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Pembrolizumab and its role in relapsed/refractory classical Hodgkin's lymphoma: evidence to date and clinical utility

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Abstract: Immune evasion is a critical mechanism of malignant cell survival, and relies in part on molecular signaling through the programmed cell death 1 (PD-1)/PD-1 ligand (PD-L1) axis that contributes to T cell exhaustion. Immune modulatory therapy with monoclonal antibodies against PD-1 designed to enhance antitumor immune response have shown promise in the treatment of advanced solid tumors and hematologic malignancies. Classical Hodgkin's lymphoma (cHL), a unique B cell malignancy characterized by an extensive but ineffective immune cell infiltrate surrounding a small number of tumor cells, has shown significant response to anti-PD-1 directed therapy. The anti-PD-1 monoclonal antibodies nivolumab and pembrolizumab have shown similarly remarkable activity in relapsed/refractory cHL and have been approved by the Food and Drug Administration for treatment of this disease. In this article we review the rationale of targeting the PD-1/PD-L1 axis in cHL and the pharmacology of pembrolizumab, and summarize the data on activity and safety profile of this agent in the treatment of relapsed/refractory cHL. We also discuss the potential benefits and pitfalls of using PD-1 blockade in the setting of allogeneic stem-cell transplantation, and summarize ongoing prospective trials of single-agent pembrolizumab and combination strategies as well as future directions.

Keywords: checkpoint inhibitor therapy, Hodgkin's lymphoma, pembrolizumab

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Classical Hodgkin's lymphoma

Classical Hodgkin's lymphoma (cHL) is a lymphoproliferative malignant neoplasm that arises from clonal germinal center B cells. It represents around 10% of newly diagnosed lymphomas, with an estimated 8000 new cases and 1000 deaths in 2017 in the United States.[1] The disease exhibits a bimodal distribution, affecting primarily young adults around 15–34 years of age and older adults around age 60.[2] For early-stage cHL, combination chemotherapy regimens such as doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD) or doxorubicin, vinblastine, mechlorethamine, vincristine, bleomycin, etoposide, prednisone (Stanford V), with or without radiation therapy, are associated with 5-year progression-free survival (PFS) rates ranging from 79% to 90% or greater, depending on risk stratification.[3,4] For advanced-stage cHL, treatment with combination chemotherapy regimens such as ABVD, Stanford V and bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone (BEACOPP) leads to a 5-year failure-free survival of 71% for both ABVD and Stanford V,[5] and a 10-year PFS of 69% and 75% for ABVD and BEACOPP, respectively.[6] Nevertheless, up to 30% of cHL patients suffer from primary refractory disease or recurrence after front-line therapy.[7] In patients with chemosensitive relapse, salvage chemotherapy followed by autologous stem-cell transplant (SCT) leads to 5-year PFS rates of 50–60%,[8–12] compared with 5-year PFS rates of 40–45% for patients with primary refractory disease.[8–10] Unfortunately, up to half of the patients treated with autologous SCT ultimately relapse.[13]

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Brentuximab vedotin (BV) (Adcetris, Seattle Genetics, Bothell, WA, USA) is an immune-toxin conjugate composed of an anti-CD30 antibody linked to monomethyl auristatin, a compound with antitubulin activity. BV is currently approved for treatment of relapsed/refractory cHL after autologous SCT, or in non-SCT candidates that failed at least two lines of combination chemotherapy. Treatment with BV in this setting demonstrated an overall response rate (ORR) of 75%, including complete remission (CR) rate of 36% with a median PFS of 9.3 months that was shown in the phase II trial that led to Food and Drug Administration (FDA) approval.[14] BV is also approved for maintenance therapy after autologous SCT in patients with a high risk of disease relapse, based on the results of the phase III AETHERA study in which treatment with BV showed improvement of PFS (43 months *versus* 24 months) compared with controls after a median observation time of 30 months, despite the latest update showing a more modest, albeit sustained benefit with 3-year PFS rate of 61% for the BV arm and 43% for the placebo arm.[15,16]

A number of therapeutic strategies for cHL patients who relapse after autologous SCT and BV are available. Allogeneic SCT represents a potentially curative approach for these patients, with reported 5-year overall survival (OS) rates ranging from 30% to 40%.[17–19] However, outside of allogeneic SCT, goals of therapy have been typically palliative until recently, as new therapeutic options are becoming available as described above. Treatment choice in this setting is strongly influenced by previous treatments, duration of response, and, more importantly, goal of care. Allogeneic SCT candidates are treated with additional multiagent systemic chemotherapy, with the goal of achieving the best possible response prior to transplant, while allogeneic SCT-ineligible patients are treated with targeted small molecules and immune-modulatory agents for prolonged disease control. Alternatively, involved field radiation therapy and single-agent chemotherapy for symptom control are also viable options.[20] A minority of asymptomatic cHL patients can be observed without treatment for a period of time.[20]

Research over the past few years has been focusing on the mechanisms through which malignant cells escape host immune surveillance. Numerous immune suppressive checkpoint molecules have been identified, with the best-characterized being the programmed cell death 1 (PD-1) and programmed death-ligand 1 (PD-L1) molecules. Inhibition of the interaction between PD-1 (on T cells) and PD-L1 (on lymphoma cells) with monoclonal antibodies leads to an enhanced antitumor response by reversing T cell exhaustion.[21] In this review, we will focus on the pharmacology, therapeutic activity and tolerability of the PD-1 monoclonal antibody, pembrolizumab, in relapsed/refractory cHL.

Pathophysiology of cHL and the role of PD-1/PD-L1 signaling

Reed–Sternberg cells are malignant B cells pathognomonic of cHL.[22] The vast majority of the tumor is composed of a mixture of immune cells and stromal cells that together form a microenvironment contributing to malignant cell survival, with CD4+ T helper and regulatory T cells representing the most abundant cellular component, while Reed–Sternberg cells only represent 1–5% of the cellularity.[23–25] The vast majority of T cells express PD-1, a molecule that promotes self-tolerance[24,26] through interaction with its ligands PD-L1 and PD-L2, which are expressed at high levels on Reed–Sternberg cells.[27,28] While in healthy individuals PD-1 is expressed on activated T cells to prevent autoimmunity, activation of the PD-1–PD-L1 pathway in cHL diminishes T cell-mediated antitumor responses, thereby promoting a 'tumor-friendly' microenvironment.[29,30] Engagement of the PD-1 receptor leads to reduction of T cell receptor-mediated cytokine secretion and T cell expansion through suppression of signaling pathways such as the phosphatidylinositol 3-kinase (PI3K)–serine-threonine kinase Akt and the Ras-mitogen-activated and extracellular signal-regulated kinase (MEC)–extracellular signal-regulated kinase (ERK) pathways.[30–32] In most cases, high levels of PD-L1 and PD-L2 expression on Reed–Sternberg cells are secondary to amplification of 9p24.1, which contains the *CD274* and *PDCD1LG2* genes encoding PD-L1 and PD-L2, respectively.[28] The 9p24.1 amplicon also contains the Janus kinase 2 (JAK2) locus, which positively contributes to PD-L1 overexpression *via* the STAT signaling pathway.[28,33] Lastly, Epstein–Barr virus, which is commonly detected in mixed-cellularity and lymphocyte-depleted cHL, can induce PD-L1 expression on Reed–Sternberg cells *via* latent membrane protein 1-mediated JAK/STAT signaling.[28,34] In a recent retrospective review of 108 newly diagnosed cHL cases, 9p24.1 amplification

was associated with advanced stage and shorter PFS,[28] suggesting that PD-L1 overexpression contributes to a more aggressive clinical course and poorer outcome.

Targeting the PD-1/PD-L1 axis in cHL

Engagement of PD-1/PD-L1 signaling is thought to facilitate the survival of malignant cells by promoting evasion of the tumor-directed immune response and immune tolerance.[35] Monoclonal antibodies against PD-1 have been successfully used in a wide range of solid tumors such as metastatic melanoma,[36] non-small cell lung cancer,[37] advanced renal cell carcinoma,[38] urothelial cancer,[39] Merkel cell carcinoma,[40] head and neck cancer,[41] microsatellite instability-high colorectal carcinoma and upper gastrointestinal cancers.[42]

PD-L1 overexpression in Reed–Steinberg cells, which is genetically mediated in many cases, renders the PD-1/PD-L1 axis an attractive target for treatment of cHL.[26] The safety and activity of nivolumab, a fully human monoclonal IgG4 antibody specific for PD-1, was tested in the phase I CheckMate-039 trial in cHL patients.[43] Twenty-three patients with relapsed or refractory cHL were enrolled in this study. Eight patients (35%) had been treated with six or more prior therapies, 18 patients (78%) received BV, and 18 patients (78%) relapsed after an autologous SCT. Patients were treated with nivolumab 3 mg/kg every 2 weeks until disease progression or unacceptable toxicity. Drug-related adverse events were reported in 18 patients (78%); the most common events included rash in five patients (22%) and thrombocytopenia in four patients (17%). Five patients (22%) experienced grade 3 drug-related adverse events which included hematologic events (myelodysplastic syndrome, leukopenia, lymphocytopenia and thrombocytopenia), gastrointestinal events (pancreatitis, increased lipase level, colitis, gastrointestinal inflammation), pneumonitis and stomatitis, with one event of each type observed in the study. Treatment with nivolumab resulted in a remarkable ORR of 87% with a CR rate of 17% at a median follow-up interval of 40 weeks. PFS was 86% at 24 weeks, and 11 patients (48%) had ongoing response at the time of analysis. At extended follow up of 86 weeks, 10 out of 20 responders had a durable remission.[44] Twelve patients (52%) ultimately discontinued treatment with nivolumab. Two of these (9%) discontinued secondary to toxicity (myelodysplastic syndrome and thrombocytopenia in one patient and pancreatitis in one patient), four patients (17%) stopped due to progressive disease (PD), and six patients (26%) pursued SCT (allogeneic in five patients and autologous in one patient).[44]

A multicenter phase II trial of nivolumab by Younes and colleagues included 80 patients with relapsed/refractory cHL who were heavily pretreated (median of four prior therapies).[17] All patients were previously treated with autologous SCT and BV. Six patients (8%) had more than two lines of prior BV. Overall, 43 patients (64%) showed no response to BV. An objective response to nivolumab was observed in 53 of 80 patients (66%) after a median follow up of 8.9 months. The most common toxicities included fatigue in 20 patients (25%), infusion-related reaction in 16 patients (20%), rash in 13 patients (16%), arthralgia in 11 patients (14%), pyrexia in 11 patients (14%), nausea in 10 patients (13%), diarrhea in 8 patients (10%) and pruritus in 8 patients (10%).[17] Grade 3 or 4 adverse events included neutropenia in 4 of 80 patients (5%) and elevated lipase in 4 of 80 patients (5%). At the time of analysis, 51 patients (64%) remained on active treatment. Of those that discontinued nivolumab, 13 of 80 patients (16%) stopped due to disease progression, and 4 (5%) stopped due to drug toxicity (one autoimmune hepatitis, one elevated alanine transaminase (ALT) level, one elevated aspartate aminotransferase (AST) level and one multiorgan failure). A total of 20 patients (25%) experienced serious adverse events of any cause, including pyrexia in 3 patients (4%) and malignant neoplasm progression, pneumonia, arrhythmia, meningitis or infusion-related reaction in 2 patients (3%) each.[17]

Based on the results of this phase II trial, nivolumab became the first FDA-approved PD-1 blocking antibody for the treatment of patients with cHL who have relapsed or progressed after autologous SCT and BV. These trials opened immune checkpoint inhibition as an effective and exciting new avenue that could revolutionize the future of cHL treatment.

Pharmacology of pembrolizumab

Pembrolizumab (Keytruda, Merck Oncology, Kenilworth, NJ, USA) is a fully humanized monoclonal IgG4 antibody that specifically binds to PD-1 with a greater affinity for PD-1 than nivolumab.[45] Pembrolizumab is currently approved by the FDA for treatment of the following solid

tumors: unresectable or metastatic melanoma; metastatic non-small cell lung cancer with evidence of PD-L1 expression; recurrent or metastatic head and neck squamous cell cancer; locally advanced or metastatic urothelial carcinoma in patients who are not candidates for cisplatin-containing therapy or that has progressed on such therapy; and microsatellite instability-high cancer that has progressed on other therapies.[46] The FDA has also recently granted an accelerated approval to pembrolizumab for the treatment of adult and pediatric patients with cHL who are refractory or have relapsed after three or more prior lines of therapy.

In the initial clinical trial that subsequently led to FDA approval in melanoma, pembrolizumab was given at 10 mg/kg every 2 weeks or 10 mg/kg every 3 weeks.[47] Three-week dosing intervals were found to be appropriate for maintaining clinically relevant concentrations between doses, while the every 2-week schedule was associated with greater toxicity.[48] In the phase Ib KEYNOTE 013 trial in relapsed/refractory cHL described below, pembrolizumab was given at a dose of 10 mg/kg every 2 weeks.[49] However, subsequent studies found a flat exposure–response in the dose range of 2–10 mg/kg; therefore, it was concluded that a fixed dose of 200 mg every 3 weeks and weight-based dose of 2 mg/kg provide similar exposure distributions.[50,51] Like other therapeutic IgG monoclonal antibodies, pembrolizumab has a low volume of distribution and a half-life of approximately 3 weeks.[48]

Activity of pembrolizumab in relapsed/refractory cHL

The initial evidence of pembrolizumab safety and activity in relapsed/refractory cHL comes from a phase Ib study (KEYNOTE-013).[49] One of the cohorts included 31 patients with relapsed or refractory cHL with failure to BV. Of these patients, 22 patients (71%) had received prior autologous SCT, 8 patients (26%) were SCT-ineligible, and 1 patient (10%) refused SCT. Patients were treated with pembrolizumab 10 mg/kg every 2 weeks (equivalent to the maximum tolerated dose determined in solid tumors)[50] for up to 2 years or until disease progression or unacceptable toxicity. Results were encouraging and comparable to nivolumab: ORR was 65%, with 5 patients (16%) achieving a CR and 15 patients (48%) attaining a partial response (PR); 16 of the 20 responding patients achieved their best response at approximately 12 weeks. PFS rates of 69% were observed at 24 weeks and 46% at 1 year. Interestingly, the ORR to pembrolizumab was lower in transplant-naïve patients, compared with patients who had failed autologous SCT (44% *versus* 73%, respectively). A total of 15 of 16 analyzed tumor samples (94%) were positive for PD-L1 expression; 9 of 10 patients (90%) were found to express PD-L2. Flow cytometric analysis showed an increase in absolute numbers of CD4 and CD8 T cells and NK cells in the peripheral blood of treated patients. Furthermore, RNA profiling using a NanoString platform on the peripheral blood of patients with paired pre- and post-treatment samples showed significant upregulation of CXCL9, CXCL10, HLA-DRA, IDO1 and STAT1, consistent with an interferon gamma (IFN-γ)-induced signature, similar to what was previously seen in melanoma.[52] These results positioned pembrolizumab as an attractive immunomodulatory agent that can induce high and durable responses in heavily pretreated cHL.

The subsequent phase II KEYNOTE-087 study investigated the activity of pembrolizumab in patients with cHL who had failed either autologous SCT, BV or both. A total of 210 patients were included in three cohorts: 69 patients had failed autologous SCT and subsequent BV therapy (cohort 1); 81 patients were ineligible for autologous SCT due to chemo-resistant disease and had failed BV therapy (cohort 2); 60 patients had progressed after autologous SCT but had not received BV after SCT, although 25 of these patients had received BV before SCT (cohort 3).[53] Overall, 67 patients had bulky lymphadenopathy and 67 patients had B symptoms at baseline. Patients received a median of four prior lines of therapy, and 76 patients had prior radiation therapy. Patients were treated with pembrolizumab 200 mg every 3 weeks for a maximum of 24 months or until discontinuation due to disease progression, intolerable toxicity or investigator decision. Median exposure to pembrolizumab was 8.3 months and patients received a median of 13 cycles. ORR was 69% across all cohorts, 74% in cohort 1 (with 15 CRs and 36 PRs), 64% in cohort 2 (with 20 CRs and 32 PRs) and 70% in cohort 3 (with 12 CRs and 30 PRs). Five patients in cohort 1 (7%), 17 patients in cohort 2 (21%) and 8 patients in cohort 3 (13%) developed disease progression. Subgroup analysis across cohorts showed similar ORRs between patients that received fewer than three *versus* three or more prior therapies (71% *versus* 69%), and a

remarkable ORR of 57% in patients who were refractory to all prior therapies. Ten patients went on to receive an allogeneic SCT, while four underwent autologous SCT. Median duration of response and OS were not reached at the time of publication, and the 9-month OS and PFS rates were 98% and 63%, respectively. Authors investigated a PD-L1 expression score that included assessments of PD-L1 expression by tumor cell staining intensity (intensity score 0–3) and membrane staining score (0%; >0 to <50%; ⩾50% to <100%, 100%), as well as histiocyte staining intensity (score 1–3), and correlated their findings with the clinical response. It was found that 64% of patients had a maximal score across all of these staining modalities, while 88% or greater stained maximally in at least one of the modalities. Patients with lower staining intensity and membrane staining scores appeared to have a greater chance of PD on pembrolizumab, although the vast majority of patients received high staining scores. Based on the results of this trial, the FDA granted expedited approval to pembrolizumab for treatment of cHL patients who are refractory or have relapsed after three or more prior therapies.

Although pembrolizumab is generally well tolerated, grade 3–4 adverse events have been described. To reduce the incidence and the severity of adverse events, low-dose pembrolizumab regimens have been investigated. In a recent report by Chan and colleagues, five patients with relapsed or refractory cHL were treated with pembrolizumab at approximately 2 mg/kg every 3 weeks.[54] All patients were refractory to at least one regimen of combination chemotherapy, and one patient had relapsed after a previous autologous SCT. The number of prior treatments ranged from one to six, and four of five patients previously received BV. ORR was 100%, with four patients (80%) achieving a CR after a median cumulative dose of 495 mg and one patient achieving a PR after a cumulative dose of 400 mg. One of the patients who achieved CR went on to autologous SCT, and the other three patients remained in CR at the time of last follow up, after a range of 14–25 cycles of pembrolizumab. The patient who achieved PR eventually developed disease progression and was started on BV. Although these results suggest that pembrolizumab treatment is highly effective at a lower (and more cost-effective) dose, this approach requires further validation in a larger cohort of cHL patients.

The studies described above are summarized in Table 1.

Safety and tolerability

Physiologically, PD-1–PD-L1 interactions lead to attenuation of immune response to prevent autoimmunity. By unbalancing the immune system, checkpoint inhibitors generate dysimmune toxicities, termed immune-related adverse events (IRAEs), which mainly include rash, acute pneumonitis, colitis, thyroiditis, hypophysitis, hepatitis, nephritis, pancreatitis, rheumatoid arthritis, type I diabetes and uveitis.[55–58] Most of these adverse events respond to discontinuation of the drug while treatment with steroids continues. Other immunosuppressive agents such as mycophenolate mofetil and tumor necrosis factor antagonists are used for more severe steroid-refractory cases.[59–61] Biopsies of affected organs have demonstrated inflammatory changes such as mucosal infiltration with neutrophils and increased CD3+ CD8+ intraepithelial lymphocytes in cases of microscopic colitis.[62] Nonetheless, treatment with pembrolizumab is generally well tolerated in both solid tumors and cHL.

In the phase I study of pembrolizumab in cHL, 68% of patients experienced at least one drug-related adverse event, with the most frequent being hypothyroidism (16%), diarrhea (16%), nausea (13%) and pneumonitis (10%).[49] Grade 3 events occurred in five patients and included colitis, transaminitis, nephrotic syndrome, joint swelling, back pain and axillary pain. Two patients discontinued pembrolizumab due to grade 2 pneumonitis and grade 3 nephrotic syndrome; both of these patients received steroid treatment. There were no grade 4 treatment-related adverse events.

In the landmark phase II study, safety analysis indicated that pembrolizumab was well tolerated.[53] Grade 1–2 infusion-related reactions occurred in 10 patients (5%). The most common drug-related adverse events included hypothyroidism (12%), pyrexia (11%), fatigue (9%) and rash (8%). The highest severity of drug-related adverse events was grade 3, with the most common being neutropenia (2%), dyspnea (1%) and diarrhea (1%). Twenty-six patients (12%) had to interrupt treatment due to drug-related adverse events, and nine patients (4%) had to discontinue treatment because of drug-related adverse events including myocarditis, myelitis, myositis, pneumonitis, infusion-related

Table 1. Published studies that tested or reviewed activity of pembrolizumab in relapsed or refractory Hodgkin's lymphoma.

ClinicalTrials.gov identifier	Type	Title	Population	Outcome	Adverse events
NCT01953692	Phase Ib	Programmed death-1 blockade with pembrolizumab in patients with classical Hodgkin's lymphoma after brentuximab vedotin failure[49]	31 relapsed or refractory cHL patients previously treated with BV and relapsed after; ineligible for or refused autologous SCT	ORR 65% (90% CI 48–79%); CR 16% (90% CI 7–31%); PR 48%; PFS 69% at 24 weeks and 46% at 52 weeks	Hypothyroidism (16%), diarrhea (16%), nausea (13%) and pneumonitis (10%); Grade 3 AEs in four patients. Two patients discontinued treatment due to AEs
NCT02453594	Phase II	Study of pembrolizumab (MK-3475) in participants with relapsed or refractory classical Hodgkin's lymphoma (MK-3475-087/KEYNOTE-087)[53]	210 patients with relapsed/refractory cHL who progressed or did not respond to either autologous SCT followed by BV (cohort 1), salvage chemotherapy followed by BV (cohort 2) or autologous SCT (cohort 3)	ORR 69.0% (95% CI 62.3–75.2%), CR 22.4% (95% CI 16.9–28.6%). ORRs were 73.9% for cohort 1, 64.2% for cohort 2, and 70.0% for cohort 3. 31 patients had a response ⩾6 months	Immune-mediated events in 28.6% of patients, most common AEs hypothyroidism (12.4%) and pyrexia (10.5%)
	Retrospective	Low-dose pembrolizumab for relapsed/refractory Hodgkin's lymphoma: high efficacy with minimal toxicity[54]	Five patients refractory to 1–6 therapy modalities. four of five patients had previously received BV	ORR 100%, CR 80% at median follow up of 18 months	Grade 1 diarrhea in 20%; grade 1 eczema (20%)

AEs, adverse events; BV, brentuximab vedotin; cHL, classical Hodgkin's lymphoma; CI, confidence interval; CR, complete remission; ORR, overall response rate; PFS, progression-free survival; PR, partial response; SCT, stem-cell transplant.

reactions and cytokine release syndrome. Notably, two patients died from sepsis and acute graft-*versus*-host disease (aGVHD) during the follow-up period, with both deaths not attributed to pembrolizumab. Finally, among five patients treated with a lower dose of pembrolizumab, adverse events included grade 1 diarrhea that responded to budesonide and grade 1 eczema that responded to local treatment.[54] None of the patients had to discontinue pembrolizumab due to intolerable adverse effects in this small case series.

Checkpoint inhibitors pre- and postallogeneic SCT

Although clinical trials with pembrolizumab have demonstrated promising results in relapsed/refractory cHL patients, the only curative approach for this patient population remains allogeneic SCT. As discussed previously, pembrolizumab can induce remissions in patients who relapse after autologous SCT and may be considered for use as salvage therapy and a bridge to allogeneic SCT for patients who show disease response and are appropriate transplant candidates. However, increased risk of aGVHD- and GVHD-related mortality after blockade of PD-1 activity has been demonstrated in murine models.[63,64]

In humans, limited data exist on the use of PD-1 inhibitors before or after allogeneic SCT for relapsed and refractory cHL, and even fewer data exist on pembrolizumab specifically. In a recent retrospective study, El Cheikh and colleagues analyzed the toxicity and outcome of 11 cHL patients who had received nivolumab before or after allogeneic SCT.[65] Nine patients received nivolumab before allogeneic SCT, and two

patients received nivolumab for relapse after allogeneic SCT. Of the nine cHL patients who received nivolumab prior to allogeneic SCT, one patient (11%) had primary refractory disease and the rest had relapsed disease following SCT, with seven (78%) who also failed BV post-autologous SCT. Patients received nivolumab for a median of eight cycles before allogeneic SCT, and the median time between the last dose of nivolumab and allogeneic SCT was 44 days. At the time of transplant, three patients (33%) were in CR, four (44%) in PR and two (22%) had PD. None of the patients experienced graft rejection; however, all the patients (100%) developed aGVHD (grade 2 in three patients, grade 3 in five patients, grade 4 in one patient), and two patients (22%) also developed mild to severe chronic GVHD. Acute GVHD resolved in six of nine patients (67%) by the end of the study (time of follow up 5–19 months). At last follow up, eight of nine patients (89%) treated with nivolumab prior to transplant were alive, seven (78%) in CR and one (11%) with stable disease. However, three patients (33%) had ongoing complications at the time of last follow up, including one (22%) with incomplete red blood cell recovery and hemolytic anemia, one (22%) with hemorrhagic cystitis, recurrent cytomegalovirus (CMV) infection and pneumonia, and one (22%) with recurrent CMV and pneumonia. Of the two patients who received nivolumab after the transplant, one patient received nivolumab upon disease relapse 10 months after a second allogeneic SCT. Within 10 days from completing cycle 1, this patient developed severe grade 3 aGVHD with ocular, liver and skin involvement. He was treated with steroids and ruxolitinib. GVHD was controlled but he died from mucormycosis 13 weeks after receiving nivolumab therapy while in CR documented by imaging. The second cHL patient also relapsed 9 months after a second allogeneic SCT. This patient was treated with nivolumab, and 3 weeks after first dose developed grade 3 steroid-responsive aGVHD of the skin and gastrointestinal tract and steroid-resistant GVHD of the liver requiring ruxolitinib, cyclosporine and extracorporeal photophoresis. At the last follow up, 8 months after nivolumab, this patient was in CR and on treatment for GVHD. Neither of these two patients had evidence of GVHD prior to nivolumab treatment.

Another retrospective study investigated the efficacy and safety of administering PD-1 inhibitors before allogeneic SCT. A total of 39 patients with lymphoma were enrolled, and 31 (79%) had relapsed or refractory cHL.[66] Overall, 28 (72%) of enrolled patients received nivolumab (in four cases, in combination with another immune checkpoint inhibitor, ipilimumab, that targets CTLA-4), and 11 (28%) received pembrolizumab. A median of eight cycles of a PD-1 inhibitor were administered. For the cHL patients, 1-year OS and PFS rates were 90% and 74%, respectively. Although survival rates were high, 14 cHL patients (45%) developed aGVHD, including 8 patients (26%) with grade 3–4 aGVHD. Three treatment-related deaths (8%) were reported in the cHL group. Two of these three patients (6%) developed a noninfectious febrile syndrome, which began approximately 1 week after transplant, followed by a fatal hyperacute grade 4 GVHD. Two cHL patients (6%) developed sinusoidal obstruction syndrome (SOS) that required treatment with steroids and defibrotide, and central venovenous hemofiltration in one case. One of these two patients ultimately died, and the other recovered completely. Acute GVHD occurred in all four patients who received nivolumab in combination with ipilimumab, leading to a significantly higher 6-month rate of grade 3–4 aGVHD in these patients compared to those who received a single PD-1 inhibitor (75% *versus* 17%, $p = 0.01$).

Overall, these results support the feasibility and the activity of PD1/PD-L1 signaling inhibitors as a bridge to allogeneic SCT. However, they also provide insight into the risks of rapid-onset, potentially fatal GVHD in this setting, and prompted the FDA to issue a warning for use of allogeneic SCT after therapy with PD-1 inhibitors. Furthermore, there was a higher incidence of rare GVHD syndromes such as SOS and noninfectious febrile syndrome, as well as signs of drug-induced necrosis observed on liver biopsy obtained from the fatal case of SOS, suggesting that these symptoms were specific to immune effects of the PD-1 blockade. Interestingly, although there is an overall higher incidence of grade 3–4 aGVHD in patients who received peripheral blood stem cells *versus* those that received bone marrow grafts and in those with an unmatched donor *versus* matched, this did not seem to result in a significant difference in outcome. Results from prospective studies are needed to definitively assess the risk of GVHD in cHL patients undergoing allogeneic SCT after treatment with checkpoint inhibitors.

Correlative studies from Merryman and colleagues showed that patients treated with checkpoint inhibitors prior to allogeneic SCT had a decreased ratio of CD4+ T regulatory cells (CD3+/CD4+/Foxp3+) to conventional CD4+ T cells (CD3+/CD4+/Foxp3−) up to 1 month after transplant.[66] Reduced ratios of regulatory *versus* conventional CD4+ T cells early after transplant have been associated with higher incidence of aGVHD in recipients of mismatched allogeneic SCT.[67] Although treatment with checkpoint inhibitors is usually held for at least a month prior to allogeneic SCT, several studies suggest that the immune impact of checkpoint inhibitors continues well beyond what is predicted by pharmacokinetic studies. Interestingly, in the retrospective study by Merryman and colleagues, analysis of clinical predictors of survival and GVHD showed that duration of time between the last dose of PD-1 blockade and allogeneic SCT did not predict GVHD incidence and did not influence disease outcomes at 1 year. Ongoing and future studies will help to better define the timing of allogeneic SCT following treatment with checkpoint inhibitors. In addition, several strategies are being explored to reduce the incidence and the severity of checkpoint-inhibitor-induced GVHD, with one of these being high-dose cyclophosphamide given as GVHD prophylaxis.[68]

Several case reports and a limited number of larger-scale retrospective studies investigated the efficacy and toxicity of checkpoint inhibitors in the postallogeneic SCT setting.[69–72] The activity and safety of single-agent nivolumab was assessed in a retrospective study of 20 cHL patients relapsing after allogeneic SCT.[73] Patients had a median of seven lines of therapy. ORR was 95% with a CR rate of 42% and a PR rate of 52%, and 1-year PFS and OS rates were 58.2% and 78.7%, respectively. Nine patients (45%) had a prior history of aGVHD, three patients (15%) had prior history of chronic GVHD (cGHVD) and one patient (5%) had both acute and chronic GVHD. Six patients (30%) developed aGVHD after a single infusion of nivolumab, which prompted discontinuation of the drug. Five of the six patients had grade 3–4 GVHD with involvement of one or both of the liver and skin. Notably, all of these patients had a history of aGVHD prior to nivolumab therapy. Overall, 95% of the patients responded to standard GVHD therapy, with two responding to high-dose steroids and three requiring intravenous cyclosporine for steroid-refractory GVHD. Two of the six patients died as a result of GVHD (febrile multiorgan dysfunction and GVHD of the liver). Patients that developed nivolumab-triggered aGVHD appeared to have a shorter time between allogeneic SCT and nivolumab administrations than did those who did not develop GVHD [median 8.5 months (range 2–19 months) *versus* 28.5 months (range 7–111 months); $p = 0.0082$]. None of the enrolled patients developed cGVHD by the time of most recent follow up.

Case reports include a report of fatal GVHD attributed to pembrolizumab therapy in a 29-year-old man who had relapsed nodular sclerosing cHL. This patient's treatment history included ABVD chemotherapy followed by salvage chemotherapy and autologous SCT at first relapse, and subsequently BV followed by allogeneic SCT with fludarabine-total body irradiation nonmyeloablative conditioning.[74] His postallogeneic SCT course was complicated by steroid-responsive GVHD. This patient developed multiorgan GVHD that started within a week of drug administration, was refractory to therapy with steroids, basiliximab and antithymocyte globulin, and was ultimately fatal. Tolerance of pembrolizumab in two patients treated for cHL relapsed after allogeneic SCT and with history of prior GVHD has also been reported. These two patients did not experience GVHD reactivation following treatment with pembrolizumab.[75]

A retrospective review of 31 patients with relapsed cHL after allogeneic SCT also showed significant response rates to single-agent PD-1 inhibitor.[76] A total of 31 patients from 10 transplant centers were reviewed; 30 of them had relapsed cHL (one had both cHL and follicular lymphoma). Of these, 87% received at least one salvage therapy that included BV (52%), lenalidomide (10%), donor lymphocyte infusion (16%) or ipilimumab (10%). Ten of these patients received pembrolizumab 200 mg every 3 weeks, while the rest were treated with nivolumab at 3 mg/kg every 2 weeks. Treatment with checkpoint inhibitors was started an average of 2.2 years after allogeneic SCT. Encouraging responses were reported, with ORR of 79% in 30 evaluable cHL patients, with 21 of 31 patients (68%) alive at median follow up of 428 days. Seventeen patients (55%) developed GVHD, with six cases of aGVHD, seven cases of cGVHD and four overlapping cases, after a median of one dose of PD-1 inhibitor for aGVHD and two doses for chronic and overlapping GVHD. Acute GVHD developed after a median of 16 days following administration of PD-1

inhibitor, overlapping GVHD after a median of 21 days, and cGVHD after a median of 14 days. Most common organs involved were liver and skin. GVHD (acute or chronic) was defined as treatment-emergent if it either occurred after starting PD-1 inhibitor in a patient without prior GVHD history or recurred in a patient with previous history of GVHD and required GVHD-directed therapy. Treatment-emergent aGVHD occurred in 10 patients (32%) and was severe in 6 (19%). Nine of 10 patients with aGVHD required a secondary GVHD-directed therapy due to inadequate response to steroids, and eventually 5 (50%) of these patients responded to treatment, achieving either a CR or PR after receiving a median of three treatment modalities (treatments included steroids, calcineurin inhibitor, mycophenolate mofetil, antithymocyte globulin and extracorporeal photopheresis). Four of five patients who did not respond to therapy died, with GVHD cited as the primary cause of death. Chronic GVHD occurred in 11 patients (31%), and in four of these patients overlapping GVHD was diagnosed. Four of seven patients who developed treatment-emergent cGVHD died, with GVHD cited as the primary cause of death, and three patients were reported to be alive at the last follow up. There were a median of two systemic cGVHD treatments, and treatment modalities included systemic steroids, mycophenolate mofetil, sirolimus and extracorporeal photopheresis.

These case reports and retrospective studies indicate that treatment of relapsed and refractory cHL patients after allogeneic SCT with checkpoint inhibitors induces high rates of durable responses. However, this approach is associated with high frequency of aGVHD, including treatment-refractory and fatal cases. The incidence of aGVHD appears to be higher in patients with prior history of GVHD, but GVHD has also been observed in cHL patients without prior GVHD. Given the fact that the largest studies described above are retrospective, randomized controlled prospective studies are needed to better evaluate the risk–benefit balance of this approach in a patient population with limited effective therapeutic options.

Ongoing trials with single-agent pembrolizumab and novel combination strategies

There are 14 ongoing clinical trials investigating the activity of pembrolizumab in cHL (summarized in Table 2), with 13 trials actively recruiting patients. While most of these trials are designed to include patients with relapsed or refractory cHL after multiple lines of therapy, 'Pembrolizumab and involved site radiation therapy for early-stage relapsed or primary refractory Hodgkin lymphoma' [ClinicalTrials.gov identifier: NCT03179917] is designed to assess pembrolizumab combined with involved field radiation therapy in patients with primary refractory early-stage cHL, and 'PET-directed therapy with pembrolizumab and combination chemotherapy in treating patients with previously untreated classical Hodgkin lymphoma' [ClinicalTrials.gov identifier: NCT03226249] is designed to test pembrolizumab in combination with adriamycin, vinblastin, dacarbazine (AVD) in previously untreated cHL. Results from the latter will provide useful information regarding the activity of pembrolizumab in patients with a nearly intact immune system. 'Pembrolizumab after ASCT for Hodgkin lymphoma, DLBCL and T-NHL' [ClinicalTrials.gov identifier: NCT02362997] is an interesting phase II study designed to determine the role of pembrolizumab administered as consolidation therapy after autologous SCT in patients with relapsed/refractory cHL or other lymphoid malignancies.

A number of ongoing studies are exploring the activity of pembrolizumab in combination with other biologic agents in relapsed/refractory cHL. KEYNOTE 145 [ClinicalTrials.gov identifier: NCT02362035] is a phase I/II clinical trial testing the safety and activity of the combination of pembrolizumab and acalabrutinib, a second-generation Bruton's tyrosine kinase inhibitor (BTK), in patients with relapsed/refractory B cell malignancies including cHL. At the time of writing, the trial is ongoing but not actively recruiting patients. It will be interesting to learn about activity of pembrolizumab combined with a selective BTK inhibitor that does not have interleukin-2-inducible T cell kinase (ITK)-inhibitory activity on which Th2 cells and possibly regulatory T cells rely for activation and proliferation.[77]

Other novel agents are also on the horizon for the treatment of cHL. Treatment with single-agent lenalidomide has been reported to induce an ORR of 19% in heavily pretreated relapsed/refractory cHL patients.[78] Lenalidomide directly induces malignant B cell death and enhances antitumor response through inhibition of regulatory T cells and stimulation of cytotoxic T and NK cells. Given the differences in mechanism of action, combination of lenalidomide with pembrolizumab may

Table 2. Ongoing trials evaluating response of Hodgkin's lymphoma to pembrolizumab at various stages of disease.

ClinicalTrials.gov identifier	Phase	Title	HL patient population	Recruiting?
Previously untreated cHL				
NCT03226249	II	Phase II study of PET-directed frontline therapy with pembrolizumab and AVD for patients with classical Hodgkin lymphoma	Previously untreated classical Hodgkin's lymphoma	Yes
Primary refractory early-stage cHL				
NCT03179917	II	Pembrolizumab and involved site radiation therapy for early stage relapsed or primary refractory Hodgkin lymphoma	Patients with relapsed or refractory stage I–II classical Hodgkin's lymphoma. Possible prior treatments include chemotherapy alone or combined with radiation. In cases of prior combined therapy, area of relapse is outside the previous radiation field	Yes
Combination with biologic agents				
NCT02665650	Ib	A phase Ib dose escalation study to assess the safety of AFM13 in combination with pembrolizumab in patients with relapsed or refractory classical Hodgkin lymphoma (KEYNOTE-206)	CD30+ classical Hodgkin's lymphoma, relapsed or refractory after standard therapy including BV, SCT, or both	Yes
NCT02875067	I/II	Safety and efficacy study of combination of pembrolizumab and lenalidomide, in patients with relapsed non-Hodgkin and Hodgkin lymphoma	History of at least two prior therapies, not eligible for SCT	Yes
NCT02362035	I/II	A phase Ib/II proof-of-concept study of the combination of ACP-196 (acalabrutinib) and pembrolizumab in subjects with hematologic malignancies	Diagnosis of a hematologic malignancy without central nervous system involvement	No
NCT03150329	I	A phase I study of pembrolizumab plus vorinostat for relapsed or refractory diffuse large B-cell lymphoma, follicular lymphoma, and Hodgkin lymphoma	Relapsed or refractory classical Hodgkin's lymphoma (all histological subtypes except nodular lymphocyte predominant), stable, partial response or disease progression after at least one prior regimen, ineligible or declining SCT	Yes
NCT03179930	II	Combination therapy with entinostat and pembrolizumab in relapsed and refractory lymphomas	Hodgkin's lymphoma patients that have received at least two prior regimens	Yes
NCT03236935	Ib	Phase Ib trial of L-NMMA in combination with pembrolizumab in patients with melanoma, non-small cell lung cancer, head and neck squamous cell carcinoma, classical Hodgkin lymphoma, urothelial carcinoma, or microsatellite instability-high/mismatch repair deficient cancer	Classical Hodgkin's lymphoma that has relapsed after three or more lines of therapy or is refractory to treatment	Not yet

Table 2. (Continued)

ClinicalTrials.gov identifier	Phase	Title	HL patient population	Recruiting?
NCT03010176	I	Study of MK-1454 alone or in combination with pembrolizumab in participants with advanced/metastatic solid tumors or lymphomas (MK-1454-001)	Histologically or cytologically confirmed advanced/metastatic solid tumor or lymphoma of any type that is refractory to all treatment known to confer clinical benefit and can be tolerated by the patient	Yes
Combination with salvage chemotherapy				
NCT03077828	II	Phase II trial of pembrolizumab in combination with ICE salvage chemotherapy for relapsed/refractory Hodgkin lymphoma	Relapsed/refractory Hodgkin's lymphoma, with at least one but no more than two lines of prior chemotherapy	Not yet
Other				
NCT02684292	III	A phase III, randomized, open-label, clinical trial to compare pembrolizumab with brentuximab vedotin in subjects with relapsed or refractory classical Hodgkin lymphoma	Relapsed/refractory classical Hodgkin's lymphoma in BV-naïve patients that progressed or did not respond to auto-SCT, or salvage chemotherapy. Patients who are not candidates for auto-SCT received at least two chemotherapy regimens and are BV-naïve are eligible	Yes
NCT02362997	II	A phase II study of pembrolizumab (MK-3475) after autologous stem-cell transplantation in patients with relapsed/refractory classical Hodgkin lymphoma and, diffuse large B cell lymphoma and T-cell non-Hodgkin lymphoma	Classical Hodgkin's lymphoma that failed to achieve CR after initial chemotherapy regimen or relapsed and was treated with auto-SCT for chemo-sensitive diseases	Yes

BV, brentuximab vedotin; CR, complete remission; SCT, stem-cell transplant.

produce an additive or even synergistic effect. At the time of writing, this approach is being investigated in a trial enrolling patients with cHL or non-Hodgkin's lymphoma who have received at least two prior therapies and are not eligible for SCT [ClinicalTrials.gov identifier: NCT02875067].

AFM13 is a bispecific anti-CD30/CD16 antibody designed to enhance NK cell-mediated antitumor activity, with activity in relapsed or refractory cHL. In a phase I trial, 3 of 26 evaluable patients (12%) treated with single-agent AFM13 achieved a PR and 13 patients (50%) achieved stable disease (SD), with an overall disease control rate of 62%.[79,80] 'Study of the combination of AFM13 and pembrolizumab in patients with relapsed or refractory classical Hodgkin lymphoma' [ClinicalTrials.gov identifier: NCT02665650] is a phase Ib trial designed to assess the safety and activity of AFM13 in combination with pembrolizumab in patients with relapsed/refractory cHL.

Other agents currently under investigation in combination with pembrolizumab include two histone deacetylase (HDAC) inhibitors, vorinostat and entinostat. It has been reported that treatment with HDAC inhibitors favors a T helper 1 immune response, enhances antitumor immunity by HDAC11-mediated upregulation of OX40L, and downregulates tumor suppressor T cells in the tumor microenvironment, in addition to directly inhibiting lymphoma cell growth.[81–83] However, treatment with single-agent HDAC inhibitors has shown modest activity in relapsed and refractory cHL patients, with ORR of just 4% (vorinostat) and 12% (entinostat). Given the ability of HDAC inhibitors to induce upregulation of PD-L1 and PD-L2,[84] one trial is investigating a combination

of vorinostat with pembrolizumab in cHL patients with SD, PR or PD after at least one prior regimen and who are ineligible for or decline SCT [ClinicalTrials.gov identifier: NCT03150329]. Another trial investigates a combination of entinostat with pembrolizumab in cHL patients who have received at least two prior regimens [ClinicalTrials.gov identifier: NCT03179930].

Additionally, L-NG-monomethyl arginine (L-NMMA), a nitric oxide synthase inhibitor thought to be able to enhance immune-mediated antitumor responses,[85] and MK-1454, an agonist of stimulator of interferon genes protein (STING) with potential immunoactivating and antineoplastic activities, are being tested in combination with pembrolizumab in cHL. Finally, because single-agent BV and single-agent nivolumab have induced high response rates in cHL, the combination of these drugs is currently being investigated in both the relapsed/refractory setting as well as newly diagnosed, elderly cHL patients. To our knowledge, the combination of pembrolizumab and BV is not currently being evaluated. However, there is an ongoing phase III study comparing the activity of single-agent BV *versus* pembrolizumab in relapsed/refractory cHL patients [ClinicalTrials.gov identifier: NCT02684292].

In summary, the role of pembrolizumab as a single agent and in combination with other biological/immunomodulatory agents is being investigated at different stages of cHL. Ongoing and future studies will clarify sequential or combined use of pembrolizumab as well as its role in treatment-naïve patients.

Pembrolizumab in other hematologic malignancies

Interestingly, pembrolizumab has shown significant activity in other hematologic malignancies.[86] A total of 42% of malignant cells in primary mediastinal B cell lymphoma (PMBCL) were found to express PD-L1.[87] A phase I trial of pembrolizumab in 17 evaluable patients with relapsed/refractory PMBCL showed an ORR of 41%, with duration of response ranging from 2.4 months to 22.5 months, and six ongoing responses at the time of report after a median follow up of 11.3 months.[88] The activity of pembrolizumab was evaluated in a phase II trial in patients with chronic lymphocytic leukemia (CLL) and Richter's transformation, showing an ORR of 44% in Richter's patients but no activity in 16 relapsed CLL patients.[89] Interestingly, the median OS in the Richter's patient cohort was 10.7 months, which is significantly longer than predicted survival in patients with Richter's transformation (about 4 months), and median OS was not reached in Richter's patients who previously progressed on ibrutinib.[89] Significant responses with ORR of 38% was also achieved in patients with mycosis fungoides or Sezary syndrome who were treated with a median of four prior therapies, and 89% of responses lasted for at least 32 weeks.[90] Lastly, a recent case report suggests that pembrolizumab may be effective in relapsed/refractory mediastinal gray-zone lymphomas.[91] The activity of single-agent pembrolizumab is currently being evaluated in relapsed/refractory gray-zone lymphoma, primary central nervous system lymphoma, and other extranodal diffuse large B cell lymphomas [ClinicalTrials.gov identifier: NCT03255018]. Further studies are required to determine the therapeutic role of pembrolizumab in these diseases.

Conclusion

The PD-1-directed monoclonal antibody pembrolizumab has shown significant activity and an acceptable toxicity profile in cHL and in a subset of non-Hodgkin's lymphoma patients.[92] Pembrolizumab is currently FDA-approved for the treatment of cHL patients who are refractory or have relapsed after three or more prior therapies. In both the phase I and II studies, CRs are achieved by only 16–20% of patients. Although more mature data are needed, it appears that heavily pretreated patients who failed both autologous SCT and BV can achieve and maintain a PR, indicating that CR is not necessary to obtain significant clinical benefit. Although pembrolizumab was reported to have greater affinity for PD-1 compared to nivolumab, recent data suggest these two drugs are interchangeable and differences in activity may be due to patient selection and trial design rather than drug-related reasons.[93]

Although the development of checkpoint inhibitors has led to the introduction of practice-changing therapies for patients with cHL, many questions remain to be answered. The rationale of combining systemic chemotherapy with a checkpoint inhibitor in treatment-naïve cHL patients is to obtain maximal therapeutic effect in patients with an intact immune system. The question that ongoing and future clinical trials will need to answer is how much improvement can be

achieved on the excellent front-line success rates with conventional systemic chemotherapy. The activity of checkpoint inhibitors may be attenuated in heavily pretreated cHL patients due to a deficient immune system. On the other hand, cHL appears in most cases to have a genetic dependence on the PD-1–PD-L1 axis, making this disease particularly sensitive to PD-1 inhibition. This may be an even bigger factor in relapsed/refractory cHL patients with higher mutational load and neoantigen expression, suggesting that checkpoint inhibition might be a better approach in the relapsed/refractory setting despite a weaker immune system. Alternatively, checkpoint inhibitors could be given prior to conventional chemotherapy to avoid their related immune suppression, or after chemotherapy to reduce the risk of relapse. Lastly, the combination of checkpoint inhibitors with biological/immune-modulatory agents is an area of active investigation, with the rationale of targeting the tumors with biologically independent but interrelated mechanisms.

Growing evidence highlights the risk of severe and occasionally fatal GVHD when pembrolizumab is given prior to or after allogeneic SCT for cHL. Lack of prospective randomized studies and relatively short follow up in the published clinical trials do not allow conclusions to be drawn. Checkpoint inhibitor therapy should be used with caution before and after allogeneic SCT, and the risk–benefit balance should be carefully evaluated on an individual basis.

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