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Two decades of single-institution data reveal rare long-term survivors of relapsed/refractory Burkitt lymphoma

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Two decades of single-institution data reveal rare long-term survivors of relapsed/refractory Burkitt lymphoma

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Data Sharing Statement:
The data that support the findings of this study are not publicly available due to institutional and patient privacy restrictions but may be shared by the corresponding author upon reasonable request.

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Burkitt lymphoma (BL) is a highly aggressive B-cell non-Hodgkin lymphoma, characterized by rapid disease progression driven by a high tumor proliferation rate (1). While intensive frontline chemoimmunotherapy has achieved 3-year overall survival (OS) rate of over 80%, a subset of patients experience refractory or relapsed (R/R) disease associated with a poor prognosis (2, 3). Patients with the highest risk of relapse include those with central nervous system (CNS), marrow or peripheral blood BL, age ≥ 40, ECOG ≥ 2, and LDH > 3× ULN as equally weighted independent factors (4, 5). Response rates to salvage therapies vary between 30%-50%, with long-term survival rates below 20% and often approaching zero. Specifically three studies reported long-term survival in 2 of 35 patients (6), 0 of 9 (7), and 0 of 10 (8), although one study noted 11/74 survivors (9).

To evaluate our own experience and ascertain clues for long-term survival, we conducted a retrospective review of Memorial Sloan Kettering Cancer Center patients with R/R BL using a database search from January 1, 1988, to December 21, 2021. This study was approved by the Institutional Review Board at Memorial Sloan Kettering Cancer Center and was conducted in accordance with the Declaration of Helsinki. We identified 276 patients with BL of whom 28 (10 %) received second line therapy for relapsed (n=8) or refractory (n=20) disease. Early and late relapse were defined as relapse <6 months and ≥6 months from the time of first remission, respectively. Overall response rate (ORR) was defined as the composite of complete remission (CR) and partial remission (PR). Relapse-free survival (RFS), and OS were calculated. RFS was defined as time from first remission or start of first-line treatment until relapse. OS was defined as time from first treatment failure or first relapse until death from any cause. Patients alive were censored at their last follow-up.

Characteristics of the evaluable population are shown in Supplemental Table 1. The median age was 37 years (21-69 years). High-risk baseline features include stage IV disease (75%), leptomeningeal disease (LMD) (29%), bone marrow disease (25%). Six patients had HIV with 3 taking antiretroviral therapy at BL diagnosis. Six patients had EBV-positive disease, defined by EBER in situ hybridization positivity on tumor specimens; twelve were EBER-negative, and ten had unknown EBV status. The vast majority received 'intensive' first line therapies, e.g., CODOX/IVAC (cyclophosphamide, vincristine, doxorubicin, and high-dose methotrexate alternating with ifosfamide, etoposide, and cytarabine), DA-EPOCH (dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin), and HyperCVAD (fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine); including 20 combined with received rituximab (R) not available in the first part of the study timeframe. Responses to first-line therapy included CR (29%), PR (36%), and progression of disease (POD) (36%). CR rates may reflect CT-defined response prior to the availability of PET. Among the 8 patients with CR, the median time to relapse was 6 months (95% CI, 5 – 14). Second line regimens included R-EPOCH (n=4), R+/- IVAC (n=6), R+/-ICE (ifosfamide, carboplatin, and etoposide) (n=4), high-dose MTX (methotrexate) +/-cytarabine (n=6), other (n=8). A patient flow diagram shows treatment overview (Figure 1). After second line therapy, CR was 0%, partial response 25% and POD 75%. The median OS for the entire cohort (measured from time of treatment failure or first relapse) was 4 months (95% CI 3 – 8), with a 6-month OS rate of 43% (95% CI 28 – 66) and 1-year OS rate of 11% (95% CI 4 – 31) (Figure 2). Four patients achieved CR after additional lines of salvage chemotherapy regimens and 1 after radiation. All five patients had previously received first-line intensive treatment (R-CODOX-M/IVAC, R-EPOCH, R-HyperCVAD) along with CNS directed treatment (intrathecal (IT)/high-dose MTX +/-cytarabine). Two patients received allogeneic stem cell transplant (SCT); however, 1 died due to complications within a week of transplant and 1 had POD 5 months after SCT. The three remaining patients were long-term survivors, and all received consolidative autologous SCT after relapse. They were all male, one had EBV+ BL, and they were the only patients to proceed to autologous SCT. At initial

diagnosis, one had stage I and two had stage IV disease with bone marrow and leptomeningeal disease (LMD). Their unique treatment trajectories are described below.

The first patient had HIV with a normal CD4 count, undetectable HIV viral load, and stage I BL with a 10 cm axillary mass. He received 3 cycles of R-Hyper-CVAD (including 3 doses of IT MTX and 3 doses of HD-MTX) with biopsy proven PR, R-ICE for 1 cycle (and 3 additional doses of IT MTX) with no response, 30 Gy radiation with pathologic CR followed by consolidative autologous SCT. Patient remains in remission 12 years later.

The second patient had radiographic testicular involvement and LMD at diagnosis and was treated with CODOX-M/IVAC-R (including 4 doses of IT MTX+ ARA-C and 2 doses of HD-MTX) followed by orchiectomy without evidence of lymphoma. Five months post therapy a liver biopsy showed only necrotic cells, and a lung nodule showed BL with no other sites of disease. Salvage therapies over 4 months consisted of gemcitabine-oxaliplatin (1 cycle) without response; R-EPOCH x 2 cycles with initial POD, but while undergoing transplant evaluation, repeat imaging revealed response, followed by R-EPOCH x2 with further response, and radiation (30 cGy hyper fractionated IFRT to residual hilar LN), leading to CR, followed by consolidative autologous SCT. Patient developed secondary AML 31 months later, underwent a 10/10 MUD transplant and remains without evidence of disease for more than 10 years.

The third surviving patient completed 5 cycles of front-line DA-EPOCH-R achieving control of stage IV disease except for progression in a single right level 2 cervical lymph node that was surgically resected showing lymphoma. For LMD at diagnosis, he received MTX/ARA-C via Ommaya twice weekly for 4 weeks with clearance, followed by maintenance weekly for 6 weeks and then monthly treatment (13 doses). After the cervical lymph node resection, he had 2 adjuvant cycles of HyperCVAD part B with MTX and high-dose cytarabine followed by followed by consolidative autologous SCT and had no evidence of disease for almost 10 years.

The ORR to all salvage chemotherapies in our series was 14% (CR, n=4; PR, N=0). Both early and late relapse patients had a median OS of 4 months. Despite advances in the molecular understanding of BL, no targeted therapies have emerged in the salvage setting. Unfortunately, chimeric antigen T-cell receptor therapies have been largely unsuccessful in adults with Burkitt lymphoma, with a retrospective analysis of 31 patients reporting an ORR of nearly 60% at one month, but a median PFS of only 2.3 months and just one survivor at 20 months. All three patients bridged to allogeneic BMT experienced a relapse. Consequently, better front-line therapies for those with high-risk features will likely reduce the risk of R/R disease. In contrast in pediatrics, a sequential CAR-T approach in 23 patients targeting CD19, CD22 and CD20 if CR was not achieved resulted in an estimated 18-month 78% PFS and CR rate including 78% in patients with bulky disease and 60% in patients with central nervous system (CNS) involvement.(11) Notably 9 patients received only a CD-19 directed CAR-T; 13 an anti-CD22; and 6 an anti-CD20. These remain investigational therapies and their broader applicability particularly in adults remains uncertain.

Regarding clinical trial participation, a total of 3 patients in our cohort were enrolled in clinical trials at some point during their therapy. One patient was enrolled in a first-line study evaluating R-CODOX-M/IVAC incorporating CNS penetration strategies and intensive intrathecal prophylaxis specifically for HIV-associated BL. (AMC 048) (12) No patients were enrolled in trials during second-line therapy (1st salvage). One patient in the third-line (2nd salvage) participated in a phase I trial with an anti-CD47 monoclonal antibody. The third patient participated in phase I studies in the fourth and fifth lines of therapy, including trials of SGN-CD19A (denintuzumab mafodotin, an ADC) followed by fimepinostat (a

PI3K/HDAC inhibitor) plus venetoclax. Challenges to trial enrollment in this population included the rarity and aggressive nature of R/R BL, limited trial options, as well as patients' rapidly deteriorating performance status. These barriers highlight the need for early-phase trial designs that accommodate patients with R/R BL, particularly those with high-risk features or rapidly progressive disease.

Importantly, this study was conducted prior to the implementation of comprehensive molecular profiling (such as the MSK-IMPACT testing, which screens for approximately 400 clinically relevant gene mutations) at our center. As a result, we unfortunately do not have detailed molecular data for these patients. In conclusion, we identified 28 patients over two decades with R/R BL of whom only three were long-term survivors. Our results are in keeping with other prior single-institution reports. Notably, two patients had LMD at first diagnosis and all three had very limited systemic disease at relapse, possibly all stage I. All three surviving patients underwent autologous SCT in second complete remission and remained BL free for 10 years. Overall, long-term survival is possible for only a minority with R/R BL, reinforcing the need for improved therapeutic strategies.

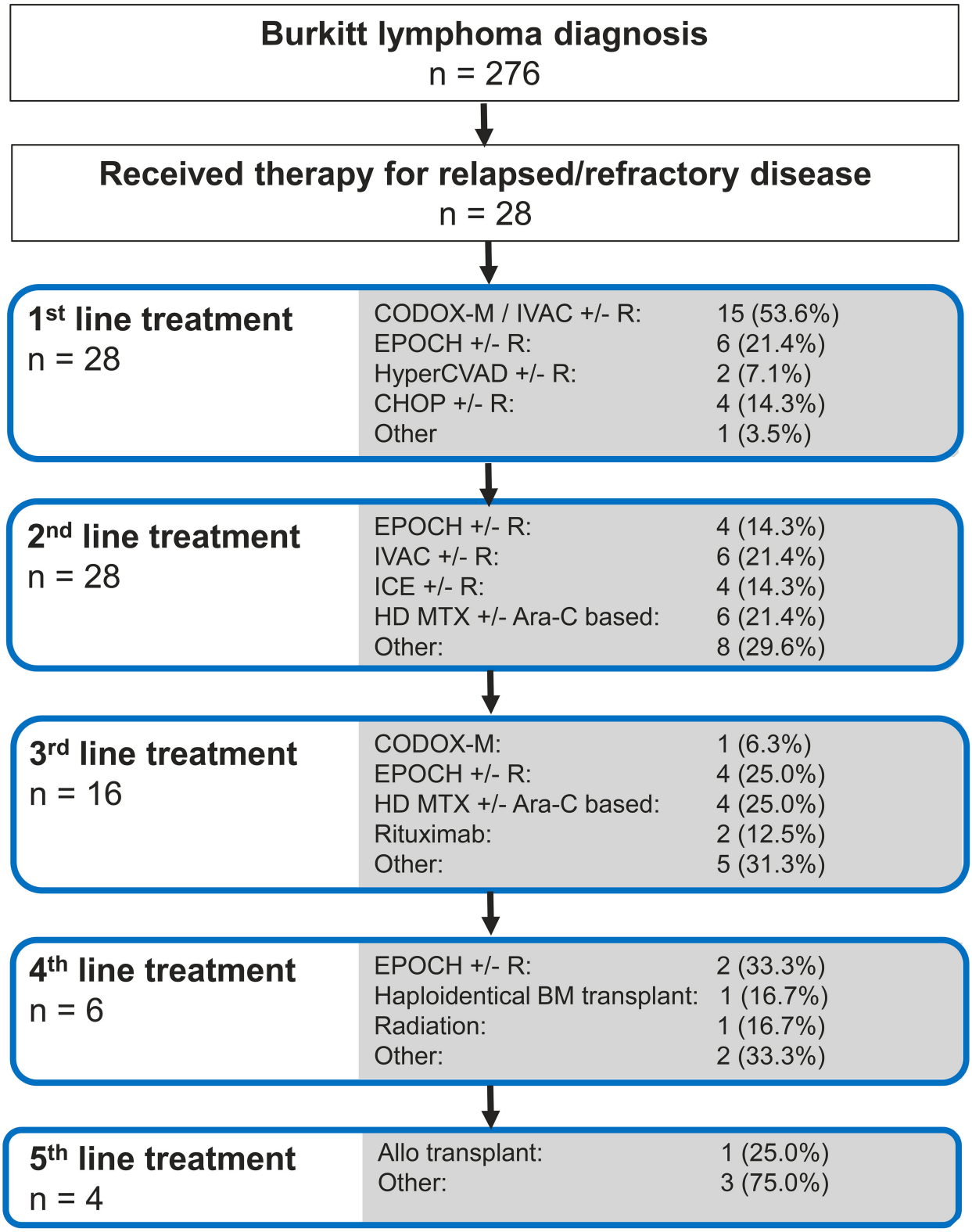
References:

1. Ferry JA. Burkitt's lymphoma: clinicopathologic features and differential diagnosis. Oncologist. 2006;11(4):375-383.
2. Thomas DA, Faderl S, O'Brien S, et al. Chemoimmunotherapy with hyper-CVAD plus rituximab for the treatment of adult Burkitt and Burkitt-type lymphoma or acute lymphoblastic leukemia. Cancer. 2006;106(7):1569-1580.
3. 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.
4. 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.
5. Olszewski AJ, Jakobsen LH, Collins GP, et al. Burkitt Lymphoma International Prognostic Index. J Clin Oncol. 2021;39(10):1129-1138.
6. Short NJ, Kantarjian HM, Ko H, et al. Outcomes of adults with relapsed or refractory Burkitt and high-grade B-cell leukemia/lymphoma. Am J Hematol. 2017;92(6):E114-E116.
7. Cremer M, Schwarzbich MA, Schoning T, et al. In Burkitt lymphoma patients who relapse after induction with a short-intensive chemoimmunotherapy protocol, aggressive salvage chemotherapy is ineffective: a single-center retrospective study. Ann Hematol. 2017;96(9):1573-1575.
8. Gamero SF, Lin Y, Kenderian SS, et al. Characteristics of patients with relapsed/refractory Burkitt non-Hodgkin lymphoma: impact on the feasibility of CAR-T cell therapy. Blood. 2019;134(Supplement_1):5352.
9. Manji F, Chow E, Gerrie AS, et al. Outcomes in relapsed/refractory Burkitt lymphoma: a multi-centre Canadian experience. Blood. 2021;138(Supplement_1):2525.
10. Samples L, Sadrzadeh H, Frigault MJ, et al. Outcomes among adult recipients of CAR T-cell therapy for Burkitt lymphoma. Blood. 2025;145(23):2762-2767.
11. 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.
12. 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.

Figure Legends:

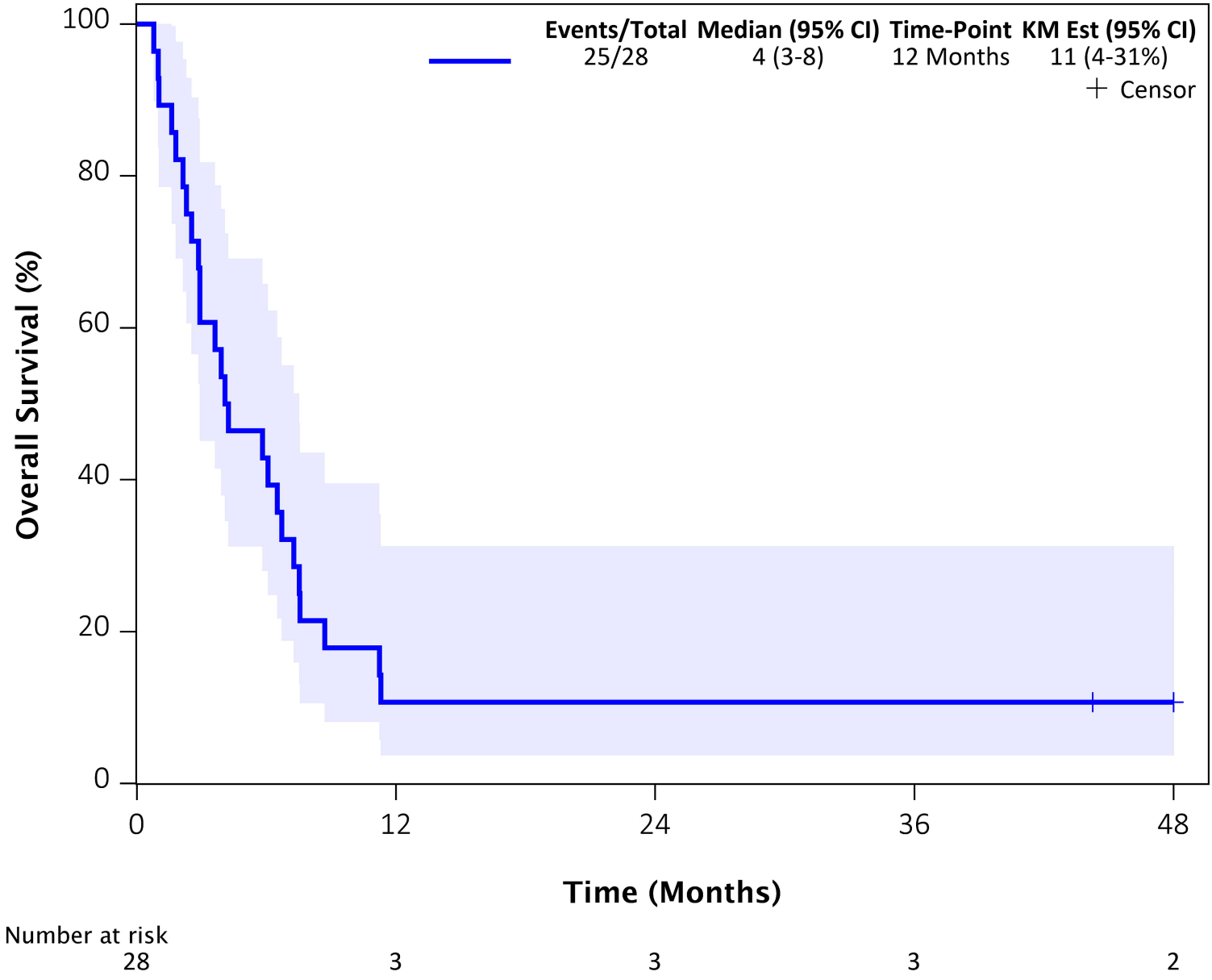
Figure 1: Patient flow diagram showing treatment overview

Figure 2: Overall Survival measured from time of treatment failure or first relapse to death, or censored at last follow-up



Autologous stem cell consolidation in CR in 3 patients:

patient 1 - two lines of chemotherapy and one radiation line to achieve a CR then autotransplant
patient 2 - two lines of chemotherapy followed by radiation to CR then autotransplant
patient 3 - resection of residual tumor followed by 2nd line chemo adjuvant while in CR and then autotransplant.


Events/Total Median (95% CI) Time-Point KM Est (95% CI)
25/28 4 (3-8) 12 Months 11 (4-31%)
Censor
Overall Survival (%)
100
80
60
40
20
0
0
12
24
36
48
Time (Months)
Number at risk
28
3
3
3
2

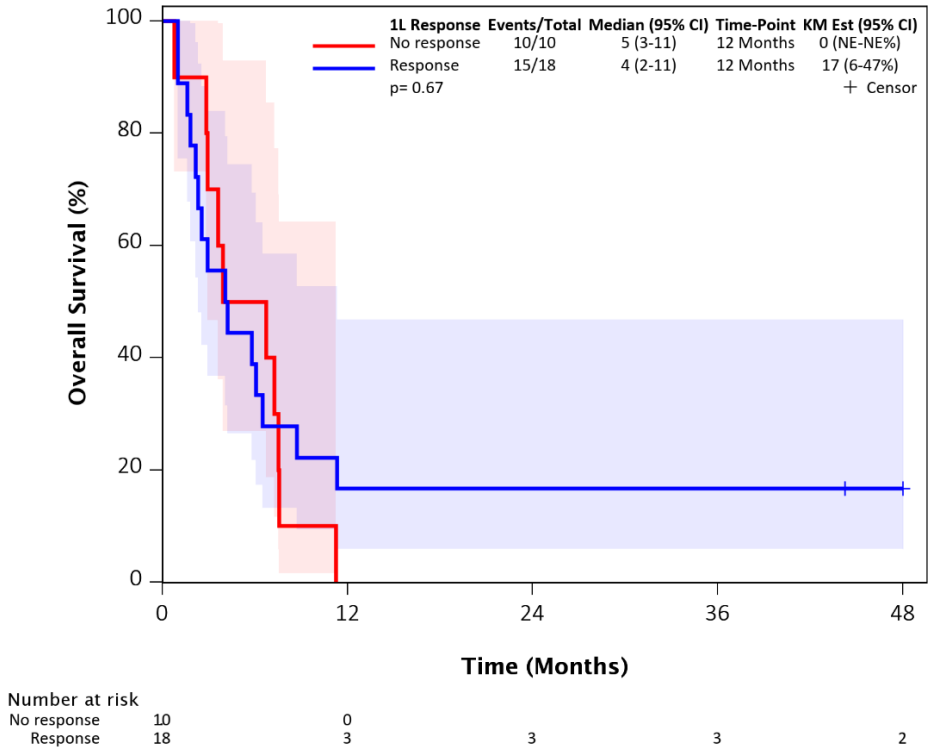
Supplemental Table 1. Clinical characteristics of 28 patients with relapsed/refractory Burkitt

Characteristic	**Value**
Age at diagnosis (years), median [range]	37 [21-69]
Overall survival from diagnosis (months), median [range]	10 [1-129 ongoing] (3 patients ongoing)
Overall survival from time of first treatment failure (months), median [range]	3.5 [0-123] (3 patients ongoing)
Disease characteristics at diagnosis, n (%)	
Stage	
I	1
II	1
III	1
IV	21
Unknown	4
Bone marrow +	7
CNS+	8
Leptomeningeal	8
Parenchymal	0
HIV+	6
EBV+	6
Initial treatment at BL diagnosis, n=28	
CHOP	1
R-CHOP	3
R-EPOCH	6
CODOXM	1
CODOXM/IVAC	7
CODOXM/IVAC-R	7
HyperCVAD-R	2
Other (Rituximab, ifosfamide, etoposide + IT cytarabine)	1
Response to initial treatment, n =28	
Complete response	8
Partial response (less than cr)	10
Progression of disease	10
Disease status at treatment failure, n (28)	
Refractory (any response other than cr)	20
Early relapse after cr 1 (<6 months)	6
Late relapse after cr1 (≥6 months)	2
Age at 1st treatment failure (years), median [range]	37.5 [21-70]
Second line treatment	N=28

R-EPOCH	4
IVAC-R	3
IVAC	3
R-ICE	2
ICE	2
HD MTX+/-Ara-C based	6
Other	8
Response to second line treatment	N=28
Partial response (<cr)	7
Progression of disease	21
Third line treatment	N=16
CODOXM	1
R- EPOCH	3
EPOCH	1
Rituximab	2
HD MTX+/-Ara-C based	4
Other	5
Response to third line treatment	
Complete response (all relapsed early)	5
Progression of disease	11
Fourth line treatment	N=6
R-EPOCH	2
Haploidentical BM transplant	1
Radiation	1
Other	2
Response to fourth line treatment	
Progression of disease	6
Fifth line treatment	N=4
Allo transplant	1
Other	3
Response to fifth line treatment	
Progression of disease	4

Supplemental Figure 1: OS (measured from time of treatment failure or first relapse) stratified by (A) response to first-line treatment (Response vs No response) and (B) early relapse (initial remission duration < 6 months) vs late relapse (initial remission duration ≥ 6 months).

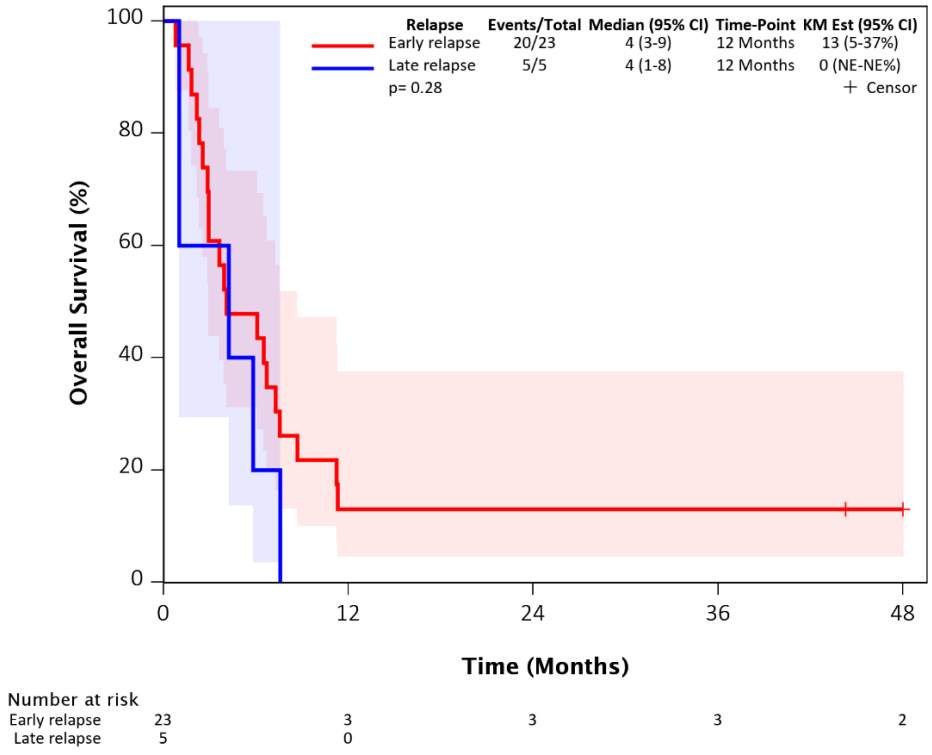
A



Number at risk

No response	10	0			
Response	18	3	3	3	2

B



Number at risk

Early relapse	23	3	3	3	2
Late relapse	5	0			

Supplemental Figure 2: RFS measured from first remission or start of first-line treatment of (A) entire cohort and (B) stratified by initial response.