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Excellent outcome of children/adolescents with primary mediastinal large B-cell lymphoma treated with FAB/LMB-based chemotherapy regimen with rituximab

by Marie Emilie Dourthe, Anne Auperin, Charlotte Rigaud, Melissa Barbati, Jacinthe Bonneau, Nimrod Buchbinder, Marie-Laure Couec, Peggy Dartigues, Stéphane Ducassou, Nathalie Garnier, Stéphanie Haouy, Bénédicte Jonca, Anne Jourdain, Amaury Leruste, Thierry Molina, Françoise Montravers, Marlène Pasquet, Aurélie Phulpin, Marilyne Poirée, Mathieu Simonin, Alexandra Spiegel, Arnauld Verschuur, Thierry Leblanc, Judith Landman-Parker, Catherine Patte, and Véronique Minard-Colin

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Primary Mediastinal (thymic) large B-cell Lymphoma (PMLBL) is a distinct pathogenetic subtype of mature B-cell neoplasms related to nodular sclerosis Hodgkin lymphoma[1]. It is a rare entity representing 2 to 4% of adult and pediatric non-Hodgkin's Lymphoma[2,3].

Treatment strategies originally designed for Burkitt lymphoma have been successfully used for children with diffuse large B-cell lymphoma (DLBCL)[4,5] but patients with PMLBL exhibited a more aggressive disease and a specific approach was needed[6,7]. In fact, the first prospective international Phase 2 study of DA-EPOCH-R regimen[8] in children and adolescents failed to replicate the exceptional survival outcomes reported in some adults studies [9,10]. Specifically, 12 out of the 46 enrolled patients experienced relapse with 3 parenchymal CNS events. We previously reported the excellent results, in a small cohort of 21 patients of the French-American-British/Lymphomes malins B (FAB/LMB) -based chemotherapy combined with rituximab. Here we expand our analysis to include a second cohort of 23 patients treated after the DA-EPOCH phase 2 reaching a total of 44 patients treated with the FAB/LMB-based chemotherapy and rituximab for PMLBL between january 2008 and december 2021.

All patients under 21years old with a confirmed diagnosis of PMLBL treated at Société Française des Cancers de l'Enfant et de l'Adolescent (SFCE) centers were included if they underwent FAB/LMB- based chemotherapy with rituximab (R). All 44 patients are registered in *The French National Registry of Childhood Cancers* (RNCE) and received information notice. This retrospective analysis has been approved by the local IRB (CLEA-2024-n°374).

The planned PMLBL treatment regimen consisted of 6 courses of Rituximab combined with chemotherapy: 2 courses of R-COPADM Group B (cyclophosphamide, vincristine,

prednisone, Adriamycin, high-dose methotrexate 3 g/m², 1 intrathecal) followed by 2 courses of R-CYVE Group C (with high-dose cytarabine, and etoposide) and 2 courses of maintenance therapy with rituximab without radiotherapy[11] (**Table 1**).

Between January 2008 and December 2021, a total of 44 patients were identified with newly diagnosed B-NHL confirmed as PMLBL either through central review in the LMB2001 prospective study (n=21) or by assessment from a referent pathologist of the French Lymphoma Study Association (LYSA) (n=23). Table 2 summarizes the baseline characteristics of patients and disease responses. The median age at diagnosis was 15.9 years (interquartile range15.0; 16.9). Twenty-seven patients were females (61%). Thirty-five patients (80%) presented with large mediastinal masses of 10 cm or more, while 18 patients (41%) exhibited elevated LDH levels (> twice the institutional upper limit of the adult normal value). One patient showed bone marrow involvement and 2 patients were considered to have CNS disease (one experienced facial paresthesia with normal MRI but CSF examination was not feasible; the other had an asymptomatic epidural mass). Overall, no patient had positive CSF. The Ann Arbor classification concluded: stage II disease in 20 patients (45.5%), stage III in 4 patients (9%), and stage IV in 20 patients (45.5%).

All patients underwent FAB/LMB-based chemotherapy, with 3 patients treated in Group B, 13 in Group C1 (supplemental Table 1) and 28 in group B/C named "FAB/LMB-based PMLBL regimen" with 2 courses of R-COPADM Group B followed by 2 courses of R-CYVE Group C and 2 courses of maintenance therapy (Table 1). Each patient received 6 doses of rituximab in combination with the chemotherapy regimen.

One patient experienced disease progression shortly after the first cycle of R-COPADM. Among the remaining 43 patients, 9 patients achieved complete response (CR) by the end of treatment while 34 (79.1%) still exhibited residual mass on imaging. Of these, 18 out of 34

underwent biopsies revealing only 1 case with viable tumor cells while histological examination indicated complete necrosis in the other 17 patients. According to the International Pediatric Non-Hodgkin Lymphoma Response Criteria (IPNHLRC), treatment responses were distributed as followed: 9 CR, 17 CRb, 10 CRu, 6 PR, 1 NR, 1 PD (**Table 2**) [12]. Ultimately, 42 patients (95%) were deemed to have achieved complete remission (CR) by the end of first line treatment with 9 showing CR on imaging, 17 with complete necrosis on histology, and 16 presenting residual masses not explored).

Thirty-six patients (82%) underwent 18F-FDG PET/CT (combined with morphological assessment via CT scan for all) after a median of 4 chemotherapy courses (range 3 to 6). Among them 14 (40%) were deemed positive according to current Cheson criteria (n=8) or Deauville score > 3 (n=6) (**supplementary Figure 1**). Of these 14 patients, 9 underwent biopsy with only 1 showing histologically positive residual disease. None of these patients experienced further progression after a follow-up period of at least 1.4 years from the initial diagnosis (predictive positive value=1/14= 7% (exact 95%CI 2%-34%). Among the 22 patients with negative 18F-FDG PET/CT results according to Cheson criteria (n=12) or with a Deauville score <4 (n=10), none experienced treatment failure (predictive negative value=100% (exact 95%CI 85%-100%)) (**supplementary Figure 1**).

The median follow-up was 4.3 years (interquartile range 2.7-6.5). A total of 3 events were observed all of which local failures (**supplementary Table 2**): One early progression during treatment (after R-COPADM1), one insufficient response with viable cells in the residual mass (after R-CYVE2), and one relapse. The patient who experienced progression after R-COPADM1 achieved CR after 3 courses of R-ICE. The patient with viable cells in the residual mass had progression after R-ICE (2 courses) but achieved CR after receiving a combination of Brentuximab-Nivolumab (4 cycles). The remaining patient, who relapsed at 6.6 months after diagnosis, had a residual mass at the end of therapy but necrosis was

observed upon histological analysis of a large biopsy. A diagnosis of high-grade B-cell lymphoma NOS was made at relapse and treatment involved R-ICE combined with ibrutinib in the SPARKLE trial [13]. All 3 patients achieved CR and underwent consolidation with high-dose BEAM chemotherapy (carmustine, etoposide, cytarabine, and melphalan) and autologous HSCT followed by local radiation therapy. They are currently alive without disease 2.7, 5 and 11 years after disease failure. The 5-year EFS and OS for the entire cohort were 93.2% (95%CI 81.8%-97.7%) and 100%, respectively (**Figure 1**).

This analysis, conducted on a larger cohort of patients with PMLBL treated in France with FAB-LMB based chemotherapy combined with rituximab confirmed the outstanding outcomes previously described. The good results of the combination immunotherapy chemotherapy are in stark contrast to those of chemotherapy alone [6,11]. These favorable outcomes stand also in contrast to the results observed with DA-EPOCH-R in 46 children and adolescents enrolled in the international phase 2 Inter B-NHL-ritux 2010 study[8]. Despite similar patients characteristics between the two studies, the phase 2 study recorded a significantly higher number of events–including 12 disease-related events with 3 (6.5%) parenchymal central nervous system relapses. This highlights the need to refine risk factors for CNS relapse, and identify patients who may benefit from CNS prophylaxis [8,14]. The phase 2 4-year EFS and OS are 69.6% (95%CI 55.2%-80.9%) and 84.8% (95%CI 71.8%-92.4%), respectively.

The BFM NHL group presented their multicentric experience spanning from 2004 to 2019: 67 patients were treated with modified DA-EPOCH-R (including the addition of at least one intrathecal triple therapy and capping the cumulative doxorubicin dose at 360mg/m2), 29 received intensified chemotherapy B-NHL BMF04 [15]. Among patients treated with DA-EPOCH-R, the 5-year EFS and OS were 84% (95%CI, 72%–91%) and 90% (CI, 79%–95%), respectively. Despite incorporation of triple intrathecal, 4 out of 11 patients experiencing

progression or relapse, presented with parenchymal CNS disease underscoring importance of CNS-directed therapy in PMLBL. Since 2008 the French recommendation described as FAB/LMB-based PMLBL regimen with rituximab, included two intrathecal therapies alongside HD MTX and high-dose cytarabine (AraC). This strategy has demonstrated its good CNS control and efficacy, with only 3 local failures and a 5-year overall survival rate of 100%. The limited number of events precludes definitive conclusions regarding the role of the different chemotherapy arms. Moreover, while the acute toxicity of FAB/LMB chemotherapy is significant [16], overall treatment burden remains manageable, with cumulative dose of cyclophosphamide at 5300mg/m^2 and adriamycin at 240mg/m^2. Additionally, only 3 patients received local radiation therapy after relapse. Regarding novel agents for PMLBL, while phase 2 results of Brentuximab-Vedotin (BV) were disappointing with an overall response rate of only 13.3%, targeted therapy such as BV combined with PD1 inhibitors could offer opportunities as a second line therapy [17–20]. One patient in our cohort benefited from this combination.

In first-line treatment outcome achieved with FAB/LMB-based PMLBL intensive regimen with rituximab is excellent with an overall survival rate of 100%. Nevertheless, new prospective studies are necessary to explore the potential for de-escalating frontline treatment through the addition of upfront immunotherapy such as anti PD1 monoclonal antibody. This will also require to identify sensitive clinical and biological predictors to allow safe de-escalation and define risk factors for CNS relapse. Conversely, for those rare patients resistant to this initial line of treatment, novel therapy such as anti PD1 monoclonal antibody or other targeted therapies based on identified molecular alterations in tumor cells could be proven beneficial in combination with chemotherapy. Moving forward, future clinical trials should ideally incorporate clinical, biological or imaging prognostic factors identified through collaborative inter groups studies.

References

1. Alaggio R, Amador C, Anagnostopoulos I, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. Leukemia. 2022;36(7):1720-1748.

2. Burkhardt B, Zimmermann M, Oschlies I, et al. The impact of age and gender on biology, clinical features and treatment outcome of non-Hodgkin lymphoma in childhood and adolescence. Br J Haematol. 2005;131(1):39-49.

3. Martelli M, Di Rocco A, Russo E, Perrone S, Foà R. Primary mediastinal lymphoma: diagnosis and treatment options. Expert Rev Hematol. 2015;8(2):173-186.

4. Patte C, Auperin A, Michon J, et al. The Société Française d'Oncologie Pédiatrique LMB89 protocol: highly effective multiagent chemotherapy tailored to the tumor burden and initial response in 561 unselected children with B-cell lymphomas and L3 leukemia. Blood. 2001;97(11):3370-3379.

5. Patte C, Auperin A, Gerrard M, et al. Results of the randomized international FAB/LMB96 trial for intermediate risk B-cell non-Hodgkin lymphoma in children and adolescents: it is possible to reduce treatment for the early responding patients. Blood. 2007;109(7):2773-2780.

6. Gerrard M, Waxman IM, Sposto R, et al. Outcome and pathologic classification of children and adolescents with mediastinal large B-cell lymphoma treated with FAB/LMB96 mature B-NHL therapy. Blood. 2013;121(2):278-285.

7. Seidemann K, Tiemann M, Lauterbach I, et al. Primary mediastinal large B-cell lymphoma with sclerosis in pediatric and adolescent patients: treatment and results from three therapeutic studies of the Berlin-Frankfurt-Münster Group. J Clin Oncol. 2003;21(9):1782-1789.

8. Burke GAA, Minard-Colin V, Aupérin A, et al. Dose-Adjusted Etoposide, Doxorubicin, and Cyclophosphamide With Vincristine and Prednisone Plus Rituximab Therapy in Children and Adolescents With Primary Mediastinal B-Cell Lymphoma: A Multicenter Phase II Trial. J Clin Oncol. 2021;39(33):3716-3724.

9. Dunleavy K, Pittaluga S, Maeda LS, et al. Dose-adjusted EPOCH-rituximab therapy in primary mediastinal B-cell lymphoma. N Engl J Med. 2013;368(15):1408-1416.

10. Giulino-Roth L, O'Donohue T, Chen Z, et al. Outcomes of adults and children with primary mediastinal B-cell lymphoma treated with dose-adjusted EPOCH-R. Br J Haematol. 2017;179(5):739-747.

11. Dourthe ME, Phulpin A, Auperin A, et al. Rituximab in addition to LMB-based chemotherapy regimen in children and adolescents with primary mediastinal large B-cell lymphoma: results of the French LMB2001 prospective study. Haematologica. 2022;107(9):2173-2182.

12. Sandlund JT, Guillerman RP, Perkins SL, et al. International Pediatric Non-Hodgkin Lymphoma Response Criteria. J Clin Oncol. 2015;33(18):2106-2111.

13. Burke GAA, Vinti L, Kabickova E, et al. Ibrutinib plus RICE or RVICI for relapsed/refractory mature B-cell non-Hodgkin lymphoma in children and young adults: SPARKLE trial. Blood Adv. 2023;7(4):602-610.

14. Gullickson C, Kersun L, Reilly A, Seif A, Chehab L. Isolated central nervous system relapse in two adolescents with primary mediastinal large B-cell lymphoma after treatment with R-DA-EPOCH. Pediatr Blood Cancer. 2024;71(8):e31065.

15. Knörr F, Zimmermann M, Attarbaschi A, et al. Dose-adjusted EPOCH-rituximab or intensified B-NHL therapy for pediatric primary mediastinal large B-cell lymphoma. Haematologica. 2021;106(12):3232-3235.

16. Minard-Colin V, Aupérin A, Pillon M, et al. Rituximab for High-Risk, Mature B-Cell Non-Hodgkin's Lymphoma in Children. N Engl J Med. 2020;382(23):2207-2219.

17. Zinzani PL, Santoro A, Gritti G, et al. Nivolumab Combined With Brentuximab Vedotin for Relapsed/Refractory Primary Mediastinal Large B-Cell Lymphoma: Efficacy and Safety From the Phase II CheckMate 436 Study. J Clin Oncol. 2019;37(33):3081-3089.

18. Armand P, Rodig S, Melnichenko V, et al. Pembrolizumab in Relapsed or Refractory Primary Mediastinal Large B-Cell Lymphoma. J Clin Oncol. 2019;37(34):3291-3299.

19. Zinzani PL, Pellegrini C, Chiappella A, et al. Brentuximab vedotin in relapsed primary mediastinal large B-cell lymphoma: results from a phase 2 clinical trial. Blood. 2017;129(16):2328-2330.

20. Zinzani PL, Santoro A, Gritti G, et al. Nivolumab combined with brentuximab vedotin for R/R primary mediastinal large B-cell lymphoma: a 3-year follow-up. Blood Adv. 2023;7(18):5272-5280.

Table 1. FAB/LMB-based PMLBL regimen

	Prephase COP*	Courses 1and 2 COPADM	Courses 3 and 4 CYVE	Courses 5 and 6 Seq3	Cumulative doses
Chemotherapy	Cy 300mg/m² D1 VCR 2mg/m² D1 IT[&] (MTX HSHC) D1 pred 60mg/m²/D D1-7	VCR 2mg/m² D1 MTX 3g/m² D1 Cy 250mg/m²/12h D2-4 adriamycin 60mg/m² D2 IT (MTX HSHC) D2 pred 60mg/m² D1-5	cytarabine 50mg/m² IVC 12h D1-5 cytarabine 3g/m² D2-5 VP16 200mg/m² D2-5	VCR 2mg/m² D1 Cy 500mg/m²/d D1-2 adriamycin 60mg/m² D1 pred 60mg/m² D1-5	cyclophosphamide= 5300mg/m² adriamycin= 240mg/m² IT= 2 to 3
Rituximab		375mg/m^2 D1	375mg/m^2 D1	375mg/m^2 D1	6 doses of 375mg/m^2

Abbreviations: Cy= cyclophosphamide, IT= intrathecal, MTX= methotrexate, pred= prednisone, VCR= vincristine.

*A COP prephase is not mandatory but may be required one week prior to commencement of course 1 for patients requiring urgent treatment whilst awaiting histological confirmation. [&]IT is optional during COP prephase.

Table 2. Baseline characteristics of the patients and disease therapy response

	All patients n=44
Clinical and biological characteristics	
Female	27 (61%)
Age, median (interquartile range) [range]	15.9 (15.0-16.9) [10.1-18.1]
10-15 years	11 (25%)
15-21 years	33 (75%)
Ann Arbor stage	
II	20 (45.5%)
III	4 (9%)
IV	20 (45.5%)
Mediastinal tumor >10cm	35 (80%)
Sites of involvement	
Sub-diaphragmatic	16 (36%)
Bone marrow involvement	1 (2%)
Central nervous system*	2 (5%)
LDH>2xupper limit of normal range**	18 (41%)
Initial therapeutic group	
Group B	**3 (7%)**
Group B/C or C	**41 (93%)**
Tumoral response	
CR	9 (21%)
CRb	17 (39%)
CRu	10 (23%)
PR	6 (13%)
NR	1 (2%)
Progressive Disease	1 (2%)

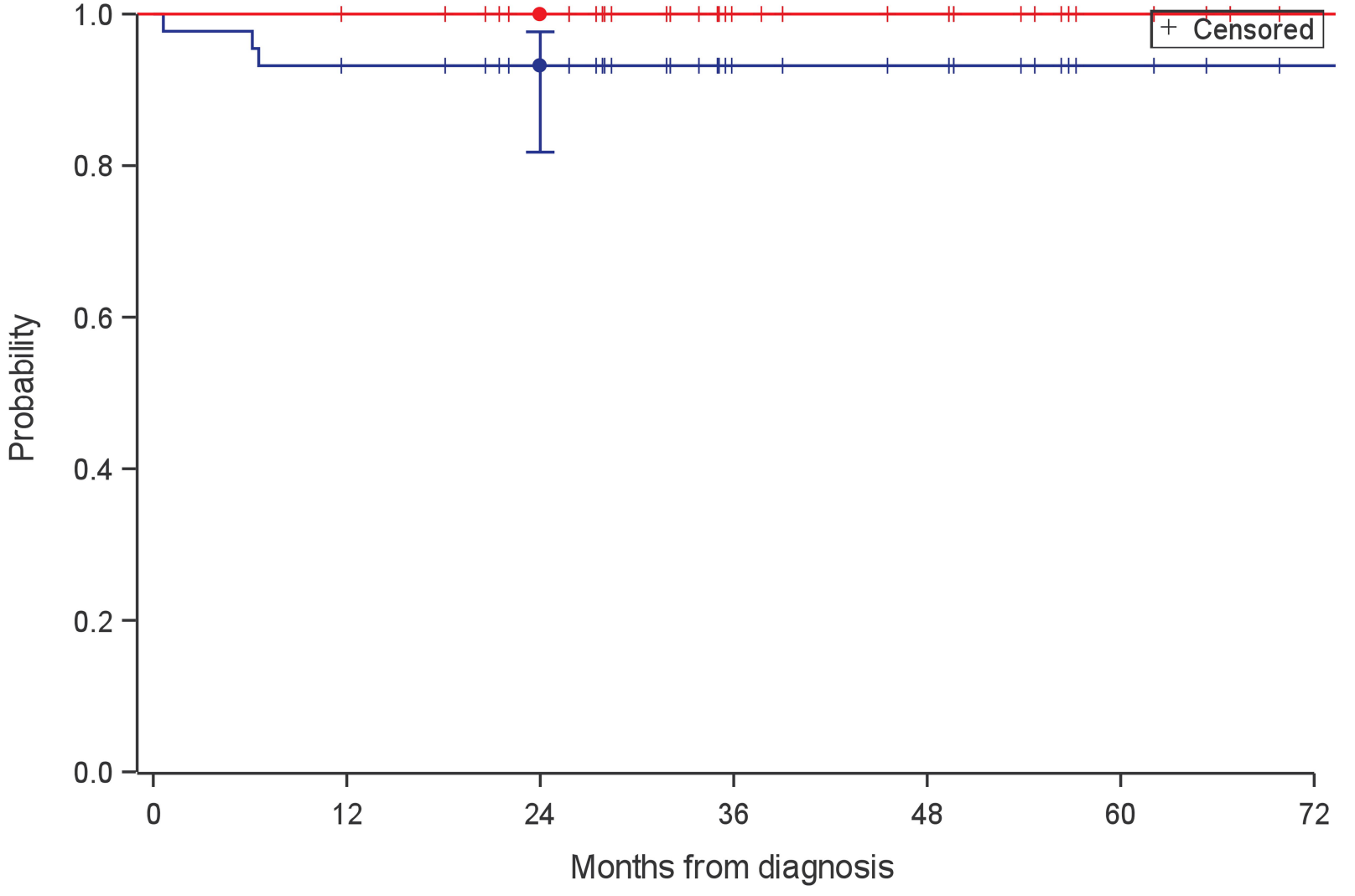
* CNS involvement consisted in: facial paresthesia with normal MRI but LCR not could be explored=1; asymptomatic epidural mass=1
** Missing data for two patients

Abbreviations: CR, complete response, CRb, complete response biopsy negative ; CRu, complete response unconfirmed ; PR, partial response, NR, non-response according to IPNHLRC.

Figure legends

Figure 1: Kaplan-Meier estimates of event-free survival and overall survival of the entire cohort

Abbreviations: EFS, Event-free-survival; OS, overall survival



Number at risk (censored)

EFS	44(0)	40(1)	36(5)	24(17)	22(19)	15(26)	12(29)
OS	44(0)	43(1)	39(5)	27(17)	24(20)	17(27)	13(31)

Supplementary results

Supplementary Table 1. Outline of the treatment for the 16 patients treated according to LMB 2001 protocol with rituximab

	Nb patients	Prephase	Course 1	Course 2	Course 3	Course 4	Course 5	Course 6	Course 7	Course 8	Cumulative dose
B	**3**	**COP*** Cy 300mg/m² D1 VCR 2mg/m² D1 IT (MTX HSHC) D1 pred 60mg/m²/D D1-7	**COPADM** VCR 2mg/m² D1 MTX 3g/m² D1 Cy 250mg/m²/12h D2-4 Adriamycin 60mg/m² D2 IT (MTX HSHC) D2;6 pred 60mg/m² D1-5	**COPADM** VCR 2mg/m² D1 MTX 3g/m² D1 Cy 250mg/m²/12h D2-4 Adriamycin 60mg/m² D2 IT (MTX HSHC) D2;6 pred 60mg/m² D1-5	**CYM** MTX 3g/m² D1 cytarabine 100mg/m²/D D2-6 IVC 24h IT (MTX HSHC D2; HSHC araC D7)	**CYM** MTX 3g/m² D1 cytarabine 100mg/m²/D D2-6 IVC 24h IT (MTX HSHC D2; HSHC araC D7)					**Cyclophosphamide= 3300mg/m² Adriamycin= 120mg/m² IT=8***
C1	**13**	**COP*** Cy 300mg/m² D1 VCR 2mg/m² D1 IT (MTX HSHC araC) D1, D3, D5 pred 60mg/m²/D D1-7	**COPADM** VCR 2mg/m² D1 MTX 8g/m² D1 Cy 250mg/m²/12h D2-4 Adriamycin 60mg/m² D2 IT (MTX HSHC AraC) D2, 4, 6 pred 60mg/m² D1-5	**COPADM** VCR 2mg/m² D1 MTX 8g/m² D1 Cy 500mg/m²/12h D2-4 Adriamycin 60mg/m² D2 IT (MTX HSHC AraC) D2, 4, 6 pred 60mg/m² D1-5	**CYVE** cytarabine 50mg/m² IVC 12h D1-5 Cytarabine 3g/m² D2-5 VP16 200mg/m² D2-5	**CYVE** cytarabine 50mg/m² IVC 12h D1-5 Cytarabine 3g/m² D2-5 VP16 200mg/m² D2-5	Seq1 VCR 2mg/m² D1 MTX 8g/m² D1 Cy 500mg/m²/d D2-3 Adriamycin 60mg/m² D2 IT (MTX HSHC AraC) D2 pred 60mg/m² D1-5	Seq2 Cytarabine 50mg/m²/12h D1-5 VP16 150mg/m² D1-3	Seq3 VCR 2mg/m² D1 Cy 500mg/m²/d D1-2 Adriamycin 60mg/m² D1 pred 60mg/m² D1-5	Seq4 Cytarabine 50mg/m²/12h D1-5 VP16 150 mg/m² D1-3	**Cyclophosphamide= 6800mg/m² Adriamycin= 240mg/m² IT=7***
R			375mg/m² D1	375mg/m² D1	375mg/m² D1	375mg/m² D1	375mg/m² D1	375mg/m² D1			

Abbreviations: Adriamycin, doxorubicin; AraC, aracytine; VCR, vincristine; MTX, methotrexate; Cy, cyclophosphamide; pred, prednisolone; IT: intrathecal; R, Rituximab; RA, remission assessment

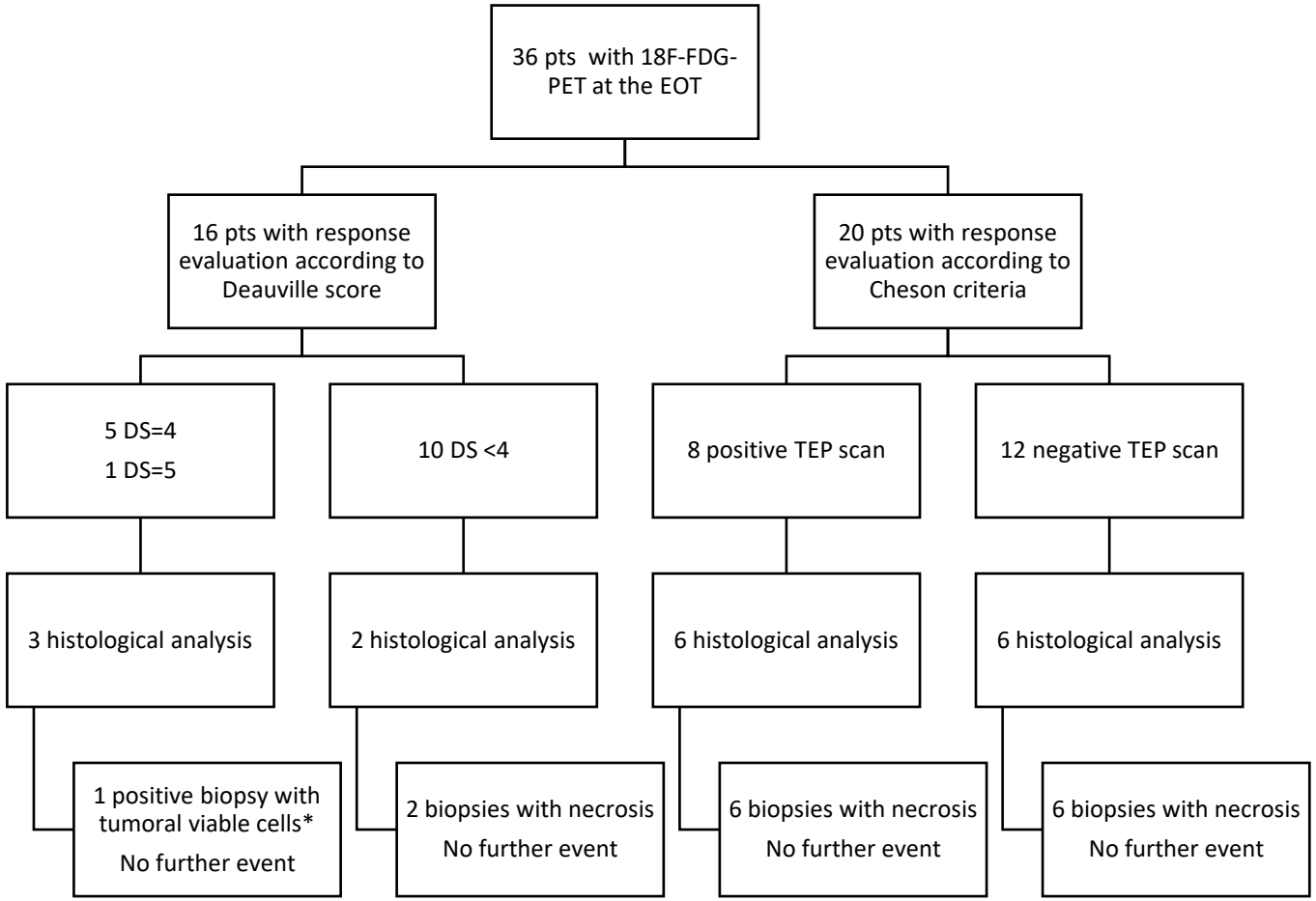
*A COP prephase is not mandatory but may be required one week prior to commencement of course 1 for patients requiring urgent treatment whilst awaiting histological confirmation. In case of COP prephase more intrathecal are administered. #remission assessment was required after 4 or 6 courses of chemotherapy. At the end of therapy, if PET-CT is positive, or a large residual tumor remains, then biopsy/removal of the residual mass is recommended. No treatment decisions were to be based on PET-CT results only.

Supplementary Table 2. Events characteristics

Patient	#2	#23	#43
Site of progression /relapse	mediastin	mediastin	mediastin*
Time from diagnosis	Viable cells in residual mass after RCYVE2 6.2 months	Progression after RCOPADM1 0.6 months	Relapse at 6.6 months
2nd line chemotherapy	R-ICE (2) Bv-Nivo (4)	R-ICE (3)	R-ICE (2) Ibrutinib (3)
High dose chemotherapy	BEAM and ASCT	BEAM and ASCT	BEAM and ASCT
Radiation therapy	yes	yes	yes
Patient status at last news	CR1 1.9 year	CR1 11 years	CR2 5.6 years

Abbreviations: ASCT, autologous stem cell transplantation; BEAM, Carmustine, etoposide, cytarabine, melphalan; Bv, Brentuximab-Vedotin; CR, complete response; ICE, ifosfamide, etoposide, carboplatin; Nivo, nivolumab ; R, Rituximab.
*Residual mass after 6 courses, necrosis at histological analysis. Relapse as « Burkitt like »/DLBCL

Supplementary Figure 1. 18F-FDG-PET results and outcome



Abbreviations: pts, patients; EOT: end of treatment; DS, Deauville score
*Deauville score =5