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Impact of FMS-like tyrosine kinase 3 inhibitor maintenance on post-transplant outcomes in acute myeloid leukemia with FMS-like tyrosine kinase 3 mutations: a real-world German registry analysis highlighting sorafenib

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Running head: Post-Allo-HCT FLT3i Maintenance: Real-World DRST

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Key words: Acute myeloid leukemia, FLT3 mutation, Allogeneic hematopoietic cell transplantation, FLT3 inhibitor maintenance, Relapse-free survival, Measurable residual disease

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Abstract:
FLT3-mutation occurs in 25-30% of AML and confers high relapse risk and inferior survival. Allogeneic hematopoietic cell transplantation (allo-HCT) offers curative potential, yet relapse remains a major post-transplant challenge. Maintenance therapy with FLT3 inhibitors (FLT3i) after allo-HCT has emerged as a promising strategy, but real-world evidence remains limited. This study aimed to assess the impact of FLT3i maintenance on transplant outcomes. We analyzed 523 adults with FLT3-ITD AML in first complete remission who underwent allo-HCT between 2011 and 2023 in 13 German transplant centers participating in the national DRST registry; 22% received FLT3i maintenance (sorafenib 49%, midostaurin 37%, gilteritinib 5%, unknown 9%). In multivariable analyses (MVA), FLT3i maintenance improved OS (HR 2.25, 95% CI [1.28; 3.95], p=0.005), RFS (HR 1.72, 95% CI [1.05; 2.81], p=0.030), non-relapse mortality (HR 3.62, 95% CI [1.08; 12.11], p=0.037), and GVHD- and relapse-free survival (HR 1.59, 95% CI [1.06; 2.40], p=0.025). The cumulative incidence of relapse did not differ. In univariate analyses (UVA), OS benefits were observed in MRD-positive (HR 2.35, 95% CI [1.04; 5.31], p=0.025) and MRD-negative patients (HR 2.64, 95% CI [1.05; 6.68], p=0.020. Sorafenib maintenance (n=50) demonstrated superior efficacy with 5-year OS of 85% versus 62% (HR 2.979, p=0.0045) and RFS of 84% versus 55% (HR 2.771, p=0.0043) compared to no maintenance. These real-world findings, while limited by the retrospective design and potential selection bias, align with randomized trial data and support the use of FLT3i maintenance as part of post-transplant care for FLT3-ITD AML.

Introduction:

Mutations in the FMS-like tyrosine kinase 3 (FLT3) gene occurs in approximately 25-30% of newly diagnosed acute myeloid leukemia (AML) patients.[1, 2] FLT3 mutations mainly comprise internal tandem duplications (ITD) or tyrosine kinase domain (TKD) point mutations, with FLT3-ITD being associated with increased relapse risk and inferior survival outcomes.[3, 4] Historically, the FLT3-ITD allelic ratio was considered an important prognostic factor, with higher allelic ratios (typically >0.5) associated with worse outcomes.[5] The 2022 European LeukemiaNet (ELN) guidelines eliminated the FLT3-ITD allelic ratio from risk stratification, with all FLT3-ITD mutations now classified as intermediate-risk regardless of allelic ratios.[6] Patients with FLT3-mutated AML typically achieve complete remission rates comparable to those without the mutation; however, they experience significantly higher relapse rates and shorter overall survival.[7] This unfavorable prognosis has driven the development of FLT3-targeted therapies, several of which are now integrated into standard AML treatment algorithms.[8, 9]

Allogeneic hematopoietic stem cell transplantation (allo-HCT) remains the most effective consolidation strategy for eligible patients with FLT3-mutated AML in first complete remission (CR1).[7] However, post-transplant relapse remains a major cause of treatment failure. [10, 11] Post-transplant FLT3-inhibitor (FLT3i) maintenance has therefore been investigated as a strategy to reduce relapse risk, with prospective trials demonstrating improved outcomes, particularly with sorafenib-based approaches. [12-14] Using the German Registry for Hematopoietic Stem Cell Transplantation and Cell Therapy (DRST), we evaluated the association of post-transplant FLT3i maintenance with survival

and relapse-related outcomes in patients with FLT3-mutated AML undergoing allo-HCT in CR1.

Methods:

Study Design and Patient Population

This multicenter cohort study was conducted on behalf of the German Registry for Hematopoietic Stem Cell Transplantation and Cell Therapy (DRST). We included adult patients (≥18 years) from 13 participating centers who underwent allogeneic stem cell transplantation (allo-HCT) for FLT3-mutated acute myeloid leukemia (AML) in first complete remission (CR1) between 2011 and 2023. A predefined subgroup analysis assessed outcomes according to post-transplant sorafenib maintenance, stratified by measurable residual disease (MRD) status at transplantation. MRD was assessed locally using multiparameter flow cytometry (MFC) and/or PCR for NPM1 mutations or leukemia-specific fusion transcripts, according to institutional standards. MFC assays typically had sensitivities of 10^{-3} -10^{-4}, and PCR assays approximately 10^{-4} -10^{-5}. MRD-negativity was defined as absence of detectable disease by the locally applied assay. Due to the registry design, platforms and thresholds varied between centers; this heterogeneity is acknowledged as a limitation. Initiation of FLT3-inhibitor (FLT3i) maintenance was at the discretion of the treating physician. Decisions reflected patient fitness, GVHD status, donor type, evolving evidence over time, drug availability and reimbursement. No standardized protocol was implemented across centers.

Only patients from centers with complete documentation of FLT3i maintenance status (maintenance vs. no maintenance) were included in the analysis.

A detailed list of participating authors, their affiliated centers, and the number of patients contributed is provided in the Supplementary Appendix.

Endpoints and Definitions

Endpoints included, overall survival (OS), relapse-free survival (RFS), non-relapse mortality (NRM), cumulative incidence of relapse (CIR), and graft-versus-host disease-and-relapse-free survival (GRFS).

To reduce immortal-time bias, all time-to-event analyses used a day+100 landmark design. Patients who relapsed or died before day+100 after allo-HCT were excluded from the analytic cohort, and follow-up for OS, RFS, GRFS, NRM and CIR was measured from day+100 onwards. This landmark was chosen because FLT3i maintenance was typically initiated between days 30 and 90 (median of 65-75 days depending on the FLT3i Type), so that most patients who could start maintenance were alive and evaluable at the time origin. Patients were censored at the last follow-up if no event occurred. OS was defined as time to death from any cause, and RFS as the time to relapse or death. GRFS was defined as time relapse, grade II-IV acute GVHD, moderate to severe chronic GVHD, or death. CIR was defined as relapse and NRM as death without prior relapse - treated as competing risks/events, and were analyzed using cumulative incidence functions. OS and RFS were estimated using Kaplan-Meier methods and compared using Cox proportional hazards models.

Univariable analyses (UVA) used Cox proportional hazards models for OS, RFS, and GRFS, and Fine-Gray competing risk models for NRM and CIR; continuous variables were categorized. Multivariable analyses (MVA) applied Cox models to estimate adjusted-hazard-ratios (HRs) with 95% confidence-intervals (CIs), with Fine-Gray-regression used for NRM and CIR. A two-sided

p-value <0.05 was considered statistically significant. Analyses were performed using R V4.0 (R-Foundation for Statistical Computing, Vienna, Austria).

Results:

Patients Donor and Transplant Characteristics

We identified 927 patients reported to the DRST who underwent allo-HCT for FLT3-mutated AML in CR1 between 2011 and 2023. After excluding 404 patients with unknown FLT3i maintenance status, the final cohort comprised 523 patients, including 116 who received FLT3i maintenance, predominantly off-label (49% Sorafenib, 37% Midostaurin, 5% Gilteritinib, 9% unknown), and 407 without maintenance. The median year of allo-HCT was 2019 (range, 2012-2021) in the maintenance group and 2018 (range, 2011-2021) in the non-maintenance group.

At allo-HCT, 39% were MRD-negative, 32% MRD-positive, and 29% had unknown MRD-status; 95% received PBSC-grafts, and 60% underwent MAC. The median time from diagnosis to transplant was 120 days (range 37-789). Median time to initiation was 74 days (range, 35-273) for sorafenib, 75 days (range, 29-303) for midostaurin, and 65 days (range, 33-215) for gilteritinib; median duration was 486 days (range, 7-909), 269 days (range, 3-520), and 287 days (range, 33-810), respectively. Patients, donors, and transplant characteristics are summarized in Table1.

Transplant outcomes

Univariable analyses are summarized in Table 2 and Multivariable Analysis are summarized in Table 3

Engraftment

Neutrophil engraftment occurred in 106 patients receiving maintenance therapy, 389 patients without maintenance, and 360 patients with unknown maintenance status. Median time to engraftment was 16 days (range, 7-30) in the maintenance group, 16 days (range, 4-47) in the non-maintenance group, and 17 days (range, 9-56) in patients with unknown maintenance status.

GVHD

Overall, 488 patients (53%) developed acute GVHD (Grades I-IV), while 249 patients (27%) did not and in 190 patients (21%) the status was unknown. The 1-year cumulative incidence from day 100 of acute GVHD grade II-IV was 7% (95% CI [0; 13]) in the maintenance group and 5% (95% CI [2; 9]) in the non-maintenance group (HR 0.84, 95% CI [0.27; 2.65], p=0.768). The corresponding 1-year cumulative incidence of acute GVHD grade III-IV was 5% (95% CI [0; 10]) in the maintenance group and 4% (95% CI [2; 7]) in the non-maintenance group (HR 0.88, 95% CI [0.28; 2.79], p=0.833).

The 5-year cumulative incidence from day 100 of chronic GVHD (all grades) was 39% (95% CI [28; 49]) in the maintenance group and 40% (95% CI [34; 46]) in the non-maintenance group (HR 0.94, 95% CI [0.64; 1.37], p=0.749). For chronic GVHD (moderate/Severe), the 5-year cumulative incidence was 21% (95% CI [12; 30]) in the maintenance group and 25% (95% CI [20; 30]) in the non-maintenance group (HR 1.18, 95% CI [0.71; 1.94], p=0.527).

OS and RFS

The 5-year OS rate for the entire cohort was 65% (95% CI [61; 70]). (Figure 1A) Patients receiving maintenance therapy exhibited a significantly higher OS compared to those who did not, with a hazard ratio (HR) of 2.37 (95% CI [1.39; 4.07]), p=0.0005. (Figure 1B) Specifically, the 5-year OS was 77% (95% CI [65; 90]) in the maintenance group versus 62% (95% CI [56; 68]) in the

non-maintenance group. This difference remained significant over time in MVA, with a HR of 2.25 (95% CI [1.28; 3.95]), p=0.005 (Table 3)

The 5-year RFS rate for the entire cohort was 60% (95% CI [56; 65]). (Figure 1C) Patients receiving maintenance therapy exhibited a significantly higher RFS compared to those who did not, with a HR of 1.81 (95% CI [1.14; 2.89]), p=0.0073. Specifically, the 5-year RFS was 75% (95% CI [66; 85]) in the maintenance group versus 55% (95% CI [48; 62]) in the non-maintenance group. (Figure 1D) This difference remained significant in MVA, with a HR of 1.72 (95% CI [1.05; 2.81]), p=0.030. (Table 3)

NRM and Relapse

The cumulative incidence of NRM at 3-years for the entire cohort was 12% (95% CI [9; 15]). (Figure 2A) Patients without maintenance had significantly higher NRM than those receiving maintenance (HR 4.42, 95% CI [1.37;14.26], p=0.013), with 5-year NRM rates of 17% (95% CI [12;22]) versus 3% (95% CI [0;7]), respectively (Figure 2B). This association remained significant in MVA (HR 3.62, 95% CI [1.08;12.11], p=0.037) (Table 3).

Sixty-Five Patients relapsed before Day 100. The 3-year CIR for the entire cohort was 28% (95% CI [24;31]) (Figure 2A). CIR did not differ between the maintenance and non-maintenance groups (HR 1.25, 95% CI [0.76;2.08], p=0.380), with 5-year CIR rates of 22% (95% CI [13;31]) and 28% (95% CI [22;34]), respectively (Figure 2B). Results were consistent in multivariable analysis (HR 1.30, 95% CI [0.76;2.23], p=0.330) (Table 3).

GRFS

The GRFS at 5-years for the entire cohort was 41% (95%CI [37; 46]). (Figure 2C) GRFS was significantly higher in the maintenance group (HR 1.45 (95%CI [1.01; 2.08], p=0.039).(Figure 2D) Specifically, the 5-year GRFS was 51% (95%CI [40; 66]) in the maintenance group vs 39% (95%CI [33; 47]) in the non-maintenance group. This difference persisted on MVA (HR 1.59 (95%CI [1.06; 2.40], p=0.025). (Table 3)

Subgroup analyses

MRD-status

In the subgroup analysis according to MRD-status at allo-HCT, MRD-positive patients receiving maintenance showed improved OS (HR 2.35, 95%CI [1.04; 5.31], p=0.025), with 5-year OS of 76% (95%CI [61; 94]) vs. 59% (95%CI [47; 73]) without maintenance. (Figure 3A) RFS at 5-years was higher with maintenance at 72% (95%CI [58; 89]) vs. 55% (95%CI [43; 70]) (Figure 3B). NRM and CIR were comparable between groups; NRM HR was 3.19 (95%CI [0.40; 25.26]), with 5-year NRM of 3% (95%CI [0; 9]) for patients receiving maintenance vs. 9% (95%CI [2; 15]) in the non-maintenance group. (Figure 3C) CIR HR was 1.22 (95%CI [0.57; 2.62]), with 5-year CIR of 25% (95%CI [11; 40]) with maintenance vs. 37% (95%CI [24; 50]) in the non-maintenance group (Figure 3C). GRFS at 5-years was 43% (95%CI [27; 66]) with maintenance vs. 31% (95%CI [20; 47]) without maintenance (Figure 3D).

Similarly, in MRD-negative patients, maintenance was associated with improved OS (HR 2.64, 95%CI [1.05; 6.68], p=0.02) and RFS (HR 2.06, 95%CI [0.97; 4.35], p=0.04). At 5-years, OS was 86% (95%CI [75; 98]) with maintenance vs. 62% (95%CI [53; 73]) without (Figure 4A), and RFS was 78%

(95%CI [65; 93]) with maintenance vs. 53% (95%CI [44; 65]) without maintenance (Figure 4B). No statistically significant difference in NRM was observed between patients receiving and not receiving maintenance (HR 7.18, 95% CI [0.95; 54.58], p=0.057), with 5-year NRM of 3% (95% CI [0; 8]) with maintenance versus 23% (95% CI [0; 29]).(Figure 4C) Although not statistically significant, the point estimate suggests a lower NRM with maintenance. Similarly, no statistically significant difference in CIR was observed between groups (HR 1.18, 95% CI [0.52; 2.66], p=0.70), with 5-year CIR rates of 20% (95% CI [6; 33]) with maintenance versus 24% (95% CI [15; 32]) without.(Figure 4C). GRFS was also similar between groups (HR 1.59, 95%CI [0.87; 2.90], p=0.11), with 5-year GRFS of 58% (95%CI [41; 81]) with maintenance vs. 45% (95%CI [35; 58]) without maintenance (Figure 4D).

Exploratory Analysis Sorafenib vs Midostaurin

In the exploratory analysis by FLT3i type, no significant differences were observed when comparing Sorafenib vs. Midostaurin maintenance for any of the transplant outcomes. Results are summarized in Supplementary Figure 1.

Sorafenib Maintenance Analysis (Exploratory)

In the overall population, 5-year OS was 85% (95% CI [73;98]) with sorafenib versus 62% (95% CI [56;68]) without maintenance (HR 2.98, 95% CI [1.22;7.30], p=0.0045) (Figure 5A). Similarly, 5-year RFS was 84% (95% CI [73;97]) versus 55% (95% CI [48;62]) (HR 2.77, 95% CI [1.22;6.30], p=0.0043) (Figure 5B).

The 5-year cumulative incidence of relapse was 13% (95% CI [2;23]) in the sorafenib group and 28% (95% CI [22;34]) in the no-maintenance group (HR 1.97, 95% CI [0.81;4.80], p=0.137). Corresponding 5-year NRM was 3% (95%

CI [0;9]) versus 17% (95% CI [12;22]) (HR 5.65, 95% CI [0.79;40.67], p=0.085) (Figure 5C).

In the exploratory analysis of MRD-Positive patients (sorafenib n=24, no maintenance n=138), none of the comparisons reached statistical significance for OS, RFS, CIR, or NRM. (Supplementary Figure 2)

In the exploratory analysis of MRD-Negative patients, Sorafenib Maintenance Subgroup Analysis (sorafenib n=24, no maintenance n=138), the 5-year OS was 90% (95% CI [77; 100]) in the sorafenib group versus 62% (95% CI [53; 73]) in the no maintenance group (HR 3.642, 95% CI [0.881; 15.053], p = 0.0284) (Supplementary Figure 3A). The 5-year RFS was 86% (95% CI [72; 100]) in the sorafenib group versus 53% (95% CI [44; 65]) in the no maintenance group (HR 3.094, 95% CI [0.963; 9.935], p = 0.0244) (Supplementary Figure 3B). There were no differences in

The 5-year NRM was 0% in the sorafenib group versus 23% (95% CI [14; 32]) in the no maintenance group (NRM analysis not calculable due to zero events in sorafenib group) (Supplementary Figure3C).

Discussion:

Our study of 523 patients with FLT3-mutated AML undergoing allo-HCT in CR1 shows that FLT3i maintenance was associated with significantly better post-transplant outcomes in this national real-world cohort. Specifically, FLT3i-mantenance was associated with superior OS and RFS, which remained significant on MVA, as well as lower NRM and improved GRFS, while VIR was comparable between the groups.

These findings align closely with prior prospective randomized trials. The SORMAIN trial demonstrated substantial benefits for sorafenib maintenance with significantly lower relapse or death compared to placebo (HR 0.39,

p=0.013) and marked improvements in RFS at 24 months (85.0% vs. 53.3%, p=0.002).[12] Similarly, the RADIUS trial reported a trend toward improved outcomes with midostaurin maintenance, although it did not reach statistical significance, highlighting a potential, albeit less pronounced, role for midostaurin compared to sorafenib.[15] Further, the large Chinese multicenter study by Xuan et al. reported significantly reduced relapse incidence and improved survival outcomes with sorafenib, reinforcing sorafenib's role as a standard maintenance option.[13] Extended 5-year follow-up data from Xuan et al. further confirmed these benefits with higher OS and lower relapse rates.[16] Additionally, the global Phase III MORPHO trial evaluating gilteritinib maintenance did not meet its primary endpoint across the entire population but suggested a greater benefit in MRD-positive patients.[14] Smaller phase studies of quizartinib and crenolanib confirmed feasibility and tolerability post-transplant, although definitive efficacy data remain limited.[17, 18]

In contrast to randomized trials and meta-analyses where reduced relapse is the principal driver of improved survival with FLT3i maintenance, we observed comparable CIR but substantially lower NRM in the maintenance group. Several factors likely explain this pattern. First, patients receiving maintenance were transplanted more recently, had better performance status, and more often had fully matched donors, introducing residual selection and era effects despite MVA adjustment. Second, the day+100 landmark design excludes early relapse events, which may attenuate detectable differences in CIR while leaving later NRM differences evident. Therefore, the lower NRM observed should be interpreted cautiously and primarily reflects selection rather than a direct therapeutic effect. This interpretation aligns with retrospective studies demonstrating no increase in NRM with FLT3i maintenance.[19-21] Our findings

complement smaller retrospective ‘real-world’ series, including the multicenter study by Shimony et al., in which 41 patients received post-transplant sorafenib (n=23) or midostaurin (n=18) and both TKIs were feasible and associated with encouraging survival outcomes.[22] Compared with such cohorts, our registry analysis includes a larger number of patients with longer follow-up but is subject to similar limitations in terms of non-standardized indication and residual confounding.

A particularly noteworthy finding in our study is the significant improvement in OS and RFS despite comparable CIR between maintenance and non-maintenance groups. The striking difference in NRM between groups (3% vs 17% at 5 years) appears to be a substantial contributor to the OS advantage. While patient selection factors likely play a role, emerging evidence suggests that FLT3i may enhance immune reconstitution and reduce infection-related mortality post-transplant. Mathew et al. demonstrated that sorafenib promotes IL-15 production, enhancing T-cell and NK cell function, which may improve infection control beyond just anti-leukemic effects. [23] These immunomodulatory benefits could help explain the reduced NRM observed in our maintenance cohort, providing a potential mechanistic explanation for the survival advantage despite comparable relapse rates. However, our registry analyses did not capture infection or cause-specific mortality data. Thus, the lower NRM observed is more likely explained by patient selection and era effects rather than direct protection from infections.

The role of MRD assessment in FLT3-mutated AML is particularly relevant in the post-transplant maintenance setting. Recent advances in next-generation sequencing and bioinformatics now enable highly sensitive detection of FLT3-ITD for MRD monitoring.[24] Although FLT3 mutations were historically

considered unsuitable MRD markers due to instability and heterogeneity, approximately 70% of FLT3-mutated AML cases harbor co-mutations amenable to MRD monitoring, most commonly NPM1 mutations or fusion genes.[25] Our observation of improved survival in MRD-positive patients receiving FLT3i maintenance is consistent with emerging evidence that FLT3 inhibitors effectively target persistent leukemic clones detected by sensitive MRD assays.[24, 26] MRD positivity after induction identifies patients at high relapse risk, and conversion from MRD-negative to MRD-positive status during follow-up strongly predicts inferior outcomes.[26] The MORPHO trial's greater benefit in MRD-positive patients suggests that maintenance therapy is particularly effective against molecularly detectable residual disease.[25, 27] This supports routine MRD assessment to guide risk-adapted post-transplant maintenance, including intensified or prolonged therapy for high-risk patients. Future trials should incorporate standardized MRD monitoring to define optimal timing, duration, and FLT3i selection based on dynamic MRD status.[24, 25]

Subgroup analyses in our cohort revealed consistent benefits of FLT3i maintenance irrespective of MRD status at transplant, with MRD-positive patients showing especially pronounced survival advantages. This aligns with findings from the MORPHO trial and the SORMAIN trial,[12, 14] advocating for the incorporation of MRD assessments in future trials to optimize personalized FLT3i therapy. The SORMAIN trial particularly highlighted significant benefits in MRD-positive patients and suggested benefits, although not statistically significant, in MRD-negative patients.[12] Notably, MRD-negative patients also benefited from maintenance therapy, with 5-year OS of 86% versus 62%

without maintenance, suggesting persistence of occult residual disease and a preventive effect of maintenance against subsequent relapse.

Our sorafenib subgroup analysis represents the first real-world large cohort study specifically examining sorafenib maintenance therapy after allogeneic hematopoietic cell transplantation in FLT3-ITD AML patients. This analysis of 50 patients receiving sorafenib maintenance versus 357 patients without maintenance provides crucial evidence for the clinical efficacy of sorafenib in the post-transplant setting and reveals important insights when compared to both our overall maintenance cohort and existing literature.

In our cohort, sorafenib was the most frequently used FLT3i and showed numerically strong associations with OS and RFS. However, subgroup numbers were limited, particularly for patients receiving gilteritinib, so these agent-specific findings are exploratory and require confirmation in prospective studies.

Our findings provide important real-world validation of prospective clinical trial results while revealing novel insights. The SORMAIN trial demonstrated substantial benefits for sorafenib maintenance with significantly lower relapse or death compared to placebo (HR 0.39, p=0.013) and marked improvements in RFS at 24 months (85.0% vs 53.3%, p=0.002).[12] Our analysis confirms the durability of these benefits with 5-year RFS of 84% versus 55% (HR 2.771, p=0.0043) and 5-year OS of 85% versus 62% (HR 2.979, p=0.0045), representing the longest follow-up data available for sorafenib maintenance in this population. The large Chinese multicenter study by Xuan et al. reported significantly reduced relapse incidence and improved survival outcomes with sorafenib,[13] with extended 5-year follow-up data confirming higher OS and lower relapse rates.[16] Our real-world cohort corroborates these findings with

consistent long-term benefits, validating the translation of controlled trial efficacy to routine clinical practice where patient selection, dosing, and duration may vary from protocol specifications.

A particularly important contrast with existing literature emerges from our MRD-stratified analysis. While the SORMAIN trial particularly highlighted significant benefits in MRD-positive patients and suggested non-significant benefits in MRD-negative patients,[12] our study demonstrates the opposite pattern. We observed significant benefits in MRD-negative patients (5-year OS: 90% vs 62%, HR 3.642, p=0.0284; RFS: 86% vs 53%, HR 3.094, p=0.0244) while MRD-positive patients showed numerical improvements that did not reach statistical significance, likely due to smaller sample size (n=19). This finding suggests that sorafenib maintenance may have broader applicability than previously demonstrated, providing substantial benefit even in patients achieving MRD-negative status post-transplant.

The absence of non-relapse mortality events among MRD-negative patients receiving sorafenib may be consistent with previously reported immunomodulatory effects of sorafenib, including IL-15-mediated enhancement of T-cell and NK-cell function,[23] but this observation remains hypothesis-generating and cannot be disentangled from selection and era effects in this registry analysis.

In this registry analysis, the favorable safety profile (5-year NRM 3% vs 17%) and superior outcomes compared with other FLT3 inhibitors support sorafenib as preferred post-transplant maintenance regardless of MRD status.

Direct comparison of sorafenib and midostaurin showed no differences in OS, RFS, NRM, CIR, or GRFS, likely due to small subgroups. However, when each was compared with no maintenance, sorafenib showed consistently

larger effect sizes, suggesting it may be the preferred agent pending larger comparative studies.

The therapeutic landscape for FLT3-mutated AML is evolving rapidly with the approval of quizartinib in the pre- and post-transplant setting. In this context, the role of sorafenib maintenance will likely be influenced by prior FLT3i exposure, patterns of resistance and toxicity, and comparative efficacy data. Our real-world findings suggest that sorafenib remains an effective option after allo-HCT, but future prospective studies are needed to determine how best to sequence sorafenib, quizartinib and other FLT3i across the transplant continuum.

Several limitations of our study warrant consideration. First, its retrospective nature introduces potential selection biases, particularly regarding which patients received maintenance therapy. Second, this is a retrospective registry analysis spanning 2011- 2023, a period during which indications for allo-HCT, supportive care, and availability of FLT3i changed substantially. Although we adjusted for year of transplant, residual era effects likely remain. In the early part of the study period almost no patients received maintenance, whereas in later years FLT3i became standard in many centers, reinforcing selection and era biases. In addition, Physicians were more likely to initiate FLT3i maintenance in patients with hematologic recovery, limited GVHD and preserved organ function, and drug access and reimbursement may have varied between centers and over time. These factors introduce substantial selection bias in favor of the maintenance group and likely contribute to the lower NRM and better survival we observed.”

The maintenance cohort was smaller than the non-maintenance group (n=116 vs n=407), limiting subgroup power. Interpretation is further constrained by

FLT3i heterogeneity (49% sorafenib, 37% midostaurin, 5% gilteritinib, 9% unknown) and exclusion of 404 patients with unknown maintenance status, which may have introduced selection bias. In addition, FLT3-ITD allelic ratio, which may influence benefit from maintenance, was not consistently available in the registry and could therefore not be incorporated into our analyses. Data on treatment at relapse, including subsequent FLT3i use and other targeted therapies, were not systematically collected, so we could not assess how prior maintenance influenced post-relapse management or outcomes.

The clinical implications of our findings are substantial. Our data supports the routine use of FLT3i maintenance after allo-HCT for FLT3-mutated AML in CR1, regardless of MRD status at transplant.

Meta-analyses by Fei et al. and Gagelmann et al. robustly confirm improved OS, RFS, and relapse prevention with FLT3i maintenance post-transplant.[28, 29] Retrospective analyses further validate these benefits, consistently showing improved OS, RFS, and reduced relapse without significant increases in NRM or toxicities.[19-21, 30-35] Additional retrospective evidence includes single-center studies demonstrating significant DFS and OS improvements upon adjustment for conditioning regimen and donor status,[36] further supporting FLT3i use post-transplant.

Collectively, these comprehensive findings across multiple study designs strongly support FLT3i maintenance as a critical therapeutic strategy to enhance survival outcomes in FLT3-mutated AML undergoing allo-HCT. Future studies should validate MRD-guided maintenance with serial monitoring, define the optimal post-transplant FLT3-i, determine maintenance duration using fixed versus MRD-adapted strategies, and refine patient selection using biomarkers beyond MRD.

In summary, FLT3i maintenance was associated with improved long-term outcomes in this real-world cohort. However, these results are hypothesis-generating and complement, evidence from prospective trials. Sorafenib was the most commonly used agent and showed favorable associations, but agent-specific differences require confirmation in adequately powered studies.

References:

1. Levis M. FLT3 mutations in acute myeloid leukemia: what is the best approach in 2013? Hematology Am Soc Hematol Educ Program. 2013;2013(1):220-226.
2. Daver N, Schlenk RF, Russell NH, Levis MJ. Targeting FLT3 mutations in AML: review of current knowledge and evidence. Leukemia. 2019;33(2):299-312.
3. Kottaridis PD, Gale RE, Frew ME, et al. The presence of a FLT3 internal tandem duplication in patients with acute myeloid leukemia (AML) adds important prognostic information to cytogenetic risk group and response to the first cycle of chemotherapy: analysis of 854 patients from the United Kingdom Medical Research Council AML 10 and 12 trials. Blood. 2001;98(6):1752-1759.
4. Thiede C, Steudel C, Mohr B, et al. Analysis of FLT3-activating mutations in 979 patients with acute myelogenous leukemia: association with FAB subtypes and identification of subgroups with poor prognosis: Presented in part at the 42nd Annual Meeting of the American Society of Hematology, December 1-5, 2000, San Francisco, CA (abstract 2334). Blood. 2002;99(12):4326-4335.
5. Dohner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood. 2017;129(4):424-447.
6. Dohner H, Wei AH, Appelbaum FR, et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. Blood. 2022;140(12):1345-1377.
7. Schlenk RF, Kayser S, Bullinger L, et al. Differential impact of allelic ratio and insertion site in FLT3-ITD-positive AML with respect to allogeneic transplantation. Blood. 2014;124(23):3441-3449.
8. Stone RM, Mandrekar SJ, Sanford BL, et al. Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation. N Engl J Med. 2017;377(5):454-464.
9. Perl AE, Martinelli G, Cortes JE, et al. Gilteritinib or chemotherapy for relapsed or refractory FLT3-mutated AML. N Engl J Med. 2019;381(18):1728-1740.
10. Brunet S, Labopin M, Esteve J, et al. Impact of FLT3 internal tandem duplication on the outcome of related and unrelated hematopoietic transplantation for adult acute myeloid leukemia in first remission: a retrospective analysis. J Clin Oncol. 2012;30(7):735-741.
11. Deol A, Sengsayadeth S, Ahn KW, et al. Does FLT3 Mutation Impact Survival after Hematopoietic Cell Transplant for AML? A CIBMTR Analysis. Cancer. 2016;122(19):3005-3014.
12. Burchert A, Bug G, Fritz LV, et al. Sorafenib maintenance after allogeneic hematopoietic stem cell transplantation for acute myeloid leukemia with FLT3-internal tandem duplication mutation (SORMAIN). J Clin Oncol. 2020;38(26):2993-3002.
13. Xuan L, Wang Y, Huang F, et al. Sorafenib maintenance in patients with FLT3-ITD acute myeloid leukaemia undergoing allogeneic haematopoietic stem-cell transplantation: an open-label, multicentre, randomised phase 3 trial. Lancet Oncol. 2020;21(9):1201-1212.
14. Levis MJ, Hamadani M, Logan B, et al. Gilteritinib as post-transplant maintenance for AML with internal tandem duplication mutation of FLT3. J Clin Oncol. 2024;42(15):1766-1775.
15. Maziarz RT, Levis M, Patnaik MM, et al. Midostaurin after allogeneic stem cell transplant in patients with FLT3-internal tandem duplication-positive acute myeloid leukemia. Bone Marrow Transplant. 2021;56(5):1180-1189.
16. Xuan L, Wang Y, Yang K, et al. Sorafenib maintenance after allogeneic haemopoietic stem-cell transplantation in patients with FLT3-ITD acute myeloid leukaemia: long-term

follow-up of an open-label, multicentre, randomised, phase 3 trial. Lancet Haematol. 2023;10(8):e600-e611.
17. Sandmaier BM, Khaled S, Oran B, Gammon G, Trone D, Frankfurt O. Results of a phase 1 study of quizartinib as maintenance therapy in subjects with acute myeloid leukemia in remission following allogeneic hematopoietic stem cell transplant. Am J Hematol. 2018;93(2):222-231.
18. Oran B, Marin D, Bashir Q, et al. Long-Term Follow-up of Crenolanib Maintenance after Allogeneic Transplantation in Newly Diagnosed and Relapsed FLT3 Mutated AML. Blood. 2024;144(Supplement 1):1497.
19. Brunner AM, Li S, Fathi AT, et al. Haematopoietic cell transplantation with and without sorafenib maintenance for patients with FLT3-ITD acute myeloid leukaemia in first complete remission. Br J Haematol. 2016;175(3):496-504.
20. Bazarbachi A, Labopin M, Battipaglia G, et al. Allogeneic Stem Cell Transplantation for FLT3-Mutated Acute Myeloid Leukemia: In vivo T-Cell Depletion and Posttransplant Sorafenib Maintenance Improve Survival. A Retrospective Acute Leukemia Working Party-European Society for Blood and Marrow Transplant Study. Clin Hematol Int. 2019;1(1):58-74.
21. Chappell G, Geer M, Gatza E, et al. Maintenance sorafenib in FLT3-ITD AML following allogeneic HCT favorably impacts relapse and overall survival. Bone Marrow Transplant. 2019;54(9):1518-1520.
22. Shimony S, Yeshurun M, Wolach O, et al. Post-transplantation maintenance with sorafenib or midostaurin for FLT3 positive AML patients-a multicenter retrospective observational study. Leuk Lymphoma. 2021;62(10):2475-2481.
23. Mathew NR, Baumgartner F, Braun L, et al. Sorafenib promotes graft-versus-leukemia activity in mice and humans through IL-15 production in FLT3-ITD-mutant leukemia cells. Nat Med. 2018;24(3):282-291.
24. Othman J, Potter N, Mokretar K, et al. FLT3 inhibitors as MRD-guided salvage treatment for molecular failure in FLT3 mutated AML. Leukemia. 2023;37(10):2066-2072.
25. Reikvam H, Dillon R. Revisiting the role of measurable residual disease in FLT3 mutated acute myelogenous leukemia. Expert Rev Hematol. 2024;17(4-5):103-106.
26. Rücker FG, Bullinger L, Cocciardi S, et al. Measurable residual disease monitoring in AML with FLT3-ITD treated with intensive chemotherapy plus midostaurin. Blood Adv. 2024;8(23):6067-6080.
27. Levis MJ, Hamadani M, Logan BR, et al. BMT CTN Protocol 1506: A phase 3, trial of gilteritinib, as maintenance therapy after allogeneic hematopoietic stem cell transplantation in patients with FLT3-ITD+ AML. Blood. 2019;134(Supplement_1):4602.
28. Gagelmann N, Wolschke C, Klyuchnikov E, Christopeit M, Ayuk F, Kröger N. TKI maintenance after stem-cell transplantation for FLT3-ITD positive acute myeloid leukemia: a systematic review and meta-analysis. Frontiers Immunol. 2021;12:630429.
29. Fei X, Zhang S, Gu J, Wang J. FLT3 inhibitors as maintenance therapy post allogeneic hematopoietic stem cell transplantation in acute myeloid leukemia patients with FLT3 mutations: A meta-analysis. Cancer Med. 2023;12(6):6877-6888.
30. Battipaglia G, Massoud R, Ahmed SO, et al. Efficacy and Feasibility of Sorafenib as a Maintenance Agent After Allogeneic Hematopoietic Stem Cell Transplantation for Fms-like Tyrosine Kinase 3 Mutated Acute Myeloid Leukemia: An Update. Clin Lymphoma Myeloma Leuk. 2019;19(8):506-508.
31. Battipaglia G, Ruggeri A, Massoud R, et al. Efficacy and feasibility of sorafenib as a maintenance agent after allogeneic hematopoietic stem cell transplantation for Fms-like tyrosine kinase 3-mutated acute myeloid leukemia. Cancer. 2017;123(15):2867-2874.

32. Griffin JD, Song Y, Yang H, Freimark J, Shah MV. Post-transplant maintenance therapy in patients with FLT3-mutated acute myeloid leukemia: Real-world treatment patterns and outcomes. Eur J Haematol. 2021;107(5):553-565.
33. Shi J, Cao L, Luo Y, et al. Maintenance sorafenib is superior to prophylactic donor lymphocyte infusion at improving the prognosis of acute myeloid leukemia with FMS-like tyrosine kinase 3 internal tandem duplication after allogeneic hematopoietic stem cell transplantation. Bone Marrow Transplant. 2021;56(1):293-296.
34. Diral E, Furnari G, Bruno A, et al. Sorafenib maintenance in FLT3-ITD mutated AML after allogeneic HCT: a real-world, single-center experience. Front Oncol. 2024;14(1391743.
35. Aydin S, Passera R, Scaldaferri M, et al. Sorafenib maintenance after hematopoietic stem cell transplantation improves outcome of FLT3-ITD-mutated acute myeloid leukemia. Int J Hematol. 2022;116(6):883-891.
36. He G, Belmont E, Karrison T, et al. FLT3 inhibitor maintenance after allogeneic stem cell transplantation in FLT3-mutated acute myeloid leukemia (AML) patients. Ann Transl Med. 2024;12(3):49.

Table 1: Patients Donor and Transplant characteristics

Variable	Value	Total N(%)	Yes N(%)	No N(%)
Age	Median (Range)	54 (18-77)	53 (18-70)	55 (20-77)
Sex	Female	276 (53%)	64 (55%)	212 (52%)
	Male	247 (47%)	52 (45%)	195 (48%)
ECOG	0	354 (68%)	79 (68%)	275 (68%)
	1	137 (26%)	35 (30%)	102 (25%)
	2	8 (2%)	0 (0%)	8 (2%)
	3	1 (0%)	0 (0%)	1 (0%)
	Unknown	23 (4%)	2 (2%)	21 (5%)
HCT-CI (NA if unknown)	0	236 (45%)	61 (53%)	175 (43%)
	2	28 (5%)	2 (2%)	26 (6%)
	3	35 (7%)	8 (7%)	27 (7%)
	4	8 (2%)	2 (2%)	6 (1%)
	5	18 (3%)	3 (3%)	15 (4%)
	6	6 (1%)	3 (3%)	3 (1%)
	7	2 (0%)	1 (1%)	1 (0%)

	8	2 (0%)	0 (0%)	2 (0%)
	10	1 (0%)	0 (0%)	1 (0%)
	Unknown	187 (36%)	36 (31%)	151 (37%)
HCT-CI (0 if unknown)	0	288 (55%)	72 (62%)	216 (53%)
	1	52 (10%)	10 (9%)	42 (10%)
	2	54 (10%)	7 (6%)	47 (12%)
	3	69 (13%)	14 (12%)	55 (14%)
	4	20 (4%)	5 (4%)	15 (4%)
	5	23 (4%)	3 (3%)	20 (5%)
	6	10 (2%)	4 (3%)	6 (1%)
	7	4 (1%)	1 (1%)	3 (1%)
	8	2 (0%)	0 (0%)	2 (0%)
	10	1 (0%)	0 (0%)	1 (0%)
Graft Source	BM (Bone Marrow)	25 (5%)	7 (6%)	18 (4%)
	CB (Cord Blood)	2 (0%)	2 (2%)	0 (0%)
	PB (Peripheral Blood)	496 (95%)	107 (92%)	389 (96%)
Type of allo-HCT	MMRD	36 (7%)	2 (2%)	34 (8%)

	MMUD	53 (10%)	8 (7%)	45 (11%)
	MRD	133 (25%)	32 (28%)	101 (25%)
	MUD	153 (29%)	42 (36%)	111 (27%)
	UD	148 (28%)	32 (28%)	116 (29%)
Conditioning Intensity	RIC	191 (37%)	27 (23%)	164 (40%)
	Unknown	17 (3%)	7 (6%)	10 (2%)
	MAC	315 (60%)	82 (71%)	233 (57%)
MRD at Tx	Negative	203 (39%)	49 (42%)	154 (38%)
	Positive	166 (32%)	47 (41%)	119 (29%)
	Unknown	154 (29%)	20 (17%)	134 (33%)
MRD 1 year post allo-HCT	Negative	263 (50%)	83 (72%)	180 (44%)
	Positive	46 (9%)	14 (12%)	32 (8%)
	Unknown	214 (41%)	19 (16%)	195 (48%)
ELN Risk Category	Adverse	83 (16%)	15 (13%)	68 (16%)
	Intermediate	440 (84%)	101 (87%)	339 (83%)

Legend: BM - Bone Marrow; CB - Cord Blood; PB - Peripheral Blood; ECOG - Eastern Cooperative Oncology Group performance status; HCT-CI - Hematopoietic Cell Transplantation-Comorbidity Index; MMRD - Mismatched Related Donor; MMUD - Mismatched Unrelated Donor; MRD - Matched Related Donor; MUD - Matched Unrelated Donor; UD - Unrelated Donor (includes MUD and MMUD); Tx - Transplantation; MRD at Tx - Minimal Residual Disease status at the time of transplantation; MRD 1 year after allo-HCT - Minimal Residual Disease status one year post-transplantation; Conditioning Intensity - MAC -myeloablative conditioning

Table 2: Univariable Analysis

	*HR [95%CI], p
OS	2.37 [1.39-4.07], 0.0005
RFS	1.81 [1.14-2.89], 0.0073
GRFS	1.45 [1.01-2.08], 0.039
Relapse	1.25 [0.76-2.08], 0.38
NRM	4.42 [1.37 -14.26],0.013

Legend: OS - Overall Survival; RFS - Relapse-Free Survival; GRFS - Graft-versus-Host Disease-Free, Relapse-Free Survival; NRM - Non-Relapse Mortality; 5Yr estimate - 5-year event rate with 95% confidence interval; HR - Hazard Ratio; CI - Confidence Interval. *-Hazard ratios, 95%CI and p refer to the overall follow-up period.

Table3: Multivariable Analysis

Variable	OS (HR [95% CI], p)	RFS (HR [95% CI], p)	GRFS (HR [95% CI], p)	Relapse (HR [95% CI], p)	NRM (HR [95% CI], p)
N	426	394	372	394	394
Events	119	128	171	87	41
Maintenance therapy (yes vs. no)	2.25 [1.28;3.95], p=0.005	1.72 [1.05;2.81], p=0.030	1.59 [1.06;2.40], p=0.025	1.30 [0.76;2.23], p=0.330	3.62 [1.08;12.11], p=0.037
Age (continuous)	1.01 [0.99;1.03]	1.00 [0.98;1.01]	1.00 [0.99;1.01]	0.99 [0.97;1.00]	1.02 [0.98;1.06]
Sex (male vs. female)	1.37 [0.95;1.99]	1.09 [0.76;1.56]	1.00 [0.73;1.37]	0.80 [0.51;1.26]	1.95 [1.00;3.78]
Conditioning (MAC vs. non-MAC)	0.96 [0.65;1.43]	0.99 [0.67;1.45]	1.01 [0.72;1.43]	0.91 [0.57;1.43]	1.08 [0.53;2.22]
ECOG (>0 vs. 0)	1.39 [0.94;2.07]	1.30 [0.89;1.90]	1.31 [0.94;1.82]	0.92 [0.57;1.49]	2.20 [1.12;4.33]
MRD at allo-HCT (positive vs. negative)	1.04 [0.66;1.64]	0.89 [0.58;1.38]	1.07 [0.74;1.55]	1.31 [0.80;2.14]	0.36 [0.14;0.95]
MRD at allo-HCT (unknown vs. negative)	1.22 [0.78;1.91]	0.99 [0.64;1.52]	1.07 [0.73;1.57]	0.99 [0.57;1.71]	1.03 [0.50;2.11]
Year of allo-HCT (continuous)	1.07 [0.99;1.16]	1.04 [0.97;1.12]	1.13 [1.05;1.21]	1.04 [0.96;1.13]	1.00 [0.86;1.15]
Donor type (MUD vs. MRD)	1.19 [0.72;1.96]	0.97 [0.60;1.58]	1.06 [0.72;1.57]	0.95 [0.54;1.67]	1.08 [0.44;2.64]
Donor type (MMUD vs. MUD)	1.73 [0.93;3.22]	1.12 [0.58;2.15]	1.07 [0.62;1.85]	0.81 [0.35;1.88]	1.72 [0.51;5.79]
Donor type (MMRD vs. MUD)	0.80 [0.33;1.93]	0.92 [0.42;2.00]	0.92 [0.49;1.74]	0.97 [0.42;2.27]	0.94 [0.19;4.70]
Donor type (UD vs. MUD)	1.30 [0.79;2.15]	1.22 [0.76;1.93]	0.75 [0.49;1.16]	1.12 [0.65;1.96]	1.28 [0.53;3.08]
ELN (adverse vs. intermediate)	0.53 [0.30;0.97]	0.80 [0.48;1.34]	1.05 [0.70;1.58]	1.12 [0.62;2.03]	0.36 [0.11;1.16]

Legend: OS - Overall Survival; RFS - Relapse-Free Survival; GRFS - GVHD-Free, Relapse-Free Survival; NRM - Non-Relapse Mortality; MRD - Minimal Residual Disease; allo-HCT - allogeneic hematopoietic cell transplantation; ECOG - Eastern Cooperative Oncology Group performance status; MUD - Matched Unrelated Donor; MRD - Matched Related Donor; MMUD - Mismatched Unrelated Donor; MMRD - Mismatched Related Donor; UD - Unrelated Donor (includes MUD and MMUD); ELN - European LeukemiaNet risk classification (2022)

Figure Legends:

- **Figure 1: Overall survival and relapse-free survival**
  - 1A: Overall survival in the entire cohort
  - 1B: Overall survival, maintenance therapy versus no maintenance therapy
  - 1C: Relapse-free survival in the entire cohort
  - 1D: Relapse-free survival, maintenance therapy versus no maintenance therapy

- **Figure 2: Non-relapse mortality, cumulative incidence of relapse, and graft-versus-host disease- and relapse-free survival**
  - 2A: Non-relapse mortality and cumulative incidence of relapse in the entire cohort
  - 2B: Non-relapse mortality and cumulative incidence of relapse, maintenance therapy versus no maintenance therapy
  - 2C: Graft-versus-host disease- and relapse-free survival in the entire cohort
  - 2D: Graft-versus-host disease- and relapse-free survival, maintenance therapy versus no maintenance therapy

- **Figure 3: Measurable residual disease-positive subgroup analysis**
  - 3A: Overall survival, maintenance therapy versus no maintenance therapy
  - 3B: Relapse-free survival, maintenance therapy versus no maintenance therapy

- 3C: Non-relapse mortality and cumulative incidence of relapse, maintenance therapy versus no maintenance therapy
- 3D: Graft-versus-host disease- and relapse-free survival, maintenance therapy versus no maintenance therapy

- **Figure 4: Measurable residual disease-negative subgroup analysis**
  - 4A: Overall survival, maintenance therapy versus no maintenance therapy
  - 4B: Relapse-free survival, maintenance therapy versus no maintenance therapy
  - 4C: Non-relapse mortality and cumulative incidence of relapse, maintenance therapy versus no maintenance therapy
  - 4D: Graft-versus-host disease- and relapse-free survival, maintenance therapy versus no maintenance therapy

- **Figure 5: Sorafenib maintenance versus no maintenance in the overall population**
  - 5A: Overall survival, sorafenib maintenance versus no maintenance
  - 5B: Relapse-free survival, sorafenib maintenance versus no maintenance
  - 5C: Non-relapse mortality and cumulative incidence of relapse, sorafenib maintenance versus no maintenance

Figure 1

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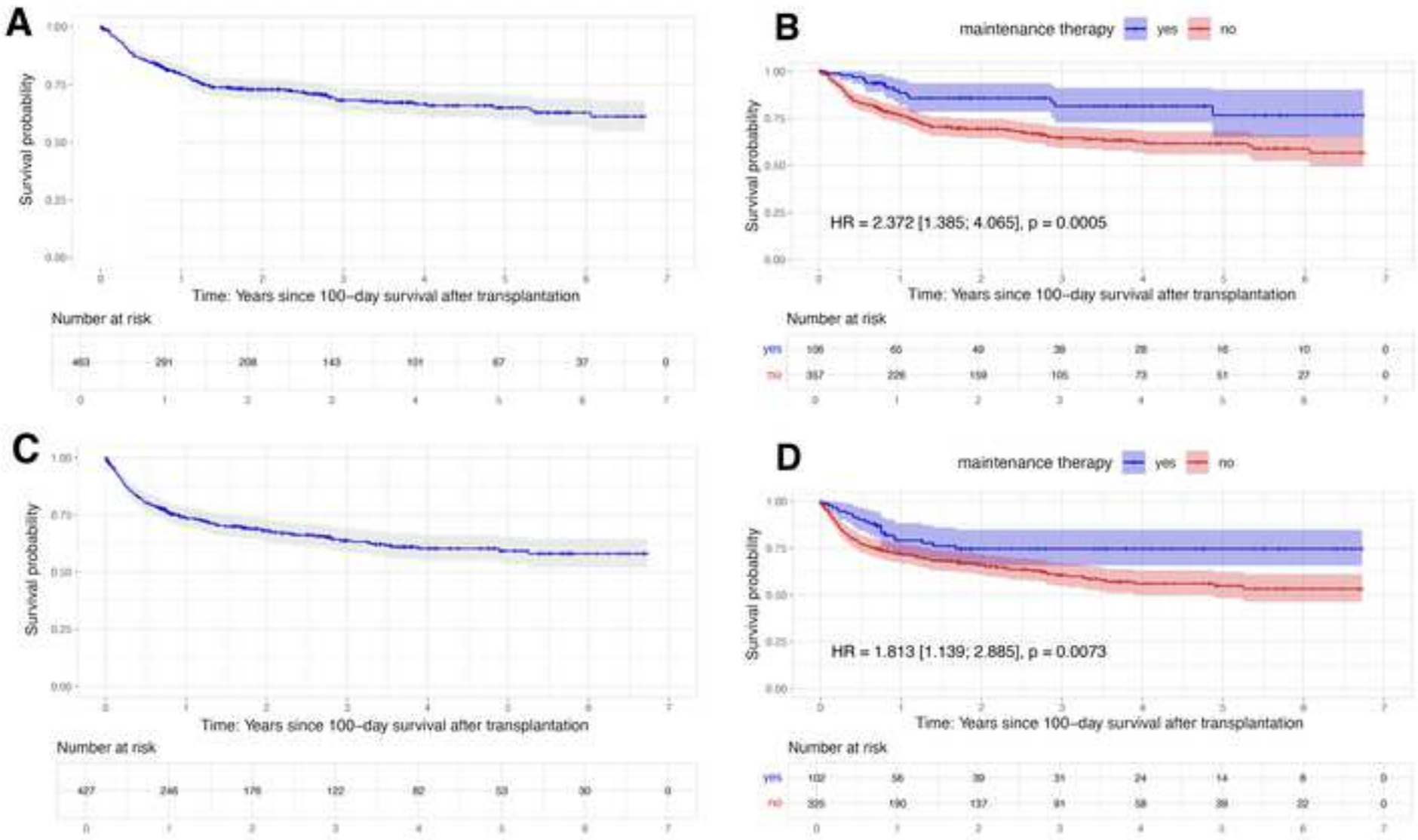

Figure 2

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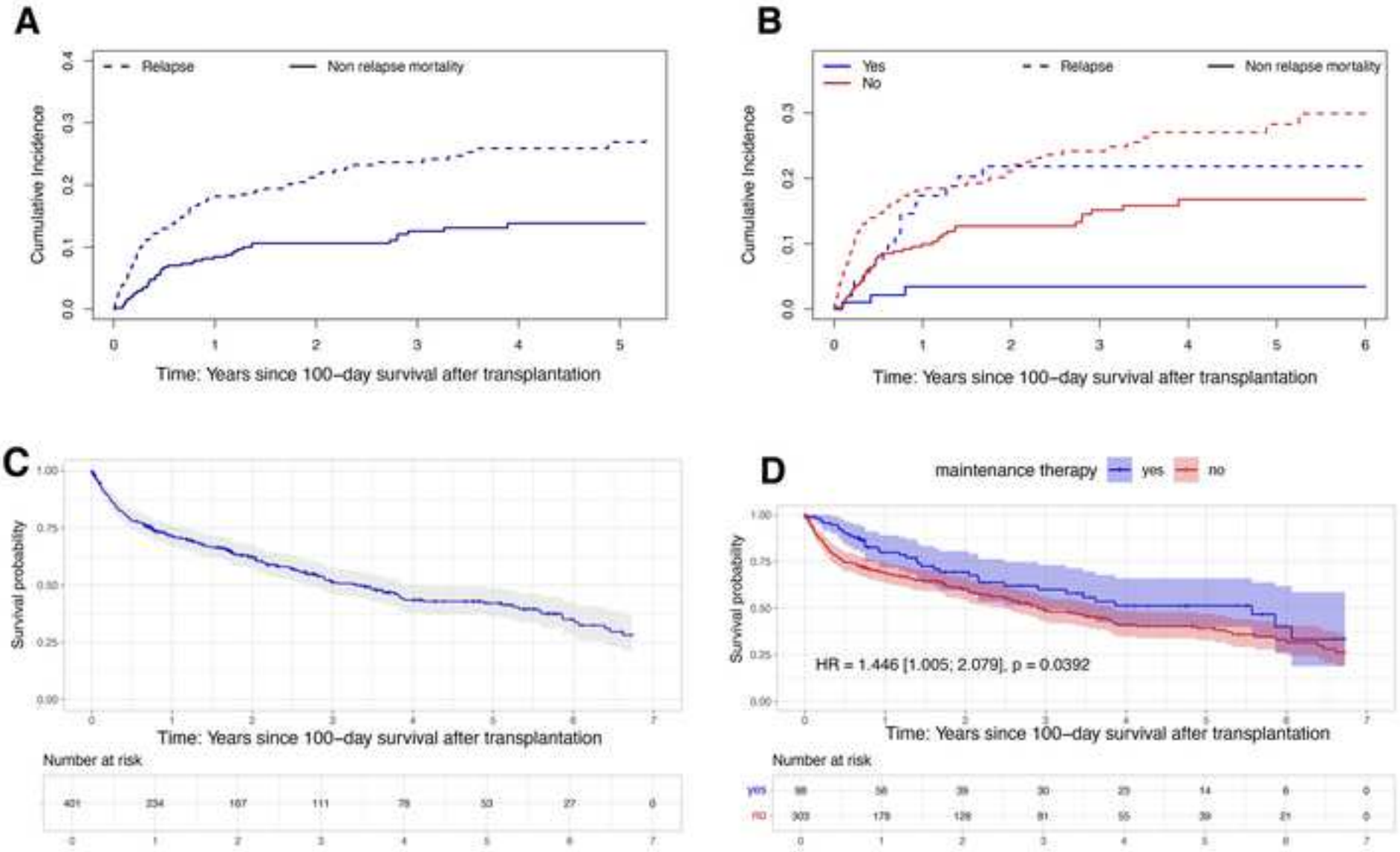

Figure 3

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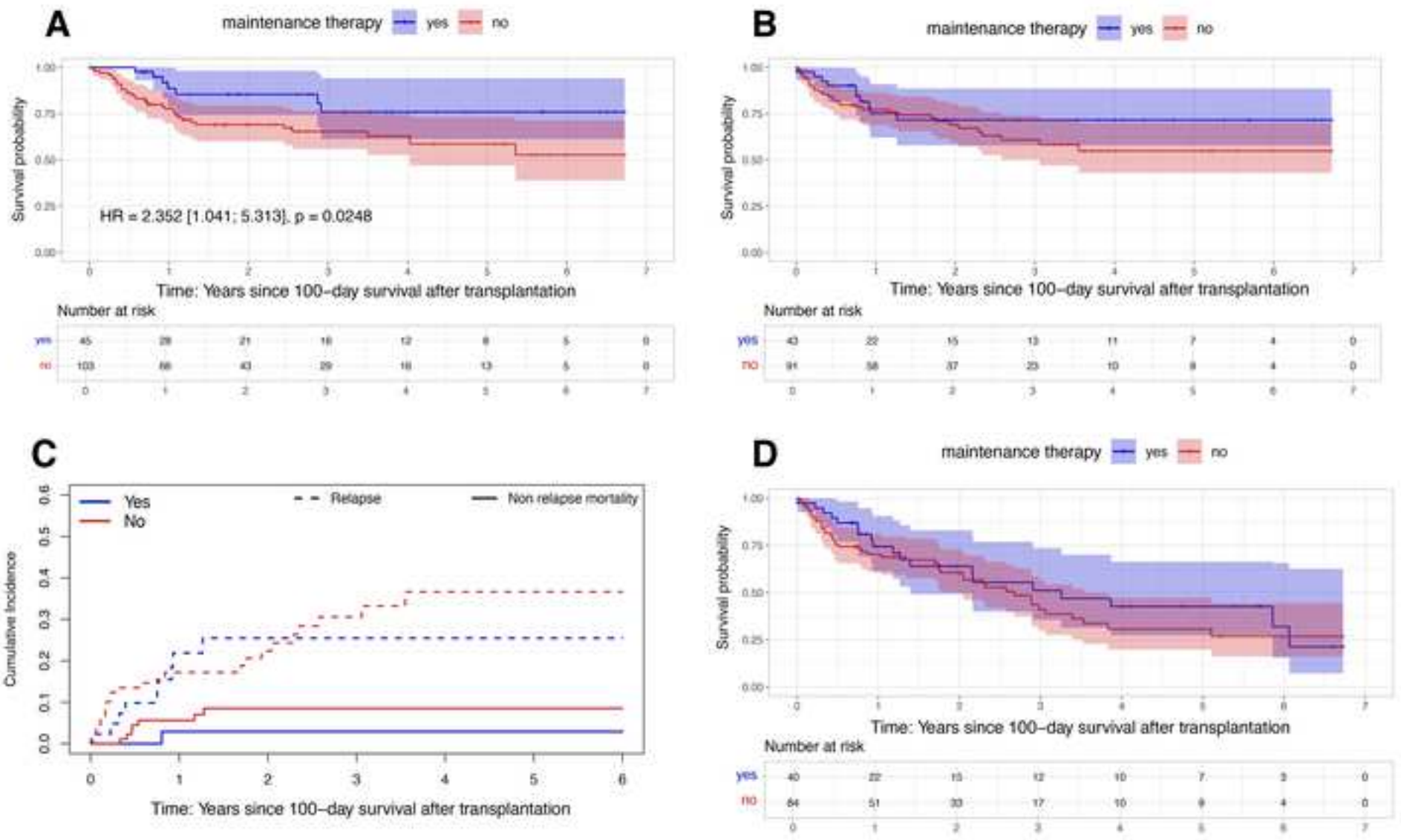

Figure 4

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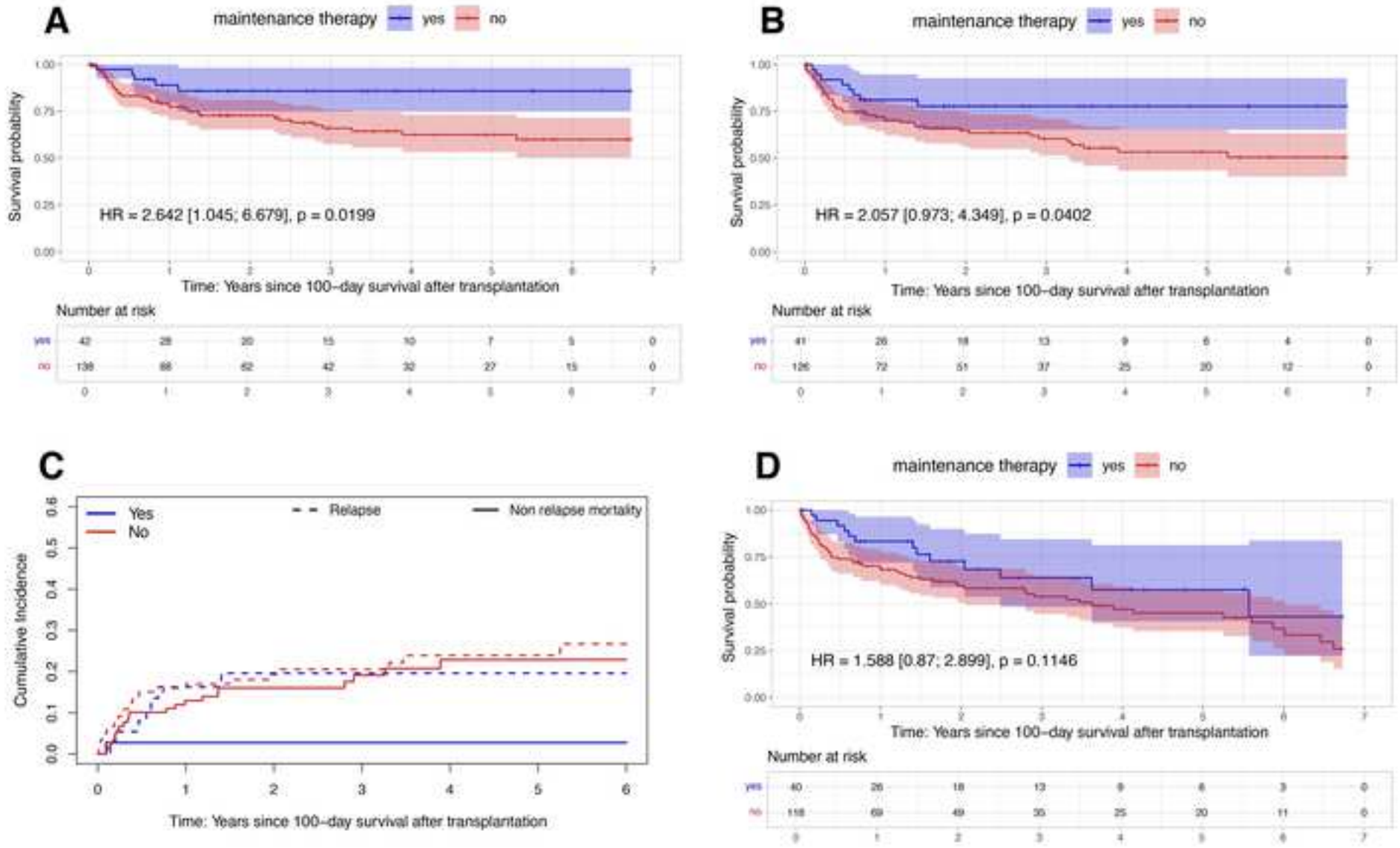

Figure 5

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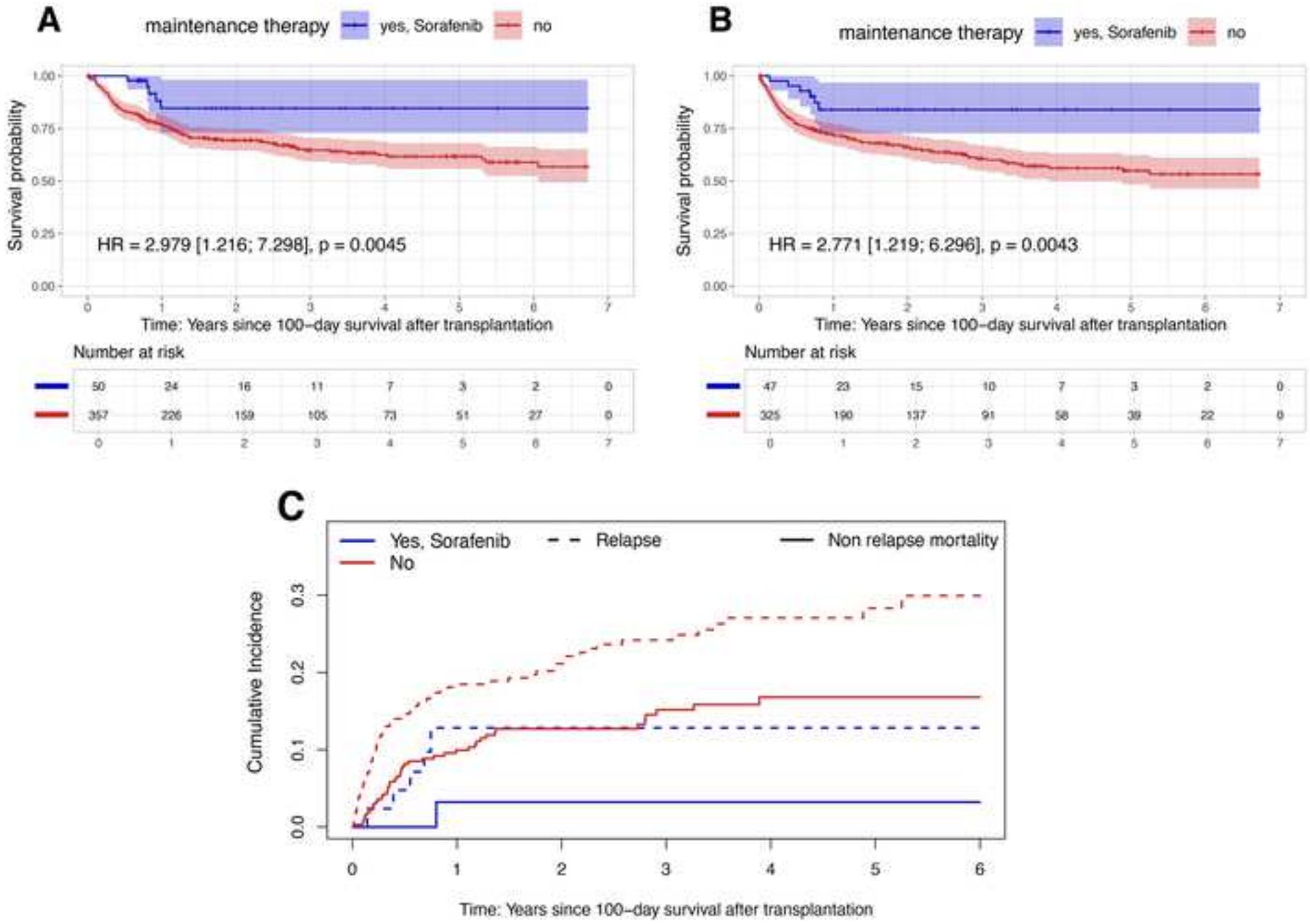


Appendix: DRST members contributing to this study

Professor Nicolaus Kröger, Universitätsklinikum Hamburg-Eppendorf, 85 patients

Professor Thomas Schroeder, Universitätsklinikum Essen, 48 patients

Professor Igor Wolfgang Blau, Charité - Universitätsmedizin Berlin, 45 patients

Professor Matthias Stelljes, Universitätsklinikum Münster, 44 patients

Professor Matthias Eder, Med. Hochschule Hannover, 42 patients

Dr. Gesine Bug, Universitätsklinikum Frankfurt (Main), 37 patients

Professor Wolfgang Bethge, Universitätsklinikum Tübingen, 36 patients

Professor Robert Zeiser, Universitätsklinikum Freiburg, 35 patients

Dr. Eva Wagner-Drouet, Universitätsmedizin Mainz, 34 patients

Professor Peter Dreger, Universitätsklinikum Heidelberg, 31 patients

Professor Gerald Wulf, Universitätsklinik Göttingen, 30 patients

Dr. Elisa Sala, Universitätsklinikum Ulm, 27 patients

Dr. Johanna Tischer, Klinikum der Universität München - Großhadern, 27 patients

Professor Inken Hilgendorf, Universitätsklinikum Jena, 27 patients

Professor Christof Scheid, Universitätsklinikum Köln, 27 patients

Professor Andreas Burchert, Universitätsklinik Marburg, 27 patients

Professor Matthias Edinger, Universitätsklinikum Regensburg, 27 patients

Professor Friedrich Stölzel, Universitätsklinikum Kiel, 23 patients

Professor Guido Kobbe, Universitätsklinikum Düsseldorf, 22 patients

Professor Uwe Platzbecker, Universitätsklinikum Leipzig, 21 patients

Dr. Jörg Thomas Bittenbring, Universitätsklinikum Homburg (Saar), 21 patients

Professor Johannes Schetelig, Universitätsklinikum Carl Gustav Carus a. d. TU Dresden, 20 patients

Dr. Tobias Holderried, Universitätsklinikum Bonn, 18 patients

Professor Michael Kiehl, Klinikum Frankfurt (Oder), 17 patients

Professor Mark Ringhoffer, Städt. Klinikum Karlsruhe gGmbH, 16 patients

Dr. Julia Winkler, Universitätsklinikum Erlangen, 16 patients

Dr. Judith Niederland, Helios Klinikum Berlin-Buch, 15 patients

Professor Christoph Schmid, Universitätsklinikum Augsburg, 14 patients

Dr. Mareike Verbeek, Klinikum rechts der Isar der TU München, 14 patients

Professor Roland Schroers, Ruhr Universität Bochum, 12 patients

Dr. Stefan Klein, Universitätsmedizin Mannheim, 12 patients

Dr. Stefan Kaun, Klinikum Bremen-Mitte, 12 patients

Professor Lutz P. Müller, Universitätsklinikum Halle (Saale), 11 patients

Dr. Denise Walther, Universitätsklinikum Magdeburg, 11 patients

Professor Edgar Jost, Universitätsklinik RWTH Aachen, 10 patients

Dr. Martin Kaufmann, Robert-Bosch-Krankenhaus Stuttgart, 8 patients

Dr. Kerstin Schäfer-Eckart, Klinikum Nürnberg Nord, 8 patients

Dr. Jakob Maucher, Diakonie-Klinikum Stuttgart, 7 patients

Dr. Frederike Wortmann, Universitätsklinikum Schleswig-Holstein / Campus Lübeck, 7 patients

Professor William Krüger, Universitätsklinikum Greifswald, 6 patients

Professor Angela Krackhardt, Malteser Krankenhaus Flensburg, 6 patients

Dr. Tobias Bartscht, Helios Klinikum Schwerin, 5 patients

Professor Gerald Illerhaus, Katharinenhospital Stuttgart, 4 patients

Dr. Arne Brecht, DKD HELIOS Klinik Wiesbaden, 4 patients

Dr. Ute Wieschermann, HELIOS Klinikum Duisburg GmbH, 4 patients

Dr. Mareike Dürholt, KEM - Kliniken Essen-Mitte, Evang. Krankenhaus Essen-Werden, 4 patients

Dr. Daniel Teschner, Universitätsklinikum Würzburg, 3 patients

Professor Jochen Casper, Klinikum Oldenburg AöR, 3 patients

Dr. Anke Morgner, Klinikum Chemnitz, 2 patients

Dr. Ralf Georg Meyer, Gem. Transpl. Dortmund-Mitte, 2 patients

Dr. Johannes Lakner, Universitätsmedizin Rostock, 2 patients

Professor Ahmet Elmaagacli, Asklepios Klinik St. Georg Hamburg, 1 patien

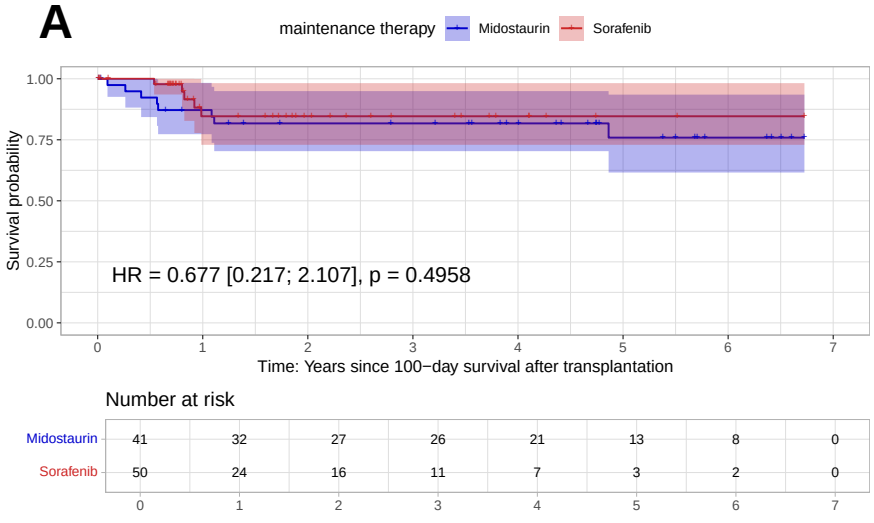
Supplementary Figures Legend

- **Supplementary Figure 1: Exploratory analysis comparing sorafenib and midostaurin**
    - 1A: Overall survival
    - 1B: Relapse-free survival
    - 1C: Non-relapse mortality and cumulative incidence of relapse
    - 1D: Graft-versus-host disease and relapse-free survival

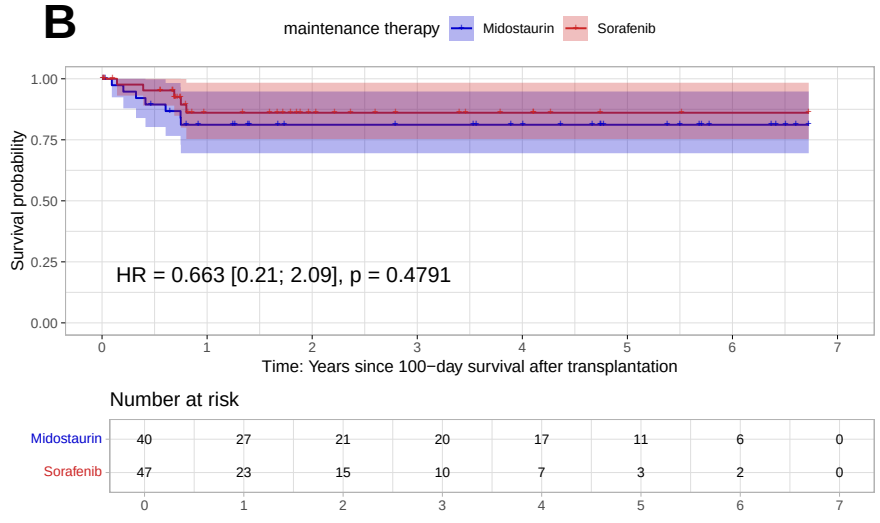
- **Supplementary Figure 2: Exploratory analysis of sorafenib maintenance versus no maintenance in the minimal residual disease positive subgroup**
    - 2A: Overall survival, sorafenib maintenance versus no maintenance
    - 2B: Relapse-free survival, sorafenib maintenance versus no maintenance
    - 2C: Non-relapse mortality and cumulative incidence of relapse, sorafenib maintenance versus no maintenance

- **Supplementary Figure 3: Exploratory analysis of sorafenib maintenance versus no maintenance in the minimal residual disease negative subgroup**
    - 3A: Overall survival, sorafenib maintenance versus no maintenance
    - 3B: Relapse-free survival, sorafenib maintenance versus no maintenance
    - 3C: Non-relapse mortality and cumulative incidence of relapse, sorafenib maintenance versus no maintenance

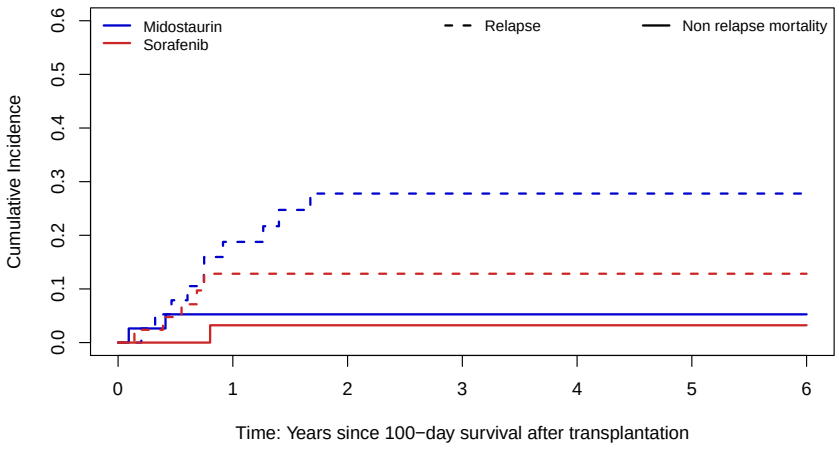
A


maintenance therapy
Midostaurin
Sorafenib
Survival probability
1.00
0.75
0.50
0.25
0.00
HR = 0.677 [0.217; 2.107], p = 0.4958
0
1
2
3
4
5
6
7
Time: Years since 100−day survival after transplantation
Number at risk
Midostaurin 41 32 27 26 21 13 8 0
Sorafenib 50 24 16 11 7 3 2 0

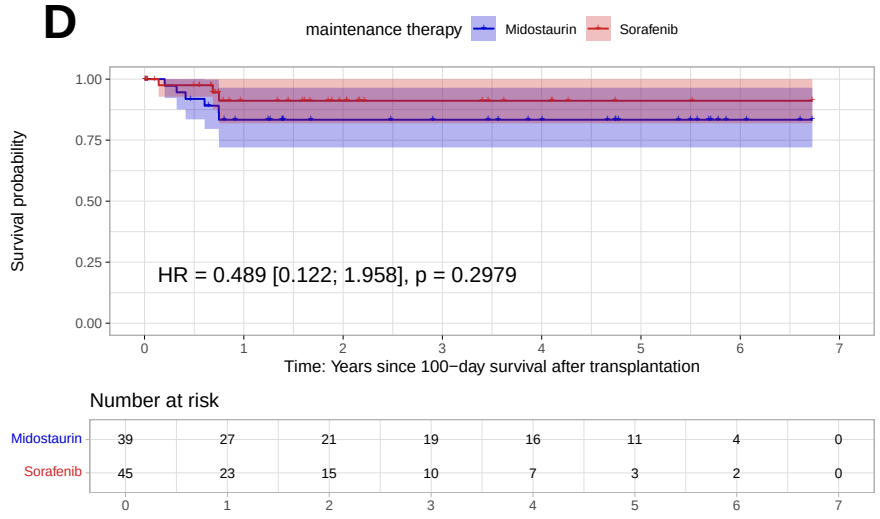
B


maintenance therapy
Midostaurin
Sorafenib
Survival probability
1.00
0.75
0.50
0.25
0.00
HR = 0.663 [0.21; 2.09], p = 0.4791
0
1
2
3
4
5
6
7
Time: Years since 100−day survival after transplantation
Number at risk
Midostaurin 40 27 21 20 17 11 6 0
Sorafenib 47 23 15 10 7 3 2 0

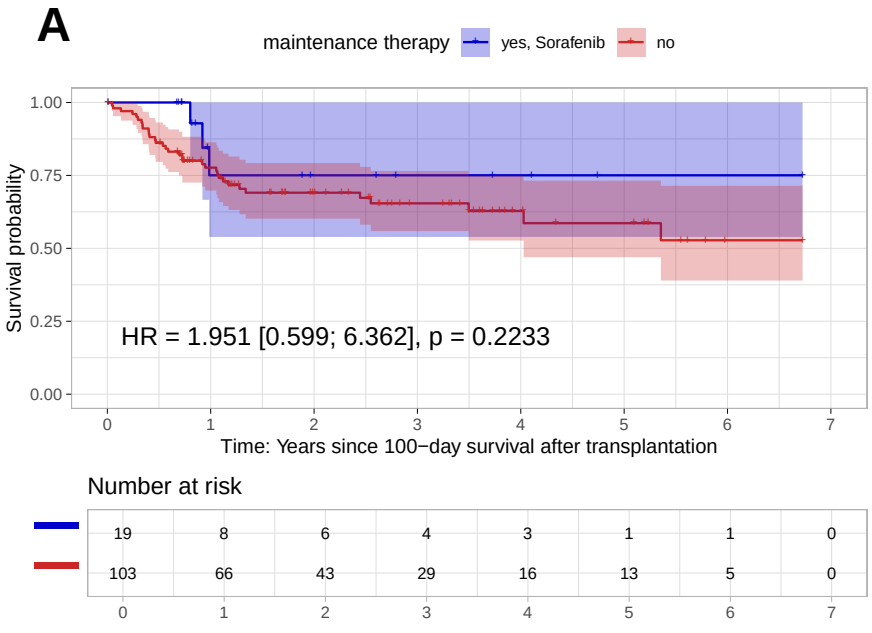
C


Midostaurin
Sorafenib
Relapse
Non relapse mortality
Cumulative Incidence
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0
1
2
3
4
5
6
Time: Years since 100−day survival after transplantation

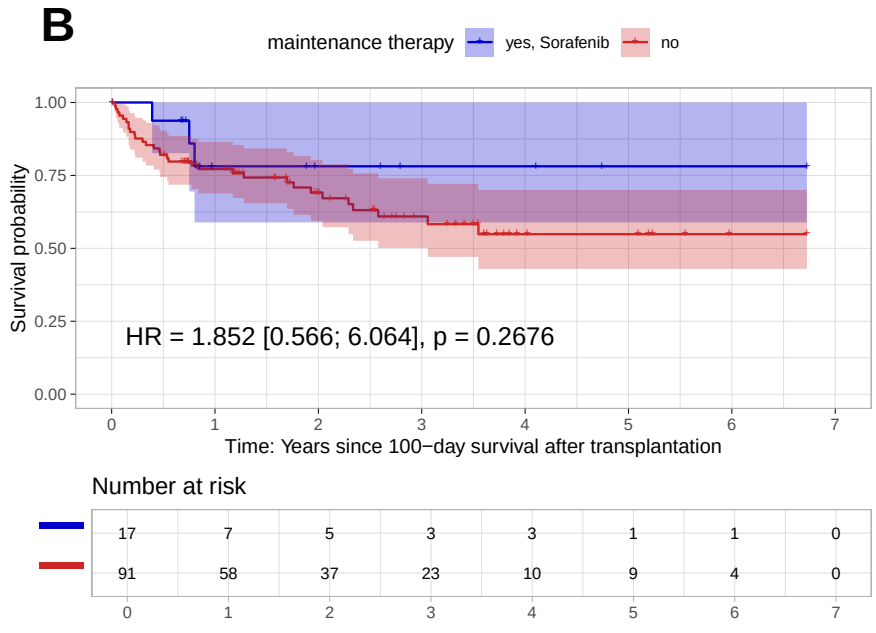
D


maintenance therapy
Midostaurin
Sorafenib
Survival probability
1.00
0.75
0.50
0.25
0.00
HR = 0.489 [0.122; 1.958], p = 0.2979
0
1
2
3
4
5
6
7
Time: Years since 100−day survival after transplantation
Number at risk
Midostaurin 39 27 21 19 16 11 4 0
Sorafenib 45 23 15 10 7 3 2 0

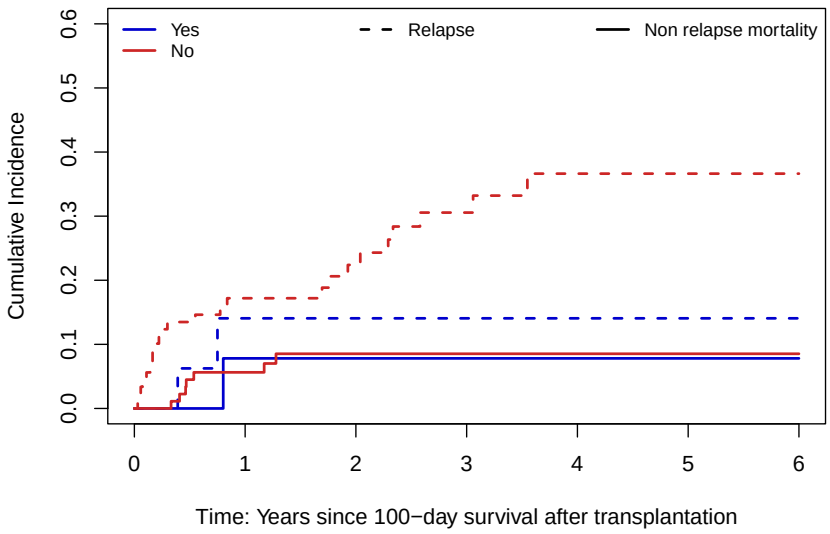
A


maintenance therapy
yes, Sorafenib
no
Survival probability
1.00
0.75
0.50
0.25
0.00
HR = 1.951 [0.599; 6.362], p = 0.2233
0
1
2
3
4
5
6
7
Time: Years since 100−day survival after transplantation
Number at risk
19 8 6 4 3 1 1 0
103 66 43 29 16 13 5 0

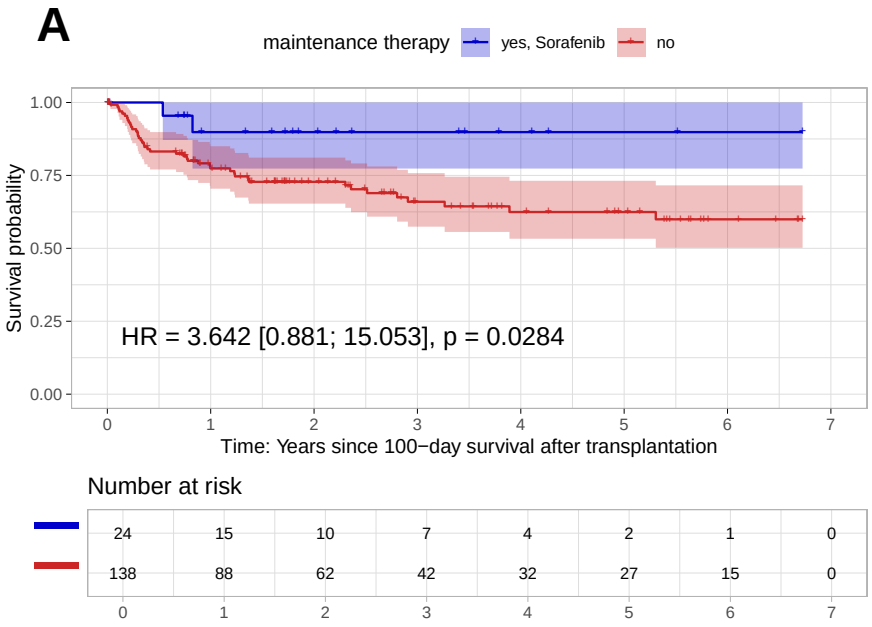
B


maintenance therapy
yes, Sorafenib
no
Survival probability
1.00
0.75
0.50
0.25
0.00
HR = 1.852 [0.566; 6.064], p = 0.2676
0
1
2
3
4
5
6
7
Time: Years since 100−day survival after transplantation
Number at risk
17 7 5 3 3 1 1 0
91 58 37 23 10 9 4 0

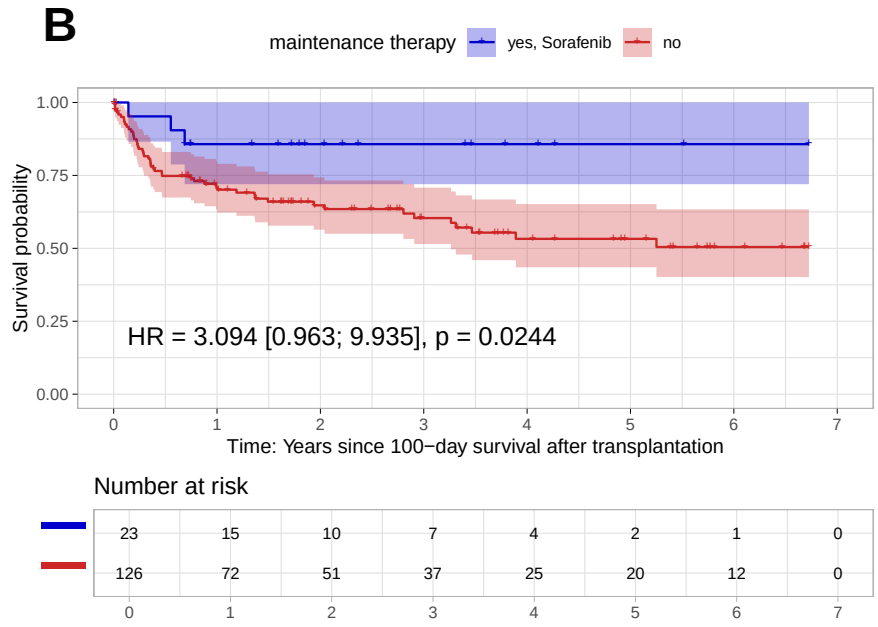
C


Yes
No
Relapse
Non relapse mortality
Cumulative Incidence
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0
1
2
3
4
5
6
Time: Years since 100−day survival after transplantation

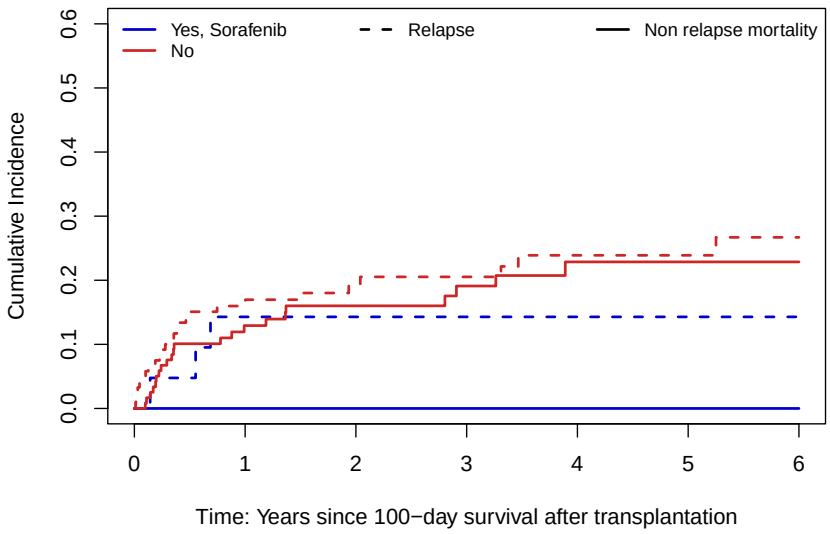
A


maintenance therapy
yes, Sorafenib
no
Survival probability
1.00
0.75
0.50
0.25
0.00
HR = 3.642 [0.881; 15.053], p = 0.0284
0
1
2
3
4
5
6
7
Time: Years since 100−day survival after transplantation
Number at risk
24 15 10 7 4 2 1 0
138 88 62 42 32 27 15 0

B


maintenance therapy
yes, Sorafenib
no
Survival probability
1.00
0.75
0.50
0.25
0.00
HR = 3.094 [0.963; 9.935], p = 0.0244
0
1
2
3
4
5
6
7
Time: Years since 100−day survival after transplantation
Number at risk
23 15 10 7 4 2 1 0
126 72 51 37 25 20 12 0

C


Yes, Sorafenib
No
Relapse
Non relapse mortality
Cumulative Incidence
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0
1
2
3
4
5
6
Time: Years since 100−day survival after transplantation