Mass General Brigham
Mass General Cancer Center

Burkitt Lymphoma

Jeremy S. Abramson, MD, MMSc
Mass General Cancer Center
Harvard Medical School

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Disclosures for Jeremy Abramson

Consulting for AbbVie, Astra-Zeneca, BeiGene, Bristol Myers Squibb, Caribou Biosciences, Cellectar, Genentech, Incyte, Interius, Janssen, Kite Pharma, Lilly, Regeneron, Takeda

Burkitt Lymphoma subtypes

2% of non-Hodgkin lymphomas

- **Endemic**
  - Equatorial Africa, Papua New Guinea
  - EBV association described in 1964
  - Median age 6-9
  - Male: Female 2:1
  - EBV+100%

- **Sporadic**
  - Median age 30
  - Male:Female 3:1
  - EBV+ 20-30%

- **Immunodeficient**
  - HIV most common (CD4 usually >200)
  - Median age 40-45
  - Male:Female 1:1
  - PTLD
  - EBV+ 25-40%

A SARCOMA INVOLVING THE JAWS IN AFRICAN CHILDREN

By DENIS BURKITT

FROM THE DEPARTMENT OF SURGERY, MAKERERE COLLEGE MEDICAL SCHOOL, AND MULAGO HOSPITAL, KAMPALA, UGANDA

MALIGNANT tumours of the jaws in children, primary or secondary, are generally regarded as rare. A sarcoma involving the jaws in African children has recently come to be recognized at Mulago Hospital as a distinctive clinical condition and certainly the commonest malignancy of childhood.

Thirty-eight patients with this sarcoma in the jaws have been seen during the past 7 years; 32 of them were seen at Mulago Hospital and 6 at district hospitals. The tumour was diagnosed clinically in a further 8 children, but these have not been included in this series owing to lack of histological confirmation.

Records of only 3 cases of this type of jaw sarcoma in children have been traced in the literature (Christiansen, 1938; Salmon and Darlington, 1944; Burford, Ackerman, and Robinson, 1944). Gelfand (1957) published an illustration of a sarcoma of the

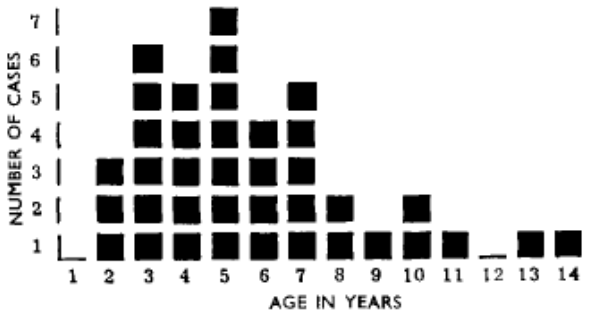
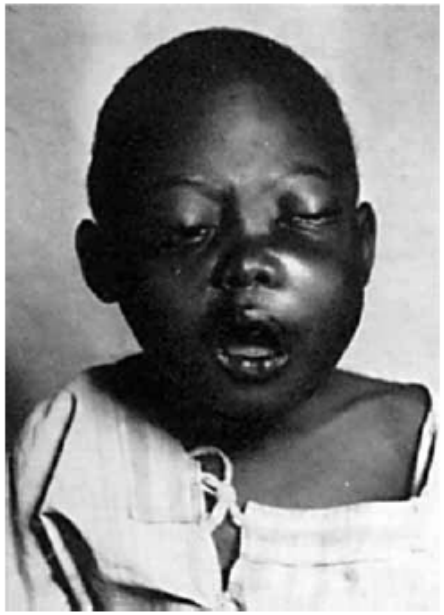


FIG. 246.—Showing age distribution in 38 cases.

In most cases the tumour started in the region of the alveolar process of a maxilla (*Fig.* 247) or the mandible (*Fig.* 249). Loosening of the deciduous molars was often the first symptom, the teeth in the involved area soon becoming embedded in tumour tissue only, and losing their insertion in bone. The next stage was irregular displacement of the teeth prior to their falling out. The tumour grew rapidly,



Burkitt D. Br J Surg 1959

Burkitt Lymphoma

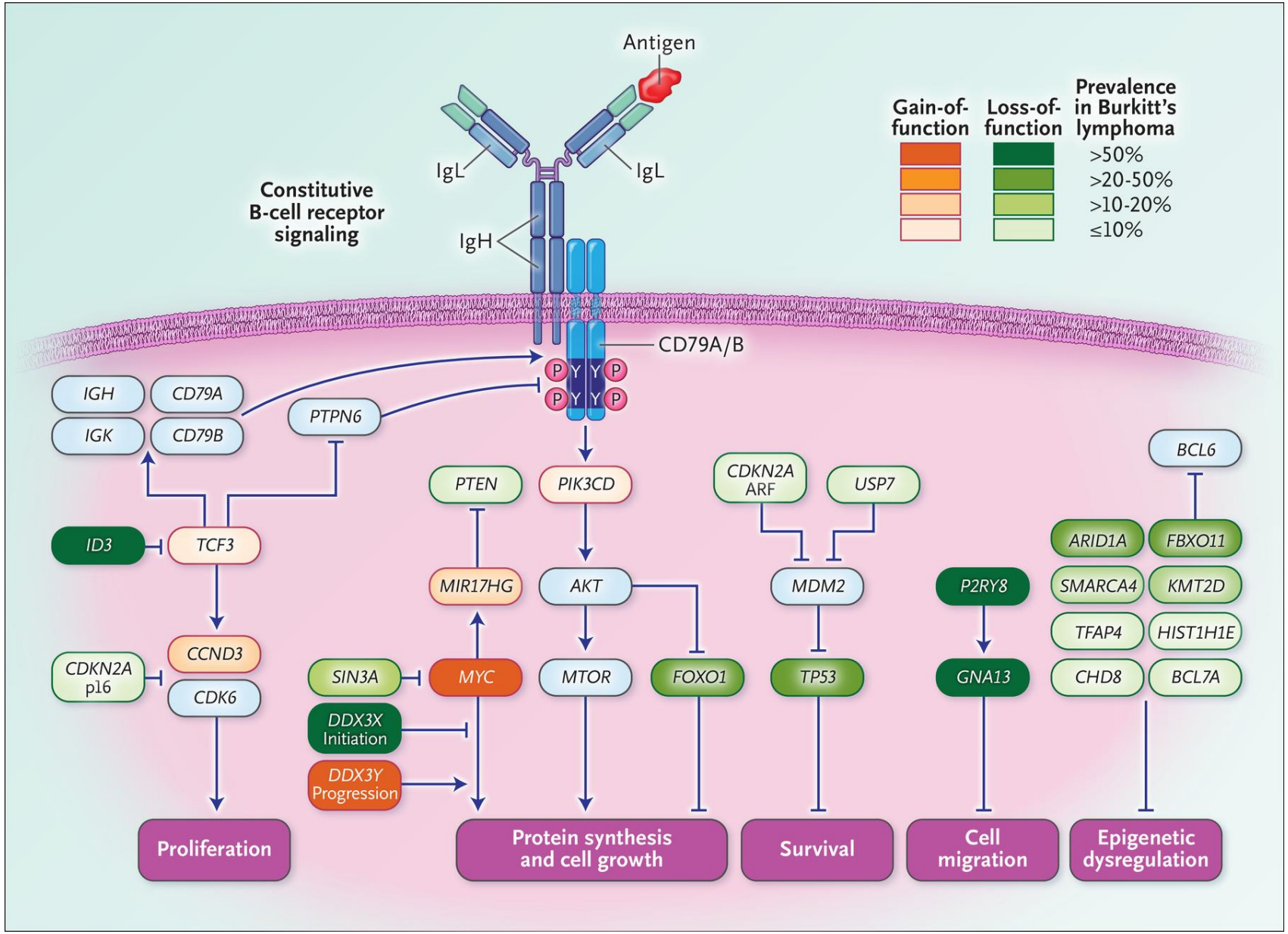
Clinical features

- Rapidly growing malignancy
- Frequently involves extranodal sites, including CNS
- Spontaneous tumor lysis syndrome may occur

Pathology

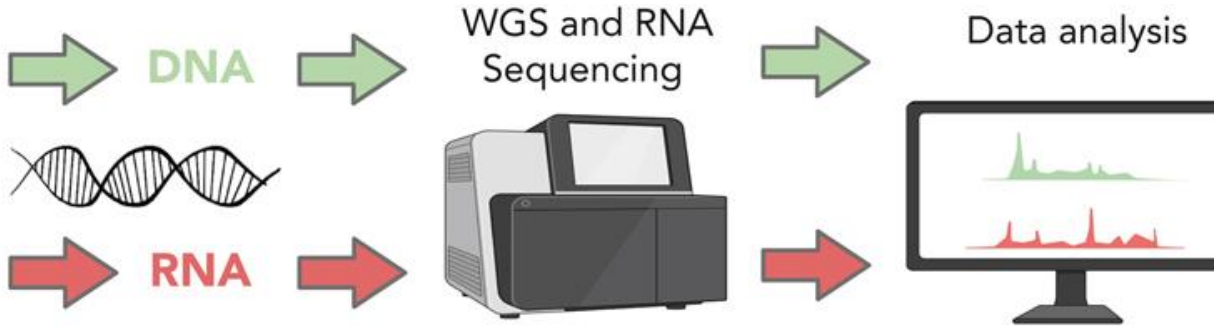
- Germinal center derived B-cell lymphoma
- Monomorphic, medium sized, round nuclei, prominent nucleoli, mitoses
- Immunophenotype: CD20+CD10+BCL6+MYC+, BCL2-, Ki67 >95%
- Deregulation of MYC is *sine qua non*, t(8;14) most common
- Simple karyotype

Genetic complexity beyond MYC



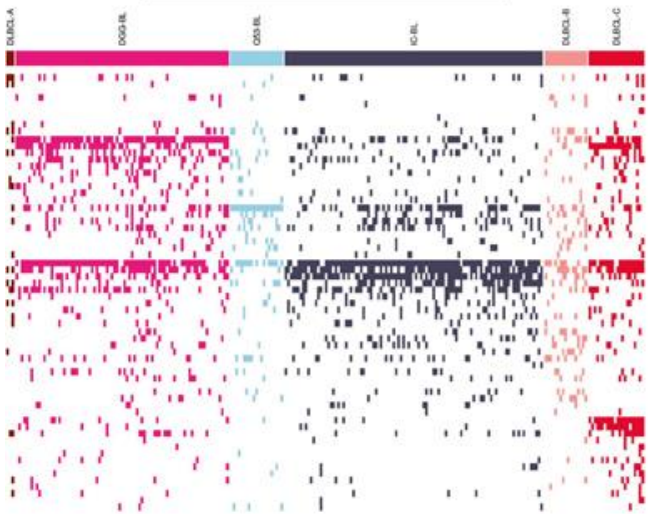
Roschewski, et al. NEJM 2022

EBV status	Adult (N = 92)	Pediatric (N = 138)
EBV+	30 (33%)	88 (64%)
EBV–	62 (67%)	50 (36%)



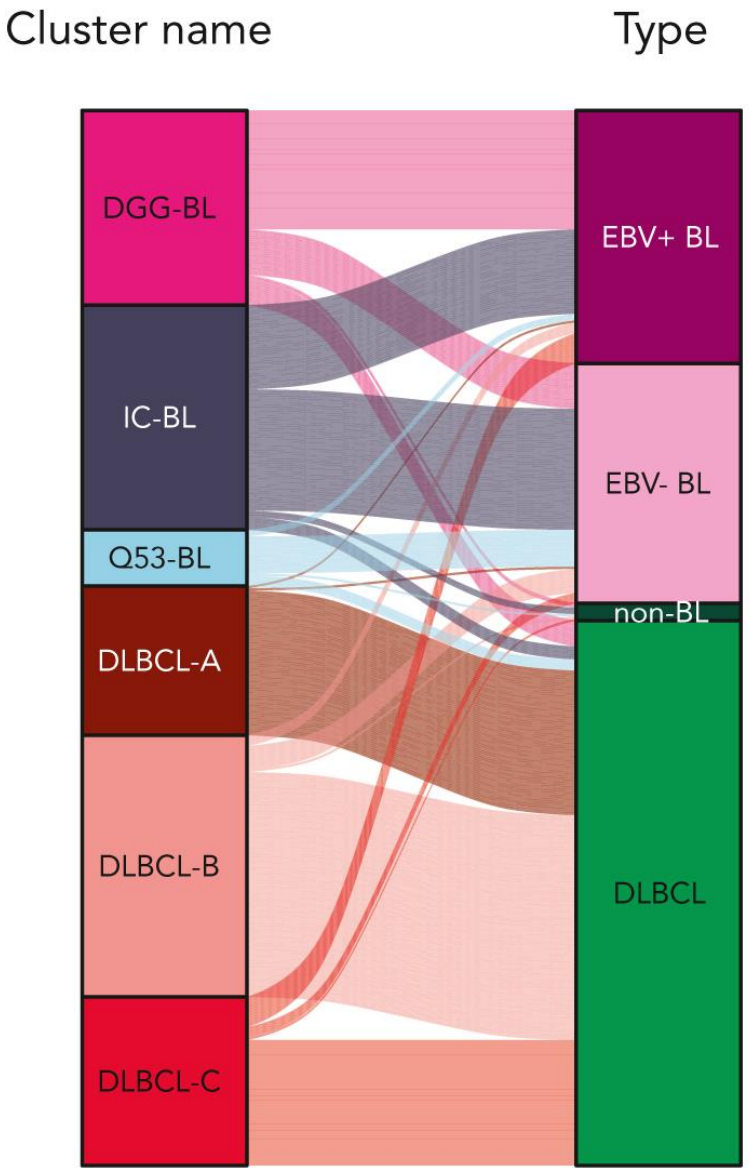
86 SMGs
16 CNVs
4 aSHM
3 oncogene Tx
2 hotspot regions
1 non-coding SSM

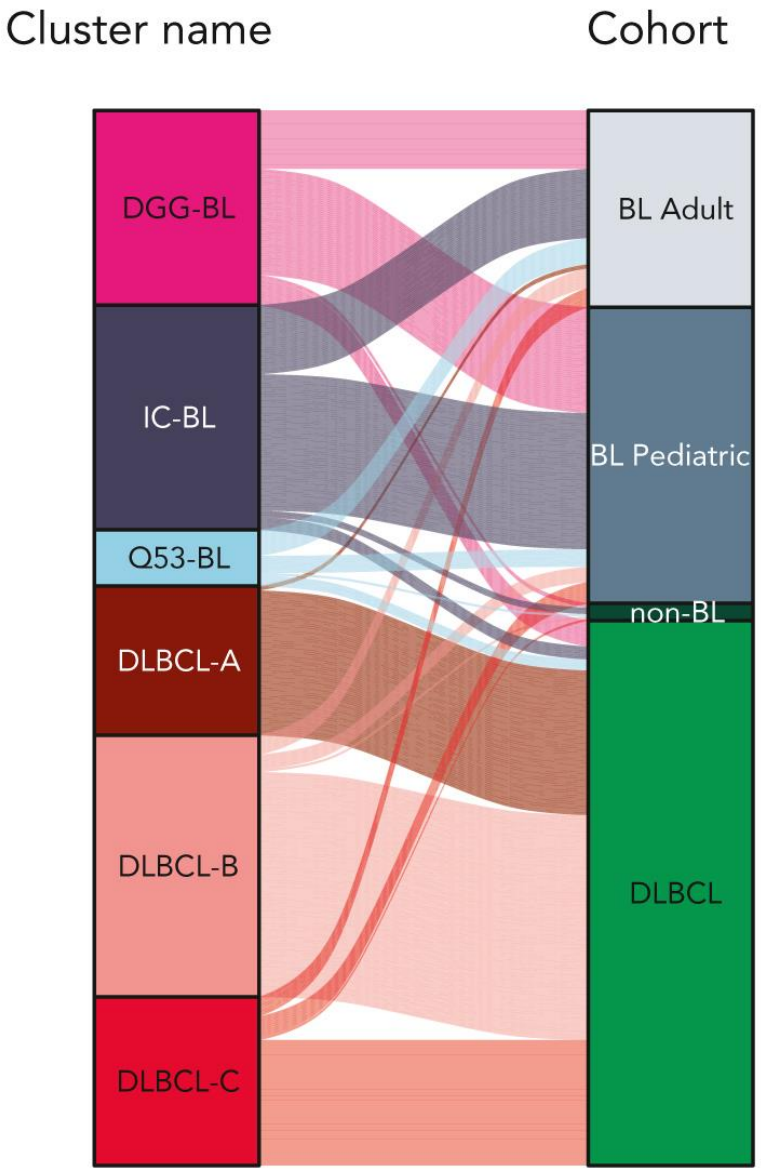
NMF

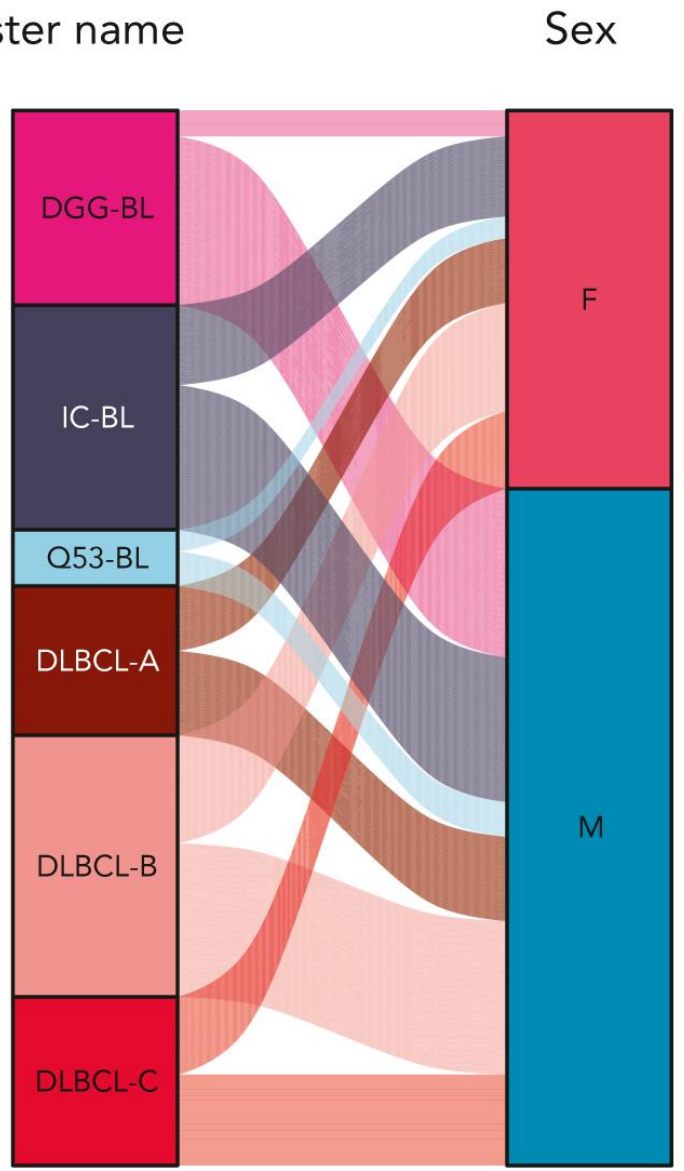


	Clinical features	Molecular features
IC-BL	Enriched for pediatric* and male* tumors	*ID3*, CCND3, and *MYC* mutations; overexpressed *IRF4* and *TNFRSF13B*
DGG-BL	Enriched for EBV+*, pediatric*, and male* tumors	*DDX3X*, *GNA13* and *GNAI2* mutations; downregulated *IRF4* and *TNFRSF13B*
Q53-BL	Enriched for EBV-*	*TP53* mutations, otherwise genetically quiet
DLBCL-like$	Equal proportions by EBV, age, and sex	High aSHM load

Thomas, et al. Blood 2023

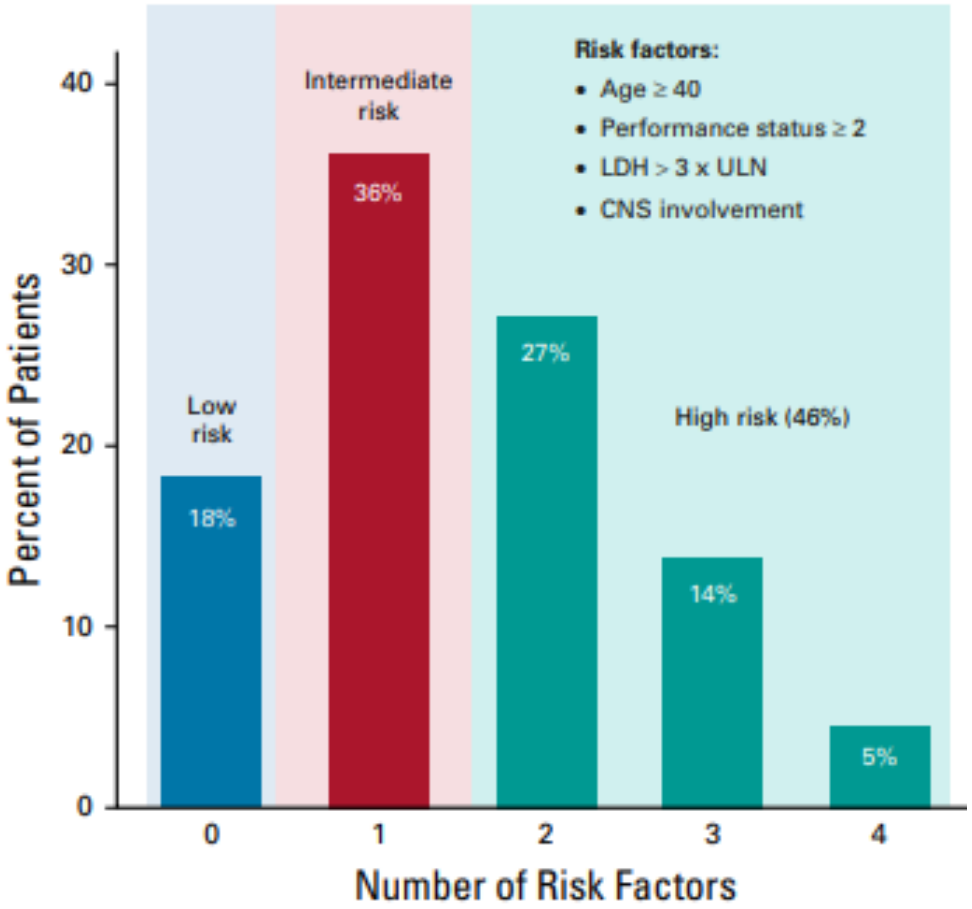






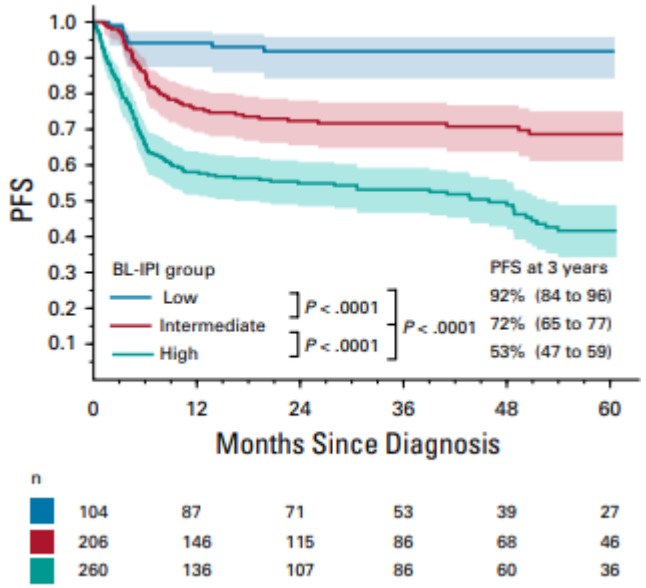
Thomas, et al. Blood 2023

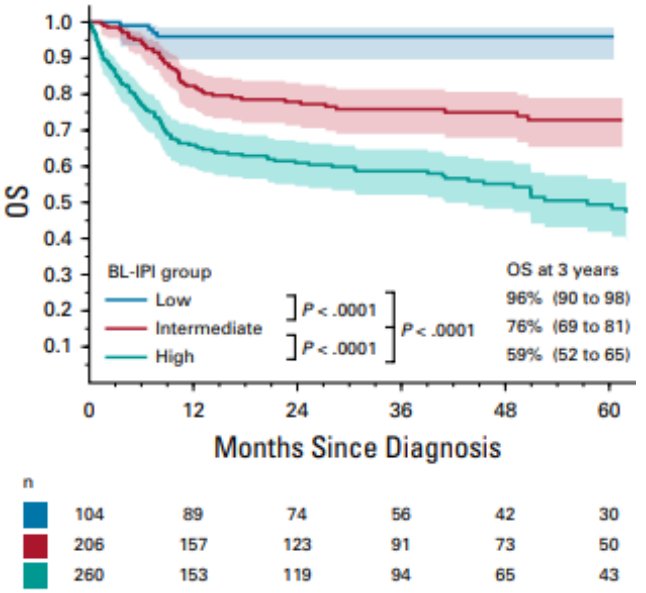
Burkitt Lymphoma International Prognostic Index (BL-IPI)



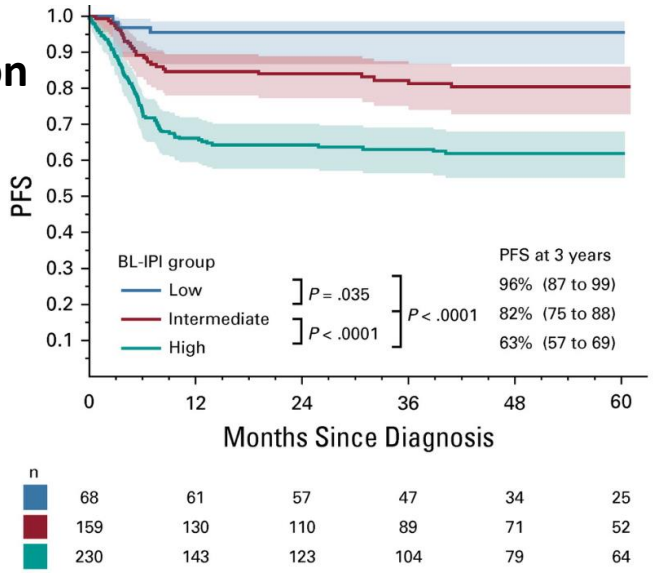
<u>Not prognostic:</u> HIV, sex, stage, marrow involvement, number of EN sites, B symptoms, anemia, hypoalbuminemia

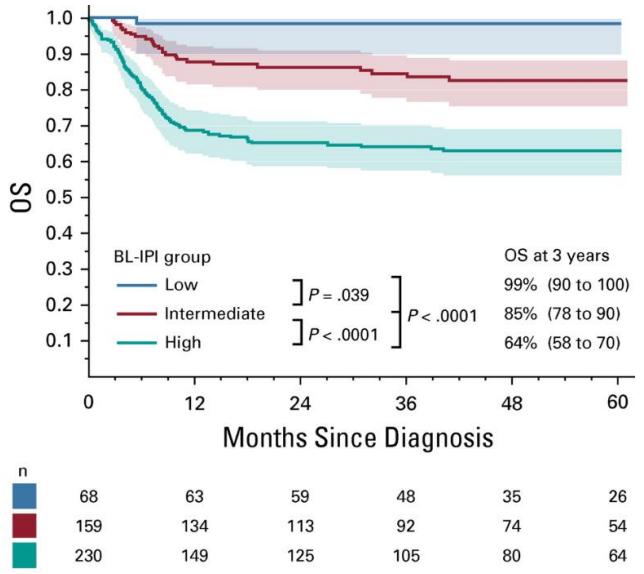
Primary (US)





Validation (Intnl)





Olszewski, et al. JCO 2021

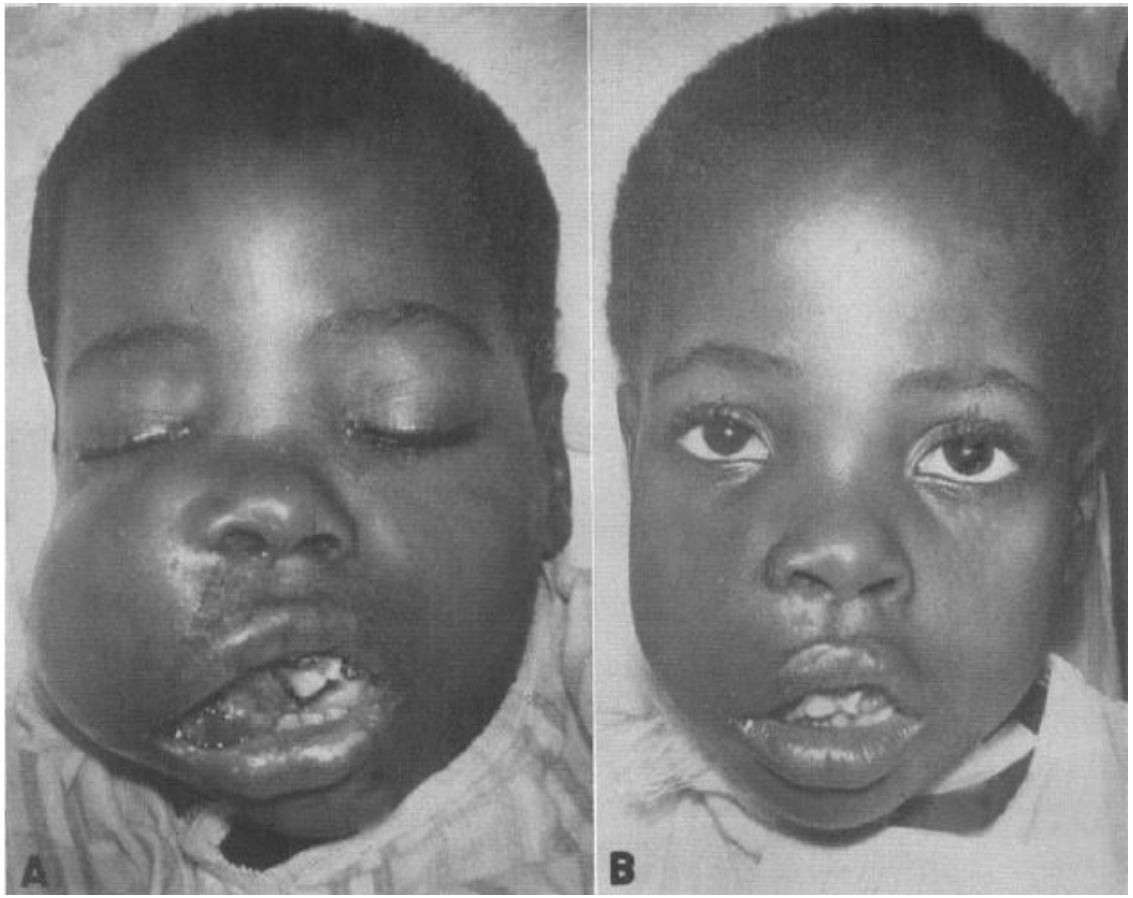
Baseline Evaluation and Pre-Treatment Management

- PET/CT scan (or CT if not able to obtain baseline PET due to acuity)
- Labs: CBC/diff, CMP, LDH, HIV, HBV, tumor lysis labs, pregnancy test
- Lumbar puncture including flow cytometry
- MRI if CNS symptoms
- Bone marrow biopsy (may not be necessary with PET)
- Peripheral blood flow cytometry if increased lymphoid forms
- Echocardiogram
- Hydration and allopurinol +/- rasburicase for TLS prophylaxis

Treatment of Burkitt Lymphoma

MALIGNANT LYMPHOMA INVOLVING THE JAW IN AFRICAN CHILDREN: TREATMENT WITH METHOTREXATE

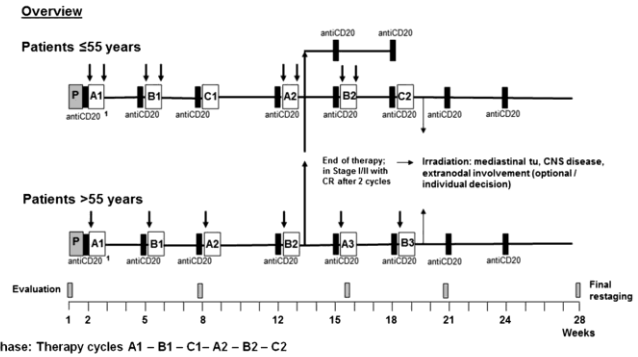
HERBERT F. OETTGEN, M.D.,* DENIS BURKITT, M.D., F.R.C.S.E., AND JOSEPH H. BURCHENAL, M.D.



Cancer 1963

Intensive Regimens Incorporating Rituximab for Adults
(derived from pediatrics)

Therapy Plan for patients aged 15-55y (GMALL-B-ALL/NHL 2002)

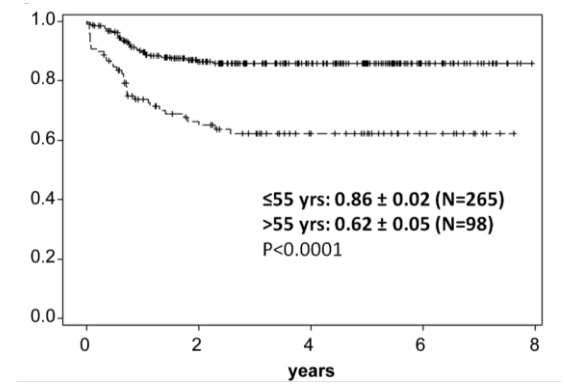


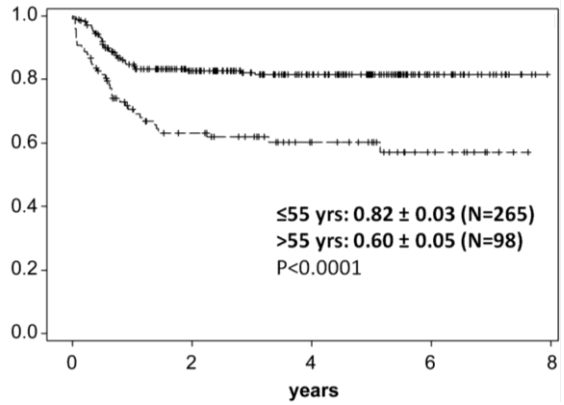
Pre-phase: Therapy cycles A1 – B1 – C1– A2 – B2 – C2

Pre-phase		
Cyclophosphamide	200 mg/m² iv (1 h)	Day 1-5
Prednisone	60 mg/m² p.o. (in 3 doses)	Day 1-5
		Day 6, break
Cycle A1, Day 7; repeated A2, Day 77		
Rituximab	375 mg/m² iv	Day 7
Dexamethasone	10 mg/m² p.o. (in 3 doses)	Day 8-12
Vincristine	2 mg iv	Day 8
Ifosfamide	800 mg/m² iv (1 h)	Day 8 -12
HD-Methotrexate*	1500 mg/m² c.i. (24 h)	Day 8
VM26	100 mg/m² iv (1 h)	Day 11 -12
Cytarabine	2x 150 mg/m² iv (1 h), every 12 h	Day 11 -12
i.th. triple prophylaxis**		
Cytarabine	40 mg i.th.	Day 8, (12)
Methotrexate	15 mg i.th.	Day 8, (12)
Dexamethasone	4 mg i.th.	Day 8, (12)
G-CSF	5 µg/kg s.c.	from Day 14

* HD-MTX: 1500 mg/m²
1/10 iv in 30 min., 9/10 c.i. in 23 ½ hours,
Leukovorin-Rescue, start at 42 h and adapted to the MTX concentrations in plasma.

Cycle B1, Day 28; repeated B2, Day 98		
Rituximab	375 mg/m² iv	Day 28
Dexamethasone	10 mg/m² p.o. (in 3 doses)	Day 29 -33
Vincristine	2 mg iv	Day 29
Cyclophosphamide	200 mg/m² iv (1 h)	Day 29 -33
HD-Methotrexate	1500 mg/m² c.i. (24 h)	Day 29
Patients > 55 years 500 mg/m²		
Adriamycin	25 mg/m² iv (15 min.)	Day 32 -33
i.th. triple prophylaxis**		
Cytarabine	40 mg i.th.	Day 29, (33)
Methotrexate	15 mg i.th.	Day 29, (33)
Dexamethasone	4 mg i.th.	Day 29, (33)
G-CSF	5 µg/kg s.c.	from Day 35
Cycle C1, Day 49; repeated C2 Day 119		
Rituximab	375 mg/m² iv	Day 49
Dexamethasone	10 mg/m² p.o. (in 3 doses)	Day 50 -54
Vindesine	3 mg/m² iv (Bolus) (max. 5 mg)	Day 50
HD-Methotrexate*	1500 mg/m² c.i. (24 h)	Day 50
VP 16 (Etoposide)	250 mg/m² c.i. (1 h)	Day 53, 54
HD-Cytarabine	2 x 2 g/m² c.i. (3 h) every 12 h	Day 54
G-CSF	5 µg/kg s.c.	from Day 56



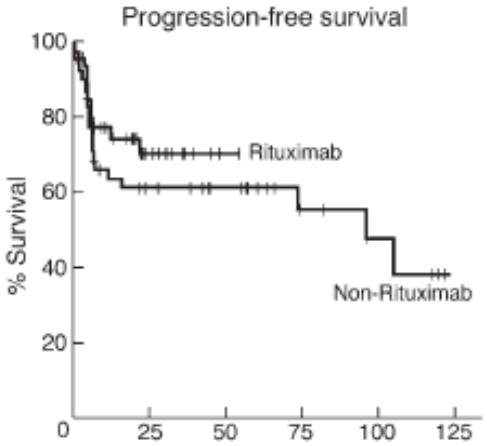


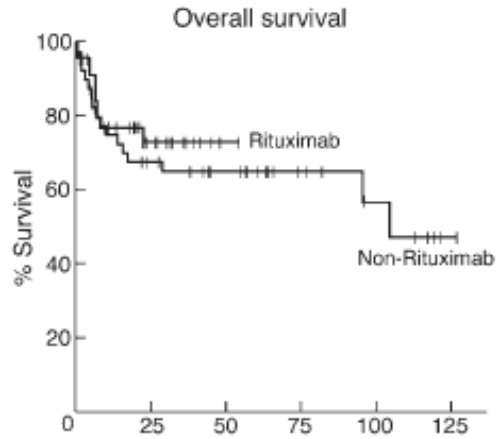
Hoelzer et al. Blood 2014

R-CODOX-M (A)
- Rituximab
- Cyclophosphamide
- Vincristine
- Doxorubicin
- High dose Methotrexate
- IT Methotrexate & cytarabine

R-IVAC (B)
- Rituximab
- Ifosfamide
- Etoposide
- Cytarabine
- IT methotrexate

To determine course:
- High risk vs. Low risk (A,B,A,B vs. A,A,A,)
- CNS +/- (increased IT therapy if +)



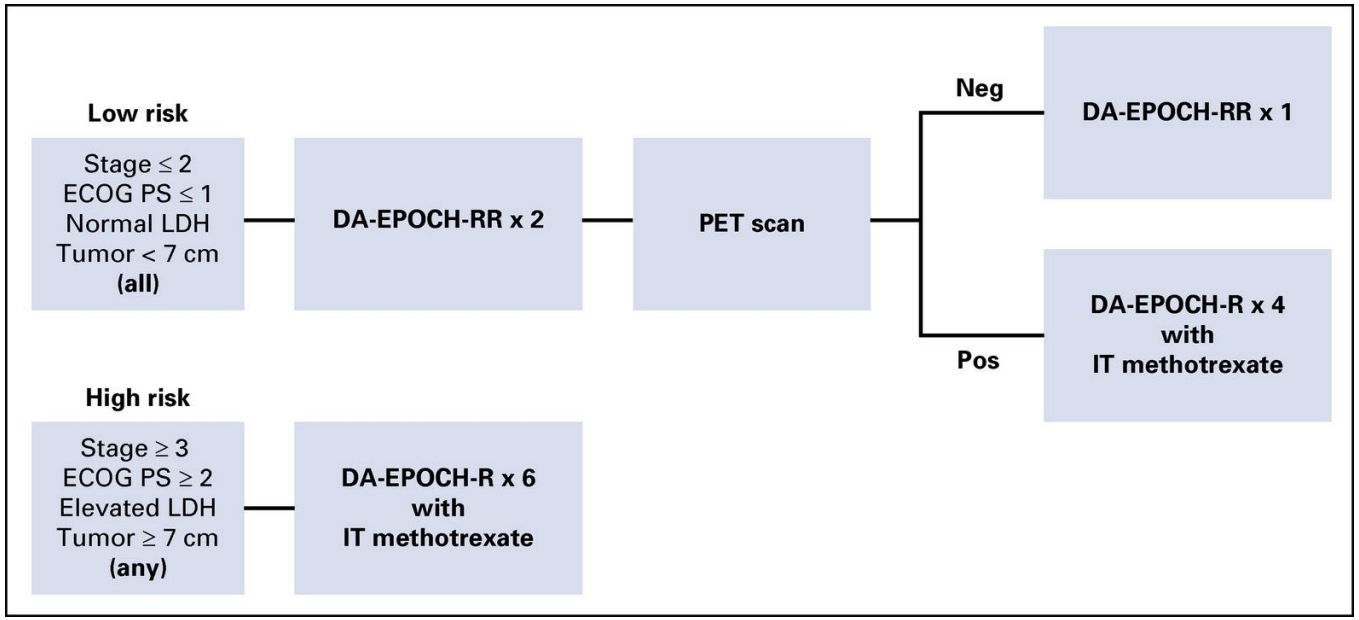


Barnes et al. Ann Onc 2010

Adverse Factors on Multivariable analysis:
- Age>60
- CNS Involvement

These are highly toxic regimens in adults

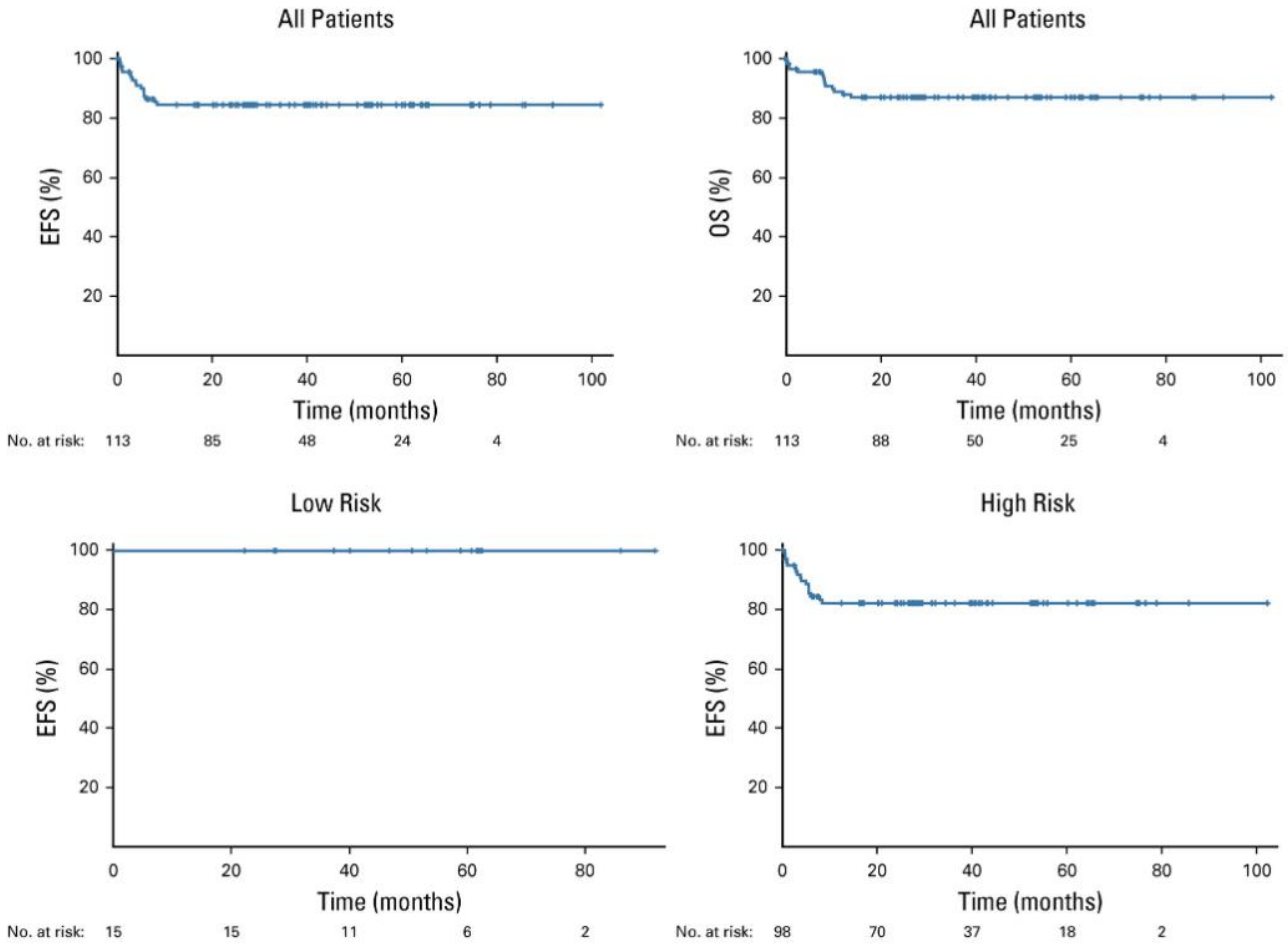
DA-EPOCH-R for Burkitt Lymphoma in Adults

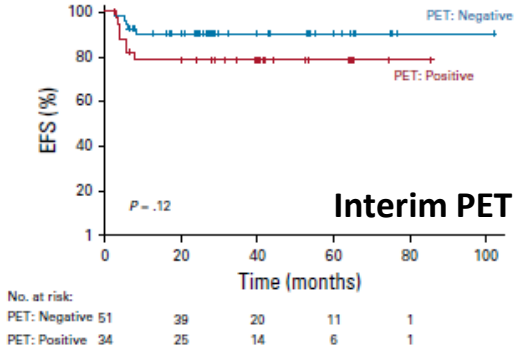


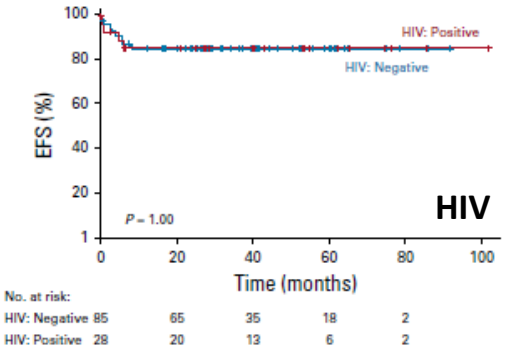
Characteristics	N= 113
Age (median, range) Age ≤ 40 years Age 40 - 60 years Age ≥ 60 years	49 years (18-86) 43 (38%) 41 (36%) 29 (26%)
Male gender	89 (79%)
Low-risk	15 (13%)
High-risk	98 (87%)
Stage III-IV	79 (70%)
Elevated LDH	69 (61%)
HIV positive	28 (25%)
Any extranodal	76 (67%)
Bone marrow and/or blood	28 (25%)
CNS involvement	11 (10%)

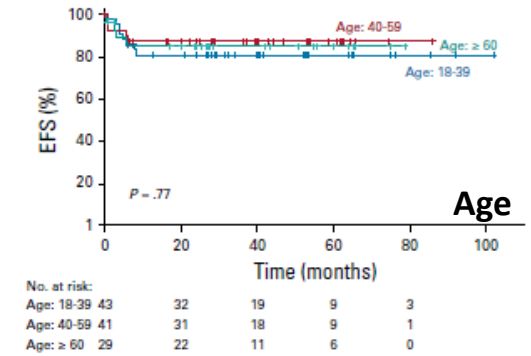
Dunleavy et al. JCO 2020.

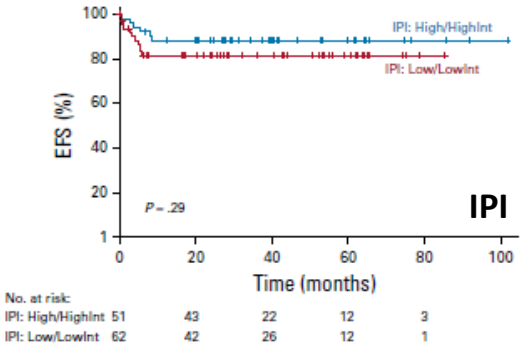
DA-EPOCH-R for Burkitt Lymphoma in Adults

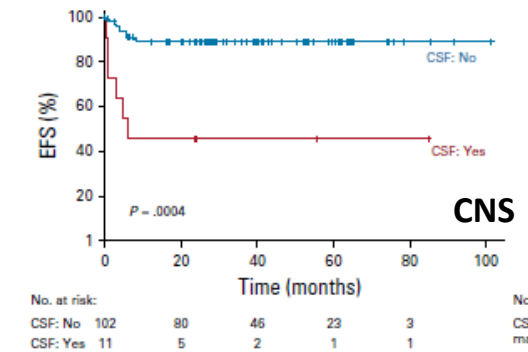


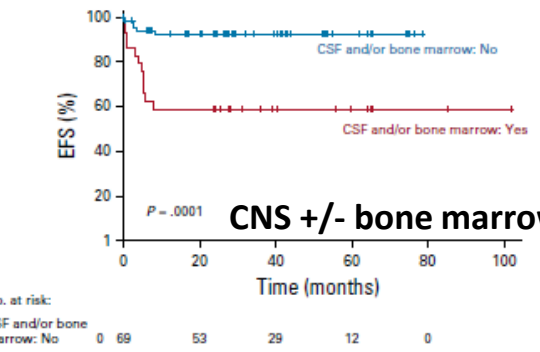








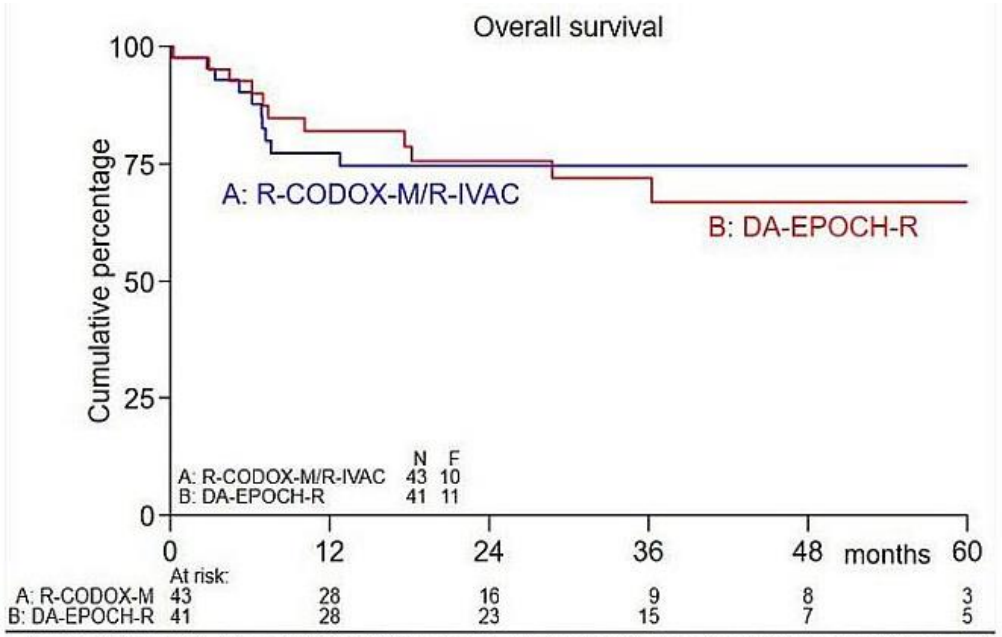




Dunleavy et al. JCO 2020.

R-CODOX-M/R-IVAC vs. DA-EPOCH-R in High Risk Burkitt Lymphoma: *HOVON/SAKK trial*

	R-CODOX-M/R-IVAC	DA-EPOCH-R
n	43	41
Median age (range)	50 yr (18-75)	56 yr (22-74)
Stage III-IV	88%	92%
CMR	**65%**	**66%**



Legend Figure 1. Overall Survival for all patients in arm A and arm B (Kaplan Meier curve). Causes of death: In arm A 10 patients died; 8 due to Burkitt Lymphoma, 1 sepsis, 1 COVID-19 infection. In arm B 11 patients died; 7 due to Burkitt Lymphoma, 1 sepsis, 1 COVID-19 infection, 1 secondary malignancy*, 1 complication of alogeneic stem cell transplantation*. *Causes of death after 24 months.

R-CODOX-M/R-IVAC was associated with excess infectious complications, transfusions and hospital days, prompting early closure of the trial

Chamuleau et al. Proc. EHA 2022

How I Treat Burkitt Lymphoma Today

- I prefer DA-EPOCH-R for most patients
  - DA-EPOCH-RR x 3 cycles in low-risk patients (BL-IPI 0, or 1 if age is only risk factor)
  - DA-EPOCH-R x 6 cycles with IT MTX prophylaxis in higher risk patients
  - Intensive IT therapy required for active CSF disease

- Where do I favor R-CODOX-M/R-IVAC?
  - Young patients with involvement of CNS, marrow or peripheral blood

- In HIV+ patients, administer concurrent ART with attention to drug-drug interactions, infectious prophylaxis and supportive care

Relapsed Burkitt Lymphoma

- Outcomes for relapsed/refractory disease are extremely poor, but are almost entirely derived from intensive chemotherapy treated patients. Will DA-EPOCH-R be different?
- Clinical trial preferred, of course
- Goal would be 2nd line chemotherapy and transplant for chemosensitive disease
- No (or minimal) data for novel agents (polatuzumab vedotin, loncastuximab tesirine, bispecific antibodies, CAR T-cells)

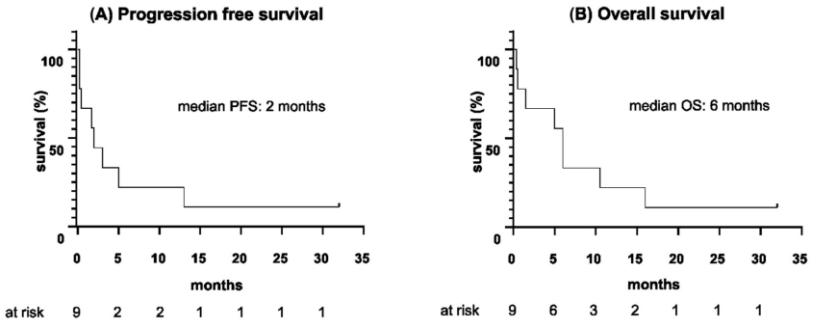
Novel agents in relapsed Burkitts

Blinatumomab

Characteristics	N=9
Median age (range)	33 (25-62
Stage III-IV	6
Marrow +/- blood involved	5/9
CNS involved	0
Median prior lines (range)	1 (1-3)

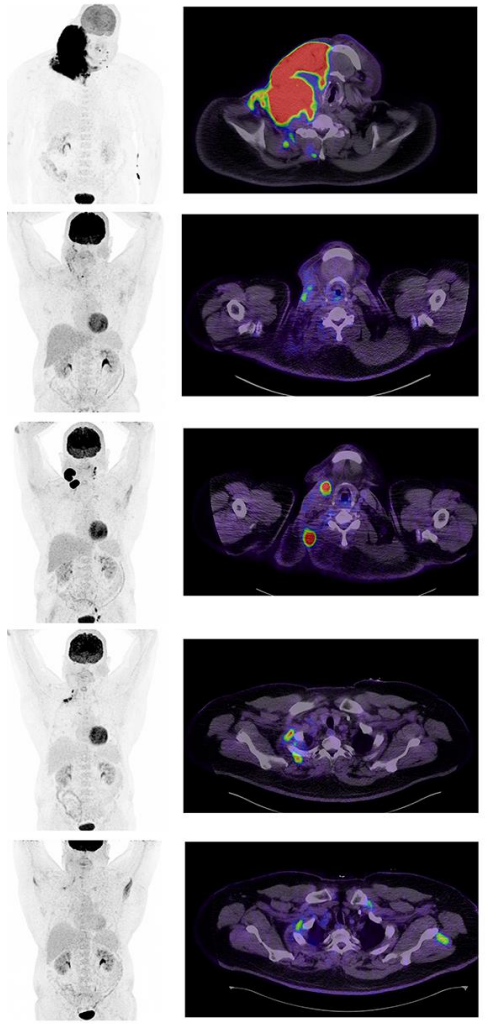
Efficacy	N=9
ORR	5 (55.5%)
CRR	3 (33.3%)
Median PFS	2 mo
Median OS	6 mo

3 patients bridged to allo



Bohler et al. Cancers 2023.

Polatuzumab-BR



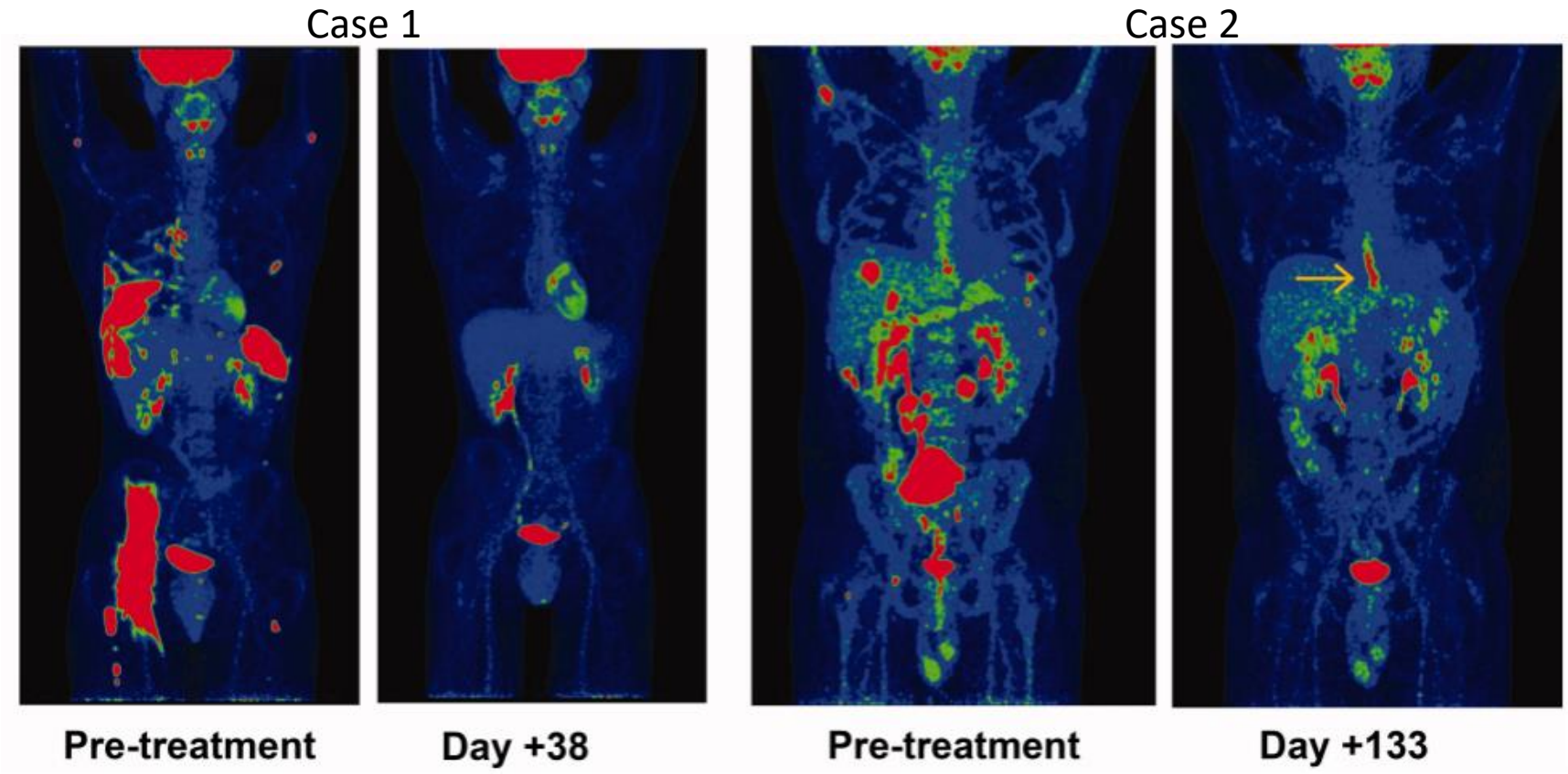
47yo man
BL, EBV+
Relapsed after R-CODOX-M/IVAC

Pola-BR x 6 -> Pola-R x 2
Remains in remission 1 year later

Alanzi et al. OncoTargets and Therapy 2023.

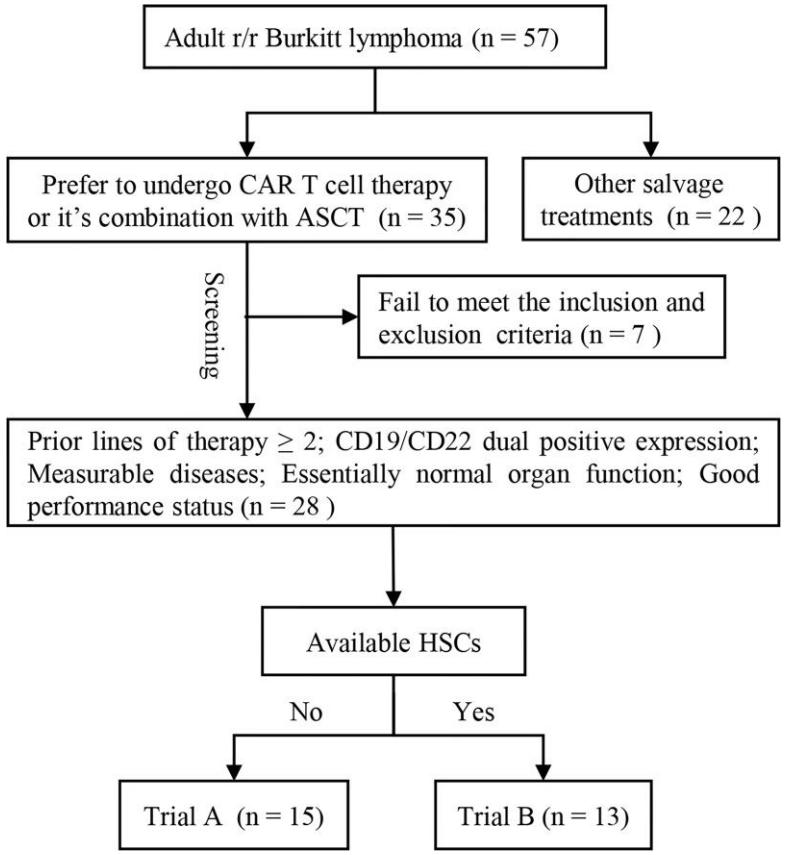
CAR-T cell case report: 2 cases at the US NCI

- 33yo man with stage IV BL treated with DA-EPOCH-R, primary refractory, received an anti-CD19 CAR (axi-cel predecessor) on clinical trial at NCI
- 45yo man R-CODOX-MR-IVAC with PR, then DA-EPOCH-R with progression, received an anti CD19 CAR (u19-CD828Z) on clinical trial at NCI
- Both achieved CR sustained at 53 and 58 months.



Seitter et al. Leuk Lymph 2022.

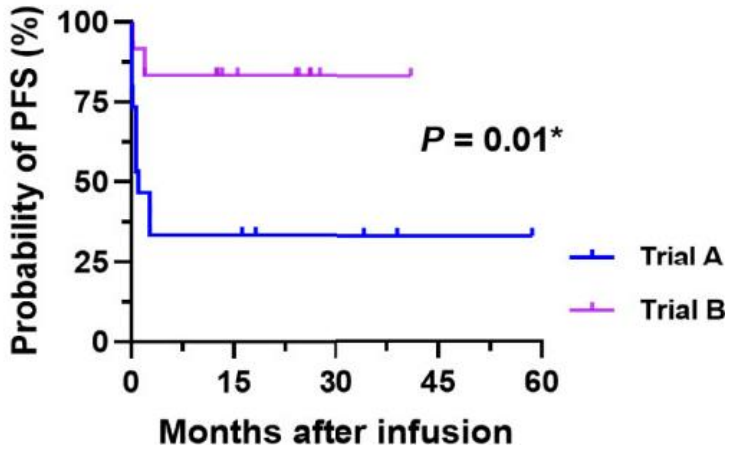
Tongji Hospital study with CD19 and CD22 CAR T-cells



CD19/CD22 CAR T cell ASCT + CD19/CD22 CAR T cell

Characteristics	Trial A	Trial B
Median age, y (range)	30 (17-62)	33 (17-70)
BL-IPI 2-4	73%	69%
Median prior lines (range)	3 (2-7)	3 (2-7)
Primary refractory	67%	85%
TP53 mutated	47%	62%

Response	Trial A	Trial B
Overall	7 (47%)	12 (92%)
Complete	5 (33%)	11 (85%)



median follow-up duration of 12.5 m

Wu et al. Front. Immunol. 2022.

Burkitt Lymphoma conclusions

- Highly aggressive lymphoma which occurs in endemic, sporadic, and immune compromised variants
- Diagnosis includes morphology, immunophenotyping and cytogenetics
- There is molecular heterogeneity beyond the MYC translocation
- Less intensive therapy with DA-EPOCH-R now preferred for most patients due to high cure rates and less toxicity
- Still consider intensive regimen (i.e. R-CODOX-M/R-IVAC) in young fit patients with high risk features (CNS involvement, blood/marrow involvement)
- HIV+ patients should be managed akin to HIV- patients with concurrent ART and special attention to drug-drug interactions and supportive care
- Little data on management of patients relapsing after DA-EPOCH-R, or with novel agents
- Additional data needed for bispecific antibodies and CAR T-cells

Thank you for your attention!

jabramson@mgh.harvard.edu