New Advances in Therapy for Lymphoma: Burkitt's Lymphoma

Leidy L. Isenalumhe MD, MS

Pediatric and Adult Hematology-Oncology

Assistant Member of Malignant Hematology Department

Director of Clinical Operation for Malignant Hematology

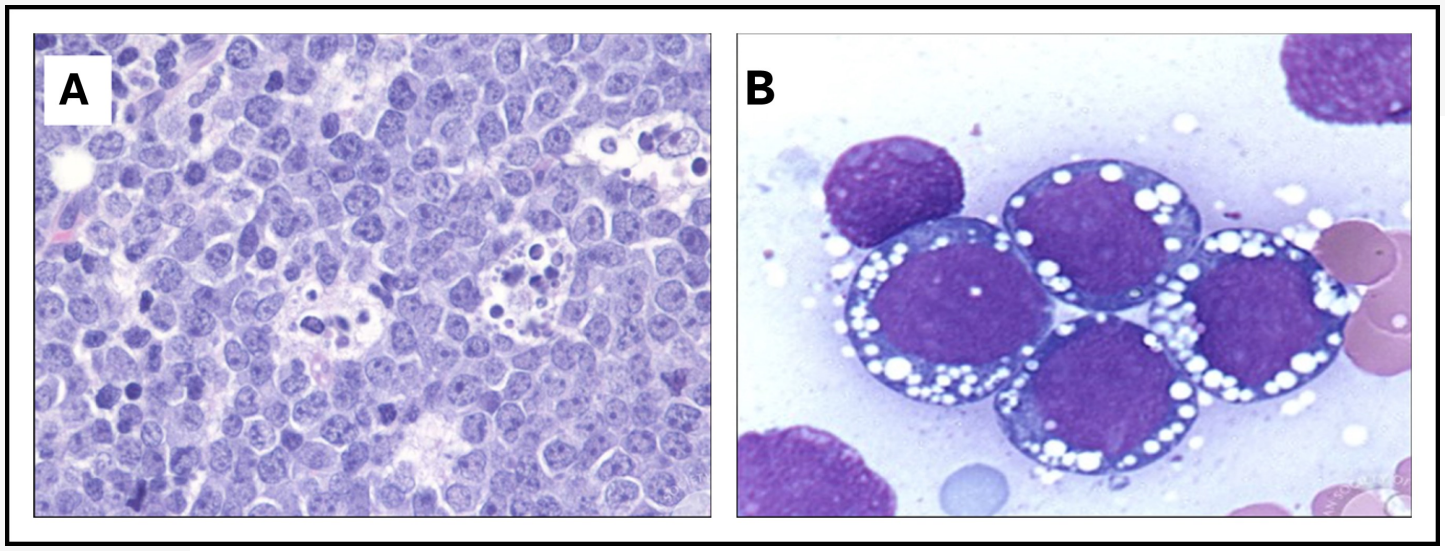
Co-Director of IPOP Service (Inpatient/Outpatient)

H. Lee Moffitt Cancer Center and Research Institute

MOFFITT CANCER CENTER

Objectives

- Review the current treatment guidelines for Burkitt's Lymphoma
    - Low risk
    - High risk
    - CNS involvement
    - HIV positive patients
- Management of Relapse/Refractory disease



Translocation of the proto-oncogene *MYC band*

- t(8;14)(q24;q32)
  8q24 to IGH region on chromosome 14q23
- t(8;22)
  IGK locus on 2p12
- t(2;8)
  IGL locus on 22q11, t(8;22)

B Cell Makers

- CD19
- CD20
- CD22
- CD79a
- PAX5

Germinal Cell Markers

- CD10
- BCL6

Strong MYC expression

Ki67 > 95%

Jennifer Crombie,Ann LaCasce, The treatment of Burkitt lymphoma in adults, Blood, 2021, Figure 1.

The Variants

Endemic

- EBV associated
- Endemic to Equatorial Africa
- Mean = 6 year of age; M>F

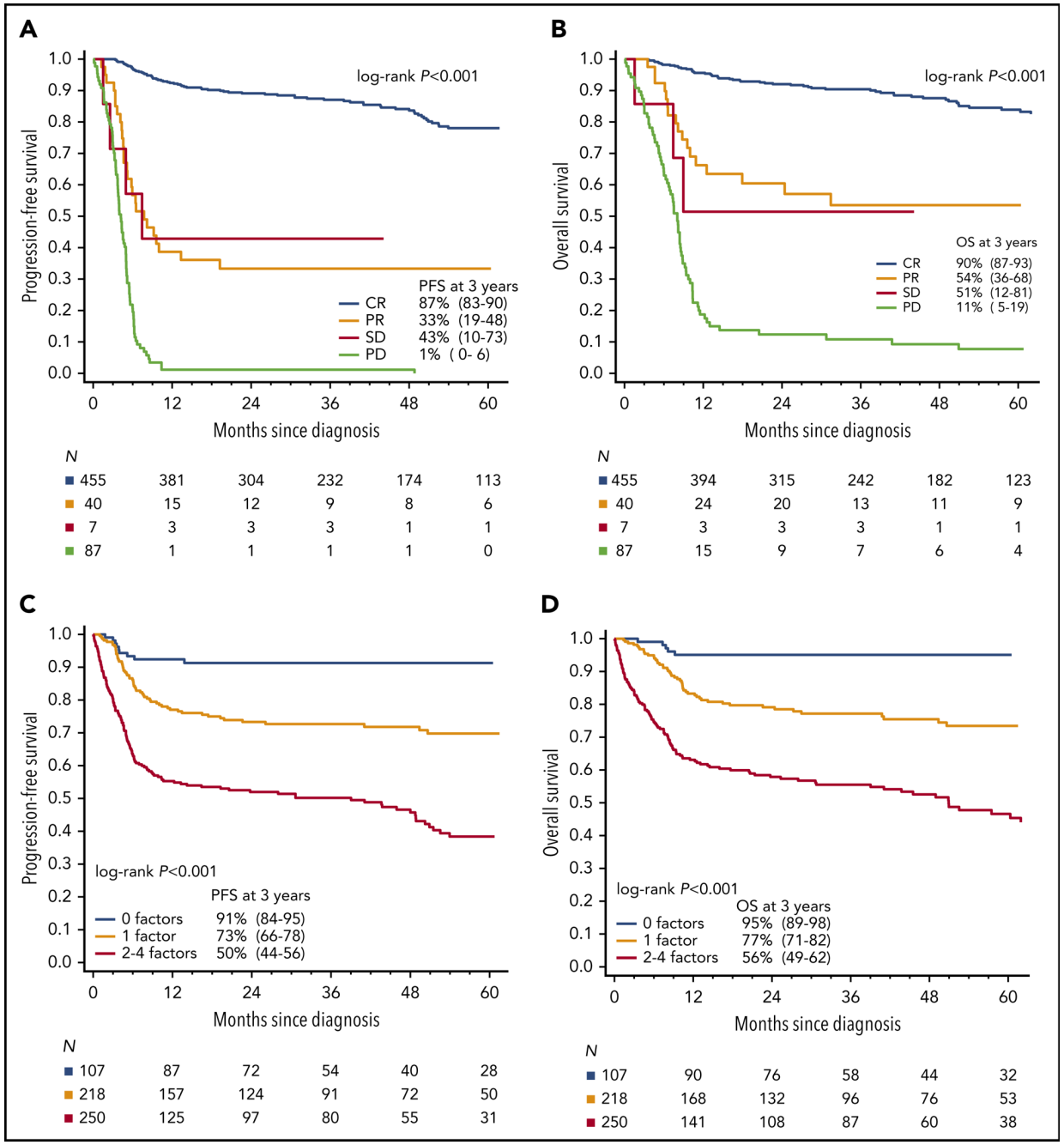
Immunodeficiency-Associated

- 20% of cases in US
- No correlation with CD4 counts or antiviral control

Sporadic

- Pediatrics and Young adults
- 1% of All NHL in adults
- Extra-nodal sites, CNS involvement

Crombie J, LaCasce. Blood. 2021;137(6):743-750)



- 641 patients
- Over 30 US centers

Prognostic Factors

- Age ≥ 40 years
- ECOG PS 2-4
- LDH > 3× normal,
- CNS involvement at diagnosis

Blood (2021) 137 (3): 374–386.

Upfront Treatment for Burkitt's Lymphoma

Treatment

- TLS management
  - Patients may require pre-treatment phase regardless of treatment regimen
  - Steroids or Cytarabine
  - Rasburicase, allopurinol and IV hydration and close monitoring of labs
- Urgent initiation of treatment is required
- Intensive multiagent chemotherapy along with adequate CNS prophylaxis
- 30-50% develop CNS disease if CNS ppx is not incorporated into treatment
  - The best method for delivery the CNS ppx has not been determined yet

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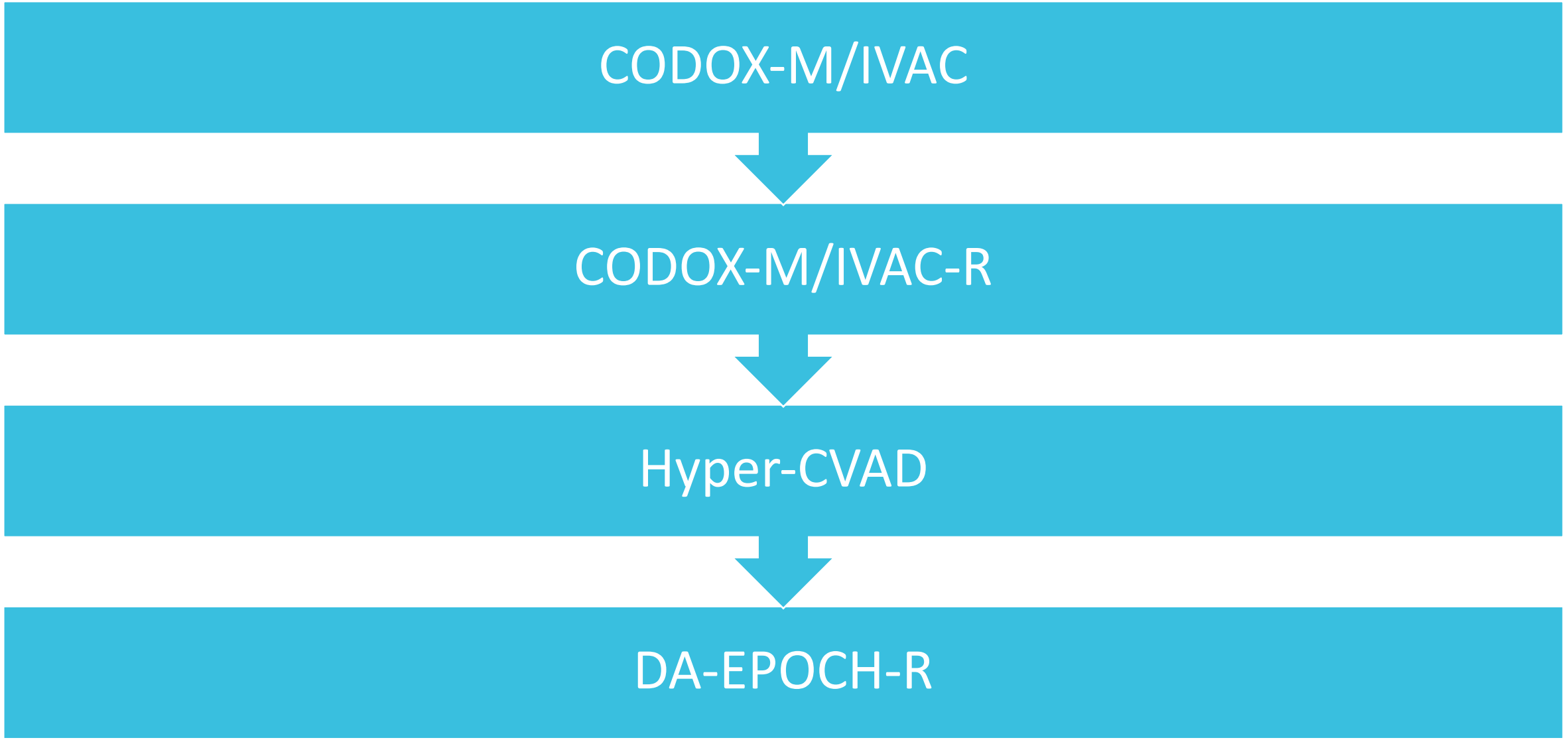
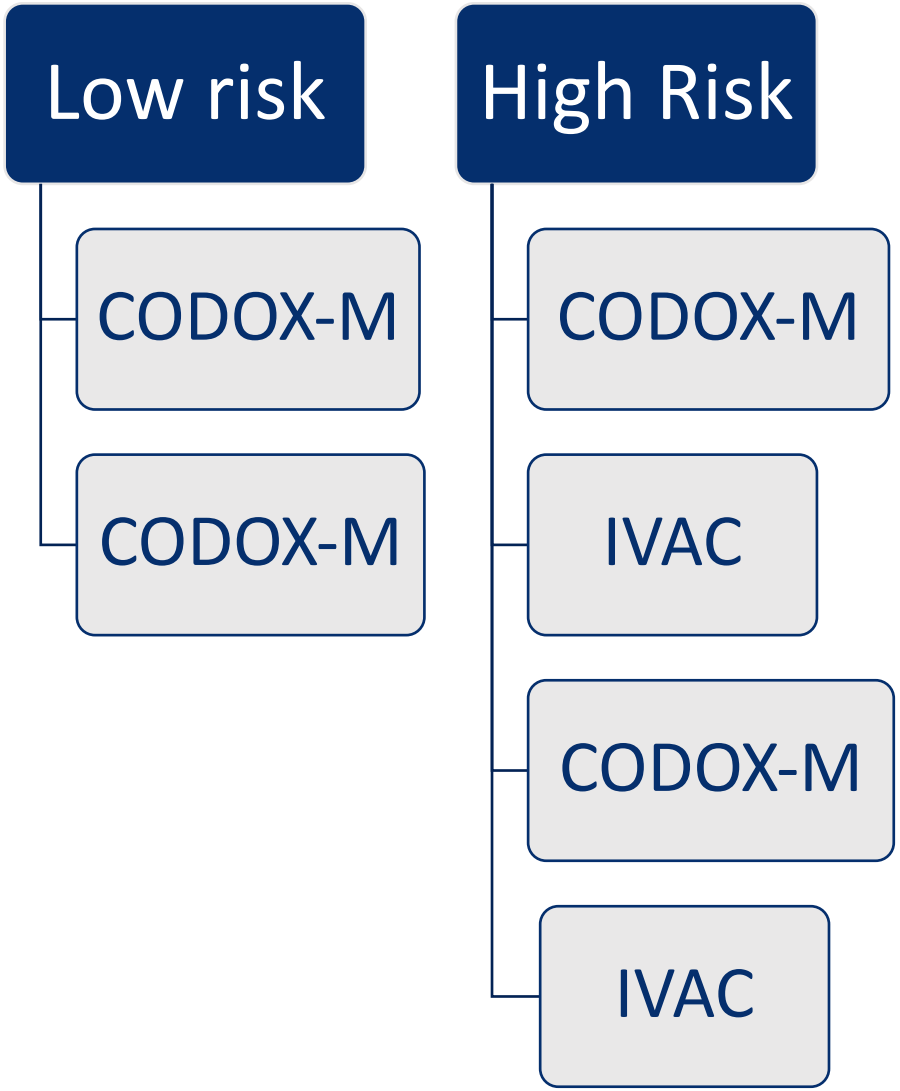
Treatment of Choice



Upfront Treatment: Magrath



(A) CODOX-M-R protocol

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Cyclophosphamide 800 mg/m² IV	x	x																
Doxorubicin 50 mg/m² IV	x																	
Vincristine 1·4 mg/m² IV	x							x										
Rituximab 375 mg/m² IV *								x										
Leucovorin (until MTX <0·1 µmol/l)											x	x	x	x				
Cytarabine 50 mg IT	x		x															
Methotrexate 3000 mg/m² IV										x								
G-CSF													x	x	x	x	x	x

(B) IVAC-R protocol

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Ifosfamide 1500 mg/m² IV	x	x	x	x	x													
Cytarabine 2000 mg/m² IV	x	x																
Mesna 375 mg/m² IV	x	x	x	x	x													
Etoposide 60 mg/m² IV	x	x	x	x	x													
Rituximab 375 mg/m² IV *				x														
Methotrexate 12 mg IT						x												x
G-CSF							x	x	x	x	x	x	x	x	x	x	x	x

1. Magrath, M, et al. J Clinic Oncol 14:925-934, 1996 2. Mead G, et al. Annals of Oncology 13: 1264-1274, 2002 (removed D15 VCR)
3. Mead G. et al. Blood 112 (6): 2248-2260, 2008 4. Evens A, et al. Annals of Oncology 24:3076-3081, 2013

Upfront Treatment: Magrath

Response	CODOX-M/IVAC[1] (1996) n=72	CODOX-M/IVAC[2] (2002) n=52	dmCODOX-M/IVAC[3] (2008) n=53 BL	dmCODOX-MR/IVAC-R[4] (2013) n=25
TRM (%) Grade ≥ 3		100 • *(Myelosuppresion, mucositis)* • *> G4 in HR patients*	61-99% *Not divided by BL*	Thrombocytopenia: 68 Anemia: 72% Mucositis
2yr EFS	92	65 LR: 83.3 HR: 59.5	64	80 (PFS)
2yr OS		73 LR: 81.5 HR: 69.9	67	84
Other	Included Peds and adults ALL and BL pts OS was not reported	Phase II trial Used prognostic groups: LR and HR BL HIV negative patients	Phase II trial Both BL and DLBCL) HIV negative patients	Phase II Safe incorporation of rituximab Rand liposomal Doxo Included HIV + patients

1. Magrath, M, et al. J Clinic Oncol 14:925-934, 1996 2. Mead G, et al. Annals of Oncology 13: 1264-1274, 2002 (removed D15 VCR)
3. Mead G. et al. Blood 112 (6): 2248-2260, 2008 4. Evens A, et al. Annals of Oncology 24:3076-3081, 2013

Upfront treatment in Adults: Hyper-CVAD

Response (%)	HyperCVAD[1] n=26	R-HyperCVAD[2] n=57
CR	81	94
3yr-EFS	49	80
5yr-EFS		
TRM	~20 *(mortality rate)	0
3yr-OS ≤60 yrs > 60 yrs	 77 **17**	**89**
5yr-OS ≤60 yrs > 60 yrs		**74** **72** **70**
		HIV negative patients

1. Thomas DA, et al. Hyper-CVAD program in Burkitt's-type adult acute lymphoblastic leukemia. J Clin Oncol 1999;17:2461-2470
2. Thomas DA, et al. Hyper-CVAD and Rituximab for De Novo Burkitt Lymphoma/Leukemia [abstract]. Blood 2011;118:Abstract 2698

Upfront treatment in Adults: DA-EPOCH-R

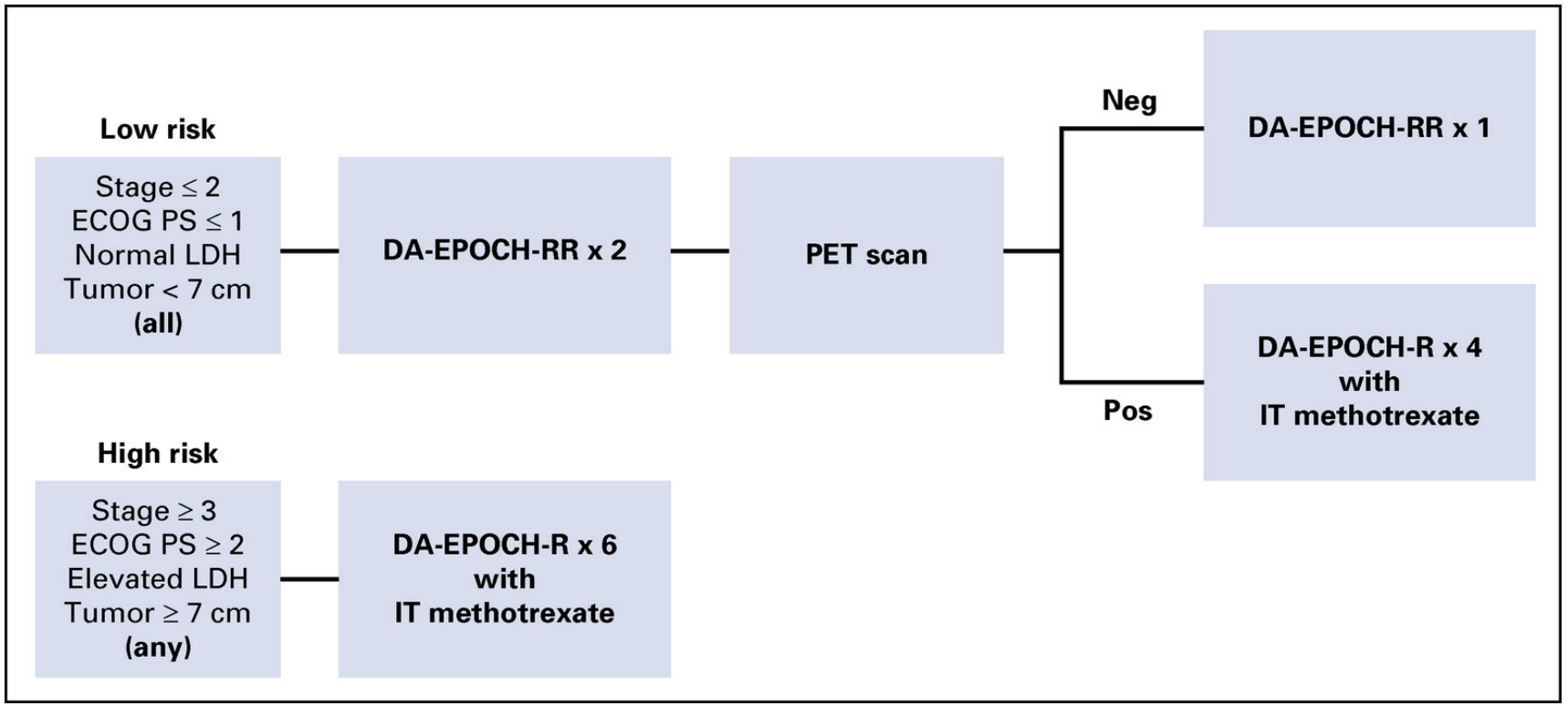


FIG 1. Treatment was risk stratified based on pretreatment characteristics. Patients were considered low risk if they had all of the following: stage I or II disease, Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1, normal serum lactate dehydrogenase (LDH) levels, and no tumor mass with a diameter ≥ 7 cm. Low-risk patients were treated with two cycles of dose-adjusted etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, and rituximab on days 1 and 5 (DA-EPOCH-RR), followed by an interim positron emission tomography (PET) scan. If the PET scan was considered negative (neg), these patients received only one additional cycle of DA-EPOCH-RR and no CNS prophylaxis. If the PET scan was considered positive (pos), patients were treated for a full six cycles of therapy and CNS prophylaxis with intrathecal (IT) methotrexate was given. Patients were considered high risk if they had any of the following: stage III or IV disease, ECOG PS of 2-4, elevated serum LDH levels, or any tumor mass ≥ 7 cm. High-risk patients were treated with six cycles of DA-EPOCH-R (rituximab on day 1 only) along with either CNS prophylaxis or active CNS therapy with IT methotrexate, as indicated.

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Upfront treatment in Adults: DA-EPOCH-R

Response	DA-EPOCH-R[1] N=19	SC-EPOCH-RR[1] N=11	DA-EPOCH-R[2] N=113
Median age	33 (40% ≥ 40yrs)	33 (40% ≥ 40yrs)	
EFS/PFS	95 (7yr PFS)	100 (6yr PFS)	86 (4yr EFS) LR: 100 HR: 82
OS	100 (7yr OS)	90(6yr OS)	87 (4yr OS) LR: 100 HR: 89
Other	HIV neg patients	**HIV pos patients**	LR and HR Included HIV pos patients

1. N Engl J Med. 2013; 369(20);2519-2529
2. J Clin Oncol. 2020; 38(22):2519-2529

Burkitt Lymphoma treatment in HIV + Patients

- CODOX-M/IVAC (modified) + IT chemotherapy
- DA-EPOCH-R + IT chemotherapy
- R-HyperCVAD + IT chemotherapy

- If CD4 <50, monitor closely for cytopenia and infections
- G-CSF for all patients
- Close collaboration with HIV specialists/Infectious Disease specialist

Jennifer Crombie,Ann LaCasce, The treatment of Burkitt lymphoma in adults, Blood, 2021.

Zaya A, et al. Haematologica volume 106(7): 1932-1942

CNS involvement in Burkitt Lymphoma

- Independently associated with:
  - HIV
  - Poor ECOG PS
  - ≥2 extra-nodal sites
  - BM involvement
  - Lower rates of CR
  - Lower OS
    - Worst OS if CNS disease at age ≥60
  - Lower PFS (regardless of tx or rituximab)

- No difference in PFS with parenchymal or leptomeningeal

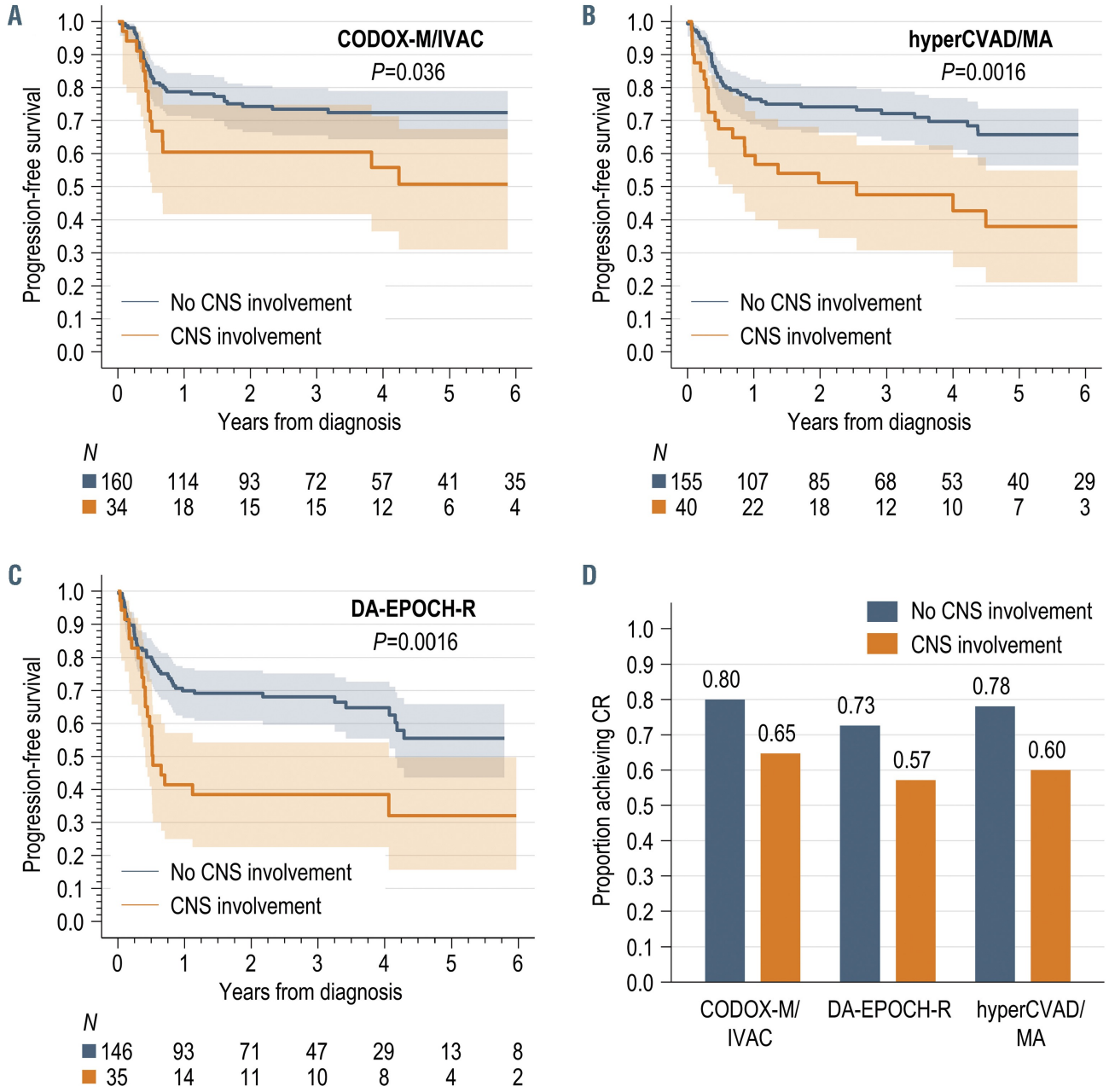
CNS recurrence

- HIV
- Poor ECOG PS
- ≥2 extra-nodal sites
- BM involvement
- Baseline CNS involvement
- Baseline testicular involvement
- HIV infection
- LDH level >3xULN

Zaya A, et al. Haematologica volume 106(7): 1932-1942

Prognostic Significance of baseline CNS involvement

- Inferior PFS with baseline CNS involvement regardless of the first-line treatment regimen given
- Lower CR rates with baseline CNS involvement across regimens



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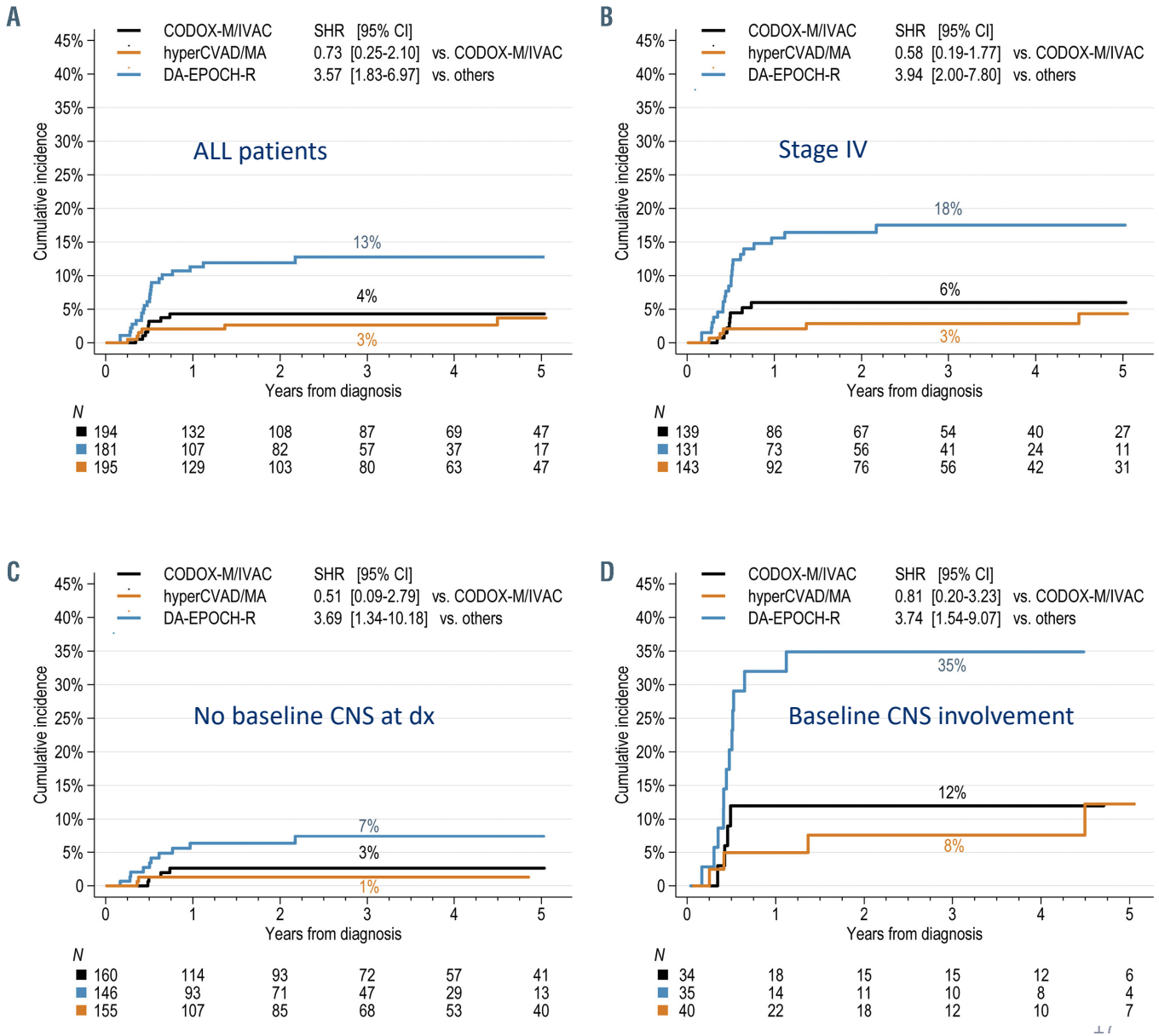
Cumulative Incidence of CNS recurrence according to first line chemotherapy regimen

ALL patients

- 3-year risk of CNS recurrence was significantly lower after CODOX-M/or hyperCVAD than after DA-EPOCH-R
- CSN recurrence more frequently after DA-EPOCH-R (40%) than after the other two regimens (16%, P<0.001)

Baseline CNS involvement

- 3- year incidence of CNS recurrence reached 35% with DA-EPOCH-R
- Risk did not differ significantly between patients treated with CODOX-M/IVAC or hyperCVAD/MA within any subset.



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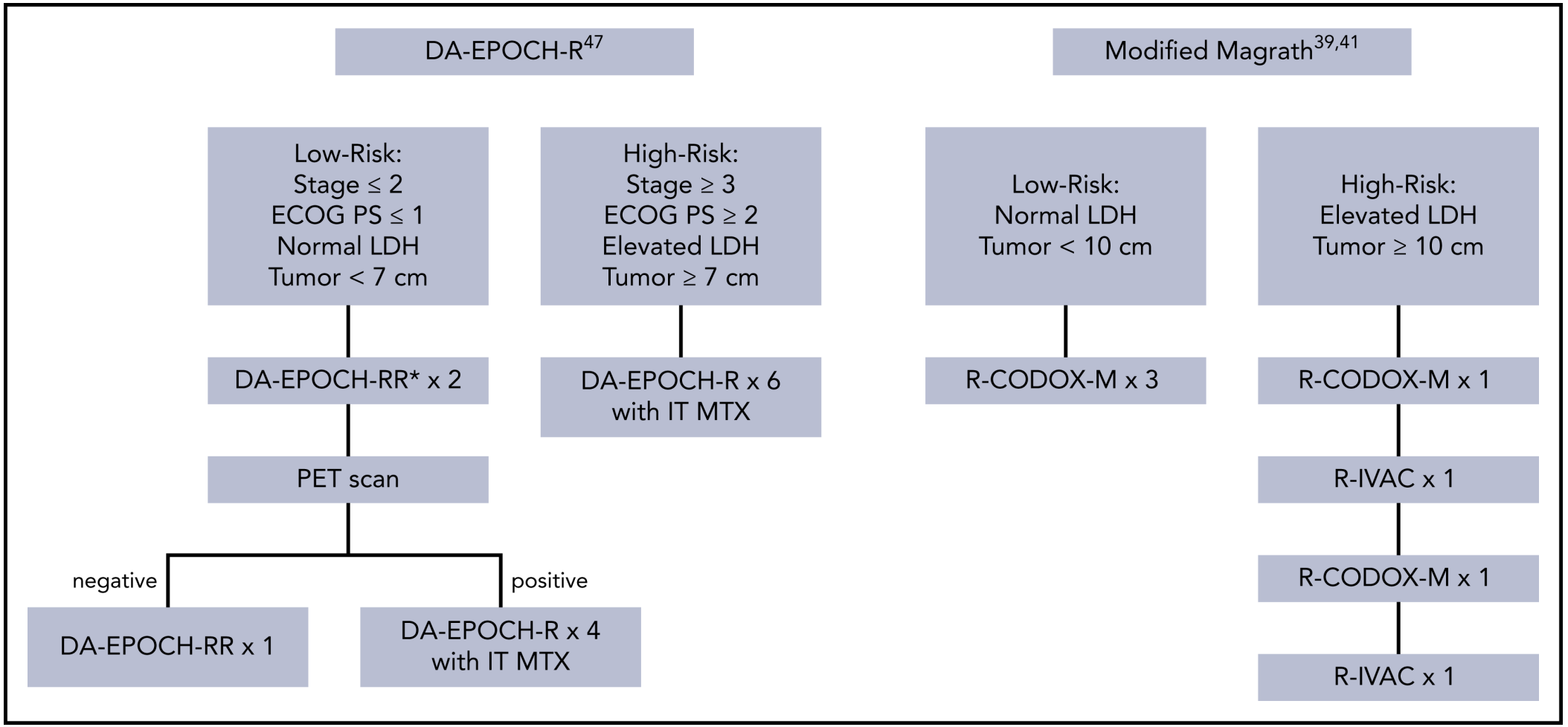
What is the best regimen for Baseline CNS Burkitt Lymphoma

- Proper work up for CNS involvement is essential at diagnosis
- Adherence to PPX regimen is important
- Start with a portion of treatment that contains CNS penetrating drugs
- If parenchymal disease: should avoid DA-EPOCH-R
- CNS recurrence higher in DA-EPOCH regardless of CNS involvement at time of presentation
  - Could be due to IT adherence
- CNS involvement was prognostically unfavorable regardless of the use of first-line rituximab or any specific regimen, including those that contained HDMTX.

Zaya A, et al. Haematologica volume 106(7): 1932-1942

The treatment of Burkitt lymphoma in adults



Jennifer Crombie,Ann LaCasce, The treatment of Burkitt lymphoma in adults, Blood, 2021, Figure 3.

Relapse/Refractory Burkitt's Lymphoma

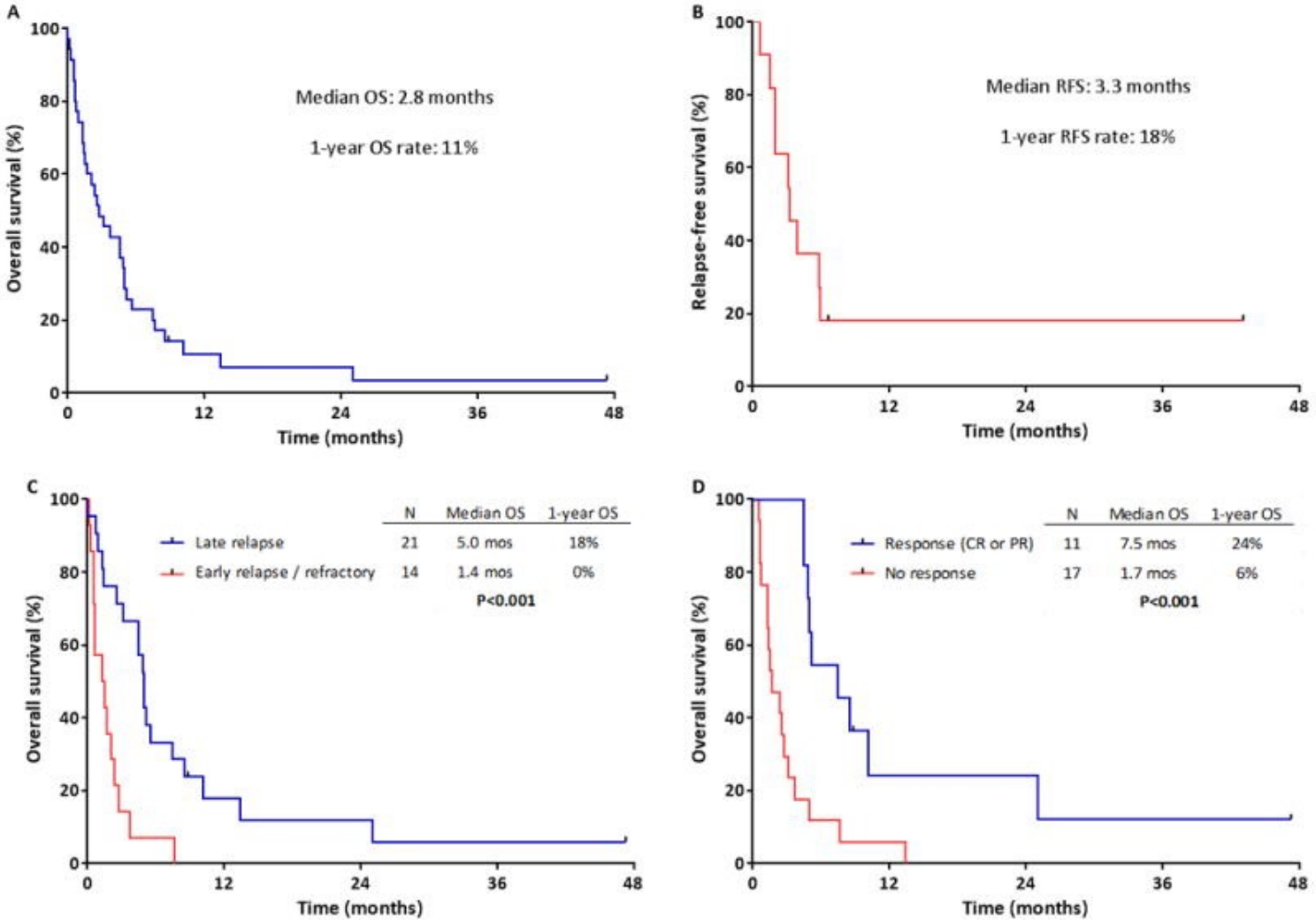
Relapse/Refractory Disease

- This study looked at outcomes in patients with disease relapse
- ALL patients treated with HyperCVAD like regimen in 1 institutions

- OS: 2.8months
- ORR: 39%

- In pediatric studies of relapsed/refractory BL, long-term survival of approximately 30-35% has been achieved with salvage chemotherapy with subsequent SCT

- Unfortunately, no standard regimens



Am J Hematol. 2017 Jun; 92(6): E114–E1

Relapse/Refractory Disease

- DA-EPOCH-R
- IVAC combined with rituximab (R-IVAC)
- R-GDP (gemcitabine, dexamethasone, cisplatin, combined with rituximab)
- R-ICE (ifosfamide, carboplatin, etoposide, combined with rituximab)
- High-dose cytarabine

- AutoSCT after salvage chemotherapy
- BIANCA trial

- Limited case reports/series and small studies in
    - Nivolumab
    - Blinatumomab
    - Polatuzumab

CAR-T in R/R Burkitt

Cancer Immunology, Immunotherapy (2021) 70:2379–2384
https://doi.org/10.1007/s00262-021-02850-6

RESEARCH REPORT

Check for updates

CAR19/22 T cell therapy in adult refractory Burkitt's lymphoma

Xiaoxi Zhou[1] · Tong Ge[1] · Tongjuan Li[1] · Liang Huang[1] · Yang Cao[1] · Yi Xiao[1] · Miao Zhen[1] · Liting Chen[1] · Jianfeng Zhou[1]

- Prospective
- CAR19/22 T cell therapy

- 21-34 yrs old
- IPI ≥3 in 4 patients
- IPI 1 in 2 patients
- All had HR genetic abnormalities
- Median: 3.5 lines of therapy

Response

- 1 CR
- 2 PR
- 1 SD
  - For 2 months, progressed and died 4.5 months later
- 2 patents failed to respond to CAR-T
- 1 death after 1 month

- Out of the 4 responses
  - 1 CR received alloSCT in remission
  - 3 pts enrolled an another clinical trial
    - autoSCT → CAR22/19T cells
    - 1 response
    - 2 no response

CRS

- No > grade 3 CRS or
- Neurotoxic events were observed in the patient cohort
- 5 pts grade 1 CRS

Zhou, X.,*Cancer Immunol Immunother* **70**, 2379–2384 (2021).

Blinatumomab

Case	Best Response to Blinatumomab	Remission Status at End of Blinatumomab	Relapse/Progress during/after Blinatumomab	Duration until Relapse/Progression*	Death	Duration until Death *	Last Follow Up *
1	CR	PD	Yes	5 m	Due to progression	6 m	6 m
2	CR	CR	No	-	No	-	32 m
3	CR	CR	Yes	13 m	Due to progression	16 m	16 m
4	PD	PD	Yes	2 m	Due to progression	5 m	5 m
5	PD	PD	Yes	5 d	Due to progression	11 d	11 d
6	PR	PR	Yes	51 d	Due to acute liver failure GvHD-related	6 m	6 m
7	PD	PD	Yes	7 d	Due to progression	14 d	14 d
8	PR	PD	Yes	3 m	Due to progression	10 m	10 m
9	PD	PD	Yes	11 d	Due to progression	46 d	46 d

*: since initiation of blinatumomab, CR: complete remission, PR: partial remission, PD: progressive disease, d: days, m: months, GvHD: graft-versus-host disease.

- Multicenter retrospective trial looking at efficacy and safety of Blinatumomab in R/R Burkitt
- Total of 9 patients
- ≥18 yrs old
- R/R after 1 line of therapy

Zhou, X.,*Cancer Immunol Immunother* **70**, 2379–2384 (2021).