

Population PK and Exposure–Response Relationships for the Antibody–Drug Conjugate Brentuximab Vedotin in CTCL Patients in the Phase III ALCANZA Study

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The antibody–drug conjugate (ADC) brentuximab vedotin consists of the CD30-directed antibody attached to the microtubule-disrupting agent monomethyl auristatin E (MMAE). In pharmacokinetic models, including data from six studies (380 patients with classical Hodgkin's, systemic anaplastic large-cell, and cutaneous T-cell (CTCL) lymphomas), lower clearance of ADC and modestly higher ADC exposure in CTCL patients did not translate into higher MMAE exposure. In CTCL patients from the phase III ALCANZA study ($n = 66$), improved progression-free survival with brentuximab vedotin vs. controls was not related to ADC exposure. ADC exposure was a predictor of grade ≥ 3 treatment-emergent adverse events (TEAEs). Results support the consistent benefit observed with brentuximab vedotin 1.8 mg/kg every 3 weeks across the range of exposures in ALCANZA and support dose reductions in patients experiencing TEAEs at the starting dose.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

✓ In Hodgkin's lymphoma (HL) and systemic anaplastic large-cell lymphoma (sALCL), pharmacokinetics (PKs) of the ADC and cytotoxic component (MMAE) of brentuximab vedotin were linear, exposures of MMAE were lower than ADC, and body size was a clinically significant covariate.

WHAT QUESTION DID THIS STUDY ADDRESS?

✓ We sought to develop two PK models (ADC and MMAE) including data from the ALCANZA study to analyze exposure–response relationships for efficacy and safety in CTCL.

WHAT THIS STUDY ADDS TO OUR KNOWLEDGE

✓ The lack of apparent exposure–efficacy relationships across the range of exposures is not due to an imbalance in potentially prognostic factors and supports the consistent treatment benefit of brentuximab vedotin 1.8 mg/kg every 3 weeks. The observed exposure–response relationship for grade ≥ 3 TEAEs supports dose reductions to 1.2 mg/kg for patients experiencing intolerable toxicities.

HOW THIS MIGHT CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE

✓ The brentuximab vedotin starting dose of 1.8 mg/kg (intravenous infusion over 30 min) every 3 weeks is appropriate in patients with CTCL as well as those with HL and sALCL.

The antibody–drug conjugate (ADC) brentuximab vedotin consists of a CD30-directed antibody, cAC10, conjugated to a microtubule-disrupting agent, monomethyl auristatin E (MMAE), by a protease-cleavable linker.¹ Following CD30 binding, brentuximab vedotin is internalized by cells and processed into lysosomal vesicles, leading to release of MMAE.² MMAE induces cell cycle arrest and cell death by inhibition of microtubule polymerization (Figure 1a).² There is limited CD30 expression on healthy tissue and cells; thus, brentuximab vedotin specifically targets cells expressing cell-surface CD30, such as Reed-Sternberg cells of classical Hodgkin's lymphoma (HL) and anaplastic large-cell lymphoma (ALCL) cells.^{1,3}

Brentuximab vedotin was initially approved for use in relapsed/refractory HL after failure of autologous hematopoietic stem cell transplantation (auto-HSCT) or after ≥ 2 prior multi-agent chemotherapy regimens in patients who are not auto-HSCT candidates, and in relapsed/refractory systemic ALCL (sALCL), based on studies demonstrating objective response rates (ORRs) of $\geq 75\%$.^{4,5} Complete remission was observed in 34% of relapsed/refractory HL patients (median duration 20.5 months) and in 57% of sALCL patients (median duration 13.2 months); treatment was well tolerated. Additionally, brentuximab vedotin is approved as consolidation treatment post-auto-HSCT in HL patients at increased risk of relapse or progression, based on the

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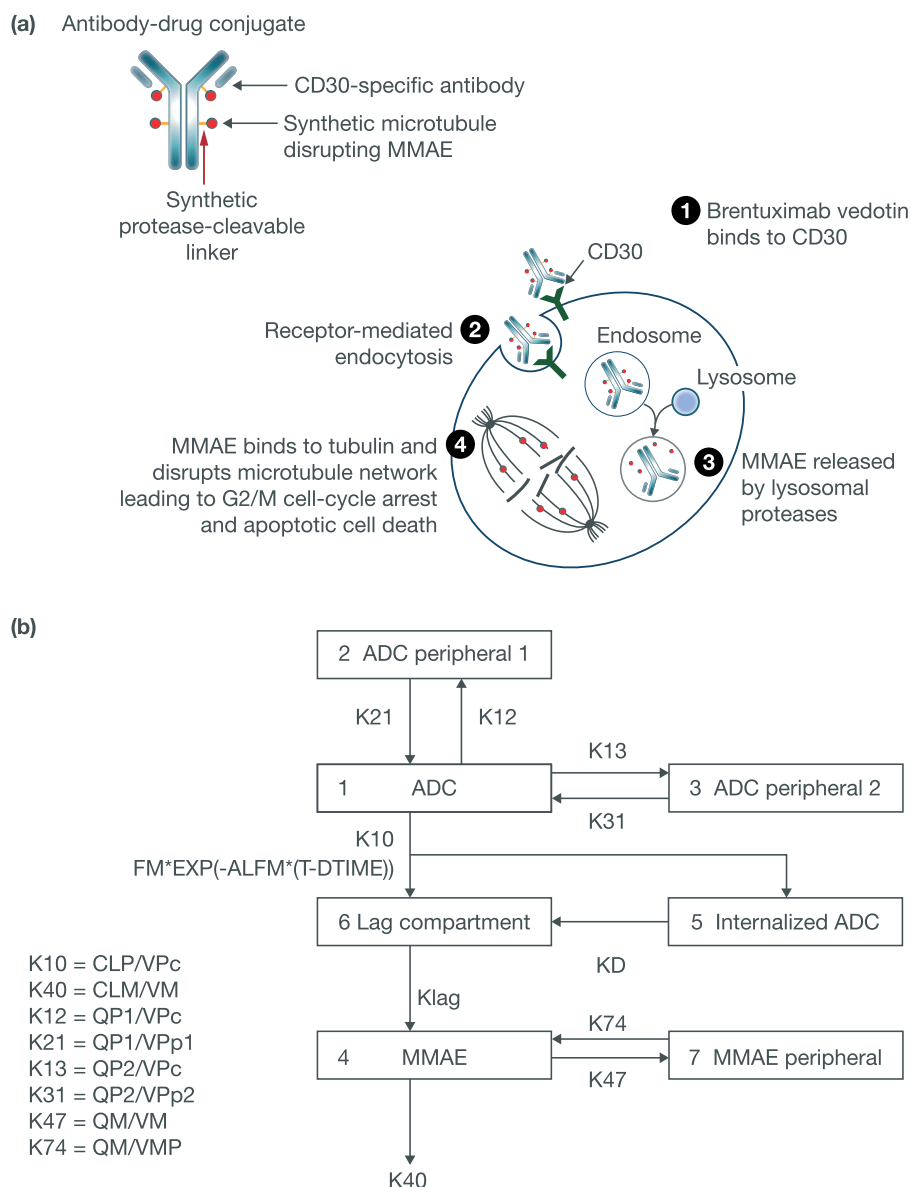


Figure 1 Brentuximab vedotin (a) mechanism of action and (b) final PK model. ADC, antibody–drug conjugate; ALFM, rate constant to describe the decline in direct conversion of ADC to MMAE following time after dose; CLM, apparent MMAE clearance; CLP, ADC clearance; KD, binding rate constant; Klag, rate constant for lag compartment; MMAE, monomethyl auristatin E; PK, pharmacokinetic; QM, apparent MMAE intercompartmental clearance; QP1 and QP2, ADC intercompartmental clearance from central to first and second peripheral compartments; VM and VMP, apparent volume of MMAE central and peripheral compartments; VPc, volume of ADC central compartment; VPp1 and VPp2, volume of ADC first and second peripheral compartments.

AETHERA trial.⁶ In this increased-risk population, brentuximab vedotin significantly improved median progression-free survival (PFS) vs. placebo.

Brentuximab vedotin is also approved in cutaneous T-cell lymphoma (CTCL), a rare family of non-Hodgkin lymphomas including mycosis fungoides (MF) and primary cutaneous ALCL (pcALCL),^{7,8} with significant clinical activity in patients with CD30-positive lymphoproliferative disorders or MF⁷ and with treatment-refractory or advanced MF or Sézary syndrome with a wide range of CD30 expression.⁸ Approval was based on the phase III ALCANZA trial in previously treated CD30-positive CTCL, which demonstrated superiority of brentuximab vedotin

over physician's choice (methotrexate or bexarotene), with significantly improved ORR lasting ≥ 4 months (ORR4) and greater symptom reduction.⁹ Frequency of grade 3/4 treatment-emergent adverse events (TEAEs) was similar with brentuximab vedotin (41%) and methotrexate or bexarotene (47%). Peripheral neuropathy (PN) occurred at >11 -fold-higher incidence with brentuximab vedotin vs. methotrexate or bexarotene (67% vs. 6%)⁹ but mostly resolved or improved after treatment cessation or completion.

The pharmacokinetics (PK) of brentuximab vedotin in HL and sALCL were described previously,^{10–14} but PK in other CD30-positive malignancies such as CTCL have not been

Table 1 Patient characteristics in the ALCANZA study and in the overall PK population

Covariate	ALCANZA (N = 66)	Overall population (N = 380)
Gender (Male/Female (%))	50/50	55/45
Race (White/Black/Asian/Other (%))	88/5/2/6	83/6/8/2
Ethnicity (Not Hispanic/Hispanic/Not reported (%))	94/3/3	91/7/2
Age (years)	59.39 (13.8) 22–83	41.57 (16.86) 12–87
Height (cm)	164.7 (23.11) 148–193	169.9 (15.96) 146–200
Weight (kg)	78.29 (17.29) 45–126	76.46 (20.31) 39–168
Body surface area (m ²)	1.839 (0.3291) 1.32–2.551	1.865 (0.2915) 1.264–2.858
Albumin (g/L)	42.38 (4.26) 29–53	36.81 (6.60) 17–53
Alanine aminotransferase (U/L)	27.17 (29.05) 8–227	24.64 (21.81) 4–232
Aspartate aminotransferase (U/L)	28.08 (25.84) 13–226	24.01 (16.97) 8–226
Bilirubin (μmol/L)	6.74 (2.63) 2–16	7.78 (7.54) 2–123
Creatinine (μmol/L)	72.3 (19.76) 40–125	72.4 (20.52) 35–159
Creatinine clearance (mL/min)	104.7 (37.2) 51–198	139.3 (54.81) 29–439

Values are mean (SD), range unless otherwise specified. PK, pharmacokinetic; SD, standard deviation.

reported. As evidence emerges for efficacy of brentuximab vedotin in these malignancies, the importance of understanding PK behavior and exposure–response relationships of the ADC and its cytotoxic component, MMAE, increases, especially because disease-related factors (e.g., tumor type/burden and target expression) may influence the PK of monoclonal antibody (mAb)-based therapeutics.^{15,16}

Here we report ADC and MMAE population PK models describing pooled concentration–time data from ALCANZA and five earlier studies of brentuximab vedotin, and patient factors (covariates) influencing the PK and PK variability of ADC and MMAE. Additionally, we conducted exposure–response analyses using ALCANZA data to identify relationships between ADC and MMAE time-averaged exposure and prespecified efficacy and safety endpoints to quantitatively characterize and support the benefit/risk profile of the proposed posology for the treatment of CTCL.

RESULTS

Population pharmacokinetic analysis dataset

PK data from 380 patients provided 22,660 records, including 3,450 dosing records and 19,210 concentration records (9,541 for ADC; 9,669 for MMAE). Approximately 3% of postdose records for both analytes (279 for ADC; 393 for MMAE) were below the limit of quantitation and were ignored (low frequency in the dataset). Overall, 246 patients had HL (64.7%), 66 had sALCL (17.4%), 50 had MF (13.2%), 16 had pcALCL (4.2%), and two had other hematologic malignancies.

The 66 patients in ALCANZA (MF and pcALCL) were generally the oldest patients in the dataset (**Table 1**): median age overall was 37 years vs. 61 years in ALCANZA. Mean creatinine clearance (CL) was lower in ALCANZA than the overall dataset, at least in part due to differences in age. Additionally, pcALCL patients were older than MF patients, and were at the lower end

of the ranges for body size, creatinine CL, and bilirubin (**Figure S1**). For albumin, patients with CTCL were at the upper end of the range.

ADC pharmacokinetic model

The final ADC PK model was a linear three-compartment model with zero-order input and first-order elimination (**Figure 1b**). Population mean estimates of model parameters (**Table S1**) were: CL 0.0478 L/h; central volume 3.5 L; peripheral volume one 3.67 L; peripheral volume two 5.79 L; intercompartmental CL one 0.0673 L/h; intercompartmental CL two 0.0125 L/h. The covariate effects in the model showed ADC CL and central volume of distribution (V_c) increasing with increasing body size and ADC CL decreasing with increasing albumin concentration (**Figure 2**; **Supplemental Table S2**). The influence of age, gender, and race was not significant. Patients with pcALCL had higher ADC concentrations and ~44% lower CL than those with other tumor types. In the most recent studies,^{9,17} which used the same updated antidrug antibody (ADA) assay with improved drug tolerance, ADC CL in pcALCL patients was 91% of that in non-pcALCL patients. Overall, ADA positivity consistently resulted in fractionally higher CLs.

Simulations of ADC concentration–time profiles and exposures

Simulation of 30 replicates using the regimen brentuximab vedotin 1.8 mg/kg every 3 weeks for three cycles showed minimal accumulation of ADC (**Figure 3**). Estimated steady-state area under the concentration–time curve (AUC) was highest for ADA-negative pcALCL patients and lowest for ADA-positive non-pcALCL patients. Of the ADA-negative patients, a 35% higher geometric mean steady-state AUC was calculated for pcALCL vs. non-pcALCL (3,742 vs. 2,772 μg·h/mL). Geometric mean steady-state AUC values for MF and pcALCL patients

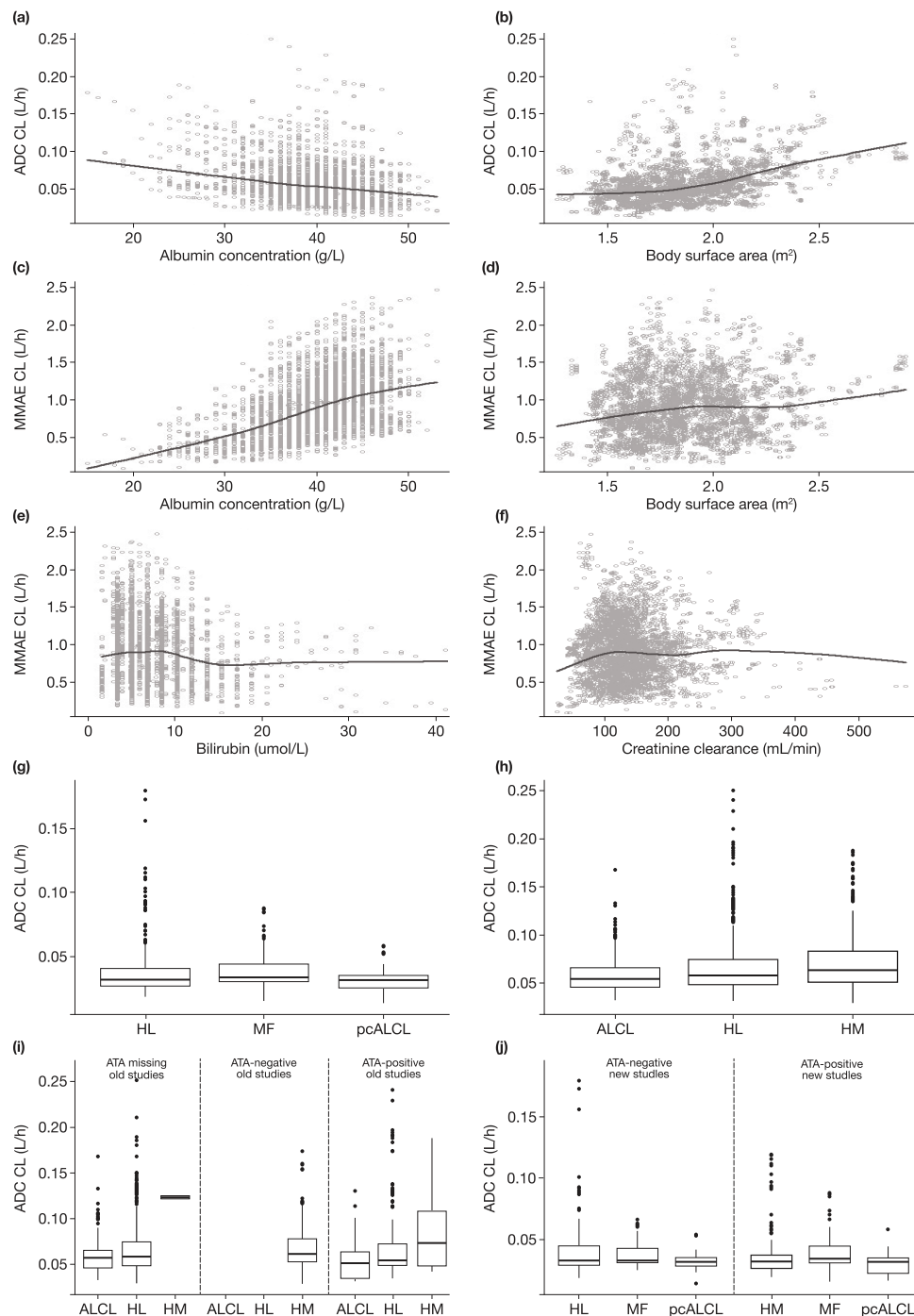


Figure 2 Scatterplots with locally weighted smoothing for ADC CL by albumin concentration (a) and body surface area (b), and for MMAE CL by albumin concentration (c), body surface area (d), bilirubin (e), and creatinine CL (f); and boxplots of ADC CL by tumor type in newer (g) and older (h) studies and by ADA status and tumor type in newer (i) and older (j) studies. In the scatterplots, open circles show individual data and the solid lines shows the locally weighted smoothing. In the boxplots, closed circles show individual data and the boxplots show the median and interquartile ranges. ADC, antibody–drug conjugate; ALCL, anaplastic large-cell lymphoma; ATA, anti-therapeutic antibody; CL, clearance; HL, Hodgkin lymphoma; HM, hematologic malignancy; MF, mycosis fungoides; MMAE, monomethyl auristatin E; pcALCL, primary cutaneous anaplastic large-cell lymphoma.

were higher than other tumor types; steady-state AUC for ADA-negative patients was 16% and 42% higher, respectively, than for HL patients (3,058, 3,742, and 2,630 μg·h/mL).

Although ADA status was a statistically significant covariate on ADC CL, the results of model-based simulations indicated

the effect on mean steady-state AUC was small (12% lower in ADA-positive vs. ADA-negative non-pcALCL (2,474 vs. 2,772 μg·h/mL); 9% lower in ADA-positive vs. ADA-negative pcALCL (3,408 vs. 3,742 μg·h/mL). Simulations of cycle 3 AUC following weight-based dosing showed trends for AUC increasing

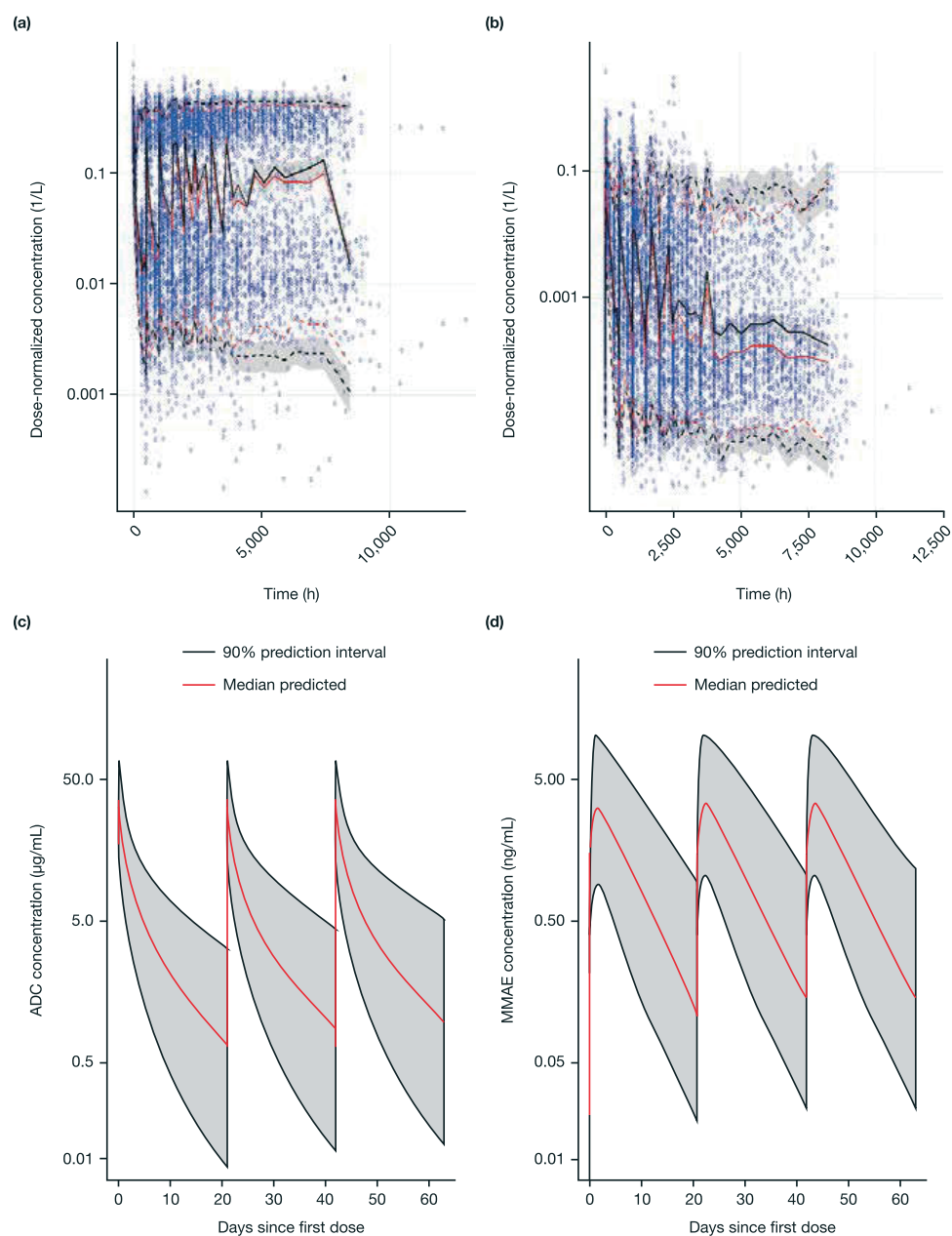


Figure 3 Visual predictive checks of (a) ADC and (b) MMAE final PK models and simulated concentration–time profiles for (c) ADC and (d) MMAE after brentuximab vedotin 1.8 mg/kg dosing every 3 weeks. In (a) and (b) the open blue symbols are the observed data. The solid red line is the median of the observed data. The dashed red lines are the lower 5th and upper 95th percentiles of the observed data. The solid black line is the median of the simulated data. The dashed black lines are the lower 5th and upper 95th percentiles of the simulated data. The shaded gray areas are the 90th percent confidence intervals of the simulated percentiles. In (c) and (d) the shaded gray area represents the simulated 95th percentile of expected concentrations. ADC, antibody–drug conjugate; MMAE, monomethyl auristatin E; PK, pharmacokinetic.

with increasing body size, although there was extensive overlap across body sizes, and the magnitude of the trend was small in relation to overall variability in exposure (Figure S2).

The visual predictive check (VPC) is shown in Figure 3, and by cycle in Figure S3. Precision-of-parameter estimates for the final ADC model and residual variability for the final ADC model were acceptable (standard errors of $\leq 16.8\%$ and 29.1% coefficient of variation). The model was well-conditioned, with a condition number of 5.8. Shrinkage for final model parameters

was low for CL (2.4%) and moderate for V_c (15.2%), and considered acceptable for simulation of ADC concentrations and subsequent estimation of AUC and maximum concentration (C_{max}).

MMAE pharmacokinetic model

The PK model for MMAE included a link to ADC elimination using individual parameter estimates from the ADC model to predict ADC concentrations in the MMAE model. MMAE PK

were described by a two-compartment model with first-order elimination and formation of MMAE both directly from ADC and through binding of ADC to a hypothetical target (Figure 1b). The model had a lag compartment to describe delay in formation of MMAE both directly from ADC and through binding to the target. The fraction of MMAE formed directly from ADC was assumed to decrease following ADC administration, relative to time after dose. Population mean values (Table S3) were: CL 0.577 L/h; central volume 16.0 L; peripheral volume 14.2 L; inter-compartmental CL 2.65 L/h; binding rate constant 0.00069 L/h; ADC-to-MMAE conversion rate 2.64 L/h; and lag compartment rate constant 15.7 L/h.

Covariate effects showed MMAE CL increasing with increasing albumin concentration and decreasing with increasing creatinine and bilirubin concentrations, although the observed covariate effects of creatinine and bilirubin were small and are inferred to not be of a clinically relevant magnitude in the context of overall variability (Figure 2; Table S2). Additionally, MMAE CL increased with increasing body surface area (BSA). There was a strong effect of body size on MMAE CL. Like the ADC model, the influence of age, gender, and race was not significant.

Simulations of MMAE concentration–time profiles and exposures

Simulations using the final PK MMAE model (after brentuximab vedotin 1.8 mg/kg every 3 weeks for three cycles) showed minimal accumulation of MMAE (Figure 3d). MMAE AUC values were comparable for pcALCL and non-pcALCL patients with ADA-negative status. Specifically, geometric mean AUC was 6% higher in ADA-negative, non-pcALCL patients vs. ADA-negative pcALCL patients (610 vs. 576 ng-h/mL). Comparison of MMAE AUC values for different tumor types showed both CTCL types (MF and pcALCL) have AUC values within 4–5% of patients without CTCL tumors (629 and 576 ng-h/mL vs. 600 ng-h/mL).

The VPC is shown in Figure 3b. Overall, the MMAE model had acceptable precision-of-parameter estimates (standard errors of $\leq 10.2\%$). Residual variability was high (42.3% coefficient of variation) and after adding the covariates, shrinkage was low for both CL (3.1%) and V_c (5.1%), and considered acceptable for estimation of AUC and C_{max} . The condition number of 2.4 indicated a well-conditioned model.

Exposure–response assessment in patients with CTCL

Associations between covariates of potential relevance to efficacy of brentuximab vedotin 1.8 mg/kg every 3 weeks in CTCL and quartiles of exposure were explored to identify imbalances in clinically relevant covariates across the quartiles of exposure. The covariates were tumor type (MF or pc-ALCL), gender, race, baseline Eastern Cooperative Oncology Group performance status (ECOG PS), and average baseline CD30. In all cases, demographic group or baseline ECOG PS was not indicative of association with a particular ADC exposure quartile ($P \geq 0.46$; two-tailed Fisher's Exact test). Average baseline CD30 was not a

statistically significant indicator of quartiles of ADC exposure ($P = 0.56$; Kruskal–Wallis test).

A Kaplan–Meier plot by exposure quartile (Figure 4a) showed improved PFS with brentuximab vedotin compared with controls across all ADC AUC/time quartiles, but continuous ADC AUC/time was not a significant predictor of PFS ($P = 0.7533$; Cox regression model). ADC time-averaged AUC (AUC/time) was not a significant predictor of ORR4 ($P = 0.3852$; Figure 4b).

As shown in Figure 4c–f, while neither ADC nor MMAE AUC/time were significant predictors of a grade ≥ 2 PN event, ADC (but not MMAE) AUC/time was a significant predictor of a grade ≥ 3 TEAE ($P = 0.03596$). Probability estimates showed, in ADA-negative, non-pcALCL patients, the mean probability of a grade ≥ 3 TEAE with brentuximab vedotin was 0.34 with 1.8 mg/kg and 0.24 with 1.2 mg/kg (Table 2).

DISCUSSION

Brentuximab vedotin has become an important treatment option for HL, and recent results of ALCANZA are considered potentially practice-changing for management of patients with CD30-positive CTCL.⁹ Our analyses characterized the PK of the ADC and its cytotoxic payload, MMAE, in cancer patients (including those with CTCL), quantified sources of PK variability, and evaluated exposure–response relationships for key efficacy and safety endpoints in ALCANZA to support the benefit/risk characterization of, and dosing recommendations for, brentuximab vedotin in CTCL.

ADC PK were described by a linear three-compartment model with zero-order input and first-order elimination. ADC CL and V_c increased with increasing body size and ADC CL decreased with increasing albumin concentration. Low albumin concentrations of mAbs are associated with increased clearance.^{18,19} Additionally, results from the hepatic impairment study show that low albumin concentrations are associated with increased clearance of brentuximab vedotin, although the potential mechanism(s) is not clear.¹¹ A similar trend of inverse relationship between clearance and albumin concentration has been reported for several biologics such as trastuzumab and ado-trastuzumab emtansine using population PK.^{16,20} Although ADA positivity resulted in fractionally higher ADC CL based on covariate analysis, the overall impact on steady-state exposure in the analysis population was minimal (9–12% lower steady-state AUC in ADA-positive patients). MMAE PK were described by a two-compartment model with first-order elimination and formation of MMAE both directly from ADC and through binding to a hypothetical target. MMAE CL increased with increasing albumin concentration and decreased with increasing creatinine and bilirubin concentration, although the effects of creatinine CL and bilirubin do not appear to be clinically relevant in the context of overall PK variability in the population.

In brentuximab vedotin, MMAE is attached to the anti-CD30 antibody via a protease-cleavable linker. The linkers used in ADCs may affect CL by impacting the rate of cleavage of the cytotoxic drug component; brentuximab vedotin contains a

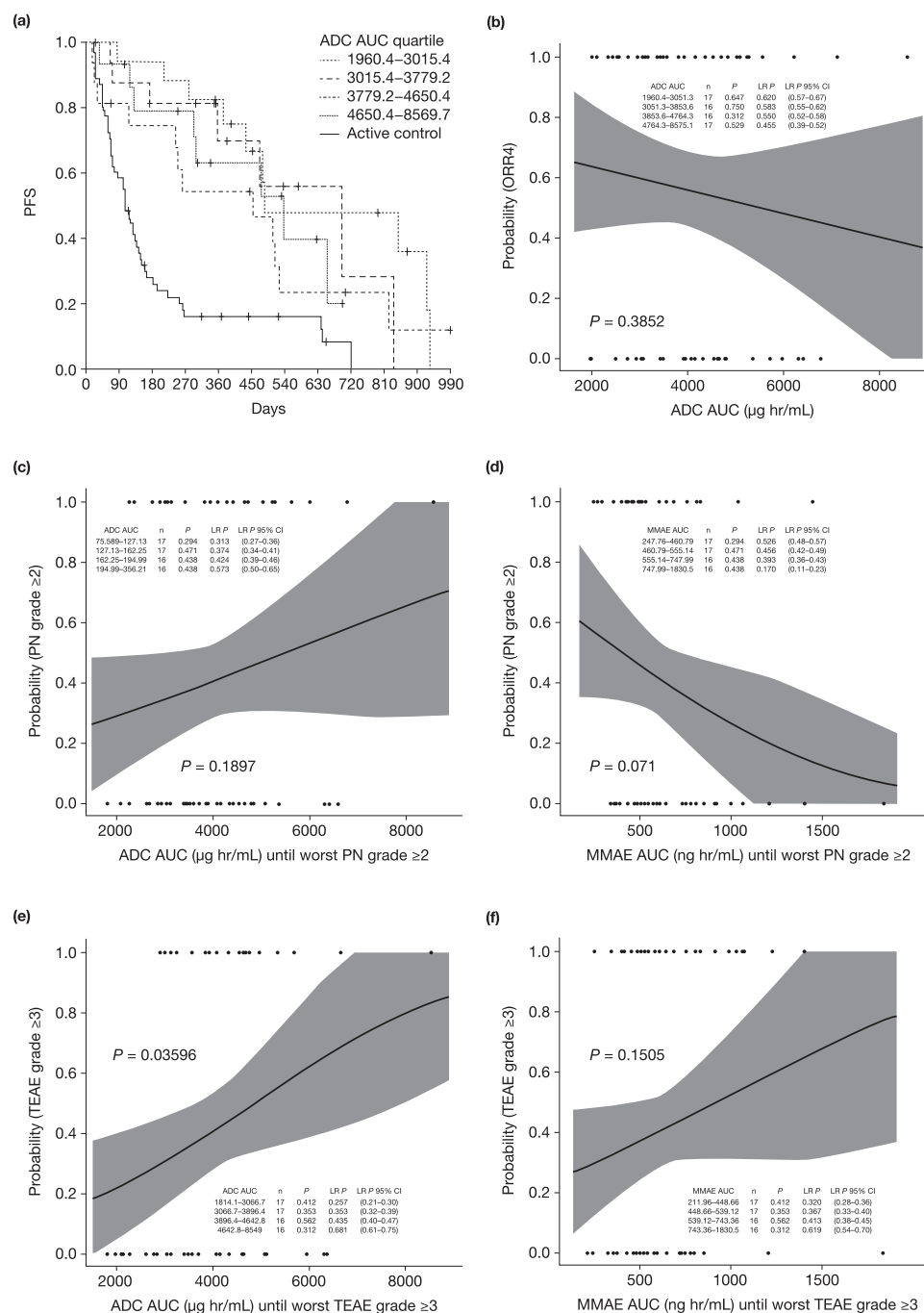


Figure 4 Exposure–response relationships for (a) ADC and PFS; (b) ADC and ORR4; (c) ADC and grade ≥ 2 PN; (d) MMAE and grade ≥ 2 PN; (e) ADC and grade ≥ 3 TEAE; and (f) MMAE and grade ≥ 3 TEAE. In (b–f), the observed values of exposure are shown by the dots for patients who did ($P = 1$) and did not ($P = 0$) experience an event. The solid line shows the model-predicted probability of the event as a function of exposure. The gray shaded area shows the 95% confidence region. ADC, antibody–drug conjugate; AUC, area under the concentration–time curve; MMAE, monomethyl auristatin E; ORR4, objective response rate lasting at least 4 months; PFS, progression-free survival; PN, peripheral neuropathy; TEAE, treatment-emergent adverse event.

protease-cleavable linker, trastuzumab emtansine contains a non-cleavable thioether linker,²¹ and inotuzumab ozogamicin and gemtuzumab ozogamicin contain acid-labile linkers.^{22,23} Notably, in our simulations, and consistent with other reports,¹⁴ there was little accumulation of MMAE following brentuximab vedotin administered every 3 weeks for three cycles.

Previous brentuximab vedotin studies showed maximum concentrations of ADC were typically observed close to the end of infusion, ADC exposures were approximately dose-proportional, and steady state was achieved within 21 days (i.e., by administration of the second dose), with little accumulation observed with multiple doses.^{10–13} Here, time to maximum concentration for

Table 2 Expected probability of grade ≥ 3 TEAEs for brentuximab vedotin doses of 1.8 mg/kg and 1.2 mg/kg administered in 21-day cycles

ADA status	Tumor type	Mean (95% CI) probability for 1.8 mg/kg dose	Mean (95% CI) probability for 1.2 mg/kg dose
Negative	Non-pcALCL	0.34 (0.20–0.47)	0.24 (0.07–0.42)
Negative	pcALCL	0.41 (0.28–0.53)	0.26 (0.09–0.43)
Positive	Non-pcALCL	0.29 (0.14–0.44)	0.22 (0.03–0.37)
Positive	pcALCL	0.38 (0.25–0.50)	0.28 (0.12–0.44)

ADA, anti-drug antibody; CI, confidence interval; pcALCL, primary cutaneous anaplastic large-cell lymphoma; TEAEs; treatment-emergent adverse events.

MMAE was 1–3 days. Similarly, MMAE steady state was achieved within 21 days.

ADC exposure in pcALCL patients was $\sim 35\%$ higher and CL was lower in CTCL patients than in patients with other hematologic tumors. Several factors may contribute to this. First, CTCL patients were older than other patients in the dataset, and patients with pcALCL were in the upper end of the range for albumin. Albumin was part of the final population PK model (Table S1) and higher albumin level can be attributed to lower ADC CL for pcALCL patients. Additionally, although brentuximab vedotin displays approximately linear PK (target-mediated disposition does not appear to markedly impact CL and result in nonlinear PK), differences in target expression could theoretically have a modest impact on CL. A relationship between circulating soluble CD30 (sCD30) concentration and overall tumor burden was previously demonstrated,²⁴ and CTCL patients are considered to have a lower CD30-related disease burden than HL populations, as evidenced by lower observed baseline sCD30 levels in ALCANZA⁹ than in the HL study by Walewski *et al.*¹⁷ (mean sCD30 value 476.3 vs. 829.1 ng/mL; unpublished data). Thus, lower tumor burden in pcALCL patients may contribute to lower CL and modestly higher systemic ADC levels compared with other tumor types. However, viewed in the context of the favorable benefit/risk profile of brentuximab vedotin established in the overall CTCL population (including both pcALCL and non-pcALCL patients),⁹ and at the same dose and regimen approved for HL and sALCL, these modest PK differences are inferred not to be clinically relevant.

While patients with pcALCL had median ADC CL $\sim 56\%$ of that in patients with other tumor types, the difference was smaller in the newer studies (NCT01990534,¹⁷ NCT01578499) (ALCANZA)⁹ using the newer ADA assay compared with the older studies (NCT00848926,⁴ NCT00866047,⁵ NCT00430846,¹⁰ NCT00649584¹³). Although ADA status was a statistically significant covariate on ADC CL, results of model-based simulations indicated the effect of ADA on steady-state AUC was small ($\sim 10\%$ variation) and well below the overall extent of interpatient variability in ADC PK. pcALCL tumor type was not found to be a predictor of MMAE CL.

ADC exposure increased with increasing body size, consistent with expectations from mg/kg dosing of brentuximab vedotin, although there was substantial overlap in exposures across body size metrics, and the magnitude of the trend was small in relation to overall variability in exposure, indicating that body weight-based

dosing (with dose capping at 180 mg for patients weighing over 100 kg) for brentuximab vedotin is appropriate in the overall adult patient population and results in reasonably consistent exposures. The MMAE model results also showed consistently larger Vc for patients with larger BSA.

Our analyses also indicated a positive relationship between MMAE CL and renal function, whereby higher values of creatinine CL resulted in higher MMAE CL. Higher bilirubin concentrations, an indicator of lower hepatic function, were associated with a trend for lower MMAE CL. These data are consistent with previous reports showing that hepatic and severe renal impairment may cause increases in MMAE exposures.¹¹ Thus, while the normal brentuximab vedotin starting dose is 1.8 mg/kg administered over 30 min every 3 weeks, in patients with hepatic or severe renal impairment, brentuximab vedotin is recommended to be administered at a lower dose (1.2 mg/kg)²⁵ or avoided entirely.²⁶

Exposure–response relationships established that ADC exposure was not a statistically significant predictor of PFS or ORR4. Although no discernible relationships between ADC exposure and efficacy outcomes were observed in exposure–response analyses, it should be noted that this inference is based on data from a single dose level (1.8 mg/kg). Despite this limitation, there was a meaningful extent of variability in time-averaged ADC systemic exposure to assess potential relationships to outcomes over the range (>4 -fold) achieved in the CTCL patient population at the 1.8 mg/kg starting dose. Further analyses indicated the lack of apparent ADC exposure–efficacy relationships was unrelated to covarying relationships between ADC exposure and demographic, molecular, or PS-related factors. This was important to rule out, as there is increasing appreciation that variability in baseline disease burden can translate into variability in the CL of mAbs; patients with more advanced disease and higher disease burden may exhibit greater target-mediated CL, leading to lower systemic exposures of antibody-based therapeutics, confounding exposure–response relationships.^{15,27} Interestingly, for both ADC and MMAE, the relationship between AUC/time and grade ≥ 2 PN was not statistically significant. However, ADC (but not MMAE) AUC/time was a significant predictor of a grade ≥ 3 TEAE.

It should be noted that AEs of ADC therapeutics are complex and can be driven by exposure to the free payload or by ADC pinocytosis, as shown in analyses of exposure–effect relationships for myelosuppression by brentuximab vedotin and trastuzumab

emtansine in murine models using mechanism-based pharmacodynamic analyses.²⁸ Specifically, whereas the myelosuppressive effects of brentuximab vedotin were best related to payload (MMAE) concentration, the same was not true for trastuzumab emtansine, for which ADC concentration was identified as the best predictor. Further understanding of PK drivers of AEs of brentuximab vedotin in the clinical setting will require larger-scale analyses across multiple studies, preferably using data from a range of doses, and methods similar to those recently reported for the investigational ADC polatuzumab vedotin leveraging a time-to-event modeling framework.²⁹

In summary, observed systemic exposures of brentuximab vedotin in CTCL patients were in the range of exposures observed in the non-CTCL population. Thus, the starting dose of 1.8 mg/kg administered as an intravenous infusion over 30 min every 3 weeks is appropriate in patients with CTCL as well as in those with HL and sALCL. The exposure–response analyses of safety data support the dose reduction strategy to manage TEAEs in patients receiving the starting 1.8 mg/kg dose. The lack of discernible associations between ADC exposure and the efficacy endpoints of ORR4 and PFS support the consistent treatment benefit observed with brentuximab vedotin 1.8 mg/kg every 3 weeks across the range of exposures in ALCANZA. The observation that ADC exposure is a significant predictor of a grade ≥ 3 TEAE supports dose reductions in patients experiencing TEAEs with brentuximab vedotin at the starting dose based on the model-based prediction of a reduced likelihood of grade ≥ 3 TEAEs at exposures achieved at a dose of 1.2 mg/kg vs. 1.8 mg/kg.

METHODS

Population pharmacokinetic analysis

For the PK analysis, data were included from 380 patients with CD30-positive malignancies who received brentuximab vedotin in phase I (NCT00430846,¹⁰ NCT00649584¹³), II (NCT00848926,⁴ NCT00866047,⁵ NCT01990534¹⁷), or III (NCT01578499); ALCANZA⁹ studies, and had ≥ 1 adequately documented ADC or MMAE concentration value and an available dosing record. Informed consent was obtained from all participants. All studies were performed in accordance with the ethical standards of the institutional and/or national research committees and with the Declaration of Helsinki, or comparable ethical standards.

Brentuximab vedotin dosing schedules and PK sampling times for each study are included in **Table S4**. ADC concentration was measured using an enzyme-linked immunosorbent assay with a lower limit of quantification of 12.5 ng/mL, and MMAE concentration (unconjugated small molecule payload) was measured using a liquid chromatography/tandem mass spectrometry assay with a lower limit of quantification of 25 pg/mL, both as previously described.³⁰ ADA in serum was detected with an electrochemiluminescence assay with a sensitivity of 4 ng/mL anti-brentuximab vedotin mAb and drug tolerance of 3,125 ng/mL brentuximab vedotin in older studies^{4,5,10,13} and 23,573 ng/mL and 25 μ g/mL, respectively, in newer studies.^{9,17} All evaluable concentration–time data were analyzed using mixed-effects modeling methods as implemented by the computer program NONMEM (v. 7.2 and 7.3, Icon Development Solutions, Dublin, Ireland). Missing data were excluded from the analyses. The first-order conditional estimation method was used for estimation. A VPC was also conducted; the simulations for VPCs were run in NONMEM, the exposure–response analysis was conducted using the open-source statistical software R (v. 3.2.0; R Foundation for Statistical

Computing, Vienna, Austria; available at: <http://www.R-project.org/>), and R was also used to generate all figures and tables.

Structural PK models for ADC and MMAE, based on previously reported models,¹⁴ consisted of three basic components: 1) the structural PK model component, defining PK parameters and describing concentration–time profiles of ADC and MMAE; 2) the interindividual error model component, describing interindividual variation in PK parameters after correction for fixed effects; and 3) the residual error model component, describing the underlying distribution of the error in the measured PK observation (i.e., intraindividual variability).

Prespecified covariates for potential inclusion in the final model were evaluated (**Table S5**). ADA status (positive vs. negative) was evaluated as a binomial time-varying covariate, with patients treated as being positive at all times following the first time when ADA positivity was detected. Those covariates showing a graphical trend or requiring further evaluation based on physiologic relevance or observations during previous analyses were tested for statistical significance as single-covariate models ($P < 0.01$). A full model of all statistically significant prespecified covariate effects was developed and a final model chosen by backward elimination ($P < 0.001$). Prior to the inclusion of covariates into the model, interindividual parameter shrinkage was evaluated. The magnitude of impact for individual covariates was also considered; if the magnitude of impact was small ($< 20\%$ change over a range of covariate values) or poorly estimated (standard error $> 45\%$) the covariate was reparameterized or discarded.

For the VPC evaluation, the 2.5th and 97.5th prediction intervals were constructed by simulating replicates of the dataset from which the model was developed. For the model to be acceptable, $\sim 2.5\%$ of observed data should lie above the 97.5th prediction interval and 2.5% below the 2.5th prediction interval.

Tables of descriptive statistics of AUC by cycle, for three cycles, were created for ADC and MMAE using brentuximab vedotin 1.8 mg/kg (maximum 180 mg for patients weighing > 100 kg).

Additional details on the PK model development and methodology are included in the **Supplementary Supporting Information**.

Exposure–response relationships

For evaluation of exposure–response relationships for safety and efficacy in CTCL patients, data were included from 66 patients with MF or pcALCL (histologically confirmed CD30-positive under the enrollment assay) who received brentuximab vedotin 1.8 mg/kg every 3 weeks in ALCANZA⁹ and who had ≥ 1 adequately documented ADC or MMAE concentration value and an available dosing record (**Figure S4**), plus information on efficacy and safety endpoints.

For exposure, AUC/time was computed using individual brentuximab vedotin doses for each cycle and ADC and MMAE CL values as determined for the ALCANZA population in the population PK analysis. AUC was calculated after appropriate unit conversion (ADC μ g-h/mL; MMAE ng-h/mL) over the entire duration of treatment or to the time of the first occurrence of the relevant event (whichever occurred first). A last-observation-carried-forward approach was used to fill cycles for which there were no individual PK parameters. To calculate AUC/time, a cycle-specific AUC value was calculated for each patient, each day over the treatment cycles for the duration of treatment. Dose reductions and delays in dosing were accounted for using individual dose records and values were averaged over the periods from start to the time of the designated event or the end of each patient's treatment.

For exposure–efficacy analyses, relationships between ADC AUC/time and two measures of efficacy (determined by independent review facility) were evaluated: ORR4, assessed by global response score, consisting of skin evaluation, nodal and visceral radiographic assessment, and detection of circulating Sézary cells (MF only); and PFS, defined as time from randomization until disease progression or death due to any cause. Model-based evaluations of ORR4 and PFS were conducted using binomial logistic regression and Cox proportional hazards modeling, respectively.

Associations between covariates of potential relevance to efficacy and quartiles of AUC/time exposure were explored to identify any imbalance in clinically relevant covariates across the quartiles of exposure. Categorical covariates were disease type (MF or pcALCL), gender, race, and baseline ECOG PS. The continuous variable was average baseline CD30.

For exposure–safety analyses, relationships between ADC and MMAE AUC/time and two measures of safety were evaluated: any grade ≥ 3 TEAE (occurring after first administration of brentuximab vedotin until 30 days after last dose), and grade ≥ 2 PN. AUC was calculated from start of treatment until the point of first occurrence of the worst (highest) grade AE. PN events included peripheral sensory neuropathy, peripheral motor neuropathy, paresthesia, hypoesthesia, polyneuropathy, muscular weakness, and demyelinating polyneuropathy. Model-based evaluations of grade ≥ 3 TEAE and grade ≥ 2 PN were conducted using binomial logistic regression.

Additional Supporting Information may be found in the online version of this article.

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CONFLICT OF INTEREST

A.S., Y.L., and K.V. are employees of Millennium Pharmaceuticals, Inc. G.J. is an employee of Seattle Genetics, Inc. D.R.M. is an employee of Projections Research, Inc. and a paid consultant for Takeda Pharmaceutical Company Limited.

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AUTHOR CONTRIBUTIONS

A.S., D.R.M., Y.L., G.J., and K.V. wrote the article; A.S., Y.L., and K.V. designed the research; A.S., D.R.M., Y.L., G.J., and K.V. performed the research; A.S., D.R.M., Y.L., G.J., and K.V. analyzed the data.

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- Berger, G.K. et al. Brentuximab vedotin for treatment of non-Hodgkin lymphomas: a systematic review. *Crit. Rev. Oncol. Hematol.* **109**, 42–50 (2017).
- Alperovich, A. & Younes, A. Targeting CD30 using brentuximab vedotin in the treatment of Hodgkin lymphoma. *Cancer J.* **22**, 23–26 (2016).
- Hsu, P.L. & Hsu, S.M. Autocrine growth regulation of CD30 ligand in CD30-expressing Reed-Sternberg cells: distinction between Hodgkin disease and anaplastic large cell lymphoma. *Lab. Invest.* **80**, 1111–1119 (2000).
- Younes, A. et al. Results of a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin lymphoma. *J. Clin. Oncol.* **30**, 2183–2189 (2012).
- Pro, B. et al. Brentuximab vedotin (SGN-35) in patients with relapsed or refractory systemic anaplastic large-cell lymphoma: results of a phase II study. *J. Clin. Oncol.* **30**, 2190–2196 (2012).
- Moskowitz, C.H. et al. Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin lymphoma at risk of relapse or progression (AETHERA): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* **385**, 1853–1862 (2015).
- Duvic, M., Tetzlaff, M.T., Gangar, P., Clos, A.L., Sui, D. & Talpur, R. Results of a phase II trial of brentuximab vedotin for CD30+ cutaneous T-cell lymphoma and lymphomatoid papulosis. *J. Clin. Oncol.* **33**, 3759–3765 (2015).
- Kim, Y.H. et al. Phase II investigator-initiated study of brentuximab vedotin in mycosis fungoides and Sézary syndrome with variable CD30 expression level: a multi-institution collaborative project. *J. Clin. Oncol.* **33**, 3750–3758 (2015).
- Prince, H.M. et al. Brentuximab vedotin or physician's choice in CD30-positive cutaneous T-cell lymphoma (ALCANZA): an international, open-label, randomised, phase 3, multicentre trial. *Lancet* **390**, 555–566 (2017).
- Younes, A. et al. Brentuximab vedotin (SGN-35) for relapsed CD30-positive lymphomas. *N. Engl. J. Med.* **363**, 1812–1821 (2010).
- Zhao, B. et al. Brentuximab vedotin, an antibody-drug conjugate, in patients with CD30-positive haematologic malignancies and hepatic or renal impairment. *Br. J. Clin. Pharmacol.* **82**, 696–705 (2016).
- Ogura, M. et al. Phase I / II study of brentuximab vedotin in Japanese patients with relapsed or refractory CD30-positive Hodgkin's lymphoma or systemic anaplastic large-cell lymphoma. *Cancer Sci.* **105**, 840–846 (2014).
- Fanale, M.A. et al. A phase I weekly dosing study of brentuximab vedotin in patients with relapsed/refractory CD30-positive hematologic malignancies. *Clin. Cancer Res.* **18**, 248–255 (2012).
- Li, H., Han, T.H., Hunder, N.N., Jang, G. & Zhao, B. Population pharmacokinetics of brentuximab vedotin in patients with CD30-expressing hematologic malignancies. *J. Clin. Pharmacol.* **57**, 1148–1158 (2017).
- Wang, Y., Booth, B., Rahman, A., Kim, G., Huang, S.M. & Zineh, I. Toward greater insights on pharmacokinetics and exposure-response relationships for therapeutic biologics in oncology drug development. *Clin. Pharmacol. Ther.* **101**, 582–584 (2017).
- Cosson, V.F., Ng, V.W., Lehle, M. & Lum, B.L. Population pharmacokinetics and exposure-response analyses of trastuzumab in patients with advanced gastric or gastroesophageal junction cancer. *Cancer Chemother. Pharmacol.* **73**, 737–747 (2014).
- Walewski, J. et al. Single-arm study of brentuximab vedotin in patients with relapsed or refractory Hodgkin lymphoma who are ineligible for stem cell transplantation or multi-agent chemotherapy. *Haematologica* **101**(s1), Abstract 104 (2016).
- Ryman, J.T. & Meibohm B. Pharmacokinetics of monoclonal antibodies. *CPT Pharmacometrics Syst. Pharmacol.* **6**, 576–588 (2017).
- Mould, D.R. & Meibohm, B. Drug development of therapeutic monoclonal antibodies. *BioDrugs* **30**, 275–293 (2016).
- Gupta, M. et al. Clinical implications of pathophysiological and demographic covariates on the population pharmacokinetics of trastuzumab emtansine, a HER2-targeted antibody-drug conjugate, in patients with HER2-positive metastatic breast cancer. *J. Clin. Pharmacol.* **52**, 691–703 (2012).
- Lu, D. et al. Population pharmacokinetics of trastuzumab emtansine (T-DM1), a HER2-targeted antibody-drug conjugate, in patients with HER2-positive metastatic breast cancer: clinical implications of the effect of covariates. *Cancer Chemother. Pharmacol.* **74**, 399–410 (2014).
- Dahl, J., Marx, K. & Jabbour, E. Inotuzumab ozogamicin in the treatment of acute lymphoblastic leukemia. *Expert Rev. Hematol.* **9**, 329–334 (2016).
- DiJoseph, J.F. et al. Antibody-targeted chemotherapy with CMC-544: a CD22-targeted immunoconjugate of calicheamicin for the treatment of B-lymphoid malignancies. *Blood* **103**, 1807–1814 (2004).
- Falini, B. et al. CD30 (Ki-1) molecule: a new cytokine receptor of the tumor necrosis factor receptor superfamily as a tool for diagnosis and immunotherapy. *Blood* **85**, 1–14 (1995).

25. European Medicines Agency. ADCETRIS Product information. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002455/WC500135055.pdf (2017). Accessed 20 September 2017.
26. Seattle Genetics. ADCETRIS Prescribing information. <https://www.adcetris.com/pdf/ADCETRIS-brentuximab-vedotin-Prescribing-Information.pdf?v=201609> (2016). Accessed 24 August 2017.
27. Bajaj, G., Wang, X., Agrawal, S., Gupta, M., Roy, A. & Feng, Y. Model-based population pharmacokinetic analysis of nivolumab in patients with solid tumors. *CPT Pharmacometrics Syst. Pharmacol.* **6**, 58–66 (2017).
28. Ait-Oudhia, S., Zhang, W. & Mager, D.E. A mechanism-based PK/PD model for hematological toxicities induced by antibody-drug conjugates. *AAPS J.* doi: 10.1208/s12248-017-0113-5 [Epub ahead of print] (2017).
29. Lu, D. *et al.* Time-to-event analysis of polatuzumab vedotin-induced peripheral neuropathy to assist in the comparison of clinical dosing regimens. *CPT Pharmacometrics Syst. Pharmacol.* **6**, 401–408 (2017).
30. Han, T.H. *et al.* CYP3A-mediated drug-drug interaction potential and excretion of brentuximab vedotin, an antibody-drug conjugate, in patients with CD30-positive hematologic malignancies. *J. Clin. Pharmacol.* **53**, 866–877 (2013).