The Oncologist®

Hematologic Malignancies

Identification of Very Low-Risk Subgroups of Patients with Primary Mediastinal Large B-Cell Lymphoma Treated with R-CHOP

Theodoros P. Vassilakopoulos,[a] Michail Michail,[e] Sotirios Papageorgiou,[f] Georgia Kourti,[g,h] Maria K. Angelopoulou,[a] Fotios Panitsas,[a] Sotirios Sachanas,[i] Christina Kalpadakis,[j] Eirini Katodritou,[k] Theoni Leonidopoulou,[l] Ioannis Kotsianidis,[m] Eleftheria Hatzimichael,[n] Maria Kotsopoulou,[o] Maria Dimou,[b] Eleni Variamis,[c] Dimitrios Boutsis,[p] Evangelos Terpos,[q] Maria N. Dimopoulou,[a] Stamatios Karakatsanis,[g] Eurydiki Michalis,[r] George Karianakis,[s] Pantelis Tsirkinidis,[t] Chryssa Vadikolia,[u] Christos Poziopoulos,[v] Anna Pigaditou,[w] Effimia Vrakidou,[s] Theophanis Economopoulos,[w] Lydia Kyriazopoulou,[n] Marina P. Siakantaris,[a] Marie-Christine Kyrtsonis,[b] Argyris Symeonidis,[x] Konstantinos Anargyrou,[y] Maria Papaioannou,[z] Evdoxia Hatjiharissi,[k,z] Elissavet Vervessou,[aa] Maria Tsirogianni,[bb] Maria Palassopoulou,[cc] Gabriella Gainaru,[s] Ekaterini Stefanoudaki,[dd] Panayiotis Zikos,[ee] Panayiotis Tsirigotis,[f] Gerasimos Tsourouflis,[d] Theodora Assimakopoulou,[l] Pavlina Konstantinidou,[k] Helen A. Papadaki,[j] Katerina Megalakaki,[o] Meletios-Athanasios Dimopoulos,[q] Vassiliki Pappa,[f] Themis Karmiris,[h] Paraskevi Roussou,[g] Panayiotis Panayiotidis,[b] Kostas Konstantopoulos,[a] Gerassimos A. Pangalis[a,i]

Departments of [a]Hematology and Bone Marrow Transplantation, [a]First Propedeutic Internal Medicine, [a]First Internal Medicine, and [a]Second Propedeutic Surgery, National and Kapodistrian University of Athens, Laikon General Hospital, Athens, Greece; [e]Department of Hematology, Nicosia General Hospital, Nicosia, Cyprus; [f]Second Propaedeutic Department of Internal Medicine, National and Kapodistrian University of Athens, Attikon Hospital, Athens, Greece; [g]Third Department of Internal Medicine, National and Kapodistrian University of Athens, Sotiria Hospital, Athens, Greece; [h]Department of Hematology and Lymphoma, Evangelismos General Hospital, Athens, Greece; [i]Department of Hematology, Athens Medical Center, Psychikon Branch, Athens, Greece; [j]Department of Hematology, University of Crete, Iraklion, Crete, Greece; [k]Department of Hematology, Theagenion Anticancer General Hospital, Thessaloniki, Greece; [l]Department of Hematology, Sismanoglion General Hospital, Athens, Greece; [m]Department of Hematology, Democritus University of Thrace, Alexandroupolis, Greece; [n]Department of Hematology, University of Ioannina, Ioannina, Greece; [o]Department of Hematology, Metaxa Anticancer Hospital, Piraeus, Greece; [p]Department of Hematology, Athens Navy Hospital, Athens, Greece; [q]Department of Therapeutics, National and Kapodistrian University of Athens, Alexandra Hospital, Athens, Greece; [r]Department of Clinical Hematology, "G.Gennimatas" Athens General Hospital, Athens, Greece; [s]Department of Hematology, HYGEIA Hospital, Athens, Greece; [t]Department of Hematology, 401 Army Hospital, Athens, Greece; [u]Department of Hematology, 424 Army Hospital, Thessaloniki, Greece; [v]Department of Hematology, Metropolitan Hospital, N. Faliron, Athens, Greece; [w]Department of Hematology, Athens Medical Center, Amaroussion Branch, Athens, Greece; [x]Hematology Division, Dept of Internal Medicine, University of Patras, Patras, Greece; [y]Department of Hematology, 251 Air Force Hospital, Athens, Greece; [z]Hematology Unit, 1st Dept of Internal Medicine, AHEPA Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece; [aa]Department of Hematology, Henry Dynant Hospital, Athens, Greece; [bb]Department of Hematology, Aghios Savvas Anticancer Hospital, Athens, Greece; [cc]Department of Hematology, University of Thessalia Hospital, Larissa, Greece; [dd]Department of Hematology, Amalia Fleming Hospital, Athens, Greece; [ee]Hematology Division, Aghios Andreas Hospital, Patras, Greece

Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Prognostic factors • Rituximab • CHOP • Large B-cell lymphoma • Primary mediastinal

Abstract

Background. R-CHOP can cure approximately 75% of patients with primary mediastinal large B-cell lymphoma (PMLBCL), but prognostic factors have not been sufficiently evaluated yet. R-da- EPOCH is potentially more effective but also more toxic than R-CHOP. Reliable prognostic classification is needed to guide treatment decisions.

Materials and Methods. We analyzed the impact of clinical prognostic factors on the outcome of 332 PMLBCL patients ≤65 years treated with R-CHOP ± radiotherapy in a multicenter setting in Greece and Cyprus.

Results. With a median follow-up of 69 months, 5-year freedom from progression (FFP) was 78% and 5-year

Correspondence: Theodoros P. Vassilakopoulos, M.D., Ph.D., Department of Hematology and Bone Marrow Transplantation, National and Kapodistrian University of Athens, School of Medicine, Laikon General Hospital, Athens, Greece 11527. Telephone: 0030213- 2061702; e-mail: tvassilak@med.uoa.gr and theopvass@hotmail.com Received July 5, 2020; accepted for publication April 2, 2021; published Online First on June 17, 2021. http://dx.doi.org/10.1002/onco.13789

lymphoma specific survival (LSS) was 89%. On multivariate analysis, extranodal involvement (E/IV) and lactate dehydrogenase (LDH) ≥2 times upper limit of normal (model A) were significantly associated with FFP; E/IV and bulky disease (model B) were associated with LSS. Both models performed better than the International Prognostic Index (IPI) and the age-adjusted IPI by Harrel's C rank parameter and Akaike information criterion. Both models A and B defined high-risk subgroups (13%–27% of patients [pts]) with approximately 19%–23% lymphoma-related mortality. They also defined subgroups composing approximately one-fourth or one-half of the patients, with 11% risk of failure and only 1% or 4% 5-year lymphoma-related mortality.

Conclusion. The combination of E/IV with either bulky disease or LDH ≥2 times upper limit of normal defined high-risk but not very-high-risk subgroups. More importantly, their absence defined subgroups comprising approximately one-fourth or one-half of the pts, with 11% risk of failure and minimal lymphoma-related mortality, who may not need more intensive treatment such as R-da-EPOCH. ***The Oncologist*** 2021;26:597–609

Implications for Practice: By analyzing the impact of baseline clinical characteristics on outcomes of a large cohort of patients with primary mediastinal large B-cell lymphoma homogeneously treated with R-CHOP with or without radiotherapy, we developed novel prognostic indices which can aid in deciding which patients can be adequately treated with R-CHOP and do not need more intensive regimens such as R-da-EPOCH. The new indices consist of objectively determined characteristics (extranodal disease or stage IV, bulky disease, and markedly elevated serum lactate dehydrogenase), which are readily available from standard initial staging procedures and offer better discrimination compared with established risk scores (International Prognostic Index [IPI] and age-adjusted IPI).

Introduction

Primary mediastinal (thymic) large B-cell lymphoma (PMLBCL) has been recognized as a distinct clinicopathologic entity in the World Health Organization (WHO) classification [1,2]. Based on unique demographic, clinical, morphologic, and immunohistochemical characteristics, it is classified separately from diffuse large B-cell lymphomas (DLBCL). Despite being an aggressive B-cell lymphoma, its molecular signature is more akin to Hodgkin lymphoma rather than DLBCL, as it is characterized by constitutive activation of NFκB and JAK-STAT pathways and programmed death ligand 1 and 2 overexpression [3,4].

PMLBCL is a highly aggressive neoplasm, characterized by a rapidly growing mediastinal tumor, usually bulky, which frequently causes superior vena cava syndrome, other compressive symptoms, and pleural and pericardial effusions. Rarely, the disease is much more extensive at the time of diagnosis involving peculiar extranodal sites, such as the kidneys, adrenals, stomach, ovary, and so on; however, bone marrow involvement is almost always absent [5–9]. The involvement of these peculiar extranodal sites or the central nervous system (CNS) is much more frequent at the time of relapse/progression [10].

Prior to the introduction of rituximab, the combination of cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) followed by radiotherapy (RT) had been considered suboptimal treatment for PMLBCL with cure rates generally not exceeding 50–60% [5,11–13]. Combinations of methotrexate (or etoposide), doxorubicin, cyclophosphamide, vincristine, prednisone and bleomycin known as M(V)ACOP-B [14,15], dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (da-EPOCH) [16], Burkitt-like or acute lymphoblastic leukemia-like regimens such as the Memorial and GMALL protocols [12,17,18], and even consolidation of first-line response with high-dose therapy and autologous stem cell transplantation [5] have all been considered superior to CHOP in rather small- to medium-sized patient series, albeit without head-to head randomized comparison. The introduction of rituximab greatly improved the results of CHOP. Rituximab-CHOP (R-CHOP) followed by RT in the majority of the patients has produced cure rates between 75% and 80% and long-term survival of 85%–90% in several small- to moderate-sized studies [13,19–25]. As a consequence, the role of more intensive immunochemotherapy regimens has been questioned [26–29]. R-CHOP-14 appeared promising in a subgroup analysis of 50 patients with PMLBCL within the large U.K. National Cancer Research Institute phase III trial [30], warranting validation in a dedicated future prospective study. Most importantly, rituximab combined with da-EPOCH (R-da-EPOCH) has produced impressive results in a phase II trial of 67 patients without the use of RT [31]. Subsequent real life data suggest that R-da-EPOCH might be only marginally better than R-CHOP but can be used to avoid RT [32–36]. However, R-da-EPOCH is a rather cumbersome regimen, requiring inpatient delivery and producing more acute hematologic toxicity and possibly late adverse effects [31,36].

Based on the above, a risk-adapted strategy would be desirable to restrict the use of more aggressive regimens to higher-risk subgroups of patients. However, prognostic factors for the outcome of PMLBCL have been mainly studied prior to the rituximab era. The International Prognostic Index (IPI) and the age-adjusted IPI (aaIPI) are used by extrapolating data applicable to DLBCL, and no prognostic model specifically applicable to PMLBCL has been developed. Very few studies have been published [21,37] or presented [19] in the rituximab era and have been based on small to moderately sized series including 123 [37], 96 [19], and 63 patients [21]. The success of R-CHOP in PMLBCL limits the number of events and makes prognostic factor analysis difficult.

The aim of the present study was to collect data on a large number of patients with PMLBCL to conduct a

powerful prognostic factor analysis and identify high- or very-low-risk subgroups for risk-adapted therapy.

Materials and Methods

Patients: Staging

Among 341 consecutive nonpediatric patients with PMLBCL, who were treated in the cooperating Hellenic and Cypriot hematology departments with R-CHOP or similar regimens with or without RT between 2001 and 2019, 332 patients ≤65 years were included in the present analysis. Only 15 of 341 patients (4.4%) were older than 60 years, which is consistent with other published data. Among the 332 eligible patients, the median age was 32 years (16–65), and 64% were female. In accordance to a previous report from our group [13], patients were eligible for inclusion if they had presented with a clinical picture (dominated by a prominent mediastinal mass) and a histology report consistent with PMLBCL according to the WHO or Revised European American Lymphoma classification [1,2,38]. Patients with minor mediastinal involvement as part of more extensive lymphoma at other sites were excluded [11]. Patients were also excluded if they had any concomitant extramediastinal mass greater in size than the primary mediastinal lesion [12].

Patients were clinically staged by standard procedures using a conservative interpretation of the Ann-Arbor definitions, as previously described [11,13,39,40]. In accordance with our previous report [13], stage IV was assigned only if noncontiguous extensive lymphoma spread to extranodal sites was documented. Contiguous spread within the thorax was considered stage II even in the presence of radiologic chest wall, osseous, lung, pleural, or pericardial involvement [11]. Patients with solitary lung lesions that were adjacent (proximal) but not contiguous to the mediastinal mass were also considered "E" and not stage IV [39,40]. Patients with multiple lung lesions were assigned as stage IV. Bulky disease was defined as a mediastinal mass ≥ 10 cm. A proportion of patients was staged with positron emission tomography (PET) in addition to conventional staging in the more recent years, but only the results of conventional staging were taken into account. Anemia was defined as hemoglobin levels <13 g/dL and < 11.5 g/dL in men and women, respectively [41]. Risk stratification was based on the IPI as well as on the age-adjusted IPI [42], because the vast majority of patients were younger than 60 years (326/332 or 98%). Exact values for IPI and aaPI were available for 309 patients. In 12 additional patients, accurate assignment in an IPI subgroup (0–1 vs. 2 vs. 3–5 for IPI or 0–1 vs. 2–3 for aaIPI) was possible, rendering 321 patients eligible for this analysis.

Treatment Strategies and Conventional Criteria of Response

Standard R-CHOP-21 and R-CHOP-14 (used in a minority of patients) as well as their variants were administered as originally described [43,44]. The treatment plan included six to eight cycles of R-CHOP–based chemotherapy. R-CHOP-21 was administered to 302 of 332 patients (91%), whereas 30 patients (9%) received R-CHOP-14. Minor deviations were recorded in a few patients as described in Table 1 and the corresponding footnote; these regimens were considered roughly equivalent to the standard ones. Patients with stable or progressive disease could be withdrawn earlier at the discretion of the treating physician. Conventional radiologic response was evaluated according to standard criteria [45]. In responding patients, RT was used at the discretion of the treating physician, but this decision was affected by PET/computed tomography (CT) results, especially in the more recent years (see Results for details) [46–49].

Retrospective medical charts review was performed by treating physicians at each of the participating centers and anonymized data were submitted for analysis. Individual patient consent was not required.

Statistical Analysis

The primary endpoint was freedom from progression (FFP), which was defined as the time interval from treatment initiation to any of the following events: disease progression, relapse, initiation of salvage therapy due to inadequate response to R-CHOP, therapy-related death without prior progression/relapse, or last follow-up. Lymphoma-specific survival (LSS) was defined as the time interval from treatment initiation until death secondary to disease progression or disease-related procedures. Unrelated deaths without prior disease progression were censored at the time of death. However, only two deaths of unrelated causes were recorded. Thus, LSS was almost identical to overall survival, which was not analyzed in this study. Similarly, FFP was analyzed instead of progression-free survival to specifically assess tumor control, but these two endpoints were almost identical, because of the very low number of deaths without prior treatment failure.

Survival curves were plotted according to the Kaplan-Meier method [50] and were compared with the log-rank test [51]. Two-sided p values less than .05 were considered significant. The identification of independent prognostic factors was performed using Cox's proportional hazards model [52]. A backward stepwise selection procedure, with entry and removal criteria of $p = .05$ and $p = .10$, respectively, was used. Based on the final multivariate models for the two main outcomes (FFP and LSS), two new risk scores were developed.

The predictive powers of alternative predictors (binary IPI, binary aaIPI, and scores derived from this study) for LSS and FFP outcomes in Cox regression models were compared using the rank parameter Harrel's C [53]. We also assessed the relative quality of Cox regression models based on each of the predictive scores for LSS and FFP using the Akaike information criterion (AIC) [54].

Results

Patients' and Treatment Characteristics

In total, 332 nonpediatric patients with PMLBCL up to 65 years were eligible to be included in this study after the exclusion of 9 older patients (66–82 years). These were consecutive patients who received R-CHOP or similar regimens

Table 1. Patients' characteristics and univariate analysis of FFP and LSS

Patients' characteristics	Patients, *n* (%)	Pts failed	5-yr FFP, %	*p* value	Pts died	5-yr LSS, %	*p* value
Age, years							
<38	242 (72.9)	55	77	.600	27	88	.491
≥38	90 (27.1)	17	80		7	91	
Gender							
Female	213 (64.2)	43	79	.35	21	90	.601
Male	119 (35.8)	29	74		13	88	
Stage							
I/II	288 (86.7)	54	81	.001	27	90	.194
III/IV	44 (13.3)	18	59		7	82	
B-symptoms							
No	225 (68.0)	43	80	.077	18	91	.043
Yes	106 (32.0)	29	72		16	85	
PS							
0–1	271 (85.5)	51	81	.071	24	91	.161
2–4	46 (14.5)	14	69		7	84	
Extranodal sites							
0–1	293 (88.5)	56	80	.007	26	91	.068
≥2	38 (11.5)	15	59		7	80	
Extranodal sites							
No	209 (63.0)	29	86	<.001	13	94	.002
Any	123 (37.0)	43	64		21	82	
IIE/IIIE	89 (26.8)	27	69	.144[a]	15	82	.943[a]
IV	34 (10.2)	16	53		6	81	
Infradiaphragmatic disease							
No	300 (90.6)	57	80	<.001	29	90	.257
Yes	31 (9.4)	15	51		5	81	
Serositis							
No	175 (55.4)	33	81	.101	12	93	.014
Any	141 (44.6)	38	72		22	83	
Serum LDH							
Normal	52 (16.4)	6	88	.013	3	94	.315
>1 to <2x ULN	176 (55.5)	32	81	.005[b]	17	90	.181[b]
≥2x ULN	89 (28.1)	27	68		12	85	
Mediastinal bulk							
No	109 (37.1)	17	84	.056	3	97	.001
Yes	185 (62.9)	46	74		28	84	
Anemia							
No	198 (62.1)	36	81	.231	14	93	.036
Yes	121 (37.9)	28	76		17	85	
White blood cells							
$<10 \times 10^9$/L	236 (74.0)	43	81	.139	23	90	.902
$\geq 10 \times 10^9$/L	83 (26.0)	21	73		8	88	
Lymphocytopenia							
$\geq 1.0 \times 10^9$/L	161(52.4)	32	79	.723	11	93	.056
$<1.0 \times 10^9$/L	146 (47.6)	31	78		19	86	
ESR							
<50 mm/h	158 (61.2)	27	83	.263	12	92	.266
≥50 mm/h	100 (38.8)	23	76		12	87	

(continued)

Table 1. (continued)

Patients' characteristics	Patients, *n* (%)	Pts failed	5-yr FFP, %	*p* value	Pts died	5-yr LSS, %	*p* value
Immunochemotherapy							
R-CHOP-21	302 (91.0)						
Standard R-CHOP-21	287						
R-CHOP-21 variants[c]	10						
Plus some additional conventional chemo[d]	5						
R-CHOP-14	30 (9.0)						
Standard R-CHOP-14	27						
R-CHOP-14 variants[e]	2						
Plus ASCT[f]	1						

[a]Comparison between stage IIE/IIIE and IV among 123 patients with any extranodal involvement.
[b]Comparison between LDH <2x ULN and ≥ 2x ULN.
[c]10/302 patients received variants of R-CHOP-21 (doxorubicin substituted with liposomal doxorubicin, epidoxorubicin, or mitoxanthrone, or addition of etoposide [R-CHOEP]).
[d]"Some additional chemotherapy" after R-CHOP-21 was given in 5 patients (high-dose methotrexate or 2 more cycles with DICE or ESHAP or da-EPOCH following 3 cycles of R-CHOP-21).
[e]2/30 patients received variants of R-CHOP-14 (liposomal doxorubicin or mitoxanthrone instead of conventional doxorubicin).
[f]A single patient received consolidation with high-dose therapy and autologous stem cell transplantation.
Abbreviations: ESR, erythrocyte sedimentation rate; FFP, freedom from progression; LDH, lactate dehydrogenase; ULN, upper limit of normal; LSS, lymphoma-specific survival; PS, ECOG performance status; Pt, patient.

with or without RT in 33 participating Centers (see also Materials and Methods).

Specifically, R-CHOP was administered at 21-day intervals in most of the patients (302/332, 91%), whereas 30 patients (9%) received R-CHOP-14. Minor deviations from these standard regimens were recorded in 18 patients (5%) in the form of alternative anthracycline or anthracenedione, addition of etoposide, or "some additional chemotherapy," as described in Table 1 and its footnote. In 42 patients, RT was not administered because of resistant disease ($n = 38$) or early death/loss to follow-up ($n = 2$); 2 patients had just completed chemotherapy and the decision regarding RT had not been made at the time of the analysis. Among 290 patients who were considered for RT after response to chemotherapy, RT was administered to 209 (72%) and spared in 81 (28%) at the discretion of the treating physician, usually in the context of a final PET-directed decision.

The baseline characteristics of the 332 patients are shown in Table 1. Briefly, median age was 32 years (16–65), 64% were female, 13% had stage III/IV and 9% infradiaphragmatic nodal and/or extranodal disease, 15% had performance status (PS) ≥2, 84% had elevated serum lactate dehydrogenase (LDH) levels (28% highly elevated, i.e., twice the upper normal limit or higher (≥2× ULN), 32% had B-symptoms, 45% had moderate or large serous effusions (pleural and/or pericardial), 63% had bulky disease, and 37% had any form of extranodal involvement (either stage IV [10%] or stages IIE/IIIE [27%]). Baseline laboratory features are also shown in Table 1. The distribution of IPI and aaIPI categories are shown in Table 2; 27% of the patients had IPI ≥2 and 22% had aaIPI ≥2.

With 72 progressions/relapses, the 5-year FFP for the whole series was 77.6%. The 5-year LSS was 89.1%, with 34 disease-related deaths recorded so far. The median follow-up of patients without progression was 68 months (2–198). Almost all treatment failures occurred within approximately 18 months from treatment initiation (69/72 or 96% within 18.6 months), with the latest relapse recorded at 46 months.

Univariate Analysis and Performance of IPI and aaPI

On univariate analysis of FFP, stage III/IV ($p = .001$), involvement of ≥2 extranodal sites ($p = .007$), elevated or highly elevated (≥2× ULN) LDH ($p = .013$ and $p = .005$), infradiaphragmatic involvement ($p < .001$), and any extranodal involvement ($p < .001$) were statistically significant prognostic factors. Tumor bulk ($p = .056$), PS ≥2 ($p = .071$), B-symptoms ($p = .077$), and any serositis ($p = .101$) were of borderline significance. Demographics and laboratory parameters other than LDH were not significant.

On univariate analysis of LSS, tumor bulk ($p = .001$), any extranodal involvement ($p = .002$), any serositis ($p = .014$), B-symptoms ($p = .043$), and anemia ($p = .036$) were statistically significant prognostic factors. Lymphocytopenia ($p = .056$) and the involvement of ≥2 extranodal sites ($p = .068$) were of borderline significance. Neither LDH, PS, stage, and infradiaphragmatic involvement nor demographics were significant.

The IPI efficiently predicted both FFP and LSS but could not identify any subgroup with very low risk of treatment failure or disease-related death (Table 2). The aaPI was less effective in the prediction of FFP and was not significantly associated with LSS (Table 2).

Multivariate Analysis

We examined a multivariate model including any extranodal involvement, infradiaphragmatic disease, highly elevated LDH (≥2× ULN), tumor bulk, B-symptoms, and any serositis as factors significant or borderline ($p \leq .1$) in univariate analysis of FFP. As shown in Table 3, only any extranodal involvement (hazard ratio 2.114, $p = .005$) and highly elevated LDH

Table 2. Performance of IPI and aaPI for the prediction of FFP and LSS in primary mediastinal (thymic) large B-cell lymphoma

Patients' characteristics	Patients, *n* (%)	Pts failed	5-yr FFP, %	*p* value	Pts died	5-yr LSS, %	*p* value
IPI							
0–1	227 (73.5)	36	84		16	93	
2	58 (18.8)	15	73	.001	10	81	.013
3–5	24 (7.8)	11	54		5	77	
IPI grouped							
0–1	234 (72.9)	37	84	.001	16	93	.002
2–5	87 (27.1)	29	66		16	80	
aaIPI							
0	46 (14.9)	5	89	.005	3	93	.290
1	195 (63.1)	36	81		18	90	
2	55 (17.8)	13	76		7	87	
3	13 (4.2)	7	46		3	73	
aaIPI grouped							
0–1	250 (77.9)	43	82	.012	21	91	.069
2–3	71 (22.1)	22	69		11	83	

Abbreviations: aaIPI, age-adjusted IPI; FFP, freedom from progression; IPI, International Prognostic Index; LSS, lymphoma-specific survival; Pt, patient.

Table 3. Multivariate Analysis of Prognostic Factors for freedom from progression and lymphoma-specific survival

Prognostic Factor	Hazard ratio (95% CI)	*p* value
Freedom from progression[a]		
Any extranodal involvement (yes vs. no)	2.114 (1.257–3.555)	.005
Highly elevated LDH (≥2x ULN vs. <2x ULN)	1.782 (1.063–2.988)	.028
Lymphoma-specific survival[b]		
Any extranodal involvement (yes vs. no)	2.445 (1.132–5.282)	.023
Bulky disease (≥10 vs. <10 cm)	4.630 (1.392–15.400)	.012

[a]Considered in the same model but not significant: B-symptoms, bulk, serositis, infradiaphragmatic disease, and performance status in addition to the previous in another model (p-to-enter>0.20 for all)
[b]Considered in the same model but not significant: B-symptoms, highly elevated LDH, anemia, serositis. Lymphocytopenia did not enter the model if added (p-to-enter 0.11 for B-symptoms and > 0.20 for all others)
Abbreviations: CI, confidence interval; LDH, lactate dehydrogenase; ULN, upper limit of normal.

(hazard ratio 1.782, $p = .028$) were independent predictors of FFP. If PS was added, it was not included in the model.

Regarding LSS, we examined a multivariate model including any extranodal involvement, tumor bulk, B-symptoms, anemia, and any serositis as factors significant or borderline in univariate analysis. Highly elevated LDH (≥2x ULN) was also included because it is an established prognostic factor in aggressive lymphomas and was an independent prognostic factor for FFP. Only any extranodal involvement (hazard ratio, 2.445; $p = .023$) and tumor bulk ≥10 cm (hazard ratio, 4.630; $p = .012$) emerged as independent predictors in the final model of LSS (table 3). If lymphocytopenia was added, it was not included in the model.

Prognostic Models

Based on the results of multivariate analysis, we constructed two separate prognostic models. The first included any extranodal involvement and highly elevated LDH (≥2× ULN), as the two independent predictors of FFP (model A). The second included any extranodal involvement and tumor bulk, the two independent predictors of LSS (model B). Subsequently, we tested the performance of model A in the prediction of LSS and that of model B in the prediction of FFP. The results are shown in Figure 1A–D.

None of these models could identify a very-high-risk subgroup of patients with PMLBCL. Indeed, high-risk subgroups defined by the presence of both adverse prognostic factors of either model A or model B included 13.2% and 27.2% of all patients, respectively, with estimated 5-year FFP ≥60% (60% and 64%) and 5-year LSS 81% and 77%, respectively.

Notably, however, both models were able to define very-low-risk groups of patients of different size with very low risk of 5-year disease-related death. These very-low-risk groups had identical risk of treatment failure of 11% at 5 years. Model A (extranodal plus LDH ≥2x ULN) resulted in a sizeable very-low-risk subgroup, those with no adverse factors, including 48.6% of all patients with 4% risk of lymphoma-related death at 5 years. Model B (extranodal plus bulk) resulted in a smaller very-low-risk subgroup, again those with no adverse factors, including 26.2% of all patients with minimal risk of lymphoma-related death at 5 years of only 1%.

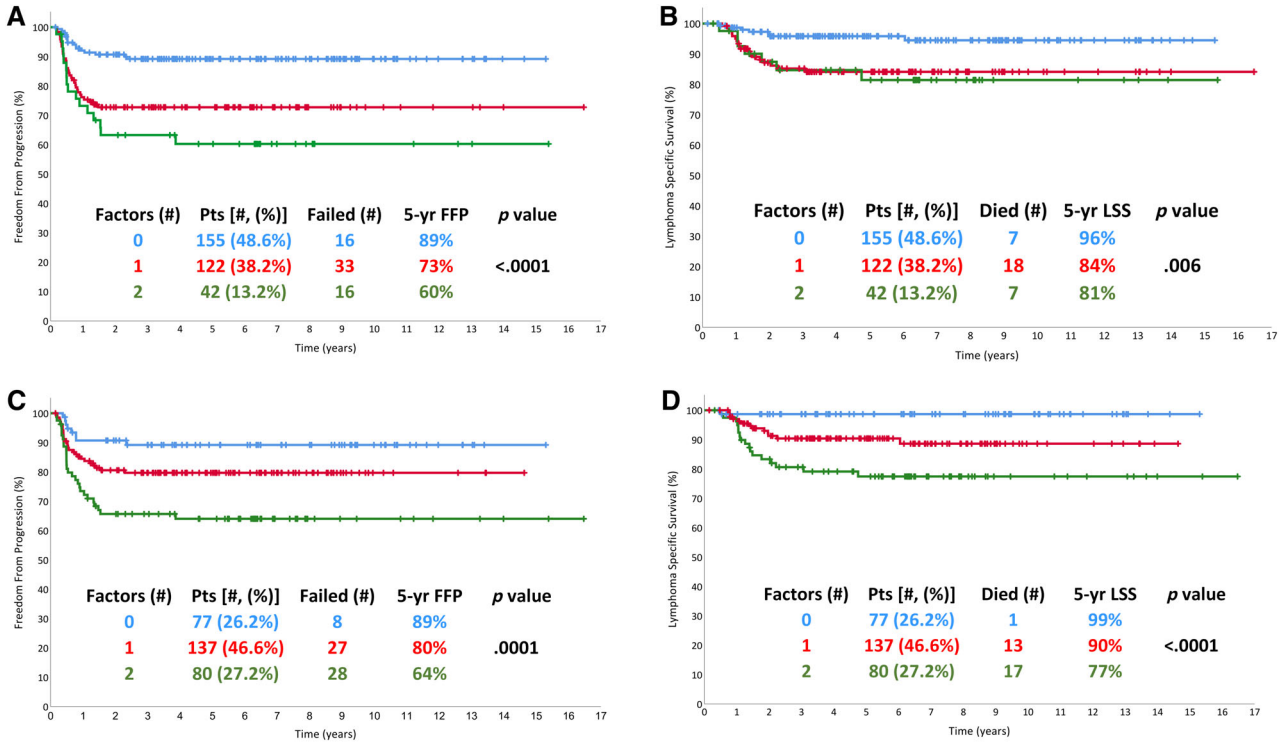

Figure 1. (A): FFP according to model A (any extranodal involvement and lactate dehydrogenase (LDH) ≥2 times). **(B):** LSS)according to model A (any extranodal involvement and LDH ≥2 times). **(C):** FFP according to model B (any extranodal involvement and bulk). **(D):** LSS according to model B (any extranodal involvement and bulk).
Abbreviations: FFP, freedom from progression; LSS, lymphoma-specific survival; Pts, patients.

Furthermore, we compared the predictive power of alternative predictors (binary IPI [0–1 vs. 2–5], binary aaIPI [0–1 vs. 2–3]) and models A and B on FFP and LSS. Both models A and B appeared to perform better compared with IPI and aaIPI based on higher Harrell's C values and lower AIC for both FFP (model A: C = 0.66, AIC = 702.1; IPI: C = 0.59, AIC = 737; aaIPI: C = 0.56, AIC = 730.4) and LSS (model B: C = 0.69, AIC = 318.4; IPI: C = 0.62, AIC = 352.7; aaIPI: C = 0.57, AIC = 358.2). Model B showed optimal characteristics among all predictive scores with regard to LSS, but model A had better predictive power for FFP (model A C = 0.66 vs. model B C = 0.62) at the cost of higher AIC compared with model B (702.1 vs 666.3).

Performance of Prognostic Models in Various Clinical Settings

Finally, we evaluated the association of the described risk models with primary treatment failure rates and the survival outcomes in the PET era and according to the use of RT.

Overall, primary refractory disease (progression at restaging after CT or CT + RT, less than partial response or initiation of salvage CT due to inadequate response) was observed in 16% of the patients, composing almost three-quarters of the total number of treatment failure events. The frequency of primary refractory disease was effectively predicted by both models: for model A (extranodal or LDH ≥2×) it was 8% versus 20% and 24% for patients with 0, 1, or 2 factors, respectively ($p = .004$). The corresponding figures for model B (extranodal or bulk) were 8% versus 15% and 27% for patients with 0, 1, or 2 factors, respectively ($p = .007$).

Because these unfavorable patients were not typically eligible for RT, we restricted further analysis only to responders to R-CHOP, who were considered for RT in the PET era. Among 188 patients, the 5-year FFP was 89% and the 5-year LSS was 96%. In this favorable prognosis subgroup of conventional responders to R-CHOP, model A (extranodal plus LDH ≥2×) effectively predicted FFP (5-year rates 96%, 84% and 76% for patients with 0, 1, or 2 factors; $p = .006$) but not LSS (5-year rates 99%, 94% and 93% for patients with 0, 1, or 2 factors; $p = .26$). Conversely, model B (extranodal plus bulk) failed to predict FFP (5-year rates 95%, 90%, and 83% for patients with 0, 1, or 2 factors, $p = .23$) but effectively predicted LSS (5-year rates 100%, 99%, and 89% for patients with 0, 1, or 2 factors; $p = .02$).

The 78 of 188 patients (41%) who remained PET-positive according to the International Harmonization Project (IHP) criteria, roughly corresponding to Deauville 5-point scale score (D5PSS) 3–5, almost invariably received RT (75/78). Taking into account the small number of events (15 FFP events and 5 lymphoma-related deaths), model A (extranodal plus LDH ≥2×) marginally predicted FFP (5-year rates 89%, 77%, and 50% for patients with 0, 1, or 2 factors; $p = .08$) but not LSS (5-year rates 96%, 91%, and 83% for patients with 0, 1, or 2 factors; $p = .68$). Conversely, model B (extranodal plus bulk) failed to predict FFP (5-year rates 92%, 81%, and 73% for patients with 0, 1, or 2 factors; $p = .57$) but marginally predicted LSS (5-year rates 100%, 97%, and 82% for patients with 0, 1, or 2 factors; $p = .15$).

In multivariate analysis of the 75 irradiated patients, a strong trend for worse FFP was seen in the presence of any of the model A adverse factors (1–2 vs. 0 factors: hazard ratio, 3.525; 95% confidence interval, 0.991–12.540; $p = .052$), adjusting for D5PSS (5 vs. ≤4; hazard ratio, 3.355; 95% confidence interval, 1.188–9.473; $p = .022$).

The 110 of 188 patients (59%) who achieved a stringent PET-negative response according to the IHP criteria, roughly corresponding to D5PSS 1–2, received ($n = 50$) or did not receive RT ($n = 60$) at the discretion of the treating physician. None of the patients who received RT relapsed. Among patients who did not receive RT, only four failures (relapses) and only one lymphoma-related death were recorded, making the analysis of LSS futile. Absence of any of model A risk factors (extranodal or LDH ≥2×) was marginally associated with better FFP (5-year rates 100%, 85%, and 83% for patients with 0, 1, or 2 factors; $p = .08$), whereas model B (extranodal plus bulk) could not discriminate FFP outcomes (5-year rates 92%, 96%, and 83% for patients with 0, 1, or 2 factors; $p = .42$).

Among very low-risk patients by model A (no risk factors), 29% of responders did not receive RT at the physician's discretion, and this figure rose to 36% in the PET era. Only 1 of 42 and 0 of 34 patients, respectively, relapsed for a 5-year FFP rate of 98% and 100% (vs. 91% and 95% for irradiated patients). Among very-low-risk patients by model B (no risk factors), 29% of responders did not receive RT (31% in the PET era). Only 1 of 21 and 1 of 14 patients, respectively, relapsed, for a 5-year FFP rate of 95% and 92% (vs. 92% and 97% for irradiated patients).

Discussion

Prognostic factors for PMLBCL have been analyzed in several studies prior to the introduction of rituximab. Generally, aaIPI had been demonstrated as a powerful prognostic factor in that era. However, the introduction of rituximab has improved the outcomes so much that a complete reassessment of prognostic factors became necessary, similarly to what was observed in DLBCL. Furthermore, it is rather clear that the reproducibility of the prognostic factors included in the IPI is not optimal, especially as far as clinical stage, number of extranodal sites, and even performance status are concerned. In Table 4, we summarize the results of several series of patients with PMLBCL under treatment with R-CHOP with respect to baseline patients' characteristics and treatment outcomes. It is obvious that easily reproducible variables, such as age and LDH, have notably similar values among all series. On the contrary, there is significant disparity in the frequency of stage III/IV among series, ranging from 7% to 48%, presumably due to the varying definitions for contiguous versus noncontiguous extranodal involvement, which can be very ambiguous in PMLBCL. Likewise, the number of involved extranodal sites may also be dubious, because of the potential contiguous involvement of multiple anatomic structures. The reported rates of poor performance status are also diverse, ranging from 0% or 12% to 59% (Table 4). Because of all the above reasons, the scoring of conventional IPI and aaIPI may not be as accurate in PMLBCL.

In the rituximab era, there are very limited data regarding prognostic factors in PMLBCL, coming from small- to moderate-sized studies [19,21,37]. In a study from Japan, only 187 of 345 patients were actually treated with R-CHOP, and prognostic factor analysis was restricted to the 123 patients, who received R-CHOP without radiotherapy [37]. However, the exclusion of patients who received RT may have resulted in selection bias. In this study, stage III/IV and the presence of serositis were independent prognostic factors, whereas IPI ≥3 and serositis were used to produce a prognostic model, based on the impact of IPI on OS in univariate analysis. The second study from British Columbia was presented as an abstract in the 2012 American Society of Hematology meeting and was based on the analysis of 96 patients [19]. Relevant prognostic factors where age > 38 years and the presence of serositis. In the last study of 63 patients from Boston, the small subgroups of patients >60 years or with multiple extranodal involvement had inferior progression-free survival (PFS) and overall survival in multivariate analysis, whereas the few patients with advanced stages also had inferior PFS irrespective of other factors [21]. All these data are summarized in Table 4.

The study reported here is the largest published to date regarding patients with PMLBCL treated in the rituximab era and specifically with R-CHOP. We tried to overcome the issues with staging arising from the definition of contiguous or noncontiguous extranodal spread by considering any extranodal involvement as a risk factor. Patients with contiguous extranodal involvement had a much poorer outcome compared with those without extranodal involvement, comparable to that of stage IV disease (Table 1). Serum LDH was prognostic in univariate analysis of FFP but not LSS, and further tiering according to the degree of elevation provided better discrimination, as was also shown for DLBCL in the NCCN-IPI [55]. Finally, any extranodal involvement and the presence of highly elevated serum LDH (≥2x ULN) emerged as independent prognostic factors for FFP. Extranodal involvement showed evident prognostic significance for both FFP and LSS, but bulky disease replaced highly elevated LDH in the analysis of LSS. Neither demographics nor any other laboratory finding except for LDH were of prognostic significance in multivariate analysis, despite significant or borderline associations of anemia and lymphocytopenia with LSS and/or FFP in univariate analysis. Interestingly, neither serositis nor age were significant for FFP or LSS in the final analysis, in disagreement with previous reports [19,37].

Based on the results of multivariate analysis, we constructed two separate models. The first included any extranodal involvement and highly elevated LDH (factors significant for FFP) and the second included any extranodal involvement and bulk (factors significant for LSS). Both models were applied for FFP and LSS prediction, as shown in Figure 1A–D. Both models proved to be very efficient in discriminating a very-low-risk group with 89% FFP at 5 years. The difference lay in the prediction of LSS: the first model (model A) delineated a sizeable very-low-risk subgroup encompassing approximately 50% of the whole patient population, with only 4% 5-year risk of disease-related death. The second model (model B) defined a smaller very-low-risk

Table 4. Summary of studies on prognostic factors and outcome after R-CHOP in patients with primary mediastinal large B-cell lymphoma

Author, year	Patients, *n*	FFP (*n* yr)	OS (*n* yr)	RT	Age >60 yr	Female sex	Stage III/IV	B-symptoms	ECOG PS ≥2	Elevated LDH	Bulky disease	Effusions	aa IPI ≥2	Prognostic factors
Ahn et al. [21], 2010	21	79 (∼3.5)	83 (∼3.5)	68 (resp) 62 (all)	10	57	48[a]	29	19	90	71[b]	48/38	37	NR separately for R-CHOP
Tai et al. [22], 2011[c]	27	88 (5)	87 (5)	100 (resp) 96 (all)	0	63	7	30	41	100	78[b]	59	41	NR separately for R-CHOP
Savage et al. [18], 2012	96	78 (5)	88 (5)	58 (all)	NR	NR	NR	NR	NR	NR	NR	NR	NR	Age>38 yr, B-symptoms, effusions
Xu et al. [23], 2013	39	77 (5)	84 (5)	82 (all)	0	62	15	46	59	72	67[b]	NR	56	NR separately for R-CHOP
Soumerai et al. [20], 2013	63	68 (5)	79 (5)	77 (resp) 59 (all)	13	40	22	NR	24	77	71[d]	NR	33	Stage, age >60 yr, multiple extranodal sites
Aoki et al. [37], 2014	187	71 (4)	90 (4)	34 (all)	16	55	28	22	22	73	47[d]	43	19[e]	stage, effusions, (IPI ≥3) among 123 pts who did not receive RT
Gleeson et al. [29], 2016[c]	50	80 (5)	84 (5)	64 (resp) 58 (all)	8	50	0	52	12	84	70	NR	16	R-CHOP-14 vs. 21: marginally better FFP and OS (22 vs 28 pts)
Lisenko et al. [25], 2017[f]	45	95 (5)	92 (5)	91	<64 yr	53	24	58	0	75	NR	NR	13 (IPI ≥3)	NR separately for R-CHOP
Vassilakopoulos et al., 2020	332	78 (5)	89 (5)	72 (resp) 63 (all)	2	64	13[a]	32	15	84	63[d]	45	22	Any extranodal disease, LDH ≥ 2 times, bulk

All numbers are percentages unless otherwise specified.
[a]The contiguous involvement of multiple extranodal anatomic structures (for example chest wall, pleura and pericardium, localized lung disease) was considered as stage IIE or IIIE.
[b]bulky disease defined as ≥10 cm or >one-third of transverse thoracic diameter.
[c]R-CHOP-21 and R-CHOP-14 were given to 13 and 14 patients, respectively, in the study by Tai et al. and 28 and 22 patients in the study by Gleeson et al.
[d]Bulky disease defined as ≥10 cm.
[e]IPI 3–5.
[f]24/45 patients (53%) received Rituximab maintenance with no difference in the outcome; 7 patients with conventional PR received ASCT consolidation without improvement in their remission status. R-CHOEP was given in 53% of the patients.
Abbreviations: aaIPI, age-adjusted IPI; ECOG PS, Eastern Cooperative Oncology Group progression status; FFP, freedom from progression; IPI, International Prognostic Index; LDH, lactate dehydrogenase; NR, not reported; OS, overall survival; RT, radiotherapy; resp, responders.

subgroup, encompassing approximately 25% of the whole patient population, with really minimal risk of disease-related death of only 1% at 5 years, despite the 11% treatment failure rate. Although IPI and aaIPI were predictive of FFP and LSS, their performance was clearly inferior to the above specified models. This permitted the omission of relatively subjective variables, such as PS and stage in PMLBCL, and the establishment of more potent and more objective prognostic models.

The prognostic models described here were highly predictive of the risk of primary progressive disease, which accounted for almost three-quarters of the observed events of treatment failure. This information is available at the time of diagnosis for treatment selection and does not depend on end-of-treatment (EOT)-PET/CT response assessment. In the PET era, the next question is whether these baseline prognostic markers can aid further management decisions at the time of the EOT-PET response assessment. Even in this large patient cohort, only 19 events were observed in patients who had already overcome the risk of primary progression and were eligible for EOT-PET evaluation as responders to R-CHOP. In patients with stringent metabolic response (IHP criteria or roughly D5PSS 1–2) who were irradiated ($n = 50$), the prognostic scores were not applicable, because no treatment failures were observed. Although only four relapses (2 CNS-only) were observed among 60 EOT-PET–negative patients, who were not irradiated at the discretion of the treating physician, model A was marginally predictive, with very-low-risk patients experiencing 100% cure rates versus 83%–85% for patients with one or two risk factors. In the PET-positive group (IHP criteria or roughly D5PSS 3–5), models A and B were marginally predictive of FFP and LSS, respectively. Larger patient numbers are probably required for more accurate estimation of the effects of these prognostic markers in each of these cohort fractions. In multivariate analysis, the level of final PET activity (D5PSS 5) was the most important factor for tumor control, whereas model A was again of borderline significance.

Based on the data presented here, the described prognostic models could mainly be used for initial treatment selection, as they are primarily predictive of the risk of primary refractory disease. Thus, it seems reasonable to speculate that very-low-risk patients would be overtreated with more intensified chemotherapy such R-da-EPOCH, with potential acute and long-term harm [31,36] abrogating any marginal benefit in terms of disease control.

In terms of clinical practice, the present study defined intermediate- and high-risk subgroups of patients with PMLBCL with 20%–40% risk of treatment failure and 10%–23% risk of disease-related death. Such patients can be considered for intensified treatment with R-da-EPOCH, given the suboptimal outcome with R-CHOP and the >90% disease control rate reported in the original NCI study, although the outcome for higher-risk patients has not been formally investigated. For this reason, a randomized comparison between R-da-EPOCH and R-CHOP is still warranted and could be more powerful if restricted to patients with one to two risk factors according to either model, who have substantially higher risk of treatment failure with R-CHOP compared with very-low-risk patients. More importantly, however, the present study permitted the objective identification of very-low-risk subgroups with 11% risk of treatment failure and minimal risk of disease-related death with R-CHOP, in whom the toxicity of R-da-EPOCH could be avoided. In our study, only 8% of such very low-risk patients were primary refractory to R-CHOP, but the risk of disease-related death was extremely low. This risk might be further substantially reduced with the use of checkpoint inhibitors and chimeric antigen receptor T cells, which can effectively salvage even heavily pretreated patients [56–59]. However, a significant issue to consider in the upfront management of these patients remains the almost universal omission of RT afforded by R-da-EPOCH, which is particularly relevant in this young population with female predominance. In the present study, RT was not used in 29%–36% of EOT-PET–negative patients, despite the prevailing trend to irradiate PMLBCL during most of the study period (data not shown), without major detrimental effect on tumor control. RT consolidation may be further limited to less than half of the patients, pending results of the IELSG-37 study in EOT-PET–negative patients [60].

Baseline prognostic information may also be derived from initial staging PET parameters [61–63] and biomarkers [64,65]. However, such approaches are still investigational and need standardization and prospective validation. In addition, baseline PET may not be feasible for logistic reasons in many patients with PMLBCL presenting with acute complications requiring urgent treatment, especially if not available on-site, whereas evaluation of biological prognostic factors may not be possible in many cases because of the small size of the biopsies. For these reasons, clinical prognostic models are expected to remain particularly useful in the specific setting of PMLBCL and may be enhanced by functional imaging and biologic markers [66].

The present study has certain limitations, which arise from its retrospective nature. Central pathology review was not performed; however, biopsy specimens were examined by expert hematopathologists. As often happens in the real world, treatment strategies were not entirely homogenous, with PET-based response assessment increasing over time and variable use of RT in patients with strictly defined PET negativity. However, both risk models offered reliable stratification of the risk of primary refractory disease, which is not affected by EOT-PET interpretation or RT strategies, and may facilitate initial treatment selection. These considerations support the applicability of our risk models in everyday clinical practice. The decision to irradiate or not after induction therapy is currently based on the initial chemotherapy regimen and the final PET result [6,31–36,60,67,68], whereas the impact of baseline prognostic markers on this decision remains to be further delineated. Obviously, the latter issue may not be applicable if patients with one or two risk factors are selected for R-da-EPOCH treatment, where RT is typically omitted.

Conclusion

The present study specifically establishes objective and easily applicable clinical prognostic models, which may help avoid exposing a considerable fraction (25%–50%) of

patients with PMLBCL to intensified regimens such as R-da-EPOCH, with only 11% resorting to salvage therapy and minimal loss in disease-specific survival.

Acknowledgments

This study was not supported, either partly or entirely, by any grant, fund, organization, or corporation.

Author Contributions

Conception/design: Theodoros P. Vassilakopoulos, Gerassimos A. Pangalis

Provision of study material or patients: Theodoros P. Vassilakopoulos, Michail Michail, Sotirios Papageorgiou, Georgia Kourti, Maria K. Angelopoulou, Sotirios Sachanas, Christina Kalpadakis, Eirini Katodritou, Theoni Leonidopoulou, Ioannis Kotsianidis, Eleftheria Hatzimichael, Maria Kotsopoulou, Maria Dimou, Eleni Variamis, Dimitrios Boutsis, Evangelos Terpos, Maria N. Dimopoulou, Evridiki Michali, George Karianakis, Pantelis Tsirkinidis, Chryssa Vadikolia, Christos Poziopoulos, Anna Pigaditou, Effimia Vrakidou, Theophanis Economopoulos, Lydia Kyriazopoulou, Marina P. Siakantaris, Marie-Christine Kyrtsonis, Argyris Symeonidis, Konstantinos Anargyrou, Maria Papaioannou, Evdoxia Chatziharissi, Elissavet Vervessou, Maria Tsirogianni, Maria Palassopoulou, Gabriella Gainaru, Ekaterini Stefanoudaki, Panayiotis Zikos, Panayiotis Tsirigotis, Gerassimos Tsourouflis, Theodora Assimakopoulou, Pavlina Konstantinidou, Helen Papadaki, Katerina Megalakaki, Meletios-Athanasios Dimopoulos, Vassiliki Pappa, Themis Karmiris, Paraskevi Roussou, Panayiotis Panayiotidis, Kostas Konstantopoulos, Gerassimos A. Pangalis

Collection and/or assembly of data: Theodoros P. Vassilakopoulos, Michail Michail, Sotirios Papageorgiou, Georgia Kourti, Maria K. Angelopoulou, Sotirios Sachanas, Christina Kalpadakis, Eirini Katodritou, Theoni Leonidopoulou, Ioannis Kotsianidis, Eleftheria Hatzimichael, Maria Kotsopoulou, Maria Dimou, Eleni Variamis, Dimitrios Boutsis, Evangelos Terpos, Maria N. Dimopoulou, Stamatios Karakatsanis, Evridiki Michali, George Karianakis, Pantelis Tsirkinidis, Chryssa Vadikolia, Christos Poziopoulos, Anna Pigaditou, Effimia Vrakidou, Theophanis Economopoulos, Lydia Kyriazopoulou, Argyris Symeonidis, Konstantinos Anargyrou, Maria Papaioannou, Evdoxia Chatziharissi, Elissavet Vervessou, Maria Tsirogianni, Maria Palassopoulou, Gabriella Gainaru, Ekaterini Stefanoudaki, Panayiotis Zikos, Pavlina Konstantinidou, Katerina Megalakaki, Paraskevi Roussou

Data analysis and interpretation: Theodoros P. Vassilakopoulos, Fotios Panitsas

Manuscript writing: Theodoros P. Vassilakopoulos

Final approval of manuscript: Theodoros P. Vassilakopoulos, Michail Michail, Sotirios Papageorgiou, Georgia Kourti, Maria K. Angelopoulou, Fotios Panitsas, Sotirios Sachanas, Christina Kalpadakis, Eirini Katodritou, Theoni Leonidopoulou, Ioannis Kotsianidis, Eleftheria Hatzimichael, Maria Kotsopoulou,Maria Dimou, Eleni Variamis, Dimitrios Boutsis, Evangelos Terpos, Maria N. Dimopoulou, Stamatios Karakatsanis, Evridiki Michali, George Karianakis, Pantelis Tsirkinidis, Chryssa Vadikolia, Christos Poziopoulos, Anna Pigaditou, Effimia Vrakidou, Theophanis Economopoulos, Lydia Kyriazopoulou, Marina P. Siakantaris, Marie-Christine Kyrtsonis, Argyris Symeonidis, Konstantinos Anargyrou, Maria Papaioannou, Evdoxia Chatziharissi, Elissavet Vervessou, Maria Tsirogianni, Maria Palassopoulou, Gabriella Gainaru, Ekaterini Stefanoudaki, Panayiotis Zikos, Panayiotis Tsirigotis, Gerassimos Tsourouflis, Theodora Assimakopoulou, Pavlina Konstantinidou, Helen Papadaki, Katerina Megalakaki, Meletios-Athanasios Dimopoulos, Vassiliki Pappa, Themis Karmiris, Paraskevi Roussou, Panayiotis Panayiotidis, Kostas Konstantopoulos, Gerassimos A. Pangalis

Disclosures

Theodoros P. Vassilakopoulos: Merck, Takeda, Amgen, Pfizer, Karyopharm (RF/PI), Takeda, Roche, Genesis Pharma, BMS, Merck, Novartis, Gilead, Sandoz, Abbvie (H), Takeda, Roche, Genesis Pharma, BMS, Merck, Novartis, Gilead (SAB); **Sotirios Papageorgiou:** Amgen, Astellas, Genesis Pharma, Sanofi (C/A), Abbvie, Amgen, BMS, Genesis Pharma, Novartis Sandoz, Pfizer, Janssen, Roche, Takeda (SAB), Abbvie, Amgen, BMS, Genesis Pharma, Gilead Sciences, Janssen, Innovis, Novartis, Pfizer, Roche, Sandoz, Winmedica (H); **Maria K. Angelopoulou:** Genesis Pharma, Novartis, Sandoz, Abbvie, Janssen, Takeda (SAB), Takeda, Pfizer, Roche, Genesis Pharma, Gilead, WinMedica, Janssen, Abbvie, BMS, Sandoz (H); **Fotios Panitsas:** Pfizer, Janssen (H); **Sotirios Sachanas:** Janssen-Cilag, Abbvie, Gilead Sciences (H), Roche (SAB); **Christina Kalpadakis:** Roche (C/A), Novartis, Gilead, Roche (H); **Eirini Katodritou:** Amgen, Takeda, Genesis-Pharma, Janssen-Cilag, Karyopharm, Abbvie, GSK, Roche (RF/PI), Amgen, Takeda, Genesis-Pharma, Janssen-Cilag, Abbvie (H); **Eleftheria Hatzimichael:** Roche, Amgen, Merck Sharpe & Dohme, Janssen Cilag, Genesis, Abbvie, Takeda, Pharmathen-Innovis, Pfizer, Abbvie (H), Roche, Genesis, Celgene, Pfizer, Amgen (SAB), Acerta-Pharma, Amgen, Boehringer-Ingelheim, Bristol-Myers Squibb, Celgene, Genesis, Glaxo, Novartis, Pharmacyclics, Roche, Takeda (RF); **Maria Kotsopoulou:** Amgen, Takeda, Genesis, Janssen, Roche (SAB), Amgen, Takeda, Genesis, Janssen, Astellas, Roche (RF); **Maria Dimou:** Roche, AbbVie, Pharmacyclics, Acerta Pharma, Osco Tec, Glaxo SmithKline, Novartis, Sandoz (RF), Roche, AbbVie, Janssen, Sandoz, Novartis, Takeda, Winmedica (H), Roche, AbbVie, Janssen, Sandoz, Takeda, Winmedica, AstraZeneca (C/A), Takeda, Roche (SAB); **Evangelos Terpos:** Amgen, GSK, Takeda, Janssen, Celgene (RF), Amgen, Bristol-Myers Squibb, Celgene, GSK, Janssen, Sanofi (H), Amgen, Bristol-Myers Squibb, GSK, Celgene, Janssen, Sanofi (SAB); **Maria N. Dimopoulou:** Bristol Myers Squibb, Novartis (H); **Stamatios Karakatsanis:** Sanofi (SAB); **Eurydiki Michalis:** Amgen, GenesisPharma, Takeda (RF); **Christos Poziopoulos:** Amgen, Novartis, Roche (SAB), Janssen, Genesis Pharma, Bristol-Myers Squibb, Pfizer, Novartis (H); **Marina P. Siakantaris:** Roche, Takeda (C/A), Winmedica, Takeda (SAB), Faran, Winmedica (RF); **Marie-Christine Kyrtsonis:** Amgen, Janssen, Celgene/Genesis Pharma (RF), Amgen, Celgene/Genesis Pharma, Janssen, Takeda (H), Amgen, Celgene/Genesis Pharma, Janssen, Sanofi (SAB); **Argyris Symeonidis:** Abbvie, Amgen, Celgene/Genesis Pharma, Gilead, Janssen, Novartis, Pfizer, Roche, Sanofi/Genzyme, Takeda (C/A), Abbvie, Amgen, Astellas, Bayer, Bristol-Myers Squibb, Apotex/Demo, GenesisPharma, Gilead, Janssen, Merck Sharpe & Dohme, Novartis, Pfizer, Roche, Sanofi/Genzyme, Takeda, WinMedica (RF), Abbvie, Amgen, Celgene/Genesis Pharma, Gilead, Jannsen, Merck Sharpe & Dohme, Novartis, Pfizer, Roche, Sanofi/Genzyme, Takeda (SAB); **Maria Papaioannou:** Novartis (H); **Evdoxia Hatjiharissi:** Abbvie, Gilead, Genesis Pharma, Janssen, Roche (H), Janssen, Genesis Pharma (SAB), Genesis Pharma (RF); **Elissavet Vervessou:** Janssen, Abbvie, Roche (SAB); **Maria Palassopoulou:** Roche, Abbvie, Takeda (SAB), Sanofi Genzyme, Abbvie, Roche, Janssen Cilag, Gilead, Takeda, Winmedica (H); **Panayiotis Zikos:** Janssen, Amgen, Genesis Pharma, Alexion (SAB), Genesis Pharma (H); **Panayiotis Tsirigotis:** Pfizer (C/A), Gilead (RF), Abbvie, Amgen, Celgene/Genesis Pharma, Gilead, Merck Sharpe & Dohme, Novartis, Pfizer, Takeda (SAB); **Pavlina Konstantinidou:** Takeda, Pfizer, Servier (SAB), Abbvie, Janssen, Gilead (H); **Helen Papadaki:** Janssen Cilag, Genesis Pharma, Abbvie, Astellas, Pfizer (RF), Gilead (H); **Katerina Megalakaki:** Genesis, Pfizer (C/A), Genesis, Amgen, GSK (RF), Amgen, Genesis (RF), Janssen, Pfizer, Gilead, Winmedica, Roche, Servier, Novartis, GSK (H); **Meletios-Athanasios Dimopoulos:** Amgen, BMS, Janssen, Takeda, Beigene (SAB); **Vassiliki Pappa:** Celgene, Janssen, Abbvie (RF/PI), Genesis Pharma, Janssen, Roche, Servier, Abbvie, Novartis, Gilead (H), Genesis Pharma, Janssen, Roche, Servier, Abbvie, Novartis, Gilead, Amgen (SAB); **Panayiotis Panayiotidis:** Roche, Abbvie, Genesis Pharma, Winmedica, Novartis, Sandoz, Jansenn, Demo (H), Roche, Abbvie, Astellas, Genesis Pharma (RF). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

References

1. Banks P, Warnke R. Mediastinal (thymic) large B-cell lymphoma. In: Jaffe E, Harris N, Stein H et al., eds. World Health Organization Classification of Tumors. Pathology and Genetics of Tumors of Haematopoietic and Lymphoid Tissues. Lyon, France: IARC Press; 2001: 175–176.

2. Swerdlow SH, Campo E, Pileri SA et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood 2016;127:2375–2390.

3. Rosenwald A, Wright G, Leroy K et al. Molecular diagnosis of primary mediastinal B cell lymphoma identifies a clinically favorable subgroup

of diffuse large B cell lymphoma related to Hodgkin lymphoma. J Exp Med 2003;198:851–862.

4. Green MR, Monti S, Rodig SJ et al. Integrative analysis reveals selective 9p24.1 amplification, increased PD-1 ligand expression, and further induction via JAK2 in nodular sclerosing Hodgkin lymphoma and primary mediastinal large B-cell lymphoma. Blood 2010;116:3268–3277.

5. Zinzani PL, Martelli M, Bertini M et al. Induction chemotherapy strategies for primary mediastinal large B-cell lymphoma with sclerosis: A retrospective multinational study on 426 previously untreated patients. Haematologica 2002; 87:1258–1264.

6. Martelli M, Ceriani L, Zucca E et al. [18F] fluorodeoxyglucose positron emission tomography predicts survival after chemoimmunotherapy for primary mediastinal large B-cell lymphoma: Results of the International Extranodal Lymphoma Study Group IELSG-26 Study. J Clin Oncol 2014;32:1769–1775.

7. Lazzarino M, Orlandi E, Paulli M et al. Treatment outcome and prognostic factors for primary mediastinal (thymic) B-cell lymphoma: A multicenter study of 106 patients. J Clin Oncol 1997;15:1646–1653.

8. Papageorgiou SG, Sachanas S, Pangalis GA et al. Gastric involvement in patients with primary mediastinal large B-cell lymphoma. Anticancer Res 2014;34:6717–6723.

9. Karakatsanis S, Papageorgiou SG, Michail M, et al. Subdiaphragmatic extranodal localizations at diagnosis of primary mediastinal large B-cell lymphoma: an impressive, rare presentation with no independent effect on prognosis. Leukemia Research 2021;107:106595. http://dx.doi.org/10.1016/j.leukres.2021.106595.

10. Papageorgiou SG, Diamantopoulos P, Levidou G et al. Isolated central nervous system relapses in primary mediastinal large B-cell lymphoma after CHOP-like chemotherapy with or without Rituximab. Hematol Oncol 2013;31: 10–17.

11. Savage KJ, Al-Rajhi N, Voss N et al. Favorable outcome of primary mediastinal large B-cell lymphoma in a single institution: The British Columbia experience. Ann Oncol 2006;17: 123–130.

12. Hamlin PA, Portlock CS, Straus DJ et al. Primary mediastinal large B-cell lymphoma: Optimal therapy and prognostic factor analysis in 141 consecutive patients treated at Memorial Sloan Kettering from 1980 to 1999. Br J Haematol 2005; 130:691–699.

13. Vassilakopoulos TP, Pangalis GA, Katsigiannis A et al. Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone with or without radiotherapy in primary mediastinal large B-cell lymphoma: The emerging standard of care. ***The Oncologist*** 2012; 17:239–249.

14. Zinzani PL, Martelli M, Bendandi M et al. Primary mediastinal large B-cell lymphoma with sclerosis: A clinical study of 89 patients treated with MACOP-B chemotherapy and radiation therapy. Haematologica 2001;86:187–191.

15. Todeschini G, Secchi S, Morra E et al. Primary mediastinal large B-cell lymphoma (PMLBCL): Long-term results from a retrospective multicentre Italian experience in 138 patients treated with CHOP or MACOP-B/VACOP-B. Br J Cancer 2004;90:372–376.

16. Dunleavy K, Pittaluga S, Janik J et al. Primary mediastinal large B-Cell lymphoma (PMBL) outcome may be significantly improved by the addition of rituximab to dose-adjusted (DA)-EPOCH and obviates the need for radiation: Results from a prospective study of 44 patients. Blood 2006; 108:209a.

17. 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-Munster Group. J Clin Oncol 2003;21:1782–1789.

18. Fietz T, Knauf WU, Hänel M et al. Treatment of primary mediastinal large B cell lymphoma with an alternating chemotherapy regimen based on high-dose methotrexate. Ann Hematol 2009;88:433–439.

19. Savage KJ, Yenson PR, Shenkier T et al. The outcome of primary mediastinal large B-cell lymphoma (PMBCL) in the R-CHOP treatment era. Blood 2012;120:303a.

20. Rieger M, Osterborg A, Pettengell R et al. Primary mediastinal B-cell lymphoma treated with CHOP-like chemotherapy with or without rituximab: Results of the Mabthera International Trial Group study. Ann Oncol 2011;22:664–670.

21. Soumerai JD, Hellmann MD, Feng Y et al. Treatment of primary mediastinal B-cell lymphoma with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone is associated with a high rate of primary refractory disease. Leuk Lymphoma 2014;55:538–543.

22. Ahn HK, Kim SJ, Yun J et al. Improved treatment outcome of primary mediastinal large B-cell lymphoma after introduction of rituximab in Korean patients. Int J Hematol 2010;91:456–463.

23. Tai WM, Quah D, Yap SP et al. Primary mediastinal large B-cell lymphoma: Optimal therapy and prognostic factors in 41 consecutive Asian patients. Leuk Lymphoma 2011;52:604–612.

24. Xu LM, Fang H, Wang WH et al. Prognostic significance of rituximab and radiotherapy for patients with primary mediastinal large B-cell lymphoma receiving doxorubicin-containing chemotherapy. Leuk Lymphoma 2013;54:1684–1690.

25. Lisenko K, Dingeldein G, Cremer M et al. Addition of rituximab to CHOP-like chemotherapy in first line treatment of primary mediastinal B-cell lymphoma. BMC Cancer 2017;17:359.

26. Zinzani PL, Stefoni V, Finolezzi E et al. Rituximab combined with MACOP-B or VACOP-B and radiation therapy in primary mediastinal large B-cell lymphoma: A retrospective study. Clin Lymphoma Myeloma 2009;9:381–385.

27. Avigdor A, Sirotkin T, Kedmi M et al. The impact of R-VACOP-B and interim FDG-PET/CT on outcome in primary mediastinal large B cell lymphoma. Ann Hematol 2014;93:1297–1304.

28. Pohlen M, Gerth HU, Liersch R et al. Efficacy and toxicity of a rituximab and methotrexate based regimen (GMALL B-ALL/NHL 2002 protocol) in Burkitt's and primary mediastinal large B-cell lymphoma. Am J Hematol 2011;86:E61–E64.

29. Moskowitz CH, Schöder H, Teruya-Feldstein J et al. Risk-adapted dose-dense immunochemotherapy determined by interim FDG-PET in advanced-stage diffuse large B-Cell lymphoma. J Clin Oncol 2010;28:1896–1903.

30. Gleeson M, Hawkes EA, Cunningham D et al. Rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP) in the management of primary mediastinal B-cell lymphoma: A subgroup analysis of the UK NCRI R-CHOP 14 versus 21 trial. Br J Haematol 2016;175: 668–672.

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

32. 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: 739–747.

33. Shah NN, Szabo A, Huntington SF et al. R-CHOP versus dose-adjusted R-EPOCH in frontline management of primary mediastinal B-cell lymphoma: A multi-centre analysis. Br J Haematol 2018;180:534–544.

34. Chan EHL, Koh LP, Lee J et al. Real world experience of R-CHOP with or without consolidative radiotherapy vs DA-EPOCH-R in the first-line treatment of primary mediastinal B-cell lymphoma. Cancer Med 2019;8:4626–4632.

35. Malenda A, Kołkowska-Leśniak A, Pula B et al. Outcomes of treatment with dose-adjusted EPOCH-R or R-CHOP in primary mediastinal large B-cell lymphoma. Eur J Haematol 2020;104: 59–66.

36. Vassilakopoulos TP, Mellios Z, Verigou E et al. Comparison of rituximab dose-adjusted EPOCH (R-DA-EPOCH) with Rituximab-CHOP (R-CHOP) chemotherapy in primary mediastinal large B-cell lymphoma (PMLBCL). HemaSphere 2019; 3(Suppl. 1): 100.

37. Aoki T, Izutsu K, Suzuki R et al. Prognostic significance of pleural or pericardial effusion and the implication of optimal treatment in primary mediastinal large B-cell lymphoma: A multicenter retrospective study in Japan. Haematologica 2014;99:1817–1825.

38. Harris NL, Jaffe ES, Stein H et al. A revised European-American classification of lymphoid neoplasms: A proposal from the International Lymphoma Study Group. Blood 1994;84:1361–1392.

39. Lister TA, Crowther D, Sutcliffe SB et al. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. J Clin Oncol 1989;7: 1630–1636.

40. Hodgson DC, Gospodarowicz MK. Clinical evaluation and staging of Hodgkin lymphoma. In: Hoppe R, Mauch P, Armitage J et al., eds. Hodgkin Lymphoma. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2007:123–132.

41. Vassilakopoulos TP, Nadali G, Angelopoulou MK et al. The prognostic significance of beta(2)-microglobulin in patients with Hodgkin's lymphoma. Haematologica 2002;87:701–708.

42. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. N Engl J Med 1993;329:987–994.

43. Coiffier B, Lepage E, Briere J et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med 2002;346:235–242.

44. Pfreundschuh M, Schubert J, Ziepert M et al. Six versus eight cycles of bi-weekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas: A randomised controlled trial (RICOVER-60). Lancet Oncol 2008;9:105–116.

45. Cheson BD, Horning SJ, Coiffier B et al. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. J Clin Oncol 1999;17:1244.

46. Cheson BD, Pfistner B, Juweid ME et al. Revised response criteria for malignant lymphoma. J Clin Oncol 2007;25:579–586.

47. Juweid ME, Stroobants S, Hoekstra OS et al. Use of positron emission tomography for response assessment of lymphoma: Consensus of the Imaging Subcommittee of International Harmonization Project in Lymphoma. J Clin Oncol 2007;25:571–578.

48. Vassilakopoulos TP, Pangalis GA, Chatziioannou S et al. PET/CT in primary mediastinal large B-cell lymphoma responding to rituximab-CHOP: An analysis of 106 patients regarding prognostic significance and implications for subsequent radiotherapy. Leukemia 2016;30:238–242.

49. Vassilakopoulos TP, Pangalis GA, Polliack A. A ''PET'' topic in primary mediastinal large B-cell lymphoma: Positive or negative, and how to handle it in the end. Leuk Lymphoma 2015;56:3–5.

50. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457–481.

51. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemother Rep 1966;50:163–170.

52. Cox DR. Regression models and life-tables. J R Stat Soc Series B Stat Methodol 1972;34:187–220.

53. Harrell Jr FE, Lee KL, Mark DB. Multivariate prognostic models: Issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 1996;15:361–387.

54. Akaike H. Information Theory and an extension of the maximum likelihood principle. In: Parzen E, Tanabe K, Kitagawa G, eds. Selected Papers of Hirotugu Akaike. New York, NY: Springer New York; 1998:199-213.

55. Zhou Z, Sehn LH, Rademaker AW et al. An enhanced International Prognostic Index (NCCN-IPI) for patients with diffuse large B-cell lymphoma treated in the rituximab era. Blood 2014;123:837–842.

56. Armand P, Rodig S, Melnichenko V et al. Pembrolizumab in relapsed or refractory primary mediastinal large B-cell lymphoma. J Clin Oncol. 2019;37:3291–3299.

57. 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;37:3081–3089.

58. Locke FL, Ghobadi A, Jacobson CA et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): A single-arm, multicentre, phase 1-2 trial. Lancet Oncol 2019;20:31-42.

59. Mei Q, Zhang W, Liu Y, et al. Camrelizumab Plus Gemcitabine, Vinorelbine, and Pegylated Liposomal Doxorubicin in Relapsed/Refractory Primary Mediastinal B-Cell Lymphoma: A Single-Arm, Open-Label, Phase II Trial. Clinical Cancer Research 2020;26:4521–4530.

60. Martelli M, Zucca E, Gospodarowicz M et al. A randomized, multicentre, two-arm phase III comparative study assessing the role of mediastinal radiotherapy after rituximab-containing chemotherapy regimens to patients with newly diagnosed primary mediastinal large B-cell lymphoma (PMLBCL): The IELSG-37 study. Hematol Oncol 2013;31:96–150.

61. Ceriani L, Martelli M, Zinzani PL, et al. Utility of baseline 18FDG-PET/CT functional parameters in defining prognosis of primary mediastinal (thymic) large B-cell lymphoma. Blood 2015;126:950–956.

62. Ceriani L, Martelli M, Conconi A et al. Prognostic models for primary mediastinal (thymic) B-cell lymphoma derived from 18-FDG PET/CT quantitative parameters in the International Extranodal Lymphoma Study Group (IELSG) 26 study. Br J Haematol 2017;178(4):588–591.

63. Ceriani L, Milan L, Martelli M et al. Metabolic heterogeneity on baseline 18FDG-PET/CT scan is a predictor of outcome in primary mediastinal B-cell lymphoma. Blood 2018;132:179–186.

64. Bledsoe JR, Redd RA, Hasserjian RP et al. The immunophenotypic spectrum of primary mediastinal large B-cell lymphoma reveals prognostic biomarkers associated with outcome. Am J Hematol 2016;91:E436–E441.

65. Mansouri L, Noerenberg D, Young E et al. Frequent NFKBIE deletions are associated with poor outcome in primary mediastinal B-cell lymphoma. Blood 2016;128:2666–2670.

66. Zhou H, Xu-Monette ZY, Xiao L, et al. Prognostic factors, therapeutic approaches, and distinct immunobiologic features in patients with primary mediastinal large B-cell lymphoma on long-term follow-up. Blood Cancer Journal 2020;10.

67. Vassilakopoulos TP, Papageorgiou SG, Angelopoulou MK, et al. Positron emission tomography after response to rituximab-CHOP in primary mediastinal large B-cell lymphoma: impact on outcomes and radiotherapy strategies. Ann Hematol 2021. http://dx.doi.org/10.1007/s00277-021-04421-2

68. Hayden AR, Tonseth P, Lee DG, et al. Outcome of primary mediastinal large B-cell lymphoma using R-CHOP: impact of a PET-adapted approach. Blood 2020;136:2803–2811.