blood advances

American Society of Hematology
2021 L Street NW, Suite 900,
Washington, DC 20036
Phone: 202-776-0544 | Fax 202-776-0545
bloodadvances@hematology.org

Defining Primary Refractory Large B-cell Lymphoma

Tracking no: ADV-2024-012760R1

Allison Bock (Huntsman Cancer Institute/University of Utah, United States) Raphael Mwangi (Mayo Clinic, United States) Yucai Wang (Mayo Clinic, United States) Arushi Khurana (Mayo Clinic, United States) Matthew Maurer (Mayo Clinic, United States) Amy Ayers (The University of Texas MD Anderson Cancer Center, United States) Brad Kahl (Washington University in St Louis, United States) Peter Martin (Weill Cornell Medical College, United States) Jonathon Cohen (Emory University, United States) Carla Casulo (University of Rochester, United States) Izidore Lossos (University of Miami, United States) Umar Farooq (University of Iowa Hospitals and Clinics, United States) Sabarish Ayyappan (University of Iowa, United States) Tanner Reicks (Mayo Clinic, United States) Thomas Habermann (Mayo Clinic, United States) Thomas Witzig (Mayo Clinic, United States) Christopher Flowers (UT MD Anderson Cancer Center, Afghanistan) James Cerhan (Huntsman Cancer Institute/University of Utah, United States) Loretta Nastoupil (UT MD Anderson Cancer Center, United States) Grzegorz Nowakowski (Mayo Clinic, United States)

Abstract:
Patients with large B-cell lymphoma (LBCL) that fail to achieve a complete response (CR) or relapse early after anthracycline-containing immunochemotherapy (IC) have a poor prognosis and are commonly considered "primary refractory disease". However, different definitions of primary refractory disease are used in the literature and clinical practice. In this study, we ex-amined variation in the time to relapse used to define refractory status and association with sur-vival outcomes in patients with primary refractory LBCL in a single-center prospective cohort with a validation in an independent multi-center cohort. Newly diagnosed LBCL patients were enrolled in the Molecular Epidemiological Resource cohort (MER; N=949) or the Lymphoma Epidemiology of Outcomes cohort (LEO; N=2,755) from 9/2002 to 5/2021. Primary refractory LBCL was defined as no response (SD) or progressive disease (PD) during or by the end of frontline (1L) IC (primary PD; PPD), partial response at end of treatment (EOT PR), or relapse within 3-12 months after achieving CR at EOT to 1L IC (early relapse). In the MER cohort, pa-tients with PPD had inferior OS (2-year OS rate 15% MER, 31% LEO) when compared to other subgroups considered in defining primary refractory disease, EOT PR (2-year OS rate 38% MER, 50% LEO) and early relapse (2-year OS rate 44% MER, 58% LEO). Among patients re-ceiving frontline IC with curative intent, we identified that patients with PPD are the key sub-group with poor outcomes. We propose a definition of primary refractory LBCL as SD or PD during or by the end of 1L treatment.

Conflict of interest: COI declared - see note

COI notes: Co-author's disclosures are detailed in the relevant section

Preprint server: No;

Author contributions and disclosures: Conception and design of research study: A.M.B, R.M., G.S.N, L.N Collection and assembly of data: All authors Data analysis and interpretation: A.M.B, R.M, M.J.M, G.S.N, L.N. Manuscript writing: All authors Final approval of manuscript: All authors Accountable for all aspects of the work: All authors

Non-author contributions and disclosures: No;

Agreement to Share Publication-Related Data and Data Sharing Statement: The datasets generated during and/or analyzed during the current study are available on request from the corresponding author on reasonable request. The data are not publicly available due to privacy or ethical restrictions.

Clinical trial registration information (if any):

Defining Primary Refractory Large B-cell lymphoma

Allison M. Bock[1,2], Raphael Mwangi[3], Yucai Wang[1], Arushi Khurana[1], Matthew J. Maurer[3], Amy Ayers[4], Brad S. Kahl[5], Peter Martin[6], Jonathon B. Cohen[7], Carla Casulo[8], Izidore S. Lossos[9], Umar Farooq[10], Sabarish Ayyappan[10], Tanner Reicks[3], Thomas M. Habermann[1], Thomas E. Witzig[1], Christopher R. Flowers[4], James R. Cerhan[2], Loretta J. Nastoupil[4], Grzegorz S. Nowakowski[1]

[1]Division of Hematology, Mayo Clinic, Rochester, MN
[2]Huntsman Cancer Institute/University of Utah, Salt Lake City, UT
[3]Department of Quantitative Health Sciences, Mayo Clinic, Rochester, MN
[4]The University of Texas MD Anderson Cancer Center, Houston, TX
[5]Washington University in St Louis, St. Louis, MO
[6]Weill Cornell Medicine, New York, NY
[7]Emory University, Atlanta, GA
[8]University of Rochester Medical Center, Rochester, NY
[9]University of Miami, Miami, FL
[10]University of Iowa, Iowa City, IA

Corresponding author:
Allison Bock, MD, Division of Hematology and Hematologic Malignancies, Huntsman Cancer Institute/University of Utah, 2000 Circle of Hope Dr, Suite 4126, Salt Lake City, UT 84112. Email: allison.bock@hci.utah.edu

and

Grzegorz S. Nowakowski, MD, Division of Hematology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905. Email: Nowakowski.grzegorz@mayo.edu

Short title: Defining Primary Refractory LBCL

Key words: primary refractory, large B-cell lymphoma, diffuse large B-cell lymphoma, high grade B-cell lymphoma, primary treatment failure

Abstract word count: 250
Word count: 3870

Figures/tables: 6
Supplementary: 3
References: 44

Data sharing statement:
The datasets generated during and/or analyzed during the current study are available on request from the corresponding author on reasonable request. The data are not publicly available due to privacy or ethical restrictions.

Key Points:

- Patients with SD/PD to 1L therapy have lower RRs to 2L therapy and poor outcomes compared to other subgroups of primary refractory disease
- We advocate for the following definition of primary refractory LBCL: patients with SD or PD during or by the end of frontline treatment.

Abstract

Patients with large B-cell lymphoma (LBCL) that fail to achieve a complete response (CR) or relapse early after anthracycline-containing immunochemotherapy (IC) have a poor prognosis and are commonly considered "primary refractory disease". However, different definitions of primary refractory disease are used in the literature and clinical practice. In this study, we examined variation in the time to relapse used to define refractory status and association with survival outcomes in patients with primary refractory LBCL in a single-center prospective cohort with a validation in an independent multi-center cohort. Newly diagnosed LBCL patients were enrolled in the Molecular Epidemiological Resource cohort (MER; N=949) or the Lymphoma Epidemiology of Outcomes cohort (LEO; N=2,755) from 9/2002 to 5/2021. Primary refractory LBCL was defined as no response (SD) or progressive disease (PD) during or by the end of frontline (1L) IC (primary PD; PPD), partial response at end of treatment (EOT PR), or relapse within 3-12 months after achieving CR at EOT to 1L IC (early relapse). In the MER cohort, patients with PPD had inferior OS (2-year OS rate 15% MER, 31% LEO) when compared to other subgroups considered in defining primary refractory disease, EOT PR (2-year OS rate 38% MER, 50% LEO) and early relapse (2-year OS rate 44% MER, 58% LEO). Among patients receiving frontline IC with curative intent, we identified that patients with PPD are the key subgroup with poor outcomes. We propose a definition of primary refractory LBCL as SD or PD during or by the end of 1L treatment.

Introduction

Patients with diffuse large B-cell lymphoma or High Grade B-cell lymphoma (collectively large B-cell lymphoma; LBCL), can be cured with frontline immunochemotherapy (IC) with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in up to 60-70% of the cases[1-3]. The clinical course following frontline IC failure is heterogeneous[4,5]. LBCL that does not respond adequately to frontline IC or that relapses early after an initial response to IC have poor outcomes and are often considered as "primary refractory disease". However, definitions of primary refractory disease have varied in the literature. The most narrow definition is failure to achieve a partial[6,7] or complete response (CR) to frontline treatment[8-10]. Another common definition includes LBCL relapsing within 3 months after an initial CR to frontline treatment[4,11]. The most broad definition also includes relapses within 3-12 months after completing IC[12-15]. Historically, patients with these varied definitions of primary refractory disease were treated similarly with salvage chemotherapy and consideration for autologous stem cell transplant (ASCT)[6,8], but the outcomes were poor overall (durable remissions in only 20% of patients), due to lack of chemosensitivity that prevents ASCT or results in relapse post ASCT[6,12,13,16]. Recently, CD19-directed chimeric antigen receptor (CAR) T-cell therapy (CAR-T) has been approved for eligible patients relapsing within 12 months as an alternative and preferred second line treatment option for these patients[17,18].

Prospective studies of primary refractory disease have been limited, possibly in part due to lack of a consensus definition. Even in recent pivotal trials evaluating CAR-T as second line therapy for patients with primary refractory or early relapsed (within 12 months) aggressive LBCLs, different definitions of primary refractory disease were used[18-20]. The international prognostic index (IPI) and its modified forms R-IPI and NCCN-IPI capture high risk clinical fea-

tures but were not developed to identify primary refractory disease[21]. Many studies have attempted to identify clinical or pathological predictors of primary refractory disease with conflicting results[4,7,22]. In addition to differences in time to treatment failure inclusion criteria, a common limitation in many prior studies is that they do not restrict based on treatment-intensity and therefore the measurements may not be entirely reflective of underlying disease biology; for example, intolerance to therapy due to an adverse event and subsequent progression is likely more of a reflection of underlying comorbidities rather than disease aggressiveness.

In this study, we evaluated clinical and pathological characteristics, second line treatment responses, and survival outcomes of patients with broadly defined primary refractory LBCL, in two large prospective cohorts: 1) the University of Iowa/Mayo Clinic Lymphoma Specialized Program of Research excellence (SPORE) Molecular Epidemiological Resource (MER) cohort and 2) the Lymphoma Epidemiology of Outcomes (LEO) cohort. The aim was to clearly define what time to relapse should be used in defining primary refractory disease to identify patients at the highest risk for poor outcomes to inform clinical practice and future research.

Methods

Patients and Methods

MER Cohort (Cohort 1)

Details on the MER cohort have previously been reported[23]. Adult patients with newly diagnosed large B-cell lymphomas (LBCL) including DLBCL and high-grade B-cell lymphomas with *MYC* and *BCL2* and/or *BCL6* rearrangements (HGBCL) were prospectively enrolled in the University of Iowa/Mayo Clinic Lymphoma Specialized Program of Research excellence (SPORE) Molecular Epidemiological Resource (MER) cohort from 9/2002 to 6/2015. Cell-of-origin determination

was performed in accordance with the Hans algorithm[24]. Immunohistochemical and fluorescence in situ hybridization (FISH) analyses were performed using available sections from formalin fixed, paraffin embedded tissue blocks that were obtained at initial diagnosis and were documented retrospectively in MER patients with available data.

LEO Cohort (Cohort 2)

We evaluated whether our definitions of primary refractory disease reflected similar outcomes in the LEO cohort of patients who were treated at 8 academic centers across the US, reflecting a more diverse patient population than our MER cohort in the Upper Midwest. The LEO prospective cohort enrolled patients between 2015 and 2021 at eight academic centers. The demographics of this overall cohort has previously been presented[25].

Patients in Cohort 1 and Cohort 2 who received curative intent anthracycline-containing IC for LBCL (R-CHOP or similar, including on trial, e.g., R-CHOP + lenalidomide or polatuzumab vedotin-R-CHP) or HGBCL (including R-CHOP and more intensive chemotherapy regimens such as EPOCH-R, R-CODOX-M/R-IVAC) were included. Interim response assessment was performed after 2 or 3 cycles in all patients and end of treatment response assessment was performed 4-8 weeks after completing chemotherapy by PET-CT scans in most patients (n=20 in MER cohort had CT only) by standard Cheson and/or Lugano response criteria[26-28]. Patients who did not complete planned IC treatment or who did not initiate anthracycline-based treatment due to intolerance or toxicity were excluded, so that our analysis would best capture patients with treatment failure rather than relapses from inadequate treatment or unrelated events. This includes patients who had planned reduced dose intensity (e.g., mini-R-CHOP), were intolerant to

and discontinued treatment prior to response assessment, who had toxicity resulting in incomplete treatment (<75% planned dose intensity), and/or who died unrelated to disease progression prior to end of treatment response assessment. Patients without complete data of response assessment were also excluded (Supplementary Figure 1). Patients with primary central nervous system (CNS) LBCL and transformed LBCL who received prior therapy for the indolent lymphoma and/or received planned consolidative ASCT were also excluded. Patients with secondary CNS involvement at diagnosis were not excluded.

We abstracted baseline data on demographics (age, sex, race), clinical features (ECOG performance status, number of extranodal sites, stage, IPI), and pathological features (cell of origin, cytogenetic and molecular characteristics such as *MYC* / *BCL2* double expressor, *MYC* and *BCL2* and/or *BCL6* rearrangements. HGBCL were assessed using WHO 2016 classification criteria which included *BCL6* rearrangements[29]. Data on which patients had a MYC/BCL2 vs MYC/BCL6 rearrangement is shown in Supplementary Table 1. Second line (2L) treatment and response and survival outcomes were abstracted.

Statistical analysis

For the analysis of relapsed patients in Cohort 1 and 2, all available patients meeting inclusion criteria were included in the analysis. We evaluated the functional form of timing of release using restricted cubic splines (Supplementary Figure 2). Then, according to different established definitions of primary refractory disease, the following cases were considered serially as components of the definition of primary refractory disease: (1) stable disease or progressive disease during or by the end of frontline IC (including transient interim PR or CR, primary progressive disease; PPD), 2) partial response (PR) as the best response by the end of treatment (EOT PR), or 3) early relapse within 3 months, 4) 3-6 months, or 5) 6-12 months after achieving CR at EOT to

frontline treatment. After individual analysis of subgroups 3-5, these were grouped together for further analysis (early relapse).

Overall survival (OS) was defined as time from relapse (or refractoriness) until death from any cause. Different combinations of primary refractory definitions were evaluated based on *a priori* definitions 1-5 as described above. OS was evaluated using Kaplan-Meier curves to visualize the survival probability over time for the different subgroups and statistical significance was quantified using long-rank test p-values at an alpha level of 0.05. An analysis of baseline features was performed among all PPD patients in Cohort 2 compared to all remaining newly diagnosed DLBCL with Chi-Square or T-test used to compare the groups and adjusted for multiple comparisons using false discovery rate (FDR). For this analysis, OS was defined from time of relapse or the end of treatment (for patients without relapse) until death from any cause. Analyses were performed using R/RStudio v4.2.2 and SAS v9.4M5.

This retrospective study was approved by Mayo Clinic IRB

Results

MER cohort (Cohort 1)

Among a total of 949 patients in the MER cohort with newly diagnosed DLBCL (N=918) or HGBCL (n=30), 132 (13.9%) met inclusion criteria for primary refractory disease (n=40 PPD, n=40 EOT PR, n=52 early relapse). Progression or persistent disease was confirmed by biopsy in addition to imaging in 59% of patients, imaging only in 35%, clinically in 2% or method not documented or missing in 4%. Baseline characteristics are described in Table 1. Median age at diagnosis was 60 years (range, 19-84) and 65% were male. Most patients (74%) had advanced

stage disease and 51% had high or high intermediate risk IPI. There were no significant differences in baseline characteristics among the three groups (Table 1). The proportions of *MYC* and *BCL2* and/or *BCL6* rearrangements (DHL/THL; 12% overall) or MYC/BCL2 double expressor (28% overall) were not different among the 3 groups. First line (1L) treatment was R-CHOP or similar treatment on a clinical trial in most patients (73%).

Second line (2L) therapies included platinum-based chemotherapy (e.g., R-ICE, R-DHAP, or similar; n=89; 69%), primarily central nervous system (CNS)-directed therapy (n=15; 12%), other systemic palliative chemotherapy (n=17; 13%), or radiotherapy or resection for localized disease (n=8; 6%) (Table 2). The response to salvage chemotherapy was significantly different between the 3 groups. The ORR/CR/PR rate to 2L was 39.5%/7.9%/31.6% for patients with PPD, 62%/10.3%/51.7% for patients with EOT PR, and 68.9%/35.6%/33.3% for patients with early relapse (Table 2). A higher proportion of patients with PPD had progressive disease as best response to second line therapy (55.3%) compared to EOT PR (27.5%) or early relapse (24.4%). Among all patients, 83% (n=105) underwent curative intent 2L therapy (defined as platinum-based chemotherapy or any therapy with intent to proceed to ASCT)(Table 3). Patients with PPD had the highest use of curative-intent 2L therapy (90%) but had significantly lower ORR/CR/PR rates compared to patients with EOT PR or early relapse (Table 3). Among all patients with complete subsequent treatment data (n=125), 42% (n=53) of patients underwent ASCT after any 2L therapy. Rates of ASCT were lower in PPD group (n=10, 26%) compared to EOT PR (n=14, 39%) and early relapse (n=29, 59%) groups.

At a median follow up of 103.2 months, 101 patients (77%) had died. The 2-year OS rate was 15% (95% CI 7-31) for patients with PPD, which was significantly worse compared to that of patients with EOT PR (2-year OS 38%, 95% CI 25-56) or early relapse (3-12 months, 2-year

OS 44%, 95% CI 33-60)(Figure 1A). In patients with early relapse, the 2-year OS rate was not appreciably different among those who relapsed within 3 months (36%, 95% CI 21-63), between 3-6 months (58%, 95% CI 36-94), or between 6-12 months (44%, 95% CI 27-75) (Figure 1B).

LEO Cohort (Validation)

A total of 2,755 patients with DLBCL (n=2522) or HGBCL (n=233) were enrolled in the LEO cohort from 2015-2021. Among 402 patients with relapse prior to 12 months, 308 (11.3%) met inclusion criteria for primary refractory disease (n=145 PPD, n=66 EOT PR, n=97 early relapse) (Supplemental Figure 1). Progression or persistent disease was confirmed by biopsy in addition to imaging in 61% of patients, imaging only in 30%, clinically in 1%, and method not documented or missing in 8%. Baseline characteristics are described in Table 1. Median age was 63 (range, 19-90) and 65% were male. Most patients (81%) had advanced disease and 52% had high or high intermediate risk IPI. Similar to MER, there were no significant differences in baseline clinical features between the 3 groups. Among patients with complete data (n=136), the proportions of DHL/THL (21% overall) or *MYC /BCL2* double expressor (41% overall) was not different among the 3 groups. Compared to MER cohort, the LEO cohort had higher inclusion of non-white races and Hispanic/Latinx ethnicity. Otherwise, baseline clinical, laboratory, and pathology features and treatment were similar between the MER and LEO cohorts.

Similar to MER, 2L treatment choices and response to second line treatment were significantly different between the 3 groups. Second line therapies included platinum-based chemotherapy in most patients (n=166, 58%), primarily CNS-directed therapy (n=33, 12%), targeted therapies (n=25; 9%), CAR-T (without bridging, n=16, 6%; with any bridging therapy, n=13, 4%), other systemic palliative chemotherapy (n=21; 7%), radiotherapy or resection (n=22; 8%) or no

treatment (n=5; 2%). Second line treatment choice was similar among subgroups except a higher use of CNS-directed therapies in those with early relapse (19%) and EOT PR (16%) compared to PPD (5%). Among all patients, 63% (n=192) underwent curative intent 2L therapy (defined as platinum-based chemotherapy or any therapy followed by ASCT or CAR-T)(Table 3). Patients with PPD had the highest use of curative-intent 2L therapy (71%) but despite this, had significantly lower ORR/CR/PR rates (46.9%/23.9%/22.9%) compared to patients with EOT PR (74.4%/38.5%/35.9%) or early relapse (78.7%/66.0%/12.7%)(Table 3). Notably, a similar trend was observed when evaluating response rate to 2L treatment groups (Table 2). For patients with PPD, the ORR was similar at approximately 40% in both MER and LEO cohorts, but the CR rate appeared higher in the LEO. Targeted therapies and CAR-T were utilized more as 2L in LEO compared to MER likely impacting overall and complete response rates and outcomes. In the PPD group, 8% of patients received targeted therapies and 7% received CAR-T, with an ORR of 27% (95% CI, 9.8-56.6%) and 87% (95% CI, 62.1-96.3%), respectively. Among all patients, 18% (n=54) patients underwent ASCT after any 2L therapy. Rates of ASCT were lower in the PPD group (n=18, 12%) compared to EOT PR (n=12, 18%) and early relapse (n=24, 25%). The lower ASCT rate than MER cohort reflects the availability of CAR-T as an alternative second line option, though notably all CAR-T patients were treated in the context of a clinical trial whereas ASCT was clinical practice.

At a median follow up of 36.6 months, 187 patients (60%) had died. The 2-year OS rate was 30% (95% CI 24-39) for patients with PPD, which was significantly worse compared to that of patients with EOT PR (2-year OS 50%, 95% CI 38-64) or early relapse (2-year OS 58%, 95% CI 49-69)(Figure 1C). In patients with early relapse, the 2-year OS rate was not significantly different among those who relapsed within 3 months (52%, 95% CI 34-79) or between 3-6 months

(56%, 95% CI 42-73) but appeared better for those relapsing between 6-12 months (66%, 95% CI 51-86%) (Figure 1D).

A clear definition of primary refractory LBCL

In both cohorts, patients with no response or progressive disease by Lugano response criteria during or by end of 1L treatment (PPD group) had inferior response rates to second line therapies and the lowest OS. Clinically, these are the patients with truly refractory disease and will herein be referred to as "primary refractory LBCL". When evaluating OS among all patients in the LEO cohort from the end of treatment or relapse, patients with primary refractory LBCL had a 2-year OS of 27% (95% CI 21-34) and a median OS of 8.4 months compared to patients with non-primary refractory LBCL who had a 2 year OS of 84% (95% CI 82-85) and the median OS at 2 years was not reached (Figure 2).

Baseline features associated with primary refractory LBCL

As patients with primary refractory LBCL have poor outcomes compared to most patients with newly diagnosed LBCLs, we evaluated baseline clinical and pathological features associated with primary refractory LBCL. Primary refractory LBCL was associated with several known adverse clinical and pathological features (Table 4). Most patients had an elevated LDH (76.9%) and advanced stage (80.3%). Patients with primary refractory LBCL had a shorter diagnosis to treatment interval (DTI) with a median DTI of 12.5 days compared to 16 in non-primary refractory patients. While there was a shift towards a higher IPI in primary refractory patients, notably 49.5% of patients had a low or low intermediate IPI. The positive predictive value of a high IPI (4-5) was only 8%. Cell of origin was not significantly different between the two groups with a similar distribution of GCB and ABC subtypes in both groups. Among patients with complete

data (n=1688), DHL/THL was observed in 26% of primary refractory patients compared to 9% in non-primary refractory patients. Presence of *Myc/Bcl2* double expressor was observed in 40% and was also significantly higher compared to non-primary refractory patients (24%).

Discussion

To the best of our knowledge, this is the largest multi-center, prospective cohort study of outcomes for patients with primary refractory LBCL. Our results showed that broadly defined primary refractory disease occurred at a similar incidence to historical rates (14% in MER and 11% in LEO, vs 10-15% historically)[11,14]. Our study is consistent with other retrospective studies in demonstrating that patients with refractory disease or early relapse have poor outcomes[13,22,30,31]. Importantly however, the large cohort sizes in our study allowed us to demonstrate that broadly defined primary refractory LBCL has heterogenous survival outcomes. In both MER and LEO cohorts, patients with no response or progression during or by the end of front-line treatment (PPD group) have significantly inferior survival compared to other subgroups of primary refractory disease, which is likely driven by poor response to salvage therapies. The particularly poor outcomes in the PPD group, even in the more recent treatment era with more novel therapies available for relapsed/refractory disease, may drive the overall poor outcomes in broadly defined primary refractory LBCL, if examined as a whole in our or other studies. Based on our results, we advocate for the following definition of primary refractory LBCL: patients with stable or progressive disease during or by the end of treatment (PPD group). This is the group of patients with clear chemoresistance and most in need of better treatment options. Patients with inadequate response or EOT PR (i.e., PR as best response by EOT) and early relapse (i.e., relapse within 12 months) have similar outcomes and may be better grouped as early relapse.

Evaluating future frontline trials by their ability to decrease patients in the PPD group should be an important clinical endpoint in future prospective studies. The lack of a consensus definition of primary refractory disease has also limited dedicated clinical trials for this important subgroup of patients and has a major impact on the interpretation of historical studies in relapsed/refractory LBCL. The phase II study of tafasitamab and lenalidomide initially excluded patients with primary refractory disease, defined as patients with relapse within 6 months of frontline treatment. The primary analysis observed a high ORR and PFS, which both declined after the inclusion of patients with primary refractory disease[32,33]. Both the ZUMA-7 and TRANSFORM trials evaluating CAR-T in the second line included primary refractory and early relapse (< 12 months) cases but the definitions for primary refractory were slightly different (lack of CR to frontline therapy in ZUMA7 and lack of CR to frontline therapy or relapse within 3 months)[17,18]. However, the subgroup analyses by refractory vs relapse status were helpful in interpreting the relative benefits of CAR-T vs standard-of-care therapy in these different subgroups[34].

The recognition of primary progressive disease may also inform future clinical practice and trial design. While better therapies are needed for all relapsed patients, selection of 2L therapy appears most crucial for patients with PPD, who had the highest rates of progressive disease to salvage chemotherapy in our study, which led to lower rates of both ASCT and CAR-T compared to patients with EOT PR or early relapse. Our findings are similar to all three of the pivotal second line CAR-T trials that observed high rates of crossover due to inability to achieve a response to salvage chemotherapy and only 33-45% of planned patients underwent ASCT[17,18,20]. Novel targeted agents may have improved efficacy compared to salvage chemotherapy for these patients and should be explored as bridging strategies for patients with PPD as progression prior

to CAR-T remains a key barrier in both trial and real-world populations[35-37]. In contrast, for patients with early relapse, chemo-containing therapies as salvage/bridging might still play a role in select cases, although incorporation of novel therapies is certainly desired as well.

Distinguishing primary progressive disease from other subgroups of broadly defined primary refractory disease has important implications in frontline treatment and trial designs as well. This is the group of patients with clear chemoresistance most in need of better treatment options given treatment failure despite optimal frontline IC. Interim PET and/or circulating tumor DNA assessment guided treatment strategies may help reduce or salvage such primary progressive cases. One example is the phase 2 ZUMA-12 study, in which high risk patients (defined as DH/THL or IPI 3-5) who had an incomplete response with positive interim PET after 2 cycles of R-CHOP were treated with axicabtagene ciloleucel. The efficacy was very encouraging, with an ORR of 89%, a CR rate of 78%, and a 12-month PFS of 75%[38], with a randomized frontline trial now enrolling (NCT05605899)[39].

Ultimately, better frontline therapies are needed to reduce the proportion of patients with primary progressive disease. Identifying patients at the highest risk for primary progressive disease prior to treatment is still challenging but becomes evident by the time of the interim PET after 2 or 3 cycles. Our results suggested that using high-intermediate or high IPI alone may miss half of patients who would have primary progressive disease, though we acknowledge the small cohort size of refractory patients compared to the total population. Biological features (DHL/THL and double expressor) may be more important than clinical features in predicting primary refractoriness. A better understanding of the molecular alterations in these patients is needed to better understand chemoresistance and risk stratification[40].

The strengths of this study include demonstration of our findings in two large prospective cohorts with detailed treatment information. We performed a comprehensive analysis of patients who received complete treatment, excluding those with incomplete treatment due to treatment intolerance or toxicity, Thus, our study captures patients whose disease is refractory despite optimal treatment, and removes possible confounding factors unrelated to inherent disease biology that may be present in prior event-based analyses[22,31]. Detailed 2L treatment and response details were available for >95% of the included patients and patients in the LEO cohort reflect the diversity representative of the US population[25]. The LEO cohort demonstrated improved outcomes compared to MER across subgroups, but OS for those with primary progressive disease still remained significantly inferior to other subgroups. The improvement in outcomes is likely multifactorial with improved supportive care and growth factor support potentially playing an important role, just as outcomes among all patients with newly diagnosed LBCL are improving over time compared to the first studies of R-CHOP[1-3,41-43]. There has also been an increase in 2L treatment options in the last 5-10 years including multiple novel targeted therapies and most recently CAR-T[17,18,32,44]. Limitations include a high number of missing data for double expressor status and *MYC*-rearrangements, mainly in MER cohort and the inclusion of MYC/BCL6 rearrangements as part of HGBCL, which was removed with the 5th edition of the WHO classification system in 2022. Outcomes are also likely impacted by subsequent lines of therapies, and we may be missing the contribution of CAR-T in later lines to improved outcomes in LEO cohort.

In summary, we evaluated outcomes of patients with primary refractory LBCL who received optimal standard frontline IC in two large prospective cohorts. Based on timing of refractoriness or relapse and the associated distinct outcomes, we propose a clear definition of primary refractory disease to frontline therapy: no response (SD) or progressive disease (PD) during or by

the end of treatment (PPD group). This definition will inform clinical practice, clinical trial design and aid in interpretation of clinical research and trial results. Better understanding of disease biology is needed to help identify patients at high risk for primary progressive disease, to facilitate investigation of novel frontline and salvage therapies.

Acknowledgements

This work was supported by a grant from the National Institutes of Health, National Cancer Institute to James Cerhan (P50 CA97274, U01 CA195568).

Author contributions:

Conception and design: A.M.B, R.M., G.S.N, L.N

Collection and assembly of data: All authors

Data analysis and interpretation: A.M.B, R.M, M.J.M, G.S.N, L.N.

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

Disclosure of Conflicts of Interest

R.M., A.K., A.A., T.R., T.E.W.: no COI to disclose

A.M.B: Consultancy or advisory role: AbbVie
Honoraria: Primum

Y. W.: Employment or leadership position: Merck - immediate family Member
Consultant or advisory role: Loxo; Incyte; Innocare; TG Therapeutics; Kite, A Gilead Company; Lilly; Janssen; BeiGene
Stock ownership: Merck - immediate family member
Honoraria: Kite, A Gilead Company

Research funding: InnoCare; Incyte; Novartis; Genentech; Loxo; MorphoSys; Genmab

M.J.M.: Employment or leadership position: Exact Sciences - immediate family member
Consultant or advisory role: Genmab; Adpative Biotechnologies
Stock ownership: Exact sciences - immediate family member
Research funding: MorphoSys; Bristol Myers Squibb; Roche/Genentech; Genmab

B.K.:
Consultant or advisory role: Celgene, AbbVie, Pharmacyclics, Acerta Pharma, ADC Therapeutics, Genentech, Roche, AstraZeneca, BeiGene, Bayer, MEI Pharma, Kite/Gilead, MorphoSys, Janssen, Celgene, Incyte, Genmab
Research Funding: Genentech, Acerta Pharma, ADC Therapeutics, Celgene

P.M.:
Consultant or advisory role: Janssen, Beigene, Karyopharm Therapeutics, Kite/Gilead, Verastem, ADC Therapeutics, Bristol Myers Squibb/Celgene, Epizyme, Merck, Morphosys, Takeda
Research funding: Karyopharm Therapeutics

J.B.C.:
Consultant or advisory role: AbbVie, Janssen, Loxo, Kite/Gilead, AstraZeneca, Aptitude Medical, Adicet Bio, Adaptive Biotechnologies
Research funding: Celgene, Janssen, Novartis, Takeda, AI Therapeutics, Genentech, ASH, Lymphoma Research Foundation, Loxo, BioInvent, AstraZeneca

C.C.:
Consultant or advisory role: Abbvie
Research funding: Gilead, SecuraBio, Genmab, Genentech.
I.L.:
Consultant or advisory role: Janssen, Seagen, Verastem
Honoraria: Janssen
Research funding: NCI

U.F.:
Consultant or advisory role: Morphosys, Caribou
Honoraria: Kite Pharma, Caribou

T.M.H.:
Consultant or advisory role: Celgene; Kite/Gilead
Research funding: Genentech
Other remuneration: Uncompensated: Tess Therapeutics; Loxo/Lilly; MorphoSys; Incyte; BeiGene

C.R.F.:

J.R.C.:
Consultant or advisory role: Bristol-Meyers-Squibb; Protagonist Therapeutics
Research funding: NanoString Technologies; Celgene; Genentech; Genmab;
Other remuneration: Uncompensated: Regeneron

L.J.N.:
Consultant or advisory role: Interius Biotherapeutics; SIRPant Immunotherapeutics
Honoraria: ADC Therapeutics, Bristol-Myers Squibb; Caribou Biosciences; Epizyme; Genentech/Roche; Genmab; Gilead Sciences; Janssen Oncology; Morphosys; Novartis; Takeda; TG Therapeutics
Research funding: Allogene Therapeutics; Bristol-Myers Squibb/Celgene; Caribou Biosciences; Epizyme; Genentech/Roche; Gilead Sciences; IgM Biosciences; Janssen Biotech; Novartis; Takeda

G.S.N.:
Consultant or advisory role: Celgene; MorphoSys; Genentech; Selvita; Debiopharm Group; Kite/Gilead; TG Therapeutics; Kymera; Karyopharm Therapeutics; Ryvu Therapeutics; Bantham
Research funding: Celgene; NanoString Technologies; MorphoSys

References:

1. Coiffier B, Lepage E, Briere J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *The New England journal of medicine*. Jan 24 2002;346(4):235-42. doi:10.1056/NEJMoa011795
2. Pfreundschuh M, Trümper L, Osterborg A, et al. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group. *The Lancet Oncology*. May 2006;7(5):379-91. doi:10.1016/s1470-2045(06)70664-7
3. Habermann TM, Weller EA, Morrison VA, et al. Rituximab-CHOP versus CHOP alone or with maintenance rituximab in older patients with diffuse large B-cell lymphoma. *J Clin Oncol*. Jul 1 2006;24(19):3121-7. doi:10.1200/jco.2005.05.1003
4. Hitz F, Connors JM, Gascoyne RD, et al. Outcome of patients with primary refractory diffuse large B cell lymphoma after R-CHOP treatment. *Annals of hematology*. Nov 2015;94(11):1839-43. doi:10.1007/s00277-015-2467-z
5. Farooq U, Maurer MJ, Thompson CA, et al. Clinical heterogeneity of diffuse large B cell lymphoma following failure of front-line immunochemotherapy. *British journal of haematology*. Oct 2017;179(1):50-60. doi:10.1111/bjh.14813
6. Mills W, Chopra R, McMillan A, Pearce R, Linch DC, Goldstone AH. BEAM chemotherapy and autologous bone marrow transplantation for patients with relapsed or refractory non-Hodgkin's lymphoma. *J Clin Oncol*. Mar 1995;13(3):588-95. doi:10.1200/jco.1995.13.3.588

7. Villela L, López-Guillermo A, Montoto S, et al. Prognostic features and outcome in patients with diffuse large B-cell lymphoma who do not achieve a complete response to first-line regimens. *Cancer*. Apr 15 2001;91(8):1557-62.
8. Philip T, Guglielmi C, Hagenbeek A, et al. Autologous Bone Marrow Transplantation as Compared with Salvage Chemotherapy in Relapses of Chemotherapy-Sensitive Non-Hodgkin's Lymphoma. *New England Journal of Medicine*. 1995;333(23):1540-1545. doi:10.1056/nejm199512073332305
9. Kewalramani T, Zelenetz AD, Hedrick EE, et al. High-dose chemoradiotherapy and autologous stem cell transplantation for patients with primary refractory aggressive non-Hodgkin lymphoma: an intention-to-treat analysis. *Blood*. Oct 1 2000;96(7):2399-404.
10. Feugier P, Van Hoof A, Sebban C, et al. Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: a study by the Groupe d'Etude des Lymphomes de l'Adulte. *J Clin Oncol*. Jun 20 2005;23(18):4117-26. doi:10.1200/jco.2005.09.131
11. Telio D, Fernandes K, Ma C, et al. Salvage chemotherapy and autologous stem cell transplant in primary refractory diffuse large B-cell lymphoma: outcomes and prognostic factors. *Leukemia & lymphoma*. May 2012;53(5):836-41. doi:10.3109/10428194.2011.643404
12. Gisselbrecht C, Glass B, Mounier N, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. *J Clin Oncol*. Sep 20 2010;28(27):4184-90. doi:10.1200/jco.2010.28.1618
13. Crump M, Neelapu SS, Farooq U, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. *Blood*. Oct 19 2017;130(16):1800-1808. doi:10.1182/blood-2017-03-769620
14. Sarkozy C, Coiffier B. Primary refractory diffuse large B cell lymphoma in the rituximab era. *Curr Opin Oncol*. Sep 2015;27(5):377-83. doi:10.1097/cco.0000000000000209
15. Shah NN, Ahn KW, Litovich C, et al. Is autologous transplant in relapsed DLBCL patients achieving only a PET+ PR appropriate in the CAR T-cell era? *Blood*. Mar 11 2021;137(10):1416-1423. doi:10.1182/blood.2020007939
16. Kewalramani T, Zelenetz AD, Nimer SD, et al. Rituximab and ICE as second-line therapy before autologous stem cell transplantation for relapsed or primary refractory diffuse large B-cell lymphoma. *Blood*. May 15 2004;103(10):3684-8. doi:10.1182/blood-2003-11-3911
17. Locke FL, Miklos DB, Jacobson CA, et al. Axicabtagene Ciloleucel as Second-Line Therapy for Large B-Cell Lymphoma. *The New England journal of medicine*. Feb 17 2022;386(7):640-654. doi:10.1056/NEJMoa2116133
18. Kamdar M, Solomon SR, Arnason J, et al. Lisocabtagene maraleucel versus standard of care with salvage chemotherapy followed by autologous stem cell transplantation as second-line treatment in patients with relapsed or refractory large B-cell lymphoma (TRANSFORM): results from an interim analysis of an open-label, randomised, phase 3 trial. *Lancet (London, England)*. Jun 18 2022;399(10343):2294-2308. doi:10.1016/s0140-6736(22)00662-6
19. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. *The New England journal of medicine*. Dec 28 2017;377(26):2531-2544. doi:10.1056/NEJMoa1707447
20. Bishop MR, Dickinson M, Purtill D, et al. Second-Line Tisagenlecleucel or Standard Care in Aggressive B-Cell Lymphoma. *The New England journal of medicine*. Feb 17 2022;386(7):629-639. doi:10.1056/NEJMoa2116596

21. Warnnissorn N, Kanitsap N, Niparuck P, et al. External validation and comparison of IPI, R-IPI, and NCCN-IPI in diffuse large B-cell lymphoma patients treated with R-CHOP to predict 2-year progression-free survival. *Hematology*. Dec 2022;27(1):1237-1245. doi:10.1080/16078454.2022.2147916
22. Hamadani M, Hari PN, Zhang Y, et al. Early failure of frontline rituximab-containing chemo-immunotherapy in diffuse large B cell lymphoma does not predict futility of autologous hematopoietic cell transplantation. *Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation*. Nov 2014;20(11):1729-36. doi:10.1016/j.bbmt.2014.06.036
23. Cerhan JR, Link BK, Habermann TM, et al. Cohort Profile: The Lymphoma Specialized Program of Research Excellence (SPORE) Molecular Epidemiology Resource (MER) Cohort Study. *International Journal of Epidemiology*. 2017;46(6):1753-1754i. doi:10.1093/ije/dyx119
24. Hans CP, Weisenburger DD, Greiner TC, et al. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. *Blood*. 2004;103(1):275-282. doi:10.1182/blood-2003-05-1545
25. Flowers CR, Link BK, Nastoupil LJ, et al. The Lymphoma Epidemiology of Outcomes (LEO) Cohort Study Reflects the Demographics and Subtypes of Patients Diagnosed with Non-Hodgkin Lymphoma in the United States. *Blood*. 2018;132(Supplement 1):1702-1702. doi:10.1182/blood-2018-99-114281
26. Cheson BD, Horning SJ, Coiffier B, et al. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. *J Clin Oncol*. Apr 1999;17(4):1244. doi:10.1200/jco.1999.17.4.1244
27. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. *J Clin Oncol*. Feb 10 2007;25(5):579-86. doi:10.1200/jco.2006.09.2403
28. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol*. Sep 20 2014;32(27):3059-68. doi:10.1200/jco.2013.54.8800
29. Jaffe ES, Barr PM, Smith SM. Understanding the New WHO Classification of Lymphoid Malignancies: Why It's Important and How It Will Affect Practice. *Am Soc Clin Oncol Educ Book*. 2017;37:535-546. doi:10.1200/edbk_175437
30. Van Den Neste E, Schmitz N, Mounier N, et al. Outcome of patients with relapsed diffuse large B-cell lymphoma who fail second-line salvage regimens in the International CORAL study. *Bone marrow transplantation*. Jan 2016;51(1):51-7. doi:10.1038/bmt.2015.213
31. Vardhana SA, Sauter CS, Matasar MJ, et al. Outcomes of primary refractory diffuse large B-cell lymphoma (DLBCL) treated with salvage chemotherapy and intention to transplant in the rituximab era. *British journal of haematology*. Feb 2017;176(4):591-599. doi:10.1111/bjh.14453
32. Duell J, Maddocks KJ, González-Barca E, et al. Long-term outcomes from the Phase II L-MIND study of tafasitamab (MOR208) plus lenalidomide in patients with relapsed or refractory diffuse large B-cell lymphoma. *Haematologica*. Sep 1 2021;106(9):2417-2426. doi:10.3324/haematol.2020.275958
33. Salles G, Duell J, González Barca E, et al. Tafasitamab plus lenalidomide in relapsed or refractory diffuse large B-cell lymphoma (L-MIND): a multicentre, prospective, single-arm, phase 2 study. *The Lancet Oncology*. Jul 2020;21(7):978-988. doi:10.1016/s1470-2045(20)30225-4
34. Kamdar MK, Chavez JC, Ghesquieres H, et al. Subgroup analyses of primary refractory (refr) vs early relapsed (rel) large B-cell lymphoma (LBCL) from the TRANSFORM study of

lisocabtagene maraleucel (liso-cel) vs standard of care (SOC) as second-line (2L) therapy. *Journal of Clinical Oncology*. 2023;41(16_suppl):7526-7526. doi:10.1200/JCO.2023.41.16_suppl.7526

35. Pinnix CC, Gunther JR, Dabaja BS, et al. Bridging therapy prior to axicabtagene ciloleucel for relapsed/refractory large B-cell lymphoma. *Blood advances*. Jul 14 2020;4(13):2871-2883. doi:10.1182/bloodadvances.2020001837

36. Lutfi F, Holtzman NG, Kansagra AJ, et al. The impact of bridging therapy prior to CD19-directed chimeric antigen receptor T-cell therapy in patients with large B-cell lymphoma. *British journal of haematology*. Sep 9 2021;doi:10.1111/bjh.17738

37. Liebers N, Duell J, Fitzgerald D, et al. Polatuzumab vedotin as a salvage and bridging treatment in relapsed or refractory large B-cell lymphomas. *Blood advances*. 2021;5(13):2707-2716. doi:10.1182/bloodadvances.2020004155

38. Neelapu SS, Dickinson M, Munoz J, et al. Axicabtagene ciloleucel as first-line therapy in high-risk large B-cell lymphoma: the phase 2 ZUMA-12 trial. *Nature medicine*. Apr 2022;28(4):735-742. doi:10.1038/s41591-022-01731-4

39. Jacobson CA, Chavez JC, Sureda A, et al. ZUMA-23: A global, phase 3, randomized controlled study of axicabtagene ciloleucel versus standard of care as first-line therapy in patients with high-risk large B-cell lymphoma. *Journal of Clinical Oncology*. 2023;41(16_suppl):TPS7578-TPS7578. doi:10.1200/JCO.2023.41.16_suppl.TPS7578

40. Bock AM, Wenzl K, Stokes ME, et al. Molecular Landscape of Primary Refractory DLBCL. *Blood*. 2022;140(Supplement 1):9221-9223. doi:10.1182/blood-2022-156497

41. Tilly H, Morschhauser F, Sehn LH, et al. Polatuzumab Vedotin in Previously Untreated Diffuse Large B-Cell Lymphoma. *The New England journal of medicine*. Jan 27 2022;386(4):351-363. doi:10.1056/NEJMoa2115304

42. McBride A, Alrawashdh N, Bartels T, Moore L, Persky D, Abraham I. Same-day versus next-day pegfilgrastim or pegfilgrastim-cbqv in patients with lymphoma receiving CHOP-like chemotherapy. *Future Oncol*. Sep 2021;17(26):3485-3497. doi:10.2217/fon-2021-0532

43. Yokoyama M, Kusano Y, Inoue N, et al. Factors for the optimal selection of granulocyte colony-stimulating factor preparations and predictors for R-CHOP dose reductions/delays among patients with non-Hodgkin B-cell lymphoma (STOP FN in NHL 2 subanalysis). *BMC Cancer*. Apr 6 2021;21(1):358. doi:10.1186/s12885-021-08068-0

44. Caimi PF, Ai W, Alderuccio JP, et al. Loncastuximab tesirine in relapsed or refractory diffuse large B-cell lymphoma (LOTIS-2): a multicentre, open-label, single-arm, phase 2 trial. *The Lancet Oncology*. Jun 2021;22(6):790-800. doi:10.1016/s1470-2045(21)00139-x

Tables

621 **Table 1. Baseline patient characteristics in different subsets of primary refractory disease**

	MER (N=949)					LEO (N=2,755)				
	PPD (n=40)	EOT PR (n=40)	Early Relapse (< 12 mo) (n=52)	Total (n=132)		PPD (n=145)	EOT PR (n=66)	Early Relapse (<12 mo) (n=97)	Total (n=308)	
Variable	n (%)	n (%)	n (%)	n (%)	P[1]	n (%)	n (%)	n (%)	n (%)	P
Age at diagnosis					0.754					
Median (range)	59.5 (19-80)	62.5 (24-84)	60.0 (21-83)	60.0 (19-84)		63 (19-88)	62 (28-90)	64 (25-83)	63 (19-90)	0.829
Gender					0.448					0.996
F	19 (47.5)	8 (20.0)	20 (38.5)	47 (35.6)		50 (34.7)	23 (34.8)	35 (36.5)	108 (35.3)	
Race					0.754					0.485
White	36 (90.0)	37 (92.5)	50 (96.2)	123 (93.2)		127 (88.2)	57 (86.4)	80 (83.3)	264 (86.3)	
African American	0 (0.0)	1 (2.5)	0 (0.0)	1 (0.8)		10 (6.9)	4 (6.1)	6 (6.3)	20 (6.5)	
Unknown/Not reported	4 (10.0)	2 (5.0)	2 (3.8)	8 (6.1)		4 (2.8)	1 (1.5)	4 (4.2)	9 (2.9)	
Ethnicity					0.754					0.889
Not Hispanic/latinx	33 (82.5)	37 (92.5)	47 (90.4)	117 (88.6)		126 (87.5)	60 (90.9)	84 (87.5)	270 (88.2)	
Hispanic/Latinx	0	0	0	0		15 (11.0)	6 (9.1)	11 (11.5)	32 (10.5)	
Unknown/not reported	7 (17.5)	3 (7.5)	5 (9.6)	15 (11.4)		3 (2.1)	0 (0)	1 (1)	4 (1.3)	
ECOG PS					0.853					0.996
<2	35 (87.5)	33 (82.5)	45 (86.5)	113 (85.6)		104 (77.0)	47 (77.0)	69 (77.5)	220 (77.2)	
LDH					0.782					0.485
>Normal	26 (78.8)	24 (77.4)	41 (85.4)	91 (81.3)		87 (76.3)	37 (66.1)	72 (80.9)	196 (75.7)	
Extranodal Sites					0.754					0.829
<=1	24 (63.2)	31 (77.5)	32 (61.5)	87 (66.9)		92 (64.8)	46 (70.8)	58 (61.70)	196 (65.1)	
Ann Arbor Stage					0.782					0.816
III-IV	32 (80.0)	29 (72.5)	37 (71.2)	98 (74.2)		107 (80.5)	46 (76.7)	80 (85.1)	233 (81.2)	
IPI Group					0.754					0.485
0-1 Low	9 (22.5)	11 (27.5)	10 (19.2)	30 (22.7)		37 (25.7)	19 (28.8)	14 (14.6)	70 (22.9)	
2 Low Intermediate	10 (25.0)	13 (32.5)	12 (23.1)	35 (26.5)		35 (24.3)	19 (28.8)	22 (22.9)	76 (24.8)	
3 High Intermediate	15 (37.5)	7 (17.5)	23 (44.2)	45 (34.1)		42 (29.2)	15 (22.7)	35 (36.5)	92 (30.1)	
4-5 High	6 (15.0)	9 (22.5)	7 (13.5)	22 (16.7)		30 (20.8)	13 (19.7)	25 (26.0)	68 (22.2)	
Diagnosis to treatment interval (DTI)					0.782					0.889
Median days (range)	12.5 (2-43)	13 (2-41)	12.5 (0-40)	12.5 (0-43)		15 (1-55)	16 (3-56)	16.5 (1-92)	15 (1-92)	
Cell of origin					0.980					0.485
Known										
Non-GCB	15 (50.0)	12 (46.2)	15 (48.4)	42 (48.3)		32 (41.5)	20 (39.2)	30 (45.4)	82 (42.2)	
GCB	15 (50.0)	14 (53.8)	16 (51.6)	45 (51.7)		45 (58.5)	31 (60.8)	36 (54.6)	112 (57.4)	
Unknown/Not done	1	1	2	4		29	8	11	48	
Double Hit/Triple Hit					0.832					0.485
Known										
Yes	4 (19.0)	1 (5)	3 (12)	8 (12.1)		23 (27.3)	7 (14.9)	11 (16.4)	41 (20.7)	
No	17 (81.0)	19 (95)	22 (88)	58 (87.9)		61 (72.7)	40 (85.1)	56 (83.6)	157 (79.3)	
Unknown/Not done	19	20	27	66		61	19	30	110	
Double expressor					0.754					0.889
Known										
Yes	6 (30)	3 (20)	5 (33.3)	14 (28.0)		25 (43.1)	12 (37.5)	19 (41.3)	56 (41.2)	
No	14 (70)	12 (80)	10 (66.7)	36 (72.0)		33 (56.9)	20 (62.5)	27 (58.7)	80 (58.8)	
Unknown/Not done	20	25	37	82		87	34	50	170	
1L treatment					0.431					0.485

	MER (N=949)				LEO (N=2,755)			
	PPD (n=40)	EOT PR (n=40)	Early Relapse (< 12 mo) (n=52)	Total (n=132)	PPD (n=145)	EOT PR (n=66)	Early Relapse (<12 mo) (n=97)	Total (n=308)
R-CHOP	27 (67.5)	32 (80.0)	37 (71.2)	96 (72.7)	112 (77.2)	46 (70.8)	64 (66.7)	221 (72.7)
Other IC*	13 (32.5)	8 (20.0)	15 (28.8)	36 (27.3)	33 (22.8)	19 (29.2)	32 (33.3)	83 (27.3)

Abbreviations: PPD: primary progressive disease; EOT PR, end of 1L treatment partial response; early relapse, relapse within 12 months after 1L treatment; ECOG PS, Eastern Cooperative Oncology Group performance status: LDH, Lactate dehydrogenase; IPI, International Prognostic Index; Double-hit/triple-hit, *MYC* rearrangement with *BCL2* and/or *BCL6*; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; Double expressor, expression of *MYC* and *BCL2* by IHC*;* IC, immunochemotherapy: GCB, germinal center B-cell; MER, Molecular Epidemiology Resource; LEO, Lymphoma Epidemiology of Outcomes; mo, months; 1L, first line.
*Other IC: includes more intensive frontline chemotherapy including DA-EPOCH-R, R-HyperCVAD, R-CODOX-M/R-IVAC or therapy as part of an investigational clinical trial (e.g., R2-CHOP)
[1]False discovery rate (FDR) correction applied to all analyses.

Table 2. Second line treatment choices and response rate in MER and LEO cohorts.

	MER (N=949)					LEO (N=2,755)				
	PPD (n=40)	**EOT PR (n=40)**	**Early relapse (n=52)**	**Total (n=132)**		**PPD (n=145)**	**EOT PR (n=66)**	**Early Relapse (n=97)**	**Total (n=308)**	
Second line therapy	n (%)	n (%)	n (%)	n (%)	P	n (%)	n (%)	n (%)	n (%)	P
Platinum-based chemotherapy	33 (82.5)	29 (76.3)	27 (52.9)	89 (69.0)	0.002	91 (64.5)	34 (59.6)	41 (45.6)	166 (57.6)	0.011
Other systemic chemotherapy	4 (10.0)	2 (5.3)	11 (21.6)	17 (13.2)		6 (4.2)	4 (7.0)	11 (12.2)	21 (7.3)	
Primarily CNS-directed	3 (7.5)	1 (2.6)	11 (21.6)	15 (11.6)		7 (4.9)	9 (15.8)	17 (18.9)	33 (11.5)	
Radiation/ Resection	0 (0)	6 (15.8)	2 (3.9)	8 (6.2)		12 (8.5)	3 (5.3)	7 (7.8)	22 (7.7)	
Targeted therapies			N/A			11 (7.8)	3 (5.3)	11 (12.2)	25 (8.7)	
CAR-T (no bridging)			N/A			10 (7.0)	4 (7.0)	2 (2.2)	16 (5.6)	
No treatment			N/A			4 (2.8)	0 (0)	1 (1.1)	5 (1.7)	
Missing/ unknown	0	2	1	3		4	9	7	20	
Response rate to 2L therapy[a]	n (%)	n (%)	n (%)	n (%)	P	n (%)	n (%)	n (%)	n (%)	P
Complete response	3 (7.9)	3 (10.3)	16 (35.6)	21 (20.0)	0.009	25 (20.8)	16 (32.7)	40 (52.6)	81 (33.1)	<0.001
Partial response	12 (31.6)	15 (51.7)	15 (33.3)	42 (40.0)		27 (22.5)	16 (32.7)	15 (19.7)	58 (23.7)	
Stable disease	2 (5.3)	3 (10.3)	3 (6.7)	8 (7.6)		9 (7.5)	4 (8.2)	4 (5.3)	17 (6.9)	
Progressive disease	21 (55.3)	8 (27.5)	11 (24.4)	34 (32.4)		59 (49.2)	13 (26.4)	17 (22.4)	89 (36.3)	
Not applicable/ missing[b]	2	11	7	27		25	17	21	63	

Abbreviations: PPD, primary progressive disease; EOT PR, partial response at end of treatment; early relapse, patients relapsing within 12 months after EOT; MER, Molecular epidemiology resource; LEO, lymphoma epidemiology of outcomes; N/A, not applicable; CAR-T, CD19-directed chimeric antigen receptor T-cell therapy; CNS, central nervous system.

Treatment groups: Platinum-based chemotherapy: R-ICE (n=172), R-DHAP(n=46), R-GDP(n=17), R-DHAX(n=9), HyperCVAD(n=3), DA-EPOCH-(R)(n=4), ESHAP-(R)(n=4); Other systemic chemotherapy: CEPP(n=2), ROAD (n=5), R-GemOx (n=16), R-cyclophosphamide(n=1), R-Bendamustine(n=1); Primarily CNS-directed: single agent high dose methotrexate (HD MTX)(n=16), HDMTX, rituximab and temozolomide (MRT)(n=21), cytarabine/HD MTX (n=7); MATRIX (n=3), Ibrutinib + intrathecal MTX (n=1), Targeted therapies: ibrutinib (n=2), polatuzumab vedotin, rituximab with and without bendamustin (n=2), Rituximab-lenalidomide (n=10), Rituximab-lenalidomide-ibrutinib(n=2) venetoclax (n=2), loncastuximab tesirine (n=1), selinexor (n=1), pembrolizumab (n=2), single agent rituximab +/- prednisone

(n=3); CAR-T: cellular therapy with axi-cel, tisa-cel directly without bridging therapy (n=15), mosunetuzumab (n=1).
[a]Response rate determined by 2014 Lugano response criteria[21]
[b]Includes patients who received radiation/resection or no treatment as 2L therapy. In LEO, also includes patients with no imaging assessment (n=9)

622
623

624

625 **Table 3. Response rates to curative-intent second line treatment in MER and LEO cohorts.**

626

	MER (N=949)					LEO (N=2,755)				
	PPD (n=40)	**EOT PR (n=40)**	**Early relapse (n=52)**	**Total (n=132)**		**PPD (n=145)**	**EOT PR (n=66)**	**Early Relapse (n=97)**	**Total (n=308)**	
Second line therapy	n (%)	n (%)	n (%)	n (%)	P	n (%)	n (%)	n (%)	n (%)	P
Curative-intent	35 (90.0)	32 (86.5)	38 (74.5)	105 (82.8)	0.174	102 (70.8)	41 (63.1)	49 (51.0)	192 (63.0)	0.040
Non-curative intent	4 (10.0)	5 (13.5)	13 (25.5)	22 (17.2)		42 (29.2)	24 (36.9)	47 (49.0)	113 (37.0)	
Missing/ n/a	1	3	1	4		1	1	1	3	
Response rate to 2L therapy[a]	n (%)	n (%)	n (%)	n (%)	P	n (%)	n (%)	n (%)	n (%)	P
Curative intent	n=35	n=32	n=38	n=105	0.002	n=102	n=41	n=49	n=192	<0.001
Complete response	3 (8.6)	5 (16.6)	16 (42.1)	24 (23.5)		23 (23.9)	15 (38.5)	31 (66.0)	69 (37.9)	
Partial response	11 (31.4)	15 (50.0)	11 (28.9)	37 (36.3)		22 (22.9)	14 (35.9)	6 (12.7)	42 (23.1)	
Stable disease	1 (2.9)	2 (6.7)	3 (7.9)	6 (5.9)		6 (6.3)	1 (2.6)	2 (4.3)	9 (4.9)	
Progressive disease	19 (57.1)	8 (26.7)	7 (18.9)	34 (34.3)		45 (46.9)	9 (23.0)	8 (17.0)	62 (34.1)	
Missing	1	2	1	4		6	2	2	10	
Non-curative intent	n=4	n=5	n=13	n=22	0.243	n=42	n=24	n=47	n=113	0.045
Complete response	0 (0)	1 (50.0)	1 (11.1)	2 (14.3)		3 (9.6)	3 (25.0)	13 (36.1)	19 (21.6)	
Partial response	1 (33.3)	0	4 (44.4)	5 (35.7)		5 (16.1)	2 (16.7)	11 (30.6)	18 (20.5)	
Stable disease	1 (33.3)	1 (50)	0	2 (14.3)		3 (9.6)	3 (25.0)	2 (5.5)	8 (9.1)	
Progressive disease	1 (33.3)	0	4 (44.4)	5 (35.7)		20 (64.5)	4 (33.3)	10 (27.8)	34 (38.6)	
Not applicable[b]/ missing	1	3	4	8		11	12	11	34	

Table 4. Baseline clinical and pathological characteristics of patients with primary progressive disease compared to all non-PPD patients in the LEO cohort.

Variable	Primary Progressive Disease (PPD) (N=145) n (%)	All non-PPD (N=2610) n (%)	Total (N=2755) n (%)	P-value
Age at Diagnosis				0.611[1]
Median (range)	62.5 (19-88)	63.0 (18-99)	63.0 (18-99)	
Gender				0.026[2]
F	50 (34.7%)	1153 (44.2%)	1203 (43.7%)	
M	94 (65.3%)	1456 (55.8%)	1550 (56.3%)	
Race				0.892[2]
White	127 (88.2%)	2217 (85.0%)	2344 (85.1%)	
Black or African American	10 (6.9%)	192 (7.4%)	202 (7.3%)	
Unknown/Not Reported	4 (2.8%)	101 (3.9%)	105 (3.8%)	
Asian	3 (2.1%)	74 (2.8%)	77 (2.8%)	
>1 Race	0 (0.0%)	17 (0.7%)	17 (0.6%)	
American Indian/Alaska Native	0 (0.0%)	4 (0.2%)	4 (0.1%)	
Native Hawaiian/Pacific Islander	0 (0.0%)	4 (0.2%)	4 (0.1%)	
Ethnicity				0.764[2]
Hispanic/Latinx	15 (10.4%)	325 (12.5%)	340 (12.4%)	
Not Hispanic or Latinx	126 (87.5%)	2227 (85.4%)	2353 (85.5%)	
Unknown/Not Reported	3 (2.1%)	57 (2.2%)	60 (2.2%)	
Diagnosis Time Interval (DTI)				<.001[2]
≤ 14 Days	68 (49.6%)	755 (30.4%)	823 (31.4%)	
> 14 Days	69 (50.4%)	1731 (69.6%)	1800 (68.6%)	
Missing	8	124	132	
ECOG PS				0.053[2]
<2	104 (77.0%)	2040 (83.4%)	2144 (83.1%)	
≥2	31 (23.0%)	405 (16.6%)	436 (16.9%)	
Missing	10	165	175	
LDH				<.001[2]
<=Normal	27 (23.7%)	1038 (45.2%)	1065 (44.2%)	
>Normal	87 (76.3%)	1256 (54.8%)	1343 (55.8%)	
Missing	31	316	347	
Extranodal Sites				0.009[2]
≤1	92 (64.8%)	1905 (74.7%)	1997 (74.2%)	
>1	50 (35.2%)	646 (25.3%)	696 (25.8%)	
Missing	3	59	62	
Ann Arbor Stage				<.001[2]
I-II	26 (19.5%)	950 (38.5%)	976 (37.5%)	
III-IV	107 (80.5%)	1520 (61.5%)	1627 (62.5%)	
Missing	12	140	152	
IPI Group				0.003[2]
0-1 Low	37 (25.7%)	956 (36.6%)	993 (36.1%)	
2 Low Intermediate	35 (24.3%)	735 (28.2%)	770 (28.0%)	
3 High Intermediate	42 (29.2%)	574 (22.0%)	616 (22.4%)	

4-5 High	30 (20.8%)	344 (13.2%)	374 (13.6%)	
Missing	1	1	2	
Cell of origin				0.285[2]
Known	45	969		
GCB	(58.4%)	(57.3%)	1014 (57.3%)	
Non-GCB	32 (41.6%)	721 (42.6%)	753 (42.6%)	
Unknown/not done	68	920	988	
Double Hit				<.001[2]
Known	23	165	188	
DHL	(27.4%)	(10.3%)	(11.1%)	
non-DHL	61 (72.6%)	1439 (89.7%)	1500 (88.9%)	
Not Done/Missing	61	1006	1067	
Double Expressor				<.001[2]
Known	25	337	362	
Positive	(43.1%)	(25.0%)	(25.8%)	
Negative	33 (56.9%)	1009 (75.0%)	1042 (74.2%)	
Not Done/Missing	87	1264	1351	

Abbreviations: PPD: primary progressive disease; ECOG PS, Eastern Cooperative Oncology Group performance status: LDH, Lactate dehydrogenase; IPI, International Prognostic Index; Double-hit, *MYC* rearrangement with *BCL2* and/or *BCL6*; Double expressor, expression of *MYC* and *BCL2*: GCB, germinal center B-cell; non-GCB, activated B-cell subtype. [1]Kruskal-Wallis p-value; [2]Chi-Square p-value

Figure Legends:

Figure 1. Overall survival from time of relapse based on timing of refractory status. Overall survival in MER (A) and (B) and LEO (C) and (D).

Figure 2. **Overall survival for primary progressive disease compared to all other newly diagnosed patients with LBCL in the LEO cohort.** OS from date of last treatment (non-relapsed patients) or date of relapse/progression (relapsed patients).

Figure 1

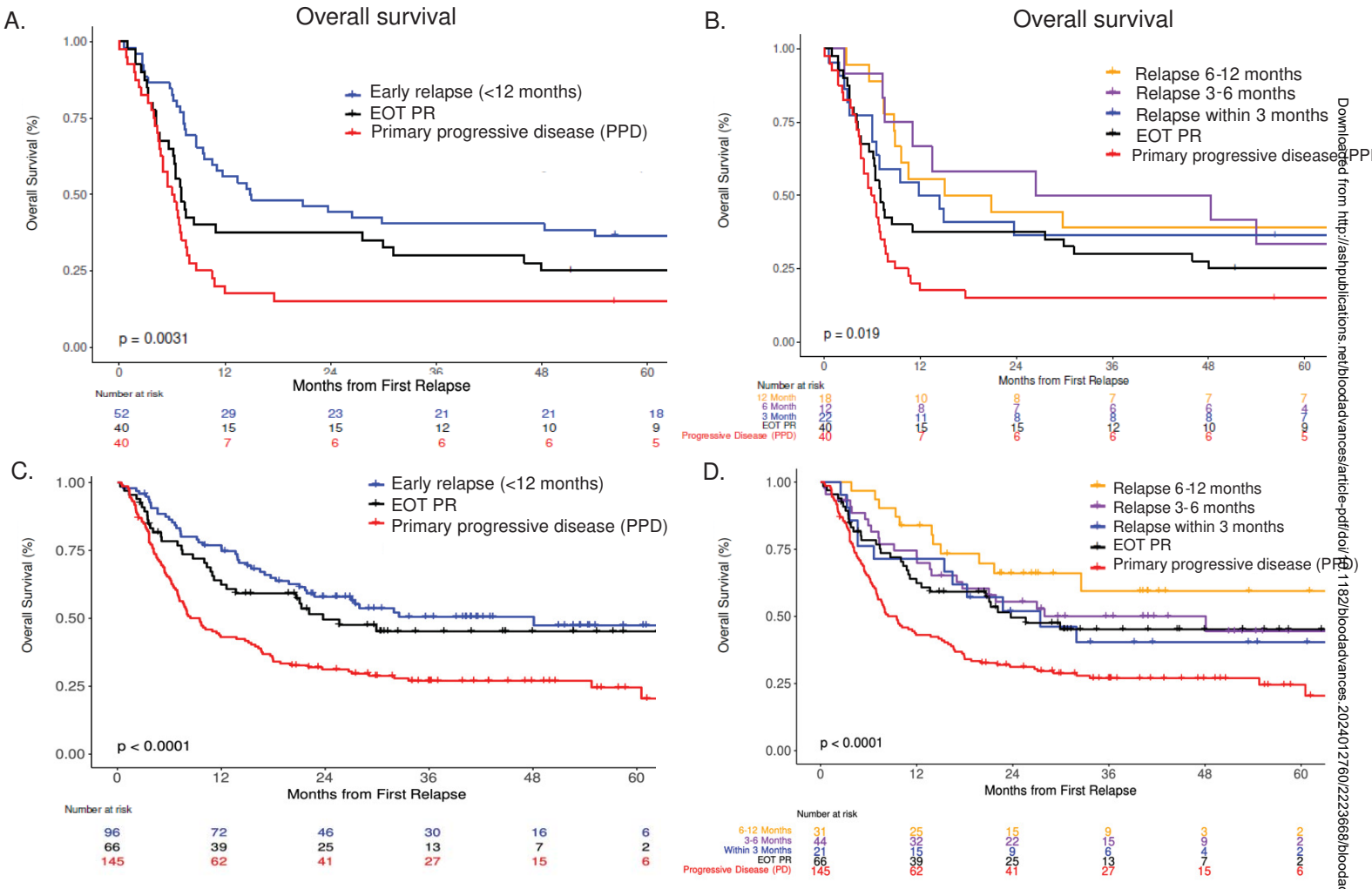
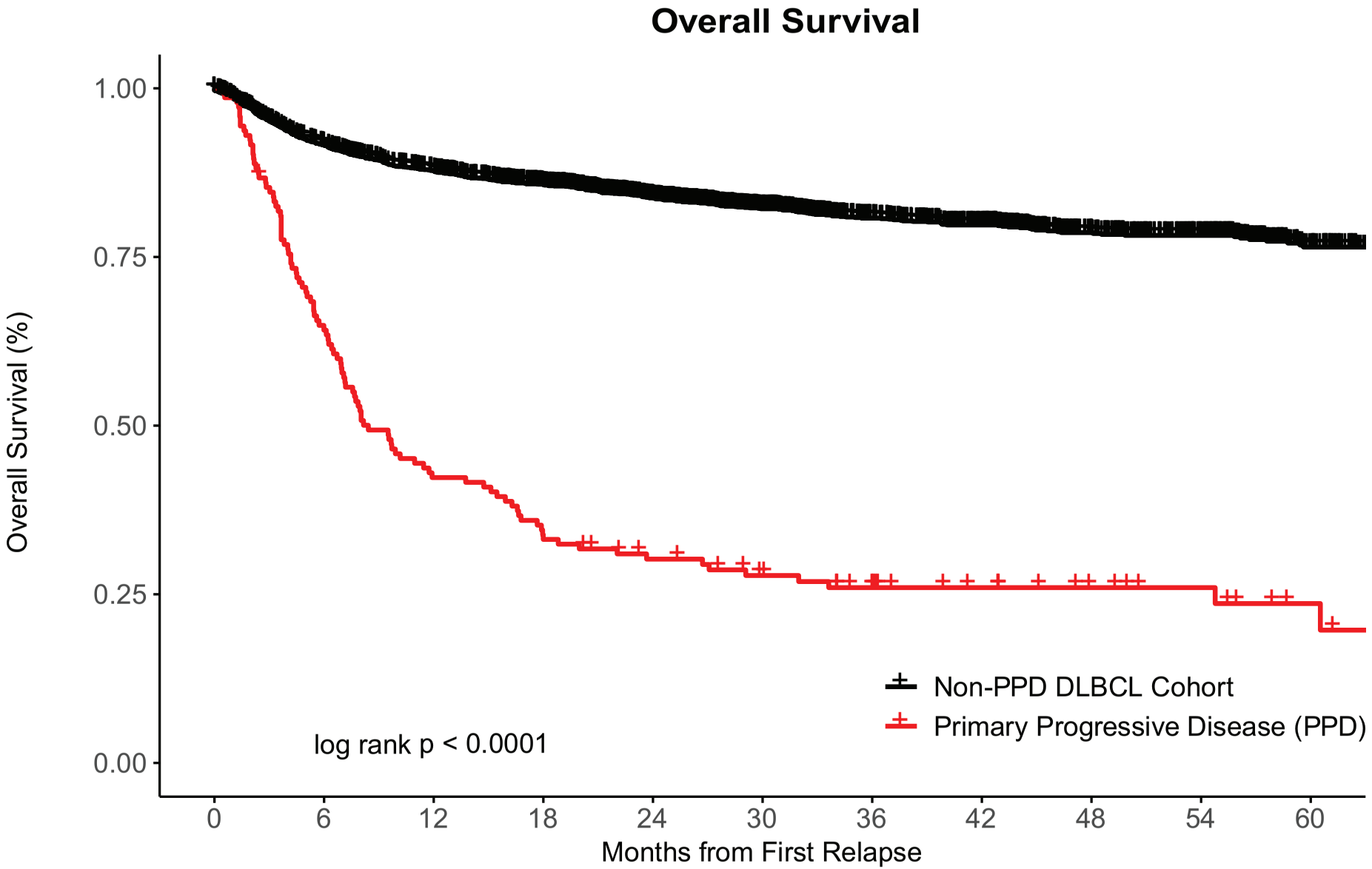


Figure 2



Number at risk											
Non-PPD DLBCL Cohort	2609	2270	2082	1887	1622	1279	996	852	586	468	253
Primary Progressive Disease (PPD)	143	91	60	47	39	32	26	19	14	11	6

Cumulative number of events											
Non-PPD DLBCL Cohort	8	214	306	353	394	422	441	453	463	466	473
Primary Progressive Disease (PPD)	0	51	82	93	99	102	104	104	104	104	105