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Signaling Pathway and Dysregulation of PD1 and its Ligands in Lymphoid Malignancies

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Abstract

Tumor cells evade immune destruction, at least partially, by upregulating inhibitory signals to limit effector T cell activation. Programmed death 1 (PD-1) is one of the most critical co-inhibitory molecules limiting the T-cell antitumor response. PD-1 and its ligands, PD-L1 and PD-L2, are overexpressed by various types of tumors as well as reactive cells in the tumor microenvironment. A growing body of evidence has shown the clinical efficiency and minimal toxicity of PD-1 pathway inhibitors in patients with solid tumors, but the role of these inhibitors in lymphoid malignancies is much less well studied. In this review, we review the pathologic role of the PD-1 pathway in most common lymphoid malignancies and we organize the clinical data from clinical trials of PD-1 pathway inhibitors. Several anti–PD-1 regimens have shown encouraging therapeutic effects in patients with relapsed/refractory Hodgkin lymphoma, follicular lymphoma, and diffuse large B cell lymphoma. Additional progress is needed to foster an improved understanding of the role of anti–PD-1 therapy in reconstituting antitumor immunity in patients with lymphoid malignancies. Upcoming trials will explore the clinical efficiency of combining PD-1 pathway inhibitors and various agents with diverse mechanisms of action and create more therapeutic possibilities for afflicted patients.

Keywords

PD-1; PD-L1; PD-L2; lymphoid malignancies; pidilizumab; nivolumab; pembrolizumab

1. Introduction

The immune system has the critical function of balancing pathogen eradication while also limiting self-reactivity to avoid collateral tissue damage. This highly organized process is controlled by complex interactions between antigen-presenting cells (APCs) and T cells and determines the intensity and eventual outcome for each immune response. In the context of

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chronic infection or cancer, failure to eliminate antigens results in progressive loss of T cell function marked by sustained overexpression of multiple inhibitory receptors, indicating an evasive mechanism co-opted by tumor cells to avoid immune destruction [1]. The observation that blocking these critical immune checkpoints led to tumor regression in mouse models has promoted further clinical investigations [2–4].

Programmed death-1 (PD-1), also known as PDCD1 or CD279, is a key regulator of tumor immune escape. PD-1 delivers a co-inhibitory signal upon binding to either of its two ligands, PD-L1 (CD274, B7-H1) or PD-L2 (PDCD1LG2, CD273, B7-DC) [5]. Blockade of the PD-1/PD-L pathway has shown great promise in the treatment of patients with various tumors, including advanced non–small cell lung cancer; prostate renal cell and colorectal carcinoma; and especially melanoma [6,7]. This review focuses on PD-1/PD-L pathway dysfunction associated with lymphoid malignancies as well as the preclinical rationale and clinical application of antibodies against PD-1 or its ligands for patients with diverse lymphoid malignancies.

2. Structural features of PD-1 and its ligands

PD-1 is encoded by *PDCD1*, located on chromosome 2q37.3. PD-L1 and PD-L2 are encoded by *CD274* and the adjacent *PDCD1LG2*, respectively, both on chromosome 9p24.1. PD-1 exists as a monomer on the cell surface of activated T cells, B cells, natural killer T cells, monocytes, and some dendritic cell subsets [5]. PD-1 is a 55-kDa type I transmembrane protein that belongs to the immunoglobulin superfamily. Structurally, PD-1 is composed of an extracellular IgV domain, a transmembrane domain, and an intracellular cytoplasmic tail that contains an immunoreceptor tyrosine-based inhibitory motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Both of these motifs can be phosphorylated upon PD-1 engagement and can then recruit Src homology region 2 domain-containing phosphatase-1 (SHP-1) and SHP-2, although ITSM seems to play the primary role in recruitment [8,9]. In contrast, the 40 kDa PD-L1 and 25 kDa PD-L2 contain extracellular IgV and IgC domains and a transmembrane domain, but lack an identifiable intracellular signaling domain [10]. PD-L1 and PD-L2 share 37% identity, but differ in their affinity for PD-1 and their expression patterns. PD-L2 has a 3-fold higher affinity [11] and is inducibly expressed on activated dendritic cells and some macrophages, whereas PD-L1 is widely expressed by both hematopoietic and non-hematopoietic cells [5].

PD-1 uses its IgV domain β-sheet to bind to the front β-sheets of PD-L1 and PD-L2, forming a surface that resembles the antigen-binding surface of antibodies and T cell receptors [12]. Six of 14 amino acids involved in binding PD-1 are fully conserved between the two ligands, suggesting their critical role in receptor recognition by both PD-L1 and PD-L2. Of note, disruption of W110, an amino acid that uniquely located only in the core of the binding interface of PD-L2, leads to significantly reduced PD-1 binding. Consequently, W110 is assumed to be an important determinant of the higher affinity of PD-L2 for PD-1 [13].

3. Inhibitory effects of PD-1 and its ligands on the immune system

3.1 Molecular mechanism of PD-1 signaling in T cells and B cells

Upon T-cell receptor (TCR) engagement, PD-1 is transcriptionally activated in an NFATc1-dependent manner [14]. In chronically activated T cells, such transcriptional activity can be prolonged by interferon-α (IFN-α) stimulation to enable the constitutive expression of PD-1 by T cells [15]. In the early activation phase, PD-1 translocates from a random membrane location to the immunological synapse and accumulates at the central supramolecular activation cluster (c-SMAC) region upon ligand binding. SHP2, and to a lesser degree SHP1, are recruited immediately to the ITSM, directly dephosphorylate proximal TCR signaling molecules; SHP1 and SHP2 also block CD28-induced co-stimulation indirectly by driving CD28 away, but not excluding it from, the c-SMAC [16,17]. PD-1 ligation also directly inhibits phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) and the downstream activity of Akt which rely on the integrity of ITSM [18]. Recently, PD-1 has been shown to increase phosphatase and tensin homologue (PTEN) activity through disruption of casein kinase 2 (CK2)-mediated phosphorylation, thereby suggesting a possible alternative means of suppressing the PI3K/Akt axis since PTEN is a crucial cellular phosphatase inhibitor of PI3K [19]. Moreover, PD-1 signaling also suppresses Ras-ERK1/2 mediated cell growth [20]. Collectively, activation of the PD-1 pathway antagonizes TCR signaling and ultimately decreases the induction of cytokines and survival proteins, leading to T cell exhaustion (Figure 1A).

PD-1 is also a negative regulator of B cells. Co-ligation of PD-1 with the B cell receptor (BCR) recruits SHP2 and subsequently attenuates the tyrosine phosphorylation of key signal transducers including Igβ and spleen tyrosine kinase (Syk), phospholipase C-gamma 2 (PLCγ2), PI3K, and vav leading to inhibition of BCR signaling [9]. Accordingly, PD-1 blockade can improve B cell responsiveness towards antigens [21]. PD-1 signaling activation is also responsible for the suppression of B-1b cell proliferation and overall B cell antibody production in response to T cell-independent type 2 antigens in normal mice (Figure 1B) [22].

3.2 Co-inhibitory network of PD-1 signaling in immunity

The phenotype of *PD-1* knockout mice is characterized by late-onset, organ-specific autoimmunity, highlighting the role of PD-1 in induction and maintenance of immune tolerance [23,24]. PD-1 ligation provides inhibitory signals that prevent self-reactive effector T cells from attacking normal tissues and regulates both central and peripheral tolerance [5,25].

Besides its inhibition of T cell survival, proliferation, and cytokine production, PD-1 signaling is assumed to shorten the duration of T cell–APC contact, which is required for the stable formation of immunological synapses [16,26]. However, this model has been challenged because a more rapid detachment of T cells from APCs was observed upon PD-1 blockade in an LCMV infection mouse model [27], implying additional complexity of the PD-1 pathway.

During the immune response, PD-L1 levels on APCs are elevated upon the secretion of inflammatory cytokines by activated T cells and natural killer (NK) cells [28,29]. Notably, PD-L1 also can bind to CD80 (B7-1), a ligand of CD28, thereby competitively antagonizing the costimulatory signal delivered by CD28-CD80 binding and further diminishing TCR signaling [30,31]. Moreover, PD-L1 may deliver reverse signals into its host cells. One group has reported that engaging PD-L1 on bone marrow–derived dendritic cells with soluble PD-1 can induce indoleamine 2,3-dioxygenase (IDO)-independent IL-10 production and dendritic cell inactivation [32]. Similar reverse signaling was also observed in PD-L1$^+$ T cells and PD-L2$^+$ dendritic cells [33,34]. Further studies are needed to confirm these observations.

The PD-1–PD-L1 interaction has been reported to play a critical role in the development and maintenance of T regulatory (Treg) cells. Francisco et al. demonstrated that PD-L1 promotes the conversion of naïve T cells into Treg cells by synergizing with TGF-β *in vitro* and that mice with PD-L1 deficiency have remarkable reductions of Treg cells [35]. However, Franceschini and colleagues showed somewhat contrary results, finding that the expansion of Treg cells was correlated inversely with PD-1 expression in patients chronically infected with hepatitis C virus (HCV) and that PD-L1 blockade can facilitate Treg cell proliferation *in vitro* [36]. A recent report suggested that the apparent contradictory effects of PD-1 signaling may be attributed to the different status of Treg cells during infection; PD-1 ligation activates Treg cells at the initial stage of infection, but also induces Treg cell apoptosis after sustained TCR stimulus (Figure 2) [37].

PD-1 regulates antibody responses. PD-1 signaling has been shown to inhibit the T cell–independent humoral response through downregulation of the BCR response in mice [22]. Nevertheless, PD-1 signaling mediates T cell–dependent humoral immunity by a completely different mechanism. In germinal centers (GCs), PD-1 is highly expressed by follicular helper T (TFH) cells and follicular regulatory T (TFR) cells, whereas PD-L1 and PD-L2 are inducibly upregulated on GC B cells and memory B cells during the primary response. PD-1–deficient mice showed greater numbers of TFR cells and qualitatively deficient TFH cells that secreted less IL-21, a cytokine essential for GC formation as well as B cell proliferation and differentiation into memory B cells and plasma cells [38–40]. Additionally, a recent report identified a specific subset of B regulatory cells that inhibits TFH cell function through elevated expression of PD-L1, further indicating the complexity of the role of PD-1 signaling in the humoral immune response (Figure 3) [41].

PD-1 expression can be induced on NK cells after prolonged exposure to antigens during chronic infection or tumor [42, 43]. Benson et al. observed a reduction of NK cell migration and deterioration of cytotoxicity towards PD-L1–bearing tumor cells upon PD-1 overexpression, both of which were reversed by PD-1 blockade [43]. In addition, the existence of PD-1 microclusters at the NK immunological synapse has been confirmed [44].

4. Expression and clinical significance of PD-1 and its ligands on lymphoid malignancies

The interaction of PD-1 and its ligands plays a pivotal role in the immune suppression associated with tumors. Persistent stimulation from tumor antigens induces PD-1 overexpression by tumor-infiltrating lymphocytes, whereas expression of PD-Ls is characteristic of malignant cells and various tumor-infiltrating APCs. In lymphoid malignancies, diverse mechanisms contribute to the constitutive expression of PD-Ls by tumor cells, including genetic alterations, transcriptional activation by certain oncogenic signaling pathways, viral infection, and induction by inflammatory cytokines [1,45,46]. Binding of PD-Ls to PD-1 on T cells functionally silences the activation of tumor-associated T cells and leads to impaired cell survival and effector function, producing a tumor-permissive microenvironment (Figure 4) [47].

4.1 Hodgkin lymphoma

In most cases of classical Hodgkin lymphoma (cHL), Reed-Sternberg and Hodgkin (RS-H) cells show strong membranous expression of PD-L1. Approximately 40% of patients of with nodular sclerosis cHL have amplification of chromosome 9p24.1, a region that includes *PD-L1* and *PD-L2*; this amplification explains the overexpression of PD-Ls at the transcriptional and protein levels. Additionally, another gene located on 9p24.1 is also amplified, Janus kinase 2 (*JAK2*), which can transcriptionally activate the candidate STAT-responsive element within the *PD-L1* and *PD-L2* promoter regions through JAK2-signal transducer and activator of transcription (JAK2-STAT) signaling, thereby further promoting overexpression of PD-Ls [45,48].

Alternative mechanisms driving PD-L1 expression by RS-H cells in cHL include Epstein-Barr virus (EBV) infection and constitutive activator protein 1 (AP-1) activity [46]. Two AP-1 components, JUNB and cJUN, are overexpressed constitutively by RS-H cells [49]; binding of either can activate the AP-1–responsive enhancer element located on intron 1 of *PD-L1* and enhance PD-L1 transcription in an AP-1–dependent manner. In contrast, there is no such enhancer for PD-L2, although PD-L2 is also upregulated in cHL cells [46]. Clinically, an increased level of PD-1^+ infiltrating lymphocytes (more than 23 cells/mm^2) has been found to be a stage-independent negative prognostic factor of overall survival for patients with cHL [50].

Much less data are available for nodular lymphocyte-predominant HL. In this disease, tumor-infiltrating T cells consistently express PD-1. In fact, PD-1^+ T-cells form rosettes around the neoplastic cells and this is a typical feature of nodular lymphocyte-predominant HL [51].

4.2 Diffuse large B-cell lymphoma

Rare cases of diffuse large B-cell lymphoma (DLBCL),-not otherwise specified, are positive for PD-Ls and expression is largely restricted to activated B cell-like DLBCL [52,53]. In addition, the level of soluble PD-L1 is remarkably elevated in the plasma of DLBCL patients compared with healthy controls independent of PD-L1 expression by the lymphoma

cells [54,55]. Increased soluble PD-L1 may be secreted by tumor-infiltrating non-malignant cells after pro-inflammatory cytokine stimulation as a feedback mechanism in response to inflammation [4,56]. In a prospective trial including 288 patients with newly diagnosed DLBCL who were treated with either rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) or R-high dose therapy, investigators found that a soluble PD-L1 level in plasma of greater than 1.52 ng/ml at time of diagnosis was associated with an inferior overall survival in patients less than 60 years old with an age-adjusted International Prognostic Index score greater than or equal to 2. These investigators also observed dynamic changes in soluble PD-L1 levels that decreased dramatically in patients who achieved complete remission (CR), indicating a treatment-related immunological effect on both the lymphoma cells and the surrounding microenvironment [55].

Primary mediastinal large B-cell lymphoma (PMBCL) is a specific subtype of DLBCL that can resemble cHL in its clinical features and histologic features of cHL and PMBCL can overlap in some cases. Approximately 70% of PMBCLs harbor amplification of chromosome 9p24.1, thereby overexpressing PD-Ls as do cHL [45,48,57]. A recent report demonstrated that translocations involving chromosome 9p24.1 (the site of the PD-L locus) occur in approximately 20% patients with PMBCL. In translocated cases, *PD-L2* transcript levels are significantly higher than in cases in which are 9p24.1 neutral, gained, or even amplified; *PD-L1* transcript levels also are higher, but to a lesser extent [58].

Robust PD-L1 expression has been reported in several other DLBCL subtypes, including T cell/histiocyte-rich B cell lymphoma, EBV-associated DLBCL, plasmablastic lymphoma, HHV8-associated primary effusion lymphoma, and primary central nervous system DLBCL [52,59]. To date, only small series of patients with these tumors have been analyzed.

4.3 Follicular lymphoma

Follicular lymphoma (FL) is derived from GC B cells that are in close contact with PD-1^+ follicular T cells. Using immunohistochemistry, Yang et al. observed that $CD4^+PD\text{-}1^{high}$ T cells reside predominantly within lymph node follicles and resemble TFH cells that support B cell growth, whereas $CD4^+PD\text{-}1^{low}$ T cells are located mainly in the interfollicular areas and display an exhausted phenotype with impaired cytokine production and signal transduction [60]. In contrast, Myklebust et al. reported that the cytokine signaling deficit was restricted in $CD4^+$ $PD\text{-}1^{high}$ tumor-infiltrating T cells that contained both TFH and non-TFH cells and displayed functional changes similar to those in exhausted T cells by phospho-flow cytometry [61]. In aggregate, these results suggest the existence of diverse PD-1^+ tumor-infiltrating T cell subsets with distinctive functions in the development of FL.

The correlation of intratumoral PD-1^+ T cells with the clinical outcome of patients with FL has been controversial. Some immunohistochemistry studies have shown that a greater number of PD-1^+ cells is associated with a better outcome independently of FL International Prognostic Index status and that patients with PD-1^+ cells less than or equal to 5% showed a worse prognosis and greater risk of high-grade transformation [62,63]. However, other investigators have observed that the number of PD-1^+ cells independently associated with poor prognosis [64]. One recent report suggested that prognostic groups can be subdivided according to the intensity of PD-1 expression and that only the amount of dimly stained cells

correlates with disease outcome [60]. Overall, considering the different methods and heterogeneity of patients in these studies, the precise function of the PD-1 signaling pathway in FL and its prognostic value remain to be elucidated in a large series of patients.

4.4 Chronic lymphocytic leukemia

Chronic lymphocytic leukemia (CLL) relies on a tumor-supportive microenvironment [65]. The development of CLL is correlates significantly with increased numbers of $CD8^+$ T cells; these cells highly express PD-1 and are skewed toward terminal differentiation. $PD1^+$ T cells are in close contact with PD-$L1^+$ CLL cells within the proliferation center and are exhausted [66]. In line with this finding, treating Eμ-TCL1 mice with PD-L1-blocking antibodies can re-activate antitumor immunity and prevent CLL development [67]. Riches et al. demonstrated that CLL-specific T cells, despite being exhausted, retain the capacity to produce IFN-γ and TNF-α, both of which have been shown to promote CLL as well as PD-L1 expression [68]; others have found contradictory results [66]. One possible explanation for these conflicting results is the heterogeneity of PD-1^+ T cells within CLL. Indeed, *in vivo* experiments using the Eμ-TCL1 mouse model suggested that CLL-induced increased T-cell proliferation favors the PD-1^{high} subset over the PD-1^{low} subset and that IFN-γ ratios are higher in PD-1^{high} than in PD-1^{low} cells. Moreover, the distribution of PD-L1 expression on CLL cells seems to be tissue specific, with the highest frequency found in the spleen, which might offer an explanation for the tumor-protecting capability of microenvironmental niches [69]. Clinically, expansion of the $CD8^+PD1^+$ T cells has been associated with a more aggressive clinical course in CLL patients [70].

4.5 Mature T-cell lymphomas

Angioimmunoblastic T-cell lymphoma and approximately 20% of peripheral T-cell lymphomas not otherwise specified are presumed to originate from TFH cells and thus express the GC T cell marker PD-1 [71,72]. Cutaneous proliferations of T cells may express markers of TFH cells. Accordingly, PD-1 is expressed by the tumor cells of patients with Sézary syndrome [73], primary cutaneous CD4+ small/medium T-cell lymphoma [74], and a rare type of CD4/CD8 double-negative mycosis fungoides [75]. Additionally, PD-L1 is overexpressed by anaplastic lymphoma kinase positive (ALK^+) anaplastic large cell lymphoma cells in a chimeric nucleophosmin/ALK-STAT3–dependent manner [76].

4.6 Virus-associated lymphomas

Viral infection induces PD-1 signaling–related immune tolerance by directly upregulating PD-L1 expression on tumor cells. Green et al. reported that LMP-1, an EBV-encoded antigen, was able to activate the promoter and enhancer of *PD-L1* by enhancing JAK3-STAT5 signaling and AP-1 activation, respectively. This observation was further confirmed by the promotion of PD-L1 expression by B cells after EBV transformation and the synchronous activity of the *PD-L1* promoter and enhancer [31]. EBV-associated lymphomas uniformly overexpress PD-L1, including EBV^+ DLBCL, cHL, post-transplant lymphoproliferative disorders, extranodal nasal-type NK/T-cell lymphoma, and angioimmunoblastic T-cell lymphoma. Burkitt lymphoma is the exception to the rule owing to its type I latency pattern of infection with absence of LMP-1 expression [52,77].

Viral infection also upregulates PD-1 expression on tumor-infiltrating T cells. Ni et al. observed increased numbers of $CD4^+CD25^+$ and $CD8^+CD25^+$ Treg cells with PD-1 overexpression in the peripheral blood of patients with HCV-associated lymphomas compared with patients without HCV infection and healthy controls [78]. Similarly, increased levels of PD-1 can be found on human T-cell leukemia virus-1 (HTLV-1)–specific $CD8^+$ T cells in patients with adult T-cell leukemia/lymphoma [63]. Interestingly, in these studies, PD-1 expression was significantly higher in cells of virus-related lymphomas compared with benign virally infected cells, reflecting a higher load of virus-associated antigens on the tumor cells [63].

The expression of components of the PD-1 signaling pathway in different lymphoid malignancies, according to the 2016 World Health Organization classification, is summarized in Table 1.

5. Targeting PD-1 and its ligand pathways

Preclinical studies of PD-1 signaling pathway blockade have shown promising clinical efficiency in a broad variety of tumors. Anti–PD-1 therapy helps to blunt the inhibition of tumor-specific immune response by enhancing T-cell activity, restoring NK cell activity, and inducing $PD\text{-}L1^+$ B-cell antibody production, thus benefiting patients with pre-existing antitumor immunity [29]. PD-1 inhibitors may be particularly attractive for patients with hematologic malignancies because the activation of adoptive immunity has long been proven effective in the form of allogeneic stem cell transplantation [79]. Diverse antibodies targeting the PD-1 pathway, by blockade of PD-1 or PD-L1, are under clinical evaluation (Table 2). Here, we focus on agents that have been used for the treatment of patients with lymphoid malignancies (Table 3).

5.1 Pidilizumab

Pidilizumab (CT-011), a humanized IgG-1 kappa recombinant monoclonal antibody, was the first PD-1 inhibitor used for hematologic malignancies. One phase I, single arm, open-label study of pidilizumab enrolled 17 patients with advanced hematologic malignancies, including eight with acute myeloid leukemia, four with non-Hodgkin lymphoma (NHL; 1 FL, 2 DLBCL, 1 anaplastic large cell lymphoma), three with CLL, one with HL, and one with multiple myeloma. All patients had relapsed disease after failure of multiple lines of chemotherapy, including six patients who had received allogeneic stem cell transplants and three who had received autologous stem cell transplants. Patients received escalating doses of pidilizumab ranging from 0.2 to 6.0 mg/kg in a single intravenous infusion. No dose-limiting toxicity or maximum tolerated dose was determined. Despite receiving only a single dose of pidilizumab, one FL patient achieved CR with prolonged remission of greater than 68 weeks. Sustained elevation in peripheral blood $CD4^+$ lymphocyte levels following treatment was observed in 15 of 17 patients from 24 hours after infusion to up to 21 days [80].

On the basis of the encouraging data from this phase I trial, a phase II trial was conducted focused on patients with recurrent DLBCL who had received autologous hematopoietic stem cell transplantation (AHSCT). The rationale of the protocol was to utilize the synergistic

effect of breaking immune tolerance through PD-1 blockade to reconstitute antitumor immunity after AHSCT. Patients with DLBCL, PMBCL, and transformed indolent B-NHL who had undergone AHSCT were eligible. Patients received pidilizumab intravenously at a dose of 1.5 mg/kg every 42 days for three cycles, beginning 30 to 90 days after AHSCT. CT scans were performed at screening, before the second and third cycles, and at 30, 44, and 69 weeks after the first administration of pidilizumab. Of 72 patients who were enrolled, 60 finished all three cycles. Among the 66 patients eligible for analysis, 35 had measurable disease by CT imaging and nine had positive results on PET scan at the time of post-AHSCT restaging. The median time to response was 30 weeks (6–69 weeks). The overall 16-month progression-free survival (PFS) was 72% (90% CI, 60%–82%), exceeding the prespecified 16-month PFS of 69%. The 16-month overall survival was 85% (90% CI, 74%–92%). Notably, among the 35 patients with residual disease after AHSCT, the overall response rate was 51%, with 12 (34%) CRs and six (17%) PRs. However, the overall response rate dropped to 33% for the nine patients with positive PET scan results. The most frequently observed grade 3 to 4 adverse effects (AEs) were neutropenia and thrombocytopenia in 19% and 8% of patients, respectively. No significant autoimmune toxicity, infusion reactions, or treatment-related mortality was observed. Treatment with pidilizumab resulted in a significant increase in the absolute number of PD-L1–bearing activated helper T cells and monocytes [79].

Another phase II trial was conducted in patients with relapsed, grade 1–2 FL treated with pidilizumab in combination with rituximab, in the hope of achieving synergistic effects via activation of both the innate (NK cells) and adaptive (T cells) immune system [81]. Pidilizumab was administered at 3 mg/kg intravenously every 4 weeks for four infusions, plus eight optional infusions every 4 weeks for patients with stable disease or better. Rituximab was given at 375 mg/m^2 intravenously weekly for 4 weeks starting 17 days after the first dose of pidilizumab. Assessments were performed at enrollment, after the second and fourth infusions of pidilizumab, and every 12 weeks thereafter for 2 years or until relapse. There were 29 evaluable patients with a median follow-up of 15.4 months; 19 (66%) responded to the therapy among which 15 (52%) achieved CR and four (14%) achieved PR. The median PFS for responders had not been reached by the time of the analysis (95% CI 18.8 months–not reached) which compared favorably with the 17.8 months reported with responders to rituximab monotherapy retreatment [82]. The median time to response was 88 days (range 53–392 days); six patients (21%) had a delayed initial response after 4 months or more. The treatment was well tolerated without any autoimmune or treatment-related AE of grade 3 or 4.

In this study, the baseline expression of PD-L1 was significantly higher in peripheral blood CD4$^+$ cells, CD8$^+$ cells, and CD14$^+$ cells of responders than that of non-responders. Gene expression profiling data suggested that baseline signatures of genes upregulated during T cell activation or repressed in regulatory T cells were predictive of longer PFS. They also showed that signatures of genes more highly expressed by effector T cells compared with TFH in sorted CD4+ T cells predicted more tumor shrinkage and longer PFS. After 14 days of infusion, the absolute numbers of CD4$^+$ effector and memory T cells increased, as did the activating receptor KLRK1 (killer cell lectin-like receptor subfamily K, member 1) on NK

cells. Similarly, increased expression of T cell activation signatures after treatment was associated with longer PFS.

5.2 Nivolumab

Nivolumab (BMS-936558, MDX-1106, ONO-4538) is a fully humanized IgG4 blocking monoclonal antibody against PD-1 that has been approved by the US Food and Drug Administration for the treatment of unresectable primary and metastatic melanoma and squamous non–small cell lung cancer.

Classical HL may be a promising target for anti-PD1 therapy because PD-L1 is overexpressed by RS-H cells and the extensive but ineffective inflammatory immune cell infiltration in the tumor microenvironment [45,46,48]. Nivolumab was tested in a phase I trial in patients with relapsed or refractory HL. The trial enrolled 23 heavily pretreated patients, of whom 87% had received at least three previous regimens. Among all patients in the trial, 78% had received brentuximab vedotin and 78% had undergone AHSCT. Nivolumab was administered at 3 mg/kg every 2 weeks until the patient experienced CR, PD or excessive toxic effects. Patients were evaluated for treatment efficacy at 4, 8, 16, and 24 weeks and every 16 weeks thereafter. Twenty (87%) patients had objective responses including four (17%) who achieved CRs. The median PFS at 24 weeks was 86% (95% CI 62–95%). With a median follow-up of 40 weeks median OS was not reached. Sixty percent of responders had an initial response within 8 weeks, whereas other patients had a delayed response up to 39 weeks. Grade 3 or 4 AEs occurred in 12 (52%) patients, five of which were reported as drug related, including one decreased lymphocyte count, one increased serum lipase level, one stomatitis, one myelodysplastic syndrome, and one pancreatitis. Notably, increased copy numbers of PD-L1 and PD-L2 with protein overexpression were observed in all 10 patient samples that underwent FISH and immunochemical testing in this study [83].

Nivolumab was also evaluated in a cohort of patients with relapsed or refractory lymphoid malignancies. This phase I clinical trial enrolled 82 patients, including 29 with B-NHL, two with PMBCL, and 23 with T-NHL. Sixty-nine percent of B-NHL patients and 78% of T-NHL patients were pretreated extensively, including prior brentuximab vedotin treatment in 7% of B-NHL patients and 26% of T-NHL patients, and AHSCT in 14% of B-NHL patients and 9% of T-NHL patients. Nivolumab was administered using a dose-escalation design (1 mg/kg and 3 mg/kg) every 2 weeks for up to 2 years. Four (36%) patients with DLBCL, four (40%) with FL, two (15%) with mycosis fungoides, and two (40%) with peripheral T-cell lymphoma responded to the therapy, among whom one patient (9%) with DBLCL and one (10%) with FL achieved CR. Drug-related AEs occurred in 72% and 65% of B-NHL and T-NHL patients, respectively [84].

5.3 Pembrolizumab

Pembrolizumab (lambrolizumab, MK-3475), a humanized IgG-4 kappa isotype monoclonal antibody, is the second anti–PD-1 drug approved by the US Food and Drug Administration for the treatment of patients with unresectable and metastatic melanoma. In a phase I clinical trial of 15 patients with relapsed or refractory cHL whose disease had failed brentuximab

vedotin therapy. Pembrolizumab was given at 10 mg/kg every 2 weeks. The preliminary results at 12 weeks showed that eight (53%) patients had objective responses including three (20%) who had CRs. The treatment was safe, with only one grade 3 AE. The trial is still ongoing [85].

In addition to anti-PD-1 agents, several antibodies targeting PD-L1 are also under clinical evaluation in patients with solid tumors and hematologic malignancies, including BMS935559 (MDX-1105), MPDL3280A, MEDI4736, and MSB0010718C (Table 4).

6. Immune-related adverse events

Although PD-1 pathway blockade can lead to significant antitumor benefits, the synchronous general immunologic enhancement may give rise to a unique set of toxicities that have been designated as immune-related AEs (irAEs). The onset of irAEs is mainly due to the elevated inflammatory cytokines released by activated T cells that infiltrate the affected areas [86,87]. In a study by the National Cancer Institute, 62% of patients with metastatic melanoma who received ipilimumab, an anti-CTLA-4 agent, experienced irAEs [88]. The irAEs observed in PD-1 pathway blockade had no apparent dose-limiting toxicities and were less severe compared with those in anti-CTLA-4 trials. In PD-1 pathway blockade, the irAEs most commonly seen have been colitis/diarrhea, dermatitis, hepatitis, and endocrinopathies [89]. Reported irAEs in the aforementioned trials included diplopia, rash, mucosal inflammation, pneumonitis, stomatitis, pancreatitis, and enteritis. Fatigue, respiratory infection, cough, diarrhea, hyperglycemia, renal failure, pain, and urinary infection were also observed. However, it would be difficult to attribute all these adverse events to irAEs [79–81,83–85]. IrAEs can be life threatening, early recognition of irAEs and initiation of treatment are critical. Oral or intravenous corticosteroids are often used to control irAEs by temporary immunosuppression. Other options include TNF-α antagonists and mycophenolate mofetil [89]. The use of immunosuppressive treatment does not seem to compromise the antitumor effect, and no solid evidence so far has correlated the occurrence of irAEs with the clinical efficacy of checkpoint blockade [89,90].

7. Biomarkers

The efficacy of PD-1 blockade regimens seems to vary among different types of lymphoma, as a relatively small dose can induce a sustained CR in patients with certain types of indolent lymphoma whereas patients with other types of lymphoma barely benefit [80,84]. A better understanding of which patients benefit from PD-1 blockade would surely help enhance clinical efficiency and reduce unnecessary overuse. Although indicators of pre-existing immunity, such as expression of PD-L1 on tumor cells and expression of PD-1 by tumor-infiltrating T cells, have been associated with better response rates for anti–PD-1 treatment in solid tumors [91], no definitive predictive biomarkers have been proposed, likely due to highly dynamic changes in the tumor microenvironment.

Little is known about predicting response to PD-1 pathway blockade in lymphoid malignancies. Pretreatment PD-L1 expression on peripheral blood CD4+ cells, CD8+ cells, and CD14+ cells seemed to be a positive biomarker for clinical response in phase II trials of patients with relapsed/refractory FL treated with pidilizumab and rituximab [81]. Likewise,

a significant increase in the absolute number of PD-L1–bearing activated helper T cells and monocytes after pidilizumab administration has been observed in patients with DLBCL after AHSCT [79]. Nevertheless, PD-L1 expression is not an absolute indicator for PD-1 blockade therapy because patients without PD-L1 expression can still have impressive clinical responses. Moreover, methodological considerations of PD-L1 assessment, such as the positive cut-off value and whether staining the tumor cells or infiltrating immune cells is relevant, remain to be determined [92]. Further investigation regarding PD-L1 and its interactions with other possible prognostic factors is needed.

8. Evaluation criteria of therapeutic response

Early experience suggests that immune checkpoint blockade agents, including anti–PD-1 and anti–CTLA-4 antibodies, are characterized by long median times before patients respond. Patients may require up to 1 year or more to achieve an objective response, although the response is durable and may exist even after withdrawal of drug [1,80,92]. Accordingly, in trials of PD-1 blockade in lymphoma patients, a considerable number of responders and even patients with stable disease have benefited with prolonged survival and remarkable reduction of tumor lesions. However, response may be obscured by early or simultaneously progressing lesions within the same patient during treatment [93]. Therefore, Wolchok et al. proposed a set of alternative evaluation criteria, specific for immunologic checkpoint blockade, called the immune-related response criteria. The immune-related response criteria allow new lesions to be included as part of the total tumor burden without being immediately considered as progressive disease, in order to avoid premature treatment withdrawal [94]. However, the immune-related response criteria are based mainly on experience using anti–CTLA-4 agents on solid tumors and are still undergoing revision and validation. All data from the clinical trials described above were evaluated by the traditional revised response evaluation criteria in solid tumors (RECIST) criteria adapted for lymphoma. An adequate evaluation system is required to better address the role of PD-1 blockade and other antibodies targeting immune checkpoint molecules in the future.

9. Opportunities for combinational therapy

9.1 Dual checkpoint blockade

As mentioned above, CTLA-4 wass the first recognized immune checkpoint molecule to play a non-redundant role with PD-1 in immune regulation. Unlike PD-1 which acts mainly as a brake on T cell effector function at a later stage of T cell activation, CTLA-4 is believed to be upregulated earlier in T cell activation, by directly blocking the costimulatory signal of CD28, and exhibits its inhibitory effect through a different mechanism [18,95]. Dual checkpoint blockade was therefore designed to synergistically remove co-inhibition signals and thus enhance antitumor immunity. Superior antitumor activity has been shown in patients with solid tumors by combining anti–CTLA-4 and anti–PD-1 agents [96,97]. Larkin et al. demonstrated a favorable median PFS of 11.5 months in previously untreated melanoma patients with nivolumab plus ipilimumab (an anti–CTLA-4 antibody) compared with 2.9 months with only ipilimumab and 6.9 months with only nivolumab. Two clinical trials of dual checkpoint blockade with nivolumab and ipilimumab for patients with relapsed/refractory NHL, HL, or multiple myeloma are currently recruiting (NCT02304458,

NCT01592370) (Table 4). Of note, a higher occurrence of irAEs has been observed during combined checkpoint blockade due to the significant activation of host immunoreaction [89].

9.2 In combination with immune modulators

The combination of immune checkpoint blockade with other immune modulators may also act in a synergistic manner. Ibrutinib is aBruton tyrosine kinase (BTK) inhibitor approved by the US Food and Drug Administration for the treatment of some types of B-cell malignancy. Ibrutinib also inhibits interleukin-2–inducible T-cell kinase (ITK), an essential enzyme for Th2 T cells and therefore ibrutinib has been purported to have an immunomodulatory effect by skewing a shift of the T-cell immune responses to a Th1 T cell bias [98]. Recently, Sagiv-Barfi et al. reported a remarkable therapeutic outcome following the combined use of anti–PD-L1 and ibrutinib in a mouse model of lymphoma that was intrinsically insensitive to ibrutinib monotherapy [99]. The antitumor effect induced by the combination depended on augmentation of host T-cell immune response rather than BTK expression on tumor cells, suggesting a wide spectrum of indications besides B-cell malignancies. Clinical trials designed to test the efficacy of this and similar combinations on patients with relapsed/refractory NHL and HL are ongoing (NCT02401048, NCT02329847, and NCT02362035) (Table 4).

Antibodies that operate as agonists of costimulatory T-cell and NK-cell receptors also show promise as agents to be tested in combination with immune checkpoint blocking agents [100]. CD137 (4-1BB), CD134 (OX40), and glucocorticoid-induced TNFR (GITR; CD357) are members of the TNF receptor family and specialize in delivering a costimulatory signal on the surface in T cells and NK cells [101]. Considering that anti–PD-1 therapies can only partially restore the function of exhausted T cells, combinations of agonists specific for these molecules with agents targeting PD-1 have been evaluated in animal models [102]. The combination has shown promising antitumor effect by further forcing exhausted $CD8^+$ T cells to exit quiescence and possibly enhance NK cell–mediated cytotoxicity [103,104]. Clinical trials combining anti– PD-1 therapy with urelumab (targeting CD137) or lirilumab (an anti-KIR antibody) are now available for patients with lymphoid malignancies (NCT02253992 and NCT01592370) (Table 4).

Indoleamine 2,3-dioxygenase (IDO) is a direct inhibitor of immune response and promotes differentiation of Treg cells [105]. Pro-inflammatory stimuli such as IFN-γ, can induce IDO potentially counteracting the effectiveness of antitumor therapy [106]. Upregulation of IDO has been assumed to be a possible mechanism of immune checkpoint blockade resistance. Dual blockade of IDO and CTLA-4 led to enhanced infiltration of tumor-specific effector T cells and tumor growth retardation in a mouse model of melanoma. Similar effects have also been observed in IDO-deficient mice treated with anti–PD-1 therapy [107]. Clinical trials evaluating combinations of INCB024360 (a small molecule inhibitor of IDO) and nivolumab are currently underway for patients with relapsed/refractory HL or NHL (NCT02327078) (Table 4).

9.3 Targeted therapy

The combination of agents that prevent immune escape with genetic or cell-target therapies may prove particularly effective in selected patients. Treatment using pidilizumab and rituximab has achieved a high overall response rate and good tolerance in patients with relapsed FL [81]. Combinations with other novel antibodies specific for diverse targets are in clinical evaluation for patients with lymphoid malignancies (NCT02220842, NCT02205333, NCT02271945, and NCT02408042) (Table 4).

Another area of active exploration includes the combination of PD-1 inhibitors with traditional cytotoxic therapies such as chemotherapy and radiotherapy. Preclinical mouse model studies have shown that traditional cytotoxic therapies induce changes that affect the antitumor immune response and may partner favorably with immunotherapies [108]. Further studies will evaluate the efficiency and safety profile of traditional cytotoxic therapies in combination with PD-1 blockade agents (NCT02408042) (Table 4).

9.4 Other approaches

The combination of PD-1 signaling inhibitors with vaccines is an attractive treatment approach, as is the application of PD-1 signaling blockade after allogeneic stem cell transplantation. Tumor-specific vaccines help to enhance tumor antigen presentation and therefore facilitate immune response in the microenvironment [109]. Concurrent peptide vaccination with immune checkpoint blockade has led to increased CTL responses in mouse models and in some patients with solid tumors [110]. Dendritic cell fusion vaccines after autologous transplantation in patients with multiple myeloma (NCT01067287) and acute myeloid leukemia (NCT01096602) are under investigation. Although anti–PD-1 therapy may aggravate graft-versus-host disease, it can also enhance the graft-versus-lymphoma effect. Koestner et al. observed restoration of graft-versus-lymphoma effect without triggering graft-versus-host disease by PD-L1 blockade in mouse models [111]. However, the optimal dose and timing for drug administration are still under preliminary study [112].

10. Concluding remarks

Although the diverse genomic landscape of each tumor creates challenges for tumor cell targeted therapies, neoantigens derived from tumor-specific mutations are potential targets for immune recognition and elimination. PD-1 pathway inhibitors are designed to unleash host immune cells to exert a tumor-specific cytotoxic effect and these inhibitors have shown encouraging therapeutic effects with minimal toxicity in patients with multiple cancer types, including lymphoid malignancies. In particular, the global activation of effector T cells induced by PD-1 blockade may overcome the development of tumor resistance and benefit patients, including those who have been heavily pretreated. Additionally, anti–PD-1 therapy may be of interest in the treatment of virus-associated lymphomas. However, many questions remain regarding the identification of biologic predictors and the establishment of criteria for evaluating clinical response. Despite the preliminary results obtained from clinical trials for relapsed/refractory DLBCL, FL, and HL, it is currently unknown whether PD-1 pathway inhibitors would be effective in other types of lymphoid malignancies or as first-line therapy. On the other hand, the multitude of available agents with various

mechanisms of action creates diverse possibilities for combination therapy; each combination is an opportunity to improve the therapeutic response for various types of lymphoid malignancies. Further knowledge of the reconstitution of antitumor immunity among different histologic tumor types and inter-patient variability is needed to shed light upon the rationale for combination regimens. PD-1 pathway modulation has a promising future for the treatment of patients with lymphoid malignancies.

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Disclosure/conflicts of interest

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Highlights

- PD-1 and its ligands are overexpressed by various types of tumors and microenvironment-supporting cells.
- Therapeutic targeting of PD-1 signaling has shown promising antitumor efficacy.

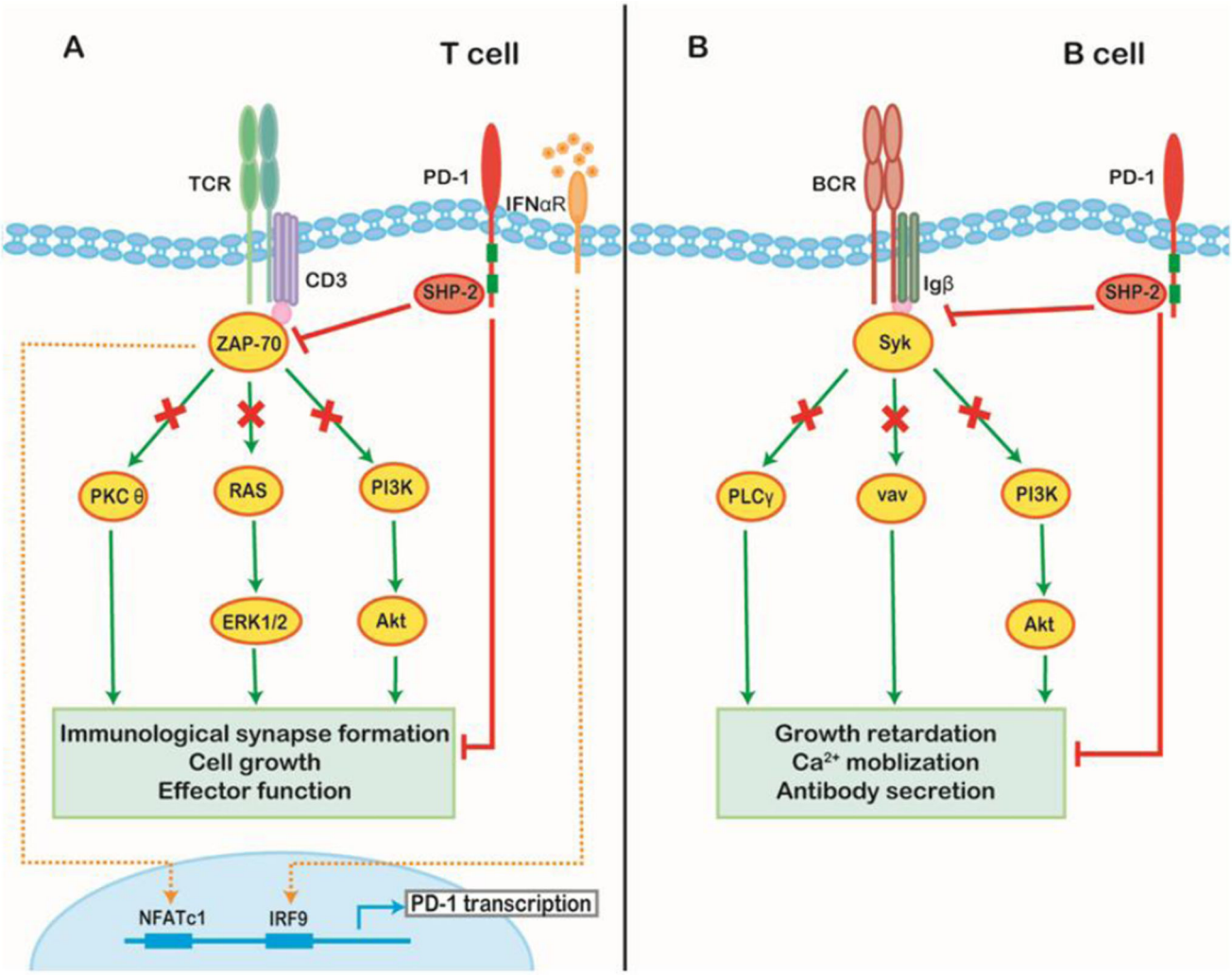

Figure 1. Downstream molecular pathway of PD-1 signaling

(A) TCR engagement initiates *PD-1* transcription through NFATc1 binding at the 5' promoter region *of PD-1*. Transcriptional activity is prolonged by sustained stimulation of interferon-α in the context of chronic infection or tumor through association of IFN-responsive factor 9 (IRF9) with the IFN stimulation response element within the *PD-1* promoter. Upon PD-1 engagement, SHP1/2 are recruited and dephosphorylate downstream members of the TCR signaling pathway (e.g. CD3δ and ZAP70) disrupting the normal TCR response as well as inhibiting PKCθ, RAS-Erk, and PI3K–Akt signaling. Consequently, PD-1 activation reduces the stability of the immunological synapse as well as the level of T cell survival proteins and leads to impaired cell growth and effector function. (B) In B cells, the recruitment of SHP-2 reduces the tyrosine phosphorylation levels of key signal transducers including the Igβ, Syk, PLCγ, vav, and PI3K pathways, thus suppressing BCR-mediated growth retardation, Ca^{2+} mobilization, and antibody secretion.

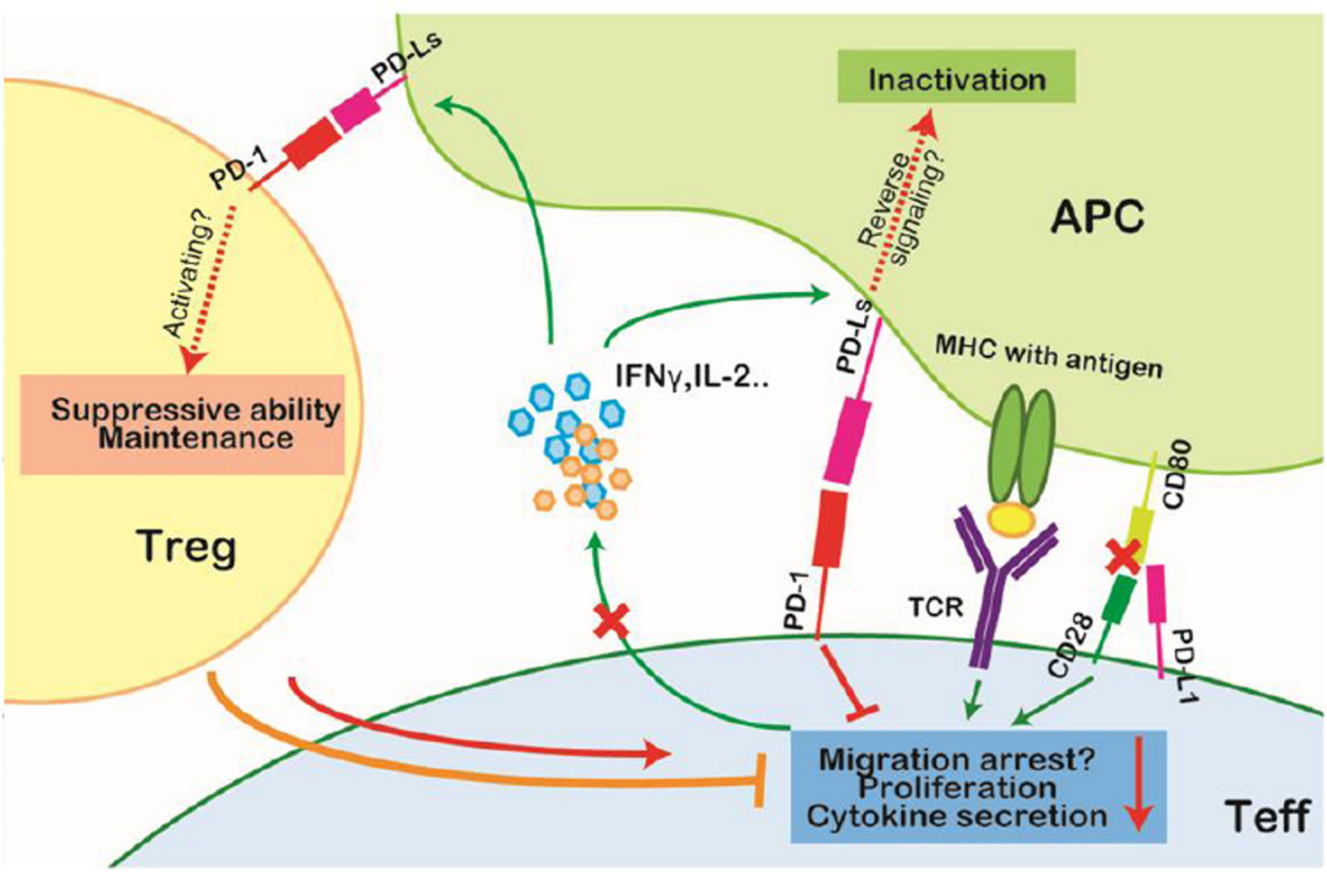

Figure 2. PD-1 signaling in the cellular immune response

In the cellular immune response, IFN-γ serves as a measure of T-cell activation. Upon initial TCR ligation, T cells secrete IFN-γ which induces PD-L1 upregulation on antigen-presenting cells (APCs). Activated T cells highly express PD-1. The activation of the PD-1 signaling pathway negatively regulates effector T (Teff) cells by limiting cytokine secretion and proliferation, and possibly affects the retention time on APCs to execute cytotoxic activity. PD-L1 also can competitively bind to CD80 and inhibit the costimulation effect of CD28. Moreover, although controversial, PD-1 signaling is presumed to promote the maintenance and suppressive ability of regulatory T (Treg) cells and thus further strengthen the inhibition of effector function. Additionally, reverse signaling through PD-Ls may deliver negative signals to the APCs.

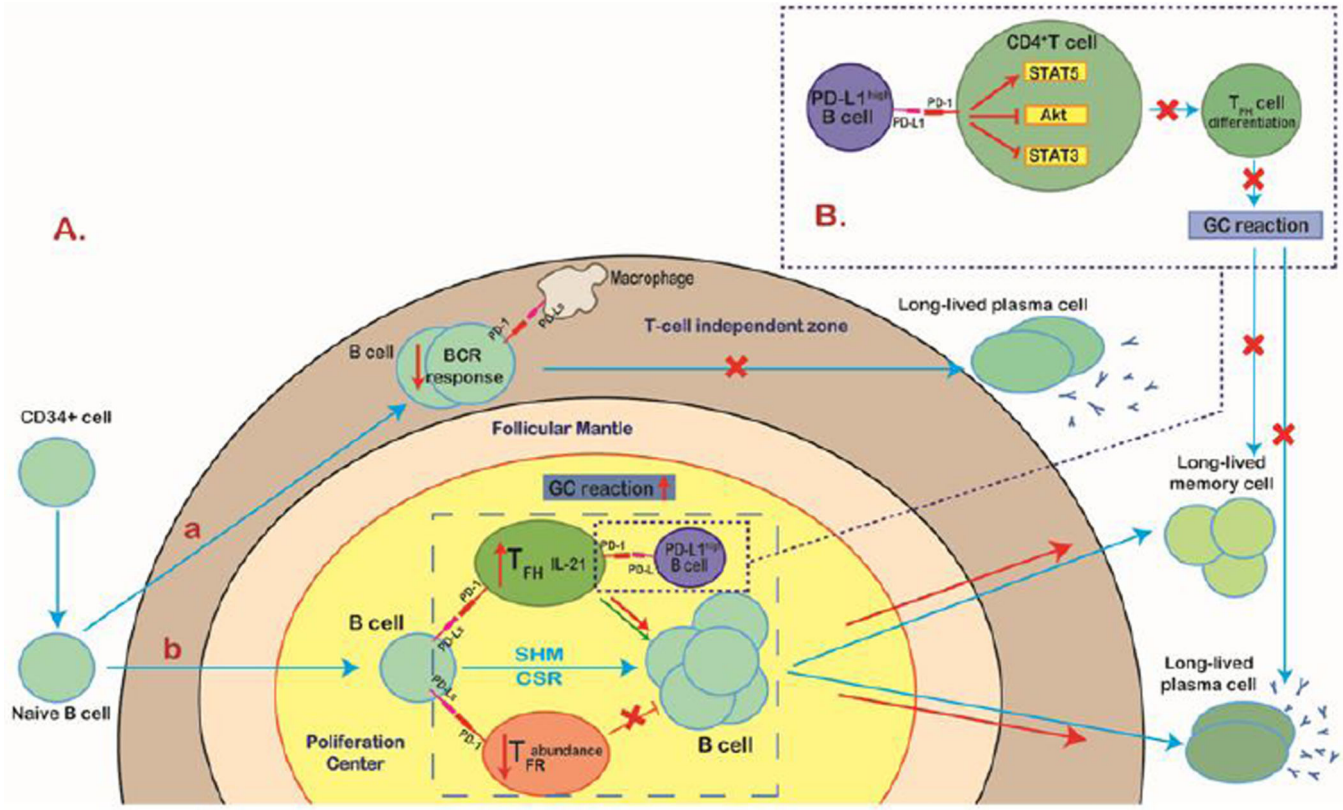

Figure 3. PD-1 signaling in the humoral immune response

A (a) PD-1 is highly expressed on naïve B cells. In T cell–independent humoral immunity, activation of PD-1 signaling inhibits the B cell receptor response and therefore suppresses B1 cell expansion and subsequent long-lived IgG production. (b) In sharp contrast with the innate-like response, PD-1 signaling acts as a promoter, at least partially, for T cell–dependent humoral immunity. Both follicular helper T (TFH) and follicular regulatory T (TFR) cells express PD-1. TFH cells, with a phenotype of $CXCR5^{+}PD\text{-}1^{hi}Foxp3^{-}$, are specialized for helping germinal center (GC) reaction, whereas TFR cells, displaying $CXCR5^{+}PD\text{-}1^{hi}Foxp3^{+}$, potently inhibit TFH cell function. In the proliferation center, the ligation of PD-1 with PD-Ls expressed on B cells profoundly reduces the abundance of TFR cells and increases the level of IL-21 produced by TFH cells, leading to an enhanced GC reaction and the formation of long-lived plasma cells and memory cells. (B) However, a specific B cell subset that highly expresses PD-L1 can suppress TFH cell function in a PD-L1–dependent manner. $PD\text{-}L1^{high}$ B cells restrict $CD4^{+}$ T cell differentiation to TFH cells by upregulating STAT5 and synchronous inhibition of Akt and STAT3 and therefore downregulate the GC reaction and reduce T cell–dependent humoral immunity.

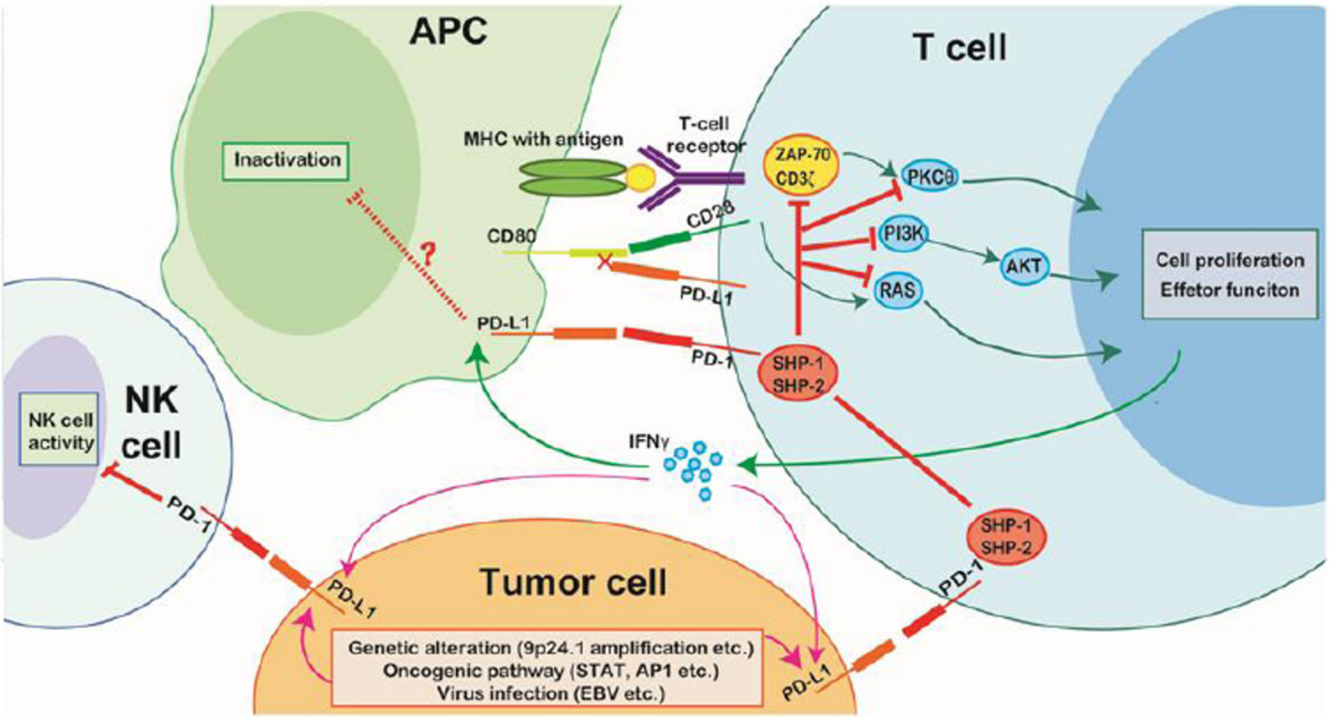

Figure 4. PD-1 signaling in the presence of tumor cells

Tumor cells typically overexpress PD-L1 due to intrinsic factors (genetic alterations, activation of certain signaling pathways, and viral infection) and extrinsic factors (cytokines, such as IFN-γ, secreted by T cells attempting to destroy tumor cells). Interactions of tumor cell PD-L1 and PD-1 on immune cells of the tumor microenvironment (T cells and NK cells) induce immune cell exhaustion and result in failure to activate antitumor immunity.

Table 1

The expression of components of PD-1 signalling pathway in different lymphoid malignancies

Lymphoma subtype	Postulated normal counterpart	Clinical features	Immuno phenotype	Tumor cells			Tumor microenvironment			Clinical significance
				PD 1	PD-L1	PD-L2	PD 1	PD L1	PD L2	
Mature B-cell neoplasms										
Small lymphocytic lymphoma/ chronic lymphocytic leukemia	Naïve or memory B-cells	• Indolent • Median age 65	$CD5^+$ CD10 $CD20^{+/-}$ $CD23^+$	+	+/−	−	+	..	..	↑PD-1+ CD8(+) T lymphocytes : more advanced stage of disease
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue	Post germinal center, marginal zone B-cell	• Indolent • Median age 61	$CD5^-$ $CD10^-$ $CD20^+$ $CD23^-$	−	−	..	+/−	..	..	
Nodal marginal zone Lymphoma	Post-germinal center marginal B-cell	• Indolent • Median age 60	$CD5^-$ $CD10^-$ $CD20^+$ $BCL2^+$ $BCL6^-$	−	−	..	..	..	..	
Follicular lymphoma	Germinal center B-cell	• Variable • Median age 60	$CD5^-$ $CD10^+$ $CD20^+$ $BCL2^+$ $BCL6^+$	III + I/II -	−	−	+	+	..	Controversy
Mantle cell Lymphoma	Peripheral B-cell of inner mantle zone	• Aggressive • Median age 60	$CD5^+$ $CD10^+$ $CD20^+$ $FMC7^+$ $CCND1^+$	−	+/−	−	−	..	..	
Diffuse large B-cell lymphomas, not other specified	Peripheral B-cells of either germinal center or post germinal center origin	• Aggressive • Median age 65	$CD5^-$ $CD10^{+/-}$ $CD20^+$ $CD22^+$	−	GCB - Non-GCB +	..	+/−	..	..	↑sPD-1 associated with inferior prognosis in young high risk patients
T-cell/histiocyte-rich B-cell lymphoma	Germinal center B cells	• Aggressive • Median age 50	$CD20^+$ $BCL\text{-}6^+$ EMA^+ $BCL\text{-}2^+$	−	+	..	+	+	..	..
Primary central nervous system lymphoma	Activated (late germinal center) B-cell	• Aggressive • Median age 60	$CD20^+$ $CD10^{+/-}$ $BCL\text{-}6^+$ $MUM\text{-}1^+$ $BCL\text{-}2^{+/-}$	+/−	+/−	..	+	+/−	..	..

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Lymphoma subtype	Postulated normal counterpart	Clinical features	Immuno phenotype	Tumor cells			Tumor microenvironment			Clinical significance
				PD 1	PD-L1	PD-L2	PD 1	PD L1	PD L2	
EBV-positive DLBCL of Elderly	Mature B lymphocyte, transformed by EBV	• Aggressive • Median age 71	$CD20^{+}$ $CD10^{-}$ BCL-6^{-} MUM-1^{+} $LMP1^{+}$ EBNA-2^{+}	−	+	..	..	..	..	
Primary mediastina large B-cell lymphoma	Thymic medullary, asteroid, (AID-positive), B-cell	• Variable • Median age 35	$CD20^{+}$ $CD10^{+/-}$ $CD30^{+}$ $CD15^{+/-}$	−	+	+	+	+	..	
Plasmablastic Lymphoma	Plasmablast	• Aggressive • Median age 50	$CD38^{+}$ $CD138^{+}$ $CD20^{+/-}$ $CD56^{+/-}$	..	+	..	..	..	..	
Primary effusion Lymphoma	Post-germinal center B-cell	• Aggressive • Young, middle-age	Lack pan-B-cell markers, BCL-6-, LANA+	..	+	..	..	..	..	
Burkitt lymphoma	Germinal center B-cell	• Aggressive • Median age 30	$CD20^{+}$ $CD10^{+}$ $BCL6^{+}$ $BCL2^{+/-}$ TdT^{-}	−	−	−	..	..	..	
Mature T- and NK-cell neoplasms										
Adult T-cell leukaemia/lymphoma	CD4+CD25+ FOXP3+ Treg	• Variable • Median age 58	$CD4^{+}$ $CD7^{+/-}$ $CD8^{+/-}$ CD25+ $CD30^{-}$ $FOXP3^{+}$	+	+/−	..	..	+	..	
Extranodal NK/T-cell Lymphoma	Activated NK cells and cytotoxic T cells	• Variable • Median age 44	CD2+ CD56+ EBER+ CD3: surface-cytoplasmic+	−	+	..	+	+	..	
Mycosis fungoides	Mature skin homing CD4+ T cell	• Variable • Mostly adults/ elderly	$CD2^{+}$ $CD3^{+}$ $CD4^{+}CD5^{+}$ $CD7^{+/-}$ $CD8^{-}$ CLA^{+}	+/−	+	..	..	..	..	
Sézary syndrome	Mature epidermotropic skin homing CD4+ T cell	• Aggressive • Median age 60	$CD2^{+}$ $CD3^{+}$ $CD5^{+}$ $CD7^{+/}$ $CD4^{+}CD8^{-}$ $TCR\beta^{+}$ $CCR4^{+}$	+	..	..	..	..	..	
Angioimmunoblastic T-cell lymphoma	germinal center TFH	• Aggressive • Median age 56	$CD4^{+}$ $CD8^{+/-}$ $CD10^{+}$ $BCL\text{-}6^{+}$ $PD\text{-}1^{+}$ $CXCL13^{+}$	+	+/−	..	..	+	..	

Lymphoma subtype	Postulated normal counterpart	Clinical features	Immuno phenotype	Tumor cells			Tumor microenvironment			Clinical significance
				PD 1	PD-L1	PD-L2	PD 1	PD L1	PD L2	
Anaplastic large cell Lymphoma	Activated mature cytotoxic T cell.	• Variable • ALK^{+}young • ALK- 40–65	CD4^{-}CD8$^{+/-}$ CD30^{+} ALK-1$^{+/-}$	+/−	+	..	..	..	..	
Hodgkin lymphoma										
Classical Hodgkin Lymphoma	Germinal center B-cell	• Indolent • Median age 18 and 45	CD30^{+} CD15^{+} CD20$^{+/-}$ PAX5^{+}	−	+	+	+	+	−	↑PD-1+>23 cells/mm^{2} stage-independent negative prognostic factor for OS
Nodular lymphocyte predominant Hodgkin lymphoma	Germinal center B-cell	• Indolent • Age 30–50y	CD15^{-} CD30^{-} CD20^{+} BCL-6^{+} AID^{+}	−	+/−	..	+	..	..	

Abbreviations: PD-1: programmed cell death-1; PD-L: programmed cell death ligand; +: expressed; -: not expressed; +/−: discordant result; ..: not reported.

Table 2

Agents of PD-1, its ligands and clinical trials

Target	Symbol	Type of construction	Developed by
PD-1	Nivolumab* (BMS-936558, MDX-1106, ONO-4538)	Fully human IgG4 mAb (Whole antibody)	Bristol-Myers Squibb
	Pembrolizumab# (lambrolizumab, MK-3475)	Humanized IgG4 mAb (Whole antibody)	Merck
	Pidilizumab (CT-011)	Humanized (from mouse) IgG1 mAb (Whole antibody)	CureTech Ltd
	AMP-224	Extracellular domain of PD-L2 and the Fc region of human IgG(fusion protein)	Amplimmune/AstraZeneca
	AMP-110	Monoclonal antibody	Amplimmune/AstraZeneca
	MEDI0680 (AMP-514)	Monoclonal antibody	Amplimmune/AstraZeneca
PD-L1	MPDL3280A (RG7446)	IgG1 mAb to PDL1 with an engineered Fc domain(Whole antibody)	Genentech/Roche
	BMS-936559 (MDX-1105)	Fully human IgG4 mAb (Whole antibody)	Bristol-Myers Squibb
	MEDI4736	IgG1 mAb to PDL1 with an engineered Fc domain (Whole antibody)	MedImmune/AstraZeneca
	MSB0010718C	Fully human IgG1 mAb	Merck KGaA

*Japan and U.S.A both approves Nivolumab (Opdivo®) for advanced melanoma.

#FDA of U.S.A approves Pembrolizumab (Keytruda®) for advanced melanoma.

Table 3

Completed Clinical Trials of anti-PD-1 and PD-L1 antibodies in patients with lymphoid malignancies

Agent tested(Phase)	Patients (No.)	Treatment arms	Response rates	Response duration	Adverse Events No. of patients
Pidilizumab(I)	Advanced stage of CLL (3), AML (7), NHL (4), HL (1) and MM (1) following chemotherapy and/or SCT.	Pidilizumab five dose groups of 0.2, 0.6, 1.5, 3, and 6 mg/kg×1 cycles	**Clinical benefit: ORR:** 33%(5/15) 1 CR(FL) 4 SD(2 CLL; 1 HL; 1 MM) 1 MR(AML)	**Mean survival time :** 25±27 weeks **Survival time:** 1.7∼77 weeks. **Averaging survival time of response patients:** > 60 weeks	All AEs: grade 1/2. **Related to treatment** 1 weakness, 1 flushing **Other:** 2 diarrhea, 1 rash, 1 urine infection, 1 pain, 1 back pain, 1 shortness of breath, 1 blurred vision, 1 pressure wound,
Pidilizumab (II)	Sixty-six patients after AHSCT from 30 to 90 days: de novo DLBCL (49); PMBCL (4); transformed indolent B-NHL (13)	Pidilizumab 1.5 mg/kg every 42 days×3 cycles	**Measurable patients:** ORR: 51% (CR:34%; PR: 17%) SD: 37% PD:11% **PET-CT positive patients:** ORR:33% SD:44%	At 16 months: **Measurable patients:** PFS: 72% (90% CI, 60% to 82%) OS: 85% (90% CI, 74% to 92% **PET-CT positive patients:** PFS: 70%(90% CI, 51% to 82%)	613 AEs occurred in 69 of patients in all 72 patients **Related to treatment:** 135 AEs **The most common AEs** **Grade 3 to 4** 14 neutropenia, 6 thrombocytopenia **Grade 2** 7 neutropenia, 5 URTI **Grade 1** 16 fatigue, 11 cough
Pidilizumab(II)	Adult patients with rituximab-sensitive follicular lymphoma relapsing after one to four previous therapies(32)	**Pidilizumab:** **All:** 3 mg/kg q 4 weeks × 4 times **Optional:** stable disease or better plus 8 times q 4 weeks **Rituximab:** 375 mg/m2 q w × 4 weeks, starting 17 days after the first pidilizumab iv.	**Median follow up 15·4 months** ORR: 66% CR: 52% PR: 14% **Measurable tumor regression:** 86%	**MTR:** All: 88 days (53 to 392 days). Delayed responsers:6/29(21%)>4m **Median PFS** all patients: 18·8 m (95% CI 14·7 to not reached) Responders: not reached (95% CI 18·8 to not reached) **Response duration:** 20.2 m (95% CI 13·9 to not reached)	No autoimmune or treatment-related AEs of grade 3 or 4. **The most common AEs:** **Grade 2**: 5 respiratory infection **Grade 1**: 14 anemia; 13 fatigue
Nivolumab(I)	Adult patients with relapsed or refractory Hodgkin's lymphoma(23)	**Nivolumab:** 3mg/kg every 2 weeks until CR, PD, or excessive toxic effects.	**Median follow up 24 months** ORR: 87% CR: 17% PR: 70% SD: 13%	**PFS: 86%** **Median overall survival:** NR **Median duration:** 10 m (0 to 18.75 m)	**Any grade AEs**: 22 (96%) **Grade 3**: 12 (52%) **Drug-related AEs**: 18 (78%) **The most common AEs:** 5(22%) rash, 4 (17%) ↓ platelet, 3(13%) fatigue; **Drug-related grade 3 AEs**: 5 patients (22%): 1. pancreatitis, pneumonitis, stomatitis, colitis, gastroenteritis; 2. ↑lipase; 3. MPN, thrombocytopenia, ↓ lymphocyte, leukopenia.

Abbreviations: AML: Acute Myeloid Leukemia; CML: Chronic Lymphocytic Leukemia; NHL: non-Hodgkin's lymphoma; HL: Hodgkin's lymphoma; MM: multiple myeloma; MPN: myelodysplastic syndrome; SCT: stem cell transplantation; AHSCT: autologous hematopoietic stem-cell transplantation; CR, complete response; PR: partial responses; SD, stable disease; MR: minimal response; NR: not reported; ORR: overall response rate; OR: objective response; MTR: median time to response; AE: adverse events; irAEs: immune-related adverse events; URTI: upper respiratory tract infection;

Table 4

Ongoing studies of anti-PD-1 and PD-L1 antibodies in patients with lymphoid malignancies

Agent	ClinicalTrial.gov ID	Phase	Additional Therapy	Disease
Pembrolizumab	NCT02362997	II	None	R/R DLBCL or cHL prior to AHSCT
Pembrolizumab	NCT02408042	Ib/II	DLBCL: RICE; cHL: ICE + Pembrolizumab or brentuximab vedotin	R/R DLBCL or cHL
Pembrolizumab	NCT02332668	I/II	None	R/R lymphoma patient less than 18 years old
Pembrolizumab	NCT01953692	I	None	R/R HL, PMBCL, MM, PD-L1+ NHL, DLBCL or FL
Pembrolizumab	NCT02332980	II	None	R/R CLL or other low grade B-NHL
Pembrolizumab	NCT02362035	Ib/II	ACP-196	NHL, MM, CLL, RS or WM
Pembrolizumab	NCT02243579	II	None	Newly diagnosed MF or SS (Except for stage IA), Recurrent MF or SS
Nivolumab	NCT02038946	II	None	Refractory FL without evidence of transformation
Nivolumab	NCT02038933	II	None	R/R DLBCL failed or not fit for AHSCT
Nivolumab	NCT02304458	I/II	Ipilimumab	Refractory HL or NHL between 12 months to 30 years old
Nivolumab	NCT02253992	I/II	Urelumab	Previously treated advanced B-NHL
Nivolumab	NCT01592370	I	Ipilimumab/lirilumab	R/R NHL, HL or MM
Nivolumab	NCT02181738	II	None	R/R HL post AHSCT
Nivolumab	NCT02327078	I/II	INCB24360	R/R HL or NHL
Nivolumab	NCT02329847	I/II	Ibrutinib	R/R B-NHL or CLL
MPDL3280A	NCT02220842	I	Obinutuzumab	R/R FL or DLBCL
MPDL3280A	NCT01375842	I	None	advanced hematologic malignancies
MEDI4736	NCT02401048	Ib/II	Ibrutinib	R/R FL or DLBCL
MEDI4736	NCT02205333	Ib/II	Rituximab	Refractory DLBCL
MEDI0680 (AMP-514)	NCT02271945	Ib/II	MEDI-551	R/R DLBCL, MCL or Grade 3B FL

Abbreviations: FL: Follicular Lymphoma; DLBCL: Diffuse Large B-Cell Lymphoma; MM: Multiple myeloma; WM: Waldenström's macroglobulinemia; RS: Richter Syndrome; MF: Mycosis fungoides; SS: Sezary syndrome; MCL: Mantle cell lymphoma; cHL: Classic Hodgkin's lymphoma; PMLBCL: Primary mediastinal large B cell lymphoma; NHL: non-Hodgkin's lymphoma; AHSCT: Autologous hematopoietic stem cell transplantation; ICE: Ifosfamide, carboplatin, and etoposide; RICE: Rituximab, ifosfamide, carboplatin, and etoposide;