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Marked survival gains in patients ≤ 65 years with advanced-stage mantle cell lymphoma: a pooled analysis of six randomized phase III trials, 1996-2020

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Author contributions

LJ, EH, and MD designed the study, interpreted the results, and reviewed the manuscript. MD, ML, OH, JCK-N, JW, JD, VV, EG, MJ, MH, MT, UM, JR, OS, MGdS, VR, CS, WK, and MU coordinated the trials, collected the data, and reviewed the manuscript. MU and EH verified the underlying data. LJ conducted data analyses and

wrote the manuscript. All authors approved the final version of the manuscript.

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Data sharing statement

Individual participant data that underlie the results reported in this article, after de-identification may be shared following article publication upon request sent to the corresponding author based on a scientific collaboration.

Abstract

Mantle cell lymphoma (MCL) remains a challenging and generally incurable disease. We aimed to evaluate survival trends in advanced-stage MCL over the past three decades, focusing on the impact of evolving first-line therapies. We pooled six randomized phase III trials of treatment-naïve, advanced-stage MCL patients enrolled between 1996 and 2020. Patients were grouped into four eras by enrollment period. Failure-free survival (FFS) and overall survival (OS) were compared across eras using Kaplan-Meier methods and Cox regression adjusted for MIPI and treatment. Dynamic survival trends were analyzed using penalized splines. Among 2,541 MCL patients, survival outcomes have improved steadily since 1996. In younger and transplant-eligible patients (≤ 65 years), median OS strongly increased from 4.9 years (5-year OS: 49%) in 1996–2000 to 13.8 years (73%) in 2004–2014 and was not reached (84%) in 2016–2020. In older and transplant-ineligible patients, median OS improved from 3.8 to 4.8 years (5-year OS: 40% to 49%) between 1996 and 2014. Dynamic trends revealed a sharp decline in treatment failure and mortality risk between 2000 and 2005, followed by sustained improvements. Patients receiving the same treatment regimens had comparable FFS and OS across eras. Adjusting for treatment eliminated most survival trends, underscoring the impact of rituximab, ASCT, high-dose cytarabine, and ibrutinib on survival improvements. In conclusion, OS in MCL has substantially improved over the past three decades, especially in younger patients, driven largely by improvements of first-line treatment. In older patients, despite significantly improved OS in recent decades, there remains an urgent need for further improvements.

Introduction

Mantle cell lymphoma (MCL) is an uncommon type of B-cell lymphoma accounting for about 3–10% of adult non-Hodgkin lymphoma cases.[1] It exhibits varied clinical presentations, from asymptomatic, indolent to highly aggressive cases with poor prognosis.[2] The incidence of MCL kept rising in the past decades and the recently reported annual incidence was 1–2 per 100,000 people.[3] The median age at diagnosis is about 70 years and the male/female ratio is 2–3:1.[4] Most patients present with stage III/IV disease with a rather aggressive clinical course, and the large majority requires treatment.[2]

The treatment landscape of MCL has been evolving since its international recognition as a distinct lymphoma subtype in 1992.[5] Before 2000, CHOP-based chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisone) was the most commonly used induction regimen,[6] until consolidation autologous stem cell transplantation (ASCT) was first introduced in younger patients.[7] After 2000, advancements were made by incorporating rituximab into the CHOP regimen,[8] followed by introducing intensified immunochemotherapy with a high-dose cytarabine-containing regimen before ASCT in younger patients,[9] and by rituximab maintenance in older patients.[10] The recent standard of care first-line treatment has been based on age and fitness – younger (≤ 65 years) and physically fit patients typically receive intensive immunochemotherapy with ASCT, while older (> 65 years) or unfit patients are treated with combined immunochemotherapy, followed by rituximab maintenance.[2,4] In the current era of

targeted therapies, Bruton's tyrosine kinase (BTK) inhibitors have demonstrated efficacy and are being incorporated into first-line treatment for MCL patients, challenging the use of ASCT in younger patients.[11,12]

Despite therapeutic advances, MCL remains generally incurable. Several studies have shown trends of improved survival over time.[6,13–27] These studies on MCL survival trends relied on population-based registries with limited details regarding treatment, prognostic factors, and less reliable MCL diagnosis without reference pathology, especially in earlier years. Only one prospective cohort study linked shifts in treatment patterns to improved event-free and overall survival in MCL patients diagnosed during 2010–2015 versus 2002–2009.[26] Another study based on clinical trial populations comparing 1975–1986 and 1996–2004 found OS increased from 2.7 to 4.8 years, with 5-year survival doubling from 22% to 47%.[14] However, no studies have examined continuous survival trends, accounting for detailed treatment regimens and clinical characteristics.

Since 1996, pivotal randomized phase III trials conducted by the German Low-Grade Lymphoma Study Group (GLSG, now German Lymphoma Alliance) and the European MCL Network have consistently advanced the standard of care for advanced-stage MCL: GLSG1996 introduced CHOP,[28] European MCL trial 1 introduced ASCT in younger patients,[7] GLSG2000 introduced R-CHOP,[8] MCL Younger introduced high-dose cytarabine-containing regimen in younger patients,[9] MCL Elderly introduced rituximab maintenance in older patients,[10] and TRIANGLE introduced ibrutinib in younger patients.[11] With the benefit of long-term follow-up from these trials, we now aimed to

explore the evolution of survival outcomes in MCL patients over the past three decades and to identify key clinical and treatment factors driving these survival trends.

Methods

Patients and Study Design

This pooled analysis included individual patient data from six randomized phase III trials: GLSG1996,[28] GLSG2000,[8] European MCL trial 1,[7] MCL Younger,[9] MCL Elderly,[10] and TRIANGLE.[11] All trials targeted treatment-naïve advanced-stage MCL patients using similar eligibility criteria. They were conducted sequentially, with the recruitment spanning nearly the entire period from 1996 to 2020 in younger and 1996–2014 in older patients. The most recent follow-up data were used, extending over previously published results for GLSG1996, GLSG2000, MCL Elderly, and TRIANGLE. We defined four eras based on trial enrollment periods (Figure 1). Trial designs are summarized in Figure 1 and the Supplementary Information (Summary of the Trial Designs and Table S1). The study population included all enrolled patients with a confirmed MCL diagnosis. Each trial received approval from local ethics committees, and all participants provided written informed consent.

Prognostic Factors and Outcomes

Patients aged under 60 or patients aged under 65 and suitable for high-dose treatment were classified as younger patients, and those over 65 or over 60 and ineligible for high-dose treatment were classified as older patients.

Treatment groups were defined as the randomized or assigned treatment, following the intention-to-treat principle. Patients lacking post-remission treatment assignments were retrospectively randomized to one of the post-remission treatments within the enrolled trial, stratified by induction treatment.

The outcomes assessed were failure-free survival (FFS) and overall survival (OS). FFS was defined as the time from study registration to stable disease at end of induction, progression, or death from any cause, whichever occurred first. Patients without events were censored at their last follow-up without treatment failure. OS was measured from study registration to death from any cause, with patients alive censored at their latest follow-up. Patients with no information available after enrollment were censored one day after registration.

Statistical Methods

FFS and OS by era were estimated by Kaplan-Meier methods and compared by log-rank tests. Hazard ratios (HR) with 95% confidence intervals (CI) and the corresponding p values from the Wald test were calculated from Cox models adjusting for Mantle Cell Lymphoma International Prognostic Index (MIPI) score, and further for the treatment groups.

To evaluate the dynamic trend of FFS and OS over time, we incorporated the time of study registration as a continuous covariate in Cox models, adjusting for MIPI score and treatment. We assessed linearity of the registration time using P-splines with AIC-optimized degrees of freedom, employing non-linear Cox models when the linearity

assumption was violated ($p < 0.05$).[29] The survival trends were visualized by plotting HRs against registration time.

We conducted all analyses separately for younger and older patients due to substantial differences in their risk profiles and treatment regimens, both within the trials and in current clinical practice. All analyses were performed using R version 4.3.2.

Results

From May 1996 to Dec 2020, 2,596 patients were enrolled in six randomized phase III trials. After excluding 55 patients without confirmed MCL diagnosis, we analyzed 2,541 MCL patients (1,763 younger, 778 older) in this study (Figure 2). The cohort had a median age of 60 years (range 27–88), with 70% younger patients, 76% males, and 85% with stage IV disease (Table 1). Younger patients (median age 56 years) were mostly enrolled in 2004–2014 (35%) and 2016–2020 (49%) and had low (61%) or intermediate (25%) risk MIPI. Over time, we observed trends of slightly increased median age and MIPI risk, less frequent B-symptoms, better ECOG (Eastern Cooperative Oncology Group) performance status, higher lactate dehydrogenase (LDH) and Ki-67 index among younger patients (Table S2). Older patients (median age 70 years) were mostly enrolled in 2004–2014 (73%), with intermediate (44%) or high (48%) risk MIPI (Table 1). There were trends of decreasing B-symptoms, increasing age, higher MIPI risk, better ECOG performance status, and increasing LDH over time among older patients (Table S3).

The median follow-up reached up to 12.6 years for FFS and 15.5 years for OS since the

1996–2000 era (Table S4). In younger MCL patients, FFS improved significantly across eras. Median FFS increased from 1.3 years (95% CI 1.0–1.8) in 1996–2000 to 2.1 years (1.7–2.7) in 2000–2004, further to 5.7 years (4.8–6.8) in 2004–2014, and has not been reached yet in the latest 2016–2020 era (Figure 3A). Corresponding 5-year FFS rose from 13% (8%–20%) in 1996–2000 to 71% (67%–74%) in 2016–2020. FFS doubled between 2000–2004 and 2004–2014 (MIPI-adjusted HR (aHR)=0.44, 95% CI 0.35–0.54, p<0.0001) and again in 2016–2020 (aHR=0.51, 0.43–0.61, p<0.0001; Table 2). Similarly, median OS improved from 4.9 years (4.3–6.7) in 1996–2000 to 13.8 years (10.8–not reached) in 2004–2014 and was not yet reached in 2016–2020, with 5-year OS improving from 49% (42%–58%) to 84% (81%–87%) (Figure 3B). Survival nearly doubled in both 2004–2014 (aHR=0.56, 0.44–0.72, p<0.0001) and 2016–2020 (aHR=0.52, 0.41–0.65, p<0.0001; Table 2).

In older MCL patients, median FFS significantly increased from 1.3 years (1.1–1.6) in 1996–2000 to 2.4 years (2.2–2.8) in 2004–2014, with 5-year FFS rising from 10% (5%–20%) to 31% (27%–36%) (Figure 3C). Median OS increased from 3.8 years (3.2–5.0) to 4.8 years (4.0–5.6), with 5-year OS increasing from 40% (30%–52%) to 49% (45%–54%, Figure 3D). Significant improvement occurred in FFS during 2004–2014 and in OS during 2000–2004 (Table 2).

The assigned treatment groups could largely explain the improved survival outcomes of MCL patients across eras. In younger patients, compared to CHOP+IFN/ASCT in 1996–2000, we observed longer FFS and OS in those assigned to R-CHOP+IFN/ASCT in 2000–2004, followed by R-CHOP+ASCT in 2004–2014, and by R-CHOP/R-

DHAP+ASCT in 2004–2014 and 2016–2020, and finally by IR-CHOP/R-DHAP+/-ASCT+I in era 2016–2020, with more than a 7-fold FFS improvement (vs. CHOP+IFN/ASCT in 1996–2000: aHR=0.14, 0.11–0.18, p<0.0001) and a 5-fold OS improvement (aHR=0.19, 0.14–0.27, p<0.0001, Figure 4A, B; Table S5). In older patients, similarly, compared to CHOP+IFN in 1996–2000, we observed significantly prolonged FFS and OS among those assigned to R-CHOP+IFN in 2000–2004, and to R-FC+IFN/R and R-CHOP+IFN/R in 2004–2014 (Figure 4C, D; Table S5). The evolution of treatment explained most of the survival trends in both younger and older patients, as the significant improvement in FFS and OS over the eras disappeared when further adjusting for the treatment groups (Table 2).

Patients assigned to the same treatment regimens demonstrated comparable FFS and OS across eras (Table S6), confirming first-line treatment as the primary contributor to survival outcomes. In younger patients, compared to induction with chemotherapy (MCP/CHOP+IFN/ASCT), immunochemotherapy with rituximab (R-CHOP+IFN/ASCT) significantly improved FFS (aHR=0.43, 0.35–0.52, p<0.001) and OS (aHR=0.59, 0.47–0.74, p<0.001), with further improvement when high-dose cytarabine (R-CHOP/R-DHAP+ASCT, FFS: aHR=0.21, 0.17–0.25, p<0.001; OS: aHR=0.38, 0.30–0.47, p<0.001) and ibrutinib (IR-CHOP/R-DHAP+/-ASCT+I, FFS: aHR=0.12, 0.10–0.16, p<0.001; OS: aHR=0.19, 0.14–0.25, p<0.001) were incorporated into the induction immunochemotherapy (Figure S1A, B).

Among younger patients who achieved a response to induction treatment, ASCT consolidation contributed to better FFS and OS compared to IFN maintenance, and a

high-dose cytarabine-containing regimen before ASCT further significantly improved FFS (Figure S2A, B). Interestingly, the contribution of ASCT to chemotherapy (OS: aHR=0.66, 0.44–0.99) was similar to that of rituximab added to chemotherapy without ASCT (OS: aHR=0.68, 0.42–1.10) (Figure S2B). Ibrutinib added to induction and maintenance treatment improved OS, whereas adding ASCT to ibrutinib-containing regimens did not further improve survival outcomes (Figure S2B). Moreover, in the 2016–2020 era, rituximab maintenance (assigned to 68% of patients) improved FFS and OS after immunochemotherapy, with or without ASCT or ibrutinib (Figure S2A, B; Figure S3A, B).

In older patients, immunochemotherapies (R-CHOP/R-FC+IFN/R) significantly prolonged FFS and OS compared to chemotherapy (MCP/CHOP+IFN), with R-CHOP (+IFN/R) demonstrating a superior OS benefit (aHR=0.54, 0.42–0.68) versus R-FC (+IFN/R, aHR=0.69, 0.54–0.89) (Figure S1C, D). Among those who achieved a response, rituximab maintenance led to better survival outcomes than IFN, especially following R-CHOP induction, where FFS and OS doubled under rituximab maintenance (FFS: aHR=0.25, 0.18–0.34; OS: aHR=0.29, 0.20–0.41) compared to IFN (FFS: aHR=0.57, 0.44–0.75; OS: aHR=0.56, 0.42–0.75) (Figure S2C, D; Figure S3C, D).

Dynamic trends of FFS (p for non-linearity < 0.0001) and OS (p=0.025) improvements were seen in younger patients from 1996 to 2020 with accelerated gains during 2000–2005 followed by sustained improvement (Figure 5A, B). The significant p-values for non-linearity indicate that the HRs varied in a non-linear pattern, rather than remaining constant over time. These trends diminished after adjusting for treatment (FFS:

aHR=0.99, 0.97–1.02, p=0.62; OS: aHR=0.98, 0.96–1.01, p=0.16, non-linear p=0.089, Figure S4A), indicating that first-line treatment drove most survival improvements (Table S7). Older patients showed similar FFS improvement during 2000-2005 before stabilizing (non-linear p=0.012), while OS improved steadily and significantly from 1996 to 2015 (non-linear p=0.70, MIPI-adjusted HR=0.95, 0.93–0.97, p<0.0001) (Figure 5C, D; Table S7). Adjusting for treatment eliminated these trends (FFS: aHR=0.98, 0.95–1.02, p=0.33; OS: aHR=0.98, 0.94–1.01, p=0.22) (Table S7).

Similar to the overall patient population, the improving survival trends diminished after adjusting for treatment across MIPI subgroups and among younger patients in the high Ki-67, cytology, and p53 expression subgroups, while younger patients with low Ki-67 showed slightly prolonged OS (MIPI and treatment-adjusted HR=0.96, 0.92–1.00, p=0.051) over time (Table S7). Among younger patients whose disease responded to induction treatment, we observed a remaining OS improvement from 2000 to 2005, after adjusting for the treatment regimens (non-linear p=0.041, Table S7; Figure S4B). The same trend was observed in the younger subgroup assigned to induction with rituximab (non-linear p=0.022, Figure S4C), but not in the ASCT subgroup (aHR=0.98, 0.95–1.01, p=0.18, Figure S4D), suggesting that OS improved from 2000 to 2005 for patients treated with rituximab-containing chemotherapy, irrespective of whether they underwent ASCT, potentially due to advancements in salvage treatments during this period.

Discussion

In this clinical trial cohort of 2,541 MCL patients, we analyzed trends in FFS and OS

across evolving first-line treatments since 1996. Among younger patients, survival improved significantly over four treatment eras, with a marked reduction in the risk of treatment failure and death between 2000 and 2005. These gains were primarily driven by the introduction of ASCT, immunochemotherapy with rituximab, high-dose cytarabine, and ibrutinib. Older patients also demonstrated improved survival across eras, with a notable FFS increase from 2000 to 2004, largely due to the integration of rituximab into both induction and post-remission therapy.

Our study extended the historical comparison in non-blastoid MCL patients showing a near doubling of median OS between the 1976–1986 and 1996–2004 eras (2.7 vs. 4.8 years).[14] By incorporating data from 2004–2020, we found that OS nearly doubled again among younger patients during 2004–2014 (median 13.8 years, 5-year OS 73%, aHR=0.56, p<0.0001) compared to 2000–2004, with further gains in 2016–2020 (median OS not reached, 5-year OS 84%), while older patients experienced more modest improvements during 2004–2014 (median 4.8 years, 5-year OS 49%, aHR=0.80, p=0.070). The comparatively longer 2004–2014 era was defined to align with trial recruitment periods, and sensitivity analysis confirmed that this uneven division of eras did not affect our findings.

A U.S. population-based study reported significant OS improvement in 2000–2003 (vs. 1992–1999: unadjusted HR 0.86) and 2004–2007 (vs. 2000–2004: 0.91) among patients with advanced disease.[6] Similarly, SEER and Texas Cancer Registry data showed significantly improved survival during 1995–2013, limited to advanced-stage MCL.[22] While neither study accounted for treatment effects, our analysis of advanced-

stage MCL also revealed mortality reductions – MIPI-adjusted HRs of 0.80 and 0.70 (2000–2004 vs. 1996–2000) and 0.56 and 0.80 (2004–2014 vs. 2000–2004) for younger and older patients, respectively – largely attributable to treatment advancements. No notable survival differences were seen among patients receiving the same regimen across eras. This aligns with a prospective cohort study reporting similar event-free survival and OS after R-CHOP-like induction in patients ≤ 65 years (2010–2015 vs. 2002–2009).[26] These results suggest no major advancements or availability of second-line treatment or supportive care during these periods. Of note, the use of second-line BTKi was too infrequent in our cohort to yield a significant impact on post-relapse survival.

After accounting for first-line treatment, we found no significant survival improvement in younger or older MCL patients since 1996. Our findings strongly suggest that the improved outcomes across eras are a direct result of specific therapeutic advances – the sequential introduction of rituximab, ASCT, high-dose cytarabine, and ibrutinib – into clinical practice, rather than any other factors that may have changed over time. This aligns with data from Swedish and Danish lymphoma registries, where mortality reduction (2006–2011 vs. 2000–2005) lost significance after adjusting for chemotherapy and rituximab.[16] They further identified rituximab as a strong predictor of improved survival (HR=0.68, p=0.001).[16] Similarly, a UK population-based cohort (2004–2015) showed significantly improved OS with chemotherapy + rituximab vs. chemotherapy alone (3-year OS: 50.3% vs. 29.1%, p=0.002).[21] In our study, rituximab added to chemotherapy significantly improved OS in younger (aHR=0.59, 95% CI 0.47–0.74) and

older patients (aHR=0.54, 0.42–0.68). Rituximab maintenance further enhanced survival in older patients who responded to immunochemotherapy, particularly after R-CHOP.

Among younger MCL patients responding to induction immunochemotherapy, ASCT demonstrated a non-significant trend toward improved survival, while adding high-dose cytarabine significantly improved FFS but not OS. In comparison, Abrahamsson et al. found a significant survival benefit from ASCT (HR=0.59, p=0.002) but no OS improvement with cytarabine.[16] Following the 2000–2004 era, ASCT became standard consolidation therapy for transplant-eligible younger MCL patients. However, its role has recently been reconsidered with the advent of BTK-inhibitors like ibrutinib.[11]

This study has several limitations. As our analysis used data from randomized trials, the patient population was highly selected based on inclusion and exclusion criteria. Although the cohort largely represents treatment-naïve, advanced-stage MCL patients eligible for therapy, the findings may not generalize to those too ill for treatment or with indolent disease. The strict age cutoff in trials may not reflect real-world practice, where fit patients over 65 may still benefit from intensive regimens. Likewise, the treatment regimens analyzed were limited to those available in the included trials and may not fully represent real-world practice. For example, R-bendamustine (R-B), now widely used in older patients, showed improved outcomes in recent trials (R-B + ibrutinib vs. R-B: median PFS 80.6 vs. 50.9 months, 7-year OS 55.0% vs. 56.8%[30]; R-B + Acalabrutinib vs. R-B + placebo: median PFS 66.4 vs. 49.6 months, 5-year OS over 60% in both groups[12]), compared to the 2004–2014 era (median FFS 28.8 months, 7-year OS 40%, 5-year OS 49%), though the risk profiles of R-B cohorts were not accounted

for. The lack of data for older patients after 2014 also prevented us from analyzing survival trends in the most recent era for this age group. Nevertheless, our landmark trials captured most of the evolution of MCL standard of care in Europe. Finally, limited follow-up in later eras and lack of data on biological or functional cures precluded identifying potentially cured cases, which falls beyond the scope of this study.

To our knowledge, this represents the first comprehensive analysis of survival trends in MCL patients across three decades of clinical trials. The study's major strengths include: (1) utilization of high-quality clinical trial data with centralized histological confirmation of MCL diagnosis, ensuring diagnostic accuracy and consistency across cohorts; (2) largely comparable patient characteristics across trial cohorts, allowing for meaningful era comparisons with minimized confounding; (3) detailed treatment information enabling the identification of key factors driving outcome improvements; (4) dynamic modeling that further captures survival trends over continuous time, providing a nuanced view of the temporal relationship between therapeutic advances and evolving MCL outcomes.

Our study highlights the remarkable survival improvements in treatment-naïve, advanced-stage MCL patients from 1996 to 2020, driven by advances in first-line therapy. The introduction of ASCT, rituximab, high-dose cytarabine, and ibrutinib has transformed MCL from a historically dismal disease into a more chronic clinical course, particularly in younger patients. However, older patients may require better first-line therapies beyond CHOP-based regimens. Further analyses including BTK inhibitor ± R-B-treated older patients may offer valuable insights.

Future research integrating both clinical trial data and real-world cohorts with extended follow-up is crucial to bridge the gap between trial outcomes and routine clinical practice. These findings will help guide the development of next-generation therapies and refine the standard of care for this challenging disease.

References

1. Alaggio R, Amador C, Anagnostopoulos I, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. Leukemia. 2022;36(7):1720-1748.

2. Silkenstedt E, Dreyling M. Mantle cell lymphoma-Update on molecular biology, prognostication and treatment approaches. Hematol Oncol. 2023;41(S1):36-42.

3. Tiemann M, Schrader C, Klapper W, et al. Histopathology, cell proliferation indices and clinical outcome in 304 patients with mantle cell lymphoma (MCL): a clinicopathological study from the European MCL Network. Br J Haematol. 2005;131(1):29-38.

4. Jain P, Wang ML. Mantle cell lymphoma in 2022-A comprehensive update on molecular pathogenesis, risk stratification, clinical approach, and current and novel treatments. Am J Hematol. 2022;97(5):638-656.

5. Banks PM, Chan J, Cleary ML, et al. Mantle cell lymphoma. A proposal for unification of morphologic, immunologic, and molecular data. Am J Surg Pathol. 1992;16(7):637-640.

6. Chandran R, Gardiner SK, Simon M, Spurgeon SE. Survival trends in mantle cell lymphoma in the United States over 16 years 1992-2007. Leuk Lymphoma. 2012;53(8):1488-1493.

7. Zoellner A-K, Unterhalt M, Stilgenbauer S, et al. Long-term survival of patients with mantle cell lymphoma after autologous haematopoietic stem-cell transplantation in first remission: a post-hoc analysis of an open-label, multicentre, randomised, phase 3 trial. Lancet Haematol. 2021;8(9):e648-657.

8. Lenz G, Dreyling M, Hoster E, et al. Immunochemotherapy With Rituximab and Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone Significantly Improves

Response and Time to Treatment Failure, But Not Long-Term Outcome in Patients With Previously Untreated Mantle Cell Lymphoma: Results of a Prospective Randomized Trial of the German Low Grade Lymphoma Study Group (GLSG). J Clin Oncol. 2005;23(9):1984-1992.

9. Hermine O, Jiang L, Walewski J, et al. High-Dose Cytarabine and Autologous Stem-Cell Transplantation in Mantle Cell Lymphoma: Long-Term Follow-Up of the Randomized Mantle Cell Lymphoma Younger Trial of the European Mantle Cell Lymphoma Network. J Clin Oncol. 2023;41(3):479-484.

10. Kluin-Nelemans HC, Hoster E, Hermine O, et al. Treatment of Older Patients With Mantle Cell Lymphoma (MCL): Long-Term Follow-Up of the Randomized European MCL Elderly Trial. J Clin Oncol. 2020;38(3):248-256.

11. Dreyling M, Doorduijn J, Giné E, et al. Ibrutinib combined with immunochemotherapy with or without autologous stem-cell transplantation versus immunochemotherapy and autologous stem-cell transplantation in previously untreated patients with mantle cell lymphoma (TRIANGLE): a three-arm, randomised, open-label, phase 3 superiority trial of the European Mantle Cell Lymphoma Network. Lancet. 2024;403(10441):2293-2306.

12. Wang M, Salek D, Belada D, et al. Acalabrutinib Plus Bendamustine-Rituximab in Untreated Mantle Cell Lymphoma. J Clin Oncol. 2025;43(20):2276-2284.

13. Wu H, Wang J, Zhang X, et al. Survival Trends in Patients Under Age 65 Years With Mantle Cell Lymphoma, 1995-2016: A SEER-Based Analysis. Front Oncol. 2020;10:588314.

14. Herrmann A, Hoster E, Zwingers T, et al. Improvement of overall survival in advanced stage mantle cell lymphoma. J Clin Oncol. 2009;27(4):511-518.

15. Abrahamsson A, Dahle N, Jerkeman M. Marked improvement of overall survival in mantle cell lymphoma: a population based study from the Swedish Lymphoma

Registry. Leuk Lymphoma. 2011;52(10):1929-1935.

16. Abrahamsson A, Albertsson-Lindblad A, Brown PN, et al. Real world data on primary treatment for mantle cell lymphoma: a Nordic Lymphoma Group observational study. Blood. 2014;124(8):1288-1295.

17. Issa DE, van de Schans SAM, Chamuleau MED, et al. Trends in incidence, treatment and survival of aggressive B-cell lymphoma in the Netherlands 1989-2010. Haematologica. 2015;100(4):525-533.

18. Al-Hamadani M, Habermann TM, Cerhan JR, Macon WR, Maurer MJ, Go RS. Non-Hodgkin lymphoma subtype distribution, geodemographic patterns, and survival in the US: A longitudinal analysis of the National Cancer Data Base from 1998 to 2011. Am J Hematol. 2015;90(9):790795.

19. Pulte D, Weberpals J, Jansen L, et al. Survival for patients with rare haematologic malignancies: Changes in the early 21st century. Eur J Cancer. 2017;84:81-87.

20. Epperla N, Hamadani M, Fenske TS, Costa LJ. Incidence and survival trends in mantle cell lymphoma. Br J Haematol. 2018;181(5):703-706.

21. Smith A, Roman E, Appleton S, et al. Impact of novel therapies for mantle cell lymphoma in the real world setting: a report from the UK's Haematological Malignancy Research Network (HMRN). Br J Haematol. 2018;181(2):215-228.

22. Fu S, Wang M, Li R, Lairson DR, Zhao B, Du XL. Increase in survival for patients with mantle cell lymphoma in the era of novel agents in 1995-2013: Findings from Texas and national SEER areas. Cancer Epidemiol. 2019;58:89-97.

23. Ekberg S, Smedby KE, Glimelius I, et al. Trends in the prevalence, incidence and survival of non-Hodgkin lymphoma subtypes during the 21st century - a Swedish lymphoma register study. Br J Haematol. 2020;189(6):1083-1092.

24. Liu W, Ji X, Song Y, et al. Improving survival of 3760 patients with lymphoma: Experience of an academic center over two decades. Cancer Med. 2020;9(11):3765-3774.

25. Villavicencio A, Solans M, Auñon-Sanz C, Roncero JM, Marcos-Gragera R. Population-based survival of lymphoid neoplasms: Twenty years of epidemiological data in the Girona province, Spain. Cancer Epidemiol. 2020;69:101841.

26. Castellino A, Wang Y, Larson MC, et al. Evolving frontline immunochemotherapy for mantle cell lymphoma and the impact on survival outcomes. Blood Adv. 2022;6(4):1350-1360.

27. Di M, Cui C, Kothari SK, et al. Survival of mantle cell lymphoma in the era of Bruton tyrosine kinase inhibitors: a population-based analysis. Blood Adv. 2022;6(11):3339-3342.

28. Nickenig C, Dreyling M, Hoster E, et al. Combined cyclophosphamide, vincristine, doxorubicin, and prednisone (CHOP) improves response rates but not survival and has lower hematologic toxicity compared with combined mitoxantrone, chlorambucil, and prednisone (MCP) in follicular and mantle cell lymphomas. Cancer. 2006;107(5):1014-1022.

29. Eilers PHC, Marx BD. Flexible smoothing with B-splines and penalties. Stat Sci. 1996;11(2):89-121.

30. Wang ML, Jurczak W, Jerkeman M, et al. Ibrutinib plus Bendamustine and Rituximab in Untreated Mantle-Cell Lymphoma. N Engl J Med. 2022;386(26):2482-2494.

Table 1. Baseline characteristics of all analyzed patients

Variable	Value	All analyzed patients (N = 2541)		Younger (< 60 or ≤ 65 and transplant-eligible) patients (N = 1763)		Older (> 65 or ≥ 60 and transplant-ineligible) patients (N = 778)	
Study era	1996–2000 (n, %)	236	9%	152	9%	84	11%
	2000–2004 (n, %)	261	10%	137	8%	124	16%
	2004–2014 (n, %)	1183	47%	613	35%	570	73%
	2016–2020 (n, %)	861	34%	861	49%	0	0%
Age (years)	Median, Min–Max	60	27–88	56	27–68	70	60–88
Sex	Male (n, %)	1928	76%	1377	78%	551	71%
Ann Arbor Stage	I (n, %)	7 (n=2536)	<1%	4 (n=1760)	<1%	3 (n=776)	0%
	II (n, %)	97 (n=2536)	4%	64 (n=1760)	4%	33 (n=776)	4%
	III (n, %)	286 (n=2536)	11%	190 (n=1760)	11%	96 (n=776)	12%
	IV (n, %)	2146 (n=2536)	85%	1502 (n=1760)	85%	644 (n=776)	83%
B-symptoms	Present (n, %)	881 (n=2520)	35%	583 (n=1749)	33%	298 (n=771)	39%
ECOG	0 (n, %)	1426 (n=2537)	56%	1103	63%	323 (n=774)	42%
	1 (n, %)	987 (n=2537)	39%	603	34%	384 (n=774)	50%
	2 (n, %)	118 (n=2537)	5%	55	3%	63 (n=774)	8%
	3 (n, %)	5 (n=2537)	< 1%	1	< 1%	4 (n=774)	1%
	4 (n, %)	1 (n=2537)	< 1%	1	< 1%	0 (n=774)	0%
LDH (ULN)	Median, Min–Max	0.91 (n=2534)	0.15–12.22	0.9	0.15–12.22	0.93 (n=771)	0.29–11.27
LDH	> ULN (n, %)	973 (n=2534)	38%	655	37%	318 (n=771)	41%

WBC count (10^9/L)	Median, Min–Max	7.6 (n=2532)	0.16–1105	7.45 (n=1761)	0.16–1105	8 (n=771)	1.04–658.8
MIPI score	Median, Min–Max	5.77 (n=2527)	4.07–9.18	5.59 (n=1761)	4.07–8.68	6.17 (n=766)	4.97–9.18
MIPI risk group	Low (n, %)	1137 (n=2527)	45%	1071 (n=1761)	61%	66 (n=766)	9%
	Intermediate (n, %)	776 (n=2527)	31%	440 (n=1761)	25%	336 (n=766)	44%
	High (n, %)	614 (n=2527)	24%	250 (n=1761)	14%	364 (n=766)	48%
Ki-67 index (%)	Median, Min–Max	18.5 (n=1623)	0–100	18 (n=1260)	0–100	19.5 (n=363)	2–91
Ki-67 index	≥ 30%	462 (n=1623)	28%	351 (n=1260)	28%	111 (n=363)	31%
Cytology	Blastoid	170 (n=1606)	11%	133 (n=1308)	10%	37 (n=298)	12%
P53 expression	> 50% (n, %)	137 (n=946)	14%	110 (n=795)	14%	27 (n=151)	18%
High risk biology	High risk (n, %)	225 (n=928)	24%	162 (n=774)	21%	63 (n=154)	41%

ECOG: Eastern Cooperative Oncology Group; LDH: lactate dehydrogenase; WBC: white blood cell; MIPI: Mantle Cell Lymphoma International Prognostic Index; high risk biology: high risk MIPI and Ki-67 ≥ 30%, or P53 expression > 50%

Table 2. Hazard ratios of FFS and OS by trial eras in younger and older patients

	Age Group	Trial Era	Median (95% CI)	5-year probability (95% CI)	10-year probability (95% CI)	Reference Era	HR adjusted for MIPI (95% CI)	p	HR adjusted for MIPI and treatment (95% CI)	p
FFS	**Younger**	**1996–2000**	1.3 (1.0–1.8)	0.13 (0.08–0.20)	0.05 (0.03–0.11)	–	–	–	–	–
	(N=1761)	**2000–2004**	2.1 (1.7–2.7)	0.24 (0.18–0.33)	0.10 (0.06–0.18)	vs. 1996–2000	0.68 (0.53–0.87)	0.0024	1.27 (0.89–1.82)	0.18
		2004–2014	5.7 (4.8–6.8)	0.54 (0.49–0.58)	0.36 (0.31–0.41)	vs. 2000–2004	0.44 (0.35–0.54)	<0.0001	0.97 (0.71–1.32)	0.85
		2016–2020	Not reached	0.71 (0.67–0.74)	Not reached	vs. 2004–2014	0.51 (0.43–0.61)	<0.0001	0.87 (0.67–1.12)	0.28
	Older	**1996–2000**	1.3 (1.1–1.6)	0.10 (0.05–0.20)	0.03 (0.01–0.10)	–	–	–	–	–
	(N=766)	**2000–2004**	1.7 (1.4–1.9)	0.10 (0.06–0.18)	0.01 (0.00–0.08)	vs. 1996–2000	0.75 (0.56–1.02)	0.065	0.99 (0.63–1.56)	0.98
		2004–2014	2.4 (2.2–2.8)	0.31 (0.27–0.36)	0.15 (0.12–0.19)	vs. 2000–2004	0.61 (0.49–0.76)	<0.0001	0.85 (0.64–1.12)	0.24
OS	**Younger**	**1996–2000**	4.9 (4.3–6.7)	0.49 (0.42–0.58)	0.27 (0.20–0.35)	–	–	–	–	–
	(N=1761)	**2000–2004**	6.4 (5.4–9.5)	0.60 (0.52–0.69)	0.36 (0.29–0.47)	vs. 1996–2000	0.80 (0.60–1.06)	0.12	1.02 (0.68–1.53)	0.94
		2004–2014	13.8 (10.8–NA)	0.73 (0.69–0.76)	0.58 (0.53–0.63)	vs. 2000–2004	0.56 (0.44–0.72)	<0.0001	0.81 (0.57–1.15)	0.23
		2016–2020	Not reached	0.84 (0.81–0.87)	Not reached	vs. 2004–2014	0.52 (0.41–0.65)	<0.0001	0.84 (0.61–1.15)	0.28
	Older	**1996–2000**	3.8 (3.2–5.0)	0.40 (0.30–0.52)	0.09 (0.05–0.19)	–	–	–	–	–
	(N=766)	**2000–2004**	4.3 (3.8–5.6)	0.43 (0.35–0.53)	0.19 (0.12–0.29)	vs. 1996–2000	0.70 (0.51–0.96)	0.025	0.91 (0.56–1.48)	0.71
		2004–2014	4.8 (4.0–5.6)	0.49 (0.45–0.54)	0.30 (0.26–0.35)	vs. 2000–2004	0.80 (0.64–1.02)	0.070	0.85 (0.62–1.16)	0.30

FFS: failure-free survival; OS: overall survival; HR: hazard ratios; CI: confidence interval

Figure Legends

Figure 1. Patients and Study Design

MCP: mitoxantrone, chlorambucil, and prednisone; CHOP: cyclophosphamide, vincristine, doxorubicin, and prednisone; IFN-α: interferon-alpha; R-CHOP: rituximab plus CHOP; ASCT: autologous stem cell transplantation; R-FC: rituximab, fludarabine, and cyclophosphamide; R-DHAP: rituximab plus dexamethasone, high-dose cytarabine, and cisplatin; IR-CHOP: ibrutinib plus R-CHOP.

Figure 2. Patient flow diagram

Figure 3. Kaplan-Meier plots by trial eras for (A) FFS in younger patients, (B) OS in younger patients, (C) FFS in older patients, and (D) OS in older patients

FFS: failure-free survival; OS: overall survival

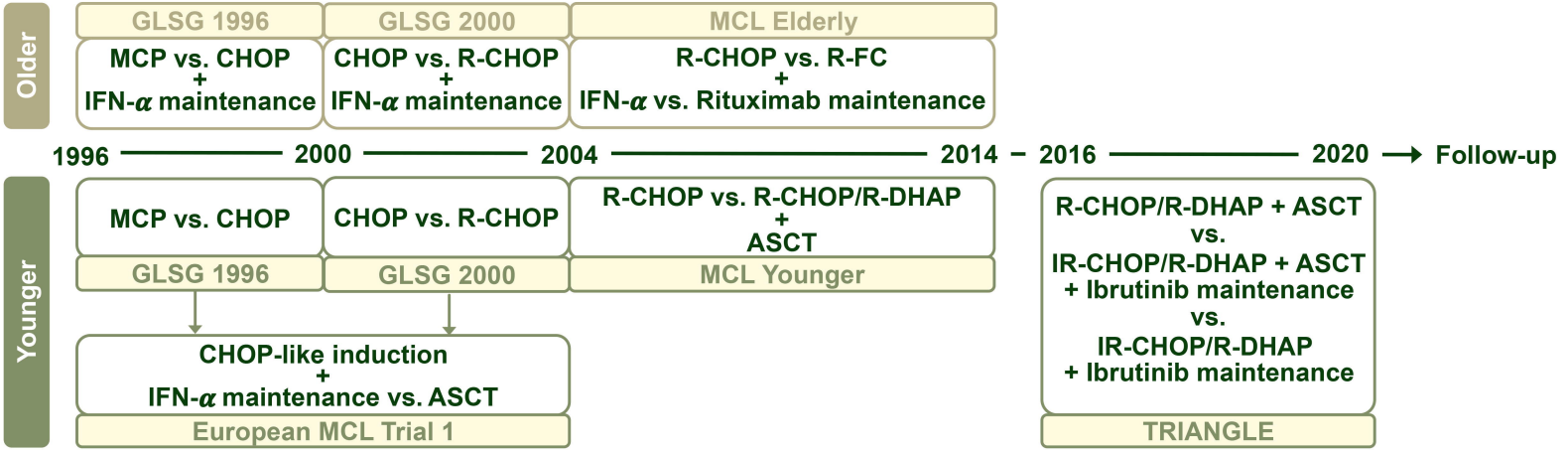
Figure 4. Kaplan-Meier plots by trial eras and treatment for (A) FFS in younger patients, (B) OS in younger patients, (C) FFS in older patients, and (D) OS in older patients

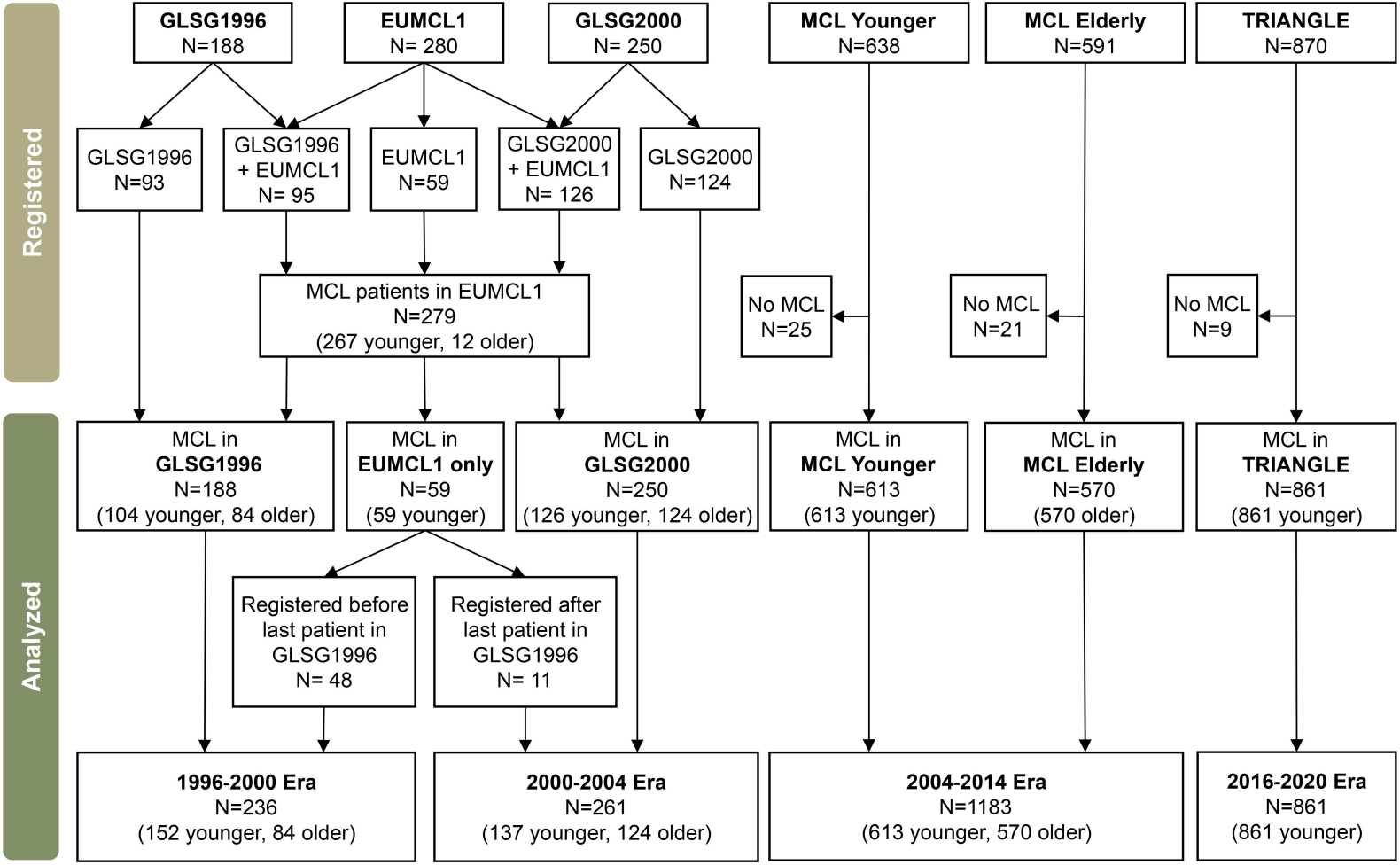
FFS: failure-free survival; OS: overall survival; MCP: mitoxantrone, chlorambucil, and prednisone; IFN: interferon-alpha; ASCT: autologous stem cell transplantation; CHOP: cyclophosphamide, vincristine, doxorubicin, and prednisone; R-CHOP: rituximab plus CHOP; R-DHAP: rituximab plus dexamethasone, high-dose cytarabine, and cisplatin; I: ibrutinib; R-FC: rituximab, fludarabine, and cyclophosphamide; Number of younger patients (in A and B): 1996−2000: MCP+IFN/ASCT (N = 28), 1996−2000: CHOP+IFN/ASCT (N = 124), 2000−2004: CHOP+IFN/ASCT (N = 45), 2000−2004: R−CHOP+IFN/ASCT (N = 92), 2004−2014: R−CHOP+ASCT (N = 237), 2004−2014: R−CHOP/R−DHAP+ASCT (N = 376), 2016−2020: R−CHOP/R−DHAP+ASCT (N = 286), 2016−2020: IR−CHOP/R−DHAP±ASCT+I (N = 575); Number of older patients (in C and D): 1996−2000: MCP+IFN (N = 25), 1996−2000: CHOP+IFN (N = 59), 2000−2004: CHOP+IFN (N = 32), 2000−2004: R−CHOP+IFN (N = 92), 2004−2014: R−CHOP+IFN/R

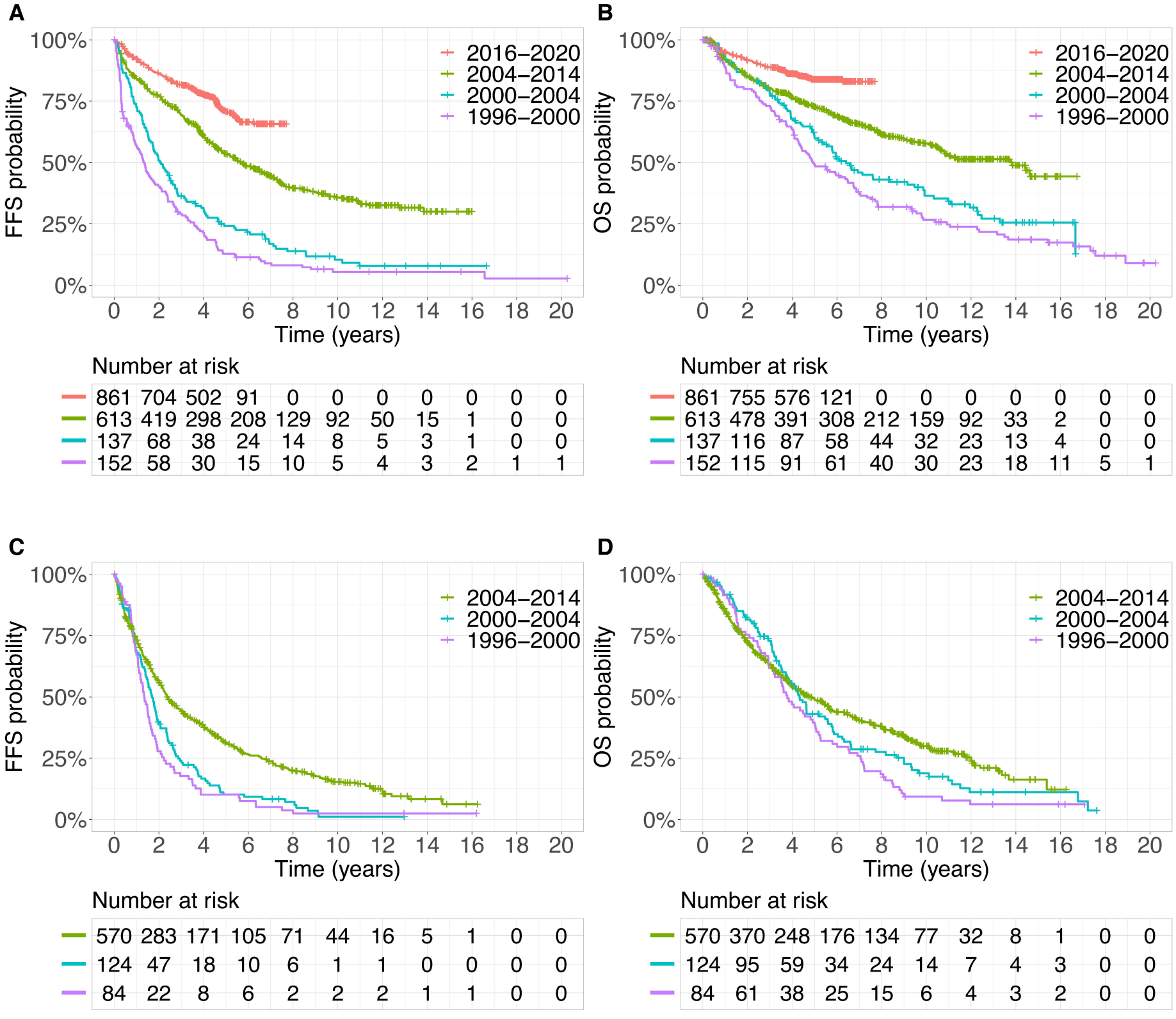
(N = 295), 2004−2014: R−FC+IFN/R (N = 275)

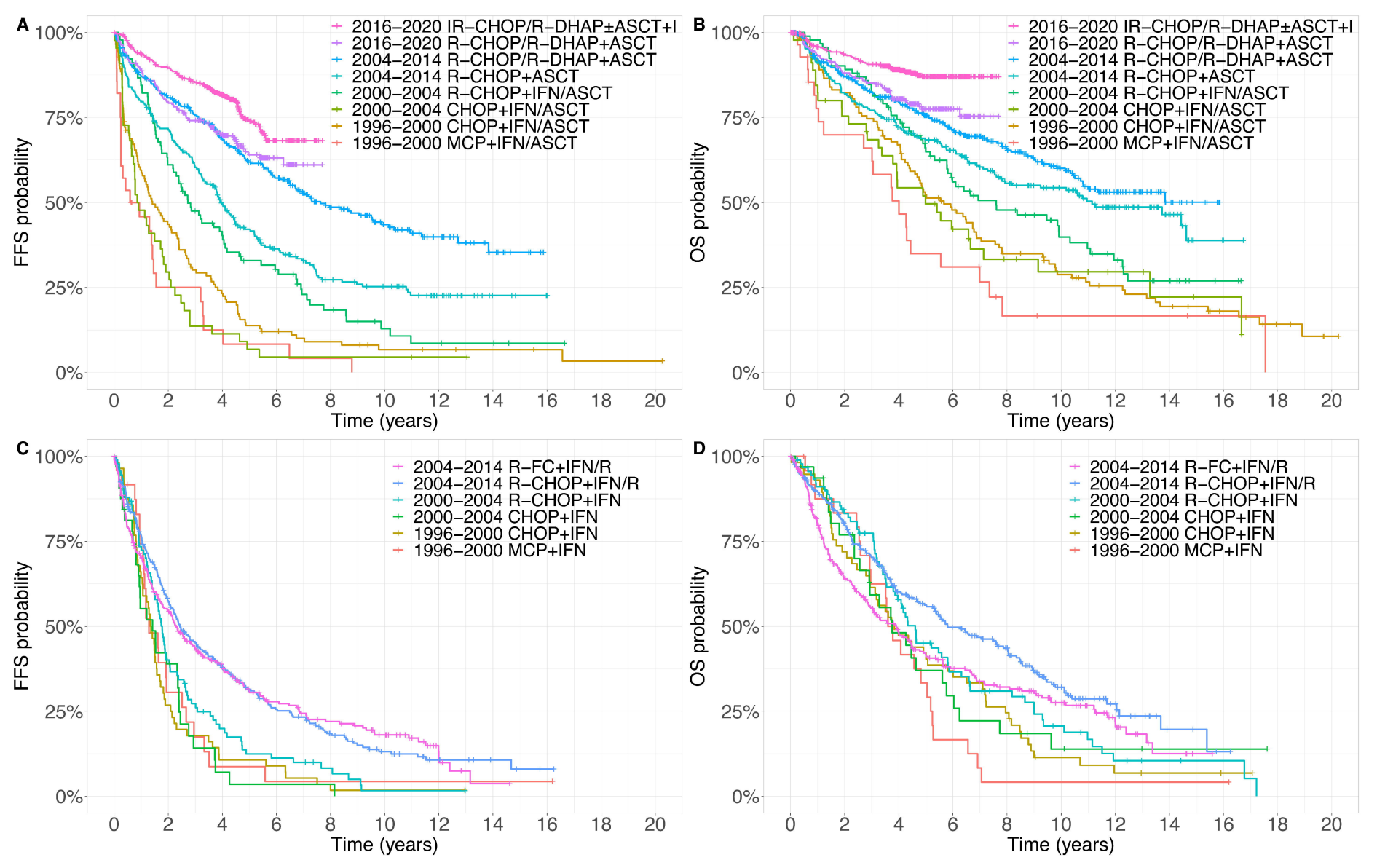
Figure 5. Dynamic trend of MIPI-adjusted hazard ratios and 95% confidence intervals over time of trial enrolment in (A) FFS of younger patients, (B) OS of younger patients, (C) FFS of older patients, and (D) OS of older patients

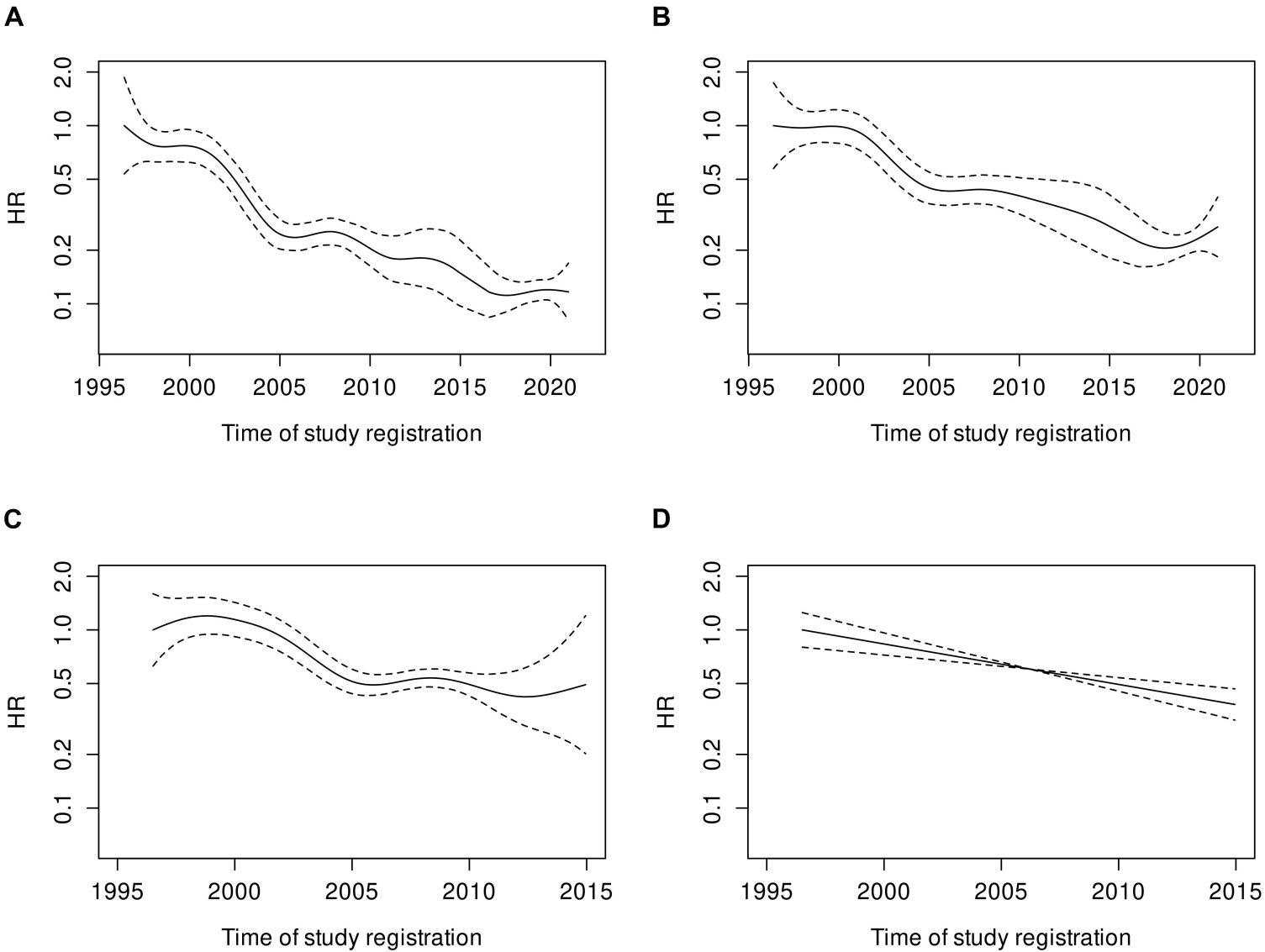
HR: hazard ratio


Older
GLSG 1996
MCP vs. CHOP
+
IFN-α maintenance
GLSG 2000
CHOP vs. R-CHOP
+
IFN-α maintenance
MCL Elderly
R-CHOP vs. R-FC
+
IFN-α vs. Rituximab maintenance
1996
2000
2004
2014
2016
2020
Follow-up
Younger
MCP vs. CHOP
CHOP vs. R-CHOP
R-CHOP vs. R-CHOP/R-DHAP
+
ASCT
GLSG 1996
GLSG 2000
MCL Younger
CHOP-like induction
+
IFN-α maintenance vs. ASCT
European MCL Trial 1
R-CHOP/R-DHAP + ASCT
vs.
IR-CHOP/R-DHAP + ASCT
+ Ibrutinib maintenance
vs.
IR-CHOP/R-DHAP
+ Ibrutinib maintenance
TRIANGLE


Registered
Analyzed
GLSG1996
N=188
EUMCL1
N= 280
GLSG2000
N= 250
MCL Younger
N=638
MCL Elderly
N=591
TRIANGLE
N=870
GLSG1996
N=93
GLSG1996
+ EUMCL1
N= 95
EUMCL1
N=59
GLSG2000
+ EUMCL1
N= 126
GLSG2000
N=124
MCL patients in EUMCL1
N=279
(267 younger, 12 older)
No MCL
N=25
No MCL
N=21
No MCL
N=9
MCL in
GLSG1996
N=188
(104 younger, 84 older)
MCL in
EUMCL1 only
N=59
(59 younger)
MCL in
GLSG2000
N=250
(126 younger, 124 older)
MCL in
MCL Younger
N=613
(613 younger)
MCL in
MCL Elderly
N=570
(570 older)
MCL in
TRIANGLE
N=861
(861 younger)
Registered before
last patient in
GLSG1996
N= 48
Registered after
last patient in
GLSG1996
N= 11
1996-2000 Era
N=236
(152 younger, 84 older)
2000-2004 Era
N=261
(137 younger, 124 older)
2004-2014 Era
N=1183
(613 younger, 570 older)
2016-2020 Era
N=861
(861 younger)


A
FFS probability
100%
75%
50%
25%
0%
0 2 4 6 8 10 12 14 16 18 20
Time (years)
2016–2020
2004–2014
2000–2004
1996–2000
Number at risk
861 704 502 91 0 0 0 0 0 0 0
613 419 298 208 129 92 50 15 1 0 0
137 68 38 24 14 8 5 3 1 0 0
152 58 30 15 10 5 4 3 2 1 1
B
OS probability
100%
75%
50%
25%
0%
0 2 4 6 8 10 12 14 16 18 20
Time (years)
2016–2020
2004–2014
2000–2004
1996–2000
Number at risk
861 755 576 121 0 0 0 0 0 0 0
613 478 391 308 212 159 92 33 2 0 0
137 116 87 58 44 32 23 13 4 0 0
152 115 91 61 40 30 23 18 11 5 1
C
FFS probability
100%
75%
50%
25%
0%
0 2 4 6 8 10 12 14 16 18 20
Time (years)
2004–2014
2000–2004
1996–2000
Number at risk
570 283 171 105 71 44 16 5 1 0 0
124 47 18 10 6 1 1 0 0 0 0
84 22 8 6 2 2 2 1 1 0 0
D
OS probability
100%
75%
50%
25%
0%
0 2 4 6 8 10 12 14 16 18 20
Time (years)
2004–2014
2000–2004
1996–2000
Number at risk
570 370 248 176 134 77 32 8 1 0 0
124 95 59 34 24 14 7 4 3 0 0
84 61 38 25 15 6 4 3 2 0 0


A
FFS probability
100%
75%
50%
25%
0%
0
2
4
6
8
10
12
14
16
18
20
Time (years)
2016–2020 IR–CHOP/R–DHAP±ASCT+I
2016–2020 R–CHOP/R–DHAP+ASCT
2004–2014 R–CHOP/R–DHAP+ASCT
2004–2014 R–CHOP+ASCT
2000–2004 R–CHOP+IFN/ASCT
2000–2004 CHOP+IFN/ASCT
1996–2000 CHOP+IFN/ASCT
1996–2000 MCP+IFN/ASCT
B
OS probability
100%
75%
50%
25%
0%
0
2
4
6
8
10
12
14
16
18
20
Time (years)
2016–2020 IR–CHOP/R–DHAP±ASCT+I
2016–2020 R–CHOP/R–DHAP+ASCT
2004–2014 R–CHOP/R–DHAP+ASCT
2004–2014 R–CHOP+ASCT
2000–2004 R–CHOP+IFN/ASCT
2000–2004 CHOP+IFN/ASCT
1996–2000 CHOP+IFN/ASCT
1996–2000 MCP+IFN/ASCT
C
FFS probability
100%
75%
50%
25%
0%
0
2
4
6
8
10
12
14
16
18
20
Time (years)
2004–2014 R–FC+IFN/R
2004–2014 R–CHOP+IFN/R
2000–2004 R–CHOP+IFN
2000–2004 CHOP+IFN
1996–2000 CHOP+IFN
1996–2000 MCP+IFN
D
OS probability
100%
75%
50%
25%
0%
0
2
4
6
8
10
12
14
16
18
20
Time (years)
2004–2014 R–FC+IFN/R
2004–2014 R–CHOP+IFN/R
2000–2004 R–CHOP+IFN
2000–2004 CHOP+IFN
1996–2000 CHOP+IFN
1996–2000 MCP+IFN


A
B
C
D
HR
0.1
0.2
0.5
1.0
2.0
1995
2000
2005
2010
2015
2020
Time of study registration

SUPPLEMENTARY INFORMATION

Summary of the Trial Designs

GLSG1996 was a randomized phase III trial comparing combined cyclophosphamide, vincristine, doxorubicin, and prednisone (CHOP) chemotherapy with combined mitoxantrone, chlorambucil, and prednisone (MCP) chemotherapy in follicular lymphoma (FL), mantle cell lymphoma (MCL), and lymphoplasmacytic lymphoma (LPL). For MCL, patients age≥18 years with previously untreated, advanced Stage III or IV disease were included. The randomization between CHOP and MCP took place between May 1996 and December 1998, then the randomization was stopped due to a higher overall response rate and a higher probability of successful stem-cell mobilization in younger patients observed with CHOP. Recruitment to the trial was continued until September 2000, with all newly recruited patients assigned to CHOP. In the end, a total of 188 MCL patients were registered to GLSG1996.

GLSG2000 was a randomized phase III trial comparing CHOP and CHOP plus Rituximab (R-CHOP) in patients with FL, MCL, or LPL. MCL patients age≥18 years with previously untreated, advanced Stage III or IV disease were included. The randomization started from May 2000 until April 2002, when the sequential test showed a significantly higher overall response rate after induction therapy with R-CHOP as compared with CHOP in MCL patients. Thus the randomization for MCL was stopped in 2002, and the newly recruited MCL patients were all assigned to R-CHOP until July 2004. In total, 250 MCL patients registered to GLSG2000.

In both GLSG1996 and GLSG2000 trials, patients older than 65 years or not suitable for high-dose treatment and in remission after first-line induction received interferon-alpha maintenance. MCL patients younger than 65 years and suitable for high-dose treatment from GLSG1996, GLSG2000, as well as international patients within the European MCL Network, were recruited to the first randomized international trial of the European MCL Network, the **European MCL trial 1**, which randomly compared ASCT to interferon-alpha maintenance in primary remission. Between September 1996 and March 2004, 280 patients from 129

institutions were registered.

MCL Younger was a randomized phase III trial conducted by European MCL network. Younger patients under 65 years old eligible for myeloablative therapy with untreated stage II-IV MCL were randomized to receive either R-CHOP followed by myeloablative radiochemotherapy and ASCT, or alternating R-CHOP or R-DHAP (rituximab plus dexamethasone, high-dose cytarabine, and cisplatin) followed by a high-dose cytarabine-containing conditioning regimen and ASCT. From 20 July 2004 to 18 March 2010, 497 patients were randomized. After the randomization stopped in 2010, all the newly recruited patients were assigned to the experimental arm until December 2014. In total, 638 patients were registered to MCL Younger.

MCL Elderly was another randomized phase III trial by European MCL network. Older patients over 65 years old or patients aged 60-65 years and not eligible for high dose chemotherapy with untreated stage II-IV MCL were randomized to either R-FC (rituximab, fludarabine, and cyclophosphamide) or R-CHOP. Patients who had a response underwent a second randomization to maintenance therapy with rituximab or interferon alfa, each given until progression. Between January 2004 and October 2010, a total of 560 patients from eight countries were randomized. After the randomization stopped in 2010, all the newly recruited patients were assigned to R-CHOP followed by rituximab maintenance until December 2014. In total, 591 patients registered to MCL Elderly.

TRIANGLE was a randomised three-arm phase III trial conducted by European MCL network. Patients with previously untreated stage II-IV MCL, up to 65 years and suitable for high-dose cytarabine and ASCT were randomized 1:1:1 to the three trial arms A (alternating R-CHOP/ R-DHAP followed by ASCT), A+I (alternating R-CHOP adding ibrutinib / R-DHAP followed by ASCT and maintenance with ibrutinib), and I (alternating R-CHOP adding ibrutinib / R-DHAP followed by maintenance with ibrutinib). Between July 2016 and December 2020, a total of 870 patients from 14 countries were randomized.

Table S1. Summary of the trials

Trial	GLSG1996	European MCL Trial 1*	GLSG2000	MCL Younger	MCL Elderly	TRIANGLE
Recruitment Period	**1996 – 2000** Randomization: May 1996 to Dec 1998 Assignment to the experimental arm: until Sep 2000.	**1996 – 2004** Randomization: Sep 1996 to Mar 2004	**2000 – 2004** Randomization: May 2000 to July 2002 Assignment to the experimental arm: until July 2004.	**2004 – 2014** Randomization: Jul 2004 to Mar 2010 Assignment to the experimental arm: until Dec 2014.	**2004 – 2014** Randomization: Jan 2004 to Oct 2010 Assignment to the experimental arm: until Dec 2014.	**2016 – 2020** Randomization: Jul 2016 to Dec 2020
Age Group	**Younger + Older**	**Younger**	**Younger + Older**	**Younger**	**Older**	**Younger**
Population	age ≥ 18 stage III-IV untreated	age 18-65 stage III-IV untreated ECOG ≤ 2	age ≥ 18 stage III-IV untreated ECOG ≤ 2	age 18-65 stage II-IV untreated ECOG ≤ 2	age ≥ 66 or 60-65 ineligible for high-dose treatment stage II-IV untreated ECOG ≤ 2	age 18-65 suitable for high-dose treatment stage II-IV untreated ECOG ≤ 2
Countries Involved	Germany	Germany, France, the Netherlands, Belgium, Italy	Germany	Germany, France, Poland, Belgium	Germany, France, the Netherlands, Poland, Belgium, Czech Republic, Denmark, Italy	Germany, Italy, the Netherlands, Spain, Sweden, Poland, Denmark, Switzerland, Norway, Czech Republic, Belgium, Israel, Portugal, Finland
Randomization(s)	Induction: **MCP vs. CHOP** Post-remission: **see European MCL Trial 1**	Post- remission: **IFN vs. ASCT**	Induction: **CHOP vs. R-CHOP** Post- remission: **see European MCL Trial 1**	Induction + post-remission: **R-CHOP+ASCT vs. R-CHOP/R-DHAP+ASCT**	Induction: **R-CHOP vs. R-FC** Post- remission: **Rituximab vs. IFN maintenance**	Induction + post-remission: **A vs. A+I vs. I**
Control Treatment	6 (CR after 4 cycles) to 8 (PR after 4 cycles) cycles of MCP if age<60: 2nd randomization for EUMCL1 after 2 cycles if age≥60: IFN-α maintenance	After PR/CR from 4-6 cycles of CHOP-like induction: consolidation with 2 cycles of chemotherapy + IFN-α maintenance	6 cycles of CHOP if age≤65: 2nd randomization for EUMCL1 if PR/CR after induction if age>65: IFN-α maintenance	6 cycles of R-CHOP + Dexa BEAM + TBI + high-dose cyclophosphamide + ASCT	1st randomization: 8 cycles of R-CHOP If PR/CR after induction: 2nd randomization: IFN-α or PegIntron maintenance	Arm A: alternating 3 cycles of R-CHOP/3 cycles of R-DHAP + ASCT

Experimental Treatment	6 (CR after 4 cycles) to 8 (PR after 4 cycles) cycles of CHOP
	
	if age<60:
	2nd randomization for EUMCL1 after 2 cycles
	
	if age≥60:
	IFN-α maintenance
		After PR/CR from 4-6 cycles of CHOP-like induction:
		Dexa BEAM + TBI + high-dose cyclophosphamide + ASCT
			6 cycles of R-CHOP
			
			if age≤65:
			2nd randomization for EUMCL1 if PR/CR after induction
			
			if age>65:
			IFN-α maintenance
				alternating 3 cycles of R-CHOP/3 cycles of R-DHAP+ TBI + high-dose cytarabine + melphalan + ASCT	1st randomization:
					6 cycles of R-FC
					
					If PR/CR after induction:
					2nd randomization:
					Rituximab maintenance
						Arm A+I:
						alternating 3 cycles of Ibrutinib+R-CHOP/3 cycles of R-DHAP + ASCT + Ibrutinib maintenance
						
						Arm I:
						alternating 3 cycles of Ibrutinib+R-CHOP/3 cycles of R-DHAP + Ibrutinib maintenance

No. of registered patients	Total: **188** Induction: <u>Control arm:</u> 51 randomized, 2 assigned <u>Experimental arm:</u> 55 randomized, 9 assigned, 71 assigned after stop of randomization Post-remission: <u>Control arm:</u> 48 randomized, 6 assigned <u>Experimental arm:</u> 41 randomized	Total: **280** (95 from GLSG1996, 126 from GLSG2000, 59 from neither) <u>Control arm:</u> 133 randomized, 18 assigned <u>Experimental arm:</u> 129 randomized	Total: **250** Induction: <u>Control arm:</u> 63 randomized, 3 assigned <u>Experimental arm:</u> 67 randomized, 117 assigned after stop of randomization Post-remission: <u>Control arm:</u> 56 randomized, 12 assigned <u>Experimental arm:</u> 58 randomized	Total: **638** <u>Control arm:</u> 249 randomized <u>Experimental arm:</u> 248 randomized, 141 assigned after stop of randomization	Total: **591** Induction: <u>Control arm:</u> 311 randomized <u>Experimental arm:</u> 249 randomized, 31 assigned after stop of randomization Post-remission: <u>Control arm:</u> 161 randomized <u>Experimental arm:</u> 156 randomized, 31 assigned	Total: **870** <u>Control arm A:</u> 288 randomized <u>Experimental arm A+I:</u> 292 randomized <u>Experimental arm I:</u> 290 randomized

* including patients from German high-dose trial with the same trial design

MCP: mitoxantrone, chlorambucil, and prednisone; CHOP: cyclophosphamide, vincristine, doxorubicin, and prednisone; CR: complete remission; PR: partial remission; IFN-α: interferon-alpha; ECOG: Eastern Cooperative Oncology Group; R-CHOP: rituximab plus CHOP; ASCT: autologous stem cell transplantation; Dexa BEAM: dexamethasone, carmustine, etoposide, cytarabine, and melphalan; TBI: Total Body Irradiation; R-DHAP: rituximab plus dexamethasone, high-dose cytarabine, and cisplatin; R-FC: rituximab, fludarabine, and cyclophosphamide

Table S2. Baseline characteristics of younger (< 60 or ≤ 65 and transplant-eligible) patients by eras

Variable	Value	1996-2000 (N =152)		2000-2004 (N = 137)		2004-2014 (N = 613)		2016-2020 (N=861)	
Age (years)	Median, Min-Max	55	36 - 66	56	35 - 65	56	30 - 67	57	27 - 68
Sex	Male (n, %)	122	80%	109	80%	490	80%	656	76%
Ann Arbor Stage	I (n, %)	0 (n=151)	0%	1 (n=136)	1%	2	0%	1 (n=860)	0%
	II (n, %)	0 (n=151)	0%	1 (n=136)	1%	27	4%	36 (n=860)	4%
	III (n, %)	19 (n=151)	13%	26 (n=136)	19%	74	12%	71 (n=860)	8%
	IV (n, %)	132 (n=151)	87%	108 (n=136)	79%	510	83%	752 (n=860)	87%
B-symptoms	Present (n, %)	63 (n=150)	42%	61 (n=134)	46%	224	37%	235 (n=852)	28%
ECOG	0 (n, %)	52	34%	53	39%	366	60%	632	73%
	1 (n, %)	84	55%	76	55%	226	37%	217	25%
	2 (n, %)	14	9%	8	6%	21	3%	12	1%
	3 (n, %)	1	1%	0	0%	0	0%	0	0%
	4 (n, %)	1	1%	0	0%	0	0%	0	0%
LDH (ULN)	Median, Min-Max	0.83	0.15 - 8.62	0.86	0.38 - 9.6	0.91	0.29 - 12.22	0.92	0.36 - 8.46
LDH	> ULN (n, %)	44	29%	47	34%	222	36%	342	40%
WBC count (10^9/L)	Median, Min-Max	8 (n = 151)	1.46 - 764	7.55 (n = 136)	1.1 - 150.4	7.53	1.05 - 1105	7.2	0.16 - 599
MIPI score	Median, Min-Max	5.58 (n = 151)	4.31 - 8.36	5.52 (n = 136)	4.52 - 8.6	5.58	4.07 - 8.68	5.62	4.25 - 8.1
MIPI	Low (n, %)	94 (n=151)	62%	99 (n=136)	73%	380	62%	498	58%
	Intermediate (n, %)	38 (n=151)	25%	25 (n=136)	18%	142	23%	235	27%
	High (n, %)	19 (n=151)	13%	12 (n=136)	9%	91	15%	128	15%
Ki-67 index (%)	Median, Min-Max	12.9 (n = 73)	1.4 - 90.9	11.4 (n = 81)	1.2 - 43.8	20 (n = 343)	0 - 97	18 (n = 763)	0 - 100
Ki-67 index	≥ 30%	11 (n=73)	15%	4 (n=81)	5%	95 (n=343)	28%	241 (n=763)	32%
Cytology	blastoid	8 (n=89)	9%	3 (n=83)	4%	30 (n=359)	8%	92 (n=777)	12%

P53 expression	> 50% (n, %)	NA	NA	NA	NA	27 (n=197)	14%	83 (n=598)	14%
High risk biology	High risk (n, %)	NA	NA	NA	NA	46 (n=171)	27%	116 (n=603)	19%
Induction treatment assigned	MCP (n, %)	28	18%	0	0%	0	0%	0	0%
	CHOP (n, %)	124	82%	45	33%	0	0%	0	0%
	R-CHOP (n, %)	0	0%	92	67%	237	39%	0	0%
	R-CHOP/R-DHAP (n, %)	0	0%	0	0%	376	61%	286	33%
	IR-CHOP/R-DHAP (n, %)	0	0%	0	0%	0	0%	575	67%
Post-remission treatment assigned	IFN-α (n, %)	87	57%	73	53%	0	0%	0	0%
	ASCT (n, %)	65	43%	64	47%	613	100%	574	67%
	Ibrutinib maintenance (n, %)	0	0%	0	0%	0	0%	575	67%

ECOG: Eastern Cooperative Oncology Group; LDH: lactate dehydrogenase; WBC: white blood cell; MIPI: Mantle Cell Lymphoma International Prognostic Index; high risk biology: high risk MIPI and Ki-67 ≥ 30%, or P53 expression > 50%; MCP: mitoxantrone, chlorambucil, and prednisone; CHOP: cyclophosphamide, vincristine, doxorubicin, and prednisone; R-CHOP: rituximab plus CHOP; R-DHAP: rituximab plus dexamethasone, high-dose cytarabine, and cisplatin; I: ibrutinib; IFN-α: interferon-alpha; ASCT: autologous stem cell transplantation

Table S3. Baseline characteristics of older (>65 or ≥60 and transplant-ineligible) patients by eras

Variable	Value	1996-2000 (N =84)		2000-2004 (N = 124)		2004-2014 (N = 570)	
Age (years)	Median, Min-Max	68	60 - 86	69	60 - 84	71	60 - 88
Sex	Male (n, %)	57	68%	93	75%	401	70%
Ann Arbor Stage	I (n, %)	0	0%	1 (n=122)	1%	2	0%
	II (n, %)	1	1%	1 (n=122)	1%	31	5%
	III (n, %)	9	11%	26 (n=122)	21%	61	11%
	IV (n, %)	74	88%	94 (n=122)	77%	476	84%
B-symptoms	Present (n, %)	39 (n=82)	48%	46 (n=119)	39%	213	37%
ECOG	0 (n, %)	19	23%	40 (n=120)	33%	264	46%
	1 (n, %)	57	68%	66 (n=120)	55%	261	46%
	2 (n, %)	4	5%	14 (n=120)	12%	45	8%
	3 (n, %)	4	5%	0 (n=120)	0%	0	0%
LDH (ULN)	Median, Min-Max	0.88 (n = 83)	0.36 - 2.17	0.87 (n = 118)	0.45 - 3.32	0.95	0.29 - 11.27
LDH	> ULN (n, %)	27 (n=83)	33%	43 (n=118)	36%	248	44%
WBC count (10^9/L)	Median, Min-Max	8.65 (n = 82)	2.6 - 86	8.1 (n = 119)	2.7 - 658.8	7.9	1.04 - 537
MIPI score	Median, Min-Max	6.03 (n = 81)	5.31 - 7.44	6.06 (n = 115)	5.47 - 9.18	6.21	4.97 - 8.84
MIPI	Low (n, %)	10 (n=81)	12%	9 (n=115)	8%	47	8%
	Intermediate (n, %)	46 (n=81)	57%	61 (n=115)	53%	229	40%
	High (n, %)	25 (n=81)	31%	45 (n=115)	39%	294	52%
Ki-67 index (%)	Median, Min-Max	20 (n = 41)	3.7 - 76	21 (n = 53)	3.65 - 90.95	19.5 (n = 269)	2 - 91
Ki-67 index	≥ 30%	9 (n=41)	22%	17 (n=53)	32%	85 (n=269)	32%
Cytology	blastoid	0 (n=3)	0%	2 (n=3)	67%	35 (n=292)	12%
P53 expression	> 50% (n, %)	NA	NA	NA	NA	27 (n=151)	18%
High risk biology	High risk (n, %)	NA	NA	NA	NA	63 (n=154)	41%

Induction treatment assigned	MCP (n, %)	25	30%	0	0%	0	0%
	CHOP (n, %)	59	70%	32	26%	0	0%
	R-CHOP (n, %)	0	0%	92	74%	295	52%
	R-FC (n, %)	0	0%	0	0%	275	48%
Post-remission treatment assigned	IFN-α (n, %)	84	100%	124	100%	158 (n=340)	46%
	Rituximab maintenance (n, %)	0	0%	0	0%	182 (n=340)	54%

ECOG: Eastern Cooperative Oncology Group; LDH: lactate dehydrogenase; WBC: white blood cell; MIPI: Mantle Cell Lymphoma International Prognostic Index; high risk biology: high risk MIPI and Ki-67 ≥ 30%, or P53 expression > 50%; MCP: mitoxantrone, chlorambucil, and prednisone; CHOP: cyclophosphamide, vincristine, doxorubicin, and prednisone; R-CHOP: rituximab plus CHOP; R-FC: rituximab, fludarabine, and cyclophosphamide; IFN-α: interferon-alpha

Table S4. Median follow-up time by trial eras

	Median follow-up in years (95% CI)	1996-2000	2000-2004	2004-2014	2016-2020
FFS	**All patients**	12.6 (9.4-NA)	11.0 (9.0-NA)	9.4 (8.5-9.9)	4.6 (4.5-4.7)
	Younger patients	11.4 (9.4-NA)	11.0 (9.0-NA)	8.9 (7.8-9.7)	4.6 (4.5-4.7)
	Older patients	13.0 (13.0-NA)	13.0 (7.4-NA)	10.0 (8.9-10.8)	-
	GLSG1996	12.6 (9.4-NA)	-	-	-
	European MCL Trial 1	12.1 (9.37-15.5)		-	-
	GLSG2000	-	11.0 (9.0-NA)	-	-
	MCL Younger	-	-	8.9 (7.8-9.7)	-
	MCL Elderly	-	-	10.0 (8.9-10.8)	-
	TRIANGLE	-	-	-	4.6 (4.5-4.7)
OS	**All patients**	15.5 (14.1-17.5)	12.1 (11.0-13.4)	9.4 (8.9-9.9)	4.6 (4.6-4.7)
	Younger patients	15.4 (14.1-18.5)	12.3 (11.0-14.3)	9.4 (8.4-10.2)	4.6 (4.6-4.7)
	Older patients	15.9 (13.0-NA)	12.4 (9.7-NA)	9.4 (8.9-10.1)	-
	GLSG1996	15.5 (14.1-17.5)	-	-	-
	European MCL Trial 1	14.0 (12.1-14.7)		-	-
	GLSG2000	-	12.3 (11.0-14.0)	-	-
	MCL Younger	-	-	9.4 (8.4-10.2)	-
	MCL Elderly	-	-	9.4 (8.9-10.1)	-
	TRIANGLE	-	-	-	4.6 (4.6-4.7)

FFS: failure-free survival; OS: overall survival; CI: confidence interval

Table S5. MIPI-adjusted hazard ratios of FFS and OS by trial eras and treatment in younger and older patients

	Age group	Trial era and treatment	Median (95% CI)	5-year probability (95% CI)	10-year probability (95% CI)	HR adjusted for MIPI (95% CI)	p
FFS	**Younger**	**1996 – 2000: MCP + IFN/ASCT**	0.8 (0.3-1.6)	0.08 (0.02 - 0.31)	NA	1.72 (1.12 - 2.64)	0.013
	(N=1761)	**1996 – 2000: CHOP + IFN/ASCT**	1.4 (1.0-2.3)	0.14 (0.09 - 0.22)	0.07 (0.03 - 0.14)	Reference	-
		2000 – 2004: CHOP + IFN/ASCT	0.9 (0.7-1.8)	0.07 (0.02 - 0.20)	0.05 (0.01 - 0.18)	1.30 (0.91 - 1.85)	0.15
		2000 – 2004: R-CHOP + IFN/ASCT	2.7 (2.2-4.1)	0.33 (0.24 - 0.45)	0.13 (0.07 - 0.24)	0.59 (0.44 - 0.79)	0.00045
		2004 – 2014: R-CHOP + ASCT	3.9 (3.4-4.6)	0.42 (0.36 - 0.49)	0.25 (0.20 - 0.32)	0.45 (0.35 - 0.57)	<0.0001
		2004 – 2014: R-CHOP/R-DHAP + ASCT	7.6 (6.5-10.1)	0.62 (0.57 - 0.68)	0.43 (0.38 - 0.50)	0.25 (0.19 - 0.31)	<0.0001
		2016 – 2020: R-CHOP/R-DHAP + ASCT	Not reached	0.64 (0.58 - 0.71)	NA	0.21 (0.16 - 0.28)	<0.0001
		2016 – 2020: IR-CHOP/R-DHAP +/- ASCT + I	Not reached	0.74 (0.70 - 0.78)	NA	0.14 (0.11 - 0.18)	<0.0001
	Older	**1996 – 2000: MCP + IFN**	1.3 (1.1-2.7)	0.09 (0.02 - 0.33)	0.04 (0.01 - 0.30)	0.82 (0.50 - 1.35)	0.44
	(N=766)	**1996 – 2000: CHOP + IFN**	1.4 (1.1-1.7)	0.11 (0.05 - 0.23)	0.02 (0.00 - 0.12)	Reference	-
		2000 – 2004: CHOP + IFN	1.4 (0.9-2.4)	0.04 (0.01 - 0.24)	NA	1.00 (0.63 - 1.57)	0.99
		2000 – 2004: R-CHOP + IFN	1.8 (1.5-2.1)	0.12 (0.07 - 0.22)	0.02 (0.00 - 0.11)	0.64 (0.45 - 0.91)	0.013
		2004 – 2014: R-CHOP + IFN/R	2.4 (2.1-3.2)	0.31 (0.26 - 0.38)	0.13 (0.09 - 0.19)	0.42 (0.31 - 0.57)	<0.0001
		2004 – 2014: R-FC + IFN/R	2.3 (1.8-3.0)	0.31 (0.26 - 0.38)	0.18 (0.13 - 0.24)	0.44 (0.32 - 0.60)	<0.0001
OS	**Younger**	**1996 – 2000: MCP + IFN/ASCT**	4.0 (3.0-7.4)	0.35 (0.21 - 0.59)	0.17 (0.07 - 0.42)	1.34 (0.84 - 2.14)	0.22
	(N=1761)	**1996 – 2000: CHOP + IFN/ASCT**	5.7 (4.7-6.9)	0.52 (0.44 - 0.62)	0.29 (0.21 - 0.39)	Reference	-
		2000 – 2004: CHOP + IFN/ASCT	5.0 (3.8-9.2)	0.50 (0.37 - 0.67)	0.30 (0.18 - 0.49)	1.04 (0.69 - 1.56)	0.86
		2000 – 2004: R-CHOP + IFN/ASCT	7.6 (5.8-11.0)	0.65 (0.56 - 0.76)	0.40 (0.30 - 0.53)	0.76 (0.54 - 1.06)	0.11
		2004 – 2014: R-CHOP + ASCT	11.1 (7.8-NA)	0.68 (0.63 - 0.75)	0.54 (0.48 - 0.62)	0.56 (0.42 - 0.74)	<0.0001
		2004 – 2014: R-CHOP/R-DHAP + ASCT	NA (10.8-NA)	0.76 (0.71 - 0.80)	0.60 (0.54 - 0.66)	0.42 (0.32 - 0.55)	<0.0001
		2016 – 2020: R-CHOP/R-DHAP + ASCT	Not reached	0.77 (0.72 - 0.83)	NA	0.35 (0.25 - 0.49)	<0.0001

	2016 – 2020: IR-CHOP/R-DHAP +/- ASCT + I	Not reached	0.87 (0.84 - 0.90)	NA	0.19 (0.14 - 0.27)	<0.0001
Older	**1996 – 2000: MCP + IFN**	3.7 (3.0-5.2)	0.33 (0.19 - 0.59)	0.04 (0.01 - 0.28)	1.10 (0.67 - 1.82)	0.70
(N=766)	**1996 – 2000: CHOP + IFN**	3.8 (2.9-6.0)	0.42 (0.31 - 0.57)	0.11 (0.05 - 0.24)	Reference	-
	2000 – 2004: CHOP + IFN	3.8 (2.9-6.0)	0.37 (0.23 - 0.60)	0.14 (0.05 - 0.37)	0.91 (0.56 - 1.49)	0.72
	2000 – 2004: R-CHOP + IFN	4.6 (3.9-5.9)	0.45 (0.35 - 0.57)	0.21 (0.13 - 0.33)	0.67 (0.46 - 0.97)	0.032
	2004 – 2014: R-CHOP + IFN/R	5.8 (5.3-8.0)	0.56 (0.50 - 0.63)	0.32 (0.26 - 0.39)	0.50 (0.36 - 0.68)	<0.0001
	2004 – 2014: R-FC + IFN/R	3.9 (2.9-4.5)	0.42 (0.36 - 0.48)	0.28 (0.22 - 0.34)	0.69 (0.50 - 0.94)	0.020

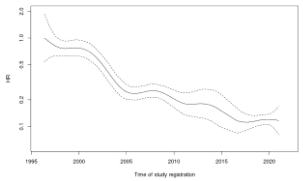
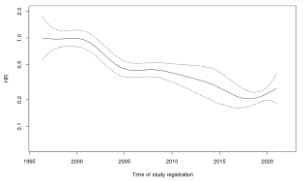
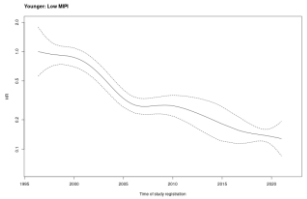
FFS: failure-free survival; OS: overall survival; HR: hazard ratio; CI: confidence interval; MCP: mitoxantrone, chlorambucil, and prednisone; IFN: interferon-alpha; ASCT: autologous stem cell transplantation; CHOP: cyclophosphamide, vincristine, doxorubicin, and prednisone; R-CHOP: rituximab plus CHOP; R-DHAP: rituximab plus dexamethasone, high-dose cytarabine, and cisplatin; I: ibrutinib; R-FC: rituximab, fludarabine, and cyclophosphamide

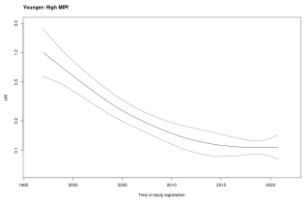
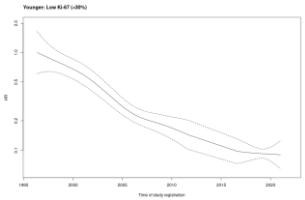
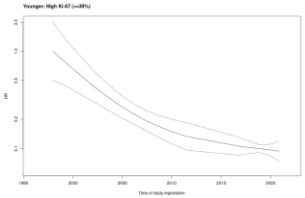
Table S6. FFS and OS of younger and older patients assigned to the same treatment regimen across trial eras

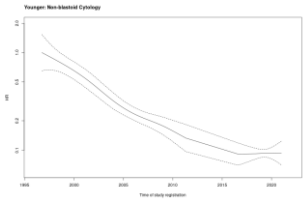
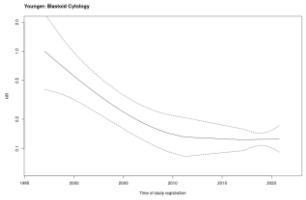
Treatment	Age group	Outcome	Trial era	N	No. of events	Median (years) (95% CI)	5- year probability (95% CI)	10- year probability (95% CI)	MIPI-adjusted HR (95% CI)	p
CHOP + IFN	**Younger**	**FFS**	**1996-2000**	71	65	1.3 (0.9-1.7)	0.06 (0.02 - 0.16)	0.02 (0.00 - 0.14)	Reference	
			2000-2004	28	27	0.8 (0.6-1.3)	0.04 (0.01 - 0.25)	Not reached	1.51 (0.96 - 2.39)	0.077
		OS	**1996-2000**	71	55	4.6 (3.7-6.5)	0.42 (0.31 - 0.56)	0.22 (0.14 - 0.35)	Reference	
			2000-2004	28	20	5.5 (2.1-NA)	0.52 (0.36 - 0.75)	0.28 (0.15 - 0.55)	1.01 (0.60 - 1.70)	0.96
	Older	**FFS**	**1996-2000**	59	55	1.4 (1.1-1.7)	0.11 (0.05 - 0.23)	0.02 (0.00 - 0.12)	Reference	
			2000-2004	32	30	1.4 (0.9-2.4)	0.04 (0.01 - 0.24)	Not reached	0.95 (0.60 - 1.51)	0.82
		OS	**1996-2000**	59	52	3.8 (2.9-6.0)	0.42 (0.31 - 0.57)	0.11 (0.05 - 0.24)	Reference	
			2000-2004	32	24	3.8 (2.9-6.0)	0.37 (0.23 - 0.60)	0.14 (0.05 - 0.37)	0.97 (0.59 - 1.59)	0.90
CHOP + ASCT	**Younger**	**FFS**	**1996-2000**	53	46	2.8 (1.2-4.1)	0.23 (0.14 - 0.38)	0.12 (0.05 - 0.27)	Reference	
			2000-2004	17	15	2.3 (0.8-3.6)	0.12 (0.03 - 0.43)	0.12 (0.03 - 0.43)	1.02 (0.56 - 1.86)	0.95
		OS	**1996-2000**	53	38	6.9 (5.7-12.3)	0.66 (0.54 - 0.81)	0.38 (0.26 - 0.55)	Reference	
			2000-2004	17	11	5.0 (3.8-NA)	0.47 (0.28 - 0.78)	0.34 (0.17 - 0.67)	1.18 (0.58 - 2.39)	0.65
R-CHOP + ASCT	**Younger**	**FFS**	**2000-2004**	47	37	3.7 (2.6-6.9)	0.42 (0.30 - 0.59)	0.18 (0.09 - 0.35)	Reference	
			2004-2014	237	162	3.9 (3.4-4.6)	0.42 (0.36 - 0.49)	0.25 (0.20 - 0.32)	1.18 (0.83 - 1.69)	0.36
		OS	**2000-2004**	47	28	9.9 (6.4-NA)	0.69 (0.57 - 0.84)	0.46 (0.33 - 0.65)	Reference	
			2004-2014	237	107	11.1 (7.8-NA)	0.68 (0.63 - 0.75)	0.54 (0.48 - 0.62)	1.35 (0.88 - 2.05)	0.17
R-CHOP/R-DHAP+ ASCT	**Younger**	**FFS**	**2004-2014**	376	162	7.6 (6.5-10.1)	0.62 (0.57 - 0.68)	0.43 (0.38 - 0.50)	Reference	
			2016-2020	286	92	Not reached	0.64 (0.58 - 0.71)	Not reached	0.89 (0.68 - 1.16)	0.39
		OS	**2004-2014**	376	123	NA (10.8-NA)	0.76 (0.71 - 0.80)	0.60 (0.54 - 0.66)	Reference	
			2016-2020	286	59	Not reached	0.77 (0.72 - 0.83)	Not reached	0.82 (0.59 - 1.14)	0.24

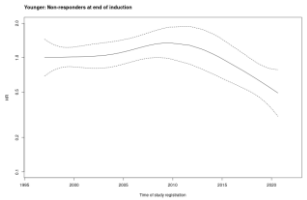
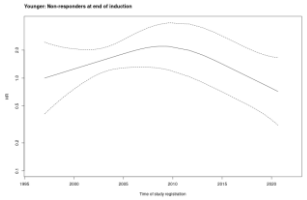
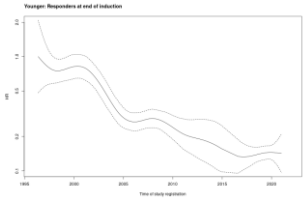
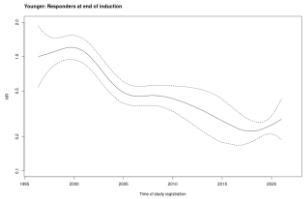
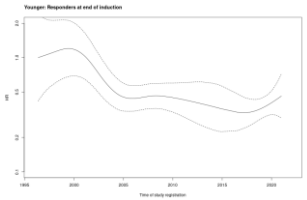
FFS: failure-free survival; OS: overall survival; HR: hazard ratio (adjusted for MIPI score); CI: confidence interval; CHOP: cyclophosphamide, vincristine, doxorubicin, prednisone; IFN: interferon-alpha; ASCT: autologous stem cell transplantation; R: rituximab; DHAP: dexamethasone, high-dose cytarabine, cisplatin

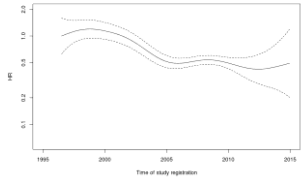
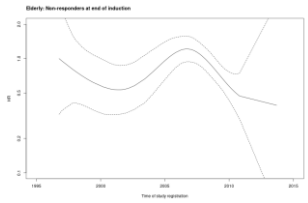
Table S7. Dynamic trend of FFS and OS over time of trial enrolment in younger and older patients and in MIPI, Ki-67, cytology, P53 expression and response subgroups

Patient group		Model	FFS			OS		
			Non-linear p value	HR (95% CI)	If linear: p value	Non-linear p value	HR (95% CI)	If linear: p value
Younger patients	All (N=1761)	adjusted for MIPI score	<0.0001			0.025		
		adjusted for MIPI score and treatment	0.859	0.99 (0.97 - 1.02)	0.62	0.089	0.98 (0.96 - 1.01)	0.16
	MIPI low (N=1071)	unadjusted	0.0016			0.062	0.93 (0.91 - 0.95)	<0.0001
		adjusted for treatment	0.77	1.00 (0.97 - 1.02)	0.79	0.14	0.98 (0.94 - 1.02)	0.25
	MIPI intermediate (N=440)	unadjusted	0.16	0.92 (0.90 - 0.93)	<0.0001	0.92	0.93 (0.91 - 0.95)	<0.0001
		adjusted for treatment	0.60	0.98 (0.94 - 1.02)	0.38	0.77	0.97 (0.93 - 1.02)	0.24

Younger patients	**MIPI high (N=250)**	**unadjusted**	0.0061			0.13	0.93 (0.91 - 0.96)	<0.0001
		adjusted for treatment	0.59	1.00 (0.95 - 1.05)	0.98	0.84	0.99 (0.93 - 1.04)	0.63
	Ki-67 low (N=909)	**adjusted for MIPI score**	<0.0001			0.49	0.91 (0.89 - 0.93)	<0.0001
		adjusted for MIPI score and treatment	0.54	0.99 (0.96 - 1.02)	0.40	0.12	0.96 (0.92 - 1.00)	0.051
	Ki-67 high (N=351)	**adjusted for MIPI score**	0.016			0.16	0.93 (0.91 - 0.96)	<0.0001
		adjusted for MIPI score and treatment	0.58	1.00 (0.96 - 1.04)	0.87	0.89	0.99 (0.95 - 1.04)	0.69

Younger patients	**Non-blastoid cytology (N=1175)**	**adjusted for MIPI score**	<0.0001			0.16	0.92 (0.91 - 0.94)	<0.0001
		adjusted for MIPI score and treatment	0.22	0.99 (0.96 - 1.01)	0.33	0.080	0.98 (0.95 - 1.01)	0.25
	Blastoid cytology (N=133)	**adjusted for MIPI score**	0.028			0.57	0.95 (0.92 - 0.99)	0.011
		adjusted for MIPI score and treatment	0.23	0.98 (0.92 - 1.05)	0.66	0.12	0.98 (0.91 - 1.06)	0.68
	P53 expression low (≤50%) (N=685)	**adjusted for MIPI score**	0.23	0.93 (0.91 - 0.95)	<0.0001	0.54	0.93 (0.90 - 0.96)	<0.0001
		adjusted for MIPI score and treatment	0.36	0.98 (0.94 - 1.01)	0.22	0.61	0.97 (0.92 - 1.02)	0.21
	P53 expression high (>50%) (N=110)	**adjusted for MIPI score**	0.59	0.96 (0.90 - 1.01)	0.12	0.40	0.93 (0.88 - 0.99)	0.029
		adjusted for MIPI score and treatment	0.19	1.08 (0.99 - 1.19)	0.083	0.56	1.08 (0.98 - 1.19)	0.11

Younger patients	**Did not respond to induction (N=140)**	**adjusted for MIPI score**	0.027		0.61	1.02 (0.99 - 1.05)	0.14	
		adjusted for MIPI score and induction treatment	0.041		0.88	0.97 (0.91 - 1.03)	0.33	
	Responded to induction (N=1545)	**adjusted for MIPI score**	0.00019		0.0083			
		adjusted for MIPI score and treatment	0.65	0.99 (0.97 - 1.02)	0.53	0.041		

Older patients	**All (N=766)**	**adjusted for MIPI score**	0.012			0.70	0.95 (0.93 - 0.97)	<0.0001
		adjusted for MIPI score and treatment	0.74	0.98 (0.95 - 1.02)	0.33	0.56	0.98 (0.94 - 1.01)	0.22
	MIPI low (N=66)	**unadjusted**	0.38	0.88 (0.82 - 0.96)	0.0030	0.12	0.94 (0.86 - 1.03)	0.19
		adjusted for treatment	0.083	0.92 (0.80 - 1.06)	0.25	0.28	1.02 (0.85 - 1.21)	0.87
	MIPI intermediate (N=336)	**unadjusted**	0.27	0.93 (0.90 - 0.96)	<0.0001	0.79	0.93 (0.90 - 0.97)	<0.0001
		adjusted for treatment	0.84	0.99 (0.93 - 1.04)	0.61	0.24	0.96 (0.90 - 1.02)	0.18
	MIPI high (N=364)	**unadjusted**	0.066	0.95 (0.91 - 0.98)	0.0020	0.21	0.97 (0.94 - 1.00)	0.061
		adjusted for treatment	0.17	0.99 (0.95 - 1.04)	0.80	0.13	0.99 (0.94 - 1.04)	0.66
	Ki-67 low (N=251)	**adjusted for MIPI score**	0.091	0.91 (0.88 - 0.95)	<0.0001	0.91	0.92 (0.88 - 0.96)	0.00012
		adjusted for MIPI score and treatment	0.60	0.99 (0.92 - 1.06)	0.74	0.69	0.95 (0.87 - 1.03)	0.18
	Ki-67 high (N=111)	**adjusted for MIPI score**	0.15	0.94 (0.88 - 1.01)	0.072	0.82	0.95 (0.89 - 1.01)	0.087
		adjusted for MIPI score and treatment	0.18	0.97 (0.87 - 1.07)	0.49	0.78	0.95 (0.86 - 1.06)	0.36
	Not responded to induction (N=120)	**adjusted for MIPI score**	0.80	0.97 (0.92 - 1.02)	0.29	0.0091		
		adjusted for MIPI score and induction treatment	0.71	0.95 (0.87 - 1.03)	0.19	0.23	0.94 (0.87 - 1.02)	0.12

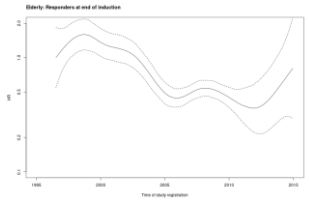
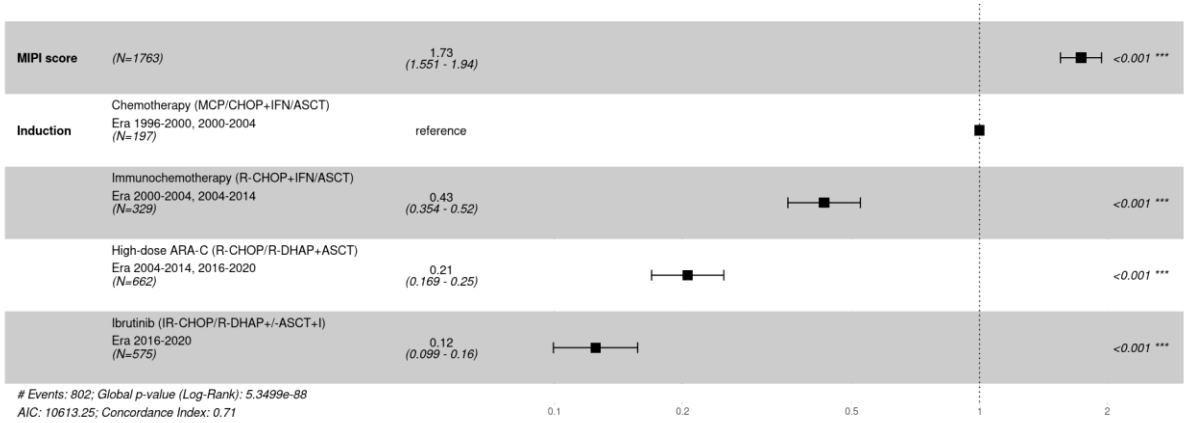
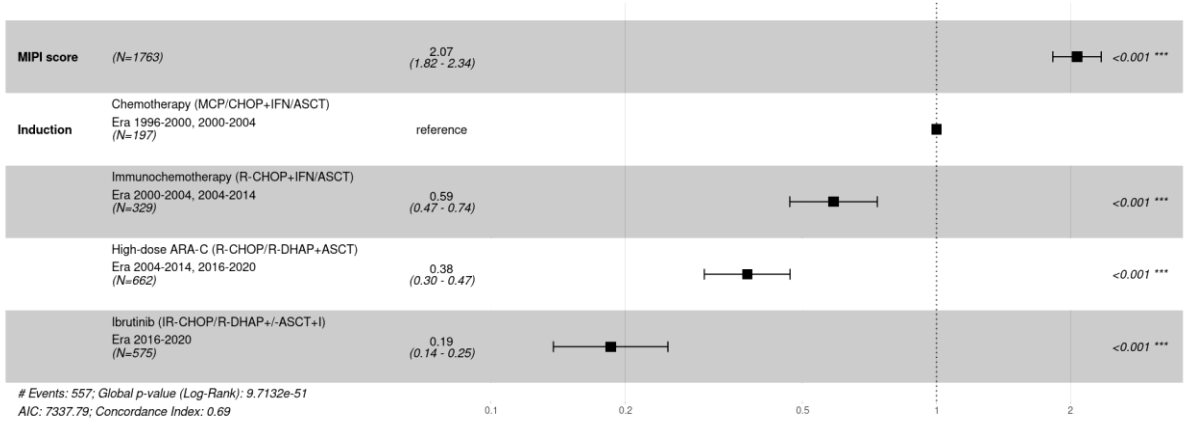
Responded to induction (N=613)	**adjusted for MIPI score**	0.0013			0.49	0.93 (0.91 - 0.95)	<0.0001
	adjusted for MIPI score and treatment (n=500)	0.13	0.99 (0.95 - 1.03)	0.61	0.78	0.98 (0.93 - 1.03)	0.42

Figure S1. MIPI-adjusted hazard ratios of induction treatment on (A) FFS in younger patients, (B) OS in younger patients, (C) FFS in older patients, and (D) OS in older patients

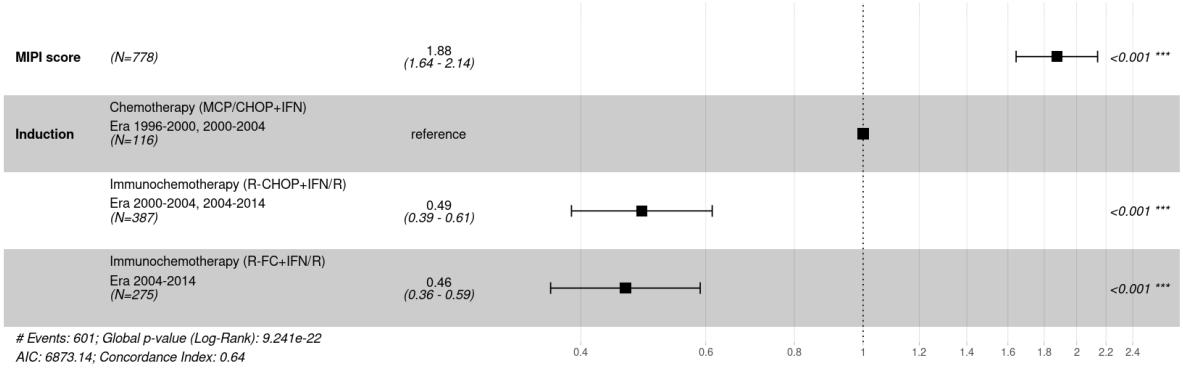
(A)



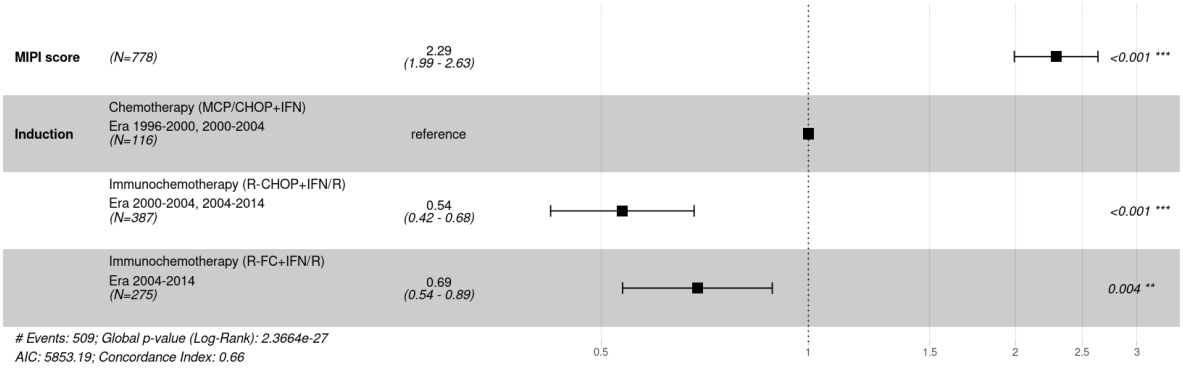
(B)



(C)



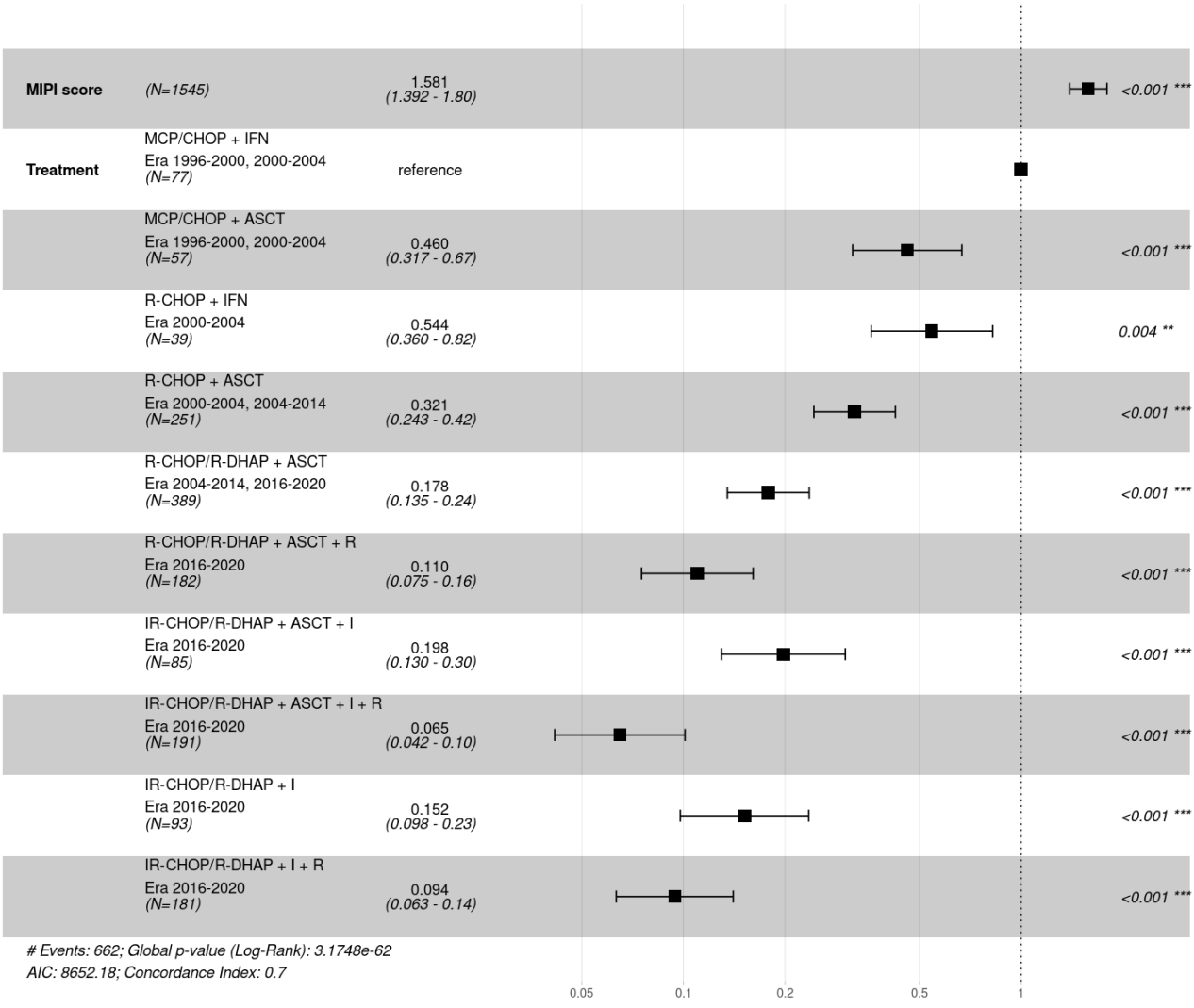
(D)



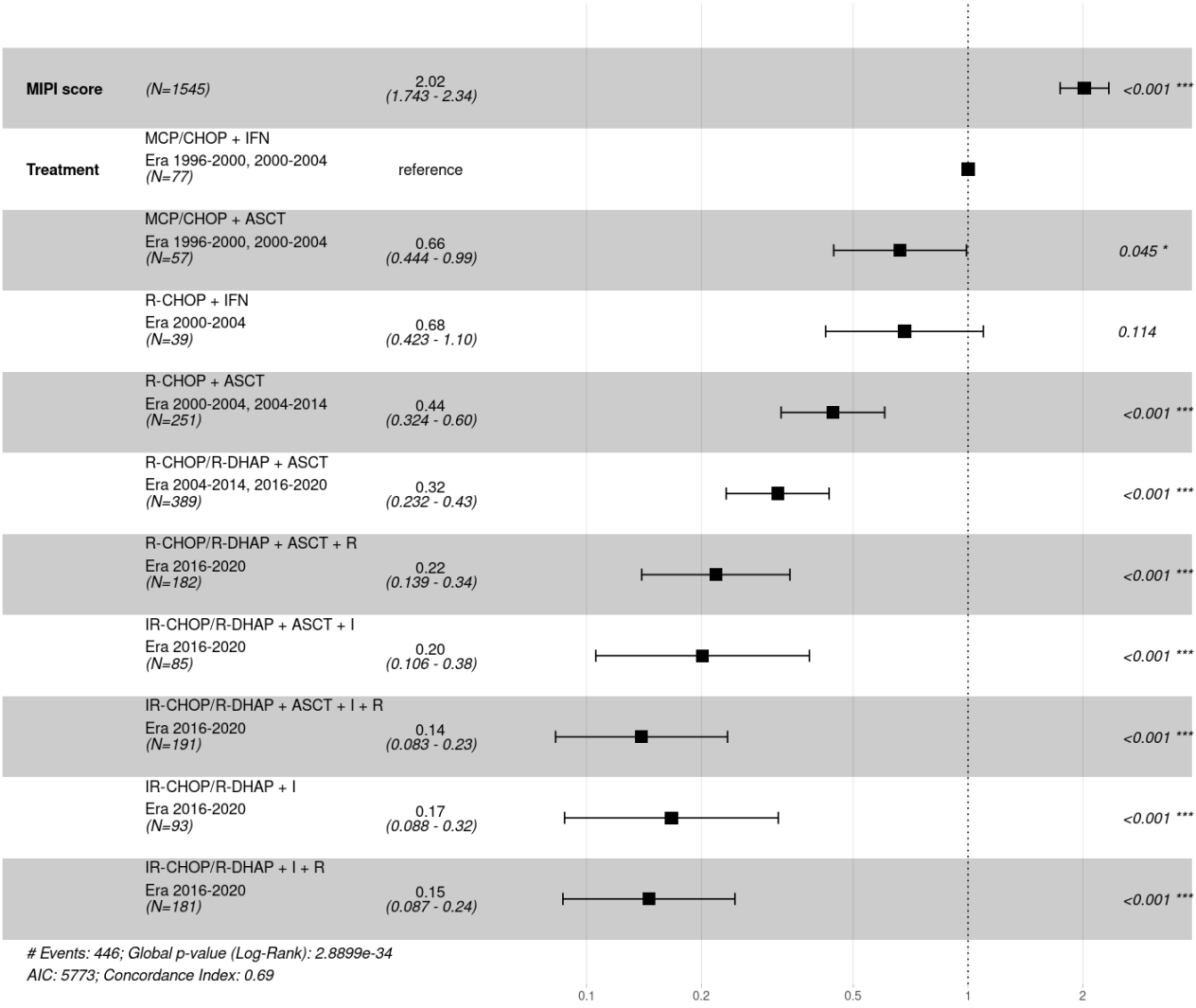
FFS: failure-free survival; OS: overall survival; MCP: mitoxantrone, chlorambucil, and prednisone; CHOP: cyclophosphamide, vincristine, doxorubicin, and prednisone; R-CHOP: rituximab plus CHOP; R-DHAP: rituximab plus dexamethasone, high-dose cytarabine, and cisplatin; I: ibrutinib; R-FC: rituximab, fludarabine, and cyclophosphamide

Figure S2. MIPI-adjusted hazard ratios of treatment regimens on (A) FFS and (B) OS in younger patients who responded to induction treatment, and (C) FFS and (D) OS in older patients who responded to induction treatment

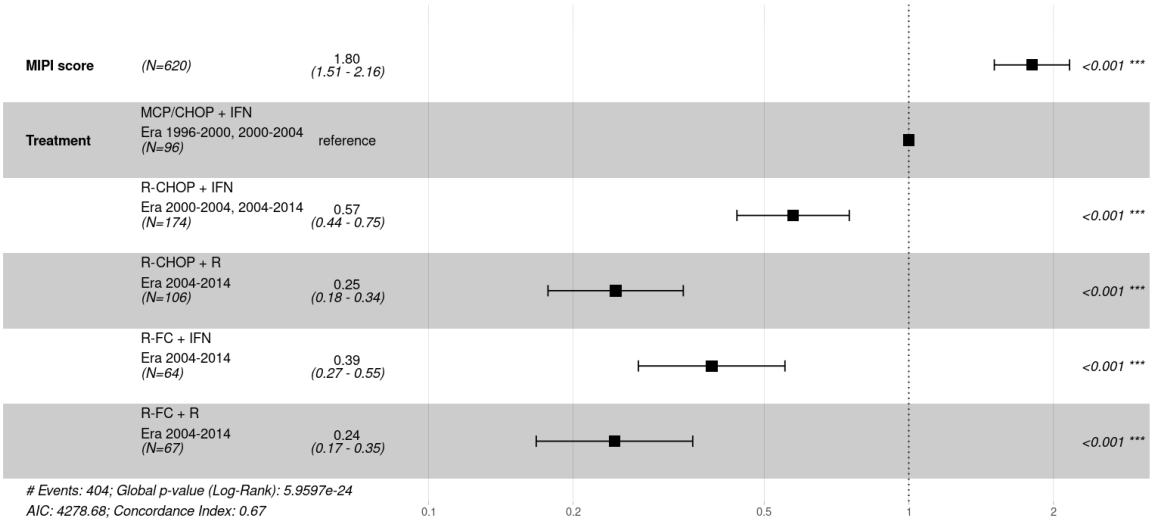
(A)



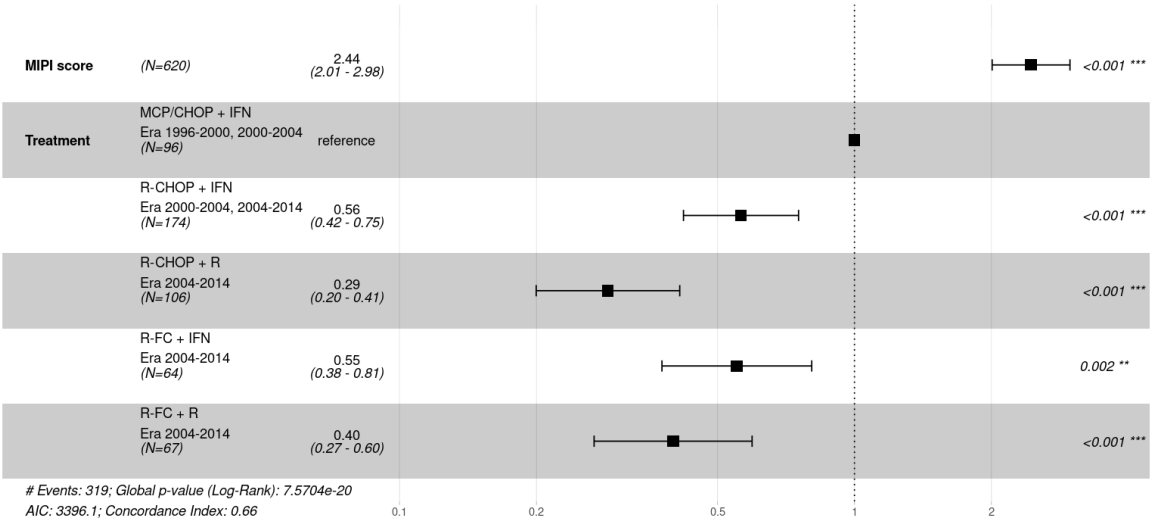
(B)


MIPI score
(N=1545)
2.02
(1.743 - 2.34)
<0.001 ***
Treatment
MCP/CHOP + IFN
Era 1996-2000, 2000-2004
(N=77)
reference
MCP/CHOP + ASCT
Era 1996-2000, 2000-2004
(N=57)
0.66
(0.444 - 0.99)
0.045 *
R-CHOP + IFN
Era 2000-2004
(N=39)
0.68
(0.423 - 1.10)
0.114
R-CHOP + ASCT
Era 2000-2004, 2004-2014
(N=251)
0.44
(0.324 - 0.60)
<0.001 ***
R-CHOP/R-DHAP + ASCT
Era 2004-2014, 2016-2020
(N=389)
0.32
(0.232 - 0.43)
<0.001 ***
R-CHOP/R-DHAP + ASCT + R
Era 2016-2020
(N=182)
0.22
(0.139 - 0.34)
<0.001 ***
IR-CHOP/R-DHAP + ASCT + I
Era 2016-2020
(N=85)
0.20
(0.106 - 0.38)
<0.001 ***
IR-CHOP/R-DHAP + ASCT + I + R
Era 2016-2020
(N=191)
0.14
(0.083 - 0.23)
<0.001 ***
IR-CHOP/R-DHAP + I
Era 2016-2020
(N=93)
0.17
(0.088 - 0.32)
<0.001 ***
IR-CHOP/R-DHAP + I + R
Era 2016-2020
(N=181)
0.15
(0.087 - 0.24)
<0.001 ***
Events: 446; Global p-value (Log-Rank): 2.8899e-34
AIC: 5773; Concordance Index: 0.69
0.1
0.2
0.5
1
2

(C)



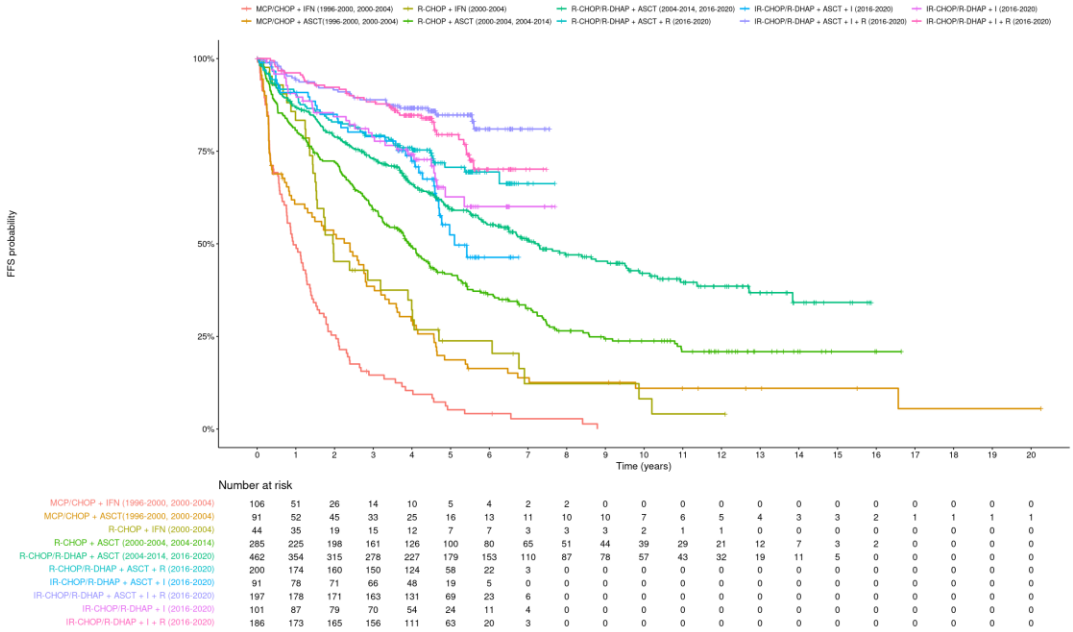
(D)



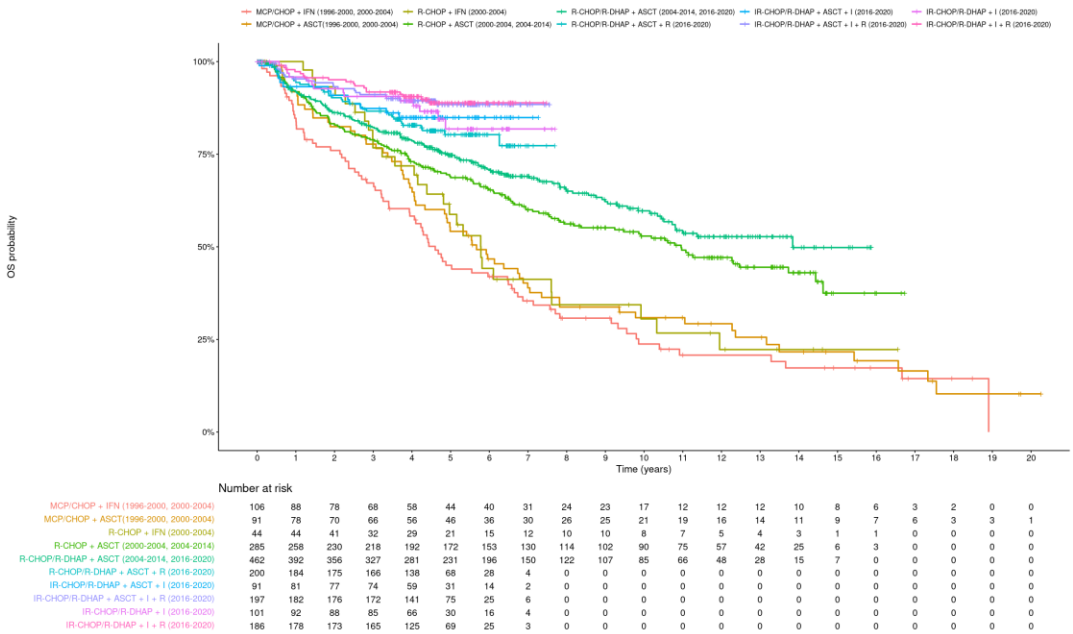
FFS: failure-free survival; OS: overall survival; MCP: mitoxantrone, chlorambucil, and prednisone; CHOP: cyclophosphamide, vincristine, doxorubicin, and prednisone; R-CHOP: rituximab plus CHOP; R-DHAP: rituximab plus dexamethasone, high-dose cytarabine, and cisplatin; I: ibrutinib; IFN: interferon-alpha; ASCT: autologous stem cell transplantation; R-FC: rituximab, fludarabine, and cyclophosphamide; R: rituximab maintenance

Figure S3. Kaplan-Meier plots by treatment regimens for (A) FFS in younger patients (B) OS in younger patients (C) FFS in older patients (D) OS in older patients

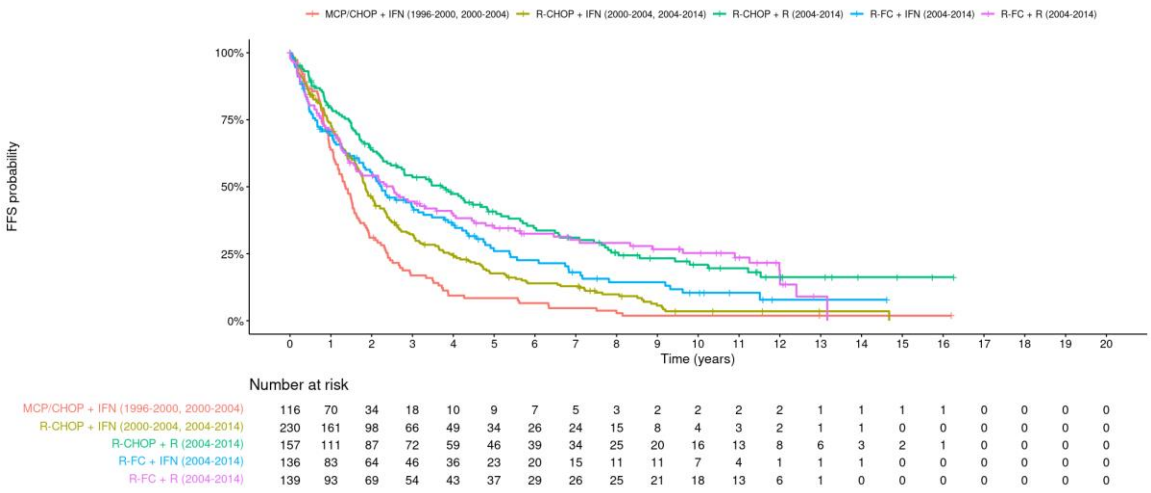
(A)



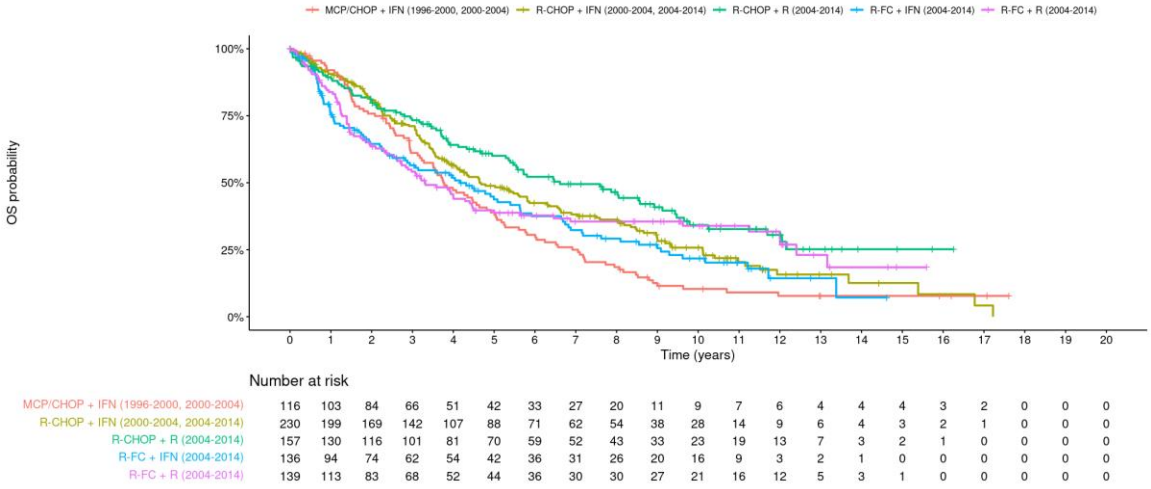
(B)



(C)



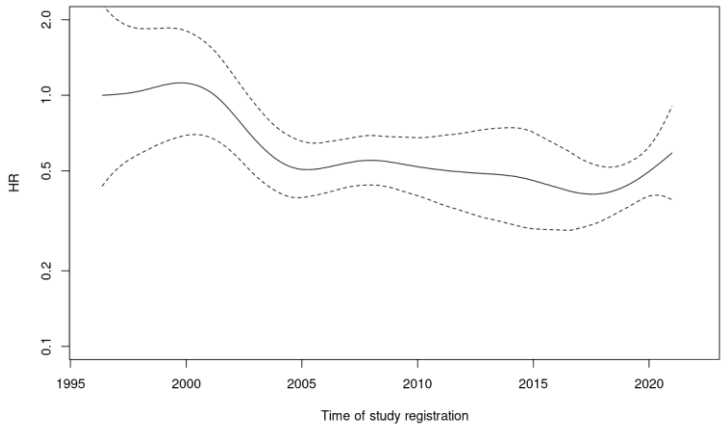
(D)



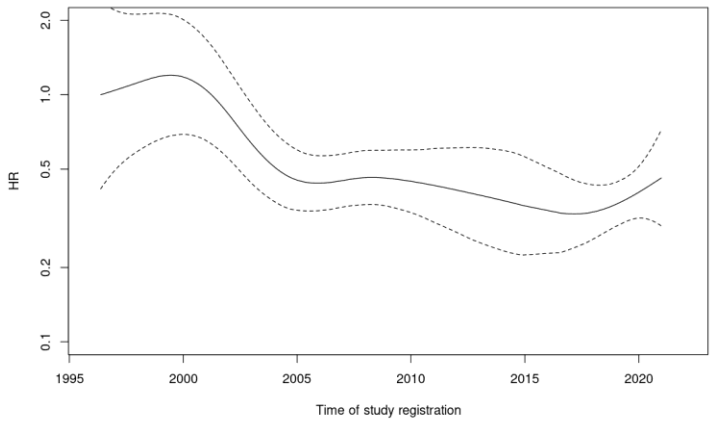
FFS: failure-free survival; OS: overall survival; MCP: mitoxantrone, chlorambucil, and prednisone; IFN: interferon-alpha; ASCT: autologous stem cell transplantation; CHOP: cyclophosphamide, vincristine, doxorubicin, and prednisone; R-CHOP: rituximab plus CHOP; R-DHAP: rituximab plus dexamethasone, high-dose cytarabine, and cisplatin; I: ibrutinib; R: rituximab; R-FC: rituximab, fludarabine, and cyclophosphamide

Figure S4. Dynamic OS trend of MIPI and treatment-adjusted hazard ratios with 95% confidence intervals over time of trial enrolment in (A) all the younger patients, (B) younger patients who responded to induction treatment, (C) younger responders who were assigned to induction with Rituximab, and (D) younger responders who were assigned to ASCT

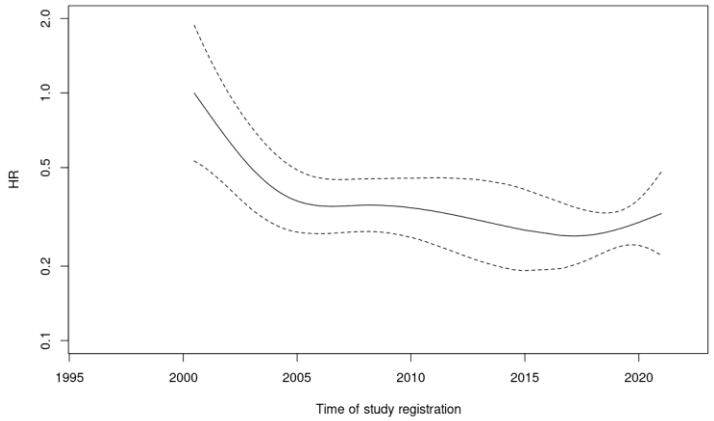
(A)



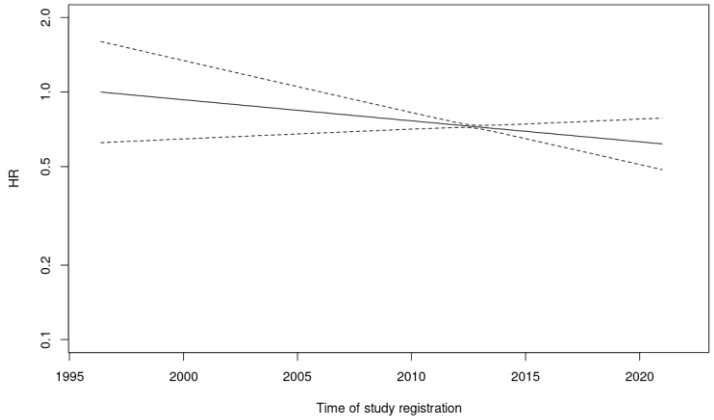
(B)



(C)



(D)



* MIPI-adjusted interaction effect between time of study registration and induction with Rituximab: p=0.38, between time of study registration and ASCT: p=0.0040.