NHS England Evidence Review:

Combination brentuximab vedotin and bendamustine for adults with relapsed or refractory classical Hodgkin lymphoma

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Prepared by Solutions for Public Health (SPH) on behalf of NHS England Specialised Commissioning

Contents

1. Introduction

This evidence review examines the clinical effectiveness, safety and cost effectiveness of combination brentuximab vedotin and bendamustine (BVB) as third or subsequent line treatment compared to standard of care in adults with relapsed or refractory classical Hodgkin lymphoma (R/R HL). A parallel review (2404b) examines the evidence in children with relapsed or refractory classical Hodgkin lymphoma.

Classical Hodgkin lymphoma is a rare blood cancer in which white blood cells start to grow in an uncontrolled way and begin to collect in parts of the lymphatic system, such as the lymph nodes. The affected white blood cells lose their infection-fighting properties, making the body more vulnerable to infection. Frontline therapy is highly effective and cures the majority of patients, but approximately 10 to 30% patients will develop relapsed or refractory disease.

Brentuximab vedotin (BV) is a CD30-targeted antibody drug conjugate which is licenced and NICE approved for use in HL (TA 524). Bendamustine is an alkylating agent. The proposed intervention is the addition of off-label bendamustine to the NICE approved dose and usage of BV in R/R HL. Combination BVB therapy may be given with or without best supportive care. Best supportive care can include steroids, analgesics, antipyretics, antibiotics, anti-emetics or granulocyte-colony stimulating factor (G-CSF). Combination BVB therapy will often be followed by stem cell transplant which may be autologous or allogenic pending on age or co-morbidities or other risk factors.

Current standard of care can include monotherapy BV, monotherapy pembrolizumab or third line chemotherapy. Standard of care may be given with or without best supportive care.

In addition, the review scope included the identification of possible subgroups of patients within the included studies who might benefit from treatment with combination BVB as third or subsequent line treatment more than others, as well as the number of cycles and the doses of combination therapy used by the included studies to treat R/R HL.

2. Executive summary of the review

This evidence review examines the clinical effectiveness, safety and cost effectiveness of combination brentuximab vedotin and bendamustine (BVB) as third or subsequent line treatment compared to standard of care in adults with relapsed or refractory classical Hodgkin lymphoma (R/R HL). The searches for evidence published since June 2014 were conducted on 12 June 2024 and identified 325 references. The titles and abstracts were screened and 29 full text papers were obtained and assessed for relevance.

Seven papers were identified for inclusion, one single arm (phase I and phase II) trial and six case series (five retrospective and one unspecified). The studies included between 20 and 65 subjects. Median follow-up ranged from 12 to 38 months where reported. The studies were carried out in Canada, Hungary, India, Italy, Turkey and the USA. No studies comparing BVB with other treatments were identified.

In terms of clinical effectiveness:

Critical outcomes

- **Overall survival**

  Six non-comparator studies of R/R HL patients receiving BVB as third or subsequent line treatment provided very low certainty evidence for overall survival.

  - One single arm (phase II) trial and one retrospective case series reported a 1-year overall survival of 86% at an unspecified follow-up and 85% at a median follow-up of 14 months.
  - One single arm (phase II) trial and two retrospective case series reported a 2-year overall survival ranging from 72% to 82% up to a median follow-up of 19 months. One retrospective case series reported a 2-year overall survival of 93% at a median follow-up of 17 months in patients receiving BVB followed by ASCT.
  - One retrospective case reported a 3-year overall survival of 75% (95% CI 59 to 95) at a median follow-up of 12 months.
  - Three retrospective case series reported a median overall survival of not reached up to a median follow-up of 38 months and one single arm (phase I-II) trial reported a median overall survival of 43.3 months (95% CI 11.3 to not reached) at phase I and not reached at phase II at an unspecified follow-up.

- **Response rate**

  Seven non-comparator studies of R/R HL patients receiving BVB as third or subsequent line treatment provided very low certainty evidence for response rate.

  - One single arm (phase I-II) trial and four retrospective case series reported an overall response rate of 71% to 82% (complete response rate 49% to 68.9% where reported) at end of BVB treatment.
  - One retrospective case series reported an overall response rate of 92.6% (complete response rate 70.7%) at end of BVB treatment in patients receiving BVB followed by ASCT.
  - One case series reported that 100% of patients achieved complete metabolic response.
  - One single arm (phase I-II) trial reported a duration of response of 4.3 months (95% CI 0 to 7.1) in the phase I trial and 3.95 months (95% CI 7.5 to not reached) in the phase II trial.

- **Eligibility for stem cell transplant**

  Five case series (four retrospective and one unspecified) of R/R HL patients receiving BVB as third or subsequent line treatment provided very low certainty evidence relating to eligibility for stem cell transplant.

  - One case series reported that 28 out of 30 patients were eligible for SCT, 25 of whom underwent SCT after BVB treatment.
  - One case series reported that out of 32 patients given BVB as a bridge to ASCT, 29 had ASCT and three had allo-SCT after BVB salvage; out of two patients given BVB as a bridge to allo-ASCT, two had allo-ASCT; out of 18 patients given BVB after ASCT relapse, seven patients had allo-SCT and nine patients were transplant ineligible due to comorbidities prior and post BVB.
  - The remaining three case series reported that 26 out of 47, 15 out of 41 and 18 out of 20 patients underwent SCT after BVB.

Important outcomes

- **Event-free survival**

  One retrospective case series of R/R HL patients receiving BVB as third or subsequent line treatment provided very low certainty relating to event-free survival.

  - The study reported a 3-year event-free survival of 58% (95% CI 37 to 90) at a median follow-up of 12 months.
- **Progression-free survival**

  Seven non-comparator studies of R/R HL patients receiving BVB as third or subsequent line treatment provided very low certainty evidence for progression-free survival.

  - One single arm (phase II) trial reported a 1-year progression-free survival of 67% at an unspecified follow-up.
  - One single arm (phase II) trial and two retrospective case series reported a 2-year progression-free survival ranging from 60% to 93.7% up to a median follow-up of 27 months. One retrospective case series reported a 2-year progression-free survival of 62% at a median follow-up of 17 months in patients receiving BVB followed by ASCT.
  - One single arm (phase I-II) trial reported a median progression-free survival of 7.5 months in the phase II trial and not reached in the phase II trial at an unspecified follow-up and three retrospective case series reported a median progression-free survival of 18 to 26 months up to a median of 38 months follow-up.
- **Disease-free survival or remission**
  - No evidence was identified for this outcome.
- **Quality of life**
  - No evidence was identified for this outcome.

In terms of safety:

One single arm (phase I-II) trial and five case series of R/R HL patients receiving BVB as third or subsequent line treatment and one case series of R/R HL patients receiving BVB as third or subsequent line treatment followed by ASCT provided very low certainty evidence relating to safety.

- Any grade AEs. One case series reported that just under half of patients (46%) experienced treatment related AEs of any grade at a median of 38 months follow-up

and one case series of patients receiving BVB followed by ASCT reported that just over half (58.5%) experienced any grade AEs.

- One single arm (phase I-II) trial and one case series reported the following most common grade 3 AEs: neutropenia (7% & 27%), anaemia (18%), infection (7% & 14%) and thrombocytopenia (14%) at a median follow-up of 38 months or unspecified follow-up. Two case series reported that 15 (34%) patients at a median follow-up of 19 months and 50% at a median follow-up of 27 months experienced grade 3 or 4 AEs. Two further case series reported the following most common grade 3 or 4 AEs: neutropenia (24.6% & 73%), lymphopenia (40%), thrombocytopenia (13.1%), anaemia (13.1%), peripheral neuropathy (13%) and clinically detected infection (13%) at a median follow-up of 12 and 14 months. One single arm trial and three case series reported on grade 4 AEs up to a median follow-up of 38 months. One study reported no grade 4 AEs and two studies reported cases of grade 4 neutropenia (3 (8%) patients & 1 patient). One case series of R/R HL patients receiving BVB followed by ASCT reported that 7.3% of patients experienced grade 3 AEs (neutropenia (4.8%) and peripheral neuropathy (2.4%)) and no patients experienced grade 4 AEs at a median follow-up of 17 months.
- Four case series of R/R HL patients receiving BVB as third or subsequent line treatment and one case series of R/R HL patients receiving BVB as third or subsequent line treatment followed by ASCT reported on discontinuation of therapy due to treatment-related AEs, with results ranging from 0% to 40% up to a median follow-up of 38 months. One case series reported on the interruption of treatment due to grade 4 toxicity, with 11% of patients affected at a median follow-up of 19 months. One case series reported that 3.3% of patients had lower drug doses due to AEs at a median follow-up of 14 months.

In terms of cost effectiveness:

- No evidence was identified for cost effectiveness

In terms of subgroups:

Four case series reported results related to those who are fit for stem cell transplant vs those who are not fit for stem cell transplant in patients with R/R classical HL receiving BVB for the outcomes overall survival (two studies), response rate (three studies), eligibility for stem cell transplant (one study) and progression-free survival (two studies). The studies reported separate results for either those fit for SCT prior to BVB, those fit for SCT post BVB, or for both subgroups. Only two case series reported statistical comparisons.

- For overall survival, one case series reported a *statistically significantly* greater 2-year overall survival for patients who received SCT post BVB compared to those who did not but reported a *statistically non-significant* association for ASCT prior to BVB with overall survival at a median follow-up of 19 months. A further case series reported a *statistically non-significant* association between patients undergoing ASCT and overall survival at a median follow-up of 14 months.
- For response rate, one case series reported that overall response rate and complete response rate were not *statistically significantly* different for patients who had previously received SCT at a median follow-up of 19 months.
- For progression-free survival, one case series reported that median progression-free survival was *statistically significantly* greater in patients who received SCT post BVB compared to those who did not and a *statistically non- significant* association of ASCT

prior to BVB with progression-free survival at a median follow-up of 19 months. A further case series reported that no *statistically significant* differences were observed between BVB responsive patients who received SCT post BVB and those who did not for median progression-free survival at a median follow-up 38 months.

In terms of the number of cycles and doses of BVB combination therapy used:

- BV was administered at a dose of 1.8 mg/kg IV on day one across all seven studies and bendamustine was administered at a dose of 90 mg/m² IV on days one and two across all the studies, except for one study which used a dose of 120 mg/m² on days two and three. The cycle length was 21 days for all studies. The number of cycles ranged from two to eight cycles, with a median of three to four cycles in most studies.

Limitations

The most important limitation relating to the evidence included is the lack of a comparator group. This means that it is not clear whether the outcomes reported for adults with R/R HL after combination BVB as third or subsequent line treatment are different from those after standard care. Other limitations that reduce the certainty in the outcomes reported include the retrospective nature of the majority of the studies; the small sample sizes, the studies not being UK based; uncertainty about whether the inclusion of participants was complete or consecutive, and limited statistical analyses or summary statistics for some of the outcomes reported.

Conclusion

This evidence review includes seven studies (one single arm trial and six case series) which reported outcomes of combination BVB as third or subsequent line treatment in adults with R/R HL up to a median of 38 months follow-up.

The studies provide very low certainty evidence for the critical outcomes of overall survival, response rate and eligibility for stem cell transplant and the important outcomes of event-free survival, progression-free survival and safety. No studies were identified that reported the important outcomes of disease-free survival or remission or quality of life. No evidence on cost effectiveness was found.

With respect to critical outcomes, the studies suggest that adults with R/R HL receiving combination BVB as third or subsequent line treatment have a 1-year overall survival ranging from 85% to 86%, a 2-year overall survival ranging from 72% to 82% (93% in patients post ASCT after BVB) and a 3-year overall survival of 75% up to a median of 19 months follow-up, an overall response rate after BVB treatment ranging from 71% to 82% (92.6% in patients post ASCT after BVB) and a complete response rate ranging from 49% to 100% (70.7% in patients post ASCT after BVB), and a wide range of patients eligible for SCT after BVB treatment of 37% to 93%. With respect to important outcomes, the studies suggest that adults with R/R HL receiving combination BVB as third or subsequent line treatment have a 3-year event-free survival of 58% at a median follow-up of 12 months, a 1-year progression-free survival of 67% at an unspecified follow-up, a 2-year progression-free survival ranging from 60% to 93.7% (62% in patients post ASCT after BVB) up to a median of 27 months follow-up, and a median progression-free survival of 7.5 months to 26 months up to a median of 38 months follow-up. With respect to safety, the studies suggest a relatively high incidence of treatment-related AEs, including severe (grade 3 or 4) AEs. Neutropenia, lymphopenia, thrombocytopenia, anaemia, infection and peripheral neuropathy were the most common severe AEs. A wide range of results for discontinuation of therapy due to treatment-related AEs were reported, ranging from 0% to 40% up to a median follow-up of 38 months.

Limited subgroup results were reported for patients fit versus unfit for SCT. One case series found significantly greater 2-year overall survival and median progression-free survival in patients who received SCT post BVB, while another found no significant differences in median progression-free survival. For patients who received SCT prior to BVB, one case series found no significant associations with overall survival, overall response rate, complete response rate, and progression-free survival.

BV was administered at a dose of 1.8 mg/kg IV on day one of a 21 day cycle across all seven studies and bendamustine was at a dose of 90 mg/m² IV on days one and two across all the studies, except for one study which used a dose of 120 mg/m² on days two and three. The number of cycles ranged from two to eight cycles, with a median of three to four cycles in most studies.

The studies were small, mostly retrospective case series with no patients from the UK. The lack of comparative studies mean that no conclusions can be drawn about the effectiveness of combination BVB as third or subsequent line treatment compared with standard care in adults with R/R HL.

3. Methodology

Review questions

The review question(s) for this evidence review are:

1. In relapsed or refractory classical Hodgkin lymphoma, what is the clinical effectiveness of combination brentuximab vedotin and bendamustine as third or subsequent line treatment compared with standard of care?
2. In relapsed or refractory classical Hodgkin lymphoma, what is the safety of combination brentuximab vedotin and bendamustine as third or subsequent line treatment compared with standard of care?
3. In relapsed or refractory classical Hodgkin lymphoma, what is the cost effectiveness of combination brentuximab vedotin and bendamustine as third or subsequent line treatment compared with standard of care?
4. From the evidence selected, are there any subgroups of patients that may benefit from combination brentuximab vedotin and bendamustine as third or subsequent line treatment more than the wider population of interest?
5. From the evidence selected, how many cycles of combination therapy were required to treat relapsed or refractory classical Hodgkin lymphoma, and what doses were used?

See Appendix A for the full PICO document.

Review process

The methodology to undertake this review is specified by NHS England in its 'Guidance on conducting evidence reviews for Specialised Services Commissioning Products' (2020).

The searches for evidence were informed by the PICO document and were conducted 12 June 2024.

See Appendix B for details of the search strategy.

Results from the literature searches were screened using their titles and abstracts for relevance against the criteria in the PICO document. Full text of potentially relevant studies were obtained and reviewed to determine whether they met the inclusion criteria for this evidence review.

See Appendix C for evidence selection details and Appendix D for the list of studies excluded from the review and the reasons for their exclusion.

Relevant details and outcomes were extracted from the included studies and were critically appraised using a checklist appropriate to the study design. See Appendices E and F for individual study and checklist details.

The available evidence was assessed by outcome for certainty using modified GRADE. See Appendix G for GRADE profiles.

4. Summary of included studies

Seven papers were identified for inclusion (Iannitto et al 2020, Moretti et al 2022, O'Connor et al 2022, Picardi et al 2019, Pinczes et al 2020, Radhakrishnan et al 2021, Uncu Ulu et al 2022). One paper reported results for a single arm phase I and phase II trial and the remaining six papers were case series (five retrospective and one unspecified). No comparative studies were identified and there were no studies reporting cost effectiveness.

Table 1 provides a summary of the included studies and full details are given in Appendix E.

Table 1: Summary of included studies

Study	Population	Intervention and comparison	Outcomes reported

Iannitto et al 2020
Retrospective case series
Italy (8 centres)
	47 adults with R/R HL[a]
	Median age: 34 years (range 18 to 76)
	Male: 31 (66%)
	Median prior therapy: 2 (range 1 to 4)
	
	Subgroups:
	• Patients receiving SCT prior to BVB
	• Patients receiving SCT post BVB
		Intervention
		BVB combination therapy
		BV (1.8 mg/kg, 30-minute infusion) on day 1 and bendamustine (90 mg/m^2, 120-minute infusion) on days 2 to 3 of a 21-day cycle
		Median number of cycles of BVB: 4 (2.5 to 97.5 percentiles 2 to 7)
		Comparison
		No comparator group
			Median follow-up of 19 months (95% CI 17.4 to 18.5) unless stated otherwise
			Critical outcomes
			• Overall survival[b]
			  ○ 2-year OS
			  ○ Median OS
			• Response rate[c]
			  ○ Overall response rate at end of BVB treatment (median 4 cycles, 2.5 to 97.5 percentiles 2 to 7)
			• Eligibility for stem cell transplant at end of BVB (median 4 cycles, 2.5 to 97.5 percentiles 2 to 7)
			
			Important outcomes
			• Progression-free survival)[d]
			  ○ Median PFS
			• Safety
			  ○ Grade >3 AEs
			  ○ Interrupting treatment due to grade 4 toxicity

Moretti et al 2022 Retrospective case series Italy (11 centres)	41 adults with R/R HL[e] Median age: 36 years (range 16 to 74) Male: 22 (54%) Median number of previous therapies: 2 (range 1 to 5)	**Intervention** BVB combination therapy BV (1.8 mg/kg IV) on day 1 and bendamustine (90 mg/m^2 IV) on days 1 and 2 of a 21-day cycle for up to 8 cycles	Median follow-up of 38 months (range 4.2 to 64, IQR 26.7) unless stated otherwise **Critical outcomes** • Overall survival[f]

Study	Population	Intervention and comparison	Outcomes reported
	Subgroups: • Patients receiving SCT post BVB • Patients not receiving SCT post BVB	19 patients received up to 4 cycles of BVB and 21 received 6 or more cycles **Comparison** No comparator group	○ Median OS • Response rate[g] ○ Overall response rate at end of BVB treatment (up to 8 cycle) • Eligibility for stem cell transplant **Important outcomes** • Progression-free survival[h] ○ Median PFS • Safety ○ Treatment emergent AEs of any grade ○ Discontinuation of therapy
O'Connor et al 2022 Single-arm trial (Phase I–II) USA (1 centre) & Canada (2 centres)	65 adults with R/R HL[i] or ALCL Phase I: n=28 Male: 18 (64%) Median age: 38 years (range 25 to 70) ALCL: 1 (4%) patient Median prior therapy: 5 (range 2-12) Phase II: n=37 Male: 23 (62%) Median age: 34 years (range 18 to 72) ALCL: 0 patients Median prior therapy: 3 (range 1 to 8) No subgroups reported	**Intervention** BVB combination therapy *Phase I:* 3+3 dose escalation design[j] Cohort 1: starting dose of 1.2 mg/kg BV and 70 mg/m^2 of bendamustine (n=7) Cohort 2: 1.2 mg/kg BV and 80 mg/m^2 of bendamustine (n=3) Cohort 3: 1.8 mg/kg BV and 80 mg/m^2 of bendamustine (n=7) Cohort 4: 1.8 mg/kg BV and 90 mg/m^2 of bendamustine (n=11) *Phase II:* BV (1.8 mg/kg) and bendamustine (90 mg/m^2) Median number of cycles: 5 (range 2 to 6) **Comparison** No comparator group	Duration of follow-up not reported **Critical outcomes** • Overall survival[k] ○ 1-year OS ○ 2-year OS ○ Median OS • Response rate ○ Overall response rate[l] ○ Duration of response[m] **Important outcomes** • Progression-free survival[n] ○ 1-year PFS ○ 2-year PFS ○ Median PFS • Safety ○ Toxicity of any grade, grade 1, 2, 3 & 4 ○ Discontinuation due to toxicity

Study	Population	Intervention and comparison	Outcomes reported

Picardi et al 2019
Case series[o]
Italy (1 centre)
	20 adults with R/R HL[p]
	Median age: 40 years (range 23 to 54)
	Male: 8 (40%)
	Primary refractory: 11 (55%)
	Relapsed: 9 (45%)
	Median prior therapy: 3 (range 2 to 6)
	
	Subgroups:
	• Patients receiving SCT post BVB
		Intervention
		BVB combination therapy
		BV (1.8 mg/kg IV) on day 1 of each 3-week cycle and bendamustine (fixed dose of 120 mg/m^2 per day)
		at least 24 hours after BV, on days 2 and 3
		
		All patients underwent 4 courses of BVB
		Comparison
		No comparator group
			Median follow-up of 27 months (range 4 to 68) unless stated otherwise
			Critical outcomes
			• Response rate
			  ○ Complete metabolic response[q] at end of BVB treatment (median 5 weeks after the 4th cycle)
			• Eligibility for stem cell transplant after 4 cycles of BVB
			
			Important outcomes
			• Progression free survival[r]
			  ○ 2-year PFS
			• Safety
			  ○ Grade 3 or 4 treatment-related AEs
			  ○ Serious infusion related reactions
			  ○ Temporary discontinuation of therapy due to treatment-related AEs

Pinczes et al 2020
Retrospective case series
Hungary (4 centres)
	41 adults with R/R HL[s]
	Median age: Not reported
	Male: 25 (61%)
	Refractory: 28 (68.3%)
	Relapse ≤12 months: 9 (22%)
	Relapse >12 months: 4 (9.7%)
	Median number of salvage therapies prior to BVB: 3 (range 1 to 6)
	
	No subgroups reported (all patients underwent ASCT
		Intervention
		BVB combination therapy followed by ASCT
		BV (1.8 mg/kg IV) on day 1 and bendamustine (90 mg/m^2 IV) on days 1 and 2 of a 21-day cycle.
		Median number of cycles of BVB: 3 (range 1 to 6)
		ASCT with BEAM (carmustine, etoposide, cytarabine and melphalan) conditioning regimen
		Comparison
		No comparator group
			Median follow-up of 17 months (range 2 to 40) unless reported otherwise
			Critical outcomes
			• Overall survival[t]
			  ○ 2-year OS
			• Response rate[u]
			  ○ Overall response rate at end of BVB treatment (median 3 cycles, range 1 to 6)
			Important outcomes
			• Progression-free survival[v]

Study	Population	Intervention and comparison	Outcomes reported
	after BVB which is a PICO subgroup of interest)		○ 2-year PFS[47] • Safety ○ Treatment-related AEs of any grade, 3 & 4 ○ Discontinuation of therapy due to treatment related AEs
Radhakrishnan et al 2021 Retrospective case series India (1 centre)	30 adults and young people with R/R[w] HL Median age: 30 years (range 15 to 59) Male: 15 (50%) Treatment lines prior to BVB, N=30: • 1: 8 (27%) • 2: 16 (53%) • 3: 4 (13%) • 4: 2 (7%) **Subgroups:** • Patients receiving SCT post BVB	**Intervention** BVB combination therapy BV (1.8 mg/kg) on day 1 with bendamustine (90 mg/m^2) on days 1 and 2 of a 21-day cycle Median number of cycles of BVB: 3 (range 1 to 6) **Comparison** No comparator group	Median follow-up time of 12 months (95% CI 5.2 to18.8) unless stated otherwise **Critical outcomes** • Overall survival[x] ○ 3-year OS • Response rate[y] ○ Overall response rate after BVB treatment (median 3, range 1 to 6) • Eligibility for stem cell transplant[z] after BVB treatment (median 3, range 1 to 6) **Important outcomes** • Event free survival[aa] ○ 3-year EFS **Safety** • Grade 1 or 2 infusion reactions • Grade 3 or 4 treatment related AEs • Discontinuations or treatment delays due to BVB toxicity
Uncu Ulu et al 2022 Retrospective case series Turkey (8 centres)	61 adults with R/R[bb] classical HL Median age of BVB initiation: 33 (range: 18 to 76) years Male: 135 (57.4%)	**Intervention** BVB combination therapy BV (1.8 mg/kg IV) on day 1 and bendamustine (90 mg/m^2) on days 1 and 2 of a 21-day cycle	Median follow-up time: 14 months (range 2 to 42) unless stated otherwise **Critical outcomes** • Overall survival[cc]

Study	Population	Intervention and comparison	Outcomes reported
	Primary refractory: 29 (47.5%) Relapsed: n=32 (52.5%) Median BVB line: 3 (range 2 to 11) **Subgroups:** • Patients transplant-ineligible • Patients receiving SCT post BVB • Patients receiving SCT prior to BVB	Median number of cycles: 4 (range 2 to 6) **Comparison** No comparator group	○ 1-year OS ○ 2-year OS ○ Median OS • Response rate[dd] ○ Overall response rate at end of BVB treatment (median 4 cycles, range 2 to 6)[ee] • Eligibility for stem cell transplant at end of BVB treatment (median of 4 cycles (range 2 to 6), **Important outcomes** • Progression-free survival[ff] ○ 2-year PFS ○ Median PFS • Safety ○ Grade 3 or 4 AEs ○ Drug cessation due to AEs ○ Lower drug doses due to AEs

Abbreviations

AE: adverse event; ALCL: anaplastic large cell lymphoma; ASCT: autologous stem cell transplant; BV: brentuximab vedotin; BVB: brentuximab vedotin and bendamustine; CI: confidence interval; CT: computed tomography; DLT: dose-limiting toxicities; EFS: event-free survival; FDG-PET: fluorodeoxyglucose positron emission tomography; HL: Hodgkin lymphoma; IQR: interquartile range; IV: intravenous; kg: kilogram; MTD: maximum tolerated dose; m: metre; mg: milligram; OS: overall survival; PFS: progression-free survival; R/R: relapsed/refractory; SCT: stem cell transplant

Footnotes

a. Primary refractory disease (defined as not achieving a complete response or relapsing within 3 months after a conventional treatment) or in second relapse or beyond

b. Defined as the time from BVB treatment initiation to the date of death from any cause

c. The response revaluation criteria in lymphoma (RECIL) were followed for clinical response coding

d. Defined as the time from BVB treatment initiation to the first documentation of progression/relapse or to death from any cause

e. After failure of ≥1 therapy including ASCT, allo-SCT, or BV

f. Calculated from the date of enrolment until death from any cause and it was censored at the date of last follow up for surviving patients

g. Responses were assessed using the 2014 Lugano criteria whereby a score of ≤3 on the Deauville 5-point scale was considered indicative of complete response

h. Defined as the time from treatment initiation to progression of disease, relapse, or death from any cause. If none of these events had occurred, PFS was censored at the date of last follow up. Patients undergoing SCT were not censored at the time of consolidation

Study	Population	Intervention and comparison	Outcomes reported
i. In Phase I, defined as having developed progressive disease following or after declining ASCT, or had at least two prior multi-agent chemotherapy regimens (if they are not ASCT candidates). In Phase 2, patients with HL were eligible if they had relapsed or refractory disease after one line of therapy (median prior therapy was 2) j. Three patients are initially enrolled into a given dose cohort. If there is no dose-limiting toxicity seen in any of these participants, the trial proceeds to enrol additional participants into the next higher dose cohort. This process continues until dose-limiting toxicities (DLTs) are observed in at least one patient. An additional three patients are accrued into that same dose cohort. Development of DLTs in two or more out of six patients at a specific dose level indicates that the maximum tolerated dose (MTD) has been exceeded. Further dose escalation is not pursued, and the prior dose level is expanded to six patients. If there is no more than one patient who experiences a DLT among those six patients, that dose level is considered the MTD k. Defined as the time from randomisation to the date of death due to any cause or last date of contact l. Defined as the percentage of patients who achieved a confirmed complete or partial response. Disease response was assessed by CT or PET/CT according to the International Harmonization Project Group 2007 International Harmonization Project Group 2007 Revised Response Criteria for Malignant Lymphoma after cycle 3 and after cycle 6 m. Defined as the time from documentation of a response to treatment to the first documentation of tumour progression or death due to any cause whichever comes first n. Defined as the time from randomisation until disease progression or death due to any cause, whichever occurred first o. The paper describes the study as a real life study. It states that consecutive eligible patients from September 2013 to November 2017 were included. The paper does not specify whether the paper is retrospective or prospective p. Defined as failure of ≥1 salvage treatments q. Defined as FDG-PET-negative result (DS ≤3) r. Defined as the time from BVB first dose to disease progression/relapse or to death from any cause s. Failure after at least one standard salvage chemotherapy regimen made relapsed or refractory classical HL patients eligible for BVB therapy t. Calculated from the day of ASCT to the last follow-up visit or death u. Evaluated regarding PET/CT status according to the Lugano Classification. A dedicated PET/CT scan was performed after cycle 2 of BVB and later as it was deemed necessary v. Defined as the time from ASCT to disease progression, to relapse, or to death w. Refractory disease defined as Deauville score > 3, after the completion of first line multi-agent chemotherapy x. Defined as the time from initiation of BVB to the event of death from any cause y. Response evaluation with FDG-PET-CT scan was done at the end of 2-3 cycles, based on the international working group (IWG) International Harmonization Project Group 2007 Revised Response Criteria for Malignant Lymphoma, and from 2015 the Lugano classification z. Patients with a complete or partial response post BVB were eligible for SCT aa. Defined as the time from initiation of BVB to the first episode of relapse, progression, or death from any cause bb. Primary refractory disease was defined as not achieving a complete remission or relapsing within three months after conventional treatment cc. Defined as the period from BVB initiation to death from any cause dd. The response evaluation was assessed using PET/CT. Response evaluation was performed after at least two cycles of combination treatment and repeated every two cycles. PET-CT scans were evaluated four to six weeks after treatment for response assessment according to the Deauville five-point scale ee. Defined as the percentage of patients who achieved a confirmed complete or partial response. Disease response was assessed by CT or PET/CT according to the International Harmonization Project Group 2007 Revised Response Criteria for Malignant Lymphoma after cycle 3 and after cycle 6 ff. Defined as the period from BVB initiation to progression or death for any reason			

5. Results

In adults with relapsed or refractory classical Hodgkin lymphoma, what is the clinical effectiveness and safety of brentuximab vedotin and bendamustine as third or subsequent line treatment compared with standard of care

Outcome	Evidence statement
Clinical Effectiveness	
Critical outcomes	
Overall survival **Certainty of evidence:** Very low	This outcome is important to patients as patients with R/R HL have a higher mortality rate due to previously failed therapy. Improved overall survival is an important marker of effective treatment, although it does not provide information about a patient's health and wellbeing during that time. In total, six studies (one phase I-II trial and five case series) provided evidence relating to overall survival. *1-year overall survival* At a median follow-up of 14 months (range 2 to 42): • One retrospective case series (Uncu Ulu et al 2022) (n=61) of adults with R/R[33] classical HL receiving BVB (at a median treatment line of 3 (range 2 to 11)) reported a 1-year overall survival[34] of 85%. **(VERY LOW)** At unspecified duration of follow-up: • One single arm phase II trial (O'Connor et al 2022) (n=37) of adults with R/R[35] CD30+ biopsy proven HL receiving BVB (median prior therapy of 3 (range 1 to 8)) reported a 1-year overall survival[36] of 86%. **(VERY LOW)** *2-year overall survival* At a median follow-up of 14 months (range 2 to 42): • One retrospective case series (Uncu Ulu et al 2022) (n=61) of adults with R/R classical HL receiving BVB (at a median treatment line of 3 (range 2 to 11)) reported a 2-year overall survival of 72%. **(VERY LOW)** At a median follow-up 17 months (range 2 to 40): • One retrospective case series (Pinczes et al 2020) (n=41) of adults with R/R[37] classical HL receiving BVB (median prior salvage therapies of 3 (range 1 to 6)) followed by ASCT reported a 2-year overall survival[38] of 93%. **(VERY LOW)** At a median follow-up of 19 months (95% CI 17.4 to 18.5): • One retrospective case series (Iannitto et al 2020) (n=47) of adults with histologically confirmed diagnosis of R/R classical HL[39] receiving BVB

[33] Primary refractory disease was defined as not achieving a complete remission or relapsing within three months after conventional treatment
[34] Defined as the period from BVB initiation to death from any cause
[35] In Phase 1, defined as having developed progressive disease following or after declining ASCT, or had at least two prior multi-agent chemotherapy regimens (if they are not ASCT candidates). In Phase 2, patients with HL were eligible if they had relapsed or refractory disease after one line of therapy (median prior therapy was 2)
[36] Defined as the time from randomisation to the date of death due to any cause or last date of contact
[37] Failure after at least one standard salvage chemotherapy regimen made relapsed or refractory classical HL patients eligible for BVB therapy
[38] Calculated from the day of ASCT to the last follow-up visit or death
[39] Primary refractory disease (defined as not achieving a CR or relapsing within 3 months after a conventional treatment) or in second relapse or beyond

Outcome	Evidence statement
	(median prior therapy of 2 (range 1 to 4)) reported a 2-year overall survival[40] of 72%. **(VERY LOW)** At unspecified duration of follow-up: • One single arm phase II trial (O'Connor et al 2022) (n=37) of adults with R/R CD30+ biopsy proven HL receiving BVB (median prior therapy of 3 (range 1 to 8)) reported a 2-year overall survival of 82%. **(VERY LOW)** *3-year overall survival* At a median follow-up 12 months (95% CI 5.2 to 18.8): • One retrospective case series (Radhakrishnan et al 2021) (n=30) of adults and young people with R/R[41] HL receiving BVB (73% of patients had 2 or more treatment lines prior to BVB) reported a 3-year overall survival[42] of 75% (95% CI 59 to 95). **(VERY LOW)** *Median overall survival* At a median follow-up of 14 months (range 2 to 42): • One retrospective case series (Uncu Ulu et al 2022) (n=61) of adults with R/R classical HL receiving BVB (at a median treatment line of 3 (range 2 to 11)) reported a median overall survival of not reached. **(VERY LOW)** At a median follow-up of 19 months (95% CI 17.4 to 18.5): • One retrospective case series (Iannitto et al 2020) (n=47) of adults with histologically confirmed diagnosis of R/R classical HL receiving BVB (median prior therapy of 2 (range 1 to 4)) reported a median overall survival of not reached. **(VERY LOW)** At a median follow-up 38 months (range 4.2 to 64, IQR 26.7): • One retrospective case series (Moretti et al 2022) (n=41) of adults with biopsy-proven, CD30-positive R/R[43] classical HL receiving BVB (median prior therapies of 2 (range 1 to 5)) reported a median overall survival of not reached. **(VERY LOW)** At unspecified duration of follow-up: • One single arm phase I-II trial (O'Connor et al 2022) (n=28 phase I & n=37 phase II) of adults with R/R CD30+ biopsy proven HL receiving BVB (median prior therapies of 3 (range 1 to 8)) reported a median overall survival of 43.3 months (95% CI 11.3 to not reached) in the phase I trial and not reached in the phase II trial. **(VERY LOW)** **Six non-comparator studies of R/R HL patients receiving BVB as third or subsequent line treatment provided very low certainty evidence for overall survival. One single arm (phase II) trial and one retrospective case series reported a 1-year overall survival of 86% at an unspecified follow-up and 85% at a median follow-up of 14 months.** **One single arm (phase II) trial and two retrospective case series reported a 2-year overall survival ranging from 72% to 82% up to a median follow-up of 19 months. One retrospective case series reported a 2-year overall survival of 93% at a median follow-up of 17 months in patients receiving BVB followed by ASCT.**

[40] Defined as the time from BVB treatment initiation to the date of death from any cause
[41] Refractory disease defined as Deauville score >3, after the completion of first line multi-agent chemotherapy
[42] Defined as the time from initiation of BVB to the event of death from any cause
[43] After failure of ≥1 therapy including ASCT, allo-SCT or BV

Outcome	Evidence statement
	One retrospective case reported a 3-year overall survival of 75% (95% CI 59 to 95) at a median follow-up of 12 months. **Three retrospective case series reported a median overall survival of not reached up to a median follow-up of 38 months and one single arm (phase I-II) trial reported a median overall survival of 43.3 months (95% CI 11.3 to not reached) at phase I and not reached at phase II at an unspecified follow-up.**
Response rate **Certainty of evidence:** Very low	This outcome is important to patients as it indicates the treatment has successfully been able to treat the cancer. Complete response rate is an important marker of effective treatment as it is associated with better survival outcomes and higher transplant rates. In total, seven studies (one phase I-II trial and six case series) provided evidence relating to response rate. *Overall response rate (complete and partial response)* At the end of BVB treatment with a median of three cycles (range 1 to 6): • One retrospective case series (Pinczes et al 2020) (n=41) of adults with R/R classical HL receiving BVB (median prior salvage therapies of 3 (range 1 to 6)) followed by ASCT reported an overall response rate[44] of 92.6% (complete response, n (%): 29 (70.7) and partial response: 9 (21.9)) before ASCT. **(VERY LOW)** • One retrospective case series (Radhakrishnan et al 2021) (n=29) of adults and young people with R/R HL receiving BVB (73% of patients had 2 or more treatment lines prior to BVB) reported an overall response rate[45] of 79% (complete metabolic response, n (%): 18 (62), partial response: 5 (17), stable disease: 1 (3), progressive disease: 5 (17)). **(VERY LOW)** At the end of BVB treatment with a median of four cycles (range 2 to 6): • One retrospective case series (Uncu Ulu et al 2022) (n=61) of adults with R/R classical HL receiving BVB (at a median treatment line of 3 (range 2 to 11)) reported an overall response rate of 82% (complete response rate, n (%): 42 (68.9), partial response rate: 8 (13.1), refractory rate: 11 (18)). **(VERY LOW)** At the end of BVB treatment with a median of four cycles (2.5 to 97.5 percentiles 2 to 7): • One retrospective case series (Iannitto et al 2020) (n=47) of adults with histologically confirmed diagnosis of R/R classical HL receiving BVB (median prior therapy of 2 (range 1 to 4)) reported an overall response rate[46] of 79% (95% CI 64 to 89) (complete response rate: 49%, (95% CI 34 to 64)). **(VERY LOW)** At the end of BVB treatment with up to eight cycles: • One retrospective case series (Moretti et al 2022) (n=40) of adults with biopsy-proven, CD30-positive R/R classical HL receiving BVB (median prior therapies of 2 (range 1 to 5)) reported an overall response rate[47] of 75% (95% CI 59% to 86%) (complete response rate: 50% (95% CI 35% to 66%)). **(VERY LOW)**

[44] Evaluated regarding PET/CT status according to the Lugano Classification. A dedicated PET/CT scan was performed after cycle 2 of BVB and later as it was deemed necessary
[45] Response evaluation with FDG-PET-CT scan was done at the end of 2-3 cycles, based on the international working group (IWG) International Harmonization Project Group 2007 Revised Response Criteria for Malignant Lymphoma, and from 2015 the Lugano classification
[46] The response revaluation criteria in lymphoma (RECIL) were followed for clinical response coding
[47] Responses were assessed using the 2014 Lugano criteria whereby a score of ≤3 on the Deauville 5-point scale was considered indicative of complete response

Outcome	Evidence statement
	At unspecified duration of follow-up: • One single arm phase I-II trial (O'Connor et al 2022) (n=28 phase I & n=37 phase II) of adults with R/R CD30+ biopsy proven HL receiving BVB (median prior therapies of 3 (range 1 to 8)) reported an overall response rate[48] of 61% (95% CI 41 to 79) in the phase I trial, 78% (95% CI 62 to 91) in the phase II trial and 71% (95% CI 58 to 81) for phase I and phase II patients combined. **(VERY LOW)** *Complete metabolic response* At a median of 5 (range 5 to 6) weeks after the 4th BVB cycle: • One case series[49] (Picardi et al 2019) (n=20) of adults with biopsy-proven CD30-positive R/R[50] classical HL receiving BVB (median prior therapy of 3 (range 2 to 6)) reported that 20 (100%) of patients achieved complete metabolic response[51] (DS scores of 1: 8 patients, 2: 8 patients, 3: 4 patients). **(VERY LOW)** *Duration of response* At unspecified duration of follow-up: • One single arm phase I-II trial (O'Connor et al 2022) (n=28 phase I & n=37 phase II) of adults with R/R CD30+ biopsy proven HL receiving BVB (median prior therapies of 3 (range 1 to 8)) reported a duration of response[52] of 4.3 months (95% CI 0 to 7.1) in the phase I trial and 3.95 months (95% CI 7.5 to not reached) in the phase II trial. **(VERY LOW)** **Seven non-comparator studies of R/R HL patients receiving BVB as third or subsequent line treatment provided very low certainty evidence for response rate.** **One single arm (phase I-II) trial and four retrospective case series reported an overall response rate of 71% to 82% (complete response rate 49% to 68.9% where reported) at end of BVB treatment. One retrospective case series reported an overall response rate of 92.6% (complete response rate 70.7%) at end of BVB treatment in patients receiving BVB followed by ASCT.** **One case series reported that 100% of patients achieved complete metabolic response.** **One single arm (phase I-II) trial reported a duration of response of 4.3 months (95% CI 0 to 7.1) in the phase I trial and 3.95 months (95% CI 7.5 to not reached) in the phase II trial.**
Eligibility for stem cell transplant **Certainty of evidence:** Very low	This outcome is important to patients as it indicates the treatment is able to progress them safely to stem cell transplant. Progression to stem cell transplant is important as this is the definitive treatment of R/R Hodgkin lymphoma and improves overall survival. In total, five case series provided evidence relating to eligibility for stem cell transplant. *Number of patients eligible for SCT after BVB*

[48] Disease response was assessed by CT or PET/CT according to the International Harmonization Project Group 2007 Revised Response Criteria for Malignant Lymphoma after cycle 3 and after cycle 6
[49] Unclear if case series was prospective or retrospective
[50] Defined as failure of ≥1 salvage treatments
[51] Defined as a FDG-PET-negative result (DS score ≤3)
[52] Defined as the time from documentation of a response to treatment to the first documentation of tumour progression or death due to any cause whichever comes first

Outcome	Evidence statement
	At the end of BVB treatment with a median of three cycles (range 1 to 6): • One retrospective case series (Radhakrishnan et al 2021) (n=30) of adults and young people with R/R HL receiving BVB (73% of patients had 2 or more treatment lines prior to BVB) reported that 28 patients were eligible for SCT[53] after BVB. **(VERY LOW)** *Number of patients undergoing SCT after BVB* At the end of BVB treatment with a median of three cycles (range 1 to 6): • One retrospective case series (Radhakrishnan et al 2021) (n=30) of adults and young people with R/R HL receiving BVB (73% of patients had 2 or more treatment lines prior to BVB) reported that 25 patients underwent SCT[54] (20 post BVB & 5 after subsequent regimens), 17 of which were ASCT and eight allo-SCT. **(VERY LOW)** At the end of BVB treatment with four cycles: • One case series (Picardi et al 2019) (n=20) of adults with biopsy-proven CD30-positive R/R classical HL receiving BVB (median prior therapy of 3 (range 2 to 6)) reported that 14 patients underwent ASCT and four patients underwent allo-SCT. **(VERY LOW)** At the end of BVB treatment with a median of four cycles (range 2 to 6): • One retrospective case series (Uncu Ulu et al 2022) (n=61) of adults with R/R classical HL receiving BVB (at a median treatment line of 3 (range 2 to 11)) reported that out of 32 patients given BVB as a bridge to ASCT, 29 had ASCT and three had allo-SCT after BVB salvage; out of two patients given BVB as a bridge to allo-ASCT, two had allo-ASCT; and out of 18 patients given BVB after ASCT relapse, seven patients had allo-SCT. Nine patients were transplant ineligible due to comorbidities prior and post BVB. **(VERY LOW)** At the end of BVB treatment with a median of four cycles (2.5 to 97.5 percentiles 2 to 7): • One retrospective case series (Iannitto et al 2020) (n=47) of adults with histologically confirmed diagnosis of R/R classical HL receiving BVB (median prior therapy of 2 (range 1 to 4)) reported that 26 patients (17 with complete response, 7 with partial response & 2 with stable disease after BVB) proceeded to a SCT (20 ASCT, 4 allo-SCT & 2; tandem ASCT-allo-SCT). **(VERY LOW)** At the end of BVB treatment with up to eight cycles: • One retrospective case series (Moretti et al 2022) (n=41) of adults with biopsy-proven, CD30-positive R/R classical HL receiving BVB (median prior therapies of 2 (range 1 to 5)) reported that 15 (36.6%) responding patientssa underwent SCT. Nine patients underwent SCT after four cycles of BVB (7 ASCT and 2 allo-SCT) and six patients underwent SCT after ≥6 cycles of BVB (1 ASCT & 5 allo-SCT). **(VERY LOW)** **Five case series (four retrospective and one unspecified) of R/R HL patients receiving BVB as third or subsequent line treatment provided very low certainty evidence relating to eligibility for stem cell transplant. One case series reported that 28 out of 30 patients were eligible for SCT, 25 of whom underwent SCT after BVB treatment. One case series reported that out of 32 patients given BVB as a bridge to ASCT, 29 had ASCT and three had allo-SCT**

[53] Patients who were ≥ partial response and willing for transplant were eligible for consolidation with ASCT or allo-SCT
[54] 2 patients dropped out due to financial constraints and 1 patient failed autologous stem cell mobilisation

Outcome	Evidence statement
	after BVB salvage; out of two patients given BVB as a bridge to allo-ASCT, two had allo-ASCT; out of 18 patients given BVB after ASCT relapse, seven patients had allo-SCT and nine patients were transplant ineligible due to comorbidities prior and post BVB. The remaining three case series reported that 26 out of 47, 15 out of 41 and 18 out of 20 patients underwent SCT after BVB.
Important outcomes	
Event-free survival **Certainty of evidence:** Very low	This outcome is important to patients because it represents the time during which their disease is not progressing. Stable disease might represent longer survival and disease stability may result in patients experiencing fewer symptoms from the disease itself. It can be determined sooner than overall survival outcome measures. In total, one case series provided evidence relating to event free survival. *3-year event-free survival* At a median follow-up 12 months (95% CI 5.2 to 18.8): • One retrospective case series (Radhakrishnan et al 2021) (n=30) of adults and young people with R/R HL receiving BVB (73% of patients had two or more treatment lines prior to BVB) reported 3-year event-free survival of 58% (95% CI 37 to 90). **(VERY LOW)** **One retrospective case series of R/R HL patients receiving BVB as third or subsequent line treatment provided very low certainty of 3-year event-free survival of 58% (95% CI 37 to 90) at a median follow-up 12 months.**
Progression-free survival **Certainty of evidence:** Very low	This outcome is important to patients because it represents the time for which their disease is not progressing. Stable disease might represent longer survival and disease stability may result in patients experiencing fewer symptoms from the disease itself. It can be determined sooner than overall survival outcome measures. In total, seven studies (one phase I-II trial and five case series) provided evidence relating to progression-free survival. *1-year progression-free survival* At unspecified duration of follow-up: • One single arm phase II trial (O'Connor et al 2022) (n=37) of adults with R/R CD30+ biopsy proven HL receiving BVB (median prior therapy of 3 (range 1 to 8)) reported a 1-year progression-free survival[55] of 67%. **(VERY LOW)** *2-year progression-free survival* At a median follow-up of 14 months (range 2 to 42): • One retrospective case series (Uncu Ulu et al 2022) (n=61) of adults with R/R classical HL receiving BVB(at a median treatment line of 3 (range 2 to 11)) reported a 2-year progression-free survival[56] of 60%. **(VERY LOW)** At a median follow-up 17 months (range 2 to 40): • One retrospective case series (Pinczes et al 2020) (n=41) of adults with R/R classical HL receiving BVB (median prior salvage therapies of 3 (range 1 to 6)) followed by ASCT reported a 2-year progression-free survival[57] of 62%. **(VERY LOW)** At a median follow-up of 27 months (range 4 to 68):

[55] Defined as the time from randomisation until disease progression or death due to any cause, whichever occurred first
[56] Defined as the period from BVB initiation to progression or death for any reason
[57] Defined as the time from ASCT to disease progression, to relapse, or to death

Outcome	Evidence statement
	• One case series (Picardi et al 2019) (n=20) of adults with biopsy-proven CD30-positive R/R classical HL receiving BVB (median prior therapy of 3 (range 2 to 6)) reported a 2-year progression-free survival[58] of 93.7% (95% CI 62.7 to 99.6). **(VERY LOW)** At unspecified duration of follow-up: • One single arm phase II trial (O'Connor et al 2022) (n=37) of adults with R/R CD30+ biopsy proven HL receiving BVB (median prior therapy of 3 (range 1 to 8)) reported a 2-year progression-free survival[59] of 62%. **(VERY LOW)** *Median progression-free survival* At a median follow-up of 14 months (range 2 to 42): • One retrospective case series (Uncu Ulu et al 2022) (n=61) of adults with R/R classical HL receiving BVB (at a median treatment line of 3 (range 2 to 11)) reported a median progression-free survival of 26 months (95% CI 13.9 to 38). **(VERY LOW)** At a median follow-up of 19 months (95% CI 17.4 to 18.5): • One retrospective case series (Iannitto et al 2020) (n=47) of adults with histologically confirmed diagnosis of R/R classical HL receiving BVB (median prior therapy of 2 (range 1 to 4)) reported a median progression-free survival[60] of 18 months (95% CI 4.5 to 31.4). **(VERY LOW)** At a median follow-up 38 months (range 4.2 to 64, IQR 26.7): • One retrospective case series (Moretti et al 2022) (n=41) of adults with biopsy-proven, CD30-positive R/R classical HL receiving BVB (median prior therapies of 2 (range 1 to 5)) reported a median progression-free survival[61] of 26 months (95% CI 7.2 to not reached). **(VERY LOW)** At unspecified duration of follow-up: • One single arm phase I-II trial (O'Connor et al 2022) (n=28 phase I & n=37 phase II) of adults with R/R CD30+ biopsy proven HL receiving BVB (median prior therapies of 3 (range 1 to 8)) reported a median progression-free survival of 7.5 months (95% CI 4.8 to 12.1) in the phase I trial and not reached in the phase II trial. **(VERY LOW)** **Seven non-comparator studies of R/R HL patients receiving BVB as third or subsequent line treatment provided very low certainty evidence for progression-free survival.** **One single arm (phase II) trial reported a 1-year progression-free survival of 67% at an unspecified follow-up.** **One single arm (phase II) trial and two retrospective case series reported a 2-year progression-free survival ranging from 60% to 93.7% up to a median follow-up of 27 months. One retrospective case series reported a 2-year progression-free survival of 62% at a median follow-up of 17 months in patients receiving BVB followed by ASCT.** **One single arm (phase I-II) trial reported a median progression-free survival of 7.5 months in the phase II trial and not reached in the phase II trial at an unspecified follow-up and three retrospective case series reported a median**

[58] Defined as the time from BVB first dose to disease progression/relapse or to death from any cause
[59] Defined as the time from randomisation until disease progression or death due to any cause, whichever occurred first
[60] Defined as the time from BVB treatment initiation to the first documentation of progression/relapse or to death from any cause
[61] Defined as the time from treatment initiation to progression of disease, relapse, or death from any cause. If none of these events had occurred, PFS was censored at the date of last follow up. Patients undergoing SCT were not censored at the time of consolidation

Outcome	Evidence statement
	progression-free survival of 18 to 26 months up to a median of 38 months follow-up.
Disease-free survival or remission **Certainty of evidence:** Not applicable	This outcome is important to patients as it means that the signs and symptoms of cancer have reduced, either partially or completely and they are free of all detectable disease. **No evidence was identified for this outcome.**
Quality of life **Certainty of evidence:** Not applicable	This is an important outcome for patients as it provides an indication of an individual's general health and self-perceived well-being and their ability to participate in activities of daily living. Validated tools for general quality of life measurements are important patient reported outcome measures to help inform patient-centred decision making and inform health policy. Treatment related impacts on specific quality of life measures are also useful for this purpose. **No evidence was identified for this outcome.**
Safety	
Safety **Certainty of evidence:** Very low	These outcomes are important to patients because they will impact on their treatment choices, recovery and could have long term sequelae if they are irreversible. They reflect the tolerability and adverse effects of the treatment. From a service delivery perspective, they reflect the additional demands placed on the health system to manage the adverse consequences of the treatment. In total, seven studies (one phase I-II trial and six case series) provided evidence relating to safety. *Adverse events (AEs) of any grade* At a median follow-up 17 months (range 2 to 40): • One retrospective case series (Pinczes et al 2020) (n=41) of adults with R/R classical HL receiving BVB (median prior salvage therapies of 3 (range 1 to 6)) followed by ASCT reported that 24 (58.5%) patients experienced treatment-related AEs of any grade. The most common AEs were neutropenia (17%), peripheral neuropathy (12.2%) and infusion-related reactions with fever, chills, flushing, or pruritus (12.2%). **(VERY LOW)** At a median follow-up 38 months (range 4.2 to 64, IQR 26.7): • One retrospective case series (Moretti et al 2022) (n=41) of adults with biopsy-proven, CD30-positive R/R classical HL receiving BVB (median prior therapies of 2 (range 1 to 5)) reported that 19 (46%) patients experienced treatment emergent AEs of any grade. **(VERY LOW)** At unspecified duration of follow-up: • One single arm phase I-II trial (O'Connor et al 2022) (n=28 phase I & n=37 phase II) of adults with R/R CD30+ biopsy proven HL receiving BVB (median prior therapies of 3 (range 1 to 8)) reported on toxicities of any grade. In the phase I trial, the most common toxicities (>25%) were, n (%): nausea 15 (54%), vomiting 10 (36%), dyspnoea 10 (36%), peripheral sensory neuropathy 9 (32%), diarrhoea 8 (29%), pruritus 8 (29%), cough 8 (29%), constipation 7 (25%), and fever 7 (25%). In the phase II trial, the most common AEs (>25%) were, n (%): fatigue 25 (68%), nausea 25 (68%), fever 15 (41%), diarrhoea 14 (38%), vomiting 12 (32%), and rash maculopapular 12 (32%). **(VERY LOW)** *Grade 1 AEs* At unspecified duration of follow-up:

Outcome	Evidence statement
	• One single arm phase I-II trial (O'Connor et al 2022) (n=28 phase I & n=37 phase II) of adults with R/R CD30+ biopsy proven HL receiving BVB (median prior therapies of 3 (range 1 to 8)) reported on grade 1 toxicities, n (%). • Phase I: chills 6 (21%), diarrhoea 6 (21%), pain 6 (21%), dysguesia 5 (18%), dyspnoea 5 (18%), fatigue 5 (18%), fever 5 (18%), nausea 5 (18%), constipation 4 (14%), cough 4 (14%), headache 4 (14%), abdominal pain 4 (14%), dyspepsia 4 (14%), pruritus 4 (14%), rash maculopapular 3 (11%), back pain 3 (11%), hot flashes 3 (11%), hyperhidrosis 3 (11%), nasal congestion 3 (11%), sore throat 3 (11%), vertigo 3 (11%), anxiety 2 (7%), vomiting 2 (7%) and infusion-related reaction 1 (4%). • Phase II: nausea 20 (54%), diarrhoea 10 (27%), fatigue 10 (27%), dyspnoea 8 (22%), headache 7 (19%), constipation 6 (16%), cough 6 (16%), pain 6 (16%), rash maculopapular 6 (16%), fever 5 (14%), vomiting 5 (14%), dysguesia 4 (11%), dyspepsia 4 (11%), chills 3 (8%), vertigo 3 (8%), anxiety 1 (3%), myalgia 2 (5%) and nasal congestion 2 (5%). **(VERY LOW)** *Grade 2 AEs* At unspecified duration of follow-up: • One single arm phase I-II trial (O'Connor et al 2022) (n=28 phase I & n=37 phase II) of adults with R/R CD30+ biopsy proven HL receiving BVB (median prior therapies of 3 (range 1 to 8)) reported on grade 2 toxicities, n (%)**.** • Phase I: fatigue 10 (36%), nausea 10 (36%), peripheral sensory neuropathy 9 (32%), vomiting 8 (29%), cough 4 (14%), pruritus 4 (14%), diarrhoea 2 (7%), constipation 3 (11%), fever 2 (7%), dyspnoea 5 (18%), and anxiety 1 (4%). • Phase II: fatigue 15 (41%), fever 10 (27%), vomiting 7 (18%), pruritus 6 (16%), rash maculopapular 6 (16%), nausea 5 (14%), lung infection 5 (14%), diarrhoea 4 (11%), abdominal pain 4 (11%), infusion-related reaction 4 (11%), back pain 2 (5%), anaemia 2 (5%), peripheral sensory neuropathy 2 (5%), and constipation 1 (3%). **(VERY LOW)** *Grade 3 AEs* At a median follow-up 17 months (range 2 to 40): • One retrospective case series (Pinczes et al 2020) (n=41) of adults with R/R classical HL receiving BVB (median prior salvage therapies of 3 (range 1 to 6)) followed by ASCT reported that 3 (7.3%) patients experienced grade 3 AEs. These were, n (%): neutropenia (2 (4.8%)) and peripheral neuropathy (1 (2.4%)). **(VERY LOW)** At a median follow-up 38 months (range 4.2 to 64, IQR 26.7): • One retrospective case series (Moretti et al 2022) (n=41) of adults with biopsy-proven, CD30-positive R/R classical HL receiving BVB (median prior therapies of 2 (range 1 to 5)) reported on the number of patients experiencing grade 3 treatment emergent AEs. These were, n (%): infections (3 (7%); 1 with CMV pneumonia, and H1N1 pneumonia, 1 with CMV pericarditis and 1 with sepsis caused by Klebsiella pneumoniae neutropenic fever), neutropenia (3 (7%)), peripheral neuropathy (2 (5%)) and febrile neutropenia (1 (2%)). **(VERY LOW)** At unspecified duration of follow-up: • One single arm phase I-II trial (O'Connor et al 2022) (n=28 phase I & n=37 phase II) of adults with R/R CD30+ biopsy proven HL receiving BVB (median prior therapies of 3 (range 1 to 8)) reported on grade 3 toxicities. For phase I these were, n (%): anaemia 5 (18%), platelet count decreased 4 (14%), neutropenia 3 (11%), and infusion-related reaction 2 (7%). For phase

Outcome	Evidence statement
	II these were, n (%): neutropenia 10 (27%) and lung infection 5 (14%). **(VERY LOW)** *Grade 3 or 4 AEs* At a median follow-up 12 months (95% CI 5.2 to 18.8)[62]: • One retrospective case series (Radhakrishnan et al 2021) (n=30) of adults and young people with R/R HL receiving BVB (73% of patients had 2 or more treatment lines prior to BVB) reported on number of patients experiencing grade 3 or 4 treatment related adverse events. These were, n (%): neutropenia 21 (70%; grade 3 (28 of 92 cycles of BVB administered (30.4%)) & 1 grade 4), peripheral neuropathy 4 (13%), clinically detected infection 4 (13%), mucositis 3 (10%), skin rash 2 (6.5%) and liver/hepatitis 2 (6.5%). **(VERY LOW)** At a median follow-up of 14 months (range 2 to 42): • One retrospective case series (Uncu Ulu et al 2022) (n=61) of adults with R/R classical HL receiving BVB (at a median treatment line of 3 (range 2 to 11)) reported on number of patients experiencing grade 3 or 4 AEs. These were, n (%): lymphopenia 25 (40%), neutropenia 15 (24.6%), thrombocytopenia 8 (13.1%), anaemia 8 (13.1%), infusion reaction 5 (8.2%), vomiting 3 (4.9%), neuropathy 4 (6.5%) and skin reactions 2 (3.2%). **(VERY LOW)** At a median follow-up of 19 months (95% CI 17.4 to 18.5)[63]: • One retrospective case series (Iannitto et al 2020) (n=47) of adults with histologically confirmed diagnosis of R/R classical HL receiving BVB (median prior therapy of 2 (range 1 to 4)) reported that 15 (34%) patients experiencing grade >3 AEs. **(VERY LOW)** At a median follow-up of 27 months (range 4 to 68): • One case series (Picardi et al 2019) (n=20) of adults with biopsy-proven CD30-positive R/R classical HL receiving BVB (median prior therapy of 3 (range 2 to 6)) reported that 10 (50%) patients experienced grade 3 or 4 treatment related adverse events. **(VERY LOW)** *Grade 4 AEs* At a median follow-up 17 months (range 2 to 40): • One retrospective case series (Pinczes et al 2020) (n=41) of adults with R/R classical HL receiving BVB (median prior salvage therapies of 3 (range 1 to 6)) followed by ASCT reported that no patients experienced grade 4 AEs. **(VERY LOW)** At a median follow-up 38 months (range 4.2 to 64, IQR 26.7): • One retrospective case series (Moretti et al 2022) (n=41) of adults with biopsy-proven, CD30-positive R/R classical HL receiving BVB (median prior therapies of 2 (range 1 to 5)) reported that no patients experienced grade 4 toxicities. **(VERY LOW)** At unspecified duration of follow-up: • One single arm phase I-II trial (O'Connor et al 2022) (n=28 phase I & n=37 phase II) of adults with R/R CD30+ biopsy proven HL receiving BVB (median prior therapies of 3 (range 1 to 8)) reported on grade 4 toxicities. For phase I

[62] F/up not reported for safety outcomes. Length of f/up assumed to be the same as that reported for survival outcomes
[63] F/up not reported for safety outcomes. Length of f/up assumed to be the same as that reported for survival outcomes

Outcome	Evidence statement
	there were no grade 4 toxicities and for phase II there were 3 (8%) patients experiencing grade 4 neutropenia. **(VERY LOW)** *Infusion reactions* At a median follow-up 12 months (95% CI 5.2 to 18.8): • One retrospective case series (Radhakrishnan et al 2021) (n=30) of adults and young people with R/R HL receiving BVB (73% of patients had 2 or more treatment lines prior to BVB) reported that 12 (40%) patients experienced grade 1 or 2 infusion reactions. **(VERY LOW)** At a median follow-up of 27 months (range 4 to 68): • One case series (Picardi et al 2019) (n=20) of adults with biopsy-proven CD30-positive R/R classical HL receiving BVB (median prior therapy of 3 (range 2 to 6)) reported that two (10%) patients experienced serious infusion related reactions. **(VERY LOW)** *Discontinuation of treatment due to AEs* At a median follow-up 12 months (95% CI 5.2 to 18.8): • One retrospective case series (Radhakrishnan et al 2021) (n=30) of adults and young people with R/R HL receiving BVB (73% of patients had 2 or more treatment lines prior to BVB) reported that no patients experienced discontinuations or treatment delays due to BVB toxicity. **(VERY LOW)** At a median follow-up of 14 months (range 2 to 42): • One retrospective case series (Uncu Ulu et al 2022) (n=61) of adults with R/R classical HL receiving BVB (at a median treatment line of 3 (range 2 to 11)) reported that 10 (16.4%) patients experienced drug cessation due to AEs. **(VERY LOW)** At a median follow-up 17 months (range 2 to 40): • One retrospective case series (Pinczes et al 2020) (n=41) of adults with R/R classical HL receiving BVB (median prior salvage therapies of 3 (range 1 to 6)) followed by ASCT reported that one patient discontinued bendamustine due to severe, treatment-related neutropenia. **(VERY LOW)** At a median follow-up of 27 months (range 4 to 68): • One case series (Picardi et al 2019) (n=20) of adults with biopsy-proven CD30-positive R/R classical HL receiving BVB (median prior therapy of 3 (range 2 to 6)) reported that eight (40%) patients temporarily discontinued therapy due to treatment-related AEs. **(VERY LOW)** At a median follow-up 38 months (range 4.2 to 64, IQR 26.7): • One retrospective case series (Moretti et al 2022) (n=41) of adults with biopsy-proven, CD30-positive R/R classical HL receiving BVB (median prior therapies of 2 (range 1 to 5)) reported that one patient discontinued therapy due to febrile neutropenia and diarrhoea after the first cycle. **(VERY LOW)** *Interrupting treatment due to grade 4 toxicity* At a median follow-up of 19 months (95% CI 17.4 to 18.5)[64]: • One retrospective case series (Iannitto et al 2020) (n=47) of adults with histologically confirmed diagnosis of R/R classical HL receiving BVB (median prior therapy of 2 (range 1 to 4)) reported that 11% of patients experienced interrupting treatment due to grade 4 toxicity. **(VERY LOW)**

[64] F/up not reported for safety outcomes. Length of f/up assumed to be the same as that reported for survival outcomes

Outcome	Evidence statement
	Lower drug doses due to AEs At a median follow-up of 14 months (range 2 to 42): • One retrospective case series (Uncu Ulu et al 2022) (n=61) of adults with R/R classical HL receiving BVB (at a median treatment line of 3 (range 2 to 11)) reported that two (3.3%) patients had lower drug doses due to AEs. **(VERY LOW)** **One single arm (phase I-II) trial and five case series of R/R HL patients receiving BVB as third or subsequent line treatment and one case series of R/R HL patients receiving BVB as third or subsequent line treatment followed by ASCT provided very low certainty evidence relating to safety.** **Any grade AEs. One case series reported that just under half of patients (46%) experienced treatment related AEs of any grade at a median of 38 months follow-up and one case series of patients receiving BVB followed by ASCT reported that just over half (58.5%) experienced any grade AEs.** **One single arm (phase I-II) trial and one case series reported the following most common grade 3 AEs: neutropenia (7% & 27%), anaemia (18%), infection (7% & 14%) and thrombocytopenia (14%) at a median follow-up of 38 months or unspecified follow-up. Two case series reported that 15 (34%) patients at a median follow-up of 19 months and 50% at a median follow-up of 27 months experienced grade 3 or 4 AEs. Two further case series reported the following most common grade 3 or 4 AEs: neutropenia (24.6% & 73%), lymphopenia (40%), thrombocytopenia (13.1%), anaemia (13.1%), peripheral neuropathy (13%) and clinically detected infection (13%) at a median follow-up of 12 and 14 months. One single arm trial and three case series reported on grade 4 AEs up to a median follow-up of 38 months. One study reported no grade 4 AEs and two studies reported cases of grade 4 neutropenia (3 (8%) patients & 1 patient). One case series of R/R HL patients receiving BVB followed by ASCT reported that 7.3% of patients experienced grade 3 AEs (neutropenia (4.8%) and peripheral neuropathy (2.4%)) and no patients experienced grade 4 AEs at a median follow-up of 17 months.** **Four case series of R/R HL patients receiving BVB as third or subsequent line treatment and one case series of R/R HL patients receiving BVB as third or subsequent line treatment followed by ASCT reported on discontinuation of therapy due to treatment-related AEs, with results ranging from 0% to 40% up to a median follow-up of 38 months. One case series reported on the interruption of treatment due to grade 4 toxicity, with 11% of patients affected at a median follow-up of 19 months. One case series reported that 3.3% of patients had lower drug doses due to AEs at a median follow-up of 14 months.**
Abbreviations AEs: adverse events; allo-SCT: allogeneic stem cell transplant; ASCT: autologous stem cell transplant; BVB: brentuximab vedotin and bendamustine; CD30: cluster of differentiation 30; CI: confidence interval; CMV: cytomegalovirus; DS: Deauville score; HL: Hodgkin lymphoma; R/R: relapsed or refractory; SCT: stem cell transplant	

In adults with relapsed or refractory classical Hodgkin lymphoma, what is the cost effectiveness of brentuximab vedotin and bendamustine as third or subsequent line treatment compared with standard of care?

Outcome	Evidence statement
Cost effectiveness	No evidence was identified for cost effectiveness

From the evidence selected, are there any subgroups of patients that may benefit from brentuximab vedotin and bendamustine as third or subsequent line treatment more than the wider population of interest?

Subgroup	Evidence statement
Those who are fit for stem cell transplant vs those who are not fit for stem cell transplant	**Overall survival** *Subgroup: patients receiving SCT prior to BVB* At a median follow-up of 19 months (95% CI 17.4 to 18.5): • One retrospective case series (Iannitto et al 2020) (n=47) of adults with histologically confirmed diagnosis of R/R classical HL receiving BVB (median prior therapy of 2 (range 1 to 4)) reported that a univariate analysis did not show a significant association of previous exposure to ASCT with overall survival (no further details reported). *Subgroup: patients receiving SCT post BVB (SCT as consolidation therapy)* At a median follow-up of 19 months (95% CI 17.4 to 18.5): • One retrospective case series (Iannitto et al 2020) (n=47) of adults with histologically confirmed diagnosis of R/R classical HL receiving BVB (median prior therapy of 2 (range 1 to 4)) reported that 2-year overall survival was statistically significantly greater in patients who received SCT post BVB compared to those who did not (85% vs 56%, p=0.008). *Subgroup: patients not receiving ASCT*[65] At a median follow-up of 14 months (range 2 to 42): • One retrospective case series (Uncu Ulu et al 2022) (n=61) of adults with R/R classical HL receiving BVB (at a median treatment line of 3 (range 2 to 11)) reported that a multivariate analysis showed that patients who did not undergo ASCT had a worse overall survival than those who did. However this result was *statistically non-significant* (HR 0.215 (95% CI 0.04 to 1.11); p=0.07). **Response rate** *Subgroup: patients receiving SCT prior to BVB* At a median follow-up of 14 months (range 2 to 42): • One retrospective case series (Uncu Ulu et al 2022) (n=61) of adults with R/R classical HL receiving BVB (at a median treatment line of 3 (range 2 to 11)) reported that out of 18 patients who received ASCT prior to BVB, 14 were in complete remission and four had refractory disease. At a median follow-up of 19 months (95% CI 17.4 to 18.5): • One retrospective case series (Iannitto et al 2020) (n=47) of adults with histologically confirmed diagnosis of R/R classical HL receiving BVB (median prior therapy of 2 (range 1 to 4)) reported that overall response rate and complete response rate were not significantly different for patients who had previously received SCT (no further details reported). Four out of 12 (33%) patients who had relapsed after SCT achieved clinical response after BVB (3 complete response and 1 partial response) and proceeded to a second transplant (3 allo-SCT and 1 ASCT). *Subgroup: patients receiving SCT post BVB* At a median follow-up of 14 months (range 2 to 42): • One retrospective case series (Uncu Ulu et al 2022) (n=61) of adults with R/R classical HL receiving BVB (at a median treatment line of 3 (range 2 to 11)) reported that out of 32 patients who received ASCT post BVB, 22

[65] Unclear whether this group relates to ASCT prior to BVB, post BVB or both

Subgroup	Evidence statement
	were in complete remission, three were in partial remission and seven had refractory disease. At a median follow-up of 14.4 months (CI 95% 6 to 23): • One retrospective case series (Radhakrishnan et al 2021) (n=30) of adults and young people with R/R HL receiving BVB (73% of patients had two or more treatment lines prior to BVB) reported an overall response rate post SCT consolidation of 91% (21 out of 23 patients[66]) for patients who had SCT post BVB: Two patients had progressive disease post SCT consolidation, one died and the other was on salvage therapy at end of follow-up. *Subgroup: patients who were transplant ineligible* At a median follow-up of 14 months (range 2 to 42): • One retrospective case series (Uncu Ulu et al 2022) (n=61) of adults with R/R classical HL receiving BVB (at a median treatment line of 3 (range 2 to 11)) reported an overall response rate of 100% (9 out of 9 patients; complete response rate: 77.7%). **Eligibility for stem cell transplant** *Subgroup: patients receiving SCT prior to BVB* At a median follow-up of 14 months (range 2 to 42): • One retrospective case series (Uncu Ulu et al 2022) (n=61) of adults with R/R classical HL receiving BVB (at a median treatment line of 3 (range 2 to 11)) reported that out of 18 patients who received ASCT prior to BVB, seven patients received allo-SCT post BVB. **Progression-free survival** *Subgroup: patients receiving SCT prior to BVB* At a median follow-up of 19 months (95% CI 17.4 to 18.5): • One retrospective case series (Iannitto et al 2020) (n=47) of adults with histologically confirmed diagnosis of R/R classical HL receiving BVB (median prior therapy of 2 (range 1 to 4)) reported that a univariate analysis did not show a significant association of previous exposure to ASCT with progression-free survival (no further details reported). *Subgroup: patients receiving SCT post BVB (SCT as consolidation therapy)* At a median follow-up of 19 months (95% CI 17.4 to 18.5): • One retrospective case series (Iannitto et al 2020) (n=47) of adults with histologically confirmed diagnosis of R/R classical HL receiving BVB (median prior therapy of 2 (range 1 to 4)) reported that median progression-free survival was *statistically significantly* greater in patients who received SCT post BVB compared to those who did not (33 months (95% CI 14.7 to 51.3) vs 7 months (95% CI 2.5 to 11.3), p<0.001)). At a median follow-up 38 months (range 4.2 to 64, IQR 26.7): • One retrospective case series (Moretti et al 2022) (n=41) of adults with biopsy-proven, CD30-positive R/R classical HL receiving BVB (median prior therapies of 2 (range 1 to 5)) reported that no *statistically significant* differences were observed between BVB responsive patients who

[66] 2 allo-SCT patients died in the peri-transplant period, 1 each of sepsis and acute severe steroid refractory GVHD and were not included in the response rate post SCT consolidation

Subgroup	Evidence statement
	received SCT post BVB and those who did not for median progression-free survival (not reached vs 28 months, no further details reported). **Four case series reported results related to those who are fit for stem cell transplant vs those who are not fit for stem cell transplant in patients with R/R classical HL receiving BVB as third or subsequent line treatment for the outcomes overall survival (two studies), response rate (three studies), eligibility for stem cell transplant (one study) and progression-free survival (two studies). The studies reported separate results for either those fit for SCT prior to BVB, those fit for SCT post BVB, or for both subgroups. Only two case series reported statistical comparisons.** **For overall survival, one case series reported a *statistically significantly* greater 2-year overall survival for patients who received SCT post BVB compared to those who did not but reported a *statistically non-significant* association for ASCT prior to BVB with overall survival at a median follow-up of 19 months. A further case series reported a *statistically non-significant* association between patients undergoing ASCT and overall survival at a median follow-up of 14 months.** **For response rate, one case series reported that overall response rate and complete response rate were not *statistically significantly* different for patients who had previously received SCT at a median follow-up of 19 months.** **For progression-free survival, one case series reported that median progression-free survival was *statistically significantly* greater in patients who received SCT post BVB compared to those who did not and a *statistically non- significant* association of ASCT prior to BVB with progression-free survival at a median follow-up of 19 months. A further case series reported that no *statistically significant* differences were observed between BVB responsive patients who received SCT post BVB and those who did not for median progression-free survival at a median follow-up 38 months.**
Abbreviations allo-SCT: allogeneic stem cell transplant; ASCT: autologous stem cell transplant; BVB: brentuximab vedotin and bendamustine; CI: confidence interval; HR: hazard ratio; HL: Hodgkin lymphoma; R/R: relapsed or refractory; SCT: stem cell transplant	

From the evidence selected, how many cycles of combination therapy were required to treat relapsed or refractory classical Hodgkin lymphoma, and what doses were used?

Outcome	Evidence statement
Number of cycles of combination therapy required to treat relapsed or refractory classical Hodgkin lymphoma, and doses used	• Iannitto et al 2020 administered BV at 1.8 mg/kg (30-minute IV infusion) on day one and bendamustine at 90 mg/m^2 (120-minute infusion) on days two to three of a 21-day cycle. The median number of cycles of BVB was four (2.5 to 97.5 percentiles 2 to 7). • Moretti et al 2022 administered BV at 1.8 mg/kg IV on day one and bendamustine at 90 mg/m^2 IV on days one and two of a 21-day cycle for up to eight cycles. Nineteen patients received up to four cycles of BVB and 21 received six or more cycles.

Outcome	Evidence statement
	• In Phase I of O'Connor et al 2018, the dose escalation proceeded according to a standard 3 + 3 dose escalation design[67] with no intra-cohort dose escalation. BV was dosed on day one, while B was dosed on days one and two, on a 21 days cycle. Four dose cohorts were enrolled, starting at a dose of 1.2 mg/kg for BV escalating to a dose of 1.8mg/kg and a starting dose of bendamustine of 70 mg/m^2 escalating to 90 mg/m^2 (Cohort 1: starting dose of 1.2 mg/kg BV and 70 mg/m^2 of bendamustine; Cohort 2: 1.2 mg/kg BV and 80 mg/m^2 of bendamustine, Cohort 3: 1.8 mg/kg BV and 80 mg/m^2 of bendamustine, Cohort 4: 1.8 mg/kg BV and 90 mg/m^2 of bendamustine). Cohorts were expanded by three patients until the maximum tolerated dose was met. A maximum of six cycles was allowed, and no dose reductions were permitted. After cycle 1, dose delays up to three weeks were allowed, while delays of more than three weeks led to study discontinuation. While the maximum tolerated dose (MTD) of BVB was not reached, the MTD of BV (1.8 mg/kg day 1) and recommended phase II dose (RP2D) of bendamustine (90 mg/m^2 days 1 and 2) were identified as the RP2D of BVB and these were used for phase II. The median number of cycles administered was five (range 2 to 6). • Picardi et al 2019 administered BV at 1.8 mg/kg IV on day one of each 3-week cycle and bendamustine at 120 mg/m^2 per day at least 24 hours after BV, on days two and three. All patients underwent four courses of BVB. • Pinczes et al 2020 administered BV at 1.8 mg/kg IV on day one and bendamustine at 90 mg/m^2 IV on days one and two of a 21-day cycle. The median number of cycles of BVB was three (range 1 to 6). • Radhakrishnan et al 2021 administered BV at 1.8 mg/kg on day one with bendamustine at 90 mg/sq.m on days one and two of a 21-day cycle. The median number of cycles of BVB was three (range 1 to 6). • Uncu Ulu et al 2022 administered BV at 1.8 mg/kg IV on day one and bendamustine at 90 mg/m^2 on days one and two of a 21-day cycle. The median number of cycles was four (range 2 to 6). **BV was administered at a dose of 1.8 mg/kg IV on day one across all seven studies and bendamustine was administered at a dose of 90 mg/m² IV on days one and two across all the studies, except for one study which used a dose of 120 mg/m² on days two and three. The cycle length was 21 days for all studies. The number of cycles ranged from two to eight cycles, with a median of three to four cycles in most studies.**
Abbreviations ASCT: autologous stem cell transplant; BVB: brentuximab vedotin and bendamustine; CD30: cluster of differentiation 30; HL: Hodgkin lymphoma; IV: intravenous; kg: kilogram; m: metre; mg: milligram; MTD: maximum tolerated dose; RP2D: recommended phase 2 dose; R/R: relapsed or refractory	

[67] Three patients are initially enrolled into a given dose cohort. If there is no dose-limiting toxicity seen in any of these participants, the trial proceeds to enrol additional participants into the next higher dose cohort. This process continues until dose-limiting toxicities (DLTs) are observed in at least one patient. An additional three patients are accrued into that same dose cohort. Development of DLTs in two or more out of six patients at a specific dose level indicates that the maximum tolerated dose (MTD) has been exceeded. Further dose escalation is not pursued, and the prior dose level is expanded to six patients. If there is no more than one patient who experiences a DLT among those six patients, that dose level is considered the MTD

6. Discussion

This evidence review considered the clinical effectiveness, safety and cost effectiveness of combination BVB as third or subsequent line treatment compared with standard of care in adults with R/R HL. The critical outcomes of interest were overall survival, response rate and eligibility for stem cell transplant. Important outcomes were event-free survival, progression-free survival, disease-free survival or remission, quality of life and safety.

Seven studies were identified for inclusion in this review, one single arm (phase I-II) trial (O'Connor et al 2022) and six case series (Iannitto et al 2020, Moretti et al 2022, Picardi et al 2019, Pinczes et al 2020, Radhakrishnan et al 2021, Uncu Ulu et al 2022). All case series were retrospective except for one where the perspective was not specified. The studies ranged in size from 20 to 65 patients and ranged in median follow-up duration from 12 to 38 months where reported. No comparator evidence or cost effectiveness evidence was identified.

The studies included adults with a histologically confirmed diagnosis of classical HL with relapsed or refractory disease following induction chemotherapy. Exceptions included the single arm trial (O'Connor et al 2022) which also included one patient with ALCL and one case series which also included young people (Radhakrishnan et al 2021; median age of 30 years (range 15 to 59). The median patient age in the included studies where reported ranged from 30 to 40 years.

BV was administered at a dose of 1.8 mg/kg IV on day one of a 21 day cycle across all seven studies and bendamustine was at a dose of 90 mg/m² IV on days one and two across all the studies, except for one study which used a dose of 120 mg/m² on days two and three. The number of cycles ranged from two to eight cycles, with a median of three to four cycles in most studies. BVB was given as third or subsequent line treatment in the majority of patients. All of the studies were either restricted to patients having had at least two previous lines of therapy (O'Connor et al 2022, Picardi et al 2019, Pinczes et al 2020, Uncu Ulu et al 2022) and therefore all patients were in scope or had a median of two or more previous lines of therapy (Iannitto et al 2020, Moretti et al 2022, Radhakrishnan et al 2021) and therefore the majority of patients were patient were in scope. One case series only included patients who went on to have ASCT after BVB and outcomes were reported post ASCT (Pinczes et al 2020).

Overall, these differences from the PICO specified population for this review were relatively small and the studies generally represented the population of interest.

Between the seven studies, the study outcomes reported included the critical outcomes of overall survival (six studies), response rate (seven studies), and eligibility for stem cell transplant (five studies) and the important outcomes of event-free survival (one study), progression-free survival (six studies) and safety (seven studies). No studies were identified that reported the important outcomes of disease-free survival or remission or quality of life.

The treatment response outcomes were evaluated in accordance with either the Lugano classification, the Response Evaluation Criteria in Lymphoma (RECIL) or the International Harmonization Project Group 2007 Revised Response Criteria for Malignant Lymphoma. Survival outcomes were calculated using the Kaplan-Meier method.

No minimal clinically important thresholds or differences were reported for the outcomes considered.

Four retrospective case series reported subgroup results related to those who are fit for stem cell transplant vs those who are not fit for stem cell transplant in patients with R/R classical HL receiving BVB for the outcomes overall survival (two studies), response rate (three studies),

eligibility for stem cell transplant (one study) and progression-free survival (two studies). Only two case series reported on statistical analyses comparing those who are fit for stem cell transplant vs those who are not fit for stem cell transplant (either pre or post BVB). For patients who received SCT post BVB, one case series (n=47) reported a statistically significantly greater 2-year overall survival and median progression-free survival in patients who received SCT post BVB compared to those who did not at a median follow-up of 19 months. However, a further case series (n=41) reported that no statistically significant differences were observed between BVB responsive patients who received SCT post BVB and those who did not for median progression-free survival at a median follow-up 38 months. For patients who received SCT prior to BVB, one case series (n=47) reported a statistically non-significant association for ASCT prior to BVB with overall survival, overall response rate, complete response rate and progression-free survival at a median follow-up of 19 months.

All seven studies were considered to be at high risk of bias and certainty about the evidence for the critical and important outcomes was very low when assessed using modified GRADE. The most important limitation relating to the evidence included is the lack of a comparator group. This means that it is not clear whether the results reported for R/R HL patients receiving BVB as third or subsequent line treatment are different from those receiving standard care. Other limitations that reduce the certainty in the outcomes reported include the small sample size of the studies, the retrospective nature of the majority of the studies, uncertainty about whether the inclusion of participants was complete or consecutive, and limited statistical analyses or summary statistics for some of the outcomes reported.

The studies were all carried out mostly across multiple centres in countries outside of the UK (Canada, Hungary, India, Italy, Turkey and the USA) and it is not clear if the patients and aspects of care in the studies reflect that seen in clinical practice in England and care is therefore needed in generalising results to the NHS.

7. Conclusion

This evidence review includes seven studies (one single arm trial and six case series) which reported outcomes of combination BVB as third or subsequent line treatment in adults with R/R HL with sample sizes ranging from 20 to 65 patients and a median follow-up of up to 38 months.

The studies provide very low certainty evidence for the critical outcomes of overall survival, response rate and eligibility for stem cell transplant and the important outcomes of event-free survival, progression-free survival and safety. No studies were identified that reported the important outcomes of disease-free survival or remission or quality of life. No evidence on cost effectiveness was found.

With respect to critical outcomes, the studies suggest that adults with R/R HL receiving combination BVB as third or subsequent line treatment have a 1-year overall survival ranging from 85% to 86%, a 2-year overall survival ranging from 72% to 82% (93% in patients post ASCT after BVB) and a 3-year overall survival of 75% up to a median of 19 months follow-up, an overall response rate after BVB treatment ranging from 71% to 82% (92.6% in patients post ASCT after BVB) and a complete response rate ranging from 49% to 100% (70.7% in patients post ASCT after BVB), and a wide range of patients eligible for SCT after BVB treatment of 37% to 93%). With respect to important outcomes, the studies suggest that adults with R/R HL receiving combination BVB as third or subsequent line treatment have a 3-year event-free survival of 58% at a median follow-up of 12 months, a 1-year progression-free survival of 67% at an unspecified follow-up, a 2-year progression-free survival ranging from 60% to 93.7% (62% in patients post ASCT after BVB) up to a median of 27 months follow-up, and a median progression-free survival of 7.5 months to 26 months up to a median of 38 months follow-up. With respect to safety, the studies suggest a relatively high incidence of treatment-related AEs, including severe (grade 3 or 4) AEs. Neutropenia, lymphopenia, thrombocytopenia, anaemia, infection and peripheral neuropathy were the most common severe AEs. A wide range of results for discontinuation of therapy due to treatment-related AEs were reported, ranging from 0% to 40% up to a median follow-up of 38 months.

Limited subgroup results were reported for patients fit versus unfit for SCT. One case series found significantly greater 2-year overall survival and median progression-free survival in patients who received SCT post BVB, while another found no significant differences in median progression-free survival. For patients who received SCT prior to BVB, one case series found no significant associations with overall survival, overall response rate, complete response rate, and progression-free survival.

BV was administered at a dose of 1.8 mg/kg IV on day one of a 21 day cycle across all seven studies and bendamustine was at a dose of 90 mg/m² IV on days one and two across all the studies, except for one study which used a dose of 120 mg/m² on days two and three. The number of cycles ranged from two to eight cycles, with a median of three to four cycles in most studies.

The studies were small, mostly retrospective case series with no patients from the UK. The lack of comparative studies mean that no conclusions can be drawn about the effectiveness of combination BVB as third or subsequent line treatment compared with standard care in adults with R/R HL.

Appendix A PICO document

The review questions for this evidence review are:

1. In relapsed or refractory classical Hodgkin lymphoma, what is the clinical effectiveness of combination brentuximab vedotin and bendamustine as third or subsequent line treatment compared with standard of care?
2. In relapsed or refractory classical Hodgkin lymphoma, what is the safety of combination brentuximab vedotin and bendamustine as third or subsequent line treatment compared with standard of care?
3. In relapsed or refractory classical Hodgkin lymphoma, what is the cost effectiveness of combination brentuximab vedotin and bendamustine as third or subsequent line treatment compared with standard of care?
4. From the evidence selected, are there any subgroups of patients that may benefit from combination brentuximab vedotin and bendamustine as third or subsequent line treatment more than the wider population of interest?
5. From the evidence selected, how many cycles of combination therapy were required to treat relapsed or refractory classical Hodgkin lymphoma, and what doses were used?

P –Population and Indication	Adult patients with relapsed or refractory (R/R) CD30^{+ve} classical Hodgkin's lymphoma who have either: • already had an autologous stem cell transplant OR • had at least two previous lines of therapy [This may be described in studies as either second line salvage therapy or third line therapy from diagnosis] [Autologous stem cell transplant is always given as second or subsequent line therapy] [Previous lines of therapy include multi-agent chemotherapy regimens] [Include studies where there are mixed populations by age and the majority of participants or the mean/median age of participants is 18 years or over] Subgroups of interest: • Those that are fit for stem cell transplant vs those who are not fit for stem cell transplant
I – Intervention	Combination brentuximab vedotin and bendamustine therapy [This may be given with or without best supportive care. Best supportive care can include steroids, analgesics, antipyretics, antibiotics, anti-emetics or G-CSF (Granulocyte-colony stimulating factor)] [Combination therapy will often be followed by stem cell transplant which may be autologous or allogenic pending on age or co-morbidities or other risk factors]
C – Comparator(s)	Standard of care [This can include: • Monotherapy brentuximab vedotin

	• Monotherapy pembrolizumab • Third line chemotherapy] [Standard of care may be given with or without best supportive care]
O – Outcomes	**<u>Clinical Effectiveness</u>** Minimally clinically important differences (MCIDs) are not known unless stated. Outcomes reported at two, five and 10 years are of particular interest. <u>*Critical to decision-making:*</u> • **Overall survival** *This outcome is important to patients as patients with R/R HL have a higher mortality rate due to previously failed therapy. Improved overall survival is an important marker of effective treatment, although it does not provide information about a patient's health and wellbeing during that time.* [Overall survival is conventionally thought of as the gold standard for assessing survival benefit of cancer drug treatments and is usually defined as time from diagnosis to death.] • **Response rate** *This outcome is important to patients as it indicates the treatment has successfully been able to treat the cancer. Complete response rate is an important marker of effective treatment as it is associated with better survival outcomes and higher transplant rates.* [Response rate may be reported as overall response rate, complete response, partial response or no response, or best response rate. This may also be reported as complete or partial remission or complete molecular remission. This may be measured using PET or CT scans, Revised Response Criteria, the Lugano 2014 classification (most widely used) or more recent RECIL criteria.] • **Eligibility for stem cell transplant** *This outcome is important to patients as it indicates the treatment is able to progress them safely to stem cell transplant. Progression to stem cell transplant is important as this is the definitive treatment of R/R Hodgkin lymphoma and improves overall survival.* [Stem cell transplant may be autologous or allogenic. Number of patients successfully undergoing autologous or allogenic stem cell transplant is a clinically important outcome. An important factor within this outcome is the number of treatment cycles with combination therapy required prior to transplant, where ≤4 treatment cycles is clinically significant.] <u>*Important to decision-making:*</u> • **Event-free survival** *This outcome is important to patients because it represents the time during which their disease is not progressing. Stable disease might represent longer survival and disease stability may result in patients experiencing fewer symptoms from the disease itself. It can be determined sooner than overall survival outcome measures.*

	[Event-free survival is a composite measure and could be defined by the following: time to treatment failure; freedom from treatment failure; disease-free survival; time from diagnosis to first event, including death during induction therapy; failure to achieve remission; relapse at any site; development of second malignant neoplasm; time from complete metabolic response to molecular relapse or death from R/R HL. This may also be represented by start of a new anti-lymphoma therapy for inadequate response.] • **Progression free survival** *This outcome is important to patients because it represents the time for which their disease is not progressing. Stable disease might represent longer survival and disease stability may result in patients experiencing fewer symptoms from the disease itself. It can be determined sooner than overall survival outcome measures.* [This may also be presented as failure-free survival, e.g. defined as time from treatment initiation to biochemical failure, local progression, distant metastases, death from lymphoma, or progression free-survival defined as failure-free survival but excluding biochemical failure.] • **Disease-free survival or remission** *This outcome is important to patients as it means that the signs and symptoms of cancer have reduced, either partially or completely and they are free of all detectable disease.* [Disease-free survival/ remission are binary measures that can be defined as the time from haematological/cytogenic/molecular complete remission (CR) to either haematological/cytogenic/molecular relapse or death from R/R HL.] • **Quality of Life** *This is an important outcome for patients as it provides an indication of an individual's general health and self-perceived well-being and their ability to participate in activities of daily living. Validated tools for general quality of life measurements are important patient reported outcome measures to help inform patient-centred decision making and inform health policy. Treatment related impacts on specific quality of life measures are also useful for this purpose.* [Examples of quality-of-life tools include but are not limited to Paediatric Quality of Life Inventory (PedsQL), the Child Health Questionnaire (CHQ), or the Quality-of-Life Scale for Children (QOL-C), QLQ-OV28, QLQ-C30, QLQ-FA12, EQ-5D and SF-36.] **<u>Safety</u>** *These outcomes are important to patients because they will impact on their treatment choices, recovery and could have long term sequelae if they are irreversible. They reflect the tolerability and adverse effects of the treatment. From a service delivery perspective, they reflect the additional demands placed on the health system to manage the adverse consequences of the treatment.* [Examples include, but not limited to:

	• Toxicity including cardiac toxicity • Frequency of adverse events • Frequency of grade 3 or 4 adverse events • Adverse events leading to discontinuation • Treatment related adverse events] **Cost effectiveness**
Inclusion criteria	
Study design	Systematic reviews, randomised controlled trials, controlled clinical trials, cohort studies. If no higher level quality evidence is found, case series can be considered.
Language	English only
Patients	Human studies only
Age	Adults
Date limits	2014-2024
Exclusion criteria	
Publication type	Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, pre-prints and guidelines
Study design	Case reports, resource utilisation studies

Appendix B Search strategy

Medline, Embase and the Cochrane Library were searched limiting the search to papers published in English language in the last 10 years. Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, pre-prints, guidelines, case reports and resource utilisation studies were excluded.

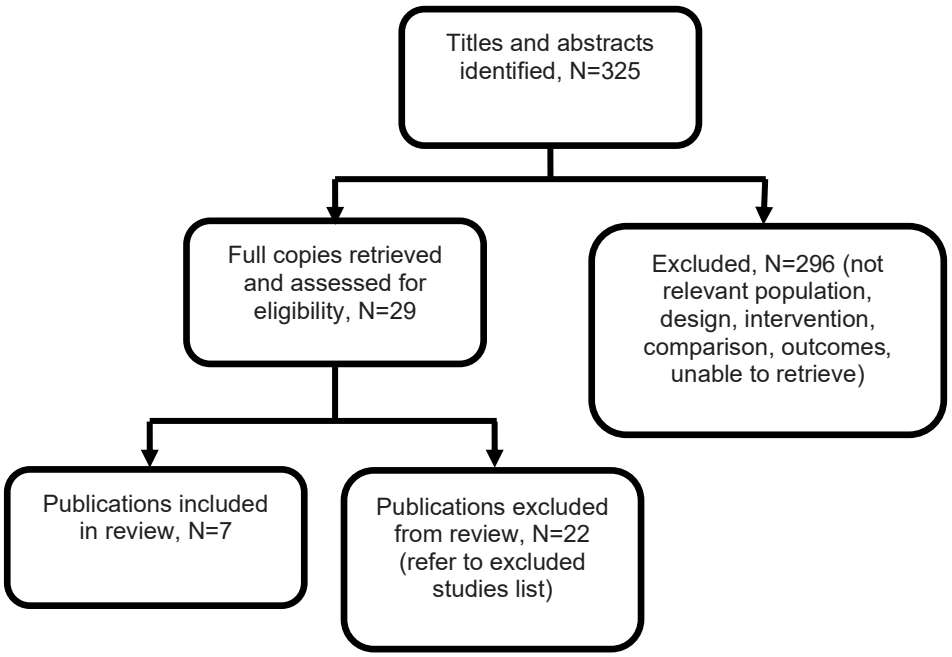
Search dates: 1 January 2014 and 12 June 2024

	Ovid MEDLINE(R) ALL <1946 to June 12, 2024>
1	Hodgkin Disease/
2	(hodgkin* adj (lymphoma? or disease?)).ti,ab,kf.
3	1 or 2
4	Bendamustine Hydrochloride/
5	(bendamustin? or cytostasan or "imet 3393" or ribomustin or treanda or "zimet 3393").mp.
6	4 or 5
7	Brentuximab Vedotin/
8	(brentuximab or adcetris or cac10 or sgn 35).mp.
9	7 or 8
10	3 and 6 and 9
11	limit 10 to (english language and yr="2014 -Current")

Appendix C Evidence selection

The literature searches identified 325 references. These were screened using their titles and abstracts and 29 references were obtained in full text and assessed for relevance. Of these, seven references are included in the evidence summary. The remaining 22 references were excluded and are listed in Appendix D.

Figure 1- Study selection flow diagram



References submitted with Preliminary Policy Proposal

Reference	Paper selection - decision and rationale if excluded
Broccoli A, Argnani L, Botto B, Corradini P, Pinto A, Re A, et al. First salvage treatment with bendamustine and brentuximab vedotin in Hodgkin lymphoma: a Phase II study of the Fondazione Italiana Linfomi. Blood Cancer J. 2019;9(12):100.	Excluded. Intervention out of scope: BVB given as first salvage treatment, not second line salvage treatment as specified in the PICO
LaCasce AS, Bociek RG, Sawas A, Caimi P, Agura E, Matous J, et al. Brentuximab vedotin plus bendamustine: a highly active first salvage regimen for relapsed or refractory Hodgkin lymphoma. Blood. 2018;132(1):40-8.	Excluded. Intervention out of scope: BVB given as first salvage treatment, not second line salvage treatment as specified in the PICO
O'Connor OA, Lue JK, Sawas A, Amengual JE, Deng C, Kalac M, et al. Brentuximab vedotin plus bendamustine in relapsed or refractory Hodgkin's lymphoma: an international, multicentre, single-arm, phase 1-2 trial. Lancet Oncol. 2018;19(2):257-66.	Included

Appendix D Excluded studies table

Study reference	Reason for exclusion
Anonymous. Brentuximab Vedotin in Combination With Dacarbazine or Bendamustine for Frontline Treatment of Hodgkin Lymphoma in Patients Aged 60 Years and Above: Interim Results of a Multi-Cohort Phase 2 Study. Clin. 2016;14(2 Suppl 1):13-5.	Publication type out of scope: Conference abstract
Broccoli A, Argnani L, Botto B, Corradini P, Pinto A, Re A, 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.	Intervention out of scope: BVB given as first salvage treatment, not second line salvage treatment as specified in the PICO
Cheah CY, Chihara D, Horowitz S, Sevin A, Oki Y, Zhou S, et al. Patients with classical Hodgkin lymphoma experiencing disease progression after treatment with brentuximab vedotin have poor outcomes. Ann Oncol. 2016;27(7):1317-23.	Intervention out of scope: 95% of patients received BV monotherapy
El Cheikh J, Massoud R, Haffar B, Fares E, Mahfouz R, Jisr T, et al. Bendamustine as a bridge to allogeneic transplant in relapsed/refractory Hodgkin lymphoma patients who failed salvage brentuximab vedotin postautologous peripheral blood stem cell transplantation. Leuk Lymphoma. 2017;58(11):2745-7.	Publication type out of scope: Letter
Forlenza CJ, Gulati N, Mauguen A, Absalon MJ, Castellino SM, Franklin A, et al. Combination brentuximab vedotin and bendamustine for pediatric patients with relapsed/refractory Hodgkin lymphoma. Blood Adv. 2021;5(24):5519-24.	Population and intervention out of scope: Children & majority of patients (72%) received BVB as first salvage treatment, not second line salvage treatment as specified in the PICO
Friedberg JW, Forero-Torres A, Bordoni RE, Cline VJM, Patel Donnelly D, Flynn PJ, et al. Frontline brentuximab vedotin in combination with dacarbazine or bendamustine in patients aged >=60 years with HL. Blood. 2017;130(26):2829-37.	Population out of scope: Treatment naïve HL
Harker-Murray P, Mauz-Korholz C, Leblanc T, Mascarin M, Michel G, Cooper S, et al. Nivolumab and brentuximab vedotin with or without bendamustine for R/R Hodgkin lymphoma in children, adolescents, and young adults. Blood. 2023;141(17):2075-84.	Population out of scope: Children. Included in children with R/R HL review
Kaloyannidis P, Al Zayer M, Al Darweesh M, Al Batran M, Al Garni A, Al Naim A, et al. Brentuximab vedotin plus bendamustine versus platinum-based regimens as 1st salvage therapy and 'bridge' to autologous hematopoietic stem cell transplantation for relapsed/refractory Hodgkin lymphoma. Leuk Lymphoma. 2023;64(3):742-5.	Publication type out of scope: Letter
Korsantya MN, Romankova YE, Myakova NV, Pshonkin AV. The experience of using the brentuximab vedotin in the treatment of children and young adults with primary refractory course and relapses of hodgkin's lymphoma. Pediatric hematology/oncology and immunopathology. 2020;19(1):47?52.	Paper in Russian

Study reference	Reason for exclusion
LaCasce AS, Bociek RG, Sawas A, Caimi P, Agura E, Matous J, et al. Brentuximab vedotin plus bendamustine: a highly active first salvage regimen for relapsed or refractory Hodgkin lymphoma. Blood. 2018;132(1):40-8.	Intervention out of scope: BVB given as first salvage treatment, not second line salvage treatment as specified in the PICO
Magyari F, Barna S, Husi K, Simon Z, Miltenyi Z, Varoczy L, et al. Alternative salvage regimens for relapsed/refractory classical Hodgkin's lymphoma. Hematol. 2016;21(7):404-10.	Intervention out of scope: Rituximab–bendamustine–BV combination therapy
Picardi M, Della Pepa R, Giordano C, Pugliese N, Mortaruolo C, Trastulli F, et al. Brentuximab vedotin followed by bendamustine supercharge for refractory or relapsed Hodgkin lymphoma. Blood Adv. 2019;3(9):1546-52.	Duplicate
Raut M, Singh G, Hiscock I, Sharma S, Pilkhwal N. A systematic literature review of the epidemiology, quality of life, and economic burden, including disease pathways and treatment patterns of relapsed/refractory classical Hodgkin lymphoma. Expert Rev Hematol. 2022;15(7):607-17.	Systematic review on the epidemiology of R/R HL, disease management, QoL and economic burden. Included references are out of scope
Rossi C, Gilhodes J, Maerevoet M, Herbaux C, Morschhauser F, Brice P, et al. Efficacy of chemotherapy or chemo-anti-PD-1 combination after failed anti-PD-1 therapy for relapsed and refractory hodgkin lymphoma: A series from lysa centers. American Journal of Hematology. 2018;93(8):1042-9.	Intervention out of scope: Anti-PD-1 monotherapy
Rutherford SC, Leonard JP. Management of relapsed and refractory hodgkin lymphoma in 2018. JAMA Oncology. 2018;4(8):1120-1.	General review on the management of R/R HL
Sawas A, Ma H, Kuruvilla J, Lue JK, Deng C, Marchi E, et al. Prolonged progression free survival in a subset of responders to the combination of brentuximab vedotin and bendamustine in heavily treated patients with relapsed or refractory Hodgkin lymphoma: updated results from an international multi-center phase I/II experience. Leuk Lymphoma. 2020;61(12):3014-7.	Publication type out of scope: Letter
Szabo SM, Hirji I, Johnston KM, Juarez-Garcia A, Connors JM. Treatment patterns and costs of care for patients with relapsed and refractory Hodgkin lymphoma treated with brentuximab vedotin in the United States: A retrospective cohort study. PLoS ONE. 2017;12(10):e0180261.	Intervention out of scope: BV monotherapy
Tacyildiz N, Cakmak HM, Unal E, Dincaslan H, Tanyildiz G, Ozdemir SI, et al. Evaluation of late effects during a 21-year follow-up of pediatric Hodgkin lymphoma survivors: Experience of a pediatric cancer center in Turkey, as a developing country model. Indian J Cancer. 2024;09:09.	Population out of scope: Children
Tacyildiz N, Tanyildiz HG, Unal E, Dincaslan H, Asarcikli F, Aksoy BA, et al. A targeted salvage therapy with Brentuximab vedotin in heavily treated refractory or relapsed pediatric Hodgkin lymphoma patients before and after stem cell transplantation. Turk J Pediatr. 2019;61(5):671-6.	Population out of scope: Children

Study reference	Reason for exclusion
Vinti L, Pagliara D, Buffardi S, Di Ruscio V, Stocchi F, Mariggio E, et al. Brentuximab vedotin in combination with bendamustine in pediatric patients or young adults with relapsed or refractory Hodgkin lymphoma. Pediatr Blood Cancer. 2022;69(4):e29557.	Population out of scope: Children. Included in children with R/R HL review
Wagner SM, Melchardt T, Egle A, Magnes T, Skrabs C, Staber P, et al. Treatment with brentuximab vedotin plus bendamustine in unselected patients with CD30-positive aggressive lymphomas. Eur J Haematol. 2020;104(3):251-8.	Population and intervention out of scope. Includes HL patients with a median of 1 treatment prior to BVB. Not R/R HL with third line BVB as specified in the PICO
Zinzani PL, Vitolo U, Viviani S, Corradini P, Motta G, Tani M, et al. Safety and efficacy of single-agent bendamustine after failure of brentuximab vedotin in patients with relapsed or refractory hodgkin's lymphoma: experience with 27 patients. Clin Lymphoma Myeloma Leuk. 2015;15(7):404-8.	Intervention out of scope: Bendamustine monotherapy

Appendix E Evidence table

For abbreviations see list after table

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Iannitto E, Romano A, Scalzulli PR, Bonanno V, Scalone R, Chiarenza A, et al. Brentuximab vedotin in association with bendamustine in refractory or multiple relapsed Hodgkin lymphoma. A retrospective real-world study. Eur J Haematol. 2020;104(6):581-7. **Study location** Italy (8 centres) **Study type** Retrospective case series **Study aim** To assess the efficacy of BVB in multiple R/R classic HL using medical records of 47 patients treated with BVB in second relapse or beyond **Study dates** October 2014 to November 2018	Adults with histologically confirmed diagnosis of R/R classical HL[68] **Inclusion criteria** • Aged ≥ 18 years • Histologically confirmed diagnosis of classical HL • 18-F fluorodeoxyglucose (FDG)-PET avid tumour • Bi-dimensionally measurable disease • Primary refractory disease (defined as not achieving a CR or relapsing within 3 months after a conventional treatment) or in second relapse or beyond **Exclusion criteria** None reported **Total sample size** N=47	**Interventions** BVB combination therapy BV at 1.8 mg/kg IV, 30-minute infusion on day 1 in association with bendamustine 90 mg/m^2, 120-minute infusion on days 2 to 3 of a 21-day cycle Median 4 cycles (2.5 to 97.5 percentiles 2-7) **Comparators** None	**Critical outcomes** **Overall survival[69]** At median follow-up of 19 months (95% CI: 17.4 to 18.5): 2-year OS: 72% Median OS: Not reached **Response rate[70]** At end of BVB treatment (median 4 cycles, 2.5 to 97.5 percentiles 2 to 7) Overall response rate (ORR; complete and partial responders): 79% (95% CI 64 to 89) Complete response rate: 49%, (95% CI 34 to 64) **Eligibility for stem cell transplant** At end of BVB treatment (median 4 cycles, 2.5 to 97.5 percentiles 2 to 7) Number of patients proceeding to a SCT: 26 (17 CR, 7 PR & 2 SD) 20 ASCT; 4 allo-SCT; 2; tandem ASCT-allo-SCT **Important outcomes**	This study was appraised using the Joanna Briggs checklist for case series. 1.YES 2.YES 3.YES 4.UNCLEAR 5. UNCLEAR 6.YES 7.YES 8.YES 9.NO 10.YES **Other comments:** This paper reports on a retrospective case series of 47 R/R classical HL patients treated with BVB in second relapse or beyond across eight centres in Italy. Inclusion and exclusion criteria were clearly defined but it was not clear if patient recruitment had been consecutive and complete. Six patients in progression at their last clinical examination (3 in progression after BVB and 3 after

[68] Primary refractory disease (defined as not achieving a CR or relapsing within 3 months after a conventional treatment) or in second relapse or beyond
[69] Defined as the time from BVB treatment initiation to the date of death from any cause
[70]The response revaluation criteria in lymphoma (RECIL) were followed for clinical response coding

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	Baseline characteristics Median age: 34 years (range 18 to 76) Male: 31 (66%) Disease characteristics: • Bulky disease at diagnosis: 14 (37%) • Bendamustine symptoms: 30 (75%) • Advanced stage at initial diagnosis: 42 (89%) • Extranodal disease: 18 (31%) First-line regimens: • ABVD (4 to 6 cycles): 38 (82%) • ABVD dose dense: 4 (8%) • ABVD (2 cycles) - escBEACOPP (4 cycles): 2 (4%) • Other: 3 (6%) • Involved-field radiotherapy: 10 (21%) BVB therapy: • Median previous lines of treatment (range): 2 (1 to 4) • BVB fourth-line treatment or later:14 (25%)		**Progression free survival**[71] At median follow-up of 19 months (95% CI: 17.4 to 18.5) Median PFS: 18 months (95% CI 4.5 to 31.4) **Safety** Length of f/up assumed to be the same as that reported for survival outcomes (median follow-up of 19 months (95% CI: 17.4 to 18.5)) Number of patients experiencing grade >3 adverse events: 15 (34%) The most common grade 3-4 adverse events were: Neutropenia: 23% Peripheral sensory neuropathy: 11% Diarrhoea: 7% Infection: 4% (1 bronchopneumonia and 1 CMV pneumonitis) % of patients with interrupting treatment due to grade 4 toxicity: (11%) **Subgroups** *Subgroup: SCT prior to BVB* **Overall survival** "Univariate analysis did not show a significant association	SCT) were lost to follow-up. These patients were included as events in OS and PFS analyses. It should be noted, that while the majority of patients were in scope for this review, 6 patients (13%) received BVB as second-line therapy and where therefore out of scope. The response evaluation criteria in lymphoma (RECIL) were followed for clinical response coding. No further details were reported on response evaluation. Survival outcomes were calculated using the Kaplan-Meier method. **Source of funding:** Supported by Associazione Italiana contro le Leucemie of Catania, Fondazione Catanese per lo Studio e la Cura delle Malattie Neoplastiche del Sangue and Collegio Ghislieri Two authors received honoraria from Takeda.

[71] Defined as the time from BVB treatment initiation to the first documentation of progression/relapse or to death from any cause

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	• BVB third-line treatment: 36 (64%) • BVB second-line treatment: 6 (13%) Disease status at start of BVB: • Relapsed/progressed after ASCT: 12 (25%) • Previous BV as single agent: 17 (36%) • Primary refractory to frontline therapy: 24 (51%) • Refractory to last treatment: 31 (66%) • Refractory to first- and second-line treatment: 24 (51%)		of previous exposure to ASCT" **Response rate** ORR and CRR were not significantly different for patients who had previously received SCT 4 out of 12 (33%) patients who had relapsed after SCT achieved clinical response after BVB (3 CR and 1 PR) and proceeded to a second transplant (3 allo-SCT and 1 ASCT) **Progression-free survival** "Univariate analysis did not show a significant association of previous exposure to ASCT" *Subgroup: SCT post BVB* **Overall survival** Consolidation SCT vs non-SCT 2-year OS: 85% vs 56%, p=0.008 **Progression-free survival** Consolidation SCT vs non-SCT Median PFS: 33 months (95% CI 14.7 to 51.3) vs 7 months (95% CI 2.5 to 11.3), p<0.001)	
Moretti M, Liberati AM, Rigacci L, Puccini B, Pulsoni A, Gini G, et al. Brentuximab vedotin and	Biopsy-proven, CD30-positive R/R classical HL after failure of ≥1 therapy including ASCT, allo-SCT, or BV	**Interventions** IV BV (1.8 mg/kg) given on day 1 and IV bendamustine (90 mg/m^2) given on days 1	Median follow-up of 38 months (range 4.2 to 64, IQR 26.7) unless stated otherwise **Critical outcomes**	This study was appraised using the Joanna Briggs checklist for case series. 1.NO

Study details	Population	Interventions	Study outcomes	Appraisal and funding
bendamustine produce long-term clinical benefit in patients with relapsed or refractory classical Hodgkin lymphoma: A multicenter real-life experience. Clin Lymphoma Myeloma Leuk. 2022;22(3):198-204. **Study location** Italy (11 centres) **Study type** Retrospective case series **Study aim** To report the analysis of a real-world experience looking at efficacy, safety and outcomes associated with the use of BVB, with an extended follow-up **Study dates** July 2015 to June 2020	**Inclusion criteria** • Biopsy-proven, CD30-positive • R/R classical HL after failure of ≥1 therapy including ASCT, allo-SCT, or BV **Exclusion criteria** Not reported **Total sample size** N=41 **Baseline characteristics** Median age: 36 years (range 16 to 74) Male: 22 (54%) Histological subtype: • Nodular sclerosis: 28 (68%) • Mixed cellularity: 6 (15%) • Lymphocyte-rich: 2 (5%) • Not classified: 5 (12%) ECOG PS: • 0 – 1: 37 (90%) • ≥2: 4 (10%) Previous ASCT: 8 (20%) Previous allo-SCT: 2 (5%) Number of previous lines of therapy: • ≤2: 28 (68%)	and 2 of a 21-day cycle for up to 8 cycles 19 patients received up to 4 cycles of BVB and 21 received 6 or more cycles **Comparators** None	**Overall survival**[72] Median OS (n=41): not reached **Response rate**[73] At the end of BVB treatment (up to 8 cycles) ORR (n=40): 75% (95% CI 59 to 86) Complete response rate (n=40): 50% (95% CI 35 to 66) **Eligibility for stem cell transplant** Number of patients undergoing SCT after BVB (n=41): 15 (36.6%) • 9 patients underwent SCT after 4 cycles of BVB (7 ASCT and 2 allo-SCT), 7 in CR and 2 in PR • 6 patients underwent SCT after ≥ 6 cycles of BVB (1 ASCT & 5 allo-SCT), 5 in CR and 1 in PR **Important outcomes** **Progression-free survival**[74] Median PFS (n=41): 26 months (95% CI 7.2 to not reached) **Safety (n=41)** Number of patients experiencing treatment emergent AEs of any grade: 19 (46%) Number of patients discontinuing therapy: 1 (due to febrile	2.YES 3.YES 4.YES 5.YES 6.YES 7.YES 8.YES 9.NO 10.YES **Other comments:** This paper reports on a case series of 41 R/R classical HL patients receiving BVB after failure of ≥1 therapy at 11 centres in Italy. Limited inclusion and exclusion criteria were reported. The paper reported that consecutive patients with biopsy-proven, CD30-positive R/R classical HL, who were deemed candidates for BVB were included. It should be noted that while the majority of patients are in scope for this review, the range of prior therapies was 1 to 5 (median 2) and therefore some patients with one prior therapy will be out of scope (number not reported). Responses were assessed at the end of the therapy using the 2014 Lugano criteria whereby a score of ≤3 on the Deauville 5-point scale

[72] Calculated from the date of enrolment until death from any cause and it was censored at the date of last follow up for surviving patients
[73] Responses were assessed using the 2014 Lugano criteria whereby a score of ≤3 on the Deauville 5-point scale was considered indicative of complete response
[74] Defined as the time from treatment initiation to progression of disease, relapse, or death from any cause. If none of these events had occurred, PFS was censored at the date of last follow up. Patients undergoing SCT were not censored at the time of consolidation

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	• ≥3: 13 (32%) Median number of previous therapies: 2 (range 1 to 5) Previous BV: 26 (63%)		neutropenia and diarrhoea after the first cycle) Grade 3 treatment emergent AE were: • Infections: 3 (7%): (1 with CMV pneumonia, and H1N1 pneumonia, 1 with CMV pericarditis and 1 with sepsis caused by Klebsiella pneumoniae neutropenic fever) • Neutropenia: 3 (7%) • Peripheral neuropathy: 2 (5%) • Febrile neutropenia: 1 (2%) There were no grade 4 toxicities **Subgroups** *Subgroup: SCT post BVB* Out of 15 patients who underwent SCT post BVB: 9 patients underwent SCT (7 HDT-ASCT & 2 allo-SCT) after 4 cycles of BVB, 7 in CR and 2 in PR. 8 patients are alive and in CR at the time of this analysis, while 1 was lost to follow-up. 6 patients underwent SCT (1 HDT-ASCT & 5 allo-SCT) after ≥ 6 cycles of BVB, 5 in CR and 1 in PR. 3 patients are alive in treatment-free remission, 2 relapsed after SCT (1 ASCT & 1 allo-SCT) and received, respectively, anti-PD-1 therapy as a bridge to allo-SCT and anti-PD-1 therapy followed by BeGEV as palliative therapy. The third patient	(DS) was considered indicative of CR. One patient discontinued treatment after one cycle due to febrile neutropenia and diarrhoea and was excluded from the response outcomes. Survival outcomes were calculated using the Kaplan-Meier method. **Source of funding:** Not reported

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			died due to post-allo-SCT infectious complications. *Subgroup: Non-SCT post BVB* 8 patients achieved CR, but did not undergo SCT. 4 are still in remission, while 4 relapsed 5, 6, 16 and 22 months after completing BVB. Among the latter, 3 are currently receiving an anti-PD-1 therapy and 1 received DHAP chemotherapy followed by HDT-ASCT. 7 patients attained PR and did not undergo ASCT consolidation. Two of them achieved CR with additional BV or bendamustine monotherapy, 4 received anti-PD-1 therapy, and one died because of CMV pericarditis. *Subgroup: SCT vs non-SCT after BVB* **Progression-free survival** *"No statistically significant differences were observed between BVB responsive patients who received ASCT or allo-SCT and those who did not, although there was a trend towards longer PFS in transplanted patients (not reached vs 28 months)"*	
O'Connor OA, Lue JK, Sawas A, Amengual JE, Deng C, Kalac M, et al. Brentuximab vedotin plus bendamustine in relapsed or refractory Hodgkin's lymphoma: an international, multicentre,	Adults with relapsed/refractory CD30+ biopsy proven HL or ALCL **Inclusion criteria** • ECOG performance status ≤2 • ≥ 18 years	**Interventions** BVB combination therapy	Duration of follow-up not reported **Critical outcomes**	This study was appraised using the Joanna Briggs checklist for case series. 1.YES 2.YES 3.YES 4.UNCLEAR

Study details	Population	Interventions	Study outcomes	Appraisal and funding
single-arm, phase 1-2 trial. Lancet Oncol. 2018;19(2):257-66. **Study location** Canada (2 centres) & USA (1 centre) **Study type** Single-arm trial (Phase I-II) **Study aim** To explore the safety and clinical activity of BV and bendamustine in combination in patients with relapsed or refractory Hodgkin Lymphoma Study dates **Study dates** 26 July 2012 to 31 May 2017	• Documented adequate organ and marrow function defined as: ANC > 1000; platelet count > 50,000; liver function tests (AST/ALT) < 2.0 x institutional upper limit of normal; total bilirubin < 1.5 x institutional limit; creatinine clearance > 50 mL/min. • Patients had an estimated life expectancy of 6 months or more Phase I only: • Developed progressive disease following or after declining ASCT, or had at least two prior multi-agent chemotherapy regimens (if they are not ASCT candidates) • Patients were required to have measurable or evaluable disease Phase II only:	*Phase I:* 3+3 dose escalation design[75] Cohort 1: starting dose of 1.2 mg/kg BV and 70mg/m^2 of bendamustine (n=7) Cohort 2: 1.2 mg/kg BV and 80mg/m^2 of bendamustine (n=3) Cohort 3: 1.8 mg/kg BV and 80mg/m^2 of bendamustine (n=7) Cohort 4: 1.8 mg/kg BV and 90mg/m^2 of bendamustine (n=11) *Phase II:* BV at a dose of 1.8 mg/kg and bendamustine at a dose of 90 mg/m^2 Median number of cycles: 5 (range 2 to 6) **Comparators** None	**Overall survival[76]** 1-year OS Phase I (n=28): NR Phase II (n=37): 86% (32 of 37 patients) All (n=65): NR 2-year OS Phase I (n=28): NR Phase II (n=37): 82% (30 of 37 patients), All (n=65): NR Median OS Phase I (n=28): 43.3 months (95% CI 11.3 to not reached) Phase II (n=37): Not reached All (n=65): NR **Response rate[77]** ORR[78] Phase I (n=28): 17 (61%, 95% CI 41 to 79) Phase II (n=37): 29 (78%, 95% CI 62 to 91)	5.UNCLEAR 6.YES 7.YES 8.YES 9.NO 10.YES **Other comments:** This paper reports on a Phase I-II single arm trial carried out across three centres in Canada and the USA. Inclusion and exclusion criteria were clearly defined but it was not clear if patient recruitment had been consecutive and complete. In Phase I, 30 patients were screened, with 2 screen fails leaving 28 patients to be included. All 28 patients were eligible for the safety analysis, and 27 for response, excluding one patient due to G-CSF during Cycle 1. In Phase II, 41 patients were screened, with 4 screen fails leaving 37 patients to be included. Of the 37 patients, 36 were evaluable for response, excluding one patient who was discontinued

[75] Three patients are initially enrolled into a given dose cohort. If there is no dose-limiting toxicity seen in any of these participants, the trial proceeds to enrol additional participants into the next higher dose cohort. This process continues until dose-limiting toxicities (DLTs) are observed in at least one patient. An additional three patients are accrued into that same dose cohort. Development of DLTs in two or more out of six patients at a specific dose level indicates that the maximum tolerated dose (MTD) has been exceeded. Further dose escalation is not pursued, and the prior dose level is expanded to six patients. If there is no more than one patient who experiences a DLT among those six patients, that dose level is considered the MTD

[76] Defined as the time from randomisation to the date of death due to any cause or last date of contact

[77] The paper states that one patient was excluded from the response outcomes in phase I due to G-CSF during Cycle 1 and one patient was excluded from the response outcomes in phase 2 due to being discontinued from the study in Cycle 2 due to toxicity. The denominators used to calculate the response % included these excluded patients in an intention to treat analysis.

[78] Defined as the percentage of patients who achieved a confirmed complete or partial response. Disease response was assessed by CT or PET/CT according to the International Harmonization Project Group 2007 Revised Response Criteria for Malignant Lymphoma after cycle 3 and after cycle 6

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	• Had relapsed or refractory disease after one line of therapy. • Eligible ALCL patients were required to have relapsed after at least one prior multi-agent chemotherapy regimen and if they were not eligible for or have declined ASCT **Exclusion criteria** • Previously treated with BVB combination, but were eligible if they had received either as a single agent • Systemic steroids were required to be stabilised to ≤10 mg/day 7 days prior to the initiation of trial • Known cerebral or meningeal disease, active concurrent malignancy, pre-existing neuropathy grade 3 or greater, HIV, hepatitis B, or C, were pregnant or nursing or had uncontrolled intercurrent **Total sample size** n=65		All (n=65): 46 (71%, 95% CI 58 to 81) Number of patients with: • Complete response Phase I (n=28): 5 (18%) Phase II (n=37): 16 (43%) All (n=65): 21 (32%) • Partial response Phase I (n=28): 12 (43%) Phase II (n=37): 13 (35%) All (n=65): 25 (38%) • Stable disease Phase I (n=28): 4 (14%) Phase II (n=37): 5 (14%) All (n=65): 9 (14%) • Progression of disease Phase I (n=28): 6 (21%) Phase II (n=37): 3 (8%) All (n=65): 9 (14%) • Not evaluable Phase I (n=28): 1 (4%) Phase II (n=37): 0 (0%) All (n=65): 1 (2%) Duration of response[79] Phase I (n=28): 4.3 months (95% CI 0 to 7.1) Phase II (n=37): 3.95 months (95% CI 7.5 to not reached) All (n=65): NR	from the study in Cycle 2 due to toxicity. It should be noted, that one patient in Phase I had ALCL and was therefore out of scope for this review. Furthermore, the range of prior therapies was 1 to 8 (median 3) in the Phase I and therefore some patients with one prior therapy will be out of scope for this review (number not reported). All had at least two prior therapies for Phase II. The majority of patients had undergone some form of stem cell transplant. The primary aim of the Phase I study was to identify the maximum tolerated dose and dose limiting toxicity and patients. The doses in Phase I started at a dose of 1.2 mg/kg for BV escalating to a dose of 1.8 mg/kg and for bendamustine a starting dose of 70 mg/m^2 escalating to 90 mg/m^2. Therefore some patients were not on the recommended dose of BVB. Patients in Phase II were on BV at a dose of 1.8 mg/kg and bendamustine at a dose of 90 mg/m^2. The duration of follow-up was not reported. Efficacy outcomes were evaluated after cycle 2 and 6. Tumour assessment was performed clinically every 3 to 6 months until progression of disease and/or subsequent therapy. Analyses were based on an intention to treat analysis.

[79] Defined as the time from documentation of a response to treatment to the first documentation of tumour progression or death due to any cause whichever comes first

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	Phase I: n=28 Phase II: n=37 **Baseline characteristics** *Phase I* Median age: 38 years (range 25 to 70) Male: 18 (64%) Ethnicity: White, non-Hispanic: 18 (64%) White Hispanic: 0 (0%) Black, non-Hispanic: 3 (11%) Asian/Indian/Pacific Islander: 1 (4%) Other: 6 (21%) Disease: HL: 27 (96%) ALCL: 1 (4%) Prior therapy: Median: 4 (range 1 to 12) ABVD/BEACOPP/EVA: 27 (96%) Platinum based: 28 (100%) Autologous stem cell transplant: 21 (75%) Allogeneic transplant: 2 (7%) Radiotherapy: 12 (43%) Alkylator based: 15 (54%) Lenalidomide: 9 (32%) Vinblastine: 10 (36%) Gemcitabine based: 9 (32%)		**Important outcomes** **Progression-free survival[80]** 1-year PFS Phase I (n=28): NR Phase II (n=37): 25 (67%) All (n=65): NR 2-year PFS Phase I (n=28): NR Phase II (n=37):23 (62%) All (n=65): NR Median PFS Phase I (n=28): 7.5 months (95% CI 4.8 to 12.1) Phase II (n=37): Not reached All (n=65): NR **Safety** Toxicities of any grade *Phase I (n=28)* Most common all grades adverse events (>25%): Fatigue: 15 (54%) Nausea: 15 (54%) Vomiting: 10 (36%) Dyspnoea: 10 (36%) Peripheral sensory neuropathy: 9 (32%)	Survival outcomes were calculated using the Kaplan-Meier method **Source of funding:** Seattle Genetics, The Lymphoma Research Fund of Columbia University and National Center for Advancing Translational Sciences, National Institutes of Health (Grant Number UL1TR001873) provided research support. Teva provided bendamustine

[80] Defined as the time from randomisation until disease progression or death due to any cause, whichever occurred first

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	Brentuximab vedotin: 8 (29%) HDAC inhibitor: 5 (18%) Experimental drug: 4 (14%) Etoposide: 2 (7%) *Phase II* Median age: 34 years (range 18 to 72) Male: 23 (62%) Ethnicity: White, non-Hispanic: 25 (68%) White Hispanic: 1 (3%) Black, non-Hispanic: 2 (5%) Asian/Indian/Pacific Islander: 5 (14%) Other: 4 (11%) Disease: HL: 37 (100%) ALCL: 0 (0%) Prior therapy: Median: 5 (range 2 to 12) ABVD/BEACOPP/EVA: 37 (100%) Platinum based: 29 (78%) Autologous stem cell transplant: 21 (57%) Allogeneic transplant: 1 (3%) Radiotherapy: 17 (46%) Alkylator based: 2 (5%) Lenalidomide: 3 (8%) Vinblastine: 2 (5%) Gemcitabine based: 1 (3%)		Diarrhoea: 8 (29%) Pruritus: 8 (29%) Cough: 8 (29%) Constipation: 7 (25%) Fever: 7 (25%) *Phase II (n=37)* Fatigue: 25 (68%) Nausea: 25 (68%) Fever: 15 (41%) Diarrhoea: 14 (38%) Vomiting: 12 (32%) Rash maculopapular: 12 (32%) Grade 1 toxicities *Phase I (n=28)* Chills: 6 (21%) Diarrhoea: 6 (21%) Pain: 6 (21%) Dysguesia: 5 (18%) Dyspnoea: 5 (18%) Fatigue: 5 (18%) Fever: 5 (18%) Nausea: 5 (18%) Constipation: 4 (14%) Cough: 4 (14%) Headache: 4 (14%) Abdominal pain: 4 (14%) Dyspepsia: 4 (14%) Pruritis: 4 (14%) Rash maculopapular: 3 (11%) Back pain: 3 (11%)	

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	BV: 3 (8%) HDAC inhibitor: 0 (0%) Experimental drug: 3 (8%) Etoposide: 0 (0%)		Hot flashes: 3 (11%) Hyperhidrosis: 3 (11%) Nasal congestion: 3 (11%) Sore throat: 3 (11%) Vertigo: 3 (11%) Anxiety: 2 (7%) Vomiting: 2 (7%) Infusion-related reaction: 1 (4%) *Phase II (n=37)* Nausea: 20 (54%) Diarrhoea: 10 (27%) Fatigue: 10 (27%) Dyspnoea: 8 (22%) Headache: 7 (19%) Constipation: 6 (16%) Cough: 6 (16%) Pain: 6 (16%) Rash maculopapular: 6 (16%) Fever: 5 (14%) Vomiting: 5 (14%) Dysguesia: 4 (11%) Dyspepsia: 4 (11%) Chills: 3 (8%) Vertigo: 3 (8%) Anxiety: 1 (3%) Myalgia: 2 (5%) Nasal congestion: 2 (5%) Grade 2 toxicities	

			Phase I (n=28) Fatigue: 10 (36%) Nausea: 10 (36%) Peripheral sensory neuropathy: 9 (32%) Vomiting: 8 (29%) Cough: 4 (14%) Pruritis: 4 (14%) Diarrhoea: 2 (7%) Constipation: 3 (11%) Fever: 2 (7%) Dyspnoea: 5 (18%) Anxiety: 1 (4%) *Phase II (n=37)* Fatigue: 15 (41%) Fever: 10 (27%) Vomiting: 7 (18%) Pruritis: 6 (16%) Rash maculopapular: 6 (16%) Nausea: 5 (14%) Lung infection: 5 (14%) Diarrhoea: 4 (11%) Abdominal pain: 4 (11%) Infusion-related reaction: 4 (11%) Back pain: 2 (5%) Anaemia: 2 (5%) Peripheral sensory neuropathy: 2 (5%) Constipation: 1 (3%) Grade 3 toxicities *Phase 1 (n=28)* Anaemia: 5 (18%)	

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			Thrombocytopenia: 4 (14%) Neutropenia: 3 (11%) Infusion-related reactions: 2 (7%) *Phase II (n=37)* Neutropenia: 10 (27%) Lung infection: 5 (14%) Grade 4 toxicities *Phase I (n=28)* None *Phase II (n=37)* Neutropenia: 3 (8%) Patients who had to discontinue drug due to toxicity *Phase I (n=28)* 2 (both at BV dose of 1.8mg/kg and B dose of 90 mg/m^2), including 1 for an infusion related reaction, 1 for an anaphylactic reaction) *Phase II (n=37)* 2 (1 for kidney infection, 1 for dehydration)	
Picardi M, Della Pepa R, Giordano C, Pugliese N, Mortaruolo C, Trastulli F, et al. Brentuximab vedotin followed by	Adults with biopsy-proven CD30-positive R/R[82] classical HL **Inclusion criteria**	**Interventions** BVB combination therapy 3-day outpatient IV infusions of 1.8 mg/kg of BV on day 1 of each 3-week cycle	**Critical outcomes** **Response rate**	This study was appraised using the Joanna Briggs checklist for case series. 1.NO

[82] Failure of ≥1 salvage treatments

Study details	Population	Interventions	Study outcomes	Appraisal and funding
bendamustine supercharge for refractory or relapsed Hodgkin lymphoma. Blood Adv. 2019;3(9):1546-52. **Study location** Italy (1 centre) **Study type** Case series[81] **Study aim** To report a real-life experience on the efficacy and safety of a salvage program based on sequential combination of BV standard dose and bendamustine supercharge for a total of 4 courses in a series of R/R classical HL patients **Study dates** September 2013 to November 2017	• Aged <60 years • Failure of ≥1 salvage treatments **Exclusion criteria** Not reported **Total sample size** N=20 **Baseline characteristics** Median age: 40 years (range 23 to 54) Male: 8 (40%) Histological subtypes: • Nodular sclerosis: 16 (80%) • Mixed cellularity: 3 (15%) • Lymphocyte rich: 1 (5%) Frontline therapy received: • ABVD, 4 courses: 5 (25%) • ABVD, 6 courses: 15 (75%) • Radiotherapy after ABVD: 6 (30%) Response to frontline therapy: • Primary refractory: 11 (55%) • Relapsed: 9 (45%)	combined in sequence with bendamustine (at least 24 hours after BV, on days 2 and 3 of the treatment cycle at a fixed dose of 120 mg/m^2 per day All patients underwent 4 courses of BVB: median-dose intensity during sequential therapy was 100% (range, 88.6% to 102.4%) for BV and 100% (range, 88.7% to 102.4%) for bendamustine **Comparators** None	At a median of 5 (range 5 to 6) weeks after the 4th cycle of immune-chemotherapy cycle Complete metabolic response (CMR)[83]: 20 (100%) DS scores of: • 1: 8 patients • 2: 8 patients • 3: 4 patients 18 patients achieved 100% decrease in lymph node size (as evaluated by morphologic imaging (CT scans) 2 patients relapsed after 13 and 33 months, respectively. Both had received ASCT after BVB. One of them was refractory to prior treatment with BV as single agent. The 2 patients had residual tissue in the initial mediastinal bulky site with a DS score of 3 at FDG-PET scans following BVB **Eligibility for stem cell transplant** After 4 cycles of BVB Bridge to ASCT, n: 14 Bridge to allo-SCT, n: 4 **Important outcome** **Progression free survival[84]**	2.YES 3.YES 4.YES 5.YES 6.YES 7.YES 8.YES 9.NO 10.UNCLEAR **Other comments:** This paper reports on a case series of 20 R/R classical HL patients receiving a BVB regimen consisting of BV standard dose and bendamustine at a supercharge dose of 120 mg/m^2 per day after failure of ≥1 salvage treatments at one centre in Italy. Limited inclusion and exclusion criteria were reported. The paper reported that consecutive biopsy-proven CD30-positive R/R classical HL patients scheduled to receive salvage treatment with BVB supercharge regimen were included. The response evaluation was assessed using PET/CT. Response evaluation was performed after at least two cycles of combination treatment and repeated every two cycles. PET-CT scans were evaluated four to

[81] The paper describes the study as a real life study. It states that consecutive eligible patients from September 2013 to November 2017 were included. The paper does not specify whether the paper is retrospective or prospective
[83] Defined as a FDG-PET-negative result (DS score ≤3)
[84] Defined as the time from BVB first dose to disease progression/relapse or to death from any cause

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	Number of previous treatments: • 2: 5 (25%) • 3-4: 14 (70%) • 4: 1 (5%) • Median (range): 3 (2 to 6) Previous salvage therapy: • IGEV: 16 (80%) • DHAP: 7 (35%) • BV: 5 (25%) • BEACOPP: 1 (5%) • Radiotherapy: 1 (5%) Transplant: • ASCT: 5 (25%) Characteristics of disease at the time of BVB start: • ≥3 nodal sites involved: 12 (60%) • Extranodal involvement: 10 (50%) • Mediastinal bulky: 6 (30%) • Bone marrow involvement: 1 (5%) • LDH > normal limits: 7 (35%) • ESR >50: 6 (30%)		Median follow-up of 27 months (range 4 to 68) 2-year PFS: 93.7% (95% CI 62.7 to 99.6) **Safety** Length of f/up assumed to be the same as that reported for survival outcomes (median follow-up of 27 months (range 4 to 68)) Number of patients experiencing treatment-related adverse (grade 3 or 4): 10 (50%) Most common grade ≥3 haematologic toxicity was neutropenia (3 patients), which required supplemental administrations of granulocyte-colony stimulating factors (G-CSF) Most common grade ≥3 extra-haematologic toxicity was CMV reactivation with viremia (median CMV-DNA, 1810 IU/mL; range, 620 to 170 000 IU/mL) with fever (5 patients), which was successfully treated with pre-emptive therapy with valganciclovir Number of serious infusion related reactions (both during cycle 2 of combination therapy) with fever, chills, and dyspnoea: 2 (10%). Number of patients temporarily discontinuing therapy due to treatment-related adverse events: 8 (40%) **Subgroups**	six weeks after treatment for response assessment according to the Deauville five-point scale. Statistical methods were not reported. **Source of funding:** Not reported

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			Subgroup: ASCT post BVB (n=14) **Response rate** Number of patients relapsing: 2 Two patients relapsed after 13 and 33 months, respectively. The 2 patients had residual tissue in the initial mediastinal bulky site with a DS score of 3 at FDG-PET scans following BVB	
Pinczes LI, Szabo R, Illes A, Foldeak D, Piukovics K, Szomor A, et al. Real-world efficacy of brentuximab vedotin plus bendamustine as a bridge to autologous hematopoietic stem cell transplantation in primary refractory or relapsed classical Hodgkin lymphoma. Ann Hematol. 2020;99(10):2385-92. **Study location** Hungary (4 centres) **Study type** Retrospective case series **Study aim** To evaluate the safety and efficacy of BVB combination therapy as a bridge to	Adults with R/R[85] classical HL **Inclusion criteria** • Aged 18 years or older • Histologically confirmed diagnosis of classical HL • Relapsed or refractory disease following standard first-line polychemotherapy • Received at least 2 cycles of a standard salvage chemotherapy regimen before the administration of BVB **Exclusion criteria**	**Interventions** BVB combination therapy followed by ASCT 1 to 6 cycles of BVB with a dose of 1.8 mg/kg IV BV on day 1 and 90 mg/m^2 of IV bendamustine on each of days 1 and 2 of a 21-day cycle. ASCT with BEAM (carmustine, etoposide, cytarabine, and melphalan) conditioning regimen Patients received a median of 3 (range 1 to 6) cycles of BVB **Comparators** None	**Critical outcomes** **Overall survival[86]** Median follow-up of 17 months (range 2 to 40) 2-year OS: 93%[87] **Response rate[88]** At end of BVB treatment (median of 3 (range 1 to 6) cycles) ORR: 92.6% Complete response, n (%): 29 (70.7%) Partial response, n (%): 9 (21.9%) **Eligibility for stem cell transplant** N/A Only patients who underwent ASCT after receiving BVB were included in the case series	This study was appraised using the Joanna Briggs checklist for case series. 1.NO 2.YES 3.YES 4.UNCLEAR 5.UNCLEAR 6.YES 7.YES 8.YES 9.NO 10. NO **Other comments:** This paper reports on a retrospective case series of 41 R/R classical HL patients receiving a BVB salvage therapy before ASCT in patients who had previously

[85] Failure after at least one standard salvage chemotherapy regimen made relapsed or refractory classical HL patients eligible for BVB therapy
[86] Calculated from the day of ASCT to the last follow-up visit or death
[87] Paper reports this statistic a "median" 2-year survival but the result is reported as a % not months so it is more likely to be a 2-year survival rate
[88] Evaluated regarding PET/CT status according to the Lugano Classification. A dedicated PET/CT scan was performed after cycle 2 of BVB and later as it was deemed necessary

Study details	Population	Interventions	Study outcomes	Appraisal and funding
transplantation in R/R classical HL patients who previously received 2 or more multiagent chemotherapy regimens **Study dates** 1 January 2016 to 31 December 2018	• The paper reported that no exclusion criteria were determined regarding marrow and other organ function, ECOG performance status, or a total number of previous therapies received. **Total sample size** N=41 **Baseline characteristics** Median age: Not reported Male: 25 (61%) Histological subtypes: • Mixed cellularity: 6 (14.6%) • Nodular sclerosis: 25 (61%) • Lymphocyte-rich: 5 (12.2%) • Lymphocyte-depleted: 1 (2.4%) • Not determined: 4 (9.8%) Refractory: 28 (68.3%) Relapse ≤12 months: 9 (22%) Relapse >12 months: 4 (9.7%) Extranodal involvement: 8 (19.5%)		29 (70.8%) patients were PET-negative (Deauville score 1–3) before ASCT 12 (29.2%) patients were PET-positive (Deauville score 4–5) before ACT Number of treatment cycles with BVB required prior to transplant: median of 3 (range 1 to 6) cycles **Important outcomes** **Progression-free survival[89]** Median follow-up of 17 months (range 2 to 40) 2-year PFS: 62%[90] **Safety** Length of f/up assumed to be the same as that reported for survival outcomes (median follow-up of 17 months (range 2 to 40)) Number of patients experiencing treatment-related AEs of any grade: 24 (58.5%) Most common AEs were: • Neutropenia (17%) • Peripheral neuropathy (12.2%) • Infusion-related reactions with fever, chills, flushing, or pruritus: 12.2% Number of patients experiencing grade 3 AEs: 3 (7.3%). These were:	received 2 or more multiagent chemotherapy regimens at 4 centres in Hungary. The aim of the study was to evaluate the safety and efficacy of BVB combination therapy as a bridge to transplantation in R/R classical HL patients. All the patients included in the series received ASCT after BVB. Survival outcomes were calculated from the day of ASCT rather than BVB initiation. Therefore although not explicitly stated in the inclusion criteria it appears that the case series only included patients who had ASCT after salvage BVB and therefore it is not possible to evaluate the PICO outcome eligibility for stem cell transplant. It was not clear if patient recruitment had been consecutive and complete. Response to the salvage therapies was assessed using the 2016 Refinement of the Lugano Classification Lymphoma Response Criteria. A dedicated PET/CT scan was performed after cycle 2 of BVB combination therapy and later as it was deemed necessary. PET-negative patients (Deauville score 1–3) underwent ASCT at any time after cycle 2, while PET-positive (Deauville score 4–5) patients were

[89] Defined as the time from ASCT to disease progression, to relapse, or to death
[90] Paper reports this statistic as “median” 2-year PFS but the result is reported as a % not months so it is more likely to be a 2-year PFS rate

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	B symptoms: 15 (36.6%) Number of salvage therapies preceding BVB: • 2: 24 (58.5%) • ≥3: 17 (41.5%) • Median: 3 (range 1 to 6)		Neutropenia: 2 (4.8%) Peripheral neuropathy: 1 (2.4%) Number of patients experiencing grade 4 AEs: 0 Number of patients discontinuing therapy due to treatment related AEs: 1 patient (discontinued bendamustine due to severe, treatment-related neutropenia)	administered further antitumour therapy. Two patients were lost to follow-up and these patients were included in the analyses. Survival outcomes were reported as medians but were given as % so have been included here as 2-year overall survival rate and progression free rate. No confidence intervals were reported. Survival outcomes were calculated using the Kaplan-Meier method **Source of funding:** Open access funding provided by University of Debrecen.
Radhakrishnan VS, Bajaj R, Raina V, Kumar J, Bhave SJ, Sukumaran Nair RK, et al. Relapsed refractory Hodgkin lymphoma and brentuximab vedotin-bendamustine combination therapy as a bridge to transplantation: Real-world evidence from a middle-income setting and literature review. Front. 2021;11:796270. **Study location** India (1 centre) **Study type**	Adults and young people with R/R[91] HL **Inclusion criteria** • 15 years or older • R/R HL • Diagnosis of HL based on biopsy performed at diagnosis and/or at relapse • Refractory disease defined as Deauville score > 3, after the completion of first line multi-agent chemotherapy	**Interventions** BV at a dose of 1.8 mg/kg, as IV infusion on day 1 along with bendamustine at a dose of 90 mg/sq.m on days 1 and 2 of a 21-day cycle Median number of cycles of BVB: 3 (range 1 to 6) **Comparators** None	Median follow-up time of 12 months (95% CI 5.2 to18.8) unless stated otherwise **Critical outcomes** **Overall survival[92] (n=30)** 3-year OS: 75% (95% CI 59 to 95) **Response rate[93]** At end of BVB treatment (median of 3 (range 1 to 6) cycles) ORR (n=29): 23 (79%) CMR (n=29), n (%): 18 (62%) Partial response (n=29), n (%): 5 (17%) Stable disease (n=29), n (%): 1 (3%)	This study was appraised using the Joanna Briggs checklist for case series. 1.YES 2.YES 3.YES 4. YES 5.YES 6.YES 7.YES 8.YES 9.NO 10.YES **Other comments:**

[91] Refractory disease defined as Deauville score >3, after the completion of first line multi-agent chemotherapy
[92] Defined as the time from initiation of BVB to the event of death from any cause
[93] Response evaluation with FDG-PET-CT scan was done at the end of 2-3 cycles, based on the international working group (IWG) International Harmonization Project Group 2007 Revised Response Criteria for Malignant Lymphoma, and from 2015 the Lugano classification

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Retrospective case series **Study aim** To audit the real-world efficacy and tolerability of the BVB regimen in R/R HL patients, either as first salvage or in subsequent lines of therapy, from a middle income country setting **Study dates** May 2011 to December 2019	**Exclusion criteria** None reported **Total sample size** N=30 **Baseline characteristics** Median age: 30 years (range 15 to 59) Male: 15 (50%) Subtype: • Mixed cellularity: 6 (20%) • Nodular sclerosis: 6 (20%) • Lymphocyte depleted: 1 (3%) • Not otherwise specified/Unassigned: 17 (57%) First line treatment, N=30: • ABVD: 27 (90%) • ABVD/BEACOPP: 1 (3.3%) • CHOEP: 1 (3.3%) • OEPA: 1 (3.3%) Second line treatment, N=22: • GDP: 14 (47%) • DHAP: 4 (13%) • ICE: 3 (10%) • Other: 1 (3%) • SCT pre BVB, N=5:		Progressive disease (n=29), n (%): 5 (17%) **Eligibility for stem cell transplant[94]** At end of BVB treatment (median of 3 (range 1 to 6) cycles) Number of patients eligible for SCT: 28 2 patients dropped out due to financial constraints and they remain in CMR at data-cutoff, over a follow-up period of 44.6 and 9.9 months each 1 patient (who received RT to achieve CMR) failed autologous stem cell mobilisation and remains in CMR Number of patients who underwent SCT: 25 • 20 post BVB & 5 after subsequent regimens • 17 ASCT & 8 allo-SCT **Important outcomes** **Event free survival[95] (n=30)** 3-year EFS: 58% (95% CI 37 to 90) **Safety** Grade I/II infusion reactions, n (%): 12 (40%) Grade 3/4 treatment related adverse events, n (%):	This paper reports on a retrospective case series of 30 R/R HL patients receiving BVB either as first salvage or in subsequent lines of therapy at one centre in India. Hospital electronic medical records were used to identify all patients, 15 years or older treated with BVB for R/R HL as part of their salvage chemotherapy. It should be noted that while the majority of patients are in scope for this review, the range of prior therapies was 1 to 4 and therefore some patients with one prior therapy are out of scope (8 patients (27%)). Response evaluation with FDG-PET-CT scan was done at the end of 2 to 3 cycles, based on the international working group (IWG) revised response criteria for malignant lymphoma, and from 2015 the Lugano classification. One patient developed febrile neutropenia and died due to septic shock after cycle 1 of BVB and was excluded from response assessment. Survival outcomes were calculated using the Kaplan-Meier method. **Source of funding:** Not reported

[94] Patients with a complete or partial response post BVB were eligible for SCT
[95] Defined as the time from initiation of BVB to the first episode of relapse, progression, or death from any cause

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	• Allo-SCT: 1 (20%) • ASCT: 4 (80%) Treatment lines prior to BVB, N=30: • 1: 8 (27%) • 2: 16 (53%) • 3: 4 (13%) • 4: 2 (7%) Bulky disease prior to BVB: 4 (13%) Extra nodal disease prior to BVB: 6 (20%) B symptoms prior to BVB: 5 (17%)		Neutropenia: 21 grade 3 (70%) (28 of 92 cycles of BVB administered (30.4%)) & 1 grade 4 Peripheral neuropathy: 4 (13%) Clinically detected infection: 4 (13%) Mucositis: 3 (10%) Skin rash: 2 (6.5%) Liver/hepatitis: 2 (6.5%) Discontinuations or treatment delays due to BVB toxicity: 0 **Subgroups** *Subgroup: SCT post BVB (n=25)* Median follow-up of 14.4 months (CI 95% 6 to 23) **Response rate** Response post SCT consolidation (n=23):[96] CMR, n (%): 21 (91%) Partial response, n (%): 0 (0%) Stable disease, n (%): 0 (0%) Progressive disease, n (%): 2 (9%) Overall response rate, n (%): 21 (91%) Of the two patients who had progression post SCT consolidation, 1 died and the other is alive (with disease) on salvage therapy.	

[96] 2 allo-SCT patients died in the peri-transplant period, 1 each of sepsis and acute severe steroid refractory GVHD and were not included in the response rate post SCT consolidation

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			None of the surviving allo-SCT patients (n=5) developed a relapse	
Uncu Ulu B, Dal MS, Yonal Hindilerden I, Akay OM, Mehtap O, Buyukkurt N, et al. Brentuximab vedotin and bendamustine: an effective salvage therapy for relapsed or refractory Hodgkin lymphoma patients. J Chemother. 2022;34(3):190-8. **Study location** Turkey (8 centres) **Study type** Retrospective case series **Study aim** To retrospectively evaluate the response rates, toxicities, and the survival of patients with R/R HL who received the BVB combination in a multi-centre study **Study dates** April 2017 to March 2020	Adults with R/R[97] classical HL **Inclusion criteria** • 18 years or older • ECOG performance status of ≤2 • Histologically confirmed classical HL as the first relapse or primary refractory status. Received BVB therapy as the second line and after • Did not receive BV monotherapy in the first or second line. • If had prior exposure to BV monotherapy as salvage, BVB combination therapy was applied for salvage in the subsequent line and BV was included as a part of the protocol **Exclusion criteria**	**Interventions** BVB combination therapy IV dose of 1.8 mg/kg of BV on day 1 and a dose of 90 mg/m^2 of bendamustine on days 1 and 2 of a 21-day cycle BVB combination was administered for at least 2 and for a maximum of 6 cycles (median of 4 cycles; (range 2 to 6) **Comparators** None	Median follow-up time: 14 months (range 2 to 42) unless stated otherwise **Critical outcomes** **Overall survival[98]** 1-year OS: 85% 2-year OS 72% Median OS: Not reached **Response rate[99]** At end of BVB treatment (median of 4 cycles (range 2 to 6)) ORR: 50 (82%) Complete response rate: 42 (68.9%) Partial response rate: 8 (13.1%) Refractory rate: 11 (18%) **Eligibility for stem cell transplant** At end of BVB treatment (median of 4 cycles (range 2 to 6)) Out of 32 (52.4%) patients given BVB as a bridge to ASCT, 29 had ASCT and 3 had allo-SCT after BVB salvage	This study was appraised using the Joanna Briggs checklist for case series. 1.YES 2.YES 3.YES 4.UNCLEAR 5. UNCLEAR 6.YES 7.YES 8.YES 9.NO 10.YES **Other comments:** This paper reports on a retrospective case series of 61 R/R HL patients treated with BVB as a second-line or beyond salvage regimen across eight centres in Turkey. Inclusion and exclusion criteria were clearly defined but it was not clear if patient recruitment had been consecutive and complete. It should be noted that while the majority of patients are in scope for

[97] Primary refractory disease was defined as not achieving a complete remission or relapsing within three months after conventional treatment
[98] Defined as the period from BVB initiation to death from any cause
[99] The response evaluation was assessed using PET/CT. Response evaluation was performed after at least two cycles of combination treatment and repeated every two cycles. PET-CT scans were evaluated four to six weeks after treatment for response assessment according to the Deauville five-point scale

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	• <18 years old • ECOG performance status of 3/4 • Received BVB therapy as first-line treatment **Total sample size** N=61 **Baseline characteristics** Median age: 29 years (range 18 to 75) Median age of BVB initiation: 33 (range: 18 to 76) years. Male: 35 (57.4%) Primary refractory: 29 (47.5%) Relapsed: n=32 (52.5%) Disease characteristics: • Bulky disease: 7 (11.5%) • B symptoms: 39 (63.9%) • Extranodal disease: 22 (36.1%) • Advanced stage at initial diagnosis: 40 (65.6%) Histology: • Mixed cellularity: 17 (27.9%)		Out of 2 patients given BVB as a bridge to allo-ASCT, 2 had allo-ASCT Out of 18 patients given BVB after ASCT relapse, 7 patients had allo-SCT Number of treatment cycles with BVB required prior to transplant: NR **Important outcomes** **Progression-free survival[100]** 2-year PFS: 60% Median PFS: 26 months (95% CI 13.9 to 38) **Safety** Adverse events (grade 3/4): Neutropenia: 15 (24.6%) Lymphopenia: 25 (40%) Thrombocytopenia: 8 (13.1%) Anaemia: 8 (13.1%) Infusion reaction: 5 (8.2%) Vomiting: 3 (4.9%) Skin reactions: 2 (3.2%) Neuropathy: 4 (6.5%) Lower drug doses due to adverse events: 2 (3.3%) Drug cessation due to adverse events: 10 (16.4%)	this review, the range of treatment line that BVB was given was 2 to 11, and therefore some patients are out of scope (6 patients (9.8%) who were given BVB as second line treatment). The response evaluation was assessed using PET/CT. Response evaluation was performed after at least two cycles of combination treatment and repeated every two cycles. PET-CT scans were evaluated four to six weeks after treatment for response assessment according to the Deauville five-point scale. Survival outcomes were calculated using the Kaplan-Meier method. No confidence intervals were reported for the majority of outcomes. **Source of funding:** Not reported

[100] Defined as the period from BVB initiation to progression or death for any reason

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	• Nodular sclerosis: 40 (65.6%) • Lymphocyte rich: 3 (4.9%) • Lymphocyte depleted: 1 (1.6%) 1st line regimens: • ABVD: 58 (95.1%) • BEACOPP: 1 (1.6%) • Gemcitabine based: 2 (3.3%) 2nd line regimens**:** • Gemcitabine based (GDP, IGEV): 13 (21.3%) • Platinum based (DHAP, ICE): 36 (59%) • IVE (ifosfamide, epirubicin, etoposide): 2 (3.3%) • ABVD/BEACOPP: 4 (6.6%) • BVB: 6 (9.8%) Transplants: • ASCT: 50 (81.9%) • Allo-SCT: 12 (19.7%) Median time from diagnosis to BVB initiation: 26 months (range: 4 to 237) BVB line, median 3 (2–11): • Second line 6 (9.8%) • Third line 25 (41%)		**Subgroups** *Subgroup: Transplant-ineligible (n=9):* **Overall survival** ASCT (ref ASCT received) Hazard ratio: 0.215 (95% CI 0.04 to 1.11; p=0.07) **Response rate** ORR: 9 (100%) Complete response rate: 77.7% *Subgroup: ASCT post BVB (n=32)* **Response rate** Complete remission: 22 Partial remission: 2 Refractory disease: 7 *Subgroup: ASCT prior to BVB (n=18)* **Response rate** Complete remission:14 Refractory disease: 4 **Eligibility for stem cell transplant** Allo-SCT: 7	

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	• Fourth line 30 (49.2%) BVB position: • Prior to ASCT: 32 (52.4%) • Relapsed after ASCT: 18 (29.6%) • Prior to Allo-SCT: 2 (3.2%) • Transplant ineligible: 9 (14.8%)			

Abbreviations

ABVD: doxorubicin, bleomycin, vinblastine, dacarbazine; AE: adverse event; ALCL: anaplastic large cell lymphoma; allo-SCT: allogeneic stem cell transplant; ALT: alanine aminotransferase; ANC: absolute neutrophil count; anti-PD-1: anti-programmed cell death protein 1; ASCT: autologous stem cell transplant; AST: aspartate aminotransferase; BEACOPP: bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; BeGEV: bendamustine, gemcitabine, vinorelbine; BV: brentuximab vedotin; BVB: brentuximab vedotin and bendamustine; CD30: cluster of differentiation 30; CHOEP: cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone; CI: confidence interval; CMR: complete metabolic response; CMV: cytomegalovirus; CR: complete response; CT: computed tomography; DHAP: dexamethasone, cytarabine and cisplatin; DS: Deauville score; ECOG: Eastern Cooperative Oncology Group; EFS: event-free survival; ESR: erythrocyte sedimentation rate; EVA: etoposide, vincristine, doxorubicin; FDG-PET: 18-F fluorodeoxyglucose positron emission tomography; G-CSF: granulocyte colony-stimulating factor; GDP: gemcitabine, dexamethasone, cisplatin; HDAC: histone deacetylase; HL: Hodgkin lymphoma; HR: hazard ratio; ICE: ifosfamide, carboplatin and etoposide; IGEV: ifosfamide, gemcitabine, vinorelbine; IQR: interquartile range; IV: intravenous; kg: kilogram; LDH: lactate dehydrogenase; mg: milligram; NR: not reported; OEPA: vincristine, etoposide, prednisone, doxorubicin; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; PR: partial response; R/R: relapsed/refractory; SCT: stem cell transplant; SD: stable disease

Appendix F Quality appraisal checklists

JBI Critical Appraisal Checklist for Case Series

1. Were there clear criteria for inclusion in the case series?
2. Was the condition measured in a standard, reliable way for all participants included in the case series
3. Were valid methods used for the identification of the condition for all participants included in the case series?
4. Did the case series have consecutive inclusion of participants?
5. Did the case series have complete inclusion of participants?
6. Was there clear reporting of the demographics of the participants in the study?
7. Was there clear reporting of clinical information of the participants?
8. Were the outcomes or follow up results of cases clearly reported?
9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?
10. Was statistical analysis appropriate?

Appendix G GRADE profiles

For abbreviations and footnotes see end of tables

Outcome measure, units and timepoint in study (for continuous outcomes indicate if benefit is indicated by higher or lower result)									
QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	BVB	No comparator	Result		
Overall survival (1 phase I–II trial & 5 case series)									
1-year overall survival[a], median follow-up 14 months (range 2 to 42); %									
Retrospective case series Uncu Ulu et al 2022	Very serious limitations[1]	Very serious indirectness[2]	Not applicable	Not calculable	61	0	85%	Critical	Very low
1-year overall survival[b], follow-up not reported; n (%)									
Single-arm study (phase I–II trial) O'Connor et al 2022	Very serious limitations[1]	Very serious indirectness[2]	Not applicable	Not calculable	37	0	Phase II: 32 (86%)	Critical	Very low
2-year overall survival, median follow-up 14 months (range 2 to 42); %									
Retrospective case series Uncu Ulu et al 2022	Very serious limitations[1]	Very serious indirectness[2]	Not applicable	Not calculable	61	0	72%	Critical	Very low

2-year overall survival[c], median follow-up 17 months (range 2 to 40); %									
Retrospective case series Pinczes et al 2020	Very serious limitations[3]	Serious indirectness[4]	Not applicable	Not calculable	41	0	93%	Critical	Very low
2-year overall survival[d], median follow-up 19 months (95% CI 17.4 to 18.5); %									
Retrospective case series Iannitto et al 2020	Very serious limitations[1]	Very serious indirectness[2]	Not applicable	Not calculable	47	0	72%	Critical	Very low
2-year overall survival, follow-up not reported; %									
Single-arm study (phase I–II trial) O'Connor et al 2022	Serious limitations[5]	Very serious indirectness[2]	Not applicable	Not calculable	37	0	Phase II: 82% (95% CI 30 of 37 patients)	Critical	Very low
3-year overall survival[e], median follow-up 12 months (95% CI 5.2 to 18.8); %									
Retrospective case series Radhakrishnan et al 2021	No serious limitations	Very serious indirectness[2]	Not applicable	Not calculable	30	0	75% (95% CI 59 to 95)	Critical	Very low

Median overall survival, median follow-up 14 months (range 2 to 42); %									
Retrospective case series Uncu Ulu et al 2022	Serious limitations[5]	Very serious indirectness[2]	Not applicable	Not calculable	61	0	Not reached	Critical	Very low
Median overall survival, median follow-up 19 months (95% CI 17.4 to 18.5); months									
Retrospective case series Iannitto et al 2020	Serious limitations[5]	Very serious indirectness[2]	Not applicable	Not calculable	47	0	Not reached	Critical	Very low
Median overall survival, median follow-up 38 months (range 4.2 to 64, IQR 26.7); months									
Retrospective case series Moretti et al 2022	Serious limitations[7]	Very serious indirectness[2]	Not applicable	Not calculable	41	0	Not reached	Critical	Very low
Median overall survival, follow-up time not reported; months									
Single-arm study (phase I–II trial) O'Connor et al 2022	Serious limitations[5]	Very serious indirectness[2]	Not applicable	Not calculable	Phase I: 28: Phase II: 37:	0	Phase I: 43.3 months (95% CI 11.3 to not reached) Phase II: Not reached	Critical	Very low
Response rate (1 phase I–II trial & 4 case series)									
Overall response rate (complete and partial responders)[f], end of BVB treatment (median of 3 cycles (range 1 to 6); %									
Retrospective case series	Very serious limitations[3]	Serious indirectness[4]	Not applicable	Not calculable	41	0	Overall response rate: 92.6%	Critical	Very low

Pinczes et al 2020							• Complete response, n (%): 29 (70.7) • Partial response, n (%): 9 (21.9)		
Overall response rate[g], end of BVB treatment (median of 3 cycles (range 1 to 6); %									
Retrospective case series Radhakrishnan et al 2021	Serious limitations[6]	Very serious indirectness[2]	Not applicable	Not calculable	29	0	Overall response rate: 79% • Complete metabolic response, n (%): 18 (62%) • Partial response, n (%): 5 (17) • Stable disease, n (%): 1 (3) • Progressive disease, n (%): 5 (17)	Critical	Very low
Overall response rate[h], end of BVB treatment (median 4 cycles (range 2 to 6); n (%)									
Retrospective case series Uncu Ulu et al 2022	Very serious limitations[3]	Very serious indirectness[2]	Not applicable	Not calculable	61	0	Overall response rate: 50 (82%) • Complete response rate: 42 (68.9%) • Partial response rate: 8 (13.1%) • Refractory rate: 11 (18%)	Critical	Very low
Overall response rate[i], end of BVB treatment (median 4 cycles (2.5 to 97.5 percentiles 2 to 7)); %									
Retrospective case series Iannitto et al 2020	Serious limitations[5]	Very serious indirectness[2]	Not applicable	Not calculable	47	0	Overall response rate: 79% (95% CI 64 to 89) • Complete response rate: 49%, (95% CI 34 to 64)	Critical	Very low
Overall response rate[j], end of BVB treatment (up to 8 cycles); %									
Retrospective case series	Serious limitations[7]	Very serious indirectness[2]	Not applicable	Not calculable	40	0	Overall response rate: 75% (95% CI 59 to 86)	Critical	Very low

Moretti et al 2022							• Complete response rate: 50% (95% CI 35 to 66)		
Overall response rate[k], follow-up not reported; %									
Single-arm study (phase I–II trial) O'Connor et al 2022	Serious limitations[5]	Very serious indirectness[2]	Not applicable	Not calculable	Phase I: 28: Phase II: 37: All: 65	0	Phase I: 61% (95% CI 41 to 79) Phase II: 78% (95% CI 62 to 91) All: 71% (95% CI 58 to 81)	Critical	Very low
n achieving complete metabolic response[l]; median of 5 (range 5 to 6) weeks after the 4th BVB cycle; n (%)									
Case series Picardi et al 2019	Very serious limitations[8]	Serious indirectness[4]	Not applicable	Not calculable	20	0	20 (100%) • DS scores of: • 1: 8 patients • 2: 8 patients • 3: 4 patients	Critical	Very low
Duration of response[m], follow-up not reported; months (benefit is indicated by higher result)									
Single-arm study (phase I–II trial) O'Connor et al 2022	Serious limitations[5]	Very serious indirectness[2]	Not applicable	Not calculable	Phase I: 28: Phase II: 37:	0	Phase I: 4.3 months (95% CI 0 to 7.1) Phase II: 3.95 months (95% CI 7.5 to not reached)	Critical	Very low
Eligibility for stem cell transplant (5 case series)									
n of patients eligible[n] for SCT after BVB, median of 3 cycles (range 1 to 6); n									

Retrospective case series Radhakrishnan et al 2021	No serious limitations	Very serious indirectness[2]	Not applicable	Not calculable	30	0	28	Critical	Very low
n of patients undergoing SCT after BVB, median of 3 cycles (range 1 to 6); n									
Retrospective case series Radhakrishnan et al 2021	No serious limitations	Very serious indirectness[2]	Not applicable	Not calculable	30	0	25	Critical	Very low
n of patients undergoing SCT after BVB, 4 cycles; n									
Case series Picardi et al 2019	Very serious limitations[8]	Serious indirectness[4]	Not applicable	Not calculable	20	0	ASCT: 14 allo-SCT: 4	Critical	Very low
n of patients undergoing SCT after BVB, median of 4 cycles (range 2 to 6); n									
Retrospective case series Uncu Ulu et al 2022	Serious limitations[5]	Very serious indirectness[2]	Not applicable	Not calculable	61	0	Out of 32 patients given BVB as a bridge to ASCT, 29 had ASCT and 3 had allo-SCT after BVB salvage Out of 2 patients given BVB as a bridge to allo-ASCT, 2 had allo-ASCT Out of 18 patients given BVB after ASCT relapse, 7 patients had allo-SCT 9 patients were transplant ineligible due to comorbidities prior and post BVB	Critical	Very low
n of patients proceeding to a SCT after BVB, median 4 cycles (2.5 to 97.5 percentiles 2 to 7); n									

Retrospective case series Iannitto et al 2020	Serious limitations[5]	Very serious indirectness[2]	Not applicable	Not calculable	47	0	26	Critical	Very low
n of responding patients undergoing SCT after BVB, up to 8 cycles; n (%)									
Retrospective case series Moretti et al 2022	Serious limitations[7]	Very serious indirectness[2]	Not applicable	Not calculable	41	0	15 (36.6%)	Critical	Very low
Event-free survival (1 case series)									
3-year event-free survival[o], median follow-up time of 12 months (95% CI 5.2 to18.8); %									
Retrospective case series Radhakrishnan et al 2021	No serious limitations	Very serious indirectness[2]	Not applicable	Not calculable	30	0	58% (95% CI 37 to 90)	Important	Very low
Progression-free survival (1 phase I–II trial & 6 case series)									
1-year progression-free survival[p], follow-up not reported; n (%)									
Single-arm study (phase I–II trial) O'Connor et al 2022	Very serious limitations[1]	Very serious indirectness[2]	Not applicable	Not calculable	Phase II: 37:	0	Phase II: 25 (67%)	Important	Very low
2-year progression-free survival[q], median follow-up time: 14 months (range 2 to 42); %									

Retrospective case series Uncu Ulu et al 2022	Very serious limitations[1]	Very serious indirectness[2]	Not applicable	Not calculable	61	0	60%	Important	Very low
2-year progression-free survival[r], median follow-up of 17 months (range 2 to 40); %									
Retrospective case series Pinczes et al 2020	Very serious limitations[3]	Serious indirectness[4]	Not applicable	Not calculable	41	0	62%	Important	Very low
2-year progression-free survival[s], median follow-up of 27 months (range 4 to 68); %									
Retrospective case series Picardi et al 2019	Very serious limitations[8]	Serious indirectness[4]	Not applicable	Not calculable	20	0	93.7% (95% CI 62.7 to 99.6)	Important	Very low
2-year progression-free survival, follow-up not reported; n (%)									
Single-arm study (phase I–II trial) O'Connor et al 2022	Very serious limitations[1]	Very serious indirectness[2]	Not applicable	Not calculable	Phase II: 37:	0	Phase II: 23 (62%)	Important	Very low
Median progression-free survival, median follow-up time: 14 months (range 2 to 42); months									
Retrospective case series	Serious limitations[5]	Very serious indirectness[2]	Not applicable	Not calculable	61	0	26 months (95% CI 13.9 to 38)	Important	Very low

Uncu Ulu et al 2022									
Median progression-free survival[t], median follow-up of 19 months (95% CI: 17.4 to 18.5); months									
Retrospective case series Iannitto et al 2020	Serious limitations[5]	Very serious indirectness[2]	Not applicable	Not calculable	47	0	18 months (95% CI 4.5 to 31.4)	Important	Very low
Median progression-free survival[u], median follow-up of 38 months (range 4.2 to 64, IQR 26.7); months									
Retrospective case series Moretti et al 2022	Serious limitations[7]	Very serious indirectness[2]	Not applicable	Not calculable	41	0	26 months (95% CI 7.2 to not reached)	Important	Very low
Median progression-free survival, follow-up not reported; months									
Single-arm study (phase I–II trial) O'Connor et al 2022	Serious limitations[5]	Very serious indirectness[2]	Not applicable	Not calculable	Phase I: 28: Phase II: 37:	0	Phase I: 7.5 months (95% CI 4.8 to 12.1) Phase II: Not reached	Important	Very low
Safety (1 phase I–II trial & 6 case series)									
Treatment-related AEs of any grade, median follow-up of 17 months (range 2 to 40)[v]; n (%)									
Retrospective case series	Very serious limitations[3]	Serious indirectness[4]	Not applicable	Not calculable	41	0	24 (58.5%)	Important	Very low

Pinczes et al 2020							Most common AEs were: Neutropenia: 17% Peripheral neuropathy: 12.2% Infusion-related reactions with fever, chills, flushing, or pruritus: 12.2%		
Treatment emergent AEs of any grade, median follow-up of 38 months (range 4.2 to 64, IQR 26.7)[R]; n (%)									
Retrospective case series Moretti et al 2022	Serious limitations[7]	Very serious indirectness[2]	Not applicable	Not calculable	41	0	19 (46%)	Important	Very low
Toxicities of any grade, follow-up not reported; n (%)									
Single-arm study (phase I–II trial) O'Connor et al 2022	Serious limitations[5]	Very serious indirectness[2]	Not applicable	Not calculable	Phase I: 28: Phase II: 37	0	Most common adverse events (>25%) Phase I Fatigue: 15 (54%) Nausea: 15 (54%) Vomiting: 10 (36%) Dyspnoea: 10 (36%) Peripheral sensory neuropathy: 9 (32%) Diarrhoea: 8 (29%) Pruritus: 8 (29%) Cough: 8 (29%) Constipation: 7 (25%) Fever: 7 (25%) Phase II Fatigue: 25 (68%) Nausea: 25 (68%) Fever: 15 (41%) Diarrhoea: 14 (38%)	Important	Very low

							Vomiting: 12 (32%) Rash maculopapular: 12 (32%)		
Grade 1 toxicities, follow-up not reported; n (%)									
Single-arm study (phase I–II trial) O'Connor et al 2022	Serious limitations[5]	Very serious indirectness[2]	Not applicable	Not calculable	Phase I: 28: Phase II: 37:	0	Phase I Chills: 6 (21%) Diarrhoea: 6 (21%) Pain: 6 (21%) Dysguesia: 5 (18%) Dyspnoea: 5 (18%) Fatigue: 5 (18%) Fever: 5 (18%) Nausea: 5 (18%) Constipation: 4 (14%) Cough: 4 (14%) Headache: 4 (14%) Abdominal pain: 4 (14%) Dyspepsia: 4 (14%) Pruritis: 4 (14%) Rash maculopapular: 3 (11%) Back pain: 3 (11%) Hot flashes: 3 (11%) Hyperhidrosis: 3 (11%) Nasal congestion: 3 (11%) Sore throat: 3 (11%) Vertigo: 3 (11%) Anxiety: 2 (7%) Vomiting: 2 (7%) Infusion-related reaction: 1 (4%) Phase II Nausea: 20 (54%) Diarrhoea: 10 (27%) Fatigue: 10 (27%) Dyspnoea: 8 (22%)	Important	Very low

							Headache: 7 (19%) Constipation: 6 (16%) Cough: 6 (16%) Pain: 6 (16%) Rash maculopapular: 6 (16%) Fever: 5 (14%) Vomiting: 5 (14%) Dysguesia: 4 (11%) Dyspepsia: 4 (11%) Chills: 3 (8%) Vertigo: 3 (8%) Anxiety: 1 (3%) Myalgia: 2 (5%) Nasal congestion: 2 (5%)		
Grade 2 toxicities, follow-up not reported; n (%)									
Single-arm study (phase I–II trial) O'Connor et al 2022	Serious limitations[5]	Very serious indirectness[2]	Not applicable	Not calculable	Phase I: 28: Phase II: 37:	**0**	Phase I Fatigue: 10 (36%) Nausea: 10 (36%) Peripheral sensory neuropathy: 9 (32%) Vomiting: 8 (29%) Cough: 4 (14%) Pruritis: 4 (14%) Diarrhoea: 2 (7%) Constipation: 3 (11%) Fever: 2 (7%) Dyspnoea: 5 (18%) Anxiety: 1 (4%) Phase II Fatigue: 15 (41%) Fever: 10 (27%) Vomiting: 7 (18%) Pruritis: 6 (16%) Rash maculopapular: 6 (16%)	Important	Very low

							Nausea: 5 (14%) Lung infection: 5 (14%) Diarrhoea: 4 (11%) Abdominal pain: 4 (11%) Infusion-related reaction: 4 (11%) Back pain: 2 (5%) Anaemia: 2 (5%) Peripheral sensory neuropathy: 2 (5%) Constipation: 1 (3%)		
Grade 3 AEs, median follow-up of 17 months (range 2 to 40); n (%)									
Retrospective case series Pinczes et al 2020	Very serious limitations[3]	Serious indirectness[4]	Not applicable	Not calculable	41	0	3 (7.3%). Neutropenia: 2 (4.8%) Peripheral neuropathy: 1 (2.4%)	Important	Very low
Grade 3 treatment emergent AEs, median follow-up of 38 months (range 4.2 to 64, IQR 26.7); n (%)									
Retrospective case series Moretti et al 2022	Serious limitations[7]	Very serious indirectness[2]	Not applicable	Not calculable	41	0	Infections: 3 (7%): (1 with CMV pneumonia, and H1N1 pneumonia, 1 with CMV pericarditis and 1 with sepsis caused by Klebsiella pneumoniae neutropenic fever) Neutropenia: 3 (7%) Peripheral neuropathy: 2 (5%) Febrile neutropenia: 1 (2%)	Important	Very low
Grade 3 toxicities, follow-up not reported; n (%)									
Single-arm study (phase I–II trial) O'Connor et al 2022	Serious limitations[5]	Very serious indirectness[2]	Not applicable	Not calculable	Phase I: 28: Phase II: 37:	0	Phase I Anaemia: 5 (18%) Neutropenia: 3 (11%) Platelet count decreased: 4 (14%) Infusion-related reaction: 2 (7%) Phase II	Important	Very low

							Neutropenia: 10 (27%) Lung infection: 5 (14%)		
Grade 3 or 4 treatment related adverse events, median follow-up time of 12 months (95% CI 5.2 to18.8)[v]; n (%)									
Retrospective case series Radhakrishnan et al 2021	No serious limitations	Very serious indirectness[2]	Not applicable	Not calculable	30	0	Neutropenia: 21 grade 3 (70%) (28 of 92 cycles of BVB administered (30.4%)) & 1 grade 4 Peripheral neuropathy: 4 (13%) Clinically detected infection: 4 (13%) Mucositis: 3 (10%) Skin rash: 2 (6.5%) Liver/hepatitis: 2 (6.5%)	Important	Very low
Grade 3 or 4 AEs, median follow-up time: 14 months (range 2 to 42); n (%)									
Retrospective case series Uncu Ulu et al 2022	Serious limitations[5]	Very serious indirectness[2]	Not applicable	Not calculable	61	0	Neutropenia: 15 (24.6%) Lymphopenia: 25 (40%) Thrombocytopenia: 8 (13.1%) Anaemia: 8 (13.1%) Infusion reaction: 5 (8.2%) Vomiting: 3 (4.9%) Skin reactions: 2 (3.2%) Neuropathy: 4 (6.5%)	Important	Very low
Grade >3 AEs, median follow-up of 19 months (95% CI 17.4 to 18.5)[v]; n (%)									
Retrospective case series Iannitto et al 2020	Serious limitations[5]	Very serious indirectness[2]	Not applicable	Not calculable	47	0	15 (34%)	Important	Very low
Grade 3 or 4 treatment-related AEs, median follow-up of 27 months (range 4 to 68)[v]; n (%)									
Retrospective case series	Very serious limitations[8]	Serious indirectness[4]	Not applicable	Not calculable	20	0	10 (50%)	Important	Very low

Picardi et al 2019									
Grade 4 AEs, median follow-up of 17 months (range 2 to 40); n									
Retrospective case series Pinczes et al 2020	Very serious limitations[3]	Serious indirectness[4]	Not applicable	Not calculable	41	0	0	Important	Very low
Grade 4 toxicities, median follow-up of 38 months (range 4.2 to 64, IQR 26.7); n									
Retrospective case series Moretti et al 2022	Serious limitations[7]	Very serious indirectness[2]	Not applicable	Not calculable	41	0	0	Important	Very low
Grade 4 toxicities, follow-up not reported; n (%)									
Single-arm study (phase I–II trial) O'Connor et al 2022	Serious limitations[5]	Very serious indirectness[2]	Not applicable	Not calculable	Phase I: 28: Phase II: 37:	0	Phase I None Phase II Neutropenia: 3 (8%)	Important	Very low
Grade 1 or 2 infusion reactions, median follow-up time of 12 months (95% CI 5.2 to18.8); n (%)									
Retrospective case series Radhakrishnan et al 2021	No serious limitations	Very serious indirectness[2]	Not applicable	Not calculable	30	0	12 (40%)	Important	Very low
Serious infusion related reactions, median follow-up of 27 months (range 4 to 68); n (%)									
Retrospective case series	Very serious limitations[8]	Serious indirectness[4]	Not applicable	Not calculable	20	0	2 (10%)	Important	Very low

Picardi et al 2019									
Discontinuations or treatment delays due to BVB toxicity, median follow-up time of 12 months (95% CI 5.2 to18.8); n									
Retrospective case series Radhakrishnan et al 2021	No serious limitations	Very serious indirectness[2]	Not applicable	Not calculable	30	0	0	Important	Very low
Drug cessation due to AEs, median follow-up time: 14 months (range 2 to 42); n (%)									
Retrospective case series Uncu Ulu et al 2022	Serious limitations[5]	Very serious indirectness[2]	Not applicable	Not calculable	61	0	10 (16.4%)	Important	Very low
Discontinuation of therapy due to treatment related AEs, median follow-up of 17 months (range 2 to 40); n									
Retrospective case series Pinczes et al 2020	Very serious limitations[3]	Serious indirectness[4]	Not applicable	Not calculable	41	0	1 Discontinued bendamustine due to severe, treatment-related neutropenia	Important	Very low
Temporary discontinuation of therapy due to treatment-related AEs, median follow-up of 27 months (range 4 to 68); n (%)									
Retrospective case series Picardi et al 2019	Very serious limitations[8]	Serious indirectness[4]	Not applicable	Not calculable	20	0	8 (40%)	Important	Very low
Discontinuation of therapy, median follow-up of 38 months (range 4.2 to 64, IQR 26.7); n									
Retrospective case series	Serious limitations[7]	Very serious indirectness[2]	Not applicable	Not calculable	41	0	1 (due to febrile neutropenia and diarrhoea after the first cycle)	Important	Very low

Moretti et al 2022									
Lower drug doses due to AEs, median follow-up time: 14 months (range 2 to 42); n (%)									
Retrospective case series Uncu Ulu et al 2022	Serious limitations[5]	Very serious indirectness[2]	Not applicable	Not calculable	61	0	2 (3.3%)	Important	Very low
Interrupting treatment due to grade 4 toxicity, median follow-up of 19 months (95% CI 17.4 to 18.5); %									
Retrospective case series Iannitto et al 2020	Serious limitations[5]	Very serious indirectness[2]	Not applicable	Not calculable	47	0	11%	Important	Very low

Abbreviations

AE: adverse event; allo-SCT: allogeneic stem cell transplant; ASCT: autologous stem cell transplant; BVB: brentuximab vedotin and bendamustine; CI: confidence interval; CMV: cytomegalovirus; DS: Deauville score; IQR: interquartile range; SCT: stem cell transplant

1. Risk of bias: very serious limitations due to unclear reporting of whether the case series included consecutive patients and complete inclusion of patients and limited statistical analysis
2. Indirectness: very serious indirectness due to lack of comparator group and inclusion of some patients who did not meet the PICO definition
3. Risk of bias: very serious limitations due to unclear reporting of inclusion criteria and whether the case series included consecutive patients and complete inclusion of patients and limited statistical analysis
4. Indirectness: serious indirectness due to lack of comparator group
5. Risk of bias: serious limitations due to unclear reporting of whether the case series included consecutive patients and complete inclusion of patients
6. Risk of bias: serious limitations due to limited statistical analysis
7. Risk of bias: serious limitations due to limited reporting of inclusion/exclusion criteria
8. Risk of bias: very serious limitations due to limited reporting of inclusion/exclusion criteria and no reporting of statistical methods

a. Defined as the period from BVB initiation to death from any cause
b. Defined as the time from randomisation to the date of death due to any cause or last date of contact
c. Calculated from the day of ASCT to the last follow-up visit or death
d. Defined as the time from BVB treatment initiation to the date of death from any cause

e. Defined as the time from initiation of BVB to the event of death from any cause
f. Evaluated regarding PET/CT status according to the Lugano Classification. A dedicated PET/CT scan was performed after cycle 2 of BVB and later as it was deemed necessary
g. Response evaluation with FDG-PET-CT scan was done at the end of 2-3 cycles, based on the international working group (IWG) revised response criteria for malignant lymphoma, and from 2015 the Lugano classification
h. The response evaluation was assessed using PET/CT. Response evaluation was performed after at least two cycles of combination treatment and repeated every two cycles. PET-CT scans were evaluated four to six weeks after treatment for response assessment according to the Deauville five-point scale
i. The response revaluation criteria in lymphoma (RECIL) were followed for clinical response coding
j. Responses were assessed using the 2014 Lugano criteria whereby a score of ≤3 on the Deauville 5-point scale was considered indicative of complete response
k. Disease response was assessed by CT or PET/CT according to the Revised Response Criteria for Malignant Lymphoma after cycle 3 and after cycle 6
l. Defined as a FDG-PET-negative result (DS score ≤3)
m. Defined as the time from documentation of a response to treatment to the first documentation of tumour progression or death due to any cause whichever comes first
n. Patients who were ≥ partial response and willing for transplant were eligible for consolidation with AHCT or allo-HCT
o. Defined as the time from initiation of BVB to the first episode of relapse, progression, or death from any cause
p. Defined as the time from randomisation until disease progression or death due to any cause, whichever occurred first
q. Defined as the period from BVB initiation to progression or death for any reason
r. Defined as the time from ASCT to disease progression, to relapse, or to death
s. Defined as the time from BVB first dose to disease progression/relapse or to death from any cause
t. Defined as the time from BVB treatment initiation to the first documentation of progression/relapse or to death from any cause
u. Defined as the time from treatment initiation to progression of disease, relapse, or death from any cause. If none of these events had occurred, PFS was censored at the date of last follow up. Patients undergoing SCT were not censored at the time of consolidation
v. F/up not reported for safety outcomes. Length of f/up assumed to be the same as that reported for survival outcomes

Glossary

Adverse event	Any undesirable event experienced by a person while they are having a drug or any other treatment or intervention, regardless of whether or not the event is suspected to be related to or caused by the drug, treatment or intervention.
Case series	Reports of several patients with a given condition, usually covering the course of the condition and the response to treatment. There is no comparison (control) group of patients.
Clinical importance	A benefit from treatment that relates to an important outcome such as length of life and is large enough to be important to patients and health professionals.
Confidence interval (CI)	A way of expressing how certain we are about the findings from a study, using statistics. It gives a range of results that is likely to include the 'true' value for the population. A wide confidence interval indicates a lack of certainty about the true effect of the test or treatment - often because a small group of patients has been studied. A narrow confidence interval indicates a more precise estimate (for example, if a large number of patients have been studied).
Control group	A group of people in a study who do not have the intervention or test being studied. Instead, they may have the standard intervention. The results for the control group are compared with those for a group having the intervention being tested. The aim is to check for any differences. Ideally, the people in the control group should be as similar as possible to those in the intervention group, to make it as easy as possible to detect any effects due to the intervention.
Cost effectiveness study	An analysis that assesses the cost of achieving a benefit by different means. The benefits are expressed in non-monetary terms related to health, such as life years gained (that is, the number of years by which life is extended as a result of the intervention). Options are often compared on the cost incurred to achieve 1 outcome (for example, cost per life year gained).
GRADE (Grading of recommendations assessment, development and evaluation)	A systematic and explicit approach to grading the quality of evidence and the strength of recommendations developed by the GRADE working group.
Hazard ratio (HR)	The hazard or chance of an event occurring in the treatment arm of a study as a ratio of the chance of an event occurring in the control arm over time.
Minimal clinically important difference	The smallest change in a treatment outcome that people with the condition would identify as important (either beneficial or harmful), and that would lead a person or their clinician to consider a change in treatment.

PICO (population, intervention, comparison and outcome) framework	A structured approach for developing review questions that divides each question into 4 components: the population (the population being studied); the interventions (what is being done); the comparators (other main treatment options); and the outcomes (measures of how effective the interventions have been).
Prospective study	A research study in which the health or other characteristic of patients is monitored (or 'followed up') for a period of time, with events recorded as they happen. This contrasts with retrospective studies.
P-value (p)	The p value is a statistical measure that indicates whether or not an effect is statistically significant. For example, if a study comparing 2 treatments found that 1 seems to be more effective than the other, the p value is the probability of obtaining these results by chance. By convention, if the p value is below 0.05 (that is, there is less than a 5% probability that the results occurred by chance), it is considered that there probably is a real difference between treatments. If the p value is 0.001 or less (less than a 0.1% probability that the results occurred by chance), the result is seen as highly significant. If the p value shows that there is likely to be a difference between treatments, the confidence interval describes how big the difference in effect might be.
Retrospective study	A research study that focuses on the past and present. The study examines past exposure to suspected risk factors for the disease or condition. Unlike prospective studies, it does not cover events that occur after the study group is selected.
Statistical significance	A statistically significant result is one that is assessed as being due to a true effect rather than random chance.

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