

Evaluation of the Relationship of Glasdegib Exposure and Safety End Points in Patients With Refractory Solid Tumors and Hematologic Malignancies

The Journal of Clinical Pharmacology
2021, 61(3) 349–359
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DOI: 10.1002/jcph.1742

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Abstract

Glasdegib is approved for treating acute myeloid leukemia in elderly patients at 100 mg once daily in combination with low-dose cytarabine. Exposure-efficacy analysis showed that the survival benefit of glasdegib was not glasdegib exposure-dependent. The relationship between glasdegib exposure and adverse event (AE) cluster terms of clinical concern was explored in this analysis. The incidence and severity of *dysgeusia*, *muscle spasms*, *renal toxicity*, and *QT interval prolonged* was modeled using ordinal logistic regression. AEs were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03). Estimated pharmacokinetic parameters were used to derive glasdegib exposure metrics. Demographic characteristics, disease factors, and other variables of interest as potential moderators of safety signals were evaluated. Clinical trial data from patients who received single-agent glasdegib (N = 70; 5–640 mg once daily); or glasdegib (N = 202, 100–200 mg once daily) with low-dose cytarabine, decitabine, or daunorubicin and cytarabine were analyzed. Glasdegib exposure was statistically significantly associated with the cluster term safety end points *dysgeusia*, *muscle spasms*, *renal toxicity*, and *QT interval prolonged*. The impact of age on *muscle spasms* and baseline body weight and creatinine clearance on *renal toxicity* helped explain the AE grade distribution. At the 100 mg once daily clinical dose, the predicted probabilities of the highest AE grade were 11.3%, 6.7%, 7.7%, and 2.5% for *dysgeusia*, *muscle spasms*, *renal toxicity*, and *QT interval prolonged*, respectively. Overall, the predicted probability of developing an AE of any severity for these safety end points was low. Therefore, no starting dose adjustments are recommended for glasdegib based on the observed safety profile.

Keywords

acute myeloid leukemia, exposure-response, hedgehog signaling, PK/PD, safety, smoothed inhibitor

Glasdegib is a selective, orally administered smoothed inhibitor. It has demonstrated potent and selective inhibition of hedgehog signaling in vitro and significant antitumor efficacy in vivo.^{1–3} Glasdegib has been investigated in clinical trials for selected solid tumors and advanced hematologic malignancies including acute myeloid leukemia (AML), chronic myeloid leukemia, chronic myelomonocytic leukemia, myelodysplastic syndrome (MDS), or myelofibrosis.^{4–10} Glasdegib is currently approved in the United States in combination with low-dose cytarabine for the treatment of newly diagnosed AML in adult patients who are ≥ 75 years old or with comorbidities that preclude the use of intensive induction chemotherapy.¹¹

The clinical safety profile of single-agent glasdegib was characterized in phase 1 studies in patients with hematologic malignancies and in patients with advanced solid tumors over a dose range of 5 to 640 mg once daily.^{4,5} The maximum tolerated dose of glasdegib in hematologic malignancies was 400 mg once daily,⁵ and the dose of glasdegib for further clinical investigation was subsequently determined to be 100 mg once daily based on evidence of no further downregulation of the hedgehog pathway at > 100 mg once daily. Additionally, consideration for the anticipated glasdegib

exposure increase with concurrent administration with cytochrome P450 3A inhibitors based on the results of a drug-drug interaction study with ketoconazole was also important in selecting a clinical dose much lower than the maximum tolerated dose.¹² In a phase 2, randomized, open-label, multicenter study, the addition of glasdegib (100 mg orally once daily) to low-dose cytarabine demonstrated superior overall survival vs low-dose cytarabine alone (hazard ratio, 0.51; 80%

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Submitted for publication 20 May 2020; accepted 26 August 2020.

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Table 1. Summary of Clinical Studies

| Study | N/n | Patient Population | Glasdegib Doses ^a | PK Sampling ^b |
|--------------------------|----------------------|----------------------|--|---|
| B1371001 (Phase 1) | 47/47 | Hematologic cancers | 5-, 10-, 20-, 40-, 80-, 120-, 180-, 270-, 400-, and 600-mg monotherapy | Single dose: Before dosing and 0.5, 1, 2, 4, 8, 24, 48, 96, and 120 h after dosing Multiple dose: Before dosing and 0.5, 1, 2, 4, 8, and 24 h after dosing |
| B1371002 (Phase 1) | 23/23 | Solid tumors | 80-, 160-, 320-, and 640-mg monotherapy | Single dose: Before dosing and 1, 2, 4, 6, 10, and 24 h after dosing Multiple dose: Before dosing and 1, 2, 4, 10, 24, 48, 72, and 96 h after dosing |
| B1371003 (Phase 1b/2) | 255/202 ^c | AML or high-risk MDS | 100, 200 mg in combination with chemotherapy (LDAC, decitabine, cytarabine + daunorubicin) | Single dose: Sparse sampling only Multiple dose: Before dosing and 0.5, 1, 2, 4, 6, and/or 24 h after dosing |

AML indicates acute myeloid leukemia; LDAC, low-dose cytarabine; MDS, myelodysplastic syndromes; N, total number of patients in the study; n, total number of patients who were included in the current analysis; PK, pharmacokinetics.

^a Glasdegib doses were administered orally once daily.

^b The intensive PK sampling schedule is shown; additional sparse sampling was also conducted. For B1371003, PK sampling schedule differed based on treatment arm.

^c Only glasdegib-treated patients for whom the safety endpoint and dose information were available were included in the current analyses.

confidence interval [CI], 0.39-0.67; $P = .0004$; median overall survival 8.8 vs 4.9 months) in patients with untreated AML or high-risk MDS, who were unsuitable for intensive chemotherapy.⁹ Based on data from >300 patients across glasdegib dose range of 5 to 640 mg once daily and multiple hematologic and solid tumor malignancies, the overall glasdegib safety profile appeared to be consistent with expected clinical symptoms related to underlying acute myeloid malignancies, backbone chemotherapy, and an elderly patient population, and with toxicities reported for other approved smoothed inhibitors (vismodegib and sonidegib).¹³ Most often, adverse events (AEs) were managed with standard symptom management interventions and/or glasdegib dose reductions and temporary discontinuations.^{4,5,7-9}

The pharmacokinetics (PK) of glasdegib has been fully characterized and reported elsewhere.¹⁴ Individual post hoc estimates based on the population PK model for glasdegib were used to derive glasdegib exposures for individual patients. Treatment-response and exposure-response analysis showed that the survival benefit of glasdegib plus low-dose cytarabine vs low-dose cytarabine alone was independent of glasdegib exposure in patients with newly diagnosed AML.¹⁵ Subsequently, the potential relationship between glasdegib exposure and safety in patients with solid tumors, AML, or high-risk MDS were characterized.

Exposure-response (E-R) modeling analysis for selected safety end points, based on incidence or clinical relevance for glasdegib-treated patients, was conducted using data from 3 clinical studies, in which glasdegib was used as monotherapy or in combination with chemotherapy. The E-R analysis aimed to estimate the association between glasdegib exposure (through several exposure metrics estimated using the

final population PK analysis¹⁴ at the time the highest event grade recorded) and the incidence of the safety cluster terms *dysgeusia*, *muscle spasms*, *renal toxicity*, and *QT interval prolonged*; it also aimed to evaluate the effect of intrinsic and extrinsic factors (covariates) on the E-R relationship for each of the safety end points.

Methods

Clinical Study Overview

A summary of the clinical studies used in the E-R analysis is presented in Table 1. Study B1371001 (NCT00953758) was a first-in-patient phase 1, dose-escalation study with a standard 3+3 design in patients with selected advanced hematologic malignancies who were refractory, resistant, or intolerant to previous treatments. Patients (N = 47) received single-agent glasdegib orally once daily in 28-day cycles continuously. Ten dose levels (5-600 mg once daily) were evaluated. The most frequently reported treatment-related AEs included *dysgeusia*, decreased appetite, and alopecia.⁵ Study B1371002 (NCT01286467) was also a phase 1, dose-escalation study with a standard 3+3 design in patients with selected advanced/metastatic solid tumors (N = 23). The starting dose of glasdegib was 80 mg once daily and additional dose levels of 160 mg once daily, 320 mg once daily, and 640 mg once daily were evaluated. *Dysgeusia*, fatigue, decreased appetite, nausea, dizziness, dehydration, and diarrhea were the most common treatment-related AEs.⁴ Study B1371003 (NCT01546038) was a phase 1b/2 study. In the phase 1b portion, 52 patients were treated with glasdegib (100 mg or 200 mg once daily) in combination with low-dose cytarabine, decitabine, or with induction chemotherapy that consisted of a chemotherapy regimen of 7 days of

standard-dose cytarabine and 3 days of daunorubicin (7+3). No unexpected safety concerns were observed.⁷ The phase 2 portion consisted of 2 parts. One part was a single arm, open-label trial of glasdegib plus “7+3” in 71 patients with AML and MDS eligible for intensive chemotherapy. The most common reported grade 3-4 all-causality AEs were febrile neutropenia, anemia, and thrombocytopenia.⁸ The second part of the phase 2 portion was a prospective, randomized (2:1), open-label trial of glasdegib plus low-dose cytarabine vs low-dose cytarabine alone in 132 patients with AML or MDS who were not considered candidates for intensive induction chemotherapy based on age or other risk factors. The addition of glasdegib 100 mg orally once daily to low-dose cytarabine resulted in a statistically significant and clinically meaningful improvement in overall survival compared with the standard therapy of low-dose cytarabine. The safety profile was consistent with elderly patients with AML receiving chemotherapy, with anemia, febrile neutropenia, and thrombocytopenia as the most frequently reported grade 3-4 all-causality AEs.⁹

All 3 studies were approved by the institutional review board or independent ethics committee at each investigational center and conducted in accordance with the Declaration of Helsinki, the International Council for Harmonisation Good Clinical Practice Guideline, and local regulatory requirements. All participating patients provided informed consent.

Data Set for E-R Analysis

Data from the 3 clinical studies were pooled. Only patients who received ≥ 1 dose of glasdegib for whom the safety end point and dose information were available were included. No data exclusions were performed. If a baseline value was missing, the first observation on treatment was carried backwards. In absence of any observation on treatment, the value was not imputed. If the amount of missing data for a covariate was high ($> 10\%$), that covariate was excluded from the analysis.

Dosing information, demographic and safety laboratory data, and disease assessments including event and time of event were derived from source data collected from the 3 clinical studies. Individual PK parameters estimated previously¹⁴ were used to derive different glasdegib exposure metrics.

Software and Strategy

The E-R analyses were performed using R version 3.4.2 (R Foundation for Statistical Computing, Vienna, Austria).¹⁶ R was used for data manipulation, logistic regression modeling, postprocessing, and generation of figures and tables. An ordinal logistic regression approach to modeling the occurrence of AEs was performed.

Ordinal logistic regression was used to assess the E-R relationship for each of the safety end points. Ordinal regression models are specialized cases of the general linear model, where the order of the categories cannot be ignored. The model is based on the assumption that there is a latent continuous outcome variable and that the observed ordinal outcome arises from discretizing the underlying continuum into j -ordered groups; it allows for various link functions and structured thresholds that restrict the thresholds or cut points to be equidistant (proportional odds) or symmetrically arranged around the central thresholds. Using the proportional odds assumption, it is assumed that the coefficients describing the relationship with the response variable (from the lowest to the highest category) are the same, and therefore there is only a set of parameters for all grade levels. In this analysis, the proportional odds assumption was tested to be reasonable as the differences between predicted logits for varying levels of a single response variable were the same.

The models developed for this analysis consisted of 3 components: the base model defining the regression parameters with no covariate influences, the full covariate model describing the influence of all identified fixed effects on regression parameters, and the final model describing the influence of all significant fixed effects on regression parameters.

An initial base model was developed to describe the overall probability of an event using ordinal logistic regression with only the corresponding intercepts and a glasdegib exposure metric. The ordinal logistic regression used a logit link function during the estimation. Safety end points were captured as ordered events based on a 5-point scale (0-4), where 0 was no AE and 4 was the highest possible grade of AE. Only the first occurrence of the highest observed AE grade was included in the analysis. All AE grades were derived using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 definitions.¹⁷ The most significant glasdegib exposure metric, as determined using the model deviance (D , a measure of goodness of fit [GOF] of the model used for statistical hypothesis testing), was selected to develop the base model for each of the safety end points. Any parameter included in the base model was not subject to removal during the development of the final model. The exposure metrics tested were maximum estimated plasma concentration before the safety event; minimum estimated plasma concentration (C_{\min}) before the safety event; cumulative area under the plasma concentration–time curve (AUC) up to the day of the safety event; average plasma concentration (C_{avg}) calculated using cumulative AUC up to the day of the event over the period of time; and, as early glasdegib exposure metric predictors cycle 1 exposure including maximum

Table 2. Covariates Explored in the Exposure-Response Analyses

| Category | Variable |
|---|---|
| Treatment | Glasdegib monotherapy, glasdegib + LDAC, glasdegib + decitabine, and glasdegib + DNR/Ara-C |
| Demographics | Sex, race, age (y), body weight (kg) |
| Safety laboratory information at baseline | ALB (g/dL), ALT (IU/L), AST (IU/L), BIL (mg/dL), CCL (mL/min), HGB (g/dL), SCr (mg/dL), and WBC (10^9 cells/L) |
| Disease status at baseline | ECOG PS |

ALB indicates albumin; ALT, alanine transaminase; Ara-C indicates cytarabine; AST, aspartate transaminase; BIL, total bilirubin; CCL, creatinine clearance; DNR, daunorubicin; ECOG PS, Eastern Cooperative Oncology Group performance status; HGB, hemoglobin; LDAC, low-dose cytarabine; SCr, serum creatinine; WBC, white blood cells.

estimated plasma concentration, C_{min} , C_{avg} , and AUC before dosing on cycle 2 day 1 were also explored. Glasdegib exposure metrics were estimated using nonlinear mixed-effects modeling (NONMEM version 7.3.0), according to the final population PK model previously reported.¹⁴

The demographic characteristics and disease factors presented in Table 2 were considered potential moderators in the severity and incidence of the defined 4 cluster terms and therefore were included in the full model. An ordinal multivariate logistic regression model was estimated using the `clm()` function with the R package `ordinal`. If 2 potential covariates were highly correlated (ie, baseline alanine transaminase and baseline aspartate transaminase, or baseline creatinine clearance and baseline serum creatinine), only 1 (baseline alanine transaminase and baseline creatinine clearance) was included in the covariate analysis. The distribution of the potential covariates was examined in the numeric and logarithmic scales; the scale that provided a distribution closer to normal was selected for the covariate analysis. Categorical covariates were included if the distribution of the different categories presented incidences >10%; otherwise, the effect of those categories could be highly biased due to the imbalance in the variable distribution. A stepwise backward covariate elimination approach was used to perform covariate selection. A significance level of $\alpha = 0.01$ was used to determine if a covariate would remain in the model. For glasdegib exposure metrics, once a metric was selected it was not considered for elimination from the model. Both categorical and continuous covariates were tested for inclusion using linear parameterization (Supplemental Information).

A final model was determined using the selected glasdegib exposure metric along with all covariates remaining after stepwise backward elimination was completed.

The safety end points were a selected set of cluster terms (*dysgeusia*, *muscle spasms*, *renal toxicity*, and *QT interval prolonged*); the selection was performed taking into consideration the adverse drug reactions and AEs of clinical interest for glasdegib based on safety assessment in cancer patients.^{4,5,7-9}

Assessment of Model Adequacy

Graphical assessments of risk score and event probability discrimination were carried out. Further, an ordinal version of the multinomial Hosmer-Lemeshow (HL) test,^{18,19} the Pulkstenis and Robinson (P-R) tests,²⁰ and the Lipsitz test²¹ were performed as appropriate. The GOF tests worked with the null hypothesis; that is, the model fits the data well. The alternative hypothesis was that there is some (unspecific) problem with the fit, which is usually referred to as “lack of fit.” Therefore, a small P value would indicate a problem with the fit and that the model needed to be modified and improved. Thus, an adequate GOF was considered to be obtained when P values for these tests were >.05.

Results

Observed Data

A total of 272 glasdegib-treated patients enrolled in studies B1371001, B1371002, and B1371003, who had safety end point and dose information available, were included in this pooled data analysis. In the overall analysis population, 66.5% (181/272) of patients were men, 86.4% (235/272) were White, the median (range) baseline age was 69 (25-92) years old, and the median (range) baseline body weight was 78.6 (43.5-145.6) kg (Table 3).

Exposure-Response Analysis

As defined in the analysis strategy, the potential covariates listed in Table 2 were explored in the numerical scale and after natural logarithmic transformation. The distribution closer to normal was selected for the covariate analysis. Thus, the natural logarithmic values were included in the full model for the following potential baseline covariates: creatinine clearance, hemoglobin, white blood cells, alanine transaminase, total bilirubin, and albumin. In the analysis data set, the distribution of race (a potential covariate) was >75% White patients in all studies, with frequencies <10% in the majority of the studies for other races. Therefore, the race variable was not included in the analysis to avoid bias due to the imbalance in the variable distribution.

Table 3. Baseline Characteristics of Patients in the Total Data Set

| | Total |
|--|-------------------|
| N | 272 |
| Age, y | |
| Mean (SD) | 67.3 (12.4) |
| Median (range) | 69.0 (25.0-92.0) |
| Sex, n (%) | |
| Male | 181 (66.5) |
| Female | 91 (33.5) |
| Race, n (%) | |
| White | 235 (86.4) |
| Black | 16 (5.9) |
| Asian | 9 (3.3) |
| Other | 12 (4.4) |
| Body weight, kg | |
| Mean (SD) | 80.2 (17.1) |
| Median (range) | 78.6 (43.5-145.6) |
| ECOG PS, n (%) | |
| 0 | 76 (27.9) |
| 1 | 131 (48.2) |
| 2 | 65 (23.9) |
| Disease, n (%) | |
| AML | 181 (66.5) |
| MDS | 21 (7.7) |
| Missing | 70 (25.7) |
| Disease history, n (%) | |
| De novo | 125 (46.0) |
| Secondary AML/MDS | 77 (28.3) |
| Missing | 70 (25.7) |
| Prior treatment with HA, n (%) | |
| No | 169 (62.1) |
| Yes | 33 (12.1) |
| Missing | 70 (25.7) |
| Creatinine clearance, mL/min | |
| Mean (SD) | 86.3 (33.1) |
| Median (range) | 81.0 (31.4-238.4) |
| Albumin, g/dL | |
| Mean (SD) | 3.7 (1.9) |
| Median (range) | 3.7 (0.0-33.0) |
| ALT, IU/L | |
| Mean (SD) | 26.4 (27.3) |
| Median (range) | 20.0 (5.0-348.0) |
| BIL, mg/dL | |
| Mean (SD) | 0.7 (0.4) |
| Median (range) | 0.6 (0.02-4.2) |
| White blood cells, 10 ⁹ cells/L | |
| Mean (SD) | 28.5 (354.4) |
| Median (range) | 3.6 (0.4-5850.0) |
| Hemoglobin, g/dL | |
| Mean (SD) | 9.5 (1.7) |
| Median (range) | 9.0 (6.9-17.2) |

ALT indicates alanine transaminase; AML, acute myeloid leukemia; BIL, total bilirubin; ECOG PS, Eastern Cooperative Oncology Group performance status; HA, hypomethylating agent; MDS, myelodysplastic syndrome; SD, standard deviation.

The safety end points of interest for the E-R analysis were *dysgeusia*, *muscle spasms*, *renal toxicity*, and *QT interval prolonged*, which are a combination of Medical Dictionary for Regulatory Activities preferred terms (Table S1). Available safety data were pooled from the trials. A summary of the frequency of the safety end

points by study, treatment (including the control group of low-dose cytarabine only of study B1371003), and grade is shown in Table 4.

To model the severity of the selected safety end points using ordinal logistic regression, low frequencies for a given grade were combined; for instance, grades 3 and 4 of all the cluster terms were very low (Table 4), and therefore, to perform the E-R analyses, grades 3 and 4 were grouped and the ordinal categorical end points were studied as grade 0 to grade 2 and grade ≥ 3 . *Dysgeusia* was analyzed by grades 0, 1, and 2 only, as no grade 3 or 4 of *dysgeusia* was reported.

Glasdegib exposure metrics were screened for each of the cluster terms to develop a base model. Both natural logarithmic transformation and nontransformed measures of exposure were evaluated. The exposure variable possessing the most significant association with the cluster term under investigation was selected (lowest *D* value).

Tables S2 and S3 show the parameter estimates or coefficients and the odds ratio (OR) for each E-R analysis. The OR was calculated by exponentiating the parameter estimates. The intercepts, also called cut points, indicated where the safety cluster term was cut to make the grades observed in the data set. These intercepts in general were not used for the interpretation of the results. The coefficients of the model could be somehow difficult to interpret because they were scaled in terms of logarithms. Converting the coefficients into OR helped with the interpretation.

Dysgeusia

Glasdegib cycle 1 AUC showed a statistically significant relationship with *dysgeusia*. For each unit increase of the natural logarithmic value of cycle 1 AUC, the probability of moving from one given *dysgeusia* grade to the immediate grade above increased approximately 1.5-fold; OR, along with its 95%CI, were 1.47 (1.08–2.02) (Table S3). The predicted probability of a given *dysgeusia* grade >0 increased with increasing glasdegib exposure. The predicted probabilities as a function of cycle 1 AUC are shown in Figure 1.

Muscle Spasms

Glasdegib cycle 1 C_{\min} showed a statistically significant relationship with *muscle spasms*. Baseline age appeared to be a statistically significant predictor of *muscle spasms*. For each unit increase of the natural logarithmic value of cycle 1 C_{\min} , the probability of moving from one given *muscle spasms* grade to the immediate grade above increased approximately 1.3-fold (OR, 1.29; 95%CI, 1.12–1.50). On the contrary, age decreased the probability of *muscle spasms*; for each additional year of age, the probability of moving from one given *muscle spasms* grade to the immediate grade

Table 4. Summary of Safety End Points by Study, Treatment, and per Grade

| Variable (Cluster Term) | Category (Grade) | B1371001 | B1371002 | B1371003 | | | Total | B1371003 |
|----------------------------|---------------------|-----------|-----------|-------------|------------|------------------|------------|-----------|
| | | Glas only | Glas only | Glas + LDAC | Glas + Dec | Glas + DNR/Ara-C | | LDAC only |
| N | | 47 | 23 | 106 | 7 | 89 | 272 | 41 |
| Dysgeusia | 0 | 34 (72.3) | 8 (34.8) | 76 (71.7) | 4 (57.1) | 59 (66.3) | 181 (66.5) | 40 (97.6) |
| | 1 | 7 (14.9) | 14 (60.9) | 18 (17.0) | 2 (28.6) | 19 (21.3) | 60 (22.1) | 0 (0) |
| | 2 | 6 (12.8) | 1 (4.3) | 12 (11.3) | 1 (14.3) | 11 (12.4) | 31 (11.4) | 1 (2.4) |
| Muscle spasms | 0 | 27 (57.4) | 14 (60.9) | 60 (56.6) | 4 (57.1) | 44 (49.4) | 149 (54.8) | 37 (90.2) |
| | 1 | 12 (25.5) | 6 (26.1) | 15 (14.2) | 1 (14.3) | 26 (29.2) | 60 (22.1) | 3 (7.3) |
| | 2 | 5 (10.6) | 3 (13.0) | 23 (21.7) | 2 (28.6) | 13 (14.6) | 46 (16.9) | 1 (2.4) |
| | 3 | 3 (6.4) | 0 (0) | 8 (7.5) | 0 (0) | 4 (4.5) | 15 (5.5) | 0 (0) |
| | 4 | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (1.1) | 1 (0.4) | 0 (0) |
| | Missing | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (1.1) | 1 (0.4) | 0 (0) |
| Renal toxicity | 0 | 35 (74.5) | 18 (78.3) | 80 (75.5) | 4 (57.1) | 59 (66.3) | 196 (72.1) | 35 (85.4) |
| | 1 | 6 (12.8) | 1 (4.3) | 13 (12.3) | 1 (14.3) | 18 (20.2) | 39 (14.3) | 3 (7.3) |
| | 2 | 6 (12.8) | 4 (17.4) | 7 (6.6) | 1 (14.3) | 10 (11.2) | 28 (10.3) | 2 (4.9) |
| | 3 | 0 (0) | 0 (0) | 5 (4.7) | 0 (0) | 2 (2.2) | 7 (2.6) | 1 (2.4) |
| | 4 | 0 (0) | 0 (0) | 1 (0.9) | 1 (14.3) | 0 (0) | 2 (0.7) | 0 (0) |
| QT interval prolonged | 0 | 39 (83) | 21 (91.3) | 98 (92.5) | 7 (100) | 80 (89.9) | 245 (90.1) | 40 (97.6) |
| | 1 | 2 (4.3) | 0 (0) | 2 (1.9) | 0 (0) | 1 (1.1) | 5 (1.8) | 0 (0) |
| | 2 | 6 (12.8) | 0 (0) | 3 (2.8) | 0 (0) | 4 (4.5) | 13 (4.8) | 0 (0) |
| | 3 | 0 (0) | 2 (8.7) | 2 (1.9) | 0 (0) | 4 (4.5) | 8 (2.9) | 1 (2.4) |
| | 4 | 0 (0) | 0 (0) | 1 (0.9) | 0 (0) | 0 (0) | 1 (0.4) | 0 (0) |

Ara-C indicates cytarabine; Dec, decitabine; Glas, glasdegib; DNR, daunorubicin; LDAC, low-dose cytarabine; N, number of trial participants enrolled; QT, measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle.

Values are n (%). Clinicaltrials.gov registration numbers are: NCT00953758 (Study B1371001), NCT01286467 (Study B1371002), and NCT01546038 (Study B1371003).

above decreased 0.97 times (OR, 0.97; 95%CI, 0.96–0.99) (Table S3). Predicted probabilities as a function of cycle 1 C_{min} and age are shown in Figure 2.

Renal Toxicity

Glasdegib cycle 1 C_{min} showed a statistically significant relationship with *renal toxicity*. Baseline body weight and baseline creatinine clearance appeared to be statistically significant predictors of *renal toxicity*. For each unit increase of the natural logarithmic value of cycle 1 C_{min} , the probability of moving from one given *renal toxicity* grade to the immediate grade above increases 1.2-fold (OR, 1.24; 95%CI, 1.04–1.49). Baseline body weight increased the probability of *renal toxicity*. For each additional kilogram of weight, the probability of moving from one given *renal toxicity* grade to the immediate grade above increased 1.04-fold (OR, 1.04; 95%CI, 1.02–1.05). Baseline renal function was a predictor of the probability of developing *renal toxicity*; as renal function worsened, the probability of developing *renal toxicity* increased (for baseline creatinine clearance, OR was 0.35; 95%CI, 0.15–0.82; Table S3). Predicted probabilities as a function of cycle 1 C_{min} , baseline body weight, and baseline creatinine clearance are shown in Figure 3.

QT Interval Prolonged

Glasdegib cycle 1 C_{avg} showed a statistically significant relationship with *QT interval prolonged*. For each unit

increase of cycle 1 C_{avg} , the probability of moving from one given *QT interval prolonged* grade to the immediate grade above increased 2.2-fold (OR, 2.18; 95%CI, 1.40–3.41; Table S3). Predicted probabilities as a function of cycle 1 C_{avg} are shown in Figure 4.

Model Adequacy Assessment

A logistic regression yields a linear predictor (commonly named a prognostic index, a diagnostic index, or a risk score) that is a weighted combination of the explanatory variables or predictors. The inverse-logit of the risk score by the variable or variables considered predictors is a model-based estimate of the event probability. The histogram of risk score by the predictor variables is an indicative measure of discrimination assessment. The more overlap between histograms of a risk score, the harder it is for the model to establish differences between values of the predictor variables. For the current analysis, the histograms of risk score by relevant glasdegib exposure measures and baseline covariates (data not shown) showed good separation, confirming that the relevant models were adequate to discriminate the cluster terms of interest.

The impact of the selected variables on the probability of developing the cluster terms of interest was also assessed using boxplots. For *dysgeusia* grade <1 (ie, no event), the highest (fourth quartile) glasdegib exposure

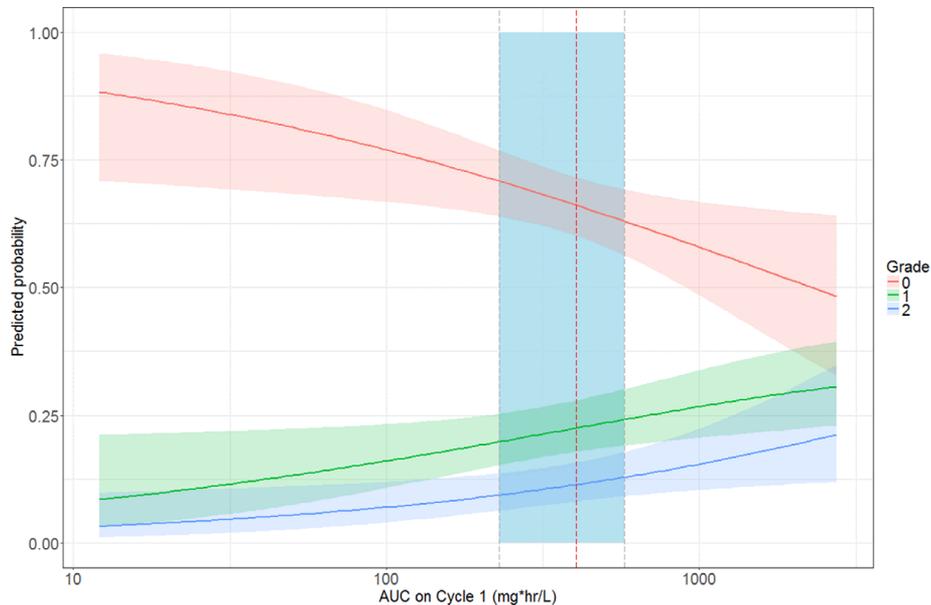


Figure 1. Predicted probability of *dysgeusia* by grade. Predicted probabilities of *dysgeusia* by grade are shown as solid lines with 95%CI as shaded areas. The red dotted vertical line represents the geometric mean value of AUC on cycle 1 simulated from trial participants in the analysis data set at a dose of 100 mg once daily. The blue shaded area represents the geometric mean value \pm the CV of the geometric mean value. The geometric mean of AUC on cycle 1 was 403.139 mg \cdot h/L, the lower bound was 229.789 mg \cdot h/L, and the upper bound was 576.488 mg \cdot h/L. AUC indicates area under the plasma concentration–time curve; CI, confidence interval; CV, coefficient of variation.

(cycle 1 AUC) had the lowest probability of grade <1 and the lowest (first quartile) glasdegib exposure had the highest probability of grade <1; this relationship reversed for *dysgeusia* grade \geq 1. The findings were similar for all cluster terms analyzed, which suggested good discrimination of the predicted probabilities by glasdegib exposure for all safety end points (data not shown).

The model adequacy of the final models for each cluster term was evaluated by statistical tests. All *P* values were $>.05$ (Table S4), and the null hypothesis for the models was considered reasonable. The P-R test is the most appropriate statistical test to assess model adequacy if the lack of fit is associated with categorical variables, whereas the HL and Lipsitz tests are appropriate for lack of fit caused by continuous covariates.^{18,22} In the absence of categorical covariates in any of the final models, the P-R test was not performed. The *P* values of the HL and Lipsitz tests were $>.05$; therefore, adequate GOF was considered to be obtained for all the final models.

Discussion

Glasdegib in combination with standard therapies was well tolerated in clinical studies,^{7–9} and glasdegib plus low-dose cytarabine has demonstrated a favorable efficacy-safety profile in patients with AML unsuitable for intensive chemotherapy.⁹ For patients treated with glasdegib plus low-dose cytarabine, the most common all-causality AEs (incidence $\geq 20\%$) include anemia,

fatigue, hemorrhage, febrile neutropenia, musculoskeletal pain, nausea, edema, thrombocytopenia, dyspnea, decreased appetite, *dysgeusia*, mucositis, constipation, and rash.¹¹ Understanding of the relationship between drug exposure and adverse reactions will provide valuable additional information to guide clinical application of glasdegib in the real-world setting. Based on the incidence and severity of the treatment-related AEs following treatment with glasdegib, 4 safety cluster terms were selected as the safety end points of interest for the E-R analysis: *dysgeusia*, *muscle spasms*, *renal toxicity*, and *QT interval prolonged*.

By analyzing the pooled data from adult patients treated with glasdegib, over the dose range of 5 to 640 mg once daily, alone or in combination with chemotherapy, glasdegib exposure appeared to have a statistically significant association with the occurrence of the safety end points *dysgeusia*, *muscle spasms*, *renal toxicity*, and *QT interval prolonged*. Treatment (monotherapy vs therapy combinations), sex, baseline safety laboratory test results, and baseline Eastern Cooperative Oncology Group Performance Status score were tested (Table 2) and were not found to be statistically significant predictors of the incidence and severity of the safety end points. This E-R analysis also showed that at the approved glasdegib dose of 100 mg once daily, the predicted probability of developing an AE of any severity (grade) for these safety end points was low, with the predicted probabilities of the highest AE grade (grade 2 for *dysgeusia*, grade ≥ 3 for the other end

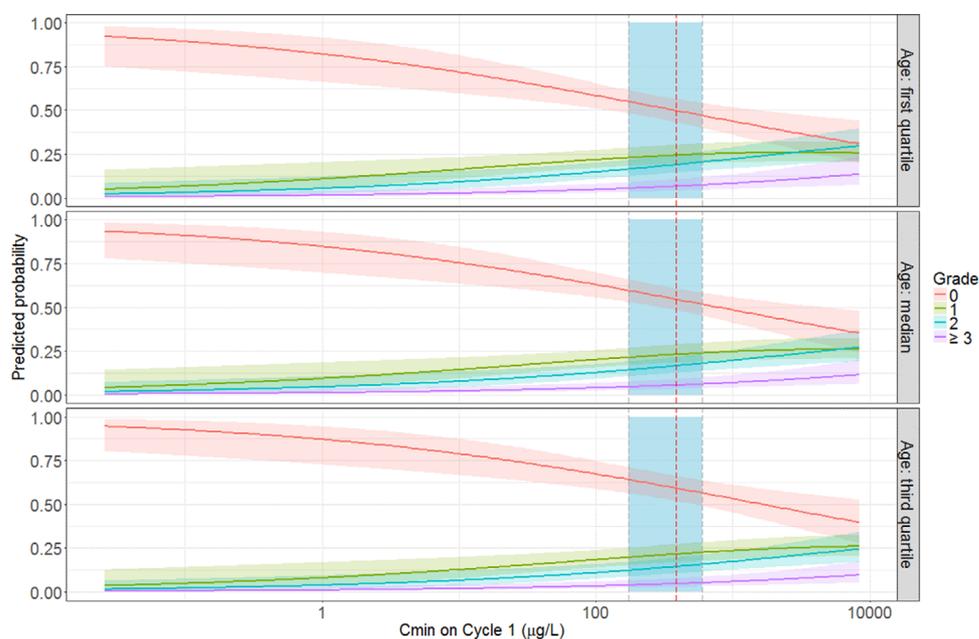


Figure 2. Predicted probability of muscle spasms by grade. Predicted probabilities of muscle spasms by grade are shown as solid lines with 95%CI as shaded areas. The red dotted vertical line represents the geometric mean value of C_{\min} on cycle 1 simulated from trial participants in the analysis data set at a dose of 100 mg once daily. The blue shaded area represents the geometric mean value \pm the CV of the geometric mean value. The geometric mean of C_{\min} on cycle 1 was 384.370 $\mu\text{g/L}$, the lower bound was 172.966 $\mu\text{g/L}$, and the upper bound was 595.774 $\mu\text{g/L}$. The first, second (median), and third age quartiles in the data set were 62, 69, and 76 years, respectively. CI indicates confidence interval; C_{\min} , minimum predicted concentration; CV, coefficient of variation.

points) at 11.3%, 6.7%, 7.7%, and 2.5% for *dysgeusia*, *muscle spasms*, *renal toxicity*, and *QT interval prolonged*, respectively. Therefore, the predicted E-R model-based probabilities for AE frequency, in concert with the observed safety profile, supported the starting dose of glasdegib.

Dysgeusia and *muscle spasms* are both mechanism of action-based adverse effects of inhibition of the smoothed pathway and have been reported for other smoothed inhibitors (vismodegib and sonidegib).¹³ *Renal toxicity* had been observed in both preclinical rat and dog species, though not in human trials, but was considered an important AE of interest and included a large number of preferred terms (Table S1). Additionally, QT prolongation potential had been observed preclinically in the human Ether-à-go-go-Related Gene assay and in the dog cardiovascular safety pharmacology studies. Some instances of grade 3 QTc prolongation had also been reported in monotherapy studies (at doses ≥ 400 mg once daily). In patients with AML and MDS deemed unfit for intensive chemotherapy, in the randomized phase 2 study of glasdegib 100 mg once daily in combination with low-dose cytarabine versus low-dose cytarabine alone, grade 3 QTc prolongation was reported in both study arms,⁹ perhaps related to the effect of comorbidities, concomitant medications, and factors such as electrolyte imbalances, which are common in this

population. While the frequency of these instances in the clinic was low, the *QT interval prolonged* cluster term (which included electrocardiogram QT prolonged) was considered important to evaluate in the E-R analysis. A formal International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use E14-compliant thorough QT clinical study, to specifically evaluate electrocardiogram QT prolonged was also conducted in healthy subjects at both therapeutic steady-state exposures and suprathreshold exposures ($2\times$ therapeutic exposures), placebo, and a positive control. The results of the study demonstrated that while glasdegib had an effect on the QTc interval, the change in baseline- and placebo-corrected QTc interval ($\Delta\Delta\text{QTcF}$) did not cross the threshold of clinical concern for oncology drugs.^{23,24}

Ordinal logistic regression was used to assess the E-R relationship for each of the safety end points. The final E-R models for *dysgeusia* and *QT interval prolonged* included only glasdegib exposure as a statistically significant relationship with safety response, that is, cycle 1 AUC for *dysgeusia* and cycle 1 C_{avg} for *QT interval prolonged*. At the glasdegib clinical dose of 100 mg once daily, the predicted probability of grade 2 *dysgeusia* and grade ≥ 3 *QT interval prolonged* was low (11.3% and 2.5%). The coefficients of the model were scaled in terms of logarithms and were converted into ORs by exponentiating the parameter estimates for

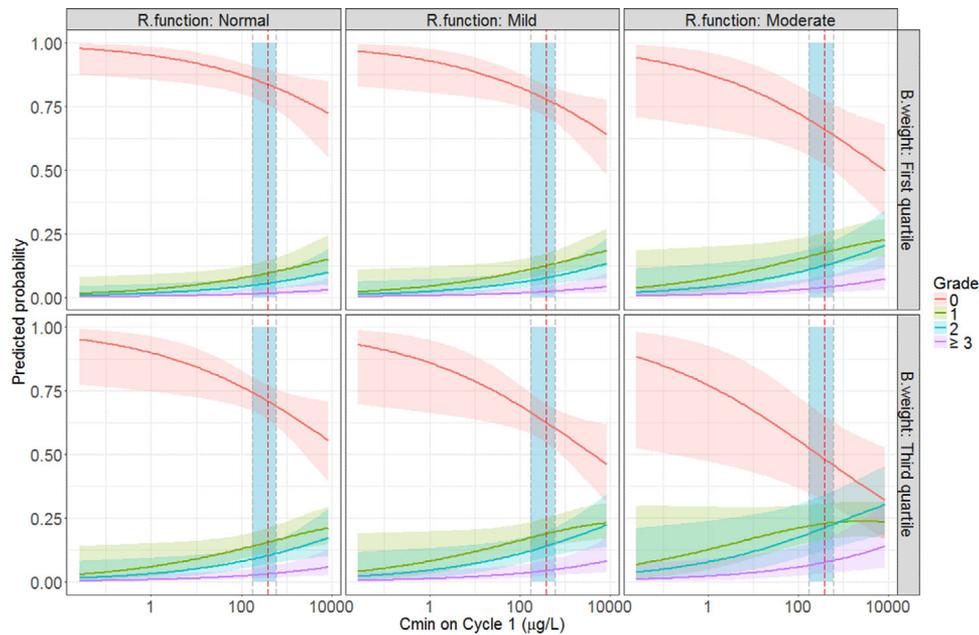


Figure 3. Predicted probability of renal toxicity by grade. Predicted probabilities of renal toxicity by grade are shown as solid lines with 95%CI as shaded areas. The red dotted vertical line represents the geometric mean value of C_{min} on cycle 1 simulated from trial participants in the analysis data set at a dose of 100 mg once daily. The blue shaded area represents the geometric mean value \pm the CV of the geometric mean value. The geometric mean of C_{min} on cycle 1 was 384.370 $\mu\text{g/L}$, the lower bound was 172.966 $\mu\text{g/L}$, and the upper bound was 595.774 $\mu\text{g/L}$. The first and third baseline body weight quartiles in the data set were 67.95 kg and 89 kg, respectively. B.weight indicates baseline body weight; CI, confidence interval; C_{min} , minimum predicted concentration; CV, coefficient of variation; R.function, renal function.

the convenience of result interpretation. Based on the ORs, the odds of moving from a given grade of cluster term to the grade immediately above were multiplied when the glasdegib exposure metric included moved up 1 unit. No sharp increase was seen in the probability of having a higher-grade *dysgeusia* or *QT interval prolonged* event when glasdegib exposure increased.

Cycle 1 C_{min} for glasdegib and age were found to be significantly associated with *muscle spasms*. The probability of having *muscle spasms* increased with increase in glasdegib exposure and decreased with increasing age. At the glasdegib clinical dose of 100 mg once daily, for a 69-year-old patient, which is the median age for the pooled data set, the probability of having *muscle spasms* grade ≥ 3 was 5.6% (95%CI, 3.4%–9.0%; Figure 2). Based on these results, the relationship between *muscle spasms* and age does not suggest that a starting dose adjustment is required.

It has been reported that urine and feces are the primary routes of elimination for glasdegib and its metabolites,²⁵ and baseline creatinine clearance has been identified as a statistically significant predictor of variability in glasdegib clearance.¹⁴ In this analysis, statistically significant relationships were found between renal toxicity and glasdegib cycle 1 C_{min} , baseline body weight, and baseline creatinine clearance. The predicted probability of developing renal toxicity increased with increasing glasdegib exposure and

baseline body weight, and decreased with increasing baseline creatinine clearance. The inverse relationship observed with baseline creatinine clearance indicated that patients with normal renal function (ie, higher values of creatinine clearance) had lower probability of renal toxicity events than those with lower values of creatinine clearance, which was reflective of mildly or moderately impaired baseline renal function. For example, at the glasdegib clinical dose of 100 mg once daily, the probability of renal toxicity grade ≥ 3 was 7.7% (95%CI, 3.3%–16.9%) and 4.4% (95%CI, 2.3%–8.3%), respectively, in heavier (89 kg; median body weight in the data set was 78.6 kg) patients with mildly and moderately impaired baseline renal function (Figure 3). Further, the impact of renal impairment on the PK of glasdegib after a single oral 100-mg dose was being investigated (NCT03596567),²⁶ findings of which will provide detailed information to guide the safe use of glasdegib in cancer patients with renal impairment.

Conclusions

E-R relationships were identified for *dysgeusia*, *muscle spasms*, *renal toxicity*, and *QT interval prolonged* with glasdegib treatment. As glasdegib exposure increased, the probability of a given grade of these safety endpoints increased. Other variables, such as age, baseline body weight, and baseline renal function, also

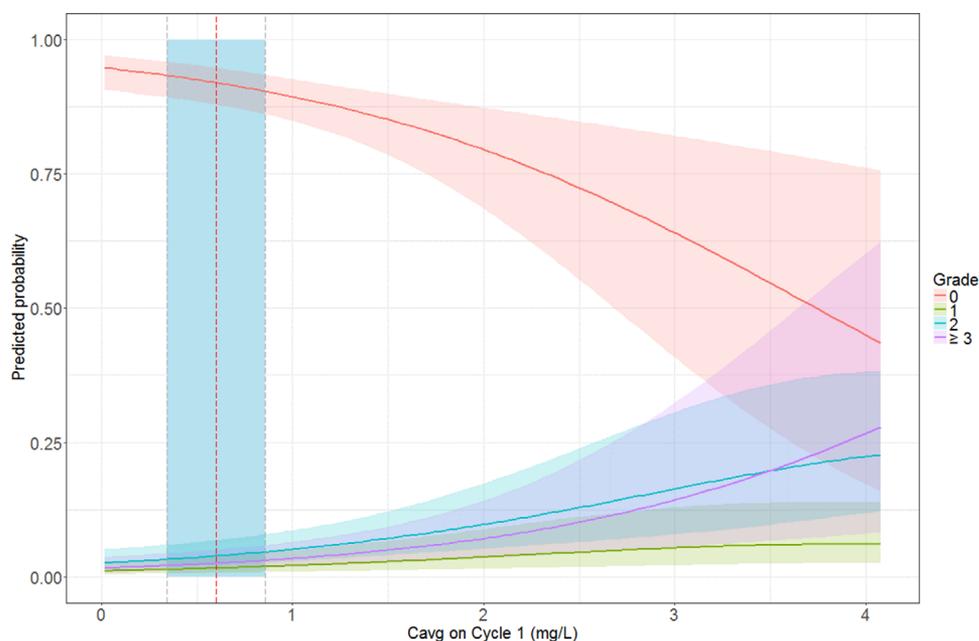


Figure 4. Predicted probability of QT interval prolonged by grade. Predicted probabilities of QT interval prolonged by grade are shown as solid lines, with 95%CI as shaded areas. The red dotted vertical line represents the geometric mean value of C_{avg} on cycle 1 simulated from trial participants in the analysis data set at a dose of 100 mg once daily. The blue shaded area represents the geometric mean value \pm the CV of the geometric mean value. The geometric mean of C_{avg} on cycle 1 was 0.600 mg/L, the lower bound was 0.342 mg/L, and the upper bound was 0.858 mg/L. AUC indicates area under the plasma concentration–time curve; C_{avg} , average concentration calculated using the cumulative AUC over the period of time; CI, confidence interval; CV, coefficient of variation.

affected the incidences of these adverse reactions of interest. However, while the relationships were statistically significant at the approved clinical dose of 100 mg once daily, the frequency and severity of these safety end points was low and did not pose a clinical safety concern to the glasdegib-treated patient population. Furthermore, exposure-efficacy analysis showed that the survival benefit of glasdegib 100 mg once daily was not glasdegib exposure-dependent.¹⁵ Overall, data suggest that there is no need for starting dose adjustments for patients who receive glasdegib treatment.

Acknowledgments

The study was sponsored by Pfizer Inc. Editorial support was provided by Shuang Li, PhD, of Engage Scientific Solutions and was funded by Pfizer.

Conflicts of Interest

A.R.G. was an employee of and owns stock in Pfizer Inc. N.S., S.L., and G.C. are employees of and own stock in Pfizer Inc. C.J. has equity ownership in Aspera Biomedicines, patents relating to Forty Seven, Inc., and previously received research funding from Celgene and Johnson & Johnson. M.H. has received consultancy and research funding from Bayer Pharma AG; consultancy, honoraria, and research funding from Novartis and Pfizer; and research funding from Tetralogic, Sunesis, Daiichi Sankyo, Karyopharm, BergenBio, Roche, and Astellas.

Funding

This study was funded by Pfizer.

Data Sharing Statement

Upon request, and subject to certain criteria, conditions and exceptions (see <https://www.pfizer.com/science/clinical-trials/trial-data-and-results> for more information), Pfizer will provide access to individual deidentified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines, and medical devices (1) for indications that have been approved in the United States and/or European Union or (2) in programs that have been terminated (ie, development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The deidentified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

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Supplemental Information

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