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Pembrolizumab in classical Hodgkin's lymphoma

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Abstract

Pembrolizumab is a humanized monoclonal antibody directed against programmed cell death protein 1 (PD-1), a key immune-inhibitory molecule expressed on T cells and implicated in CD4+ T-cell exhaustion and tumor immune-escape mechanisms. Classical Hodgkin's lymphoma (cHL) is a unique B-cell malignancy in the sense that malignant Reed–Sternberg (RS) cells represent a small percentage of cells within an extensive immune cell infiltrate. PD-1 ligands are upregulated on RS cells as a consequence of both chromosome 9p24.1 amplification and Epstein–Barr virus infection and by interacting with PD-1 promote an immune-suppressive effect. By augmenting antitumor immune response, pembrolizumab and nivolumab, another monoclonal antibody against PD-1, have shown significant activity in patients with relapsed/refractory cHL as well as an acceptable toxicity profile with immune-related adverse events that are generally manageable. In this review, we explore the rationale for targeting PD-1 in cHL, review the clinical trial results supporting the use of checkpoint inhibitors in this disease, and present future directions for investigation in which this approach may be used.

Keywords

Hodgkin's lymphoma; immune checkpoint inhibitors; pembrolizumab

Classical Hodgkin's lymphoma

Classical Hodgkin's lymphoma (cHL) is a monoclonal B-cell lymphoid neoplasm characterized by the presence of a variable percentage of malignant Reed–Sternberg (RS) cells within an extensive immune cell infiltrate (1, 2). Patients with newly diagnosed limited-stage cHL treated with standard frontline chemotherapy have 5-yr progression-free survival (PFS) rates of 83–98% (3, 4), while those with advanced-stage cHL have 5-yr PFS rates of 71–86% (5, 6). The standard treatment approach for medically fit patients with relapsed/refractory disease is salvage chemotherapy followed by autologous stem cell transplant (ASCT) which provides 5-yr PFS rates of 50–60% for those patients with chemosensitive

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disease, and 40–45% in patients with primary refractory cHL (7–9). Depending on the presence of risk factors at the time of transplant, nearly half patients with cHL undergo high-dose chemotherapy followed by ASCT relapse (10, 11).

The outcome for patients with cHL relapsing after ASCT is poor with a median overall survival (OS) of 1–2 yr (12). Although the existence and importance of graft-versus-lymphoma effect remains debatable and supported only by indirect evidence, retrospective and small prospective studies support the role of allogeneic stem cell transplant as the only curative option for these patients (13, 14). The relapse rate post-allogeneic transplant differs slightly depending on the conditioning regimen used (i.e., myeloablative vs. reduced intensity), but the 3-yr OS rates are similar (45–66%) (14–16).

In the non-curative setting, many agents can be used in sequence or in combination to provide disease control. Specific options include single-agent chemotherapy (e.g., gemcitabine, vinblastine, etoposide, vinorelbine, liposomal doxorubicin, bendamustine), immunomodulatory agents (e.g., lenalidomide), histone deacetylase inhibitors (vorinostat and panobinostat), mechanistic target of rapamycin inhibitors (e.g., everolimus), involved-field radiation, enrollment in a clinical trial, and observation (17–23). Combination chemotherapy regimens can be considered in selected patients, specifically for those who are symptomatic and/or need to achieve optimal pre-allogeneic transplant cytoreduction; however, this approach is associated with significant hematologic and non-hematologic toxicity (24–26). The sequence of these agents depends on goal of treatment, patient's performance status, physician preference, and risk of therapy-related toxicity such as myelodysplastic syndrome/acute myeloid leukemia (27), but clearly the treatment of this patient population remains challenging (12, 27, 28).

Recent advances in our understanding of cHL pathogenesis, interaction with tumor microenvironment, and immune-escape mechanisms have led to the identification of novel therapeutic targets. A breakthrough in the treatment of patients with relapsed/refractory cHL came with the introduction of brentuximab vedotin (BV) which is a monoclonal antibody anti-cluster of differentiation (CD) 30 conjugated to monomethyl auristatin E, a microtubule-disrupting agent. BV was approved by the Food and Drug Administration (FDA) in 2011 based on the results of a phase II trial in which 102 patients with relapsed/refractory cHL were treated with 1.8 mg/kg every 3 wk for a maximum of 16 cycles. BV was overall well tolerated, the overall response rate (ORR) was 75% [34% complete response (CR)], the median PFS was 9.3 months, and the median duration of response was 22.4 months with prolonged response in those patients achieving a CR (29, 30).

In general, the tumor microenvironment is characterized by the presence of tumor-infiltrating immune cells. This immune cell population is comprised of a variable percentage of 'tolerant T cells' due to the interaction between inhibitory molecules on tumor cells surface and their corresponding targets on T cells (T-cell exhaustion) (31). Specifically in cHL, RS cells aberrantly express programmed cell death-1 ligand (PD-L1) on the cell surface, and by engaging PD-1 on immune effector cells, RS cells evade antitumor immune response (32–34).

Therapeutic strategies targeting immune checkpoints have shown significant clinical activity in solid tumors and hematologic malignancies by enhancing T-cell activation and inducing T-cell-mediated antitumor response (34–44). In cHL, 2 monoclonal antibodies directed against PD-1, nivolumab and pembrolizumab, are the most promising thus far (34, 45–50). Herein, we describe the rationale for utilizing immune checkpoint inhibitors in patients with relapsed/refractory cHL focusing on the novel monoclonal antibody pembrolizumab and how the development of these new agents is reshaping the care of this patient population.

Biology of immune checkpoints and RS cells' immune-escape mechanisms

T-cell activation requires an antigen-specific signal provided through the interaction of the T-cell receptor and the antigen-containing major histocompatibility complex (MHC). Additionally, antigen-independent signaling is also required and mediated by the interaction of costimulatory molecules on antigen-presenting cells (APCs) [CD80 and CD86, CD70, B- and T-lymphocyte attenuator (BTLA), inducible costimulator ligand, OX40L (CD134L), CD153] and their corresponding receptors on T cells [CD28, CD27, herpesvirus entry mediator (HVEM), inducible costimulator, OX40 (CD134), CD30] (Table 1) (51). T cells also express a number of surface co-inhibitory receptors [PD-1, cytotoxic T-lymphocyte-associated protein 4 (CTLA4), lymphocyte-activation gene 3, BTLA, T-cell immunoglobulin and mucin domain-containing-3 (TIM-3)] and by interacting with their corresponding ligands on APCs [PD-L1 and PD-L2, CD80 and CD86, MHC class II, HVEM, galectin-9] attenuate T-cell response and promote T-cell tolerance (Table 1) (51).

The most clinically relevant checkpoint molecules to date are PD-1 and CTLA4 with preclinical data suggesting that the inhibitory signal mediated by PD-1 interaction is more effective than that mediated by CTLA4 engagement (52–54). The gene encoding PD-L1 is located on chromosome 9 which is the target of recurrent genetic abnormalities more commonly seen in nodular sclerosis cHL (34). Polysomy of chromosome 9p, 9p copy gain, and 9p24.1 amplification lead to PD-L1 overexpression in cHL (32, 34). Furthermore, the 9p24.1 amplicon also includes the gene encoding janus kinase 2 whose overexpression further increases PD-L1 transcription (32, 34, 37). Epstein–Barr virus (EBV) which is implicated in the pathogenesis of 10–40% of cHLs depending on subtype (1) also induces PD-L1 expression via activator protein-1 and JAK/signal transducers and activators of transcription (STAT) signaling (33). By engaging with PD-1, PD-L1 delivers a potent immune-suppressive signal characterized by decreased T-cell proliferation, modulation of cytokine release, and increased susceptibility to apoptosis (Fig. 1) (55, 56). In addition, PD-L1 also competitively binds to the CD28 ligand, CD80, decreasing the stimulatory signal mediated by CD80/CD28 interaction and further inhibiting T-cell proliferation and cytokine production (Fig. 1) (57, 58).

The most abundant cells found in the surrounding inflammatory cHL infiltrate consist of CD4+ T cells with a T-helper 2 (Th2) and T regulatory (Treg) phenotype (59). RS cells typically secrete cytokines [chemokine (C-C motif) ligand 5 (CCL5), chemokine (C-C motif) ligand 22 (CCL22), chemokine (C-C motif) ligand 17 (CCL17)] that attract Th2 and Tregs to the tumor microenvironment (58). In turn, these Th2 cells provide continuous CD40L stimulation and release a number of cytokines [interleukin-4 (IL-4), interleukin-5

(IL-5), interleukin-6 (IL-6), interleukin-10 (IL-10), interleukin-13 (IL-13)] that promote RS cells survival and proliferation (59). By inhibiting cytotoxic T lymphocytes and disrupting the Th1/Th2 balance, the interaction between Th2, Tregs, and RS cells facilitates tumor cells' immunologic escape and suggests that cHL cells might be vulnerable to agents capable of restoring the host immune system.

Anti-PD-1 monoclonal antibodies in cHL

Nivolumab

Nivolumab (formerly ONO-4538, BMS-936558, MDX1106, trade name Opdivo; Bristol-Myers Squibb), a fully human IgG4 monoclonal antibody directed against PD-1 (58), initially demonstrated single-agent activity in solid tumors. Two trials, the CheckMate 057 for patients with advanced previously treated non-small-cell lung carcinoma (NSCLC) (40) and the CheckMate 066 for patients with untreated unresectable stage III–IV melanoma (44), led to FDA approval of nivolumab at a dose of 3 mg/kg every 2 wk in these diseases.

The importance of microenvironment in the maintenance of RS cells' survival and proliferation and the presence of tolerant T cells in the immune cell infiltrate, as well as PD-L1 overexpression on a subset of RS cells, led to the inclusion of patients with relapsed/refractory cHL in a phase I dose-escalation trial of single agent nivolumab in patients with relapsed/refractory hematologic malignancies. The results of this trial published in 2015 (34) were recently updated at the 2015 American Society of Hematology (ASH) Annual Meeting (45). Twenty-three patients with cHL (22 with nodular sclerosis and 1 with mixed cellularity) were enrolled in this study: 15 of them (65%) received >4 lines of chemotherapy prior to enrollment, 18 patients (78%) received previous treatment with BV, and 18 patients (78%) had undergone previous ASCT. Patients were treated with single agent nivolumab at 3 mg/kg at week 1 and 4, then every 2 wk until disease progression or CR or for a maximum of 2 yr. The median number of doses received during study was 16 (range 6–37). The ORR was 87% with six patients achieving a CR (26%). Of the 20 patients who responded, only 12 (60%) had the first response by week 8 suggesting a delayed effect, and 10 of these achieved durable responses (median 65 wk, range 41.7–90.7). Of the 10 remaining patients, four progressed, one discontinued treatment with no evidence of disease progression, and five patients discontinued to undergo stem cell transplant. Interestingly, one patient who originally achieved a CR and discontinued therapy was successfully retreated at relapse 43 wk later and again achieved a CR (34).

Seventy-eight percent of the patients experienced grade 2–3 drug-related toxicity, most common being rash (22%) and thrombocytopenia (17%) with three patients discontinuing treatment due to adverse events (grade 2 peripheral neuropathy, grade 3 myelodysplastic syndrome, grade 3 pancreatitis). Grade 3 or 4 adverse events were observed in 12 patients (52%) although none of the grade 4 events were thought to be related to nivolumab treatment, and the incidence of drug-related adverse events did not increase with time on treatment (34, 45). Correlative assessment from 10 cHL patients with available tumor specimens showed copy number gains in PD-L1/PD-L2 genes, overexpression of PD-L1 and PD-L2 on RS cells, active JAK/STAT signaling, and low levels of PD-1 on infiltrating T cells. Only one of 10 tumor samples was determined to be EBV-positive. These results

prompted the FDA to designate nivolumab as a breakthrough therapy for cHL following ASCT and BV, and a confirmatory phase II study with nivolumab in patients with relapsed/refractory cHL is under way (NCT02181738).

Pembrolizumab

Pembrolizumab (formerly MK-3475 and lambrolizumab, trade name Keytruda; Merck Oncology) is a humanized IgG4 antibody directed against PD-1 and, as nivolumab, blocks the binding of both PD-L1 and PD-L2 to their target (60). However, compared to nivolumab, pembrolizumab has been shown to have higher affinity to PD-1 (KD, equilibrium dissociation constant, for pembrolizumab 0.028 nM compared to 2.6 nM for nivolumab) (61). Similar to nivolumab, pembrolizumab is currently FDA approved for treatment of patients with relapsed/refractory melanoma who are no longer responding to other drugs (42) and patients with metastatic NSCLC whose tumors express PD-L1 and have failed prior standard chemotherapy (43).

In the initial clinical trial that subsequently led to FDA approval, pembrolizumab was given at 10 mg/kg every 2 wk, 10 and 2 mg/kg every 3 wk to 135 patients with metastatic melanoma. The study was not powered to compare the efficacy between study arms, and although the 10 mg/kg every 2 wk schedule was associated with higher response rates, it was also associated with higher prevalence of adverse events (23% vs. 4% vs. 9%, respectively). The ORR was 38% and the PFS longer than 7 months. Overall, 13% of the patients reported drug-related adverse events, and grade 3–4 treatment-related autoimmune processes were uncommon (AST increase two patients; nephritis two patients; hypothyroidism one patient; colitis one patient). Based on these results, the dosing schedule of 2 mg/kg every 3 wk was chosen for FDA approval (39).

In NSCLC, the KEYNOTE-001 trial led to pembrolizumab approval in this disease as it demonstrated an acceptable side-effect profile and showed significant antitumor activity. Pembrolizumab was given at 10 mg/kg every 2 wk, 10 and 2 mg/kg every 3 wk to 495 patients with advanced NSCLC (43). The ORR was 19.4%, and the PFS was 3.7 months with longer duration of response in those patients who had at least 50% pf tumor cells positive for PD-L1. Overall, 9.5% of the patients reported adverse events of grade 3 or higher. Grade 3–4 treatment-related autoimmune/inflammatory processes were uncommon (infusion reaction in 1 patient; elevation of AST/ALT in five patients; hypothyroidism in one patient; pneumonitis in nine patients; colitis in three patients). The recommended dosing schedule based on this study was also 2 mg/kg every 3 wk.

Given the responses in solid tumors and the emerging clinical data in cHL, patients with relapsed/refractory cHL were included as a cohort of an ongoing, multicenter, phase Ib trial of pembrolizumab in hematologic malignancies (NCT01953692, KEYNOTE-013). Thirty-one patients were evaluable for analysis at the most recent update (48). Median age was 32, 21 patients (68%) received greater than three lines of chemotherapy, by design all the patients had failed prior treatment with BV and 22 patients (71%) had failed prior ASCT, 10 patients (32%) received prior radiation therapy. Patients were treated with single agent pembrolizumab at 10 mg/kg administered every 2 wk until disease progression or up to 2 yr or unacceptable toxicity. Treatment response was evaluated by computed tomography/

positron emission tomography at 12 wk and then every 8 wk. The ORR at 12 wk was 65% with five patients achieving a CR (16%) and 15 a partial response (PR) (48%). ORR was 73% (CR 14%) for patients who failed ASCT compared to 44% (CR 22%) for those who were transplant ineligible or refused ASCT. Additionally, the rate of progressive disease while on therapy was higher in the ASCT ineligible/refusal group (22%) compared to the ASCT failure group (9%). Eighty percent of responses occurred by week 12, and PFS at 24 wk was 69% (62). At the time data were presented, the median duration of response was not reached. Two patients (6%) discontinued for toxicity, 12 (39%) for disease progression, and 3 (10%) for reasons that were not reported (47, 48).

Treatment with pembrolizumab was overall well tolerated. The most common treatment-related adverse events were hypothyroidism (16%), diarrhea (13%), and pneumonitis (10%). Although no grade 4 or 5 adverse events were reported, 5 patients (16%) experienced grade 3 adverse events including elevated liver enzymes (one patient), colitis (one patient), nephrotic syndrome (one patient), and axillary pain (one patient). Two patients discontinued treatment due to grade 3 adverse events, one pneumonitis, and one nephrotic syndrome (47, 48).

Immunohistochemistry of pretreatment tumor tissue from 11 evaluable patients showed that 10 (91%) were positive for PD-L1 and all of them were positive for PD-L2. Peripheral blood immunophenotyping in these patients demonstrated an increase in absolute numbers of circulating CD4+ and CD8+ T cells and natural killer cells. Further, gene expression studies showed that pembrolizumab promoted the activation of interferon-gamma and other pathways involved in regulation and differentiation of immune cells (47, 48).

Although pembrolizumab was overall well tolerated in a limited series of patients with relapsed/refractory cHL (48), treatment has been associated with a variety of immune adverse reaction that usually can be managed with close observation/supportive care, steroids, or treatment delay depending on the severity of the reaction. In the attempt to reduce the incidence of adverse reaction as well as the high cost of immunotherapy, ongoing efforts are examining the activity of lower doses/shorter course of pembrolizumab in this patient population. In a recently published case report, two patients with relapsed/refractory cHL were treated with 2 mg/kg every 3 wk of pembrolizumab for 4–6 doses. Both patients received prior treatment with BV, and only one patient underwent prior ASCT. One patient achieved a CR and the other a near CR, and both patients tolerated treatment well with no adverse events reported and remained asymptomatic at 23 and 28 wk after initial treatment, suggesting that this approach warrants further investigation (49).

Anti-PD-1 monoclonal antibodies in combination with other agents

While we are waiting for more mature data on safety and activity of single agent pembrolizumab in relapsed/refractory cHL after ASCT, there are ongoing efforts to assess the activity of this antibody as pre-ASCT salvage therapy as well as its use in combination with other agents in this patient population (Table 2).

The rationale of combining immune checkpoint inhibitors with conventional chemotherapy is to enhance antitumor activity and to consolidate the response obtained with chemotherapy without significantly increasing the toxicity. As of today, no data are available if treatment with immune checkpoint inhibitors should precede, be concomitant, or follow conventional chemotherapy. Actively recruiting and future clinical trials will most likely address most of these questions.

Another interesting area of ongoing research is the possibility of combining different immune checkpoint inhibitors given concomitantly or sequentially in the attempt to maximize the immune-mediated antitumor response. This has been done in melanoma patients treated with nivolumab and ipilimumab, an anti-CTLA4 antibody, and although the PFS was longer in the combination treatment arm, also the treatment-related adverse events were significantly higher in this group, compared to either single-agent approach (41).

Ongoing preclinical and clinical research has been exploring the activity of checkpoint inhibitors in combination with immune modulators and targeted therapies in hematologic malignancies. Lenalidomide is an immune modulator with single-agent activity in relapsed/refractory cHL patients with a reported ORR ranging from 14% to 50% (17). Correlative studies in a trial of lenalidomide and rituximab in relapsed low grade B-cell non-Hodgkin's lymphoma demonstrated increased CD8+ T cells, PD-1+ T cells, and NK cells as well as decreased Tregs in the peripheral blood of patients receiving lenalidomide providing the rationale of combining lenalidomide with checkpoint inhibitors (63). This combination is currently being explored in multiple myeloma (pembrolizumab + lenalidomide, NCT02036502, NCT0257 9863) and in patients with lymphoid malignancies post-allogeneic or ASCT (lenalidomide + ipilimumab, NCT01 919619).

Despite the lack of a number of components of the B-cell receptor machinery (BCR), preclinical studies in RS cells have demonstrated heterogeneous expression of components of the BCR signaling pathway such as Bruton tyrosine kinase (Btk), Lck/Yes novel tyrosine kinase (Lyn), and spleen tyrosine kinase (Syk) and constitutive activation of BCR downstream pathways such as phosphatidylinositol-3-kinase/protein kinase B (PI3K/AKT) and that inhibition of PI3K leads to cell cycle arrest and apoptosis of RS cells (64–66). Ibrutinib, an irreversible Btk inhibitor, has the ability to inhibit other kinases such as Lyn, Syk, Fyn, PI3K (66) as well as inhibits interleukin-2-inducible kinase (ITK) which is necessary for Th2 signaling and proliferation (67). As of today, there is only one case report describing the activity of single agent ibrutinib in two patients with relapsed/refractory cHL after allogeneic stem cell transplant (68); however, its potential cytotoxic effect on RS cells as well as its ability to cause a shift from Th2-mediated immunity to a Th1 response with prevention of tumor cells immunologic escape provides the rationale of combining ibrutinib with immune checkpoint inhibitors. The combination of ACP-196, a second-generation BTK inhibitor, and pembrolizumab is currently being explored in B-cell malignancies including cHL (NCT02362035).

Anti-PD-1 monoclonal antibody treatment before and after allogeneic stem cell transplant for cHL

Given that PD-1 inhibitors are now being used in hematologic malignancies in which allogeneic stem cell transplant is a viable treatment option, the effect of these agents on the incidence and severity of graft-versus-host disease (GVHD) as well as on graft-versus-tumor is an active area of investigation. Recently, the safety and efficacy of nivolumab has been evaluated in 12 relapsed/refractory cHL after allogeneic stem cell transplant. Seven of the eight evaluable patients had clinical benefit from treatment (4 PR and 3 CR). Grade III–IV skin acute GVHD occurred in two patients; however, both patients had prior history of grade II acute GVHD. One patient developed grade IV neutropenia and one patient grade III thrombocytopenia. At 60-month follow-up, nine patients are still on nivolumab, one patient discontinued due to progressive disease, and two patients discontinued due to acute GVHD (46). The safety and efficacy of reduced-intensity conditioning regimen (RIC) allogeneic stem cell transplant after treatment with PD-1 inhibitors was also recently evaluated in patients with lymphoid malignancies, including 11 patients with cHL. Although the patient population was small and heterogeneous and with a limited follow-up, this study suggests the efficacy of this approach in these patients as the relapse rate compares favorably to that expected for this cohort. Due to the reported risks of fatal GVHD and veno-occlusive disease, more safety data are needed before routinely planning allogeneic transplant after treatment with checkpoint inhibitors (69). Both these studies are retrospective in nature and include a small number of patients with a short follow-up; however, while we wait for more mature data, they do provide useful preliminary information about the use of PD-1 inhibitors before and after allogeneic stem cell transplant.

Conclusions and future perspectives

Both nivolumab and pembrolizumab have shown significant activity and acceptable toxicity profile in relapsed/refractory cHL, and although not yet FDA approved, PD-1 blocking agents already represent a viable, important treatment option for this difficult-to-treat patient population. By inhibiting the interaction between PD-L1 on tumor cells and PD-1 on T cells, these agents block one of the most important mechanisms known thus far to evade antitumor immune response (Fig. 1). Although response to PD-1 blocking agents seems to positively correlate with intensity of PD-L1 expression in solid tumors, limited data exist in cHL and correlation between PD-1 expression on tumor-infiltrating T cells, PD-L1 expression on RS cells, and treatment outcome needs to be evaluated in larger prospective studies. Both nivolumab and pembrolizumab are IgG4 monoclonal antibodies, and this structure presumably decreases the risk of classical complement pathway activation and subsequent inflammatory response without limiting their activity (70). Although pembrolizumab is reported to have higher affinity for its target compared to nivolumab (61), whether this translates into higher efficacy remains to be verified.

Despite our basic understanding of the mechanism of action of immune checkpoint inhibitors, their effect at protein and molecular level in immune cell subsets is incompletely characterized. Ongoing research in hematologic malignancies is focused on the ability of

novel agents such as epigenetic regulators to modulate the expression of targetable checkpoint molecules on the surface of either T cells or tumor cells, providing the rationale for combining these agents with immune checkpoint inhibitors (71–73). Furthermore, although much of the preclinical/clinical research has been focusing on the PD-1/PD-L1 and on the CTLA4/CD80–86 axis, as our knowledge of T-cell costimulatory and inhibitory molecules improves, many other potentially targetable molecules are being discovered and tested in preclinical studies (Table 1) opening the doors to future clinical studies.

We are just beginning to understand the complex interaction between tumor cells and immune system, and although there are many questions that remain to be answered, identification of novel targetable checkpoint molecules with development of new agents, prospective ongoing clinical trials on larger patient sample, and longer follow-up will add insight to the landscape of immunotherapy in lymphoid malignancies. For these reasons, continued participation in clinical trials should be encouraged.

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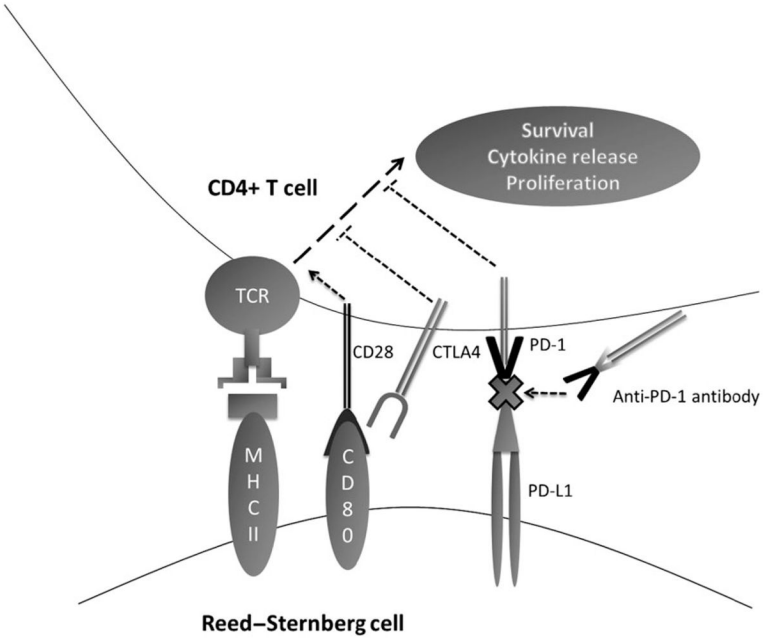

Figure 1.

This figure depicts the basic interaction between Reed–Sternberg cells and tumor-infiltrating CD4+ T cells. PD-1/PD-L1 interaction initiates a cascade of events that ultimately lead to T-cell exhaustion. This interaction is interrupted by the monoclonal antibodies against PD-1. CTLA4 competes with CD28 for the costimulatory ligand CD80. TCR, T-cell receptor; MHC II, major histocompatibility complex class II; PD-1/PD-L1, programmed cell death-1/programmed cell death-1 ligand; CTLA4, cytotoxic T-lymphocyte antigen; ⇢|, inhibitory signal; ⇢, stimulatory signal.

Table 1

Checkpoint molecules and ligands

T-cell molecules	Ligands on APCs	Type of signal
PD-1	PD-L1 and PD-L2	Inhibitory
CTLA4	CD80 and CD86	Inhibitory
BTLA	HVEM	Inhibitory
LAG-3	MHC class II	Inhibitory
TIM-3	Galectin-9	Inhibitory
CD134	CD134L	Stimulatory
CD30	CD30L	Stimulatory
ICOS	ICOSL	Stimulatory
CD28	CD80 and CD86	Stimulatory
CD27	CD70	Stimulatory
HVEM	BTLA	Stimulatory

APCs, antigen-presenting cells; PD-1, programmed cell death-1; PD-L1 and 2, programmed cell death ligands 1 and 2; CTLA4, cytotoxic T-lymphocyte antigen-4; BTLA, B- and T-lymphocyte attenuator; HVEM, herpesvirus entry mediator; LAG-3, lymphocyte-activation gene 3; MHC class II, major histocompatibility complex class II; TIM-3, T-cell immunoglobulin and mucin domain-containing-3; ICOS, inducible costimulator; ICOSL, inducible costimulator ligand.

Table 2

Clinical trials with pembrolizumab in cHL

Identifier	Phase	Population	Regimen	Status
NCT02453594	II	Relapsed or Refractory Classical Hodgkin Lymphoma	Monotherapy	Active, not recruiting
NCT02684292	II	Relapsed or Refractory Classical Hodgkin Lymphoma	Pembrolizumab vs. Brentuximab Vedotin	Not yet recruiting
NCT02362997	II	Consolidation after ASCT for Hodgkin Lymphoma and DLBCL	Consolidation therapy after autologous stem cell transplant (ASCT)	Recruiting
NCT02665650	I	Relapsed or Refractory Classical Hodgkin Lymphoma	Combination of AFM13 and Pembrolizumab	Not yet recruiting
NCT02595866	I	HIV and Relapsed/Refractory, or Disseminated Malignant Neoplasms (including cHL)	Monotherapy	Not yet recruiting
NCT02362035	I, II	B-cell Malignancies (including cHL)	Combination of ACP-196 and Pembrolizumab	Recruiting
NCT01953692	I	Hematologic Malignancies (including cHL)	Combination of Pembrolizumab and Epacadostat	Recruiting
NCT02453594	II	Hodgkin’s Lymphoma	Monotherapy	Ongoing, not recruiting