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Autologous stem cell transplant in fit patients with refractory or early relapsed diffuse large B-cell lymphoma that responded to salvage chemotherapy

Aung M. Tun1,2*, Yucai Wang1*, Seth Maliske3, Ivana Micallef1, David J. Inwards1, Thomas M. Habermann1, Luis Porrata1, Jonas Paludo1, Jose Villasboas Bisneto1, Allison Rosenthal1, Mohamed A Kharfan-Dabaja6, Stephen M. Ansell1, Grzegorz S. Nowakowski1, Umar Farooq3, Patrick B. Johnston1

1 Division of Hematology, Mayo Clinic, Rochester, Minnesota
2 Division of Hematologic Malignancies and Cellular Therapeutics, The University of Kansas, Kansas City, Kansas
3 Division of Hematology, Oncology, and Blood & Marrow Transplantation, University of Iowa, Iowa City, Iowa
4 Internal Medicine, Division of Hematology/Oncology, Mayo Clinic Arizona, Scottsdale, Arizona
5 Division of Hematology-Oncology and Blood and Marrow Transplantation and Cellular Therapy Program, Mayo Clinic, Jacksonville, Florida

* AMT and YW contributed equally.

Corresponding Author: Aung M. Tun, MD (atun@kumc.edu) or Patrick B. Johnston, MD, PhD

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Conception and design: Aung M. Tun, Yucai Wang, and Patrick B. Johnston
Collection and assembly of data: Aung M. Tun and Seth Maliske
Data analysis and Interpretation: All authors
Manuscript writing: The first draft was prepared by Aung M. Tun, Yucai Wang, and Patrick B. Johnston. All authors reviewed and revised the manuscript.
Final approval of manuscript: All authors

Data-Sharing statement
This article includes the data supporting the findings and interpretation of the results. Please contact the corresponding authors for additional data.
Abstract

Chimeric antigen receptor T-cell (CAR-T) therapy is the new standard of care in fit patients with refractory or early relapsed diffuse large B-cell lymphoma (DLBCL). However, there may still be a role for salvage chemotherapy (ST) and autologous stem cell transplant (ASCT) in certain circumstances (eg, lack of CAR-T resources, chemosensitive relapses, etc). We retrospectively studied 230 patients with refractory or early relapsed DLBCL who underwent ST and ASCT. Median line of ST was 1 (range 1-3). Best response before ASCT was complete response (CR) in 106 (46%) and partial response (PR) in 124 (54%) patients. Median follow-up after ASCT was 89.4 months. The median progression-free (PFS) and overall survival (OS) were 16.1 and 43.3 months, respectively. Patients relapsing between 6 to 12 months after frontline therapy had numerically better median PFS (29.6 months) and OS (88.5 months). Patients who required 1 line of ST, compared to those requiring >1 line, had better median PFS (37.9 vs 3.9 months; \( P = 0.0005 \)) and OS (68.3 vs 12.0 months; \( P = 0.0005 \)). Patients who achieved CR had better median PFS (71.1 vs 6.3 months; \( P<0.0001 \)) and OS (110.3 vs 18.9 months; \( P<0.0001 \)) than those in PR. Patients who achieved CR after 1 line of ST had the most favorable median PFS (88.5 months) and OS (117.2 months). Post-ASCT survival outcomes of patients with refractory or early relapsed DLBCL appeared reasonable and were particularly favorable in those who required only 1 line of ST to achieve CR before ASCT, highlighting its role in select patients with chemosensitive disease.

Introduction

Diffuse large B-cell lymphoma (DLBCL), the most common type of aggressive non-Hodgkin lymphoma (NHL), constitutes approximately 30% of newly diagnosed NHL cases each year in the United States.\(^1,2\) Approximately 30–40% of patients encounter relapsed or refractory (RR) disease after frontline immunochemotherapy (IC), and their survival outcomes are generally unfavorable — particularly in those with refractory disease or an early relapse occurring within 12 months of initial diagnosis (or frontline treatment), as reported by multiple studies including Center for International Blood and Marrow Transplant Research (CIBMTR), the Molecular Epidemiology Resource (MER) of the University of Iowa/Mayo Clinic Lymphoma Specialized Program of Research Excellence, as well as the CORAL study.\(^3,4,13,14,5–12\) To improve outcomes of such patients, three phase 3 randomized clinical trials (RCTs) were conducted in patients with refractory or an early relapse within 12 months of treatment completion, comparing chimeric antigen receptor T-cell (CAR-T) products (axicabtagene ciloleucel in ZUMA-7, tisagenlecleucel in BELINDA, lisocabtagene maraleucel in TRANSFORM) to then standard-of-care of salvage chemotherapy (ST) followed by high dose chemotherapy (HDT) and autologous stem cell transplant (ASCT), which established axicabtagene ciloleucel and lisocabtagene maraleucel as the new standard of care in second line setting.\(^15–17\)

However, significant challenges and barriers remain for timely delivery of CAR-T therapy in routine clinical practice. CAR-T therapy, to date, is mainly offered in major referral centers, and patients often need to travel long distance for CAR-T therapy evaluation. Patients also need to spend weeks to months for eligibility and fitness assessment, insurance approval, CAR-T manufacturing, and other logistical planning.\(^18,19\) A substantial number of patients, before receiving CAR-T therapy, experience symptomatic, life threatening progressive disease and often require urgent systemic chemotherapy in a form of a salvage or bridging therapy.\(^19\) Moreover, clinical activities of CAR-T therapy remain modest in the second line setting, with the median event-free survival of only 8.3 months with axicabtagene ciloleucel in ZUMA-7 and 10.1 months with lisocabtagene maraleucel in TRANSFORM, and the majority of patients treated with CAR-T in both studies experienced a relapse.\(^15,17\) Furthermore, CAR-T therapy is associated with significant morbidities such as cytokine release syndrome, neurotoxicities, and cytopenia, and its long-term complications remain a major concern.\(^19\)
Given challenges and barriers as well as modest clinical activities of CAR-T, there is a need to explore alternative strategies and identify patients who can truly benefit from HDT and ASCT. It is well understood that ASCT (or rescue) enables the use of HDT, in patients with proven chemosensitive disease, to eradicate residual lymphoma cells that have evaded ST.\(^{20}\) Whereas autologous CAR-T therapy utilizes genetically modified patient’s T-cells, directing against CD19 antigen on lymphoma cells, for its therapeutic effect.\(^{15,17}\) Accordingly, fit patients with chemosensitive disease can benefit from consolidation with HDT and ASCT, unlike those with chemoresistant disease.\(^{11,21}\) We, therefore, hypothesize that HDT and ASCT is beneficial and preferable in patients with proven chemosensitive disease after 1 line of ST, and those with a later relapse 6–12 months of completing frontline IC. Hence we conducted a retrospective study of patients with refractory disease or relapse within 12 months of completing frontline IC from the Mayo Clinic (MC) and the University of Iowa (IA) lymphoma and transplant databases.

Methods

**Patients**

The institutional review boards at MC and IA approved this study. Data were abstracted on consecutive adult patients who underwent ASCT for DLBCL between July 2000 and December 2017 at MC or between April 2003 and April 2020 at IA. Clinical, pathological, molecular characteristics, cell of origin by Hans algorithm, as well as treatment course, clinical response to treatment (as determined by treating physician), and clinical outcome data were extracted by chart reviews.

For this study, eligible patients were those who were treated with frontline R-CHOP or R-CHOP-like IC, had refractory disease (i.e. disease progression during frontline IC or persistent disease after completion of frontline therapy) or an early relapse occurring within 12 months of frontline IC completion, and underwent ST and ASCT. Patients who had response assessment to ST done by positron emission tomography (PET)-computed tomography (CT) scan and achieved CR or PR, as determined by treating physicians, were included. DLBCL was classified as per hematopathologists in MC and IA. Patients with MYC and BCL2 and/or BCL6 rearrangements (i.e. double-hit or triple-hit lymphoma) and transformed indolent lymphoma at diagnosis, unless previously treated with IC, were also included. Patients who did not receive frontline rituximab and those who underwent hematopoietic stem cell transplant in the frontline (after achieving complete remission to frontline IC) were excluded.

**Statistical analysis**

Descriptive statistics was used to report baseline characteristics, treatment information, and response status. The reverse Kaplan-Meier method was used to estimate median follow up time.\(^{22,23}\) Duration of response (DOR) was defined as time from initial response after ASCT to disease progression, relapse, or death. Post-ASCT progression-free survival (PFS) was defined as time from ASCT until progression, relapse, or death from any cause. Post-ASCT overall survival (OS) was defined as time from ASCT to death from any cause. Post-ASCT PFS and OS were plotted by Kaplan-Meier method. Log-rank test and Cox proportional hazards models were used to evaluate the impact of clinicopathological characteristics, treatment variables, and response status on PFS and OS. \(P\)-value of <0.05 was considered statistically significant. Cumulative incidences of relapse and nonrelapse mortality as well as causes of death were analyzed with competing risk models.\(^{24}\) Cause of death was categorized as deaths as a result of lymphoma progression, treatment-related toxicities, non-lymphoma related causes (other causes), and unknown causes. Statistical analyses were performed in JMP v16 and XLSTAT v2021.2.

Results

**Clinicopathological characteristics of the study population and treatment**
A total of 230 eligible patients were included in the study (Supplementary Figure 1). Baseline characteristics of patients at initial diagnosis are summarized in Supplementary Table 1. Clinical characteristics at relapse are described in Table 1. 157 (68%) patients had refractory disease or relapsed within 6 months of completing the frontline therapy and 73 (32%) had a relapse between 6 to 12 months of frontline therapy. The median age at relapse/ST was 60 years (range 19–78), and 107 (47%) patients were of age >60 years. The Eastern Cooperative Oncology Group performance status (ECOG PS) was ≤1 in 181 (97%) patients. 56 (39%) had an elevated lactate dehydrogenase (LDH) level, 21 (12%) had >1 extranodal site involvement, and 109 (61%) had advanced stage disease. Treatment pattern and responses to therapy are shown in Supplementary Table 2. 201 (87%) had platinum or high dose cytarabine containing chemotherapy as a first line ST. A median of 1 line (range 1–3) of ST was required. The lines of ST were 1 in 178 (77%) and >1 in 52 (23%) patients. Response before ASCT was CR in 106 (46%) and PR in 124 (54%) patients. Median age at ASCT was 60 years (range 19–78). Carmustine (BCNU), etoposide, cytarabine (Ara-C), and melphalan conditioning regimen was used in 213 (93%) patients. Following ASCT, 123 (56%) patients achieved CR, and 18 (8%) patients had consolidative radiation therapy post-ASCT.

Post-ASCT outcomes

Median follow-up after ASCT was 89.4 months (95% confidence interval [CI] 73.5–99.2), and post-ASCT outcomes at 12 months, 24 months, and 60 months are summarized in Supplementary Table 3. The median PFS and OS after ASCT were 16.1 months (95% CI 9.3–43.3) and 43.3 months (95% CI 24.2–75.5), respectively. The 24-month PFS and OS rates were 47% and 57%, respectively (Figure 1A & 1B). The median DOR in patients who achieved CR or PR after ASCT was 96.4 months (95% CI 61.6–160.6), with a 24-month DOR rate of 72%. The cumulative incidence of post-ASCT relapse and nonrelapse mortality rates were 43.4% and 3.9% at 12 months (Figure 1C). 118 patients had a relapse (see Supplementary Table 4 for their subsequent management), with median post relapse OS of 6.0 months (95% CI 3.8–8.3) (Supplementary Figure 2), and 136 died during the follow up (see Supplementary Table 5 for causes of death). Lymphoma was the primary cause of death after ASCT, with a 12-month estimated death rate of 28.5% due to lymphoma, 2.1% due to therapies, 1.3% due to other causes, and 0.9% of unknown causes (Figure 1D).

Outcomes according to clinicopathological characteristics

No statistically significant difference in PFS and OS was seen based on age at relapse, sex, ECOG PS, serum LDH, extranodal site involvement, and stage at relapse (Table 2). Time to first relapse/refractory status (relapse 6–12 months vs refractory or relapse <6 months after frontline therapy) was not associated with a significant difference in PFS (median PFS 29.6 vs 10.1 months; \(P = 0.47\)) (Figure 2A) (Table 2), but there was a trend for improvement in OS (median OS 88.5 vs 28.0 months; \(P = 0.07\)) (Figure 2B) (Table 2). Patients who required 1 line of ST, compared to those who required >1 line of ST, had significantly better PFS (median PFS 37.9 vs 3.9 months; \(P = 0.0005\)) (Figure 2C) (Table 2) and OS (median OS 68.3 vs 12.0 months; \(P = 0.0005\)) (Figure 2D) (Table 2). In addition, patients who achieved CR prior to ASCT, compared to those who achieved PR, had significantly better PFS (median PFS 71.1 vs 6.3 months; \(P<0.0001\)) (Figure 3A) (Table 2) and OS (median OS 110.3 vs 18.9 months; \(P<0.0001\)) (Figure 3B) (Table 2). Patients who achieved CR after 1 line of ST had the most favorable PFS and OS, with median PFS of 88.5 vs 9.1 vs 12.0 vs 3.2 months (\(P<0.0001\)) and median OS of 117.2 vs 28.8 vs 32.5 vs 7.1 months (\(P<0.0001\)) in cases with CR after 1 line of ST vs PR after 1 line of ST vs CR after >1 line of ST vs PR after >1 line of ST (Figure 3C & 3D) (Table 2). In multivariate Cox regression models adjusted for age at ASCT and sex, lines of ST and response to ST before ASCT remained prognostic for PFS (1 line of ST: HR 0.53 (95% CI 0.36–0.77); \(P = 0.0008\) and CR: HR 0.49 (95% CI 0.35–0.69); \(P<0.0001\)) and OS (1 line of ST: HR 0.51 (95% CI 0.35–0.74); \(P = 0.0005\) and CR: HR 0.46 (95% CI
Additionally, in this multivariate model, time to first relapse/refractory status (relapse between 6 to 12 months vs refractory or relapse <6 months of frontline therapy) showed a trend for improvement in PFS, HR 0.83 (95% CI 0.59–1.18); \( P = 0.31 \) and a statistically significant improvement in OS, HR 0.67 (95% CI 0.46–0.98); \( P = 0.04 \) (Supplementary Table 6).

Note that patients with a MYC rearrangement status, compared to those without, had significantly inferior PFS (median PFS 3.1 vs 43.3 months; \( P = 0.0001 \)) and OS (median OS 6.2 vs 67.4 months; \( P<0.0001 \)) (Table 2; Supplementary Figure 3).

**Discussion**

The new standard of care in fit patients with primary refractory or early relapsed DLBCL occurring within 12 months of completing frontline IC is CAR-T therapy with axicabtagene ciloleucel or lisocabtagene maraleucel according to the results of the contemporary ZUMA-7 and TRANSFORM studies.\(^{15,17}\) Our study of such patients, treated with ST and ASCT, reported reasonable survival outcomes with the median PFS of 16.1 months and the 24-month PFS of 47%. The results from our study are in keeping with those of CIBMTR that reported a 3-year post-ASCT PFS rate of 44% despite early IC failure within 12 months of initial diagnosis and another study from CIBMTR, in patients with primary refractory DLBCL, that reported a 3-year post-ASCT PFS rate of 46.8%.\(^{10,25}\) The median DOR in our patients who achieved CR or PR after ASCT was 96.4 months (24-month DOR, 72%). These results indicate that patients with chemosensitive RR disease, despite having primary refractory disease to frontline IC or an early relapse, can expect durable disease control with ASCT consolidation. These findings are further supported by durable responses seen in patients assigned to the standard of care group of the ZUMA-7 and TRANSFORM studies, with the former resulting in the median DOR of 8.9 months in patients who had a response (i.e. CR or PR) and the latter reporting the median DOR of 14.5 months (12-month DOR rate, 54.7%) in patients achieving CR.\(^{15,17}\) More favorable survival outcomes were observed in our patients who required only 1 line of ST and those who achieved CR, with the median PFS of 37.9 months (24-month PFS, 52%) and 71.1 months (24-month PFS, 62%), respectively. Most importantly, survival outcomes were excellent in patients who had only 1 line of ST and resulted in CR, with the median PFS of 88.5 months (24-month PFS, 65%). These findings imply that HDT, followed by ASCT rescue, confers complete eradication of lymphoma cells that are biologically sensitive to chemotherapy.

In patients who achieved PR after 1 line of ST, our study showed the median PFS of 9.1 months, with the 24-month PFS of 39%. The CIBMTR study reported a 5-year post-ASCT PFS rate of 41% in patients with early frontline IC failure (i.e. primary refractory disease or relapse within 12 months of diagnosis).\(^{12}\) A similar result was reported from MD Anderson Cancer Center (MDACC) with a 5-year post-ASCT PFS rate of 40% in patients with RR DLBCL who had residual disease before ASCT.\(^{26}\) Variations in survival rates among these studies are due, in part, to different study populations, study eras, patterns of relapse, and management approaches.\(^{12,26}\) In addition, defining PR by treating physicians is subjective, and varies depending on imaging modality (i.e. CT or PET-CT scans).\(^{27}\) Nevertheless, despite achieving only PR, their survival outcomes after ASCT are reasonable, with a long term remission rate of ~40%, supporting the role of ASCT consolidation.\(^{12,26}\) In the CAR-T therapy era, the role of ASCT consolidation in patients achieving PR to ST was reported by CIBMTR.\(^{28}\) In this study, the efficacy of ASCT was compared with that of axicabtagene ciloleucel in a total of 411 patients of which 266 undergoing ASCT consolidation and 145 receiving axicabtagene ciloleucel.\(^{28}\) The study found that ASCT consolidation, compared to axicabtagene ciloleucel, was associated with a lower rate of relapse/progression (2-year rate, 40% vs 53%; \( P = 0.05 \)), a trend for superior PFS (2-year rate, 52% vs 42%; \( P = 0.1 \)), and a superior OS rate (2-year rate, 69% vs 47%; \( P = 0.004 \)).\(^{28}\) The caveat with this study was that median line of therapy was higher in patients receiving axicabtagene ciloleucel, and the difference was no longer seen when the
analysis was done in patients who received ≤2 lines of therapy (1-year PFS, 59% in the ASCT group vs 65% in the axicabtagene ciloleucel group; \( P = 0.5 \)).28

There is no consensus among lymphoma clinicians when defining early treatment failure. Most historical studies, such as CIBMTR, MER, and CORAL, identified patients with refractory or relapse within 12 months of initial diagnosis as an unfavorable risk factor.\(^7,10,12,13\) In contrast, the 3 RCTs (ZUMA-7, TRANSFORM, and BELINDA) and the NCIC-CTG LY.12 study determined patients with refractory or relapse within 12 months of completing frontline therapy as high risk.\(^15–17,29\) Consequently, selection of optimal treatment strategy becomes challenging for patients relapsing 6 to 12 months of frontline therapy completion.\(^19\) It is noteworthy that these patients achieve a remission duration of at least 6 months after completing frontline IC, indicating chemosensitive biology, and are more likely to respond to ST and be able to proceed with HDT and ASCT.\(^7\) In our study, patients that relapsed between 6 to 12 months of frontline therapy, compared to those with refractory or relapse <6 months, did not have a statistically significant improvement in PFS after ASCT (\( P = 0.47 \)), albeit numerically better PFS in the former (median PFS 29.6 vs 10.1 months). Additionally, there was a trend for improvement in OS in the univariate analysis (\( P = 0.07 \)), and a statistically significant improvement in OS, after adjusted for age at ASCT and sex, in the multivariate model (\( P = 0.04 \)). Therefore, after establishing chemosensitive disease, careful consideration between HDT followed by ASCT and CAR-T is warranted in such patients due to their favorable survival rate after ASCT (24-month PFS, 52%), though the findings from our study population, receiving care at MC and IA, may limit broader generalization.

There remain logistical and financial barriers that prevent timely access to CAR-T therapy.\(^30\) Patients often need to wait weeks to months for frailty and fitness assessment, overcoming logistical and financial barriers, as well as CAR-T manufacturing (though a significantly shorter wait time is anticipated with the use of allogeneic CAR-T products).\(^16,30,31\) Moreover, patients with relapsed or progressive disease are often symptomatic requiring immediate intervention. Thus, it is reasonable to initiate ST especially in resource limited setting. Those who achieved PR can consider proceeding with ASCT based on reasonable survival outcomes, and this practice is supported by the report from CIBMTR, favoring ASCT consolidation, as discussed earlier.\(^15,28\) For those achieving CR, ASCT consolidation seems favored over CAR-T, in patients with early treatment failure, as per the recent study from CIBMTR reporting a lower 2-year relapse rate (22.8% vs 45.9%; \( P<0.001 \)) and a superior 2-year PFS rate (70.9% vs 48.3%; \( P<0.001 \)), though it is difficult to draw definitive conclusions due to its retrospective study design.\(^32\) Similar survival outcomes were reported, after receiving CAR-T therapy while in CR, with a 2-year PFS rate of 44% in the MDACC cohort and a 1-year PFS rate of 59.6% in the study from 8 US academic centers.\(^33,34\) Notably, patients relapsing or progressing after CAR-T therapy have unfavorable outcomes due to the limited availability and efficacy of subsequent STs.\(^19\) After CAR-T therapy, cytopenias and patient intolerance to intensified therapy and the potential of stem cell mobilization failure make ASCT less feasible.\(^19,35\) Although ASCT consolidation generally is favored in patients with established chemosensitive disease, post-ASCT outcomes of those with \( MYC \) rearrangement are poor, despite having chemosensitive disease, with median PFS of only 3.1 months, and CAR-T therapy may be preferred in such patients.\(^36,37\)

It is, however, worth noting that only about half of patients with RR DLBCL treated with intensified therapy are able to proceed with ASCT consolidation, though higher response rates can be expected with the incorporation of novel therapeutic agents.\(^7,13,15,17,29,38,39\) In the CORAL study, ~63% of patients achieved CR or PR to ST, namely rituximab, ifosfamide, carboplatin, and etoposide (RICE) and rituximab, dexamethasone, high-dose cytarabine, and cisplatin (R-DHAP), and ~53% of patients subsequently proceeded with ASCT. In NCIC-CTG LY.12, ~45% of patients had responses to ST regimens gemcitabine, dexamethasone, and cisplatin (GDP) and DHAP.\(^7,29\) The real world analysis of the MER database reported that 40% of patients treated aggressively with the second line ST for RR DLBCL were
able to proceed with ASCT. In participants of ZUMA-7 and TRANSFORM trials, who were then randomized to the ST group, ASCT consolidation was done in 38% and 46% of patients, respectively. However, response to ST can be improved with the incorporation of novel therapy; notably, polatuzumab vedotin added to RICE achieved an overall response rate (i.e. CR or PR) of 92%, with an acceptable toxicity profile, in a multicenter phase II study. Response rates could also improve with incorporation of bispecific CD20xCD3 monoclonal antibodies to ST, and these strategies are being evaluated by currently ongoing clinical studies such as glofitamab plus RICE (NCT05364424) and epcoritamab plus GDP (NCT05852717).

The strengths of our study include systematic review of large number of patients with RR DLBCL following failure of frontline R-CHOP or R-CHOP-like IC who then underwent ASCT after the first, early relapse or refractory status, with the availability of the long-term follow up data. However, our study has limitations due to its retrospective study design with potential selection bias, geographical bias with limited generalizability, and lack of centralized histopathology review, as well as some missing information and long study period that spans over two decades with potential heterogeneity in management approaches.

Conclusions

In summary, survival outcomes after ASCT are favorable in at least a subset of patients with primary refractory or early relapsed DLBCL. Post-ASCT survival outcomes are more favorable in patients who require only 1 line of ST and those achieved CR to ST. Furthermore, survival outcomes after ASCT are excellent in patients achieving CR after 1 line of ST. In patients who relapsed between 6 to 12 months of completing frontline therapy, careful consideration between CAR-T therapy and ST followed by HDT and ASCT should be done. These data support the role of ST and ASCT consolidation as a second line treatment strategy in select patients with primary refractory or early relapsed DLBCL in an appropriate clinical context.
References:


Table 1. Characteristics of RR DLBCL patients at relapse/salvage therapy

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† Primary refractory DLBCL (n=106) and relapsed <6 months (n=51)

Abbreviations: RR, relapsed or refractory; DLBCL, diffuse large B-cell lymphoma; ASCT, autologous stem cell transplant; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase
Table 2. Survival after ASCT by clinicopathological characteristics and response status

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<th>Median PFS in months (95% CI)</th>
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<td>&gt;6 months† (n = 157)</td>
<td>10.1 (5.8–43.3)</td>
<td>45% (38–53)</td>
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<td>28.0 (14.5–67.4)</td>
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<td>6–12 months (n = 73)</td>
<td>29.6 (12.1–64.9)</td>
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<td>≤60 (n = 123)</td>
<td>12.2 (6.7–110.3)</td>
<td>47% (38–56)</td>
<td>0.33</td>
<td>48.5 (18.9–143.0)</td>
<td>57% (48–66)</td>
<td>0.37</td>
</tr>
<tr>
<td>&gt;60 (n = 107)</td>
<td>16.2 (8.4–48.1)</td>
<td>47% (38–57)</td>
<td></td>
<td>39.4 (21.2–71.1)</td>
<td>57% (47–66)</td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Male (n = 149)</td>
<td>14.6 (8.9–37.9)</td>
<td>46% (38–54)</td>
<td>0.08</td>
<td>43.3 (27.3–71.1)</td>
<td>59% (51–67)</td>
<td>0.34</td>
</tr>
<tr>
<td>Female (n = 81)</td>
<td>16.2 (6.1–NR)</td>
<td>49% (38–60)</td>
<td></td>
<td>55.0 (14.5–NR)</td>
<td>53% (42–64)</td>
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<tr>
<td><strong>ECOG PS scale</strong></td>
<td></td>
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<tr>
<td>≤1 (n = 181)</td>
<td>18.5 (10.1–54.4)</td>
<td>49% (41–56)</td>
<td>0.80</td>
<td>62.9 (28.1–88.5)</td>
<td>59% (52–66)</td>
<td>0.52</td>
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<tr>
<td>&gt;1 (n = 5)</td>
<td>6.3 (1.6–NR)</td>
<td>40% (0–83)</td>
<td></td>
<td>8.1 (2.1–NR)</td>
<td>40% (0–83)</td>
<td></td>
</tr>
<tr>
<td><strong>LDH</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal (n = 87)</td>
<td>48.9 (10.1–71.1)</td>
<td>55% (46–56)</td>
<td>0.17</td>
<td>68.3 (55.0–110.3)</td>
<td>70% (60–80)</td>
<td>0.07</td>
</tr>
<tr>
<td>Elevated (n = 56)</td>
<td>7.7 (3.7–37.8)</td>
<td>41% (28–54)</td>
<td></td>
<td>20.5 (9.1–43.3)</td>
<td>48% (35–61)</td>
<td></td>
</tr>
<tr>
<td><strong>Extranodal sites</strong></td>
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<td></td>
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</tr>
<tr>
<td>≤1 (n = 161)</td>
<td>28.7 (11.7–59.5)</td>
<td>50% (43–58)</td>
<td>0.50</td>
<td>64.8 (28.8–95.5)</td>
<td>60% (53–68)</td>
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<tr>
<td>&gt;1 (n = 21)</td>
<td>8.2 (3.1–NR)</td>
<td>38% (17–59)</td>
<td></td>
<td>32.5 (7.9–110.3)</td>
<td>52% (31–74)</td>
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</tr>
<tr>
<td><strong>Stage at relapse</strong></td>
<td></td>
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<tr>
<td>I-II (n = 70)</td>
<td>55.0 (14.4–95.5)</td>
<td>57% (45–69)</td>
<td>0.17</td>
<td>71.1 (31.5–145.2)</td>
<td>70% (59–81)</td>
<td>0.15</td>
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<tr>
<td>III-IV (n = 109)</td>
<td>12.0 (5.4–48.1)</td>
<td>43% (34–52)</td>
<td></td>
<td>37.1 (13.9–75.5)</td>
<td>52% (43–62)</td>
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<tr>
<td><strong>MYC rearrangement</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Present (n = 9)</td>
<td>3.1 (1.9–7.7)</td>
<td>13% (0–35)</td>
<td>0.0001</td>
<td>6.2 (3.4–13.8)</td>
<td>13% (0–35)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Absent (n = 53)</td>
<td>43.3 (8.9–NR)</td>
<td>54% (41–68)</td>
<td></td>
<td>67.4 (22.9–NR)</td>
<td>64% (50–77)</td>
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</tr>
<tr>
<td><strong>Lines of ST</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>0.0005</td>
</tr>
<tr>
<td>1 (n = 178)</td>
<td>37.9 (14.4–84.0)</td>
<td>52% (45–60)</td>
<td>0.0005</td>
<td>68.3 (33.0–117.2)</td>
<td>63% (56–70)</td>
<td></td>
</tr>
<tr>
<td>&gt;1 (n = 52)</td>
<td>3.9 (3.0–9.3)</td>
<td>31% (18–43)</td>
<td></td>
<td>12.0 (6.8–23.2)</td>
<td>37% (23–50)</td>
<td></td>
</tr>
<tr>
<td><strong>Response to ST</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CR (n = 106)</td>
<td>71.1 (29.6–118.6)</td>
<td>62% (53–71)</td>
<td>&lt;0.0001</td>
<td>110.3 (64.9–NR)</td>
<td>68% (59–77)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PR (n = 124)</td>
<td>6.3 (4.2–9.7)</td>
<td>35% (27–43)</td>
<td></td>
<td>18.9 (9.1–31.5)</td>
<td>47% (38–56)</td>
<td></td>
</tr>
<tr>
<td><strong>Lines of ST and response status</strong></td>
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<td>&lt;0.0001</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
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<tr>
<td>CR after 1 line of ST (n = 90)</td>
<td>88.5 (43.3–NR)</td>
<td>65% (55–75)</td>
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<td>117.2 (75.5–NR)</td>
<td>70% (61–80)</td>
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<tr>
<td>PR after 1 line of ST (n = 88)</td>
<td>9.1 (5.4–16.2)</td>
<td>39% (29–49)</td>
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<td>28.8 (13.4–64.8)</td>
<td>55% (45–66)</td>
<td></td>
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<tr>
<td>CR after &gt;1 line of ST (n = 16)</td>
<td>12.0 (3.5–163.8)</td>
<td>44% (19–68)</td>
<td></td>
<td>32.5 (19.1–163.8)</td>
<td>56% (32–81)</td>
<td></td>
</tr>
<tr>
<td>PR after &gt;1 line of ST (n = 36)</td>
<td>3.2 (2.8–5.4)</td>
<td>25% (11–39)</td>
<td></td>
<td>7.1 (4.7–14.4)</td>
<td>28% (13–43)</td>
<td></td>
</tr>
</tbody>
</table>

†Time to relapse from completion of first line therapy
‡This category included patients with primary refractory disease.

Abbreviations: ASCT, autologous stem cell transplant; PFS, progression-free survival; OS, overall survival; CI, confidence interval; NR, not reached; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; ST, salvage chemotherapy; CR, complete response; PR, partial response
Figure 1. Outcomes after ASCT in patients with refractory or early relapsed DLBCL: (A) PFS, (B) OS, (C) cumulative incidence of relapse and nonrelapse mortality, and (D) cumulative incidence of causes of death

Abbreviations: PFS, progression-free survival; OS, overall survival; ASCT, autologous stem cell transplant; DLBCL, diffuse large B-cell lymphoma

Figure 2. Post-ASCT outcomes according to refractory and/or time to relapse status and line of ST: (A) PFS and (B) OS by refractory and/or time to relapse status; (C) PFS and (D) OS by line of ST

Abbreviations: PFS, progression-free survival; OS, overall survival; ASCT, autologous stem cell transplant; ST, salvage chemotherapy

Figure 3. Post-ASCT outcomes according to line of ST and response status: (A) PFS and (B) OS by response status; (C) PFS and (D) OS by line of ST and response status

Abbreviations: PFS, progression-free survival; OS, overall survival; ASCT, autologous stem cell transplant; CR, complete response; PR, partial response; ST, salvage chemotherapy
Supplementary Figure 1. Description of study patient selection

Abbreviations: DLBCL, diffuse large B-cell lymphoma; MC, Mayo Clinic; IA, University of Iowa; CR, complete response; RR, relapsed or refractory; ASCT, autologous stem cell transplant; IC, immunochemotherapy; ST, salvage chemotherapy; PET/CT, positron emission tomography-computed tomography
Supplementary Figure 2. OS of study patients after post-ASCT relapse
Abbreviations: OS, overall survival; ASCT, autologous stem cell transplant

Supplementary Figure 3. Post-ASCT outcomes according to MYC rearrangement status: (A) PFS and (B) OS
Abbreviations: PFS, progression-free survival; OS, overall survival; ASCT, autologous stem cell transplant
Supplementary Table 1. Characteristics of patients with DLBCL at initial diagnosis in MC and IA transplant database treated in the rituximab era

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>(n = 230)</th>
<th>%</th>
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<td><strong>Age at diagnosis, years</strong></td>
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<tr>
<td>≤60</td>
<td>128</td>
<td>56</td>
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<tr>
<td>&gt;60</td>
<td>102</td>
<td>44</td>
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<tr>
<td><strong>Sex</strong></td>
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<td>149</td>
<td>65</td>
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<tr>
<td>Female</td>
<td>81</td>
<td>35</td>
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<tr>
<td><strong>ECOG PS scale</strong></td>
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<tr>
<td>≤1</td>
<td>201</td>
<td>91</td>
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<tr>
<td>&gt;1</td>
<td>21</td>
<td>9</td>
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<td><strong>LDH</strong></td>
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<td></td>
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<tr>
<td>Normal</td>
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<td>21</td>
</tr>
<tr>
<td>Elevated</td>
<td>135</td>
<td>79</td>
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<tr>
<td>Missing</td>
<td>60</td>
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<td><strong>Extranodal sites</strong></td>
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<td>≤1</td>
<td>167</td>
<td>74</td>
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<td>&gt;1</td>
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<td><strong>Ann Arbor Stage</strong></td>
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<td>I-II</td>
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<td>18</td>
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<tr>
<td>III-IV</td>
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<td>82</td>
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<td><strong>IPI risk classification</strong></td>
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<td>Low</td>
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<tr>
<td>Low-intermediate</td>
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<td>34</td>
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<tr>
<td>High-intermediate</td>
<td>67</td>
<td>40</td>
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<td>High</td>
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<td>14</td>
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<td>Missing/incomplete evaluation</td>
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<td><strong>Cell of origin</strong></td>
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<tr>
<td>GCB</td>
<td>73</td>
<td>60</td>
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<tr>
<td>Non-GCB</td>
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<td>40</td>
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<tr>
<td>Missing/not performed</td>
<td>108</td>
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<td><strong>MYC rearrangement status</strong></td>
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<tr>
<td>Present*</td>
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<td>15</td>
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<tr>
<td>Absent</td>
<td>53</td>
<td>85</td>
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<tr>
<td>Missing/not performed</td>
<td>168</td>
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</tbody>
</table>

*4 patients had MYC and BCL2 rearrangements; 3 had MYC, BCL2, and BCL6 rearrangements; 1 had MYC and BCL6 rearrangements; and 1 had MYC rearrangement.

Abbreviations: DLBCL, diffuse large B-cell lymphoma; MC, Mayo Clinic; IA, University of Iowa; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; IPI, international prognostic index; GCB, germinal center B-cell
Supplementary Table 2. Treatment pattern and response to therapy in study patients with RR DLBCL

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<tr>
<th>First line salvage regimen</th>
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<tr>
<td>Platinum or high dose cytarabine containing chemotherapy(^1)</td>
<td>201</td>
<td>87</td>
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<tr>
<td>High dose methotrexate based chemotherapy(^2)</td>
<td>26</td>
<td>11</td>
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<td>Other chemotherapy(^3)</td>
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<td>1</td>
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<th>Lines of ST</th>
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<td>1</td>
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<td>&gt;1</td>
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<td>23</td>
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<th>Response to ST</th>
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<td>CR</td>
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<td>46</td>
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<tr>
<td>PR</td>
<td>124</td>
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<th>Conditioning Regimen</th>
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<tr>
<td>BEAM</td>
<td>213</td>
<td>93</td>
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<td>Other regimens(^†)</td>
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<td>7</td>
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<table>
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<tr>
<th>Disease Status Post-ASCT</th>
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<tr>
<td>CR</td>
<td>123</td>
<td>56</td>
</tr>
<tr>
<td>Non-CR</td>
<td>96</td>
<td>44</td>
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<table>
<thead>
<tr>
<th>Radiation post-ASCT (consolidation)</th>
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<tr>
<td>Yes</td>
<td>18</td>
<td>8</td>
</tr>
<tr>
<td>No</td>
<td>212</td>
<td>92</td>
</tr>
</tbody>
</table>

\(^1\)(R-)ICE, rituximab, ifosfamide, carboplatin, etoposide; (R-)DHAP, rituximab, dexamethasone, Ara-C, cisplatin; RGDP, rituximab, gemcitabine, dexamethasone, cisplatin; ROAD, rituximab, oxaliplatin, Ara-C, dexamethasone; (R-)ESHAP, rituximab, etoposide, methylprednisone, Ara-C, cisplatin; and RGemOx, rituximab, gemcitabine, oxaliplatin

\(^2\)methotrexate with or without rituximab and/or temozolomide

\(^3\)R-CDE, rituximab, cyclophosphamide, doxorubicin, etoposide; rituximab, mitoxantrone, and fludarabine; R-EPOCH; rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin

\(^†\)BCNU and Thiotepa; BVAC, BCNU, etoposide, Ara-C, cyclophosphamide; and BEC, BCNU, etoposide, and cyclophosphamide

Abbreviations: RR, relapsed or refractory; DLBCL, diffuse large B-cell lymphoma; ST, salvage chemotherapy; CR, complete response; PR, partial response; BEAM, BCNU, etoposide, Ara-C, and melphalan; and ASCT, autologous stem cell transplant

Supplementary Table 3. Post-ASCT outcomes at 12 months, 24 months, and 60 months

<table>
<thead>
<tr>
<th></th>
<th>At 12 months (95% CI)</th>
<th>At 24 months (95% CI)</th>
<th>At 60 months (95% CI)</th>
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<tbody>
<tr>
<td>PFS</td>
<td>53% (47–60)</td>
<td>47% (41–54)</td>
<td>41% (34–47),</td>
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<tr>
<td>OS</td>
<td>66% (61–74)</td>
<td>57% (50–63)</td>
<td>48% (41–55),</td>
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<tr>
<td>DOR</td>
<td>78% (70–85)</td>
<td>72% (64–80)</td>
<td>61% (52–70),</td>
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<tr>
<td>Relapse</td>
<td>43.4% (37.5–50.2)</td>
<td>47.8% (41.8–54.6)</td>
<td>52.0% (45.8–58.9)</td>
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<tr>
<td>Nonrelapse mortality</td>
<td>3.9% (2.7–4.5)</td>
<td>4.8% (2.7–8.5)</td>
<td>7.3% (4.5–11.7)</td>
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<table>
<thead>
<tr>
<th>Causes of death</th>
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<tbody>
<tr>
<td>Lymphoma</td>
<td>28.5% (23.2–35.0)</td>
<td>37.8% (32.0–44.7)</td>
</tr>
<tr>
<td>Treatment-related deaths</td>
<td>2.1% (0.9–5.2)</td>
<td>3.1% (1.5–6.4)</td>
</tr>
<tr>
<td>Other causes</td>
<td>1.3% (0.4–4.1)</td>
<td>1.8% (0.7–4.7)</td>
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<tr>
<td>Unknown</td>
<td>0.9% (0.2–3.5)</td>
<td>0.9% (0.2–3.5)</td>
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</table>

Abbreviations: ASCT, autologous stem cell transplant; CI, confidence interval; PFS, progression-free survival; OS, overall survival; DOR, duration of response
Supplementary Table 4. Subsequent first line treatment after post-ASCT relapse

<table>
<thead>
<tr>
<th>Subsequent first line treatment after post-ASCT relapse</th>
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<td></td>
<td>N=118</td>
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<td>Systemic chemotherapy</td>
<td>25</td>
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<td>CNS directed chemotherapy</td>
<td>9</td>
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<tr>
<td>Cellular therapy</td>
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<tr>
<td>Radiation/surgery</td>
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<tr>
<td>Lenalidomide containing therapy</td>
<td>5</td>
</tr>
<tr>
<td>Others</td>
<td>25</td>
</tr>
<tr>
<td>Radioimmunotherapy/single agent rituximab</td>
<td>5</td>
</tr>
<tr>
<td>Palliative care</td>
<td>19</td>
</tr>
<tr>
<td>Unknown</td>
<td>7</td>
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</table>

Abbreviation used: ASCT, autologous stem cell transplant; DLBCL, diffuse large B-cell lymphoma; CNS, central nervous system.
Systemic chemotherapy: rituximab, gemcitabine, cisplatin, and dexamethasone (R-GDP); rituximab, ifosfamide, carboplatin, and etoposide (RICE); rituximab, gemcitabine, vinorelbine, and prednisone (R-GVP); rituximab, dexamethasone, cytarabine, and cisplatin (R-DHAP); cyclophosphamide, doxorubicin, etoposide, bleomycin, vincristine, methotrexate, and prednisone (ProMACE CytaBOM); nitrogen mustard and solumedrol; cyclophosphamide, fludarabine, and rituximab; bendamustine and rituximab (BR); rituximab, gemcitabine, and oxaliplatin (R-GemOx), rituximab, etoposide, methylprednisolone, high dose cytarabine, and cisplatin (R-ESHAP); dose-adjusted rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (EPOCH-R); and polatuzumab vedotin plus BR
CNS directed chemotherapy: methotrexate, temozolomide, and rituximab (MTR)
Cellular therapy: chimeric antigen receptor T-cell therapy and allogeneic stem cell transplant
Others: everolimus, sorafenib, panobinostat, nivolumab, pembrolizumab, ipilimumab, anti-TRAIL antibody, acalabrutinib, ruxolitinib, pixantrone, and fostamatinib

Supplementary Table 5. Causes of Death

<table>
<thead>
<tr>
<th>Causes</th>
<th>N = 136</th>
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<tbody>
<tr>
<td>Lymphoma</td>
<td>101</td>
</tr>
<tr>
<td>Treatment-related deaths†</td>
<td>11</td>
</tr>
<tr>
<td>Other causes‡</td>
<td>13</td>
</tr>
<tr>
<td>Unknown causes</td>
<td>11</td>
</tr>
</tbody>
</table>

†Infection (n = 3); myelodysplastic syndrome (n = 3); pulmonary toxicity (n = 2); cardiotoxicity (n = 1); cytokine release syndrome (n = 1); and microangiopathy (n = 1)
‡Gastrointestinal malignancy (n = 4); infection (n = 2); stroke/status epilepticus (n = 2); aortic aneurysm (n = 1); gastrointestinal bleeding (n = 1); suicide (n = 1); sudden cardiac arrest (n = 1); and general debility (n = 1)

Supplementary Table 6. Multivariate analyses adjusted for age at ASCT and sex

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>HR for PFS (95% CI)</th>
<th>P value</th>
<th>HR for OS (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapse between 6 to 12 months of frontline therapy completion (vs refractory/relapse &lt;6 months)</td>
<td>0.83 (0.59–1.18)</td>
<td>0.31</td>
<td>0.67 (0.46–0.98)</td>
<td>0.04</td>
</tr>
<tr>
<td>1 line of ST (vs &gt;1)</td>
<td>0.53 (0.36–0.77)</td>
<td>0.0008</td>
<td>0.51 (0.35–0.74)</td>
<td>0.0005</td>
</tr>
<tr>
<td>CR to ST (vs PR)</td>
<td>0.49 (0.35–0.69)</td>
<td>&lt;0.0001</td>
<td>0.46 (0.32–0.66)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Abbreviations: ASCT, autologous stem cell transplant; PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; ST, salvage chemotherapy; CR, complete response; PR, partial response