ImmunoTargets and Therapy

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

Immune Checkpoint Blockade for the Treatment of Hodgkin Lymphoma

Adam Yuh Lin[1], Joseph Michael Schnitter[2], Leo I Gordon[1]

[1]Division of Hematology Oncology, Department of Medicine, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA; [2]Department of Medicine, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA

Correspondence: Adam Yuh Lin, Division of Hematology Oncology, Department of Medicine, Feinberg School of Medicine, Northwestern University, Arkes Pavilion, 676 N St Clair Street Suite 850, Chicago, IL, 60611, USA, Email adam.lin@northwestern.edu

Abstract: Classical Hodgkin lymphoma is biologically different than other lymphomas. The cancer cells only occupy a small amount of the lymph node and evade the immune system by amplification of PD-L1 and PD-L2. Therefore, checkpoint inhibitors are a logical treatment option for Hodgkin lymphoma patients to unlock the immune system. Checkpoint inhibitors have shown high response rates in clinical trials in advanced-stage Hodgkin lymphoma. The two most commonly used checkpoint inhibitors are pembrolizumab and nivolumab, both FDA approved as third-line therapy. There is increasing interest in the use of checkpoint inhibitors with combination chemotherapy or with other targeted agents in the second-line or even frontline setting. In this review, we will highlight the clinical trials that led to approvals of checkpoint inhibitors for Hodgkin lymphoma.

Keywords: checkpoint inhibitor, pembrolizumab, nivolumab, Hodgkin lymphoma

Introduction

Classical Hodgkin lymphoma (cHL) is largely curable with conventional chemotherapy, with an estimated 5-year survival of approximately 88%.[1] Treatment algorithms in cHL depend in part on the clinical stage at the time of diagnosis. In early-stage disease (stage I/II), using the National Comprehensive Cancer Network guidelines, patients are separated into favorable or unfavorable characteristics, depending on several factors including erythrocyte sedimentation rate, bulky disease (greater than one-third of the thoracic width or ≥10 cm in diameter) and number of nodal sites.[2] Most early-stage patients can be cured by reduced cycles (two to four cycles) of chemotherapy combined with involved field radiation, though the optimal number of cycles and the need for combined modality therapy remain controversial. The chemotherapy regimen used in trials for early-stage disease is mostly ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) with possible escalation to BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) if the interim positron emission tomography noted residual or progressive disease. The research focus for the treatment of early-stage disease cHL is to minimize therapy to mitigate the secondary cancer and cardiovascular risks.[3,4]

For advanced disease, frontline therapy for cHL has changed over the years. In addition to ABVD, BV-AVD (brentuximab vedotin, doxorubicin, vinblastine, and dacarbazine) has become an option, based on the results of the ECHLON-1 trial.[5,6] Brentuximab vedotin (BV), which is an antibody drug conjugate, replaced bleomycin to reduce the risk of significant lung injury. A more intensive chemotherapy regimen, escalated BEACOPP, is often used in Germany, with similar results to ABVD. Despite this high response rate, a significant number of patients will not respond to frontline therapy or will have relapsed disease. Options for relapsed/refractory cHL patients include high-dose salvage intensive chemotherapy followed by high-dose chemotherapy and autologous hematopoietic stem cell transplantation (HSCT). The optimum second-line salvage chemotherapy regimen is not standardized and is still the subject of debate and investigation. Castagna et al detailed and categorized the second-line chemotherapy options into 1) platinum-based regimens such as ifosfamide, carboplatin, etoposide (ICE),[7] with an overall response rate (ORR) of 72% and a complete

Received: 25 November 2021
Accepted: 2 February 2022
Published: 23 February 2022

response (CR) rate of 26%; 2) gemcitabine-based regimens such as gemcitabine, vinorelbine, pegylated liposomal doxorubicin (GVD),[8] with an ORR of 70% and a CR of 19%; and 3) others, namely non-platinum or gemcitabine regimens.[9] Our institution often uses ICE as salvage chemotherapy as it has the benefit of stem cell collection between cycles.

The unique biology of cHL can drive novel treatments. The malignant cell, the Reed–Sternberg cell (RSC), makes up only a small portion of the involved lymph nodes, while the majority are reactive T cells and other immune cells. Further evaluation of the RSCs found overexpression of PD-L1 and PD-L2 due to genetic amplification of the 9p24.1 locus.[10]

The overexpression of the PD-1 ligand leads to a T-cell-exhausted tumor microenvironment.[11] The RSCs with copy number alterations of 9p24.1/CD274(PD-L1)/PDCD1LG2(PD-L2) are surrounded by PD-L1-positive tumor-associated macrophages.[12] This is often described as a "castle and moat" model as the RSCs are surrounded by inactivated innate immune cells to protect them from the immune system, specifically, activated T cells. Importantly, alterations of PD-L1 and PD-L2 have correlated with reduced progression-free survival (PFS) when treated with standard chemotherapy regimens.[13] Also, these RSCs had overall high mutational burden and microsatellite instability (MSI)-associated hypermutation, biological markers that correlate with the response to checkpoint inhibitor (CPI) therapy in other malignancies.[14] Therefore, anti-PD-1/PD-L1 CPI therapy is a rational approach to the treatment of cHL.[15–19] The success of PD-1 blockade suggests that some of these T cells are reversibly exhausted. RSCs with β_2-microglobulin/major histocompatibility complex (MHC) class I loss are noted to have more durable responses.[11] In addition to MHC class I, newly diagnosed cHLs had a higher prevalence of NF-kB genetic alterations. Wienand et al also found a mutational signature of spontaneous deamination of cytosine-phosphate-guanines, apolipoprotein B mRNA editing catalytic polypeptide-like, activation-induced cytidine deaminase, and MSI-associated hypermutation.[14]

Clinical trial data have shown that anti-PD-1/PD-L1 monotherapy is an effective option for patients who have failed first-line chemotherapy. Thus far, two main CPIs – nivolumab and pembrolizumab, both of which are anti-PD-1 monoclonal antibodies – have been approved by the FDA for relapsed/refractory cHL. In this review, we will discuss the clinical trials for CPI in cHL, organized by the sequence of treatments.

Third or Greater Line of Therapy

In a 2015 study in which 23 patients with previously heavily treated (more than two lines of therapy) relapsed/refractory cHL were administered nivolumab every 2 weeks until they had evidence of CR, tumor progression, or severe toxicity, 80% of patients demonstrated an objective response, including 17% with CR and 70% with partial response (PR), with a rate of PFS of 86% at 24 weeks.[20] A multicenter phase II study of nivolumab monotherapy in 17 Japanese patients with relapsed/refractory cHL who had all previously received BV demonstrated an objective response rate of 81.3% among the 16 patients included in the efficacy analysis. Among these 16 patients, four had complete remission and nine had partial remission.[21] In another phase II study from 34 hospitals across Europe and North America, in which nivolumab monotherapy was administered to 80 patients with recurrent cHL who had progressed after autologous stem cell transplantation (ASCT) and either failed to respond to or relapsed following BV administration, 53 patients (66.3%, 95% CI 54.8–76.4%) demonstrated an objective response based on review from an independent radiological review committee (IRRC).[22]

The phase II CheckMate 205 trial also examined the efficacy of nivolumab in relapsed/refractory cHL, but further separated patients into three groups based on treatment history: BV-naïve, autologous hematopoietic cell transplantation (auto-HCT) followed by BV, and BV received before and/or after auto-HCT.[23] In total, 243 patients were treated with nivolumab and the overall objective response rate was 69% (95% CI 63–75%), ranging from 65% to 73% in each cohort. The median response duration among all 243 patients was 16.6 months (95% CI 12.2–20.3 months) and median PFS was 14.7 months (95% CI 11.3–18.5 months). This trial, along with the 2015 trial,[20] led to the FDA approval of nivolumab single agent for the treatment of relapsed cHL which had progressed after autologous HSCT and post-transplantation BV. Notably, this was the first FDA application for a PD-1 inhibitor in hematologic malignancies.

Around the same time, in 2017, the FDA also approved pembrolizumab for adults and children with cHL refractory to or which has relapsed after at least three prior therapies based on the initial results from KEYNOTE-087.[24] The patients were divided into three cohorts: 1) patients with progression after ASCT and subsequent BV administration (n=69); 2)

patients with progression following salvage chemotherapy and BV who were not candidates for ASCT (n=81); and 3) patients with progression after ASCT without exposure to BV (n=60). Cohort 1 had an ORR of 73.9% and a CR rate of 21.7%. Cohort 2 had an ORR of 64.2% and a CR rate of 24.7%. Cohort 3 had an ORR of 70% and a CR rate of 20%. For all the patients included, the ORR was 69% and the CR rate was 22.4%. A 5-year follow-up of KEYNOTE-087 reaffirmed the benefit of pembrolizumab in both BV-naïve patients and those with previous exposure.[25] Out of the 210 patients evaluated, 46 patients completed 2 years of pembrolizumab. The ORR was 71%, with a CR rate of 27.6%. The ORR increased to 84.1% for cohort 1 and 67.9% for cohort 2, and there was a slight decrease to 68.3% for cohort 3 at the data cut-off. Furthermore, the median PFS was 56.5 months and the 5-year PFS rate was 44.3%, while the median overall survival (OS) was not reached and the 5-year OS was impressive, at 82.8%.

Before that trial, the phase Ib study KEYNOTE-013 helped open the door for the use of pembrolizumab in this population.[23,26] The study consisted of 31 patients with relapsed/refractory cHL, all of whom had disease progression while on or after treatment with BV, where 55% had more than four previous lines of therapy, and 71% had relapsed following ASCT. Among this group, the ORR was 65% (90% CI 48–79%), with complete remission in 16% (90% CI 7–31%) and partial remission in 48% of patients. PFS was 69% at 24 weeks and 46% at 52 weeks.

Data from clinical trials have shown that anti-PD-1 therapies in combination with other agents are effective in relapsed/refractory cHL. A phase I trial investigated pembrolizumab plus vorinostat in patients with DLBCL, follicular lymphoma, and cHL who had failed one or more prior lines of treatment (with a median of four) and were not candidates for stem cell transplantation.[27] In total, 30 patients were enrolled in the trial, 12 of whom had cHL. Among these 12, 11 had previously received BV, seven had been treated previously with anti-PD-1 therapy, and three were refractory to prior anti-PD-1 therapy. Ultimately, among the nine evaluable cHL patients, four achieved CR and five had a PR. Perhaps most notably, these data suggest that patients with refractory disease to anti-PD-1 therapy should not necessarily be excluded from receiving further treatment with anti-PD-1 treatment, particularly when administered in combination with other agents.

A 2020 phase Ib dose-escalating study further explored the benefits of combination therapy in 30 patients with relapsed/refractory CHL.[28] In this trial, patients received pembrolizumab in combination with AFM13, a bispecific tetravalent antibody that targets CD30 on tumor cells and CD16A on natural killer cells and macrophages to induce tumor cell killing. In this study, patients who had received prior anti-PD-1, anti-PD-L1, or anti-PD-1-L2 treatment were excluded. Overall, the study population had an 83% objective response rate, with 37% showing a complete metabolic response and 47% a partial metabolic response. Among those who received the highest treatment dose, the objective response rate was 88%.

Bolstered by the encouraging data above, two clinical trials investigating anti-PD-1 therapy in combination with radiotherapy for patients with relapsed/refractory cHL are ongoing. NCT04419441 is exploring whether radiotherapy will improve the rate of complete remission in patients receiving anti-PD-L1 therapy. NCT03480334 has the same hypothesis, but its study population is comprised specifically of patients who have recently progressed on anti-PD-1 therapy.

CPI for Maintenance Strategy

A multicohort phase II study by Armand et al evaluated pembrolizumab as a maintenance strategy post-ASCT. These patients consisted of a particularly high-risk group, with 90% of the 30 patients deemed high risk by clinical criteria. The maintenance pembrolizumab therapy lasted for eight cycles every 3 weeks. Among 28 evaluable patients, the rate of PFS was 82% at 18 months, satisfying the investigators' hypothesis that pembrolizumab would improve PFS from 60% to 80%.[29] Similarly, maintenance nivolumab (6 months) post-ASCT was also tested in patients with Hodgkin lymphoma (HL).[30] The data are immature, but out of the 37 patients enrolled on this trial, the 6-month or end of therapy PFS is 92.1% and the 12-month OS is 100%. The median PFS and OS have not been reached, with a median follow-up of 9.2 months. Only four discontinued the nivolumab owing to adverse events and two patients progressed while on the nivolumab. Both of these trials suggest that maintenance CPIs are tolerable, and mature data are needed for them to become the standard of care.

Second-Line Therapy

Several studies have also demonstrated the effectiveness of checkpoint inhibition in combination with other agents as second-line therapy in cHL. In one phase I/II study, a total of 91 patients with relapsed/refractory disease were treated with combination BV plus nivolumab. Patients in this study were divided into two cohorts: one group that received BV and nivolumab in a staggered schedule, and a second group that received therapy concurrently. Therapy proved effective in both cohorts; the rate of CR for treated patients was 67% and the objective response rate was 85%.[31,32] Given these encouraging results, BV plus nivolumab is now approved for use as second-line therapy in relapsed/refractory cHL, establishing an alternative to chemotherapy for consolidation prior to ASCT.

Another trial addressed the question of whether immunotherapy in combination with chemotherapy could safely be tolerated prior to ASCT, without adversely affecting peripheral blood progenitor cell mobilization and engraftment. Patients were treated with a regimen of pembrolizumab plus ifosfamide, carboplatin, and etoposide (ICE). Among the 40 patients with relapsed/refractory cHL recruited, 23 were evaluable. All but one patient in this group had successful stem cell mobilization and harvest (this patient had a severe allergic response to filgrastim and instead had a bone marrow harvest), and all patients who underwent stem cell reinfusion successfully engrafted, with a median time of 11 days for absolute neutrophil recovery and 12 days for platelet recovery. Notably, the therapy was well tolerated in this group, with no reports of the more serious adverse immune CPI toxicities of pneumonitis, colitis, hepatitis, or endocrinopathies.[33] Therefore, these data further support the feasibility of immunotherapy as second-line therapy in relapsed/refractory cHL prior to ASCT.

The randomized, open-label phase III trial entitled KEYNOTE-204 demonstrated that pembrolizumab monotherapy was superior to BV in patients with relapsed/refractory cHL.[34] This trial was a head-to-head comparison of pembrolizumab and BV, and included both patients with and those without prior BV exposure. All participants were either post-ASCT or ineligible for transplant. In a head-to-head comparison, patients who received pembrolizumab had higher rates of PFS compared to those who had received BV (HR 0.65, 95% CI 0.46–0.85), with PFS rates of 53.9% in patients given pembrolizumab versus 35.6% in the BV group. Pembrolizumab was superior in all of the study's subgroups, including those who had not previously undergone ASCT, those with primary refractory disease, prior exposure to BV, and no prior exposure to BV. This study led to the extended FDA approval in 2020 of pembrolizumab for adult cHL patients as second-line therapy and pediatric patients as third-line therapy.

In a similar vein, a subsequent phase II study investigated whether pembrolizumab plus gemcitabine, vinorelbine, and liposomal doxorubicin (GVD) would be effective as second-line therapy prior to ASCT. Thirty-seven patients were recruited for the study, and 34 were eligible for analysis. Among this group, 31 achieved a CR after two cycles and three achieved a PR. One of these three partial responders ultimately achieved CR after four cycles of therapy. At the time of publication, 32 patients have undergone ASCT, one is awaiting transplantation, and one declined transplantation and instead opted for maintenance pembrolizumab therapy. All patients were still in remission at the time of publication.[35] No dose-limiting toxicities were noted in the safety phase of the trial. Grade 3 toxicities include elevated liver enzymes (four patients), neutropenia (four patients), oral mucositis (two patients), rash (one patient), and hyperthyroidism (one patient).

One study pursued a unique angle by having a cohort of patients who received a combination of immunotherapy agents: nivolumab and ipilimumab. Ipilimumab is a monoclonal antibody targeted against CTLA-4, an immune checkpoint receptor on T cells.[36] Using multiplex immunofluorescence microscopy with digital image analysis, Patel et al found that the tumor microenvironment in cHL is enriched for non-T-regulatory, cytotoxic T-lymphocyte-associated protein-4 (CTLA-4)-positive T cells that outnumber PD-1-positive T cells.[37] Unlike the tumor-associated macrophages that express PD-L1, T cells that surround the RSCs are more often positive for CTLA-4 than PD-1. The patients included in this trial had wide variance in prior treatments; some had as few as one prior line of therapy while others had received nine lines of therapy (median of 2). Of the 64 patients enrolled in this phase I trial, 61 were evaluable. These patients were separated into three cohorts: one group received BV and ipilimumab; a second received BV and nivolumab; and the final group received BV, ipilimumab, and nivolumab. Each of these cohorts demonstrated robust objective response rates and CR rates: 76% and 57%, respectively, in the BV/ipilimumab group; 88% and 61%, respectively, in the BV/nivolumab group; and 82% and 73%, respectively, in the BV/nivolumab/ipilimumab group.

The most significant toxicities occurred in the BV/nivolumab and BV/nivolumab/ipilimumab groups, each of which had one grade 5 pneumonitis death and five dose-limiting toxicities between the two of them. Common grade 1–2 toxicities included fatigue, elevation of liver transaminases, peripheral neuropathy, and diarrhea. For grade 3 or 4 adverse events, 10 (43%) of the ipilimumab group, three (16%) of the nivolumab group, and 11 (50%) of the triple-therapy patients experienced high-grade toxicities.

Frontline Therapy

More recently, Allen et al pursued CPI therapy as a component of frontline therapy, given its effectiveness in relapsed/refractory disease.[38] In this multicenter phase II study, 30 patients with untreated, early, unfavorable, or advanced-stage disease were treated with pembrolizumab and doxorubicin, vinblastine, and dacarbazine (AVD) chemotherapy. These patients first received three cycles of pembrolizumab monotherapy, followed by AVD for four to six cycles depending on the stage and bulk of disease. After pembrolizumab monotherapy, 11 patients had a complete metabolic response, and an additional seven patients had >90% reduction in metabolic tumor volume based on PET/CT. All patients in the study attained a complete metabolic response after two cycles of AVD, and at median follow-up of 22.5 months there were no cases of disease progression, death, or further therapy. Furthermore, the therapy was well tolerated, with the most notable adverse effects being six patients with grade 1 rash, four patients with grade 2 transfusion reactions, one patient with reversible grade 4 transaminitis, and one patient with reversible Bell's palsy.[39]

This trial by Allen et al used a lead-in or sequential strategy of CPIs prior to chemotherapy, with high response rates. However, the question of concurrent versus sequential use of CPIs with chemotherapy remains. The German Hodgkin Study Group led by Bröckelmann et al performed a phase II study looking at early-stage unfavorable disease patients, with a 1:1 assignment to either concurrent treatment with four cycles of nivolumab and AVD or sequential treatment with four doses of nivolumab, two cycles of N-AVD, and two cycles of AVD, followed by involved-site radiotherapy.[40] There were 109 patients included in this study, with a 90% CR rate in the concurrent arm and 94% CR in the sequential arm. The one-year PFS rates were 100% and 98% for the concurrent arm and sequential arm, respectively. These results suggest that both options are reasonable, but the single-agent nivolumab (four cycles) lead-in had a 96% response rate, which, along with the pembrolizumab data from Allen et al,[39] will require further investigation to minimize toxicities.

The CheckMate 205 trial referenced above (in the section "Third or Greater Line of Therapy") also included a cohort of patients who received immunotherapy with chemotherapy as frontline therapy for newly diagnosed cHL.[41,42] In this study, 51 patients with stage IIB with unfavorable risk, III, or IV cHL underwent treatment. The investigators planned for four doses of nivolumab monotherapy followed by nivolumab plus doxorubicin, vinblastine, and dacarbazine combination therapy for six cycles. After two combination cycles, the rate of complete remission was 51% (and 71% complete metabolic response) via an independent review committee and 71% per investigator. On a more recent trial result update, the ORR was 84% (95% CI 71–93%), including 67% of the patients reaching a CR.[43] At 21-month follow-up, the rate of PFS was 83% per investigator. Furthermore, Roemer et al found that responses in this trial correlated with a higher level of 9p24.1 copy gain and increased PD-L1 expression on RSCs.[44] Surprisingly, major histocompatibility complex (MHC) class II on the RSCs was predictive of the responses, whereas β_2-microglobulin/MHC class I was not.

Other Checkpoint Inhibitors

Though other anti-PD-1 immunotherapy agents have not been approved by the FDA for use in relapsed/refractory cHL, studies indicate that sintilimab, tislelizumab, and camrelizumab are effective in these patients. Sintilimab, a fully humanized IgG_4 monoclonal antibody toward PD-1, was administered to patients taking part in ORIENT-1, a phase II trial consisting of 96 patients from 18 hospitals in China who had relapsed/refractory disease following two or more lines of therapy.[45] In total, 74 patients among the 92 analyzed (80.4%, 95% CI 70.9–88.0%) demonstrated an objective response via review from an independent committee. In another phase II study among 70 Chinese patients with relapsed/refractory HL who received tislelizumab, a humanized anti-PD-1 antibody that is designed to bind less to Fc gamma receptors, 61 (87.1%) of the patients assessed by an independent review committee had an objective response, with a 9-month PFS rate of 74.5%.[46]

Table 1 Active or Recently Completed Clinical Trials Using Checkpoint Inhibitors (CPIs) in Hodgkin Lymphoma

Title	Line	Phase	NCT	Status	Notes
Phase II Trial of Individualized Immunotherapy in Early-Stage Unfavorable Classical Hodgkin Lymphoma (INDIE)	Frontline	II	NCT04837859	Recruiting	Tislelizumab alone or in combination with AVD followed by RT if PET positive after therapy
Immunotherapy (Nivolumab or Brentuximab Vedotin) plus Combination Chemotherapy in Treating Patients with Newly Diagnosed Stage III–IV Classic Hodgkin Lymphoma	Frontline	III	NCT03907488	Recruiting	BV+AVD is used as standard of care cohort
Nivolumab and Brentuximab Vedotin in Treating Older Patients with Untreated Hodgkin Lymphoma	Frontline	II	NCT02758717	Active, not recruiting	Age >60 years or unsuitable for standard chemotherapy
Brentuximab Vedotin and Nivolumab in Treating Patients with Early-Stage Classic Hodgkin Lymphoma	Frontline	II	NCT03712202	Recruiting	Arms: Nivo+BV, Nivo+ABVD, Nivo+BV+AVD
Nivolumab, Ifosfamide, Carboplatin, and Etoposide as Second-Line Therapy in Treating Patients with Refractory or Relapsed HL (NICE Trial)	Second-line therapy	II	NCT03016871	Recruiting	Nivolumab given concurrently with chemotherapy
A Study of Brentuximab Vedotin Combined with Nivolumab for Relapsed or Refractory Hodgkin Lymphoma	Second-line therapy	I/II	NCT02572167	Recently completed	Previously treated with BV, immune-oncology agents, or SCT excluded
Immune Checkpoint Inhibitors and Radiotherapy in Relapsed/Refractory Hodgkin Lymphoma (ICI-RT-1)	At least 1 prior line	R	NCT04419441	Recruiting	No other therapies allowed outside of CPI and RT
Umbralisib and Pembrolizumab in Treating Patients with Relapsed or Refractory Classical Hodgkin Lymphoma	At least 1 prior line	II	NCT03776864	Recruiting	Prior CPI use allowed
Brentuximab Vedotin and Nivolumab with or Without Ipilimumab in Treating Patients with Relapsed or Refractory Hodgkin Lymphoma	At least 1 prior line	I/II	NCT01896999	Recruiting	12 arms during phase I. Two arms during phase II
Gemcitabine, Bendamustine, and Nivolumab in Patients with Relapsed or Refractory Classical Hodgkin Lymphoma	At least 1 prior line	I/II	NCT03739619	Active, not recruiting	Previously allogeneic SCT excluded
Pembrolizumab and Vorinostat in Treating Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma, Follicular Lymphoma, or Hodgkin Lymphoma	At least 1 prior line	I	NCT03150329	Recruiting	Not candidates for ASCT or declined ASCT
Nivolumab and Ipilimumab in Treating Patients with HIV Associated Relapsed or Refractory Classical Hodgkin Lymphoma or Solid Tumors That Are Metastatic or Cannot Be Removed by Surgery	At least 1 prior line	I	NCT02408861	Recruiting	Includes cohort of HIV-associated classical Hodgkin lymphoma
RadVax for Relapsed/Refractory Hodgkin's Lymphoma: A Phase II Trial of Nivolumab + Low Dose Radiotherapy for Incomplete Responders	At least 1 prior line	II	NCT03495713	Recruiting	Radiotherapy given if not in CR by week 8. Need >2 sites of measurable disease

https://doi.org/10.2147/ITT.S284988 DovePress

Brentuximab Vedotin and Nivolumab for the Treatment of Relapsed/Refractory Classic Hodgkin Lymphoma Previously Treated with Brentuximab Vedotin or Checkpoint Inhibitors	At least 1 prior line	II	NCT05039073	Not yet recruiting	Previously treated with brentuximab vedotin or CPIs
Tumor Associated Antigen Specific T Cells (TAA-T) With PD1 Inhibitor for Lymphoma	At least 2 prior lines	I	NCT03843294	Recruiting	Includes post-ASCT consolidation for high-risk patients. Prior allogeneic SCT and solid organ transplant excluded
A Study of Nivolumab Plus Brentuximab Vedotin Versus Brentuximab Vedotin Alone in Patients with Advanced Stage Classical Hodgkin Lymphoma, Who Are Relapsed/ Refractory or Who Are Not Eligible for Autologous Stem Cell Transplant (CheckMate 812)	Ineligible or relapse after ASCT	III	NCT03138499	Recently completed	Must have at least one lesion that is >15 mm in the longest diameter
Ipilimumab or Nivolumab in Treating Patients with Relapsed Hematologic Malignancies After Donor Stem Cell Transplant	Post allogeneic SCT relapse	I	NCT01822509	Recently completed	Must have baseline donor T-cell chimerism of ≥20%
Nivolumab and Brentuximab Vedotin After Stem Cell Transplant in Treating Patients with Relapsed or Refractory High-Risk Classical Hodgkin Lymphoma	Post ASCT	II	NCT03057795	Active, not recruiting	Complex high-risk disease definition in trial details
A Study of Anti-PD-1 AK105 in Patients with Relapsed or Refractory Classic Hodgkin Lymphoma	Post ASCT or at least 2 lines of prior therapy	I/II	NCT03722147	Unknown	AK105 is an anti-PD-1 antibody

Abbreviations: AVD, adriamycin, vinblastine, dacarbazine; ABVD, adriamycin, bleomycin, vinblastine, dacarbazine; ASCT, autologous stem cell transplant; SCT, stem cell transplant; BV, brentuximab vedotin; R, retrospective; CR, complete response; Nivo, nivolumab; PD, programmed cell death; CPI, checkpoint inhibitor; PET, positron emission tomography; mm, millimeter; RT, radiation therapy; HIV, human immunodeficiency virus.

https://doi.org/10.2147/ITT.S284988

Camrelizumab, another anti-PD-1 antibody, was administered to 75 Chinese patients with relapsed/refractory cHL after ASCT or who had received two or more lines of chemotherapy, among whom 57 (76.0%, 95% CI 64.7–85.1%) achieved an objective response based on review by an independent review committee.[47] A two-arm, open-label phase II study consisting of 86 relapsed/refractory cHL patients who had already undergone at least two lines of therapy reaffirmed the efficacy of camrelizumab, though it also suggested that co-administration of decitabine improves the clinical response. Among the patients who were naïve to anti-PD-1 therapy, six of 19 (32%) achieved complete remission with camrelizumab monotherapy, compared with 30 of 42 patients (71%) who received decitabine plus camrelizumab. In patients who had previously been treated with anti-PD-1 therapy, 28% achieved complete remission, while PR was seen in 24% of these patients, suggesting that co-administration of decitabine could bypass PD-1 resistance in patients who had previously been treated with anti-PD-1 therapy.[48]

JAVELIN Hodgkins, a phase Ib trial for patients with relapsed/refractory cHL, showed that avelumab, an anti-PD-L1 monoclonal antibody, is also effective in this patient population.[49] In this study of 31 heavily pretreated patients, nine had received three prior treatments and 20 had received four or more treatments. The objective response rate among all patients was 41.9%, with a CR rate of 19.4%, and the objective response rate among patients who had previously received an allogeneic hematopoietic stem cell transplant was even more significant, at 55.6%.

Conclusion

CPIs are destined to be active agents in HL owing to the biological nature of 9p24.1 amplification. Both pembrolizumab and nivolumab have been successful in treating cHL patients as single agents or as combination therapy with brentuximab vedotin or chemotherapy in the third line. Growing evidence suggests that CPIs in the first or second line may improve outcomes. Additional clinical trials are needed and are ongoing to evaluate the best time to use CPIs in these patient populations (Table 1). CPIs in combination with newer targeting agents will also be a point of further trials, especially since the PD-1/PD-2 pathway is not the only method of immune evasion by RSCs.[50] Furthermore, a better understanding of the systemic and tumor microenvironment will help us predict which patients will respond to CPI therapy.[51]

Disclosure

Dr. Leo I Gordon reports consulting fees from Astra Zeneca, consulting fees from Karyopharm Therapeutics, consulting fees from Epizyme, consulting fees from Janssen Research and Development, and consulting fees from Janssen Research and Development, outside the submitted work; in addition, Dr Leo I Gordon has a patent for Gold Nanoparticles for Lymphoma, issued to Application Serial No. 62/902,342. The authors report no other conflicts of interest in this work.

References

1. Hodgkin Lymphoma Cancer stat facts; [cited 2022 February 10]. Available from: https://seer.cancer.gov/statfacts/html/ hodg.html
2. Hodgkin Lymphoma. NCCN clinical practice guidelines in oncology (NCCN guidelines ®) NCCN.org NCCN guidelines for patients ®; 2021. Available from: www.nccn.org/patients. Accessed February 2, 2022.
3. van Leeuwen FE, Ng AK. Late sequelae in Hodgkin lymphoma survivors. *Hematol Oncol*. 2017;35:60–66. doi:10.1002/hon.2402
4. van Nimwegen FA, Ntentas G, Darby SC. Risk of heart failure in survivors of Hodgkin lymphoma: effects of cardiac exposure to radiation and anthracyclines. *Blood*. 2017;129(16):2257–2265. doi:10.1182/blood-2016-09-740332
5. Connors JM, Jurczak W, Straus DJ, et al. Brentuximab vedotin with chemotherapy for stage III or IV Hodgkin's lymphoma. *N Engl J Med*. 2018;378(4):331–344. doi:10.1056/NEJMoa1708984
6. Straus DJ, Długosz-Danecka M, Connors JM, et al. Brentuximab vedotin with chemotherapy for stage III or IV classical Hodgkin lymphoma (ECHELON-1): 5-year update of an international, open-label, randomised, phase 3 trial. *Lancet Haematol*. 2021;8(6):e410–e421. doi:10.1016/S2352-3026(21)00102-2
7. Zelenetz AD, Hamlin P, Kewalramani T, et al. Ifosfamide, carboplatin, etoposide (ICE)-based second-line chemotherapy for the management of relapsed and refractory aggressive non-Hodgkin's lymphoma. *Ann Oncol*. 2003;14(SUPPL. 1):i5–i10. doi:10.1093/annonc/mdg702
8. Bartlett NL, Niedzwiecki D, Johnson JL, et al. Gemcitabine, vinorelbine, and pegylated liposomal doxorubicin (GVD), a salvage regimen in relapsed Hodgkin's lymphoma: CALGB 59804. *Ann Oncol*. 2007;18(6):1071–1079. doi:10.1093/annonc/mdm090
9. Castagna L, Santoro A, Carlo-Stella C. Salvage therapy for Hodgkin's lymphoma: a review of current regimens and outcomes. *J Blood Med*. 2020;11:389–403. doi:10.2147/JBM.S250581
10. Chen BJ, Chapuy B, Ouyang J, et al. PD-L1 expression is characteristic of a subset of aggressive B-cell lymphomas and virus-associated malignancies. *Clin Cancer Res*. 2013;19(13):3462–3473. doi:10.1158/1078-0432.CCR-13-0855

11. Cader FZ, Schackmann RCJ, Hu X, et al. Mass cytometry of Hodgkin lymphoma reveals a CD4+ regulatory T-cell-rich and exhausted T-effector microenvironment. *Blood*. 2018;132(8):825–836. doi:10.1182/blood-2018-04-843714
12. Carey CD, Gusenleitner D, Lipschitz M, et al. Topological analysis reveals a PD-L1-associated microenvironmental niche for Reed-Sternberg cells in Hodgkin lymphoma. *Blood*. 2017;130(22):2420–2430. doi:10.1182/blood-2017-03-770719
13. Roemer MG, Advani RH, Ligon AH, et al. PD-L1 and PD-L2 genetic alterations define classical Hodgkin lymphoma and predict outcome. *J Clin Oncol*. 2016;34(23):2690–2697. doi:10.1200/JCO.2016.66.4482
14. Wienand K, Chapuy B, Stewart C, et al. Genomic analyses of flow-sorted Hodgkin Reed-Sternberg cells reveal complementary mechanisms of immune evasion. *Blood Adv*. 2019;3(23):4065–4080. doi:10.1182/bloodadvances.2019001012
15. Batlevi CL, Matsuki E, Brentjens RJ, Younes A. Novel immunotherapies in lymphoid malignancies. *Nat Rev Clin Oncol*. 2015;13(1):25–40. doi:10.1038/nrclinonc.2015.187
16. Pezeshki PS, Eskian M, Hamblin MR, Rezaei N. Immune checkpoint inhibition in classical Hodgkin lymphoma. *Expert Rev Anticancer Ther*. 2021;00(00):1–14.
17. Al-Hadidi SA, Chuang HH, Miranda RN, Lee HJ. Programmed cell death-one inhibition therapy in classical Hodgkin lymphoma. *Clin Lymphoma Myeloma Leuk*. 2021;21(2):e105–e111. doi:10.1016/j.clml.2020.08.031
18. Savage KJ, Steidl C. Immune checkpoint inhibitors in Hodgkin and non-Hodgkin lymphoma: how they work and when to use them. *Expert Rev Hematol*. 2016;9(11):1007–1009. doi:10.1080/17474086.2016.1242404
19. Lin RJ, Diefenbach CS. Checkpoint inhibition in Hodgkin lymphoma: saving the best for last? *Oncology (Williston Park)*. 2016;30(10):914–920.
20. Ansell SM, Lesokhin AM, Borrello I, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. *N Engl J Med*. 2015;372(4):311–319. doi:10.1056/NEJMoa1411087
21. Maruyama D, Hatake K, Kinoshita T, et al. Multicenter phase II study of nivolumab in Japanese patients with relapsed or refractory classical Hodgkin lymphoma. *Cancer Sci*. 2017;108(5):1007–1012. doi:10.1111/cas.13230
22. Younes A, Santoro A, Shipp M, et al. Nivolumab for classical Hodgkin's lymphoma after failure of both autologous stem-cell transplantation and brentuximab vedotin: a multicentre, multicohort, single-arm phase 2 trial. *Lancet Oncol*. 2016;17(9):1283–1294. doi:10.1016/S1470-2045(16)30167-X
23. Armand P, Shipp MA, Ribrag V, et al. Programmed death-1 blockade with pembrolizumab in patients with classical Hodgkin lymphoma after brentuximab vedotin failure. *J Clin Oncol*. 2016;34(31):3733–3739. doi:10.1200/JCO.2016.67.3467
24. Chen R, Zinzani PL, Fanale MA, et al. Phase II study of the efficacy and safety of pembrolizumab for relapsed/refractory classic Hodgkin lymphoma. *J Clin Oncol*. 2017;35(19):2125–2132. doi:10.1200/JCO.2016.72.1316
25. Armand P, Zinzani PLL, Lee HJ, et al. Five-year follow-up of keynote-087: pembrolizumab monotherapy in relapsed/refractory classical Hodgkin lymphoma (R/R cHL). *Blood*. 2021;138(Supplement 1):1366. doi:10.1182/blood-2021-147881
26. Armand P, Kuruvilla J, Michot JM, et al. KEYNOTE-013 4-year follow-up of pembrolizumab in classical Hodgkin lymphoma after brentuximab vedotin failure. *Blood Adv*. 2020;4(12):2617–2622. doi:10.1182/bloodadvances.2019001367
27. Herrera AF, Chen L, Popplewell LL, et al. Preliminary results from a phase I trial of pembrolizumab plus vorinostat in patients with relapsed or refractory diffuse large B-cell lymphoma, follicular lymphoma, and Hodgkin lymphoma. *Blood*. 2019;134(Supplement_1):759. doi:10.1182/blood-2019-123163
28. Bartlett NL, Herrera AF, Domingo-Domenech E, et al. A phase 1b study of AFM13 in combination with pembrolizumab in patients with relapsed or refractory Hodgkin lymphoma. *Blood*. 2020;136(21):2401–2409. doi:10.1182/blood.2019004701
29. Armand P, Bin CY, Redd RA, et al. PD-1 blockade with pembrolizumab for classical Hodgkin lymphoma after autologous stem cell transplantation. *Blood*. 2019;134(1):22–29. doi:10.1182/blood.2019000215
30. Bachier C, Schade H, Zoghi B, Ramakrishnan A, Shah NN. A phase II single arm study of nivolumab as maintenance therapy after autologous stem cell transplantation in patients with Hodgkin lymphoma at risk of relapse or progression. *Blood*. 2021;138(Supplement 1):2455. doi:10.1182/blood-2021-148139
31. Herrera AF, Moskowitz AJ, Bartlett NL, et al. Interim results of brentuximab vedotin in combination with nivolumab in patients with relapsed or refractory Hodgkin lymphoma. *Blood*. 2018;131(11):1183–1194. doi:10.1182/blood-2017-10-811224
32. Moskowitz AJ, Advani RH, Bartlett NL, et al. Brentuximab vedotin and nivolumab for relapsed or refractory classic Hodgkin lymphoma: long-term follow-up results from the single-arm phase 1/2 study. *Blood*. 2019;134(Supplement_1):238. doi:10.1182/blood-2019-122576
33. Bryan LJ, Smith SE, Allen P, et al. Safety and toxicity profile of pembrolizumab (PEM) in combination with ICE chemotherapy followed by autologous stem cell transplantation for relapsed/refractory classical Hodgkin lymphoma: no impairment in stem cell mobilization or engraftment. *Blood*. 2019;134(Supplement_1):4029. doi:10.1182/blood-2019-123879
34. Kuruvilla J, Ramchandren R, Santoro A, et al. KEYNOTE-204: randomized, open-label, phase III study of pembrolizumab (pembro) versus brentuximab vedotin (BV) in relapsed or refractory classic Hodgkin lymphoma (R/R cHL). *ASCO Ann Meet*. 2020;38(15_suppl):8005. doi:10.1200/JCO.2020.38.15_suppl.8005
35. Moskowitz AJ, Shah G, Schöder H, et al. Phase II trial of pembrolizumab plus gemcitabine, vinorelbine, and liposomal doxorubicin as second-line therapy for relapsed or refractory classical Hodgkin lymphoma. *J Clin Oncol*. 2021;39:3109–3117. doi:10.1200/JCO.21.01056
36. Diefenbach CS, Hong F, Ambinder RF, et al. Ipilimumab, nivolumab, and brentuximab vedotin combination therapies in patients with relapsed or refractory Hodgkin lymphoma: phase 1 results of an open-label, multicentre, phase 1/2 trial. *Lancet Haematol*. 2020;7(9):e660–e670. doi:10.1016/S2352-3026(20)30221-0
37. Patel SS, Weirather JL, Lipschitz M, et al. The microenvironmental niche in classic Hodgkin lymphoma is enriched for CTLA-4–positive T cells that are PD-1–negative. *Blood*. 2019;134(23):2059–2069. doi:10.1182/blood.2019002206
38. Alencar AJ, Moskowitz CH. Immune-checkpoint inhibition as first-line therapy for Hodgkin lymphoma. *Nat Rev Clin Oncol*. 2019;16(10):599–600. doi:10.1038/s41571-019-0255-8
39. Allen PB, Savas H, Evens AM, et al. Pembrolizumab followed by AVD in untreated early unfavorable and advanced-stage classical Hodgkin lymphoma. *Blood*. 2021;137(10):1318–1326. doi:10.1182/blood.2020007400
40. Bröckelmann PJ, Goergen H, Keller U. Efficacy of nivolumab and AVD in early-stage unfavorable classic Hodgkin lymphoma: the randomized phase 2 German Hodgkin study group NIVAHL trial. *JAMA Oncol*. 2020;6(6):872–880. doi:10.1001/jamaoncol.2020.0750

41. Ramchandren R, Fanale MA, Rueda A, et al. Nivolumab for newly diagnosed advanced-stage classical Hodgkin lymphoma (cHL): results from the phase 2 checkmate 205 study. *Blood*. 2017;130(Suppl 1):651. doi:10.1182/blood.V130.Suppl_1.651.651
42. Ansell S, Ramchandren R, Domingo-Domènech E, et al. Nivolumab plus doxorubicin, vinblastine and dacarbazine for newly diagnosed advanced-stage classical Hodgkin lymphoma: checkmate 205 cohort D 2-year follow-up. *Hematol Oncol*. 2019;37:146–147. doi:10.1002/hon.104_2629
43. Ramchandren R, Domingo-Domènech E, Rueda A. Nivolumab for newly diagnosed advanced-stage classic Hodgkin lymphoma: safety and efficacy in the phase II checkMate 205 study. *J Clin Oncol*. 2019;37(23):1997–2007. doi:10.1200/JCO.19.00315
44. Roemer MGM, Redd RA, Cader FZ, et al. Major histocompatibility complex class II and programmed death ligand 1 expression predict outcome after programmed death 1 blockade in classic Hodgkin lymphoma. *J Clin Oncol*. 2018;36(10):942–950. doi:10.1200/JCO.2017.77.3994
45. Shi Y, Su H, Song Y, et al. Safety and activity of sintilimab in patients with relapsed or refractory classical Hodgkin lymphoma (ORIENT-1): a multicentre, single-arm, phase 2 trial. *Lancet Haematol*. 2019;6(1):e12–e19. doi:10.1016/S2352-3026(18)30192-3
46. Song Y, Gao Q, Zhang H. Treatment of relapsed or refractory classical Hodgkin lymphoma with the anti-PD-1, tislelizumab: results of a phase 2, single-arm, multicenter study. *Leukemia*. 2020;34(2):533–542. doi:10.1038/s41375-019-0545-2
47. Song Y, Wu J, Chen X. A single-arm, multicenter, phase II study of camrelizumab in relapsed or refractory classical Hodgkin lymphoma. *Clin Cancer Res*. 2019;25(24):7363–7369. doi:10.1158/1078-0432.CCR-19-1680
48. Nie J, Wang C, Liu Y, et al. Addition of low-dose decitabine to anti–PD-1 antibody camrelizumab in relapsed/refractory classical Hodgkin lymphoma. *J Clin Oncol*. 2019;37(17):1479–1489. doi:10.1200/JCO.18.02151
49. Herrera AF, Burton C, Radford J, et al. Avelumab in relapsed/refractory classical Hodgkin lymphoma: phase 1b results from the JAVELIN Hodgkins trial. *Blood Adv*. 2021;5(17):3387–3396. doi:10.1182/bloodadvances.2021004511
50. Green MR, Monti S, Rodig SJ, et al. Integrative analysis reveals selective 9p24.1 amplification, increased PD-1 ligand expression, and further induction via JAK2 in nodular sclerosing Hodgkin lymphoma and primary mediastinal large B-cell lymphoma. *Blood*. 2010;116(17):3268–3277. doi:10.1182/blood-2010-05-282780
51. Cader FZ, Hu X, Goh WL, et al. A peripheral immune signature of responsiveness to PD-1 blockade in patients with classical Hodgkin lymphoma. *Nat Med*. 2020;26(9):1468–1479. doi:10.1038/s41591-020-1006-1