REGULAR ARTICLE

blood advances

Interim PET after 4 cycles predicts outcome in histomolecularly confirmed primary mediastinal B-cell lymphoma

Vincent Camus,[1,2] Thierry Molina,[3,*] Fabienne Desmots,[4,*] Paul Blanc-Durand,[5,†] Salim Kanoun,[6,†] Amine Moslemi,[7] Philippe Ruminy,[2] Steven Le Gouill,[8] Hervé Ghesquières,[9] Lucie Oberic,[10] Franck Morschhauser,[11] Hervé Tilly,[1,2] Vincent Ribrag,[12] Roch Houot,[13] Catherine Thieblemont,[14] Hervé Maisonneuve,[15] Fabien Claves,[16] Krimo Bouabdallah,[17] Corinne Haioun,[18] Gandhi Laurent Damaj,[19] Luc-Matthieu Fornecker,[20] Robin Noel,[21] Pierre Feugier,[22] David Sibon,[23] Guillaume Cartron,[24] Christophe Bonnet,[25] Wivine Bernard,[26] Françoise Kraeber-Bodéré,[27] Caroline Bodet-Milin,[27] Jean-Philippe Jais,[28] Josette Brière,[29] Cedric Rossi,[30] Mad-Hélénie Elsensohn,[31] Loïc Chartier,[31] Emmanuel Itti,[5] Fabrice Jardin,[1,2,‡] and Thierry Fest[4,‡]

[1]Department of Hematology, Centre Henri Becquerel, Rouen, France; [2]INSERM U1245, Centre Henri Becquerel, University of Rouen, Rouen, France; [3]Department of Pathology, Assistance Publique–Hôpitaux de Paris, Necker and Robert Debré Hospital, Université Paris Cité, Paris, France; [4]Laboratoire d'Hématologie, Team B_DEVIL, UMR_S1236, Centre Hospitalier Universitaire de Rennes, Université de Rennes 1, INSERM, Établissement Français du Sang de Bretagne, Rennes, France; [5]Department of Nuclear Medicine, CHU Henri Mondor, Nuclear Medicine, Paris-Est University, Créteil, France; [6]INSERM, UMR 1037, Cancer Research Center of Toulouse, Toulouse, France; [7]Department of Pathology, Centre Hospitalier Universitaire Amiens, Amiens, France; [8]Department of Hematology, Institut Curie, Paris, France; [9]Department of Hematology, Centre Hospitalier Lyon-Sud, Hospices Civils de Lyon, Université Claude Bernard Lyon 1, Lyon, France; [10]Department of Hematology, Institut Universitaire du Cancer, Toulouse-Oncopole, Toulouse, France; [11]Department of Hematology, Claude Huriez Hospital, Lille University Hospital, Lille, France; [12]Department of Hematology, Gustave Roussy, Villejuif, France; [13]Department of Hematology, Centre Hospitalier Universitaire Rennes, University of Rennes, INSERM U1236, Etablissement Français du Sang, Rennes, France; [14]Department of Hemato-oncology, Assistance Publique–Hôpitaux de Paris, Hôpital Saint-Louis, Université de Paris, Paris, France; [15]Department of Hematology, Centre Hospitalier Departemental de Vendée, La Roche sur Yon, France; [16]Department of Hematology, Grenoble University Hospital, Grenoble, France; [17]Department of Hematology, Bordeaux University Hospital, Bordeaux, France; [18]Department of Hematology, Henri Mondor University Hospital, Créteil, France; [19]Department of Hematology, Caen University Hospital, Caen, France; [20]Department of Hematology, Strasbourg University Hospital, Strasbourg, France; [21]Department of Hematology, Institut Paoli-Calmettes, Marseille, France; [22]Department of Hematology, Hôpital de Brabois, Nancy University Hospital, Nancy, France; [23]Department of Hematology, Assistance Publique–Hôpitaux de Paris, Hôpital Necker, Université de Paris, Paris, France; [24]Department of Hematology, Montpellier University Hospital, Montpellier, France; [25]Department of Hematology, Centre Hospitalier Universitaire Liege, Liege, Belgium; [26]Department of Hematology, CHU Université Catholique de Louvain Namur, Site Godinne, Namur, Belgium; [27]Department of Nuclear Medicine, University Hospital of Nantes, Nantes, France; [28]Department of Biostatistics, Hôpital Necker, Institut Imagine, Unité INSERM 1163, University of Paris, Paris, France; [29]Department of Hematology, Hôpital Saint-Louis, Assistance Publique–Hôpitaux de Paris, Université Paris Diderot, Paris, France; [30]Department of Hematology, Dijon University Hospital, Dijon, France; and [31]Biostatistics Department, The Lymphoma Academic Research Organisation, Lyon-Sud Hospital, Pierre-Bénite, France

Submitted 10 December 2024; accepted 5 February 2025; prepublished online on *Blood Advances* First Edition 3 March 2025. https://doi.org/10.1182/bloodadvances.2024015577.

*T.M. and F.D contributed equally to this study.

†P.B.-D and S.K. contributed equally to this study.

‡F.J. and T.F. contributed equally to this study.

Presented in abstract form at the 66th American Society of Hematology Annual Meeting & Exposition, San Diego, CA, 7 to 10 December 2024.

The sequencing data are publicly available on the European Genome-phenome Archive (EGA; https://ega-archive.org/; accession numbers

EGAP50000000485 [corresponds to the data policy access, which is related to the corresponding data access committee (DAC)]; and

EGAC50000000540 [DAC related to the data set on the EGA platform]).

For access to other original data, please contact dpo@lysarc.org. They will respond to your request in compliance with applicable data protection regulations, data security requirements, the principle of data minimization, and the relevant contractual provisions.

The full-text version of this article contains a data supplement.

Key Points

- Favorable outcomes were observed with dose-dense induction and PET-driven consolidation, with 2-year PFS at 86.2% and OS at 93.2%.
- The interim PET response, based on ΔSUVmax at PET4 (threshold, ≤70% vs >70%), emerged as the most robust predictor of outcomes.

The GAINED study was a randomized phase 3 trial comparing obinutuzumab (G) with rituximab (R) plus ACVBP (doxorubicin, cyclophosphamide, and prednisone, combined with either vindesine or bleomycin) or CHOP14 (cyclophosphamide, doxorubicin, vincristine, and prednisone, administered on a 14-day schedule) induction, followed by positron emission tomography (PET)–guided consolidation. This post hoc analysis aimed to detail the outcomes of patients with primary mediastinal B-cell lymphoma (PMBL), verified through expert pathological review and the use of gene expression profiling (GEP) and next-generation sequencing. Of 620 centrally reviewed patients, 138 (22.3%) confirmed PMBL cases were analyzed. Baseline characteristics included a median age of 33.5 years, 63.8% female, 55.1% stage III to IV, 90.6% elevated lactate dehydrogenase, 87.6% Eastern Cooperative Oncology Group performance status score of 0 to 1, 62.3% extranodal involvement, 52.6% age-adjusted International Prognostic Index (aaIPI) of 2% to 3%, and 53.6% bulk (>10 cm). Induction regimens were R/G-CHOP14 (56.9%) and R/G-ACVBP (43.1%). Postinduction treatments, based on interim PET results, included: standard consolidation chemotherapy (59.8%) if change in maximum standardized uptake value (ΔSUVmax) of >66% after cycle 2 and >70% after cycle 4 ($PET2^-/4^-$), intensive treatment and autologous transplantation (26.8%) if $PET2^+/4^-$, and salvage therapy (13.4%) if $PET4^+$ (ΔSUVmax of ≤70%). Among patients with GEP data (n = 107), 38 (35.5%) were $PDL1^{high}/PDL2^{high}$. Key somatic mutations data (n = 87) included *SOCS1* (70.1%), *B2M* (56.3%), *STAT6* (49.4%), *TNFAIP3* (47.1%), *GNA13* (39.1%), *CIITA* (37.9%), *CD58* (36.8%), and *TP53* (29.9%). After a median follow-up of 39.5 months, 2-year progression-free survival (PFS) and overall survival (OS) rates were 86.2% and 93.2%, respectively. In a multivariate model including bulk, aaIPI, and ΔSUVmax PET2/PET4, only bulk and ΔSUVmax PET4 of ≤70% were associated with shorter PFS (hazard ratio, 4.39 [95% confidence interval (CI), 1.28-15.11] and 4.95 [95% CI, 1.71-14.3], respectively), whereas none were associated with OS. The ΔSUVmax-based interim PET4 response emerged as the strongest predictor of patient outcomes in this selected clinical trial population. This trial was registered at www.ClinicalTrials.gov as #NCT01659099.

Introduction

The latest World Health Organization (WHO) and International Consensus classifications defined primary mediastinal B-cell lymphoma (PMBL) as a distinct entity of mature aggressive large B-cell lymphoma (LBCL) of supposed thymic B-cell origin that mostly locates in the anterior mediastinum.[1,2] Patients with PMBL are poorly represented in clinical trials for several reasons: (1) diagnosis often occurs in emergency settings because of severe clinical presentations, including symptoms related to tumor mass, with 30% to 40% of patients developing superior vena cava syndrome[3]; (2) the mediastinum, a challenging anatomical site to biopsy, frequently yields samples with suboptimal quality or quantity for definitive histopathological diagnosis[4-6]; (3) PMBL exhibits a unique biological complexity, characterized by an immune escape profile more akin to classical Hodgkin lymphoma and driven by specific genetic and molecular alterations that set it apart from other LBCL[7-9]; and (4) despite being a subtype of LBCL, PMBL shows an atypical favorable prognosis in first-line treatment, with 5-year survival rates of >80%.[9-11] Molecular classifiers can distinguish PMBL from LBCL using RNA extracted from formalin-fixed paraffin-embedded (FFPE) tissue samples.[9,12,13] Next-generation sequencing (NGS)–based studies have further clarified the genetic landscape of PMBL, identifying recurrent somatic mutations (*SOCS1*, *STAT6*, *ITPKB*, *IGLL5*, *CIITA*, *TNFAIP3*, *ARID1A*, *CD58*, *IRF4*, *B2M*, *GNA13*, *NFKBIE*, *XPO1*, and *IL4R*), which can aid pathologists in diagnosing PMBL.[4,5,12,14-16] Whole-exome sequencing and NGS serve as valuable tools for risk stratification, with recent findings suggesting that mutations in *DUSP2* and *CD58* may correlate with patient outcomes and guide treatment decisions.[16] Furthermore, using gene expression profiling (GEP), the PMBL Lymphoma Study Association (LYSA) study recently identified a subset (23%-30%) of patients with PMBL with high expression of both *PDL1* and *PDL2* genes who exhibit poor responses to first-line standard immunochemotherapy with anthracyclines and anti-CD20 monoclonal antibody.[4] This real-life study, similar to many other studies within patients with PMBL, was conducted retrospectively, carrying an inherent risk of selection and sampling bias. In addition, because of the rarity of the disease and limited availability of biological samples, cases are often collected over extended periods, with variations in treatments and therapeutic response assessments

across time and institutions. This can create challenges in generalizing the findings. Notably, in the PMBL LYSA study, no blood samples were available at diagnosis to assess correlations between *PDL1/PDL2* gene expression and soluble PDL1 (sPDL1) protein levels, a promising disease biomarker in classical Hodgkin lymphoma[17-19] and LBCL.[20]

The GA IN NEWLY DIAGNOSED DLBCL (GAINED) study (ClinicalTrials.gov identifier: NCT01659099) was a randomized phase 3 trial comparing obinutuzumab (G) with rituximab (R), both combined with standard chemotherapy. No significant difference in progression-free survival (PFS) or overall survival (OS) rates was observed between the R or G treatment arms.[21] Eligible patients were young (aged 18-60 years), fit for high-dose chemotherapy intensification followed by autologous stem cell transplant (ASCT), and diagnosed with $CD20^+$ diffuse LBCL (DLBCL) according to the 2008 WHO classification.[22] At that time, PMBL was often considered a subtype of DLBCL; however, PMBL cases were later confirmed via centralized histopathological review, integrating GEP and NGS for diagnosis.[23]

This post hoc analysis aimed to characterize the clinical, imaging, and biological features of this patient population and evaluate treatment responses, by performing correlations between patient outcomes and GEP, NGS, radiomics parameters, cell-free DNA (cfDNA), and sPDL1 data in a well-annotated, prospective cohort of PMBL enrolled in a multicenter phase 3 trial.

Methods

Patients, procedures, and data collection

Details of the GAINED study design have been published previously.[21] It was an open-label multicenter randomized study conducted by the LYSA in 99 centers in Belgium and France. Eligible patients were aged 18 to 60 years with newly diagnosed, untreated, histologically proven $CD20^+$ DLBCL (2008 WHO classification), age-adjusted International Prognostic Index (aaIPI) of $\geq$1, at least 1 hypermetabolic lesion at baseline positron emission tomography (PET), eligibility for ASCT, and those who had a life expectancy of $\geq$3 months. Study design is shown in supplemental Figure 1. The treatment plan was divided into 2 phases: induction and consolidation. The induction phase included 4 cycles of doxorubicin, cyclophosphamide, and prednisone, combined with either vindesine and bleomycin (ACVBP) or vincristine, administered on a 14-day schedule (CHOP14). Treatment responses during the induction phase were evaluated using PET after the second and fourth cycles (PET2/PET4), with thresholds for change in maximum standardized uptake value (ΔSUVmax) set at 66% for PET2 and 70% for PET4.[24] Patients then received a PET-driven consolidation with either R/G-CHOP14 ×4 or the conventional post-ACVBP consolidation strategy if PET2 and PET4 were negative, or therapeutic intensification followed by ASCT if $PET2^{+/}PET4^-$, or salvage treatment if $PET2^+/PET4^+$. PET at the end of treatment (EoT) was not performed (response evaluated by computed tomography scan).

The study protocol received approval from the appropriate local or national ethics committees in compliance with the legal requirements of each country. The research was conducted in line with the principles outlined in the Declaration of Helsinki. All patients provided written informed consent before their enrollment in the study. The data cutoff date for the present analyses was the same as for the final analysis of the GAINED study: 1 December 2017.

GEP

A 137–gene expression assay combining reverse transcriptase multiplex ligation-dependent probe amplification and high-throughput sequencing was applied as previously described (LymphoSign; Genexpath, Rouen, France).[4,13]

Expert pathologic review

The process of FFPE review was organized and coordinated by the LYSA pathology platform (Henri Mondor University Hospital, Créteil, France). The histopathologic review of all cases with available material was performed by 3 expert hematopathologists and 1 molecular biologist following the diagnostic criteria established by WHO and International Consensus classifications.[1,2,25] The final diagnosis of PMBL in this study was established by combining histological findings with available GEP and NGS data, resulting in a reconciled, integrated histomolecular diagnosis[23] (supplemental Methods).

NGS

Targeted DNA sequencing was performed on DNA extracted from FFPE samples using a custom "Lymphopanel" to identify mutations in 70 genes related to lymphomagenesis. Library preparation, exome capture, sequencing, and analysis were carried out by IntegraGen SA (Evry, France), with sequencing done on an Illumina HiSeq4000 platform. Bioinformatic analysis, including variant calling and annotation, was performed using established tools such as MuTect and Ensembl Variant Effect Predictor (VEP) (supplemental Table 1; supplemental Methods).

Baseline cfDNA

Plasma samples were collected at the time of randomization using BD P100 tubes (BD Diagnostics, Le Pont-De-Claix, France). These samples were shipped at room temperature to the core laboratory in Rennes (France) within 24 hours, then centrifuged and stored at −80°C. The concentration of cfDNA was measured based on DNA fragments within the 90- to 320-bp range. A high cfDNA concentration was defined as >55 ng/mL, following previous studies.[26]

sPDL1

Baseline sPDL1 levels were measured using an enzyme-linked immunosorbent assay (PDCD1LG1 enzyme-linked immunosorbent assay kit; USCN Life Science, Wuhan, China), following the manufacturer's instructions. The assay had a minimum detectable concentration of 0.057 ng/mL and a quantifiable range starting at 0.156 ng/mL. A threshold of 1.52 ng/mL was used to classify patients with elevated baseline sPDL1 levels, as defined in previous research.[20]

Centralized PET review

Details of PET review process were previously described (supplemental Methods).[21,24] In addition, as a post hoc analysis, whole-body PET volumes were semiautomatically segmented using the total metabolic tumor volume (TMTV) protocol from Local Image Features Extraction (LIFEx).[27] Above the fixed SUV detection threshold of 4, connected regions were extracted and were individually pruned by 3 experienced physicians (P.B.-D., S.K., and

E.I.) to assess baseline TMTV and total lesion glycolysis (TLG), as previously described.[28-30] We previously observed that patients with a baseline TMTV of ≥360 cm^3 had poorer outcomes.[4,11]

Statistical analysis

Variables were summarized by numbers and percentages for categorical data and by the mean and standard deviation (SD) and median and quartiles for quantitative data. The tests for the comparisons of the different subpopulations were not corrected for multiple testing. Categorical variables were compared using Fisher or $\chi 2$ tests and quantitative variables using Kruskal-Wallis or Wilcoxon tests. Survival curves with 95% confidence intervals (CIs) were generated using the Kaplan-Meier method. Difference in survival was assessed by log-rank test and hazard rates with their 95% CIs calculated from Cox proportional hazard regression models. Univariate Cox models were built using clinical interest variables. A false discovery rate correction for multiple testing were applied separately by type of data (clinical, biological, and radiomic) on univariate Cox models. The variables with a significant effect after false discovery rate correction or well-known to affect PFS (aaIPI) were retained for building the multivariate Cox model. However, TMTV was not retained because of its strong correlation with bulk. For OS, the multivariate analysis (MVA) was constructed using the same variables as in the PFS model to ensure consistency. All statistical analyses were performed using Statistical Analysis System (SAS) (version 9.4 or higher) and R (version 4.3.1).

Results

Patients disposition and characteristics

From September 2012 to July 2015, 670 patients were enrolled in the GAINED study and randomized to receive either R (n = 334) or G (n = 336). Overall, 620 (92.5%) cases underwent centralized histopathological review and molecular profiling through GEP and/or NGS when available. Of these, 138 patients (22.3%) were identified as having PMBL (Figure 1). These 138 patients with PMBL, referred to as the "PMBL set" were included for further analysis. Baseline characteristics of this cohort included: median age, 33.5 years (range, 18-60); female, 63.8%; Eastern Cooperative Oncology Group performance status score of 0 to 1, 87.6%; stage III to IV, 55.1%; elevated lactate dehydrogenase (LDH), 90.6%; extranodal involvement, 62.3%; aaIPI of 2 to 3, 52.6%; bulk (mediastinal mass of >10cm), 53.6%; median TMTV, 388.6 cm^3; TMTV of ≥360 cm^3, 53%; and median TLG, 4440.2 g (Table 1). Bulk was strongly associated with higher TMTV and TLG ($P <$ .001; supplemental Table 2). Indeed, 70% of patients with TMTV of ≥360 cm^3 also had bulk of >10 cm.

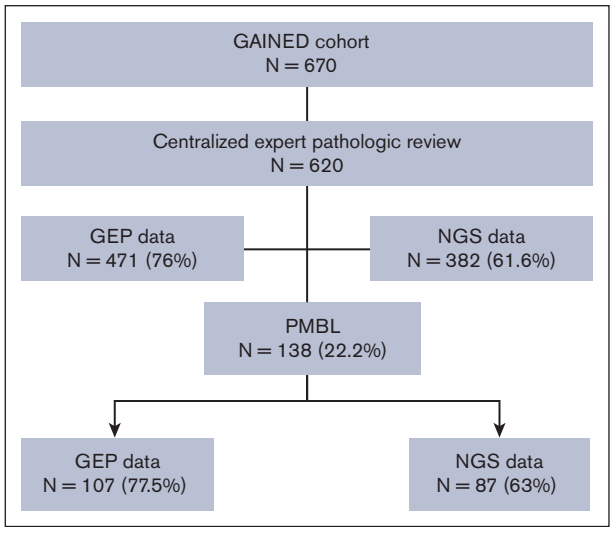


Figure 1. Population selection from the GAINED cohort.

Induction regimens were R-CHOP14 (31%), G-CHOP14 (26%), G-ACVBP (23%), and R-ACVBP (20%; supplemental Figure 2). We did not observe any significant differences in patient characteristics nor protocol consolidation treatment between those who received CHOP14- or ACVBP-based induction (supplemental Table 3).

Biological features of the PMBL population

Supplemental Figure 3 summarizes the number of patients with available GEP, NGS, sPDL1, and cfDNA data.

Among 107 patients with PMBL with available GEP data, 38 patients (35.5%) were identified as *PDL1*^{high}/*PDL2*^{high}, that is, expression of *PDL1* of >0.402 and *PDL2* of >9.147, as previously described.[4] A trend toward more frequent extranodal involvement was noted in the *PDL1*^{high}/*PDL2*^{high} group (73.7%) compared with the non-*PDL1*^{high}/*PDL2*^{high} group (55.1%; $P = .065$). In addition, the IPI score was significantly higher in the *PDL1*^{high}/*PDL2*^{high} group, with 54.1% of these patients having an IPI of ≥3, compared with the non-*PDL1*^{high}/*PDL2*^{high} group (23.2%; $P = .002$). Finally, pleural and/or pericardial involvement were significantly more common in the *PDL1*^{high}/*PDL2*^{high} group (42.1%) compared with the non-*PDL1*^{high}/*PDL2*^{high} group (15.9%; $P = .005$), suggesting a more aggressive disease in this subgroup (supplemental Table 4). We also observed a higher proportion of *PIM1* and *SETD1B* mutations in the *PDL1*^{high}/*PDL2*^{high} group (supplemental Figure 4). This finding suggests that patients with elevated *PDL1* and *PDL2* expression may exhibit distinct genetic alterations that could influence the disease's pathobiology, specifically, the *PIM1* gene, known for its role in promoting cell proliferation and survival,[31] along with *SETD1B*, a chromatin modifier involved in apoptosis resistance and B-cell lymphoma 2 independence.[32] In addition, the tumor mutational burden, defined as the number of somatic mutations per megabase of analyzed genomic sequence, was significantly higher in the *PDL1*^{high}/*PDL2*^{high} group (supplemental Figure 5; $P < .01$). Furthermore, among the 4 immune escape–associated genes tested, we observed higher variant allele frequencies (VAFs) for *CD58* and *CIITA* in the *PDL1*^{high}/*PDL2*^{high} group ($P < .05$; supplemental Figure 5).

sPDL1 level and cfDNA level were classified as high in 45 (52.3%) and 7 (16%) patients, respectively (supplemental Table 5). Of note, no correlation between sPDL1 and *PDL1*/*PDL2* gene expression was observed (supplemental Figure 6).

With a mean read depth of 255× and a panel size of 0.453 gigabase, NGS mutational analysis (n = 87) highlights recurrent somatic mutations in key PMBL-associated genes: *SOCS1* (70.1%), *B2M* (56.3%), *STAT6* (49.4%), *TNFAIP3* (47.1%), *GNA13* (39.1%), *CIITA* (37.9%), and *CD58* (36.8%; Figure 2; supplemental Tables 6 and 7). Mutations were identified in all

Table 1. Patient characteristics at baseline

	PMBL set n = 138	
Age at randomization, y		
n	138	
Mean (SD)	34.1 (9.98)	
Median	33.5	
Q1-Q3	26-40	
Min-max	18-60	
Sex, female, n (%)	88	(63.8)
Elevated LDH (greater than the upper limit), n (%)	125	(90.6)
ECOG performance status score of 0-1, n (%)	120	(87.6)
Missing	1	–
Ann Arbor stage in class, n (%)		
I-II	62	(44.9)
III-IV	76	(55.1)
Patients with at least 1 extranodal involvement, n (%)	86	(62.3)
aaIPI in class, n (%)		
0-1	65	(47.4)
2-3	72	(52.6)
Missing	1	–
IPI, n (%)		
1	58	(42.3)
2	31	(22.6)
3	43	(31.4)
4	5	(3.6)
Missing	1	–
IPI in class, n (%)		
0-2	89	(65)
3-5	48	(35)
Missing	1	–
CNS IPI score in class, n (%)		
0-1	58	(42.3)
2-3	66	(48.2)
4-6	13	(9.5)
Missing	1	–
Presence of B symptoms, n (%)	56	(40.6)
Bulk, mediastinal mass maximal diameter >10 cm, n (%)	74	(53.6)
Pleura and/or pericardium involvement, n (%)	37	(26.8)
Presence of an anterior mediastinal mass, n (%)	137	(99.3)
Baseline TMTV, cm^3		
n	132	
Missing	6	
Mean (SD)	453.4273 (292.919 71)	
Median	388.640 0	
Q1-Q3	233.720-611.080	
Min-max	20.150-1 551.280	
TMTV of ≥360 cm^3, n (%)	70	(53)
TLG, g		
n	132	
Missing	6	
Mean (SD)	5 038.596 6 (3 599.432 52)	
Median	4 440.215 0	
Q1-Q3	2 486.945-6 897.395	
Min-Max	103.500-16 571.940	

CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; max, maximum; min, minimum; Q1/3, First quartile/Third quartile.

coding regions of the panel except for the *MIR17HG* gene, with a median of 24 variants per case. Additionally, pathogenic *TP53* variants were identified in 29.9% of patients. Early or driver mutations, such as those affecting *SOCS1*, *TNFAIP3*, *STAT6*, *CIITA*, *CD58*, and *B2M* were observed with high median VAFs (~30%), supporting their role in the early pathogenesis of PMBL. In contrast, mutations in genes such as *BCL2*, which displayed a lower median VAF (6.9%), are considered late or subclonal mutations (supplemental Table 8).

Interim PET response rates and postinduction treatment

PET2 and PET4 were performed in 129 (93.5%) and 128 (92.8%) patients, respectively. As shown in Table 2 and Figure 3, 77 patients (60.2%) had ΔSUVmax PET2 of >66%, of whom 76 (98.7%) received the planned immunochemotherapy. Thirty-four patients (26.5%) had ΔSUVmax PET2 of ≤66% and ΔSUVmax PET4 of >70%, and all of them received the planned consolidation therapy followed by ASCT. Seventeen patients (13.3%) had ΔSUVmax PET4 of ≤70%, and all received salvage chemotherapy (supplemental Table 9). In detail, these patients were categorized as having disease progression in 5 patients (29.4%) and insufficient response in 12 patients (70.6%), as determined by physician judgment based on PET4 (partial metabolic response or no metabolic response). Salvage chemotherapy regimens included R-DHAX–like therapies (R, dexamethasone, high-dose cytarabine, and a platinum salt [oxaliplatin, cisplatin, or carboplatin]) in 14 patients (82%) and high-dose methotrexate in 3 patients (18%). Mediastinal radiotherapy was performed in 3 patients (18%), and 12 patients (71%) underwent second-line consolidation with ASCT.

When evaluating interim PET (iPET) responses across the induction regimens, no significant differences were observed. PET2 and PET4 negativity rates were slightly higher in the ACVBP subgroups but did not reach statistical significance, and response rates according to Cheson 2007 criteria[33] were similar across all subgroups (supplemental Table 10). Notably, Deauville score (DS) was missing in 108 cases (78.3%) at PET2 and 127 cases (92%) at PET4 because the protocol recommended using ΔSUVmax to assess treatment response, meaning this variable was mostly not collected. No significant association was observed between

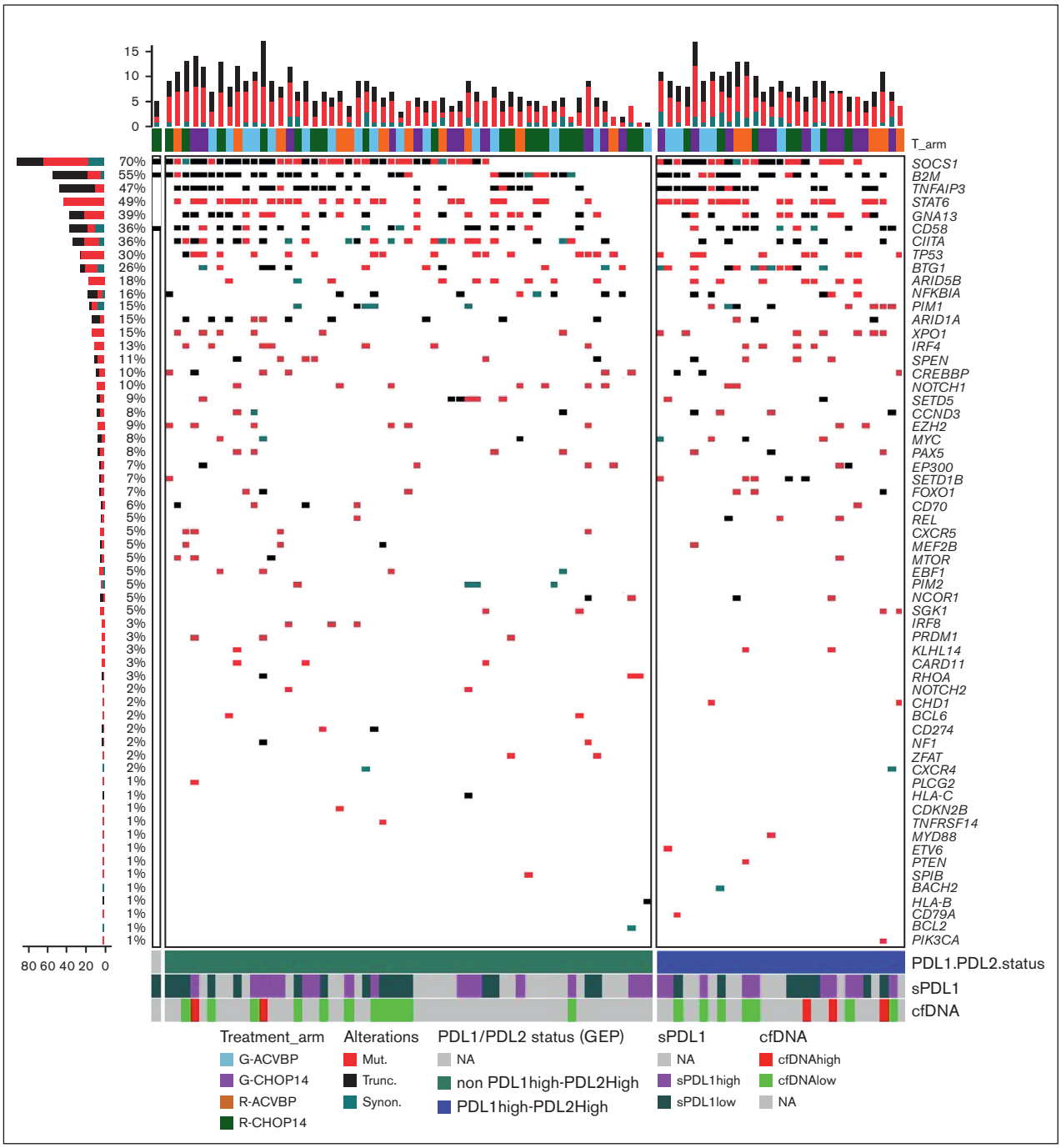


Figure 2. Oncoprint showing the distribution of genomic alterations in patients with PMBL from the GAINED cohort with available targeted NGS (n = 87), clustered based on the *PDL1/PDL2* gene expression status (GEP). cfDNA, baseline cfDNA level; Mut, Mutation; NA, Not available; sPDL1, baseline sPDL1 level; Synon, Synonymous mutation; Trunc, Truncating mutation.

baseline TMTV and PET2/PET4 responses (supplemental Table 11).

PET responses and proportion of salvage therapy rates were analyzed according to *PDL1/PDL2* gene expression status. No statistically significant differences were observed across the analyzed characteristics (supplemental Tables 4 and 12).

Patient outcome

After a median follow-up of 39.5 months, 2-year and 4-year PFS rates were 86.2% (95% CI, 79.2-91) and 83.9% (95% CI, 76.5-89.1), respectively. The 2-year and 4-year OS rates were 93.2% (95% CI, 87.3-96.4) and 90.8% (95% CI, 84.3-94.7; Figure 4), respectively. Of 138 patients, 12 (8.7%) deaths were recorded.

Table 2. iPET results

	PMBL set
	n = 138
ΔSUVmax PET2	
n	130
Missing	8
Mean (SD)	77.504 (14.9323)
Median	80.240
Q1-Q3	74.88-86.93
Min-max	4.96-96.35
PET2 response, n (%)	
ΔSUVmax PET2, >66%	80 (62)
ΔSUVmax PET2, ≤66%	49 (38)
Missing	9
ΔSUVmax PET4	
n	128
Missing	10
Mean (SD)	84.042 (8.9557)
Median	85.85
Q1-Q3	81.18-89.44
Min-max	28.75-96.06
PET4 response, n (%)	
ΔSUVmax PET4, >70%	111 (86.7)
ΔSUVmax PET4, ≤70%	17 (13.3)
Missing	10
PET2/PET4 response, n (%)	
ΔSUVmax PET2, >66% ($PET2^-$)	77 (60.2)
ΔSUVmax PET2, ≤66% and ΔSUVmax PET4, >70% ($PET2^+/PET4^-$)	34 (26.5)
ΔSUVmax PET4, ≤70% ($PET4^+$)	17 (13.3)
Missing	10

Causes of death included lymphoma in 7 patients (58.3%), toxicity of study treatment (including related cancers) in 3 patients (25%), concurrent illness in 1 patient, and other reasons in 1 patient (supplemental Table 13). Only 1 patient experienced a relapse in the central nervous system.

A stratified analysis of patients based on iPET results revealed notable differences in PFS. Patients with $PET4^+$ results had significantly worse PFS compared with patients with $PET2^-/4^-$ and $PET2^+/4^-$ results ($P < .001$). Because of consolidation ASCT, the difference between $PET2^-/4^-$ and $PET2^+/4^-$ was not statistically significant ($P = .193$; Table 3). The 2-year PFS rates were 93.5% for $PET2^-/4^-$ patients, 82.4% for $PET2^+/4^-$ patients, and 58.8% for $PET4^+$ (Figure 5).

The differences in OS were not statistically significant, with 2-year OS rates of 96% for $PET2^-/4^-$ patients, 90.9% for $PET2^+/4^-$ patients, and 85.6% for $PET4^+$ patients ($P = .123$; Figure 5).

Univariate and MVA

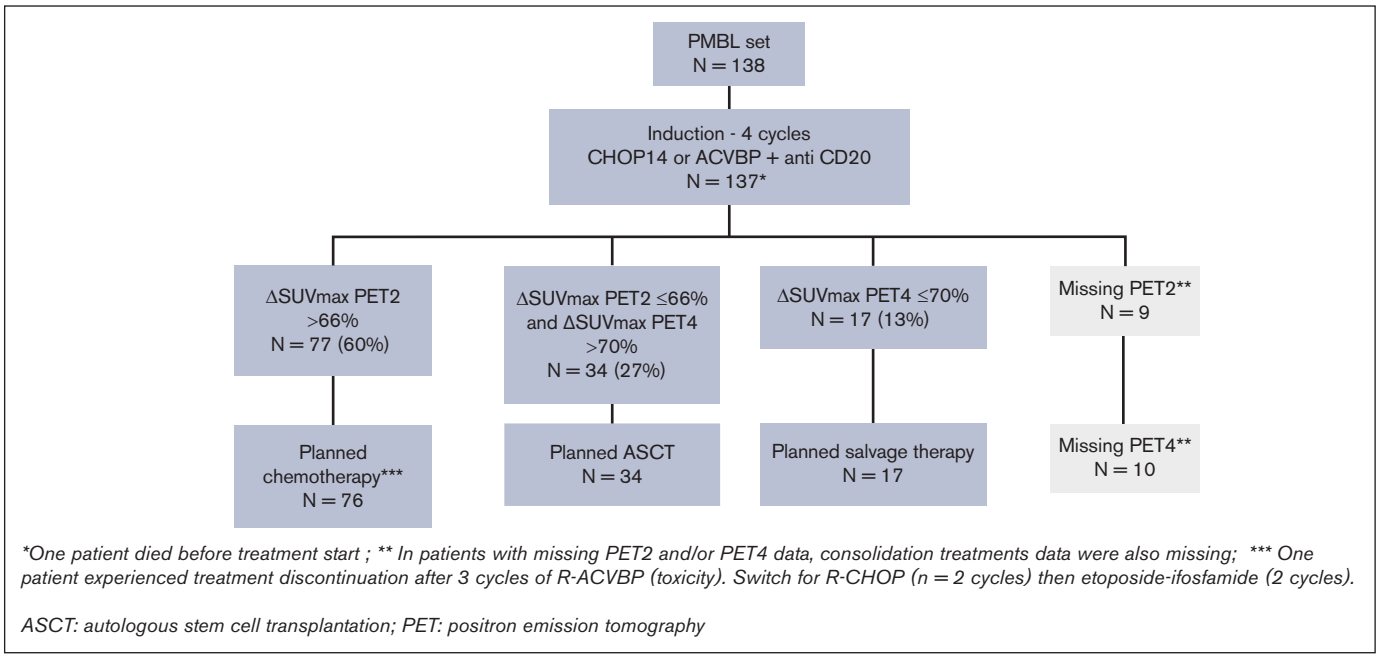
Univariate analysis highlighted that bulk of >10 cm (hazard ratio [HR], 4.37; 95% CI, 1.48-12.92), TMTV of ≥360 cm^3 (HR, 3.91; 95% CI, 1.31-11.7), stage III to IV (HR, 4.06; 95% CI, 1.38-12.01), and ΔSUVmax of ≤70% ($PET4^+$, 6.6; 95% CI, 2.3-18.77) were associated with shorter PFS, whereas ΔSUVmax PET4 (continuous variable) was associated with longer PFS (HR, 0.26; 95% CI, 0.15-0.43; for an increase of a SD). Additionally, stage III to IV (HR, 9.9; 95% CI, 1.28-76.57) and TMTV of ≥360 cm^3 (HR, 8.57; 95% CI, 1.09-67.62) were linked to shorter OS, whereas ΔSUVmax PET4 (continuous variable) was associated with longer OS (HR, 0.36; 95% CI, 0.21-0.62; for an increase of a SD). None of the other factors assessed (induction regimen; anti-CD20 monoclonal antibody; cfDNA and sPDL1 levels; *PDL1*^{high}/*PDL2*^{high} status; *B2M*, *CD58*, *TP53* alterations; and TLG) were significantly associated with outcomes (Tables 3 and 4).

Finally, in a MVA including bulk, aaIPI (which includes stage), and ΔSUVmax PET2/PET4, only bulk and ΔSUVmax PET4 of ≤70% were associated with shorter PFS (HR, 4.39; 95% CI, 1.28-15.11; and HR, 4.95; 95% CI, 1.71-14.3, respectively), whereas none were associated with OS (Tables 3 and 4).

Discussion

We conducted a post hoc analysis of a large international phase 3 trial to focus on the outcome of patients with newly diagnosed PMBL treated with R/G-CHOP14 or R/G-ACVBP induction and iPET-driven consolidation strategies without radiotherapy. PMBL was a common diagnosis (~22%) among the centrally reviewed cases in the GAINED study. Because of the primary focus on DLBCL in the GAINED study, a potential selection bias cannot be excluded as some centers may have omitted patients with PMBL. Compared with previous PMBL reports, this may partly explain the higher proportion of stage IV and extranodal involvement observed in our cohort.[10,11,34-36] This entity exhibited markedly different biology and clinical course, further supporting the need for precise diagnosis and distinction of PMBL from other LBCL subtypes, as is now clearly established in international classifications.[1,2] We emphasize the importance of an integrated diagnostic approach that combines expert histological analysis with at least 1 molecular technique, such as GEP or NGS, to achieve a precise diagnosis of PMBL. This approach is essential because it directly influences treatment decisions: patients with PMBL benefit from dose-dense regimens,[10,37] unlike patients with DLBCL.[38-40] In this study, we used the LymphoSign GEP panel alongside NGS to aid pathologists in distinguishing PMBL from other lymphoma subtypes, forming an integrated histomolecular diagnostic procedure.[23] Adopting this strategy into routine practice could significantly improve patient outcomes by ensuring accurate diagnoses and appropriate therapeutic approaches.

Overall, PFS and OS were favorable in this PMBL population (2-year PFS, 86.2%; 2-year OS, 93.2%) and consistent with other published studies, reinforcing the excellent outcomes of patients treated with frontline dose-dense immunochemotherapy without radiotherapy.[10,11,37,41] In treatment subgroups, G demonstrated efficacy comparable with R, as previously observed in DLBCL.[21,42] Similarly, no significant difference in outcomes was found between CHOP14 and ACVBP induction regimens, aligning with findings from a pooled analysis of 5 clinical trials conducted by LYSA[41] and our previous earlier retrospective study, which analyzed real-world data from a large nontrial population.[11] The rate of consolidation with ASCT was twice as high in the PMBL population (26.5%) compared with the overall GAINED study population,[21] reflecting a



*One patient died before treatment start ; ** In patients with missing PET2 and/or PET4 data, consolidation treatments data were also missing; *** One patient experienced treatment discontinuation after 3 cycles of R-ACVBP (toxicity). Switch for R-CHOP (n = 2 cycles) then etoposide-ifosfamide (2 cycles).*

ASCT: autologous stem cell transplantation; PET: positron emission tomography

Figure 3. Treatments received according to iPET responses. *One patient died before treatment start. **In patients with missing PET2 and/or PET4 data, consolidation treatments data were also missing. ***One patient experienced treatment discontinuation after 3 cycles of R-ACVBP (toxicity). Switch for R-CHOP (n = 2 cycles) then etoposide-ifosfamide (2 cycles).

greater frequency of positive iPET in PMBL, even when ΔSUVmax was used for interpretation.

ΔSUVmax PET2 of >66% and ΔSUVmax PET4 of >70% were achieved in 62% and 87% of patients with iPET data, respectively, which was higher than expected for a PMBL population. In comparison, previous studies reported complete metabolic response (CMR) rates (based on DS) ranging from 10% to 47.8% at PET2[11,43] and 52.8% to 73.2% at PET4.[11,44] Notably, PET4 response (ΔSUVmax of ≤70%) emerged as the strongest dynamic predictor of shorter PFS (HR, 6.6; 95% CO, 2.3-18.77), regardless of the treatment group.

The lack of prognostic impact for aaIPI in MVA may be attributed to limited statistical power, the small sample size, and the low number of events. Additionally, the use of ASCT may have mitigated the influence of baseline prognostic factors. Bulk (tumor mass of >10 cm) emerged as a strong baseline prognostic marker, a finding not previously reported in other recent studies.[11,45-49] This may indicate increased chemotherapy resistance in these patients,

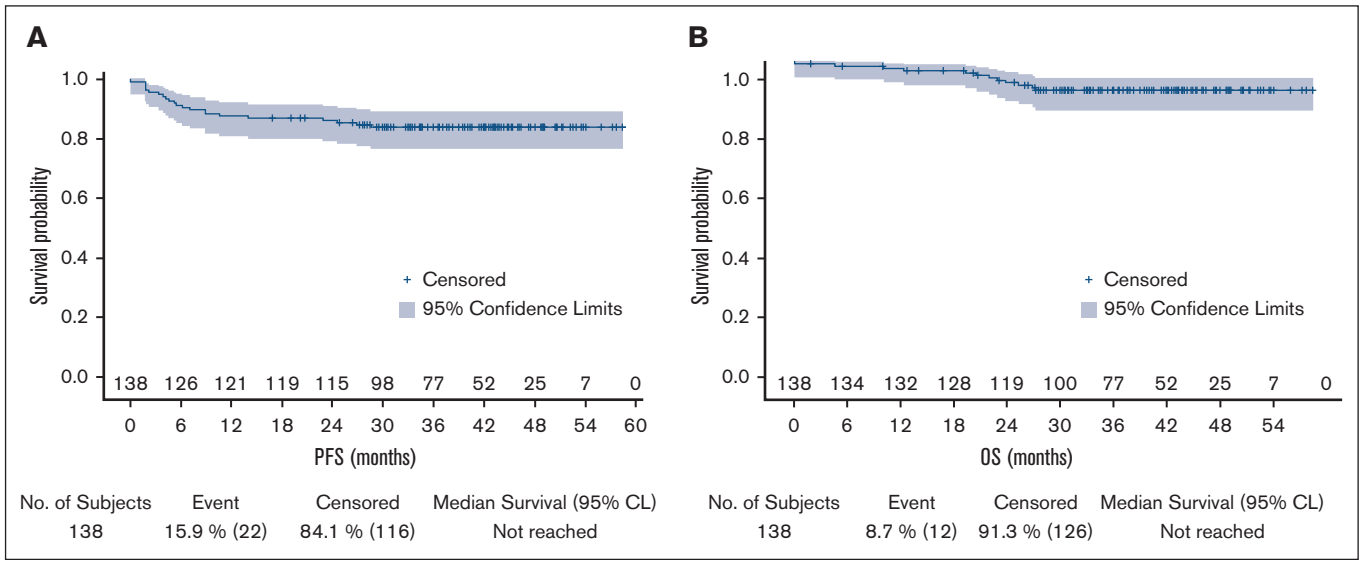


Figure 4. Progression-Free Survival and Overall Survival Curves (Kaplan-Meier Analysis). (A) PFS and (B) OS in the PMBL set.

Table 3. Univariate and MVA of prognostic factors associated with PFS

		Univariate analysis					MVA			
Variable	**Modality**	**HR**	**95% lower confidence limit for HR**	**95% upper confidence limit for HR**	**Raw *P* value**	**FDR *P* value**	**HR**	**95% lower confidence limit for HR**	**95% upper confidence limit for HR**	***P* value**
ΔSUVmax PET2	Continuous	0.785	0.548	1.124	.2285	.228				
ΔSUVmax PET4	Continuous	0.256	0.151	0.434	<.0001	<.0001				
ΔSUVmax (cutoff)					.0041	.012				
	ΔSUVmax PET2 of ≤66% ($PET2^-$)	Reference	–	–	–	–	Reference	–	–	–
	ΔSUVmax PET2 of ≤66% and ΔSUVmax PET4 of >70% ($PET2^+/PET4^-$)	2.065	0.694	6.146	.1925	–	2.309	0.771	6.913	.1348
	ΔSUVmax of ≤70% ($PET4^+$)	6.566	2.298	18.767	.0004	–	4.952	1.714	14.305	.0031
Bulk	>10 cm	4.37	1.479	12.916	.0024	.02	4.388	1.275	15.106	.019
Ann Arbor stage	III-IV	4.064	1.375	12.012	.004	.02				
aaIPI	2-3	2.653	1.038	6.782	.0308	.103	2.303	0.817	6.495	.1148
TMTV*	Continuous	1.267	0.996	1.61	.0724	.109				
TMTV cutoff	≥360 cm^3	3.91	1.307	11.699	.0064	.013				
TLG†	Continuous	1.078	0.971	1.196	.1815	.218				
ECOG PS score	2-4	2.878	1.125	7.363	.044	.11				
Pleura and/or pericardium involvement	Absence	0.502	0.214	1.174	.1227	.245				
B symptoms	Presence	1.853	0.801	4.29	.1491	.248				
Induction chemotherapy	CHOP14	1.609	0.649	3.986	.2937	.42				
Monoclonal antibody	R	1.125	0.486	2.604	.7826	.783				
Age	Continuous	1.145	0.759	1.729	.5226	.621				
LDH level	Elevated	0.683	0.202	2.31	.5586	.621				
Baseline cfDNA level	Continuous	2.502	0.291	21.525	.4595	.715				
cfDNA cutoff	cfDNA low	0.689	0.143	3.319	.6543	.727				
sPDL1	Continuous	0.694	0.34	1.419	.2493	.715				
sPDL1 cutoff	sPDL1 low	2.058	0.69	6.143	.1848	.715				
PDL1/PDL2 gene expression	$PDL1^{high}/PDL2^{high}$	2.274	0.877	5.897	.0929	.715				
TP53	Mutated	0.703	0.193	2.553	.5806	.726				
CD58	Mutated	1.023	0.335	3.128	.9679	.968				
B2M	Mutated	0.688	0.231	2.048	.5007	.715				

ECOG PS, Eastern Cooperative Oncology Group performance status; FDR, false discovery rate.

*The TMTV effect corresponds to an increase of 200 cm^3. We did not include TMTV of ≥360 cm^3 in the MVA because the model lacked sufficient power to estimate both parameters (TMTV of ≥360 cm^3 and bulk of >10 cm), which are highly correlated. Indeed, 70% of patients with PMBL with TMTV of ≥360 cm^3 also had bulk of >10 cm. Given the limited sample size, the model could not simultaneously estimate the effects of these 2 variables. Therefore, we retained bulk of >10 cm in the MVA, as it had higher HR in the univariate analysis.

†The TLG effect corresponds to an increase of 1000.

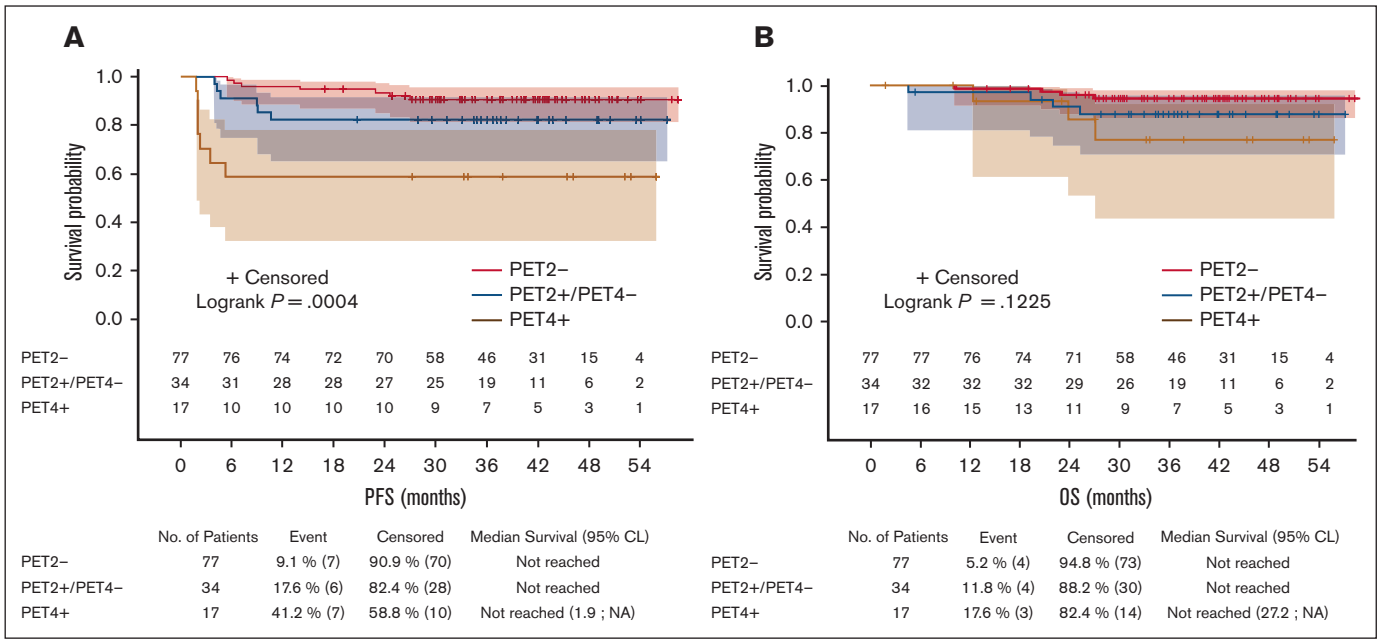


Figure 5. Progression-Free Survival and Overall Survival According to Interim PET2 and PET4 Response (Kaplan-Meier Analysis). (A) PFS and (B) OS according to interim PET2 and PET4 response in the PMBL set.

potentially because of anatomical characteristics of large mediastinal tumors, in which the substantial volume, and dense, fibrotic, and compartmentalized structure may impair the penetration and distribution of chemotherapeutic agents, including those in ASCT conditioning regimens. Such limited drug diffusion could affect local pharmacodynamics, especially in patients not exposed to radiotherapy, as suggested by preclinical models of solid tumors.[50-53] We did not include TMTV of ≥360 cm^3 in the MVA because the model lacked sufficient power to estimate both parameters (TMTV of ≥360 cm^3 and bulk of >10 cm), which are highly correlated. Indeed, 70% of patients with PMBL with TMTV of ≥360 cm^3 also had bulk of >10 cm. Given the limited sample size, the model could not simultaneously estimate the effects of these 2 variables. Therefore, we retained bulk in the MVA, because it had a higher HR in the univariate analysis. Other studies have proposed alternative thresholds, such as 25% or 41% of SUVmax or fixed SUV of ≥2.5.[11,21,24,54-57] However, in our series, the correlation between the 41% of SUVmax and fixed SUV4 segmentation approaches was ~90% (data not shown), resulting in comparable outcomes. Moreover, recent data presented as an abstract at the American Society of Hematology 2024 conference further support the use of an SUV of ≥4 threshold for volumetric measurements in PMBL, reporting a median TMTV value of 396 mL, which is very close to that of our cohort.[58] Further research is needed to evaluate whether bulk of >10 cm could serve as a surrogate marker for more advanced tumor volume or metabolic distribution tools, such as metabolic heterogeneity or TLG.[30,49,59]

A limitation of our study is that DS was largely unrecorded, as the protocol recommended using ΔSUVmax to evaluate treatment response. This omission prevents analysis of DS predictive value on iPET, as has been conducted in other studies.[11,43,44] Furthermore, EoT CMR was not assessed in the GAINED trial. By contrast, in our earlier retrospective study, we reported similar ~86% CMR rates across the R-ACVBP and R-CHOP14 groups.[11] Consequently, we are unable to directly compare our results with those of the International Extranodal Lymphoma Study Group 37 (IELSG37) trial, which assessed the omission of radiotherapy in patients achieving CMR at EoT.[35]

Regarding biological features, the mutational profile identified in this study perfectly aligns with the existing literature on PMBL. We observed recurrent mutations in genes such as *SOCS1* (70.1%), *B2M* (56.3%), *STAT6* (49.4%), *TNFAIP3* (47.1%), *GNA13* (39.1%), *CIITA* (37.9%), and *CD58* (36.8%), all of which are well-established genetic alterations associated with PMBL. In addition, we observed a higher tumor mutational burden in the $PDL1^{high}$/$PDL2^{high}$ group, a feature known to correlate with responses to checkpoint inhibitors.[60-62] These findings further support the characterization of PMBL as having a distinct genetic landscape compared with other LBCL, as described in previous genomic studies.[5,15,16]

Patients with $PDL1^{high}$/$PDL2^{high}$ status exhibited worse clinical characteristics (eg, elevated LDH, higher aaIPI scores, and Eastern Cooperative Oncology Group performance status score of ≥2), and a higher incidence of $PET4^{+}$ (23.5% vs 9.5%), correlating with a trend toward poorer outcomes (PFS: HR, 2.27; OS: HR, 3.87), consistent with, but not as pronounced as, findings from our previous report.[4] Approximately 25% of patients with PMBL underwent ASCT, a higher rate than in the overall GAINED trial population (~15%)[21] and slightly higher than in our previously retrospective study (22%).[11] This may have influenced the lack of significant associations between baseline factors and outcomes. We acknowledge that interpreting the predictive capacity of iPET results is limited by our study design, in which treatment was adapted based on iPET findings. The iPET-guided strategy aimed to reduce PFS/OS differences between risk groups defined by

Table 4. Univariate analyses and MVA of prognostic factors associated with OS

		Univariate analysis					MVA			
Variable	**Modality**	**HR**	**95% lower confidence limit for HR**	**95% upper confidence limit for HR**	**Raw *P* value**	**FDR *P* value**	**HR**	**95% lower confidence limit for HR**	**95% upper confidence limit for HR**	***P* value**
ΔSUVmax PET2	Continuous	0.736	0.471	1.15	.2304	.346				
ΔSUVmax PET4	Continuous	0.361	0.211	0.616	.0024	.014				
ΔSUVmax (cutoff)					.1635	.327				
	ΔSUVmax PET2 of ≤66%	Reference	–	–	–	–	Reference	–	–	–
	ΔSUVmax PET2 of ≤66% and ΔSUVmax PET4 of >70% ($PET2^+/PET4^-$)	2.376	0.594	9.500	.2211	–	3.008	0.737	12.285	.125
	ΔSUVmax of ≤70% ($PET4^+$)	4.217	0.943	18.860	.0597	–	3.175	0.7	14.395	.1342
Bulk	>10 cm	2.875	0.778	10.624	.0893	.179	1.908	0.496	7.341	.3476
Ann Arbor stage	III-IV	9.885	1.276	76.572	.0032	.032				
aaIPI	2-3	4.885	1.07	22.297	.0176	.059	4.292	0.885	20.809	.0705
TMTV*	Continuous	1.161	0.803	1.677	.4483	.501				
TMTV cutoff	≥360 cm^3	8.566	1.085	67.618	.0083	.025				
TLG†	Continuous	1.056	0.906	1.231	.5012	.501				
ECOG PS score	2-4	2.477	0.67	9.155	.2106	.351				
Pleura and/or pericardium involvement	Absence	0.341	0.11	1.058	.0686	.172				
B symptoms	Presence	4.541	1.23	16.775	.0132	.059				
Induction chemotherapy	CHOP14	1.368	0.4	4.674	.6126	.613				
Monoclonal antibody	R	0.665	0.211	2.097	.4833	.537				
Age	Continuous	1.251	0.722	2.168	.4303	.537				
LDH level	Elevated	0.518	0.114	2.365	.4308	.537				
Baseline cfDNA level	Continuous	3.047	0.316	29.339	.3975	.497				
cfDNA cutoff	cfDNA low	0.447	0.082	2.445	.379	.497				
sPDL1	Continuous	0.425	0.13	1.388	.0776	.259				
sPDL1 cutoff	sPDL1 low	2.705	0.7	10.462	.1299	.325				
PDL1/PDL2 gene expression	$PDL1^{high}/PDL2^{high}$	3.873	0.968	15.498	.0465	.249				
TP53	Mutated	0.477	0.056	4.08	.4646	.516				
CD58	Mutated	0.825	0.151	4.506	.8227	.823				
B2M	Mutated	0.402	0.074	2.194	.2757	.459				

*The TMTV effect corresponds to an increase of 200 cm^3.
†The TLG effect corresponds to an increase of 1000.

iPET. As observed in the GAINED study, no significant difference in PFS was reported between $PET2^{-}$ and $PET2^{+}$ patients among $PET4^{-}$ patients, suggesting that ASCT may mitigate the risk in $PET2^{+}$ patients. However, no PFS improvement was observed in $PET4^{+}$ patients, even when treated with salvage therapy. These findings suggest that PET4 results remain a prognostic factor for identifying high-risk patients, despite treatment adaptations in our study. In addition, growing evidence supports the use of iPET as a predictive tool in other LBCLs. For instance, a study by Sun et al demonstrated that iPET using ΔSUVmax was predictive of PFS (HR, 20.4) and OS (HR, 12.7) in non–germinal center B-cell DLBCL.[63] Additionally, a study by Johansson et al investigated iPET in DLBCL using ΔSUVmax in a MVA integrating baseline clinical factors and the time-dependent variable iPET. The authors observed that iPET positivity was associated with adverse outcomes (HR, 6.1 for time to progression; and HR, 5.5 for OS).[64]

Furthermore, the small group of patients with GEP data and the PET-driven consolidation (in which $PET4^{+}$ patients received salvage therapy) may explain the limited prognostic impact of $PDL1^{high}/PDL2^{high}$ status, a feature previously shown to be strongly unfavorable in non-PET–driven trial settings. It is plausible that $PDL1^{high}/PDL2^{high}$ patients represent those with highly symptomatic disease and/or high tumor burden at diagnosis, which could preclude them from waiting for phase 3 trial enrollment. Indeed, in our previous study, $PDL1^{high/}PDL2^{high}$ patients had a higher proportion of elevated LDH (94.6% vs 77.1%) and greater baseline TMTV (358.5 vs 255.7 cm^3) than other patients.[4] Consequently, prognostic factors identified in real-world settings may not be fully replicated in controlled clinical trial environments. The lack of statistical significance in this analysis may also stem from the limited sample size and the nonrandom distribution of patients with available GEP data. Similarly, the small number of patients with NGS data limits the ability to draw robust conclusions regarding the prognostic significance of specific genetic alterations, such as *CD58*, *TP53*, or *B2M* mutations, which have been previously reported as unfavorable features in other studies.[4,16,65]

Finally, regarding the broader implications of our findings, it is worth noting that ASCT is no longer recommended as a first-line consolidation treatment for DLBCL and has never been a standard for PMBL.[66-68] The PET2/PET4-guided strategy, hindered by a high rate of PET2 positivity (~38%, according to ΔSUVmax of ≤66%), does not reliably discriminate patients at risk of progression or relapse. A PET4-only strategy could offer greater utility, enabling the identification of slow responders or patients with progressive disease, whose prognosis is notably worse, and guiding them toward salvage therapies including, for instance radiotherapy, anti-PD1 immunotherapy, and/or chimeric antigen receptor T-cell treatments in cases of PET4 positivity (ΔSUVmax of ≤70%). These approaches have demonstrated promising results for patients with PMBL in several recent studies,[69-73] and this strategy warrants further exploration in future clinical trials targeting high-risk, $PET4^{+}$ populations.

In conclusion, this analysis underscores the strong representation, distinct characteristics, and excellent outcomes of patients with PMBL in the GAINED trial. It highlights the importance of expert histopathological and molecular characterization for accurate diagnosis, which is crucial for ensuring these patients receive appropriate dose-dense treatments. Genetics were not associated with outcomes within the context of a PET-driven strategy whereas iPET response, particularly ΔSUVmax PET4, emerged as a key predictor of outcomes in this carefully selected clinical trial population, in which consolidation treatments were tailored based on iPET results.

Acknowledgments

The authors thank the patients who participated in this study and their families, as well as Jean Galtier who reviewed this manuscript on behalf of the Lymphoma Study Association scientific committee, and all of the investigators and staff at GAINED clinical sites. The authors also acknowledge The Lymphoma Academic Research Organisation (LYSARC) and all research teams and nurses at the participating centers. The authors thank René-Olivier Casasnovas for support and contribution to the conduct of the GAINED study. The authors thank Anne-Ségolène Cottereau for her review of the manuscript. Roche Pharma provided obinutuzumab.

Roche Pharma funded the GAINED trial, and LYSARC served as the sponsor of the study.

The funder had no role in the trial design, data collection, data analysis, data interpretation, or the writing of the present report.

Authorship

Contribution: V.C. designed and supervised this work, collected, analyzed, interpreted the data, and wrote the manuscript, had full access to all data in this post hoc analysis of the study, and held final responsibility for the decision to submit for publication; S.L.G. designed the GAINED trial in collaboration with J.-P.J., C.H., and E.I., conducted the study, analyzed the results, and enrolled and treated patients; H.G., L.O., F.M., H.T., V.R., R.H., C.T., H.M., F.C., K.B., G.L.D, L.-M.F., R.N., P.F., D.S., G.C., C.B., W.B., and C.R. enrolled and treated patients; T.M., A.M., and J.B. performed the expert pathological review and interpreted the data; F.D. conducted the next-generation sequencing experiments, interpreted the biological data, and participated in the integrated histomolecular diagnosis process; P.R. carried out and analyzed the gene expression profiling experiments and contributed to the integrated histomolecular diagnosis process; P.B.-D., F.K.-B., C.B.-M., S.K., and E.I. centrally reviewed the positron emission tomography results; P.B.-D., S.K., and E.I. conducted the total metabolic tumor volume and total lesion glycolysis assessments; M.-H.E. and L.C. performed the statistical analysis; F.J., T.M., and T.F designed and supervised the present work, analyzed, and interpreted the data, and edited the manuscript; and all authors approved the manuscript.

Conflict-of-interest disclosure: V.C. has received honoraria from AbbVie, AstraZeneca, Bristol Myers Squibb (BMS), Ideogen, Janssen, Kiowa Kirin, Kite/Gilead, Novartis, Pfizer, Sanofi, and Takeda. R.H. has received honoraria from Kite/Gilead, Novartis, BMS/Celgene, Incyte, Janssen, Merck Sharp & Dohme., Takeda, Amgen, AbbVie, and Roche; and is a member on an entity's board of directors or advisory committees of Kite/Gilead, Novartis, BMS/Celgene, Tessa Therapeutics, AbbVie, and Roche. W.B. has received travel grants from Leo Pharma, Roche, and Takeda; and honoraria from Leo Pharma and BMS. The remaining authors declare no competing financial interests.

ORCID profiles: V.C., 0000-0002-1559-007X; F.D., 0009-0009-9161-6903; S.L.G., 0000-0001-9840-2128; L.O., 0000-0002-0039-1983; F.M., 0000-0002-3714-9824; V.R., 0000-0002-5221-353X; R.H., 0000-0003-1729-8213; G.L.D., 0000-0002-4689-3882; R.N., 0000-0002-7048-5491; D.S., 0000-0002-9205-625X; G.C., 0000-0003-0659-9635; W.B., 0000-0001-7415-9549; F.K.-B., 0000-0002-3417-0759; C.B.-M., 0000-0002-8219-3592; C.R., 0000-0003-3717-7961; E.I., 0000-0003-1578-4058; T.F., 0000-0002-6437-4189.

Correspondence: Vincent Camus, Department of Hematology, Centre Henri Becquerel, 1, rue d'Amiens, 76000 Rouen, France; email: vincent.camus@chb.unicancer.fr.

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