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Beta-blocker use and survival in diffuse large B-cell lymphoma: a post hoc analysis of the RICOVER-60 trial

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Authorship Contributions

M.B. and Y.B. contributed equally to this work and share first authorship. K.C. and L.T. contributed equally and share senior authorship.

M.B., Y.B., M.Bö., and L.T. conceived the study. M.B., Y.B., K.C., and L.T. designed the study. F.N., C.S., M.H., and C.B. performed the in vitro experiments. M.B., Y.B., V.L., I.A.K., M.K., and D.K.-M. collected data. P.M., V.L., and C.B. performed the statistical analyses. P.M., M.H., and M.Bö. contributed clinical data and resources.

M.B., Y.B., M.Bö., L.T., and K.C. drafted the manuscript. M.B., Y.B., and F.N. performed data analysis and interpretation. K.C. and L.T. supervised the study.

All other authors critically revised the manuscript for important intellectual content and approved the final version.

Disclosure of Conflicts of Interest

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Data sharing statement

The original data underlying this study are available upon reasonable request. Requests for data access should be directed to the corresponding author.

Artificial intelligence (AI) statement

AI was used solely for checking grammar and spelling

Positive associations between beta blocker (BB) intake and survival outcomes in cancer patients have been reported. We performed a post hoc analysis of the RICOVER-60 trial (NCT00052936) and evaluated whether baseline BB use is associated with survival outcomes in patients with diffuse large B-cell lymphoma (DLBCL) treated with the immunochemotherapy regimen R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone). Baseline BB use was associated with improved survival outcomes in DLBCL patients treated with 6xR-CHOP-14. The association was not observed with the more intensive 8xR-CHOP-14 regimen and in regimens without rituximab.

Interactions between the immune system and the sympathetic nervous system (SNS) are complex and incompletely understood. After release of catecholamines (epinephrine, norepinephrine) their effects are mediated by alpha (αAR) and beta (βAR) adrenergic receptors.[1] βAR activation typically exerts immunosuppressive effects.[2] Beta-blockers (BBs) are classified as selective (targeting β1AR) or non-selective (targeting both β1AR and β2AR). Retrospective studies suggest beneficial association between BB intake and survival outcomes in cancer patients, potentially mediated by immunomodulatory effects.[3–10] Data on the interaction of BB and rituximab + CHOP chemotherapy in lymphoma patient are not available.

The RICOVER-60 trial enrolled 1222 patients aged 61–80 years with newly diagnosed, CD20-positive, aggressive B-cell lymphoma.[11] Patients were randomized to receive six or eight cycles of CHOP chemotherapy every two weeks (-14), with or without rituximab (6xCHOP-14, 6xCHOP-14 + 8xR, 8xCHOP-14, 8xCHOP-14 + 8xR). The trial was registered under NCT00052936 and conducted in accordance with the Declaration of Helsinki. The protocol was approved by the ethics committees of all participating centers. Written informed consent was obtained from all patients.

Since six cycles of R-CHOP represent one of the contemporary standard regimens, we centered the clinical analyses on the 6xR-CHOP-14 subgroup and treated corresponding analyses for 8xR-CHOP-14 patients and cohorts treated without rituximab as exploratory assessments of effect heterogeneity by chemotherapy intensity. Baseline BB use was defined at randomization and analyzed as a fixed exposure, leaving some room for exposure misclassification as changes in BB exposure were not assessed during the treatment period. Outcomes were overall survival (OS), progression-free survival (PFS), and event-free survival (EFS). Unadjusted associations of BB use and outcomes were examined using Kaplan-Meier analyses with log-rank testing and Cox proportional hazards models. The 6xR-CHOP-14 cohort included 306 patients, of whom 75 (24.5%) used BB at baseline (Table 1). Baseline BB use was strongly associated with cardiovascular comorbidity, including higher prevalence of cardiovascular risk factors (58.7% vs 28.6%; SMD 0.637), and manifest cardiovascular disease (36% vs 13.9%; SMD 0.53), whereas lymphoma-related characteristics were generally comparable (Table 1). For RICOVER-60 patients treated with 6xR-CHOP-14, unadjusted Kaplan–Meier curves separated in favor of BB users, with statistically significance for OS (log-rank p = 0.026) and PFS (log-rank p = 0.0036), but not for EFS (log-rank p = 0.074) (Figure 1A). Since BB use was not randomized, propensity score-based inverse probability tilting (IPT) weights targeting the average treatment effect were applied. The propensity score model included age, sex, study arm (6 vs 8 CHOP cycles), IPI factors, bulky disease, B symptoms, cardiovascular risk factors, and manifest cardiovascular disease. After propensity score-based IPT-weighting, baseline covariates were well balanced between groups (Figure S1A) and propensity score overlap was acceptable (Figure S1B). In IPT-weighted Cox models, baseline BB use was associated with improved outcomes (aHR 0.43 [95% CI 0.21–0.90], p = 0.025 for OS; aHR 0.38 [95% CI 0.19–0.77], p = 0.0074 for PFS; and aHR 0.54 [95% CI 0.30–

0.97], p = 0.04 for EFS). In contrast, no benefit was observed in the 8xR-CHOP-14 cohort in either unadjusted analyses (Figure S2A) or after IPT-weighted adjustment. When both rituximab-containing arms were pooled, again no association was seen (aHR 0.82 [95% CI 0.49–1.35] for OS; aHR 0.79 [95% CI 0.49–1.28] for PFS; and aHR 0.88 [95% CI 0.58–1.34] for EFS). However, estimates for influence of BB use on rituximab treatment effect differed by CHOP cycle number (6xCHOP vs 8xCHOP), with significant interactions for OS (p = 0.035), PFS (p = 0.011), and EFS (p = 0.041) (Figure 1B).

Taken together, in the 6xR-CHOP-14 cohort, baseline BB use was associated with prolonged survival compared to non-use. This was not true when patients received 8 cycles of R-CHOP. A potential explanation is that any immunologic advantage could be outweighed by treatment-related toxicity in patients with cardiovascular comorbidity. Consistent with this, BB users had higher prevalences of cardiovascular risk factors and manifest cardiovascular disease in both the overall and rituximab-treated cohorts. However, this interpretation remains speculative, as comparative data on treatment-related mortality and treatment intensity according to beta-blocker exposure were not available. Therefore, alternative explanations, including residual confounding and multiple testing with chance findings, cannot be excluded.

Notably, a positive association between BB use and outcomes was not observed in patients treated with chemotherapy alone without rituximab (Figure S2B). In exploratory analyses across the whole RICOVER-60 trial (n = 1,222), rituximab was associated with improved outcomes within each CHOP cycle stratum (OS HR: 0.76 [95% CI 0.61–0.94]; PFS HR: 0.62 [95% CI 0.51–0.76]; EFS HR: 0.64 [95% CI 0.53–0.76]) (Figure S3A). Within 6-cycle regimens, the rituximab benefit appeared larger among baseline BB users than non-users (OS HR: 0.34 [95% CI 0.16–0.70] vs 0.83 [95% CI 0.59–1.18], p for interaction = 0.028; PFS HR: 0.21 [95% CI 0.11–0.42] vs 0.72

[95% CI 0.53–0.98], p for interaction = 0.0012; EFS HR: 0.33 [95% CI 0.19–0.57] vs 0.63 [95% CI 0.48–0.84], p for interaction = 0.036). No evidence of effect modification was observed within 8-cycle regimens (p for interaction = 0.71 for OS, 0.73 for PFS, and 0.49 for EFS) (Figure S3A). The 3-way interaction testing whether this modification differed by CHOP cycle number was most pronounced for PFS (p=0.0087), with borderline signals for OS (p=0.056) and EFS (p=0.053) (Figure S3A). Sensitivity analyses using IPT-weighted association of baseline beta blocker use with outcomes by rituximab application (yes/no) and CHOP cycle number (6 vs 8) showed similar results (Figure S3B). These findings support the hypothesis that BB may act through immune effector mechanisms involved in ADCC, such as NK cells and NKT cells, both of which express Fc receptors.[12]

Therefore, in-vitro experiments were performed to assess the effects of catecholamines and BBs on NK cell function. NK cell-mediated cytotoxicity against Daudi B-cell lymphoma cells was measured using LDH release assays after rituximab exposure (0.0001 – 1.0 μg/ml). NK cells were isolated from the peripheral blood mononuclear cells (PBMCs) of healthy donors. NK cells were exposed to the β1-specific AR blockers CPG-20712A methanesulfonate (0.9 nM) and bisoprolol (0.5 nM and 1 nM) or the β2-specific AR blocker ICI-118.551 (0.6 nM). After one, 24, 48, and 72 h isoprenaline (4 nM) was added. After 72 h, NK cells were co-incubated with rituximab-labeled target cells at an effector-to-target (E:T) ratio of 2:1. ADCC activity was quantified after 4 h by measuring LDH release into the supernatant. Incubation with isoprenaline significantly reduced ADCC capability of NK cells. BB addition mitigated the inhibitory effects of isoprenaline and restored NK cell function. Treatment with the β1-selective blocker CPG-20712A or the β2-selective blocker ICI-118.551 both increased NK cell-mediated cytotoxicity. Without isoprenaline or BB treatment, rituximab-induced lysis of DAUDI cells ranged from 4.2% to 75.3% at rituximab

doses from 0.0001 μg/ml to 1.0 μg/ml. After isoprenaline exposure, lysis decreased to 2.6%–42.3%. Pre-treatment with CPG-20712A before isoprenaline restored lysis rates to 2.7%–62.0%. Likewise, blocking β2AR signaling with ICI-118.551 increased lysis to 3.9%–67.1% (Figure 2A). Concomitant use of CPG-20712A and ICI-118.551 did not show additive effects, with lysis rates of 3.0%–50.9% (Figure 2A). In addition, bisoprolol, a β1-selective AR blocker, was tested for its ability to restore NK cell function as it was frequently used in the RICOVER-60 trial. Among the 273 patients receiving a beta-blocker at baseline, 239 (87.5%) received a β1-selective beta-blocker and 34 (12.5%) received a non-selective beta-blocker. The most frequently used agents were metoprolol (n=130; 47.6% of BB users) and bisoprolol (n=81; 29.7%). Adding bisoprolol led to similar improvements in NK cell function following isoprenaline treatment as CPG-20712A and ICI-118.551 (Figure 2B). It is well established that active cancer and cancer therapies can increase catecholamine release as part of stress response.[13] Since NK cells mediate antibody effects through ADCC, it seems possible that BBs improve NK cell functionality by inhibiting beta-adrenergic signaling pathways leading to improved survival of lymphoma patients treated with immunotherapy. However, these findings do not prove that this mechanism accounts for the differences observed between the treatment subgroups.

Even though our results do not represent direct evidence for a causal relation between BB-induced improved NK cell function and better survival outcomes in DLBCL patients treated with R-CHOP, they still provide biological plausibility. Nevertheless, these clinical findings should be interpreted cautiously. All analyses of BB exposure were post hoc, multiple endpoints were tested (possibility for type I error), and residual confounding cannot be excluded despite propensity-score weighting. Also, RICOVER-60 evaluated CHOP-14-based regimens and did not include R-CHOP-21 or other contemporary DLBCL regimens, limiting the generalizability of our findings.

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Table 1

Baseline Characteristics of the 6xR-CHOP-14 cohort

Variable	Overall (n=306)	No Beta Blocker (n=231)	Beta Blocker (n=75)	SMD
Age, years (SD)	68.93 (5.18)	68.84 (5.29)	69.21 (4.84)	0.075
Male (%)	138 (45.1)	101 (43.7)	37 (49.3)	0.113
IPI (%)				0.288
1	94 (30.7)	69 (29.9)	25 (33.3)	
2	89 (29.1)	67 (29.0)	22 (29.3)	
3	78 (25.5)	56 (24.2)	22 (29.3)	
4	26 (8.5)	22 (9.5)	4 (5.3)	
5	19 (6.2)	17 (7.4)	2 (2.7)	
Bulky disease (%)	117 (38.2)	89 (38.5)	28 (37.3)	0.025
B symptoms (%)	98 (32.0)	74 (32.0)	24 (32.0)	0.001
Extranodal involvement (%)	161 (52.6)	124 (53.7)	37 (49.3)	0.087
CV risk factor (%)	110 (35.9)	66 (28.6)	44 (58.7)	0.637
Manifest CVD	59 (19.3)	32 (13.9)	27 (36.0)	0.530

Data are shown as mean (SD), or n (%), as appropriate. Standardized mean differences (SMD) compare baseline beta blocker users vs non-users.

Figure legends

Figure 1

Survival outcomes according to baseline beta blocker use

(A) Kaplan–Meier estimates by beta blocker use of patients treated with 6xR-CHOP-14 in the RICOVER-60 trial for (A) overall survival, (B) progression-free survival, and (C) event-free survival are shown. Patients with (n=75) and without (n=231) beta blocker use at baseline are compared. P values were calculated using the log-rank test.

(B) IPT-weighted associations of baseline beta blocker use with outcomes by CHOP cycle number among rituximab-treated patients are presented. Forest plots show IPT-weighted hazard ratios (HRs) with 95% confidence intervals for baseline beta-blocker use (yes vs no) for overall survival, progression-free survival, and event-free survival. Results are shown overall and separately for patients receiving 6 CHOP cycles with 8 doses of rituximab (6xR-CHOP-14) and 8 CHOP cycles with 8 doses of rituximab (8xR-CHOP-14). Patients in both arms received rituximab (8 doses). Interaction p values test whether the beta blocker association differs between 6 and 8 CHOP cycles (BB×CHOP-cycle interaction).

Figure 2

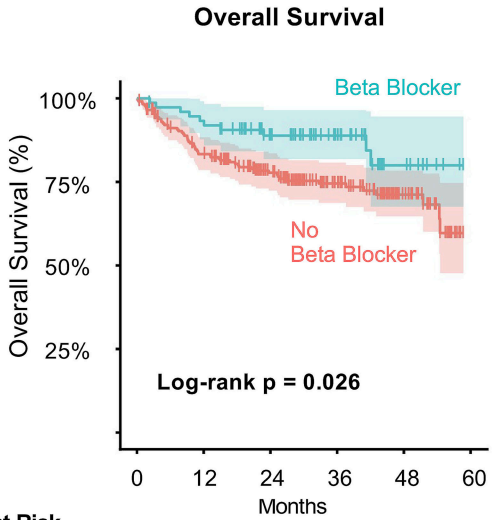
LDH release assays to assess the influence of isoprenaline with and without the addition of a BB on NK cell function.

Lysis rates of lymphoma cells (DAUDI) were evaluated. Rituximab was used at concentrations of 0 µg/ml, 0.0001 µg/ml, 0.001 µg/ml, 0.01 µg/ml, 0.1 µg/ml, and 1 µg/ml.

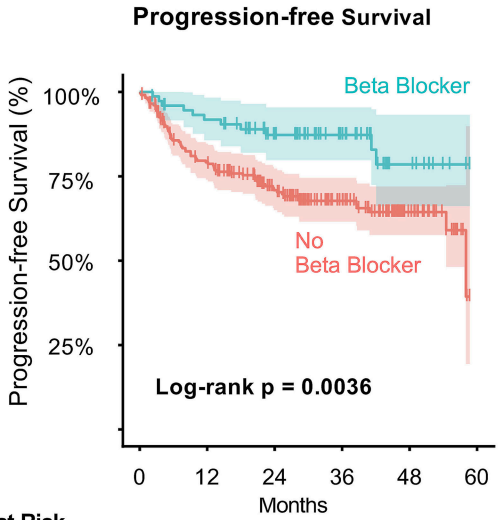
(A) When NK cells were not treated before LDH release assays, the lysis rates of the lymphoma target cells ranged from 4.2–75.3% depending on the rituximab concentration. After the addition of isoprenaline, rituximab-induced lymphoma cell lysis was reduced significantly. When the beta-1 selective BB CPG-20712A and the beta-2 selective BB ICI-118.551 were added to block the isoprenaline effect, NK cell function was restored. Concomitant use of CPG-20712A and ICI-118.551 showed no additive effects.

(B) The selective BB bisoprolol was used to block isoprenaline effects because it is one of the most commonly used BBs in clinical practice. At 0.5 nM and 1.0 nM, bisoprolol showed similar results to CPG-20712A and ICI-118.551, restoring isoprenaline-impaired NK cell function.

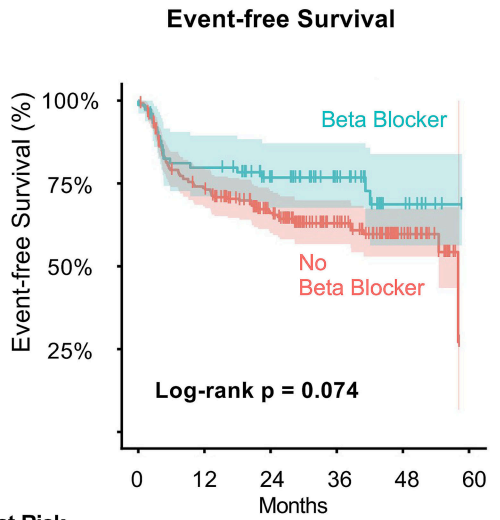
A



No. at Risk						
Beta Blocker	75	69	50	30	11	1
No Beta Blocker	231	181	133	80	33	0



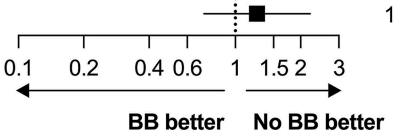
No. at Risk						
Beta Blocker	75	66	49	30	11	1
No Beta Blocker	231	170	120	70	26	0

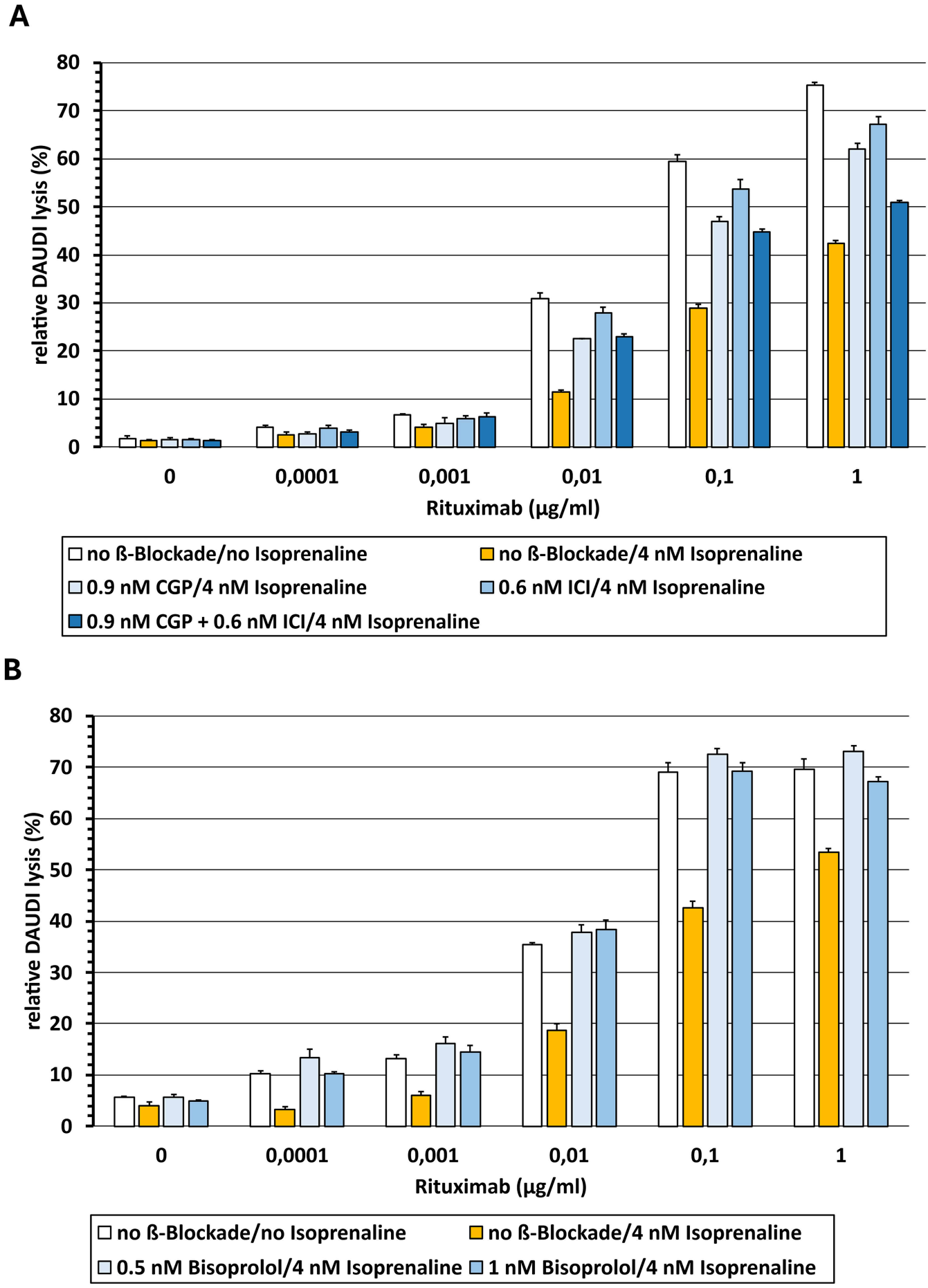


No. at Risk						
Beta Blocker	75	59	45	28	10	1
No Beta Blocker	231	161	114	67	24	0

B

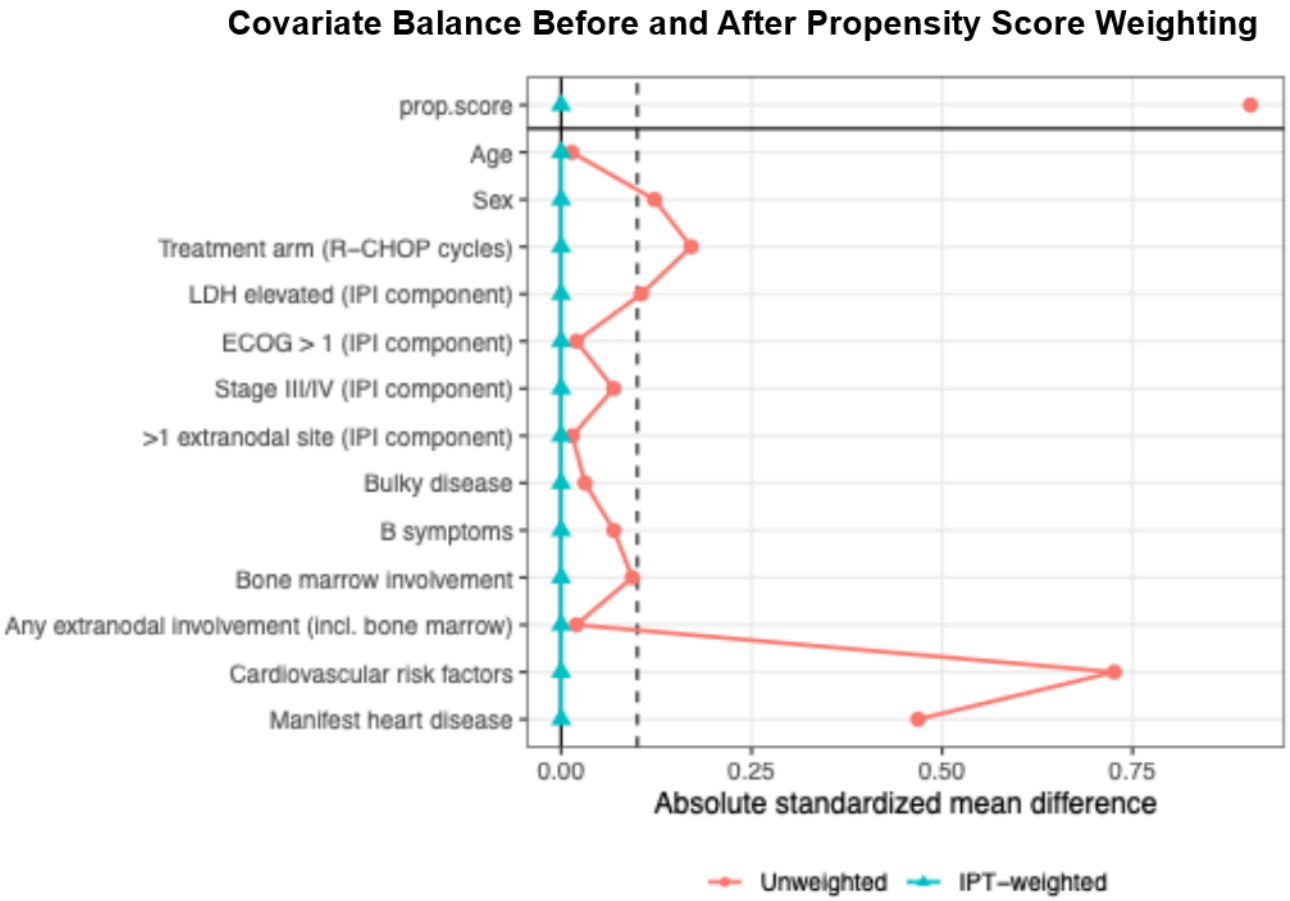
Outcome	Beta Blocker	No Beta Blocker	IPT-weighted HR (95% CI)	P value for interaction
	no. of patients with outcome/total no. (%)			
Overall survival				0.035
Overall	30/132 (22.7)	122/478 (25.5)	0.82 (0.49–1.35)	
6xR-CHOP-14	10/75 (13.3)	59/231 (25.5)	0.43 (0.21–0.90)	
8xR-CHOP-14	20/57 (35.1)	63/247 (25.5)	1.24 (0.65–2.37)	
Progression-free survival				0.011
Overall	32/132 (24.2)	144/478 (30.1)	0.79 (0.49–1.28)	
6xR-CHOP-14	11/75 (14.7)	72/231 (31.2)	0.38 (0.19–0.77)	
8xR-CHOP-14	21/57 (36.8)	72/247 (29.1)	1.29 (0.70–2.35)	
Event-free survival				0.041
Overall	44/132 (33.3)	169/478 (35.4)	0.88 (0.58–1.34)	
6xR-CHOP-14	19/75 (25.3)	84/231 (36.4)	0.54 (0.30–0.97)	
8xR-CHOP-14	25/57 (43.9)	85/247 (34.4)	1.28 (0.73–2.22)	




A
80
70
60
50
40
30
20
10
0
relative DAUDI lysis (%)
0
0,0001
0,001
0,01
0,1
1
Rituximab (µg/ml)
no ß-Blockade/no Isoprenaline
no ß-Blockade/4 nM Isoprenaline
0.9 nM CGP/4 nM Isoprenaline
0.6 nM ICI/4 nM Isoprenaline
0.9 nM CGP + 0.6 nM ICI/4 nM Isoprenaline
B
80
70
60
50
40
30
20
10
0
relative DAUDI lysis (%)
0
0,0001
0,001
0,01
0,1
1
Rituximab (µg/ml)
no ß-Blockade/no Isoprenaline
no ß-Blockade/4 nM Isoprenaline
0.5 nM Bisoprolol/4 nM Isoprenaline
1 nM Bisoprolol/4 nM Isoprenaline

Supplemental Figures

A



B

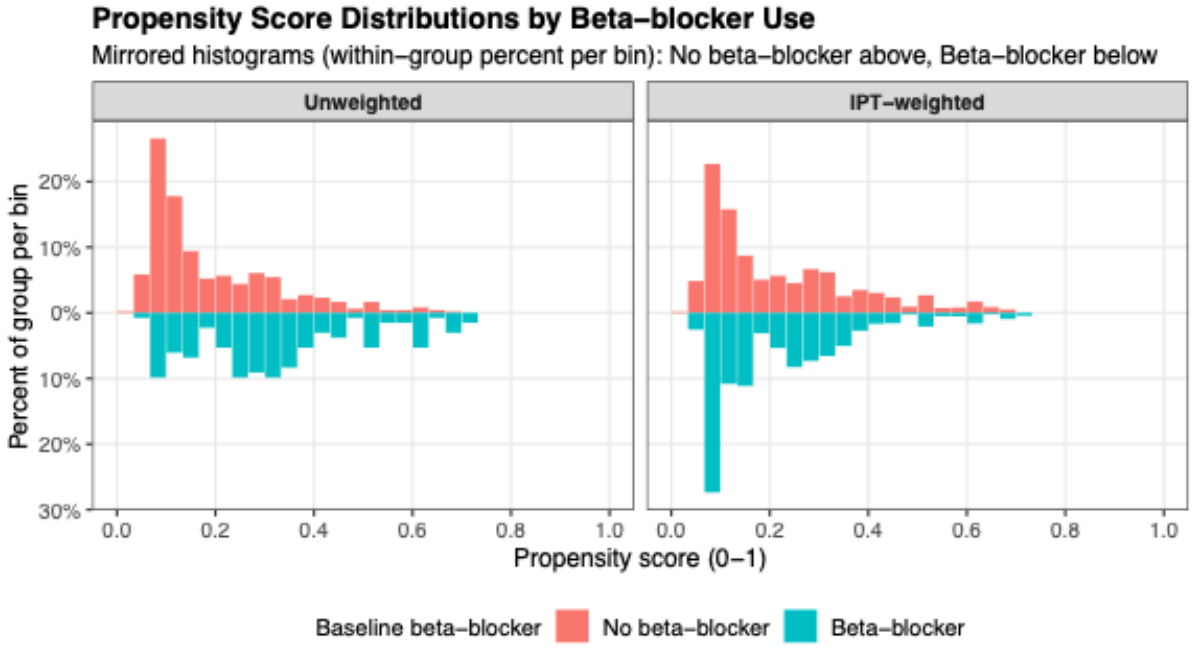


Figure S1. Evaluation of group imbalances

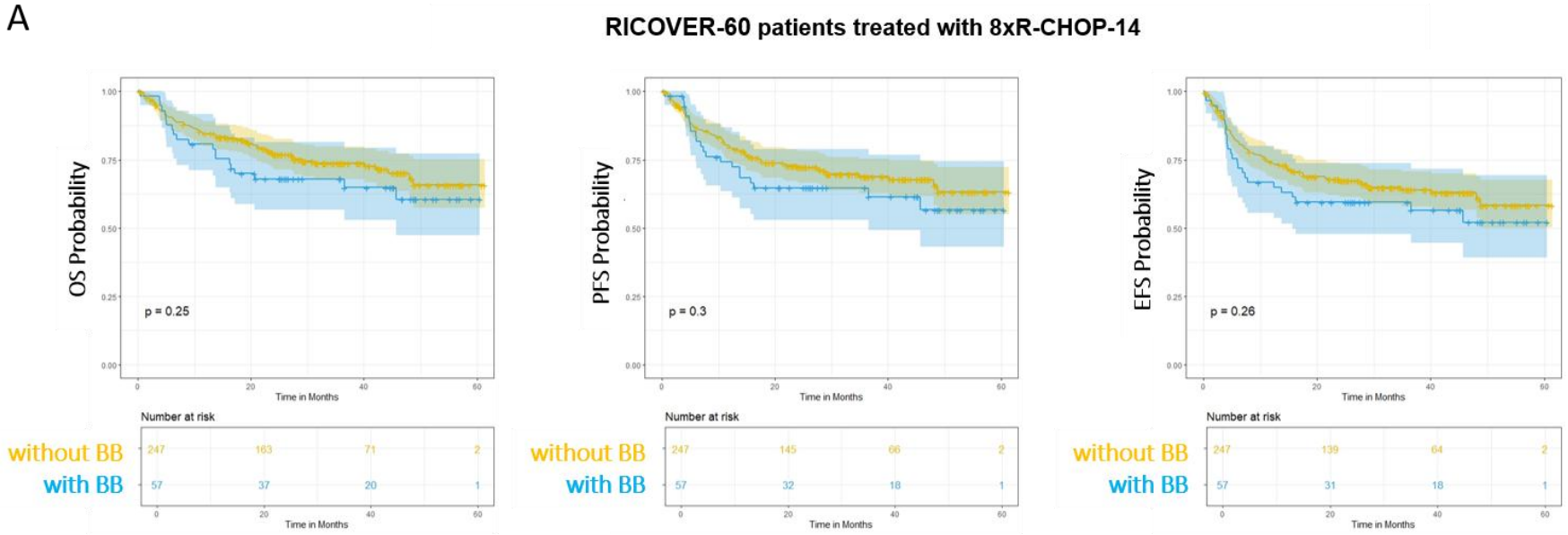
A. Covariate balance before and after propensity-score weighting for the 6xR-CHOP-14 cohort of the RICOVER-60 trial

Standardized mean differences (SMD) for baseline covariates comparing patients with versus without baseline beta blocker use are shown before weighting (unweighted) and after inverse probability tilting (IPT) weighting.

B. Propensity score overlap by baseline beta blocker use in patients receiving 6xR-CHOP-14

Mirrored histograms display the distribution of the estimated propensity score (0–1) for baseline beta blocker use in beta blocker non-users (shown above the zero line) and beta blocker users (shown below the zero line), with bars representing the within-group percentage per bin. Distributions are shown before weighting (unweighted) and after inverse probability tilting (IPT) weighting.

A


RICOVER-60 patients treated with 8xR-CHOP-14
OS Probability
p = 0.25
PFS Probability
p = 0.3
EFS Probability
p = 0.26
Time in Months
Number at risk
without BB
with BB
247 163 71 2
57 37 20 1
247 145 66 2
57 32 18 1
247 139 64 2
57 31 18 1

B

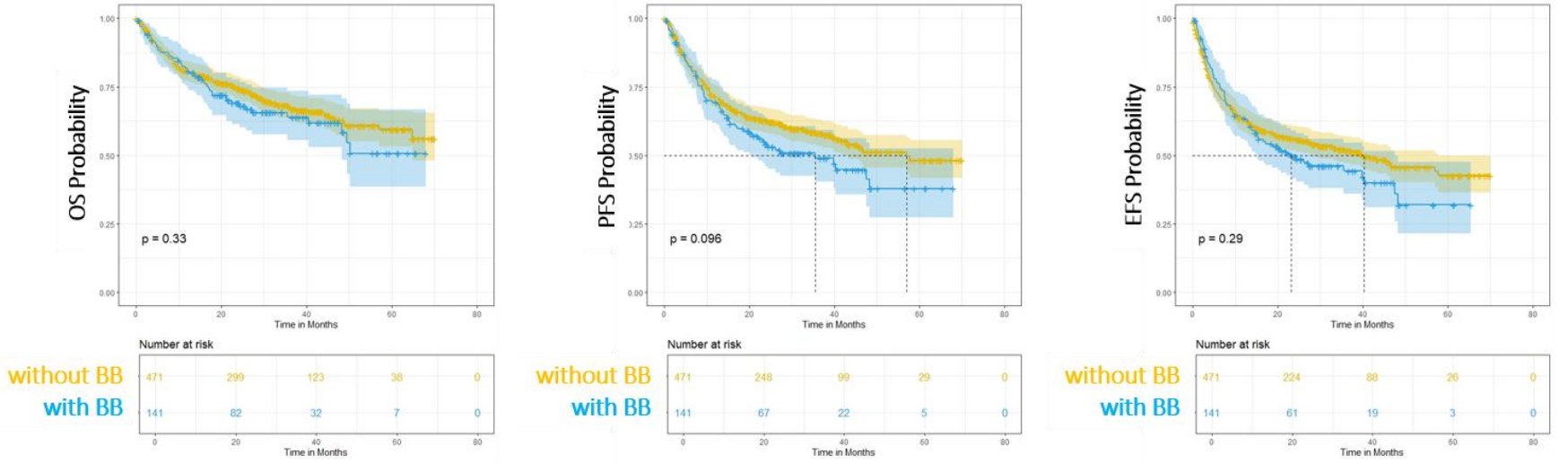

RICOVER-60 patients treated without Rituximab
OS Probability
p = 0.33
PFS Probability
p = 0.096
EFS Probability
p = 0.29
Time in Months
Number at risk
without BB
with BB
471 299 123 38 0
141 82 32 7 0
471 248 99 29 0
141 67 22 5 0
471 224 88 26 0
141 61 19 3 0

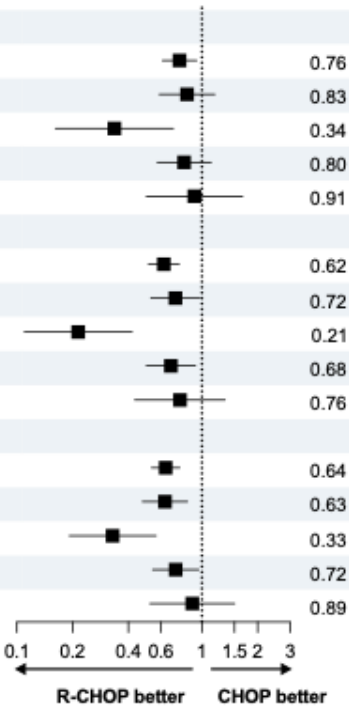
Figure S2.

A. For patients receiving eight cycles of R-CHOP, intake of beta-blocker had no statistically significant impact on OS but showed a trend favoring patients taking no BB (HR: 1.34; 95% CI: 0.81 – 2.23; p = 0.25). Also, intake of beta-blocker had no bearing on PFS (HR: 1.29; 95% CI: 0.79 – 2.1; p=0.3) and EFS (HR: 1.29; 95% CI: 0.83 – 2.02; p = 0.26) with the same trend favoring patients without BB intake.

B. In RICOVER-60, no significant differences regarding survival outcomes overall survival (OS), progression-free survival (PFS) and event-free survival (EFS) were observed for patients treated with and without documented BB intake. Since one proposed mechanism of action of beta-blocker is its effect on immune cells, patients were analyzed separately according to rituximab medication (yes/no). Patients who received no rituximab for lymphoma treatment seemed to fair slightly worse when BB intake was documented.

A

Outcome	No. of CHOP cycles	Beta Blocker	R-CHOP *no. of patients with outcome/total no. (%)*	CHOP *no. of patients with outcome/total no. (%)*	HR (95% CI)	P two way interaction	P three way interaction
Overall survival							
Overall			152/610 (24.9)	194/612 (31.7)	0.76 (0.61–0.94)		0.056
	6	No	59/231 (25.5)	71/232 (30.6)	0.83 (0.59–1.18)	0.028	
	6	Yes	10/75 (13.3)	25/75 (33.3)	0.34 (0.16–0.70)		
	8	No	63/247 (25.5)	75/239 (31.3)	0.80 (0.57–1.12)	0.71	
	8	Yes	20/57 (35.1)	23/66 (34.9)	0.91 (0.50–1.66)		
Progression-free survival							
Overall			176/610 (28.9)	259/612 (42.3)	0.62 (0.51–0.76)		0.0087
	6	No	72/231 (31.2)	95/232 (40.9)	0.72 (0.53–0.98)	0.0012	
	6	Yes	11/75 (14.7)	38/75 (50.7)	0.21 (0.11–0.42)		
	8	No	72/247 (29.1)	97/239 (40.6)	0.68 (0.50–0.92)	0.73	
	8	Yes	21/57 (36.8)	29/66 (44.0)	0.76 (0.43–1.34)		
Event-free survival							
Overall			213/610 (34.9)	297/612 (48.5)	0.64 (0.53–0.76)		0.053
	6	No	84/231 (36.4)	117/232 (50.4)	0.63 (0.48–0.84)	0.036	
	6	Yes	19/75 (25.3)	43/75 (57.3)	0.33 (0.19–0.57)		
	8	No	85/247 (34.4)	106/239 (44.4)	0.72 (0.54–0.96)	0.49	
	8	Yes	25/57 (43.9)	31/66 (47.0)	0.89 (0.52–1.50)		



B

Outcome	No. of CHOPCycles	Received Rituximab	Beta Blocker *no. of patients with outcome/total no. (%)*	No Beta Blocker *no. of patients with outcome/total no. (%)*	IPT-weighted HR (95% CI)	P two way interaction	P three way interaction
Overall survival							
Overall			78/273 (28.6)	268/949 (28.2)	0.83 (0.61–1.14)		0.039
	6	No	25/75 (33.3)	71/232 (30.6)	0.98 (0.55–1.74)	0.12	
	6	Yes	10/75 (13.3)	59/231 (25.5)	0.42 (0.16–1.06)		
	8	No	23/66 (34.8)	75/239 (31.4)	0.80 (0.44–1.44)	0.63	
	8	Yes	20/57 (35.1)	63/247 (25.5)	0.98 (0.52–1.85)		
Progression-free survival							
Overall			99/273 (36.3)	336/949 (35.4)	0.90 (0.68–1.18)		0.0076
	6	No	38/75 (50.7)	95/232 (40.9)	1.27 (0.80–2.00)	0.016	
	6	Yes	11/75 (14.7)	72/231 (31.2)	0.36 (0.15–0.91)		
	8	No	29/66 (43.9)	97/239 (40.6)	0.94 (0.58–1.52)	0.85	
	8	Yes	21/57 (36.8)	72/247 (29.1)	1.01 (0.55–1.86)		
Event-free survival							
Overall			118/273 (43.2)	392/949 (41.3)	0.93 (0.72–1.19)		0.012
	6	No	43/75 (57.3)	117/232 (50.4)	1.19 (0.79–1.81)	0.054	
	6	Yes	19/75 (25.3)	84/231 (36.4)	0.54 (0.27–1.08)		
	8	No	31/66 (47.0)	106/239 (44.4)	0.84 (0.53–1.33)	0.69	
	8	Yes	25/57 (43.9)	85/247 (34.4)	0.97 (0.55–1.71)		

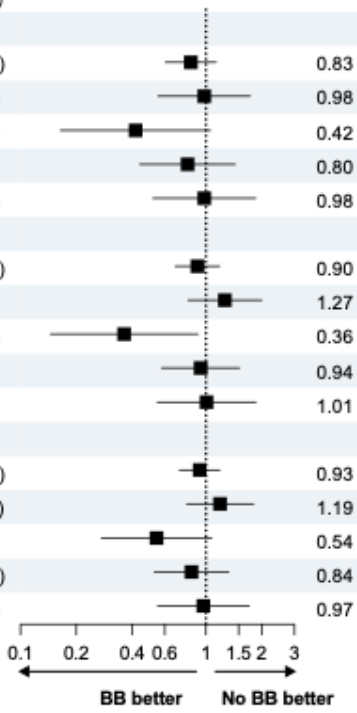


Figure S3.

A. Rituximab treatment effect (R-CHOP vs CHOP) by baseline beta blocker use and CHOP cycle number (6 vs 8)

Unadjusted rituximab treatment effect across beta blocker subgroups and cycle strata. Forest plots show hazard ratios (HRs) with 95% confidence intervals comparing R-CHOP versus CHOP for OS, PFS, and EFS overall and within strata defined by cycle number (6 vs 8) and baseline beta blocker use (yes vs no). Two-way interaction p values assess effect modification of the rituximab treatment effect by beta blocker use within each cycle stratum (Ritux×BB). Three-way interaction p values test whether this interaction differs between 6 and 8 cycles (Ritux×BB×cycle).

B. Sensitivity analysis: IPT-weighted association of baseline beta blocker use with outcomes by regimen (CHOP vs R-CHOP) and CHOP cycle number (6 vs 8)

IPT-weighted beta blocker association by treatment regimen and cycle strata. Forest plots show IPT-weighted HRs (95% CI) for baseline beta blocker use (yes vs no) for OS, PFS, and EFS, presented overall and separately for 6-cycle and 8-cycle regimens with and without rituximab. Two-way interaction p values test whether the beta blocker association differs between CHOP and R-CHOP within each cycle stratum (BB×Ritux). Three-way interaction p values test whether this interaction differs between 6 and 8 cycles (BB×Ritux×cycle).