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## Allogeneic Hematopoietic Cell Transplantation Compared to Chemotherapy Consolidation in older Acute Myeloid Leukemia (AML) Patients 60–75 Years in First Complete Remission (CR1): An Alliance (A151509), SWOG, ECOG-ACRIN and CIBMTR Study

Celalettin Ustun<sup>1,2</sup>, Jennifer Le-Rademacher<sup>3</sup>, Hai-Lin Wang<sup>4</sup>, Megan Othus<sup>5</sup>, Zhuoxin Sun<sup>6</sup>, Brittany Major<sup>7</sup>, Mei-Jie Zhang<sup>4</sup>, Elizabeth Storricks<sup>8</sup>, Jacqueline M Lafky<sup>9</sup>, Selina Chow<sup>10</sup>, Krzysztof Mrózek<sup>11</sup>, Eyal C. Attar<sup>12,13</sup>, Such Nand<sup>14</sup>, Clara D. Bloomfield<sup>15</sup>, Larry D. Cripe<sup>16</sup>, Martin S. Tallman<sup>17</sup>, Frederick Appelbaum<sup>18</sup>, Richard A. Larson<sup>19</sup>, Guido Marcucci<sup>20</sup>, Gail J. Roboz<sup>21</sup>, Geoffrey L. Uy<sup>22</sup>, Richard M. Stone<sup>23</sup>, Aminah Jatoi<sup>9</sup>, Thomas C. Shea<sup>24</sup>, Marcos de Lima<sup>25</sup>, James M. Foran<sup>26</sup>, Brenda M. Sandmaier<sup>18</sup>, Mark R. Litzow<sup>27</sup>, Harry P. Erba<sup>28</sup>, Arti Hurria<sup>29</sup>, Daniel J. Weisdorf<sup>1,4</sup>, Andrew S. Artz<sup>16</sup>

<sup>1</sup>Blood and Marrow Transplant Program, University of Minnesota, Minneapolis, MN;

<sup>2</sup>Rush University, Division of Hematology, Oncology and Cellular Therapy, Chicago, IL,

<sup>3</sup>Dept of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, MN;

<sup>4</sup>CIBMTR (Center for International Blood and Marrow Transplant Research), Department of Medicine, Medical College of Wisconsin, Milwaukee, WI;

<sup>5</sup>Public Health Sciences Division, Fred Hutchinson Cancer Research Center, Seattle;

<sup>6</sup>Harvard T.H. Chan School of Public Health, Boston;

<sup>7</sup>Department of Health Sciences Research, Mayo Clinic, Rochester;

<sup>8</sup>Alliance Statistics and Data Center, Mayo Clinic, Rochester, MN;

<sup>9</sup>Mayo Clinic, Rochester;

<sup>10</sup>University of Chicago Comprehensive Cancer Center, Chicago;

<sup>11</sup>The Ohio State University Comprehensive Cancer Center, Columbus, OH;

<sup>12</sup>Massachusetts General Hospital, Boston;

<sup>13</sup>Agios Pharmaceuticals, Inc., Cambridge, MA;

**Corresponding Author and Address:** Celalettin Ustun, MD, Associate Professor of Medicine, Division of Hematology Oncology and Cellular Therapy, Department of Medicine, Rush University, 1725 W Harrison St Suit 39, Chicago, IL 60612, USA, Tel: 612-624-0123, celalettin\_ustun@rush.edu.

Contribution to the Study:

CU and AA conceived the idea, searched literature, analyzed data, wrote and edited the manuscript.

JLR, BM, ES, HLW, MJZ, DJW collected data, analyzed data, wrote and edited the manuscript.

RS, RAL, AH, TCS, MDL, AJW, HPE, MST, FA, CDB, MO, JML, SC, GM, KM, BS, ECA, ML, ZS helped data collection, wrote and edited the manuscript

SN, GJR, GLU, JMF, LDC, AJ was a principal investigator of the relevant cooperative group studies, and wrote and edited the manuscript.

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- <sup>14</sup>Loyola University Medical Center, Chicago, IL;
- <sup>15</sup>Comprehensive Cancer Center, The Ohio State University, Columbus, OH;
- <sup>16</sup>Indiana University Simon Cancer Center, Indianapolis;
- <sup>17</sup>Memorial Sloan Kettering Cancer Center, New York, NY;
- <sup>18</sup>Fred Hutchinson Cancer Research Center and Division of Oncology, University of Washington, Seattle, WA.
- <sup>19</sup>Department of Medicine and Comprehensive Cancer Center, University of Chicago, Chicago, IL;
- <sup>20</sup>Department of Hematological Malignancies Translational Science, Gehr Family Center for Leukemia Research, Hematologic Malignancies and Stem Cell Transplantation Institute, Beckman Research Institute, City of Hope, Duarte, CA;
- <sup>21</sup>Weill-Cornell Medical College, New York, NY;
- <sup>22</sup>Washington University School of Medicine, Saint Louis, MO;
- <sup>23</sup>Dana-Farber Cancer Institute, Boston, MA;
- <sup>24</sup>Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC;
- <sup>25</sup>Adult Hematologic Malignancies & Stem Cell Transplant Section, University Hospitals Seidman Cancer Center, Cleveland, OH;
- <sup>26</sup>Division of Hematology and Medical Oncology, Department of Medicine, Mayo Clinic Florida, Jacksonville, FL;
- <sup>27</sup>Division of Hematology, Department of Internal Medicine, Mayo Clinic, Rochester, MN;
- <sup>28</sup>Duke University, Durham, NC;
- <sup>29</sup>City of Hope, Duarte, CA

## Abstract

The preferred post-remission therapy for older patients with acute myeloid leukemia (AML) in first complete remission (CR1) remains uncertain. In this retrospective, multicenter study, we compared outcomes for older AML patients (age 60–77 years) receiving allogeneic hematopoietic cell transplantation (alloHCT) (n=431) with those treated on prospective National Clinical Trials Network induction and non-transplantation chemotherapy consolidation (CT) trials (n=211). AlloHCT patients were younger (median age: 64.2 vs. 67.9 years,  $p<0.001$ ), but more frequently had high-risk AML (high WBC, secondary AML and unfavorable cytogenetics). Overall survival (OS) was worse in alloHCT during the first 9 months after CR1 (HR=1.52,  $p=0.02$ ), but was significantly better thereafter (HR= 0.53,  $p<0.0001$ ) relative to CT. Treatment-related mortality (TRM) following HCT was worse in the first 9 months (HR=2.8, CI: 1.5 –5.2,  $p=0.0009$ ), while post-HCT relapse was significantly less frequent beyond 9 months (HR = 0.42, CI: 0.29 to 0.61,  $p<0.0001$ ). Despite higher early TRM, alloHCT recipients had superior long-term OS [29% (24–34%) vs. CT 13.8% (9 –21%) at 5-year]. Although this is a retrospective analysis with potential biases, it indicates that alloHCT led to heightened early risks from TRM, yet reduced relapse and superior long-term survival relative to CT in older AML patients in CR1.

## Keywords

Acute myeloid leukemia; older; elderly; relapse; non-relapse mortality; complete remission; consolidation; allogeneic hematopoietic cell transplantation; survival

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## Introduction :

Acute myeloid leukemia (AML) most often affects older patients ( > 60 years) with a median age of 68 years,<sup>1-3</sup> who generally have worse outcomes.<sup>4</sup> Overall survival (OS) remains dismal due to frequent disease relapse.<sup>5, 6</sup> Although intensive remission induction regimens can induce complete remission (CR) in 45 to 65% of patients,<sup>7, 8</sup> relapse frequently occurs within the first 12–18 months.<sup>9</sup> Adverse disease biology of AML in older patients drives high relapse as a consequence of unfavorable cytogenetics/molecular profile, intolerance to intensive chemotherapy and overexpression of multidrug resistance genes.<sup>4, 5, 10-13</sup>

Allogeneic hematopoietic cell transplantation (AlloHCT) is a highly potent antileukemic consolidation strategy; however, treatment-related mortality (TRM) presents a major limitation, particularly in older patients.<sup>14</sup> Advances in alloHCT using nonmyeloablative/reduced-intensity conditioning (NMA/RIC) regimens<sup>15, 16</sup> have permitted more widespread HCT application, even in the eighth decade of life.<sup>17, 18</sup> Several studies have shown that when compared with conventional myeloablative conditioning (MAC) regimens, RIC HCT yields comparable or lower peri-HCT toxicities but higher relapse rates (CTN 0910) - despite its use in older patients or those with high pre-HCT comorbidity scores.<sup>19-22</sup>

The benefit of alloHCT in younger AML patients has been evaluated in biologic randomization studies of those with and without an available HLA matched donor.<sup>14, 23, 24</sup> Studies among older AML patients reporting 30–50% 2-year survival after RIC appear promising relative to non-HCT chemotherapy (CT) approaches<sup>25, 26</sup> but are hampered by the lack of control groups. Since most older AML patients never pursue alloHCT<sup>3, 27</sup>, adjusting for selection bias among older alloHCT recipients poses a major limitation in generalizing transplantation results. Studies addressing the benefits of alloHCT in an older AML population compared to CT consolidations are limited and no well-designed prospective studies have been reported<sup>28-30</sup>. To better delineate the risks and benefits of alloHCT, here, we compare AML outcomes in older patients receiving alloHCT with those receiving CT consolidation in prospective cooperative group trials.

## Materials and Methods:

### Patients

Patients 60 to 75 years of age with AML in CR1 receiving a first alloHCT between 2008 and 2013 included in the Center for International Blood and Marrow Transplantation (CIBMTR) database comprised the alloHCT cohort. As reporting of allogeneic stem cell transplant outcomes is a federal requirement in the US, this data set includes almost all such transplants performed in the US during this time. Older AML patients enrolled on US cooperative group trials (now National Clinical Trials Network, NCTN) achieving CR1 receiving postinduction therapy in Alliance for Clinical Trials in Oncology (Alliance)/

Cancer and Leukemia Group B trials [10502, 10801, 11001<sup>31, 32</sup> and 11002 (<https://clinicaltrials.gov/ct2/show/NCT01420926>)] between and 2008 and 2013, ECOG-ACRIN Cancer Research Group trial E3999<sup>33</sup> between 2002 and 2005 and Southwest Oncology Group (SWOG) protocols (S0432 and S0703)<sup>34, 35</sup> between 2005 and 2012 constituted the chemotherapy (CT) consolidation group (Supplemental Table 1). All subjects signed written informed consent for treatment trials in the cooperative groups and for data capture in the CIBMTR. Each NCTN and the CIBMTR approved this retrospective study. Any patient in the CT group who later underwent alloHCT was excluded in an attempt to preserve homogeneity within each cohort.

*De novo* or treatment-associated AML or AML evolving from a previous myelodysplastic (MDS) or myeloproliferative (MPN) disorder were eligible. All types of donors [sibling, unrelated (URD), and umbilical cord blood (UCB)] except haploidentical donors, and any conditioning intensity regimens were eligible.<sup>36</sup> Cytogenetic reports from the Alliance studies were reviewed and categorized by the 2016 European Leukemia Net although molecular data were not included since this information was not available for the majority of patients enrolled in these studies.<sup>37</sup> Cytogenetic risk classification generally followed the classification by Slovak for ECOG-ACRIN and SWOG.<sup>38</sup> The CIBMTR cytogenetic characterization mirrored the Alliance schema (Supplemental Table 2).

Karnofsky (or Zubrod for only in the SWOG study) performance score (KPS) for CT cohort was collected prior to induction therapy while alloHCT cohort KPS was reported before alloHCT.

### Statistical Considerations:

Categorical variables were summarized by frequency (percent) and compared using a Chi-square or Fisher exact test as appropriate. Continuous variables were summarized by median (range) and compared using a two-sample t-test or a Wilcoxon rank-sum test.

The time to event for all outcomes started at the time of CR1. Left-truncation was used in all analyses to account for administration of either alloHCT or CT at differing times after CR1 and thus delayed entry into the study. AlloHCT patients enter the risk group at the time of alloHCT and CT patients enter the risk group at the start of first consolidation therapy. Disease-free survival (DFS) was recorded until time of disease relapse or death, whichever occurred first. Overall survival (OS) and DFS were estimated for each cohort using the left-truncated version of the Kaplan-Meier estimator.<sup>39</sup> The cumulative incidence of relapse and all-cause treatment related mortality (TRM) estimates used the cumulative incidence function with the risk sets adjusted for left truncation. Relapse was the competing risk for TRM and vice versa; Cox model for cause-specific hazards was used. Outcomes were compared between cohorts using the Cox proportional hazards model with left-truncation. AlloHCT versus consolidation therapy was the primary study comparison with OS as the primary endpoint. The potential confounding effect of age, KPS and cytogenetic risk classification were adjusted for in the multivariate model. Of note, we chose to adjust for these factors as covariates in the multivariate model instead of a stratified analysis so that the interaction between these factors and the main effect (AlloHCT vs. CT) can be evaluated. The proportional hazards assumption comparing alloHCT versus CT was not met for OS and

DFS. The maximum partial likelihood approach was then used to determine a cut-point of 9 months post treatment which best segregated post treatment time periods.<sup>39</sup> Statistical analyses were conducted by the Alliance Statistics and Data Center. All analyses were based on the study database frozen on January 2<sup>nd</sup>, 2018.

## Results:

### Baseline Characteristics:

The study evaluated 642 patients comprised of 431 patients in the alloHCT group and 211 patients in the CT group (Supplemental Table 3 **for selection**). Of note, pruning of the datasets to meet eligibility varied and ultimately relatively few patients met criteria of consolidation therapy on an NCTN trial while in CR1 without subsequent alloHCT. Table 1 summarizes patients' baseline characteristics. AlloHCT patients were younger, had more secondary AML, more often had high WBC > 100 × 10<sup>9</sup>/L at diagnosis, worse performance scores, less frequent extramedullary disease (EMD) at diagnosis, and less frequent FLT3 mutation in tested patients. Adverse karyotype among those evaluable was similar between alloHCT recipients (38%) versus CT (30%) (p= 0.072). Supplemental Table 2 shows the cytogenetic risk groups among NCTN studies and the alloHCT group. CT patients had more frequent favorable risk cytogenetics 11.3% (17/150) versus only 1.7% (7/416) in the alloHCT cohort (p<0.001). Because of few patients in the favorable cytogenetic risk group, subsequent analyses merged Favorable and intermediate risk groups.

The majority (60%) of alloHCT patients received at least one cycle of pre-alloHCT consolidation therapy. As a result, time from CR1 to alloHCT (median 3.2 months, IQR 1.9 – 4.7) was longer than the time from CR1 to consolidation therapy [median 0.5 months, interquartile range (IQR) 0.2 – 0.7, p<0.0001].

### Outcomes:

The study took advantage of the long median follow of 56.9 (2–96.3) and 53.1 (8.6 –84.5) months for alloHCT and CT, respectively. The comparison of alloHCT relative to CT outcomes differed over time as OS and DFS did not meet the proportional hazards assumptions (Figure 1A and Figure 1D, respectively) prompting creation of an early and later period at the 9 month timepoint. In the early consolidation period (within the first 9 months), alloHCT resulted in lower OS (HR, 1.52, 95%CI: 1.07 – 2.07, p=0.02) due to higher TRM (HR, 2.81, 95%CI: 1.53 – 5.16, p=0.001) (Table 2, Figures 1A and 1B, respectively). In contrast, beyond 9 months after CR1, alloHCT achieved superior OS (Figure 1A, HR, 0.53, 95%CI 0.40 – 0.70, p<0.0001) and DFS (Figure 1D, HR, 0.53, 95%CI 0.40 – 0.70, p<0.0001) due to a significantly lower incidence of relapse (Figure 1C, HR, 0.42, 95%CI 0.29 – 0.61, p<0.0001). After 9 months, the incidence of TRM (Figure 1B) did not differ between the alloHCT and CT groups. The long-term benefit of alloHCT was more apparent among patients with poor risk cytogenetics (Figures 2A and B). Time point estimates of OS and DFS at years 1, 2, 3 and 5 for each group are shown under Figure 1A and 1D, respectively. Of note, at 5-years OS and DFS significantly favored alloHCT: 5-year OS alloHCT of 28.6% (CI: 24.4–33.6) compared to CT of 13.8% (CI: 9.2–20.7) and 5-year DFS of 23.7% (CI 19.9–28.3) versus CT at 11.1% (CI: 7 – 17.6). In the alloHCT group, OS

did not significantly differ by receiving consolidation or consolidation number (Supplemental Figure 1).

In multivariate analysis, patients harboring poor cytogenetics had higher risks of relapse (HR, 2.12, 95%CI 1.65 – 2.73,  $p < 0.0001$ ), lower DFS (HR, 1.74, 95%CI 1.42 – 2.13,  $p < 0.0001$ ), and OS (HR, 1.74, 95%CI 1.41 – 2.14,  $p < 0.0001$ ) compared with those with favorable or intermediate cytogenetics (Table 2). No significant associations existed for age and KPS with any outcome. The interaction between treatment effect was evaluated for age, KPS and disease risk group and no interactions found (data not shown). In addition, a Forest plot analysis was performed to compare alloHCT vs. CT for subgroup analysis by age, KPS, and cytogenetic risk classification (Figure 3), which confirmed our findings. Adjusted overall survival curves and time-point estimates were also very similar to unadjusted findings (Supplemental Figure 2A and B).

### Transplantation Characteristics

Among the 431 patients receiving alloHCT (Table 3), RIC/NMA was used most often (79%), although 21% received MAC. Most received HLA matched related or URD grafts (66%), but 34% received alternative donor grafts: 24% UCB; 10% partially matched URD. Peripheral blood stem cells were used most often (71%) along with tacrolimus-based graft-versus host disease (GVHD) prophylaxis (65%) and *in vivo* anti-T cell therapies with ATG or alemtuzumab (42%).

### Risk Factors following AlloHCT

Multivariate risk factor analysis showed that UCB grafts were associated with higher TRM, and lower OS (Table 4). Conditioning intensity, age and KPS had no significant impact on any outcome.

### Discussion:

In this study, alloHCT for older AML patients in CR1 resulted in significantly better long-term DFS and OS relative to chemotherapy consolidation. The rates of failure differed by treatment approach: alloHCT patients suffered from higher rates of early TRM while patients after CT had higher rates of relapse, even beyond the first year (Figure 1C).

Compared to prior studies, the major strengths of this study are inclusion of older patients (17% were 70 years and older), large sample size, available cytogenetic data, and derivation from a recent era reflecting modern treatment and supportive care practices. In addition, the alloHCT cohort represented broad clinical practice by including different donor types and conditioning regimens. The study populations were chosen to minimize bias in comparing the different consolidation strategies. While selection of appropriate alloHCT patients reflected the screening and eligibility at each HCT center, the control comparators also underwent eligibility screening for contemporaneous NCTN group trial participation. We accounted for the delay in alloHCT after CR1 by including only patients receiving chemotherapy on a cooperative group trial study and adjusting for the time to consolidation or HCT.

High quality prospective studies have been primarily conducted in younger patients comparing those with an HLA-matched donor to those without (a.k.a., biologic randomization) showing improved survival in CR1 for intermediate and high-risk disease with an overall hazard ratio of 0.87 to 0.9 in a meta-analysis by Koreth et al.<sup>24</sup> Uncontrolled studies among older adults with AML have shown promising survival relative to historical expectations.<sup>26, 40, 41</sup> Generalizing the benefits of alloHCT from younger adults to older AML patients is problematic. The higher prevalence of comorbidities and functional impairments influences patient selection for treatments and treatment intensity. However, the more adverse disease biology and higher relapse risks counterbalances efforts to minimize treatment intensity in older patients.<sup>21</sup>

With inclusion of different donor types, HLA matching and conditioning regimens, the magnitude of benefit observed in our study was similar to prior studies comparing alloHCT to CT consolidation in older adults.<sup>28, 29, 42</sup> A retrospective European study compared alloHCT with CT (i.e., additional chemotherapy or autologous HCT) versus no further therapy in 640 older patients (range-62 to 71 years) with AML in CR1. Similar to our results, 5-year overall survival was 35% in the subset of 97 patients receiving HLA matched alloHCT, 26% in the CT, 21% in those receiving no post-remission therapy.<sup>42</sup> A retrospective study from Japan including somewhat younger patients (50–70 years) demonstrated higher 3-year OS after alloHCT (n=152) compared to chemotherapy (62% versus 51%,  $P<0.012$ ).<sup>29</sup> Farag et al. compared alloHCT reported to the CIBMTR from an earlier time period (1999 to 2005) to consolidation on CALGB chemotherapy protocols in elderly AML patients in CR1.<sup>28</sup> Patients aged 60–70 years who survived at least 4 months in CR1 received either RIC allogeneic HCT (n=96) or chemotherapy (n=94). OS at 3-year was 37% (95% CI, 27%–47%) for alloHCT versus 25% (95% CI, 17%–34%) for chemotherapy ( $P=0.08$ ). These studies underscore the major value of alloHCT to mitigate relapse evidenced by relapse incidence rates of 22–50% at 3–5 years post alloHCT compared to 66–81% for CT consolidation,<sup>25, 28, 29, 42</sup> similar to the relapse reduction that we observed of 66.5% after CT compared to 44.3% for alloHCT. Likewise, these studies also showed increased TRM after alloHCT, especially in the early post HCT months.<sup>25, 28, 29, 42</sup>

Even though adverse cytogenetics posed the major independent risk for treatment failure among all patients due to higher relapse rates, outcomes were particularly improved in the alloHCT subgroup; 5-year estimated OS and DFS in these high-risk patients were 20.2% and 15.9% after alloHCT compared with 2.6% and 0% after CT, respectively. However, this should be taken cautiously given the small number of patients in the subsets. The Koreth meta-analysis in younger AML patients showed a similar pattern of stronger advantage for alloHCT for adverse karyotype AML with an estimated absolute 11% 5-year OS benefit.<sup>24</sup> Patients with favorable or intermediate risk cytogenetics experienced 5-year OS of 33.3% (95% CI 27.5 – 40.3) and DFS of 28.3% (95% CI 22.7 – 35.4) after alloHCT compared to 5 year OS of 19% (95% CI 10.2 – 35.9) and DFS of 15.9 (95% CI 7.5 – 33) for CT. An imbalance in favorable cytogenetics favored CT (11%) compared to alloHCT (1.6%).<sup>24</sup>

Seventeen percent of our study patients were 70 years and older (33% in CT group and 9% in the alloHCT group). Patients aged 70 years and older did not experience worse overall outcomes in either the transplant or CT groups. While a limited sample size, this still

represents the largest comparative study including those in their eighth decade and supports efforts to utilize fitness rather than age alone in determining transplant candidacy.

These data also suggest pathways to improve the poor long-term outcomes of older AML patients. This older group still requires special attention in recipient selection and treatment especially among alloHCT to reduce TRM<sup>43</sup> perhaps by applying better geriatric performance assessment,<sup>44</sup> donor selection<sup>16</sup> and education about alloHCT.<sup>45</sup>

Alternative donors (haploidentical donors, UCB, or combinations of these) have also been increasingly used and can result in approximately 40% 2 year DFS and 50% OS in older patients with AML.<sup>17, 46–49</sup> We found that UCB grafts were associated with higher TRM, and thus lower DFS and OS compared to the other donor grafts in the study. However, additional studies will be needed to delineate optimal alloHCT graft and donor type, including newer platforms such as haploidentical T-replete alloHCT.<sup>50</sup> With the availability and improved outcomes of alternative donor grafts, prospective donor versus no donor studies have become even more difficult as nearly all patients have a suitable and available donor and reinforce the need for future comparative effectiveness studies of consolidation strategies

Important limitations in this study included the lack of comprehensive data on molecular profiling or minimal residual disease status for either population and having only cytogenetic data for disease characterization. Additionally, both cohorts lacked data on patient health including comorbidities or geriatric assessments. It should also be pointed out that the small number of older patients in the chemotherapy group reflects the relative paucity of cooperative group trials for older AML patients. In this regard, this patient population is likely to be highly selected for eligibility characteristics and likely reflects a healthier population of older AML patients who may not accurately represent the majority of older AML patients. By using left truncation, we excluded early deaths (prior to consolidation for the CT group and prior to HCT in the transplant group); however, this can also had a bias because CT group received consolidation earlier than allogeneic HCT. Regardless of these limitations, we found alloHCT as consolidation for AML patients 60 years and older improved long-term survival and DFS, primarily in the cytogenetically and clinically higher risk populations. We believe alloHCT should be actively considered for older AML patients in first remission with early donor identification and planning for the possibility of alloHCT soon after diagnosis,<sup>51</sup> except in those with good or intermediate risk cytogenetics who also have co-morbidities that would increase transplant-related risks. Future studies to reduce TRM among alloHCT recipients and to reduce relapse after HCT or CT consolidation remain high priorities.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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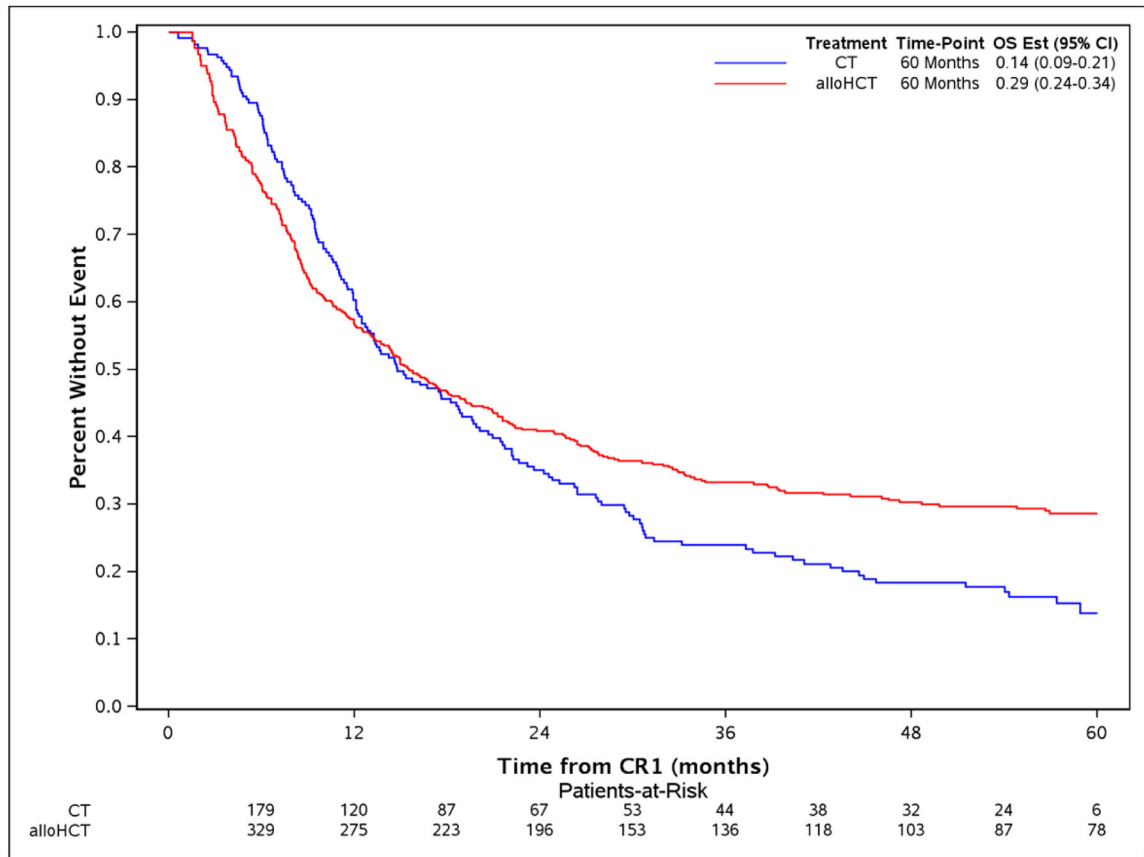
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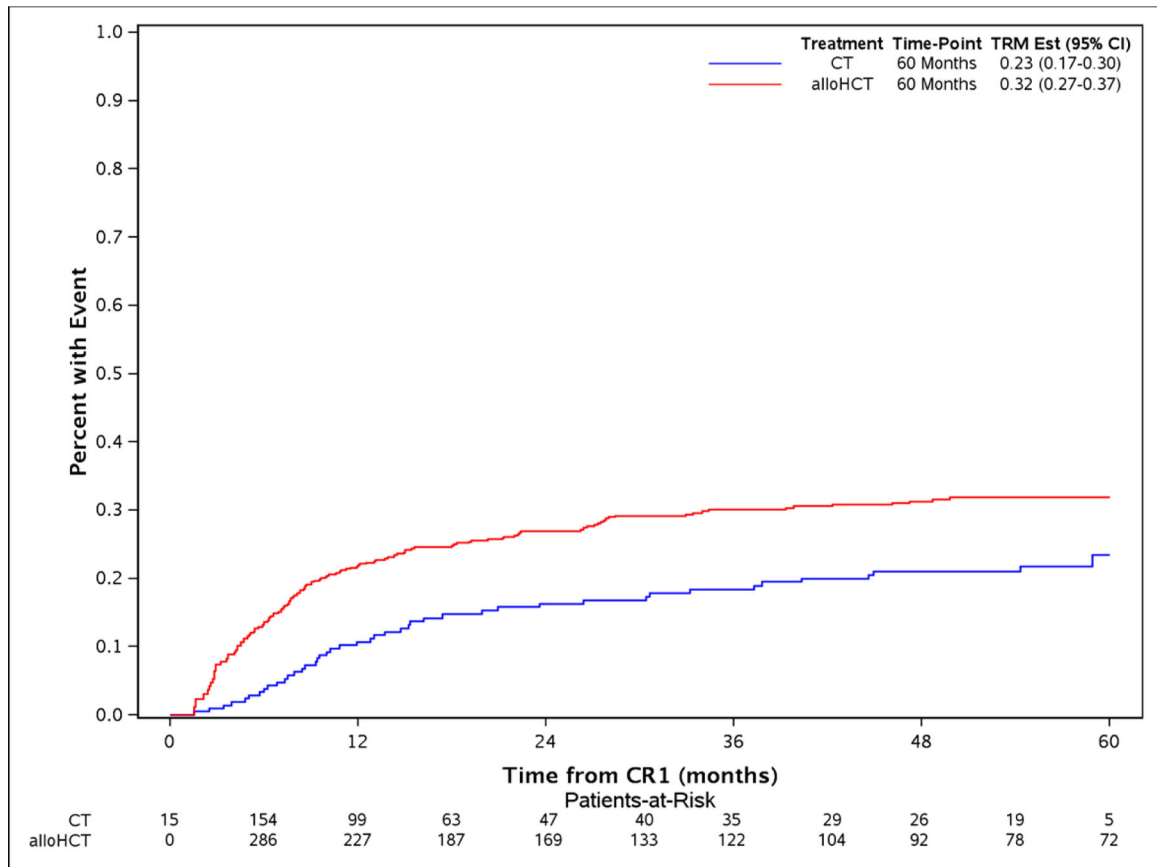
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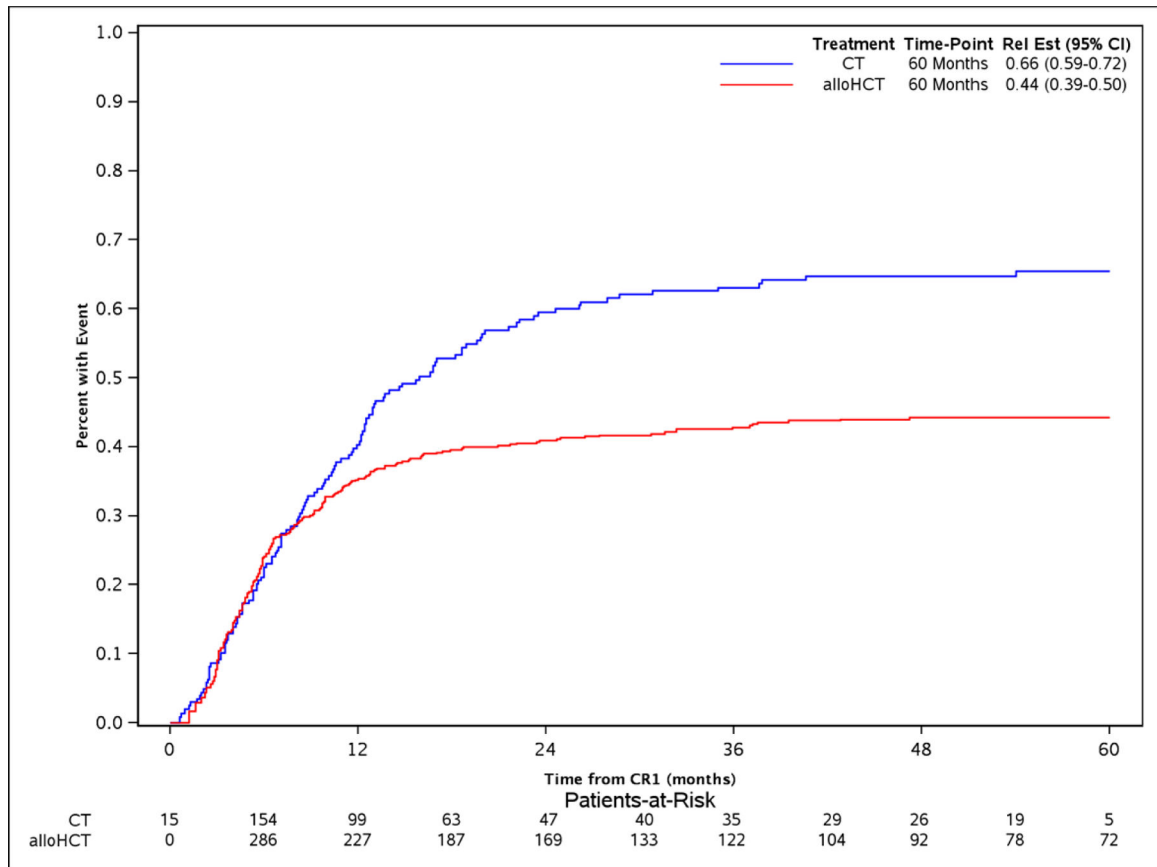
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Time Point (years)	CT	AlloHCT
<b>OS</b>		
1	60.3% (53.9%-67.5%)	56.8% (51.6%-62.6%)
2	35.1% (29%-42.5%)	40.8% (36.2%-46.1%)
3	23.9% (18.6%-30.8%)	33.3% (28.9%-38.3%)
5	13.8% (9.2%-20.7%)	28.6% (24.4%-33.6%)



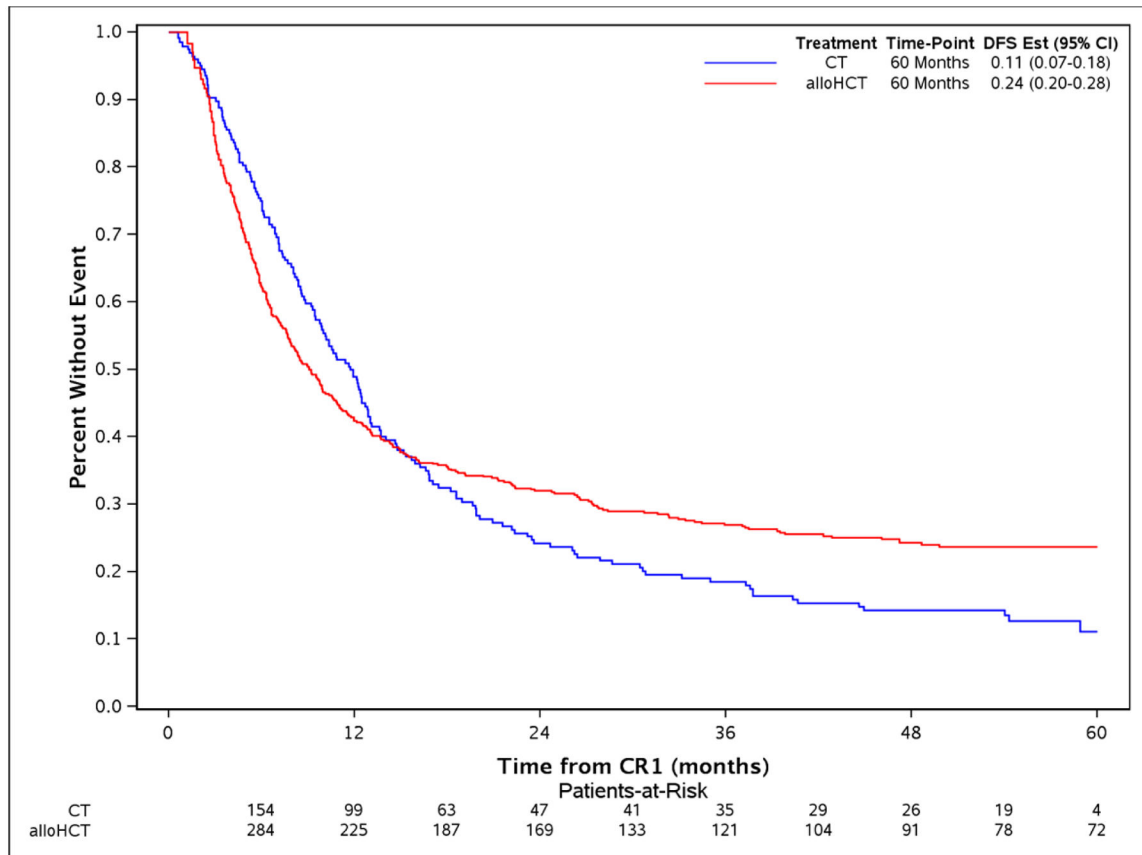


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Time Point (years)	CT	AlloHCT
<b>DFS</b>		
1	48.9% (42.5%-56.3%)	42.4% (37.3%-48.2%)
2	24.2% (18.9%-30.9%)	32% (27.6%-37.1%)
3	18.5% (13.8%-24.8%)	26.9% (22.9%-31.7%)
5	11.1% (7%-17.6%)	23.7% (19.9%-28.3%)

**Figure 1:** Overall survival for alloHCT and CT with 5-year point estimate (**1A**), treatment-related mortality for alloHCT and CT with 5-year point estimate (**1B**), cumulative incidence of relapse for alloHCT and CT with 5-year point estimate (**1C**), disease-free survival for alloHCT and CT with 5-year point estimate (**1D**)

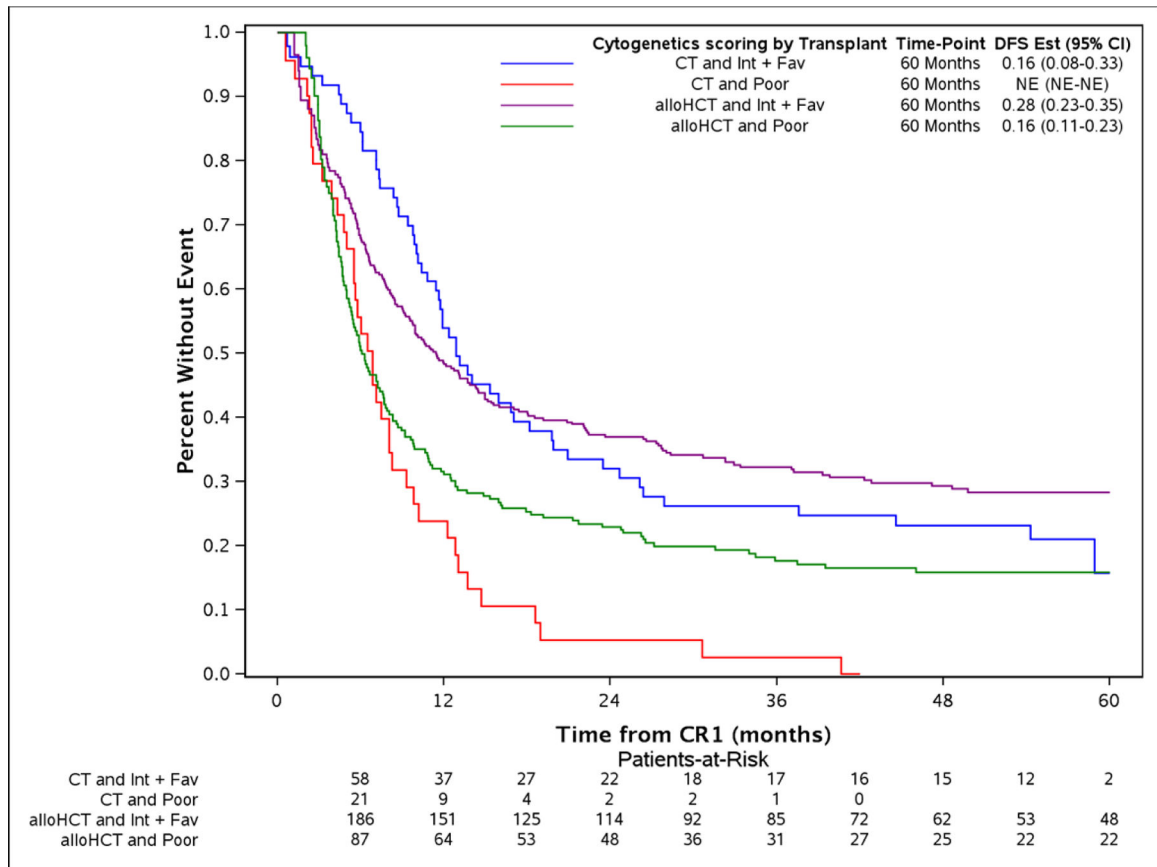


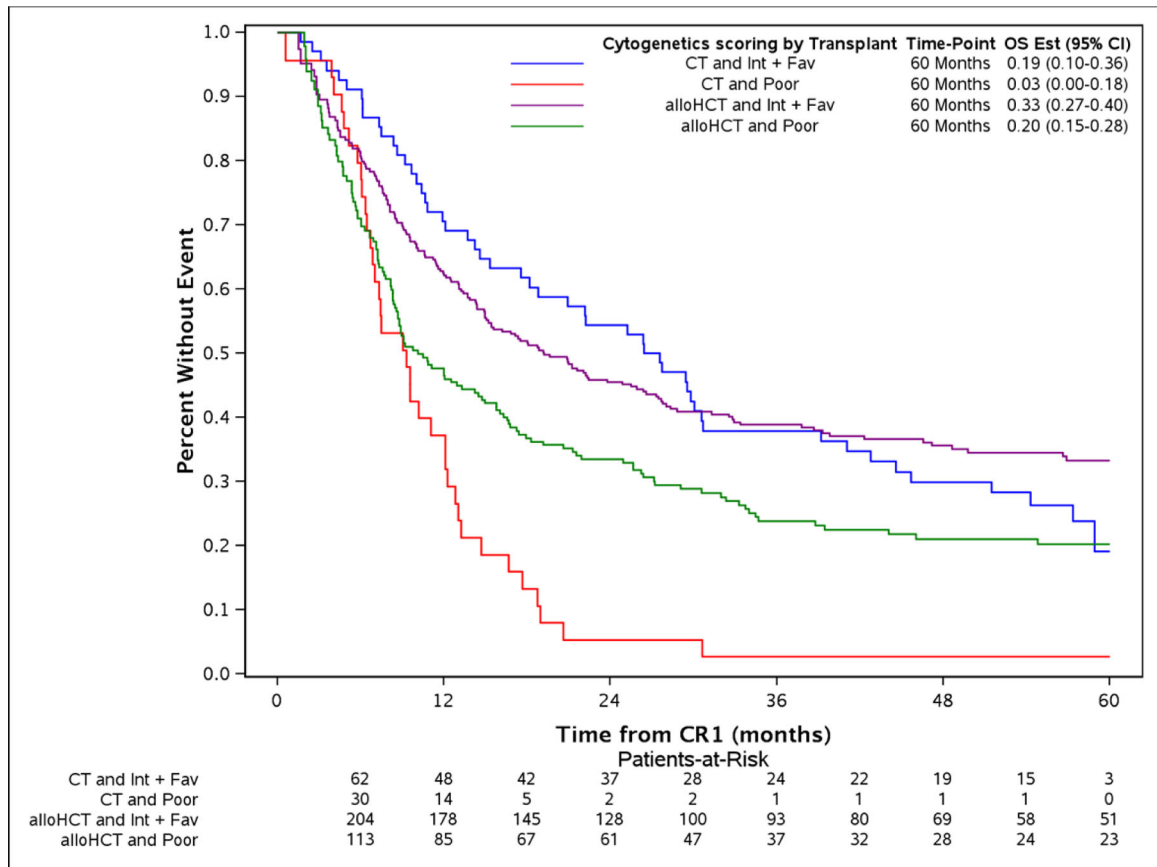
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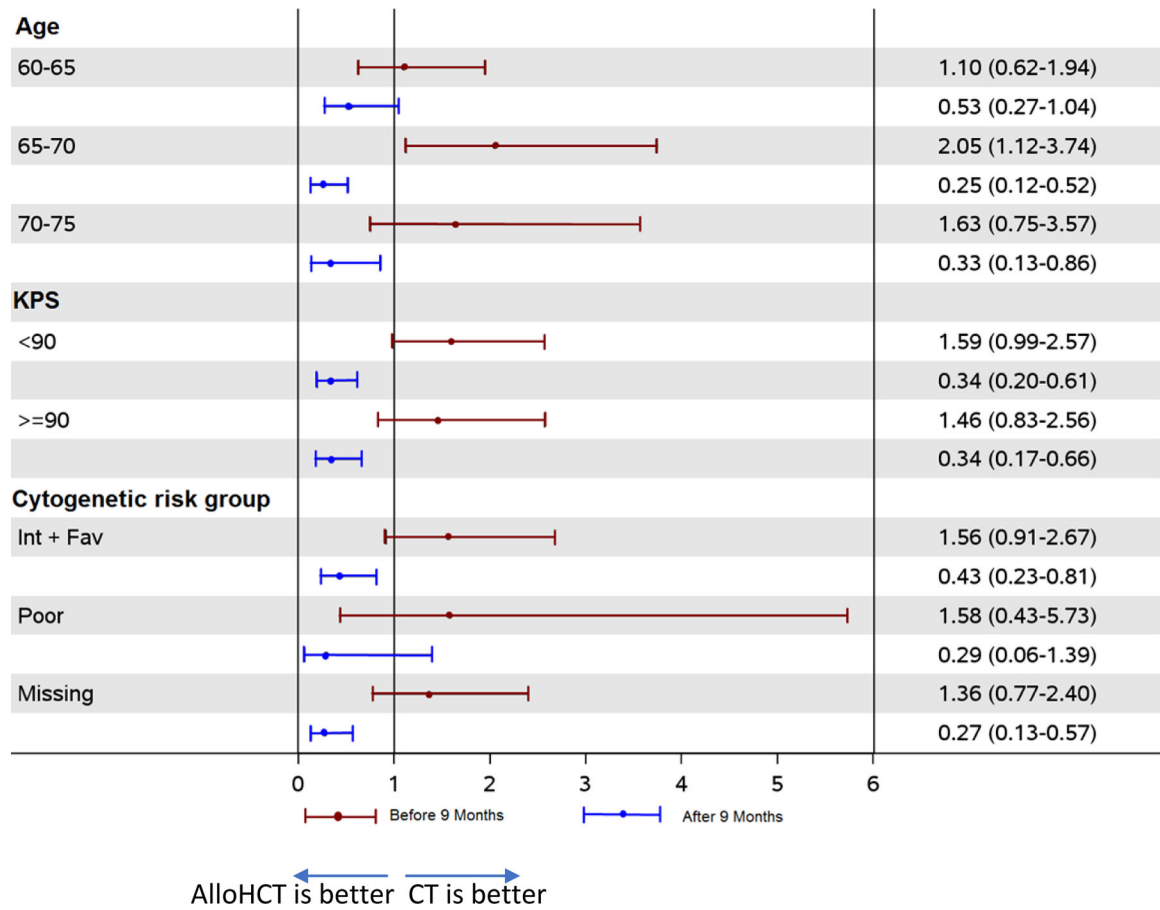
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**Figure 2:** Disease-free survival by alloHCT or CT stratified by intermediate or poor cytogenetic categories and 5-year point estimates (2A), overall survival by alloHCT or CT stratified by intermediate or poor cytogenetic categories and 5-year point estimates (2B).



**Figure 3.** The Forest Plot represents the effect of each characteristic (age, Karnofsky Performance Status, and cytogenetic risk group) on overall survival per treatment before and after 9 months.

**Table 1.**

## Baseline Characteristics

Patient Characteristics by Treatment			
	CT (N=211)	alloHCT (N=431)	P value
<b>Age</b>			<0.001
60–65	66 (31%)	234 (54%)	
65–70	74 (35%)	157 (36%)	
70–75	70 (33%)	40 (9%)	
Missing	1	0	
<b>Gender</b>			0.07
Male	114 (54%)	265 (61%)	
Female	97 (46%)	166 (39%)	
<b>Karnofsky score</b>			<0.001
<90	135 (64%)	152 (36%)	
≥90	76 (36%)	266 (64%)	
Missing	0	13	
<b>White Blood Count at diagnosis</b>			0.01
≤ 10	145 (69%)	268 (69%)	
10 – 100	64 (30%)	97 (25%)	
> 100	2 (1%)	21 (5%)	
Missing	0	45	
<b>Extramedullary disease at diagnosis</b>			<0.001
No	161 (87%)	415 (97%)	
Yes	24 (13%)	11 (3%)	
Missing	26	5	
<b>Cytogenetics scoring</b>			<0.001
Normal, Intermediate or Favorable	105 (50%)	257 (60%)	
Poor	45 (21%)	159 (37%)	
Missing	61 (29%)	15 (3%)	
<b>FLT3 mutation</b>			<0.001
No	10 (43%)	223 (82%)	
Yes	13 (57%)	48 (18%)	
Missing	188	160	
<b>Type of AML</b>			<0.001
De-novo	170 (81%)	262 (61%)	
Secondary	41 (19%)	169 (39%)	
<b>Consolidation type</b>			<0.001
HiDAC	183 (87%)	132 (31%)	
Other, non-HiDAC	28 (13%)	127 (30%)	
None	0 (0%)	171 (40%)	
Missing	0	1	
<b>Other consolidations</b>			

<b>Patient Characteristics by Treatment</b>			
	<b>CT (N=211)</b>	<b>alloHCT (N=431)</b>	<b>P value</b>
Azacitine plus gemtuzumab	15 (54%)		
Tipifarnib	9 (32%)		
Other	4 (14%)		
Not applicable	183		
<b>Number of consolidation cycles</b>			<0.001
0	0 (0%)	171 (43%)	
1	56 (27%)	96 (24%)	
2+	155 (73%)	132 (33%)	
Missing	0	32	
<b>Donor Grouping</b>			
HLA-identical sibling		107 (25%)	
Well-matched unrelated		178 (41%)	
Partially matched unrelated		39 (9%)	
Mismatched unrelated		3 (1%)	
Unrelated matching unknown		2 (0%)	
Cord blood		102 (24%)	
<b>Time from Diagnosis to CR1</b>			0.24
N	209	428	
Mean (SD)	2.0 (1.8)	2.1 (2.2)	
Median	1.6	1.5	
Q1, Q3	1.3, 2.2	1.0, 2.4	
Range	(0.6–22.5)	(0.2–21.5)	
<b>Time from CR1 to consolidation or HCT (months)</b>			<0.001
N	211	431	
Mean (SD)	0.5 (0.5)	3.5 (2.5)	
Median	0.5	3.2	
Q1, Q3	0.2, 0.7	1.9, 4.7	
Range	(0.0–3.7)	(0.2–20.6)	

**Abbreviations:** AlloHCT: allogeneic hematopoietic cell transplantation, CT: chemotherapy consolidation, CR1: first complete remission, HiDac: high dose cytarabine, SD: standard deviation.

**Table 2.**

Multivariate analysis for TRM, relapse, DFS and OS

Variables	TRM		Relapse		DFS		OS	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (99% CI)	P-value
<b>Therapy</b>		0.0003 <sup>‡</sup>		0.0002 <sup>‡</sup>		<0.0001 <sup>‡</sup>		<0.0001 <sup>‡</sup>
CT before 9 mo	1		1		1		1	
AlloHCT before 9 mo	2.81 (1.53–5.16)	0.001	1.04 (0.73–1.48)	0.82	1.38 (1.03–1.87)	0.03	1.52 (1.07–2.17)	0.02
CT after 9 mo	1		1		1		1	
AlloHCT after 9 mo	0.74 (0.45,1.20)	0.22	0.42 (0.29–0.61)	<0.0001	0.52 (0.39–0.70)	<0.0001	0.53 (0.40–0.70)	<0.0001
<b>Age</b>		0.5		0.77		0.57		0.28
60–65 years	1		1		1		1	
65–70	1.22 (0.87–1.71)	0.25	0.99 (0.76–1.29)	0.96	1.08 (0.87–1.32)	0.49	1.10 (0.89–1.37)	0.37
70–75	1.18 (0.74–1.89)	0.49	1.11 (0.8–1.54)	0.52	1.15 (0.88–1.5)	0.31	1.25 (0.95–1.64)	0.11
<b>KPS</b>								
KPS >90	1		1		1		1	
KPS 90	0.99 (0.72–1.36)	0.94	1.22 (0.97–1.55)	0.1	1.13 (0.94–1.37)	0.2	1.15 (0.94–1.39)	0.17
<b>Cytogenetic risk group</b>		0.52		<0.0001		<0.0001		<0.0001
Favorable/intermediate	1		1		1		1	
Poor	1.23 (0.87–1.74)	0.25	2.12 (1.65–2.73)	<0.0001	1.74 (1.42–2.13)	<0.0001	1.74 (1.41–2.14)	<0.0001
Missing	1.03 (0.6–1.77)	0.91	1.32 (0.93–1.89)	0.12	1.20 (0.90–1.62)	0.22	1.13 (0.83–1.54)	0.43

**Abbreviations:** TRM: treatment-related mortality, DFS: Disease free survival, OS: Overall survival, AlloHCT: Allogeneic hematopoietic cell transplantation, CT-chemotherapy alone for consolidation, KPS: Karnofsky performance status

<sup>‡</sup> early vs. late effect

**Table 3:**

## Transplantation Characteristics

<b>N</b>	<b>431</b>
<b>Conditioning intensity</b>	
MAC	92 (21%)
RIC/NMA	337 (79%)
Missing	2
<b>Type of Donor</b>	
HLA-identical sibling	107 (25%)
HLA Well-matched unrelated	178 (41%)
Partially matched unrelated/Mismatched unrelated	42 (10%)
UCB	102 (24%)
Missing	2
<b>Graft Source</b>	
Bone marrow	25 (6%)
Peripheral blood	304 (71%)
UCB	102 (24%)
<b>UCB HLA matching</b>	
<=4/6 HLA locus match	57 (58%)
5/6	36 (37%)
6/6	5 (5%)
Missing	4
<b>GVHD prophylaxis</b>	
Ex-vivo TCD	13 (3%)
Tac based	280 (65%)
CsA based	120 (28%)
Other	18 (4%)
<b>In-vivo TCD (ATG or alemtuzumab)</b>	
No	251 (58%)
Yes	180 (42%)

**Abbreviations:** MAC: myeloablative conditioning, RIC/NMA: reduced-intensity or nonmyeloablative regimens, UCB: umbilical cord blood, CMV: cytomegalovirus seropositivity, D: donor, R: recipient, GVHD: graft-versus-host disease, TCD: t-cell depletion, tac: Tacrolimus, CsA: cyclosporine A, ATG: antithymocyte globulin.

**Table 4.**

Multivariate analysis for TRM, relapse, DFS and OS within the AlloHCT group

Variables	TRM			Relapse			DFS			OS		
	HR (95% CI)	P-value		HR (95% CI)	P-value		HR (95% CI)	P-value		HR (95% CI)	P-value	
<b>Conditioning Intensity</b>												
MAC	1			1			1			1		
NMA/RIC	0.99 (0.65–1.51)	0.95		1.39 (0.93–2.08)	0.11		1.19 (0.89–1.59)	0.24		1.14 (0.85–1.54)	0.39	
<b>Donor Type</b>												
HLA-identical sibling	1	0.0004		1	0.07		1	0.0003		1	<0.0001	
HLA-Partially MURD/MMURD	1.47 (0.75–2.88)	0.26		0.70 (0.38–1.26)	0.23		0.94 (0.61–1.46)	0.79		1.05 (0.66–1.65)	0.85	
HLA-Well-matched URD	1.23 (0.74–2.04)	0.42		0.73 (0.5–1.06)	0.1		0.88 (0.66–1.20)	0.44		0.97 (0.71–1.33)	0.85	
UCB	2.69 (1.59–4.55)	0.0002		1.18 (0.77–1.8)	0.45		1.65 (1.19–2.28)	0.003		1.87 (1.34–2.60)	0.0002	

**Abbreviations:** TRM: treatment-related mortality, DFS: disease-free survival, OS: overall survival, HR: hazard ratio, MAC: myeloablative conditioning, NMA: nonmyeloablative, RIC: reduced-intensity conditioning, MURD: matched unrelated donor, MMURD: mismatched unrelated donor, URD: unrelated donor, UCB: umbilical cord blood.