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Original Article

Brentuximab Vedotin Compared with Other Therapies in Relapsed/Refractory Hodgkin Lymphoma Post ASCT: Median Overall Survival Meta-Analysis

Vijayveer Bonthapally, Hongbo Yang, Rajeev Ayyagari, Ruo-Ding Tan, Sean Cai, Eric Wu, Ashish Gautam, Andy Chi, Dirk Huebner

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Abstract

Objective: This meta-analysis compared the median overall survival (mOS) of brentuximab vedotin reported in the pivotal phase 2 study with published results of other therapies for the treatment of relapsed/refractory (R/R) Hodgkin lymphoma (HL) post-autologous stem cell transplant (ASCT).

Research design and methods: A systematic literature review identified studies that reported survival outcomes following conventional/experimental therapies in R/R HL patients, with ≥50% having failed ≥1 ASCT. Kaplan–Meier curves were used to reconstruct individual patient level survival data. Patients were grouped by treatment type and reconstructed data were used to estimate the mOS. Censored median regression modelling was used to compare mOS in each group with the mOS in the pivotal brentuximab vedotin trial. All patients in the pivotal trial had undergone ASCT, therefore a sensitivity analysis was conducted among studies with a 100% post-ASCT patient population.

Results: The mOS reported for brentuximab vedotin was 40.5 (95% CI 30.8-NA) compared with 26.4 months (95% CI 23.5-28.5) across all 40 studies identified (n=2518 excluding the brentuximab vedotin trial) (p<0.0001). The difference in mOS between brentuximab vedotin and chemotherapy, allogeneic stem cell transplant (allo-SCT), and other therapies, was 17.7 (95% CI 10.6-24.7; p<0.0001), 12.5 (95% CI 8.2-16.9; p<0.0001), and 15.2 months (95% CI 4.9-25.5; p=0.0037), respectively. For the 11 studies reporting a 100% prior-ASCT rate (n=662 excluding the brentuximab vedotin trial), the mOS was 28.1 months (95% CI 23.9-34.5), and the difference in mOS between brentuximab vedotin, chemotherapy, allo-SCT, and other therapies was 19.0 (95% CI 12.9-25.1; p<0.0001), 9.4 (p>0.05), and 6.8 months (95% CI 1.2-12.5; p=0.0018), respectively.

Conclusions: While some selection bias may occur when comparing trials with heterogeneous eligibility criteria, in the absence of randomized controlled trial data these results suggest brentuximab vedotin improves long-term survival and is associated with longer mOS in R/R HL post-ASCT compared with other therapies.

ORIGINAL ARTICLE

Brentuximab Vedotin Compared with Other Therapies in Relapsed/Refractory Hodgkin Lymphoma Post ASCT: Median Overall Survival Meta-Analysis

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Key words: Meta-analysis, Hodgkin lymphoma, Antigens, CD30, Hematopoietic Stem Cell Transplantation, Overall survival, Brentuximab vedotin.

[Short title: Brentuximab vedotin in relapsed/refractory Hodgkin lymphoma

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Research design and methods: A systematic literature review identified studies that reported survival outcomes following conventional/experimental therapies in R/R HL patients, with ≥50% having failed ≥1 ASCT. Kaplan–Meier curves were used to reconstruct individual patient level survival data. Patients were grouped by treatment type and reconstructed data were used to estimate the mOS. Censored median regression modelling was used to compare mOS in each group with the mOS in the pivotal brentuximab vedotin trial. All patients in the pivotal trial had undergone ASCT, therefore a sensitivity analysis was conducted among studies with a 100% post-ASCT patient population.

Results: The mOS reported for brentuximab vedotin was 40.5 (95% CI 30.8-NA) compared with 26.4 months (95% CI 23.5-28.5) across all 40 studies identified (n=2518 excluding the brentuximab vedotin trial) (p<0.0001). The difference in mOS between brentuximab vedotin and chemotherapy, allogeneic stem cell transplant (allo-SCT), and other therapies, was 17.7 (95% CI 10.6-24.7; p<0.0001), 12.5 (95% CI 8.2-16.9; p<0.0001), and 15.2 months (95% CI 4.9-25.5; p=0.0037),

respectively. For the 11 studies reporting a 100% prior-ASCT rate (n=662 excluding the brentuximab vedotin trial), the mOS was 28.1 months (95% CI 23.9-34.5), and the difference in mOS between brentuximab vedotin, chemotherapy, allo-SCT, and other therapies was 19.0 (95% CI 12.9-25.1; p<0.0001), 9.4 (p>0.05), and 6.8 months (95% CI 1.2-12.5; p=0.0018), respectively.

Conclusions: While some selection bias may occur when comparing trials with heterogeneous eligibility criteria, in the absence of randomized controlled trial data these results suggest brentuximab vedotin improves long-term survival and is associated with longer mOS in R/R HL post-ASCT compared with other therapies.

Introduction

Hodgkin lymphoma (HL) is a rare clonal lymphoid malignancy, with an annual incidence rate of 2.90 and 2.49 per 100,000 in the US and Europe, respectively[1, 2]. It is estimated that in 2014 there will be 9,190 new HL diagnoses and 1,180 deaths in the US alone[3]. Currently, more than 80% of all newly diagnosed HL patients, aged ≤60 years, are likely to be cured following front-line therapy consisting of multi-agent chemotherapy and radiotherapy[4, 5]. However, depending on the initial stage of the disease at diagnosis as well as the various prognostic factors, up to 30% of patients who achieve remission, relapse or are refractory to frontline therapy[6, 7]. For patients with relapsed/refractory (R/R) HL, standard treatment involves second-line, salvage combination chemotherapy followed by high-dose chemotherapy and autologous stem cell transplant (HDT-ASCT)[8, 9]. Unfortunately, approximately 50% of HL patients relapse after ASCT[10, 11] and their prognosis is generally poor with a median survival of 25 months[12]. Treatment options for R/R HL patients post-ASCT are limited and include additional chemotherapy, allogeneic stem cell transplant (allo-SCT), recurrent ASCT, radiotherapy, and immunotherapy. The management of this subset of patients remains a significant challenge.

Brentuximab vedotin is an antibody-drug conjugate that targets CD30[13, 14], a cell-surface antigen expressed on the malignant Hodgkin's Reed-Sternberg cells of classical HL[15]. It consists of a CD30-targeted monoclonal antibody (cAC10) covalently linked to the microtubule-disrupting agent monomethyl auristatin E (MMAE) by a protease-cleavable linker[13, 14, 16, 17]. It received accelerated approval from the US Food and Drug Administration in 2011 for the treatment of HL patients that have relapsed after ASCT or after at least two prior multi-agent chemotherapy regimens with ineligibility for ASCT[18]. Subsequently, brentuximab vedotin received conditional approval from the European Commission in 2012 for the treatment of CD30-positive R/R HL patients after ASCT or after failure of at least two prior multi-agent chemotherapy regimens when ASCT or multi-agent chemotherapy is not a treatment option[19].

The efficacy and safety of brentuximab vedotin in R/R HL post-ASCT was demonstrated in a single-arm, multicentre, pivotal phase 2 clinical trial (SG035-0003; NCT00848926)[20]. A total of 102 patients with R/R HL following ASCT were treated with brentuximab vedotin 1.8 mg/kg by intravenous infusion every 21 days for a maximum of 16 cycles. The objective response rate was 75%, with complete remission (CR) in 33% of patients[20, 21]. Recent long term follow-up data from the pivotal phase 2 trial, with a median observation time of 32.7 months, reported a median overall survival (mOS) of 40.5 months[22].

The US and European approval of brentuximab vedotin for the treatment of R/R HL was based on the results of the pivotal phase 2 study. In the absence of head-to-head, randomized, controlled, phase 3 trials, no comparative efficacy data for brentuximab vedotin and existing therapies in the R/R setting are available. A recent meta-analysis compared the antitumor activity of brentuximab vedotin in terms of CR rate as reported in the phase 2 study, with existing drug therapies or experimental agents, for the treatment of R/R HL post-ASCT. Brentuximab vedotin was associated with a significantly higher CR rate compared with other therapies (33.3% vs. 11.1%, $p<0.0001$)[23]. Now that long-term survival data are available for patients treated with brentuximab vedotin in the pivotal phase 2 study, we conducted a systematic literature review to identify studies which reported survival outcomes for other therapies among adult R/R HL patients post-ASCT. We then performed a meta-analysis to compare the mOS of brentuximab vedotin as reported in the pivotal study to that of other therapies reported in the literature for the treatment of R/R HL post-ASCT patients.

Patients and methods

Systematic literature review

Per pre-specified criteria, a systematic literature review was undertaken to identify studies that reported survival outcomes following conventional and experimental therapies in R/R HL patients

post-ASCT. Indexed search terms and free text terms were used to identify 'relapsed', 'refractory', 'HL', and 'ASCT' in studies published between February 2013 and January 2014 in six electronic databases: MEDLINE, MEDLINE In-Process and other non-indexed citations, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), Cumulative Index to Nursing and Allied Health Literature (CINAHL), and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP). Recent conference proceedings (2011 to 2013) from American Society for Clinical Oncology (ASCO), American Society of Hematology (ASH), European Society of Medical Oncology (ESMO), and European Hemtology Association (EHA) were also included. There were no restrictions regarding study design or type of treatment in the initial search, and English-language studies involving human subjects were selected for review. A comprehensive summary of the search strategies with detailed search terms is provided in the supplementary appendix. Relevant studies published from January 1993 to January 2013, identified from a prior systematic literature review that was conducted using the same search strategy as the current study, were included in the final analysis.

Studies identified from both the current and prior systematic literature review were selected for relevance for the subsequent meta-analysis, by a two level screening process, according to pre-determined inclusion and exclusion criteria. The results are reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement[24]. Studies were screened by title and/or abstract at the first level followed by full text screening at the second level. Clinical trials from the ICTRP were screened by title, by trial description, and by full text of any linked publication. The inclusion criteria required that the study population include ≥20 R/R HL patients, of whom ≥80% were ≥12 years of age and ≥50% had failed at least one ASCT. Included studies were to report survival outcomes, specifically Kaplan–Meier (KM) curves, mOS, and survival rates. Kin studies deemed non-primary publications for a study and not reporting relevant outcomes were excluded, as were studies reporting survival time from time points other than the start of the treatment under evaluation and studies reporting actuarial survival rate. Certain publication types were

excluded including reviews, meta-analyses, comments, recommendations/guidelines, study protocols, and case reports.

Data collection

Two reviewers independently extracted data from each eligible study which were collected in a pre-specified extraction table. Where available, extracted data included bibliographic information, study description and design (type of study, time frame, location of study, condition, number of HL patients, and number of study arms), patient baseline demographics and disease characteristics, study treatment(s), and clinical outcomes (KM curves and/or mOS). Any discrepancies were discussed or a third reviewer was consulted to reach a consensus.

Statistical analysis

Studies that included KM curves of OS, estimated from the start of treatment under evaluation, were used to reconstruct pseudo-individual patient level survival data survival or censoring times at the pseudo-individual patient level. Engauge digitization software (v4.1) was used to extract time points and survival probabilities from the published KM curves. Pseudo-individual patient level data were reconstructed from the digitized curves using the published algorithm recommended by the National Institute for Health and Care Excellence (NICE), UK[25, 26]. Patients were grouped according to the type of post-ASCT treatment they received (brentuximab vedotin, chemotherapies, allo-SCT, or other therapies), and the reconstructed pooled datasets were used to plot a single KM curve and estimate the mOS and 95% confidence interval (CI) for each treatment group identified. Reconstructed survival data was validated by comparing the estimated mOS with those reported in published studies (or derived from published KM curves using pixel analysis). In addition, reproduced KM curves from four randomly selected studies (one from each treatment group) were overlaid on top of the original published curves and the level of agreement was visually assessed.

A censored quantile regression model[27] was used to estimate the difference in mOS obtained from the long-term follow-up results for the pivotal phase 2 brentuximab vedotin trial with the other treatment groups, and the p-value of the difference. A log-rank test was also performed to test for overall differences between the KM curves of brentuximab vedotin versus alternative treatment groups as a whole. All analyses were carried out using the statistical software R (v2.15.2). Two sensitivity analyses were carried out; one including only those studies reporting a 100% prior-ASCT patient population to assess the impact of prior-ASCT on the estimated mOS for each treatment group, and one using a relaxed classification for chemotherapy including all studies reporting either sole chemotherapy regimens or chemotherapy in combination with other treatments to better reflect the diverse treatment regimens that patients may receive in clinical practice.

Results

Selection of studies

The systematic literature search process is shown in Figure 1. Our initial search identified a total of 787 potentially relevant records. An additional 121 records published between January 1993 and February 2013 were obtained from the prior systematic literature review. Forty-eight studies met the required criteria after full-text screening. The most frequent reasons for exclusion were studies without relevant populations (*n*=48) or outcomes (*n*=20). Forty one of these 48 studies, including the brentuximab vedotin pivotal trial, with a total of 2,619 evaluable R/R HL patients, reported KM curves of OS among R/R HL post-ASCT patients and were included in the meta-analysis[22, 28-67]. The study design and key patient characteristics for all 41 studies included in the meta-analysis are described in Table 1. They consisted of 1 phase 1/2, 11 phase 2, 8 prospective cohort, and 21 retrospective studies. The most commonly observed treatment types were allo-SCT and chemotherapy with 21 and 8 studies reporting survival outcomes, respectively. Chemotherapy under evaluation

included single sequential or multi-agent treatments, and the agent used varied, including gemcitabine (*n*=3), bendamustine (*n*=3), vinorelbine (*n*=4), and pegylated liposomal doxorubicin (*n*=2). The remaining 11 studies reported outcomes for other therapies including radiation therapy, immunotherapies such as donor leukocyte infusions, and mixed treatments such as radiation therapy in combination with salvage chemotherapy.

The studies varied in size, with the number of HL patients in each study ranging from 21 to 285. The median age of all patients ranged from 25 to 51 years, the median number of prior regimens ranged from ≤2–5, and the number of patients with previous ASCT ranged from 52 to 100%. In the pivotal study of brentuximab vedotin, the median age was 31 years (range: 15–77), the median number of prior chemotherapy regimens was 3.5 (range: 1–13), and all patients had undergone ASCT[22]. Twelve studies, including the brentuximab vedotin phase 2 trial, with a total of 763 evaluable R/R HL patients, reported a 100% prior-ASCT rate and were included in the sensitivity analysis. Of these 11 remaining studies, 4 reported outcomes for chemotherapy, 3 for allo-SCT, and 4 for other therapies.

Analysis of mOS

The estimated mOS in R/R HL post-ASCT patients across the 40 pooled studies of current treatment was 26.4 months (95% CI 23.5-28.5). This was significantly lower than the reported mOS of 40.5 months (95% CI 30.8-NA; $p<0.0001$) for patients receiving brentuximab vedotin in the pivotal phase 2 trial. The results of the meta-analysis are presented in Figure 2. The estimated mOS for chemotherapy, allo-SCT, and other treatment regimens was 23.0 months (95% CI 21.0-28.1), 27.9 months (95% CI 23.9-30.2), and 23.9 months (95% CI 21.0-28.0), respectively. Brentuximab vedotin-treated patients experienced significantly longer mOS compared with patients on chemotherapies, allo-SCT, and other treatment regimens as demonstrated by differences in mOS of 17.7 months (95%

CI 10.6-24.7; $p<0.0001$) (Figure 2a), 12.5 months (95% CI 8.2-16.9; $p<0.0001$) (Figure 2b), and 15.2 months (95% CI 4.9-25.5; $p=0.0037$) (Figure 2c), respectively.

The sensitivity meta-analysis, which included only those studies that reported a 100% prior-ASCT rate, showed a significant difference between the reported mOS of 40.5 months in the brentuximab vedotin trial and the estimated mOS across the 11 pooled studies of 28.1 months (95% CI 23.9-34.5; $p<0.0001$). The results of this sensitivity meta-analysis are presented in Figure 3. The estimated mOS for chemotherapy, allo-SCT, and other treatment regimens in the sensitivity meta-analysis was 21.1 months (95% CI 17.0-28.1), 31.1 months (95% CI 23.9-62.1), and 34.1 months (95% CI 29.5-41.5), respectively. Brentuximab vedotin-treated patients experienced significantly longer mOS compared with patients on chemotherapies, and other treatment regimens as demonstrated by differences in mOS of 19.0 months (95% CI 12.9-25.1; $p<0.0001$), and 6.8 months (95% CI 1.2-12.5; $p=0.0018$), respectively. The median difference in mOS estimated from the censored quantile regression method between patients receiving brentuximab vedotin and allo-SCT was not reported as the assumption of monotonicity for quantile difference was not met; however, the raw numeric difference of 9.4 months was not statistically significant ($p>0.05$).

The sensitivity meta-analysis, which grouped studies using a relaxed classification for chemotherapy, further demonstrated that brentuximab vedotin-treated patients experienced a significantly longer mOS compared with patients on chemotherapies. The estimated mOS for the broad chemotherapies group was 22.2 months (95% CI 21.0-27.5). The difference in mOS between brentuximab vedotin and broad chemotherapies was 17.3 months (95% CI 9.9-24.7; $p<0.0001$) (Figure 4).

Discussion

This meta-analysis is the first study to compare mOS between brentuximab vedotin and other therapies for the treatment of adult patients with R/R HL post-ASCT. In the absence of randomized controlled trial data, this study allows for an indirect comparison of survival outcome between brentuximab vedotin and current therapies used in the R/R setting. Brentuximab vedotin was associated with a significantly longer mOS compared with that of other therapies reported in the literature (40.5 months vs. 26.4 months, $p<0.0001$). The difference in mOS between brentuximab vedotin and chemotherapy, allo-SCT, and other therapies was 17.7 months ($p<0.0001$), 12.5 months ($p<0.0001$), and 15.2 months ($p=0.0037$), respectively. Our results suggest brentuximab vedotin improves long-term survival in adult R/R HL patients.

The results of this meta-analysis are consistent with those reported from previous meta-analyses. Using a similar methodological approach, Bonthapally et al. conducted a meta-analysis to evaluate the antitumor activity of brentuximab vedotin as reported in the pivotal phase 2 study versus the activity of other drug therapies and experimental agents as reported in 17 evaluable studies identified from the literature, in patients with R/R HL post-ASCT. CR rate was selected as the most appropriate endpoint for the study due to the lack of long-term survival data for patients treated with brentuximab vedotin. Brentuximab vedotin was associated with a significantly higher CR rate compared with other therapies in the treatment of R/R HL post-ASCT patients (33.3% vs. 11.1%, $p<0.0001$)[23]. Karuturi et al. compared OS from the pivotal brentuximab vedotin study with 756 R/R HL historical control post-ASCT patients from 6 international centres, prior to the approval and widespread availability of brentuximab vedotin. Brentuximab vedotin was associated with prolonged mOS, measured from the point of ASCT, when compared with historical control patients (91.49 months vs. 27.99 months, $p<0.0001$). Improvement in OS was irrespective of time to relapse post-ASCT, age, or sex[68]. These findings further support the results of our study suggesting that brentuximab vedotin's antitumor activity exceeds that of other therapies currently used in the treatment of R/R HL post-ASCT. Our study provides a comprehensive review of the literature to date, comparing brentuximab vedotin's efficacy, in terms of mOS, with other therapies used to treat R/R HL post-ASCT using long-term survival data over a 24-month period.

In the absence of well controlled head-to-head comparisons, meta-analyses such as this provide valuable insights; however, results should obviously be interpreted with caution. We acknowledge the potential for patient selection bias that may occur when comparing trials with heterogeneous eligibility criteria. The systemic literature review identified 41 studies that met all eligibility criteria and presented KM curves of OS for inclusion in the meta-analysis. There was substantial heterogeneity in the mOS reported within each treatment group. In the studies for chemotherapy, allo-SCT, and other therapies, mOS ranged from 12[58] to 42[35, 39] months, 6.7[62] to 55[51] months, and 14.8[36] to 40.8[46] months, respectively. Nine studies had relatively short follow-up time so that mOS were not reached by the end of the study period[29, 30, 45, 48, 50, 53, 54, 66, 67]. With the inclusion of these immature data, the censored quantile regression model was likely to over-estimate mOS for the treatment group; however, the final impact of these immature data on the meta-analysis is unclear. Survival data for brentuximab vedotin were obtained from the pivotal phase 2 trial, where all 102 patients had undergone ASCT prior to receiving brentuximab vedotin; however, only 11 out of the 40 pooled studies of other treatments reported a 100% prior-ASCT rate. Therefore, we conducted a sensitivity analysis among only those studies reporting a 100% post-ASCT population, to examine the effect of ASCT status on the primary result. Our findings confirmed the robustness of the brentuximab vedotin mOS result compared with that of other therapies reported in the literature (40.5 months vs. 28.1 months, $p<0.0001$). The median difference in mOS between brentuximab vedotin and chemotherapy, and other therapies for the 100% prior-ASCT patient population was 19.0 months ($p<0.0001$), and 6.8 months ($p=0.0018$), respectively, further suggesting brentuximab vedotin improves long-term survival compared to other treatment types. The raw numeric difference of 9.4 months ($p>0.05$) between 100% prior-ASCT patient receiving brentuximab vedotin and allo-SCT was not statistically significant; however, this may be due to the low number of allo-SCT studies reporting survival outcomes for a 100% prior-ASCT patient population.

Due to the lack of individual patient baseline characteristics reported in the studies, they could not be adjusted for effect modifiers in the censored quantile regression model to account for differences in observed baseline characteristics. This could have led to biased estimates. Furthermore,

as the studies included in the meta-analysis were either single-arm or lacked common comparator arms, it was not possible to make adjustments to account for differences in unobserved baseline characteristics. Finally, it is important to note that this meta-analysis compared three alternative treatment groups to brentuximab vedotin: chemotherapies, allo-SCT, and other therapies. The chemotherapy group included studies where patients only received chemotherapy agents. Mixed treatments, such as chemotherapies in combination with salvage radiation therapy were categorized in the other therapies group. In clinical practice, patients do not fall exclusively into one treatment category, but receive multiple salvage treatment regimens depending on their age, performance status, disease type and stage, and time to relapse[69]. We therefore conducted a sensitivity analysis using a relaxed classification for chemotherapy to better reflect clinical practice. The estimated mOS for the broad chemotherapies group was 22.2 months (95% CI 21.0-27.5), which was significantly lower compared to patients receiving brentuximab vedotin as demonstrated by a difference in mOS of 17.3 months (95% CI 9.9-24.7; $p<0.0001$). Analysis of safety data was beyond the scope of this meta-analysis.

Future analyses which can prospectively compare brentuximab vedotin to alternative therapies using a randomized design are needed to verify the findings from the current study. Two randomized, multicentre phase 3 brentuximab vedotin studies are ongoing; however, these are not in the R/R HL post-ASCT population. AETHERA (NCT01100502) is a double-blind, placebo-controlled study investigating brentuximab vedotin and best supportive care (BSC) versus placebo and BSC in the treatment of HL patients at risk of progression following ASCT. Efficacy data were recently published. As of August 2013, all patients have completed or discontinued study treatment[70]. ECHELON-1 (NCT01712490) is an open-label study, investigating the safety and efficacy of front-line brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine (A+AVD) versus doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) in patients with advanced-stage classical HL. As of June 23, 2014, 444 patients have been randomized at 195 sites; data is expected to be published in the near future.

Conclusion

Results of this meta-analysis suggest that brentuximab vedotin is associated with a longer mOS compared with other therapies among patients with R/R HL post-ASCT. In the absence of randomized clinical trials, our findings suggest brentuximab vedotin improves long-term survival and provides meaningful clinical benefit in adult R/R HL patients.

Transparency

Declaration of funding:

The analysis was funded by Millennium Pharmaceuticals Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited.

Declaration of financial/other relationships:

VB, AC, DH are employed by Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited; VB owns stocks in Takeda Pharmaceutical Company Limited; AG is employed by Millennium Pharmaceuticals, Inc.; HY, RA, RDT, SC, EW are employees of Analysis Group Inc., which has received a consultancy fee from Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited. CMRO Peer Reviewers on this manuscript have received an honorarium from CMRO for their review work, but have no other relevant financial relationships to disclose.

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Figure 1. PRISMA for selecting studies for inclusion in the meta-analysis.

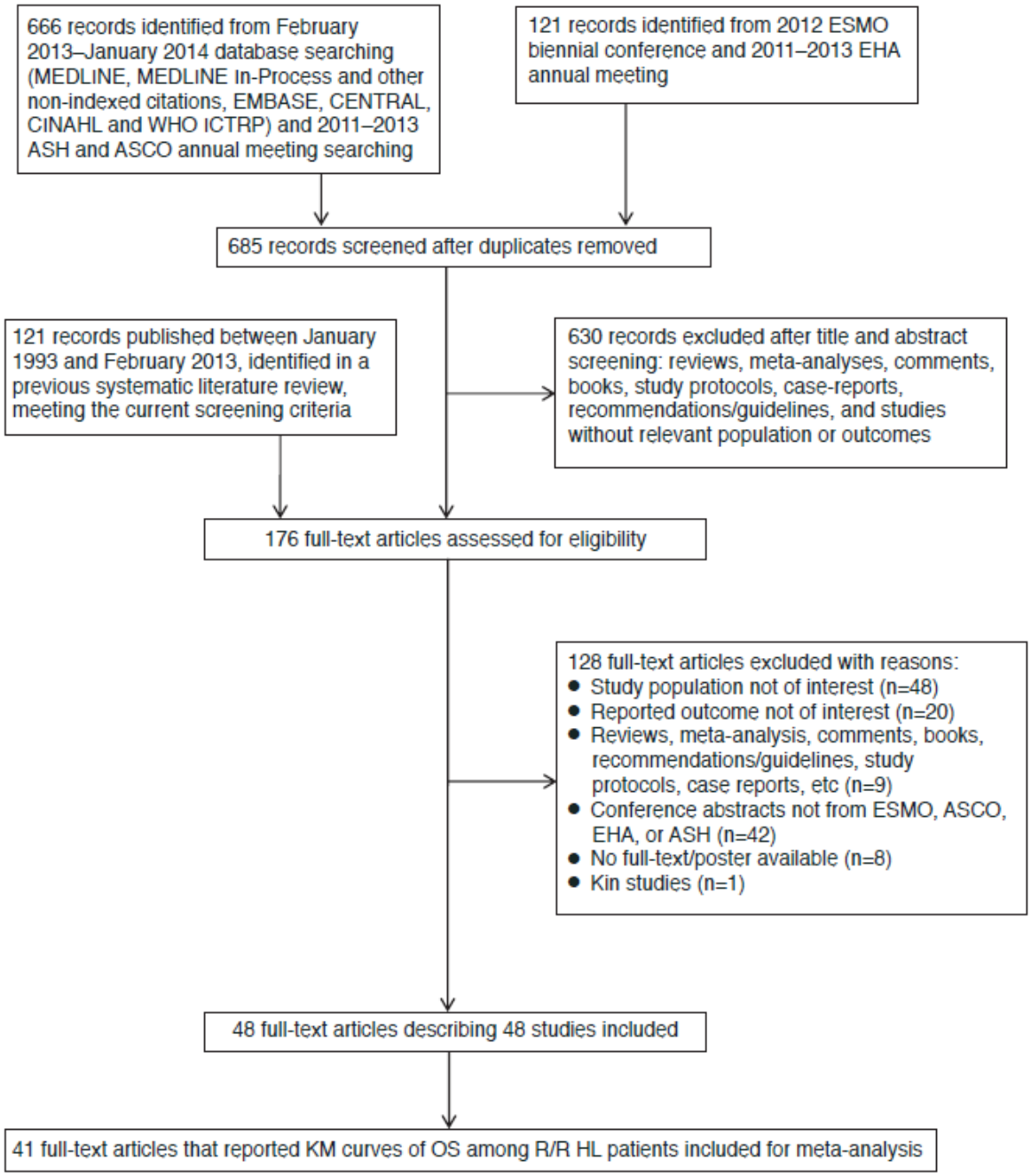
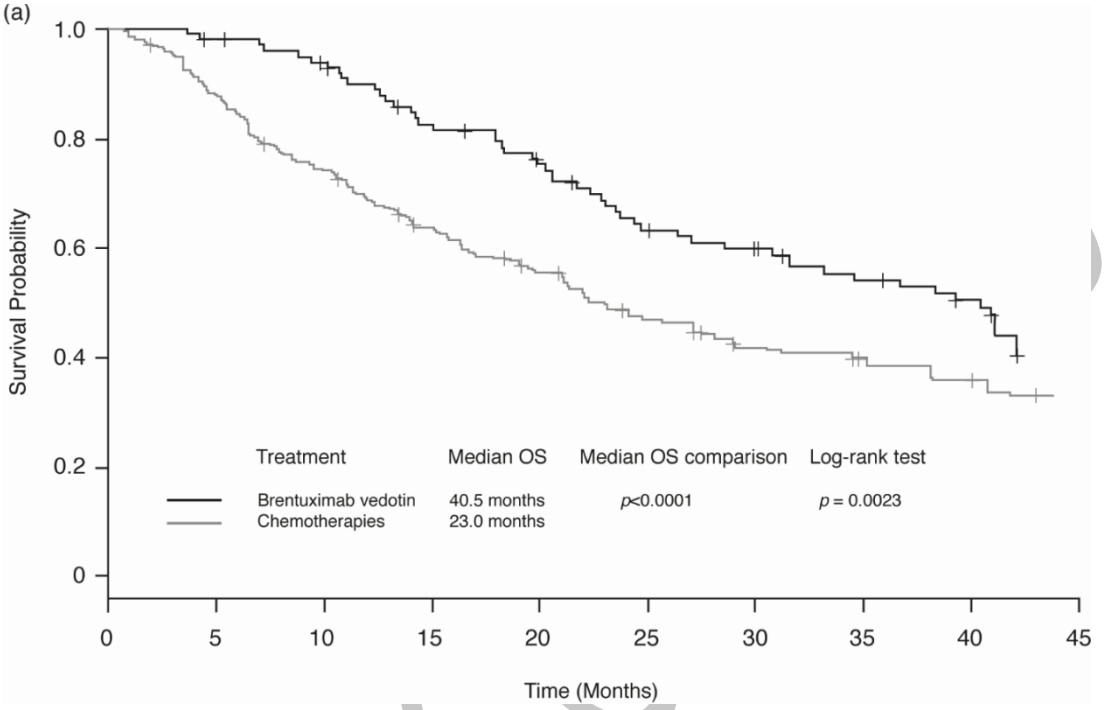
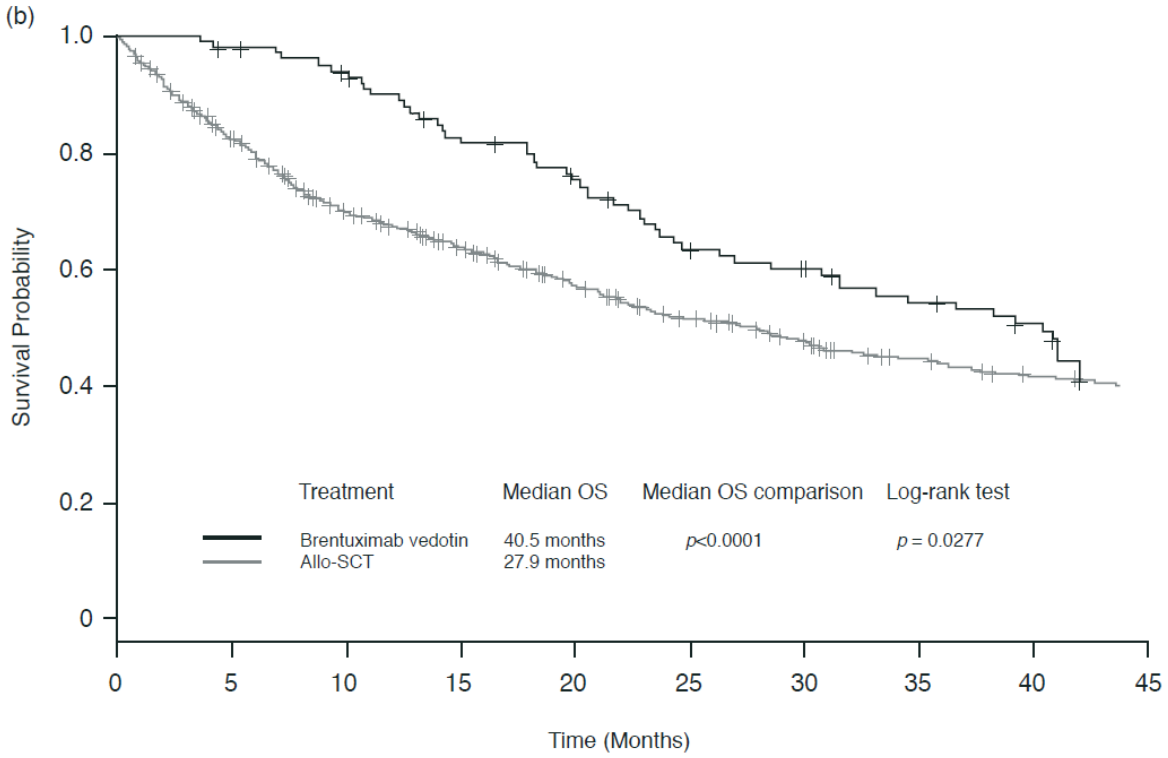


Figure 2. Comparison of mOS for brentuximab vedotin versus (A) chemotherapy, (B) allo-SCT, and (C) other therapies.





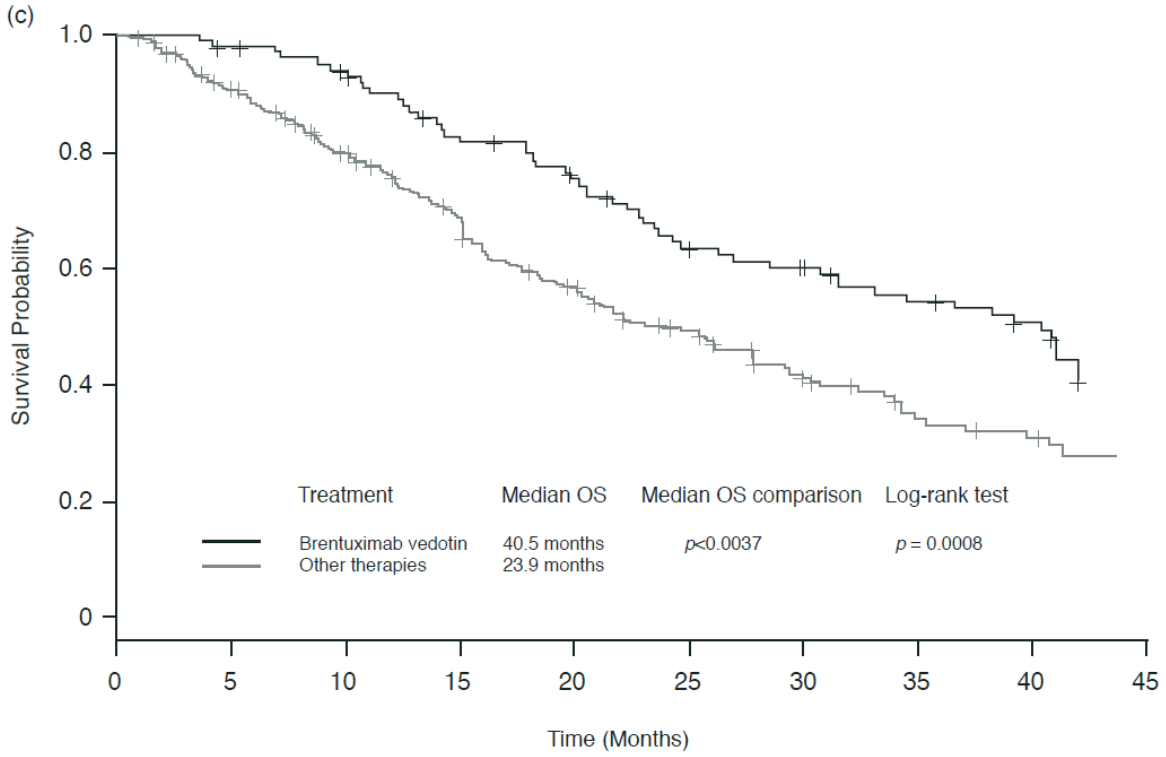
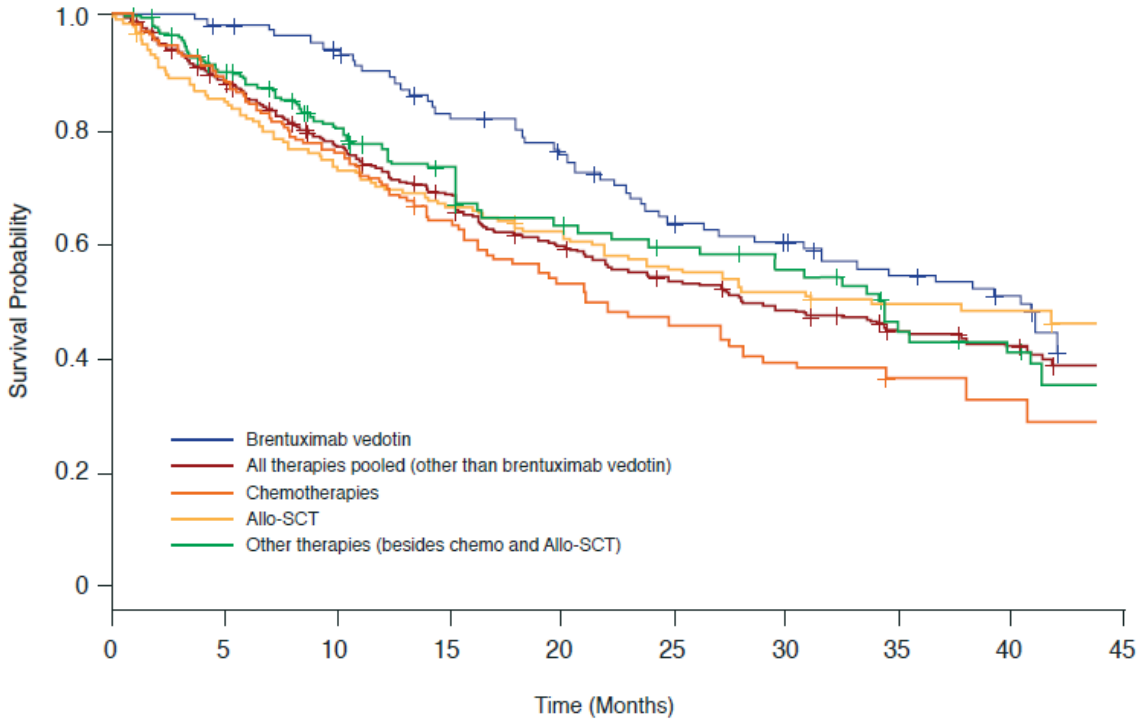


Figure 3. Sensitivity meta-analysis comparison of mOS for brentuximab vedotin versus



chemotherapy, allo-SCT, and other therapies in patients with a 100% prior-ASCT rate

Figure 4. Sensitivity meta-analysis comparison of mOS for brentuximab vedotin versus chemotherapy using a relaxed classification for chemotherapy

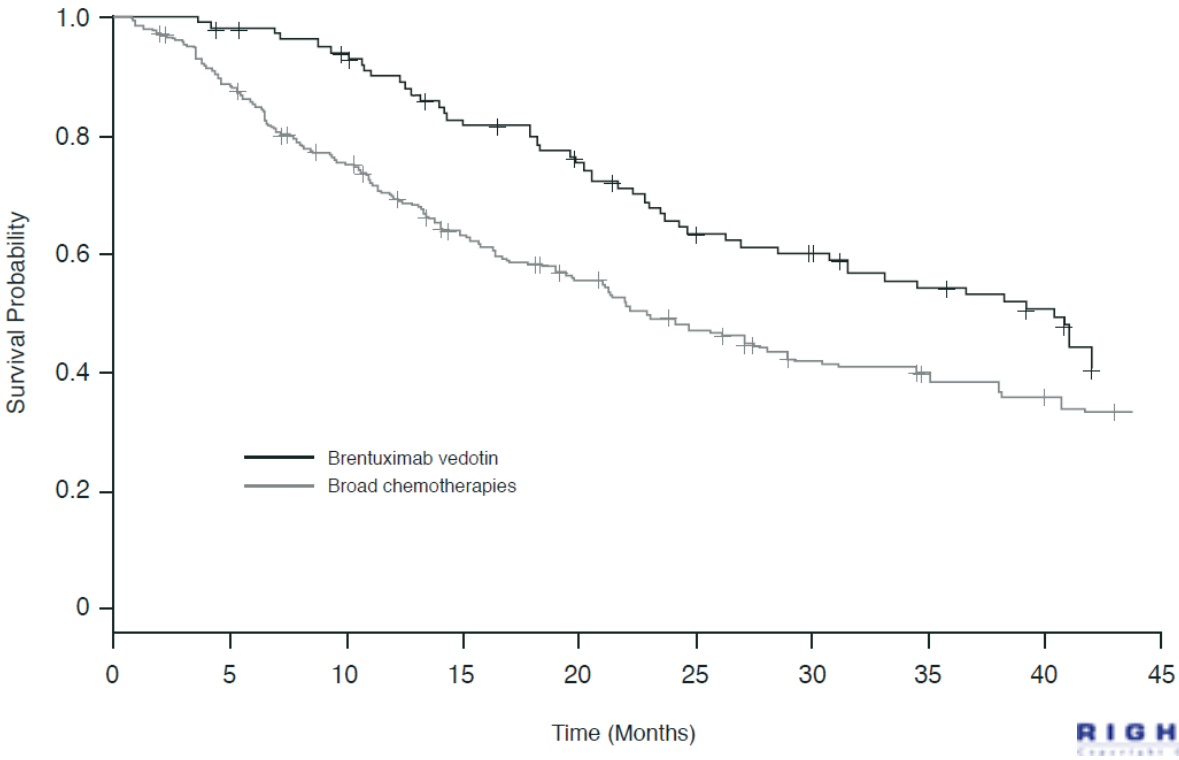


Table 1 Study design and key patient characteristics of 41 identified studies included in the meta-analysis.

Study	Study design	Regimen	Number of evaluable HL patients	Median baseline age, years	Number of HL patients with prior ASCT, *n* (%)	Median follow up (months)	Reported median OS (or derived from KM curve[†]), month
Alvarez et al[28]	Prospective cohort	Allo-SCT with RIC	40	35	29 (73)	8.5	20[†]
Anastasia et al[29]	Prospective cohort	Bendamustine	69/73	34	73 (100)[‡]	13	Not reached
Anderlini et al[30]	Retrospective	Allo-SCT with RIC	40	31	30 (75)	12 (all patients) 13 (survivors)	Not reached
Anderlini et al[31]	Prospective cohort	Allo-SCT with RIC	58	32	48 (83)	24 (survivors)	33.6[†]
Anderlini *et al*[32]	Retrospective	Donor leukocyte infusion	27	30	21 (78)	41 (5 survivors)	17.6[†]

Study	Study design	Regimen	Number of evaluable HL patients	Median baseline age, years	Number of HL patients with prior ASCT, *n* (%)	Median follow up (months)	Reported median OS (or derived from KM curve†), month
Armand et al[33]	Retrospective	Allo-SCT with RIC	36	31	34 (94)	26 (survivors)	48.3†
Baron et al[34]	Prospective cohort	Allo-SCT following nonmyeloablative conditioning	35/147*	46 (all patients)	NR (~92) (all patients)	26.7 (survivors)	22.3†
Bartlett et al[35]	Phase 1/2	GVD	91 (40 with previous ASCT)	33 (all patients)	40 (44)	43.2 (survivors)	42
Blum et al[36]	Phase 2	Bortezomib	30	35	24 (80)	18 (all patients)	14.8
Burroughs et al[37]	Retrospective	Allo-SCT following nonmyeloablative conditioning	90 total HLA-matched: 38 Unrelated: 24 HLA-haploidentical: 28	HLA-matched: 33 Unrelated: 28 HLA-haploidentical: 32	HLA-matched: 34 (89) Unrelated: 24 (100) HLA-haploidentical: 25 (89)	Survivors: HLA-matched: 24 Unrelated: 38 HLA-haploidentical: 22	HLA-matched: 26.4† Unrelated: 46.5† HLA-haploidentical: 47.5†
Chen et al[38]	Retrospective	Allo-SCT with RIC	24	35	20 (83)	27.2 (all patients)	39.6†

Study	Study design	Regimen	Number of evaluable HL patients	Median baseline age, years	Number of HL patients with prior ASCT, *n* (%)	Median follow up (months)	Reported median OS (or derived from KM curve[†]), month
Clozel et al[39]	Retrospective	PLD or PLD+MOPP/GVD/ BEACOPP/vinblastine	47	25	47 (100)[‡]	36	42[†]
Corazzelli et al[40]	Retrospective	Bendamustine and allo-SCT	41	33	35 (85)	Not reported	21.4
Corradini et al[41]	Phase 2	Allo-SCT with RIC	32/170*	51 (all patients)	25 (78)	33 (all patients)	26.9[†]
Czyz et al[42]	Retrospective	GCS or GV	37	32	37 (100)[‡]	26.4 (survivors)	15.5
Devetten et al[43]	Retrospective	RIC and nonmyeloablative SCT	143	30	127 (89)	25 (survivors)	14.8[†]
Fehniger et al[44]	Phase 2	Lenalidomide	36/38	34	29 (76)	20	20

Study	Study design	Regimen	Number of evaluable HL patients	Median baseline age, years	Number of HL patients with prior ASCT, *n* (%)	Median follow up (months)	Reported median OS (or derived from KM curve[†]), month
Ghesquieres et al[45]	Retrospective study	Bendamustine or bendamustine + rituximab or vinorelbine	28	32	25 (89)	16.5	Not reached
Goda et al[46]	Retrospective study	Salvage RT or RT with salvage CT	56	30	56 (100)[‡]	31.3	40.8
Gopal et al[22]	Pivotal Phase 2	Brentuximab vedotin	102	31	102 (100)[‡]	32.7	40.5
Guidetti et al[47]	Phase 2	Perifosine and perifosine + sorafenib	25/40*	42 (all patients)	27 (67) (all patients)	14 (all patients)	16
Harrison et al[48]	Prospective cohort	Panobinostat	129	32	129 (100)[‡]	NA	Not reached
Johansson et al[49]	Retrospective	Allo-SCT with RIC	23	36	20 (87)	25 (all patients) 46 (survivors)	52.1[†]

Study	Study design	Regimen	Number of evaluable HL patients	Median baseline age, years	Number of HL patients with prior ASCT, *n* (%)	Median follow up (months)	Reported median OS (or derived from KM curve[†]), month
Majhail et al[50]	Prospective cohort	UCB or MSD allo-SCT with RIC	21 total UCB: 9 MSD:12	UCB: 28 MSD:42	UCB: 7 (78) MSD: 7 (58)	UCB: 17 MSD:24	UCB: Not reached MSD: 16.2[†]
Marcais et al[51]	Retrospective	Allo-SCT	191	31	174 (92)	36	55
Moskowitz et al[52]	Phase 2	Bendamustine	34/36	34	27 (75)	19 (all patients) 36 (survivors)	29[†]
Peggs et al[53]	Prospective cohort	Allo-SCT with RIC	49 total Unrelated donors: 18 Related donors: 31	32	44 (90)	31.8 (survivors)	Unrelated donors: 14[†] Related donors: Not reached

Study	Study design	Regimen	Number of evaluable HL patients	Median baseline age, years	Number of HL patients with prior ASCT, *n* (%)	Median follow up (months)	Reported median OS (or derived from KM curve[†]), month
Peggs et al[54]	Retrospective	Allo-SCT with RIC followed by GvHD prophylaxis with MF-A or MF	67 total MF-A: 31 MF: 36	MF-A: 36 MF: 35	MF-A: 27 (87) MF: 26 (72)	MF-A: 58.6 (survivors) MF: 41.7 (survivors)	MF-A: Not reached MF: 25[†]
Robinson et al[55]	Retrospective	Allo-SCT with RIC	272/285	31.2	229 (80)	26 (all patients)	28.4[†]
Sarina et al[56]	Retrospective	Donor group: conditioning regimen No donor group: salvage chemotherapy or radiotherapy	104	31.9	104 (100)[‡]	47.9 (all patients)	Allo-SCT patients: 37.9[†]
Schmitz et al[57]	Retrospective	Nonmyeloablative conditioning + allo-SCT	80/94	30	NR (~50)	NR	18.6[†]

Study	Study design	Regimen	Number of evaluable HL patients	Median baseline age, years	Number of HL patients with prior ASCT, *n* (%)	Median follow up (months)	Reported median OS (or derived from KM curve[†]), month
Shamash et al[58]	Retrospective	HDCT with autologous haematopoietic support	37 total Single sequential chemotherapy: 20 multiple agent group: 17	28	37 (100)[‡]	24	Single sequential chemotherapy: 12.0 multiple agent group: 21.9
Smith et al[59]	Retrospective	Second ASCT	21/40*	38 (all patients)	40 (100)[‡] (all patients)	72 (survivors)	24[†]
Smith et al[60]	Phase 2	Galiximab	29/30	36	21 (70)	13.6	23.2
Sobol et al[61]	Prospective cohort	Allo-SCT with RIC	31	36	100[‡]	84	Chemorefractory bulky: 19.4, Chemorefractory nonbulky: NA, Chemosensitive bulky: 18.4, Chemosensitive nonbulky: NA

Study	Study design	Regimen	Number of evaluable HL patients	Median baseline age, years	Number of HL patients with prior ASCT, *n* (%)	Median follow up (months)	Reported median OS (or derived from KM curve[†]), month
Sureda et al[62]	Retrospective	Allo-SCT with RIC or myeloablative conditioning	168 total RIC: 89 Myeloablative:79	RIC: 26 Myeloablative:27	RIC: 55 (61.8) Myeloablative: 32 (40.5)	RIC: 73 Myeloablative: 76	RIC: 14.6 Myeloablative: 6.7
Sureda et al[63]	Phase 2	Allo-SCT with RIC	78/92	28	79 (86)	32 (all patients) 48 (survivors)	30.1[†]
Thomson et al[64]	Phase 2	Allo-SCT with RIC	38	31	38 (100)[‡]	49 (survivors)	46[†]
Validire et al[65]	Retrospective	Gemcitabine-based regimen	55	29	34 (62)	14 (all patients)	20.7[†]

Study	Study design	Regimen	Number of evaluable HL patients	Median baseline age, years	Number of HL patients with prior ASCT, *n* (%)	Median follow up (months)	Reported median OS (or derived from KM curve[†]), month
Younes et al[66]	Phase 2	Mocetinostat	51 total 85mg: 28 110mg: 23	85mg: 34 110mg: 28	85mg: 23 (82) 110mg: 20 (87)	NR	85mg: Not reached 110mg: 20.3[†]
Younes et al[67]	Phase 2	Panobinostat	129	32	129 (100)[‡]	9.6 (all patients)	Not reached

*Mixed lymphoma populations; [†]Median overall survival derived from KM curve; [‡]Studies reporting a 100% prior-ASCT rate and included in the sensitivity analysis

Allo-SCT = allogeneic stem cell transplant; ASCT = autologous stem cell transplant; BEACOPP = bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; CT = chemotherapy; GCS = gemcitabine, cisplatin, and methylprednisolone or dexamethasone; GV = gemcitabine and vinorelbine; GVD = gemcitabine, vinorelbine, and pegylated liposomal doxorubicin; GvHD = graft versus host disease; HDCT = high

dose chemotherapy; MF-A = cyclosporine, alemtuzumab; MF = closporine, methotrexate; MOPP = mechlorethamine, vincristine, procarbazine, prednisone; MSD = matched-sibling donors; NR = not reported; PLD = pegylated liposomal doxorubicin; RIC = reduced-intensity conditioning; RT = radiotherapy; SCT = stem cell transplant; UCB = umbilical cord blood

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Study	Study design	Regimen	Number of evaluable HL patients	Median baseline age, years	Number of HL patients with prior ASCT, *n* (%)	Median follow up (months)	Reported median OS (or derived from KM curve†), month
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Bartlett et al[35]	Phase 1/2	GVD	91 (40 with previous ASCT)	33 (all patients)	40 (44)	43.2 (survivors)	42
Blum et al[36]	Phase 2	Bortezomib	30	35	24 (80)	18 (all patients)	14.8

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Burroughs et al[37]	Retrospective	Allo-SCT following nonmyeloablative conditioning	90 total HLA-matched: 38 Unrelated: 24 HLA-haploidentical: 28	HLA-matched: 33 Unrelated: 28 HLA-haploidentical: 32	HLA-matched: 34 (89) Unrelated: 24 (100) HLA-haploidentical: 25 (89)	Survivors: HLA-matched: 24 Unrelated: 38 HLA-haploidentical: 22	HLA-matched: 26.4[†] Unrelated: 46.5[†] HLA-haploidentical: 47.5[†]
Chen et al[38]	Retrospective	Allo-SCT with RIC	24	35	20 (83)	27.2 (all patients)	39.6[†]
Clozel et al[39]	Retrospective	PLD or PLD+MOPP/GVD/ BEACOPP/vinblastine	47	25	47 (100)[‡]	36	42[†]
Corazzelli et al[40]	Retrospective	Bendamustine and allo-SCT	41	33	35 (85)	Not reported	21.4
Corradini et al[41]	Phase 2	Allo-SCT with RIC	32/170*	51 (all patients)	25 (78)	33 (all patients)	26.9[†]

Study	Study design	Regimen	Number of evaluable HL patients	Median baseline age, years	Number of HL patients with prior ASCT, *n* (%)	Median follow up (months)	Reported median OS (or derived from KM curve[†]), month
Czyz et al[42]	Retrospective	GCS or GV	37	32	37 (100)[‡]	26.4 (survivors)	15.5
Devetten et al[43]	Retrospective	RIC and nonmyeloablative SCT	143	30	127 (89)	25 (survivors)	14.8[†]
Fehniger et al[44]	Phase 2	Lenalidomide	36/38	34	29 (76)	20	20
Ghesquieres et al[45]	Retrospective study	Bendamustine or bendamustine + rituximab or vinorelbine	28	32	25 (89)	16.5	Not reached
Goda et al[46]	Retrospective study	Salvage RT or RT with salvage CT	56	30	56 (100)[‡]	31.3	40.8
Gopal et al[22]	Pivotal Phase 2	Brentuximab vedotin	102	31	102 (100)[‡]	32.7	40.5
Guidetti et al[47]	Phase 2	Perifosine and perifosine + sorafenib	25/40*	42 (all patients)	27 (67) (all patients)	14 (all patients)	16

Study	Study design	Regimen	Number of evaluable HL patients	Median baseline age, years	Number of HL patients with prior ASCT, *n* (%)	Median follow up (months)	Reported median OS (or derived from KM curve[†]), month
Harrison et al[48]	Prospective cohort	Panobinostat	129	32	129 (100)[‡]	NA	Not reached
Johansson et al[49]	Retrospective	Allo-SCT with RIC	23	36	20 (87)	25 (all patients) 46 (survivors)	52.1[†]
Majhail et al[50]	Prospective cohort	UCB or MSD allo-SCT with RIC	21 total UCB: 9 MSD:12	UCB: 28 MSD:42	UCB: 7 (78) MSD: 7 (58)	UCB: 17 MSD:24	UCB: Not reached MSD: 16.2[†]
Marcais et al[51]	Retrospective	Allo-SCT	191	31	174 (92)	36	55
Moskowitz et al[52]	Phase 2	Bendamustine	34/36	34	27 (75)	19 (all patients) 36 (survivors)	29[†]

Study	Study design	Regimen	Number of evaluable HL patients	Median baseline age, years	Number of HL patients with prior ASCT, *n* (%)	Median follow up (months)	Reported median OS (or derived from KM curve[†]), month
Peggs et al[53]	Prospective cohort	Allo-SCT with RIC	49 total Unrelated donors: 18 Related donors: 31	32	44 (90)	31.8 (survivors)	Unrelated donors: 14[†] Related donors: Not reached
Peggs et al[54]	Retrospective	Allo-SCT with RIC followed by GvHD prophylaxis with MF-A or MF	67 total MF-A: 31 MF: 36	MF-A: 36 MF: 35	MF-A: 27 (87) MF: 26 (72)	MF-A: 58.6 (survivors) MF: 41.7 (survivors)	MF-A: Not reached MF: 25[†]
Robinson et al[55]	Retrospective	Allo-SCT with RIC	272/285	31.2	229 (80)	26 (all patients)	28.4[†]
Sarina et al[56]	Retrospective	Donor group: conditioning regimen No donor group: salvage chemotherapy or radiotherapy	104	31.9	104 (100)[‡]	47.9 (all patients)	Allo-SCT patients: 37.9[†]

Study	Study design	Regimen	Number of evaluable HL patients	Median baseline age, years	Number of HL patients with prior ASCT, *n* (%)	Median follow up (months)	Reported median OS (or derived from KM curve[†]), month
Schmitz et al[57]	Retrospective	Nonmyleoablative conditioning + allo-SCT	80/94	30	NR (~50)	NR	18.6[†]
Shamash et al[58]	Retrospective	HDCT with autologous haematopoietic support	37 total Single sequential chemotherapy: 20 multiple agent group: 17	28	37 (100)[‡]	24	Single sequential chemotherapy: 12.0 multiple agent group: 21.9
Smith et al[59]	Retrospective	Second ASCT	21/40*	38 (all patients)	40 (100)[‡] (all patients)	72 (survivors)	24[†]
Smith et al[60]	Phase 2	Galiximab	29/30	36	21 (70)	13.6	23.2
Sobol et al[61]	Prospective cohort	Allo-SCT with RIC	31	36	100[‡]	84	Chemorefractory bulky: 19.4, Chemorefractory nonbulky: NA, Chemosensitive bulky: 18.4, Chemosensitive nonbulky: NA

Study	Study design	Regimen	Number of evaluable HL patients	Median baseline age, years	Number of HL patients with prior ASCT, *n* (%)	Median follow up (months)	Reported median OS (or derived from KM curve[†]), month
Sureda et al[62]	Retrospective	Allo-SCT with RIC or myeloablative conditioning	168 total RIC: 89 Myeloablative:79	RIC: 26 Myeloablative:27	RIC: 55 (61.8) Myeloablative: 32 (40.5)	RIC: 73 Myeloablative: 76	RIC: 14.6 Myeloablative: 6.7
Sureda et al[63]	Phase 2	Allo-SCT with RIC	78/92	28	79 (86)	32 (all patients) 48 (survivors)	30.1[†]
Thomson et al[64]	Phase 2	Allo-SCT with RIC	38	31	38 (100)[‡]	49 (survivors)	46[†]
Validire et al[65]	Retrospective	Gemcitabine-based regimen	55	29	34 (62)	14 (all patients)	20.7[†]

Study	Study design	Regimen	Number of evaluable HL patients	Median baseline age, years	Number of HL patients with prior ASCT, *n* (%)	Median follow up (months)	Reported median OS (or derived from KM curve[†]), month
Younes et al[66]	Phase 2	Mocetinostat	51 total 85mg: 28 110mg: 23	85mg: 34 110mg: 28	85mg: 23 (82) 110mg: 20 (87)	NR	85mg: Not reached 110mg: 20.3[†]
Younes et al[67]	Phase 2	Panobinostat	129	32	129 (100)[‡]	9.6 (all patients)	Not reached

*Mixed lymphoma populations; [†]Median overall survival derived from KM curve; [‡]Studies reporting a 100% prior-ASCT rate and included in the sensitivity analysis

Allo-SCT = allogeneic stem cell transplant; ASCT = autologous stem cell transplant; BEACOPP = bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; CT = chemotherapy; GCS = gemcitabine, cisplatin, and methylprednisolone or dexamethasone; GV = gemcitabine and vinorelbine; GVD = gemcitabine, vinorelbine, and pegylated liposomal doxorubicin; GvHD = graft versus host disease; HDCT = high

dose chemotherapy; MF-A = cyclosporine, alemtuzumab; MF = closporine, methotrexate; MOPP = mechlorethamine, vincristine, procarbazine, prednisone; MSD = matched-sibling donors; NR = not reported; PLD = pegylated liposomal doxorubicin; RIC = reduced-intensity conditioning; RT = radiotherapy; SCT = stem cell transplant; UCB = umbilical cord blood