# Central nervous system relapse in younger patients with diffuse large B-cell lymphoma - a LYSA and GLA/ DSHNHL analysis

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# Abstract

The majority of patients with diffuse large B-cell lymphoma (DLBCL) can be cured with immunochemotherapy comprising rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). Patients suffering progression or relapse in the central nervous system (CNS) face dismal outcomes. The impact of more aggressive regimens used in front-line therapy has not systematically been investigated in this context. To this end, we analyzed a large cohort of 2203 younger DLBCL patients treated on ten German and French prospective phase II and III trials following first-line therapy with R-CHOP, R-CHOEP (R-CHOP + etoposide), dose-escalated R-CHOEP followed by repetitive stem cell transplantation (R-MegaCHOEP), or rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycine, prednisone (R-ACVBP) followed by consolidation including multiple drugs crossing the blood-brain-barrier (BBB). DLBCL patients with age-adjusted International Prognostic Index (aaIPI) of 0–1 showed very low cumulative incidence (CI) rates of CNS relapse regardless of first-line therapy and CNS prophylaxis (3-year CI 0% – 1%). Younger high-risk patients with aaIPI of 2–3 had 3-year CI rates of 1.6% and 4% after R-ACVBP plus consolidation or R-(Mega)CHO(E)P, respectively (Hazard Ratio 2.4 (95% confidence interval: 0.8–7.4), p = 0.118). Thus, for younger high-risk patients, front-line regimens incorporating multiple agents crossing the BBB may reduce often fatal CNS relapse.


# Introduction

Relapse in the central nervous system (CNS) is an important cause of treatment failure in patients with diffuse large B-cell lymphoma (DLBCL) (1). Patients experiencing CNS relapse continue to show dismal outcomes emphasizing the unmet need to better understand and prevent CNS relapse. We recently reported that in younger patients with high-risk aggressive B-cell lymphoma (age-adjusted International Prognostic Index (aaIPI) 2 or 3) failing conventional or high-dose chemotherapy up to one third of all progressions and relapses occurred in the CNS highlighting that in order to improve results of modern DLBCL therapy better prognostication of CNS relapse risk remains of paramount importance (2). The now widely used CNS-International Prognostic Index (CNS-IPI) based on simple clinical parameters (age > 60 years, LDH > normal, ECOG performance status > 1, advanced stage, extranodal involvement > 1, and involvement of kidney and/ or adrenal glands) and developed in patients treated with R-CHOP defines three risk groups (low-, intermediate-, and high-risk) featuring CNS relapse rates between 0.6% and 10.2% at 2 years (1). In addition to these clinical risk factors, molecular subtyping of the lymphoma may help to improve identification of DLBCL patients at high risk for relapse in the CNS (3, 4). Beyond all models, consequent imaging of the brain and flow cytometry of the cerebrospinal fluid (CSF) in any high-risk patient remain important diagnostic tools. More sensitive technologies including the search for cell-free tumor DNA in the CSF may foster the early detection of CNS involvement (5).

While prophylactic intrathecal (IT) injections of methotrexate (MTX) (+/- cytarabine and prednisolone) are of limited if any effect to prevent CNS relapse (6–8) systemic administration of high-dose (HD) MTX and other cytotoxic drugs (e.g. cytarabine, ifosfamide, etoposide) crossing the blood-brain barrier (BBB) seemed more promising (7, 9). However, randomized studies comparing prophylactic strategies have not

been reported and more recent analyses shed doubts if IV HD MTX is more effective than IT MTX or has any preventive effect at all (10–12).

If first-line therapy other than standard R-CHOP influences the frequency of CNS relapse has not thoroughly been addressed. In the pre-rituximab era, Bernstein et al. were unable to demonstrate that aggressive multi-agent chemotherapy (m-BACOD, ProMACE-CytaBOM, MACOP-B) significantly reduced the frequency of CNS relapse as compared to patients treated with CHOP (13). In 2003 already, the French study group reported that patients treated with the ACVBP regimen experienced significantly less CNS relapses than patients treated with CHOP (14) while Boehme et al. for the German high-grade lymphoma study group showed that the addition of etoposide to CHOP (CHOEP) significantly reduced the number of CNS relapses (15). With the advent of rituximab we and others showed that the addition of rituximab to CHOP reduces the risk of CNS relapse albeit moderately (6, 16). If more aggressive systemic chemotherapy in combination with rituximab (R-CHOEP, R-ACVBP) compared to standard R-CHOP reduces the risk of CNS relapse has not been investigated. R-CHOEP combining drugs identical to DA-EPOCH-R albeit given at different doses and route of administration continues to be used in Germany and Scandinavian countries (2, 17) while R-ACVBP combining an induction phase of rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycine, and prednisone with a consolidation phase comprising HD-MTX, rituximab, etoposide, ifosfamide, and cytarabine is used in the French-speaking world (18, 19). Here, we report on the risk of CNS relapse in large cohorts of younger patients from prospective phase II and III trials treated with R-CHOP, R-CHOEP, or R-ACVBP and compare the incidence and quality of CNS relapses.

# Methods

**Patients and Treatment**. This study represents a joint analysis of the French Lymphoma Study Alliance (LYSA) and the German Lymphoma Alliance (GLA), formerly Deutsche Studiengruppe Hochmaligne Non-Hodgkin Lymphome (DSHNHL). All patients in this analysis were treated on prospective clinical trials LNH03-1B (20), LNH03-2B (18), LNH03-3B (21), LNH07-3B (22), FLYER (23), MInT (24), UNFOLDER (25), MegaCHOEP phase II (26) and phase III (27), and DENSE-R-MegaCHOEP (28) launched by LYSA or GLA/ DSHNHL.

HIV-negative patients with newly diagnosed DLBCL, aged between 18 and 60 years, covering all risk groups of the age-adjusted International Prognostic Index (aaIPI) were included in this analysis. Patients with CNS involvement at diagnosis as well as patients with a history of transformed lymphoma were excluded. CNS involvement was diagnosed if patients presented with typical clinical symptoms and/ or imaging suggested brain lesions compatible with CNS lymphoma and/ or lymphoma cells were detected in the CSF.

The respective study designs including the modalities used to prevent CNS relapse are summarized in **Supplementary Table S1**. In brief, first-line therapy comprised 4–8 courses of standard CHOP or 6–8 cycles of CHOP plus etoposide (CHOEP) given at 2- or 3-week intervals in combination with rituximab. In the R-MegaCHOEP trial, patients randomized to high-dose therapy received 4 courses of dose-escalated

CHOEP (MegaCHOEP) necessitating infusion of autologous hematopoietic stem cells in combination with rituximab (27). Patients on DSHNHL studies received CNS prophylaxis with IT MTX only if bone marrow, testes, or lymph nodes in the upper neck or head were involved.

The R-ACVBP regimen comprised 3 or 4 courses of rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone (R-ACVBP) followed by consolidation depending on risk profile of patients. Patients with IPI 0 or 1 received consolidation with two cycles of HD- MTX (3g/$m^2$), four cycles of rituximab (375 mg/$m^2$), etoposide (300mg/$m^2$), and ifosfamide (1500mg/$m^2$), followed by 2 cycles of cytarabine (100mg/$m^2$) subcutaneously for 4 days (18, 20). Patients with aaIPI 2–3 received two cycles of HD MTX followed by carmustine, etoposide, cytarabine, melphalan (BEAM) and autologous stem cell transplantation (ASCT) for consolidation (21, 22). Patients treated with R-ACVBP were to receive four prophylactic intrathecal (IT) injections of 15 mg of methotrexate (MTX) during courses 1–4 of systemic chemotherapy.

Baseline patient characteristics, treatment and outcome details were retrieved from the LYSA data files at the LYSARC, and the DSHNHL data center at the Institute for Medical Informatics, Statistics, and Epidemiology, University of Leipzig, Leipzig, Germany. All patients gave informed consent. This analysis was done according to the Helsinki declaration and guidelines of Good Clinical Practice.

# Statistical analysis

Progression-free survival (PFS), defined as time from study inclusion (randomization/ registration) to progression, relapse, or death from any cause, and overall survival (OS), defined as time from inclusion to death from any cause, were estimated according to Kaplan-Meier, differences between groups were compared by log-rank test. Kaplan-Meier estimates at 3 years, with 95% confidence intervals (95%CI), were calculated. Multivariable analyses were done using Cox proportional hazard models adjusted for the factors of the age adjusted International Prognostic Index (aaIPI: lactate dehydrogenase (LDH) > normal, Eastern Cooperative Oncology Group performance score (ECOG PS) > 1, stage III/IV), extralymphatic involvement, sex, B symptoms, bone marrow involvement, and bulky disease > 10 cm.

Any CNS involvement with or without progression or relapse at other localisations defined a CNS event. CNS events occurred as first progression/ relapse (“CNS relapse”) or as later event after involvement of other regions. Cumulative incidence curves of CNS relapse were calculated, with “CNS relapse” as event, and PFS events without CNS involvement as competing events. All other patients were censored with PFS time. Three-year cumulative incidence rates are presented. Analyzing the time to CNS relapse for patients with aaIPI 2–3, cause-specific hazard models were used taking into account competing risk events adjusted for ECOG > 1, more than one extralymphatic involvement, sex, B symptoms, bone marrow involvement, bulky disease > 10 cm, and additionally for involvement of kidney and/ or adrenal gland. Analyses were performed for aaIPI groups (0, 1, 2–3) separately to investigate the treatment effects (R-ACVBP versus R-CHO(E)P) in comparable trial populations. A sensitivity analysis was done for aaIPI 2–3

excluding patients from LNH07-3B because this study followed a PET-guided approach in order to select therapy.

OS after a CNS event, defined as time from CNS event to death from any cause, was estimated according to Kaplan-Meier and 1-year rates with 95%CI are presented. For comparison of patient characteristics, chi-square and, if necessary, Fisher's exact test were used. For comparison of age, Mann-Whitney U test was used. The two-sided significance level was set at $p < 0.050$. No adjustments were made for multiple comparisons. Statistical analyses were performed with IBM SPSS Statistics 26 and 28 software (SPSS, Chicago, IL) and R (version 3.6.0, package 'cuminc').

## Results

# Survival analysis

A total of 2,203 DLBCL patients between 18 and 60 years treated on German and French clinical phase II or III trials were included in this analysis. Study designs are summarized in **Supplementary Table S1**. Overall, 455 French patients were treated with R-ACVBP including consolidation, 1,304 patients from France and Germany received R-CHOP at 2- or 3-week intervals, and 444 patients from Germany received R-CHOEP (n = 305) or R-MegaCHOEP (n = 139) (Table 1). Because PFS and OS did not show significant differences, patients treated with R-CHOEP or R-MegaCHOEP were analyzed together.

Table 1
Overview of included patients according to aaIPI and first-line therapy.

| Number of patients | R-ACVBP (n = 455) | R-CHOP (n = 1304) | R-CHOEP (n = 444) |
|---|---|---|---|
| **aaIPI 0 without bulk (n = 652)** | | | |
| LNH03-1B | 76 | | |
| FLYER | – | 399 | |
| MInT | – | 58 | 55 |
| UNFOLDER | – | 64 | – |
| **aaIPI 1 (n = 924)** | | | |
| LNH03-2B | 134 | 134 | – |
| MInT | – | 105 | 85 |
| UNFOLDER | – | 466 | – |
| **aaIPI 2–3 (n = 627)** | | | |
| LNH03-3B | 164 | – | – |
| LNH07-3B | 81 | 78 | |
| MegaCHOEP phase II | – | – | 47 |
| MegaCHOEP phase III | – | – | 189 |
| DENSE-R-MegaCHOEP | – | – | 68 |

First, we compared PFS and OS according to aaIPI risk groups and first-line therapy (Fig. 1). For patients with aaIPI 0 and no bulk, 3-year-PFS rates was 99% (95%CI: 96% − 100%) and 96% (94% − 98%) following R-ACVBP (n = 76) and R-CHO(E)P (n = 576), respectively, without any significant differences between treatment groups. Three-year OS was 100% and 98% (97% − 99%), respectively. (Fig. 1A, B). For patients with aaIPI 1, 3-year PFS- and OS-rates were estimated at 85% (79% − 92%) / 84% (82% − 87%) and 91% (86% − 96%) / 91% (89% − 93%) following R-ACVBP (n = 134) and R-CHO(E)P (n = 790), respectively (Fig. 1C, D). Patients with aaIPI 2–3 showed 3-year PFS rates of 78% (73% − 83%) and 74% (69% − 78%) and 3-year OS rates of 81% (76% − 86%) and 82% (78% − 86%) following first-line therapy with R-ACVBP (n = 245) or R-(Mega)CHO(E)P (n = 382), respectively (Fig. 1E, F). In multivariable analyses adjusted for extralymphatic involvement, sex, B symptoms (aaIPI 0), elevated LDH, stage III/IV, extralymphatic involvement, sex, B symptoms, bone marrow involvement, and bulky disease (aaIPI 1), or ECOG > 1, extralymphatic involvement, sex, B symptoms, bone marrow involvement, and bulky disease (aaIPI 2–3), there was no significant difference of PFS and OS according to treatment arms. A separate analysis of

the three treatment strategies R-ACVBP, R-CHOP, and R-CHOEP showed comparable results (**Supplementary Fig. S1**, **Supplementary Table S2**).

# Baseline Characteristics Of Patients With Cns Event

Overall, 40 of 2,203 young DLBCL patients (1.8%) experienced progression or relapse in the CNS. Thirty-three CNS events (82%) represented the first progression or relapse for affected patients. As expected, 27 of these 33 CNS relapses occurred within the first 12 months after study inclusion. Interestingly, the six remaining CNS relapses (18%) occurred later than 40 months after study inclusion. For 34 of 40 patients with CNS event the precise sites of CNS involvement were reported at initial diagnosis: in 56% (19/34) a meningeal, in 47% (16/34) an intracerebral, in 9% of cases (3/34) an intraspinal solid lymphoma manifestation, and in one case eye involvement (3%) were reported. Combined involvement occurred in 5 cases.

Comparing patients with (n = 40) and without CNS event (n = 2163) revealed several baseline characteristics significantly associated with CNS event (Table 2). Overall, patients with CNS event showed a higher aaIPI at initial diagnosis ($p < 0.001$). Each factor of the aaIPI: elevated LDH (49% vs. 80%, $p < 0.001$), poor ECOG performance status (8% vs. 25%, $p = 0.002$), and advanced stage III/ IV disease (46% vs. 70%, $p = 0.003$) conveyed a significantly higher risk for CNS events compared to patients lacking the respective characteristics. Other significant factors were bulky disease > 10 cm (21% vs. 35%, $p = 0.029$), B-symptoms (29% vs. 49%, $p = 0.009$), and bone marrow involvement (6% vs. 18%, $p = 0.012$). Involvement of the kidney and/ or adrenal gland occurred in 4% of patients without CNS event compared to 10% of patients with CNS event ($p = 0.057$). Patients with CNS event showed a higher CNS IPI at initial diagnosis ($p < 0.001$). In the entire study cohort, only one of 640 patients with CNS IPI of 0 experienced a late CNS event (0.2%) more than 4 years after study inclusion. In 1399 patients with CNS IPI 0 or 1, 16 CNS events occurred (1.1%). 665 patients of intermediate risk with CNS IPI 2–3 showed 17 CNS events (2.6%). Finally, 139 patients showed a high CNS IPI (4–5) with 7 patients (5%) experiencing a CNS event. Twenty patients displayed a CNS IPI of 5 with four patients (20%) showing a CNS event.

Table 2
Main characteristics of DLBCL patients according to the occurrence of CNS event.

| | All patients n = 2203 | Patients without CNS event n = 2163 | Patients with CNS event n = 40 | p-value* |
|---|---|---|---|---|
| Male | 1292 (59%) | 1266 (59%) | 26 (65%) | 0.410 |
| Female | 911 (41%) | 897 (41%) | 14 (35%) | |
| Age, median (range) | 47 (18, 60) | 47 (18, 60) | 51 (19, 60) | 0.370 |
| LDH > UNV | 1102 (50%) | 1070 (49%) | 32 (80%) | < 0.001 |
| ECOG > 1 | 193 (9%) | 183 (8%) | 10 (25%) | 0.002 |
| Stage III/ IV | 1031 (47%) | 1003 (46%) | 28 (70%) | 0.003 |
| aaIPI0 | 652 (30%) | 651 (30%) | 1 (2%) | < 0.001 |
| 1 | 924 (42%) | 906 (42%) | 18 (45%) | |
| 2 | 479 (22%) | 468 (22%) | 11 (28%) | |
| 3 | 148 (7%) | 138 (6%) | 10 (25%) | |
| Extralymph. involvement | 1210 (55%) | 1183 (55%) | 27 (68%) | 0.107 |
| Extralymph. involvement > 1 | 509 (23%) | 496 (23%) | 13 (32%) | 0.155 |
| Bulky disease** (> 10 cm) | 462 (21%) | 448 (21%) | 14 (35%) | 0.029 |
| B symptoms** | 654 (30%) | 635 (29%) | 19 (49%) | 0.009 |
| BM involvement | 142 (6%) | 135 (6%) | 7 (18%) | 0.012 |
| Kidney inv. at staging | 56 (3%) | 53 (2%) | 3 (8%) | 0.079 |
| Adrenal gland inv. at staging | 33 (1%) | 31 (1%) | 2 (5%) | 0.119 |
| Kidney and/or adrenal gland inv. at staging | 81 (4%) | 77 (4%) | 4 (10%) | 0.057 |

* p-value for the comparison of patients with CNS failure versus patients without CNS event

** some missing values: bulky disease (9/9/0), B symptoms (7/6/1), MTX IT (143/138/5)

| | All patients n = 2203 | Patients without CNS event n = 2163 | Patients with CNS event n = 40 | p-value* |
|---|---|---|---|---|
| CNS IPI0 | 640 (29%) | 639 (30%) | 1 (2%) | < 0.001 |
| 1 | 759 (34%) | 744 (34%) | 15 (38%) | |
| 2 | 414 (19%) | 403 (19%) | 11 (28%) | |
| 3 | 251 (11%) | 245 (11%) | 6 (15%) | |
| 4 | 119 (5%) | 116 (5%) | 3 (8%) | |
| 5 | 20 (1%) | 16 (1%) | 4 (10%) | |
| CNS IPI groups | 1399 (64%) | 1383 (64%) | 16 (40%) | 0.002 |
| 0–1 – low risk | 665 (30%) | 648 (30%) | 17 (42%) | |
| 2–3 – intermediate risk | 139 (6%) | 132 (6%) | 7 (18%) | |
| 4–5 – high risk | | | | |
| MTX prophylaxis | 780 (38%) | 766 (38%) | 14 (40%) | – |
| (at least one course) | 344 (16%) | 342 (16%) | 2 (5%) | |
| MTX IT** | | | | |
| HD MTX IV | | | | |
| CNS event at 1st prog/rel | 33 (1.5%) | – | 33 (82%) | – |
| (within the first 3 years) | (27) | | (27) | |
| after 1st prog/rel | 7 (0.3%) | | 7 (18%) | |
| (within the first 3 years) | (4) | | (4) | |
| * p-value for the comparison of patients with CNS failure versus patients without CNS event | | | | |
| ** some missing values: bulky disease (9/9/0), B symptoms (7/6/1), MTX IT (143/138/5) | | | | |

# Cumulative Incidence Of Cns Relapse According To Aaipi And First-line Therapy

Next, we compared the cumulative incidences of CNS relapse according to aaIPI risk factors and first-line therapy administered. The different median observation time for OS in patients treated with R-ACVBP or R-CHO(E)P (aaIPI 0 without bulky disease: 43 vs. 68 months; aaIPI 1: 43 vs. 67 months; aaIPI 2–3: 45 vs. 41 months) should be recognized. Among patients with aaIPI 0 without bulky disease (n = 652), one

single patient (0.2%) experienced a late CNS relapse (**Supplementary Table S3**). The 3-year cumulative incidences of CNS relapse were 0% in all treatment arms.

Among patients with aaIPI 1, 134 patients treated with R-ACVBP did not experience any CNS relapse. 705 patients treated with R-CHOP showed 11 CNS relapses (1.6%) and 85 patients treated with R-CHOEP showed two CNS relapses (2.4%) (**Supplementary Table S4**). The 3-year cumulative incidences of CNS relapse were 0%, 1.0% (0.3% − 1.7%), and 1.2% (0% − 3.6%), respectively.

245 patients with aaIPI 2 or 3 received treatment with R-ACVBP including consolidation. Four CNS relapses were recognized (1.6%) and the 3-year cumulative incidence following R-ACVBP was 1.6% (0% − 3.2%, Fig. 2). 382 patients with aaIPI 2 or 3 were treated with R-CHOP (n = 78), R-CHOEP (n = 165), or R-MegaCHOEP (n = 139). Fifteen CNS relapses (3.9%) were noticed (**Supplementary Table S5**). The corresponding 3-year cumulative incidence of CNS relapse for R-CHO(E)P was 4% (2.0% − 6.0%) (Fig. 2). Comparing the time to CNS relapse for R-(Mega)CHO(E)P vs. R-ACVBP, the multivariable, cause-specific, hazard model adjusted for prognostic factors showed a trend for less CNS relapses in the R-ACVBP group (R-(Mega)CHO(E)P vs. R-ACVBP, HR 2.4 (95%CI 0.8–7.4), p = 0.118). Comparing only R-ACVBP and R-(Mega)CHOEP patients the corresponding 3-year cumulative incidence of CNS relapse for R-(Mega)CHOEP was 5% (2.5%-7.5%) and the HR almost reached statistical significance (R-(Mega)CHOEP vs. R-ACVBP, HR 3.0 (95%CI 1.0-9.3), p = 0.052) (**Supplementary Fig. S2A**). Notably, the patients treated with R-ACVBP or R-CHOP within the LNH07-3B trial received salvage therapy in case of positive PET4.[21] Considering only the 164 R-ACVBP treated patients within the LNH03-3B trial, the corresponding 3-year cumulative incidence of CNS relapse was 1.2% (0% − 2.9%) with a HR of R-(Mega)CHO(E)P vs. R-ACVBP accounting 4.1 (95%CI 0.9–18.2), p = 0.062) (**Supplementary Fig. S2B**).

As expected, patients experiencing CNS events showed very unfavorable outcomes (Fig. 3). With a median time of observation of 18 months, 1-year OS after CNS event was 20% (6% − 33%).

# Discussion

Since our initial report in 2009 (6), most retrospective analyses failed to show that DLBCL patients benefit from CNS prophylaxis with IT MTX (3, 29, 30). More recently, the efficacy of prophylaxis with IV HD MTX has also been questioned (10, 12). Taken together, the lack of progress in establishing more effective CNS prophylaxis emphasizes the necessity to continue searching for alternative strategies to reduce the frequency of CNS relapse. Here we demonstrate that the incidence of CNS relapse in younger, well-documented study patients with aaIPI 0 or 1 is very low making further efforts to reduce their number challenging to impossible. Patients falling into these low-risk groups mostly presenting also with a low CNS-IPI can be spared any CNS-directed diagnostic and prophylactic procedures. Attempts to improve the situation would also be hampered by the necessity to treat very high numbers of patients to document any statistically significant improvement.

For younger patients with aaIPI 2 or 3 and treated with the R-ACVBP regimen the 3- year cumulative incidence rate of CNS relapse was intriguingly low (1.6%) and lower than observed with the R-CHO(E)P regimen (4.0%). It should be mentioned that the overall CNS relapse rates observed in this analysis are lower than expected, e.g. by applying the CNS-IPI, possibly reflecting the superiority of aggressive regimens over R-CHOP especially when patients are treated on clinical studies. Taking into account earlier reports on the ACVBP regimen before rituximab was added to chemotherapy (14) the aggregate data available today suggest that (R-)ACVBP can effectively prevent CNS relapse also in younger high-risk DLBCL patients (aaIPI 2 or 3) who run the highest risk of CNS relapse of all patients amenable to more aggressive chemotherapy. R-ACVBP in comparison to other aggressive therapies such as R-CHOEP or DA-EPOCH-R not only comprises dose-escalated induction chemotherapy but includes a distinct consolidation part consisting of HD-MTX, ifosfamide, etoposide, and cytarabine, or HD-MTX, BEAM (including escalated etoposide and cytarabine) and ASCT (18). Moreover, R-ACVBP includes 4 IT injections of MTX administered to all patients regardless of specific region(s) involved by lymphoma. Although the benefit of IT MTX remains controversial, the combination of aggressive systemic therapy, intrathecal prophylaxis for all patients, and consolidation with multiple drugs crossing the BBB effectively reduces the incidence of CNS relapse. Which of the unique therapeutic features of R-ACVBP actually make the difference is impossible to decide; rather, the combination of all consolidation elements may be necessary to obtain optimal results with R-ACVBP.

Unfortunately, the majority of elderly patients with DLBCL and high risk of CNS relapse may not be able to benefit from being treated with R-ACVBP or other regimens more aggressive than R-CHOP because of toxicities precluding their routine administration to older and unfit patients (18, 31). Despite improved overall survival rates reported for younger patients with aaIPI of 1, R-ACVBP was associated with significantly increased hematological toxicity (18). It must be weighed up individually whether the potential benefit of preventing CNS relapse justifies more treatment-related toxicity. Therefore, the search for better diagnostic and prognostic markers as well as optimizing systemic therapy including new drugs with less toxicity crossing the BBB must continue (32, 33). A GLA phase II study investigating R-CHOEP plus the BTK-inhibitor ibrutinib in young, high-risk DLBCL patients completed patient accrual and awaits analysis (EudraCT-No. 2017-003256-22).

# Conclusions

We demonstrate that the risk of relapse in the CNS for younger patients with low-risk DLBCL (aaIPI 0 and 1) is very low and further efforts to improve CNS prophylaxis may neither be warranted nor feasible. Younger patients with high-risk (aaIPI 2 and 3) disease may benefit from aggressive immunochemotherapy including consolidation with multiple drugs crossing the BBB. Because the toxicities observed with aggressive chemotherapy remain significant and may preclude such treatment in the elderly the search for more effective and less toxic CNS prophylaxis must continue to improve the overall results of first-line therapy in DLBCL.

# Declarations

### Competing interests

Catherine Thieblemont: honoraria from Roche, Amgen, Janssen, Celgene, Gilead Science/ Kyte Beigene; consulting/ advisory role for Roche, Gilead Sciences, Janssen, Celgene, Novartis, Beigene, BMS/ Celgene research funding and travel, accommodations, expenses from Roche, Novartis outside the submitted work.

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Final approval of manuscript: all authors.

Accountable for all aspects of the work: all authors.

Catherine Thieblemont, Bettina Altmann, and Fabian Frontzek contributed equally. Marita Ziepert and Norbert Schmitz contributed equally.

### Data availability

The datasets of this study will be provided on request by the corresponding author.

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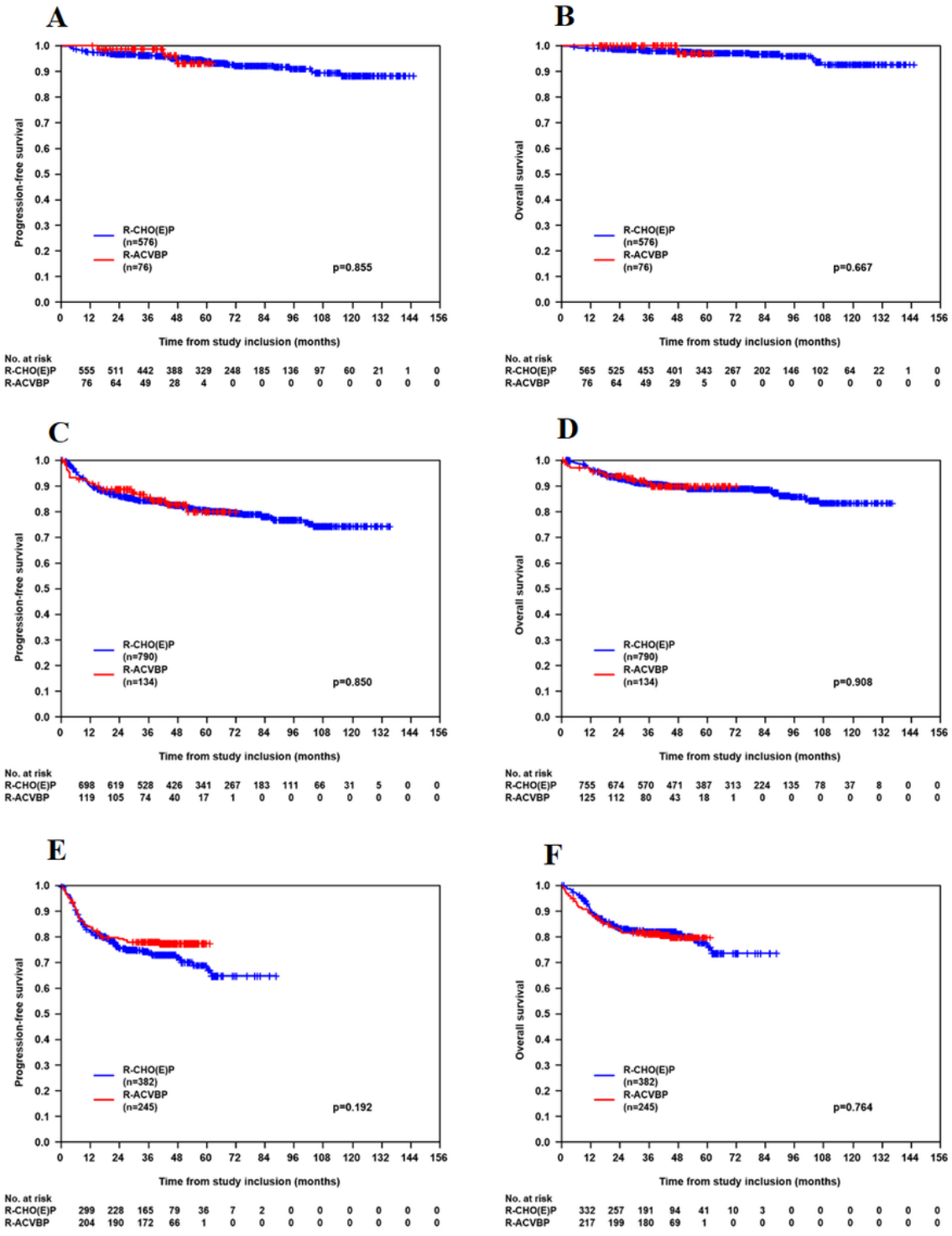
# Figures




## Figure 1

PFS (A, C, E) and OS (B, D, F) for patients with aaIPI 0 without bulk (A, B), aaIPI 1 (C, D), and aaIPI 2-3 (E, F) according to first-line therapy (R-ACVBP versus R-CHO(E)P). Log-rank p-values are presented.

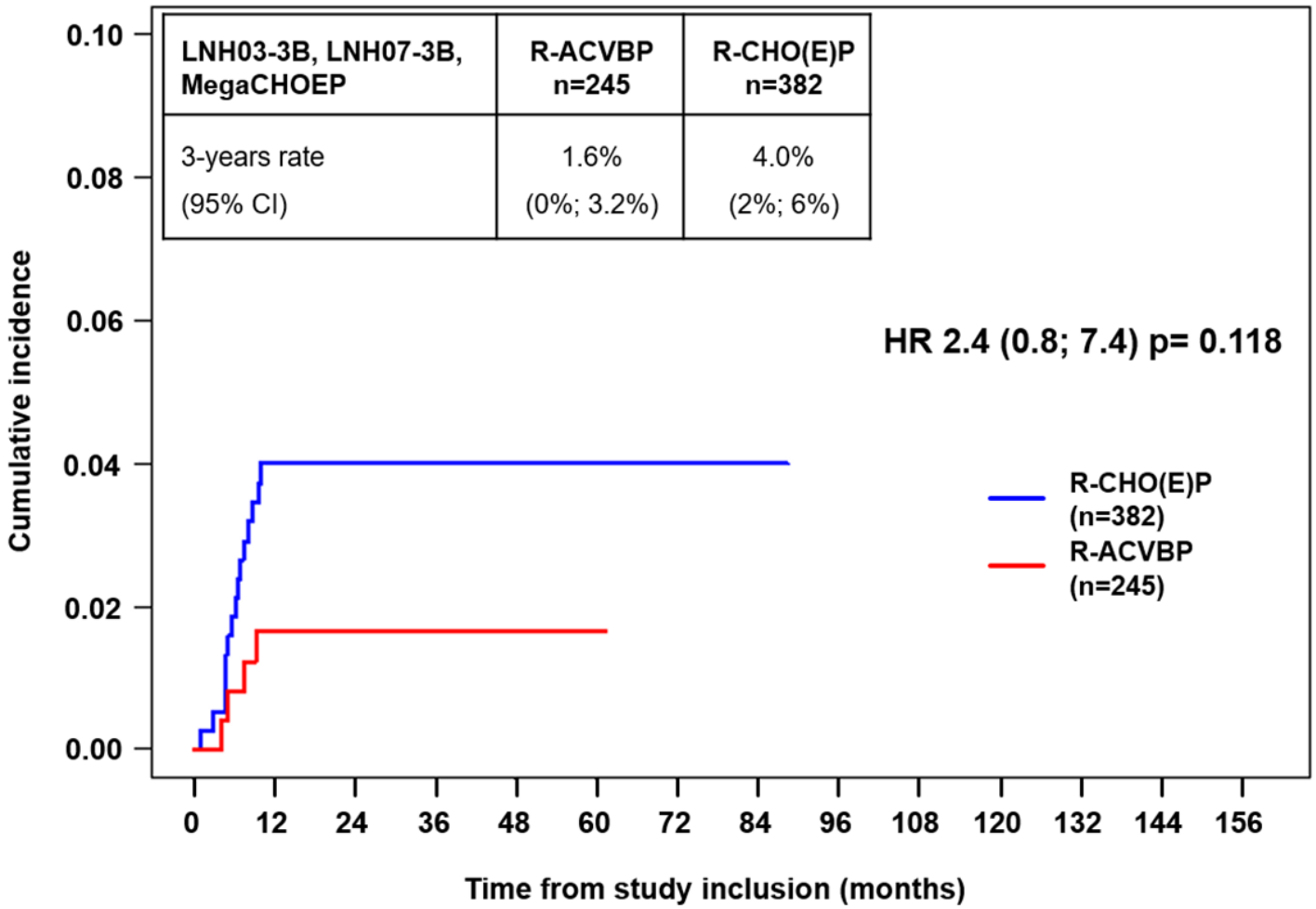



**Figure 2**

Cumulative Incidence of CNS relapse for patients with aaIPI 2-3 according to first-line therapy (R-ACVBP versus R-CHO(E)P). Adjusted HR with 95%CI is presented.

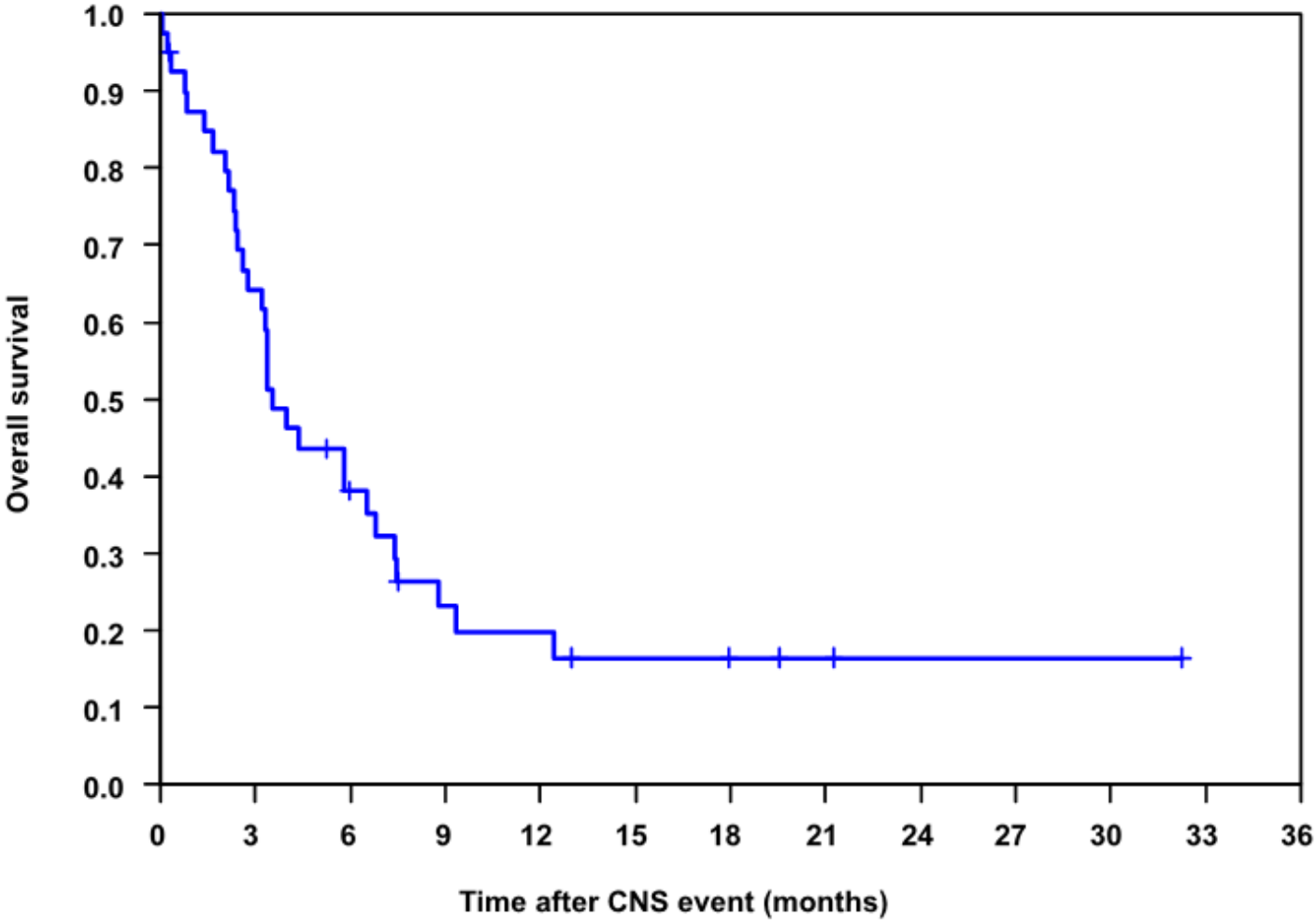



**Figure 3**

OS of young DLBCL patients after CNS event (n=40).

## Supplementary Files

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