A cancer and leukemia group B multi-center study of DA-EPOCH-rituximab in untreated diffuse large B-cell lymphoma with analysis of outcome by molecular subtype

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Haematologica 2011 [Epub ahead of print]


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A cancer and leukemia group B multi-center study of DA-EPOCH-rituximab in untreated diffuse large B-cell lymphoma with analysis of outcome by molecular subtype

Running head: Dose-adjusted EPOCH-R in diffuse large B-cell lymphoma

Wyndham H. Wilson1, Sin-Ho Jung2, Pierluigi Porcu3, David Hurd4, Jeffrey Johnson2, S. Eric Martin5, Myron Czuczman6, Raymond Lai7, Jonathan Said8, Amy Chadburn9, Dan Jones10, Kieron Dunleavy1, George Canellos11, Andrew D. Zelenetz12, Bruce D. Cheson,13 and Eric D. Hsi14 for the Cancer and Leukemia Group B

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ABSTRACT

Background. A phase II trial of dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin and rituximab (DA-EPOCH-R) from the National Cancer Institute showed promising activity in untreated diffuse large B-cell lymphoma. The Cancer and Leukemia Group B conducted a study to determine if these results could be reproduced in a multi-institutional setting.

Design and Methods. This is a phase II study of 69 patients with untreated diffuse large B-cell lymphoma of at least 18 years of age and at least stage II. Radiation was not permitted. Patients had a median age of 58 (range: 23-83) years and 40% had high-intermediate or high International Prognostic Index risk. Immunohistochemical biomarkers for cell or origin and proliferation were performed.

Results. With a median follow-up of 62 months, time to progression and overall survival were 81% and 84%, respectively, and time to progression was 87%, 92% and 54% for low/low-intermediate, high-intermediate and high international prognostic index risk groups, respectively, at five-years and beyond. The time to progression and event-free survival of germinal center B-cell were 100% and 94%, respectively, and non-germinal center B-cell GCB diffuse large B-cell lymphoma were 67% and 58%, respectively, at 62 months (germinal center versus non-germinal center B-cell p=0.008). DA-EPOCH-R was tolerated without significant grade 4 non-hematological toxicities.
**Conclusions.** These results provide the first confirmation by a multi-institutional group that DA-EPOCH-R provides high durable remissions in diffuse large B-cell lymphoma and is effective in both germinal center and non-germinal center B-cell subtypes. *The trial was registered at ClinicalTrials.Gov (NCT00032019).*

**INTRODUCTION**

Efforts to improve the chemotherapy for DLBCL have met with limited success over the past 30 years(1-3). While modifications of CHOP chemotherapy led to modest improvements in outcome, these were generally overcome by the addition of rituximab(4, 5). Alternative regimens based on aggressive treatment platforms such as ACVBP have improved outcomes in select patient groups, even in the rituximab era, but their applicability is restricted to younger patients due to high acute and long-term toxicities(6-9). The bases for these strategies have generally derived from the hypothesis that “non-cross resistant” drugs and dose intensity will overcome drug resistance, but this has generally not borne out(10, 11). It is now recognized that treatment failure depends on a complex interplay of factors including tumor biology, tumor volume, pharmacokinetics, and pharmacogenomics(10).

Investigators at the National Cancer Institute (NCI) pursued a therapeutic strategy that drew on concepts of drug resistance and pharmacokinetics. Based on studies that showed high tumor proliferation is an adverse prognostic factor in DLBCL, they modeled the effect of drug schedule on tumor cell kill and showed that continuous low dose drug
exposure enhances cell kill of rapidly proliferating tumor cells in vitro(12-14). Furthermore, they hypothesized that variations in drug clearance among patients would significantly impact the drug concentration-response curve in the setting of low steady state concentrations (Css) that are achieved during prolonged continuous infusion schedules. These concepts formed the basis for the dose adjusted (DA)-EPOCH regimen in which doxorubicin, vincristine and etoposide are infused over 96 hours, cyclophosphamide and prednisone are administered on a bolus schedule, and doxorubicin, etoposide and cyclophosphamide are pharmacodynamically dose-adjusted based on the neutrophil nadir(15-18). The NCI initially performed a phase II study of DA-EPOCH followed by a study of DA-EPOCH with rituximab in untreated DLBCL, both of which performed well compared to reported outcomes with CHOP and R-CHOP, respectively, in similar patient groups(2-5, 17, 19). To determine if the results of the NCI DA-EPOCH-R study were robust and generalizable to the community setting, the CALGB performed an independent multi-institutional study of DA-EPOCH-R with analysis of molecular subtype. Herein, we present the mature outcome of this multi-center study.
DESIGN AND METHODS

Study Design

This multi-center phase II study of DA-EPOCH-R in untreated de novo CD20+ DLBCL enrolled patients at 18 institutions between February 15, 2002 and May 28, 2004. To assure an independent assessment of DA-EPOCH-R, the NCI did not enroll patients on this multicenter study. The minimum follow-up required for each patient was 3 years or until death, whichever occurred first. Data collection was stopped on 4/15/2009 when this requirement was met. Clinical objectives included response rate, progression-free and overall survival and toxicity, and experimental endpoints included tumor immunohistochemical (IHC) biomarker analysis. Seventy-eight patients were enrolled, of which 9 were ineligible; two did not start protocol treatment, one patient was taken off study on day one due to rituximab intolerance, one patient refused treatment after one cycle, and five patients had ineligible histologies. Central pathology review was conducted by EH in 62 patients.

Eligibility included stages II-IV, human immunodeficiency virus (HIV) negative, negative pregnancy test, adequate major organ function, no central nervous system (CNS) lymphoma, and no evidence of low-grade lymphoma(15, 17). Initial evaluation included standard blood tests, whole body computed tomography (CT), and bone marrow biopsy. Standard staging and response criteria were employed(20, 21). Disease sites were restaged after cycles 4, 6 and 8 (if administered). The study was approved by the Institutional Review Boards of all participating institutions, complied with the Declaration of Helsinki and all patients gave written informed consent. All authors had access to the primary data and approved the manuscript.
Chemotherapy and Dose Adjustments

DA-EPOCH-R was administered as previously described (15, 17). Patients received 2 cycles beyond CR or stable changes for a minimum of 6 and a maximum of 8 cycles. Pharmacodynamic dose adjustment was based on twice weekly complete blood counts to achieve limited absolute neutropenia count (ANC) < 500/µl with the administration of filgrastim 300 mg from day 5 until the ANC > 5000/µl past the nadir counts (15, 17). Strict adherence to the dose adjustment paradigm is mandatory to achieve the results reported herein. Patients with > 1 extranodal site and elevated LDH and/or bone marrow involvement by DLBCL received CNS prophylaxis consisting of intrathecal methotrexate 12 mg given on day 1 (or day 2) of Cycles 3, 4, 5, and 6. Radiation was not permitted on study. Bactrim® DS was administered twice daily for 3 days per week.

Biomarkers

Immunostaining on whole tissue sections with appropriate primary antibodies was performed at the Pathology Coordinating Office of the CALGB (CD10 [clone 56C6], BCL6 [PG-B6p], MUM1 [clone MUM1p], BCL2 [clone 124], Ki67 [clone MIB1]) using automated immunostainers (Dako, Carpenteria, CA). High pH (9.0) antigen retrieval (Dako) was used for BCL6 and MUM1 while low pH (6.1) was used for CD10, BCL2, and Ki67. LMO2 (clone 1A9-1) was performed at the Cleveland Clinic (Benchmark XT, Ventana Medical Systems, Tucson AZ). Slides were scored independently in 10% increments by two pathologists, with a third review in case of disagreement of >20% for
all immunostains (mean score used as final value) except Ki67, for which image analysis (IA, Aperio, Scanscope) and a visual estimate (0=<10%, 1+=10-24%, 2+ - 25-49%, 3+=50-74%, 4+=75-100%) was used. A 30% cutoff for positive staining was used for CD10, BCL6, and MUM1, 40% was used for BCL2 and 60% for Ki67. Classification of tumor biopsies into GCB or non-GCB (i.e. ABC surrogate) subtypes was determined using CD10, BCL6, and MUM1 IHC markers by the validated method of Hans et al(22).

**Statistical analysis**

Overall (OS), time to progression (TTP) and event-free (EFS) survivals were calculated using the Kaplan-Meier method and the significance between Kaplan-Meier curves was calculated using log-rank procedure(23, 24). Survival endpoints were calculated from on-study date until death, relapse, progression or last follow-up as appropriate. For TTP, deaths among patients without progression or relapse were censored. IPI could not be determined in two patients due to missing data. Follow-up was calculated from study entry until death or close of study analysis for each patient. The analysis of biomarkers was not adjusted for multiple comparisons as they were prespecified(15). The SAS v9.2 (Cary, NC) statistical package was used for analyses. Patient registration and data collection were managed by the CALGB Statistical Center. Data quality was ensured by careful review of data by CALGB Statistical Center staff and by the study chairperson. CALGB statisticians performed all statistical analyses.
RESULTS

Clinical characteristics and outcome

Sixty-nine eligible patients with untreated DLBCL were enrolled (Table 1). The patients had a median age of 58 years (range 23-83), and 59% were in advanced stage, 72% had an elevated serum lactate dehydrogenase (LDH) level, and 40% had high-intermediate/high risk IPI scores (25). Overall, 58 (84%) patients achieved a complete response (CR), which includes those with CR unconfirmed, and 10 (15%) achieved a partial response (PR). Ten (17%) of the CR's and 3 (30%) of the PR's have relapsed, half of which occurred in patients with high IPI scores. All episodes of disease progression except one occurred within the first 1.6 years.

The median (range) follow-up of living patients is 5.2 (3.4-6.8) years. At five-years and beyond, the TTP, EFS and OS are 81%, 75% and 84%, respectively (Figure 1A, 1B, 1C). Three patients died without progression, one on treatment and two during follow-up from respiratory and cardiac failure. Only high IPI patients were at major risk of progression. At 5 years, the TTP was 54% in high IPI patients, whereas those with low/low-intermediate and high-intermediate IPI had low rates of progression with TTP of 87% and 92%, respectively (Figure 1D). Estimates of EFS and OS revealed similar findings (Figure 1E, 1F).
Clinical and biological prognostic factors

The IPI was significantly associated with TTP ($p = 0.0085$), EFS ($p < 0.0013$) and OS ($p < 0.0001$), which was all driven by the poorer outcome of high-risk patients. Biomarkers were also analyzed in tumor tissue from 52 (76%) patients. To accurately determine the prognostic influence of the cell of origin as defined by the GCB versus non-GCB (ABC surrogate) subgroups, the 10 patients with PMBL were excluded; 9 from the IHC group and one from the group without IHC (Table 1)(26). Patient characteristics were similar in the groups with and without tissue for IHC (Table 1). Tissue was analyzed with biomarkers of cellular differentiation (CD10, LMO2, BCL6, and MUM1), proliferation (Ki67) and apoptosis inhibition (BCL2), and categorized as GCB or non-GCB DLBCL by the Hans method (Table 2)(10, 14, 22). All survival endpoints were significantly worse in non-GCB compared to GCB DLBCL, though both groups fared well (Table 2; Figure 2A and 2B). Remarkably, no patients with GCB DLBCL progressed. To control for error in cell categorization by the Hans method, we also assessed outcome using individual markers of cellular differentiation. From 95 to 100% of patients with tumors that expressed LMO2 or CD10, specific markers of germinal center differentiation, are free of progression (Table 2). The less differentiation-specific markers for GCB and non-GCB DLBCL, BCL6 and MUM1, respectively, showed similar results (Table 2). Interestingly, while we observed a significant association between high tumor proliferation (Ki67 $\geq 60\%$) and survival outcomes, this was only seen in patients with non-GCB DLBCL (Table 2; Figure 2D, 2E and 2F). BCL2 expression was not associated with any survival outcome measure in the combined GCB and non-GCB DLBCL groups (Table 2) or in the non-GCB DLBCL group (data not shown). There
were too few events to construct a meaningful multivariate analysis that included IPI and biomarkers.

**Treatment and Toxicity**

Toxicity was assessed in all 69 patients on study. Sixty-three (91%) patients completed all treatment cycles. Fifty (72%) patients underwent at least one dose escalation to achieve a nadir ANC<500/µL, and 65 (94%) patients achieved the desired pharmacodynamic endpoint. Overall, 25 (36%) patients had fever with neutropenia, 5 (7%) of which were grade 4. Platelet and red cells transfusions were administered to 9 (13%) and 21 (30%) patients, respectively. Gastrointestinal toxicity, such as mucositis or nausea/vomiting, was infrequent and occurred in ≤5 patients. Similarly, there were infrequent cardiac events, and only included grade 3 arrhythmia in 4 patients. There was a relatively modest incidence of neuropathy given that vincristine was not capped. Overall, grade 3 motor or sensory neuropathies occurred in 10 (14%) and 7 (10%) patients, respectively, and one patient developed grade 4 motor neuropathy. Most patients experienced significant improvement following treatment. Grade 3 fatigue was observed in 11 (16%) patients. One patient died from a brain hemorrhage during the first cycle.
DISCUSSION

An important goal of this study was to determine if the outcome of the NCI trial of DA-EPOCH-R could be achieved in a multi-institutional setting(17). Indeed, the positive outcomes of other single institution studies using novel chemotherapy in aggressive lymphomas, including DLBCL, Burkitt lymphoma and mantle cell lymphoma, could not be confirmed by multi-institutional studies(1, 27, 28). In the present study, the TTP and OS were 81% and 84%, respectively, at 5-years with no late events. Notably, the outcome of DA-EPOCH-R was similar in the low/low-intermediate and high-intermediate IPI groups with 87% and 92% of patients, respectively, progression free at 5-years. Patients with high IPI had the least favorable outcome with a 5-year TTP of 54%. In the NCI trial of 72 patients, the 5-year TTP and OS were 79% and 80%, respectively, with a median follow-up of 54 months. The outcome by IPI was also similar in the NCI trial. Among patients with low/low-intermediate and high IPI, the 5-year TTP was 90% and 47%, respectively. Patients with high-intermediate IPI faired less well in the NCI trial with a 5-year TTP of 67%, but the results are within the confidence intervals of the present study. Notably, in another study of DA-EPOCH-R in high-intermediate and high IPI risk DLBCL, the EFS and OS were of 68% and 75%, respectively, at 2 years(29). The toxicity profile of DA-EPOCH-R was similar in the CALGB and NCI trials(17). Overall, 91% and 100% of patients in the CALGB and NCI trials, respectively, achieved ANC nadirs < 500 cells/µl, which is the pharmacodynamic endpoint. The incidence of fever and neutropenia was also similar and occurred in 36% and 47% of patients, respectively. The incidence of gastrointestinal side effects, neuropathy and fatigue were also similar between the two trials.
This CALGB trial provides further evidence that DA-EPOCH-R provides favorable outcomes in DLBCL. Although there are no comparable therapeutic trials with R-CHOP, two retrospective studies and four randomized studies provide outcome results with R-CHOP-based treatment in untreated DLBCL(4, 5, 30-33). Among these is a retrospective study from the British Columbia Cancer Agency of R-CHOP in 152 patients with a median age of 63 years and high-intermediate/high IPI in 49%(33). In this study, the 3-year progression free survival (defined as TTP) was 65%. In a follow-up paper, this group reported the outcome of R-CHOP at a median follow-up of 33 months using the standard and a revised IPI(34). Employing the standard IPI, they reported a 4-year PFS (TTP) of 57% and 51% for high-intermediate and high-risk patients. Among the high-risk patients, DA-EPOCH-R had a similar TTP of 54%, albeit with a significantly longer follow-up. In contrast, high-intermediate risk patients had an excellent TTP of 92% with DA-EPOCH-R. It should be noted that this study is limited by its short 2-year median follow-up and retrospective study design. The randomized MabThera International Trial (MInT) of R-CHOP versus CHOP-like treatments, which included radiotherapy in approximately half of patients, provides outcome results for patients ≤ 60 years with low (0-1) age-adjusted IPI(5). With a median follow-up of 34 months, the EFS was 75% at 4-years with R-CHOP. Patients on the DA-EPOCH-R study, however, were significantly poorer prognosis with 40% high-intermediate/high IPI and 43% greater than 60 years of age.

Analysis of biomarkers confirm previous findings that DA-EPOCH-R performs better in GCB compared to non-GCB DLBCL(17, 35). The robustness of these results is supported by the association of individual markers of cell of origin and outcome in the
present study. Our findings are also consistent with the study by Lenz et al that showed a significant association between outcome and GCB and ABC (i.e. non-GCB by IHC) DLBCL determined by GEP(36). Interestingly, unlike previous results with DA-EPOCH-R, we observed a significant association between high tumor proliferation and poorer outcome in the present study(16, 17, 35). However, the adverse effect of high tumor proliferation was only present in the non-GCB DLBCL group, which may explain the discordant results with our earlier trials. We did not find any association between BCL2 expression and outcome, which is similar to our previous results(17). It is now recognized that several mechanisms lead to BCL2 over expression and confer different prognoses, making it an unreliable biomarker of outcome(15, 37, 38).

The favorable outcome of GCB DLBCL as identified by the Hans algorithm in the present study is consistent with prior findings with DA-EPOCH-R(22). In the NCI phase II study of DA-EPOCH-R, GCB DLBCL had a 79% PFS at 5 years(17). Additionally, a NCI study of DA-EPOCH-R in HIV-associated DLBCL reported a 5-year PFS of 95% in patients with GCB DLBCL(35). Other studies employing the Hans algorithm suggest that GCB DLBCL does not have as favorable an outcome with R-CHOP(39, 40). In a recent study from the University of Barcelona, 149 patients with newly diagnosed DLBCL categorized by the Hans algorithm showed no difference in outcome between GCB and non-GCB DLBCL with a 5-year PFS of 54% and 52%, respectively(39). Analysis of the RICOVER-60 trial from the German High-Grade Lymphoma Study Group found a 5-year survival of approximately 50% and 58%, respectively, for GCB and non-GCB DLBCL(40). Furthermore, a trial in 131 patients from the University of Nebraska reported a 3-year EFS of 67% and 52% in GCB and non-GCB DLBCL, respectively(41).
It is notable that most clinical studies that have used IHC algorithms to categorize DLBCL as GCB or non-GCB DLBCL have not found a difference in outcome with R-CHOP based treatments (39-42). However, two clinical studies that employed GEP, the gold standard for molecular classification, have shown differences in outcome of GCB and ABC DLBCL with R-CHOP (36, 39). The reason for this discordance may be due to technical variability that might lower accuracy of IHC classification for GCB and ABC (i.e. non-GCB) DLBCL (43). Nonetheless, studies using IHC algorithms with DA-EPOCH-R have shown significantly better disease outcome in GCB compared to non-GCB DLBCL similar to the results with GEP (17, 35).

We hypothesize that the efficacy of DA-EPOCH-R in GCB-DLBCL may be related to its effect on BCL6 (44, 45). BCL6 is a key germinal center B-cell transcription factor that suppresses genes involved in lymphocyte activation, differentiation, cell cycle arrest (p21 and p27Kip1) and DNA damage response genes (p53 and ATR) (44). In GCB DLBCL, chromosomal translocations and/or somatic mutations affecting BCL6 enhance its inhibitory effect on the apoptotic stress response and promote proliferation, which are associated with treatment failure (14, 44, 46-48). Interestingly, inhibition of topoisomerase II leads to down regulation of BCL6 expression by ubiquitin-mediated protein degradation and possibly through transcriptional inhibition (49). This may partially account for the in vitro finding that sustained exposure of tumor cells to the topoisomerase inhibitors, etoposide and doxorubicin, promotes the p53-p21 pathway and activates the check-point kinase (Chk2), effects that are inhibited in cells engineered to over express BCL6 (50, 51). The association between topoisomerase II inhibition and BCL6 expression raises the hypothesis that regimens directed against topoisomerase II
may be more effective in GCB DLBCL. In this regard, DA-EPOCH-R was designed to inhibit topoisomerase II through several strategies: incorporates two topoisomerase II inhibitors, etoposide and doxorubicin; optimizes topoisomerase II inhibition through a prolonged 96-hour infusion; and maximizes steady state concentrations through pharmacodynamic dose adjustment(16).

The present study provides the first multi-institutional evidence that DA-EPOCH-R has a favorable outcome in newly diagnosed DLBCL, and confirms the biomarker results from the NCI study. DA-EPOCH-R compares favorably with historical data with R-CHOP, particularly for the treatment of GCB DLBCL. An ongoing phase III trial comparing the outcome of DA-EPOCH-R and R-CHOP in DLBCL within the GCB and ABC DLBCL molecular subtypes will provide a definitive comparison of these regimens (CALGB 50303).
AUTHORSHIP AND DISCLOSURES

Wyndham Wilson designed the study, analyzed and collected the data and wrote the study and manuscript. Sin-Ho Jung analyzed and collected the data and helped write the manuscript. Pierluigi Porcu performed the research and reviewed the manuscript. David Hurd performed the research and reviewed the manuscript. Jeffrey Johnson analyzed and collected the data and reviewed the manuscript. S. Eric Martin performed the research and reviewed the manuscript. Myron Czuczman performed the research and reviewed the manuscript. Raymond Lai performed research on specimens performed the research and reviewed the manuscript. Jonathan Said performed the research and reviewed the manuscript. Amy Chadburn performed the research and reviewed the manuscript. Dan Jones performed the research and reviewed the manuscript. Kieron Dunleavy reviewed and analyzed data and reviewed the manuscript. George Canellos helped conceive the study and reviewed the manuscript. Andrew Zelenetz helped conceive the study and reviewed the manuscript. Bruce D. Cheson performed the research and reviewed the manuscript. Eric Hsi performed the research, analyzed data and helped write the manuscript. The authors have no conflict of interest disclosures.
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of ATM/ATR. Biochemical and Biophysical Research Communications. 2001;289(5):1199-204.

Table 1. Patient Characteristics.

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>All Patients</th>
<th>Patients With Biomarkers Excluding PMBL</th>
<th>Patients Without Biomarkers Excluding PMBL</th>
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<tr>
<td></td>
<td>No.</td>
<td>%</td>
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</tr>
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<tr>
<td>PMBL</td>
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<tr>
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<tr>
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<tr>
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PMBL-Primary mediastinal B-cell lymphoma; DLBCL-Diffuse large B-cell lymphoma; NOS-Not otherwise specified; ECOG-Eastern Cooperative Oncology Group; LDH: Lactate dehydrogenase; IPI: International prognostic index.

1No significant difference in distribution of patient characteristics among patients with or without tissue for biomarker analysis.
2Two patients missing values for number of extra-nodal sites and IPI.
Table 2. Biomarkers in GCB and non-GCB DLBCL and outcome.

<table>
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<tr>
<th>Characteristics</th>
<th>No.</th>
<th>%</th>
<th>(^1)TTP % 5 years (95% CI)</th>
<th>(^2)P</th>
<th>(^1)EFS % 5 years (95% CI)</th>
<th>(^2)P</th>
<th>(^1)OS % 5 years (95% CI)</th>
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<tr>
<td>&lt; 30%</td>
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<td>71</td>
<td>0.75 (0.55, 0.87)</td>
<td>0.06</td>
<td>0.66 (0.45, 0.80)</td>
<td>0.02</td>
<td>0.72 (0.52, 0.85)</td>
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<td>≥ 30%</td>
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<td>29</td>
<td>1.00 (---)</td>
<td>6</td>
<td>1.00 (---)</td>
<td>7</td>
<td>1.00 (---)</td>
<td>3</td>
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<td>0%</td>
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<td>0.05</td>
<td>0.65 (0.40, 0.82)</td>
<td>0.04</td>
<td>0.75 (0.50, 0.89)</td>
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<td>21</td>
<td>51</td>
<td>0.95 (0.71, 0.99)</td>
<td>8</td>
<td>0.90 (0.67, 0.98)</td>
<td>6</td>
<td>0.90 (0.67, 0.98)</td>
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<tr>
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<tr>
<td>&lt; 30%</td>
<td>22</td>
<td>61</td>
<td>0.76 (0.52, 0.89)</td>
<td>0.19</td>
<td>68 (0.45, 0.83)</td>
<td>0.21</td>
<td>0.77 (0.54, 0.90)</td>
<td>0.49</td>
</tr>
<tr>
<td>≥ 30%</td>
<td>14</td>
<td>39</td>
<td>0.93 (0.59, 0.99)</td>
<td>8</td>
<td>86 (0.54, 0.96)</td>
<td>0</td>
<td>0.86 (0.54, 0.96)</td>
<td>7</td>
</tr>
<tr>
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<tr>
<td>&lt; 30%</td>
<td>36</td>
<td>88</td>
<td>0.89 (0.72, 0.96)</td>
<td>0.00</td>
<td>83 (0.66, 0.92)</td>
<td>0.00</td>
<td>0.86 (0.70, 0.94)</td>
<td>0.01</td>
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<tr>
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<td>12</td>
<td>0.40 (0.05, 0.75)</td>
<td>5</td>
<td>20 (0.01, 0.58)</td>
<td>1</td>
<td>0.40 (0.05, 0.75)</td>
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<tr>
<td>GCB</td>
<td>18</td>
<td>49</td>
<td>100 (---)</td>
<td>0.00</td>
<td>0.94 (0.65,0.99)</td>
<td>0.00</td>
<td>0.94 (0.65,0.99)</td>
<td>0.04</td>
</tr>
<tr>
<td>Non-GCB</td>
<td>19</td>
<td>51</td>
<td>0.67 (0.40, 0.83)</td>
<td>8</td>
<td>0.58 (0.33, 0.76)</td>
<td>8</td>
<td>0.68 (0.43, 0.84)</td>
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<tr>
<td>&lt; 60%</td>
<td>26</td>
<td>65</td>
<td>0.92 (0.72, 0.98)</td>
<td>0.02</td>
<td>0.84 (0.64, 0.94)</td>
<td>0.04</td>
<td>0.88 (0.68, 0.96)</td>
<td>0.06</td>
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<tr>
<td>≥ 60%</td>
<td>14</td>
<td>35</td>
<td>0.64 (0.34, 0.83)</td>
<td>0</td>
<td>0.57 (0.28, 0.78)</td>
<td>2</td>
<td>0.64 (0.34, 0.83)</td>
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<tr>
<td>BCL2</td>
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<tr>
<td>&lt; 30%</td>
<td>15</td>
<td>36</td>
<td>0.93 (0.61, 0.99)</td>
<td>0.19</td>
<td>0.87 (0.56, 0.96)</td>
<td>0.23</td>
<td>0.86 (0.56, 0.96)</td>
<td>0.46</td>
</tr>
<tr>
<td>≥ 30%</td>
<td>27</td>
<td>64</td>
<td>0.77 (0.56, 0.89)</td>
<td>6</td>
<td>0.70 (0.49, 0.84)</td>
<td>2</td>
<td>0.78 (0.57, 0.89)</td>
<td>5</td>
</tr>
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</table>

\(^1\)Kaplan-Meier estimates at 5 years. \(^2\)P = two-tailed p-value, derived from log-rank test based on Kaplan-Meier curves. Abbreviations: TTP: Time to progression; OS: Overall survival; GCB DLBCL: Germinal Center B-cell diffuse large B-cell lymphoma.
FIGURE LEGENDS

Figure 1. Kaplan-Meier Plots of Survival Outcomes of All Patients. Outcomes are reported at 5-years (95% Confidence Interval (CI)) and CI range is shown on the curves. A. PFS 81% (69, 88). B. EFS 75% (63, 84). C. OS 84% (73, 91). D. PFS for IPI risk groups: low/low-intermediate ( ) 87% (72, 94), high-intermediate ( ) 92% (57, 99) and high risk ( ) 54% (25, 76)(p=0.0085). E. EFS for IPI risk groups: low/low-intermediate 85% (69, 93), high-intermediate 85% (51, 96) and high risk 43% (18, 66)(p<0.0013). F. OS for IPI risk groups: low/low-intermediate 95% (80, 99), high-intermediate 92% (57, 99) and high risk 43% (18, 66)(p<0.0001).

Figure 2. Kaplan-Meier Plots of Survival Outcomes Patients with Biomarkers. A. PFS of GCB ( ) and non-GCB ( ) DLBCL (p=0.008). B. EFS of GCB and non-GCB DLBCL (p=0.008). C. OS of GCB and non-GCB DLBCL (p=0.04). D. PFS of Ki67 < 60% ( ) and Ki67 ≥ 60% ( ) in non-GCB DLBCL (p=0.03). E. EFS of Ki67 < 60% and Ki67 ≥ 60% in non-GCB DLBCL (p=0.04). F. OS of Ki67 < 60% and Ki67 ≥ 60% in non-GCB DLBCL (p=0.05).
Figure 1

A. Time to Progression

B. Event-Free Survival

C. Overall Survival

D. Time to Progression by IPI

E. Event-Free Survival by IPI

F. Overall Survival by IPI