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Racial and Ethnic Disparities in Pediatric Acute Myeloid Leukemia Outcome

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# Racial and Ethnic Disparities in Pediatric Acute Myeloid Leukemia Outcome

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M.D., Case Western Reserve University School of Medicine, 2008
B.A., Skidmore College, 2004

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An abstract of
A thesis submitted to the Faculty of the
James T. Laney School of Graduate Studies of Emory University
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in Clinical Research
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ABSTRACT

Racial and Ethnic Disparities in Pediatric Acute Myeloid Leukemia Outcome

By Joanna G. Newton, M.D.

In the U.S., Black and Hispanic children with cancer are less likely to survive than White children. In acute myeloid leukemia (AML), Black race and Hispanic ethnicity have, likewise, been associated with a poor prognosis. It remains unclear, however, whether the association between race/ethnicity and outcome, could be explained by differences in other relevant variables, such as socioeconomic status (SES), age, obesity, and disease characteristics, or whether the association is simply due to worse outcome following stem cell transplant (SCT), often included in AML treatment, and known to be inferior for Black and Hispanic patients. In order to examine these and other potential explanatory variables, we did a secondary analysis of the data collected during the Children's Oncology Group phase 3 clinical trial AAML0531. The primary outcome was event-free survival (EFS), censored at the time of per-protocol SCT. We hypothesized an association between race/ethnicity and response to chemotherapy and survival; and moreover, that it would be explained by racial/ethnic differences in patient characteristics such as weight and SES and disease characteristics such as the presence of risk-stratifying cytogenetic/molecular abnormalities. A total of 1022 patients were included in the analysis, but only 914 could be classified into one of 4 meaningful racial/ethnic groups (White, Black, Asian, Hispanic-White). Kaplan-Meier survival analysis showed significantly worse 5-year EFS for Black patients compared to White (39.07% ± 4.89 vs 50.84% ± 2.23; p=0.035); however, there was no difference in remission or relapse rate between groups. In the multivariate analysis, controlling for age, cytogenetic/molecular disease characteristics, weight, and SES did not affect the association between Black race and poor EFS (HR=1.49, 95% CI: 1.10-2.00; p=0.009). Surprisingly, Black patients had significantly worse treatment related mortality (TRM) compared to White (15.21% ± 3.54 vs 5.66% ± 1.01; p=0.0006), although no consistent cause of death was identified. Therefore, we conclude that the poor outcome for Black children with AML treated on this regimen is due to excess TRM and not due to baseline differences in disease characteristics, response to therapy, or complications from SCT. Future research should be aimed at determining the underlying reason for this observation.

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# INTRODUCTION

Each year in the U.S., there are 13,500 children diagnosed with cancer (incidence ~ 1-2/10,000), and cancer is the leading cause of death from disease in this age group. There has been a significant improvement in 5-year overall survival (OS) for all children with any primary cancer from 63% (1975-1979) to 79% (1995-1999) (1). However, data from SEER indicates that, in general, Hispanic and Black children are less likely to survive than White children (74% and 73% vs 81%, respectively, $p<0.0001$). More specifically, this appears to be true in acute myeloid leukemia (AML) as well.

In 2006, Aplenc *et al* published a paper in Blood showing that among children with newly diagnosed AML treated on two large, consecutive multicenter trials, Hispanic and Black children had worse OS compared to White children, and Black children also had worse event-free survival (EFS) compared to White children (2). However, since that study was published, there has been substantial progress made in understanding the predictors of outcome in childhood AML. Furthermore, the treatment strategy utilized in the U.S. has been revised in an attempt to improve outcome for all children affected. Therefore, we had three main questions for the present study: 1) Do these survival disparities still exist with contemporary therapy; 2) If so, why; and 3) Are racial/ethnic survival disparities independent of disparities related to outcome following SCT?

While race/ethnicity is not often thought of as a true "predictor" of disease or outcome following treatment, in this case, it is thought that there could be biological differences between patients of different races/ethnicities that mediate the survival differences observed. If the biological underpinnings of this relationship were understood, it would allow treatment to be modified for those at highest risk for poor outcome in such a way that survival is maximized while toxicity is minimized. This strategy is used in the treatment of other pediatric malignancies. For example, it has been observed that boys with pediatric acute lymphoblastic leukemia (ALL)

have worse survival compared to girls when they are treated for the same amount of time, but this disparity is eliminated when boys receive an extra year of treatment (3). Thus, the standard of care is for boys to receive an extra year of therapy.

In order to begin to understand the relationship between race/ethnicity and AML treatment outcome, our first aim was to estimate the association between race/ethnicity and the response to chemotherapy among newly diagnosed pediatric AML patients. Secondly, we intended to estimate the association between race/ethnicity and survival among newly diagnosed pediatric AML patients. Thirdly, we planned to determine if there is an association between race/ethnicity and patient-related variables (e.g. weight, SES), disease-related variables (e.g. cytogenetics, molecular characteristics), and treatment-related factors (e.g. receipt of SCT). And finally, we planned to identify the underlying factors that explain the association between race/ethnicity, response to chemotherapy, and survival, if such an association is observed.

In order to accomplish these goals, it is critical to tease out the relationship between race/ethnicity, response to chemotherapy and survival from outcomes related to the effects of SCT. SCT continues to be part of the treatment protocol for children with Intermediate and High Risk disease in this study. There are well documented racial/ethnic disparities related to SCT access, including decreased availability of matched family stem cell donors for Black patients, decreased unrelated donor availability for Blacks (Hispanics and Asians to a lesser degree) compared to Whites, and decreased access to SCT for Black patients due to SES factors (location, lack of means to pay) (4). In fact, Aplenc *et* al did find that Black patients had far fewer available SCT donors than White patients, so it is possible that lack of available donors, and thus the inability to provide SCTs to Black patients who required them, negatively impacted their survival. However, it is also well documented that Black and Hispanic patients have decreased survival and increased treatment related mortality (TRM) compared to White patients following allogeneic SCT, but the reasons for this are not fully understood and are believed to be multifactorial (4).

One major limitation of the study done by Aplenc *et al* was in their inability to separate whether the disparities in outcome that they observed were due to SCT-related differences. Therefore, in our investigation, it is critical to separate out the effect of transplant on survival from the effect of chemotherapy on survival in assessing the relationship between race/ethnicity and survival in children with AML. To do this, we will use EFS, censored at the time of per-protocol transplant in CR-1, as our primary endpoint (see "Methods" for a complete explanation of the rationale for this). We hypothesize that, among pediatric AML patients, there is an association between race/ethnicity and response to chemotherapy and survival. Moreover, this association is, in part, explained by racial/ethnic differences in patient characteristics such as weight and SES and disease characteristics such as the presence of risk-stratifying cytogenetic and molecular abnormalities Inversion 16, FLT3/ITD-HAR, t(8;21), monosomy 7, monosomy 5/del 5q, CEBPA, and NPM1.

# BACKGROUND

In 2006, Aplenc *et al* published a paper in Blood showing that among children with newly diagnosed AML, Hispanic and Black children compared to White children treated on the Children's Cancer Group trial CCG 2891 had significantly decreased OS (37% ± 9% vs 48% ± 4%; p=0.016 and 34% ± 10% vs 48 ± 4%; p=0.007, respectively) (2). Additionally, Black children had decreased event-free survival (EFS) compared to White children (25% ± 9% vs 36% ± 4%; p=0.044). When they did a confirmatory analysis utilizing data from the subsequent CCG trail, CCG 2961, they again found that Black children had significantly decreased EFS and OS compared to White children (28% ± 11% vs 46% ± 4%; p=0.006 and 45% ± 12% vs 60% ± 4%; p=0.007, respectively), and there was a non-significant trend toward decreased EFS and OS in Hispanic compared to White children (40% ± 8% vs 46% ± 4%; p=0.101 and 51% ± 8% vs 60% ± 4%; p=0.065, respectively).

The only concrete explanation investigators could offer for the survival disparities they observed was that there was a significant difference in infection rate between Black and Hispanic children compared to White. However, they did suggest other explanations worthy of exploration in future research including the possibility of pharmacogenetic differences in drug metabolism between racial/ethnic groups that may contribute to differences in toxicity, the possible role of SES as it relates to nutrition, health prior to diagnosis, and prompt access to care at disease onset, differential access to stem cell transplant (SCT) – a treatment often used in conjunction with chemotherapy to treat childhood AML, differential survival following SCT, and increased treatment-related toxicity.

The outcome disparities Aplenc *et al* observed were in children treated on two consecutive phase III randomized control trials of primary therapy for AML, CCG 2891 and CCG 2961, that accrued patients from 1989-1995 and from 1996-2002, respectively (2). Since these data were published, the Children's Oncology Group (COG) completed a new, large phase III

trial for de novo childhood AML, AAML0531, in which they adopted a treatment strategy similar to that of the British Medical Research Council (MRC) 10 protocol (5,6). COG study AAML03P1 was the pilot study from 2003-2005 that led to study AAML0531, which accrued patients from 2006-2010. This new protocol was among the first to implement MRC-based therapy in the United States and was also the largest clinical trial for primary therapy for pediatric AML since the closure of CCG 2961 (6).

Cooper *et al* recently published data showing that Black patients treated on study AAML03P1 had worse EFS and OS than patients of other racial groups (HR=1.93; p=0.044 and HR=2.48; p<0.001, respectively) (6). However, no one has yet to explore whether there were any survival differences between different racial or ethnic groups enrolled on AAML0531, which accrued over 1000 patients, compared to the 340 patients included in the AAML03P1 analysis. Therefore, the primary aim of the present study is to confirm that the differences observed by Aplenc *et al* and Cooper *et al* persist in the most recent phase III study of primary therapy for children with AML. Additionally, we intend to extend our understanding of this relationship by assessing whether this effect may be mediated by differences in the patient-related variables socioeconomic status (SES) and weight (obesity), disease-related variables, including a variety of cytogenetic and molecular abnormalities now known to predict outcome, the presence of minimal residual disease (MRD), and treatment-related factors, including the receipt of allogeneic stem cell transplant (SCT) in first complete remission (CR-1). These factors have not been accounted for in any other analysis looking at the impact of race and ethnicity on outcomes in pediatric AML.

In their study, Aplenc *et al* cite their inability to capture SES as an important limitation, as differences in SES between racial groups have influenced disparities in outcomes in the treatment of other pediatric cancers (2). In a large, multicenter, retrospective analysis of patients treated according to a Pediatric Oncology Group protocol for acute lymphoblastic leukemia (ALL), Hispanics had 33% excess mortality and Blacks had 42% excess mortality compared to

Whites (1). However, in a single-center study using contemporary protocol-based therapy, investigators found no difference in outcome based on race/ethnicity. They explain that this difference may be due to a single institution's ability ensure close individual care, regardless of a patient's ability to pay. However, a key difference between the treatment of pediatric ALL and AML is that the former is primarily treated in the outpatient setting, while the latter is treated almost entirely in the inpatient hospital setting. While one might expect the influence of SES to be mitigated in the context of hospital-based AML treatment, this is yet unknown. And, given that there is an opportunity to intervene should SES play a significant role in the disparate outcomes between patients with AML of different ethnicities, it is crucial to investigate the role this plays. AAML0531 captured data regarding the type of insurance used by patients enrolled on the study, so we will use payment type as a surrogate indicator of SES.

Additionally, other variables have been previously shown to affect outcome in patients treated with AML that were not taken into account in the analysis done by Aplenc *et al*. For example, in 2005, Lange *et al* did an analysis of the same CCG2961 data set to look at the effect of BMI on outcomes and found that underweight patients (BMI<$10^{th}$ percentile) were less likely to survive (HR=1.85, 95% CI: 1.19-2.87; p=0.006) and more likely to experience treatment-related mortality (TRM) (HR=2.66, 95% CI: 1.38-5.11; p=0.003) and overweight patients (BMI≥$95^{th}$ percentile) were similarly less likely to survive (HR=1.88, 95% CI: 1.25-2.83; p=0.002) and more likely to experience TRM (HR=3.49, 95% CI: 1.99-6.1; p<0.001) than their middleweight counterparts (7). While it had been well known at the time of that publication that underweight patients did worse than healthy-weight patients, that publication was the first to show that overweight patients had a worse outcome than healthy-weight patients. The etiology of the inferior outcome in overweight patients is as yet unknown; however, if the effect of malnutrition or obesity contributes to the differences in outcomes between racial/ethnic groups, it provides a prime target for intervention and for improving those differences.

Since Aplenc *et al* published their data, other leukemia-related predictors of better or worse outcome have been identified, including the molecular abnormalities FLT3/ITD-high allelic ratio (HAR), nucleophosmin gene mutation (NPM1), and CEBPA gene mutation, as well as the treatment response characteristic, minimal residual disease (MRD) (8-10). In fact, the successor study to AAML0531, AAML1031, utilizes these indicators, among others, in risk stratification for treatment, which in that protocol, substantially changes the treatment and contributes to the decision to transplant a patient in CR-1. The presence of CEBPA or NPM1 gene mutations portends a better prognosis whereas the presence of FLT3/ITD-HAR portends a worse prognosis. And, while the prevalence of these mutations have been examined based on demographic variables such as age and gender, no one has yet examined whether there is a difference in the frequency of these cytogenetic abnormalities between different racial/ethnic groups.

There are two main sources of treatment failure in AML, leukemic relapse and treatment related mortality (TRM). MRD, which can be viewed as an endpoint of response to induction therapy, has recently been recognized as an important predictor of relapse. Those patients who are MRD positive at the end of induction, that is, who have leukemia cells detectable in marrow specimens obtained at the end of their first cycle of induction, are much more likely to suffer relapse (10). Importantly, MRD testing was not performed on patients in the two studies examined by Aplenc *et al*; however, it was on AAML0531. No one has yet looked at whether or not there are differences in MRD status between different racial groups. This is critical to understand, as it could have implications for decisions regarding risk stratification or therapy intensity at the start of treatment. TRM, often thought of as "death in remission," in children with AML is often caused by infection stemming from prolonged neutropenia (11). While Aplenc *et al* found a non-significant trend toward worse TRM in Black and Hispanic patients, they noted that those patients had a significantly higher mortality rate from infection when treated on CCG2961 compared to White children (13% and 16% vs 9%, respectively; p=0.035). Apart from this

observation, they did not offer any other explanation for the survival differences they observed in their study (2).

Allogeneic stem cell transplant (SCT) plays an important role in the treatment of children with AML. In the CCG2891, CCG2961, and AAML03P1 trials, for example, any child with an HLA-matched related donor was assigned to SCT as consolidation therapy following several cycles of induction chemotherapy. In the AAML0531 trial, the use of SCT differed but still played a pivotal role. In that trial, patients with Intermediate Risk disease were assigned to SCT for consolidation if they had a matched related donor; patients with High Risk disease were assigned to SCT if they had a matched related donor or an acceptable alternative donor (unrelated or mismatched related). Moreover, SCT figures prominently in the treatment of children who suffer relapse (12).

Strong racial disparities exist in access to and outcome after SCT. Black patients are not only less likely to have a matched related donor, an optimal unrelated adult donor, or a cord blood unit available, but also Black patients receiving allogeneic transplants have inferior outcomes (13-15). While it is likely that these transplant-related racial disparities contribute to the inferior OS of Black children with AML, it is less clear how race/ethnicity affects the outcome of treatment with chemotherapy, independent of survival disparities related to the use of SCT. Thus, the primary aim of this study is to assess the relationship between race and ethnicity and outcome following chemotherapy treatment.

# METHODS

**Hypothesis:** Among pediatric AML patients, there is an association between race/ethnicity and response to chemotherapy and survival. Moreover, this association is, in part, explained by racial/ethnic differences in patient characteristics such as weight and SES and disease characteristics such as the presence of risk-stratifying cytogenetic and molecular abnormalities t(8;21), Inversion 16, FLT3/ITD-HAR, monosomy 7, monosomy 5/del 5q, CEBPA, and NPM1.

**Study Design:** This is a secondary data analysis (cohort study) of data from a Children's Oncology Group phase III randomized control trial, AAML0531.

**Patients:** All patients eligible for participation and inclusion in the primary analysis of the clinical trial were eligible for inclusion in this analysis. Per the AAML0531 study protocol, patients were eligible if they were ≥ 1 month old and < 30 years old, had a new diagnosis of AML, and had not received any prior chemotherapy or radiation for any other malignancy. All parents signed informed consent and all children of appropriate age signed informed assent prior to enrollment. During the enrollment process, parents/patients were asked to identify themselves with one racial and one ethnic group as follows:

- **Race:** White, Black or African American, Asian, Native Hawaiian or Other Pacific Islander, American Indian or Alaska Native, Other, Unknown
- **Ethnicity:** Hispanic or Latino, Not Hispanic or Latino, Other

In order to create meaningful groups for statistical comparison, patients were re-categorized into the following groups: White, Black, Asian, Hispanic-White, and Other. Patients who identified themselves as race, "Native Hawaiian or Other Pacific Islander," "American Indian or Alaska Native," "Other," and "Unknown" were re-classified as race, "Other." Patients ultimately

classified as race "Other" were not included in most statistical analyses. With the exception of Hispanic-White patients, all patients of ethnicity, "Hispanic or Latino" and "Other" were analyzed with their respective racial group. For example, patients of Black race who were also of Hispanic ethnicity were analyzed together with Black non-Hispanic patients.

**Measurements**

**Outcomes:** The primary outcome measure was event-free survival (EFS), censored at the time of per-protocol SCT in first complete remission (CR-1). EFS was defined as the time from study enrollment to the time of induction failure, relapse, or death. This was not a repeating measure; the occurrence of any one of the above outcomes constituted an EFS event. EFS, as opposed to overall survival (OS), was chosen as the primary endpoint because SCT is often used as salvage therapy for AML patients who relapse. Because information on the type of salvage therapy given after relapse is not available for patients included on this trial, the impact of SCT on OS cannot be completely assessed and confuses the relationship between race/ethnicity and outcome. In addition, it is important to note that SCT in CR-1 is part of the treatment protocol for Intermediate and High Risk patients treated on AAML0531. Prior studies have shown that Black and Hispanic patients have decreased survival following SCT; therefore, patients who received per-protocol SCT in CR-1 were censored in order to eliminate the influence of SCT on outcome. Secondary outcomes included OS, defined as the time from study enrollment to death or study completion, minimal residual disease (MRD) following Induction 1, treatment response following 2 courses of induction chemotherapy (remission induction), early death, by definition, within the first 3 courses of chemotherapy, cumulative incidence of relapse (relapse rate or RR), TRM, defined as death at any time due to treatment toxicity (also known as death in remission: non-relapse, non-AML-related death), and cause of death.

**Predictor:** Race/ethnicity, as defined above

**Covariates:** For the multivariate analysis, we controlled for age, weight, SES, and risk group. Prior studies have shown that both age (≥ 16 years old predicts poor prognosis) and weight (obesity predicts poor prognosis) impact survival. Conversely, a limitation of prior work in this area is that researchers failed to control for SES, so its impact on racial/ethnic survival disparities in childhood AML has never been examined. Pediatric AML is a unique disease in that it is treated almost exclusively in the inpatient hospital setting. Because all treatment is administered by hospital nurses and does not rely on parental involvement, home medication compliance, or transportation to and from appointments, it is not expected that SES would have an impact on outcome; however, SES may have unmeasured effects owing to differences in home environment prior to AML diagnosis, nutrition, or other psychosocial factors, so it is important to control for its potential influence on survival. In this study, we used payment type as a surrogate for SES. SES, as reflected by payment type, was categorized as follows:

- High SES: patients with "Self Pay" or "Private Insurance." Patients who were "Self Pay" had means to pay, in contrast to those with "No Insurance" who did not.
- Low SES: patients with "Medicaid" or "No Insurance." Medicaid patients may or may not have had additional Medicare insurance. Patients with "No Insurance" had no insurance and no means to pay, in contrast to "Self Pay" patients.
- Patients with other types of insurance, including Medicare and Military insurance, were not excluded from the analysis but these types of insurance were not considered to be reflective of SES.

**Sample-size and Power:** The results of CCG2961 showed an 18% difference in EFS between White and Black patients. To identify the same degree of disparity at a type-1 error rate of 5%, we have 80% power to detect a difference in survival, using a Log-rank statistic, if there are at least 54 patients in each racial/ethnic group.

**Analytic plan**

**Descriptive statistics:** Frequency tables were calculated to describe the racial/ethnic distribution of patients included in the study. Patients were classified into one of 5 different racial/ethnic groups: White, Black, Asian, Hispanic-White, and "Other". Patients classified as "Other" were excluded from the analysis, as described above. Additionally, only frequency tables were calculated for cause of death, stratified by race/ethnicity, because over-parameterization prevented the meaningful use of a statistical test.

**Bivariate Analysis of Baseline Characteristics:** Baseline patient, disease, and treatment characteristics, stratified by race/ethnicity, were assessed and a Pearson chi-square test was used to compare differences between groups. The patient characteristics that were examined included age, gender, weight, and payment type (surrogate for SES, as described above). The disease characteristics we assessed included, the presence of CNS disease, cytogenetic risk group, overall risk group (see below for description), and the presence of the following individual cytogenetic/molecular characteristics: t(8;21), inversion 16, CEBPA, NPM1, trisomy 8, t(6;9)(p23;q34), t(9;11)(p22;q23), 11q23 abnormality (MLL-rearrangment), t(15;17), monosomy 7, monosomy 5, deletion 5q-, FLT3/ITD-HAR, and accumulated, identifiable, "other cytogenetic abnormalities." Treatment characteristics included study treatment arm, receipt of per-protocol SCT, and if transplanted, transplant donor type and stem cell source. In circumstances where cell counts were sufficiently low that the Pearson Chi-square test was not a reliable statistic, the Monte-Carlo estimate of the exact test was reported.

**Bivariate Analysis of Selected Outcome Measures:** a Pearson Chi-square test was used to compare the proportion of patients from each racial/ethnic group with MRD following induction 1 and who experienced early death, and to compare their responses to 2 cycles of induction chemotherapy as well as their overall response to treatment – remission, induction failure, relapse, or death.

**Odds Ratios for Selected Outcomes:** A univariate logistic regression model was used to calculate the odds ratio, compared to White race, for the outcomes MRD positivity and early death. The ORs with the 95% Wald Confidence Limits were reported. The following models were used:

- MRD: Logit $P(MRD = 1) = \beta_0 + \beta_1 RaceEth1 + \beta_2 RaceEth2 + \beta_3 RaceEth3$; where RaceEth1 = Asian, RaceEth2 = Black, and RaceEth3 = Hispanic-White. White patients were the reference group (reference coding used).
- Early Death: Logit $P(EarlyDeath = 1) = \beta_0 + \beta_1 RaceEth1 + \beta_2 RaceEth2 + \beta_3 RaceEth3$; where RaceEth1 = Asian, RaceEth2 = Black, and RaceEth3 = Hispanic-White. White patients were the reference group (reference coding used).

**Survival Analysis:** The Kaplan-Meier Method was used to construct survival curves and calculate survival estimates stratified by racial/ethnic group for both EFS and OS, censored at the time of per-protocol SCT (see section "Outcomes" above for explanation of rationale for censoring). Three and 5-year EFS and OS (± Standard Error) and median survival times for each group were reported. The Log-rank test was performed, $\alpha = 0.05$, and the Sidak adjustment for multiple comparisons was used to compare the survival estimates for each racial/ethnic group to those for patients of White race.

**Cumulative Incidence of Selected Outcomes:** When assessing RR and TRM, it is best to use a competing risk model. In the case of RR, patients who die or fail to achieve remission after induction therapy are not at risk for relapse, so the rate of relapse is affected by both the induction failure and death rate; thus, these events are competing risks to relapse. Conversely, relapse and induction failure are a competing risks to TRM, also known as death in remission. The toxic effects of chemotherapy in the absence of disease cannot be accurately assessed for patients who do not achieve remission or who relapse and are no longer in remission; induction failure and relapse are competing risks to TRM. In this study, a cumulative incidence function accounting for

competing risks was used to calculate the RR and TRM for each racial/ethnic group **(citation for macro)**. Gray's Test, $\alpha = 0.05$, was used to compare the 3-year RR and TRM (± Standard Error) between racial/ethnic groups.

**Hazard Ratios for EFS (primary outcome):** The HR (± 95% Confidence Interval) for EFS events (induction failure, relapse, or death), censored at the time of per-protocol transplant, were calculated using a Cox Proportional Hazards Model. Log-log survival curves for EFS, stratified by race/ethnicity, were assessed to verify that the assumptions of the Cox Proportional Hazards Model were met. In order to determine which covariates should be included in the final multivariate model, each was added sequentially to a model that contained only race/ethnicity as a predictor and the subsequent impact on the HRs for each racial/ethnic group compared to White race was assessed. Candidate covariates included those that are known to be predictors of outcome such as age, weight, the cytogenetic/molecular characteristics t(8;21), inversion 16, CEBPA, NPM1, monosomy 7, monosomy 5, deletion 5q-, FLT3/ITD-HAR, MRD positivity after induction 1 (also examined as an outcome measure), as well as those that we think may have an impact on outcome such as SES, or disease characteristics that were differentially represented between racial/ethnic groups, such as the 11q23 abnormality. The following univariate Cox Proportional Hazards Models were used to assess the relationship between race/ethnicity and EFS, censored at the time of per-protocol transplant, as well as the individual relationships between each of the above mentioned candidate covariates and EFS, censored at the time of per-protocol transplant:

- Primary Predictor: Race/Ethnicity
    - $h(t) = h_0(t)\exp(\beta_1 \text{RaceEth1} + \beta_2 \text{RaceEth2} + \beta_3 \text{RaceEth3})$; where RaceEth1 = Asian, RaceEth2 = Black, and RaceEth3 = Hispanic-White, and White patients were the reference group (reference coding used).

- Univariate models for covariates: $h(t) = h_0(t)\exp(\beta_1 Covariate1 + \beta_2 Covariate2 + \ldots + \beta_N CovariateX)$; where "Covariate1" – "CovariateX" = specific covariate of interest with levels indicated by dummy variables "1-X," and parameter estimates $\beta_1 - \beta_N$.

Including each of the known cytogenetic/molecular predictors of outcome in the final multivariate analysis is important in order to fully understand the relationship between race/ethnicity and EFS. To decrease model parameterization and to reflect the most recent risk group classification system used by COG in their study AAML1031, we created a summary Risk Group variable that incorporated each patient's results for the following disease characteristics t(8;21), inversion 16, CEBPA, NPM1, monosomy 7, monosomy 5, deletion 5q, FLT3/ITD-HAR, and MRD. The Risk Group summary variable was constructed as follows **(citation – include table in appendix?)**:

- Low Risk: Group 1: any patient with "good risk markers" - t(8;21), inversion 16, CEBPA, NPM1 - regardless of the presence of "bad risk markers" - monosomy 7, monosomy 5, deletion 5q - or MRD positivity, as long as FLT3/ITD-HAR is negative. Group 2: any patient who is negative for FLT3/ITD-HAR and also lacks "good risk markers" as well as "bad risk markers" monosomy 7, monosomy 5, deletion 5q, and is also MRD negative.
- High Risk: Group 1: any patient who is FLT3/ITD-HAR positive, regardless of the presence of "good risk markers." Group 2: any patient who is FLT3/ITD-HAR negative but has "bad risk markers" and no "good risk markers," regardless of MRD status. Group 3: any patient who is FLT3/ITD-HAR negative and has neither "good risk makers" nor "bad risk markers," but is MRD positive.

- Patients with missing or incomplete information are defaulted to classification in the "Low Risk" group.

The final multivariate Cox Proportional Hazards Model describes the relationship between race/ethnicity and EFS, censored at the time of per-protocol transplant, controlling for age, weight, SES (via payment type), and Risk Group:

- $h(t) = h_0(t)\exp(\beta_1 RaceEth1 + \beta_2 RaceEth2 + \beta_3 RaceEth3 + \beta_4 Age1 + \beta_5 Age2 + \beta_6 Age3 + \beta_7 Weight1 + \beta_8 Weight2 + \beta_9 Weight3 + \beta_{10} Payment1 + \beta_{11} Payment2 + \beta_{12} Payment3 + \beta_{13} RiskGroup1)$; where RaceEth1 = Asian, RaceEth2 = Black, and RaceEth3 = Hispanic-White, and White patients were the reference group, Age1 = < 1 yo, Age2 = 10-15.99 yo, Age3 = ≥ 16 yo, and patients age 1-9.99 were the reference group, Weight1 = "Overweight," Weight2 = "Underweight," Weight3 = "Unable to Classify," and patients of "Middleweight" were the reference group, Payment1 = "Medicaid or No insurance," Payment2 = "Medicare," Payment3 = "Military," and patients who were "Self Pay or Private Insurance" were the reference group, and RiskGroup1 = "High Risk" patients with "Low Risk" patients as the reference group.

It is important to note that patients of weight "Unable to Classify" were included in the model because nearly all of them were patients < 1 yo; therefore, excluding those patients would also inadvertently exclude all patients < 1 yo.

**Interactions:** While no interactions were included in the final model, we did look for the presence of interaction between race/ethnicity and the following covariates: t(8;21), inversion 16, Payment Type, and Risk Group. Interaction models were assessed using race/ethnicity and just one other covariate at a time. The model is as follows:

- $h(t) = h_0(t)\exp(\beta_1 RaceEth1 + \beta_2 RaceEth2 + \beta_3 RaceEth3 + \beta_4 Covariate1 + \beta_5 Covariate2 + \ldots + \beta_N CovariateX + \beta_{N+1} RaceEth1*Covariate1 + \beta_{N+2} RaceEth2*Covariate2 + \ldots + \beta_{N+Y} RaceEth3*CovariateX)$; where RaceEth1 = Asian, RaceEth2 = Black, and RaceEth3 = Hispanic-White, and White patients were the reference group, and "Covariate1" – "CovariateX" = specific covariate of interest with levels indicated by dummy variables "1-X," and parameter estimates $\beta_1 - \beta_N$.

**Assessment of Potential Bias:** Because the primary outcome of interest was EFS censored at the time of per-protocol transplant, if a disproportionate number of patients from one racial/ethnic group were censored, our interpretation of the relationship between race/ethnicity and EFS would be biased. To verify that our censorship method did not introduce bias, we verified that the proportion of patients censored from each racial/ethnic group was similar by comparing the frequency of EFS outcomes (induction failure, relapse, and death), stratified by race/ethnicity, with censoring to the frequency of EFS outcomes without censoring.

# RESULTS

## Patients

A total of 1070 patients were enrolled on COG AAML0531, but only 1022 were eligible for inclusion in this analysis. Of those included, 748 (73.18%) were White, 116 (11.35%) were Black, 50 (4.89%) were Asian, 137 (18.30%) were Hispanic-White, and 108 (10.57%) were classified as "Other" (Table 1). "Other" patients were excluded from further analysis, leaving a total of 914 patients in the study group.

Table 2a shows patient characteristics, stratified by race/ethnicity. Age and gender were evenly distributed between groups, but there were significant differences in the distribution of weight and payment type comparing different racial/ethnic groups to patients of White race ($p=0.001$ and $p<0.0001$, respectively). The difference in weight was due to the presence of significantly more "Middleweight" Asian and "Overweight" Hispanic-White patients compared to White. The difference in payment type was due to significantly more Black and Hispanic-White patients with Medicaid or no insurance compared to White and significantly more White patients with Private Insurance or "self pay" compared to Black and Hispanic-White patients.

Of the 16 different disease characteristics examined in this study, only 3 were significantly differently distributed between racial/ethnic groups: t(8;21) ($p=0.054$), 11q23 ($p=0.015$), and the presence of "other cytogenetic abnormalitites" ($p=0.003$) (Table 2b). A greater proportion of Black patients (26.14%) than any other group had the low risk cytogenetic feature t(8;21); however, Black patients also had many more accumulated "other cytogenetic abnormalities" than any other group (53.45% compared to 36.17% of Whites, 30% of Asians, and 40.88% of Hispanic-Whites). Abnormalities of 11q23 were over-represented in White patients (32.44%) compared to patients in the other racial/ethnic groups. Importantly, racial/ethnic groups were evenly represented in summary High Risk and Low Risk groups created by taking into account each of the disease and treatment-related factors thought to affect outcome.

There were no differences in the racial/ethnic distribution of any of the 4 treatment characteristics evaluated in this study. Most notably, there was no racial/ethnic disparity with regard to receipt of per-protocol SCT.

**Response to Induction Chemotherapy**

There was a significant difference in the proportion of patients with MRD positivity following the first cycle of induction chemotherapy between racial/ethnic groups ($p = 0.013$) (Table 3b). This difference was due solely to the disparity between Asian and White patients; the odds ratio of MRD positivity for Asian compared to White patients was 2.72 (95% CI: 1.40-5.31; $p = 0.003$) (Table 3a). However, by the time the second cycle of induction chemotherapy was complete, there were no longer any differences in treatment response between groups for the endpoints remission, relapse, or death (Table 4). Additionally, there was no statistically detectable difference in the occurrence of early death – death within the first 3 cycles of chemotherapy – between groups (Table 5b); but, there was a trend toward increased early death for Black (OR 2.25, 95% CI: 0.78-6.51) and Asian patients (OR 2.08, 95% CI: 0.45-9.56) compared to White (Table 5a).

**Survival Analysis**

**Event-free Survival:** The entire cohort of patients had a 3-year and 5-year EFS, censored at the time of per-protocol transplant, of 49.40% ± 1.83 and 48.06% ± 1.92, respectively, with a median survival time of 902 days (Figure 1). A stratified Kaplan-Meier survival analysis using the Sidak adjustment for multiple comparisons showed that both 3 and 5-year EFS were significantly different for Black compared to White patients (3-year EFS: 39.07% ± 4.89 vs 51.94% ± 2.25 and 5-year EFS: 39.07% ± 4.89 vs 50.84% ± 2.35; $p = 0.035$) (Figure 2). While there were no statistically detectable differences in survival comparing any other group to White patients, there

was a trend toward worse EFS at 5 years for Asian patients (5-year EFS 34.58% ± 8.43 vs 50.84% ± 2.35; p = 0.095).

**Overall Survival:** The entire cohort of patients had a 3-year and 5-year EFS, censored at the time of per-protocol transplant, of 67.02% ± 1.74 and 62.40% ± 2.10, respectively (Figure 3). Median survival time was not reached by the end of the study period. A stratified Kaplan-Meier survival analysis using the Sidak adjustment for multiple comparisons showed that all racial/ethnic groups had significantly worse 3 and 5-year OS compared to White patients (Figure 4).

**Assessment of Potential Bias in EFS Results Due To Censoring:** Table 6 shows the proportion of patients from each racial/ethnic group who experienced each type of EFS event (induction failure, relapse, or death), excluding those patients who had per-protocol SCT; whereas Table 7 shows the proportion of patients from each group who experienced each type of EFS event *including* those who had per-protocol SCT. In comparing the two tables, a similar proportion of patients from each racial/ethnic group were excluded when censorship at the time of per-protocol SCT was imposed. For the outcome "relapse," censorship eliminated 4.91% of White patients, 4.31% of Black patients, 4% of Asian patients, and 6.57% of Hispanic-White patients. For the outcome "death as an only event," 1.47% of White patients, 0.87% of Black patients, 2% of Asian patients, and 0.73% of Hispanic-White patients were excluded by censoring at the time of per-protocol SCT.

**Relapse Rate**

A cumulative incidence function, taking into account the competing risks of death and induction failure, was used to assess the rate of relapse for each racial/ethnic group (Figure 5). There was no difference in relapse rate for any racial/ethnic group compared to White patients (p=0.5801).

**Treatment-Related Mortality and Cause of Death**

The TRM rate was assessed for each racial/ethnic group using a cumulative incidence function that accounted for the competing risks of death and relapse (Figure 6). There was a very significant disparity in TRM between groups ($p = 0.0044$), but it was solely due to the very large difference in TRM between Black and White patients ($15.21\% \pm 3.54$ vs $5.66\% \pm 1.01$; $p = 0.0006$). Table 8 shows the causes of death for patients who experienced TRM, stratified by race/ethnicity. There was no apparent pattern in the cause of death for any particular racial/ethnic group.

**Race/Ethnicity as a Predictor of EFS: Cox Proportional Hazards Models**

**Univariate Models:** Race/ethnicity, age, weight, payment type (as a surrogate for SES), and risk group were assessed as univariate predictors of EFS using Cox Proportional Hazards Models (Table 9). Black patients compared to White patients, patients < 1 year old compared to patients 1-9.99 years old, and High Risk compared to Low Risk patients all had a significantly worse hazard of experiencing an EFS event (Black: HR 1.41, 95% CI: 1.07-1.86, $p = 0.015$; <1 yo: HR 1.51, 95% CI: 1.08-2.10, $p = 0.015$; High Risk: HR 2.51, 95% CI: 2.03-3.11, $p < 0.0001$). Patients of weight "Unable to Classify" also had significantly worse EFS compared to Middleweight patients (HR 1.34, 95% CI: 1.03-1.84, $p = 0.031$); however, this group was comprised mostly of patients < 1 year old. SES, as reflected by payment type, was not a statistically significant predictor of EFS.

**Interactions:** Tables 10a-13b show the results of Cox Proportional Hazards Models exploring whether the effect of race/ethnicity on EFS is affected by the presence or absence of t(8;21) (Tables 10a and 10b), inversion 16 (Tables 11a and 11b), Risk Group classification (Tables 12a and 12b), or payment type (Tables 13a and 13b). Among White and Black patients, the presence of t(8;21) significantly predicts good outcome to a similar degree (White: HR 0.28, 95%CI: 0.16-0.49, $p<0.0001$; Black: HR 0.36, 95% CI: 0.16-0.79, $p=0.012$). Among Hispanic-White patients, the presence of t(8;21) tends to predict good outcome (HR 0.59, 95% CI: 0.28-1.27; $p = 0.178$),

but the difference was not statistically detectable, and among Asian patients, the presence of t(8;21) did not significantly predict outcome. In this cohort, compared to White patients with t(8;21), both Asian and Hispanic-White patients with t(8;21) had significantly worse EFS (HR 1.45, 95% CI: 1.13-10.60; p=0.030 and HR 2.48, 95% CI: 1.03-5.97; p=0.044, respectively). Finally, in the absence of t(8;21), Black patients tended to have worse EFS than White patients (HR 1.40, 95% CI: 0.99-1.98, p = 0.054).

The presence of inversion 16 tends to predict improved EFS among White, Black, and Hispanic-White patients, although this improvement only reached statistical significance for Hispanic-White patients (HR 0.33, 95% CI: 0.12-0.92; p=0.034) (Table 11a). Conversely, Hispanic-White patients without inversion 16 tended to have worse outcome compared to White patients without inversion 16 (HR 1.39, 95% CI: 0.99-1.94, p=0.054) (Table 11b).

Risk group similarly predicts outcome within each racial/ethnic group (Table 12a). Moreover, Table 12b shows that Low Risk Black patients have a significantly worse outcome than Low Risk White patients (HR 1.41, 95% CI: 1.00-1.97; p=0.047); thus, Black patients have significantly worse outcome than White patients, regardless of Risk Group classification.

Payment type did not affect EFS when controlling for race/ethnicity (Table 13a). However, Black patients compared to White patients with “Medicaid or No Means of Payment” had worse EFS (HR 1.81, 95% CI: 1.15-2.87; p=0.011) (Table 13b).

**Multivariate Model:** Race/ethnicity continued to be a predictor of worse outcome, even when controlling for age, weight, payment type, and risk group in the same model (Table 14). Black patients had significantly worse hazard of experiencing an EFS event compared to White patients (HR 1.49, 95% CI: 1.10-2.00; p=0.009). There was a trend toward worse outcome for Asian patients in this model as well; however, the difference was not statistically detectable.

# DISCUSSION

Since Aplenc *et al* first reported worse survival for Black and Hispanic children with AML in their 2006 publication, this is the first time racial/ethnic survival disparities have been reported for pediatric AML patients treated on a large, multicenter, contemporary phase III trial. In this study, we have shown that Black patients have significantly worse EFS than White patients (39.07% ± 4.89 vs 50.84% ± 2.35; p = 0.035), and that this difference is due to markedly excessive TRM (15.21% ± 3.54 vs 5.66% ± 1.01; p=0.0006). In using EFS as our primary endpoint and censoring patients at the time of per-protocol SCT in CR-1, we were able to remove the influence of SCT complications on survival, well known to be worse for Black compared to White patients, in order to assess the relationship between race/ethnicity, chemotherapy, and outcome. Furthermore, we verified that our use of censorship in this way to tease out this relationship did not introduce bias into our results; a similar proportion of patients from each racial/ethnic group was censored at the time of per-protocol SCT in CR-1.

While we hypothesized that racial/ethnic differences in patient, disease, and treatment characteristics would be, at least in part, responsible for survival disparities, we did not find this to be the case. In fact, there were very few differences in the distribution of specific patient and disease characteristics between groups, and there were no differences in treatment characteristics between racial/ethnic groups. With the exception of t(8;21), none of the other cytogenetic/molecular characteristics known to be reliable predictors of outcome including inversion 16, FLT3/ITD-HAR, monosomy 7, monosomy 5/del 5q, CEBPA, and NPM1, that we hypothesized might contribute to racial/ethnic disparities in outcome due to imbalanced distribution between groups were differentially represented. Notably, Black patients more frequently had the low risk cytogenetic abnormality t(8;21), but this did not lead to an increased proportion of Black patients being classified as Low Risk – similar proportions of patients were classified as Low and High Risk from each racial/ethnic group. In examining Cox Proportional

Hazards Models looking for an interaction between race/ethnicity and t(8;21) and race/ethnicity and Risk Group, there was no interaction observed – both predictors of outcome had similar effects on survival for all racial/ethnic groups.

MRD positivity has recently been recognized as an important predictor of EFS, and our univariate analysis again shows this to be true (HR=2.59, 95% CI: 2.06-3.27; p<0.0001). Additionally, we found that Asians are significantly more likely than Whites to be MRD positive following Induction I of chemotherapy (OR=2.72, 95% CI: 1.40-5.31; p=0.003). However, by the end of the second cycle of induction, there were no racial/ethnic differences in chemotherapy response and patients in all groups had similar rates of remission. This is consistent with the findings of the study by Aplenc *et al.* Thus, the disparity in EFS that we observed was not due to a differential response to induction chemotherapy.

Relapse and TRM are the two causes of treatment failure in AML. In our study, we found no difference in the rate of relapse between racial/ethnic groups; however, as previously mentioned, there was excessive TRM for Black patients compared to White patients. Aplenc *et al.* also observed a difference in TRM for both Black and Hispanic patients, but not nearly to the degree that we observed. Additionally, they observed significantly more induction death among Black and Hispanic patients compared to White patients. We examined "early death" – death within the first 3 cycles of chemotherapy – and while we could not statistically detect a difference in the occurrence of early death due to its fortunate rarity, the odds of early death for both Black and Asian patients were over twice that of White patients. Thus, early death due to the toxic effects of treatment likely contributes to some degree to the excessive TRM we observe for Black patients. Unfortunately, in looking at the causes of death for patients of any race/ethnicity who had TRM, we were unable to identify a single underlying cause.

A limitation of prior work in this area was in the failure to evaluate the impact of SES on outcome. Low SES has been shown to affect the outcome of treatment for other types of cancer due to a negative influence on nutrition, reduced compliance with therapy, and decreased access

to care, among other reasons. We did not expect that SES would impact the outcome of AML treatment, because unlike for other types of cancer, pediatric AML treatment is administered exclusively in the inpatient hospital setting. In our study, we used payment type as a surrogate indicator of SES, with "Private Insurance/Self Pay" indicating high SES and "Medicaid or No Insurance" indicating low SES. In a univariate model, we confirmed that SES, as represented by payment type, does not predict EFS in children with AML treated on this protocol (p=0.914). Despite the absence of a main effect, we further explored whether there was an interaction between race/ethnicity and payment type. We found that Black patients compared to White patients with "Medicaid or No Insurance" had a significantly worse EFS (HR= 1.81, 95% CI: 1.15-2.87; p=0.011). However, importantly, significantly more Black patients than White patients enrolled on this study had "Medicaid or No Insurance" (42.24% vs 19.80%; p<0.0001), which is not surprising because it reflects a demographic truth about race/ethnicity and SES in the U.S. Thus, the apparent disparity in outcome between Black and White patients of low SES does not have to do with an effect of SES on outcome that varies by race/ethnicity, but is simply due to the fact that there are many more Black patients than White patients of low SES enrolled on this study and that Black patients have poorer survival due to the disproportionate occurrence of TRM. Therefore, we can conclude that SES does not contribute to the racial/ethnic disparities in EFS we observe.

Our ability to show that racial/ethnic disparities in AML treatment outcome are independent both of SES and of complications related to SCT is a major strength of this study and, to our knowledge, is the first time this has been reported. Furthermore, while others have described excessive TRM for Black patients, our study is the first to show such an extreme difference and to isolate TRM as the likely cause of racial/ethnic disparities in AML outcome, independent of other patient, disease, and treatment characteristics known to predict prognosis. However, one limitation to our analysis is that almost 1/3 of the patients included had incomplete cytogenetic and molecular testing results, so it is possible that disparities in other disease

characteristics may have been identified, given more complete testing results. Our study is also limited by our inability to determine from our cause of death data the underlying reason for the excess TRM experienced by Black patients. Thus, future research should be aimed at determining the underlying reason for this so that therapy can be modified or appropriate interventions can be designed to mitigate this adverse outcome.

# CONCLUSION

Black children with newly diagnosed AML continue to have worse outcome than White children, despite contemporary changes in treatment approach. This disparity cannot be explained entirely be racial differences in access to SCT or transplant-related outcomes. Mortality during chemotherapy treatment from complications, rather than from disease, is also more common among Black children, and this disparity does not appear to be mediated by SES. Future research should be directed toward understanding the reasons for the disproportionate TRM experienced by Black patients so that appropriate treatment modifications or other interventions can be designed to mitigate this adverse outcome.

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TABLES AND FIGURES

Table 1. Race and ethnicity of patients enrolled on study AAML0531

| | White n (%) | Black n (%) | Asian n (%) | Other n (%) | Total Patients n (%) |
|---|---|---|---|---|---|
| **Race** | 748 (73.18) | 116 (11.35) | 50 (4.89) | 108 (10.57) | 1022 |
| **Ethnicity** | | | | | |
| **Hispanic** | 137 (18.30) | 8 (6.90) | 2 (4.00) | 42 (38.89) | 189 (18.50) |
| **Not Hispanic** | 600 (80.21) | 104 (89.66) | 48 (96.00) | 42 (38.89) | 794 (77.69) |
| **Unknown** | 11 (1.47) | 4 (3.45) | 0 | 24 (22.22) | 39 (3.82) |

Table 2a. Patient characteristics by race/ethnicity

| | White n (%) | Black n (%) | Asian n (%) | Hispanic-White n (%) | P-Value |
|---|---|---|---|---|---|
| **Patient Characteristics** | | | | | |
| **Total Patients (n=914)** | **611 (59.78)** | **116 (11.35)** | **50 (4.89)** | **137 (13.41)** | |
| **Age** | | | | | 0.539 |
| **<1 yo** | 66 (10.8) | 11 (9.48) | 1 (2.00) | 14 (10.22) | |
| **1-9.99 yo** | 247 (40.43) | 40 (34.48) | 22 (44.00) | 55 (40.15) | |
| **10-15.99 yo** | 193 (31.59) | 46 (39.66) | 19 (38.00) | 49 (35.77) | |
| **≥ 16 yo** | 105 (17.18) | 19 (16.38) | 8 (16.00) | 19 (13.87) | |
| **Gender (male)** | 317 (51.88) | 53 (45.69) | 22 (44.00) | 67 (48.91) | 0.476 |
| **Weight** | | | | | **0.001*** |
| **Underweight** | 46 (7.53) | 5 (4.31) | 4 (8.00) | 6 (4.38) | |
| **Middleweight** | 397 (64.98) | 76 (65.52) | 40 (80.00) | 78 (56.93) | |
| **Overweight** | 89 (14.57) | 21 (18.10) | 2 (4.00) | 38 (27.74) | |
| **Not Classified** | 79 (12.93) | 14 (12.07) | 4 (8.00) | 15 (10.95) | |
| **Payment Type[¥]** | | | | | **<0.0001*[§]** |
| **Self Pay or Private Insurance** | 383 (62.68) | 52 (44.83) | 33 (66.00) | 39 (28.47) | |
| **Medicaid or No Insurance** | 121 (19.80) | 49 (42.24) | 7 (14.00) | 77 (56.20) | |
| **Medicare** | 8 (1.31) | 1 (0.86) | 0 | 1 (0.73) | |
| **Military** | 6 (0.98) | 2 (1.72) | 1 (2.00) | 0 | |
| **Uncategorized** | 93 (15.22) | 12 (10.34) | 9 (18.00) | 20 (14.60) | |

*Denotes significant p-value, α=0.05; Pearson Chi Square probability is reported
[§]p-value is the Monte-Carlo estimate for the exact test
[¥]Payment Type categories: Self Pay or Private Insurance = Self pay or no insurance but with means to pay or Private Insurance; Medicaid or No Insurance = Medicaid with or without medicare or no insurance without means of payment; Medicare = Medicare with or without additional private insurance; Military Insurance = any military insurance including Champus, Tricare, and Veterans

Table 2b. Disease characteristics by race/ethnicity

| | White n (%) | Black n (%) | Asian n (%) | Hispanic-White n (%) | P-Value* |
|---|---|---|---|---|---|
| **Disease Characteristics Total Patients (n=914)** | **611** | **116** | **50** | **137** | |
| **CNS Disease (n=914)** | 43/611 (7.04) | 11/116 (9.48) | 2/50 (4.00) | 7/137 (5.11) | 0.464 |
| **Cytogenetic Risk (n=878)** | | | | | 0.178§ |
| **High** | 20/592 (3.37) | 7/113 (6.20) | 3/47 (6.38) | 2/126 (1.59) | |
| **Standard** | 440/592 (74.32) | 75/113 (66.37) | 37/47 (78.72) | 90/126 (71.43) | |
| **Low** | 132/592 (22.30) | 31/113 (27.43) | 7/47 (14.89) | 34/126 (26.98) | |
| **CEBPA Mutation (n=794)** | 29/531 (5.46) | 6/102 (5.88) | 5/41 (12.20) | 6/120 (5.00) | 0.344 |
| **NPM1 Mutation (n=796)** | 41/532 (7.71) | 5/102 (4.90) | 3/41 (7.31) | 10/121 (8.26) | 0.769 |
| **Trisomy 8 (n=664)** | 77/446 (17.26) | 14/88 (15.91) | 4/31 (12.90) | 12/99 (12.12) | 0.606 |
| **Inv(16)/t(16;16) (n=664)** | 67/446 (15.02) | 8/88 (9.09) | 1/31 (3.23) | 15/99 (15.15) | 0.152 |
| **t(8;21) (n=664)** | 65/447 (14.54) | 23/88 (26.14) | 6/31 (19.35) | 19/98 (19.39) | **0.054*** |
| **-5/5q- (n=914)** | 10/611 (1.64) | 1/116 (0.86) | 1/50 (2.00) | 0/137 | 0.446§ |
| **FLT3/ITD-HAR¥ (n=803)** | 52/538 (9.66) | 6/103 (5.82) | 6/42 (14.28) | 11/120 (9.17) | 0.825 |
| **Monosomy 7 (n=664)** | 15/446 (3.36) | 4/88 (4.54) | 2/31 (6.45) | 1/99 (1.01) | 0.379§ |
| **t(6;9)(p23;q34) (n=665)** | 12/447 (2.68) | 3/88 (3.41) | 2/31 (6.45) | 1/99 (1.01) | 0.383§ |
| **t(9;11)(p22;q23) (n=665)** | 54/447 (12.08) | 8/88 (9.09) | 2/31 (6.45) | 9/99 (9.09) | 0.596 |
| **11q23 Abnormality (n=665)** | 145/447 (32.44) | 20/88 (22.73) | 5/31 (16.13) | 20/99 (20.20) | **0.015*** |
| **Other Cytogenetic Abnormality (n=914)** | 221/611 (36.17) | 62/116 (53.45) | 15/50 (30.00) | 56/137 (40.88) | **0.003*** |
| **Risk Group (n=914)** | | | | | 0.099 |
| **Low (n=684)** | 461/611 (75.45) | 89/116 (76.82) | 30/50 (60.00) | 104/137 (75.91) | |
| **High (n=230)** | 150/611 (24.55) | 27/116 (23.28) | 20/50 (40.00) | 33/137 (24.09) | |

*Denotes significant p-value, $\alpha$=0.05

§Indicates that the p-value is the Monte-Carlo estimate for the exact test, otherwise, Pearson Chi Square probability is reported

¥FLT3/ITD-HAR (FLT3 Internal Tandem Duplication/High allelic ratio). Allelic ratio only evaluated for patients found to be FLT3/ITD positive.

£Patient with t(15;17) also had t(8;21) so met criteria to be treated on study.

Table 2c. Treatment characteristics by race/ethnicity

| | White n (%) | Black n (%) | Asian n (%) | Hispanic-White n (%) | P-Value |
|---|---|---|---|---|---|
| **Treatment Characteristics** | | | | | |
| **Total Patients (n=914)** | **611 (59.78)** | **116 (11.35)** | **50 (4.89)** | **137 (13.41)** | |
| **Treatment Arm** | | | | | 0.665 |
| **Arm A (Standard)** | 296 (48.45) | 61 (52.59) | 27 (54.00 | 72 (52.55) | |
| **Arm B (Experimental)** | 315 (51.55) | 55 (47.41) | 23 (46.00) | 65 (47.45) | |
| **Received Stem Cell Transplant**[¥] | 102 (16.69) | 12 (10.34) | 8 (16.00) | 21 (15.33) | 0.393 |
| **Transplant Donor Type** | | | | | 0.956[§] |
| **Sibling** | 71 (11.62) | 7 (6.03) | 7 (14.00) | 15 (10.95) | |
| **Parent** | 3 (0.49) | 1 (0.86) | 0 | 1 (0.73) | |
| **Unrelated Donor** | 26 (4.26) | 3 (2.59) | 1 (2.00) | 5 (3.65) | |
| **Other** | 3 (0.49) | 1 (0.86) | 0 | 1 (0.73) | |
| **Stem Cell Source** | | | | | 0.530[§] |
| **Bone Marrow** | 83 (13.58) | 11 (9.48) | 7 (14.00) | 16 (11.68) | |
| **Umbilical Cord Blood** | 15 (2.46) | 1 (0.86) | 1 (2.00) | 6 (4.38) | |
| **Peripheral Blood Stem Cells** | 5 (0.82) | 0 | 0 | 0 | |

[§]Indicates that the p-value is the Monte-Carlo estimate for the exact test, otherwise, Pearson Chi Square probability is reported

[¥]3 patients with documented donors and stem cell sources never were documented as having received transplants (2 sibling bone marrow, 1 unrelated umbilical cord blood; 1 White, 2 Hispanic patients)

Tables 3a and b. MRD positivity following Induction 1, comparing patients of different races/ethnicities

3a. Odds ratio of being MRD positive at the end of Induction 1, compared to patients of White race.

| | White OR | Black OR (95% CI) | Asian OR (95% CI) | Hispanic-White OR (95% CI) | P-Value |
|---|---|---|---|---|---|
| **MRD Positive** | 1 | 1.36 (0.84-2.20) | 2.72*§ (1.40-5.31) | 0.92 (0.58-1.48) | **0.017*§** |

White = Reference group
*Denotes significant p-value, α=0.05
§The significant p-value is due to the contribution of the comparison of Asian to White, where p=0.0032. All other comparisons were not statistically significant.

3b. Proportion of patients who were MRD positive at the end of Induction 1, by race/ethnicity.

| | White n (%) | Black n (%) | Asian n (%) | Hispanic-White n (%) | P-Value* |
|---|---|---|---|---|---|
| **MRD Status** | | | | | **0.013*** |
| **Positive** | 137 (22.42) | 31 (26.72) | 20 (40.00) | 29 (21.17) | -- |
| **Negative** | 336 (54.99) | 56 (48.28) | 18 (36.00) | 77 (56.20) | -- |
| **Unknown†** | 138 (22.59) | 29 (25.00) | 12 (24.00) | 31 (22.63) | -- |

*Denotes significant p-value, α=0.05
†These values not included in chi-square test (test only compares proportion of positive to negative)

Table 4. Outcomes by race/ethnicity following 2 cycles of induction chemotherapy.

| | White n (%) | Black n (%) | Asian n (%) | Hispanic-White n (%) | P-Value |
|---|---|---|---|---|---|
| **End Induction 2 Marrow Result (n=914)** | 611 (59.78) | 116 (11.35) | 50 (4.89) | 137 (13.41) | 0.144[§] |
| **Complete Remission** | 514 (84.12) | 93 (80.17) | 37 (74.00) | 108 (78.83) | -- |
| **Relapse** | 24 (3.93) | 1 (0.86) | 0 | 7 (5.11) | -- |
| **Refractory Disease** | 40 (6.55) | 10 (8.62) | 6 (12.00) | 13 (9.49) | -- |
| **Death** | 10 (1.64) | 5 (4.31) | 2 (4.00) | 3 (2.19) | -- |
| **Unevaluable*** | 23 (3.76) | 7 (6.03) | 5 (10.00) | 6 (4.38) | -- |

The Bonferroni Adjustment for multiple comparisons did not yield any significant differences between any racial/ethnic groups

[*]Unevaluable patients were not included in the statistical comparison

[§]Indicates that the p-value is the Monte-Carlo estimate for the exact test for the Pearson Chi Square probability

Tables 5a and b. Occurrence of early death, comparing patients of different races/ethnicities

5a. Odds ratio of early death, compared to patients of White race.

| | White OR (95% CI) | Black OR (95% CI) | Asian OR (95% CI) | Hispanic-White OR (95% CI) | P-Value |
|---|---|---|---|---|---|
| **Early Death** | 1 | 2.25 (0.78-6.51) | 2.08 (0.45-9.56) | 1.12 (0.31-4.02) | 0.434 |

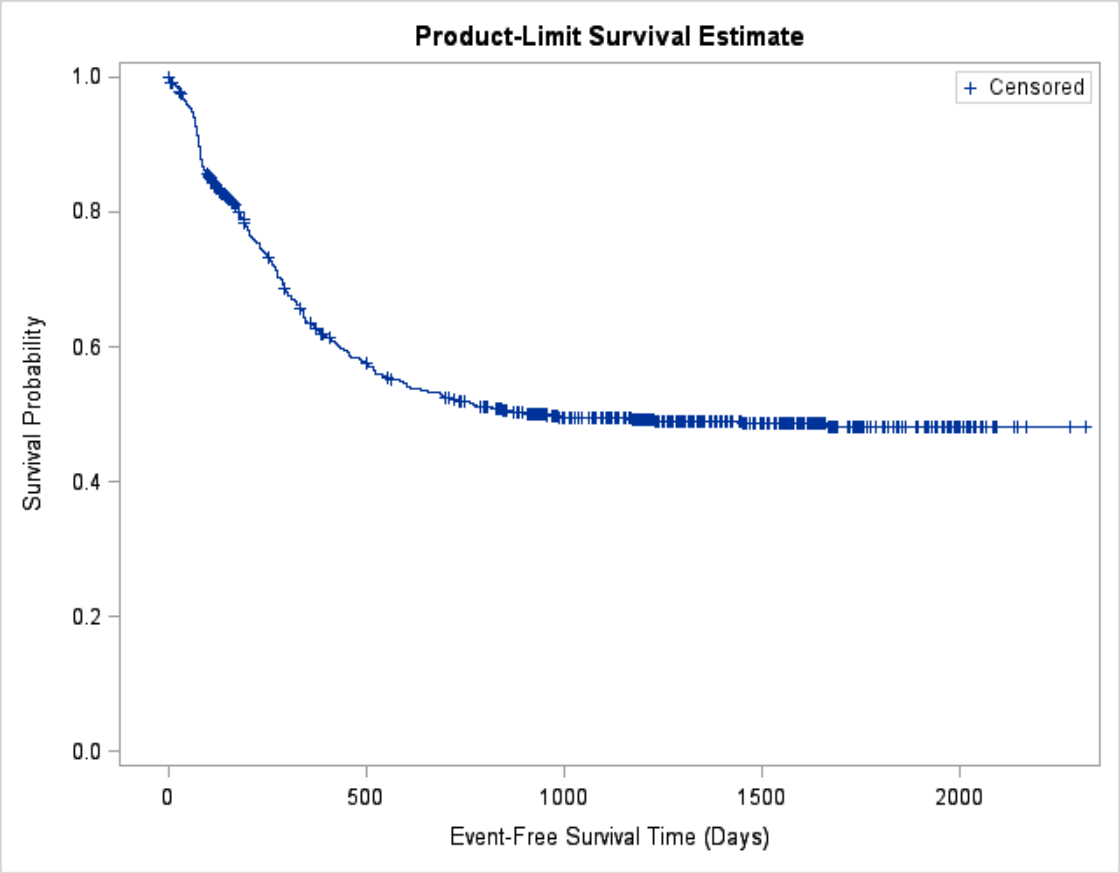
White = Reference group
Early Death = Death during first 3 cycles of chemotherapy

5b. Proportion of patients who had early death, by race/ethnicity.

| | White n (%) | Black n (%) | Asian n (%) | Hispanic-White n (%) | P-Value |
|---|---|---|---|---|---|
| **Status** | | | | | 0.408 |
| **Alive** | 599 (98.04) | 111 (95.69) | 48 (4.00) | 134 (97.81) | -- |
| **Dead** | 12 (1.96) | 5 (4.31) | 2 (4.00) | 3 (2.19) | -- |

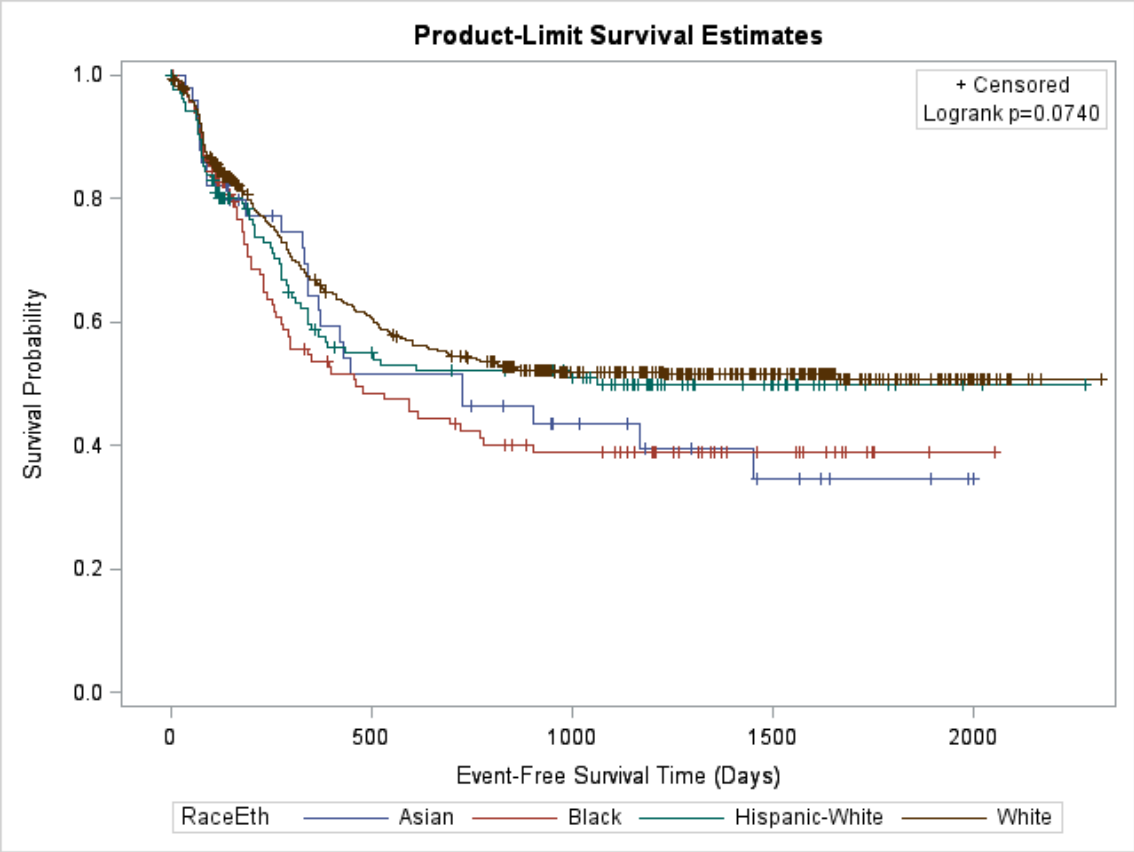
White = Reference group
Early Death = Death during first 3 cycles of chemotherapy
Pearson Chi-square p-value reported

Figure 1. Event-free survival, censored at the time of per-protocol transplant in CR-1.




3-year EFS = 49.40% ± 1.83; 5-year EFS = 48.06% ± 1.92 ; Median survival = 902 days

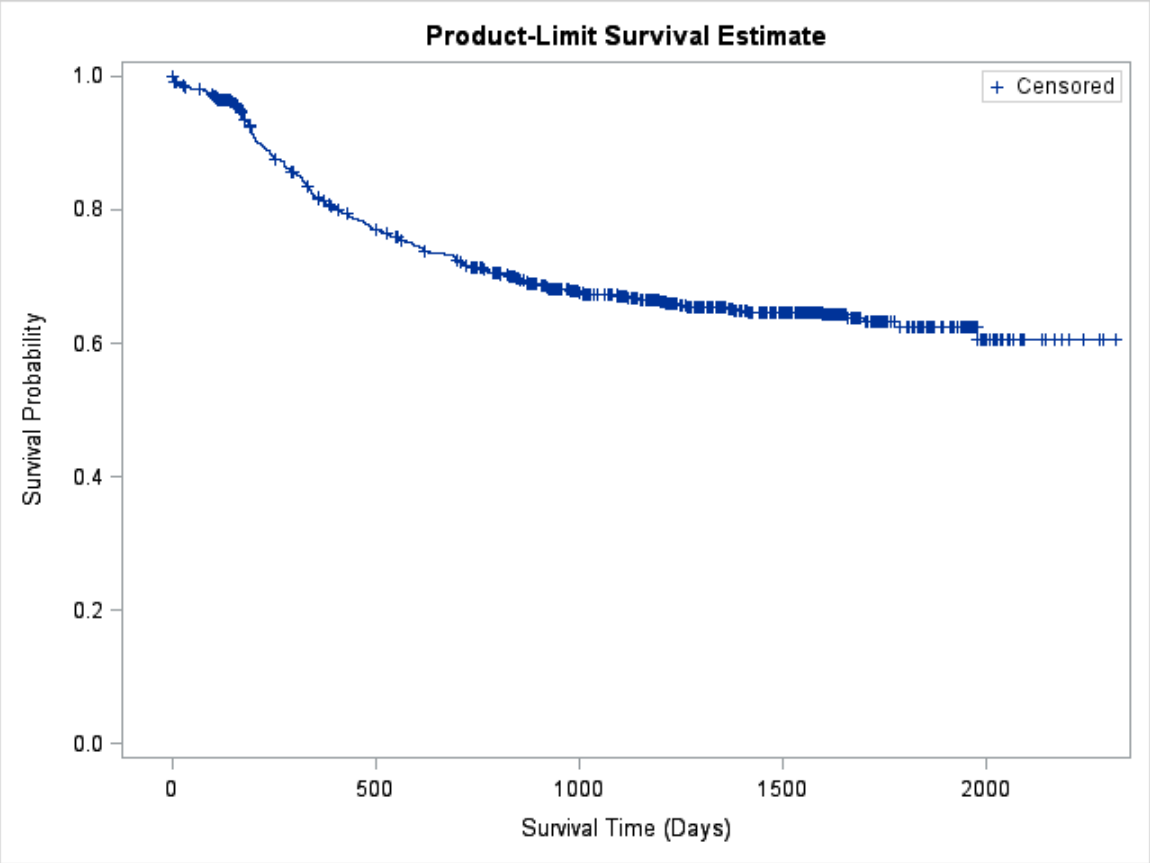
Figure 2. Event-free survival, censored at the time of per-protocol transplant in CR-1, comparing racial/ethnic groups.




| Race/Ethnicity | 3-year EFS ± SE | 5-year EFS ± SE | Median Survival Time (Days) | P-Value*§ |
|---|---|---|---|---|
| **White**# | 51.94% ± 2.25 | 50.84% ± 2.35 | ¥ | -- |
| **Black** | 39.07% ± 4.89 | 39.07% ± 4.89 | 460 | **0.035*** |
| **Asian** | 43.48% ± 7.84 | 34.58% ± 8.43 | 724 | 0.095 |
| **Hispanic-White** | 49.81% ± 4.71 | 49.81% ± 4.71 | 1060 | 0.348 |

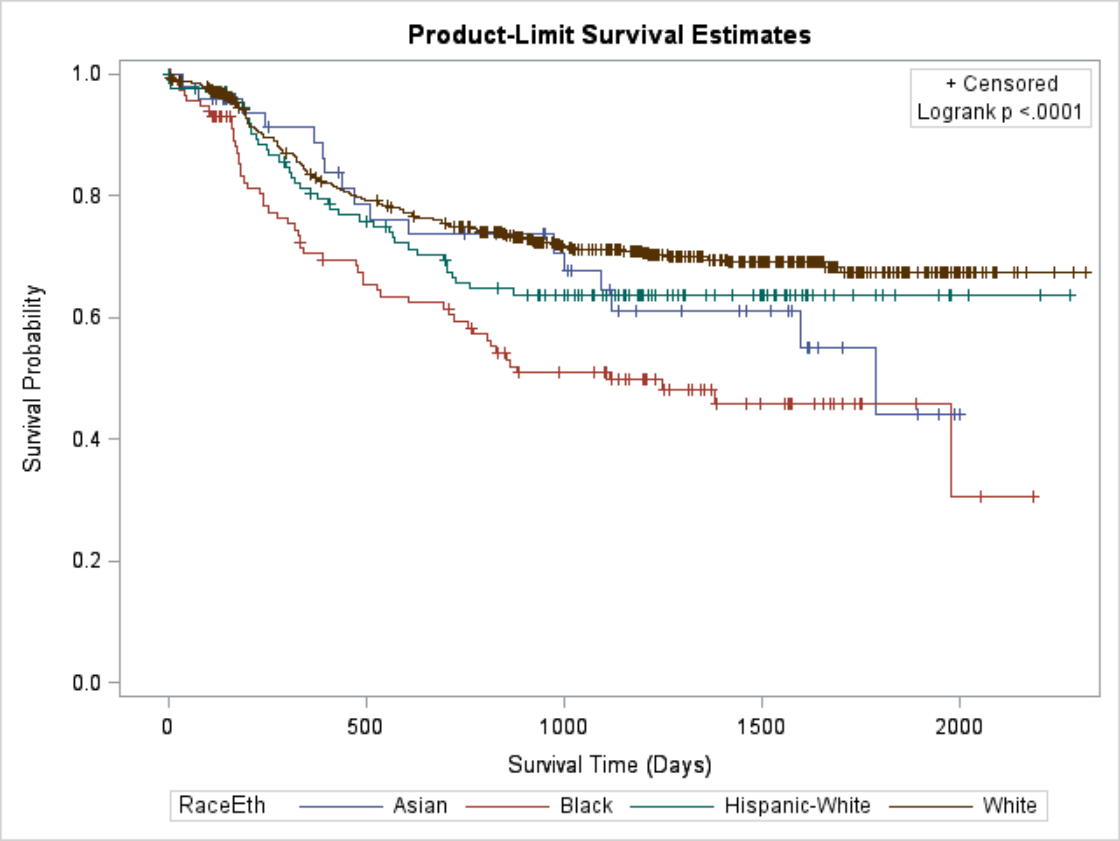
#White race used as reference group for reporting of p-values
*Denotes significant p-value, $\alpha = 0.05$
§Sidak adjustment for multiple comparisons for the Logrank test is reported
¥Median survival time not reached by the end of the study period

Figure 3. Overall survival, censored at the time of per-protocol transplant in CR-1.




3-year OS = 67.02% ± 1.74; 5-year OS = 62.40% ± 2.10
*Median survival time not reached

Figure 4. Overall survival, censored at the time of per-protocol transplant in CR-1, comparing racial/ethnic groups.




| Race/Ethnicity | 3-year OS ± SE | 5-year OS ± SE | Median Survival Time (Days) | P-Value*§ |
|---|---|---|---|---|
| **White**# | 71.22% ± 2.06 | 67.52% ± 2.39 | ¥ | -- |
| **Black** | 50.94% ± 5.01 | 45.78% ± 5.37 | 1117 | **<0.0001*** |
| **Asian** | 64.53% ± 7.79 | 44.02% ± 1.23 | 1787 | **0.006*** |
| **Hispanic-White** | 63.81% ± 4.55 | 63.81% ± 4.55 | ¥ | **0.035*** |

#White race used as reference group for reporting of p-values
*Denotes significant p-value, $\alpha = 0.05$
§Sidak adjustment for multiple comparisons for the Logrank test is reported
¥Median survival time not reached by the end of the study period

Table 6. EFS outcomes by race/ethnicity, excluding patients who had per-protocol transplant in CR-1.

| | White n (%) | Black n (%) | Asian n (%) | Hispanic-White n (%) | P-Value |
|---|---|---|---|---|---|
| **Total Patients (n=399)** | | | | | 0.086 |
| **Relapse** | 156 (25.53) | 36 (31.03) | 17 (34.00) | 34 (24.82) | 0.734 |
| **Refractory Disease** | 64 (10.47) | 11 (9.48) | 6 (12.00) | 20 (14.60) | 0.243 |
| **Death as Only Event[§]** | 30 (4.91) | 16 (13.79) | 3 (6.00) | 6 (4.38) | **0.034*** |

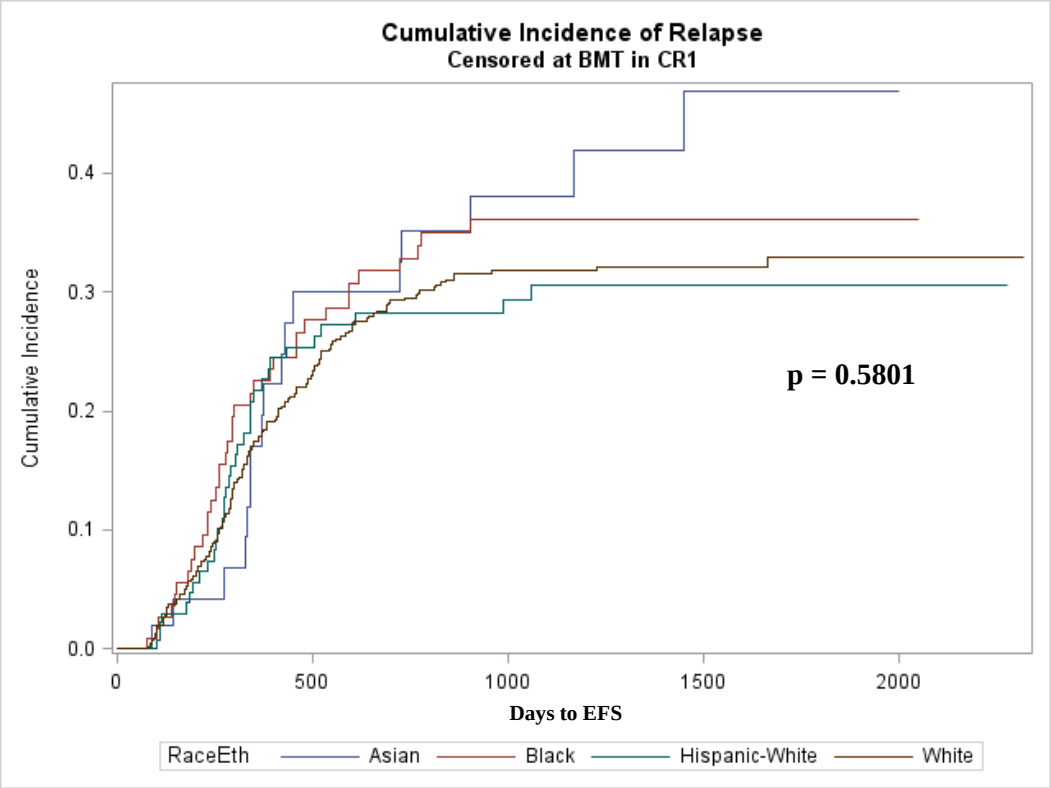
*Denotes significant Pearson Chi-square p-value, $\alpha$=0.05. P-value is for comparison of specific EFS event to all other EFS events
[£]These relapsed patients received ONLY chemotherapy, per protocol, prior to relapse (no HSCT).
[§]Patients in this group did not relapse, have refractory disease, or receive per-protocol transplant prior to death

Table 7. EFS outcomes by race/ethnicity, NOT excluding patients who had per-protocol transplant in CR-1.

| | White n (%) | Black n (%) | Asian n (%) | Hispanic-White n (%) | P-Value |
|---|---|---|---|---|---|
| **Total Patients (n=457)** | | | | | 0.184 |
| **Relapse** | 186 (30.44) | 41 (35.34) | 19 (38.00) | 43 (31.39) | 0.556 |
| **Refractory Disease** | 64 (10.47) | 11 (9.48) | 6 (12.00) | 20 (14.60) | 0.513 |
| **Death as Only Event[§]** | 39 (6.38) | 17 (14.66) | 4 (8.00) | 7 (5.11) | **0.012*** |

*Denotes significant Pearson Chi-square p-value, $\alpha$=0.05.
[§]Patients in the group did not relapse prior to death

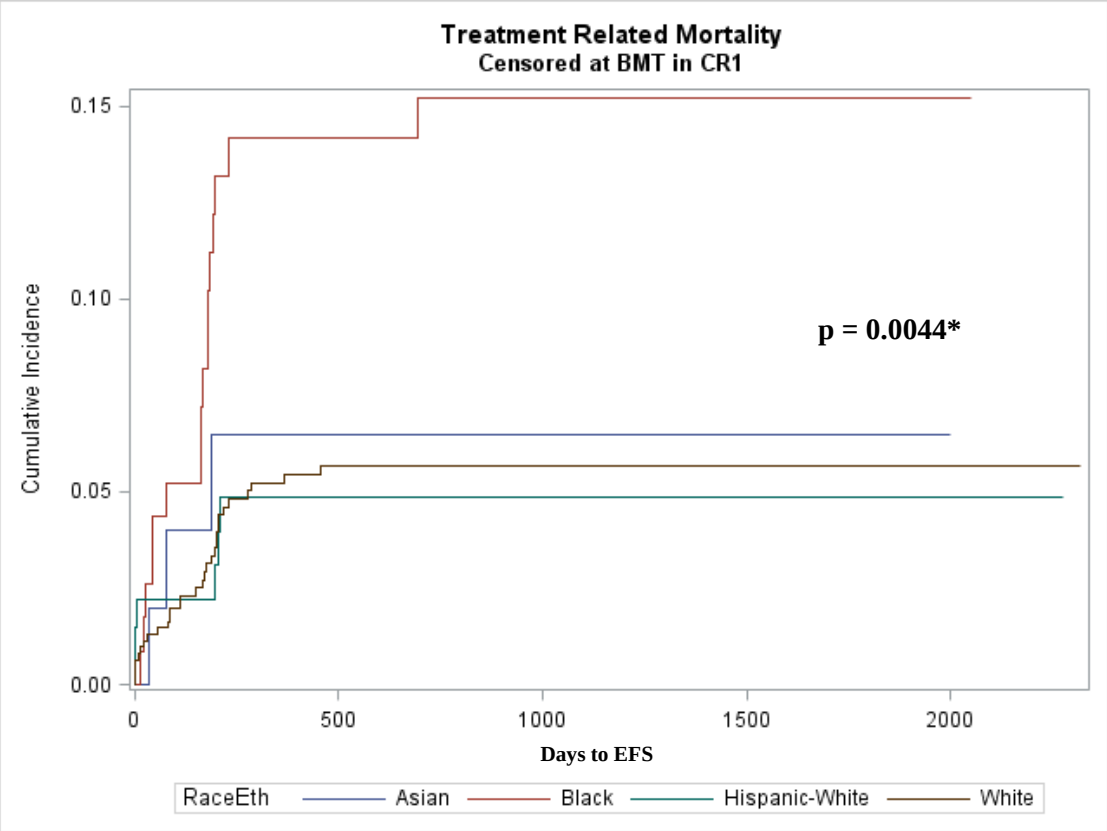
Figure 5. Cumulative incidence of relapse, censored at the time of per-protocol transplant in CR-1.




| Race/Ethnicity | 3-year RR ± SE | P-Value |
|---|---|---|
| **White**[#] | 31.79% ± 2.12 | -- |
| **Black** | 36.13% ± 4.86 | 0.398 |
| **Asian** | 38.03% ± 7.87 | 0.261 |
| **Hispanic-White** | 30.57% ± 4.43 | 0.831 |

RR = relapse rate
[#]Reference group

Figure 6. Treatment-related mortality, censored at the time of per-protocol transplant in CR-1.




| Race/Ethnicity | 3-year TRM ± SE | P-Value |
|---|---|---|
| **White**[#] | 5.66% ± 1.01 | -- |
| **Black** | **15.21% ± 3.54** | **0.0006*** |
| **Asian** | 6.49% ± 3.70 | 0.744 |
| **Hispanic-White** | 4.88% ± 1.96 | 0.755 |

TRM = treatment-related mortality
[#]Reference group

Table 8. Cause of death when death was the only event (descriptive).

| | White n (%) | Black n (%) | Asian n (%) | Hispanic-White n (%) |
|---|---|---|---|---|
| **Cause of Death as Only Event** | | | | |
| **Total Deaths (n=55)** | 30 | 16 | 3 | 6 |
| **AML** | 1 (3.33) | 2 (12.5) | 1 (33.33) | 3 (50.00) |
| **Infection** | 13 (43.33) | 5 (31.25) | 0 | 2 (33.33) |
| **Toxicity** | 0 | 0 | 0 | 0 |
| **Hemorrhage** | 2 (6.67) | 2 (12.5) | 1 (33.33) | 0 |
| **GVHD**[†] | 0 | 1 (6.25) | 0 | 0 |
| **ARDS** | 1 (3.33) | 0 | 0 | 0 |
| **Multiorgan Failure** | 12 (40.00) | 6 (37.50) | 0 | 1 (16.67) |
| **Other Cause** | 0 | 0 | 0 | 0 |
| **Unknown** | 1 (3.33) | 0 | 1 (33.33) | 0 |

[†]One black patient documented as dying from GVHD but not noted to have been transplanted in data set

Table 9. Univariate predictors of EFS parameters (induction failure, relapse, death)

| Variable | Hazard Ratio | Hazard Ratio 95% CI | P-Value |
|---|---|---|---|
| **Race/Ethnicity** | | | 0.076 |
| **Black** | **1.41** | **1.07-1.86** | **0.015*** |
| **Asian** | 1.30 | 0.87-1.95 | 0.198 |
| **Hispanic-White** | 1.11 | 0.84-1.47 | 0.466 |
| **Age** | | | 0.115 |
| **< 1 year** | **1.51** | **1.08-2.10** | **0.015*** |
| **10-15.99 years** | 1.11 | 0.88-1.40 | 0.393 |
| **≥ 16 years** | 1.11 | 0.84-1.48 | 0.472 |
| **Weight** | | | 0.103 |
| **Overweight** | 1.08 | 0.83-1.41 | 0.552 |
| **Underweight** | 0.80 | 0.51-1.27 | 0.344 |
| **Unable to Classify**[†] | **1.34** | **1.03-1.84** | **0.031*** |
| **Payment Type** | | | 0.914 |
| **Medicaid or No Insurance** | 1.03 | 0.82-1.30 | 0.792 |
| **Medicare** | 1.02 | 0.33-3.20 | 0.978 |
| **Military** | 1.37 | 0.56-3.12 | 0.488 |
| **MRD = Yes** | **2.59** | **2.06-3.27** | **<0.0001*** |
| **Risk Group = High** | **2.51** | **2.03-3.11** | **<0.0001*** |

Patients censored at the time of per protocol HSCT in CR-1
Reference Groups: Race/Ethnicity - White, Age 1-9.99, Weight - Middleweight, Payment - Self Pay/Private Insurance, MRD – No, Risk Group - Low
*Significant p-value, $\alpha$=0.05
[†]Majority of patients of weight "unable to classify" < 1 year old

Tables 10a and b. Cox Proportional Hazards Model of the effect of the interaction between race/ethnicity and t(8;21) on EFS.

10a. Hazard ratios for EFS parameters (induction failure, relapse, death), comparing patients with t(8;21) to those without, controlling for race

| Race/Ethnicity | Hazard Ratio | Hazard Ratio 95% CI | P-Value |
|---|---|---|---|
| **White** | **0.28** | **0.16-0.49** | **<0.0001*** |
| **Black** | **0.36** | **0.16-0.79** | **0.012*** |
| **Asian** | 0.97 | 0.31-3.01 | 0.959 |
| **Hispanic-White** | 0.59 | 0.28-1.27 | 0.178 |

Patients censored at the time of per protocol HSCT in CR-1
*Significant p-value, α=0.05

10b. Hazard ratios for EFS parameters (induction failure, relapse, death), comparing patients of different racial/ethnic groups to White patients, controlling for the presence of t(8;21).

| Race/Ethnicity | Hazard Ratio | Hazard Ratio 95% CI | P-Value |
|---|---|---|---|
| **t(8;21) Positive** | | | |
| **Black** | 1.77 | 0.71-4.43 | 0.224 |
| **Asian** | **3.45** | **1.13-10.60** | **0.030*** |
| **Hispanic-White** | **2.48** | **1.03-5.97** | **0.044*** |
| **t(8;21) Negative** | | | |
| **Black** | **1.40** | **0.99-1.98** | **0.054*** |
| **Asian** | 1.00 | 0.56-1.80 | 0.996 |
| **Hispanic-White** | 1.17 | 0.83-1.66 | 0.362 |

Patients censored at the time of per protocol HSCT in CR-1
*Significant p-value, α=0.05

Tables 11a and b. Cox Proportional Hazards Model of the effect of the interaction between race/ethnicity and Inversion 16 on EFS.

11a. Hazard ratios for EFS parameters (induction failure, relapse, death), comparing patients with Inversion 16 to those without, controlling for race.

| Race/Ethnicity | Hazard Ratio | Hazard Ratio 95% CI | P-Value |
|---|---|---|---|
| **White** | 0.80 | 0.54-1.19 | 0.268 |
| **Black** | 0.69 | 0.25-1.93 | 0.485 |
| **Hispanic-White** | **0.33** | **0.12-0.92** | **0.034*** |

Asian patients excluded because only 1 patient had inversion 16
*Significant p-value, α=0.05

11b. Hazard ratios for EFS parameters (induction failure, relapse, death), comparing patients of different racial/ethnic groups to White patients, controlling for the presence of Inversion 16.

| Race/Ethnicity | Hazard Ratio | Hazard Ratio 95% CI | P-Value |
|---|---|---|---|
| **Inversion 16 Positive**[†] | | | |
| **Black** | 1.13 | 0.40-3.20 | 0.824 |
| **Hispanic-White** | 0.57 | 0.20-1.63 | 0.298 |
| **Inversion 16 Negative** | | | |
| **Black** | 1.30 | 0.93-1.82 | 0.131 |
| **Asian** | 1.18 | 0.71-1.98 | 0.522 |
| **Hispanic-White** | **1.39** | **0.99-1.94** | **0.054*** |

[†]Asian patients excluded because only 1 patient had inversion 16
*Significant p-value, α=0.05

Tables 12a and b. Cox Proportional Hazards Model of the effect of the interaction between race/ethnicity and Risk Group on EFS.

Table 12a. Hazard ratios for EFS parameters (induction failure, relapse, death), comparing High Risk to Low Risk patients, controlling for race/ethnicity.

| Race/Ethnicity | Hazard Ratio | Hazard Ratio 95% CI | P-Value |
|---|---|---|---|
| **White** | 2.37 | 1.80-3.11 | **<0.0001*** |
| **Black** | 2.16 | 1.28-3.66 | **0.004*** |
| **Asian** | 3.19 | 1.47-6.89 | **0.003*** |
| **Hispanic-White** | 3.43 | 2.00-5.89 | **<0.0001*** |

Patients censored at the time of per protocol HSCT in CR-1
*Significant p-value, α=0.05

Table 12b. Hazard ratios for EFS parameters (induction failure, relapse, death), comparing patients of different racial/ethnic groups, controlling for Risk Group.

| Race/Ethnicity | Hazard Ratio | Hazard Ratio 95% CI | P-Value |
|---|---|---|---|
| **Low Risk** | | | |
| **Black** | 1.41 | 1.00-1.97 | **0.047*** |
| **Asian** | 1.00 | 0.56-1.79 | 0.997 |
| **Hispanic-White** | 1.03 | 0.73-1.45 | 0.866 |
| **High Risk** | | | |
| **Black** | 1.29 | 0.79-2.09 | 0.306 |
| **Asian** | 1.34 | 0.76-2.38 | 0.309 |
| **Hispanic-White** | 1.49 | 0.91-2.44 | 0.111 |

Patients censored at the time of per protocol HSCT in CR-1
*Significant p-value, α=0.05

Tables 13a and b. Cox Proportional Hazards Model of the effect of the interaction between race/ethnicity and payment type on EFS.

13a. Hazard ratios for EFS parameters (induction failure, relapse, death), comparing patients with Medicaid/no means of payment to those with private insurance/self pay, controlling for race/ethnicity.

| Race/Ethnicity | Hazard Ratio | Hazard Ratio 95% CI | P-Value |
|---|---|---|---|
| **White** | 0.97 | 0.70-1.34 | 0.847 |
| **Black** | 1.36 | 0.81-2.30 | 0.241 |
| **Asian** | 0.79 | 0.24-2.69 | 0.714 |
| **Hispanic-White** | 0.71 | 0.41-1.24 | 0.228 |

13b. Hazard ratios for EFS parameters (induction failure, relapse, death), comparing patients of different racial/ethnic groups to White patients, controlling for payment type.

| Race/Ethnicity | Hazard Ratio | Hazard Ratio 95% CI | P-Value |
|---|---|---|---|
| **Medicaid/No means of payment** | | | |
| **Black** | **1.81** | **1.15-2.87** | **0.011*** |
| **Asian** | 1.27 | 0.40-4.09 | 0.686 |
| **Hispanic-White** | 1.05 | 0.67-1.66 | 0.819 |
| **Private Insurance/Self Pay** | | | |
| **Black** | 1.29 | 0.85-1.94 | 0.228 |
| **Asian** | 1.55 | 0.96-2.49 | 0.073 |
| **Hispanic-White** | 1.44 | 0.91-2.27 | 0.120 |

*Significant p-value, $\alpha$=0.05
Overall effect of the interaction was not significant

Table 14. Multivariate Cox Proportional Hazards Model: Race/Ethnicity as a predictor of EFS, controlling for age, weight, payment type, and risk classification.

| Race/Ethnicity | Hazard Ratio | Hazard Ratio 95% CI | P-Value |
|---|---|---|---|
| **Black** | **1.49** | **1.10-2.00** | **0.009*** |
| **Asian** | 1.40 | 0.90-2.17 | 0.138 |
| **Hispanic-White** | 1.16 | 0.84-1.61 | 0.370 |

White patients used as reference group
Patients censored at the time of per protocol HSCT in CR-1
*Denotes significant p-value, $\alpha = 0.05$