Soochow University, Suzhou, Jiangsu, P. R. China

Correspondence
Xin Wang, M.D., Ph.D., Director & Professor of the Department of Hematology, Shandong Provincial Hospital, Shandong University, No.324, Jingwu Road, Jinan, Shandong, 250021, P. R. China.
Email: xinw007@126.com

Shunfeng Hu, M.D., Ph.D., Department of Hematology, Shandong Provincial Hospital Affiliated to Shandong First Medical University, No.324, Jingwu Road, Jinan, Shandong, 250021, P. R. China.
Email: HuShunFeng0409@163.com

Abstract

Immune checkpoints are differentially expressed on various immune cells to regulate immune responses in tumor microenvironment. Tumor cells can activate the immune checkpoint pathway to establish an immunosuppressive tumor microenvironment and inhibit the anti-tumor immune response, which may lead to tumor progression by evading immune surveillance. Interrupting co-inhibitory signaling pathways with immune checkpoint inhibitors (ICIs) could reinvigorate the anti-tumor immune response and promote immune-mediated eradication of tumor cells. As a milestone in tumor treatment, ICIs have been firstly used in solid tumors and subsequently expanded to hematological malig-

Abbreviations: ADCC, antibody-dependent cell-mediated cytotoxicity; ALL, acute lymphoblastic leukemia; allo-HCT, allogeneic hematopoietic cell transplantation; AML, acute myeloid leukemia; APCs, antigen-presenting cells; ATLL, adult T-cell leukemia-lymphoma; auto-HCT, autologous hematopoietic cell transplantation; B-NHL, B-cell non-Hodgkin lymphoma; B2M, Beta-2-microglobulin; BM, bone marrow; BiTE, bispecific T cell engager; BSA, body surface area; bsAb, bispecific antibody; BTLA, B and T lymphocyte attenuator; c-HL, classic Hodgkin lymphoma; c-MYC, c-myelocytomatosis viral oncogene homolog; CAR-T, chimeric antigen receptor T-cell; CD, cluster of differentiation; cDCs, conventional DCs; CIK, cytokine-induced killer; CiTE, checkpoint inhibitory T cell-engaging; CML, chronic myeloid leukemia; CoA, acetyl coenzyme A; CRR, complete response rate; CTLA-4, cytotoxic T lymphocyte-associated antigen 4; DCs, dendritic cells; DLBCL, diffuse large B-cell lymphoma; ENKTCL, extra-nodal natural killer/T cell lymphoma; ESMO, European Society for Medical Oncology; Fc, crystalline fragment; FDA, Food and Drug Administration; FL, follicular lymphoma; Foxp3, forkhead box protein P3; GPI, glycosyl-phosphatidylinositol; HIV, human immunodeficiency virus; HL, Hodgkin lymphoma; HO-1, Heme oxygenase-1; HVEM, herpes virus entry mediator; ICB, immune checkpoint blockade; ICIs, immune checkpoint inhibitors; IFN-γ, interferon-γ; IgG, immunoglobulin G; IL, interleukin; irAEs, immune-related adverse events; JAK, Janus kinase; LAG-3, lymphocyte activation gene 3; L1LRB1, leukocyte immunoglobulin-like receptor subfamily B member 1; mAbs, monoclonal antibodies; MCL, mantle cell lymphoma; MDS, myelodysplastic syndromes; MHC, major histocompatibility complex; MM, multiple myeloma; mRNA, messenger RNA; MSCs, Mesenchymal stromal cells; NK cells, natural killer cells; NKG2D, NK receptor group 2 member D; NPs, nanoparticles; ORR, objective response rate; OVs, oncolytic viruses; OX40L, tumor necrosis factor receptor superfamily member 4 ligand; PB, peripheral blood; PCNSL, primary central nervous system lymphoma; pDCs, plasmacytoid DCs; PD-1, programmed cell death protein 1; PD-L1, programmed cell death 1 ligand 1; PFS, progression-free survival; PVRIG, poliovirus receptor-associated immunoglobulin domain-containing; PVRL2, poliovirus receptor-related 2; r/r, relapsed/refractory; RS, Richter syndrome; sCTLA-4, soluble CTLA-4; SIRPα, signal regulatory protein α; sPD-L1, soluble PD-L1; T-NHL, T-cell non-Hodgkin lymphoma; TAAs, tumor-associated antigens; T-VEC, talimogene laherparepvec; TGF-β, transforming growth factor-β; TIM-3, T cell immunoglobulin domain and mucin domain 3; TIPE2, Tumor necrosis factor-alpha-inducible protein 8-like 2; TNF, tumor necrosis factor; Tregs, regulatory T cells; VISTA, V-domain Ig suppressor of T cell activation; VSV, vesicular stomatitis virus.

Funding information
National Natural Science Foundation, Grant/Award Numbers: 82270200, 82070203, 81770210; Key Research and Development Program of Shandong Province, Grant/Award Number: 2018CXGC1213; Taishan Scholars Program of Shandong Province, Grant/Award Numbers: tspd20230610, tsqnz20231251; Translational Research Grant of NCRCH, Grant/Award Numbers: 2021WWB02, 2020ZKMB01; Shandong Provincial Engineering Research Center of Lymphoma; Academic Promotion Programme of Shandong First Medical University, Grant/Award Number: 2019QL018; China Postdoctoral Science Foundation, Grant/Award Number: 2023M741506; Shandong Provincial Natural Science Foundation, Grant/Award Number: ZR2023QH193

nancies, which are in their infancy. Currently, immune checkpoints have been investigated as promising biomarkers and therapeutic targets in hematological malignancies, and novel immune checkpoints, such as signal regulatory protein α (SIRPα) and tumor necrosis factor-alpha-inducible protein 8-like 2 (TIPE2), are constantly being discovered. Numerous ICIs have received clinical approval for clinical application in the treatment of hematological malignancies, especially when used in combination with other strategies, including oncolytic viruses (OVs), neoantigen vaccines, bispecific antibodies (bsAb), bio-nanomaterials, tumor vaccines, and cytokine-induced killer (CIK) cells. Moreover, the proportion of individuals with hematological malignancies benefiting from ICIs remains lower than expected due to multiple mechanisms of drug resistance and immune-related adverse events (irAEs). Close monitoring and appropriate intervention are needed to mitigate irAEs while using ICIs. This review provided a comprehensive overview of immune checkpoints on different immune cells, the latest advances of ICIs and highlighted the clinical applications of immune checkpoints in hematological malignancies, including biomarkers, targets, combination of ICIs with other therapies, mechanisms of resistance to ICIs, and irAEs, which can provide novel insight into the future exploration of ICIs in tumor treatment.

KEYWORDS
Immune checkpoint, hematological malignancies, biomarkers, therapeutic targets, drug resistance

1 | BACKGROUND

Immune homeostasis can be influenced by immune checkpoint molecules that are expressed on immune cells and tumor cells, which regulate the immune system, and targeting immune checkpoints could affect immune homeostasis [1]. Ligand-receptor pairs that exert inhibitory effects on immune responses are referred to as immune checkpoint molecules. Additionally, the inhibitory pathways may uphold self-tolerance and counteract the activation procedure to prevent excessive harm, which also promotes tumor cells to evade immune destruction, also called immune escape. In recent years, new advances in the mechanisms of tumor promotion by immune checkpoints have emerged continuously. For example, a new study demonstrates that programmed cell death protein 1 (PD-1) signaling inhibits T-cell tumors by restricting the production of glycolytic energy and acetyl coenzyme A (CoA) in a mouse model of T-cell non-Hodgkin lymphoma (T-NHL) and tumor cells from patients with T-NHL [2]. Monoclonal antibodies (mAbs) have been recognized as a means of immune checkpoint blockade (ICB), which could relieve the immune cells from suppression and enable them to identify and eliminate tumor cells [3].

Promising tumor immunotherapies known as immune checkpoint inhibitors (ICIs) have been recognized for their ability to enhance anti-tumor immune responses by targeting immune checkpoints present on both immune cells and tumor cells [4]. A variety of ICIs targeting specific immune checkpoints are currently available in the clinic. In 2011, ipilimumab, the first block antibody against immune checkpoint cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), was authorized for treating melanoma [5]. In 2014, the first PD-1 targeting agent, pembrolizumab, was approved by U.S. Food and Drug Administration (FDA) for melanoma treatment [6, 7]. In 2016, nivolumab, the first PD-1 inhibitor approved to treat hematological malignancies, was approved for treating individuals with relapsed classic Hodgkin lymphoma (c-HL) after autologous hematopoietic stem cell transplantation (auto-HCT). In 2017, approval for the treatment of relapsed/refractory c-HL (r/r c-HL) was granted to pembrolizumab in 2017, after undergoing more previous treatment regimens [8]. At the present time, ICIs have become the most widely used anti-tumor therapy [4], which have enhanced the clinical management of aggressive tumors, including improving patient survival, changing the way to assess efficacy and manage adverse

effects, especially in metastatic melanoma [7]. Additionally, promising progress has been made in the application and research of ICIs independently and in combination with other drugs in hematological malignancies [9, 10].

As numerous studies have verified the clinical significance and prognostic value of ICIs, the expressions of immune checkpoints may have the potential to become significant biomarkers in forecasting prognosis and responsiveness to ICIs. In addition to classical immune checkpoints like PD-1 [11] and CTLA-4 [12], emerging immune checkpoints have been gradually revealed to be prognostic biomarkers for tumors, including V-domain Ig suppressor of T cell activation (VISTA) in extranodal natural killer/T-cell lymphoma [13], lymphocyte activation gene 3 (LAG-3) [14] in diffuse large B-cell lymphoma (DLBCL).

Despite the promising future of ICIs, a considerable proportion of tumor patients fail to show a positive response to ICIs therapy or respond briefly before developing resistance, with significant variation among different types of tumors [15]. Perturbations of any steps of anti-tumor immunity can contribute to ICIs resistance, including the recruitment and stimulation of T cells, the induction of T cell effector activities, and the formation of effector memory T cells [16]. The approaches to overcome drug resistance include focusing on other checkpoint molecules, enhancing T cell exposure to antigens, or combining ICIs with other therapeutic modalities, including cytokine therapies. ICIs treatment can lead to a range of immune-related adverse events (irAEs) that collectively manifest as various side effects. The future application of ICIs in tumor treatment may involve predictive models that rely on the theory of integrated biomarker determination. Combination therapy presents new opportunities for the use of ICIs in tumor therapy, including oncolytic viruses (OVs) [17], neoantigen vaccines [18], bsAb [19], bio-nanomaterials [20], tumor vaccines [21], and cytokine-induced killer (CIK) cells [22].

Given the emerging research of immune checkpoints in the field of hematological malignancies in recent years, we focused on the current advances and potential clinical applications of ICIs in hematological malignancies, including the identification and utilization of biomarkers, the clinical studies of ICIs as standalone treatments or in combination, and the possible obstacles.

2 | IMMUNE CHECKPOINTS IN DIFFERENT IMMUNE CELLS

Immune checkpoints, which have both similarities and differences on the surface of immune cells, antigen-presenting cells (APCs), or tumor cells, have been extensively studied in the last decade [23–25]. Their types and distribution, which will be described separately in the following sections, are shown in Figure 1.

2.1 | Natural killer cells (NK cells)

NK cells, whose chief effector functions are cell killing and the releasement of pro-inflammatory cytokine, can respond to virally infected cells [26, 27].

Additional inhibitory immune checkpoints related to NK cells, apart from the inhibitory receptors linked to the major histocompatibility complex (MHC) class I, have been discovered, including the well-known checkpoints like CTLA-4, PD-1, LAG-3, and T cell immunoglobulin domain and mucin domain 3 (TIM-3) [28]. Recent reports have identified B7- cluster of differentiation (CD) 28 family members, including B7-H3, B7-H7, and VISTA, as potential candidates for inhibiting NK cells. NK cell-based immune checkpoint targets, including siglec-7 and -9, CD200, and CD47, have recently been discovered within the siglec family receptors [28]. CD200 is regarded as a marker of tumor progression due to its elevated expression in different types of tumors in both non-hematological [29] and hematological malignancies, including multiple myeloma (MM) [30] and acute myeloid leukemia (AML) [31]. Evidence suggests that the CD200-CD200 receptor (CD200R) inhibitory pathway directly contributes to suppressing NK cells. The overexpression of CD200 in AML patients suppressed the anti-tumor responses of NK cells, consequently elevating the likelihood of relapse in these individuals. These findings clearly demonstrated that the inhibition of NK cell cytotoxicity could be achieved by targeting cells that express CD200 [32], leading to immune escape and tumor progression.

Recently, a novel immune checkpoint signal regulatory protein α (SIRPα) was reported in NK cells, which could interact with target CD47 and counter other signals, such as interleukin 2 (IL-2) and CD16. Overexpression of CD47 in the NK-sensitive erythroleukemia cell line K562 significantly attenuated the killing of K562 by NK cells. Moreover, SIRPα deficiency or blockage increased the cytotoxic ability of rhesus monkey NK cells, which suggested that the disruption of the SIRPα-CD47 immune checkpoint could enhance the immune response of NK cells against tumors and inhibit NK cell-mediated tumor-killing effects [23].

The formation of tumors has been linked to the existence of malfunctioning NK cells, including aberrant activation of inhibitory immune checkpoints [28]. Hence, ICIs that can restore the anti-tumor activity of NK cells may serve as a viable choice for immunotherapy against tumors. In addition, combining anti-PD-1 or anti-PD-L1 inhibitors and NK cell-specific checkpoint inhibitors, such as anti-KIR or anti-NKG2A inhibitors, can be used for

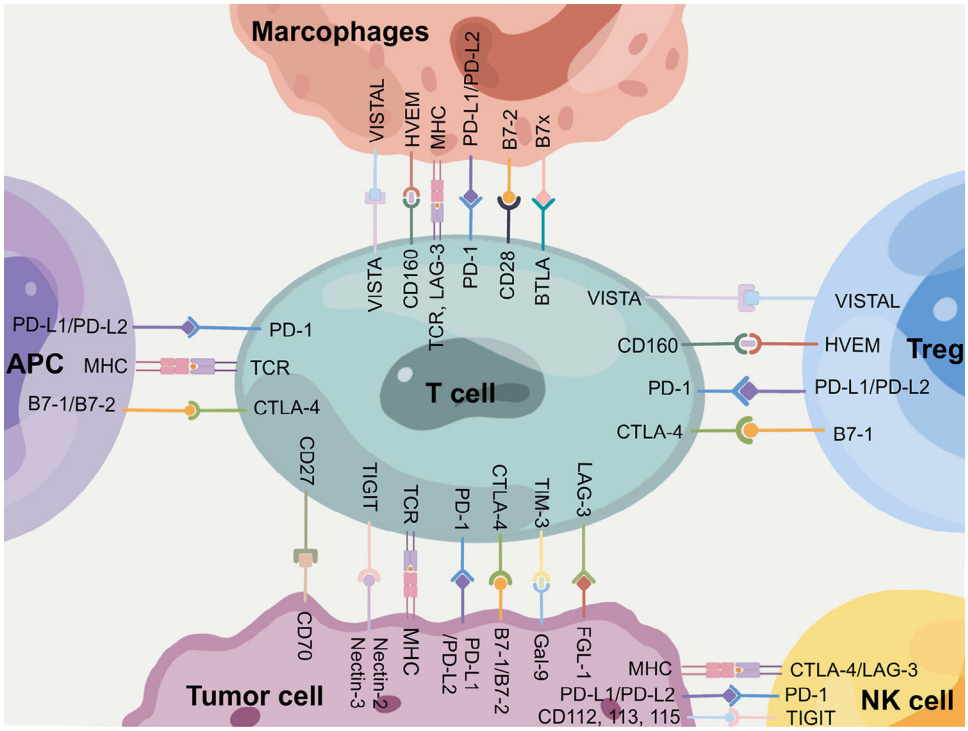

FIGURE 1 The interaction between immune cells and tumor cells through immune checkpoints. The immune component in the tumor microenvironment consists of different types of immune cells, which are highly associated with the anti-tumor immunological state. The expression of immune checkpoint proteins by tumor cells dysregulates the anti-tumor immunity, suppresses the immune function of T cells, and favors the growth and expansion of cancer tumor cells. Abbreviation: APC, antigen-presenting cells; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; FGL-1, fibrinogen-like protein 1; Gal-9, galectin-9; HVEM, herpes virus entry mediator; LAG-3, lymphocyte activation gene 3; MHC, major histocompatibility complex; NK cells, natural killer cells; PD-1, programmed cell death protein 1; PD-L1/2, programmed death-ligand 1/2; Treg, regulatory T cells. TCR, T cell receptor; TIM-3, T cell immunoglobulin domain and mucin domain 3; TIGIT, T cell Ig and ITIM domain; VISTA, V-domain Ig suppressor of T cell activation; VISTAL, VISTA ligand.

combination immunotherapy in hematological malignancies based on checkpoint inhibition. With the development of novel checkpoints, combining these checkpoints for synergistic anti-tumor responses is a future direction to fully utilize the tumor-killing role of NK cells.

2.2 | Regulatory T cells (Tregs)

Tregs have crucial functions in balancing immune homeostasis and suppressing autoimmune responses [33] because they can regulate T cells, B cells, NK cells, dendritic cells (DCs), and macrophages through both humoral and direct cell interactions [34]. However, Tregs impede immune surveillance against tumors in healthy patients and hinder the formation of potent immune responses against tumors in individuals with tumors by inhibiting the growth of cytotoxic $CD8^+$ T cells [33, 35]. Treg-mediated suppression mechanisms encompass a range of molecules, including CTLA-4, LAG-3, IL-10, IL-35, IL-2, forkhead box protein P3 (Foxp3), transforming growth factor-β (TGF-β), and others [36].

Previous studies have unveiled the impact of ICIs on T effector cells, but there is limited understanding regarding their influence on Tregs [33]. In a novel study, Bauer et al. [24] treated transgenic mice that spontaneously developed B cell lymphomas due to restricted overexpression of the proto-oncogene c-myelocytomatosis viral oncogene homolog (*c-MYC*) in B cells with anti-PD-1 (clone J43) and anti-CTLA-4 (clone UC10-4B9), resulting in reduced upregulation of Foxp3, CD25, and IL-10 in Tregs, as well as a decrease in their inhibitory ability. During B cell lymphoma progression, intratumoral Tregs showed elevated expression of Foxp3, CD25, CTLA-4, and IL-10 compared to Tregs from healthy mice, which exhibited a positive association with heightened immunosuppressive capabilities. This function could be attributed to the change towards a pro-inflammatory environment promoted by ICIs [24]. It has been reported that in c-HL and NHL, such as DLBCL, ICIs therapy reduced the infiltration of immunosuppressive $CD4^+/CD25^+/Foxp3^+$ Tregs [37, 38]. As discussed above, targeting immune checkpoints on Tregs may offer a hopeful strategy for effective tumor immunotherapy.

2.3 | DCs

DCs, B cells, and macrophages are typically regarded as the three significant groups of APCs. However, DCs can convey tumor antigens to the draining lymph nodes, thereby triggering the activation of T cells, an essential step for the development of T cell-mediated immunity [39]. Conventional DCs (cDCs) especially excel in presenting exogenous and endogenous antigens to T cells and regulating the proliferation, survival, and effectiveness of T cells [40]. Antigens from tumor cells could be captured by cDCs and presented to T cells within the tumor microenvironment or when cDCs moved to lymph nodes connected to the tumor [41].

Although the response to PD-1/programmed cell death 1 ligand 1 (PD-L1) blocking can be promoted by anti-TIM-3 antibodies through reducing T cell exhaustion, the effectiveness of TIM-3 blockade may extend to patients with tumors lacking significant T cell infiltration [42]. In co-stimulatory molecules, CD80 and CD86 expressed by DCs controlled activation or suppression of T cells through the interaction between CD28 or CTLA4 [43]. Peng et al. [25] found that DCs infiltrating the expressed a high level of PD-L1, which played a crucial role in limiting anti-tumor immune responses. PD-L1 expression on DCs was increased during antigen presentation in order to shield DCs from the cytotoxic effects of activated T cells. A high density of DCs has been correlated with favorable prognosis in c-HL [44] and cutaneous T cell lymphoma (CTCL) [45]. Plasmacytoid DCs (pDCs), which are closely related to the AML and chronic myeloid leukemia (CML) progression, are hematopoietic cells, mainly developed from a myeloid branch including the macrophage DC progenitor with monocytes, cDCs and pDCs differentiation potential [46]. Therefore, although the mechanism behind immune checkpoints in DCs remains unclear, DCs still have the potential to act as target cells for ICIs to improve efficacy in tumor treatment.

2.4 | Macrophages

Macrophages are an important cell type in the innate immune response, with CD47 serving as the main regulator for macrophages. Blocking CD47 allows macrophages to phagocytose leukemia cells for therapeutic purposes [47]. Since first confirmed as a tumor antigen in human ovarian tumors [48], CD47 has been progressively shown to be overexpressed in a wide range of hematological malignancies, such as acute lymphoblastic leukemia (ALL) [49], AML [50] and CML [51], which appears to be a universal indication for tumor cells to avoid phagocytosis by the innate immune system, particularly macrophages [52]. In addition, higher CD47 expression levels were negatively associated with good treatment response and prognosis in patients with acute myeloid leukemia and CML [51]. Previous studies have confirmed that CD47 messenger RNA (mRNA) and protein levels are higher in leukemic stem cells of AML patients than in normal healthy stem cells, and elevated CD47 was highly correlated with poor prognosis [49].

The involvement of CD47 in the tumor-mediated evasion of phagocytosis was initially reported in cases of AML. Compared to normal cell counterparts, both mouse and human AML cells exhibited increased expression of CD47, which was directly linked to disease pathogenesis through the evasion of macrophages [53]. Consequently, clinical studies of CD47-targeted agents have been underway for AML and myelodysplastic syndromes (MDS), either as monotherapy or in combination therapy. Macrophages exhibited strong phagocytosis of primary AML patient leukemic cells when exposed to the anti-CD47 blocking antibody (clone B6H12), whereas the immunoglobulin G (IgG) control or a non-blocking anti-CD47 antibody did not show the same effect. Within 14 days of treatment, anti-CD47 antibody treatment eliminated tumor cells of peripheral blood (PB) and bone marrow (BM) in primary AML patient-derived xenografted mice in vivo. Furthermore, an anti-CD47 antibody (magrolimab) that has been humanized for clinical purposes exhibited comparable elimination of leukemia and prolonged survival in vivo [54]. In addition to AML, similar pre-clinical observations were noted in MDS patients [52].

Recently, new immune checkpoints have been identified in macrophages, including the cell surface glycoprotein CD137, also called 4-1BB, which is a member of the tumor necrosis factor (TNF) receptor superfamily [55, 56]. Stoll et al. [57] discovered that CD137 was expressed on circulating monocytes of healthy individuals and at even greater levels on cells derived from tumor patients. Monocytes that exhibit elevated levels of CD137 demonstrate enhanced ability to engulf MM and lymphoma cells treated with anti-CD38 or anti-CD20 mAbs, respectively, due to their heightened phagocytic capacity for antibody-dependent phagocytosis [57]. Therefore, CD137 was identified as a new potential immune checkpoint on human macrophages, suggesting possible therapeutic benefits in the treatment of tumors.

In summary, tumor cells mediate immune escape through various immune checkpoints located on the surface of immune cells, and ICIs targeting these immune checkpoints may have better efficacy. In addition, cellular immunotherapies are evolving in hematological malignancies as novel therapies, mainly including chimeric antigen receptor T-cell (CAR-T) therapy, NK-cell-based immunotherapy (CAR-NK therapy), and allogeneic

hematopoietic stem cell transplantation (allo-HSCT). DC vaccines are also being experimented in murine T cell lymphoma models [58] and AML patients [59]. Therefore, both immune cells themselves and ICIs targeting immune checkpoints of immune cells have great therapeutic potential in hematological malignancies. Meanwhile, combining ICIs with targeted immune cell chemotherapeutic agents is a promising strategy to improve the treatment response rate of hematological malignancies.

3 | APPLICATION OF IMMUNE CHECKPOINTS IN HEMATOLOGICAL MALIGNANCIES

ICIs have been rapidly developed in solid tumors while are less effective in hematological malignancies, which has been rapid progress in recent years. However, numerous unsatisfactory clinical problems still need to be solved in the application of ICIs due to immature technology and other reasons, such as resistance and adverse effects. In recent years, there has been a growing focus on researching immune checkpoints, including biomarkers, combination therapies with ICIs, resistance, and toxicities.

3.1 | Prognostic biomarkers

The lack of specific biomarkers for prognostic stratification and accurate diagnosis makes hematological malignancies the most challenging type of tumor to diagnose. It is worth noting that researchers have proved that immune checkpoints could be used as promising biomarkers for diagnosis and prognosis prediction in hematological malignancies.

3.1.1 | PD-1/PD-L1

According to recent research, higher levels of immune checkpoints have been linked to poor prognosis and worse treatment efficacy in hematological malignancies. For example, PD-1 and PD-L1 expression were poor prognostic indicators in patients with aggressive adult T-cell leukemia-lymphoma (ATLL) [12]. Cuccaro et al. [11] found that increased PD-L1 expression in PB was associated with advanced disease, systemic symptoms, and inferior progression-free survival (PFS) in HL patients, which proved that PD-L1 expression in PB might be a potential indicator for prognosis in HL. High PD-1/PD-L1 expression was associated with poor prognosis in aggressive acquired immunodeficiency syndrome (AIDS)-associated non-Hodgkin's lymphoma (NHL) [60]. The high level of $CD4^+$ $PD1^+$ and $CD8^+$ $PD1^+$ T lymphocytes were both prognostic factors of AML patients and ALL patients [61]. Elevated levels of soluble PD-L1 (sPD-L1) were associated with poor prognosis in MM [62].

In addition to prognostic markers, the researchers explored the potential of PD-1 and PD-L1 as biomarkers in predicting treatment response, testing safety, and detecting disease progression [63–65]. In research for cutaneous T cell lymphoma, $PD\text{-}1^+$ T cells were involved in the formation of spatial biomarkers that could be strongly associated with response to pembrolizumab treatment [65]. In another study, by quantifying PD-1 in patients with FL and those who converted to DLBCL, researchers found that high levels of PD-1 in the follicles were associated with a significantly shorter time to transformation-free survival, indicating that PD-1 expression in follicular lymphoma (FL) tumor tissues prior to treatment could be used as a risk-predictive biomarker for transformation to DLBCL [63]. Through analysis of metabolic markers on immune cells from lymphoma patients undergoing autologous transplantation, including DLBCL, FL, and T-NHL, other researchers found that lymphoma patients with a sustained increase in PD-1 expression on T cells had a shorter median survival after autologous transplantation, suggesting that PD-1 expression on T cells could be used as an unfavorable biomarker for lymphoma patients undergoing autologous transplantation [64].

All of the above studies suggested that PD-1 and PD-L1 may serve as potential biomarkers in hematological malignancies. Based on these results, a large number of studies have come to explore the potential of targeting PD-1 and PD-L1 for the treatment of hematologic malignancies. However, since the therapeutic effect of anti-PD-1/PD-L1 therapy varies considerably in hematological malignancies with high heterogeneity, it is necessary to detect the expression level of PD-1 and PD-L1 to decide whether to use ICIs targeting PD-1 and PD-L1, as well as to predict their therapeutic responses. Furthermore, larger sample size experiments need to be used to validate their potential as prognostic markers for hematological malignancies.

3.1.2 | CTLA-4

CTLA-4 has been reported to be a poor prognostic indicator in patients with aggressive ATLL [12]. Previous analysis indicated that unsuitable manifestation of CTLA-4 on $CD4^+$ T cells in active MM was linked to unfavorable clinical outcomes. MM patients with decreased CTLA-4 levels expression may be prone to experiencing early relapse [66]. In a research on MDS patients, soluble CTLA-4 (sCTLA-4) levels were higher in MDS patients compared to controls, and sCTLA-4 levels were significantly higher in patients with high-risk MDS compared to the intermediate-risk

group [67]. The higher the patient's CTLA-4 levels, the higher the risk of transformation to AML and the higher the mortality rate after follow-up, suggesting that elevated sCTLA-4 levels in MDS patients are an indicator of poor prognosis in MDS [67]. In another study of AML patients, the mRNA expression of CTLA-4 was significantly upregulated in AML patients compared to healthy controls. In addition, CTLA-4 expression was found to be associated with poor prognosis, and regression analysis revealed that CTLA-4 expression level was an independent predictor of prognosis in AML patients [68].

Based on these results, a large number of studies have begun to explore the potential of targeting CTLA-4 for the treatment of hematological malignancies, with promising results. However, similar to the results of anti-PD-1/PD-L1 therapy, anti-CTLA-4 therapy in hematological malignancies has shown markedly variable results. For example, in a phase 1 clinical study of ipilimumab in B-cell non-Hodgkin lymphoma (B-NHL) patients, the complete response rate (CRR) was only 5.6% [69]. However, in another phase 1 clinical study of ipilimumab in allo-HSCT patients, the CRR could reach 23% [70]. Therefore, in order to confirm the potential of CTLA-4 as a prognostic biomarker in hematological malignancies, it is necessary to conduct studies with a larger sample size.

3.1.3 | TIM-3

In addition, microenvironmental expressions of TIM-3 were strongly correlated with better overall survival, which were important prognostic factors in patients with ATLL [71]. NK cells play a crucial role in immune responses against AML, and the expression of TIM-3 is significantly high in NK cells derived from AML individuals, which is associated with enhanced functional authorization and superior capabilities as effectors. Racova et al. [72] constructed prognosis-related biomarkers of active immunity against AML by NK cell frequency and TIM-3 expression levels. Similarly, Tim-3$^+$ Foxp3$^+$ Treg cells were highly enriched in the tumor microenvironment (TME) of DLBCL patients, which were correlated with the poor prognosis [73]. In addition to prognostic biomarkers, TIM-3 has potential as a biomarker for predicting chemotherapy efficacy. In a study of DLBCL patients, TIM-3 expression was increased in CD3$^+$ T cells from DLBCL patients compared to healthy controls, and the level of TIM-3 expression was decreased after four courses of standard chemotherapy. Patients with low TIM-3 expression had a higher treatment efficacy than patients with high TIM-3 expression, indicating that TIM-3 may serve as a potential indicator of chemotherapy efficacy in DLBCL patients [74]. Another study also demonstrated that, after three years of follow-up, the rate of Tim-3 positive expression was higher in treatment-effective DLBCL patients than in treatment-ineffective patients, and Tim-3 positivity was an independent risk factor for the prognosis of DLBCL [75].

Collectively, TIM-3 has the potential to serve as a potential biomarker for hematological malignancies. Furthermore, we need more research with larger sample sizes to demonstrate the ability of TIM-3 as a biomarker and the reliability of predicting treatment efficacy for different hematological malignancies.

3.1.4 | Others

In addition to the above familiar immune checkpoints, novel immune checkpoints are constantly being identified as potential biomarkers in hematological malignancies. For example, microenvironmental expressions of tumor necrosis factor receptor superfamily member 4 ligand (OX40L) were strongly correlated with better overall survival, which were important prognostic factors in patients with ATLL [71]. Moreover, AML patients with high levels of OX40L expression on tumor cells had significantly worse survival than patients with low OX40 expression, suggesting OX40 was a novel prognostic marker for AML patients [76].

Several studies have demonstrated that high expression of LAG-3 was correlated with worse outcomes and functioned as an independent prognostic indicator in DLBCL and MDS patients [14, 77, 78]. Moreover, VISTA was an independent prognostic factor for patients with extranodal natural killer/T cell lymphoma (ENKTCL), providing that VISTA could be a promising immune biomarker to perform prognostic stratification or diagnosis for ENKTCL [13].

Another study in AML patients showed an imbalance in the distribution of TIGIT and CD226 (the competitive co-stimulatory receptor for TIGIT) on $\gamma\delta$ T cells, with a decrease in CD226$^+$ $\gamma\delta$ T cells and an increase in TIGIT$^+$ $\gamma\delta$ T cells in patients with de novo AML, whereas TIGIT-CD226$^+$ $\gamma\delta$ T cells were restored in patients with AML who reached complete response after chemotherapy [79]. In addition, non-M3 AML patients with higher TIGIT$^+$ CD226$^-$ $\gamma\delta$ T cells had lower overall survival [79].

Tumor necrosis factor-alpha-inducible protein 8-like 2 (TIPE2) is a newly identified negative regulator of antitumor immunity that plays a crucial function in preserving immune homeostasis. It has been shown in pan-cancer studies that TIPE2 might be a promising immune checkpoint biomarker in different hematological malignancy types, including AML, and might serve as a promising target for immunotherapy [80]. The high expression of the novel immune checkpoint molecule, siglec-15, on

peritumoral macrophage predicted the positive outcome in primary central nervous system lymphoma (PCNSL), indicating that siglec-15 might represent an independent prognostic factor [81].

Taken together, immune checkpoints have been demonstrated to be prognostically relevant in hematological malignancies, particularly in lymphoma and leukemia, which potentially improve the prognosis and stratification accuracy. In addition, a large amount of prognosis-related statistics could help researchers make useful references for the development of new ICIs and select the immune targets and directions for research and development. Immune checkpoints are no longer to be used merely as prognostic biomarkers for hematological malignancies, and new studies have expanded to explore their potential as biomarkers for safety and clinical outcomes. There are individualized differences in the efficacy of ICIs among patients with hematological malignancy, so more experiments with larger sample sizes are needed to repeatedly validate the ability of immune checkpoints to be clinical biomarkers. Meanwhile, two or more immune checkpoints have been found to be concurrently associated with the prognosis in hematological malignancies and may have a synergistic effect, which also provides a mechanistic basis for the subsequent combined application of ICIs targeting different immune checkpoints.

3.2 | The advances of ICIs in hematological malignancies

A variety of ICIs targeting specific immune checkpoints have been currently available in the clinic, including anti-CTLA-4 and anti-PD-1 [82]. Recent clinical studies on ICIs in hematological malignancies are shown in Table 1.

3.2.1 | PD-1/PD-L1

A phase II study evaluated pembrolizumab for r/r c-HL patients in complete response who discontinued treatment and subsequently experienced partial response were eligible for second-course pembrolizumab, and objective response rate (ORR) was achieved in 71.4%, while CRR was achieved in 27.6% [83]. In another single-arm phase II study of pembrolizumab in individuals with r/r HL, ORR was 69.0%, and CRR was 22.4% [84], while another similar phase II trial showed 60% ORR [10]. According to the trials above, the ORR of pembrolizumab for r/r HL was approximately 60% [85]. However, a phase Ib study of pembrolizumab showed an ORR of 0% in r/r MM [86]. Moreover, in a phase II trial to evaluate the effectiveness of nivolumab in r/r FL patients, the ORR was 4% [87]. A phase II study of nivolumab in r/r c-HL after auto-HCT demonstrated an ORR of 69% [88]. Another phase I trial evaluated the efficacy of nivolumab, with ORR of 40%, 36%, and 40% observed in individuals diagnosed with FL, DLBCL, and peripheral T-cell lymphoma, and adverse events occurred in 51 (63%) patients [89]. A prospective phase I clinical trial of nivolumab for relapsed hematological malignancies, including chronic lymphocytic leukemia (CLL), HL, MM, AML, ALL, MDS, and CML, after allo-HCT showed an ORR of 32% [90]. A phase Ia/Ib study evaluated the primary anti-tumor effects of GLS-010, a monoclonal antibody that specifically inhibited the PD-1/PD-L1 axis, in patients with refractory lymphoma, and the ORR was 23.6% [91]. A study of anti-PD-1 efficacy in pediatric malignancies showed that the survival rate of pediatric patients with HL was the highest among pediatric malignancies when pembrolizumab was used alone or when nivolumab was combined with brentuximab vedotin, a CD30-directed antibody-drug conjugate linked to monomethyl auristatin E [92]. Another study of anti-PD-1 efficacy in pediatric hematological malignancies demonstrated that nivolumab plus brentuximab vedotin was an effective and safe treatment for inducing remission in pediatric r/r c-HL patients [93]. In conclusion, ICIs targeting PD-1 and PD-L1 could exert anti-tumor effects in hematological malignancies. However, both response rates and efficacy differed in the treatment of hematological malignancies. Moreover, a significant proportion of patients with hematological malignancies do not respond well to ICIs therapy. Therefore, subsequent studies are needed to explore the resistance mechanisms of ICIs targeting PD-1 and PD-L1, identify more effective markers for medicine guidance, and explore more effective combination strategies in hematological malignancies.

3.2.2 | TIM-3

TIM-3 is still a newly identified target for ICIs with numerous active early-phase trials. A phase I trial investigated Sym023 as monotherapy for lymphoma. According to initial data, individuals who received the maximum dosage of Sym023 reported an ORR of 66.7% within a treatment duration of 16 weeks (NCT03489343). In a phase II trial (NCT04623216), an anti-TIM-3 agent sabatolimab (MBG4530) was assessed as a monotherapy or in combination with azacitidine to enhance the graft-vs-leukemia effectiveness in AML patients who received allo-HCT and achieved CR. Moreover, NCT04266301, NCT03066648 and NCT05367401 are evaluating the efficacy of sabatolimab along with other treatments for MDS, CLL and AML. A phase I study, NCT05357651, is assessing a bsAb, LB1410 (anti-PD-1/anti-TIM-3), in the treatment of lymphoma.

TABLE 1 The clinical advances of ICIs in hematological malignancies.

Immune checkpoints	Inhibitors	Conditions	Patients Numbers	Phase	Status	NCT number	Brief profile
PD-1	Pembrolizumab	HL	211	II	Active, not recruiting	NCT02453594 [83]	ORR: 71.4%, CRR: 27.6%
		HL	340	II	Recruiting	NCT03407144	Examining the safety and efficacy of pembrolizumab (MK-3475) in combination with chemotherapy
		r/r HL	370	II	Recruiting	NCT02332668 [10]	ORR (r/r HL): 60%
		Lymphoma	157	I	Completed	NCT03010176	Evaluating the safety and efficacy of ulevostinag via intratumoral injection in combination with pembrolizumab
		HL	360	III	Recruiting	NCT05508867	Comparing the efficacy of co-formulated favezelimab/pembrolizumab (MK-4280A) with physician's choice chemotherapy of bendamustine or gemcitabine
		NHL	378	I	Active, not recruiting	NCT03454451	Evaluating CPI-006 as a single agent, in combination with ciforadenant, in combination with pembrolizumab, and in combination with ciforadenant and pembrolizumab.
		r/r HL r/r MM	197	I	Completed	NCT01953692 [85, 86]	ORR (r/r HL): 65% ORR (r/r MM): 0%
	Nivolumab	r/r FL	116	II	Completed	NCT02038946 [87]	ORR:4%
		HL	294	II	Completed	NCT02181738 [88]	ORR (r/r c-HL):69%,
		NHL MM	316	II	Active, not recruiting	NCT01592370 [89]	ORR (FL): 40%, ORR (DLBCL): 36%, ORR (peripheral T-cell lymphoma): 40%
		B-ALL	550	II	Recruiting	NCT04546399	Studying the effect of nivolumab in combination with blinatumomab compared to blinatumomab alone
		Lymphoma, NHL	388	III	Recruiting	NCT03366272	Evaluating the addition of nivolumab to gemcitabine, oxaliplatin plus rituximab
		ALL, AML, CLL, CML, HL, NHL, MDS	71	I	Completed	NCT01822509 [90]	ORR: 32%
	GLS-010 (zimberelimab)	lymphoma	289	I	Active, not recruiting	NCT03713905 [91]	ORR: 23.6%
	Camrelizumab	HL	200	II	Recruiting	NCT04514081	Comparing the ORR obtained with Chidamide+Decitabine+Camrelizumab against with Decitabine+Camrelizumab

(Continues)

TABLE 1 (Continued)

Immune checkpoints	Inhibitors	Conditions	Patients Numbers	Phase	Status	NCT number	Brief profile
	Toripalimab	NK/T Cell Lymphoma	207	III	Recruiting	NCT04365036	Comparing the safety and efficacy of sequential chemoradiotherapy with or without toripalimab
	AZD7789	c-HL	180	II	Recruiting	NCT05216835	Assessing the safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of AZD7789
	IBI363	Lymphoma	260	I	Not yet recruiting	NCT05460767	Evaluating the safety, tolerability, and preliminary efficacy of IBI363, determine the maximum tolerated dose (MTD) or maximum administered dose
	TY101	Lymphoma	268	II	Recruiting	NCT04458389	Evaluating TY101 safety, tolerability, pharmacokinetic characteristics, effectiveness, and immunogenicity
	PDR001 (Spartalizumab)	AML MDS CML	242	I	Active, not recruiting	NCT03066648	Characterizing the safety and tolerability of 1) MBG453 as a single agent or in combination with PDR001 or 2) PDR001 and/or MBG453 in combination with decitabine or azacitidine
PD-L1	CK-301 (cosibelimab)	c-HL NHL	500	I	Recruiting	NCT03212404	Assessing the safety, tolerability, and efficacy of CK-301 when administered intravenously as a single agent
CTLA-4	Ipilimumab	Lymphoma	300	II	Completed	NCT03013491 [187]	ORR: 19%
		Lymphoma	110	II	Completed	NCT03058289	Evaluating the intratumoral administration of escalating doses of a novel, experimental drug, INT230-6
		MDS AML	55	I	Recruiting	NCT03600155	Studying the side effects and best dose of nivolumab and ipilimumab after donor stem cell transplant
		AML, CML, MDS	182	II	Recruiting	NCT02397720	Studying the side effects and best dose of nivolumab and azacitidine with or without ipilimumab
		CLL	50	I	Recruiting	NCT04781855	Evaluating the best dose and side effects of ipilimumab in combination with ibrutinib or with ibrutinib and nivolumab
		Leukemia MDS	160	II	Active, not recruiting	NCT02530463	Studying the side effects of nivolumab and/or ipilimumab with or without azacitidine

(Continues)

TABLE 1 (Continued)

Immune checkpoints	Inhibitors	Conditions	Patients Numbers	Phase	Status	NCT number	Brief profile
LAG-3	Sym022	Lymphoma	15	I	Completed	NCT03489369	Evaluating if Sym022 is safe and tolerable for patients with locally advanced/unresectable lymphomas that are refractory to available therapy or for which no standard therapy is available.
		Lymphoma	91	I	Completed	NCT03311412	Seeing if Sym021 is safe and tolerable as monotherapy, in combination with either Sym022 or Sym023, and in combination with both Sym022 and Sym023
	LAG525	DLBCL	76	II	Completed	NCT03365791	Determining whether treatment with PDR001 and LAG525 demonstrates sufficient efficacy
	Relatlimab	AML	30	II	Recruiting	NCT04913922	Testing the safety and tolerability of combination therapy (nivolumab and relatlimab) in patients with AML.
		Lymphoma NHL	68	II	Recruiting	NCT05255601	Assessing the safety, tolerability, drug levels, and preliminary efficacy of relatlimab plus nivolumab
		MM	104	II	Recruiting	NCT04150965	Evaluating anti-LAG-3 and anti-TIGIT to understand their immunologic effects and safety both as single agents and in combination with pomalidomide and dexamethasone.
	HLX26	Lymphoma	11	I	Active, not recruiting	NCT05078593	Evaluating the safety and tolerability of HLX26 with escalated doses in the treatment of patients with lymphoma.
TIM-3	Sym023	Lymphoma	24	I	Completed	NCT03489343	Evaluating if Sym023 is safe and tolerable for patients with lymphomas that are refractory to available therapy or for which no standard therapy is available.
	MBG453 (Sabatolimab)	AML	59	II	Recruiting	NCT04623216	Completing remission after allogeneic hematopoietic stem cell transplantation with preemptive treatment with sabatolimab alone or in combination with azacitidine enhances the graft-versus-leukemia (GvL) response.

(Continues)

TABLE 1 (Continued)

Immune checkpoints	Inhibitors	Conditions	Patients Numbers	Phase	Status	NCT number	Brief profile
		MDS CMML	530	III	Active, not recruiting	NCT04266301	Assessing clinical effects of MBG453 in combination with azacitidine
		Leukemia MDS CLL	242	I	Active, not recruiting	NCT03066648	Characterizing the safety of 1) MBG453 as a single agent or in combination with PDR001 or 2) PDR001 and/or MBG453 in combination with decitabine or azacitidine
		MDS AML	63	II	Not yet recruiting	NCT05367401	Determining the safety and preliminary efficacy of sabatolimab with magrolimab and azacitidine in MDS and AML and sabatolimab in combination with magrolimab in AML
	TQB2618	r/r Lymphoma	92	II	Recruiting	NCT05400876	Evaluating the safety and efficacy of TQB2618 injection combined with Penpulimab
		r/r AML MDS	73	I	Recruiting	NCT05426798	Evaluating the tolerability and initially evaluating the anti-tumor efficacy of TQB2618 injection combined with demethylation drugs
	LB1410	Lymphoma	100	I	Recruiting	NCT05357651	Evaluating if experimental anti-PD-1 and anti-TIM-3 bispecific antibody, LB1410, is safe, tolerable, and efficacious
	AZD7789	r/r c-HL	180	II	Recruiting	NCT05216835	Assessing safety, pharmacokinetics, pharmacodynamics, and efficacy of AZD7789

Abbreviations: AML, acute myeloid leukemia; B-ALL, B-cell acute lymphoblastic leukemia; c-HL, classic Hodgkin lymphoma; CML, chronic myeloid leukemia; CMML, Chronic myelomonocytic leukemia; CLL, chronic lymphocytic leukemia; CRR, complete response rate; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; c-HL, classic Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HL, Hodgkin lymphoma; LAG-3, lymphocyte activation gene 3; MDS, myelodysplastic syndromes; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; ORR, objective response rate; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; r/r, relapsed or refractory; TIM-3, T cell immunoglobulin domain and mucin domain 3.

NCT05216835 is another phase I trial that evaluated anti-PD-1 and anti-TIM-3 bsAb (AZD7789) in r/r HL patients. Another phase I is an open-label clinical trial to evaluate the efficacy of TQB2618 injection, an inhibitor of TIM-3, combined with penpulimab in individuals with r/r lymphoma (NCT05400876). Moreover, in NCT03311412, the researchers further assessed anti-PD-1 (Sym021) therapy in combination with Sym022 or anti-TIM-3 (Sym023) in lymphoma.

3.2.3 | LAG-3

Ongoing active trials about LAG-3 include NCT05078593, a phase I trial investigating HLX26, an anti-LAG-3 agent, to evaluate the safety and tolerability in lymphomas. Another phase I, open-label trial NCT03489369, evaluated the anti-tumor activity of an anti-LAG-3 mAb (Sym022) in lymphomas. A phase II trial, NCT04913922, is examining the potential of combining relatlimab, nivolumab, and azacytidine as a therapy for AML, lymphoma, and NHL. Another phase II trial (NCT04150965) was conducted to evaluate anti-LAG-3 (relatlimab) and anti-TIGIT (BMS-986207) to assess their effectiveness as single agents or when combined with pomalidomide and dexamethasone. Furthermore, LAG-3 protein was highly expressed on malignant Richter syndrome (RS) cells and tumor-infiltrating lymphocytes, supporting the possibility of LAG3 inhibition to enhance anti-tumor responses in RS [94]. LAG-3 studies have also focused on the efficacy, safety, and tolerability of ICIs. Large sample-size studies are still needed to investigate drug resistance and potential biomarkers. Most of the clinical trials on ICIs targeting LAG-3 in hematological malignancies are still under investigation, and few results have been reported.

3.2.4 | TIGIT

In addition to numerous classic ICIs in clinical trials [83, 84], numerous novel targets have been investigated with positive results. A novel study demonstrated that TIGIT was widely expressed on lymphoma-infiltrating T cells (LITs) in a variety of human lymphomas and was frequently co-expressed with PD-1 [95]. Moreover, in a syngeneic A20 B-cell lymphoma mouse model, blockade of PD-1 or TIGIT alone retarded tumor progression. In contrast, simultaneous blockade of PD-1 and TIGIT resulted in complete rejection and significantly prolonged survival, providing a rationale for research on TIGIT and PD-1 blockade in lymphoma [95]. In addition, another study on the expression of TIGIT in biopsy tissues of human hematologic malignancies showed that chronic lymphocytic leukemia/small lymphocytic lymphoma and anaplastic large cell lymphoma demonstrated high TME TIGIT expression compared with PD-L1, with a high proportion of dual TIGIT and PD-L1-positivity, which is likely to contribute to the design and correlative study of therapeutic response in clinical trials targeting TIGIT alone or in combination with PD1/PDL1 [96].

3.2.5 | Leukocyte immunoglobulin-like receptor subfamily B member 1 (LILRB1)

LILRB1, widely expressed in human immune cells, is an inhibitory patterned receptor based on the immune receptor tyrosine whose ligands, such as MHC-I molecules, could activate LILRB1 and transmit inhibitory signals, thereby suppressing the immune response. Chen et al. [97] discovered that the proportion of LILRB1$^+$ NK cells was higher in patients with MM after treatment compared to that in healthy donors. Furthermore, specific antagonistic anti-LILRB1 monoclonal antibodies developed by them enhanced the anti-tumor activity of NK cells against various hematological malignancies, including MM, leukemia, and lymphoma, suggesting that LILRB1 blockade on immune effector cells like NK cells may offer a new approach in anti-tumor therapy [97]. Furthermore, dual blockade of crystalline fragment (Fc)-silencing antibodies (LILRB1-IgGσ and LILRB2-IgGσ) against LILRB with CD47 antibodies enhanced antibody-dependent cellular phagocytosis (ADCP) by macrophages and improved treatment effect of CD20 antibody therapy in CLL and lymphomas, whereas LILRB blockers alone were ineffective [98].

3.2.6 | Others

Extensive research has been conducted on CD24, a highly glycosylated protein attached to cell membranes through glycosyl-phosphatidylinositol (GPI) anchor [99]. Freile et al. [100] found that CD24 was heavily expressed on mantle cell lymphoma (MCL) cells, and the therapy with CD24 mAbs was more effective compared to CD47 mAbs in MCL, suggesting that CD24 was a promising immunotherapeutic target in MCL patients.

A study revealed the role of new immune checkpoint B and T lymphocyte attenuator (BTLA) and its ligand herpes virus entry mediator (HVEM) in suppressing immune responses mediated by NK cells and its association with poor prognosis in CLL [101]. BTLA blockade reduced CLL cells and enhanced NK cell-mediated responses ex vivo by increasing interferon-γ (IFN-γ) production, cytotoxic capability, and antibody-dependent cell-mediated cytotoxicity

(ADCC), indicating that the BTLA may be a promising target for CLL [101].

The poliovirus receptor-associated immunoglobulin domain-containing (PVRIG) is a novel immune checkpoint whose ligand is poliovirus receptor-related 2 (PVRL2) [102]. The inhibition of PVRIG greatly enhanced NK cell killing of PVRL2$^+$ AML cells. Therefore, the PVRIG-PVRL2 pathway can be targeted with PVRIG-blocking antibodies for NK-mediated immunotherapy of PVRL2$^+$ AML [102].

In summary, most of the clinical trials are still focused on approved and marketed drugs, and due to the presence of adverse effects and drug resistance, how to control the dose and increase the efficacy by combining with other chemotherapeutic agents is the focus of the research. In addition, new ICIs targeting old and new immune checkpoints are also being actively put into clinical trials, and some of them have already achieved encouraging results. Concurrent basic research and clinical studies of new immune checkpoints and ICIs can effectively promote their clinical application, thereby benefiting more patients with hematological malignancies in the future. Moreover, large sample size experiments are needed to further validate the predictive ability of immune checkpoint expression on drug efficacy and explore the mechanism of drug resistance to ICIs in hematological malignancies, which are the aspects lacking in the current studies.

Human immunodeficiency virus (HIV)-infected patients, as well as those with congenital immunosuppression, are far more likely to develop hematological malignancies such as HL than the general population [103]. However, compared with people living without HIV, people living with HIV and tumors have traditionally been excluded from ICI trials. Therefore, there is a paucity of real-world data on the use of ICIs in people living with HIV and tumors [104]. Recently, newer retrospective and prospective studies have shown that ICIs are a safe and effective cancer treatment for people with HIV. Numerous studies have shown that HIV patients with hematological malignancies, including HL and NHL, who received ICIs, such as anti-PD-1 and anti-CTLA-4 drugs, generally tolerated the drugs well [105]. Considering that hematological malignancy patients with HIV infection are inherently immunosuppressed, previous treatment regimens and dosages of ICIs may no longer be applicable and lead to more serious side effects. Therefore, the irAEs in patients with specific underlying diseases, such as AIDS, should be given extra attention. We need more data to compare the safety of ICIs in this population. Lurain K et al. [106] reported that the response rate of pembrolizumab was up to 50% in patients with HIV-associated NHL. Moreover, ICIs therapy not only provided relief from cancer in HIV-infected individuals but also served as a therapeutic intervention to restore the immune response to HIV, reverse HIV latency, and achieve a functional cure for HIV infection [107].

3.3 | Combination of ICIs with other therapies

As a single therapy, the effectiveness of ICIs is restricted due to a low rate of response and immune-related side effects, and combination therapies provide new opportunities for the application of ICIs in tumor therapy. This section briefly describes several avenues combined with ICIs and other therapies.

3.3.1 | OVs

OVs have emerged as another therapeutic agent for tumor treatment. Combining OVs and ICIs could improve outcomes, which may be related to the mechanism of CD8$^+$ T cell infiltration and enhanced IL-1α expression [108]. For immune 'cold tumors', the efficacy of ICIs is poor, and OVs can stimulate the tumor immune microenvironment to improve the anti-tumor effect of ICIs, so the combination of ICIs and OVs can have a synergistic effect on the enhancement of anti-tumor immunity. OVs are mostly utilized for research in tumor treatment in combination with ICIs, and vesicular stomatitis virus (VSV) has also been demonstrated to be effective in hematological malignancies models, such as ALL [109] and c-HL [110] combined with ICIs. Shen et al. [17] illuminated that the combination of VSV and anti-PD-L1 antibody enhanced therapeutic outcomes in murine AML. A recent study has also explored the improvement of CAR-T cell responses in B cell lymphoma through the use of lysosomal viral therapies that also target 4-1BB, a novel immune checkpoint as an inducible costimulatory receptor [111]. Similarly, an immunostimulatory Lokon oncolytic adenovirus (LOAd) targeting 4-1BB has been used to evaluate the efficacy of treating MM, with encouraging results from cell experiments [112]. Moreover, there are also a series of ongoing experiments. A phase I clinical study (NCT03605719) has combined nivolumab and pelareorep (AN1004) to treat recurrent plasma cell myeloma. Another phase I clinical study combined ipilimumab, nivolumab, and recombinant VSV to treat B-NHL, T-NHL, AML, MDS, and MM. A phase II trial (NCT02978625) of talimogene laherparepvec (T-VEC) combined with nivolumab was performed in treating patients with refractory lymphomas such as T cell and NK cell lymphoma, anaplastic large cell lymphoma, and Sezary syndrome, etc. In summary, the combination of OVs and ICIs has a promising perspective on hematologi-

cal malignancies. OVs are also one of the therapies with the highest number of ongoing clinical trials of combination therapies with ICIs.

3.3.2 | Neoantigen vaccines

Neoantigens resulting from tumor-specific somatic alterations are more favorable therapeutic targets compared to traditional tumor-associated antigens (TAAs) like NY-ESO-1 and MUC-1. This is due to the ongoing difficulties in developing vaccines targeting TAAs, which raise concerns about potential autoimmunity [113]. Tumor-specific neoantigens formed by somatic mutations in tumor cells are generally not immune-tolerant and are, therefore, considered to be highly promising therapeutic targets for tumor vaccines. Both tumor vaccines and ICIs therapies can exert anti-tumor effects by expanding and/or inducing maintenance of tumor-specific T cells. A multidimensional comparative study revealed that the neoantigen vaccines combined with ICBs had a stronger ability to activate the immune response than either the vaccines or ICBs alone [114]. At the same time, ICIs therapy, together with neoantigen vaccines, could successfully induce anti-tumor-specific T cell immunity while reducing the probability of triggering immune-related adverse events [113]. Nevertheless, the neoantigen vaccine alone exhibited a restricted anti-tumor impact, as no tumor regression was detected. Meanwhile, based on the results that PD-1 and TIM-3 expression was elevated on neoantigen-specific T cells, immunosuppressive TME could limit the effectiveness of neoantigen vaccination by manipulating the functional states of T cells, possibly through the PD-L1/PD-1 [113]. After being treated with the combination of ICIs and vaccines, complete tumor regression and substantial enhancement survival were observed [113]. These findings suggested that combining ICIs with the neoantigen vaccine could greatly enhance its anti-tumor efficacy. Research on neoantigen vaccines is currently focused on solid tumors, but there has been a gradual rise in hematological malignancies in recent years, including AML [115], T cell lymphoma [18] and MM (NCT03631043). Further investigation is needed to explore the potential value of combining neoantigen vaccines with ICIs in treating hematological malignancies.

3.3.3 | BsAb

BsAb therapy is a type of tumor immunotherapies currently approved for clinical application [116]. BsAb enhances the ability of T cells to kill tumor cells by connecting T cells and tumor antigens [117]. Combining ICIs and bsAb has the potential to overcome the resistance to ICIs immunotherapy. The approval for the treatment of ALL was granted to blinatumomab, a bispecific T cell engager (BiTE) that targets both CD19 and CD3 in 2014 [116]. Most anti-CD3 pan-T cell engagers have been developed to treat hematological malignancies, such as targeting CD20 for NHL and targeting B cell maturation antigen for MM [118, 119]. Unfortunately, ongoing clinical trials found that only a limited proportion of individuals can benefit from bsAb therapy. T cell anergy and exhaustion is a main obstacle caused by inhibitory immune checkpoint pathways, including the PD-L1/PD-1 axis [87]. As the use of bsAb essentially lead to strong T cell activation and production of proinflammatory cytokines [120], such therapies might also trigger tumor cells to employ immunosuppressive strategies to escape antibody-mediated cell lysis. For instance, CD33/CD3 BiTE antibody treatment could induce high expression of PD-L1 on AML cells, which could lead to T-cell-induced immune escape [121]. Enlightened by the inhibitory function of PD-1/PD-L1 pathway in AML, a cellular experiment combining PD-1/PD-L1 blockade with CD33/CD3 BiTE antibody showed enhanced T cell proliferation and IFN-γ production, which resulted in enhanced AML cells lysis [121]. Moreover, a bifunctional checkpoint inhibitory T cell-engaging (CiTE) antibody was found to induce complete AML eradication in a mice xenograft model [19]. Currently, bsAb, which engages patient's T cells or NK cells to combat tumor cells, is gaining interest in the treatment of hematological malignancies.

3.3.4 | Bio-nanomaterials

The progress made in nanotechnology has played a crucial role in the creation of effective, secure, and productive drug systems against tumors based on nanoparticles (NPs). Studies have demonstrated that ICIs delivered by NPs can improve the effectiveness of T cell-focused immunotherapy [122, 123]. Currently, novel ICIs have been used to investigate whether they can bind to NPs to enhance the efficacy of ICIs themselves. For example, Heme oxygenase-1 (HO-1), an antioxidant and immunosuppressive enzyme expressed in many types of tumors, has been considered a potential target in the context of a chemotherapy-induced anti-tumor immune response [20, 124]. Yong et al. [20] conducted a study where a hybrid nanoparticle consisting of lipids and polymers (hNP) was utilized to carry mesoporphyrin (SnMP), an inhibitor of HO-1. Additionally, the hNP was modified with an engineered antibody to enable targeted delivery to leukemic cells. HO-1-inhibiting T-hNP improved the sensitivity of human leukemia cells to chemotherapy in a mouse model of AML [20]. This

novel therapeutic approach for AML showed promising potential [20, 125], and considering the pharmacokinetic mechanism of the bio-nanomaterials and their metabolism through the liver, the following clinical trials will most likely focus on reducing the liver damage of this drug as well as investigating new drug delivery systems [125]. The findings also provide fresh ideas for nanotechnology to be used in combination with ICIs in treating hematological malignancies.

3.3.5 | Other therapies

Mesenchymal stromal cells (MSCs) have been used as new vaccine carriers. Unlike neoantigen vaccines, Abusarah et al. [21] constructed a vaccination strategy by utilizing engineered MSCs to express the immunoproteasome complex (MSC-IPr). The ability of MSC-IPr to present a significantly diverse epitope repertoire resulted in a strong reactivation of T cell immunity against lymphoma [21]. Vaccination of mice T cell and B cell lymphoma models effectively controlled tumor progression and combined with antibodies targeting PD-1, CTLA-4, LAG-3, or 4-1BB under autologous and allogeneic settings could enhance its effects, demonstrating that MSC-IPr constitutes a hopeful subgroup of non-blood-related APCs suitable for creating universal cell-based tumor vaccines, and it is also promising to enhance the efficacy by combining those vaccines with ICIs [21].

CIK cells, a heterogeneous subset of T lymphocytes expanded outside the body, primarily exert their cytotoxic effects by recognizing NK receptor group 2 member D (NKG2D) instead of the T cell receptor [126]. They also display tumor-killing abilities, thereby aiding in the prolonged survival of individuals with tumors [127]. When CIK cells came into contact with B-NHL cells, the expression of PD-1 on CIK cells and PD-L1 on tumor cells were both upregulated, suggesting that CIK had the potential to be used in combination with ICIs targeting PD-1/PD-L1 [128]. The use of CIK cells in research on AML [129], CML [130], and CLL [22] has already been demonstrated to be an innovative clinical perspective. Data from a current study showed that the survival rate in two NHL cell lines (DAUDI and SU-DHL-4) was significantly affected when they were co-cultured with CIK cells activated by PD-1 blockade. In a word, the combination of PD-1 inhibitors and CIK cells could offer a therapeutic alternative for NHL [128].

Numerous studies have evaluated innovative combinations of targeted therapies, epigenetic therapies, and immunotherapy treatments to improve treatment response and combat drug resistance [131]. For example, HBI-8000 is a novel orally bioavailable class I selective histone deacetylase inhibitor that directly alters anti-tumor activity by inducing apoptosis in adult T-cell lymphoma patients, among other mechanisms. Bissonnette et al. [132] treated mice bearing syngeneic B-cell lymphoma daily with HBI-8000, either by itself or in conjunction with PD-1, PD-L1, or CTLA-4 antibodies. The results showed that the activity of ICIs antibodies targeting these immune checkpoints was enhanced by HBI-8000, leading to a notable increase in tumor regression in the mice models. HBI-8000 augmented the activity of ICIs antibodies targeting these immune checkpoints and significantly increased tumor regression in the mice models, which strongly supported the use of combination therapies involving ICIs and HBI-8000 [132].

Recent investigations have demonstrated that the combination of ICIs with other immunotherapies is a major trend in the immunotherapy of hematological malignancies [133, 134]. However, further investigations are necessary to explore and demonstrate the efficacy and safety of those combined therapies. In the future, researchers should explore more combination regimens based on ICIs, test the anti-tumor effects of combinations in ex vivo experiments and explore the underlying molecular mechanisms. At the same time, a large number of preclinical and clinical studies should be performed to evaluate their efficacy and adverse effects and search for biomarkers to guide the selection of combination regimens so as to promote the clinical application of ICIs combination therapy in hematological malignancies.

4 | BARRIERS TO THE APPLICATION OF IMMUNE CHECKPOINT INHIBITORS IN HEMATOLOGICAL MALIGNANCIES

4.1 | Drug resistance of ICIs in hematological malignancies

Drug resistance, which is primarily associated with biological processes related to tumor immunity, is an important factor affecting the effectiveness of ICIs. The speculated mechanisms of resistance to ICIs can be broadly categorized into several groups, including inadequate tumor antigenicity, tumor-intrinsic IFN-γ signaling, loss of MHC, and disordered regulation of oncogenic signaling [135]. The mechanism of tumor resistance to ICIs is systematically illustrated in Figure 2.

Firstly, following treatment with ICIs, loss of function mutations in Beta-2-microglobulin (B2M) could lead to MHC I loss and represent a molecular route of immune escape [136]. Recently, truncation changes in B2M have been repeatedly found in acquired resistance to ICIs [137–139]. The absence of MHC I and II expression may also be due to the loss-of-function mutations in Janus

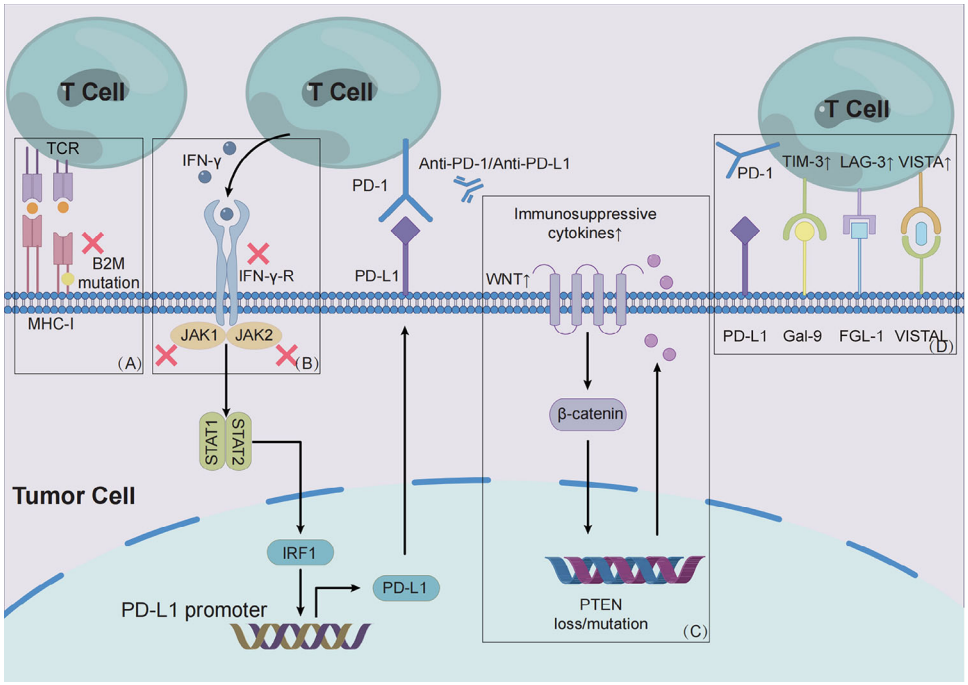

FIGURE 2 The molecular mechanisms of acquired resistance to ICIs in tumor cells. (A)The disruption and downregulation of antigen presentation machinery: the mutations and expression loss of MHC-I or *B2M* lead to the inhibition of tumor antigen presentation and the decrease of TCR engagement. (B)The loss of IFN-γ sensitivity: the mutations and expression loss of IFN-γ-R or JAK1/2 lead to the insensitivity to IFN-γ in tumor microenvironment and the resistance to anti-PD-1/anti-PD-L1 treatment mediated by T cell response. (C)Tumor-mediated immunosuppression and exclusion: activated WNT signaling leads to the augment of β-catenin or the mutations and loss of *PTEN*, which can ultimately promote the production of immune-suppressive cytokines that reduce the infiltration and function of $CD8^+$ T cells in tumor microenvironment. (D)Additional inhibitory checkpoints: the upregulation of additional immune checkpoints such as TIM-3, LAG-3, and VISTA can be found at the time of acquired resistance to PD-1 inhibitors. Abbreviation: B2M, Beta-2-microglobulin; IFN-γ, interferon-γ; IFN-γ-R, interferon-γ receptor; IRF1, interferon regulatory factor; JAK1, Janus kinase 1; JAK2, Janus kinase 2; LAG-3, lymphocyte activation gene 3; MHC-I, major histocompatibility complex I; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PTEN, phosphatase and tensin homolog; STAT1, signal transducer and activator of transcription 1; STAT2, signal transducer and activator of transcription 2; TIM-3, T cell immunoglobulin domain and mucin domain 3; VISTA, V-domain Ig suppressor of T cell activation.

kinase (JAK) 1/2 and *B2M* genes. It has been reported that the expression of MHC molecules can be induced by several drugs, such as Toll-like receptor agonists, histone deacetylase (HDAC) inhibitors, etc. [140]. Cellular therapies, such as CD40 agonists or CAR-T, can also be effective in tumors with impaired expression of such MHC molecules [141].

Secondly, the essential initial process in the JAK-STAT pathway, which triggered the apoptosis of tumor cells, was the activation of receptor-associated kinases JAK1 and JAK2 binding to the IFN-γ-receptor 1/ receptor 2 (R1/R2) [15]. Several cases of inactivating mutations in JAK1 or JAK2 suggested that mutations in this pathway may lead to the progression of ICIs resistance [137, 142, 143]. A study in NK cell/T-cell lymphoma found that the HDAC inhibitor chidamide, recently approved for the treatment of patients with r/r peripheral T-cell lymphoma (PTCL), was associated with an ORR and CRR of 39% and 18%, respectively [144]. In-vitro studies have shown that overactive JAK-STAT signaling in NKTL cell lines is associated with resistance to chidamide [144]. Another study in cutaneous T-cell lymphoma showed that n-(4-ethoxycarbophenyl) retinamide (ECPIRM), the 13-cis retinoic acid derivative, inhibited the expression of the JAK/STAT pathway, thereby inhibiting cell proliferation and promoting apoptosis, which may also address the resistance to ICIs triggered by the JAK/STAT pathway [145]. Therefore, inhibition of JAK-STAT activity could reprogram chromatin from a drug-resistant to a sensitive state, overcome drug resistance to ICIs and produce synergistic anti-tumor effects in vitro and in vivo.

Thirdly, the absence of the tumor suppressor phosphatase and tensin homolog (*PTEN*), which regulated phosphatidylinositol 3-kinase (PI3K) activity, had also been observed in cases of acquired resistance to ICIs [146–148]. *PTEN* deficiency in lymphoid malignancies has been associated with advanced disease, chemotherapy resistance, and poor survival [149]. The combination of PI3K inhibitors and ICIs could be a potential strategy to improve the drug resistance to ICIs in hematological

malignancies, but a large number of clinical trials are still needed to further validate the feasibility.

Lastly, several studies have reported the increased expression of other immune checkpoints at the time of acquired resistance, including TIM3 [150], VISTA [151], and LAG-3 [139]. As mechanisms of resistance were inferred from circumstantial data in some reports, the exact mechanism of resistance to ICIs remains uncertain. One study included 19 AML patients treated with azacitidine and avelumab, and the findings demonstrated that PD-L2 expression was increased during treatment in both BM and PB [152]. Therefore, high expression of PD-L2 in BM may be an essential mechanism for the resistance to anti-PD-L1 therapy in AML patients [152]. In general, unremitting research on tumor resistance to ICIs will expand the spectrum of patients who can benefit from ICIs. Though the mechanism of ICIs resistance in hematological malignancies is still unclear, there are still feasible solutions, such as the combination of ICIs with chemotherapeutic agents, antiangiogenic agents, or radiotherapy. Combination application is the current research hotspot for resisting and reversing immune resistance, which still needs further clinical research. In view of the possible increased risk of toxicities, the combination of multiple ICIs requires careful assessments of benefits and risks before determining the treatment regimen.

4.2 | Toxicity of ICIs in hematological malignancies

So far, an unavoidable problem with ICIs is irAEs [153, 154]. The mechanisms of irAEs related to ICIs are complex and not fully comprehended but are currently known to be associated with aberrant T cell activity [133, 155]. Shared antigens between tumor and normal tissue have been thought to activate nascent T cell response [133]. Nascent alterations in the peripheral B cell pool can also be used to explain the mechanisms of irAEs related to ICIs [156]. IrAEs related to ICIs can manifest in different human systems due to the disruption of the body's immune balance by ICIs [133]. IrAEs related to ICIs consist of dozens of different conditions that affect almost every organ system, including the skin, endocrine system, digestive system, etc. [157, 158]. ICIs-related irAEs of hematological malignancies are shown systematically in Figure 3. IrAEs related to ICIs can be severe and even lethal in certain instances, especially in patients with underlying diseases [159].

Skin toxicity is the most common type of irAE related to ICIs in hematological malignancies, especially MM [160]. The usual and typical manifestations are maculopapular rash, pruritus, and exfoliative dermatitis [161, 162], but rare skin necrosis [163] and Stevens-Johnson syndrome [164] may also occur. Rash and pruritus occurred in 0%-17% of patients receiving ipilimumab monotherapy and were mostly mild, usually defined as body surface area (BSA) grade 1-2. Another PD-1 inhibitor, pembrolizumab, can also cause skin toxicity [165]. Grade 1 (affecting <10% of BSA) and grade 2 (10%–30% BSA) skin irAEs are generally treated symptomatically and usually do not affect the continued use of ICIs. In a word, skin toxicity of hematological malignancies is diverse and variable in severity, with a high degree of individual variability. Skin toxicity is not as severe compared to other tissue toxicities, but it can have an impact on a patient's quality of life.

Endocrine organs, such as the thyroid, pituitary, adrenal, and pancreas, are frequently affected in patients who receive ICIs, leading to the development of irAEs [166, 167]. Osteomalacia, thyroid dysfunction, insulin-deficient diabetes mellitus, and primary adrenal insufficiency are among the reported ICIs-related irAEs. Hypophysitis was associated with anti-CTLA-4 therapy [69], while thyroid dysfunction was associated with anti-PD-1 therapy [168]. Diabetes and adrenal insufficiency are comparatively rare but can be fatal if left untreated [167]. The use of ipilimumab, either alone or in combination with other therapies, was linked to the occurrence of thyroid dysfunction (0%-6%) in cases of hematological malignancies such as CLL [162] and AML [70] after allo-HSCT. There was a comparable occurrence of thyroid toxicity in cases where nivolumab and pembrolizumab were administered. Hypothyroidism was reported in 0%-29% and 0%-17% [169] of cases, respectively, while hyperthyroidism occurred in 0%-13%[168] and 0%-17% [170]of cases. Both of these two agents above also showed the occurrence of adrenal insufficiency with a maximum incidence of 6% [86, 161]. Thyroid diseases generally do not require ICIs discontinuation. Cortisol levels should be tested to prevent adrenal crisis when TSH is decreasing [160]. Overall, endocrine toxicities are diverse, highly variable, and potentially fatal, requiring electrolyte and hormone examinations to detect this kind of irAEs.

Frequent occurrences of gastrointestinal (GI) irAEs to ICIs have been found particularly during anti-CTLA-4 therapy [166, 171]. The clinical manifestations are diversified, including diarrhea, abdominal pain, hematuria, and even some extraintestinal manifestations. Meanwhile, upper gastrointestinal symptoms such as nausea and vomiting are less common [153, 171]. Mild colitis is usually treated symptomatically with fluid and electrolyte repletion [153]. If symptoms get worse, ICIs need to be stopped immediately, and steroids should be given orally or intravenously as appropriate [172].

In general, pulmonary symptoms were more noticeable with anti-PD-1 or anti-PD-L1 monoclonal antibodies than with anti-CTLA-4 inhibitors. Pulmonary toxicity in

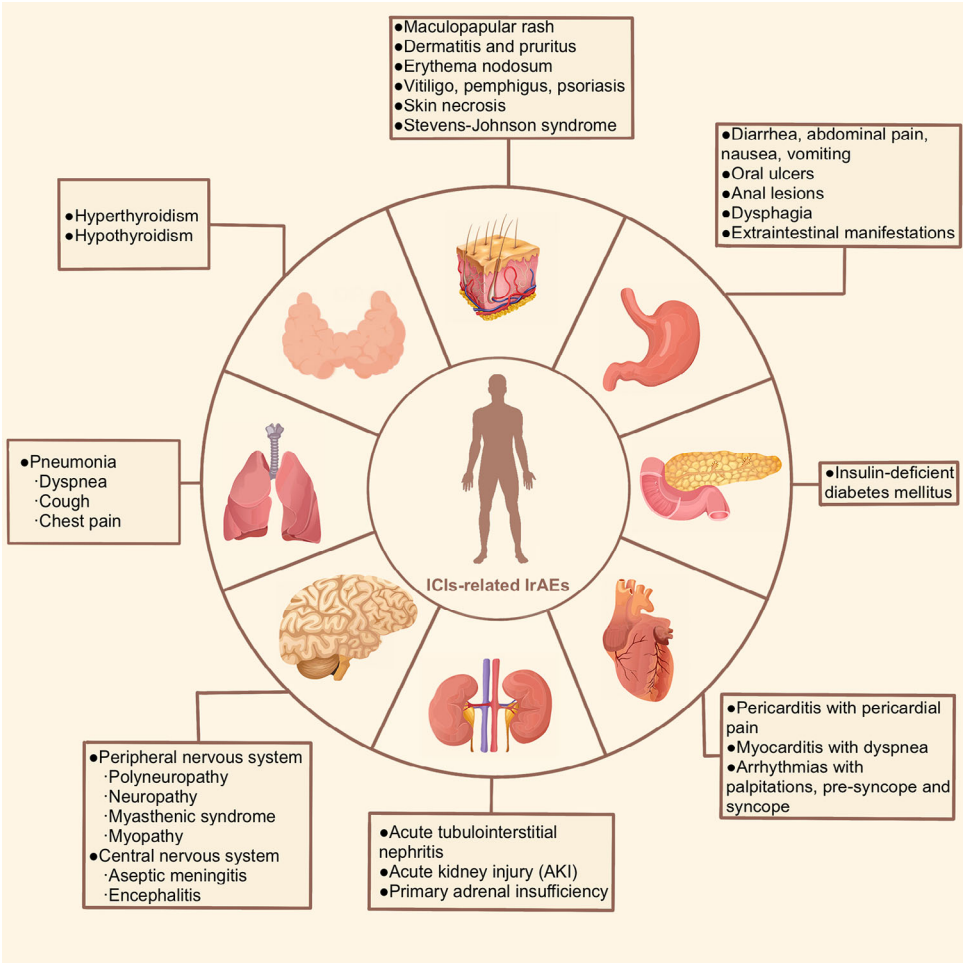

FIGURE 3 ICIs-related IrAEs in a variety of systems in hematological malignancies. Several systems can be affected by ICI-related irAEs in hematological malignancies, including the skin, digestive system, respiratory system, endocrine system, cardiovascular system, urinary system, and central nervous system. In comparison, cutaneous toxicity and gastrointestinal toxicity are more common but less severe, while pulmonary toxicity, cardiotoxicity, neurological toxicity, and nephrotoxicity are rare but more severe, even fatal. Abbreviation: ICIs, immune checkpoint inhibitors; irAEs, immune-related adverse events.

ICIs is uncommon, but when present, it has the potential to worsen rapidly or even be fatal [166]. Pneumonia is one of the most common causes of ICIs discontinuation and is the primary cause of treatment-related mortality in hematological malignancies. Clinical symptoms include dyspnea, cough, and chest pain, usually appearing about 10-12 weeks after ICIs treatment [160]. The incidence of pulmonary toxicity for ipilimumab monotherapy was 0%-11%. Nivolumab and pembrolizumab caused pneumonitis or upper respiratory tract infection in 0%-24% [69] and 0%-13% [161] of patients.

Cardiotoxicity in hematological malignancies occurs occasionally. The incidence rate of myocarditis was predicted to be 1.14%, with a median time to onset of 34 days [173]. Cases of myocarditis were observed in hematological malignancy patients such as r/r MM receiving ICIs therapy, and two cases were fatal and were caused by the combination of pembrolizumab and dexamethasone [174–176]. Pericarditis with pericardial pain, myocarditis with difficulty breathing caused by fluid accumulation in the lungs or arrhythmias with heart palpitations and fainting may indicate cardiotoxicity [177, 178]. Therefore, the incidence of cardiac irAEs is low, but the mortality rate is high [179]. European Society for Medical Oncology (ESMO) Clinical Practice Guidelines recommend electrocardiography and troponin for all individuals [153]. When myocarditis is confirmed, it is necessary to discontinue ICIs and administer high-dose corticosteroids to patients [172].

Other rare irAEs to hematological malignancies include nephrotoxicity and rheumatologic toxicity [180, 181]. Arthralgia and myalgia are the most commonly reported rheumatic irAEs, while arthritis, myositis and vasculitis were also observed in trials of hematological malignancies treated with ICIs, such as CLL [90], r/r HL [182], AML [90], MDS [90], CML [90], r/r primary mediastinal

B-cell lymphoma [183], r/r peripheral T cell lymphoma [180]. These adverse events are more likely to occur in anti-PD-1 ICIs and may occur later than other irAEs [166]. The most common manifestation of nephrotoxicity is acute kidney injury (AKI) due to acute tubulointerstitial nephritis [166, 181].

In general, irAEs to hematological malignancies can occur in all systems, among which cardiotoxicity and pulmonary toxicity, as well as endocrine toxicity, are more dangerous and require close monitoring of patients. The current strategy for dealing with irAEs is based on timely monitoring, early detection, and effective intervention [133]. While searching for alternatives to high-dose corticosteroids to develop unique strategies for the treatment of irAEs [155, 184], more scientific prevention and monitoring measures are also necessary. So, is it necessary to resume the use of ICIs after control of irAEs? There is still controversy over this question. The general recommendation is based on the grade determination of irAEs. For patients with grade 2 irAEs, ICIs can be reintroduced after the adverse effects have resolved to grade 1, and for grade 3 irAEs, it is generally recommended that ICIs should be discontinued. Importantly, restarting ICIs after the interruption of ICIs due to irAEs should be done in consultation with a specialist physician. If severe or life-threatening irAEs have occurred, treatment with these ICIs must be permanently discontinued, and restarting ICIs should be done by choosing a different type of ICIs as much as possible. Besides, restarting ICIs should be done by monitoring the recurrence of previous irAEs and considering permanently discontinuing the treatment with these ICIs if irAEs are present again. It is more important to individualize the decision based on patient outcomes and whether irAEs are controlled.

5 | PERSPECTIVES AND CONCLUSIONS

Immune checkpoints have been studied for almost four decades and still remain a hot topic in tumor treatment. Currently, the inhibitors of PD-1 and CTLA-4 have been widely used in HL [83, 89, 185] with favorable efficacy, which has been achieved in other lymphoma subgroups, such as r/r B-NHL [69], primary mediastinal large B-cell lymphoma [165] and NK/T-cell lymphoma [186]. Immune checkpoints like PD-1 have been identified to serve as potential biomarkers for hematological malignancies, and a large number of studies have been performed to explore the potential of targeting these immune checkpoints for the treatment of hematologic malignancies. [11, 12, 60]. In recent years, the emergence of novel immunotherapies, such as double antibiotics [118, 119] and lysosomal viruses [111], has brought many new ideas for the application of ICIs. Moreover, there have been numerous attempts to address the issue of drug resistance to ICIs, and most researchers have taken the approach of combining ICIs with drugs that target specific pathways of resistance mechanisms, such as HDAC inhibitors that induce the expression of MHC molecules [144]. It is now generally accepted that close monitoring and appropriate intervention while using ICIs can mitigate irAEs. For example, according to recommendations of ESMO Clinical Practice Guidelines, it is advisable to administer concurrent broad-spectrum antibiotics and immune suppression to mitigate pulmonary toxicity [153].

In conclusion, since the efficacy of ICIs therapy in hematological malignancies varies considerably, it is necessary to explore the potential of immune checkpoints as biomarkers to decide whether to use ICIs, as well as to predict their therapeutic responses. The underlying mechanism of immune checkpoints is yet to be dug deeper, and new immune checkpoints are urgently needed to be discovered and applied to provide biomarkers and molecular targets for tumor treatment. Although new ICIs are undergoing a large number of clinical trials, whether already approved ICIs can be used in combination and the effect of the combination are still the factors that most directly affect the outcome of patients with hematological malignancies. At the same time, we cannot ignore the fact that a significant proportion of patients with hematological malignancies do not respond to ICIs therapies. However, due to the unclear mechanism of drug resistance and the lack of validation trials with large sample sizes, the strategy of combining drugs to combat resistance to ICIs remains to be validated and explored in hematological malignancies. In addition, facing irAEs, how to avoid or minimize the harm of side effects is also the most concerned part of researchers. We believe that persistent research on ICIs will increase their effectiveness, mitigate adverse effects, and ultimately expand the percentage of patients who can benefit from ICIs.

AUTHOR CONTRIBUTIONS

Wenyue Sun wrote this manuscript and created figures and tables. Xin Wang and Shunfeng Hu revised the manuscript. Xin Wang provided guidance throughout the preparation of the manuscript. All authors read and approved the final manuscript.

ACKNOWLEDGMENTS

This study was funded by the National Natural Science Foundation (No.82270200, No.82070203 and No.81770210); Key Research and Development Program of Shandong Province (No.2018CXGC1213); Taishan Scholars Program of Shandong Province (No.tspd20230610, NO.tsqnz20231251); Translational Research Grant of

NCRCH (No.2021WWB02, No.2020ZKMB01); Shandong Provincial Engineering Research Center of Lymphoma; Academic Promotion Programme of Shandong First Medical University (No. 2019QL018); China Postdoctoral Science Foundation (No. 2023M741506); Shandong Provincial Natural Science Foundation (No. ZR2023QH193).

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

Not applicable.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

ORCID

Xin Wang https://orcid.org/0000-0001-8051-1481

REFERENCES

1. Zhang Y, Zheng J. Functions of Immune Checkpoint Molecules Beyond Immune Evasion. Adv Exp Med Biol. 2020;1248:201-26.
2. Wartewig T, Daniels J, Schulz M, Hameister E, Joshi A, Park J, et al. PD-1 instructs a tumor-suppressive metabolic program that restricts glycolysis and restrains AP-1 activity in T cell lymphoma. Nat Cancer. 2023;4(10):1508-25.
3. Topalian SL, Drake CG, Pardoll DM. Immune checkpoint blockade: a common denominator approach to cancer therapy. Cancer Cell. 2015;27(4):450-61.
4. Robert C. A decade of immune-checkpoint inhibitors in cancer therapy. Nat Commun. 2020;11(1):3801.
5. Korman AJ, Garrett-Thomson SC, Lonberg N. The foundations of immune checkpoint blockade and the ipilimumab approval decennial. Nat Rev Drug Discov. 2022;21(7):509-28.
6. Robert C, Schachter J, Long GV, Arance A, Grob JJ, Mortier L, et al. Pembrolizumab versus Ipilimumab in Advanced Melanoma. N Engl J Med. 2015;372(26):2521-32.
7. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Rutkowski P, Lao CD, et al. Five-Year Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. N Engl J Med. 2019;381(16):1535-46.
8. Vaddepally RK, Kharel P, Pandey R, Garje R, Chandra AB. Review of Indications of FDA-Approved Immune Checkpoint Inhibitors per NCCN Guidelines with the Level of Evidence. Cancers (Basel). 2020;12(3):738.
9. Chen R, Zinzani PL, Lee HJ, Armand P, Johnson NA, Brice P, et al. Pembrolizumab in relapsed or refractory Hodgkin lymphoma: 2-year follow-up of KEYNOTE-087. Blood. 2019;134(14):1144-53.
10. Geoerger B, Kang HJ, Yalon-Oren M, Marshall LV, Vezina C, Pappo A, et al. Pembrolizumab in paediatric patients with advanced melanoma or a PD-L1-positive, advanced, relapsed, or refractory solid tumour or lymphoma (KEYNOTE-051): interim analysis of an open-label, single-arm, phase 1-2 trial. Lancet Oncol. 2020;21(1):121-33.
11. Cuccaro A, Bellesi S, Galli E, Zangrilli I, Corrente F, Cupelli E, et al. PD-L1 expression in peripheral blood granulocytes at diagnosis as prognostic factor in classical Hodgkin lymphoma. J Leukoc Biol. 2022;112(3):539-45.
12. Onishi A, Fuji S, Kitano S, Maeshima AM, Tajima K, Yamaguchi J, et al. Prognostic implication of CTLA-4, PD-1, and PD-L1 expression in aggressive adult T-cell leukemia-lymphoma. Ann Hematol. 2022;101(4):799-810.
13. He HX, Gao Y, Fu JC, Zhou QH, Wang XX, Bai B, et al. VISTA and PD-L1 synergistically predict poor prognosis in patients with extranodal natural killer/T-cell lymphoma. Oncoimmunology. 2021;10(1):1907059.
14. Keane C, Law SC, Gould C, Birch S, Sabdia MB, Merida de Long L, et al. LAG3: a novel immune checkpoint expressed by multiple lymphocyte subsets in diffuse large B-cell lymphoma. Blood Adv. 2020;4(7):1367-77.
15. Schoenfeld AJ, Hellmann MD. Acquired Resistance to Immune Checkpoint Inhibitors. Cancer Cell. 2020;37(4):443-55.
16. Veldman J, Visser L, Berg AVD, Diepstra A. Primary and acquired resistance mechanisms to immune checkpoint inhibition in Hodgkin lymphoma. Cancer Treat Rev. 2020;82:101931.
17. Shen W, Patnaik MM, Ruiz A, Russell SJ, Peng KW. Immunovirotherapy with vesicular stomatitis virus and PD-L1 blockade enhances therapeutic outcome in murine acute myeloid leukemia. Blood. 2016;127(11):1449-58.
18. Jing Z, Wang S, Xu K, Tang Q, Li W, Zheng W, et al. A Potent Micron Neoantigen Tumor Vaccine GP-Neoantigen Induces Robust Antitumor Activity in Multiple Tumor Models. Adv Sci (Weinh). 2022;9(24):e2201496.
19. Herrmann M, Krupka C, Deiser K, Brauchle B, Marcinek A, Ogrinc Wagner A, et al. Bifunctional PD-1 × αCD3 × αCD33 fusion protein reverses adaptive immune escape in acute myeloid leukemia. Blood. 2018;132(23):2484-94.
20. Yong SB, Kim J, Chung JY, Ra S, Kim SS, Kim YH. Heme Oxygenase 1-Targeted Hybrid Nanoparticle for Chemo- and Immuno-Combination Therapy in Acute Myelogenous Leukemia. Adv Sci (Weinh). 2020;7(13):2000487.
21. Abusarah J, Khodayarian F, El-Hachem N, Salame N, Olivier M, Balood M, et al. Engineering immunoproteasome-expressing mesenchymal stromal cells: A potent cellular vaccine for lymphoma and melanoma in mice. Cell Rep Med. 2021;2(12):100455.
22. Kornacker M, Moldenhauer G, Herbst M, Weilguni E, Tita-Nwa F, Harter C, et al. Cytokine-induced killer cells against autologous CLL: direct cytotoxic effects and induction of immune accessory molecules by interferon-gamma. Int J Cancer. 2006;119(6):1377-82.
23. Deuse T, Hu X, Agbor-Enoh S, Jang MK, Alawi M, Saygi C, et al. The SIRPα-CD47 immune checkpoint in NK cells. J Exp Med. 2021;218(3):e20200839.
24. Bauer V, Ahmetlić F, Hömberg N, Geishauser A, Röcken M, Mocikat R. Immune checkpoint blockade impairs immunosuppressive mechanisms of regulatory T cells in B-cell lymphoma. Transl Oncol. 2021;14(9):101170.
25. Peng Q, Qiu X, Zhang Z, Zhang S, Zhang Y, Liang Y, et al. PD-L1 on dendritic cells attenuates T cell activation and regu-

lates response to immune checkpoint blockade. Nat Commun. 2020;11(1):4835.
26. Kiessling R, Klein E, Wigzell H. "Natural" killer cells in the mouse. I. Cytotoxic cells with specificity for mouse Moloney leukemia cells. Specificity and distribution according to genotype. Eur J Immunol. 1975;5(2):112-7.
27. Herberman RB, Nunn ME, Holden HT, Lavrin DH. Natural cytotoxic reactivity of mouse lymphoid cells against syngeneic and allogeneic tumors. II. Characterization of effector cells. Int J Cancer. 1975;16(2):230-9.
28. Khan M, Arooj S, Wang H. NK Cell-Based Immune Checkpoint Inhibition. Front Immunol. 2020;11:167.
29. Liu JQ, Talebian F, Wu L, Liu Z, Li MS, Wu L, et al. A Critical Role for CD200R Signaling in Limiting the Growth and Metastasis of CD200+ Melanoma. J Immunol. 2016;197(4):1489-97.
30. Moreaux J, Hose D, Reme T, Jourdan E, Hundemer M, Legouffe E, et al. CD200 is a new prognostic factor in multiple myeloma. Blood. 2006;108(13):4194-7.
31. Tonks A, Hills R, White P, Rosie B, Mills KI, Burnett AK, et al. CD200 as a prognostic factor in acute myeloid leukaemia. Leukemia. 2007;21(3):566-8.
32. Coles SJ, Wang EC, Man S, Hills RK, Burnett AK, Tonks A, et al. CD200 expression suppresses natural killer cell function and directly inhibits patient anti-tumor response in acute myeloid leukemia. Leukemia. 2011;25(5):792-9.
33. Sasidharan Nair V, Elkord E. Immune checkpoint inhibitors in cancer therapy: a focus on T-regulatory cells. Immunol Cell Biol. 2018;96(1):21-33.
34. Sakaguchi S, Yamaguchi T, Nomura T, Ono M. Regulatory T cells and immune tolerance. Cell. 2008;133(5):775-87.
35. Ohue Y, Nishikawa H. Regulatory T (Treg) cells in cancer: Can Treg cells be a new therapeutic target? Cancer Sci. 2019;110(7):2080-9.
36. Tanaka A, Sakaguchi S. Regulatory T cells in cancer immunotherapy. Cell Res. 2017;27(1):109-18.
37. Dehghani M, Kalani M, Golmoghaddam H, Ramzi M, Arandi N. Aberrant peripheral blood CD4(+) CD25(+) FOXP3(+) regulatory T cells/T helper-17 number is associated with the outcome of patients with lymphoma. Cancer Immunol Immunother. 2020;69(9):1917-28.
38. Mittal S, Marshall NA, Duncan L, Culligan DJ, Barker RN, Vickers MA. Local and systemic induction of CD4+CD25+ regulatory T-cell population by non-Hodgkin lymphoma. Blood. 2008;111(11):5359-70.
39. Gardner A, de Mingo Pulido Á, Ruffell B. Dendritic Cells and Their Role in Immunotherapy. Front Immunol. 2020;11:924.
40. Wculek SK, Cueto FJ, Mujal AM, Melero I, Krummel MF, Sancho D. Dendritic cells in cancer immunology and immunotherapy. Nat Rev Immunol. 2020;20(1):7-24.
41. Böttcher JP, Reis e Sousa C. The Role of Type 1 Conventional Dendritic Cells in Cancer Immunity. Trends Cancer. 2018;4(11):784-92.
42. Sakuishi K, Apetoh L, Sullivan JM, Blazar BR, Kuchroo VK, Anderson AC. Targeting Tim-3 and PD-1 pathways to reverse T cell exhaustion and restore anti-tumor immunity. J Exp Med. 2010;207(10):2187-94.
43. Rowshanravan B, Halliday N, Sansom DM. CTLA-4: a moving target in immunotherapy. Blood. 2018;131(1):58-67.
44. Abdou AG, Asaad NY, Loay I, Shabaan M, Badr N. The prognostic role of tumor-associated macrophages and dendritic cells in classic Hodgkin's lymphoma. J Environ Pathol Toxicol Oncol. 2013;32(4):289-305.
45. Huang S, Liao M, Chen S, Zhang P, Xu F, Zhang H. Immune signatures of CD4 and CD68 predicts disease progression in cutaneous T cell lymphoma. Am J Transl Res. 2022;14(5):3037-51.
46. Zalmaï L, Viailly PJ, Biichle S, Cheok M, Soret L, Angelot-Delettre F, et al. Plasmacytoid dendritic cells proliferation associated with acute myeloid leukemia: phenotype profile and mutation landscape. Haematologica. 2021;106(12):3056-66.
47. Chao MP, Takimoto CH, Feng DD, McKenna K, Gip P, Liu J, et al. Therapeutic Targeting of the Macrophage Immune Checkpoint CD47 in Myeloid Malignancies. Front Oncol. 2019;9:1380.
48. Poels LG, Peters D, van Megen Y, Vooijs GP, Verheyen RN, Willemen A, et al. Monoclonal antibody against human ovarian tumor-associated antigens. J Natl Cancer Inst. 1986;76(5):781-91.
49. Yang K, Xu J, Liu Q, Li J, Xi Y. Expression and significance of CD47, PD1 and PDL1 in T-cell acute lymphoblastic lymphoma/leukemia. Pathol Res Pract. 2019;215(2):265-71.
50. Majeti R, Chao MP, Alizadeh AA, Pang WW, Jaiswal S, Gibbs KD, Jr., et al. CD47 is an adverse prognostic factor and therapeutic antibody target on human acute myeloid leukemia stem cells. Cell. 2009;138(2):286-99.
51. Russ A, Hua AB, Montfort WR, Rahman B, Riaz IB, Khalid MU, et al. Blocking "don't eat me" signal of CD47-SIRPα in hematological malignancies, an in-depth review. Blood Rev. 2018;32(6):480-9.
52. Pang WW, Pluvinage JV, Price EA, Sridhar K, Arber DA, Greenberg PL, et al. Hematopoietic stem cell and progenitor cell mechanisms in myelodysplastic syndromes. Proc Natl Acad Sci U S A. 2013;110(8):3011-6.
53. Jaiswal S, Jamieson CH, Pang WW, Park CY, Chao MP, Majeti R, et al. CD47 is upregulated on circulating hematopoietic stem cells and leukemia cells to avoid phagocytosis. Cell. 2009;138(2):271-85.
54. Liu J, Wang L, Zhao F, Tseng S, Narayanan C, Shura L, et al. Pre-Clinical Development of a Humanized Anti-CD47 Antibody with Anti-Cancer Therapeutic Potential. PLoS One. 2015;10(9):e0137345.
55. Wolfl M, Kuball J, Ho WY, Nguyen H, Manley TJ, Bleakley M, et al. Activation-induced expression of CD137 permits detection, isolation, and expansion of the full repertoire of CD8+ T cells responding to antigen without requiring knowledge of epitope specificities. Blood. 2007;110(1):201-10.
56. Makkouk A, Chester C, Kohrt HE. Rationale for anti-CD137 cancer immunotherapy. Eur J Cancer. 2016;54:112-9.
57. Stoll A, Bruns H, Fuchs M, Völkl S, Nimmerjahn F, Kunz M, et al. CD137 (4-1BB) stimulation leads to metabolic and functional reprogramming of human monocytes/macrophages enhancing their tumoricidal activity. Leukemia. 2021;35(12):3482-96.
58. Shi Y, Liu Y, Huang J, Luo Z, Guo X, Jiang M, et al. Optimized mobilization of MHC class I- and II- restricted immunity by dendritic cell vaccine potentiates cancer therapy. Theranostics. 2022;12(7):3488-502.
59. Fløisand Y, Remberger M, Bigalke I, Josefsen D, Vålerhaugen H, Inderberg EM, et al. WT1 and PRAME RNA-loaded

dendritic cell vaccine as maintenance therapy in de novo AML after intensive induction chemotherapy. Leukemia. 2023;37(9): 1842-9.

60. Zhao H, Cai S, Xiao Y, Xia M, Chen H, Xie Z, et al. Expression and prognostic significance of the PD-1/PD-L1 pathway in AIDS-related non-Hodgkin lymphoma. Cancer Med. 2024;13(7):e7195.
61. Ruan Y, Wang J, Zhang Q, Wang H, Li C, Xu X, et al. Clinical implications of aberrant PD-1 expression for acute leukemia prognosis. Eur J Med Res. 2023;28(1):383.
62. Wang L, Wang H, Chen H, Wang WD, Chen XQ, Geng QR, et al. Serum levels of soluble programmed death ligand 1 predict treatment response and progression free survival in multiple myeloma. Oncotarget. 2015;6(38):41228-36.
63. Beck Enemark M, Monrad I, Madsen C, Lystlund Lauridsen K, Honoré B, Plesner TL, et al. PD-1 Expression in Pre-Treatment Follicular Lymphoma Predicts the Risk of Subsequent High-Grade Transformation. Onco Targets Ther. 2021;14:481-9.
64. Richter S, Böttcher M, Stoll A, Zeremski V, Völkl S, Mackensen A, et al. Increased PD-1 Expression on Circulating T Cells Correlates with Inferior Outcome after Autologous Stem Cell Transplantation. Transplant Cell Ther. 2024;30(6):628.e1-.e9.
65. Phillips D, Matusiak M, Gutierrez BR, Bhate SS, Barlow GL, Jiang S, et al. Immune cell topography predicts response to PD-1 blockade in cutaneous T cell lymphoma. Nat Commun. 2021;12(1):6726.
66. Kulikowska de Nałęcz A, Ciszak L, Usnarska-Zubkiewicz L, Pawlak E, Frydecka I, Szmyrka M, et al. Inappropriate Expression of PD-1 and CTLA-4 Checkpoints in Myeloma Patients Is More Pronounced at Diagnosis: Implications for Time to Progression and Response to Therapeutic Checkpoint Inhibitors. Int J Mol Sci. 2023;24(6):5730.
67. Aref S, El Agdar M, El Sebaie A, Abouzeid T, Sabry M, Ibrahim L. Prognostic Value of CD200 Expression and Soluble CTLA-4 Concentrations in Intermediate and High-Risk Myelodysplastic Syndrome Patients. Asian Pac J Cancer Prev. 2020;21(8):2225-30.
68. Radwan SM, Elleboudy NS, Nabih NA, Kamal AM. The immune checkpoints Cytotoxic T lymphocyte antigen-4 and Lymphocyte activation gene-3 expression is up-regulated in acute myeloid leukemia. Hla. 2020;96(1):3-12.
69. Ansell SM, Hurvitz SA, Koenig PA, LaPlant BR, Kabat BF, Fernando D, et al. Phase I study of ipilimumab, an anti-CTLA-4 monoclonal antibody, in patients with relapsed and refractory B-cell non-Hodgkin lymphoma. Clin Cancer Res. 2009;15(20):6446-53.
70. Davids MS, Kim HT, Bachireddy P, Costello C, Liguori R, Savell A, et al. Ipilimumab for Patients with Relapse after Allogeneic Transplantation. N Engl J Med. 2016;375(2):143-53.
71. Takeuchi M, Miyoshi H, Nakashima K, Kawamoto K, Yamada K, Yanagida E, et al. Comprehensive immunohistochemical analysis of immune checkpoint molecules in adult T cell leukemia/lymphoma. Ann Hematol. 2020;99(5):1093-8.
72. Rakova J, Truxova I, Holicek P, Salek C, Hensler M, Kasikova L, et al. TIM-3 levels correlate with enhanced NK cell cytotoxicity and improved clinical outcome in AML patients. Oncoimmunology. 2021;10(1):1889822.
73. Zhong W, Liu X, Zhu Z, Li Q, Li K. High levels of Tim-3(+)Foxp3(+)Treg cells in the tumor microenvironment is a prognostic indicator of poor survival of diffuse large B cell lymphoma patients. Int Immunopharmacol. 2021;96:107662.
74. Zhang L, Du H, Xiao TW, Liu JZ, Liu GZ, Wang JX, et al. Prognostic value of PD-1 and TIM-3 on CD3+ T cells from diffuse large B-cell lymphoma. Biomed Pharmacother. 2015;75:83-7.
75. Wu H, Sun HC, Ouyang GF. T-cell immunoglobulin mucin molecule-3, transformation growth factor β, and chemokine-12 and the prognostic status of diffuse large B-cell lymphoma. World J Clin Cases. 2022;10(32):11804-11.
76. Marconato M, Kauer J, Salih HR, Märklin M, Heitmann JS. Expression of the immune checkpoint modulator OX40 indicates poor survival in acute myeloid leukemia. Sci Rep. 2022;12(1):15856.
77. Ma J, Pang X, Li J, Zhang W, Cui W. The immune checkpoint expression in the tumor immune microenvironment of DLBCL: Clinicopathologic features and prognosis. Front Oncol. 2022;12:1069378.
78. Moiseev I, Tcvetkov N, Epifanovskaya O, Babenko E, Parfenenkova A, Bakin E, et al. Landscape of alterations in the checkpoint system in myelodysplastic syndrome and implications for prognosis. PLoS One. 2022;17(10):e0275399.
79. Jin Z, Lan T, Zhao Y, Du J, Chen J, Lai J, et al. Higher TIGIT(+)CD226(-) $\gamma\delta$ T cells in Patients with Acute Myeloid Leukemia. Immunol Invest. 2022;51(1):40-50.
80. Bai KH, Zhang YY, Li XP, Tian XP, Pan MM, Wang DW, et al. Comprehensive analysis of tumor necrosis factor-α-inducible protein 8-like 2 (TIPE2): A potential novel pan-cancer immune checkpoint. Comput Struct Biotechnol J. 2022;20:5226-34.
81. Fudaba H, Momii Y, Hirakawa T, Onishi K, Asou D, Matsushita W, et al. Sialic acid-binding immunoglobulin-like lectin-15 expression on peritumoral macrophages is a favorable prognostic factor for primary central nervous system lymphoma patients. Sci Rep. 2021;11(1):1206.
82. Hatic H, Sampat D, Goyal G. Immune checkpoint inhibitors in lymphoma: challenges and opportunities. Ann Transl Med. 2021;9(12):1037.
83. Armand P, Zinzani PL, Lee HJ, Johnson NA, Brice P, Radford J, et al. Five-year follow-up of KEYNOTE-087: pembrolizumab monotherapy for relapsed/refractory classical Hodgkin lymphoma. Blood. 2023;142(10):878-86.
84. Chen R, Zinzani PL, Fanale MA, Armand P, Johnson NA, Brice P, et al. Phase II Study of the Efficacy and Safety of Pembrolizumab for Relapsed/Refractory Classic Hodgkin Lymphoma. J Clin Oncol. 2017;35(19):2125-32.
85. Armand P, Shipp MA, Ribrag V, Michot JM, Zinzani PL, Kuruvilla J, et al. Programmed Death-1 Blockade With Pembrolizumab in Patients With Classical Hodgkin Lymphoma After Brentuximab Vedotin Failure. J Clin Oncol. 2016;34(31):3733-9.
86. Ribrag V, Avigan DE, Green DJ, Wise-Draper T, Posada JG, Vij R, et al. Phase 1b trial of pembrolizumab monotherapy for relapsed/refractory multiple myeloma: KEYNOTE-013. Br J Haematol. 2019;186(3):e41-e4.
87. Armand P, Janssens A, Gritti G, Radford J, Timmerman J, Pinto A, et al. Efficacy and safety results from CheckMate 140, a phase 2 study of nivolumab for relapsed/refractory follicular lymphoma. Blood. 2021;137(5):637-45.
88. Armand P, Engert A, Younes A, Fanale M, Santoro A, Zinzani PL, et al. 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. 2018;36(14):1428-39.
89. Lesokhin AM, Ansell SM, Armand P, Scott EC, Halwani A, Gutierrez M, et al. Nivolumab in Patients With Relapsed or Refractory Hematologic Malignancy: Preliminary Results of a Phase Ib Study. J Clin Oncol. 2016;34(23):2698-704.
90. Davids MS, Kim HT, Costello C, Herrera AF, Locke FL, Maegawa RO, et al. A multicenter phase 1 study of nivolumab for relapsed hematologic malignancies after allogeneic transplantation. Blood. 2020;135(24):2182-91.
91. Liu D, Ma C, Lu P, Gong J, Ye D, Wang S, et al. Dose escalation and expansion (phase Ia/Ib) study of GLS-010, a recombinant fully human antiprogrammed death-1 monoclonal antibody for advanced solid tumors or lymphoma. Eur J Cancer. 2021;148:1-13.
92. Marjańska A, Pawińska-Wąsikowska K, Wieczorek A, Drogosiewicz M, Dembowska-Bagińska B, Bobeff K, et al. Anti-PD-1 Therapy in Advanced Pediatric Malignancies in Nationwide Study: Good Outcome in Skin Melanoma and Hodgkin Lymphoma. Cancers (Basel). 2024;16(5):968.
93. Greve P, Beishuizen A, Hagleitner M, Loeffen J, Veening M, Boes M, et al. Nivolumab plus Brentuximab vedotin +/- bendamustine combination therapy: a safe and effective treatment in pediatric recurrent and refractory classical Hodgkin lymphoma. Front Immunol. 2023;14:1229558.
94. Gould C, Lickiss J, Kankanige Y, Yerneni S, Lade S, Gandhi MK, et al. Characterisation of immune checkpoints in Richter syndrome identifies LAG3 as a potential therapeutic target. Br J Haematol. 2021;195(1):113-8.
95. Godfrey J, Chen X, Sunseri N, Cooper A, Yu J, Varlamova A, et al. TIGIT is a key inhibitory checkpoint receptor in lymphoma. J Immunother Cancer. 2023;11(6):e006582.
96. Libert D, Zhao S, Younes S, Mosquera AP, Bharadwaj S, Ferreira C, et al. TIGIT is Frequently Expressed in the Tumor Microenvironment of Select Lymphomas: Implications for Targeted Therapy. Am J Surg Pathol. 2024;48(3):337-52.
97. Chen H, Chen Y, Deng M, John S, Gui X, Kansagra A, et al. Antagonistic anti-LILRB1 monoclonal antibody regulates antitumor functions of natural killer cells. J Immunother Cancer. 2020;8(2):e000515.
98. Zeller T, Lutz S, Münnich IA, Windisch R, Hilger P, Herold T, et al. Dual checkpoint blockade of CD47 and LILRB1 enhances CD20 antibody-dependent phagocytosis of lymphoma cells by macrophages. Front Immunol. 2022;13:929339.
99. Kay R, Rosten PM, Humphries RK. CD24, a signal transducer modulating B cell activation responses, is a very short peptide with a glycosyl phosphatidylinositol membrane anchor. J Immunol. 1991;147(4):1412-6.
100. Freile J, Ustyanovska Avtenyuk N, Corrales MG, Lourens HJ, Huls G, van Meerten T, et al. CD24 Is a Potential Immunotherapeutic Target for Mantle Cell Lymphoma. Biomedicines. 2022;10(5):1175.
101. Sordo-Bahamonde C, Lorenzo-Herrero S, Gonzalez-Rodriguez AP, Á RP, González-García E, López-Soto A, et al. BTLA/HVEM Axis Induces NK Cell Immunosuppression and Poor Outcome in Chronic Lymphocytic Leukemia. Cancers (Basel). 2021;13(8):1766.
102. Li J, Whelan S, Kotturi MF, Meyran D, D'Souza C, Hansen K, et al. PVRIG is a novel natural killer cell immune checkpoint receptor in acute myeloid leukemia. Haematologica. 2021;106(12):3115-24.
103. Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. Lancet. 2007;370(9581):59-67.
104. El Zarif T, Nassar AH, Adib E, Fitzgerald BG, Huang J, Mouhieddine TH, et al. Safety and Activity of Immune Checkpoint Inhibitors in People Living With HIV and Cancer: A Real-World Report From the Cancer Therapy Using Checkpoint Inhibitors in People Living With HIV-International (CATCH-IT) Consortium. J Clin Oncol. 2023;41(21):3712-23.
105. Cook MR, Kim C. Safety and Efficacy of Immune Checkpoint Inhibitor Therapy in Patients With HIV Infection and Advanced-Stage Cancer: A Systematic Review. JAMA Oncol. 2019;5(7):1049-54.
106. Lurain K, Ramaswami R, Mangusan R, Widell A, Ekwede I, George J, et al. Use of pembrolizumab with or without pomalidomide in HIV-associated non-Hodgkin's lymphoma. J Immunother Cancer. 2021;9(2):e002097.
107. Benito JM, Restrepo C, García-Foncillas J, Rallón N. Immune checkpoint inhibitors as potential therapy for reverting T-cell exhaustion and reverting HIV latency in people living with HIV. Front Immunol. 2023;14:1270881.
108. Jhawar SR, Wang SJ, Thandoni A, Bommareddy PK, Newman JH, Marzo AL, et al. Combination oncolytic virus, radiation therapy, and immune checkpoint inhibitor treatment in anti-PD-1-refractory cancer. J Immunother Cancer. 2023;11(7):e006780corr1.
109. Conrad DP, Tsang J, Maclean M, Diallo JS, Le Boeuf F, Lemay CG, et al. Leukemia cell-rhabdovirus vaccine: personalized immunotherapy for acute lymphoblastic leukemia. Clin Cancer Res. 2013;19(14):3832-43.
110. Hanauer JDS, Rengstl B, Kleinlützum D, Reul J, Pfeiffer A, Friedel T, et al. CD30-targeted oncolytic viruses as novel therapeutic approach against classical Hodgkin lymphoma. Oncotarget. 2018;9(16):12971-81.
111. Wenthe J, Naseri S, Labani-Motlagh A, Enblad G, Wikström KI, Eriksson E, et al. Boosting CAR T-cell responses in lymphoma by simultaneous targeting of CD40/4-1BB using oncolytic viral gene therapy. Cancer Immunol Immunother. 2021;70(10):2851-65.
112. Wenthe J, Naseri S, Hellström AC, Wiklund HJ, Eriksson E, Loskog A. Immunostimulatory oncolytic virotherapy for multiple myeloma targeting 4-1BB and/or CD40. Cancer Gene Ther. 2020;27(12):948-59.
113. Liu L, Chen J, Zhang H, Ye J, Moore C, Lu C, et al. Concurrent delivery of immune checkpoint blockade modulates T cell dynamics to enhance neoantigen vaccine-generated antitumor immunity. Nat Cancer. 2022;3(4):437-52.
114. Keshari S, Shavkunov AS, Miao Q, Saha A, Williams CD, Highsmith AM, et al. Neoantigen Cancer Vaccines and Different Immune Checkpoint Therapies Each Utilize Both Converging and Distinct Mechanisms that in Combination Enable Synergistic Therapeutic Efficacy. bioRxiv. 2024.
115. Biernacki MA, Foster KA, Woodward KB, Coon ME, Cummings C, Cunningham TM, et al. CBFB-MYH11 fusion

neoantigen enables T cell recognition and killing of acute myeloid leukemia. J Clin Invest. 2020;130(10):5127-41.
116. Blanco B, Domínguez-Alonso C, Alvarez-Vallina L. Bispecific Immunomodulatory Antibodies for Cancer Immunotherapy. Clin Cancer Res. 2021;27(20):5457-64.
117. Waite JC, Wang B, Haber L, Hermann A, Ullman E, Ye X, et al. Tumor-targeted CD28 bispecific antibodies enhance the antitumor efficacy of PD-1 immunotherapy. Sci Transl Med. 2020;12(549):eaba2325.
118. Clynes RA, Desjarlais JR. Redirected T Cell Cytotoxicity in Cancer Therapy. Annu Rev Med. 2019;70:437-50.
119. Aigner M, Feulner J, Schaffer S, Kischel R, Kufer P, Schneider K, et al. T lymphocytes can be effectively recruited for ex vivo and in vivo lysis of AML blasts by a novel CD33/CD3-bispecific BiTE antibody construct. Leukemia. 2013;27(5):1107-15.
120. Krupka C, Kufer P, Kischel R, Zugmaier G, Bögeholz J, Köhnke T, et al. CD33 target validation and sustained depletion of AML blasts in long-term cultures by the bispecific T-cell-engaging antibody AMG 330. Blood. 2014;123(3):356-65.
121. Krupka C, Kufer P, Kischel R, Zugmaier G, Lichtenegger FS, Köhnke T, et al. Blockade of the PD-1/PD-L1 axis augments lysis of AML cells by the CD33/CD3 BiTE antibody construct AMG 330: reversing a T-cell-induced immune escape mechanism. Leukemia. 2016;30(2):484-91.
122. Riley RS, June CH, Langer R, Mitchell MJ. Delivery technologies for cancer immunotherapy. Nat Rev Drug Discov. 2019;18(3):175-96.
123. Deng H, Zhang Z. The application of nanotechnology in immune checkpoint blockade for cancer treatment. J Control Release. 2018;290:28-45.
124. Muliaditan T, Opzoomer JW, Caron J, Okesola M, Kosti P, Lall S, et al. Repurposing Tin Mesoporphyrin as an Immune Checkpoint Inhibitor Shows Therapeutic Efficacy in Preclinical Models of Cancer. Clin Cancer Res. 2018;24(7):1617-28.
125. Bai H, Sun Q, Kong F, Dong H, Ma M, Liu F, et al. Zwitterion-functionalized hollow mesoporous Prussian blue nanoparticles for targeted and synergetic chemo-photothermal treatment of acute myeloid leukemia. J Mater Chem B. 2021;9(26):5245-54.
126. Jamieson AM, Diefenbach A, McMahon CW, Xiong N, Carlyle JR, Raulet DH. The role of the NKG2D immunoreceptor in immune cell activation and natural killing. Immunity. 2002;17(1):19-29.
127. Zhang Y, Ellinger J, Ritter M, Schmidt-Wolf IGH. Clinical Studies Applying Cytokine-Induced Killer Cells for the Treatment of Renal Cell Carcinoma. Cancers (Basel). 2020;12(9).
128. Li Y, Sharma A, Bloemendal M, Schmidt-Wolf R, Kornek M, Schmidt-Wolf IGH. PD-1 blockade enhances cytokine-induced killer cell-mediated cytotoxicity in B-cell non-Hodgkin lymphoma cell lines. Oncol Lett. 2021;22(2):613.
129. Linn YC, Lau LC, Hui KM. Generation of cytokine-induced killer cells from leukaemic samples with in vitro cytotoxicity against autologous and allogeneic leukaemic blasts. Br J Haematol. 2002;116(1):78-86.
130. Hoyle C, Bangs CD, Chang P, Kamel O, Mehta B, Negrin RS. Expansion of Philadelphia chromosome-negative CD3(+)CD56(+) cytotoxic cells from chronic myeloid leukemia patients: in vitro and in vivo efficacy in severe combined immunodeficiency disease mice. Blood. 1998;92(9):3318-27.
131. Yi M, Zheng X, Niu M, Zhu S, Ge H, Wu K. Combination strategies with PD-1/PD-L1 blockade: current advances and future directions. Mol Cancer. 2022;21(1):28.
132. Bissonnette RP, Cesario RM, Goodenow B, Shojaei F, Gillings M. The epigenetic immunomodulator, HBI-8000, enhances the response and reverses resistance to checkpoint inhibitors. BMC Cancer. 2021;21(1):969.
133. Morad G, Helmink BA, Sharma P, Wargo JA. Hallmarks of response, resistance, and toxicity to immune checkpoint blockade. Cell. 2021;184(21):5309-37.
134. Yap TA, Parkes EE, Peng W, Moyers JT, Curran MA, Tawbi HA. Development of Immunotherapy Combination Strategies in Cancer. Cancer Discov. 2021;11(6):1368-97.
135. Kalbasi A, Ribas A. Tumour-intrinsic resistance to immune checkpoint blockade. Nat Rev Immunol. 2020;20(1):25-39.
136. Restifo NP, Marincola FM, Kawakami Y, Taubenberger J, Yannelli JR, Rosenberg SA. Loss of functional beta 2-microglobulin in metastatic melanomas from five patients receiving immunotherapy. J Natl Cancer Inst. 1996;88(2):100-8.
137. Shin DS, Zaretsky JM, Escuin-Ordinas H, Garcia-Diaz A, Hu-Lieskovan S, Kalbasi A, et al. Primary Resistance to PD-1 Blockade Mediated by JAK1/2 Mutations. Cancer Discov. 2017;7(2):188-201.
138. Sade-Feldman M, Jiao YJ, Chen JH, Rooney MS, Barzily-Rokni M, Eliane JP, et al. Resistance to checkpoint blockade therapy through inactivation of antigen presentation. Nat Commun. 2017;8(1):1136.
139. Gettinger S, Choi J, Hastings K, Truini A, Datar I, Sowell R, et al. Impaired HLA Class I Antigen Processing and Presentation as a Mechanism of Acquired Resistance to Immune Checkpoint Inhibitors in Lung Cancer. Cancer Discov. 2017;7(12):1420-35.
140. Cycon KA, Mulvaney K, Rimsza LM, Persky D, Murphy SP. Histone deacetylase inhibitors activate CIITA and MHC class II antigen expression in diffuse large B-cell lymphoma. Immunology. 2013;140(2):259-72.
141. Gladue RP, Paradis T, Cole SH, Donovan C, Nelson R, Alpert R, et al. The CD40 agonist antibody CP-870,893 enhances dendritic cell and B-cell activity and promotes anti-tumor efficacy in SCID-hu mice. Cancer Immunol Immunother. 2011;60(7):1009-17.
142. Gao J, Shi LZ, Zhao H, Chen J, Xiong L, He Q, et al. Loss of IFN-γ Pathway Genes in Tumor Cells as a Mechanism of Resistance to Anti-CTLA-4 Therapy. Cell. 2016;167(2):397-404.e9.
143. Sucker A, Zhao F, Pieper N, Heeke C, Maltaner R, Stadtler N, et al. Acquired IFNγ resistance impairs anti-tumor immunity and gives rise to T-cell-resistant melanoma lesions. Nat Commun. 2017;8:15440.
144. Chen J, Zuo Z, Gao Y, Yao X, Guan P, Wang Y, et al. Aberrant JAK-STAT signaling-mediated chromatin remodeling impairs the sensitivity of NK/T-cell lymphoma to chidamide. Clin Epigenetics. 2023;15(1):19.
145. Yang H, Ma P, Cao Y, Zhang M, Li L, Wei J, et al. ECPIRM, a Potential Therapeutic Agent for Cutaneous T-Cell Lymphoma, Inhibits Cell Proliferation and Promotes Apoptosis via a JAK/STAT Pathway. Anticancer Agents Med Chem. 2018;18(3):401-11.
146. Peng W, Chen JQ, Liu C, Malu S, Creasy C, Tetzlaff MT, et al. Loss of PTEN Promotes Resistance to T Cell-Mediated Immunotherapy. Cancer Discov. 2016;6(2):202-16.

147. George S, Miao D, Demetri GD, Adeegbe D, Rodig SJ, Shukla S, et al. Loss of PTEN Is Associated with Resistance to Anti-PD-1 Checkpoint Blockade Therapy in Metastatic Uterine Leiomyosarcoma. Immunity. 2017;46(2):197-204.
148. Trujillo JA, Luke JJ, Zha Y, Segal JP, Ritterhouse LL, Spranger S, et al. Secondary resistance to immunotherapy associated with β-catenin pathway activation or PTEN loss in metastatic melanoma. J Immunother Cancer. 2019;7(1):295.
149. Wang X, Huang H, Young KH. The PTEN tumor suppressor gene and its role in lymphoma pathogenesis. Aging (Albany NY). 2015;7(12):1032-49.
150. Koyama S, Akbay EA, Li YY, Herter-Sprie GS, Buczkowski KA, Richards WG, et al. Adaptive resistance to therapeutic PD-1 blockade is associated with upregulation of alternative immune checkpoints. Nat Commun. 2016;7:10501.
151. Kakavand H, Jackett LA, Menzies AM, Gide TN, Carlino MS, Saw RPM, et al. Negative immune checkpoint regulation by VISTA: a mechanism of acquired resistance to anti-PD-1 therapy in metastatic melanoma patients. Mod Pathol. 2017;30(12):1666-76.
152. Saxena K, Herbrich SM, Pemmaraju N, Kadia TM, DiNardo CD, Borthakur G, et al. A phase 1b/2 study of azacitidine with PD-L1 antibody avelumab in relapsed/refractory acute myeloid leukemia. Cancer. 2021;127(20):3761-71.
153. Haanen J, Carbonnel F, Robert C, Kerr KM, Peters S, Larkin J, et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017;28(suppl_4):iv119-iv42.
154. Fan Y, Xie W, Huang H, Wang Y, Li G, Geng Y, et al. Association of Immune Related Adverse Events With Efficacy of Immune Checkpoint Inhibitors and Overall Survival in Cancers: A Systemic Review and Meta-analysis. Front Oncol. 2021;11:633032.
155. Dougan M, Luoma AM, Dougan SK, Wucherpfennig KW. Understanding and treating the inflammatory adverse events of cancer immunotherapy. Cell. 2021;184(6):1575-88.
156. Das R, Bar N, Ferreira M, Newman AM, Zhang L, Bailur JK, et al. Early B cell changes predict autoimmunity following combination immune checkpoint blockade. J Clin Invest. 2018;128(2):715-20.
157. Postow MA, Sidlow R, Hellmann MD. Immune-Related Adverse Events Associated with Immune Checkpoint Blockade. N Engl J Med. 2018;378(2):158-68.
158. Pauken KE, Dougan M, Rose NR, Lichtman AH, Sharpe AH. Adverse Events Following Cancer Immunotherapy: Obstacles and Opportunities. Trends Immunol. 2019;40(6):511-23.
159. Wang DY, Salem JE, Cohen JV, Chandra S, Menzer C, Ye F, et al. Fatal Toxic Effects Associated With Immune Checkpoint Inhibitors: A Systematic Review and Meta-analysis. JAMA Oncol. 2018;4(12):1721-8.
160. Hradska K, Hajek R, Jelinek T. Toxicity of Immune-Checkpoint Inhibitors in Hematological Malignancies. Front Pharmacol. 2021;12:733890.
161. Badros A, Hyjek E, Ma N, Lesokhin A, Dogan A, Rapoport AP, et al. Pembrolizumab, pomalidomide, and low-dose dexamethasone for relapsed/refractory multiple myeloma. Blood. 2017;130(10):1189-97.
162. Khouri IF, Fernandez Curbelo I, Turturro F, Jabbour EJ, Milton DR, Bassett RL, Jr., et al. Ipilimumab plus Lenalidomide after Allogeneic and Autologous Stem Cell Transplantation for Patients with Lymphoid Malignancies. Clin Cancer Res. 2018;24(5):1011-8.
163. Bray ER, Lin RR, Li JN, Elgart GW, Elman SA, Maderal AD. Immune checkpoint inhibitor associated epidermal necrosis, beyond SJS and TEN: a review of 98 cases. Arch Dermatol Res. 2024;316(6):233.
164. Coleman E, Ko C, Dai F, Tomayko MM, Kluger H, Leventhal JS. Inflammatory eruptions associated with immune checkpoint inhibitor therapy: A single-institution retrospective analysis with stratification of reactions by toxicity and implications for management. J Am Acad Dermatol. 2019;80(4):990-7.
165. Armand P, Rodig S, Melnichenko V, Thieblemont C, Bouabdallah K, Tumyan G, et al. Pembrolizumab in Relapsed or Refractory Primary Mediastinal Large B-Cell Lymphoma. J Clin Oncol. 2019;37(34):3291-9.
166. Chhabra N, Kennedy J. A Review of Cancer Immunotherapy Toxicity: Immune Checkpoint Inhibitors. J Med Toxicol. 2021;17(4):411-24.
167. Chang LS, Barroso-Sousa R, Tolaney SM, Hodi FS, Kaiser UB, Min L. Endocrine Toxicity of Cancer Immunotherapy Targeting Immune Checkpoints. Endocr Rev. 2019;40(1):17-65.
168. Zinzani PL, Santoro A, Gritti G, Brice P, Barr PM, Kuruvilla J, et al. 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. 2019;37(33):3081-9.
169. Younes A, Brody J, Carpio C, Lopez-Guillermo A, Ben-Yehuda D, Ferhanoglu B, et al. Safety and activity of ibrutinib in combination with nivolumab in patients with relapsed non-Hodgkin lymphoma or chronic lymphocytic leukaemia: a phase 1/2a study. Lancet Haematol. 2019;6(2):e67-e78.
170. Maruyama D, Terui Y, Yamamoto K, Fukuhara N, Choi I, Kuroda J, et al. Final results of a phase II study of nivolumab in Japanese patients with relapsed or refractory classical Hodgkin lymphoma. Jpn J Clin Oncol. 2020;50(11):1265-73.
171. Rocha M, Correia de Sousa J, Salgado M, Araújo A, Pedroto I. Management of Gastrointestinal Toxicity from Immune Checkpoint Inhibitor. GE Port J Gastroenterol. 2019;26(4):268-74.
172. Kennedy LB, Salama AKS. A review of cancer immunotherapy toxicity. CA Cancer J Clin. 2020;70(2):86-104.
173. Mahmood SS, Fradley MG, Cohen JV, Nohria A, Reynolds KL, Heinzerling LM, et al. Myocarditis in Patients Treated With Immune Checkpoint Inhibitors. J Am Coll Cardiol. 2018;71(16):1755-64.
174. Martinez-Calle N, Rodriguez-Otero P, Villar S, Mejías L, Melero I, Prosper F, et al. Anti-PD1 associated fulminant myocarditis after a single pembrolizumab dose: the role of occult pre-existing autoimmunity. Haematologica. 2018;103(7):e318-e21.
175. Mateos MV, Blacklock H, Schjesvold F, Oriol A, Simpson D, George A, et al. Pembrolizumab plus pomalidomide and dexamethasone for patients with relapsed or refractory multiple myeloma (KEYNOTE-183): a randomised, open-label, phase 3 trial. Lancet Haematol. 2019;6(9):e459-e69.
176. Usmani SZ, Schjesvold F, Oriol A, Karlin L, Cavo M, Rifkin RM, et al. Pembrolizumab plus lenalidomide and dexamethasone for patients with treatment-naive multiple myeloma (KEYNOTE-185): a randomised, open-label, phase 3 trial. Lancet Haematol. 2019;6(9):e448-e58.

177. Tocchetti CG, Cadeddu C, Di Lisi D, Femminò S, Madonna R, Mele D, et al. From Molecular Mechanisms to Clinical Management of Antineoplastic Drug-Induced Cardiovascular Toxicity: A Translational Overview. Antioxid Redox Signal. 2019;30(18):2110-53.
178. Upadhrasta S, Elias H, Patel K, Zheng L. Managing cardiotoxicity associated with immune checkpoint inhibitors. Chronic Dis Transl Med. 2019;5(1):6-14.
179. Čelutkienė J, Pudil R, López-Fernández T, Grapsa J, Nihoyannopoulos P, Bergler-Klein J, et al. Role of cardiovascular imaging in cancer patients receiving cardiotoxic therapies: a position statement on behalf of the Heart Failure Association (HFA), the European Association of Cardiovascular Imaging (EACVI) and the Cardio-Oncology Council of the European Society of Cardiology (ESC). Eur J Heart Fail. 2020;22(9):1504-24.
180. Shi Y, Wu J, Wang Z, Zhang L, Wang Z, Zhang M, et al. 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. 2021;14(1):12.
181. Tinawi M, Bastani B. Nephrotoxicity of Immune Checkpoint Inhibitors: Acute Kidney Injury and Beyond. Cureus. 2020;12(12):e12204.
182. Liu Y, Wang C, Li X, Dong L, Yang Q, Chen M, et al. Improved clinical outcome in a randomized phase II study of anti-PD-1 camrelizumab plus decitabine in relapsed/refractory Hodgkin lymphoma. J Immunother Cancer. 2021;9(4):e002347.
183. Mei Q, Zhang W, Liu Y, Yang Q, Rasko JEJ, Nie J, et al. Camrelizumab Plus Gemcitabine, Vinorelbine, and Pegylated Liposomal Doxorubicin in Relapsed/Refractory Primary Mediastinal B-Cell Lymphoma: A Single-Arm, Open-Label, Phase II Trial. Clin Cancer Res. 2020;26(17):4521-30.
184. Esfahani K, Elkrief A, Calabrese C, Lapointe R, Hudson M, Routy B, et al. Moving towards personalized treatments of immune-related adverse events. Nat Rev Clin Oncol. 2020;17(8):504-15.
185. Sakamuri D, Glitza IC, Betancourt Cuellar SL, Subbiah V, Fu S, Tsimberidou AM, et al. Phase I Dose-Escalation Study of Anti-CTLA-4 Antibody Ipilimumab and Lenalidomide in Patients with Advanced Cancers. Mol Cancer Ther. 2018;17(3):671-6.
186. Tao R, Fan L, Song Y, Hu Y, Zhang W, Wang Y, et al. Sintilimab for relapsed/refractory extranodal NK/T cell lymphoma: a multicenter, single-arm, phase 2 trial (ORIENT-4). Signal Transduct Target Ther. 2021;6(1):365.
187. Sanborn RE, Hamid O, de Vries EG, Ott PA, Garcia-Corbacho J, Boni V, et al. CX-072 (pacmilimab), a Probody PD-L1 inhibitor, in combination with ipilimumab in patients with advanced solid tumors (PROCLAIM-CX-072): a first-in-human, dose-finding study. J Immunother Cancer. 2021;9(7):e002446.

How to cite this article: Sun W, Hu S, Wang X. Advances and clinical applications of immune checkpoint inhibitors in hematological malignancies. Cancer Commun. 2024;1–27. https://doi.org/10.1002/cac2.12587