Rituximab maintenance improves clinical outcome of relapsed/resistant follicular non-Hodgkin’s lymphoma, both in patients with and without rituximab during induction: results of a prospective randomized phase III intergroup trial

Short Title: Rituximab maintenance in follicular lymphoma

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MHJvO, RK, REM, MW, EK and AH formed the writing committee designing the study, and were principal investigators of the participating lymphoma groups. RDG and AJ performed the major part of pathology review. MvG did all statistical analyses. IT and CR performed all data analysis. MvG, AV and HH included most patients and MHJvO wrote the paper.

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Scientific heading: Clinical Observations, Interventions and Therapeutic trials
Abstract
We evaluated the role of rituximab (R) both in remission induction and maintenance treatment of relapsed/resistant follicular lymphoma (FL). 465 patients were randomized to induction with 6 cycles of CHOP (3-weekly) or R-CHOP (R: 375 mg/m² i.v. day 1). Those in complete (CR) or partial remission (PR) were randomized to maintenance with R (375 mg/m² i.v. once every 3 months for a maximum of two years) or observation. R-CHOP induction yielded an increased overall response rate (CHOP 72.3%; R-CHOP 85.1%; p<0.0001) and CR rate (CHOP 15.6%; R-CHOP 29.5%; p<0.0001). Median progression free survival (PFS) from first randomization was 20.2 months after CHOP versus 33.1 months after R-CHOP (HR 0.65; p=0.0003).
Rituximab maintenance yielded a median PFS from second randomization of 51.5 months versus 14.9 months with observation (HR 0.40; p<0.0001). Improved PFS was found both after induction with CHOP (HR 0.30; p< 0.0001) and R-CHOP (HR 0.54; p=0.0043). R maintenance also improved overall survival from second randomization: 85% at 3 years versus 77% with observation (HR 0.52; p= 0.0111). This is the first trial showing that in relapsed/resistant FL rituximab maintenance considerably improves PFS not only after CHOP but also after R-CHOP induction.
Introduction

For patients with follicular lymphoma (FL) chemotherapy alone has not resulted in improved overall survival over the past 30 years. Although in the vast majority of the patients complete or partial remissions can be obtained with either single agents or combination chemotherapy, the clinical course is characterized by a high relapse rate. After relapse, both the response rate and relapse free survival after subsequent salvage treatment regimens steadily decrease, resulting in a median survival of only 4-5 years after first relapse. Therefore new treatment modalities resulting in increased progression free and overall survival are urgently required. Optimal treatment of patients relapsed after one or two chemotherapy regimens is largely unknown.

Rituximab (R) is a chimeric murine/human anti-CD20 monoclonal antibody capable of killing CD20-positive lymphoma cells. Effector mechanisms include complement-mediated cytotoxicity, antibody dependent cellular cytotoxicity and possibly direct induction of apoptosis. In the non-randomized pivotal study in 166 relapsed low grade lymphoma patients, monotherapy with rituximab resulted in a response rate of 48% with 6% CR rate and a median time to progression in responding patients of 13 months. Toxicity was generally mild to moderate (grade 1 or 2) and occurred primarily with the first infusion. In a subsequent small phase II study, the combination of rituximab and CHOP was shown to be safe and effective.

Treatment results in FL might not only be improved by more effective induction regimens but also by maintenance treatment - defined as continued treatment beyond induction therapy. Maintenance treatment with cytotoxic agents has been shown to improve PFS but not OS. This prolongation of PFS was achieved at the costs of increased toxicity, reduced patient well being and increased risk for secondary malignancies. In a recent meta-analysis, interferon maintenance treatment showed a survival benefit in FL when given in conjunction with intensive chemotherapy and at certain dose levels. However, the benefit of maintenance was not
consistent across all studies and toxicity was considerable \textsuperscript{17}. Because of its efficacy as monotherapy and its favorable pharmacokinetic and safety profile, maintenance treatment with R might be both effective and well tolerated.

In view of a) the efficacy of R monotherapy in relapsed low grade lymphoma \textsuperscript{11}, b) the feasibility of combining R with cytotoxic drugs \textsuperscript{12}, c) the theoretical potential of such combinations to clear minimal residual disease, we decided in 1998 to launch a phase III randomized clinical trial in patients with relapsed or resistant FL with 2 main objectives. First: to compare response rates to CHOP and R-CHOP and second: to establish the effect of maintenance treatment with R on progression free survival (PFS).

\section*{Methods}

\textbf{Patients.} This randomized (1:1) open label phase III Intergroup study was conducted at 130 centers in Canada, Australia/New Zealand, Europe and South Africa, from November 1998 to April 2004. Patients eligible for the study were those over 18 years of age with a CD20 positive grade 1-3 follicular lymphoma, Ann Arbor stage III or IV at initial diagnosis, and relapsed after or resistant to a maximum of 2 non-anthracycline containing systemic chemotherapy regimens. A previous regimen was defined as at least 2 months of single agent therapy (e.g. chlorambucil) and / or at least 2 consecutive cycles of polychemotherapy (e.g. CVP) or purine analogues. Patients had to have at least one bi-dimensional measurable mass by either clinical or radiological examination. WHO performance status had to be \( \leq 2 \). Major exclusion criteria were: prior treatment with anthracyclines, rituximab, autologous or allogeneic stem cell transplantation; circulating tumor cells \( >10 \times 10^9/l \); histological transformation; known HIV positivity; symptomatic CNS lymphoma; IgG levels \( <3 \text{ g/l} \); severe concomitant disease. Patient information and written informed consent were obtained
according to the rules of the respective country and institute. The study was conducted according to the Declaration of Helsinki and the Guidelines for Good Clinical Practice.

**Study design and Treatment.** Eligible patients were randomized to remission induction with either 6 cycles of standard CHOP (Cyclophosphamide 750 mg/m² i.v. day 1; Doxorubicin 50 mg/m² i.v. day 1; Vincristine 1.4 mg/m² (max 2 mg) day 1 and Prednisone 100 mg/dy orally days 1-5; once every 3 weeks) or CHOP + rituximab (R) (375 mg/m² i.v. at day 1 of each cycle of CHOP).

After 3 cycles of CHOP ± R, patients were evaluated for response. Those with stable disease or progression went off study. Responders received another 3 cycles of the assigned treatment. Patients with a complete or partial remission after 6 cycles of therapy underwent a second randomization to either no further treatment (observation) or maintenance treatment with rituximab (375 mg/m² i.v. once every 3 months until relapse or for a maximum period of two years). Exclusion criteria for second randomization were: no CR or PR upon induction treatment, IgG levels below 3 g/l, and active infection.

First randomization was stratified by centre, previous treatment with purine analogues, age, number of previous induction treatments and best response previously obtained (CR/PR/NC/PD), time since diagnosis (≤ or > 2 years), and bulky disease (≤ or > 10 cm), using a minimization procedure. The second randomization was stratified according to the treatment allocated by the first randomization, the quality of the response obtained after induction (CR/PR), and center.

Responses after induction treatment were evaluated by physical examination, hematology and chemistry, CT scans (obligatory) and bone marrow biopsies (when indicated) and assessed according to the LEXCOR criteria 18. Patients lacking bone marrow evaluation, but without evidence of disease on physical examination and CT scans, were scored as partial remissions.

During the 2 years of R maintenance/observation, physical examination, hematology and chemistry were performed at least every 3 months, and thereafter once every 4-6 months. In this large multicenter international study it was decided to adhere as much as possible to the daily
practice in the participating countries. Thus, during maintenance/observation CT and bone marrow examinations were performed only on indication. A central pathology review was performed by all participating groups.

The trial was designed to detect a 10% difference (from 70% to 80%) in the overall response rate to induction chemotherapy and had to recruit 600 patients (alpha=0.05, beta=0.22, two-sided test). The final analysis of maintenance was foreseen after 201 progressions or deaths, to detect a 14% difference in the 2-years PFS (from 40% to 54%; alpha=0.05, beta=0.2, two-sided test). An interim analysis of safety was planned after inclusion of 50 patients and two interim analyses of efficacy after inclusion of 200 and 400 patients (Haybittle and Peto strategy, p<0.001).

**Statistical analysis.** All primary analyses were conducted following the intention to treat (ITT) principle. The primary endpoint for the induction phase was the response to treatment. Secondary endpoints were PFS and overall survival from first randomization. Response rates were compared using the Mantel-Haenszel test for trend on 4 ordered categories (CR/PR/NC/PD). For the primary analysis non-assessable patients were excluded. For sensitivity analyses, non-assessable cases were considered as progressions. The primary endpoint for the maintenance phase was progression free survival (defined as interval between the date of second randomization and date of first relapse, progression, or death), and the secondary endpoint was OS from second randomization. The principal analysis of PFS and OS was done with the logrank test, and sensitivity analyses with Cox regression analysis with adjustment for type of induction treatment and response. Kaplan Meier curves were calculated to graphically show the differences between the treatment arms. All P values given are two-sided.

In February 2004, a preplanned second interim analysis of the present study was reviewed by the Independent Data Monitoring Committee (IDMC) of this study. At that time 461 patients had been included (369 evaluable for response) and 319 patients had been randomized for
maintenance treatment (268 evaluable). The results revealed that the primary endpoints for both the induction and maintenance part of the study had been reached, and the formal criteria for stopping the trial had been met. Subgroup analysis as requested by the IDMC confirmed the benefit of R maintenance in the CHOP subgroup, but not yet in the R-CHOP subgroup. It was therefore suggested to amend the protocol with all patients receiving R-CHOP for induction treatment followed by randomization to R maintenance therapy or no further treatment. Hence, recruitment to the trial was suspended in April 2004 while preparing a major protocol amendment. In the meantime, all data were retrospectively monitored on site and all pending queries were solved to perform a final analysis including all patients recruited to the study by April 2004. As the study was conducted at 130 sites and by 8 clinical study groups, the monitoring and data cleaning process was only completed in September 2005. Thus an updated data set with additional 19 months of median follow up was available for the final analysis. After reviewing the data of this final analysis the IDMC recommended not to reopen the trial as the primary question of the amended protocol had already been answered.

Results

Patients

A total of 474 patients with relapsed/resistant follicular lymphoma were randomly assigned to receive induction treatment with CHOP or R-CHOP. Nine patients had to be excluded because of missing informed consent forms. Therefore, all analyses are restricted to 465 patients (231 CHOP and 234 R-CHOP). Recruitment was stopped after the preplanned second interim analysis for efficacy because the criteria for early discontinuation were met both for induction and maintenance. Baseline demographics and other characteristics of the two groups were well balanced (table 1). Because the Follicular Lymphoma International Prognostic Index (FLIPI) was
only published in 2004 \textsuperscript{19}, the FLIPI score was assessed retrospectively for our patients, and thus was not used as stratification factor. However, both study arms were well balanced, with 70% of the patients having intermediate (FLIPI score 2) or high risk (FLIPI score $\geq 3$) disease at study entry (table 1). According to local pathology, 98% of the patients had follicular lymphoma. Central pathology data are available for 82% of all patients. Overall concordance rate between local and central assessment for all subtypes of follicular lymphoma was 93% in both treatment arms.

In both groups, about 80% had received only one prior treatment, almost equally consisting of single agent therapy or polychemotherapy. In both arms, only 9% of the patients had been treated previously with purine analogs. Best response to prior treatment was similar in both study arms. There were 17% and 16% of patients resistant to their prior treatment in the CHOP and R-CHOP arm, respectively (table 1). Three randomized patients never started protocol treatment; 1 because of rapid progression, and 2 refusals. The 6 cycles of protocol therapy could be completed in 81% of the patients in the CHOP arm and in 89% in the R-CHOP arm. Dose density for doxorubicin and cyclophosphamide was similar in both arms. Most protocol discontinuations occurred at the time of the first response evaluation, after the third cycle of treatment.

The 334 patients randomized to the maintenance phase were well balanced for baseline characteristics at study entry, FLIPI score (\geq 2 in 70 and 66 % in the observation and maintenance arm respectively), type of induction treatment received, and response to induction (in both arms 29 % CR and 71 % PR). In both arms, more patients had received R-CHOP during induction (59 % in the observation arm and 55% in the maintenance arm), reflecting the higher efficacy of R-CHOP as compared to CHOP in terms of response induction. Maintenance treatment was started a median of 7 weeks (range 3-16) after the end of the last induction cycle.
Efficacy: induction phase

The addition of rituximab significantly increased both overall and complete response rates. Overall response rates were 72.3% and 85.1% after CHOP and R-CHOP induction treatment, respectively (p<0.0001). The CR rate was 15.6% in patients receiving CHOP and 29.5% in patients treated with R-CHOP (p<0.0001) (table2).The partial response rate was 56.7% in the CHOP arm and 55.6% in the R-CHOP arm (NS). With a median follow up from first randomization of 39.4 months, median PFS from first randomization was 20.2 months in the CHOP group versus 33.1 months in the R-CHOP group (p=0.0003 log rank test; fig 1A). Hazard ratio (HR) for the R-CHOP group was 0.65. Overall survival (OS) at 3 years from first randomization was 71.9% in the CHOP arm and 82.5% in the R-CHOP arm (p=0.096 log rank test; HR 0.74; fig 1B).

Efficacy: maintenance phase

Of the 366 patients having responded to induction treatment (with either CHOP or R-CHOP) 32 were not randomized for maintenance treatment: 17 because of low IG levels (9 in the CHOP arm, and 8 in the R-CHOP); 8 patients because they were still on CHOP induction when the trial was put on hold because of the results of the first interim analysis (these patients received rituximab maintenance treatment on a compassionate need basis; they were included in the analysis of response to induction but were excluded from the analysis of maintenance treatment); 1 patient was not randomized because of a secondary neoplasia and 1 patient because of active infection. There were three refusals and two ineligibilities due to administrative problems.

334 eligible patients were randomly assigned to R maintenance treatment (n=167) for 2 years or observation (n=167). In each study arm, one patient did not start allocated treatment because of
progression immediately after randomization. At the time of last follow up, 41 patients were still under maintenance treatment or observation. With a median follow-up from second randomization of 33.3 months, median PFS from second randomization was 51.5 months in the R maintenance arm versus 14.9 months in the observation arm (p<0.0001 log rank test). The hazard ratio for R maintenance treatment compared to observation was 0.40; p< 0.0001) (fig 2A). As the difference in PFS was highly significant, a further analysis was carried out to evaluate whether the benefits of maintenance applied to patients treated both with CHOP and R-CHOP. After CHOP induction, R maintenance resulted in a median PFS from second randomization of 42.2 months, versus 11.6 months in the observation arm (HR 0.30; p<0.0001). After R-CHOP induction, these figures were 51.8 months and 23.0 months respectively (HR 0.54; p=0.0043) (fig 3). Similarly, R maintenance resulted in a highly significant increase in PFS both in patients who had a partial remission after induction treatment and those who had obtained a complete remission (data not shown).

Rituximab maintenance treatment increased 3-year overall survival rates (from second randomization) from 77.1% in the observation group to 85.1% in the R maintenance group (p=0.0111 log rank test; fig 2B). The hazard ratio for R maintenance compared to observation is 0.52. All sensitivity analyses confirmed the results of the principal analyses.

Safety

Induction. Grade 3-4 neutropenia was the most frequent adverse event (AE): 48.2% grade 3-4 in the CHOP arm and 54.7 % in the R-CHOP arm (NS). More patients on R-CHOP experienced grade 3-4 allergy (CHOP: 0 patients vs R-CHOP 8) and skin reactions (CHOP: 17 patients vs. R-CHOP 31 patients). Six patients in the CHOP arm and 8 patients in the R-CHOP arm withdrew from treatment because of toxicity. Treatment related mortality occurred in 2 patients in the CHOP group (1 sepsis, 1 respiratory distress syndrome) and in 1 patient in the R-CHOP group (pneumonia). During induction hypogammaglobulinemia developed in about 5% of the patients.
Indeed 17 out of the 366 responders to induction treatment were not eligible for second randomization because of immunoglobulin G (IgG) levels below the predefined threshold of 3 g/l. However we did not find a correlation between the incidence of bacterial infections and decreased IgG levels.

**Maintenance.** During R maintenance treatment, neutropenia was the only significant AE: 10.8 % in the R maintenance arm versus 5.4 % in the observation arm (NS; p=0.07 chi-square). This probably contributed to the increased grade 3-4 infection rate: 9% in the maintenance group and 2.4% (p=0.009 chi-square) during observation, the majority of these in the ear-nose-throat area. During maintenance 6 patients with therapy related grade 3 to 4 adverse events (infection) were hospitalized. They fully recovered.

Only 6 of the 167 patients withdrew from R maintenance treatment because of toxicity (4/6 due to infections). According to protocol IgG (but not IgA and IgM) levels were measured every 3 months during maintenance treatment/observation. At second randomization the median IgG levels were just below the normal range in both arms (6.6 g/l in the observation arm, and 6.5 g/l in the maintenance arm). Whereas during 2 years of observation the median IgG levels increased to within the normal range (7.3 g/l), IgG levels remained stable in the maintenance arm (6.3 g/l). Maintenance dose was delayed in only one patient and omitted in two patients at least once, because of low (<3/l) IgG levels. No patient had to be withdrawn from rituximab maintenance treatment due to persisting IgG levels below 3g/l. There were no deaths related to R maintenance treatment.

**Discussion**

The final analysis of the EORTC 20981 Intergroup study has shown several important findings. Firstly, in patients with relapsed/resistant follicular lymphoma, remission induction with R-CHOP
results in a highly significant increase in CR rate as compared to CHOP; secondly, rituximab maintenance treatment significantly improves PFS and OS in patients responding to induction treatment; and thirdly, R maintenance treatment achieves a considerable increase in PFS not only after remission induction with chemotherapy (CHOP) but also after immunochemotherapy (R-CHOP).

Since the start of the trial in late 1998, a considerable amount of data on efficacy and safety of rituximab in combination with different chemotherapy regimens as induction therapy for both previously untreated and pretreated patients has been published. There is a strong rationale for this combination because cytotoxic drugs and rituximab both have proven efficacy, yet different mechanisms of action and non-overlapping toxicities. In addition, in vitro data have shown that rituximab may increase sensitivity of lymphoma cells to cytotoxic agents.

In indolent lymphoma, remission induction with the combination of rituximab and chemotherapy has been shown to be superior to chemotherapy alone in several randomized phase III trials, both in previously untreated as well as in relapsed patients. In previously untreated patients, the addition of R to chemotherapy results in significantly better overall and complete response rates, improved PFS and OS. Our finding of a superior CR rate after R-CHOP in relapsed follicular lymphoma patients is in line with the results of the German Low Grade Lymphoma Study Group who showed in a mixed group of relapsed/refractory indolent NHL and mantle cell lymphoma patients that R-FCM (Fludarabine, Cyclophosphamide and Mitoxantrone) yields significantly higher ORR and CR rates, and prolongs PFS and OS when compared to FCM alone. In all these studies, addition of rituximab to chemotherapy did not result in increased toxicity.

In the past decades, maintenance therapy over a period of 12-24 months after induction treatment was evaluated using cytotoxic agents such as chlorambucil or cyclophosphamide or interferon-alpha. However, no consistent long-term benefit in terms of overall survival
could be demonstrated, and prolonged administration of both chemotherapy and interferon-alpha are associated with significant toxicity and patient inconvenience.

Two randomized trials have investigated the efficacy of induction therapy with single-agent rituximab followed by rituximab maintenance treatment. Hainsworth et al. randomized patients with relapsed or refractory indolent NHL to rituximab maintenance or rituximab retreatment at disease progression and found an approximate 4-fold increase in PFS for the former (31.1 months versus 7.4 months) \(^{33}\). However, the rituximab benefit (defined as date of study entry to date of next lymphoma treatment) was similar in both groups (31.3 vs. 27.4 months respectively). Because this was not part of our study, we do not have systematic information on the retreatment of patients who relapsed after either rituximab maintenance or observation. However, because rituximab was registered and available in all participating countries, it has to be assumed that many patients will have received a rituximab containing regimen, notably those who did neither receive rituximab during induction nor maintenance. Indeed, a preliminary analysis showed that in the patients in the observation arm, first post protocol treatment (n=85) was rituximab monotherapy in 29% and R-chemo in 11 %, versus 11% and 5 % respectively in patients in the maintenance arm requiring post protocol treatment (n=56). The SAKK 35-98 study showed an almost 2-fold increase in median EFS by rituximab maintenance in patients with untreated and relapsed FL (23 months versus 12 months) \(^{34}\).

The efficacy of rituximab maintenance therapy has also been investigated following treatment with different chemotherapy regimens. In previously untreated patients with indolent lymphoma (ECOG 1496), rituximab maintenance treatment after remission induction with CVP increased PFS by almost 3 years and improved overall survival in patients with high tumor burden \(^{35}\). In all these studies, rituximab maintenance treatment was well tolerated and did not lead to significantly higher rates of neutropenia, thrombocytopenia and/or infection as compared to observation.
Our study is the first large randomized trial to show that in patients with relapsed/resistant follicular lymphoma, rituximab maintenance treatment achieves a statistically highly significant and clinically very relevant improvement in PFS after induction treatment with chemotherapy plus rituximab. For the pooled CHOP and R-CHOP patients R maintenance also improved overall survival: 85% at 3 years versus 77% with observation (HR 0.52; p= 0.0111). Of course follow-up is still rather short for patients with FL, and longer follow-up is required to know whether the survival benefit will stand. Recently, a preliminary report of a randomized study by Hiddemann et al in a mixed population of relapsed FL and MCL also showed a significant improvement in response duration for patients receiving R maintenance after induction therapy with R-FCM (n=119) 36. In relapsed FL there has only been one randomized trial comparing chemotherapy and autologous stem cell transplantation 37. Although the number of patients was small and not balanced as to prognostic factors between the study arms, a clear benefit for AuSCT as to PFS and OS was shown. In view of the excellent PFS obtained with R-CHOP induction followed by R maintenance, future trials in relapsed FL should compare this(or a comparable) regimen with an optimal transplantation approach: R-chemo induction and R – myeloablative treatment, and R maintenance after transplantation. This probably also applies to future trials in FL of autologous transplantation in first remission.

In conclusion, we have shown that rituximab maintenance treatment results in a major improvement in PFS both after chemotherapy and immuno-chemotherapy, and - most importantly - also in a better overall survival. Questions still to be answered relate to the optimal schedule (e.g. single infusions every 2-3 months or 4 weekly infusion every 6 months) and duration of R maintenance (e.g. 2 years or until progression) and whether the results of R-chemo induction and R maintenance in relapsed/resistant FL will be similar in patients who have already received prior rituximab containing regimens.
APPENDIX

The following investigators (listed in alphabetical order) included patients in the study:


BNLI  D. Bareford, City Hospital, Birmingham. K. Benstead, Cheltenham General Hospital, Cheltenham. P.C. Bevan, St. Richards hospital, Chichester. N. Blessing, The Great Western Hospital, Swindon Wiltshire. A.K. Burnett, University Of Wales College Of Medicine, Cardiff. A. O’ Callaghan, St. Mary’s Hospital, Porthmouth Hants. R. Chasty, North Staffordshire Hospital, Stoke on Trent. J. Cullis, Salisbury District Hospital, Salisbury. D. Cunningham, Royal Marsden Hospital, Sutton. D. Dunlop, Royal Infirmary, University Of Glasgow, Glasgow, Scotland. M.S. Dyer, Leicester Royal Infirmary, Leicester. B. Hancock, Weston Park Hospital, Sheffield. C. Hatton, John Radcliffe Hospital, Oxford. A.M. O Hea, Stoke Mandeville Hospital, Aylesbury Bucks. P.J. Hoskin, Mount Vernon Hospital, Northwood. Al-Ismail, Singleton Hospital, Swansea. E. Lee, Countess Of Chester Hospital, Chester. M. Lyttelton, Kettering General Hospital, Kettering. M. Mackie, Western General Hospital, Edinburgh. R. Marcus, Addenbrookes Hospital, Cambridge. E. Marshall, Clatterbridge Hospital, Bebington Wirral. T. Maughan, Velindre Hospital, Cardiff. G.J. Morgan, Leeds General Infirmary, Leeds. A. Morrison, Southern General Hospital, Glasgow. T.C.M. Morris, Belfast City Hospital, Belfast. J.T. Neilson, Russels Hall Hospital, Dudley. D.H. Parry, North West Wales Nhs Trust – Bangor Hospital, Gwynned Bangor. R. Patmore, Hull Royal Infirmary, Hull. A. Pettit, Royal Liverpool University Hospital, Liverpool. S.J. Proctor, Royal Victoria Infirmary, Newcastle-Upon-Tyne. A.J. Rathmell, The James Cook University Hospital, Cleveland. G. Satchi, Whiston Hospital, Prescot Merseyside. P.J. Stableforth, Sandwell District General Hospital, Rhyl Denbighshire. A. Vranovsky, National Cancer Institute, Bratislava. J. Wimperis, Norfolk and Norwich Hospital, Norwich.

Legends to Figures

Fig 1  Effect of addition of R (rituximab) to CHOP remission induction on progression free survival and overall survival

Kaplan-Meier plots of progression free survival and overall survival from first randomization. Panel A shows the progression free survival after CHOP (n=231) and R-CHOP (n=234) remission induction treatment. Panel B shows the overall survival after CHOP (n=231) and R-CHOP (n=234) remission induction treatment.

Fig 2  Effect of R (rituximab) maintenance treatment on progression free survival and overall survival

Kaplan-Meier plots of progression free survival and overall survival from second randomization. Panel A shows the progression free survival after R maintenance therapy (n=167) and observation (n=167). Panel B shows the overall survival after R maintenance therapy (n=167) and observation (n=167).

Fig 3  Effect of R (rituximab) maintenance treatment on progression free survival after remission induction with either CHOP or R-CHOP

Kaplan-Meier plots of progression free survival from second randomization. Upper panel shows the progression free survival after CHOP remission induction (n=145). Lower panel shows the progression free survival after R-CHOP remission induction (n=189).
Table 1 Baseline characteristics according to treatment group

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<th>R-CHOP (n=234)</th>
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* assessed retrospectively
Table 2  Response to induction treatment

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<th>R-CHOP (n=234) %</th>
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<td>0.4</td>
</tr>
<tr>
<td>Not assessable</td>
<td>6.9</td>
<td>6.4</td>
</tr>
</tbody>
</table>

* Mantel-Haenszel test for trend
**FIG 1A**

**Progression free survival**

from first randomization

Overall Logrank test: p=0.0003

<table>
<thead>
<tr>
<th></th>
<th>Number of patients at risk</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>O</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>149</td>
<td>231</td>
<td>CHOP</td>
</tr>
<tr>
<td>122</td>
<td>234</td>
<td>R-CHOP</td>
</tr>
</tbody>
</table>

**FIG 1B**

**Overall survival**

from first randomization

Overall Logrank test: p=0.096

<table>
<thead>
<tr>
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<td>O</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>65</td>
<td>231</td>
<td>CHOP</td>
</tr>
<tr>
<td>52</td>
<td>234</td>
<td>R-CHOP</td>
</tr>
</tbody>
</table>
FIG 2 A

Progression free survival from 2nd randomization

Overall Logrank test: p<0.0001

Number of patients at risk:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Observation</th>
<th>Rituximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>110 167</td>
<td>90 42 17</td>
<td>5</td>
</tr>
<tr>
<td>66 167</td>
<td>126 86 47</td>
<td>12</td>
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</tbody>
</table>

FIG 2 B

Overall survival from 2nd randomization

Overall Logrank test: p=0.011

Number of patients at risk:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Observation</th>
<th>Rituximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>39 167</td>
<td>148 99 50</td>
<td>14 2</td>
</tr>
<tr>
<td>23 167</td>
<td>155 112 69</td>
<td>19 4</td>
</tr>
</tbody>
</table>
FIG 3

Progression free survival after CHOP

Overall Logrank test: p<0.0001

Number of patients at risk:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation</td>
<td>55</td>
<td>69</td>
<td>31</td>
<td>11</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Rituximab</td>
<td>32</td>
<td>76</td>
<td>61</td>
<td>38</td>
<td>20</td>
<td>4</td>
</tr>
</tbody>
</table>

Progression free survival after R-CHOP

Overall Logrank test: p=0.004

Number of patients at risk:

<table>
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<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation</td>
<td>55</td>
<td>98</td>
<td>59</td>
<td>31</td>
<td>13</td>
<td>4</td>
</tr>
<tr>
<td>Rituximab</td>
<td>34</td>
<td>91</td>
<td>65</td>
<td>48</td>
<td>27</td>
<td>8</td>
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</tbody>
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Reference List


34. Ghielmini M, Schmitz SF, Cogliatti SB et al. Prolonged treatment with rituximab in patients with follicular lymphoma significantly increases event-free survival and response duration compared with the standard weekly x 4 schedule. Blood 2004;103:4416-4423.


36. Hiddemann W, Forstpointner R, Dreyling M et al. Rituximab maintenance following a rituximab containing chemotherapy significantly prolongs the duration of response in
patients with relapsed follicular and mantle cell lymphomas: Results of a prospective randomized trial of the German Low Grade Lymphoma Study Group (GLSG). J Clin Oncol (Meeting Abstracts) 2005;23:6527.

Rituximab maintenance improves clinical outcome of relapsed/resistant follicular non-Hodgkin's lymphoma, both in patients with and without rituximab during induction: results of a prospective randomized phase III intergroup trial

Marinus H van Oers, Richard Klasa, Robert E Marcus, Max Wolf, Eva Kimby, Randy D Gascoyne, Andrew Jack, Mars van t Veer, Andrej Vranovsky, Harald Holte, Martine van Glabbeke, Ivana Teodorovic, Cynthia Rozewicz and Anton Hagenbeek