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Outcomes of synchronous systemic and central nervous system (CNS) involvement of diffuse large B-cell lymphoma are dictated by the CNS disease: A collaborative study of the Australasian Lymphoma Alliance

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Summary

De novo diffuse large B-cell lymphoma (DLBCL) presenting with synchronous central nervous system (CNS) and systemic disease (synDLBCL) is not well described and is excluded from clinical trials. We performed a retrospective analysis of 80 synDLBCL patients treated across 10 Australian and UK centres. Of these patients, 96% had extranodal systemic disease. CNS-directed treatment with combination intravenous cytarabine and high-dose methotrexate

("CNS-intensive") (n=38) was associated with favourable survival outcomes compared with "CNS-conservative" strategies such as intravenous high-dose methotrexate monotherapy, intrathecal therapy and/or radiotherapy (2-year progression-free survival [PFS] 50% versus 31%, p=0.006; 2-year overall survival [OS] 54% versus 44%, p=0.037). Outcomes were primarily dictated by the ability to control the CNS disease, with 2-year cumulative CNS relapse incidence of 42% and non-CNS relapse 21%. Two-year OS for CNS-relapse patients was 13% versus 36% for non-CNS relapses (p=0.02). Autologous stem cell transplantation as consolidation (n=14) was not observed to improve survival in those patients who received CNS-intensive induction when matched for induction outcomes (2-year PFS 69% versus 56%, p=0.99; 2-year OS 66% versus 56%, p=0.98). Hyperfractionated or infusional systemic treatment did not improve survival compared to R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone) (2-year OS 49% for both groups). Our study suggests that adequate control of the CNS disease is paramount and is best achieved by intensive CNS-directed induction.

Introduction:

Diffuse large B-cell lymphoma (DLBCL) is a biologically and clinically heterogenous malignancy. It commonly presents solely outside of the central nervous system (CNS), or is less frequently isolated to the CNS (primary CNS lymphoma; PCNSL). CNS involvement of systemic DLBCL at diagnosis (synDLBCL) is rare but results in poor outcomes. SynDLBCL is typically excluded from clinical trials, so data are limited (Chihara et al., 2017; Ferreri et al., 2015; Nijland et al., 2017). Whilst the treatments of systemic DLBCL and PCNSL are well established (Cunningham et al., 2013; Ferreri et al., 2016), high-dose methotrexate (HDMTX)-based therapy, used to treat PCNSL, does not provide adequate systemic control, and drugs for systemic disease, such as R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone), have insufficient CNS penetration. Hence, defining optimal management proves challenging, and most patients receive a combination of systemic and CNS-directed therapy.

CNS dissemination of systemic disease occurs in up to 5% of all patients with DLBCL (Ferreri *et al*, 2009a; Ghose et al., 2015), however asymptomatic presence at diagnosis is not well documented, as magnetic resonance imaging and lumbar puncture staging of the CNS is not routine. A recent study described baseline CNS involvement in 2-3% of systemic DLBCL cases, though the number of patients formally evaluated for CNS disease was not reported and the primary focus was molecular prognostication (Reddy et al., 2017). Whether CNS-relapse predictors, such as presence of a high-risk CNS International Prognostic Index (IPI) or sites associated with CNS relapse, e.g. testes, kidneys and adrenal glands, predicts for synDLBCL has not been comprehensively studied (El-Galaly et al., 2017; Ollila & Olszewski, 2018; Schmitz et al., 2016).

The largest reported retrospective cohort of synchronous systemic and CNS lymphoma (n=60) included non-DLBCL subtypes and analysed patients according to consolidative autologous stem cell transplantation (AuSCT) in first response rather than by induction regimen. The study reported a 3-year overall survival (OS) of 75% in the transplanted patients versus 29% in non-transplanted (Damaj et al., 2015), however selection bias inherent in choosing patients for intensive therapy and the inclusion of multiple histological subtypes are likely to contribute to the difference. Smaller retrospective series of similar cohorts report superior non-transplant outcomes (3-year OS 49% in the largest) from various induction regimens, including R-CODOX-M (rituximab, cyclophosphamide, cytarabine, vincristine, doxorubicin, methotrexate)/ IVAC (ifosfamide, etoposide, cytarabine), though patient numbers are low (Chihara et al., 2017; Maciocia et al., 2016; Nijland et al., 2017; Phillips et al., 2018; Yoo et al., 2015). To date, the clinical and biological features of this rare entity have not been comprehensively described. The role of intensified (e.g. hyperfractionated, such as HyperCVAD [hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate, cytarabine], CODOX-M/IVAC, or infusional e.g. DA-EPOCH-R [dose-adjusted eptposide, prednisolone, vincristine, cyclophosphamide, doxorubicin, rituximab) systemic induction therapy, multi-agent CNS-directed chemotherapy and the role of AuSCT in consolidation of patients with adequate CNS-directed treatment in induction are not established.

Synchronous CNS and systemic presentation of non-Hodgkin lymphoma (NHL) was evaluated in a small, single-arm phase II study (n=38) however the study included follicular,

mantle cell lymphoma and aggressive NHL subtypes, in newly-diagnosed and relapsed patients. Treatment entailed intravenous (IV) high-dose methotrexate (HDMTX) plus cytarabine followed by intensification with high doses of cyclophosphamide, cytarabine and etoposide, followed by a carmustine (BCNU)/thiotepa-conditioned (i.e. CNS-penetrating) AuSCT (Ferreri et al., 2015). It should be noted that the regimen omitted anthracyclines other than a single cycle of R-CHOP for debulking, which was only delivered in 2 patients; only 16 patients had synchronous disease at initial diagnosis and detailed outcomes according to histology were not reported. Nonetheless, OS for the whole group was 45% at 5 years and treatment-related mortality (TRM) was 10.5%.

This international, multicentre study reports the largest cohort of *de novo* synDLBCL including detailed assessment of clinical features, treatment regimens, toxicities and outcomes for this rare entity.

Methods:

Patients

Eligible patients had treatment-naïve, histologically-proven DLBCL according to the relevant World Health Organisation classification at the time of diagnosis. Cases were identified by a systematic search of lymphoma databases and pharmacy records from the rituximab era for patients receiving CNS-directed intravenous or intrathecal chemotherapy. Cases diagnosed as high-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* (HGBL-DH) rearrangements were included. Burkitt lymphoma, lymphoblastic lymphoma/acute lymphoblastic leukaemia, mantle cell lymphoma and low-grade lymphomas were excluded, though transformed low-grade lymphomas were included if completely treatment-naïve. CNS involvement was confirmed by histological biopsy, cerebrospinal fluid (CSF) cytology and/or flow cytometry, and/or definitive radiological evidence. Where the only evidence of CNS disease was radiological, it was sufficiently convincing for CNS-directed treatment (rather than prophylaxis alone) to be administered. Patients with discrete CNS lesions or direct CNS invasion from a systemic site were eligible; however, patients with clinical features due to external compression only (i.e. lesions only on the systemic side of the blood brain barrier) were excluded.

All patients received rituximab-containing immuno-chemotherapy incorporating CNS-directed and systemically efficacious therapy.

Study design

This was an international, multicentre, retrospective study. Patients treated from 2003 to 2017 were identified from 10 participating Australian and United Kingdom sites using local hospital and pharmacy records. The research was approved by the Austin Hospital human research and ethics committee (LNR/17/Austin/186) and conducted in accordance with the declaration of Helsinki.

Data collection

Collected data included patient demographics, results of baseline investigations and treatment details, including number of cycles, dose reductions, intrathecal therapy, site and dose of radiation, transplant conditioning (if performed), TRM and response to therapy. IPI, National Comprehensive Cancer Network (NCCN)-IPI (Zhou et al., 2014) and CNS-IPI (Schmitz et al., 2016) were also calculated. Data on cell of origin (COO) according to Hans algorithm (Hans et al., 2004), immunohistochemical expression of MYC (>40%) and BCL2 (>50%), and fluorescence in-situ hybridisation (FISH) for identifying *MYC*, *BCL2* and *BCL6* rearrangements were also collected where available. Response assessments were assigned at the point of completion of planned primary therapy and prior to consolidative AuSCT in patients who received this treatment. Primary refractory disease was defined as failure to achieve at least a partial response or progression within 3 months of therapy.

Statistical analysis:

Data were analysed by treatment group. The 'CNS-intensive' group was defined by treatment with established multi-agent intravenous chemotherapy regimens with ≥2 CNS penetrating drugs (i.e. HDMTX [≥1 g/m^2] and cytarabine [≥2 g/m^2]), with or without intrathecal chemotherapy (ITC) and/or radiotherapy (RT) in addition to systemic chemotherapy. The 'CNS-conservative' group was defined by use of ≤1 IV CNS penetrating chemotherapy agents in induction (i.e. HDMTX), administered with or without ITC and/or RT in addition to systemic therapy. Comparison by systemic induction regimen (R-CHOP versus R-HyperCVAD or CODOX-M/IVAC) and by consolidative AuSCT was also performed. To

reduce selection bias, transplant outcomes were further analysed by induction regimen and putative transplant eligibility (i.e. age ≤70 years and chemosensitive to induction) in the control group.

Fisher's exact test was used to compare categorical variables. Responses were defined by the internationally recognised criteria applied at the time the patient was treated, and both CNS and systemic compartments must have met the criteria for response. Progression-free survival (PFS) was defined as the time from diagnostic biopsy to the time of radiologically or histologically proven progression, death or last follow-up, and OS was defined as the time from diagnostic biopsy to death or last follow-up. Cox proportional hazard model was used to determine factors associated with OS and PFS and their 95% confidence interval (95%CI). A parsimonious multivariable model was constructed based upon treatment modalities and anticipated confounders. The Kaplan-Meier method was used to determine survival distribution and log-rank test to determine survival differences between groups. When comparing transplant outcomes, a "delayed entry" model using transplant date was used to eliminate immortal time bias. Competing risk analysis was used to determine cumulative incidences. Two-sided p-values of <0.05 were considered significant. SPSS version 25 (IBM, Armonk, NY, USA) was used for analysis.

Results:

Patient characteristics

Eighty patients were eligible. Baseline characteristics are described in Table I. The diagnosis was DLBCL not otherwise specified (NOS) in 67 patients (84%), HGBL-DH or HGBL in 12 (15%) and T-cell histiocyte-rich DLBCL in one (1%). Median age was 64 years for the whole cohort, and 54 versus 69 for the CNS-intensive and CNS-conservative groups, respectively (p<0.001); 68% were male (Table I). High-risk cases (score ≥4) by NCCN-IPI and CNS-IPI comprised 68% and 70% of cases respectively, with differences between treatment groups related exclusively to age (Table I). Systemic extranodal disease was present in 77/80 (96%), and 56/80 (70%) had more than one extranodal site in addition to CNS involvement (Table I). Fifty-eight (73%) had at least one extranodal site considered of special interest due to its

association with CNS relapse (bone marrow, adrenal glands, kidneys, testes, uterus and sinuses) (El-Galaly et al., 2017; Kridel et al., 2017; Schmitz et al., 2016).

COO was available in 62 patients (78%); 29 (47%) were germinal-centre origin (GC) and 33 (53%) were non-GC. MYC and BCL2 expression by immunohistochemistry (IHC) was performed in 42 (53%) and co-expressed in 17 (40%); 12/17 (71%) were non-GC origin. FISH for *MYC* and *BCL2* translocations was performed in 26 (33%) and both were rearranged in 6 (7% of total; 23% of cases tested); 5/6 were GC origin.

The distribution of CNS involvement was parenchymal-only in 30 (38%), leptomeningeal/CSF-only in 40 (50%) and both in 10 (12%). More leptomeningeal disease was present in the CNS-intensive group (66% versus 33%, $p<0.001$), however a higher number of patients had lumbar punctures as part of chemotherapy in this group (97% versus 60%, $p<0.001$). Sixty-four cases (80%) had discrete CNS lesions non-contiguous with a systemic site; 16 (20%) had direct invasion into the CNS from a systemic site, such as paranasal sinuses or vertebrae. Focal CNS symptoms were present in 65 (81%).

Treatment:

Treatment details, including CNS-directed therapies are described in Table II. Systemic induction in the CNS-intensive group was R-HyperCVAD in 66%; R-CODOX-M-IVAC in 24%; R-CHOP plus HDMTX and cytarabine in 5%; MATRix (methotrexate, cytarabine, thiotepa, rituximab) in 3%; and R-DHAP (rituximab, dexamethasone, cytarabine, cisplatin) plus HDMTX in 3%. Systemic induction in the CNS-conservative group included R-CHOP/CHOP-like in 83%; R-CODOX-M and DA-EPOCH-R in 5% each; and R-MPV (rituximab, methotrexate, procarbazine, vincristine), R-bendamustine and R-HDMTX only in 3% each. Two patients in the CNS-conservative group received radiotherapy as the sole CNS-directed therapy (whole brain and involved-field in one each). A further two patients progressed in the CNS and died prior to receiving planned CNS-directed therapy (HDMTX was planned for both). These cases were included in the analysis as treatment intent was curative. CNS-directed therapy was intercalated with systemic therapy in almost all cases.

The first cycle of chemotherapy contained IV CNS-penetrating agents in 38 (48%); the remaining 42 (52%) received systemic-only IV therapy +/- ITC. Six patients had a “debulking”

cycle of R-CHOP prior to commencing intensive systemic treatment with infusional or hyperfractionated induction.

Fourteen patients underwent consolidative AuSCT. Conditioning included carmustine + thiotepa in 7, BEAM (carmustine, etoposide, cytarabine and melphalan) in six and 1 Stanford variant CBV (Horning et al., 1991) in one. Thirteen received CNS-intensive induction and one received R-CHOP with HDMTX.

Outcomes

Within the CNS-intensive group, dose-reduction occurred in seven patients (18%) and seven (18%) had to cease therapy early either due to toxicity or lack of efficacy. In contrast, 20 patients (48%) treated with CNS-conservative therapy required dose reductions (p=0.009), and 22 (52%) required early cessation (p=0.002).

There were four treatment-related deaths in the CNS-intensive group; two during induction and two during consolidative AuSCT. Three induction-related deaths occurred in the CNS-conservative group (11% versus 7%, p=0.70). There were a further three late treatment-related deaths due to salvage therapy (n=2, one in each group) or from therapy-related myeloid neoplasm (n=1, in the CNS-conservative group).

The overall response rate (ORR) was 80% for CNS-intensive and 63% for CNS-conservative, and complete response (CR) rates were higher in CNS-intensive group but this was not statistically significant (69% versus 51%, p=0.16). Primary refractory disease occurred in 19% of CNS-intensive and 38% of CNS-conservative (p=0.07). Two-year PFS and OS for the whole group was 40% and 49% respectively. 2-year PFS for CNS-intensive and conservative respectively were 50% and 31% (p=0.006) and 2-year OS was 54% versus 44% (p=0.037, Figure 1A-1B). Hyperfractionated or infusional regimens (R-HyperCVAD, DA-EPOCH-R, R-CODOX-M/IVAC) were not observed to reduce systemic relapses relative to R-CHOP/R-CHOP-like induction (p=0.76). Outcomes for individual regimens are included in Table SI.

Patients who underwent consolidative AuSCT all achieved a response (11 CR, 3 partial response) post-induction. Two-year PFS was 70% versus 34%, favouring those transplanted when compared with the rest of the cohort, though this was not statistically significant when adjusted for immortal time bias (p=0.079, Figure 2A); 2-year OS was 66% in the

transplant group versus 45% in non-transplanted (p=0.13, Figure 2B). Thirteen of 14 transplant patients received CNS-intensive induction.

Within the CNS-intensive group, 32 patients met the criteria for "transplant-eligible" analysis (age ≤70 years and chemosensitive to induction); 13 were transplanted and 19 not transplanted. When compared directly, no difference was observed between those transplanted versus those not transplanted in PFS (2-year PFS 69% versus 56%, p=0.99, Figure 2C) or OS (2-year OS 66% versus 56%, p=0.98, Figure 2D).

The most common site of relapse or progression was the CNS (n=28). 2-year cumulative incidence of CNS relapse was 42% (Figure 3A), with fewer CNS relapses observed in the CNS-intensive arm (25% versus 49%, p=0.03). Five systemic-only relapses occurred in each treatment group (n=10). CNS progressions were associated with a 2-year OS of 13% versus 36% for systemic-only relapses (p=0.02, Figure 3B).

The parsimonious multivariable model included age, receipt of IV CNS penetrating agents, receipt of CNS-intensive induction and receipt of CNS radiotherapy. Autologous transplantation in first response was not included in the multivariate model as the number of patients needing to be removed due to transplant ineligibility (e.g. early progression or death) was substantial. CNS-intensive induction had the largest impact on survival in the model, though it failed to achieve statistical significance (Hazard ratio [HR] for PFS 0.48 (95%CI 0.22-1.07, p=0.07); HR for OS 0.57 (95%CI 0.26-1.27, p=0.17; Table III). Analysis of the CNS-conservative patients who received IV HDMTX (as opposed to those who received IT MTX or RT only) also showed inferior outcomes compared to those who received CNS-intensive treatment (2-year PFS 28% versus 50%, p=0.02), despite higher cumulative HDMTX in those treated with monotherapy (10.5 g/m^2 versus 6 g/m^2, p=0.027).

There was no PFS advantage for patients treated with IV CNS-directed treatment in the first cycle (HR 0.65, 95%CI 0.36-1.16, p=0.14). However, death from CNS progression occurred in six cases prior to delivery of planned IV CNS-directed chemotherapy. Other predictors of survival outcome are described in Table III.

Discussion

This is the largest reported study of synDLBCL - a group almost uniformly excluded from clinical trials. Results from our 80 patients demonstrate that this rare phenomenon occurs almost exclusively in the setting of systemic, often extensive, extranodal disease (El-Galaly et al., 2017; Kridel et al., 2017; Schmitz et al., 2016). Treatment is heterogeneous, with no emerging standard of care. The 2-year OS for the whole cohort was only 49%, which was improved by the use of combination HDMTX and cytarabine-containing induction therapy compared to HDMTX alone and other conservative CNS strategies (OS 54% versus 44%; p=0.037).

The high rate of extranodal systemic disease in this cohort reinforces known risk factors for CNS relapse, and patients with extranodal disease should be carefully evaluated for CNS involvement at baseline. Whilst most of our cohort (81%) had focal CNS symptoms, the presence of CNS symptoms may be over-estimated, as symptomatic patients are more likely to be identified.

Due to the extended period of the study, complete pathobiological data were not available for all patients. Nonetheless, poor-risk biological features, such as double-expression of MYC and BCL2 and non-GC subtype by the Hans algorithm were present more frequently than expected from a general DLBCL population, consistent with previous reports of cohorts with high-risk of CNS relapse (Hans et al., 2004; Klanova et al., 2019; Savage et al., 2016). Though over-represented compared with a systemic DLBCL population, IHC-defined non-GC subtype was relatively less frequent when compared to PCNSL, where the vast majority are ABC subtype (Rubenstein, 2017). This may be partly explained by the relatively high percentage of HGBL-DH in our cohort (23% of cases tested), which are usually GC phenotype and have CNS risk (Rosenthal & Younes, 2017). Ultimately, gene expression profiling and analysis of the genetic and functional drivers is required to optimally define this entity.

Comparing our data with reports of DLBCL relapsing in the CNS, the clinicopathological features of synDLBCL are similar to systemic DLBCL that bears high-risk features for subsequent CNS relapse with regard to CNS-IPI, extranodal disease and involvement of high-risk sites (El-Galaly et al., 2017). A comprehensive genomic analysis of the genetic and functional drivers of CNS presentations of systemic DLBCL, either synchronously or at relapse, with comparison to PCNSL has not previously been performed and is ongoing by our group (Chapuy et al., 2016; Kraan et al., 2013). This may ultimately provide a rationale for

the addition of novel agents, such as ibrutinib and lenalidomide, which have known CNS penetration and single-agent activity primarily in ABC-subtype systemic disease, which is likely to be an independent risk factor for CNS relapse of systemic DLBCL (Klanova et al., 2019; Wilson et al., 2015). Ibrutinib has also been studied in PCNSL with promising results, probably due to high number of nuclear factor-κB-activating B-cell receptor pathway mutations such as *MYD88* and *CD79B* (Lionakis et al., 2017).

Optimal therapy for synDLBCL has not been established. R-CHOP-based immunochemotherapy is standard treatment for systemic DLCBL but has poor CNS penetration. Aggressive combination chemotherapy with MATRix, with or without AuSCT or whole-brain RT, has become standard of care for fit PCNSL patients (Ferreri et al., 2016). However, it is unclear if this regimen provides equivalent systemic control to anthracycline-containing regimens. The two main approaches in our cohort were adding HDMTX to R-CHOP, and regimens developed for Burkitt lymphoma, such as R-CODOX-M/IVAC, or lymphoblastic leukaemia, such as R-HyperCVAD, which contain CNS-penetrating agents. These intensive regimens are not tolerated by elderly or poor performance status patients. Additionally, the dose of methotrexate in R-HyperCVAD is substantially lower than doses commonly used in PCNSL, though this did not appear to affect outcomes in our cohort (Table SI).

The primary determinant of prognosis in our cohort was the behaviour of the CNS disease. CNS progression or relapse occurred early, and before CNS-directed treatment was delivered in a small but significant number (7.5%) of patients who were not salvageable.

The most significant factor affecting survival was the ability to control the CNS disease, which was improved by the addition of IV cytarabine to HDMTX (CNS-intensive). Given the significant amount of overlap between those treated with CNS-intensive induction and those receiving hyperfractionated, infusional and dose-intensified induction, we cannot conclude definitively that it is the addition of cytarabine that improved outcomes. As expected, patients receiving intensive poly-drug regimens in our cohort were younger on average than their CNS-conservative counterparts. Whilst the younger age and more intensive systemic treatment of the CNS-intensive group may have contributed to the

improved survival, it is clear that CNS disease control was substantially improved by the addition of cytarabine with lower rates of CNS relapse/progression observed (25% versus 49%, p=0.03). The discrepancy in survival between CNS relapses and systemic relapses is evidence that the CNS component of the disease dictates survival. Thus, it is likely that the improvement in survival in SynDLBCL is related to combination CNS-directed chemotherapy (i.e. HDMTX plus cytarabine) rather than dose intensification or hyperfractionation of agents that do not have substantial CNS penetration. This is supported by PCNSL data, where the addition of cytarabine to HDMTX gives superior disease control in PCNSL compared to HDMTX alone (Ferreri, 2009b). Therefore, optimal CNS disease control should be a focus of efforts to improve outcomes, regardless of age. Our data suggest early and aggressive multi-agent CNS-directed treatment should be considered the first priority in patients with synDLBCL. Whether the inclusion of additional CNS-penetrating agents, such as thiotepa, adds benefit is uncertain, but it may ultimately provide better CNS control, as it does in PCNSL (Ferreri et al., 2016).

Up-front consolidation with AuSCT in high-risk DLBCL is controversial. No randomised data demonstrate OS benefit using consolidative AuSCT in first remission, even in selected high-risk populations (Greb et al., 2008; Stiff et al., 2013). In PCNSL, consolidating MATRix with AuSCT or RT is a current standard of care, yet the study evaluating this did not have a chemotherapy-alone control arm (Ferreri et al., 2017). The toxicity of AuSCT is not insubstantial, with 2/14 patient deaths from toxicity in our report. Favourable transplant outcomes have been reported in smaller series of synchronous CNS and systemic NHL (Damaj et al., 2015). Comparing transplant outcomes in non-randomised, retrospective data is difficult, as there are unknown confounders that cannot be adjusted for in patient selection. The PFS and OS reported in our transplanted patients was similar to this previous report and appeared better than the non-transplanted patients, though the results were not statistically significant when adjusted for immortal time bias. Additionally, no benefit was observed when compared only in patients responding to CNS-intensive induction who were not transplanted. This suggests that the potential benefit of up-front AuSCT was due the to selection of relatively favourable-risk chemo-sensitive patients.

The major limitation of our study is the heterogeneity of treatment and the discrepancy in ages between treatment groups, with more conservative approaches being taken in older patients. Unknown confounding factors may have influenced patient selection for aggressive versus conservative therapy. Importantly, other IPI risk factors including ECOG performance status were similar between groups. Whilst this may confound the survival data, the lower rates of CNS relapse/progression in intensively treated patients do suggest that better disease control is achieved by this approach. While our study is limited by the retrospective nature of data collection and the heterogenous treatment inherent to this rare entity, it is the largest to report clinicopathological features, therapeutic strategies prescribed and outcomes, including site and timing of relapse, in a pure DLBCL cohort, from 10 expert tertiary centres. Prospective randomised trials in this disease entity are unlikely given its rarity and the need for urgent treatment.

In conclusion, synDLBCL almost universally involves extranodal sites outside the CNS and is associated with suboptimal outcomes. The prognosis is determined by the ability to achieve early control of CNS disease, and therefore rapid delivery of combination, CNS-penetrating agents is warranted in fit patients. Combination cytarabine and HDMTX-containing induction regimens may provide superior outcomes to those incorporating only HDMTX or intrathecal therapy.

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Author contributions:

Joel Wight and Eliza Hawkes designed the research protocol

All authors contributed to data collection and a critical review of the manuscript

Joel Wight analysed the data and prepared the manuscript

References

Chapuy, B., Roemer, M. G., Stewart, C., Tan, Y., Abo, R. P., Zhang, L., Dunford, A. J., Meredith, D. M., Thorner, A. R., Jordanova, E. S., Liu, G., Feuerhake, F., Ducar, M. D., Illerhaus, G., Gusenleitner, D., Linden, E. A., Sun, H. H., Homer, H., Aono, M., Pinkus, G. S., Ligon, A. H., Ligon, K. L., Ferry, J. A., Freeman, G. J., van Hummelen, P., Golub, T. R., Getz, G., Rodig, S. J., de Jong, D., Monti, S., & Shipp, M. A. (2016). Targetable genetic features of primary testicular and primary central nervous system lymphomas. *Blood, 127*(7), 869-881.

Chihara, D., Fowler, N. H., Oki, Y., Fanale, M. A., Fayad, L. E., Westin, J. R., & Hagemeister, F. B. (2017). Dose-Adjusted EPOCH-R and Mid-Cycle High Dose Methotrexate for Patients with Systemic Lymphoma and secondary CNS Involvement. *British Journal of Haematology, 179*(5), 851-854.

Cunningham, D., Hawkes, E. A., Jack, A., Qian, W., Smith, P., Mouncey, P., Pocock, C., Ardeshna, K. M., Radford, J. A., McMillan, A., Davies, J., Turner, D., Kruger, A., Johnson, P., Gambell, J., & Linch, D. (2013). Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone in patients with newly diagnosed diffuse large B-cell non-Hodgkin lymphoma: a phase 3 comparison of dose intensification with 14-day versus 21-day cycles. *Lancet, 381*(9880), 1817-1826.

Damaj, G., Ivanoff, S., Coso, D., Ysaebert, L., Choquet, S., Houillier, C., Parcelier, A., Abarah, W., Marjanovic, Z., Gressin, R., Garidi, R., Diouf, M., Gac, A. C., Dupuis, J., Troussard, X., Morschhauseur, F., Ghesquieres, H., Soussain, C., Lysa, & Loc network, F. (2015). Concomitant systemic and central nervous system non-Hodgkin lymphoma: the role of consolidation in terms of high dose therapy and autologous stem cell transplantation. A 60-case retrospective study from LYSA and the LOC network. *Haematologica, 100*(9), 1199-1206.

El-Galaly, T. C., Villa, D., Michaelsen, T. Y., Hutchings, M., Mikhaeel, N. G., Savage, K. J., Sehn, L. H., Barrington, S., Hansen, J. W., Smith, D., Rady, K., Mylam, K. J., Larsen, T. S., Holmberg, S., Juul, M. B., Cordua, S., Clausen, M. R., Jensen, K. B., Johnsen, H. E., Seymour, J. F., Connors, J. M., de Nully Brown, P., Bogsted, M., & Cheah, C. Y. (2017). The number of extranodal sites assessed by PET/CT scan is a powerful predictor of CNS relapse for patients with diffuse large B-cell lymphoma: An international multicenter study of 1532 patients treated with chemoimmunotherapy. *European Journal of Cancer, 75*, 195-203.

Ferreri, A. J., Assanelli, A., Crocchiolo, R., & Ciceri, F. (2009a). Central nervous system dissemination in immunocompetent patients with aggressive lymphomas: incidence, risk factors and therapeutic options. *Hematological Oncology, 27*(2), 61-70.

Ferreri, A. J., Reni, M., Foppoli, M., Martelli, M., Pangalis, G. A., Frezzato, M., Cabras, M. G., Fabbri, A., Corazzelli, G., Ilariucci, F., Rossi, G., Soffietti, R., Stelitano, C., Vallisa, D., Zaja, F., Zoppegno, L., Aondio, G. M., Avvisati, G., Balzarotti, M., Brandes, A. A., Fajardo, J., Gomez, H., Guarini, A., Pinotti, G., Rigacci, L., Uhlmann, C., Picozzi, P., Vezzulli, P., Ponzoni, M., Zucca, E., Caligaris-Cappio, F., Cavalli, F., & International Extranodal Lymphoma Study Group. (2009b). High-dose cytarabine plus high-dose methotrexate versus high-dose methotrexate alone in patients with primary CNS lymphoma: a randomised phase 2 trial. *Lancet, 374*(9700), 1512-1520.

Ferreri, A. J., Donadoni, G., Cabras, M. G., Patti, C., Mian, M., Zambello, R., Tarella, C., Di Nicola, M., D'Arco, A. M., Doa, G., Bruno-Ventre, M., Assanelli, A., Foppoli, M., Citterio, G., Fanni, A., Mule, A., Caligaris-Cappio, F., & Ciceri, F. (2015). High Doses of Antimetabolites Followed by High-Dose Sequential Chemoimmunotherapy and Autologous Stem-Cell Transplantation in Patients With Systemic B-Cell Lymphoma and Secondary CNS Involvement: Final Results of a Multicenter Phase II Trial. *Journal of Clinical Oncology, 33*(33), 3903-3910.

Ferreri, A. J., Cwynarski, K., Pulczynski, E., Ponzoni, M., Deckert, M., Politi, L. S., Torri, V., Fox, C. P., Rosee, P. L., Schorb, E., Ambrosetti, A., Roth, A., Hemmaway, C., Ferrari, A., Linton, K. M., Ruda, R., Binder, M., Pukrop, T., Balzarotti, M., Fabbri, A., Johnson, P., Gorlov, J. S., Hess, G., Panse, J., Pisani, F., Tucci, A., Stilgenbauer, S., Hertenstein, B., Keller, U., Krause, S. W., Levis, A., Schmoll, H. J., Cavalli, F., Finke, J., Reni, M., Zucca, E., Illerhaus, G., & International Extranodal Lymphoma Study Group. (2016). Chemoimmunotherapy with methotrexate, cytarabine, thiotepa, and rituximab (MATRix regimen) in patients with primary CNS lymphoma: results of the first randomisation of the International Extranodal Lymphoma Study Group-32 (IELSG32) phase 2 trial. *Lancet Haematol, 3*(5), e217-227.

Ferreri, A. J. M., Cwynarski, K., Pulczynski, E., Fox, C. P., Schorb, E., La Rosee, P., Binder, M., Fabbri, A., Torri, V., Minacapelli, E., Falautano, M., Ilariucci, F., Ambrosetti, A., Roth, A., Hemmaway, C., Johnson, P., Linton, K. M., Pukrop, T., Sonderskov Gorlov, J., Balzarotti, M., Hess, G., Keller, U., Stilgenbauer, S., Panse, J., Tucci, A., Orsucci, L., Pisani, F., Levis, A., Krause, S. W., Schmoll, H. J., Hertenstein, B., Rummel, M., Smith, J., Pfreundschuh, M., Cabras, G., Angrilli, F., Ponzoni, M., Deckert, M., Politi, L. S., Finke, J., Reni, M., Cavalli, F., Zucca, E., Illerhaus, G., & International Extranodal Lymphoma Study Group. (2017). Whole-brain radiotherapy or autologous stem-cell transplantation as consolidation strategies after high-dose

methotrexate-based chemoimmunotherapy in patients with primary CNS lymphoma: results of the second randomisation of the International Extranodal Lymphoma Study Group-32 phase 2 trial. *Lancet Haematol, 4*(11), e510-e523.

Ghose, A., Elias, H. K., Guha, G., Yellu, M., Kundu, R., & Latif, T. (2015). Influence of Rituximab on Central Nervous System Relapse in Diffuse Large B-Cell Lymphoma and Role of Prophylaxis--A Systematic Review of Prospective Studies. *Clinical Lymphoma, Myeloma & Leukemia, 15*(8), 451-457.

Greb, A., Bohlius, J., Schiefer, D., Schwarzer, G., Schulz, H., & Engert, A. (2008). High-dose chemotherapy with autologous stem cell transplantation in the first line treatment of aggressive non-Hodgkin lymphoma (NHL) in adults. *Cochrane Database of Systematic Reviews*(1), CD004024.

Hans, C. P., Weisenburger, D. D., Greiner, T. C., Gascoyne, R. D., Delabie, J., Ott, G., Muller-Hermelink, H. K., Campo, E., Braziel, R. M., Jaffe, E. S., Pan, Z., Farinha, P., Smith, L. M., Falini, B., Banham, A. H., Rosenwald, A., Staudt, L. M., Connors, J. M., Armitage, J. O., & Chan, W. C. (2004). Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. *Blood, 103*(1), 275-282.

Horning, S. J., Chao, N. J., Negrin, R. S., Hoppe, R. T., Kwak, L. W., Long, G. D., Stallbaum, B., O'Connor, P., & Blume, K. G. (1991). The Stanford experience with high-dose etoposide cytoreductive regimens and autologous bone marrow transplantation in Hodgkin's disease and non-Hodgkin's lymphoma: preliminary data. *Annals of Oncology, 2 Suppl 1*, 47-50.

Klanova, M., Sehn, L. H., Bence-Bruckler, I., Cavallo, F., Jin, J., Martelli, M., Stewart, D., Vitolo, U., Zaja, F., Zhang, Q., Mattiello, F., Sellam, G., Punnoose, E. A., Szafer-Glusman, E., Bolen, C. R., Oestergaard, M. Z., Fingerle-Rowson, G. R., Nielsen, T., & Trneny, M. (2019). Integration of cell of origin into the clinical CNS International Prognostic Index improves CNS relapse prediction in DLBCL. *Blood, 133*(9), 919-926.

Kraan, W., Horlings, H. M., van Keimpema, M., Schilder-Tol, E. J., Oud, M. E., Scheepstra, C., Kluin, P. M., Kersten, M. J., Spaargaren, M., & Pals, S. T. (2013). High prevalence of oncogenic MYD88 and CD79B mutations in diffuse large B-cell lymphomas presenting at immune-privileged sites. *Blood Cancer J, 3*, e139.

Kridel, R., Telio, D., Villa, D., Sehn, L. H., Gerrie, A. S., Shenkier, T., Klasa, R., Slack, G. W., Tan, K., Gascoyne, R. D., Connors, J. M., & Savage, K. J. (2017). Diffuse large B-cell lymphoma with testicular involvement: outcome and risk of CNS relapse in the rituximab era. *British Journal of Haematology, 176*(2), 210-221.

Lionakis, M. S., Dunleavy, K., Roschewski, M., Widemann, B. C., Butman, J. A., Schmitz, R., Yang, Y., Cole, D. E., Melani, C., Higham, C. S., Desai, J. V., Ceribelli, M., Chen, L., Thomas, C. J., Little, R. F., Gea-Banacloche, J., Bhaumik, S., Stetler-Stevenson, M., Pittaluga, S., Jaffe, E. S., Heiss, J., Lucas, N., Steinberg, S. M., Staudt, L. M., & Wilson, W. H. (2017). Inhibition of B Cell Receptor Signaling by Ibrutinib in Primary CNS Lymphoma. *Cancer Cell, 31*(6), 833-843 e835.

Maciocia, P., Badat, M., Cheesman, S., D'Sa, S., Joshi, R., Lambert, J., Mohamedbhai, S., Pule, M., Linch, D., & Ardeshna, K. (2016). Treatment of diffuse large B-cell lymphoma with secondary central nervous system involvement: encouraging efficacy using CNS-penetrating R-IDARAM chemotherapy. *British Journal of Haematology, 172*(4), 545-553.

Nijland, M., Jansen, A., Doorduijn, J. K., Enting, R. H., Bromberg, J. E. C., & Kluin-Nelemans, H. C. (2017). Treatment of initial parenchymal central nervous system involvement in systemic aggressive B-cell lymphoma. *Leukemia and Lymphoma, 58*(9), 1-6.

Ollila, T. A., & Olszewski, A. J. (2018). Extranodal Diffuse Large B Cell Lymphoma: Molecular Features, Prognosis, and Risk of Central Nervous System Recurrence. *Current Treatment Options in Oncology, 19*(8), 38.

Phillips, E. H., Burton, C., Kirkwood, A., Barrans, S., Lawrie, A., Rule, S., Patmore, R., Pettengell, R., Ardeshna, K., Montoto, S., Paneesha, S., Clifton-Hadley, L., Linch, D., & McMillan, A. (2018). Favourable Outcomes with R-CODOX-M/R-IVAC Across all Subgroups of Aggressive High-Grade B-Cell Lymphoma: Pathology and Updated Survival Resulst from a Phase 1 UK NCRI/LLR Trial. Abstract s1548. Presented at the 23rd annual congress of the European Haematology Association, Stockholm. EHA Learning Center, Jun 17, 2018; 214487. https://learningcenter.ehaweb.org/eha/2018/stockholm/214487/elizabeth.phillips.favourable.outcomes.with.r-codox-m.r-ivac.across.all.html?f=listing%3D4%2Abrowseby%3D8%2Asortby%3D2%2Amedia%3D3%2Aspeaker%3D587589

Reddy, A., Zhang, J., Davis, N. S., Moffitt, A. B., Love, C. L., Waldrop, A., Leppa, S., Pasanen, A., Meriranta, L., Karjalainen-Lindsberg, M. L., Norgaard, P., Pedersen, M., Gang, A. O., Hogdall, E., Heavican, T. B., Lone, W., Iqbal, J., Qin, Q., Li, G., Kim, S. Y., Healy, J., Richards, K. L., Fedoriw, Y., Bernal-Mizrachi, L., Koff, J. L., Staton, A. D., Flowers, C. R., Paltiel, O., Goldschmidt, N., Calaminici, M., Clear, A., Gribben, J., Nguyen, E., Czader, M. B., Ondrejka, S. L., Collie, A., Hsi, E. D., Tse, E., Au-Yeung, R. K. H., Kwong, Y. L., Srivastava, G., Choi, W. W. L., Evens, A. M., Pilichowska, M., Sengar, M., Reddy, N., Li, S., Chadburn, A., Gordon, L. I., Jaffe, E. S., Levy, S., Rempel, R., Tzeng, T., Happ, L. E., Dave, T., Rajagopalan, D., Datta, J., Dunson,

D. B., & Dave, S. S. (2017). Genetic and Functional Drivers of Diffuse Large B Cell Lymphoma. *Cell, 171*(2), 481-494 e415.

Rosenthal, A., & Younes, A. (2017). High grade B-cell lymphoma with rearrangements of MYC and BCL2 and/or BCL6: Double hit and triple hit lymphomas and double expressing lymphoma. *Blood Reviews, 31*(2), 37-42.

Rubenstein, J. L. (2017). Biology of CNS lymphoma and the potential of novel agents. *Hematology: The Education Program of the American Society of Hematology, 2017*(1), 556-564.

Savage, K. J., Slack, G. W., Mottok, A., Sehn, L. H., Villa, D., Kansara, R., Kridel, R., Steidl, C., Ennishi, D., Tan, K. L., Ben-Neriah, S., Johnson, N. A., Connors, J. M., Farinha, P., Scott, D. W., & Gascoyne, R. D. (2016). Impact of dual expression of MYC and BCL2 by immunohistochemistry on the risk of CNS relapse in DLBCL. *Blood, 127*(18), 2182-2188.

Schmitz, N., Zeynalova, S., Nickelsen, M., Kansara, R., Villa, D., Sehn, L. H., Glass, B., Scott, D. W., Gascoyne, R. D., Connors, J. M., Ziepert, M., Pfreundschuh, M., Loeffler, M., & Savage, K. J. (2016). CNS International Prognostic Index: A Risk Model for CNS Relapse in Patients With Diffuse Large B-Cell Lymphoma Treated With R-CHOP. *Journal of Clinical Oncology, 34*(26), 3150-3156.

Stiff, P. J., Unger, J. M., Cook, J. R., Constine, L. S., Couban, S., Stewart, D. A., Shea, T. C., Porcu, P., Winter, J. N., Kahl, B. S., Miller, T. P., Tubbs, R. R., Marcellus, D., Friedberg, J. W., Barton, K. P., Mills, G. M., LeBlanc, M., Rimsza, L. M., Forman, S. J., & Fisher, R. I. (2013). Autologous transplantation as consolidation for aggressive non-Hodgkin's lymphoma. *New England Journal of Medicine, 369*(18), 1681-1690.

Wilson, W. H., Young, R. M., Schmitz, R., Yang, Y., Pittaluga, S., Wright, G., Lih, C. J., Williams, P. M., Shaffer, A. L., Gerecitano, J., de Vos, S., Goy, A., Kenkre, V. P., Barr, P. M., Blum, K. A., Shustov, A., Advani, R., Fowler, N. H., Vose, J. M., Elstrom, R. L., Habermann, T. M., Barrientos, J. C., McGreivy, J., Fardis, M., Chang, B. Y., Clow, F., Munneke, B., Moussa, D., Beaupre, D. M., & Staudt, L. M. (2015). Targeting B cell receptor signaling with ibrutinib in diffuse large B cell lymphoma. *Nature Medicine, 21*(8), 922-926.

Yoo, K. H., Lee, J. Y., Lim, S. H., Ko, Y. H., Kim, S. J., & Kim, W. S. (2015). Pilot trial of systemic methotrexate plus R-CHOP regimen with intrathecal methotrexate for simultaneous central nervous system and systemic diffuse large B cell lymphoma. *Acta Haematologica, 133*(2), 179-182.

Zhou, Z., Sehn, L. H., Rademaker, A. W., Gordon, L. I., Lacasce, A. S., Crosby-Thompson, A., Vanderplas, A., Zelenetz, A. D., Abel, G. A., Rodriguez, M. A., Nademanee, A., Kaminski, M. S., Czuczman, M. S., Millenson, M., Niland, J., Gascoyne, R. D., Connors, J. M., Friedberg, J. W.,

& Winter, J. N. (2014). An enhanced International Prognostic Index (NCCN-IPI) for patients with diffuse large B-cell lymphoma treated in the rituximab era. *Blood, 123*(6), 837-842.

Table I. Baseline characteristics

Variable	**All (n=80)**	**CNS-intensive (n=38)**	**CNS-conservative (n=42)**	**P value**
Median age (years) (range)	64 (18-87)	54 (18-75)	69 (45-86)	**<0.001**
Male gender	54 (68%)	26 (68%)	28 (67%)	1
ECOG PS ≥2	44 (55%)	21 (55%)	23 (55%)	1
NCCN IPI ≥4	54 (68%)	20 (53%)	34 (81%)	**0.009**
High-risk CNS IPI	56 (70%)	21 (55%)	34 (81%)	**0.01**
Non-CNS extranodal disease	77 (96%)	38 (100%)	39 (93%)	0.24
Median extranodal sites outside CNS (range)	2 (0->10)	2 (1->10)	2 (0->7)	0.91
Leptomeningeal disease only	39 (49%)	25 (66%)	14 (33%)	**<0.001**
Direct invasion only	16 (20%)	5 (13%)	11 (26%)	0.17
Concordant bone/BM involvement	27 (34%)	14 (37%)	13 (31%)	0.64
Adrenal gland involvement	13 (16%)	5 (13%)	8 (19%)	0.55
Renal involvement	13 (16%)	8 (21%)	5 (12%)	0.36
Sinus involvement	12 (15%)	7 (18%)	5 (12%)	0.53
Testicular involvement	10 (19% of males)	5 (19% of males)	5 (19% of males)	1
Uterine involvement	3 (12% of	1 (9% of females)	2 (14% of	1

	females)		females)	

BM = bone marrow; CNS = central nervous system; ECOG PS= Eastern Cooperative Oncology Group performance status; IPI = International Prognostic Index; NCCN = National Comprehensive Cancer Network.

Table II. Treatment and responses by group

Treatment and outcome	**CNS-intensive (N, %)**	**CNS-conservative (N, %)**	**P value**
Systemic therapy	R-HyperCVAD = 25 (66%) R-CODOX-M/IVAC = 9 (24%) R-CHOP = 2 (5%) R-DHAC = 1 (3%) MATRix = 1 (3%)	R-CHOP = 35 (83%) R-CODOX-M = 2 (5%) DA-EPOCH-R = 2 (5%) R-Bendamustine = 1 (2%) R-MPV = 1 (2%) R-HDMTX = 1 (2%)	N/A
CNS-directed IV therapy	IV MTX + Ara-C = 37 (97%) MATRix = 1 (3%)	HDMTX = 25 (60%)	**<0.001** (for any IV therapy)
Intrathecal chemotherapy	37 (97%)	25 (60%)	**<0.001**
CNS-directed radiation therapy	12 (32%)	8 (19%)	0.21
AuSCT in 1st response	13 (34%)	0 (0%)	**<0.001**
Median cumulative dose of IV MTX (g/m^2)	6 (1-14)	3.15 (0-64)$^{€}$ 10.5 (3-64)$^{£}$	0.11$^{€}$ **0.027**
IV CNS-directed 1st cycle	28 (74%)	10 (24%)	**<0.001**
Treatment-related mortality$^{\#}$	5 (13%)	5 (12%)	1
Dose reductions required	7 (18%)	20 (48%)	**0.009**

Early cessation of chemotherapy[¥]	7 (18%)	22 (52%)	**0.002**
Complete responses at EOI	25/36* (69%)	20/38* (51%)	0.16
Primary refractory	7/36* (19%)	15/38* (38%)	0.07
CNS progression or relapse	9/36* (25%)	19/38* (49%)	**0.03**

*Denominator reduced due to early induction deaths prior to first disease assessment

[#]Includes deaths in salvage/consolidation

¥ Includes cessation for toxicity and futility

€ In all CNS-conservative patients

£ In patients receiving HDMTX

AraC = cytarabine (variable doses); AuSCT; autologous stem cell transplantation; BR = bendamustine, rituximab; CNS = central nervous system; DA-EPOCH-R = Dose-adjusted etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin, rituximab; EOI = end of induction; HDMTX: high-dose methotrexate; IV = intravenous; MATRix = methotrexate (3.5 g/m^2), cytarabine (2 g/m^2 BD days 2 and 3), thiotepa (30 mg/m^2); MTX = methotrexate (variable doses); N/A: not available; R-CHOP = Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; R-CODOX-M = rituximab, hyperfractionated cyclophosphamide, vincristine, doxorubicin, methotrexate (3 g/m^2); R-DHAC = rituximab, dexamethasone, cytarabine (2 g/m^2 BD days 1 and 2); R-HyperCVAD = rituximab, hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone alternating with IV methotrexate (1 g/m^2) and cytarabine (3 g/m^2 BD days 2 and 3); R-IVAC = rituximab, ifosfamide, etoposide, cytarabine (2 g/m^2 BD days 1 and 2); R-MPV = rituximab, methotrexate (3.5 g/m^2), procarbazine, vincristine.

Table III. Analysis of factors predicting survival outcomes.

Variable	**PFS HR (95% CI)**	**p value**	**OS HR**	**p value**
Univariate analysis				
Age >60 years	**1.93 (1.04-3.57)**	**0.037**	**2.11 (1.11-4.01)**	**0.022**
ECOG PS ≥2	1.74 (0.95-3.19)	0.07	**2.05 (1.09-3.87)**	**0.027**

NCCN IPI >4	1.33 (0.75-2.36)	0.33	1.37 (0.75-2.48)	0.30
High-risk CNS-IPI	1.58 (0.8-3.1)	0.19	1.42 (0.72-2.81)	0.31
DPE DLBCL	2.03 (0.89-4.65)	0.09	2.05 (0.85-4.96)	0.11
CNS-intensive induction	**0.45 (0.25-0.81)**	**0.01**	**0.53 (0.29-0.97)**	**0.04**
IV HDMTX monotherapy	1.5 (0.81-2.75)	0.20	1.1 (0.58-2.08)	0.77
CNS RT	0.81 (0.43-1.54)	0.53	0.95 (0.5-1.83)	0.89
AuSCT in 1st response	**0.30 (0.11-0.84)**	**0.022**	**0.34 (0.12-0.95)**	**0.04**
Hyperfractionated or infusional induction*	**0.55 (0.31-0.99)**	**0.045**	0.66 (0.36-1.29)	0.185
Leptomeningeal only	1.02 (0.58-1.79)	0.95	1.00 (0.56-1.8)	0.99
Direct invasion	0.68 (0.32-1.45)	0.32	0.78 (0.36-1.69)	0.53
IV CNS Rx 1st cycle	0.65 (0.36-1.16)	0.14	0.84 (0.47-1.52)	0.57
Multivariate analysis				
Age >60 years	1.35 (0.66-2.76)	0.47	1.68 (0.8-3.5)	0.17
CNS-intensive induction	0.43 (0.22-1.07)	0.07	0.57 (0.26-1.27)	0.17
CNS radiotherapy	0.89 (0.49-1.79)	0.75	0.99 (0.5-1.99)	0.99
Any IV CNS-directed chemotherapy	0.86 (0.39-1.86)	0.71	0.7 (0.32-1.56)	0.39

*This included regimens HyperCVAD, CODOX-M, CODOX-M/IVAC, DA-EPOCH-R, DHAC, MATRix. It was excluded from multivariable analysis due to significant cross-over between this group and "CNS-intensive" induction, such that they could not be considered truly independent of one another; thus, the most significant of the two was used in the multivariable analysis

AraC = cytarabine (variable doses); AuSCT = autologous stem cell transplantation; CNS = central nervous system; CODOX-M = hyperfractionated cyclophosphamide, vincristine, doxorubicin, methotrexate; DA-EPOCH-R = Dose-adjusted etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin, rituximab; DHAC = dexamethasone, cytarabine; DPE DLBCL = dual protein expression of MYC and BCL2; Complete data available for 42 patients (53%); ECOG PS= Eastern Cooperative Oncology Group performance status; HDMTX = high dose

methotrexate (variable doses); HR = hazard ratio; HyperCVAD = hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone alternating with IV methotrexate and cytarabine; IPI = International Prognostic Index; IV = intravenous; IVAC = ifosfamide, etoposide, cytarabine; MATRix = methotrexate, cytarabine, thiotepa; NCCN = National Comprehensive Cancer Network; OS = overall survival; PFS = progression-free survival; RT = radiotherapy; Rx = treatment

Figure legends

Figure 1.

A. Progression-free survival according to treatment with CNS-intensive (IV HDMTX plus cytarabine) versus CNS-conservative. B. Overall survival according to treatment with CNS-intensive versus CNS-conservative. CNS = central nervous system; HDMTX = high dose methotrexate (variable doses); IV = intravenous; OS = overall survival; PFS = progression-free survival.

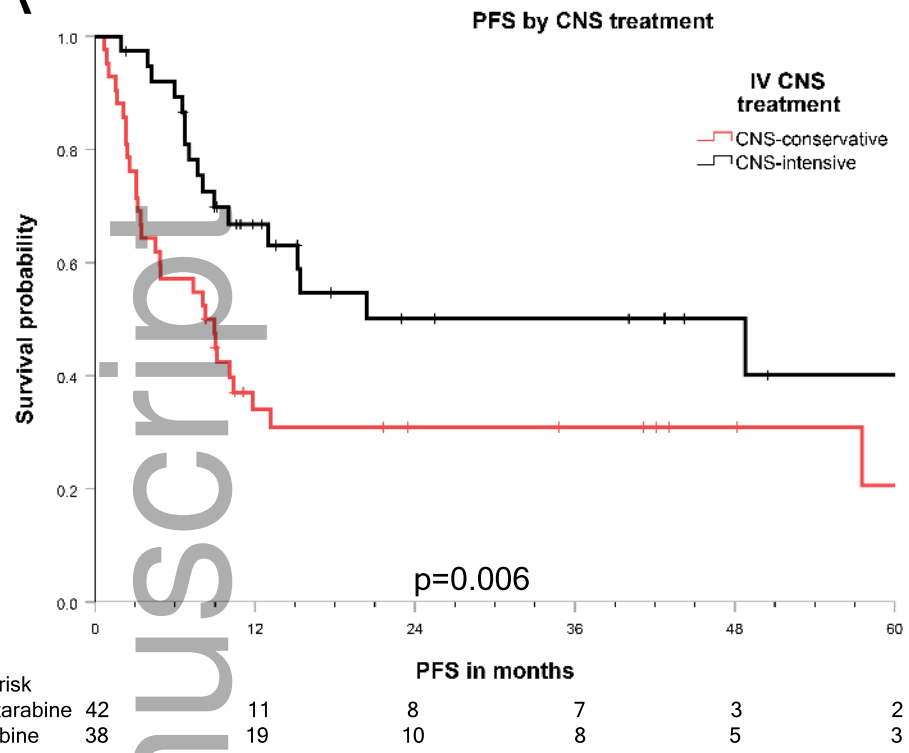
Figure 2.

A. Progression-free survival according to receipt of consolidative AuSCT in first response for all patients. B. Overall survival according to receipt of consolidative AuSCT in first response for all patients. C. Progression-free survival according to receipt of AuSCT in patients responding to CNS-intensive induction. D. Overall survival according to receipt of in patients responding to CNS-intensive induction. AuSCT = autologous stem cell transplantation; CNS = central nervous system; OS = overall survival; PFS = progression-free survival.

Figure 3.

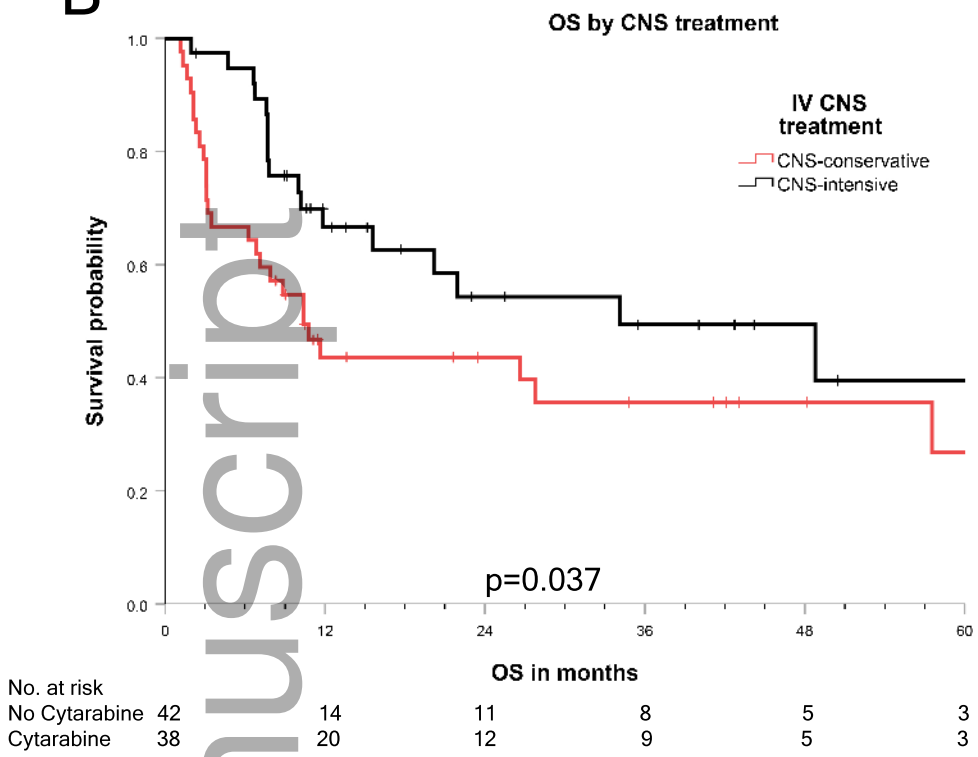
A. Cumulative incidence of CNS relapse/progression. B. Overall survival by site of relapse or progression: CNS, non-CNS and progression-free. CNS = central nervous system; OS = overall survival.

A



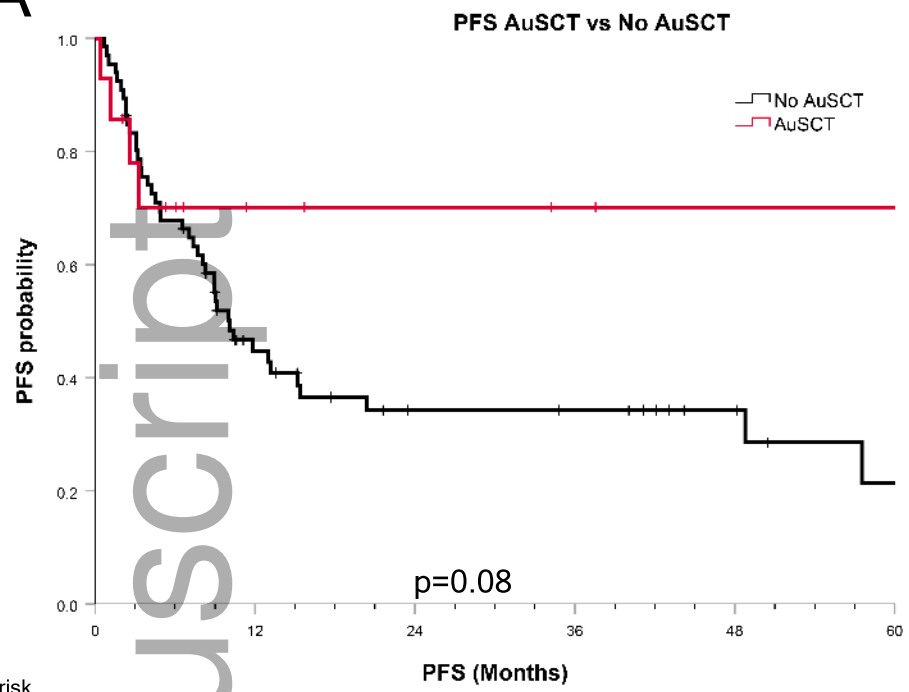
No. at risk						
No Cytarabine	42	11	8	7	3	2
Cytarabine	38	19	10	8	5	3

B



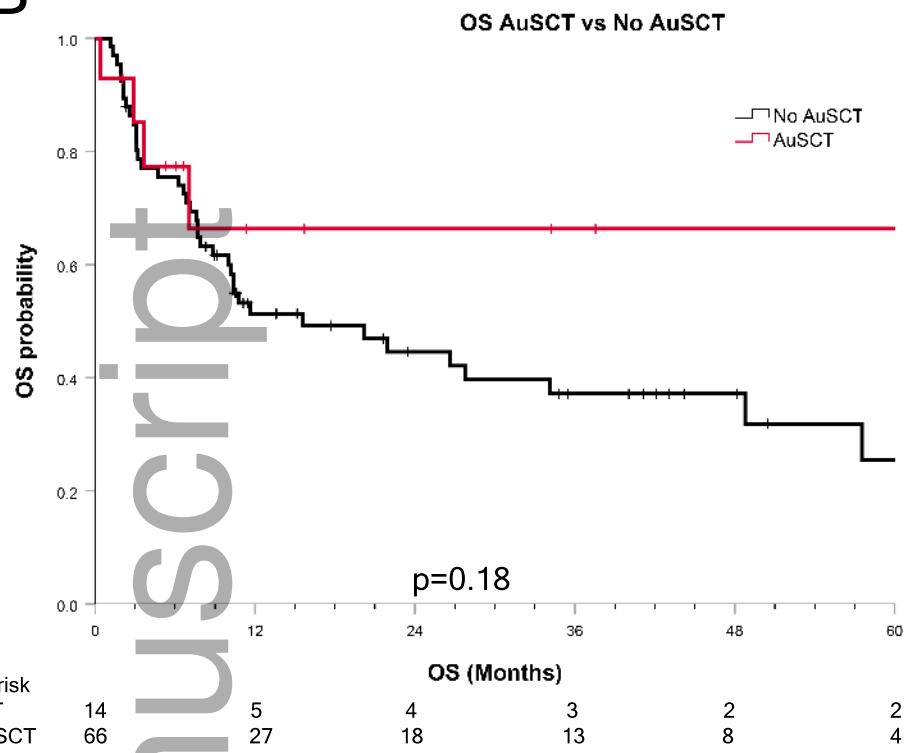
No. at risk						
No Cytarabine	42	14	11	8	5	3
Cytarabine	38	20	12	9	5	3

A



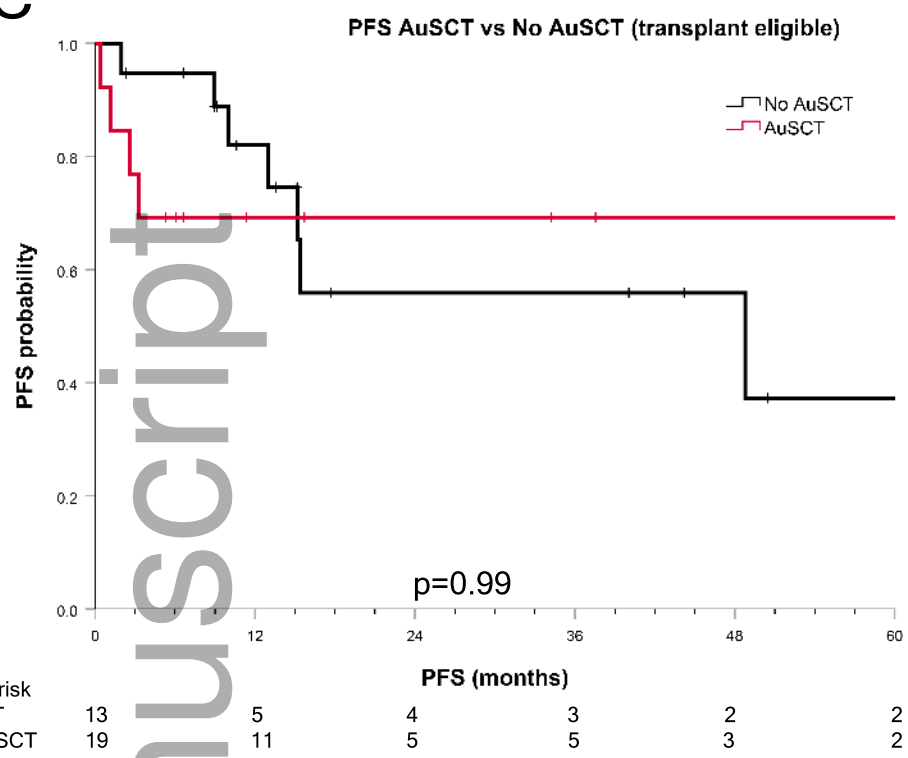
No. at risk						
AuSCT	14	5	4	3	2	2
No AuSCT	66	23	13	12	7	3

B



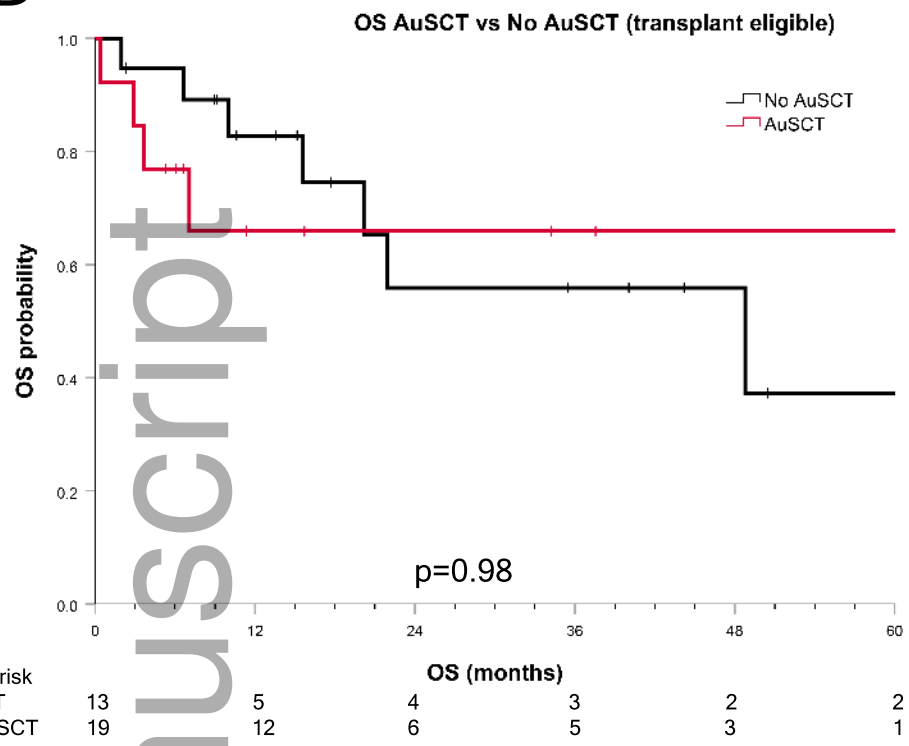
No. at risk						
AuSCT	14	5	4	3	2	2
No AuSCT	66	27	18	13	8	4

C



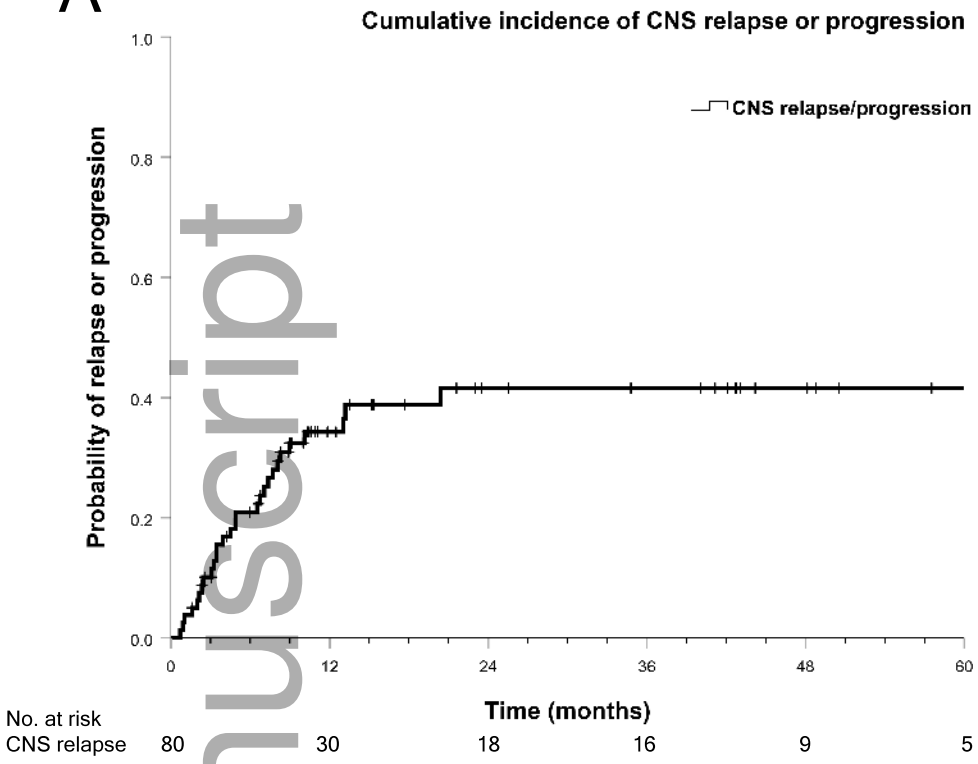
No. at risk						
AuSCT	13	5	4	3	2	2
No AuSCT	19	11	5	5	3	2

D

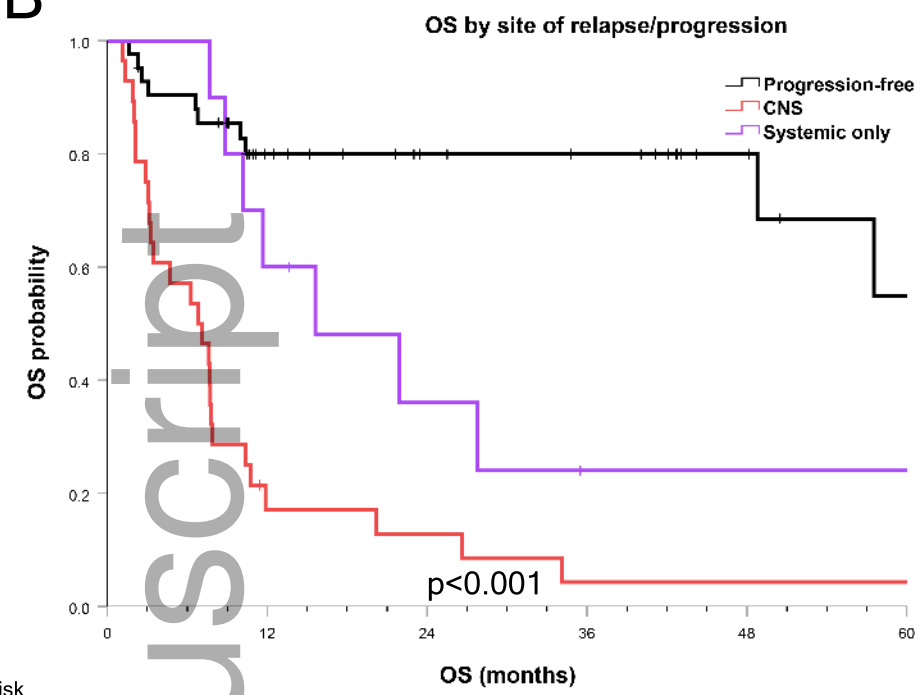


No. at risk						
AuSCT	13	5	4	3	2	2
No AuSCT	19	12	6	5	3	1

A



B



No. at risk						
Progression-free	42	24	17	15	8	4
CNS	28	4	1	1	1	1
Systemic only	10	6	3	1	1	1