Optimizing Brentuximab Vedotin Dosing in Pediatric Patients with Advanced Hodgkin Lymphoma: A Population Pharmacokinetic and Exposure-Response Analysis

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Pediatric patients with advanced-stage newly diagnosed Hodgkin lymphoma (HL) were treated with brentuximab vedotin (BV) combined with adriamycin, vinblastine, and dacarbazine (A + AVD). Weight-based BV dosing is employed in adult patients, while both body weight- and body surface area (BSA)-based dosing are used in pediatric patients. Data from two pediatric studies were used for a population pharmacokinetics (PK) analysis. Study 1 was a phase I/II dose-escalation study in which patients with relapsed or refractory systemic anaplastic large-cell lymphoma or HL received single-agent weight-based BV 1.4–1.8 mg/kg every 3 weeks. Study 2 tested BSA-based BV 48 mg/m^2 every 2 weeks with AVD in patients with advanced-stage, newly diagnosed HL. Sources of PK variability were quantified using nonlinear mixed-effects modeling. The relationships between antibody-drug conjugate (ADC) or payload monomethyl auristatin E (MMAE) exposures and progression-free survival (PFS) or incidence of adverse events were analyzed by Cox proportional hazards and logistic regression, respectively. Population PK models of ADC and MMAE were developed using data from 95 patients. BSA was identified as a significant covariate for the clearance of ADC and MMAE. BSA-based BV dosing resulted in similar systemic exposures of ADC and MMAE in pediatric patients across age groups (< 12, 12–16, and > 16 years). A significant increase ($P < 0.05$) in the incidence of febrile neutropenia was related to increasing exposure of MMAE. No apparent relationship was identified between ADC or MMAE exposures and PFS. The analyses support BSA-based BV dosing in combination with AVD in pediatric patients.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Weight-based dosing has been utilized in adult patients with hematological malignancies. However, weight-based dosing of brentuximab vedotin (BV) in a pediatric study resulted in lower antibody-drug conjugate (ADC) exposures in small/medium-sized pediatric patients (< 28 kg and 28–49 kg, respectively).

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ Does body surface area (BSA)-based dosing of BV result in similar ADC exposures in pediatric patients across age groups, and what is the optimal way of dosing BV in pediatric patients?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ BSA is a significant covariate for ADC and monomethyl auristatin E (MMAE) clearance in pediatric patients receiving concurrent adriamycin, vinblastine, and dacarbazine (AVD). BSA-based dosing of BV 48 mg/m^2 + AVD in pediatric patients resulted in systemic exposures of ADC and MMAE that were similar across age groups and comparable with those in adults who received BV 1.2 mg/kg + AVD.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ The BSA-based dosing regimen of BV in combination with AVD informs posology in pediatric patients with advanced-stage newly diagnosed Hodgkin lymphoma. This regimen is prescribed in frontline Hodgkin lymphoma in Japan.

Brentuximab vedotin (BV) is an antibody-drug conjugate (ADC) consisting of the monoclonal antibody cAC10, targeting the CD30 antigen on Hodgkin lymphoma (HL) and systemic anaplastic large-cell lymphoma (sALCL) cells, a valine-citrulline linker, and a cytotoxic antimicrotubule agent monomethyl auristatin E (MMAE). It is indicated for multiple types of lymphoma

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Received October 21, 2024; accepted February 24, 2025. doi:10.1002/cpt.3629

in adults.[1] Based on the final analyses, BV administered as a single agent at 1.8 mg/kg every 3 weeks (Q3W) achieved improved, clinically meaningful, durable responses and longer progression-free survival (PFS) vs. physician's therapy of choice for patients with CD30-expressing mycosis fungoides or primary cutaneous anaplastic large-cell lymphoma.[2] BV 1.2 mg/kg every 2 weeks (Q2W) in combination with 25 mg/m^2 doxorubicin, 6 mg/m^2 vinblastine, and 375 mg/m^2 dacarbazine (A + AVD) showed durable improvement in PFS in adult patients with previously untreated stage III or IV classical HL (cHL).[3] Combined with cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, and prednisone 100 mg, BV at 1.8 mg/kg Q3W yielded clinically meaningful survival benefit in adult patients with untreated sALCL or other CD30-expressing peripheral T-cell lymphomas.[4] BV has also been administered in pediatric patients with cHL or sALCL. In a phase I/II open-label, single-agent multicenter dose-escalation study (NCT01492088), patients aged 7–18 years who had relapse or refractory classical HL or sALCL received the adult dose of 1.8 mg/kg Q3W. In that study, BV had a manageable safety profile with clinically meaningful responses (overall response rate [ORR] of 47% in patients with cHL and 53% for those with sALCL).[5] Prior noncompartmental pharmacokinetic (PK) analysis of this study suggested a trend for lower ADC and MMAE exposures in patients aged < 12 years. The population PK analysis suggested that body surface area (BSA)-based dosing of BV as an alternate dosing regimen may normalize ADC and MMAE exposures across all body weights.[6] Simulations indicated that BV 48 mg/m^2 Q2W in pediatric patients would achieve equivalent ADC exposures at 1.2 mg/kg Q2W in adult patients. Subsequently, a phase I/II, open-label, multicenter study (NCT02979522) of BV 48 mg/m^2 plus AVD was conducted in pediatric patients with advanced-stage, newly diagnosed, CD30+ cHL. BV 48 mg/m^2 plus AVD showed efficacy and an acceptable safety profile in treatment-naïve pediatric patients with advanced cHL. ORR was 88%; the 24-month PFS rate confirmed by independent review was 72.6%.[7]

It is widely recognized that doses of many oncology agents used for registrational studies may not be optimal, and the lack of dose optimization during early clinical development has occasionally resulted in a post-marketing requirement or post-marketing commitment for further dose optimization.[8,9] Project Optimus, introduced by the US Food and Drug Administration, is an endeavor that aims to reform the dose selection paradigm in the evaluation of oncology drugs. Workshops, webinars, publications, and public meetings to facilitate engagement, share updates, and gather feedback from the public have focused on dose optimization for drugs indicated for adult patients.[10–14]

As described herein, population PK models using data from two pediatric studies (NCT01492088 and NCT02979522) were developed to characterize the intrinsic and extrinsic factors that affect the PK of ADC and MMAE in pediatric patients. Exposure-response analyses were performed to assess benefit/risk profiles of A + AVD in pediatric patients with advanced-stage newly diagnosed HL. To our knowledge, this may be one of the very few cases of an oncology drug where posology in pediatric patients with advanced-stage newly diagnosed HL was optimized during drug development to maximize safety, efficacy, and tolerability in this specific population.

METHODS

BV and MMAE PK measurements and population PK analyses

Clinical studies and sample collections. Study 1 (NCT01492088) was an open-label phase I/II dose-escalation study in which patients aged 7–18 years with relapsed or refractory sALCL or HL received BV as a single agent 1.4–1.8 mg/kg Q3W (**Figure 1**). Study 2 (NCT02979522) was an open-label phase I/II study in patients 5 to < 18 years with advanced-stage, CD30+, newly diagnosed HL in which BV 48 mg/m^2 was coadministered with doxorubicin 25 mg/m^2, vinblastine 6 mg/m^2, and dacarbazine 375 mg/m^2 (**Figure 1**). Both studies were institutional review board approved. Data from these two pediatric studies were used for the population analysis. For study 1, samples for measuring ADC and MMAE concentrations and immunogenicity assessment were collected

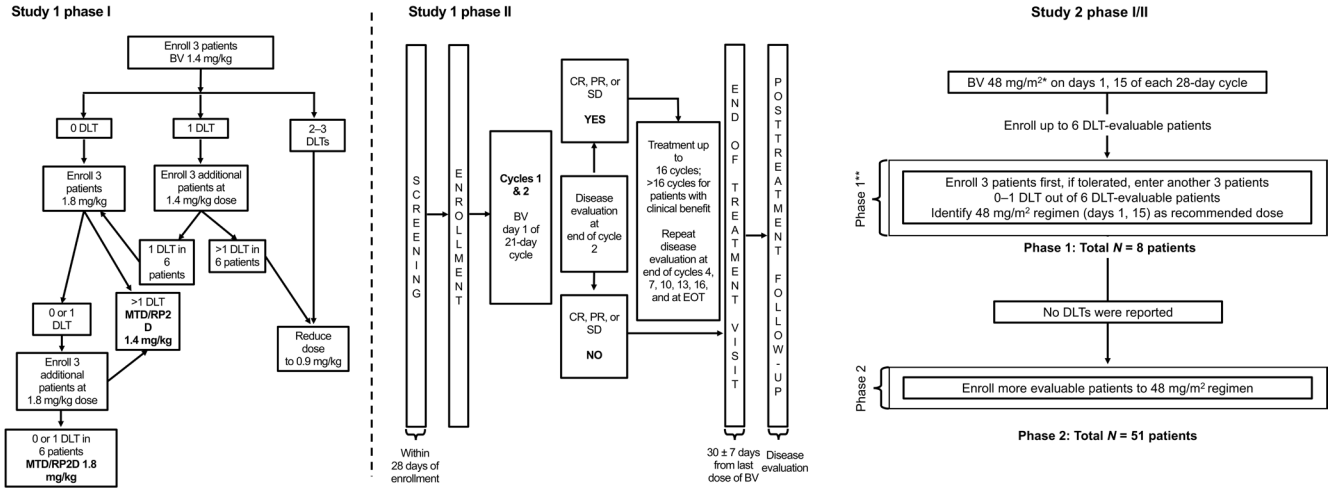

Figure 1 Study design. *A BV dose reduction to 36 mg/m^2 was permitted if needed. **Patients treated at RP2D will be carried over to phase 2 and receive up to 6 cycles of BV. BV, brentuximab vedotin; CR, complete remission; DLT, dose-limiting toxicity; EOT, end of treatment; MTD, maximum tolerated dose; PR, partial remission; RP2D, recommended phase 2 dose; SD, stable disease.

at all cycles pre-dose on day 1 and 5 minutes after the end of BV infusion; 24 hours (±4 hours) from the start of the day 1 intravenous infusion of BV (phase I only); at cycles 1 and 8: 24, 48, 96, and 312 hours from the start of the day 1 intravenous infusion. For study 2, samples were collected at cycles 1 through 6 predose and at the end of infusion on days 1 and 15. Additionally, samples were collected in cycles 1 and 3 at 24, 48, 72, and 168 hours post-infusion. A validated enzyme-linked immunosorbent assay was used to measure ADC concentrations, and unconjugated MMAE concentrations were measured using a validated liquid chromatography–tandem mass spectrometry assay, as reported previously.[15]

Population PK model development and covariate assessment. The structure model for ADC and MMAE was based on previously reported models[16] and a schematic representation of the model is presented in **Figure 2**. After the ADC model was finalized, a model for MMAE was developed where MMAE formation was linked to ADC elimination using the individual parameter estimates from the ADC model to predict the ADC concentrations in the MMAE model. ADC and MMAE concentration-time data were analyzed using mixed-effects modeling methods as implemented by NONMEM (version 7.4; Icon Development Solutions, Dublin, Ireland) with Intel® Visual Fortran Intel® 64 Compiler XE, Version 12.0.0.104, Build 20101006 (Santa Clara, CA). A log-transform both sides approach was used. Modeling was performed using the first-order conditional estimation method.

Age, weight, BSA, body mass index, albumin, alanine aminotransferase, aspartate aminotransferase, bilirubin, creatinine, concurrent chemotherapy (AVD), disease type (HL vs. non-HL), sex, race, ethnicity, and lymphoma volume (disease burden) were evaluated as covariates on the clearance of ADC and MMAE. General goodness-of-fit of the final PK models was evaluated by examining a variety of diagnostic and summary graphics. For the prediction-corrected visual predictive check (pcVPC) evaluation, the median, 5th and 95th prediction intervals were constructed by simulating replicates of the dataset from which the model was developed. The observed data were then overlaid and compared to the prediction intervals.

Model-based simulations. Simulations using the final ADC and MMAE models were performed with pediatric patients in study 2 who received BV 48 mg/m^2 Q2W compared to 1.2 mg/kg Q2W in adult patients in ECHELON-1. The simulated ADC and MMAE exposures in pediatric patients were summarized as three age groups of < 12 years, 12–16 years, and > 16–18 years.

Exposure-response analyses

Exposure-response (efficacy and safety) analyses were performed using data from study 2 in which patients were treated with A+AVD for newly diagnosed, advanced-stage cHL. The time-averaged area under the concentration-time curve (AUC/time, dose intensity) was used as exposure metrics in the analyses, in which time-averaged ADC and MMAE AUC at steady-state were calculated for the dose interval (from day 1 to day 15, i.e., $\tau = 14$ days). These exposure metrics were obtained from the individual predicted concentration-time profiles for 1 cycle (day 1 to day 15) at steady-state, using individual post-hoc PK parameter estimates derived from the final population PK model. The exposure-response relationship for PFS was explored using Cox proportional hazard analysis. Adverse events (AEs) of interest were grade 3 and higher neutropenia, febrile neutropenia, peripheral neuropathy, and grade 3 and higher treatment-emergent AEs (TEAEs). The relationships between the incidence of AEs and ADC/MMAE exposures were analyzed by logistic regression.

RESULTS

Population PK of ADC and MMAE

The population PK dataset included 95 patients with 9,479 concentration records: 2,608 from study 1 and 6,871 from study 2. Patient baseline demographics and disease characteristics are summarized in **Table 1**. ADC PK was a linear three-compartment model with zero-order input and first-order elimination (**Figure 2**). Inter-individual variability was included on clearance rate (CL), inter-compartment clearance (Q2), and volume of distribution (V3). The covariates on CL included an increasing CL with increasing BSA and tumor size, decreasing CL with increasing albumin concentration, and a higher CL for patients on concurrent AVD treatment. Patients with non-HL had approximately

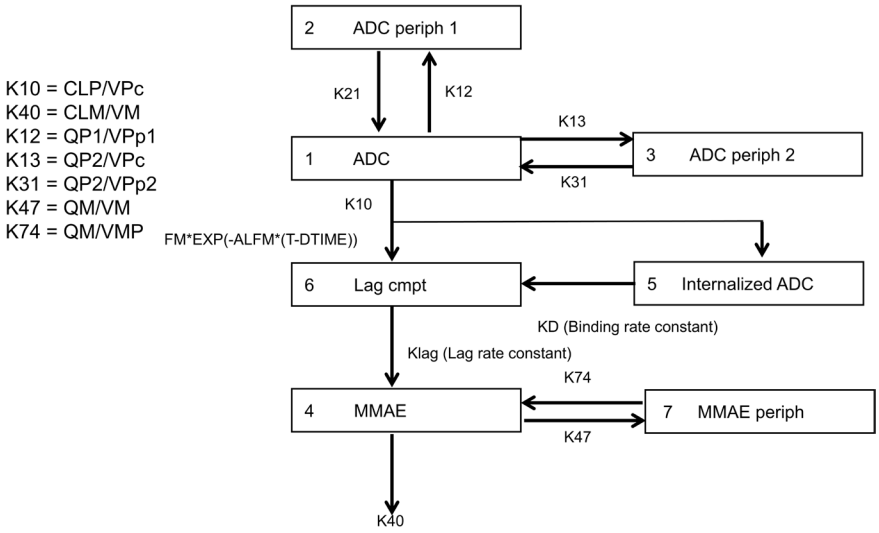

Figure 2 Pharmacokinetic structure model. ADC, antibody-drug conjugate; CLM, apparent MMAE clearance; CLP, ADC clearance; KD, binding rate constant; Klag, constant for lag compartment; MMAE, monomethyl auristatin E; QM, apparent MMAE inter-compartmental clearance; QP1 and QP2, ADC inter-compartmental clearance from central to 1st and 2nd peripheral compartments, respectively; VM and VMP, apparent volume of MMAE central and peripheral compartments, respectively; VPc, volume of ADC central compartment; VPp1 and VPp2, volume of ADC 1st and 2nd peripheral compartments, respectively; DTIME, time after dose.

Table 1 Patient demographics and baseline characteristics

	Study	
	C25002 ($n=36$)	C25004 ($n=59$)
Age, years		
Mean (SD)	13.1 (3.2)	13.7 (3.0)
Median (min–max)	14.0 (7.0–18.0)	14.0 (6.0–17.0)
Sex, *n* (%)		
Male	25 (69.4)	31 (52.5)
Female	11 (30.6)	28 (47.5)
Weight, kg		
Mean (SD)	50.0 (17.4)	49.4 (16.0)
Median (min–max)	49.9 (21.2–87.0)	49.0 (18.8–81.0)
BSA, m^2		
Mean (SD)	1.48 (0.32)	1.47 (0.29)
Median (min–max)	1.52 (0.89–2.03)	1.52 (0.79–2.03)
Albumin, g/L		
Mean (SD)	40.9 (5.9)	38.1 (5.3)
Median (min–max)	40.5 (27.0–51.0)	39.0 (23.0–46.0)
Bilirubin, µmol/L		
Mean (SD)	6.60 (4.15)	7.75 (5.95)
Median (min–max)	5.15 (1.71–20.0)	6.84 (1.71–45.2)
Creatine clearance (Cockroft), mL/min		
Mean (SD)	166.7 (45.7)	144.5 (35.9)
Median (min–max)	165.3 (102.0–301.4)	132.3 (85.5–251.2)
Race, *n* (%)		
White	31 (86.1)	34 (57.6)
Black	0 (0.0)	12 (20.3)
Asian	2 (5.6)	3 (5.1)
Other	3 (8.3)	10 (16.9)
Sum of tumor area, mm^2		
Mean (SD)	2,158 (1,890)	2,317 (2,095)
Median (min–max)	1,581 (555–6,515)	1,639 (455–9,792)

BSA, body surface area; Max, maximum value; Min, minimum value; SD, standard deviation.

50% reduced Q2 parameter compared to that of HL patients. V3 increased with increasing BSA. Parameter precision as standard error was 32.2% or less. Residual variability was 32.1%, and the condition number was 14. Final model parameters for ADC and MMAE are listed in **Tables S1 and S2**, respectively.

pcVPC plots for ADC and MMAE concentrations vs. time since the last dose (**Figure S1**) showed that the observed concentrations overlaid model-predicted intervals. The observed 95% and median intervals are within the shaded prediction intervals, indicating that the model predicted the observed ADC and MMAE concentrations adequately.

Effect of age, body size, and tumor size on the clearance of ADC and MMAE

Effects of age, body size (body weight and BSA), and tumor size on clearance of ADC and MMAE were evaluated based on simulations using final model parameters. **Figure 3** illustrates the magnitude of selected covariates on clearance of ADC and MMAE. As concurrent chemotherapy treatment with AVD resulted in higher ADC clearance, the forest plots for ADC are presented with and without concurrent AVD, respectively. Age (7–17 years) had no clinically meaningful impact on ADC and MMAE clearance. The range of ADC clearance at 5th and 95th percentile of body weight were similar, indicating that body weight was not an important predictor for ADC clearance in pediatric patients. As expected, BSA (0.79–2.03 m^2) had a significant effect on the clearance of both ADC and MMAE. Pediatric patients with larger BSA resulted in higher clearance of ADC and MMAE. Lymphoma volume (i.e., tumor linear diameter) and albumin were also included as covariates on ADC clearance in the final model, with larger tumor burden resulting in higher ADC clearance, and lower albumin levels associated with higher ADC clearance.

Exposure-PFS analyses

The analysis dataset for the exposure-efficacy analyses included 59 patients with cHL receiving A + AVD. As all patients survived (no deaths) and responded to the treatment (either complete remission or partial remission) for the study duration (including treatment cycles and two-year follow-up period), analyses for exposure-overall survival and exposure-ORR were not performed. **Figure 4** depicts Kaplan–Meier curves for PFS stratified by AUC (tertiles) of ADC and MMAE, which showed substantial overlap. A log-rank test indicated that systemic exposures of ADC or MMAE were not significantly related to PFS of pediatric patients with advanced-stage newly diagnosed HL who received A + AVD ($P > 0.05$).

Exposure-safety analyses

The incidence of febrile neutropenia was significantly increased with increasing MMAE exposure ($P < 0.05$, **Figure 5**). Peripheral neuropathy also showed a non-significant relationship with MMAE exposure ($P < 0.1$), similar to that observed in adult patients. The incidence of grade 3 or higher neutropenia or grade 3 or higher TEAEs was not significantly related to MMAE exposure with currently available data ($N = 59$). No AEs of interest (grade 3 or higher neutropenia, febrile neutropenia, peripheral neuropathy, or grade 3 or higher TEAE) were related to ADC exposure.

DISCUSSION

Dose optimization is key to maximizing the benefit/risk ratio of new medicines for pediatric patients with cancer and is an integral part of oncology drug development. Unique considerations associated with dose selection and optimization for pediatric patients with cancer include variability in PK and pharmacodynamic parameters by age and body size, the need for age-appropriate formulations, potential for toxicities associated with long-term use, and the rarity of pediatric cancers. BV was administered in adult patients with weight-based dosing, and population PK and exposure-response analyses were previously reported for adult cancer patients with BV as monotherapy or in combination with chemotherapy.[2,3,6] Weight-based

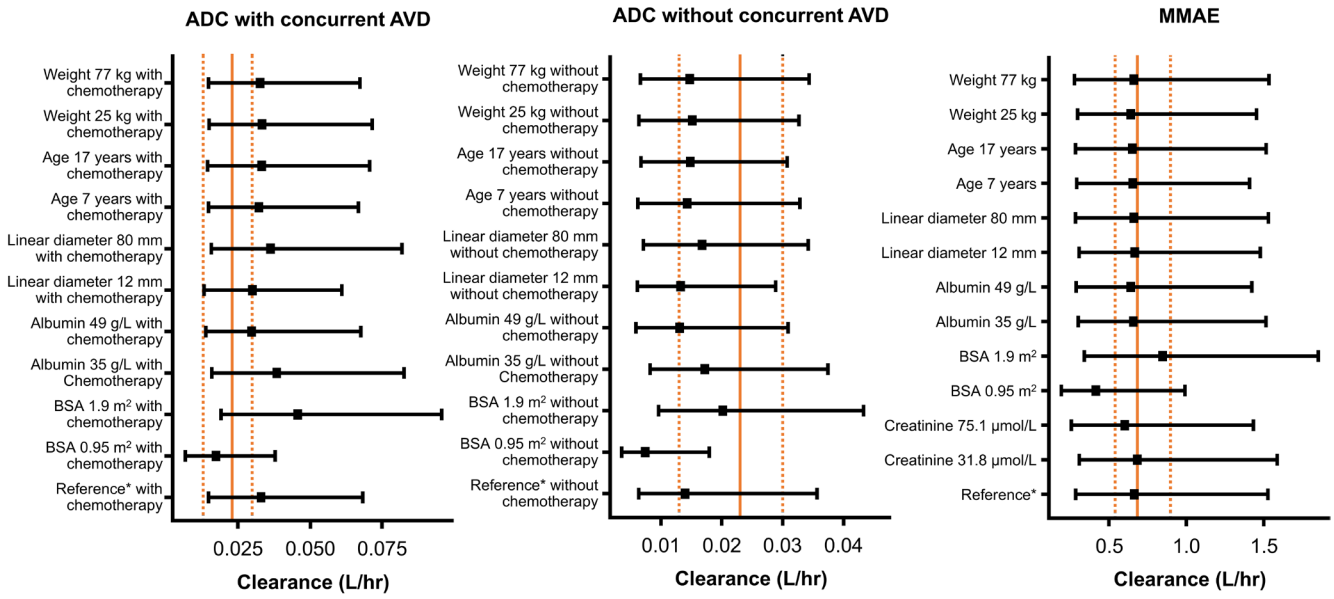

Figure 3 Effect of covariates on ADC and MMAE clearance. The horizontal black lines and box display the 5th, 95th quantiles, and the median, respectively, ADC CL values for the median, 5th, and 95th quantiles of various continuous covariate values shown on the left panel of the plot. In these plots, the vertical red dashed lines are the 5th and 95th bootstrap confidence intervals of ADC CL. The solid red line is the median of the bootstrap CL estimates. The reference (ref) patient is a virtual patient with median covariate values. ADC, antibody-drug conjugate; AVD, adriamycin, vinblastine, and dacarbazine; BSA, body surface area; MMAE, monomethyl auristatin E.

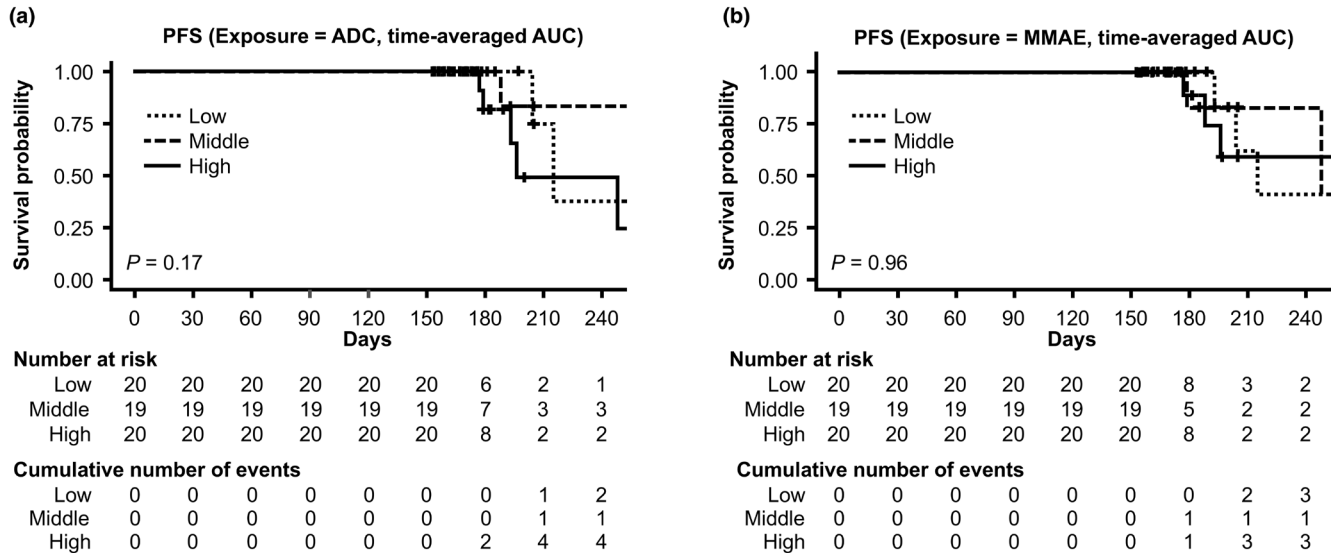

Figure 4 Kaplan–Meier plots of PFS by tertiles of ADC (**a**) and MMAE (**b**) exposures. ADC, antibody-drug conjugate; AUC, area under the concentration-time curve; MMAE, monomethyl auristatin E; PFS, progression-free survival.

dosing of BV in pediatric patients has been approved in the United States.[4] Pediatric patients demonstrate a wide range of body weight across age groups, and a study of BV administered 1.8 mg/kg in patients aged 7–18 years suggested a trend for lower ADC and MMAE exposures in patients aged < 12 years. BSA was identified as an important covariate on the clearance of ADC and MMAE, and simulations suggested that BSA-based dosing of BV may be able to address BV PK variabilities and normalize ADC and MMAE exposures across pediatric age groups with a wide range of body sizes.

This population PK analysis used data from two pediatric studies, one utilizing weight-based dosing of BV as a single agent, and the other with BSA-based dosing of BV in combination with AVD. BSA was confirmed as an important predictor for the PK of ADC and MMAE. As illustrated in **Figure S2** (**panels A and B**), after normalizing the BSA, ADC clearance (L/h/m^2) was similar across three pediatric age groups (< 12 years, 12–16 years and > 16 years). Systemic exposures of ADC and MMAE following BV administration at 48 mg/m^2 Q2W in combination with AVD in pediatric patients are comparable to those in adults receiving 1.2 mg/kg BV

Q2W with AVD in the ECHELON-1 study (**Figure 6**, **Figure S2**, **panels C and D**).

In the population PK analysis of BV in adult patients, BSA was a significant covariate.[17] The weight-based dosing of BV has some disadvantages in pediatric patients because the range of body weight in pediatric patients is larger than that in adults due to substantial variability in growth rate at young ages, resulting in a tendency to under-dose very young patients and/or those with low weight. For pediatrics, BSA has a relatively narrower distribution than body weight. Therefore, the BSA-based dosing of BV resulted in comparable systemic exposure of ADC and MMAE across different age groups in pediatric populations. The tiered weight-based dosing of therapeutic proteins may be the most widely used dosing approach in pediatric populations.[18] The disadvantage of this dosing strategy is that it necessitates the development of multiple dosage strengths with pediatric-suitable formulations[19] or leads to drug waste due to a lack of specific strengths.

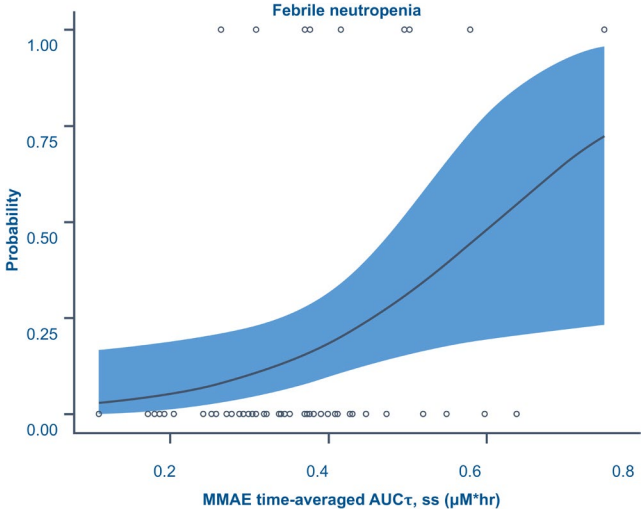

Figure 5 Relationship between MMAE exposure and the incidence of febrile neutropenia. The black circles represent observed incidence. The solid line and gray shade represent predicted incidence of febrile neutropenia and the associated 95% confidence interval, respectively. ADC, antibody-drug conjugate; AUC, area under the concentration-time curve; MMAE, monomethyl auristatin E; Q2W, every 2 weeks.

The PK of BV is characterized by a three-compartment model with first-order elimination, as described previously.[20,21] The PK of MMAE was described by a two-compartment model with first-order elimination, and the decrease in payload is estimated empirically to be like the conversion of ADC to MMAE following each dose administration. Based on a recently published analysis, following repeated BV dosing, a time-varying formation rate for MMAE was reported, accounting for a decline in MMAE exposure over time, which possibly reflected disease status improvement.[6] The analysis indicated that higher serum albumin concentrations were associated with lower ADC clearance, consistent with that observed in adult patients treated with A + AVD in ECHELON-1.[22] BV is formed by an anti-CD30 chimeric immunoglobulin G (IgG) 1 conjugated with MMAE. Since albumin and IgG share the same neonatal Fc receptor salvaging pathway, serum albumin level could reflect the IgG catabolic rate, which directly affects the clearance of IgG antibodies, consistent with reports that the clearance of IgG antibodies is faster in patients with lower serum albumin levels.[6,23] The effect of lymphoma volume or disease burden on ADC clearance was explored, with increased ADC clearance observed with increasing tumor burden. This may be due to increased ADC internalization due to high tumor burden.[24] BV acts through the binding of the ADC to CD30-positive cells, followed by receptor endocytosis and release of MMAE upon exposure to intracellular lysozymes. Endocytosis is regulated by various cellular factors, including membrane composition, cytoskeletal dynamics, and signaling pathways. Tumor cells diverging from normal cells and

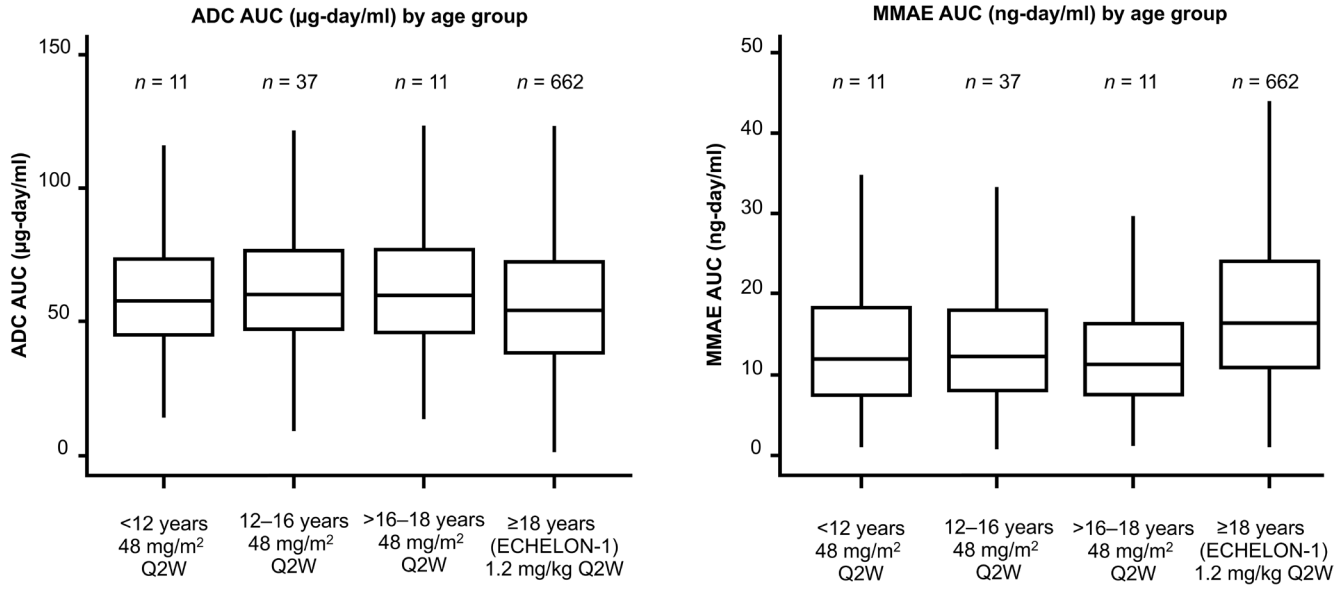

Figure 6 After BSA-based dosing of BV 48 mg/m^2 in combination with AVD, systemic exposures of ADC and MMAE were similar across age groups and comparable with those in adults (BV 1.2 mg/kg). AUC, area under the concentration-time curve; Q2W, once every 2 weeks.

various tumor types are different in their cell membrane's structure and composition; this may be the possible reason to impact the receptor endocytosis and the conversion rate from ADC to MMAE (ALFM). The inter-individual variability of the binding rate constant, Kd, is estimated to be 147% with the shrinkage of 7.8% (**Table S2**). Similarly, the CV of ALFM is estimated to be close to 90% with shrinkage of 18.8%, indicating that the model is stable and not over-parameterized for the data that is available. Anti-drug antibody (ADA) positivity was identified as a statistically significant covariate on ADC clearance, suggesting that ADA positivity increases ADC clearance. Because of the low observed incidence of immunogenicity in these two pediatric studies, these results support the lack of clinically meaningful immunogenicity during BV treatment, consistent with observations in adult patients.[25]

The limitation of this analysis is that for these two pediatric studies, one is a BV single agent with weight-based dosing and the other is an A + AVD combination study with BSA-based dosing. The sample size (36 patients for single agent and 59 for the combination) is small for both studies. There are no sufficient data to investigate the effects of covariates on ALFM. The final model used the covariate effect of concurrent treatment with AVD on the clearance of ADC, accounting for lower ADC exposures in the combination study, which have not adequately addressed ADC exposure differences between these two studies due to the limited sample size of the analysis dataset. In addition, tiered weight-based dosing or the flat dosing of BV has not been evaluated in pediatric patients.

Exposure-safety analyses suggested a significantly increased incidence of febrile neutropenia with increased MMAE exposure in pediatric patients, consistent with the observed myelosuppression in adult patients due to blocking the polymerization of tubulin,[26] supporting the protocol-specified dose modification guidance to mitigate hematological toxicities. No significant relationship for PFS and ADC exposures was observed, supporting consistent clinical benefit across the range of ADC exposures after a dose of 48 mg/m^2 BV in combination with AVD in pediatric patients with advanced-stage newly diagnosed HL.

CONCLUSIONS

Population PK and exposure-response analyses support a 48 mg/m^2 Q2W dose of BV in combination with AVD as a treatment option for pediatric patients with advanced-stage newly diagnosed HL. Aligned with Project Optimus recommendations, this work highlights the importance of dose optimization for pediatric patients during clinical development.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

ACKNOWLEDGMENTS

The authors thank the patients and their families and caregivers for their participation in the studies used for this analysis, along with all investigators and site personnel. Editorial support was provided by Helen Johns, PhD, of Ashfield MedComms, an Inizio Company, funded by Takeda Pharmaceuticals U.S.A., Inc., Lexington, MA, and complied with the Good Publication Practice 3 ethical guidelines (DeTora LM, et al. Ann Intern Med 2022;175:1298–1304).

FUNDING

The study was sponsored by Takeda Development Center Americas, Inc., Lexington, MA. Editorial assistance was provided by Helen Johns, PhD, Ashfield MedComms, an Inizio Company, and funded by Takeda Development Center Americas, Inc., Lexington, MA.

CONFLICTS OF INTEREST

X.Z., X.B., and N.G. are employees of Takeda. D.R.M. was a paid consultant for Takeda. L.G. declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

All authors contributed to the writing and review of the manuscript. X.Z., D.R.M., L.G., and N.G. designed the research. All authors performed the research. X.Z., D.R.M., X.B., and N.G. analyzed thedata.

DATA AVAILABILITY STATEMENT

All authors had full access to the data and accept responsibility for its presentation herein. The datasets, including the redacted study protocol, redacted statistical analysis plan, and individual participants' data supporting the results reported in this article, will be made available within 3 months from the initial request to researchers who provide a methodologically sound proposal. The data will be provided after its de-identification in compliance with applicable privacy laws, data protection, and requirements for consent and anonymization.

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