# Feasibility and outcomes after dose reduction of immunochemotherapy in young adults with Burkitt lymphoma and leukemia: results of the BURKIMAB14 trial

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**Received:** April 19, 2023.
**Accepted:** July 31, 2023.
**Early view:** August 10, 2023.

**https://doi.org/10.3324/haematol.2023.283342**



## Abstract

High dose-intensive or infusional intermediate-dose immunochemotherapy is highly effective treatment for Burkitt lymphoma irrespective of human immunodeficiency virus (HIV) infection. However, toxicities of these regimens are relevant, especially in older adults and elderly patients. The prospective multicenter BURKIMAB14 trial included four to six blocks of immunochemotherapy according to stage (localized: 1 and 2 non-bulky; advanced: 2 bulky, 3, 4) and age, with dose reduction in patients >55 years old. Dose-intensity of chemotherapy was reduced in patients ≤55 years old after achieving complete metabolic response (CMR). Their outcomes were compared with those of similar patients included in the former BURKIMAB08 trial, in which there was no dose reduction. CMR was attained in 86 of 107 (80%) patients (17/19 in localized stages and 69/88 in advanced stages). Patients from the BURKIMAB14 trial ≤55 years old showed similar overall survival (OS), fewer

infections and cytopenias than patients from the BURKIMAB08 trial. Patients >55 years old had a significantly higher treatment-related mortality despite dose reduction of chemotherapy. With a median follow-up of 3.61 years the 4-year OS probability was 73% (range, 63-81%). Age (≤55 *vs*. >55 years) and stage (localized *vs*. advanced) had prognostic significance. No significant differences in OS were observed in HIV-positive *versus* HIV-negative patients. The results of BURKIMAB14 are similar to those of other dose-intensive immunochemotherapy trials. Age >55 years and advanced stage, but not HIV infection, were associated with poor survival. Dose reduction of chemotherapy in young adults in CMR is safe and does not impact outcomes (*clinicaltrials gov. Identifier: NCT05049473*).

## Introduction

Burkitt's lymphoma or leukemia (BL) is a highly aggressive mature B-cell non-Hodgkin lymphoma (NHL), that represents 1-2% of NHL in adults from western countries.[1] BL accounts for nearly 40% of lymphomas that arise in human immunodeficiency virus (HIV)-infected patients and occurs in those with relatively normal CD4 lymphocyte counts. Whereas more than 90% of children and adolescents are cured with high-dose intensive chemotherapy, the cure rate in adults ranges from 75% to 85% in prospective trials using high-dose[2-13] or infusional intermediate-dose immunochemotherapy.[14,15] In HIV-associated BL the use of combination antiretroviral therapy (cART) has led to improved tolerance to full-dose chemotherapy, which has translated into outcomes similar to those of non-immunosuppressed patients. Despite highly effective front-line therapy, the incidence of treatment failure among adults may be as high as 20-30%, especially in older adults and elderly people.[16,17] To date, there are no effective rescue therapies for patients with refractory disease or relapse.[18,19]

The BURKIMAB08 trial of the Spanish PETHEMA (Programa Español de Tratamientos en Hematología) and GELTAMO (Grupo Español de Linfomas y Trasplantes de Medula Ósea) cooperative groups included 118 evaluable adult patients with BL irrespective of their HIV infection status.[8] The intensity of the therapy was adapted to age, with a cutoff point of 55 years (yrs). The response rate was 85% and the 4-year overall survival (OS) was 73%. Toxicity was relevant especially in older as well as in HIV-infected patients. In the BURKIMAB14 trial, the dose of cyclophosphamide, methotrexate and cytarabine was reduced in young adults aged up to 55 yrs after achieving response, whereas no modifications were performed for patients older than 55 yrs. Herein we report the efficacy and toxicity of this trial and compare these with the results observed in the BURKIMAB08 trial in young adults.

## Methods

Eligibility criteria included age ≥18 yrs, confirmed histologic and immune cytologic or histochemical diagnosis, including cytogenetics and/or *MYC* gene rearrangement. HIV-infected patients had to be on treatment with or had to begin combined cART at BL diagnosis. Exclusion criteria included patients with t(8;14), t(2;8) or t(8;22) with additional cytogenetic abnormalities, patients with *BCL-2* and/or *BCL-6* gene rearrangements, organ failure not due to BL, previous organ transplant and previous radiotherapy or chemotherapy. The study was approved by the Spanish Health Ministry on May 23, 2014 (reference 14155/RG44063). Accrual began in January 2014, and the study was closed for follow-up in June 2022. The study was registered as *clinicaltrials gov. Identifier: NCT05049473*. The Ann Arbor staging system was used to define stage. The International Prognostic Index (IPI) and the Burkitt lymphoma International Prognostic Index (BL-IPI)[20] were used to stratify risk. Table 1 shows the therapy of the BURKIMAB14 trial. Patients in advanced stage (2 with bulky disease or 3-4) ≤55 yrs received two courses of alternating cycles A, B and C, whereas patients >55 yrs received three courses of alternating cycles A and B, for a total of six cycles in both groups. Patients with localized stage (non-bulky stages 1-2) received four cycles of treatment (A, B, C and A for younger adults and A, B, A and B for older patients). A single dose of rituximab was administered before each cycle. Compared with the BURKIMAB08 trial, after achievement of complete response (CR) for patients ≤55 yrs intravenous methotrexate for cycles A, B and C was reduced 33%, iphosphamide 28% in cycle A and cytarabine 25% in cycle C. Central nervous system (CNS) prophylaxis consisted of triple intrathecal therapy (TIT) administered in the pre-phase and twice in each cycle A and B, for a total of nine doses in all patients. Positron-emission tomography-computed tomography (PET-CT) scans were performed after cycle 2 in all patients and after cycle 4 for patients in localized stages and after cycle 6 for patients in advanced stages. Early complete metabolic response (CMR) was defined as the disappearance of marrow and extramedullary disease after two cycles. Patients in partial metabolic remission (PMR, defined as >50% reduction of all measurable lesions) after two cycles continued therapy and were re-evaluated at the end of the fourth or the sixth cycle, in patients in early or advanced stages, respectively. The overall CMR rate was calculated as the sum of early CMR and CMR attained at the end of the fourth or sixth cycle, respectively. Treatment failure was defined when a patient did not achieve at least PMR after the first two cycles or CMR after six, respectively. Toxicity was evaluated according to the Common Terminology Cri-

teria for Adverse Events (CTCAE v 6.0) criteria.
The primary objective of the study was to assess OS and to compare the OS and toxicity with those observed in patients aged 18 to 55 yrs from the BURKIMAB08 trial. Survival curves were plotted according to the Kaplan-Meier method and were compared by the log-rank test. Median follow-up was calculated for alive patients.

# Results

## Patients

One hundred eleven patients were registered at 26 Spanish centers, of whom 107 were valid for this study. Reasons for exclusion of the remaining four patients were previous therapy (n=2) and treatment not given according to the age range (n=2). Sixty-eight patients were aged ≤55 yrs and 24 were HIV-positive. Table 2 shows the characteristics of the whole series and compares them according to age and HIV infection. Patients >55 yrs showed a significantly higher frequency of BL, high serum lactate dehydrogenase (LDH) level and higher frequency of poor IPI and BL-IPI risk groups, whereas the cohorts of HIV-positive and HIV-negative patients were comparable for the main clinical and biological parameters at diagnosis. In HIV-positive patients, the CD4 lymphocyte count was < 200/μL in nine of 20 cases (45%) (median 204; range, 0-773/μL), the HIV viral load was detectable in 12 of 22 patients (55%) and BL led to the diagnosis of HIV infection in 11 patients (46%).

## Response to treatment, survival and toxicity

Figure 1 shows the study flow chart. Following two cycles of chemotherapy early CMR and PMR were attained in 15 and four patients with localized stages and in 54 and 23 patients with advanced stages, respectively. At the end of therapy, the overall CMR rates were 17 of 19 (89%) and 69 of 88 (78%), respectively. For the whole series, the overall CMR rate was 80%. No relapses or deaths by toxicity were observed in patients with localized stages, whereas the main events registered in patients in advanced stages

**Table 1.** BURKIMAB08 and BURKIMAB14 protocol treatment[a].

| Cycle Day | Drug | Dose (mg/m²) BURKIMAB08 15-55 yrs | Dose (mg/m²) BURKIMAB14 18-55 yrs | Dose (mg/m²) BURKIMAB08 & BURKIMAB14 >55 yrs | Route (time in hrs) |
|---|---|---|---|---|---|
| Pre-phase | | | | | |
| 1-5 | Cyclophosphamide | 200 | 200 | 200 | IV (1) |
| 1-5 | Prednisone | 60 | 60 | 60 | IV bolus |
| Cycle A | | | | | |
| 7 | Rituximab | 375 | 375 | 375 | IV (4) |
| 8 | Vincristine | 2 (absolute) | 2 (absolute) | - | IV bolus |
| 8 | Methotrexate | 1,500[b] | 1,000[b] | 500[b] | IV (24)[b] |
| 8-12 | Iphosphamide | 800 | 500 | 400 | IV (1) |
| 8-12 | Dexamethasone | 10 | 10 | 10 | IV bolus |
| 11-12 | Etoposide | 100 | 100 | 60 | IV (1) |
| 11-12 | Cytarabine | 150 | 150 | 60 | IV (1 every 12) |
| Cycle B | | | | | |
| 28 | Rituximab | 375 | 375 | 375 | IV (4) |
| 29 | Vincristine | 2 (absolute) | 2 (absolute) | 1 (absolute) | IV bolus |
| 29 | Methotrexate | 1,500[b] | 1,000[b] | 500[b] | IV (24)[b] |
| 29-33 | Cyclophosphamide | 200 | 200 | 200 | IV (1) |
| 29-33 | Dexamethasone | 10 | 10 | 10 | IV bolus |
| 32-33 | Doxorubicin | 25 | 25 | 25 | IV (15 min) |
| Cycle C[c] | | | | | |
| 49 | Rituximab | 375 | 375 | - | IV (4) |
| 50 | Vindesine | 3 (max. 5) | 3 (max. 5) | - | IV bolus |
| 50 | Methotrexate | 1,500[b] | 1,000[b] | - | IV (24)[b] |
| 50-54 | Dexamethasone | 10 | 10 | - | IV bolus |
| 53-54 | Etoposide | 250 | 250 | - | IV (1) |
| 54 | Cytarabine | 2,000 | 1,500 | - | IV (3 every 12) |
| CNS prophylaxis | | | | | |
| 1, 8, 12, 29, 33 | Methotrexate | 15 | 15 | 15 | IT |
| | Cytarabine | 40 | 40 | - | IT |
| | Dexamethasone | 20 | 20 | - | IT |

[a]Patients with localized stage (non-bulky stages 1-2I) received 4 cycles of treatment (A, B, C and A for younger adults and A, B, A and B for older patients). [b]Folinic acid rescue from 12 hours after the end of infusion. [c]Omitted for patients >55 years (yrs) old. IV: intravenous; IT: intrathecal; hrs: hours; min: minutes; CNS: central nervous system.

were resistance (n=2), death by toxicity (n=13), withdrawal for toxicity (n=5) and relapse or progression during therapy (n=8, 4 patients each). Sixty-three of 69 patients who completed the therapy remain alive in CMR. The main events in patients off therapy were relapse (n=4) and non-relapse mortality (n=2, neuroblastoma and infection, 1 patient each). With a median follow-up of 3.61 (range, 0.1-7.42) yrs the 4-year disease-free survival was 86% (95% confidence interval [CI]: 76-92) and the 4-year OS was 73% (95% CI: 63-81) (Figure 2A, B). No differences in OS were observed in patients who attained CMR (n=69) *versus* those in PMR (n=17) after two cycles of therapy (4-year OS: 87% [95% CI: 76-93] *vs*. 88% [95% CI: 59-97]). The death rate by toxicity was significantly higher in patients with advanced age (3/68 patients ≤55 yrs *vs*. 11/39 patients >55 yrs; *P*<0.001). In patients >55 yrs, death by toxicity was most frequent in the early phase of the therapy (pre-phase and cycle A, 8/11 deaths). The overall causes of death (n=28) were relapse/resistance (n=7 and n=5, respectively), infection (n=13), tumor lysis syndrome (n=1), hemorrhage (n=1) and second cancer (n=1). Both the toxic deaths in general and the deaths by infection were significantly higher in older *versus* younger patients (4/68 *vs*. 11/38; *P*=0.001 for toxic deaths and 3/68 *vs*. 10/38; *P*=0.002 for infections). On the contrary, the deaths by disease progression were not significantly different according to age (7/68 *vs*. 5/38; *P*=0.752). The deaths by infections were due to bacteria (*E. coli* n=2, *Enterobacter cloacae* n=3, *Klebsiella pneumoniae* n=1, *Pseudomonas aeruginosa* n=1, *Serratia marcesens* n=1) followed by fungal infections (*Candida* spp n=2, *Aspergillus* spp n=1). There was one death due to syncytial respiratory virus and another by COVID-19 infection. Relapses (n=8) were localized in the CNS (n=4) and in bone marrow combined with lymph nodes (n=3) or CNS (n=1). The median time to CNS relapses was 4 (range, 2-9) months. Age (≤55 yrs *vs*. >55 yrs), stage (localized *vs*. advanced), IPI (low-low intermediate *vs*. intermediate-high) and BL-IPI (low *vs*. intermediate *vs*. high) had prognostic significance in this series (Figure 3A-D). No significant differences in OS were observed in HIV-positive *versus* HIV-negative patients (62% [95% CI: 38-79] *vs*. 76% [95% CI: 65-84], respectively) or in patients with Burkitt leukemia *versus* those with BL in stages 3 and 4 (62% [95%

**Table 2.** Patient characteristics in the series.

| | Whole series N=107 | Patients ≤55 yrs old N=68 | Patients >55 yrs old N=39 | *P* | HIV-infected N=24 | Non-HIV-infected N=83 | *P* |
|---|---|---|---|---|---|---|---|
| Sex: male, N (%) | 82 (77) | 55 (81) | 27 (69) | 0.170 | 20 (83) | 62 (75) | 0.379 |
| Age in yrs, median (min, max) | 51 (18, 80) | - | - | - | 46 (30, 74) | 52 (18, 80) | 0.258 |
| Age in yrs, N (%)<br>≤55<br>>55 | <br>68 (64)<br>39 (36) | <br>-<br>- | <br>-<br>- | <br>-<br>- | <br>17 (71)<br>7 (29) | <br>61 (61)<br>32 (39) | 0.400 |
| Diagnosis, N (%)<br>Burkitt's leukemia<br>Burkitt Lymphoma | <br>38 (35)<br>69 (65) | <br>19 (28)<br>49 (72) | <br>19 (49)<br>20 (51) | 0.031 | <br>5 (21)<br>19 (79) | <br>33 (40)<br>50 (60) | 0.088 |
| Ann Arbor stage, N (%)<br>1-2<br>3-4 | <br>29 (27)<br>78 (73) | <br>21 (31)<br>47 (69) | <br>8 (20)<br>31 (80) | 0.245 | <br>5 (21)<br>19 (79) | <br>24 (29)<br>59 (71) | 0.433 |
| HIV-infected, N (%) | 24 (22) | 17 (25) | 7 (18) | 0.400 | - | - | - |
| ECOG <2, N (%) | 71/105 (68) | 48/66 (73) | 23 (59) | 0.146 | 15 (65) | 56/82 (68) | 0.781 |
| ≥2 extranodal involvements, N (%) | 54 (51) | 34 (50) | 20 (51) | 0.898 | 16 (67) | 38 (46) | 0.072 |
| CNS involvement, N (%) | 19 (18) | 10 (15) | 9 (23) | 0.275 | 5 (21) | 14 (17) | 0.762 |
| Bulky mass (>10 cm), N (%) | 31/102 (30) | 24/65 (37) | 7/37 (19) | 0.057 | 5 (21) | 26/78 (33) | 0.244 |
| High LDH, N (%) | 80/105 (76) | 46/66 (70) | 34 (87) | 0.042 | 19/23 (83) | 61/82 (74) | 0.413 |
| IPI, N (%)<br>Low / Low-intermediate<br>Intermediate / Intermediate-high | <br>44/106 (41)<br>62/106 (59) | <br>35/67 (52)<br>32/67 (48) | <br>9 (23)<br>30 (77) | 0.003 | <br>7 (29)<br>17 (71) | <br>37/82 (45)<br>45/82 (55) | 0.163 |
| BL-IPI, N (%)<br>Low<br>Intermediate<br>High | <br>16/105 (15)<br>31/105 (30)<br>58/105 (55) | <br>16/66 (24)<br>21/66 (32)<br>29/66 (44) | <br>0<br>10 (26)<br>29 (74) | 0.001 | <br>3/23 (13)<br>8/23 (35)<br>12/23 (52) | <br>13/82 (16)<br>23/82 (28)<br>46/82 (56) | 0.811 |

HIV: human immunodeficiency virus; ECOG: Eastern Cooperative Oncology Group; CNS: central nervous system; LDH: lactate dehydrogenase; IPI: International Prognostic Index; min: minimum; max: maximum; BL-IPI: Burkitt Lymphoma International Prognostic Index; yrs: years.

CI: 44-75] *vs*. 72% [95% CI: 57-83], respectively).
Table 3 shows the main grade ≥3 toxic events according to age and stage of BL. Neutropenia and thrombocytopenia were the most frequent events, with a significantly longer duration in patients >55 yrs in advanced stages. Hepatic and renal toxicity were also higher in the latter group of patients.

### Outcomes and toxicity of the BURKIMAB14 *versus* BURKIMAB08 trials in patients aged 18-55 years

*Online Supplementary Table S1* shows the comparison of the main clinical and biologic characteristics of patients included in both protocols. Compared with the BURKIMAB08 trial patients from the BURKIMAB14 trial showed a lower frequency of HIV infection and a higher frequency of patients belonging to the low-risk category. Table 4 compares the main outcomes of these patients. No significant differences were found for any outcome measure. However, there were fewer deaths in CMR in the BURKIMAB14 trial (3/60 [5%] *vs*. 8/74 [11%]). The 4-year OS probabilities in the BURKIMAB 08 and BURKIMAB14 trails were 72% (95% CI: 61-80) and 82% (95% CI: 70-90), respectively (Figure 4). *Online Supplementary Table S2* compares the main toxic events in both trials. The duration of thrombocytopenia as well as the number of grade>2 infections and the deaths by infection were significantly lower in the BURKIMAB14 trial.

## Discussion

This study shows that the results of BURKIMAB14 are similar to those of other dose-intensive immunochemotherapy trials. Age >55 years and advanced stage were associated with poor survival. In contrast, HIV infection did not show different outcome. It is of note that the reduction of chemotherapy in young adults in CMR did not negatively impact outcome and was associated with a reduced frequency and mortality by infections.
Prospective studies on the treatment of BL used at least six different regimens (LMB, GMALL, CALGB, R-CODOX-M/R-IVAC, DA-EPOCH-R, HD-MTX-CHP [BASIC]).[2-15] Treatment schedules using high-dose intensive immunochemotherapy (R-CODOX-M/R-IVAC being the most frequently used) show considerable differences in the drugs and dosages used, age of patients included, HIV infection status, risk definition, days of hospitalization and follow-up. The response rate and the OS probability in the different trials range from 80-90% and 70-95%, respectively. Only one study randomly compared R-CODOX-M/R-IVAC *versus* DA-EPOCH-R in newly diagnosed patients with high-risk BL, and reported a similar CMR (79% *vs*. 73%) and 2-year OS probability (75% *vs*. 76%) but a lower frequency of infections/febrile neutropenia, platelet transfusions, and fewer days of hospitalization were observed in patients treated with

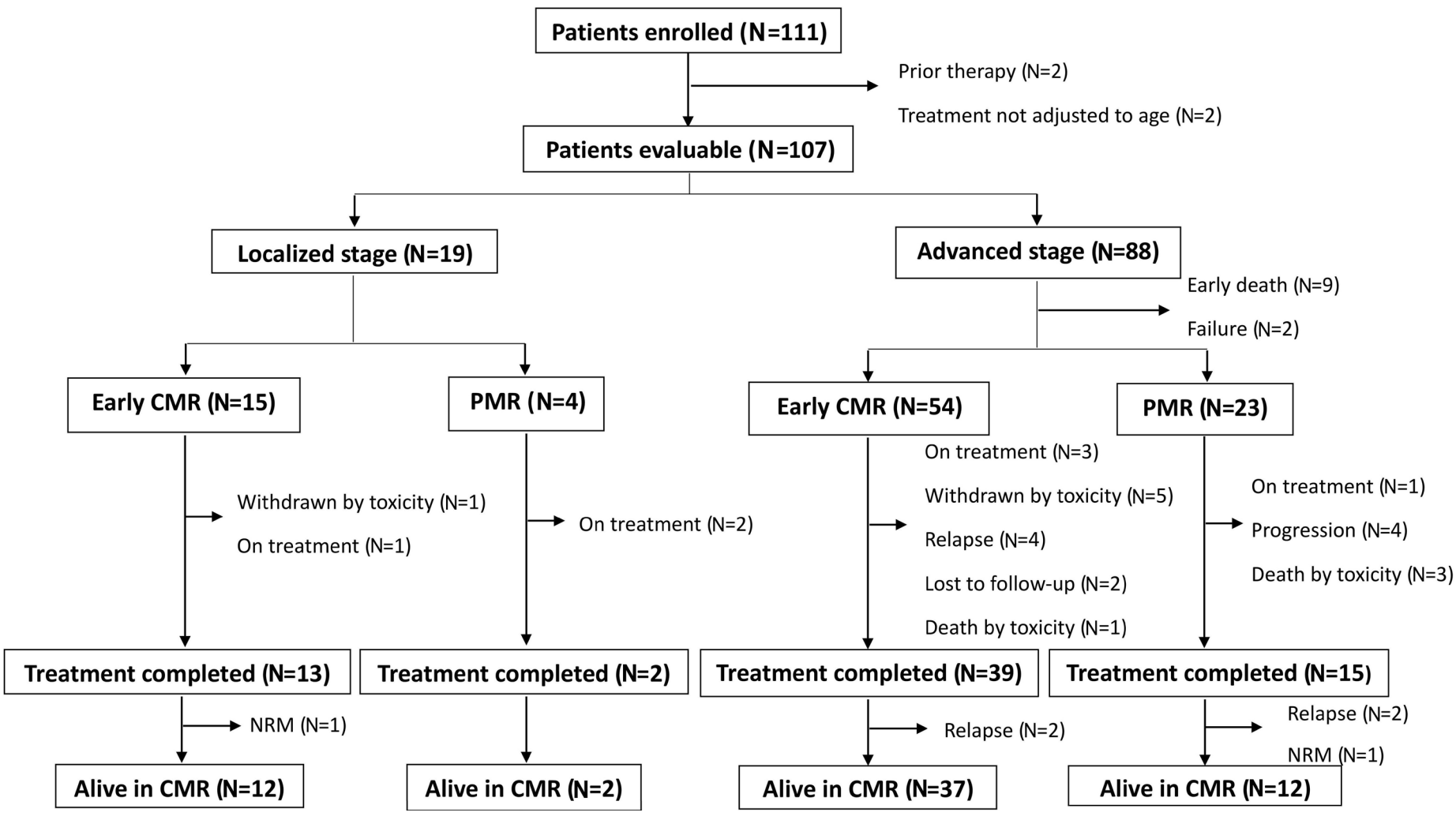


**Figure 1. Flowchart of the study.** This figure summarizes the distribution of patients according to their stage and the metabolic response. Most patients were diagnosed in advanced-stage disease and showed early complete metabolic response (CMR). PMR: partial metabolic remission; NMR: no metabolic response.

DA-EPOCH-R.[21] However, this trial was prematurely closed due to low accrual rate when only 89 out of planned 260 patients were included. On the other hand, a retrospective study of 641 adult patients treated in 30 centers from US showed a non-significant advantage of the CODOX-M/R-IVAC regimen over DA-EPOCH-R or hyperCVAD/MA regimens in terms of progression-free survival and OS.[16] The BURKIMAB14 trial showed CMR rates of 80% and a 4-year OS probability of 73%. Early *versus* late attainment of CMR did not impact the OS. The OS probability was influenced by age and stage but not by HIV infection status. Despite a significant dose reduction for patients >55 yrs old, a high mortality rate was observed, being concentrated in the pre-phase and the first cycle of chemotherapy. This could be explained by the poorer BL characteristics in patients >55 yrs old and by the lack of delay between the pre-phase and the first block of chemotherapy, a feature inducing an accumulation of toxicity. Dose reduction of drugs included in the first block A for older patients (e.g., eliminating iphosphamide [as cyclophosphamide has been given in the prephase] and also eliminating the doses of cytarabine and etoposide) could reduce the death rate, mainly due to infections in the neutropenic period, and simplify the implementation of the trial.

The BURKIMAB14 trial aimed to evaluate the efficacy and tolerability of dose reduction of chemotherapy in young patients in CMR, in order to reduce toxicity and mortality compared with those of the BURKIMAB08 trial without hampering the efficacy. In the BURKIMAB14 trial, the mortality of CMR patients (5% *vs*. 11%), the frequency of grade >2 infections and the duration of thrombocytopenia were reduced, and the OS showed a non-significant increase (82% *vs*. 72%). This difference could be explained by the reduction of mortality as well as by better disease characteristics of young patients in the BURKIMAB14 trial. These differences in patients' inclusion in both trials could be due in part by chance and in part by unknown biases from physicians after having acquired experience with the BURKIMAB08 trial. Overall, these data suggest that a dose reduction is feasible and safe for young BL patients after CMR achievement. CNS relapse is a matter of concern in this and other BL trials, although was not apparently related with the reduction of chemotherapy in older patients from our trial. The possible inclusion of cranial irradiation could increase the toxicity and could influence the timely delivery of the chemotherapy. Better efforts are needed to provide adequate protection of this sanctuary, as alternative approached such as DA-EPOCH-R do not protect adequately from CNS relapse.

This study has some limitations; first, the selection of the chemotherapy according only to stage and age, without considering other risk factors such as lactate dehydrogenase levels, CNS involvement or performance status, which are variables included in BL-IPI; second, the lack of centralized review of the PET-CT scans. The value of complete metabolic response by PET-TC imaging in Burkitt lymphoma not involving the bone marrow is uncertain. However, this is currently the only available tool for response evaluation. Data on the value of circulating tumor DNA could represent a promising tool for residual disease assessment but solid data are not available for BL; third, the lack of review of pathologic samples, although stringent criteria for BL

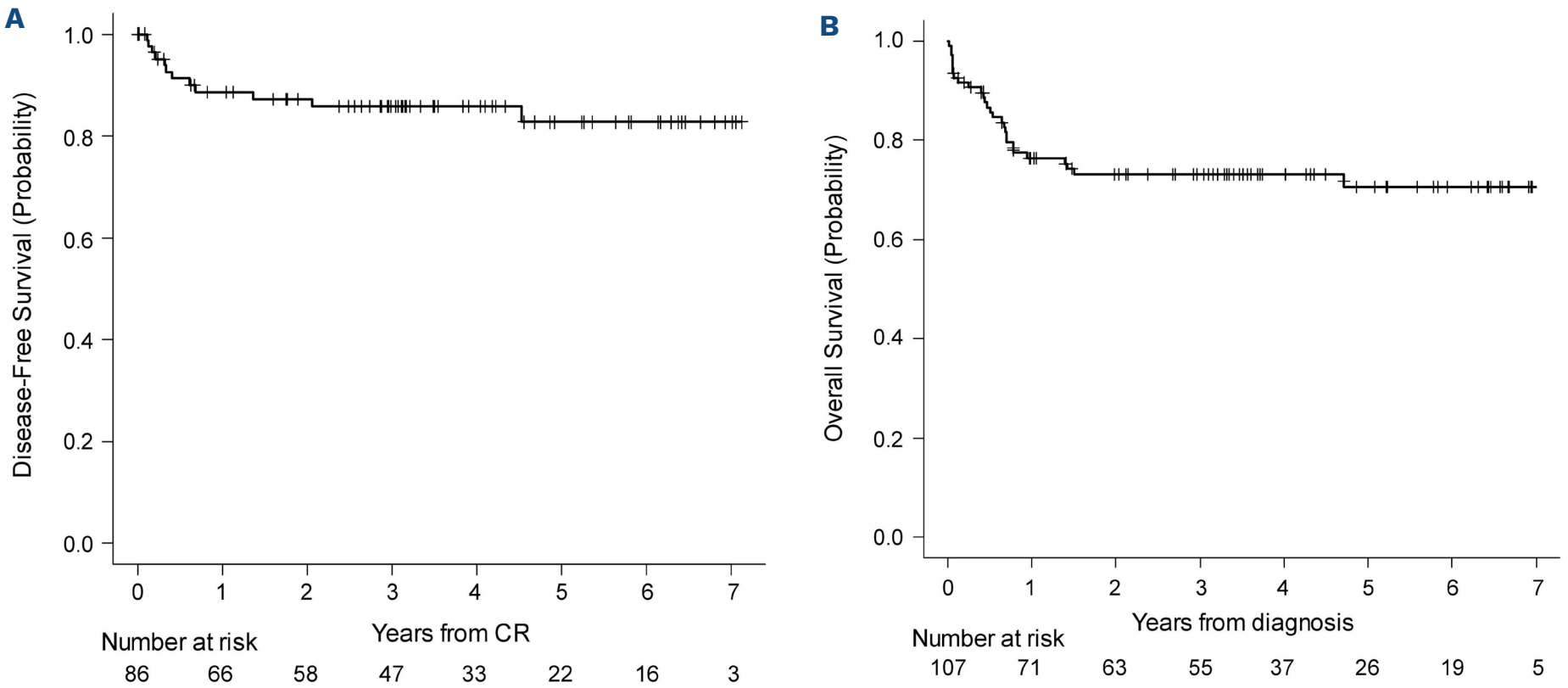


**Figure 2. Disease-free survival and overall survival in the whole series.** Panel (A) shows the disease-free survival of 86 patients in complete response (CR), the probability of disease-free survival at 4 years was 86% (95% confidence interval [CI]: 76-92). Panel (B) shows the overall survival of 107 patients, the probability of overall survival at 4 years was 73% (95% CI: 63-81).

diagnosis were used in this trial. Additional limitations include the lack of sample size calculation (the comparison was established when similar number of patients were recruited in BURKIMAB 08 and BURKIMAB14 trials) and the lack of multivariable analysis of prognostic factors, as we validated the well-established BL-IPI as a prognostic index for BL in our series.

The immunochemotherapy results of BL should be improved

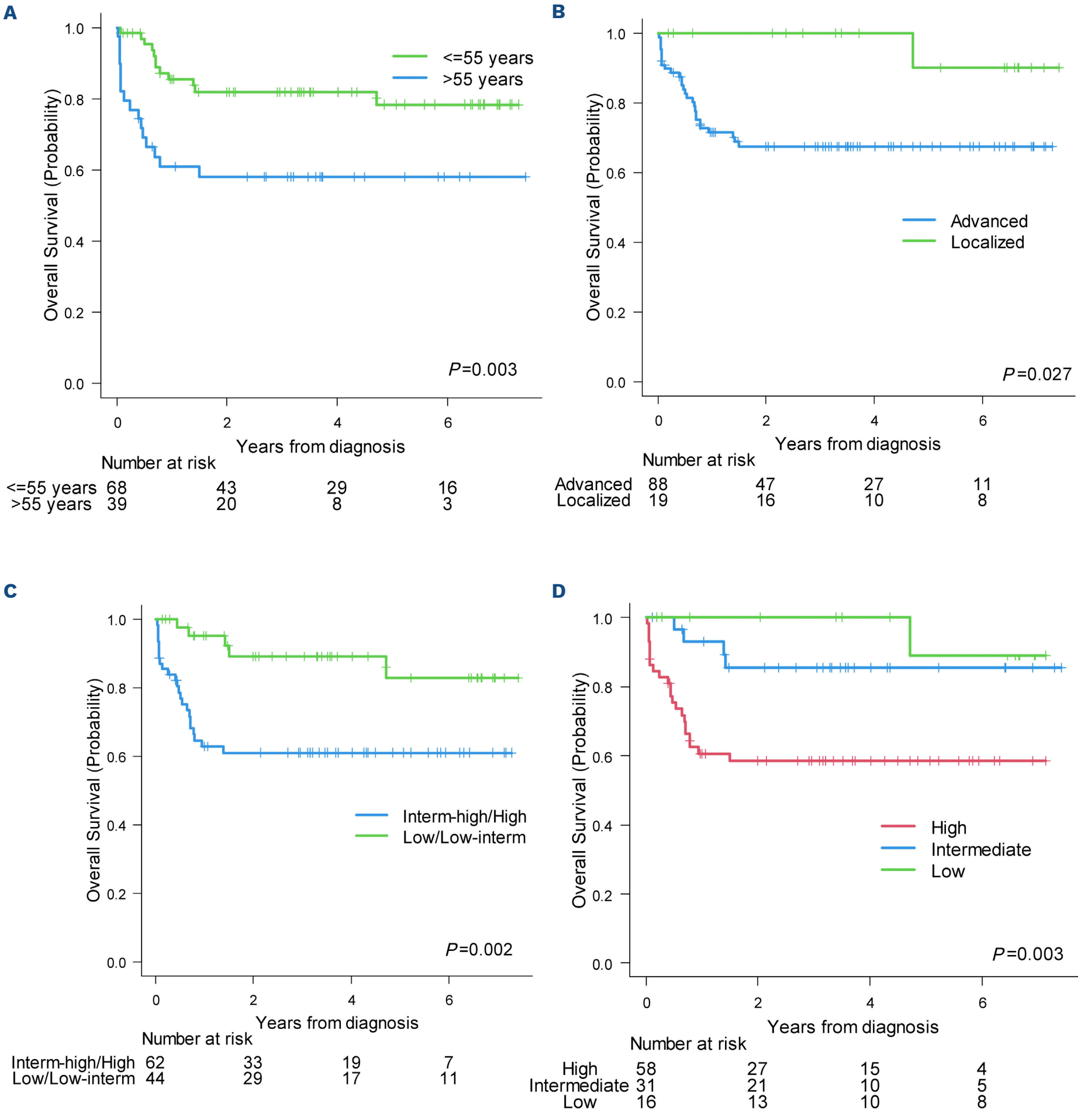


**Figure 3. Overall survival according to age, stage, International Prognostic Index and the Burkitt lymphoma International Prognostic Index.** Panel (A) shows a significantly poorer survival of patients aged >55 years. Panel (B) shows the prognostic influence of stage at diagnosis, with poorer survival of patients in advanced stages. Panel (C) shows the prognostic significance of the International Prognostic Index (IPI) with poorer outcome of patients with intermediate-high and high IPI score. Panel (D) shows the reproducibility of the three groups of the Burkitt lymphoma IPI in this series of patients. interm: intermediate.

in older patients and in those who relapse. In our series, patients >55 years old showed a significantly higher frequency of Burkitt leukemia and a higher frequency of poor IPI and BL-IPI risk groups. These features, together with the high mortality rate, explain their poor prognosis. DA-EPOCH-R is best tolerated in patients with advanced age and should probably be the treatment of choice.[1] The frequent CNS relapse also points out the need for improvement of CNS prophylaxis.[22] To date, no rescue chemotherapies have demonstrated efficacy, and allogeneic or autologous stem cell transplantation do not seem to be effective, with a survival rate less than 20%. Patients with relapsed or refractory disease should be included in clinical trials. Therapies based on the improved knowledge of the genetic background of BL[23] including those targeting the PI3Kδ, AKT, mTOR complex 1 (mTORC1) or CDK6 inhibitors, among others, are currently being evaluated. Immunotherapeutic approaches such as bispecific anti CD20-CD3 monoclonal antibodies or chimeric antigen receptor T-cell therapy[24,25] are also under investigation.

## Disclosures

*JMR receives consultancy fees, research funding and speaker's bureau fees from Pfizer and Amgen; receives consultancy and speakers bureau fees from Ariad and Novartis. PA receives honoraria from Janssen, Celgene, AbbVie, AstraZeneca, Gilead*

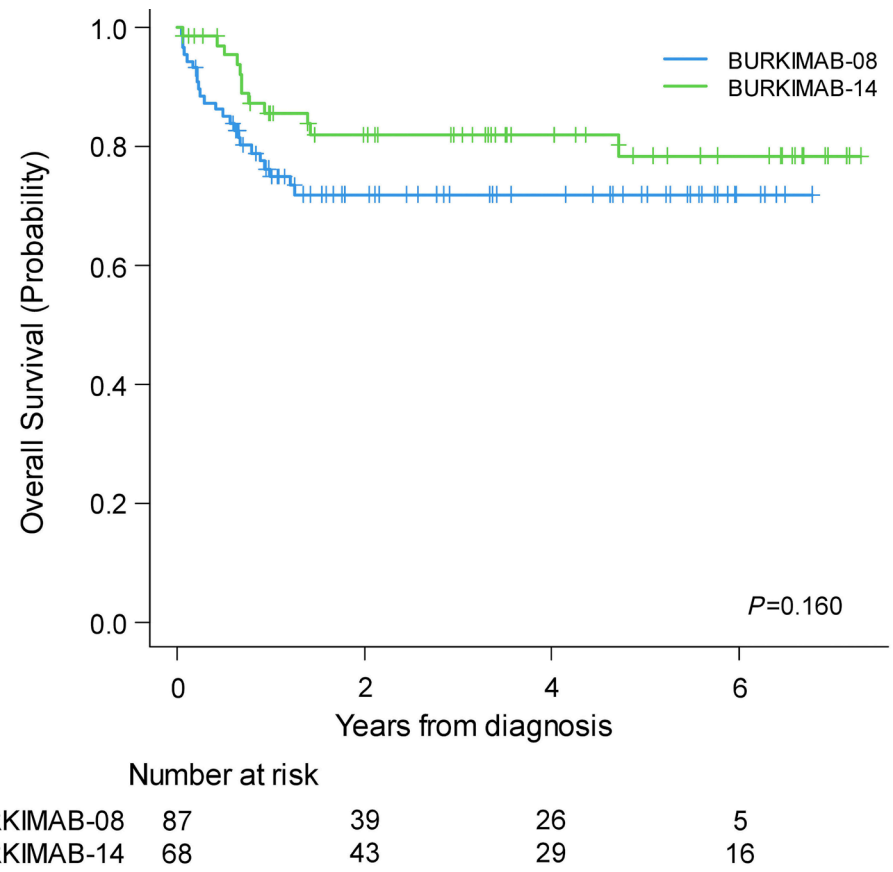


**Figure 4. Overall survival of patients aged 18-55 years in the BURKIMAB14 and BURKIMAB08 trials.** In the BURKIMAB14 trial the 4-year overall survival probability was 82% (95% confidence interval [CI]: 70-90) *versus* 72% (95% CI: 61-80) for patients included in the BURKIMAB08 trial.

**Table 3.** Grade >2 toxicity according to age and stage in patients from the BURKIMAB14 trial.

| | Patients ≤55 yrs old | | Patients >55 yrs old | |
|---|---|---|---|---|
| | Localized stage N=12 | Advanced stage N=56 | Localized stage N=7 | Advanced stage N=32 |
| Neutropenia, N/N (%)<br>Median days (min, max) | 11/12 (92)<br>4 (2, 7) | 53/54 (98)<br>7 (1, 21)[1] | 6/7 (86)<br>7 (3, 13) | 30/31 (97)<br>10.5 (2, 24)[1] |
| Thrombocytopenia, N/N (%)<br>Median days (min, max) | 7/12 (58)<br>2 (1, 5) | 41/54 (76)<br>3 (1, 31)[2] | 4/7 (57)<br>4 (2, 16) | 25/31 (81)<br>11 (1, 28)[2] |
| Hepatic toxicity, N (%) | 1 (8) | 4 (7)[3] | 0 | 6 (19)[3] |
| Renal toxicity, N (%) | 0 | 3 (5)[4] | 0 | 9 (28)[4] |
| Mucositis, N (%) | 4 (33) | 25 (45) | 4 (57) | 19 (59) |
| Neurologic toxicity, N (%) | 0 | 2 (4) | 1 (14) | 2 (6) |
| Infections, N (%) | 3 (25) | 42 (75) | 3 (43) | 28 (88) |
| Death by infection, N (%) | 0 | 2 (4)[5] | 0 | 10 (31)[5] |

[1]*P*=0.227; [2]*P*=0.004; [3]*P*=0.160; [4]*P*=0.007; [5]*P*=0.001. yrs: years; min: minimum; max: maximum.

**Table 4.** Main outcomes of patients from the BURKIMAB08 and BURKIMAB14 trials in patients aged 18-55 years.

| | BURKIMAB08 N=87 | BURKIMAB14 N=68 | *P* |
|---|---|---|---|
| Early death, N (%) | 6 (7) | 1 (2) | 0.136 |
| Failure, N (%) | 6 (7) | 4 (6) | 1.000 |
| CMR, N (%) | 74 (85) | 60 (88) | 0.566 |
| Relapse, N/N (%) | 5/74 (7) | 5/60 (8) | 0.752 |
| Death in CMR, N/N (%) | 8/74 (11) | 3/60 (5) | 0.344 |
| 4-year OS, % (95% CI) | 72 (61-80) | 82 (70-90) | 0.160 |
| 4-year DFS, % (95% CI) | 83 (73-90) | 87 (74-93) | 0.495 |

The final response was not evaluated (due to withdrawal without response assessment or partial response on treatment or death in partial response) in 1 and 3 patients in the BURKIMAB08 and BURKIMAB14 trials, respectively. CMR: complete metabolic response; OS: overall survival; DFS: disease-free survival; CI: confidence interval.

*and Incyte; has a consulting/advisory role at Janssen, Celgene, AbbVie, AstraZeneca; is part of the speakers' bureau of Janssen, Celgene, AbbVie, AstraZeneca and Gilead. MB receives research funding from Roche and Kite/Gilead; receives honoraria from Roche, Kite/Gilead, Novartis, Janssen, Incyte and BMS/Celgene; is on the advisory board of Roche, Kite/Gilead, Novartis, Janssen, Incyte and BMS/Celgene. MJT has as consultancy (advisory) at Roche, Gilead, Janssen, Takeda, Abbvie and Lilly; discloses educational activities for Roche, Gilead, Janssen, Takeda, Abbvie and Lilly. EG serves as consultant and/or on the speaker's bureau for/of AbbVie, Janssen-Cilag and AstraZeneca; has received travel grants from AbbVie, Janssen-Cilag and AstraZeneca. SM receives research funding from Roche and honoraria from Roche, Gilead, Janssen and Servier. JMS receives honoraria for a consultancy or advisory role from Roche, Janssen, Gilead-Kite, Novartis, Celgene-BMS, Incyte, Beigene, Miltenyi Biomedicine, Celltrion and Kern-Pharma; receives honoraria as a speaker in educational events from Roche, Janssen, Gilead-Kite, Novartis, Celgene-BMS, Incyte, Takeda and Kern-Pharma. The remaining authors have no conflicts of interest to disclose.*

**Contributions**

*JMR and JMS designed the trial and contributed to the analysis. JMR wrote the paper. MM and OGC collected the data, created the database and performed the statistical analysis. MS, BB, MC, HL, JMHR, MS, IGC, PA, PM, MB, MPQL, PB, AT, PH, AGG, FVLJS, MJT, JMB, AGN, CB, LL, DGB, EG, AC and SM qualify for authorship according to the WAME criteria, and were involved in patient inclusion, data collection and data acquisition. All authors approved the final version of the manuscript.*

**Funding**

*The research was supported in part by the grant 2021 SGR 00771, AGAUR, Generalitat de Catalunya, Spain.*

**Data-sharing statement**

*For original data, please contact the corresponding author or mmorgades@iconcologia.net. De-identified individual participant data are available indefinitely at www.pethema.org. The study protocol is also available at the same website.*

# References

1. Roschewski M, Staudt LM, Wilson WH. Burkitt's lymphoma. N Engl J Med. 2022;387(12):1111-1122.
2. Ribrag V, Koscielny S, Bosq J, et al. Rituximab and dose-dense chemotherapy for adults with Burkitt's lymphoma: a randomised, controlled, open-label, phase 3 trial. Lancet. 2016;387(10036):2402-2411.
3. Mead GM, Barrans SL, Qian W, et al. A prospective clinicopathologic study of dose-modified CODOX-M/IVAC in patients with sporadic Burkitt lymphoma defined using cytogenetic and immunophenotypic criteria (MRC/NCRI LY10 trial). Blood. 2008;112(6):2248-2260.
4. Corazzelli G, Frigeri F, Russo F, et al. RD-CODOX-M/IVAC with rituximab and intrathecal liposomal cytarabine in adult Burkitt lymphoma and 'unclassifiable' highly aggressive B-cell lymphoma. Br J Haematol. 2012;156(2):234-244.
5. Evens AM, Carson KR, Kolesar J, et al. A multicenter phase II study incorporating high-dose rituximab and liposomal doxorubicin into the CODOX-M/IVAC regimen for untreated Burkitt's lymphoma. Ann Oncol. 2013; 24(12):3076-3081.
6. Noy A, Lee JY, Cesarman E, et al. AMC 048: modified CODOX-M/IVAC-rituximab is safe and effective for HIV-associated Burkitt lymphoma. Blood. 2015;126(2):160-166.
7. Intermesoli T, Rambaldi A, Rossi G, et al. High cure rates in Burkitt lymphoma and leukemia: a Northern Italy Leukemia Group study of the German short intensive rituximab-chemotherapy program. Haematologica. 2013;98(11):1718-1725.

8. Ribera JM, García O, Grande C, et al. Dose-intensive chemotherapy including rituximab in Burkitt's leukemia or lymphoma regardless of human immunodeficiency virus infection status: final results of a phase 2 study (Burkimab). Cancer. 2013;119(9):1660-1668.
9. Hoelzer D, Walewski J, Döhner H, et al. Improved outcome of adult Burkitt lymphoma/leukemia with rituximab and chemotherapy: report of a large prospective multicenter trial. Blood. 2014;124(26):3870-3879.
10. Rizzieri DA, Johnson JL, Byrd JC, et al. Improved efficacy using rituximab and brief duration, high intensity chemotherapy with filgrastim support for Burkitt or aggressive lymphomas: cancer and Leukemia Group B study 10002. Br J Haematol. 2014;165(1):102-111.
11. Kasamon YL, Brodsky RA, Borowitz MJ, et al. Brief intensive therapy for older adults with newly diagnosed Burkitt or atypical Burkitt lymphoma/leukemia. Leuk Lymphoma. 2013;54(3):483-490.
12. Kujawski LA, Longo WL, Williams EC, et al. A 5-drug regimen maximizing the dose of cyclophosphamide is effective therapy for adult Burkitt or Burkitt-like lymphomas. Cancer Invest. 2007;25(2):87-93.
13. Ferreri AJM, Angelillo P, Erbella F, et al. Safety and efficacy of a dose-dense short-term therapy in patients with MYC-translocated aggressive lymphoma. Blood Adv. 2022;6(22):5811-5820.
14. Dunleavy K, Pittaluga S, Shovlin M, et al. Low-intensity therapy in adults with Burkitt's lymphoma. N Engl J Med. 2013;369(20):1915-1925.
15. Roschewski M, Dunleavy K, Abramson JS, et al. Multicenter study of risk-adapted therapy with dose-adjusted EPOCH-R in adults with untreated Burkitt lymphoma. J Clin Oncol. 2020;38(22):2519-2529.
16. Evens AM, Danilov A, Jagadeesh D, et al. Burkitt lymphoma in the modern era: real-world outcomes and prognostication across 30 US cancer centers. Blood. 2021;137(3):374-386.
17. Crombie J, LaCasce A. The treatment of Burkitt lymphoma in adults. Blood. 2021;137(6):743-750.
18. Woessmann W, Zimmermann M, Meinhardt A, et al. Progressive or relapsed Burkitt lymphoma or leukemia in children and adolescents after BFM-type first-line therapy. Blood. 2020;135(14):1124-1132.
19. Cremer M, Schwarzbich MA, Schöning T, Lisenko K, Ho AD, Witzens-Harig M. In Burkitt lymphoma patients who relapse after induction with a short-intensive chemoimmunotherapy protocol, aggressive salvage chemotherapy therapy is ineffective: a single-center retrospective study. Ann Hematol. 2017;96(9):1573-1575.
20. Olszewski AJ, Jakobsen LH, Collins GP, et al. Burkitt Lymphoma International Prognostic Index. J Clin Oncol. 2021;39(10):1129-1138.
21. Chamuleau M, Stenner F, Chityu D, et al. R-CODOX-M/R-IVAC versus dose-adjusted (DA)-EPOCH-R in patients with newly diagnosed high-risk Burkitt lymphoma: first results of a multi-center randomized HOVON/SAKK trial. Hemasphere. 2022;6:S3:LB2370.
22. Zayac AS, Evens AM, Danilov A, et al. Outcomes of Burkitt lymphoma with central nervous system involvement: evidence from a large multicenter cohort study. Haematologica. 2021;106(7):1932-1942.
23. Thomas N, Dreval K, Gerhard DS, et al. Genetic subgroups inform on pathobiology in adult and pediatric Burkitt lymphoma. Blood. 2023;141(8):904-916.
24. Liu Y, Deng B, Hu B, et al. Sequential different B-cell antigen-targeted CAR T-cell therapy for pediatric refractory/relapsed Burkitt lymphoma. Blood Adv. 2022;6(3):717-730.
25. Zhang W, Yang J, Zhou C, et al. Early response observed in pediatric patients with relapsed/refractory Burkitt lymphoma treated with chimeric antigen receptor T cells. Blood. 2020;135(26):2425-2427.