UCCH Universitäres Cancer Center Hamburg
UCCSH Universitäres Cancer Center Schleswig-Holstein

UCCH / UCCSH Pathway

Guideline
ZNS Non Hodgkin Lymphoma

Version Januar/2024

Guideline ZNS - Non Hodgkin Lymphoma

Version 01, Januar/2024

According to the 5th edition of the WHO classification of haematolymphoid tumours: lymphoid neoplasms

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Revised	
Next planned review	Nov/2025

Legend of Colours

= Therapeutic procedure

= Clinical or diagnostical condition

= Diagnostic procedure

= Clinical trial

= Supportive measure

= Referral

TB

= Tumorboard (including post tumorboard interaction with patient that follows the principles of shared decision-making)

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Pathway: ZNS-NHL

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Page 1: Work up

Work up	Remarks
History	• B-symptoms? • Neurological Symptoms? • Immunosupression? • Headache? • Nausea/Vomiting? • ECOG? • Personality Changes? • Neurocognitive Decline?
Clinical examination	• Splenomegaly, hepatomegaly, lymphadenopathy? • Opthalmological examination • Neurological examination • Lumbal Punction for CSF Analysis • Bone Marrow Punction
Laboratory	• Differential blood count • LDH • GOT, GPT, AP, γ-GT, bilirubin, creatinine, uric acid • Quick/INR, PTT • Quantitative immunoglobulines (IgG, IgA, IgM) in serum • HBV, HCV, HIV screening • Lymphocytesubpopulation (CD4, CD8) (only at HIV-Infection / Immunosuppression) • Liquor: Cell Count, Protein, Cytomorphology
Histology	• **Avoid administering steroids before obtaining histology** • Stereotactic Biopsy of the Brain Lesion -> PCNSL
Bone marrow punction	• Cytomorphology, FACS, Cytogenetic, Histology
Imaging	• CT of the Neck/Chest/Abdomen or Whole-Body PET-CT • spinal MRI (only in symptomatic cases or with CSF positivity) • MRI of the Brain with Contrast • Testical sonography
Other	• Informing about possible inclusion in a study, tumor bank, samples for scientific use including UCCH biobank

Risk factors for the Definition of the Prognostic Index of the IELSG

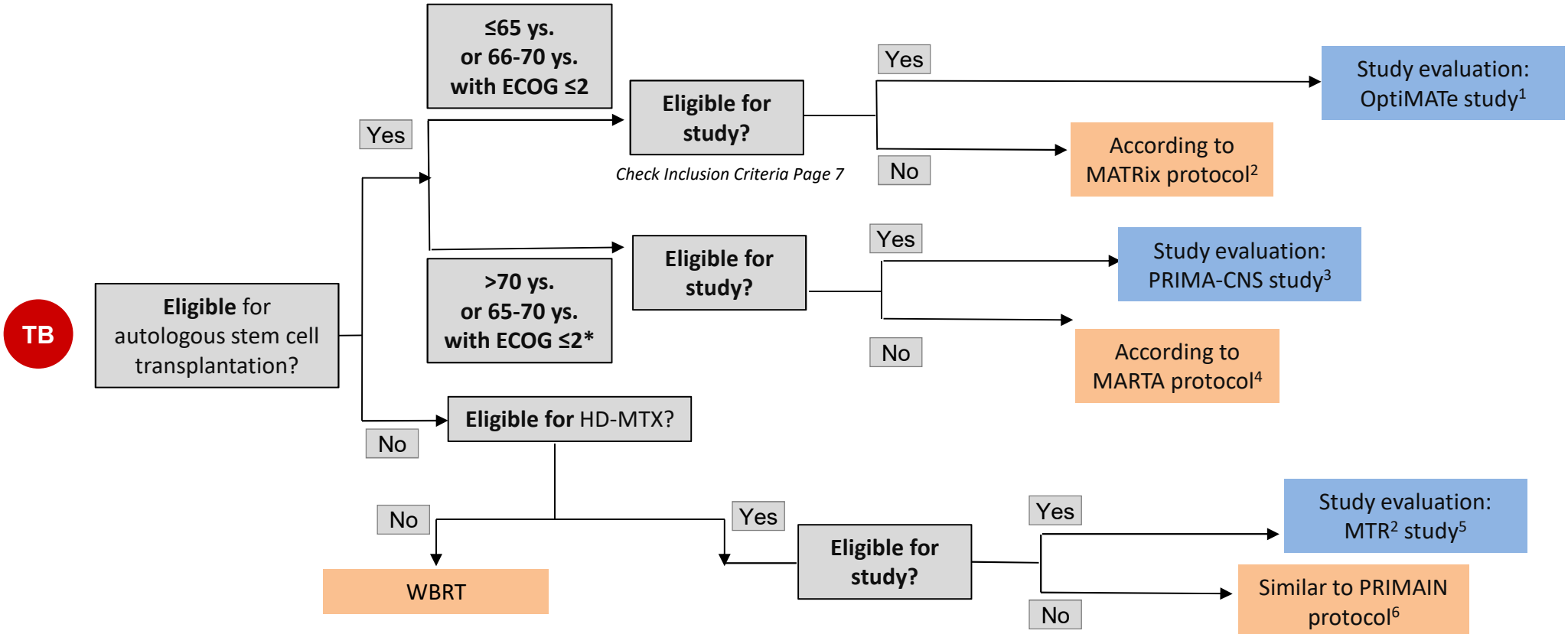
Points	Parameter	Remarks
1	Age > 60y	None
1	PS 2-4	ECOG Performance Score
1	Serum LDH elevated	above upper normal
1	Cerebrospinal fluid protein elevated	above upper normal
1	Deep structures involved	basal ganglia, corpus callosum, brain stem, or cerebellum

# of Risk Factors - General index	Risk Group
0 - 1	1 = low
2 - 3	2 = intermediate
4 - 5	3 = high

Ferreri AJM et al: Prognostic Scoring System for Primary CNS Lymphomas: The International Extranodal Lymphoma Study Group Experience J Clin Oncol Vol.21 (2), 2003: 266-272.

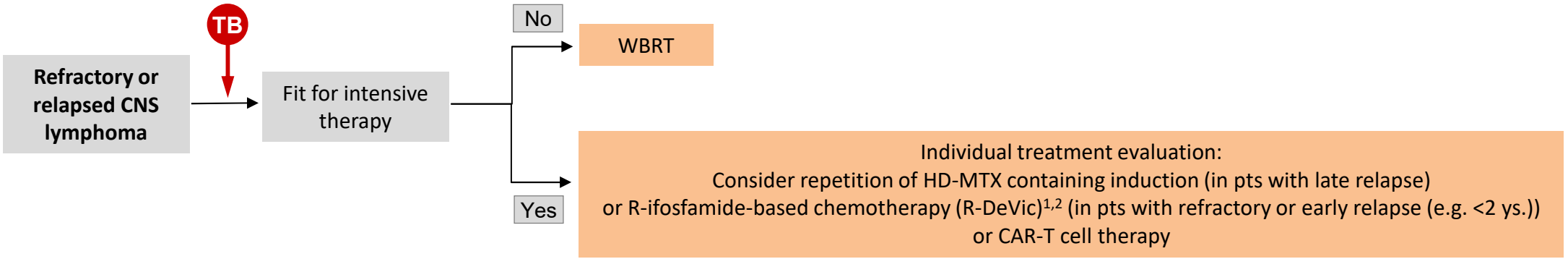
Page 2: First line therapy

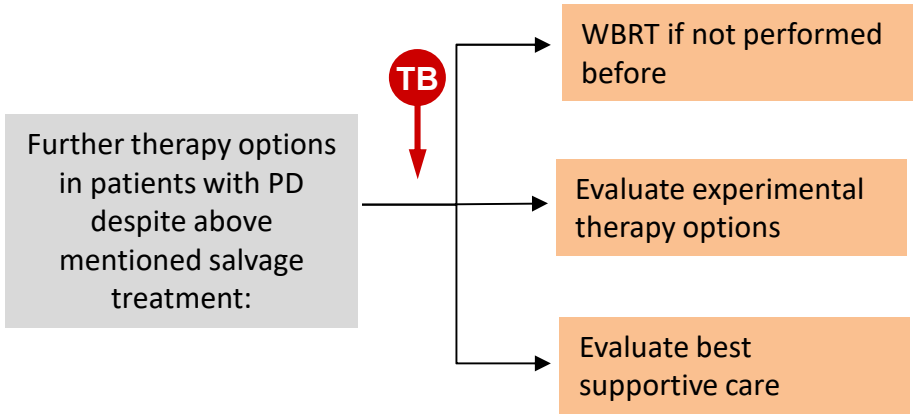
*and not eligible for intensified therapy (e.g. Optimate study / MATRix protocol)



[1]Multicentre randomized phase III trial; control intervention (response assumed): 2x MATRix > stem cell harvest > 2x MATRix > HCT-ASCT; experimental intervention: 1x R-MTX > 1x MATRix > stem cell harvest > 1x MATRIX > HCT-AST (Wendler et al. BMC Cancer 2022; 22, 971)
[2]Treatment with 4x MATRix with stem cell harvest after 2nd cycle and subsequently HCT-AST (Ferreri et al. Leukemia. 2022 Jul;36(7):1870-1878), see therapy protocol page 9
[3]Multicentre randomized phase III trial; all patients: Pre-treatment with 1x R-MTX, subsequently randomization; control intervention (response assumed): 3x R-MTX/Procarbazine with maintenance with Procarbazine (6# à 43 days); experimental intervention: 2x R-MTX/AraC > HCT-AST (Isbell et al. BMC Cancer 2023;23(1):767)
[4]Treatment with 2x R-MTX/AraC with stem cell harvest after 1st cycle and subsequently HCT-AST (Schorb et al. Blood 2022;140 (Suppl 1):1773-1774), see therapy protocol page 9
[5]Multicentre single-arm phase II trial; 4x R-MTX, Tafasitamab, Lenalidomid
[6]Treatment with 3x R-MTX/Procarbazine with maintenance with Procarbazine (6# à 43 days) (Fritsch et al. Leukemia 2017;31:846-852), see therapy protocol page 9

Page 3: Second line therapy





[1]Scholl et al, BMC Cancer 2016;16:282
[2]SMoll et al, Blood 2018;132(Suppl 1), 1705

Page 4: Palliative care screening tool

Screening items			Points
1.	• Presence of metastatic or locally advanced cancer		**2**
2.	• ECOG score (functional status score, performance status)		**0-4**
3.	• Presence of one or more serious complications of advanced cancer usually associated with a prognosis of < 12 months (e.g. brain metastases, hypercalcemia, delirium, spinal cord compression, cachexia)		**1**
4.	• Presence of one or more serious comorbid diseases also associated with poor prognosis (e.g. moderate-severe COPD or CHF, dementia, AIDS, end stage renal failure end stage liver cirrhosis)		**1**
5.	• Presence of palliative care problems		**1**
	a.	• Symptoms uncontrolled by standard approaches	**1**
	b.	• Moderate to severe distress in patient or family, related to cancer diagnosis or therapy (personal targets and expectations, educational and informational requirements, cultural factors)	**1**
	c.	• Patient/family requests palliative care consult	**1**
	d.	• Team needs assistance with complex decision making or determing goals of care (benefit/side effects of treatment)	**1**
	e.	• Instable or deficient network especially for emergency situation or 24-h care	**1**

A total of > 5 points signalizes need for supportive palliative care

According to Glare et al. (2011); NCCN Clinical Practice guidelines in Oncology 2015

Page 5: Inclusion and exclusion criteria Optimate study[1]

Inclusion criteria

1. Immunocompetent patients with newly diagnosed primary diffuse large B-cell lymphoma (DLBCL) of the central nervous system (CNS)
2. Male or female patients aged 18–65 years irrespective of ECOG PS or 66–70 years with ECOG PS ≤ 2
3. Histologically or cytologically assessed diagnosis of B-cell lymphoma by local pathologist. Diagnostic sample obtained by stereotactic or surgical biopsy, CSF cytology examination or vitrectomy
4. Disease exclusively located in the CNS
5. At least one measurable lesion
6. Previously untreated patients (previous or ongoing steroid treatment admitted)
7. Negative pregnancy test
8. Written informed consent obtained according to international guidelines and local laws by patient or authorized legal representative in case patient is temporarily legally not competent due to his or her disease
9. Ability to understand the nature of the trial and the trial related procedures and to comply with them

Exclusion criteria

1.Congenital or acquired immunodeficiency including human immunodeficiency virus (HIV) infection and previous organ transplantation
2. Systemic lymphoma manifestation (outside the CNS)
3. Primary vitreoretinal lymphoma without manifestation in the brain parenchyma or spinal cord
4. Previous or concurrent malignancies with the exception of surgically cured carcinoma in situ of the cervix, carcinoma of the skin or other kinds of cancer without evidence of disease for at least 5 years
5. Previous Non-Hodgkin lymphoma at any time
6. Inadequate renal function (creatinine clearance < 60 ml/min)
7. Inadequate bone marrow, cardiac, pulmonary or hepatic function according to investigator´s decision
8. Active hepatitis B or C disease
9. Concurrent treatment with other experimental drugs or participation in an interventional clinical trial with study medication being administered within the last 30 days before the start of this study
10. Third space fluid accumulation > 500 ml
11. Hypersensitivity to study treatment or any component of the formulation
12. Taking any medications that are likely to cause interactions with the study medication
13. Known or persistent abuse of medication, drugs or alcohol
14. Active COVID-19-infection or non-compliance with the prevailing hygiene measures regarding the COVID-19 pandemic
15. Patients without legal capacity who are unable to understand the nature, significance and consequences of the trial and without designated legal representative
16. Previous participation in this trial
17. Persons who are in a relationship of dependency/ employment with the sponsor and/ or the investigator
18. Any familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule
19. Current or planned pregnancy, nursing period
20. For fertile patients: Failure to use one of the following safe methods of contraception: intra-uterine device or hormonal contraception in combination with a mechanical method of contraception

[1]Wendler et al. BMC Cancer 2022; 22, 971 (2022)

Page 6: Treatment protocols

MATRix q3w

Methotrexat	3,5mg/m2	D1
Cytarabin	2 x 2g/m2	D2,3
Thiotepa	30mg/m2	D4
Rituximab	375mg/m2	D0,5

HD-Protocol (following MATRix)

BCNU	400mg/m2	D-6
Thiotepa	2x 5mg/Kg	D-5,-4
Reinfusion stem cells		D0

R-MTX/AraC (MARTA) q3w

Methotrexat	3,5mg/m2	D1
Cytarabin	2 x 2g/m2	D2,3
Rituximab	375mg/m2	D0,4

HD-Protocol (following MARTA)

Rituximab	375 mg/m2	D-8
Busulfan	3.2 mg/kg	D-7,-6
Thiotepa	5mg/Kg	D-5,-4
Reinfusion stem cells		D0

R-MP (PRIMAIN) repetition on d43

Methotrexat	3,0mg/m2	D2,16,30
Procarbazine	60mg/m2	D2-11
Rituximab	375mg/m2	D-6 (cycle 1),1,15,29

Procarbazine maintenance (following PRIMAIN) repetition on d43

Procarbazine	100mg abs.	D1-5