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Brentuximab vedotin does not cause clinically relevant QTc interval prolongation in patients with CD30-positive hematologic malignancies

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Abstract

Purpose—Brentuximab vedotin (ADCETRIS®), an antibody–drug conjugate, comprises an anti-CD30 antibody conjugated by a protease-cleavable linker to a microtubule-disrupting agent, monomethyl auristatin E (MMAE). In vitro studies showed that MMAE does not interfere with hERG K⁺ channels at clinically relevant concentrations. In pivotal phase 2 clinical trials in

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Conflict of interest None.

patients with relapsed or refractory Hodgkin lymphoma and systemic anaplastic large cell lymphoma, brentuximab vedotin has shown substantial efficacy and an acceptable safety profile. This phase 1 open-label study was designed to evaluate the effect of brentuximab vedotin on the duration of cardiac ventricular repolarization.

Methods—Patients with CD30-positive hematologic malignancies were treated with 1.8 mg/kg brentuximab vedotin by intravenous infusion every 3 weeks for up to 16 cycles. The primary endpoint was the change from baseline to Cycle 1 Days 2, 3, and 4 in the duration of ventricular repolarization using Fridericia's corrected QT interval (QTcF).

Results—There was no clinically meaningful change from baseline in the duration of ventricular repolarization as measured by QTcF in the 46 evaluable patients out of 52 total patients treated with brentuximab vedotin. There was no evidence of treatment-emergent cardiac safety abnormalities. Brentuximab vedotin was generally well tolerated with a response rate and an adverse event profile consistent with prior studies.

Conclusion—There is no significant prolongation of the QT/QTc interval with brentuximab vedotin in patients with CD30-positive hematologic malignancies.

Keywords

Brentuximab vedotin; Antibody–drug conjugate; QT interval; CD30-positive hematologic malignancies

Introduction

Antibody drug conjugates (ADCs) consist of cytotoxic agents or toxins chemically conjugated to monoclonal antibodies [1, 2]. ADCs represent an advantage over treatment with traditional chemotherapy because they are designed to deliver the cytotoxic agent specifically to tumor cells, thereby potentially resulting in a more favorable therapeutic window compared to the administration of the cytotoxic agent alone.

Brentuximab vedotin (ADCETRIS®; Seattle Genetics, Inc., United States) is an ADC comprising a chimeric anti-CD30 antibody conjugated by a protease-cleavable linker to the microtubule-disrupting agent, MMAE. Following binding of the ADC to CD30 on the cell surface, the ADCCD30 complex is internalized and trafficked to the lysosomal compartment, releasing MMAE via proteolytic cleavage [3]. Binding of MMAE to tubulin disrupts the microtubule network, induces cell cycle arrest, and results in apoptotic death of the CD30-expressing cell [4]. Maximum MMAE concentrations are achieved approximately 1–3 days following administration of brentuximab vedotin in humans.

In vitro studies conducted with MMAE demonstrated that MMAE does not interfere with hERG K⁺ channels at concentrations well above those that are clinically relevant. Additionally, in vivo studies were performed to evaluate the potential of MMAE to prolong the QTc interval. In monkeys, no arrhythmias were noted following IV administration of brentuximab vedotin. Based on these findings (unpublished data), it was not anticipated that brentuximab vedotin would have an effect on QT/QTc interval prolongation and proarrhythmic potential in human patients.

The International Conference on Harmonisation (ICH) E14 guideline, “The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs,” calls for a “thorough QT/QTc study” for most drugs [5]. The form of QT investigation depends on the class of drug and mechanism of action. The cytotoxic nature of the MMAE component of brentuximab vedotin precludes testing in healthy

volunteers. Patients with CD30-positive hematologic malignancies require active treatment, which renders treatment with a placebo unacceptable to patients and their physicians. In addition, there are no approved therapies to use as a positive control to induce QT prolongation that would be appropriate for the treatment of CD30-positive hematologic malignancies. For these reasons, a thorough QT/QTc study was not possible and an “intensive” QT/QTc trial was determined to be appropriate for this study.

The primary objective of this phase 1 study was to evaluate the effect of treatment with brentuximab vedotin on cardiac ventricular repolarization in patients with CD30-positive hematologic malignancies. These evaluations were performed during peak MMAE concentrations following the first and third dose of brentuximab vedotin to assess both potential direct and delayed effects.

Methods

Study design

This study was conducted at 8 US sites and 1 site in Germany (ClinicalTrials.gov identifier: NCT01026233). Patients in this multicenter, open-label study received 1.8 mg/kg brentuximab vedotin IV on Day 1 of each 21-day treatment cycle. Patients could remain on study for up to 16 cycles (approximately 12 months) or until disease progression, whichever occurred first.

Patients were treated from February 2010 through August 2011. Primary data analysis was performed after the last patient's Cycle 2 Day 1 visit, which occurred in December 2010. A subsequent analysis was performed in December 2011 after all patients had completed treatment and follow-up evaluations 30 days after the last dose of study drug. These data are presented in the current manuscript.

The protocol for this study was designed in accordance with the general ethical principles outlined in the Declaration of Helsinki. The conduct of all aspects of the study, including methods for obtaining informed consent, were also in accordance with the principles enunciated in the declaration, the ICH Good Clinical Practices (GCP), and applicable Food and Drug Administration (FDA) regulations/guidelines set forth in Title 21 CFR Parts 11, 50, 54, 56, and 312. The study was registered on ClinicalTrials.Gov, and the protocol was approved by the institutional review board or independent ethics committee for each study site; all patients provided written informed consent before any study-specific procedures began.

Patient population

Men and women at least 18 years of age with histologically confirmed CD30-positive hematologic malignancies who had relapsed, refractory, or progressive disease following at least one prior systemic therapy were enrolled. Patients must have completed any treatment with radiotherapy, chemotherapy, biologics, prior immunotherapy, radioisotope therapy, and/or any other investigational agent at least 4 weeks prior to the first dose of study drug and also recovered from any treatment-related toxicities. In addition to an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, patients must have had adequate organ function based on baseline laboratory data. Female patients of childbearing potential and males with partners of childbearing potential must have agreed to use an effective contraceptive method during the study and for 30 days following the last dose of study drug. Patients with any of the following cardiac abnormalities were to be excluded from the study: QRS duration of >120 ms; QTcF >470 ms; abnormal rhythm at screening; clinically significant cardiac valve abnormality (e.g., stenosis, regurgitation); history of left ventricular ejection fraction <0.30; or a history of cardiac event within 6 months, including

heart failure, myocardial infarction, unstable angina, congestive heart failure, or cardiac arrhythmia. Any medications known to affect QTc interval were prohibited, unless patients were on a stable dose for at least 3 weeks prior to study entry through the Cycle 3 Day 4 ECG monitoring period; a list of these medications was provided in the protocol for reference.

Electrocardiogram assessments

Intensive electrocardiogram (ECG) monitoring was conducted during the first week of Cycles 1 and 3 using an ambulatory 12-lead Holter monitor applied to the patient. Holter recording, which used a Mason-Likar system of electrode placement, was conducted for approximately 2 h prior to the first dose of brentuximab vedotin; post-dose Holter monitoring continued for at least 2 more hours after study drug administration and pharmacokinetic (PK) draws. Post-dose monitoring was also conducted on Days 2, 3, and 4 of Cycles 1 and 3. The Holter monitor was reapplied to the patient and recording was conducted for at least 2 h. The start time for these ECGs was to be as close as possible to the start time of the pre-dose ECGs on Day 1.

At 30, 60, 90, and 120 min after the start of ECG monitoring pre-dose Cycles 1 and 3, as well as 30, 60, 90, and 120 min after the start of ECG monitoring post-dose Cycles 1 and 3 Days 1–4, flashcards were analyzed and 12-lead ECGs obtained from the Holter recording were extracted in quadruplicate with approximately 1–2 min between ECGs. ECGs from a single patient were read by a single, board-certified cardiologist who was responsible for annotating each ECG and conducting an arrhythmia analysis (Biomedical Systems Corporation; St. Louis, MO, USA).

Evaluations included Fridericia's corrected QT interval (QTcF); Bazett's corrected QT interval, as recommended per ICH E14, was also used. Other standard ECG parameters (HR, RR, PR, QRS, QT), morphologic ECG waveform abnormalities, and proarrhythmic AEs were also evaluated.

Pharmacokinetic assessments

Blood samples for the investigation of QT interval and MMAE concentration relationship were obtained at each ECG monitoring period. Post-infusion PK sampling was performed after the initial 2-hour Holter recordings were taken.

Assessments included serum and plasma samples for PK (MMAE, ADC, and TAb) and immunogenicity (anti-therapeutic antibodies; ATA).

Safety assessments

Qualitative follow-up safety ECG monitoring, consisting of a 12-lead Holter monitor applied for at least 2 min, was performed pre-dose at Cycles 2 and 4. Adverse events were collected over the course of the study and reviewed to identify proarrhythmic events and any association with QT interval.

Other safety evaluations included the incidence of any AEs, serious AEs, and changes in laboratory values. Investigator-assessed relationship was recorded and the severity of AEs was graded using the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE version 3.0). Additionally, concomitant medications were summarized using the WHO Drug (version June 2009) substance name; measurements of physical examination findings were also evaluated.

Efficacy evaluations

Assessment of disease status was performed by the investigator per the institutional standard of care and was based on the Revised Response Criteria for Malignant Lymphoma [6].

Statistical methods

The primary endpoint for this study was the change from baseline to Cycle 1 Days 2, 3, and 4 (at each of 12 post-baseline ECG sampling timepoints) in the duration of ventricular repolarization using QTcF. Analysis of the primary endpoint was performed on the evaluable patients set, defined as all eligible patients who received the intended dose of brentuximab vedotin, had a baseline and at least 1 quadruplicate Cycle 1 Day 2, 3, or 4 ECG measurement, and did not have protocol-prohibited concomitant medications or disallowed changes in concomitant medications. Based on ICH E14 Guidance, the Intersection–Union test was used to assess the following hypothesis by observing if the change in QTcF at any of the timepoints had a one-sided 95 % (i.e., two-sided 90 %) upper confidence bound equal to or exceeding 20 ms. At each of the 12 post-baseline ECG sampling timepoints (4 each on Cycle 1 Days 2, 3, and 4), the 90 % CI around the average change from baseline was presented. An upper 90 % CI of <20 ms at each of the post-baseline timepoints would indicate the absence of QTc prolongation due to brentuximab vedotin.

Additional analyses included standard categorical absolute changes in QTcF intervals (<30 ms, >30–60 ms, or >60 ms) and binary categorical changes in QTcF intervals (>450 ms, >480 ms, or >500 ms). The number and percent of patients in each of the categories were summarized at each of the 12 post-baseline ECG sampling timepoints. Additionally, the maximum change from baseline and the maximum QTcF across all timepoints for a patient were determined and the criteria above utilized to categorize the maximum values at the patient-level. The number and percent of patients in each of the categories were summarized.

Summaries of other ECG parameters included heart rate (HR), RR interval, PR interval, QRS duration, and uncorrected QT interval. Measures of central tendencies were calculated for these parameters at baseline and at each of the 12 post-baseline ECG sampling timepoints. The average change from baseline for HR, RR, PR, QRS, and QT was also calculated. The categories based on change from baseline were also created as follows: change from baseline PR interval >0.25 and <–0.25 ms, change from baseline QRS duration >0.25 and <–0.25 ms, change from baseline HR <–0.25 and <50 bpm, and change from baseline HR >0.25 and >100 bpm. The number and percent of patients in each of these binary categories were calculated at each of the 12 post-baseline ECG sampling timepoints. Additionally, the maximum change from baseline across all time-points for a patient was determined and the criteria above utilized to categorize the maximum values at the patient-level. The number and percent of patients in each of the categories were summarized.

Morphological analyses of ECG waveforms were performed for the following abnormalities: atrial fibrillation or flutter, second-degree heart block, third-degree heart block, complete right bundle branch block, complete left bundle branch block, ST segment depression, negative T wave abnormalities, myocardial infarction pattern, and abnormal U waves. Incidence of these abnormalities, presented as number and percent, was summarized for baseline and post-baseline timepoints. Additionally, any changes from baseline that represented the appearance of a morphological abnormality were summarized.

Proarrhythmic AEs of interest included Torsade de Pointes, sudden death, ventricular tachycardia, ventricular fibrillation and/or flutter, syncope, seizures, palpitations, and dizziness. The incidence of these events as associated with ECG parameters (e.g., QTcF interval, PR interval, QRS interval, and heart rate) was assessed at each timepoint.

The correlation between the change from baseline interval of QTcF and plasma concentration of MMAE was examined using all plasma MMAE concentrations and matched Cycle 1 Days 1, 2, 3, and 4 ECG data. Descriptive/graphical presentations of the QTcF changes from baseline versus MMAE concentration were generated. Additional approaches such as the linear mixed effects modeling described by Garnett et al. [7] were used to estimate the relationship between the change in the QTcF interval from baseline and plasma MMAE concentration, as appropriate.

The pharmacokinetic/pharmacodynamic (PK/PD) analysis explored the relationship between the change from baseline in QTc intervals and plasma concentrations of MMAE. For this PK/PD analysis, a linear mixed effects modeling approach was taken using plasma MMAE concentration as a fixed effect and the intercept and patient as random effects. This model was used to estimate the population slope (β) and the standard error of the slope ($SE\beta$) of the relationship between plasma concentrations of MMAE and the change from baseline in QTcF interval.

The all-treated patients analysis set was used to summarize all safety and efficacy endpoints and included all patients who receive at least 1 dose of brentuximab vedotin. The incidence of AEs was summarized using frequencies and percentages. For peripheral neuropathy events, the standardized MedDRA query (SMQ) Peripheral Neuropathy (version 13.0, broad search) was used to summarize the events of treatment-emergent peripheral neuropathy.

Results

Patient characteristics

As shown in Table 1, for all patients enrolled and treated ($N = 52$), the median age of this population was 35 years (range 19–76 years), 48 % of patients were male, and 73 % were white. Patients entering the study had an ECOG performance status of 0 (44 %) or 1 (56 %). Forty-nine patients (94 %) had HL, 2 patients (4 %) had systemic ALCL, and 1 patient (2 %) had gray zone lymphoma. The median time from the patient's initial disease diagnosis to the patient's first dose of brentuximab vedotin in this study was 36 months (range 6–186). These patients had received a median of 4 prior systemic chemotherapy regimens (range 1–11), and 43 patients (83 %) had received prior autologous and/or allogeneic hematopoietic stem cell transplant.

Electrocardiogram results

Of the 52 patients enrolled and treated, 46 patients were eligible for inclusion in the primary analyses for at least one ECG evaluation post-dose (i.e., the evaluable patient set). Of the 6 non-eligible patients, 1 patient was excluded for violating eligibility criteria (QRS was >120 ms at baseline) and 5 patients were excluded for intermittent use of a protocol-prohibited medication in the 3 weeks prior to first dose. Although included in the primary analysis for timepoints where there was no violation, an additional 3 patients had protocol deviations that excluded them from the ECG analyses at Cycle 1 Days 3 and/or 4: 1 patient started a protocol-prohibited medication after the Cycle 1 Day 2 ECG, and 2 patients did not have an ECG measurement captured on either Cycle 1 Day 3 or Day 4. Additional patients may have been excluded from ECG analyses for a particular timepoint if they were missing ECG values for that timepoint during Cycles 1 or 3 Days 1, 2, 3, and/or 4 (i.e., missing values were not imputed).

QTcF duration changes from baseline

As noted in Fig. 1, the change from baseline in QTcF interval was less than 10 ms at each timepoint. At Cycle 1, the maximum mean QTcF increase from baseline was 0.2 ms at

Cycle 1 Day 1 at the 30 min timepoint; the minimum QTcF interval was 348.5 ms at Cycle 1 Day 2 at the 60 min timepoint. Use of the Intersection–Union test showed that the upper bound of each 90 % CI around the mean effect on QTcF was <10 ms at each timepoint, indicating the absence of QTcF prolongation due to brentuximab vedotin or MMAE. The largest upper bound 90 % CI was 2.4 ms seen at Cycle 1 Day 1 at the 30 and 60 min timepoint.

At Cycle 3, the maximum mean QTcF increase from baseline was 4.8 ms at the Cycle 3 Day 1 at the 30 min timepoint; the minimum QTcF interval was 361.5 ms at Cycle 3 Day 4 at the 60-min timepoint. Use of the Intersection–Union test showed that the upper bound of each 90 % CI around the mean effect on QTcF was <10 ms at each timepoint, indicating the absence of QTcF prolongation due to brentuximab vedotin. The largest upper bound 90 % CI was 9.5 ms seen at Cycle 3 Day 1 at the 30-min timepoint.

Heart rate, PR interval, QRS duration, and changes in ECG status

Brentuximab vedotin did not cause clinically meaningful changes for any of the additional ECG parameters evaluated, including HR, PR interval, RR interval, QRS duration, uncorrected QT interval, and Bazett's QTc duration. Brentuximab vedotin was not associated with the appearance or worsening of clinically notable proarrhythmic AEs. Brentuximab vedotin was not associated with the appearance or worsening of morphological abnormalities of interest, including second- and third-degree heart block, complete bundle branch block, ST segment depression, or T wave abnormalities. A myocardial infarction pattern was observed in the ECG of one patient; however, this was a transient finding that is likely to have been due to electrode misplacement. The incident was not considered to be a true myocardial infarction and was thus not reported as an AE or considered to be otherwise clinically meaningful. There were no other AEs suggestive of a myocardial infarction associated with this finding.

Concentration–QTcF analysis results

Using the data from Cycle 1, there was not a significant positive or negative linear relationship between plasma MMAE concentration and the change in QTcF from baseline (Fig. 2). The estimated geometric mean maximum concentration (C_{max}) of brentuximab vedotin in Cycle 1 and Cycle 3 was 5.16 and 3.41 ng/mL, respectively. When comparing the change from baseline in the QTcF duration against the plasma concentration of MMAE for Cycle 1 and Cycle 3, the slope estimate was -0.53 ms/ng/mL of MMAE and -3.29 ms/ng/mL of MMAE, respectively (Table 2). The estimated change in QTcF duration from baseline using the geometric mean MMAE concentration of Cycle 1 and Cycle 3 data was -4.16 and -6.28 ms, respectively.

Figure 2 also shows plots of the observed change from baseline in QTcF values compared with both MMAE plasma and ADC serum concentrations; the plots for MMAE plasma are overlaid with model-predicted values. No concentration-dependent effect on the QTcF interval was observed.

Immunogenicity results

Based on patients' post-baseline ATA assessments, patients were considered negative for ATA, transiently positive for ATA if they had 1–2 positive samples at any time during the study, or persistently positive for ATA if they had more than 2 positive samples at any time during the study. Patients who were categorized as persistently positive did not necessarily need to have a positive ATA sample at the end of the treatment to be considered “persistent” for ATA.

A total of 24 patients (46 %; $N = 52$) tested positive for ATA at some point during the study. Of the 24 patients who tested positive at some point, 20 patients tested negative for ATA at baseline. Of the 4 patients who tested positive at baseline, 2 patients were transiently positive and 2 patients were persistently positive. Of the 20 patients who tested negative at baseline but then tested positive for ATA at some point during the study, 14 patients were transiently positive and 6 patients were persistently positive.

Response results

For all-treated patients ($N = 52$), the ORR was 67 % [95 % CI (52.9, 79.7)]: 38 % of all patients achieved a CR [95 % CI (25.3, 53)] (Table 3). For HL patients ($n = 49$), the ORR was 69 % [95 % CI (54.6, 81.7)]: 41 % of HL patients achieved a CR [95 % CI (27, 55.8)]. Of the 2 patients with systemic ALCL, 1 patient achieved a PR and 1 patient had a best response of progressive disease. The patient with gray zone lymphoma achieved SD.

Safety results

All 52 patients enrolled in this study received at least one infusion of brentuximab vedotin. The median duration of treatment for all patients treated was 25 weeks (range 3–63 weeks) and the median number of treatment cycles per patient was 8 (range 1–16 cycles).

One death of recurrent Hodgkin disease considered unrelated to study drug occurred during the study. All patients had at least one treatment-emergent AE. Adverse events that occurred in 20 % of patients were peripheral sensory neuropathy (50 %); fatigue, nausea, and pyrexia (38 % each); cough (25 %); diarrhea, dyspnea, and vomiting (23 % each); and arthralgia, neutropenia, and upper respiratory tract infection (21 % each) (Fig. 3).

The highest incidences of Grade 3 AEs were for neutropenia (31 %), anemia (17 %), and peripheral sensory neuropathy (10 %). Treatment-related Grade 4 events were febrile neutropenia, hypoxia, leukopenia, neutropenia, and thrombocytopenia.

Serious AEs occurred in 19 patients (37 %). Serious AE preferred terms reported for 2 patients were pyrexia (4 patients); recurrent Hodgkin disease (3 patients); and dyspnea, hypoxia, muscular weakness, nausea, peripheral sensory neuropathy, pneumonia, and vomiting (2 patients each).

Treatment-emergent AEs of peripheral neuropathy (per MedDRA SMQ) that occurred in more than 1 patient were peripheral sensory neuropathy (26 patients, 50 %); paresthesia (8 patients, 15 %); muscular weakness (5 patients, 10 %), and peripheral motor neuropathy (4 patients, 8 %). Planned dose reductions due to peripheral neuropathy AEs occurred in 7 patients (13 %) for paresthesia, peripheral sensory neuropathy, and peripheral motor neuropathy. Five patients (10 %) discontinued treatment due to peripheral neuropathy.

Infusion-related reactions occurred in a total of 11 patients (21 %). Of these 11 patients with infusion-related reactions, AE preferred terms that occurred in more than 1 patient each were dyspnea, nausea, and pruritus. Most events were Grade 1 or Grade 2, with the exception of Grade 3 anaphylactic reaction, dyspnea, hypoxia, pruritus, and urticaria that occurred once each in a total of 3 patients. Six of 8 patients with persistently positive ATA and 2 of 16 patients with transiently positive ATA experienced AEs consistent with infusion reactions. Of the 28 patients who tested ATA negative throughout the study, 3 patients experienced AEs consistent with infusion reactions.

Discussion

Identifying a potential effect on QTc is considered an important part of the development of a new drug candidate. An undesirable property of some non-antiarrhythmic drugs is their ability to delay cardiac repolarization. A delay in cardiac repolarization creates an electrophysiological environment that favors the development of cardiac arrhythmias, most clearly Torsade de Pointes, but possibly other ventricular tachyarrhythmias as well. Although drug-induced prolongation of the QT/QTc interval is usually asymptomatic, an increased rate of certain AEs, including Torsade de Pointes, ventricular tachycardia, and syncope, in patients taking an investigational agent can signal potential proarrhythmic effects. For example, Torsade de Pointes can degenerate into ventricular fibrillation and lead to sudden cardiac death [5].

Although there was no evidence of QTc prolongation in either preclinical or prior clinical studies of brentuximab vedotin, this study was performed to provide a more rigorous assessment of the potential for brentuximab vedotin to prolong ventricular repolarization. Per ICH E14, results of QTc evaluation in drugs that are known to prolong the mean QT/QTc interval by more than around 5 ms and less than 20 ms are generally inconclusive, but drugs that prolong the mean QT/QTc interval by more than 20 ms may have a substantially increased likelihood of being proarrhythmic and might have clinical arrhythmic events captured during AE reporting.

The ECG recordings from the Holter monitoring at and around the time of maximum MMAE plasma concentration and brentuximab vedotin concentrations were used to evaluate whether there was a brentuximab vedotin effect on the QTc interval. Typically, plasma concentrations of free MMAE, the cytotoxic small molecule component of brentuximab vedotin, increase following infusion and reach C_{max} between 24 and 72 h post-dose (Days 2–4). ECG recordings from the Holter monitoring on Days 2, 3, and 4 of Cycles 1 and 3 were used to evaluate whether there was an MMAE effect on QTc interval. Brentuximab vedotin concentrations are maximal post-infusion; therefore, ECG recordings from the Holter monitoring on Day 1 post-infusion were used to evaluate whether there was a brentuximab vedotin effect on the QTc interval.

Exploring the relationship between drug concentration and change in QT interval may provide important additional information to evaluate QT risk [7]; therefore, an exploratory assessment of the MMAE concentration and QTc relationship was conducted. Unlike a typical small molecule drug where drug concentrations change rapidly over a span of hours, the change in free MMAE concentration is small between study Days 2 and 4. The 4 ECGs recorded over a 2-hour interval were planned since free MMAE concentrations were expected to be at or near peak and not change significantly over the 2-hour ECG monitoring window.

For QT correction, using both Fridericia's formula and Bazett's formula (Bazett's data not shown; results were similar), there was no clinically meaningful change from baseline in the duration of ventricular repolarization in patients treated with brentuximab vedotin. The upper bound of each 90 % CI around the mean effect on QTcF was less than 10 ms at each timepoint, indicating the absence of QT prolongation due to brentuximab vedotin. The QTc interval was observed to be slightly shorter following administration of brentuximab vedotin; the maximum mean decrease from baseline was 7 ms. However, a decrease in QTcF this small in magnitude is of uncertain clinical significance [8, 9]. Furthermore, because this study was primarily designed to evaluate QTc prolongation, additional contributing factors cannot be ruled out. Brentuximab vedotin did not cause clinically meaningful changes for any of the additional ECG parameters evaluated, including HR, PR

interval, RR interval, QRS duration, or uncorrected QT interval. For the categorical change from baseline in QTcF, no patient had a QTcF change <60 ms at any timepoint. For absolute QTcF duration, no patient had a QTcF <500 ms at any timepoint. Brentuximab vedotin was not associated with the appearance or worsening of clinically notable proarrhythmic AEs. Brentuximab vedotin was not associated with the appearance or worsening of morphological abnormalities of interest, including second- and third-degree heart block, complete bundle branch block, ST segment depression, or T wave abnormalities.

Generally, the incidence and severity of treatment-emergent AEs reported were consistent to those seen in other studies of brentuximab vedotin [10, 11]. Of note, preexisting neuropathy was seen in 29 % of patients at baseline. Treatment-emergent peripheral sensory neuropathy was the most frequently reported treatment-emergent AE and most dose reductions were due to peripheral neuropathies. Despite the incidence, peripheral sensory neuropathy Grade 3 was seen in only 10 % of patients.

Immunogenicity results were consistent with those seen in other studies [10, 11]. Less than half of the patients tested positive for ATA at some point during the study. Infusion-related reactions were reported in 21 % of patients; most events were Grade 1 or Grade 2 in severity.

Response results for the 49 HL patients were consistent with the pivotal study of brentuximab vedotin in this population [11]. As the number of sALCL and gray zone lymphoma patients was sparse, no conclusions can be drawn in these populations.

In conclusion, there is no significant prolongation of the QT/QTc interval with brentuximab vedotin in patients with CD30-positive hematologic malignancies. No positive relationship between the change in QTcF and MMAE plasma concentration was observed. These results, along with a tolerable safety profile and demonstrated response, indicate that brentuximab vedotin does not affect the cardiac ventricular repolarization in humans to an extent that would impact risk–benefit considerations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1. QTcF interval change from baseline. Results were based on the mean of baseline (pre-dose on Cycle 1 Day 1) and each timepoint mean ECG post-dose. *Error bars* represent the *lower/upper* two-sided 90 % data-based confidence limit around the mean change from baseline

Fig. 2. Plasma MMAE concentration and serum ADC concentration: change from baseline in QTcF. Symbols represent QTcF/MMAE time-matched individual patient observations post-dose at Days 1, 2, 3, and 4. Observed values of MMAE plasma concentration (ng/mL) are overlaid with mixed effects model-predicted values

Fig. 3.
Treatment-emergent adverse events by severity in 15 % of patients, regardless of relationship

Table 1

Patient demographics and baseline characteristics

	All patients (<i>N</i> = 52)
Age (years)	
Median	34.5
Min, max	19, 76
>65	3 (6 %)
Gender, <i>n</i> (%)	
Female	27 (52 %)
Male	25 (48 %)
Race, <i>n</i> (%)	
White	38 (73 %)
Asian	6 (12 %)
Black or African American	5 (10 %)
Other	3 (6 %)
ECOG performance status, <i>n</i> (%)	
0	23 (44 %)
1	29 (56 %)
Initial diagnosis, <i>n</i> (%)	
HL	49 (94 %)
ALCL	2 (4 %)
Other CD30-positive malignancy ^a	1 (2 %)
Time from initial diagnosis to first dose (months)	
<i>n</i>	52
Median	36.0
Min, max	6, 186
Stage at initial diagnosis, <i>n</i> (%)	
Stage I	1 (2 %)
Stage II	26 (50 %)
Stage III	14 (27 %)
Stage IV	8 (15 %)
Unknown	3 (6 %)
Any prior cancer-related radiotherapy, <i>n</i> (%)	40 (77 %)
Number of prior cancer-related systemic therapy regimens	
Median	4.0
Min, max	1, 11
Any prior hematopoietic stem cell transplantation, <i>n</i> (%)	43 (83 %)
Type of stem cell transplantation, <i>n</i> (%) ^b	
Autologous	41 (95 %)
Allogeneic	11 (26 %)

^a Patient had CD30-positive gray zone lymphoma

^b Denominator was the number of patients with a prior hematopoietic stem cell transplantation

Table 2

Plasma MMAE concentration and change from baseline in QTcF

	Cycle 1 only	Cycle 3 only	Cycles 1 and 3
MMAE slope estimate	−0.53	−3.29	−1.07
Standard error	0.34	0.76	0.34
<i>P</i> value	0.1278	0.0001	0.0031
Estimated change from baseline QTcF ^a ,ms	−4.16	−6.28	−3.96
Estimated <i>C</i> _{max} , ng/mL	5.16	3.41	4.15
One-sided upper 95 % confidence bound ^b ,ms	−1.29	−1.87	−1.33

^aEstimated change from baseline QTcF at geometric mean MMAE^bUpper bound = upper one-sided linear mixed model-based confidence limit

Table 3

Response results

	HL patients (N = 49)	All patients (N = 52)
	n (%)	n (%)
Best clinical response ^a		
Complete remission (CR)	20 (41)	20 (38)
Partial remission (PR)	14 (29)	15 (29)
Stable disease (SD)	12 (24)	13 (25)
Progressive disease (PD)	3 (6)	4 (8)
Not evaluable (NE)	0	0
Objective response rate (CR + PR)	34 (69)	35 (67)
95 % CI ^b for objective response	54.6, 81.7	52.9, 79.7
95 % CI ^b for complete remission	27, 55.8	25.3, 53

^aBest response according to Cheson et al. [6] prior to the start of any new antitumor treatment (inclusive of stem cell transplant)

^bTwo-sided 95 % exact confidence interval, computed using the F distribution method [13]