Synopsis

TITLE OF TRIAL	Age-adjusted high-dose chemotherapy followed by autologous stem cell transplantation or conventional chemotherapy with R-MP as first-line treatment in elderly primary CNS lymphoma patients – a randomized phase III trial
SHORT TITLE	PRIMA-CNS
PROTOCOL NUMBER	P003077
EUDRACT NO	2020-001181-10
MAIN DIAGNOSIS	Primary Central Nervous System Lymphoma
PHASE	Phase III
OBJECTIVE(S)	The primary objective of this study is to demonstrate that intensified chemotherapy followed by consolidating high-dose chemotherapy and autologous stem-cell transplantation (HCT-ASCT) is superior to conventional chemotherapy with R-MP followed by maintenance in elderly patients with newly diagnosed PCNSL regarding progression free survival (PFS). Secondary objectives are the comparison of the two treatment arms with respect to quality of life, remission after treatment, event free survival, overall survival (OS) and treatment related morbidities (neurotoxicity and adverse events).
INTERVENTION(S)	**All patients:** Pre-phase with **1 cycle of R-MTX** (rituximab 375 mg/m² d-8 HD-MTX 3.5 g/m² d-7) followed by an assessment regarding eligibility for stem cell transplantation; afterwards, patients will be randomized: **Arm A - control intervention:** Patients in the control intervention (Arm A) will receive 3 cycles (28 days cycle) of R-MP (rituximab 375 mg/m² i.v. d0,14; HD-MTX 3.5 g/m² i.v. d1,15; procarbazine 60 mg/m²/d p.o. d2-11) followed by maintenance therapy with procarbazine 100 mg absolute/d p.o. d1-5 for additional 6 cycles. **Arm B - experimental intervention:** Patients in the experimental intervention (Arm B) will receive 2 cycles (21 days cycle) of R-MTX/AraC (rituximab 375 mg/m² i.v. d0, 4 HD-MTX 3.5 g/m² i.v. d1, AraC 2x2 g/m² i.v. d2+d3) followed by consolidating HCT-ASCT with rituximab 375 mg/m² d-8, busulfan 3.2 mg/kg/d i.v. d-7 and d-6 and thiotepa 5 mg/kg/d i.v. d-5 and d-4. **All patients** must at least achieve stable disease (SD) to proceed with 3rd cycle of R-MP (Arm A) or with HCT-ASCT (Arm B) and patients in arm A must achieve at least complete or partial remission (CR, PR) to continue with maintenance therapy. Duration of intervention per patient: Arm A: 37 weeks Arm B: 11 weeks

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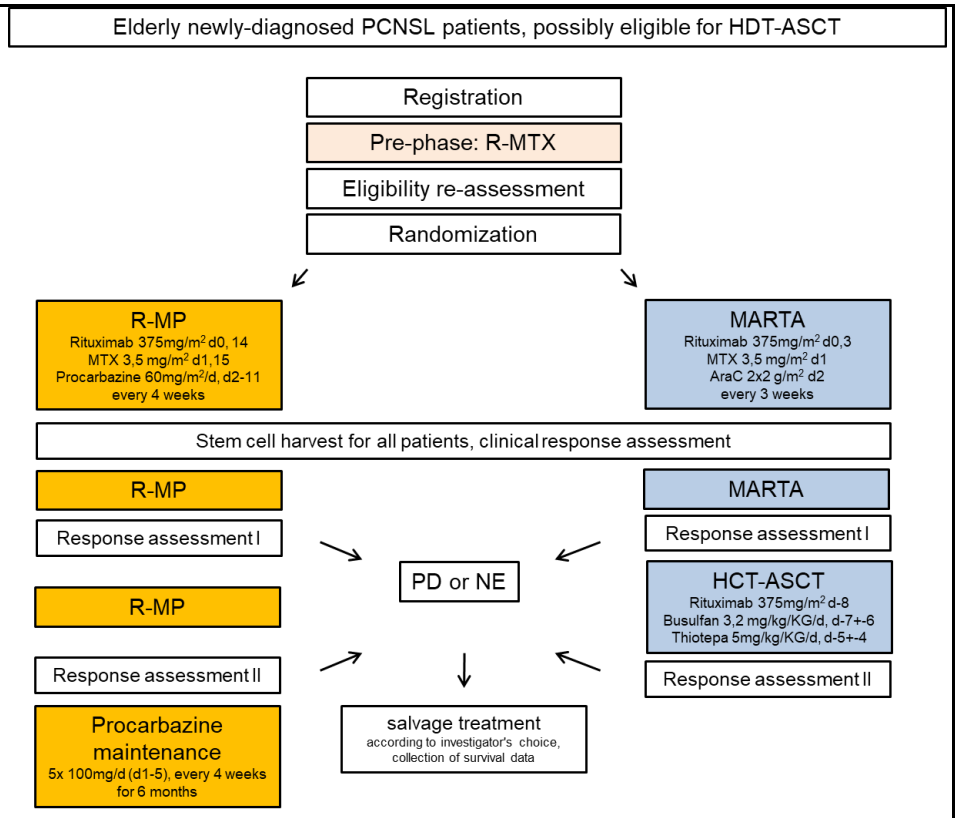

<u>Follow up per patient</u>:
Patients will proceed to a follow-up phase which will last until at least 12 months after response assessment II.
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<td>KEY INCLUSION CRITERIA</td>
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1. Immunocompetent patients with newly-diagnosed primary DLBCL of the central nervous system.
2. Age >70 years or age 65-70 years if not eligible for more intensive treatment (e.g. OptiMATe trial).
3. Histologically or cytologically assessed diagnosis of B-cell lymphoma by local pathologist.
4. Diagnostic sample obtained by stereotactic or surgical biopsy, CSF cytology examination or vitrectomy.
5. Disease exclusively located in the CNS.
6. At least one measurable lesion.
7. ECOG-Performance Status ≤2.
8. Patients eligible for HCT-ASCT according to physician's choice.
9. 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.</td>
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<td>KEY EXCLUSION CRITERIA</td>
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1. Congenital or acquired immunodeficiency including 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.</td>
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	5. Previous systemic Non-Hodgkin lymphoma at any time. 6. Inadequate renal function (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 thirty 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 likely to cause interactions with the study medication. 13. Known or persistent abuse of medication, drugs or alcohol. 14. Patients without legal capacity and who are unable to understand the nature, significance and consequences of the study and without designated legal representative. 15. Persons who are in a relationship of dependency/employment to the sponsor and/ or investigator. 16. Any familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule.
ENDPOINTS	Primary endpoint: PFS (defined as the time from randomization to disease progression or death of any cause) Key secondary endpoints: Quality of life (QoL), Remission after treatment, Event free survival (EFS; defined as time from randomization to premature end of treatment due to any reason, new anti-lymphoma treatment, lymphoma progression or death, whichever occurs first), Overall survival (OS), serious adverse events, neurotoxicity by serial neuropsychological tests according to a modified version of the standardized IPCG test battery as well as unplanned hospital admissions and length of hospital stays. Assessment of safety: Criteria for assessment of safety will be based on standard criteria for monitoring, assessing, and reporting of adverse events (CTCAE criteria v. 5.0). Toxicity will be monitored by taking vital signs, blood samples (laboratory parameters), lung function tests and neuropsychological evaluation.
TRIAL DESIGN	Multicenter, open-label, randomized, with two parallel arms, phase III
STATISTICAL ANALYSIS EFFICACY	Sample size consideration: The sample size of the trial is calculated based on the primary endpoint PFS. We assume a PFS rate at 1 year of 55% for the control arm and a PFS rate above 65% (67, 5% for calculation) for the experimental arm 12 months after randomization. The corresponding hazard ratio of experimental versus control is 0.66. Considering an exponential survival time distribution with two-sided alpha = 0.05 and power = 0.8 (recruitment time 60 months, follow-up time from randomization between 12 and 72 months), 178 events need to be observed, and 118 patients per arm need to be randomized in a 1:1 ratio (total N=236). To account for possible drop outs, we aim to randomize 260 patients. Primary endpoint: The primary analysis of the primary endpoint PFS will be conducted in the full analysis set (FAS) including all randomized patients according to the intention-to-treat principle. Patients will be randomized as late as possible to achieve a high compliance. The treatment effect will be estimated and tested by Cox regression. The regression model will include treatment and, for adjustment, the stratification variable ECOG (0/1 vs. 2) as independent variables. As estimate of the effect size, the hazard ratio (arm B vs. arm A) will be calculated with corresponding asymptotic two-sided 95% confidence intervals (CIs). The two-sided test on the difference between the experimental arm B and

	the control arm A at two-sided significance level of 5% will be based on the corresponding asymptotic two-sided 95% CIs from the Cox regression model. PFS, EFS, and OS rates in the two treatment arms will be estimated by the Kaplan-Meier method. Secondary endpoints: OS and EFS will be analysed with a Cox regression model as described for the analysis of PFS. Remission rates after end of treatment will be displayed with absolute and relative frequencies. Standardized questionnaires on quality of life will be analysed descriptively in compliance with the EORTC manual.	
STATISTICAL ANALYSIS SAFETY	Safety analysis will be performed for all patients for whom treatment was started. Adverse events and serious adverse events will be registered and reported according to the guidelines of ICH/GCP. Rates of adverse events and of serious adverse events will be calculated with corresponding two-sided 95% CIs. Toxicity and neurotoxicity will be analyzed descriptively.	
SAMPLE SIZE	To be assessed for eligibility:	n = 300
	To be allocated to trial:	n = 260
	To be analyzed:	n = 260
TRIAL DURATION	Recruitment period (months): (first patient signed PIC until last patient included)	60 months
	First patient in to last patient out (months): (First patient signed PIC until last patient last visit incl. 1 year of follow up)	72 months
	Duration of the entire trial (months):	96 months
	Treatment duration per patient (weeks):	Arm A: 37 weeks Arm B: 11 weeks
	FU duration per patient:	at least 12 months
TIMETABLE	Enrolment of first patient (FPFV)	4th quarter 2021
	Enrolment of last patient (registration)	4th quarter 2026
	End of trial for last patient (LPLV)	1st quarter 2028
	Final statistical analysis	4th quarter 2028
	Planned interim analysis	NA
PARTICIPATING CENTRES	About 35-40 sites in Germany and possibly additional international sites	