Synopsis

TITLE OF TRIAL	**Optimizing MATRix as remission induction in PCNSL: De-escalated induction treatment in newly diagnosed primary CNS lymphoma – a randomized phase III trial**
SHORT TITLE	**OptiMATe**
EUDRACT NO	2018-002115-96
PROTOCOL NUMBER	SCC215/P002900
HEALTH CONDITION STUDIED	Primary central nervous system lymphoma (PCNSL)
PHASE	Phase III
OBJECTIVE(S)	Primary: To demonstrate superiority of a de-escalated induction treatment strategy followed by autologous stem cell transplantation compared to the standard MATRix protocol in terms of event free survival (EFS) Secondary: To compare overall survival, progression free survival, remission rate prior to consolidation and after consolidation, rate of patients reaching consolidation, complication rate, neurocognitive impairment and quality of life between both treatment arms
TREATMENT(S)	Randomization takes place after completion of screening procedures. **Control treatment (Arm A):** Patients receive four cycles of MATRix (rituximab 2 x 375 mg/m^2, HD-MTX 3.5 g/m^2, HD-AraC 4 x 2 g/m^2, thiotepa 30 mg/m^2; i.v.) as induction treatment. Response assessment with gadolinium-enhanced brain MRI (centrally reviewed) takes place after cycles two and four. Patients with at least PR proceed to 3rd cycle of MATRix after first response assessment and to HCT-ASCT (BCNU 400 mg/m^2, thiotepa 4 x 5 mg/kg; i.v.) after second response assessment. Collection of autologous stem cells is planned after the second cycle of MATRix. **Experimental treatment (Arm B):** As induction treatment, patients receive a pre-phase treatment with R/HD-MTX (rituximab 375 mg/m^2, HD-MTX 3.5 g/m^2; i.v.). In the absence of clinical signs of progression, patients proceed to two cycles of MATRix, followed by a response assessment with gadolinium-enhanced brain MRI (centrally reviewed). Patients achieving at least PR will proceed to HCT-ASCT (BCNU 400 mg/m2, thiotepa 4 x 5 mg/kg; i.v.). Collection of autologous stem cells is planned after the first cycle of MATRix. **Duration of treatment per patient:** Control treatment (Arm A): 15 weeks (first cycle until bone marrow recovery after ASCT) Experimental treatment (Arm B): 11 weeks (first cycle until bone marrow recovery)

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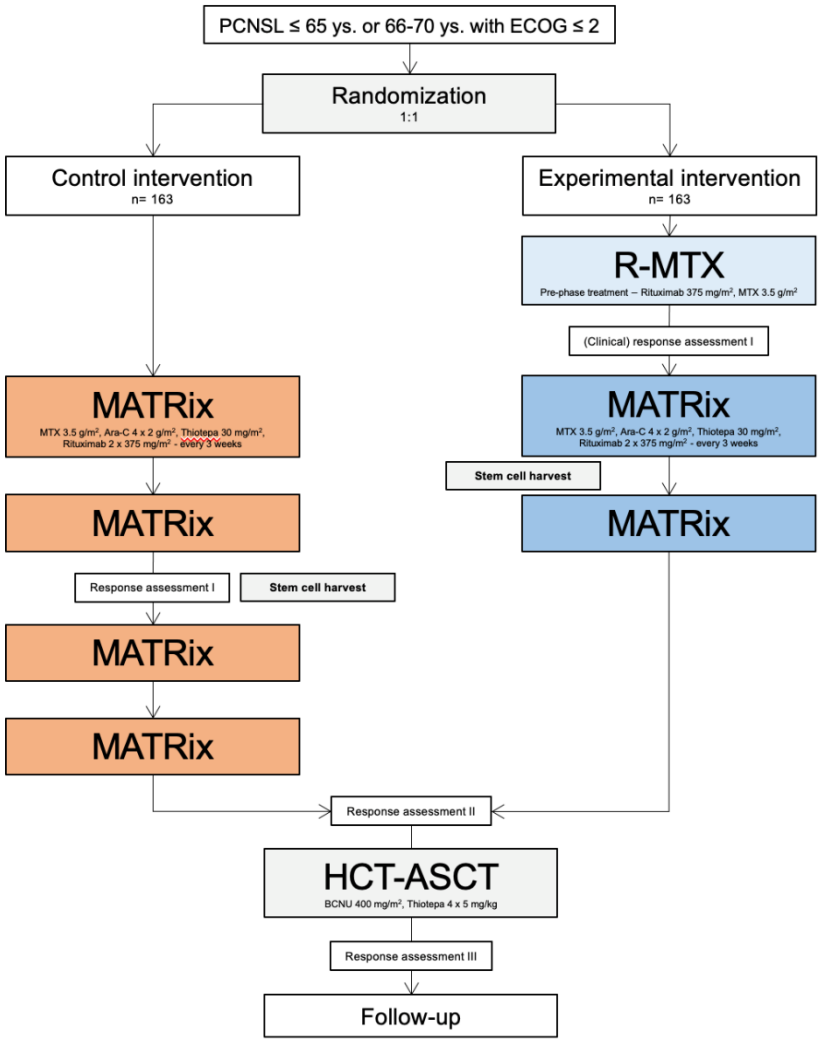

Follow-up per patient: Patients will proceed to a follow-up phase which will last until at least 24 months after completion of treatment
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<td>**KEY INCLUSION CRITERIA**</td>
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1. Immunocompetent patients with newly diagnosed primary diffuse large B-cell lymphoma of the central nervous system (PCNSL).
2. Male or female patients aged 18-65 years irrespective of ECOG or 66-70 years with ECOG Performance Status ≤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.
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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 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 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 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.
ENDPOINTS	**Primary efficacy endpoint:** Event-free survival (EFS, defined as time from randomization to premature end of treatment due to any reason, lymphoma progression or death, whichever occurs first). **Secondary endpoints:** ● Overall survival (OS) ● Progression free survival (PFS) ● Remission prior to consolidation therapy – RA II

	● Remission after consolidation – 30 days after ASCT ● Rate of patients reaching consolidation ● Quality of life (QoL): EORTC QLQ-C30, EORTC QLQ-BN20; measured during screening period, at EOT (30 days after ASCT) 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 (CTC-AE criteria v5.0) ● 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 two parallel arms
STATISTICAL ANALYSIS	The sample size calculation is based on the primary endpoint EFS. In the international IELSG32 trial, the 2-year PFS rate in the best arm was 61%. An EFS rate similar to PFS in the IELSG32 trial is expected in the standard intervention group. It is noted that EFS includes more events than PFS. We aim to increase the 2-year EFS by at least 12% to 73% patients being event-free after 2 years with the experimental intervention. This corresponds to a hazard ratio of 0.636. Then, 153 events need to be observed to detect this difference with 80% power at a 2-sided significance level of 5%. Assuming an exponential model for survival, an accrual period of 4 years and an additional follow-up time of 2 years, 292 patients (146 per arm) patients should be included in the analysis (calculated with nQuery 7.0). Assuming a dropout rate of around 10%, we aim to include 326 patients. Efficacy: The primary efficacy endpoint EFS will be analysed with a Cox proportional hazards regression model. The regression model will include treatment and for adjustment, the following independent variables: the stratification variable trial center, further: age (<60 years vs. ≥60 years), and ECOG performance status (0/1 vs. ≥2). Description of the primary efficacy analysis and population: The primary analysis will be conducted according to the intention-to-treat principle Safety: Safety analyses will be performed for patients who received at least one dose of treatment medication. Rates of adverse events and of serious adverse events will be presented with two sided 95% confidence intervals Secondary endpoints: OS and PFS will be analysed in the same way as described above for EFS; Rate of patients reaching consolidation and rate of remission prior and after consolidation, measured at RAII/30 days after ASCT, will be analysed using a logistic regression model with treatment assignment and the same covariates as in the primary analysis of EFS as independent variable. Crude proportions will be presented with two sided 95% confidence intervals. Descriptive analyses will be presented for length of hospital stays, quality of life and neurocognitive impairment

SAMPLE SIZE	To be assessed for eligibility:	n = 360
	To be allocated/randomized to trial (1:1):	n = 326
	To be analysed:	n = 326
TRIAL DURATION	Recruitment period (months):	48
	First patient in to last patient out (months):	76
	Treatment duration per patient (weeks):	Arm A: 15 Arm B: 11
	Follow up duration per patient (months):	At least 24 (last patient), max. 72 (first patient)
PLANNED DATES	Enrolment of first patient, first patient in (FPI)	2nd quarter 2021
	Enrolment of last patient, last patient in (LPI)	2nd quarter 2025
	End of trial defined as last patient last visit (LPLV)	3rd quarter 2027
	Final statistical analysis	2nd quarter 2028
	Planned interim analysis	n.a.
PARTICIPATING SITES	35-40 German sites, 12-16 sites in the United Kingdom (UK), 7 Italian (IELSG) sites and one Austrian site are planned. Additional international sites planned	
FUNDER(S)	”Bundesministerium für Bildung und Forschung” BMBF (project number FKZ 01KG2001). UK funding is provided by Cancer Research UK through a research grant from the Clinical Research Committee (reference CRCPJT\100010).	