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Matthew Mei

Raju Pillai

Soyoung Kim

Noel Estrada-Merly

Michelle Afkhami

See next page for additional authors

Authors

Matthew Mei, Raju Pillai, Soyoung Kim, Noel Estrada-Merly, Michelle Afkhami, Lixin Yang, Zhuo Meng, Muhammad Bilal Abid, Mahmoud Aljurf, Ulrike Bacher, Amer Beitinjaneh, Christopher Bredeson, Jean-Yves Cahn, Jan Cerny, Edward Copelan, Corey Cutler, Zachariah DeFilipp, Miguel Angel Diaz Perez, Nosha Farhadfar, César O Freytes, Shahinaz M Gadalla, Siddhartha Ganguly, Robert Peter Gale, Usama Gergis, Michael R Grunwald, Betty K Hamilton, Shahrukh Hashmi, Gerhard C Hildebrandt, Hillard M Lazarus, Mark Litzow, Reinhold Munker, Hemant S Murthy, Sunita Nathan, Taiga Nishihori, Sagar S Patel, David Rizzieri, Sachiko Seo, Mithun Vinod Shah, Melhem Solh, Leo F Verdonck, Ravi Vij, Ronald M Sobecks, Betul Oran, Bart L Scott, Wael Saber, and Ryotaro Nakamura

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Matthew Mei,[1*] Raju Pillai,[2*] Soyoung Kim,[3,4] Noel Estrada-Merly,[4] Michelle Afkhami,[2] Lixin Yang,[2] Zhuo Meng,[5] Muhammad Bilal Abid,[6] Mahmoud Aljurf,[7] Ulrike Bacher,[8] Amer Beitinjaneh,[9] Christopher Bredeson,[10] Jean-Yves Cahn,[11] Jan Cerny,[12] Edward Copelan,[13] Corey Cutler,[14] Zachariah DeFilipp,[15] Miguel Angel Diaz Perez,[16] Nosha Farhadfar,[17] César O. Freytes,[18] Shahinaz M. Gadalla,[19] Siddhartha Ganguly,[20] Robert Peter Gale,[21] Usama Gergis,[22] Michael R. Grunwald,[13] Betty K. Hamilton,[23] Shahrukh Hashmi,[24,25] Gerhard C. Hildebrandt,[26] Hillard M. Lazarus,[27] Mark Litzow,[28] Reinhold Munker,[29] Hemant S. Murthy,[30] Sunita Nathan,[31] Taiga Nishihori,[32] Sagar S. Patel,[33] David Rizzieri,[34] Sachiko Seo,[35] Mithun Vinod Shah,[36] Melhem Solh,[37] Leo F. Verdonck,[38] Ravi Vij,[39] Ronald M. Sobecks,[40] Betul Oran,[41] Bart L. Scott,[42] Wael Saber[4*] and Ryotaro Nakamura[1*]

[1]Department of Hematology/HCT, City of Hope National Medical Center, Duarte, CA, USA; [2]Department of Pathology, City of Hope, Duarte, CA, USA; [3]Division of Biostatistics, Institute for Health and Equity, Medical College of Wisconsin, Milwaukee, WI, USA; [4]CIBMTR® (Center for International Blood and Marrow Transplant Research), Department of Medicine, Medical College of Wisconsin, Milwaukee, WI, USA; [5]Beckman Research Institute, City of Hope, Duarte, CA, USA; [6]Divisions of Hematology/Oncology & Infectious Diseases, Department of Medicine, Medical College of Wisconsin, Milwaukee, WI, USA; [7]Department of Oncology, King Faisal Specialist Hospital Center & Research, Riyadh, Saudi Arabia; [8]Department of Hematology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland; [9]Division of Transplantation and Cellular Therapy, University of Miami Hospital and Clinics, Sylvester Comprehensive Cancer Center, Miami, Fl, USA; [10]The Ottawa Hospital Transplant & Cellular Therapy Program, Ottawa, Ontario, Canada; [11]Department of Hematology, CHU Grenoble Alpes, Université Grenoble Alpes, Grenoble, France; [12]Division of Hematology/Oncology, Department of Medicine, University of Massachusetts Medical Center, Worcester, MA, USA; [13]Department of Hematologic Oncology and Blood Disorders, Levine Cancer Institute, Atrium Health, Charlotte, NC, USA; [14]Stem Cell Transplantation and Cellular Therapy, Dana-Farber Cancer Institute, Boston, MA, USA; [15]Hematopoietic Cell Transplant and Cellular Therapy Program, Massachusetts General Hospital, Boston, MA, USA; [16]Department of Hematology/Oncology, Hospital Infantil Universitario Niño Jesús, Madrid, Spain; [17]Division of Hematology/Oncology, University of Florida College of Medicine, Gainesville, FL, USA; [18]University of Texas Health Science Center at San Antonio, San Antonio, TX, USA; [19]Divsion of Cancer Epidemiology & Genetics, NIH-NCI Clinical Genetics Branch, Rockville, MD, USA; [20]Division of Hematological Malignancy and Cellular Therapeutics, University of Kansas Health System, Kansas City, KS, USA; [21]Haematology Research Centre, Department of Immunology and Inflammation, Imperial College London, London, UK; [22]Department of Medical Oncology, Division of Hematological Malignancies, Thomas Jefferson University, Philadelphia, PA USA; [23]Blood & Marrow Transplant Program, Department of Hematology and Medical Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, USA; [24]Department of Internal Medicine, Mayo Clinic, Rochester, MN, USA; [25]Department of Medicine, Sheikh Shakhbout Medical City, Abu Dhabi, United Arab Emirates; [26]Markey Cancer Center, University of Kentucky, Lexington, KY, USA; [27]University Hospitals Cleveland Medical Center, Case Western Reserve University, Cleveland, OH, USA; [28]Division of Hematology and Transplant Center, Mayo Clinic Rochester, Rochester, MN, USA; [29]Markey Cancer Center, University of Kentucky, Lexington, KY, USA; [30]Division of Hematology-Oncology, Blood and Marrow Transplantation Program, Mayo Clinic, Jacksonville, FL, USA; [31]Section of Bone Marrow Transplant and Cell Therapy, Rush University Medical Center, Chicago, IL, USA; [32]Department of Blood & Marrow Transplant and Cellular Immunotherapy (BMT CI), Moffitt Cancer Center, Tampa, FL, USA; [33]Blood and Marrow Transplant Program, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA; [34]Novant Health Cancer Institute; Charlotte, NC, USA; [35]Department of Hematology and Oncology, Dokkyo Medical University, Tochigi, Japan; [36]Mayo Clinic, Rochester, MN, USA; [37]The Blood and Marrow Transplant Group of Georgia, Northside Hospital, Atlanta, GA, USA; [38]Department of Hematology/Oncology, Isala Clinic, Zwolle, The Netherlands; [39]Division of Medical Oncology, Washington University School of Medicine, St. Louis, MO, USA; [40]Cleveland Clinic, Cleveland, OH, USA; [41]Department of Stem Cell Transplantation, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX USA and [42]Fred Hutchinson Cancer Research Center, Seattle, WA, USA

**MM, RP, WS and RN contributed equally to this work.*

Correspondence: M. Mei
mamei@coh.org

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Abstract

Somatic mutations are recognized as an important prognostic factor in chronic myelomonocytic leukemia (CMML). However, limited data are available regarding their impact on outcomes after allogeneic hematopoietic cell transplantation (HCT). In this registry analysis conducted in collaboration with the Center for International Blood and Marrow Transplantation Registry database/sample repository, we identified 313 adult patients with CMML (median age: 64 years, range, 28-77) who underwent allogeneic HCT during 2001-2017 and had an available biospecimen in the form of a peripheral blood sample obtained prior to the start of conditioning. In multivariate analysis, a CMML-specific prognostic scoring system (CPSS) score of intermediate-2 (HR=1.46, *P*=0.049) or high (HR=3.22, *P*=0.0004) correlated significantly with overall survival. When the molecularly informed CPSS-Mol prognostic model was applied, a high CPSS-Mol score (HR=2 *P*=0.0079) correlated significantly with overall survival. The most common somatic mutations were in *ASXL1* (62%), *TET2* (35%), *KRAS/NRAS* (33% combined), and *SRSF2* (31%). *DNMT3A* and *TP53* mutations were associated with decreased overall survival (HR=1.70 [95% CI: 1.11-2.60], *P*=0.0147 and HR=2.72 [95% CI: 1.37-5.39], *P*=0.0042, respectively) while *DNMT3A*, *JAK2*, and *TP53* mutations were associated with decreased disease-free survival (HR=1.66 [95% CI: 1.11-2.49], *P*=0.0138, HR=1.79 [95% CI: 1.06-3.03], *P*=0.0293, and HR=2.94 [95% CI: 1.50-5.79], *P*=0.0018, respectively). The only mutation associated with increased relapse was *TP53* (HR=2.94, *P*=0.0201). Nonetheless, the impact of *TP53* mutations specifically should be interpreted cautiously given their rarity in CMML. We calculated the goodness of fit measured by Harrell's C-index for both the CPSS and CPSS-Mol, which were very similar. In summary, via registry data we have determined the mutational landscape in patients with CMML who underwent allogeneic HCT, and demonstrated an association between CPSS-Mol and transplant outcomes although without major improvement in the risk prediction beyond that provided by the CPSS.

Introduction

Chronic myelomonocytic leukemia (CMML) is a clonal myeloid neoplasm sharing clinical and pathological features of both myeloproliferative neoplasms and myelodysplastic syndromes and is classified by the World Health Organization (WHO) in the category of myelodysplastic syndrome/myeloproliferative neoplasm.[1] While rare with an annual incidence in the USA of 4.1 cases per 100,000 person-years,[2] it is nonetheless the most common of the adult-onset overlap myelodysplastic sydnrome/myeloproliferative neoplasm syndromes and occurs at a median age of 71-75 years.[3] CMML has a heterogenous clinical course, with prognosis and risk of transformation to acute myeloid leukemia being dependent on a number of clinical and molecular factors.[4,5] At present, the optimal treatment of CMML is not well defined as systemic therapies such as hypomethylating agents exert a limited effect on the natural history of the disease, and overall survival (OS) remains poor.[6-9]

Allogeneic hematopoietic cell transplantation (HCT) represents the only potentially curative treatment but is associated with high risks of morbidity and mortality. To date, transplant outcome data in CMML are limited to a few retrospective series mainly due to the relative rarity of the disease.[10-16] The largest retrospective study in the literature of 513 patients was conducted by the European Group for Blood and Marrow Transplantation (EBMT), which demonstrated a 4-year OS of 33%.[15] However, robust data regarding prognostic factors for allogeneic HCT outcomes in CMML remain lacking. A previous analysis by the Center for International Blood and Marrow Transplant Research (CIBMTR) demonstrated that OS correlated with the CMML-specific Prognostic Scoring System (CPSS) score, although the CPSS was not predictive for relapse, disease-free survival (DFS) or non-relapse mortality, and its impact on OS was chiefly due to its effect on post-relapse survival.[16] The impact of the MD Anderson Prognostic Score (MDAPS) on outcomes following allogeneic HCT has been evaluated in two smaller studies, neither of which showed a significant association with OS.[17] Therefore, improved risk stratification for CMML patients considered for allogeneic HCT is still needed.

Among the multiple prognostic scores developed for CMML, three incorporate information on recurrent somatic mutations. These are the Groupe Francophone des Myélodysplasies (GFM) score, the Mayo Molecular Model (MMM), and the clinical/molecular CPSS (CPSS-Mol) score.[18-20] While there are accumulating data regarding the impact of somatic mutations in a non-transplant setting,[21] limited data are available regarding the impact of somatic mutations or these molecularly informed prognostic models in CMML patients undergoing allogeneic HCT. Therefore, in this registry analysis conducted in collaboration with the CIBMTR database/sample repository, we sought to determine the landscape of somatic mutations in patients with CMML who underwent allogeneic HCT and their post-transplant outcomes, with an analysis of clinical and molecular prognostic factors.

Methods

Data source

The CIBMTR is a research collaboration between the Medical College of Wisconsin and the National Marrow Donor Program (NMDP)/Be the Match and consists of a voluntary network of more than 330 transplantation centers worldwide that contribute detailed data on allogeneic and autologous HCT to a centralized statistical center. Observational studies conducted by the CIBMTR are performed in compliance with all applicable federal regulations pertaining to the protection of human research participants. Protected health information issued in the performance of such research is collected and maintained in CIBMTR's capacity as a Public Health Authority under the Health Insurance Portability and Accountability Act Privacy Rule. Additional details regarding the data source are described elsewhere.[22] Patients' samples were obtained from the NMDP biospecimen repository.

Eligibility for study participation

Adult patients (age ≥18 years) with CMML who underwent allogeneic HCT during 2001-2017 and who had an available specimen in the NMDP biospecimen repository were included in this analysis. Patients who received umbilical cord blood HCT, syngeneic HCT, or haploidentical HCT, or patients who experienced disease transformation to secondary acute myeloid leukemia at any time prior to allogeneic HCT were excluded (n=56).

Study endpoints

The primary endpoint was OS, and secondary endpoints were DFS, relapse/progression, and treatment-related mortality (TRM). OS was defined as time to death from any cause, and DFS was defined as the time to relapse or death from any cause. TRM was defined as death from any cause in the first 28 days after transplantation, regardless of relapse status, or death beyond day 28 without disease recurrence; relapse was considered a competing event. Relapse/progression was reported by the transplantation centers. CPSS, CPSS-Mol, GFM, and MMM scores were calculated at the time of transplant per published references.[18,20,23,24]

Statistical analysis

Descriptive statistics tables of patients including demographics, disease-related factors, and transplant-related factors were prepared. The median and range were listed for continuous variables. The total number of patients and the percentage of each subgroup were calculated for categorical variables. Probabilities of DFS and OS were calculated using the Kaplan-Meier estimator, with the variance estimated by the Greenwood formula. Probabilities of relapse and TRM were generated using cumulative incidence estimates to accommodate competing risk events.

The primary objective of the study was to evaluate whether the CPSS-Mol score is associated with OS in allogeneic HCT patients. This was determined through multivariate Cox regression, with CPSS score adjusting for other clinical covariates. The proportional hazard of assumptions was tested in the Cox regression model. Stepwise selection was applied to the adjusting variables. The association of OS with other somatic mutations was examined using the log-rank test, and the *P* values were adjusted for multiple comparisons using the Holm procedure.

The secondary objective was to examine whether the CPSS-Mol is more predictive than the CPSS score for transplant outcomes. We used the C-index to compare the CPSS-Mol and CPSS scores in predicting survival outcomes and competing risk outcomes (relapse and TRM) using the SAS 9.4.[25]

Mutation analysis

Details of the mutation analysis are provided in the *Online Supplementary Material*.

Results

Study participants

We identified a total of 313 patients across 78 centers with CMML who met the inclusion criteria and had an available sample of peripheral blood collected immediately prior to the beginning of the conditioning regimen. A summary of their demographic information is given in Table 1 (full demographic information is provided in *Online Supplementary Table S1*). The median age was 64 years (range, 28-77) and 69% of the patients were male. Splenomegaly was documented in 84 patients (27%), and 166 patients (53%) had CMML-0 at the time of allogeneic HCT, as defined by WHO criteria. The majority of patients had 5% or fewer blasts both in the peripheral blood (82%) and bone marrow (71%). A hypomethylating agent (either 5-azacytidine or decitabine) was given to 61% of patients prior to allogeneic HCT. Slightly more than half of the patients (54%, n=170) received a reduced-intensity conditioning regimen. Nearly half of the patients (45%, n=134) had a Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI) of 3 or greater, and 41% of patients (n=128) had a Karnofsky Performance Score under 90%. The majority of patients received an allograft from a matched unrelated donor (76%, n=238) with the source of stem cells being peripheral blood (85%, n=267), and received tacrolimus-based graft-*versus*-host disease prophylaxis (81%, n=253) without *in vivo* T-cell depletion (60%, n=188). CPSS scores calculated at the time of transplantation were available

Table 1. Summary of baseline characteristics.

Patients' characteristics	Total
Number of patients	313
Number of centers	78
Median age in years, (range)	64 (28-77)
Age in years at HCT, N (%)	
<50	33 (11)
50-59	75 (24)
60-69	165 (53)
≥ 70	40 (13)
Sex, N (%)	
Male	215 (69)
Female	98 (31)
HCT-CI score, N (%)	
0	55 (18)
1-2	67 (21)
≥ 3	134 (43)
Not available / Before 2007	57 (18)
Disease-specific characteristics	
CMML status: WHO criteria at transplant, N of patients (%)	
CMML-0 (<2% blasts in PB and <5% blasts in BM)	166 (53)
CMML-1 (2–4% blasts in PB and/or 5–9% blasts in BM)	62 (20)
CMML-2 (5–19% blasts in PB, 10–19% blasts in BM)	27 (9)
Not reported	58 (19)
Therapy prior to HCT, N of patients (%)	
Hypomethylating agent	190 (61)
Chemotherapy	10 (3)
Hypomethylating agent + chemotherapy	27 (9)
Not reported	86 (27)
CPSS prior to transplant, N of patients (%)	
Low	91 (29)
Intermediate-1	77 (25)
Intermediate-2	96 (31)
High	14 (4)
Not reported	35 (11)
Transplant-related characteristics	
Time from diagnosis to transplant, months	9 (<1-112)
Donor type, N of patients (%)	
Matched related	20 (6)
Matched unrelated	238 (76)
Mismatch unrelated	52 (17)
Not reported	3 (<1)
Conditioning intensity, N of patients (%)	
Myeloablating conditionig	135 (43)
Reduced intensity conditioning	170 (54)
Not reported	8 (3)
Year of transplant, N of patients (%)	
2001-2011	108 (35)
2012-2014	84 (27)
2015-2017	121 (39)
Median follow-up of survivors, months (range)	47 (3-192)

HCT: allogeneic hematopoietic cell transplantation; CI: comorbidity index; CMML: chronic myelomonocytic leukemia; WHO: World Health Organization PB; peripheral blood;; BM: bone marrow; CPSS: Chronic Myelomonocytic Leukemia-Specific Prognostic Scoring System.

for 89% (n=278) of the subjects, and the distribution of scores was as follows: low in 32.7% (n=91), intermediate-1 in 27.7% (n=77), intermediate-2 in 34.5% (n=96), and high in 5% (n=14). The median follow-up was 47 months (range, 3-192 months).

Genetic characteristics and spectrum of mutations

Of the 313 patients examined, 290 (93%) had at least one

pathogenic mutation identified in one of the assayed genes, and the median number of mutations was three (range, 0-10). The most common somatic mutations were in *ASXL1* (61%), *TET2* (35%), *KRAS/NRAS* (33% combined), and *SRSF2* (31%). A *TP53* mutation was found in ten patients (3%) (*Online Supplementary Figure S1*, *Online Supplementary Table S3*). As previously reported,[19,31] a significant association was found between *TET2* and splicing factor gene mutations: 54 patients had co-occurring *TET2* and *SRSF2* mutations and 71 patients had co-occurrence of mutations in *TET2* and one or more of *SRSF2*, *ZSRF2*, *U2AF1*, and *SF3B1* (*Online Supplementary Figure S2*). In the double mutant (*TET2*/splicing factor gene) cases, the variant allele frequency of *TET2* was higher than that of the splicing factor gene in more cases (n=39) than the converse (variant allele frequency of splicing factor gene greater than that of *TET2*, n=23), which suggests that *TET2* mutations precede splicing factor mutations in the majority of cases (*Online Supplementary Figure S2*). CPSS-Mol, GFM, and MMM scores were derived for 92% (n=287), 98% (n=306), and 95% (n=296) of subjects, respectively. The distribution of patients according to the CPSS-Mol, GFM, and MMM scores is shown in Table 2. Distribution across risk classes by the CPSS and GFM is similar to what was reported in the original studies for both scoring systems,[18,23] whereas patients in our cohort appeared to be significantly higher risk than those in the original studies for the CPSS-Mol and MMM, both of which were focused on non-transplant patients.[18,20]

Clinical correlation between mutations and disease phenotype

We also examined the correlation between the mutational profile and disease phenotype. *U2AF1* mutations were correlated with myelodysplastic CMML (white blood cell count ≥13×10^9/L) while myeloproliferative CMML (white blood cell count <13×10^9/L) was found to associated with mutations in *ASXL1*, *EZH2*, *KIT*, and *SRSF2*. A significant correlation was also found between mutational burden and both age and myeloproliferative CMML. (*Online Supplementary Table S4A*). Positive interactions with the WHO subtype (CMML-0, -1, -2) were found with mutations in *ASXL1*, *BCOR*, *BRAF*, *CEBPA*, *CSF3R*, *FLT3*, *GATA2*, *IDH1/2*, *NRAS*, *STAG2*, and *TET2* although relative frequencies were low for most of these except *ASXL1*, *NRAS*, and *TET2* (*Online Supplementary Table S4B*).

Table 2. Molecularly informed prognostic scores for chronic myelomonocytic leukemia.

Characteristic	N (%)
CPSS-Mol score prior to transplant	
Low	39 (12)
Intermediate-1	52 (17)
Intermediate-2	118 (38)
High	78 (25)
Not reported	26 (8)
GFM score prior to transplant	
Low (0-4)	133 (42)
Intermediate (5-7)	108 (35)
High (8-12)	65 (21)
Not reported	7 (2)
MMM score prior to transplant	
Low	1 (<1)
Intermediate-1	13 (4)
Intermediate-2	62 (20)
High	220 (70)
Not reported	17 (5)

CPSS-Mol: Clinical/Molecular Chronic Myelomonocytic Leukemia-Specific Prognostic Scoring System; GFM, Groupe Francophone des Myélodysplasies; MMM, Mayo Molecular Model.

Univariate analysis

On univariate analysis, both the CPSS and CPSS-Mol scores correlated significantly with 4-year OS, DFS, and TRM. Notably, neither scoring system was predictive for disease progression/relapse. Data for the univariate analysis stratified by CPSS and CPSS-Mol scores are given in Table 3. Kaplan-Meier curves for OS and DFS, and cumulative incidence curves for relapse and TRM, are displayed according to the CPSS score in Figure 1A-D, and according to the CPSS-Mol score in Figure 2A-D. According to the CPSS, the 4-year OS was 41.1% (95% CI: 29.5-53.3) for low-risk, 36.5% (95% CI: 25.1-48.6) for intermediate-1-risk, 26.6% (95% CI: 17.1-37.2) for intermediate-2-risk, and 10.7% (95% CI: 0.1-34.7) for high-risk patients (*P*=0.029) (Figure 1A, Table 3). By CPSS-Mol score, the 4-year OS was 47.5% (95% CI: 31.1-64.1) for low-riks, 39.7% (95% CI: 25-55.4) for intermediate-1-risk, 37.6% (95% CI: 28.1-47.6) for intermediate-2-risk, and 16% (95% CI:7.4-27) for high-risk patients (*P*=0.001) (Figure 1B, Table 4). Outcomes for the entire cohort are provided in *Online Supplementary Table S5*.

Multivariate analysis

On multivariate analysis, a CPSS score of intermediate-2 or high correlated significantly with OS (CPSS score intermediate-2: HR=1.46 [95% CI: 1.001-2.134], *P*=0.0494, CPSS score high: HR=3.22 [95% CI: 1.685-6.154], *P*=0.0004]) as did a higher HCT-CI (HCT-CI 1-2: HR=1.71 [95% CI: 1.02-2.86], *P*=0.0406, HCT-CI 3+, HR=2.05 [95% CI: 1.29-3.25], *P*=0.0024). A matched unrelated donor *versus* mismatched unrelated donor (HR=0.53 [95% CI: 0.67-0.76], *P*=0.0005) also significantly correlated with OS. A CPSS score of high correlated significantly with both DFS (HR=2.24 [95% CI: 1.20-4.19], *P*=0.012) and relapse/progression (HR=2.73 [95% CI: 1.25-5.99], *P*=0.012), and a CPSS score of intermediate-2 (HR=1.93 [95% CI: 1.11-3.37], *P*=0.021) and number of mutations (HR=1.17 [95% CI: 1.06-1.31], *P*=0.0031) were both correlated with TRM.

A high CPSS-Mol score correlated significantly with OS (HR=2 [95% CI: 1.12-3.34], *P*=0.0079) and DFS (HR=1.73

Table 3. Univariable estimates for CPSS score at time of hematopoietic stem cell transplantation.

	Low (N = 91)		Intermediate-1 (N = 77)		Intermediate-2 (N = 96)		High (N = 14)		
Outcomes	**N**	**Prob % (95% CI)**	**N**	**Prob % (95% CI)**	**N**	**Prob % (95% CI)**	**N**	**Prob % (95% CI)**	**P value**
Overall survival	91		77		96		14		0.005
100-day		87.9 (80.5-93.8)		87 (78.6-93.5)		84.4 (76.5-90.9)		71.4 (46-91.2)	0.566
4-year		41.1 (29.5-53.3)		36.5 (25.1-48.6)		26.6 (17.1-37.2)		10.7 (0.1-34.7)	0.029
Relapse	88		77		95		13		0.508
100-day		8 (3.2-14.5)		6.5 (2.1-13.1)		15.8 (9.2-23.9)		30.8 (8.8-58.9)	0.082
4-year		44.5 (33.6-55.8)		43.4 (32-55.2)		40.7 (30.7-51.2)		61.5 (31.1-87.7)	0.642
Treatment-related mortality	88		77		95		13		0.146
100-day		9.1 (4-16)		13 (6.4-21.4)		11.6 (5.9-18.8)		15.4 (1.4-40.3)	0.837
4-year		19.4 (11.5-28.7)		29.7 (19.6-40.8)		38.9 (28.5-49.9)		30.8 (8.6-59.3)	0.050
Disease-free survival	88		77		95		13		0.035
100-day		83 (74.4-90)		80.5 (71-88.5)		72.6 (63.2-81.1)		53.8 (27.5-79.1)	0.099
4-year		36.1 (25.7-47.2)		26.9 (17-38.1)		20.4 (12-30.3)		7.7 (0-27.6)	0.015

CPSS: Chronic Myelomonocytic Leukemia-Specific Prognostic Scoring System, 95% CI: 95% confidence interval.

[95% CI: 1.07-2.80], *P*=0.024) as did an HCT-CI score of three or more (HR=1.99 [95%CI: 1.26-3.14], *P*=0.003) and matched unrelated donor *versus* mismatched unrelated donor (HR=0.535 [95% CI: 0.37-0.77], *P*=0.0007). Finally, intermediate-1-risk and intermediate-2-risk CPSS-Mol scores were associated with lower TRM compared to a high-risk CPSS-Mol score (HR=0.32 for both, *P*=0.0078). Results for the multivariate analyses incorporating the CPSS and CPSS-Mol scores are described in *Online Supplementary Table S7*.

Goodness of fit

We calculated the goodness-of-fit measure by Harrell's C-index[26] for both the CPSS and CPSS-Mol for all four outcomes of interest. The C-index scores for the CPSS for OS, DFS, relapse, and TRM were 0.56, 0.55, 0.52, and 0.56, respectively. The C-index scores for the CPSS-Mol for OS, DFS, relapse, and TRM were 0.57, 0.55, 0.55, and 0.58, respectively.

Causes of mortality

Given the high rates of TRM seen in the cohort, the causes of death were investigated further. Overall, 40% (n=68) of patients died due to the primary disease, whereas 15% (n=26) died of infection, 13% (n=23) from graft-*versus*-host disease, 13% (n=22) from organ failure, and 9% (n= 6) from other causes.

Prognostic value of individual somatic mutations

Full results of the multivariate analysis of the impact of somatic mutations on the primary and secondary endpoints are shown in *Online Supplementary Table S6A-D*. In multivariate analysis, *DNMT3A* and *TP53* mutations correlated with decreased OS (HR=1.70 [95% CI: 1.11-2.60], *P*=0.0147 and HR=2.72 [95% CI: 1.37-5.39], *P*=0.0042, respectively) while *DNMT3A*, *JAK2*, and *TP53* mutations were associated with decreased DFS (HR=1.66 [95% CI: 1.11-2.49], *P*=0.0138, HR=1.79 [95% CI: 1.06-3.03], *P*=0.0293, and HR=2.94 [95% CI: 1.50-5.79], *P*=0.0018, respectively). The only mutation associated with increased relapse was *TP53* (HR=2.94 [95% CI: 1.18-7.28], *P*=0.0201). Finally, *DNMT3A* mutations were associated with increased TRM (HR=1.89 [95% CI: 1.03-3.44], *P*=0.039) whereas *PTPN11* mutations were associated with decreased TRM (HR=0.21 [95% CI: 0.05-0.86], *P*=0.03).

Discussion

Our data represent the largest study of CMML patients who underwent allogeneic HCT and who had a comprehensive somatic mutation analysis. The mutation landscape observed in our study was largely consistent with that of prior reports in CMML[20,27] including the most common somatic mutations (*ASXL1*, *TET2*, *KRAS/NRAS*, and *SRSF2*), with an association between *TET2* and splicing factor gene mutations, and an association with clinical subtypes (*U2AF1* mutations with myelodysplastic CMML, and *ASXL1*, *EZH2*, *KIT*, and *SRSF2* mutations with myeloproliferative CMML.[28] As expected, our transplant cohort had a greater proportion of patients with high-risk mutations than cohorts in non-transplant studies as it was enriched for patients with *ASXL1* mutations compared to historical data.[29] Although the results were disappointing, especially in the CPSS and CPSS-Mol high-risk groups (4-year OS of 10.7% and 16%, respectively), they are reflective of real-world data derived from a very high-risk population. Also, 66% of patients were at least 60 years of age,

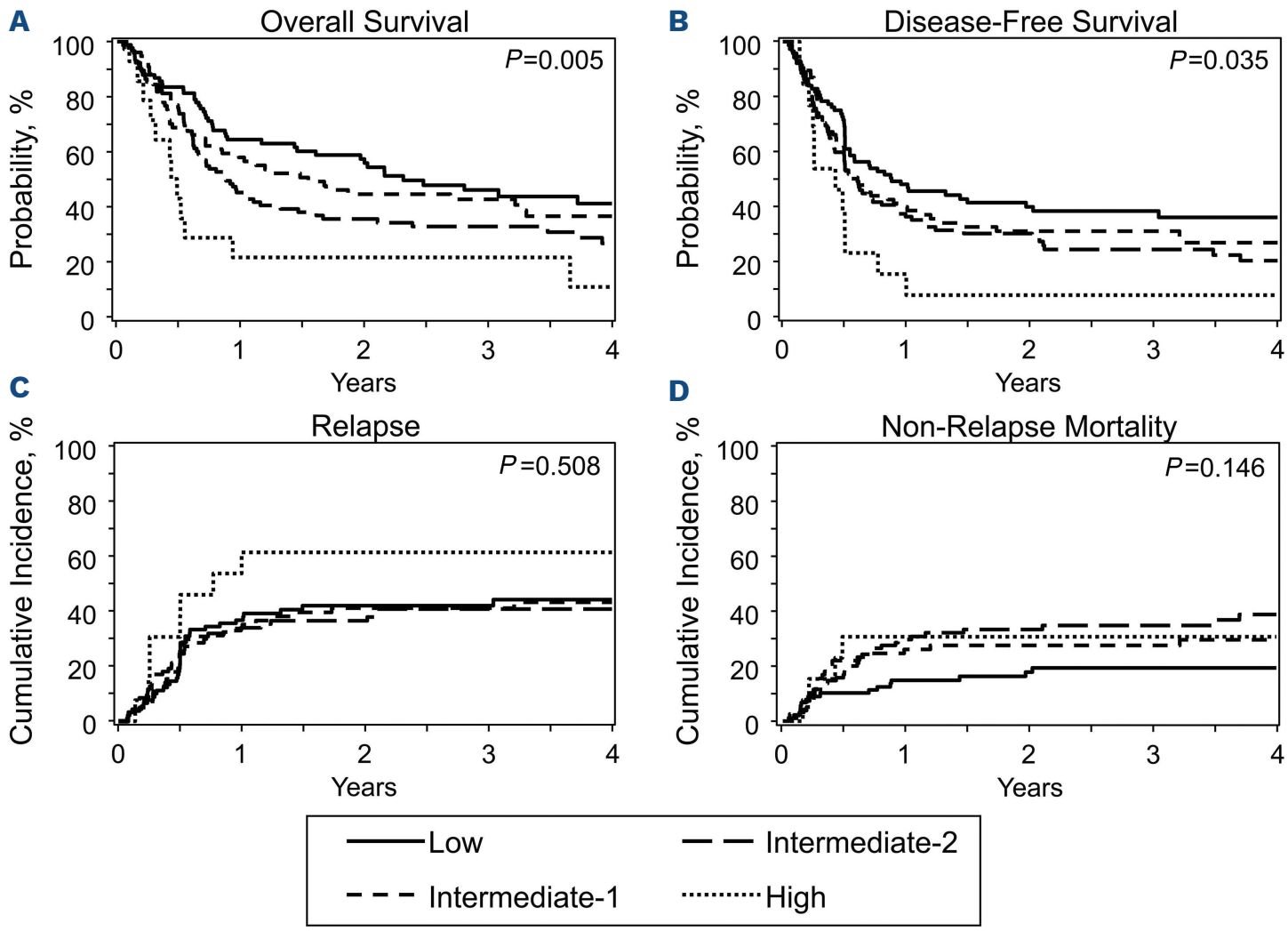

Figure 1. Univariate analysis of post-transplant outcomes by CPSS score. (A) Overall survival. (B) Disease-free survival. (C) Relapse/progression. (D) Transplant-related mortality. CPSS: Chronic Myelomonocytic Leukemia-Specific Prognostic Scoring System.

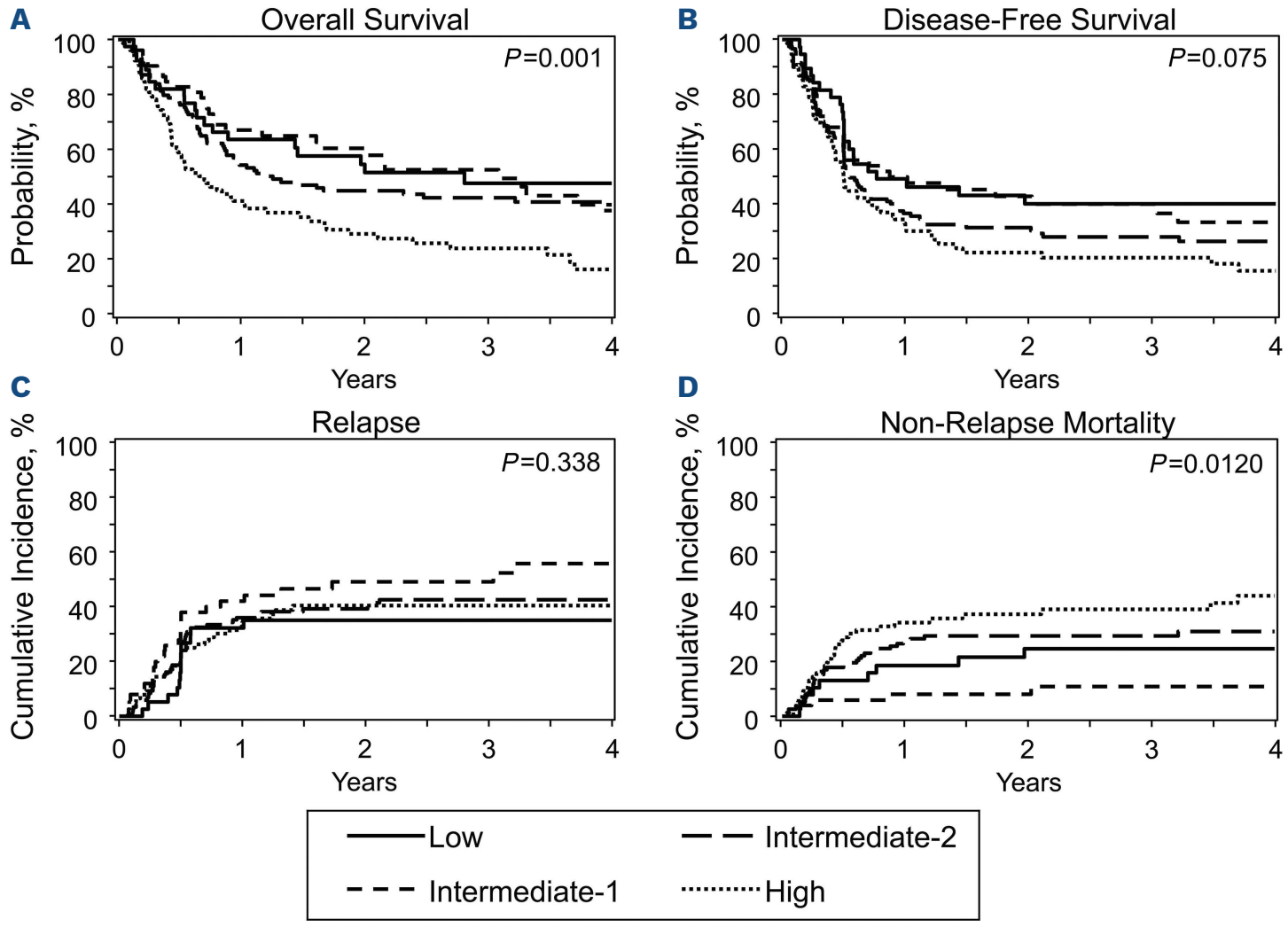

Figure 2. Univariate analysis of post-transplant outcomes by CPSS-Mol score. A) Overall survival. (B) Disease-free survival. (C) Relapse/progression. (D) Transplant-related mortality. CPSS-Mol: Chronic Myelomonocytic Leukemia-Specific Prognostic Scoring System Molecular.

41% had a Karnofsky Performance Score <90%, 43% had an HCT-CI of 3+, and only 6% received a graft from a matched sibling; all of these factors likely contributed to the overall high TRM in this study.

We found both the CPSS and CPSS-Mol scores to be significantly associated with post-allogeneic HCT OS and DFS. In contrast, the GFM and MMM scores correlated poorly with transplant outcomes. One interesting observation was the variable segregation of disease risk by the different models. The CPSS, CPSS-Mol, and MMM models each stratify patients into four risk groups, whereas the GFM has three risk groups. However, as stratified by the MMM, the overwhelming majority of patients had intermediate-2 or high-risk disease (90% combined) with only one patient having low-risk disease and 4% (n=13) of patients having intermediate-1-risk disease; therefore, the MMM functionally stratified patients into two groups. Similarly, only 4% (n=13) of patients had high-risk disease by the CPSS whereas at least 10% of patients fell into each of the risk categories as defined by the CPSS-Mol and GFM scores.

In this study, we had hypothesized that the CPSS-Mol score, which incorporates the impact of four separate somatic mutations (*ASXL1*, *NRAS*, *RUNX1*, and *SETBP1*), would provide better prognostication than the CPSS score, which uses only clinical variables along with cytogenetic data. However, we found that there was no improvement in the prognostic model by having additional molecular data on the CPSS, as the C-index scores for the two models were not appreciably different and were under 0.7 for all outcomes, indicative of relatively poor discriminatory value. In a prior CIBMTR analysis, the CPSS had correlated with OS but primarily exerted its effect through prolonged post-relapse survival.[16] As such, we hypothesized that the incorporation of molecular data in the form of the CPSS-Mol, which has been validated in the non-transplant setting, would refine risk stratification for disease relapse, especially as patients with low and intermediate-1 CPSS-Mol scores have a very low risk of acute leukemic evolution.[20] However, this did not translate into a significantly diminished risk of post-transplant relapse: patients with CPSS-Mol low- and intermediate-1-risk disease had a relatively high 4-year incidence of relapse of 35.2% and 55.9%, respectively. We found that TRM correlated with both CPSS and CPSS-Mol scores here, which had not been seen in the earlier CIBMTR analysis on CMML;[16] this is similar to what has been seen in myelofibrosis with an increased Dynamic International Prognostic Scoring System (DIPPS) score being associated with increased TRM and may be reflective of other unknown biological correlates.[30]

While the overwhelming majority of patients with CMML have at least one recurrent somatic driver mutation,[27] the spectrum of molecular mutations seen in CMML is more restricted than that in other myeloid disorders such as myelodysplastic syndrome or acute myeloid leukemia. It has been observed that the heterogeneity of clinical behavior is in excess of that predicted by the impact of somatic mutations alone, and the impact of somatic mutations in CMML may be less than in other diseases.[31] The impact of acquired somatic mutations on post-transplant outcomes in other myeloid malignancies has been previously examined. For instance, a study of 401 patients with myelodysplastic syndrome and secondary acute myeloid leukemia evolving out of prior myelodysplastic syndrome found that mutations in *ASXL1*, *RUNX1*, and *TP53* were independently predictive of OS after allogeneic HCT.[32] Another study of 234 patients with acute myeloid leukemia who were stratified by the European Leukemia-

Table 4. Univariable estimates for CPSS-Mol score at time of hematopoietic stem cell transplantation.

	Low (N = 39)		Intermediate-1 (N = 52)		Intermediate-2 (N = 118)		High (N = 78)		
Outcomes	**N**	**Prob % (95% CI)**	**N**	**Prob % (95% CI)**	**N**	**Outcomes**	**N**	**Prob % (95% CI)**	**P value**
Overall survival	39		52		118		78		0.001
100-day		84.6 (71.8-94.1)		90.4 (81-96.8)		84.7 (77.7-90.6)		79.5 (69.9-87.7)	0.362
4-year		47.5 (31.1-64.1)		39.7 (25-55.4)		37.6 (28.1-47.6)		16 (7.4-27)	0.001
Relapse	38		50		118		76		0.373
100-day		5.3 (0.5-14.6)		12 (4.5-22.5)		11 (6-17.3)		14.5 (7.5-23.3)	0.283
4-year		35.2 (20.5-51.5)		55.9 (40.4-70.7)		42.7 (33.5-52.1)		40.5 (29.4-52.1)	0.012
Treatment-related mortality	38		50		118		76		
100-day		10.5 (2.8-22.3)		6 (1.1-14.3)		14.4 (8.7-21.3)		14.5 (7.5-23.3)	0.263
4-year		24.8 (12-40.3)		10.9 (3.5-21.9)		31.1 (22.6-40.2)		44 (32-56.5)	<0.001
Disease-free survival	38		50		118		76		0.075
100-day		84.2 (71.1-93.9)		82 (70.3-91.3)		74.5 (66.3-82)		71.1 (60.4-80.6)	0.260
4-year		40 (24.8-56.3)		33.2 (19.7-48.3)		26.3 (18.2-35.3)		15.5 (7.4-25.8)	0.034

CPSS-Mol: Chronic Myelomonocytic Leukemia-Specific Prognostic Scoring System Molecular, 95% CI: 95% confidence interval.

Net (ELN) risk classification, a system which includes only cytogenetic and molecular data, found that the ELN2017 risk class was highly correlated with post-allogeneic HCT outcomes; a *TP53* mutation was found to confer an independent negative effect even in the ELN2017 adverse-risk group.[33] In contrast, the limited impact of molecular data in our study mirrors the results seen in myelofibrosis, in which none of the high molecular risk mutations (*ASXL1*, *SRSF2*, *U2AF1*, *EZH2*, or *IDH1/2*) was correlated with allogeneic HCT outcomes.[34]

Other groups have also examined the impact of mutational status on allogeneic HCT outcomes in patients with CMML. In a single-center retrospective analysis from the University of Washington, 129 patients with CMML who underwent allogeneic HCT were analyzed, including 52 with comprehensive somatic mutation data. Mutations in *NRAS*, *ATRX*, and *WT1* were associated with increased relapse, and the latter two were associated with inferior survival, and an increasing number of mutations correlated with relapse as well.[35] Another study of 70 CMML patients who underwent allogeneic HCT at the Mayo Clinic, 24 of whom had experienced prior transformation to acute myeloid leukemia, found no impact of mutational status on post-transplant outcomes.[36]

Finally, a recent ten-center study by Gagelman *et al*., evaluating 240 CMML patients who underwent allogeneic HCT, found that the CPSS-Mol, GFM, and MMM scores were all significantly associated with OS, whereas neither the CPSS nor the MDAPS correlated with OS.[37] In this study, a CMML transplant-specific score was developed with incorporation of *ASXL1* and/or *NRAS* mutation status, bone marrow blasts, and HCT-CI, which outperformed the existing prognostic models. We observed key differences between the cohort reported by Gagelmann *et al*. and ours. For instance, the distribution by WHO classification was dissimilar as CMML-0, -1, and -2 patients accounted for 53%, 20%, and 9% (19% not reported) of cases, respectively, in our cohort, whereas the corresponding figures for the cohort studied by Gagelmann *et al*. were 10%, 50%, and 40%, respectively; this marked difference possibly resulted in the bone marrow blast percentage not being significantly associated with post-allogeneic HCT survival in our cohort. There were also important differences in the genetic profiling of the two cohorts, as 62% of our patients had *ASXL1* mutations (all nonsense) compared to 34.2% in the EBMT cohort.

Our data need to be interpreted with caution given the limitations of this retrospective study. The clinical data are from the time immediately prior to transplantation, so they may have been affected by pre-allogeneic HCT therapy, although hypomethylating agents do not appear to significantly alter the mutational landscape in CMML.[9] The somatic mutations were analyzed from peripheral blood rather than bone marrow; however, there is excellent concordance between the two in chronic myeloid disorders.[38] Additionally, the impact of individual somatic mutations might reflect other confounding variables; for instance, there is no clear biological basis for an association between *DNMT3A* mutations and increased TRM. Nonetheless, results are largely in keeping with existing data, suggesting that somatic mutations in CMML exert only a limited effect on post-allogeneic HCT outcomes. Future studies with characterization of structural variations, epigenetic profiling and transcriptomics including the contribution of non-coding RNA as well as longitudinal analysis of molecular data at the time of relapse may provide additional insight into ways to decrease relapse.

In summary, our registry data provided the mutational landscape in CMML patients undergoing allogeneic HCT, and demonstrated an association between CPSS-Mol score and transplant outcomes although this was driven by the CPSS without a significant contribution from the additional molecular data. While this study cannot answer the question as to whether a specific patient with CMML should undergo allogeneic HCT, the fact that allogeneic HCT outcomes are not greatly influenced by specific molecular mutations in CMML is relevant especially in centers lacking ready access to next-generation sequencing. On the other hand, given the favorable natural history of CPSS-Mol low- and intermediate-1 disease with low risk of evolution to acute myeloid leukemia, the decision to perform allogeneic HCT in these patients should be made very carefully. As allogeneic HCT outcomes are still poor in CMML, other molecular and hematologic data are needed to understand resistance mechanisms in this challenging disease, as well as to prevent post-allogeneic HCT relapse and decrease treatment toxicity.

Disclosures

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Contributions

MM, RN and WS designed the protocol; RP, MAfkhami, LY and ZM were responsible for the molecular analyses; SK and NE-M analyzed the data; MM, RN and WS wrote the article. All authors interpreted the data and revised the manuscript.

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Data-sharing statement

The CIBMTR supports accessibility of research in accord with the National Institutes of Health (NIH) Data Sharing Policy and the National Cancer Institute (NCI) Cancer Moonshot Public Access and Data Sharing Policy. The CIBMTR only releases de-identified datasets that comply with all relevant global regulations regarding privacy and confidentiality.

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