CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

Statistical Review and Evaluation
Clinical Studies

NDA Number	210656
Drug Name	DAURISMO (glasdegib)
Indication	Treatment of newly diagnosed AML
Sponsor	Pfizer
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1 Executive Summary

The efficacy of glasdegib (G) in combination with low-dose cytarabine (LDAC) was studied in a Phase 2 randomized open-label study (B1371003) of previously untreated AML and high-risk MDS patients for whom high-dose chemotherapy was not administered. The study randomized 132 patients in a 2:1 ratio (88 to the G+LDAC arm and 44 to the LDAC arm). The primary endpoint was overall survival (OS).

For the set of randomized AML and MDS patients, G+LDAC demonstrated superiority over LDAC with respect to overall survival (OS):

- hazard ratio (95% CI) = 0.51 (0.34, 0.77) in favor of G+LDAC.
- one-sided log-rank $p = 0.0004$.
- median time to OS and 95% CI of
  - 8.8 (5.0, 11.7) months for G+LDAC
  - 4.9 (2.9, 6.5) months for LDAC

To the extent that MDS and AML are two distinct diseases, the amount of statistical information for making statements about the efficacy of G+LDAC within the MDS subgroup was inadequate as there were only 10 MDS patients in the G+LDAC arm and 6 in the LDAC arm.

Focusing only on patients with FDA-adjudicated AML status, the superiority of G+LDAC over LDAC with respect to OS continued to hold:

- hazard ratio (95% CI) = 0.46 (0.3, 0.71) in favor of G+LDAC
- one-sided log-rank $p = 0.0002$.
- median time to OS of 8.3 months for G+LDAC and 4.3 months for LDAC.

With respect to complete remission rates, G+LDAC also demonstrated superiority over LDAC alone among patients with confirmed AML:

- LDAC: CR = 1/37 (2.6%)
- G+LDAC: CR = 14/77 (18.2%)
- Difference (Exact 95% CI): -15.6% (-26.6%, -1.0%)

In sum, the efficacy of G+LDAC is demonstrated in both the as-randomized cohort (consisting of both AML and MDS patients) and the subgroup consisting of patients with confirmed AML.

Whether the results from Study B1371003 provide a favorable benefit to risk ratio to support an approval of glasdegib in combination with low-dose cytarabine for the proposed indication will be deferred to the clinical review team.

2 Introduction

2.1 Overview

Study B1371003 is the basis of the NDA and upon which efficacy of glasdegib (G), in combination with other therapies, is to be determined. It is a Phase 1b/2, open-label, international, multi-center, safety and efficacy study of G in combination with

- intensive chemotherapy regimen based on cytarabine and daunorubicin,
- low dose cytarabine (LDAC), or
- decitabine

in *previously untreated patients with AML or high-risk MDS*. The patient population includes those who

- are newly-diagnosed,
- are previously untreated, or
- have had one prior regimen with commercially-available agents for their antecedent hematologic disease.

The primary objectives of B1371003 are to evaluate the safety and efficacy of G when administered in combination with first-line treatment regimens for AML and high-risk MDS.

Study B1371003 includes two phases: Phase 1b and Phase 2. See Figure 1 for a summary of the design schema. Additionally, the Phase 2 portion contains two sub-studies:

- a randomized study among *unfit* (defined in Section 3.1.2.1) patients, hereafter referred to as P2Unfit.
- a single arm study among *fit* patients.

While Study B1371003 consists of multiple phases, the review of the efficacy of G will focus only on the P2Unfit sub-study within the Phase 2 portion. The reason for this focus is that the primary efficacy evidence as well as the basis of approval and labeling stem from this Phase 2 sub-study.

This document is organized as follows:

- Section 3 summarizes features of the P2Unfit sub-study with respect to
  - Design
  - Endpoints
  - Methods of analyses
  - Baseline characteristics

  - Patient disposition
  - Results and conclusions

- Section 4 summarizes analyses results by subgroups including those based on age, race, gender, and region.
- Section 5 discusses some important issues that came up during the review, the collective evidence, and the final conclusion.

And finally, the Appendix (Section 6) provides additional FDA-generated results. These results may be of interest in their own right but those pertaining to subgroup evaluations are not meant to be used or interpreted in any formal sense as the statistical requirements to support such usage or interpretation are not adequate.

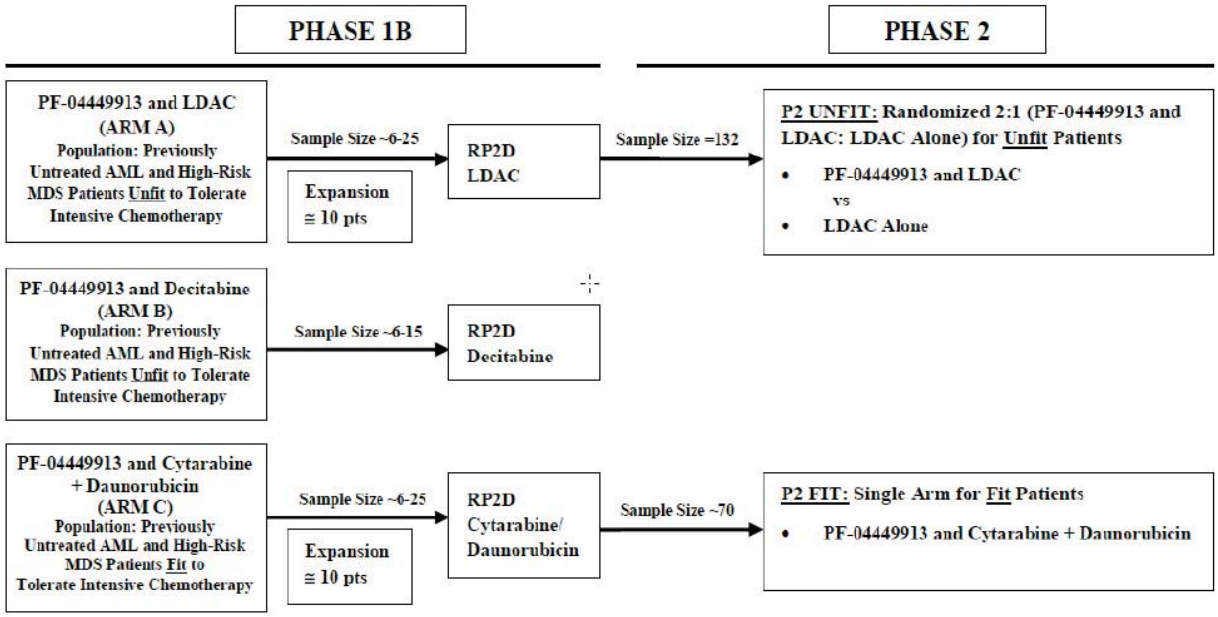

Figure 1 : Design schema for Study B1371003. **SOURCE** Pfizer (2016a, p. 9)

2.2 Data Sources

2.2.1 Data Sets Analyzed

The statistical review interacts with the following SAS data sets (XPT format), located at //CDSESUB1/evsprod/NDA210656/0001/m5/datasets/b1371003/analysis/legacy/datasets/phase-2-unfit:

- EESRV

- EFFR3
- EFFR1
- IVRS
- PRGFAC
- DEMOG
- ECOG
- LABS
- PRDIAG
- DISCON
- HRCV
- CYCLES

2.2.2 Documents Reviewed

The following documents were also reviewed:

- Clinical Study Report
- Study Protocol
- Statistical Analysis Plan

3 Statistical Evaluation

3.1 Evaluation of Efficacy

3.1.1 Study Objectives

Primary. The primary objective is to compare the overall survival (OS) between glasdegib + LDAC (G+LDAC) and LDAC alone in unfit patients with previously untreated AML or high-risk MDS.

Secondary. Secondary objectives include the following:

- To assess clinical efficacy measures (including disease-specific measures) of G+LDAC versus LDAC alone in unfit patients with previously untreated AML or high risk MDS.
- To assess the safety and tolerability of G+LDAC versus LDAC alone in unfit patients with previously untreated AML or high risk MDS.

- To evaluate the pharmacodynamics of G+LDAC versus LDAC alone in unfit patients with previously untreated AML or high risk MDS.
- To evaluate the pharmacokinetics of G
- To characterize the effects of G on QTc interval.

3.1.2 Study Design

P2Unfit initiates after Phase 1b identifies the RP2D. It is a Phase 2, randomized (2:1 ratio), open-label study that directly compares the efficacy and safety of G+LDAC to LDAC alone. Randomization is stratified by cytogenetic risk (poor vs good/intermediate). Any individual that has any of the following cytogenetic features are classified as having *poor* cytogenetic risk:

- inv(3)
- t(6;9)
- 11q23
- -5
- 05q
- -7
- abnl(17p)
- complex karyotype ($\geq$ 3 clonal abnormalities)

All others are classified as *good/intermediate*[1]. Patients are treated with G+LDAC for up to 1 year (12 cycles) or until the earlier of

- disease progression/relapse,
- patient refusal,
- unacceptable toxicity.

Upon completion of 1 year of treatment with LDAC, patients are considered to have completed the trial. Post-treatment survival status will be followed for 4 years from 1st dose. Patients who are randomized but do not start treatment will also be followed for survival.

[1] Patient risk status is captured in the Interactive Voice Registration System (IVRS) and the factors that characterize patient risk are captured in the CRF (Pfizer, 2016b Section 5.1.2).

3.1.2.1 Study Population

The study population is characterized by the inclusion (Section 6.1) and exclusion criteria (Section 6.2). Per inclusion criterion 6, a patient is classified as unfit for intensive chemotherapy if one or more of the following criteria are met:

- Age ≥ 75
- ECOG of 2
- Serum creatinine > 1.3 mg/dL
- Severe cardiac disease (eg, LVEF <45% by multi-gated acquisition [MUGA] or echocardiography [ECHO] at screening).

Per inclusion criterion 7, patients with *none* of the following criteria are considered fit for intensive chemotherapy:

- ECOG of 2
- Serum creatinine > 1.3 mg/dL
- Severe cardiac disease (eg, LVEF <45% by MUGA or ECHO at screening).

3.1.2.2 Sample Size Determination

The historical median OS for LDAC was estimated at 5 months and the expected median OS for G+LDAC is 8 months, which induces an expected HR=0.625. Based on the following design parameters

- 2:1 randomization,
- a planned accrual period of approximately 13 months,
- a follow-up period of approximately 6 months,
- a 1-sided log-rank test with one-sided $\alpha = 0.1$ (type I error) and
- one futility analysis when 46 OS events are observed (50% information, rho(1) beta spending function),

a total of 92 OS events provide 80% power to detect a hazard ratio of 0.625. A total of 132 subjects (88 in the G+LDAC arm and 44 in the LDAC arm) were randomized.

3.1.3 Study Endpoints

Primary and secondary endpoints for the P2Unfit sub-study are summarized in Table 1.

Table 1 : Endpoints of the Phase 2 randomized study among unfit patients in Study B1371003. **SOURCE** FDA-generated based on SAP.

	Endpoints
Primary	- Overall Survival (OS)
Secondary	- Complete response (CR)
	- CR with incomplete blood count recovery (CRi)
	- Morphologic Leukemia-Free State (MLFS)
	- Partial Remission (PR)
	- Partial Remission with incomplete blood count recovery (PRi)
	- Minor Response (MR)
	- Stable Disease (SD)
	- Cytogenetic Complete Response (CRc)
	- Molecular Complete Response (CRm)
	- Type, incidence, severity (graded by the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE], Version 4.0), timing, seriousness, and relatedness of adverse events.
	- Pharmacodynamic biomarkers
	- Pharmacokinetic parameters of glasdegib
	- QTc interval

Overall survival is defined as time from the date of randomization to the date of death from any cause. Patients not known to have died at the last follow-up are censored on the date they were last known to be alive.

Overall survival status is assessed every month for the first two months after discontinuation of study treatment and every two months thereafter. Assessment will continue until death or 4 years from first dose (or from time of randomization if treatment was never initiated)

3.1.4 Statistical Methodologies

3.1.4.1 Overview

As noted in the Introduction, the primary evidence of efficacy comes from the P2Unfit sub-study. As such, the summary of the statistical analyses as documented in this section pertains only to this sub-study.

3.1.4.2 Analysis Populations

The following analysis populations are used in the analyses of efficacy and safety:

- **Full Analysis Set (FAS)**. FAS consists of *all randomized patients*. Efficacy analyses of OS and response-based endpoints are FAS-based.
- **Safety Analysis Set (SaS)**. SaS consists of all enrolled patients who receive at least one dose of any study drug. Safety analyses are SaS-based.

3.1.4.3 Missingness

If missing

- **day of month**, impute as 1st day of month.
- **day and month**, impute as January 1 as long as time duration > 0. For OS, the latest contact date in that year will be used as the date of death for patients with partial death date.

Other than the date imputation listed above, there is no imputation of missing data for the primary and secondary efficacy analyses.

3.1.4.4 Analyses of Efficacy

Efficacy analyses specified in the SAP are summarized in Table 2 below. For response-based secondary efficacy endpoints such as CR, primary analyses are based on derived response while secondary analyses are based on investigator assessment.

Table 2 : Summary of efficacy analyses to be performed for the P2 Unfit sub-study. **SOURCE** Excerpted from Table 2 in the statistical analysis plan.

Endpoint	**Analysis Population**	**Method**	**Missing Data**	**Objective**
OS	FAS	Stratified log-rank test (1-sided, $\alpha = 0.10$) Kaplan-Meier estimate	Censoring rules apply	Primary analysis
OS	FAS	Unstratified log-rank test (1-sided, $\alpha = 0.10$), Cox model, Kaplan-Meier estimate	Censoring rules apply	Secondary analysis of primary endpoint. Cox model to be run with two different set of stratification factors: as per IVRS (main Cox model analysis) and as per CRF (secondary Cox model analysis)
OS	FAS	Stratified log-rank test (1-sided, $\alpha = 0.10$) Kaplan-Meier estimate	Censoring upon receiving transplant	Sensitivity Analysis of primary endpoint
CR	FAS	χ^2 test, CMH test, Proportion with CI using normal approximation	Without known CR as non-responders	Secondary analysis (derived response and investigator data separately)
AML-specific endpoints, CRi, CR/CRi, Morphologic Leukemia-Free State, Partial Remission (PR), Partial	AML patients in FAS	Proportion with exact CI	N/A	Secondary Analysis (derived response and investigator data separately). Note: CRm

Remission with incomplete blood count recovery (PRi), Minor Response (MR), Stable Disease (SD), Cytogenetic Complete Response, and Molecular Complete Response (CRm)				exists only as investigator data
MDS-specific endpoints, CRi(derived only), marrow CR , Partial Remission (PR), Stable Disease (SD), Partial or Complete Cytogenetic Response,	MDS patients in FAS	Proportion with exact CI	N/A	Secondary Analysis (derived response and investigator data separately). Note: Partial Cytogenetic Response will only exist as investigator data

3.1.5 Baseline Characteristics

Table 3 summarizes some relevant baseline characteristics by treatment arms. In general, baseline factors seem balance. However, several features are noticeably unbalanced:

- Gender. G+LDAC has a higher proportion of male patients.
- Cytogenetic Risk. LDAC has a higher proportion of Poor cytogenetic risk.
- European Leukemia Network (ELN) Criteria. LDAC arm has a higher proportion of Adverse patients.

Table 3 : Baseline factors among unfit AML patients in Study B1371003. **SOURCE** FDA-generated.

Subgroup	G+LDAC	LDAC	Total
Overall	78 (67.2%)	38 (32.8%)	116 (100%)
Age Group			
Age < 65	1 (1.3%)	1 (2.6%)	2 (1.7%)
65 ≤ Age < 75	29 (37.2%)	14 (36.8%)	43 (37.1%)
75 ≤ Age < 85	41 (52.6%)	23 (60.5%)	64 (55.2%)
Age ≥ 85	7 (9%)		7 (6%)
Gender			
Female	19 (24.4%)	15 (39.5%)	34 (29.3%)
Male	59 (75.6%)	23 (60.5%)	82 (70.7%)
Race			
Asian	2 (2.6%)		2 (1.7%)
Black	1 (1.3%)		1 (0.9%)
White	75 (96.2%)	38 (100%)	113 (97.4%)
ECOG Status			
0	10 (12.8%)	3 (7.9%)	13 (11.2%)
1	26 (33.3%)	17 (44.7%)	43 (37.1%)
2	41 (52.6%)	18 (47.4%)	59 (50.9%)
Missing	1 (1.3%)		1 (0.9%)
Cytogenetic Risk			

Good/Intermediate	49 (62.8%)	21 (55.3%)	70 (60.3%)
Poor	29 (37.2%)	17 (44.7%)	46 (39.7%)
ELN			
Favorable	5 (6.4%)	3 (7.9%)	8 (6.9%)
Intermediate-I	27 (34.6%)	11 (28.9%)	38 (32.8%)
Intermediate-II	21 (26.9%)	8 (21.1%)	29 (25%)
Adverse	25 (32.1%)	16 (42.1%)	41 (35.3%)
Haeme History			
2ndary AML	40 (51.3%)	20 (52.6%)	60 (51.7%)
de Novo AML	38 (48.7%)	18 (47.4%)	56 (48.3%)

As the P2Unfit sub-study enrolls patients who are unfit for high-dose chemotherapy, Table 4 summarizes the unfit criteria distributions by treatment arms. Unfit criteria seem reasonably balance across the two arms. However, the G+LDAC arm has a higher proportion of patients with severe cardiac disease and having two or more unfit criteria.

Table 4 : Baseline unfit criteria among AML patients in Study B1371003. **SOURCE** FDA-generated.

Subgroup	G+LDAC	LDAC	Total
Overall	78 (67.2%)	38 (32.8%)	116 (100%)
Age Group			
≥ 75	48 (61.5%)	23 (60.5%)	71 (61.2%)
< 75	30 (38.5%)	15 (39.5%)	45 (38.8%)
Serum Creatinine			
≤ 1.3 mg/dL	63 (80.8%)	33 (86.8%)	96 (82.8%)
> 1.3 mg/dL	15 (19.2%)	5 (13.2%)	20 (17.2%)
ECOG Status			
ECOG = 0,1	37 (47.4%)	20 (52.6%)	57 (49.1%)
ECOG = 2	41 (52.6%)	18 (47.4%)	59 (50.9%)
Cardiac Disease			
Not Severe	26 (33.3%)	18 (47.4%)	44 (37.9%)

Severe	52 (66.7%)	20 (52.6%)	72 (62.1%)
No. Unfit Criteria			
1 Unfit Criterion	23 (29.5%)	17 (44.7%)	40 (34.5%)
2+ Unfit Criteria	55 (70.5%)	21 (55.3%)	76 (65.5%)
No. Unfit Criteria Met			
1	23 (29.5%)	17 (44.7%)	40 (34.5%)
2	34 (43.6%)	15 (39.5%)	49 (42.2%)
3	19 (24.4%)	5 (13.2%)	24 (20.7%)
4	2 (2.6%)	1 (2.6%)	3 (2.6%)

3.1.6 Patient Disposition

Patient disposition is summarized in Figure 2.

Number (%) of patients		Glasdegib 100 mg+LDAC	LDAC Alone
Screened	132		
Assigned to study treatment		88	44
Treated		84	41
Treatment completed		0	0
Treatment discontinued		80 (95.2)	41 (100.0)
Patient died		10 (11.9)	11 (26.8)
Global deterioration of health status		3 (3.6)	1 (2.4)
Insufficient clinical response		37 (44.0)	15 (36.6)
Other		3 (3.6)	0
Protocol violation		1 (1.2)	0
Patient refused continued treatment for reason other than AE		5 (6.0)	2 (4.9)
AEs - relation to study treatments[a] not defined		13 (15.5)	10 (24.4)
AEs - related to study treatments[a]		8 (9.5)	2 (4.9)
Treatment ongoing at cutoff date		4 (4.8)	0
Study completed		0	0
Study discontinued		72 (81.8)	43 (97.7)
Patient died		68 (77.3)	41 (93.2)
Lost to follow-up		1 (1.1)	0
Patient refused further follow-up		3 (3.4)	2 (4.5)
Study ongoing at cutoff date		16 (18.2)	1 (2.3)

Figure 2 : Patient disposition. **SOURCE** Table 6 from CSR (p. 108).

3.1.7 Results and Conclusions

3.1.7.1 Overview

The clinical study report (CSR) summarizes the results based on one-sided $\alpha = 0.10$ and 80% confidence intervals. The analysis results presented in this section use one-sided $\alpha = 0.025$ and 95% confidence intervals.

As noted earlier, the P2Unfit sub-study randomizes patients who either have MDS or AML disease. However, the proportion of MDS patients in the study cohort is small relative to the entire study cohort:

- Of 132 randomized patients, 16 (or 12%) are MDS patients.
- Of 16 MDS patients, 10 are in the G+LDAC arm and 6 are in the LDAC arm.

To the extent that MDS is viewed as a distinct disease population different from AML, it follows that the size of the MDS cohort is not adequate to support statements about efficacy of G+LDAC among MDS patients. Therefore, results summarized in this section pertain only to AML patients.

For completeness however, note that the P2Unfit sub-study, as designed, is positive in the sense that G+LDAC is superior to LDAC alone with respect to OS among randomized patients who either have MDS or AML. These results are provided in Section 6.6 and are consistent with those presented by the sponsor.

> ***Reviewer Comment****: The Agency recognizes that focusing on the AML subgroup may present conceptual challenges as these analyses are not prespecified; nominal analyses and post-hoc multiplicity adjustments are not defensible. However, the proportion of statistical information leading to statistical significance of the overall FAS results comes mostly from the AML cohort. Therefore, it is not statistically clear that these results can be extended to the MDS cohort. Hence, we focus on the AML subset and the statistical approaches as specified in the SAP are kept as-is.*

3.1.7.2 Overall Survival: AML Only

The primary endpoint is overall survival. The following analysis results use IVRS-based cytogenetic risk information. Median follow-up times, as computed by reverse[2] Kaplan-Meier, are

- G+LDAC: 21.7 months.
- LDAC: 20.1 months.

[2] The approach examines the censoring distribution over time. Median follow-up time is interpreted as time to which half of the patients are censored. In general, this is not very accurate if there are few censoring.

Figure 3 summarizes the OS experience of AML patients. The stratified log-rank test and the estimated hazard ratio aggregated over the cytogenetic risk-strata suggest superiority of G+LDAC over LDAC.

Figure 4 and Figure 5 summarize the stratum-specific OS experience of the AML patients. **NOTE** Due to low event counts within each stratum, the statistical bases for making formal statements about the differences between the two arms may not be adequate. Nevertheless, stratum-specific results do not appear to contradict the overall result.

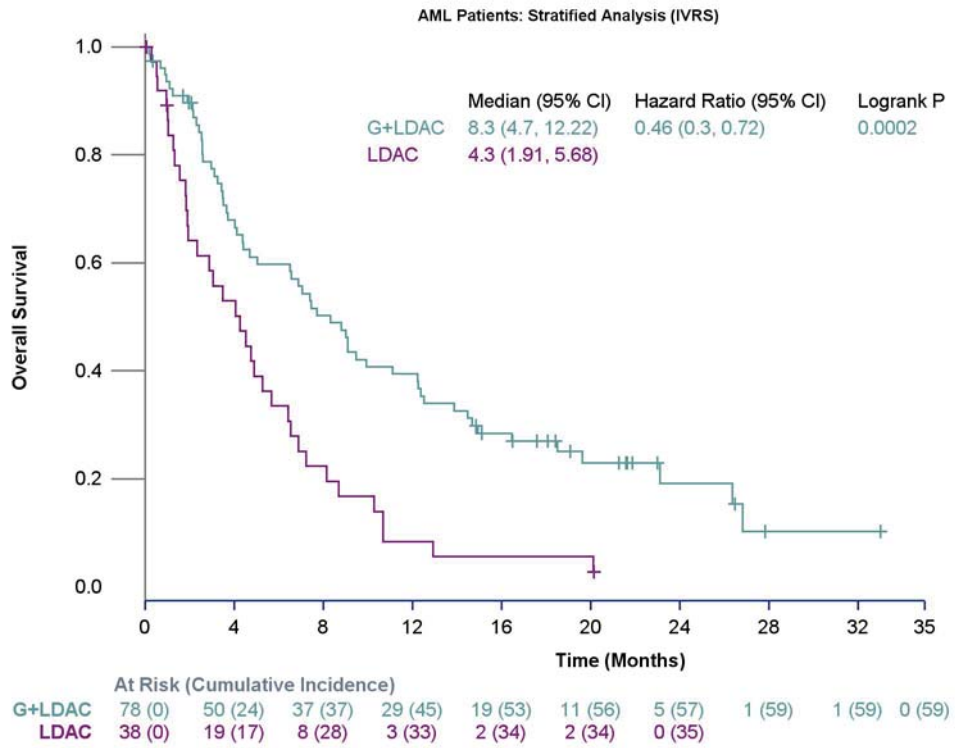

Figure 3 : Overall survival contours for AML patients. The hazard ratio and the log-rank test (1-sided p) are calculated by incorporating cytogenetic risk strata. **SOURCE** FDA-generated.

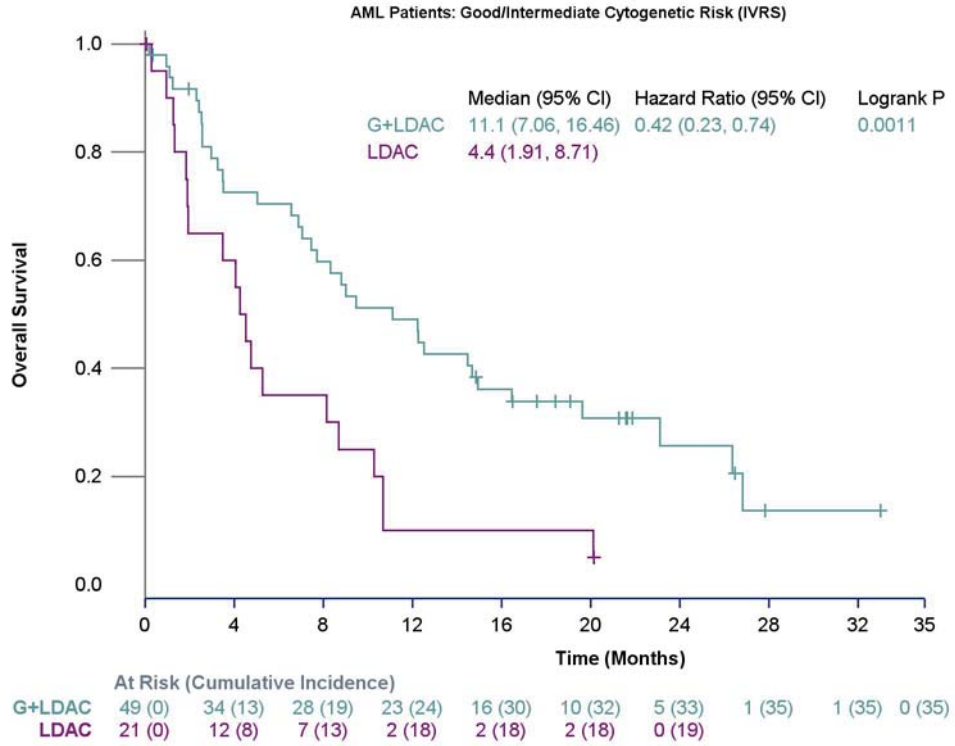

Figure 4 : Overall survival contours among AML patients within the Good/Intermediate cytogenetic risk stratum. **SOURCE** FDA-generated.

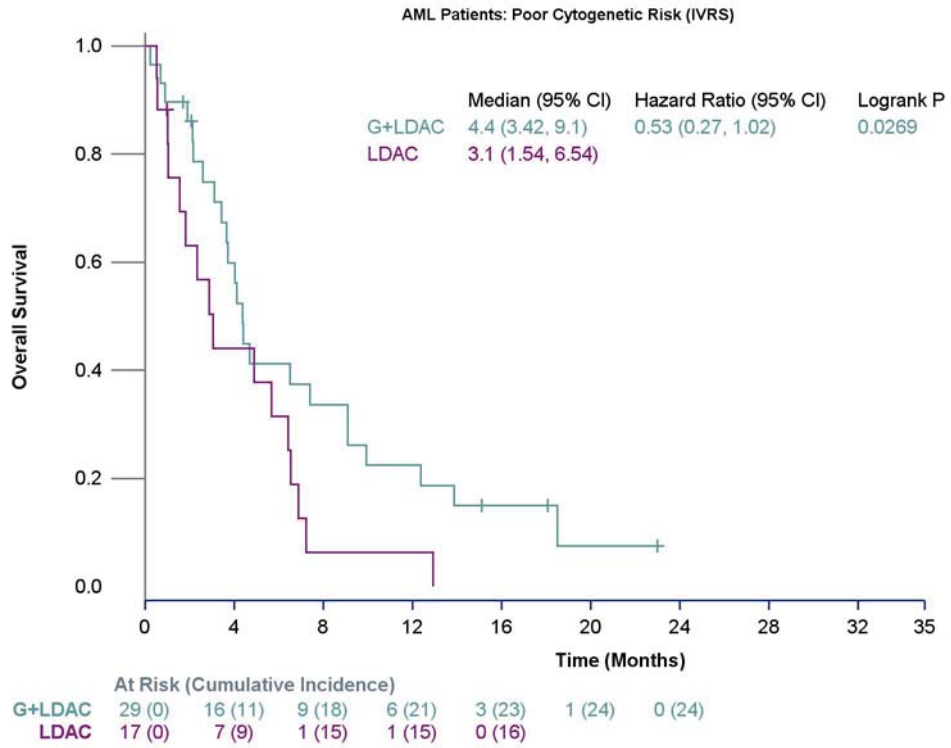

Figure 5 : Overall survival contours among AML patients within the Poor cytogenetic risk stratum. **SOURCE** FDA-generated.

For AML results in which cytogenetic risk information is determined by CRF, see Section 6.3. The overall conclusion regarding efficacy of G+LDAC is invariant whether the source of the cytogenetic risk is IVRS- or CRF- based.

3.1.7.3 Complete Remission: AML Only

Morphologic complete remission (CR) is a secondary endpoint and rates are summarized in Figure 6. The estimated difference in CR proportions and 95% CI are:

- difference in CR proportions: -15.3% (<0 favors G+LDAC)
- exact 95% CI for difference in proportions: (-25.9%, -3.0%)

Some additional subgroup context is also provided in Figure 6. Although sample size and the number of CRs are small, subgroup CR results appear consistent with the overall CR result.

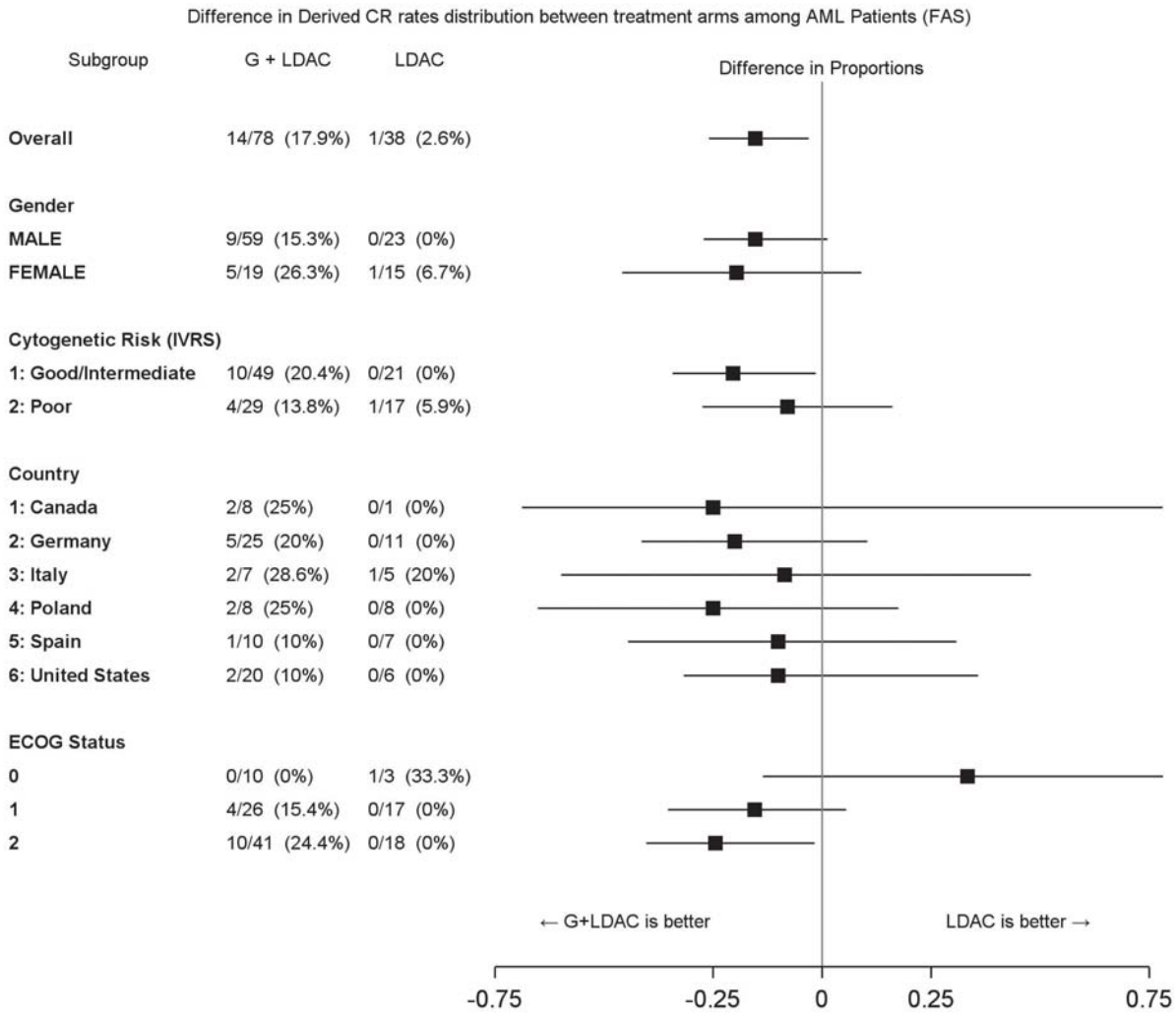

Figure 6 : Complete remission among AML patients. Confidence intervals are calculated using an exact method. **SOURCE** FDA-generated.

***Reviewer Comment**: For labeling purpose, FDA-adjudicated AML status is used (see Section 5.1.4 and Section 6.4.3 for additional details). Although the FDA-adjudicated CR rates and their difference are different from those presented here, the difference is not meaningful.*

Additional characterization of complete remission across treatment arms are provided in Table 5. Among responders,

- G+LDAC

  - Median time to CR is 60 days.
  - Median duration of CR is about 299 days.
- LDAC
  - Median time to CR is 170 days.
  - Median duration of CR is 91 days.

***Reviewer Comment**: As there is only one CR in the LDAC arm, any statistical characterization of time to CR or duration of CR for the LDAC arm in this study is highly imprecise and potentially misleading.*

Table 5 : Complete remission among AML patients in Study B1371003 using derived response. **SOURCE** FDA-generated.

	G+LDAC	**LDAC**
Time to CR (Days)		
N	14	1
Mean (Stddev)	71.29 (33.17)	170 (.)
Min / Max	36 / 170	170 / 170
Q1 / Median / Q3 / P90	57 / 59.5 / 68 / 111	170 / 170 / 170 / 170
Duration of CR (Days)		
N	14	1
Mean (Stddev)	339.07 (241.84)	91 (.)
Min / Max	1 / 841	91 / 91
Q1 / Median / Q3 / P90	175 / 299 / 489 / 610	91 / 91 / 91 / 91

4 Subgroup Findings

4.1 By Gender, Race, Age, and Region

Table 6 summarizes the hazard ratio for OS by age, gender, race, and region. For race, there are only 3 non-whites which render the hazard ratio in the non-whites subset numerically infeasible. Overall, the amount of statistical information within each subgroup is small. As

such, the point estimates are likely to be unstable and the confidence intervals are unlikely to be valid. In general, there is little basis for concluding subgroup differences with respect to age, gender, race, and region.

Table 6 : Hazard ratios by Age, Race, Gender, and Region. The treatment columns have the format A/B/C where A = Number of deaths, B = Number censored, and C = Total number of patients. **SOURCE** FDA-generated.

Subgroup	G + LDAC	LDAC	HR	Lower95	Upper95
Overall	59/19/78	35/3/38	0.46	0.2988	0.7166
Age					
< 75	21/9/30	13/2/15	0.27	0.1303	0.565
>= 75	38/10/48	22/1/23	0.6	0.3494	1.02
Gender					
Female	13/6/19	13/2/15	0.5	0.2298	1.095
Male	46/13/59	22/1/23	0.42	0.2483	0.7195
Race					
Other	3/0/3	0/0/0	-	-	-
White	56/19/75	35/3/38	0.46	0.2972	0.7167
Region					
North America	24/4/28	7/0/7	0.54	0.2278	1.301
Europe	35/15/50	28/3/31	0.41	0.2442	0.6838

4.2 Other Subgroup Populations

The Agency also explored additional analyses in which subgroups were defined by levels of the unfit criteria. These results are presented in the Appendix (see Section 6.5).

5 Summary and Conclusions

5.1 Statistical and Other Issues

5.1.1 Overview

There are no major statistical issues that have the potential to invalidate the overall efficacy conclusion that glasdegib, in combination with low-dose cytarabine, is superior to low-dose cytarabine alone as characterized by overall survival and complete remission. Although the sponsor presented results based on one-sided $\alpha = 0.10$ in the CSR, the conclusion remains intact under the more stringent one-sided $\alpha = 0.025$ criterion.

Cytogenetic risk levels are used to specify baseline hazards in the estimation of the hazard ratio and to compute the stratified logrank test. While there are some differences between IVRS-identified and CRF-identified cytognetic risk status, these differences have little impact on the overall conclusion that glasdegib, in combination with low-dose cytarabine, is superior to low-dose cytarabine alone.

There are however some issues that should be mentioned as part of this review. Some of them have previously been raised in the form of **Reviewer Comment** throughout the document.

5.1.2 Multiple Endpoints

As noted in Section 3.1.3, the primary endpoint is OS and there are multiple secondary endpoints with no formal plan to address multiple testing. Without such a plan, complete remission and other endpoints can reasonably be viewed as exploratory endpoints. Nevertheless, the CR rates between the two arms are very different in favor of G+LDAC. As noted earlier, characterization of duration of CR for the LDAC arm is difficult as there is only one CR.

5.1.3 Baseline Imbalance

An examination of baseline characteristics in Section 3.1.5 identified notable differences in the baseline distributions of various attributes between the two arms; for example,

- Gender,
- ECOG status, and
- Cardiac disease severity.

It is not clear as to the reasons for the observed imbalance as the study was randomized. It is possible that the small sample size in LDAC arm may have contributed to the imbalance. The Agency conducted additional sensitivity analyses to examine the behavior of the hazard ratio under various models:

- Model 1: Trt + G (Gender)
- Model 2: Trt + S (Serum Creatinine)
- Model 3: Trt + E (ECOG)
- Model 4: Trt + C (Cardiac Disease Severity)
- Model 5: Trt + A (Age)
- Model 6: Trt + G + S + E + C + A

The variable Trt is a treatment indicator with value 1 for the combination therapy and 0 for the monotherapy. As shown in Table 7, the superiority of G+LDAC over LDAC alone continues to hold after adjusting for potentially imbalanced covariates. Whether these additional adjusted analyses adequately address the imbalance problem is an open question. What these results provide is a sense of robustness. These results seem to suggest that the degree of baseline imbalance is unlikely to invalidate the efficacy conclusion.

Table 7 : Sensitivity analyses adjusting for baseline attributes. Hazard ratios are estimated by Cox regression, stratified by cytogenetic risk. **SOURCE** FDA-generated.

Model	**Hazard Ratio**	**Lower 95**	**Upper 95**
Models			
1: Trt + G	0.44	0.28	0.69
2: Trt + S	0.46	0.30	0.71
3: Trt + E	0.46	0.29	0.73
4: Trt + C	0.46	0.30	0.72
5: Trt + A	0.46	0.29	0.71
6: Trt + G + S + E + C + A	0.44	0.28	0.71

5.1.4 Unconfirmed AML Status

Per the clinical review, one patient[3] in the G+LDAC arm was classified as having AML. However, the Agency could not confirm this patient's AML status. Additional analyses were undertaken in which the patient in question was removed from the study cohort. The

[3] PID = B1371003 1056 10562001.

overall survival results, presented in Section 6.4, indicate that statements about the superiority of glasdegib, in combination with LDAC, over LDAC alone, continue to hold.

CR conclusions excluding the patient in question also continue to suggest the superiority of G+LDAC over LDAC.

5.2 Collective Evidence

The pivotal study in which the efficacy of glasdegib in combination with low-dose cytarabine (G+LDAC) is established is a randomized sub-study within Study B1371003, a Phase 1b/2 study comparing the efficacy of G+LDAC to that of LDAC alone. The patient population consists of AML and MDS patients who are not eligible for high-dose chemotherapy or for whom high-dose chemotherapy is not administered. Per the sponsor's terminology, these patients are considered *unfit* for high-dose chemotherapy.

The primary endpoint is overall survival (OS).

For the set of randomized AML/MDS patients, the B1371003 randomized sub-study met its primary OS endpoint:

- HR (95% CI) = 0.51 (0.34, 0.77) in favor of G+LDAC.
- one-sided log-rank $p = 0.0004$.
- median time to OS favoring G+LDAC
  - 8.8 (5.0, 11.7) months for G+LDAC
  - 4.9 (2.9, 6.5) months for LDAC

The focus of this review, however, is not the set of all randomized AML and MDS patients. Rather, the review focuses on the set of all randomized AML patients. The reason for this focus stems from the fact that the size of the MDS disease subcohort is approximately 12% of the entire study cohort: 10 in the G+LDAC arm and 6 in the LDAC arm. With respect to OS (excluding one patient whose baseline AML status was indeterminate per FDA's assessment), G+LDAC is superior to LDAC alone as characterized by the following metrics:

- HR = 0.46 (0.3, 0.71).
- one-sided log-rank $p = 0.0002$.
- median time to OS of 8.3 months for G+LDAC and 4.3 months for LDAC.

An analysis comparing the rate of complete remission (excluding one patient whose baseline AML status was indeterminate per FDA's assessment) also supports the position that G+LDAC is superior to LDAC alone:

- LDAC: CR = 1/37 (2.6%)
- G+LDAC: CR = 14/77 (18.2%)
- Difference (Exact 95% CI): -15.6% (-26.6%, -1.0%)

5.3 Conclusions and Recommendations

Based on the results submitted by the sponsor and the additional results stemming from the Agency's own analyses, the data provide adequate evidence to support the claim that glasdegib in combination with low-dose cytarabine is efficacious in the sense that it is superior to low-dose cytarabine alone with respect to overall survival.

6 Appendix

6.1 A: Inclusion Criteria

Table 8 : Inclusion criteria for Study B1371003. Patients must meet all of these criteria to be eligible for enrollment into the study.

Criteria	Description
1	Patients with AML or RAEB-2 High-Risk MDS who are newly diagnosed according to the WHO 2008 Classification and previously untreated. Eligible patients with MDS, as well as eligible patients with AML arising from an antecedent hematologic disease (AHD) or MDS, may have had one prior regimen with commercially-available agent(s) (eg, azacitidine or decitabine) for the treatment of their prior hematologic disease. The patients may not have had any prior therapy for their AML.
2	AML patients include de-novo AML, AML evolving from MDS or other AHD and AML after previous cytotoxic therapy or radiation (secondary AML). - For a diagnosis of AML, a bone marrow blast count of 20% or more is required. - For AML defined by cytogenetic aberrations t(8;21), inv(16) or t(16;16) and some cases of erythroleukemia, the proportion of bone marrow blasts may be <20%. - In AML FAB M6a (erythroid leukemia) $\geq$ 20% of non-erythroid cells in the bone marrow must be leukemic blasts and $\geq$ 50% of the cells are erythroid precursors. - In AML with monocytic or myelomonocytic differentiation, monoblasts and promonocytes, but not abnormal monocytes, are counted as blast equivalents.
3	For a diagnosis of high-risk Myelodysplastic Syndrome RAEB-2 the patient must have 10-19% bone marrow blasts.
4	$\geq$ 18 years old for patients enrolled in Phase 1B and P2 Fit Arm. $\geq$ 55 years old for patients enrolled in the P2 Unfit Arms.
5	ECOG Performance status of 0, 1, 2
6	For patients with AML or High-Risk MDS who have one or more of the criteria below are considered unfit for intensive chemotherapy and are eligible for Phase 1B Arms A and B or P2 Unfit Arms:

	- Age ≥ 75 years. - ECOG of 2. - Serum creatinine >1.3 mg/dL. - Severe cardiac disease (eg, LVEF <45% by multi-gated acquisition [MUGA] or echocardiography [ECHO] at screening).
7	Patients with AML or high risk MDS and have none of the following criteria are considered fit for more intensive chemotherapy and are only eligible for Phase 1B Arm C or P2 Fit Arm: - ECOG of 2. - Serum creatinine >1.3 mg/dL. - Severe cardiac disease (eg, LVEF <45% by MUGA or ECHO at screening).
8	Adequate Organ Function as defined by the following: - Serum aspartate aminotransferase (AST) and serum alanine aminotransferase (ALT) ≤ 3 x upper limit of normal (ULN), or AST and ALT ≤ 5 x ULN if liver function abnormalities are due to underlying malignancy. - Total serum bilirubin ≤ 2 x ULN (except patients with documented Gilbert's syndrome). - Serum creatinine ≤ 1.5 x ULN or estimated creatinine clearance ≥ 60 mL/min as calculated using the method standard for the institution.
9	All anti-cancer treatments (unless specified) should be discontinued ≥ 2 weeks from study entry, for example: targeted chemotherapy, radiotherapy, investigational agents, hormones, anagrelide or cytokines. - For control of rapidly progressing leukemia, hydroxyurea or leukopheresis may be used before and for up to 1 week after first dose of PF-04449913. - Patients with controlled CNS leukemia (documented by two consecutive assessments of zero blast count in cerebrospinal fluid), and who are still receiving intra-thecal (IT) therapy at study entry are considered eligible, and will continue to receive IT therapy.
10	Resolved acute effects of any prior therapy to baseline severity or Grade ≤ 1 CTCAE except for AEs not constituting a safety risk by investigator judgement.

11	Serum/urine pregnancy test (for females of childbearing potential) that is negative at screening and immediately prior to initiation of treatment (first dose). Male and female patients of childbearing potential must agree to use a highly effective method of contraception throughout the study and for at least 180 days after the last dose of assigned treatment. A patient is of childbearing potential if, in the opinion of the investigator, he/she is biologically capable of having children and is sexually active.
12	Evidence of a personally signed and dated informed consent document indicating that the patient (or a legal representative) has been informed of all pertinent aspects of the study.
13	Willingness and ability to comply with the study scheduled visits, treatment plans, laboratory tests and other procedures.

6.2 B: Exclusion Criteria

Table 9 : Exclusion criteria for Study B1371003. Patients who meet any one of these criteria are ineligible for enrollment.

Criteria	Description
1	Acute Promyelocytic Leukemia (APL) patients with t(15;17) or patients with a t(9:22) cytogenetic translocation for any component of the study.
2	Hyperleukocytosis (leukocytes $\geq$ 30 x 10^9/L) at study entry. These patients may be treated with hydroxyurea or receive leukopheresis treatment according to routine practice, and enrolled in the study when the leukocyte count falls below 30 x 109/L.
3	Patients known to be refractory to platelet or packed red cell transfusions per Institutional Guidelines, or a patient who refuses blood product support.
4	Patients with active malignancy with the exception of basal cell carcinoma, non-melanoma skin cancer, cervical carcinoma-in-situ. Other prior or concurrent malignancies will be considered on a case-by-case basis.
5	For fit patients (Phase 1B Arm C or P2 Fit Arm): - LVEF <45% by ECHO or MUGA scan - Cumulative anthracyline dose equivalent of $\geq$ 250 mg/m2 of daunorubicin or $\geq$ 125mg/m2 of idarubicin

6	Any one of the following currently or in the previous 6 months: myocardial infarction, congenital long QT syndrome, torsades de pointes or clinically significant ventricular arrhythmias.
7	QTc interval >470 msec using the Fridericia (QTcF).
8	Patients with an active, life threatening or clinically significant uncontrolled systemic infection.
9	Patients with known active uncontrolled central nervous system (CNS) leukemia.
10	Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness or active Hepatitis B or C infection.
11	Known malabsorption syndrome or other condition that may impair absorption of study medication (eg, gastrectomy or lap band).
12	Major surgery or radiation within 4 weeks of starting study treatment.
13	Prior treatment with: - a Hedgehog inhibitor at any time. - an investigational agent for the treatment of an antecedent hematologic disease (AHD).
14	treatment of primary diagnosis or AHD with decitabine or azacitidine (Phase 1B Arm B only), or cytarabine (Phase 1B Arm A and P2 Unfit only).
15	The presence of any one of the following hypersensitivities: - For patients receiving cytarabine on study (Phase 1B Arm A, P2 Fit, and P2 Unfit Arms only): Hypersensitivity to cytarabine (not including drug fever or exanthema). rm C and P2 Fit Arm): hypersensitivity to daunorubicin. - For patients receiving decitabine on study (Phase 1B Arm B): hypersensitivity to decitabine. - For patients receiving daunorubicin on study (Phase 1B Arm C and P2 Fit Arm): hypersensitivity to daunorubicin.
16	Concurrent treatment with any investigational or approved oncology agents (unless specified in the protocol).
17	Concurrent administration of herbal preparations.
18	Current use at time of study entry (defined in Section 6) or anticipated need for drugs that are known strong CYP3A4/5 inducers. Please refer to Section 5.5 for list of prohibited inducers.

19	Current drug or alcohol abuse.
20	Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and
21	Patients who are investigational site staff members or relatives of those site staff members or patients who are Pfizer employees directly involved in the conduct of the trial.
22	Pregnant females; breastfeeding females; males and females of childbearing potential not using highly effective contraception or not agreeing to continue highly effective contraception for at least 180 days after last dose of investigational product; male
23	Recent or active suicidal ideation or behavior.

6.3 C: Overall Survival for AML Patients per CRF-Based Cytogenetic Risk

The following analysis results use cytogenetic risk information as determined by CRF. The results are consistent with IVRS as presented in Section 3.1.7.2.

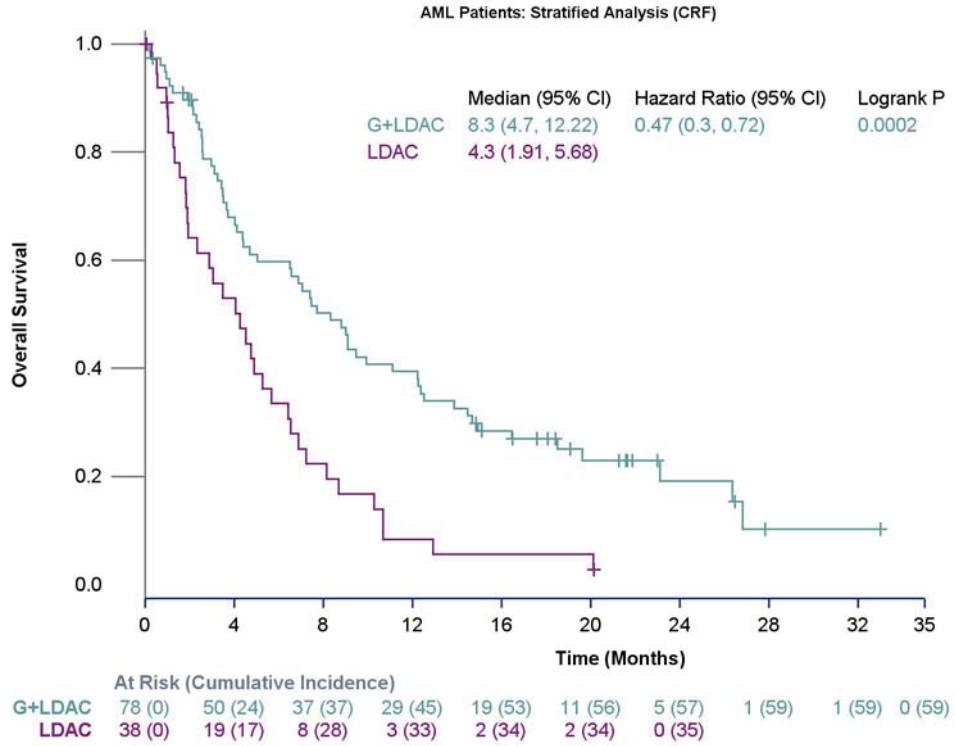

Figure 7 : Overall survival contours for AML patients. Hazard ratio and log-rank test are calculated by aggregating over cytogenetic risk strata. **SOURCE** FDA-generated.

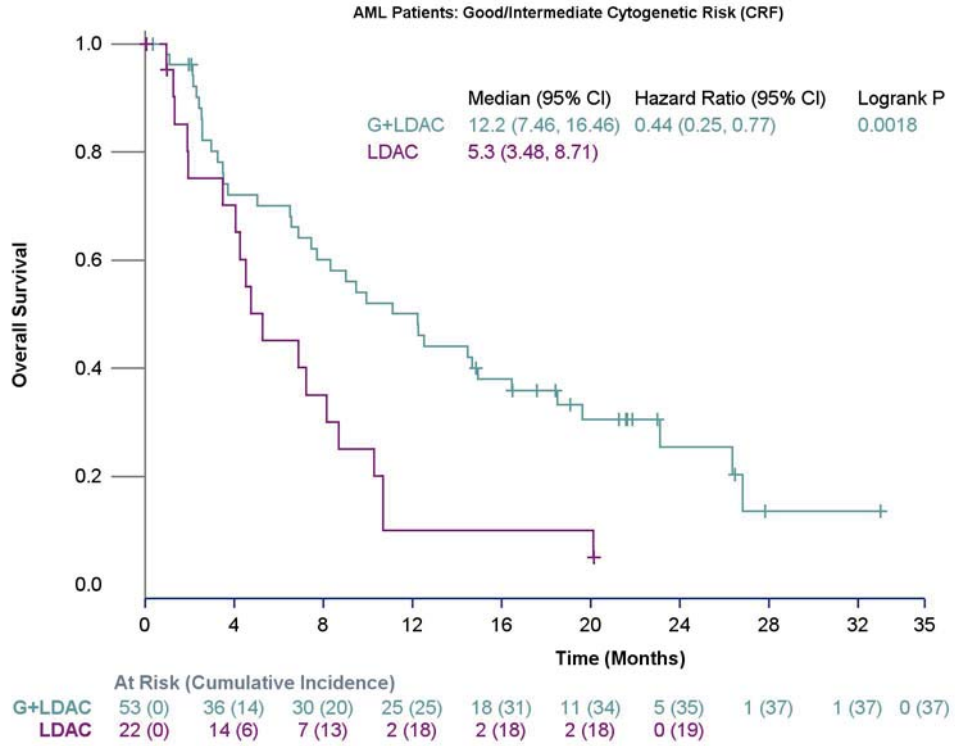

Figure 8 : Overall survival contours among AML patients within the Good/Intermediate cytogenetic risk stratum. **SOURCE** FDA-generated.

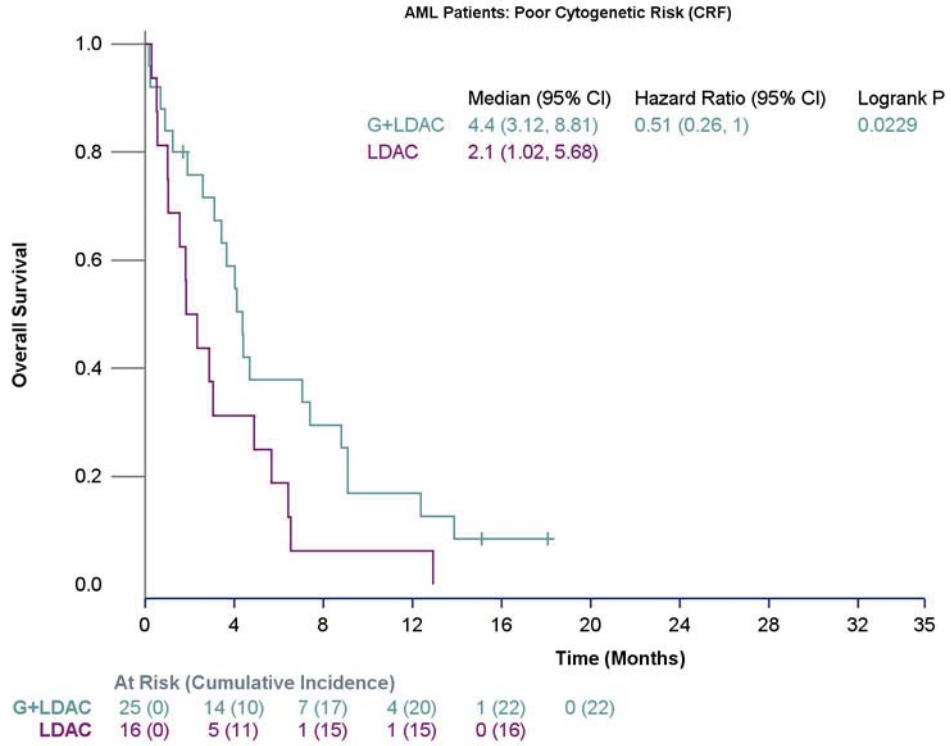

Figure 9 : Overall survival contours among AML patients within the Poor cytogenetic risk stratum. **SOURCE** FDA-generated.

6.4 D: Excluding Patient (b) (4)

6.4.1 OS: IVRS-Based Cytogenetic Risk

The following analysis results use cytogenetic risk information as determined by IVRS.

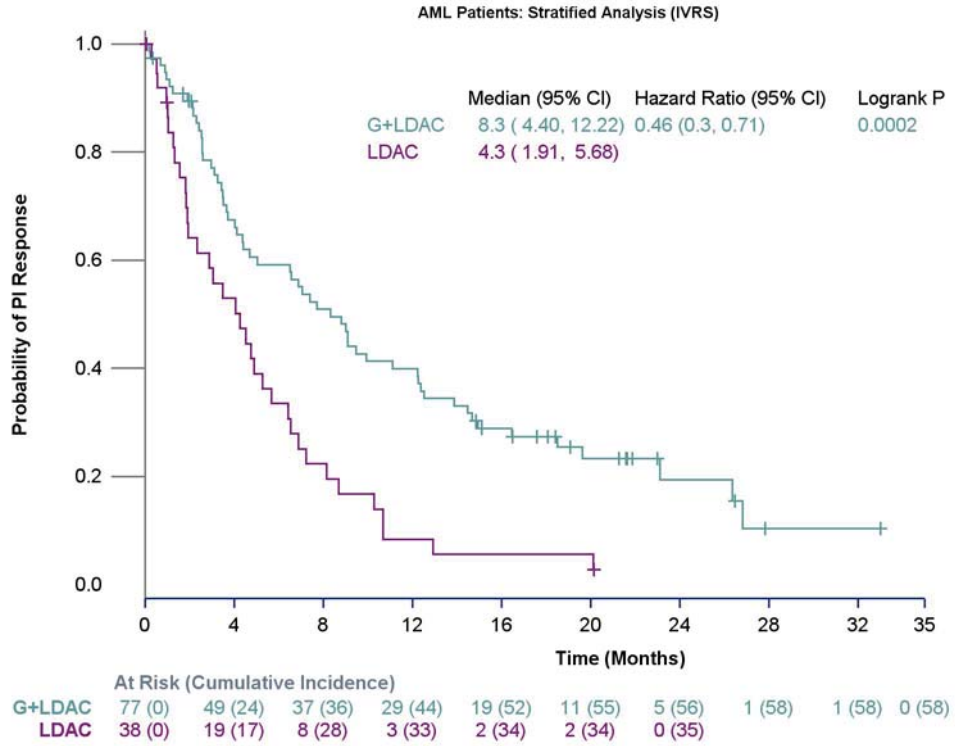

Figure 10 : Overall survival contours for AML patients (excluding patient (b) (6)). Hazard ratio and log-rank test are calculated by aggregating over cytogenetic risk strata.
SOURCE FDA-generated.

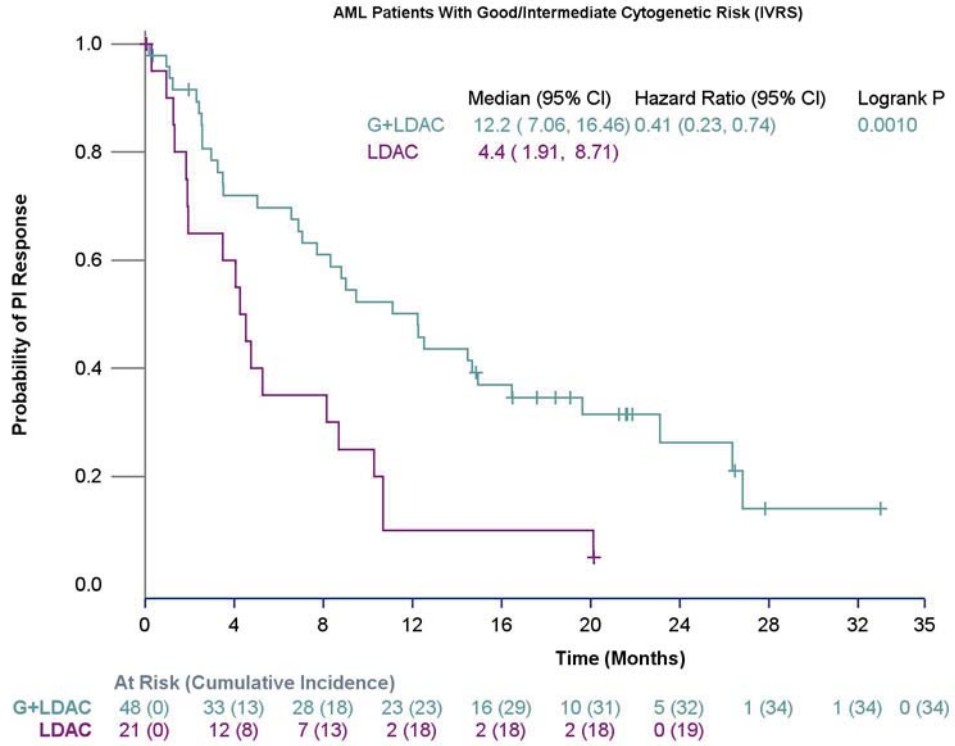

Figure 11 : Overall survival contours among AML patients (excluding patient (b) (6)) within the Good/Intermediate cytogenetic risk stratum. **SOURCE** FDA-generated.

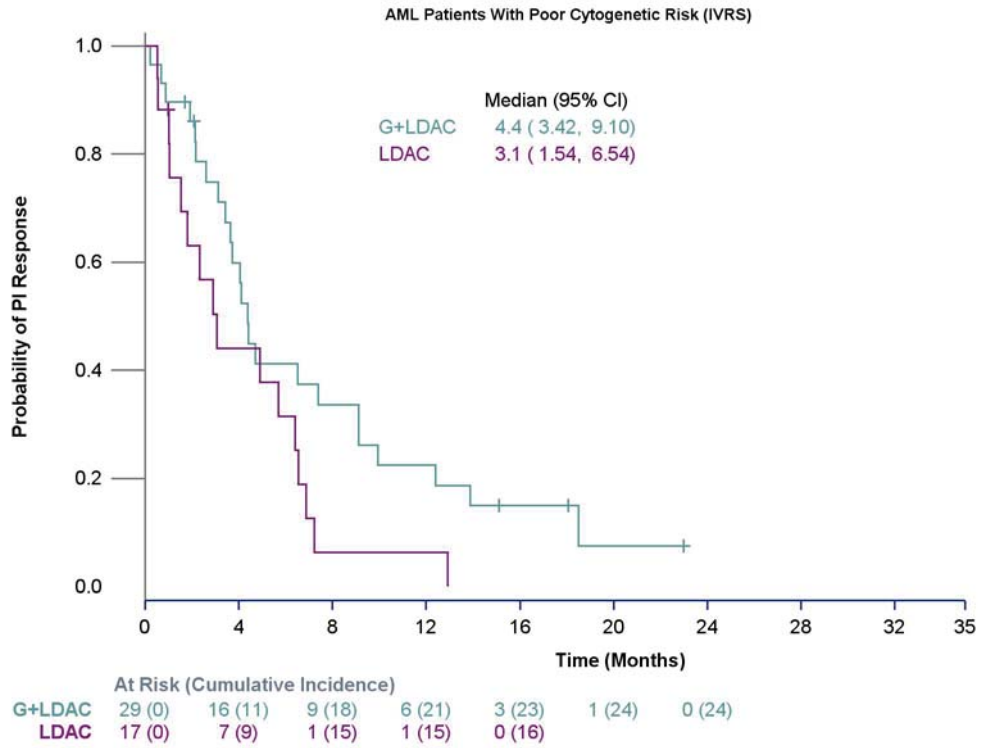

Figure 12 : Overall survival contours among AML patients (excluding patient (b) (6)) within the Poor cytogenetic risk stratum. **SOURCE** FDA-generated.

6.4.2 OS: CRF-Based Cytogenetic Risk

The following analysis results use cytogenetic risk information as determined by the CRF.

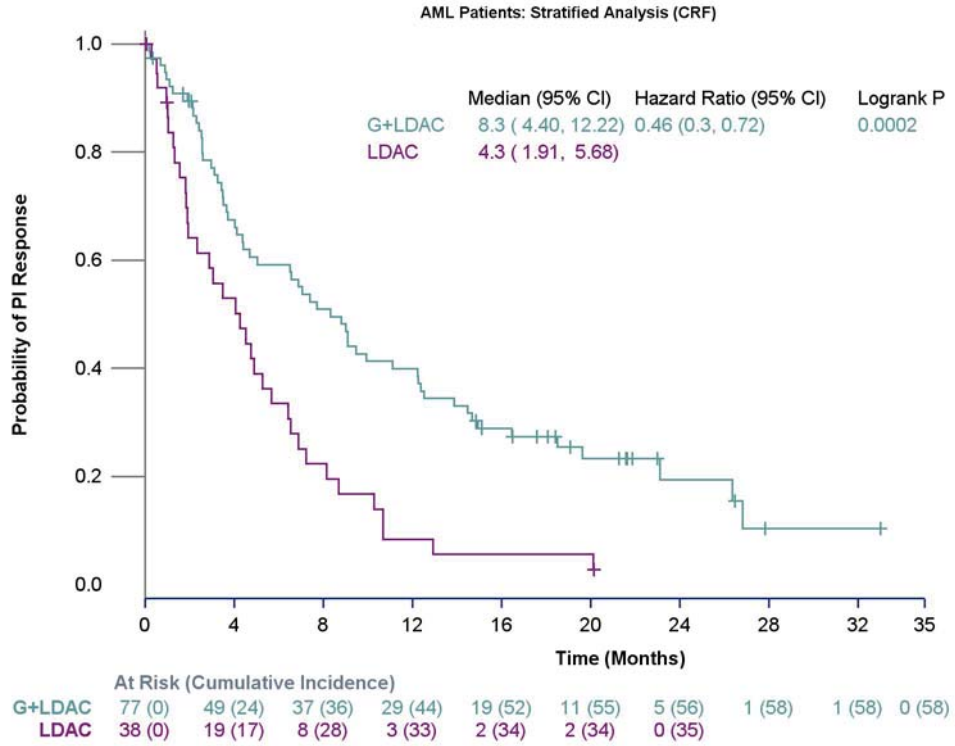

Figure 13 : Overall survival contours for AML patients (excluding patient (b) (6)). Hazard ratio and log-rank test are calculated by aggregating over cytogenetic risk strata.
SOURCE FDA-generated.

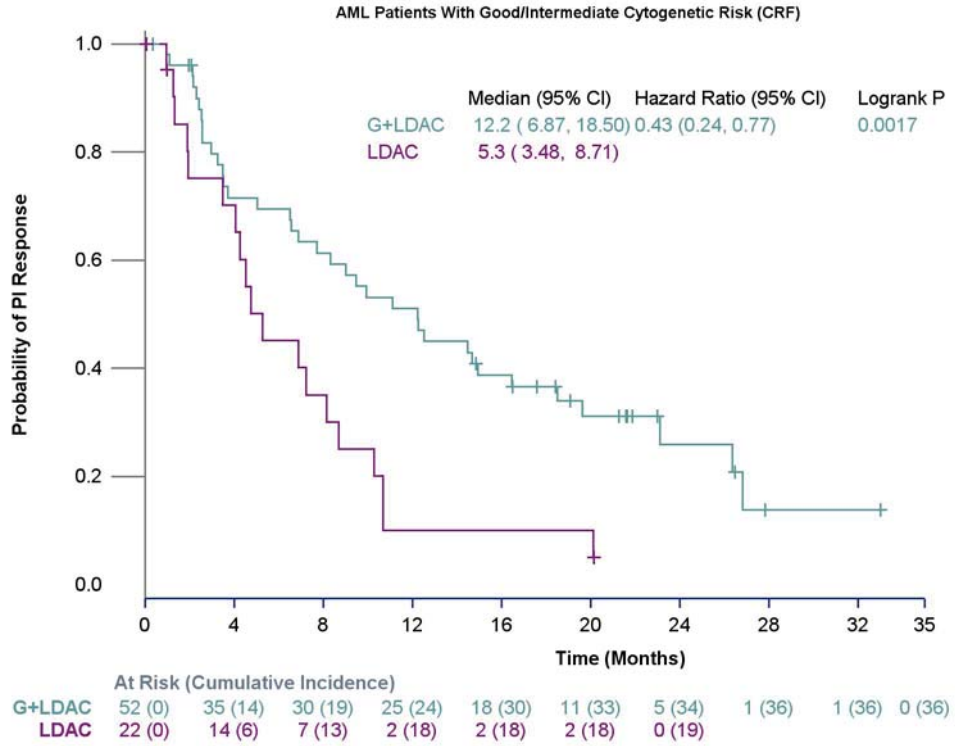

Figure 14 : Overall survival contours among AML patients (excluding patient (b) (6)) within the Good/Intermediate cytogenetic risk stratum. **SOURCE** FDA-generated.

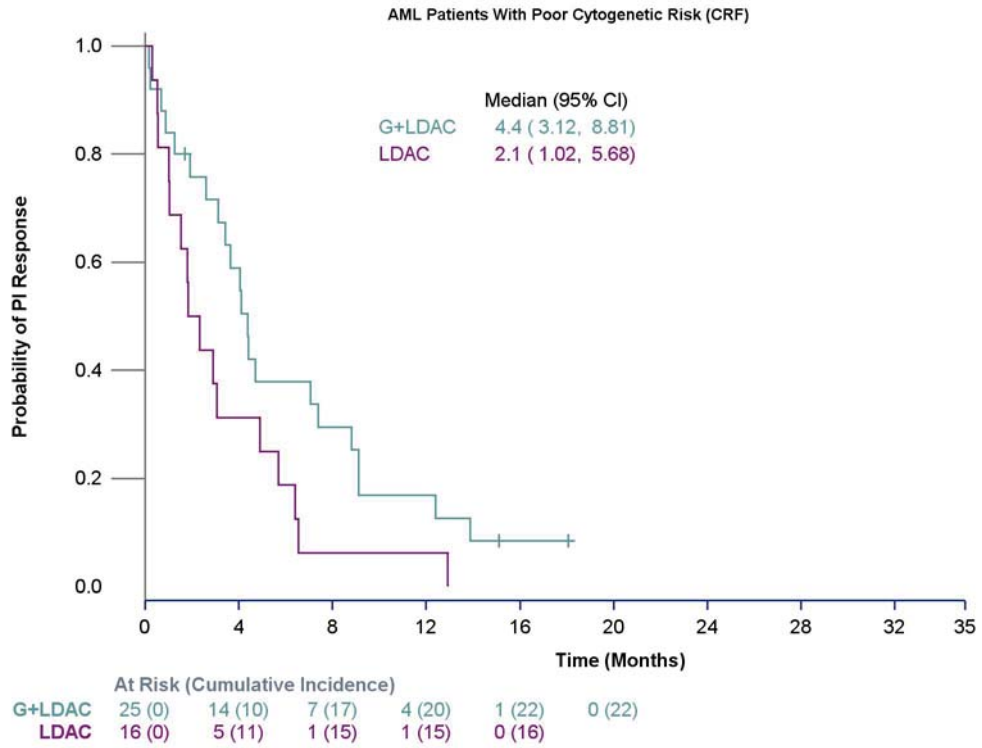

Figure 15 : Overall survival contours among AML patients (excluding patient (b) (6)) within the Poor cytogenetic risk stratum. **SOURCE** FDA-generated.

6.4.3 Complete Remission

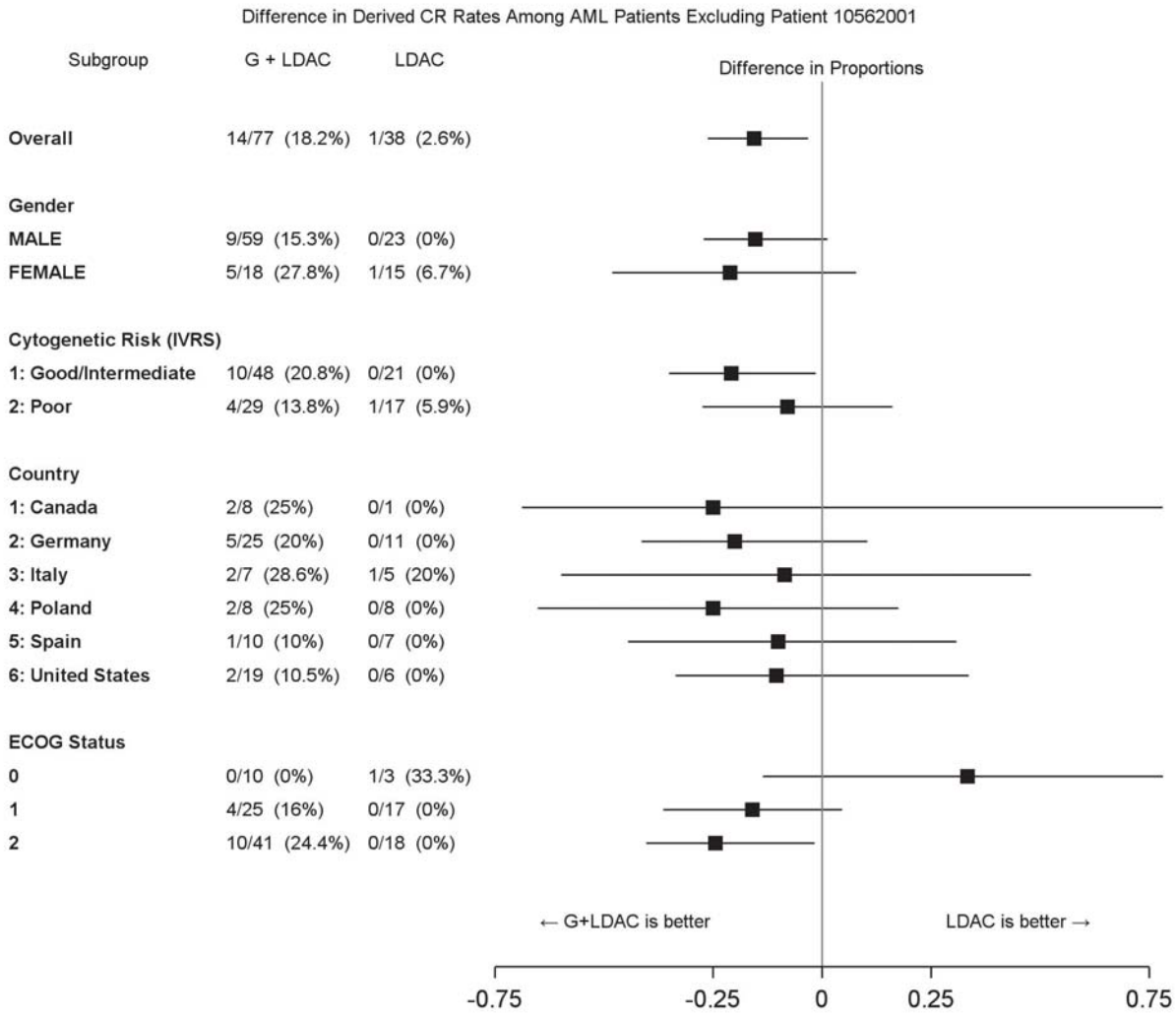

Figure 16 : Complete remission among AML patients (excluding patient (b) (6)).
SOURCE FDA-generated.

6.5 E: Overall Survival for AML Patients by Unfit Criteria

6.5.1 Overview

This section presents overall survival results by each of the unfit criteria:

- Age: < 75 versus ≥ 75
- Serum Creatinine: ≤ 1.3 mg/dL versus > 1.3 mg/dL
- ECOG Status: < 2 versus 2

- Cardiovascular Disease Severity: Not Severe versus Severe

Quantatively, the KM contours may not be consistent in the statistical sense as the sample size is small. This implies that the estimated median survival time is likely to be unstable and the confidence intervals are likely to be invalid. As such, formal statements about efficacy within each of the subgroup levels are potentially misleading.

6.5.2 By Age

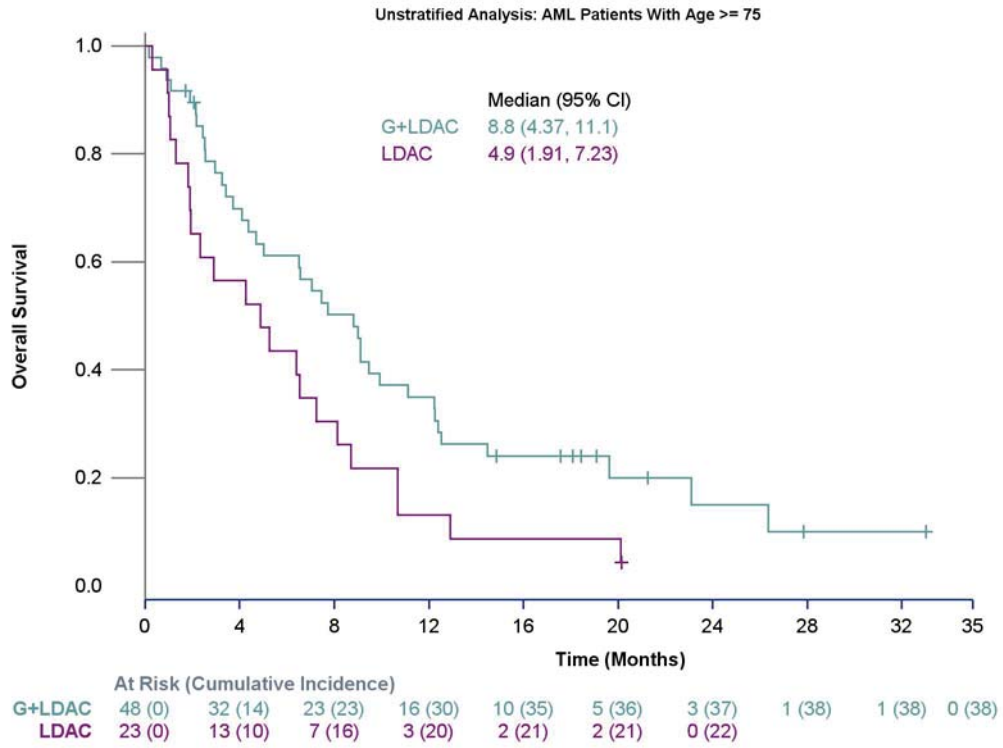

Figure 17 : Overall survival contours for AML patients at least 75 years old. **SOURCE** FDA-generated.

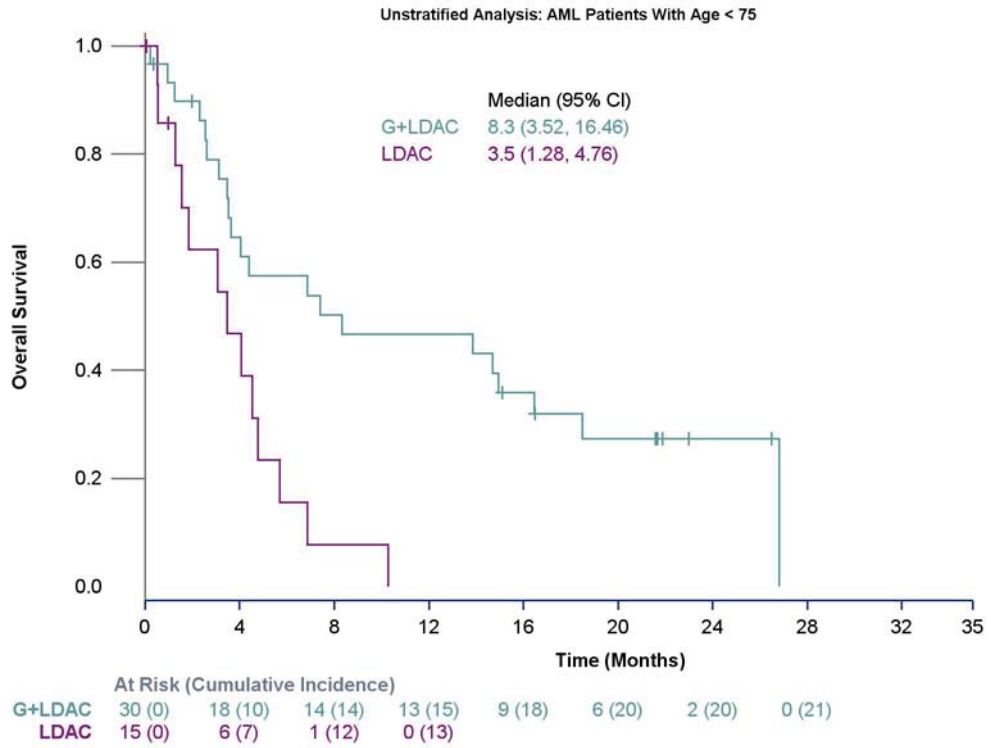

Figure 18 : Overall survival contours for AML patients less than 75 years old. **SOURCE** FDA-generated.

6.5.3 By Serum Creatinine

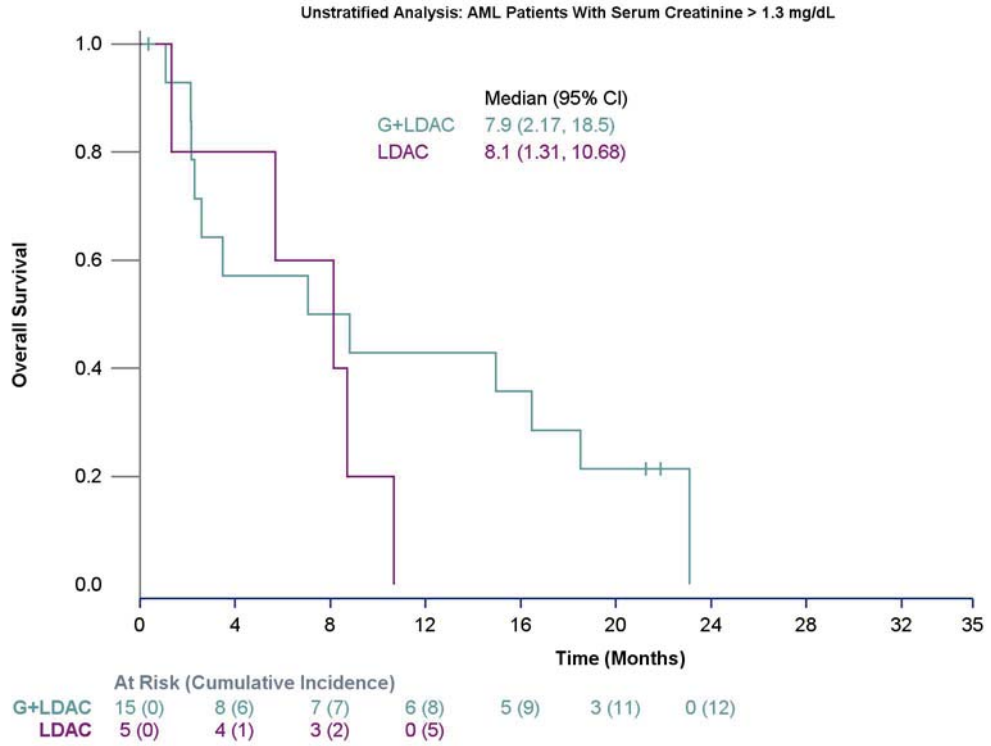

Figure 19 : Overall survival contours for AML patients with serum creatinine > 1.3 mg/dL.
SOURCE FDA-generated.

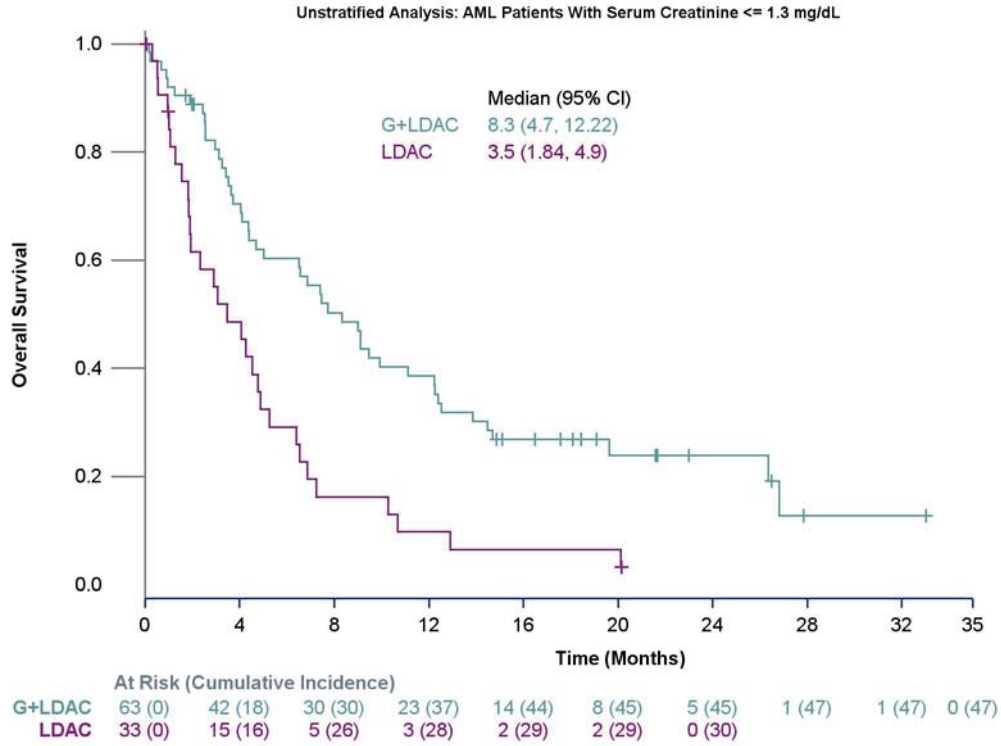

Figure 20 : Overall survival contours for AML patients with serum creatinine <= 1.3 mg/dL.
SOURCE FDA-generated.

6.5.4 By ECOG

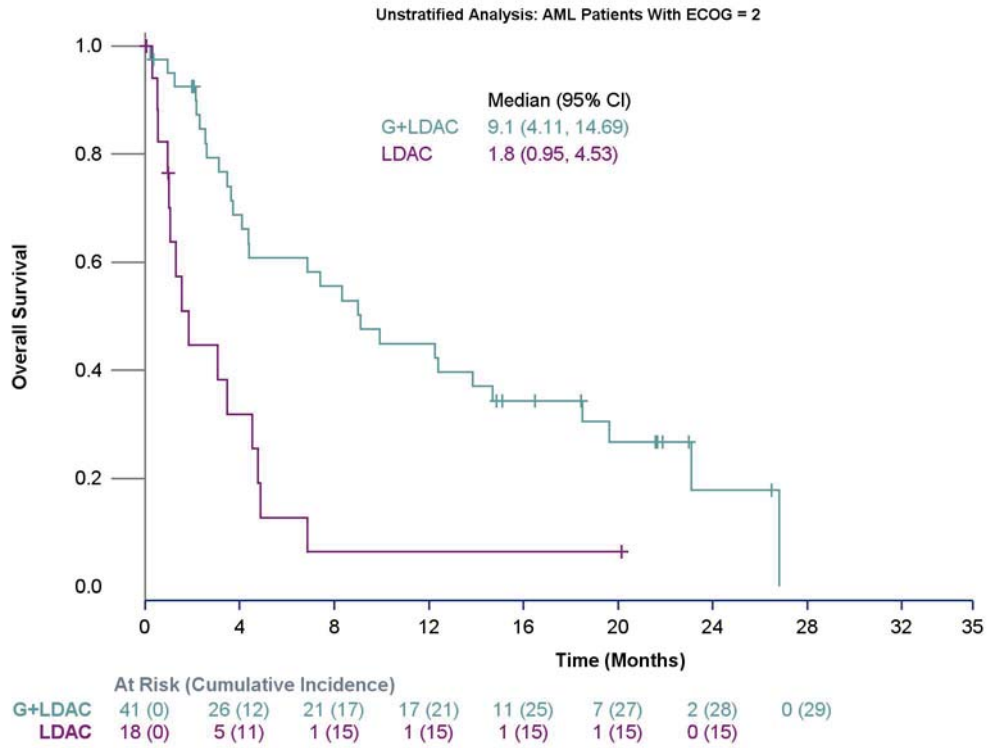

Figure 21 : Overall survival contours for AML patients with ECOG of 2. **SOURCE** FDA-generated.

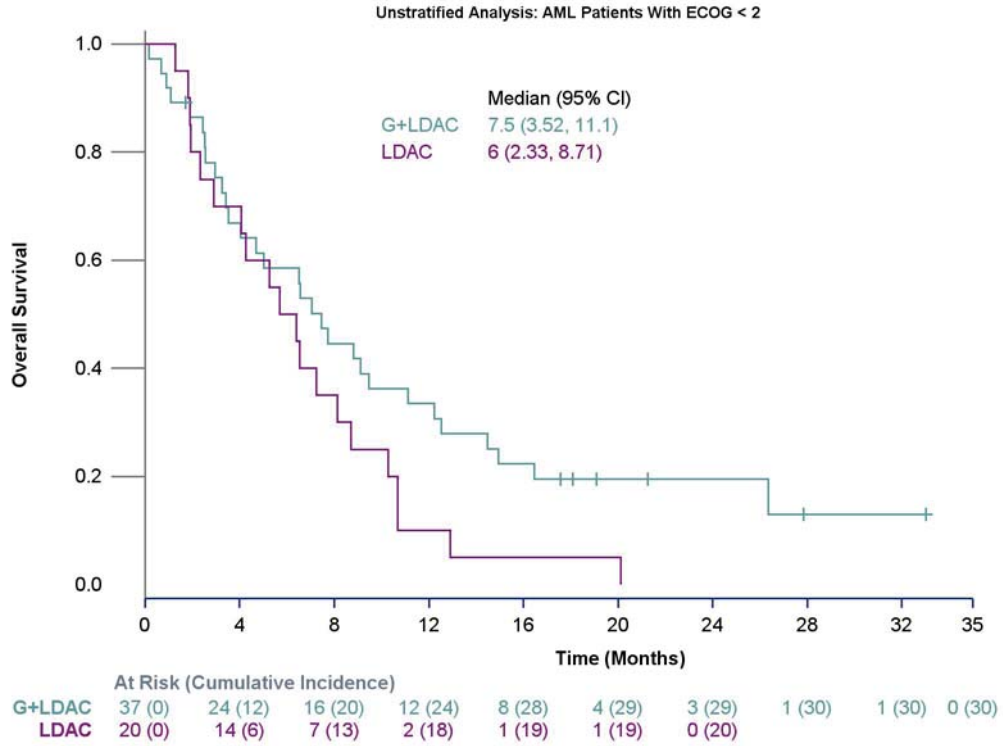

Figure 22 : Overall survival contours for AML patients with ECOG < 2. **SOURCE** FDA-generated.

6.5.5 By Severity of Cardiac Disease

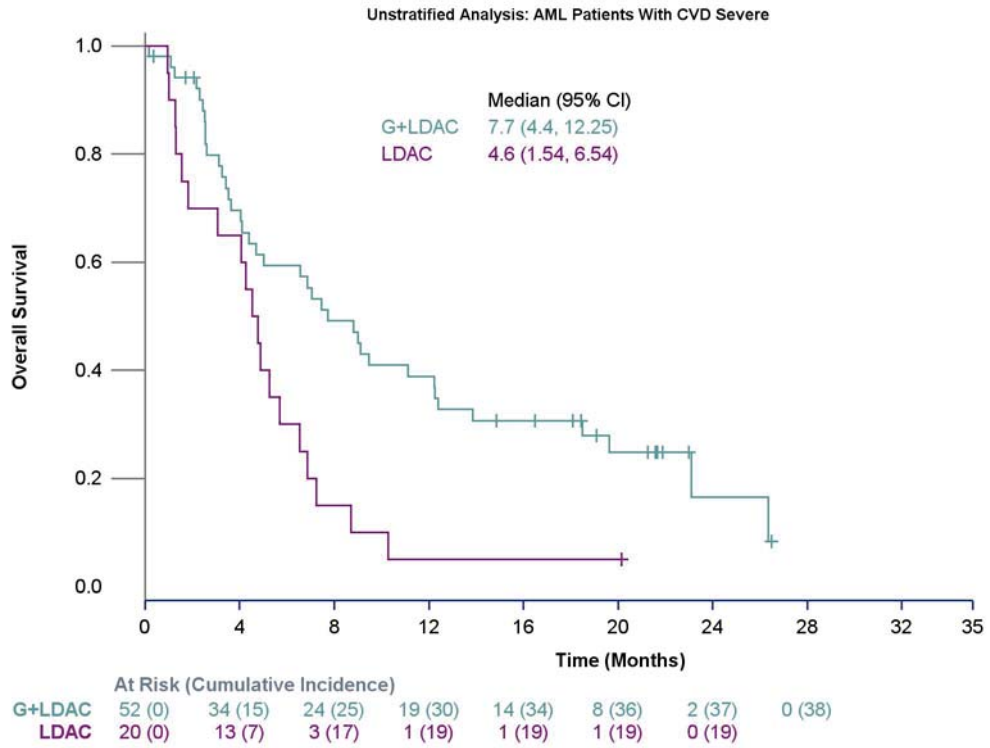

Figure 23 : Overall survival contours for AML patients with severe CVD. **SOURCE** FDA-generated.

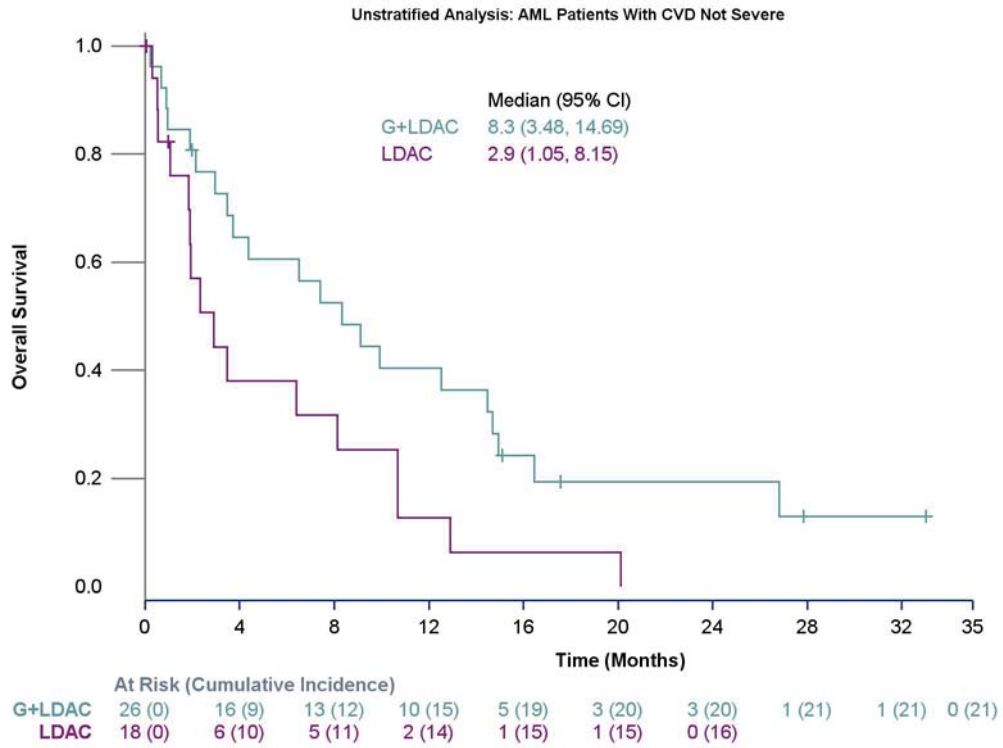

Figure 24 : Overall survival contours for AML patients with CVD not severe. **SOURCE** FDA-generated.

6.5.6 By Number of Unfit Criteria

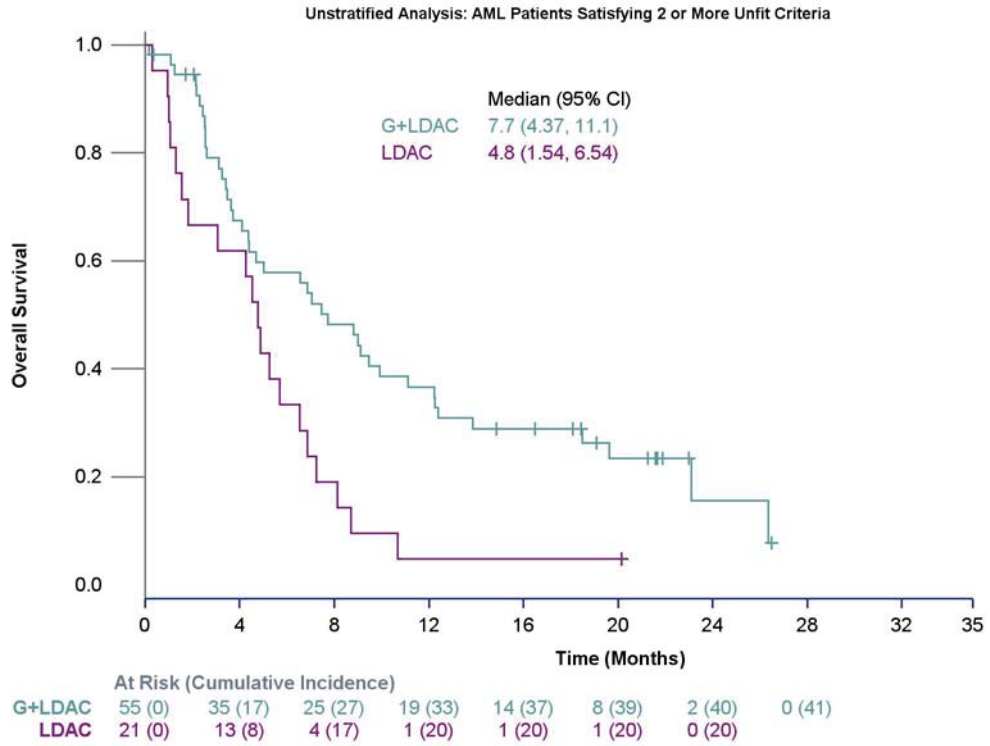

Figure 25 : Overall survival contours for AML patients having 2+ unfit criteria. **SOURCE** FDA-generated.

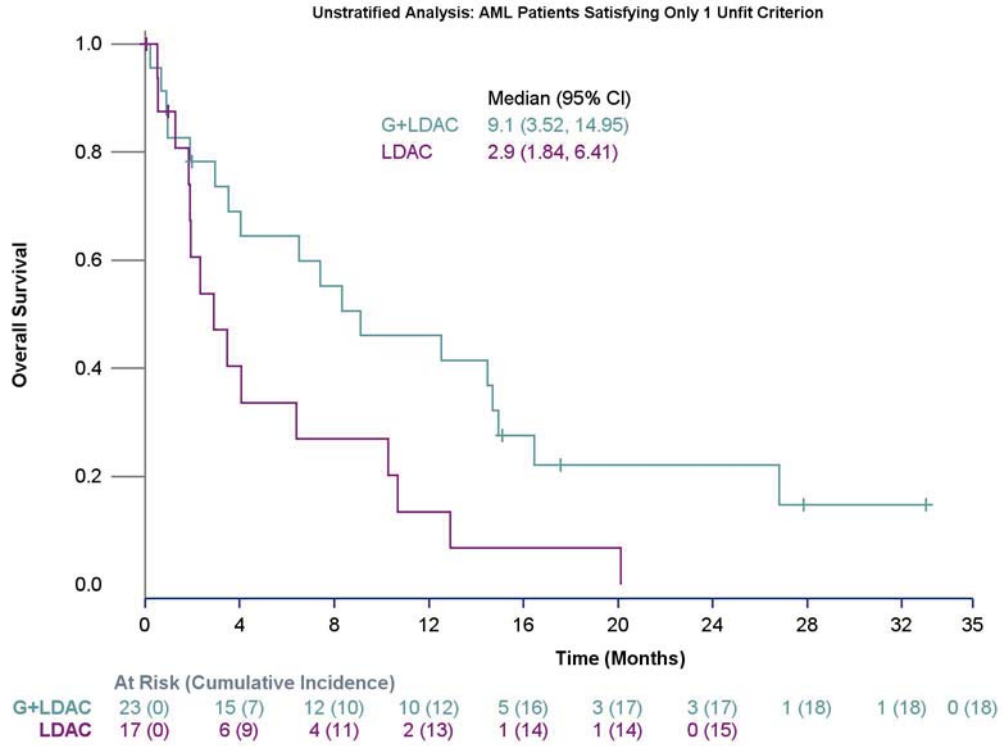

Figure 26 : Overall survival contours for AML patients having only 1 unfit criterion.
SOURCE FDA-generated.

6.5.7 Hazard Ratios by Unfit Criteria

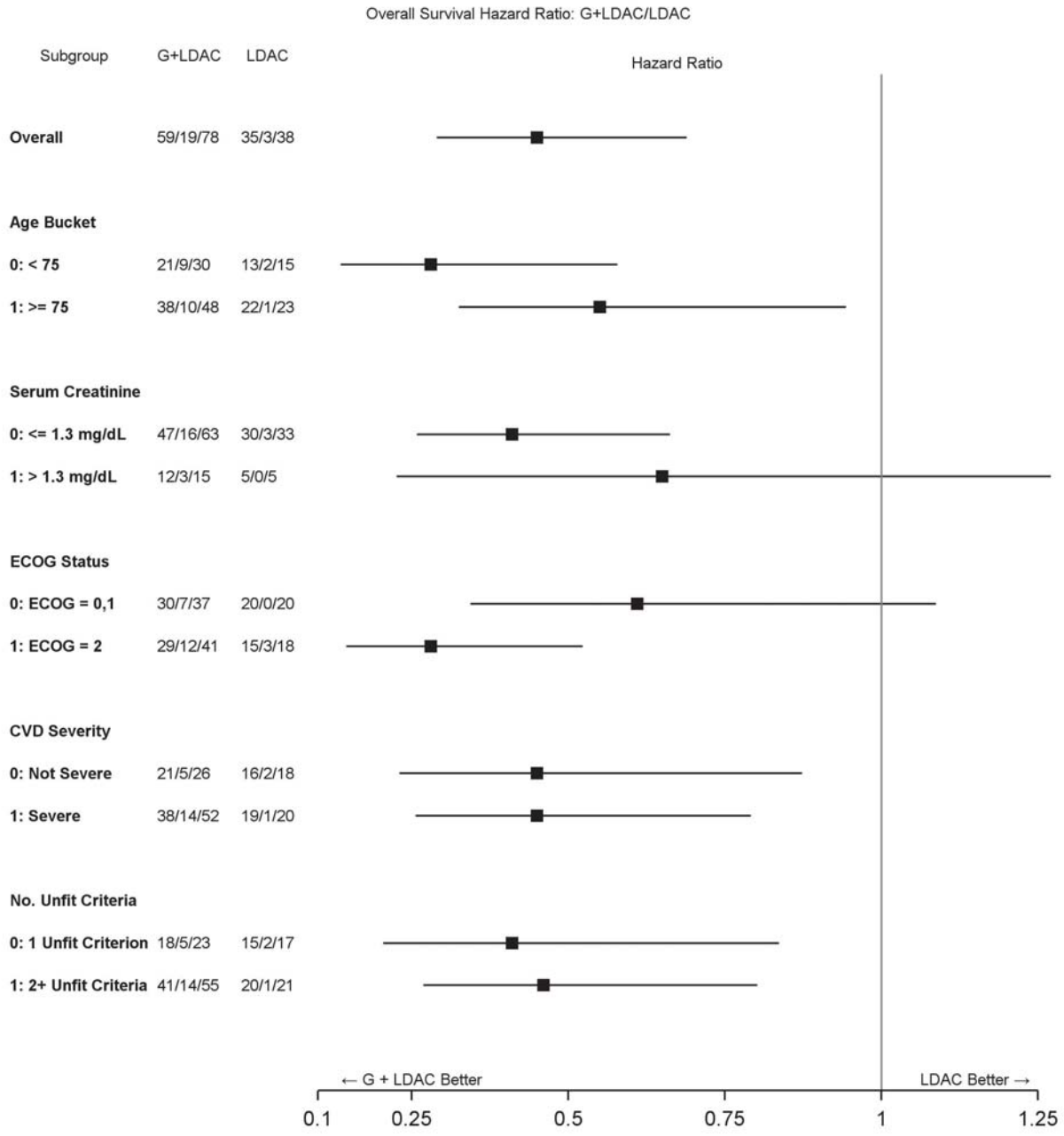

Figure 27 : Hazard ratios between G+LDAC and LDAC among AML patients by unfit criteria.
SOURCE FDA-generated.

6.6 F: Overall Survival for AML+MDS Patients

6.6.1 IVRS-Based Cytogenetic Risk

The following analysis results use cytogenetic risk information as determined by IVRS.

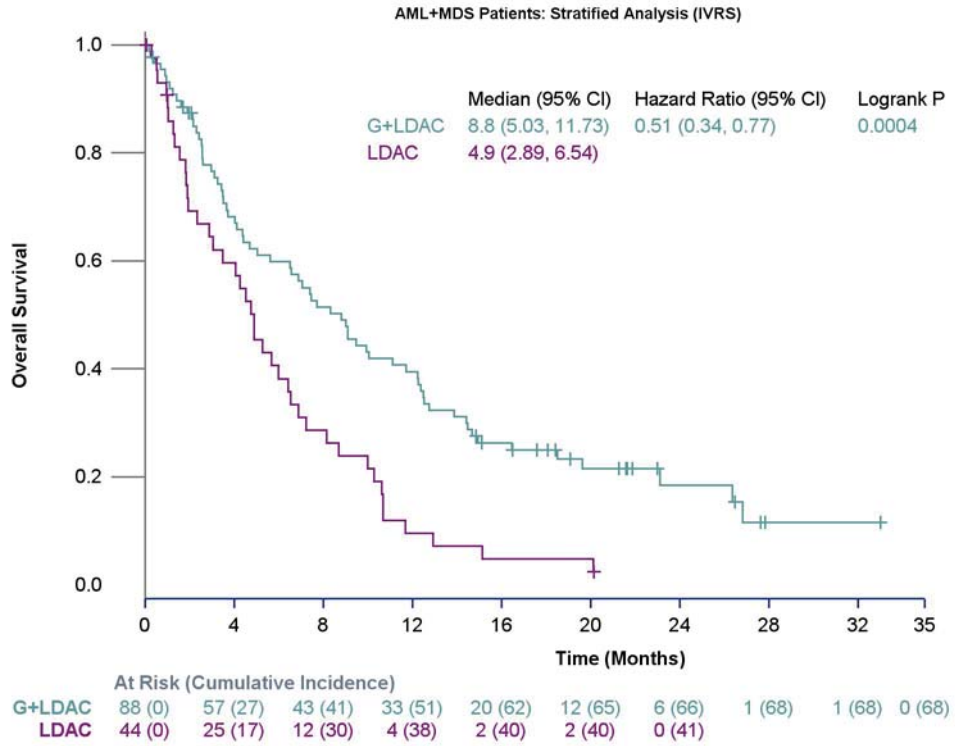

Figure 28 : Overall survival contours for AML+MDS patients. Hazard ratio and log-rank test are calculated by aggregating over cytogenetic risk strata. **SOURCE** FDA-generated.

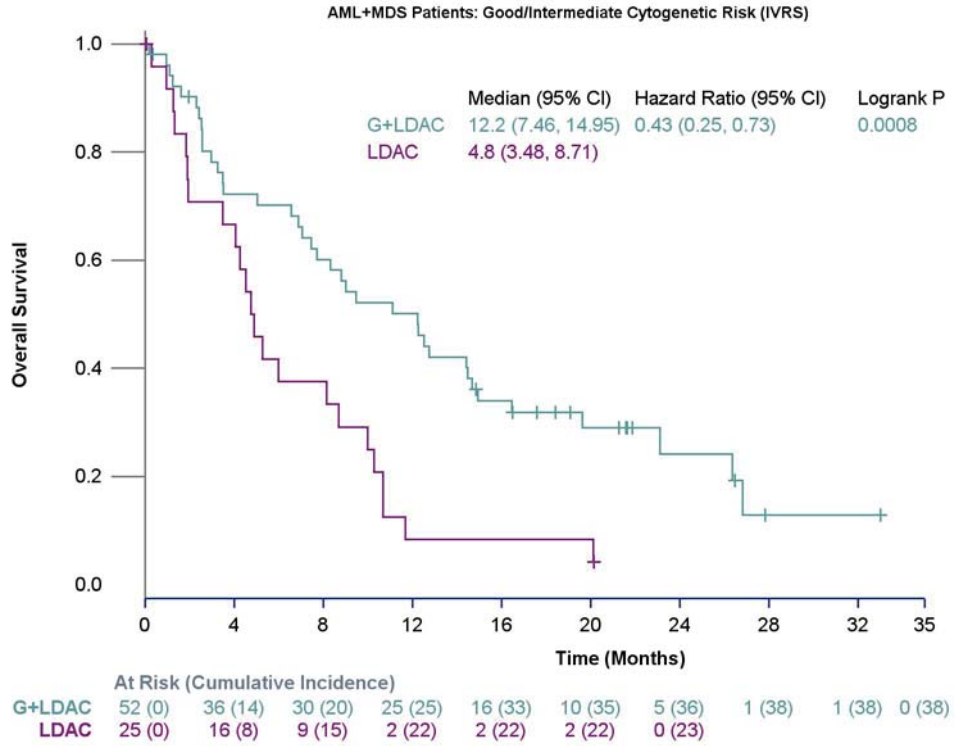

Figure 29 : Overall survival contours among AML+MDS patients within the Good/Intermediate cytogenetic risk stratum. **SOURCE** FDA-generated.

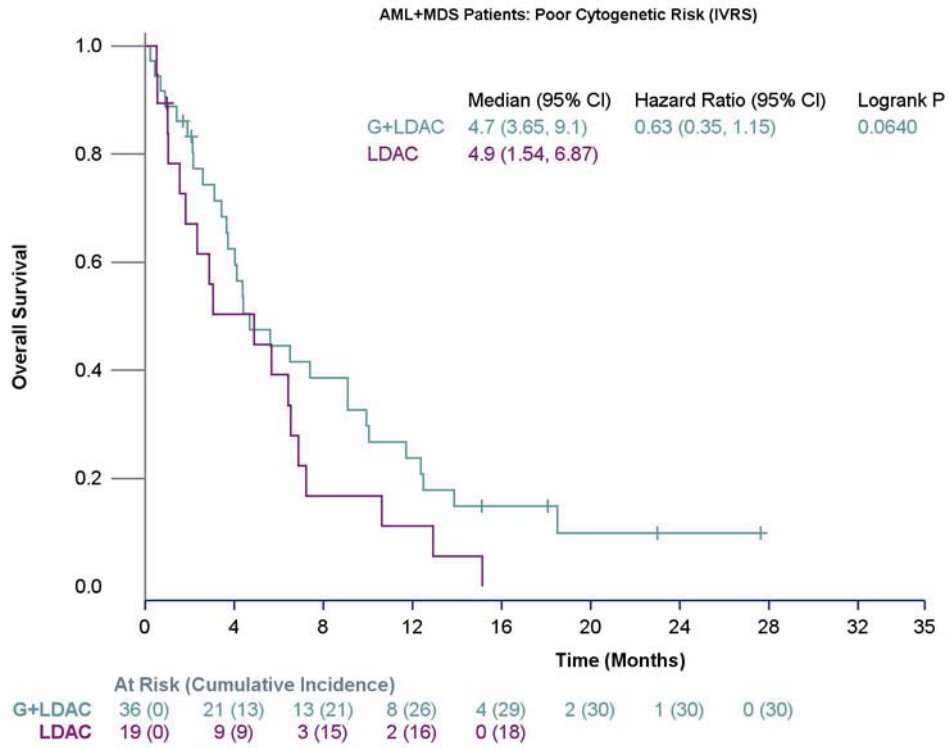

Figure 30 : Overall survival contours among AML+MDS patients within the Poor cytogenetic risk stratum. **SOURCE** FDA-generated.

6.6.2 CRF-Based Cytogenetic Risk

The following analysis results use cytogenetic risk information as determined by CRF.

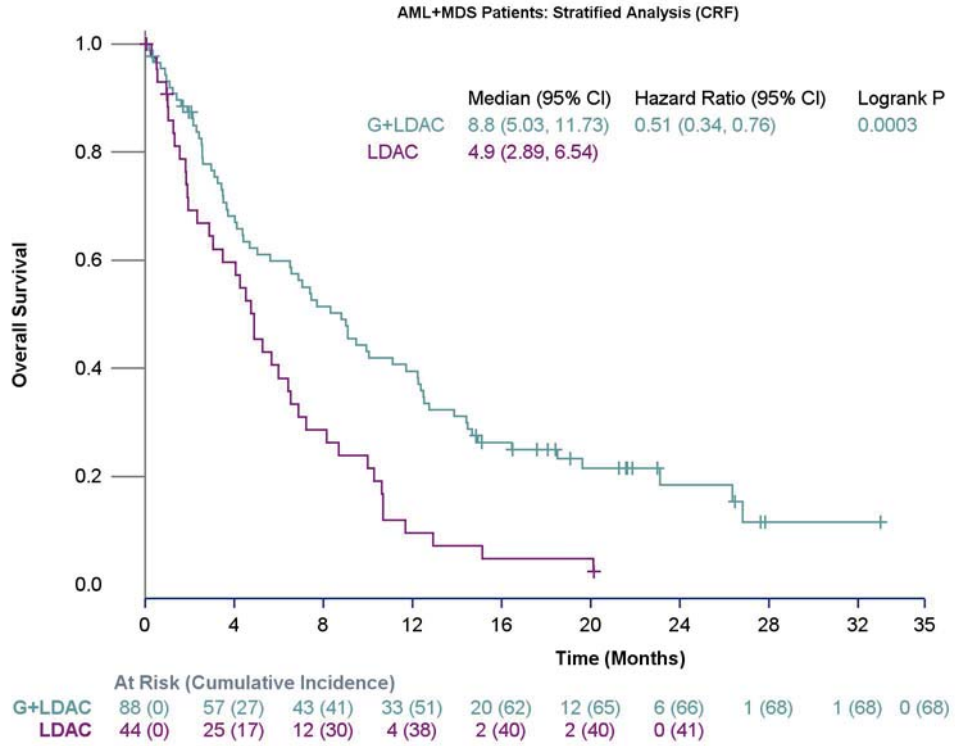

Figure 31 : Overall survival contours for AML+MDS patients. Hazard ratio and log-rank test are calculated by aggregating over cytogenetic risk strata. **SOURCE** FDA-generated.

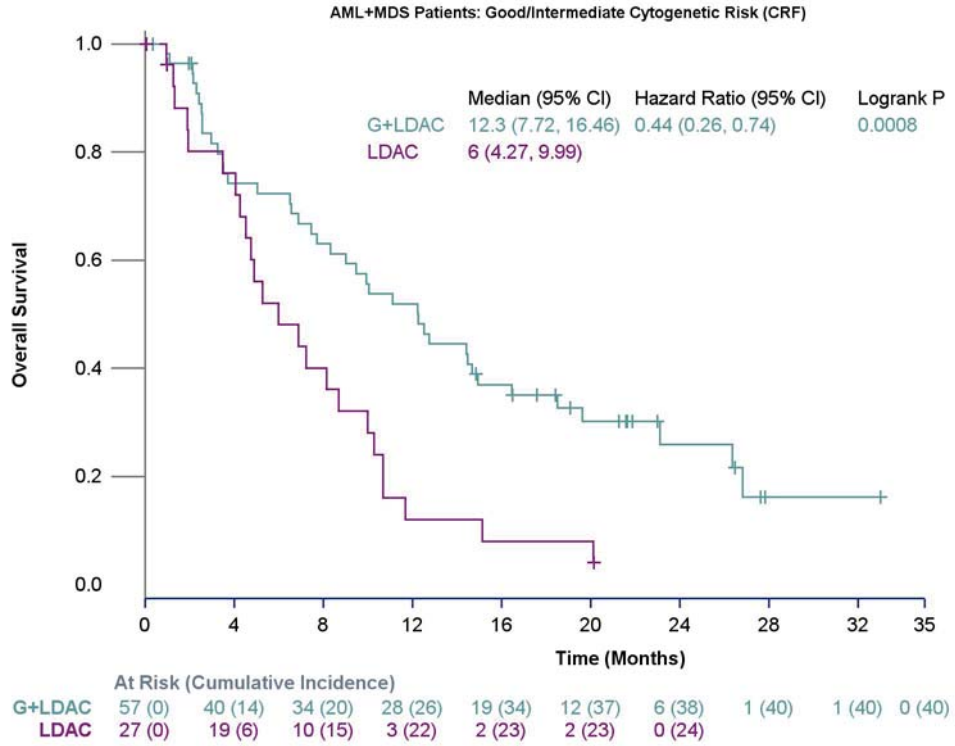

Figure 32 : Overall survival contours among AML+MDS patients within the Good/Intermediate cytogenetic risk stratum. **SOURCE** FDA-generated.

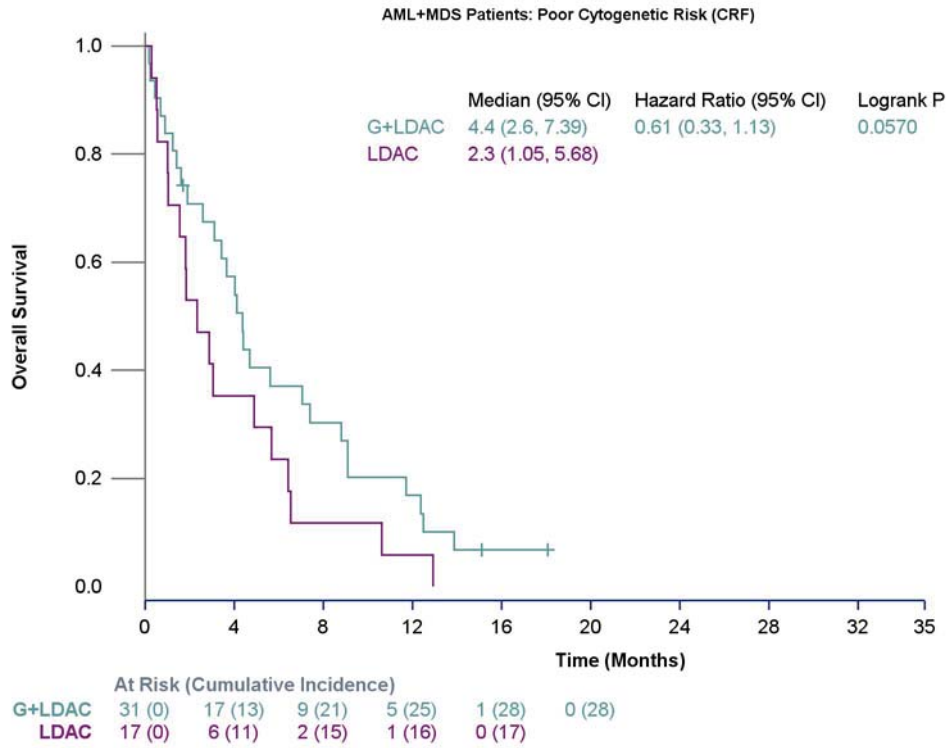

Figure 33 : Overall survival contours among AML+MDS patients within the Poor cytogenetic risk stratum. **SOURCE** FDA-generated.

7 Bibliography

Pfizer. (2016a) A phase 1B/2 study to evaluate the safety and efficacy of pf-04449913, an oral hedgehog inhibitor, in combination with intensive chemotherapy, low dose ara-c or decitabine in patients with acute myeloid leukemia or high-risk myelodysplastic syndrome. *Statistical Analysis Plan: Study B1371003*, **11MAR2016**.

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