REMUNOM
ISSN 2178-6925

Received: 22/01/2026 - **Accepted:** 18/02/2026
Vol: 02.02
DOI: 10.61164/0sbasb69
Pages: 1 - 23

SAFETY, EFFICACY, AND EFFECTIVENESS OF BRENTUXIMAB VEDOTIN IN THE TREATMENT OF RELAPSED OR REFRACTORY CD30+ HODGKIN LYMPHOMA AFTER AUTOLOGOUS STEM CELL TRANSPLANTATION: A SYSTEMATIC REVIEW

SEGURANÇA, EFICÁCIA E EFETIVIDADE DO BRENTUXIMABE VEDOTINA NO TRATAMENTO DO LINFOMA DE HODGKIN CD30+ RECIDIVADO OU REFRATÁRIO APÓS TRANSPLANTE AUTÓLOGO DE CÉLULAS-TRONCO: UMA REVISÃO SISTEMÁTICA

SEGURIDAD, EFICACIA Y EFECTIVIDAD DE BRENTUXIMAB VEDOTIN EN EL TRATAMIENTO DEL LINFOMA DE HODGKIN CD30+ RECIDIVANTE O REFRACTARIO DESPUÉS DEL TRASPLANTE AUTÓLOGO DE CÉLULAS MADRE: UNA REVISIÓN SISTEMÁTICA

Ms Joyce da Silva Guimarães
Federal University of Paraná, Postgraduate Program in Pharmaceutical Services and Policies, Curitiba, PR, Brazil
E-mail: joyce.0002jsg@gmail.com

Ms. Paulo Henrique Gouveia
Federal University of Paraná, Postgraduate Program in Pharmaceutical Sciences, Curitiba, PR, Brazil
E-mail: gouveiaph1@gmail.com

Layssa Andrade Oliveira
Federal University of Paraná, Postgraduate Program in Pharmaceutical Sciences, Curitiba, PR, Brazil
E-mail: layssaandradeoliveira@gmail.com

Fernanda Stumpf Tonin
Pharmacy and Pharmaceutical Technology Department, Social and Legal Pharmacy Section, University of Granada, Granada, Spain.
E-mail: fer_stumpf_tonin@hotmail.com

Dr. Roberto Pontarolo
Federal University of Paraná, Department of Pharmacy, Curitiba, PR, Brazil
E-mail: pontarolo@ufpr.br

Dra. Yara Maria da Silva Pires
Federal University of Paraná, Postgraduate Program in Pharmaceutical Sciences,
E-mail: yah.pires@hotmail.com

Dra. Astrid Wiens
Federal University of Paraná, Department of Pharmacy, Curitiba, PR, Brazil

REMUNOM
ISSN 2178-6925

Received: 22/01/2026 - **Accepted:** 18/02/2026
Vol: 02.02
DOI: 10.61164/0sbasb69
Pages: 1 - 23

E-mail: astrid@ufpr.br

ABSTRACT
This systematic review reassessed the efficacy, safety, and impact on quality of life of Brentuximab Vedotin (BV) in treating relapsed/refractory (R/R) CD30+ Hodgkin lymphoma after autologous stem cell transplantation (ASCT). The review followed the Cochrane Handbook for Systematic Reviews of Interventions, with results reported according to PRISMA guidelines. The initial search was conducted on December 11, 2024. A total of 2291 studies were identified; eight met the eligibility criteria, including one phase 3 randomized controlled trial (RCT) and seven retrospective observational studies. In total, 1628 patients received BV after relapse or progression post ASCT, while 924 received comparator therapies such as chemotherapy, checkpoint inhibitors, anthracyclines, gemcitabine, pembrolizumab, and radiotherapy. Risk of bias assessments using RoB 2.0 and ROBINS-I indicated variable risk, ranging from some concerns to moderate or serious. The certainty of evidence, assessed using the GRADE approach, ranged from moderate to low, resulting in a weak recommendation. Overall, BV either as monotherapy or combined with other treatments, showed promising potential for inducing disease remission in patients with R/R CD30+ Hodgkin lymphoma after ASCT. However, limitations in the current evidence underscore the need for more robust, high-quality studies to confirm and strengthen these findings.
Keywords: Hodgkin lymphoma; Brentuximab Vedotin; treatment; systematic review.
RESUMO
Esta revisão sistemática reavaliou a eficácia, segurança e impacto na qualidade de vida do brentuximabe vedotina (BV) no tratamento do linfoma de Hodgkin CD30+ recidivado/refratário (R/R) após transplante autólogo de células-tronco (TACT). A revisão seguiu o Manual Cochrane para Revisões Sistemáticas de Intervenções, com os resultados relatados de acordo com as diretrizes PRISMA. A busca inicial foi realizada em 11 de dezembro de 2024. Um total de 2.291 estudos foram identificados; oito atenderam aos critérios de elegibilidade, incluindo um ensaio clínico randomizado (ECR) de fase 3 e sete estudos observacionais retrospectivos. No total, 1.628 pacientes receberam BV após recidiva ou progressão pós-TACT, enquanto 924 receberam terapias comparadoras, como quimioterapia, inibidores de checkpoint, antraciclinas, gencitabina, pembrolizumabe e radioterapia. As avaliações de risco de viés usando RoB 2.0 e ROBINS-I indicaram risco variável, desde alguma preocupação até risco moderado ou grave. A certeza da evidência, avaliada pela abordagem GRADE, variou de moderada a baixa, resultando em uma recomendação fraca. No geral, o brentuximabe vedotina (BV), tanto em monoterapia quanto em combinação com outros tratamentos, mostrou potencial promissor para induzir remissão da doença em pacientes com linfoma de Hodgkin CD30+ recidivado/refratário após transplante autólogo de células-tronco hematopoiéticas (TCTH). No entanto, as limitações das evidências atuais ressaltam a necessidade de estudos mais robustos e de alta qualidade para confirmar e fortalecer esses achados.
Palavras-chave: linfoma de Hodgkin; brentuximabe vedotina; tratamento; revisão sistemática.
RESUMEN
Esta revisión sistemática reevaluó la eficacia, la seguridad y el impacto en la calidad de vida de Brentuximab Vedotin (BV) en el tratamiento del linfoma de Hodgkin CD30+ recidivante/refractario (R/R) tras un trasplante autólogo de células madre (TACM). La revisión siguió el Manual Cochrane para Revisiones Sistemáticas de Intervenciones, y los resultados se informaron según las directrices PRISMA. La búsqueda inicial se realizó el 11 de diciembre de 2024. Se identificaron 2291 estudios; ocho cumplieron los criterios de elegibilidad, incluyendo un ensayo controlado aleatorizado (ECA) de fase III y siete estudios observacionales retrospectivos. En total, 1628 pacientes recibieron BV tras una recaída o progresión tras un TCM, mientras que 924 recibieron terapias de comparación como quimioterapia, inhibidores de puntos de control, antraciclinas, gemcitabina, pembrolizumab y radioterapia. Las evaluaciones del riesgo de sesgo con RoB 2.0 y ROBINS-I indicaron un riesgo variable, desde leve hasta moderado o grave. La certeza de la evidencia, evaluada mediante el método GRADE, varió de moderada a baja, lo que resultó en una recomendación débil. En general, la VB, ya sea en monoterapia o en combinación con otros tratamientos, mostró un potencial prometedor para inducir la remisión de la enfermedad en pacientes con linfoma de Hodgkin R/R CD30+ tras un trasplante autólogo de células madre. Sin embargo, las limitaciones de la evidencia actual subrayan la necesidad de estudios más sólidos y de alta calidad para confirmar y reforzar

REMUNOM
ISSN 2178-6925

Received: 22/01/2026 - **Accepted:** 18/02/2026
Vol: 02.02
DOI: 10.61164/0sbasb69
Pages: 1 - 23

estos hallazgos.
Palabras clave: linfoma de Hodgkin; brentuximab vedotina; tratamiento; revisión sistemática.

1. INTRODUCTION

Hodgkin lymphoma (HL) is characterized by the malignant proliferation of B lymphocytes, giving rise to Reed-Sternberg cells [1]. The incidence of HL shows a bimodal age distribution, affecting adolescents, young adults, and the elderly, with variations influenced by geographic, socioeconomic, and genetic factors. Despite therapeutic advances, there are still persistent mortality rates in the relapsed or refractory (R/R) setting [2].

Standard treatment usually involves a multi-modal approach including chemotherapy, radiotherapy, and, in selected cases, autologous stem cell transplantation (ASCT). A distinguishing feature of HL is the high expression of the CD30 protein on malignant cells, making targeted therapies such as Brentuximab Vedotin (BV) an effective therapeutic option [3]. Nevertheless, the therapeutic landscape is rapidly evolving. The emergence of immune checkpoint inhibitors (CPIs) has raised questions about the optimal treatment sequencing between targeted therapy and immunotherapy.

Given the therapeutic complexity of relapsed or refractory Hodgkin lymphoma, the real-world effectiveness of BV needs careful synthesis to guide evidence-based decisions. Thus, this systematic review aims to evaluate the efficacy, safety, and effectiveness of BV in patients with R/R CD30+ HL following ASCT.

2. METHODS

This systematic review followed the methodological guidelines of Cochrane Handbook [4], and the results were reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [5]. The full protocol was registered in PROSPERO (CRD42022306761).

A meta-analysis was not performed due to substantial clinical and methodological heterogeneity across studies, in accordance with PRISMA and Cochrane recommendations.

REMUNOM
ISSN 2178-6925

Received: 22/01/2026 - **Accepted:** 18/02/2026
Vol: 02.02
DOI: 10.61164/0sbasb69
Pages: 1 - 23

2.1. Eligibility Criteria

Studies were considered eligible if they included patients diagnosed with CD30+ relapsed or refractory (R/R) HL ASCT, regardless of age or sex; evaluating the safety profile, efficacy, and/or effectiveness of BV at any dose or regimen; or reported data on quality of life or treatment adherence. Studies with any active comparator (any therapeutic regimen/scheme) or with placebo, the best supportive care, or no treatment were included. Eligible study designs include comparative interventional studies (randomized and non-randomized controlled trials) and observational cohort studies. Studies that did not meet these criteria or were published using non-Roman characters were excluded.

2.2 Information Sources and Search Strategy

A comprehensive search was performed through PubMed, Embase, Cochrane Library, LILACS, and SciELO databases on December 11, 2024. The search strategy incorporated MeSH terms and descriptors related to the disease (Hodgkin disease or lymphoma) and treatment (brentuximab), combined using the Boolean operators AND and OR. Detailed search strategies and additional information are presented in Table 1.

2.3. Selection Process

All identified studies were imported into Rayyan software [6] for duplicate removal and screening. Titles and abstracts were screened independently by two reviewers. Full-text articles were subsequently assessed for eligibility by the same reviewers. Discrepancies were resolved through consensus with a third reviewer.

2.4. Data Collection Process and Data Items

Data were extracted independently by two reviewers using a standardized form. Extracted information included: first author, year of publication, study design, year of study conduction, participant characteristics (number, sex, age), intervention details (dose and administration regimen), duration of follow-up, and outcomes of interest, including overall survival, progression-free survival, objective response

REMUNOM
ISSN 2178-6925

Received: 22/01/2026 - **Accepted:** 18/02/2026
Vol: 02.02
DOI: 10.61164/0sbasb69
Pages: 1 - 23

rate, remission rate, quality of life (measured by any reported instrument), treatment adherence (treatment discontinuation), and safety (incidence of serious adverse events).

2.5. Risk of Bias Assessment and Certainty of Evidence

The risk of bias for each included study was assessed independently by two reviewers using the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2.0) for randomized controlled trials and the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) for observational or non-randomized studies [7,8]. The certainty of the evidence for each outcome was assessed using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach [9].

2.5. Synthesis Methods

Findings were synthesized and presented narratively, supplemented by tables and graphs summarizing descriptive statistical analyses for all outcomes of interest and available comparisons identified in literature.

3. RESULTS

3.1. Study selection

A total of 3,297 records were identified through systematic search. After removing 1,006 duplicates, 2,291 studies remained for eligibility screening (title and abstract review).

A number of 2232 records were excluded based on title and/or abstract review. The full text for each of the remaining 59 studies was assessed, and 8 studies met the eligibility criteria. The data were extracted and synthesized, as depicted in the systematic review flowchart shown in Figure 1.

3.2. Study Characteristics and Results of Individual Studies

One RCT and seven observational studies were included in this review. One observational study evaluated BV as post-ASCT consolidation rather than

REMUNOM
ISSN 2178-6925
Received: 22/01/2026 - **Accepted:** 18/02/2026
Vol: 02.02
DOI: 10.61164/0sbasb69
Pages: 1 - 23

treatment of relapses and was therefore interpreted separately. Due to the substantial variability in comparators and the number of treatment cycles used across the studies, conducting a meta-analysis was not feasible. Methodological heterogeneity among the studies compromised the possibility of robust statistical comparison, making the data consolidation into a single quantitative estimate inappropriate. Consequently, the results were interpreted qualitatively, considering the specific characteristics of each study.

3.2.1. Randomized Clinical Trial

A phase 3 RCT conducted by Kuruvilla et al. [10] enrolled participants 304. Participants were divided into two treatment groups: (i) Pembrolizumab (n=151) and (ii) Brentuximab Vedotin (BV) (n=152). The median treatment duration was 305 days (interquartile range [IQR] 131.5–635.0) with a median of 15 cycles (IQR 7–30.5) for pembrolizumab, and 146.5 days (IQR 65.0–232.5) with a median of 7 cycles (IQR 4–12) for BV. Treatment discontinuation occurred in 74% of the pembrolizumab group and 96% of the BV group, mainly due to disease progression (39% vs. 49%) and adverse events (14% vs. 19%).

The primary and secondary outcomes assessed in the Kuruvilla et al. [10] study were progression-free survival (PFS). The primary PFS included evaluation by clinical examinations and imaging post-ASCT, while the secondary PFS did not. Overall, there was a significant improvement of approximately 5 months in primary PFS for patients receiving pembrolizumab (median primary PFS 13.2 months vs. 8.3 months for BV; hazard ratio [HR] 0.65 [95% confidence interval – CI, 0.48–0.88]; p=0.002) and about 4 months for secondary PFS (12.6 months vs. 8.2 months; HR 0.62 [95% CI 0.46–0.85]).

The only randomized controlled trial included demonstrated superior progression-free survival with pembrolizumab compared to brentuximab vedotin.

3.2.2. Observational Studies

A retrospective cohort study [11] evaluated 156 patients with a median age of 35 years, divided into two groups: those who received BV consolidation (n=62) and

REMUNOM
ISSN 2178-6925

Received: 22/01/2026 - **Accepted:** 18/02/2026
Vol: 02.02
DOI: 10.61164/0sbasb69
Pages: 1 - 23

those who did not (untreated group, n=94), with a median of 14 cycles of drug administration (range 2–16). Three-year PFS rates demonstrated a significant clinical benefit, with an HR of 0.39 (95% CI: 0.21–0.80; p=0.01) in the BV group compared to the untreated group, indicating a substantial reduction in the risk of disease progression or death. PFS rates were significantly higher in patients undergoing BV consolidation compared to those in the untreated group.

Desai et al. [12] conducted a retrospective cohort study, with a median follow-up of 48.1 months. A total of 344 patients with a median age of 34 years were included, divided into three groups: CPI (checkpoint inhibitors) (n=70); BV (n=157); and no CPI/BV (n=117). The outcome assessed was post-progression survival (PPS), the time from progression post-ASCT to death or last follow-up. Patients receiving CPI showed higher survival rates compared to those who received no novel agents, with HR: 2.4 [1.1–5.23]; p=0.03 for BV, and HR: 3.4 [1.5–7.8]; p=0.002 for neither CPI nor BV.

Tun et al. [13] retrospectively evaluated patients at three Mayo Clinic locations: 32 received BV, 38 received chemotherapy, 19 received radiotherapy (RT), 17 received investigational agents, and 8 received immune checkpoint inhibitors (ICI). The median age was 34 years, and both genders were represented. During the 6-month therapeutic follow-up, 12 deaths occurred. Survival outcomes were as follows: chemotherapy (95% CI: 0.85 [0.46–1.2]), BV (HR 1.11 [95% CI: 0.60–2.19]), RT (HR 0.78 [95% CI: 0.26–2.17]), investigational agents (HR 0.50 [95% CI: 0.13–1.71]), and ICI (NR [0.46–NR]), with a p-value of 0.006.

Badar et al. [14] conducted a retrospective observational study, evaluating 215 patients with a median age of 35 years. Patients were divided into four groups: BV (n=98); checkpoint inhibitors (n=39); gemcitabine (n=53); and anthracyclines (n=31). Outcomes assessed included PFS, overall response rate (ORR), and complete response (CR) rate. Checkpoint inhibitors demonstrated superior outcomes compared to comparators (PFS of 9 months vs. 7.3 months with BV; ORR of 74% vs. 71%), although no comparative statistical analysis was presented. Subgroup analysis indicated better ORR (70%-75% vs. 60%-68%) and PFS (7.0–9.0 months vs. 4.5 months) with novel therapies compared to chemotherapy.

REMUNOM
ISSN 2178-6925
Received: 22/01/2026 - **Accepted:** 18/02/2026
Vol: 02.02
DOI: 10.61164/0sbasb69
Pages: 1 - 23

Tsirigotis et al. [15] retrospectively assessed 214 patients. Patients were divided into Cohort 1 (n=146; no access to BV) and Cohort 2 (n=68; received BV). Notably, only 37% of Cohort 2 used BV as first-line therapy. Median overall survival (OS) was significantly longer for BV-treated patients (57 months [95% CI 38–not reached]) compared to Cohort 1 (31 months [95% CI 25–42]). Multivariate analysis confirmed a significant survival benefit with BV use (HR = 0.34 [95% CI 0.15–0.80]; p=0.013), further supporting the conclusion that BV is associated with a marked reduction in the risk of death.

Between January 2008 and June 2014, Zagadailov et al. [16] conducted a multicenter retrospective study across 50 clinics in the UK and Germany, evaluating 312 patients, of whom 196 (62.8%) received BV and 116 received standard chemotherapy. Median age was 45.7 and 47.8 years, respectively, with a predominance of males. At one year, BV patients received an average of 7.5 infusion cycles with an ORR of 80.6% and CR of 45.4%, compared to 4 cycles, 68.2% ORR, and 44.2% CR for chemotherapy patients. Significant PFS improvements were seen with BV (27 months vs. 13.4 months; p=0.0441), along with superior ORR (80.6% vs. 68.2%; p=0.0165) and a lower disease progression rate (7.7% vs. 22.3; p=0.0165).

Bair et al. [17] retrospectively evaluated 87 patients, with a median age of 35.6 years, 54% male. Fifty-five patients received conventional cytotoxic chemotherapy, while 38 received novel therapeutic agents (BV [n=22]; lenalidomide [n=5]; nivolumab [n=6]; panobinostat [n=5]). Improved OS was observed in patients receiving novel agents compared to chemotherapy (85.6 vs. 17.1 months; p<0.001). Subgroup analysis showed a favorable HR for BV (HR 0.22 [95% CI 0.009–0.51]; p<0.001).

3.4. Risk of bias

The risk of bias of the only RCT Kuruvilla et al. was rated as moderate. Concerns about risk of bias were mainly related to survival outcome measurement [7-10]. Detailed in Table 2: The ROB 2.0 analysis is described in Table 2.

REMUNOM
ISSN 2178-6925

Received: 22/01/2026 - **Accepted:** 18/02/2026
Vol: 02.02
DOI: 10.61164/0sbasb69
Pages: 1 - 23

The ROBINS-I tool indicated moderate to serious bias in several areas of observational studies, mainly due to confounding, selection bias, and variations in intervention classification. Deviations in doses and treatment regimens, missing data, inconsistent outcome measurement, and lack of standardized definitions further complicated study comparisons. Overall, the risk of bias was considered moderate to serious [8,11-17] (Table 3).

3.5. Certainty of Evidence

Outcomes for pembrolizumab vs. BV comparison, derived from the KEYNOTE-204 RCT, were evaluated using the GRADE. Certainty of evidence was downgraded one level to "moderate" for survival outcomes. For response rates and adverse events, the evidence was downgraded two levels to "low" certainty due to concerns about result imprecision. The observational studies included in this review were judged to have "low" to "moderate" certainty of evidence, primarily due to bias, data inconsistency, and result imprecision. Table 01 of the supplementary material provides a detailed breakdown of evidence quality ratings [9-10].

4. DISCUSSION

The present systematic review evaluated the safety, efficacy, and effectiveness of BV in patients with relapsed or refractory R/R CD30+ HL after ASCT, synthesizing evidence from randomized and observational studies with different methodological designs.

Evidence from observational studies suggests an association between BV exposure and improved overall survival; however, these findings are subject to confounding and should be interpreted with caution. In these studies, the observed benefits were attributed to BV, with reported overall response rates reaching 80.6% and complete response rates of 45.4% within the first year of treatment, indicating clinically relevant antitumor activity. Nevertheless, the absence of randomized comparators limits the ability to establish causal inference regarding survival benefits [15,16].

REMUNOM
ISSN 2178-6925

Received: 22/01/2026 - **Accepted:** 18/02/2026
Vol: 02.02
DOI: 10.61164/0sbasb69
Pages: 1 - 23

BV gained clinical relevance primarily through early single-arm and observational studies that demonstrated meaningful activity in heavily pretreated patients with R/R CD30+ HL after ASCT. A pivotal phase II trial reported substantial response rates, while subsequent prospective observational cohorts, including studies conducted in Italy and France, confirmed manageable toxicity profiles and consistent response outcomes. However, despite their contribution to understanding feasibility and safety, these single-arm studies were excluded from the quantitative synthesis of this review in order to prioritize comparative evidence and reduce selection bias [18,19].

Larger observational cohorts evaluating BV monotherapy reported objective response rates ranging from approximately 60%, with complete response rates around 30% and median progression-free survival between 6 and 8 months. While these findings support BV biological activity, the lack of control groups and the retrospective nature of these analyses limit direct comparison with alternative therapies [20].

Comparative evidence identified three therapeutic perspectives. First, observational comparative studies suggest that BV monotherapy may offer survival benefits, particularly when administered early after ASCT. Second, combination strategies involving BV and ICIs were associated with improved PFS and OS in non-randomized settings, suggesting potential additive or synergistic effects; however, these findings are derived predominantly from observational data and should not be interpreted as definitive evidence of superiority. Third, randomized evidence indicates that isolated ICI therapy, particularly pembrolizumab, demonstrates superior PFS compared with BV, positioning BV as a secondary option in treatment sequencing according to current RCT data. These findings are consistent with recent literature emphasizing therapeutic sequencing strategies, in which ICIs are preferentially positioned earlier in the post ASCT setting, while BV is often reserved for selected clinical contexts, such as contraindications to immunotherapy or limited access to CPIs [10–11,13,16–17].

Kuruvilla et al. proposed pembrolizumab as an alternative to BV, acknowledging safety concerns and uncertainties in long-term outcomes. While

REMUNOM
ISSN 2178-6925

Received: 22/01/2026 - **Accepted:** 18/02/2026
Vol: 02.02
DOI: 10.61164/0sbasb69
Pages: 1 - 23

real-world studies frequently report objective response rates exceeding 80% for BV, such estimates may be inflated due to selection bias inherent in observational designs. In contrast, RCT evidence places BV behind ICIs in terms of disease control, reinforcing the importance of distinguishing between efficacy demonstrated under controlled conditions and effectiveness observed in real-world practice [10].

In the current therapeutic landscape, BV remains a relevant option, particularly in contexts with limited access to ICIs or in patients with contraindications to immunotherapy. Its role is supported mainly by observational evidence rather than robust randomized comparisons [10,12].

Regarding safety, BV demonstrated a consistent adverse event profile across studies, with neuropathy and neutropenia being the most frequently reported events. Although generally manageable, these toxicities may compromise treatment continuity and necessitate dose adjustments or discontinuation, underscoring the importance of careful patient monitoring [11, 21-23].

The risk of bias assessment revealed significant methodological limitations. Two studies were classified as having a serious risk of bias [11,17]. While the remaining studies presented moderate risk, mainly due to confounding, non-randomized allocation, retrospective data collection, and heterogeneous outcome definitions. These limitations reduce confidence in effect estimates and restrict the generalizability of findings.

Although the RCT by Kuruvilla et al. represents the highest level of evidence included in this review, several outcomes presented some concerns regarding risk of bias, particularly related to outcome measurement and selective reporting. These issues affected both efficacy endpoints, such as primary and secondary PFS, and safety outcomes, including treatment-related adverse events and grade 3–5 toxicities. While the superiority of pembrolizumab over BV in PFS appears robust, caution is warranted when interpreting secondary efficacy and safety estimates, as measurement and reporting biases may have influenced the magnitude of observed effects [10].

Among the observational studies, those conducted by Martínez et al., Desai et al., and Bair et al. were classified as having a serious risk of bias, mainly due to

REMUNOM
ISSN 2178-6925
Received: 22/01/2026 - **Accepted:** 18/02/2026
Vol: 02.02
DOI: 10.61164/0sbasb69
Pages: 1 - 23

confounding, participant selection, missing data, and selective outcome reporting. In these studies, patients who received BV were more likely to present favorable baseline characteristics, such as better performance status or access to subsequent lines of therapy, which may have led to an overestimation OS benefits attributed to BV. Consequently, direct comparisons with untreated or conventionally treated cohorts should be interpreted with caution, limiting the internal validity of the reported effect estimates [11,12,17].

Studies classified as having a moderate risk of bias, including those by Tun et al., Badar et al., Tsirigotis et al., and Zagadailov et al., were primarily affected by confounding, intervention misclassification, outcome measurement limitations, and selective reporting. These methodological issues particularly impact ORR and PFS estimates, which may reflect real-world effectiveness but cannot be interpreted as definitive evidence of comparative efficacy due to the absence of randomized allocation and standardized outcome assessment [13–16].

Taken together, the presence of outcome-specific bias across studies, combined with substantial clinical and methodological heterogeneity, reinforces the need for cautious interpretation of apparent survival and response benefits associated with BV. These findings highlight the importance of distinguishing between signals of clinical activity and robust comparative effectiveness, which remains insufficiently established in the current evidence base.

In addition to methodological limitations, substantial clinical and substantial clinical and methodological heterogeneity was observed among the included studies, justifying the decision not to perform a meta-analysis. The main sources of variability included differences in the treatment context (BV as consolidation versus treatment in relapse), months of treatment and doses of prior chemotherapy, patient clinical status at the start of BV treatment, comparator therapies, number of cycles and dosage regimens, as well as discontinuation rates due to adverse events [10, 11-17].

Additional heterogeneity arose from variations in safety reports, including the incidence of anemia, diarrhea, fever, pruritus, nausea, vomiting, hypothyroidism,

REMUNOM
ISSN 2178-6925

Received: 22/01/2026 - **Accepted:** 18/02/2026
Vol: 02.02
DOI: 10.61164/0sbasb69
Pages: 1 - 23

leukopenia, mucositis, infection, thrombocytopenia, in addition to the two prevalent adverse events, neutropenia and peripheral neuropathy [10-11, 16].

Studies also compared BV with a wide range of alternative treatments, including ICIs, chemotherapy-based regimens, or no active treatment, and reported heterogeneous outcomes such as overall response rate, progression-free survival, overall survival, and safety outcomes [10, 11-17].

Taken together, these variations limit direct comparability between studies and may partially explain the discrepancies in reported efficacy results. However, they reflect real-world clinical diversity and highlight the need for future randomized trials with standardized comparators, dosing strategies, outcome definitions, and longer follow-up.

Furthermore, the certainty of the evidence assessed using the GRADE framework ranged from moderate to low, primarily due to limitations in study design, imprecision, and inconsistency. Short follow-up periods and reliance on medical records further compromised the assessment of outcomes in several studies. However, none of the included observational studies reported a priori statistical power calculations, which limits the interpretability of neutral or negative findings and increases the risk of type II error, particularly for OS.

In the context of R/R CD30+ LH, cumulative toxicity and peripheral neuropathy associated with BV may significantly affect daily functioning and long-term treatment tolerability, influencing therapeutic sequencing and discontinuation rates. Therefore, future studies should systematically incorporate patient-centered outcomes, such as health-related quality of life, symptom burden, and treatment adherence, to better support individualized treatment decisions.

Despite these limitations, BV was incorporated into the Brazilian Unified Health System (SUS) in 2019, expanding access to treatment for patients with R/R CD30+ HL. Post-marketing observational studies continue to contribute valuable real-world safety data; however, high-quality randomized trials with extended follow-up remain essential to better define BV's comparative role [25].

5. CONCLUSION

REMUNOM
ISSN 2178-6925

Received: 22/01/2026 - **Accepted:** 18/02/2026
Vol: 02.02
DOI: 10.61164/0sbasb69
Pages: 1 - 23

BV represents a therapeutic option for patients with R/R CD30+ Hodgkin lymphoma after ASCT, based primarily on observational evidence. Although clinical activity and manageable safety have been consistently reported in real-world settings, the overall certainty of the evidence remains moderate to low due to methodological limitations and risk of bias. Randomized evidence indicates superior disease control with ICI compared to BV, suggesting that it should not be interpreted as a clearly superior or equivalent alternative based on current evidence. Consequently, conclusions about comparative efficacy should be drawn with caution. The findings highlight the need for well-designed randomized clinical trials with longer follow-up periods, standardized outcome definitions, and patient-centered outcomes, including quality of life and treatment adherence. Such studies are essential to more precisely define the role of BV in contemporary treatment strategies for R/R CD30+ Hodgkin lymphoma.

References

1. Mantey NRC, Muller EV, Montenegro MLV, Mantey JMC. Temporal trend of mortality due to Hodgkin and non-Hodgkin lymphoma in Brazil, 2001 to 2018. Saude Desenv Hum. 2023;11(1):1-12. https//doi.org/10.18316/sdh.v11i1.8929.

2. Moreira GS, Fernandes CLA, Andrade IKB, Leite RP, Oliveira MER, et al. Clinical and epidemiological profile of Hodgkin lymphoma cases in Brazil and their association with systemic lupus erythematosus. Research, Society and Development. 2024;13(4). https//doi.org/10.33448/rsd-v13i4.45391.

3. Araújo JAF, Firmino TAB, Santana FAA, Claudino KCS, Aoyama EA. Hodgkin lymphoma: the importance of early diagnosis by the nursing team. Brazilian Journal of Health Review. 2019;2(1):171–176. Available from: https://ojs.brazilianjournals.com.br/ojs/index.php/BJHR/article/view/878/759.

4. Higgins J, Thomas J, et al. Cochrane handbook for systematic reviews of interventions. Cochrane. 2024;6,5. Available from: https://www.training.cochrane.org/handbook.

5. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. PLoS Medicine. 2021;18(3). https//doi.org/10.1371/journal.pmed.1003583.

REMUNOM
ISSN 2178-6925

Received: 22/01/2026 - **Accepted:** 18/02/2026
Vol: 02.02
DOI: 10.61164/0sbasb69
Pages: 1 - 23

6. RAYYAN – Intelligent Systematic Review. Available from: https://www.rayyan.ai.

7. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366. https//doi.org/10.1136/bmj.l4898.

8. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016;355. https//doi.org/10.1136/bmj.i4919.

9. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336 (7650):924–926. https//doi.org/10.1136/bmj.39489.470347.AD.

10. Kuruvilla J, Ramchandren R, Santoro A, Paszkiewicz-Kozik E, Gasiorowski R, et al. Pembrolizumab versus brentuximab vedotin in relapsed or refractory classical Hodgkin lymphoma (KEYNOTE-204): an interim analysis of a multicentre, randomised, open-label, phase 3 study. Lancet Oncology. 2021;22(4):512–524. https//doi.org/ 10.1016/S1470-2045(21)00005-X.

11. Martínez C, de Haro ME, Romero S, Gutiérrez A, Domingo-Domènech E, et al. Impact of pre- and/or post-autologous stem cell transplantation exposure to brentuximab vedotin on survival outcomes in patients with high-risk Hodgkin lymphoma. Annals of Hematology. 2023;102(2):429–437. https//doi.org/10.1007/s00277-022-05011-6.

12. Desai SH, Spinner MA, Evens AM, Sykorova A, Bachanova V, et al. Overall survival of patients with cHL who progress after autologous stem cell transplant: results in the novel agent era. Blood Advances. 2023;7(23):7295–7303. https//doi.org/10.1182/bloodadvances.2023011205.

13. Tun AM, Wang Y, Matin A, Inwards DJ, Habermann TM, et al. Outcomes of patients with classic Hodgkin lymphoma who relapsed after autologous stem cell transplant. HemaSphere. 2023;7(4):869. https//doi.org/10.1097/HS9.0000000000000869.

14. Badar T, Epperla N, Szabo A, Borson S, Vaughn J, et al. Trends in postrelapse survival in classic Hodgkin lymphoma patients after experiencing therapy failure following auto-HCT. Blood Advances. 2020;4(1):47–54. https//doi.org/10.1182/bloodadvances.2019000981.

15. Tsirigotis P, Vassilakopoulos T, Batsis I, Bousiou Z, Gkirkas K, et al. Positive impact of brentuximab vedotin on overall survival of patients with classical

REMUNOM
ISSN 2178-6925

Received: 22/01/2026 - **Accepted:** 18/02/2026
Vol: 02.02
DOI: 10.61164/0sbasb69
Pages: 1 - 23

Hodgkin lymphoma who relapse or progress after autologous stem cell transplantation: a nationwide analysis. Hematology Oncology. 2018;36(4):645–650. https//doi.org/10.1002/hon.2541.

16. Zagadailov EA, Corman S, Chirikov V, Johnson C, Macahilig C, et al. Real-world effectiveness of brentuximab vedotin versus physician's choice chemotherapy in patients with relapsed/refractory Hodgkin lymphoma following autologous stem cell transplantation in the United Kingdom and Germany. Leukemia & Lymphoma. 2018;59(6):1413-1419. https//doi.org/10.1080/10428194.2017.1382698.

17. Bair SM, Strelec L, Nagle SJ, Nasta SD, Landsburg DJ, et al. Outcomes of patients with relapsed/refractory Hodgkin lymphoma progressing after autologous stem cell transplant in the current era of novel therapeutics: a retrospective analysis. American Journal of Hematology. 2017;92(9):879–884. https//doi.org/ 10.1002/ajh.24792.

18. Younes A, Gopal AK, Smith SE, Ansell SM, Rosenblatt JD, et al. Results of a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's lymphoma. J Clin Oncol. 2012;30(18)2183-9. https//doi.org/10.1200/JCO.2011.38.0410.

19. Zinzani PL, Viviani S, Anastasia A, Vitolo U, Luminari S, et al. Brentuximab vedotin in relapsed/refractory Hodgkin's lymphoma: the Italian experience and results of its use in daily clinical practice outside clinical trials. Haematologica. 2013;98(8):1232-6. https//doi.org/ 10.3324/haematol.2012.083048.

20. Perrot A, Monjanel H, Bouabdallah R, Quittet P, Sarkozy C, et al. Impact of post-brentuximab vedotin consolidation on relapsed/refractory CD30+ Hodgkin lymphomas: a large retrospective study on 240 patients enrolled in the French Named-Patient Program. Haematologica. 2016;101:466-73.

21. Massaro F, Pavone V, Stefani PM, Botto B, Pulsoni A, et al. Brentuximab vedotin consolidation after autologous stem cell transplantation for Hodgkin lymphoma: a Fondazione Italiana Linfomi real-life experience. Hematology Oncology. 2022;40(1):31–39. https//doi.org/10.1002/hon.2939.

22. Moretti M, Liberati AM, Rigacci L, Puccini B, Pulsoni A, et al. Brentuximab vedotin and bendamustine produce long-term clinical benefit in patients with relapsed or refractory classical Hodgkin lymphoma: a multicenter real-life experience. Clinical Lymphoma Myeloma and Leukemia. 2022;22(3):198–204. https// doi.org/10.1016/j.clml.2021.09.018.

23. NATIONAL COMMISSION FOR THE INCORPORATION OF HEALTH TECHNOLOGIES (CONITEC). Brentuximab vedotin for the treatment of adult

REMUNOM
ISSN 2178-6925

Received: 22/01/2026 - **Accepted:** 18/02/2026
Vol: 02.02
DOI: 10.61164/0sbasb69
Pages: 1 - 23

patients with refractory or relapsed CD30+ Hodgkin lymphoma after autologous hematopoietic stem cell transplantation. Ministry of Health, 2019. Available from: http://conitec.gov.br/images/Relatorios/2019/Relatorio_Brentuximabe_LinfomaHodgkin.pdf. Accessed on: July 19, 2022.

24. Uncu Ulu B, Dal MS, Yönal Hindilerden İ, Akay OM, Mehtap Ö, et al. Brentuximab vedotin and bendamustine: an effective salvage therapy for relapsed or refractory Hodgkin lymphoma patients. Journal of Chemotherapy. 2022;34(3):190–198. https//doi.org/10.1080/1120009X.2021.1976912.

25. Wagner CB, Boucher K, Nedved A, Micallef IN, Desai S, et al. Effect of cumulative dose of brentuximab vedotin maintenance in relapsed/refractory classical Hodgkin lymphoma after autologous stem cell transplant: an analysis of real-world outcomes. Haematologica. 2023;108(11):3025–3032. https//doi.org/10.3324/haematol.2023.282780.

REMUNOM
ISSN 2178-6925

Received: 22/01/2026 - **Accepted:** 18/02/2026
Vol: 02.02
DOI: 10.61164/0sbasb69
Pages: 1 - 23

TABLES AND FIGURES

TABLE 1.

Search Strategies and Results in the Databases Consulted

Database	Search Strategy
Pubmed	#1 “Hodgkin disease”[TIAB] OR “Hodgkin Disease”[MH] OR “Hodgkin lymphoma”[TIAB] OR “Hodgkin granuloma”[TIAB] OR (Hodgkin[TIAB] AND (cancer[TIAB] OR lymphogranuloma[TIAB] OR malignant[TIAB])) #2 brentuximab[TIAB] OR adcetris[TIAB] OR “Brentuximab Vedotin”[MH] #1 AND #2
Embase	(‘Hodgkin disease’:ab,ti OR ‘Hodgkin lymphoma’:ab,ti OR ‘Hodgkin granuloma’:ab,ti) AND (brentuximab:ab,ti OR adcetris:ab,ti)
Lilacs	Brentuximab (título, resumo, assunto)
Scielo	Brentuximab (todos os índices)
Cochrane Library	(‘Hodgkin disease’:ab,ti OR ‘Hodgkin lymphoma’:ab,ti OR ‘Hodgkin granuloma’:ab,ti) AND (Brentuximab:ab,ti OR Adcetris:ab,ti)

REMUNOM
ISSN 2178-6925

Received: 22/01/2026 - **Accepted:** 18/02/2026
Vol: 02.02
DOI: 10.61164/0sbasb69
Pages: 1 - 23

TABLE 2. RISK OF BIAS ASSESSMENT USING THE ROB 2.0 TOOL

Study	Outcomes	Randomization	Deviation from intended intervention	Missing outcome data	Outcome measurement	Selection of the reported result	Overall risk of bias
Kuruvilla *et al*., 2021. (10)	Primary progression-free survival (PFS)				1		Some concerns
	Secondary progression-free survival (PFS)				1		Some concerns
	Complete response rate (CRR)					2	Some concerns
	Partial response rate (PRR)					2	Some concerns
	Stable disease rate (SDR)					2	Some concerns
	Progressive disease rate (PDR)					2	Some concerns
	Treatment-related adverse events (TRAEs)					3	Some concerns
	Grade 3–5 adverse events					3	Some concerns

PFS: Progression-free survival; OS: Overall survival; 1 = Disease progression (primary PFS) and progression excluding clinical and imaging data (secondary PFS) were subject to interpretation bias by the assessor; 2 = There are discrepancies in the reporting of results (for these outcomes, a total of 103 patients were reported in the pembrolizumab group and 92 in the brentuximab group in the text; however, the tables show 99 and 83 patients, respectively); 3 = The authors report 24 serious adverse events in the pembrolizumab group and 16 in the brentuximab group, but the table shows 28 grade 3–4 events in the pembrolizumab group and 38 in the brentuximab group. Green color: Low riskYellow color: Some concerns;
Red color: High risk.

REMUNOM
ISSN 2178-6925

Received: 22/01/2026 - **Accepted:** 18/02/2026
Vol: 02.02
DOI: 10.61164/0sbasb69
Pages: 1 - 23

TABLE 3. RISK OF BIAS ASSESSMENT USING THE ROBINS-I TOOL

Study	Outcomes	Confounding	Participant selection	Intervention classification	Deviation from intended intervention	Missing data	Outcome measurement	Selection of the reported result	Overall risk of bias
Martínez *et al*., 2023. (11)	PFS	15	14			17		16	Serious
	OS	15	14			17		16	Serious
Desai *et al*., 2023. (12)	OS	12	11	13					Moderate
Tun *et al*., 2023. (13)	PFS	20	18				19		Moderate
	OS	20	18				19		Moderate
Badar *et al*., 2020. (14)	OS	1					2		Moderate
	PFS	1					2		Moderate
	Complete response rate	1					2		Moderate
Tsirigotis *et al*., 2018.	OS						3	4	Moderate

REMUNOM
ISSN 2178-6925

Received: 22/01/2026 - **Accepted:** 18/02/2026
Vol: 02.02
DOI: 10.61164/0sbasb69
Pages: 1 - 23

(15)									
Zagadailov *et al*., 2018. (16)	OS	5					6		Moderate
	PFS	5					6		Moderate
	Patients alive at 12 months	5					6		Moderate
	Overall response rate	5					6		Moderate
	Complete response rate	5					6		Moderate
	Partial response rate	5					6		Moderate
	Stable disease rate	5					6		Moderate
	Progressive disease rate	5					6		Moderate
Bair *et al*., 2017. (17)	OS		7	8		9		10	Serious

PFS: Progression-free survival; OS: Overall survival. 1. Retrospective comparative cohorts with time cutoff; patients stratified into cohorts 1 and 2, results by intervention. 2. Wide confidence intervals. 3. Variability in outcome reporting, no standardization. 4. Insufficient follow-up to determine survival. 5. No standardization in chemotherapy choice (clinical judgment). 6. Results reported only in percentages, no statistical analysis. 7. Discrepancy in patient numbers (text: n=88; table: n=87). 8. Unclear intervention distribution; 60/87 no intervention, 38 new agents; possible multiple interventions per patient. 9. No information on dosage and cycles. 10. Multiple outcome analyses. 11. Retrospective design, no randomization; treatment choices based on clinical judgment may bias results. 12. Unmeasured confounders (e.g., initial response, comorbidities). 13. Reliance on retrospective data with possible incomplete/inconsistent

REMUNOM
ISSN 2178-6925

Received: 22/01/2026 - **Accepted:** 18/02/2026
Vol: 02.02
DOI: 10.61164/0sbasb69
Pages: 1 - 23

records. 14. Selection bias: BV-treated patients may differ in clinical characteristics. 15. Insufficient adjustment for confounders despite multivariate analysis (e.g., PET-CT staging, prior BV use). 16. PET-CT-based success assessment subjective, varies by interpreter experience. 17. Inconsistencies in medical records (treatment history, BV adverse event management). 18. Selection bias: all patients post-ASCT; those receiving BV/ICIs may differ from chemotherapy group. 19. Information bias: gaps/inconsistencies in clinical records. 20. Inadequate control of unmeasured confounders (performance status, comorbidities, additional treatments). Risk Levels: Green: Low; Yellow: Moderate; Orange: Severe; Red: Critical; White/Gray: Not reported.

REMUNOM
ISSN 2178-6925

Received: 22/01/2026 - **Accepted:** 18/02/2026
Vol: 02.02
DOI: 10.61164/0sbasb69
Pages: 1 - 23

Figure 1.
Flowchart of the Systematic Review