Rituximab maintenance for patients with aggressive B-cell lymphoma in first remission: results of the randomized NHL13 trial

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**Listed in Appendix 1*

ABSTRACT

We investigated rituximab maintenance therapy in patients with diffuse large B-cell lymphoma (n=662) or follicular lymphoma grade 3b (n=21) in first complete remission. Patients were randomized to rituximab maintenance (n=338) or observation (n=345). At a median follow-up of 45 months, the event-free survival rate (the primary endpoint) at 3 years was 80.1% for rituximab maintenance *versus* 76.5% for observation. This difference was not statistically significant for the intent-to-treat population (likelihood ratio *P*=0.0670). The hazard ratio by treatment arm was 0.79 (95% confidence interval 0.57-1.08; *P*=0.1433). The secondary endpoint, progression-free survival was also not met for the whole statistical model (likelihood ratio *P*=0.3646). Of note, rituximab maintenance was superior to observation when treatment arms only were compared (hazard ratio: 0.62; 95% confidence interval 0.43-0.90; *P*=0.0120). Overall survival remained unchanged (92.0 *versus* 90.3%). In subgroup analysis male patients benefited from rituximab maintenance with regards to both event-free survival (84.1% *versus* 74.4%) (hazard ratio: 0.58; 95% confidence interval 0.36-0.94; *P*=0.0267) and progression-free survival (89.0% *versus* 77.6%) (hazard ratio: 0.45; 95% confidence interval 0.25-0.79; *P*=0.0058). Women had more grade 3/4 adverse events (*P*=0.0297) and infections (*P*=0.0341). Men with a low International Prognostic Index treated with rituximab had the best outcome. In summary, rituximab maintenance in first remission after R-CHOP-like treatment did not prolong event-free, progression-free or overall survival of patients with aggressive B-non-Hodgkin lymphoma. The significantly better outcome of men warrants further studies prior to the routine use of rituximab maintenance in men with low International Prognostic Index. This trial is registered under EUDRACT #2005-005187-90 and *www.clinicaltrials.gov* as *#NCT00400478*.

Introduction

The addition of rituximab to induction chemotherapy has greatly improved the outcome of patients with diffuse large B-cell lymphoma (DLBCL).[1,2] However, relapse prevention with anti-CD20 antibody maintenance therapy is not established for DLBCL or other aggressive lymphomas (follicular lymphoma grade 3b, FLG3b).[3-8] Rituximab maintenance after R-CHOP first-line treatment provided no benefit in patients older than 60 years in a randomized trial (ECOG 4494).[9] On the other hand, improved progression-free survival (PFS) in DLBCL after R-CHOP induction was reported in a smaller retrospective study.[10] In relapsed DLBCL prolonged event-free survival (EFS) has been observed with autologous stem cell transplantation and in women receiving rituximab maintenance after second-line autologous stem cell transplantation.[11,12] This is in line with data from a meta-analysis showing that male sex is a poor risk factor in DLBCL.[13] The superior outcome of female lymphoma patients is supported by higher rituximab serum concentrations in women than in men.[14,15]

We investigated the ability of rituximab maintenance given every 2 months to prolong EFS (and PFS) in patients with DLBCL or FLG3b in complete remission (CR) or CR unconfirmed (CRu) after R-CHOP induction.[16] The NHL13 study was designed for patients with a variety of R-CHOP-like treatment modalities (4 to 8 cycles of rituximab-containing treatment with or without planned involved field radiothera-

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py) representative of clinical practice at the time of initiation (2004): 21 patients received fewer than six cycles, 308 received six cycles and 354 received more than 6 cycles. All patients received eight doses of rituximab before randomization to maintenance or observation. Adult patients of all ages, clinical stages and International Prognostic Index (IPI) risk groups were included.[17] Unrestricted inclusion was intended to provide clues on the effect of rituximab maintenance in the whole population as well as in subgroups.

Methods

Patients and study design

Previously untreated adult patients over 18 years old were eligible for this open label multicenter phase III randomized trial if they had a diagnosis of CD20-positive aggressive lymphoma (DLBCL or FLG3b defined by the local pathologist according to the World Health Organization classification) and had reached a CR or CRu according to the 1999 response criteria for malignant lymphoma.[16] The study was performed in accordance with the Helsinki Declaration, the protocol was approved by the ethics review committee of each participating center, and all patients gave written informed consent. Central pathology review was performed for Austrian patients. Patients received eight infusions of rituximab (375 mg/m^2 i.v.) plus four to eight cycles of CHOP-like chemotherapy (i.e. 12 to 24 weeks of a CHOP-like regimen, including, but not limited to CEOP/IMVP, CHOEP, iCHOP, ESHAP, CNOP, MACOP-B, VACOP-B, and ProMaceCytaBOM, as first-line therapy. Induction treatment had to have been completed 12 to 4 weeks before starting the trial treatment. CR or CRu was documented prior to starting trial treatment by computed tomography (CT) scanning through investigator assessment. Patients had to have an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0, 1 or 2 at the time of inclusion and a known IPI prior to induction.

Patients with first-line therapy other than specified, transformed lymphoma, evidence of central nervous system involvement, uncontrolled cardiac disease, hematopoietic insufficiency,

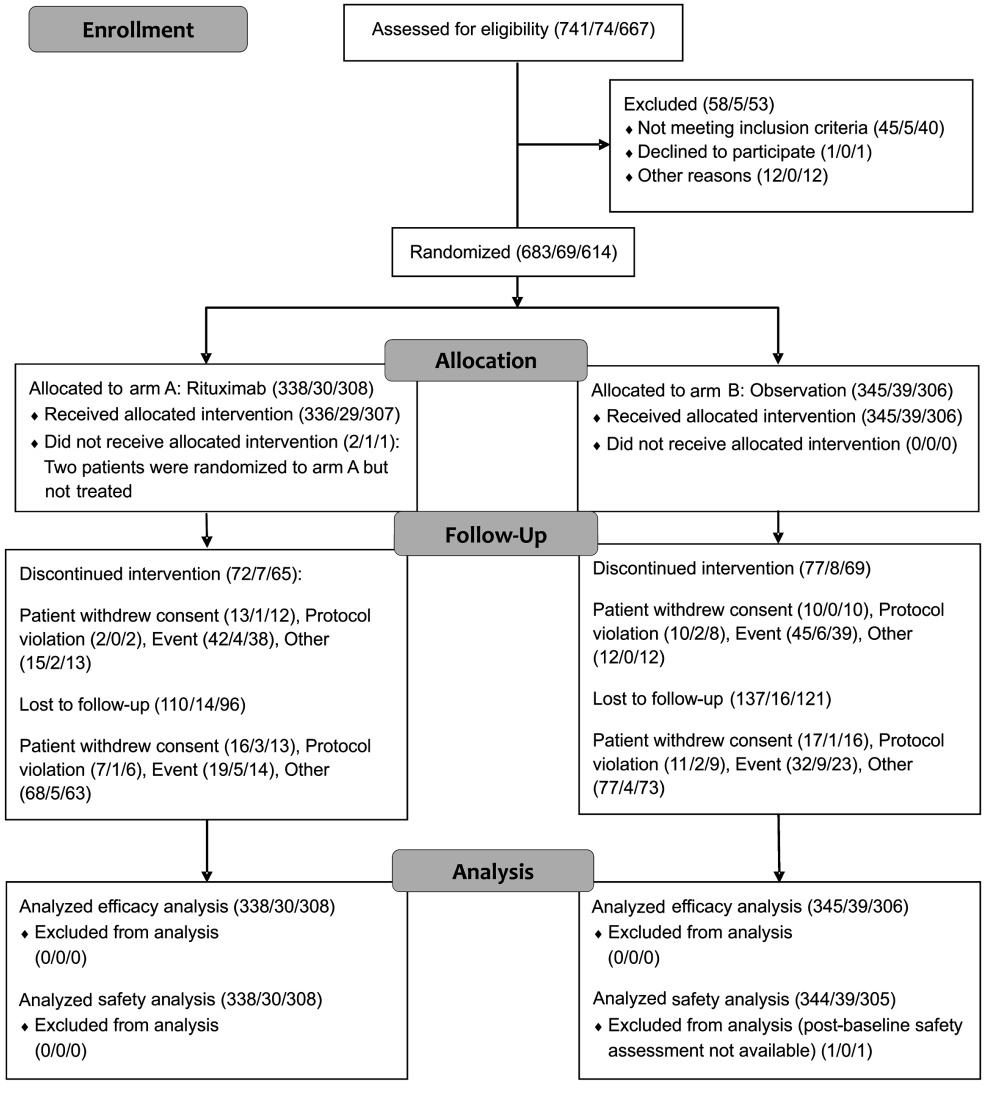

Figure 1. CONSORT 2010 study flow diagram.

abnormal renal or liver function, active opportunistic infections, active hepatitis B or C, or positivity for human immunodeficiency virus were excluded. More detailed descriptions are provided in the study protocol (*Online Supplementary Appendix* and *Online Supplementary Figure S1*).

Rituximab was given by intravenous infusion at a dose of 375 mg/m^2 every 2 months. Sixty-nine patients were randomized before the first protocol amendment in 2006 to maintenance for 1 year (6 doses) *versus* observation. Patients were stratified for type of chemotherapy, number of therapy cycles (≤6 *versus* >6) and geographic region. After the first amendment, all patients were randomized to 2 years (12 doses) of rituximab maintenance *versus* observation. Clinical response was evaluated according to the 1999 criteria and included CT scans every 4 months and bone marrow biopsies in the case of initial infiltration.[16]

As shown in Figure 1 (CONSORT flow diagram), 741 patients were assessed for eligibility and 683 patients were randomized. Patients were included at 134 sites in 26 countries. The first patient was included in June 2004 and the last patient received treatment in December 2010. The study was monitored on site.

Sample size calculation

A difference in median EFS with rituximab maintenance *versus* observation was estimated to be 74.6 months (treatment arm A) *versus* 46.6 months (observation arm B), i.e. an approximately 60% improvement in terms of EFS [hazard ratio (HR)=0.625]. Assuming an exponential distribution of survival time and a recruitment ratio of 1:1 for patients, a total of 148 events were considered necessary to achieve 80% power with a two-sided test and significance level of 5%. It was planned to enroll 600 patients (300 per arm) with DLBCL or FLG3b over a recruitment period of 2 years with a minimum follow-up of 2 years. Prior to the final analysis after 148 events two interim analyses were planned after one-third and two-third of all events had been observed. These analyses were planned to reject the null-hypothesis only with a Lan-DeMets alpha spending function resembling an O'Brien & Fleming boundary for group sequential tests.

Statistical methods

The efficacy analyses were performed for the intent-to-treat population and statistical tests were two-sided with a significance level of 5%. A per-protocol analysis was not performed since less than 10% of patients had major protocol deviations which would have excluded them from this analysis.

EFS (events: progressive disease, death from any cause, initiation of new anticancer treatment, secondary malignancy, unacceptable toxicity), PFS (events: progressive disease or relapse, death from any cause), and overall survival (OS) were analyzed using a Cox regression model with the factors geographical region and type as well as number of cycles of induction therapy (i.e. the factors used for stratification of randomization) as covariates together with the factor treatment group. Additionally, these survival parameters were presented graphically using the Kaplan-Meier method. Other factors included in the statistical analysis plan (not the study protocol) were age, body weight, sex, body mass index, and ECOG status.

The prognostic influence of the IPI (assessed at initial diagnosis) was evaluated with the same Cox regression model and IPI as an additional factor. For these analyses, all patients were classified according to whether they had IPI ≤1 or IPI >1 in order to compare two similarly large subgroups. Analyses of the four IPI categories (low, low-intermediate, high-intermediate, high) were also performed and showed similar results.

After completion of the planned statistical analysis, Cox regression models with factor treatment group and single other factors were applied for EFS, PFS and OS as post-hoc analyses. Significant factors from these models were entered into multivariate models (factors which are used for the calculation of the IPI were not entered into a multivariate model together with the IPI).

Adverse event rates were also compared post-hoc with a Fisher exact test.

Statistical analyses were performed using Statistical Analysis Software (SAS) version 9.2.

Role of the funding source

The study started as a Roche Austria sponsored trial. After the first amendment in 2006, AGMT became the sponsor with full responsibility for the study including control of collection, analysis, and interpretation of data, writing of reports, manuscripts, and presentation at meetings. The study was conducted in cooperation with the Czech Lymphoma Study Group (CLSG) and is registered under EUDRACT n. 2005-005187-90 and *ClinicalTrials.gov: NCT00400478.*

Results

Patients were balanced regarding demographics, disease characteristics at initial diagnosis, type of induction treat-

Table 1. Patients' characteristics and response to R-CHOP-like induction therapy.

	Maintenance n = 338	Observation n = 345	*P* value
Median age, years (range)	57 (19-87)	58 (19-88)	n.s.
Sex (male)	163 (48.2%)	182 (52.8%)	n.s.
Median body mass index	25.9	25.6	n.s.
At least one concomitant disease	231 (68.3%)	230 (66.7%)	n.s.
DLBCL	329 (97.3%)	333 (96.5%)	n.s.
FL grade 3	9 (2.7%)	12 (3.5%)	n.s.
Ann Arbor I	59 (17.5%)	67 (19.5%)	n.s.
Ann Arbor II	110 (32.5%)	116 (33.7%)	n.s.
Ann Arbor III	83 (24.6%)	77 (22.4%)	n.s.
Ann Arbor IV	86 (25.4%)	84 (24.4%)	n.s.
Diameter of largest lymph node:			
> 5 cm	126 (37.3%)	124 (36%)	n.s.
> 10 cm	33 (9.8%)	44 (12.8%)	n.s.
Bone marrow involvement	41 (12.1%)	33 (9.6%)	n.s.
LDH > upper limit of normal	154 (45.6%)	163 (47.2%)	n.s.
IPI: 0,1 (low)	161 (47.6%)	165 (48.0%)	n.s.
2 (low-intermediate)	96 (28.4%)	82 (23.8%)	n.s.
3 (high-intermediate)	59 (17.5%)	67 (19.5%)	n.s.
4,5 (high)	22 (6.5%)	30 (8.7%)	
Number of initial chemotherapy cycles			
< 6	149 (44.0%)	161 (46.7%)	n.s.
> 6	189 (56.0%)	184 (53.3%)	n.s.
Received all 8 planned rituximab infusions prior to randomization	334 (98.8%)	343 (99.4%)	n.s.
R-CHOP 21	250 (74.0%)	268 (77.7%)	n.s.
R-CHOP 14	41 (12.1%)	39(11.3%)	n.s.
Other CHOP-like	47 (13.9%)	38(11.0%)	n.s.
Response status at randomization			n.s.
CR	282 (83.4%)	293 (84.9%)	n.s.
CRu	56 (16.6%)	52 (15.1%)	n.s.
Planned radiotherapy	13 (3.8%)	3 (0.9%)	0.0110

n.s.: not statistically significant.

ment, and clinical response except for an imbalance regarding planned radiotherapy (3.8% in rituximab maintenance *versus* 0.9% for observation) (Table 1). The median age was 57 and 58 years, respectively, with approximately half of the patients being male in both arms. The vast majority of patients had DLBCL (97.3% and 96.5%) with 47.6% and 48% in the low IPI group. Forty-four percent and 46.7% had received up to six cycles of rituximab chemotherapy and 74% and 77.7% were treated with R-CHOP-21. At randomization, 83.4% and 84.9% were in CR, while the rest were in CRu. Adherence to the study was high with a median exposure to study medication of 20.5 months.

Event-free survival (primary endpoint)

After a median follow-up of 45 months the EFS rate (for all 683 patients) was 80.1% in the rituximab maintenance arm *versus* 76.5% in the observation arm at 3 years (Figure 2A). Cox regression analysis with factors being treatment group, geographical region, type of induction therapy and number of cycles of induction therapy was applied on the EFS for all patients. The model did not show significance (likelihood ratio P=0.0670). The hazard ratio (HR) by treatment arm was 0.79; 95% confidence interval (CI) 0.57-1.08; P=0.1433. Thus, the primary endpoint of the study was not met, indicating that rituximab maintenance did not provide an advantage for the intent-to-treat population as a whole.

Progression-free survival (secondary endpoint)

The PFS rate for rituximab maintenance *versus* observation was 86.3 *versus* 79% at 3 years (Figure 2B). This difference was not significant for all patients in the whole model (likelihood ratio P=0.3646). However, rituximab maintenance was superior to observation when treatment arms were compared (HR: 0.62; 95% CI 0.43-0.90; P=0.0120). This corresponds to a lower number of lymphoma relapses in the rituximab maintenance arm (36 *versus* 64 or 10.7% *versus* 18.6%) (Figure 2C).

Overall survival (secondary endpoint)

The OS rate at 3 years was not different between the rituximab maintenance (92.0%) and observation (90.3%) arms (likelihood ratio P=0.3184; HR by treatment arm 0.81; 95% CI 0.49-1.34; P=0.4145) (Figure 2D).

The first 69 Austrian patients were randomized to 12

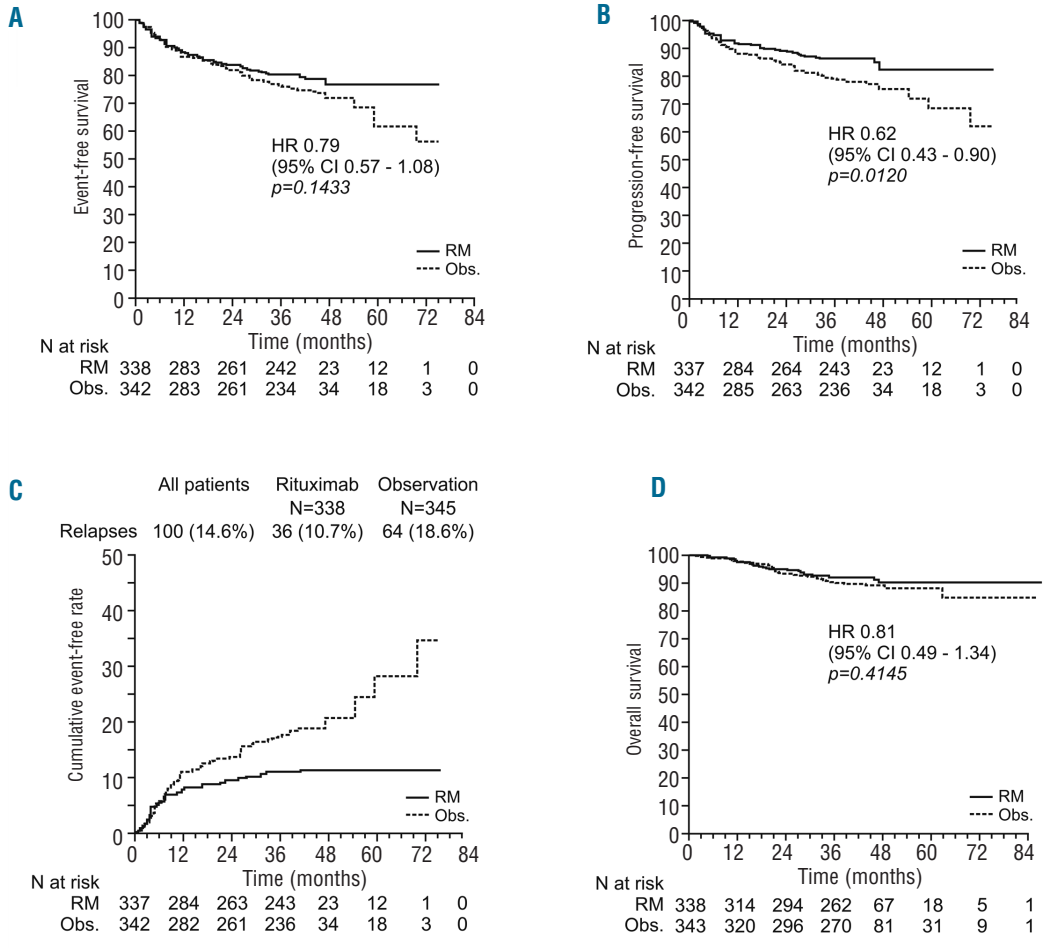

Figure 2. Survival analysis of all patients by treatment arm (intention-to-treat population) (n=683). (A) Event-free survival: the effect of treatment [rituximab maintenance (RM) *vs.* observation (obs.)] is indicated by hazard ratio (HR), 95% confidence interval (CI), and the corresponding *P* value; (B) Progression-free survival; (C) Relapses and cumulative event-free rate by treatment arm; (D) Overall survival.

months (6 doses) of rituximab while the following 614 patients (after amendment 1) were randomized to 24 months of rituximab maintenance. For statistical reasons all 683 patients were included in the final analysis. However, we also performed a separate analysis for these two groups. Results for the post-amendment 1 patients corresponded well to those of the whole group with regards to EFS (likelihood ratio *P*=0.0651), PFS (likelihood *P*=0.3923; HR by treatment arm 0.59; 95% CI 0.39-0.88; *P*=0.0108), and OS (likelihood *P*=0.3707).

Safety

Toxicity was generally mild and equal between the treatment and observation arms with 17.2% and 16.3% of patients experiencing at least one Common Toxicity Criteria (CTC) grade 3/4 adverse event (6.8% and 3.5% grade 3/4 infections). Adverse events CTC grade 3/4 classified as related to rituximab maintenance were 6.5%.

Seven patients positive for hepatitis B virus antigen were included in this study. An increase to 18 positive patients was observed at the end of treatment (from 2 to 9 with rituximab maintenance and from 5 to 9 in the observation arm).

Subgroup analysis

In a Forest plot of univariate analyses on EFS we noted a difference in response between female and male patients (Figure 3).

The Cox regression model was not significant for female patients (likelihood ratio *P*=0.4638) but highly significant for male patients (likelihood ratio *P*=0.0002). The 3-year EFS for rituximab maintenance *versus* observation was 76.8% *versus* 78.7% in female patients but 84.1% *versus* 74.4% in male patients (Figure 4A,B). Rituximab maintenance treatment had a significant effect on EFS in men (HR: 0.58; 95% CI 0.36-0.94; *P*=0.0267), but not in women (HR: 1.05; 95% CI 0.67-1.66; *P*=0.8246). The major differences in events were a higher lymphoma relapse rate (22 *versus* 14) as well as a higher rate of unacceptable toxicities (8 *versus* 4) in women (*Online Supplementary Table S1*).

There was no difference in PFS for female patients (likelihood ratio *P*=0.6816) (Figure 4C). Again, the whole model was significant for men (likelihood ratio *P*=0.0122): among men, the rituximab maintenance group had a lower hazard than the observation group (3-year PFS 89.0% *versus* 77.6%; HR: 0.45; 95% CI 0.25-0.79; *P*=0.0058) (Figure 4D).

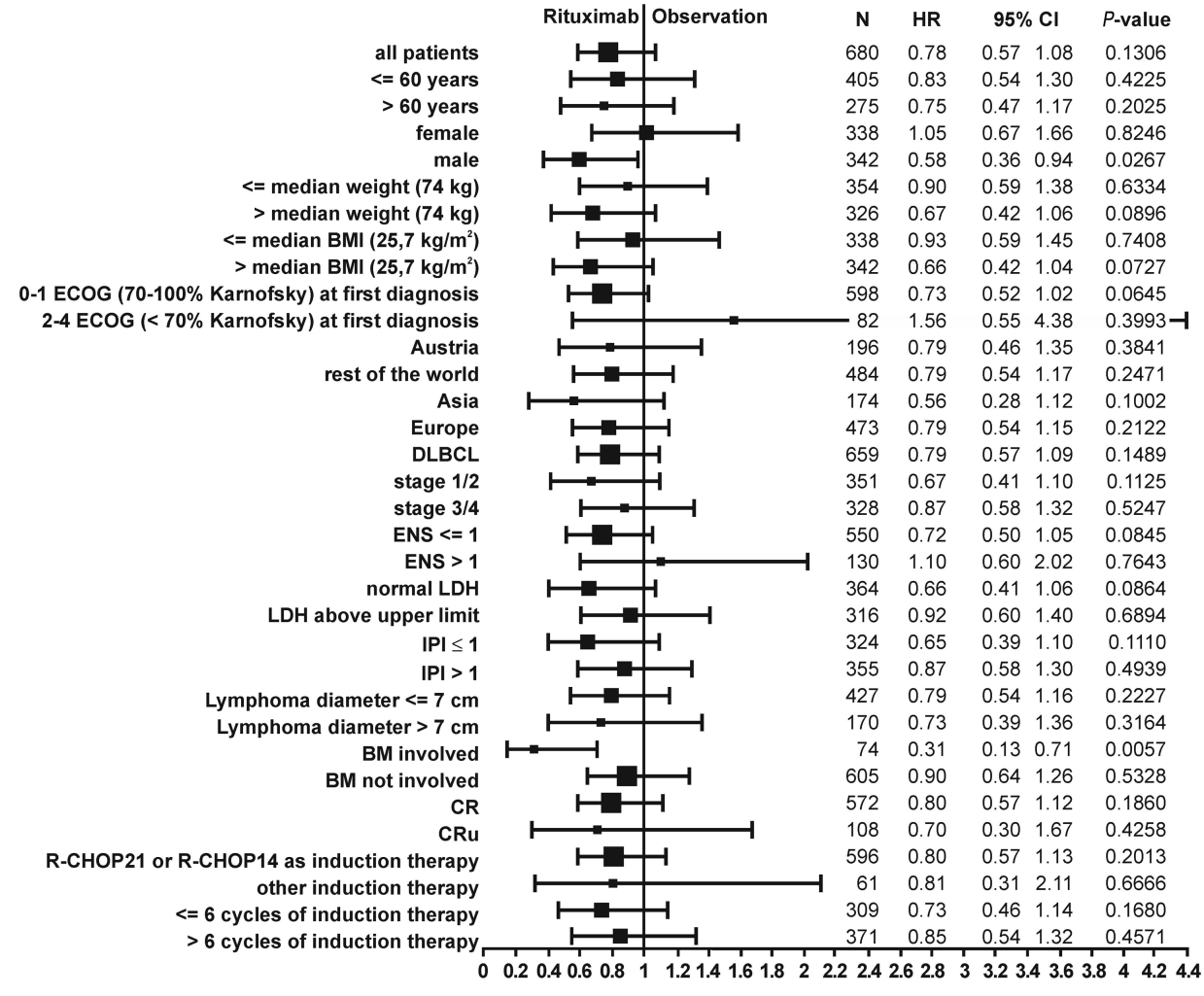

Figure 3. Forest plot of univariate analysis on EFS of selected subgroups. A shift to the left favors rituximab maintenance. X-axis: hazard ratio.

Interestingly, more women receiving rituximab maintenance had at least one grade 3/4 adverse event CTC (21.7% *versus* 12.3% in males, *P*=0.0297). Infections and infestations (all grades) occurred most frequently in female patients in the rituximab maintenance arm (40.6% *versus* 29.4% in males with rituximab maintenance; *P*=0.0341) (*Online Supplementary Table S2*).

As expected, the IPI also had a significant influence on EFS in the whole population of patients (likelihood ratio *P*=0.0121) and particularly in men (likelihood ratio *P*<0.0001), but interestingly not in women (likelihood ratio *P*=0.3712) (Figure 5A-C). Men with a low IPI treated with rituximab had the most favorable outcome (likelihood ratio *P*=0.0268) with an EFS of 91.2% (rituximab maintenance *versus* observation: HR: 0.46; 95% CI 0.19-1.16; *P*=0.0993).

In multivariate analysis for male patients, rituximab treatment, age ≤60 years, and stage 1/2 remained independent factors for EFS. When IPI was included as a single variable, rituximab maintenance (*P*=0.0217) and low IPI (*P*=0.0062) remained statistically significant (*Online Supplementary Tables S3* and *S4*).

The model was also significant regarding PFS of male patients (likelihood ratio *P*=0.0042). The hazard ratio for rituximab maintenance was lower than that for observation (*P*=0.0033) and patients with IPI≤1 had a lower hazard than the IPI>1 group (*P*=0.0254). This effect was particularly pronounced in male patients with an IPI≤1 in whom only few relapses occurred after rituximab maintenance (PFS 96.1% *versus* 80.5%, likelihood ratio *P*=0.0140) (HR: 0.26; 95% CI: 0.07-0.93; *P*=0.0388) (Figure 5D).

Another small subgroup of patients who benefited significantly from rituximab were subjects with initial bone marrow involvement (HR: 0.31; 95% CI 0.13-0.71; *P*=0.0057).

In multivariate analysis of factors potentially influencing PFS in male patients rituximab (*P*=0.0102) and low IPI (*P*=0.0229) remained statistically significant (*Online Supplementary Table S5*).

Discussion

The results of this study indicate that rituximab maintenance treatment does not significantly prolong overall EFS or PFS of patients in CR or CRu after R-CHOP-like induction treatment for aggressive B-cell lymphoma. This is in line with the results of the ECOG 4494 trial.[9] Thus, our study too does not allow rituximab maintenance to be recommended for patients with DLBCL or FLG3b in first remission.

However, the study showed interesting signs towards

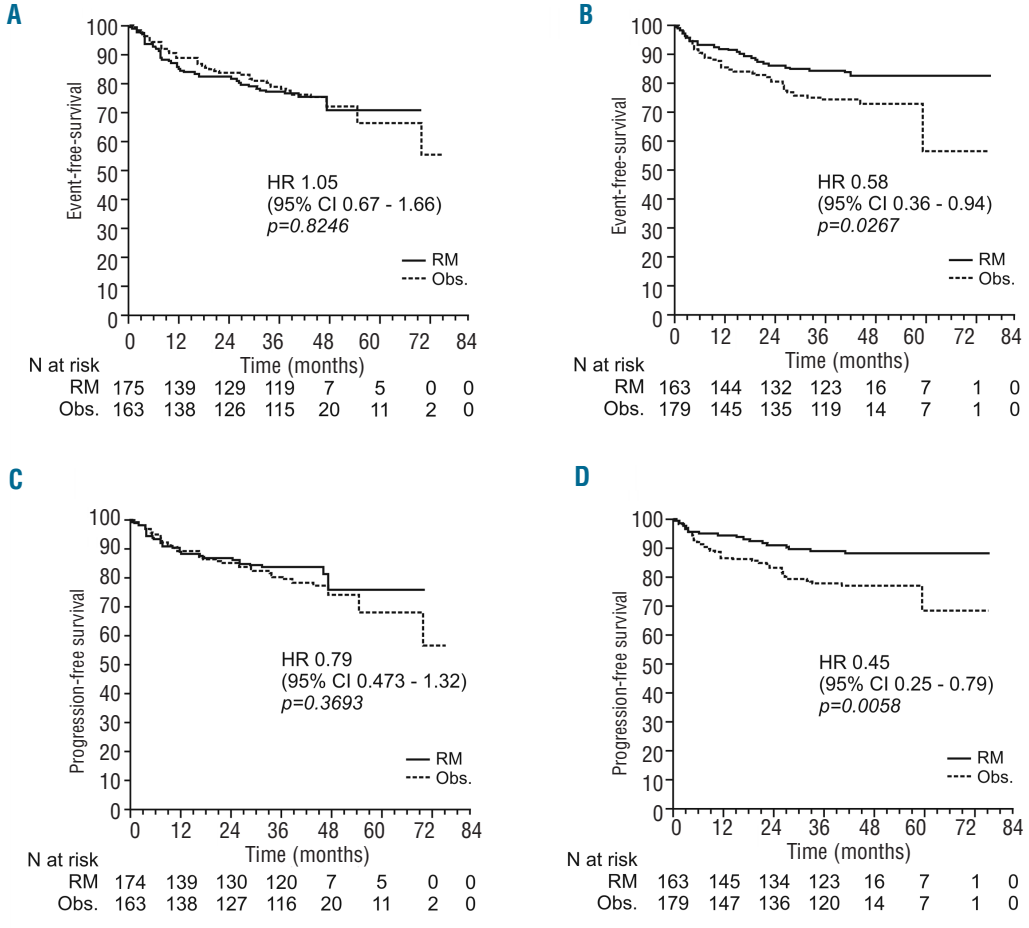

Figure 4. Subgroup analysis by sex, IPI, and treatment arm. (A) EFS: all female patients; (B) EFS: all male patients; (C) PFS: all female patients; (D) PFS: all male patients. RM: rituximab maintenance; Obs: observation.

an improved outcome of patients receiving rituximab in several ways. The *P*-value of the likelihood ratio for the primary endpoint, EFS, was 0.0670 and a shift in favor of rituximab maintenance was observed in some subgroups (male patients, patients with initial bone marrow involvement). The total lymphoma relapse rate was 14.6%. This is in line with a recently reported decline in relapse rate after completion of induction therapy.[18] However, the number of relapses in the rituximab arm decreased considerably resulting in a significantly improved PFS when treatment and observation arms were compared (HR 0.62; *P*=0.0120). Overall survival was good in this population of patients who were already in CT-assessed CR or CRu at study entry. The lack of difference in OS indicates that relapsing patients in the observation arm can be salvaged by other therapies.[11,19] On the other hand, rituximab maintenance could spare patients aggressive second-line chemotherapy or autologous stem cell transplantation.

Subgroup analysis revealed a striking sex-specific outcome: While women had no benefit from rituximab maintenance, men had a significantly prolonged EFS and PFS. This indicates that rituximab maintenance is able to reverse the poor prognostic impact of male sex in DLBCL (and FLG3b).[13,14] This is surprising since all previous evidence suggests that female lymphoma patients have a better outcome with rituximab-containing therapy.[4,11-15] Male sex was identified as a poor prognostic factor in the RICOVER-60 study as well as in a recent meta-analysis of three major trials in R-CHOP-treated DLBCL patients older than 60 years.[13,14,20,21] The clinical phenomenon is supported by pharmacokinetic data showing higher rituximab serum concentrations in female patients.[14,15] Pfreundschuh and colleagues suggested that the sex-specific difference in response is stronger because of a diminished rituximab clearance in older female patients.[14,20,21] The German DSHNHL recently reported that increasing the rituximab dose to 500 mg/m^2 eliminated the poor risk of elderly male patients in the SEXIE-R-CHOP-14 trial.[22] In our study young and old men (≤60 *versus* >60) benefited from rituximab maintenance with regards to PFS (*data not shown*) while there was no difference between rituximab maintenance and observation in women of both age groups. Thus, it seems reasonable to explore higher rituximab doses also in younger male patients in a prospective

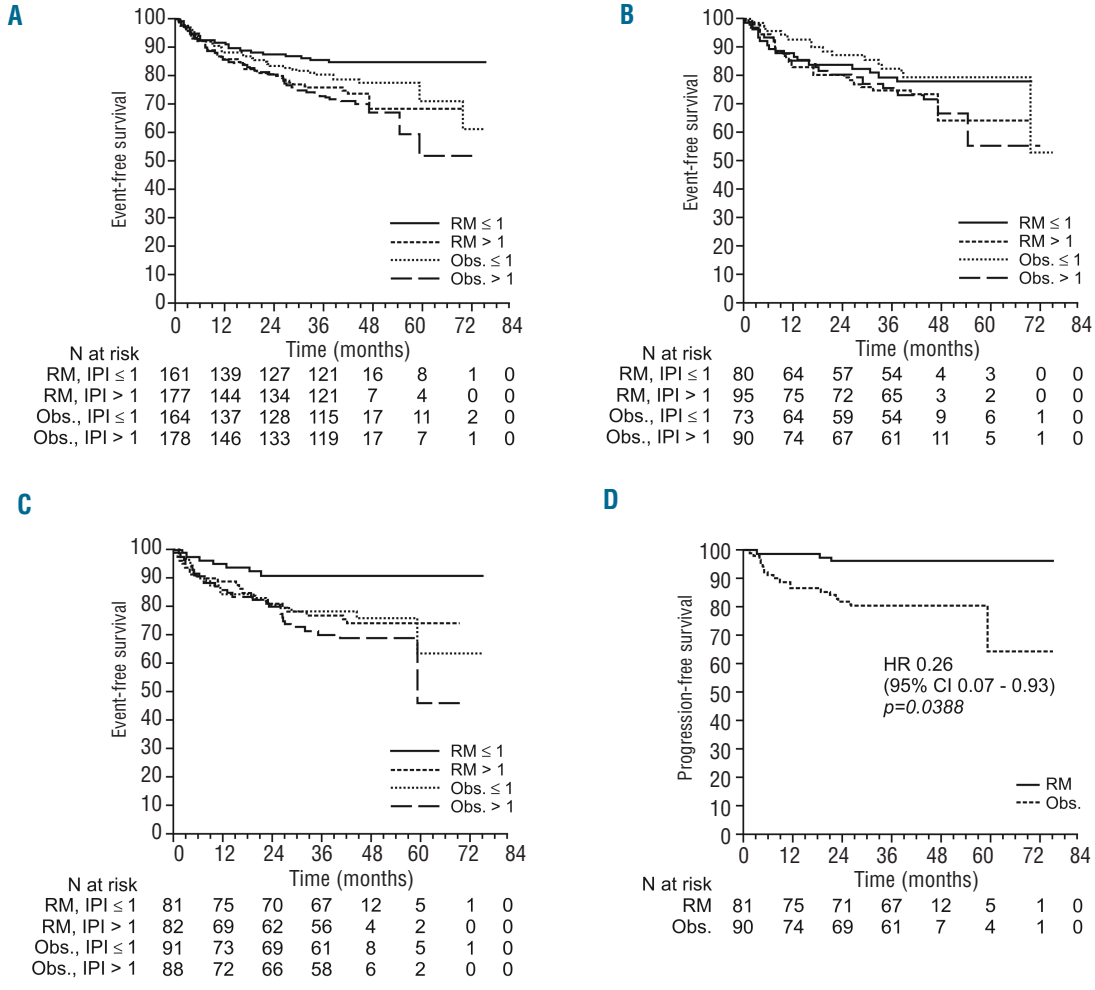

Figure 5. Subgroup analysis by IPI and treatment arm. (A) EFS: all patients; (B) EFS: all female patients; (C) EFS: all male patients; (D) PFS: male patients with IPI≤1. RM: rituximab maintenance; Obs: observation.

trial. Patients with higher body weight and higher body mass index have been shown to profit from prolonged rituximab treatment.[14,23] Men in the NHL13 had a significantly higher body mass index (median 26 *versus* 25.4, *P*=0.045; *data not shown*).

A possible explanation for the better outcome of men in our study is that female patients with DLBCL in CR may have deeper remissions and already saturated rituximab serum levels after induction treatment.[15] This could explain the higher number of infections in women. On the other hand, male patients may be underdosed with the current rituximab standard regimen of 375 mg/m^2 in R-CHOP induction.[20,21] We hypothesize that rituximab maintenance could equalize this lack of rituximab and eliminate residual lymphoma cells. Another possible explanation is a selection of good-risk male patients achieving a CR after induction. Men with a low IPI had a nearly optimal outcome with a 3-year PFS of 96.1%. These patients were younger (81.5% <60 years *versus* 40.2% in the IPI>1 group) and had received six cycles of R-CHOP more frequently (46.9% *versus* 40.7%) compared to the IPI>1 group (34.1 *versus* 62.2%) (*data not shown*). Patients with low IPI are treated with six cycles of R-CHOP according to current standards.[5,24-26] Consolidation therapy with radiation has shown a benefit for R-CHOP-treated patients with limited stage disease.[27-29] However, less than 3% of patients in NHL13 received planned radiation therapy. This may be important for further studies in patients with bulky disease.[30]

There are some differences with regard to other rituximab maintenance studies. In the ECOG 4494 trial patients were >60 years old with less early stage disease, Patients in partial remission were also included, and the rituximab regimen was different (4 x rituximab weekly with 6 months interval).[9] The Chinese retrospective study included patients under 60 years treated with six cycles of R-CHOP-14 regardless of remission status after induction. Rituximab was administered every month for the first year and every 3 months for the second year. Numbers in subgroups (e.g. sex, IPI) were small and gender outcome was not reported.[10] This also raises the question as to the optimal way of dosing and scheduling rituximab during DLBCL treatment. When we compared the 69 initial patients who received only 12 months of maintenance, we noted a trend for improved EFS in men who received 24 months of maintenance. Dose-dense application of rituximab did not significantly alter outcome of elderly patients with DLBCL.[31] It will be worth comparing rituximab maintenance with extended rituximab treatment after induction, as studied by the DSHNHL.[32]

Our study has some weaknesses. There was no upfront stratification for gender. However, sex-specific statistical analysis was pre-planned and the study is sufficiently large to exclude major biases. Central histopathological review was performed only for the Austrian patients. The fact that there were no significant differences in outcome between the Austrian and all other patients argues for the validity of the data (Figure 3). FLG3b patients were included since at the time of study initiation it was believed that FLG3b behaves similarly to DLBCL. This has recently been questioned.[8,33] In our study there was a relatively higher percentage of patients with bone marrow infiltration in the FLG3b group (6 of 14). On the other hand, only 3% of the study population had FLG3b and the results remained unchanged when only DLBCL patients were considered. Some regional differences were seen. A minority of patients were treated with R-CHOP-like regimens. However, when we analyzed R-CHOP patients only, the results remained unchanged. The response before inclusion in the study was investigator-assessed and not centrally reviewed. Importantly, positron emission tomography scans were not used since this was not included in the response assessment guidelines at the start of the study. The results may, therefore, be different with the introduction of the novel response criteria including positron emission tomography-CT.[34] We note that the outcome of patients with CR and CRu was not significantly different and the adherence to CT scans was high (median number of CT scans by attended visit was 90%, *data not shown*). These facts make it rather unlikely that the results of the study were significantly skewed. Moreover, the NHL13 data may serve as a reference for ongoing maintenance studies with other drugs such as lenalidomide (REMARC study) or enzastaurin.[35]

In conclusion, the results from NHL13 show that rituximab maintenance in first remission does not significantly alter the outcome of patients with aggressive B-non-Hodgkin lymphoma in first remission in general. However, subgroup analysis suggests that rituximab maintenance for aggressive B-cell lymphoma in CR or CRu after R-CHOP induction may be able to reverse the less favorable prognosis of male patients, particularly in the low IPI group. This finding warrants evaluation in further studies.

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