Epratuzumab with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy (ER-CHOP) in patients with previously untreated diffuse large B-cell lymphoma

Ivana N. M. Micallef, M.D. 1
Matthew J. Maurer, M.S. 1
Gregory A. Wiseman, M.D. 1
Daniel A. Nikcevich, M.D., Ph.D. 2
Paul J. Kurtin, M.D. 1
Michael W. Cannon, M.D. 3
Domingo G. Perez, M.D. 4
Gamini S. Soori, M.D. 5
Brian K. Link, M.D. 6
Thomas M. Habermann, M.D 1
Thomas E. Witzig, M.D. 1

2. Duluth CCOP, Duluth, MN 55805.
4. Metro-Minnesota Community Clinical Oncology Program, St. Louis Park, MN 55416.
5. Missouri Valley Cancer Consortium, Omaha, NE 68106.
6. University of Iowa Hospitals and Clinics, Iowa City, Iowa

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Running Title: ER-CHOP for DLBCL
Corresponding author:
Thomas E. Witzig, MD
Mayo Clinic
200 First Street, SW
Rochester, MN 55905
Email: witzig@mayo.edu
Phone: (507) 284-0527
Fax: (507) 266-4972

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For a complete list of participating institutions, see the supplemental appendix.
ABSTRACT

Approximately 60% of patients with diffuse large B-cell non-Hodgkin lymphoma (DLBCL) are curable with rituximab-CHOP chemoimmunotherapy; new treatments building on the R-CHOP backbone are needed. Epratuzumab (E) is an unlabeled anti-CD22 monoclonal antibody with efficacy in relapsed DLBCL. This phase II trial tested the safety and efficacy of combining E with R-CHOP (ER-CHOP) in patients with untreated DLBCL. A secondary aim was to assess the efficacy of interim PET to predict outcome in DLBCL. Standard R-CHOP with the addition of E 360 mg/m² IV was administered for 6 cycles. 107 patients were enrolled on the study. The regimen was well tolerated and toxicity was similar to standard R-CHOP. ORR in the 81 eligible patients was 96% (74% CR/CRu,) by CT scan and 88% by PET. By intention to treat analysis, at a median follow-up of 43 months, the EFS and OS at 3 years in all 107 patients were 70% and 80%, respectively. Interim PET was not associated with EFS or OS. Comparison with a cohort of 215 pts who were treated with R-CHOP showed an improved EFS in the ER-CHOP patients. ER-CHOP is well-tolerated and phase II results appear promising as a combination therapy. This study is registered at http://Clinicaltrials.gov as NCT00301821.
INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) remains the most common type of non-Hodgkin lymphoma (NHL) in North America. The standard of care has evolved from combination chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) to the addition of rituximab (R-CHOP). Various studies have demonstrated the benefit of adding rituximab to CHOP in both elderly and young patients.\(^1\)\(^-\)\(^4\) While R-CHOP improves both the overall response rate (ORR) and overall survival (OS), there remains room for improvement since approximately 20-40% of patients still relapse after R-CHOP.\(^1\)\(^-\)\(^4\)

Epratuzumab is a humanized monoclonal IgG1 antibody directed against the B-cell specific antigen, CD22.\(^5\)\(^,\)\(^6\) CD22 is a 135-kD trans-membrane phosphoglycoprotein expressed by pre-B and mature, normal B-cells. CD22 is a signaling molecule that plays a role in cellular adhesion, regulation of B-cell homing and modulation of B-cell activation, and is internalized into the cell when bound by antibody. In vitro data have shown that pre-treatment of B-cell lines with epratuzumab does not affect CD20 antigen expression; by contrast pre-treatment of the same cell lines with rituximab results in a slight increase in CD22 expression.\(^5\)\(^-\)\(^7\) The mechanism of action of epratuzumab is unknown; postulated mechanisms include antibody-dependent, cell mediated cytotoxicity (ADCC) and apoptosis. In clinical studies, epratuzumab has shown efficacy across various B-cell histologies. The phase I/II dose escalation trial by Leonard et al showed an ORR of 18% in heavily pretreated NHL patients and established the therapeutic dose of 360 mg/m\(^2\) weekly x 4 doses.\(^8\)\(^,\)\(^9\) Combination antibody studies with
epratuzumab and rituximab produced promising results with an ORR of 67% (CR 50%) in DLBCL\textsuperscript{10} and in a European study the ORR was 47% (CR 33%).\textsuperscript{11}

Since the addition of rituximab increased the efficacy of CHOP chemotherapy, we postulated that adding another antibody to target CD22 would further increase efficacy in DLBCL. A pilot (phase I) study tested ER-CHOP in 15 patients with untreated DLBCL and determined the regimen was safe. The ORR was 87% (CR 67%) with a 1-year PFS and OS of 93% and 100%, respectively.\textsuperscript{12}

PET imaging is recommended at baseline and end of treatment for DLBCL patients.\textsuperscript{13} Retrospective studies have shown the interim PET scans appear to be prognostic. In one study, PET scan after 2 cycles was highly predictive of outcome with the 2 year PFS for the PET negative patients being 84% vs 0 for the PET positive patients.\textsuperscript{14} However, recent reports have raised concerns about the false-positive rate of interim PET.\textsuperscript{15,16} In a report utilizing PET scan in a risk adapted study, 38 patients with a positive interim PET scan underwent repeat biopsy and 33 were negative for residual lymphoma.\textsuperscript{17} The PETAL Trial (PET Guided Therapy of Aggressive non-Hodgkin's lymphomas) is a multicenter prospective trial in aggressive lymphoma exploring the prognostic value of interim PET. In this study, interim PET is performed after 2 cycles of therapy. The interval between chemotherapy and interim PET is more than 2 weeks and G-CSF is not permitted for the treatment cycle preceding interim PET. Quantitative SUV based assessment, rather than qualitative visual assessment, is applied. PET responsivity is defined as reduction of the maximum SUV at interim-PET by >65% in
comparison to the maximum pre-treatment SUV. Using these criteria, treatment failure has been observed in 23% of the PET non-responders vs. only 8% of the PET responders.\textsuperscript{18,19}

Based on the promising results of the phase I/pilot trial of ER-CHOP, we tested the regimen in a multicenter, phase II study through the North Central Cancer Treatment Group (NCCTG). The goals were to provide further data regarding the safety and efficacy of the regimen that would support a commitment to a large, definitive, phase III trial of ER-CHOP vs R-CHOP, and to provide important data on the role of functional imaging, both at interim PET scan and end of treatment in predicting EFS in DLBCL.

**PATIENTS AND METHODS**

**Study Design**

This was a one-arm open label phase II multicenter study thru the NCCTG to assess the safety and efficacy of combination ER-CHOP in patients with newly diagnosed DLBCL. The objectives were to evaluate the efficacy as measured by 12-month EFS, PFS, OS and response rates. In addition, functional CR rate (PET negative) early (after 2 cycles, PET2) and at completion of therapy (after 6 cycles, PET6) was also studied.

Post protocol completion, the results of the ER-CHOP treated patients were compared to patients enrolled on a prospective, epidemiology study of the University of Iowa and Mayo Clinic SPORE Molecular Epidemiology Resource.\textsuperscript{20,21} The SPORE cohort consisted of all pathology confirmed DLBCL patients enrolled between September 2002
and February 2008, who met ER-CHOP trial eligibility criteria, were treated with R-CHOP, and were followed every 6 months for 3 years and annually thereafter.

**Patients and Methods**

Eligible patients were ≥18 years with previously untreated, CD20-positive DLBCL. Patients were required to have measurable disease, an absolute neutrophil count ≥1500/µl, platelets ≥100,000/µl, bilirubin ≤2mg/dl, and creatinine ≤2x upper limit of normal. Patients were excluded if they had a prior diagnosis of NHL, evidence of indolent lymphoma on the biopsy or bone marrow, an ECOG performance status of 3 or 4, active serious infection, poor cardiac function defined as an ejection fraction <45%, central nervous system NHL, positive human immunodeficiency virus status, or another primary malignancy within the preceding 5 years other than non-melanomatous skin cancers, in situ carcinoma of the cervix or treated prostate cancer with a stable PSA, history of prior pelvic irradiation and known hepatitis B or C infection. Staging and pre-treatment assessment included clinical examination; CT scans of the chest, abdomen and pelvis; and a PET scan. Lumbar puncture was not required but was recommended in patients with known bone marrow or sinus involvement; patients who had positive CSF cytology for lymphoma were excluded. A pregnancy test was required in women of child-bearing potential. The international prognostic index (IPI) was calculated based on age, serum LDH, performance status, extranodal disease, and stage. Extranodal sites of disease and stage were based on the CT scan results.
This study was conducted in accordance with the ethical guidelines mandated by the Declaration of Helsinki. All patients signed informed consent that was approved by the institutional review board at each participating site. In addition, all SPORE participants signed informed consent for inclusion in the prospective epidemiology study.

Epratuzumab (Immunomedics, Morris Plains, NJ) 360 mg/m² was administered intravenously over 1 hour followed 30-60 minutes later by rituximab 375 mg/m² and CHOP chemotherapy (cyclophosphamide 750 mg/m² iv day 1, adriamycin 50 mg/m² iv day 1, vincristine 1.4 mg/m² (maximum 2 mg) iv day 1 and prednisone 100 mg/m² orally days 1-5). For cycle 1, rituximab could be divided into 2 days; if so, the second half of rituximab was given on day 2 followed by CHOP chemotherapy. For subsequent cycles, all therapy was administered on Day 1. Premedication with acetaminophen and diphenhydramine was given prior to epratuzumab and repeated if necessary. Infusion-related side effects were treated per physician's discretion, including the use of corticosteroids. Routine use of antiemetics and G-CSF were at physician's discretion and could be used prophylactically. Allopurinol was recommended during cycle 1 to prevent tumor lysis syndrome. Prophylactic intrathecal methotrexate was suggested but not required if there was involvement of sinuses, bone marrow, epidural space or testicular sites.

Toxicity was graded according to NCI CTC v3.0, with dose modifications based on adverse events. If patients experienced grade 4 neutropenia, G-CSF was added to
subsequent cycles. If hematologic toxicity was still present at day 1 of the next cycle (ANC ≤ 1500/µl, or platelets ≤ 100 000/µl), then treatment was delayed by 1 week. If hematologic toxicity did not resolve after 3 weeks, the patient was removed from the study.

All biopsies were to be sent for central review (PJK) within 7 days of registration and treatment was initiated during central pathology review. Pathology criteria for the diagnosis of DLBCL was defined by the World Health Organization.22 Paraffin-embedded biopsies were stained for CD22 by immunohistochemistry using clones FPC1 (Novocastra) and TO15 (Dako-Cytomation). The lymphomas were judged to be CD22 positive if >20% of the tumor cells were CD22+. Patients whose tumors did not meet the study criteria for DLBCL or whose lymphomas were CD22 negative were deemed ineligible. Epratuzumab was discontinued in these patients and further therapy was at the discretion of the treating physician; however most patients received R-CHOP.

Response assessment occurred after 2 and 6 cycles. Patients were observed for up to five years after treatment or until progression or death. CT scans were performed every 3 months year 1, every 4 months year 2, and every 6 months for years 3 - 5. PET scans were performed at baseline and after cycles 2 and 6. All PET scans were centrally reviewed without knowledge of patient's clinical course (GAW) and were interpreted qualitatively as positive or negative. FDG PET scan negativity was defined on the scan done after 2 cycles for therapy monitoring as no FDG uptake greater than
the liver. On the FDG PET scan done after cycle 6 for restaging the scan was read as negative if the tumor FDG uptake had returned to background.

**Statistical Methods**

A one-stage phase-II design with an interim analysis based on a Fleming design was utilized. The primary decision endpoint of the trial was the percentage of the first 67 eligible patients who were alive and event-free 12 months after enrollment to the study (EFS12). Secondary objectives included ORR, PFS, OS, functional CR, and safety. The design tested the null hypothesis that the EFS12 rate was $\leq 60\%$, based on the results of the GELA, ECOG, and BCCA studies. The statistical design had 91% power, with an alpha of 0.10, to declare the regimen was active if the true EFS12 rate was at least 75%.

EFS was defined as the time from study entry to the first event, with an event defined as tumor progression or relapse by CT scan, initiation of subsequent lymphoma therapy following ER-CHOP study therapy, or death due to any cause. OS was defined as time from study entry to death due to any cause. PFS was defined as the time from study entry to progression or death due to lymphoma. Patients who had not experienced an event, death, or progression were censored at the last known follow-up. Response and progression were assessed by CT. Functional response was defined as PET negative. Associations of categorical variables were compared using chi-squared and Fisher’s exact test. Comparisons of continuous variables were tested with the Wilcoxon rank-sum test. Survival, EFS, and progression curves were compared via
Kaplan-Meier and the log-rank test; Cox proportional hazards models were used to assess the relationship between time-to-event endpoints and outcome. All analyses were performed using SAS v9.1.3.

**RESULTS**

**Patient Characteristics**

Between February 2006 and August 2007, 107 patients with newly diagnosed DLBCL were enrolled. On-study patient characteristics are summarized in Table 1. Twenty-six (24%) patients were declared ineligible based on pathology review (25); one patient canceled prior to beginning treatment. The reasons for ineligibility due to pathology issues were: CD22 negative (11 patients), follicular lymphoma component in DLBCL sample (4), not DLBCL (3 grade III follicular lymphoma, 1 atypical Burkitt, 3 B-cell unclassifiable lymphoma), inadequate specimen (1), DLBCL with low grade in the marrow (1), and removal from study by treating physician due to c-myc translocation by FISH (1). Baseline characteristics between the eligible patients and ineligible patients were similar (Table 1). At the time of this analysis, the median follow-up was 43 months (range, 7-58); 31 patients (29%) had an event and 22 patients (21%) had died.

**Safety**

In general, ER-CHOP treatment was well tolerated. One-hundred six patients received at least 1 cycle and 505 treatment cycles were analyzed for toxicity. Seventy-two of the 81 eligible patients (89%) received all 6 cycles of therapy on study. Three patients went off study for progression; other reasons included adverse event (1), patient refusal (2),
death on study (1), and clinical deterioration (2). Hematological toxicity was monitored with weekly CBC. The rates of grades 3 or 4 hematological toxicity were 14% for anemia, 85% for neutropenia, and 14% for thrombocytopenia. Despite the substantial incidence of neutropenia, febrile neutropenia was observed in 16% (17/106) of cases. Other toxicities (Table 2) were typical for CHOP-based therapy. Overall, 45 patients (42%) experienced at least 1 grade 3 or higher toxicity and 13 patients (12%) experienced grade 4 or 5 treatment-related toxicity. Three patients died on study; one patient died 12 days after day 1 cycle 1 due to exacerbation of COPD; one patient died of pneumonia during cycle 6, and one patient died of ventricular dysfunction 1 month after completing therapy.

Treatment cycles were able to be delivered on schedule in 72% (76/106) of cases and 93% (469/505) of treatment cycles. The most common single reason for delay was hematological toxicity (11). Dose reductions were required in 25% (26/106) of patients and in 9% (43/505) of treatment cycles primarily for cyclophosphamide and doxorubicin (20 cycles) and prednisone (10 cycles).

Response and Outcome Assessment
The study met the pre-specified study design criteria for efficacy at the interim and final analyses. Survival results are presented as intention to treat for all 107 patients. The OS, PFS, and EFS at 36 months were 80%, 76%, and 70% in all patients and 79%, 75% and 69% eligible patients, respectively (Figure 1). By IPI, 25 (23%) patients were
low-risk (IPI 0-1), 68 (64%) patients were intermediate-risk, and 14 (13%) were high-risk (IPI 4-5). The outcomes by IPI sub-group are shown in Figure 2.

CT and PET results are available for the eligible patients as per study design. All PET scans were centrally reviewed (Table 3). The ORR was 96% (74% CR/CRu; 22% PR) using standard response assessment by CT (Table 3). Functional CR as defined by PET negativity was assessed after 2 cycles and after completion of treatment. PET scans were available in 94% (76/81) of eligible patients. Early PET (PET2) was negative in 78% (54/69) and PET after completion of therapy (PET6) was negative in 88% (61/69). Overall, 87% of patients (67/77) achieved PET negative status during the study. PET2 negativity was not associated with a statistically significant improvement in EFS ($P=0.31$) or OS ($P=0.24$). However, PET6 negativity was associated with a statistically significant improvement in EFS ($P=0.02$) and OS ($P=0.002$). At 3 years, the EFS if PET6 negative was 78% compared to 50% if still PET6 positive; OS was 90% for PET6 negative compared to 50% for PET6 positive (Figure 3). Overall, 3-year survival in the 67 patients achieving a PET2 or PET6 negative status was 73% compared to 44% in the patients who did not achieve a PET negative status ($P=0.02$). Of the 15 patients that were PET2 positive, 8 became PET6 negative, of which 5 remain in CR. Of the 54 patients that were PET2 negative, 48 (89%) completed treatment in PET CR; 3 year EFS and OS were 79% and 92%, respectively, in these 48 patients.

**Comparison to SPORE cohort**

The cohort of R-CHOP treated patients in the SPORE had similar baseline characteristics to the ER-CHOP trial patients, with the exception of ER-CHOP patients
being higher stage (Table 4). After adjusting for IPI, the ER-CHOP patients had improved EFS (HR = 0.65, 95% CI: 0.43-0.98, p=0.04) (Figure 4). Improvement in overall survival was similar (HR=0.68, 95% CI: 0.42-1.11, p=0.12), though the association was not statistically significant due to fewer number of events in the overall survival analysis (Figure 4). The improved outcome of patients treated with ER-CHOP compared to the patients treated with R-CHOP (SPORE cohort) was similar across IPI groups; however, the statistical power was inadequate to make definitive conclusions (data not shown).

DISCUSSION

The results of this phase II study reported herein demonstrate an ORR of 96% to ER-CHOP, a functional CR rate (PET negative) of 88%, three year EFS of 70%, and OS of 80%. The strengths of the study include the large sample size from a multicenter cooperative group clinical trial and mature follow-up of trial participants. Although the limitations of the study include the lack of a randomized arm of patients treated with standard R-CHOP therapy and the ineligibility of CD22 negative patients, we attempt to address these issues by intent to treat analysis and comparison to other R-CHOP patient data sets, including a prospectively enrolled cohort of DLBCL patients from our SPORE who fulfilled the ER-CHOP trial eligibility criteria. Therapy with R-CHOP delivered every 21 days is the standard of care for patients with untreated DLBCL with adequate cardiac function that permits anthracycline use. Improving R-CHOP for DLBCL is very important. Salvage therapy for those that relapse, especially patients over age 70 and refractory/early relapse patients, is toxic and is associated with very
poor outcomes. Recently the GELA group reported 10 year long term follow up of the original R-CHOP vs CHOP study patients. The median OS after progression was 0.6 and 0.7 months for the CHOP and R-CHOP arms.

Various studies have tried to improve the results of treating DLBCL by either adding chemotherapeutic agents such as etoposide (CHOEP), by increasing dose density (administering chemotherapy every 14 days) or utilizing infusional regimens (DA-EPOCH). Phase III studies evaluating R-CHOP-14 vs R-CHOP-21 and the infusional chemotherapy regimen of dose-adjusted EPOCH-R vs R-CHOP-21 are ongoing. Cunningham et al reported the preliminary results of the UK study comparing eight cycles of R-CHOP-21 vs six cycles of R-CHOP-14 plus 2 additional cycles of rituximab. The ORR were equivalent at 88% for R-CHOP-21 vs 91% for R-CHOP-14. There was also no advantage to R-CHOP14 vs R-CHOP21 in the French study. We await long term follow up to determine if there will be a difference in relapse and/or survival.

In this study we used the approach of targeting another cell surface antigen (CD22) with epratuzumab combined with standard R-CHOP. The CD22 antigen is an attractive additional target to CD20, because of different mechanisms of action and possible additive or synergistic effects. This dual antibody targeting may help to overcome antibody resistance and therefore improve responses and ultimately survival without complicating the R-CHOP schedule nor adding significant toxicity.
The results with ER-CHOP suggest an improvement in OS, EFS and PFS compared to the initial randomized clinical trials using R-CHOP. However, those studies were in older patients. The population-based BCCA data, which are in all ages, have a OS and PFS at 4 years of approximately 70% compared to 79% and 76%, respectively, in our study of ER-CHOP. We also compared the ER-CHOP trial results to patients prospectively enrolled to the University of Iowa and Mayo Clinic Lymphoma SPORE Molecular Epidemiology Resource. Although the survival curves are similar for the first 2 years, the curves diverge at 2 years favoring patients treated with ER-CHOP. This suggests that epratuzumab may decrease late relapses.

The ER-CHOP results evaluated by IPI status also show an improvement, especially in the high-risk patients. Four year OS in the high-intermediate and high-risk IPI (3-5) was 55% in the BCCA cohort and 58% in the SPORE cohort compared to 72% at 4 years with ER-CHOP. Improvement was similar for 4-year PFS (53% in BCCA vs 71% ER-CHOP) and EFS (41% in SPORE vs 65% with ER-CHOP) as well. At a median follow-up of nearly 4 years, 1 patient has progressed after 24 months following initiation of ER-CHOP on our study, suggesting that there is a plateau. In the GELA 10 year follow up analysis, 87% of relapses occurred during the first 3 years of follow-up. Therefore a large number of late relapses would not be expected for this analysis.

Approximately 85% of patients with DLBCL are CD22 positive. We defined CD22 positivity by immunohistochemistry (IHC) as >20% positive staining on tumor cells. This cut-off was chosen because it is a cut-off commonly used in
hematopathology to determine antigen expression by IHC. We found that in nearly all cases the tumor cells were either positive or negative by IHC. By gene profiling CD22 parallels CD20, thus the CD22 negative cases by IHC in our study may represent staining below the level of detection of IHC. There have been no reports of CD22 as a prognostic marker and, therefore, by removing CD22 negative patients in this study, it is unlikely that a poor prognostic group was removed. Interestingly, by intention to treat analysis, there was no difference in survival outcomes between the eligible and ineligible patients. In the previous pilot study, 11 of 15 patients had CD22 status assessed. Of these 11, all were CD22 positive; 2 of whom were weakly positive. Both of these weakly positive patients achieved a CR and remain alive without disease. In the single agent radioimmunotherapy studies utilizing $^{90}$Y-epratuzumab tetraxetan in 64 patients with relapsed/refractory NHL, 98% of patients demonstrated tumor targeting on $^{111}$In imaging.\textsuperscript{37}

In this study, we also found that outside of clear-cut progression, utilizing a positive PET2 to change therapy is not supported. Fifteen patients were PET2 positive, of which 8 became PET6 negative and 5 remain progression-free. Quantitative SUV based interpretation showing PET responsiveness may however be more important than qualitative interim PET assessment where a scan is interpreted as positive or negative. In a post hoc analysis, the interim positive PET2 scans were reviewed as a quantitative SUV based assessment. As per the PETAL trial, PET non-response was defined as active disease by visual criteria and a maximum SUV reduction of $\leq 65\%$.\textsuperscript{18} Fifteen patients had an interim PET2 scan that was originally read as positive. Twelve
of these were available for review; in these 12 patients, 9 were classified as PET responders and 3 non-responders. Of the 3 non-responders 2 progressed early and 1 continues in remission (>2 years).

PET negativity at completion of therapy (PET6) was associated with an improved EFS and OS. The EFS and OS at 3 years in patients who are PET6 negative are 78% and 90%, respectively. Of the 8 patients who were PET6 positive, 4 remain alive without progression. In contrast, of the 61 patients who were PET6 negative, 6 (10%) have relapsed. Thus, negative PET6 serves as a valuable surrogate marker for EFS and a valid study endpoint for future clinical trials.

In conclusion, the addition of epratuzumab may increase the efficacy of R-CHOP without added toxicity. This benefit is especially evident in the high-intermediate and high-risk IPI patients. A randomized phase III trial of R-CHOP vs ER-CHOP is required to definitively demonstrate that dual antibody targeting in combination with CHOP results in improved outcomes.
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AUTHORSHIP

Contribution: I.N.M.M. was the principal investigator of the study. She designed the study, analyzed the data, and wrote the manuscript. M.J.M. was the biostatistician. G.A.W. was the central reviewer for the PET scans. D.A.N. provided patients and manuscript review. P.J.K. reviewed pathology specimens and reviewed the manuscript. M.W.C., D.G.P., G.S.S. T.M.H. and B.K.L. provided patients and reviewed the manuscript. T.E.W. assisted in the clinical trial development; supplied patients; and participated in writing the manuscript.

Conflict-of-interest disclosure: No authors had any disclosures to declare.
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Table 1. Baseline Clinical Characteristics

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<td>64 (29-81)</td>
<td>62 (21-82)</td>
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Table 2. Most Common (>10%) Adverse Events Without Regard to Grade and Attribution

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<td>Hyperglycemia</td>
<td>18</td>
<td>17.0</td>
</tr>
<tr>
<td>Febrile Neutropenia</td>
<td>17</td>
<td>16.0</td>
</tr>
<tr>
<td>Cytokine Release</td>
<td>15</td>
<td>14.2</td>
</tr>
<tr>
<td>Nausea</td>
<td>13</td>
<td>12.3</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>11</td>
<td>10.4</td>
</tr>
</tbody>
</table>
Table 3. Response Assessment

<table>
<thead>
<tr>
<th>CT (n=81)</th>
<th>Post cycle 2 scan</th>
<th>Post cycle 6 scan</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>12 (15%)</td>
<td>27 (33%)</td>
</tr>
<tr>
<td>CRu</td>
<td>9 (11%)</td>
<td>18 (22%)</td>
</tr>
<tr>
<td>PR</td>
<td>49 (60%)</td>
<td>32 (40%)</td>
</tr>
<tr>
<td>SD</td>
<td>8 (10%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>NA</td>
<td>3 (4%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>CR/Cru</td>
<td>21 (26%)</td>
<td>45 (55%)</td>
</tr>
<tr>
<td>ORR</td>
<td>70 (86%)</td>
<td>77 (95%)</td>
</tr>
<tr>
<td>PET POSITIVE</td>
<td>15 (22%)</td>
<td>8 (11%)</td>
</tr>
<tr>
<td>PET Negative</td>
<td>54 (78%)</td>
<td>61 (88%)*</td>
</tr>
</tbody>
</table>

*Patients who were PET negative after 2 cycles and completed treatment and did not have a post-treatment PET scan were considered PET negative post treatment if post-treatment CT scan did not show progression.
Table 4. Baseline clinical characteristics of ER-CHOP patients and SPORE patients.

<table>
<thead>
<tr>
<th></th>
<th>ER-CHOP (n=107)</th>
<th>SPORE R-CHOP (n=215)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), median (range)</td>
<td>62 (21-82)</td>
<td>62 (21-92)</td>
<td></td>
</tr>
<tr>
<td>Age ≥ 60</td>
<td>58 (54%)</td>
<td>121 (56%)</td>
<td>0.72</td>
</tr>
<tr>
<td>Sex, female</td>
<td>48 (45%)</td>
<td>100 (47%)</td>
<td>0.78</td>
</tr>
<tr>
<td>PS 0-1</td>
<td>94 (88%)</td>
<td>179 (83%)</td>
<td>0.28</td>
</tr>
<tr>
<td>Stage III-IV</td>
<td>86 (80%)</td>
<td>144 (67%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Elevated LDH</td>
<td>72 (67%)</td>
<td>118 (58%)</td>
<td>0.13</td>
</tr>
<tr>
<td>≥2 Extranodal Sites</td>
<td>32 (30%)</td>
<td>55 (26%)</td>
<td>0.45</td>
</tr>
<tr>
<td>IPI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1</td>
<td>25 (23%)</td>
<td>61 (28%)</td>
<td>0.33</td>
</tr>
<tr>
<td>2</td>
<td>27 (25%)</td>
<td>63 (29%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>41 (38%)</td>
<td>61 (28%)</td>
<td></td>
</tr>
<tr>
<td>4-5</td>
<td>14 (13%)</td>
<td>30 (14%)</td>
<td></td>
</tr>
<tr>
<td>0-2</td>
<td>52 (49%)</td>
<td>124 (58%)</td>
<td>0.12</td>
</tr>
<tr>
<td>3-5</td>
<td>55 (51%)</td>
<td>91 (42%)</td>
<td></td>
</tr>
<tr>
<td>B Symptoms</td>
<td>45 (42%)</td>
<td>64 (30%)</td>
<td>0.12</td>
</tr>
<tr>
<td>Bulky disease (&gt;10cm)</td>
<td>19 (18%)</td>
<td>33 (15%)</td>
<td>0.62</td>
</tr>
</tbody>
</table>
Figure 1. Time-to-event curves for event-free (EFS), progression-free (PFS), and overall survival (OS)

Intent To Treat (All Patients)

Eligible Patients
Figure 2a. Time-to-event curve by International Prognostic Index status for event-free survival (EFS)
Figure 2b. Time-to-event curve by International Prognostic Index status for overall survival
Figure 3a. Event-free survival based on interim PET (PET2) results

% Event-free

p=0.31

- Interim PET Negative
- Interim PET Positive

Months

0 6 12 18 24 30 36 42 48 54

0 10 20 30 40 50 60 70 80 90 100
Figure 3b. Event-free survival based on post-treatment PET (PET6) results

![Graph showing event-free survival based on post-treatment PET (PET6) results. The graph displays two curves: one for Post-treatment PET Negative and another for Post-treatment PET Positive. The p-value is 0.02.]

% Event-free

Post-treatment PET Negative

Post-treatment PET Positive

p=0.02

Months

0 6 12 18 24 30 36 42 48 54

0 10 20 30 40 50 60 70 80 90 100
Figure 4. Comparison of ER-CHOP ITT results to R-CHOP treated patients from the University of Iowa/Mayo Clinic SPORE Molecular Epidemiology Resource.

**Event-free Survival**

- ER-CHOP
- SPORE R-CHOP

IPI adjusted p=0.04

**Overall Survival**

- ER-CHOP
- SPORE R-CHOP

IPI adjusted p=0.12
Epratuzumab with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy (ER-CHOP) in patients with previously untreated diffuse large B-cell lymphoma

Ivana N. M. Micallef, Matthew J. Maurer, Gregory A. Wiseman, Daniel A. Nikcevich, Paul J. Kurtin, Michael W. Cannon, Domingo G. Perez, Gamini S. Soori, Brian K. Link, Thomas M. Habermann and Thomas E. Witzig