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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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 the Mantle Cell Lymphoma International Prognostic Index (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), there was a strong increase in median OS from 4.9 years (5-year OS: 49%) in the period 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: 40-49%) 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 in 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] In the past decades, the incidence of MCL has continued to rise, 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 require 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 have 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 survival (EFS) and overall survival (OS) 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 the 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 a 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 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 *Online Supplementary Appendix* (Summary of the Trial Designs and *Online Supplementary 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 years or patients aged under 65 years for whom high-dose treatment was indicated 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.

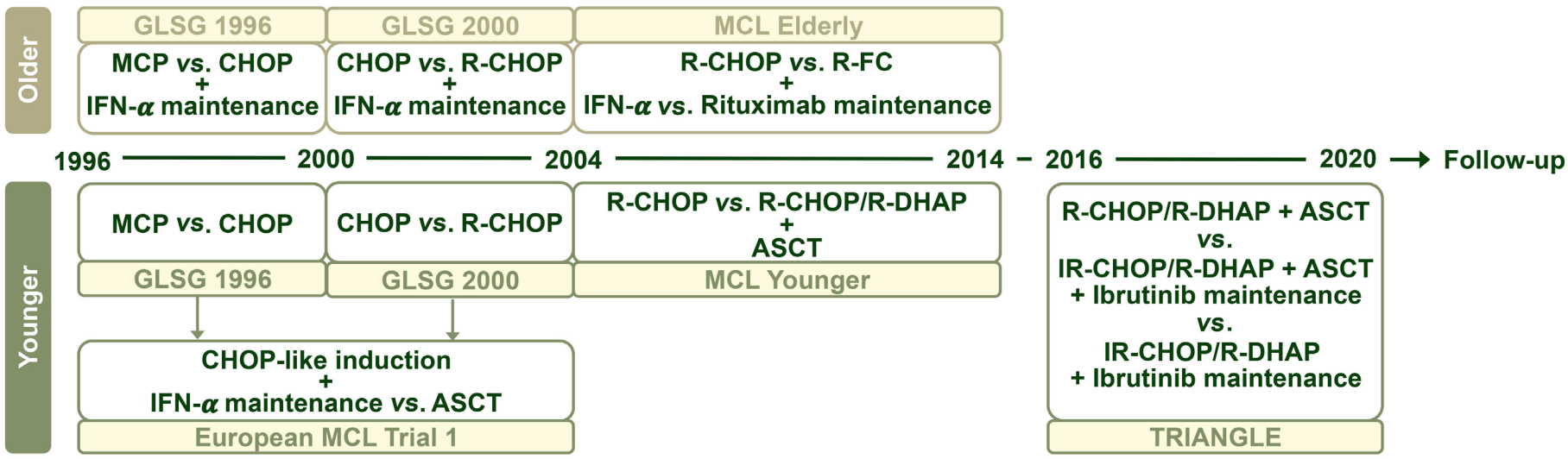

Figure 1. Patients and study design. ASCT: autologous stem cell transplantation; CHOP: cyclophosphamide, vincristine, doxorubicin, and prednisone; IFN-α: interferon-alpha; IR-CHOP: ibrutinib plus R-CHOP; MCP: mitoxantrone, chlorambucil, and prednisone; R-CHOP: rituximab plus CHOP; R-FC: rituximab, fludarabine, and cyclophosphamide; R-DHAP: rituximab plus dexamethasone, high-dose cytarabine, and cisplatin.

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 analysis

Failure-free survival 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 co-variate in Cox models, adjusting for MIPI score and treatment. We assessed linearity of the registration time using penalized (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 HR 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 December 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, and higher lactate dehydrogenase (LDH) and Ki-67 index among younger patients (*Online Supplementary 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 (*Online Supplementary 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 (*Online Supplementary 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, again to 5.7 years (4.8-6.8) in 2004-2014, and has not yet been reached 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 had not

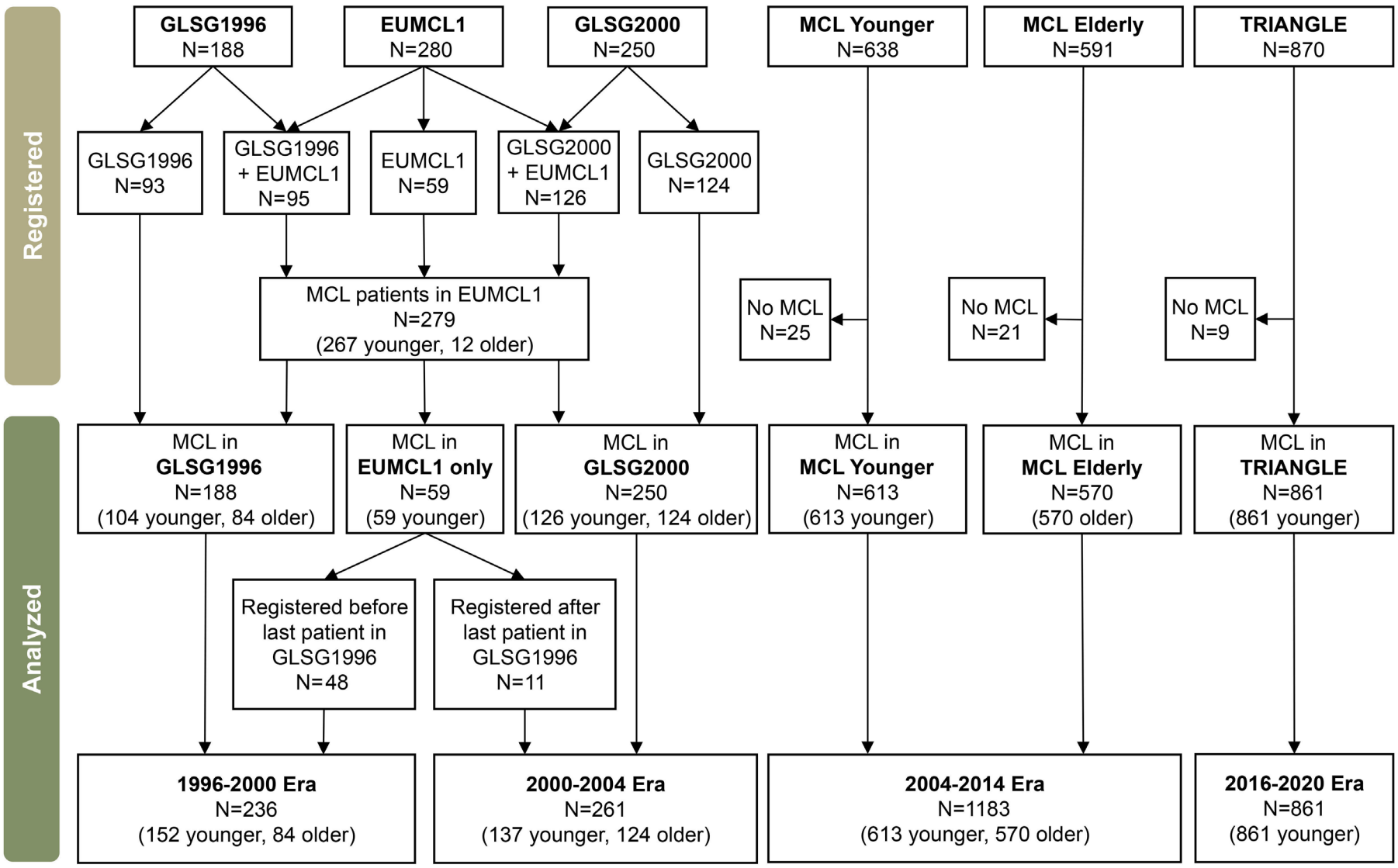

Figure 2. Patient flow diagram.

yet been 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 (95% CI: 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). There was significant improvement 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 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 and *Online Supplementary 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 and *Online Supplementary 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 (*Online Supplementary 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 (*Online Supplementary 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 (*Online Supplementary 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) (*Online Supplementary Figure S2B*). Ibrutinib added to induction and maintenance treatment

Table 1. Baseline characteristics of all analyzed patients.

Variable	All analyzed patients N=2,541	Younger patients N=1,763	Older patients N=778
Study era, N (%)			
1996-2000	236 (9)	152 (9)	84 (11)
2000-2004	261 (10)	137 (8)	124 (16)
2004-2014	1,183 (47)	613 (35)	570 (73)
2016-2020	861 (34)	861 (49)	0 (0)
Age in years			
Median (Min-Max)	60 (27-88)	56 (27-68)	70 (60-88)
Sex, N (%)			
Male	1,928 (76)	1,377 (78)	551 (71)
Ann Arbor Stage, N (%)	N=2,536	N=1,760	N=776
I	7 (<1)	4 (<1)	3 (0)
II	97 (4)	64 (4)	33 (4)
III	286 (11)	190 (11)	96 (12)
IV	2,146 (85)	1,502 (85)	644 (83)
B-symptoms , N (%)	N=2,520	N=1,749	N=771
Present	881 (35)	583 (33)	298 (39)
ECOG, N (%)	N=2,537		N=774
0	1,426 (56)	1,103 (63)	323 (42)
1	987 (39)	603 (34)	384 (50)
2	118 (5)	55 (3)	63 (8)
3	5 (<1)	1 (<1)	4 (1)
4	1 (<1)	1 (<1)	0 (0)
LDH (ULN)	N=2,534		N=771
Median (Min-Max)	0.91 (0.15-12.22)	0.9 (0.15-12.22)	0.93 (0.29-11.27)
LDH, N (%)	N=2,534		N=771
> ULN	973 (38)	655 (37)	318 (41)
WBC count, x10^9/L	N=2,532	N=1,761	N=771
Median (Min-Max)	7.6 (0.16-1,105)	7.45 (0.16-1,105)	8 (1.04-658.8)
MIPI score	N=2,527	N=1,761	N=766
Median (Min-Max)	5.77 (4.07-9.18)	5.59 (4.07-8.68)	6.17 (4.97-9.18)
MIPI risk group, N (%)	N=2,527	N=1,761	N=766
Low	1,137 (45)	1,071 (61)	66 (9)
Intermediate	776 (31)	440 (25)	336 (44)
High	614 (24)	250 (14)	364 (48)
Ki-67 index	N=1,623	N=1,260	N=363
Median (Min-Max)	18.5 (0-100)	18 (0-100)	19.5 (2-91)
Ki-67 index, N (%)	N=1,623	N=1,260	N=363
≥ 30%	462 (28)	351 (28)	111 (31)
Cytology, N (%)	N=1,606	N=1,308	N=298
Blastoid	170 (11)	133 (10)	37 (12)
P53 expression, N (%)	N=946	N=795	N=151
> 50%	137 (14)	110 (14)	27 (18)
High risk biology, N (%)	N=928	N=774	N=154
High risk	225 (24)	162 (21)	63 (41)

Younger patients are defined as those aged <60 or ≤65 years and who are transplant-eligible. Older patients are defined as those aged >65 or ≥60 years and who are transplant-ineligible. ECOG: Eastern Cooperative Oncology Group; LDH: lactate dehydrogenase; MIPI: Mantle Cell Lymphoma International Prognostic Index; high risk biology: high risk MIPI and Ki-67 ≥30%, or P53 expression >50%; WBC: white blood cell.

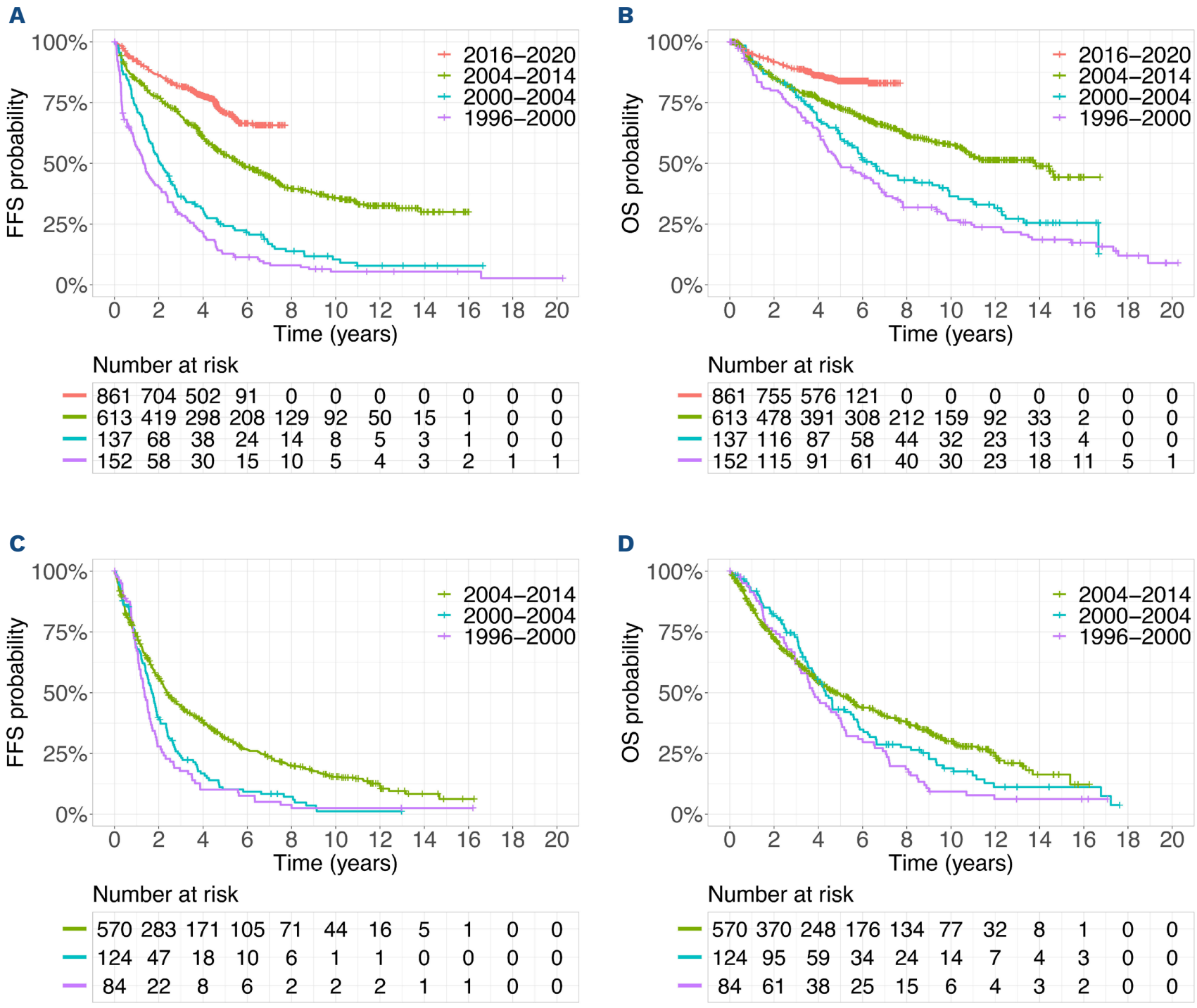

Figure 3. Kaplan-Meier plots by trial eras. (A) Failure-free survival (FFS) and (B) overall survival (OS) in younger patients. (C) FFS and (D) OS in older patients.

improved OS, whereas adding ASCT to ibrutinib-containing regimens did not further improve survival outcomes (*Online Supplementary 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 (*Online Supplementary Figures S2A, B* and *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) (*Online Supplementary 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) (*Online Supplementary Figures S2C, D* and *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 HR 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), (*Online Supplementary Figure S4A*), indicating that first-line treatment drove most survival improvements (*Online Supplementary 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

Table 2. Hazard ratios of failure-free survival and overall survival 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 N=1,761	1996-2000	1.3 (1.0-1.8)	0.13 (0.08-0.20)	0.05 (0.03-0.11)	-	-	-	-	-
		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 N=766	1996-2000	1.3 (1.1-1.6)	0.10 (0.05-0.20)	0.03 (0.01-0.10)	-	-	-	-	-
		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 N=1,761	1996-2000	4.9 (4.3-6.7)	0.49 (0.42-0.58)	0.27 (0.20-0.35)	-	-	-	-	-
		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 N=766	1996-2000	3.8 (3.2-5.0)	0.40 (0.30-0.52)	0.09 (0.05-0.19)	-	-	-	-	-
		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

CI: confidence interval; FFS: failure-free survival; HR: hazard ratios; MIPI: Mantle Cell Lymphoma International Prognostic Index; N: number; NA: not available; OS: overall survival.

1996 to 2015 (non-linear *P*=0.70, MIPI-adjusted HR=0.95, 0.930.97, *P*<0.0001) (Figure 5C, D and *Online Supplementary 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) (*Online Supplementary 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 (*Online Supplementary 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) (*Online Supplementary Table S7* and *Online Supplementary Figure S4B*). The same trend was observed in the younger subgroup assigned to induction with rituximab (non-linear *P*=0.022) (*Online Supplementary Figure S4C*), but not in the ASCT subgroup (aHR=0.98, 0.95-1.01, *P*=0.18) (*Online Supplementary 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

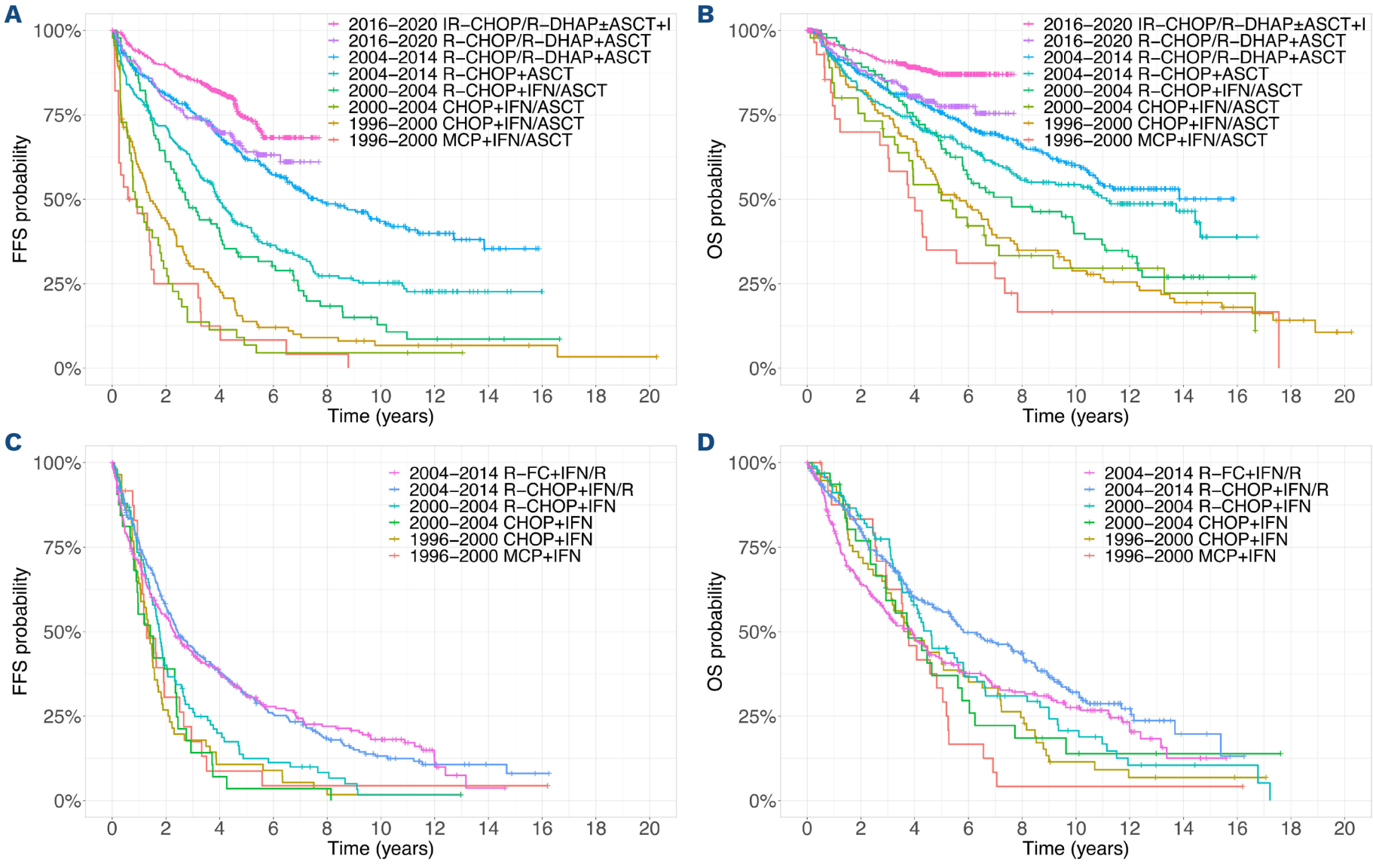

Figure 4. Kaplan-Meier plots by trial eras and treatment. (A) Failure-free survival (FFS) and (B) overall survival (OS) in younger patients. (C) FFS and (D) OS in older patients. ASCT: autologous stem cell transplantation; CHOP: cyclophosphamide, vincristine, doxorubicin, and prednisone; IFN: interferon-alpha; MCP: mitoxantrone, chlorambucil, 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).

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 US 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 HR 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

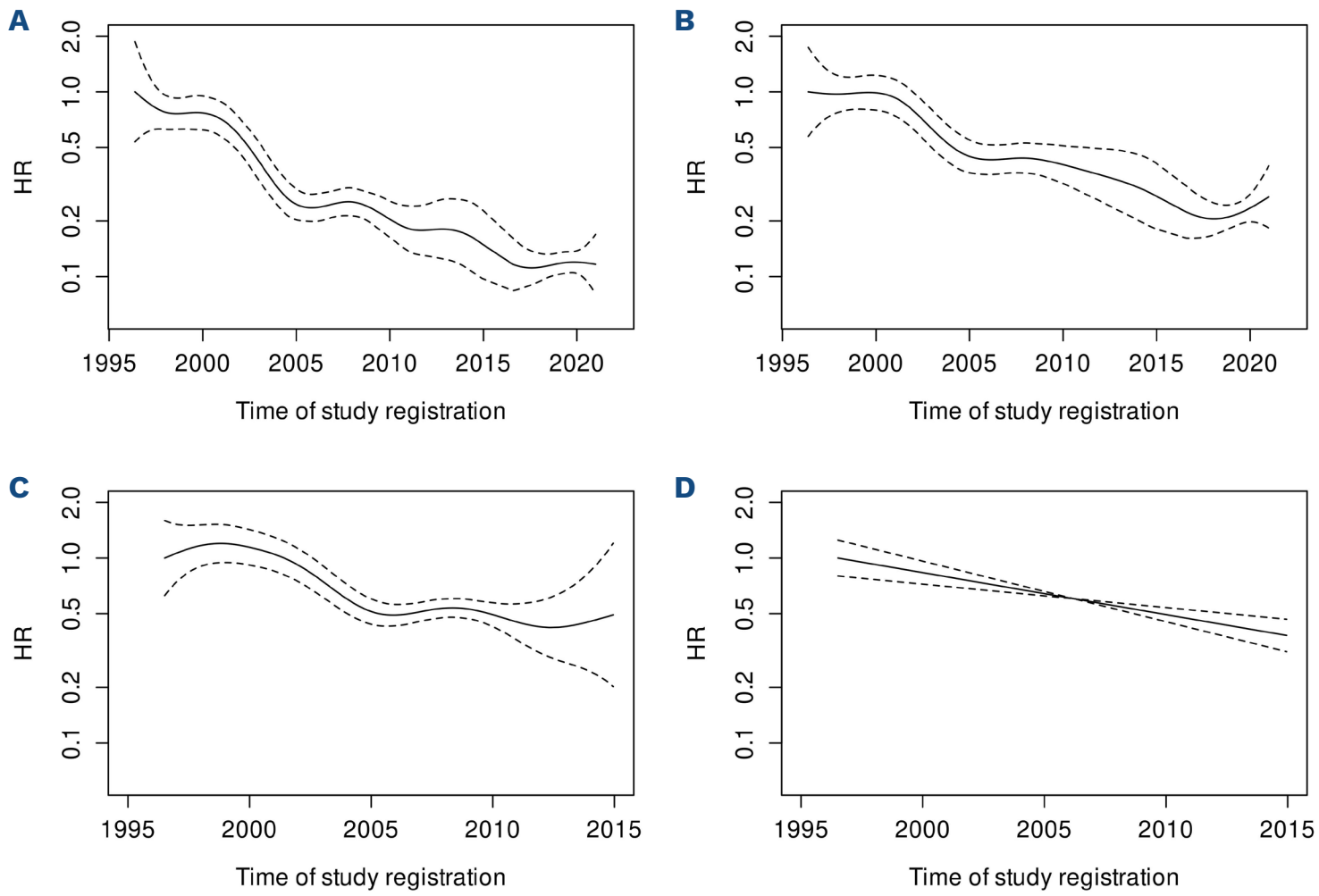

Figure 5. Dynamic trend of Mantle Cell Lymphoma International Prognostic Index-adjusted hazard ratios and 95% confidence intervals over time of trial enrolment. (A) Failure-free survival (FFS) and (B) overall survival (OS) in younger patients. (C) FFS and (D) OS in older patients.

a prospective cohort study reporting similar EFS 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 there had been 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 into clinical practice – the sequential introduction of rituximab, ASCT, high-dose cytarabine, and ibrutinib – 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 *versus* 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 years of age 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) the use 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 comparisons between eras with minimized confounding; 3) detailed treatment information enabling the identification of key factors driving outcome improvements; and 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.

Disclosures

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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 co-ordinated 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 for publication.

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.

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.