RESEARCH ARTICLE

DOI: 10.4274/tjh.galenos.2025.2025.0352
Turk J Hematol 2025;42:265-280

A Large Room for Improvement in the Management of Relapsed/Refractory Large B-Cell Lymphoma in Türkiye: Real-World Outcomes in a Setting Without Access to T-Cell Redirecting Therapies

Nüks/Dirençli Büyük B-Hücreli Lenfomanın Tedavisinde Katedilecek Çok Yol Var: Bispesifik ve CAR-T Erişimi Olmayan Hastalarda Gerçek Yaşam Sonuçları

Umut Yılmaz[1], Mehmet Sinan Dal[2], Turgay Ulaş[2], Elif Birtaş Ateşoğlu[3], Fatma Keklik Karadağ[4], Meral Uluköylü Mengüç[5], Esra Terzi Demirsoy[6], Simge Erdem[7], Ebru Pekgüç[8], Taner Tan[9], Uğur Hatipoğlu[2], Eda Nuhoğlu Kantarcı[1], Merve Apaydın Kayer[2], Ahmet Bahadır Ak[9], Serdar Örnek[8], Ali Durdu[2], Abdulkadir Şahin[2], Emre Osmanbaşoğlu[9], Nazik Okumuş[2], Tuğba Zorlu[2], Mert Seyhan[2], Mustafa Murat Özbalak[7], Tuğrul Elverdi[1], Asu Fergün Yılmaz[10], Derya Demir[11], Deniz Gören[12], Sinem Civriz Bozdağ[9], Tayfur Toptaş[10], Işık Atagündüz[10], Mustafa Nuri Yenerel[7], Olga Meltem Akay[9], Öner Doğan[13], Muhlis Cem Ar[1], Özgür Mehtap[6], Güray Saydam[4], Fevzi Altuntaş[2,14], Burhan Ferhanoğlu[9]

[1]*İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Internal Medicine, Division of Hematology, İstanbul, Türkiye*
[2]*University of Health Sciences Türkiye, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Hematology and Stem Cell Transplantation/Apheresis Unit, Ankara, Türkiye*
[3]*Yeditepe University Faculty of Medicine, Department of Internal Medicine, Division of Hematology, İstanbul, Türkiye*
[4]*Ege University Faculty of Medicine, Department of Internal Medicine, Division of Hematology, İzmir, Türkiye*
[5]*Marmara University, Pendik Training and Research Hospital, Department of Internal Medicine, Division of Hematology, İstanbul, Türkiye*
[6]*Kocaeli University Faculty of Medicine, Department of Internal Medicine, Division of Hematology, Kocaeli, Türkiye*
[7]*İstanbul University, İstanbul Faculty of Medicine, Department of Internal Medicine, Division of Hematology, İstanbul, Türkiye*
[8]*VKV American Hospital, Clinic of Internal Medicine, Division of Hematology, İstanbul, Türkiye*
[9]*Koç University Faculty of Medicine, Department of Internal Medicine, Division of Hematology, İstanbul, Türkiye*
[10]*Marmara University Faculty of Medicine, Department of Internal Medicine, Division of Hematology, İstanbul, Türkiye*
[11]*Ege University Faculty of Medicine, Department of Pathology, İzmir, Türkiye*
[12]*Haliç University Faculty of Medicine; Memorial Şişli Hospital, Department of Hematology, İstanbul, Türkiye*
[13]*Koç University Faculty of Medicine, Department of Pathology, İstanbul, Türkiye*
[14]*Ankara Yıldırım Beyazıt University Faculty of Medicine, Department of Internal Medicine, Division of Hematology, Ankara, Türkiye*

Abstract

Objective: Patients with large B-cell lymphoma (LBCL) who are relapsed/refractory (R/R) after frontline therapy have traditionally experienced highly unfavorable outcomes. The development of T-cell redirecting therapies is rapidly changing that outlook, but costs and infrastructural challenges limit access to these innovative therapies. This study was conducted to document the shortcomings of management in the absence of regular access to T-cell redirecting therapies in a contemporary patient population and define the

Öz

Amaç: Birinci sıra tedavi sonrası nükseden/tedaviye dirençli (R/R) büyük B-hücreli lenfoma (BBHL) hastalarında prognoz kötüdür. Bispesifik ve CAR-T tedavilerin geliştirilmesi bu tabloyu hızla değiştirmektedir, ancak maliyetler ve altyapısal zorluklar bu yenilikçi tedavilere erişimi sınırlamaktadır. Bu çalışma, güncel bir hasta popülasyonunda bispesifik ve CAR-T tedavilerine rutin erişimin olmadığı bir sağlık sistemindeki eksikliklerini ortaya koymak ve yenilikçi tedavilere erişime en acil ihtiyaç duyan alt grupları tanımlamak amacıyla gerçekleştirilmiştir.

Address for Correspondence/Yazışma Adresi: Prof. Burhan Ferhanoğlu, M.D., Koç University Faculty of Medicine, Department of Internal Medicine, Division of Hematology, İstanbul, Türkiye
E-mail: bferhan@gmail.com - bferhanoglu@ku.edu.tr **ORCID:** orcid.org/0000-0002-4257-549X

Received/Geliş tarihi: August 15, 2025
Accepted/Kabul tarihi: November 5, 2025
Epub: November 7, 2025

Abstract

subgroups with the most urgent need for accessing innovative treatments.

Materials and Methods: The second-line management strategies and outcomes of a large real-world LBCL cohort from Türkiye were retrospectively analyzed with the participation of 9 centers from 4 different geographical regions.

Results: Despite the contemporary nature of the treatment strategies (2012-2024), there was no regular access to novel agents. The median progression-free survival after the first progression (PFS-2) was 6.9 months. Fewer than one-fourth of all patients (24.3%) received transplantation following a response to second-line therapy, constituting the only subgroup to benefit from standard care (2-year PFS-2: 67.8%). The remaining 295 patients (75.7% of the cohort) had median survival of 6.1 months and 2-year PFS-2 of 10.3%. Progression within a year from diagnosis, non-curative intent at the second line of therapy, and failure of curative second-line therapy were key adverse features for a dismal prognosis, with median survival durations of 8.8, 2, and 7.4 months, respectively.

Conclusion: The current therapeutic strategy of intensive chemoimmunotherapy followed by autologous transplantation yields a reasonable chance of survival for only one-fifth of patients. The findings of this study emphasize the urgent need for expanding access to T-cell redirecting approaches in R/R LBCL for early progressors, transplant-ineligible cases, and patients who fail intensive second-line regimens.

Keywords: Lymphoma, Large B-cell lymphoma, Relapsed/refractory, LBCL, DLBCL, Second-line, Autologous transplantation

Öz

Gereç ve Yöntemler: Türkiye'den 4 farklı coğrafi bölgedeki 9 merkezin katılımıyla geniş bir gerçek yaşam BBHL kohortunun ikinci basamak tedavi stratejileri ve sonuçları geriye dönük olarak analiz edilmiştir.

Bulgular: Tedavi döneminin günümüzü temsil etmesine rağmen (2012-2024) yeni ajanlara rutin erişim olmadığı belgelenmiştir. İlk progresyondan sonraki medyan progresyonsuz sağkalım (PFS-2) 6,9 ay olarak saptanmıştır. Tüm hastaların dörtte birinden daha azı (%24,3) ikinci basamak tedaviye yanıt sonrası transplantasyona ilerleyebilmiş ve bu grup standart yaklaşımlardan fayda gören tek alt grubu oluşturmuştur (2 yıllık PFS-2: %67,8). Kohortun geri kalanını oluşturan 295 hastanın (%75,7) medyan sağkalımı 6,1 ay ve 2 yıllık PFS-2'si %10,3 saptanmıştır. Tanıdan sonraki bir yıl içinde progresyon, ikinci basamak tedavinin küratif potansiyelli olmaması ve küratif ikinci basamak tedavilerin başarısızlığı kötü prognoz için temel olumsuz özellikler olup; bu gruplarda medyan sağkalım süreleri sırasıyla 8,8 ay, 2 ay ve 7,4 ay olarak bulunmuştur.

Sonuç: Yoğun kemo-imünoterapiyi takiben otolog transplantasyondan oluşan güncel tedavi stratejisi, hastaların yalnızca beşte biri için makul bir sağkalım şansı sunmaktadır. Bu çalışmanın bulguları, erken progresyon gösteren hastalar, transplantasyona uygun olmayan hastalar ve yoğun ikinci basamak rejimlere yanıt vermeyen hastalar için R/R BBHL'de bispesifik ve CAR-T tedavilerine erişimin acil bir ihtiyaç olduğunu vurgulamaktadır.

Anahtar Sözcükler: Lenfoma, Büyük B-hücreli lenfoma, Nüks/dirençli, DBBHL, İkinci sıra tedaviler, Otolog nakil

Introduction

Large B-cell lymphoma (LBCL) is among the most common hematological malignancies and is considered a high-grade lymphoma [1,2]. LBCL is a curable disease with systemic therapy [1,3,4] and its incidence in Europe is 1 in 28,000 [4]. The exact incidence of LBCL in Türkiye is unknown; however, it has been recognized as the most common form of lymphoma, accounting for up to one-third of all lymphoma diagnoses [5]. The odds of survival for patients patients who fail first-line treatment have been dismal with standard approaches involving platinum-based combination therapy followed by autologous stem cell transplantation (ASCT) [6,7,8,9]. Complete response (CR) rates were reported to be lower than 30% across various subgroups and the median overall survival (OS) was 6.3 months in relapsed/refractory (R/R) cases of LBCL with standard therapies in the pivotal SCHOLAR-1 study [6]. However, the development of CAR-T cells and bispecific antibodies over the last decade has raised hopes for improving the outcomes of R/R LBCL [10,11,12]. Regulatory authorities in the United States and Europe have granted approval for these T-cell redirecting therapies, generating a paradigm shift in the standard of care (SOC) for R/R LBCL [9,10,12]. Ongoing studies are exploring the optimal sequencing and combinations for these innovative therapies [13,14,15,16].

T-cell redirecting therapies were not being reimbursed in the Turkish healthcare system as of July 2025, limiting the options for R/R LBCL to intensive cytotoxic therapies, ASCT, and, in selected cases, allogeneic stem cell transplantation (allo-SCT). The necessity of infrastructural investments and the high costs of these T-cell redirecting therapies are the likely reasons for the lag in the availability of these options in many developing countries [17,18].

This study was designed in the context of the evolving treatment landscape of LBCL to define the most urgent unmet needs in Türkiye and guide the incorporation of these innovative therapies in the most responsible way possible. The characteristics of R/R LBCL patients and therapeutic interventions in Türkiye are described. The outcomes following various second-line (2L) treatments are compared and clinical markers for prognosis in this setting are explored.

Materials and Methods

Nine centers representing multiple geographic regions of Türkiye participated in this project to document demographic features and descriptive data on the histological subtypes, treatments, and outcomes of LBCL. An in-depth methodological description of this project was previously published [19]. Consecutive patients diagnosed between 2012 and 2024 were retrospectively included. Second-line regimens were pre-stratified as platinum-based curative therapy, non-platinum-based curative therapy, and non-curative therapy. As 2L regimens were expected to be highly heterogeneous in the absence of recognized standards, a pre-planned preliminary evaluation of the spectrum of administered 2L regimens was performed to allocate rarely used regimens into these pre-defined groups (Supplementary Figure 1).

The analysis focused on real-world R/R LBCL cases. Patients without documented active disease after the completion of first-line therapy and patients enrolled in 2L trials were excluded. Patients who had stable disease as the best response to first-line therapy were considered as primary refractory cases as previously defined in the SCHOLAR-1 study [6]. The timing of progression was stratified using a 12-month cut-off from the initial diagnosis. Response states were defined according to local reports based on the Lugano 2014 criteria with positron emission tomography (PET) [20], or with computed tomography results based on the IWG 2007 criteria when PET data were unavailable [21]. The primary endpoint was progression-free survival after the first progression (PFS-2) for each group of 2L therapies. Secondary endpoints were response rates and OS. PFS-2 and OS were analyzed according to the timing of progression, ASCT performance, and response to 2L therapy. Exploratory endpoints were response rates, PFS-2, and OS based on the 2L regimen.

This study was approved by the Non-Interventional Research Committee of the Institutional Review Board of Kocaeli University with decision number KÜ GOKAEK-2025/02/13 and project number 2025/27 (16 January 2025). All participating researchers complied with good clinical practice in accordance with the Declaration of Helsinki.

Statistical Analysis

For continuous descriptive data, median values and ranges were reported, while for categorical descriptive data, numbers and frequencies were reported. OS was defined as the time from the start of 2L therapy to death. PFS-2 was defined as the time from the start of 2L therapy to disease progression, relapse, death, or the onset of a third line of therapy for active disease at the end of 2L treatment. For OS and PFS-2, cases without an event were censored at the time of the last clinical visit. Time-to-event plots were generated and median survival durations were calculated using the Kaplan-Meier method with 95% confidence intervals (CIs) and log-rank testing to determine significance. Hazard ratios (HRs) for the risk of progression and/or death were generated using Cox regression analysis for the type of therapy, timing of progression, ASCT performance, response before ASCT, type of regimen, and year of therapy as categorical variables in univariate comparisons. Type of therapy within four categories (platinum-based, non-platinum-based, non-curative, no therapy), International Prognostic Index (IPI) score at diagnosis, cell of origin, timing of progression (12-month cut-off), and age at the time of progression within three categories (<50, 50-70, >70 years) were included as covariates in multivariate analysis for the risk of death. For all comparative analyses, the CI was 95% and p values of <0.05 were considered significant. IBM SPSS Statistics 22.0 was used for statistical analysis.

Results

Baseline Features and Distribution of Treatment

First-line therapy was administered to 1369 consecutive patients in the entire cohort. Of these, 1278 had completed frontline therapy and 436 had a progression event, corresponding to a 34.1% rate of first-line treatment failure per protocol after a median follow-up of 39 months from the initial diagnosis (Supplementary Table 1). The real-world R/R cohort analyzed in this study comprised 390 patients when lymphoma-unrelated deaths after frontline treatment (n=37) and patients enrolled in clinical trials (n=9) were excluded (Figure 1a).

Slightly more than half of the R/R LBCL patients (52.3%, n=204) had a previously documented response to frontline therapy and most progression events (68.2%, n=266) were documented within the first 12 months after diagnosis (Figure 1a). Selected baseline features at the time of relapse are summarized in Table 1. Platinum-based combination therapy was administered to 51.8% (n=202) of R/R LBCL patients as 2L therapy (Figure 1b; Table 2). Non-platinum-based therapies, most commonly involving the combination of an anti-CD20 antibody with either bendamustine (n=27) or high-dose methotrexate-based regimens for central nervous system involvement (n=18), were administered to 14.6% (n=57) of patients during 2L treatment (Table 2; Supplementary Tables 2 and 3). These two groups were considered to have received therapy with a curative intent and most of these patients (247 of 259) had received regimens pre-defined as curative (Supplementary Figure 1). The remaining 131 patients (33.6%) either died due to disease before a specific anti-lymphoma regimen was administered (n=58) or received management with a regimen of negligible curative potential (n=73) (Table 2).

Outcomes for the Entire Cohort and Based on the Timing of Progression

The median PFS-2 and OS for the entire R/R LBCL cohort were respectively 6.9 (95% CI: 5.7-7.4) and 14.1 (95% CI: 9.9-16.3) months after a median follow-up period of 8.7 months (range: 4 days to 8.1 years). Among 160 patients who were censored for OS analysis, 132 had follow-up data within 12 months of the data cut-off point and 28 had been lost to follow-up. Those missing 28 cases were likely to have entailed inferior outcomes; however, they had to be censored based on the available data, possibly resulting in the overestimation of survival probabilities. Prognosis was significantly worse following an early progression after frontline therapy (<12 months) with median PFS-2 of 5.9 months (95% CI: 4.4-7.1) versus 13.7 (95% CI: 10-17.7) (HR: 1.8, 95% CI: 1.4-2.4, p<0.0001; Figure 2a) and median OS of 8.8 months (95% CI: 5.8-10.9) versus 39.2 (95% CI: 15.5-73.2) (HR: 2.2, 95% CI: 1.6-2.9, p<0.0001; Figure 2b). There was also a significant difference in outcomes between patients with primary refractory disease, early relapse, and late relapse (Supplementary Figure 2).

Outcomes Following Curative Therapies

The overall response rate (ORR) was 55.9% (39.1% CR and 16.8% partial response [PR]) after platinum-based therapies and 74.1% of these responders went on to receive ASCT. The most common reasons for not undergoing ASCT after a response were a rapid second relapse (within 2 months, n=5) or mobilization failure (n=4). The median PFS-2 after a 2L platinum-based therapy was 8.3 months (95% CI: 6.1-10.6) with 2-year PFS-2 and OS rates of 35.3% and 55.3%, respectively (Figure 3). Interestingly, there were no significant differences in response rates, PFS-2, or OS between different platinum-based regimens (Table 2; Supplementary Figure 3). The ORR for the group of patients receiving non-platinum-based regimens in 2L treatment was 47.4% (35.1% CR, 12.3% PR; Table 2). The median PFS-2 was 8.3

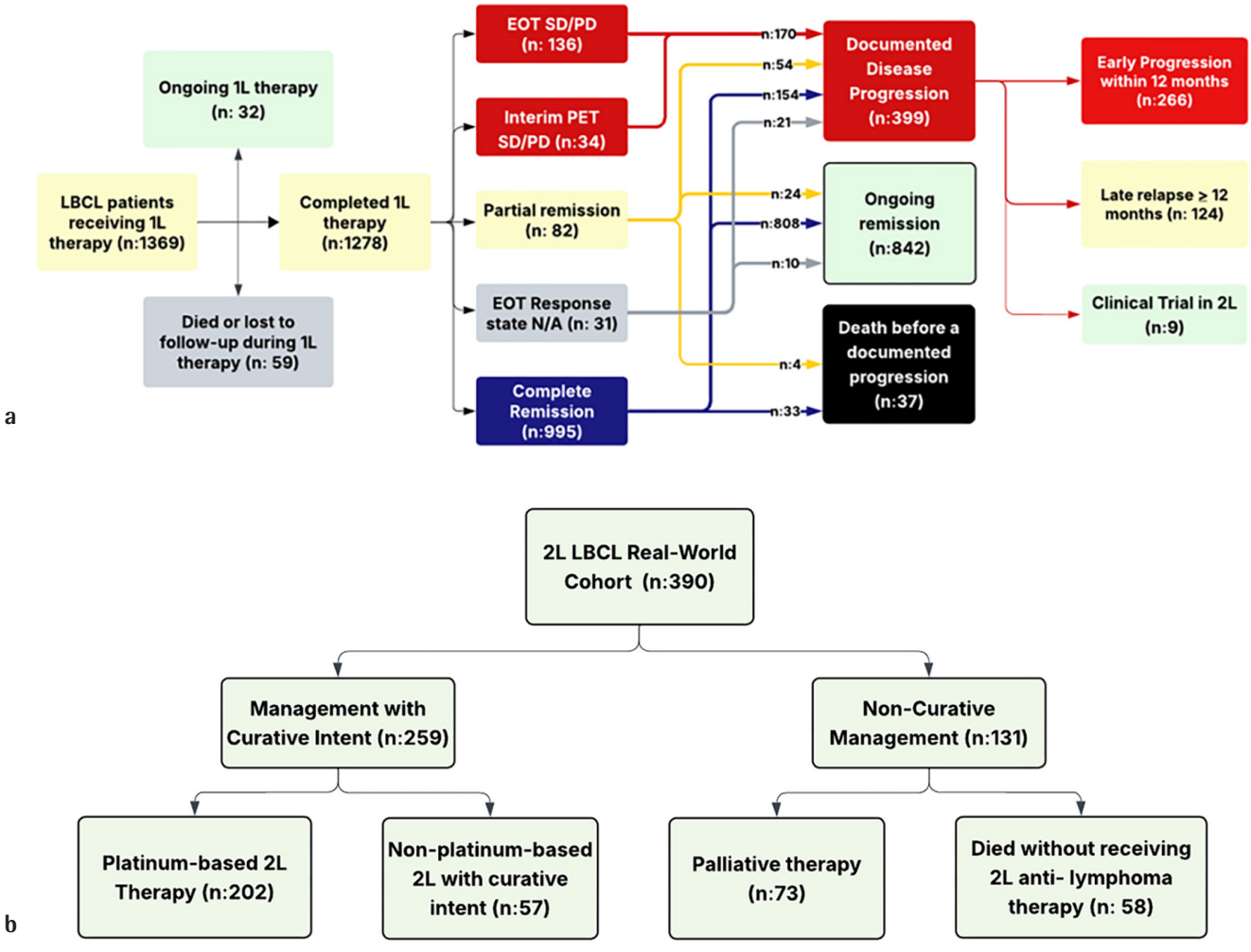


Figure 1. Flowchart following the clinical course of all 1369 patients included in the cohort (a) and the initial management of the 390 patients managed with second-line treatment in a real-world setting (b).

1L: First-line treatment; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; EOT: end of therapy; 2L: second-line treatment.

months (95% CI: 4.6-12.2) with 2-year PFS-2 and OS estimates of 35.4% and 43.2%, respectively, for patients undergoing non-platinum-based therapy with a curative intent (Figure 3).

Outcomes Following Non-curative Management

Of the 131 patients in the third group that did not receive therapy with a curative intent, 58 (44.3%) died before a treatment other than glucocorticoids was initiated, most often within 2 months of progression. All but 3 of these cases had early progression after frontline therapy and most cases were primary refractory. The remaining 73 patients in this group received treatment with regimens of negligible curative potential (Supplementary Table 2) with treatment outcomes as summarized in Table 2. The most commonly administered non-curative regimens entailed

Table 1. Selected baseline features, treatment data, response rates, autologous stem cell transplantation rates, and survival data across the entire cohort and between three groups based on second-line therapy.

Feature	R/R LBCL cohort (n=390)	Platinum-based (n=202)	Non-platinum-based (n=57)	Palliative (n=131)
Age at progression				
Median, years (range)	61 (18-93)	57 (19-86)	57 (18-92)	70 (25-92)
Sex, n (%)				
Female	170 (43.6%)	84 (41.6%)	23 (39.6%)	64 (48.9%)
Male	220 (56.4%)	118 (58.4%)	34 (61.4%)	67 (51.1%)
Histological subtype, n (%)				
DLBCL-NOS	278 (71.3%)	154 (76.1%)	35 (61.4%)	89 (68.3%)
Transformed LBCL	34 (8.6%)	16 (8.1%)	5 (8.8%)	12 (8.8%)
High-grade LBCL	33 (8.4%)	15 (7.2%)	5 (8.8%)	14 (10.4%)
TCHRBCL	9 (2.4%)	7 (3.6%)	1 (1.8%)	1 (0.8%)
PMBCL	10 (2.6%)	4 (2%)	5 (8.8%)	1 (0.8%)
Cell of origin, n (%)				
GCB	147 (37.7%)	68 (33.7%)	22 (38.6%)	44 (33.5%)
Non-GCB	149 (38.1%)	81 (40.1%)	18 (31.5%)	47 (36.1%)
Timing of progression, n (%)				
<12 months	266 (68.5%)	129 (63.9%)	36 (63.2%)	102 (77.9%)
≥12 months	124 (31.5%)	73 (36.1%)	21 (36.8%)	29 (22.1%)
Response rates, n (%)				
CR	107 (27.4%)	79 (39.1%)	20 (35.1%)	8 (6.1%)
PR	46 (11.8%)	34 (16.8%)	7 (12.3%)	5 (3.8%)
ASCT, n (%)	118 (30.3%)	102 (50.5%)	14 (24.6%)	2 (1.5%)
Median PFS, months	6.9	8.3	8.3	N/A
Median OS, months	14.1	38.1	24.6	2

R/R: Relapsed/refractory; LBCL: large B-cell lymphoma; DLBCL-NOS: diffuse large B-cell lymphoma-not otherwise specified; TCHRBCL: T-cell histiocyte-rich B-cell lymphoma; PMBCL: primary mediastinal B-cell lymphoma; GCB: germinal center B-cell; CR: complete response, PR: partial response; ASCT: autologous stem cell transplantation; PFS: progression-free survival; OS: overall survival.

Table 2. Response rates, autologous stem cell transplantation, and progression-free survival based on treatment regimen in second-line therapy and the timing of first progression.

Feature	CR rate	PR rate	ASCT	2-year PFS
Platinum-based 2L therapy				
R-ICE (n=82)	45.1%	14.6%	53.7%	35.3%
R-DHAP/DHAOx (n=49)	38.8%	18.4%	55.1%	32.5%
R-GDP (n=49)	30.6%	24.5%	49%	37.7%
Others* (n=22)	36.4%	4.5%	31.8%	31.3%
Non-platinum-based 2L therapy				
R-bendamustine (n=27)	37.0%	7.4%	7.4%	25.8%
High-dose MTX-based (n=18)	38.9%	16.7%	38.9%	34.2%
Other intensive therapies (n=12)	41.7%	16.7%	58.3%	36.7%
Non-curative intent (n=73)	9.6%	6.8%	2.7%	13.4%
Timing of first progression				
<12 months	18.4%	10.9%	25.1%	20.7%
≥12 months	47.2%	13.8%	45.1%	36.8%

CR: complete response; PR: partial response: ASCT: autologous stem cell transplantation; PFS: progression-free survival; 2L: second-line; R: rituximab; ICE: ifosfamide, carboplatin, etoposide; MTX: methotrexate; DHAP: dexamethasone-cytarabine and cisplatin; GDP: gemcitabine-dexamethasone-cisplatin.

glucocorticoids and rituximab with or without modest doses of cytotoxic drugs (gemcitabine, cyclophosphamide, vincristine), lenalidomide (n=6), or ibrutinib (n=6). The 6 patients receiving R-miniCHOP as 2L therapy were included in the non-curative group after a preliminary evaluation because dose intensity was not maintained and none of these patients completed more than 2 cycles or went on to receive ASCT. The median OS was 55 days (95% CI: 43-66) for this group with only 13.4% alive at 12 months from progression. Ten of 12 patients receiving ibrutinib or lenalidomide progressed within a year. To understand the independent impact of non-curative therapies, we performed sensitivity analyses within the non-curative therapy group, comparing the findings between patients who died before treatment and those who received therapy. This explorative analysis showed only modest differences. The median age was 70 and 72 years and the median time to first progression was 5 and 8 months, respectively. The median OS from progression was 44 days (95% CI: 35-52) and 92 days (95% CI: 17-188), respectively. Furthermore, after excluding the 58 patients who died without treatment in this group, the risk of death for the 73 patients receiving non-curative regimens remained significantly high compared to patients receiving platinum-based therapy (median OS: 92 days vs. 2.8 years, 1-year OS: 27.9% vs. 68.4%, HR: 3.5, 95% CI: 2.5-4.9, p<0.0001; Supplementary Figure 4).

Autologous Stem Cell Transplantation

ASCT was performed for 118 patients (30.3% of the cohort). Most patients (n=95) undergoing ASCT had a response to 2L therapy. These 95 patients, representing only 24.3% of the R/R LBCL cohort, constituted the only subgroup demonstrating a relatively favorable prognosis with 24-month PFS-2 and OS estimates of 67.8% and 81.9% (Figure 4). The 24-month PFS-2

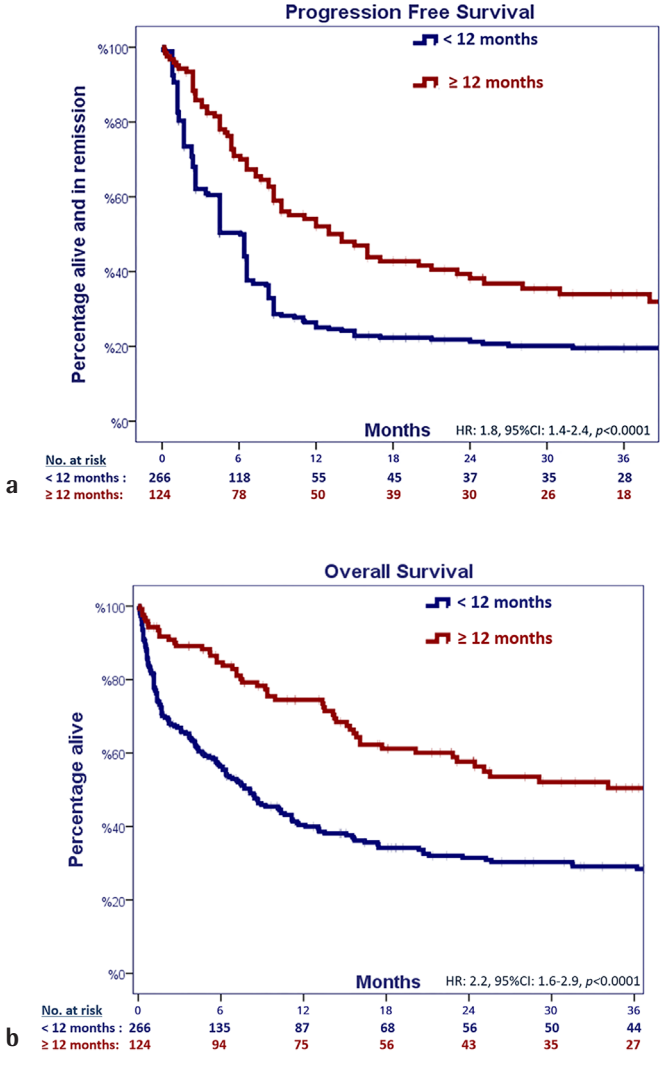


Figure 2. Comparison of progression-free survival after the first progression (a) and overall survival (b) between patients showing early progression (<12 months) after frontline therapy and those with later relapses.

2L: Second-line; HR: hazard ratio; CI: confidence interval.

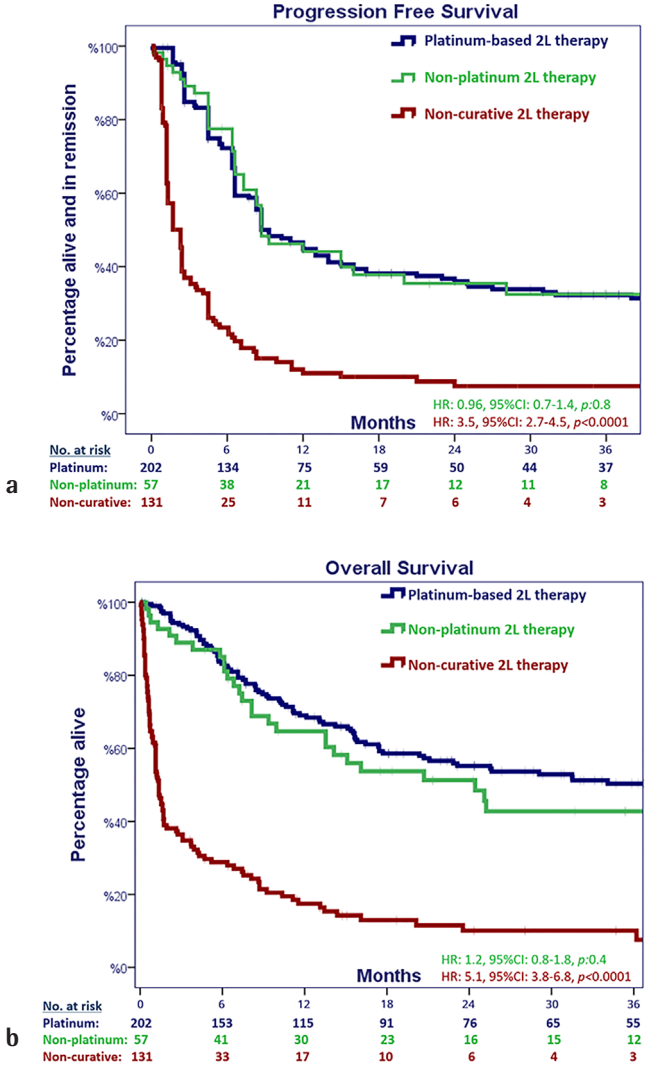


Figure 3. Comparison of progression-free survival after the first progression (a) and overall survival (b) between patients treated with platinum-based regimens, non-platinum-based regimens, and non-curative intent in second-line therapy

2L: Second-line; HR: hazard ratio; CI: confidence interval.

and OS rates were 10.7% (HR: 5.6, 95% CI: 3.8-8.1) and 20.5% (HR: 7.3, 95% CI: 4.6-11.6), respectively, for the remaining 295 patients (75.7% of the cohort) who had no objective response at the time of ASCT or did not undergo ASCT due to various reasons. Response state at the time of transplantation was the key determinant of ASCT outcomes (Supplementary Figure 5). The median OS for patients relapsing after ASCT was 8.8 months (95% CI: 3.4-12.9) and only 23.7% remained alive 2 years after ASCT failure.

Multivariate Analysis

Multivariate analysis including therapy type, age at first progression, timing of progression, IPI score at diagnosis, and cell of origin confirmed the independent risk of death related to the use of non-curative therapies (HR: 4.41 95% CI: 2.78-6.98), no treatment (HR: 9.53, 95% CI: 5.66-16.05), and early progression (HR: 1.58, 95% CI: 1.05-2.38; Supplementary Figure 6).

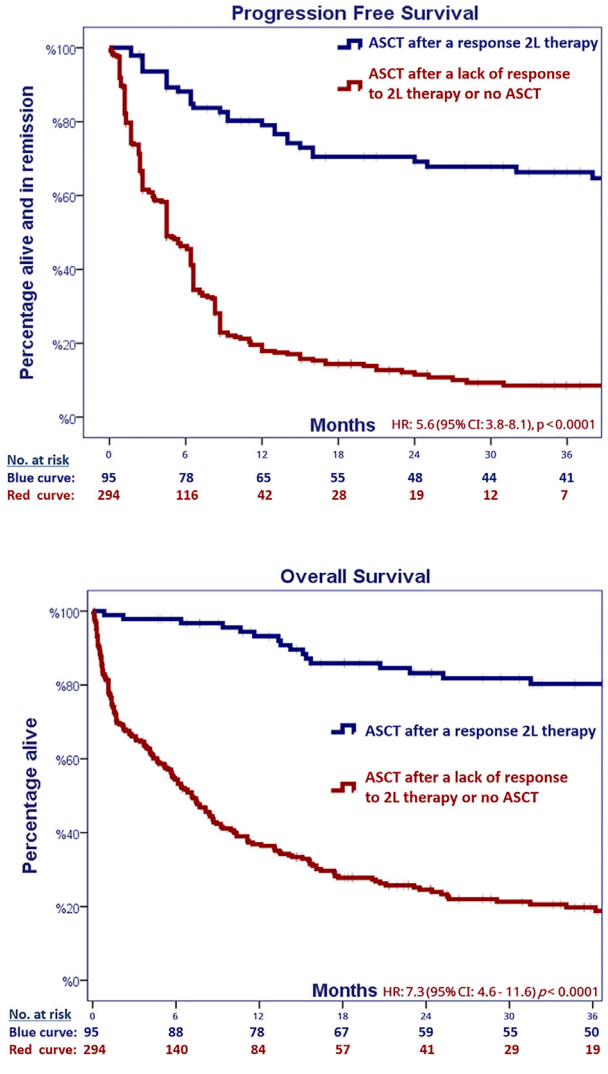


Figure 4. Comparison of progression-free survival after the first progression (a) and overall survival (b) between patients who received autologous stem cell transplantation following a response to second-line therapy and the rest of the cohort.

ASCT: Autologous stem cell transplantation; 2L: second-line; HR: hazard ratio; CI: confidence interval.

Beyond Second-Line Therapy

Among the 272 patients who had failed 2L therapy, 23 patients (8.5%) went on to receive allo-SCT in subsequent lines. Only 4 of these allo-SCT patients had documented long-term remissions, with the remaining patients either being in early stages of follow-up or having died within a year of the transplant. Nine patients (3.3%) received bispecific antibodies in the third line through participation in clinical trials or compassionate programs, with 2 achieving CR and 3 continuing treatment at the data cut-off point. None of the patients had received CAR-T cell therapy at the time of data cut-off.

Discussion

The patient characteristics, treatment modalities, and outcomes of 2L treatment for LBCL were investigated in this study. The findings confirmed the limitations in access to T-cell redirecting therapies in Türkiye. Platinum-based combination chemotherapy followed by ASCT, constituting the SOC approach before the advent of T-cell redirecting therapies, was successful for only a small minority of R/R LBCL patients. The only patients to derive significant benefit from this strategy were those who achieved a response after combination chemotherapy and went on to receive ASCT, representing less than one-quarter of the R/R LBCL population. For the remaining majority, only 1 in 5 remained alive 2 years after the first progression. The strongest variables favoring survival in this cohort were late relapse and undergoing ASCT with an objective response.

T-cell redirecting therapies have revolutionized the management of R/R LBCL over the last decade [9,10,11]. Their first regulatory approval in LBCL was issued in 2017 [22]. Since then, their indications, along with their use in various combinations and in different lines of treatment, have been evolving rapidly [13,14,16,23]. These therapies are increasingly recognized as tolerable for patients who are otherwise considered unfit for combination chemotherapies or ASCT [11,13,23,24,25]. There is a strong argument that these innovative therapies improve the outcomes of LBCL [12]. The most compelling evidence for this claim comes from the phase-3 ZUMA-7, TRANSFORM, and STARGLO trials, where significant PFS-2 and OS benefits were demonstrated for the experimental arms involving T-cell redirecting approaches [13,14,26,27]. CR rates were 65%, 74%, and 58.5% for the experimental arms versus 32%, 43%, and 25.3% for SOC arms in ZUMA-7, TRANSFORM, and STARGLO, respectively. Other T-cell redirecting options have demonstrated similarly highly promising rates of durable responses in phase-2 trials [16,23,28]. One recent example is the epcoritamab combination with gemcitabine and oxaliplatin, which yielded

CR and 12-month PFS-2 rates of over 60% in the 2L cohort [23]. In addition to T-cell redirecting therapies, polatuzumab-vedotin was also utilized as an active novel drug in R/R LBCL [29,30,31]. Despite the remarkable advances in drug development, however, challenges related to the accessibility of these innovative therapies remain largely unresolved. Recent reports make it clear that difficulties in access are not limited to developing countries; they remain a serious issue in many countries regardless of the level of economic prosperity [32,33,34,35,36]. A responsible approach to overcoming financial obstacles could entail limiting T-cell redirecting therapy reimbursements to particularly high-risk groups as defined in this study (early first progression, transplant ineligibility, 2L failures, etc.), prioritizing fixed-duration options, and securing investments for academic CAR-T products [37,38,39]. The findings of this study clearly reflect the shortcomings of cytotoxic therapy in R/R LBCL in a contemporary real-world cohort and confirm the need for global efforts to expand access to T-cell redirecting therapies.

Regarding non-T-cell redirecting targeted agents in lymphoma, the agents commercially available in Türkiye, ibrutinib and lenalidomide, have failed to demonstrate benefit in LBCL frontline trials [40,41], with modest activity restricted to particular subgroups. Their use in R/R LBCL has been sporadic, as in our cohort, and they have not produced satisfactory rates of success. However, ibrutinib and lenalidomide may regain popularity in certain molecular subgroups based on promising data from the GUIDANCE-01 trial [42]. Recent developments in LBCL with two agents targeting CD19, tafasitamab and loncastuximab, were promising in phase-2 trials [43,44]; however, real-life data have been disappointing [45,46]. Based on the evidence presented above, the worldwide trend in R/R LBCL entails a shift away from the cytotoxic or targeted drugs mentioned above, toward T-cell redirecting therapies [11,47,48].

Our real-world data on CR rates and PFS-2 outcomes align well with the results obtained for SOC arms in the large phase-3 trials mentioned above and confirm the limitations of the previous SOC approaches in contemporary real-world settings where innovative therapies are locally unavailable [6,13,14,26,27]. Most notable among these trials is SCHOLAR-1, which addressed the limitations of historical therapies. The median OS in the SCHOLAR-1 study was 6.3 months for the entire R/R LBCL group and 5 to 8 months across various subgroups [6,49]. This is consistent with the 6.1-month median OS obtained in our study for a cohort in which the majority of patients did not undergo ASCT following a response to 2L therapy. The lack of a difference between platinum-based regimens also confirms the results of two comparative trials [50,51]. Furthermore, the poor prognostic impact of a primary refractory state or very early relapse was clearly demonstrated in our cohort, comprising patients with urgent unmet needs in 2L therapy.

Study Limitations

The retrospective nature of this study, constituting its key limitation, should be considered while interpreting the results as it raises a risk of selection bias. This is most evident for the 28 patients who were censored as they were lost to follow-up before the data cut-off point of 12 months. Furthermore, since 6 of the 9 participating centers also have a transplant unit, transplant-eligible patients may have been slightly overrepresented in the cohort and the survival durations may be overestimated. However, both of these selection biases emphasize the main theme of this study concerning the shortcomings of cytotoxic therapy-based approaches in R/R LBCL.

As this study presented real-world analysis, the timing of imaging examinations was not controlled. Thus, the definition of PFS-2 events was modified to include the onset of a third line of therapy for active disease, which may have resulted in a slight underestimation of time to progression. However, this was not expected to have a large impact due to the aggressive nature of LBCL, considering that stable disease is widely recognized as treatment failure.

The therapies administered in 2L were highly heterogeneous. Therefore, a preliminary evaluation was planned to allocate rarely used regimens into predefined curative and non-curative treatment groups. The heterogeneity also limited more comprehensive comparisons of individual regimens. We were not able to use the widely recognized transplant eligibility categorization due to the absence of data regarding formal frailty assessments. Patients with more aggressive tumors were likely to be overrepresented among the 58 patients who died without receiving specific anti-lymphoma therapy, which may have resulted in underestimation of the survival probability of the non-curative therapy group (Group 3). The reason why these 58 patients were not administered therapy (e.g., highly aggressive tumor, lack of appropriate options for the patient's condition, or patient's choice) could not be discerned with the available data, limiting the interpretation of the independent impact of disease management in this subgroup. However, the exploratory analysis performed after excluding these 58 cases clearly demonstrated inferior prognosis for the 73 patients who received therapy without curative intent, confirming the main conclusions of the study.

Conclusion

Therapeutic options when T-cell redirecting therapies are inaccessible provide a reasonable chance of survival for only a minority of R/R LBCL patients. The findings of this study highlight the most urgent unmet needs of patients with early progression (within 1 year of diagnosis), those who are unable to tolerate intensive chemotherapy, and those who fail intensive 2L therapies. Determined effort is needed to overcome financial obstacles and deliver efficient therapies to those who need them the most.

Ethics

Ethics Committee Approval: This study was approved by the Non-Interventional Research Committee of the Institutional Review Board of Kocaeli University with decision number KÜ GOKAEK-2025/02/13 and project number 2025/27 (16 January 2025). All participating researchers complied with good clinical practice in accordance with the Declaration of Helsinki.

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: B.F.; Design: U.Y., M.M.Ö., S.C.B., E.B.A., O.M.A., B.F.; Data Collection or Processing: U.Y., M.S.D., T.U., E.B.A., F.K.K., S.E., M.U.M., E.T.D., E.P., T.T., U.H., E.N.K., M.A.K., A.B.A., S.Ö., A.D., A.Ş., E.O., N.O., M.N.Y., T.Z., M.S., M.M.Ö., T.E., A.F.Y., D.D., D.G., S.C.B., T.T., I.A., O.M.A., Ö.D., M.C.A., Ö.M., G.S., F.A., B.F.; Analysis or Interpretation: U.Y., E.B.A., B.F., Ö.M., A.B.A.; Literature Search: U.Y., E.B.A., D.D., B.F.; Writing: U.Y., E.B.A., B.F.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Tilly H, Gomes da Silva M, Vitolo U, Jack A, Meignan M, Lopez-Guillermo A, Walewski J, André M, Johnson PW, Pfreundschuh M, Ladetto M; ESMO Guidelines Committee. Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26(Suppl 5):v116-v125.
2. Sehn LH, Salles G. Diffuse large B-cell lymphoma. N Engl J Med. 2021;384:842-858.
3. Melchardt T, Egle A, Greil R. How I treat diffuse large B-cell lymphoma. ESMO Open. 2023;8:100750.
4. Thieblemont C, Gomes Da Silva M, Leppä S, Lenz G, Cottereau AS, Fox C, Lopez-Guillermo A, Illidge T, Jurczak W, Eich H, Aurer I, Trneny M, Rosenwald AA, Davies A, Zwezerijnen BG, Bolanos N, Marković M, Jais JP, Broussais F, Dreyling M, Vitolo U, Tilly H, Kersten MJ. Large B-cell lymphoma (LBCL): EHA Clinical Practice Guidelines for diagnosis, treatment, and follow-up. Hemasphere. 2025;9:e70207.
5. Sağlam A, Esin E, Hayran M, Boyraz B, Üner A. Distribution of lymphomas in Turkey: data of 4239 cases from a single institution using the WHO classification. Turk J Med Sci. 2018;48:1013-1023.
6. Crump M, Neelapu SS, Farooq U, Van Den Neste E, Kuruvilla J, Westin J, Link BK, Hay A, Cerhan JR, Zhu L, Boussetta S, Feng L, Maurer MJ, Navale L, Wiezorek J, Go WY, Gisselbrecht C. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. Blood. 2017;130:1800-1808.
7. Munshi PN, Chen Y, Ahn KW, Awan FT, Cashen A, Shouse G, Shadman M, Shaughnessy P, Zurko J, Locke FL, Goodman AM, Bisneto JCV, Sauter C, Kharfan-Dabaja MA, Meyers G, Jaglowski S, Herrera A, Hamadani M. Outcomes of autologous hematopoietic cell transplantation in older patients with diffuse large B-cell lymphoma. Transplant Cell Ther. 2022;28:487.e1-487.e7.
8. Renders S, Ngoya M, Finel H, Rubio MT, Townsend W, Schroers R, Novak U, Schaap N, Aljurf M, Helbig G, Collin M, Kobbe G, Huynh A, Pérez-Simón JA, Bloor A, Ghesquieres H, Sureda A, Schmitz N, Glass B, Dreger P. Autologous stem cell transplantation in T-cell/histiocyte-rich large B-cell lymphoma: EBMT Lymphoma Working Party study. Blood Adv. 2024;8:5571-5578.
9. Westin J, Sehn LH. CAR T cells as a second-line therapy for large B-cell lymphoma: a paradigm shift? Blood. 2022;139:2737-2746.
10. Iacoboni G. T-cell redirecting strategies in large B-cell lymphoma and follicular lymphoma. Hematol Oncol. 2025;43(Suppl 2):e70068.
11. Wallace DS, Loh KP, Casulo C. How I treat older patients with relapsed/refractory diffuse large B-cell lymphoma. Blood. 2025;145:277-289.
12. Duell J, Westin J. The future of immunotherapy for diffuse large B-cell lymphoma. Int J Cancer. 2025;156:251-261.
13. Abramson JS, Ku M, Hertzberg M, Huang HQ, Fox CP, Zhang H, Yoon DH, Kim WS, Abdulhaq H, Townsend W, Herbaux C, Zaucha JM, Zhang QY, Chang H, Liu Y, Cheah CY, Ghesquieres H, Simko S, Orellana-Noia V, Ta R, Relf J, Dixon M, Kallemeijn M, Mulvihill E, Huang H, Lundberg L, Gregory GP. Glofitamab plus gemcitabine and oxaliplatin (GemOx) versus rituximab-GemOx for relapsed or refractory diffuse large B-cell lymphoma (STARGLO): a global phase 3, randomised, open-label trial. Lancet. 2024;404:1940-1954.
14. Abramson JS, Solomon SR, Arnason J, Johnston PB, Glass B, Bachanova V, Ibrahimi S, Mielke S, Mutsaers P, Hernandez-Ilizaliturri F, Izutsu K, Morschhauser F, Lunning M, Crotta A, Montheard S, Previtali A, Ogasawara K, Kamdar M. Lisocabtagene maraleucel as second-line therapy for large B-cell lymphoma: primary analysis of the phase 3 TRANSFORM study. Blood. 2023;141:1675-1684.
15. Messerli C, Wiedemann G, Porret N, Nagler M, Seipel K, Jeker B, Novak U, Zeerleder S, Bacher U, Pabst T. Correlation of peripheral chimeric antigen receptor T-cell (CAR-T cell) mRNA expression levels with toxicities and outcomes in patients with diffuse large B-cell lymphoma. Turk J Hematol. 2023;40:187-196.
16. Kim WS, Kim TM, Cho SG, Jarque I, Iskierka-Jażdżewska E, Poon LM, Prince HM, Zhang H, Cao J, Zhang M, Tessoulin B, Oh SY, Lim F, Carpio C, Tan TD, Ayyappan S, Gutierrez A, Cai J, Ufkin M, Shariff S, Brouwer-Visser J, Chaudhry A, Mohamed H, Ambati S, Walewski J; ELM-2 Investigators. Odronextamab monotherapy in patients with relapsed/refractory diffuse large B cell lymphoma: primary efficacy and safety analysis in phase 2 ELM-2 trial. Nat Cancer. 2025;6:528-539.
17. Burki TK. CAR T-cell therapy roll-out in low-income and middle-income countries. Lancet Haematol. 2021;8:e252-e253.
18. Lei M, Li Q, O'Day K, Meyer K, Wang A, Jun MP. Practice efficiency and total cost of care with bispecifics and CAR-T in relapsed/refractory diffuse large B-cell lymphoma: an institutional perspective. Future Oncol. 2024;20:2189-2201.
19. Yılmaz U, Terzi Demirsoy E, Keklik Karadağ F, Hatipoğlu U, Uluköylü Mengüç M, Pekgüç E, Tan T, Nuhoğlu Kantarcı E, Mastanzade M, Durdu A, Apaydın Kayer M, Özbalak M, Elverdi T, Yılmaz AF, Gören D, Toptaş T, Ulaş T, Mehtap Ö, Dal MS, Akay OM, Ar MC, Saydam G, Altuntaş F, Birtaş Ateşoğlu E, Ferhanoğlu B. Simplified Molecular International Prognostic Index as an eligibility criterion for clinical trials: analysis of the Turkish Lymphoma Study Group's large B-cell lymphoma cohort. Br J Haematol. (in press). doi: 10.1111/bjh.20111.
20. Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, Lister TA; Alliance, Australasian Leukaemia and Lymphoma Group; Eastern Cooperative Oncology Group; European Mantle Cell Lymphoma Consortium; Italian Lymphoma Foundation; European Organisation for Research; Treatment of Cancer/Dutch Hemato-Oncology Group; Grupo Español de Médula Ósea; German High-Grade Lymphoma Study Group; German Hodgkin's Study Group; Japanese Lymphorra Study Group; Lymphoma Study Association; NCIC Clinical Trials Group; Nordic Lymphoma Study Group; Southwest Oncology Group; United Kingdom National Cancer Research Institute. Recommendations for initial evaluation, staging, and response assessment

of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014;32:3059-3068.

21. Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, Coiffier B, Fisher RI, Hagenbeek A, Zucca E, Rosen ST, Stroobants S, Lister TA, Hoppe RT, Dreyling M, Tobinai K, Vose JM, Connors JM, Federico M, Diehl V; International Harmonization Project on Lymphoma. Revised response criteria for malignant lymphoma. J Clin Oncol. 2007;25:579-586.
22. Bouchkouj N, Kasamon YL, de Claro RA, George B, Lin X, Lee S, Blumenthal GM, Bryan W, McKee AE, Pazdur R. FDA approval summary: axicabtagene ciloleucel for relapsed or refractory large B-cell lymphoma. Clin Cancer Res. 2019;25:1702-1708.
23. Brody JD, Jørgensen J, Belada D, Costello R, Trněný M, Vitolo U, Lewis DJ, Karimi YH, Sureda A, André M, Wahlin BE, Lugtenburg PJ, Jiang T, Karagoz K, Steele AJ, Abbas A, Wang L, Risum M, Cordoba R. Epcoritamab plus GemOx in transplant-ineligible relapsed/refractory DLBCL: results from the EPCORE NHL-2 trial. Blood. 2025;145:1621-1631.
24. Menez S, Bourbon E, Gounot R, Tudesq JJ, Moya N, Houot R, Bachy E. CAR T-cells in very elderly (≥80 years) lymphoma patients: a DESCAR-T analysis. Leuk Lymphoma. 2024;65:2048-2051.
25. Chihara D, Liao L, Tkacz J, Franco A, Lewing B, Kilgore KM, Nastoupil LJ, Chen L. Real-world experience of CAR T-cell therapy in older patients with relapsed/refractory diffuse large B-cell lymphoma. Blood. 2023;142:1047-1055.
26. Locke FL, Miklos DB, Jacobson CA, Perales MA, Kersten MJ, Oluwole OO, Ghobadi A, Rapoport AP, McGuirk J, Pagel JM, Muñoz J, Farooq U, van Meerten T, Reagan PM, Sureda A, Flinn IW, Vandenberghe P, Song KW, Dickinson M, Minnema MC, Riedell PA, Leslie LA, Chaganti S, Yang Y, Filosto S, Shah J, Schupp M, To C, Cheng P, Gordon LI, Westin JR; All ZUMA-7 Investigators and Contributing Kite Members. Axicabtagene ciloleucel as second-line therapy for large B-cell lymphoma. N Engl J Med. 2022;386:640-654.
27. Westin JR, Oluwole OO, Kersten MJ, Miklos DB, Perales MA, Ghobadi A, Rapoport AP, Sureda A, Jacobson CA, Farooq U, van Meerten T, Ulrickson M, Elsawy M, Leslie LA, Chaganti S, Dickinson M, Dorritie K, Reagan PM, McGuirk J, Song KW, Riedell PA, Minnema MC, Yang Y, Vardhanabhuti S, Filosto S, Cheng P, Shahani SA, Schupp M, To C, Locke FL; ZUMA-7 Investigators; Kite Members. Survival with axicabtagene ciloleucel in large B-cell lymphoma. N Engl J Med. 2023;389:148-157.
28. Schuster SJ, Bishop MR, Tam CS, Waller EK, Borchmann P, McGuirk JP, Jäger U, Jaglowski S, Andreadis C, Westin JR, Fleury I, Bachanova V, Foley SR, Ho PJ, Mielke S, Magenau JM, Holte H, Pantano S, Pacaud LB, Awasthi R, Chu J, Anak Ö, Salles G, Maziarz RT; JULIET Investigators. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. N Engl J Med. 2019;380:45-56.
29. Matasar M, Li ZM, Vassilakopoulos TP, Sancho Cia JM, Viardot A, McMillan A, Dal MS, Pereira J, Kim JS, Qiu L, Batlevi C, Ibrahim R, Hernandez J, McCall B, Jiang Y, Yan M, Harris W, Musick L, Haioun C. Polatuzumab vedotin, rituximab, gemcitabine and oxaliplatin (POLA-R-GEMOX) for relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL): phase III POLARGO trial. European Hematology Association Plenary Abstracts Session, 2025, Abstract S101.
30. Sehn LH, Hertzberg M, Opat S, Herrera AF, Assouline S, Flowers CR, Kim TM, McMillan A, Ozcan M, Safar V, Salles G, Ku G, Hirata J, Chang YM, Musick L, Matasar MJ. Polatuzumab vedotin plus bendamustine and rituximab in relapsed/refractory DLBCL: survival update and new extension cohort data. Blood Adv. 2022;6:533-543.
31. Matasar MJ, Haioun C, Sancho JM, Viardot A, Hirata J, Perretti T, Musick L, McMillan AK. POLARGO: randomized phase III study of polatuzumab vedotin plus rituximab, gemcitabine, and oxaliplatin in relapsed/refractory diffuse large B-cell lymphoma. Blood. 2021;138(Suppl 1):3568.
32. Haydu JE, Abramson JS. The rules of T-cell engagement: current state of CAR T cells and bispecific antibodies in B-cell lymphomas. Blood Adv. 2024;8:4700-4710.
33. Auletta JJ, Sandmaier BM, Jensen E, Majhail NS, Knutson J, Nemecek E, Ajayi-Hackworth F, Davies SM; ACCESS Workshop Team. The ASTCT-NMDP ACCESS Initiative: a collaboration to address and sustain equal outcomes for all across the hematopoietic cell transplantation and cellular therapy ecosystem. Transplant Cell Ther. 2022;28:802-809.
34. Jommi C, Bramanti S, Pani M, Ghirardini A, Santoro A. CAR T-cell therapies in Italy: patient access barriers and recommendations for health system solutions. Front Pharmacol. 2022;13:915342.
35. Hu B, Vaidya R, Ahmed F, Ehsan H, Moyo TK, Jacobs RW, et al. Real-world analysis of barriers to timely administration of chimeric antigen receptor T cell (CAR T) therapy in diffuse large B-cell lymphoma. Transplant Cell Ther. 2024;30:1082.e1-1082.e10.
36. Sureda A, Adam SE, Yang S, Griffin E, Baker J, Johnston K, Navarro FR, Alhasani S, Chhibber A, Wang A, Mutebi A. Logistical challenges of CAR T-cell therapy in non-Hodgkin lymphoma: a survey of healthcare professionals. Future Oncol. 2024;20:2855-2868.
37. Lei M, Li Q, O'Day K, Meyer K, Wang A, Jun MP. Practice efficiency and total cost of care with bispecifics and CAR-T in relapsed/refractory diffuse large B-cell lymphoma: an institutional perspective. Future Oncol. 2024;20:2189-2201.
38. Cliff ERS, Kelkar AH, Russler-Germain DA, Tessema FA, Raymakers AJN, Feldman WB, Kesselheim AS. High cost of chimeric antigen receptor T-cells: challenges and solutions. Am Soc Clin Oncol Educ Book. 2023;43:e397912.
39. Abdo L, Batista-Silva LR, Bonamino MH. Cost-effective strategies for CAR-T cell therapy manufacturing. Mol Ther Oncol. 2025;33:200980.
40. Younes A, Sehn LH, Johnson P, Zinzani PL, Hong X, Zhu J, Patti C, Belada D, Samoilova O, Suh C, Leppä S, Rai S, Turgut M, Jurczak W, Cheung MC, Gurion R, Yeh SP, Lopez-Hernandez A, Dührsen U, Thieblemont C, Chiattone CS, Balasubramanian S, Carey J, Liu G, Shreeve SM, Sun S, Zhuang SH, Vermeulen J, Staudt LM, Wilson W; PHOENIX investigators.. Randomized phase III trial of ibrutinib and rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone in non-germinal center B-cell diffuse large B-cell lymphoma. J Clin Oncol. 2019;37:1285-1295.
41. Nowakowski GS, Chiappella A, Gascoyne RD, Scott DW, Zhang Q, Jurczak W, Özcan M, Hong X, Zhu J, Jin J, Belada D, Bergua JM, Piazza F, Mócikova H, Molinari AL, Yoon DH, Cavallo F, Tani M, Yamamoto K, Izutsu K, Kato K, Czuczman M, Hersey S, Kilcoyne A, Russo J, Hudak K, Zhang J, Wade S, Witzig TE, Vitolo U. ROBUST: a phase III study of lenalidomide plus R-CHOP versus placebo plus R-CHOP in previously untreated patients with ABC-type diffuse large B-cell lymphoma. J Clin Oncol. 2021;39:1317-1328.
42. Zhang MC, Tian S, Fu D, Wang L, Cheng S, Yi HM, Jiang XF, Song Q, Zhao Y, He Y, Li JF, Mu RJ, Fang H, Yu H, Xiong H, Li B, Chen SJ, Xu PP, Zhao WL. Genetic subtype-guided immunochemotherapy in diffuse large B cell lymphoma: the randomized GUIDANCE-01 trial. Cancer Cell. 2023;41:1705-1716.e5.
43. Salles G, Duell J, González Barca E, Tournilhac O, Jurczak W, Liberati AM, Nagy Z, Obr A, Gaidano G, André M, Kalakonda N, Dreyling M, Weirather J, Dirnberger-Hertweck M, Ambarkhane S, Fingerle-Rowson G, Maddocks K. Tafasitamab plus lenalidomide in relapsed or refractory diffuse large B-cell lymphoma (L-MIND): a multicentre, prospective, single-arm, phase 2 study. Lancet Oncol. 2020;21:978-988.
44. Caimi PF, Ai W, Alderuccio JP, Ardeshna KM, Hamadani M, Hess B, Kahl BS, Radford J, Solh M, Stathis A, Zinzani PL, Havenith K, Feingold J, He S, Qin Y, Ungar D, Zhang X, Carlo-Stella C. Loncastuximab tesirine in relapsed or refractory diffuse large B-cell lymphoma (LOTIS-2): a multicentre, open-label, single-arm, phase 2 trial. Lancet Oncol. 2021;22:790-800.
45. Ayers E, Zelikson V, Gurumurthi A, Sawalha Y, Annunzio K, Saha A, Dong N, Qualls DA, Amoozgar B, Kahl BS, Baird JH, Challa P, Huntington SF, Santos J, Bair SM, Narkhede MS, Li S, Frosch ZAK, Ho CI, Smith SD, Winter A, Landsburg DJ, Furqan F, Hamadani M, Baird K, Romancik JT, Alharthy H, Law J, Bojanini L, Advani RH, Hu B, Johnson PC, Grover NS, Kundu D, Merrill MH, Crombie JL, Shafagati N, Sterling C, Nastoupil LJ, Epperla N. Loncastuximab in high-risk and heavily-pretreated relapsed/refractory diffuse large B-cell

lymphoma: a real world analysis from 21 US centers. Blood. 2023;142(Suppl 1):312.

46. Qualls DA, Lambert N, Caimi PF, Merrill M, Pullarkat P, Godby RC, Bond DA, Wehmeyer GT, Romancik J, Amoozgar B, Leslie L, Nastoupil LJ, Crombie JL, Abramson JS, Khurana A, Nowakowski GS, Maddocks K, Rutherford SC, Kahl B, Okwali M, Buege MJ, Seshan V, Batlevi CL, Salles G. Tafasitamab and lenalidomide in large B-cell lymphoma: real-world outcomes in a multicenter retrospective study. Blood. 2023;142:2327-2331.
47. Strüßmann T, Marks R, Wäsch R. Relapsed/refractory diffuse large B-cell lymphoma: is there still a role for autologous stem cell transplantation in the CAR T-cell era? Cancers (Basel). 2024;16:1987.
48. Barraclough A, Hawkes E, Sehn LH, Smith SM. Diffuse large B-cell lymphoma. Hematol Oncol. 2024;42:e3202.
49. Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Reagan PM, Miklos DB, Jacobson CA, Braunschweig I, Oluwole OO, Siddiqi T, Lin Y, Crump M, Kuruvilla J, Van Den Neste E, Farooq U, Navale L, DePuy V, Kim JJ, Gisselbrecht C. Comparison of 2-year outcomes with CAR T cells (ZUMA-1) vs salvage chemotherapy in refractory large B-cell lymphoma. Blood Adv. 2021;5:4149-155.
50. Gisselbrecht C, Glass B, Mounier N, Singh Gill D, Linch DC, Trneny M, Bosly A, Ketterer N, Shpilberg O, Hagberg H, Ma D, Brière J, Moskowitz CH, Schmitz N. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. J Clin Oncol. 2010;28:4184-4190.
51. Crump M, Kuruvilla J, Couban S, MacDonald DA, Kukreti V, Kouroukis CT, Rubinger M, Buckstein R, Imrie KR, Federico M, Di Renzo N, Howson-Jan K, Baetz T, Kaizer L, Voralia M, Olney HJ, Turner AR, Sussman J, Hay AE, Djurfeldt MS, Meyer RM, Chen BE, Shepherd LE. Randomized comparison of gemcitabine, dexamethasone, and cisplatin versus dexamethasone, cytarabine, and cisplatin chemotherapy before autologous stem-cell transplantation for relapsed and refractory aggressive lymphomas: NCIC-CTG LY.12. J Clin Oncol. 2014;32:3490-3496.

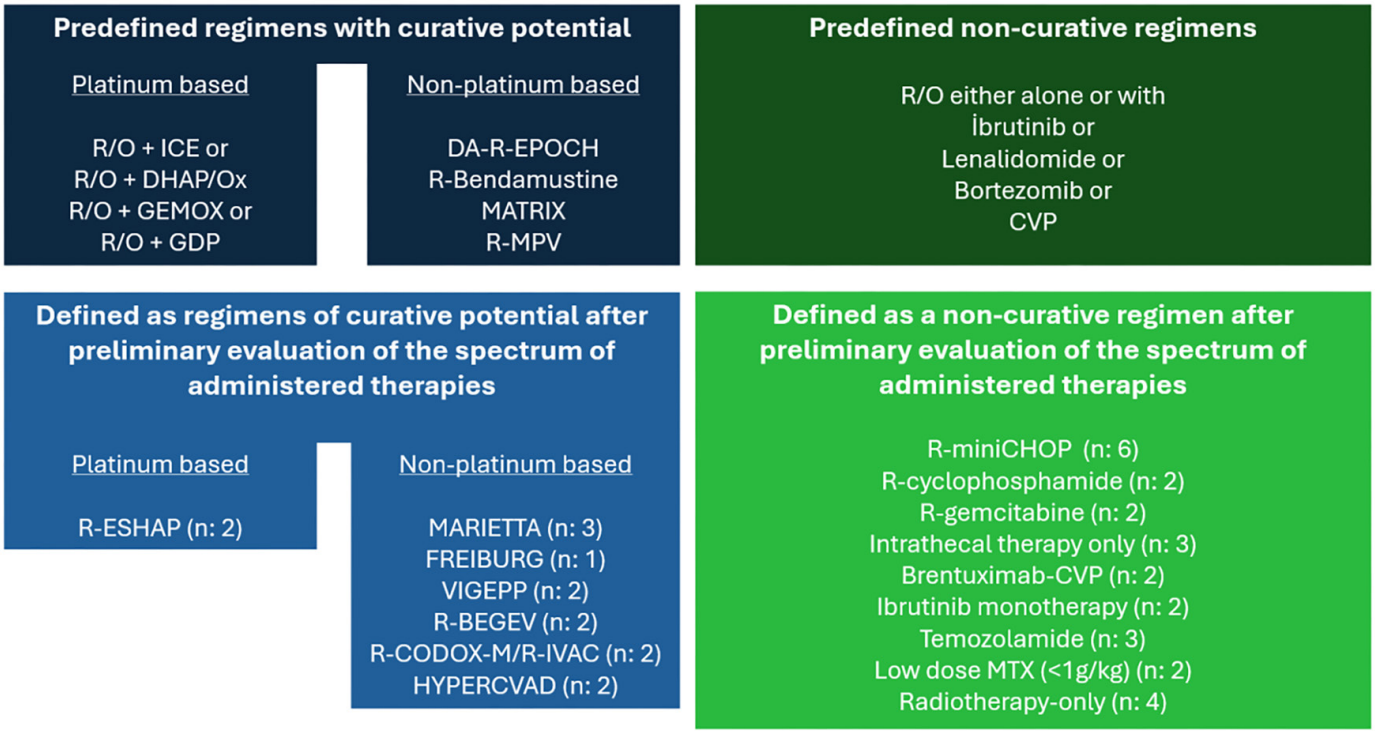
Supplementary Table 1. The distribution of first-line therapies among the 436 patients who failed frontline therapy.
Regimens
R-CHOP (n=302, 69.3%)
R-miniCHOP (n=55, 12.6%)
DA-R-EPOCH (n=50 ,11.5%)
R-CVP (n=11, 2.5%)
High-dose methotrexate based (n=9, 2.1%)
R-bendamustine (n=4, 0.9%)
Others (n=5, 1.2%)

Supplementary Table 2. Non-platinum-based and non-curative-intent regimens in 2L.
Non-platinum-based 2L therapy
R-bendamustine (n=27)
MATRIX (n=8 alone, n=3 as MARIETTA)
R-MPV (n=4)
VIGEPP (n=2)
FREIBURG (n=1)
BEGEV (n=2)
R-CODOX-M / IVAC (n=2)
R-EPOCH (n=6)
HyperCVAD (n=2)
Non-curative-intent 2L therapy (n=73)
Anti-CD 20 (n=17)
R-miniCHOP (n=6)
R-CVP (n=4)
R-cyclophosphamide (n=2)
R-gemcitabine (n=2)
IT MTX + ARA-C (n=3)
Brentuximab + CVP (n=2)
R-lenalidomide (n=6)
Ibrutinib (n=2)
R-ibrutinib (n=4)
Radiotherapy-only (n=4)
Temozolomide (n=3)
Cranial RT and low-dose methotrexate (n=2)
Unknown palliative (n=16)
2L: Second-line; RT: radiotherapy.

Supplementary Table 3. The distribution of second-line therapies among the 266 patients who progressed within 12 months of initial diagnosis.

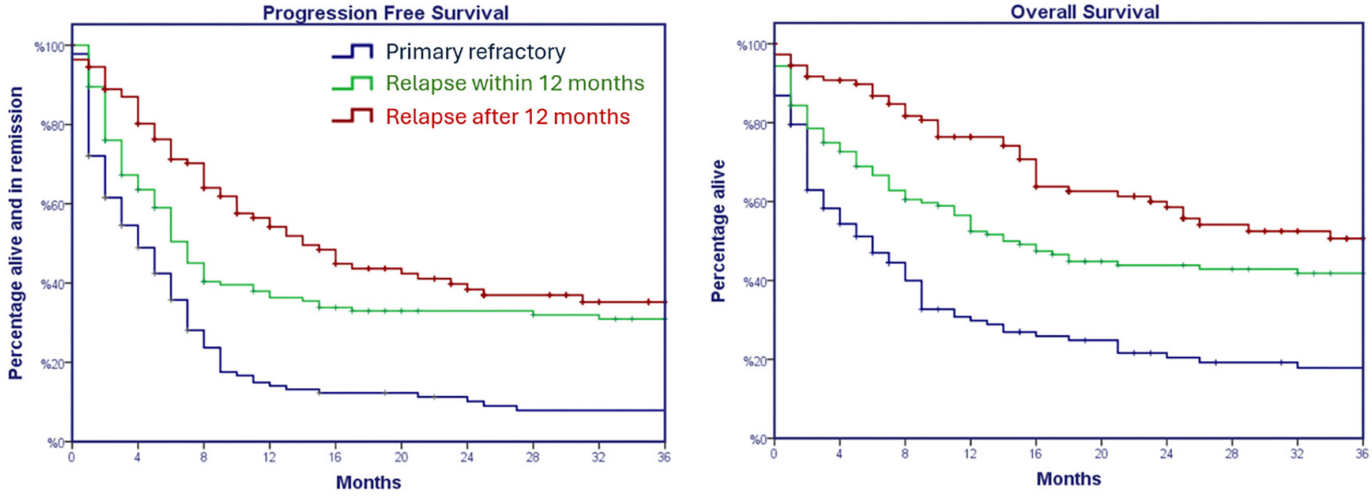
Regimens
R-ICE (n=51, 19.1%)
R-DHAP/Ox (n=34, 12.7%)
R-GDP (n=30 11.2%)
R-bendamustine (n=17, 6.4%)
High-dose methotrexate-based (n=8, 3%)
Other curative regimens (n=24, 9.1%)
Non-curative (n=48, 17.9%)
No therapy (n=54, 20.3%)

R: Rituximab; ICE: ifosfamide, carboplatin, etoposide; DHAP/Ox: dexamethasone-cytarabine and cisplatin or oxaliplatin; GDP: gemcitabine-dexamethasone-cisplatin.



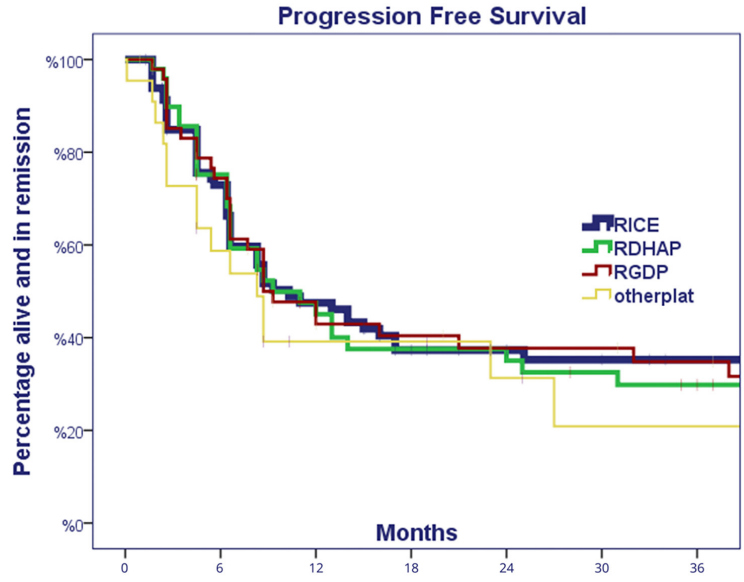
Supplementary Figure 1. Allocation of various regimens into three treatment groups.

R: Rituximab, O: obinutuzumab; ICE: ifosfomide-carboplatin-etoposide; DHAP/Ox: dexamethasone-cytarabine and cisplatin or oxaliplatin; GEMOX: gemcitabine-oxaliplatin; GDP: gemcitabine-dexamethasone-cisplatin; DA-EPOCH: dose-adjusted rituximab-etoposide-prednisolone-vincristine-cyclophosphamide-doxorubicin; MATRIX: methotrexate, cytarabine, thiotepa, and rituximab; MPV: methotrexate, procarbazine, vincristine; ESHAP: Etoposide-methylprednisolone-cytarabine-cisplatin; MARIETTA: MATRIX and ICE alternating regimen; FREIBURG: a modified MATRIX protocol; VIGEPP: vinorelbine, gemcitabine, procarbazine, and prednisone; R-CODOX-M/R-IVAC: Burkitt lymphoma standard treatment protocol; HYPERCVAD: standard treatment protocol for acute lymphoblastic leukemia.



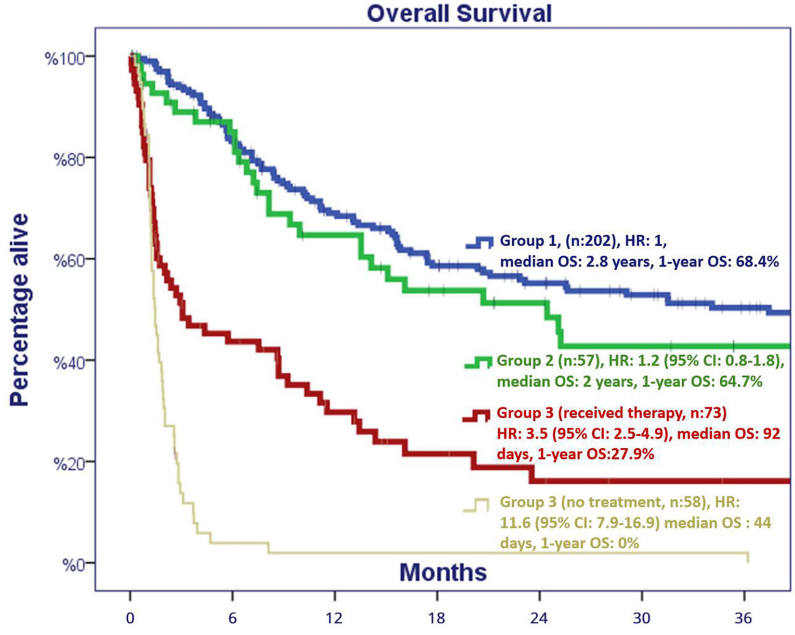
Supplementary Figure 2. PFS and OS curves comparing the outcomes depending on the refractoriness to 1L therapy, early relapse, and late relapse.

PFS: Progression-free survival; OS: overall survival; 1L: first-line.



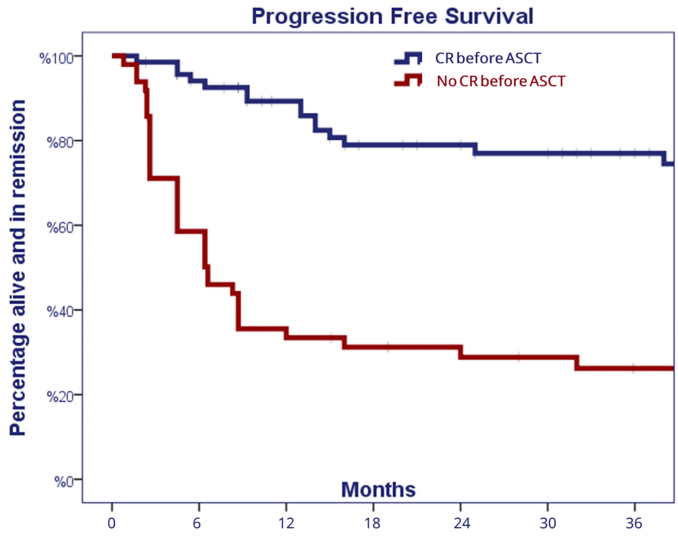
Supplementary Figure 3. PFS curves comparing different platinum-based regimens at 2L.

PFS: Progression-free survival; 2L: second-line.



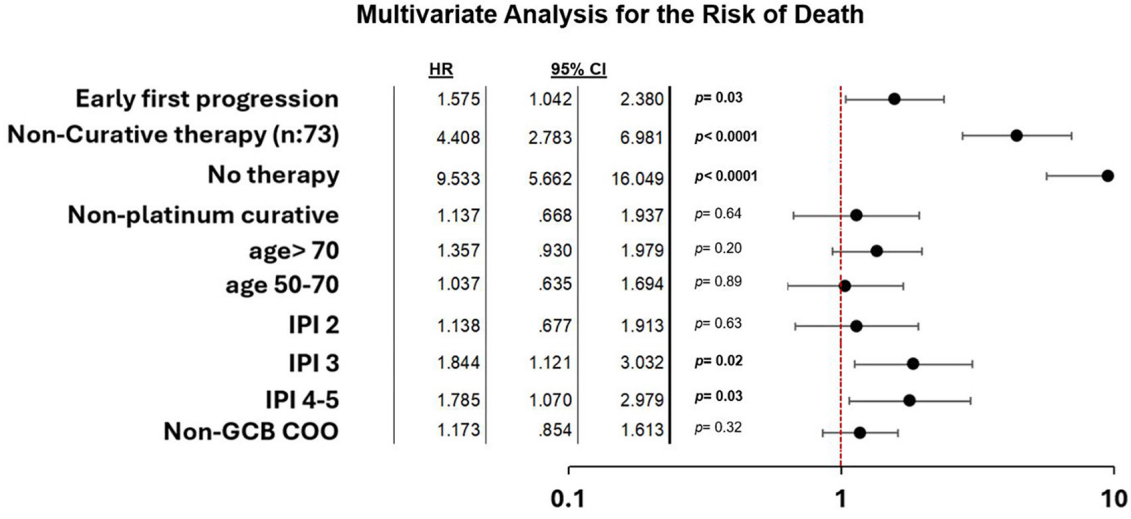
Supplementary Figure 4. OS curves after first progression with the third group separated into two based on whether a specific anti-lymphoma treatment was administered or not.

OS: Overall survival; HR: hazard ratio; CI, confidence interval.



Supplementary Figure 5. PFS curves comparing patients achieving CR before ASCT to those undergoing ASCT with a response of PR or worse.

PFS: Progression-free survival; CR: complete response; ASCT: autologous stem cell transplantation; PR: partial response.



Supplementary Figure 6. Multivariate analysis for the risk of death using the timing of progression (12-month cut-off, reference: >12 months), type of therapy (reference: platinum-based-curative), age at relapse/progression (reference: >50 years), IPI at diagnosis (0,1 reference), and cell-of-origin (GCB reference).

IPI: International Prognostic Index; GCB: germinal center B-cell.