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

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Author Contributions

MAS and LB designed the study. MAS, ATT, AHS, RAM, JT, KD, CT, KHM, TH, FD, RA, JML, KIM, JS, SL, MGDP, JM, DR, RSR, MB, JMHR, BJPH, GO, HD and LB performed data

collection. 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 model development. DDO, ES, GC and AB contributed further statistical and data science expertise to the data analysis core team. MAS, ATT, AB, KD, MB, JMHR, BJPH, GO, HD provided clinical expertise. MAS, ATT AVR and LB interpreted the data. AB, KD, MB, JMHR, BJPH, GO, HD contributed to data interpretation. ATT, MAS and LB wrote the manuscript. AVR contributed to write 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, read and approved the final manuscript.

Conflict of interest disclosures

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Sharing data statement

Data request may be addressed to the HARMONY Alliance coordination office and are subject to approval of the data access committee.

Abstract

Since 2017, targeted therapies combined with conventional intensive chemotherapy have started to improve outcome of patients with acute myeloid leukemia (AML). However, even before these innovations outcomes with intensive chemotherapy have 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 5359 AML patients, we compared 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 has 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, 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 overall have a 20% survival benefit at 5 years if received 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 multi-center 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 (Ara-C) in combination with anthracyclines: daunorubicin (DNR) or idarubicin (IDA) 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 Ara-C.[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 7+3.[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 IDH inhibition in combination with 7+3 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, the 5-year OS rates are only 30-39%[14] and for patients ≥60 years 10-25%;[15] which could be further improved by dosing DNR higher than 45mg/m².[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 at large scale. The use of consolidating alloHCT in AML patients has seen an impressive improvement, with more alloHCT being performed also at an older age[19]. In parallel to this rise, the toxicity of the intervention has decreased, which makes this intervention safer for its application to 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 (HMA) since 2004,[22] and more recently the combination of HMAs with the BCL2 inhibitor venetoclax,[23] the question, 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 of which elderly patients should start on intensive therapy. However, this decision still largely depends on many individual factors.

With this background, this study compared 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 with intensive induction chemotherapy for analysis that 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 to improve the outcome of patients with hematologic malignancies. Its database includes patient data provided by 140 organizations from >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 Supplemental Figure 1).

Following the OMOP process, patients were identified from the HARMONY database by the time of diagnosis, from 1997 to 2016, and by their documented intensive chemotherapy protocols (n=4286 independent of their age with detailed protocols as in Supplemental Table 1, and n=1072 aged 18-70 years without detailed chemotherapy information on their intensive regimen yet known to be intensively treated). In total, n=5359 cases were identified stemming from retrospective real-world data (n=1689, 31.5%) and data from prospective clinical trials (n=3670, 68.5%). The baseline variables age, sex, Eastern Cooperative Oncology Group (ECOG) performance index, hemoglobin, platelets, leucocytes and bone marrow blasts counts did not differ between these source groups (Supplemental Table 2). 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 diagnosis of acute promyelocytic leukemia, mixed phenotype leukemia and 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, no patients are included receiving 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 the ELN 2022 genetic risk groups[7].

Therapy, outcomes and statistical analysis

The sections on Therapy and Outcomes and Statistical analysis are detailed in the Supplemental 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 the primary data use 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 5359 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=3745) and older patients between 60 and 69 years of age (22.9%, n=1229) and ≥70 years (7.2%, n=385). The patients were well distributed across the four consecutive calendar periods studied: 1127 patients in period 1997-2001, 1294 patients in period 2002-2006, 1821 patients in period 2007-2011, and 1117 patients in period 2012-2016.

There was no difference in sex between the four periods, yet small but significant differences in age, leucocyte 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-D). This proportionality was also similar with ELN

2022 (Supplemental Figure 2). 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 1A-D). 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%, Supplemental Figure 3). The landscape of molecular (Figure 1E-H) and cytogenetic (Supplemental Figure 3A-D) abnormalities were stable over the four calendar periods.

Patient outcomes improved over time

The median overall survival (OS) time increased significantly from 15.5 months (95% confidence interval (CI) 13.8-17.6) to 37.8 months (95% CI 31.6-49.2) over the four calendar periods (Figure 2A, p<0.0001). 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, their shape globally were 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 two 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 (Table 1, p=0.0002 and p<0.0001, respectively). The outcome of AML patients was also influenced by the anthracycline dose. Among patients with documented anthracycline dose, those with higher doses presented better OS respect to those with lower ones (p<0.0001) (Supplemental Figure 4). 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 (Figures 2C-D) and with alloHCT in CR1 (Figures 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 patients receiving alloHCT increased from 24.1% to 39.0%, its proportion was comparatively low (27.1%) in patients from 2012-2016. Five-year OS significantly improved over the calendar periods for both, the groups without (25.4% vs 40.0%, p<0.0001, Figure 2C) and with alloHCT (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 without alloHCT (Figure 2D), however, it shifted towards significantly higher age in those that received an alloHCT (median age increased from 42.1 years, over 46.9, 49.9 to

53.0 years, Figure 2F), indicating that consolidating alloHCT was increasingly performed in older patients during more recent calendar periods.

Relapse in CR1 was reduced with consolidating chemotherapy along with improved OS following consolidating alloHCT

For patients in CR1, relapse rates declined over the four calendar periods (Figure 3 A, B). Given decreasing relapse the median relapse free survival (RFS) of CR1 patients significantly improved over the calendar periods (20.1 months vs. not reached, $p<0.0001$, Figure 3 A). This effect was most prominent for patients without 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 with alloHCT (23.5 months vs. not reached, $p=0.0294$, Figure 3E) did not linearly decline 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, with 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 landscape 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 without alloHCT in CR1 had a significant improvement in OS across calendar periods ($p<0.0001$, Figure 4A), those of the same ELN risk with alloHCT did not continuously improve ($p=0.458$, Figure 4B). For patients with intermediate risk AML, the picture was similar. Patients without alloHCT in CR1 had a strong increase in 5-year OS from 22% to 45% ($p<0.0001$, Figure 4C), while those with alloHCT did not significantly improve, despite a trend towards higher OS (Figure 4D). Only for adverse-risk ELN, the differences across the calendar periods were significant, both in patients without ($p<0.0001$, Figure 4E) and with alloHCT ($p=0.0151$, Figure 4F).

Multivariate Cox regression models confirm an improved OS over time

In order to verify these findings, we created several multivariate Cox-regression models. Given that some potentially relevant information (logWBC, percentage of BM 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 less covariates. The calendar period of AML diagnosis, ELN classification, age, log WBC at diagnosis each significantly impacted OS (Figure 5), hence 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 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 ≥60 patient cohort, less so in the ≥70 years cohort.

When we accounted for the effect of consolidating alloHCT on OS in patients ≥60 years, we found significantly higher OS in those with 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 (Figures 6B-D). While in the alloHCT cohort likely selection bias translated into excluding patients with very early relapse, still a subgroup analysis excluding patients with early relapse in the no alloHCT cohort revealed significantly higher OS in patients ≥60 years with alloHCT, confirming the relevance of consolidation for patients ≥60 years. The most frequent mutations in this population were evenly distributed between patients without and with alloHCT, with the exception of *FLT3*-ITD and *NRAS* (Figure 6E). Improved OS with alloHCT was also found in AML patients ≥70 years (Supplemental Figure 5), 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 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 with and without consolidating alloHCT. Third, our study clearly underlines the importance of alloHCT to consolidate CR1 in intensively treated patients ≥60

years as the outcome in this age subset was substantially higher 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 still are the backbone of today‘s intensive induction treatments.[5-7] Concordant to 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 ED 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 DNR[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 subsequent transplant had the largest benefit.

As the disease-related genetics have not changed among of the different calendar periods, the CR rates with standard 7+3 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 receiving 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 patient selection for this procedure based on molecular and cytogenetic risk factors.[5-7]

Over the past decades, the number of alloHSCT has continuously increased, 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 (MRD)[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 slight decreasing between 2012 and 2016. In the ELN intermediate- or adverse-risk groups, the outcome of patients consolidated with an alloHCT was significantly superior to the outcome of patients without alloHCT. Furthermore, our data confirmed the current recommendations for ELN favorable risk patients, who should only receive an alloHCT in constellations of inadequate MRD clearance 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 alloHCT[12,34]. Recent advances in more intensive induction therapies using CPX-315,[37] the classical 7+3 regimen in a new formulation, significantly improved outcome in adults with newly diagnosed, therapy-related acute myeloid leukemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC) patients. Furthermore, recent developments in maintenance treatment strategies, e.g. using sorafenib or gilteritinib post alloHCT in FLT3 mutant AML, are promising approaches to further improve outcome.[38]

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 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, which, however, 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 (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 of age with comorbidities and in patients ≥70 years[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 e.g. 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, which group of older patients benefit most from conventional induction therapy and this study offers some evidence to this important issue. Patients ≥60 years 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 with alloHCT was seen across all ELN risk groups. High-resolution HLA matching, reduced intensity conditioning and improved supportive care have allowed us to more safely perform alloHCT and also at a more advanced age. Consistent with a recent study focusing on health impairment[21,24-25,31] related to comorbidity, fitness and performance status on alloHCT outcome, patients ≥70 years benefited less from an alloHCT than those between 60 and 70 years. However, consolidation with an alloHCT remains the only way to cure these patients and the quality of remission has to be taken into account. In resume, alloHCT may clearly improve outcome of elderly AML population. Nevertheless, recommendations for choosing intensive or non-intensive chemotherapy in older population before alloHCT still need to be established with growing evidence on non-intensive approaches, as specific variables (including genetic ones) may helping to guide treatment decisions.[49-50]

Our study does also have some limitations including its retrospective character, as well as the heterogeneity of the multi-center real-world cohort. This includes the lack of more 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 >2. Furthermore, the patient group ≥70 years was comparatively small. Nevertheless, we could make important observations in terms of patient and disease characteristics and treatment results. While the HARMONY data readily provides broad multi-center 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 overall survival 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. While further outcome improvement in intensively treated AML patients will likely be driven by targeted therapies and including MRD status as a real time prognostic factor for treatment response, this pan-European HARMONY dataset can serve as a real-word comparator for such studies in the future.

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Tables

Table 1. Baseline characteristics of the cohort at AML diagnosis according to different time periods.

Characteristics	Total n=5359 (100%)	1997-2001 n=1127	2002-2006 n=1294	2007-2011 n=1821	2012-2016 n=1117	*p*
Age, median (range)	53 (18-85)	55 (17-84)	51 (15-85)	53 (16-86)	55 (17-85)	
<60 years, n (%) 60-69, n (%) ≥70 years, n (%)	3745 (69.8) 1229 (22.9) 385 (7.2)	689 (61.1) 307 (27.2) 131 (11.6)	1012 (78.2) 206 (16) 76 (5.8)	1312 (72) 403 (22.1) 106 (5.9)	732 (65.5) 313 (28) 72 (6.5)	< 0.0001 < 0.0001 < 0.0001
Female sex, n (%)	2498 (46.6)	509 (45.2)	620 (47.9)	853 (46.8)	516 (46.2)	0.5835
ECOG 0-1, n (%)	2325 (78.3)	660 (70.3)	835 (81.4)	671 (84.7)	159 (75)	< 0.001
ELN 2017 favorable intermediate adverse	1790 (33.4) 1977 (36.9) 1592 (29.7)	398 (33.3) 353 (35.3) 376 (31.3)	484 (28.2) 445 (37.4) 365 (34.4)	601 (29.5) 682 (33) 538 (37.5)	307 (28) 497 (27.5) 313 (44.5)	< 0.0001 < 0.0001 0.0173
Hb, median (range) g/dl, n=2598	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, median (IQR) ($x10^6$/mL), n=4356	16000 (Q1=4500-Q3=49900)	18320 (Q1=4900-Q3=53975)	18755 (Q1=5300-Q3=55950)	14930 (Q1=4300-Q3=46000)	12250 (Q1=3685-Q3=35000)	< 0.0001
Platelets, median (range) ($x10^6$/mL), n=4171	53000 (122-1000000)	50000 (997-746000)	53000 (122-688000)	54000 (997-950000)	54000 (3000-1000000)	0.5290
Percentage of bone marrow blasts, median (IQR), n=3552	70 (Q1=46,5-Q3=85)	70 [Q1=48,5-Q3=85] [N=1040]	75 [Q1=48-Q3=90] [N=1096]	70 [Q1=46-Q3=85] [N=1067]	63 [Q1=40-Q3=80] [N=349]	< 0.0001
Intensive regimens <70 years ≥70 years	4974 (92.82) 385 (7.18)	996 (88.4) 131 (11.6)	1218 (94.2) 76 (5.8)	1715 (94.1) 106 (5.9)	1045 (93.5) 72 (6.5)	< 0.0001 < 0.0001
Early death ≤ 14 days ≤ 30 days ≤ 60 days	96 (1.79%) 232 (4.33%) 435 (8.12%)	34 (3.01%) 71 (6.3%) 147 (13.04%)	22 (1.7%) 57 (4.4%) 105 (8.11%)	31 (2.7%) 76 (4.17%) 130 (7.14%)	9 (0.81%) 28 (2.5%) 53 (4.74%)	0.0002 < 0.0001 < 0.0001

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ELN, European LeukemiaNet; Hb, hemoglobin; WBC, white blood count. IQR, interquartile range.

Figure Legends

Figure 1. Homogeneous distribution of ELN (European LeukemiaNet) 2017 categories and stable proportion of molecular abnormalities over calendar periods.

A: Pie chart showing the proportion of patients in each calendar period according to ELN 2017 classification via its angle, absolute patient numbers are shown. Patient distribution into favorable (green), intermediate (blue) and adverse (red) risk categories. Observation periods are indicated in figure legend: 1997-2001, 2002-2006, 2007-2011, 2012-2017. **B**: Comparative illustration of the main molecular abnormalities across four calendar periods. Absolute numbers of detected genes are shown in blue bar charts. Grey chart indicates missing sample information on presence or absence of the mutation. Genes are shown in decreasing number starting with the most frequently detected gene on top.

Figure 2. Overall survival of intensively treated AML (acute myeloid leukemia) patients over calendar periods.

A: Comparison of five year overall survival (OS) of all patients (n=5359) stratified per calendar periods. Kaplan-Meier OS curve, comparison of strata with log rank test. Calendar periods are indicated in figure legend: 1997-2001 red, 2002-2006 light green, 2007-2011 blue, 2012-2017 violet. **B**: Comparison of density plots of age distributions under a smoothed curve and medians at diagnosis over calendar periods, colors as in A. Age distribution of AML patients remains stable over the calendar periods. **C:** Comparison of five year OS of intensively treated AML patients without subsequent alloHCT (allogeneic hematopoietic stem cell transplantation) in CR1 (n=2589) stratified per calendar period. Kaplan-Meier OS curve, comparison of strata with log-rank test. Observation periods are indicated in figure legend: 1997-2001 red, 2002-2006 light green, 2007-2011 blue, 2012-2017 violet. **D**: Comparison of density plots of age distributions under a smoothed curve and medians at diagnosis over calendar periods, colors as in A. **E:** Comparison of five year OS of AML patients with consolidating alloHCT (n=1770) stratified per calendar period. Kaplan-Meier OS curve, comparison of strata with log-rank test. Observation periods are indicated in figure legend:

1997-2001 red, 2002-2006 light green, 2007-2011 blue, 2012-2017 violet. **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, colors as in A.

Figure 3. **Relapse free survival after first complete remission (CR1) of intensively treated AML patients over calendar periods.**

A: Comparison of five year relapse-free survival (RFS) of AML patients in CR1 (n=3377) stratified per calendar period. Kaplan-Meier curve, comparison of strata with log-rank test. Observation periods as in A. **B**: Comparison of five year cumulative incidence of relapse of AML patients from achievement of CR1. Colors as in A.

C: Comparison of five year RFS of AML patients in CR1 without alloHCT (n=1808) stratified per calendar period. Kaplan-Meier curve, comparison of strata with logrank test. Observation periods as in A. **D**: Comparison of five year cumulative incidence of relapse of CR1 AML patients without alloHCT over calendar periods, colors as in A. **E**: Comparison of five year RFS of intensively treated CR1 AML patients with subsequent alloHCT (n=1569) stratified per calendar group. Kaplan-Meier curve, comparison of strata with log-rank test. Observation periods as in A. **F**: Comparison of five year cumulative incidence of relapse of CR1 AML patients with alloHCT, colors as in A.

Figure 4. Changes in overall survival stratified according to ELN 2017 risk groups and use of consolidating alloHCT.

The improvement in overall survival (OS) is dependent on the ELN risk group and the use of consolidating alloHCT. **A:** Kaplan Meier OS curves of ELN 2017 favorable risk patients without alloHCT is compared to **B:** ELN2017 favorable risk patients with alloHCT, strata according to the calendar periods derived from the time-point of initial diagnosis as in Figure 2. **C:** OS of ELN 2017 intermediate risk patients without alloHCT **D:** intermediate risk with

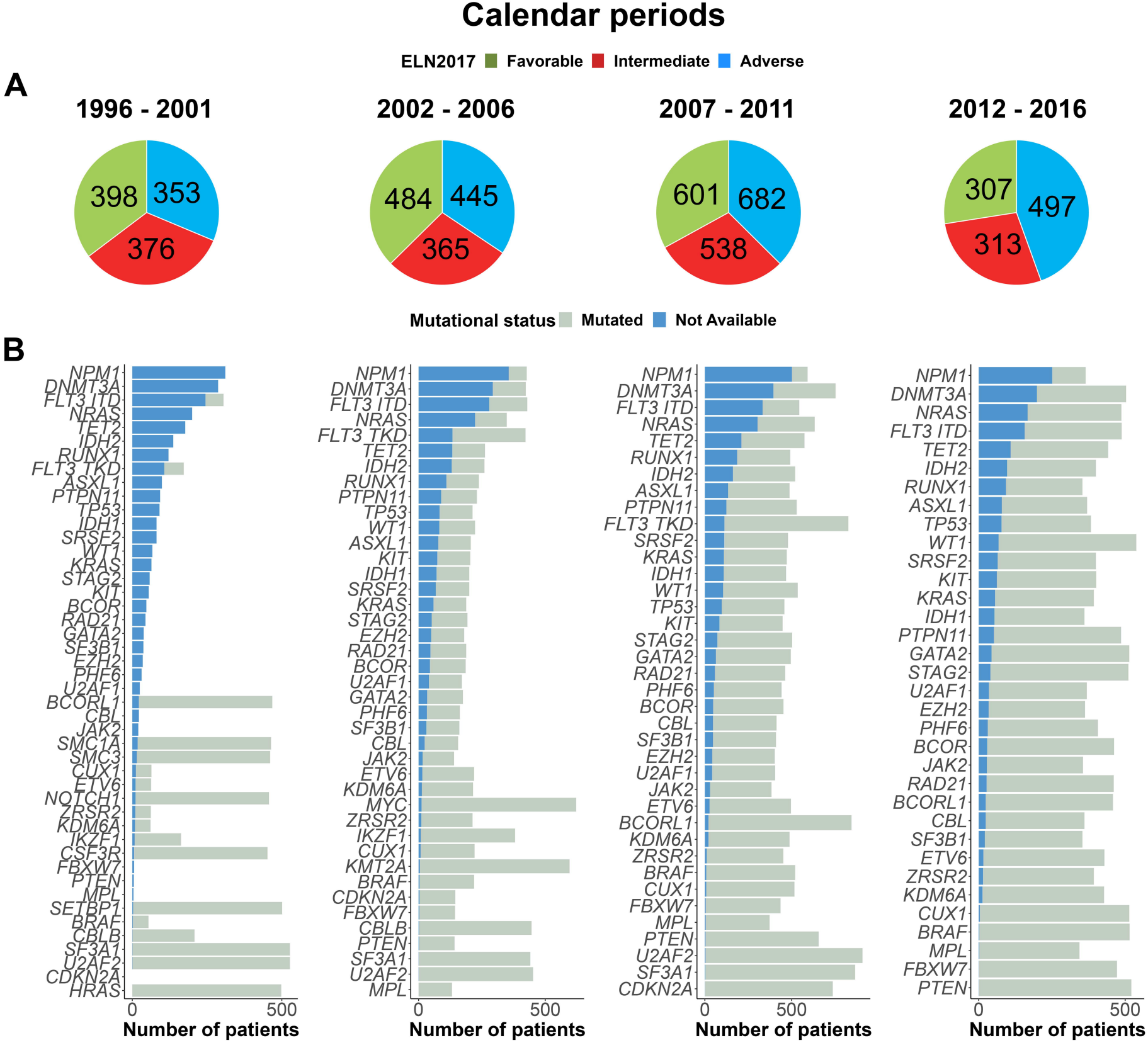
alloHCT **E:** ELN 2017 adverse risk patients without allogeneic alloHCT and **F:** adverse risk patients with alloHCT. Strata are compared with the log-rank test.

Figure 5. Multivariate Analysis confirms significant independent impact of calendar periods on outcome of intensively treated AML patients.

Multivariate Cox-regression analysis including the covariates: Age, sex, four treatment periods: 1997-2001, 2002-2006, 2007-2011 and 2012-2016; three ELN 2017 risk groups: favorable, intermediate, adverse, bone marrow myeloid blast count at AML diagnosis and logarithmic (log)white blood cell count at AML diagnosis. Age is measured as continuous risk factor, its hazard corresponds to one year increase. The bone marrow (BM) blast count and logarithmic white blood count (logWBC) are also considered as continuous variables, all other variables are used as categorical variables.

Figure 6. Comparison of overall survival and genetic features of intensively treated AML patients aged ≥60 years according to performance of alloHCT.

A-D: Comparison of patients receiving alloHCT (blue line) versus no alloHCT (red line) in all patients, Kaplan-Meier overall survival curve of intensively treated AML patients ≥60 years with alloHCT across ELN risk groups. The landmark for analysis was set after the median time from diagnosis to HCT (143 days), patients in both groups who were censored or dead before landmark were not considered for analysis. The curves were compared with the log rank test. A: All patients ≥60 years B: ELN favorable risk patients ≥60 years C: ELN intermediate risk patients ≥60 years D: ELN adverse risk patients ≥60 years. E: Genomic landscape description of patients ≥60 years. Comparison of the proportion of the most frequent gene mutations between patients ≥60 years with and without alloHCT. Absolute numbers and percentages. Colors as in A.


Calendar periods
ELN2017 Favorable Intermediate Adverse
A
1996 - 2001
398
353
376
2002 - 2006
484
445
365
2007 - 2011
601
682
538
2012 - 2016
307
497
313
Mutational status Mutated Not Available
B
NPM1
DNMT3A
FLT3 ITD
NRAS
TET2
IDH2
RUNX1
FLT3 TKD
ASXL1
PTPN11
TP53
IDH1
SRSF2
WT1
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U2AF1
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CBL
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SMC3
CUX1
ETV6
NOTCH1
ZRSR2
KDM6A
IKZF1
CSF3R
FBXW7
PTEN
MPL
SETBP1
BRAF
CBLB
SF3A1
U2AF2
CDKN2A
HRAS
0
500
Number of patients
NPM1
DNMT3A
FLT3 ITD
NRAS
FLT3 TKD
TET2
IDH2
RUNX1
PTPN11
TP53
WT1
ASXL1
KIT
IDH1
SRSF2
KRAS
STAG2
EZH2
RAD21
BCOR
U2AF1
GATA2
PHF6
SF3B1
CBL
JAK2
ETV6
KDM6A
MYC
ZRSR2
IKZF1
CUX1
KMT2A
BRAF
CDKN2A
FBXW7
CBLB
PTEN
SF3A1
U2AF2
MPL
0
500
Number of patients
NPM1
DNMT3A
FLT3 ITD
NRAS
TET2
RUNX1
IDH2
ASXL1
PTPN11
FLT3 TKD
SRSF2
KRAS
IDH1
WT1
TP53
KIT
STAG2
GATA2
RAD21
PHF6
BCOR
CBL
SF3B1
EZH2
U2AF1
JAK2
ETV6
BCORL1
KDM6A
ZRSR2
BRAF
CUX1
FBXW7
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PTEN
U2AF2
SF3A1
CDKN2A
0
500
Number of patients
NPM1
DNMT3A
NRAS
FLT3 ITD
TET2
IDH2
RUNX1
ASXL1
TP53
WT1
SRSF2
KIT
KRAS
IDH1
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GATA2
STAG2
U2AF1
EZH2
PHF6
BCOR
JAK2
RAD21
BCORL1
CBL
SF3B1
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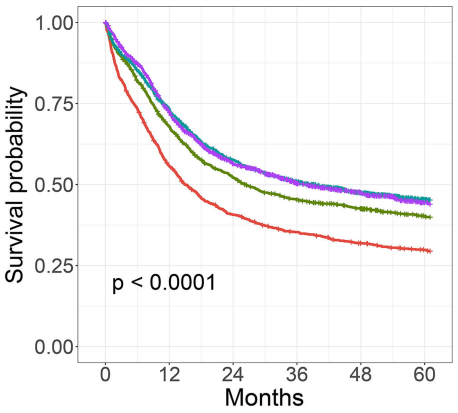
KDM6A
CUX1
BRAF
MPL
FBXW7
PTEN
0
500
Number of patients

All Patients

A



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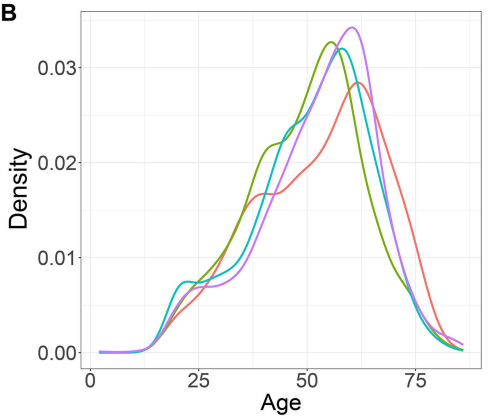


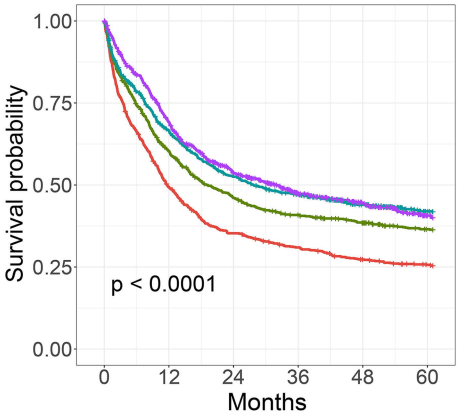
Number of patients

1997-2001	1127	624	452	387	342	310
2002-2006	1294	864	653	556	501	435
2007-2011	1821	1306	1007	871	703	539
2012-2016	1117	774	549	402	305	187

Calendar Period	1997-2001	2002-2006	2007-2011	2012-2016
Median Age	55	51	53	55

Patients without alloHCT

C



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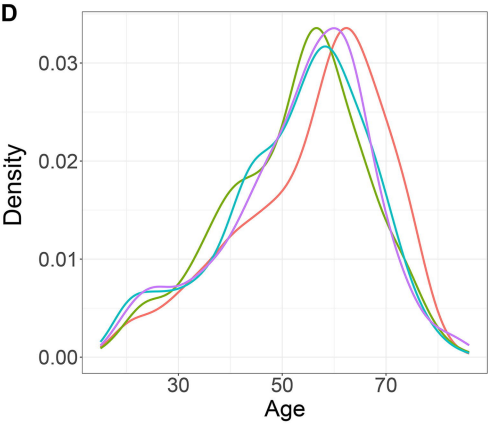


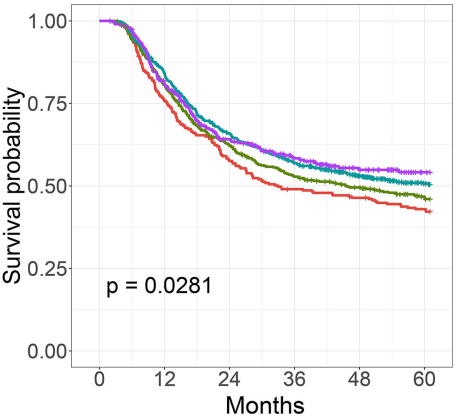
Number of patients

1997-2001	855	418	297	256	219	197
2002-2006	809	478	359	309	279	242
2007-2011	1085	697	541	473	383	312
2012-2016	777	512	365	264	202	124

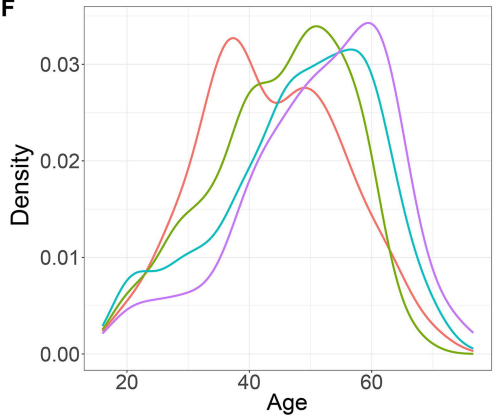
Calendar Period	1997-2001	2002-2006	2007-2011	2012-2016
Median Age	59	55	55	56

Patients with alloHCT

E



F

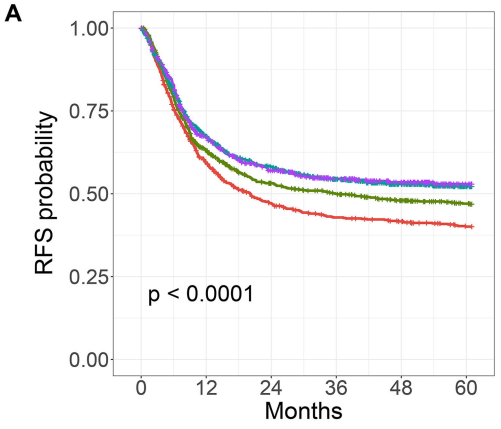


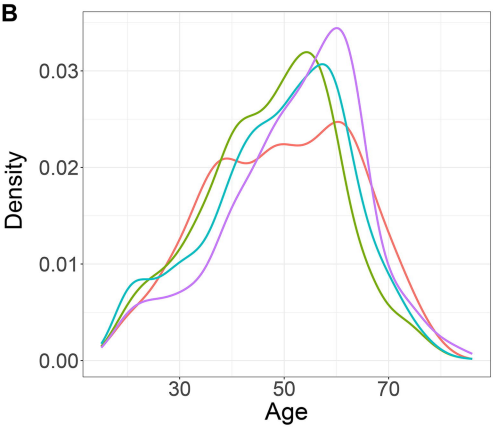
Number of patients

1997-2001	272	206	155	131	123	113
2002-2006	485	386	294	247	222	193
2007-2011	710	594	455	387	309	216
2012-2016	303	238	168	128	96	63

Calendar Period	1997-2001	2002-2006	2007-2011	2012-2016
Median Age	42	47	50	53

All Patients



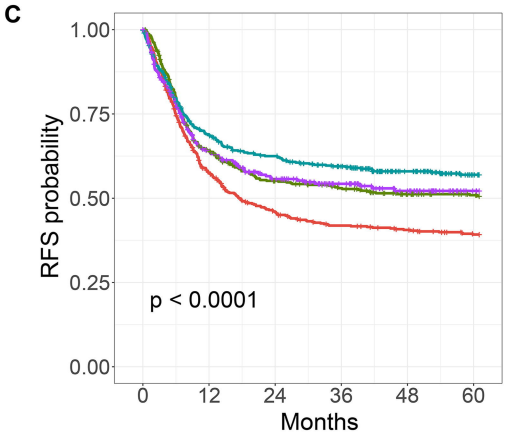


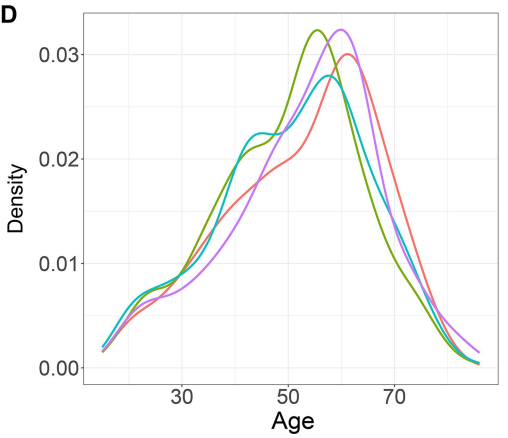
Number of patients

1997-2001	774	441	330	292	276	250
2002-2006	898	524	403	365	321	283
2007-2011	1118	684	551	471	365	256
2012-2016	587	345	255	189	136	74

Calendar Period	1997-2001	2002-2006	2007-2011	2012-2016
Median Age	50	50	51	54

Patients without alloHCT



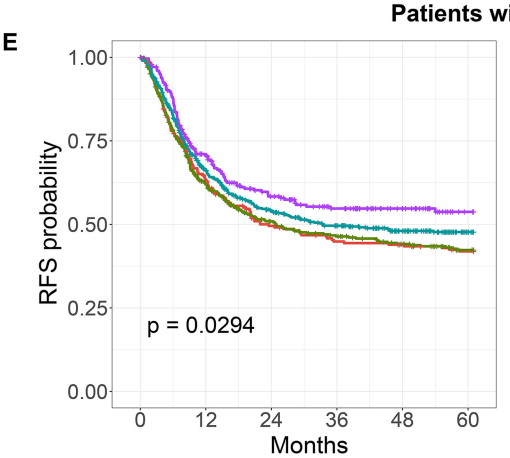


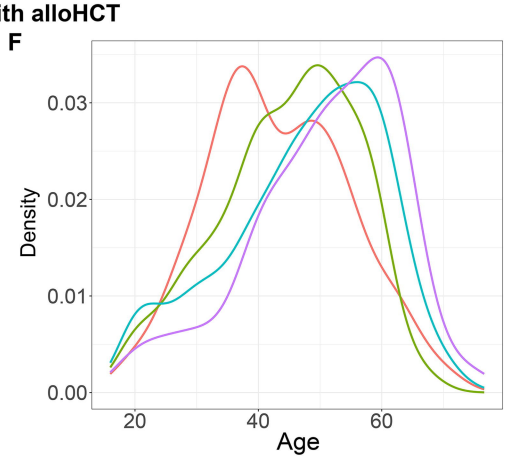
Number of patients

1997-2001	526	292	223	197	185	168
2002-2006	464	285	232	215	189	171
2007-2011	512	334	293	258	199	147
2012-2016	306	175	131	93	67	32

Calendar Period	1997-2001	2002-2006	2007-2011	2012-2016
Median Age	56	52	52	56

Patients with alloHCT

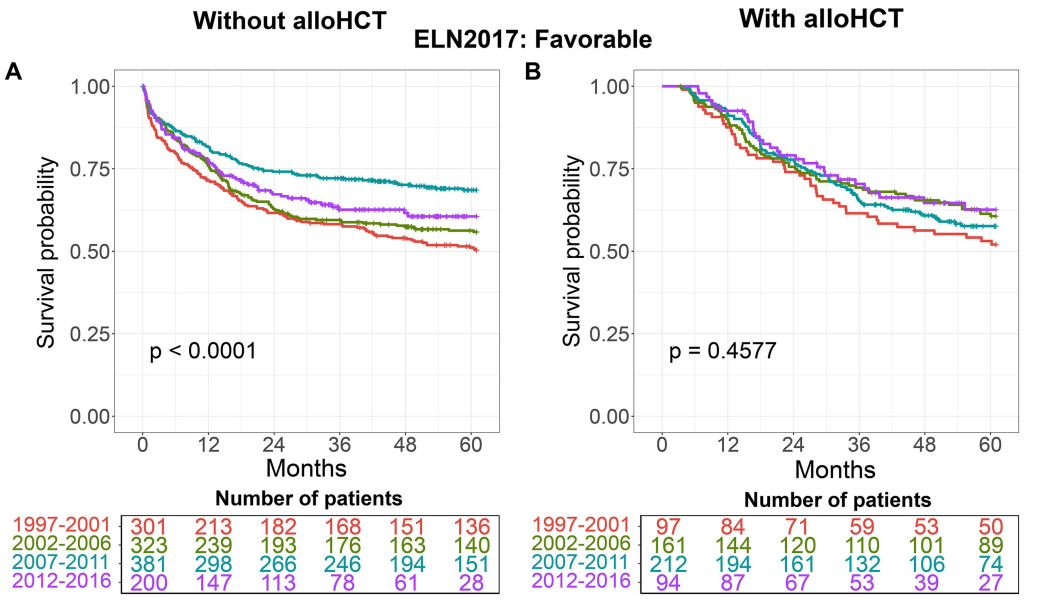


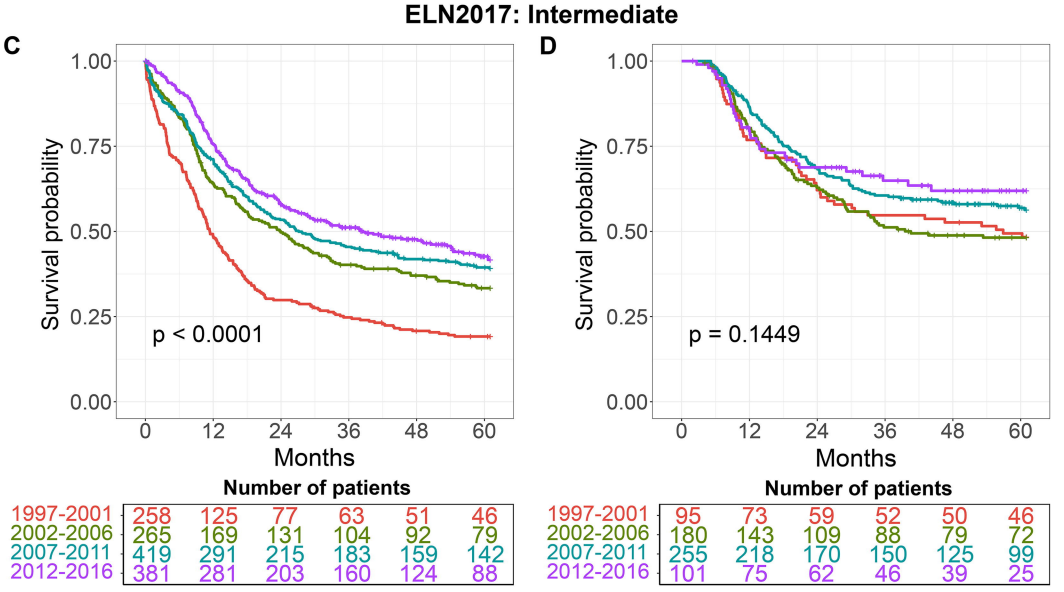


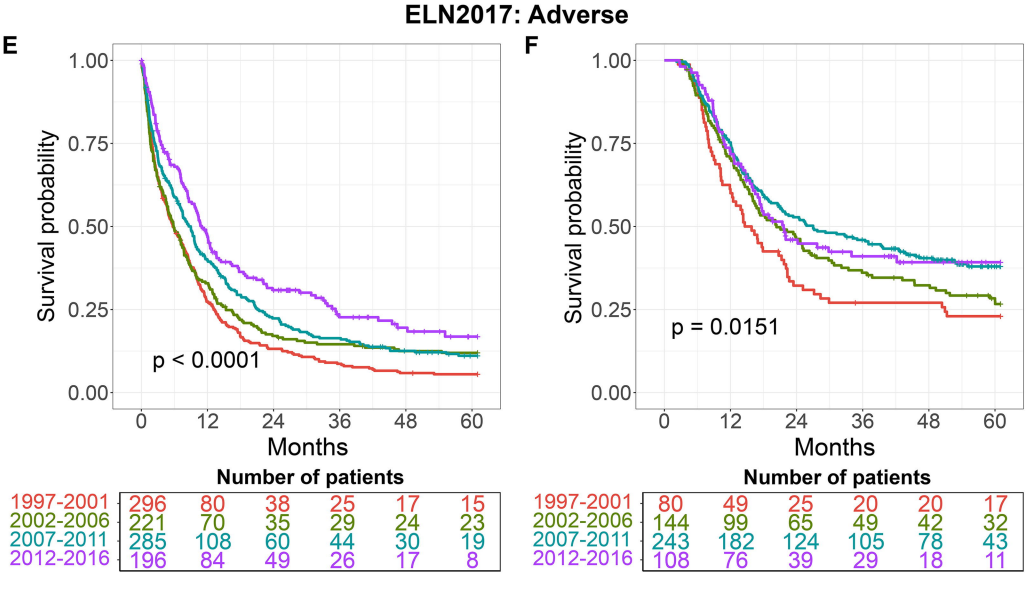
Number of patients

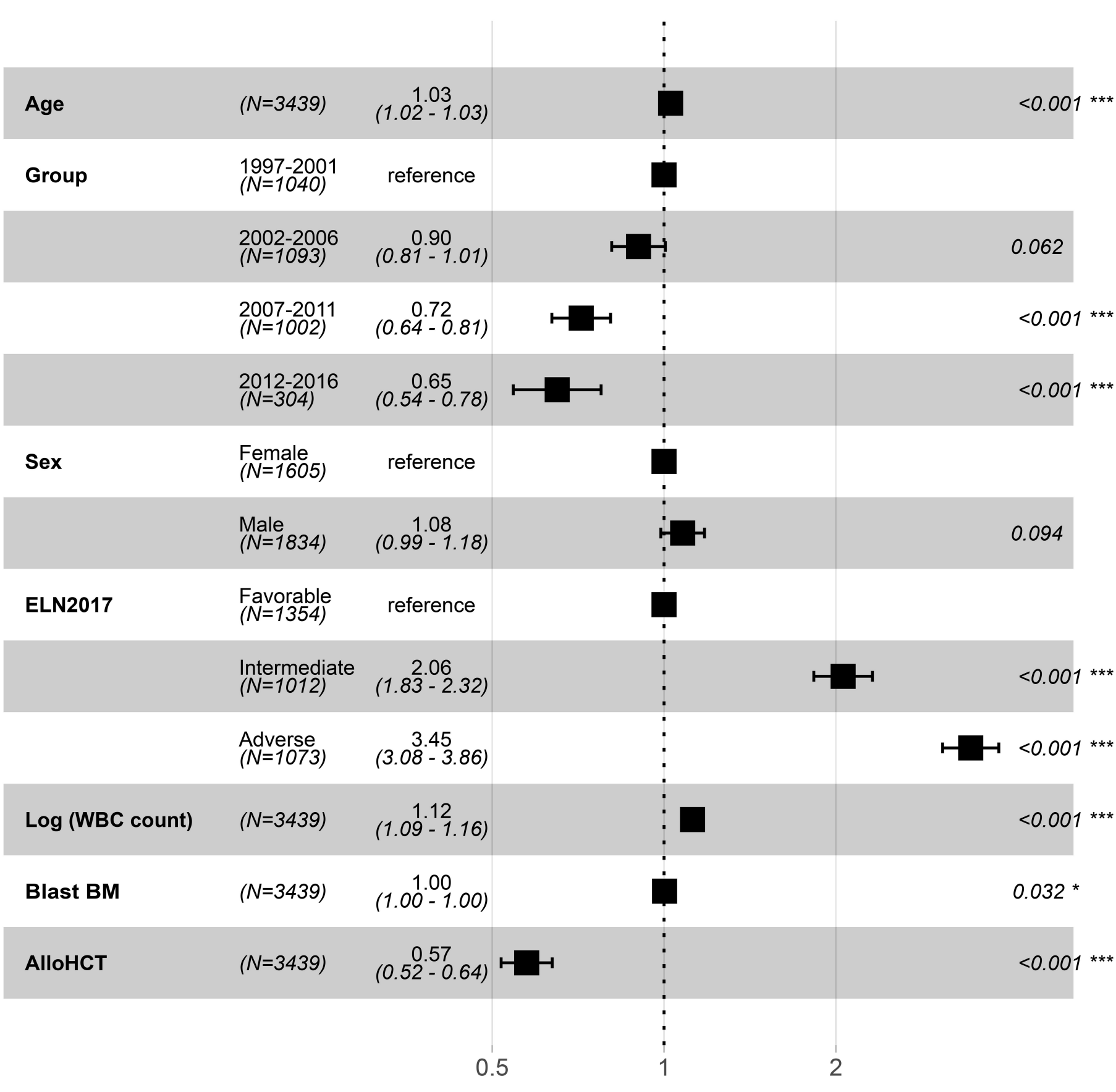
1997-2001	248	149	107	95	91	82
2002-2006	434	239	171	150	132	112
2007-2011	606	350	258	213	166	109
2012-2016	281	170	124	96	69	42

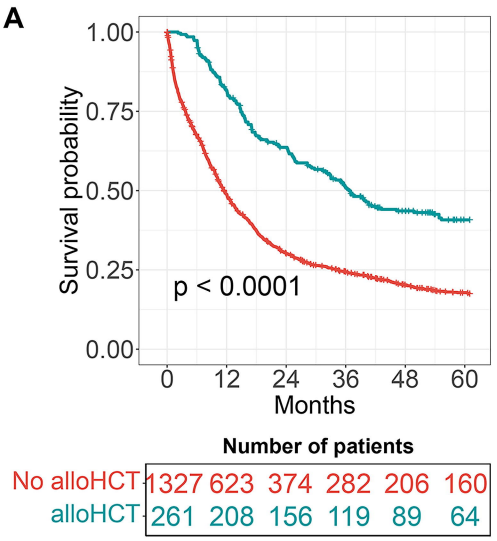
Calendar Period	1997-2001	2002-2006	2007-2011	2012-2016
Median Age	42	46	50	53

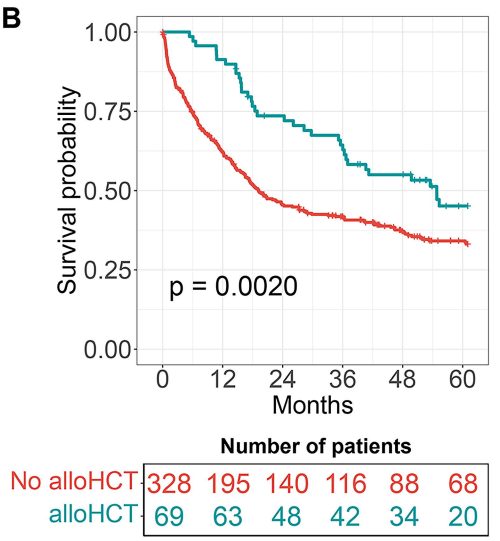

Without alloHCT
With alloHCT
ELN2017: Favorable
A
B
Survival probability
1.00
0.75
0.50
0.25
0.00
p < 0.0001
p = 0.4577
0
12
24
36
48
60
Months
Number of patients
1997-2001 301 213 182 168 151 136
2002-2006 323 239 193 176 163 140
2007-2011 381 298 266 246 194 151
2012-2016 200 147 113 78 61 28
1997-2001 97 84 71 59 53 50
2002-2006 161 144 120 110 101 89
2007-2011 212 194 161 132 106 74
2012-2016 94 87 67 53 39 27

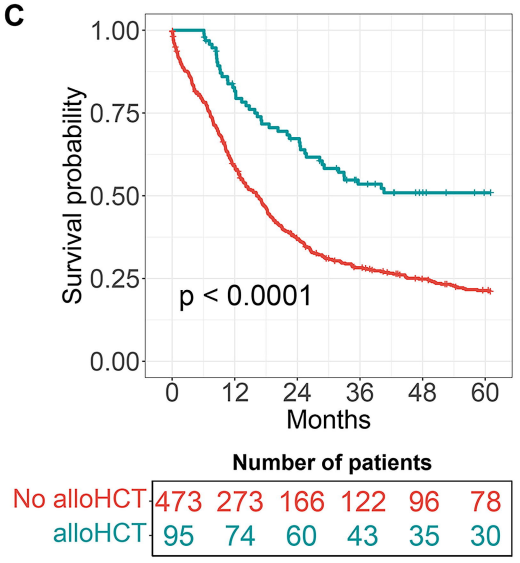

ELN2017: Intermediate
C
D
Survival probability
1.00
0.75
0.50
0.25
0.00
p < 0.0001
p = 0.1449
0
12
24
36
48
60
Months
Number of patients
1997-2001 258 125 77 63 51 46
2002-2006 265 169 131 104 92 79
2007-2011 419 291 215 183 159 142
2012-2016 381 281 203 160 124 88
1997-2001 95 73 59 52 50 46
2002-2006 180 143 109 88 79 72
2007-2011 255 218 170 150 125 99
2012-2016 101 75 62 46 39 25

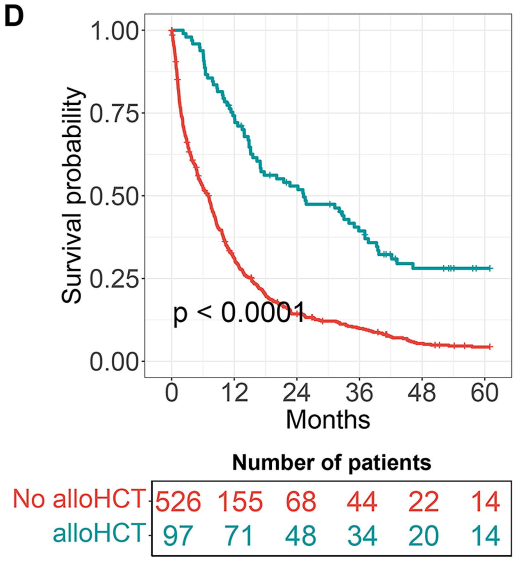

ELN2017: Adverse
E
F
Survival probability
1.00
0.75
0.50
0.25
0.00
p < 0.0001
p = 0.0151
0
12
24
36
48
60
Months
Number of patients
1997-2001 296 80 38 25 17 15
2002-2006 221 70 35 29 24 23
2007-2011 285 108 60 44 30 19
2012-2016 196 84 49 26 17 8
1997-2001 80 49 25 20 20 17
2002-2006 144 99 65 49 42 32
2007-2011 243 182 124 105 78 43
2012-2016 108 76 39 29 18 11

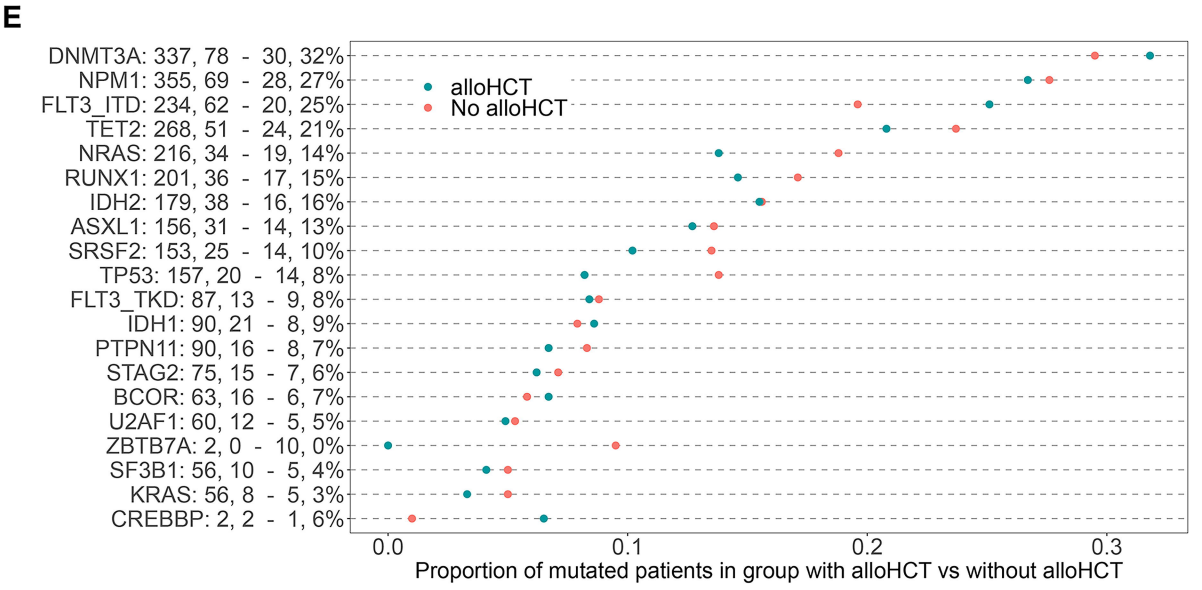

Hazard ratio
Age
(N=3439)
1.03
(1.02 - 1.03)
<0.001 ***
Group
1997-2001
(N=1040)
reference
2002-2006
(N=1093)
0.90
(0.81 - 1.01)
0.062
2007-2011
(N=1002)
0.72
(0.64 - 0.81)
<0.001 ***
2012-2016
(N=304)
0.65
(0.54 - 0.78)
<0.001 ***
Sex
Female
(N=1605)
reference
Male
(N=1834)
1.08
(0.99 - 1.18)
0.094
ELN2017
Favorable
(N=1354)
reference
Intermediate
(N=1012)
2.06
(1.83 - 2.32)
<0.001 ***
Adverse
(N=1073)
3.45
(3.08 - 3.86)
<0.001 ***
Log (WBC count)
(N=3439)
1.12
(1.09 - 1.16)
<0.001 ***
Blast BM
(N=3439)
1.00
(1.00 - 1.00)
0.032 *
AlloHCT
(N=3439)
0.57
(0.52 - 0.64)
<0.001 ***
0.5
1
2


A
Survival probability
1.00
0.75
0.50
0.25
0.00
p < 0.0001
0
12
24
36
48
60
Months
Number of patients
No alloHCT 1327 623 374 282 206 160
alloHCT 261 208 156 119 89 64


B
Survival probability
1.00
0.75
0.50
0.25
0.00
p = 0.0020
0
12
24
36
48
60
Months
Number of patients
No alloHCT 328 195 140 116 88 68
alloHCT 69 63 48 42 34 20


C
Survival probability
1.00
0.75
0.50
0.25
0.00
p < 0.0001
0
12
24
36
48
60
Months
Number of patients
No alloHCT 473 273 166 122 96 78
alloHCT 95 74 60 43 35 30


D
Survival probability
1.00
0.75
0.50
0.25
0.00
p < 0.0001
0
12
24
36
48
60
Months
Number of patients
No alloHCT 526 155 68 44 22 14
alloHCT 97 71 48 34 20 14


E
DNMT3A: 337, 78 - 30, 32%
NPM1: 355, 69 - 28, 27%
FLT3_ITD: 234, 62 - 20, 25%
TET2: 268, 51 - 24, 21%
NRAS: 216, 34 - 19, 14%
RUNX1: 201, 36 - 17, 15%
IDH2: 179, 38 - 16, 16%
ASXL1: 156, 31 - 14, 13%
SRSF2: 153, 25 - 14, 10%
TP53: 157, 20 - 14, 8%
FLT3_TKD: 87, 13 - 9, 8%
IDH1: 90, 21 - 8, 9%
PTPN11: 90, 16 - 8, 7%
STAG2: 75, 15 - 7, 6%
BCOR: 63, 16 - 6, 7%
U2AF1: 60, 12 - 5, 5%
ZBTB7A: 2, 0 - 10, 0%
SF3B1: 56, 10 - 5, 4%
KRAS: 56, 8 - 5, 3%
CREBBP: 2, 2 - 1, 6%
alloHCT
No alloHCT
0.0
0.1
0.2
0.3
Proportion of mutated patients in group with alloHCT vs without alloHCT

Supplemental Data to

Outcomes with intensive treatment for acute myeloid leukemia over two decades: An analysis from the HARMONY Alliance.

Running title: Intensive treatment for acute myeloid leukemia over two decades.

Marta Anna Sobas[1]‡, Amin T. Turki[2]‡, Angela Villaverde Ramiro[3,4], Alberto Hernández Sánchez[3,4,5,], 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].

‡ equal contribution, shared first authorship

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Hematology and Oncology, University Hospital Brno and Masaryk University; [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, United Kingdom; [27]Center, Amsterdam UMC,location VUMC, Netherlands.

Supplemental Methods

Therapy

Intensive induction regimen was defined based on the use of cytarabine (Ara-C) at 100-200 mg/m² daily over 5-7 days. Induction therapy varied by treatment period and local protocols. Variations in these regimens included different anthracyclines (daunorubicin, idarubicin, mitoxantrone), the addition of other types of chemotherapy, such as thioguanine, etoposide, nucleoside analogues (fludarabine, clofarabine, cladribine), or differentiating agents such as valproate, tretinoin plus valproate, with or without granulocyte colony-stimulating-factor. Patients receiving non-cytarabine based regimens, and those treated with epigenetic (hypomethylating) or targeted therapy (anti CD-33 or genetically targeted) were excluded from the analysis. Response to therapy was defined according to the Cheson[29] and ELN criteria[6]. Early death was defined as the death within 14, 30 and 60 days from diagnosis. Patients receiving consolidating allogeneic hematopoietic cell transplantation (alloHCT) were included independent of alloHCT type, including grafts from related or unrelated donors without and with HLA mismatch. The remission status at alloHCT was CR1 for the majority of patients. Myeloablative and reduced intensity conditioning regimens were permitted.

Outcomes and Statistical analysis

The main clinical outcome parameters were overall survival (OS) and relapse-free survival (RFS) as determined by Kaplan-Meier analysis. The observation period was 5 years. The OS was calculated from the date of AML diagnosis to death from any cause, censoring patients who were alive at the time of last follow up. The RFS was calculated for patients achieving complete remission (CR) measured from the date of achievement of remission until the date of hematologic relapse or death from any cause, censoring patients who were not known to have relapsed or who were alive at last follow-up. In addition, relapse and death were considered as competing events and were analyzed by competing risk analysis. Cumulative incidences were compared by Gray's test. P-values <0.05 were considered statistically significant. Both OS and RFS (primary endpoints) were compared between the four treatment periods using the log-rank test. Associations between patients' features and time-to-event endpoints (OS, RFS) were determined by multivariable Cox regression analysis[24]. Several multivariable Cox regression models including 5359 patients (10 covariates), 4356 (11 covariates) and 3439 patients (12 covariates) were constructed and compared using the Akaike information criterion[25]. All covariates entered the first model. Variables were selected

by retaining significant variables in univariate Cox analysis and clinically relevant variables for the multivariate models. The strongest OS model was retained as final and is displayed in the results (Figure 5). The following covariates entered multivariate analysis: age, gender, ELN risk, calendar treatment period of 5 years each (1997-2001, 2002-2006, 2007-2011, 2012-2016), ECOG performance index, logarithm (log) of white blood cell (WBC) counts, hemoglobin and platelet levels, the percentage of bone marrow blasts at diagnosis and the performance of alloHCT. AlloHCT was analyzed as time-dependent co-variate in Cox-regression analysis. For the direct head-to-head comparison of patients aged 60 years and older with and without alloHCT using Kaplan Meier survival analysis we employed the landmark analysis as previously described[30]. The median time from diagnosis to alloHCT was 143 days, the landmark was also set at 143 days. Patients in both groups that died or were censored before that date were not considered in this analysis.

Calculations were performed with *R*[36] (version 4.1.3, R Core team 2020, https://www.r-project.org) using the following libraries: *ggplot2, surviva*[37]*, survminer*[38]*, cmprsk*[39].

Supplemental Tables

Supplemental Table 1. List of chemotherapy regimens (n=4286).

Induction chemotherapy	***n* (%)**
DNR/IDA + Ara-C	1227 (28.7%)
DNR/IDA + Ara-C + Miscellaneous	2265 (52.9%)
Mitoxantrone + Ara-C	409 (9.5%)
Mitoxantrone + Ara-C + Miscellaneous	380 (8.8%)
HD Ara-C	5 (0.1%)

Abbreviations: Ara-C, cytarabine, DNR, daunorubicin; and IDA, idarubicin.

Supplemental Table 2. Comparison of baseline characteristics between all patients and separate for those with documented intensive chemotherapy regimen and for those aged <70 years.

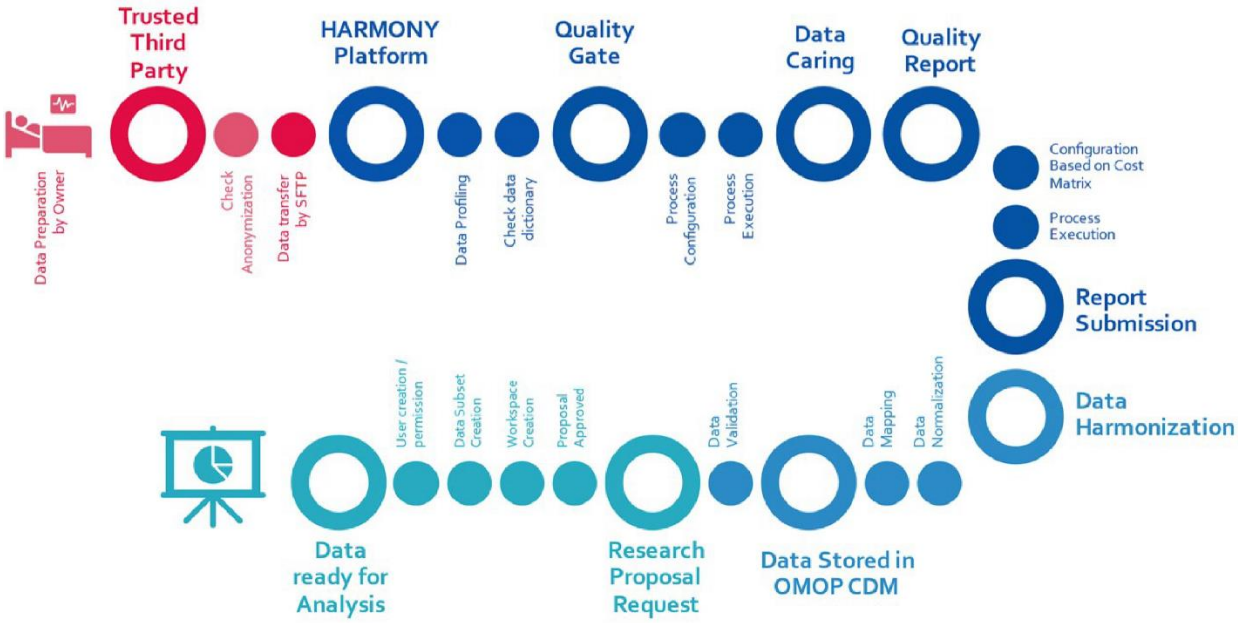
Characteristics	Total (n=5359)	With detailed chemotherapy (n=4287)	Patients ≤70 (n=1072)	*p*
Age, median (range)	53 (18-85)	53 (18-85)	54 (18-70)	0.6796
Female sex, n (%)	2498 (46.6)	1995 (46.5)	503 (46.9)	0.8476
ECOG 0-1, n (%) (n = 2934)	2325 (78.3)	2293 (79.1)	32 (91.4)	0.1144
ELN 2017 favorable intermediate adverse	 1790 1977 1592	 1631 (38%) 1257 (29%) 1399 (33%)	 159 (15%) 720 (67%) 193 (18%)	< 0.01
Hb, median (range) g/dl n=2598	9 (2.5-19)	9 (2.5-19)	9 (3.4-15.4)	0.7593
WBC, median (IQR) (x10^6/mL) n=4356	16000 [Q1=4,500-Q3=49,900]	16200 [Q1 = 4,500 – Q3 = 50,867.5]	12100 [Q1 = 4,850 – Q3 = 31,450]	0.07322
Platelets, median (IQR) (x10^6/mL) n=4171	53000 (Q1=29,000 – Q3=100,000)	53000 (Q1=29,000 – Q3=100,000)	49000 (Q1=26,000 - Q3=98,000)	0.3051
Bone marrow blasts, %, median (IQR) n=3552	70 [Q1=46.5 - Q3=85]	70 [Q1=47 - Q3=85]	63 [Q1=40 - Q3=82.5]	0.02271

Abbreviations: ECOG, Eastern Cooperative Oncology Group performance index; IQR, interquartile range; Q, quartile; ELN, European LeukemiaNet; Hb, hemoglobin; WBC, white blood cells.

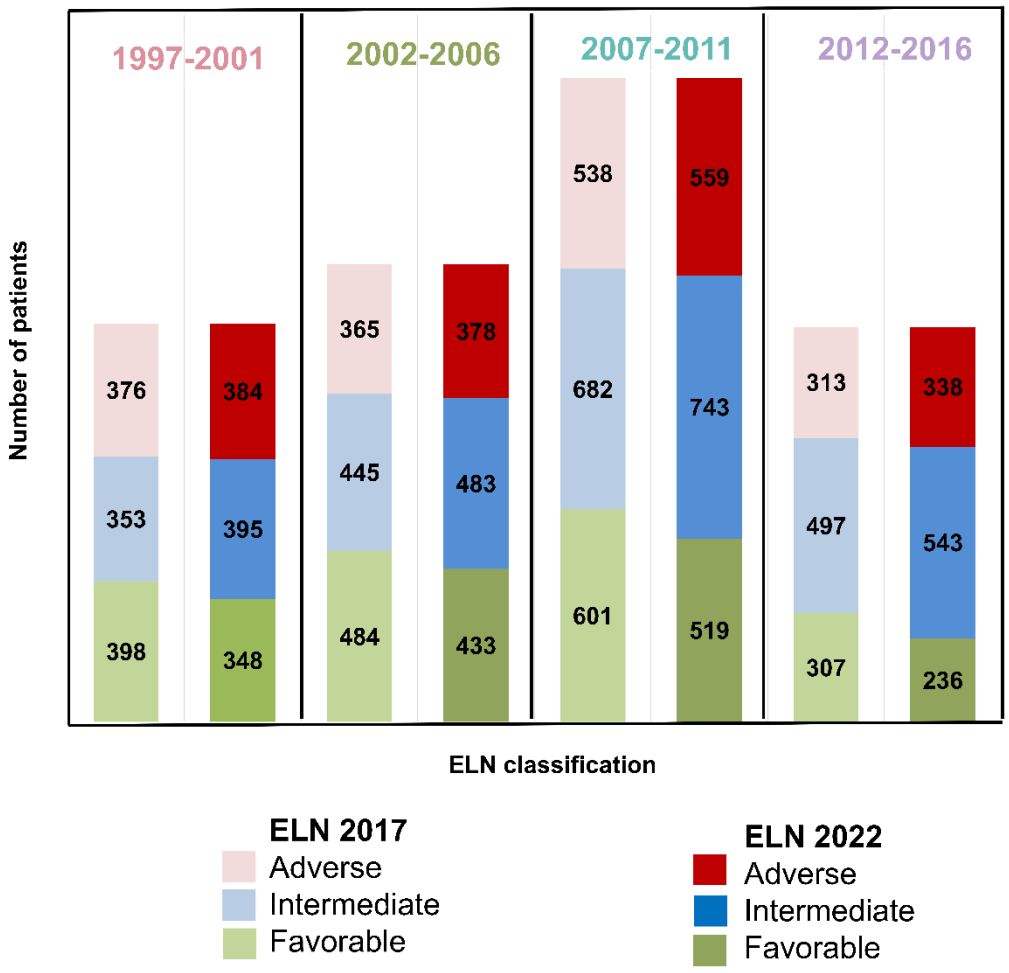
Supplemental Figures

Supplemental Figure 1. Data anonymization and harmonization process.

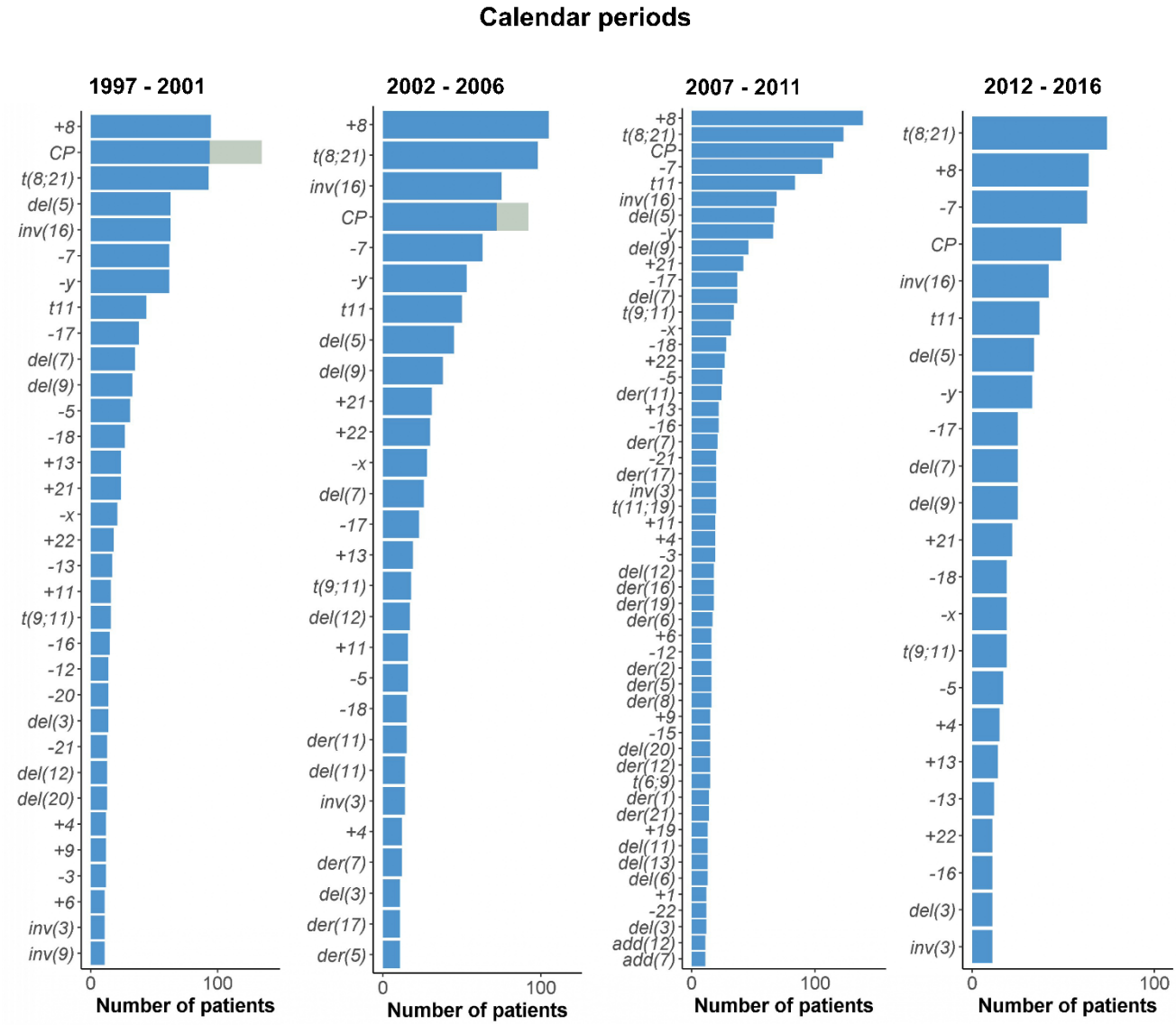
Data providers share de-identified datasets with the trusted third party (TTP). TTP provides second pseudonymization (unknown to the data provider) and transfers the data to the HARMONY platform. Quality gating evaluates and maps the data dictionary with the provided data. Quality report is provided before further data processing. Research proposals for the data in HARMONY are submitted to and evaluated by the Harmony steering committee. Only de-identified data from the HARMONY database is provided for researchers on a need-to-know basis.



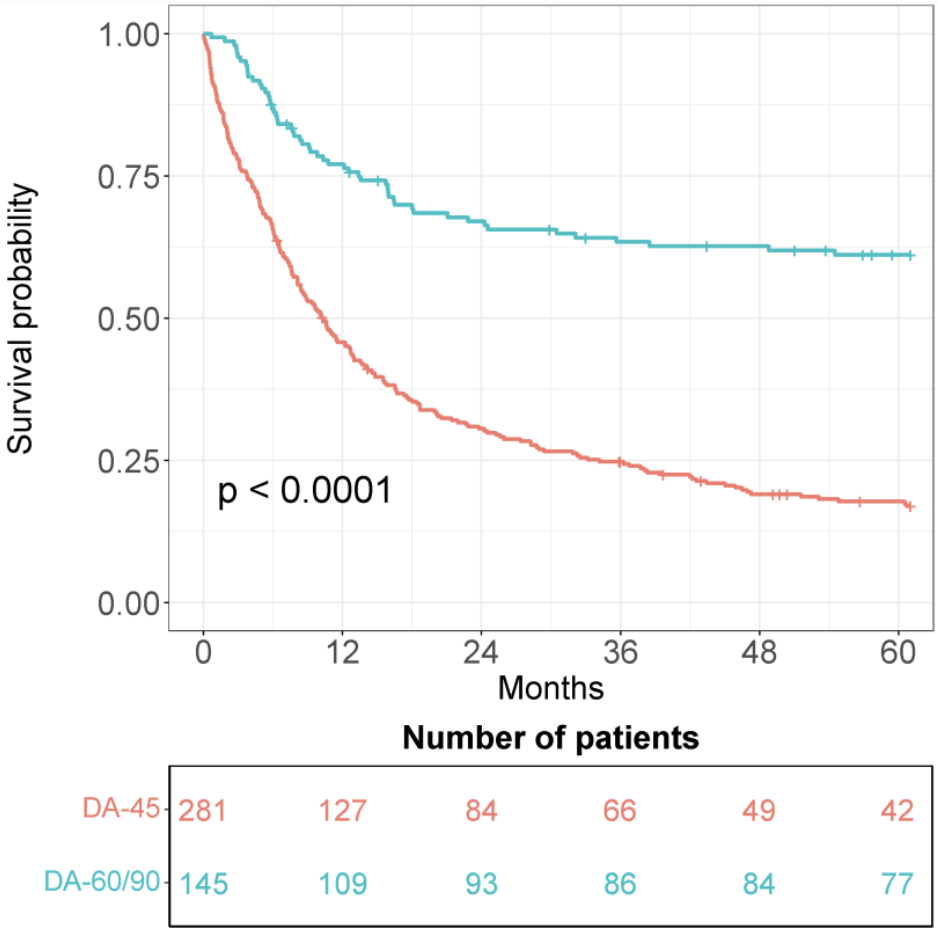
Supplemental Figure 2. Proportion of patients according to ELN 2017 and ELN 2022 for each calendar period.



Supplemental Figure 3. Stable proportion of main cytogenetic abnormalities across four calendar periods.



Supplemental Figure 4. Impact of doses of daunorubicin on overall survival of AML patients.



Supplemental Figure 5. Comparison of OS in patients aged ≥70 years (n=385).

A Comparison of OS across 4 calendar periods, **B** Comparison of OS in patients ≥70 years with alloHCT (n=21, blue) and without alloHCT (n=364, red)