Optimization of Rituximab for the Treatment of Diffuse Large B-Cell Lymphoma (II): Extended Rituximab Exposure Time in the SMARTE-R-CHOP-14 Trial of the German High-Grade Non-Hodgkin Lymphoma Study Group


ABSTRACT

Purpose
To study pharmacokinetics, toxicity, and efficacy of prolonged rituximab exposure in elderly patients with diffuse large B-cell lymphoma (DLBCL).

Patients and Methods
In the SMARTE-R-CHOP-14 trial, rituximab 375 mg/m² was administered, together with six cycles of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone on a 14-day schedule (6×R-CHOP-14), on days −4, 0, 10, 29, 57, 99, 155, and 239. Pharmacokinetics and outcome were to be compared with those of patients who had received 6×R-CHOP-14 in combination with eight 2-week applications of rituximab in the RICOVER-60 (Rituximab With CHOP Over Age 60 Years) trial.

Results
The complete response (CR)/unconfirmed CR rate was 85% in 189 evaluable patients, 90% for 90 good-prognosis patients (International Prognostic Index [IPI], 1 or 2), and 81% for 99 poor-prognosis patients (IPI, 3 to 5); 3-year event-free survival (EFS) was 71%, 75%, and 67%, respectively, and 3-year overall survival (OS) was 84%, 88%, and 80%, respectively, with no differences between men and women. The preplanned historical comparison with 306 RICOVER-60 patients (good prognosis, n = 183; poor prognosis, n = 123) revealed no outcome differences for all and good-prognosis patients; however, the longer exposure time in SMARTE-R-CHOP-14 compared with RICOVER-60 was associated with better 3-year EFS (67% vs 54%) and OS (80% vs 67%) in poor-prognosis patients.

Conclusion
Extended rituximab exposure compared with eight 2-week applications in combination with 6×R-CHOP-14 significantly improved outcome of elderly poor-prognosis patients without increasing toxicity. To our knowledge, results obtained with the SMARTE-R-CHOP-14 rituximab schedule are the best reported for elderly patients with DLBCL to date. In the subgroup of poor-prognosis patients treated with extended rituximab exposure, the outcome seemed superior to that of a similar historical cohort of patients treated with 6×R-CHOP-14 plus 2-week rituximab, with similar toxicity. A randomized comparison of the two schedules is warranted.

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INTRODUCTION

The combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) with rituximab is considered standard treatment for diffuse large B-cell lymphoma (DLBCL). After we had shown that rituximab was suboptimally dosed in the majority of patients with DLBCL when administered synchronously with a 14-day schedule of CHOP (CHOP-14) at a dose of 375 mg/m², we performed several phase II studies with different rituximab schedules to determine the most promising approach for a subsequent randomized comparison with the standard six cycles of CHOP-14 plus rituximab (6×R-CHOP-14) plus two additional applications of rituximab (6×R-CHOP-14 + 2R). Twelve dose-dense applications of rituximab in the DENSE-R-14 trial resulted in higher rituximab serum levels and were associated with higher complete response (CR) rates in poor-prognosis patients, but...
this did not translate into better outcome.\(^6\) After R-CHOP-14 was shown not to be superior to eight cycles of R-CHOP on a 21-day schedule (R-CHOP-21) in two randomized trials,\(^7,8\) even though CHOP-14 had been shown to be superior to CHOP-21 in the NHL-B2 (Non-Hodgkin Lymphoma–B2) trial,\(^9\) we hypothesized that rituximab exposure time might be too short when administered eight times every 2 weeks. On the basis of these pharmacokinetic considerations,\(^5,10\) we designed the SMARTe-R-CHOP-14 study, in which elderly patients with DLBCL received six cycles of CHOP-14 together with eight applications of rituximab administered over a prolonged period of time.

**PATIENTS AND METHODS**

**Patients**

The study was conducted in accordance with the Helsinki Declaration. The protocol was approved by the ethics review committee of each participating center. All patients provided written informed consent. Inclusion and exclusion criteria were identical to those in the RICOVER-60 (Rituximab With CHOP Over Age 60 Years) trial; patients were eligible if they had previously untreated, biopsy-confirmed aggressive non-Hodgkin lymphoma of the B-cell type according to WHO classification\(^11\) and were between ages 61 and 80 years. Histologic diagnosis was reviewed centrally by a panel of five expert hematopathologists. Patients with previous lymphoma associated with AIDS; a diagnosis of history of indolent lymphoma or other neoplasms; marked impairment of cardiac, pulmonary, hepatic, or renal function; WHO performance status \(\geq 2\); initial WBC \(< 2.5 \times 10^9/\text{L}\); initial platelet \(< 100 \times 10^9/\text{L}\); or inability to comply with study requirements were excluded. Patients underwent mandatory baseline examinations, which included clinical examination; relevant laboratory tests; computed tomography (CT) of the neck, chest, abdomen, and pelvis; and bone marrow biopsy.

**Treatment**

A prephase treatment (single injection of vincristine 1 mg intravenously [IV] and prednisone 100 mg orally for 7 days) was mandatory to improve the performance status of patients and to ameliorate the adverse effects of the first chemotherapy cycle. Levofloxacin 500 mg was recommended when leukocytes dropped below 1,000/\(\mu\)L. Cytomegalovirus and *Pneumocystis jiroveci* prophylaxes with aciclovir (400 mg orally four times per day) and cotrimoxazole (two double-strength tablets every Saturday and Sunday), respectively, were recommended in the SMARTe-R trial only. The CHOP regimen consisted of cyclophosphamide 750 mg/m\(^2\) IV, doxorubicin 50 mg/m\(^2\) IV, vincristine 2 mg IV on day 1, and prednisone 100 mg orally administered on days 1 to 5. CHOP-14 was recycled every 2 weeks for a total of six cycles on days 1, 15, 29, 43, 57, and 71. Rituximab 375 mg/m\(^2\) was administered on days \(4, 0, 10, 29, 57, 99, 155,\) and 239. All patients received filgrastim or lenograstim starting on day 4 of each cycle until recovery of leukocytes. The next chemotherapy cycle was scheduled for day 15, after recovery of WBC \((> 2.5 \times 10^9/\text{L})\) and platelets \((> 80 \times 10^9/\text{L})\). Patients with initial bulky disease (defined as lymphoma masses or conglomerates with diameter \(\geq 7.5 \text{ cm}\)) or extranodal involvement received radiotherapy (36 Gy) to these areas irrespective of chemotherapy results. All patients underwent restaging after three cycles of therapy and after the end of therapy. Follow-up examinations were performed every 3 months during the first 2 years and every 6 months during years 3 to 5; these included physical examination, relevant laboratory tests, and CT of the chest and abdomen. Response was assessed by the treating physician and classified as CR, unconfirmed CR (CRu), partial response, stable disease, or progressive disease according to International Workshop criteria.\(^12\) Adverse events reported were coded on the patient case report forms according to National Cancer Institute Common Toxicity Criteria (version 2.0) grades.

**Study Design and Statistical Analysis**

The primary end point was evaluation of the pharmacokinetics, safety, and toxicity of the SMARTe-R-CHOP-14 schedule of rituximab. Secondary end points were complete remission rate (CR/CRu), rate of primary progression, event-free survival (EFS), and overall survival (OS). In the RICOVER-60 trial, we observed 6% treatment-related deaths with six cycles R-CHOP-14. By means of an exact binomial test, with 125 patients, we would be able to detect the difference between the null-hypothesis proportion (P0) of 6% and the alternative proportion (PA) of 12.5% with a power of 79% and a nominal 5% one-sided significance level. Rate of CR was 78% for 6 \(\times\) R-CHOP-14 in the RICOVER-60 trial. Supposing the rate of complete remission in this trial to be 88%, the 95% CI for the CR/CRu rate could be estimated with a precision of \(\pm 6\%\). When the interim analysis of 125 patients showed decreased rather than increased toxicity and better efficacy of the SMARTe-R-CHOP-14 schedule, the Data Safety Monitoring Board recommended increasing the number of patients to decrease the CIs and consolidate the results. Therefore, we increased the number of patients to 190, the maximum number or patients covered by the SMARTe-R insurance. Because SMARTe-R-CHOP-14 was performed as one of several phase II studies to identify the most promising rituximab schedule for a subsequent randomized comparison with standard 6 \(\times\) R-CHOP-14+2R, the results of the SMARTe-R-CHOP-14 trial were to be compared with the results of patients treated in the RICOVER-60 trial with 6 \(\times\) R-CHOP-14+2R.\(^4\) All tests for significance were two sided and were adjusted for multiple comparisons of treatment arms. Patient characteristics, National Cancer Institute Common Toxicity Criteria toxicities, therapeutic interventions, and responses between treatment arms were compared using \(\chi\)^2 tests and, if required, Fisher’s exact tests. Statistical analyses were performed with SPSS software (version 19.0; IBM, Ehningen, Germany). SMARTe-R-CHOP-14 was performed as amendment sixth to eighth to the RICOVER-60 protocol after RICOVER-NoRTh (no radiotherapy)\(^13\) and DENSE-R-CHOP-14\(^14\) and was registered as DSINHL (German High-Grade Non-Hodgkin Lymphoma Study Group)–2004-1.

**Rituximab Pharmacokinetics**

A pharmacokinetic study was performed in six men and seven women. All patients included in the pharmacokinetic study had normal kidney and liver functions. Blood sampling and rituximab enzyme-linked immunosorbent assay were performed as described previously.\(^15\) Pharmacokinetic properties (population model building, pharmacokinetic analysis, and model validation) of rituximab were processed and analyzed using the nonlinear mixed-effects approach in NONMEM software version VI level 2.0 (Globomax, Hanover, MD) as described.\(^10\) Statistical analysis of the demographic data of the pharmacokinetic study was performed using IBM SPSS software (version 19.0).

**RESULTS**

Between July 2007 and September 2009, 42 centers recruited 190 consecutive patients with DLBCL age 61 to 80 years. For one patient, the informed-consent form was missing, leaving 189 patients evaluable for response and toxicity. Characteristics of these patients are listed in Table 1.

**Toxicity and Adherence to Protocol**

Grade 3 and 4 toxicities are listed in Table 2. Protocol adherence was excellent, with 99% median relative doses for rituximab, doxorubicin, cyclophosphamide, and prednisone; because of polyneuropathy, this was only 75% for vincristine (data not shown).

**Rituximab Pharmacokinetics**

The measured trough and simulated rituximab serum levels are shown in Figure 1. Rituximab trough serum levels in SMARTe-R were
highest before the third application on day 15 (90 μg/mL). Serum levels > 25 μg/mL and > 50 μg/mL were observed until days 340 and 280, respectively.

Response to Therapy

Rate of CR/Cru in SMARTE-R was 85% for all 189 patients (Table 3), 90% for the 90 good-prognosis patients (International Prognostic Index [IPI], 1 or 2), and 81% for the 99 poor-prognosis patients (IPI, 3 to 5). After a median observation time of 37 months, 3-year EFS was 71% for all, 75% for good-prognosis, and 67% for poor-prognosis patients; 3-year progression-free survival (PFS) was 75%, 79%, and 71%, respectively, and 3-year OS was 84%, 88%, and 80%, respectively.

Because elderly men have a significantly faster rituximab clearance than elderly women (P = .003), which was associated with worse outcome in RICOVER-60 for patients treated with rituximab (EFS hazard ratio [HR], 1.5 [P = .004]; PFS HR, 1.7 [P = .001]; OS HR, 0.01),10 we compared the outcome of elderly women and men in SMARTE-R. This planned subgroup analysis revealed an identical outcome for elderly men and women with respect to 3-year EFS, PFS, and OS in the entire cohort as well as in the good- and poor-prognosis subpopulations.

Comparison of SMART-E-R-CHOP-14 With RICOVER-60

SMARTE-R was one of several phase II studies designed to identify the most promising rituximab regimen for a subsequent randomized phase III comparison with standard eight 2-week applications of rituximab. For all these phase II studies, 306 patients, treated in the best of the four arms of the randomized RICOVER-60 trial with 6 × R-CHOP-14 + 2R, served as the comparator. During the first 4 weeks, rituximab levels in SMARTE-R with the loading schedule of two applications before the first CHOP cycle were higher than in RICOVER-60, where the highest trough serum levels were not observed until the last application on day 98. Serum levels > 25 μg/mL and > 50 μg/mL were observed longer in SMARTE-R than in RICOVER-60 (340 v 250 and 280 v 205 days, respectively; Fig 1). Despite the worse prognostic profile of the SMARTE-R compared with the RICOVER population, there were no significant differences with respect to grade 3 and 4 toxicities (Table 2), except for leukocytopenia (42% v 52%) and infections (19% v 28%), which were less frequent in SMARTE-R. Therapy-associated death rates were lower in SMARTE-R (where anti-infective prophylaxes with aciclovir and cotrimoxazole were mandatory) compared with RICOVER (3% v 6%). Rate of CR/Cru was significantly higher in SMARTE-R (85% v 78%; Table 3). After a median observation time of 37 and 34 months in SMARTE-R-CHOP-14 and RICOVER-60, respectively, outcome was nonsignificantly better in SMARTE-R than in RICOVER-60 when the entire study populations were compared (Fig 2) with respect to 3-year EFS (71% v 66%), 3-year PFS (75% v 73%), and 3-year OS (84% v 78%). A similar picture emerged with respect to 3-year EFS (75% v 75%), 3-year PFS (79% v 82%), and 3-year OS (88% v 86%) when the 90 good-prognosis patients in SMARTE-R were compared with the respective subpopulation in RICOVER-60 (n = 183). The SMARTE-R rituximab schedule also resulted in significantly better outcome for 99 patients with IPI of 3 to 5 compared with 123 patients with IPI of 3 to 5 in RICOVER-60 with respect to 3-year EFS (67% v 54%), 3-year PFS (71% v 59%), and 3-year OS (80% v 67%).

Although there was no difference for elderly good-prognosis patients, elderly poor-prognosis women benefitted only marginally from the SMARTE-R rituximab schedule (3-year EFS, 67% v 61%; 3-year PFS, 71% v 67%; 3-year OS, 80% v 76%; Fig 3). In contrast, elderly men with poor prognosis benefitted considerably more from the SMARTE-R rituximab schedule than women (3-year EFS, 67% v 47%; 3-year PFS, 71% v 53%; 3-year OS, 80% v 60%; Fig 3). The differences between poor-prognosis elderly women and men observed in RICOVER-60, which were 14%, 14%, and 16% for 3-year EFS, 3-year PFS, and 3-year OS, respectively, were abolished in SMARTE-R (0%, 0%, and 0% for 3-year EFS, 3-year PFS, and 3-year OS, respectively).

DISCUSSION

Rituximab serum levels were higher in SMARTE-R than those observed in RICOVER-60 during the first 4 weeks of CHOP-14 treatment but...
were considerably lower thereafter until approximately day 240. The simulated courses of the serum levels also showed that relevant trough serum levels with the 2-week regimen were not achieved until day 15, suggesting that most of the first rituximab dose was trapped by the circulating B cells, and it was only with the second application of rituximab that therapeutic serum levels were achieved. The early high serum levels might have been responsible for the higher CR/CRu rate in SMARTE-R, despite the worse prognostic profile of the SMARTE-R population. A similar trend was observed in the DENSE-R trial,6 with four additional rituximab applications during the first 3 weeks compared with the 2-week schedule, which also resulted in higher response rates in DENSE-R compared with RICOVER-60, but these were associated with more early relapses, suggesting that the observed responses were not deep enough to translate into better long-term outcome. The early relapses might have been avoided in SMARTE-R by the two consolidating rituximab applications on days 155 and 250, respectively. Although the minimum serum levels necessary for an anti-DLBCL effect are unknown and might be between 25 and 50 µg/mL,14 eight SMARTE-R applications maintained serum levels > 25 µg/mL 90 days and > 50 µg/mL 75 days longer than eight 2-week applications in RICOVER-60.

The SMARTE-R schedule did not change the outcome of elderly good-prognosis patients (IPI, 0 or 1), but it significantly improved all outcome parameters for elderly poor-prognosis patients (IPI, 3 to 5) compared with RICOVER-60, suggesting that the pharmacokinetics of eight applications of rituximab administered every 2 weeks are adequate for patients with good-prognosis IPI or low tumor burden but not for those with poor-prognosis IPI or high tumor loads. Multivariable analyses performed separately for SMARTE-R and RICOVER-60 (Appendix Table A1, online only) showed that lactate dehydrogenase, stage, and male sex were significant risk factors for PFS only in RICOVER-60, but not in SMARTE-R. Multivariable analyses both without (Appendix Table A2, online only) and with the interaction between the SMARTE-R schedule and male sex (Appendix Table A3, online only) showed an interaction term with an HR of 0.540, which is remarkable, even though this interaction failed to become significant (P = .106) because of the limited number of patients.

The results observed in SMARTE-R are by far the best reported to date for elderly poor-prognosis patients, to our knowledge. Interestingly, elderly men, who have a significantly faster rituximab clearance and hence shorter rituximab exposure, benefited considerably more from the prolonged rituximab exposure time than elderly women—to such a degree that the inferior outcome of elderly men compared with women, observed in RICOVER-60 and confirmed in other studies with rituximab,15 was completely abolished, and no differences between elderly men and women were observed with the SMARTE-R schedule. The positive effect of the higher serum levels during the first 4 weeks of treatment might have been responsible for the higher response rates in SMARTE-R, similar to the DENSE-R-CHOP-14 study,6 where higher response rates were also observed but did not translate into a better outcome because of an increased rate of early

Table 3. Response to Therapy in SMARTE-R-CHOP-14 and RICOVER-60 Reference Populations

<table>
<thead>
<tr>
<th>Response</th>
<th>SMARTE-R-CHOP-14 (n = 189)</th>
<th>RICOVER-60 (n = 306)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>CR/CRu</td>
<td>161</td>
<td>85</td>
</tr>
<tr>
<td>CR</td>
<td>43</td>
<td>35</td>
</tr>
<tr>
<td>PR or NC</td>
<td>1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>PD</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Therapy-associated death</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Unknown</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>CR/CRu after additional treatment</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

NOTE: Patients received six cycles of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone on 14-day schedule with 12 additional applications of rituximab in SMARTE-R-CHOP-14 and eight additional applications in RICOVER-60.

Abbreviations: CR, complete response; CRu, unconfirmed complete response; NC, no change; PD, progressive disease; PR, partial response; RICOVER-60, Rituximab With CHOP Over Age 60 Years.
relapses. The latter was not observed in SMARTER-R, most likely because of the two consolidation rituximab applications on days 155 and 239, respectively. The worse outcome of poor-prognosis men in RICOVER-60 was most likely the result of rituximab exposure time being too short for this population with a fast rituximab clearance under the 2-week schedule, which obviously does not exploit the full potential of this antibody when administered at 375 mg/m² and synchronously with CHOP-14. This insufficient exposure time would also explain why 8×R-CHOP-14 or 6×R-CHOP-14+2R, with the last rituximab dose administered on day 98, failed to be superior to 8×R-CHOP-21, where the last application of rituximab was administered on day 148. Obviously, the more efficacious CHOP-14 chemotherapy is compromised by the inferior pharmacokinetics and shorter exposure time of rituximab when administered at 2- instead of 3-week intervals, despite the fact that the 2-week regimen achieves higher and earlier serum levels. Although long-term rituximab maintenance therapy has failed to date, rituximab exposure time, which should not fall below a certain minimum, seems to be more important than higher serum levels, when results of the RICOVER-60, DENSE-R-CHOP-14, and SMARTER-R-CHOP-14 are weighted against one another. This is also supported by the NHL-13 (Non-Hodgkin Lymphoma–13) study, where a positive effect of rituximab maintenance administered every 2 months over 2 years improved outcome for men but not women. Whether the minimum exposure time requires 2-year maintenance, as in NHL-13, or whether a last application on day 239, as in SMARTER-R, or on day 148, as with eight 3-week applications, in R-CHOP-21 is late enough, is unclear and difficult to determine through a clinical study; however, it is obvious

Fig 2. For (A) to (C) all patients (SMARTER-R-CHOP-14, n = 189; RICOVER-60 [Rituximab With CHOP Over Age 60 Years], n = 306), (D) to (F) patients with International Prognostic Index (IPI) of 1 or 2 (SMARTER-R-CHOP-14, n = 90; RICOVER-60, n = 183), and (G) to (I) patients with IPI of 3 to 5 (SMARTER-R-CHOP-14, n = 99; RICOVER-60, n = 123), (A, D, G) event-free, (B, E, H) progression-free, and (C, F, I) overall survival are shown.
that R-CHOP-21 would not be improved as much as R-CHOP-14 by prolonged rituximab exposure time, because such a prolonged exposure time would extend rituximab exposure less in 8×R-CHOP-21 (last application, day 148) than in R-CHOP-14+2R (last application, day 99). Six cycles of CHOP-14 with a SMARTe-R schedule of eight rituximab applications would also be expected to be considerably better than 8×R-CHOP-21, which was not superior to 6×CHOP-14 in combination with eight 2-week applications of rituximab in two randomized studies.7,8

Toxicity was not higher in SMARTe-R compared with RICOVER-60; indeed, rate of leukopenia was considerably lower and rate of grade 3 and 4 infections was significantly lower in SMARTe-R. The latter is not likely to have been only the result of the different rituximab schedule or pharmacokinetics; rather, prophylaxes with aciclovir and cotrimoxazole likely also played a role; these were mandatory only in the SMARTe-R trial after they were shown to significantly reduce infections in the DENSE-R study,6 where they were introduced for the first time.

European Society for Medical Oncology guidelines recommend 8×R-CHOP-21 or 6×R-CHOP-14+2R for the treatment of elderly patients with DLBCL, because they have equal efficacy and (acute) toxicity features. The results of SMARTe-R, a large phase II study with 189 patients, strongly suggest that outcome with R-CHOP-14 can be improved with a modified rituximab schedule with no increase in toxicity or cost, resulting in the best results ever reported for elderly patients with DLBCL to date, to our knowledge. Despite the size of this phase II study, all the caveats of a historical comparison apply when the results are compared with the respective population treated in the RICOVER-60 study. The combination of 6×CHOP-14 with eight pharmacokinetics-based applications of rituximab in the SMARTe-R schedule can only become the new treatment of choice for elderly patients with DLBCL if the superiority of the SMARTe-R approach is confirmed in the ongoing OPTIMAL > 60 study of the DSHNHL, which is comparing an optimized schedule of 12 rituximab applications composed of elements from DENSE-R (four additional applications during first 3 weeks) and SMARTe-R (two consolidations on days 155 and 239, respectively) with eight 2-week applications of rituximab in combination with 6×CHOP-14 in elderly patients with DLBCL in a prospective and randomized fashion.

**AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

Although all authors completed the disclosure declaration, the following author(s) and/or an author’s immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO’s conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

**Employment or Leadership Position:** None

**Consultant or Advisory Role:** Michael Pfueehnduch, Boehringer Ingelheim (C), Celgenc (C), Pfizer (C), Onyx Pharmaceuticals (C), Roche (C); Norbert Schmitz, Roche (C); Andreas Viardot, Roche (C), Gilead Sciences (C), Janssen (C); Ulrich Keller, Roche (C)

**Stock Ownership:** None

**Honoraria:** Norbert Schmitz, Roche; Andreas Viardot, Roche, Pfizer; Martin H. Dreyling, Roche; Carsten Mueller, Pfizer; Ulrich Keller, Roche

**Research**
Conception and design: Michael Pfreibundschuh, Viola Poeschel, Carsten Zwick, Niels Murawski

References

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Appendix

### Table A1. Multivariable Analysis of Risk Factors in RICOVER-60 and SMARTE-R-CHOP-14 for PFS

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>SMARTER-CHOP-14 (n = 189)</th>
<th>RICOVER-60 (n = 306)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>LDH &gt; UNV</td>
<td>1.3</td>
<td>0.7 to 2.3</td>
</tr>
<tr>
<td>ECOG PS &gt; 1</td>
<td>0.7</td>
<td>0.2 to 1.9</td>
</tr>
<tr>
<td>Disease stage III or IV</td>
<td>4.0</td>
<td>1.7 to 9.1</td>
</tr>
<tr>
<td>Extralymphatic involvement &gt; 1</td>
<td>0.6</td>
<td>0.3 to 1.1</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.0</td>
<td>0.5 to 1.8</td>
</tr>
</tbody>
</table>

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; LDH, lactate dehydrogenase; PFS, progression-free survival; RICOVER-60, Rituximab With CHOP Over Age 60 Years; UNV, upper normal value.

### Table A2. Multivariable Analysis of Risk Factors for PFS in RICOVER-60 and SMARTE-R-CHOP-14 (pooled data)

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDH &gt; UNV</td>
<td>1.9</td>
<td>1.3 to 2.7</td>
<td>.001</td>
</tr>
<tr>
<td>ECOG PS &gt; 1</td>
<td>1.2</td>
<td>0.8 to 2.0</td>
<td>.388</td>
</tr>
<tr>
<td>Disease stage III or IV</td>
<td>1.9</td>
<td>1.2 to 2.9</td>
<td>.003</td>
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<tr>
<td>Extralymphatic involvement &gt; 1</td>
<td>0.8</td>
<td>0.5 to 1.3</td>
<td>.435</td>
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<tr>
<td>Male sex</td>
<td>1.5</td>
<td>1.1 to 2.2</td>
<td>.025</td>
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<tr>
<td>SMARTE-R-CHOP-14</td>
<td>0.8</td>
<td>0.5 to 1.2</td>
<td>.222</td>
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NOTE: Without interaction between SMARTER-R-CHOP-14 rituximab schedule and male sex.

### Table A3. Multivariable Analysis of Risk Factors for PFS in RICOVER-60 and SMARTE-R-CHOP-14 (pooled data)

<table>
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<th>Risk Factor</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
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<tr>
<td>LDH &gt; UNV</td>
<td>1.9</td>
<td>1.3 to 2.7</td>
<td>.002</td>
</tr>
<tr>
<td>ECOG PS &gt; 1</td>
<td>1.3</td>
<td>0.8 to 2.0</td>
<td>.362</td>
</tr>
<tr>
<td>Disease stage III or IV</td>
<td>1.9</td>
<td>1.3 to 3.0</td>
<td>.002</td>
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<tr>
<td>Extralymphatic involvement &gt; 1</td>
<td>0.8</td>
<td>0.5 to 1.3</td>
<td>.336</td>
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<tr>
<td>Male sex</td>
<td>1.9</td>
<td>1.2 to 3.0</td>
<td>.007</td>
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<tr>
<td>SMARTER-R-CHOP-14</td>
<td>1.1</td>
<td>0.6 to 2.0</td>
<td>.684</td>
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<tr>
<td>Interaction of sex and rituximab</td>
<td>0.5</td>
<td>0.3 to 1.1</td>
<td>.106</td>
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</tbody>
</table>

NOTE: With interactions between SMARTER-R-CHOP-14 rituximab schedule and male sex. Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; LDH, lactate dehydrogenase; PFS, progression-free survival; UNV, upper normal value.