

# Checkpoint Inhibitors in Relapsed/Refractory Classical Hodgkin Lymphoma

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## Abstract

Even though classical Hodgkin lymphoma is highly curable, the outcome of patients with a refractory or relapsed disease has been disappointing. Multiple lines of therapy are available for patients after their first failure, and most respond to subsequent therapies. However, there is a sizable proportion that remains relapsing/recurrent even after several lines of therapy. The overall prognosis of patients with relapsing and recurrent classical Hodgkin lymphoma (rrcHL) has been very disappointing until recently. Immune checkpoint inhibitors such as the anti-programmed death 1 (PD-1) receptor antibodies have recently been approved to treat relapsed and refractory cHL and have significantly improved the outcome of patients with rrcHL. The approved immune checkpoint inhibitors for relapsed and refractory cHL are nivolumab and pembrolizumab. In the Checkmate 205 study nivolumab demonstrated an objective response rate of 69% with an acceptable safety profile. Similarly, pembrolizumab demonstrated an overall response rate (ORR) of 69% with a complete remission rate (CRR) of 22.4% in the KEYNOTE-087 study in heavily pretreated patients with rrcHL.

**Keywords:** Checkpoint inhibitors; Nivolumab; Pembrolizumab; Relapsed/refractory classical Hodgkin lymphoma

## Introduction

The development in the treatment of Hodgkin lymphoma has been an amazing multidisciplinary effort throughout history.

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The present modalities of therapy have converted a fatal disease to one that is curable in most patients. The current guidelines for the treatment of Hodgkin lymphoma rely mostly on the stage of the disease at first presentation and the prognostic factors, which may be favorable or unfavorable. It is important to make this distinction because the therapy tends to be more aggressive in the unfavorable group. The core of classical Hodgkin lymphoma (cHL) management is based on the ABVD therapy combination (doxorubicin, bleomycin, vinblastine, dacarbazine) followed by the recommended form of radiation in the early and advanced stages of the disease [1]. Other therapies available for advanced stages such as escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone) and brentuximab vedotin (BV) + AVD, saved for more aggressive presentation, have a longer progression-free survival without any impact in the overall survival. Stanford V (doxorubicin, vinblastine, mechlorethamine, vincristine, bleomycin, etoposide and prednisone) is another therapeutic option that incorporates radiation therapy for all patients. However, there is no advantage compared to ABVD [2-4].

Even though cHL is highly curable, around 25% of the patients with cHL have a refractory or relapsed disease after the first-line therapy [5]. High-dose chemotherapy (using a different chemotherapeutic agent) and autologous stem cell transplantation (SCT) is considered the treatment of choice in a subset of patients. However, in these patients, conventional-dose chemotherapy regimens induce low remission rates, resulting in long-term remissions in approximately 40-50% of relapsed patients and in up to 25-30% of those with primary refractory disease. Lately, cancer immunotherapy has shown promising results in high-risk relapsed/refractory cHL (rrcHL) patients using strategies to overcome the evasion of immune surveillance that can be classified as passive (administration of agents such as monoclonal antibodies, lymphocytes or cytokines that potentiate existing anti-tumor response) or active immunotherapy (the stimulation of self-immune system to attack tumor cells via vaccination, non-specific immunomodulation, or targeting specific antigen receptors). In this review, we will present the scientific rationale for the currently available immunotherapies in rrcHL.

## Checkpoint Inhibitors Therapy

The overall prognosis of patients with cHL has improved over

the decades with most patients responding well to the standard means of therapy [6]. However, there is a subgroup of patients who will have relapsed and refractory disease with poor outcomes. The goal for the treatment in the first relapsed/refractory episode in cHL is to achieve long-term disease control, which may be accomplished in most cases through the application of autologous SCT. The pre-transplant positron emission tomography (PET) negativity is one of the most crucial predictors of the outcome after autologous SCT in patients with relapsed or refractory cHL [1]. A state of complete remission before autologous SCT may be achieved using intensive combination or targeted chemotherapy.

Immune checkpoint inhibitors such as the anti-programmed death 1 (PD-1) receptor antibodies have recently been approved for the treatment of relapsed and refractory cHL and have shown to be effective [7]. The malignant Reed Sternberg cells in cHL overexpress programmed death-ligand 1 (PD-L1) and PD-L2, which confer them with several mechanisms to escape immune clearance [8]. One of the hallmarks of this escape is that the tumor cells are capable of immune suppressing the highly inflamed tumor microenvironment composed of T cells, B cells, macrophages, natural killer (NK) cells and neutrophils. Targeting PD-1 will restore immune function in the tumor microenvironment. This is the rationale for the use of these types of drugs in cHL.

The approved immune checkpoint inhibitors for relapsed and refractory cHL are nivolumab and pembrolizumab with demonstrated high response rates in several retrospective studies. Other immune checkpoint inhibitors including ipilimumab, sintilimab and tislelizumab have also been tried [9, 10].

## Nivolumab

Nivolumab is a fully human immunoglobulin G4 (IgG4) monoclonal antibody selectively targeting the PD-1 receptor to block the ligands PD-L1 and PD-L2 from binding. It has been previously used in other solid tumors. Nivolumab was first evaluated in a phase I trial which enrolled 23 patients who received extensive prior treatment regimens including BV and autologous SCT. Treatment with nivolumab had an overall response rate (ORR) of 87% and progression-free survival of 86% in 24 months follow-up. Nivolumab exhibited an acceptable safety profile with most adverse events being grade one and two [11]. Subsequently, the phase II study which enrolled 243 patients (Checkmate 205) was developed to further assess the clinical activity and safety of nivolumab. Checkmate 205 is a multi-center phase II study that enrolled 243 patients with rrcHL, who have failed after autologous SCT and treatment with BV, grouped into three cohorts according to their prior therapies. Most of the participants were heavily treated before enrollment, with the median number of prior lines of therapy being four. The objective response rate as assessed by an independent radiologic review committee (IRRC) was 69%. It was very promising to note more than two-thirds of patients who failed BV treatment responded to nivolumab. The study also showed that nivolumab has an acceptable safety profile with most reported adverse event (AE) being grade one to two.

Subjectively patients overall reported improved quality of life [12]. Moreover, extended follow-up of Checkmate 205 study concluded that the response to nivolumab was frequent and durable. The ORR in the cohorts divided according to pretreatment regimen was 69% [13]. The promising results of these trials led to the US Food and Drug Administration (FDA) approval of nivolumab for patients with rrcHL.

## Pembrolizumab

Pembrolizumab is another humanized, high-affinity, IgG4 monoclonal antibody directed against PD-1. Pembrolizumab was evaluated in the phase IB study, KEYNOTE-013 (ClinicalTrials.gov, NCT01953692), designed to evaluate its safety and anti-tumor activity. Based on the knowledge of the role of PD-1 signaling pathway in the pathogenesis of Hodgkin lymphoma the study had an independent cohort of patients with Hodgkin lymphoma. The cohort had 31 patients. The participants had received multiple prior treatments with 55% receiving greater than or equal to five lines of therapy and all had received BV. Pembrolizumab had a high ORR of 65% at 12 weeks and has demonstrated a favorable safety profile. The median survival at the time of the study cutoff was 17.6 months. Although the 16% complete remission rate (CRR) in this study was low, the durability of the partial response (PR) (48 %) achieved in this study was very promising. This shows in line with other studies, that achievement of complete remission with checkpoint blockade might not be necessary to derive significant clinical outcome. The progression-free survival and overall survival rates at 24 weeks were 69% and 100%, respectively. Progression-free survival at 52 weeks was 46% [14]. Subsequently, a multicenter, single-arm phase II study (KEYNOTE-087) enrolled 210 patients who either had autologous SCT or are ineligible to evaluate the clinical activity of pembrolizumab in patients with rrcHL. The study grouped subjects into three cohorts based on disease progression and prior line of therapy. Similar to the studies with nivolumab, the study subjects had multiple prior lines of therapy with the median number of prior lines of therapy being four. In this study, the ORR was 69% with a CRR of 22.4%; and interestingly, ORR did not vary based on the number of prior lines of therapy. Moreover, pembrolizumab has demonstrated an acceptable safety profile. Compared to nivolumab, pembrolizumab has shown to have better CRR [15]. Like nivolumab, the promising results of these trials led to the US FDA approval of pembrolizumab for patients with rrcHL.

## Combination Therapy

The immune checkpoint inhibitors (nivolumab and pembrolizumab) have significantly improved the prognosis of relapsed and refractory cHL. While the improvement in overall response achieved by PD-1 blockade had been promising, there are a sizable proportion of patients who would not have a durable response [16]. Given this, combination therapy has been pursued. Combination therapies involving BV (a CD30-direct-

ed antibody-drug conjugate) and nivolumab and ipilimumab; nivolumab and bendamustine; nivolumab with radiation therapy are being developed [17-20].

## Conclusions

Over the last few years, checkpoint inhibitors have significantly changed the prognosis of patients with rrcHL. The checkpoint inhibitors, nivolumab and pembrolizumab, have demonstrated outstanding results in heavily pretreated (including BV and autologous SCT) patients with rrcHL in the Checkmate 205 and KEYNOTE-087 studies. Combination therapies involving checkpoint inhibitors are being pursued to fill the gap that remains in the management of rrcHL after checkpoint inhibitors.

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None to declare.

## Conflict of Interest

None to declare.

## Author Contributions

All authors contributed to conception, design, manuscript writing and final approval of the manuscript. All authors are accountable for all aspects of the work.

## Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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