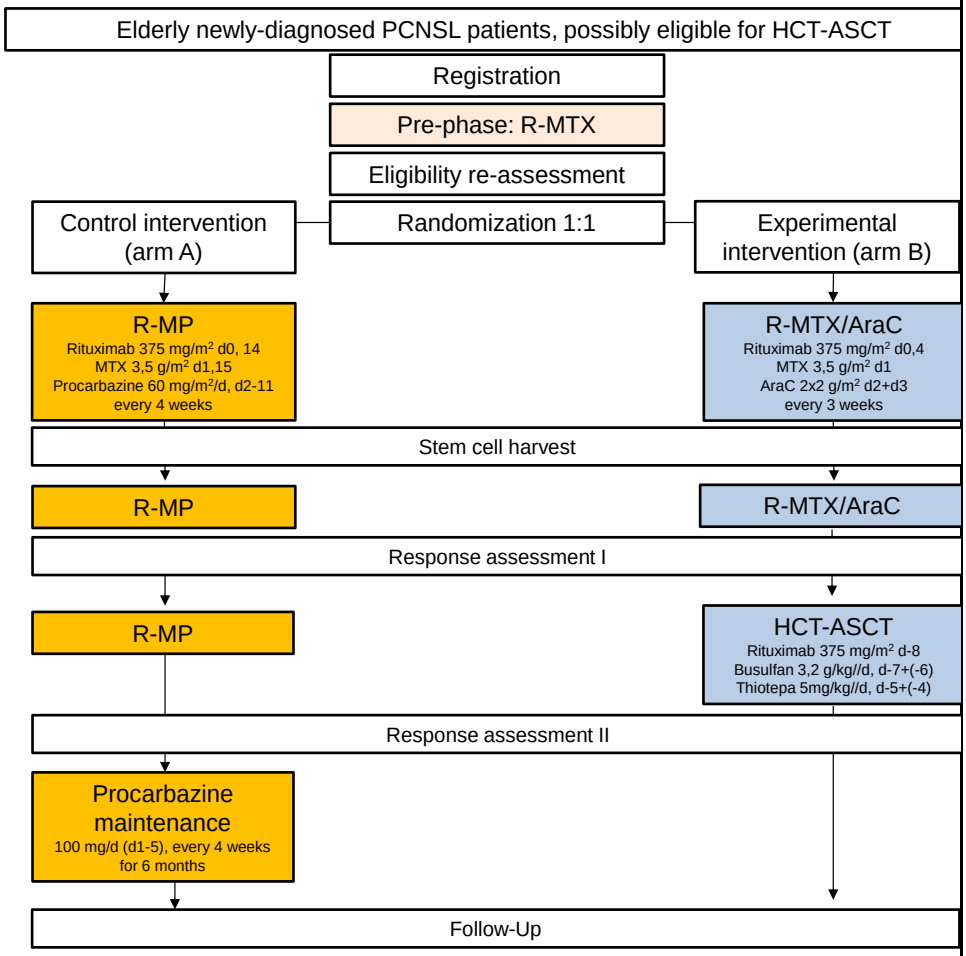
Synopsis

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 (PCNSL)
PHASE	Phase III
OBJECTIVE(S)	Primary: 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 in terms of progression free survival (PFS). Secondary: To compare quality of life, remission after induction treatment, remission after maintenance treatment (arm A) / consolidation treatment (arm B), event free survival, overall survival and treatment related morbidities (neurotoxicity and adverse events) between both treatment arms.
INTERVENTION(S)	**Pre-phase treatment all patients:** **1 cycle of R-MTX** (rituximab 375 mg/m² i.v. d0; MTX 3.5 g/m² i.v. d1) followed by an assessment regarding eligibility for stem cell transplantation. On day 10-14 of pre-phase treatment, 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; 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 (28 days cycle). **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; 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: 38 weeks (pre-phase treatment until end of maintenance treatment) Arm B: 12 weeks (pre-phase treatment until bone marrow recovery after ASCT)



Follow-up per patient:
Patients will proceed to a follow-up (FU) phase which will last until at least 12 months after response assessment (RA) II.

KEY INCLUSION CRITERIA

Key Inclusion criteria:

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 1 measurable lesion.
7. ECOG-Performance Status ≤2.
8. Patients possibly eligible for HCT-ASCT as judged by the treating physician.
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.

Additional randomization criteria:

1. Patients eligible for HCT-ASCT defined by the EBL score (at most one of the 3 following conditions may apply: ECOG PS > 1, Barthel Index of ADL < 20 and Lachs geriatric screening > 3), improvement of PS after pre-

	phase treatment or clinical judgement by the treating physician after discussion with the study expert team. 2. No evidence of disease progression after pre-phase treatment.
KEY EXCLUSION CRITERIA	Key Exclusion criteria: 1. Congenital or acquired immunodeficiency including HIV infection and previous organ transplantation. 2. Systemic lymphoma manifestation (outside the CNS). 3. Primary vitreoretinal lymphoma or primary leptomeningeal lymphoma without manifestation in the brain parenchyma or spinal cord. 4. Previous or concurrent malignancies with the exception of surgically cured carcinoma *in situ* or other kinds of cancer without evidence of disease for at least 5 years. 5. Previous systemic 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 administration of study medication within the last 30 days before the start of this study. 10. Clinically relevant third space fluid accumulation according to the investigator's discretion. 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. Active COVID-19-infection or non-compliance with the prevailing hygiene measures regarding the COVID-19 pandemic. 15. Patients without legal capacity and who are unable to understand the nature, significance and consequences of the study and without designated legal representative. 16. Previous participation in this trial. 17. Persons who are in a relationship of dependency/employment to the sponsor and/ or investigator. 18. Any familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule. 19. Fertile patients refusing to use safe contraceptive methods during the study.
ENDPOINTS	<u>Primary endpoint:</u> PFS (defined as the time from randomization to disease progression or death of any cause) <u>Key secondary endpoints</u>: • Overall survival (OS) • Event free survival (EFS; defined as time from randomization to premature end of treatment (EOT) due to any reason, lymphoma progression or death, whichever occurs first) • Remission during and after induction treatment • Remission after maintenance: 6 months after RAII • Quality of life (QoL): EORTC QLQ-C30, EORTC QLQ-BN20; measured during screening period, at RAII and premature EOT visit and thereafter every 12 months during follow-up.

	Assessment of safety: • Safety: based on standard criteria for monitoring, assessing and reporting of (serious) adverse events (CTCAE criteria v. 5.0) • Toxicity will be monitored by taking vital signs and laboratory parameters • Neurotoxicity will be assessed by MoCA / TMT-A and -B and a neuropsychological test battery • Rate of unplanned hospital admissions • Length of hospital stays (nights in hospital)	
TRIAL DESIGN	Randomized, controlled, open-label, multicenter phase III trial with 2 parallel arms	
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 12 months after randomization of 55% for the control arm and above 65% (67, 5% for calculation) for the experimental arm. 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 Eastern Cooperative Performance Status (ECOG PS) (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 a corresponding asymptotic two-sided 95% confidence interval (CI). 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 induction and maintenance / consolidation 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 = 340
	To be included in trial pre-phase:	n = 310
	To be randomized:	n = 260
	To be analyzed:	n = 260
TRIAL DURATION	Recruitment period (months): (first patient signed PIC until last patient included)	60

	First patient in to last patient out (months): (First patient signed PIC until last patient last visit incl. 1 year of follow-up)	75
	Duration of the entire trial (months):	96
	Treatment duration per patient (weeks):	Arm A: 38 Arm B: 12
	FU duration per patient (months):	at least 12 after RA II (last patient), max. 72 after RA II (first patient)
TIMETABLE	Enrolment of first patient (FPFV)	4th quarter 2022
	Enrolment of last patient (registration)	4th quarter 2027
	End of trial for last patient (LPLV)	1st quarter 2029
	Final statistical analysis	1st quarter 2030
	Planned interim analysis	Not applicable
PARTICIPATING CENTRES	About 42 sites in Germany, 1 site in Austria, 1 site in Switzerland and possibly additional international sites	
FUNDER(S)	”Bundesministerium für Bildung und Forschung” BMBF project number 01KD2203	