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The mTORC1 Inhibitor Everolimus Combined with R-CHOP-21 for New Untreated Diffuse Large B-Cell Lymphoma (DLBCL): Safety and Efficacy Results of a Phase I and Feasibility Trial NCCTG 1085 (Alliance)

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Abstract

Background—The PI3K/mTORC pathway is upregulated in diffuse large B-cell lymphoma (DLBCL) and can be targeted with the mTORC1 inhibitor everolimus. Everolimus has activity in relapsed DLBCL. These data provide the rationale to combine everolimus with standard R-CHOP-21.

Methods—The primary endpoint of this study was to determine the maximum tolerated dose of everolimus 10 mg days 1-10 or 1-14 in combination with R-CHOP-21 for 6 cycles along with a feasibility cohort for response assessment in patients with new, untreated DLBCL. Secondary endpoints were the rate of event-free survival 12 months from registration and overall survival. Patients were considered evaluable for the primary endpoint in the phase I portion if they completed the first cycle as planned. In the feasibility portion all patients who received at least one dose of everolimus were included. This completed trial is registered with [ClinicalTrials.gov](https://clinicaltrials.gov) as NCT01334502.

Findings—Nine patients were enrolled into the phase I trial without dose-limiting toxicities; therefore, everolimus 10 mg days 1-14 with standard R-CHOP-21 was tested in 15 additional patients for a total of 24 patients. The median age was 58.5 years (IQR, 49.5-71.5); 18 (75%) stages III/IV; 13 (54%) with elevated lactate dehydrogenase; 29% with high International

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Author contribution: PBJ and TEW designed and conducted the clinical trial study, and wrote the report. BL did the statistical analysis. EM did the pathology review. TMH, DJI, IM, PBJ, JPC, SMA, GN, and TEW enrolled patients on to the trial and reviewed the manuscript.

Conflicts of interest: Novartis provided everolimus for the trial. No investigator received funding for the trial. Drs. Witzig and Johnston have participated in Advisory Boards for Novartis but were personally uncompensated. None of the authors have any financial conflict of interests.

Prognostic Index; and 54% (13/24) non-GCB by immunohistochemistry. The overall response rate was 96% (23/24; 95% CI: 79 – 100%) with 23 attaining functional complete remission by PET/CT (96%, 95% CI: 79 – 100%). The remaining patient went off study for refusal in cycle 1 and attained a complete response with RCHOP. The median follow-up is now 21.5 months (IQR, 17 - 29) with all 24 patients meeting EFS12. None of the 24 patients have died, and none have experienced relapse with DLBCL. The most common grade 3/4 toxicity was hematologic with 18 patients (75%) with grade 4 neutropenia of which five (21%) experienced grade 3 febrile neutropenia.

Interpretation—Everolimus for 14 days in combination with R-CHOP-21 is safe and produced a 96% CR rate in both GCB and non-GCB DLBCL. With a median follow-up of 21.5 months and all patients meeting EFS12, the lack of DLBCL relapse is of special interest. A randomized trial will be necessary to confirm the benefits of this novel combination.

Funding—National Cancer Institute of the United States; Novartis provided everolimus.

Keywords

Everolimus; mTORC1; DLBCL

Introduction

Lymphoma ranks sixth in the incidence of cancer and diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma (NHL). The addition of rituximab to cyclophosphamide, doxorubicin, vincristine and prednisone delivered every 21 days for 6 cycles (R-CHOP-21) improved overall response rates (ORR) and overall survival (OS) compared to CHOP.^{1,2} R-CHOP-21 is the current standard of care and cures approximately 60% of patients; novel approaches incorporating recent DLBCL research findings are needed to increase the cure rate. Investigations into DLBCL biology have identified molecularly distinct forms - germinal center B-cell (GCB), activated B-cell (ABC), primary mediastinal B-cell, and unclassifiable.^{3,4} This classification can be performed by gene expression profiling (GEP), immunohistochemistry (IHC) or with NanoString techniques using the Lymph2CX algorithm.⁴ The recognition of the importance of the negative prognostic impact of double hit DLBCL as identified by *MYC* plus *BCL2* and/or *BCL6* translocations has led to proposals to treat these patients differently. The relevance of event-free status (EFS) at 12 and 24 months in predicting long-term outcome of DLBCL provides a new method for early evaluation of novel regimens.⁵ Lastly, the elucidation of key signal pathways used by DLBCL cells⁶ has led to the testing of agents that target these pathways.⁷ We are currently in the R(X)CHOP era with trials testing the addition of agents such as bortezomib, ibrutinib, or lenalidomide that target different signaling pathways in the tumor to standard R-CHOP-21.⁸

This study reports the results of adding the mTORC1 inhibitor everolimus to R-CHOP-21. The rationale for this trial was based on the role of the PI3K/Akt/mTOR pathway in cancer in general⁹ and specifically in lymphoma.⁶ We have demonstrated that the PI3K/mTOR pathway is activated in NHL cells^{10,11} and that mTORC1 inhibitors have single-agent activity in relapsed B-cell¹² and T-cell NHL.¹³ Everolimus has also been shown to be safe

and effective when combined with rituximab in relapsed DLBCL patients.¹⁴ Inhibition of the pathway at the PI3K level is effective and idelalisib is now approved for relapsed CLL and indolent B-cell NHL.¹⁵ This biology and the clinical activity of everolimus in relapsed patients led to this study of everolimus/RCHOP.

Material and Methods

Patient selection

N1085 was a phase I and feasibility study for untreated DLBCL patients otherwise eligible for R-CHOP immunochemotherapy. The study was designed in the North Central Cancer Treatment Group (NCCTG) as N1085 (NCT01334502) and transitioned to the Alliance for Clinical Trials in Oncology (Alliance) after the merger of NCCTG, Cancer and Leukemia Group B, and the American College of Surgeons Oncology Group. All patients were accrued from the Mayo Clinic Rochester, Minnesota site. The Mayo Clinic Institutional Review Board approved the study and each patient provided written informed consent. The R-CHOP drugs were supplied commercially and were the responsibility of the patient.

Patients were required to have untreated CD20+ DLBCL; ≥ 18 years, stages II-IV, ECOG performance status 0-2, and have measurable disease by CT or MRI with ≥ 1 lesion with a single diameter of ≥ 2 cm. All patients had bone marrow examination pre-treatment and if positive a repeat marrow at end of treatment. FDG-PET imaging was performed pre-treatment, before cycle 3, and end of therapy. Required laboratory tests were: absolute neutrophil count (ANC) ≥ 1,500/μL; platelets ≥ 100,000/μL; hemoglobin ≥ 9 g/dL (transfusions allowed); creatinine ≤ the upper limit of normal (ULN); bilirubin ≤ 1.5 × ULN (if total ≤ 1.5 then a normal direct bilirubin); alkaline phosphatase and AST ≤ 3 × ULN (≤ 5 × ULN if liver involvement). Patients with known HIV infection were eligible if CD4 count was ≥ 400/μL. Patients with diabetes mellitus receiving therapy were required to have a HbA1C ≤ 8% or a fasting serum glucose ≤ 110% ULN. Patients with central nervous system (CNS) lymphoma were ineligible.

Treatment—Patients received standard R-CHOP-21² with scheduled pegfilgrastim 6 mg SQ on day 2 for 6 cycles. Everolimus 10 mg/day dose was selected as it is the standard FDA-approved daily dose for other cancers. Because we did not want to compromise the RCHOP dose intensity and since everolimus is myelosuppressive, we aimed to provide at least 1 week off per cycle. Thus, for the phase I portion, two schedules were tested – 10 mg PO daily in the fasting state days 1-10 or days 1-14; there was no CNS prophylaxis. Patients could be on anticoagulants.

Adverse Event Assessment—Adverse events were graded using the NCI Common Terminology Criteria for Adverse Events v4.0. A CBC was performed weekly. A toxicity was defined as an adverse event at least possibly related to treatment. Dose limiting toxicity (DLT) was defined as any of the following during cycle 1: platelet count <25,000/μL for ≥ 7 days; platelet nadir <10,000/μL any time during the cycle; failure to recover platelet count >75,000/μL and/or ANC ≥ 1500/μL by day 28 after cycle 1; grade 4 febrile neutropenia; grade 4 infection; any grade 3 non-hematologic toxicity; and any toxicity causing a dose delay >1 week. Rituximab infusion reactions were not considered DLTs. A significant

toxicity was defined as a grade 4 or higher non-hematologic adverse event at least possibly related to treatment with everolimus or a dose reduction or delay > 7 days of any agent of RCHOP at least possibly related to the addition of everolimus. At retreatment, the ANC was required to be $1500/\mu\text{L}$ and the platelet count $75,000/\mu\text{L}$. Patients not meeting those requirements on day 21 were allowed up to day 28 to recover and still receive 100% of drug doses. Treatment delays longer than day 28 required everolimus dose reductions to 5 mg days 1-14 and 5 mg days 1-10.

Response Assessment—Responses were categorized using the Revised Response Criteria for Malignant Lymphoma that incorporated PET results.¹⁶ Patients progressing at any time went off study to event monitoring. Patients were evaluated every three months during year 1 post-therapy and every four months during year 2. Tumor imaging was performed with the technique of choice during these follow-up time points. Two years post-therapy patients went off protocol treatment and entered event monitoring every 6 months until 5 years from registration.

Translational Research—We measured the absolute lymphocyte count (ALC) and monocyte count (AMC) from the CBC and WBC differential and calculated the ALC/AMC ratio. $\text{ALC} > 1000/\mu\text{L}$, $\text{AMC} < 630/\mu\text{L}$, and an ALC/AMC ratio < 1.1 at baseline are all predictive of a favorable outcome.¹⁷ As described in the protocol, DLBCL tumors were to be classified as GCB or non-GCB by Hans criteria and vitamin D levels measured by standard laboratory assays. In addition, we measured Bcl-2 and Myc protein expression on primary tumor cells by IHC; 70% and 40% were used as cutoffs for Bcl-2 and Myc, respectively.

Statistical Design

The phase I portion utilized a standard cohort of 3 design to determine the MTD of everolimus/RCHOP. The MTD was defined as the highest safely tolerated dose where at most 1 of 6 patients experience DLT with the next higher dose having at least 2 patients who experience DLT (unless it is the maximum dose level). The 6 patients treated at the MTD in Phase I were also included in the feasibility portion. In the feasibility portion of the study, 15 additional patients were accrued at the MTD to better assess efficacy and toxicity with this regimen. Feasibility was assessed by determining the proportion of patients experiencing a significant toxicity at least possibly related to the addition of everolimus to RCHOP. If 20% of patients had a significant toxicity then this regimen would not be considered feasible. Patients were considered evaluable in the phase I portion if they completed the first cycle as planned. In the feasibility portion all patients who were treated at the MTD and took at least one dose of everolimus were included. Study progress was monitored via regularly scheduled meetings involving the study chair, statisticians and data manager. Time-to-event measures were estimated using the Kaplan-Meier method.¹⁸ Event-free survival (EFS) was measured from registration with death due to any cause, tumor progression or relapse, or initiation of subsequent anti-lymphoma therapy considered events.⁵

Role of Funding Source

The trial was designed by the authors in collaboration with leadership at the National Cancer Institute and the NCCTG (Alliance). Everolimus was supplied by Novartis Pharmaceuticals (IND111801). The study was supported by the National Cancer Institute without additional pharmaceutical support. All data was available to study personnel and were kept at the Mayo Clinic and NCCTG/(Alliance) statistical center. The results and the manuscript were provided to NCCTG (Alliance), NCI, and Novartis for review prior to submission. The corresponding author had full access to all of the data and the final responsibility to write and submit for publication.

Results

Twenty-six patients were enrolled between March 21, 2012 and September 15, 2014 (**Figure 1**). One patient at dose level 1 did not complete cycle 1 because of insurance company refusal for participation in a research trial. A second patient at dose level 2 withdrew consent and failed to return for adverse event assessment after R-CHOP and 4 days of everolimus because of a desire to be treated closer to home. Thus, 24 eligible patients are summarized in this report. The median age was 58.5 years (IQR, 49.5-71.5); 46% (11/24) were 60 years old and 38% (9/24) 70 years old (**Table 1**). All patients were HIV negative. Five patients (21%) had bulky disease (a mass >10cm); however, no patients with primary mediastinal B-cell lymphoma were enrolled.

Phase 1

Three patients were accrued to dose level 1 and six to level 2. There were no DLTs; therefore, everolimus 10 mg days 1-14 of each 21 day R-CHOP cycle was selected for the feasibility phase.

Feasibility Phase

Fifteen patients were enrolled and treated for a total of 21 patients in the feasibility phase and overall 24 patients were eligible for response assessment. Twenty-two (92%) received all six cycles; 1 patient received 3 cycles and became ill due to a biliary stent malfunction and further chemotherapy administration was discontinued due to treatment delay. This patient had achieved a complete response (CR) after 3 cycles, received no further therapy and remains in CR two years from diagnosis. The other patient received one full cycle of everolimus/R-CHOP, then withdrew consent and received three additional cycles of R-CHOP and attained a CR that persists >18 months from diagnosis. This patient was considered evaluable for toxicity and response.

The ORR in all patients was 96% (23/24; 95% CI: 79 – 100%) with 23 patients attaining functional CR by PET/CT (96%; 95% CI: 79 – 100%) while on study. The remaining patient as noted above went off study for refusal in cycle 1 but attained a CR with further R-CHOP-21; thus, all 24 patients achieved a CR. The median follow-up for all 24 patients is 21.5 months (IQR, 17 - 29). All 24 (100%) were event-free at 12 months post-diagnosis (EFS12), and 9 had sufficient follow-up to be event-free at 24 months (EFS24). To date, none of the 24 patients have died and none have experienced relapse of DLBCL (**Figure 2**).

Thus, the median duration of response and progression-free survival for DLBCL have not been reached, as there are no events yet. One patient relapsed with biopsy-proven follicular grade I NHL 16 months from DLBCL diagnosis and achieved a second CR with standard salvage therapy. One of the original 26 patients who received one tablet of everolimus and then withdrew from the study has died of relapsed DLBCL. There have been no CNS relapses.

Adverse Events

Adverse events are reported from all 24 patients evaluated during treatment (**Table 2**). The most common grade 3/4 toxicity was neutropenia with 75% (18/24) grade 4. Five (21%) patients had grade 3 febrile neutropenia. One patient (4%) had grade 3 hyperglycemia, and 3 (13%) patients had grade 3 hypertriglyceridemia. Grade 3 reversible rash and pneumonitis were observed in 1 (4%) case each. The case of pneumonitis developed after cycle 3 in association with grade 3 ANC and bilateral pulmonary infiltrates on CT. She was successfully treated with oral antibiotics. One patient in the feasibility phase had a treatment delay of 12 days due to grade 3 hypokalemia possibly related to everolimus, for a significant toxicity rate of 5% (1/21; 95% CI: 0 – 24%) in patients treated at dose level 2 in the feasibility phase. An additional two patients treated at dose level 1 in the phase I portion also met the significant toxicity definition: 1 patient had a grade 4 sepsis possibly related to treatment and one patient had a treatment delay of 10 days due to grade 3 infection possibly related to everolimus. Ten patients (42%) experienced a dose reduction in everolimus - eight patients reduced one dose level (10 mg days 1-10) and two reduced two dose levels (5 mg days 1-14). Two patients permanently discontinued everolimus after cycles 3 and 4, respectively; two additional patients omitted everolimus for 1 and 2 cycles, respectively, during treatment then resumed everolimus for subsequent cycles. There were no treatment related deaths.

Translational Research

Ten (42%) patients had a low pretreatment ALC; 10 (42%) had a high pretreatment AMC; however, only 2 had a low (<1.1, unfavorable) ALC/AMC ratio. The single patient who relapsed with a follicular NHL had a low baseline ALC (670/ μ L). Molecular classification by IHC revealed 54% (13/24) to be non-GCB. FISH for double hit cytogenetic abnormalities was performed in 18 cases (8 GCB, 10 non-GCB) and all were negative. The tumors were Bcl-2 protein positive in 71% (15/21); Myc protein positive in 13% (2/13); and double protein positive in 2 cases. Nineteen patients had 25-hydroxyvitamin D [25(OH)D] levels (normal, 25-80 ng/mL) measured at baseline and eight (42%) were insufficient (mean, 15.5 ng/mL; median, 16.5, IQR 12.5-19).¹⁹

Discussion

This study demonstrated that combining the oral mTORC1 inhibitor everolimus at 10 mg/day for 14 days to standard RCHOP-21 is feasible with acceptable toxicity and produces a 96% functional CR rate with no DLBCL relapses at a median follow-up of the cohort of 21.5 months. Everolimus was chosen for combination with RCHOP based on studies demonstrating mTORC1 pathway activation in DLBCL tumors, cytostatic activity in vitro

on DLBCL cell lines and primary samples,¹⁰ and demonstration of single-agent activity (ORR 30%) in a clinical trial of everolimus 10 mg/d in 47 patients with relapsed DLBCL.¹² In addition, none of the other agents in R-CHOP specifically target the PI3K/mTORC1 pathway.

In the current trial, everolimus was incorporated upfront in untreated DLBCL patients in combination with R-CHOP-21. This was a different approach than the PILLAR2 (NCT00790036) trial that studied everolimus vs placebo maintenance for one-year following achievement of CR after R-CHOP (trial complete but not reported). The characteristics of the 24 patients enrolled were typical for DLBCL with a high LDH in 50%, 29% IPI 3/4, 42% with a low ALC, 42% a high AMC, non-GCB in 54%, and 42% vitamin D insufficient. In patients with DLBCL, a low ALC²⁰ and a high ALC/AMC ratio¹⁷ predict relapse and inferior OS. There were two cases that were double protein (Bcl-2/Myc) positive but all 18 cases tested for translocations by FISH were negative. Thus, we have no data on the efficacy of this regimen in double hit DLBCL. The protocol eligibility was more stringent than usual in that the baseline creatinine was required to be normal. Most DLBCL studies allow creatinine levels of $1.5\text{--}2.0 \times \text{UNL}$.²¹⁻²⁴

Everolimus/R-CHOP-21 had a reasonable toxicity profile with the most common grade 3/4 toxicity being hematologic with 75% of patients experiencing grade 4 neutropenia. Despite prophylactic pegfilgrastim, 5 patients (21%) had grade 3 febrile neutropenia during the 6 cycles. This is slightly higher than the rate of 19% found in a large study of patients treated with standard R-CHOP.²⁵ Hyperglycemia and hyperlipidemia - toxicities observed in studies of continuous everolimus - were not a major issue (1 patient with grade 3 hyperglycemia; 3 with grade 3 hypertriglyceridemia) despite everolimus being administered with 5 days of prednisone. Everolimus can induce a drug rash and non-specific pneumonitis. Neither of these complications were problematic, likely prevented by the concomitant corticosteroids in the R-CHOP regimen. A 15 patient phase 1 trial of everolimus with CHOP (without pegfilgrastim) for T-cell NHL found 5 mg days 1-14 to be the MTD for future trials. The lower MTD in that trial may reflect a biologic difference in patients with T cell NHL, the lack of mandated pegfilgrastim, or the ethnic background of the study cohort.²⁶

Studies to improve DLBCL outcome by increasing the intensity of R-CHOP rather than adding new agents have not been successful.²⁷ Other studies have also built on standard R-CHOP-21 by adding novel agents. The NCCTG performed an 81 patient phase II trial that combined the anti-CD22 monoclonal antibody epratuzumab with R-CHOP-21.²¹ The ORR was 88% as determined by PET imaging. At a median follow-up of 43 months, the EFS and OS in all patients was 70% and 80%, respectively. The NF-KB signal pathway is activated in ABC-type DLBCL, providing rationale to study the NF-KB inhibitor bortezomib. Bortezomib/R-CHOP-21 cycle was found safe and efficacious in DLBCL with an ORR of 100% and a 2-year PFS of 64%.²⁸ However, a recent trial comparing standard R-CHOP with the VR-CAP regimen that substitutes bortezomib for vincristine showed similar CR rates (approximately 65%) for both arms and a similar PFS24 of approximately 77%.²² Thus, despite compelling biology to target NF-KB, the addition of bortezomib did not provide additional benefit in this randomized trial. The ongoing REMoDL-B (NCT01324596) trial is

testing bortezomib-R-CHOP vs R-CHOP in patients with GCB or ABC-type DLBCL as determined by Affymetrix GEP performed prior to randomization.

Ibrutinib is an oral Bruton's tyrosine kinase inhibitor that has demonstrated single-agent activity primarily in ABC-type DLBCL.²⁹ This led to a phase I trial of continuous ibrutinib with standard R-CHOP (IRCHOP) in 32 patients (23 with untreated DLBCL) and the ORR was 95%.³⁰ At the time of that report the duration of response was not available. These results have led to a large randomized trial of R-CHOP vs ibrutinib/R-CHOP for non-GCB DLBCL that has yet to be reported (NCT01855750).

Two phase I^{23,31} and a phase II trial²⁴ demonstrated that the immunomodulatory agent lenalidomide could be safely combined with R-CHOP and produce results superior to historical controls. This has led to a prospective phase II trial (ECOG-ACRIN E1412, NCT01856192) of R-CHOP or R2CHOP. The trial is determining DLBCL cell of origin by NanoString with specific analyses for the GCB and non-GCB subgroups. A second trial (ROBUST, NCT02285602) is recruiting patients with non-GCB type DLBCL as determined by NanoString with randomization to either standard R-CHOP or R2CHOP.

The results of these ongoing studies will clarify the roles of IR/CHOP, R2CHOP, and BorRCHOP. In general these regimens, similar to everolimus/RCHOP, appear safe when compared to RCHOP and when given to patients eligible for aggressive therapy. The toxic death rate with standard RCHOP is in the 4-10% range;^{1,2,22} it was 0-5% in the novel RCHOP combinations reviewed above.^{22,24,28,30,31} The rates of febrile neutropenia with RCHOP are typically in the 20% range^{22,25} and were no higher in VR-CAP (9%),²² R2CHOP (5-9%),^{24,31} and IRCHOP (18%).³⁰

The strengths of this study of everolimus/RCHOP are the impressive ORR results and that all patients have achieved EFS12 by PET/CT with respect to DLBCL. EFS12 is an early marker of OS.⁵ Achieving EFS24 is an even better predictor, and we acknowledge that although all patients are past 12 months, only 9 patients are 24 months. The value of EFS12/24 is that it allows an earlier evaluation of a new regimen such as Everolimus/RCHOP so that decisions can be made more expeditiously regarding phase III trials. The weaknesses of the study are that it was small, single center, and eligibility was restricted to those patients with normal serum creatinine. Everolimus/RCHOP is the only regimen tested to date that integrates a PI3K/mTORC1 agent with standard RCHOP. The encouraging outcome results and toxicity profile of this novel combination along with the worldwide availability of everolimus make this combination potentially applicable to the large population of DLBCL patients. Our results require validation in a randomized phase III trial for both GCB and non-GCB types vs R-CHOP or vs the winner of one of the ongoing trials as described above.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Research in Context

Evidence before this study

The standard accepted treatment for diffuse large B-cell lymphoma (DLBCL) is a combination of rituximab immunotherapy and chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone (RCHOP) delivered on a 21-day cycle length for 6 cycles. This regimen typically cures approximately 60% of patients. There is an unmet need to develop new therapies based on the RCHOP-21 backbone to try and improve the cure rate for DLBCL. This study tested the addition of the mTORC1 inhibitor everolimus to standard RCHOP-21 for previously untreated DLBCL. The importance of the PI3K/mTOR signal pathway in the pathogenesis of DLBCL cells demonstrated in the literature, and the documented single-agent efficacy of everolimus in relapsed DLBCL provided the rationale for choosing everolimus to be combined with standard RCHOP.

Added value of this study

Our study demonstrates that everolimus can be safely combined with RCHOP. The response rate was high at 96% with all responders achieving a functional CR. More importantly, there have been no relapses to date with DLBCL. All patients have achieved the important predictive milestone of being event free at 12 months from registration (EFS12).

Implications of all the available evidence

To our knowledge, this is the first study to combine an mTORC1 inhibitor with RCHOP and has demonstrated that this regimen is safe. The high ORR and durability of responses suggests that agents that target the PI3K/mTOR pathway may add value when combined with standard RCHOP. The everolimus/RCHOP regimen should be tested in a randomized clinical trial vs standard RCHOP.

Figure 1.

Flow chart of the 26 patients enrolled in the study of everolimus/RCHOP for new, untreated diffuse large B-cell lymphoma. All 24 eligible treated patients remain on study.

Figure 2.

(A) Overall survival of the 24 eligible patients treated with everolimus/RCHOP; (B) Event-free survival. The histology of the one relapse was follicular lymphoma.

Table 1

Patient Characteristics of the 24 Eligible Patients in N1085

Parameter	Result
Age – median, IQR in years	58.5 (49.5-71.5)
Age ≥ 60 years	11 (46%)
Age ≥ 70 years	9 (38%)
Sex – female	10 (42%)
Sex – male	14 (58%)
Clinical stage	
I	0
II	6 (25%)
III	5 (21%)
IV	13 (54%)
B-Symptoms	4 (17%)
Elevated LDH	13 (54%)
ECOG Performance Status score	
0	14 (58%)
1	10 (42%)
Bulky disease (>10 cm)	5 (21%)
International Prognostic Index	
Low (1-2 points)	17 (71%)
High (3-5 points)	7 (29%)
Tumor genotype by Hans criteria	
Germinal center type	11 (46%)
Non-Germinal center type	13 (54%)

Table 2

Adverse events at least possibly related to treatment in 24 evaluable patients treated with at least one cycle of everolimus/RCHOP-21. Includes All Grade 3+; and Grades 1 and 2 if combined incidence >10%. No grade 5 adverse events were observed.

	Adverse Event	Highest Grade/Patient					
		1-2		3		4	
		N	%	N	%	N	%
Hematologic	Anemia	9	38	3	12	0	
	Leukocytosis	0		2	8	0	
	Leukopenia	4	17	7	29	2	8
	Lymphopenia	0		4	17	0	
	Neutropenia	4	17	0		18	75
	Thrombocytopenia	15	63	3	13	3	13
Non-Hematologic	Febrile neutropenia	0		5	21	0	
	Hypercholesterolemia	14	58	0		0	
	Hypertriglyceridemia	15	63	3	13	0	
	Hyperglycemia	0		1	4	0	
	Diarrhea	12	50	0		0	
	Nausea	3	13	0		0	
	Pneumonitis	3	12	1	4	0	
	Rash (acneiform)	0		1	4	0	
	Rash (maculopapular)	5	21	0		0	
	Dry skin	0		1	4	0	
	Fatigue	11	46	1	4	0	
	Infection	0		1	4	0	
	Sepsis	0		0		1	4
	Urinary tract infection	0		1	4	0	
	Lung infection	0		1	4	0	
	Hypocalcemia	0		1	4	0	
	Hypokalemia	0		1	4	0	
	Hyponatremia	0		1	4	0	
	Hypophosphatemia	0		1	4	0	
	Seizure	0		1	4	0	
	Thromboembolic event	0		1	4	0	
	Alopecia	15	63	0		0	
	Weight loss	5	21	1	4	0	
	Hypoxia	0		1	4	0	