Synopsis

TITLE OF TRIAL	AGE-ADJUSTED HIGH-DOSE CHEMOTHERAPY AND AUTOLOGOUS STEM CELL TRANSPLANT IN ELDERLY AND FIT PRIMARY CNS LYMPHOMA PATIENTS
SHORT TITLE	MARTA
PROTOCOL NUMBER	P001317
EUDRACT NO	2016-001628-72
MAIN DIAGNOSIS	Primary Central Nervous System Lymphoma
PHASE	Phase II
OBJECTIVE(S)	The primary objective of the study is to investigate the efficacy of age-adapted induction treatment followed by high-dose chemotherapy and autologous stem cell transplantation regarding 1-year PFS in elderly and fit patients with primary CNS lymphoma. Secondary objectives are the investigation of OS, treatment response (rate of complete responses on day 30 after HDT-ASCT) and treatment related morbidities (neurotoxicity and adverse advents).
INTERVENTION(S)	**Induction treatment:** 2 cycles (every 3 weeks), stem-cell harvest after first cycle: - Rituximab 375 mg/m²/d i.v. (d0,4) - MTX 3,5 g/m² i.v. (d1) - AraC 2x2 g/m²/d i.v. (d2-3) **Consolidation:** High-dose chemotherapy: - Rituximab 375 mg/m² i.v. (d-8) - Busulfan 3,2 mg/kg/d i.v. (d-7 and d-6) - Thiotepa 5 mg/kg/d i.v. (d-5 and d-4) - ASCT (d0) Duration of intervention per patient: 10 weeks Follow-up per patient: 12 months
(KEY) INCLUSION CRITERIA	Key inclusion criteria: 1. Immunocompetent patients with newly-diagnosed primary central nervous system B-cell lymphoma. 2. Age > 65 years not eligible for treatment within the MATRix/IELSG43 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 intensive treatment 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.
(KEY) EXCLUSION CRITERIA	Key exclusion criteria: 1. Congenital or acquired immunodeficiency. 2. Systemic lymphoma manifestation (outside the CNS). 3. Isolated ocular 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 systemic Non-Hodgkin lymphoma at any time. 6. Inadequate renal function (creatinine clearance <60 ml/min). 7. Inadequate hepatic, cardiac or pulmonary function according to physician`s decision. 8. Active hepatitis B or C disease. 9. HIV infection, previous organ transplantation or other clinical evident form of immunodeficiency. 10. Concurrent treatment with other experimental drugs or participation in a clinical trial within the last thirty days before the start of this study. 11. Third space fluid accumulation >500 ml. 12. Hypersensitivity to study treatment or any component of the formulation. 13. Taking any medications likely to cause interactions with the study medication. 14. Known or persistent abuse of medication, drugs or alcohol. 15. Patient without legal capacity and who is unable to understand the nature, significance and consequences of the study and without designated legal representative. 16. Persons who are in a relationship of dependency/employment to the sponsor and/ or investigator. 17. Any familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule.
ENDPOINTS	Primary endpoint: progression free survival (PFS) at 1 year: time from start of treatment until disease progression or death from any cause, whichever occurs first. Key secondary endpoint(s): • Rate of complete responses (CR) on day +30 after HDT-ASCT • Progression-free survival (PFS) as time from start of treatment until progression, relapse or death from any cause, whatever happens first • Overall survival (OS) as time from start of treatment until death from any cause • Rate of neurotoxicity on day + 30 after HDT-ASCT and continuously thereafter • Non relapse mortality (NRM) • (Serious) adverse events ([S]AEs): from the first administration of the study medication until day 30 after HDT-ASCT 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. 4.0) Toxicity will be monitored by taking continuous blood samples (i.e. full blood-count, kidney and liver-markers…), lung function tests and neuropsychological evaluation.	
TRIAL DESIGN	This is an open-label, prospective, multicentric, non-randomized, single arm phase II trial using Fleming one stage design	
STATISTICAL ANALYSIS **EFFICACY**	Sample size consideration: The sample size of the trial is calculated based on the primary endpoint PFS probability at 1 year. The following assumptions are used: Treatment with MARTA is considered to be not successful if the 1 year PFS probability is 50% or lower. Treatment with MARTA is considered to be successful if the 1 year PFS probability is 70% or higher. The type I error rate α, i.e. the error probability of regarding the treatment regimen as successful when it is not (probability of PFS is 50% or lower), is set to 10%. The type II error rate β, i.e. the error probability of regarding the treatment regimen as not successful when it is successful (probability of PFS is 70% or higher), is set to 10%. For the purpose of sample size calculation, 1 year PFS is considered as a binary endpoint, and the exact binomial distribution is used to test H0: p<= 0.5 vs H1: p>=0.7 with α and β as defined above, where p denotes the 1 year PFS probability. The required sample size is n=39, and the treatment will be considered as successful, when the number of patients who are progression free and alive after 1 year is 24 or higher. As we assume that the disease status after one year will not be available for a few patients (maximal 30%), 51 patients will be included in the trial. Primary endpoint: If no censored observations before 1 year occur, the primary analysis will be conducted using the exact binomial distribution. If the number of evaluable patients progression-free and alive one year after start of treatment will be 24 or higher, treatment will be considered as successful. Two-sided confidence intervals will be derived from the exact binomial distribution for the confidence level 80% (in accordance with the specified α) and 95% (for comparability to the literature). If censored observations occur, the 1 year PFS rate will be estimated using the Kaplan Meier method, and confidence intervals will be derived using the Greenwood formula. The treatment will be considered as successful, if the two-sided 80% confidence interval lies completely above 50%. Secondary endpoints: Endpoints of survival, where no competing risks are present (OS, PFS), will be analysed by means of the Kaplan Meier method. In order to analyse potentially prognostic factors to a broader extend, cox regression models are applied. Standardised questionnaires on quality of life will be analysed descriptively in compliance with the EORCT manual.	
STATISTICAL ANALYSIS **SAFETY**	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 (serious) adverse events will be calculated with corresponding two-sided 95% confidence intervals. Toxicity and neurotoxicity will be analysed descriptively.	
SAMPLE SIZE	To be assessed for eligibility:	n = 60
	To be allocated to trial:	n = 51
	To be analysed:	n = 51
TRIAL DURATION	Recruitment period (months): (first patient signed PIC until last patient included)	36 months
	First patient in to last patient out (months):	51 months

	(First patient signed PIC until last patient last visit incl. 1 year of follow up)	
	Duration of the entire trial (months):	63 months
	Treatment duration per patient (weeks): (e.g. 6 months after inclusion in the study or until relapse/progression, unacceptable toxicity or death)	10 weeks
TIMETABLE	Enrolment of first patient (FPFV)	2nd quarter 2017
	Enrolment of last patient (registration)	2nd quarter 2020
	End of trial for last patient (LPLV) (Follow up per patient: After one year of follow-up every 3 months, control examinations are recommended to take place every six months within years 3 to 5 and annually thereafter.)	3rd quarter 2021
	Final statistical analysis	3rd quarter 2022
	Planned interim analysis	No interim analyses will be performed
PARTICIPATING CENTRES	12 sites in Germany	