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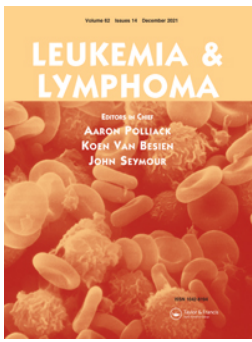
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## Effectiveness of brentuximab vedotin monotherapy in relapsed or refractory Hodgkin lymphoma: a systematic review and meta-analysis

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## Effectiveness of brentuximab vedotin monotherapy in relapsed or refractory Hodgkin lymphoma: a systematic review and meta-analysis

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### ABSTRACT

This systematic review and meta-analysis aimed to determine the effectiveness of brentuximab vedotin (BV) in relapsed/refractory classical Hodgkin lymphoma (R/R cHL) in the clinical practice setting using most recent results. A total of 32 observational studies reporting on treatment patterns, overall response rate (ORR), complete response (CR) rate, progression-free survival (PFS), overall survival (OS), and adverse events were found. After four cycles, a random-effect model yielded pooled ORR and CR rates of 62.6% (95% confidence interval (CI): 56.0–68.9;  $I^2 = 9.7%$ ) and 32.9% (95% CI, 20.8–46.3,  $I^2 = 64.8%$ ), respectively. Regarding survival, 1-year, 2-year, and 5-year PFS ranged from 52.1% to 63.2%, 45.2% to 56.2%, and 31.9% to 33.0%, respectively. OS rates were 68.2–82.7%, 58.0–81.9%, and 58.0–62.0%, respectively. Most common adverse events were hematological toxicities (neutropenia: 13.3–23%, anemia: 8.8–39.0%, and thrombocytopenia: 4–4.6%), and grade  $\geq 3$  peripheral neuropathy (3.3–7.3%). This study supports the effectiveness and safety of BV in R/R cHL patients in the real-world setting.

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### Introduction

Hodgkin lymphoma (HL) is a cancer of the lymphatic system characterized by the presence of Reed-Sternberg cells [1]. Although modern chemotherapy and radiotherapy regimens have made HL one of the most curable malignancies, 10–15% of early stage and 20–30% of advanced stage patients experience relapse after the initial treatment [2]. Only 50% of patients with relapsed or refractory classical Hodgkin lymphoma (R/R cHL) achieve a prolonged complete remission with high-dose chemotherapy and autologous stem cell transplantation (ASCT) [3], representing an important unmet medical need.

Brentuximab vedotin (BV, ADCETRIS<sup>®</sup>), an anti-CD30 antibody drug conjugate, was shown to be effective

and well-tolerated for the treatment of R/R cHL. In a pivotal phase II trial, the overall response rate (ORR) was 75% and complete response (CR) was observed in 34% of patients [4]. Previous meta-analyses compared these results to the activity of other drug therapies or experimental agents used for R/R cHL in the post ASCT setting and found that BV was superior to other therapies in terms of CR and overall survival (OS) [5,6]. In these analyses, BV data originated from the pivotal phase II trial only. Similar findings to the pivotal phase II trial were since obtained in observational studies; however, due to limited sample size (51–196 patients treated with BV), effectiveness estimates lacked precision [7,8]. To enhance the strength of evidence on the effectiveness of BV in the clinical practice setting for the treatment of R/R cHL in the adult population (age

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 Supplemental data for this article can be accessed [here](#).

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≥18 years), a systematic review of observational studies was undertaken, followed by a meta-analysis of effectiveness outcomes.

## Methods

The systematic review was conducted according to a protocol developed a priori and registered in PROSPERO (CRD42020173134).

### Systematic review

Three sources of information were used: (i) literature search; (ii) pragmatic searches of web sources; and (iii) screening of reference list of retained studies (i.e. snowballing). Search period covered the past 10 years (1 January 2010 to 6 February 2020). The literature search was conducted in Ovid MEDLINE, Embase, and Web of Science using free-text keywords and thesaurus terms (i.e. MeSH and Emtree terms, respectively, for MEDLINE and Embase). Pragmatic searches involved a review of websites of relevant learned or clinical societies and related conference proceedings. Sources identified were screened independently by two reviewers (with conflicts resolved by a third independent assessor) using the following pre-defined inclusion criteria: (i) observational (non-interventional) studies including registries and case series; (ii) studies that included adult patients (age ≥18 years) with R/R cHL; (iii) sample size ≥20 patients; (iv) studies that reported effectiveness outcomes of BV used as a single agent; (v) original studies, conference proceedings, abstracts, reviews, or meta-analyses; (vi) publications written in English, French, or Spanish. Expert opinions, editorials, non-clinical studies, phase I–III clinical trials, and case reports were excluded. Data of interest were patterns of BV use, ORR, CR rate, progression-free survival (PFS), OS, and adverse events. Data extraction was conducted independently by two assessors (with conflicts resolved by a third) and the data extraction form was piloted prior to the start of data extraction. The review was conducted according to the methods proposed by the Cochrane group [9] and the Institute of Medicine (IOM) of the National Academy of Medicine (NAM) [10]. The methodological quality of retained full-text publications was assessed using the Joanna Briggs Institute (JBI) critical appraisal tools for original studies [11]. To be considered of good methodological quality, studies were required to meet at least seven of the criteria from the checklist for cohort studies (11 items) or for case series (10 items). Owing to insufficient information, the methodological quality of studies published as abstracts only could not be determined.

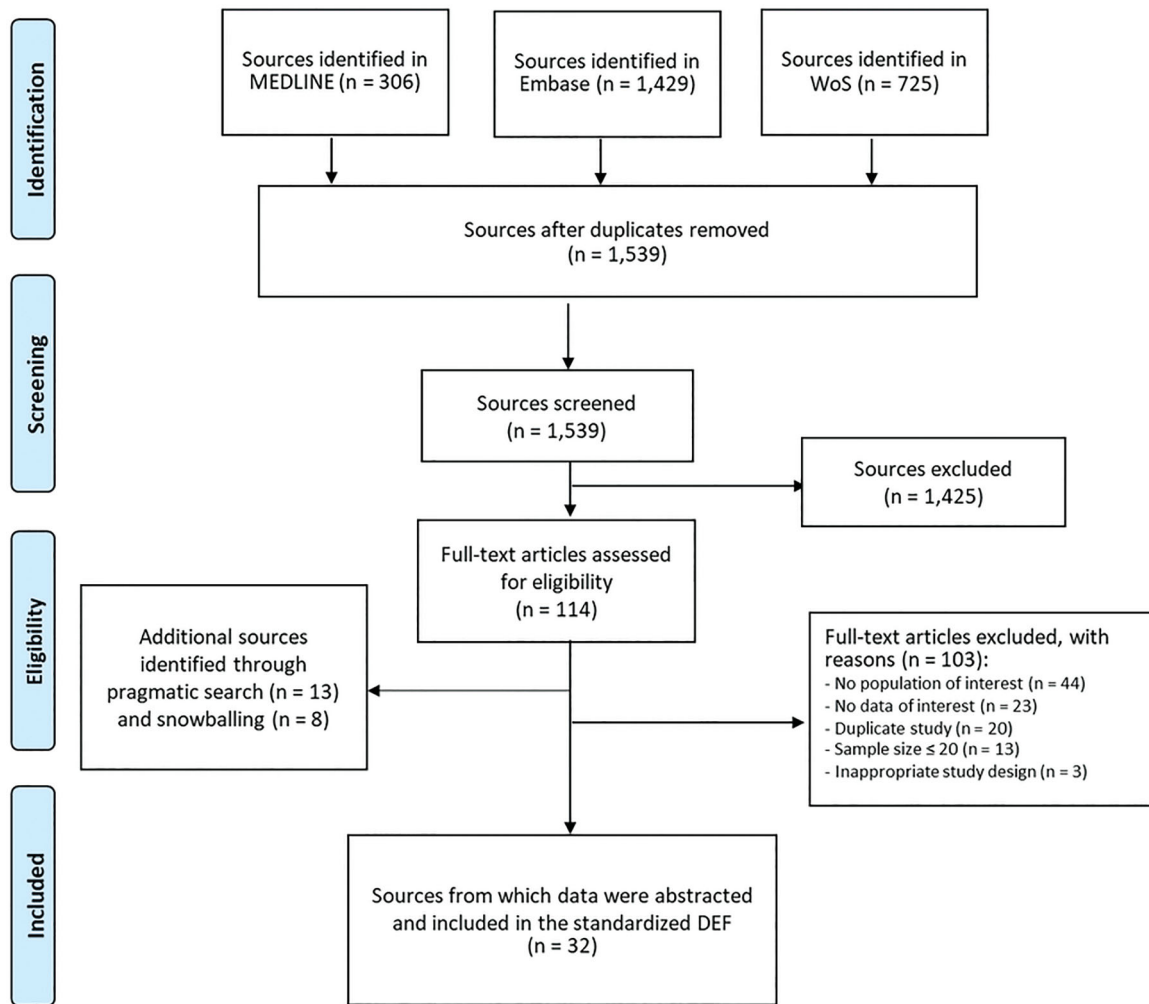
## Meta-analysis

For each effectiveness outcome of interest (ORR, CR, PFS, and OS), a qualitative assessment of the clinical and methodological heterogeneity of retained studies was conducted. Statistical heterogeneity was quantified through the  $I^2$  statistics, which is the percentage of variation across studies that is due to heterogeneity rather than chance. According to the Cochrane recommendations, when the  $I^2$  exceeds 50%, heterogeneity is considered substantial, and estimates should not be pooled [12]. When heterogeneity exceeded the threshold, alternative subgroups analyses based on study design, populations, or BV treatment schedule were explored. Primary meta-analyses included studies of good methodological quality only. Two sets of sensitivity analyses were conducted: the first included studies of good and moderate quality, and the second included previous estimates as well as those published as abstracts only. When appropriate, estimates were pooled using a random effects model. The presence of publication bias was determined using a funnel plot. All statistical analyses were performed using MetaXL, version 5.3 [13].

## Results

### Search results

The selection of sources through the different phases of the search is presented in the PRISMA flowchart (Figure 1). The literature search yielded 2460 sources, of which 114 were retained for in-depth review. There were 103 sources that were further excluded at this stage for reasons listed in Figure 1. Pragmatic searches and snowballing yielded 21 additional sources. Data were thus abstracted from 32 sources (13 original studies, 17 abstracts, one letter to the editors, and one website). The majority of studies originated from Europe ( $n=24$ ; 75.0%). Countries covered included France ( $n=3$ ), Germany ( $n=2$ ), Greece ( $n=2$ ), Italy ( $n=4$ ), Poland ( $n=2$ ), the United Kingdom (UK) ( $n=5$ ), and other countries ( $n=6$ ; Bulgaria, Czech Republic, Portugal, Slovakia, and Sweden). The remainder were from North America ( $n=4$ ; 12.5%, all from the United States) and Asia ( $n=3$ ; 9.4%, one from Kazakhstan, one from Japan and one from Taiwan). Also, a multiregional study conducted in six national centers was identified (countries not specified). Patient populations were relatively homogenous across studies. Specifically, the median age ranged between 27 years and 45.7 years, and most studies included a majority of patients who underwent ASCT prior to



**Figure 1.** PRISMA flowchart of search results. DEF: data extraction form; WoS: Web of Science.

initiating BV. In the few studies that reported the Eastern Cooperative Oncology Group (ECOG) performance status, most patients had a score  $\leq 2$ . A summary of study characteristics is presented in Table 1. Details regarding patient populations are summarized in Table 2.

### **Patterns of BV use in R/R cHL patients**

According to 26 sources that reported patterns of BV usage in R/R cHL patients ( $n = 18$  [22] to 241 patients [29]), BV was used as a single agent after a median of 3 prior regimens (range: 2–4). Dosing regimen was 1.8 mg/kg every three weeks and the median number of BV cycles administered ranged from 4 [18,32,35] to 8 [7,14,16,20].

### **Treatment response**

To evaluate treatment response, most studies relied on positron emission tomography (PET) or computed

tomography (CT) scans, with most centers using either technique depending on availability. Also, a majority of studies based this assessment on the 2007 revised response criteria for malignant lymphoma from the International Working Group [44] while a minority of studies considered the Lugano Classification (2014) [20,39]. Across studies, response was typically assessed after several cycles of BV treatment, ranging from two cycles to the end of treatment.

Based on results reported in 24 studies, the ORR of BV in R/R cHL patients ranged from 46.6% [26] to 84.0% [19]. In these studies, the study populations were representative of patients who are eligible to BV, according to the approved indication. Specifically, the proportion of patients who received previous ASCT ranged from 25.5% [24] to 100% [8,17,36] and 37.5% [27] to 81% [42] patients had refractory HL, defined as stable or progressive disease during first-line or salvage chemotherapy. However, almost half studies ( $n = 10$ ; 41.7%) did not provide any details regarding the distribution of patients according to relapse or

**Table 1.** Characteristics of studies included in the systematic review on the effectiveness and safety of BV in R/R cHL patients (N = 32).

Study authors	Country	Year	Design	Study period	Data source	Sample size	Response assessment	Effectiveness and safety parameter(s)
<i>Europe (n = 24)</i> Angelopoulou et al. [14]	Greece	2018	CS	June 2011–April 2015	Medical chart review	95	International Working Group Criteria (2007) – as reported by treating physicians	ORR, CR, OS, PFS
Bazarbachi et al. [15]	Multinational	2019	RC	2010–2014	Registry (disease)	80	International Working Group Criteria (2007) – assessed retrospectively	ORR, CR, OS
Brockelmann et al. [16]	Germany, United Kingdom	2017	CS	January 2008–June 2014	Medical chart review	136	NR	ORR, CR, OS, PFS, AEs
Chavda et al. [17]	Multinational	2019	CS	2012–2019	Registry (disease)	101	NR	ORR, CR, AEs
Czay et al. [18]	Poland	2018	RC	2018 <sup>a</sup>	Medical chart review	57	PET scan – assessed retrospectively	ORR, CR, OS, PFS, AEs
Czay et al. [19]	Poland	2019	RC	2012–2018	Medical chart review	44	CT or PET scan	ORR, OS, PFS
Gandolfi et al. [20]	Italy	2016	CS	2016 <sup>b</sup>	EMRs	43	International Working Group Criteria (2007) and Lugano Classification (2014) – assessed retrospectively	ORR, CR, OS, PFS
Gardiaz et al. [21]	France	2014	CS	July 2009–November 2012	Medical chart review	24	International Working Group Criteria (2007) – assessed retrospectively	ORR, CR, OS, PFS, AEs
Gibb et al. [22]	United Kingdom	2013	CS	December 2010–August 2011	Medical chart review	18	International Working Group Criteria (2007) – as reported by treating physicians	ORR, CR
Goranova-Marinova et al. [23]	Bulgaria	2019	CS	2019 <sup>a</sup>	Medical chart review	64	NR	ORR, CR, PFS
Ionova et al. [24]	Russia	2019	CS	2019 <sup>b</sup>	Ad hoc data collection	55	RECIST Criteria v1.0 – as reported by treating physicians	ORR, CR, AEs
Jansson et al. [25]	Sweden	2018	CS	2011–2017	Medical chart review	39	NR	ORR, CR, OS, PFS
Kral et al. [26]	Czech Republic, Slovakia	2019	CS	2012–2016	Registry (disease)	58	International Working Group Criteria (2007) – assessed retrospectively	ORR, CR, OS, PFS, AEs
Ladicka et al. [7]	Slovakia	2018	CS	July 2012–February 2017	Medical chart review	51	NR	NR
Monjanel et al. [27]	France	2014	CS	June 2009–October 2012	Medical chart review	32	International Working Group Criteria (2007) – assessed retrospectively	ORR, CR, PFS
Pellegrini et al. [28]	Italy	2017	CS	November 2012–July 2014	Medical chart review	234	International Working Group Criteria (2007) – assessed retrospectively	ORR, CR, OS, PFS, AEs
Perrot et al. [29]	France	2014	CS	2011–2014	Medical chart review	241	International Working Group Criteria (2007) – assessed retrospectively	ORR, CR, OS, PFS
Piddock et al. [30]	United Kingdom	2017	CS	2017 <sup>a</sup>	Medical chart review	24	International Working Group Criteria (2007) – as reported by treating physicians	ORR, CR
Pierdomenico et al. [31]	Portugal	2016	CS	September 2011–February 2016	Medical chart review	34	PET-CT scan – assessed retrospectively	ORR, CR, OS, PFS, AEs
Sarma et al. [32]	United Kingdom	2016	CS	2013–2015	Medical chart review	26	FDG-PET/CT scan – assessed retrospectively	ORR, CR
Tsirigotis et al. [33]	Greece	2018	RC	1995–2015	Registry (disease)	68	NA	OS
Viviani et al. [34]	Italy	2015	RC	January 2011–April 2014	Medical chart review	45	PET scan – assessed retrospectively	ORR, CR, OS, PFS, AEs
Zagadailov et al. [8]	Germany, United Kingdom	2018	RC	January 2008–June 2014	Medical chart review	196	NR	ORR, CR, PFS, AEs
Zinzani et al. [35]	Italy	2015	CS	2011–2014	Medical chart review	30	International Working Group Criteria (2007) – assessed retrospectively	ORR, CR, AEs
<i>North America (n = 4)</i> Badar et al. [36]	United States	2020	RC	2005–2016	Medical chart review	98	PET scan – assessed retrospectively	ORR, CR, PFS
Houk et al. [37]	United States	2014	RC	2009–2014	Medical chart review	43	NA	PFS
Rajeev et al. [38]	United States	2018	CS	2008–2015	Medical chart review	21	NR	ORR, CR
Svoboda et al. [39]	United States	2019	RC	2013–2018	Medical chart review	21	Lugano Classification (2014) – as reported by treating physicians	ORR, CR
<i>Asia-Pacific (n = 2)</i> NCT02139592 [40]	Japan	NA	PC	April 2014–June 2017	Ad hoc data collection	182	PET scan – as reported by treating physicians	ORR, OS

(continued)



Table 1. Continued.

Study authors	Country	Year	Design	Study period	Data source	Sample size	Response assessment	Effectiveness and safety parameter(s)
Tien et al. [41] Central Asia ( <i>n</i> = 1)	Taiwan	2019	CS	May 2016–October 2018	Medical chart review	20	PET scan – assessed retrospectively	ORR, CR, OS, PFS, AEs
Jazylytayeva et al. [42]	Kazakhstan	2019	CS	2015–2018	Medical chart review	21	NR	ORR, CR, OS
Multi-regions ( <i>n</i> = 1) Karuturi et al. [43]	Multinational	2012	RC	1996–2009	Medical chart review	102	NA	OS

AEs: adverse events; CS: case series; CR: complete response; CT: computed tomography; EMBs: electronic medical records; FDG: fluorodeoxyglucose; NA: not applicable; NR: not reported; ORR: overall response rate; OS: overall survival; PC: prospective cohort; PET: positron emission tomography; PFS: progression-free survival; RC: retrospective cohort.  
<sup>a</sup>Year of publication.

refractory status. Lower estimates of ORR (20.6% [31] to 40.0% [35]) were reported in case series from France [29], Italy [35], Portugal [31], and the UK [32]. In the case series from France (*n* = 241) and Portugal (*n* = 34), the estimates of ORR after 2–4 cycles of BV were within the previously reported range (58% [29] and 67% [31], respectively). However, at the end of treatment with BV, the ORR was 32% in France (median number of BV cycles = 6, range: 1–16) [29] and 20.6% in Portugal (median number of BV cycles = 7.5) [31]. In the case series from Italy (*n* = 30) [35] and the UK (*n* = 26) [32], BV was evaluated as a bridge to ASCT for R/R cHL patients who achieved a suboptimal response to salvage treatment, with reported ORR estimates of 40.0% and 38.5%, respectively, after four cycles.

According to 22 studies, 21.1% [41] to 45.8% [21] R/R cHL patients treated with BV achieved CR. Lower estimates (14.3% [42] to 16.7% [21,22]) were found in four case series that included either small sample sizes (*n* = 21 [27], *n* = 24 [30], and *n* = 18 [22]) or covered a specific population [31]. Conversely, in a conference proceeding that reported on a study conducted at the Memorial Sloan Kettering Cancer Center (MKSCC) in the United States, 13 (61.9%) of the 21 R/R cHL patients who received BV post-ASCT relapse achieved CR [38].

Out of the 26 studies that reported estimates of ORR or CR, there were 12 full-text publications. These were considered for the meta-analysis and the qualitative assessment of clinical and methodological heterogeneity revealed no major differences across those 12 studies. In all studies, patients received BV in monotherapy, and the majority of patients (range: 50% [21] to 87.5% [27]) had advanced disease (stage III or IV) and a previous ASCT (range: 33.3% [22] to 100% [8,36]). As the time period for the assessment of treatment response varied across studies, three subgroups were defined: (i) assessment after four cycles; (ii) assessment after 4–6 cycles; and (iii) assessment after more than six cycles. Seven of these 12 studies were deemed of good methodological quality [8,14,15,20,22,28,36] and were included in the primary meta-analysis while the remaining five studies were of moderate methodological quality and hence, were only considered for the sensitivity analyses [16,21,26,27,41]. In addition, there were 14 studies which consisted of abstracts or conference proceedings that were included in a second set of sensitivity analyses [17–19,23–25,29–32,34,38,39,42].

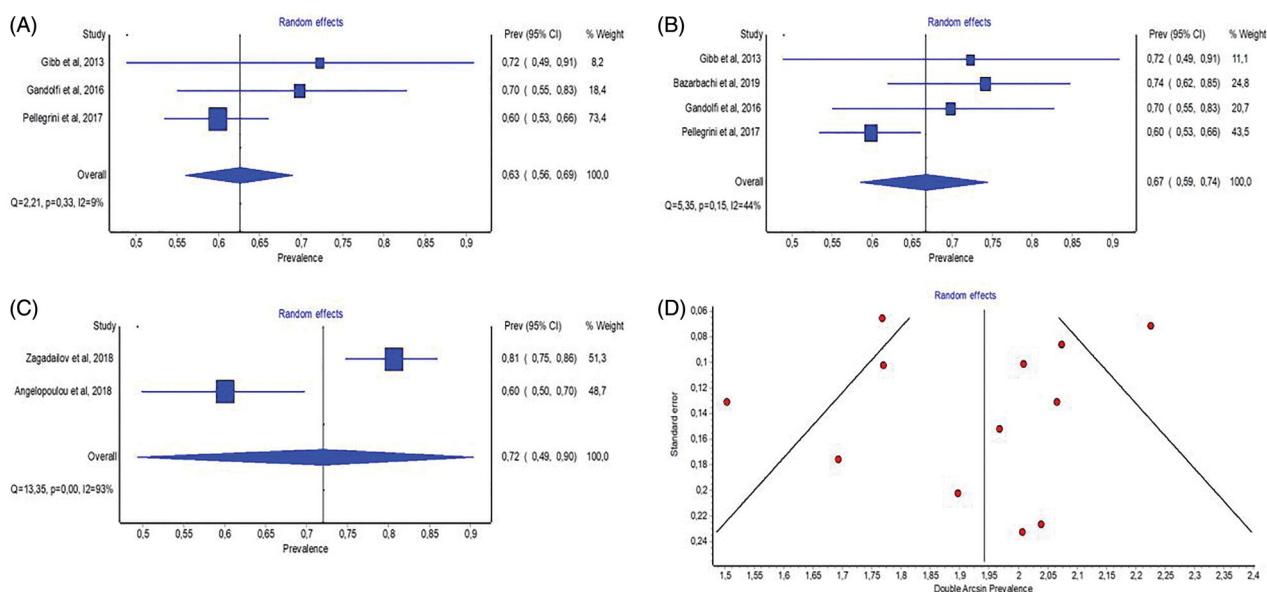
Pooled estimates of ORR according to the number of BV cycles are summarized in Figure 2 with details

**Table 2.** Patient characteristics in studies included in the systematic review on the effectiveness and safety of BV in R/R cHL patients ( $N = 32$ ).

Study reference	Age distribution	Comorbidities	ECOG PS	Prior SCT
<i>Europe (n = 24)</i>				
Angelopoulou et al. [14]	Median: 33 years	NR	NR	ASCT: 70% ( $n = 67$ ) Allo-SCT: 2.1% ( $n = 2$ ) ASCT: 77.2% ( $n = 142$ )
Bazarbachi et al. [15]	Median: 30 years (19–59)	NR	NR	NR
Brockelmann et al. [16]	Mean: 66.7 ± 11.7 years	Mean Charlson Comorbidity Index: 2.3 ± 2.0	0: 2.2% ( $n = 3$ ) 1: 35.3% ( $n = 48$ ) 2: 51.5% ( $n = 70$ ) 3: 8.8% ( $n = 12$ ) 4: 0.7% ( $n = 1$ )	
Chavda et al. [17]	Median: 34 years (range, 19–65)	NR	NR	ASCT: 100%
Czyz et al. [18]	Median: 33 years (range, 18–68)	NR	NR	ASCT: 36.2% ( $n = 34$ )
Czyz et al. [19]	NR	NR	NR	ASCT: 100%
Gandolfi et al. [20]	Median: 33.4 years (range, 18.2–79.4)	NR	0: 60.5% ( $n = 26$ ) 1: 39.5% ( $n = 17$ )	ASCT: 60.5% ( $n = 26$ )
Garciaz et al. [21]	Median: 35 years (range, 20–60)	NR	0–1: 95.8% ( $n = 23$ )	ASCT: 41.7% ( $n = 10$ ) Allo-SCT: 16.7%
Gibb et al. [22]	NR	NR	NR	ASCT: 33% ( $n = 6$ )
Goranova-Marinova et al. [23]	Mean: 40.7 ± 13.1 years	NR	NR	ASCT: 70.3% ( $n = 45$ )
Ionova et al. [24]	Median: 28 years (range, 18–67)	NR	0–1: 82% ( $n = 45$ )	ASCT: 25.5% ( $n = 14$ )
Jansson et al. [25]	Median: 41 years (range, 17–78)	NR	NR	ASCT: 43.6% ( $n = 17$ ) ASCT + allo-SCT: 7.7% ( $n = 3$ )
Král et al. [26]	Median: 30.5 years (range, 20.0–53.0)	NR	NR	ASCT: 91.4% ( $n = 53$ ) 1 ASCT: 79.3% ( $n = 46$ ) 2 ASCT: 12.1% ( $n = 7$ ) Allo-SCT: 12.1% ( $n = 7$ )
Ladicka et al. [7]	Median: 38.8 years	NR	NR	NR
Monjanel et al. [27]	Median: 35 years (range, 20–69)	NR	NR	ASCT: 87.5% ( $n = 28$ ) Allo-SCT: 15.6% ( $n = 5$ )
Pellegrini et al. [28]	Median: 35.4 years (range, 18.0–79.0)	NR	0: 60.5% ( $n = 26$ ) 1: 39.5% ( $n = 17$ )	ASCT: 69.8% ( $n = 163$ )
Perrot et al. [29]	Median: 34 years (range, 17–79)	Pre-existent peripheral neuropathy: 8% ( $n = 20$ )	0–1: 81% ( $n = 196$ )	At least 1 SCT: 61% ( $n = 147$ ) 2 SCT: 36% ( $n = 87$ ) Allo-SCT: 16% ( $n = 39$ )
Piddock et al. [30]	Median: 40 years (range, 21–77)	NR	NR	ASCT: 27.3% ( $n = 9$ )
Pierdomenico et al. [31]	Median: 34.5 years (range, 23–69)	NR	NR	SCT: 64% ( $n = 22$ )
Sarma et al. [32]	Median: 36 years (range, 23–63)	NR	NR	ASCT: 11.5% ( $n = 3$ )
Tsirigotis et al. [33]	Median: 31 years (range, 19–68)	NR	NR	ASCT: 100%
Viviani et al. [34]	Median: ASCT-ineligible: 38 years (range, 20–76) Failed ASCT: 39 years (range, 16–64)	NR	NR	ASCT: 55.6% ( $n = 25$ )
Zagadailov et al. [8]	Mean: 45.7 ± 15.4 years	NR	>1: 75.5% ( $n = 148$ )	ASCT: 100%
Zinzani et al. [35]	Median: 27 years	NR	NR	0%
<i>North America (n = 4)</i>				
Badar et al. [36]	Median at time of ASCT: 35 years (range, 19–73)	NR	NR	ASCT: 100%
Houk et al. [37]	Median: 34 years (range, 17–80)	NR	NR	ASCT: 72.1% ( $n = 31$ ) Allo-SCT: 23.3% ( $n = 10$ )
Rajeev et al. [38]	Median: 40 years (range, 21–66)	NR	NR	ASCT: 100%
Svoboda et al. [39]	Median: 31 years (range, 18–76)	NR	NR	0%
<i>Asia-Pacific (n = 2)</i>				
NCT02139592 [40]	Mean: 56.7 ± 19.8 years	Hepatic disorder: 8.8% ( $n = 25$ ) Renal disorder: 7.0% ( $n = 20$ )	0: 40.1% ( $n = 114$ ) 1: 36.6% ( $n = 104$ ) 2: 11.3% ( $n = 32$ ) 3: 6.7% ( $n = 19$ ) 4: 5.3% ( $n = 15$ )	ASCT: 15.1% ( $n = 43$ ) Allo-SCT: 3.2% ( $n = 9$ ) ASCT + allo-SCT: 4.2% ( $n = 12$ )
Tien et al. [41]	Median: 28 years (range, 18–85)	NR	NR	ASCT: 60.0% ( $n = 12$ )
<i>Central Asia (n = 1)</i>				
Jazylytayeva et al. [42]	Mean: 34.5 years (range, 20–69)	NR	NR	NR
<i>Multi-regions (n = 1)</i>				
Karuturi et al. [43]	NR	NR	NR	ASCT: 100%

Allo-SCT: allogeneic stem cell transplant; ASCT: autologous stem cell transplant; ECOG PS: Eastern Cooperative Oncology Group Performance Status; NR: not reported; SCT: stem cell transplant.





**Figure 2.** Meta-analysis of overall response rates. (A) Forest plot of estimates of overall response rates after 4 cycles of treatment with BV (1st subgroup); (B) forest plot of estimates of overall response rates after 4–6 cycles of treatment with BV (2nd subgroup); (C) forest plot of estimates of overall response rates after 6 or more cycles of treatment with BV (3rd subgroup); (D) funnel plot of full-text publications reporting overall response rate estimates ( $n = 12$  publications).

**Table 3.** Pooled estimates of complete response.

Subgroups	Primary analysis (full-text publications of good methodological quality)		
	Number of studies (R/R cHL patients treated with BV)	Pooled CR (95% CI)	Heterogeneity statistics
1st subgroup (CR after 4 cycles)	3 ( $n = 295$ )	32.9% (20.8–46.3)	$I^2=64.8\%$ (95% CI: 0–89.9) Cochran's $Q = 5.7$ ; $p=.05$
2nd subgroup (CR after 4–6 cycles)	4 ( $n = 353$ )	32.4% (24.3–41.1)	$I^2=49.3\%$ (95% CI: 0–83.2) Cochran's $Q = 5.9$ ; $p=.12$
3rd subgroup (CR after 6 or more cycles)	2 ( $n = 291$ )	33.4% (13.0–57.3)	$I^2=92.9\%$ (95% CI: 76.4–97.9) Cochran's $Q = 14.1$ ; $p=.0002$

BV: brentuximab vedotin; CI: confidence interval; CR: complete response; R/R cHL: relapsed/refractory classical Hodgkin lymphoma.

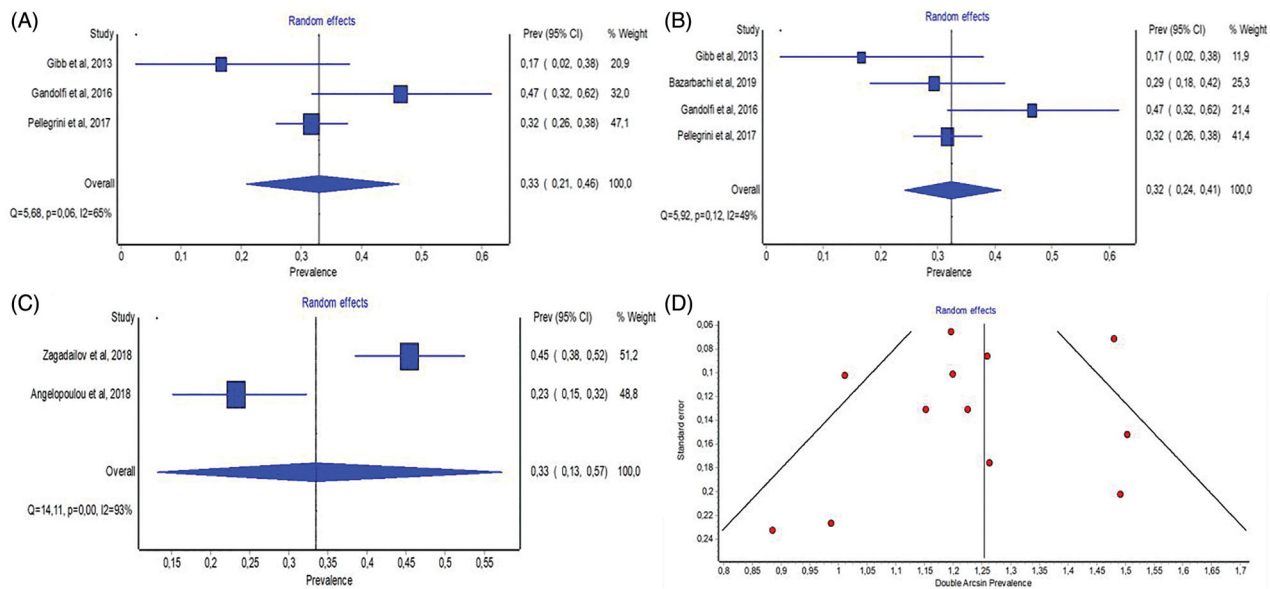
provided in [Supplementary Table 1](#). The pooled estimate was 62.6% (95% confidence interval (CI), 56.0–68.9;  $I^2 = 9.5\%$ ) after four cycles, 66.7% (95% CI, 58.5–74.5;  $I^2 = 43.9\%$ ) after 4–6 cycles and 72.0% (95% CI, 49.3–90.4,  $I^2 = 92.5\%$ ) after more than six cycles. Pooled estimates originating from good and moderate quality studies (sensitivity analysis 1) as well as those including data published as abstracts (sensitivity analysis 2) were similar to results of the main meta-analysis, thus confirming the robustness of findings ([Supplementary Table 2](#)). Also, as shown in the funnel plot ([Figure 2\(D\)](#)), the distribution of studies around the average estimate is relatively symmetrical, therefore, suggesting no or minor publication bias.

Pooled estimates of CR are summarized in [Table 3](#) and in [Figure 3](#). Results from the primary meta-analysis were 32.9% (95% CI, 20.8–46.3,  $I^2 = 64.8\%$ ), 32.4% (95% CI, 24.3–41.1;  $I^2 = 49.3\%$ ), and 33.4% (95% CI, 13.0–57.3,  $I^2 = 92.9\%$ ), respectively, for each subgroup

of cycles. Despite the substantial statistical heterogeneity ( $I^2 > 50\%$ ) associated with two pooled estimates, both sensitivity analyses led to similar pooled estimates ([Table 4](#)). According to the funnel plot presented in [Figure 3\(D\)](#), there was no or minor publication bias.

### Survival in R/R cHL patients treated with BV

A total of 18 sources documented PFS in R/R cHL patients treated with BV. Twelve studies (66.7%) defined this parameter as the median duration from BV initiation until disease progression, relapse, or death from any cause, with estimates ranging from 5 [34] to 16.6 [26] months. Other measures of PFS identified included 1-year PFS (two studies, 52.1% [16], and 63.2% [26]), 2-year PFS (three studies, 45.2% [26], 51% [18], and 56.2% [19]), 3-year PFS (one study, 36.7% [20]), and 5-year PFS (two studies, 31.9% [28] and 33.0% [25]).



**Figure 3.** Meta-analysis of complete response rates. (A) Forest plot of estimates of complete response after 4 cycles of treatment with BV (1st subgroup); (B) forest plot of estimates of complete response after 4–6 cycles of treatment with BV (2nd subgroup); (C) forest plot of estimates of complete response after 6 or more cycles of treatment with BV (3rd subgroup); (D) funnel plot of full-text publications reporting complete response estimates ( $n = 12$  publications).

Nine full-text publications that reported estimates of the median PFS were considered for the meta-analysis. The qualitative assessment of clinical heterogeneity revealed no major differences across studies. However, in all these studies, only point estimates of PFS were reported. Therefore, a meta-analysis could not be conducted due to the lack of information on the distribution of data (i.e. interquartile range, 95% CI).

A total of 18 publications reported estimates of OS in R/R cHL patients treated with BV, with five reporting median OS: 17.8 [16], 26.5 [14], 33.2 [42], 57.0 [33], and 91.5 months [43]. The lowest estimate was found in a case series of 136 R/R cHL patients ineligible to ASCT identified in Germany and the UK [16] and, the highest estimate was reported in a conference proceeding describing patients treated with BV following a relapse after ASCT over a median follow-up period of 49.4 months [43]. In four studies, median OS was not reached. In these studies, follow-up periods following BV initiation were 14 months (range: 1–36) [34], 16 months [29], 18.1 months (range: 1.5–26.3) [41], and 55 months [28]. Other studies reported estimates of 1-year OS (six studies, range: 68.2% [16] to 82.7% [15,16,26,29,31,40]), 2-year OS (seven studies, range: 58.0% [29] to 81.9% [14,18,19,26,29,34,41]), 3-year OS (two studies, 41% [26] and 74.6% [20]), 5-year OS (three studies, range: 58% [43] to 62.0% [25]), and 10-year OS (one study, 33.0%) [43].

Among full-text publications, the most commonly reported parameter was median OS ( $n = 3$  studies).

Hence, the qualitative assessment of clinical heterogeneity was conducted for these three studies only as for other estimates data were scarce with only one study each reporting 1-year OS [15], 2-year OS [14], and 3-year OS [20]. The qualitative assessment of study methods and populations revealed no major heterogeneity. However, since the two studies deemed of good methodological quality [14,33] used different definition of OS, no meta-analysis could be conducted. The first defined OS as the time from BV initiation to death of any cause [14] while the second defined it as the time from relapse/progression after ASCT until death of any cause or last follow-up [23].

### Safety of BV in R/R cHL patients

A total of 12 studies reported safety data on BV in R/R cHL patients. The most common adverse events, as obtained from medical charts or disease registries, consisted of hematological toxicities: Neutropenia (13.3% [35] to 23% [29] patients), anemia (8.8% [16] to 39.0% [29]), and thrombocytopenia (4% [18] to 4.6% [8]). Occurrence of peripheral neuropathy in BV-treated patients was reported in 11 sources. The estimated frequency of grade 1 or 2 peripheral neuropathy, as identified in a disease registry, was 36.2%, [26], and that of grade 3 or higher found in medical charts (details not provided) ranged from 3.3% [35] to 7.3% [28]. As reported in an Italian series of 234 patients, resolution or improvement of peripheral neuropathy

**Table 4.** Sensitivity analysis of pooled estimates of complete response.

Subgroup	Sensitivity analysis 1 (original articles of good or moderate quality)			Sensitivity analysis 2 (original articles of good or moderate quality + conference proceedings)		
	Number of studies (patients treated with BV)	Pooled CR (95% CI)	Heterogeneity statistics	Number of studies (patients treated with BV)	Pooled CR (95% CI)	Heterogeneity statistics
1st subgroup (CR after 4 cycles)	4 ( <i>n</i> = 319)	35.5% (24.8–46.9)	<i>I</i> <sup>2</sup> = 59.0% (95% CI: 0–86.3) Cochran's <i>Q</i> = 7.3; <i>p</i> = .06	5 ( <i>n</i> = 542)	34.1% (27.7–40.8)	<i>I</i> <sup>2</sup> = 47.0% (95% CI: 0–80.6) Cochran's <i>Q</i> = 7.5; <i>p</i> = .11
2nd subgroup (CR after 4–6 cycles)	6 ( <i>n</i> = 396)	32.9% (25.7–40.5)	<i>I</i> <sup>2</sup> = 43.2% (95% CI: 0–77.5) Cochran's <i>Q</i> = 8.8; <i>p</i> = .12	13 ( <i>n</i> = 831)	32.4% (26.6–38.5)	<i>I</i> <sup>2</sup> = 63.3% (95% CI: 33.4–79.8) Cochran's <i>Q</i> = 32.7; <i>p</i> = .001
3rd subgroup (CR after 6 or more cycles)	5 ( <i>n</i> = 517)	34.3% (26.1–43.0)	<i>I</i> <sup>2</sup> = 73.1% (95% CI: 32.8–89.3) Cochran's <i>Q</i> = 14.9; <i>p</i> = .005	NA	NA	NA

BV: brentuximab vedotin; CI: confidence interval; CR: complete response.

was observed in 90% of patients with a median time to resolution or improvement of 12 weeks [28].

## Discussion

This review identified 32 observational studies that reported on the effectiveness or safety of BV used as a single agent in R/R cHL patients, which enables synthesis of evidence without the inclusion of clinical trial results. The dosing regimen of BV used in the clinical practice setting is aligned with that used in the pivotal phase II trial and the recommendations included in the summary of product characteristics [4]. In addition, reported estimates of treatment response measured using the ORR, CR, PFS, and OS are consistent with results reported in the pivotal trial, even though patients treated in the real-world clinical practice setting may include subgroups of patients with a worse prognosis. In the pivotal phase II trial, the ORR was 75%, which is similar to the pooled estimate of 72.0% after more than six cycles found in the present meta-analysis. Similar results were observed for the CR rate (34% in the clinical trial versus 33.4% in the meta-analysis) [4]. In the pivotal phase II trial, the study population was restricted to patients with an ECOG performance status score of 0 or 1, while some observational studies included patients with ECOG PS 2 or higher [16,24]. Also, patients with previous allogeneic SCT were excluded from the trial, whereas several studies identified in the systematic review included patients with such history of transplantation [14,21,25–27,29,37]. In four case series, lower estimates of ORR were reported (20.6% [31] to 40.0% [29,31,32,35]). However, these results may be explained by characteristics of the study populations (i.e. heavily pretreated patients refractory to previous salvage treatments or patients ineligible to ASCT due to the persistence of the disease). Similarly for CR rate, lower estimates reported in four case series (14.3% [42] to 16.7% [22,30]) can be explained by small sample sizes (*n* = 21 [42], *n* = 24 [30], and *n* = 18 [22]) or specific patient populations (heavily pretreated patients who received a median of four prior regimens and were refractory to previous salvage therapies [31]). Of note, the majority of studies retained in this review assessed treatment response based on the 2007 International Working Group criteria, while these criteria have been updated in 2014, known as the Lugano Classification. Despite safety data being relatively scarce in the literature, results were consistent with those reported in the pivotal phase II trial. The most common BV-related adverse events observed in

the real-world clinical practice setting were neutropenia, anemia, thrombocytopenia, and peripheral neuropathy. For the latter, most patients had grade 1 or 2 toxicity and only a minority experienced grade 3 or 4 adverse events.

Similar results were observed in two previous reviews conducted by Zinzani et al. [45,46], in which the pooled ORR and CR rates were 67% and 26%, respectively. In these studies, only BV data originating from published reports of the BV Named Patient Program, up to the year 2015 were included whereas in the current review a larger scope was considered. Specifically, the search period spanned through the year 2019 and various study designs such as retrospective and prospective cohort studies as well as case series were considered. Also, in previous reviews, the timing of response evaluation was not considered in the pooled analyses of ORR and CR rates, while in the current review pooled estimates were stratified according to timing of evaluation of treatment response or the mean/median number of BV cycles received by patients, following a formal assessment of clinical heterogeneity. In addition, Dada et al. [47] also conducted a systematic review and meta-analysis to evaluate the impact of BV on outcomes in pretreated patients with R/R cHL. Based on this meta-analysis, the pooled ORR and CR rates were 62.7% and 31.8%, respectively. In this review, both observational studies and clinical trials published between 2012 and 2015 were included. The current review therefore offers an update of findings on BV treatment response using only real-world evidence data obtained in observational studies.

This review presents several strengths. First, the methodological quality of studies was evaluated using validated assessment tools based on expert critical review. Second, the screening and data extraction processes were performed independently by two reviewers with discrepancies resolved by a third independent assessor. Third, this review includes data on the use of BV in the real-world setting over more than a decade (1996–2019), therefore, supporting its effectiveness in clinical practice. Finally, sensitivity analyses led to estimates that were similar to those obtained in the primary analyses which demonstrates the robustness of results.

Several limitations of this review should be considered. First, identified studies were mostly those that led to publications in the scientific literature and that have been indexed in MEDLINE, Embase, or Web of Science using pre-defined MeSH terms and keywords. To mitigate this limitation, pragmatic searches, as well

as snowballing were conducted. Another limitation consisted of the absence of pooled estimates for survival outcomes for which a meta-analysis was not feasible due to the heterogeneous definitions considered for OS and the lack of data on the distribution of median PFS estimates. In order to address this limitation, additional efforts including contacts with corresponding authors of publications reporting PFS estimates were conducted. However, no additional data regarding interquartile ranges or 95% CIs of median PFS estimates were available, and analysis could therefore not be conducted. Third, while the current review focused on the use of BV in R/R cHL alone, recent guidelines recommend its use in combination with other chemotherapy regimens such as doxorubicin, vinblastine, and dacarbazine in the first-line setting or as consolidation after ASCT [48,49]. Moreover, BV is also being used as a combination partner for salvage chemotherapy at first relapse in patients eligible for ASCT [50–54]. This use of BV in earlier lines limits the generalizability of our current findings [55], although retreatment with BV in patients who have previously obtained a response has been shown [54,56]. In addition, as the main focus of this review was to evaluate the effectiveness of BV in the real-life practice setting, safety data were relatively scarce and originated from studies which were not aimed to explore this outcome.

According to identified observational studies, covering a total of 2303 R/R cHL patients, reported estimates of treatment response measured through ORR, CR, PFS, and OS were consistent with those reported in the pivotal phase II trial as were safety results despite the fact that observational studies include broader and more heterogeneous populations. Specifically, in studies that were conducted in the clinical practice setting, patients with a worse prognosis or higher risk cHL than those included in the phase II trial could be included (i.e. patients with ECOG PS 2 or higher, patients who failed allogeneic SCT, patients ineligible for transplant). As a consequence, although lower estimates of ORR or CR may sometimes be reported in these specific populations, this study supports the effectiveness and safety of BV in R/R cHL patients in the real-world setting.

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