

LETTER TO THE EDITOR

High rate of event-free survival at 24 months with everolimus/RCHOP for untreated diffuse large B-cell lymphoma: updated results from NCCTG N1085 (Alliance)

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The purpose of this letter is to update the event-free (EFS) and overall (OS) survival data from North Central Cancer Treatment Group (NCCTG) N1085 (NCT01334502)—a phase I and feasibility trial of everolimus combined with standard RCHOP for patients with untreated diffuse large B-cell lymphoma (DLBCL).¹ NCCTG is now part of the Alliance for Clinical Trials in Oncology (Alliance). Event-free survival at 24 months (EFS24) is a surrogate for long-term outcome² and this end point is being used in newer trials for DLBCL. In addition, we report the time from diagnosis to day 1 of treatment (DtT) for this cohort. DtT has recently been shown to influence the rate of achieving EFS24 in DLBCL patients accrued to the University of Iowa/Mayo Clinic Lymphoma SPORE Molecular Epidemiology Resource.³ The DtT is a continuous variable, with patients initiating chemoimmunotherapy ≤ 14 days from the date of biopsy having inferior EFS compared to those with a DtT ≥ 15 days ($P < 0.0001$). In order for the lymphoma investigators to make decisions regarding the EFS/OS end points for the design of the next large-phase III trial, it is important to have, at a minimum, EFS24 and DtT data from the regimens to be tested.

The PI3K/mTOR pathway is a key signal transduction pathway used by DLBCL cells (reviewed in Roschewski *et al.*⁴). Studies in relapsed DLBCL demonstrate single-agent activity of everolimus.⁵ These data provided the rationale to test everolimus with RCHOP in a phase I and feasibility study in the NCCTG (Alliance) NCTN group. The trial, which accrued 26 patients between 21 March 2012 and 15 September 2014, was designed to determine the maximum tolerated dose of everolimus 10 mg days 1–10 (level 1) or 1–14 (level 2) in combination with R-CHOP-21 and pegfilgrastim for six cycles in patients with newly diagnosed DLBCL. Eligible patients were required to have new, untreated, CD20-positive DLBCL (stages II–IV, ECOG performance status 0–2), be eligible for R-CHOP chemotherapy, aged at least 18 years, and have measurable disease by computed tomography (CT) or magnetic resonance imaging with at least one lesion of more than 2 cm diameter. Each participant signed an IRB-approved, protocol-specific informed consent in accordance with federal and institutional guidelines. Two were patients were ineligible; therefore results were presented for 24 eligible patients. Data collection and statistical analyses were conducted by the Alliance Statistics and Data Center. The early results of that trial have been published¹ and demonstrated that the combination of everolimus 10 mg days 1–14 with standard RCHOP-21 with prophylactic pegfilgrastim was safe and efficacious. The overall response rate was 96% (23/24), with 23 patients attaining functional complete remission (CR) by positron emission tomography/CT. The remaining patient went off study treatment but attained a CR off study with additional cycles of RCHOP. At the time of the initial report¹ all 24 patients had met EFS12, but only nine patients had long-enough follow-up to assess EFS24. As of February 2017 the median follow-up for the 24 patients was 37.2 months (range, 26.9–56.3) and all patients had been assessed for EFS24 with no

DLBCL relapses (Figure 1). As previously mentioned,¹ one patient relapsed with low-grade follicular lymphoma but is now in a second CR with radioimmunotherapy and rituximab. The median DtT of the 24 eligible patients was 14 days (mean, 16 days; range, 5–48 days).

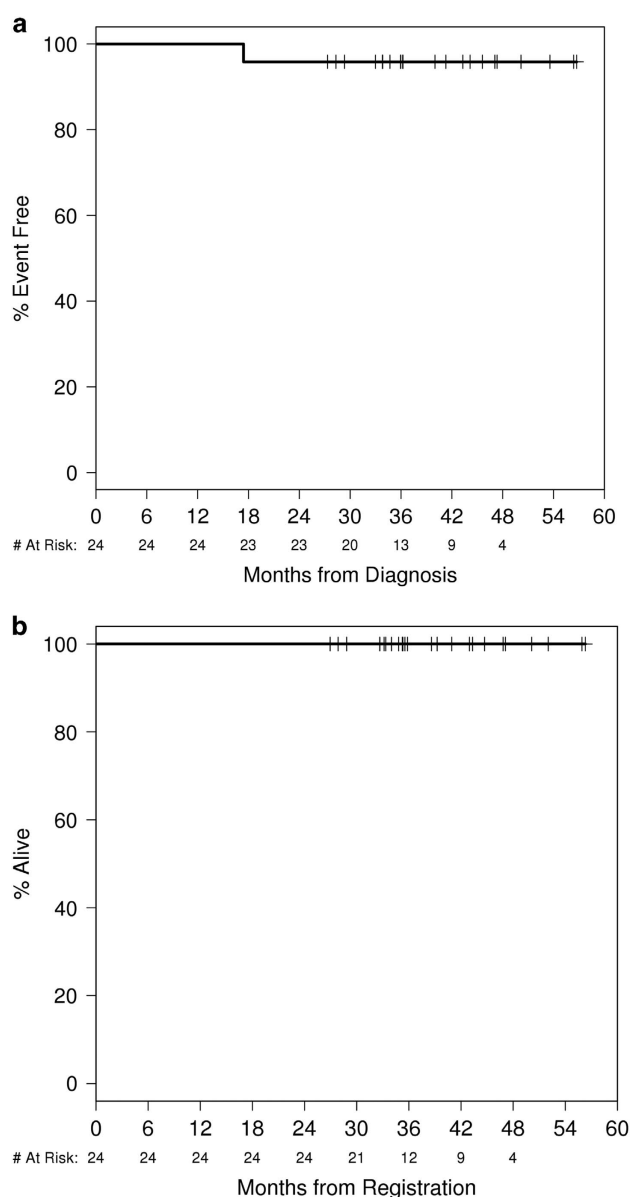


Figure 1. Event-free (a) and overall survival (b) of the 24 patients treated with everolimus and RCHOP on N1085 as updated through February 2017.

The results from this small study of everolimus/RCHOP continue to be very promising, especially since the median DtT of the patients on this trial was 14 days. Based on our recent data, patients with DtT \leq 14 days treated with RCHOP would have an expected EFS24 failure rate of 44%.³ We recommend further testing of this regimen in a randomized trial to learn if the results will be significant when compared head to head with RCHOP or other novel regimens. We also recommend that the DtT be used as a stratification factor given its influence on EFS24.

These data are also important when placed in context with other efforts to improve the OS of patients with DLBCL. For the last 15 years the standard of care has been chemoimmunotherapy with RCHOP, which cures ~60% of all patients. Multiple attempts to improve on the RCHOP backbone have been unsuccessful. The results of Cancer and Leukemia Group B 50303 were reported at the 2016 American Society of Hematology meeting and demonstrated that both RCHOP and DA-REPOCH had similar rates of PFS and OS with more toxicity in the DA-EPOCH arm.⁶ Eighty percent of patients in the RCHOP arm achieved EFS24, much higher than predicted at the start of the trial. The trial had important goals with respect to tumor assessment of cell of origin. It is possible that these requirements led to a long DtT, thus inadvertently accruing a more favorable group of patients. The recent GOYA study tested a new anti-CD20 antibody (obintuzumab) with CHOP vs RCHOP, and this study was also negative.⁷ Attempts to provide some form of adjuvant therapy to high-risk DLBCL patients with a CR after RCHOP have also been unsuccessful. These include trials of up to 3 years of oral enzastaurin,⁸ 1 year of everolimus⁹ or autologous stem cell transplant.¹⁰

Current efforts similar to our everolimus/RCHOP study are combining novel agents with standard RCHOP.¹¹ The choice of these agents is based on biology, the demonstration of single-agent activity in patients with relapsed DLBCL and pilot studies of the combination that have shown them to be reasonably safe. Trials adding bortezomib¹² or ibrutinib¹³ to RCHOP have been enrolled but not fully reported. Ongoing trials ECOG E1412 (NCT01856192) and ROBUST (NCT02285062) are testing R2CHOP^{14,15} vs RCHOP. We recommend that all these trials begin to report EFS24 and DtT results to allow better comparison across studies. It is hoped that these or forthcoming trials will be successful at improving OS in DLBCL.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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DISCLAIMER

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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REFERENCES

- Johnston PB, LaPlant B, McPhail E, Habermann TM, Inwards DJ, Micallef IN *et al.* Everolimus combined with R-CHOP-21 for new, untreated, diffuse large B-cell lymphoma (NCCTG 1085 [Alliance]): safety and efficacy results of a phase 1 and feasibility trial. *Lancet* 2016; **3**: e309–e316.
- Maurer MJ, Ghesquieres H, Jais JP, Witzig TE, Haioun C, Thompson CA *et al.* Event-free survival at 24 months is a robust end point for disease-related outcome in diffuse large B-cell lymphoma treated with immunochemotherapy. *J Clin Oncol* 2014; **32**: 1066–1073.
- Maurer M, Link B, Habermann T, Thompson C, Allmer C, Johnston P *et al.* Time from diagnosis to initiation of treatment of DLBCL and implication for potential selection bias in clinical trials. Clinically relevant abstract. *Blood* 2016; **128**: 3034.
- Roschewski M, Staudt LM, Wilson WH. Diffuse large B-cell lymphoma-treatment approaches in the molecular era. *Nat Rev Clin Oncol* 2014; **11**: 12–23.
- Witzig TE, Reeder CB, LaPlant BR, Gupta M, Johnston PB, Micallef IN *et al.* A phase II trial of the oral mTOR inhibitor everolimus in relapsed aggressive lymphoma. *Leukemia* 2011; **25**: 341–347.
- Wilson W, Jung S-H, Pitcher B, Hsi E, Friedberg J, Cheson B *et al.* Phase III randomized study of R-CHOP vs. DA-EPOCH-R and molecular analysis of untreated large B-Cell lymphoma: CALGB/Alliance 50303. *Blood* 2016; **128**: 469.
- Vitolo U, Trneny M, Belada D, Carella A, Chua N, Abrisqueta P *et al.* Obinutuzumab or rituximab plus CHOP in patients with previously untreated diffuse large B-cell lymphoma: final results from an open-label, randomized Phase III study (GOYA). *Blood* 2016; **34**: 470.
- Crump M, Leppa S, Fayad L, Lee JJ, Di Rocco A, Ogura M *et al.* Randomized, double-blind, Phase III trial of enzastaurin versus placebo in patients achieving remission after first-line therapy for high-risk diffuse large B-cell lymphoma. *J Clin Oncol* 2016; **34**: 2484–2492.
- Witzig T, Tobinai K, Rigacci L, Lin T, Ikeda T, Vanazzi A *et al.* PILLAR-2: A randomized, double-blind, placebo-controlled, phase III study of adjuvant everolimus (EVE) in patients (pts) with poor-risk diffuse large B-cell lymphoma (DLBCL). *J Clin Oncol* 2016; **34**(Suppl): 7506.
- Cortelazzo S, Tarella C, Gianni AM, Ladetto M, Barbui AM, Rossi A *et al.* Randomized trial comparing R-CHOP versus high-dose sequential chemotherapy in high-risk patients with diffuse large B-cell lymphomas. *J Clin Oncol* 2016; **34**: 4015–4022.
- Vaidya R, Witzig TE. Prognostic factors for diffuse large B-cell lymphoma in the R (X)CHOP era. *Ann Oncol* 2014; **25**: 2124–2133.
- Ruan J, Martin P, Furman RR, Lee SM, Cheung K, Vose JM *et al.* Bortezomib plus CHOP-rituximab for previously untreated diffuse large B-cell lymphoma and mantle cell lymphoma. *J Clin Oncol* 2011; **29**: 690–697.
- Younes A, Thieblemont C, Morschhauser F, Flinn I, Friedberg JW, Amorim S *et al.* Combination of ibrutinib with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) for treatment-naïve patients with CD20-positive B-cell non-Hodgkin lymphoma: a non-randomised, phase 1b study. *Lancet Oncol* 2014; **15**: 1019–1026.
- Nowakowski GS, LaPlant B, Macon WR, Reeder CB, Foran JM, Nelson GD *et al.* Lenalidomide combined with R-CHOP overcomes negative prognostic impact of non-germinal center B-cell phenotype in newly diagnosed diffuse large B-Cell lymphoma: a phase II study. *J Clin Oncol* 2015; **33**: 251–257.
- Vitolo U, Chiappella A, Franceschetti S, Carella AM, Baldi I, Inghirami G *et al.* Lenalidomide plus R-CHOP21 in elderly patients with untreated diffuse large B-cell lymphoma: results of the REAL07 open-label, multicentre, phase 2 trial. *Lancet Oncol* 2014; **15**: 730–737.



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