Poster 595

Quality-Adjusted Survival for Low-Dose Cytarabine (LDAC) versus Glasdegib+LDAC among Newly Diagnosed Acute Myeloid Leukemia Patients who are not Candidates for Intensive Chemotherapy: A Q-TWiST Analysis

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Introduction

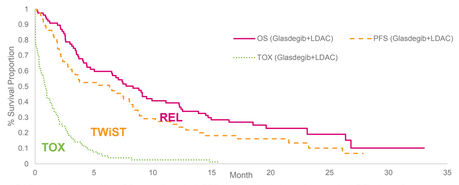
- In a randomized, phase 2 trial of newly diagnosed acute myeloid leukemia (AML) patients (BRIGHT AML 1003; NCT01546038), patients receiving glasdegib (a selective oral inhibitor of hedgehog signaling pathway) in combination with low-dose cytarabine (LDAC) experienced statistically significant and meaningful gains in survival compared with patients receiving LDAC alone[1].
- This analysis assessed using a Q-TWiST approach[2] the possible trade-offs between time with adverse events (toxicities) and after relapse/progression (i.e., with symptoms of disease) as compared to 'good' survival (i.e., time without toxicities or symptoms of progression [TWiST]) when comparing regimens.

Materials and Methods

STUDY DESIGN

- Overall survival in the BRIGHT AML 1003 trial, restricted to a follow-up of 20 months, was partitioned into **(Figure 1)**
  - **TOX**: Time with toxicity, defined as grade ≥ 3 adverse events [AE] prior to progression
  - **TWiST**: Time without symptoms of disease progression or toxicity; this is the most desirable time period
  - **REL**: Time post-progression, where progression was defined as treatment discontinuation due to insufficient clinical response or death; patients who discontinued for other reasons (including AEs) were censored at the date of discontinuation unless death occurred within 28 days of discontinuation.

Figure 1. Partitioned Survival Curve for Glasdegib+ LDAC



Abbreviations: LDAC, low-dose cytarabine; OS, overall survival; PFS, progression/relapse-free survival; REL, time after progression/relapse; TOX, time with grade ≥ 3 toxicity; TWiST, time without symptoms of disease progression or toxicity.

Figure 1 depicts the OS and PFS Kaplan-meier curves survival as well as the curve representing total days with grade ≥ 3 adverse events, which are used to partition survival into TOX, TWiST, and REL health states in the calculation of Q-TWiST. The area under each of these curves is equal to the mean time in each state and are equivalent to the respective means presented in Figure 2.

STATISTICAL ANALYSIS

- Q-TWiST was calculated by multiplying restricted mean time in each state by respective utilities (U) and then summing up the utility-adjusted time.
- Base case analysis used U(TOX)=U(REL)=0.5 and U(TWiST)=1.0; threshold analyses were performed varying U(TOX) and U(REL) jointly each from 0 to 1 (Table 1).
- Relative gains in Q-TWiST, calculated as Q-TWiST difference/overall survival in LDAC arm were calculated; relative gains ≥ 15% were considered clearly clinically meaningful per the clinical literature.[3]
- Sensitivity analysis varied the length of follow-up and AE definitions; prespecified subgroup analyses were also performed.
- A bootstrap procedure was used to obtain 95% confidence intervals (95% CI).

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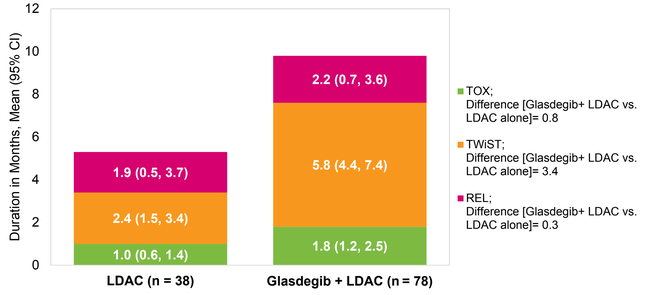
Results

BASE CASE ANALYSIS

- At 20 months of follow-up, the survival rate for glasdegib + LDAC and LDAC arm was 28.2% and 7.9%, respectively.
- While glasdegib + LDAC vs. LDAC alone patients experienced a longer time with toxicities (as expected since glasdegib is an add-on therapy), the majority of the additional time that glasdegib+LDAC patients experienced was TWiST time, which represents added time in relatively 'good' health **(Figure 2).**

Figure 2. Restricted Mean Duration of Health States



Abbreviations: LDAC, low-dose cytarabine; REL, time after progression; TOX, time with grade ≥ 3 toxicity; TWiST, time without symptoms of disease progression or toxicity.

Figure 2 shows the overall survival through 20 months, divided into time spent in TOX, TWiST, and REL health states. These are not multiplied by any utilities, but represent the full time in each state. Glasdegib+LDAC patients spent a significantly longer time in TOX and TWiST health states versus LDAC alone.

- Q-TWiST was 4.0 [95% CI: 2.1, 5.8] months longer for glasdegib+LDAC, translating into a 75% relative improvement in quality-adjusted survival relative to LDAC alone **(Table 1)**.

Table 1. Q-TWiST Threshold Analysis

Utility		Q-TWiST, Mean (95% CI), Months			
TOX	REL	LDAC (n = 38)	Glasdegib + 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
0.5	0.5	3.8 (2.8, 4.9)	7.8 (6.5, 9.3)	4.00 (2.11, 5.78)	75
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

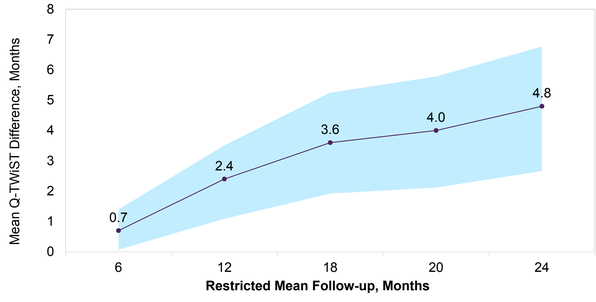
Abbreviations: LDAC, low-dose cytarabine; Q-TWiST, quality-adjusted time without symptoms of disease progression or toxicity; REL, utility of time after progression; TOX, utility of time with grade ≥ 3 toxicity.

Table 1 depicts quality-adjusted survival (Q-TWiST) for LDAC, glasdegib+LDAC, and the difference between these cohorts using a range of utilities. The green row represents base case results. Quality-adjusted survival results were robust to utilities used for TOX and REL states. Relative gains, calculated as difference in quality adjusted survival relative to overall survival in the LDAC group, and is a metric used to compare across studies.

SENSITIVITY ANALYSIS

- Q-TWiST gains exceeded the clinically meaningful threshold and were statistically significant across all combinations of U(TOX) and U(REL) (**Table 1**).
- Results were robust to length of follow-up from 6 to 24 months (**Figure 3**) and remained significant when including all adverse events regardless of grade.
- Q-TWiST differences were significantly greater or trended towards having more quality adjusted survival for glasdegib+ LDAC versus LDAC alone in all subgroups (**Figure 4).**

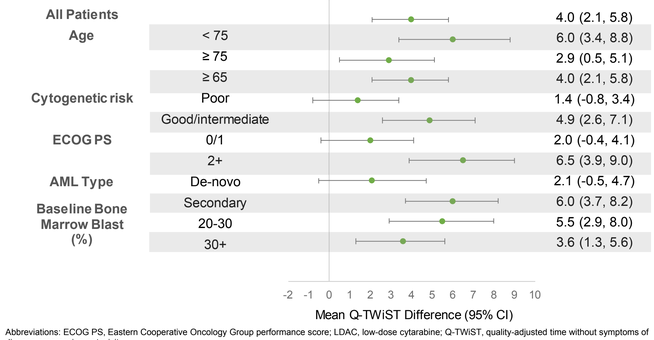
Figure 3. Q-TWiST Gain Function Over Time



Abbreviations: Q-TWiST, quality-adjusted time without symptoms of disease progression or toxicity. The shaded blue area represents 95% confidence bands at each follow-up month.

Figure 4 illustrates that as more time is included within the measurement period for Q-TWiST analysis, the difference in Q-TWiST between glasdegib+LDAC vs. LDAC alone increases. However, even with short intervals (e.g., 6 months), quality-adjusted survival was longer for glasdegib+LDAC.

Figure 4. Subgroup Analyses of Q-TWiST Difference



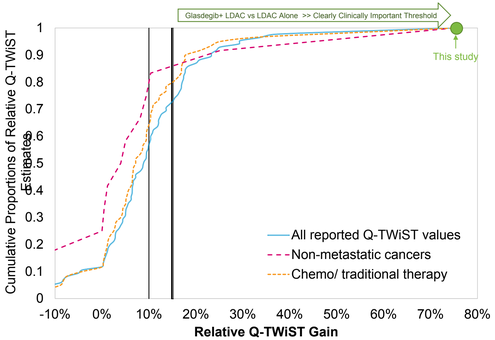
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance score; LDAC, low-dose cytarabine; Q-TWiST, quality-adjusted time without symptoms of disease progression or toxicity.

Figure 5 summarizes the Q-TWiST difference for glasdegib+LDAC vs. LDAC alone in different subgroups of the sample. In all sugroups, there was greater quality adjusted survival in the glasdegib+LDAC arm, although some confidence intervals did overlap 0 (indicating the difference may not be statistically significantly different)

Discussion and Conclusions

- Glasdegib+LDAC demonstrated significant quality-adjusted survival benefits for newly diagnosed AML patients who are unable to receive intensive chemotherapy.
- In this cohort, the relative gains in quality-adjusted survival greatly exceeded previously established thresholds[3] for being clearly clinically meaningful **(Figure 5)**, which suggests that the benefits of glasdegib + LDAC vs LDAC alone outweigh the risks.

Figure 5. Relative Gain Versus Q-TWiST Literature



Abbreviations: Q-TWiST, quality-adjusted time without symptoms of disease progression or toxicity.

Figure 3 contextualizes the current study results as compared to what has been previously observed within the Q-TWiST literature regarding relative Q-TWiST gains. Black lines at 10% and 15% represent clinically important and clearly clinically important thresholds.[3] The relative gains observed for glasdegib+LDAC vs. LDAC alone (i.e., 75% in the base case) exceeded the relative gains observed in all published studies to date.

References:

1. Cortes JE, Heidel FH, Hellmann A, et al. Randomized comparison of low dose cytarabine with or without glasdegib in patients with newly diagnosed acute myeloid leukemia or high-risk myelodysplastic syndrome. Leukemia 2019;33:379-89.
2. Solem CT, Kwon Y, Shah RM, Aly A, Botteman MF. Systematic review and benchmarking of Quality-Adjusted Time Without Symptoms or Toxicity (Q-TWiST) in oncology. Expert Rev Pharmacoecon Outcomes Res 2018:1-9.
3. Revicki DA, Feeny D, Hunt TL, Cole BF. Analyzing oncology clinical trial data using the Q-TWiST method: clinical importance and sources for health state preference data. Qual Life Res 2006;15:411-23.

Disclosures: C. Solem is an employee of Pharmerit International, which was paid to conduct the research herein. Y Kwon and C Johnson were employees of Pharmerit International at the time the research was conducted. T. Bell, J Cappelleri, H Bhattacharyya, and C Hoang are employees of Pfizer Inc. J Cortes was paid by Pfizer Inc to consult on this research.

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