NHS England Evidence Review:

Combination brentuximab vedotin and bendamustine for children 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 children with relapsed or refractory classical Hodgkin lymphoma (R/R HL). A parallel review (2404a) examines the evidence in adults 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 G-CSF (Granulocyte-colony stimulating factor). 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 BVB 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 children 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.

Two papers were identified for inclusion, one single arm (phase II) trial and one retrospective case series. The single arm trial administered nivolumab plus brentuximab vedotin (BV) to 43 children and young adults (CYA) with pathologically confirmed HL with failure or non-response to first-line therapy**,** followed by intensification with BVB for 11 patients who did not achieve complete metabolic response after four cycles of nivolumab plus BV. These 11 patients were considered in scope for this review and outcomes have been extracted for this subgroup only. The retrospective case series included 32 pathologically confirmed HL CYA with primary refractory disease (defined as progressive disease during or three months after first-line chemotherapy) who were given BVB after a median of two prior therapies. Median follow-up was 20.9 (range 2.6 to 29.2) months for the single arm trial and 42 (range 11 to 94) months for the case series. The studies were carried out in Canada, France, Germany, Ireland, Italy, the Netherlands, the UK and the USA. No studies comparing BVB with other treatments were identified.

In terms of clinical effectiveness:

Critical outcomes

- **Overall survival**

  One retrospective case series of CYA with R/R HL receiving BVB after a median of two prior therapies provided very low certainty evidence on overall survival.

  - The study reported a 3-year overall survival of 78.1% (95% CI 59.5 to 88.9) at a median follow-up of 42 months (range 11 to 94).

- **Response rate**

  One subgroup of a single arm trial and one retrospective case series of CYA with R/R HL receiving BVB as third or subsequent line treatment provided very low certainty evidence on response rate.

  - The subgroup of the single arm trial of R/R HL standard risk patients receiving BVB intensification after induction with nivolumab plus BV reported an objective response rate of 100% (complete response rate of 82% per blinded independent central review (BICR) and 100% per investigator assessment) after two cycles of BVB intensification and 100% (complete response rate of 67% per BICR and 100% per investigator assessment) after four cycles of BVB intensification.
  - The retrospective case series of CYA with R/R HL receiving BVB after a median of two prior therapies reported that 15 (54%) patients had a complete response (partial response: 13 (46%)) after the first two cycles of BVB treatment and an overall response rate of 81% (95% CI 67 to 96) (n=26) (complete response rate: 69% (95% CI 52 to 86) (n=22), partial response rate: 12% (95% CI 0.5 to 25) (n=4) & progressive disease/relapse rate: 19% (95% CI 5 to 33) (n=6)) at the end of BVB treatment (median of 4 (range 2 to 6) cycles).

- **Eligibility for stem cell transplant**

  One retrospective case series of CYA with R/R HL receiving BVB after a median of two prior therapies provided very low certainty evidence on eligibility for SCT.

  - The study reported on the progression to SCT for three groups: all patients at the end of BVB treatment, those who had an objective response post BVB, and those with disease progression/relapse post BVB. At end of BVB treatment (median of 4 (range 2 to 6) cycles), the study reported that 24 patients underwent autologous stem cell transplant (ASCT), five patients underwent allo-SCT (allogeneic stem cell transplant), four patients underwent a subsequent allo-SCT after ASCT and three patients had no SCT. Out of 26 patients in whom an objective response was observed post BVB, 22 patients underwent ASCT, four patients underwent allo-SCT and four patients underwent a subsequent allo-SCT after ASCT. Out of six patients in whom a progressive disease/relapse was observed post BVB, two patients underwent ASCT and one patient underwent allo-SCT.

Important outcomes

- **Event-free survival**
  - No evidence was identified for this outcome.
- **Progression-free survival**

  One retrospective case series of CYA with R/R HL receiving BVB after a median of two prior therapies provided very low certainty evidence on progression-free survival.
  - The study reported a 3-year progression-free survival: 67% (95% CI 47.2 to 80.7) at a median follow-up of 42 months (range 11 to 94).
- **Disease-free survival or remission**

  One retrospective case series of CYA with R/R HL receiving BVB after a median of two prior therapies provided very low certainty evidence on disease-free survival or remission.
  - The study reported a 3-year disease-free survival: 62.3% (95% CI 43.3 to 76.6) at a median follow-up of 42 months (range 11 to 94).
- **Quality of life**
  - No evidence was identified for this outcome.

In terms of safety:

One subgroup of a single arm trial and one retrospective case series of CYA with R/R HL receiving BVB as third or subsequent line treatment provided very low certainty evidence on safety.

- The subgroup of the single arm trial of R/R HL standard risk patients receiving BVB intensification after induction with nivolumab plus BV reported that eight (72.7%) patients experienced a treatment related AE (any grade) and three (27.3%) patients experienced a treatment related AE (grade 3 or 4) at a median follow-up of 20.9 months (range 2.6 to 29.2 months). The most common AEs (any grade) were vomiting (54.5%) and nausea (45.5%), followed by infusion-related reaction (18.2%) and headache (18.2%).
- The retrospective case series of R/R HL patients receiving BVB after a median of two prior therapies reported that the most common grade 2 AEs were anaemia (25%), nausea/vomiting (18.2%), thrombocytopenia (15.9%) and neutropenia (11.4%) and the most common grade 3 to 4 AEs were neutropenia (52.3%), anaemia (18.2%) and thrombocytopenia (18.2%) at a median follow-up of 42 months (range 11 to 94). The

study also reported that no patients discontinued treatment due to grades 3 to 4 and there were no fatal events related to treatment.

In terms of cost effectiveness:

- No evidence was identified for cost effectiveness

In terms of subgroups:

- One retrospective case series reported results related to those who were fit for stem cell transplant vs those who were not fit for stem cell transplant in patients with R/R classical HL receiving BVB after a median of two prior therapies. However no formal subgroup analyses were conducted.

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 on day 1 in both studies and bendamustine was administered at a dose of 90 mg/m² on days 1 and 2 in the single arm trial and 120 mg/m² on days 2 and 3 in the case series. The single arm trial administered BVB for 2 cycles (plus an additional 2 cycles if approved by study medical monitor). The case series administered BVB for a median of 4 cycles (range 2 to 6).

Please see the results table (section 5) in the review for further details of outcomes and definitions.

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 CYA with R/R HL after combination BVB as third or subsequent line treatment are different from those who did not receive this treatment Other limitations that reduce the certainty in the outcomes reported include the small sample sizes with one study of 32 patients and another study where only a subgroup of 11 patients were in scope; one study being retrospective; uncertainty about whether the inclusion of participants was complete or consecutive; discrepancies in the reporting of the length of follow-up for survival outcomes and eligibility for SCT and grade 3-4 AE results in one study; and limited statistical analyses or summary statistics for some of the outcomes reported. . In terms of generalisability, although the median age of both studies was 16, the range was wide and included adults up to the age of 25 and 30 and therefore some of the results are not wholly generalisable to children only, and the studies mostly included non-UK patients.

Conclusion

This evidence review includes one subgroup (n=11) of a single arm trial and one retrospective case series (n=32) which reported outcomes of combination BVB as third or subsequent line treatment in children with R/R HL with a median of 20.9 and 42 months follow-up. No studies comparing BVB with other treatments were identified.

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 progression-free survival, disease-free survival or remission and safety. No studies were identified that

reported the important outcomes of event-free survival or quality of life. No evidence on cost effectiveness was found.

With respect to critical outcomes, the studies suggest that BVB combination therapy as third or subsequent line treatment for CYA with R/R HL resulted in 3-year overall survival of 78.1% (95% CI 59.5 to 88.9) at a median follow-up of 42 months, an overall response rate ranging from 81% to 100% (complete response rate: 54% to 100%), and 24/32 CYA going on to have ASCT and 9/32 allo-SCT (including 4 patient who first had ASCT) after BVB treatment.

With respect to important outcomes, one retrospective case series suggests that at median follow-up of 42 months, BVB combination therapy as third or subsequent line treatment for CYA with R/R HL resulted in 3-year progression-free survival of 67% (95% CI 47.2 to 80.7), and 3-year disease-free survival of 62.3% (95% CI 43.3 to 76.6).

With respect to safety, one single arm phase II trial (subgroup n=11) reported that 72.7% of patients experienced a treatment related any grade AE and 27.3% patients experienced a grade 3 or 4 treatment related AE at a median follow-up of 20.9 months. The most common AEs were vomiting and nausea, anaemia, thrombocytopenia, neutropenia, infusion-related reaction and headache across the two studies and one study reported that the most common grade 3 to 4 AEs were neutropenia (52.3%), anaemia (18.2%) and thrombocytopenia (18.2%). There were no reports of discontinued treatment due to severe AEs, or fatal events related to the treatment.

No subgroups were identified from either study as although the 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, no formal subgroup analyses were conducted.

BV was administered at a dose of 1.8 mg/kg on day 1 in both studies and bendamustine was administered at a dose of 90 mg/m² on days 1 and 2 in the single arm trial and 120 mg/m² on days 2 and 3 in the case series. The single arm trial administered BVB for 2 cycles (plus an additional 2 cycles if approved by study medical monitor). The case series administered BVB for a median of 4 cycles (range 2 to 6).

The studies identified for this review were small and lacked a control group and results should therefore be treated with caution. It was not possible to draw reliable conclusions about the clinical effectiveness, safety or cost effectiveness of combination BVB as third or subsequent line treatment compared with standard care in children 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 on 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

Two papers were identified for inclusion (Harker-Murray et al 2023 & Vinti et al 2022). Harker-Murray et al 2023 reported results for a single arm (phase II) study with a subgroup of patients in scope for this review; Vinti et al 2022 reported on a retrospective case series with the majority of patients in scope for this review. 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

Harker-Murray et al 2023
Single arm trial (Phase II)
International (multi-centre)
Canada, France, Germany, Ireland, Italy, the Netherlands, UK, USA
	43 CYA with standard risk[a] R/R HL[b]
	
	Subgroup of 11 patients in scope who received BVB intensification
	
	• Median age: 16 years (range 9 to 30)
	• Male: 29 (66%)
	• Primary refractory: 24 (55%)
	• Relapsed: 20 (45%)
	
	No subgroups reported
		Intervention
		BVB intensification after induction with nivolumab plus BV
		Induction: nivolumab (3 mg/kg, day 8 of cycle 1; day 1 thereafter) plus BV (1.8 mg/kg, day 1 of every cycle) for all patients
		Intensification: BV (1.8 mg/kg, day 1 of every cycle) plus bendamustine (90 mg/m^2, days 1 and 2 of every cycle) for 2 cycles[c] for patients with less than CMR[d] following 4 cycles of induction
		Comparison
		No comparator group
			Critical outcomes
			• Response rate[e]
			  ○ Objective response rate[f] after 2 cycles & 4 cycles of BVB intensification
			Important outcomes
			Median follow-up of 20.9 months (range 2.6 to 29.2 months)
			• Safety
			  ○ Treatment related AEs of any grade; grade 3-4

Vinti et al 2022
Retrospective case series
Italy (2 centres)
	32 CYA with R/R HL[g]
	• Median age: 16 years (range 8 to 25)
	• Male: 18
	• Median number of prior therapies: 2 (range 1 to 10)
	• 1-2 lines of prior therapy: 18
	• ≥3 lines of prior therapy: 14
	• Primary refractory: 17
	• Relapsed disease: 15
		Intervention
		BVB
		BV (1.8 mg/kg BV on day 1) plus bendamustine[h] (120 mg/m^2 on days 2 and 3)
		Median cycles administered: 4 (range 2 to 6)
		Comparison
		No comparator group
			Median follow-up of 42 months (range 11 to 94) unless stated otherwise
			Critical outcomes
			• Overall survival[i]
			  ○ 3-year OS
			• Response rate[j]
			  ○ Overall response rate at end of BVB treatment (median of 4 (range 2 to 6) cycles
			• Eligibility for stem cell transplant at end of BVB treatment (median of 4 (range 2 to 6) cycles
			Important outcomes
			• Progression-free survival[k]
			  ○ 3-year PFS
			• Disease-free survival[l]
			  ○ 3-year DFS
			• Safety

Study	Population	Intervention and comparison	Outcomes reported
			○ AEs of grade 2, grades 3-4 ○ Discontinuing treatment due to grades 3–4 ○ Fatal events related to treatment

Abbreviations

AE: adverse event; BVB: brentuximab vedotin and bendamustine; BV: brentuximab vedotin; CMR: complete metabolic response; CT: computed tomography; CYA: children and young adults; DFS: disease-free survival; FDG-PET: fluorodeoxyglucose positron emission tomography; HL: Hodgkin lymphoma; kg: kilogram; m: metre; mg: milligram; OS: overall survival; PFS: progression-free survival; R/R: relapsed/refractory; RT: radiotherapy

Footnotes

a. Standard risk was defined as having ≥1 of the following: primary refractory disease, high stage at initial diagnosis, short time to relapse, presence of B symptoms or extranodal disease at relapse, extensive disease (where RT was contraindicated at relapse), or relapse in a prior radiation field. Patients not eligible for the standard-risk cohort were eligible for a separate, low-risk cohort (results were not reported for this cohort)

b. Pathologically confirmed classical HL (excluding nodular lymphocyte-predominant HL) after failure or non-response to first-line therapy

c. Up to 2 additional cycles of BVB were permitted if approved by the study medical monitor

d. Complete metabolic response defined as Deauville Score ≤3 per Lugano 2014 criteria per blinded independent central review

e. Complete metabolic response was defined as a Deauville score of ≤3 per Lugano 2014 criteria per blinded independent central review.

f. Complete response plus partial response

g. Primary refractory disease defined as progressive disease during first-line chemotherapy or within 3 months after completion of the treatment

h. Six patients received 90 mg/m^2/day of bendamustine for medical decision, mainly because they had been heavily pretreated

i. Defined as the time from study enrolment to death due to any cause or last follow-up

j. Objective response was assessed through CT and FDG-PET scans and patients were evaluated for treatment response according to Cheson's Criteria. Patients with all target lesions Deauville score 3 or less were considered to have a complete response regardless of residual mass size

k. Defined as time from study enrolment to the date of first event or last follow-up. Events were either disease progression or death due to any cause

l. Defined as time from complete response to recurrence of tumour or death

5. Results

In children 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, one retrospective case series provided evidence relating to overall survival. *3-year overall survival* At a median follow-up of 42 months (range 11 to 94)[1]: • One retrospective case series (Vinti et al 2022) (n=32) of CYA with R/R HL[2] receiving BVB (median prior therapies of 2 (range 1 to 10)) reported a 3-year overall survival[3] of 78.1% (95% CI 59.5 to 88.9). **(VERY LOW)** **One retrospective case series of CYA with R/R HL receiving BVB after a median of two prior therapies provided very low certainty evidence of a 3-year overall survival of 78.1% (95% CI 59.5 to 88.9) at a median follow-up of 42 months (range 11 to 94).**
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, two studies (one subgroup of a single arm trial and one retrospective case series) provided evidence relating to response rate. After two cycles of BVB intensification: • One subgroup of a single arm (phase II) trial (Harker-Murray et al 2023) (n=11) of CYA with standard risk[4] R/R HL[5] receiving BVB intensification after induction with nivolumab plus BV reported an objective response rate[6] per BICR of 100% (complete metabolic response[7] : 82% (n=9) & partial metabolic response: 18% (n=2)). **(VERY LOW)** • The study also reported an objective response rate per investigator assessment of 100% (complete metabolic response: 91% (n=10) & partial metabolic response: 9% (1)). **(VERY LOW)**

[1] This follow-up was reported in the results section in the published paper. However it is worth noting that a different follow-up length was reported in the discussion for survival outcomes (median of 36 months (range 8.7 to 86))
[2] Primary refractory disease defined as progressive disease during first-line chemotherapy or within 3 months after completion of the treatment
[3] Defined as the time from study enrolment to death due to any cause or last follow-up
[4] Standard risk was defined as having ≥1 of the following: primary refractory disease, high stage at initial diagnosis, short time to relapse, presence of B symptoms or extranodal disease at relapse, extensive disease (where RT was contraindicated at relapse), or relapse in a prior radiation field. Patients not eligible for the standard-risk cohort were eligible for a separate, low-risk cohort (results were not reported for this cohort)
[5] Pathologically confirmed classical HL (excluding nodular lymphocyte-predominant HL) after failure or non-response to first-line therapy
[6] Complete response plus partial response
[7] Defined as Deauville ≤3 per Lugano 2014 criteria

Outcome	Evidence statement
	After four cycles of BVB intensification: • One subgroup of a single arm (phase II) trial (Harker-Murray et al 2023) (n=3) of CYA with standard risk R/R HL receiving BVB intensification after induction with nivolumab plus BV reported an objective response rate per BICR of 100% (complete metabolic response: 67% (n=2) & partial metabolic response: 33% (n=1).) **(VERY LOW)** • The study also reported an objective response rate per investigator assessment of 100% (n=2) (complete metabolic response: 100% (n=2) & partial metabolic response: 0% (0)). **(VERY LOW)** At the end of BVB treatment (median of 4 (range 2 to 6) cycles): • One retrospective case series (Vinti et al 2022) (n=32) of CYA with R/R HL receiving BVB (median prior therapies of 2 (range 1 to 10)) reported an overall response[8] rate of 81% (95% CI 67 to 96) (n=26) (complete response rate[9]: 69% (95% CI 52 to 86) (n=22), partial response rate: 12% (95% CI 0.5 to 25) (n=4) & progressive disease/relapse rate: 19% (95% CI 5 to 33) (n=6)) . **(VERY LOW)** After first two cycles of BVB treatment: • One retrospective case series (Vinti et al 2022) (n=32) of CYA with R/R HL receiving BVB (median prior therapies of 2 (range 1 to 10)) reported that 15 (54%) patients had a complete response (partial response: 13 (46%)). **(VERY LOW)** **One subgroup of a single arm trial and one retrospective case series of CYA with R/R HL receiving BVB as third or subsequent line treatment provided very low certainty evidence on response rate. The subgroup of the single arm trial of R/R HL standard risk patients receiving BVB intensification after induction with nivolumab plus BV reported an objective response rate of 100% (complete response rate of 82% per BICR and 100% per investigator assessment) after two cycles of BVB intensification and 100% (complete response rate of 67% per BICR and 100% per investigator assessment) after four cycles of BVB intensification. The retrospective case series of R/R HL patients receiving BVB after a median of two prior therapies reported that 15 (54%) patients had a complete response (partial response: 13 (46%)) after the first two cycles of BVB treatment and an overall response rate of 81% (95% CI 67 to 96) (n=26) (complete response rate: 69% (95% CI 52 to 86) (n=22)), partial response rate: 12% (95% CI 0.5 to 25) (n=4) & progressive disease/relapse rate: 19% (95% CI 5 to 33) (n=6)) at the end of BVB treatment (median of 4 (range 2 to 6) cycles).**
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. At end of BVB treatment (median of 4 (range 2 to 6) cycles): • One retrospective case series (Vinti et al 2022) (n=32) of CYA with R/R HL[10] receiving BVB (median prior therapies of 2 (range 1 to 10)) reported that 24 patients underwent ASCT, nine patients underwent allo-SCT and three patients had no SCT. **(VERY LOW)** • The study also reported that out of 26 patients in whom an objective response was observed post BVB, 22 patients underwent ASCT, four patients underwent allo-SCT (three for having previously failed an ASCT prior to BVB & one for a medical decision), four patients underwent a

[8] Complete response plus partial response
[9] Defined as all target lesions with a Deauville score of 3 or less regardless of residual mass size
[10] Primary refractory disease defined as progressive disease during first-line chemotherapy or within 3 months after completion of the treatment

Outcome	Evidence statement
	subsequent allo-SCT after ASCT (three patients for relapse or progressive disease after BVB-post ASCT or radiotherapy & one patient for consolidation of a partial response achieved with ASCT post initial BVB). **(VERY LOW)** • The study also reported that out of six patients in whom a progressive disease/relapse was observed post BVB, two patients underwent ASCT and one patient underwent allo-SCT. **(VERY LOW)** **One retrospective case series of CYA with R/R HL receiving BVB after a median of two prior therapies provided very low certainty evidence on eligibility for SCT. The study reported on the progression to SCT for three groups: all patients at the end of BVB treatment, those who had an objective response post BVB, and those with disease progression/relapse post BVB. At end of BVB treatment (median of 4 (range 2 to 6) cycles), the study reported that 24 patients underwent ASCT, nine patients underwent allo-SCT and three patients had no SCT. Out of 26 patients in whom an objective response was observed post BVB, 22 patients underwent ASCT, four patients underwent allo-SCT and four patients underwent a subsequent allo-SCT after ASCT. Out of six patients in whom a progressive disease/relapse was observed post BVB, two patients underwent ASCT and one patient underwent allo-SCT.**
Important outcomes	
Event-free survival **Certainty of evidence:** Not applicable	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. **No evidence was identified for this outcome.**
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, one retrospective case series provided evidence relating to progression-free survival. *3-year progression-free survival* At a median follow-up of 42 months (range 11 to 94): One retrospective case series (Vinti et al 2022) (n=32) of CYA with R/R HL receiving BVB (median prior therapies of 2 (range 1 to 10)) reported a 3-year progression-free survival[11] of 67% (95% CI 47.2 to 80.7). **(VERY LOW)** **One retrospective case series of CYA with R/R HL receiving BVB after a median of two prior therapies provided very low certainty evidence of a 3-year progression-free survival of 67% (95% CI 47.2 to 80.7) at a median follow-up of 42 months (range 11 to 94).**
Disease-free survival or remission **Certainty of evidence:** Very low	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. In total, one retrospective case series provided evidence relating to disease-free survival. *3-year disease-free survival* At a median follow-up of 42 months (range 11 to 94):

[11] Defined as time from study enrolment to the date of first event or last follow-up. Events were either disease progression or death due to any cause

Outcome	Evidence statement
	• One retrospective case series (Vinti et al 2022) (n=32) of CYA with R/R HL receiving BVB (median prior therapies of 2 (range 1 to 10)) reported a 3-year disease-free survival[12] of 62.3% (95% CI 43.3 to 76.6). **(VERY LOW)** **One retrospective case series of CYA with R/R HL receiving BVB after a median of two prior therapies provided very low certainty evidence of a 3-year disease-free survival of 62.3% (95% CI 43.3 to 76.6) at a median follow-up of 42 months (range 11 to 94).**
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, two studies (one subgroup of a single arm trial and one retrospective case series) provided evidence relating to safety. At a median follow-up of 20.9 months (range 2.6 to 29.2 months): • One subgroup of a single arm (phase II) trial (Harker-Murray et al 2023) (n=11) of CYA with standard risk R/R HL receiving BVB intensification after induction with nivolumab plus BV reported that eight (72.7%) patients experienced a treatment related AE (any grade). **(VERY LOW)** • This study also reported that three (27.3%) patients experienced a treatment related AE (grade 3 or 4). **(VERY LOW)** • The study also reported on treatment related AEs with ≥2 patients in either the induction or intensification phase and reported the following for the 11 patients receiving BVB intensification, n (%): vomiting (any grade): 6 (54.5%); nausea (any grade): 5 (45.5%); infusion-related reaction (any grade): 2 (18.2%); headache (any grade): 2 (18.2%); vomiting (grade 3/4): 1 (9.1%); hypersensitivity (any grade): 1 (9.1%); diarrhoea (any grade): 1 (9.1%) ; pyrexia (any grade): 1 (9.1%); increased AST (any grade): 1 (9.1%). **(VERY LOW)** At a median follow-up of 42 months (range 11 to 94): • One retrospective case series (Vinti et al 2022) (n=32) of CYA with R/R HL receiving BVB (median prior therapies of 2 (range 1 to 10)) reported on grade 2 AEs and reported the following, n (%): nausea/vomiting: 8 (18.2%); erythema: 2 (4.5%); anaemia: 11 (25%); neutropenia: 5 (11.4%); thrombocytopenia: 7 (15.9%); peripheral neuropathy: 3 (6.8%). **(VERY LOW)** • The study also reported on grade 3-4 AEs[13] and reported the following, n (%): anaemia: 8 (18.2%), neutropenia: 23 (52.3%) and thrombocytopenia: 8 (18.2%). **(VERY LOW)**

[12] Defined as time from complete response to recurrence of tumour or death
[13] These results were extracted from Table 2 on adverse events. It should be noted that the text in the paper reports that *"the most common treatment-related AE was grades 3–4 hematological toxicity in 14 patients (44%)"* which is inconsistent with the results presented in Table 2 of the paper

Outcome	Evidence statement
	• The study also reported that no patients discontinued treatment due to grades 3 to 4. **(VERY LOW)** • The study also reported that there were no fatal events related to treatment. **(VERY LOW)** **One subgroup of a single arm trial and one retrospective case series of CYA with R/R HL receiving BVB as third or subsequent line treatment provided very low certainty evidence on safety. The subgroup of a single arm trial of R/R HL standard risk patients receiving BVB intensification after induction with nivolumab plus BV reported that eight (72.7%) patients experienced a treatment related AE (any grade) and three (27.3%) patients experienced a treatment related AE (grade 3 or 4) at a median follow-up of 20.9 months (range 2.6 to 29.2 months). The most common AEs (any grade) were vomiting (54.5%) and nausea (45.5%), followed by infusion-related reaction (18.2%) and headache (18.2%). The retrospective case series of R/R HL patients receiving BVB after a median of two prior therapies reported that the most common grade 2 AEs were anaemia (25%), nausea/vomiting (18.2%), thrombocytopenia (15.9%) and neutropenia (11.4%) and the most common grade 3 to 4 AEs were neutropenia (52.3%), anaemia (18.2%) and thrombocytopenia (18.2%) at a median follow-up of 42 months (range 11 to 94). The study also reported that no patients discontinued treatment due to grades 3 to 4 and there were no fatal events related to treatment.**
Abbreviations AE: adverse event; allo-SCT: allogeneic stem cell transplant; ASCT: autologous stem cell transplant; BICR: blinded independent central review; BV: brentuximab vedotin; BVB: brentuximab vedotin and bendamustine; CI: confidence interval; CYA: children and young adults; HL: Hodgkin lymphoma; R/R: relapsed/refractory; RT: radiotherapy; SCT: stem cell transplant	

In children 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 that are fit for stem cell transplant vs those who are not fit for stem cell transplant	**Response rate** *Subgroup: patients with overall response after BVB treatment who had ASCT post BVB* Out of 22 patients who underwent ASCT after achieving overall response post BVB treatment, one patient achieved partial response (patient went on to have allo-SCT), 17 patients achieved complete response and five patients had

Subgroup	Evidence statement
	progressive disease or relapse[14]. Out of the five patients with progressive disease or relapse post ASCT, three patients went on to have further treatment followed by allo-SCT and two patients had further treatment followed by progressive disease or relapse. *Subgroup: patients with progressive disease or relapse after BVB who had ASCT post BVB and further treatment* Two patients with progressive disease post BVB underwent ASCT and both patients achieved partial response after further treatment and ASCT. *Subgroup: patients with progressive disease or relapse after BVB who had an allo-SCT post BVB and further treatment* One patient with progressive disease post BVB underwent allo-SCT and this patient continued to have progressive disease after further treatment and allo-SCT. *Subgroup: patients with progressive disease or relapse after BVB who had no SCT post BVB and further treatment* Three patients with progressive disease post BVB did not have SCT and two of these patients had progressive disease and one patient had complete response after further treatment. **One retrospective case series reported results related to those who were fit for stem cell transplant vs those who were not fit for stem cell transplant in patients with R/R classical HL receiving BVB as third or subsequent line treatment. However no formal subgroup analyses were conducted.**
Abbreviations allo-SCT: allogeneic stem cell transplant; ASCT: autologous stem cell transplant; BVB: brentuximab vedotin and bendamustine; 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	• Harker-Murray et al 2023, a single arm trial, administered BV at 1.8 mg/kg on day 1 plus bendamustine at 90 mg/m^2 on days 1 and 2 of every cycle for 2 cycles for patients with less than CMR (plus an additional 2 cycles if approved by study medical monitor) following 4 cycles of induction (nivolumab plus BV). • Vinti et al 2022, a retrospective case series, administered BV at 1.8 mg/kg on day 1 and 120 mg/m^2 bendamustine on days 2 and 3 (6 out of 32 patients received 90 mg/m^2/day of bendamustine for medical decision, mainly because they had been heavily pretreated). The median cycles administered was 4 (range 2 to 6) **BV was administered at a dose of 1.8 mg/kg on day 1 in both studies and bendamustine was administered at a dose of 90 mg/m² on days 1 and 2 in the single arm trial and 120 mg/m² on days 2 and 3 in the case series. The single arm trial administered BVB for 2 cycles (plus an additional 2 cycles if approved by study medical monitor). The case series administered BVB for a median of 4 cycles (range 2 to 6).**
Abbreviations	

[14] Results taken from Figure 2. Eight patients also had BV post ASCT and six patients had radiotherapy post ASCT. There is an anomaly in the results, with the total number of patients having complete response (n=17), partial response (n=1) and progressive disease/relapse (n=5) after ASCT in patients who achieved an overall response post BVB being more that the total number of patients who achieved an overall response and subsequently underwent ASCT (n=22)

BVB: brentuximab vedotin and bendamustine; CMR: complete metabolic response; kg: kilogram; m: metre; mg: milligram

6. Discussion

This evidence review considered the clinical effectiveness, safety and cost effectiveness of combination BVB as third or subsequent line treatment compared to with standard of care in children 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.

Two studies were identified for inclusion in this review, a single arm (phase II) trial (Harker-Murray et al 2023) with a median follow-up of 20.9 months (range 2.6 to 29.2 months) and one retrospective case series with a median follow-up 42 months (range 11 to 94) (Vinti et al 2022). No comparator evidence or cost effectiveness evidence was identified.

The single arm trial administered induction therapy of nivolumab plus BV to 43 pathologically confirmed HL patients with failure or non-response to first-line therapy followed by intensification with BVB in 11 patients who did not achieve complete metabolic response after four cycles of induction. These 11 patients were considered in scope for this review and outcomes have been extracted for this subgroup only.

The retrospective case series included 32 pathologically confirmed HL with primary refractory disease (defined as progressive disease during first-line chemotherapy or within three months after completion of the treatment) who received BVB after a median of two prior therapies. Prior therapies ranged from one to ten and therefore some patients with one prior therapy (number not reported) will be out of scope for this review. Results were not reported separately for patients with two or more prior therapies. The results for the total sample have been included in this review as the majority of patients were considered in scope.

BV was administered at a dose of 1.8 mg/kg on day one in both studies and bendamustine was administered at a dose of 90 mg/m² on days one and two in the single arm trial and 120 mg/m² on days two and three in the case series. The single arm trial administered BVB for two cycles (plus an additional two cycles if approved by study medical monitor). The case series administered BVB for a median of four cycles (range 2 to 6).

Both studies focussed on children and young people and had a median age of 16 years. However, the age range of the included patients was nine to 30 for the total sample of the single arm trial (baseline characteristics not reported for the in-scope subgroup) and eight to 25 years for the case series and therefore an unknown proportion of patients will have been over 18 years and out of scope for this review.

Both studies defined complete metabolic response as a Deauville score of ≤3 per Lugano 2014 or Cheson's Criteria.

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

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

The 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 but no formal subgroup analyses were conducted so no conclusions could be drawn.

Both 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 who did not receive this treatment. Other limitations that reduce the certainty in the outcomes reported include the small sample size of the studies, the retrospective nature of the case series, uncertainty about whether the inclusion of participants was complete or consecutive, discrepancies in the reporting of the length of follow-up for survival outcomes and eligibility for SCT and grade 3-4 AE results in one study, and limited statistical analyses or summary statistics for some of the outcomes reported.

The single arm trial included patients from centres in Canada, France, Germany, Ireland, Italy, the Netherlands, the UK, the USA and the case series included patients from two centres in Italy. As the majority of patients were from outside of the UK 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 one subgroup (n=11) of a single arm trial and one retrospective case series (n=32) which reported outcomes of combination BVB as third or subsequent line treatment in children with R/R HL with a median of 20.9 and 42 months follow-up. No studies comparing BVB with other treatments were identified.

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, progression-free survival, disease-free survival or remission and safety. No studies were identified that reported the important outcomes of event-free survival or quality of life. No evidence on cost effectiveness was found.

With respect to critical outcomes, the studies suggest that BVB combination therapy as third or subsequent line treatment for CYA with R/R HL resulted in 3-year overall survival of 78.1% (95% CI 59.5 to 88.9) at a median follow-up of 42 months, an overall response rate ranging from 81% to 100% (complete response rate: 54% to 100%), and 24/32 CYA going on to have ASCT and 9/32 allo-SCT (including 4 patient who first had ASCT) after BVB treatment.

With respect to important outcomes, one retrospective case series suggests that at median follow-up of 42 months, BVB combination therapy as third or subsequent line treatment for CYA with R/R HL resulted in 3-year progression-free survival of 67% (95% CI 47.2 to 80.7), and 3-year disease-free survival of 62.3% (95% CI 43.3 to 76.6).

With respect to safety, one single arm phase II trial (subgroup n=11) reported that 72.7% of patients experienced a treatment related any grade AE and 27.3% patients experienced a grade 3 or 4 treatment related AE at a median follow-up of 20.9 months. The most common AEs were vomiting and nausea, anaemia, thrombocytopenia, neutropenia, infusion-related reaction and headache across the two studies and one study reported that the most common grade 3 to 4 AEs were neutropenia (52.3%), anaemia (18.2%) and thrombocytopenia (18.2%). There were no reports of discontinued treatment due to severe AEs, or fatal events related to the treatment.

No subgroups were identified from either study as although the 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, no formal subgroup analyses were conducted.

BV was administered at a dose of 1.8 mg/kg on day 1 in both studies and bendamustine was administered at a dose of 90 mg/m² on days 1 and 2 in the single arm trial and 120 mg/m² on days 2 and 3 in the case series. The single arm trial administered BVB for 2 cycles (plus an additional 2 cycles if approved by study medical monitor). The case series administered BVB for a median of 4 cycles (range 2 to 6).

The studies identified for this review were small and lacked a control group and results should therefore be treated with caution. It was not possible to draw reliable conclusions about the clinical effectiveness, safety or cost effectiveness of combination BVB as third or subsequent line treatment compared with standard care in children 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	Children aged <18 years old 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 under 18 years] 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	Children aged <18 years old
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.

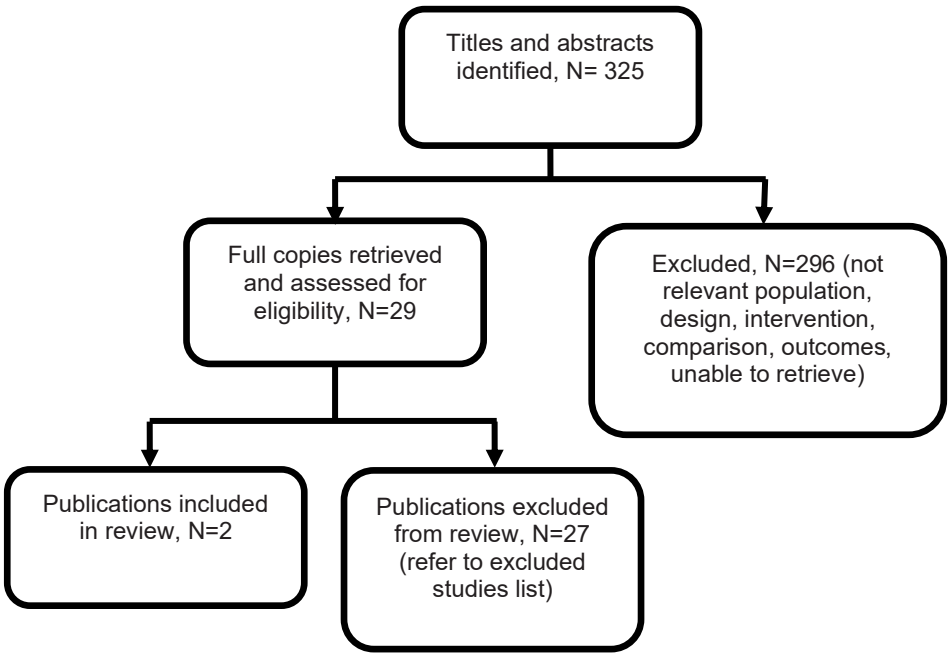
Search dates: 1 January 2014 and 12 June 2024

	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, 2 references are included in the evidence summary. The remaining 27 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 2 study of the Fondazione Italiana Linfomi. Blood Cancer J. 2019;9(12):100.	Excluded. Population out of scope: adults. 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. Population out of scope: adults. 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.	Excluded. Population out of scope: adults. Included in adults with R/R HL review

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.	Intervention out of scope: 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: Adults & treatment naïve HL
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.	Population out of scope: Adults. Included in adults 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

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.	Population and intervention out of scope: Adults & 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
Moretti M, Liberati AM, Rigacci L, Puccini B, Pulsoni A, Gini G, et al. Brentuximab Vedotin and Bendamustine Produce Long-Term Clinical Benefit in Patients With Relapsed or Refractory Classical Hodgkin Lymphoma: A Multicenter Real-Life Experience. Clin Lymphoma Myeloma Leuk. 2022;22(3):198-204.	Population out of scope: Adults. Included in adults with R/R HL review
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.	Population out of scope: Adults. Included in adults with R/R HL review
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
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.	Population out of scope: Adults. Included in adults with R/R HL review
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.	Population out of scope: Adults. Included in adults with R/R HL review
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.	Population out of scope: Adults. Included in adults with R/R HL review
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.	Publication type out of scope: 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.	A subgroup of 9 patients received BV but not all received bendamustine and results were not reported separately for in scope patients
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.	A subgroup of 2 patients were in scope. Larger studies available. No additional outcomes presented
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.	Population out of scope: Adults. Included in adults 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
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. **Study location** International (multi-centre) Canada, France, Germany, Ireland, Italy, the Netherlands, the UK, the USA **Study type** Single arm trial (Phase II; CheckMate 744) **Study aim** To determine whether nivolumab plus brentuximab vedotin (followed by brentuximab vedotin plus	CYA with standard risk[15] R/R classical HL **Inclusion criteria** • Aged 5 to 30 years • Measurable disease documented by pathologic and radiographic criteria including FDG-PET–avid and bidimensional measurable disease of ≥1.5 cm in the longest axis. • Pathologically confirmed classical HL (excluding nodular lymphocyte-predominant HL) after failure or non-response to first-line therapy (i.e, relapsed or refractory disease) • Karnofsky (for patients aged >16 years) or Lansky (for patients aged ≤16 years) performance status ≥50 • Standard risk	**Interventions** BVB intensification after induction with nivolumab plus BV Induction: nivolumab (3 mg/kg, day 8 of cycle 1; day1 thereafter) plus BV (1.8 mg/kg, day 1 of every cycle) for all patients Intensification: BV (1.8 mg/kg, day 1 of every cycle) plus bendamustine (90 mg/m^2, days 1 and 2 of every cycle) for 2 cycles[17] for patients with less than CMR[18] following 4 cycles of induction **Comparators** None	**Critical outcomes** **Response rate** After 2 cycles BVB intensification (n=11) Objective response rate[19]: Per blinded independent central review (BICR): 100% (11) Per investigator assessment: 100% (11) Complete metabolic response[20] Per BICR: 82% (9) Per investigator: 91% (10) Partial metabolic response: Per BICR: 18% (2) Per investigator: 9% (1) After 4 cycles BVB intensification (n=3) Objective response rate: Per BICR: 100% (3) Per investigator: 100% (2)	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.NO **Other comments:** This paper reports on a single arm (phase II) trial of 43 CYA (median age 16 years) with R/R classical HL. During the induction phase of the study, all patients were given nivolumab plus BV. Patients who did not achieve complete metabolic response after 4 cycles of induction received intensification with BVB. These 11 patients were in scope for

[15] Standard risk was defined as having ≥1 of the following: primary refractory disease, high stage at initial diagnosis, short time to relapse, presence of B symptoms or extranodal disease at relapse, extensive disease (where RT was contraindicated at relapse), or relapse in a prior radiation field. Patients not eligible for the standard-risk cohort were eligible for a separate, low-risk cohort (results were not reported for this cohort)
[17] up to 2 additional cycles of BVB were permitted if approved by the study medical monitor
[18] CMR defined as Deauville Score ≤3 per Lugano 2014 criteria per blinded independent central review
[19] Complete response plus partial response
[20] Defined as Deauville ≤3 per Lugano 2014 criteria

Study details	Population	Interventions	Study outcomes	Appraisal and funding
bendamustine in patient with suboptimal response) is safe and effective in treating patients with Hodgkin's lymphoma **Study dates** Not reported	**Exclusion criteria** • Prior treatment with checkpoint inhibitors, radiation therapy within 3 weeks (or chest radiation within 12 weeks), bendamustine, auto-SCT or allo-SCT **Total sample size** N=43 (all patients) N=11 (in scope patients receiving BVB intensification) **Baseline characteristics** N=43[16] Median age: 16 years (range 9 to 30) <18 years: 31 (70%) Male: 29 (66%) Performance status, median (range): • Lansky (n=26): 100 (70 to 100) • Karnofsky (n=18): 100 (80 to 100) Stage at initial diagnosis: • Stage II: 21 (48%) • Stage III: 7 (16%) • Stage IV: 16 (36%) Response to first-line therapy: • Primary refractory: 24 (55%) • Relapsed: 20 (45%)		Complete metabolic response Per BICR: 67% (2) Per investigator: 100% (2) Partial metabolic response Per BICR: 33% (1) Per investigator: 0% (0) **Safety** Median follow-up of 20.9 months (range 2.6 to 29.2 months) TRAE (any grade): 8 (72.7%) TRAE (grade 3/4): 3 (27.3%) One patient experienced vomiting and decreased white blood cell count; one experienced increased lipase; and one experienced neutropenia TRAEs with ≥2 patients in either the induction or intensification phase:	this review and outcomes have been extracted for this subgroup only. Inclusion and exclusion criteria were clearly defined but it was not clear if patient recruitment had been consecutive and complete for each centre. Baseline characteristics were clearly reported for all patients but not for the subgroup of patients in scope for this review. As the age range of all the study patients was 9 to 30 years, it is possible that some of the subgroup patients may be >18 years and therefore out of scope for this review. The median number of prior therapies was not reported. Despite this, it is clear that patients received BVB as a third or subsequent line treatment because BVB was given after nivolumab plus BV to patients with failure or non-response to first-line therapy. PET–computed tomography/magnetic resonance imaging (real-time BICR) was performed after 4 cycles of nivolumab plus BV and after every 2 cycles of BVB before consolidation. Complete metabolic response was defined as a Deauville score of ≤3 per Lugano 2014 criteria per blinded independent central review. One patient discontinued because of study drug toxicity after 2 cycles of induction with nivolumab plus BV. This patient was included in the total

[16] Baseline characteristics were not reported separately for the 11 in scope patients

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	○ 3-12 months: 14 (32%) ○ ≥12 months: 6 (14%) • Prior auto-HCT: 0 • Prior BV: 0 Prior systemic therapy: 44 (100%) • OEPA/COPDAC: 20 (46%) • OEPA: 6 (14%) • ABVE-PC: 6 (14%) • ABV/COPP: 4 (9%) • ABVD: 4 (9%) • ABVE: 2 (5%) • Other: 2 (5%) Prior radiation therapy: 16 (36%) B symptoms or extranodal disease at relapse, extensive disease (RT contraindicated), or relapse in a prior radiation field: 28 (64%) Bone marrow involvement: 5 (11%) Stage IV disease at relapse: 16 (36%)		Vomiting (any grade): 6 (54.5%) Nausea (any grade): 5 (45.5%) Infusion-related reaction (any grade): 2 (18.2%) Headache (any grade): 2 (18.2%) Vomiting (grade 3/4): 1 (9.1%) Hypersensitivity (any grade): 1 (9.1%) Diarrhoea (any grade): 1 (9.1%) Pyrexia (any grade): 1 (9.1%) Increased AST (any grade): 1 (9.1%)	number of patients for the response and safety results. Confidence intervals were not reported for the in-scope patient subgroup outcomes of interest. **Source of funding:** The research was funded by Bristol Myers Squibb, in collaboration with Seagen. Professional medical writing and editorial support were funded by Bristol Myers Squibb.
Vinti L, Pagliara D, Buffardi S, Di Ruscio V, Stocchi F, Mariggio E, et al. Brentuximab vedotin in	CYA with pathologically confirmed CD30-positive R/R HL **Inclusion criteria**	**Interventions** BVB 1.8 mg/kg BV on day 1 and 120 mg/m^2	**Critical outcomes** **Overall survival[21]** At a median follow-up of 42 months (range 11 to 94)[22]	This study was appraised using the Joanna Briggs checklist for case series. 1.YES

[21] Defined as time from study enrolment to death due to any cause or last follow-up
[22] This follow-up was reported in the results section in the paper. However it is worth noting that a different follow-up length was reported in the discussion for survival outcomes (median of 36 months (range 8.7 to 86))

Study details	Population	Interventions	Study outcomes	Appraisal and funding
combination with bendamustine in pediatric patients or young adults with relapsed or refractory Hodgkin lymphoma. Pediatr Blood Cancer. 2022;69(4):e29557. **Study location** Italy (2 centres) **Study type** Retrospective case series **Study aim** To describe the results of a retrospective analysis carried out in two Italian centres where paediatric patients and young adults with R/R HL received the combination of BVB with the aim of obtaining a durable remission as bridge to transplant **Study dates** Between December 2013 and April 2019	• Aged 20 years or less at time of diagnosis and 25 years or less at time of treatment • Primary refractory disease defined as progressive disease during first-line chemotherapy or within 3 months after completion of the treatment **Exclusion criteria** None reported **Total sample size** N=32 **Baseline characteristics** Median age: 16 years (range 8 to 25) Performance status (Lansky/Karnofsky score) >60: 32 Male: 18 Histology (WHO classification): Classical HL, nodular sclerosis: 30 Classical HL, mixed cellularity: 2 B symptoms: 24 Disease stage at diagnosis: • Stage II: 16 • Stage III: 8 • Stage IV: 8	bendamustine on days 2 and 3 (6 patients received 90 mg/m^2/day of bendamustine for medical decision, mainly because they had been heavily pretreated) Median cycles administered: 4 (range 2 to 6) Premedication with paracetamol and antihistamines was administered on days 1 to 3 in order to reduce BVB infusion-related adverse reactions and selective 5-HT3 receptor antagonists were administered for preventing nausea and vomiting Supportive therapy was administered according to institutional practice. G-CSF was used in case of febrile neutropenia **Comparators** None	3-year OS: 78.1% (95% CI 59.5 to 88.9) **Response rate[23]** After the first 2 cycles of BVB treatment (early response assessment); n=28 Complete response, n (%): 15 (54%) Partial response, n (%): 13 (46%) At the end of BVB treatment (median of 4 (range 2 to 6) cycles; n=32 Overall response rate (ORR): 81% (95% CI 67 to 96); 26 patients Complete response rate: 69% (95% CI 52 to 86); 22 patients Partial response rate: 12% (95% CI 0.5 to 25); 4 patients Progressive disease/relapse rate: 19% (95% CI 5 to 33); 6 patients *"No statistically significant difference in treatment response was observed when comparing the six heavily pretreated patients receiving the lower dose of bendamustine (90 mg/m^2/day) and the remaining subjects (p=0.14 for CR; p=0.56 for ORR)"* **Eligibility for stem cell transplant** At end of BVB treatment (median of 4 (range 2 to 6) cycles) Among all patients (n=32) • ASCT: 24 patients • Allo-SCT: 9 patients (including 4 patients who had ASCT first post BVB) • No SCT: 3 patients	2. YES 3.YES 4.UNCLEAR 5.UNCLEAR 6.YES 7.YES 8.NO 9.NO 10.YES **Other comments:** This paper reports on a retrospective case series of 32 CYA (median age 16 years) with pathologically confirmed CD30-positive R/R HL. Inclusion and exclusion criteria were clearly defined but it was not clear if patient recruitment had been consecutive and complete for each centre. Baseline characteristics were clearly reported. It should be noted that while the majority of patients are in scope for this review, the range of prior therapies was 1 to 10 (median 2) and therefore some patients with 1 prior therapy will be out of scope (number not reported). Furthermore the age range was 8 to 25 years so some patients with be >18 years and therefore out of scope for this review. Objective response was assessed through CT and FDG-PET scans and patients were evaluated for

[23] Objective response was assessed through CT and FDG-PET scans and patients were evaluated for treatment response according to Cheson's Criteria. Patients with all target lesions Deauville score 3 or less were considered to have a complete response regardless of residual mass size

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	Extra-nodal involvement at treatment: 21 Median number of prior therapies: 2 (range 1 to 10) 1-2 lines of prior therapy: 18 ≥3 lines of prior therapy: 14 First line therapy: • COPP/ABV: 24 • ABVD: 3 • OEPA/COPDAC: 5 Other lines of therapy: • IEP: 15 • DHAP: 13 • BEACOPP: 3 • IGEV: 7 • BV monotherapy: 3 • Bendamustine monotherapy: 1 • Other: 14 Radiotherapy: 16 SCT: • Autologous: 5 • Allogeneic: 1 Response to prior therapies: • Primary refractory: 17 • Relapsed disease: 15		Among patients in whom an objective response was observed post BVB (n=26):[24] • ASCT: 22 patients • Allo-SCT: 4 patients; for having previously failed an ASCT prior to BVB (3 patients) or for medical decision (1 patient) • Subsequent allo-SCT after ASCT: 4; for relapse or progressive disease after BV-post ASCT or radiotherapy (3 patients), for consolidation of a partial response achieved with ASCT post initial BVB (1 patient) Among patients in whom a progressive disease/relapse was observed post BVB: (n=6) and after further treatment: • ASCT: 2 • Allo-SCT: 1 **Important outcomes** **Progression-free survival[25]** At a median follow-up of 42 months (range 11 to 94)[26] 3-year PFS: 67% (95% CI 47.2 to 80.7) **Disease-free survival[27]**	treatment response according to Cheson's Criteria. Patients with all target lesions Deauville score 3 or less were considered to have a complete response regardless of residual mass size. There were discrepancies in the reporting of some results including the median follow-up for survival outcomes, eligibility for SCT results and grade 3-4 AEs. Survival outcomes were calculated using the Kaplan-Meier method. **Source of funding:** Not reported

[24] Results taken from Figure 2 in the paper. The subsequent allo-SCT results differ slightly from those reported in the main text which reported that five patients received a subsequent allo-SCT: three patients for relapse, one patient for progressive disease (after two more lines of chemotherapy), and one patient as consolidation of a progressive response achieved with ASCT

[25] Defined as time from study enrolment to the date of first event or last follow-up. Events were either disease progression or death due to any cause.

[26]This follow-up was reported in the results section in the paper. However it is worth noting that a different follow-up length was reported in the discussion for survival outcomes (median of 36 months (range 8.7 to 86))

[27] Defined as time from complete response to recurrence of tumour or death.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			At a median follow-up of 42 months (range 11 to 94)[28] 3-year DFS: 62.3% (95% CI 43.3 to 76.6) **Safety** At a median follow-up of 42 months (range 11 to 94)[29] Grade 2 AEs: • Nausea/vomiting: 8 (18.2%) • Erythema: 2 (4.5%) • Anaemia: 11 (25%) • Neutropenia: 5 (11.4%) • Thrombocytopenia: 7 (15.9%) • Peripheral neuropathy: 3 (6.8%) Grades 3-4 AEs:[30] • Anaemia: 8 (18.2%) • Neutropenia: 23 (52.3%) • Thrombocytopenia: 8 (18.2%) *"No statistically significant difference was detected in grades 3–4 haematological toxicity when comparing the 6 heavily pretreated patients receiving the lower dose of bendamustine (90 mg/m^2/day) and the remaining subjects"* Number of patients discontinuing treatment due to grades 3–4: 0 Number of fatal events related to treatment: 0	

[28]This follow-up was reported in the results section in the paper. However it is worth noting that a different follow-up length was reported in the discussion for survival outcomes (median of 36 months (range 8.7 to 86))
[29] Follow-up for safety outcomes not reported. The follow-up for survival outcomes has been used.
[30] These results were extracted from Table 2 on adverse events. It should be noted that the text in the paper reports that *"the most common treatment-related AE was grades 3–4 hematological toxicity in 14 patients (44%)"* which is inconsistent with the results presented in Table 2 of the paper.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			Subgroups **Response rate** *ASCT post BVB in patients achieving overall response after BVB treatment (n=22)* [31] Partial response: 1 patient (patient went on to have allo-SCT) Complete response: 17 patients after either BV-post ASCT or radiotherapy post BVB Progressive disease or relapse: 5 patients after either BV-post ASCT or radiotherapy post BVB (3 patients went on to have further treatment followed by allo-SCT and 2 patients had further treatment followed by progressive disease or relapse) *ASCT post BVB and further treatment in patients with progressive disease or relapse after BVB treatment (n=2)* Partial response: 2 patients Allo-*SCT post BVB and further treatment in patients with progressive disease or relapse after BVB treatment (n=1)* Progressive disease: 1 patient *No SCT post BVB and further treatment in patients with progressive disease or relapse after BVB treatment (n=3)* Progressive disease or relapse: 2 patients Complete response: 1 patient	

Abbreviations

ABV/COPP: doxorubicin, bleomycin, vinblastine/cyclophosphamide, vincristine, procarbazine, prednisone; ABVD: doxorubicin, bleomycin, vinblastine, dacarbazine; ABVE: doxorubicin, bleomycin, vincristine, etoposide; ABVE-PC: doxorubicin, bleomycin, vincristine, etoposide, prednisone, cyclophosphamide; AE: adverse event; allo-SCT:

[31] Results taken from Figure 2. Eight patients also had BV post ASCT and six patients had radiotherapy post ASCT. There is an anomaly in the results, with the total number of patients having complete response (n=17), partial response (n=1) and progressive disease/relapse (n=5) after ASCT in patients who achieved an overall response post BVB being more that the total number of patients who achieved an overall response and subsequently underwent ASCT (n=22)

Study details	Population	Interventions	Study outcomes	Appraisal and funding
allogeneic stem cell transplant; ASCT: autologous stem cell transplant; BICR: blinded independent central review; BV: brentuximab vedotin; BVB: brentuximab vedotin and bendamustine; CD30: cluster of differentiation 30; CI: confidence interval; COPDAC: cyclophosphamide, vincristine, prednisone, and dacarbazine; COPP: cyclophosphamide, vincristine, procarbazine, and prednisone; CR: complete response; CT: computed tomography; CYA: children and young adults; DFS: disease-free survival; DHAP: dexamethasone, cytarabine, and cisplatin; FDG-PET: fluorodeoxyglucose positron emission tomography; G-CSF: granulocyte-colony stimulating factor; HL: Hodgkin lymphoma; IEP: ifosfamide, etoposide, and prednisone; IGEV: ifosfamide, gemcitabine, vinorelbine and prednisone; IQR: interquartile range; kg: kilogram; m: metre; mg: milligram; OEPA: vincristine, etoposide, prednisone, doxorubicin; OEPA/COPDAC: vincristine, etoposide, prednisone, doxorubicin/cyclophosphamide, vincristine, prednisone, dacarbazine; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; R/R: relapsed/refractory; SCT: stem cell transplant; TRAE: treatment-related adverse event				

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 case series)									
3-year overall survival[a] at a median follow-up of 42 months (range 11 to 94)[b]; %									
Retrospective case series Vinti et al 2022	Very serious limitations[1]	Very serious indirectness[2]	Not applicable	Not calculable	32	0	78.1% (95% CI 59.5 to 88.9)	Critical	Very low
Response rate (1 single arm trial & 1 case series)									
Objective response rate[c] per BICR after 2 cycles BVB intensification; % (n)									
Single arm trial (phase II) Harker-Murray et al 2023	Very serious limitations[3]	Very serious indirectness[4]	Not applicable	Not calculable	11	0	100% (11) • Complete metabolic response : 82% (9) • Partial metabolic response: 18% (2)	Critical	Very low
Objective response rate per investigator assessment after 2 cycles BVB intensification; % (n)									
Single arm trial (phase II)	Very serious limitations[3]	Very serious indirectness[4]	Not applicable	Not calculable	11	0	100% (11)	Critical	Very low

Harker-Murray et al 2023							• Complete metabolic response: 91% (10) • Partial metabolic response: 9% (1)		
Objective response rate per BICR after 4 cycles BVB intensification; % (n)									
Single arm trial (phase II) Harker-Murray et al 2023	Very serious limitations[3]	Very serious indirectness[4]	Not applicable	Not calculable	3	0	100% (3) • Complete metabolic response: 67% (2) • Partial metabolic response: 33% (1)	Critical	Very low
Objective response rate per investigator assessment after 4 cycles BVB intensification; % (n)									
Single arm trial (phase II) Harker-Murray et al 2023	Very serious limitations[3]	Very serious indirectness[4]	Not applicable	Not calculable	2	0	100% (2) • Complete metabolic response: 100% (2) • Partial metabolic response: 0% (0)	Critical	Very low
Overall response[d] rate at the end of BVB treatment (median of 4 (range 2 to 6) cycles; %									
Retrospective case series Vinti et al 2022	Serious limitations[5]	Very serious indirectness[2]	Not applicable	Not calculable	32	0	81% (95% CI 67 to 96); 26 patients Complete response rate[e]: 69% (95% CI 52 to 86); 22 patients • Partial response rate: 12% (95% CI 0.5 to 25); 4 patients • Progressive disease/relapse rate: 19% (95% CI 5 to 33); 6 patients	Critical	Very low

Complete response after first 2 cycles of BVB treatment; n (%)									
Retrospective case series Vinti et al 2022	Very serious limitations[3]	Very serious indirectness[2]	Not applicable	Not calculable	28	0	15 (54%) Partial response: 13 (46%)	Critical	Very low
Eligibility for stem cell transplant (1 case series)									
n of patients undergoing SCT[f] at end of BVB treatment (median of 4 (range 2 to 6) cycles); n									
Retrospective case series Vinti et al 2022	Very serious limitations[6]	Very serious indirectness[2]	Not applicable	Not calculable	32	0	• ASCT: 24 patients • Allo-SCT: 9 patients • No SCT: 3 patients	Critical	Very low
n of patients in whom an objective response was observed post BVB undergoing SCT at end of BVB treatment (median of 4 (range 2 to 6) cycles); n									
Retrospective case series Vinti et al 2022	Very serious limitations[6]	Very serious indirectness[2]	Not applicable	Not calculable	26	0	• ASCT: 22 patients • Allo-SCT: 4 patients (3 for having previously failed an ASCT prior to BVB & 1 for medical decision) • Subsequent allo-SCT after ASCT: 4 patients (3 for relapse or progressive disease after BVB-post ASCT or radiotherapy & 1 for consolidation of a partial response achieved with ASCT post initial BVB)	Critical	Very low
n of patients in whom a progressive disease/relapse was observed post BVB undergoing SCT at end of BVB treatment (median of 4 (range 2 to 6) cycles); n									
Retrospective case series Vinti et al 2022	Very serious limitations[6]	Very serious indirectness[2]	Not applicable	Not calculable	6	0	• ASCT: 2 • Allo-SCT: 1	Critical	Very low

Progression-free survival (1 case series)									
3-year progression-free survival[g] at a median follow-up of 42 months; %									
Retrospective case series Vinti et al 2022	Very serious limitations[1]	Very serious indirectness[2]	Not applicable	Not calculable	32	0	67% (95% CI 47.2 to 80.7)	Important	Very low
Disease-free survival (1 case series)									
3-year disease-free survival[h] at a median follow-up of 42 months; %									
Retrospective case series Vinti et al 2022	Very serious limitations[1]	Very serious indirectness[2]	Not applicable	Not calculable	32	0	62.3% (95% CI 43.3 to 76.6)	Important	Very low
Safety (1 single arm trial & 1 case series)									
Treatment related AEs (any grade) at a median follow-up of 20.9 months (range 2.6 to 29.2 months), n (%)									
Single arm trial (phase II) Harker-Murray et al 2023	Serious limitations[5]	Very serious indirectness[4]	Not applicable	Not calculable	11	0	8 (72.7%)	Important	Very low
Treatment related AEs (grade 3 or 4) at a median follow-up of 20.9 months (range 2.6 to 29.2 months), n (%)									
Single arm trial (phase II) Harker-Murray et al 2023	Serious limitations[5]	Very serious indirectness[4]	Not applicable	Not calculable	11	0	3 (27.3%) One patient experienced vomiting and decreased white blood cell count; one experienced increased lipase; and one experienced neutropenia	Important	Very low

Treatment related AEs with ≥2 patients in either the induction or intensification phase at a median follow-up of 20.9 months (range 2.6 to 29.2 months), n (%)									
Single arm trial (phase II) Harker-Murray et al 2023	Serious limitations[5]	Very serious indirectness[4]	Not applicable	Not calculable	11	0	Vomiting (any grade): 6 (54.5%) Nausea (any grade): 5 (45.5%) Infusion-related reaction (any grade): 2 (18.2%) Headache (any grade): 2 (18.2%) Vomiting (grade 3/4): 1 (9.1%) Hypersensitivity (any grade): 1 (9.1%) Diarrhoea (any grade): 1 (9.1%) Pyrexia (any grade): 1 (9.1%) Increased AST (any grade): 1 (9.1%)	Important	Very low
Grade 2 AEs at a median follow-up of 42 months (range 11 to 94)[i]; n (%)									
Retrospective case series Vinti et al 2022	Very serious limitations[1]	Very serious indirectness[2]	Not applicable	Not calculable	32	0	Nausea/vomiting: 8 (18.2%) Erythema: 2 (4.5%) Anaemia: 11 (25%) Neutropenia: 5 (11.4%) Thrombocytopenia: 7 (15.9%) Peripheral neuropathy: 3 (6.8%)	Important	Very low
Grades 3-4 AEs[j] at a median follow-up of 42 months (range 11 to 94); n (%)									
Retrospective case series Vinti et al 2022	Very serious limitations[7]	Very serious indirectness[2]	Not applicable	Not calculable	32	0	Anaemia: 8 (18.2%) Neutropenia: 23 (52.3%) Thrombocytopenia: 8 (18.2%)	Important	Very low
Number of patients discontinuing treatment due to grades 3–4 at a median follow-up of 42 months (range 11 to 94); n									

Retrospective case series Vinti et al 2022	Very serious limitations[1]	Very serious indirectness[2]	Not applicable	Not calculable	32	0	0	Important	Very low
Number of fatal events related to treatment at a median follow-up of 42 months (range 11 to 94); n									
Retrospective case series Vinti et al 2022	Very serious limitations[1]	Very serious indirectness[2]	Not applicable	Not calculable	32	0	0	Important	Very low
Abbreviations: AE: adverse event; allo-SCT: allogeneic stem cell transplant; ASCT: autologous stem cell transplant; BICR: blinded independent central review; BVB: brentuximab vedotin and bendamustine; CI: confidence interval; SCT: stem cell transplant									

1. Risk of bias: very serious limitations due to unclear reporting of whether the study included consecutive patients and complete inclusion of patients and no follow-up length reported or inconsistent reporting of follow-up length
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 whether the study included consecutive patients and complete inclusion of patients and no confidence intervals reported
4. Indirectness: very serious indirectness due to lack of comparator group and results relating to a subgroup of in scope patients
5. Risk of bias: serious limitations due to unclear reporting of whether the study included consecutive patients and complete inclusion of patients
6. Risk of bias: very serious limitations due to unclear reporting of whether the study included consecutive patients and complete inclusion of patients and inconsistent reporting of results
7. Risk of bias: very serious limitations due to unclear reporting of whether the study included consecutive patients and complete inclusion of patients and inconsistent reporting of results and no follow-up length reported

a. Defined as the time from study enrolment to death due to any cause or last follow-up
b. This follow-up was reported in the results section in the paper. However it is worth noting that a different follow-up length was reported in the discussion for survival outcomes (median of 36 months (range 8.7 to 86))
c. Complete response plus partial response
d. Defined as Deauville ≤3 per Lugano 2014 criteria
e. Complete response plus partial response
f. Defined as all target lesions with a Deauville score of 3 or less regardless of residual mass size
g. Results taken from Figure 2 in the paper. The subsequent allo-SCT results differ slightly from those reported in the main text which reported that five patients received a subsequent allo-SCT: three patients for relapse, one patient for progressive disease (after two more lines of chemotherapy), and one patient as consolidation of a progressive response achieved with ASCT
h. Defined as time from study enrolment to the date of first event or last follow-up. Events were either disease progression or death due to any cause
i. Defined as time from complete response to recurrence of tumour or death
j. Follow-up for safety outcomes not reported. The follow-up for survival outcomes has been used.
k. These results were extracted from Table 2 on adverse events. It should be noted that the text in the paper reports that *"the most common treatment-related AE was grades 3–4 hematological toxicity in 14 patients (44%)"* which is inconsistent with the results presented in Table 2 of the paper.

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.
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.
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.

References

Included studies

- 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.
- 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.

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