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

Nüks/Dirençli Büyük B-Hücreli Lenfomanın Tedavisinde Karşılanmamış İhtiyaçlar: Bispesifik ve CAR-T Erişimi Olmayan Çok Merkezli 1369 Hasta Kohortunda İkinci Sıra Tedavilerinin İncelenmesi

Yılmaz U. et al.: Real-World Unmet Needs in R/R LBCL

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Abstract
Objectives: Large B-cell lymphoma (LBCL) patients who fail frontline therapy (R/R-LBCL) experience highly unfavorable outcomes. The development of T-cell redirecting therapies is rapidly evolving this outlook. However, costs and infrastructural challenges limit access to such 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 subgroups with the most urgent need for accessing innovative treatments.
Methods: The second-line management and outcomes of a large real-world LBCL cohort from Türkiye were retrospectively analyzed with the participation of nine centers from four different geographical regions.
Results: Despite the contemporary period (2012-24), there was no regular access to novel agents. The median PFS-2 was 6.9 months. Less than a quarter of patients (24.3%) received transplantation following a response to second-line therapy, the only subgroup who benefited from the standard care (2-year PFS-2: 67.8%). The remaining 295 patients (75.7% of the cohort) had a median survival of 6.1 months and a 2-year PFS-2 of 10.3%. Progression within a year from diagnosis, non-curative intent at second line, 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.
Conclusions: The current therapeutic strategy of intensive chemoimmunotherapy followed by autologous transplantation yields a reasonable chance of survival for only a fifth of patients. The findings emphasize the urgent need for expanding access to T-cell redirecting approaches in R/R LBCL for early progressors, transplant-ineligible cases, those who fail intensive second-line regimens.
Keywords: Lymphoma, Large B-cell lymphoma, relapsed/refractory, LBCL, DLBCL, second-line, autologous transplantation

Öz
Giriş: Nüks/dirençli büyük B-hücreli lenfomanın (R/R-BBHL) kötü prognozlu olduğu bilinmektedir. Son yıllarda geliştirilen bispesifik antikor ve CAR-T tedavileri sağkalımı uzatmaktadır. Finansal ve altyapısal engeller, bu tedavilerin ulaşılabilirliğini kısıtlamaktadır. Ülkemizde 2025 yılı itibariyle, bu tedaviler geri ödeme kapsamında değildir. Bu kısıtlılığın getirdiği sonuçları günümüz şartlarında belgelemek ve yeni tedavilere en çok ihtiyaç duyan hasta alt gruplarını tanımlamak amaçlı bu çalışmayı tasarladık.
Yöntem: Çalışma, çok merkezli geriye dönük tasarlanmıştır. R/R-BBHL'de ikinci sıra tedaviler ve bunların sonuçları incelenmiştir.
Bulgular: 2012-2024 arasında tanı almış 1369 hastalık bu kohortta, 436 hastada progresyon olayı izlenmiştir. Lenfoma nüksü öncesi ölen ve ikinci sırada klinik çalışmalara katılanlar hariç bırakılarak 390 hastanın gerçek-yaşam ikinci sıra tedavileri analiz edilmiştir.
Türkiye'de bispesifik ve CAR-T tedavilerine rutin olarak ulaşılamadığı çalışma verileriyle doğrulanmıştır. İlk progresyonun tanımlanmasını takiben ortanca progresyonsuz sağkalım (PFS) 6.9 ay, sağkalım 14,1 aydır. 266 (%68,2) hastada erken progresyon (<12 ay) olduğu gözlenmiştir ve bu grupta ortanca sağkalım 8.8 aydır. 95 hastada (%24,3) yanıt elde edilerek otolog nakle ilerlenebilmiştir. Standart terapötik strateji yalnızca bu 95 hastada başarılı olmuştur (2-yıl-PFS: %67,8). Geri kalan 295 hastada (kohortun %75,7'si) ortanca sağkalım 6.1 ay ve 2-yıl-PFS %10,3'tür. Nakil sonrası nüks eden olgularda ortanca TS 8.8 aydır.
Küratif tedavi uygulanmayan 131 hastada düşük yoğunluklu sitotoksik kombinasyon rejimleri, ibrutinib ve lenalidomid gibi hedefe yönelik moleküller tedavi tercihinde öne çıkmıştır. Bu grupta ortanca sağkalım 2 ay olarak gözlenmiştir ve 1 yıl toplam sağkalım %13,4 bulunmuştur.
Sonuç: Türkiye'de R/R BBHL tedavisinde yoğun sitotoksik tedavi ve otolog nakil stratejisinin beş hastanın yalnızca birinde başarılı olduğu bu çalışmanın verileriyle belgelenmiştir. Tanı sonrası ilk bir yılda progresyon gösteren veya transplant adayı olmayan olgular, yeni tedavilere en öncelikli olarak ihtiyaç duyulan alt gruplar olarak belirlenmiştir. İkinci sıra tedavilere yanıtsız veya otolog nakil sonrası nüks olgularda da standart yaklaşımlar yetersizdir. Bispesifik ve CAR-T tedavilerinin ulaşılabilir hale getirilmesi öncelikli bir klinik ihtiyaçtır.

Introduction
Large B-cell lymphoma (LBCL) is among the most common hematologic malignancies, and it 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 comprising up to a third of all lymphoma diagnoses(5). Odds of survival for patients failing first-line treatment have been dismal with standard approaches of platinum-based combination therapy followed by autologous stem cell transplantation (ASCT)(6–9). The complete remission (CR) rates were lower than 30% across various subgroups, and the median overall survival (OS) was 6.3 months in

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relapsed/refractory LBCL with standard therapies in the pivotal SCHOLAR-1 study(6). The development of CAR-T cells and bispecific antibodies over the last decade have raised hopes for improving the outcomes in relapsed/refractory (R/R) LBCL(10–12). Regulatory authorities in the USA and/or Europe have granted approvals 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 with these innovative therapies(13–16).

T-cell redirecting therapies are yet to be reimbursed in the Turkish Health Care system as of July 2025, limiting options in R/R LBCL to intensive cytotoxic therapies, ASCT, and in selected cases allogeneic stem cell transplantation (allo-SCT). The necessity for 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 nations(17,18).

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

Materials and Methods

Nine centers representing multiple geographic regions of Türkiye participated to this project to document the demographic features and descriptive data on histological subtypes, treatment, and outcomes of LBCL. An in depth methodological description of this project was previously published(19). Consecutive patients diagnosed between 2012 to 2024 were retrospectively included. Second-line regimens were pre-stratified into platinum-based curative therapy, non-platinum-based curative therapy, and non-curative therapy. As 2L regimens were anticipated 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 predefined groups (Supplemental Figure-1).

This analysis was focused on real-world R/R LBCL cases and patients without a documented active disease after the completion of first-line therapy, and patients enrolled in 2L trials were excluded. Patients who had stable disease as best response to first line therapy were considered primary refractory 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. The response states were defined according to local reports based on the Lugano 2014 criteria with positron emission tomography (PET)(20), or computed tomography (CT) results based on IWG 2007 criteria when PET data was unavailable(21). The primary endpoint was progression-free survival after the first progression (PFS-2) per group of 2L therapy. Secondary endpoints were response rates and OS. PFS-2 and OS based on the timing of progression, performance of ASCT, and response to second-line therapy. Exploratory endpoints were response rates, PFS-2 and OS based on the 2L regimen.

Statistics

For continuous descriptive data, the median values and range; for categorical descriptive data the number and frequency 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 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 and log-rank test to determine significance. Hazard ratios (HR) for the risk of progression and/or death were generated using Cox regression analysis using either the type of therapy, timing of progression, performance of ASCT, response before ASCT, type of regimen, or the year of therapy as categorical variables in univariate comparisons. Type of therapy in four categories (platinum-based, non-platinum-based, non-curative-no therapy), IPI and cell-of-origin from diagnosis, timing of progression (12-month cut-off) and age at the time of progression in three categories (<50, 50-70, >70 years) were included as covariates in the multivariate analysis for the risk of death. For all comparative analyses, the confidence interval was 95%, and p values <0.05 were considered significant. IBM SPSS version 22.0 was used for statistical analysis.

Results

Baseline features and distribution of treatment

A 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 initial diagnosis (Supplemental Table-1). The real-world R/R cohort analyzed in this study was composed of 390 patients, when lymphoma-unrelated deaths after frontline treatment (n: 37) and those enrolled in clinical trials (n: 9) were excluded (Figure-1a).

Slightly over half of R/R LBCL cases (52.3%, n:204) had previously documented response to frontline therapy and most progression events (68.2%, n:266) were documented within the first 12 months of diagnosis (Figure 1a). Selected baseline features at the time of relapse are summarized in Table-1. Platinum-based combination

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therapy was administered to 51.8% (n:202) of R/R LBCL cases as 2L therapy (Figure 1b, Table 2). Non-platinum-based therapies, most commonly by combining an anti-CD20 antibody with either bendamustine (n:27) or high-dose methotrexate-based regimens for CNS involvement (n:18) were administered to 14.6% (n:57) of cases in the 2L (Table-2, Supplemental Table-2,3). These two groups were considered to have received therapy with a curative intent and most of these cases (247 of 259) had received regimens predefined as curative (Supplemental Figure-1). The remaining 131 patients (33.6%) either succumbed 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 was 6.9 (95%CI: 5.7-7.4) , and 14.1 (95%CI: 9.9-16.3) months, respectively after a median follow-up of 8.7 months (range: 4 days – 8.1 years). Among 160 patients who were censored for OS analysis, 132 had a follow-up data within 12 months of data cut-off and 28 had been lost to follow-up. These missing 28 cases were likely to have experienced inferior outcomes; however, had to be censored based on available data, possibly resulting in the overestimation of survival probabilities. The prognosis was significantly worse following an early progression after frontline therapy (<12 months) with a median PFS-2 of 5.9 (95%CI: 4.4-7.1) versus 13.7 (95%CI: 10- 17.7) months (Figure 2a, HR: 1.8, 95%CI: 1.4-2.4, p<0.0001) and a median OS of 8.8 (95%CI: 5.8-10.9) months versus 39.2 (95%CI: 15.5- 73.2) months (Figure 2b, HR: 2.2, 95% CI: 1.6-2.9, p<0.0001). There was also a significant difference in outcomes between those with primary refractory disease, early relapse, and late relapse (Supplemental Figure-2).

Outcomes after curative therapies

The overall response rate (ORR) was 55.9% (39.1% CR and 16.8% PR) after platinum-based therapies, and 74.1% of these responders went on to receive ASCT. Most common reasons for not undergoing ASCT after a response were a rapid second relapse (within 2 months, n:5), or a mobilization failure (n:4). The median PFS-2 after a 2L platinum-based therapy was 8.3 (95%CI: 6.1-10.6) months 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, and OS between various platinum-based regimens (Table-2, Supplemental Figure-3). The ORR for the group of patients receiving non-platinum-based regimens in the 2L was 47.4% (35.1% CR, 12.3% PR, Table-2). The median PFS-2 was 8.3 (95%CI: 4.6-12.2) months 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

Concerning the 131 patients in the third group who did not receive therapy with a curative intent, 58 (44.3%) died before a treatment other than glucocorticoids was initiated, most within 2 months of progression. All but three of these cases had early progression after frontline therapy and most were primary refractive. The remaining 73 patients in this group received treatment with regimens of negligible curative potential (Supplemental Table-2) and the treatment outcomes of these cases are summarized in Table-2. Most commonly administered non-curative regimens were glucocorticoids and rituximab with or without either modest doses of cytotoxic drugs (gemcitabine, cyclophosphamide, vincristine), lenalidomide (n:6) or ibrutinib (n:6). The six patients receiving R-miniCHOP as 2L therapy were considered in the non-curative group after a preliminary evaluation, since dose intensity was not maintained and none of these cases completed more than 2 cycles or went on to receive ASCT. The median OS was 55 days (95%CI: 43-66 days) for this group with only 13.4% remaining alive at 12 months from progression. Ten of twelve cases under ibrutinib or lenalidomide progressed within a year. To understand the impact of noncurative therapies more independently, we performed sensitivity analyses within this 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 and the median time to first progression was 5 and 8 months, respectively. The median OS from progression was 44 (95%CI: 35-52) and 92 (95%CI: 17-188) days, respectively. Furthermore, after separating the 58 cases 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 (Supplemental Figure-4).

Autologous stem cell transplantation

ASCT was performed to 118 (30.3% of the cohort) patients. Most patients (n:95) undergoing ASCT had a response to 2L therapy. These 95 patients, representing only the 24.3% of the R/R LBCL cohort, comprised the only subgroup demonstrating a relatively favorable prognosis with a 24-month PFS-2 and OS estimates of 67.8% and 81.9% **(Figure-4).** The 24-month PFS-2 and OS 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) without an 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 (Supplemental Figure-5). The median OS for patients relapsing after ASCT was 8.8 (95%CI: 3.4-12.9) months and only 23.7% remained alive after 2 years of ASCT-failure.

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Multivariate analysis

Multivariate analysis using the therapy type, patient age at first progression, timing of progression, IPI at diagnosis, and the 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 the early timing of progression (HR:1.58, 95% CI: 1.05-2.38 , Supplemental Figure-6)

Beyond second-line therapy

Among the 272 patients who failed 2L therapy, 23 patients (8.5%) went on to receive an allo-SCT in subsequent lines. Only four of these allo-SCT patients have documented long term remissions, with the remaining either early in their follow-up or died within a year of transplant. Nine patients (3.3%) received bispecific antibodies in the third line through participation in clinical trials or compassionate programs, with two achieving CR and three continuing treatment at data cut-off. 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 for the 2L treatment of 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, the standard of care approach before the advent of T-cell redirecting therapies, provided a reassuring chance of success to only a small minority of R/R LBCL patients. The only subset who derived significant benefit from this strategy were those who achieved a response after a combination chemotherapy and went on to receive ASCT, representing less than a quarter of the R/R LBCL population. For the remaining majority, only one-in-five remained alive after two years of first progression. The two strongest aspects favoring survival in this cohort were late relapses and undergoing ASCT with an objective response.

T-cell redirecting therapies have revolutionized the management of R/R LBCL over the last decade(9–11). 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 that can be offered to patients who are otherwise considered unfit for combination chemotherapies or ASCT(11,13,23–25). There is a strong argument that these innovative therapies improve the outcomes in LBCL(12). The most compelling evidence for this claim come from the phase-3 ZUMA-7, TRANSFORM and STARGLO trials where significant PFS-2 and OS benefits were demonstrated favoring the experimental arms containing 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 similarly demonstrated highly promising rates of durable responses in phase-2 trials(16,23,28). One recent example is the epcoritamab combination with gemcitabine and oxaliplatin yielding a CR and 12-month PFS-2 rates of over 60% in the 2L cohort(23). In addition to T-cell redirecting therapies polatuzumab-vedotin has also proved itself as an active novel drug in R/R LBCL(29–31). Despite the remarkable advances in drug development, the challenges with accessibility of these innovative therapies remain largely unmet. Recent reports make it clear that difficulties in access is not limited to developing nations but remains a serios issue in many nations regardless of economic prosperity(32–36). A responsible approach to overcome financial obstacles can be 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 investments for academic CAR-T products(37–39). The findings of this study clearly document the shortcomings of cytotoxic therapy in R/R LBCL in a contemporary real-world cohort and echo the urge for a global effort to expand access to T-cell redirecting therapies.

Regarding non-T-cell redirecting targeted agents in lymphoma, the two 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 without satisfactory rates of success. 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 CD-19 (tafasitamab and loncastuximab) were promising in phase-2 trials(43,44); however, real-life data have been disappointing(45,46). Based on the evidence listed above, the trend worldwide in R/R LBCL is fading away from cytotoxic or targeted drugs mentioned above, towards T-cell redirecting therapies(11,47,48). Our real-world data in terms of CR rates and PFS-2 outcomes align well with the SOC arms from the large phase-3 trials mentioned above and confirm the limitations of the previous SOC approaches in the contemporary real-world setting where innovative therapies were locally unavailable(6,13,14,26,27). Most notable among these is the SCHOLAR-1 study reporting 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 between 5 to 8 months across various subgroups analyzed(6,49). This was largely along the line of 6.1-month median OS reported in our results concerning the majority of the cohort who did not undergo ASCT following a response to 2L therapy. The lack of a difference between platinum-based regimens confirms the results of two comparative trials (50,51). Furthermore, the poorly

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prognostic impact of the primary refractory state or very early relapse is clearly demonstrated in this cohort, highlighting a group with urgent unmet needs in the 2L of therapy.

Limitations

The key limitation of this study, its retrospective nature, should be considered in interpreting results as it exposes analyses to selection bias. This was most evident for the 28 patients who were censored as they were lost to follow-up over 12 months from data cut-off. Furthermore, since six of the nine 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 only further emphasize the main theme of the study concerning the shortcomings of cytotoxic therapy-based approaches in R/R LBCL.

As a real-world analysis, the timing of imaging studies were not controlled. Thus, the definition of PFS-2 events were 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 a treatment failure.

The therapies administered in 2L were highly heterogeneous. Therefore, a preliminary evaluation was planned to allocate rarely used regimens into predefined curative/non-curative treatment groups. The heterogeneity also limited more comprehensive comparison 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 cases were not administered therapy (e.g. highly aggressive tumor, lack of appropriate options for patient's fitness, or patient choice) could not be discerned with the available data, limiting the interpretation of the independent impact of management in this subgroup. However, the exploratory analysis performed after separating these 58 cases clearly demonstrated the inferior prognosis for the 73 patients that received therapy without a 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. Findings highlight the most urgent unmet needs in patients with early progression (within one year of diagnosis), lack of fitness to tolerate intensive chemotherapy, and those who fail intensive second-line therapies. A determined effort is desperately needed to overcome financial obstacles and deliver efficient therapies to those who need them the most.

Conflict of Interest Statement

No conflicts of interest declared

Funding: The study has not received financial support

Novelty Statement

1- The first report of second-line outcomes of LBCL among a large real-world cohort without regular access to T-cell redirecting therapies in the 2020s.

2- There are urgent unmet needs in LBCL that can be partially covered by expanding access to T-cell redirecting therapies.

3- The first extensive analysis representing multiple geographic regions of Türkiye for R/R LBCL features, management, and outcomes

Ethics Approval Statement

The study was approved with the number 2025/27 by the Non-Interventional Research Committee of the Institutional Review Board of Kocaeli University on the 16th of January. All researchers complied with good clinical practice in accordance with the Declaration of Helsinki. All patient data were anonymized before analysis and no identifier of any sort including any images were used in the study. All authors have approved the final version of this manuscript.

Patient Consent Statement

Due to the retrospective nature of this non-interventional study spanning back to 2012, individual consent was not deemed necessary by the ethical board. All patient data were anonymized before analysis. No patient photo or radiologic image were collected, and no individual identifier of any sort has been included in the manuscript.

Funding Sources

No funding was received for the conduct or publication of this study.

Data Availability Statement

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The data is not publicly available due to local regulations; however, raw data can be shared with peers upon reasonable request.

Permission to reproduce material from other sources

No material from other sources have been used in this manuscript

Clinical Trial Registration Number

Not applicable

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Table 1.

Feature	**R/R LBCL Cohort** (n:390)	**Platinum-based** (n:202)	**Non-platinum based** (n:57)	**Palliative** (n:131)
Age at progression				
Median / Range	61 (18-93)	57 (19-86)	57 (18-92)	70 (25-92)
Gender				
Female	n:170 (43.6%)	n: 84 (41.6%)	n: 23 (39.6%)	n: 64 (48.9%)
Male	n:220 (56.4%)	n: 118 (58.4%)	n: 34 (61.4%)	n: 67 (51.1%)
Histological subtype				
DLBCL-NOS	n: 278 (71.3%)	n:154 (76.1%)	n: 35 (61.4%)	n: 89 (68.3%)
Transformed LBCL	n: 34 (8.6%)	n: 16 (8.1%)	n: 5 (8.8%)	n: 12 (8.8%)
High Grade LBCL	n: 33 (8.4%)	n:15 (7.2%)	n: 5 (8.8%)	n:14 (10.4%)
TCHRBCL	n: 9 (2.4%)	n:7 (3.6%)	n:1 (1.8%)	n: 1 (0.8%)
PMBCL	n: 10 (2.6%)	n:4 (2%)	n:5 (8.8%)	n: 1 (0.8%)
Cell of origin				
GCB	n: 147 (37.7%)	n:68 (33.7%)	n: 22 (38.6%)	n: 44 (33.5%)
Non-GCB	n: 149 (38.1%)	n: 81 (40.1%)	n: 18 (31.5%)	n: 47 (36.1%)
Timing of progression				
<12 months	n: 266 (68.5%)	n:129 (63.9%)	n: 36 (63.2%)	n: 102 77.9%
≥12 months	n: 124 (31.5%)	n:73 (36.1%)	n: 21 (36.8%)	n: 29 (22.1%)

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Response rates				
CR	n: 107 (27.4%)	n: 79 (39.1%)	n:20 (35.1%)	n: 8 (6.1%)
PR	n: 46 (11.8%)	n:34 (16.8%)	n: 7 (12.3%)	n: 5 (3.8%)
ASCT	n: 118 (30.3%)	n: 102 (50.5%)	n: 14 (24.6%)	n:2 (1.5%)
Median PFS (months)	6.9	8.3	8.3	N/A
Median OS (months)	14.1	38.1	24.6	2

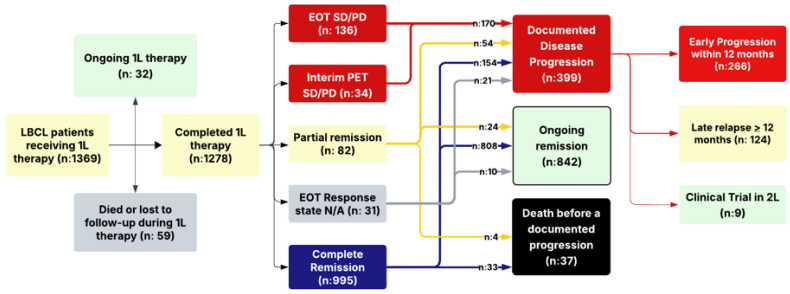
Selected baseline features, treatment data, response rates, ASCT rates, PFS, and OS data across the entire cohort and between the three groups based on second-line therapy

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

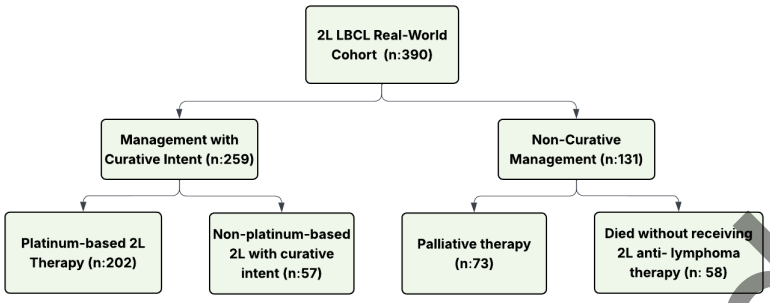
Table 2. Response rates, ASCT, and PFS based on the treatment regimen in second-line therapy and the timing of first progression

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%

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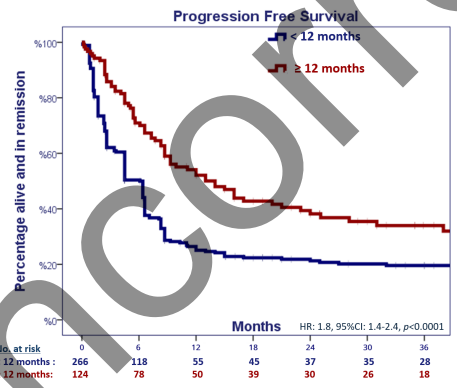


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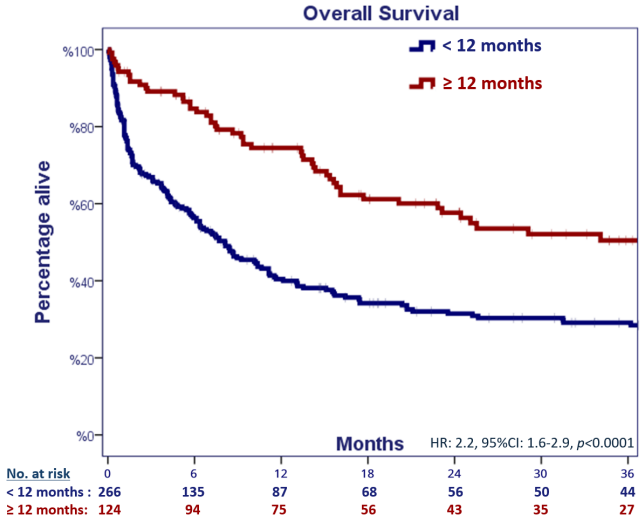
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Figure 1 Flowchart following the clinical course of all 1369 patients involved in the cohort (1a) and the initial management of the 390 cases managed in second-line in the real-world setting (1b).
Abbreviation: 1L; first-line treatment, CR; complete remission, PR; partial remission, SD; stable disease, PD; progressive disease, EOT; end of therapy, 2L; second-line treatment



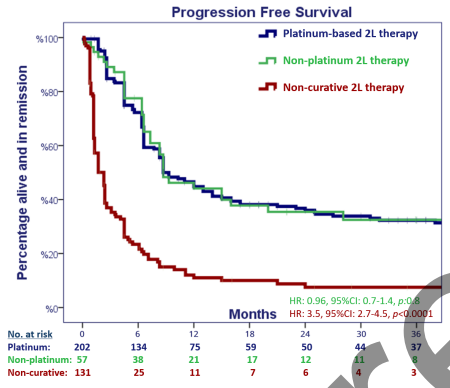
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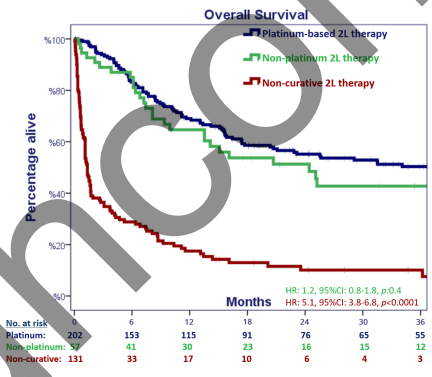


b

Figure 2 Comparison of PFS-2 (2a) and OS(2b) between patients showing early progression (<12 months) after frontline therapy and those with later relapses.



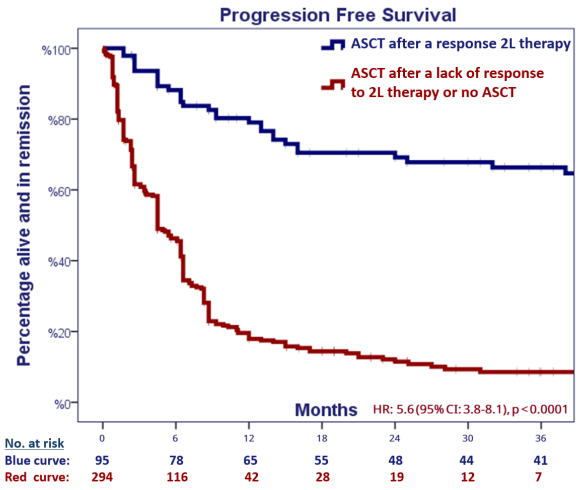
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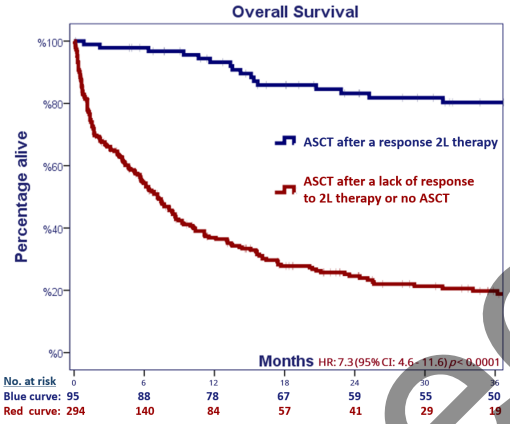
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Figure 3 Comparison of PFS-2 (3a) and OS(3b) between patients treated with a platinum based regimen, a non-platinum-based regimen, and non-curative intent in second line therapy
Abbreviation: 2L; second-line

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a



b

Figure 4. Comparison of PFS-2(4a) and OS (4b) between patients who received ASCT following a response to second line therapy and the rest of the cohort
Abbreviations: ASCT; autologous stem cell transplantation, 2L; second-line

Supplementary Table: Non-Platinum based and Non-Curative Intent Regimens in 2L

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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)

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)

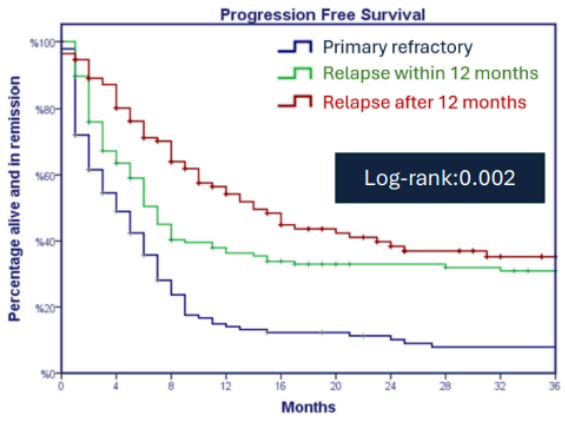
IT MTX + ARA-C (n:3)

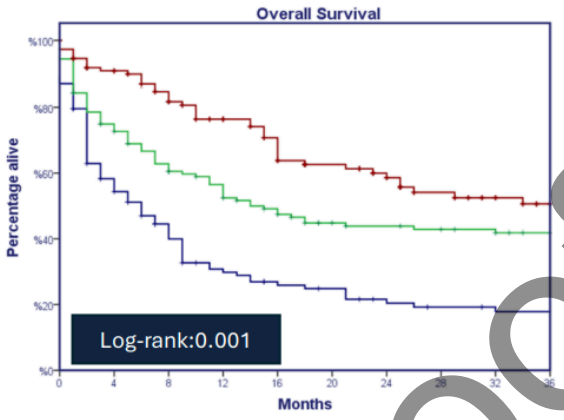
Brentuximab + CVP
(n:2) R-lenalidomide
(n:6) Ibrutinib (n:2)

R- ibrutinib (n:4)
Radiotherapy-only
(n:4) Temozolomide
(n:3)

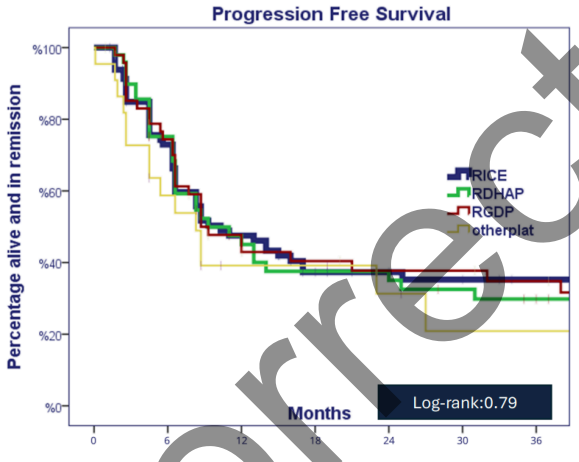
Cranial RT and low-dose methotrexate (n:2)
Unknown palliative (n:16)

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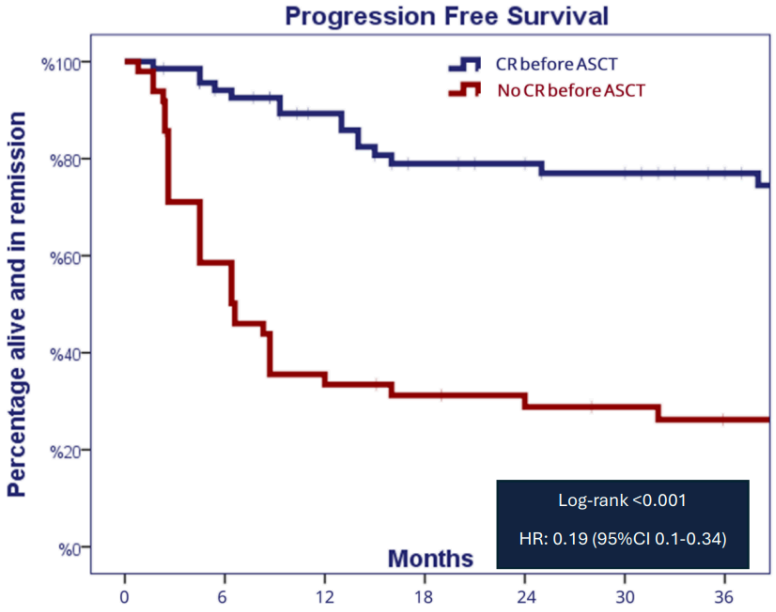


Supplementary Figure 1 – PFS and OS curves comparing the outcomes depending on the refractoriness to 1L therapy, early relapse, and late relapse

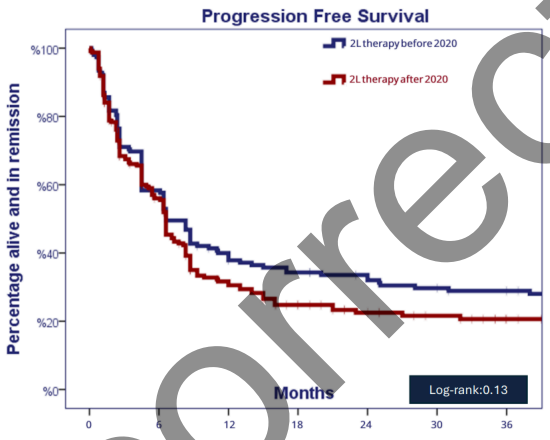


Supplementary Figure 2 – PFS curves comparing different platinum-based regimens at 2L

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Supplementary Figure 3 - PFS curves comparing patients achieving CR before ASCT to those undergoing ASCT with a response of PR or worse



Supplementary Figure 4 - PFS curves comparing patients grouped based on the year of 2L therapy onset

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