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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

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Conflicts of interest:

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 declare no competing financial interests with regard to the present study.

Author 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.

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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, supplementary information, or supplementary data files.

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 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 that were treated January 2017 - 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 must have received a pre-phase treatment consisting of rituximab (R) 375mg/m^2 and HD-MTX (≥3g/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 (≥1.5g/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 (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 4.1.2 and RStudio 2024.04.1+748.

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 out 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. CFSs 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, 48/83 (58%) patients were delivered into intensive induction treatment and 30/48 (63%) patients ultimately proceeded to HCT-ASCT. 19/48 (40%) of 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]. 28/83 (34%) patients proceeded to less intensive treatment regimen and 7/83 (8%) stopped further anti-lymphoma treatment due to treatment-related toxicity [n=4], PD [n=2] or other reasons [n=1]; (**Supplementary figure (SF) 1)**. Main reasons for proceeding to non-intensive treatment were lack of substantial PS improvement and treatment-related toxicities. Of note, 4 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 2/83 (2%) and 5/83 (6%) of patients. Although 5 patients died treatment-related during subsequent induction treatment, no treatment-related death was observed following HCT-ASCT; (**Table 2**). 10/83 (12%) patients experienced severe infections that led to intensive care unit admission in 3 patients, dose modification/delay of subsequent treatment in 4, treatment discontinuation in 2 and death in 1 patients. Of note, severe infections were not associated with leukopenia <2000/µL (p=0.718). However, all 10 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); (**SF 2**)**.** 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 (**SF 3A/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, **SF 3B/F**). The choice of subsequent treatment regimen significantly influenced PFS and OS (p=0.009 and p=0.0094, **SF 3C/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, **SF 3D/H**).

R-MTX pre-phase was tolerable in our study, although it included a significant proportion of frail patients in regard 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 third 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 into 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-MP were promising, suggesting potential benefits from R-MTX pre-phase in the context of less intensive treatment regimen.[1] These results emphasize 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 magnet 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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Tables and Figures

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

Patient characteristics	**n= 83**
Age at diagnosis	
- Median (range)	72 years (35-84)
Gender	
- female	38 (45 %)
CNS lymphoma type	
- PCNSL	54 (65 %)
- rrPCNSL	7 (8 %)
- SCNSL	22 (27 %)
Time to subsequent treatment cycle	
- median (range)	14 days (7-35)

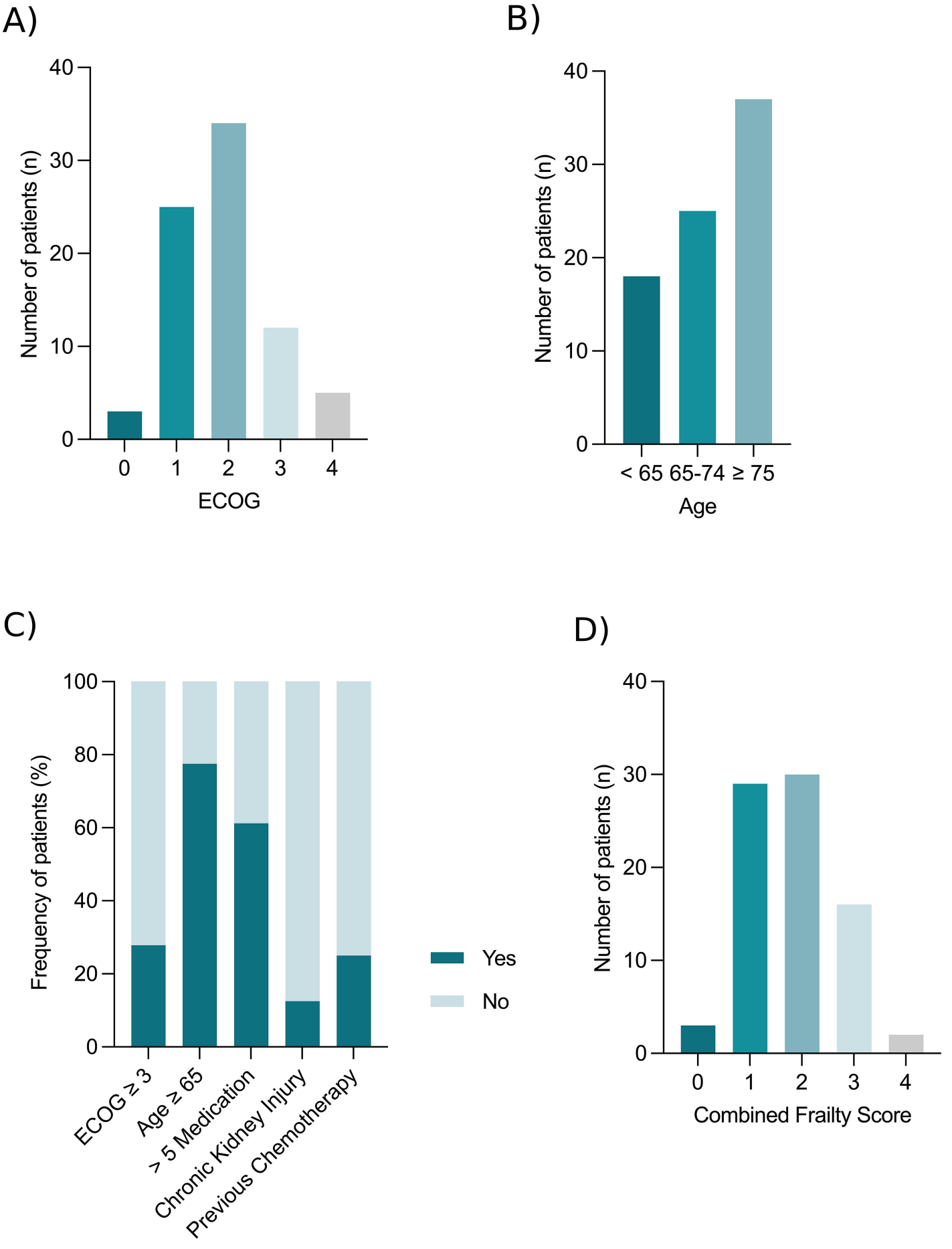
n=number; CNS=central nervous system; PCNSL=primary central nervous system lymphoma; rrPCNSL=refractory/relapsed primary central nervous system lymphoma; SCNSL=secondary central nervous system lymphoma

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

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

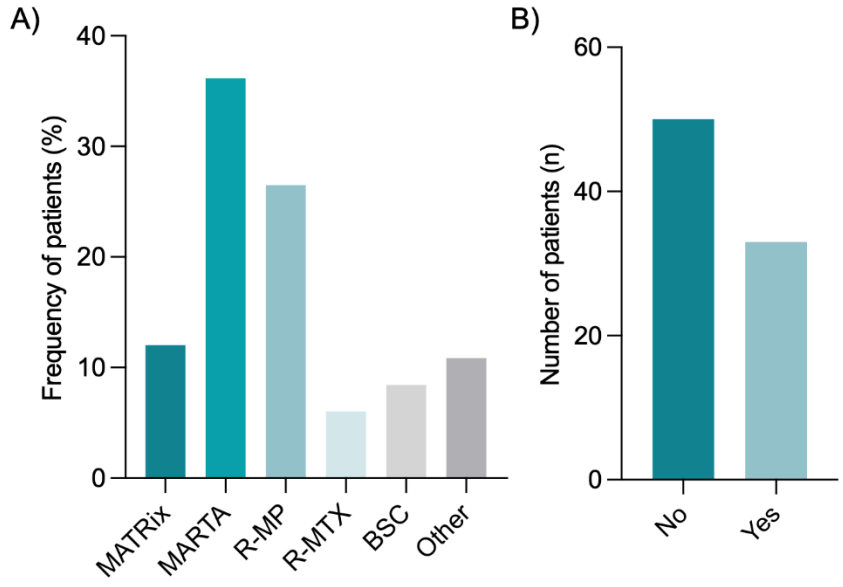
Figure 1 Patient frailty prior to pre-phase with rituximab/high-dose methotrexate. Patient frailty in regard to: (A) Eastern Cooperative Oncology Group Performance Status (n=83 patients); (B) age in years (n=83 patients); (C) individual parameters of the combined frailty score and (D) the combined frailty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


A)
Number of patients (n)
40
30
20
10
0
0
1
2
3
4
ECOG
B)
Number of patients (n)
40
30
20
10
0
< 65
65-74
≥ 75
Age
C)
Frequency of patients (%)
100
80
60
40
20
0
ECOG ≥ 3
Age ≥ 65
> 5 Medication
Chronic Kidney Injury
Previous Chemotherapy
Yes
No
D)
Number of patients (n)
40
30
20
10
0
0
1
2
3
4
Combined Frailty Score

Supplementary Material

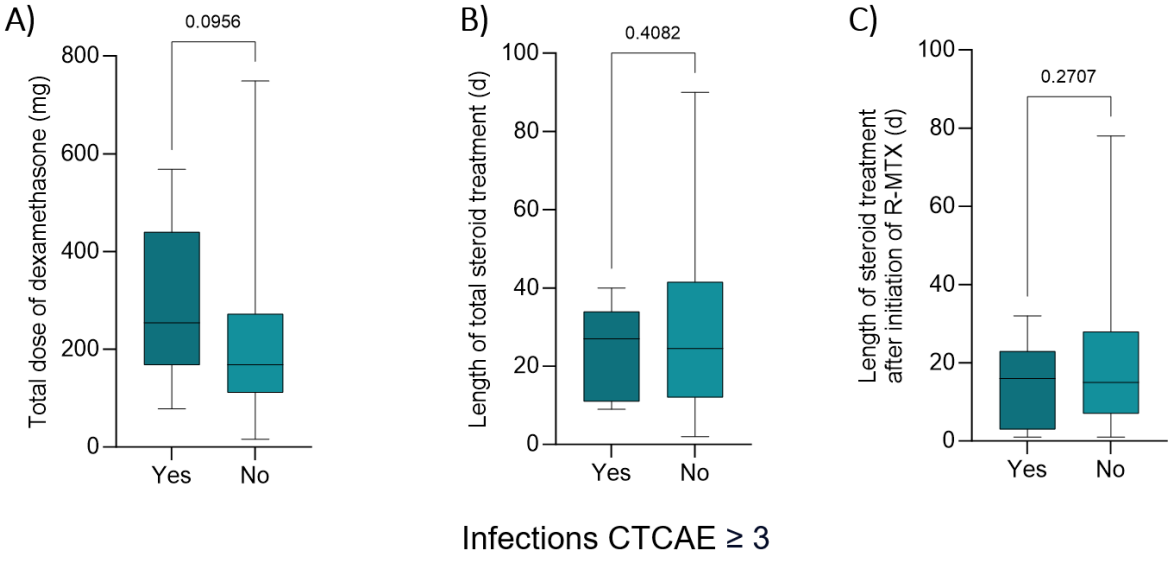
Supplementary Figures (SF)

SF 1 Subsequent treatment regimen following rituximab/high-dose methotrexate. A) Proportion of patients receiving respective treatment regimen; B) number of patients ultimately proceeding to ASCT



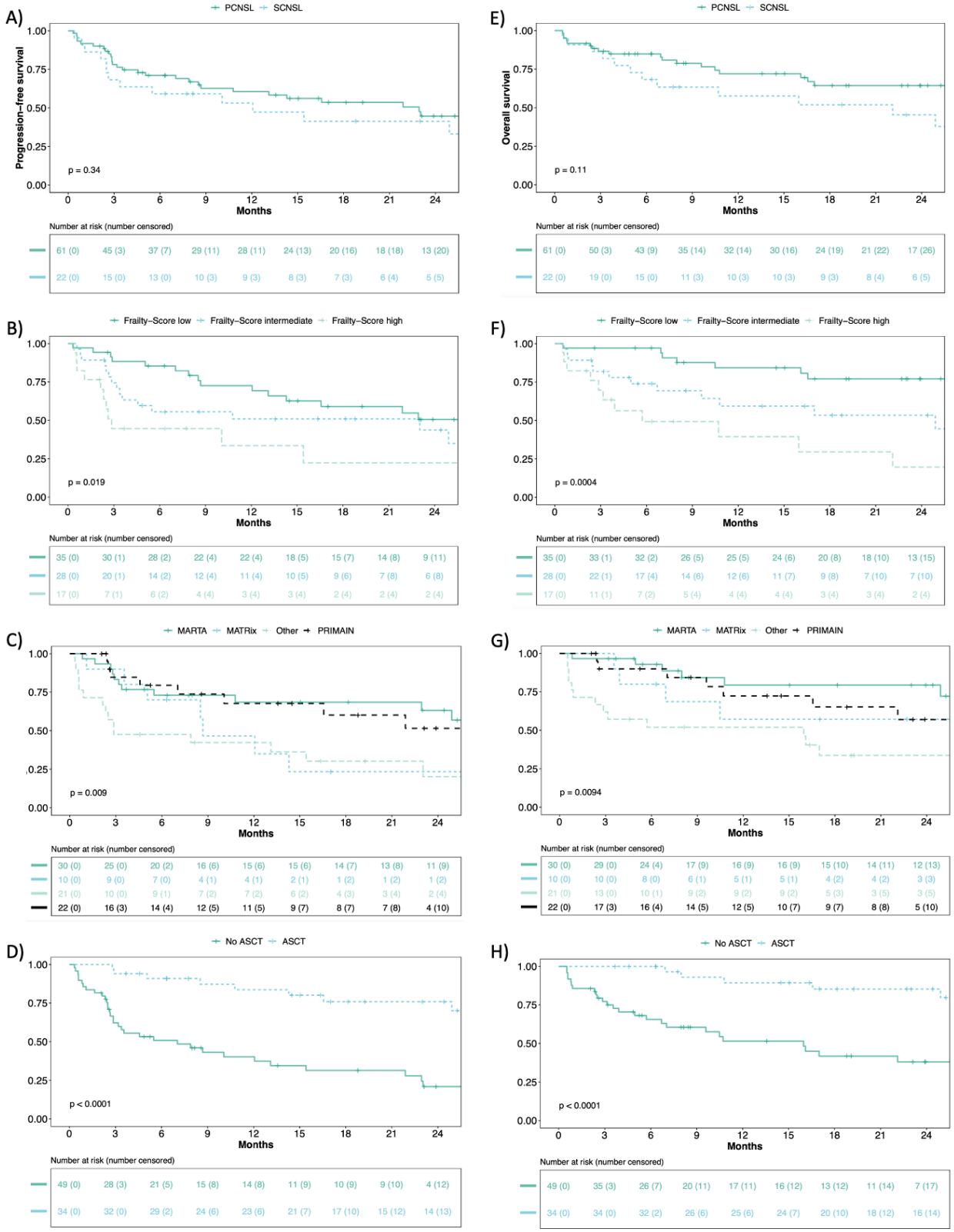
MATRix=high-dose methotrexate, high-dose cytarabine, thiotepa, rituximab; MARTA=high-dose methotrexate; high-dose cytarabine, rituximab; R-MP=rituximab, high-dose methotrexate, procarbazine, R-MTX=rituximab, high-dose methotrexate; BSC=best supportive care

SF 2 Occurrence of severe (≥ grade 3) infections. Grade ≥3 infections yes versus no following rituximab/high-dose methotrexate in regard to: A) total dose of dexamethasone; B) total duration of corticosteroid treatment; and C) time of corticosteroid treatment after rituximab/high-dose methotrexate initiation for n=83 patients that received initial corticosteroid treatment



mg=milligrams; d=day(s); R-MTX=rituximab/high-dose methotrexate; CTCAE=Common Terminology Criteria for Adverse Events

SF 3 Progression-free survival following pre-phase with rituximab/high-dose methotrexate. Progression-free survival in regard to: A) central nervous system lymphoma type; B) combined frailty score; C) subsequent induction treatment regimen; D) Autologous stem cell transplantation versus no autologous stem cell transplantation and overall survival in regard to E) central nervous system lymphoma type; F) combined frailty score; G) subsequent induction treatment regimen; H) Autologous stem cell transplantation versus no autologous stem cell transplantation



PCNSL=primary central nervous system lymphoma; SCNSL=secondary central nervous system lymphoma; MATRix=high-dose methotrexate, high-dose cytarabine, thiotepa, rituximab; MARTA=high-dose methotrexate; high-dose cytarabine, rituximab; PRIMAIN=rituximab, high-dose methotrexate, procarbazine; ASCT=autologous stem cell transplantation