ORIGINAL ARTICLE

Time-to-Event Analysis of Polatuzumab Vedotin-Induced Peripheral Neuropathy to Assist in the Comparison of Clinical Dosing Regimens

D Lu[1]*, WR Gillespie[2], S Girish[1], P Agarwal[1], C Li[1], J Hirata[1], Y-W Chu[1], M Kagedal[1], L Leon[1], V Maiya[1] and JY Jin[1]

Polatuzumab vedotin, an antibody-drug conjugate containing monomethyl auristatin E, was associated with an incidence of grade ≥ 2 peripheral neuropathy (PN) of 55–72% in patients with indolent non-Hodgkin lymphoma in a phase II study, when dosed 1.8–2.4 mg/kg every 3 weeks until progression or for a maximum of 17 cycles. To quantify the correlation of conjugate exposure and treatment duration with PN risk, a time-to-event model was developed using data from phase I and II studies. The model suggested that PN risk increased with conjugate exposure and treatment cycles, and a trend for increased risk with body weight and albumin concentration. When capping the treatment duration to six to eight cycles, the risk ratio of a dose of 2.4 mg/kg vs. 1.8 mg/kg was ≥ 1.29; the predicted incidence of grade ≥ 2 PN at 1.8–2.4 mg/kg dose levels was 17.8–37.2%, which is comparable with other antimicrotubule agents for lymphoma treatment.
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Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
☑ The PN risk factors related to patient baseline characteristics and drug dose and regimen for vc-MMAE ADCs such as pola are not well understood.

WHAT QUESTIONS DID THIS STUDY ADDRESS?
☑ What are the key risk factors that contribute to pola-induced PN? Can an optimal dosing regimen be identified/supported by applying a TTE model?

WHAT THIS STUDY ADDS TO OUR KNOWLEDGE
☑ Pola-induced PN increased with conjugate exposure and treatment duration. Capping pola treatment to six to eight cycles might enable better tolerability and compliance of 1.8–2.4 mg/kg q3w dose by reducing PN risks.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?
☑ A TTE modeling approach helps with managing long-term toxicities such as PN that do not appear within the dose-limiting toxicity observation window.

Antibody-drug conjugates (ADCs) are comprised of a cytotoxic agent linked to a monoclonal antibody (mAb) via a chemical linker.[1] The linker characteristics of ADCs ensure both relative stability in the circulation and release of the cytotoxin predominantly within the tumor microenvironment.[2] Currently, over 50 different ADCs are in various stages of clinical development in oncology.[3] Two ADCs have regulatory approval: the cluster-of-differentiation (CD) 30-targeted brentuximab vedotin (Adcetris) in Hodgkin lymphoma (HL) and systemic anaplastic large cell lymphoma (sALCL) and the HER2-targeted ado-trastuzumab emtansine (Kadcyla) in breast cancer. A third ADC, CD33-targeted gemtuzumab ozogamicin (Mylotarg), was approved in the year 2000 for use in relapsed acute myeloid leukemia in patients aged 60 years and over, but was withdrawn due to safety concerns in 2010, although it remains an investigational drug.

Polatuzumab vedotin (pola) is an ADC that contains a humanized immunoglobulin-G1 (IgG1) mAb targeting the human B-cell surface antigen CD79b and a potent antimitotic agent, monomethyl auristatin E (MMAE), linked through a protease labile linker, maleimidocaproyl valine citrulline p aminobenzyloxycarbonyl (MC-VC-PABC).[4] MMAE is a synthetic auristatin derivative that inhibits cell division and promotes apoptosis by binding to tubulin and disrupting the microtubule network.[5]

Clinical activity of pola has been demonstrated in phase I and II studies in B-cell non-Hodgkin lymphoma (NHL), at doses of 1.8 mg/kg and 2.4 mg/kg, as a single agent or in combination with rituximab.[6–8] Peripheral neuropathy (PN), an adverse event (AE) typical of microtubule inhibitors,[9] including vincristine,[10,11] taxanes,[12,13] and brentuximab vedotin,[14] was also observed in clinical studies of pola.[6–8,15] In these studies, the PN events observed were chronic, with delayed emergence and progressive worsening following multiple treatment cycles; a higher dose was generally associated with increased incidence.[16] A higher incidence of PN was seen in indolent NHL (iNHL) as compared with diffuse large B-cell lymphoma (DLBCL), possibly due to earlier progression for DLBCL and overall shorter treatment duration. In a phase II study in which patients with iNHL were treated with pola until progression or for a maximum of 17 cycles, the incidence of grade ≥ 2 PN was 55% for patients treated with 1.8 mg/kg, and 72% for those treated with 2.4 mg/kg.[17] Furthermore, PN was the most common reason for pola treatment discontinuation in the

phase I and II studies.[6–8] Some clinical evidence suggests that the PN induced by antimicrotubule agents is reversible after dose reduction or treatment discontinuation. In the phase I trial of pola, there was documented resolution of pola-induced PN in 54% of patients who had dose delays, reductions, or treatment discontinuation due to PN[8]; in the clinical trials of brentuximab vedotin in relapsed HL and sALCL, PN (which affected 54% of patients) was reported to improve partially in 31% and completely in 49% of patients.[18]

An exposure–response analysis of pola data by logistic regression suggested that a higher conjugate (antibody-conjugated MMAE, acMMAE) plasma exposure was associated with a higher incidence of grade ≥ 2 PN.[19] In contrast, no correlation was observed for unconjugated MMAE plasma exposure. However, this analysis was limited in that it did not include a component of treatment duration, which is potentially important in order to infer the treatment duration of pola for a clinically acceptable PN risk.

The hypothesis of the current work was that PN risk can be managed by capping the treatment duration at clinically efficacious doses. Thus, our objective was to establish a time-to-event (TTE) model to: 1) quantify the correlation between acMMAE exposure and treatment duration with the risk of developing clinically significant PN (grade ≥ 2); 2) explore the effects of potential baseline risk factors on the incidence of grade ≥ 2 PN induced by pola treatment; and 3) assist inference of grade ≥ 2 PN incidence at clinically relevant dose levels in order to manage PN risk.

METHODS
Study design
Data from two clinical studies in patients with relapsed/refractory (R/R) NHL were used in this analysis. The studies were approved by the Medical Ethics Committee and were carried out according to the International Conference on Harmonization Guidelines for Good Clinical Practice (http://www.ich.org/home.html). In the phase I study, DCS4968g (NCT01290549), pola was administered as a single agent or in combination with rituximab at doses ranging from 0.1–2.4 mg/kg q3w to NHL patients ($N = 77$; 76 patients included in this analysis).[8] In the phase II study, GO27834 (ROMULUS; NCT01691898), pola was administered in combination with rituximab at a dose of 2.4 mg/kg every 3 weeks (q3w) to patients with follicular lymphoma (FL) or DLBCL ($N = 60$); a lower dose of 1.8 mg/kg q3w was administered in another subset ($N = 20$; 19 patients included in this analysis) of patients with FL.[6,7,20] In both studies, q3w dosing proceeded until the occurrence of progressive disease or unacceptable toxicity, or for a maximum of 17 cycles in the phase II study. Patients treated at the 2.4 mg/kg dose level were permitted a dose reduction to 1.8 mg/kg for treatment-emergent toxicity, including new or worsening grade 2 or 3 PN and other AEs; dose reductions to levels less than 1.8 mg/kg were not permitted. Data from 155 patients, from all treatment cycles, were used for this analysis, with a data cut date of July 2014. All patients, including the patients with dose reduction due to AE, were included in the analysis.

Exploratory data analysis and establishment of base model
The PN events were grouped based on terms in the broad categories of PN defined by Standardized MedDRA Queries (SMQ Version 17.0).[21] PN was graded according to the Common Terminology Criteria for Adverse Events (CTCAE, v. 4.0, 2010).[22] Grade ≥ 2 PN was considered clinically relevant (moderate intensity and limiting age-appropriate instrumental activities of daily living). The probability for the onset of grade ≥ 2 PN is the pharmacodynamics (PD) endpoint modeled here, based on the fact that it is most clinically relevant for the selection of dose level and treatment duration.

An exploratory data analysis was conducted to assess whether the incidence of grade ≥ 2 PN increased with time after repeated pola treatment. Multiple strategies were explored to relate plasma acMMAE concentration–time profiles to the hazard rate of grade ≥ 2 PN, which changes with time. Models that directly link concentrations with hazard rate at the same time did not describe the observed data, suggesting that the hazard for emergence of grade ≥ 2 PN is delayed relative to plasma acMMAE concentrations. Thus, a parametric TTE analysis that appropriately accounted for right censoring was performed to describe the time to first occurrence of grade ≥ 2 PN events as a function of various measures of acMMAE pharmacokinetic (PK) exposure. A semiparametric proportional hazard model using PK exposures as a covariate was not used, as it cannot model the delay between PK and PD, and was not ideal for simulations. The acMMAE exposures resulting from pola administration were calculated using individual empirical Bayes estimates (EBE) PK parameters from a previously developed population PK model.[19] There were cases where the dose was reduced for AEs other than PN, and the predicted PK exposures take these dose reductions into account. The covariates for the population PK model parameters were previously identified using the stepwise hypothesis-testing approach.[19] The TTE models were fitted via maximum likelihood estimation by Nonlinear Mixed Effects Modeling (NONMEM; v. 7.3) (ICON, Hanover, MD). The likelihood (L) for time to first grade ≥ 2 PN event in the ith patient is expressed by (Eq. 1):

$$L\big(\theta | t_{PN,i}, \ \text{censor}_i, \ X_i\big)$$

$$= \begin{cases} h_i\big(t_{PN,i}|\theta, X_i\big) e^{-\int_0^{t_{PN,i}} h_i\ (u|\theta, X_i)\,du}, & \text{censor}_i = 0 \\ e^{-\int_0^{t_{PN,i}} h_i\ (u|\theta, X_i)\,du}, & \text{censor}_i = 1 \end{cases} \quad (1)$$

where: t_{PN}: time to first grade ≥ 2 PN or right censoring event; θ: model parameters; X: independent variables/covariates; $h_i\big(t_{PN,i}|\theta, X_i\big)$: hazard rate at time t; $e^{-\int_0^{t_{PN,i}} h_i\ (u|\theta, X_i)\,du}$: survival function at time t.

$$\text{censor}_i \ \equiv \ \begin{cases} 1, & \text{if grade } \geq 2 \text{ PN event is right censored} \\ 0, & \text{if grade } \geq 2 \text{ PN event is observed} \end{cases}$$

Four base models that could describe this delay were selected for full model evaluation:

Model 1: h(t) = function of cumulative area under the plasma concentration–time curve (AUC) of acMMAE (**Supplemental Materials S1:** Eq. 1)

Model 2: h(t) = The numerical value in the hypothetical effect compartment (**S1:** Eq. 2)

Model 3: h(t) = The numerical value in the hypothetical indirect response compartment in excess of baseline, with acMMAE plasma concentrations inhibiting the elimination rate of the compartment (**S1:** Eq. 3)

Model 4: h(t) = the function of the conjugate concentrations in the hypothetical effect compartment and with time-dependent change by Weibull distribution. This model was selected as the final model, and the equations (see also **S1:** Eq. 4) are presented in the Results section, below.

The NONMEM codes for the final model are described in **Supplemental Materials S2**.

Assessment of covariates and determination of the final model

The effects of 11 baseline covariates were explored for each model, in addition to acMMAE exposures after treatment. Four full models including all of these covariates were constructed to support inference about these covariates, which is considered a less biased way than the classic stepwise hypothesis testing strategy for the covariate model.[23] Since EBE PK estimates for each patient were used to drive the TTE model, the inference for these covariates in the TTE model would not reflect an effect mediated by PK parameters. These covariates, selected on the basis of clinical experience, were potential risk factors for PN, and included demographics, prior treatment history, and baseline pathophysiological conditions and treatment combinations: body weight; sex; age; baseline albumin concentrations; baseline sum of product of tumor dimensions; tumor histology; prior platinum-based treatment (yes/no); prior vinca alkaloids treatment (yes/no); prior radiotherapy (yes/no); active PN at study entry (yes/no); and rituximab combination (yes/no). As the studies allowed patients with grade 1 PN to be enrolled, some patients had active grade 1 PN at study entry. Effects of the covariates were estimated using a proportional hazard submodel with the following equation (Eq. 2).

$$h(t) = h_{base}(t) *$$

$$\exp\left(\theta_{age}(age - 65) + \theta_{bodyWeight}(bodyWeight - 80) + \theta_{female}(female) + \right.$$

$$\theta_{baselinePN}(baselinePN) + \theta_{priorRadioTx}(priorRadioTx) +$$

$$\theta_{priorVinca}(priorVinca) + \theta_{Platin}(priorPlatin) + \theta_{rituximab}(rituximab) +$$

$$\theta_{DLBCL}(DLBCL) + \theta_{otherNonFL}(otherNonFL) +$$

$$\theta_{baseTumorSum} \log\left(\frac{baseTumorSum}{3000}\right) + \theta_{albumin}(albumin - 39) \quad (2)$$

where $h_{base}(t)$ is the base model hazard function modeled by the Equations for Models 1–4 (S1: Equations 1–4) without including covariates; θ_{age}: effect of age; $\theta_{bodyWeight}$: effect of body weight; θ_{female}: effect of sex (female vs. male); $\theta_{baselinePN}$: effect of grade 1 PN at baseline (yes/no); $\theta_{priorRadioTx}$: effect of prior radiotherapy (yes/no); $\theta_{priorVinca}$: effect of prior vinca alkaloids (yes/no); θ_{Platin}: effect of prior

platinum (yes/no); $\theta_{rituximab}$: effect of combination of pola with rituximab (yes/no); θ_{DLBCL}, $\theta_{otherNonFL}$: effect of tumor histology (FL, DLBCL, others); $\theta_{baseTumorSum}$: effect of baseline sum of product of longest tumor dimensions; $\theta_{albumin}$: effect of baseline albumin concentrations.

Some covariates were correlated with the ones listed above, so the following sensitivity test was also performed. First, the covariate of history of prior PN (yes/no) was highly correlated with active PN at study entry (yes/no), and was tested in replacement of the later one. Second, the baseline B-cell count appeared to be higher in patients with FL and other histologies than in those with DLBCL, and was tested in replacement of tumor histology. Simulation methods were used to estimate the magnitude of effect for each covariate on hazard rate, by simulating the hazard ratio (HR) of two levels for each covariate. The distribution of HR was estimated based on the covariate parameter uncertainty (asymptotic variance-covariance matrix), using R (available at www.r-project.org).

Comparison of models 1–4 was performed with all covariates included to determine the final model, which was chosen based on the NONMEM objective function value (OFV), Akaike information criterion (AIC), and visual predictive check (VPC). VPC was simulated using R, based on *post hoc* PK parameter estimates, parameter uncertainty of the TTE model, sampling from the TTE model, and covariate of each patient. The simulation assumed that the patients' treatment durations matched those observed for each individual in the actual trial. For a simulated PN event time greater than the treatment duration, the PN event was treated as right-censored.

Model application to compare pola dosing regimens

Simulations were performed in the final model at two clinically relevant doses (1.8 and 2.4 mg/kg) given q3w and two treatment durations (six and eight cycles), typical durations for NHL using chemotherapeutic agents. This simulation is not extrapolated outside the dose level or time range of data for the model building. Simulations using R software were performed based on nominal doses, or observed doses accounting for the actual dose reduction in patients receiving 2.4 mg/kg pola. In total, eight scenarios with 250 trials in each scenario were simulated. The risk ratio (RR) for 2.4 vs. 1.8 mg/kg was estimated to infer the relationship of dose–response. The incidence of PN with each scenario was estimated after accounting for all sources of variability and uncertainty: interindividual variability of the PK model, parameter uncertainty of the TTE model, and sampling from the TTE model. For each vector of the TTE parameters obtained from the uncertainty distribution (multivariate normal using the covariance matrix of the model parameter estimates), the probability of PN incidence at each time was simulated for 500 patients and averaged at that time. The covariates were resampled from the patients used for model building. Parameter uncertainty for the PK model was not included for model simulation, because a sequential analysis was used in which EBE PK parameters were fixed for the TTE model fitting. Censoring was not included because the objective was to simulate the TTE (grade ≥2 PN) or to
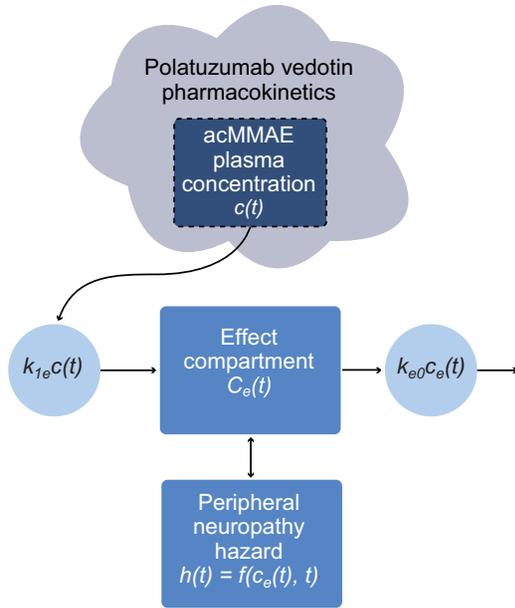
Figure 1 Scheme of the selected base model (Model 4). *h(t)*: hazard rate of grade ≥2 PN at time *t* after start of pola treatment (1/*h*); *β*: Weibull function parameter (unitless); *k1e*: distribution rate constant of acMMAE to the effect compartment (1/*h*); *ke0*: elimination rate constant of acMMAE from the effect compartment (1/*h*); *Ce(t)*: concentration of acMMAE in the effect compartment (ng/mL); *α*: drug effect parameter (1/(*h**ng/mL)). acMMAE, antibody-conjugated monomethyl auristatin E; PN, peripheral neuropathy; pola, polatuzumab vedotin.

completion of the predefined number of treatment cycles (six or eight cycles), whichever occurred first.

RESULTS
Final model

Data exploration by Kaplan–Meier (K-M) plot suggested that grade ≥2 PN incidence increased with treatment duration (**Supplemental Figure S1**). Among the four potential base models with covariates, Model 4 (described by Eq. 3 and in **Figure 1**) resulted in the lowest OFV and AIC values.

Model 4: h(t) = the function of the conjugate concentrations in the hypothetical effect compartment and with time-dependent change by Weibull distribution:

$$h(t) = \beta E_{drug}(t)^{\beta} t^{(\beta-1)}$$

$$E_{drug}(t) = \alpha C_e(t)$$

$$\frac{dCe(t)}{dt} = k_{1e} C(t) - k_{e0} C_e(t)$$

$$k_{1e} = k_{e0} \qquad (3)$$

h(t): hazard rate of grade ≥2 PN at time t after pola treatment (1/h); *α*: drug effect parameter (1/(h*ng/mL)); *β*: Weibull function parameter (unitless); k_{1e}: distribution rate constant of acMMAE to the effect compartment (1/h);

k_{e0}: elimination rate constant of acMMAE from the effect compartment (1/h); C_e(t): concentration of acMMAE in the effect compartment (ng/mL); $E_{drug}(t)$: function of acMMAE exposure effect on h(t).

VPC plots also suggested that Model 4 best described the observed K-M plot of the incidence of grade ≥2 PN up to the first eight cycles (∼168 days) after pola treatment (**Figure 2**), and this model was selected as the final model. The hazard is described as a function of the amount of drug in a hypothetical effect compartment, with a time-dependent increase not completely explained by drug exposure and clinically relevant covariates. The model confirmed that the hazard of grade ≥2 PN increases with conjugate exposure. The final model parameter estimates are listed in **Table 1**. The change in acMMAE plasma concentrations, amount in the effect compartment, hazard rate, and cumulative probability of grade ≥2 PN with time were simulated (**Supplemental Figure S2**).

The distribution of all covariates assessed is summarized in **Supplemental Table S1**. Grade ≥2 PN hazard had a trend of increasing with body weight and serum albumin concentrations, after accounting for conjugate exposure. Concomitant rituximab appeared to be associated with lower grade ≥2 PN hazard (**Figure 3**, **Table 1**). However, the rituximab effect was highly correlated with study (phase I vs. phase II) and should be interpreted with caution (see Discussion and Conclusion, below). Evidence for potential effects of the other eight evaluated covariates on grade ≥2 PN hazard was not apparent/inconclusive based on
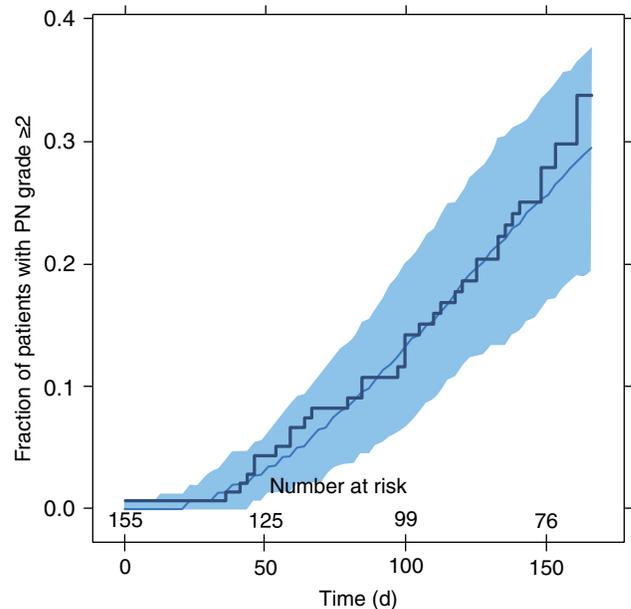
Figure 2 Visual predictive check for the model fitting of the observed K-M plot (patient number = 155) of fraction of grade ≥2 PN adjusted for censoring over the first eight cycles (168 days). Thick blue line: the K-M curve based on the observed fraction of patients (*n* = 155) with grade ≥2 PN vs. time; thin blue line: the TTE model estimated median K-M curve; shaded areas: the TTE model estimated 90% confidence intervals of the K-M curve. K-M, Kaplan-Meier; PN, peripheral neuropathy.

Table 1 Final model (Model 4) parameter estimates for the structure model

Parameter (unit)	Parameter name	Estimation value (RSE%)[a]	Estimation value (SE)[b]
α (1/(hour*ng/mL))	Drug effect parameter	$2.26*10^{-6}$ (49.2%)	–
β	Weibull function parameter	1.37 (15.1%)	–
k_{1e} (1/hour)	Distribution rate constant of acMMAE to the effect compartment	$3.60*10^{-4}$ (73.8%)	–
k_{e0} (1/hour)	Elimination rate constant of acMMAE from the effect compartment	$= k_{1e}$	–
THETA(4) (1/years)	Effect of age on hazard rate	–	$-2.55*10^{-3}$ (0.0120)
THETA(5) (1/kg)	Effect of body weight on hazard rate	–	0.0219 (0.0111)
THETA(6)	Effect of sex on hazard rate	–	0.296 (0.373)
THETA(7)	Effect of active grade 1 PN at baseline (yes/no) on hazard rate	–	−0.222 (0.324)
THETA(8)	Effect of prior radiotherapy (yes/no) on hazard rate	–	$-7.94*10^{-3}$ (0.319)
THETA(9)	Effect of prior vinca alkaloid (yes/no) on hazard rate	–	−0.102 (0.469)
THETA(10)	Effect of prior platinum treatment (yes/no) on hazard rate	–	0.159 (0.345)
THETA(11)	Effect of combination with rituximab (yes/no) on hazard rate	–	−0.577 (0.325)
THETA(12)	Effect of tumor histology as DLBCL on hazard rate	–	−0.0697 (0.365)
THETA(13)	Effect of tumor histology as non-FL on hazard rate	–	0.688 (0.758)
THETA(14)	Effect of baseline sum of product of longest tumor dimensions	–	0.169 (0.178)
THETA(15)	Effect of serum albumin concentrations on hazard rate	–	0.0582 (0.0362)

acMMAE, antibody-conjugated monomethyl auristatin E; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; NONMEM, nonlinear mixed effects modeling; PN, peripheral neuropathy; RSE, relative standard error; SE, standard error.
[a]For structure model parameters α, β, k_{1e}, they are estimated in the log domain by NONMEM, thus RSE% is presented.
[b]For parameters for covariates' effect, they are estimated in the normal domain by NONMEM, and some values are negative, thus SE is presented.

available data, as indicated by the median HR and/or relatively large degree of uncertainty (**Figure 3**, **Table 1**). Active PN at study entry (yes/no) appeared to have no apparent effect. A sensitivity analysis in which this covariate was replaced with history of prior PN (yes/no) and tumor histology was replaced with baseline B-cell count did not identify conclusive effects for these covariates based on current data (**Supplemental Figure S3**).

Model application
The RR for 2.4 vs. 1.8 mg/kg and the model-estimated grade ≥2 PN incidences of eight scenarios (see Methods section) are summarized in **Table 2** and **Figure 4**. Simulations based on nominal doses (**Figure 4a**), and actual doses accounting for the observed dose reductions in the 2.4 mg/kg arm (**Figure 4b**), suggested that the 2.4 mg/kg dose induced a greater risk of grade ≥2 PN than 1.8 mg/kg: risk ratio ≥1.29
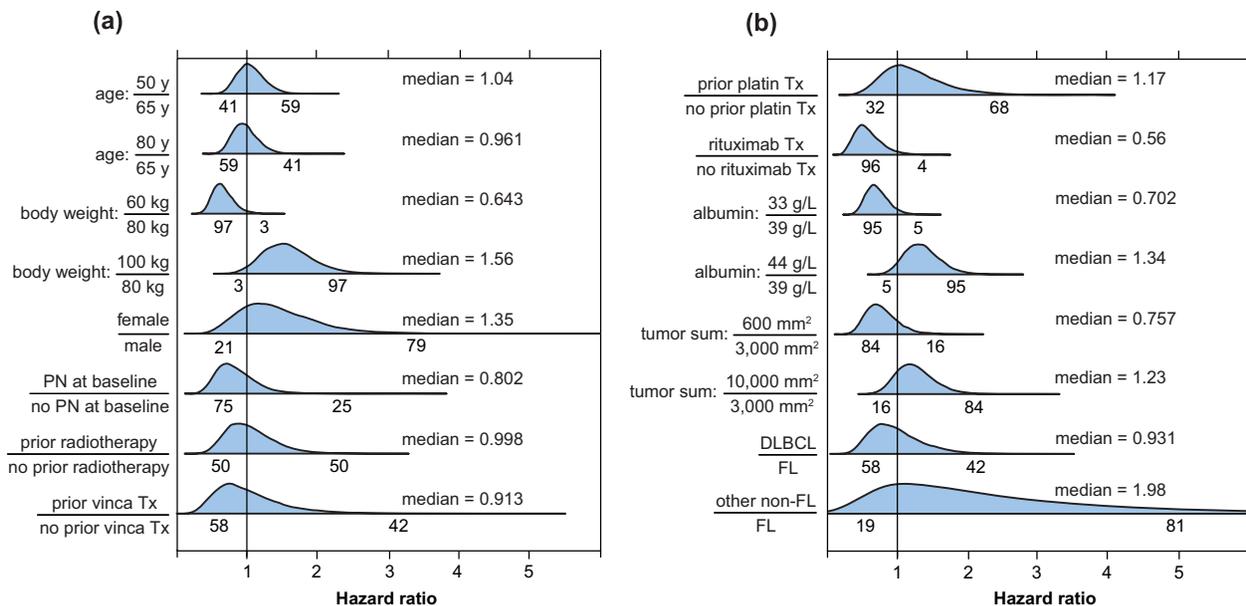
Figure 3 Covariate effects on hazard ratio distributions. Each bell-shaped curve: the distribution of HR for each covariate of interest; median of the estimated HR distribution: the point estimate of median HR for each covariate; corresponding horizontal line under each bell shaped curve: degree of uncertainty in the estimated HR for that covariate; numbers below each distribution: probability (%) of a HR of <1 (left side) or >1 (right side). DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; platin, platinum; HR, hazard ratio; PN, peripheral neuropathy; TX, treatment; vinca, vinca alkaloids.

Table 2 Model predicted incidence of Grade ≥2 peripheral neuropathy for pola treatment of six or eight cycles and the risk ratio for 2.4 vs. 1.8 mg/kg

	Estimate (90% CI)	
Variable	126 days (6 cycles)	168 days (8 cycles)
PN grade ≥2 (Pr, %)		
Nominal dose 1.8 mg/kg	19.0 (13.5, 24.7)	30.7 (21.9, 38.6)
Observed dose 1.8 mg/kg[a]	17.8 (12.4, 23.2)	28.8 (21.3, 36.2)
Nominal dose 2.4 mg/kg	26.6 (19.4, 33.4)	40.9 (30.9, 49.5)
Observed dose 2.4 mg/kg[a]	24.1 (17.8, 31.1)	37.2 (28.6, 45.7)
Risk ratio (2.4 vs. 1.8 mg/kg)		
Nominal doses	1.38 (1.30,1.55)	1.32 (1.25,1.47)
Observed doses[a]	1.35 (1.28,1.48)	1.29 (1.23,1.41)

CI, confidence interval; pola, polatuzumab vedotin; Pr, probability; PN, peripheral neuropathy.
[a]Observed doses account for dose reduction at 2.4 mg/kg.

with confidence intervals (CIs) not including 1 (**Table 2**). Based on nominal doses, the risk ratio for 2.4 vs. 1.8 mg/kg was 1.38 (90% CI: 1.30–1.55) and 1.32 (90% CI: 1.25–1.47), for six or eight cycles of treatment, respectively. After accounting for dose reductions at 2.4 mg/kg, as informed by actual dosing history, the risk ratio was 1.35 (90% CI: 1.28–1.48) and 1.29 (90% CI: 1.23–1.41), respectively.

For treatment of up to eight cycles, based on model simulation using nominal doses, the incidence of grade ≥2 PN was estimated to be 40.9% (90% CI: 30.9–49.5%) for 2.4 mg/kg and 30.7% (90% CI: 21.9–38.6%) for 1.8 mg/kg. After accounting for dose reductions at 2.4 mg/kg (per actual dosing history), the incidence of grade ≥2 PN was 37.2% (90% CI: 28.6–45.7%) for patients initially assigned to 2.4 mg/kg and 28.8% (90% CI: 21.3–36.2%) for 1.8 mg/kg (**Table 2**). The incidence was lower for treatment duration of six cycles, as shown in **Table 2**.

DISCUSSION AND CONCLUSION

Grade ≥2 PN is considered clinically relevant, given the impact it has on patients' quality of life and the consequent need for dose modifications per protocol or standard clinical practice (e.g., dose delay/reduction, or drug discontinuation). Previously, we conducted a logistical analysis to explore the relationship between conjugate exposure and grade ≥2 PN; however, that analysis did not account for the time-dependent increase of PN risk during treatment with pola.[19] In addition, there was limited capacity to directly compare the impact of the 1.8 and 2.4 mg/kg doses of pola on the risk of grade ≥2 PN based on observed data, due to the limited number of patients (26 of 155) initially assigned to receive 1.8 mg/kg, and the absence of randomization between the two dose levels of interest. The patients were treated until progression or unacceptable toxicity without a prespecified dosing duration. Thus, we sought to infer the dose–response and treatment duration–response relationships by constructing a TTE model to describe the relationship between acMMAE plasma concentrations and time to grade ≥2 PN event, to assist in the comparison of different pola dosing regimens in the context of minimizing PN risk. As the current standard of care for NHL typically involves six to eight cycles of rituximab in combination with chemotherapeutic agents, [24] the PN rate with treatment duration capped at six to eight cycles was assessed.

We found that systemic exposure to acMMAE, rather than unconjugated MMAE, is positively correlated with PN risk.[19,25] Following its uptake from the systemic circulation by body tissues and target-expressing cells, the conjugate is likely internalized and further degraded within lysosomes to release unconjugated MMAE. Unconjugated MMAE may subsequently distribute to nearby neurons following cell death to cause PN. Thus, circulating acMMAE may play an
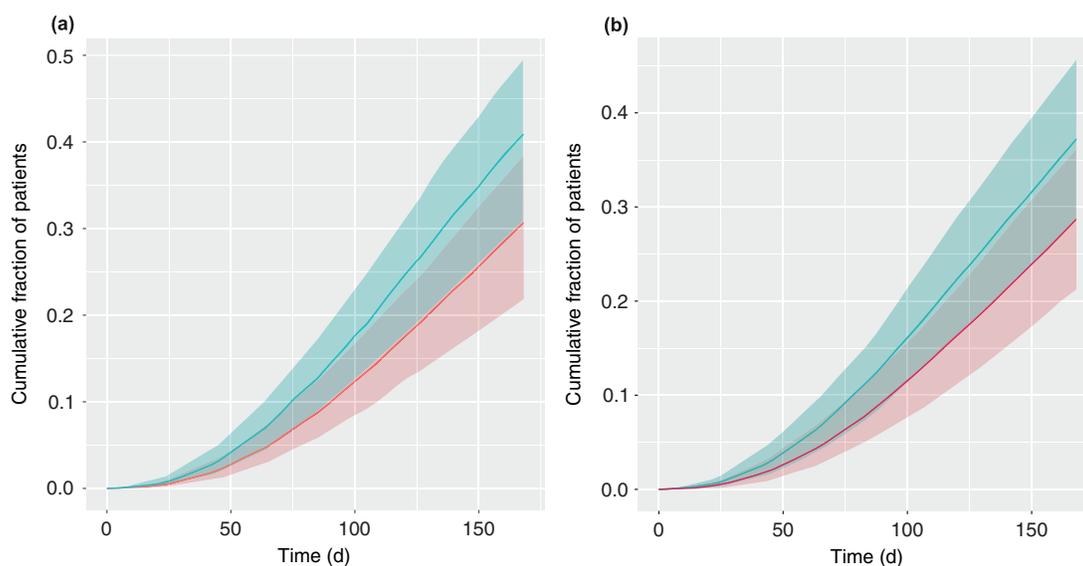
Figure 4 Model-predicted incidence of grade ≥2 PN given (**a**) nominal dose of 1.8 and 2.4 mg/kg q3w pola regimens for six to eight cycles; (**b**) observed pola dosing regimens in patients initially assigned to 1.8 and 2.4 mg/kg q3w for six to eight cycles. Blue line, 2.4 mg/kg dose; orange/red line, 1.8 mg/kg dose; PN, peripheral neuropathy; pola, polatuzumab vedotin.

important role in delivery of MMAE to tissues, resulting in the observed correlation with the incidence of PN. On the other hand, the systemic level of unconjugated MMAE is very low and may not correlate well with the tissue level. Nonetheless, although indirect uptake of MMAE by neurons following initial adjacent tissue-uptake likely contributes to PN development, direct uptake of conjugate by neurons cannot be ruled out as an additional potential contributing factor.

A sequential PK-PD modeling approach was used in this case. There is more confidence in the systemic PK model with rich time-course data, while less certainty in the PD model with less than one observation per individual. Thus, the sequential approach prevents PD model misspecification from "contaminating" the PK model fitting, which is possible if a simultaneous fitting is used. We acknowledge that this is at the risk of biasing statistical inference related to the PD parameter estimates, likely misrepresenting the uncertainty in those parameter estimates.

This analysis confirmed that the PN hazard is delayed relative to acMMAE plasma concentrations, as a model with direct link between plasma concentrations and hazard rate did not describe the data. PN resulting from ADC treatment may take time to develop after the distribution of conjugate to tissues and release of unconjugated MMAE. Furthermore, clinical evidence has suggested that patients undergo at least partial recovery when pola is discontinued following onset of clinically significant PN,[8] and this recovery may take time to occur (data not shown). This exposure–response relationship may be described by the effect compartment model (Models 2 and 4) and the indirect response model (Model 3). However, Model 1, despite fitting well to the observed data, would not be mechanistically plausible, as it does not allow for reversibility of PN. Model 4 improved fitting to the observed data compared with Model 2. The additional time-dependence of hazard rate described by the Weibull function is a largely empirical choice that attempts to account for the effects of time that are not completely explained by drug exposure. The Weibull distribution parameter β was estimated to be 1.32 (Model 4), suggesting that the hazard rate increases over time more than can be explained by the amount in the effect compartment.

Various modeling strategies were considered including using a Markov model to model the transition between grades of PN. Discussion with clinical experts identified the onset of grade ≥ 2 PN event being the most clinically relevant to impact the selection of treatment durations. In addition, the current data are limited regarding the time of grade transition following the initial grade ≥ 2 PN event. If these data were available in future trials, modeling of transitions in PN grades over time will be useful to describe the onset, severity, and recovery of PN.

It should be noted that our model underestimated the risk of grade ≥ 2 PN after eight cycles (see **Supplemental Figure S4**), potentially due to the small number of events and patients at risk at later timepoints. Therefore, subsequent model applications were restricted to no more than eight cycles of pola treatment. It is also apparent from the observed data that PN risks increase with time; the model is more valuable to infer the relationship between exposure and PN risks.

Body weight was identified as a positive risk factor for PN after accounting for conjugate exposure. This finding is supported by another analysis in which the TTE model was expanded to include eight MMAE-containing ADCs.[26] It was reported that height, which is highly correlated with body weight, is an important and independent risk factor for PN.[27] There is also a trend for higher risk with increasing serum albumin concentrations. Hypothetically, ADC may undergo maleimide exchange with albumin to form albumin-conjugated MMAE.[28] How this would correlate with the incidence of PN is not known. Our analysis suggested a trend towards lower risk for grade ≥ 2 PN for treatment with pola in combination with rituximab. However, all patients in the phase II study were given pola in combination with rituximab, whereas all but eight of 76 patients in the phase I study were given single-agent pola. Thus, this observation should be interpreted with caution, as other patient characteristics in each study might covary with the factor of rituximab combination. Although patients with DLBCL appear to have a lower PN incidence compared with patients with FL,[7] this might result from earlier disease progression, resulting in overall shorter treatment duration. In fact, tumor histology was not identified as a covariate impacting hazard rate when treatment duration was accounted for by the TTE model.

The final model predicted grade ≥ 2 PN incidences of 17.8–37.2% for 1.8–2.4 mg/kg q3w treatment of six to eight cycles, accounting for the observed dose reductions (for 2.4 mg/kg). Censoring was not accounted for in this simulation, given that most patients in the clinical trials completed at least six to eight cycles.[17] These predicted incidences of grade ≥ 2 PN are comparable to those observed with other antimicrotubule agents.[11,14,29] For brentuximab vedotin, a grade ≥ 2 PN rate of 31% was reported in patients with R/R HL with up to 16 cycles of q3w dosing.[14] The median times to onset of grade 2 and grade 3 PN events were 27.3 and 38.0 weeks, respectively.[14] For vincristine sulfate liposome injection (Marqibo), in the studies of R/R adult acute lymphoblastic leukemia, the incidence of grade ≥ 3 PN was 32.5% in 83 patients.[29] When Marqibo was used in 22 patients with R/R NHL (in combination with rituximab), the incidence of all grades PN (sensory) was 36%.[11]

In conclusion, the risk of grade ≥ 2 PN increased with increasing conjugate exposure and treatment duration. Higher body weight and serum albumin concentrations appeared associated with increased PN risk. Pola 2.4 mg/kg was found to confer a higher risk of grade ≥ 2 PN than 1.8 mg/kg. When accounting for all sources of variability, the model-estimated PN incidence suggested that capping treatment duration to six to eight cycles at doses of 1.8–2.4 mg/kg would result in PN incidences comparable to those associated with other antimicrotubule agents. Taken together, the present modeling results support the ongoing clinical trial strategy for PN risk-mitigation of combining pola 1.8 mg/kg, limited to six to eight cycles, with an anti-CD20 mAb and a chemotherapeutic, immunotherapeutic, or novel small molecule pathway inhibitor agent (Genentech data on file).

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