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Investigational PD-1 inhibitors in HL and NHL and biomarkers for predictors of response and outcome

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Abstract

Introduction—Inhibitors against the PD-1/PD-L1 pathway are revolutionizing the treatment and management of malignancies.

Areas covered—We summarize our current understanding of the function of PD-1, its role in immune evasion, the clinical data available that support the use of PD-1 antagonist in Hodgkin and non-Hodgkin lymphomas, and potential predictors of response.

Expert opinion—We anticipate that in the next 10 years, agents that modulate the immune system such as PD-1 antagonists will be increasingly used in favor over traditional cytotoxic chemotherapeutic agents. PD-1 antagonists will be combined with future immunotherapies or used as adjuncts to cellular therapy to boost tumor-specific immune responses.

Keywords

PD-1; PD-L1; non-Hodgkin lymphoma; Hodgkin lymphoma; immunotherapy; PD-1 inhibitor

1.0 Introduction

The discovery of pathways that dampen T-cell-mediated immune responses, and the development of inhibitors that interfere with this process have revolutionized the field of oncology. Of the known pathways that restrain T-cell-mediated immune responses, the Programmed Cell Death 1 (PD-1) pathway has gained the most notoriety given its impressive response rates across solid tumors and hematologic malignancies. Indeed, PD-1

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Declaration of Interest

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inhibitors are the first drug class to be granted a tissue and histology agnostic approval by the FDA. Multiple studies are underway to expand the use of this powerful new class of medications in the treatment and management of lymphomas. Lymphomas are a heterogeneous group of malignancies that together have an estimated annual incidence rate between 80,000 and 136,000 new cases in the United States alone[1,2]. Despite their common origin in lymphatic tissue, the clinical course of lymphomas vary considerably from indolent to rapidly aggressive[3]. Treatment ranges from surveillance for indolent disease to multi-agent chemotherapy and allogeneic stem cell transplant for patients with aggressive or refractory disease. Initial treatment with combination chemo-immunotherapy results in long term disease-free survival in approximately 70–90% of Hodgkin[4,5] and 36–80% of diffuse large B-cell lymphoma (DLBCL) patients,[6,7] depending on stage and prognostic factors. Even though the prognosis of many forms of lymphoma is favorable compared to solid tumors, aggressive subtypes have suboptimal response to upfront therapy and many patients experience relapses. The response to salvage chemotherapy is often poor and many patients eventually succumb to their disease. PD-1 inhibitors initially emerged as treatments for solid tumors. However, accumulating data demonstrated a range of efficacy across multiple hematologic malignancies including lymphoma (Table 1). In this review, we aim to further define the role of these agents in the treatment of lymphomas by discussing the biology of the PD-1/PD-L1 pathway, current data for PD-1 inhibitors in lymphoma, biomarkers of treatment outcome, and future directions for clinical development.

2.0 The Biology of PD-1 and Its Application in Oncology

T-cells require two signals for activation and effector functions implementations: the interaction between the T-cell receptor (TCR) and its target antigen bound to a major histocompatibility complex (MHCs) provides the first signal; the second is a co-stimulatory signal that usually involves engagement of CD28 on the surface of a T-cell with either CD80 or CD86 on the antigen-presenting cell (Figure 1). Without this second signal, TCR activation results in T-cell anergy[9]. Upon activation, T-cells also express inhibitory receptors whose purpose is to restrain and prevent overactivation of the immune response[9]. These receptors, also known as “immune checkpoints”, play an essential role in the prevention of the autoimmune diseases but are also implicated in immune escape of chronic infections and malignancies. Of these immune checkpoints, the PD-1/PD-L1 pathway is arguably the best understood. PD-1 was first identified in 1992 as a member of the immunoglobulin gene superfamily whose expression was associated with increased levels of apoptosis in T-cells[10] but was subsequently shown to be a negative regulator of the immune response[11]. PD-1-deficient mice were more prone to develop autoimmune diseases such as lupus-like arthritis, glomerulonephritis, dilated cardiomyopathy, and type I diabetes mellitus[11–14]. PD-1 was later found to bind to PD-L1 and PD-L2, B7-like molecules that expressed on a variety of benign and malignant tissues[15–18].

PD-1 is a 288-amino acid, type I, single-pass transmembrane protein with an extracellular Ig-variable domain (IgV) which harbors the sites of interaction with PD-L1 and PD-L2[17–19]. Unlike other proteins in the family, which have SH2 and SH3-binding motifs in their cytoplasmic tails, PD-1 contains an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITISM) which is essential for the

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inhibitory function of PD-1[20]. PD-1 is predominantly expressed on activated CD4+ and CD8+ T-cells but is also found on B-cells, monocytes, natural killer cells, and dendritic cells among others[21]. It is also expressed in CD4-CD8- (double-negative) thymocytes and plays an important role in their selection process[22]. PD-1 expression is actively regulated by transcription factors like NFATc1, FOXO1, Notch, IRF9, and the members of the STAT family of proteins[23–27] while the transcription factor T-bet is a repressor[28].

PD-L1 and PD-L2 demonstrate distinct patterns of expression. PD-L1 is expressed in antigen-presenting cells, as well as many non-hematopoietic cells including the lung, endothelial cells, and immune privileged sites such as placenta and eye. It is also expressed in some malignancies[20,21,29–31]. PD-L2, on the other hand, is expressed mainly on dendritic cells, macrophages, and some B-cells after activation[32]. Both ligands are upregulated in T-cells by proinflammatory cytokines such as interferon-γ[33]. In addition to binding to PD-1, PD-L1 also interacts with CD80 on the surface of T-cells, providing an additional inhibitory signal[34,35].

Engagement of PD-1 with its ligand results in the phosphorylation of the tyrosine residues in the ITIM and ITSM, recruiting tyrosine phosphatases to the immune receptor complex, leading to a cascade of interactions that ultimately result in loss of T-cell effector function and T-cell exhaustion[36] (Figure 1). Activation of PD-1 inhibits the activation of the PI3k-AKt pathway and decreases the phosphorylation of CD3, ZAP70, and PKCθ[37,38]. Additionally, PD-1 impairs the activation of the MEK-ERK-MAP kinase pathway by inhibiting the activation of RAS and PLC-γ1[39,40]. Both pathways are required for T-cell activation. Furthermore, PD-1 activation alters the metabolic program of the T-cell, promoting the use of fatty acids in beta-oxidation and generating a more oxidative environment that disfavors the differentiation into effector T-cells[41,42]. The consequences of PD-1 activation on T-cell function depends in part on the degree of PD-1 expression. While low levels are required to block interferon-γ, TNF-α, and interleukin-2 production, higher expression of PD-1 is needed to inhibit macrophage inflammatory protein 1 beta (Mip-1b) production, a chemokine important for the recruitment of T-cells to the tissue microenvironment[43,44].

PD-1 play important roles in the regulation of the immune response against infection and malignancy. During an acute viral infection, naïve antigen-specific CD8+ T-cells are activated, proliferate, and differentiate into effector CD8+ T-cells, most of which undergo apoptosis once the infection is cleared though some turn into long-lived memory cells[45]. In chronic infection, however, T-cells lose effector function and become exhausted[46]. Importantly, these exhausted T-cells overexpress PD-1, and PD-1-blocking antibodies can restore effector function[47–49]. Analogous to chronic infections, various types of human cancers use PD-1 to evade the immune system and blocking the interaction between PD-1 and PD-L1 have resulted in decreased tumor burden in a T-cell-dependent manner[50,51]. Monoclonal antibodies targeting this pathway are now approved for treatment of malignancies such as melanoma, non-small cell lung cancer, renal cell carcinoma, urothelial carcinoma, tumors with mismatch repair deficiencies, head and neck cancers, Merkel cell carcinoma, gastric adenocarcinoma, and relapsed Hodgkin lymphoma (Table 2)[31,52–69].

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3.0 Targeting PD-1 in Hodgkin Lymphoma

The application of PD-1 antagonists in lymphomas was first approved by the U.S. FDA in 2016 for use in patients with classical Hodgkin lymphoma (cHL) that relapsed or progressed after autologous stem cell transplant. This was based on phase I and II studies showing an overall response rate (ORR) of 65–87% and a complete response rate (CR) of 17–22.4%[55,68–71]. To date, two PD-1 inhibitors, nivolumab and pembrolizumab, have received accelerated approval for use in cHL and are available commercially for clinical use. PD-1 inhibition in cHL is intriguing given the immune background of cHL tumors containing few neoplastic Reed-Sternberg cells surrounded by a non-malignant but dysfunctional immune-cell infiltrate[72–75]. This inflammatory morphology with low tumor-to-immune-cell ratio creates a perfect backdrop for immunotherapy. Furthermore, alterations in chromosome 9p24.1, which houses the genes for PD-L1, PD-L2, and JAK2, are ubiquitous in cHL[72,76,77]. Indeed, a study found that up to 97% of cHLs had alterations in this locus, most of which were copy gain but polysomy and amplifications were also observed[55,76]. Consistent with these genetic alterations, virtually all Reed-Sternberg cells express high levels of PD-L1[55,75]. Additionally, the tumor-associated macrophages also have significant PD-L1 expression and are in close proximity to PD-1-expressing T-cells[78]. The high response rates observed with anti-PD-1 antibody treatment in patients who progressed through multiple lines of treatments suggest that the PD-1 pathway plays an essential role in the pathogenesis of cHL. Interestingly, some have successfully used lower doses of both pembrolizumab and nivolumab to treat cHL, indicating enhanced susceptibility to PD-1 inhibition compared to other malignancies[79–81].

In spite of its high clinical efficacy, questions regarding the optimal timing and combination of PD-1 blockade in the treatment of cHL remain. Clinical trials are underway combining PD-1 antagonists with brentuximab vedotin, ibrutinib, lenalidomide, vorinostat, ipilimumab, as well as traditional cytotoxic chemotherapeutic agents in the relapsed and upfront settings. Checkpoint inhibition is also being studied in the posttransplant setting and in combination with radiotherapy. Preliminary results from some of these studies have been encouraging. In NCT02572167, for instance, the combination of nivolumab and the anti-CD30 antibody-drug conjugate brentuximab vedotin produced an ORR of 100% and a 50% complete metabolic response in the 6 patients with relapsed or primary refractory disease that completed treatment[82]. This combination resulted in similar response rates in a heavily pretreated population in NCT01896999 as well[83].

As mentioned previously, chromosome 9p24.1 also harbors the gene for JAK2, which is a member of the JAK family of kinases shown to up-regulate the transcription of PD-L1 and PD-L2[72]. Thus, inhibition of JAK2 can lead to decreased levels of PD-L1 and may be a valuable therapeutic strategy. The use of the JAK2 inhibitor ruxolitinib as a single agent in heavily pretreated patients with cHL (NCT01965119) showed a response rate of 54% and a median duration of response of 5 months, though only one of the thirteen patients achieved complete response (CR)[84]. While results of this pilot study are relatively modest compared to those observed with direct PD-1 antagonists, the anti-tumor activity of JAK2 inhibition observed as a single agent may be synergistic with PD-1 inhibition and is being further explored.

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4.0 PD-1 as a Potential Therapeutic Target in Non-Hodgkin Lymphoma

4.1 Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL)

CLL cells express PD-1 and PD-L1, and T-cells in these patients exhibit exhausted effector function and defects in immunologic synapse formation[85–87]. Preclinical data showed that blockade of the PD-1/PD-L1 interaction with an anti-PD-L1 antibody normalized immune effector function and prevented CLL development in a mouse model[88], setting up the stage for clinical studies. Pembrolizumab was studied in a phase 2 trial of 25 subjects with relapsed or refractory CLL, including 9 subjects with Richter's transformation (RT) (NCT02332980). No subjects with CLL achieved CR or partial response (PR). Among patients with RT, there was one CR (11%), 3 PR (33%), 3 subjects with stable disease (33%), and two patients with progressive disease, for an overall response rate (ORR) of 44%[89]. In two patients with PR to the Richter's component of disease, progression of bone marrow CLL involvement resulted in thrombocytopenia. The protocol was subsequently amended to allow the addition of CLL-directed therapy with ibrutinib or idelalisib to provide additional control of the CLL component of disease[89]. These findings suggest heterogeneity of response between CLL and RT, with no observed single-agent activity of pembrolizumab in CLL. Studies are ongoing to further evaluate the use of single-agent pembrolizumab in RT (NCT02576990) as well as in combination with BTK and PI3K inhibitors (NCT03153202, NCT02362035, NCT03283137, NCT02535286, NCT03204188).

Nivolumab has been studied in combination with ibrutinib in a phase 2 study (NCT02420912). Preliminary results from five patients in cohort 1 (relapsed/refractory CLL or RT) and three patients in cohort 2 (CLL with PR on ibrutinib) showed PR in 3 patients and 2 patients, respectively. No CRs were observed, although recruitment is still ongoing[90]. Antibodies targeting PD-L1 are also under investigation in CLL. Ongoing trials include atezolizumab in combination with obinutuzumab and ibrutinib (NCT02846623), and a phase 1/2 study of durvalumab as monotherapy and in combination with ibrutinib, bendamustine/rituximab, or lenalidomide/rituximab (NCT02733042)[91].

4.2 Follicular Lymphoma (FL)

Responses to PD-1 targeted therapy have been reported in follicular lymphoma. A phase 1 study of nivolumab in relapsed or refractory hematologic malignancies included 10 patients with relapsed FL who had received a median of three previous therapies. The ORR was 40% (4/10), with one CR[92]. The phase 2 Checkmate-140 trial will seek to confirm the efficacy of nivolumab monotherapy in patients with FL who have failed a CD20 antibody and an alkylating agent (NCT02038946). Other ongoing studies will evaluate nivolumab combinations in both newly-diagnosed and relapsed FL (NCT03245021, NCT03015896, NCT03121677).

Preliminary results of a phase 2 study of pembrolizumab in combination with rituximab have shown promising results as well (NCT02446457). Twenty-seven patients with a median of one prior therapy initiated therapy, and interim analysis of 15 patients demonstrated an ORR of 80% and CR rate of 60%. Median PFS and OS were not reached at a median of 7 months of follow-up[93]. Pembrolizumab is also being studied in combination with a variety

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of treatment modalities including intratumoral injections (NCT02501473, NCT02677155), vorinostat (NCT03150329), and BTK or PI3K inhibitors (NCT02950220, NCT02332980).

The PD-L1 inhibitor atezolizumab was studied in combination with obinutuzumab in a phase 1b trial of patients with relapsed or refractory FL or DLBCL, with a median of four prior therapies. Preliminary results from three patients with FL demonstrated one PR (33%)[94]. A phase 2 expansion cohort study in FL is ongoing (NCT02631577). Additional studies of atezolizumab in combination with obinutuzumab and a variety of third agents including bendamustine, tazemetostat, polatuzumab vedotin, and venetoclax are planned (NCT02596971, NCT02220842, NCT02729896, NCT03276468).

4.3 Diffuse Large B-Cell Lymphoma (DLBCL) and other B-Cell NHL

Initial trials showed limited efficacy of PD-1 inhibitors against DLBCL. Eleven patients with relapsed or refractory DLBCL were included in the phase 1 study of nivolumab monotherapy, along with 10 patients with other B-cell lymphomas. Among patients with DLBCL, there was a 36% ORR, with two CRs (18%). There were no objective responses observed in patients with other B-cell lymphomas[92]. A second cohort of patients received nivolumab in combination with the anti-CTLA-4 antibody ipilimumab, including 15 patients with B-cell NHL (10 DLBCL, 5 FL). Three partial responses (20%) and no complete responses were observed[95]. Further studies are ongoing including CheckMate 139 (NCT02038933), which has enrolled 161 patients with relapsed or refractory DLBCL to receive nivolumab monotherapy. Phase 1 and 2 studies evaluating nivolumab in combination with chemotherapy or other novel targeted therapies are also underway (NCT03259529, NCT02327078, NCT03038672, NCT03015896). Interestingly, recent studies since have shown a differential expression of PD-L1 among patients with DLBCL. Tumors that area associated with EBV or have an activated-B-cell (ABC) phenotype have higher expression of PD-L1 than their counterparts[96,97]. It was also shown that PD-L1 expression in DLBCL was associated with inferior overall survival[97], suggesting that PD-L1 expression is a poor prognostic marker. However, these observations are in patients who were not treated with PD-1 inhibitors. Thus, it remains to be seen whether outcomes in these patients change with the introduction of agents against PD-1 to their treatment regimen.

Additionally, lymphomas arising in immune privileged sites such as primary central nervous system lymphoma (PCNSL) and primary testicular DLBCL demonstrated increased PDL-1 expression owing to alterations in chromosome 9p24.1[98], making PD-1 inhibitors particularly appealing in light of the successes seen in cHL. Consistent with preclinical data, preliminary results displayed favorable activity of nivolumab in relapsed/refractory PCNSL and primary testicular lymphoma (PTL). Among four patients with multiply relapsed disease and one patient with primary refractory PCNSL, treatment with nivolumab resulted in four complete and one partial response. All patients with neurologic symptoms at initiation of treatment had at least near-complete resolution of those symptoms[99]. We anticipate further results of single agent nivolumab from Checkmate 647, a phase 2, single arm study of 65 patients with relapsed/refractory PCNSL and PTL, which is actively enrolling (NCT02857426)[99].

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The KEYNOTE-013 trial is an ongoing phase 1b study of pembrolizumab in patients with hematologic malignancies including FL, DLBCL, and primary mediastinal large B cell lymphoma (PMBCL) (NCT01953692). Special attention has been given to PMBCL owing to its clinical and genetic resemblance to cHL, including alterations in chromosome 9p24.1 leading to overexpression of PD-1 ligands[72,100,101]. Preliminary results from the first 19 patients enrolled in the PMBCL cohort have been reported, with an ORR of 41% (7/17 patients evaluable for response), including 2 CRs and 5 PRs. With a median 11.3 months of follow-up median duration of response was not reached, with 6 ongoing responses[102]. Interestingly, studies with ruxolitinib, an inhibitor of JAK2, was very disappointing in patients with PMBCL as patients showed disease progression after 1–2 cycles[84]. Nonetheless, in light of response to direct PD-1 inhibition, the use of pembrolizumab in PMBCL will be further evaluated in KEYNOTE-170, a multicenter phase 2 study (NCT02576990). Other notable ongoing studies of pembrolizumab include its use in combination with standard chemotherapy (NCT02541565) and in combination with external beam radiation therapy (EBRT) (NCT03210662) in DLBCL. There are also ongoing studies evaluating monotherapy in recurrent PCNSL (NCT02779101), HIV-related lymphoma (NCT02595866), after ASCT (NCT02362997), and in patients relapsed or refractory to treatment with CD19+ CAR T cells (NCT02650999).

PD-L1 inhibitors are also being studied for use in these types of lymphomas. Preliminary results of atezolizumab in combination with obinutuzumab in 23 patients with heavily pretreated DLBCL demonstrated a 16% ORR. No subgroup analysis were reported in this preliminary study[103]. Other ongoing studies in relapsed/refractory DLBCL are evaluating atezolizumab in combination with obinutuzumab and polatuzumab vedotin (NCT02926833), and in combination with CD19 CAR T cells (NCT02926833). A phase 2 study of durvalumab in combination with RCHOP or RCHOP/lenalidomide in newly diagnosed DLBCL is currently recruiting, with a target enrollment of 120 subjects (NCT03003520)[104]. Avelumab in combination with RCHOP in DLBCL (NCT03244176), and in a variety of combinations with chemotherapy and utomilumab, an anti-4-1BB antibody (NCT02951156) are also being studied.

4.4 T-cell Lymphomas

T-cell lymphomas (TCLs) constitute 15% of all NHLs but carry a significantly worse prognosis owing to their aggressive course, frequent relapses, and limited targeted options[2,105]. Overall response rates to front line chemotherapy are typically in the range of 50%, with relapse as a rule of thumb[106]. Like their B-cell counterparts, TCLs may be associated with EBV and many overexpress PD-1[107–109]. Targeting the PD-1 pathway is particularly appealing in this group of lymphomas given that both PD-1 and PD-L1 can be expressed in the surface of T-cells. A total of 23 patients with relapsed/refractory TCLs were included in the phase 1 study of nivolumab in hematologic malignancies: 13 patients with mycosis fungoides (MF), 5 peripheral T-cell lymphoma (PTCL), 2 Sezary syndrome, and 3 with other non-CTCL (cutaneous T-cell lymphoma). Eighty-seven percent of patients had received two or more previous treatments. The ORR in this group of patients with TCLs was 17%, with two PRs in MF patients (15%) and two PRs in PTCL patients (40%). Three of the four T-cell patients with PR had ongoing responses at 24.3+, 50.0+, and 78.6+ weeks[92].

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Preliminary results of a phase 2 study of pembrolizumab in 24 patients with relapsed/refractory MF and Sezary syndrome demonstrated an ORR of 38% with one CR and 8 PRs. Six patients experienced 90% or greater improvement in skin disease, although of note six patients with Sezary syndrome experienced an immune-mediated skin flare reaction[110]. Additional planned studies of pembrolizumab in PTCL and CTCL include combinations with decitabine and pralatrexate (NCT03240211) and romidepsin (NCT03278782).

PD-1 inhibitors have also been studied in aggressive TCLs including NK/T cell lymphoma and HTLV-associated T-cell leukemia/lymphoma. Promisingly, a retrospective case series of seven patients with relapsed or refractory NK/T-cell lymphoma treated with pembrolizumab reported a 100% ORR after a median of seven cycles of treatment (CR = 2; clinical + radiologic CR = 3; PR = 2). All five patients remained in CR at a median 6 months of follow-up[109]. Studies are ongoing to further evaluate the use of pembrolizumab in this aggressive disease (NCT03107962, NCT03021057).

Phase 2 studies of nivolumab in relapsed/refractory PTCL and in HTLV-associated T cell leukemia/lymphoma are ongoing (NCT03075553, NCT02631746). The PD-L1 inhibitors durvalumab and avelumab are also under investigation in TCLs, both as single agents and in combination with existing treatments (NCT03011814, NCT03161223, NCT03046953).

5.0 Adverse Effects of PD-1 Therapy

The conglomerate experience within the field of oncology have shown that monoclonal antibodies targeting PD-1 or PD-L1 are very well tolerated. The known adverse event profiles in solid tumors have been consistent in hematologic malignancies as well and include autoimmune-mediated hypothyroidism, pyrexia, rash, diarrhea, and neutropenia[55,69,102]. The most common adverse events reported are skin rash and GI symptoms, affecting about 19–26% of patients[111]. Occasionally, patients may have more severe side effects such as autoimmune myocarditis, pneumonitis, colitis, hepatitis, and hypophysitis, though these have not yet been reported in lymphoma, likely owing to the limited number of patients treated thus far[63,112]. Grade 3/4 adverse events occurred in 6% of the patients treated with PD-1 antagonists as monotherapy. The rates of significant adverse events, however, increased significantly when PD-1 antagonists were used in combination with the CTLA-4 antagonist ipilimumab[62,111]. Most of the adverse events occur during the first 12–14 weeks of treatment although they can occur at any time. Most of the events reported, except for endocrinopathies, resolve within a median of 5 weeks.

In the transplant setting, an increased incidence of graft-versus-host disease (GVHD) in patients who received PD-1 inhibitors before or after allogeneic stem cell transplant has been reported[71,113]. Haverkos *et. al.* conducted a retrospective study of 31 patients that received PD-1 inhibitors after allogeneic stem cell transplant and found that 17 (55%) developed treatment-emergent GVHD, 9 of which were grade 3/4 acute or severe chronic GVHD. Only 2 of these patients responded completely to GVHD treatment and most required multiple systemic treatments for GVHD. This is particularly concerning given that stem cell transplantation is a treatment modality often used in the treatment of lymphomas. Further studies are needed to define the optimal timing and use of PD-1 inhibitors in the

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setting of bone marrow transplantation as well as the optimal management of GVHD related to the use of PD-1 inhibitors.

6.0 Predictors of treatment response and resistance

Despite the high response rate seen in multiple clinical trials using PD-1 antagonist in Hodgkin and non-Hodgkin lymphomas, a significant number of patients do not respond to treatment with PD-1 antagonists and many others progress. Biomarkers capable of identifying the patients likely to benefit from treatment as well as resistance mechanisms are a critical area of investigation. Many have naturally looked at the expression of PD-L1 in the tumor and/or PD-1 in tumor-infiltrating lymphocytes (TILs) as a potential biomarker to predict treatment response. For pembrolizumab, a companion test measuring PD-L1 in tumors by immunohistochemistry was even developed in attempts to screen for patients who are more likely to respond to therapy. In addition to cHL, PD-1 and/or PD-1 ligands are also overexpressed in PMBCL, T-cell/histiocyte-rich-B-cell lymphoma, EBV-associated DLBCL, plasmablastic lymphoma, extranodal NK/T-cell lymphoma, anaplastic large cell lymphoma, and CLL/SLL[86,87,96,107,109,114,115]. Others like Burkitt lymphoma and FL showed little to no PD-L1 expression [96,116]. In FL, however, PD-L1 can be found in histiocytes within the tumor microenvironment and TILs are PD-1 positive[116]. Indeed, many attribute the high treatment response rates seen in cHL to the high expression of PD-L1 and PD-1 in the tumor and the TILs respectively[55,68,72]. Several reports have documented responses to PD-1 antagonist in many lymphomas expressing high PD-1 and/or PD-L1 (summarized in Table 1)[55,70,99,108,109]. Unfortunately, response to treatment with PD-1 inhibitors does not always correlate with expression of these surface proteins in the tumor microenvironment[55,117]. In CLL, for example, no objective responses have been noted to date when treated with PD-1 antagonists as monotherapy in the absence of CLL transformation[89,97], despite having promising preclinical studies[88] and expression of both PD-1 and PD-L1[85–87,118,119] in malignant cells. Across all tumor types, response to PD-1 therapy ranges from 0–17% in PD-L1 negative tumors and 36–100% in PD-L1 positive tumors[120]. Thus, current approaches to test for PD-1/PD-L1 expression have suboptimal positive and negative predictive value for use as a stand-alone biomarker.

The discovery of chromosome 9p24.1 alterations and corresponding overexpression of PD-1 ligands in several lymphomas including cHL[76], primary mediastinal[121], grey zone[122], PCNSL[98], PTL[98], and some solid tumors[123–127] have prompted further investigations of these alterations as a possible genetic biomarker. In cHL, genetic alterations corresponding to the highest expression of PD-L1, amplifications, correlated with advanced stage, inferior treatment outcomes with standard therapy, but increased sensitivity to PD-1 blockade[69,70,76]. Clinical development of quick and reliable testing for abnormalities in this locus are currently in progress[128] but further testing and validation is required prior to its application in the clinical setting.

Overexpression of PD-L1 has also been reported in the setting of infections. It is well established that Epstein-Barr virus (EBV) infection increases the risk of developing several types of lymphomas and other solid tumors, particularly in patients with concomitant infections such as HIV and malaria[129–133]. EBV resides in memory B-cells but can also

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infect T-cells[134] and NK cells, and disruptions in these cells can eventually lead to lymphomagenesis. Although the precise mechanism and extent by which EBV contributes to oncogenesis is not fully understood, chromosomal abnormalities such as translocation of chromosome 14 and 8 (leading to overexpression of MYC) and gain/amplification of 9p24.1 likely contribute to the pathogenesis of the disease[129–131]. Of note, EBV+ lymphomas show high expression of PD-L1[96] and testing for EBV may be of use as a predictor of response to PD-1 inhibition. Other infections such as H. pylori[135], HIV[48,136], and hepatitis B[137] are also associated with increased expression of PD-L1. Further studies are needed to determine the relevance of testing for these viruses as a prognostic biomarker that predict response to treatment with PD-1 inhibitors.

The value TILs as a prognostic marker for treatment response has also been assessed in multiple cancers. The goal of inhibition of the PD-1/PD-L1 pathway is to “reinvigorate” T-cells to react against tumor-specific antigens; logically, the immune cells in closest proximity to the tumor would have the highest likelihood of response. Studies in solid tumors have found that patients with high numbers of lymphocytes in their tumors are more likely to respond to treatment[138–141]. Thus, in addition to overexpression of PD-1 ligands, the high ratio of inflammatory-to-malignant cells in cHL likely contributes to the high response rates seen in patients treated with PD-1 antagonists. The role of TILs as predictors of treatment response in lymphomas needs to be further explored.

7.0 Conclusion

The advent of checkpoint inhibitors is radically changing the management of many types of cancer. Their ability to modulate the immune system to eradicate the disease makes them potentially useful in virtually all types of malignancies. This class of agents is expected to supersede and may eventually replace traditional chemotherapy in certain settings. While many responses are seen, cures are still rare and long term follow up data is lacking. Current available data shows the highest response rates in cHL, likely because of their high level of PD-1 ligand expression and genetic reliance on the PD-1 pathway through alterations of chromosome 9p24.1. The PD-1 antibodies, nivolumab and pembrolizumab, are now approved for use in the relapsed setting. However, emerging data demonstrating increased adverse events in the peri-transplant setting recommend continued caution. As current trials mature, we are likely to see benefits in other types of lymphomas. Efforts are undergoing to identify biomarkers that can predict response and studies in this area will become paramount in the identification of patients who will benefit most from these agents.

8.0 Expert Opinion

PD-1 inhibitors represent a major advance within the field of lymphoma and oncology in general. While initial response rates have been impressive, the efficacy of single agent PD-1 inhibition is widely disparate between each lymphoma subtype, and reliable biomarkers predicting response or resistance are lacking. Mechanisms highlighting sensitivity to PD-1 blockade such as genetic alterations in the chromosome region encoding the PD-1 ligands has highlighted several lymphomas with unique susceptibility to PD-1 blockade. However, alternative mechanisms such as increased PD-1 expression in the microenvironment and

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proximity of immune cells to cancer cells seem to also predict response. The high responses in aggressive lymphomas such as PTLs, PCNSL, and NK/T cell lymphoma on initial small trials, certainly warrants further study. Nevertheless, broad inhibition of the PD-1 pathway fails to cure most lymphoma patients. Even in cHL, where PD-1 expression is ubiquitous, complete responses beyond 2 years are observed in less than 20% of patients on clinical trials[142]. While advances have been swift, further immunology research has proven to highlight our inadequate understanding of the complex mechanisms involved in the tumor immune response and the role of the immune environment in tumorigenesis. Even within the PD-1 system, scientists have only recently discovered the binding sites of PD-1 with PD-L1 and its monoclonal antagonists[143–146]. Pembrolizumab and nivolumab were found to bind to loops outside the IgV. The clinical implications of this binding site discovery are manifold: the loop regions are not subject to conformational switching as can happen in the IgV, therefore resistance is unlikely to develop through this mechanism. Furthermore, the epitopes of pembrolizumab and nivolumab are distinct and *in vitro* studies showed that both antibodies could be bound to PD-1 at the same time[143]. This suggests that combining PD-1 inhibitors or sequential treatment with another PD-1 inhibitor after progression on the first one could be feasible, assuming that PD-1 remains a functional protein and the signaling pathway is intact. Furthermore, this knowledge could aid in the development of future generations of PD-1 inhibitors, which may seek to further exploit this stable binding region.

Additional advances in the understanding of the PD-1 pathway would include an expanded understanding of the profile of reinvigorated T-cells, the elements outside of PD-1 inhibition that are necessary for an effective immune response, and alternative mechanisms for PD-1 immune evasion. The development of resistance to PD-1 therapy presents another major hurdle. The longest follow up in lymphoma is among Hodgkin patients treated with nivolumab. It appears that while some responses are durable, most relapses occur following initial response[147]. A few studies have begun to elucidate mechanisms of primary resistance as well as immune escape. PD-1 inhibition relies on an intact antigen presentation system between T-cells and tumor cells for the TCR engagement. Tumors with deficient antigen presentation have a diminished predicted response to therapy. For example, the Reed Sternberg cells of cHL downregulate MHC class I expression[148]. Similarly, Beta-2 microglobulin (B2M), which serves as a scaffolding protein for MHC-1, is also diminished. Those tumors with the lowest levels of MHC expression experienced inferior prognosis overall among a cohort of cHL patients with uniform treatment. The reduction in antigen presentation in Hodgkin's lymphoma in light of it's high overall response rate challenges our understanding of the mechanisms of PD-1 inhibition. Further studies assessing how changes in antigen presentation impact response to PD-1 inhibition in lymphoma are needed. Studies in melanoma have identified acquired resistance patterns either through upregulation of alternative checkpoints such as CTLA-4, abrogating dependence on the PD-1 pathway, or similar mutations in B2M, or JAK1/2 that allow tumors to bypass the negative regulation of PD-1 inhibition[150,151]. Specifically, JAK1 and 2 mutations decrease response to interferon-γ, a negative regulator of tumor growth and inducer of PD-1 ligand expression. Meanwhile, B2M truncating mutations reduced surface MHC-1 expression, as seen similarly in cHL. Potential pathways to circumvent these resistance patterns include combination immunotherapy or using B2M and MHC-1 expression as a potential resistance biomarker.

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Drugs targeting other immune checkpoints and activators are currently under study. For example, drugs have targeted the killer-immune globulin receptors (kir) on NK-cells, the so-called “NK- checkpoint inhibitors”[152]. Additionally, toll-like receptor agonists and dendritic cell vaccines attempt to improve the presentation of tumor antigens to increase the amplitude and specificity of the T- and B-cell immune responses. Pre-clinical studies are ongoing using tumor-specific proteins as synthetic peptide vaccines combined with checkpoint blockade, allowing personalized cancer-specific vaccines augmented by anti-PD-1 therapies[153]. Ultimately, the goal of any cancer therapy is cure. Whether PD-1 antagonists will result in significant cure rates when combined with the right partners and longer follow up, remains to be seen.

8.1 Future directions

Antagonists to the PD-1 pathway were the first and most robust type of immune therapy, yet their future role in lymphoma remains unclear. Many forms of lymphoma such as cHL and PMBCL are highly curable, and therefore 1 to 5-year disease control is not an adequate benchmark for novel therapies. We foresee the immediate role of immunotherapy in lymphoma as diminishing the use of multi-drug salvage therapy, and simultaneously reducing the number of patients requiring autologous and allogeneic stem cell transplantation. As it stands, PD-1 inhibitors might be best used as immune adjuncts, alongside curative consolidation therapies, or as single agents in those with limited options or unable to tolerate conventional curative therapy. Improved understanding of tumor immunology will allow for rational immune combinations, as well as appropriate stopping points for PD-1 therapies in the future by consolidating with curative therapy, or by combining with tumor-specific immune responses through the use of unique tumor antigens or tumor-specific vaccines. One such approach currently under investigation involves immune stimulation with PD-1 inhibition combined with CAR-T cell therapy to serve the ultimate “one-two-punch”[154,155]. As the intersection between immunology and oncology continues to converge, the efficacy and selectivity of immune therapies, such as those targeting the PD-1 pathway, must improve. PD-1 therapy as a single agent has proven efficacious in a limited number of lymphoma subtypes including, cHL, PMBCL, NK/T cell lymphoma, and certain DLBCL subgroups. One common finding among many of these lymphoma subgroups is an inflammatory phenotype and often the presence of 9q24.1 alterations. The refinement of currently available biomarkers such as expression patterns of PD-1 and PDL-1, as well as genetic signatures such as the 9p alterations, may allow more selective use of PD-1 inhibition in the future as well as selection of populations most susceptible to this therapy.

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Article Highlights

- PD-1 is a surface receptor on T-cells. Binding to its ligands, PD-L1 or PD-L2, leads to a cascade of interactions that dampens the immune response and thus preventing overactivation of the immune system.
- Several lymphomas overexpress PD-1 ligands as a method for immune evasion. These include classical Hodgkin lymphoma, primary mediastinal B-cell lymphoma, T-cell lymphomas, and those associated with infections like EBV. In some cases, overexpression of PD-1 ligands are due to alterations in chromosome 9p24.1, which contains the genetic loci for PD-L1, PD-L2, and Jak2.
- PD-1 inhibitors, pembrolizumab and nivolumab, are FDA-approved for use in many tumors including relapsed classical Hodgkin lymphoma.
- Many studies are underway to assess the role of inhibitors of the PD-1/PD-L1 pathway in the treatment of lymphomas, including some with very promising results.
- We foresee that PD1/PD-L1 inhibitors may be used alongside curative therapies, as immune adjuncts, or as single agents for those who cannot tolerate conventional therapy. They will likely provide alternative options forsalvage therapy in the treatment of relapsed disease.
- Further studies are needed to understand the complexity of immune regulation in the setting of malignancy to optimize outcome and minimize treatment-related adverse events.

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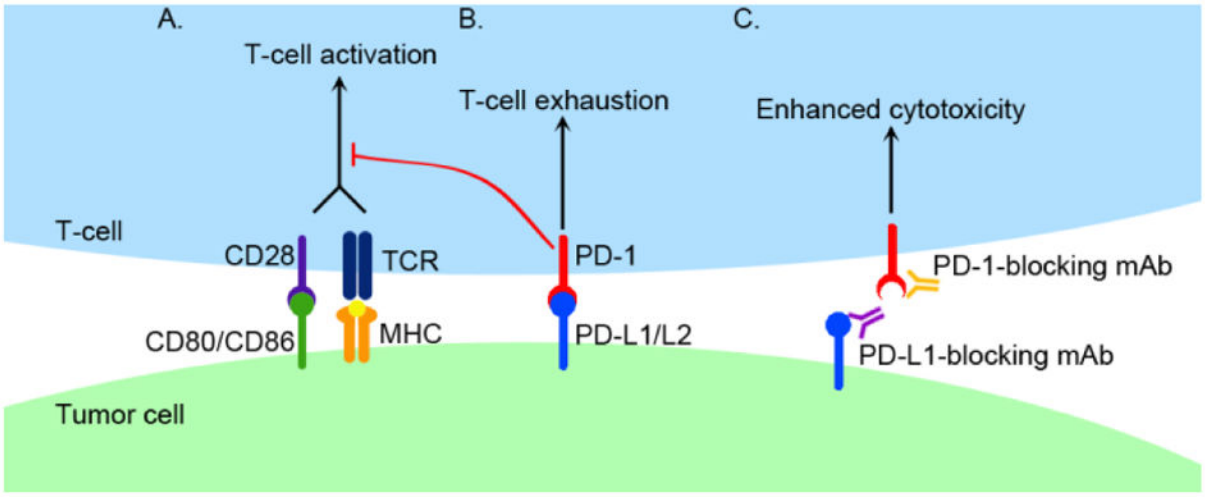

Figure 1.

Effects of PD-1 and PD-1 inhibition on T-cell activation. A. Antigen (yellow) presentation by MHC (orange) to the T-cell receptor (TCR, dark blue) and interaction between CD28 (purple) and CD80 or CD86 (green) leads to T-cell activation. B. Engagement of PD-1 (red) with PD-L1 or PD-L2 (light blue) inhibits T-cell activation and promotes T-cell exhaustion. C. Blockade of the interaction between PD-1 and its ligands by anti-PD1 and anti-PD-L1 monoclonal antibodies restores T-cell function and leads to enhanced cytotoxicity.

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Table 1

Available Clinical Trial Results of PD-1 and PD-L1 in lymphoma

Study Title	Identifier	Intervention	Planned enrollment	Population(s) (n)	ORR n (%)	CR n (%)	SD n (%)	PFS	OS	AEs n (%)	
Nivolumab											
Multiple Phase 1 Safety Cohorts of Nivolumab Monotherapy or Nivolumab Combination Regimens Across Relapsed/Refractory Hematologic Malignancies[55,92,95]	NCT01592370 Phase 1	Nivolumab 1 or 3 mg/kg weeks 1 and 4, then q 2 wk	375	rr cHL (23)	20/23 (87%)	5/23 (17%)	3/23 (13%)	86% (6 mo)	--	**Grade ≥3**	
				rr B-NHL (31)	8/31 (26%)	3/31 (10%)	16/31 (52%)	23 wk		Pneumonitis	3 (4%)
				DLBCL (11)	4/11 (36%)	2/11 (18%)	3/11 (27%)	7 wk		Anemia	3 (4%)
				FL (10)	4/10 (40%)	1/10 (10%)	6/10 (60%)	NR		Leukopenia	3 (4%)
				Other B-NHL (10)	0/10 (0%)	0/10 (0%)	7/10 (70%)	11 wk		Rash	1 (1%)
				rr T-NHL (23)	4/23 (17%)	0/23 (0%)	10/23 43%)	10 wk		Blood creatine phosphokinase increased	1 (1%)
				MF (13)	2/13 (15%)	0/13 (0%)	9/13 (69%)	10 wk		Lipase increased	1 (1%)
				PTCL (5)	2/5 (40%)	0/5 (0%)	0/5 (0%)	14 wk		Mucosal	1 (1%)
				Other CTCL (3)	0/3 (0%)	0/3 (0%)	0/3 (0%)	7 wk		Inflammation	
				Other non-CTCL (2)	0/2 (0%)	0/2 (0%)	1/2 (50%)	10 wk		Stomatitis	1 (1%)
										Diplopia	1 (1%)
				rr MM (27)	1/27 (4%)	1/27 (4%)	17/27 (63%)	10 wk		Pneumonia	1 (1%)
										Pulmonary embolism	1 (1%)
										Sepsis	1 (1%)
										ARDS	1 (1%)
										Lymphopenia	1 (1%)
										Neutropenia	1 (1%)
										Eosinophilia	1 (1%)
		Nivolumab 3 mg/kg + ipilimumab 1 mg/kg IV q 3 weeks × 4 doses, then nivo monotherapy (3 mg/kg) every 2 weeks		rr cHL (31)	23/31 (74%)	6/31 (19%)	3/31 (10%)	NR	NR	**All Grades**	
				rr B-NHL (15)	3/15 (20%)	0/15 (0%)	1/15 (7%)	1.5 mo	2.9 mo	Fatigue	17 (26%)
				DLBCL (10)	--	--	--	--	--	Pyrexia	15 (23%)
				FL (5)	--	--	--	--	--	Diarrhea	12 (18%)
				rr T-NHL (11)	1/11 (9%)	0/11 (0%)	4/11 (36%)	2 mo	13.2 mo		
				CTCL (7)	--	--	--	--	--		
				PTCL (4)	--	--	--	--	--		

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Study Title	Identifier	Intervention	Planned enrollment	Population(s) (n)	ORR n (%)	CR n (%)	SD n (%)	PFS	OS	AEs n (%)	
				rr MM (7)	0/7 (0%)	0/7 (0%)	1/7 (14%)	2.2 mo	7.6 mo		
Study of Nivolumab in Patients With Classical Hodgkin's Lymphoma (Registrational) (CheckMate 205)[70]	NCT02181738 Phase 2	Nivolumab 3 mg/kg q 2 weeks	294	rr cHL (failure to ASCT and BV) (80)	53/80 (66.3%)	7/80 (8.8%)	46/80 (57.5%)	76.9% (6 mo)	98.7% (6 mo)	**All Grades**	
										Fatigue	20 (25%)
										Infusion reaction	16 (20%)
										Rash	13 (16%)
										Arthralgia	11 (14%)
										Pyrexia	11 (14%)
										Nausea	10 (13%)
										Diarrhea	8 (10%)
										Pruritus	8 (10%)
A Study of Brentuximab Vedotin Combined With Nivolumab for Relapsed or Refractory Hodgkin Lymphoma[82]	NCT02572167 Phase 1/2	Nivolumab 3 mg/kg + BV 1.8 mg/kg	92	rr cHL (25 enrolled; 23 received treatment; 6 completed)	6/6 (100%)	3/6 (50%)	--	--	--	**All Grades**	
										Fatigue	8 (35%)
										Nausea	6 (26%)
										Rash	5 (22%)
										Dyspnea	4 (17%)
										Myalgia	4 (17%)
										Pruritus	4 (17%)
Brentuximab Vedotin and Nivolumab With or Without Ipilimumab in Treating Patients With Relapsed or Refractory Hodgkin Lymphoma[83]	NCT01896999	Nivolumab 3 mg/kg + BV 1.2 mg/kg or 1.8 mg/kg	189	rr cHL (19; 12 evaluable for response)	12/12 (100%)	8/12 (66%)	--	8.5 mo	NR	**Grade ≥3**	
										1.2 mg/kg	
										Pruritus	1
										Rash	1
										1.8 mg/kg	
										Typhilitis	1
										Pneumonitis	1
Nivolumab With Ibrutinib for Relapsed, Refractory or High-Risk	NCT02420912 Phase 2	Nivolumab 3 mg/kg q 2 wk + ibrutinib 420 mg daily	72	Relapsed CLL (5)	3/5 (60%)	0/5 (0%)	1/5 (20%)	--	--	**All Grades**	
				RT (4)	2/4 (50%)	0/4 (0%)	1/4 (25%)			Thyroiditis	1 (8%)

Study Title	Identifier	Intervention	Planned enrollment	Population(s) (n)	ORR n (%)	CR n (%)	SD n (%)	PFS	OS	AEs n (%)	
Untreated Patients With Chronic Lymphocytic Leukemia (CLL)[90]				CLL with PR on ibrutinib (3)	3/3 (100%)	0/3 (0%)	0/3 (0%)			Tumor flare	1 (8%)
PD-1 blockade with nivolumab in relapsed/refractory primary central nervous system and testicular lymphoma[99]	Case series	Nivolumab 3 mg/kg q 2 weeks ± rituximab or radiation	5	Primary refractory PCNSL (1) Recurrent PCNSL (3) CNS recurrence of PTL (1)	5/5 (100%) [radiographic response]	4/5 (80%) [radiographic response]	--	13+ to 17+ mo	--	**All Grades** Pruritus – G2 Fatigue – G2 Worsened baseline renal insufficiency – G4	 1 1 1
Pembrolizumab											
A Trial of Pembrolizumab (MK-3475) in Participants With Blood Cancers (MK-3475-013) (KEYNOTE-013)[68,102]	NCT01953692 Phase 1b	Pembrolizumab 10 mg/kg q 2 weeks	222	rr cHL (after BV) (31)	20/31 (65%)	5/31 (16%)	7/31 (23%)	69% (24 wk)	100% (24 wk)	**Grade ≥ 3** AST/ALT increased Axillary pain Back pain Colitis Joint swelling Nephrotic syndrome	 1 (3%) 1 (3%) 1 (3%) 1 (3%) 1 (3%) 1 (3%)
		Pembrolizumab 200 mg q 3 weeks	222	rrPMBCL (19)	7/17 (41%)	2/17 (12%)	6/17 (35%)	--	--	**Grade ≥3** Neutropenia VOD	 1 (6%) 1 (6%)
Study of Pembrolizumab (MK-3475) in Participants With Relapsed or Refractory Classical Hodgkin Lymphoma (MK-3475-087/ KEYNOTE-087)[69]	NCT02453594 Phase 2	Pembrolizumab 200 mg q 3 weeks	210	rr cHL (210) ASCT+BV (69) Salvage +BV (81) ASCT (60)	145/210(69%) 51/69 (73.9%) 52/81 (64.2%) 42/60 (70%)	47 (22%) 15/69 (22%) 20/81 (25%) 12/60 (20%)	31 (15%) 11 (16%) 10 (12%) 10 (17%)	63.4% (9 mo)	97.5% (9 mo)	**Grade ≥3** Neutropenia Vomiting Dyspnea Hypothyroidism Pyrexia Cough Fatigue	 5 (2%) 2 (1%) 2 (1%) 1 (0.5%) 1 (0.5%) 1 (0.5%) 1 (0.5%)

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Study Title	Identifier	Intervention	Planned enrollment	Population(s) (n)	ORR n (%)	CR n (%)	SD n (%)	PFS	OS	AEs n (%)	
Pembrolizumab Alone or With Idelalisib or Ibrutinib in Treating Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia or Other Low-Grade B-Cell Non-Hodgkin Lymphomas[89]	NCT02332980 Phase 2	Pembrolizumab 200 mg q 3 weeks (± ibrutinib or idelalisib)	68	Relapsed CLL (16) RT (9)	0/16 (0%) 4/9 (44%)	0/16 (0%) 1/9 (11%)	5/13 (38%) 4/9 (44%)	2.4 mo 5.4 mo	11.2 mo 10.7 mo	**Grade ≥3** Platelet count decreased Anemia Neutrophil count decreased Dyspnea Fatigue Febrile neutropenia Fever Hypoxia Rash maculopapular	 5 (20%) 5 (20%) 5 (20%) 2 (8%) 2 (8%) 2 (8%) 1 (4%) 2 (8%) 1 (4%)
Study of Rituximab Plus Pembrolizumab (MK-3475) in Subjects With Relapsed Follicular Lymphoma[93]	NCT02446457 Phase 2	Rituximab 375 mg/m2 IV weekly × 4 doses + Pembrolizumab 200 mg q 3 weeks	100	FL (27)	12/15 (80%)	9/15 (60%)	--	NR	NR	**Grade ≥3** Nausea Infusion reaction Aseptic meningitis Pneumonia	 2 (8%) 2 (8%) 1 (4%) 1 (4%)
Pembrolizumab in Treating Patients With Relapsed or Refractory Stage IB-IVB Mycosis Fungoides or Sezary Syndrome[110]	NCT02243579 Phase 2	Pembrolizumab 2 mg/kg q 3 weeks	24	SS (15) MF (9)	4/15 (27%) 5/9 (56%)	0/15 (0%) 1/9 (11%)	7/15 (47%) 2/9 (22%)	NR	--	**Grade ≥3** Skin flare reaction Diarrhea	 4 (17%) 2 (8%)
PD1 blockade with pembrolizumab is highly effective in relapsed or refractory NK/T-cell lymphoma failing l-asparaginase[109]	Case series	Pembrolizumab 2 mg/kg q 3 weeks (1 patient received q 2 weeks)	7	NK/T lymphoma (7)	7/7 (100%)	5/7 (71%) 3/7(clinical + radiologic CR only)	--	--	--	**All Grades** Skin GVHD—G2	 1
Atezolizumab											
A Safety and Pharmacology Study of Atezolizumab (MPDL3280A) Administered With Obinutuzumab or Tazemetostat in Participants With Relapsed/Refractory Follicular Lymphoma and Diffuse Large B-cell Lymphoma[94,103]	NCT02220842 Phase 1b	Cycle 1: Obinutuzumab Days 1, 2, 8, and 15 Cycles 2–8: atezolizumab 1200 mg + obinutuzumab 1000 mg Day 1 q 3 weeks Consolidation: atezolizumab 1200 mg q3 weeks × 6 mo	92	FL (26) DLBCL (23)	(57%) (16%)	--	--	--	--	**Grade ≥3** Pain Anemia Neutropenia	 4 (8.2%) 3 (6.1%) 3 (6.1%)

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AE = adverse event; ASCT = autologous stem cell transplant; B-NHL = B cell non Hodgkin lymphoma; BV = brentuximab vedotin; cHL = classic Hodgkin lymphoma; CLL = chronic lymphocytic leukemia; CR = complete response; DLBCL = diffuse large B cell lymphoma; FL = follicular lymphoma; MM = multiple myeloma; MF = mycosis fungoides; NR = not reached; ORR = objective response rate; OS = overall survival; PMBCL = primary mediastinal B cell lymphoma; PCNSL = primary CNS lymphoma; PFS = progression free survival; PR = partial response; PTL = primary testicular lymphoma PTCL = peripheral T cell lymphoma; RR = relapsed/refractory; RT = Richter transformation; SD = stable disease; SS = Sezary syndrome; T-NHL = T cell non Hodgkin lymphoma; VOD = veno-occlusive disease

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Table 2

PD-1 and PD-L1 inhibitors approved for clinical use

Drug	Mechanism/Target	FDA-Labeled Indications (September 2017)
Nivolumab (Opdivo, BMS-936558, MDX-1106, ONO-4538)	Human IgG4 antibody directed against PD-1 receptor	• Classical Hodgkin lymphoma (relapsed or refractory) • Colorectal cancer (metastatic, microsatellite instability-high or mismatch repair deficient) • Melanoma (unresectable or metastatic) • Non-small cell lung cancer (metastatic, progressive) • Renal cell cancer (advanced) • Squamous cell head and neck cancer (recurrent or metastatic) • Urothelial carcinoma (locally advanced or metastatic)
Pembrolizumab (Keytruda, MK-3475, SCH 900475)	Humanized IgG4 antibody directed against PD-1 receptor	• Classical Hodgkin lymphoma (relapsed or refractory) • Melanoma (unresectable or metastatic) • Microsatellite instability-high cancer (unresectable or metastatic) • Non-small cell lung cancer (metastatic) • Squamous cell head and neck cancer (recurrent or metastatic) • Urothelial carcinoma (locally advanced or metastatic) • Gastric or gastroesophageal junction adenocarcinoma (Recurrent locally advanced or metastatic)
Atezolizumab (Tecentriq, MPDL3280A, RG7446, RO5541267)	Human Fc optimized monoclonal antibody directed against PD-L1	• Non-small cell lung cancer (metastatic) • Urothelial carcinoma (locally advanced or metastatic)
Durvalumab (Imfinzi, MEDI4736)	Fc optimized monoclonal antibody directed against PD-L1	• Urothelial carcinoma (locally advanced or metastatic)
Avelumab (Bavencio, MSB0010718C)	Human IgG1 monoclonal antibody directed against PD-L1	• Merkel cell carcinoma (metastatic) • Urothelial carcinoma (locally advanced or metastatic)