haematologica
Journal of the Ferrata Storti Foundation

# Relapsed classic Hodgkin lymphoma; should all patients receive an autologous stem cell transplant? – the PRO

*by Chathuri Abeyakoon and John Kuruvilla*

*Received: January 21, 2026.*
*Accepted: March 25, 2026.*

*Citation: Chathuri Abeyakoon and John Kuruvilla. Relapsed classic Hodgkin lymphoma; should all patients receive an autologous stem cell transplant? – the PRO Haematologica. 2026 Apr 2. doi: 10.3324/haematol.2026.300574 [Epub ahead of print]*

**Relapsed classic Hodgkin lymphoma; should all patients receive an autologous stem cell transplant? – the PRO**

Chathuri Abeyakoon[1,2,3], John Kuruvilla[4]

1. Monash Haematology, Monash Health, Melbourne, VIC, Australia
2. Epworth HealthCare, Melbourne, VIC, Australia
3. Department of Medicine, School of Clinical Sciences at Monash Health, Monash University, Melbourne, VIC, Australia
4. Division of Medical Oncology and Haematology, Princess Margaret Cancer Centre, Toronto ON, Canada

Corresponding author: John Kuruvilla

Email: john.kuruvilla@uhn.ca

Author contributions: CA and JK conducted the literature search and wrote the manuscript.

High-dose chemotherapy followed by autologous stem cell transplantation (ASCT) has long been the cornerstone of curative therapy for eligible patients with relapsed or refractory classical Hodgkin lymphoma (RR-cHL) who demonstrate treatment sensitive disease.[1-3] Over the past decade, the therapeutic landscape of cHL has evolved substantially. The incorporation of the CD30-directed antibody–drug conjugate brentuximab vedotin (BV) and immune checkpoint inhibitors (CPIs) targeting programmed cell death protein-1 (PD-1) into frontline, salvage, and post-transplant settings has significantly improved outcomes. These advances have ignited debate regarding the ongoing role of ASCT: does high-dose therapy remain necessary for all patients with RR-cHL, or can selected subgroups be safely spared this intensive approach?

While this question is timely and important, the available evidence strongly supports the continued central role of ASCT as consolidative therapy for the majority of patients with RR-cHL in the current era.

**The curative paradigm and historical evidence supporting ASCT**

Contemporary frontline strategies cure approximately 80–95% of patients with early- and advanced-stage cHL.[4-9] Modern clinical trials in the primary treatment setting have sought to improve or maintain high cure rates while attempting to minimize treatment exposure to reduce rates of both acute and delayed toxicities. Cure remains the overarching goal for patient management even in the relapsed/refractory setting. For the 10-20% of patients who are not cured with primary therapy, historical data have demonstrated that approximately 50% of patients can expect durable remission and cure with salvage therapy followed by consolidative ASCT.[10-14]

The role of ASCT is supported by two randomised controlled trials (RCTs) conducted in the pre-novel agent era, which consistently demonstrated superior freedom from treatment failure (FFTF) or event-free survival (EFS) compared with conventional-dose chemotherapy alone, albeit without a clear overall survival (OS) advantage.[10,11] The largest of these, the German Hodgkin Study Group (GHSG) HD-R1 trial, randomised 161 patients aged 16–60 years to receive two cycles of dexamethasone, BCNU, etoposide, cytarabine, and melphalan (Dexa-BEAM) followed by either two additional cycles of Dexa-BEAM or high-dose BEAM

with ASCT. Among the 117 patients with chemosensitive disease, 7-year FFTF was significantly improved with ASCT (49% versus 32%; $p$ = 0.02) at a median follow-up of 83 months.[10] It is important to highlight that these trials were not powered to look at OS as the primary endpoint and that maintained EFS or FFTF (ongoing longer term disease remission) is indicative of cure as relapse following second-line therapy is uncommon beyond 2-years.[15] Patients in the non-ASCT arm of these trials would have gone on to receive additional therapy (radiation, further chemotherapy etc.) that may provide the potential for some disease control but treatment typically would no longer be given with curative intent.

These findings are reinforced by pooled analyses from GHSG trials, which demonstrated superior long-term outcomes among patients able to proceed to ASCT. Ten-year progression-free survival (PFS) and OS were 49% and 62%, respectively, in transplanted patients, compared with 31% and 41% in those unable to undergo ASCT.[13] Retrospective analysis of 501 patients treated on three prospective phase II trials and prospectively registered in the database at the MD Anderson Cancer Centre demonstrated a 5-year PFS and OS of 55% (95% CI 50 – 59%) and 73%, respectively with improvement in both endpoints over time.[14] Collectively, these data established ASCT as the standard consolidative strategy for chemosensitive RR-cHL.

With the arrival of the CD30 antibody drug conjugate BV and the first CPIs developed in cHL (nivolumab and pembrolizumab), agents with impressive single agent activity in the palliative setting were identified. The goal of subsequent drug development was to incorporate these agents earlier into the disease course, particularly into the curative treatment setting.

**Consolidation Therapy post-ASCT**

The confirmatory randomized trial for BV was the AETHERA study. This study randomized high risk patients defined as primary refractory disease, relapsed disease with an initial remission duration of less than 12-months or extranodal involvement at the start of pre-transplantation salvage chemotherapy to receive BV monotherapy up to 16 cycles versus placebo.[12] Long-term follow-up demonstrated a 5-year PFS of 59% (95% CI 55 – 66%) with BV maintenance versus 41% (95% CI 33 – 49%) with placebo.[16] These results demonstrate

that in a modern cohort of patients with RR-cHL, BV maintenance improves outcomes post ASCT, with cure rates appearing superior to the approximate 50% reported in historical cohorts, even in high-risk disease.

**Prognostic importance of PET response and optimisation of salvage therapy**

A key advance in the modern era has been the recognition of pre-transplant metabolic response as the strongest predictor of post-ASCT outcomes. Achievement of a complete metabolic response (CMR), most commonly defined as a Deauville score of 1–3 on 18F-flurodeoxyglucose positron emission tomography (FDG-PET) imaging, is consistently associated with superior PFS and OS.[17-20] Importantly, the number of salvage regimens required to achieve FDG-PET-defined CMR does not appear to adversely affect transplant outcomes, underscoring the importance of response rather than regimen sequence.[19]

Traditional salvage chemotherapy regimens incorporating gemcitabine-, platinum-, or ifosfamide-based backbones historically yielded overall response rates (ORR) of 60–70% and complete response (CR) rates of 20–25% by computed tomography (CT) criteria.[21] The integration of functional imaging has revealed substantially higher CR rates, even with conventional chemotherapy. Notably, the BeGEV regimen (bendamustine, gemcitabine, vinorelbine) achieved a PET-defined CR rate of 75%, with 5-year PFS and OS of 77% and 91%, respectively, among patients proceeding to ASCT.[22]

Given the central prognostic importance of PET-defined CR, novel agents have increasingly been explored and incorporated into salvage strategies to optimise pre-transplant disease control and improve subsequent post-ASCT outcomes.

**Expected current outcomes with salvage and ASCT strategies incorporating novel agents**

Both BV and PD-1 inhibitors have been successfully integrated into salvage regimens demonstrating high CR rates. Initial experience with BV and CPIs in the salvage setting involved the use of these agents as monotherapy in patients not responding to second-line (typically platinum-containing) regimens.[23,24] Although safe and effective, it was evident that using these agents as part of second-line therapy would likely lead to more favourable patient outcomes. BV combined with conventional chemotherapy backbones including

ESHAP (etoposide, methylprednisolone, high-dose cytarabine, cisplatin), IGeV (ifosfamide, gemcitabine, vinorelbine, prednisolone), and DHAP (dexamethasone, cytarabine, cisplatin), or with single-agent gemcitabine or bendamustine, has produced CR rates of 67–79%.[21] Similarly, CPI-based salvage regimens have yielded striking results. Pembrolizumab combined with ICE (ifosfamide, carboplatin, etoposide) or GVD (gemcitabine, vinorelbine, liposomal doxorubicin) has demonstrated CR rates of 86–95% and ORRs approaching 100%.[25,26] It is important to highlight that these trials did not describe any concerning safety signals although grade 3-4 neutropenia was more common with BV combinations and immune related adverse events can occur with CPIs in the salvage setting, these complications are uncommon.[26-29]

Furthermore, sequential strategies using BV or nivolumab monotherapy upfront to induce CR, reserving multi-agent chemotherapy for non-responders has also been explored. Complete remission rates of 28–77% with novel agents alone and 65–85% following subsequent chemotherapy have been described.[29-31] These trials highlight that approximately 25-75% of can directly proceeded to an ASCT without exposure to chemotherapy-based salvage therapy. Novel–novel combinations have further expanded therapeutic options: BV plus nivolumab achieved a CR rate of 67% respectively, while the triplet of nivolumab, BV, and ipilimumab yielded CR rates of 73%.[32-34] These regimens are also appealing as they do not include traditional chemotherapy agents but it remains unclear in the absence of randomized comparisons if there is an optimal combination approach with the highest CR rate and most favourable toxicity profile prior to ASCT.

High CR rates achieved with novel salvage regimens appear to translate into favourable PFS outcomes post ASCT. BV-incorporating savage regimens have demonstrated 2-year PFS rates of 63-78% and a retrospective analysis have demonstrated superior 2-year EFS with CPI-based salvage therapy compared to conventional chemotherapy, BV and chemotherapy or BV monotherapy (79.7%, 49.6%, 62.3%, and 36.9%, respectively, $p < 0.0001$).[21,35] As mentioned previously, patients with high-risk disease features at relapse can go on to receive post-ASCT BV maintenance with the aim to further improve PFS outcomes which can make interpretation of the impact of salvage therapy on post-ASCT PFS more challenging given the use of additional therapy. The only RCT to date comparing novel salvage therapy

against conventional chemotherapy is an ongoing Canadian Cancer Trials Group randomised study (CCTG HD.11, NCT05180097) comparing pembrolizumab–BV with GDP (gemcitabine, dexamethasone, cisplatin) followed by ASCT which has completed accrual in 2025.

Although long-term follow-up of these single arm phase II or retrospective studies evaluating the efficacy of salvage regimens incorporating novel agents are relatively short (typically reporting 2-year time to event outcomes), the data remain encouraging. It will be important to review the long-term follow-up of these studies to report late toxicities to better understand if these approaches also favourably impact secondary cancer rates or cardiovascular outcomes.

Recent trials evaluating non-ASCT based approaches provide some expectations for such an approach in the current era. A non-randomised phase II trial is assessing 4 cycles of pembrolizumab-GVD followed by 13 cycles of pembrolizumab maintenance with the omission of an ASCT in those able to achieve a CR after the initial 4 induction cycles. Interim results have demonstrated a 2-year PFS of 51% (95% CI 33 – 80%) with higher risk of progression in patients with stage IV disease at trial enrolment.[36] These results highlight the importance of enrolling patients on well-designed prospective clinical trials as the impact on OS and cure for a non-ASCT based approach remains an unanswered question.

**Evolving primary therapy approaches and new questions**

The incorporation of BV-AVD (brentuximab vedotin, doxorubicin, vinblastine, dacarbazine), N-AVD (nivolumab, doxorubicin, vinblastine, dacarbazine) and BrECADD (brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone) into frontline therapy has further improved outcomes in cHL.[8,9,37] While these advances represent a major success, they introduce new uncertainties in the relapsed/refractory setting. The impact of prior exposure to novel agents on salvage response, transplant outcomes, and long-term cure remains largely unknown. These regimens were tested in stage III-IV patients and are typically approved/reimbursed (or pending approval and reimbursement) in many countries in this setting. Given traditional inclusion of stage IIB bulky patients with advanced stage disease, it would be reasonable to anticipate that many of these patients would also receive novel therapy in combination with chemotherapy.

However, the role of BV and CPIs in patients with stage I-II disease is less clear. Phase II data have demonstrated excellent results with the incorporation of novel agents in this setting.[38-40] Randomized controlled trials are currently underway.[41,42]

It is important to recognise that, over the coming years, clinicians will increasingly be required to manage two distinct patient populations in the second-line relapsed/refractory setting: (1) patients without prior exposure to novel agents, and (2) patients with prior exposure to novel therapies, including BV, CPIs, or both. In light of the impressive safety and efficacy outcomes from the S1826 trial, it is likely that many patients will have received N–AVD in the frontline setting, with a smaller proportion treated with BrECADD. Consequently, the results of second-line salvage strategies incorporating novel agents will primarily be applicable to patients who are novel agent–naïve at relapse. As disease progression typically occurs within 12–24 months of frontline therapy, large datasets (prospective or retrospective) evaluating second-line approaches in patients progressing after frontline BV or CPI exposure are not yet available.

Limited prospective and real-world data suggest that retreatment with BV or CPI monotherapy is feasible, with ORRs of approximately 50–60% for BV and 75–100% for CPIs in selected patients.[43-46] This is suggestive of the feasibility of retreatment in combination approaches from an efficacy perspective, but there are also important factors to consider in the clinic. Cumulative toxicities (particularly peripheral neuropathy with BV) and prior immune related adverse events or history of autoimmune disease (for CPIs) may be key factors when selecting second-line regimens in patients with prior novel agent exposure. More importantly, the durability of responses achieved with novel salvage regimens alone remain uncertain. In a BV-AVD or BrECADD exposed patient, a nivolumab or pembrolizumab based approach is rational. Conversely, in a nivolumab or pembrolizumab exposed patient, a BV-based approach is rational.

**Can ASCT be omitted in selected patients?**

The desire to reduce treatment intensity where safely possible is appropriate. Paediatric and adolescent guidelines from the EuroNet group already recommend non-transplant approaches for carefully selected low-risk patients based on time to relapse, stage at

relapse, prior therapy, and achievement of early PET-defined CR (post 2 cycles of savage therapy).[47] Whether similar strategies can be safely extrapolated to adults remains an open question.

Early-phase studies exploring ASCT omission are promising but immature. In the phase IIb BRESELIBET trial, BV-ESHAP (brentuximab vedotin, etoposide, methylprednisolone, high-dose cytarabine, cisplatin) improved CR rates compared with ESHAP alone, with patients achieving CR receiving BV consolidation without ASCT.[48] A RCT evaluating ASCT versus pembrolizumab maintenance in patients that achieve a CR to induction cycles of pembrolizumab-GVD is underway.[26,36] However, long-term PFS and OS data are not yet available, and these studies largely exclude patients treated with frontline novel agents.

Until mature randomised data demonstrate non-inferiority of ASCT-free strategies, omission of transplant should remain investigational and limited to carefully selected patients within clinical trials. Importantly, patients with high-risk features—early relapse, primary refractory disease, advanced stage, or extranodal involvement—are unlikely to be adequately treated without ASCT consolidation. Furthermore, patients who do not proceed to second-line ASCT consolidation and subsequently relapse, will most likely go onto receive ASCT as part of third-line treatment strategies.

**Health economics and global equity considerations**

Historically, ASCT had risks even in younger patients including a 100-day non-relapse mortality of approximately 5-6%.[49,50] However, the safety of ASCT has improved substantially given advances in supportive care and the routine use of peripheral blood stem cells, and this is now in the range of 1-2%, particularly in patients under the age of 60 years.[51,52] While cost analyses are complex, ASCT has been shown to be cost-effective compared to conventional chemotherapy and transplant is a time limited therapy.[53] In contrast, multiple rounds of subsequent treatment, prolonged use of novel agents as maintenance or sequential therapy and the potential need for an allogeneic stem cell transplantation are likely to incur substantial cumulative costs, particularly in the absence of definitive cure.

From a global perspective, access to BV and CPIs remains limited and largely confined to high-income countries, with significant disparities even within these settings. Moreover, short-course exposure (2–4 cycles) to novel agents as salvage therapy to optimise ASCT outcomes represents a more cost-effective strategy than prolonged novel agent therapy, potentially improving feasibility and accessibility in low- and middle-income countries. Additionally, conventional chemotherapy and ASCT are available in most regions worldwide, underscoring their continued relevance and importance in achieving equitable cHL directed care.[54,55] A systematic review performed by Craven et al. exploring cHL treatment patterns and outcome disparities in low- and middle- income countries demonstrate that ASCT is the most commonly used treatment modality in the relapsed/refractory setting (62%) in comparison to novel agents (29%).[55]

**Conclusion**

The modern therapeutic era has transformed outcomes for patients with cHL, and novel agents have undeniably improved the efficacy of salvage approaches. However, these advances should be viewed as complementary to, rather than replacements for, ASCT. At present, ASCT remains the only consolidative strategy with robust long-term evidence for durable remission and cure in RR-cHL. Until prospective randomised data demonstrate equivalent long-term outcomes without transplant, ASCT should remain standard of care for the majority of transplant-eligible patients with relapsed disease. In the enthusiasm for therapeutic innovation, we must be careful not to discard a curative modality with decades of proven benefit.

**References**


1. Eichenauer DA, Aleman BMP, André M, et al. Hodgkin lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018;29(Suppl 4):iv19-iv29.
2. Aurer I, Zing N, Federico M. Hodgkin lymphoma: Comments on ESMO Clinical Practice Guidelines. Hemasphere. 2020;4(4):e458.
3. Hoppe RT, Advani RH, Ai WZ, et al. Hodgkin Lymphoma, Version 2.2020, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2020;18(6):755-781.
4. Fuchs M, Goergen H, Kobe C, et al. Positron emission tomography-guided treatment in early-stage favorable Hodgkin lymphoma: final results of the international, randomized phase III HD16 trial by the German Hodgkin Study Group. J Clin Oncol. 2019;37(31):2835-2845.
5. Borchmann P, Plütschow A, Kobe C, et al. PET-guided omission of radiotherapy in early-stage unfavourable Hodgkin lymphoma (GHSG HD17): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2021;22(2):223-234.
6. Kreissl S, Goergen H, Buehnen I, et al. PET-guided eBEACOPP treatment of advanced-stage Hodgkin lymphoma (HD18): follow-up analysis of an international, open-label, randomised, phase 3 trial. Lancet Haematol. 2021;8(6):e398-e409.
7. Luminari S, Fossa A, Trotman J, et al. Long-term follow-up of the response-adjusted therapy for advanced Hodgkin lymphoma trial. J Clin Oncol. 2024;42(1):13-18.
8. Herrera AF, LeBlanc M, Castellino SM, et al. Nivolumab+AVD in advanced-stage classic Hodgkin's lymphoma. N Engl J Med. 2024;391(15):1379-1389.
9. Ansell SM, Radford J, Connors JM, et al. Overall survival with brentuximab vedotin in stage III or IV Hodgkin’s lymphoma. N Engl J Med. 2022;387(4):310-320.
10. Schmitz N, Haverkamp H, Josting A, et al. Long term follow up in relapsed Hodgkin’s disease (HD): Updated results of the HD-R1 study comparing conventional chemotherapy (cCT) to high-dose chemotherapy (HDCT) with autologous haemopoetic stem cell transplantation (ASCT) of the German Hodgkin Study Group (GHSG) and the Working Party Lymphoma of the European Group for Blood and Marrow Transplantation (EBMT). J Clin Oncol. 2005;23(16_suppl):6508.
11. Linch DC, Winfield D, Goldstone AH, et al. Dose intensification with autologous bone-marrow transplantation in relapsed and resistant Hodgkin's disease: results of a BNLI randomised trial. Lancet. 1993;341(8852):1051-1054.
12. Moskowitz CH, Nademanee A, Masszi T, et al. Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2015;385(9980):1853-1862.
13. Bröckelmann PJ, Müller H, Gillessen S, et al. Clinical outcomes of relapsed and refractory Hodgkin lymphoma patients after contemporary first-line treatment: a German Hodgkin Study Group analysis. Leukemia. 2022;36(3):772-780.
14. Nieto Y, Gruschkus S, Valdez BC, et al. Improved outcomes of high-risk relapsed Hodgkin lymphoma patients after high-dose chemotherapy: a 15-year analysis. Haematologica. 2022;107(4):899-908.
15. Sureda A, Pavlovsky A, Haidar D, Kristo F, Stache V, Zomas A. Real-world outcomes of brentuximab vedotin as consolidation therapy after autologous stem cell transplantation in

relapsed/refractory Hodgkin lymphoma: A systematic review and meta-analysis. Bone Marrow Transplant. 2025;60(6):820-831.
16. Moskowitz CH, Walewski J, Nademanee A, et al. Five-year PFS from the AETHERA trial of brentuximab vedotin for Hodgkin lymphoma at high risk of progression or relapse. Blood. 2018;132(25):2639-2642.
17. Moskowitz AJ, Yahalom J, Kewalramani T, et al. Pretransplantation functional imaging predicts outcome following autologous stem cell transplantation for relapsed and refractory Hodgkin lymphoma. Blood. 2010;116(23):4934-4937.
18. Mocikova H, Pytlik R, Markova J, et al. Pre-transplant positron emission tomography in patients with relapsed Hodgkin lymphoma. Leuk Lymphoma. 2011;52(9):1668-1674.
19. Moskowitz CH, Matasar MJ, Zelenetz AD, et al. Normalization of pre-ASCT, FDG-PET imaging with second-line, non-cross-resistant, chemotherapy programs improves event-free survival in patients with Hodgkin lymphoma. Blood. 2012;119(7):1665-1670.
20. Moskowitz CH, Yahalom J, Zelenetz AD, et al. High-dose chemo-radiotherapy for relapsed or refractory Hodgkin lymphoma and the significance of pre-transplant functional imaging. Br J Haematol. 2010;148(6):890-897.
21. Abeyakoon C, Kuruvilla J. Optimizing salvage therapy for Hodgkin lymphoma: progress and future challenges. Expert Rev Hematol. 2024;17(8):467-478.
22. Santoro A, Mazza R, Pulsoni A, et al. Five-year results of the BEGEV salvage regimen in relapsed/refractory classical Hodgkin lymphoma. Blood Adv. 2020;4(1):136-140.
23. Merryman RW, Redd RA, Nishihori T, et al. Autologous stem cell transplantation after anti-PD-1 therapy for multiply relapsed or refractory Hodgkin lymphoma. Blood Adv. 2021;5(6):1648-1659.
24. Onishi M, Graf SA, Holmberg L, et al. Brentuximab vedotin administered to platinum-refractory, transplant-naïve Hodgkin lymphoma patients can increase the proportion achieving FDG PET negative status. Hematol Oncol. 2015;33(4):187-191.
25. Bryan LJ, Casulo C, Allen PB, et al. Pembrolizumab added to ifosfamide, carboplatin, and etoposide chemotherapy for relapsed or refractory classic Hodgkin lymphoma: a multi-institutional Phase 2 investigator-initiated nonrandomized clinical trial. JAMA Oncol. 2023;9(5):683-691.
26. 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(28):3109-3117.
27. Abuelgasim KA, Alzahrani M, Alsharhan Y, et al. Chemoimmunotherapy with brentuximab vedotin combined with ifosfamide, gemcitabine, and vinorelbine is highly active in relapsed or refractory classical Hodgkin lymphoma. Bone Marrow Transplant. 2019;54(7):1168-1172.
28. Kersten MJ, Driessen J, Zijlstra JM, et al. Combining brentuximab vedotin with dexamethasone, high-dose cytarabine and cisplatin as salvage treatment in relapsed or refractory Hodgkin lymphoma: the phase II HOVON/LLPC Transplant BRaVE study. Haematologica. 2021;106(4):1129-1137.
29. Mei MG, Lee HJ, Palmer JM, et al. Response-adapted anti-PD-1-based salvage therapy for Hodgkin lymphoma with nivolumab alone or in combination with ICE. Blood. 2022;139(25):3605-3616.
30. Herrera AF, Palmer J, Martin P, et al. Autologous stem-cell transplantation after second-line brentuximab vedotin in relapsed or refractory Hodgkin lymphoma. Ann Oncol. 2018;29(3):724-730.

31. Chen R, Palmer JM, Martin P, et al. Results of a multicenter phase II trial of brentuximab vedotin as second-line therapy before autologous transplantation in relapsed/refractory Hodgkin lymphoma. Biol Blood Marrow Transplant. 2015;21(12):2136-2140.
32. Advani RH, Moskowitz AJ, Bartlett NL, et al. Brentuximab vedotin in combination with nivolumab in relapsed or refractory Hodgkin lymphoma: 3-year study results. Blood. 2021;138(6):427-438.
33. 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.
34. Diefenbach CS, Jegede O, Ansell SM, et al. Results from an intergroup randomized phase II study of the combinations of ipilimumab, nivolumab and brentuximab vedotin in patients with relapsed/refractory classic Hodgkin lymphoma: a trial of the ECOG-ACRIN Research Group (E4412). Blood. 2023;142(Supplement 1):607.
35. Desai SH, Spinner MA, David K, et al. Checkpoint inhibitor-based salvage regimens prior to autologous stem cell transplant improve event-free survival in relapsed/refractory classic Hodgkin lymphoma. Am J Hematol. 2023;98(3):464-471.
36. Moskowitz A, Shah GL, Ganesan N, et al. Pembrolizumab maintenance instead of autologous hematopoietic cell transplantation for patients with relapsed or refractory Hodgkin Lymphoma in Complete Response after Pembrolizumab, Gemcitabine, Vinorelbine, and liposomal doxorubicin. Blood. 2024;144(Supplement 1):569.
37. Borchmann P, Ferdinandus J, Schneider G, et al. Assessing the efficacy and tolerability of PET-guided BrECADD versus eBEACOPP in advanced-stage, classical Hodgkin lymphoma (HD21): a randomised, multicentre, parallel, open-label, phase 3 trial. Lancet. 2024;404(10450):341-352.
38. Abramson JS, Straus DJ, Bartlett NL, et al. Updated analysis of brentuximab vedotin, nivolumab, doxorubicin, and dacarbazine for nonbulky, early-stage classical Hodgkin lymphoma. Blood. 2024;144(Supplement 1):460.
39. Bröckelmann PJ, Bühnen I, Meissner J, et al. Nivolumab and doxorubicin, vinblastine, and dacarbazine in early-stage unfavorable Hodgkin lymphoma: final analysis of the randomized German Hodgkin study group phase II NIVAHL trial. J Clin Oncol. 2023;41(6):1193-1199.
40. Fornecker LM, Lazarovici J, Aurer I, et al. Brentuximab vedotin plus AVD for first-line treatment of early-stage unfavorable Hodgkin lymphoma (BREACH): a multicenter, open-label, randomized, phase II trial. J Clin Oncol. 2023;41(2):327-335.
41. Radford J, Adedayo T, Ardavan A, et al. P025: RADAR: An international phase III, PET response-adapted, randomised trial in progress, comparing ABVD±ISRT with brentuximab vedotin+AVD±ISRT in patients with previously untreated limited-stage classical Hodgkin lymphoma. Hemasphere. 2022;6:12-13.
42. Henderson TO, Hu B, Keller F, et al. AHOD2131: a randomized phase 3 response-adapted trial comparing standard therapy with immuno-oncology therapy for children and adults with newly diagnosed stage I and II classic Hodgkin lymphoma. Blood. 2023;142(Supplement 1):3084.
43. Sureda A, García-Sanz R, Domingo-Domenech E, et al. Retreatment with brentuximab vedotin in patients with relapsed/refractory CD30+ malignancies: a retrospective medical chart review study in Spain-The BELIEVE Study. Cancers (Basel). 2025;17(7):1137.

44. Sano D, Liu N, Knowles S, et al. Brentuximab vedotin retreatment in patients with relapsed or refractory classical Hodgkin lymphoma or peripheral T-cell lymphoma: a retrospective United States claims analysis. Curr Oncol. 2024;31(5):2598-2609.
45. Ansell SM, Bröckelmann PJ, von Keudell G, et al. Nivolumab for relapsed/refractory classical Hodgkin lymphoma: 5-year survival from the pivotal phase 2 CheckMate 205 study. Blood Adv. 2023;7(20):6266-6274.
46. Armand P, Zinzani PL, Lee HJ, et al. Five-year follow-up of KEYNOTE-087: pembrolizumab monotherapy for relapsed/refractory classical Hodgkin lymphoma. Blood. 2023;142(10):878-886.
47. Daw S, Hasenclever D, Mascarin M, et al. Risk and response adapted treatment guidelines for managing first relapsed and refractory classical Hodgkin lymphoma in children and young people. Recommendations from the EuroNet Pediatric Hodgkin Lymphoma Group. Hemasphere. 2020;4(1):e329.
48. Sureda Balarí AM, Nuñez Cespedes J, Terol Castera MJ, et al. The addition of brentuximab vedotin to ESHAP significantly increases the rate of metabolic complete remissions vs chemotherapy alone. in patients with relapsed/refractory classical Hodgkin's lymphoma. Final results of a phase IIb prospective randomized clinical trial (BRESELIBET). Blood. 2024;144(Supplement 1):3049.
49. Carlsten M, Jädersten M, Hellström A, et al. The Karolinska experience of autologous stem-cell transplantation for lymphoma: a population-based study of all 433 patients 1994–2016. Exp Hematol Oncol. 2019;8:7.
50. Sirohi B, Cunningham D, Powles R, et al. Long-term outcome of autologous stem-cell transplantation in relapsed or refractory Hodgkin's lymphoma. Ann Oncol. 2008;19(7):1312-1319.
51. Spinner MA, Sica RA, Tamaresis JS, et al. Improved outcomes for relapsed/refractory Hodgkin lymphoma after autologous transplantation in the era of novel agents. Blood. 2023;141(22):2727-2737.
52. Zektser M, Hueniken K, Crump M, et al. Considering older patients as candidates for auto stem cell transplants: a comprehensive study on toxicities and survival analysis. Blood. 2023;142(Supplement 1):4964.
53. Sweetenham JW. Economics of stem cell transplantation for lymphoma: counting the cost of living. Br J Cancer. 2000;82(1):4-6.
54. Baig A, Kaur S, Verma N, et al. Curable but not equal: Survival disparities in classic Hodgkin lymphoma by treatment facility type in the United States. Blood. 2025;146(Supplement 1):5396.
55. Craven DM, Harrington MJ, Sansbury GM, et al. Hodgkin lymphoma treatment patterns and outcome disparities in low- and middle-income countries. Blood Global Hematol. 2025;1(3):100021
56. Cole PD, McCarten KM, Pei Q, et al. Brentuximab vedotin with gemcitabine for paediatric and young adult patients with relapsed or refractory Hodgkin's lymphoma (AHOD1221): a Children's Oncology Group, multicentre single-arm, phase 1-2 trial. Lancet Oncol. 2018;19(9):1229-1238.
57. Broccoli A, Argnani L, Botto B, et al. First salvage treatment with bendamustine and brentuximab vedotin in Hodgkin lymphoma: a phase 2 study of the Fondazione Italiana Linfomi. Blood Cancer J. 2019;9(12):100.

58. LaCasce AS, Bociek RG, Sawas A, et al. Brentuximab vedotin plus bendamustine: a highly active first salvage regimen for relapsed or refractory Hodgkin lymphoma. Blood. 2018;132(1):40-48.
59. Garcia-Sanz R, Sureda A, de la Cruz F, et al. Brentuximab vedotin and ESHAP is highly effective as second-line therapy for Hodgkin lymphoma patients (long-term results of a trial by the Spanish GELTAMO Group). Ann Oncol. 2019;30(4):612-620.
60. Moskowitz AJ, Schöder H, Gavane S, et al. Prognostic significance of baseline metabolic tumor volume in relapsed and refractory Hodgkin lymphoma. Blood. 2017;130(20):2196-2203.

Table 1: Salvage regimens incorporating novel agents

| Salvage regimen | Reference | No. of patients | CR % | PFS % | OS % |
|---|---|---|---|---|---|
| **Salvage regimens incorporating BV** | | | | | |
| BV + gemcitabine | [56] | 45 | 57 | NR | 1-year 95 |
| BV + bendamustine | [57]<br>[58] | 55<br>40 | 74<br>79 | 2-year 63<br>2-year 67 | 2-year 94<br>3-year 88 |
| BV + ESHAP | [59] | 66 | 70 | 30-months 71 | 2-month 90 |
| BV + IGEV | [27] | 28 | 70 | 2-year 73.5 | 2-year 87.1 |
| BV + DHAP | [28] | 67 | 81 | 2-year 74 | 2-year 95 |
| BV + sequential augmented ICE | [60] | 65 | 75 (28 post BV alone) | 3-year 82 | 3-year 95 |
| BV + sequential ICE/GVD | [30] | 57 | 65 | 2-year 67 | 2-year 93 |
| BV + sequential physicians choice salvage regimen | [31] | 37 | 61 | NR | NR |
| **Salvage regimens incorporating CPIs** | | | | | |
| Pembrolizumab + ICE | [25] | 42 | 86.5 | Median 26 months | 2-year 88.2 |
| Pembrolizumab + GVD | [26] | 39 | 95 | 1-year 100 | 1-year 100 |
| Nivolumab + sequential NICE | [29] | 43 | 71 post cycles of Nivo<br>98 post NICE | 2-year 72 | 2-year 95 |
| **Salvage regimens incorporating BV in combination with CPIs** | | | | | |
| BV + nivolumab | [32] | 91 | 67 | 2-year 78 | 2-year 93 |
| Nivolumab + BV + ipilimumab | [33] | 64 | BV-Ipi 57<br>BV-Nivo 61<br>BV-Nivo-Ipi 73 | 1-year<br>BV-Ipi 61<br>BV-Nivo 70<br>BV-Nivo-Ipi 80 | Median OS not reached |

BV: brentuximab vedotin; CR: complete response; PFS: progression free survival; OS: overall survival; NR: not reported; ESHAP: etoposide, methylprednisolone, high-dose cytarabine, cisplatin; IGEV: ifosfamide, gemcitabine, vinorelbine, prednisolone; DHAP: dexamethasone, cytarabine, cisplatin; ICE: ifosfamide, carboplatin, etoposide: GVD: gemcitabine, vinorelbine, liposomal doxorubicin; BV-Ipi: brentuximab vedotin, ipilimumab; BV-Nivo: brentuximab vedotin, nivolumab; BV-Nivo-Ipi: brentuximab vedotin, nivolumab, ipilimumab; ICE: ifosfamide, carboplatin, etoposide; NICE: nivolumab, ifosfamide, carboplatin, etoposide

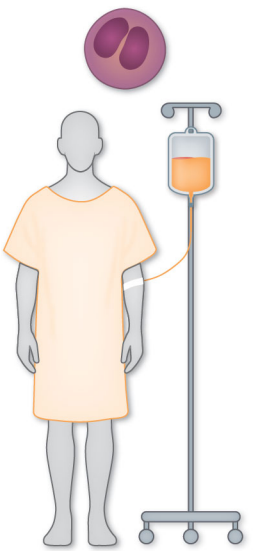
Figure 1: ASCT Remains an Important Therapeutic Modality in the Management of RR-cHL

ASCT: autologous stem cell transplantation; RR-cHL: relapsed or refractory classical Hodgkin Lymphoma; RCT: randomised controlled trial; CMR: complete metabolic remission; BV: brentuximab vedotin; CPI: checkpoint inhibitor; TRM: transplant related mortality; alloSCT: allogeneic stem cell transplantation; PET: 18F-flurodeoxyglucose positron emission tomography; PFS: progression free survival

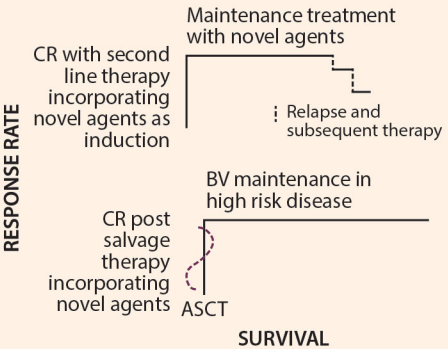
## Historical Outcomes with Salvage Therapy and ASCT

- ASCT in second-line therapy is supported by two RCTs demonstrating ~50% durable remission/cure with ASCT, superior to conventional chemotherapy.

10-20% of patients are refractory or will relapse following frontline therapy



## Long-term Outcomes Demonstrating Cure With the Omission of ASCT are Lacking




## Outcomes with Salvage Therapy and ASCT Strategies Incorporating Novel Agents

- PET CMR is the strongest prognostic factor for post-ASCT surival.
- BV and CPI-based salvage regimens improve pre-ASCT PET CMR rate to ~80-95%, compared with ~70-75% using conventional chemotherapy.
- Encouraging 2-year PFS rates of ~63-80%.
- Post-ASCT BV maintenance has the potential to further improve PFS.
- Despite increasing frontline use of novel agents, limited prospective and retrospective data suggest re-treatment with novel agents remain feasible.

## Health Economics and Global Health Perspective

- ASCT TRM 1-2% in modern era.
- ASCT is cost effective when compared to prolonged use of novel agents, and the potential need for successive rounds of treatment for relapsed disease including the need for alloSCT.
- Use of novel agents as short courses of savage pre-ASCT improves accessibility and feasibility of novel agents in low-/middle-income countries to improve survival outcomes.
- ASCT is a time limited therapy.