


# A Quality-Adjusted Survival Time Without Symptoms or Toxicities Analysis of Glasdegib Plus Low-Dose Cytarabine Versus Low-Dose Cytarabine as Initial Therapy for Acute Myeloid Leukemia in Patients Who Are Not Considered Candidates for Intensive Chemotherapy

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**BACKGROUND:** In a randomized study, glasdegib (a hedgehog inhibitor) plus low-dose cytarabine (LDAC) significantly prolonged survival in comparison with LDAC in patients with acute myeloid leukemia (AML). A quality-adjusted time without symptoms of disease progression or toxicity (Q-TWiST) approach was used to evaluate comparative quality-adjusted survival. **METHODS:** Overall survival was partitioned into the following: time with any treatment-emergent grade 3 or higher adverse events (TOX); time without symptoms of disease progression or toxicity (TWiST); and time after treatment discontinuation due to insufficient clinical response, relapse, or death time after progression (REL). Q-TWiST was calculated by multiplying the restricted mean time in each state by respective utilities and then summing up the utility-adjusted time. **RESULTS:** At 20 months of follow-up, the survival probabilities for the glasdegib-LDAC arm and the LDAC arm were 28.2% and 7.9%, respectively. Glasdegib-LDAC patients (n = 78), in comparison with LDAC patients (n = 38), had significantly longer mean TWiST (+3.4 months; 95% confidence interval [CI], 1.8-5.2 months) and TOX (+0.8 months; 95% CI, 0.1-1.6 months) and longer but nonsignificant REL (+0.3 months; 95% CI, -1.9 to 2.3 months). Q-TWiST was 4.0 months (95% CI, 2.1-5.8 months) longer with glasdegib plus LDAC, and this translated into a 75% relative improvement in quality-adjusted survival with respect to LDAC. Results were robust to the length of follow-up (6-24 months) and remained significant when all adverse events, regardless of grade, were included. **CONCLUSIONS:** These results suggest that most of the survival benefit from glasdegib plus LDAC versus LDAC alone is TWiST, and this represents added time in relatively “good” health. These results support the clinical value of glasdegib plus LDAC as initial therapy for AML in patients for whom intensive chemotherapy is not an option. *Cancer* 2020;126:4315-4321. © 2020 The Authors. *Cancer* published by Wiley Periodicals LLC on behalf of American Cancer Society. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

**KEYWORDS:** acute myeloid leukemia, glasdegib, low-dose cytarabine, quality-adjusted survival, quality-adjusted time without symptoms of disease progression or toxicity (Q-TWiST), quality of life.

## INTRODUCTION

Glasdegib, a hedgehog pathway inhibitor, in combination with low-dose cytarabine (LDAC) was approved by the US Food and Drug Administration in 2018 for the treatment of newly diagnosed acute myeloid leukemia (AML) in adult patients who are 75 years old or older or have comorbidities that preclude the use of intensive induction chemotherapy.<sup>1</sup> Glasdegib binds to and inhibits Smoothened, a transmembrane protein involved in hedgehog signal transduction. In murine studies, glasdegib with LDAC has prevented tumor growth and reduced blasts in the bone marrow.<sup>1</sup> A recent randomized, open-label, multicenter, phase 2 study (BRIGHT AML 1003; NCT01546038) evaluated the efficacy of glasdegib plus LDAC in comparison with LDAC alone in patients with AML or myelodysplastic syndrome who were not considered candidates for intensive chemotherapy.<sup>2</sup> The primary endpoint of overall survival (OS) was met with a median OS of 8.8 months (6.9-9.9 months) with glasdegib plus LDAC and a median OS of 4.9 months (3.5-6.0 months) with LDAC (hazard ratio, 0.51; 80% confidence interval [CI], 0.39-0.67;  $P = .0004$ ). The addition of glasdegib to LDAC was generally well tolerated with a manageable safety profile consistent with elderly patients receiving chemotherapy

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and toxicities reported for other marketed Smoothened inhibitors. The frequencies of alopecia, muscle spasms, and dysgeusia were numerically lower than what had been previously reported for Smoothened inhibitors.

Although BRIGHT AML 1003 results clearly demonstrate a survival advantage of glasdegib plus LDAC versus LDAC alone, the quality of that extended life is less understood in terms of the benefit-risk tradeoff that may be associated with additional side effects versus an extension of life. It is thus important to determine whether prolongation of survival results from more time with symptoms of progression or adverse events (AEs) or from “quality” added time. The quality-adjusted time without symptoms of disease progression or toxicity (Q-TWiST) method<sup>3,4</sup> provides one tool for assessing the net benefits of oncology treatments in terms of the quantity of survival (OS, relapse-free survival, and AEs) and the quality of survival (patient health utilities) gained across 50 cancers,<sup>5,6</sup> including AML,<sup>7</sup> chronic lymphocytic leukemia,<sup>8-10</sup> and other hematologic cancers.<sup>11-15</sup> The Q-TWiST method allows physicians and patients who are considering a given treatment approach to incorporate into their decision making the relative value of time spent with AEs, time after disease relapse, and “good” time that is not in either of these health states. We thus performed a post hoc analysis of the BRIGHT AML 1003 trial data to examine the quality-adjusted survival time associated with glasdegib-LDAC therapy and LDAC therapy among previously untreated patients with AML who were not eligible for intensive chemotherapy.

## MATERIALS AND METHODS

### Overview/Data Source

Patient-level data used for this secondary post hoc analysis were obtained from the phase 2 BRIGHT AML 1003 trial (NCT01546038), a randomized, open-label, multicenter study that enrolled patients with AML or myelodysplastic syndrome who were unsuitable for intensive chemotherapy, as previously described.<sup>2</sup> For this analysis, the AML-only cohort of the full analysis set ( $n = 116$ ) was used. Patients were randomized in a 2:1 ratio and stratified by cytogenetic risk to receive LDAC (20 mg subcutaneously twice daily for 10 days for 28-day cycles) or glasdegib (100 mg orally daily in 28-day cycles) plus LDAC. Patients continued treatment until disease progression, unacceptable toxicity, or patient refusal and were followed for 4 years for post-treatment survival status. The primary objective of the BRIGHT AML 1003 trial was OS, which was defined as the time from the date of randomization to death from any cause at any time. Secondary objectives included clinical efficacy endpoints, safety and tolerability, pharmacokinetics,

and pharmacodynamics. The final study protocol, amendments, and informed consent documents were approved by institutional review boards or independent ethics committees at each investigational center.

### Statistical Analysis

#### Q-TWiST method

Survival time was partitioned into 3 health states: time with any treatment-emergent grade 3 or higher adverse events (TOX); time without symptoms of disease progression or toxicity (TWiST); and time after treatment discontinuation due to insufficient clinical response, relapse, or death (REL). For the REL definition, patients who discontinued treatment for other reasons (including AEs) were censored at the date of discontinuation unless death occurred within 28 days of discontinuation. For TOX, the duration of an AE was calculated as the difference between the AE start and end dates. If the end date occurred on the same date as or after REL, the end date for the AE was imputed as the REL date and was counted as an event in order to not double-count time after REL. A patient in this circumstance would have no TWiST by definition. AEs with overlapping duration were also truncated; only unique AE days were counted toward TOX to avoid redundancy or double counting.

Each health state's restricted mean duration was obtained by calculation of the area under the Kaplan-Meier curve. A 20-month cutoff for the maximum follow-up was used to estimate restricted means based on the median OS in the trial. Differences in mean health state durations between treatment arms were tested with log-rank tests. We then calculated the Q-TWiST by summing up the time in each health state multiplied by its respective utility weight (range, 0-1) to reflect patient preferences for time spent in each health state according to the following equation:

$$\text{QTWiST} = (\text{TOX} \times U_{\text{TOX}}) + (\text{TWiST} \times U_{\text{TWiST}}) + (\text{REL} \times U_{\text{REL}})$$

where  $U_{\text{TWiST}}$  is the utility weight for TWiST,  $U_{\text{TOX}}$  is the utility weight for TOX, and  $U_{\text{REL}}$  is the utility weight for REL. In the base-case scenario,  $U_{\text{TWiST}}$  was assumed to be equal to 1 and represented a “perfect” or “best” state of health/quality of life (QOL), and the utility weight was 0.5 for TOX and REL, which was consistent with the utility weights often used within the Q-TWiST literature.<sup>6</sup> To assess the precision of the mean restricted time in each health state, the overall Q-TWiST, and the difference in Q-TWiST, 95% CIs were computed with 1000 bootstrapped samples (with replacement) of trial patients. Finally, we calculated the relative Q-TWiST

gain (ie, difference in Q-TWiST between arms divided by the mean OS of the LDAC group). According to Revicki et al's criteria,<sup>16</sup> a relative Q-TWiST gain  $\geq 10\%$  was considered "clinically important," and  $\geq 15\%$  was considered "clearly clinically important."

### Threshold analysis and Q-TWiST gain function

A threshold analysis was conducted whereby the utility values for TOX and REL were varied between 0 and 1 (ie, to cover the range of possible values) in steps of 0.5.

### Sensitivity analyses

#### TOX definition

Several TOX definitions were included for sensitivity analyses. The calculation of TOX was conducted with 2 separate definitions beyond the base case (ie, grade 3 or higher AEs before progression): the first limited TOX time included only symptomatic grade 3 or higher AEs, which excluded AEs that were listed as laboratory investigations (eg, "blood fibrinogen decreased" or "red blood cells urine positive") according to the Medical Dictionary for Regulatory Activities preferred category term, and the second definition included any all-cause AE, regardless of grade (grades 1-5).

#### Varying time horizon

The BRIGHT AML 1003 trial followed up patients receiving glasdegib plus LDAC for a median of 21.7 months and patients receiving LDAC for a median 20.1 months.<sup>2</sup> For this analysis, we used a base-case follow-up time of 20 months. In a sensitivity analysis, the follow-up time was modified to 6, 12, 18, and 24 months to understand the impact of various time horizons on overall Q-TWiST.

#### Subgroup analyses

In the BRIGHT AML 1003 trial, patients were stratified by cytogenetic risk based on their profile at study entry as either poor risk (ie, inv(3), t(6;9), 11q23, -5, -5q, -7, abnormal [17p], or a complex karyotype [3 or more clonal abnormalities]) or good/intermediate risk (ie, lacking the features of poor-risk patients).<sup>2</sup> Analyses were also performed for the following prespecified subgroups: age (<75,  $\geq 75$ , or  $\geq 65$  years), Eastern Cooperative Oncology Group (ECOG) performance status (PS; 0-1 vs  $\geq 2$ ), AML (de novo vs secondary), and bone marrow blast count at the baseline (20%-30% vs  $\geq 30\%$ ).

## RESULTS

Of the 116 patients with AML enrolled in BRIGHT AML 1003, 78 received glasdegib plus LDAC, and 38 received LDAC; this full analysis set was the focus of

this analysis. Almost all patients (95.7%; 96.1% of the glasdegib-LDAC patients and 94.7% of the LDAC patients) experienced some AEs, with 88.4% of the glasdegib-LDAC patients and 92.1% of the LDAC patients experiencing grade 3 or 4 treatment-emergent AEs. At 20 months of follow-up, 28.2% of the patients treated with glasdegib plus LDAC were alive, whereas 7.9% of the LDAC-treated patients were .

### Base-Case Q-TWiST Analysis

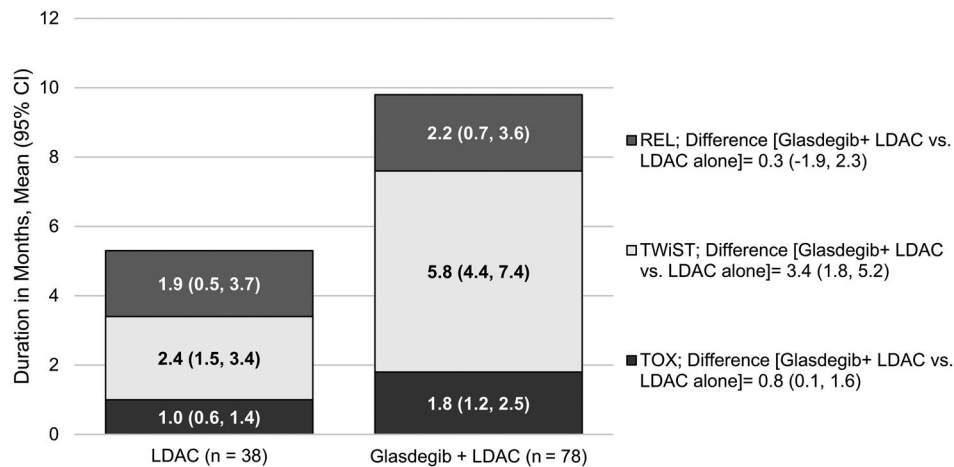
Patients receiving glasdegib plus LDAC had significantly longer TWiST (mean difference, 3.4 months; 95% CI, 1.8-5.2 months) and TOX (mean difference, 0.8 months; 95% CI, 0.1-1.6 months) in comparison with patients receiving LDAC (Fig. 1). A longer REL (mean difference, 0.3 months) was seen in the glasdegib-LDAC group versus the LDAC group, but the difference was not statistically significant. Patients in the glasdegib-LDAC group also had a significantly longer Q-TWiST quality-adjusted survival time in comparison with the LDAC group (7.8 vs 3.8 months; Q-TWiST difference, 4.0 months; 95% CI, 2.1-5.8 months), which corresponded to a 75% relative gain in quality-adjusted survival (Table 1).

Threshold analyses showed significantly positive Q-TWiST differences between glasdegib plus LDAC and LDAC across the full range of TOX and REL utility values (Table 1). Mean absolute Q-TWiST gains ranged from 3.5 to 4.5 months, and relative Q-TWiST gains ranged from 66% to 85% at 20 months of follow-up. The relative Q-TWiST gains were statistically significant, regardless of the utilities used for REL and TOX (Table 1).

### Sensitivity Analyses

The observed Q-TWiST gains were statistically significant, regardless of the TOX definition used (grade 3 or higher AEs [base case], all-cause AEs, or symptomatic grade 3 or higher AEs). When all-cause AEs were included, there was a Q-TWiST difference of 2.9 months (95% CI, 1.4-4.4 months), which represented a 55% gain in quality-adjusted survival; as before, this had the greatest amount of added survival occurring in TWiST. When only symptomatic AEs were included, the Q-TWiST difference was 4.10 months (95% CI, 2.23-5.96 months), which represented a 77% gain in quality-adjusted survival.

Various follow-up times demonstrated that relative gains in Q-TWiST increased over time, with a relative gain of 0.7 months (95% CI, 0.1-1.4 months) at 6 months of follow-up increasing to 4.8 months (95% CI, 2.7-6.8 months) at 24 months of follow-up; Q-TWiST gains were statistically significant at all specified time points (Fig. 2).



**Figure 1.** Restricted mean duration of health states at 20 months (base case). Labels represent the mean durations and 95% CIs. CI indicates confidence interval; LDAC, low-dose cytarabine; RFS, relapse-free survival; REL, time after treatment discontinuation due to insufficient clinical response, relapse, or death; TOX, time with any treatment-emergent grade 3 or higher adverse events; TWiST, time without symptoms of disease progression or toxicity.

**TABLE 1.** Q-TWiST Threshold Analysis

Utility		Q-TWiST, Mean (95% CI), mo			
TOX	REL	LDAC (n = 38)	Glasdegib Plus LDAC (n = 78)	Difference	Relative Gain, %
0	0	2.4 (1.5-3.4)	5.9 (4.4-7.4)	3.50 (1.77-5.19)	66
0	0.5	3.3 (2.4-4.5)	6.9 (5.7-8.3)	3.60 (1.77-5.23)	68
0	1	4.3 (2.8-6.1)	8.0 (6.6-9.6)	3.70 (1.43-5.87)	70
0.5	0	2.9 (2.0-3.8)	6.8 (5.2-8.4)	3.90 (2.08-5.69)	74
<b>0.5</b>	<b>0.5</b>	<b>3.8 (2.8-4.9)</b>	<b>7.8 (6.5-9.3)</b>	<b>4.00 (2.11-5.78)</b>	<b>75</b>
0.5	1	4.8 (3.4-6.6)	8.9 (7.4-10.6)	4.10 (1.72-6.35)	77
1	0	3.4 (2.4-4.4)	7.6 (6.0-9.4)	4.20 (2.37-6.34)	79
1	0.5	4.3 (3.3-5.5)	8.7 (7.3-10.3)	4.40 (2.45-6.36)	83
1	1	5.3 (3.9-7.1)	9.8 (8.2-11.5)	4.50 (2.04-6.86)	85

Abbreviations: CI, confidence interval; LDAC, low-dose cytarabine; Q-TWiST, quality-adjusted time without symptoms of disease progression or toxicity; REL, time after treatment discontinuation due to insufficient clinical response, relapse, or death; TOX, time with any treatment-emergent grade 3 or higher adverse events. Bolded data represent the base case.

**Subgroup Analyses**

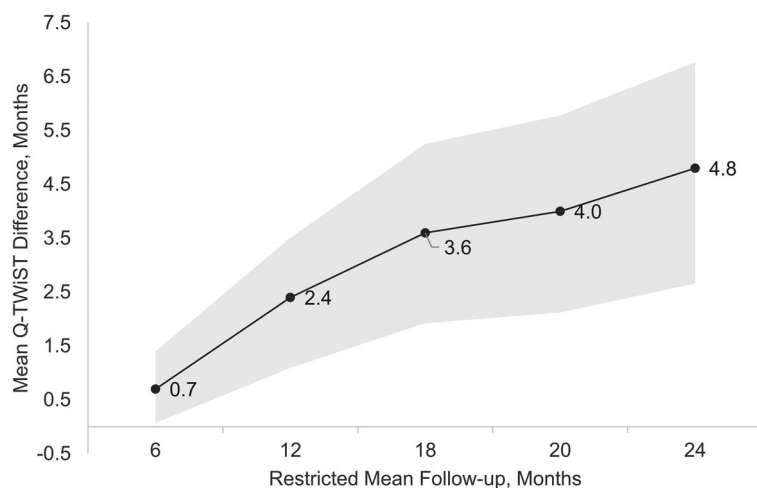
The Q-TWiST gains with glasdegib plus LDAC versus LDAC varied across subgroups from 1.4 months (poor cytogenetic risk) to 6.5 months (ECOG PS ≥2; Fig. 3). Despite the small sample sizes for each subgroup (and the corresponding wide 95% CIs), Q-TWiST differences were statistically significant for all age groups, the good/intermediate cytogenetic risk group, the ECOG PS ≥2 group, the secondary AML group, and all baseline bone marrow blast count groups in favor of glasdegib plus LDAC. For the groups with poor cytogenetic risk, a PS of 0 to 1, and de novo AML, the difference also favored the glasdegib-based combination, but the 95% CIs crossed the neutral value.

**DISCUSSION**

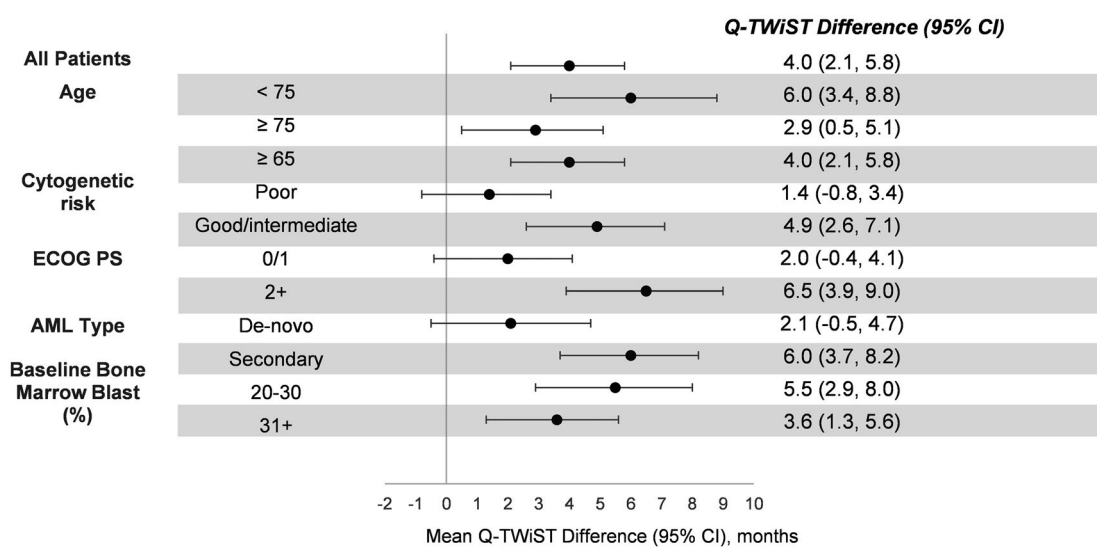
BRIGHT AML 1003 showed a significant survival benefit from glasdegib plus LDAC in comparison with LDAC

alone. Our post hoc Q-TWiST analysis demonstrates that most of the prolonged survival time corresponds to TWiST (3.4 months), which leads to a Q-TWiST quality-adjusted survival difference of 4.0 months. This translates into a 75% relative gain in quality-adjusted survival in comparison with the OS of LDAC patients. This result exceeds the clinical significance threshold of 10% 5-fold and confirms the benefits seen with glasdegib in the BRIGHT AML 1003 study and previous studies.<sup>17,18</sup> The Q-TWiST method has been used to analyze the quality-adjusted benefit of other treatments in oncology. Compared with results from a systematic review of 81 Q-TWiST analyses in oncology, our relative survival gains were substantially higher than those of all previous studies, regardless of the utilities applied to TOX or REL.<sup>6</sup>

This is the first Q-TWiST analysis performed in adults 65 years old or older with AML. More than half of



**Figure 2.** Q-TWiST gain function over time. The shaded area represents 95% confidence bands at each follow-up month. Q-TWiST indicates quality-adjusted time without symptoms of disease progression or toxicity.



**Figure 3.** Subgroup analyses of the Q-TWiST difference. AML indicates acute myeloid leukemia; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; LDAC, low-dose cytarabine; PS, performance status; Q-TWiST, quality-adjusted time without symptoms of disease progression or toxicity.

AML cases are diagnosed in older adults (>65 years old),<sup>19</sup> and intensive chemotherapy may not be a treatment option for these patients because of comorbidities and/or poor PS (ie, ECOG PS  $\leq 2$ ).<sup>20</sup> Until recently, low-intensity therapy was limited to LDAC and hypomethylating agents in the absence of clinical trials, but these therapies are associated with low response rates and minimal improvement in OS.<sup>21</sup> At the time of its approval in the United States, glasdegib was the first novel agent to show a survival advantage in combination with LDAC in comparison with LDAC alone in a randomized study.

The goals of treatment in patients with AML for whom intensive chemotherapy is not an option, however, are 2-fold: prolonging survival and maintaining/improving QOL. Assessing QOL is becoming increasingly important to patients, particularly to older patients, who may spend a large proportion of time after treatment for AML experiencing AEs, being admitted to the hospital, or experiencing active disease.<sup>22</sup> Few studies have reviewed QOL in patients with AML for whom intensive chemotherapy is not an option, possibly because of the poor prognosis and short survival time in this population.<sup>22</sup> Results of a

systematic review of 10 articles assessing QOL in patients with AML showed that low-intensity therapy maintains some measures of QOL but does not improve QOL.<sup>22</sup> Our analysis adds significant data regarding quality-adjusted survival for older patients with AML who are unable to receive intensive regimens. More importantly, our results add a measure of value for a novel, recently approved therapy to better assess what a longer life may represent for patients treated with glasdegib plus LDAC.

Observed results were robust to the TOX definition used and to the time horizon for analysis. Subgroup analyses showed that glasdegib plus LDAC was beneficial, particularly for patients 75 years old or older, patients with an ECOG PS  $\geq 2$ , and patients with secondary AML; these characteristics are considered poor prognostic factors related to AML.<sup>21</sup> The Q-TWiST relative gains were 2.9 months for patients 75 years old or older, 6.5 months for patients with an ECOG PS  $\geq 2$ , and 6.0 months for patients with secondary AML.

This analysis and the Q-TWiST methodology are not without limitations. Although our base-case analysis, consistent with previous Q-TWiST analyses, used grade 3 or higher AEs to calculate TOX,<sup>6</sup> this approach to defining TOX does not distinguish between different types of AEs and would not reflect potential differences that the type of AE and the AE severity might have on utility (eg, the utility of grade 3 pneumonia vs grade 3 fatigue), whether these AEs might require hospitalization, or the impact of having multiple AEs at the same time, which may be associated with greater disutility. Another limitation of Q-TWiST studies is the perceived arbitrary choice for utilities, which has been addressed through threshold analyses that can address such limitations by allowing users to give their personal utility to time in REL and TOX states and see the corresponding changes in quality-adjusted survival. In this way, patients can personalize their decision to their own perception of how much they would value (or devalue) TOX and REL. Additional studies analyzing real-world evidence are needed to understand QOL impacts from the patient perspective, and these in turn could provide real-world utilities. This is particularly relevant with respect to AEs, which may have a significant impact on a patient's QOL even if they are not grade 3 AEs. In addition, for patients with more than 1 concomitant AE, there was not a further discount in utility associated with experiencing more than 1 AE at a time. The perceived utility of a TOX day may be different when 2 or more AEs co-exist than when only 1 exists. We also did not incorporate interventions that might modulate the impact of a given grade 3 AE. For example, grade 3 anemia not resulting

in a transfusion may not have the same impact as grade 3 anemia requiring a transfusion because of the time spent in the clinic, the need for additional needle sticks, costs, and so forth. A final limitation is that information was not available for the relapse date if a patient discontinued treatment and subsequently relapsed, and this could affect TWiST.

Despite these limitations, Q-TWiST analyses help to fill a gap in our understanding of the tradeoffs in clinical risk and benefit of various oncology therapies from a patient perspective. These tradeoffs are receiving increasing attention from regulators and physicians, including the European Medicine Agency,<sup>23-25</sup> the US Food and Drug Administration,<sup>26</sup> and the American Society of Clinical Oncology,<sup>27</sup> which formally define a net health benefit score based on clinical benefits and toxicities. The Q-TWiST approach makes it possible for any physician or patient to tailor the results to his or her own personal value placed on TOX, TWiST, and REL and adapt the survival analysis to reflect his or her own personal situation and beliefs. The results presented herein clearly convey that in the case of glasdegib, the majority of the extension of life is happening in "good" TWiST in the absence of AEs and disease progression.

In conclusion, glasdegib plus LDAC demonstrated significant survival benefits for newly diagnosed patients with AML who were not considered candidates for intensive chemotherapy. Although patients treated with glasdegib plus LDAC versus LDAC alone experienced an increase in time with toxicities (which might be expected for a 2-drug therapy in comparison with a single-agent therapy), the majority of the additional survival time that glasdegib-LDAC patients experienced was TWiST, which represented added time in relatively "good" health. The relative gains in OS with glasdegib plus LDAC in this analysis greatly exceeded previously established thresholds considered to confer a clinical benefit, and they confirm the value of glasdegib plus LDAC over LDAC alone in this patient population and support its role in the management of patients with AML for whom intensive chemotherapy is not an option.

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#### CONFLICT OF INTEREST DISCLOSURES

Caitlyn T. Solem is an employee of Pharmerit International, LP, which was paid to conduct the research herein. Timothy J. Bell, Joseph C. Cappelleri, Helen Bhattacharyya, and Caroline J. Hoang are employees of and

stockholders in Pfizer, Inc. Youngmin Kwon and Courtney Johnson were employees of Pharmerit International, LP, at the time the research was conducted. Jorge E. Cortes reports grants and personal fees from Pfizer during the conduct of the study; grants and personal fees from Novartis, Takeda, Biopath Holdings, and Jazz outside the submitted work; and grants from Amphivena and Merus outside the submitted work.

## AUTHOR CONTRIBUTIONS

**Caitlyn T. Solem:** Conceptualization, formal analysis, methodology, project administration, supervision, validation, and writing—original draft. **Timothy J. Bell:** Conceptualization, funding acquisition, methodology, project administration, supervision, validation, and writing—review and editing. **Youngmin Kwon:** Methodology, formal analysis, project administration, and writing—review and editing. **Joseph C. Cappelleri:** Conceptualization, methodology, validation, and writing—review and editing. **Courtney Johnson:** Formal analysis, project administration, and writing—review and editing. **Helen Bhattacharyya:** Conceptualization, methodology, validation, and writing—review and editing. **Caroline J. Hoang:** Conceptualization, methodology, validation, and writing—review and editing. **Jorge E. Cortes:** Conceptualization, methodology, validation, and writing—review and editing.

## DATA AVAILABILITY

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 de-identified 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 the 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 de-identified 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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