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MEDICINE & BIOLOGICAL SCIENCES

Prognostication and treatment of Burkitt lymphoma in the modern era

Adam J Olszewski

Brown University / Rhode Island Hospital

19TH ULTMANN

adamo@brown.edu

@ lymphomatic

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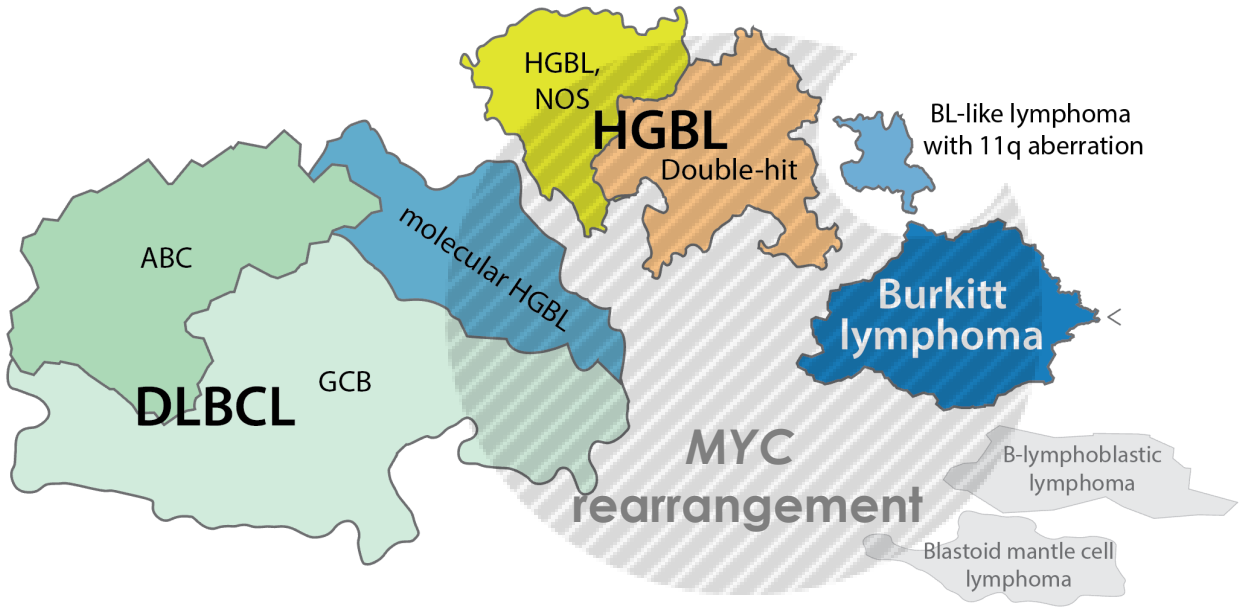
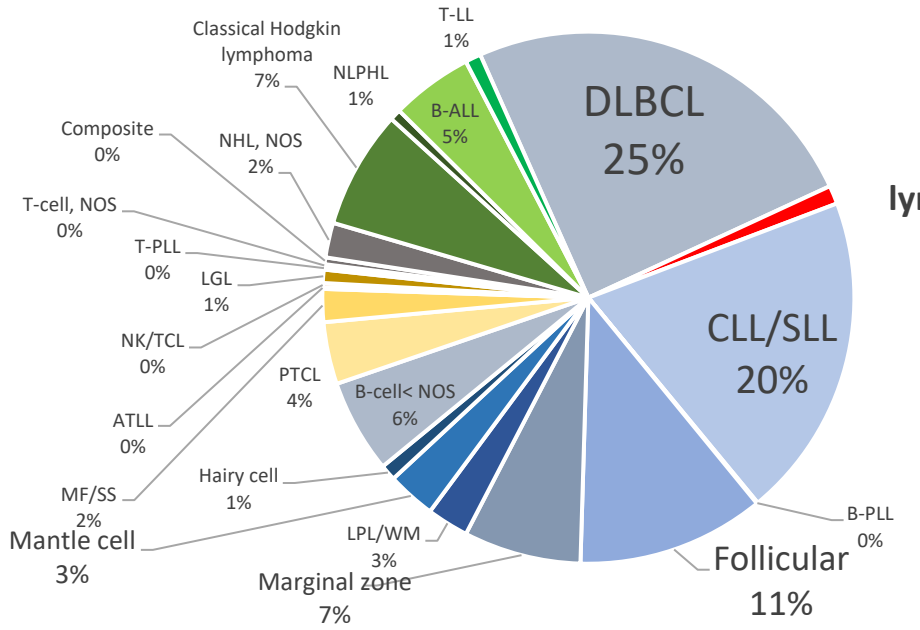
Disclosures

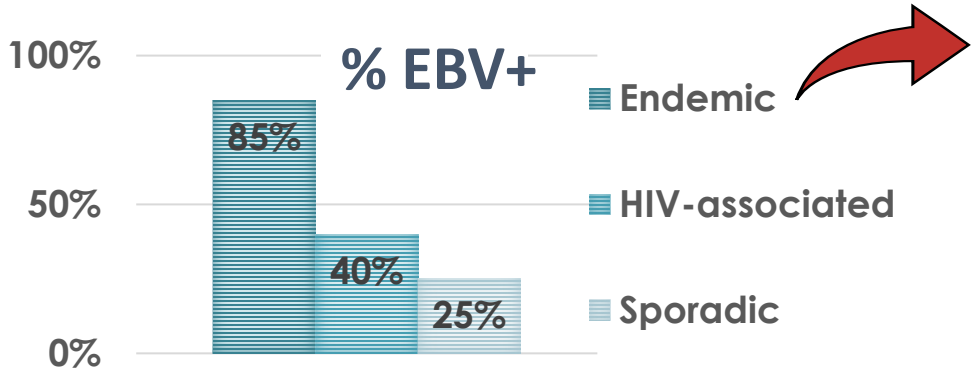
- Research funding: Acrotech, Adaptive Biotechnologies, Celldex, Genentech/Roche, Genmab, Precision Biosciences, TG Therapeutics,
- Consulting: Blue Cross and Blue Shield of Rhode Island, Genmab, Schrodinger, TG Therapeutics

Burkitt lymphoma

- 1,250 cases per year in the US
- 11,285 globally





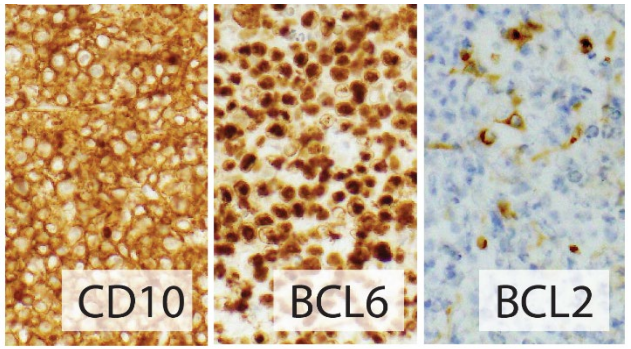


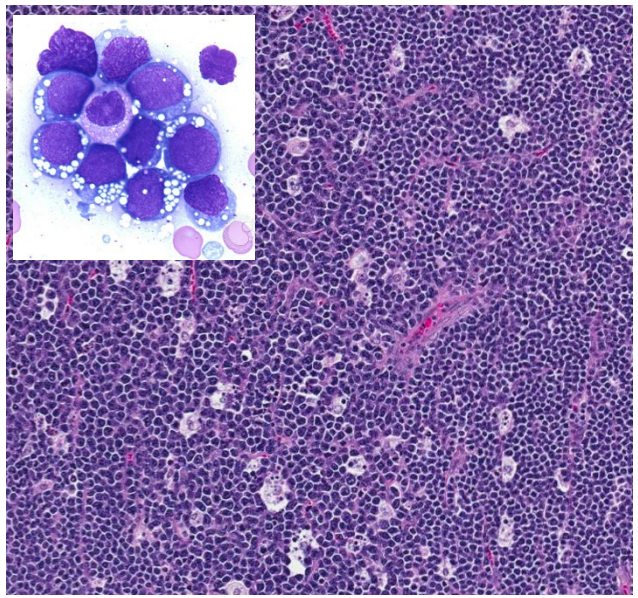
Swerdlow SH, World Health Organization, IARC; 2017

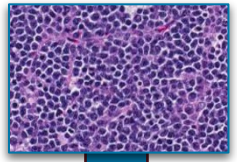
Molyneux et al., Lancet. 2012

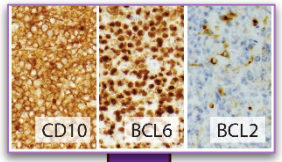
SEER data, 2015-2018

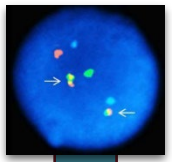
Diagnosis





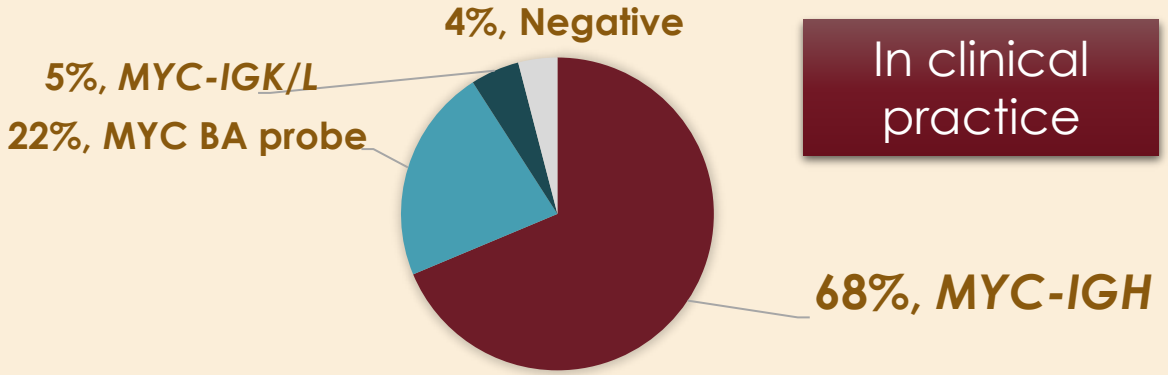




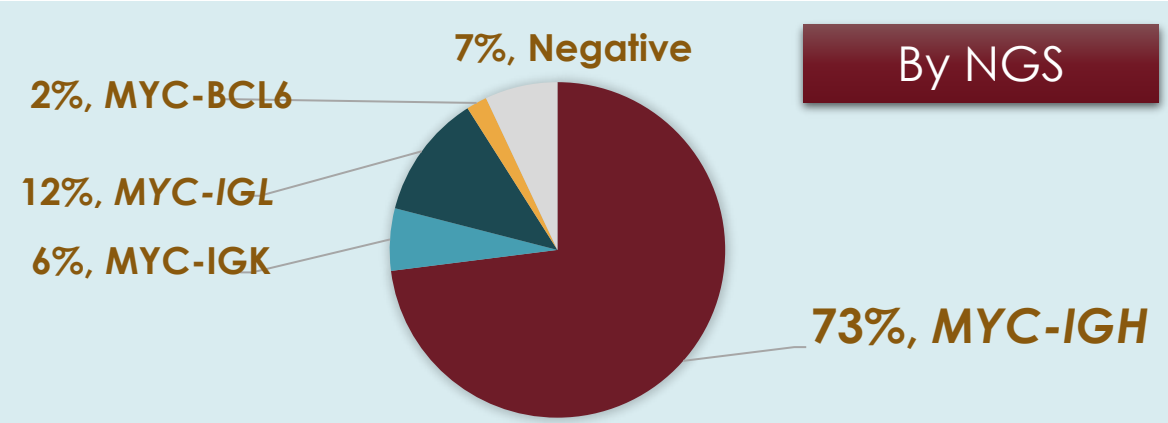


Disease	Cyto-morphology	IHC			FISH		Karyo-type
		CD10	BCL6	BCL2	*MYC*	*BCL2/ BCL6*	
Burkitt lymphoma	**Small / int. cells** starry sky	+	+	-	+	-	**Simple**
HGBCL with *MYC* and *BCL2* and/or *BCL6* rearrangements	Large / medium cells starry sky	75-90%	typically +	+ if rearranged	+	+	May be **complex**
HGBCL, NOS	More pleomorphic starry sky	+ > -	+ > -	+ > -	+ 40%	+/-	May be **complex**
DLBCL with MYC rearrangement	Large cells	+/-	+/-	+/-	+	-	May be **complex**
Lymphoblastic lymphoma	Large lymphoblasts **TdT+**	+/-	+/-	+/-	rare	-	Variable

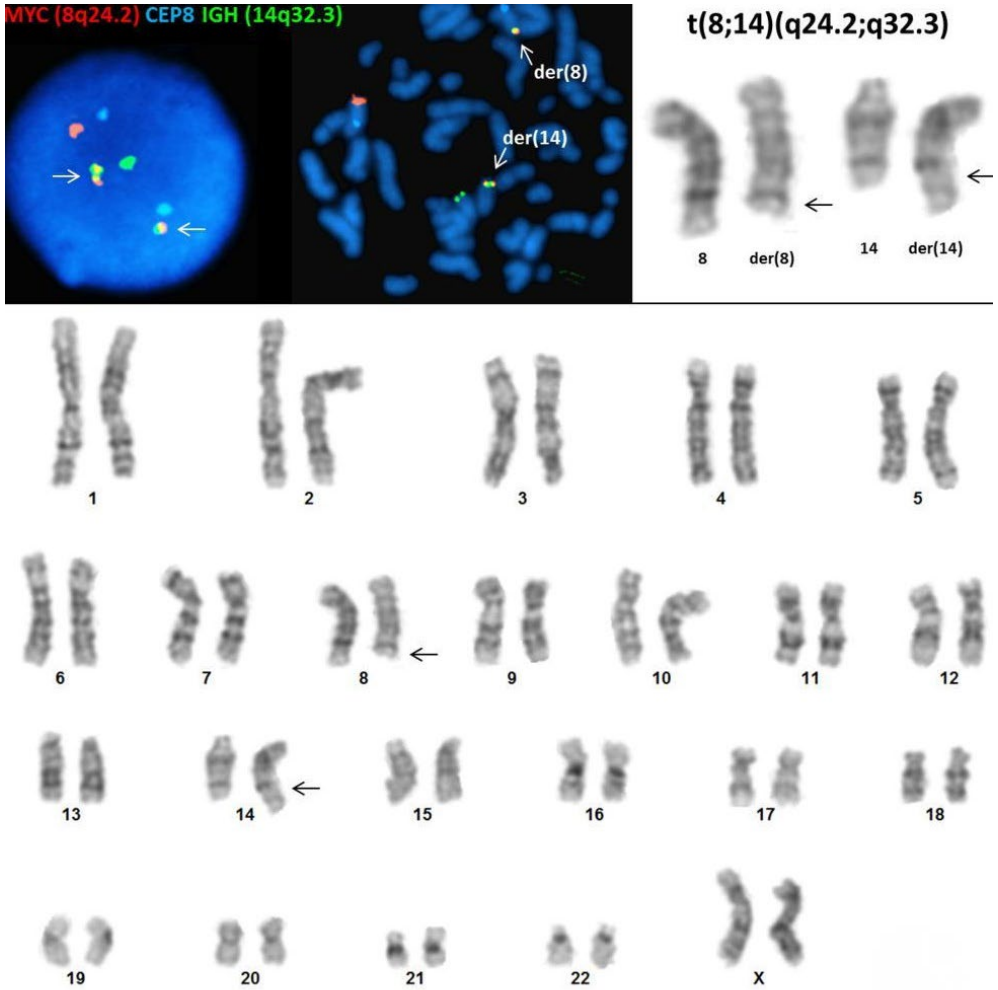
MYC rearrangement



In clinical practice

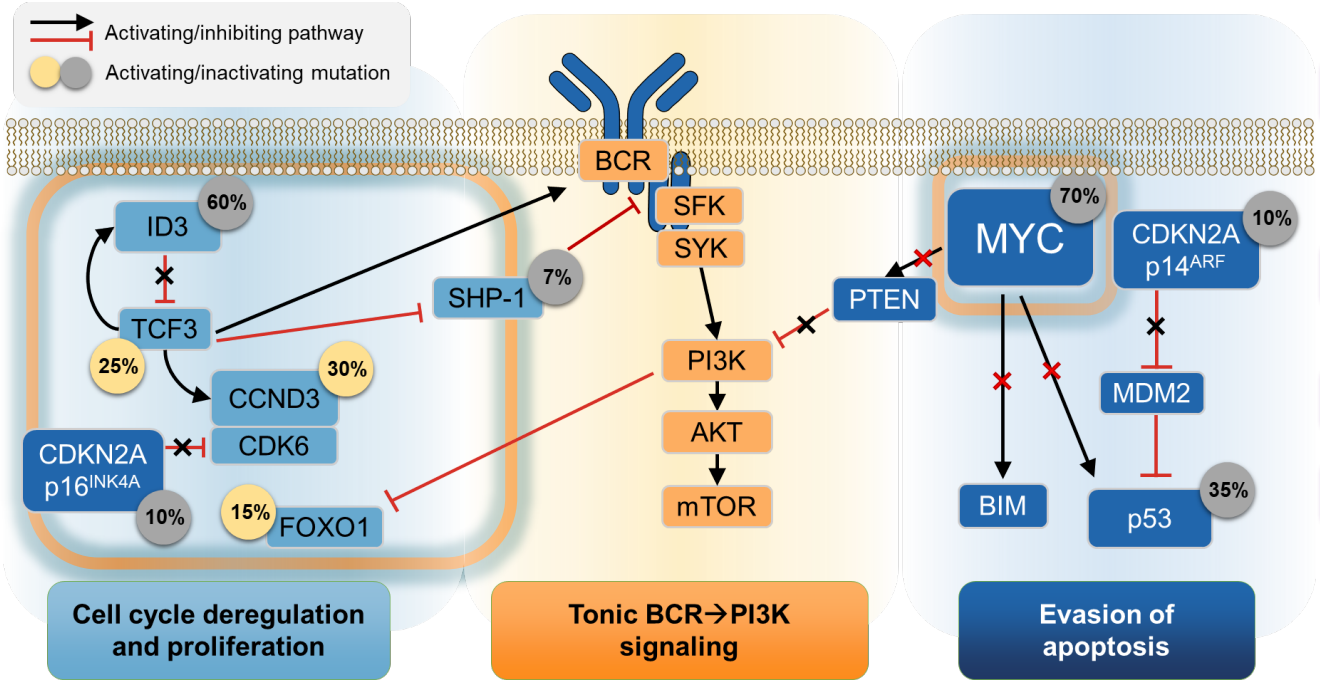


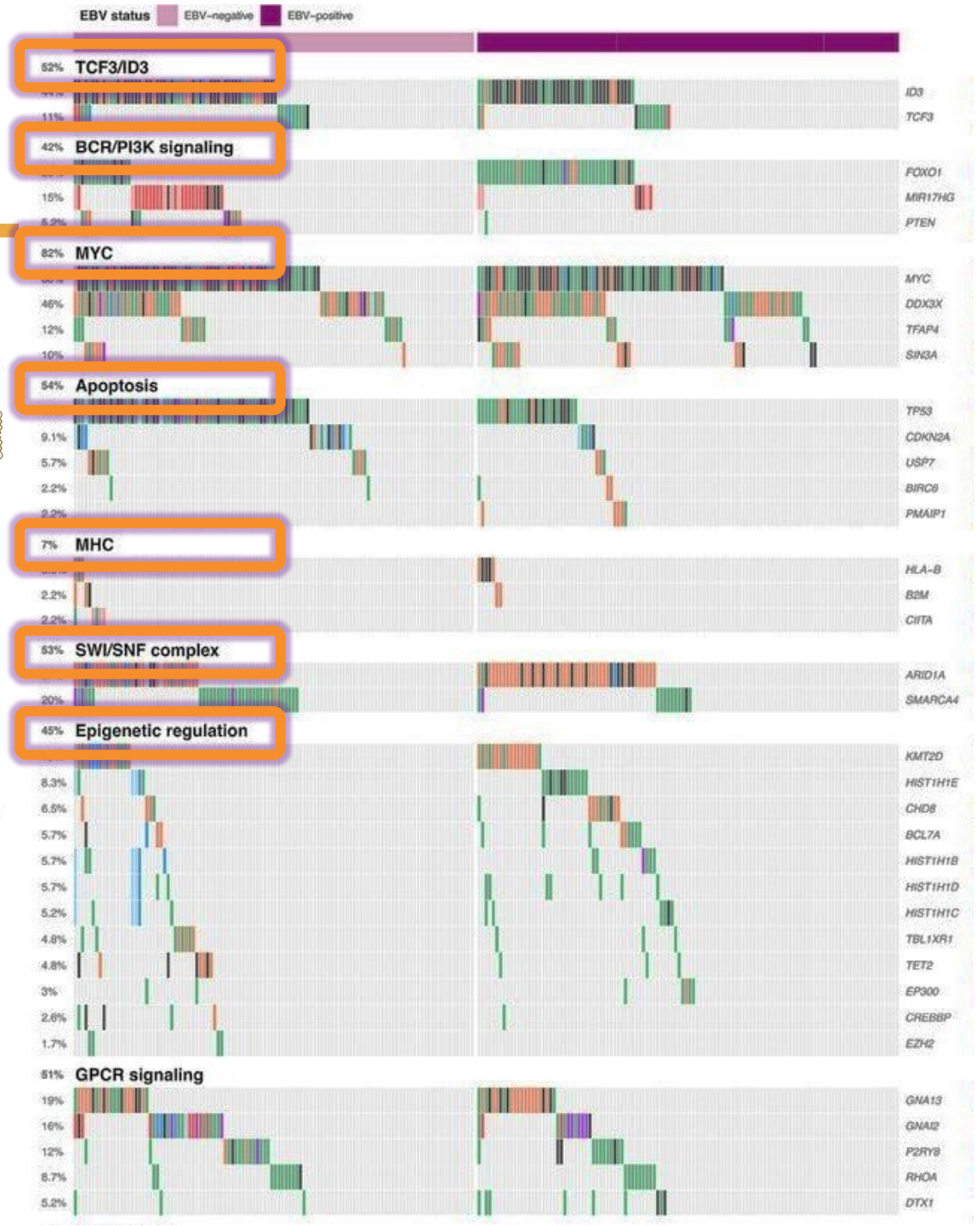
By NGS



Evens AM, et al. *Blood* 2021
Thomas et al. ASH 2021/ medRxiv

Molecular features





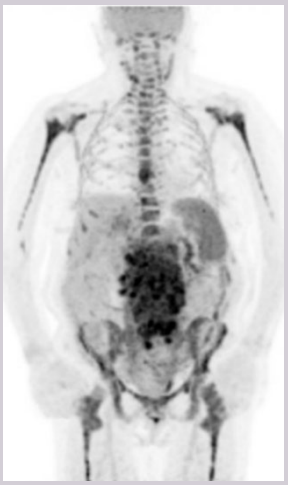
Schmitz R, et al., Nature. 2012
Sander S, et al., Cancer Cell. 2012
Zayac & Olszewski. Leuk Lymphoma 2020
Thomas et al. ASH 2021 / medRxiv

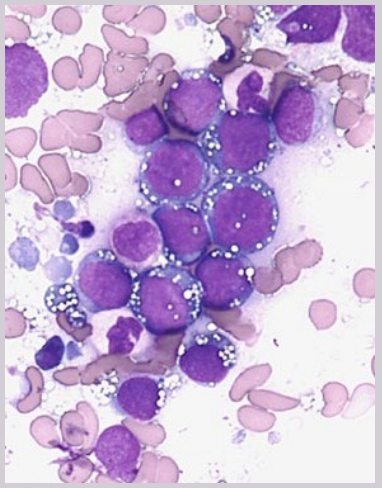
Clinical presentation

Localized: 10%

Single mass – typically cecum/appendix
Sometimes resected
Normal LDH

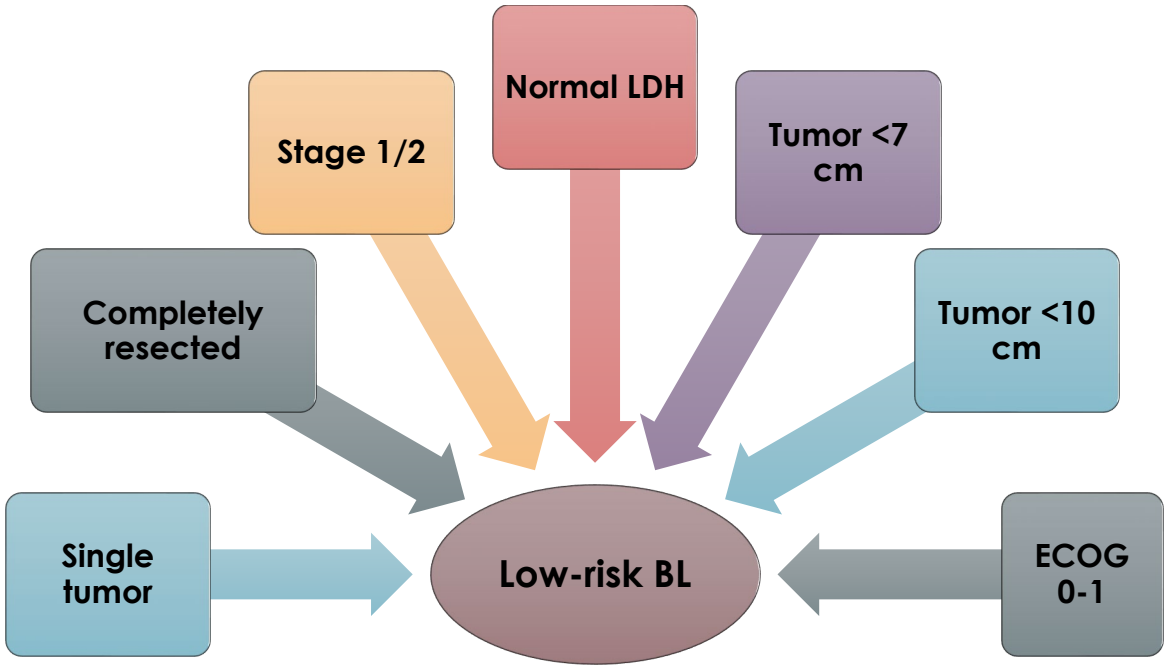
Disseminated: 90%





Widely disseminated disease
Extranodal, leukemic

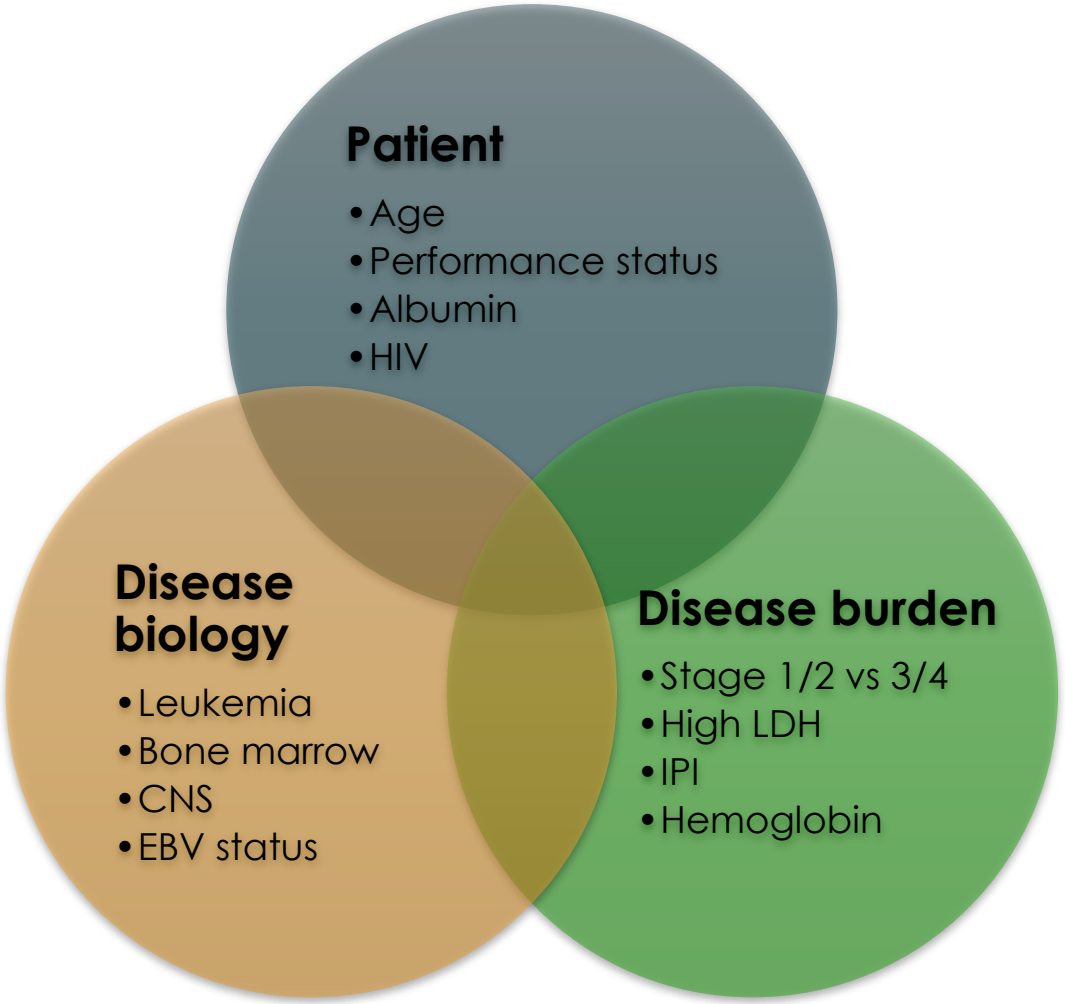
Prognosis: low-risk BL

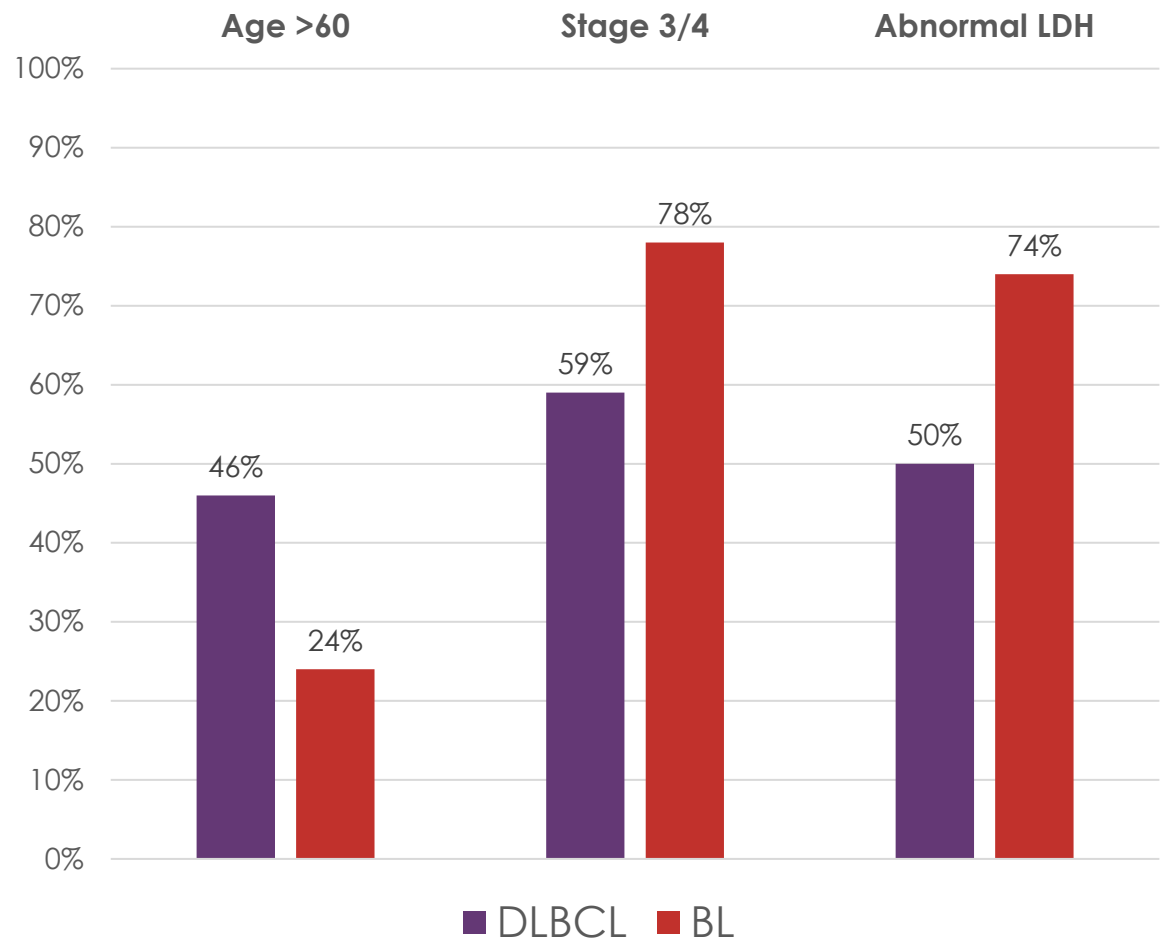


Study	Low-risk BL	Low risk %
Magrath et al., 1996	▪ Single extra-abdominal mass or resected abdominal disease ▪ LDH <ULN	17%
Mead et al., 2002	▪ Stage I or II ▪ No tumor ≥10 cm ▪ PS 0 or 1 ▪ LDH <ULN	23%
Wang et al., 2003	▪ Single extra-abdominal mass or resected abdominal disease ▪ LDH <ULN	37%
LaCasce et al., 2004	▪ Single site of disease <10 cm ▪ LDH <ULN	21%
Evens et al., 2006	▪ Stage I or II ▪ Tumor <10 cm ▪ PS 0 or 1 ▪ LDH <ULN	20%
Ribera et al., 2013	▪ "Non-bulky" stage I/II	22%
Dunleavy et al., 2013	▪ Resected stage I or abdominal st. II disease	17%
Ribrag et al., 2016	▪ B: No bone marrow or CNS involvement	48%
Noy et al., 2015	▪ Stage I with single tumor <10 cm ▪ or resected intra-abdominal disease ▪ LDH <ULN	6%
Roschewski et al., 2020	▪ Stage I or II ▪ Tumor <7 cm ▪ PS 0 or 1 ▪ LDH <ULN	13%

Olszewski AJ, et al. J Clin Oncol 2021

Multiple overlapping prognostic factors

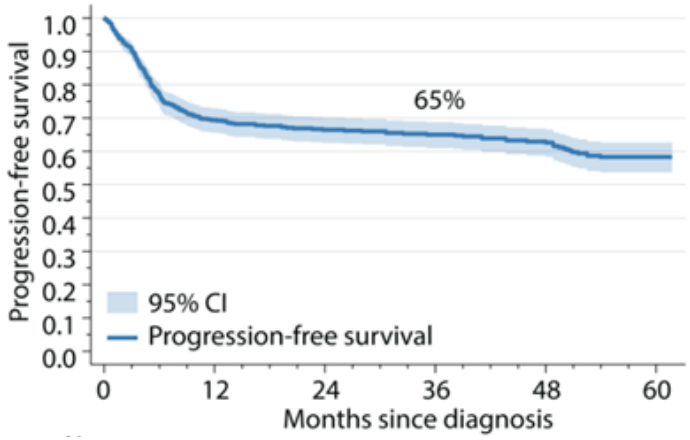


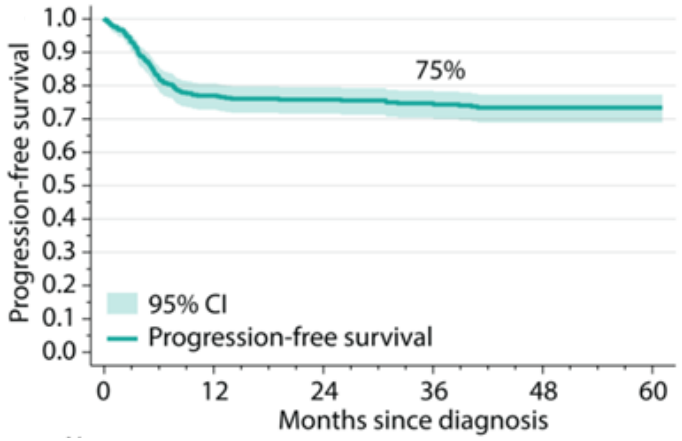


Evens AM, et al. *Blood* 2021

Burkitt lymphoma International Prognostic index

Variable	Derivation US	Validation International
N	633	457
Age, median (IQR)	**47** (33-59)	**46** (34-59)
Age ≥40, %	**63%**	**64%**
Age ≥60, %	**23%**	**24%**
Male sex, %	**76%**	**77%**
HIV+, %	**22%**	**23%**
PS ECOG ≥2, %	22%	35%
Stage 3/4, %	**78%**	**79%**
>1 extranodal site, %	43%	54%
CNS involvement, %	**19%**	**10%**
LDH > ULN, %	**74%**	**77%**
LDH >3x ULN, %	42%	46%
Stage 1 or 2 with LDH ≤ULN, %	**8%**	**13%**

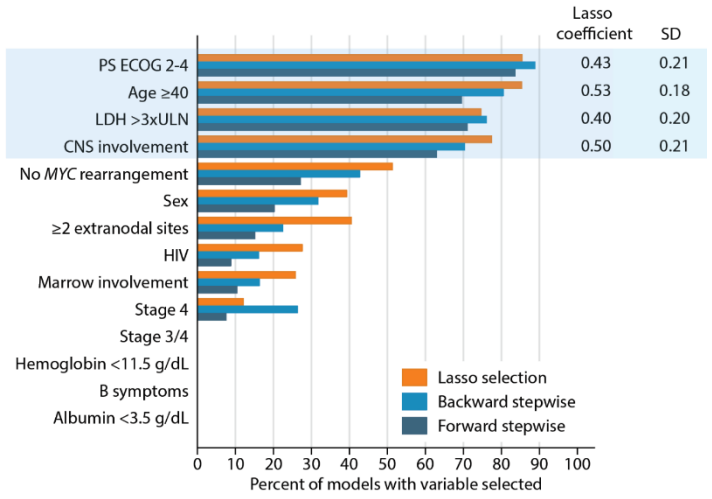




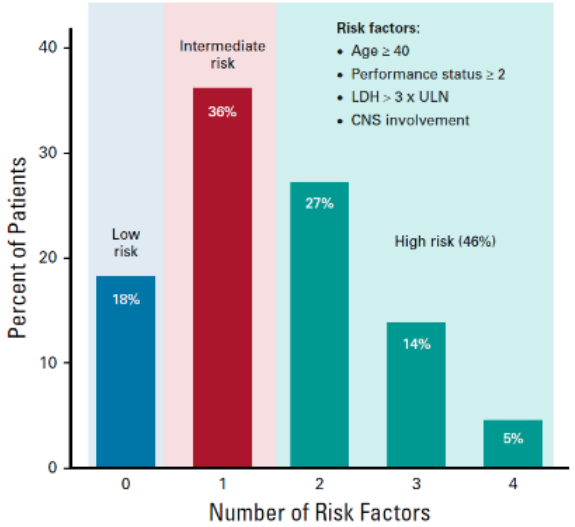
Olszewski AJ, et al. J Clin Oncol 2021

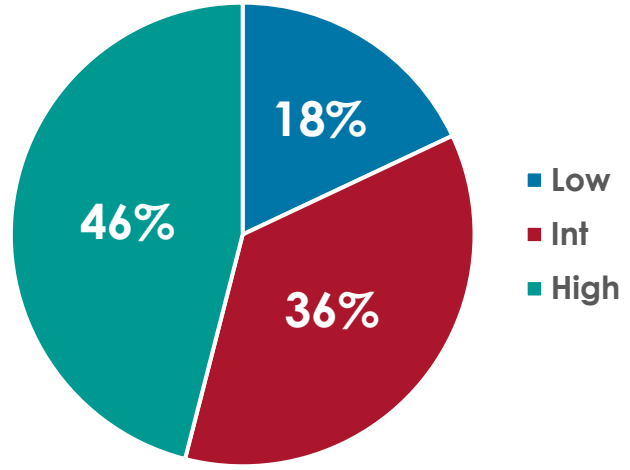
BL-IPI

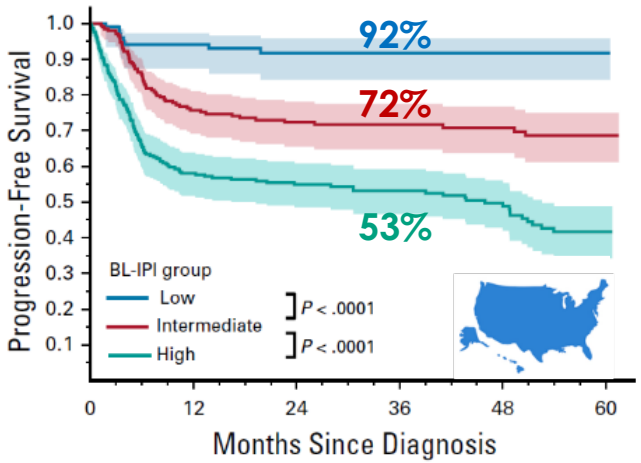
- Age ≥40
- Poor performance status
- LDH > 3x ULN
- CNS involvement

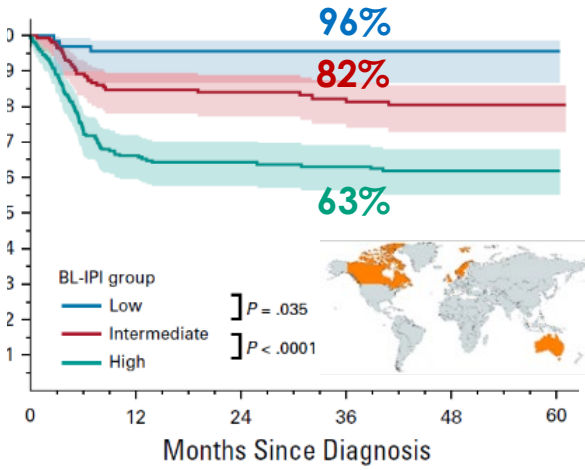


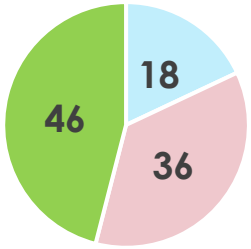
Olszewski AJ, et al. J Clin Oncol 2021







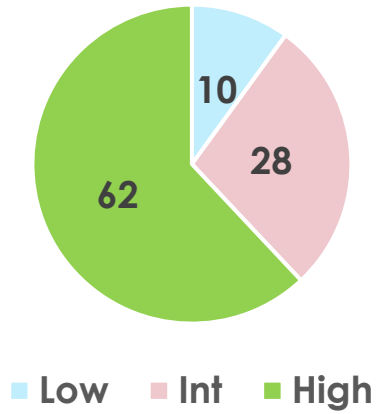


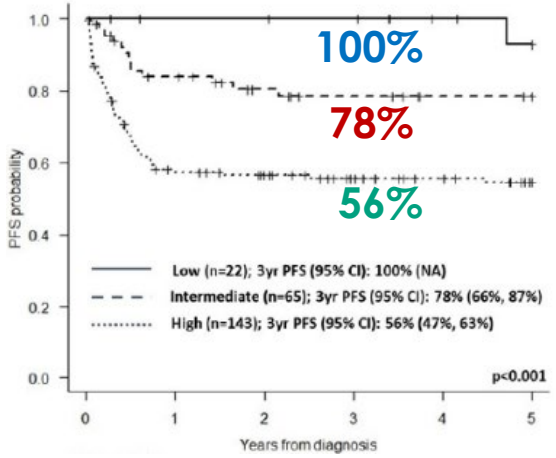


BL-IPI: validation in clinical trials

- **BURKIMAB** n=277

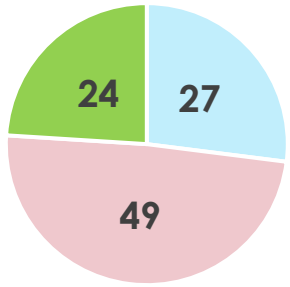
BLIPI	%	PFS	OS
Low	10%	**100%**	100%
Intermediate	28%	**78%**	82%
High	62%	**56%**	56%

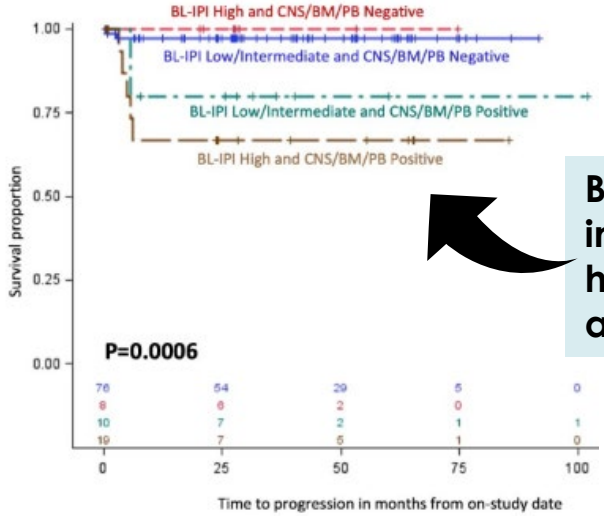




- **DA-EPOCH-R** n=113

BLIPI	%	EFS	OS
Low	27%	**84%**	*NR*
Intermediate	49%	**94%**	*NR*
High	24%	**67%**	*NR*





Blood and marrow involvement are highly prognostic after DA-EPOCH-R

Ribera et al., Leuk Lym 2022; Lakhotia et al., ASH 2021

Historical approach to treatment of Burkitt lymphoma

One shot: either cure or death

Start immediately: deal with tumor lysis

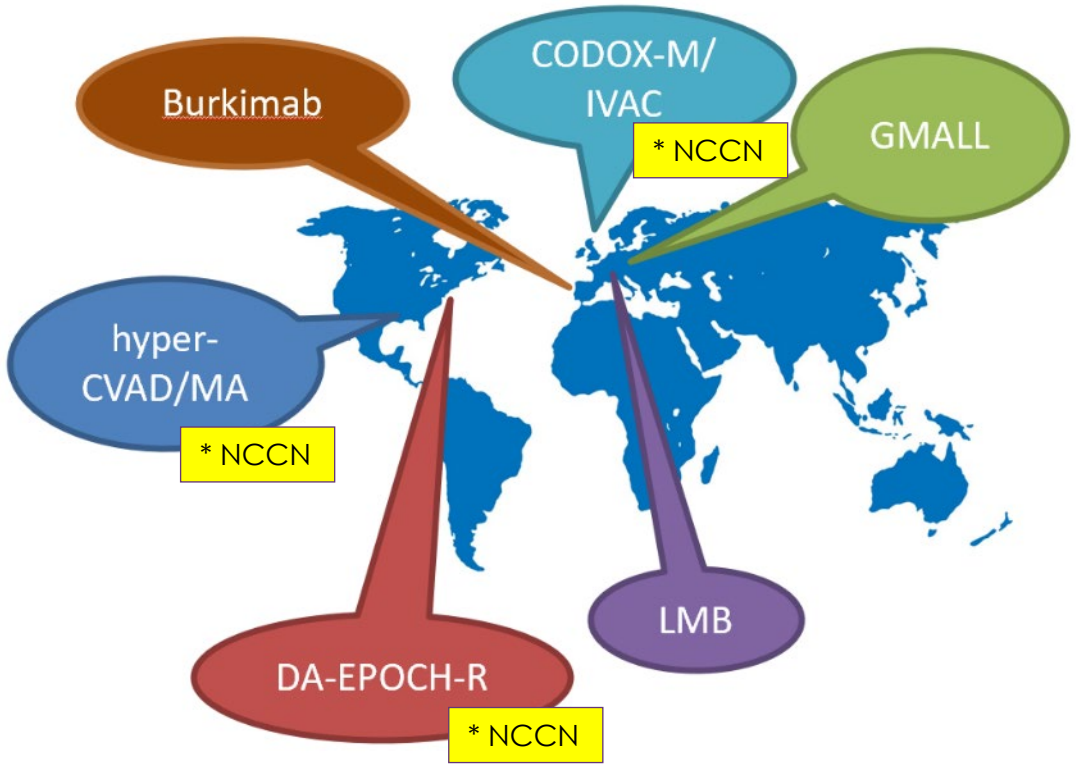
Intensive “short-course” chemotherapy

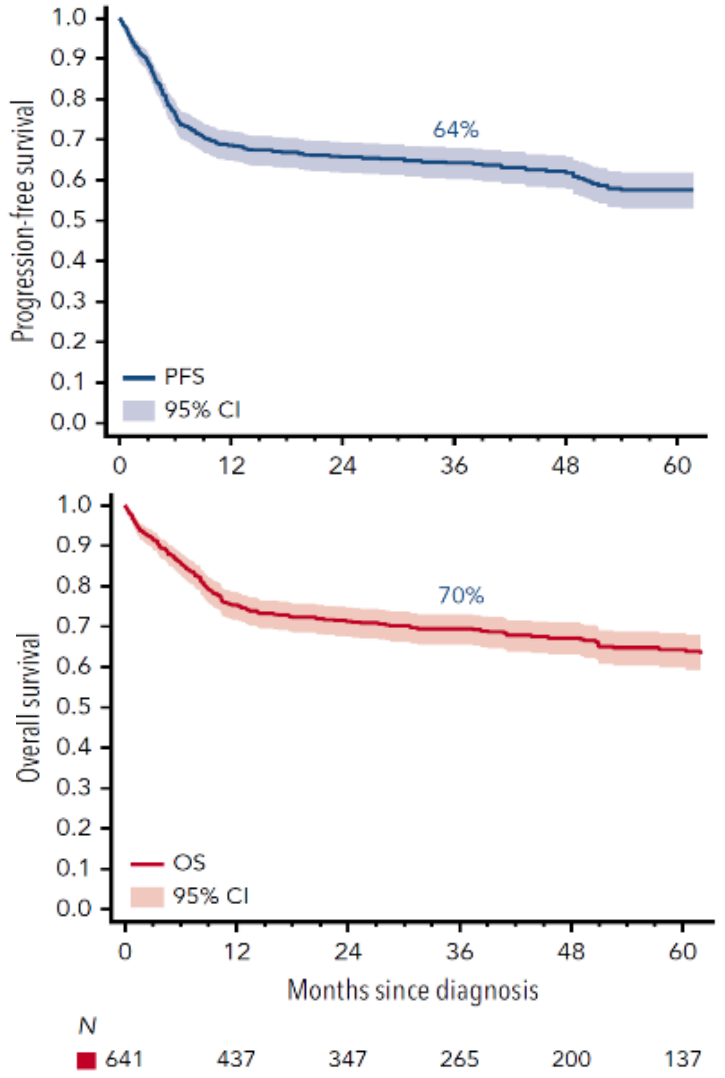
Short duration: no maintenance

Prevent CNS recurrence

Prevent death from sepsis

Treatment: short, intensive chemotherapy

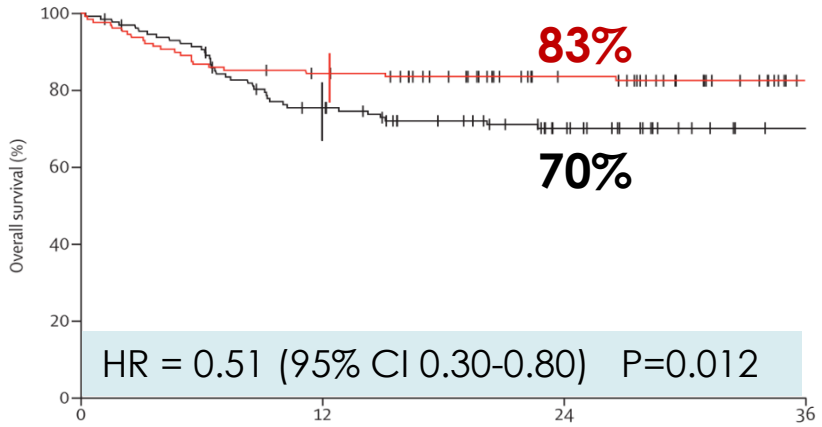


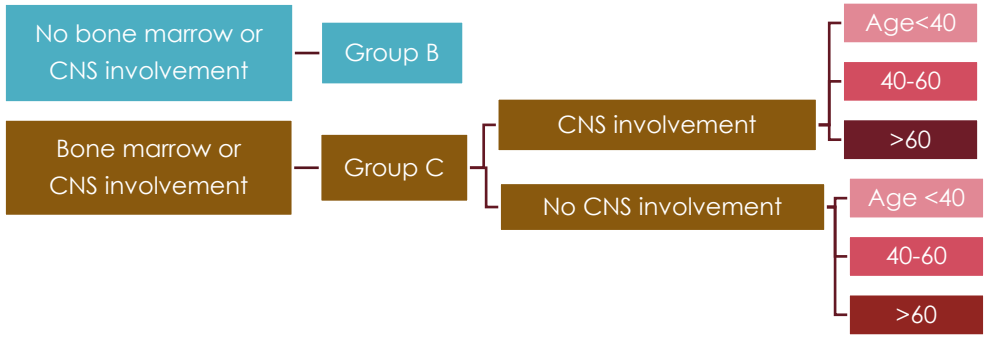


Evens AM, et al. Blood 2021

Largest clinical trials in Burkitt lymphoma

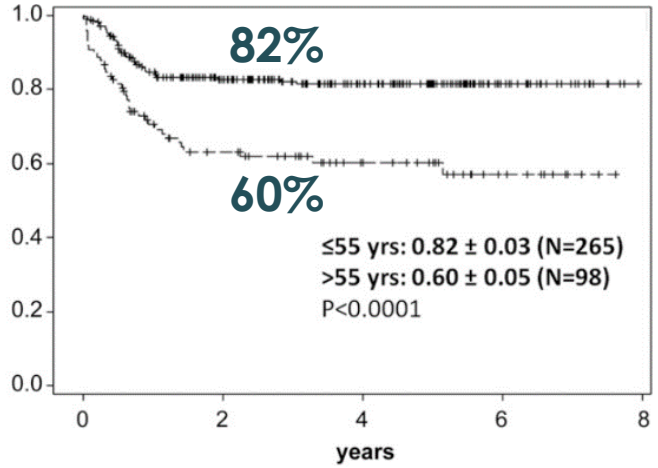
- Phase 3: LMB ± rituximab
- N=258





Ribrag V, et al. Lancet 2016

- Phase 2 GMALL regimen
- N= 363

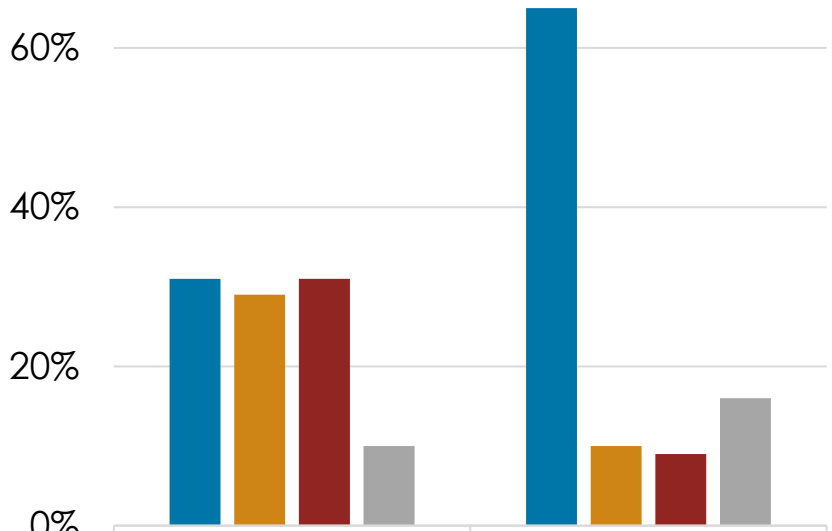


Risk factors for OS:
- Age >55 years
- LDH > 250
- Bone marrow involvement
- Male sex

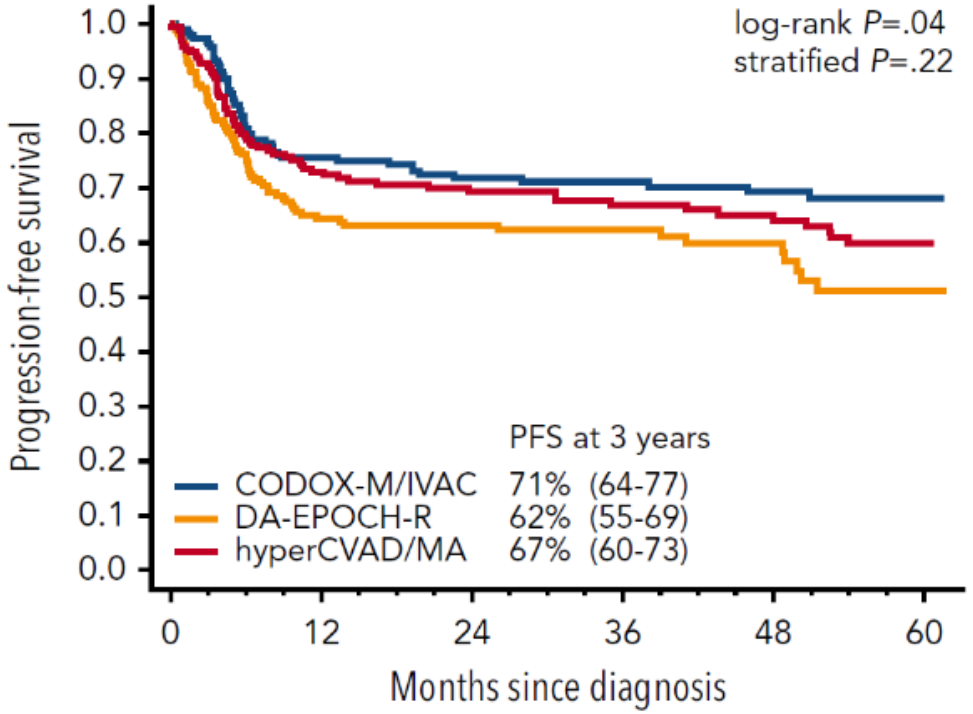
Hoelzer D, et al. Blood 2014

Treatment in the real world

First-line therapy

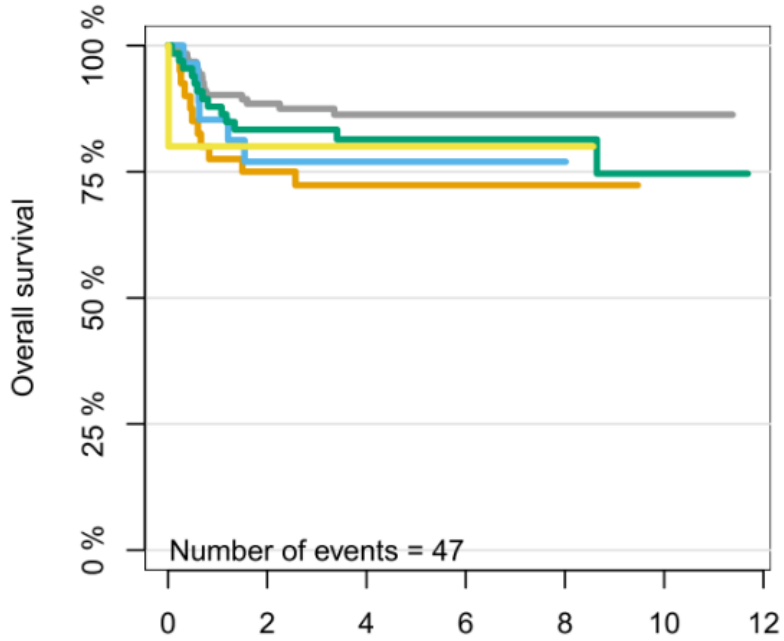


	US	International
CODOX-M/IVAC	31%	65%
DA-EPOCH-R	29%	10%
hCVAD/MA	31%	9%
Other	10%	16%

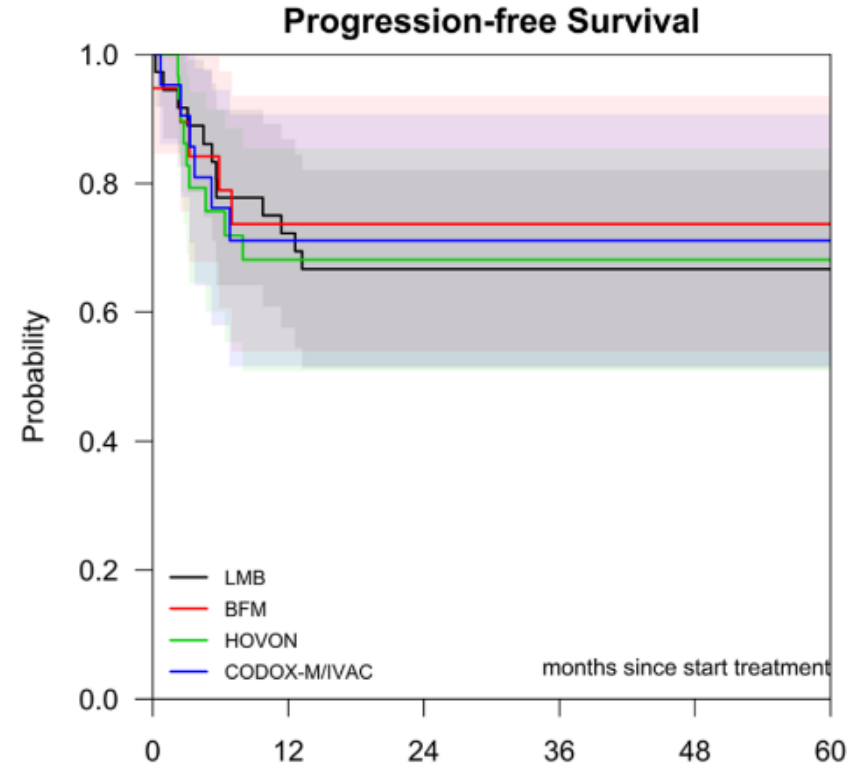


Evens AM, et al. Blood 2021

Other retrospective studies



CODOX−M/IVAC	124	96	59	33	17	5	0
Hyper−CVAD	41	29	20	7	2	0	0
DA−EPOCH	28	17	10	3	1	0	0
BFM/GMALL	66	53	38	19	14	7	0
Other	5	4	3	2	1	0	0



treat						
LMB	36	26	20	16	14	12
BFM	19	14	14	12	8	5
HOVON	29	17	12	11	7	7
CODOX-M/IVAC	21	14	10	8	4	2

Jakobsen LH, et al. Br J Haematol 2020; Oosten LEM, et al. Ann Hematol 2018

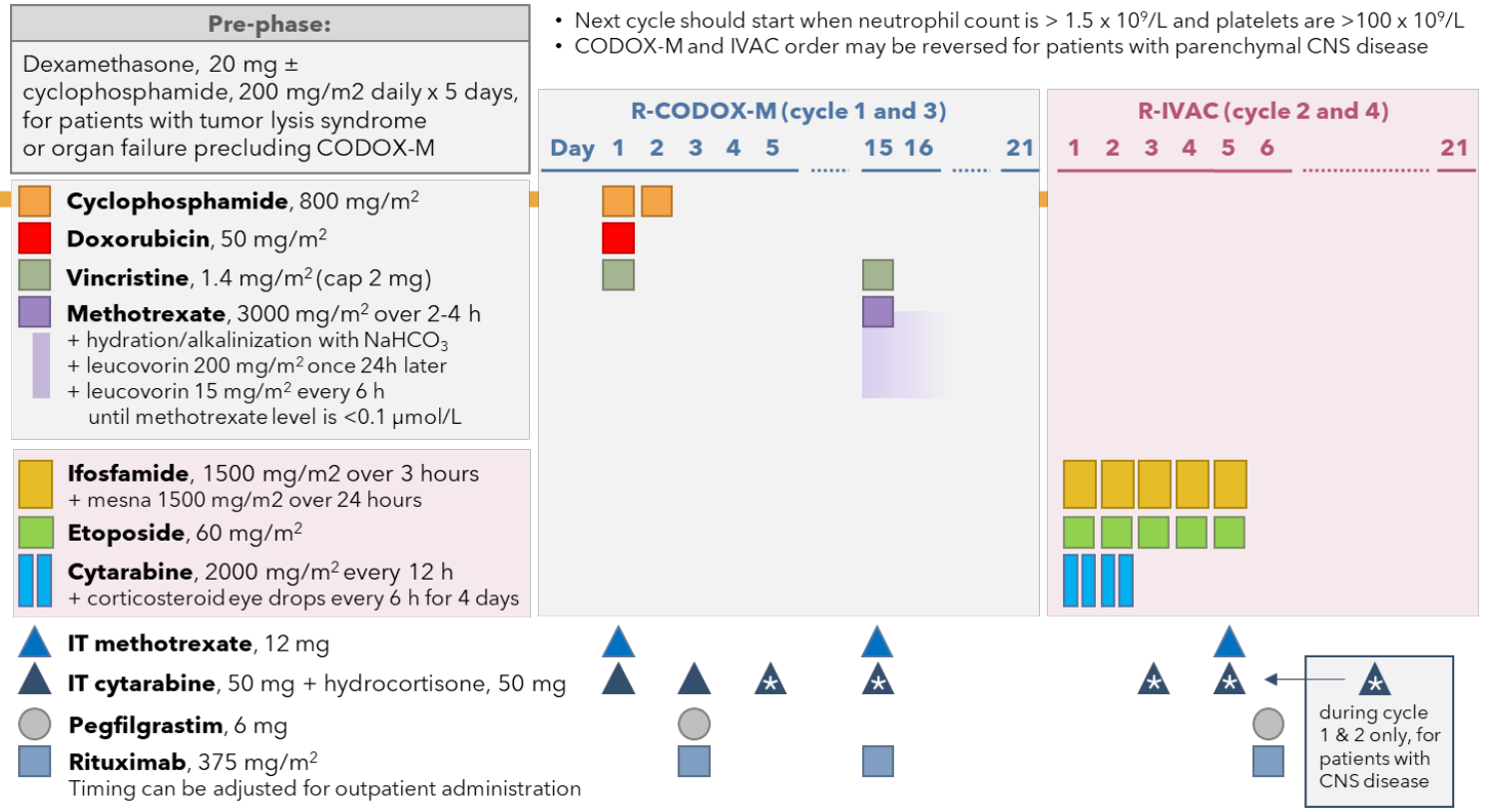
R-CODOX-M/IVAC

- Dose intense – inpatient
- Short: **3 months**
  - Low risk → **3 x CODOX**
  - High risk → **4 cycles**

- Excellent CNS control
  - Early high-dose methotrexate
  - IVAC – CNS penetrant

- Best delivered in academic setting
- OK for HIV+
- Not for age > 50-55 ?

Jacobson & LaCasce, Blood 2014



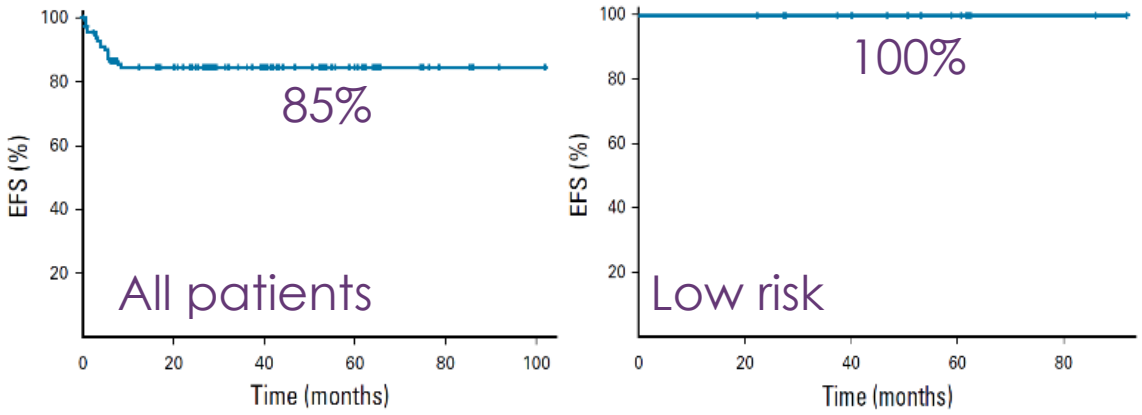
Regimen	Age	CR	EFS/PFS at 2 years	OS at 2 years	TRM
Magrath, Blood 1984	16 [2-35]	95%	**92%**	NR	3%
Mead, Blood 2008	37 [17-76]	77%	**65%**	73%	8%
AMC-048, Noy. Blood 2015	42 [19-55]	NR	**69%**	69%	3%
Lacasce, Leuk Lym 2004	47 [18-65]	90%	**64%**	71%	0%
Evens, Blood 2020	44 [23-70]	80%	**80%**	84%	5%

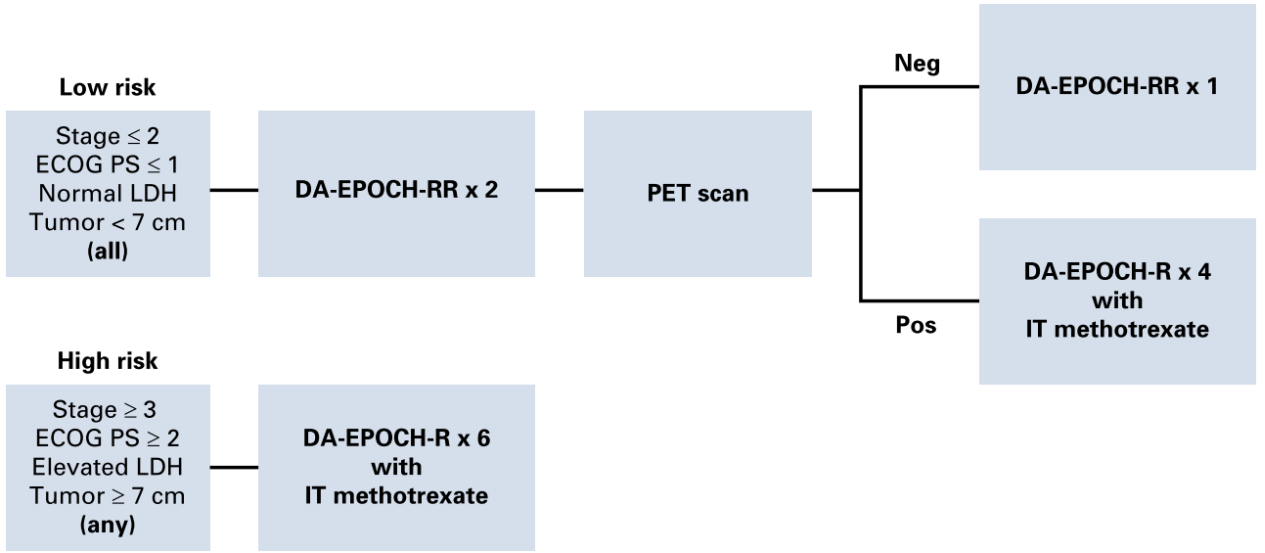
DA-EPOCH-R: lower intensity, high cure rate

- OK up to age 85 years
- OK for HIV+ patients
  - SC-EPOCH-RR

- Low-risk: **3 cycles → 100% EFS!**
  - No intrathecal injections
- High-risk: 6 cycles
  - Cabe delivered as outpatient
  - Requires very close monitoring

- BUT….
  - Not for parenchymal CNS disease
  - Strict intrathecal schedule
  - Requires expertise in dose adjustments



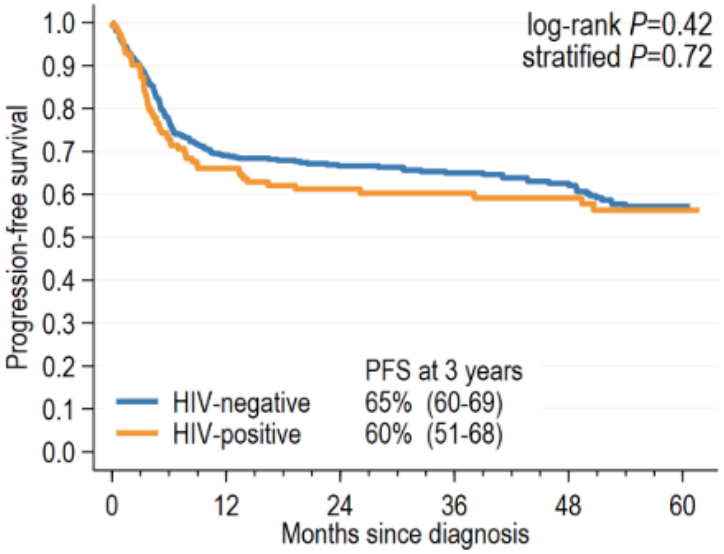


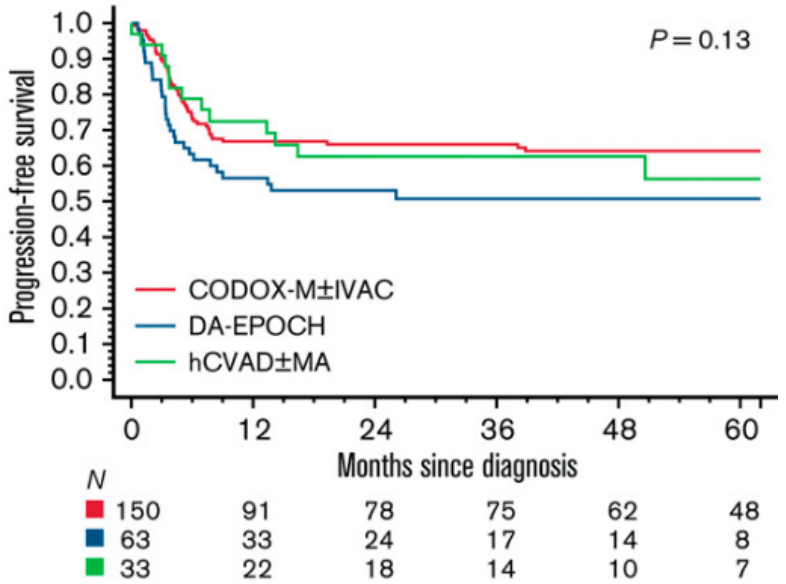
Roschewski M, et al. JCO 2020 Dunleavy K, et al. NEJM 2013

HIV-associated BL

Median CD4 count	**217** /mm^3
VL undetectable	**21%**
HAART	**39%**

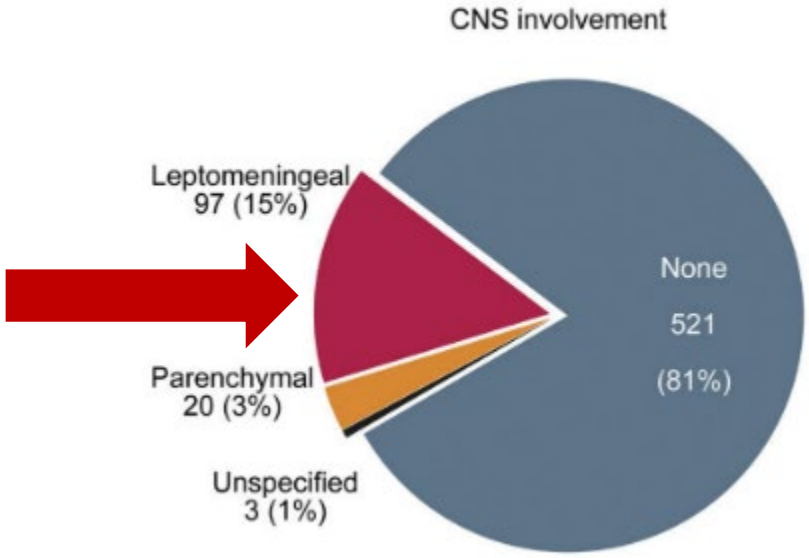
- Worse outcomes with low CD4
- No significant difference ± rituximab

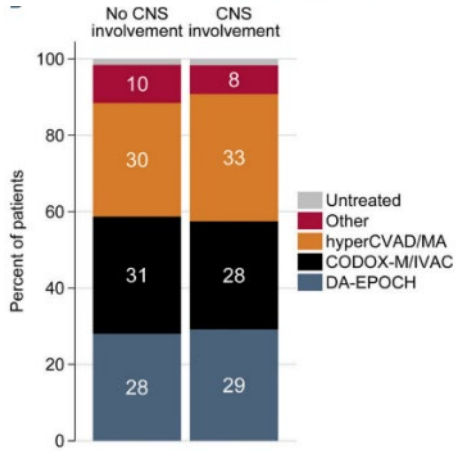




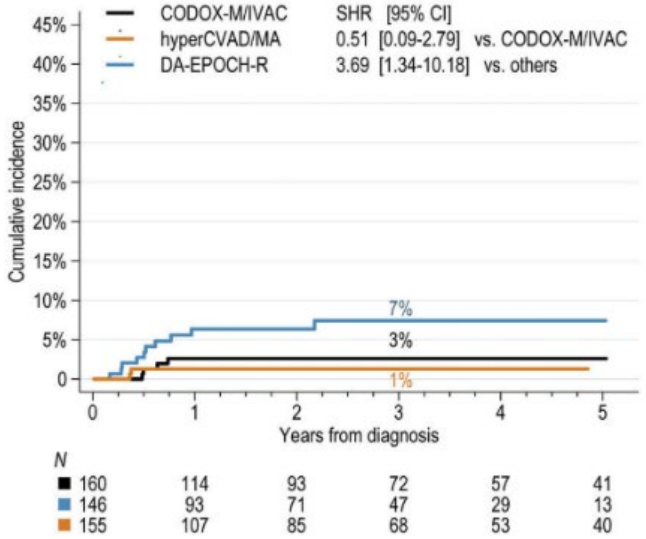
Atallah-Yunes SA, et al., Lancet Haematol. 2020 Alderuccio JP, et al., Blood Adv. 2021

CNS control in Burkitt lymphoma

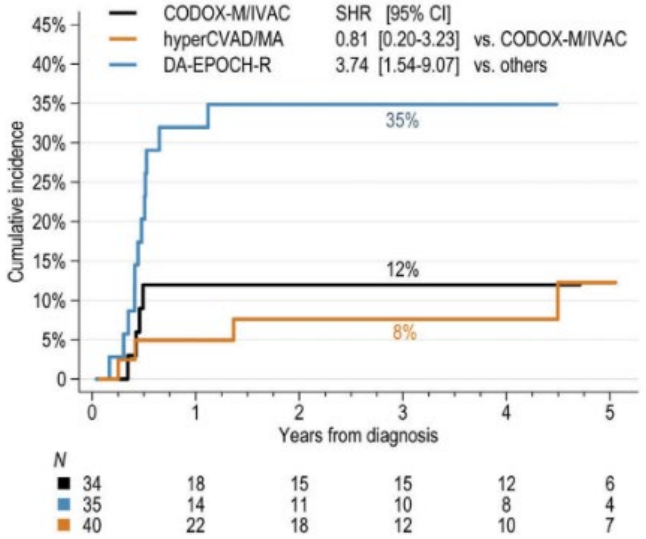




No CNS involvement



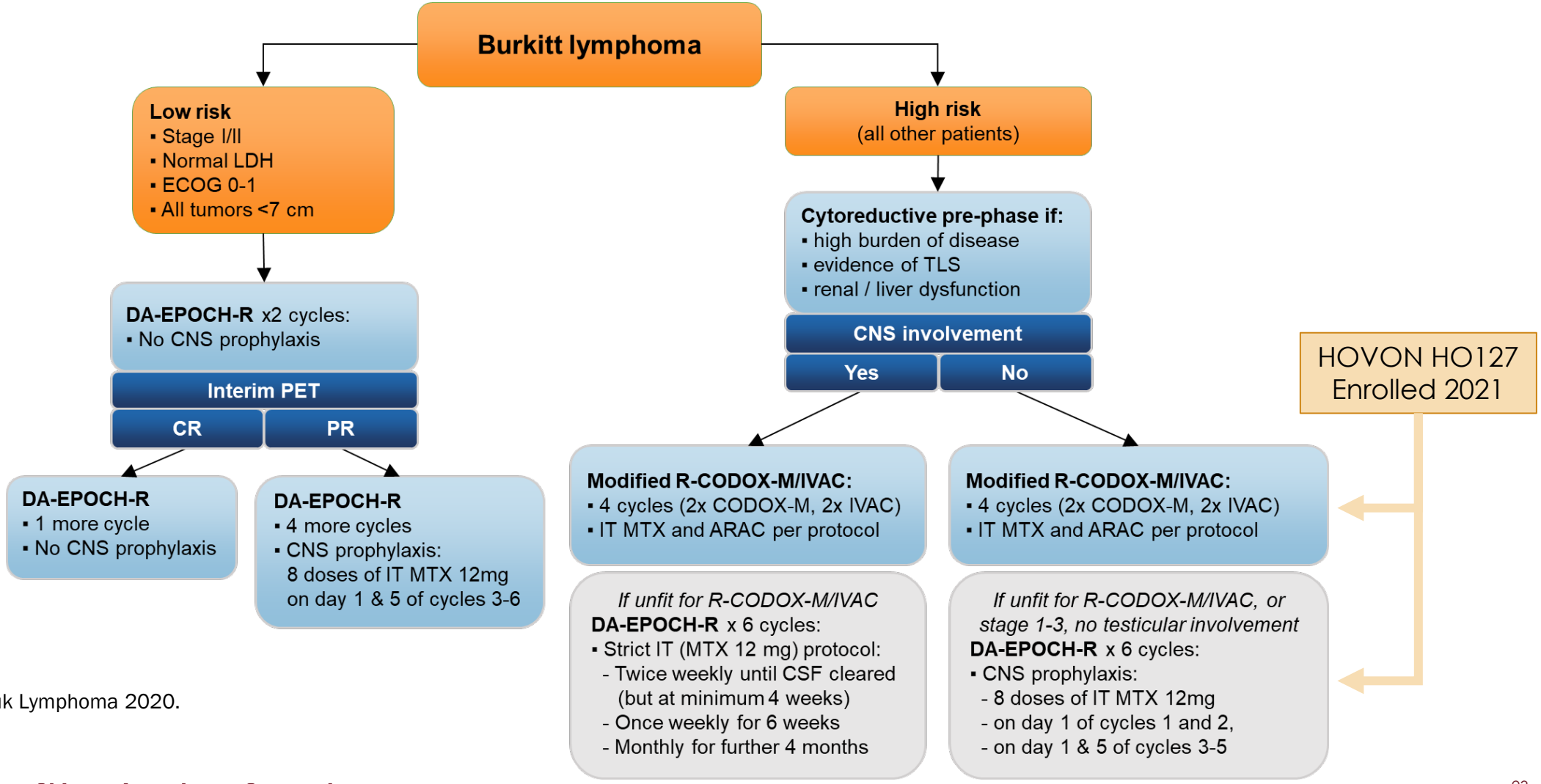
Baseline CNS involvement



- All patients with CNS recurrence after DA-EPOCH-R had IT MTX
- Only 57% had strict adherence to protocol schedule
- Only 45% who had <u>baseline</u> CNS involvement followed the protocol schedule

Zayac AS, et al., Haematologica. 2021

First-line therapy: 2022

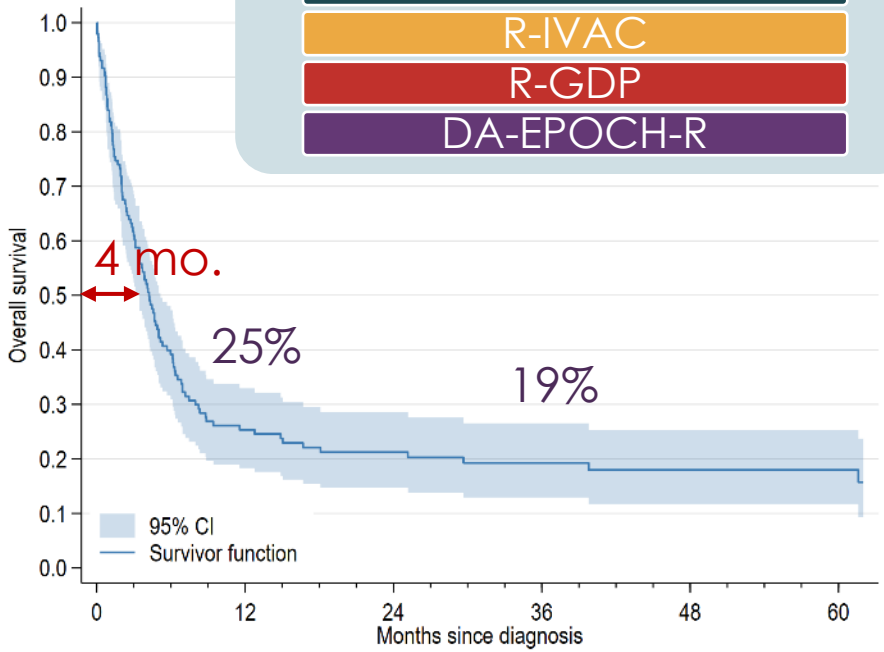


Zayac & Olszewski. Leuk Lymphoma 2020.

Relapsed/refractory Burkitt lymphoma

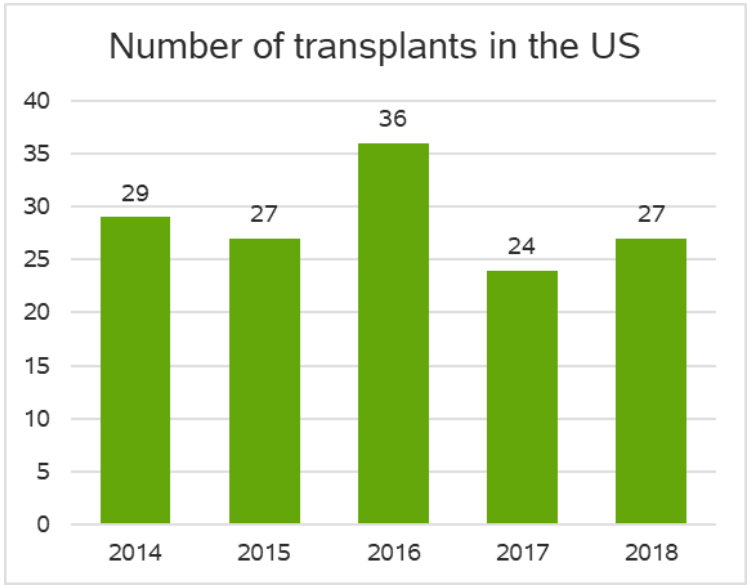
Salvage regimens

- R-DHAP
- R-ICE
- R-IVAC
- R-GDP
- DA-EPOCH-R



5-year PFS after transplantation

	CR1	>CR1	CR2+	Not iCR
Auto	78%	27%	**44%**	**19%**
Allo	50%	19%	**27%**	**11%**



Evens AM, et al. Blood 2021 Maramattom LV, et al., BBMT 2013 CIBMTR data

CAR T-cell therapy for Burkitt lymphoma?

- BL **excluded** from CAR T-cell trials

- Challenges:
  - ➢ Time to production
  - ➢ Need for bridging therapy
  - ➢ CNS involvement
  - ➢ Immune evasion?
    - Downregulated MHC I

- **Case reports**

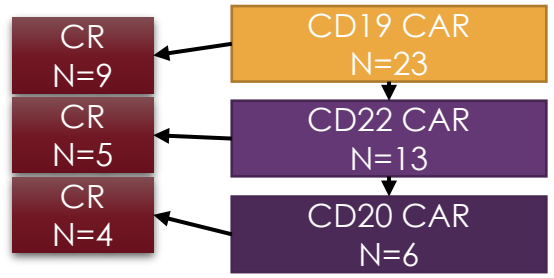
Patient refractory to:
- R-CODOX-M/IVAC
- R-ESHAP
- Allo-BMT

Avigdor A, et al., Bone Marrow Transplant. 2018

- **Case series**
  - N=6 R/R adults, CD19/CD22 CARs
  - 1 CR, 2 PR, 3 no response

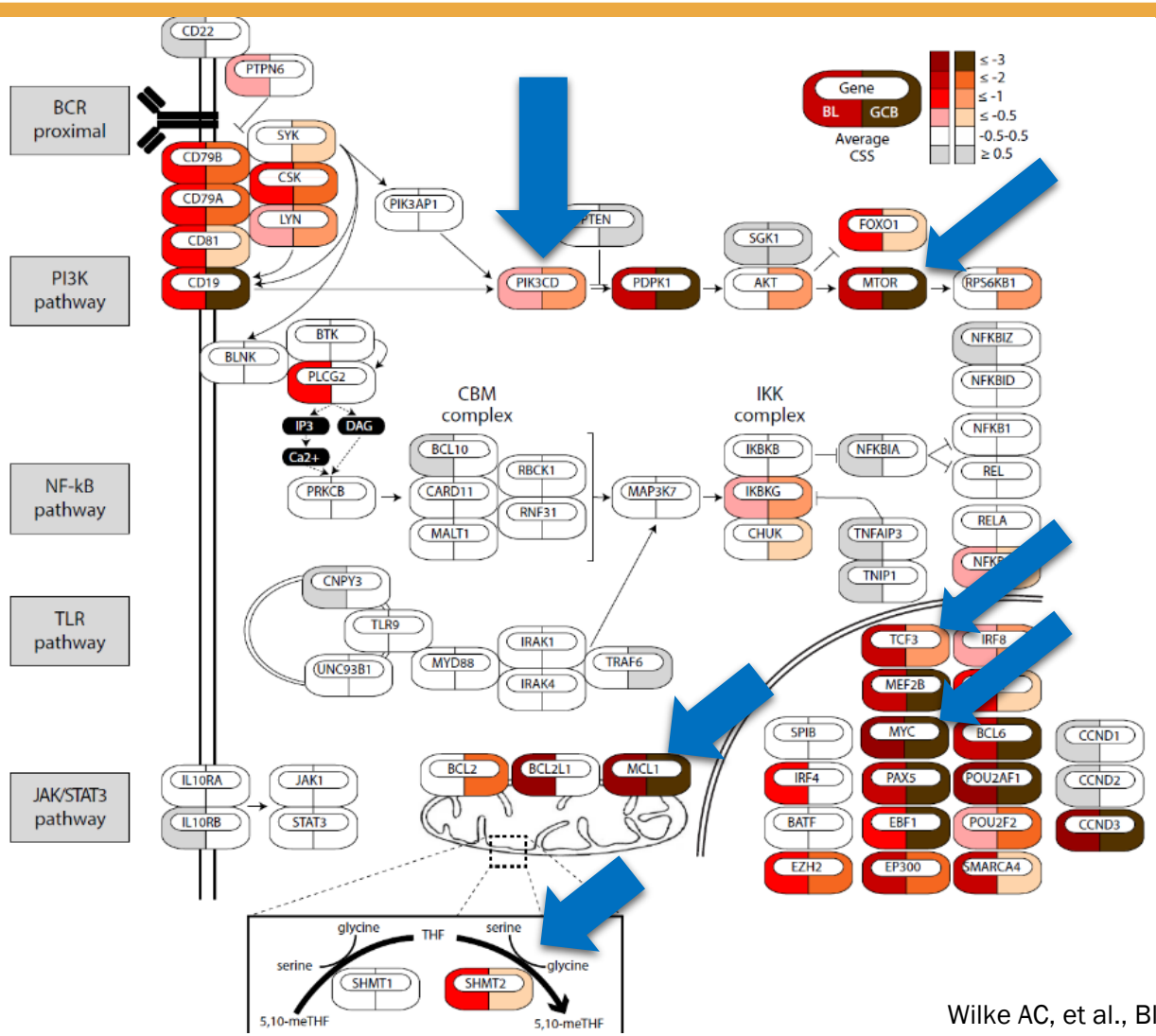
Zhou X, et al., Cancer Immunol Immunother. 2021

- **Phase 1 trial**
  - Pediatric patients
  - CR rate: **78%**
  - PFS @1.5y: **78%**



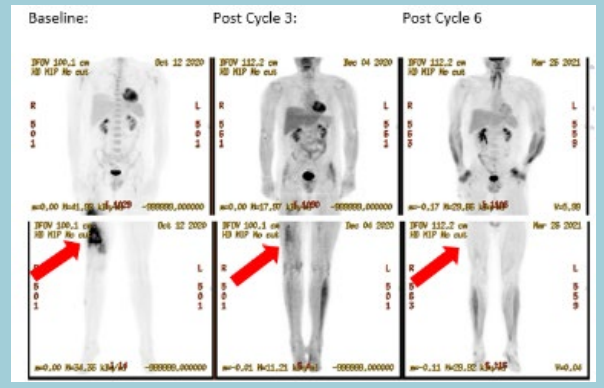
Liu Y, et al., Blood Adv. 2022

Targeted agents in Burkitt lymphoma



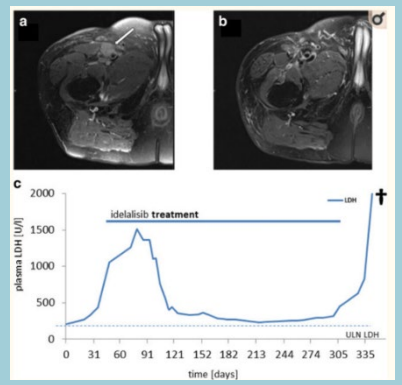
Devimistat
mitochondrial disruptor

1 out of 7 patients responded



Idelalisib
PI3K inhibitor

Case report: Non-sustained response



Wilke AC, et al., Blood. 2022 Nikolaenko et al., ASH 2021 BleckmanA, et al., AnHematol. 2021

Conclusions

- BL-IPI provides consistent prognostication
  - ✓Not ready to modify therapy in clinical practice → For future clinical trials

- Current treatment relies on R + chemotherapy:
  - ✓R-CODOX-M/IVAC: excellent outcomes for all younger patients
  - ✓DA-EPOCH-R: high cure rate for **low-risk** BL (NCI definition)

- Priorities for research:
  - ✓incorporate rational targeted agents in first-line and R/R therapy
  - ✓Immunotherapy for R/R disease

adamo@brown.edu

ARS question

What therapy would you recommend to this patient?

- previously healthy 50-year-old man – presented with acute bowel obstruction
- Now 3 weeks after an emergency resection of a 6 cm intestinal mass
- pathology shows Burkitt lymphoma with *MYC-IGH*
- post-operative PET-CT shows no FDG-avid lesions

1. R-Hyper-CVAD/MA x 4 cycles + intrathecal MTX
2. R-CODOX-M x 3 cycles + intrathecal MTX
3. DA-EPOCH-R x 6 cycles + intrathecal MTX
4. DA-EPOCH-R x 3 cycles, no intrathecal MTX
5. No further therapy