# Synopsis

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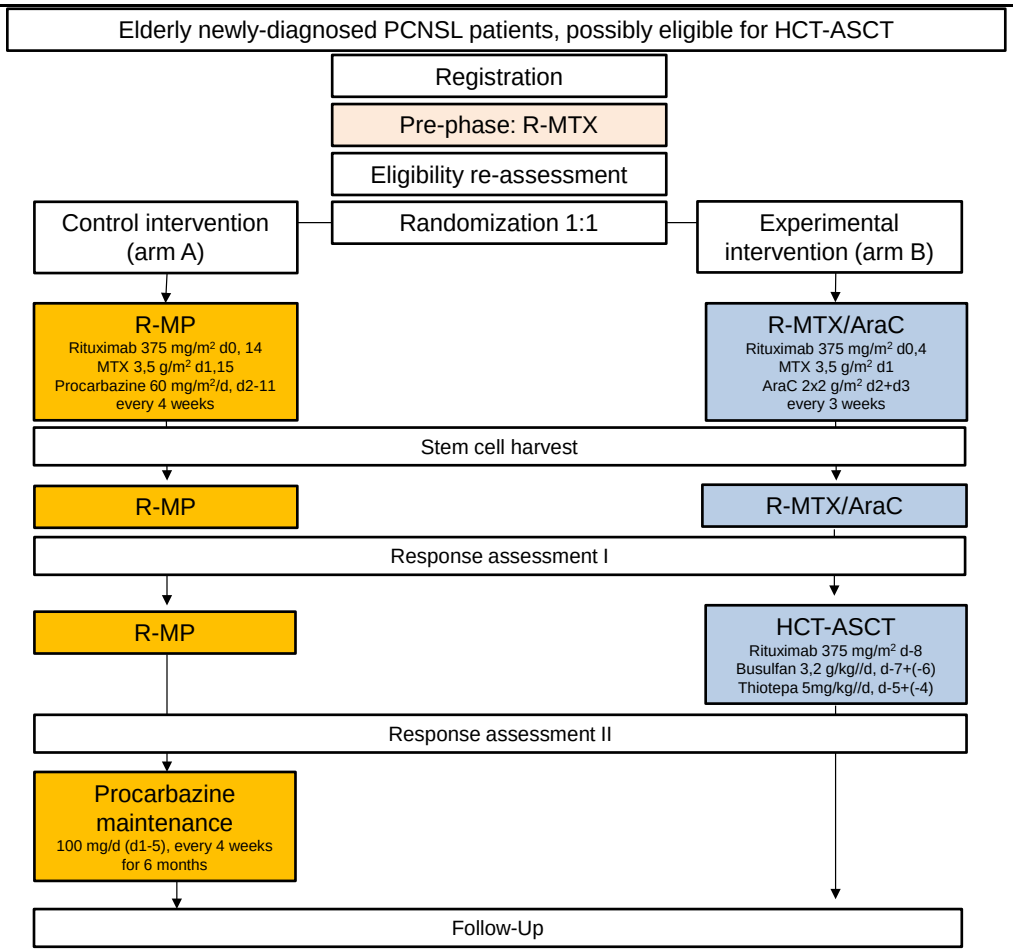
| **TITLE OF TRIAL** | Age-adjusted high-dose chemotherapy followed by autologous stem cell transplantation or conventional chemotherapy with R-MP as first-line treatment in elderly primary CNS lymphoma patients – a randomized phase III trial |
| **SHORT TITLE** | PRIMA-CNS |
| **PROTOCOL NUMBER** | 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).<br>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:**<br>**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:<br>**Arm A - control intervention:**<br>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).<br>**Arm B - experimental intervention:**<br>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.<br>**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.<br><br>Duration of intervention per patient:<br>Arm A: 38 weeks (pre-phase treatment until end of maintenance treatment)<br>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 1 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.

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| **KEY EXCLUSION CRITERIA** | Key Exclusion criteria:<br>1. Congenital or acquired immunodeficiency including HIV infection and previous organ transplantation.<br>2. Systemic lymphoma manifestation (outside the CNS).<br>3. Primary vitreoretinal lymphoma or primary leptomeningeal lymphoma without manifestation in the brain parenchyma or spinal cord.<br>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.<br>5. Previous systemic Non-Hodgkin lymphoma at any time.<br>6. Inadequate renal function (creatinine clearance <60 ml/min).<br>7. Inadequate bone marrow, cardiac, pulmonary or hepatic function according to investigator´s decision.<br>8. Active hepatitis B or C disease.<br>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.<br>10. Clinically relevant third space fluid accumulation according to the investigator's discretion.<br>11. Hypersensitivity to study treatment or any component of the formulation.<br>12. Taking any medications likely to cause interactions with the study medication.<br>13. Known or persistent abuse of medication, drugs or alcohol.<br>14. Active COVID-19-infection or non-compliance with the prevailing hygiene measures regarding the COVID-19 pandemic.<br>15. Patients without legal capacity and who are unable to understand the nature, significance and consequences of the study and without designated legal representative.<br>16. Previous participation in this trial.<br>17. Persons who are in a relationship of dependency/employment to the sponsor and/ or investigator.<br>18. Any familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule.<br>19. Fertile patients refusing to use safe contraceptive methods during the study. |
| **ENDPOINTS** | Primary endpoint: PFS (defined as the time from randomization to disease progression or death of any cause)<br>Key secondary endpoints:<br>• Overall survival (OS), with censoring at the last date the patient was seen alive<br>• 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), with censoring at the last date the patient was seen event-free<br>• Remission during and after induction treatment<br>• Remission after maintenance: 6 months after RAII<br>• 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.<br>Assessment of safety:<br>• Safety: based on standard criteria for monitoring, assessing and reporting of (serious) adverse events (CTCAE criteria v. 5.0)<br>• Toxicity will be monitored by taking vital signs and laboratory parameters<br>• Neurotoxicity will be assessed by MoCA and a neuropsychological test battery<br>• Rate of unplanned hospital admissions<br>• Length of hospital stays (nights in hospital) |
| **TRIAL DESIGN** | Randomized, controlled, open-label, multicenter phase III trial with 2 parallel arms |

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| **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.<br>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.<br>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.<br>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):<br>(first patient signed PIC until last patient included) | 60 |
| | First patient in to last patient out (months):<br>(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<br>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) | 1st quarter 2023 |
| | Enrolment of last patient (registration) | 1st quarter 2028 |
| | End of trial for last patient (LPLV) | 2 nd quarter 2029 |
| | Final statistical analysis | 2 nd quarter 2030 |
| | Planned interim analysis | Not applicable |
| **PARTICIPATING CENTRES** | About 44 sites in Germany, Austria, Switzerland and possibly additional international sites | |
| **FUNDER(S)** | ”Bundesministerium für Bildung und Forschung” BMBF<br>project number 01KD2203 | |

Table 1 Visit schedule and assessments – Flowchart: Control Treatment - Arm A

| **PERIODS** | | **SCREENING** | **TREATMENT – ARM A including MAINTENANCE** | | | | | | | | **EOT** | | **FOLLOW-UP** | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Duration | 14 days | 10-14 days | | 28 days | 28 days | | 28 days | | 6 months | | | at least 1 (max. 6) year(s) after RA II | |
| **Visits** | **Title in eCRF** | **Screening** | **Pre-phase** | **Rando-mization** | **Visit 1[1]** | **Visit 2[1]** | **RA I[1]** | **Visit 3[1]** | **RA II[1]** | **Maintenance Visits** | **EOT Visit[1]** | **Pre-mat-ure EOT[1]** | **FU Yr 1-2** | **FU from Yr3[2]** |
| **Time window for assessments / Interval of treatment administration** | Time / Section of CTP | d-14 until d0 | d0-1 | d10-14 | d0-15[3] of cycle 1 | d0-15[3] of cycle 2 | d25-27 of cycle 2 | d0-15[3] of cycle 3 | d25-27 of cycle 3 | Visits every 3 months/ Treatment d1-5 every 4 weeks | d30 after last administration of IMP | | every 3 mo (± 14 d) | every 6 mo (± 30 d) |
| **Informed consent**[5] | 15.3 | x | | | | | | | | | | | | |
| **Inclusion/exclusion criteria** | 4.2, 4.3, | x | | x | | | | | | | | | | |
| **Registration** | 5.2.1 | x | | | | | | | | | | | | |
| **Treatment administration** | 6.1 | | x | | x | x | | x | x[6] | x[6] | | | | |
| **Demographics, Medical History** | 7.8.1 7.8.2 | x | | | | | | | | | | | | |
| **Physical and neurological examination*/**** | 7.8.3 | x | x | | x | x | | x | x | x | x | x | x | x |
| **Vital signs*** | 7.8.4 | x | x | | x | x | | x | x | x | x | x | x | x |
| **Body height and weight** | 7.8.4 | x | x | | x | x | | x | x | x | | | | |
| **Performance status (Karnofsky and ECOG)** | 7.8.5 | x | | | x | x | | x | x | x | x | x | x | x |
| **Premorbid performance status (Karnofsky and ECOG)** | 7.8.5 | x | | | | | | | | | | | | |
| **Lachs geriatric screening** | 7.8.6 | x | | x | | | | | | | | | | |
| **Barthel Index of ADL** | 7.8.6 | x | | x | | | | | x | x | x | x | x[13] | x[13] |
| **IADL (premorbid + current status)** | 7.8.6 | x | | | | | | | | | | | | |
| **Weight loss questionnaire** | 7.8.6 | x | | | | | | | | | | | | |
| **CIRS-G** | 7.8.6 | x | | | | | | | | | | | | |
| **Charlson Comorbidity Index (CCI)** | 7.8.6 | x | | | | | | | | | | | | |
| **HCT-ASCT eligibility assessment[26]** | 7.8.14 | | | x | | | | | | | | | | |
| **Hematology[7]/Clinical chemistry[8]*** | 7.8.15 | x | x | x | x | x | | x | x | x | x | x | x | x |
| **Creatinine, estimated GFR (MDRD)[8]** | 7.8.15 | x | x | | x | x | | x | | | | | | |
| **Hepatitis B/C and HIV serology*** | 7.8.15 | x | | | | | | | | | | | | |

| **PERIODS** | | **SCREENING** | **TREATMENT – ARM A including MAINTENANCE** | | | | | | | | **EOT** | | **FOLLOW-UP** | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Duration | 14 days | 10-14 days | | 28 days | 28 days | | 28 days | | 6 months | | | at least 1 (max. 6) year(s) after RA II | |
| **Visits** | **Title in eCRF** | **Screening** | **Pre-phase** | **Rando-mization** | **Visit 1[1]** | **Visit 2[1]** | **RA I[1]** | **Visit 3[1]** | **RA II[1]** | **Maintenance Visits** | **EOT Visit[1]** | **Pre-mat-ure EOT[1]** | **FU Yr 1-2** | **FU from Yr3[2]** |
| **Time window for assessments / Interval of treatment administration** | Time / Section of CTP | d-14 until d0 | d0-1 | d10-14 | d0-15[3] of cycle 1 | d0-15[3] of cycle 2 | d25-27 of cycle 2 | d0-15[3] of cycle 3 | d25-27 of cycle 3 | Visits every 3 months/ Treatment d1-5 every 4 weeks | d30 after last administration of IMP | | every 3 mo (± 14 d) | every 6 mo (± 30 d) |
| **Electrocardiogram (ECG)*** | 7.8.16 | x | | | | | | | | | | | | |
| **Whole body plethysmography[24]** | 7.8.16 | x | | | | | | | | | | | | |
| **Echocardiography*** | 7.8.16 | x | | | | | | | | | | | | |
| **Testicular ultrasound*** | 7.8.17 | x | | | | | | | | | | | | |
| **Abdominal ultrasound[9]*** | 7.8.18 | | x | | x | x | | x | | | | | | |
| **Whole brain MRI and response statement according to IPCG (local and central radiology)** | 7.8.19 | x | | | | | x | | x | x[14] | x | x[15] | x[16] | x[16] |
| **Imaging (CT neck to pelvis)[10]*** | 7.8.19 | x | | | | | | | | | | | | |
| **Shipment to central pathology[25]** | 7.8.20 | x | | | | | | | | | | | | |
| **Bone marrow examination[27]*** | 7.8.21 | x | | | | | | | | | | | | |
| **Slit lamp examination[11]** | 7.8.22 | x | | | | | x [11] | | x [11] | | x [11] | x[11] | | |
| **CSF examination[12]** | 7.8.23 | x | | (x)[22] | | | x[11] | | x[11] | | x[11] | x[11] | | |
| **MoCA[13]** | 7.8.8.1 | x | | | | | | | x | | | x | x[13] | x[13] |
| **PHQ9[13], GAD7[13], SSUK[13]** | | x | | | | | | | x | | | x | x[13] | x[13] |
| **QLQ (EORTC QLQ-C30 BN20)[13]** | 7.8.24 | x | | | | | | | x | | | x | x[13] | x[13] |
| **Neuropsychological battery[17]** | 7.8.8.2 | x | | | | | | | x | | | (x)[17] | (x)[13] | (x)[13] |
| **NANO** | | x | | x | | | | x | x | | | x | x[13] | x[13] |
| **Subjective evaluation of trial participation** | 7.8.9 | x[18] | | | | | | | x[19] | | x[19] | x[19] | | |
| **Stem cell harvest** | 7.8.24 | | | | x[20] | | | | | | | | | |
| **HCT-CI** | 7.8.6.2 | x | | | | | | | | | | | | |
| **Translational program[21]** | 7.9 | x[21] | | x[21] | | | | | x[21] | (x)[21] | x[21] | (x)[21] | (x)[21] | (x)[21] |
| **Concomitant medication** | 6.3 | x | x | | | | | | | | | | | |
| **Adverse events (CTCAE v. 5.0)** | 10 | x | x | | | | | | | | | | x[23] | |

ADL=Activities of daily living; AE=Adverse Event; ASCT=Autologous stem cell transplantation; CIRS-G = Cumulative Illness Rating Scale Geriatric; CSF=Cerebrospinal fluid; CT=Computed Tomography; CTCAE v.5.0=Common Terminology Criteria for Adverse Events version 5.0; d=Day(s); EORTC QLQ-C30=Quality of Live Questionnaire; EOT=End of Treatment; FU=Follow-up; GAD7=General Anxiety Disorder 7; GFR=Glomerular Filtration Rate; HCT-ASCT=High-dose chemotherapy and autologous stem-cell transplantation; HCT-CI=Hematopoietic Cell Transplantation- Comorbidity Index; HIV=Human immunodeficiency virus; IADL= Instrumental Activities of Daily Living; IMP=Investigational Medicinal Product; IPCG=International PCNSL Collaborative Group; LDH=Lactate dehydrogenase; MDRD=Modification of Diet in Renal Disease; mo=Month(s); MoCA=Montreal Cognitive Assessment; MRI=Magnetic Resonance Imaging; NANO= Neurologic Assessment in Neuro-Oncology; PHQ9=Personal Health Questionnaire form 9; QLQ-BN 20=brain tumor module Questionnaire; QOQ=Quality of Life Questionnaire; SSUK=Social Support in Chronic Illness Questionnaire; yr=Year; RA=Response Assessment; For additional details see corresponding numbering (footnotes).

Table 2 Visit schedule and assessments – Flowchart: Experimental Treatment - Arm B

| **PERIODS** | | **Screening** | **TREATMENT – ARM B** | | | | | | **EOT** | | **FOLLOW-UP** | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Duration | 14 days | 10-14 days | | 21 days | 21 days | | 39 days | | | at least 1 (max. 6) year(s) after RA II | |
| **Visits** | **Title in eCRF** | **Screening** | **Pre-phase** | **Rando-mization** | **Visit 1[1]** | **Visit 2[1]** | **RA I[1]** | **Visit 3[1]** | **RA II = EOT Visit[1]** | **premature EOT Visit[1]** | **FU Yr 1-2** | **FU from Yr3[2]** |
| **Time window for assessments / Interval of treatment administration** | Time / Section | d-14 until day 0 | d0-1 | d10-14 | d0-4[3] of cycle 1 | d0-4[3] of cycle 2 | d18-20 of cycle 2 | d-8 to d0 of HCT-ASCT[4] | d30 after ASCT | d30 after last adminis-tration of IMP | every 3 mo (± 14 d) | every 6 mo (± 30 d) |
| **Informed consent**[5] | 15.3 | x | | | | | | | | | | |
| **Inclusion/exclusion criteria** | 4.2, 4.3, | x | | x | | | | | | | | |
| **Registration** | 7.3.4 | x | | | | | | | | | | |
| **Treatment administration** | 6.1 | | x | | x | x | | x | | | | |
| **Demographics, Medical History** | 7.8.1, 7.8.2 | x | | | | | | | | | | |
| **Physical and neurological examination*** | 7.8.3 | x | x | | x | x | | x | x | x | x | x |
| **Vital signs*** | 7.8.4 | x | x | | x | x | | x | x | x | x | x |
| **Body height and weight** | 7.8.4 | x | x | | x | x | | x | | | | |
| **Performance status (Karnofsky and ECOG)** | 7.8.5 | x | | | x | x | | x | x | x | x | x |
| **Premorbid performance status (Karnofsky and ECOG)** | 7.8.5 | x | | | | | | | | | | |
| **Lachs geriatric screening** | 7.8.6 | x | | x | | | | | | | | |
| **Barthel Index of ADL** | 7.8.6 | x | | x | | | | | x | x | x[13] | x[13] |
| **IADL (premorbid + current status)** | 7.8.6 | x | | | | | | | | | | |
| **Weight loss questionnaire** | 7.8.6 | x | | | | | | | | | | |
| **CIRS-G** | 7.8.6 | x | | | | | | | | | | |
| **Charlson Comorbidity Index (CCI)** | 7.8.6 | x | | | | | | | | | | |
| **HCT-ASCT eligibility assessment[26]** | 7.8.14 | | | x | | | | | | | | |
| **Hematology[7]/Clinical chemistry[8]*** | 7.8.15 | x | x | x | x | x | | x | x | x | x | x |
| **Creatinine, estimated GFR (MDRD)[8]** | 7.8.15 | x | x | | x | x | | x | | | | |
| **Hepatitis B/C and HIV serology*** | 7.8.15 | x | | | | | | | | | | |
| **Electrocardiogram (ECG)*** | 7.8.16 | x | | | | | | x | | | | |

| **PERIODS** | | **Screening** | **TREATMENT – ARM B** | | | | | | **EOT** | | **FOLLOW-UP** | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Duration | 14 days | 10-14 days | | 21 days | 21 days | | 39 days | | | at least 1 (max. 6) year(s) after RA II | |
| **Visits** | **Title in eCRF** | **Screening** | **Pre-phase** | **Rando-mization** | **Visit 1[1]** | **Visit 2[1]** | **RA I[1]** | **Visit 3[1]** | **RA II = EOT Visit[1]** | **premature EOT Visit[1]** | **FU Yr 1-2** | **FU from Yr3[2]** |
| **Time window for assessments / Interval of treatment administration** | Time / Section | d-14 until day 0 | d0-1 | d10-14 | d0-4[3] of cycle 1 | d0-4[3] of cycle 2 | d18-20 of cycle 2 | d-8 to d0 of HCT-ASCT[4] | d30 after ASCT | d30 after last adminis-tration of IMP | every 3 mo (± 14 d) | every 6 mo (± 30 d) |
| **Whole body plethysmography[24]*** | 7.8.16 | x | | | | | | x | | | | |
| **Echocardiography*** | 7.8.16 | x | | | | | | x | | | | |
| **Testicular ultrasound*** | 7.8.17 | x | | | | | | | | | | |
| **Abdominal ultrasound[9]*** | 7.8.18 | | x | | x | x | | | | | | |
| **Whole brain MRI and response statement according to IPCG (local and central radiology)** | 7.8.19 | x | | | | | x | | x | x[15] | x[16] | x[16] |
| **Imaging (CT neck to pelvis)[10]*** | 7.8.19 | x | | | | | | | | | | |
| **Shipment to central pathology[25]** | 7.8.20 | x | | | | | | | | | | |
| **Bone marrow examination[27]*** | 7.8.21 | x | | | | | | | | | | |
| **Slit lamp examination[11]** | 7.8.22 | x | | | | | x[11] | | x[11] | x[11] | | |
| **CSF examination[12]** | 7.8.23 | x | | (x)[22] | | | x[11] | | x[11] | x[11] | | |
| **MoCA[13]** | 7.8.8.1 | x | | | | | | | x | x | x[13] | x[13] |
| **PHQ9[13], GAD7[13], SSUK[13]** | | x | | | | | | | x | x | x[13] | x[13] |
| **QLQ (EORTC QLQ-C30 + BN20)[13]** | 7.8.7 | x | | | | | | | x | x | x[13] | x[13] |
| **Neuropsychological battery[17]** | 7.8.8.2 | x | | | | | | | x | x | (x)[13] | (x)[13] |
| **NANO** | | x | | x | | | | x | x | x | x[13] | x[13] |
| **Subjective evaluation of trial participation** | 7.8.9 | x[18] | | | | | | | x[19] | x[19] | x[19] | |
| **Stem cell harvest** | 7.8.24 | | | | x[20] | | | | | | | |
| **HCT-CI** | 7.8.6.2 | x | | | | | | x | | | | |
| **Translational program[21]** | 7.9 | x[21] | | x[21] | | | x[21] | | x[21] | (x)[21] | (x)[21] | (x)[21] |
| **Concomitant medication** | 6.3 | x | x | | | | | | | | | |
| **Adverse events (CTCAE V. 5.0)** | 10 | x | x | | | | | | | | x [23] | |

ADL=Activities of daily living; AE=Adverse Event; ASCT=Autologous stem cell transplantation; CIRS-G = Cumulative Illness Rating Scale Geriatric; CSF=Cerebrospinal fluid; CT=Computed Tomography; CTCAE v. 5.0=Common Terminology Criteria for Adverse Events version 5.0; d=Day(s); EORTC QLQ-C30=Quality of Live Questionnaire; EOT=End of Treatment; FU=Follow-up; GAD7=General Anxiety Disorder 7; GFR=Glomerular Filtration Rate; HCT-ASCT=High-dose chemotherapy and autologous stem-cell transplantation; HCT-CI=Hematopoietic Cell Transplantation- Comorbidity Index; HIV=Human immunodeficiency virus; IADL=Instrumental Activities of Daily Living; IMP=Investigational Medicinal Product; IPCG=International PCNSL Collaborative Group; LDH=Lactate dehydrogenase; MDRD=Modification of Diet in Renal Disease; mo=Month(s); MoCA=Montreal Cognitive Assessment; MRI=Magnetic Resonance Imaging; NANO=Neurologic Assessment in Neuro-Oncology; PHQ9=Personal Health

Questionnaire form 9; QLQ-BN 20=brain tumor module Questionnaire; QOQ=Quality of Life Questionnaire; SSUK=Social Support in Chronic Illness Questionnaire; yr=Year; RA=Response Assessment; For additional details see corresponding numbering (footnotes).

* not to be documented in the eCRF
** Physical examination is recommended to be performed according to the flow chart; detailed findings concerning these examinations must only be documented in the eCRF at screening. At other visits, in case of clinically relevant abnormal findings, the investigator has to document an AE on the AE-page in the eCRF

[1] Deviations ± 5 days are allowed

[2] Also after termination of study, follow up every 3 months (year 2), every 6 months (year 3-5) and annually (after year 5) is recommended for evaluation of overall survival and late toxicities (see section 7.7.)

[3] Interval of treatment administration, max. delay of therapy 4 weeks (for details see section 6.2). Additional gadolinium-enhanced brain MRI in case delay exceeds 2 weeks. Restart of treatment only in case of at least SD

[4] d-8 of HCT matches d22 of last cycle of MARTA. Max. delay of therapy 4 weeks (for details see section 6.2.1). Additional gadolinium-enhanced brain MRI in case delay exceeds 2 weeks. Restart of treatment only in case of at least SD

[5] Informed consent must be obtained before any study specific screening examination

[6] Maintenance treatment administration day 1-5 every 4 weeks for 6 months. Beginning within 5 days after RA II. Max. delay of therapy 4 weeks (for details see section 6.2). Unless clinically indicated otherwise, visits will be performed every 3 months during maintenance therapy.

[7] Hematology: white blood count (WBC), neutrophils, hemoglobin and platelets

[8] Blood chemistry: creatinine, total bilirubin, ALAT, ASAT, LDH, estimated GFR (MDRD), (and Gamma-GT only performed at screening); only LDH (at screening), estimated GFR (MDRD) and creatinine have to be documented in eCRF.

[9] Ultrasound to exclude third space fluid accumulation prior to MTX administration. If third space fluid accumulation has already been excluded during the screening period by means of (PET-) CT and clinically no new suspicious indications arise, a renewed evaluation before the start of the pre-phase therapy is not mandatory. This examination can also be omitted if the patient's medical history and thorough physical examination do not suggest any third space fluid accumulation.

[10] If CT is suspicious at diagnosis: adequate further diagnostics by investigator's decision, e.g. FDG-PET, biopsy. Note: FDG-PET-/CT can be performed at screening instead of CT neck to pelvis, refer to section 7.8.15.

[11] Only performed if positive at previous examination/clinically indicated; until results are negative or in case of participation in the translational program on condition that additional informed consent is available

[12] Only performed after excluding increased intracranial pressure by brain MRI; cytology, FACS and protein examination

[13] Beginning with RA II / premature EOT every 12 months during follow-up period

[14] During maintenance treatment in arm A, MRT assessment will be done every 3 months, unless it is clinically indicated otherwise

[15] If clinically indicated

[16] Central radiology assessment in the maintenance and/or follow-up period only if measureable lesions are still present and in case of recurrence. Shipment for central review as soon as possible after screening and after RA II (including assessments at RA I), after EOT (arm A) and in case of recurrence for the individual patient. In case of persisting measurable lesions, shipment during follow-up will be performed once at the end of the study for each trial site.

[17] Beginning with Follow-up MoCA every 12 months as screening test; subsequent neuropsychological battery only if 24-26 points in MoCA or if MoCA result deviates ≥4 points in comparison to previous test. If premature EOT occurs during maintenance treatment the neuropsychological battery does not have to be performed if it was done at RAII. (for details see 5.2.2)

[18] Subjective evaluation of trial participation questionnaire Q1 will be done after the patient was informed about the trial and has given informed consent, it may be done after start of treatment during the pre-phase treatment in-patient visit.

[19] Subjective evaluation of trial participation questionnaire Q2_Q3 will be done in arm A at RA II, EOT Visit (6 months after RA II) and premature EOT Visit. In arm B at RA II, premature EOT Visit and onetime during FU (6 months after RA II).

[20] Stem cell harvest is planned after the first cycle of R-MP in the control arm and after first cycle of R-MTX-AraC in the experimental arm. If stem cell harvest is unsuccessful at this time point further attempts can be made after cycle 2 and 3 in arm A or after cycle 2 in arm B before HCT.

[21] During screening period on condition that additional informed consent is available, additional biological specimen have to be taken before IMP administration (1 EDTA tube à 9 ml, 3 streck tubes à 10 mL, 1 Serum tube à 9 mL, 1 CSF à 4-5mL, tumor FFPE, bone marrow).

In arm **A** blood and CSF samples will be taken at randomization, RA II and EOT and in case of relapse and progressive disease. At premature end of treatment visit and during follow up period these samples will be taken only in case of relapse or progressive disease (1 EDTA à 9 mL, 3 streck tubes à 10 mL, 1 Serum tube à 9 mL, 1 CSF à 4-5mL).
In arm **B** blood and CSF samples will be taken at randomization, RAI and RAII (EOT) and in case of relapse and progressive disease. At premature end of treatment visit and during follow up period these samples will be taken only in case of relapse and progressive disease. (1 EDTA à 9 mL, 3 streck tubes à 10 mL, 1 Serum tube à 9 mL, 1 CSF à 4-5mL).
Respective collecting and shipping material will be provided by the University Hospital Freiburg. For details on translational project and sample handling and logistics see section 7.9 and study specific instruction sheet for shipping and sample handling respectively.

[22] Only performed if patient participates in the translational program (additional informed consent required); cytology, FACS and protein examination not mandatory.

[23] Only serious adverse events related to IMP as per investigator's judgement

[24] Where this is not considered standard evaluation for pulmonary function: Comparable pulmonary function tests can be used (refer to section 7.8.12).

[25] Shipping to central pathology should be arranged as soon as possible after registration in this trial.

[26] Patients eligible for HCT-ASCT defined by the EBL score (at most 1 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. Discussion with the study expert team should take place from day 7-14 of prephase treatment in a weekly organised virtual meeting.

[27] If PET-CT was done at screening, bone marrow examination is not mandatory at screening.