

Bendamustine and rituximab as induction therapy in both transplant eligible and ineligible patients with mantle cell lymphoma

Supplementary file

The seven tables in this Supplementary file describe univariate and multivariate analyses performed in subgroups defined by treatment and/or age, as well as in the overall study dataset. Baseline patient or disease characteristics with $p < 0.1$ in univariate analysis were entered into the multivariate models, and results with $p < 0.05$ were considered statistically significant in the final models. ASCT was not entered into the multivariate models due to strong selection bias. To account for guarantee time bias in analyses exploring the impact of receipt of maintenance rituximab on outcomes, univariate landmark analyses were performed by excluding patients with PD, death, or loss to follow-up within 18 months of BR/R-CHOP initiation. Additionally, maintenance rituximab was analyzed as a time-dependent covariate in the multivariate models. Coefficients of all variables were calculated under the assumption of a constant hazard ratio except the time-dependent adjustment term.

1. Univariate and multivariate analyses for PFS and OS in all BR-treated patients

Characteristic	PFS	OS
	HR (95% CI), p	HR (95% CI), p
Univariate analysis (n=190)		
Age >65 years at BR start	1.84 (1.13-2.99), p=0.014	2.22 (1.24-3.95), p=0.005
Male	0.85 (0.43-1.37), p=0.512	0.92 (0.53-1.59), p=0.752
Performance status >1	3.67 (2.19-6.13), p<0.001	4.89 (2.76-8.67), p<0.001
Elevated LDH	2.43 (1.35-4.37), p=0.003	1.93 (0.94-3.96), p=0.074
Ann Arbor stage III/IV	1.04 (0.42-2.58), p=0.940	1.04 (0.38-2.89), p=0.939
Marrow/blood involvement	0.75 (0.46-1.22), p=0.254	0.88 (0.49-1.56), p=0.659
B symptoms	1.32 (0.77-2.26), p=0.314	1.61 (0.88-2.94), p=0.125
Largest mass ≥5cm	1.61 (0.86-2.99), p=0.135	2.10 (0.97-4.55), p=0.060
High risk MIPI	3.22 (1.72-6.02), p<0.001	4.28 (2.09-8.78), p<0.001
Blastoid/pleomorphic	2.73 (1.35-5.50), p=0.013	3.03 (1.42-6.43), p=0.011
Ki67 ≥30%	1.29 (0.78-2.14), p=0.330	1.26 (0.69-2.28), p=0.454
Ki67 ≥50%	1.80 (1.07-3.02), p=0.026	1.97 (1.08-3.57), p=0.026
Maintenance rituximab		
Unadjusted analysis	0.11 (0.68-0.19), p<0.001	0.10 (0.06-0.18), p<0.001
Landmark analysis	1.03 (0.24-4.40), p=0.969	1.13 (0.15-8.67), p=0.905
Multivariate analysis excluding maintenance rituximab (n=113 PFS, n=81 OS)		
Age >65 years at BR start	Not significant	Not significant
Performance status >1	4.47 (2.29-8.70), p<0.001	9.47 (3.53-25.40), p<0.001
Elevated LDH	2.54 (1.34-4.83), p=0.004	Not significant
Largest mass ≥5cm	Not included	Not significant
High risk MIPI	Not significant	Not significant
Blastoid/pleomorphic	Not significant	Not significant
Ki67 ≥50%	2.30 (1.19-4.44), p=0.013	4.48 (1.68-11.96), p=0.003
Multivariate analysis including maintenance rituximab (n=113 PFS, n=81 OS)		
Age >65 years at BR start	Not significant	Not significant
Performance status >1	Not significant	2.56 (1.09-6.01), p=0.032
Elevated LDH	2.81 (1.40-5.63), p=0.004	Not significant
Largest mass ≥5cm	Not included	Not significant
High risk MIPI	Not significant	Not significant
Blastoid/pleomorphic	Not significant	Not significant
Ki67 ≥50%	Not significant	Not significant
Maintenance rituximab	0.01 (0.002-0.11), p<0.001	0.02 (0.002-0.12), p<0.001

2. Univariate and multivariate analyses for PFS and OS in BR-treated patients age ≤65 years

Characteristic	PFS	OS
	HR (95% CI), p	HR (95% CI), p
Univariate analysis (n=89)		
Male	0.78 (0.36-1.68), p=0.517	0.59 (0.23-1.52), p=0.272
Performance status >1	3.95 (1.63-9.56), p=0.002	6.38 (2.35-17.33), p<0.001
Elevated LDH	3.97 (1.56-10.09), p=0.004	3.96 (1.16-13.55), p=0.028
Ann Arbor stage III/IV	1.44 (0.20-10.70), p=0.720	0.93 (1.22-7.05), p=0.943
Marrow/blood involvement	0.92 (0.39-2.19), p=0.845	1.10 (0.36-3.38), p=0.870
B symptoms	1.34 (0.58-3.10), p=0.497	1.30 (0.45-3.75), p=0.624
Largest mass ≥5cm	2.03 (0.74-5.55), p=0.166	1.65 (0.46-5.86), p=0.441
High risk MIPI	3.56 (1.33-9.55), p=0.012	7.08 (2.15-23.37), p<0.001
Blastoid/pleomorphic	3.20 (1.19-8.60), p=0.021	3.95 (1.28-12.14), p=0.017
Ki67 ≥30%	1.49 (0.66-3.36), p=0.332	1.95 (0.69-5.49), p=0.204
Ki67 ≥50%	1.90 (0.81-4.50), p=0.143	2.66 (0.95-7.48), p=0.063
Maintenance rituximab		
Unadjusted analysis	0.12 (0.05-0.28), p<0.001	0.15 (0.06-0.39), p<0.001
Landmark analysis	Not evaluable*	Not evaluable*
Multivariate analysis excluding maintenance rituximab (n=64 PFS, n=42 OS)		
Performance status >1	5.88 (2.0-17.3), p=0.001	10.04 (1.63-61.71), p=0.013
Largest mass ≥5cm	Not included	Not significant
Elevated LDH	Not significant	Not significant
High risk MIPI	Not significant	Not significant
Blastoid/pleomorphic	8.61 (2.49-29.75), p=0.001	20.26 (3.29-124.5), p=0.001
Ki67 ≥50%	Not included	Not significant
Multivariate analysis including maintenance rituximab (n=64 PFS, n=42 OS)		
Performance status >1	Not significant	8.77 (1.36-56.64), p=0.022
Largest mass ≥5cm	Not included	Not significant
Elevated LDH	Not significant	Not significant
High risk MIPI	Not significant	Not significant
Blastoid/pleomorphic	5.60 (1.50-20.85), p=0.010	10.39 (1.43-75.31), p=0.021
Ki67 ≥50%	Not included	Not significant
Maintenance rituximab	0.13 (0.04-0.41), p<0.001	Not significant

*All patients received MR after the 18 month landmark.

3. Univariate and multivariate analyses for PFS and OS in BR-treated patients age >65 years

Characteristic	PFS	OS
	HR (95% CI), p	HR (95% CI), p
Univariate analysis (n=101)		
Male	0.85 (0.47-1.56), p=0.607	1.09 (0.55-2.19), p=0.800
Performance status >1	3.33 (1.76-6.30), p<0.001	3.84 (1.91-7.73), p<0.001
Elevated LDH	2.01 (0.88-4.62), p=0.098	1.63 (0.59-4.53), p=0.346
Ann Arbor stage III/IV	0.99 (0.35-2.77), p=0.981	1.24 (0.38-4.06), p=0.722
Marrow/blood involvement	0.71 (0.39-1.30), p=0.268	0.89 (0.45-1.76), p=0.737
B symptoms	1.64 (0.80-3.33), p=0.174	2.16 (1.03-4.53), p=0.041
Largest mass ≥5cm	1.64 (0.73-3.72), p=0.235	2.45 (0.92-6.55), p=0.074
High risk MIPI	2.75 (1.21-6.26), p=0.016	2.89 (1.16-7.18), p=0.023
Blastoid/pleomorphic	2.43 (0.67-6.81), p=0.092	3.18 (1.12-9.07), p=0.030
Ki67 ≥30%	0.98 (0.51-1.90), p=0.948	0.77 (0.37-1.61), p=0.491
Ki67 ≥50%	1.60 (0.84-3.05), p=0.155	1.50 (0.72-3.12), p=0.275
Maintenance rituximab		
Unadjusted analysis	0.11 (0.06-0.21), p<0.001	0.09 (0.05-0.19), p<0.001
Landmark analysis	1.16 (0.15-9.05), p=0.889	0.48 (0.06-4.18), p=0.506
Multivariate analysis excluding maintenance rituximab (n=60 PFS, n=42 OS)		
Performance status >1	4.17 (1.95-8.91), p<0.001	Not significant
Elevated LDH	3.04 (1.23-7.50), p=0.016	Not included
B symptoms	Not included	6.20 (1.69-22.85), p=0.006
Largest mass ≥5cm	Not included	Not significant
High risk MIPI	Not significant	4.83 (1.42-16.45), p=0.012
Blastoid/pleomorphic	Not significant	Not significant
Multivariate analysis including maintenance rituximab (n=60 PFS, n=42 OS)		
Performance status >1	2.80 (1.22-6.42), p=0.015	Not significant
Elevated LDH	Not significant	Not included
B symptoms	Not included	Not significant
Largest mass ≥5cm	Not included	4.0 (1.15-13.89), p=0.029
High risk MIPI	Not significant	Not significant
Blastoid/pleomorphic	Not significant	Not significant
Maintenance rituximab	0.10 (0.04-0.26), p<0.001	0.06 (0.02-0.20), p<0.001

4. Univariate and multivariate analyses for PFS and OS in the entire study cohort including BR-treated and R-CHOP-treated patients

Characteristic	PFS	OS
	HR (95% CI), p	HR (95% CI), p
Univariate analysis (n=438)		
Age >65 years at chemo start	1.99 (1.55-2.55), p<0.001	2.26 (1.71-2.99), p<0.001
Male	0.98 (0.75-1.28), p=0.871	1.04 (0.77-1.40), p=0.809
Performance status >1	2.72 (2.06-3.59), p<0.001	2.78 (2.09-3.68), p<0.001
Elevated LDH	1.85 (1.39-2.45), p<0.001	1.74 (1.28-2.35), p<0.001
Ann Arbor stage III/IV	1.82 (1.10-3.0-2), p=0.021	1.88 (1.07-3.31), p=0.027
Marrow/blood involvement	1.26 (0.95-1.67), p=0.116	1.35 (0.97-1.86), p=0.072
B symptoms	1.64 (1.26-2.14), p<0.001	1.67 (1.26-2.23), p<0.001
Largest mass ≥5cm	1.37 (1.04-1.81), p=0.027	1.35 (0.99-1.84), p=0.056
High risk MIPI	3.03 (2.21-4.16), p<0.001	3.98 (2.82-5.60), p<0.001
Blastoid/pleomorphic	2.12 (1.48-3.05), p<0.001	2.26 (1.54-3.31), p<0.001
Ki67 ≥30%	1.18 (0.88-1.59), p=0.279	1.30 (0.93-1.82), p=0.126
Ki67 ≥50%	1.21 (0.88-1.70), p=0.237	1.35 (0.95-1.91), p=0.098
BR	0.65 (0.49-0.86), p=0.003	0.73 (0.53-1.01), p=0.055
Maintenance rituximab		
Unadjusted analysis	0.26 (0.20-0.34), p<0.001	0.24 (0.18-0.32), p<0.001
Landmark analysis	0.53 (0.38-0.74), p<0.001	0.50 (0.34-0.74), p=0.001
Multivariate analysis excluding maintenance rituximab (n=262 PFS, n=193 OS)		
Age >65 years at chemo start	2.44 (1.75-3.40), p<0.001	2.01 (1.25-3.24), p=0.004
Performance status >1	1.51 (1.04-2.20), p=0.032	2.22 (1.32-3.75), p=0.003
Elevated LDH	1.43 (1.02-2.01), p=0.038	Not significant
Ann Arbor stage III/IV	1.86 (1.02-3.42), p=0.045	Not significant
Marrow/blood involvement	Not included	1.73 (1.05-2.85), p=0.032
B symptoms	Not significant	Not significant
Largest mass ≥5cm	Not significant	Not significant
High risk MIPI	Not significant	2.61 (1.45-4.70), p=0.001
Blastoid/pleomorphic	1.97 (1.24-3.14), p=0.004	Not significant
Ki67 ≥50%	Not included	Not significant
BR	0.58 (0.39-0.86), p=0.007	0.49 (0.29-0.84), p=0.010
Multivariate analysis including maintenance rituximab (n=262 PFS, n=193 OS)		
Age >65 years at chemo start	1.50 (1.06-2.11), p=0.023	Not significant
Performance status >1	1.57 (1.09-2.56), p=0.016	2.43 (1.44-4.08), p=0.001
Ann Arbor stage III/IV	2.63 (1.42-4.83), p=0.001	Not significant
Marrow/blood involvement	Not included	1.85 (1.13-3.04), p=0.015
B symptoms	Not significant	Not significant
Largest mass ≥5cm	Not significant	Not significant
High risk MIPI	Not significant	3.64 (2.01-6.58), p<0.001
Blastoid/pleomorphic	3.07 (1.94-4.86), p<0.001	Not significant
Ki67 ≥50%	Not included	Not significant
BR	1.20 (0.78-1.85), p=0.408	1.0 (0.56-1.78), p=0.99
Maintenance rituximab	0.09 (0.05-0.17), p<0.001	0.18 (0.11-0.28), p<0.001

5. Univariate and multivariate analyses for PFS and OS in BR-treated and R-CHOP-treated patients age ≤65 years

Characteristic	PFS	OS
	HR (95% CI), p	HR (95% CI), p
Univariate analysis (n=231)		
Male	1.14 (0.76-1.71), p=0.544	1.10 (0.69-1.76), p=0.676
Performance status >1	2.44 (1.59-3.75), p<0.001	2.82 (1.79-4.44), p<0.001
Elevated LDH	2.47 (1.67-3.66), p<0.001	2.17 (1.38-3.40), p=0.001
Ann Arbor stage III/IV	2.35 (1.03-5.34), p=0.043	2.77 (1.01-7.55), p=0.047
Marrow/blood involvement	1.62 (1.0-2.63), p=0.050	1.70 (0.95-2.97), p=0.075
B symptoms	2.05 (1.41-2.98), p<0.001	1.86 (1.22-2.83), p=0.004
Largest mass ≥5cm	1.57 (1.06-2.33), p=0.026	1.30 (0.83-2.05), p=0.255
High risk MIPI	2.57 (1.52-4.34), p<0.001	3.38 (1.93-5.92), p<0.001
Blastoid/pleomorphic	3.06 (1.84-5.07), p<0.001	3.02 (1.73-5.27), p<0.001
Ki67 ≥30%	1.27 (0.81-1.97), p=0.297	1.39 (0.83-2.33), p=0.210
Ki67 ≥50%	1.16 (0.72-1.89), p=0.545	1.37 (0.79-2.38), p=0.264
BR	0.69 (0.42-1.03), p=0.069	0.64 (0.37-1.11), p=0.115
Maintenance rituximab		
Unadjusted analysis	0.34 (0.23-0.48), p<0.001	0.29 (0.19-0.43), p<0.001
Landmark analysis	0.73 (0.45-1.18), p=0.194	0.65 (0.37-1.14), p=0.129
Multivariate analysis excluding maintenance rituximab (n=154 PFS, n=184 OS)		
Performance status >1	Not significant	2.08 (1.19-3.64), p=0.010
Elevated LDH	1.86 (1.17-2.96), p=0.009	Not significant
Ann Arbor stage III/IV	Not significant	Not significant
Marrow/blood involvement	Not significant	Not significant
B symptoms	Not significant	Not significant
Largest mass ≥5cm	Not significant	Not included
High risk MIPI	Not significant	2.49 (1.32-4.69), p=0.005
Blastoid/pleomorphic	2.87 (1.54-5.36), p=0.001	3.29 (1.71-6.32), p<0.001
BR	0.74 (0.41-1.34), p=0.324	0.57 (0.29-1.10), p=0.094
Multivariate analysis including maintenance rituximab (n= 154 PFS, n=184 OS)		
Performance status >1	Not significant	2.24 (1.27-3.96), p=0.006
Elevated LDH	1.65 (1.04-2.62), p=0.034	Not significant
Ann Arbor stage III/IV	Not significant	4.85 (1.68-13.96), p=0.003
Marrow/blood involvement	2.33 (1.31-4.12), p=0.004	Not significant
B symptoms	Not significant	Not significant
Largest mass ≥5cm	Not significant	Not included
High risk MIPI	Not significant	Not significant
Blastoid/pleomorphic	2.77 (1.47-5.23), p=0.002	3.42 (1.76-6.65), p<0.001
BR	1.06 (0.58-1.96), p=0.851	0.70 (0.36-1.38), p=0.303
Maintenance rituximab	0.12 (0.05-0.27), p<0.001	0.21 (0.13-0.35), p<0.001

6. Univariate and multivariate analyses for PFS and OS in BR-treated and R-CHOP-treated patients age >65 years

Characteristic	PFS	OS
	HR (95% CI), p	HR (95% CI), p
Univariate analysis (n=207)		
Male	0.90 (0.63-1.29), p=0.563	1.03 (0.70-1.53), p=0.872
Performance status >1	2.77 (1.91-4.02), p<0.001	2.42 (1.64-3.58), p<0.001
Elevated LDH	1.37 (0.91-2.08), p=0.132	1.45 (0.93-2.27), p=0.104
Ann Arbor stage III/IV	1.52 (0.80-2.91), p=0.202	1.52 (0.77-2.99), p=0.233
Marrow/blood involvement	1.19 (0.83-1.70), p=0.351	1.40 (0.94-2.08), p=0.100
B symptoms	1.56 (1.05-2.30), p=0.028	1.77 (1.18-2.65), p=0.006
Largest mass ≥5cm	1.18 (0.80-1.74), p=0.403	1.37 (0.90-2.09), p=0.139
High risk MIPI	2.63 (1.73-3.99), p<0.001	3.57 (2.25-5.67), p<0.001
Blastoid/pleomorphic	1.39 (0.82-2.36), p=0.223	1.59 (0.93-2.70), p=0.087
Ki67 ≥30%	0.95 (0.63-1.43), p=0.805	1.11 (0.71-1.73), p=0.658
Ki67 ≥50%	1.17 (0.76-1.79), p=0.480	1.24 (0.78-1.96), p=0.360
BR	0.55 (0.39-0.79), p=0.001	0.68 (0.46-1.02), p=0.065
Maintenance rituximab		
Unadjusted analysis	0.24 (0.16-0.35), p<0.001	0.25 (0.16-0.38), p<0.001
Landmark analysis	0.44 (0.26-0.73), p=0.001	0.54 (0.29-0.99), p=0.049
Multivariate analysis excluding maintenance rituximab (n=131 PFS and OS)		
Performance status >1	2.10 (1.32-3.36), p=0.002	Not significant
B symptoms	Not significant	1.94 (1.16-3.23), p=0.012
High risk MIPI	1.73 (1.07-2.79), p=0.025	3.46 (2.15-5.58), p<0.001
Blastoid/pleomorphic	Not included	Not significant
BR	0.57 (0.36-0.90), p=0.015	0.73 (0.43-1.27), p=0.266
Multivariate analysis including maintenance rituximab (n=131 PFS and OS)		
Performance status >1	1.90 (1.19-3.03), p=0.007	Not significant
B symptoms	Not significant	Not significant
High risk MIPI	1.77 (1.11-2.84), p=0.018	3.13 (1.88-5.19), p<0.001
Blastoid/pleomorphic	Not included	2.60 (1.21-5.61), p=0.015
BR	0.68 (0.40-1.15), p=0.149	0.59 (0.33-1.07), p=0.084
Maintenance rituximab	0.21 (0.13-0.33), p<0.001	0.16 (0.08-0.30), p<0.001

7. Univariate and multivariate analyses for PFS and OS in BR-treated and R-CHOP-treated patients who received ASCT

Characteristic	PFS	OS
	HR (95% CI), p	HR (95% CI), p
Univariate analysis (n=157)		
Age >65 years at chemo start	1.78 (0.81-3.94), p=0.152	2.34 (0.97-5.61), p=0.057
Male	1.13 (0.63-2.02), p=0.687	1.03 (0.51-2.10), p=0.935
Performance status >1	1.97 (1.02-3.81), p=0.045	2.36 (1.14-4.86), p=0.020
Elevated LDH	1.98 (1.14-3.44), p=0.015	1.42 (0.73-2.77), p=0.304
Marrow/blood involvement	2.69 (1.08-6.72), p=0.034	2.58 (0.79-8.37), p=0.115
B symptoms	2.66 (1.58-4.46), p<0.001	2.12 (1.14-3.92), p=0.017
Largest mass ≥5cm	2.08 (1.20-3.64), p=0.010	1.47 (0.77-2.80), p=0.248
High risk MIPI	1.90 (0.86-4.21), p=0.114	2.36 (0.97-5.78), p=0.059
Blastoid/pleomorphic	1.70 (0.68-4.24), p=0.258	1.75 (0.62-4.93), p=0.288
Ki67 ≥30%	1.27 (0.71-2.27), p=0.419	1.38 (0.68-2.79), p=0.373
Ki67 ≥50%	1.22 (0.61-2.44), p=0.569	1.07 (0.48-2.40), p=0.870
BR	0.63 (0.34-1.16), p=0.139	0.66 (0.29-1.48), p=0.308
Maintenance rituximab		
Unadjusted analysis	0.61 (0.26-1.41), p=0.248	0.45 (0.17-1.14), p=0.092
Landmark analysis	0.80 (0.29-2.21), p=0.661	0.58 (0.18-1.92), p=0.375
Multivariate analysis excluding maintenance rituximab (n=108 PFS, n=126 OS)		
Age >65 at chemo start	Not included	Not significant
Performance status >1	Not significant	2.38 (1.14-4.96), p=0.021
Elevated LDH	Not significant	Not included
Marrow/blood involvement	Not significant	Not included
B symptoms	2.30 (1.30-4.08), p=0.004	Not significant
Largest mass ≥5cm	Not significant	Not included
High risk MIPI	Not included	Not significant
BR	0.40 (0.17-0.94), p=0.036	0.33 (0.10-1.10), p=0.070
Multivariate analysis including maintenance rituximab (n=108 PFS, n=126 OS)		
Age >65 at chemo start	Not included	Not significant
Performance status >1	Not significant	2.45 (1.17-5.12), p=0.018
Elevated LDH	Not significant	Not included
Marrow/blood involvement	Not significant	Not included
B symptoms	2.15 (1.20-3.85), p=0.010	Not significant
Largest mass ≥5cm	Not significant	Not included
High risk MIPI	Not included	Not significant
BR	0.42 (0.17-0.99), p=0.047	0.32 (0.09-1.07), p=0.064
Maintenance rituximab	0.26 (0.09-0.76), p=0.014	0.34 (0.13-0.89), p=0.028