



European
Reference
Network

for rare or low prevalence
complex diseases

 Network
Paediatric Cancer
(ERN PaedCan)

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ESCP Webinar – Non-Hodgkin Lymphoma

Moderation:

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COI declaration

- PP: Nothing to disclose
- VT: Nothing to disclose
- AA: Jazz, Amgen, Novartis, Gilead

NHL

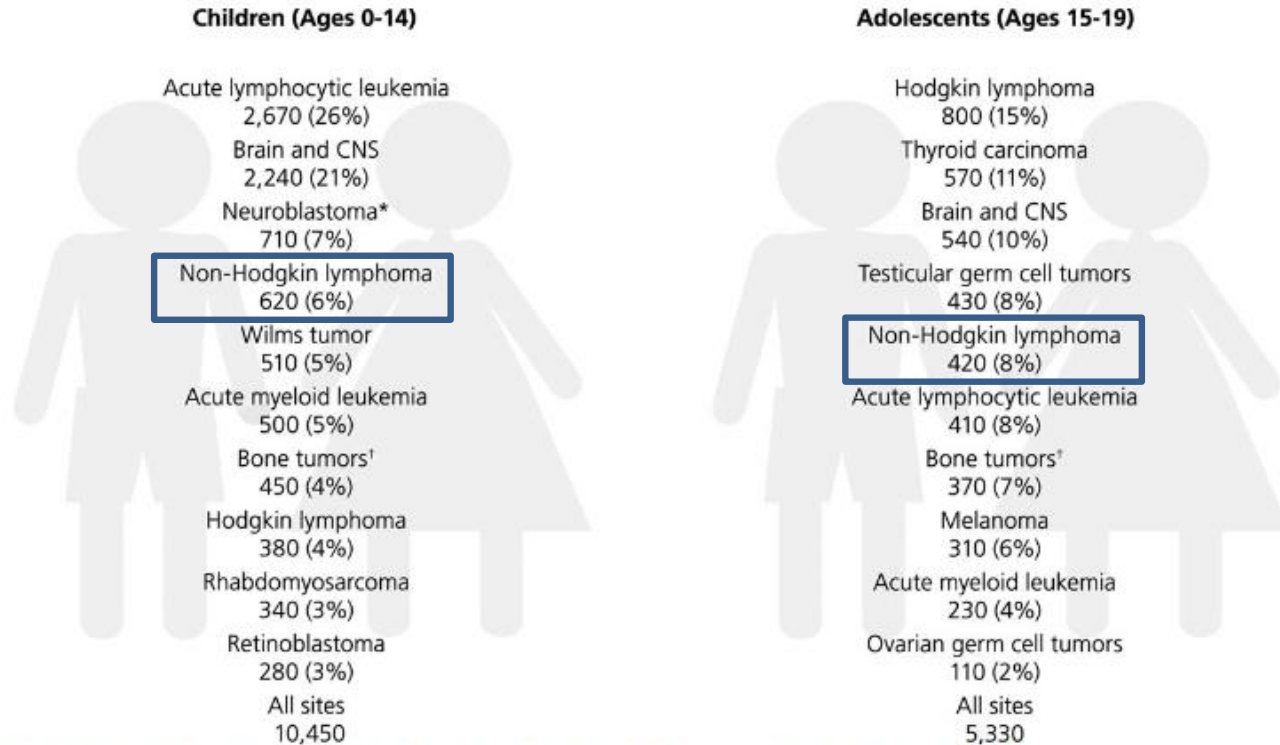
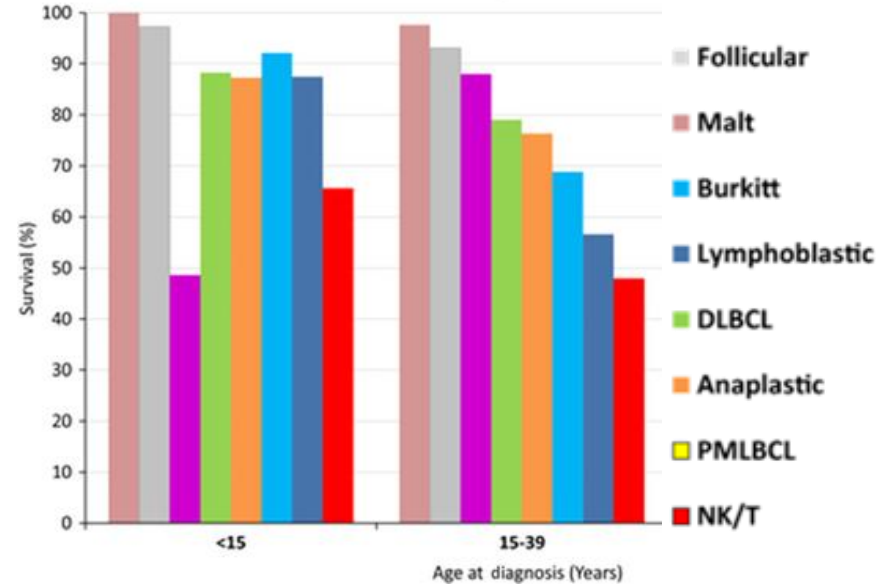
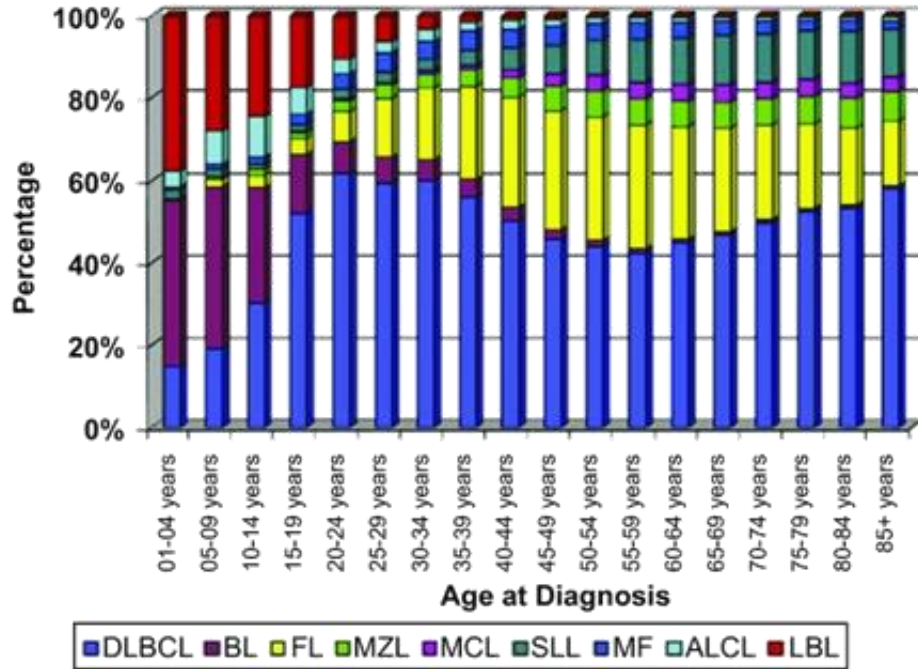


FIGURE 1. Estimated New Cases of Childhood and Adolescent Cancers, United States, 2014.

Ward E et al. Childhood and adolescent cancer statistics, 2014. CA Cancer J Clin. PMID: 24488779.

NHL

Relative Frequency of NHL Subtypes by Age at Diagnosis



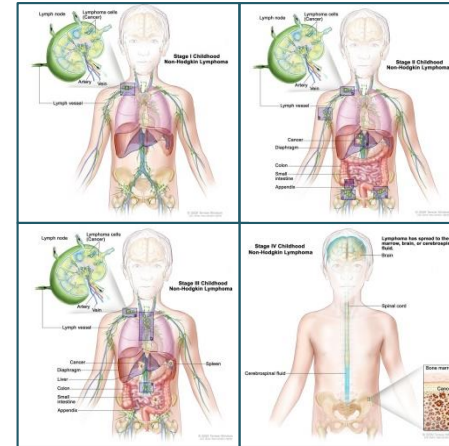
Cairo MS, Beishuizen. 2019 PMID: 30729513

NHL Staging

Table 6. International Paediatric Non-Hodgkin Lymphoma Staging System

Criteria for extent of disease

- | | |
|------------|--|
| I | <ul style="list-style-type: none"> • Single tumour with exclusion of the mediastinum and abdomen |
| II | <ul style="list-style-type: none"> • Single extranodal tumour with regional node involvement • \geq Two nodal areas on the same side of diaphragm • Primary gastrointestinal tract tumour (usually in ileocecal area), \pm involvement of associated mesenteric nodes, that is completely resectable (without malignant ascites or extension to adjacent organs) |
| III | <ul style="list-style-type: none"> • \geq Two extranodal tumours above and/or below the diaphragm • \geq Two nodal areas above and below the diaphragm • Intrathoracic tumour (mediastinal, hilar, pulmonary, pleural, or thymic) • Intra-abdominal and retroperitoneal disease, including liver, spleen, kidney, and/or ovary localizations, regardless of degree of resection (except primary GI tract tumour \pm associated mesenteric nodes that is completely resectable) • Any paraspinal or epidural tumour +/- other locations • A single bone lesion with concomitant involvement of extranodal and/or non-regional nodal sites (also, for mature B-NHL: multilocular bone disease) |
| IV | <ul style="list-style-type: none"> • Any of the above findings with initial involvement of CNS (stage IV CNS), BM (stage IV BM), or both (stage IV combined) based on conventional methods |



NHL Staging

Table 6. International Paediatric Non-Hodgkin Lymphoma Staging System

	Criteria for extent of disease
I	<ul style="list-style-type: none"> • Single tumour with exclusion of the mediastinum and abdomen
II	<ul style="list-style-type: none"> • Single extranodal tumour with regional node involvement • ≥ Two nodal areas on the same side of diaphragm • Primary gastrointestinal tract tumour (usually in ileocecal area), ± involvement of associated mesenteric nodes, that is completely resectable (without malignant ascites or extension to adjacent organs)
III	<ul style="list-style-type: none"> • ≥ Two extranodal tumours above and/or below the diaphragm • ≥ Two nodal areas above and below the diaphragm • Intrathoracic tumour (mediastinal, hilar, pulmonary, pleural, or thymic) • Intra-abdominal and retroperitoneal disease, including liver, spleen, kidney, and/or ovary localizations, regardless of degree of resection (except primary GI tract tumour ± associated mesenteric nodes that is completely resectable) • Any paraspinal or epidural tumour +/- other locations • A single bone lesion with concomitant involvement of extranodal and/or non-regional nodal sites (also, for mature B-NHL: multilocular bone disease)
IV	<ul style="list-style-type: none"> • Any of the above findings with initial involvement of CNS (stage IV CNS), BM (stage IV BM), or both (stage IV combined) based on conventional methods

Organ involvement	
CNS	CNS-1: negative: no blast in CSF, no infiltrates in cranio-spinal MRI and no intradural cranial nerve palsy
	CNS-2: < 5 cells/μl CSF, but blasts (only for LBL)
	CNS-3: CSF with blast (and > 5 cells/μl in LBL), MRI infiltrates, cranial nerve palsy not due extradural lesions
BM	≥5% and <25% blasts in BM aspiration
	Leukaemia: ≥ 25% blasts in BM aspiration
Mediastinal	Confirmed by MRI or CT scan
Lung	Confirmed by CT scan
Bone	Bone lesions on x-ray or MRI
Testicular	Painless enlargement of one or both testicles
Skin	If relevant (i.e. ALCL): confirmed by biopsy (not secondary to continuous tumour growth)

Therapy strategy of the NHL-BFM group for lymphoblastic lymphoma (LBL)



NHL-BFM Group Therapeutic Strategy for Aggressive Mature B-Cell Non-Hodgkin Lymphoma/Burkitt Leukemia (B-AL)

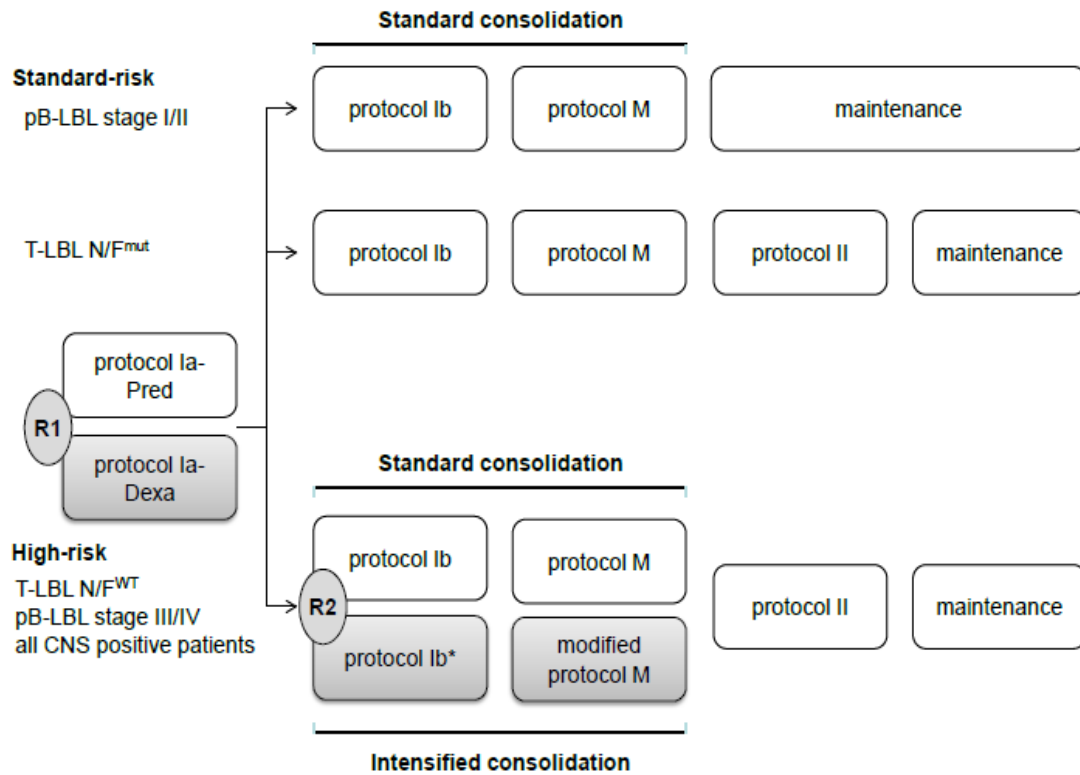
R1	Completely resected	A ⁴	B ⁴					
R2	Not resected, Stage I + II, Stage III and LDH <500 U/L	V	A ⁴	B ⁴	A ⁴	B ⁴		
R3	Stage III and LDH >500 but <1000 U/L, Stage IV/B-AL and LDH <1000 U/L and CNS negative	V	AA ²⁴	BB ²⁴	CC	AA ²⁴	BB ²⁴	
R4 ZNS-	Stage III and LDH ≥1000 U/L, Stage IV/B-AL and LDH ≥1000 U/L and CNS negative	V	AA ²⁴	BB ²⁴	CC	AA ²⁴	BB ²⁴	CC
R4 ZNS+	Stage IV/B-AL and CNS positive	VZ	AAZ1	BBZ1 ²⁴	CC	AAZ2 ²⁴	BBZ2 ²⁴	CC

Therapy strategy of the NHL-BFM group for anaplastic large cell lymphoma (ALCL)

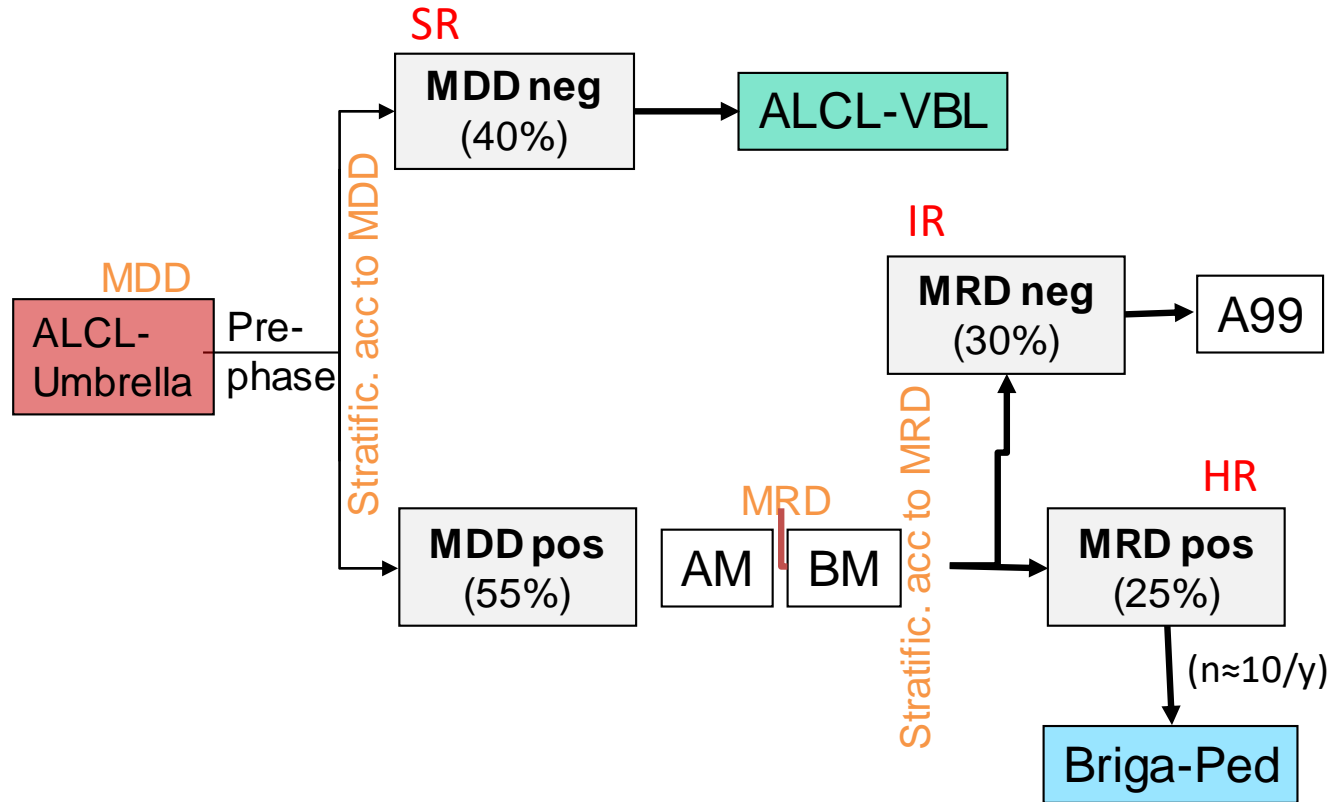
ALCL with isolated skin manifestation	watch and wait Strategie							
Completely resected ALCL		V	AM	BM	AM			
Not completely resected ALCL		V	AM	BM	AM	BM	AM	BM
ALCL CNS-pos.		VZ	AAZ1	BBZ1 ²⁴	CC	AAZ2 ²⁴	BBZ2 ²⁴	CC

* Cranial irradiation

LBL 2018 – Treatment plan



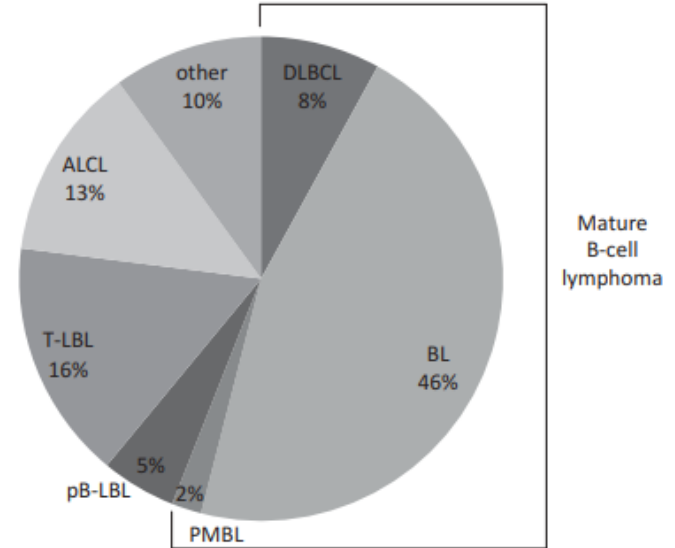
Overall Frontline strategy ALCL 2022



Mature aggressive B-cell lymphoma/leukemia

- NHL is the fourth most common malignancy in children (age 0-14y)
- Mature aggressive B-cell lymphoma/leukemia accounts for approximately 60% of NHL in childhood and adolescence
- The main histological subtypes are:
 - Burkitt lymphoma (BL)
 - Diffuse large B cell lymphoma (DLBCL)
 - Primary mediastinal large B cell lymphoma (PMLBCL)
- Recent advances have improved overall survival to 90%

Subtypes of NHL in children and adolescent



Lange J et al. Mature aggressive B-cell lymphoma across age groups - molecular advances and therapeutic implications. Expert Rev Hematol. 2017. PMID: 27936978.

General principles on diagnostic and surgical approach

Procedure for biopsy	the least invasive
Needle biopsy	restricted only when more invasive procedure is contraindicated
Alternative approaches	examination of peripheral blood, bone marrow, pleural, pericardial effusion or ascites
Mediastinal tumor	try to avoid surgery under general anesthesia if not possible, ventilation should continue post-operatively with initiation of cytoreductive therapy
In critical clinical status	start cytoreductive therapy with prednisone ± cyclophosphamide

Diagnostics work-up

Complete history including B-symptoms
(fever $>38^{\circ}\text{C}$ $>7\text{d}$, drenching night sweats, unintentional weight
loss $>10\%$ $<6\text{mo}$)

Physical examination and performance status

Bone marrow aspirate from two sites: morphology,
immunology and genetics (if $>20\%$ blasts)

Bone marrow biopsy: immunohistochemistry

CSF analysis: cell count, cytopsin, glucose, protein

Echocardiography and ECG

Fertility preservation

Imaging

Ultrasound of the abdomen, lymph nodes, testis, thorax	
MRI of the involved region	
Chest x-ray	
Cranial MRI	In case of symptoms or lymphoma manifestations close to CNS
Chest CT or MRI with contrast	In case of mediastinal involvement
X-ray/MRI/bone scan	In case of suspected bone lesions
Spinal MRI	In case of symptoms
PET-CT	Not standard, at diagnosis if no delays occur. Not used for staging

Laboratory investigations

Full blood count, differential and platelet count, reticulocytes, blood smears

Electrolytes, urea, creatinine, uric acid, calcium, phosphorous, albumin

SGOT, SGPT, gamma GT, bilirubin

LDH level

Hemostasis/coagulation tests

HIV antibody test

Serum level of HB Ags, anti-HBs antibodies, anti-HBc IgG, IgM;
Viral serology including EBV, CMV

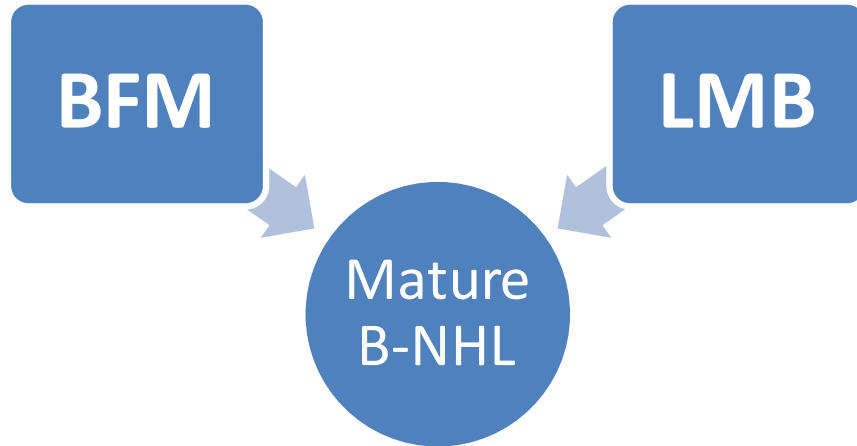
Pregnancy test for girls/female adolescents with signs of puberty

Organ involvement

CNS	CNS negative: no blast in CSF, no infiltrates in cranio-spinal MRI and no intradural cranial nerve palsy
	CNS positive: CSF with blast (any count), cerebral or medullary infiltrates on MRI, cranial nerve palsy not due extradural lesions
BM	≥5% and <25% blasts in BM aspiration
	Leukaemia: ≥ 25% blasts in BM aspiration
Mediastinal	Confirmed by MRI or CT scan
Lung	Confirmed by Chest CT
Bone	Bone lesions on x-ray or MRI, biopsy if it is the only disease manifestation
Testicular	Painless enlargement of one or both testicles

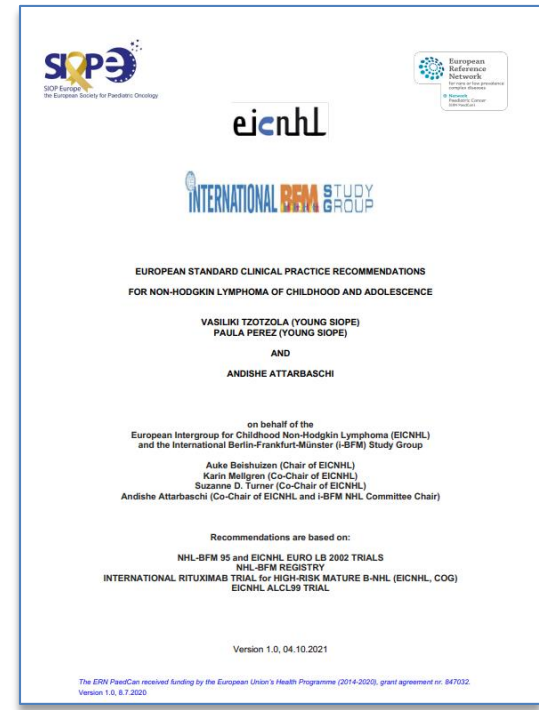
ESCP for NHL

Mature aggressive B-NHL/lymphoma



BFM approach

- Based on the NHL BFM 2013 registry
- Published data so at that time



Therapeutic groups

Table 8. Risk group stratification for mature aggressive B-NHL according to the BFM concept

Risk group	Resection status	Stage and initial serum LDH level
R1	Complete	
R2	Incomplete	Stage I, II; stage III and LDH < 2 x ULN
R3	Incomplete	stage III and LDH > 2 x ULN but < 4 x ULN stage IV/B-AL and LDH < 4 x ULN and CNS negative
R4	Incomplete	stage III and LDH ≥ 4 x ULN stage IV/B-AL and LDH ≥ 4 x ULN and CNS negative
R4 CNS+	Incomplete	stage IV/B-AL and CNS positive

Treatment

R1	A4	b4					
R2	P	A4	B4	A4	B4		
R3/R4 CNS-	P	AA24	BB24	CC	AA24	BB24	CC (only in R4)
R4 CNS+	P(IT)	AAZ124	BBZ124	CC	AAZ224	BBZ224	CC
R4 CNS+ (stage IV B-AL with CSF blasts)	P(IT)	AA8Z1	BBZ124	CC	AAZ224	BBZ224	CC

- MTX 8gr/m2 in the first schema (AA8Z1) for patients with stage IV/ B-AL and presence of blasts in CSF
- Triple IT in a single dose for compliance reasons

Treatment

R1	A4	b4					
R2	P	A4	B4	A4	B4		
R3/R4 CNS-	P	AA24	BB24	CC	AA24	BB24	CC (only in R4)
R4 CNS+	P(IT)	AAZ124	BBZ124	CC	AAZ224	BBZ224	CC
R4 CNS+ (stage IV B-AL with CSF blasts)	P(IT)	AA8Z1	BBZ124	CC	AAZ224	BBZ224	CC

- P: Dexa-Cyclo
- A4: Dexa-VCR-MTX-Ifo-ARAC-VP16-IT
- B4: Dexa-VCR-MTX-Doxo-Cyclo-IT
- CC: Dexa-VDS-ARAC-VP16-IT

Treatment

R1	A4	b4					
R2	P	A4	B4	A4	B4		
R3/R4 CNS-	P	AA24	BB24	CC	AA24	BB24	CC (only in R4)
R4 CNS+	P(IT)	AAZ124	BBZ124	CC	AAZ224	BBZ224	CC
R4 CNS+ (stage IV B-AL with CSF blasts)	P(IT)	AA8Z1	BBZ124	CC	AAZ224	BBZ224	CC

- A4/B4/b4: MTX 1gr/m2 iv over 4 hours, ITx1

Treatment

R1	A4	b4					
R2	P	A4	B4	A4	B4		
R3/R4 CNS-	P	AA24	BB24	CC	AA24	BB24	CC (only in R4)
R4 CNS+	P(IT)	AAZ124	BBZ124	CC	AAZ224	BBZ224	CC
R4 CNS+ (stage IV B-AL with CSF blasts)	P(IT)	AA8Z1	BBZ124	CC	AAZ224	BBZ224	CC

- AA24/BB24: MTX 5gr/m2 iv over 24 hours, ITx1

Treatment

R1	A4	b4					
R2	P	A4	B4	A4	B4		
R3/R4 CNS-	P	AA24	BB24	CC	AA24	BB24	CC (only in R4)
R4 CNS+	P(IT)	AAZ124	BBZ124	CC	AAZ224	BBZ224	CC
R4 CNS+ (stage IV B-AL with CSF blasts)	P(IT)	AA8Z1	BBZ124	CC	AAZ224	BBZ224	CC

- AAZ124/BBZ124: MTX 5gr/m2 iv over 24 hours and ITx3
- AAZ224/BBZ224: MTX 5gr/m2 iv over 24 hours and ITx2

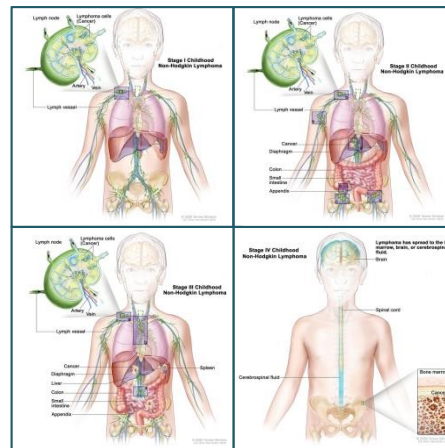
Treatment

R1	A4	b4					
R2	P	A4	B4	A4	B4		
R3/R4 CNS-	P	AA24	BB24	CC	AA24	BB24	CC (only in R4)
R4 CNS+	P(IT)	AAZ124	BBZ124	CC	AAZ224	BBZ224	CC
R4 CNS+ (stage IV B-AL with CSF blasts)	P(IT)	AA8Z1	BBZ124	CC	AAZ224	BBZ224	CC

- AA8Z1: MTX 8gr/m2 iv over 24 hours and ITx3

Mature-B NHL EICNHL Staging

- A Completely resected
- B I Stage I, II and III with LDH $< 2 \times$ UNL and good response to COP ($\geq 20\%$ reduction)
- B II (high risk) B I with poor response to COP ($< 20\%$ reduction)
Stage III with LDH $\geq 2 \times$ UNL and stage IV CNS negative
- C1 Stage IV CNS positive and CSF negative and B-AL CNS negative
- C3 B-AL CNS positive (with blasts) in CSF



Mature-B NHL EICNHL Treatment

Appendix D: Therapeutic strategy for mature B-NHL and B-AL according to the EICNHL

A	Completely resected	COPAD	COPAD						
B I	Stage I, II and III with LDH <2 x UNL and good response to COP (≥20% reduction)	COP	COPADM	COPADM	CYM	CYM			
B II (high risk)	B I with poor response to COP (<20% reduction) Stage III with LDH ≥2x UNL and stage IV CNS negative	COP	R-COPADM	R-COPADM	R-CYM	R-CYM			
C1	Stage IV CNS positive and CSF negative and B-AL CNS negative	COP	R-COPADM	R-COPADM2	R-CYVE	R-CYVE	m1	m2	
C3	B-AL CNS positive (with blasts) in CSF	COP	R-COPADM	R-COPADM2	R-IT-CYVE-MTX	R-IT-CYVE	m1	m2	

Group A

A Completely resected

COPAD

COPAD

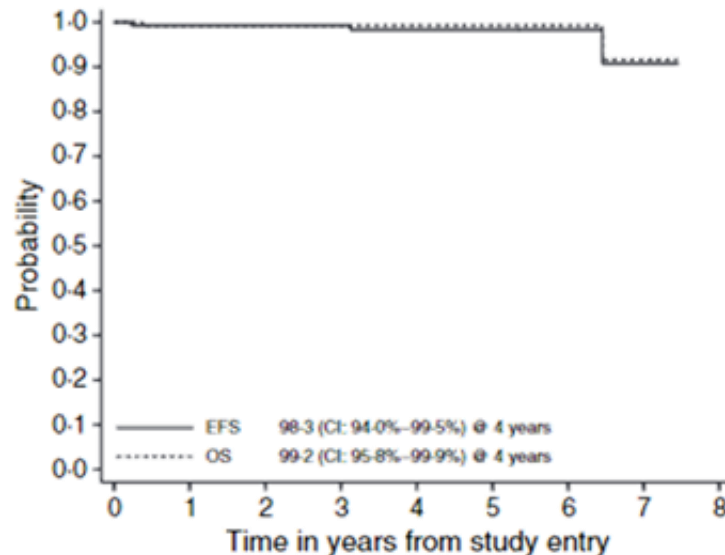
FAB/LMB Limited Treatment for Localized Resected B-cell NHL

COPAD

Cyclophosphamide 250 mg/m²/12 hours IV D1-3 (6 doses)
Vincristine 2 mg/m²/d (max. 2 mg) IV D1 and D6
Prednisone 60 mg/m²/d PO D1-5 and reduce to stop on D10
Doxorubicin 60 mg/m²/d IV D1



Ardicli, 2018

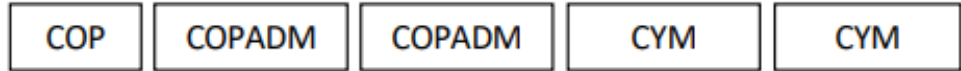


FAB/LMB96 trial. Gerrard et al. Br J Haematol. 2008. PMID: 18371107.

Group B1

B I

Stage I, II and III with LDH <2 x UNL and good response to COP (≥20% reduction)



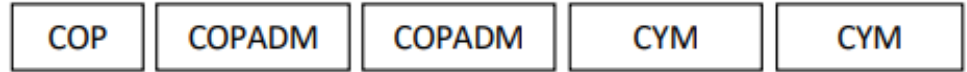
COP	Prednisone 60 mg/m ² /d PO D1-7 Vincristine 1 mg/m ² /d (max. 2 mg) IV D1 Cyclophosphamide 300 mg/m ² /d IV D1 Intrathecal chemotherapy D1 (methotrexate + hydrocortisone)
COPADM	Prednisone 60 mg/m ² /d PO D1-5 and reduce to stop on D9 Vincristine 2 mg/m ² /d (max. 2 mg) IV D1 Methotrexate (MTX) 3 g/m ² IV over 3 hours D1. <i>Folinic acid rescue 24 h.</i> Doxorubicin 60 mg/m ² /d IV D2 Cyclophosphamide 250 mg/m ² /12 hours IV D2-4 (6 doses) Intrathecal chemotherapy D1 and D6 (MTX+HC)
CYM	Methotrexate (MTX) 3 g/m ² IV over 3 hours D1. <i>Folinic acid rescue 24 h.</i> Cytarabine (ARA-C) 100 mg/m ² /d IV over 24 hours D2-6 (5 doses) Intrathecal chemotherapy D1 (MTX+HC) and D7 (ARAC-HC)

Age	Methotrexate IT [mg]	Hydrocortisone IT [mg]	Cytarabine IT [mg]
< 1 y	8	8	15
1 - < 2 y	10	10	20
2 - < 3 y	12	12	25
≥ 3 y	15	15	30

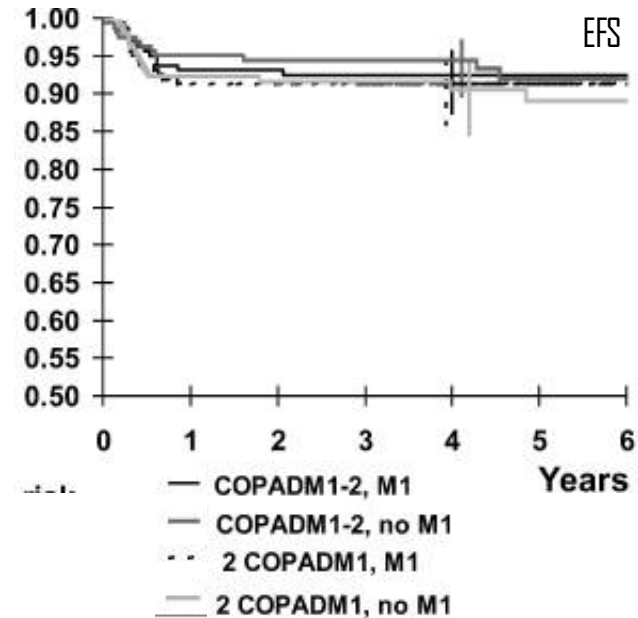
Group B1

B I

Stage I, II and III with LDH <2 x UNL and good response to COP (≥20% reduction)



COP	Prednisone 60 mg/m ² /d PO D1-7 Vincristine 1 mg/m ² /d (max. 2 mg) IV D1 Cyclophosphamide 300 mg/m ² /d IV D1 Intrathecal chemotherapy D1 (methotrexate + hydrocortisone)
COPADM	Prednisone 60 mg/m ² /d PO D1-5 and reduce to stop on D9 Vincristine 2 mg/m ² /d (max. 2 mg) IV D1 Methotrexate (MTX) 3 g/m ² IV over 3 hours D1. <i>Folinic acid rescue 24 h.</i> Doxorubicin 60 mg/m ² /d IV D2 Cyclophosphamide 250 mg/m ² /12 hours IV D2-4 (6 doses) Intrathecal chemotherapy D1 and D6 (MTX+HC)
CYM	Methotrexate (MTX) 3 g/m ² IV over 3 hours D1. <i>Folinic acid rescue 24 h.</i> Cytarabine (ARA-C) 100 mg/m ² /d IV over 24 hours D2-6 (5 doses) Intrathecal chemotherapy D1 (MTX+HC) and D7 (ARAC-HC)



FAB/LMB96 trial. Patte C et al. Blood. 2007. PMID: 17132719.

Therapeutic strategy EICNHL for HR mature B-NHL

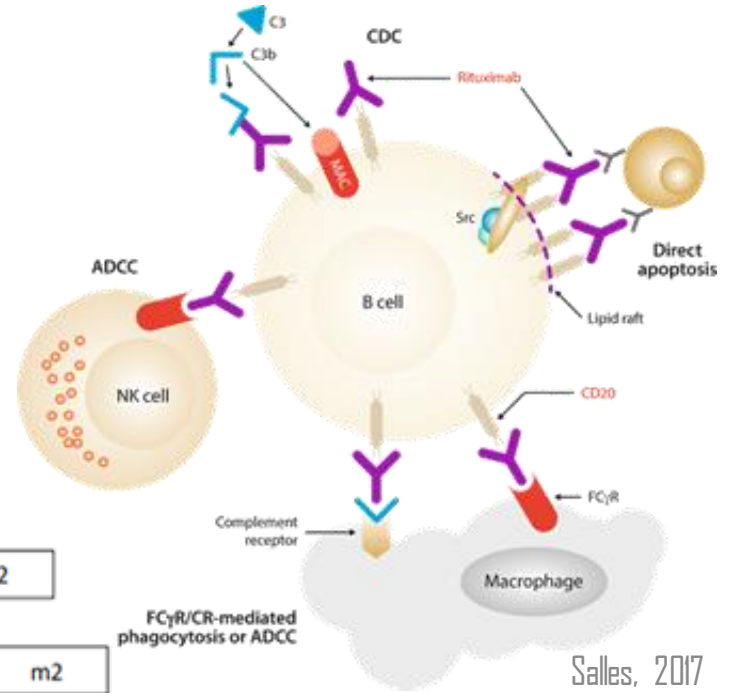
The addition of Rituximab

B II (high risk) B I with poor response to COP (<20% reduction)
Stage III with LDH $\geq 2x$ UNL and stage IV CNS negative

C1 Stage IV CNS positive and CSF negative and B-AL CNS negative

C3 B-AL CNS positive (with blasts) in CSF

B II (high risk)	COP	R-COPADM	R-COPADM	R-CYM	R-CYM		
C1	COP	R-COPADM	R-COPADM2	R-CYVE	R-CYVE	m1	m2
C3	COP	R-COPADM	R-COPADM2	R-IT-CYVE-MTX	R-IT-CYVE	m1	m2



Salles, 2017

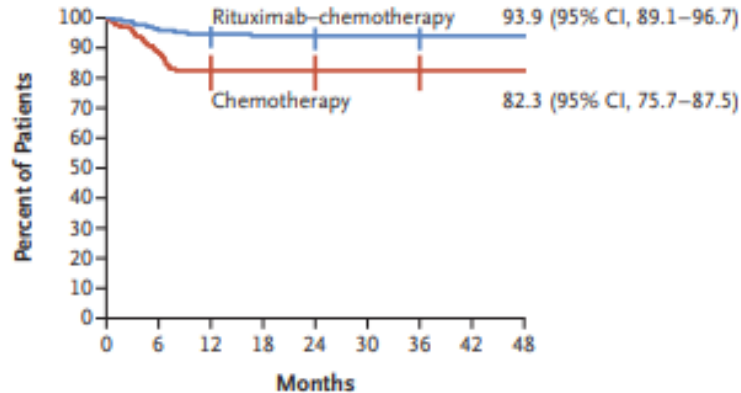
Therapeutic strategy EICNHL for HR mature B-NHL

The addition of Rituximab

R

Rituximab 375 mg/m²/d IV D-2 and D1 of R-COPADM and D1 of R-CYM (6 doses)

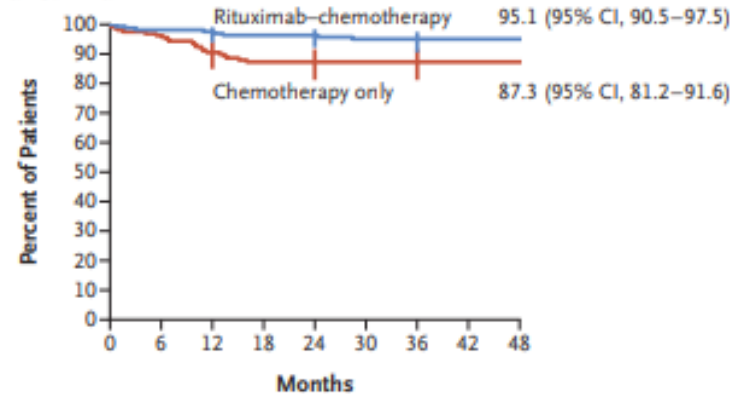
A Event-free Survival



No. at Risk

Rituximab-chemotherapy	164	157	155	154	150	138	102	74	42
Chemotherapy	164	140	128	127	122	112	82	52	38

B Overall Survival



No. at Risk

Rituximab-chemotherapy	164	161	160	158	154	140	103	75	43
Chemotherapy	164	152	141	135	130	119	89	57	42

Group BII

B II (high risk)

B I with poor response to COP
 (<20% reduction)
 Stage III with LDH $\geq 2x$ UNL and
 stage IV CNS negative



COP	Prednisone 60 mg/m ² /d PO D1-7 Vincristine 1 mg/m ² /d (max. 2 mg) IV D1 Cyclophosphamide 300 mg/m ² /d IV D1 Intrathecal chemotherapy D1 (MTX+HC)
R	Rituximab 375 mg/m ² /d IV D-2 and D1 of R-COPADM and D1 of R-CYM
COPADM	Prednisone 60 mg/m ² /d PO D1-5 and reduce to stop on D9 Vincristine 2 mg/m ² /d (max. 2 mg) IV D1 Methotrexate (MTX) 3 g/m ² IV over 3 hours D1. <i>Folinic acid rescue 24 h.</i> Doxorubicin 60 mg/m ² /d IV D2 Cyclophosphamide 250 mg/m ² /12 hours IV D2-4 (6 doses) Intrathecal chemotherapy D1 and D6 (MTX+HC)
CYM	Methotrexate (MTX) 3 g/m ² IV over 3 hours D1. <i>Folinic acid rescue 24 h.</i> Cytarabine (ARA-C) 100 mg/m ² /d IV over 24 hours D2-6 (5 doses) Intrathecal chemotherapy D1 (MTX+HC) and D7 (ARAC-HC)

Age	Methotrexate IT [mg]	Hydrocortisone IT [mg]	Cytarabine IT [mg]
< 1 y	8	8	15
1 - < 2 y	10	10	20
2 - < 3 y	12	12	25
≥ 3 y	15	15	30

Group C1

C1

Stage IV CNS positive and CSF negative and B-AL CNS negative

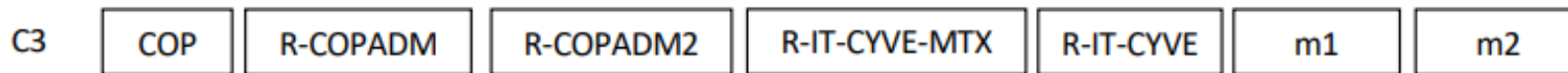
COP	R-COPADM	R-COPADM2	R-CYVE	R-CYVE	m1	m2
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COP	<p>Prednisone 60 mg/m²/d PO D1-7 Vincristine 1 mg/m²/d (max. 2 mg) IV D1 Cyclophosphamide 300 mg/m²/d IV D1 Intrathecal chemotherapy D1 (3 drugs MTX+ARAC+HC)</p>
R	<p>Rituximab 375 mg/m²/d IV D-2 and D1 of R-COPADM and D1 of R-CYVE</p>
COPADM COPADM2	<p>Prednisone 60 mg/m²/d PO D1-5 and reduce to stop on D9 Vincristine 2 mg/m²/d (max. 2 mg) IV D1 Methotrexate (MTX) 8 g/m² IV over 4 hours D1 <i>Folinic acid rescue 24 h.</i> Doxorubicin 60 mg/m²/d IV D2 Cyclophosphamide 250 (500 in COPADAM2) mg/m²/12 hours IV D2-4 (6 doses) Intrathecal chemotherapy D2, D4 and D6 (3 drugs: MTX+ARAC+HC)</p>
(IT)-CYVE- (MTX)	<p>Cytarabine (ARA-C) 50 mg/m²/d IV over 12 hours D1-6 (5 doses) Cytarabine HD (ARA-C) 3 g/m²/d IV over 3 hours D2-5 (4 doses) Etoposide 200 mg/m² IV D 2-5 Intrathecal chemotherapy D1 (2 drugs) Only 1st cycle for CNS ±: Methotrexate (MTX) 8 g/m² IV over 4 hours D18. <i>Folinic acid rescue 24 h + Intrathecal chemotherapy D19 (3 drugs) (IT-CYVE-MTX)</i></p>

Age	Methotrexate IT [mg]	Hydrocortisone IT [mg]	Cytarabine IT [mg]
< 1 y	8	8	15
1 - < 2 y	10	10	20
2 - < 3 y	12	12	25
≥ 3 y	15	15	30

m1	<p>Prednisone 60 mg/m²/d PO D1-5 and reduce to stop on D9 Vincristine 2 mg/m²/d (max. 2 mg) IV D1 Methotrexate (MTX) 8 g/m² IV over 4 hours D1. <i>Folinic acid rescue 24 h.</i> Doxorubicin 60 mg/m²/d IV D2 Cyclophosphamide 500 mg/m²/d D2-3 Intrathecal chemotherapy D2 (3 drugs)</p>
m2	<p>Cytarabine 50 mg/m²/12 hours sc D1-5 Etoposide 150 mg/m² IV D1-3</p>

Group C3



B-AL CNS positive (with blasts) in CSF

Age	Methotrexate IT [mg]	Hydrocortisone IT [mg]	Cytarabine IT [mg]
< 1 y	8	8	15
1 - < 2 y	10	10	20
2 - < 3 y	12	12	25
≥ 3 y	15	15	30

COP	<p>Prednisone 60 mg/m²/d PO D1-7</p> <p>Vincristine 1 mg/m²/d (max. 2 mg) IV D1</p> <p>Cyclophosphamide 300 mg/m²/d IV D1</p> <p>Intrathecal chemotherapy D1 (3 drugs MTX+ARAC+HC)</p>
R	<p>Rituximab 375 mg/m²/d IV D-2 and D1 of R-COPADM and D1 of R-CYVE</p>
COPADM COPADM2	<p>Prednisone 60 mg/m²/d PO D1-5 and reduce to stop on D9</p> <p>Vincristine 2 mg/m²/d (max. 2 mg) IV D1</p> <p>Methotrexate (MTX) 8 g/m² IV over 4 hours D1. Folinic acid rescue 24 h.</p> <p>Doxorubicin 60 mg/m²/d IV D2</p> <p>Cyclophosphamide 250 (500 in COPADAM2) mg/m²/12 hours IV D2-4 (6 doses)</p> <p>Intrathecal chemotherapy D2, D4 and D6 (3 drugs: MTX+ARAC+HC)</p>
IT-CYVE- MTX	<p>Cytarabine (ARA-C) 50 mg/m²/d IV over 12 hours D1-6 (5 doses)</p> <p>Cytarabine HD (ARA-C) 3 g/m²/d IV over 3 hours D2-5 (4 doses)</p> <p>Etoposide 200 mg/m² IV D 2-5</p> <p>Intrathecal chemotherapy D1 (2 drugs)</p>
IT-CYVE	<p>Only 1st cycle (IT-CYVE-MTX): Methotrexate (MTX) 8 g/m² IV over 24 hours D18. Folinic acid rescue 36 h + Intrathecal chemotherapy D19 (3 drugs) (IT-CYVE-MTX)</p>

m1	<p>Prednisone 60 mg/m²/d PO D1-5 and reduce to stop on D9</p> <p>Vincristine 2 mg/m²/d (max. 2 mg) IV D1</p> <p>Methotrexate (MTX) 8 g/m² IV over 24 hours D1. Folinic acid rescue 36 h.</p> <p>Doxorubicin 60 mg/m²/d IV D2</p> <p>Cyclophosphamide 500 mg/m²/d D2-3</p> <p>Intrathecal chemotherapy D2 (3 drugs)</p>
m2	<p>Cytarabine 50 mg/m²/12 hours sc D1-5</p> <p>Etoposide 150 mg/m² IV D1-3</p>