Outcomes with intensive treatment for acute myeloid leukemia: an analysis of two decades of data from the HARMONY Alliance

Marta Anna Sobas,[1*] Amin T. Turki,[2*] Angela Villaverde Ramiro,[3,4] Alberto Hernández-Sánchez,[3-5] Javier Martinez Elicegui,[3,4] Teresa González,[3,4] Raúl Azibeiro Melchor,[5] María Abáigar,[3,4] Laura Tur,[6] Daniele Dall'Olio,[7] Eric Sträng,[8] Jesse M. Tettero,[9] Gastone Castellani,[10] Axel Benner,[11] Konstanze Döhner,[12] Christian Thiede,[13] Klaus H. Metzeler,[14] Torsten Haferlach,[15] Frederik Damm,[8,16] Rosa Ayala,[17] Joaquín Martínez-López,[17] Ken I. Mills,[18] Jorge Sierra,[19] Sören Lehmann,[20] Matteo G. Della Porta,[21] Jiri Mayer,[22] Dirk Reinhardt,[23] Rubén Villoria Medina,[6] Renate Schulze-Rath,[24] Martje Barbus,[25] Jesús María Hernández-Rivas,[3,5] Brian J.P. Huntly,[26] Gert Ossenkoppele,[27] Hartmut Döhner[12] and Lars Bullinger[8,16]

[1]Department of Hematology, Blood Neoplasm and Bone Marrow Transplantation, Wroclaw Medical University, Wroclaw, Poland; [2]Department of Hematology and Oncology, Marienhospital University Hospital, Ruhr-University Bochum, Bochum, Germany; [3]Institute of Biomedical Research of Salamanca (IBSAL), Salamanca, Spain; [4]Cancer Research Center of Salamanca (USAL-CSIC), Salamanca, Spain; [5]Hematology Department, University Hospital of Salamanca, Salamanca, Spain; [6]GMV Innovating Solutions, Valencia, Spain; [7]IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy; [8]Department of Hematology, Oncology and Cancer Immunology, Campus Virchow, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany; [9]Department of Hematology, Amsterdam University Medical Center location Vrije Universiteit Amsterdam, Amsterdam, the Netherlands; [10]Department of Medical and Surgical Sciences - DIMEC, University of Bologna, Bologna, Italy; [11]Division of Biostatistics, German Cancer Research Center (DKFZ), Heidelberg, Germany; [12]Department of Internal Medicine III, University Hospital Ulm, Ulm, Germany; [13]Department of Internal Medicine I, University Hospital Dresden, Dresden, Germany; [14]Department for Hematology, Cell Therapy and Hemostaseology, University of Leipzig Medical Center, Leipzig, Germany; [15]MLL Munich Leukemia Laboratory, Munich, Germany; [16]German Cancer Consortium (DKTK) and German Cancer Research Center (DKFZ), Heidelberg, Germany; [17]Hematology Department, Hospital Universitario 12 de Octubre, Complutense University CNIO Madrid, Madrid, Spain; [18]Patrick G Johnston Centre for Cancer Research, Queen's University Belfast, Belfast, UK; [19]Hospital Santa Creu Sant Pau, Barcelona, Spain; [20]Uppsala University Hospital, Uppsala, Sweden; [21]IRCCS Humanitas Research Hospital and Department of Biomedical Sciences, Humanitas University, Milan, Italy; [22]Department of Internal Medicine, Hematology and Oncology, University Hospital Brno and Masaryk University, Brno, Czech Republic; [23]Department of Pediatrics III, University Hospital Essen, University Duisburg-Essen, Essen, Germany; [24]Bayer AG, Pharmaceuticals Division, Berlin, Germany; [25]AbbVie Deutschland GmbH & Co KG, Wiesbaden, Germany; [26]Department of Haematology and Wellcome-MRC Cambridge Stem Cell Institute, University of Cambridge, Cambridge, UK and [27]Amsterdam University Medical Center, location VUMC, Amsterdam, the Netherlands

**MAS and ATT contributed equally as first authors.*

Correspondence: L. Bullinger
lars.bullinger@charite.de

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Abstract

Since 2017, targeted therapies combined with conventional intensive chemotherapy have started to improve outcomes of patients with acute myeloid leukemia (AML). However, even before these innovations, outcomes with intensive chemotherapy had improved, which has not yet been extensively studied. Thus, we used a large pan-European multicenter dataset of the HARMONY Alliance to evaluate treatment-time dependent outcomes over two decades. In 5,359 AML patients, we com-

pared the impact of intensive induction therapy on outcome over four consecutive 5-year calendar periods from 1997 to 2016. During that time, the 5-year survival of AML patients improved significantly, also across different genetic risk groups. In particular, the 60-day mortality rate dropped from 13.0% to 4.7% over time. The independent effect of calendar periods on outcome was confirmed in multivariate models. Improvements were documented both for patients <60 and ≥60 years old, and in those treated with and without consolidating allogeneic hematopoietic stem cell transplantation (alloHCT). While survival of AML elderly patients remains poor, patients ≥60 years old overall have a 20% survival benefit at 5 years if they receive an alloHCT. While further outcome improvement in intensively treated AML patients will likely be driven by targeted treatment approaches, this pan-European HARMONY dataset can serve as a multicenter comparator for future studies.

Introduction

Since 1973, the standard intensive chemotherapy ("7+3" protocol) for patients with acute myeloid leukemia (AML) is based on cytosine arabinoside in combination with anthracyclines: daunorubicin or idarubicin and these drugs still provide the backbone of today's intensive induction treatments.[1] Clinical results of intensive therapy improved with consolidation treatments using high-dose/intermediate-dose cytosine arabinoside[2] or allogeneic stem cell transplantation (alloHCT) in first complete remission (CR1).[3,4] In 2010, the European LeukemiaNet (ELN) composed a prognostic score consisting of cytogenetic and molecular genetic characteristics to guide treatment decisions for AML.[5] This score was revised in 2017[6] and 2022[7] to address the growing knowledge of the genetic complexity of AML. Our better understanding of the complex biology underlying AML added novel targeted therapies to the "7+3" regimen.[8-11] This further improved the results for AML patients with *FLT3* mutations,[9] or in young patients with favorable cytogenetics and CD33 antigen expression.[10] In addition, there is emerging promising data for inhibition of isocitrate dehydrogenase (IDH) in combination with the "7+3" regimen in patients with *IDH1/IDH2* mutations.[11]

While the impact of these new therapeutic approaches on outcome remains to be determined in the real-world-setting, recently reported 5-year overall survival (OS) rates in intensively treated AML patients up to the age of their fifties remained in the range of 40-45%.[12,13] For patients up to the age of 60 years old, the 5-year OS rates are only 30-39%[14] and for patients ≥60 years, 10-25%,[15] which could be further improved by increasing the daunorubicin dose to higher than 45 mg/m^2.[16]

While differences in outcome between younger and older AML patients are multifactorial and can be divided into patient-related[17] and disease-related[18] factors, the impact of improved supportive therapies as well as age-adjusted alloHCT protocols has not been sufficiently studied in the multinational setting on a large scale. The use of consolidating alloHCT in AML patients has seen impressive improvement, with more alloHCT being performed also at an older age.[19] In parallel to this increase in use, the toxicity of the intervention has decreased, which makes this procedure safer for application in older patients.[20] However, the benefit of alloHCT still remains controversial in older patients.[21] Given evolving knowledge of leukemogenic mechanisms and the availability of less intense treatment approaches using hypomethylating agents since 2004,[22] and more recently the combination of hypomethylating agents with the BCL2 inhibitor venetoclax,[23] the question of which patients benefit most from intensive therapy has been repeatedly raised.[12,13,15,18,24,25] Risk scores have been provided to support physicians in their decision-making regarding which elderly patients should start on intensive therapy. However, this decision still largely depends on many individual factors.

On this background, this study compared the characteristics and outcomes of intensively treated patients over four consecutive 5-year calendar periods from 1997 to 2016. Our aim was to identify relevant covariates for long-term OS as well as early mortality, and to study the impact of alloHCT and age on outcome in a large pan-European multicenter real-world and multi-trial dataset of the Healthcare Alliance for Resourceful Medicines Offensive against Neoplasms in Hematology (HARMONY).

Methods

Patients

This study included AML patients given intensive induction chemotherapy who had entered the HARMONY database by October 2022. The HARMONY Alliance is a pan-European public-private partnership funded by the Innovative Medicines Initiative with the aim of improving the outcome of patients with hematologic malignancies. Its database includes data from patients provided by 140 organizations from more than 26 countries in Europe and overseas. Prior to inclusion into the HARMONY database, data pass through processes of independent quality control, *de-facto* anonymization[26] and harmonization using the Observational Medical Outcomes Partnership (OMOP) Common Data Model[27] (this process is illustrated by *Online Supplementary Figure S1*).

Following the OMOP process, patients were identified from the HARMONY database by time of diagnosis, from 1997 to 2016, and by their documented intensive chemotherapy protocols (N=4,286 independent of their age with detailed protocols as in *Online Supplementary Table S1*, and N=1,072

aged 18-70 years without detailed information on their intensive chemotherapy regimen although known to have been intensively treated). In total, 5,359 cases were identified, of which 1,689 (31.5%) stemmed from retrospective real-world cases and 3,670 (68.5%) from prospective clinical trials. The baseline variables age, sex, Eastern Cooperative Oncology Group (ECOG) performance status, hemoglobin concentration, and platelet, leukocyte and bone marrow blast counts did not differ between these source groups (*Online Supplementary Table S2*). The 5-year OS of patients in the age-determined source group was slightly higher, as was the proportion of patients with ELN intermediate risk. AML was originally classified according to the criteria at the time of diagnosis and was reclassified for this analysis according to the World Health Organization (WHO) 2016 criteria.[28] Patients with a diagnosis of acute promyelocytic leukemia, mixed phenotype leukemia or acute leukemia of ambiguous lineage were excluded.

To account for potential heterogeneity related to the time of diagnosis and treatment, patients were categorized into four consecutive 5-year calendar periods: 1997-2001, 2002-2006, 2007-2011 and 2012-2016. Since the calendar period ended in 2016, the study population did not include any patients who received new targeted agents (e.g. midostaurin). The ELN 2017 risk classification[6] was used throughout the study. We additionally verified the proportional distribution of risk groups across the 5-year calendar periods according to ELN 2022 genetic risk groups.[7]

Therapy, outcomes and statistical analysis

Detailed information on therapy and outcomes and the statistical analysis are provided in the *Online Supplementary Methods*.

Ethics

This study was performed in accordance with the Helsinki declaration and approved by the HARMONY steering committee. The HARMONY research project was reviewed and approved by the Medicinal Research Ethics Committee (CEIM) of the University of Salamanca (Reference no. PI 2018 10 128). For its studies, HARMONY provides an ethical and data-protection framework for the secondary use of data including a *de-facto* anonymization step. Written informed consent was collected from all patients in the respective HARMONY partner institution for use of the primary data prior to *de-facto* anonymization, which ensures that no patient can be identified.

Results

Patient and disease characteristics: genetic risk groups remained equally distributed across calendar periods

A total of 5,359 intensively treated AML patients with a median age of 53 years (range, 18-86 years) were analyzed. Their characteristics are detailed in Table 1. The cohort covered all age groups including younger <60 years (69.9%, N=3,745) and older patients between 60 and 69 years of age (22.9%, N=1,229) and ≥70 years (7.2%, N=385). The patients were well distributed across the four consecutive calendar periods studied: 1,127 patients in the period 1997-2001, 1,294 patients in the period 2002-2006, 1,821 patients in the period 2007-2011, and 1,117 patients in the period 2012-2016. There was no difference in sex between the four periods, yet small but significant differences in age, leukocyte counts, and percentage of bone marrow blasts were noted (Table 1). Globally, the proportion of ELN 2017 risk categories was comparable over the four consecutive calendar periods (Figure 1A). This proportionality was also similar with ELN 2022 (*Online Supplementary Figure S2*). The most frequently detected genetic abnormalities were mutations of *NPM1* (28%), *DNMT3A* (26%), *FLT3*-ITD (22%), *NRAS* (19%), *FLT3*-TKD (11%), *TET2* (14%), *IDH2* (12%) and *RUNX1* (11%) (Figure 1B). For cytogenetic abnormalities, the most frequent were trisomy 8 (7.8%), t(8;21) (7.6%), complex karyotype (6.5%), del(7q) (5.7%) and inv(16) (4.9%) (*Online Supplementary Figure S3*). The landscapes of molecular (Figure 1B) and cytogenetic (*Online Supplementary Figure S3A-D*) abnormalities were stable over the four calendar periods.

Patient outcomes improved over time

The median OS time increased significantly from 15.5 months (95% confidence interval [95% CI]: 13.8-17.6) to 37.8 months (95% CI: 31.6-49.2) over the four calendar periods (P<0.0001) (Figure 2A). Most of the known relevant factors associated with OS, including genetic aberrations (see above) and age, were stable. The age density plots at AML diagnosis peaked between 55 and 65 years and, their shapes were globally comparable across periods (Figure 2B).

One relevant factor accounting for improved OS was the early death rate within 30 days after AML diagnosis, which decreased significantly over time from 6.3% during 1997-2001 to 2.5% during 2012-2016 (P<0.0001). The same pattern was observed for early death within 2 weeks, 30 days or 60 days from AML diagnosis, which improved from 3.0% to 0.8%, 6.3% to 2.5% and 13.0% to 4.7%, respectively (P=0.0002 and P<0.0001, respectively) (Table 1). The outcome of AML patients was also influenced by the anthracycline dose. Among patients for whom the anthracycline dose was documented, those given higher doses had better OS with respect to those given lower ones (P<0.0001) (*Online Supplementary Figure S4*). Lower doses of anthracyclines were more frequently used during the first two periods. Given the relevance of consolidating alloHCT for long-term remissions - especially in intermediate- and high-risk AML, we compared OS in the four calendar periods for intensively treated AML patients without alloHCT (Figure 2C, D) and with alloHCT in CR1 (Figure 2E, F). Across all time periods, alloHCT in CR1 was performed in 33.0% of all patients. Between the 5-year intervals from 1997 and from 2007, the proportion of

Table 1. Baseline characteristics of the cohort at acute myeloid leukemia diagnosis according to different time periods.

Characteristics	Total patients N=5,359	Calendar time period				*P*
		1997-2001 N=1,127	2002-2006 N=1,294	2007-2011 N=1,821	2012-2016 N=1,117	
Age in years, median (range)	53 (18-85)	55 (17-84)	51 (15-85)	53 (16-86)	55 (17-85)	
<60 years, N (%)	3,745 (69.8)	689 (61.1)	1,012 (78.2)	1,312 (72)	732 (65.5)	<0.0001
60-69, N (%)	1,229 (22.9)	307 (27.2)	206 (16)	403 (22.1)	313 (28)	<0.0001
≥70 years, N (%)	385 (7.2)	131 (11.6)	76 (5.8)	106 (5.9)	72 (6.5)	<0.0001
Female sex, N (%)	2,498 (46.6)	509 (45.2)	620 (47.9)	853 (46.8)	516 (46.2)	0.5835
ECOG PS 0-1, N (%)	2,325 (78.3)	660 (70.3)	835 (81.4)	671 (84.7)	159 (75)	<0.001
ELN 2017 risk category, N (%)						
favorable	1,790 (33.4)	398 (33.3)	484 (28.2)	601 (29.5)	307 (28)	<0.0001
intermediate	1,977 (36.9)	353 (35.3)	445 (37.4)	682 (33)	497 (27.5)	<0.0001
adverse	1,592 (29.7)	376 (31.3)	365 (34.4)	538 (37.5)	313 (44.5)	0.0173
Hb, g/dL, median (range), N=2,598	9 (2.5-19)	8.9 (2.7-15.4)	9 (2.5-17.6)	9 (2.5-19)	9 (3.7-14.4)	0.4180
WBC x10^6/mL, median (IQR), N=4,356	16,000 (4,500-49,900)	18,320 (4,900-53,975)	18,755 (5,300-55,950)	14,930 (4,300-46,000)	12,250 (3,685-35,000)	<0.0001
Platelets x10^6/mL, median (range), N=4,171	53,000 (122-1,000,000)	50,000 (997-746,000)	53,000 (122-688,000)	54,000 (997-950,000)	54,000 (3,000-1,000,000)	0.5290
Percentage of BM blasts, median (IQR), N=3,552	70 (46.5-85)	70 (48.5-85) N=1,040	75 (48-90) N=1,096	70 (46-85) N=1,067	63 (40-80) N=349	<0.0001
Intensive regimens, N (%)						
<70 years	4,974 (92.82)	996 (88.4)	1,218 (94.2)	1,715 (94.1)	1,045 (93.5)	<0.0001
≥70 years	385 (7.18)	131 (11.6)	76 (5.8)	106 (5.9)	72 (6.5)	<0.0001
Early death, N (%)						
≤ 14 days	96 (1.79)	34 (3.01)	22 (1.7)	31 (2.7)	9 (0.81)	0.0002
≤ 30 days	232 (4.33)	71 (6.3)	57 (4.4)	76 (4.17)	28 (2.5)	<0.0001
≤ 60 days	435 (8.12)	147 (13.04)	105 (8.11)	130 (7.14)	53 (4.74)	<0.0001

ECOG PS: Eastern Cooperative Oncology Group performance status; ELN: European LeukemiaNet; Hb: hemoglobin; WBC: white blood cell count; IQR: interquartile range; BM: bone marrow.

patients receiving alloHCT increased from 24.1% to 39.0%, with the proportion being comparatively low (27.1%) in patients from 2012-2016. Five-year OS improved significantly over the calendar periods for both the group that did not undergo alloHCT (25.4% *vs*. 40.0%, *P*<0.0001) (Figure 2C) and the group that did (42.2% *vs*. 54.1%, *P*=0.0281) (Figure 2E). The age distribution represented by density plots was stable over the four time periods for patients who did not undergo alloHCT (Figure 2D), however, it shifted towards significantly higher age in those who received an alloHCT (median age increased from 42.1 years. to 46.9, 49.9 and 53.0 years) (Figure 2F), indicating that consolidating alloHCT was increasingly performed in older patients during more recent calendar periods.

Relapse in first complete remission was reduced with consolidating chemotherapy along with improved overall survival following consolidating allogeneic hematopoietic cell transplantation

For patients in CR1, relapse rates declined over the four calendar periods (Figure 3A, B). Given decreasing relapse the median relapse-free survival of CR1 patients improved significantly over the calendar periods (20.1 months *vs*. not reached, *P*<0.0001) (Figure 3A). This effect was most prominent for patients who did not undergo alloHCT (17.4 months *vs*. not reached, *P*<0.0001) (Figure 3C), who had continuously decreasing relapse rates over three calendar periods (Figure 3D), while those who did receive alloHCT (23.5 months *vs*. not reached, *P*=0.0294) (Figure 3E) did not decline linearly but revealed a significant difference in the overall test (Figure 3F). Heterogeneity in ELN risk among subgroups may also have contributed to this observation in CR1 patients receiving consolidating chemotherapy. Yet, the overall relapse rate was 37.5% and remained stable across the studied calendar periods, being 37.4% in patients diagnosed between 1997-2001, over 39.6% between 2002-2006, 36.0% between 2007-2011, and 37.4% between 2012-2016. Still, the overall genetic and cytogenetic landscapes of the studied population remained stable over two decades. However, the improvement in OS was not equally distributed among patients. It depended on ELN risk categories and on whether patients were consolidated with alloHCT. While patients with favorable ELN risk who did not undergo alloHCT in CR1 had a significant improvement in

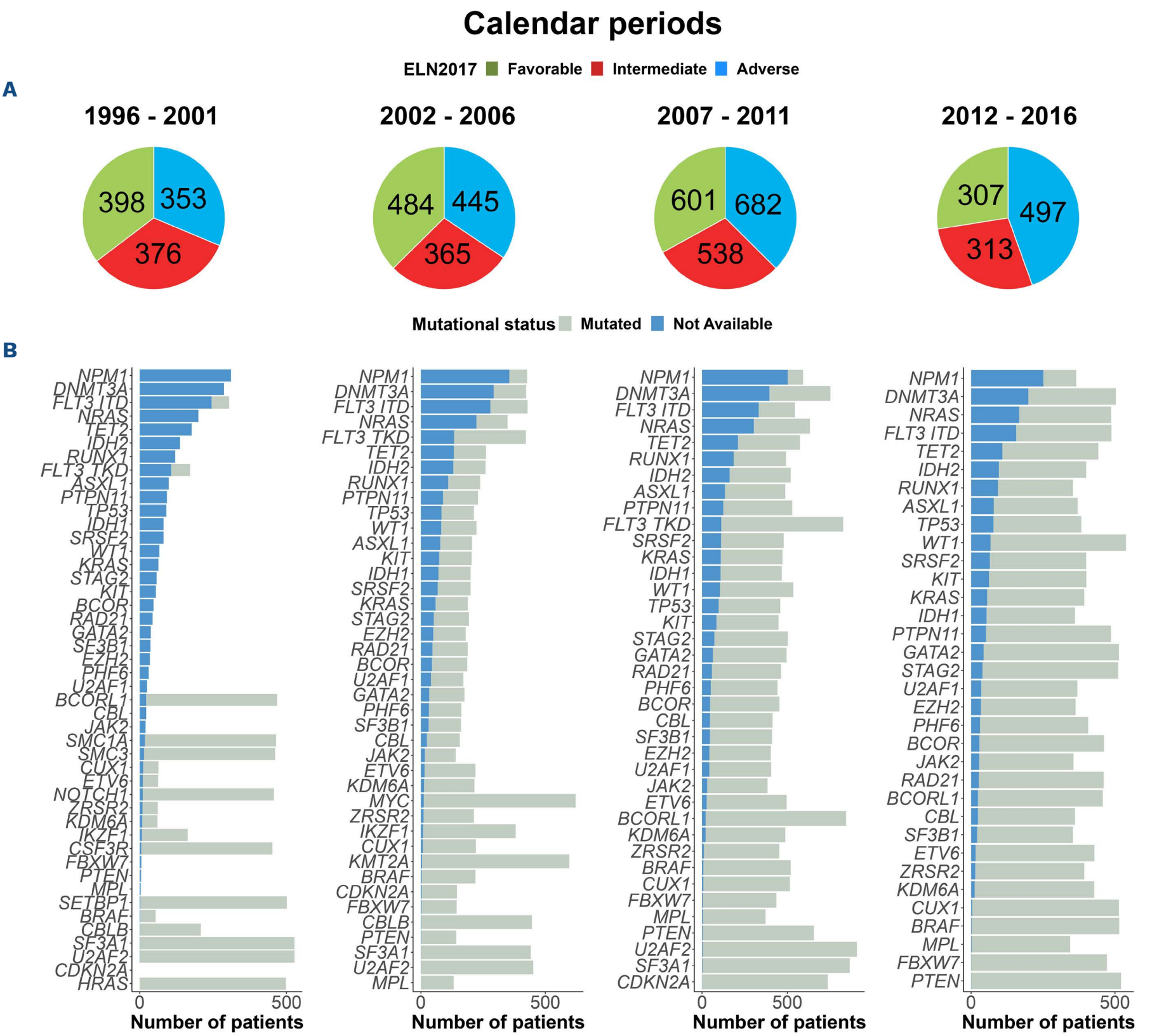
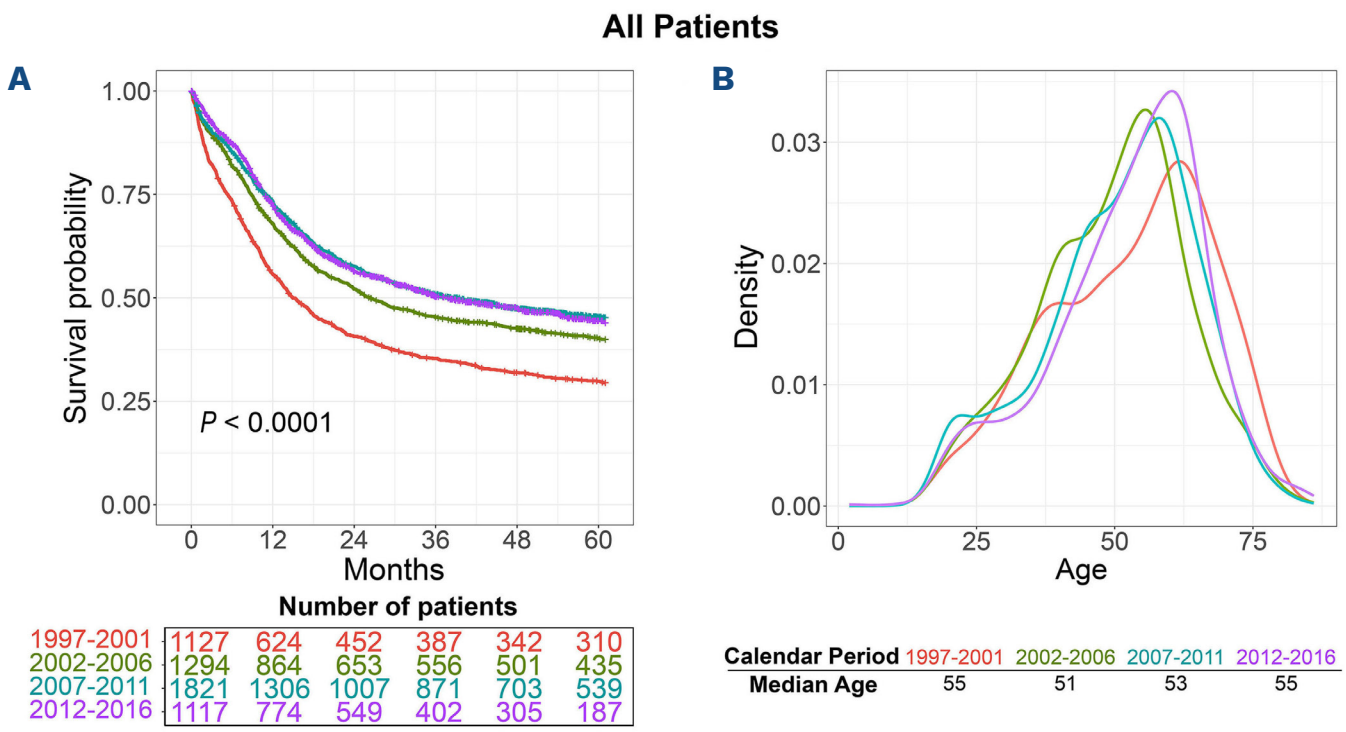


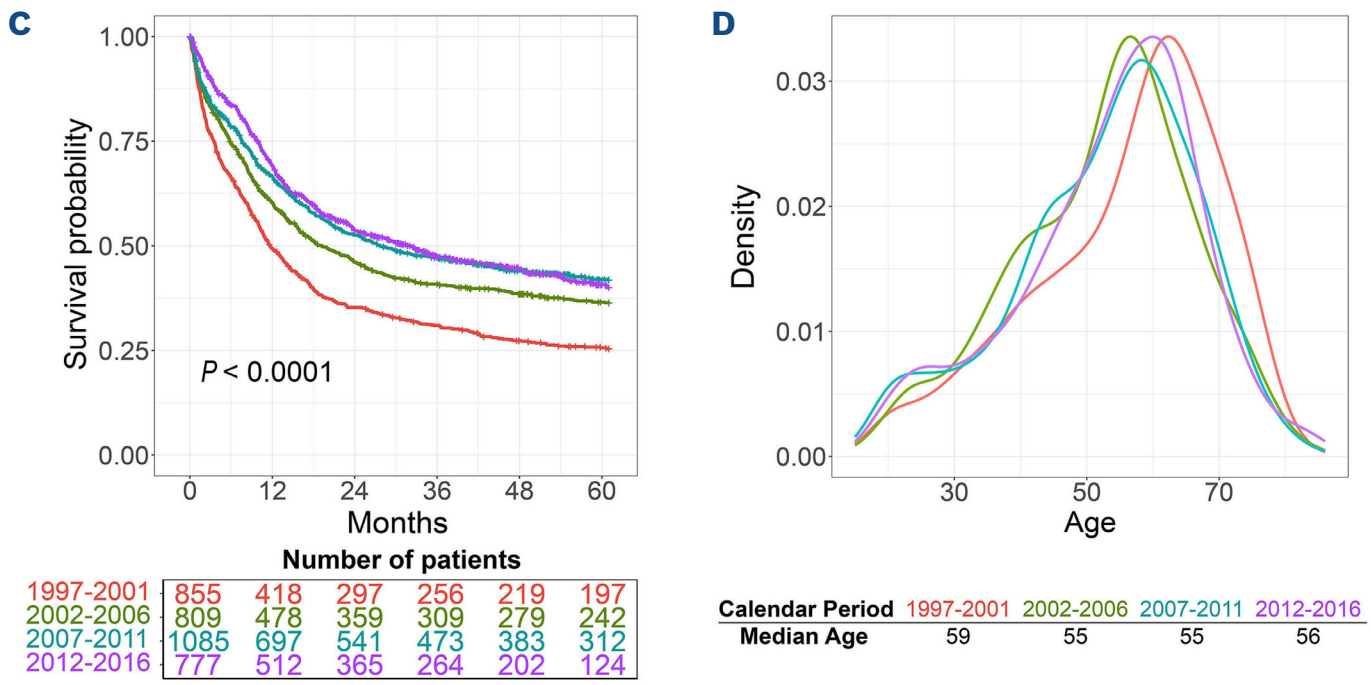
Figure 1. Homogeneous distribution of European LeukemiaNet 2017 categories and stable proportions of molecular abnormalities over calendar periods. (A) Pie charts showing the proportions of patients in each calendar period according to ELN 2017 classification: favorable (green), intermediate (blue) and adverse (red) risk categories. Absolute patient numbers are shown. (B) Comparative illustration of the main molecular abnormalities across the same four calendar periods. Absolute numbers of detected genes are represented by blue bars. Gray bars indicate missing sample information on the presence or absence of the mutation. Genes are shown in decreasing order, starting with the most frequently detected gene at the top.

OS across calendar periods (P<0.0001) (Figure 4A), those of the same ELN risk group who did not receive alloHCT did not improve continuously (P=0.458) (Figure 4B). The picture was similar for patients with intermediate-risk AML. Patients who did not have alloHCT in CR1 had a strong increase in 5-year OS from 22% to 45% (P<0.0001) (Figure 4C), while those who did receive alloHCT did not improve significantly, despite a trend towards higher OS (Figure 4D). Only for adverse-risk ELN were the differences across the calendar periods significant, both in patients who did not undergo alloHCT (P<0.0001) (Figure 4E) and in those who did (P=0.0151) (Figure 4F).

Multivariate Cox regression models confirm an improved overall survival over time

In order to verify these findings, we created several multivariate Cox-regression models. Given that some potentially relevant information (logWBC, percentage of bone marrow





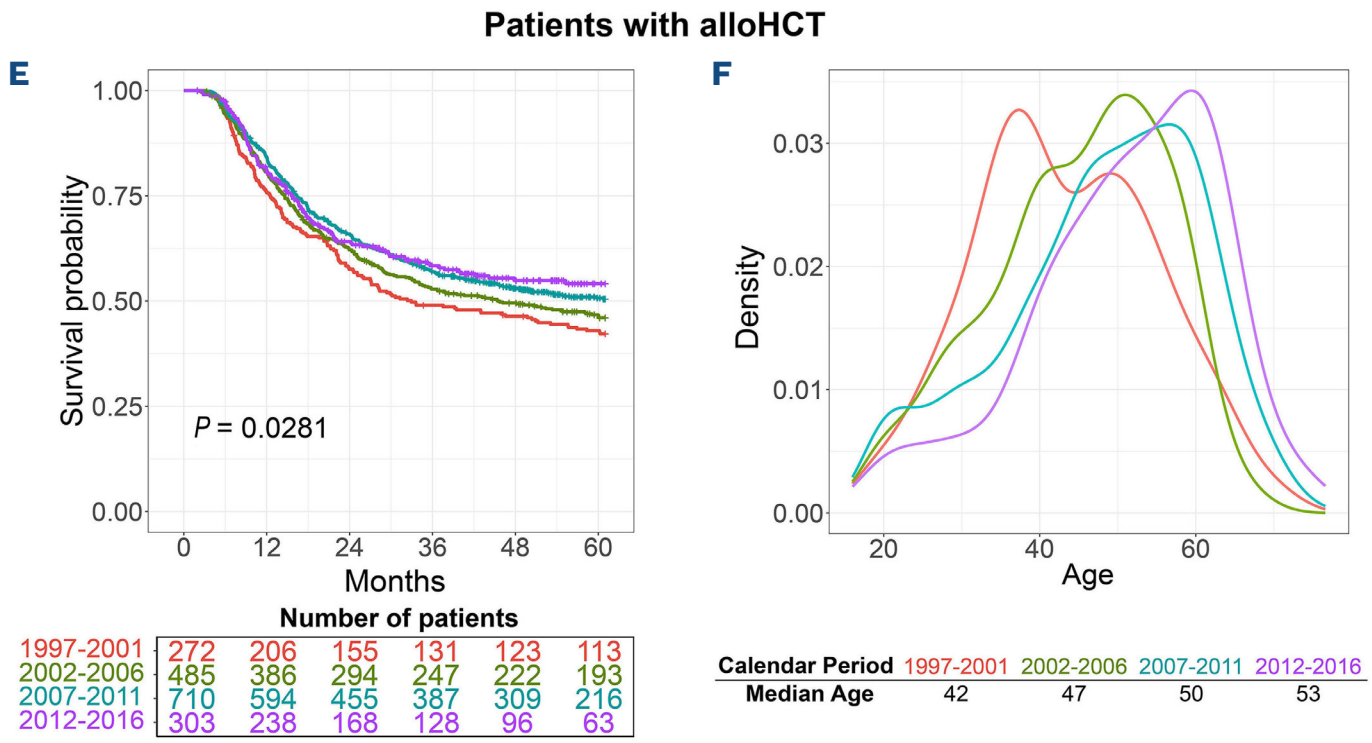


Figure 2. Overall survival of intensively treated acute myeloid leukemia patients over calendar periods. (A) Comparison of 5-year overall survival (OS) of all patients (N=5,359) with acute myeloid leukemia (AML) stratified per calendar periods. Kaplan-Meier OS curve, strata compared using the log-rank test. (B) Comparison of density plots of age distributions under a smoothed curve and medians at diagnosis over calendar periods. The age distribution of AML patients remains stable over the calendar periods. (C) Comparison of 5-year OS of intensively treated AML patients who did not subsequently undergo allogeneic hematopoietic stem cell transplantation (alloHCT) in first complete remission (N=2,589) stratified per calendar period. Kaplan-Meier OS curve, strata compared using the log-rank test. (D) Comparison of density plots of age distributions under a smoothed curve and medians at diagnosis over calendar periods. (E) Comparison of 5-year OS of AML patients with consolidating alloHCT (N=1,770) stratified per calendar period. Kaplan-Meier OS curve, strata compared using the log-rank test. (F) Age distribution of AML patients with alloHCT shifts over observation periods towards higher age. Comparison of density plots of age distributions under a smoothed curve and medians at diagnosis over calendar periods. Calendar periods are indicated under each figure: 1997-2001 red, 2002-2006 light green, 2007-2011 blue, 2012-2016 violet.

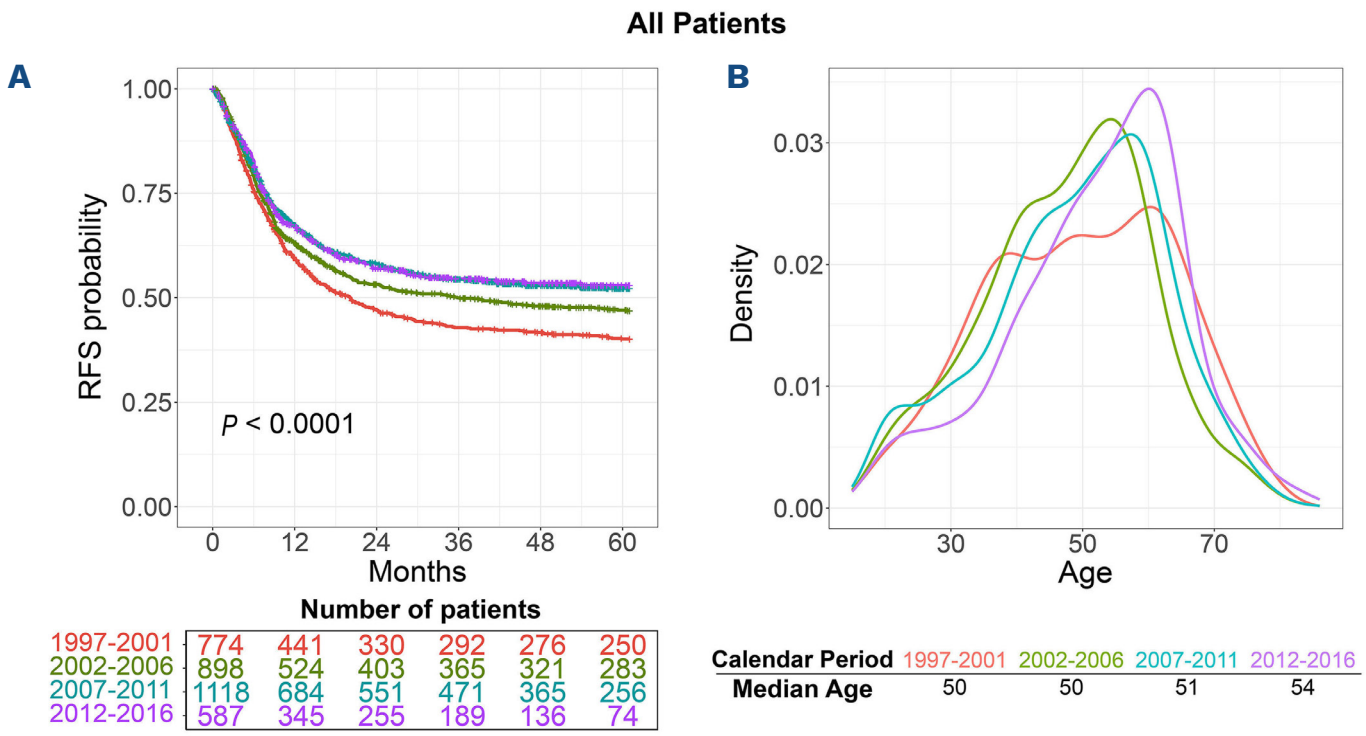


Figure 3. Relapse-free survival after first complete remission of intensively treated acute myeloid leukemia patients over calendar periods. (A) Comparison of 5-year relapse-free survival (RFS) of patients with acute myeloid leukemia (AML) in first complete remission (CR1) (N=3,377) stratified per calendar period. Kaplan-Meier curve, strata compared using the log-rank test. (B) Comparison of 5-year cumulative incidence of relapse of AML patients from achievement of CR1. (C) Comparison of 5-year RFS of AML patients in CR1 without alloHCT (N=1,808) stratified per calendar period. Kaplan-Meier curve, comparison of strata with log-rank test. (D) Comparison of 5-year cumulative incidence of relapse of CR1 AML patients who did not undergo allogeneic hematopoietic cell transplantation (alloHCT) over calendar periods. (E) Comparison of 5-year RFS of intensively treated CR1 AML patients who subsequently underwent alloHCT (N=1,569) stratified per calendar group. Kaplan-Meier curve, strata compared using the log-rank test. (F) Comparison of 5-year cumulative incidence of relapse of CR1 AML patients treated with alloHCT. Calendar periods are indicated under each figure: 1997-2001 red, 2002-2006 light green, 2007-2011 blue, 2012-2016 violet.

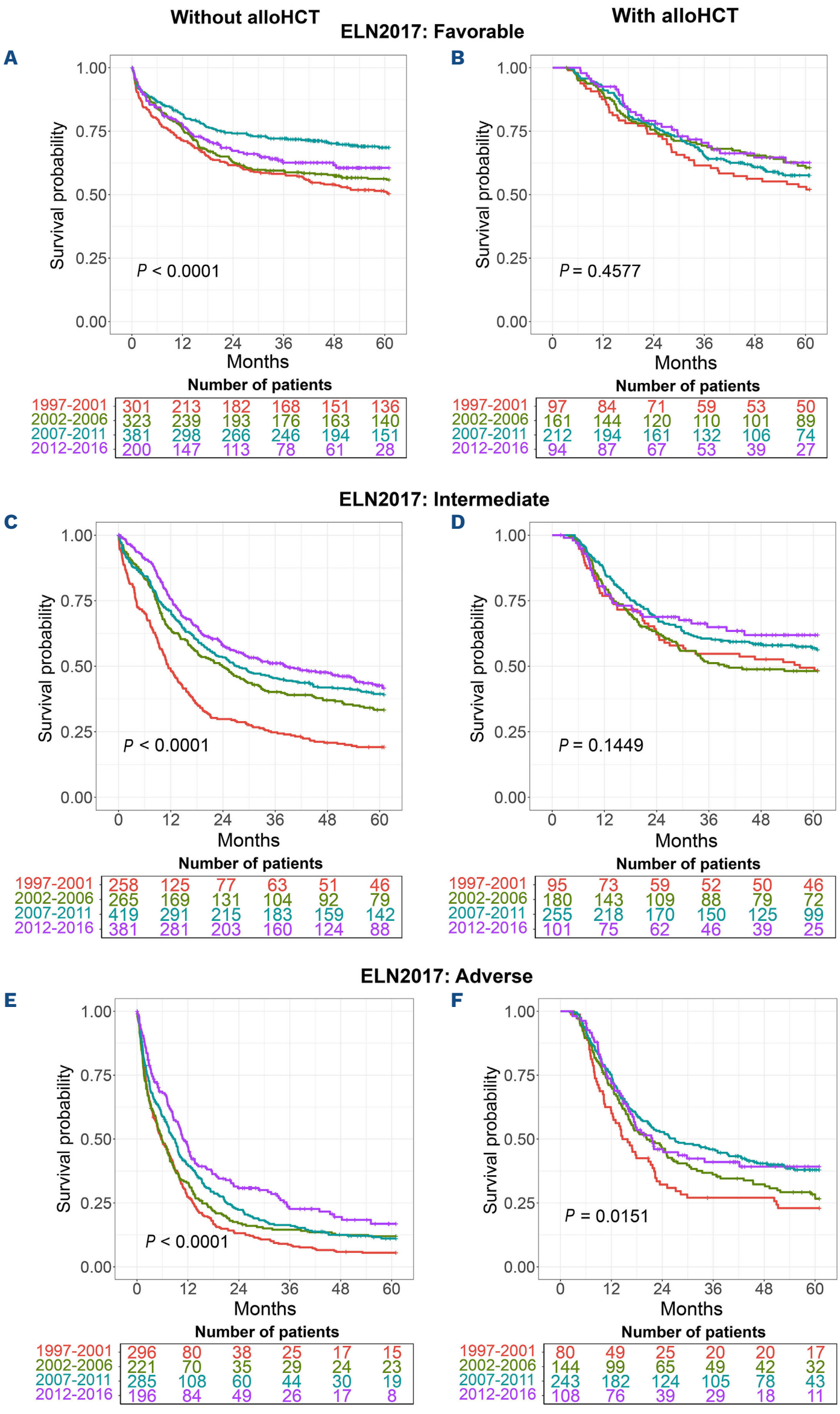


Figure 4. Changes in overall survival stratified according to European LeukemiaNet 2017 risk groups and use of consolidating allogeneic hematopoietic cell transplantation. The improvement in overall survival (OS) is dependent on European LeukemiaNet (ELN) risk group and the use of consolidating allogeneic hematopoietic cell transplantation (alloHCT). (A, B) Kaplan-Meier OS curves of ELN 2017 favorable-risk patients comparing those who did not receive alloHCT (A) and those who did receive alloHCT (B) stratified according to calendar periods derived from the time-point of initial diagnosis as in Figure 2. (C, D) OS of ELN 2017 intermediate-risk patients who did not undergo alloHCT (C) compared to those who did receive alloHCT (D). (E, F) OS of ELN 2017 adverse-risk patients who did not undergo alloHCT (E) and those who did (F). Strata are compared with the log-rank test. Calendar periods are indicated under each figure: 1997-2001 red, 2002-2006 light green, 2007-2011 blue, 2012-2016 violet.

blasts) was not available for all patients, we compared the models with increasing number of covariates and used the Akaike information criterion to select the strongest model. The final multivariate model including more covariates was most accurate and attributed similar hazards for the calendar periods to models covering all patients with fewer covariates. The calendar period of AML diagnosis, ELN classification, age, and logWBC at diagnosis each significantly impacted OS (Figure 5), confirming the independent effect of the calendar periods on OS. The percentage of bone marrow blasts at diagnosis did not significantly impact OS in intensively treated AML underlining the potency of intensive chemotherapy.

The role and benefits of intensive induction therapy are currently debated, especially in older AML patients, aged between 60-69 years and ≥70 years, as new, less-intense treatments offer the possibility for lasting remissions.[32] Yet, improved management and supportive care in intensively treated patients ≥60 (and ≥70) years old resulted in significantly higher OS in the most recent calendar period compared to the first calendar period. However, this OS benefit was mainly seen in the cohort of patients ≥60 years old and less so in the ≥70-year-old cohort.

When we accounted for the effect of consolidating alloHCT on OS in patients ≥60 years old, we found significantly

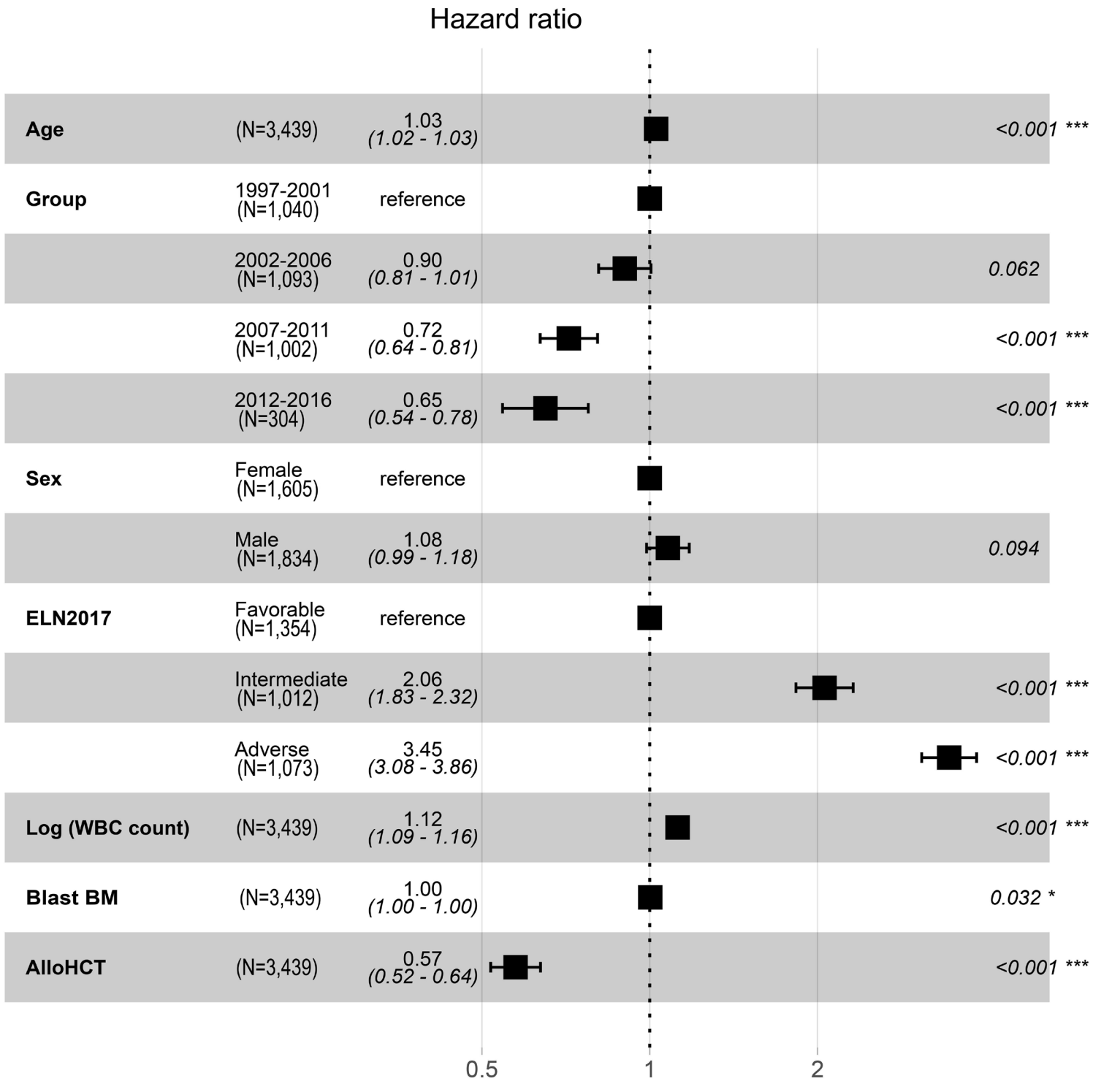


Figure 5. Multivariate analysis confirms a significant independent impact of calendar periods on outcome of intensively treated acute myeloid leukemia patients. Multivariate Cox regression analysis including the covariates age, sex, four treatment periods (1997-2001, 2002-2006, 2007-2011 and 2012-2016), three European LeukemiaNet (ELN) 2017 risk groups (favorable, intermediate, adverse), bone marrow (BM) myeloid blast count at acute myeloid leukemia (AML) diagnosis and logarithmic (log)white blood cell count (WBC) at AML diagnosis. Age is measured as a continuous risk factor, its hazard corresponds to a 1-year increase. The BM blast count and logWBC are also considered as continuous variables; all other variables are treated as categorical variables. ***P<0.001.

higher OS in those who underwent alloHCT (P<0.0001) (Figure 6A). The difference was observed for the intermediate- and adverse-risk ELN 2017 subgroups, but not for patients with favorable risk (Figure 6B-D). Although a likely selection bias in the alloHCT cohort translated into the exclusion of patients who had a very early relapse, a subgroup analysis excluding patients who relapsed early in the no alloHCT cohort revealed significantly higher OS in patients ≥60 years old who underwent alloHCT, confirming the relevance of consolidation for patients ≥60 years old. The most frequent mutations in this population were evenly distributed between patients who did or did not undergo alloHCT, with the exception of *FLT3*-ITD and *NRAS* (Figure 6E). Improved OS with alloHCT was also found in AML patients ≥70 years old (*Online Supplementary Figure S5*); however, this result was based on a very small subset of patients, and the difference was not maintained beyond 36 months of follow-up.

Discussion

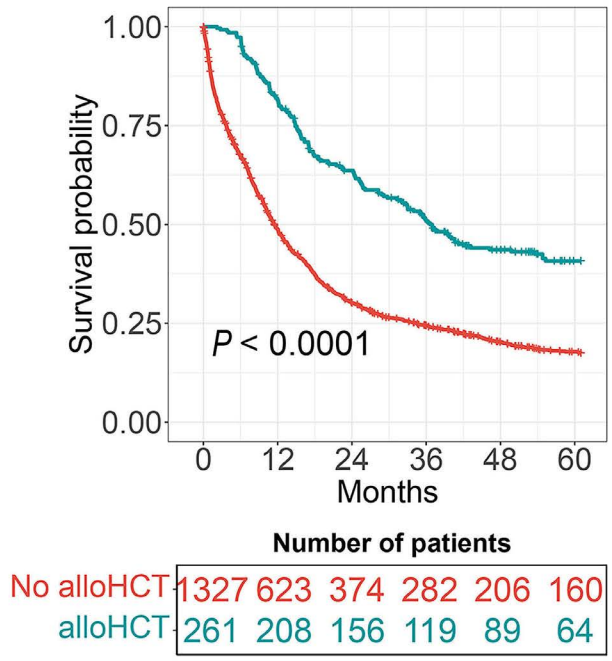
To the best of our knowledge, the present study is the largest analysis of intensively-induced AML patients stratified for treatment calendar periods and AML genetic risk. Our investigation covered patients from both clinical trials and the real-world setting in over 100 European centers. Important findings of our study include that OS of intensively treated AML patients in the pre-targeted therapy era increased significantly increased over four consecutive 5-year calendar periods, while the distribution of underlying AML-related genetic abnormalities in these patients remained stable. Second, improved OS was observed across patient age groups and both in patients who did and did not undergo consolidating alloHCT. Third, our study clearly underlines the importance of alloHCT for consolidating CR1 in intensively treated patients ≥60 years old as the outcome in this age subset was substantially better for patients who were consolidated with an alloHCT.

For decades, the induction chemotherapy of AML patients was based on the combination of cytarabine with an anthracycline, which are still the backbone of today's intensive induction treatments.[5-7] Concordant with published studies,[12,13,31] our data show that OS in intensively treated AML patients improved over four consecutive calendar periods from 1997 to 2016, even before targeted therapies became available. This improvement is mainly explained by the reduction of early deaths from 13.0% in the first calendar period to 4.7% in the last, indicating better patient management during the early induction treatment phase and likely reflecting better supportive treatment options for these patients.[12,13,32] Improvements in care structures and management, e.g., increasing numbers of patients being treated in specialized comprehensive cancer centers as well as early intensive care referral practices, have likely contributed to reduced complications.[33] As time has progressed, it appears that intensive induction treatment, also with higher, standardized doses of daunorubicin,[16] has become safer, potentially retaining its efficacy for older AML patients. In accordance, the improved OS was observed across all patient age groups, irrespective of whether patients received consolidative alloHCT, although in older patients those treated with a subsequent transplant had the largest benefit.

As the disease-related genetics have not changed among the different calendar periods, the CR rates with the standard "7+3" regimen were also stable over time. Hence novel combinations are definitely needed to further improve AML outcome in the future. Interestingly, prior to the availability of targeted treatments and novel maintenance therapy options, the overall relapse rates of the population including all remission status and repeated relapses remained quite stable around 37% across the last 20 years, which is clearly unsatisfactory but in line with published data.[34] Interestingly, relapse of CR1 patients who received only consolidating chemotherapy significantly decreased transplant-related mortality, probably due to improved genetic testing, refined ELN risk stratification and referral for alloHCT, which may prevent relapse in patients with higher risk.[3] The 2017 ELN risk classification and its current update have improved the selection of patients for this procedure based on molecular and cytogenetic risk factors.[5-7]

Over the past decades, the number of alloHSCT has increased continuously, while transplant-related mortality has decreased.[20,35] Patient selection for alloHCT changed with the recognized importance of the *FLT3*-ITD mutation[36] and minimal residual disease analysis[4] allowed timely referral to alloHCT. This observation is also mirrored by the results of our study, which show an increasing fraction of patients treated with alloHCT from 1997 to 2011 and a slight decrease between 2012 and 2016. In the ELN intermediate- and adverse-risk groups, the outcome of patients consolidated with an alloHCT was significantly superior to the outcome of patients who did not undergo alloHCT. Furthermore, our data confirmed the current recommendations for ELN favorable-risk patients, who should only receive an alloHCT in constellations of inadequate clearance of minimal residual disease or relapse.[7] While adverse-risk AML patients do benefit from alloHCT, their outcomes still remain unsatisfactory, the main reason being high relapse rates even after alloHCT, most likely due to poorly controlled disease prior to the transplant.[12,34] Recent advances in more intensive induction therapies using CPX-315,[37] the classical "7+3" regimen in a new formulation, significantly improved outcomes in adults with newly diagnosed, therapy-related AML or AML with myelodysplasia-related changes. Furthermore, recent developments in maintenance treatment strategies, e.g., using sorafenib or gilteritinib after alloHCT in *FLT3*-mutated AML, are promising approaches to further improve outcome.[38]

A



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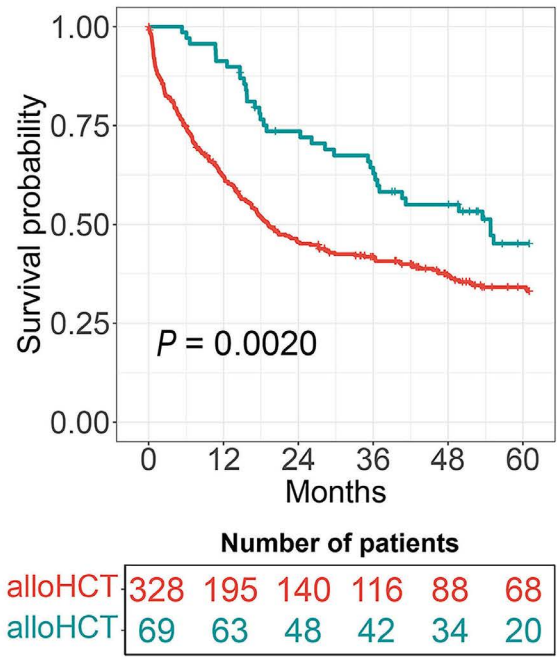

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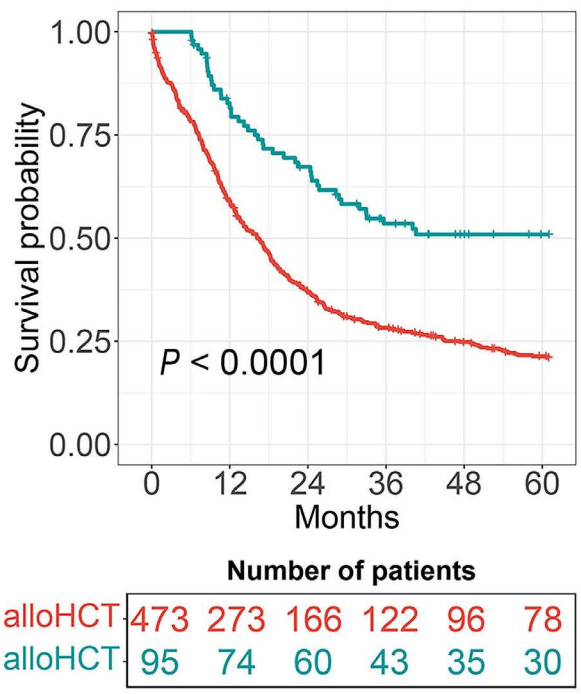

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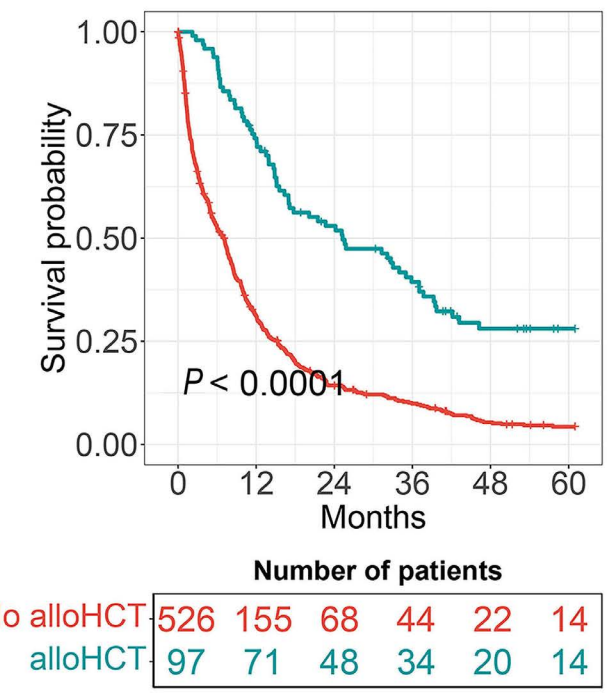

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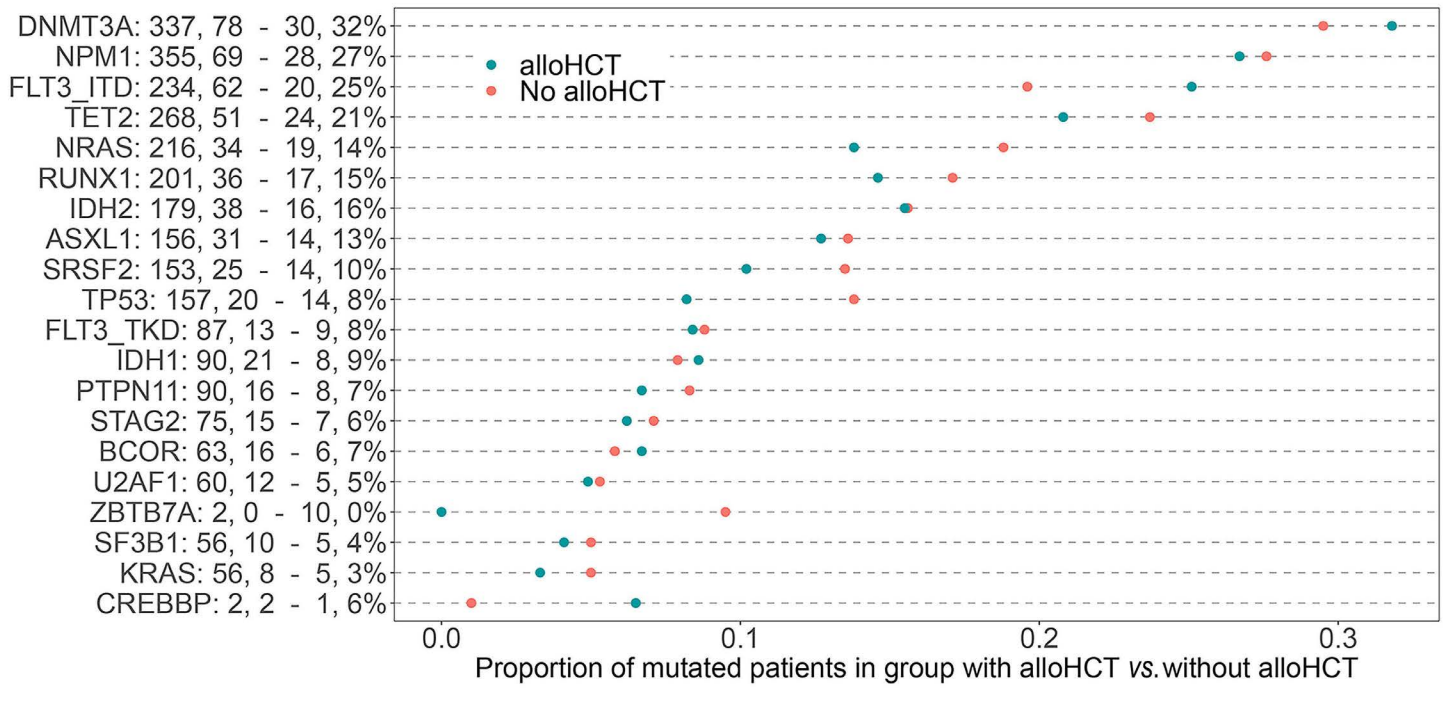

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Figure 6. Comparison of overall survival and genetic features of intensively treated acute myeloid leukemia patients aged ≥60 years according to performance of allogeneic hematopoietic cell transplantation. (A-D) Comparison of intensively treated acute myeloid leukemia patients ≥60 years old receiving allogeneic hematopoietic cell transplantation (alloHCT) (blue line) *versus* no alloHCT (red line). Kaplan-Meier overall survival curves. The landmark for analysis was set after the median time from diagnosis to alloHCT (143 days): patients in both groups who were censored or dead before the landmark were not considered for analysis. The curves were compared with the log-rank test. (A) All patients ≥60 years old. (B) European LeukemiaNet (ELN) favorable-risk patients ≥60 years old. (C) ELN intermediate-risk patients ≥60 years old. (D) ELN adverse-risk patients ≥60 years old. (E) Genomic landscape of acute myeloid leukemia patients ≥60 years old. Comparison of the proportions of the most frequent gene mutations between patients ≥60 years who did or did not receive alloHCT. Absolute numbers and percentages are shown.

While the 5-year OS of intensively treated young patients (<40 years) is around 60%,[31] the majority of AML patients are diagnosed at an older age.[39] Age is a significant risk factor for reduced OS,[40] which is also confirmed by our multivariate analysis. One reason is that genetic risk profiles are poorer[18] and that response rates to treatment of patients aged ≥60 years remain inferior to those of younger patients.[12,13,15,17,18,25] In patients of more advanced age, comorbidities are also more frequent and physicians may be more reluctant to use intensive chemotherapy. Nevertheless, it has been repeatedly shown that the early death rate is lower in elderly AML patients treated with intensive chemotherapy than in those receiving only best supportive care[41,42] – likely biased by the selection of patients entering intensive treatments. Several prospective trials confirmed that it is possible to treat elderly patients intensively[12,13,41-44] Based on such studies, the National Comprehensive Cancer Network (NCCN) recommends geriatric assessments for patients with AML ≥60 years of age and in the case of no contraindication, intensive induction therapy should be used rather than less intensive therapy or palliative care.[45,46] Similar recommendations are issued in Europe. According to the ELN, there are no generally validated criteria to consider a patient ineligible for intensive chemotherapy, except for age ≥75 years, although even this is not an absolute criterion.[7] Indeed, our data support these views also in the context of structurally improved care settings. Over the calendar periods we observed improved OS and reduced early mortality with intensive chemotherapy, even in patients ≥60 years old (2 and 5-year OS were 52.2% and 40.3%, respectively).

Despite this evidence, the use of intensive induction therapy has been and is still controversial in patients aged between 60-69 years old with comorbidities and in patients ≥70 years old[47,48] regardless of condition. Criticism primarily relates to the early toxicity of the intensive therapy and to difficulties in assessing patients' fitness for treatment. Geriatric scores have shown promising results for selecting patients for appropriate regimens.[45] The available less-intense but potent alternatives for these patients combine hypomethylating agents with, for example, venetoclax.[23,49] However, this novel treatment option exhibits a comparable level of toxicity in terms of the duration of neutropenia when compared to intensive induction therapy.

Hence, the question remains of which group of older patients benefits most from conventional induction therapy and this study offers some evidence regarding this important issue. Patients ≥60 years old who received an alloHCT following induction therapy had a significant OS benefit, likely relating to age-dependent differences in disease biology, which translate into higher relapse rates in this age group.[12,13,40] Alternatively, this finding may relate to better disease control prior to alloHCT. Interestingly, this OS benefit for older patients consolidated with alloHCT was seen across all ELN risk groups. High-resolution HLA matching, reduced intensity conditioning and improved supportive care have allowed us to perform alloHCT more safely and also at a more advanced age. Consistent with the findings of a recent study focusing on health impairment[21,24,25,31] related to comorbidity, fitness and performance status on alloHCT outcome, patients ≥70 years old benefited less from an alloHCT than those between 60 and 70 years old. However, consolidation with an alloHCT remains the only way to cure these patients and the quality of remission must be taken into account. In summary, alloHCT may clearly improve outcome of the elderly AML population. Nevertheless, recommendations for choosing intensive or non-intensive chemotherapy in older patients before alloHCT still need to be established with growing evidence on non-intensive approaches, as specific variables (including genetic ones) may help to guide treatment decisions.[49,50]

Our study does have some limitations including its retrospective character, as well as the heterogeneity of the multicenter, real-world cohort. There is a lack of detailed information on therapies (especially on supportive care) and comorbidities, as well as limited follow-up in some cases and a comparatively small proportion of patients with ECOG performance status >2. Furthermore, the group of patients ≥70 years old was comparatively small. Nevertheless, we could make important observations in terms of patient and disease characteristics and treatment results. While the HARMONY data readily provide broad multicenter coverage, these findings should still be confirmed by additional independent datasets, especially those from the era of targeted AML therapy.

In summary, this study shows that outcomes of AML patients treated with conventional intensive therapy improved significantly across all AML risk groups over two decades, yet it also points to the impact of different calendar periods. The significantly reduced early death rates indicate that better therapy management and supportive care are

driving this improvement. The OS of patients in CR1 was also improved, likely due to the increasing referral to alloHCT. The safer application of alloHCT has specifically improved the outcomes of patients aged 60-69 years old. While further outcome improvement in intensively treated AML patients will likely be driven by targeted therapies and including minimal residual disease status as a real-time prognostic factor for treatment response, this pan-European HARMONY dataset can serve as a real-word comparator for future studie.

Disclosures

MAS has received honoraria from Novartis, Celgene, AOP Orphan and AbbVie. ATT has provided consultancy services for CSL Behring, Maat Pharma, Biomarin, Pfizer and Onkowissen and has had travel costs reimbursed by Neovii Biotech, Novartis and Janssen. CT is co-owner and CEO of AgenDix GmbH, has received lecture fees from and/or participated in advisory boards for Novartis, Jazz, Astellas, Janssen and Illumina and has received research funding from Novartis and Bayer. RA has received honoraria from Astellas, BMS, Incyte and Novartis. KHM has received honoraria from AbbVie, Bristol Myers Squibb, Celgene, Janssen, Novartis, Pfizer and Otsuka and has received research support from AbbVie. JS has received honoraria from AbbVie, Jazz Pharmaceuticals, Astellas and Daiichi Sankyo and grant support from Pfizer and Jazz Pharmaceuticals. BJPH has received honoraria from Pfizer, BMS and Novartis and research support from AstraZeneca. GO has received honoraria from AbbVie, Jazz Pharmaceuticals, Astellas, Gilead, BMS, Servier and Roche. HD has had advisory roles for AbbVie, Agios, Amgen, Astellas, AstraZeneca, Berlin-Chimie, Bristol Myers Squibb, Celgene, GEMoaB, Gilead Sciences, Janssen, Jazz Pharmaceuticals, Novartis and Syndax and has received research funding from AbbVie, Agios, Amgen, Astellas, Bristol Myers Squibb, Jazz Pharmaceuticals, Kronos-Bio and Novartis. LB has received honoraria from AbbVie, Amgen, Astellas, Bristol Myers Squibb, Celgene, Daiichi Sankyo, Gilead, Hexal, Janssen, Jazz Pharmaceuticals, Menarini, Novartis, Pfizer, Roche and Sanofi, as well as research support from Bayer and Jazz Pharmaceuticals. FD reports personal fees outside the submitted work from AbbVie, Amgen, AstraZeneca, BeiGene, Gilead, Incyte, Roche and Novartis. MGDP and GC have no conflicts of interest to disclose.

Contributions

MAS and LB designed the study. MAS, ATT, AHS, RAM, JMT, KD, CT, KHM, TH, FD, RA, JM-L, KIM, JS, SL, MGDP, JM, DR, RS-R, MB, JMH-R, BJPH, GO, HD and LB collected data. MA, LT and RVM processed anonymized data on the OMOP model. AVR, JME and TG performed data preprocessing, statistical analysis, and data-driven and predictive risk model development. ATT and MAS contributed to the model development. DD'O, ES, GC and AB contributed further statistical and data science expertise to the data analysis core team. MAS, ATT, AB, KD, MB, JMH-R, BJPH, GO and HD provided clinical expertise. MAS, ATT AVR and LB interpreted the data. AB, KD, MB, JMH-R, BJPH, GO and HD contributed to data interpretation. ATT, MAS and LB wrote the manuscript. AVR contributed to writing the manuscript. BJPH, GO and HD critically reviewed the manuscript. LB supervised research and coordinated the HARMONY AML group. All authors had access to primary data, and read and approved the final manuscript.

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Data-sharing statement

Requests for data may be addressed to the HARMONY Alliance coordination office. Release of data is subject to approval from the data access committee.

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