Pre-phase treatment with rituximab and high-dose methotrexate to re-evaluate eligibility for intensive induction treatment of frail patients with central nervous system lymphoma

High-dose (HD) methotrexate (MTX)-based induction treatment followed by consolidating high-dose chemotherapy and autologous stem cell transplantation (HCT-ASCT) has been established for eligible patients with primary and secondary large B-cell lymphoma of the central nervous system (PCNSL/SCNSL), but eligibility is questionable in a substantial proportion of patients due to age, reduced performance status (PS), the underlying lymphoma with corresponding neurological symptoms, comorbidities, pre-treatment corticosteroids and prior (immuno)-chemotherapy.[1-4] Patients deemed ineligible for HCT-ASCT have inferior outcomes.[1,4,5] In the absence of established objective criteria, the evaluation of HCT-ASCT eligibility is often challenging and mainly left to the treating physician's discretion. However, the impairment of PS may rather be influenced by the underlying lymphoma than age or comorbidities, thus misleading the treating physician into underestimating the eligibility for intensive treatment strategies. Consequently, experts suggest to consider premorbid PS and regularly reassess PS during treatment.[6] Moreover, the development of novel treatment strategies for patients questionably eligible for HCT-ASCT is a high unmet medical need. This retrospective multicenter study evaluated whether a rapid improvement of PS following pre-phase rituximab/high-dose MTX (R-MTX) might enable re-evaluation of eligibility for HCT-ASCT. This study was approved by the ethic committee of the Landesärztekammer Baden-Württemberg (F-2023-043) and conducted according to institutional board requirements and the Declaration of Helsinki.

Patients with histologically proven PCNSL/SCNSL who were treated between January 2027 and May 2024 at three German tertiary referral centers were included. Patients further fulfilled the following inclusion criteria: expert consensus at the respective center stated that eligibility for intensive induction treatment followed by HCT-ASCT was questionable, acknowledging patient's age, (premorbid) PS, comorbidities, pre-treatment corticosteroids and prior (immuno)-chemotherapy. Patients had to have received a pre-phase treatment consisting of rituximab (R) 375 mg/m^2) and HD-MTX (≥3 g/m^2) at initial or relapse diagnosis in the intent to re-evaluate treatment eligibility. Patients with chronic kidney injury (CKI), defined as decreased glomerular filtration rate ≤60 mL/min/1.73m^2 (CKD-EPI) for ≥3 months, were allowed to receive reduced MTX doses (≥1.5 g/m^2). Patients receiving R-MTX pre-phase within a prospective

trial (e.g., OptiMATe or PRIMA-CNS[7,8]) were excluded. The primary endpoint was to assess the proportion of patients that were delivered into intensive treatment protocols, defined as receiving at least one cycle of MATRix (HD-MTX, HD-cytarabine [AraC], thiotepa [TT], R), MARTA (HD-MTX, HD-Ara-C, R), HD-AraC/TT, or R-DeVIC (R, dexamethasone, etoposide, ifosfamide, carboplatin), as well as the proportion of patients ultimately receiving HCT-ASCT. Secondary endpoints were: tolerability as assessed by the proportion of patients suffering treatment-related toxicities up to 14 days after R-MTX or until start of subsequent treatment as well as until 30 days after ASCT or until hospital discharge for patients reaching HCT-ASCT, and graded according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0; progression-free survival (PFS) and overall survival (OS) rates, defined as progressive disease (PD) or death from any cause, and death from any cause after the application of R-MTX. Patients without a respective event were censored at the last follow-up. Data analysis was performed descriptively, thus *P* values were considered exploratory. Continuous variables were described by median and absolute range, categorical variables by frequency and proportion. Time-to-event analysis were displayed by Kaplan-Meier method and groups were compared by log-rank test and *post hoc* analysis if applicable. Risk factors were assessed using *t* test for independent samples. Statistical analyses were performed using GraphPad Prism version 10.2.0, R version

Table 1. Patient characteristics prior to pre-phase with rituximab/high-dose methotrexate.

Patient characteristics	N=83
Age in years at diagnosis, median (range)	72 (35-84)
Female sex, N (%)	38 (45)

CNS lymphoma type, N (%)
  PCNSL
  rrPCNSL
  SCNSL
	
	54 (65)
	7 (8)
	22 (27)

Time in days to subsequent treatment cycle, median (range)	14 (7-35)

CNS: central nervous system; PCNSL: primary central nervous system lymphoma; rrPCNSL: refractory/relapsed primary central nervous system lymphoma; SCNSL: secondary central nervous system lymphoma.

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Clinical characteristics of the study population (83 patients) are shown in Table 1. Reasons for which patients were considered questionably eligible for intensive treatment regimen prior to R-MTX were one or multiple of the following factors: age, Eastern Cooperative Oncology Group (ECOG) PS, comorbidities as assessed by the number of drugs (not lymphoma-related) prescribed per day, CKI, and previous (immuno-)chemotherapy (Figure 1). In the absence of established objective measures, we developed a combined frailty score (CFS) where every item (ECOG PS 3-4; age ≥65 years; ≥5 drugs/day; CKI; prior (immuno-)chemotherapy) equals one point. CFS were grouped into low (0-1), intermediate (2), and high (3-5). Three patients were excluded from analyses as ECOG PS was not assessed. The proportion of patients presenting with low, intermediate, and high CFS was 42%, 34% and 20%. Of note, the CFS was 0 in three patients who had significant other comorbidities not displayed by the number of drugs/day. Following R-MTX, 48 of 83 (58%)

patients were delivered into intensive induction treatment and 30 of 48 (63%) patients ultimately proceeded to HCT-ASCT. Nineteen of 48 (40%) patients who started intensive induction did not proceed to HCT-ASCT due to PD (N=9), treatment-related toxicities (N=7) and other reasons (N=3). Twenty-eight of 83 (34%) patients proceeded to less intensive treatment regimen and seven of 83 (8%) stopped further anti-lymphoma treatment due to treatment-related toxicity (N=4), PD (N=2) or other reasons (N=1) (*Online Supplementary Figure S1*). Main reasons for proceeding to non-intensive treatment were lack of substantial PS improvement and treatment-related toxicities. Of note, four patients ultimately proceeded to HCT-ASCT following non-intensive induction treatment. Dose modification/delay of subsequent treatment was documented due to severe (grade ≥3) hepatotoxicity and prolonged MTX clearance in two of 83 (2%) and five of 83 (6%) patients. Altough five patients died treatment-related during subsequent treatment, no treatment-related death was observed following
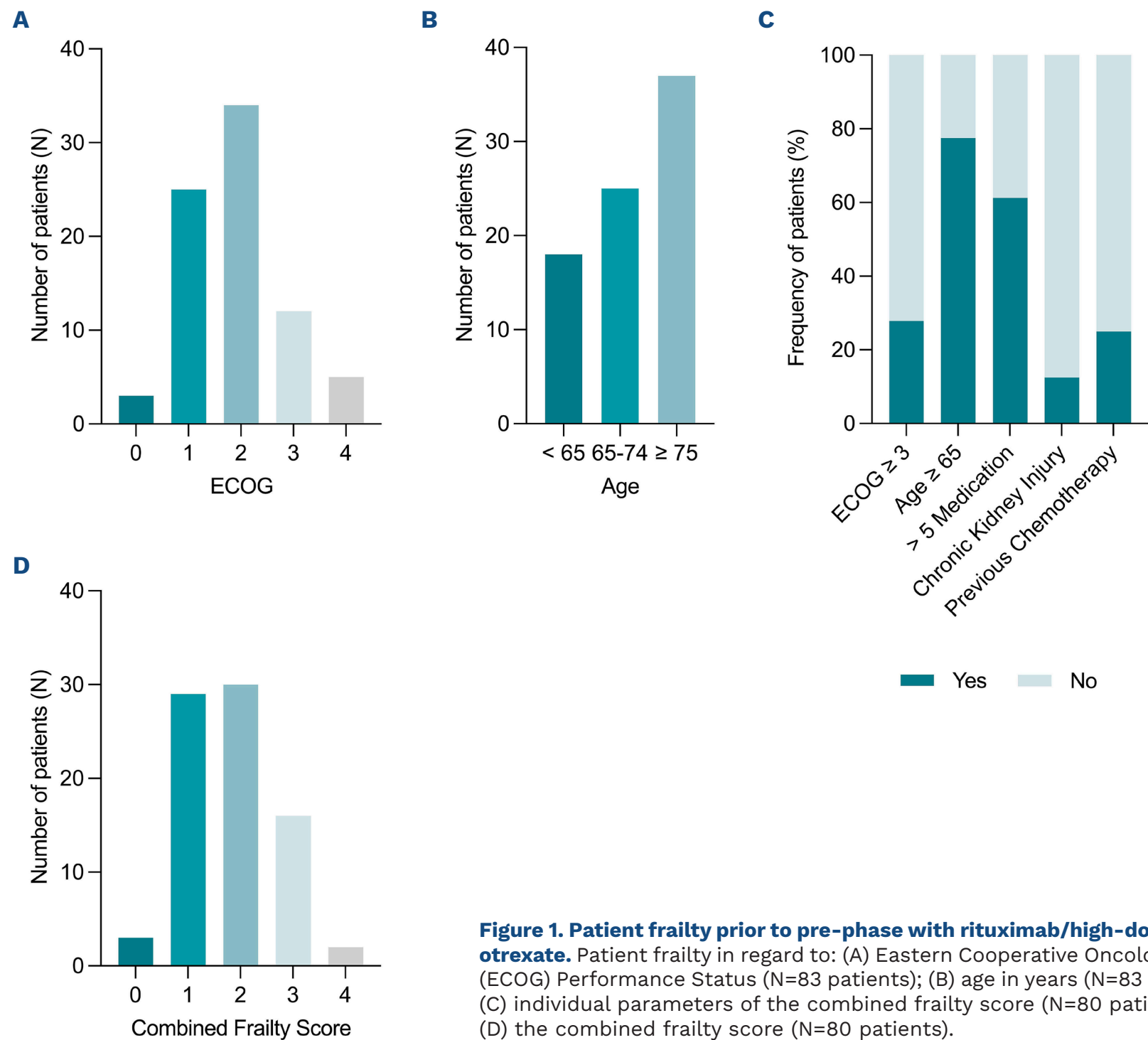

Figure 1. Patient frailty prior to pre-phase with rituximab/high-dose methotrexate. Patient frailty in regard to: (A) Eastern Cooperative Oncology Group (ECOG) Performance Status (N=83 patients); (B) age in years (N=83 patients); (C) individual parameters of the combined frailty score (N=80 patients) and (D) the combined frailty score (N=80 patients).

HCT-ASCT (Table 2). Ten of 83 (12%) patients experienced severe infections that led to intensive care unit admission in three patients, dose modification/delay of subsequent treatment in four, treatment discontinuation in two patients and death in one patient. Of note, severe infections were not associated with leukopenia <2,000/μL (*P*=0.718). However, all ten patients continued corticosteroids after R-MTX with a median number of 14 days (range, 2-32) and a median cumulative dexamethasone dose of 164 mg (range, 40-568). Severe infections were rather associated with the cumulative dose of corticosteroid application (*P*=0.096) than treatment duration (*P*=0.408) and continuation after R-MTX (*P*=0.271) (*Online Supplementary Figure S2*). Patients who stopped further anti-lymphoma treatment following R-MTX and patients suffering from severe infections had a higher mean CFS (mean CFS 1.64 *vs.* 2.29; *P*=0.034 and mean CFS 1.61 *vs.* 2.20; *P*=0.011). Within a median follow-up of 13.5 (range, 0.5-62.2) months from R-MTX administration, 31 deaths were observed (non-relapse mortality [N=11] - 5 patients died treatment-related, 6 due to other reasons). There was no significant difference in PFS and OS between PCNSL and SCNSL patients (*Online Supplementary Figure S3A, E*). Patients with low CFS had significantly superior PFS and OS compared to patients with intermediate/high CFS (*P*=0.019 and *P*=0.0004; *Online Supplementary Figure S3B, F*). The choice of subsequent treatment regimen significantly influenced PFS and OS (*P*=0.009 and *P*=0.0094; *Online Supplementary Figure S3C, G*). Of note, several events occurred following MATRix, suggesting this regimen should be chosen with caution among frail patients. As expected, patients ultimately proceeding to HCT-ASCT had significantly improved PFS and OS (both *P*<0.0001; *Online Supplementary Figure S3D, H*).

R-MTX pre-phase was tolerable in our study, although it included a significant proportion of frail patients with regards to age, PS, comorbidities and prior (immuno-)chemotherapy. The rate of severe infections following R-MTX seems expectable in this frail patient population and is superior compared to pivotal trials testing upfront intensive induction regimen.[4,5] Severe infections were significantly associated with a higher CFS and likely associated with high cumulative corticosteroid doses at treatment initiation, thus emphasizing the importance of rapid corticosteroid tapering, particularly in patients with multiple risk factors. Almost two thirds of patients proceeded to intensive induction treatment following R-MTX pre-phase and 41% ultimately reached consolidating HCT-ASCT, although none of the patients included in the present study was considered eligible for upfront intensive induction followed by HCT-ASCT at diagnosis. The application of HCT-ASCT was feasible, safe and outcomes were comparable to subgroup analyses in pivotal trials despite higher frailty in the present study.[4,9] Moreover, outcomes of patients subsequently receiving R-MTX plus procarbazine (R-MP) were promising, suggesting potential benefits from R-MTX pre-phase in the context of less intensive treatment regimen.[1] These results emphasize

Table 2. Toxicity after pre-phase with rituximab/high-dose methotrexate (N=83) and after high-dose chemotherapy and autologous stem cell transplantation (N=33).

Toxicity, CTCAE v5.0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
After R-MTX, N=83					
Infection/infestation, N (%)	2 (2)	1 (1)	5 (6)	4 (5)	1 (1)
Admission to ICU, N (%)			3 (4)		
WBC decreased, N (%)	15 (18)	4 (5)	5 (6)	1 (1)	0 (0)
Anemia, N (%)	23 (28)	19 (23)	8 (10)	0 (0)	0 (0)
Platelets decreased, N (%)	28 (34)	10 (12)	3 (4)	0 (0)	0 (0)
Hepatotoxicity,[1] N (%)	30 (36)	19 (23)	16 (19)	0 (0)	0 (0)
Acute kidney injury, N (%)	10 (12)	5 (6)	0 (0)	0 (0)	0 (0)
Prolonged MTX clearance,[2] N (%)			14 (17)		
After HCT-ASCT, N=33					
Mucositis, N (%)	0 (0)	6 (18)	19 (58)	1 (1)	0 (0)
Enterocolitis, N (%)	0 (0)	0 (0)	6 (18)	0 (0)	0 (0)
Febrile neutropenia, N (%)	0 (0)	0 (0)	24 (73)	4 (12)	0 (0)
Netropenic Sepsis, N (%)	0 (0)	0 (0)	6 (18)	5 (15)	0 (0)
Hepatotoxicity, N (%)	11 (33)	2 (6)	1 (1)	0 (0)	0 (0)
Acute kidney injury, N (%)	3 (9)	2 (6)	1 (3)	0 (0)	0 (0)

[1]Defined as increase in alanine/aspartate aminotransferase and/or bilirubin; [2]defined as methotrexate (MTX) blood level ≥1 μmol/L at 48 hours after administration. CTCAE v5.0: Common Terminology Criteria for Adverse Events version 5.0; R-MTX: rituximab/high-dose methotrexate; ICU: intensive care unit; WBC: white blood count; HCT-ASCT: high-dose chemotherapy and autologous stem cell transplantation.

that the CFS and R-MTX pre-phase might substantially guide treatment decisions in patients with questionable eligibility for intensive treatment approaches at diagnosis. The current study has several limitations: in addition to its retrospective character, the follow-up period is rather short. Furthermore, defining eligibility for intensive treatment in CNSL patients at diagnosis and following R-MTX pre-phase is never fully objective and represents the major limitation of this study. All patients received corticosteroid treatment in addition to R-MTX. Thus, PS improvement cannot be solely attributed to R-MTX. Moreover, no standardized protocol was used for the choice and timing of subsequent treatment following R-MTX and outcomes in regard to subsequent treatment might thus be influenced by only selecting patients for intensive induction treatment with substantial PS improvement following R-MTX pre-phase. Acknowledging the significant proportion of patients with reduced PS upon treatment initiation in CNSL, future studies should incorporate objective measures such as geriatric assessments to objectively assess HCT-ASCT eligibility.[8] Moreover, novel techniques such as the assessment of circulating tumor DNA[10,11] or magnetic-resonance imaging-based 3D tumor volume reduction[12] might further improve risk stratification and allow for short or less intensive induction treatment approaches in a certain patient population, both, subsequently improving treatment-related morbidity and mortality. Whether a R-MTX pre-phase effectively reduces treatment-related morbidity and mortality in fit patients with PCNSL (OptiMATe, DRKS00022768)[7] and is safe for elderly, fit patients with PCNSL (PRIMA-CNS, DRKS00024085)[8] is currently evaluated in ongoing phase III trials.

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Disclosures
JMH is an advisor or consultant for Miltenyi, Genmab, Incyte, SOBI, SERB pharmaceuticals and Novartis; reports research funding from Incyte and Novartis (Inst); and reports travel support from SOBI, SERB pharmaceuticals and Novartis. The remaining authors have no conflicts of interest to disclose.

Contributions
The study was developed by JW, JMH, GI and ES. Patients and resources were provided by JW, RIL, AK, MK, LKI, EV, PB, JMH, GI, and ES. Patient data was collected and analyzed by JW, RIL, AK and LKI. The manuscript was written by JW, JMH, GI, and ES. All authors revised and agreed to the final version of the manuscript.

Data-sharing statement
Primary individual participant data may be shared to researchers whose proposed use of the data has been approved by an independent review committee identified for this purpose upon request. All secondary data derived from primary individual participant data are available within the article or the *Online Supplementary Appendix*.

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