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Induction therapy with the MATRix regimen in patients with newly diagnosed primary diffuse large B-cell lymphoma of the central nervous system – an international study of feasibility and efficacy in routine clinical practice

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Summary

The MATRix chemoimmunotherapy regimen is highly effective in patients with newly diagnosed primary diffuse large B-cell lymphoma of the central nervous system (PCNSL). However, nothing is known about its feasibility and efficacy in everyday practice, where patients are more often older/frailer than those enrolled in clinical trials. We conducted a retrospective study addressing tolerability/efficacy of MATRix in 156 consecutive patients with newly diagnosed PCNSL treated outside a clinical trial. Median age and ECOG Performance Status of considered patients were 62 years (range 28–78) and 2 (range 0–4). The overall response rate after MATRix was 79%. Nine (6%) treatment-related deaths were recorded. After a median follow-up of 27.4 months (95% confidence interval [CI] 24.4–31.9%), the two-year progression-free and overall survival were 56% (95% CI 48.4–64.9%) and 64.1% (95% CI 56.7–72.5%) respectively. Patients not eligible for the IELSG32 trial were treated with lower dose intensity and had substantially worse outcomes than those fulfilling inclusion criteria. This is the largest series of PCNSL patients treated with MATRix outside a trial and recapitulates the IELSG32 trial outcomes in the non-trial setting for patients who fit the trial criteria. These data underscore the feasibility and efficacy of MATRix as induction treatment for fit patients in routine practice.

Keywords: primary diffuse large B-cell lymphoma of the central nervous system, induction treatment, MATRix regimen, routine clinical practice, IELSG32 trial.

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Primary diffuse large B-cell lymphoma (DLBCL) of the central nervous system (PCNSL) is an aggressive disease, which accounts for 2–3% of all non-Hodgkin lymphomas and approximately 4% of all primary CNS tumours (Ferreri *et al.*, 2003a; Rubenstein *et al.*, 2008). Its incidence has risen over the past 30 years, particularly in immunocompetent individuals (Makino *et al.*, 2006; Haldorsen *et al.*, 2007). High-dose methotrexate (HD-MTX)-based chemoimmunotherapy is a widely accepted induction treatment approach (Ferreri *et al.*, 2009; Morris *et al.*, 2013; Rubenstein *et al.*, 2013; Glass *et al.*, 2016). IELSG32, a randomized trial from the International Extranodal Lymphoma Study Group (IELSG), compared three different induction chemoimmunotherapy regimens in patients with newly diagnosed PCNSL. This trial clearly showed that the MATRix combination (HD-MTX, cytarabine [AraC], thiotepa [TT], and rituximab) followed by consolidation therapy significantly improved outcomes in eligible patients aged 70 years or younger (Ferreri *et al.*, 2016, 2017). The MATRix protocol (four cycles administered every three weeks) followed by consolidation high-dose chemotherapy and autologous stem cell transplantation (HDT-ASCT) or whole-brain radiotherapy (WBRT) is now a widely used treatment regimen in newly diagnosed PCNSL and serves as a benchmark for future randomized trials. However, the IELSG32 trial was restricted to patients aged 70 years or younger with Eastern Cooperative Oncology Group Performance Status (ECOG PS) $\leq$2 (and <65 years with ECOG PS $\leq$3), whereas many patients encountered in routine practice are older and/or frailer than those treated in prospective trials. Given that previous studies (Ferreri *et al.*, 2003b; Abrey *et al.*, 2006; Schorb *et al.*, 2013) have demonstrated inferior outcomes for PCNSL patients who present with a poor ECOG PS and older age, clinicians may be concerned about using such an intensive regimen in this patient population. Furthermore, the outcome of PCNSL patients treated outside the clinical trial setting is inferior and not solely attributable to advanced age and poorer ECOG PS (Zeremski *et al.*, 2016). Thus, we investigated clinical outcomes in routine practice of patients with newly diagnosed PCNSL treated with the MATRix combination as induction treatment.

Methods

Patient selection criteria and data collection

Inclusion criteria for this retrospective multicentre analysis were: (i) *de novo*, histologically or cytologically proven PCNSL, (ii) exclusion of systemic lymphoma by CT body scan and bone marrow examination or PET scan, (iii) administration of at least one cycle of the MATRix regimen; and (iv) MATRix delivered outside a clinical trial. We included consecutive patients treated at participating centres from the time when MATRix was adopted in routine practice (four centres prior to 2014, and nine centres after 2014). Patients were selected for treatment by the treating clinician, with no upper age limit or exclusions based on ECOG PS, co-morbidities or other patient-related characteristics. Individual patient data from 13 co-operating centres, treated by clinicians experienced in PCNSL therapy, were collected using a pre-specified data extraction tool including details on baseline characteristics, treatment, toxicities, objective response, progression-free and overall survival (75 variables in total). In addition, the total denominator of all patients with newly diagnosed PCNSL at the participating centres during the study period was recorded to estimate the proportion of patients being considered for treatment on a trial protocol or with treatment other than MATRix. Data were checked for consistency and queries clarified with the local treating physician before inclusion in the central database. The study was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with Good Clinical Practice (GCP). The study protocol was approved by the ethics committee of the University of Freiburg Medical Center.

PCNSL assessment

Staging work-up aimed to exclude systemic disease and to define involvement of different CNS structures (i.e., brain, eyes, meninges, spine, cranial nerves) followed recommendations of the International PCNSL Collaborative Group (Abrey *et al.*, 2005). Baseline and response assessment imaging were performed in line with standard of care and in accordance with international guidelines using gadolinium-

enhanced brain MRI scans evaluated by experienced local (neuro-)radiologists at each centre (Abrey *et al.*, 2005). Patients achieving complete remission (CR) or partial remission (PR) were categorized as treatment responders, whereas stable disease (SD) or progressive disease (PD) were considered non-responders. The worst toxicity per organ, per patient was considered. Effects of treatment on cognitive function and quality of life were not routinely assessed.

Statistical analysis

We used descriptive statistics (frequencies with proportions, medians and ranges where appropriate) to summarize patient demographics, treatments and outcomes. A 'dose reduction' was defined as at least a 25% reduction of at least one MATRix drug. The primary endpoint of this study was feasibility of the MATRix protocol in routine practice including treatment delivery rate, main toxicities and rate of successful stem cell mobilization. Secondary endpoints included objective response rate, overall survival (OS; defined as time from day 1 of first MATRix course to death or date of last follow-up visit) and progression-free survival (PFS; defined as the time from day 1 of first MATRix course to date of PD, relapse or death, whichever occurred first, or date of last follow-up visit). Both time-to-event endpoints were estimated using the Kaplan–Meier method; all Kaplan–Meier plots were created with 95% CIs for the respective survival estimate.

The principal eligibility criteria for the IELSG32 trial were immunocompetent patients aged up to 65 years with ECOG PS ≤3 or aged up to 70 years if ECOG PS was ≤2. Additional exclusion criteria were relevant co-morbidities such as glomerular filtration rate <60 ml/min, active hepatitis, concomitant cancer, and cardiac/pulmonary or hepatic co-morbidities. To investigate a possible prognostic impact of these key criteria, we stratified the cohort into patients that would/would not have fulfilled these criteria. In an additional sensitivity analysis, we conducted the same analysis as described above, but only considered the combination of age and ECOG PS to define eligibility (age up to 65 years with ECOG PS ≤3 or age up to 70 years if ECOG PS was ≤2). We used a Cox regression model to investigate the prognostic impact of dose reductions (as defined above: yes *versus* no) during the first cycle in a landmark analysis in which we restricted the analysis to those patients treated with at least two cycles of treatment. This model was adjusted for the IELSG32 trial eligibility criteria. Follow-up was estimated using the inverse Kaplan–Meier method (Schemper & Smith, 1996). We followed an intention-to-treat approach considering all included patients in the denominator in our calculations. We describe proportions irrespective of missing data which are also outlined separately.

We did not plan any formal statistical hypothesis testing; therefore, all *P* values were considered exploratory. All survival estimates and hazard ratios (HRs) were accompanied by 95% CIs. Statistical analyses were carried out using the statistical software R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria; www.r-project.org).

Results

Patient selection and baseline characteristics

Medical records of 427 potentially eligible patients were screened at 13 European centres from three different countries for the period July 2010 to June 2018. In total, 198/427 (46·4%) patients fulfilled the IELSG32 trial eligibility criteria and 164 (83%) of those patients were treated with the MATRix regimen of whom 54 patients were not included in our analysis due to enrolment in the IELSG32 or IELSG43 trial. Furthermore, 229/427 (53·6%) patients did not fulfil IELSG32 trial inclusion criteria and 46 (20%) of those patients were also successfully treated with MATRix. The remaining 183 patients were not considered eligible for the MATRix regimen by the investigators for the following reasons: advanced age +/− impaired ECOG PS (>70 years, or >65 years with ECOG PS >2) in 154 patients (84·1%), ECOG PS = 4 in six patients (3·3%), co-morbidities in 17 patients (9·3%), and immunosuppression in six patients (3·3%). Moreover, 34 of the 198 patients fulfilling IELSG32 trial eligibility criteria were not treated with MATRix as an individual decision of the treating physician in 22 patients (64·7%), due to death or pre-treatment complications in eight patients (23·5%) and due to refusal of therapy of one patient (3%). Three additional patients (8·8%) were treated with other protocols as the histology revealed low grade lymphoma in two and Burkitt lymphoma in one patient (Fig 1). The median age of the 154 patients not treated with MATRix due to advanced age +/− reduced PS was 77 years (range 65–91). In total, 156 of 427 (36·5%) screened patients were finally included. Latest follow-up data were collected in August 2019; following which the study database was locked. The median age and ECOG Performance Status of the 156 patients were 62 years (range 28–78) and 2 (range 0–4) respectively. Characteristics of the 156 included patients stratified by the IELSG32 trial eligibility criteria are summarized in Table I. Overall, 110 (70·5%) would have met the IELSG32 trial eligibility criteria whereas 46 (29·5%) would have not. The main reasons for not meeting the IELSG32 trial criteria were: age over 70 years (21/156; 13·5%) and impaired performance status (7/156; 4·5%). Among the 18 (11·5%) other reasons, there were 13 patients with relevant co-morbidities and five patients with acquired immunodeficiency (four human immunodeficiency virus (HIV)-positive patients and one case of post-transplant lymphoproliferative disorder) (Fig 1).

Treatment delivery of the MATRix regimen

Overall, 99/156 (62·8%) patients (including the reported four HIV-positive patients) received all four planned cycles (Table II). The main reasons for treatment interruption were PD ($n = 14$), severe infectious complications ($n = 15$) and haematological

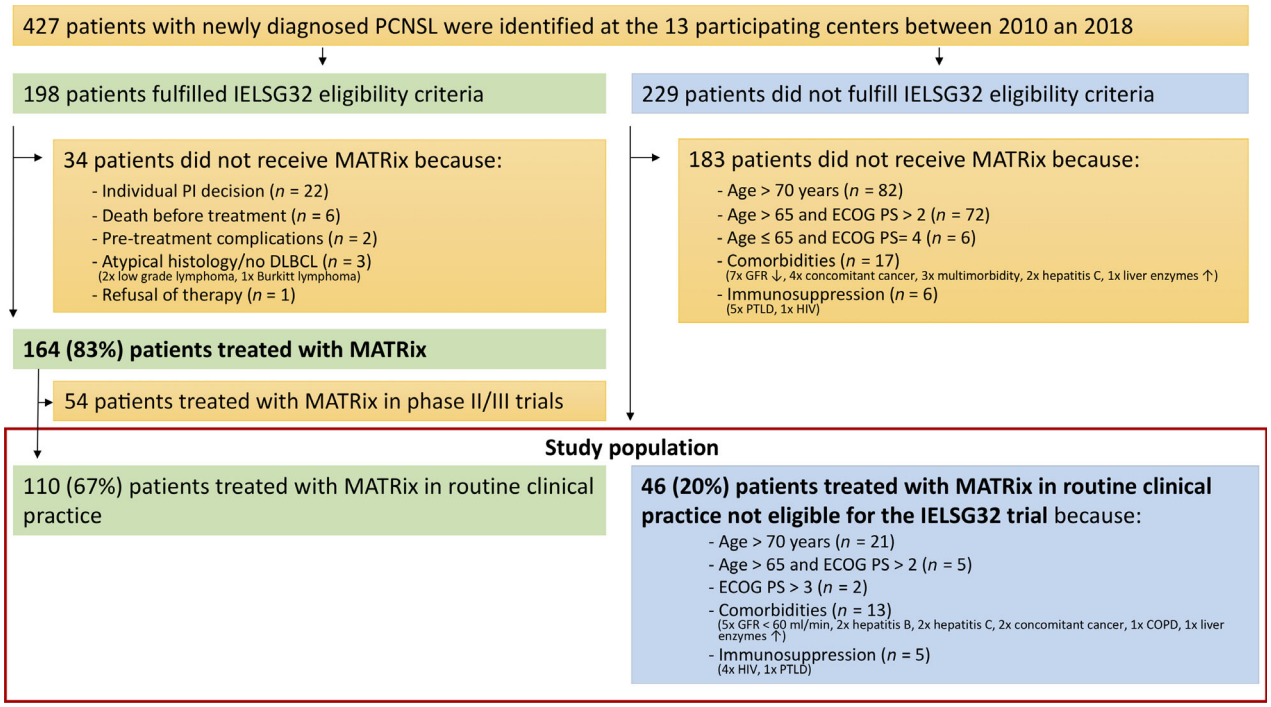

Fig 1. Flow chart of patient selection from 13 different European centres. In total, 210 (156 + 54) patients (49%) received the MATRix regimen, whereas 83% of the patients eligible for the IELSG32 trial received MATRix and this regimen was also successfully delivered in 20% of the patients who did not fulfil IELSG32 eligibility criteria. Abbreviations: PCNSL = primary diffuse large B-cell lymphoma of the central nervous system; IELSG = International Extranodal Lymphoma Study Group; MATRix = high-dose-methotrexate, cytarabine, thiotepa, and rituximab; PI = principal investigator; DLBCL = diffuse large B-cell lymphoma; ECOG PS = Eastern Cooperative Group Performance Status; GFR = Glomerular filtration rate; PTLD = Post-transplant lymphoproliferative disorder; HIV = Human immunodeficiency virus; COPD = Chronic obstructive pulmonary disease. [Colour figure can be viewed at wileyonlinelibrary.com]

toxicity (n = 2). During the first cycle, 93/156 (59·6%) patients received the full doses of each MATRix component; in 2/156 (1·3%) patients, information on dose was missing, because they were treated at a peripheral centre. The second cycle was given to 136 patients, and of these 69 (50·7%) received the full dose. Rates were similar for patients who received three (62/116 [53·5%] patients) or four (49/97 [50·5%] patients) MATRix courses. In total, 37/156 (23·7%) received all four cycles without dose reductions. For all cycles, patients who would have not fulfilled the IELSG32 trial eligibility criteria were more likely to receive reduced doses compared to those fulfilling IELSG32 eligibility (Table II). Only 5/46 (11%) patients who did not meet IELSG32 trial eligibility criteria received all four MATRix cycles at full dose. The most common reasons for dose reduction during the first cycle were reduced ECOG PS, co-existing co-morbidities and age. Main reasons for dose reduction during subsequent chemotherapy cycles were haematological toxicities, infectious complications and reduced ECOG PS.

Toxicities of the MATRix regimen

The first cycle of MATRix was associated with the most severe toxicities with 10/156 (6%) patients requiring an admission to the intensive-care unit (ICU) because of life-threatening infections, which was recorded in five of 46 (11%) patients who did not meet IELSG32 trial eligibility criteria and in five of 110 (5%) patients who would have been eligible. By contrast, there was only one ICU admission during cycles 2–4. Severe complications (mostly infectious) that did not require admission to ICU were reported in 44/156 (28%) patients after the first course, in 23/136 (17%) after the second, in 19/117 (16%) after the third, and in 11/97 (11%) patients after the fourth course. None of the HIV-positive patients suffered severe treatment-related complications. Other less severe side effects including haematological toxicities and minor infections were recorded in 23 (15%) (first course), 19 (14%) (second course), 16 (14%) (third course), and 14 (14%) (fourth course) patients respectively.

Nine out of 156 patients died of toxicity during MATRix treatment, equating to a treatment-related mortality (TRM) of 6%: six died from infectious complications and three following cardiovascular events (clinical suspicion of fatal pulmonary embolism in two patients, fatal stroke in one patient). Seven patients died during cycle 1 (three had received dose reductions due to advanced age/reduced ECOG PS; five would have fulfilled IELSG32 trial eligibility criteria) and two patients died during cycle 2 (one had received dose-reduced therapy due to advanced age and co-morbidities; the other one would have fulfilled IELSG32 trial eligibility criteria).

Table I. Patient baseline characteristics stratified by the IELSG32 trial eligibility criteria. Numbers are frequencies (column percentage) unless otherwise specified.

Characteristics	Inclusion criteria fulfilled (n = 110)	Inclusion criteria not fulfilled (n = 46)	All (n = 156)
Age median (range)	60 (30–70)	70 (28–78)	62 (28–78)
Male	57 (51·8)	24 (52·2)	81 (51·9)
ECOG PS			
ECOG 0	5 (4·5)	2 (4·3)	7 (4·5)
ECOG 1	55 (50·0)	13 (28·3)	68 (43·6)
ECOG 2	31 (28·2)	13 (28·3)	44 (28·2)
ECOG 3	17 (15·5)	12 (26·1)	27 (17·3)
ECOG 4	0 (0)	6 (13·0)	8 (5·1)
ECOG missing	2 (1·8)	0 (0)	2 (1·3)
MSKCC prognostic score			
class 1	21 (19·1)	6 (13·0)	27 (17·3)
class 2	60 (54·5)	22 (47·8)	82 (52·6)
class 3	29 (26·4)	18 (39·1)	47 (30·1)
Histology			
DLBCL	110 (100)	39 (84·8)	149 (95·5)
DLBCL – HIV associated	0	4 (8·7)	4 (2·6)
DLBCL – PTLD	0	1 (2·2)	1 (0·6)
Cytology/ immunophenotyping/ clinical-radiological diagnosis	0	2 (4·3)	2 (1·3)
Country			
Germany	5 (4·5)	4 (8·7)	9 (5·8)
Italy	23 (20·9)	10 (21·7)	33 (21·2)
UK	82 (74·5)	32 (69·6)	114 (73·1)

DLBCL = diffuse large B-cell lymphoma; ECOG PS = Eastern Cooperative Group Performance Status; MSKCC = Memorial Sloan-Kettering Cancer Center; PTLD = post-transplant lymphoproliferative disorder.

There were three further deaths not related to lymphoma relapse (hepatic failure, septic encephalitis, and sudden death) over six months after MATRix and all considered unrelated to induction therapy. All three patients had undergone HDT-ASCT consolidation and were in remission of PCNSL.

Treatment response to MATRix induction and type of consolidation treatment

Results from brain MRI were available in 145 of 156 patients (93%). Overall, 123 of 156 patients (79%; 95% CI 71–85%) achieved an objective response (54 patients with CR and 69 with PR), six (4%) patients were reported with SD and 16 (10%) had documented PD. In 10 (6%) patients no data on lymphoma response were available because of death or evidence of clinical progression before first MRI assessment; all 10 cases were classified as non-responders for this analysis. In one patient without clinical suspicion for progression, brain MRI was still awaited at time of data lock. Successful stem cell mobilization was performed in 116 of 123 (94%) responders. In three of 123 patients (2·5%) stem cell harvest was insufficient, the remaining four patients (3·5%) were judged ineligible for HDT-ASCT and thus stem cell harvest was not attempted. Different types of consolidation treatment stratified by the IELSG32 trial eligibility criteria for all patients are summarized in Table III.

Of those 123 patients achieving an objective response, 83 (67·5%) received consolidation treatment: 60 (48·8%) patients underwent HDT-ASCT, 20 (16·2%) received WBRT, two received conventionally dosed chemotherapy, and one patient had lenalidomide maintenance treatment. Forty of the 123 responding patients (32·5%) did not receive consolidation treatment due to infectious complications during induction treatment, worsening ECOG PS, co-morbidities, or individual decision of the patient or the treating physician. Among those 40 patients, 14 achieved CR and 26 PR. Overall 21 of 40 (52·2%) had a PFS-defining event (four documented progressions and 17 deaths) after a short follow-up time (median 14·1 months; range 1·5–49·3 months). Fifteen of 123 (12·2%) responding patients received all four planned MATRix cycles, but received no consolidation treatment. Among those 15 patients, six achieved CR and nine PR. Eight of 15 patients (53%) had a PFS-defining event (two documented progressions, six deaths) after a short follow-up time (median 13·9 months; range 3·5–45·6 months).

Progression-free and overall survival

After an estimated median follow-up of 27·4 months (95% CI 24·4–31·9), 100/156 patients were alive. Median PFS was 42·1 months (95% CI 21·3 to not calculable) and median OS was not reached. The two-year PFS and OS rates were 56% (95% CI 48·4–64·9%) and 64·1% (95% CI 56·7–72·5%) respectively (Fig 2A, B). Notably, when comparing patients regarding eligibility criteria for IELSG32 (eligible *versus* not eligible), there was a substantial difference in PFS (HR 2·03 [95% CI 1·24–3·32]) and OS (HR 2·25 [95% CI 1·31–3·85]). The respective two-year PFS and OS rates by eligibility criteria were 63·2% (95% CI 54·5–73·4%) vs. 37·7% (95% CI 25·1–56·6%) and 72·2% (95% CI 64·1–81·4%) vs. 42·2% (95% CI 28·8–61·9%) (Fig 2C, D). A similar pattern was seen when grouping patients by eligibility defined as combination of age and ECOG PS in the sensitivity analysis (Figures S1 and S2). In a landmark analysis restricted to patients who proceeded to a second cycle of MATRix there was no prognostic impact of dose reduction during the first cycle on PFS or OS. However, IELSG32 trial eligibility criteria retained their substantial effect on PFS and OS (Table IV).

Discussion

The IELSG32 study demonstrated the efficacy and feasibility of the MATRix protocol in an international randomized trial, conferring significant improvements in the outcome of

Table II. Dose reductions of the MATRix protocol grouped by cycle and stratified by IELSG32 trial eligibility criteria. Dose reduction was defined as at least 25% reduction of at least one MATRix component.

Cycles	Inclusion criteria fulfilled (n = 110)	Inclusion criteria not fulfilled (n = 46)	All (n = 156)	P value
One cycle delivered	12 (10·9)	6 (13·0)	18 (11·5)	0·012
Two cycles delivered	8 (7·2)	12 (26·1)	20 (12·8)	
Three cycles delivered	13 (11·8)	6 (13·0)	19 (12·2)	
Four cycles delivered	77 (70·0)	22 (47·8)	99 (62·8)	
Cycle 1	Inclusion criteria fulfilled (n = 110)	Inclusion criteria not fulfilled (n = 46)	All (n = 156)	P value
Patients with dose reduced 25% or more	28 (25·5)	35 (76·1)	63 (40·4)	0·001
Cycle 2	Inclusion criteria fulfilled (n = 96)	Inclusion criteria not fulfilled (n = 40)	All (n = 136)	P value
Patients with dose reduced 25% or more	41 (42·7)	26 (65·0)	67 (49·3)	0·02918
Cycle 3	Inclusion criteria fulfilled (n = 88)	Inclusion criteria not fulfilled (n = 28)	All (n = 116)	P value
Patients with dose reduced 25% or more	37 (42·0)	17 (60·7)	54 (46·6)	0·1317
Cycle 4	Inclusion criteria fulfilled (n = 75)	Inclusion criteria not fulfilled (n = 22)	All (n = 97)	P value
Patients with dose reduced 25% or more	34 (45·3)	14 (63·6)	48 (49·5)	0·205

Numbers are frequencies (column percentages).

Table III. Type of consolidation treatment stratified by IELSG32 trial eligibility criteria for all patients irrespective of response achieved with MATRix. Numbers are frequencies (column percentages).

Consolidation treatment	Inclusion criteria fulfilled (n = 110)	Inclusion criteria not fulfilled (n = 46)	All (n = 156)
HDT-ASCT	53 (48·2)	11 (23·9)	64 (41·0)
WBRT	17 (15·5)	4 (8·7)	21 (13·5)
Conventionally dosed chemotherapy	0	2 (4·3)	2 (1·3)
Lenalidomide	0	1 (2·2)	1 (0·6)
No consolidation	40 (36·4)	28 (60·9)	68 (43·6)

HDT-ASCT = high-dose chemotherapy with autologous stem cell transplantation; WBRT = whole-brain radiotherapy.

patients with PCNSL up to the age of 70 years, as compared to induction treatment with HD-MTX/AraC and rituximab/MTX/AraC (Ferreri *et al.*, 2009; Ferreri *et al.*, 2016). Subsequently, the MATRix combination is a widely used induction treatment approach at many centres for patients with newly diagnosed PCNSL. The currently recruiting randomized MATRix/IELSG43 trial, with similar eligibility criteria, employs the MATRix regimen as induction treatment prior to different consolidation approaches (NCT02531841) (Schorb *et al.*, 2016). However, feasibility, tolerability and efficacy of MATRix outside a prospective trial setting have not been assessed to date. In the present study, we show that applying the MATRix protocol for patients with PCNSL in routine practice can reproduce the toxicity and efficacy outcomes similar to the IELGS32 trial: response rate 79% vs. 86%, two-year PFS 56% vs. 61%, two-year OS 64·1% vs. 69%, and TRM 6% in both groups. However, patients who would have not fulfilled the IELSG32 trial inclusion criteria (predominantly those over 70 years or with impaired ECOG PS) were treated with lower dose intensity and experienced a significantly inferior outcome. Of note, inter-study comparison of the cohort reported herein with results from the IELSG32 trial still needs to be considered with care; especially regarding outcomes such as lymphoma response and PFS, which can be different, because of per protocol timing and data quality in contrast to routine care, where some scans may have been conducted at other time points.

Our study has a few limitations. First, patients were only included in the study if they underwent at least one cycle of the MATRix regimen which applies only for about 50% of all screened patients. This number is in line with previous publications and is mainly explained by the fact that patients older than 65 years account for 50% of all PCNSL cases and that those patients are likely to be considered not eligible for intensive treatment approaches (Abrey *et al.*, 2000; Kasenda *et al.*, 2015). Thus, the cohort cannot be strictly considered an intention-to-treat population; eligibility and intention-to-treat were determined by PCNSL-experienced clinicians rather than a pre-determined protocol, we

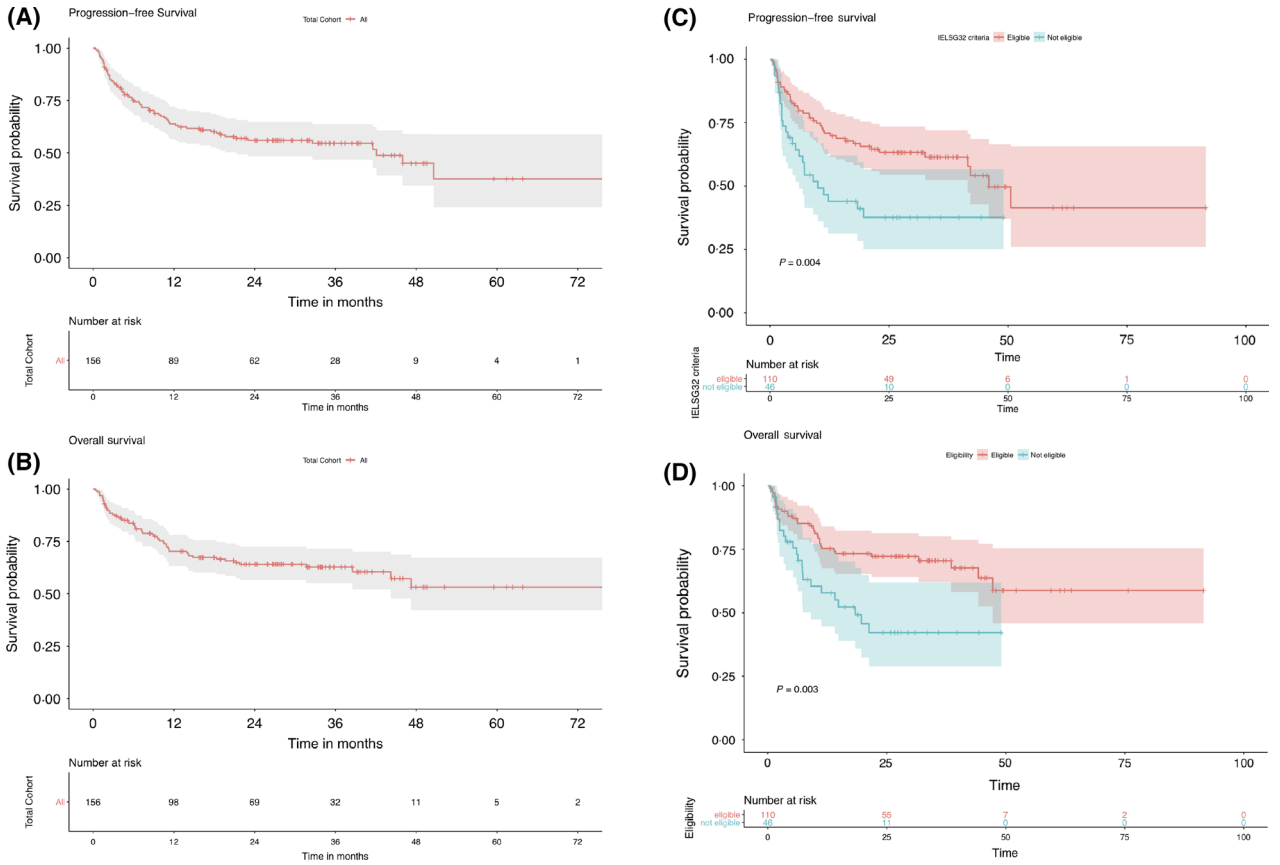

Fig 2. (A) Progression-free survival of the whole cohort. (B) Overall survival of the whole cohort. (C) Progression-free survival of the whole cohort stratified by the IELSG32 trial eligibility criteria. (D) Overall survival of the whole cohort stratified by the IELSG32 trial eligibility criteria. [Colour figure can be viewed at wileyonlinelibrary.com]

Table IV. Two multivariable Cox regression analyses to investigate the prognostic impact of dose reduction (25% or more of at least one MATRix component) during the first cycle in a landmark analysis restricted to 136 patients who at least started the second cycle of treatment with the MATRix protocol.

	Variables	Hazard ratio	95% confidence interval	*P* value
PFS	Dose reduction first cycle (yes *versus* no)	1·16	0·64–2·11	0·6360
	IELSG32 trial inclusion criteria not met (yes *versus* no)	2·37	1·28–4·38	0·0061
OS	Dose reduction first cycle (yes *versus* no)	1·03	0·51–2·06	0·9427
	IELSG32 trial inclusion criteria not met (yes *versus* no)	2·97	1·47–6·02	0·0025

had to fully rely on the information documented in the medical records and it remains possible that some patients who may be 'considered eligible' for MATRix were treated with other regimens. This may be partly explained by the fact that MATRix was only adopted in routine practice in many centres after publication of the IELSG32 trial in 2016. Second, participating centres were experienced in treating PCNSL patients and familiar with the MATRix protocol; 11 of 13 participating centres had enrolled and treated at least three patients within the IELSG32 trial. This is relevant to patient selection and may translate into clinical outcomes; patients being treated at less experienced centres may have an inferior prognosis. Finally, we had to rely on toxicity assessment as documented at the respective centres during routine care, which is different to prospective toxicity assessment within a clinical trial. Thus, toxicity in this real-world cohort may be underestimated.

Overall, feasibility and efficacy of the MATRix regimen in this real-world cohort compare well with reported outcomes from the IELSG32 trial. Notably, patients from this cohort were older and frailer than those treated within the IELSG32 trial, with 30% of patients failing to fulfil the IELSG32 inclusion criteria due to advanced age, reduced ECOG PS and/or co-morbidities. Notably, notwithstanding an older and frailer patient population, the TRM and stem cell mobilization rates were comparable.

Of note, patients not fulfilling the eligibility criteria of the IELSG32 trial could be expected to have an inferior

prognosis compared to those meeting the trial's inclusion criteria. Increased age and worse ECOG PS are known to have impact on prognosis in PCNSL (Ferreri *et al.*, 2003b; Abrey *et al.*, 2006). Additionally, in patients not fulfilling the IELSG32 trial inclusion criteria the treating physicians were more likely to administer reduced doses during induction treatment and only 39% of those patients underwent consolidation treatment. Together, these factors are likely to explain the inferior outcomes for IELSG32-ineligible patients. However, severe complications were mainly reported during the first treatment course with 7% of the patients requiring intensive-care support and 40% had dose reductions. Moreover, in our landmark analysis including all patients who started the second cycle, dose reductions during the first cycle did not have an impact on PFS or OS suggesting that careful dose adjustments are feasible without compromising treatment efficacy. This is important, because patients with newly diagnosed PCNSL often have impaired performance status at presentation suggesting consideration of dose reductions. However, the aim should always be to deliver all planned courses and, importantly, consolidation treatment, because of the substantial risk for relapse. Whether de-escalation strategies in responding patients are feasible requires further well-designed randomized trials.

We also included a small number of HIV-positive patients in our primary analysis in whom the MATRix combination was also shown to be feasible. Aetiology is different in this sub-entity associated with ineffective immunoregulation of Epstein–Barr-virus-associated B-cell proliferation. Of note, less intensive treatment regimens in combination with antiretroviral therapy have recently been shown to be effective (Gupta *et al.*, 2017; Moulignier *et al.*, 2017) and should therefore also be considered in this particular subgroup of PCNSL patients.

This large series underscores the feasibility and efficacy of chemoimmunotherapy with MATRix as induction treatment prior to HDT-ASCT for newly diagnosed PCNSL in routine practice. Overall, clinical outcomes are similar to those reported in the pivotal IELSG32 trial for those patients fulfilling key IELSG32 trial inclusion criteria. Conversely, older patients with impaired performance status experience inferior outcomes and should therefore be considered for age-adapted regimens. Importantly, for all patients, diligent attention to supportive care and consideration of dose reductions, especially during cycle 1, are strongly recommended to mitigate against treatment-associated complications.

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Authorship contributions

ES was the principal investigator and takes primary responsibility for the paper. ES, CPF, KL, NMC, TC, SN, TAE, TC, JS, DY, BDM, MK, ST, LO, AF, GI, KC, and AF collected the patient data. BK performed the statistical analysis. ES, CPF, BK, GI, AJMF and KC coordinated the research. ES, CPF, BK and KC wrote the paper. All authors reviewed the manuscript.

Conflicts of interest

The following potential conflicts of interest were reported by the authors: ES: research funding and consultancy fees from Riemser. CPF: research funding, consultancy fees and travel support from Roche and Adienne. BK: Travel support from Riemser, consultancy for Roche, research Grant from Roche/AbbVie. TC: research funding from Roche. TAE: honorarium from Roche. JS: consultancy fees and travel support from Abbvie. GI: research funding and consultancy fees from Riemser and Roche. KC: research funding, consultancy fees and travel support from Roche and Adienne. AJMF: research funding from Roche and Celgene, consultancy fees from Gilead and Celgene and travel support from Roche, Gilead and Adienne.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Fig S1. Results from sensitivity analyses. Progression-free survival. Eligibility defined as combination of age and ECOG PS. In these analyses, patients were considered eligible with age up to 65 with ECOG PS $\leq$3 or age up to 70 years if ECOG PS was $\leq$2; all other patients were considered not eligible.

Fig S2. Results from sensitivity analyses. Overall survival Eligibility defined as combination of age and ECOG PS. In these analyses, patients were considered eligible with age up to 65 with ECOG PS $\leq$3 or age up to 70 years if ECOG PS was $\leq$2; all other patients were considered not eligible.

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