Population Pharmacokinetic Modeling and Exposure–Response Assessment for the Antibody-Drug Conjugate Brentuximab Vedotin in Hodgkin's Lymphoma in the Phase III ECHELON-1 Study

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The efficacy of the CD30-directed antibody-drug conjugate (ADC) brentuximab vedotin was established in combination with chemotherapy as frontline treatment for advanced classical Hodgkin's lymphoma in the randomized phase III ECHELON-1 study. Population pharmacokinetic (PK) and exposure–response models were developed to quantify sources of PK variability and relationships between exposure and safety/efficacy end points in ECHELON-1. The influence of patient-specific factors on the PK of the ADC and the microtubule-disrupting payload monomethyl auristatin E (MMAE) was investigated; none of the significant covariates had a clinically relevant impact. Exposure–response analyses evaluated relationships between time-averaged area under the curve (AUC; ADC, MMAE) and efficacy end points (ADC) or safety parameters (ADC, MMAE). Exposure–efficacy analyses supported consistent treatment benefit with brentuximab vedotin across observed exposure ranges. Exposure-safety analyses supported the recommended brentuximab vedotin starting dose (1.2 mg/kg every 2 weeks), and effective management of peripheral neuropathy and neutropenia with dose modification/reduction and febrile neutropenia with granulocyte colony-stimulating factor primary prophylaxis.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ In relapsed/refractory classical Hodgkin's lymphoma (cHL), systemic anaplastic large cell lymphoma, and cutaneous T-cell lymphoma, the pharmacokinetics (PK) of the antibody-drug conjugate (ADC) and free monomethyl auristatin E (MMAE) were linear, and ADC exposures were higher than MMAE exposures. In the ECHELON-1 trial, frontline brentuximab vedotin in combination with doxorubicin, vinblastine, and dacarbazine (A+AVD) significantly improved outcomes in stage III or IV cHL compared with doxorubicin, bleomycin, vinblastine, and dacarbazine.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ PK models for ADC and MMAE were developed using ECHELON-1 data and used to analyze exposure–response relationships for efficacy and safety.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ The lack of relationship between ADC area under the curve (AUC)/time and modified progression-free survival supports consistent benefits across the brentuximab vedotin exposure range seen in ECHELON-1. Observed relationships between ADC and MMAE AUC/time and adverse event incidence validate protocol-specified dose modification and granulocyte colony-stimulating factor (G-CSF) primary prophylaxis for patients experiencing treatment-related toxicities at the brentuximab vedotin starting dose.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ The brentuximab vedotin starting dose of 1.2 mg/kg every 2 weeks in combination with AVD is appropriate for frontline treatment of stage III or IV cHL, and dose reduction/modification and G-CSF primary prophylaxis are relevant in management of treatment-emergent peripheral neuropathy and neutropenia, respectively.

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Brentuximab vedotin is a CD30-directed antibody-drug conjugate (ADC), composed of a monoclonal human/murine chimeric antibody conjugated to the microtubule-disrupting agent monomethyl auristatin E (MMAE) via a protease-cleavable linker.[1] Following binding of the ADC to cell surface CD30, the ADC-CD30 complex is internalized and traffics to the lysosome. Proteolytic cleavage releases MMAE into the cytoplasm, where it binds to tubulin to inhibit microtubule polymerization, resulting in cell cycle arrest and apoptosis (**Figure 1a**).[2] Brentuximab vedotin specifically targets cells that overexpress CD30, such as those in classical Hodgkin's lymphoma (cHL), anaplastic large cell lymphoma, and cutaneous T-cell lymphoma (CTCL).[2,3]

Brentuximab vedotin was first approved for relapsed cHL treatment after failure of autologous stem cell transplantation (ASCT) or failure of at least two prior multi-agent therapies in ASCT-ineligible patients, based on the results of a pivotal phase II study.[4,5] Five-year follow-up data demonstrated long-term remission for subsets of patients with this condition when treated with brentuximab vedotin (5-year progression-free survival (PFS) estimates of 52% in patients who achieved complete response (CR), with median PFS not reached) and a good tolerability profile.[6] Brentuximab vedotin is also approved as post-ASCT consolidation in patients with cHL at high risk of relapse or progression, as treatment for primary cutaneous anaplastic large cell lymphoma or CD30-expressing mycosis fungoides after prior systemic therapy, for treatment of adult patients with relapsed/refractory (R/R) CD30-expressing systemic anaplastic large cell lymphoma (sALCL) and those with previously untreated sALCL or other CD30-expressing peripheral T-cell lymphomas in combination with cyclophosphamide, doxorubicin, and prednisone.[4,7–9] Across these indications, single-agent brentuximab vedotin is approved as a 1.8 mg/kg intravenous infusion once every 3 weeks (q3w).

A phase I open-label study showed preliminary evidence of clinical efficacy of frontline brentuximab vedotin (1.2 mg/kg on days 1 and 15 of 28-day cycles) in combination with doxorubicin, vinblastine, and dacarbazine (A+AVD) in patients with advanced-stage cHL: 96% of patients treated with A+AVD achieved a CR.[10] The dosing schedule of once every 2 weeks (q2w) for A+AVD was used to align with that for doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD). The maximum planned dose of 1.2 mg/kg brentuximab vedotin given q2w was selected to achieve the same dose intensity and time-averaged exposure as the approved single-agent dose of 1.8 mg/kg q3w; the maximum tolerated dose was not exceeded at this maximum planned dose.[10] These findings provided the rationale for designing a larger-scale study in the frontline setting. The open-label, international, randomized ECHELON-1 study evaluated the efficacy and safety of A+AVD compared with ABVD in patients with previously untreated stage III or IV cHL. A+AVD significantly improved outcomes compared with ABVD (2-year modified PFS (mPFS) rates: 82% vs. 77%; $P = 0.035$).[11] On the basis of these positive findings, brentuximab vedotin has been approved as a treatment for previously untreated cHL (United States, stage III or IV disease; European Union, stage IV disease; and Japan, CD30-positive disease), in combination with AVD.[4,9,12]

Population pharmacokinetic (PopPK) and exposure–response modeling are crucial in anticancer drug development to characterize the mechanistically and clinically relevant determinants of systemic drug exposure, to identify patient factors (covariates) that influence response and toxicity, and to optimize posology for maximizing benefit vs. risk.[13–17] The pharmacokinetics (PK) of brentuximab vedotin have previously been reported in sALCL,[18–22] R/R cHL,[18–22] and CTCL[23] but not in the setting of frontline treatment of advanced-stage cHL in combination with AVD.

Here, we report PopPK and exposure–response analyses for brentuximab vedotin in combination with AVD in the ECHELON-1 study. These analyses quantitatively supported the benefit-risk profile of the recommended posology for brentuximab vedotin in the A+AVD regimen, including the risk mitigation and dose modification guidelines for treatment-related toxicities associated with this novel ADC-based combination therapy in the frontline cHL setting.

RESULTS

PopPK analysis dataset

The patient flow for ECHELON-1 has been previously reported by Connors *et al.*[11] PK data from 661 patients in the A+AVD arm provided 40,373 records, consisting of 7,209 dosing records and 33,164 concentration records (16,536 for ADC and 16,628 for MMAE). A total of 347 postdose records were excluded from the analyses due to being below the limit of quantitation (42 for ADC and 305 for MMAE). Mean age was 38.7 years (range: 18–82 years), 56.9% of patients were male, and 84.3% were white (**Table 1**). Mean albumin concentration, creatinine clearance (CrCl), and bilirubin concentration were 39.1 g/L (range: 17–53), 134.1 mL/minute (29.2–476.7), and 7.1 μmol/L (2–82), respectively.

ADC PK model

The structural model for ADC PK was a linear three-compartment model with zero-order input and first-order elimination (**Figure 1b**) based on previous PopPK models for single-agent brentuximab vedotin.[19,23] In the final model, covariate analyses included the effects of body surface area (BSA) on clearance, central volume of distribution (Vc), and first peripheral volume (V2), effect of albumin concentration on clearance, and effect of sex on Vc (**Table 2**).

Both the central and first peripheral volume of distribution increased with body size and ADC clearance decreased with increasing albumin concentration. Simulations used to compare the area under the curve (AUC) for dose 5 (cycle 3 of dosing at 1.2 mg/kg q2w in 28-day cycles) by the significant covariates in the analysis suggested an increasing AUC with increasing body size (BSA or body weight; **Figure 2a,b**) but with a substantial overlap in predicted exposures across the BSA range. AUC was ~ 30% lower for patients weighing <61.0 kg (48.8 μg-day/mL) compared with patients in the >83 kg to ≤100 kg body weight range (63.6 μg-day/mL), although the fixed dose of 120 mg for patients who weighed >100kg attenuated this observation at higher values (**Figure 2b**). AUC was ~ 20% lower for patients with an albumin concentration < 37 g/L(49.5 μg-day/mL) compared with those with an albumin concentration ≥ 43 g/L (59.6 μg-day/mL; **Figure 2c**). Vc was ~ 20% lower in female patients than in male patients (data not shown). The magnitude of

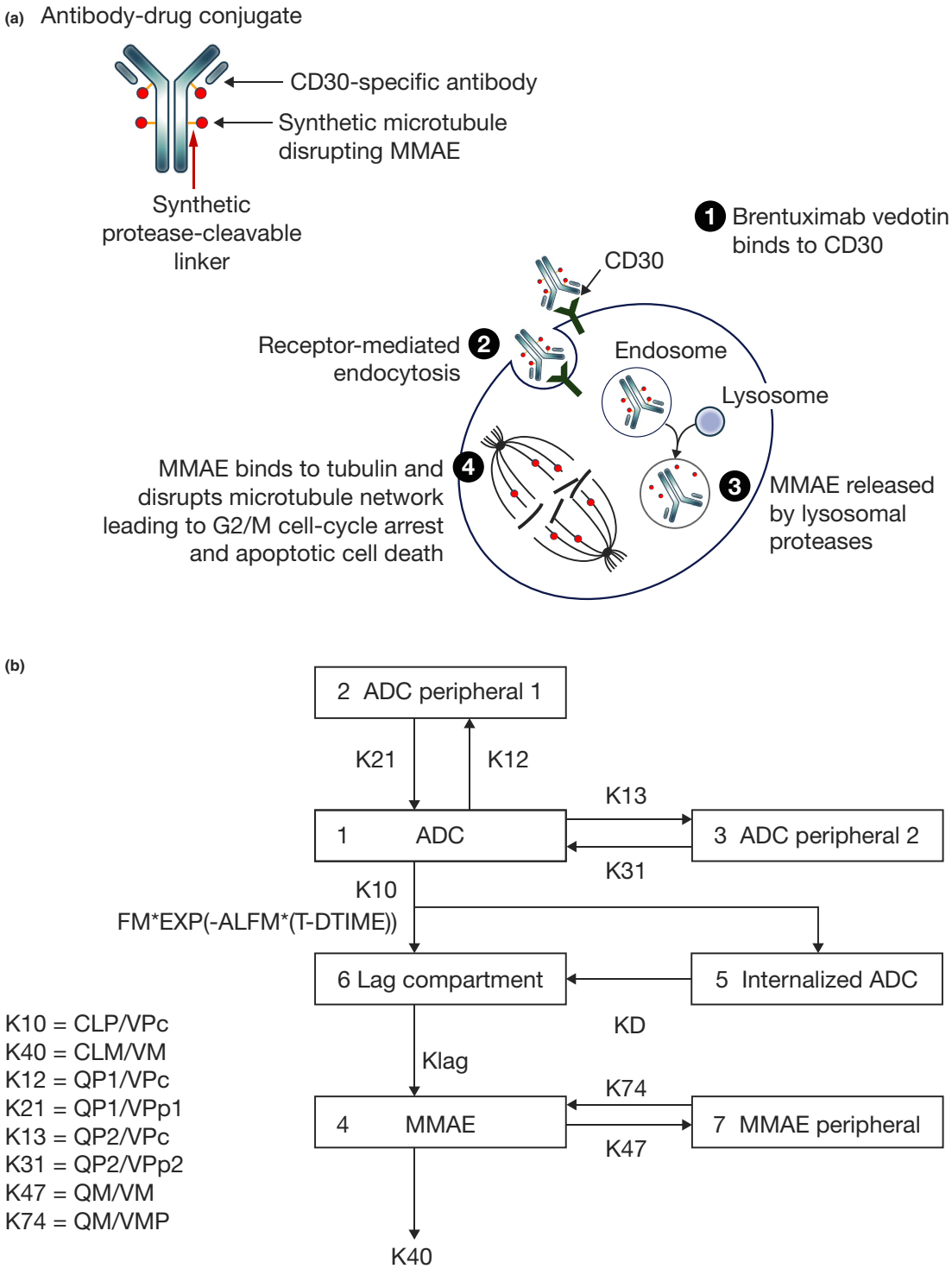

Figure 1 Brentuximab vedotin (**a**) mechanism of action and (**b**) final PK model. ADC, antibody-drug conjugate; ALFM, ADC to MMAE conversion rate; CLM, apparent MMAE clearance; CLP, ADC clearance; FM, fraction metabolized; KD, binding rate constant; Klag, rate constant for lag compartment; MMAE, monomethyl 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. Reproduced with permission from Suri A, Mould DR, Liu Y, *et al.* Population PK and Exposure-Response Relationships for the Antibody-Drug Conjugate Brentuximab Vedotin in CTCL Patients in the Phase III ALCANZA Study. Clin Pharmacol Ther 2018;104:989-999.

Table 1 Demographics and disease characteristics for PK-evaluable patients

Total patients in PK analysis (*N* = 661)	
Sex, *n* (%)	
Male	376 (56.9)
Female	285 (43.1)
Age, years	
Mean (SD)	38.7 (15.8)
Range	18–82
Race, *n* (%)	
White	557 (84.3)
Black	20 (3.0)
Asian	56 (8.5)
Other	18 (2.7)
Not reported	10 (1.5)
Weight,[a] kg	
Mean (SD)	73.5 (18.0)
Range	40.8–165.5
Body surface area,[a] m^2	
Mean (SD)	1.8 (0.3)
Range	1.3–2.8
Albumin, g/L	
Mean (SD)	39.1 (5.3)
Range	17–53
Creatinine, µmol/L	
Mean (SD)	66.2 (16.3)
Range	32–222
Creatinine clearance,[a,b] mL/minute	
Mean (SD)	134.1 (45.4)
Range	29.2–476.7
Bilirubin, µmol/L	
Mean (SD)	7.1 (5.4)
Range	2–82

This table provides the patient counts for categorical covariates and the summary statistics for the continuous covariates for all the patients in the database. There were 42 (6.4%) patients aged 65–74 years, inclusive, and 17 (2.6%) patients aged ≥ 75 years. Values of 0 in the range column indicate the value was missing for some patients.
PK, pharmacokinetic; SD, standard deviation.
[a]One patient was missing data for weight, body surface area, and creatinine clearance. During the pharmacokinetic modeling, the population median values were used for this patient. [b]Creatinine clearance was calculated using the Cockcroft–Gault equation.

change in exposure for each of these covariates was not expected to be clinically relevant when viewed in relation to overall variability (21.4–24.0% coefficient of variation in AUC).

Race (Asian vs. non-Asian), age, anti-drug antibody (ADA) titer, including neutralizing ADA (nADA) titer, and International Prognostic Factor Project (IPFP) score had no discernible effect on ADC PK parameters (data not shown). Of 632 patients assessed at baseline, 64 (10.1%) were ADA-positive (nADA-positive, $n = 4$; nADA-negative, $n = 57$; not reported, $n = 3$), and 568 (89.9%) patients were ADA-negative. Two (0.4%) and 77 patients (13.5%) who were ADA-negative at baseline developed ADA after administration of brentuximab vedotin and became persistently (>2 post baseline measurements) or transiently (1 or 2 postbaseline measurements) ADA-positive postbaseline, respectively. At the end of treatment, 550 patients were assessed for ADA status: 42 (7.6%) were ADA-positive and 2 of these patients were nADA-positive. Overall, 12 of the 109 ADA-positive patients (11.0%) were nADA-positive at any postbaseline visit. Immunogenicity (ADA and nADA) status was not identified as a covariate on ADC clearance in the PopPK analysis and had no effect on systemic exposure of brentuximab vedotin. In patients treated with A+AVD, no association was observed between ADA or nADA status and response or safety (data not shown).

ADC PK model evaluation and simulations of ADC concentration-time profiles and exposures

The visual predictive check of the ADC model is presented in **Figure 3a**. The precision of parameter estimates and residual variability for the final ADC model were considered acceptable (standard errors (SEs) were ≤8.5% and coefficient of variation was 18.1%; **Table 2**). The model was well conditioned, with a condition number of 3.4. Shrinkage was low for clearance (7.7%) and Vc (8.7%) and moderate for second compartmental volume (14.5%), whereas it was higher for V2 and intercompartmental clearance 2 (Q3; 41.2% and 25.0%, respectively). These values were considered acceptable for estimation of individual AUC values.

Simulation of 150 replicates using a 1.2 mg/kg dose of brentuximab vedotin (patients with a body weight > 100 kg capped at a 120 mg dose) q2w for five doses showed an accumulation (estimated based on AUC) of ADC by 1.27-fold between cycles 1 and 3 (**Figure 3b**). As expected, steadystate was reached by cycle 3 (**Figure 3b**).

MMAE PK model

The PK of MMAE was 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 fraction metabolized was fixed to 1 and was not estimated because the data were too sparse to estimate this parameter. The model had a lag compartment to describe the expected delay in formation of MMAE both directly from ADC and through binding of ADC to the target. The fraction of MMAE formed directly from ADC was assumed to decrease following ADC administration, relative to time after dose.

The final PK model for MMAE included covariate effects of BSA, albumin, and CrCl on clearance and was used to simulate the concentrations produced after a 1.2 mg/kg dose of brentuximab vedotin q2w for five doses (**Table 2**). Simulations showed a trend to an increasing MMAE clearance with body size and with increasing CrCl (**Figure 3d–f**, **Supplementary Supporting Information and Tables S1 and S2**). MMAE clearance also increased very slightly with increasing albumin concentration (median clearance: 1.30 L/hour (albumin < 37 g/L) vs. 1.51 L/hour (albumin ≥ 43 g/L); **Supplementary Supporting Information and Table S3**). MMAE AUC increased slightly with increasing body size (**Figure 2d,e**), although this observation

Table 2 ADC and MMAE final PK model parameters

	ADC		MMAE	
Parameter	Population mean (SE %)	% CV IIV (shrinkage)	Population mean (SE %)	% CV IIV (shrinkage)
Clearance (L/hour)	0.0615 (1.0%)	19.8 (7.7%)	1.45 (0.2%)	38.6 (2.0%)
Central volume (Vc) (L)	3.58 (0.9%)	14.0 (8.7%)	35.5 (0.3%)	68.6 (17.9%)
Intercompartmental clearance 1 (Q2) (L/hour)	0.113 (3.0%)	—	13.2 (0.3%)	—
Peripheral volume 1 (V2) (L)	3.26 (1.9%)	25.5 (41.2%)	17.7 (0.3%)	—
Intercompartmental clearance 2 (Q3) (L/hour)	0.0239 (2.3%)	41.4 (25.0%)	—	—
Peripheral volume 2 (V3) (L)	15.7 (4.0%)	77.7 (14.5%)	—	—
Albumin on clearance	−0.477 (2.2%)	—	—	—
BSA on clearance	1.1 (4.9%)	—	1.04 (1%)	—
BSA on central volume	0.893 (6.3%)	—	—	—
Sex on central volume	0.934 (1.4%)	—	—	—
BSA on peripheral volume 2	1.47 (8.5%)	—	—	—
Binding rate constant (KD 1/hour)	—	—	0.0376 (0.3%)	101.0 (8.8%)
Fraction metabolized	—	—	1 FIX	—
ADC to MMAE conversion rate (ALFM 1/hour)	—	—	2.35 (0.2%)	—
Lag compartment rate constant (Klag 1/hour)	—	—	4.51 (0.3%)	—
Creatinine clearance on clearance	—	—	0.125 (3.3%)	—
Albumin concentration on clearance	—	—	0.0275 (2.8%)	—
Residual variability	18.1% CV (0.4%)	—	39.5% CV (0.3%)	—

ADC, antibody-drug conjugate; ALFM, rate constant to describe the decline in direct conversion of ADC to MMAE following time after dose; BSA, body surface area; CV, coefficient of variation; IIV, interindividual variability; KD, binding rate constant; Klag, rate constant for lag compartment; MMAE, monomethyl auristatin E; PK, pharmacokinetic; SE, standard error; Vc, central volume of distribution.

was attenuated with the inclusion of the dose cap for patients weighing >100 kg (**Figure 2e**). AUC was 13% lower for patients weighing <61.0 kg (10.0 ng-day/mL) compared with patients weighing 83–100 kg (11.3 ng-day/mL; **Figure 2e**), and similar observations were made across the BSA range (**Figure 2d**). These differences were unlikely to be clinically meaningful given the significant overlap in exposure between the body size ranges. Additionally, MMAE AUC increased with decreasing CrCl (**Figure 2f**); AUC was 23% greater for patients with CrCl of 30 to <44 mL/minute (13.9 ng-day/mL) compared with patients with CrCl ≥ 90 mL/minute (11.3 ng-day/mL). Consistent with the observations for ADC PK, age, race, ADA and nADA titer, and IPFP score did not significantly affect MMAE PK (data not shown).

MMAE PK model evaluation and simulations of MMAE concentration-time profiles and exposures

The visual predictive check of the MMAE model is presented in **Figure 3c**. Model parameters had acceptable precision (SE ≤ 3.3%), whereas residual variability was high (39.5% coefficient of variation; **Table 2**). The model was well-conditioned (condition number = 16.6). Shrinkage was low for clearance (2.0%) and binding rate constant (8.8%) and moderate for Vc (17.9%), and considered acceptable for estimation of AUC.

Simulation of 150 replicates using a 1.2 mg/kg dose of brentuximab vedotin (patients with body weight > 100 kg capped at a 120 mg dose) q2w for five doses showed that the exposure of MMAE seemed to reduce by 49% from dose 1 (cycle 1) to dose 5 (cycle 3; **Figure 3d**).

Exposure–response assessment

Associations between covariates of potential relevance to efficacy and the quartiles of exposure (AUC/time) were explored to verify that there was no readily apparent imbalance in clinically relevant covariates across exposure quartiles. The categorical covariates were IPFP score, region (America vs. Europe vs. Asia), extranodal involvement, primary prophylactic use of granulocyte colony-stimulating factor (G-CSF), and baseline Eastern Cooperative Oncology Group (ECOG) performance status, whereas the continuous covariate was average baseline CD30. IPFP score by quartile of ADC AUC/time was the only statistically significant covariate ($P = 0.011$, two-tailed Fisher's Exact test), suggesting some imbalance in the data. Average baseline CD30 was not a statistically significant indicator of quartiles of ADC AUC/time ($P = 0.51$, Kruskal–Wallis test).

The exposure–efficacy analysis was performed using mPFS (previously defined as the time to progression, death, or non complete response and use of subsequent anticancer therapy) by independent review facility (IRF) as the efficacy end point.[11] Kaplan–Meier analysis by exposure quartile (**Figure 4a**) suggested an improved mPFS with brentuximab vedotin compared with ABVD across all quartiles of the ADC AUC/time. Consistently, continuous ADC

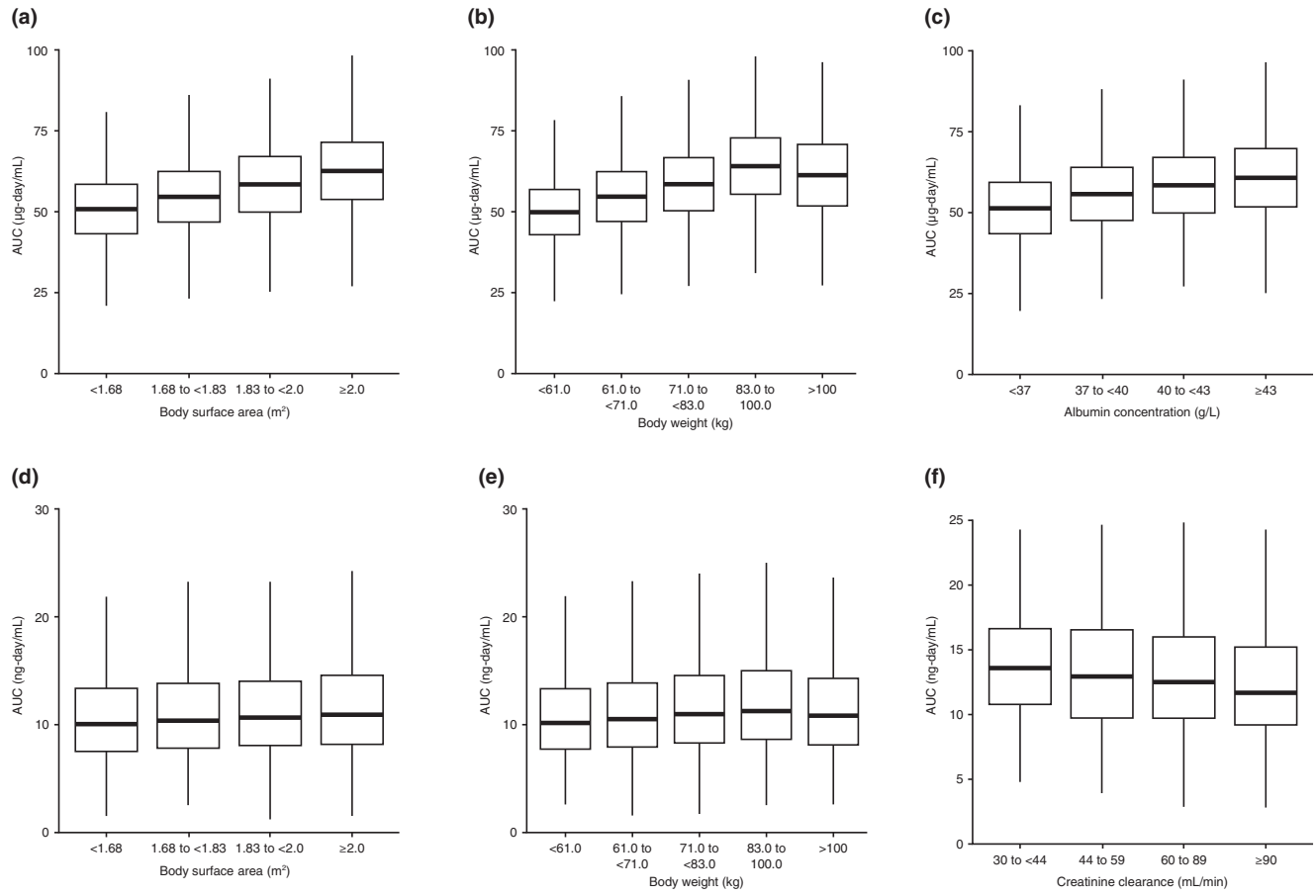

Figure 2 Simulated ADC AUC by (**a**) body surface area, (**b**) body weight, (**c**) albumin concentration and simulated MMAE AUC by (**d**) body surface area, (**e**) body weight, (**f**) creatinine clearance, for cycle 3 following administration of a 1.2 mg/kg dose every 14 days. Doses were capped at 120 mg for patients weighing >100 kg, consistent with the dosing strategy used in ECHELON-1. Closed circles show individual data, and the box plots show the median and interquartile ranges. ADC, antibody-drug conjugate; AUC, area under the concentration time curve days 0–14; MMAE, monomethyl auristatin E.

AUC/time was not a statistically significant predictor of mPFS with A+AVD ($P = 0.701$, Cox regression model).

ADC AUC/time was significantly associated with probabilities of grade ≥ 2 peripheral neuropathy (PN; **Figure 4b**) and febrile neutropenia (FN; **Figure 4c**) ($P = 0.004$ and $P = 0.001$, respectively). ADC AUC/time was not a significant predictor of grade ≥ 4 neutropenia or grade ≥ 3 treatment-emergent adverse events (TEAEs; **Figure S1a and S1b**). MMAE AUC/time was found to be a predictor of FN ($P < 0.001$; **Figure 4d**), grade ≥ 4 neutropenia events ($P = 0.021$; **Figure 4e**), and grade ≥ 3 TEAEs ($P = 0.016$; **Figure 4f**). MMAE AUC/time was not a predictor of grade ≥ 2 PN events (**Figure S1c**). Additionally, as a high proportion of grade ≥ 3 TEAEs were neutropenia-related events, G-CSF primary prophylaxis was included as a fixed covariate. Covariate analyses concluded that G-CSF primary prophylaxis significantly reduced the probability of FN, grade ≥ 4 neutropenia, and grade ≥ 3 TEAE by 55–81% ($P < 0.02$).

DISCUSSION

cHL is characterized by CD30 positivity and, as such, is a candidate for treatment with the CD30-directed ADC brentuximab vedotin, which is approved in R/R cHL as a single agent at a dose of 1.8 mg/kg q3w.[4] Until recently, the standard of care for frontline therapy of cHL was ABVD. The outcomes of a phase I safety study determined that brentuximab vedotin must not be used in combination with bleomycin due to pulmonary toxicity.[10] As a result, the randomized phase III ECHELON-1 study was designed to compare the efficacy of A+AVD (brentuximab vedotin at a dose of 1.2 mg/kg q2w combined with multi agent therapy without bleomycin in 28-day cycles) with ABVD in 1,334 treatment-naive patients with advanced-stage cHL. The brentuximab vedotin dose of 1.2 mg/kg q2w was established for the A+AVD combination from the phase I dose-escalation study and targets an overall dose intensity of brentuximab vedotin that is similar to that achieved for single-agent brentuximab vedotin at a dose of 1.8 mg q3w.[4,5,10]

Based on the results of ECHELON-1,[11] brentuximab vedotin has been approved as frontline therapy in combination with AVD for cHL (United States, stage III or IV disease; European Union, stage IV disease; and Japan, CD30-positive disease).[4,9,12] Our analyses aimed to develop PopPK models to describe the ADC and MMAE concentration-time data collected in patients with cHL enrolled in ECHELON-1. Using estimated individual systemic exposures from these models, ADC and/or

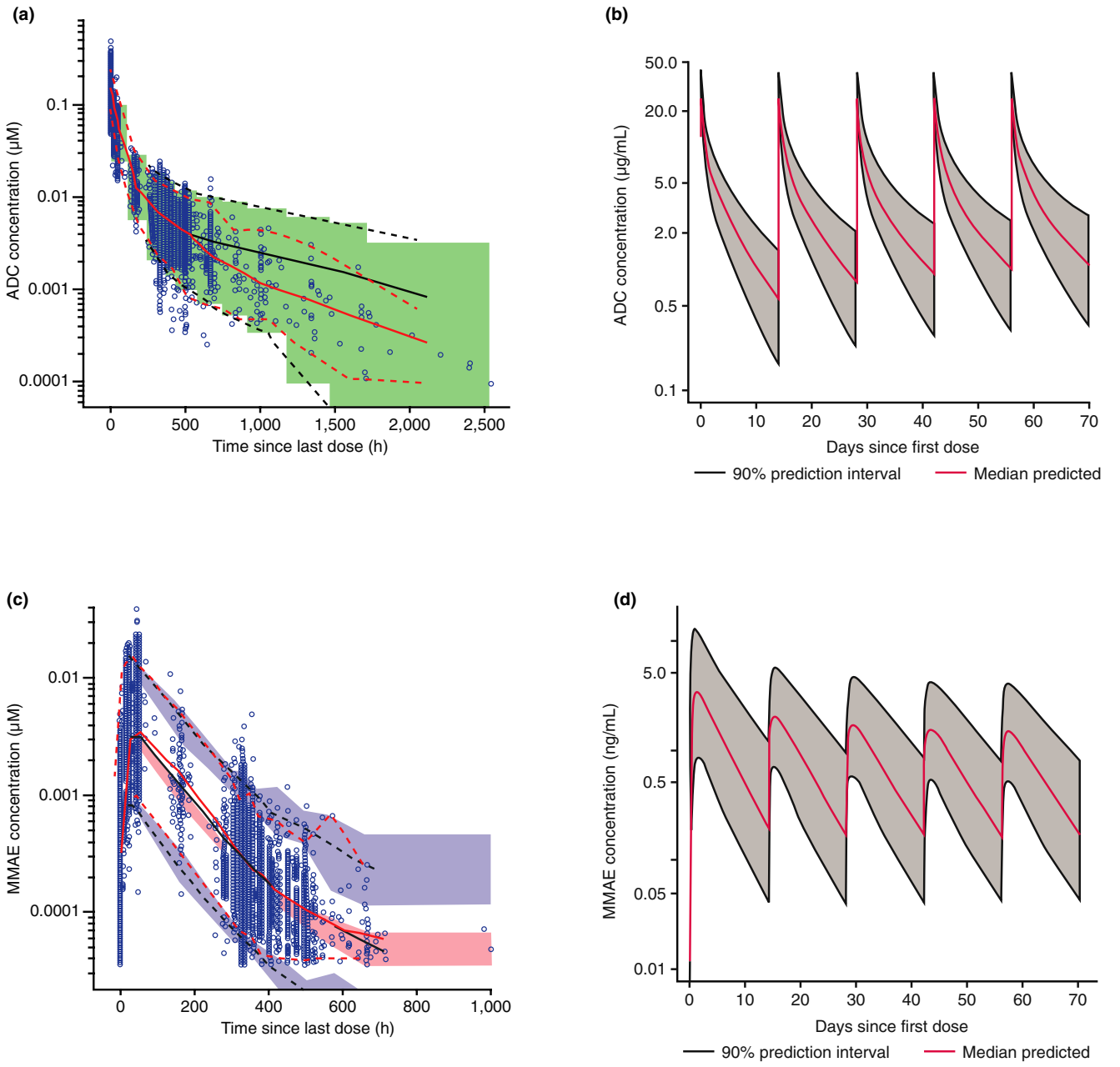

Figure 3 Final pharmacokinetic models for brentuximab vedotin administered as a 1.2 mg/kg dose every 2 weeks: (**a**) visual predictive check of ADC model and (**b**) simulated concentration-time profile from the ADC model; (**c**) visual predictive check of MMAE model and (**d**) simulated concentration-time profile from the MMAE model. **a** and **c**: the open blue symbols represent observed data. The solid red line is the median of the observed data. The dashed red lines are the lower 2.5th and upper 97.5th percentiles of the observed data. The solid black line is the median of the simulated data. The dashed black lines are the lower 2.5th and upper 97.5th percentiles of the simulated data. **a**: the shaded green area is the simulated 95% prediction interval. **c**: the shaded red area is the 95% confidence interval of the simulated median and the shaded purple areas are the 95% confidence interval of the simulated 2.5th and 97.5th percentiles. **b** and **d**: the solid red line is the simulated median, shaded gray area represents the simulated 95% prediction interval of expected concentrations. ADC, antibody-drug conjugate; h, hours; MMAE, monomethyl auristatin E.

MMAE exposure–response relationships with key efficacy and safety endpoints from ECHELON-1 were evaluated for the patients in the study. The PopPK models were built with data from 661 patients with cHL and based on a previously developed model that included data from multiple clinical studies of brentuximab vedotin, including the ALCANZA study in patients with CTCL.[8,19,23] ADC PK were described by a linear three-compartment model with zero-order input and first-order elimination. ADC clearance, Vc, and V2 increased with increasing body size, and ADC clearance decreased with increasing albumin concentration. Low albumin concentrations of monoclonal antibodies are associated with increased clearance.[24,25] Albumin is recycled via the neonatal Fc receptor, and cleared largely by proteolysis; because of these shared pathways, albumin

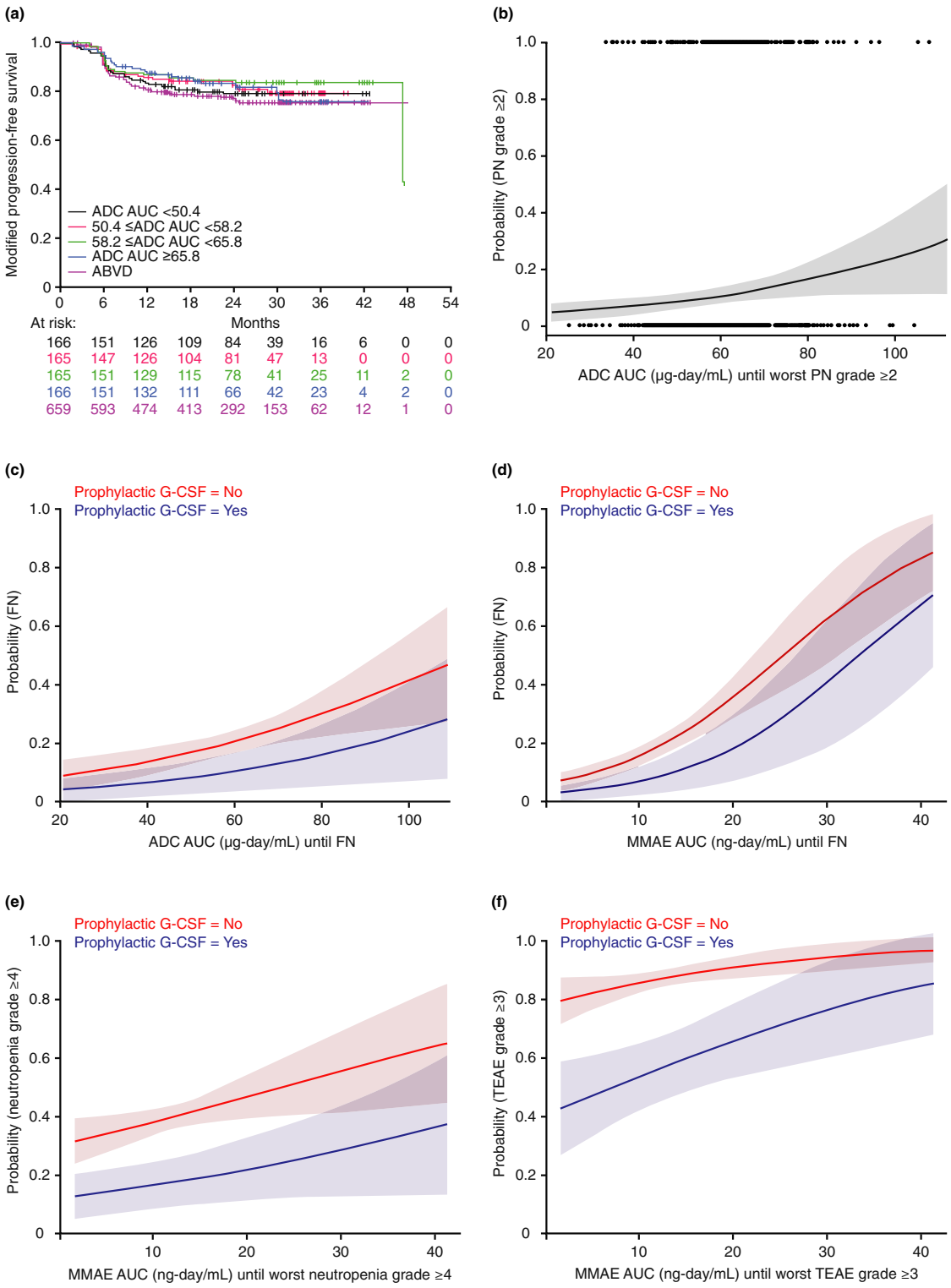

Figure 4 Exposure-response relationships for (**a**) ADC AUC and modified progression-free survival; (**b**) ADC AUC and grade ≥ 2 peripheral neuropathy; (**c**) ADC AUC and febrile neutropenia; (**d**) MMAE AUC and febrile neutropenia; (**e**) MMAE AUC and grade ≥ 4 neutropenia; (**f**) MMAE AUC and grade ≥ 3 TEAE. **c–f**: The red curve represents the probability of the relevant safety event as a function of ADC or MMAE AUC/time for non-G-CSF- treated patients, and the blue curve represents the values for patients who received prophylactic G-CSF. ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; ADC, antibody-drug conjugate; AUC, time-averaged area under the concentration time curve; FN, febrile neutropenia; G-CSF, granulocyte-colony stimulating factor; MMAE, monomethyl auristatin E; PN, peripheral neuropathy; TEAE, treatment-emergent adverse event.

is often reflective of what would happen with a monoclonal antibody in the same physiologic environment.[25–27] In addition, results from the hepatic impairment study demonstrate that low albumin concentrations are associated with increased clearance of brentuximab vedotin, although the potential mechanism(s) for this is unclear.[22] A similar trend of inverse relationship between clearance and albumin concentration has been reported for a number of biologics, including trastuzumab and ado-trastuzumab emtansine.[28,29]

The exposure–efficacy analyses aimed to assess relationships between ADC AUC/time and mPFS per IRF. Although no discernible relationships between ADC exposure and efficacy outcomes were observed in exposure–response analyses, this inference is based on data from a single dose level (1.2 mg/kg). Despite this limitation, there was a meaningful extent of variability in time-averaged ADC and MMAE systemic exposure to assess potential relationships to outcomes over the ranges (>4-fold for ADC AUC/time and >11-fold for MMAE AUC/time) achieved in the frontline advanced-stage cHL patient population at the 1.2 mg/kg starting dose. There was no statistically significant relationship between ADC AUC/time either as a continuous variable or when considered as quartiles on mPFS, and there was no improvement when including extranodal involvement or primary prophylactic G-CSF use as covariates in the model. Exposures achieved with 1.2 mg/kg brentuximab vedotin q2w resulted in similar efficacy across all quartiles of the ADC AUC/time, suggesting that increasing the dose of brentuximab vedotin would have been unlikely to lead to any further improvement in efficacy. Although a statistically significant association with baseline IPFP score was apparent, there was no evidence to show that the patients' demographic group or baseline ECOG status was indicative of a particular ADC AUC/time quartile, suggesting that these factors were well balanced across all quartiles of ADC AUC/time. Additionally, results from a Kruskal–Wallis test showed that average baseline CD30 expression was well-balanced across all quartiles of ADC AUC/time. Therefore, the lack of apparent exposure–efficacy (mPFS) relationships was not related to covarying relationships between ADC AUC/time and demographic, molecular, or performance status-related factors. The lack of discernible association with baseline CD30 expression is of particular importance and is consistent with prior experience in the CTCL population.[23] Taken together with the time-independent PK of ADC, supported by the lack of discernible bias in conditional weighted residual diagnostic plots over time, these findings support the lack of clinically relevant nonlinearities related to target expression or disease burden in brentuximab vedotin PK—an assessment that is of importance for monoclonal antibody-based therapeutics.[30]

The PK of MMAE was described by a two-compartment model with first-order elimination and formation of MMAE both directly from ADC and through binding of ADC to the target. MMAE clearance increased with increasing albumin concentration and BSA in an approximately linear fashion. The relationship between MMAE clearance and CrCl was asymptotic, with a steeper increase in MMAE clearance at lower CrCl values than at higher CrCl values. Both of these findings were consistent with previously reported results.[19] The effect of albumin concentration on clearance was small (~ 3% increase over the range of albumin concentrations—17–53 g/L—in the dataset) but was highly significant ($P < 0.0001$) and was thus kept in the model. MMAE levels at cycle 3 were 49% lower than at cycle 1; this reduction in MMAE exposure between the first and subsequent doses is a function of time, is consistent with previous findings in other indications, and is noted in the US prescribing information.[4] The effects of patient-specific factors (body weight, BSA, and CrCl) were all minimal, with variations on MMAE AUC across the range of covariate values (40.8–165.5 kg, 1.3–2.8 m^2, and 29.2–476.7 mL/minute, respectively) inferred as not being clinically significant when viewed in relation to the overall variability in MMAE exposure (46–54% coefficient of variation).

There was a statistically significant body size effect on ADC and MMAE exposure. Brentuximab vedotin is dosed by body weight, and the results showed that AUC following administration of the 1.2 mg/kg q2w dose increased with increasing body size, although this increase was attenuated with the dose cap for patients weighing >100 kg. The substantial overlap in exposures across the body size metrics and the small magnitude of the trend in relation to overall variability in exposure indicate that weight-based dosing, up to a maximum dose of 120 mg for a body weight of 100 kg, is appropriate in the overall adult population.

Because age, race, ADA titer, and IPFP score were not identified as significant covariates impacting the PK of the ADC or MMAE, no dosing adjustment based on these intrinsic or extrinsic patient factors evaluated is recommended for brentuximab vedotin in adult patients. The absence of ADA effects on PK observed in this analysis in the cHL patient population is consistent with what has been previously reported in patients with CTCL.[23] Taken together with the low observed incidence of immunogenicity in ECHELON-1, these results support the lack of clinically meaningful immunogenicity during treatment with the A+AVD regimen in adult patients with cHL.

There were 56 Asian patients (8%) in the dataset; the ADC and MMAE clearance values for all Asian and non-Asian races overlapped, suggesting no effect of Asian race on PK. A quantitative evaluation of race effects on PK of anticancer agents is essential to optimizing the benefit/risk profile of these drugs across global patient populations.[31] Here, the lack of ethnic sensitivity in PK supports the use of a common global dose for brentuximab vedotin. Overall, the PopPK model structure and parameter estimates for both the ADC and MMAE obtained from ECHELON-1 were consistent with those previously observed for monotherapy.[23]

Relationships between ADC and MMAE AUC/time and the four metrics of safety (adverse events (AEs))—grade ≥ 2 PN, grade ≥ 4 neutropenia, FN, and any grade ≥ 3 TEAE—were evaluated by exposure-safety logistic regression analyses. ADC AUC/time was a significant predictor of FN and grade ≥ 2 PN, but not of grade ≥ 4 neutropenia or grade ≥ 3 TEAEs, whereas MMAE AUC/time was a predictor of FN, grade ≥ 4 neutropenia, and grade ≥ 3 TEAEs but not of grade ≥ 2 PN. The positive exposure–safety relationships observed for key AEs, such as neutropenia, supports that reducing the dose of

brentuximab vedotin in those patients with increased severity of such events can be an appropriate clinical strategy to manage the event while maintaining exposures in the efficacious range. Importantly, primary prophylaxis with G-CSF for patients receiving A+AVD, which was introduced as a recommendation after 75% of enrollment to ECHELON-1 was complete due to the higher incidence of FN with A+AVD compared with ABVD,[11] is now recommended during A+AVD therapy.[4,9] Our analyses support that concomitant primary prophylactic use of G-CSF was protective in ECHELON-1, reducing the probability of FN, grade ≥ 4 neutropenia, and grade ≥ 3 TEAEs. The overall findings from the exposure–safety analyses were consistent with the safety results previously reported from ECHELON-1: FN and PN events were more frequent in the A+AVD vs. ABVD arms of ECHELON-1 (FN: 19% vs. 8%; PN: 67% vs. 43%) but were largely reversible or ameliorable, in particular with G-CSF prophylactic treatment, which reduced the incidence of FN events (11% of FN events in G-CSF-treated patients vs. 21% in patients who had not received prophylactic G-CSF treatment).[11] Importantly, the identification of a protective effect of G-CSF in the exposure-safety analyses for FN, grade ≥ 4 neutropenia, and grade ≥ 3 TEAE supports the recommendation of prophylactic G-CSF administration during A+AVD therapy.[4,9] Primary prophylaxis with G-CSF may reduce the need for dose modifications in patients receiving A+AVD, thereby allowing them to maintain their dose of brentuximab vedotin.

In summary, exposure–efficacy analyses, by demonstrating similar efficacy across quartiles of exposure, support the consistent treatment benefits observed with the recommended starting dose of 1.2 mg/kg brentuximab vedotin q2w. The positive exposure–safety relationships observed indicates that the risks of PN and FN can be adequately managed by dose modification/dose reduction. Importantly, exposure–safety modeling supports the protective effect of G-CSF observed in ECHELON-1, and the recommendation for G-CSF primary prophylaxis during therapy with A+AVD.

METHODS

PopPK analysis

PK data were collected from 661 adult patients enrolled in the phase III ECHELON-1 study (NCT01712490). All patients had histologically confirmed stage III or IV cHL who had not been previously treated with systemic chemotherapy or radiotherapy. Informed consent was obtained from all participants. The study was 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.

Detailed PK sampling schedules and analyses are described in **Table S4** and in the **Supplementary Supporting Information**. Patients were evaluable for PK analysis if they had at least one adequately documented ADC or MMAE concentration. Furthermore, individual ADC PK parameter estimates had to be available for MMAE PK to be evaluated. Outliers were defined as observation records associated with an absolute value of conditional weighted residuals > 5. For consistency, models previously developed for the concentrations of ADC and MMAE after treatment with single-agent brentuximab vedotin were used as the structural base models for this analysis.[19,23] Additional details on the PopPK model development and methodology are included in the **Supplementary Supporting Information**.

Exposure–response relationship assessment

Data from 661 patients were used to analyze exposure–response relationships for efficacy and safety. Patients were evaluable for exposure–response analysis if they had individual PK parameter estimates for ADC (for efficacy and safety end points) and/or MMAE (for safety end points) and adequate dose records to determine derived metrics of exposure (e.g., AUC/time). Because the timing of event occurrence was different for efficacy or the various safety events, the selected metric for conducting each of the analyses was time-averaged AUC to the point of progression or censoring (for efficacy) and over the duration of treatment or time of first occurrence of each AE (for safety). Further details are provided in the **Supplementary Supporting Information**. AUC/time was computed to the time of the first occurrence of the worst (highest) grade AE, as appropriate (i.e., grade ≥ 2 PN, grade ≥ 3 TEAE, and grade ≥ 4 neutropenia).

Exposure–efficacy analyses

Relationships between AUC/time and mPFS by IRF (defined as time from randomization until disease progression, death due to any cause, or receipt of anticancer chemotherapy or radiotherapy for patients not in CR after the completion of frontline therapy) were evaluated using a Cox proportional hazards model stratified by geographic region and IPFP score. Associations between covariates of potential relevance to efficacy and quartiles of AUC/time were evaluated to identify any imbalance in clinically relevant covariates across the quartiles of exposure. The categorical covariates were IPFP score, region, extranodal involvement, primary prophylactic use of G-CSF, and baseline ECOG performance status, whereas the continuous covariate was average baseline CD30.

Exposure–safety analyses

Relationships between ADC and MMAE AUC/time and four safety parameters—grade ≥ 4 neutropenia, FN, grade ≥ 2 PN, and grade ≥ 3 TEAE (occurring after first administration of randomized therapy until 30 days after last dose of frontline therapy)—were evaluated by binomial logistic regression. Grade ≥ 2 PN events included peripheral sensory neuropathy, peripheral motor neuropathy, paresthesia, hypoesthesia, polyneuropathy, muscular weakness, and demyelinating polyneuropathy per Common Terminology Criteria for Adverse Events.

SUPPORTING INFORMATION

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

Figure. S1
Table. S1
Table. S2
Table. S3
Table. S4
Supplementary Supporting Information

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CONFLICTS OF INTEREST

A.S., G.S., J.G.-N., and K.V. are employees of Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited. D.R.M. is an employee of Projections Research, Inc. and a paid consultant for Takeda Pharmaceutical Company Limited. G.P.C. reports honoraria from Gilead, Roche, and Takeda; consulting/advisory roles with Gilead, Roche, Takeda, Bristol-Myers Squibb, Pfizer, MSD, and Celleron Therapeutics; speakers' bureau from Gilead, Takeda, and Roche; research funding from Celgene, MSD, and Amgen; and travel/accommodation/expenses from Napp Pharmaceuticals, Roche, and Takeda. C.J.E. is an employee of Seattle Genetics, Inc. As an Associate Editor for *Clinical Pharmacology & Therapeutics*, Karthik Venkatakrishnan was not involved in the review or decision process for this paper.

AUTHOR CONTRIBUTIONS

A.S., D.R.M., G.S., G.P.C., C.J.E., J.G.-N., and K.V. wrote the manuscript. A.S., G.S., and K.V. designed the research. A.S., D.R.M., G.S., C.J.E., J.G.-N., and K.V. performed the research. A.S., D.R.M., G.S., C.J.E., J.G.-N., and K.V. analyzed the data.

DATA SHARING STATEMENT

Takeda makes patient-level, deidentified datasets and associated documents available after applicable marketing approvals and commercial availability have been received, an opportunity for the primary publication of the research has been allowed, and other criteria have been met as set forth in Takeda's Data Sharing Policy (see https://www.takedaclinicaltrials.com for details). To obtain access, researchers must submit a legitimate academic research proposal for adjudication by an independent review panel, who will review the scientific merit of the research and the requestor's qualifications and conflict of interest that can result in potential bias. Once approved, qualified researchers who sign a data sharing agreement are provided access to these data in a secure research environment.

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