

## BRENTUXIMAB VEDOTIN AS A BRIDGE TO TRANSPLANT IN HODGKIN LYMPHOMA PATIENTS. EXPERIENCE FROM TREATED PATIENTS IN NORTH MACEDONIA

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### Abstract

**Background:** The treatment of Hodgkin lymphoma (HL) has evolved significantly since the discovery of monoclonal antibodies (mAbs), which have been promising in improving outcomes, particularly in relapsed/refractory cases. Brentuximab vedotin (BV), an antibody-drug conjugate (ADC) targeting the CD30 antigen, has emerged as an effective treatment for HL, demonstrating improved survival outcomes in patients who have failed conventional chemotherapy regimens.

**Objective:** This study aims to evaluate the efficacy and clinical outcomes of BV-based salvage therapy followed by autologous stem cell transplantation (auto-PBSCT) in patients with relapsed or refractory Hodgkin lymphoma (R/R HL) in North Macedonia.

**Methods:** A retrospective analysis was conducted involving 47 patients treated with BV at the Clinic of Hematology in Skopje starting from the drug's approval in December 2022 to the latest review of patient histories in December 2024. The study primarily focused on patients initially treated with the ABVD regimen, followed by BV-based salvage therapy and subsequent auto-PBSCT.

**Results:** Out of the 47 patients, 53% were male and 47% were female, with a median age of 36 at diagnosis. The most common histopathological subtype was nodular sclerosis HL (60%), consistent with national data. Most patients (87%) received the ABVD regimen as initial treatment. In 5 patients (10.6%) a subsequent second-line salvage BV-DHAP therapy with following auto-PBSCT was applied, and in these patients, no detectable PET/CT progression was observed and the treatment was continued with a BV maintenance therapy.

In 12 patients (25.5%), BV-DHAP was used as a second-line therapy, with failure to achieve remission, which was the reason to switch the regimen to BEGEV followed by auto-PBSCT in three of the patients, whereas the rest of the patients were treated with augmented ICE, BV-ICE or escalated to the escalated BEACOPP regimen. Most of these patients are currently being administered a maintenance therapy with BV or Nivolumab. Only one of the patients that was given an augmented ICE protocol had a fatal outcome due to refractoriness of the disease.

In 9 patients (19%), the escalated BEACOPP protocol was used as a second-line therapeutic regimen. All of them achieved clinical remission and afterwards were subjected to salvage therapy with BV-DHAP/BV-BEGEV and subsequent auto-PBSCT.

The treatment outcomes, including progression-free survival (PFS), are consistent with global studies demonstrating the benefit of BV in R/R cases of HL.

**Conclusion:** BV-based salvage therapy followed by auto-PBSCT is an effective treatment strategy for R/R HL, with promising outcomes in patients who fail ABVD. Our findings support the growing evidence for BV as a key component in the treatment of R/R HL, particularly in the case of high-risk patients. Further studies are needed to explore optimal dosing regimens and long-term survival outcomes.

**Keywords:** brentuximab vedotin, CD30, CD30 targeting.

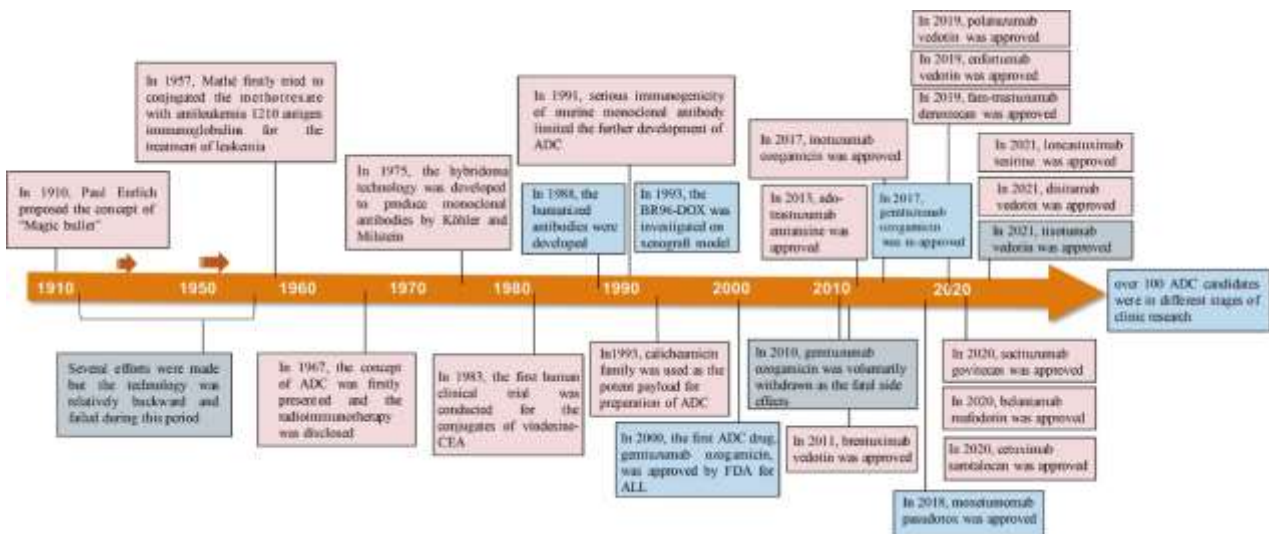
## Introduction

Since the 1975 discovery by Kohler and Milstein, scientists have been striving to improve the targeting of mAbs with the goal of achieving better outcomes in cancer treatment. The aim is to offer patients longer disease-free survival and improved quality of life. By fusing B cells and by utilizing genetic engineering, mAbs can exert their cytotoxic effects on cancer cells.

These effects occur through mechanisms like complement-mediated and antibody-dependent cell-mediated cytotoxicity, as well as by blocking signalling pathways initiated by their target antigens. [1].

Over the years, several strategies have been proposed to optimize the use of mAbs. For instance, *Khouri I.F. et al.* [2] suggested that higher doses of mAbs during autologous stem cell transplantation could be a promising treatment option for patients with aggressive B-cell lymphomas. Another strategy is the use of ADCs, which combine the targeting specificity of mAbs with the potent cytotoxic effects of chemotherapy agents. This approach enables more precise ablation of cancer cells while minimizing damage to surrounding healthy tissue [3].

Fig. 1. Timeline of developmental spurts of ADCs [4].



**Figure 1.** ADC, antibody-drug conjugate; CEA, Carcinoembryonic antigen; ALL, acute lymphoid leukaemia; BR96, an antibody binding to Lewis Y; DOX, doxorubicin; FDA, the U.S. Food and Drug Administration

HL, a disease with significant potential for treatment via ADCs, is still largely treated with the conventional frontline ABVD regimen (doxorubicin, bleomycin, vinblastine and dacarbazine), which has remained unchanged since its introduction in 1975. However, up to 30% of patients with stage III or IV Hodgkin’s lymphoma experience refractory disease or relapse after frontline treatment with ABVD [5].

Despite this, recent advances in treatment strategies have led to improved outcomes for patients with Hodgkin lymphoma over the past few decades.

## The CD30 Antigen

The CD30 antigen, a member of the tumor necrosis factor (TNF) receptor superfamily, was first identified as a cell surface antigen on primary and cultured Hodgkin’s and Reed-Sternberg cells using the monoclonal antibody Ki-1[6].

CD30 is normally expressed by a subset (15–20%) of CD45RO+ T cells following activation by various stimuli [7]. It plays a role in signal transduction through the activation of the NF-κB pathway and mitogen-activated protein kinases (MAPKs), ultimately regulating cell growth, proliferation and apoptosis.

Figure 2. Understanding CD30 biology and therapeutic targeting: a historical perspective providing insight into future directions [8].

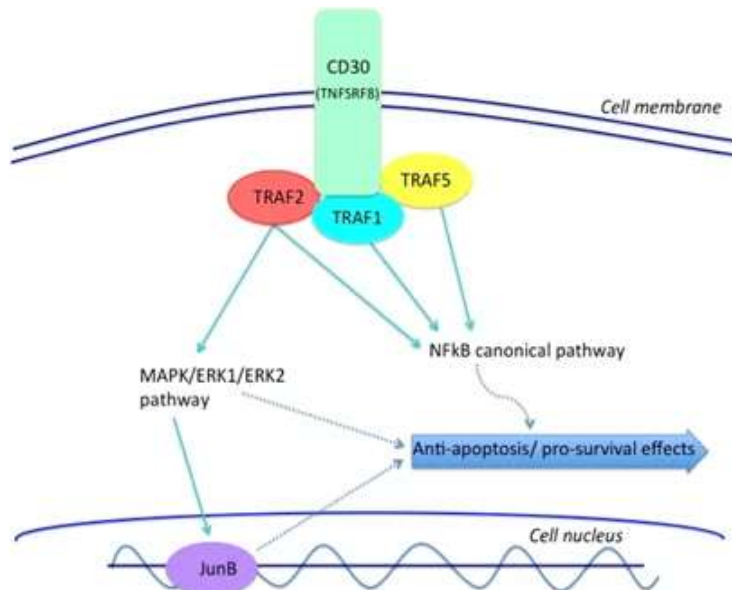


Figure 2. Blood Cancer Journal (Blood Cancer J.) ISSN 2044-5385 (online).

### Brentuximab Vedotin: The Anti-CD30 Monoclonal Antibody – A Promise for Better Horizons

Peter D. Senter and Eric L. Sievers first described cAC10-Val-Cit-PABC-MMAE, now known as brentuximab vedotin (BV), as a targeted therapy for relapsed HL and systemic anaplastic large cell lymphoma (ALCL). BV consists of approximately four molecules of monomethyl auristatin E (MMAE) conjugated to cAC10 interchain cysteine residues via a protease-cleavable ValCit-PABC linker [9].

It is approved for treating HL in adult patients with previously untreated systemic anaplastic large cell lymphoma (sALCL) or other CD30-expressing peripheral T-cell lymphomas (PTCL), including angioimmunoblastic T-cell lymphoma and PTCL not otherwise specified, in combination with cyclophosphamide, doxorubicin and prednisone; previously untreated Stage III or IV classical Hodgkin lymphoma (cHL), in combination with doxorubicin, vinblastine and dacarbazine; cHL at high risk of relapse or progression as post-autologous hematopoietic stem cell transplantation (auto-PBSCT) consolidation; cHL after failure of auto-PBSCT or failure of at least two prior multi-agent chemotherapy regimens in patients who are not auto-PBSCT candidates; sALCL after failure of at least one prior multi-agent chemotherapy regimen and for primary cutaneous anaplastic large cell lymphoma (pcALCL) or CD30-expressing mycosis fungoides (MF) who have been administered prior systemic therapy [10].

The main toxicity of BV is cumulative peripheral neuropathy.

Early clinical trials have demonstrated robust direct cytotoxicity of this antibody-drug conjugate in patients with relapsed or refractory CD30+ lymphomas, with complete remission rates of approximately 60% patients [11].

In addition to its direct cytotoxic effects, BV may activate the innate immune system, triggering an antitumor immune response by inducing immunogenic cell death via endoplasmic reticulum stress [12].

The cost-effectiveness of BV compared to chemotherapy with or without radiotherapy (and/or autologous stem cell transplantation - ASCT) in the treatment of R/R cHL has been demonstrated in multiple countries, including Scotland, Canada, Mexico, Venezuela and Sweden. All studies, except one from the healthcare perspective in Canada, found that BV is a cost-effective treatment relative to chemotherapy comparators [13].

### Our modest experience with BV as a salvage therapy followed by auto-PBSCT

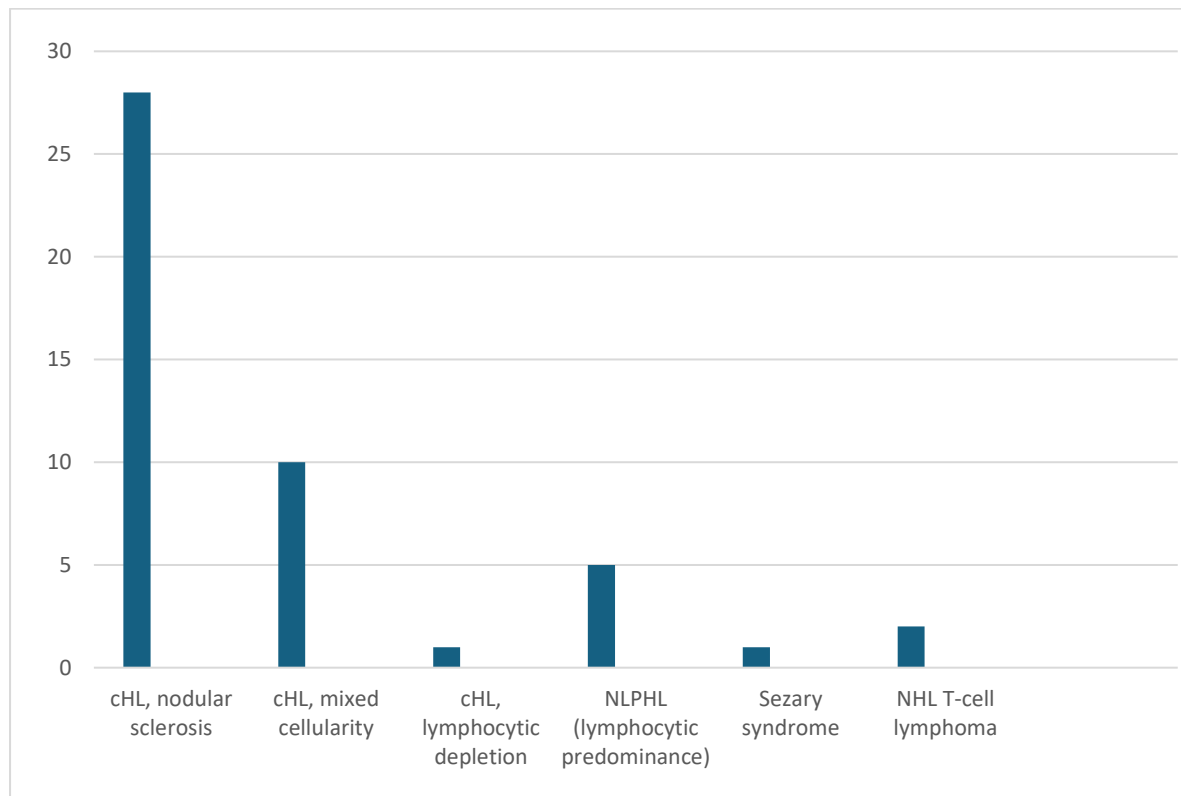
In North Macedonia, treatment recommendations for both early and advanced HL are based on the guidelines set by the European Society for Medical Oncology (ESMO) 2018, the National Comprehensive Cancer Network (NCCN), the British Society for Hematology (BSH) and the German Hodgkin's Lymphoma Group (GHSG) [14-17].

Salvage therapy, followed by high-dose chemotherapy with auto-PBSCT, remains the standard approach for treating patients with R/R HL. This approach should be tailored to the individual patient, considering factors such as the patient's initial therapy, the risk of cumulative non-hematological toxicity and the possibility of collecting stem cells.

In Macedonia, common salvage therapy regimens include combinations such as BV-DHAP, BV-ICE and BV-ESHAP. For patients not eligible for auto-PBSCT, BV is used following first-line treatment failure, with an objective response rate (ORR) of 50% and a complete response (CR) rate of 12%.

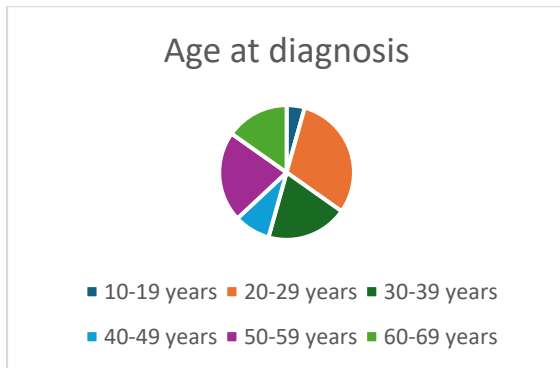
We conducted a retrospective analysis of patients treated with BV at the Clinic of Hematology in Skopje starting from the drug's approval in December 2022 until the most recent review of patient histories in December 2024. We examined 47 patients who were subjected to the nationally approved BV therapy at various stages of treatment for different diagnoses, with a specific focus on those initially treated with the ABVD regimen, followed by BV-based salvage therapy and subsequent auto-PBSCT.

Out of the examined patient cohort, 53% were male and 47% were female, with the majority diagnosed in 2019 (17%) and 2022 (17%). The most common histopathology result in 60% of patients was nodular sclerosis cHL, which aligns with the National Cancer Institute (NCI) data, where nodular sclerosis accounts for approximately 70% of all classical HL cases [18].

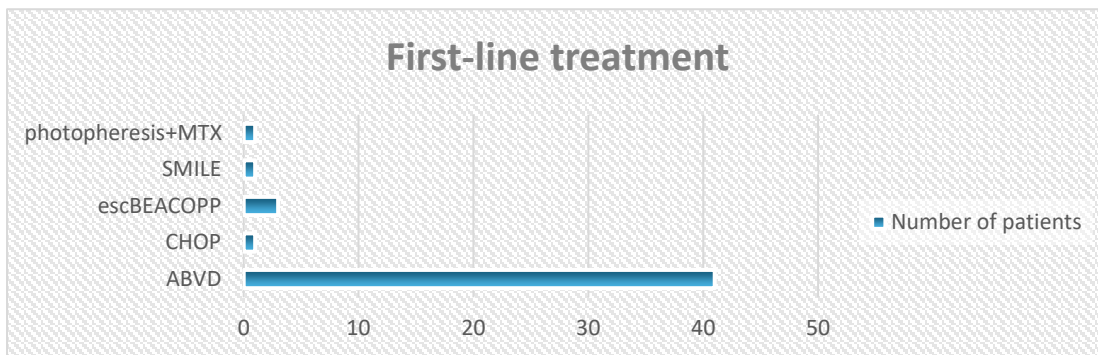


**Figure 3.** Type of diagnosis and number of patients diagnosed.

The age at diagnosis of the patients with HL corresponds to the two peaks of incidence of HL described in the literature. (Figure 4) Twenty-three patients (48%) belong to the age group of 15 to 34 years, whereas seven patients (14%) are older than 60 years. The median age at the time of diagnosis was 36 years.



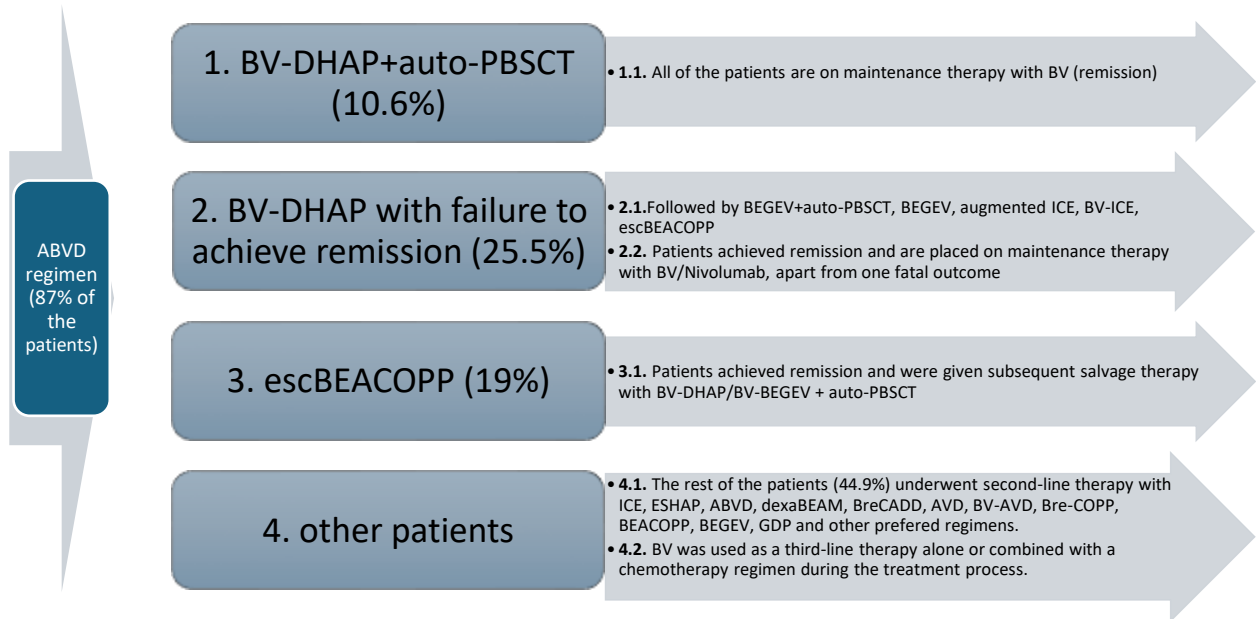
**Figure 4.** Age at diagnosis



**Figure 5.** First-line treatment

The initial prescribed therapy in 41 (87%) patients was ABVD regimen:

1. In 5 patients (10.6%) BV-DHAP therapy with subsequent auto-PBSCT was applied. In all patients subject to this protocol, remission of the disease was achieved and the treatment was followed up with maintenance therapy with BV.
2. In 12 patients (25.5%) BV-DHAP was used as a second-line therapy, with failure to achieve remission, which was a reason to switch the regimen to BEGEV followed by auto-PBSCT in three of the patients, whereas the rest of the patients were treated with augmented ICE, BV-ICE, or escalated to the esc. BEACOPP regimen. Most of these patients are currently being administered maintenance therapy with BV or Nivolumab. Only one of the patients that was given an augmented ICE protocol had a fatal outcome due to refractoriness of the disease.
3. In 9 patients (19%), the escalated BEACOPP protocol was used. All of them achieved clinical remission and afterwards were given salvage therapy with BV-DHAP/BV-BEGEV and auto-PBSCT.
4. The remaining part of the patients were given different second-line therapies including ICE, ESHAP, ABVD, dexaBEAM, BreCADD, AVD, BV-AVD, Bre-COPP, BEACOPP, BEGEV, GDP and other preferred regimens. BV was used as a third-line therapy alone or combined with a chemotherapy regimen during the treatment process.



**Figure 6.** Second-line treatment after ABVD initiation of therapy.

### Discussion

The median age of our study (36) and bimodal pattern (many in the 15–34 age group and some >60) match the classical epidemiology of HL described internationally. Nodular sclerosis predominance (~60–70%) is also typical and aligns with national registry expectations. These demographic similarities support generalizability of treatment strategies used internationally [21].

When comparing our cohort to international trials, we must acknowledge several limitations. Our sample of 47 patients is modest and influenced by clinical heterogeneity, including variations in salvage regimens, prior treatment lines and selection biases regarding who receives BV and who proceeds to transplant.

As a retrospective, single-center analysis, our data limit causal interpretation and direct comparison with long-term outcomes from prospective trials. In addition, our follow-up duration is relatively short, which may underestimate late relapses or delayed toxicities such as neuropathy. Differences in response assessment—particularly between trial-grade PET/CT evaluation and routine clinical practice—may also impact the reported rates. The acknowledgement of these limitations strengthens the interpretation of our findings and supports the value of presenting real-world national data.

Treatment recommendations suggest up to sixteen (16) cycles of BV after auto PBSCT in high-risk relapsed/refractory classical Hodgkin lymphoma. Sixteen cycles of brentuximab vedotin (BV) administered after autologous stem cell transplantation (ASCT) have shown to improve 2-year progression-free survival (PFS) in high-risk relapsed/refractory classical Hodgkin lymphoma, compared with placebo. Nevertheless, many patients are unable to complete all 16 full-dose cycles because of treatment-related toxicity [19].

BV-induced peripheral neurotoxicity (BVIN) is a major concern in Hodgkin lymphoma because it is common and often leads to dose reductions or treatment discontinuation. It can involve sensory, motor or autonomic nerve dysfunction and may become severely disabling in some patients. Although usually reversible, BVIN can persist for months or years, thus significantly impacting quality of life in the typically young HL population [20].

When we compare our outcomes with major clinical trials and real-world evidence, we can observe clear differences that help us interpret our results. The pivotal phase II trial of single-agent BV in heavily pretreated relapsed/refractory HL demonstrated strong activity, with an overall response rate

of about 75% and durable complete responses in a meaningful subset of patients—findings that established BV as an effective option for both bridging to transplant and for patients unable to undergo transplant [22].

In contrast, our real-world cohort showed an ORR (objective response rate) of roughly 50% and a CR (complete remission) rate of about 12% when BV was used after first-line therapy. Several factors likely explain this gap, including the broader and more heterogeneous patient population we treat, the use of BV later in therapy or in combination regimens, older or clinically more complex patients, and variations in real-world response assessment. These differences are consistent with other international real-world studies, where ORRs are often lower than those reported in controlled clinical trials.

When we compare our findings with international data on BV-based platinum salvage regimens, we can notice strong alignment but also expected real-world variability. Published phase II and single-arm series of BV-ICE, BV-DHAP, and BV-BEGEV consistently report high CMR/CR rates—often between 60% and 90%—and excellent bridge-to-transplant success after only one or two cycles [23].

In our cohort, all patients who received BV-DHAP followed by auto-PBSCT achieved remission and moved on to maintenance, which mirrors global evidence that adding BV improves the likelihood of reaching a transplant-eligible remission.

At the same time, the subgroup of patients who did not respond to BV-DHAP and required alternative regimens (BEGEV, ICE-based adjustments or escalated BEACOPP) reflects the heterogeneity seen in real-world practice.

International series similarly indicate that while BV-based salvage works well for many, a meaningful subset remains refractory and requires sequential salvage strategies. Overall, our results correspond to the international experience and reinforce the role of BV-containing regimens as an effective part of modern salvage therapy.

When we compare our practice with the evidence from the AETHERA trial, we can observe a clear alignment. AETHERA demonstrated that BV consolidation after autologous transplant significantly improves progression-free survival in high-risk patients, establishing BV as the standard post-transplant maintenance option in this setting [24].

In our cohort, we similarly continued BV maintenance after successful BV-based salvage and auto-PBSCT, following the same rationale used in AETHERA. By doing so, we apply an evidence-based approach that supports better disease control in patients with high-risk features, fully consistent with international recommendations.

Recent studies indicate that PD-1 inhibitors such as nivolumab and pembrolizumab, as well as combinations like BV + bendamustine or BV + PD-1 blockade, are increasingly used worldwide for challenging R/R HL because they produce high response rates and can serve as effective bridging or maintenance options [25].

In our cohort, several patients continued therapy with BV or nivolumab maintenance, which places our real-world practice in line with these international treatment trends where PD-1 inhibitors are now routinely integrated into salvage and maintenance strategies for patients who respond incompletely to BV-based regimens.

Our practical conclusions and recommendations for Macedonian practice are that BV-based salvage regimens (BV-ICE, BV-DHAP, BV-BEGEV) in our cohort showed outcomes similar to international reports and helped many patients reach auto-PBSCT, supporting the BV's role in the salvage setting. Using BV maintenance after auto-PBSCT for high-risk patients is evidence-based, consistent with the AETHERA trial, and aligns with current guidelines.

For patients who cannot undergo transplant, single-agent BV can achieve meaningful responses, although real-world ORR/CR rates are often lower than in pivotal trials; therefore, we should consider earlier use, combination approaches or referral to clinical trials/PD-1 inhibitors when possible. Finally, the establishment of prospective national data collection—with standardized PET/CT response assessment, toxicity reporting and long-term follow-up—would allow stronger comparison with international cohorts.

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## Conclusion

Brentuximab vedotin-based salvage therapy followed by autologous stem cell transplantation provides an effective and well-tolerated therapeutic strategy for relapsed/refractory classical Hodgkin lymphoma in the North Macedonian real-world setting.

Our single-center experience demonstrates that BV-containing salvage regimens increase the likelihood of achieving transplantable remission and that BV consolidation after transplant is implemented in accordance with evidence showing PFS benefit.

Discrepancies between real-world ORR/CR and pivotal clinical trial results underscore the impact of patient selection and treatment heterogeneity outside trial settings.

Prospective multicenter registries and longer follow-up are required to refine optimal sequencing, dosing and combinations (including integration of PD-1 inhibitors) and to fully characterize long-term survival and toxicity outcomes in our population.

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