

## REVIEW

# Current directions in the treatment of classical Hodgkin lymphoma

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**Abstract**

Optimal management of patients who present with Hodgkin lymphoma continues to evolve. Most patients are cured with current treatment strategies, some but both short and long-term morbidity and mortality from treatment have particular relevance given the youth of the patient population. Combinations of targeted agents together with conventional chemotherapy have recently been investigated in phase 3 clinical trials for advanced-stage Hodgkin lymphoma, and have demonstrated improved efficacy compared with chemotherapy alone. These include both antibody-drug conjugates and PD-1 blockade. Treatment approaches have historically differed between pediatric and adult groups, but recent collaborations between adult and pediatric groups via the NCTN mechanism have resulted in the successful completion of enrollment in an advanced-stage Hodgkin lymphoma and the opening of an early-stage trial that will enroll patients across a broad age spectrum. Novel approaches incorporating targeted and immunomodulatory agents in the relapse setting are being actively investigated in the relapse setting as well.

**KEYWORDS**

chemotherapy, classical Hodgkin lymphoma, treatment

## 1 | ADVANCED STAGE CLASSICAL HODGKIN LYMPHOMA

Optimal management of patients who present with advanced-stage Hodgkin lymphoma remains a challenge. Most patients are cured with current treatment strategies, but approximately 20% of patients will experience disease progression. Additionally, both short and long-term morbidity and mortality from treatment have particular relevance given the youth of the patient population. Chemotherapy backbones for advanced-stage Hodgkin lymphoma have historically differed between adult and pediatric treatment settings. In the United States, pediatric patients with advanced-stage presentations are generally treated with doxorubicin, bleomycin, vinblastine, etoposide,

prednisone, cyclophosphamide (ABVE-PC), and more than half receive consolidative radiation therapy. Adult patients have been treated with either response-adapted doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD) or, in some cases, dose-escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone (BEACOPP), with minimal use of radiation therapy. More recent studies in both adult and pediatric settings have demonstrated improved progression-free survival (PFS) and overall survival (OS) with the substitution of brentuximab vedotin for bleomycin in advanced-stage disease, and this agent is now routinely incorporated into all of the aforementioned chemotherapy treatment paradigms.

The PD-1 pathway is central to the pathogenesis of Hodgkin lymphoma and PD-1 blockade with pembrolizumab or nivolumab is highly

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effective in relapsed or refractory disease. These agents have been demonstrated to be safe in both pediatric and adult populations, and small phase 2 studies demonstrated a high level of efficacy with combinations of checkpoint inhibitors and conventional chemotherapy. In 2018, SWOG convened a clinical trials planning meeting among all of the National Cancer Institute-funded National Clinical Trial Network (NCTN) groups (Alliance, CCTG, COG, ECOG-Acrin, and SWOG). There was a uniform agreement to develop a phase 3 definitive trial testing AVD with nivolumab. However, there was initial controversy and extended discussion over control arm choices and chemotherapy backbone, as well as the use of radiation therapy. The final study, S1826 emerged as a phase III randomized trial of nivolumab or brentuximab vedotin plus AVD in patients (age  $\geq 12$  years) with newly diagnosed advanced-stage cHL, with very limited and strict criteria regarding consolidative radiation therapy. In September 2019 the first patient was enrolled, and the last patient was enrolled in October 2022, completing therapy in April 2023. In addition to the primary endpoint of PFS and secondary endpoints of event-free survival (EFS), OS, and CR, planned exploratory analyses include correlative biologic studies (circulating tumor DNA), imaging studies, quality-of-life (QoL), and patient-reported outcomes, as well as economic outcomes.

This study is unique in that it captures the full adolescent and young adult (AYA) population and can serve as an example of the rapid implementation of a clinical study that serves AYA patients. The pediatric COG group enrolled approximately one-third of the patients in this trial, and almost no patients received radiation therapy. The study accrued very rapidly and serves as a model to harmonize pediatric and adult approaches to treatment. Preliminary results of the trial were presented at the ASCO meeting in 2023 reporting on the primary endpoint, and long-term follow-up is planned to capture late effects of treatment. The fruitful collaboration between the NCTN groups has now extended to trials in early-stage disease and relapsed disease.

## 2 | EARLY-STAGE CLASSICAL HODGKIN LYMPHOMA

Early-stage Hodgkin lymphoma is a highly curable cancer, but late effects of treatment have been significant causes of morbidity and mortality, leading to ongoing efforts to effect cure while minimizing treatment-related toxicities [1, 2]. The standard approach to the treatment of early-stage classical Hodgkin lymphoma in adult patients has been the ABVD regimen with or without radiation therapy. Modifications to this decades-old combined modality approach have included therapy modifications based on initial risk stratification (Early-favorable vs. Unfavorable), early metabolic response determined chemotherapy escalation (e.g., escBEACOPP), or application of radiation therapy after completing chemotherapy, modification of radiation fields and techniques, and the introduction of proton based radiation therapy. Pediatric approaches have differed from the adult approaches in terms of risk stratification based on initial factors (low-risk vs. intermediate-risk). Compared with the treatment of adult patients pediatric chemotherapy protocols have

been less standardized, with a variety of regimens including VAMP (vincristine, doxorubicin, methotrexate, prednisone), AVPC (doxorubicin, vincristine, prednisone, cyclophosphamide), ABVE-PC, OEPA (vincristine, etoposide, prednisone, doxorubicin), COPDac (cyclophosphamide, vincristine, prednisone, dacarbazine) having been used by treatment groups. Reports utilizing the ABVD regimen in pediatric patients have been limited but do suggest that the safety, tolerability, and outcomes are similar to adult patients [3–5].

Based on the introduction of targeted therapy with brentuximab vedotin and the emerging data regarding the use of check point inhibition in advanced-stage classical Hodgkin lymphoma, as well as the success of the S1826 study that demonstrated the feasibility of pediatric and adult collaboration in Hodgkin lymphoma via the NCTN mechanism, AHOD2131 has been developed to investigate the use of an immune-oncology (IO) approach for newly diagnosed early-stage Hodgkin lymphoma. This protocol, open to all NCTN participating groups, opened in March 2023 and prescribes two cycles of ABVD to all subjects followed by response-based randomization to either continue conventional chemo/radiotherapy approaches or to receive an IO-based regimen using nivolumab and brentuximab vedotin. Eligibility criteria include ages 5–60 years with favorable or unfavorable early-stage classical Hodgkin lymphoma. The primary aims of the study relate to PFS for subjects with rapid and slow early response, and important secondary aims include overall survival at 12 years and an emphasis on the collection of patient-reported outcomes over that time period. The longer time frame for outcomes collection is an important mechanism for determining the overall impact of the disease and treatment effects in this predominantly younger patient population who may be vulnerable to financial and social disruptions in addition to the health effects of the lymphoma diagnosis.

## 3 | RELAPSED AND REFRACTORY CLASSICAL HODGKIN LYMPHOMA

Fortunately, the majority of patients diagnosed with Hodgkin lymphoma will be cured with frontline therapy. For patients who relapse after frontline therapy, the goal remains to cure, but approximately only 50% of patients achieve this goal. The most common strategy pursued involves some form of salvage chemotherapy followed by autologous stem cell transplantation (ASCT). However, the disease must respond to the salvage chemotherapy to be considered for ASCT. Traditional salvage regimens, salvage regimens such as ICE or GVD produce overall responses in 70%–80% of patients and complete responses in 50%–60% of patients. Improving the overall response rate and complete response rate to salvage therapy could improve outcomes in this population.

The introduction of checkpoint inhibitors into salvage regimens may be the strategy that may ultimately cure more patients in the relapsed setting. Several phase 2 studies have demonstrated highly promising results. For example, the combination of brentuximab vedotin combined with nivolumab generated overall response rates of 82%, complete response rates of 61%, and 2-year EFS rates of 78% in a

**TABLE 1** Active and recent phase 3 trials for classical Hodgkin lymphoma.

Study	Eligibility	Randomized question	Ages	Status
S1826	Advanced stage	BV-AVD vs. Nivolumab-AVD	≥12 years	Completed enrollment. Preliminary results expected at ASCO, July 2023
AHOD2131	Early stage	Conventional Chemotherapy vs. chemotherapy plus nivolumab/BV.	5–60 years	Opened as NCTN trial in March 2023
EA4211	Relapse	Conventional chemotherapy vs. pembrolizumab plus conventional chemotherapy	5–75 years	Pending

Abbreviations: ASCO, American Society Clinical Oncology; AVD, doxorubicin, vinblastine, dacarbazine; BV, Brentuximab vedotin; NCTN, National Clinical Trials Network.

cohort of 61 patients with relapsed and refractory Hodgkin lymphoma [6]. A second study in a similar population evaluated the combination of pembrolizumab plus gemcitabine, vinorelbine, and liposomal doxorubicin (pembro-GVD) [7]. A total of 39 patients were enrolled, and 38 were evaluable for response. The overall response rate was 100% and the complete response rate was 95%. Of the 36 patients who went on to ASCT, all remained in remission with 13 months median follow-up. The third promising phase II study was a multi-institutional effort evaluating the combination of pembrolizumab plus ifosfamide, carboplatin, and etoposide chemotherapy (pembro-ICE) [8]. The trial enrolled 42 patients with 37 evaluable for response. The overall response rate was 97% and the complete response rate was 86%. The 2-year PFS rate was 87%. The results of these three phase 2 studies of checkpoint inhibition plus standard therapy compare favorably to historical controls of conventional therapy.

Based upon these highly encouraging phase 2 studies, the National Clinical Trials Network (NCTN) has proposed a randomized phase III clinical trial testing conventional chemotherapy against checkpoint inhibition plus conventional chemotherapy as salvage therapy prior to planned ASCT. The trial, EA4211, allows for three different chemotherapy regimens to be selected (GVD, ICE, or BV/Bendamustine) at the treating physician's discretion. The primary endpoint of the study is the 2-year event-free survival. Events include failure to respond to the salvage regimen, failure to achieve complete remission post-ASCT, disease progression at any time, or death from any cause. The trial is designed to show an improvement in the 2-year EFS from 65% with conventional therapy to 79% with the addition of the checkpoint inhibitor pembrolizumab to conventional therapy. EA4211 will plan to enroll 334 patients to achieve 312 eligible randomized patients. To be eligible, patients must be at least 5 years of age and less than 76 years of age. They must have relapsed classic Hodgkin lymphoma and be considered appropriate candidates for ASCT.

In summary, classical Hodgkin lymphoma can be successfully treated in the substantial majority of patients, but also represents a paradigm for long-term complications of cancer treatment due in part to this successful treatment in the adolescent/young adult age range, many of whom have otherwise good health prior to their lymphoma diagnosis. The AYA predilection of Hodgkin lymphoma has also created an opportunity to develop trials that enroll both pediatric and adult patients. Investigations of improved strategies for initial and sal-

vage treatments are focused in large part on minimizing these adverse treatment effects while maintaining or improving disease-free survival. Hodgkin lymphoma appears to be highly responsive to IO, and current active trials are investigating how best to incorporate IO into established approaches to the treatment of newly diagnosed and relapsed disease (Table 1).

#### AUTHOR CONTRIBUTIONS

All authors contributed equally to the writing of this manuscript.

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The authors declare no conflict of interest.

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The authors have confirmed ethical approval statement is not needed for this submission.

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The authors have confirmed patient consent statement is not needed for this submission

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