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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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

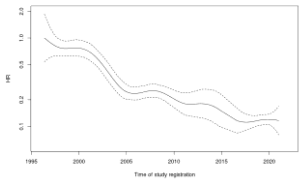
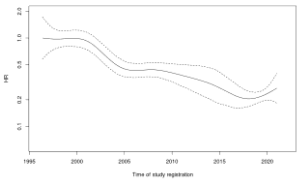
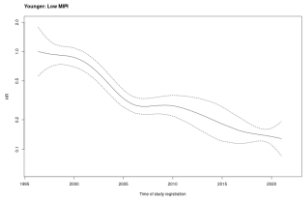
FFS: failure-free survival; OS: overall survival; HR: hazard ratio; CI: confidence interval; MCP: mitoxantrone, chlorambucil, and prednisone; IFN: interferon-alpha; ASCT: autologous stem cell transplantation; CHOP: cyclophosphamide, vincristine, doxorubicin, and prednisone; R-CHOP: rituximab plus CHOP;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

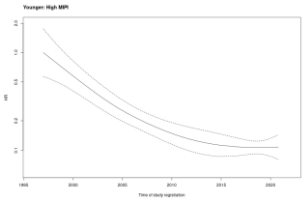
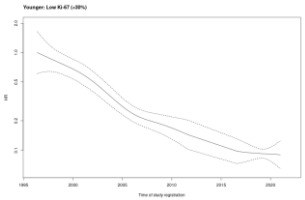
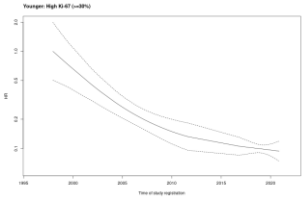
Table S6. FFS and OS of younger and older patients assigned to the same treatment regimen across trial eras

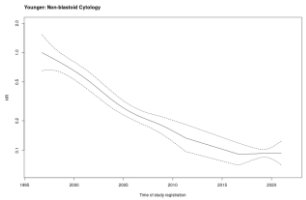
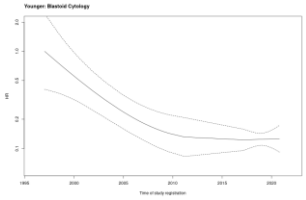
Treatment	Age group	Outcome	Trial era	N	No. of events	Median (years) (95% CI)	5- year probability (95% CI)	10- year probability (95% CI)	MIPI-adjusted HR (95% CI)	p
CHOP + IFN	**Younger**	**FFS**	**1996-2000**	71	65	1.3 (0.9-1.7)	0.06 (0.02 - 0.16)	0.02 (0.00 - 0.14)	Reference	
			2000-2004	28	27	0.8 (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

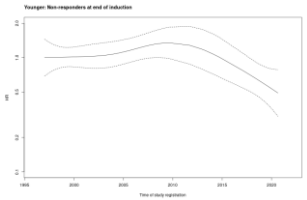
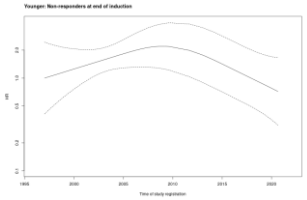
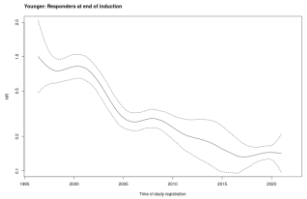
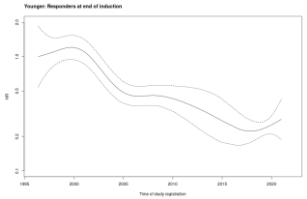
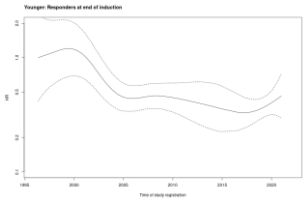
FFS: failure-free survival; OS: overall survival; HR: hazard ratio (adjusted for MIPI score); CI: confidence interval; CHOP: cyclophosphamide, vincristine, doxorubicin, prednisone; IFN: interferon-alpha; ASCT: autologous stem cell transplantation; R: rituximab; DHAP: dexamethasone, high-dose cytarabine,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

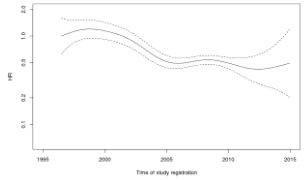
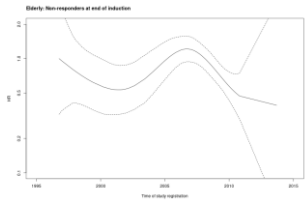
Table S7. Dynamic trend of FFS and OS over time of trial enrolment in younger and older patients and in MIPI, Ki-67, cytology, P53 expression and response subgroups

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

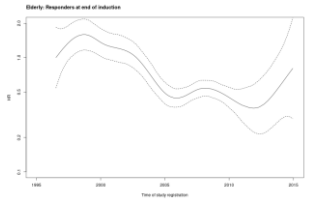
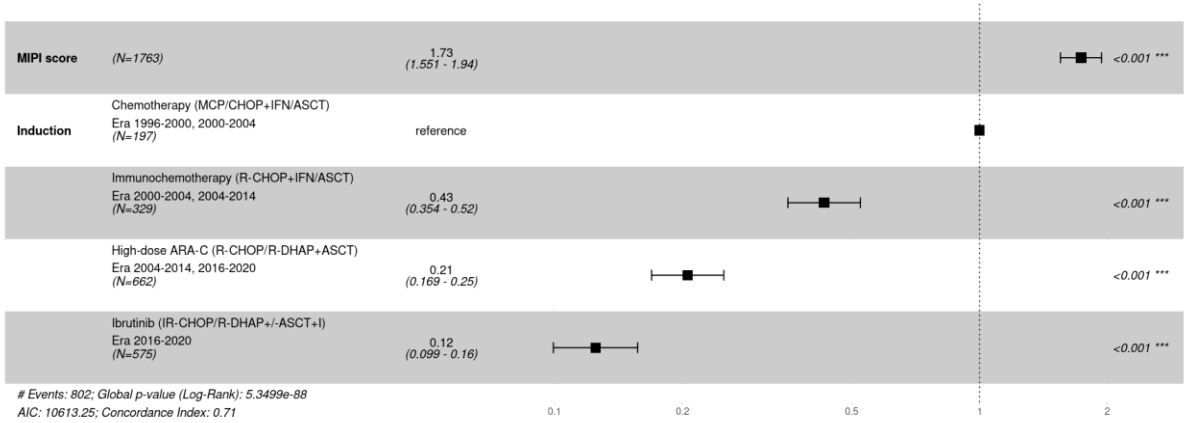
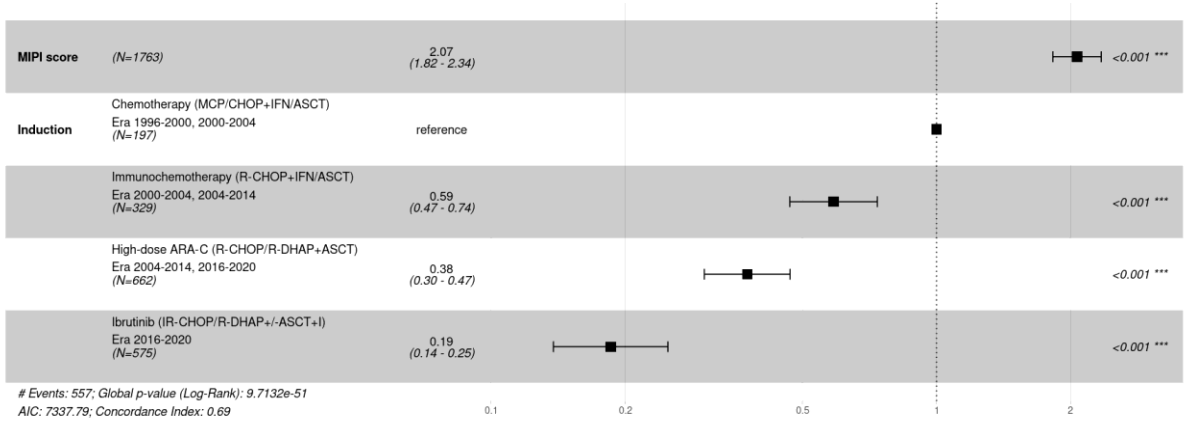
Responded to induction (N=613)	**adjusted for MIPI score**	0.0013			0.49	0.93 (0.91 - 0.95)	<0.0001
	adjusted for MIPI score and treatment (n=500)	0.13	0.99 (0.95 - 1.03)	0.61	0.78	0.98 (0.93 - 1.03)	0.42

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

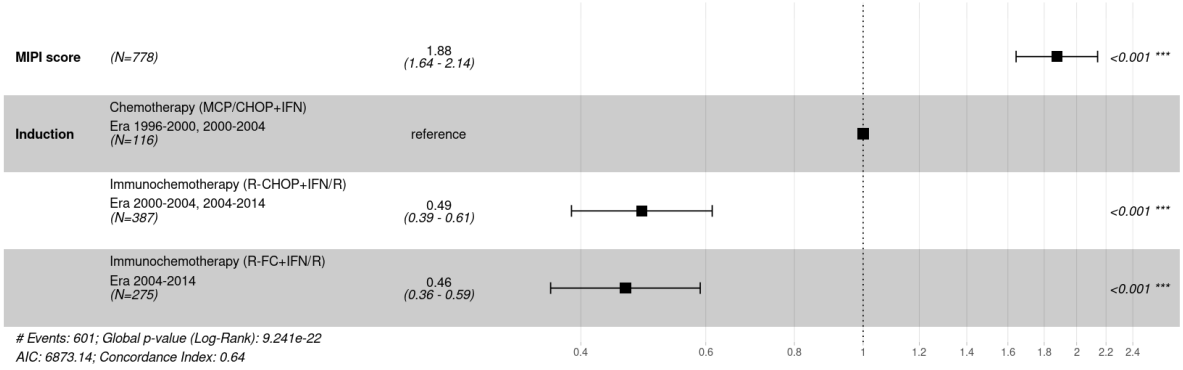
(A)



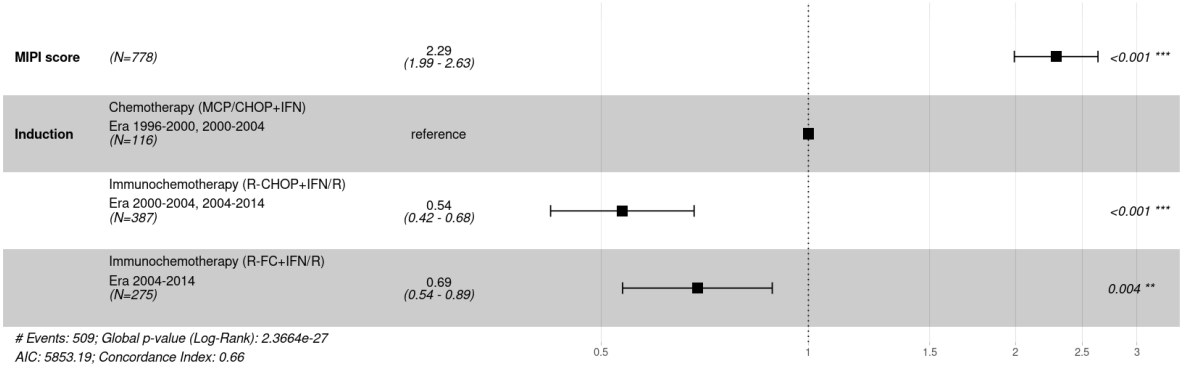
(B)



(C)



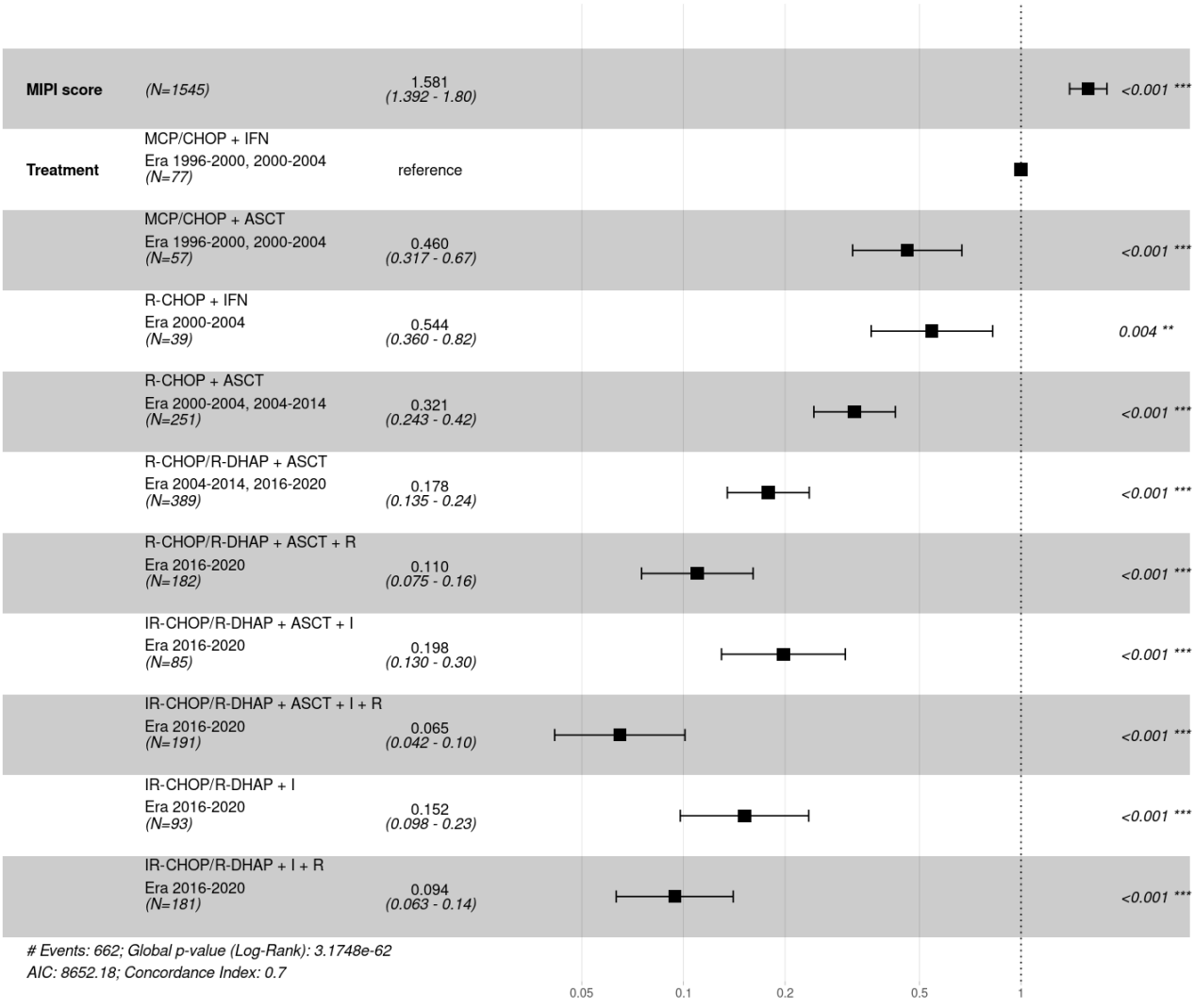
(D)



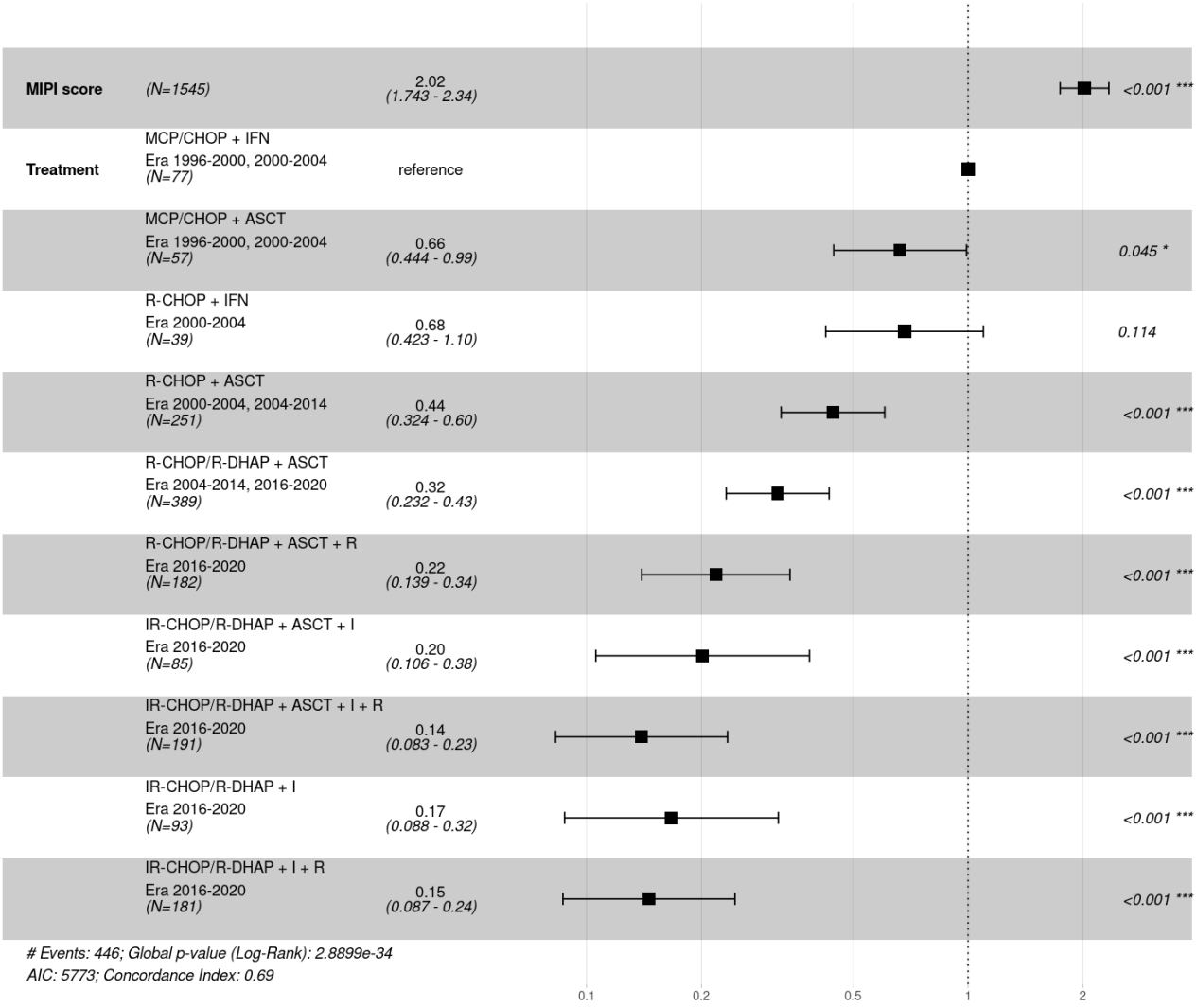
FFS: failure-free survival; OS: overall survival; MCP: mitoxantrone, chlorambucil, and prednisone; CHOP: cyclophosphamide, vincristine, doxorubicin, and prednisone; R-CHOP: rituximab plus CHOP; R-DHAP: rituximab plus dexamethasone, high-dose cytarabine, and cisplatin; I: ibrutinib; R-FC: rituximab, fludarabine,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

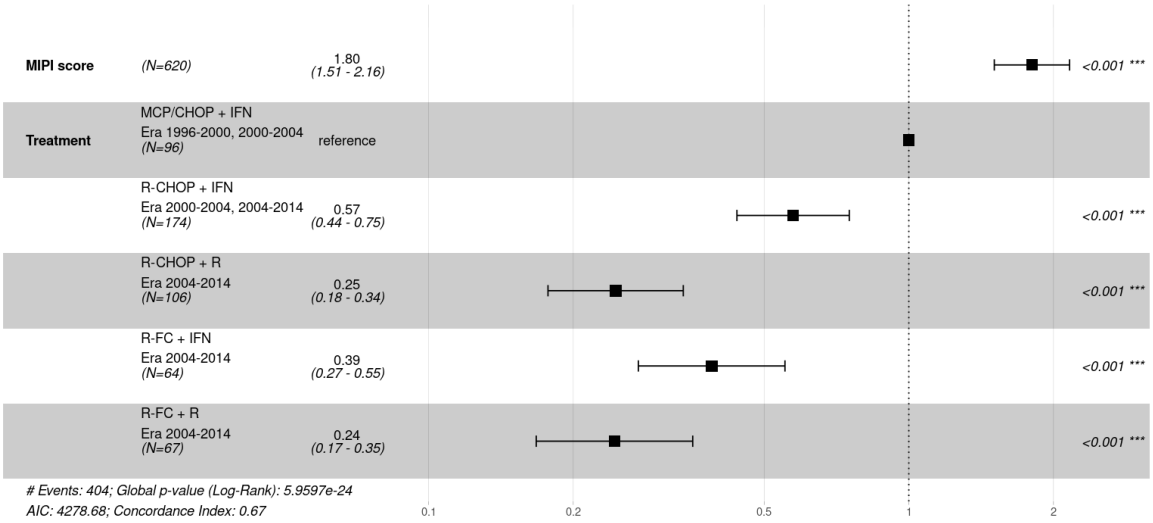
(A)



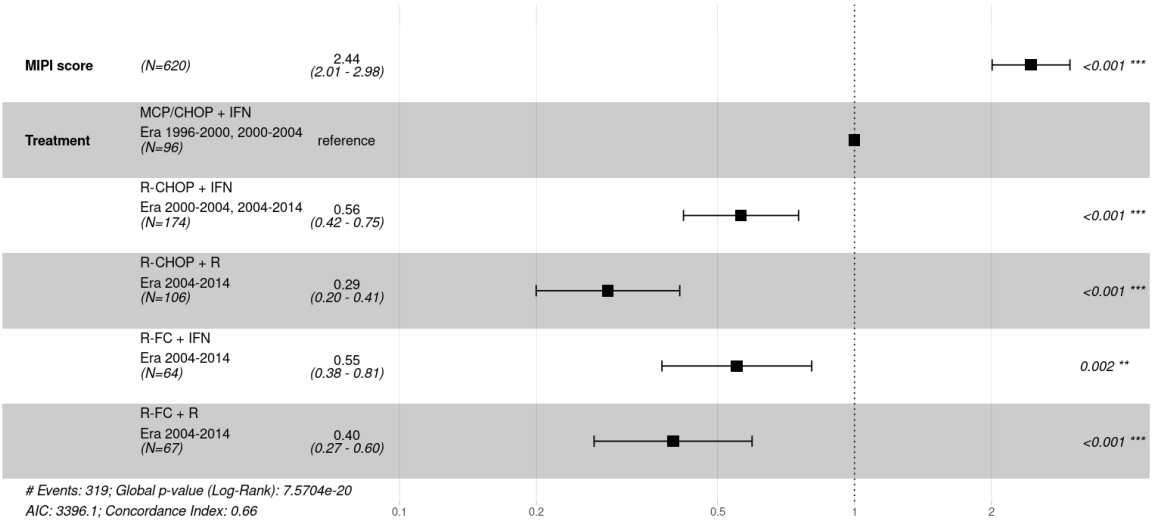
(B)


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)



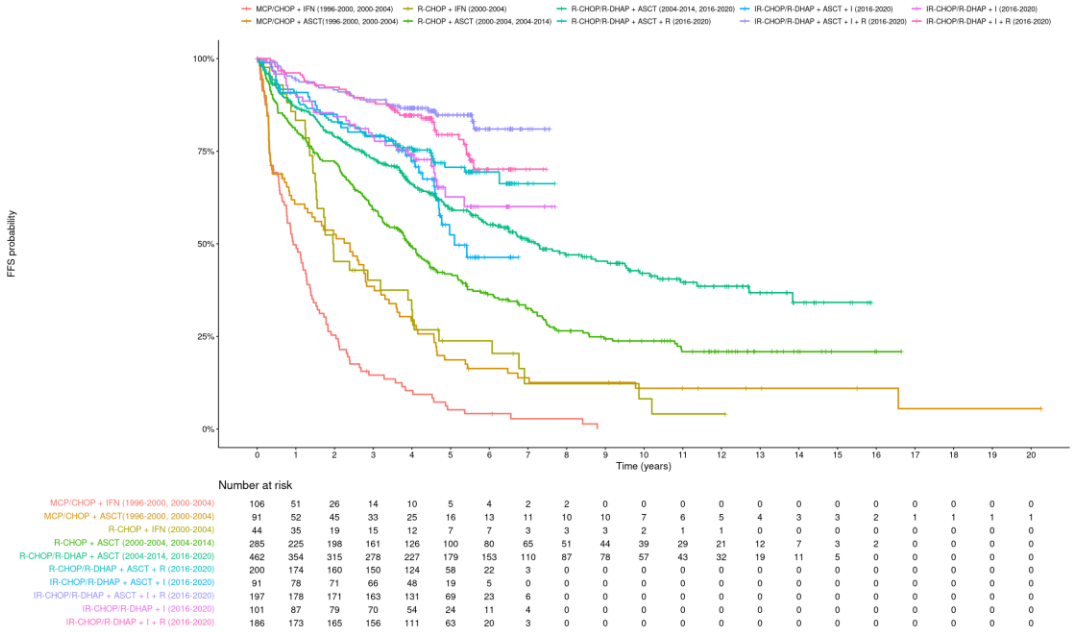
(D)



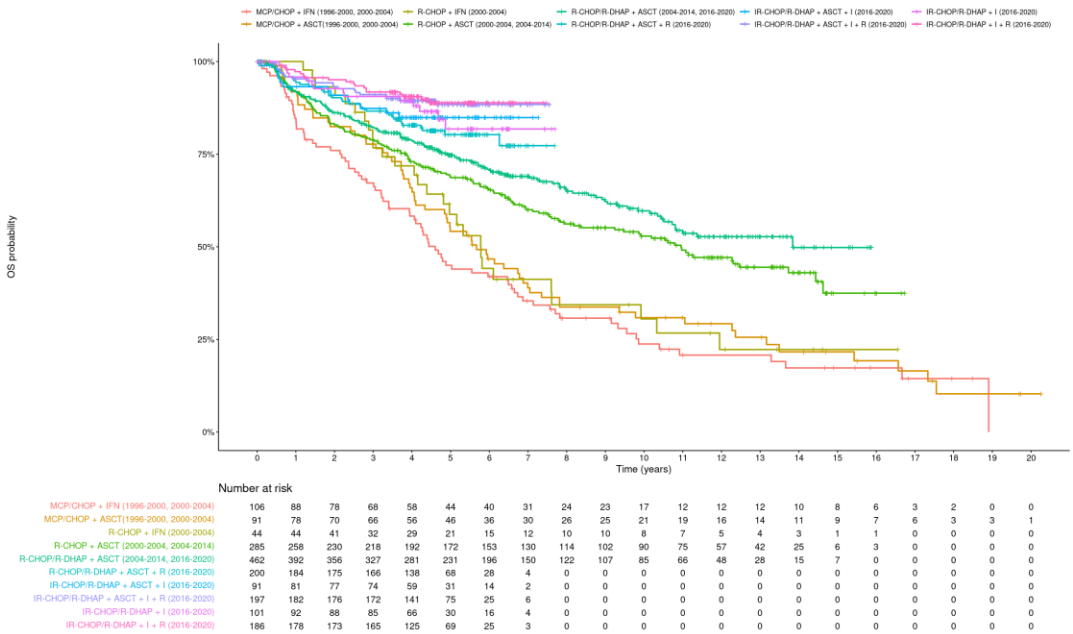
FFS: failure-free survival; OS: overall survival; MCP: mitoxantrone, chlorambucil, and prednisone; CHOP: cyclophosphamide, vincristine, doxorubicin, and prednisone; R-CHOP: rituximab plus CHOP; R-DHAP: rituximab plus dexamethasone, high-dose cytarabine, and cisplatin; I: ibrutinib; IFN: interferon-alpha;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

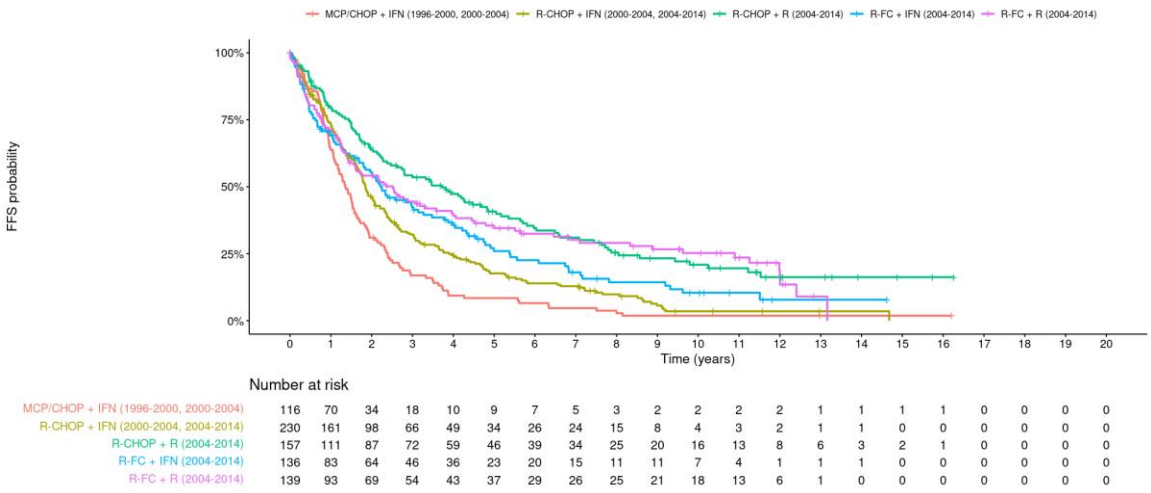
(A)



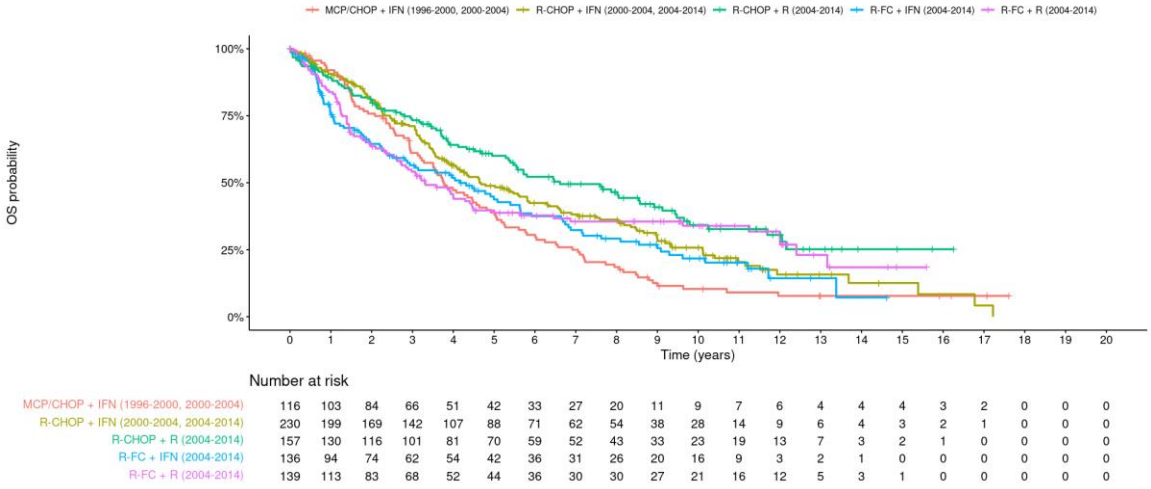
(B)



(C)



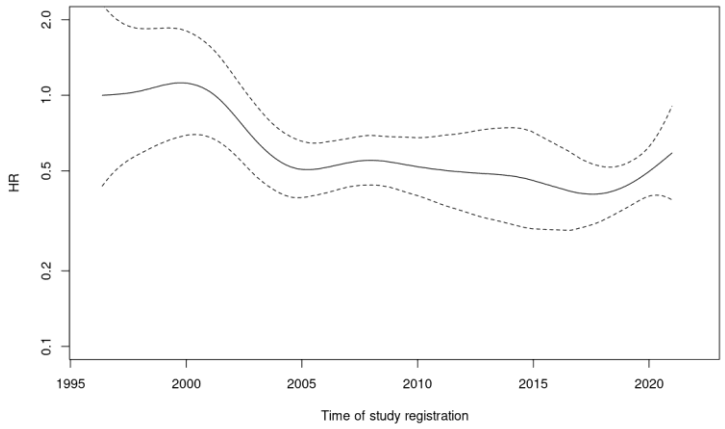
(D)



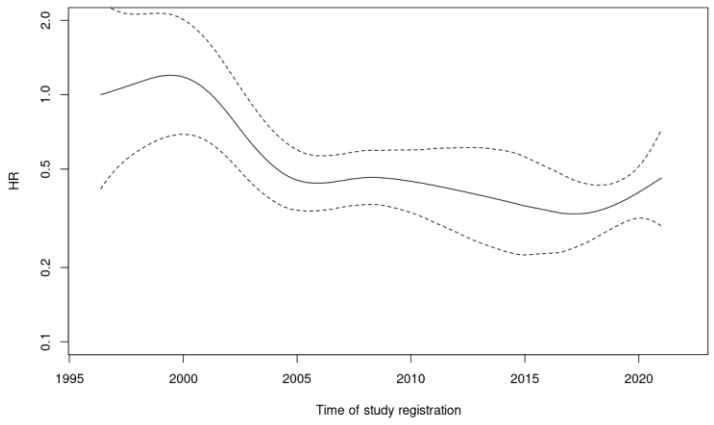
FFS: failure-free survival; OS: overall survival; MCP: mitoxantrone, chlorambucil, and prednisone; IFN: interferon-alpha; ASCT: autologous stem cell transplantation; CHOP: cyclophosphamide, vincristine, doxorubicin, and prednisone; R-CHOP: rituximab plus CHOP; R-DHAP: rituximab plus dexamethasone, high-dose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

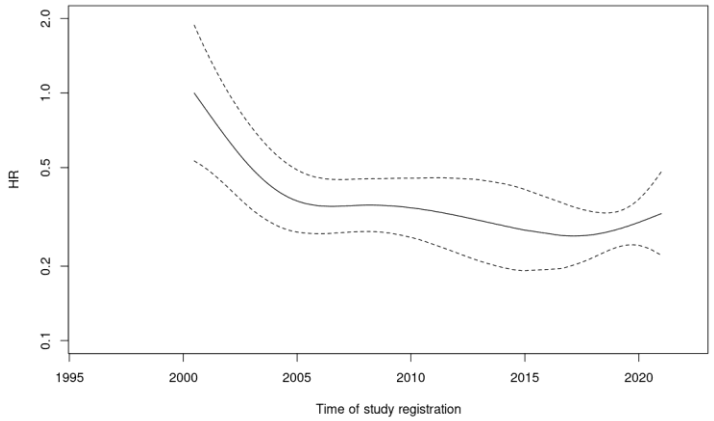
(A)



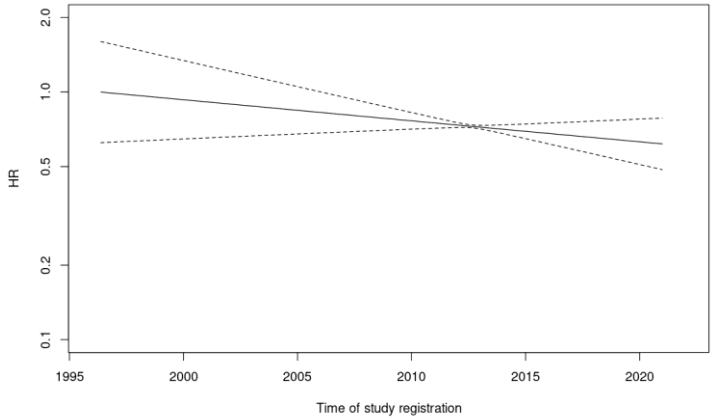
(B)



(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.