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A phase 1/2 study of lenalidomide and obinutuzumab with CHOP for newly diagnosed DLBCL

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Key Points

- Lenalidomide, obintuzumab, and CHOP chemotherapy are efficacious and well tolerated treatments for newly diagnosed DLBCL.
- LO-CHOP led to high molecular response rates based on circulating tumor DNA sequencing during and after treatment in this phase 1b/2 study.

Diffuse large B-cell lymphoma (DLBCL) can be cured with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP); however, one-third of patients experience refractory or relapsed disease. Studies comparing R-CHOP with modified regimens replacing R with obinutuzumab (O) or adding lenalidomide (L) did not result in improved outcomes; however, L and O together may enhance natural killer-cell mediated antibody-dependent cellular toxicity when paired with CHOP. Here, we report on a phase 1b/2 study of 53 patients with newly diagnosed DLBCL who received 6 cycles of LO-CHOP. The end of treatment overall and complete response rates of the 50 evaluable patients were 98% and 90%, respectively. After a median follow-up of 4.5 years, the 4-year progression free and overall survival rates were 87.4% and 91.3%, respectively. Grade 3 to 4 adverse events were experienced by 70% of patients, including neutropenia (38%), thrombocytopenia (17%), fatigue (13%), and neutropenic fever (13%). Of the 33 patients profiled with circulating tumor DNA (ctDNA) sequencing, 31 (94%) had detectable pretreatment ctDNA with cancer personalized profiling by deep sequencing, 24 (73%) were classifiable by the LymphGen classifier, and 15/20 (75%) and 12/17 (71%) patients achieved early and major molecular responses after 1 and 2 cycles, respectively. Using phased variant enrichment and detection sequencing, 16/18 evaluable patients (89%) showed no detectable ctDNA after at least 5 cycles of LO-CHOP. LO-CHOP demonstrates high efficacy and tolerability in newly diagnosed DLBCL, leading to a high rate of undetectable minimal residual disease by ctDNA. This trial has been registered at www.clinicaltrials.gov as NCT02529852.

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Data are available on request from the corresponding author, Jason R. Westin (jwestin@mdanderson.org).

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Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of lymphoma,[1] cured in approximately two-thirds of newly diagnosed patients with the immunochemotherapy regimen of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP).[2,3] Multiple randomized studies investigating the addition of novel agents to the R-CHOP backbone have not definitively improved on R-CHOP as the prevailing standard-of-care frontline regimen[4-8] before the recent POLARIX trial.[9] The replacement of vincristine with the antibody-drug conjugate polatuzumab vedotin led to a modest progression free survival (PFS) improvement over R-CHOP for intermediate and high-risk disease, representing a shift in the preferred treatment of some patients.

Notable previous studies comparing R-CHOP to modified regimens include the GOYA trial (Obinutuzumab [O] with CHOP)[6] and the ROBUST[7] and Eastern Cooperative Oncology Group-ACRIN E1412[8] trials (lenalidomide [L] with R-CHOP). O is a glycoengineered type II antibody targeting CD20 that induces improved antibody-dependent cellular cytotoxicity, phagocytosis, and direct cell death compared with rituximab.[10,11] The GOYA study was a randomized phase 3 trial that compared O-CHOP to R-CHOP in patients with untreated DLBCL. No difference was observed in the three-year PFS rates (70% vs 67%), response rates, or overall survival (OS), however, grade 3 to 5 adverse events (AEs) and discontinuation of any component of therapy were more common with O-CHOP.[6]

L is an immunomodulatory agent that activates interferon signaling, inhibits the NF-κβ pathway,[12] and promotes natural killer (NK) cell activity.[13] In the setting of relapsed and refractory DLBCL, L monotherapy has shown activity, particularly for the activated B-cell (ABC) subtype.[14] ROBUST was a phase 3 trial that randomized patients with treatment-naïve ABC DLBCL to LR-CHOP or R-CHOP. PFS and OS were not significantly different between the 2 arms; however, hematologic toxicities were more common with the addition of L. E1412 was a randomized phase 2 study that assigned patients with any subtype of untreated DLBCL to either LR-CHOP or R-CHOP. PFS was greater with LR-CHOP than with R-CHOP, with a hazard ratio of 0.67 and a 95% confidence interval (CI) of 0.44 to 1.03. The factors influencing the differential outcomes between these 2 trials may include a greater enrichment of high-risk patients in the E1412 study,[15] differences in L administration, time to treatment, or other study population differences.

Neither O nor L alone have been adopted as part of frontline DLBCL therapy; however, the 2 agents may demonstrate synergistic activity when combined. The GALEN study investigated this combination in patients with relapsed or refractory follicular lymphoma[16] or DLBCL,[17] leading to overall response rates (ORR) of 81% and 35%, respectively. Excluding DLBCL patients with disease refractory to the last therapy or autologous stem cell transplant, the ORR was 61%, with a median PFS of 11.7 months. Patients treated with the combination experienced activation of NK cells and reversal of an immature NK cell phenotype as determined by cell surface markers.[18] Administering the combination to newly diagnosed follicular lymphoma patients led to an ORR of 94%.[19] We hypothesized that combining L and O with CHOP chemotherapy would demonstrate high efficacy with a tolerable toxicity profile. Herein, we report the results of a phase 1b/2 single center clinical trial (NCT02529852) evaluating LO-CHOP for the treatment of patients with newly diagnosed DLBCL. Circulating tumor DNA (ctDNA) profiling was performed to measure the baseline tumor burden, molecular response, and molecular subtypes.

Methods

Study design

This investigator initiated, open label, single-arm phase 1b/2 study was conducted at the University of Texas MD Anderson Cancer Center. The primary end point of the phase Ib portion was to evaluate the safety of LO-CHOP and the primary end point of the phase 2 portion was to evaluate the clinical efficacy of LO-CHOP at the end of therapy. The safety evaluation in phase 1b was defined as the lack of any grade ≥3 nonhematologic toxicity unmanageable with aggressive supportive care or toxicity, resulting in a delay of over 7 days of cycle 2. The efficacy evaluation in phase 2 was defined as the ORR and complete response rate (CRR) at the end of therapy assessment with positron emission tomography/computed tomography (PET/CT) imaging, as defined by the Lugano 2014 classification.[20] Secondary endpoints for the study included rates of AEs, PFS, and OS. PFS was defined as the time from the start of therapy until the date of disease progression or death as a result of any cause and censored at the last follow-up date in disease remission, and OS was defined as the time from the start of therapy until the date of death as a result of any cause and censored at the last follow-up date while alive. AEs were defined according to the National Cancer Institute Common Terminology Criteria for Adverse Events v4.0. This study was approved by the Institutional Review Board of the MD Anderson Cancer Center under protocol 2015-0069 and conducted in accordance with the Declaration of Helsinki.

Key eligibility criteria

Eligible patients were aged ≥18 years with newly diagnosed untreated CD20+ DLBCL. Patients with stage I DLBCL were eligible only if 6 cycles of chemotherapy were planned. Measurable disease of at least 1.5 cm in longest diameter on imaging was required, as was an Eastern Cooperative Oncology Group performance status of 2 or less, unless the previously performance status was 0 to 1 and deterioration was felt to be due to lymphoma and reversible with therapy. Patients were required to have adequate organ and bone marrow function. Patients were ineligible if they were pregnant or nursing women, had a prior diagnosis of low-grade lymphoma, had central nervous system involvement, active HIV infection, active Hepatitis B or C infection, or were unwilling to take aspirin for venous thrombosis prophylaxis.

Pathology review

All diagnostic tumor biopsies were reviewed by expert hematopathologists at the University of Texas MD Anderson Cancer Center for confirmation of DLBCL using the standard WHO diagnostic criteria. The cell of origin (COO) was determined via immunohistochemistry (IHC) using the Hans algorithm.[21] When adequate tissue was available for standard testing, double expressor lymphoma was defined as positivity by IHC staining for MYC and BCL2, and double-hit lymphoma was defined as DLBCL

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with a rearrangement of *MYC* with concurrent rearrangement of *BCL2* and/or *BCL6* by fluorescence in situ hybridization.

Treatment

Patients were treated with L 15 mg orally daily on days 1 through 14 of each 21-day cycle, O 1000 mg intravenously on days 1, 8, and 15 of cycle 1 and day 1 only for all additional cycles, and standard CHOP (cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, vincristine 1.4 mg/m^2 [capped at 2.0 mg], and prednisone 100 mg by mouth daily on days 1 through 5) starting on day 1 of all cycles. Hematologic AEs that required dose reduction of L were recurrent grade 3 neutropenia (sustained for ≥7 days or with fever), recurrent grade 4 neutropenia, or recurrent grade ≥3 thrombocytopenia. All patients were scheduled to receive 6 cycles if no progression occurred, and no maintenance therapy was administered. All patients were required to receive granulocyte colony stimulating factor, aspirin 81 mg if not already receiving anticoagulation, and *Pneumocystis jirovecii* pneumonia prophylaxis therapy. Intrathecal chemotherapy was allowed if the treating physician deemed the patient at risk for central nervous system involvement because of standard risk factors.[22]

ctDNA profiling

Plasma samples were collected in EDTA tubes. Cell-free DNA (cfDNA) was extracted from 1 to 5 mL of plasma using a Qiagen QIAamp Circulating Nucleic Acid Kit. Somatic alterations were called from cfDNA using cancer personalized profiling by deep sequencing, as previously described.[23-26] Hybrid-capture was performed using targeted panels optimized for B-cell lymphomas. Quantitative levels of ctDNA were measured in haploid genome equivalents per milliliter (hGE/mL), determined as the product of total cfDNA concentration and the mean allele fraction of somatic mutations, expressed in log scale (log hGE/mL), as previously reported.[25,27] Patients with ≥20 coding and silent mutations detected by noninvasive genotyping were subjected to genotypic classification using the LymphGen online tool (https://llmpp.nih.gov/lymphgen/index.php).[28] For this purpose, mutations were integrated with genome-wide copy number alterations called from on- and off-target sequencing reads as previously described.[26]

We applied "phased variant enrichment and detection sequencing" (PhasED-Seq) to track minimal residual disease (MRD) in on-treatment samples[29] from patients with available baseline samples. Patients were stratified using previously established molecular milestones, where early molecular response (EMR) was defined as a 2 log drop in ctDNA after 1 cycle of therapy, and major molecular response (MMR) as a 2.5 log drop in ctDNA after 2 cycles of therapy.[25]

Statistical considerations

Descriptive statistics were used to define baseline characteristics and treatment response/outcomes. Fisher exact test and Wilcoxon rank-sum test were used to evaluate the association between the end of therapy response with categorical variables and continuous variables, respectively. The Kaplan-Meier method was used to estimate the probabilities of PFS/OS, and the log-rank test was used to evaluate differences in PFS/OS. The cox proportional hazards model was used to estimate the hazard ratio for the covariates. Statistical software used included SAS 9.4 (SAS Institute Inc, Cary, NC), S-Plus 8.2 (TIBCO Software Inc, Palo Alto, CA), and R 4.1.2 (R Core Team, Vienna, Austria).

Results

Patients

Fifty-three patients were enrolled, 6 in the phase 1b portion and 47 in the phase 2 portion. Patients started treatment between 12 November 2015 and 30 March 2017. The median patient age was 62 years (range 26-83), 35 (66%) had stage III/IV disease, 26 (49%) had elevated lactate dehydrogenase, 12 (23%) had an international prognostic index (IPI) >2, 26 (49%) had germinal center (GC), 22 (42%) had non-GC subtype, and 5 were unable to be subtyped. Detailed baseline characteristics are summarized in Table 1.

Safety

Treatment related AEs occurred in all patients, and 37 (70%) patients experienced at least 1 grade 3 to 4 treatment related AE. None of the patients experienced fatal AE. There were no dose limiting toxicities for the 6 patients enrolled in the phase I\1b portion at a maximum tolerated dose of L at 15 mg. Common any grade AEs included fatigue (96%), constipation (85%), nausea (72%), anemia (62%), myalgia (59%), and dizziness (57%). Common grade 3 to 4 AEs included neutropenia (38%), thrombocytopenia (17%), fatigue (13%), febrile neutropenia (13%), and

Table 1. Baseline patient characteristics

Characteristics	All patients [N = 53], N (%)
Median age, y (range)	62 (26-83)
Age >60 y	28 (53)
Male sex	30 (57)
Ann Arbor stage	
I	2 (4)
II	16 (30)
III	18 (34)
IV	17 (32)
Extranodal sites >1	4 (8)
ECOG performance status	
0	24 (45)
1	27 (51)
2	2 (4)
Lactate dehydrogenase > upper limit normal	26 (49)
IPI	
0	2 (4)
1-2	39 (74)
3-4	12 (23)
Bulky disease >10 cm	5 (9)
Double expressor lymphoma (N = 32)	9 (28)
Double hit lymphoma (N = 34)	3 (9)
Cell-of-origin	
GCB	26 (49)
Non-GCB	22 (42)
NA	5 (9)

ECOG, Eastern Cooperative Oncology Group; GCB, germinal center B-cell; N, number; NA, not applicable.

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Table 2. Summary of grade 3 to 4 treatment emergent AEs (≥5%) and AEs of interest

AE	Any grade	Grade 3-4
Most common AEs		
Neutropenia	21 (40)	20 (38)
Thrombocytopenia	15 (28)	9 (17)
Fatigue	51 (96)	7 (13)
Febrile neutropenia	7 (13)	7 (13)
Infection	12 (23)	5 (9)
Myalgia	31 (59)	4 (8)
Pain	18 (34)	3 (6)
AEs of interest		
Constipation	45 (85)	1 (2)
Nausea	38 (72)	2 (4)
Anemia	33 (62)	1 (2)
Peripheral sensory neuropathy	22 (42)	1 (2)
Diarrhea	21 (40)	1 (2)
Venous thromboembolism	4 (8)	0 (0)

infection (9%). Grades 3 to 4 infections included cellulitis, urinary tract infection, pneumonia, and *Clostridium difficile* colitis. Four patients (8%) experienced thromboembolism. The AEs are summarized in Table 2.

Because of AEs, 23 (43%) patients experienced L interruption (mainly owing to midcycle neutropenia or thrombocytopenia), 11 (21%) required a dose reduction of L, and 3 (6%) discontinued L. One patient required a delay of >7 days in their next cycle of LO-CHOP. The reasons for dose reduction were as follows: recurrent grade ≥3 neutropenia in 6 patients, and 1 patient each experienced a single episode of concurrent grade ≥3 neutropenia and thrombocytopenia, a single episode of febrile neutropenia, colitis, hospitalization for weakness, and recurrent infections. Of the 3 patients who discontinued L for AEs, 1 patient discontinued after 5 cycles and still completed a sixth cycle of O-CHOP, 1 patient came off the study after 3 cycles and completed another 3 cycles of R-CHOP without vincristine, and 1 patient discontinued therapy after 1 cycle.

Efficacy

Fifty-one patients were evaluated using interim PET/CT after 2 cycles of LO-CHOP (2 patients could not be evaluated because of study withdrawal, 1 because of AEs, and 1 per patient preference). The ORR was 51/51 (100%) at the interim assessment and the CRR was 43/51 (84%; 95% CI, 71-93) whereas the partial response rate was 8/51 (16%). Fifty patients were evaluated at the end of therapy after 6 cycles of LO-CHOP with PET/CT (an additional patient withdrew because of AEs). The ORR at the end of therapy was 49/50 (98%; 95% CI, 89-100) and 45/50 (90%; 95% CI, 78-97), 4 (8%), and 1 (2%) patient experienced CR, partial response, or progressive disease, respectively.

After a median follow-up of 4.5 years (range 1.1-5.8), 6 patients experienced disease progression or relapse, and 4 patients died. The median PFS and OS were not reached, and the 4-year PFS and OS rates were 87.4% (95% CI, 78.4-97.5) and 91.3% (95% CI, 83.5-99.9), respectively (Figure 1A-B). Two patients received high dose chemotherapy, followed by autologous stem cell transplant after progression. No baseline patient or disease characteristics were associated with the ORR, CRR, PFS, or OS. The causes of death were progressive lymphoma, transformed myelodysplastic syndrome, cerebrovascular accident, and unknown.

ctDNA profiling

Baseline plasma samples were retrieved from of 33/53 patients (62%). A total of 31/33 (94%) of the profiled patients had baseline ctDNA detectable with cancer personalized profiling by deep sequencing. The median baseline log ctDNA concentration was 2.02 log hGE/mL (range 0-3.29), and 8/33 (24%) of the patients had high baseline ctDNA levels by a previously established threshold of 2.5 log hGE/mL.[25,27] Nine patients were not evaluable for genotyping and molecular response assessment owing to low pretreatment ctDNA levels, which, in the absence of matched tumor tissue, precluded the identification of sufficient reporters. Of these, only 1 patient experienced a PFS event during follow-up at 3.8 years, reflective of the overall favorable risk profile of patients with low levels of pretreatment ctDNA. A total of 24/33 (73%) patients were successfully evaluated using the LymphGen

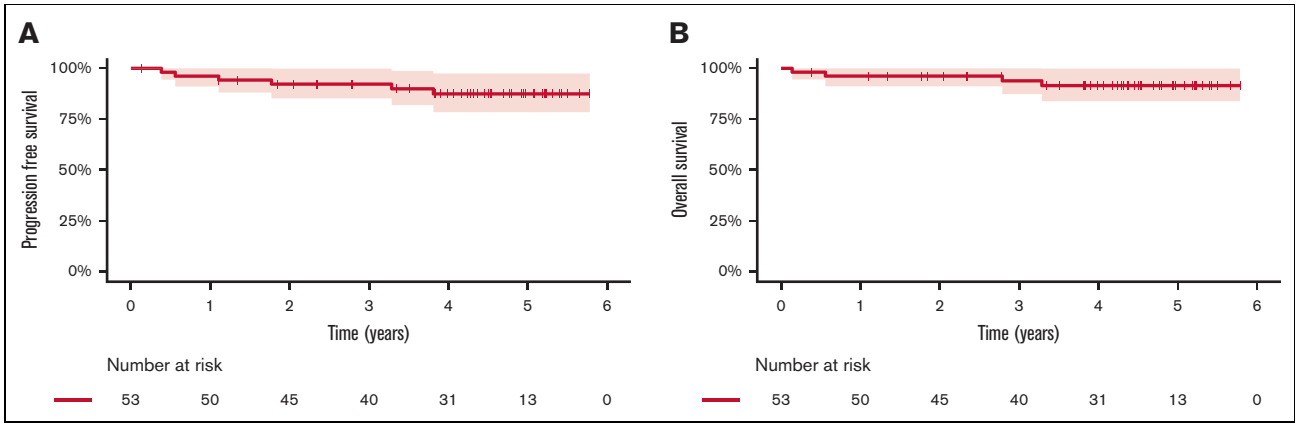

Figure 1. Time-to-event survival outcomes. PFS (A) and OS (B) of the entire cohort.

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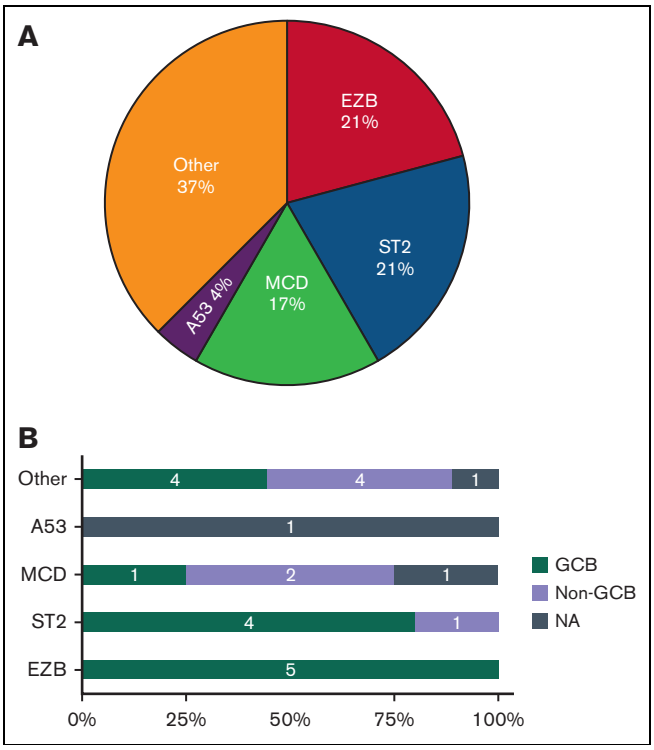

Figure 2. Description of molecular subtypes by LymphGen classifier. Frequency of molecular subtypes (A). Prevalence of COO subtypes within molecular subtypes (B).

classifier. Molecular subtypes, in order of decreasing prevalence, included other (9, 38%), EZB (5, 21%), ST2 (5, 21%), MCD (4, 17%), and A53 (1, 4%) (Figure 2A). Two patients had composite subtypes (EZB/ST2 and EZB/A53), and were classified as EZB here. As expected, all 5 EZB and 4/5 ST2-classified patients were classified as having the GC subtype, whereas only 2/4 MCD patients were non-GC according to the Hans algorithm. The genotypes of the 2 remaining patients with MCD were manually reviewed, and their classification as MCD was deemed appropriate based on the presence of canonical hotspot mutations, suggesting that these cases may have been misclassified as COO by IHC. The prevalence of COO subgroups within each genetic subtype is shown in Figure 2B.

The samples used to evaluate EMR and MMR were available for 20 and 17 of the 24 eligible patients, respectively. The EMR and MMR rates were 15/20 (75%) and 12/17 (71%) (Figure 3A-B). Among the 15 patients evaluable for both EMR and MMR, the concordance between the 2 endpoints was 13/15 (87%). The fold change in ctDNA levels through all time points is depicted in Figure 3C. Of the 3 profiled cases with progression/relapse events, 1 did not achieve EMR and MMR, 1 initially cleared their ctDNA at the EMR and MMR time points but had detectable ctDNA after cycle 3, and 1 did not have detectable pretreatment ctDNA. These patients did not have the end of treatment samples available. A total of 18 patients were evaluated for ctDNA assessment after at least 5 cycles of therapy. Of these, 16 (89%) were undetectable for ctDNA by PhasED-seq, whereas 2 patients had detectable ctDNA at this late time point; one of these patients was diagnosed with a previously unknown concurrent localized follicular lymphoma after the end of therapy, which was successfully treated with radiation alone, and had not experienced relapse of DLBCL or follicular lymphoma. The other patient remained in CR with 55 months of follow-up after achieving EMR, with a 700-fold reduction in the tumor burden during LO-CHOP. No ctDNA-based characteristics, including molecular subtype, EMR, MMR, or late time point MRD by PhasED-Seq, were associated with significant differences in response rates, PFS, or OS in the profiled patients.

Discussion

The combination of L and O with CHOP chemotherapy in this phase 1b/2 study for the treatment of newly diagnosed DLBCL was highly efficacious, leading to end of therapy overall and CR rates of 96% and 90%, and 4-year PFS and OS rates of 87% and 91%, respectively. LO-CHOP was similarly efficacious in high-risk patient subsets, including those with elevated IPI, non-GCB COO, high pretreatment ctDNA levels, and MCD and EZB molecular subtypes.[28] Rates of EMR and MMR after 1 or 2 cycles of LO-CHOP were 75% and 71%, respectively, with high concordance between these 2 endpoints in patients with both assessments performed. Encouragingly, end of therapy assessment with PhasED-seq demonstrated a high rate of undetectable MRD (89%), with 1 detectable patient being diagnosed with indolent lymphoma after therapy. Here, we demonstrate that targeted ctDNA sequencing allows for noninvasive molecular classification of patients treated in a prospective clinical trial by genetic subtype.

The safety profile of LO-CHOP did not result in any unexpected toxicities; with mandated growth factor support, the rate of grade 3 to 4 AEs, such as neutropenia, thrombocytopenia, and febrile neutropenia, compared favorably to those seen in LR-CHOP and O-CHOP treated patients.[6-8] The rate of any-grade thromboembolism may have been higher than that in the ROBUST study, although it is difficult to draw conclusions with small patient numbers. The rates of AEs of any grade, such as fatigue, nausea, and constipation, were higher than expected, but a lack of dose limiting toxicities, low rate of treatment discontinuation or delay, and similar incidence of cytopenias compared with other studies suggest that this discrepancy could be related to differences in reporting rather than excessive toxicity compared with R-CHOP or LR-CHOP.

The limitations of this study stemmed from its single-arm design. Without a comparator arm, we could not determine whether LO-CHOP could improve the efficacy compared with R-CHOP. The low number of progression events precluded the analysis of baseline or molecular characteristics, leading to the differential efficacy of LO-CHOP, including ctDNA sequencing. Only 3 patients who experienced disease progression had ctDNA profiled. Furthermore, our cohort was a relatively low-risk population with a lower proportion of patients with negative prognostic features such as advanced stage, elevated lactate dehydrogenase, extranodal sites, or IPI score.

The GOYA, E1412, and ROBUST studies did not support the replacement of R-CHOP as the standard treatment for newly diagnosed DLBCL. Other randomized studies evaluating the

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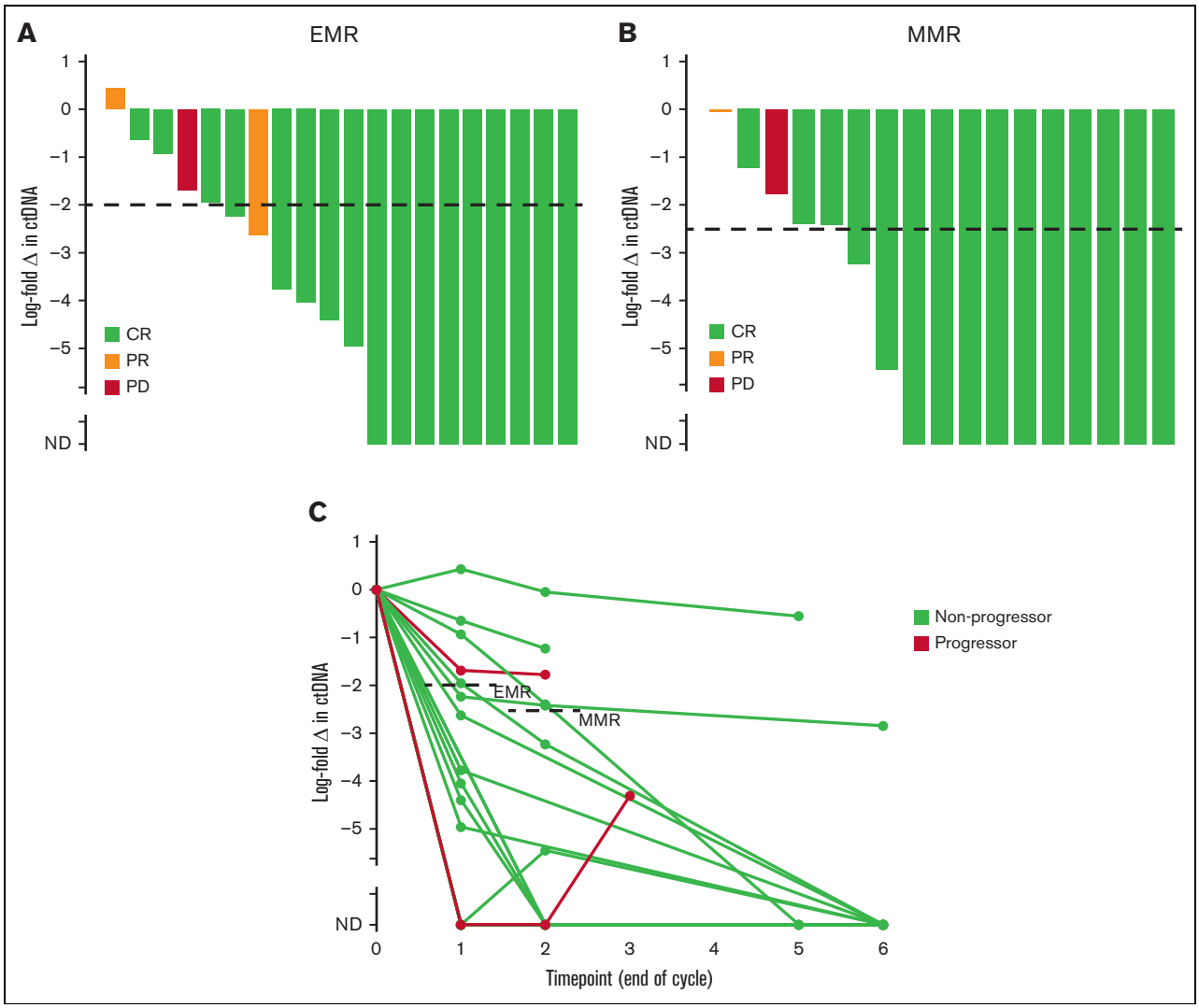

Figure 3. ctDNA-defined molecular response dynamics. Waterfall plots depicting the log-fold change in ctDNA levels from pretreatment to after cycle 1 (A) and after cycle 2 (B). Bars are colored in accordance with the end-of-therapy response. Dashed lines signify the EMR (2 log-fold decrease) and MMR (2.5 log-fold decrease) thresholds. Spider plot (C) depicting ctDNA level dynamics across all time points when the samples were available. Lines are colored in accordance with disease status at time of data censoring. The dashed lines signify the EMR and MMR thresholds at their respective time points. ND, not detected.

additive benefits of L in frontline therapy include the REMARC[30] and SENIOR[31] studies. The former found that L maintenance after R-CHOP in elderly patients improved PFS but not OS, whereas the latter demonstrated that the addition of L to dose-reduced R-CHOP (R-miniCHOP) in elderly patients did not improve PFS or OS. Despite the high-efficacy of LO-CHOP in this study, based on the published results of other trials, it appears that L and O, on their own or in combination, may still be better reserved for the treatment of indolent lymphomas.[16,19,32-35] Encouraging single-arm phase 2 results when adding novel agents to R-CHOP has not been translated into positive phase 3 studies in most cases, potentially because of patient selection pitfalls and failure to enrich high-risk patients.[36,37] Although the patients treated in the current study achieved excellent outcomes, it is not clear how this would have differed from treatment with R-CHOP.

Emerging evidence suggests that transcriptionally and genetically defined DLBCL subtypes do not only have prognostic and predictive significances. Although the PFS improvement with the use of polatuzumab vedotin over vincristine was only 6.5% in the full POLARIX study cohort, the effect was more pronounced in the ABC subset.[9] Similarly, MCD and BN2 subtypes may be more susceptible to transcriptional changes induced by L or B-cell receptor signaling inhibition through ibrutinib.[28,38] Of note, none of the 4 MCD patients in this study progressed. In the future, treatment may be guided by molecular profiling.

Although studies targeting molecular subgroups to date have uniformly utilized tumor tissue for this purpose,[4,5,7,38] liquid biopsies have several advantages. For example, liquid biopsies could facilitate molecularly-guided studies, given their noninvasive character, better capture of tumor heterogeneity, and allow access

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to abundant fresh, nonfixed specimens exclusively dedicated to molecular analyses. Separately, molecular response assessment using ctDNA may prove to be an effective early surrogate end point to uncover differences in efficacy and lead to accelerated decision making and drug approval.[39]

A limitation of studies abstaining from tumor tissue is that sufficient levels of pretreatment ctDNA are needed for the de novo identification of somatic alterations. Specifically, ctDNA assays typically require variant allele frequencies of ≥0.5% to reliably call mutations.[40] This is especially relevant for lower-risk cohorts, such as those in which only 24% of profiled patients had high ctDNA levels, compared with ~40% to 50% in previous cohorts.[25,27] Therefore, a fully noninvasive approach carries the risk of excluding cases with low baseline ctDNA levels from downstream analyses, which may ultimately require the integration of plasma and tumor sequencing in a subset of cases.

Leveraging synergistic combinations of novel agents to exploit synthetic lethality[12] may be more effective than adding "X" novel agent alone to R-CHOP if additional toxicity can be managed. Promising combination regimens include tafasitamab and L with R-CHOP[41,42] and ibrutinib and L with R-CHOP.[43]

In summary, LO-CHOP as a modified frontline regimen for DLBCL in this single-arm phase 1b/2 study showed high rates of radiographic and molecular responses, durable remission with long-term follow-up, and an expected safety profile. The design approaches included in this study, including novel-novel combinations and ctDNA-based genetic classification, may be essential to further improve frontline therapy in DLBCL.

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Authorship

Contribution: H.-J.J.C., S.K.A., A.F.M.C., and C.W.M. collected and analyzed data; H.-J.J.C. and S.A. wrote the manuscript; Y.O., L.J.N., L.F., S.S.N., F.T., F.H., M.A.R., H.J.L., and C.R.F. cared for patients and critically reviewed the manuscript; S.K.A., A.F.M.C., C.W.M., M.R.G., A.A.A., and R.E.D. performed experiments; T.J.M. and F.V. performed histopathologic analysis; L.F. analyzed data; J.R.W. designed the study, collected and analyzed data, and wrote the manuscript; and all authors approved the final version of the manuscript.

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