



UNIVERSITÄT  
DES  
SAARLANDES



GMALL  
German Multicenter Study Group for  
Adult Acute Lymphoblastic Leukemia



# Burkitt-Lymphom im Erwachsenenalter

DGHO Onkopedia-Webinar  
12. April 2024

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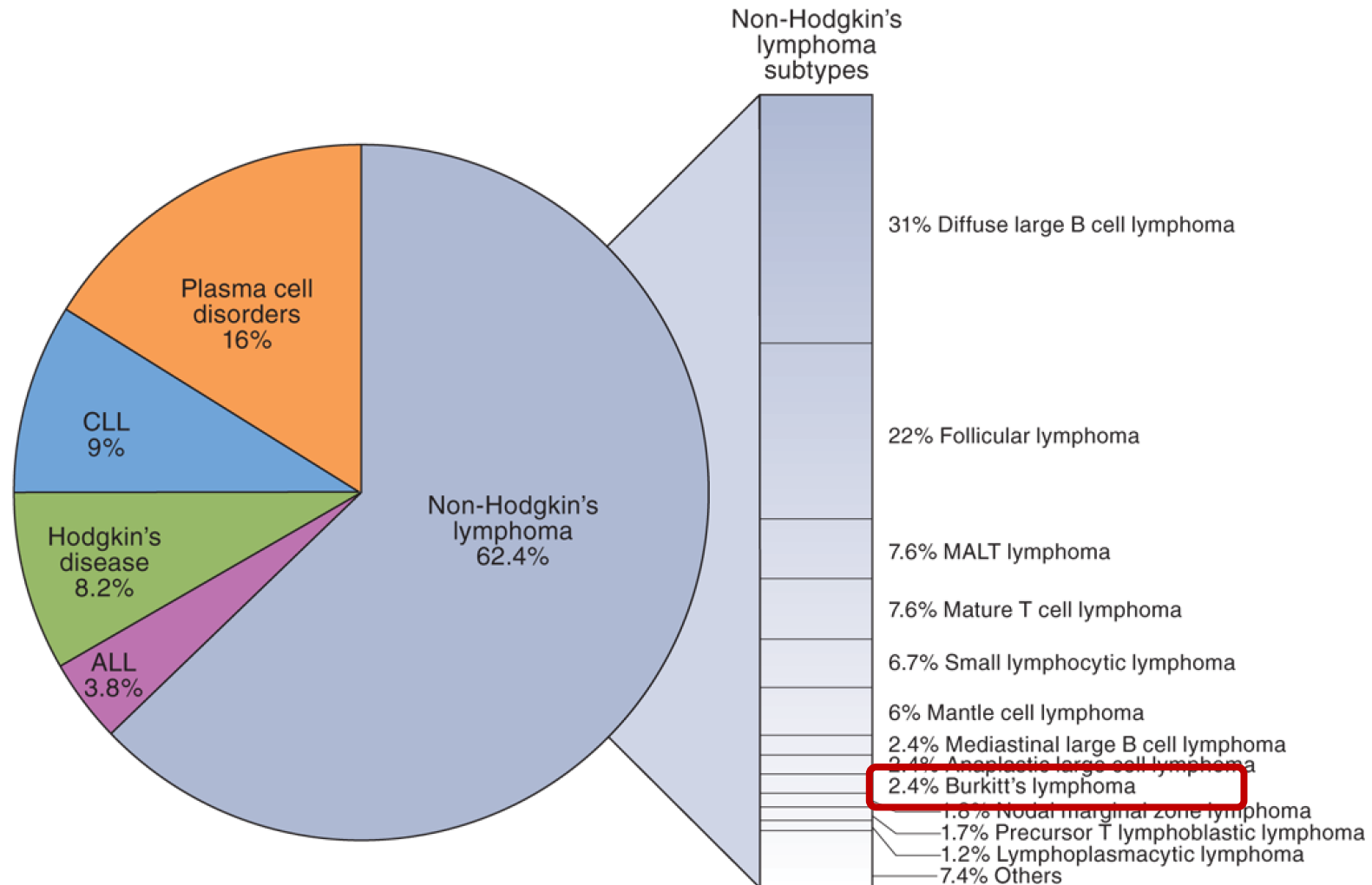


# Burkitt-Lymphom

- Einführung
  - Epidemiologie und Pathophysiologie des Burkitt-Lymphoms
- Diagnostik
  - Diagnostik Algorithmus
  - Klassifikation: Pathologie: 4<sup>th</sup> WHO vs. 5<sup>th</sup> WHO vs. ICC
- Therapie
  - Therapieprinzipien
  - 1<sup>st</sup>-line (intensive Polychemotherapie (GMALL) vs. DA-EPOCH-R)
  - Rezidivtherapie



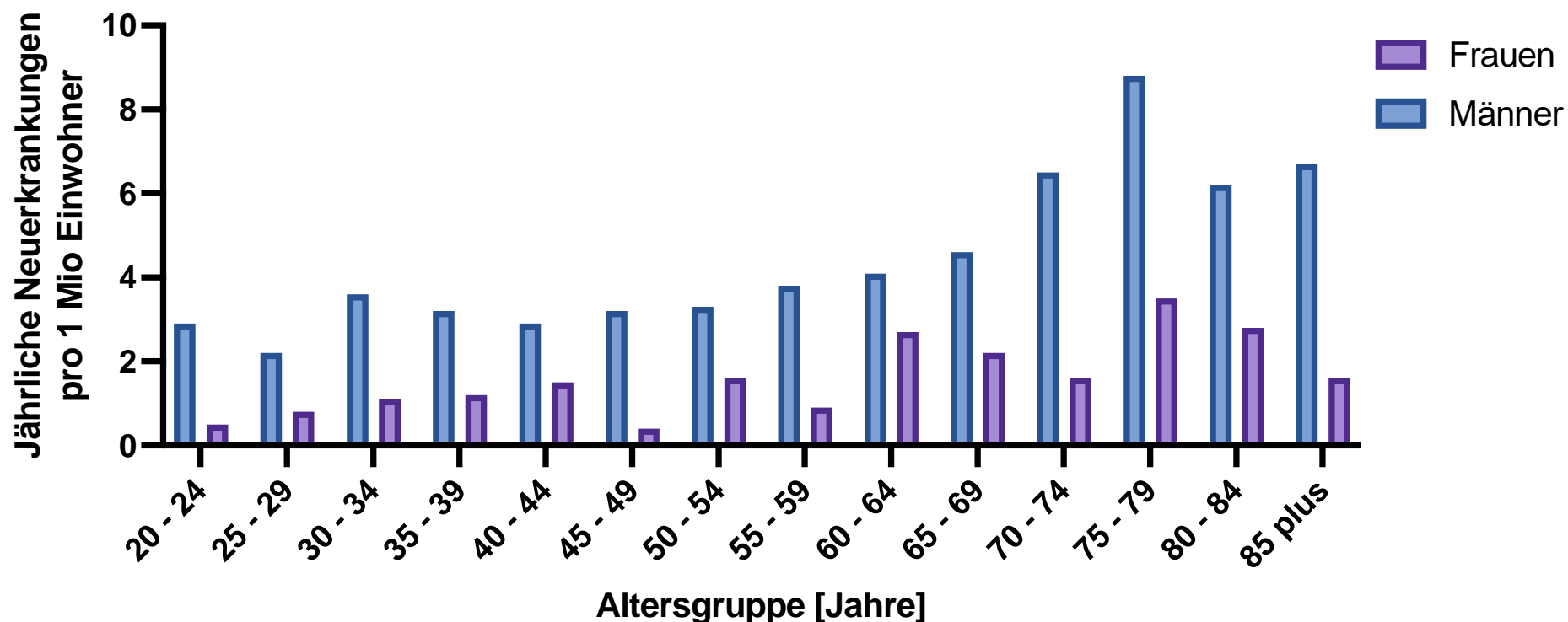
# Burkitt-Lymphom





# Epidemiologie Deutschland 2018 & 2019

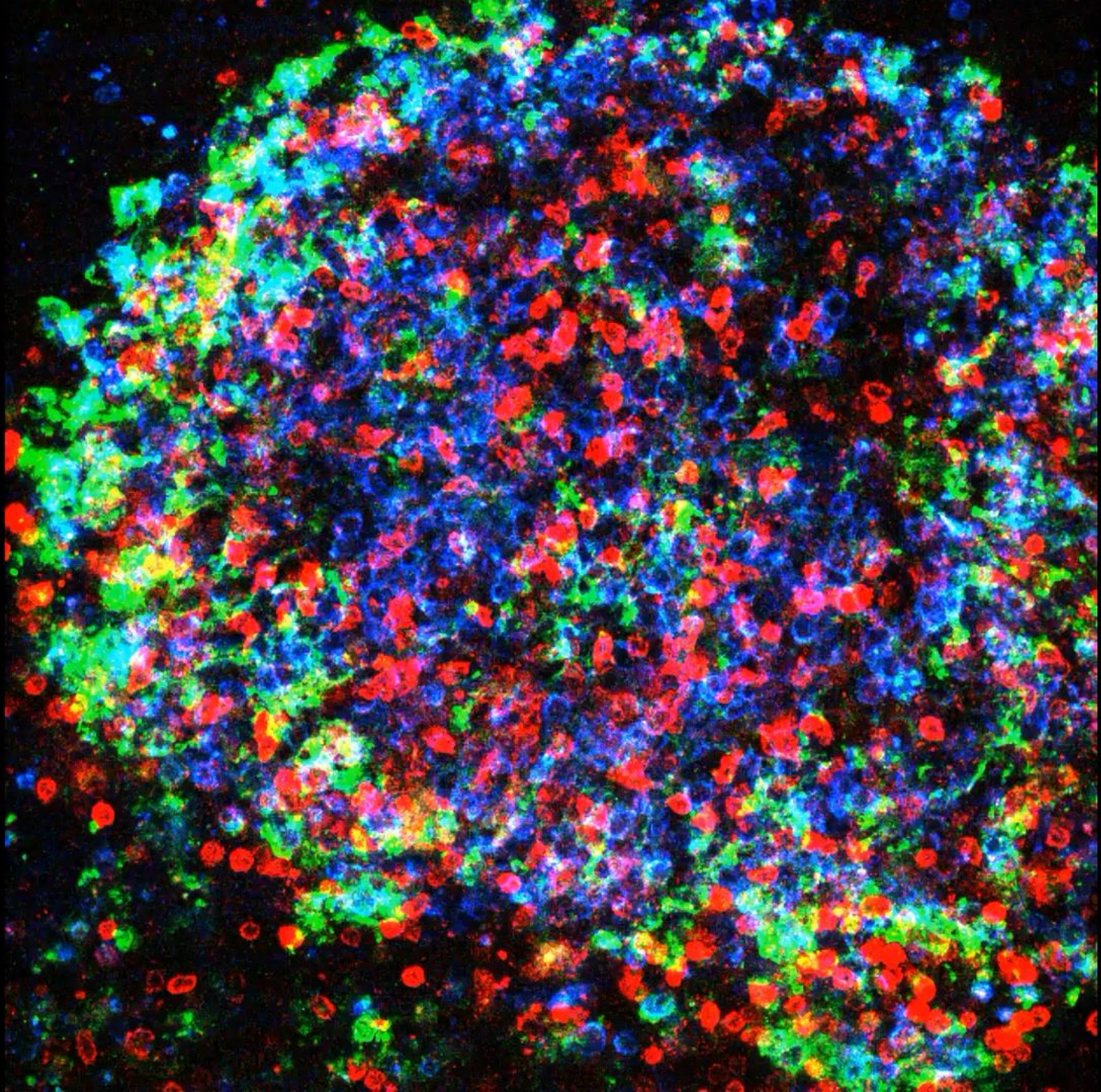
## Altersspezifische Inzidenz des Burkitt- Lymphoms (ICD-O-3: 9687.3 und 9826.3)





4D-Studie: Martin-Leo  
Hansmann und Sylvia  
Hartmann

FDCs: grün  
B-cells: blau  
T-cells (PD1): rot

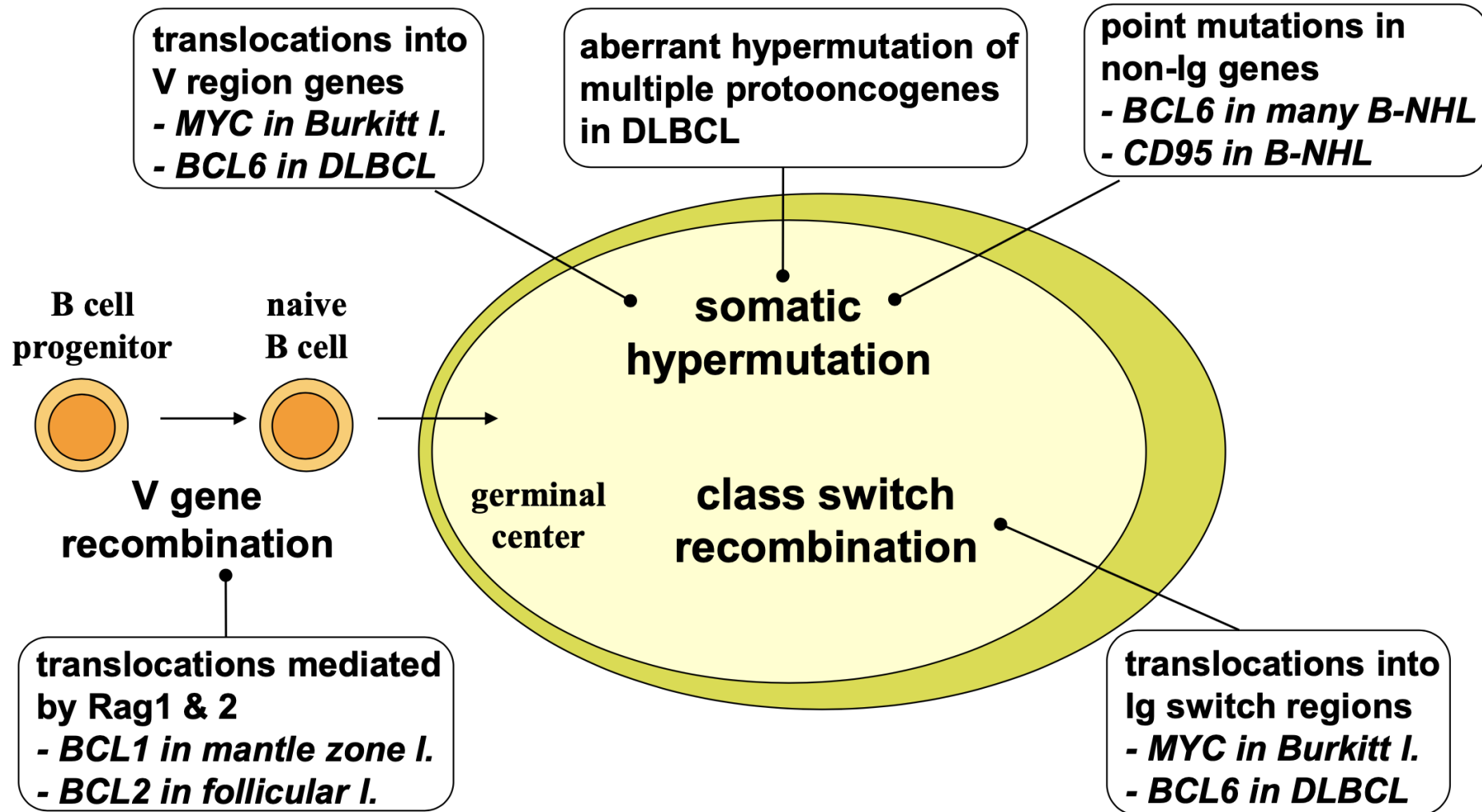


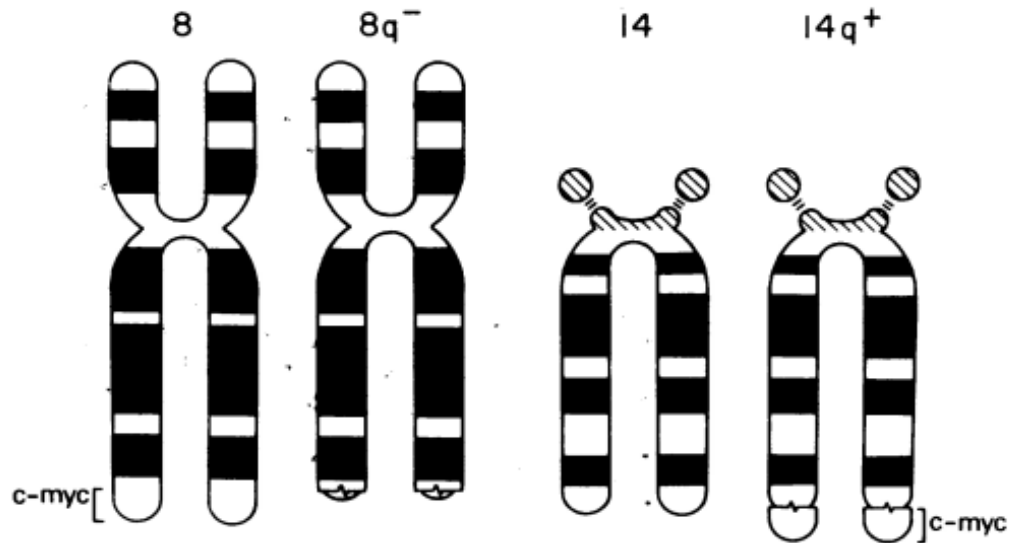
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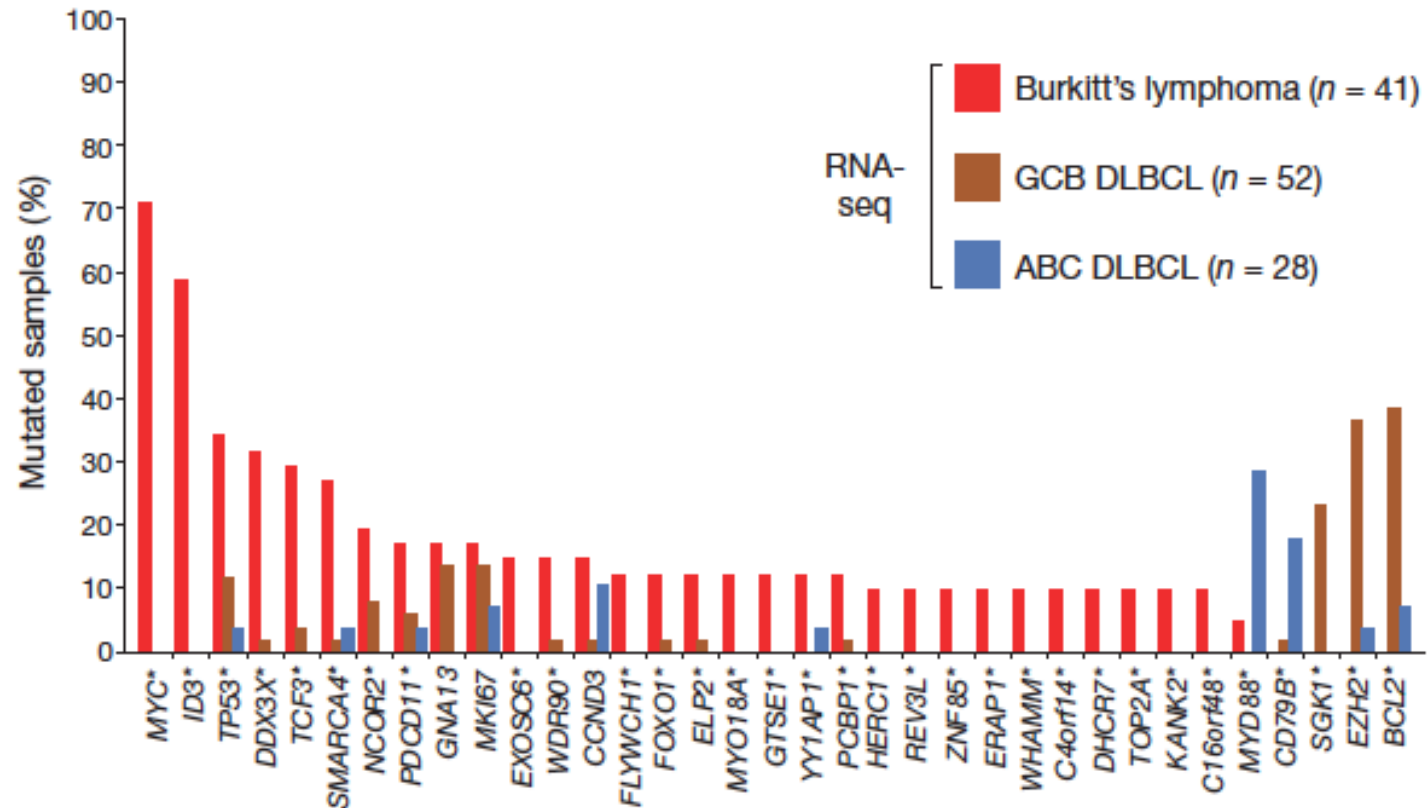


# Involvement of Molecular Processes Acting at Ig Loci in the Pathogenesis of B Cell Lymphomas





**FIG. 5.** Diagram of the t(8;14) chromosome translocation observed in Burkitt lymphoma. The reciprocal translocation results in the formation of two marker chromosomes:  $8q^-$  and  $14q^+$ . The results of the experiments described in Table 1 indicate that the human *c-myc* homologue is distal to the breakpoint on human chromosome 8 in both Burkitt lymphoma cell lines that were analyzed.



**Obituary**

# Sir Anthony Epstein obituary

**British pathologist who helped to uncover the first evidence that cancer in humans could be caused by a virus**



Using an electron microscope Anthony Epstein and his graduate student Yvonne Barr found an outline that looked like one of the family of herpes viruses. It was given the name Epstein-Barr. Photograph: Stuart Bebb/Wolfson College Archives, Oxford

It did not seem like a good thing when a precious consignment of human tumour samples on its way from Kampala, Uganda, to Heathrow was diverted to Manchester. When the samples finally arrived at the Middlesex hospital in London, they were swimming in murky fluid in their vials as though they had been infected with bacteria.

But when the pathologist Anthony Epstein looked at the fluid under the microscope he saw no bacteria, just individual cells that had been shaken loose from the tumours. And that was just what he needed in order to search for elusive virus particles and test his hunch that they were causing cancer.

In the early 1960s Epstein, who has died aged 102, had heard a lecture by **Denis Burkitt**, an Irish surgeon working in Kampala, that described strange tumours (now known as Burkitt lymphoma) growing around the jaws of children in equatorial Africa.

# Epstein-Barr Virus (EBV oder HHV 4)

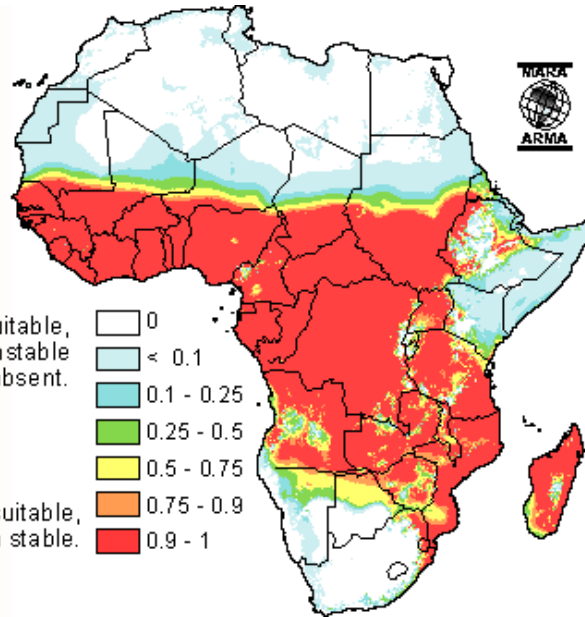
**TABLE 1.** EXPRESSION OF EBV LATENT GENES IN DISEASE.\*

PATTERN OF LATENCY	EBNA-1	EBNA-2	EBNA-3	LMP-1	LMP-2	EBER	DISEASE
Type 1	+	-	-	-	-	+	Burkitt's lymphoma
Type 2	+	-	-	+	+	+	Nasopharyngeal carcinoma, Hodgkin's disease, peripheral T-cell lymphoma
Type 3	+	+	+	+	+	+	Lymphoproliferative disease, X-linked lymphoproliferative disease, infectious mononucleosis
Other	±	-	-	-	+	+	Healthy carrier

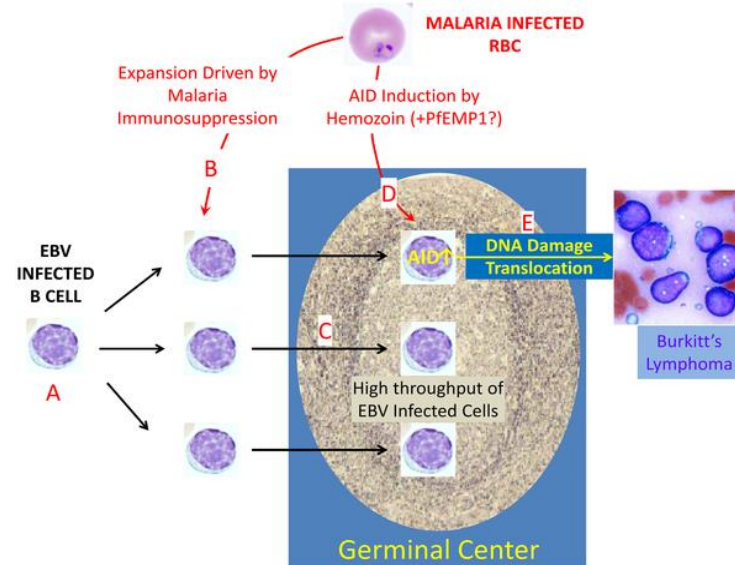
\*EBV denotes Epstein-Barr virus, EBNA Epstein-Barr virus nuclear antigen, LMP latent membrane protein, and EBER Epstein-Barr virus-encoded RNA. A plus sign indicates that the gene is expressed in the disease, a minus sign that it is not expressed, and the two together that the gene may or may not be expressed.



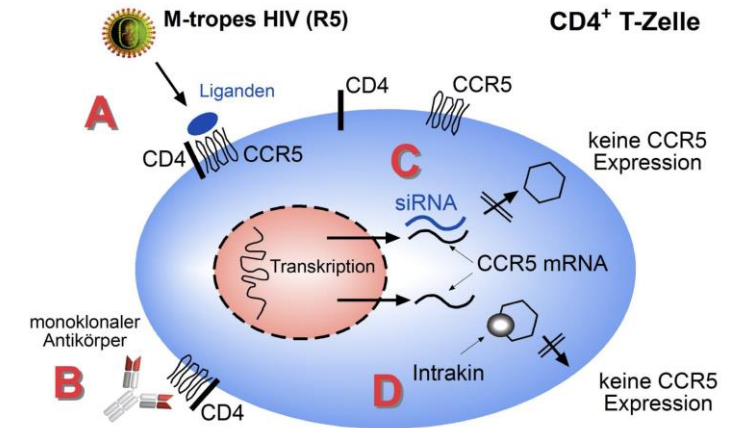
## Malariagürtel in Afrika



## Plasmodium falciparum.- und EBV-Koinfektion

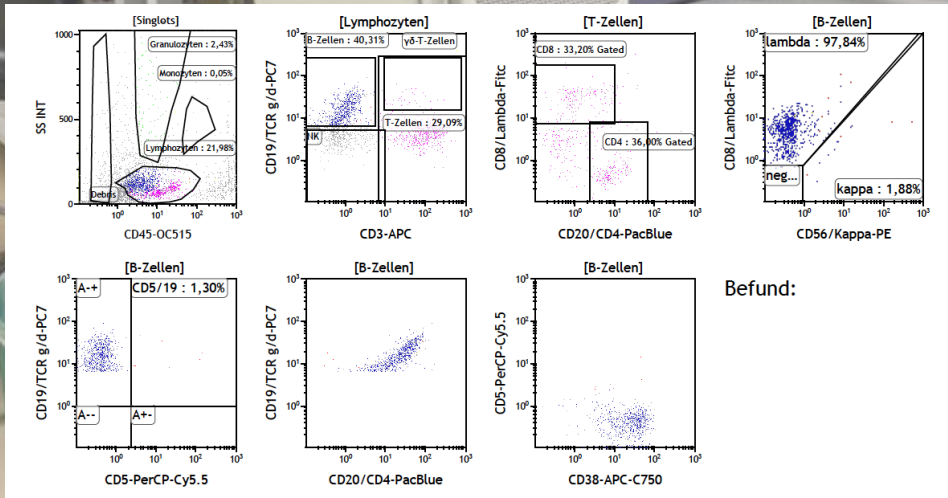
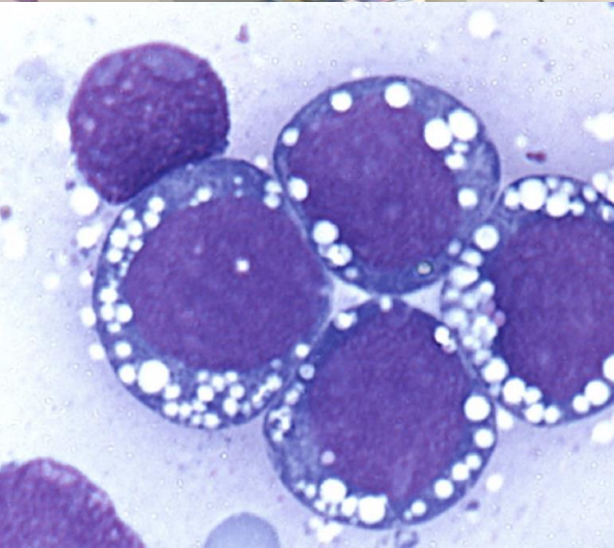


## HIV





# DIAGNOSTIK



Befund:



## Untersuchungen

### Diagnosesicherung und Staging

#### Histologie, Zytologie, Immunphänotypisierung

- Standard: **LK-Exstirpation und -Teilexstirpation bzw. Biopsie** (nach klinischem Ermessen) zur zeitnahen primärpathologischen Beurteilung und **Veranlassung der Referenzpathologie** (damit **nicht** Therapieeinleitung **verzögern**), **MYC-Expressionsanalyse** (ergänzt durch FISH zum Nachweis einer **MYC-Translokation**, sowie Ausschluss double/triple-hit Lymphom)
  - **Knochenmarkpunktion mit Zytologie, Histologie, Immunphänotypisierung**, ggf. **Etablierung von MRD-Markern** aus Primärmaterial bei Diagnosestellung
  - Zytologie von Ergüssen, ggf. auch therapeutische Punktion zur Vermeidung eines dritten Raums vor einer Therapie mit hochdosiertem Methotrexat (HD-MTX)
  - **Liquordiagnostik:** zuvor zerebrale Bildgebung zum Hirndruck-Ausschluss; Zytologie, wenn möglich mit Immunphänotypisierung
- Bildgebung - Basis
- **CT-Hals/Thorax/Abdomen** oder **FDG-PET-CT (wenn zeitlich möglich)** oder **Ganzkörper-MRT (wenn zeitlich möglich)**
  - **cMRT, ggf. alternativ CCT, MRT Wirbelsäule**
- Weitere Untersuchungen bei klinischem Verdacht:
    - Bei ZNS-Befall: ophthalmologisches Konsil (Augenhintergrund)
    - Hoden-Sonographie
    - ÖGD und/oder Koloskopie
    - Mamma-MRT, Mamma-Sonographie, Mammographie



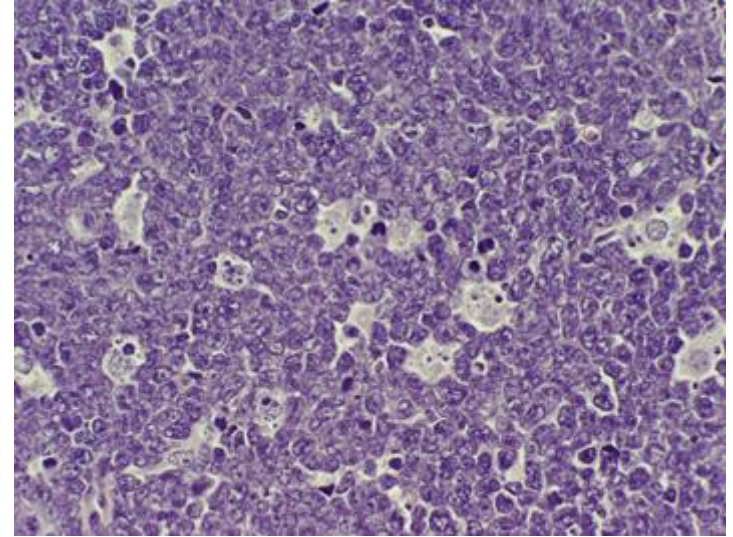
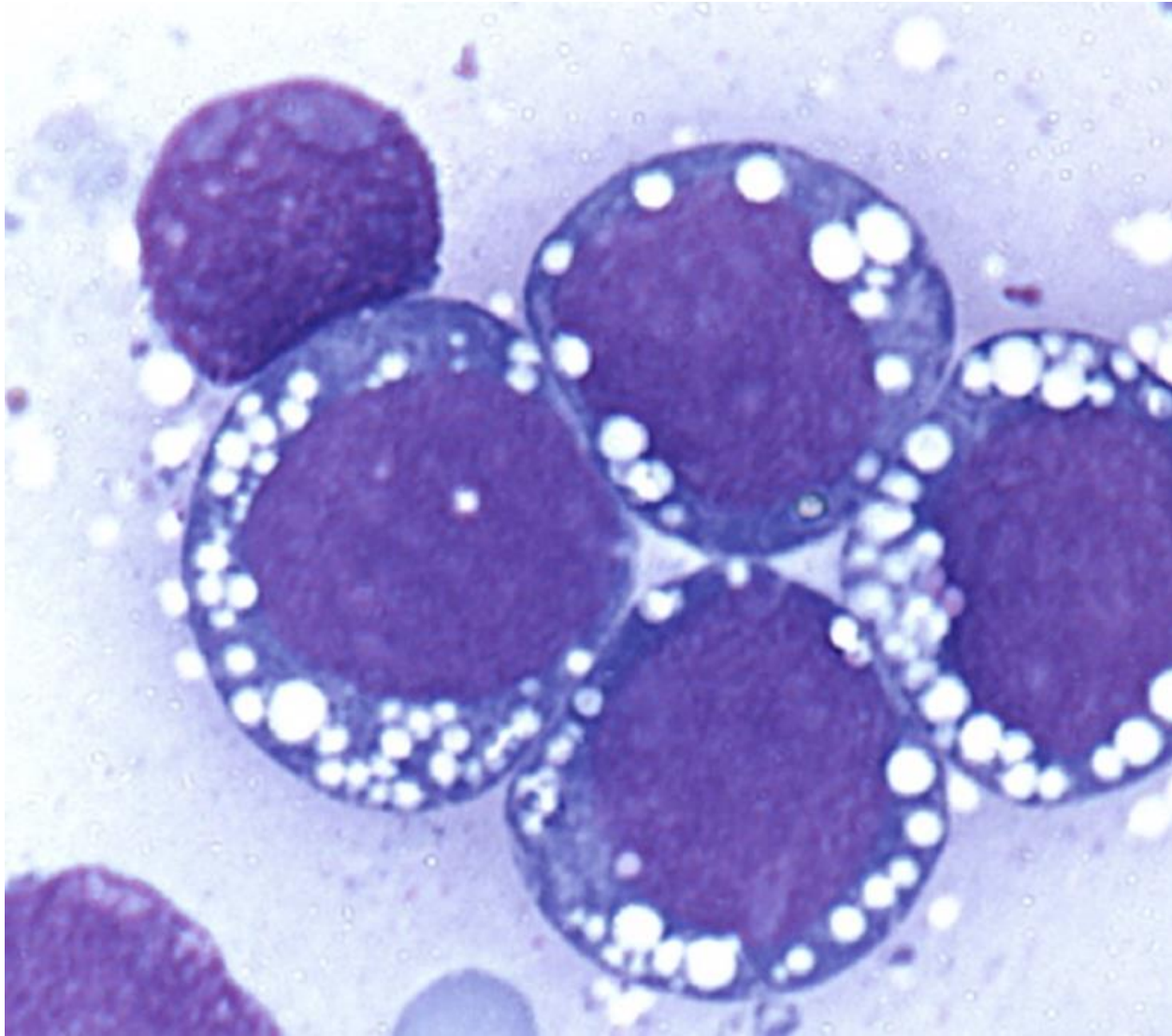


Untersuchungen	
<b>Labor</b>	<ul style="list-style-type: none"> <li>• <b>Blutbild</b> inklusive Differenzialblutbild (mikroskopische Differenzierung), und Retikulozyten</li> <li>• Durchflusszytometrische Immunphänotypisierung</li> <li>• <b>Tumorlyse-Marker:</b> LDH, Harnsäure, Phosphat, BGA</li> <li>• <b>Leberfunktion:</b> Bilirubin, GOT, GPT, alkalische Phosphatase, Gamma-GT, Albumin</li> <li>• <b>Nierenfunktion:</b> Kreatinin und Cystatin, GFR, Elektrolyte</li> <li>• Gerinnung: aPTT, TZ, Quick (INR), ggf. Faktor XIII, Fibrinogen und AT-III</li> <li>• <b>Infektionsdiagnostik:</b> HIV-, HBV- (einschließlich Anti-HBc-Ak), HCV-, CMV- und EBV-Serologie sowie ggf. direkter Erregernachweis im peripheren Blut</li> <li>• <b>bei HIV-assoziiertem BL: CD4-Status</b>, Toxoplasmose-Serologie, ggf. Kryptokokken-Antigen, Lues-Serologie, HIV-Resistenztestung, ggf. HLA-B57-Typisierung, Testung auf weitere STDs, ggf. Testung auf weitere opportunistische Infektionen.</li> <li>• ggf. Schwangerschaftstest (vor Therapieeinleitung)</li> <li>• Urin-pH</li> </ul>
<b>weitere Analysen</b>	<ul style="list-style-type: none"> <li>• Ruhe-EKG mit Ausmessung der QTc-Zeit</li> <li>• Echokardiographie</li> <li>• Lungenfunktion (Bodyplethysmographie und Diffusionskapazität)</li> <li>• Fertilität: Vorstellung in der Reproduktionsmedizin, falls erwünscht und falls kein unmittelbarer Therapiebeginn erforderlich;</li> </ul>

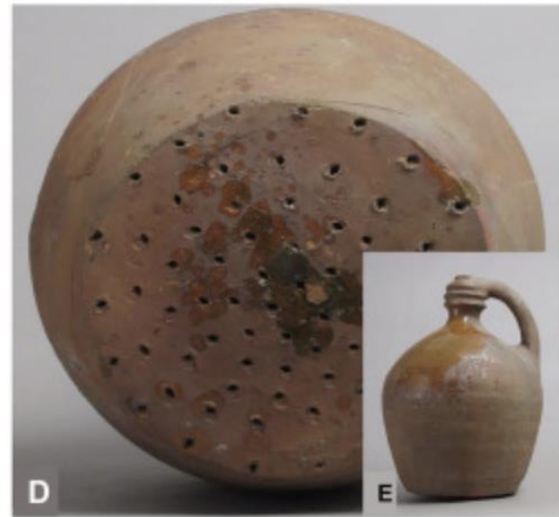




- **Zytologisch L3-Blasten:** basophiles Zytoplasma, deutliche Vakuolisierung von Zytoplasma und Nucleus (zytologisch Verwechslungsgefahr mit monozytärer AML, Vorläufer-ALL oder andern High-grade NHL)
- **Histologisch „Sternenhimmel-Muster“** - Lymphoblasten-Rasen mit eingestreuten Makrophagen, Ki-67 nahezu 100%. MYC-IHC + FISH-Analyse zum Nachweis einer MYC-Translokation
- Immunphänotypisch:
  - Abgrenzung zu Vorläuferneoplasien: Abwesenheit von TdT, aber vorhandene Expression von slg.
  - B-Zell Marker (CD20, CD19) und Keimzentrumsmarker (CD10 oder BCL6), und Negativität für BCL2, CD5 und CD23
- **Traditionell Burkitt-Leukämie ab Knochenmarkbefall >25%** oder bei Ausschwemmung (basiert auf St. Jude-Staging System für pädiatrische NHL (Murphy et al.)), nicht definiert in WHO- oder ICC-Klassifikationen



Burkitt Lymphom, HE, Lawrence Weiss



D



E



y

Zhang et al, Pathology, 2023



# BL vs. BLL vs. DHT vs. 11q // WHO vs. ICC

	4 <sup>th</sup> WHO-Klassifikation von 2016
<b>Pathogenetische Einteilung</b>	I. endemisch II. sporadisch III. Immunsuppressions-assoziiertes
<b>Abgrenzung des BL (TdT<sup>-</sup>) zu B-Vorläufer-Neoplasien</b>	Blastäre TdT <sup>+</sup> Neoplasien werden als B-LBL benannt
<b>Abgrenzung BL (IG:MYC) zu aggress. B-Zell-Lymphom mit 11q-Aberration</b>	Provisorische Entität von Burkitt-like Lymphomen mit 11q-Aberration ohne MYC-Rearrangement
<b>Abgrenzung BL (IG:MYC) zu Double/Triple hit (IG::MYC, BCL2, BCL6)</b>	BL (IG::MYC; ohne BCL2- oder BCL6-Translokation) vs. double/Triple hit HGBCL: Blastäre TdT <sup>-</sup> Neoplasien mit IG::MYC <u>und</u> BCL2- <u>und/oder</u> BCL6-Rearrangements

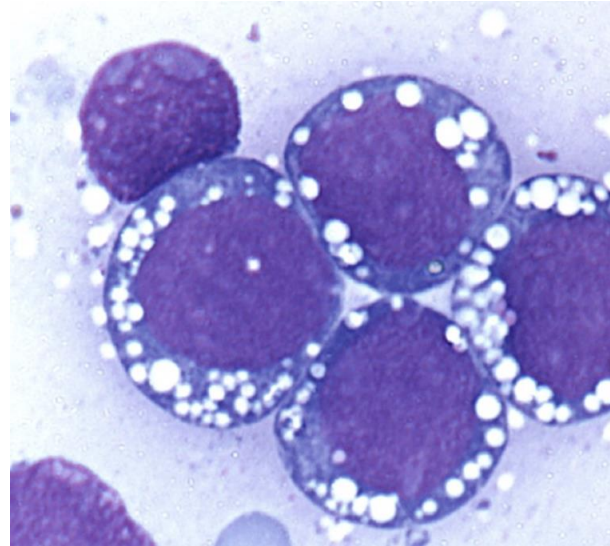
- Swerdlow SH, Campo E, Pileri SA, et al. THE UPDATED WHO CLASSIFICATION OF HEMATOLOGICAL MALIGNANCIES: The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood*. 2016;127(20):.
- Alaggio R, Amador C, Anagnostopoulos I, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. *Leukemia*. 2022;36(7):1720–1748
- Campo E, Jaffe ES, Cook JR, et al. The International Consensus Classification of Mature Lymphoid Neoplasms: a report from the Clinical Advisory Committee. *Blood*. 2022;140(11):1229–1253.



# Therapie des Burkitt-Lymphoms

## Klinik:

- massive Proliferation und Tumorlast
- 20% ZNS-Befall
- 20-40% KM-Infiltration
- Häufig E-Befälle, z.B. GI-Trakt, häufig als Bulk



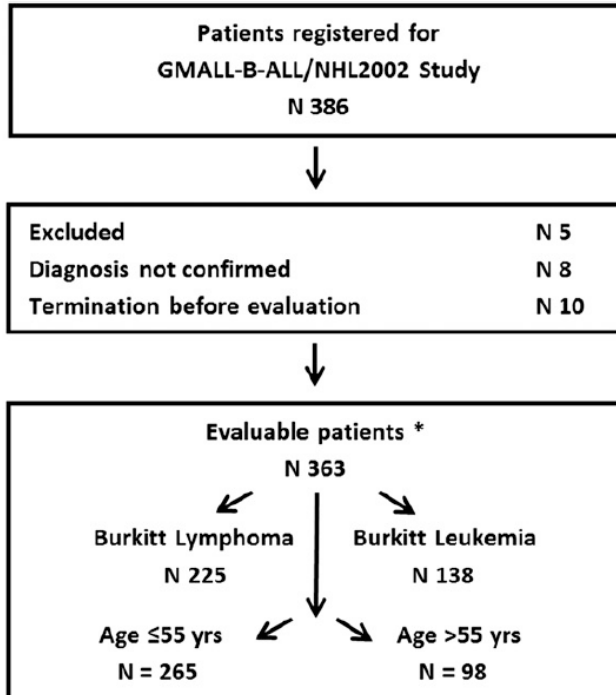
## Therapie-Prinzipien

- I. Vorphase-Therapie
- II. Intensive Polychemotherapie-Protokolle vs. DA-EPOCH-R
- III. ZNS-Prophylaxe/-Therapie





# Erstlinientherapie

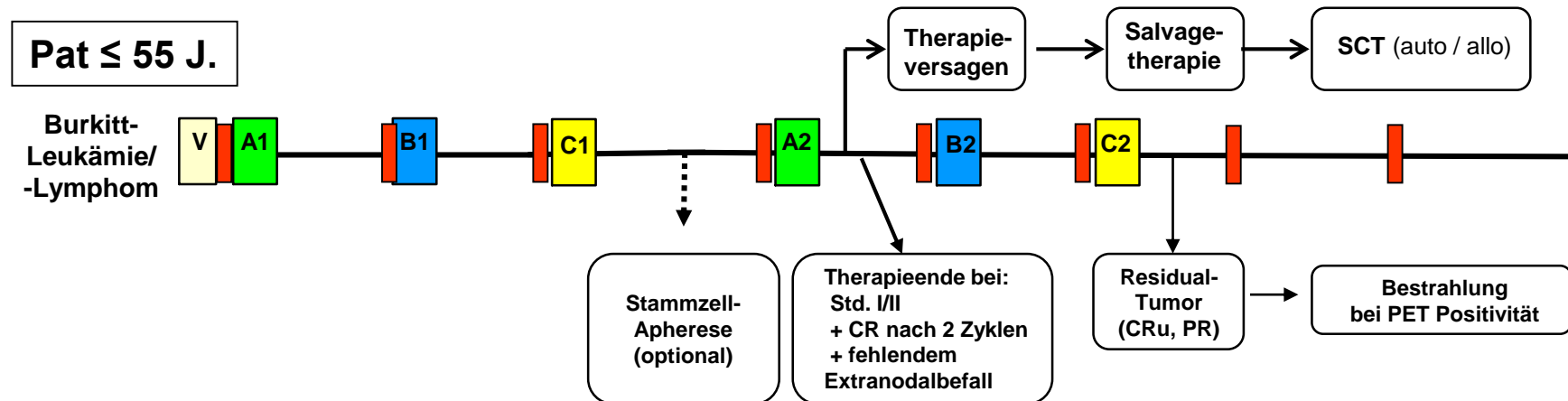


Treatment realization **	
N 341	
End of therapy Stage III/IV 6 cycles according to protocol	274
End of therapy Stage I/II 4 cycles according to protocol (no MedTU, no EN)	18
Reasons for failure to complete therapy	
Early relapse:	4
Progression under therapy:	8
Early death:	14
Withdrawal or protocol violation in CR / PR:	12 / 7
Auto-SCT in CR:	3
Death in CR	2

\* No. of patients included in the analysis

\*\* No. of patients with complete information of treatment realisation

Involved localizations			
Lymph node			
Yes	261 (77)	83 ± 2	.20
No	79 (23)	76 ± 5	
Extranodal involvement			
Yes	297 (86)	79 ± 3	.08
No	49 (14)	91 ± 4	
CNS			
Yes	35 (10)	67 ± 8	.02
No	306 (90)	82 ± 2	
Bone marrow			
Yes	143 (42)	67 ± 4	<.0001
No	201 (58)	90 ± 2	
Other localizations			
Mediastinal tumor	26 (8)		
Pleura	55 (16)		
Pericardium	11 (3)		
Spleen	43 (13)		
Liver	49 (14)		
Tonsils	16 (5)		
Thyroid	7 (2)		
Uterus/adnexa	13 (4)		
Testes/ovaries	23 (7)		
Kidney	16 (5)		
Lung	8 (2)		
Stomach	31 (9)		
Gut	85 (25)		
Bone	28 (8)		
Other	76 (23)		
Stage			
I-II	100 (29)	90 ± 3	.002
III-IV	249 (71)	76 ± 3	
IPI			
low (0-2)	140 (49)	90 ± 3	.0005
high (3-5)	146 (51)	75 ± 4	
aaIPI			
low (0-1)	111 (37)	93 ± 3	<.0001
high (2-3)	192 (63)	74 ± 3	

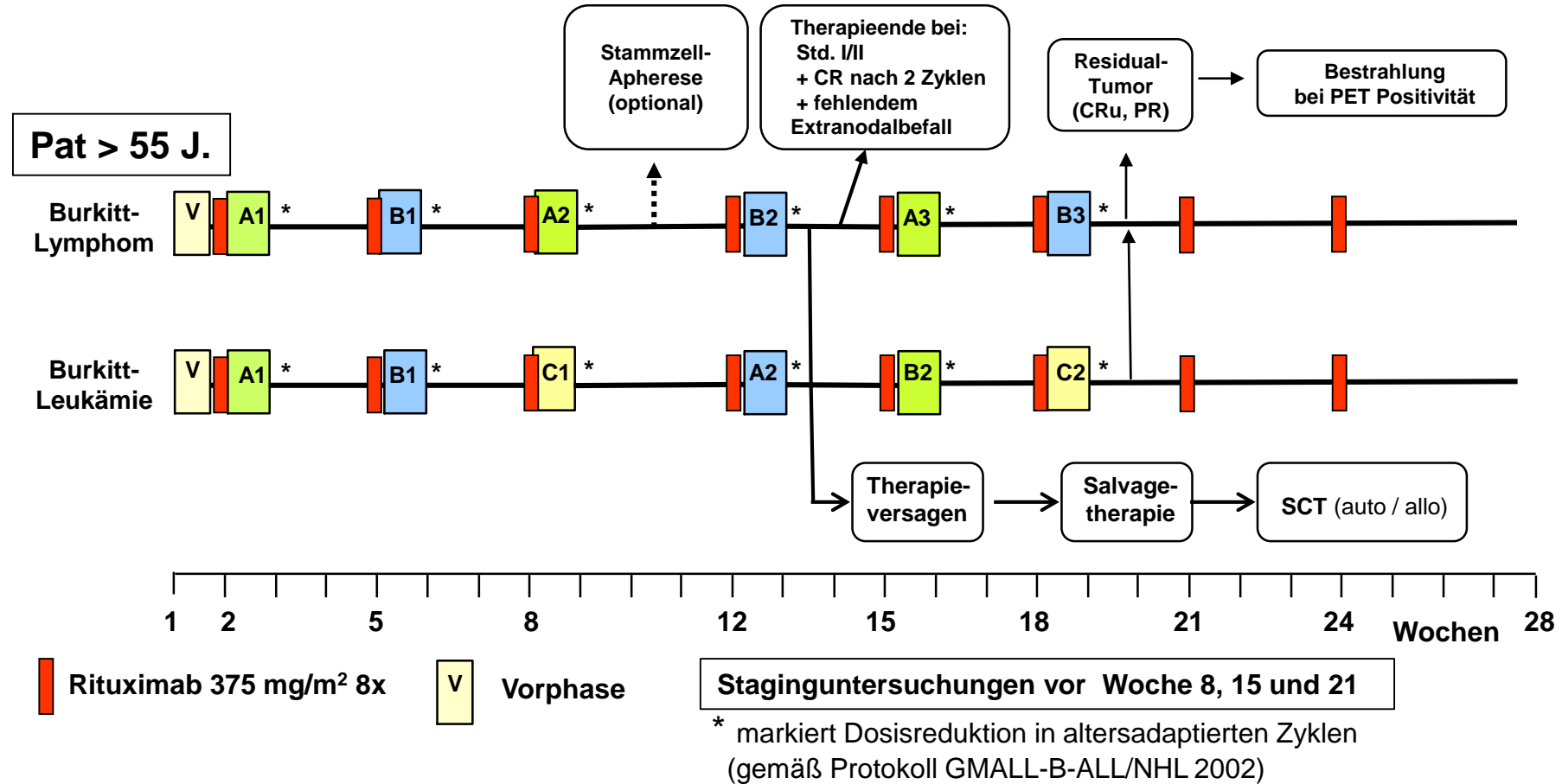


█ Rituximab 375 mg/m<sup>2</sup> (8x)

█ Vorphase



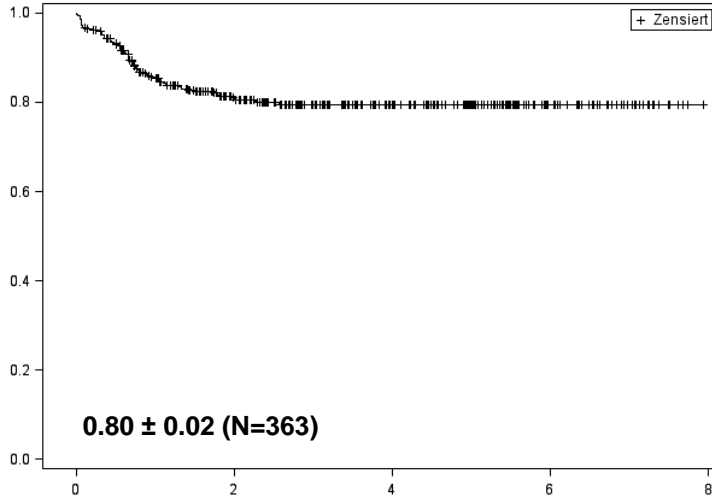
# Erstlinientherapie – GMALL B-ALL/NHL 2002



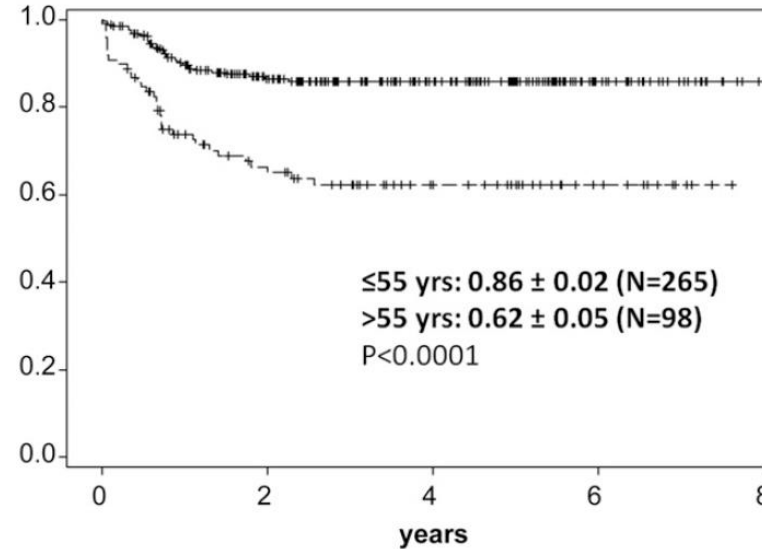


# Outcome – GMALL B-ALL/NHL 2002

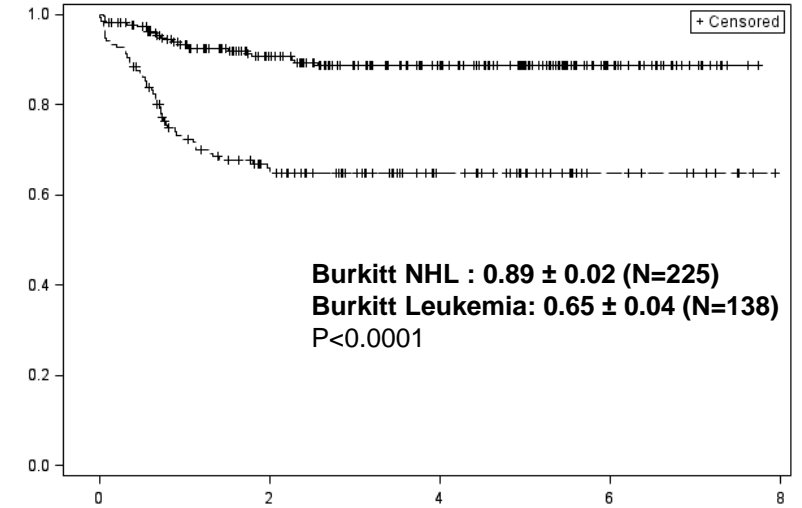
OS



OS



OS



- CR rate: 88%
- Relapse after CR rate: 12%
- TRM:
  - Pat ≤ 55y 2%
  - Pat > 55y 11%

## Risikofaktoren

- Alter >55 Jahre
- LDH > 250
- KM-Befall (Burkitt-Leukämie)
- Geschlecht (weiblich)



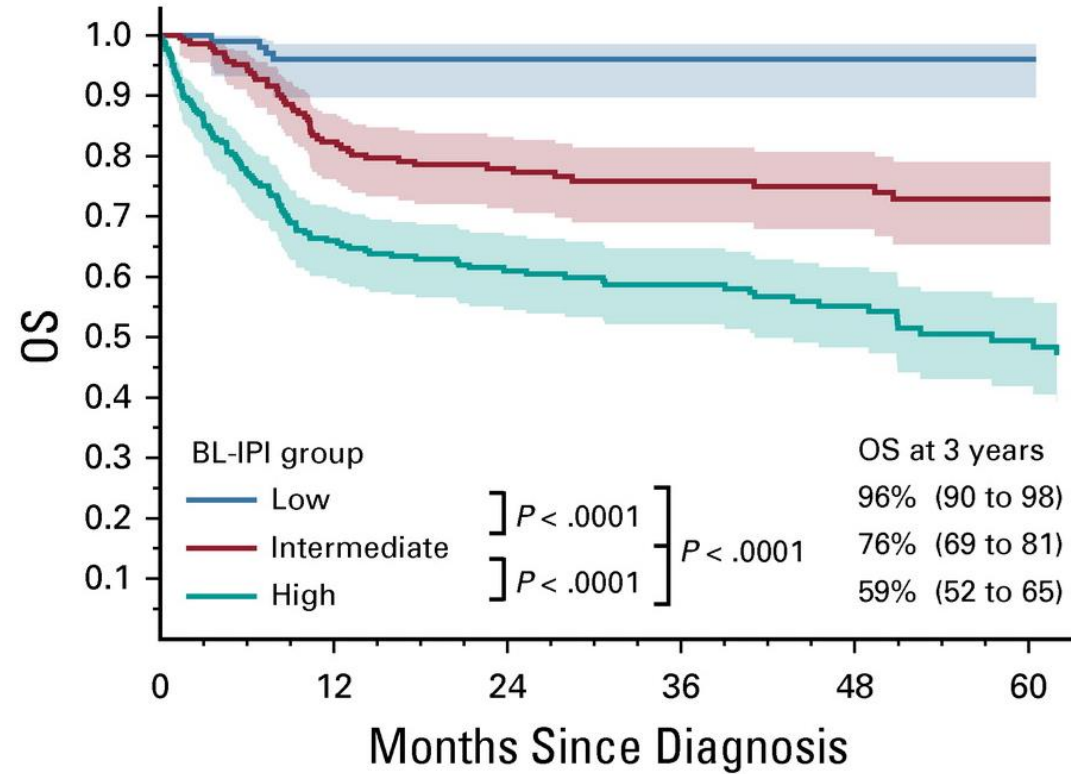


# Burkitt IPI

## BL - IPI

- age >40
- ECOG ≥ 2
- LDH > 3x ULN
- CNS involvement

Low = 0  
Intermediate = 1  
High ≥ 2

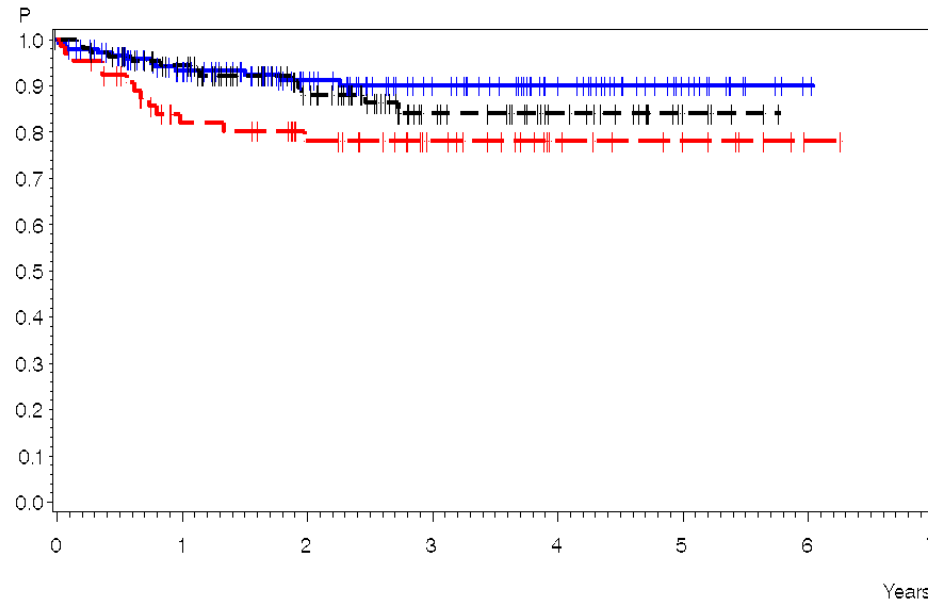


n	0	12	24	36	48	60
Low	104	89	74	56	42	30
Intermediate	206	157	123	91	73	50
High	260	153	119	94	65	43



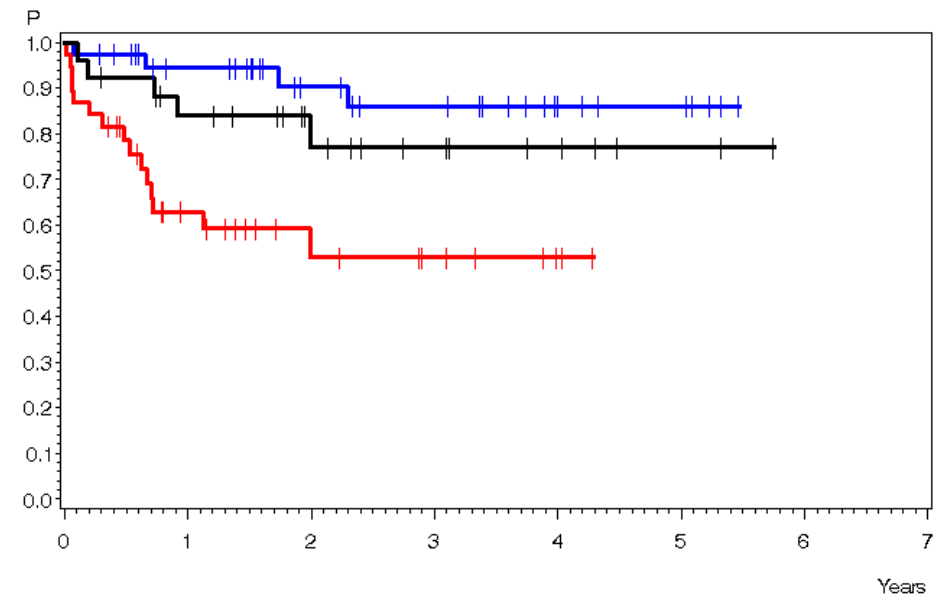
# Outcome – GMALL B-ALL/NHL 2002

15-55 years



<span style="color: blue;">—</span> Burkitt	<b>0.90</b>	<b>(N=144)</b>
<span style="color: red;">—</span> Burkitt Leukemia	<b>0.78</b>	<b>(N=65)</b>
<span style="color: black;">—</span> DLBCL	<b>0.84</b>	<b>(N=110)</b>

>55 years



<span style="color: blue;">—</span> Burkitt	<b>0.86</b>	<b>(N=39)</b>
<span style="color: red;">—</span> Burkitt Leukemia	<b>0.53</b>	<b>(N=38)</b>
<span style="color: black;">—</span> DLBCL	<b>0.77</b>	<b>(N=26)</b>



# Toxizitätsprofil

## GMALL B-ALL/NHL 2002

### GMALL B-ALL/NHL 2002 (15-55 y)

#### Toxicity Grade III/IV

	R+Cycle A1	R+Cycle B1	R+Cycle C1
<b>Evaluable</b>	<b>77</b>	<b>70</b>	<b>68</b>
<b>WBC &lt; 1.0</b>	<b>71%</b>	<b>21%</b>	<b>57%</b>
<b>Gran. &lt; 0.5</b>	<b>65%</b>	<b>20%</b>	<b>60%</b>
<b>Infection</b>	<b>22%</b>	<b>13%</b>	<b>12%</b>
<b>Thrombopenia °4</b>	<b>1 d (1-9)</b>	<b>2 d (1-2)</b>	<b>2 (1-7)</b>
<b>GOT/GPT &gt; 5xN</b>	<b>29%</b>	<b>10%</b>	<b>9%</b>
<b>Mucositis</b>	<b>36%</b>	<b>37%</b>	<b>28%</b>



## Options ?

- **Reduced dose of MTX ?**  
Favourable survival in elderly Burkitt 's NHL (0.5 g MTX)  
but CNS relapses in elderly B-ALL
- **Reduced infusion time of MTX (4 h vs 24 hrs) ?**  
HDMTX 4 hr infusion less toxic  
Equally effective in low risk but less effective in high risk
- **Reduced number of cycles ?**  
Equally effective in low risk but less effective in high risk  
Cairo et al, Blood 2007, Patte et al, Blood 2007





# Risikofaktoren für verzögerte MTX Clearance

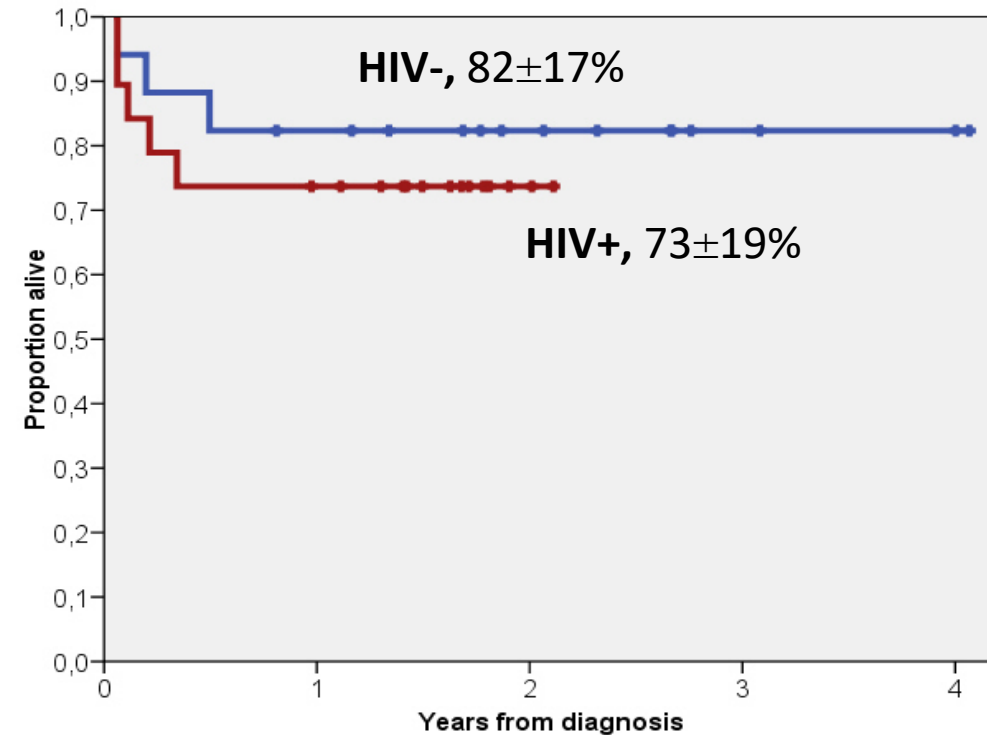
- 3rd space e.g pleural effusion
- urine pH<7
- overweight
- comedication (MTX-interference, nephrotoxic, Vitamin C, iv. contrast CT)
- advanced age
- baseline hepatic dysfunction
- baseline renal insufficiency
- **In case of delayed clearance: Carboxypeptidase**

siehe GMALL Empfehlung  
zur Durchführung der MTX Therapie



# PETHEMA Group: BURKIMAB bei HIV<sup>+</sup> BL

	HIV+	HIV-
Total	19	17
CR	79%	88%
Early Death	16%	12%
Death CR	11%	0



- HIV+:**
- 15 on parallel HAART, 4 started HAART with chemo
  - Higher incidence of mucositis and infections
  - More treatment delays
  - No difference in overall outcome

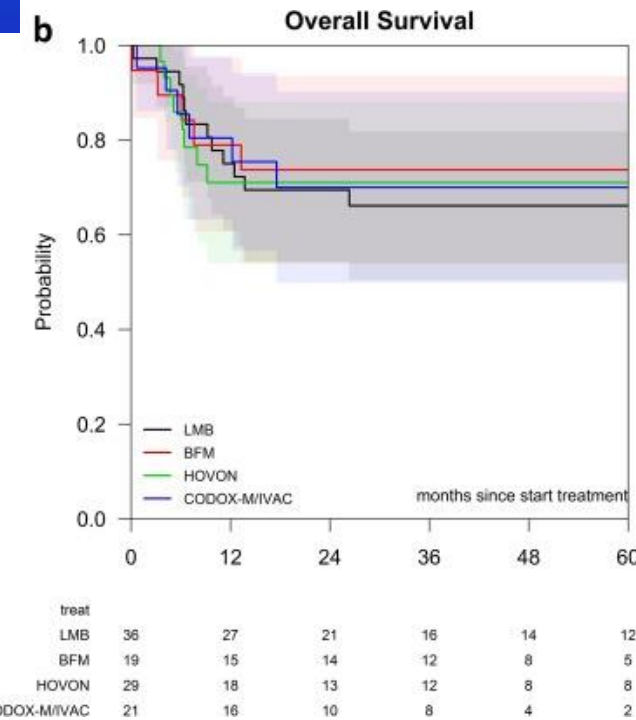
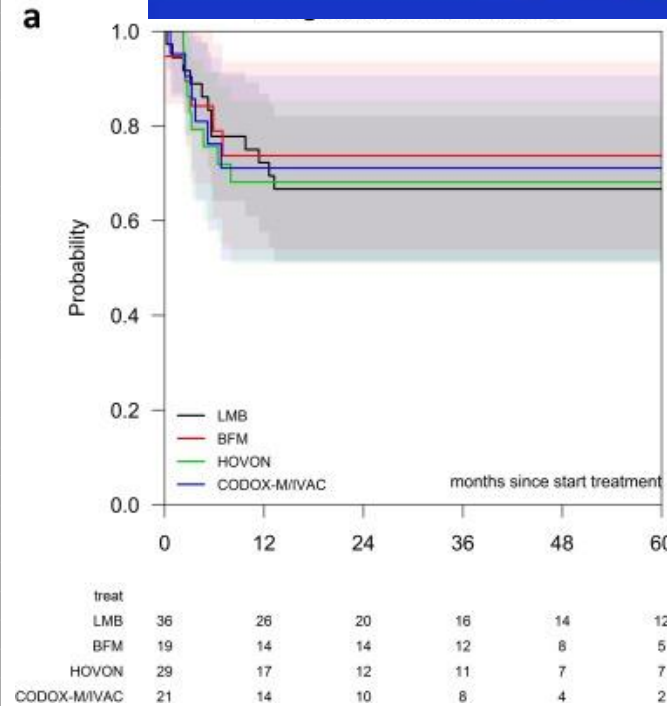


# Verschiedene intensive Protokolle

	LMB C	Hoelzer (GMALL)	up front PSCT according to HOVON 40/63 protocol	dm R-CODOX-M/R-IVAC*	DA-EPOCH-R	
	full protocol	full protocol	full protocol	2 courses	6 courses maximal dose escalation	
<b>cyclophosphamide</b>	5800	3000	7000	3200	7447	mg/m <sup>2</sup>
<b>doxorubicin</b>	240	100	280	80	397	mg/m <sup>2</sup>
<b>vincristine</b>	8	8	4.2	6	9,6	mg/m <sup>2</sup>
<b>etoposide</b>	2500	1000	2800	600	1986	mg/m <sup>2</sup>
<b>rituximab</b>	3000	3000	2875	2875	2250	mg/m <sup>2</sup>
<b>MTX iv</b>	27000	9000		6000		mg/m <sup>2</sup>
<b>cytarabine iv</b>	25000	8600	800	16000		mg/m <sup>2</sup>
<b>cytarabine sc</b>	1000					
<b>prednisone</b>	1620	300	1250		3600	mg/m <sup>2</sup>
<b>dexamethasone</b>		100				mg/m <sup>2</sup>
<b>mitoxantrone</b>			30			mg/m <sup>2</sup>
<b>melphalan</b>			140			mg/m <sup>2</sup>
<b>ifosfamide</b>		8000		15000		mg/m <sup>2</sup>
<b>teniposide</b>		200				mg/m <sup>2</sup>
<b>vindesine</b>		6				mg/m <sup>2</sup>
<b>VM26</b>		200				mg/m <sup>2</sup>
<b>MTX it</b>	135	120	75	96	90	mg
<b>cytarabine it</b>	200	320		560		mg
<b>duration of protocol</b>	30	21	20	12	18	weeks
<b>in hospital</b>	24	21	9	8	0	weeks
<b>out of hospital</b>	6	0	11	4	18	weeks

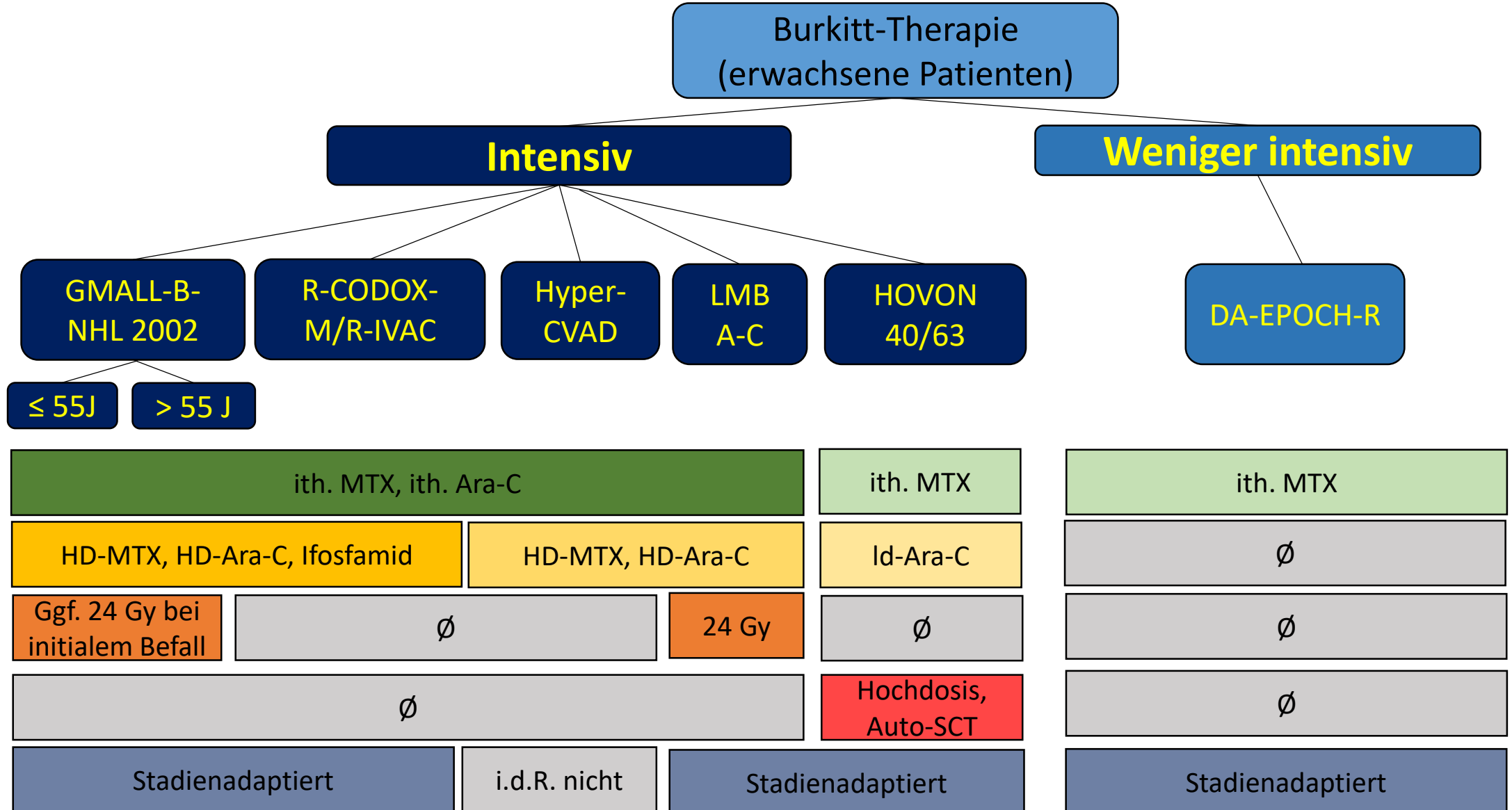


er komplexen  
derlanden, N= 147





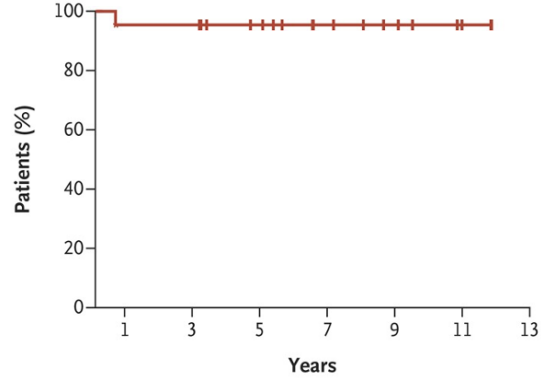
# Unterschiede: Burkitt-Protokolle



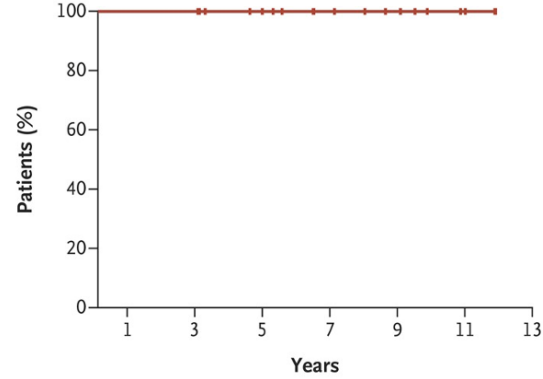


# Unizentrisch

A Freedom from Progression (DA-EPOCH-R)

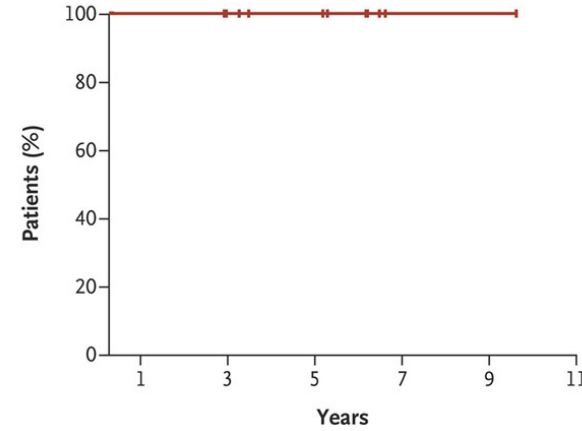


B Overall Survival (DA-EPOCH-R)

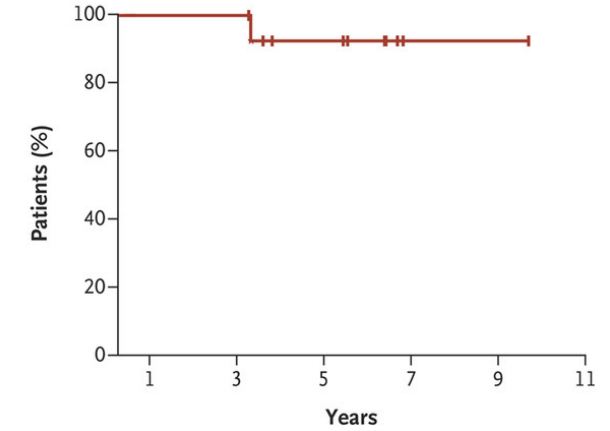


n: 19; DA-EPOCH-R

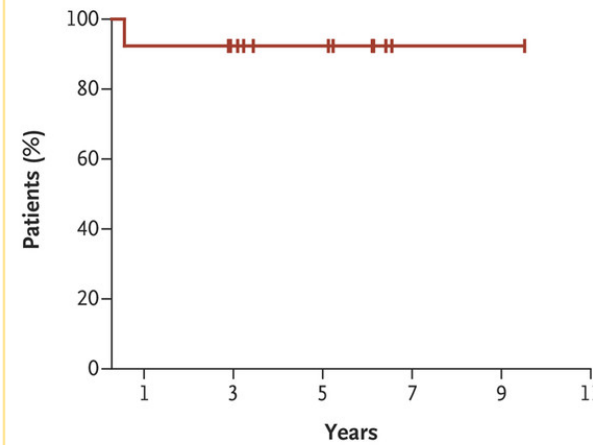
C Freedom from Progression (SC-EPOCH-RR)



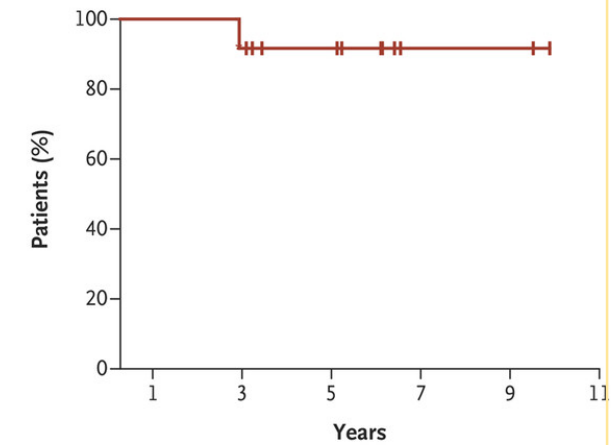
D Overall Survival (SC-EPOCH-RR)



E Freedom from Progression (Immunodeficiency-Associated Variant)



F Overall Survival (Immunodeficiency-Associated Variant)



n: 11; SC-EPOCH-RR HIV<sup>+</sup>

## EPOCH-R cycle 1

Days	Drug	Dose	Route
1-5	Prednisolone	60mg/m <sup>2</sup> <b>BD</b>	PO
1	Rituximab	375mg/m <sup>2</sup>	IV infusion
1-4	Doxorubicin	10mg/m <sup>2</sup> /day	IV infusion
1-4	Vincristine	0.4mg/m <sup>2</sup> /day	IV infusion
1-4	Etoposide	50mg/m <sup>2</sup> /day	IV infusion
5	Cyclophosphamide	750mg/m <sup>2</sup>	IV
6 onwards	GCSF (as per local policy)	Daily until neutrophils >1.0 x 10 <sup>9</sup> /L	SC

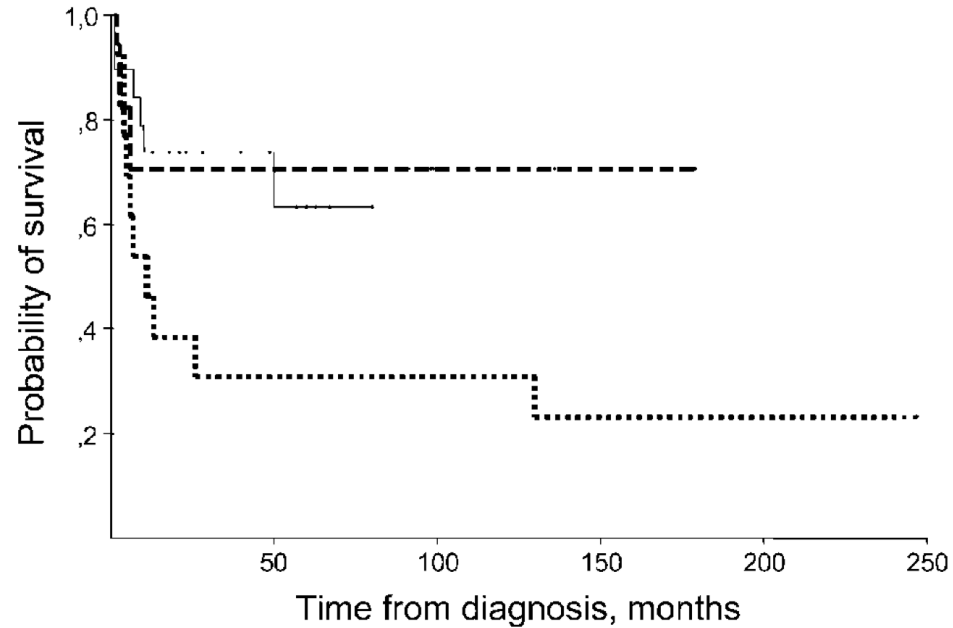
- Rituximab d1
- Doxorubicin, Vincristin und Etoposid werden an d1-4 gleichzeitig über 24 Stunden verabreicht. CAVE: sicherer Zugang!!
- Cyclophosphamid an d5 als Bolus.

## HIGH RATE OF MORBID CENTRAL LINEAS SOCIATED COMPLICATIONS DURING TREATMENT WITH DOSE-ADJUSTED R-EPOCH THERAPY FOR NON-HODGKINLYMPHOMA

**P. Peagan, ..., and J. Friedberg, ICML 2017  
(Abstract 482)**

- n=43 mit DA-R-EPOCH
  - 17 Patienten (39,5%, 95% CI 0,25–0,56) hatten mind. eine Zugang-assozierte Komplikation (LAC):
    - 15 Patienten (35%, 95% CI 0,21–0,51) hatten VTE; BMI  $\geq 35$  kg/m<sup>2</sup> und PICC (p= 0,04 bzw. p= 0,02; univariate Analyse)
    - 3 Patienten hatten eine Kather-assozierten Infekt
    - 2 Patienten hatten Extravasate (beide mit Ports)
- -> Ca. 40% der Patienten mit DA-EPOCH-R hatten Katheter-assozierte Komplikationen, die Hälfte Grad 3.

# DA-EPOCH-R in BL – warum kein R-CHO(E)P?

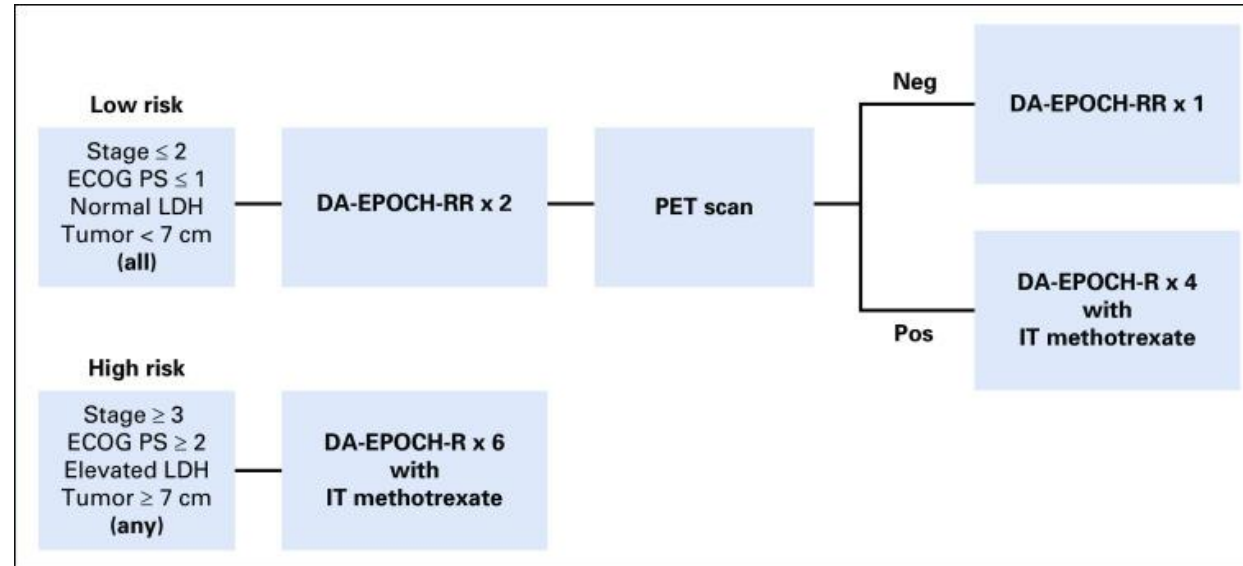


**Figure 3.** Burkitt's/Burkitt-like lymphoma: Kaplan–Meier plot of overall survival according to treatment regimen (intention to treat). . . . ., Mm CHOP; - - - -, Mm CHOP + HDT; —, BFM.

Treatment	MmCHOP	MmCHOP+HDT	BFM
No. of patients	13	17	19
Treatment period	1982–1987	1988–1994	1995–2001
Gender			
Female	4	6	6
Male	9	11	13
Age, years, median (range)	30 (15–44)	31 (15–56)	36 (17–69)
Follow-up, months (range)	218 (190–247)	127 (71–179)	49 (13–80)
Burkitt's lymphoma	12	14	13
Burkitt-like lymphoma	1	3	6
Stage I	4 [0] <sup>a</sup>	4 [0]	4 [2]
Stage II	1 [1]	3 [0]	7 [1]
Stage III	1 [0]	0	1 [0]
Stage IV	7 [0]	10 [3]	7 [3]
Bulky tumours	5 [0]	7 [2]	8 [4]
Elevated LDH	9 [1]	11 [3]	11 [5]
ECOG >2	4 [0]	6 [1]	8 [4]
Age >40 years	3 [0]	6 [3]	9 [4]
IPI score <1	5 [1]	7 [0]	9 [2]
IPI score >1	8 [0]	10 [3]	10 [4]



## Risiko-adaptiert



Niedrig-Risiko: 3 Zyklen ohne ZNS-Prophylaxe

Hoch-Risiko: 6 Zyklen mit intrathekaler ZNS-Prophylaxe oder erweiterte intrathekale Behandlung erhielten, wenn die Leptomeningeale Beteiligung.

Prim. Endpunkt: (EFS),

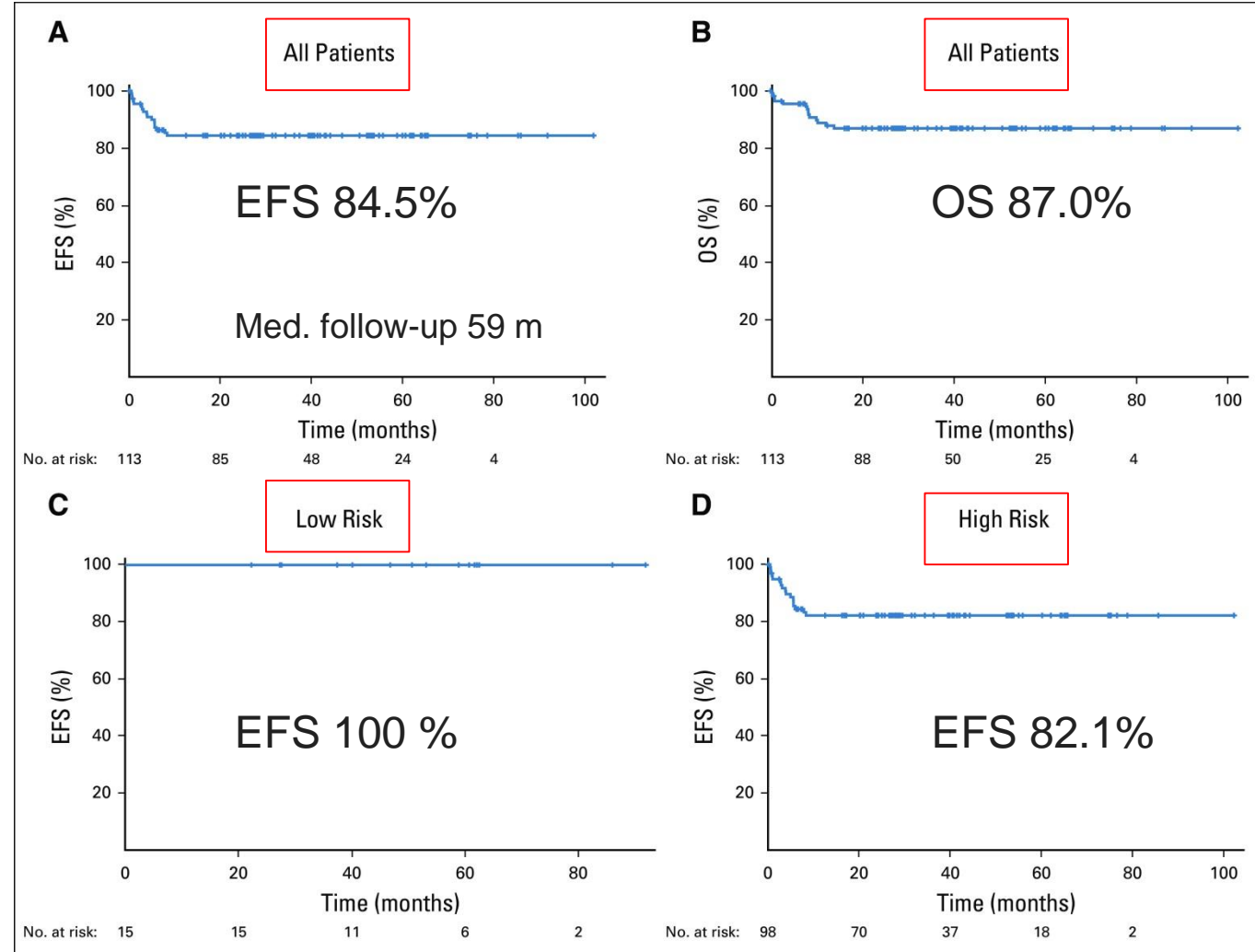
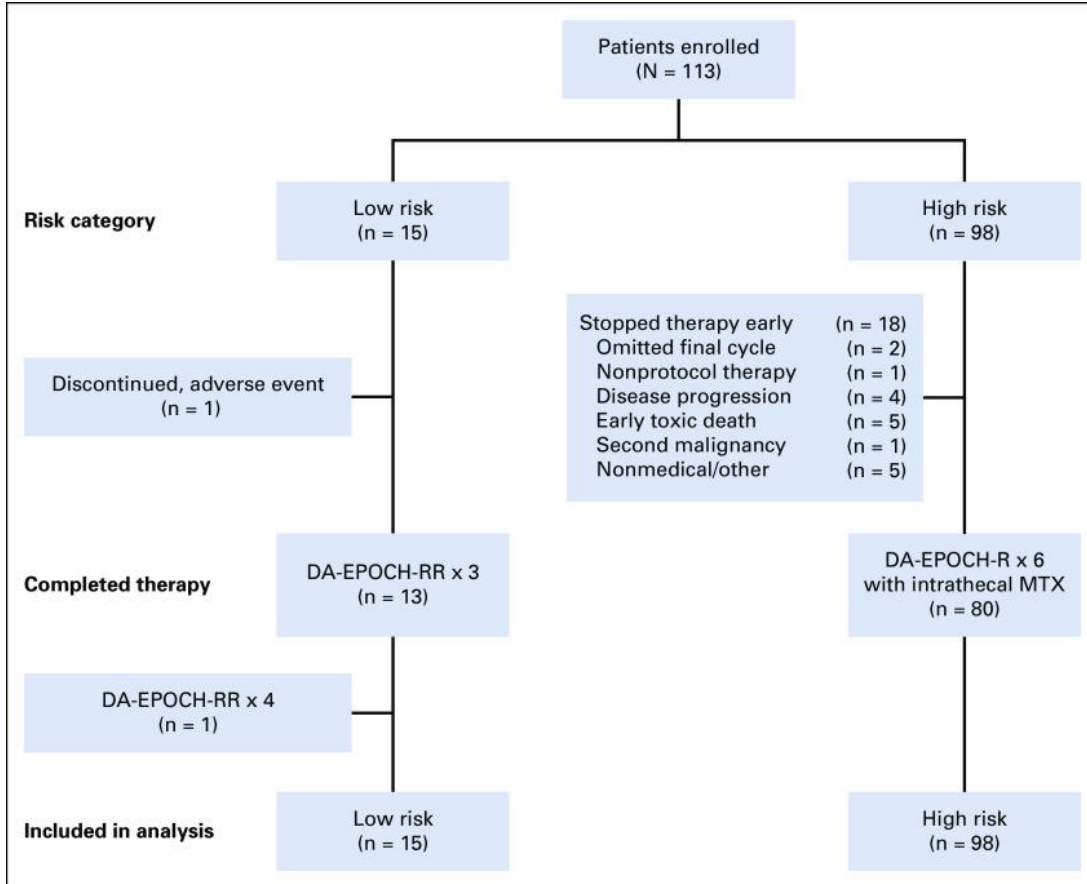
seku. Endpunkte: Toxizität und Prädiktoren für EFS und Gesamtüberleben (OS)

TABLE 1. Patient Characteristics

Characteristic	No.	%
Patients enrolled	113	
Male sex	89	79
ECOG performance status		
0-1	92	81
2	14	12
3-4	7	6
HIV status		
Negative	85	75
Positive	28	25
Age, years		
Median (range)	49 (18-86)	
< 40	43	38
40-59	41	36
≥ 60	29	26
Baseline risk stratification		
Low risk	15	13
High risk	98	87
Ann Arbor stage III or IV	79	70
Extranodal disease, any site involved	76	67
Bowel	27	24
Liver	16	14
Bone marrow or peripheral blood	28	25
CSF	11	10
Serum lactate dehydrogenase > ULN	69	61
IPI, risk group		
Low	42	37
Low intermediate	20	18
High intermediate	24	21
High	27	24

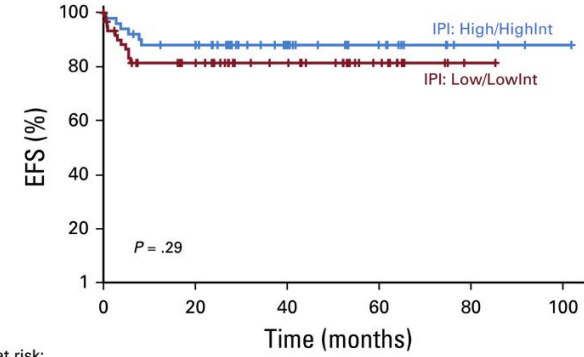
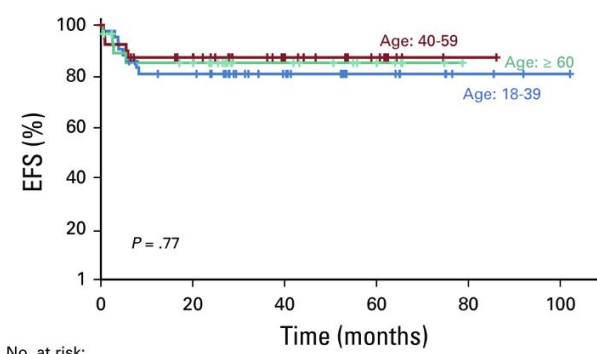
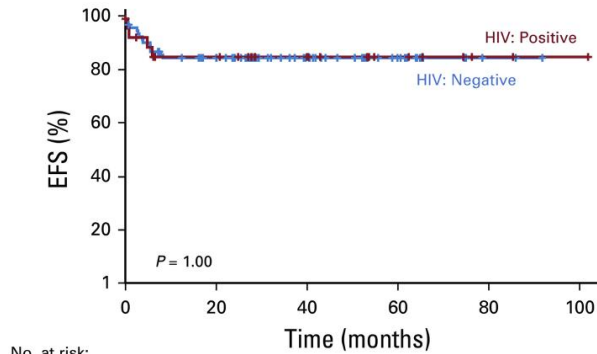
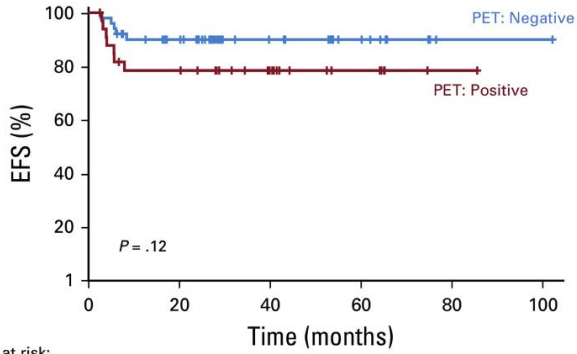


# DA-EPOCH-R bei BL





# DA-EPOCH-R bei BL



No. at risk:

PET: Negative	51	39	20	11	1
PET: Positive	34	25	14	6	1

No. at risk:

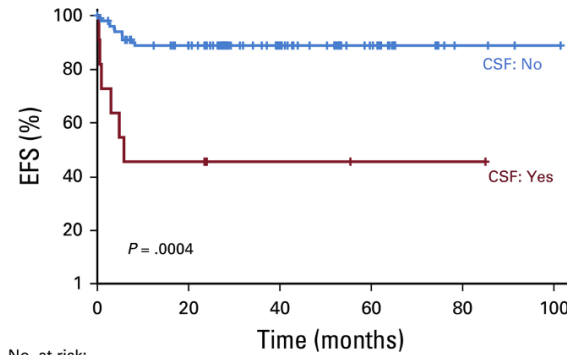
HIV: Negative	85	65	35	18	2
HIV: Positive	28	20	13	6	2

No. at risk:

Age: 18-39	43	32	19	9	3
Age: 40-59	41	31	18	9	1
Age: ≥ 60	29	22	11	6	0

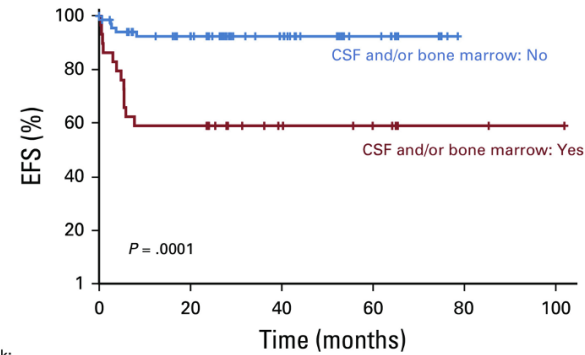
No. at risk:

IPI: High/HighInt	51	43	22	12	3
IPI: Low/LowInt	62	42	26	12	1



No. at risk:

CSF: No	102	80	46	23	3
CSF: Yes	11	5	2	1	1



No. at risk:

CSF and/or bone marrow: No	0	69	53	29	12	0
CSF and/or bone marrow: Yes	1	29	17	8	6	2

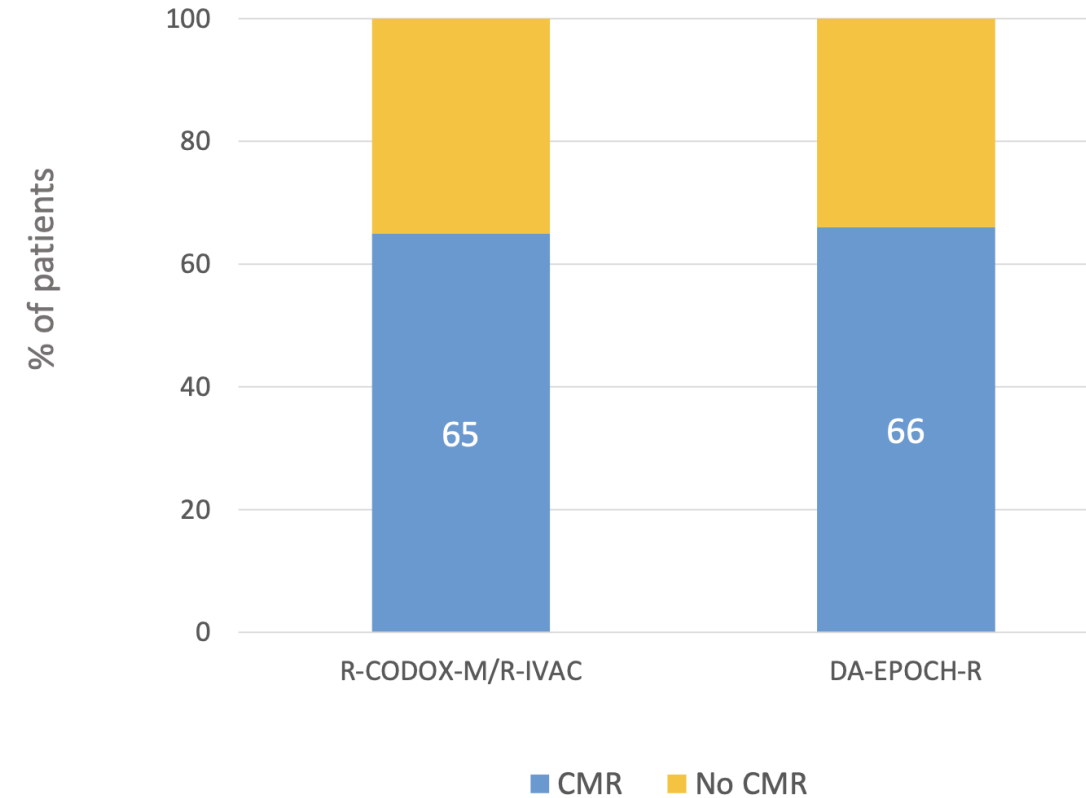
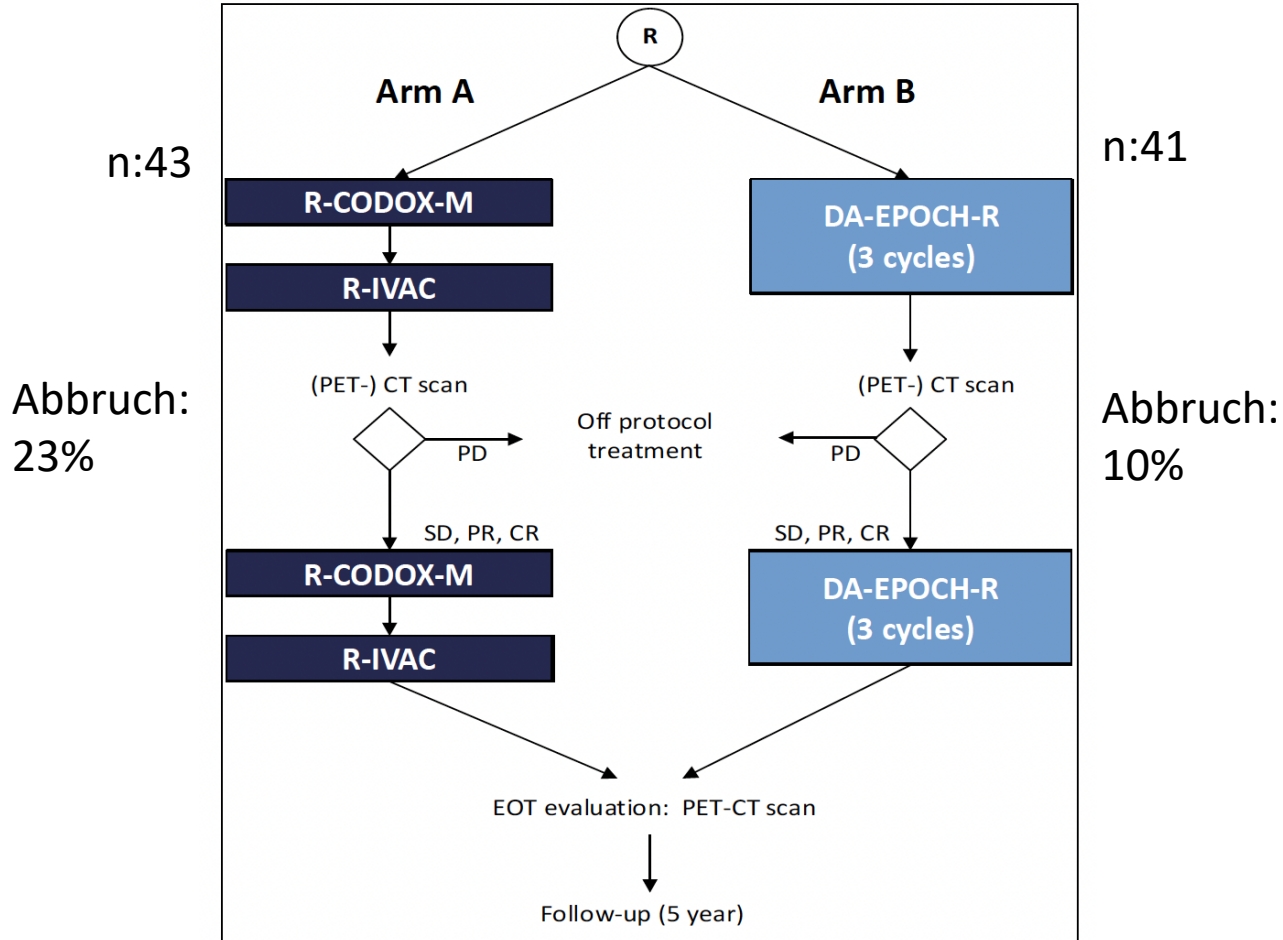


# HOVON/SAKK: R-CODOX-M/IVAC-R vs. DA-R-EPOCH

Frage: 2y-PFS von 70% mit int. Therapie zu 85% mit DA-EPOCH-R?  
-> 2014 bis 2021: 89 Patienten, 84 randomisiert

Ansprechen

## PET-CT scan



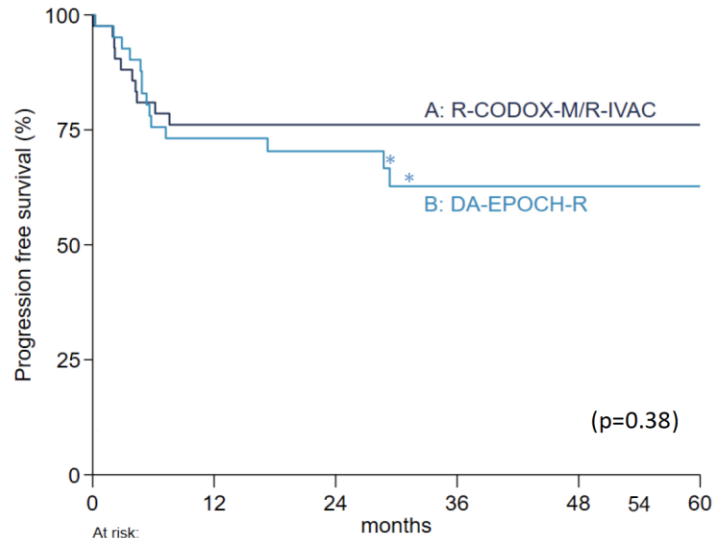




# HOVON/SAKK Studie: R-CODOX-M/IVAC-R vs. DA-R-EPOCH

## PFS

2J-PFS: 76% (95% CI: 60%–86%)  
2J-PFS: 70% (95% CI: 54%–82%)



### ARM A: R-CODOX-M/R-IVAC

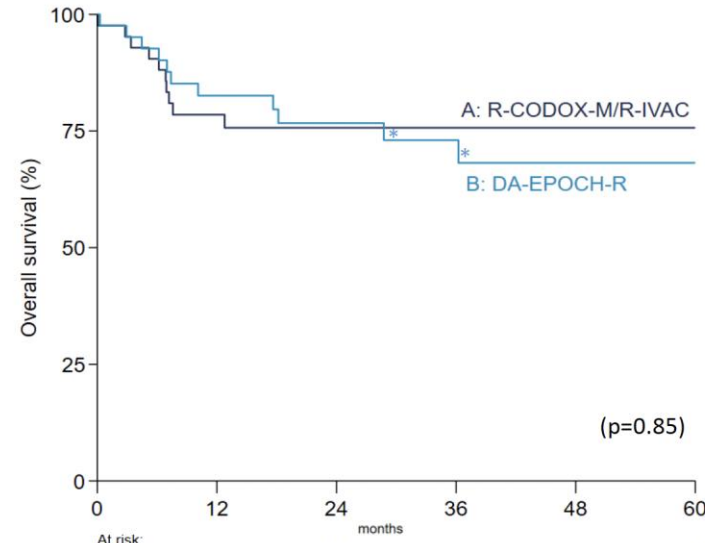
- 10 events:
- 7 BL (progression/relapse)
  - 3 death (in remission)

### ARM B: DA-EPOCH-R

- 14 events:
- 12 BL (progression/relapse)
  - 2 death (in remission)

## OS

2J-OS: 76% (95% CI 60%–86%)  
2J-OS: 75% (95% CI 59%–86%)



### ARM A: R-CODOX-M/R-IVAC

- 10 deaths:
- 8 Burkitt Lymphoma
  - 2 infections (sepsis, COVID)

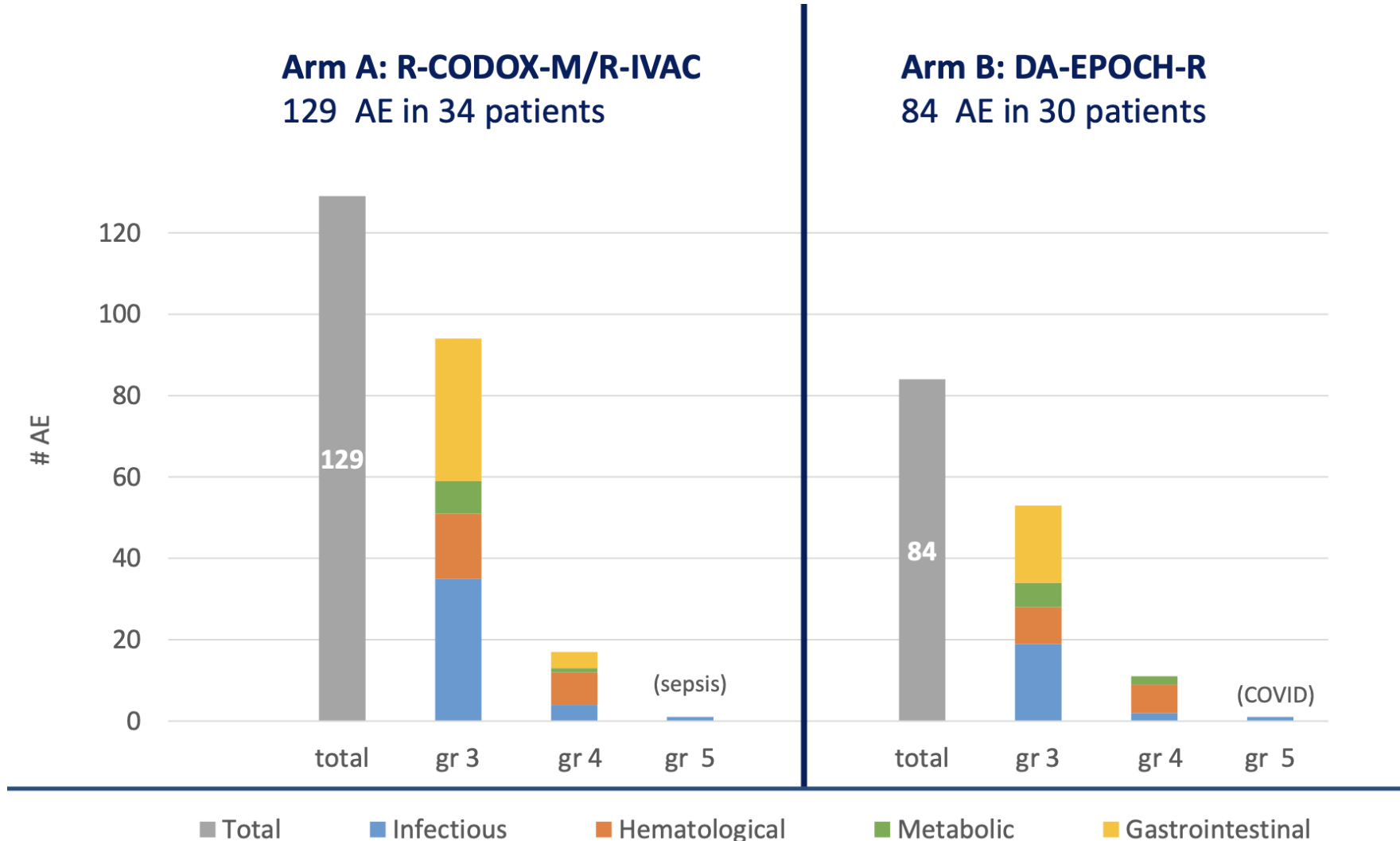
### ARM B: DA-EPOCH-R

- 11 deaths:
- 7 Burkitt Lymphoma
  - 2 infections (sepsis, COVID)
  - 1 secondary malignancy\*
  - 1 complication allo-PSCT\*



# HOVON/SAKK Studie: Toxizität I

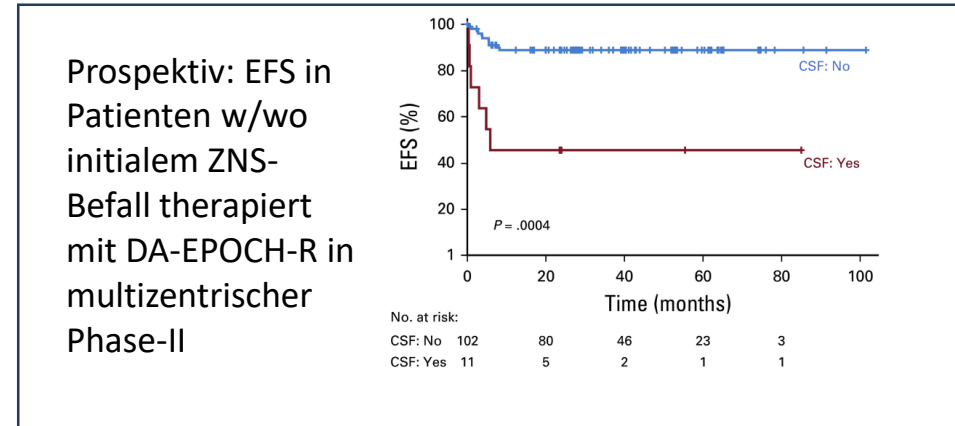
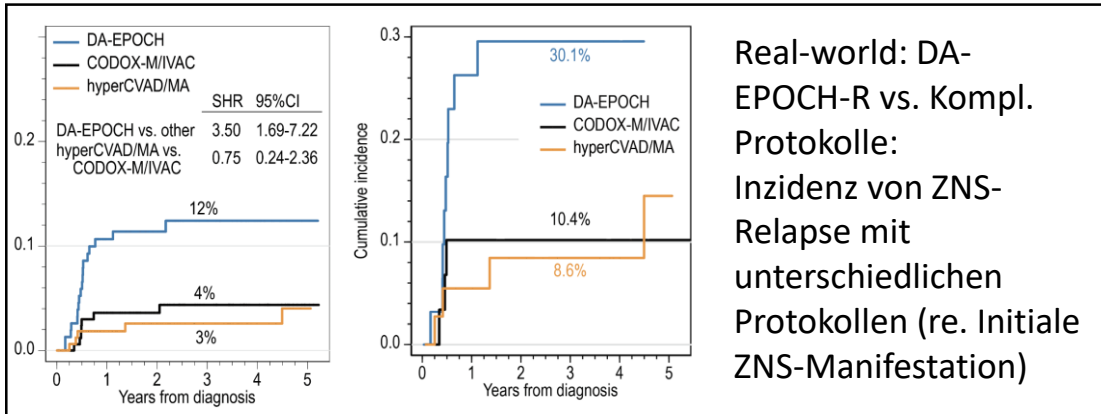
## R-CODOX-M/IVAC-R vs. DA-R-EPOCH



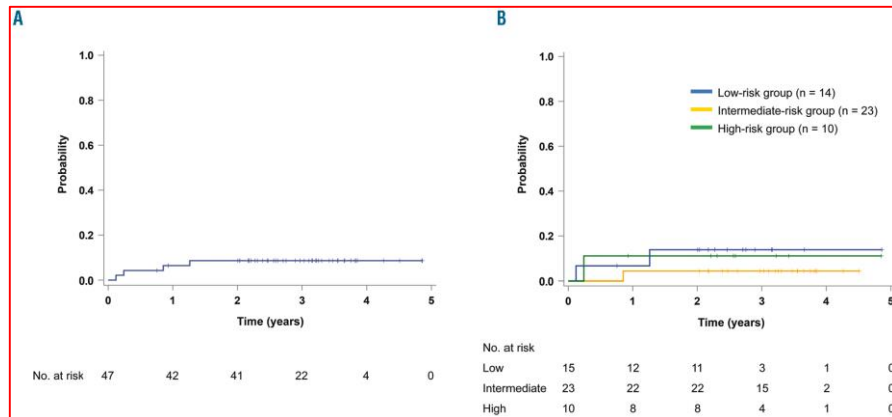


# Burkitt-Lymphom: ZNS-Prophylaxe/Therapie

- Hinzunahme ZNS-gängiger Substanzen bei BL essentiell
- ithr. MTX v.a. bei ZNS-Befall unzureichend



- DA-EPOCH-R combined with HD-MTX in CD5<sup>+</sup> DLBCL (phase-II, n=47 Patienten, kein TRM),



## GMALL B-NHL 2002:

Ggf. ZNS-Radiatio mit 24 Gy nach RS

CAVE: für >55 Jahre

-> **Amendment IX:** zusätzliche i.th. Prophylaxe und bei leukämisch **dosisreduziert Block C** auch für >55J

# Burkitt-Lymphom/ Burkitt-Leukämie

## Erstlinientherapie

### GMALL-B-ALL/NHL 2002

- Für  $\leq 55$  J: A1 B1 C1 A2 B2 C2 +2xR
- Wenn frühes Stadium UND kein extranodaler Befall UND CR nach Zyklus 2: 4 statt 6 Zyklen +2xR

### GMALL-B-ALL/NHL 2002

- Für  $> 55$  J: A1\*B1\*A2\*B2\*A3\*B3\* +2xR
- Wenn frühes Stadium UND kein extranodaler Befall UND CR nach Zyklus 2: 4 statt 6 Zyklen +2xR
- Burkitt-Leukämie:  
A1\*, B1\*, C1\*, A2\*, B2\*, C2\* +2xR

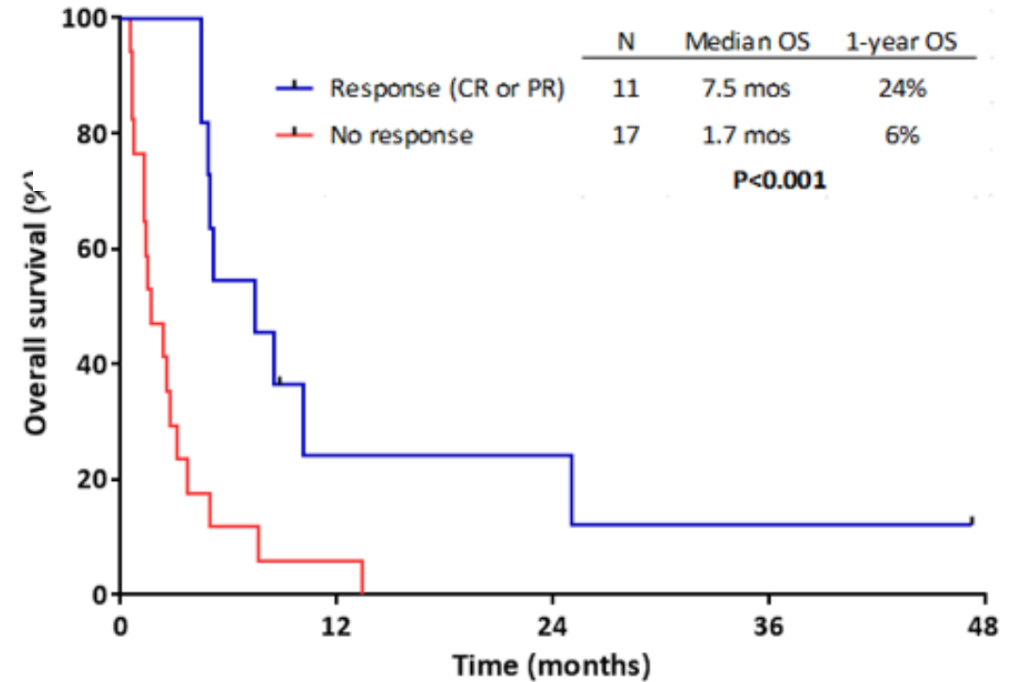
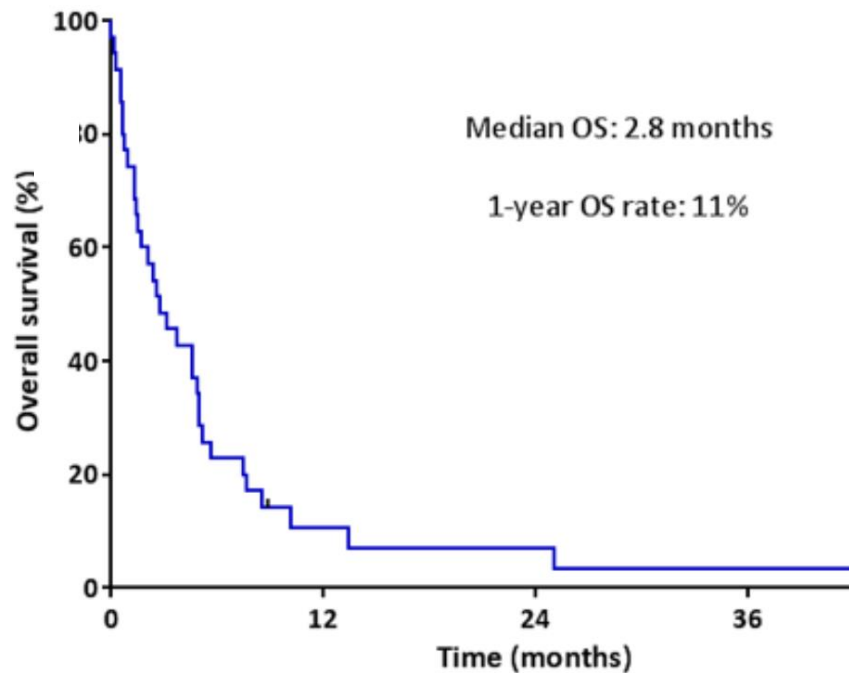
## Alternative Therapie bei z.B. Kontraindikationen oder entsprechender Komorbidität

### 6x DA-EPOCH-R mit i. th. MTX

- Wenn frühes Stadium (Stadium  $\leq 2$ ; ECOG PS  $\leq 1$ ; normale LDH; kein Bulk) UND CR in PET(2): nur 3x DA-EPOCH-RR ohne i.th. MTX Therapie



# Burkitt-Lymphom: Rezidiv-Therapie



- Chemo-sensitive r/r BL after autoTx: 3y OS 37%
- Chemo-resistant r/r BL after auto-Tx: 3y OS 7%





# BFM-Analyse

## Reinduction therapies, stem cell transplantations, treatment-related deaths, relapse, and survival for 75 patients\* with relapsed BL/B-AL between 2001 and 2016

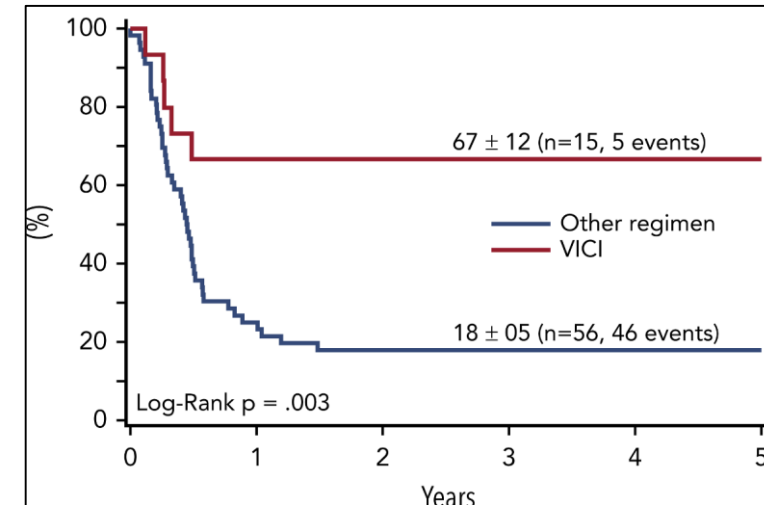
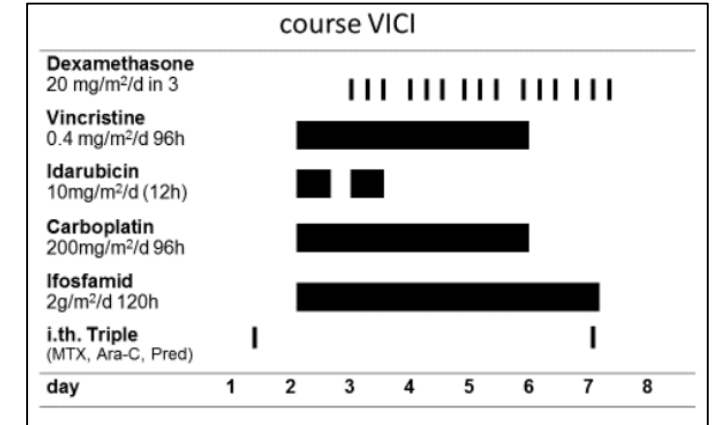
Reinduction	CC/AA-based		R-ICE		R-ICI/ICN		VICI/ICIT		EPOCH		Other	
	Auto	Allo	Auto	Allo	Auto	Allo	Auto	Allo	Auto	Allo	Auto	Allo
Patients	27		10		6		15		4		11	
Rituximab	16 (/25)		10		6		15		4		9	
TRD before SCT	0		0		0		1		0		0	
Progression before SCT	13		6		3		3		2		8	
SCT	20*		6*		3		11		2		4	
Kind of SCT	Auto	Allo	Auto	Allo	Auto	Allo	Auto	Allo	Auto	Allo	Auto	Allo
	12†	8†	4	2†	1	2	0	11	0	2	3	1
TRD after SCT	2	1	0	0	0	0	0	0	1	0	0	0
Relapse after SCT	8	3	2	2	1	1	1	1	0	2	1	1
Survival	2	4*	2‡	0	0	1		10		1	1	0

allo, allogeneic SCT; auto, autologous SCT; CR, complete remission; TRD, treatment-related death.

\* Exclusion: 1 patient without data on treatment, 1 patient who died immediately at relapse, 2 patients who received palliative care.

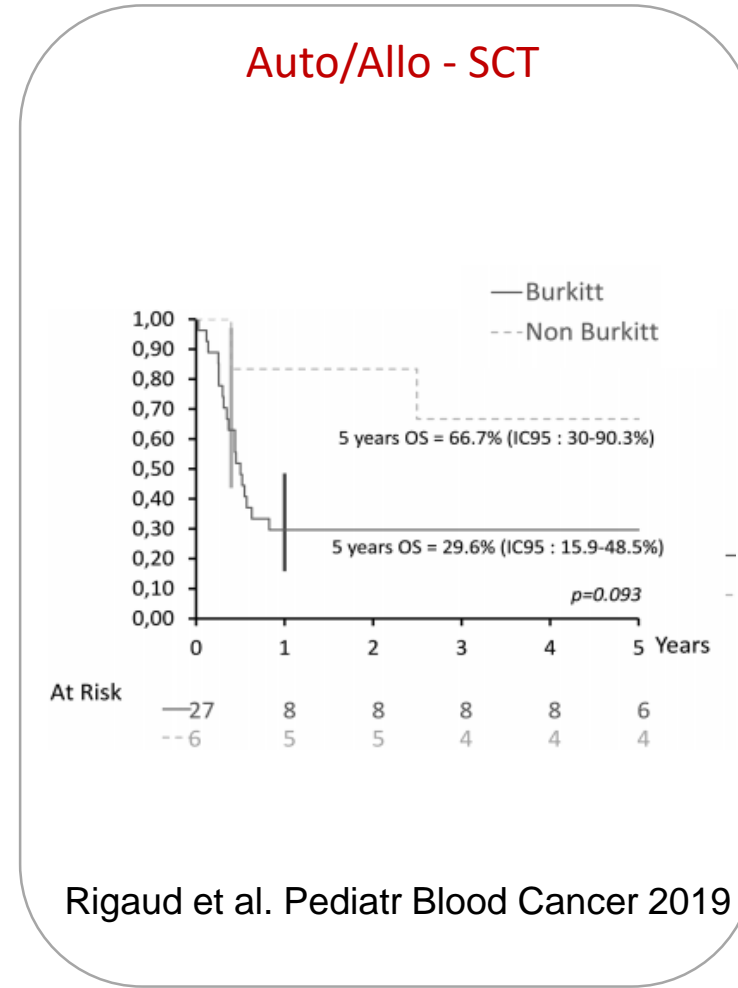
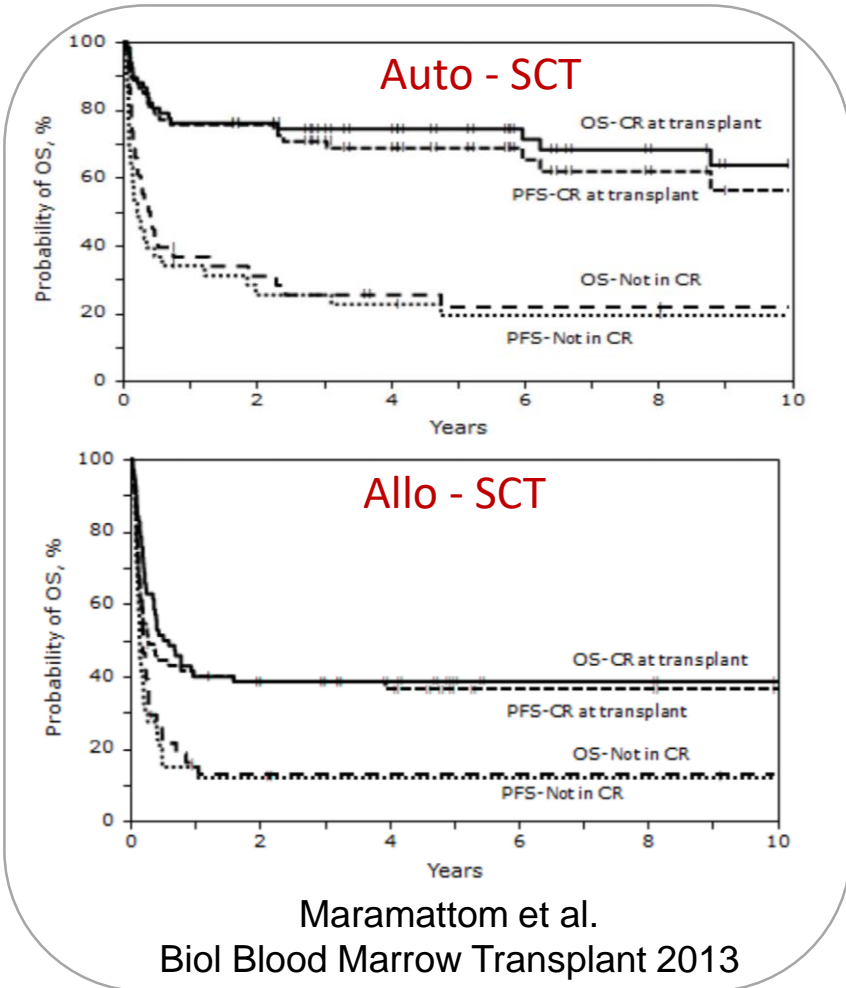
† SCT after second relapse/progression during reinduction: CC: 3 patients (2x auto - death of disease, 1x allo - CR), ICE: 2 patients (2x allo - death of disease).

‡ One patient: isolated testicular relapse.





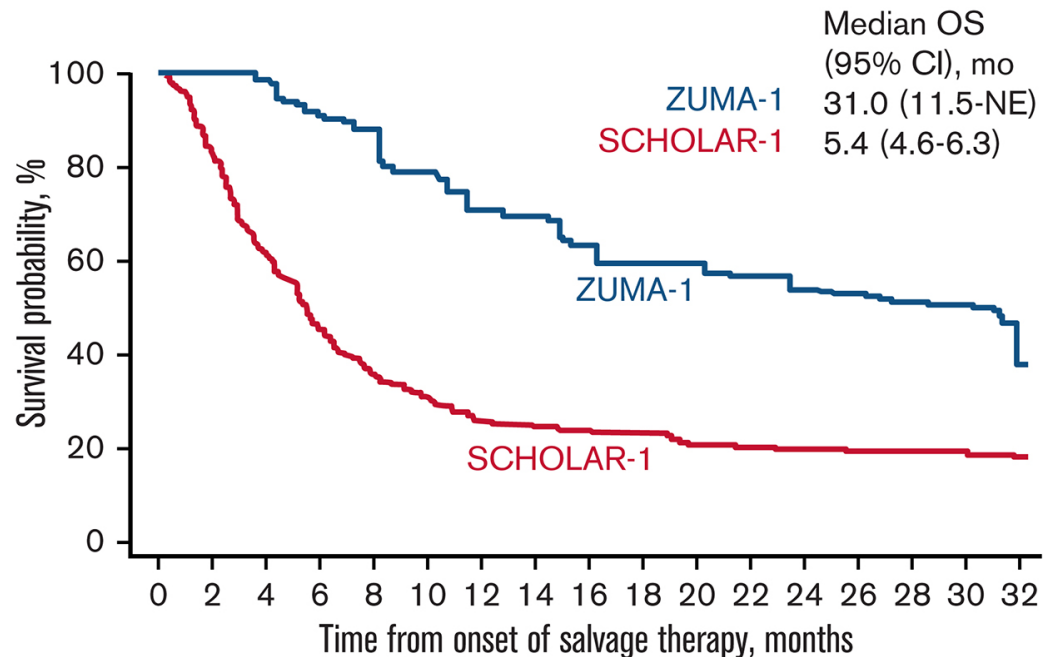
# Burkitt-Lymphom: Rezidiv-Therapie



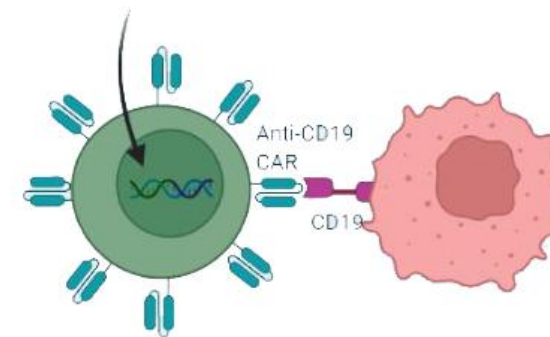


# Burkitt-Lymphom: Rezidiv-Therapie

Prolonged survival with axi-cel versus (ZUMA-1; N=81)  
standard salvage regimens (SCHOLAR-1; N=331)  
in a propensity-balanced comparison

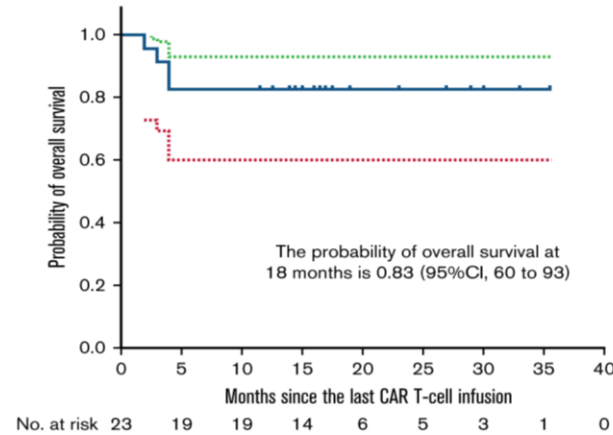
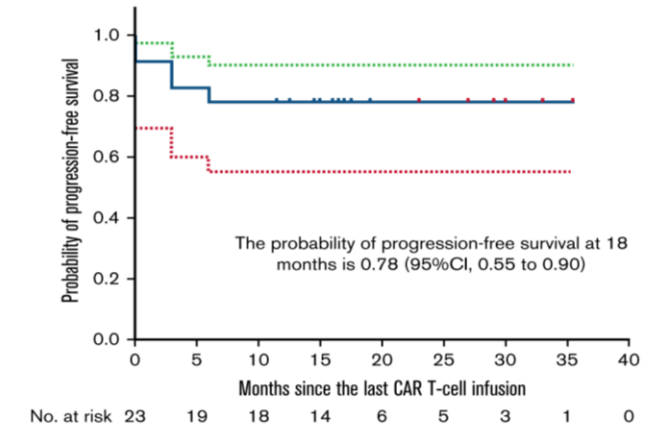
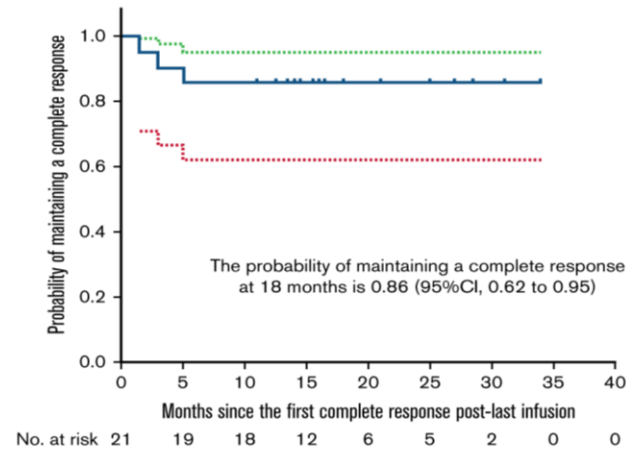
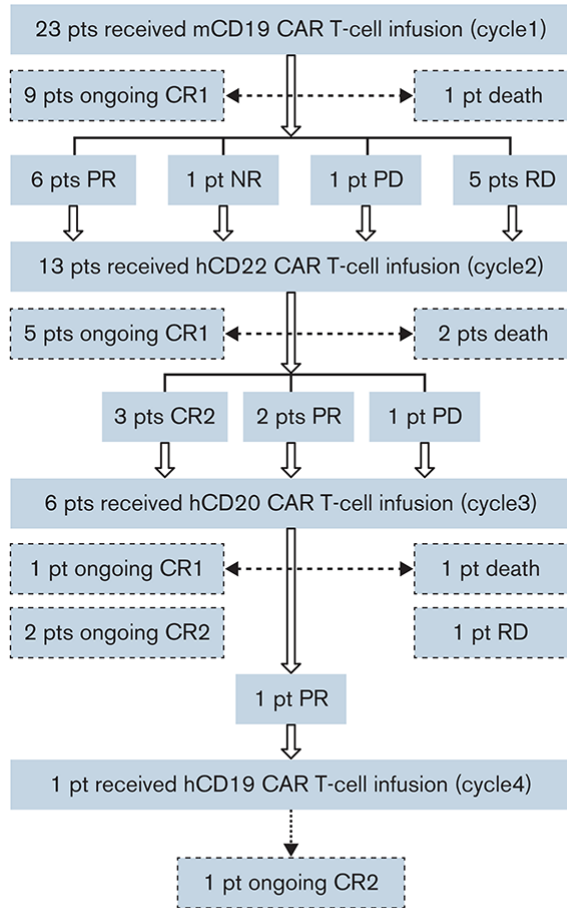


**ZUMA-25:**  
Phase 2 trial:  
**Brexucabtagene Autoleucel**  
in  
**rare B-cell malignancies (r/r)**  
**(including Burkitt)**  
Recruitment ongoing  
Est prim. completion: Nov 2029





# Burkitt-Lymphom: Rezidiv-Therapie





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SAARLANDES



UNIVERSITÄTS  
KLINIKUM FRANKFURT  
GOETHE-UNIVERSITÄT

GMALL  
German Multicenter Study Group for  
Adult Acute Lymphoblastic Leukemia



Vielen Dank für die Aufmerksamkeit