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Optimally Delivered R-da-EPOCH Versus R-CHOP-21 in Primary Mediastinal Large B-Cell Lymphoma: A Real-Life Comparison in a Single Academic Center

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Simple Summary: R-CHOP + consolidative radiotherapy (RT) has been historically the usual treatment option for PMLBCL with a cure rate of 75–80%. The National Cancer Institute introduced the intensified R-da-EPOCH regimen, which produced better outcomes compared to R-CHOP, while minimizing RT. However, there is no direct randomized comparison of R-da-EPOCH vs. R-CHOP and the majority of the comparative supporting data comes from retrospective series, where the comparisons performed demonstrated only marginally better outcomes. Herein, we report a large, real-life, single-center study aiming to compare R-da-EPOCH with R-CHOP in patients with PMLBCL of a single referral center, where the R-da-EPOCH escalation schedule was strictly followed almost universally. According to our findings, R-da-EPOCH if delivered optimally, eliminates the need for RT and might provide a benefit in disease control and potentially improved survival at the expense of a small, but measurable risk of long-term side effects.

Abstract: Background/Objectives: The National Cancer Institute introduced the intensified R-da-EPOCH regimen in primary mediastinal large B-cell lymphoma (PMLBCL) to improve outcomes while minimizing radiotherapy use. However, there is no randomized comparison of R-da-EPOCH vs. R-CHOP-21. The objective of this study was to compare R-da-EPOCH with R-CHOP-21 in consecutive patients with PMLBCL of a single, large referral center, where the R-da-EPOCH escalation schedule was strictly followed. Methods: We retrospectively analyzed all 35 consecutive patients who received R-da-EPOCH (2017–2022) compared to 35 consecutive patients treated with R-CHOP-21 arm at the same Department, starting from the most recent patient and going backwards (2005–2017). Results: R-da-EPOCH was given strictly in 33/35 (94%) patients. The 5-year freedom from progression (FFP) was 91% vs. 69% (p = 0.027). The 5-year event-free survival (EFS) was 84% vs. 69% (p = 0.124). The 5-year overall survival (OS) was 97% vs. 80% (p = 0.063). Among R-CHOP-21-responders, 20/29 (69%) received RT compared to 2/34 (6%) R-da-EPOCH-responders. In multivariate analysis, R-da-EPOCH remained better than R-CHOP-21 in terms of FFP [hazard ratios (HRs) 0.21–0.26, all $p < 0.05$] and was associated with very favorable HR for EFS and OS. Conclusions: Opti-

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Academic Editor: Alessandro Pileri

Received: 27 March 2025
Revised: 5 May 2025
Accepted: 6 May 2025
Published: 19 May 2025

Citation: Piperidou, A.; Angelopoulou, M.K.; Chatzidimitriou, C.; Asimakopoulos, J.V.; Arapaki, M.; Panitsas, F.; Tsourouflis, G.; Belia, M.; Konstantinou, I.; Kopsaftopoulou, A.; et al. Optimally Delivered R-da-EPOCH Versus R-CHOP-21 in Primary Mediastinal Large B-Cell Lymphoma: A Real-Life Comparison in a Single Academic Center. *Cancers* **2025**, *17*, 1699. https://doi.org/10.3390/cancers17101699

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mally delivered R-da-EPOCH minimized the use of RT in a real-life setting and provided superior outcomes than R-CHOP-21.

Keywords: Primary mediastinal; Large cell lymphoma; B-cell; R-da-EPOCH; R-CHOP-21; RT

1. Introduction

Primary mediastinal large B-cell lymphoma (PMLBCL) is a rare aggressive B-cell lymphoma, recognized as a distinct entity based on clinical, morphologic, immunophenotypic and cytogenetic characteristics [1]. It accounts for approximately 2.5% of non-Hodgkin Lymphomas (NHLs) with an annual incidence rate of 0.4 new cases per million [1–6]. PMLBCL typically affects young and middle-aged women, who present, in the majority of cases, with bulky mediastinal lymphadenopathy, which is often mildly or severely symptomatic. Involvement of extrathoracic distal extranodal sites is a rare event at presentation, while bone marrow involvement is extremely rare [7].

First-line treatment is of critical importance in PMLBCL. The efficacy of salvage therapy is often limited, at least prior to the introduction of innovative therapies [8]. Initial therapy includes anthracycline-based chemotherapy combined with rituximab, which has revolutionized the treatment of PMLBCL, producing a significant improvement in disease control and overall survival (OS) [9–14]. However, R-CHOP-21 alone is associated with a 20–30% probability of treatment failure and has been traditionally used along with consolidative radiotherapy (RT) in many patients, even in the positron emission tomography (PET) era [12,15–19]. Other, more intensive regimens, such as R-CHOP-14 or R-M(V)ACOP-B, have been used followed by RT or even consolidation with autologous stem cell transplantation (ASCT) but their superiority over R-CHOP-21 is doubtful and has not been tested in randomized trials [13,20–28]. The IELSG37 study was suggestive of the potential superiority of more intensive regimens over R-CHOP-21 in terms of a highly reduced rate of a Deauville score of 5 at the end of treatment, but result was not based on the randomized part of the study [25,29].

The long-term consequences of treatment have very rarely been described in PMLBCL, but it is widely known from the experience with Hodgkin Lymphoma (HL) that mediastinal RT is associated with increased risk of secondary malignancies and cardiovascular toxicity, so current research focuses on minimizing RT use [30–38].

In order to increase the success rate and reduce the use of RT, the National Cancer Institute (NCI) introduced the intensified R-da-EPOCH regimen, which produced better outcomes than those historically achieved with R-CHOP-21 whilst also minimizing consolidative RT in a phase 2 trial. According to the initially published data, R-da-EPOCH resulted in impressive disease control, with event-free survival (EFS) of 93%, long-term overall survival (OS) rates of 97% at a median follow-up of 63 months and minimal use of RT in only 2/52 patients [39,40]. Following the impressive NCI data, several real-life studies confirmed the efficacy of R-da-EPOCH in the elimination of RT, demonstrating somewhat lower—but still high—disease control rates. However, formal superiority of R-da-EPOCH over R-CHOP-21 has not been clearly demonstrated in retrospective studies [41–48]. Such studies are further compromised by the fact that the R-da-EPOCH regimen is not optimally delivered in a sizeable proportion of patients, since the escalation process is not strictly followed in real-life settings [41,46], while this information was not recorded in detail in other studies [42,44,45,47,48]. Notably, there is no direct randomized comparison of the two protocols except of the preliminary results of an Ukrainian trial, which are in favor of R-da-EPOCH in terms of both disease control and OS [49].

In the Hellenic retrospective comparison, which has not been fully published yet, protocol deviations of variable degrees were recorded in slightly more than 50% of patients [46]. As the reasons of protocol deviations are left to the discretion of the treating physicians and may not be clearly declared in a retrospective setting, it is not scientifically reasonable to compare the optimally treated subgroup of R-da-EPOCH patients with any R-CHOP-21-treated population, because it is impossible to select an appropriate control group. For this reason, we conducted a real-life comparison of R-da-EPOCH versus R-CHOP-21 in patients with PMLBCL treated at a single, large referral academic center, where the R-da-EPOCH escalation schedule was strictly followed in 33/35 patients, i.e., almost universally.

2. Patients and Methods

We retrospectively analyzed all 35 consecutive patients who received R-da-EPOCH in the Department of Haematology and Bone Marrow Transplantation of the National and Kapodistrian University of Athens, Laikon General Hospital between 2017 and 2022. A single patient who received R-CHOP-21 in the context of a completely resected mediastinal mass during the same period was excluded. An identical number of 35 consecutive PMLBCL patients served as R-CHOP-21 controls. All 35 patients received R-CHOP-21, since R-CHOP-14 has not been used in our Department for PMLBCL. All patients were treated at the same Department and were selected in a sequential manner, starting from the most recent patient and going backwards (December 2005–2017). As the Department of Haematology was founded in 2008, patients diagnosed between December 2005 and May 2008 were similarly selected by the same database among those treated at the First Department of Internal Medicine of the National and Kapodistrian University of Athens, Laikon General Hospital, which was the "progenitor" of the Department of Haematology with similar referral patterns. Using this strategy of sequential patient analysis to identify the optimal controls, the selection bias was expected to be minimal and potential sources of bias were limited to supportive care and salvage therapy options. Consolidative RT was used at the discretion of the treating physician, usually based on PET/CT results, but was systematically avoided after R-da-EPOCH in case of a Deauville score of 1–4. RT strategies after R-CHOP-21 varied with time with gradual omission of RT in the event of a Deauville score of 1–2 at the end of treatment [15,16,50].

Patients were clinically staged according to Ann-Arbor classification. In accordance with our previous reports, stage IV was defined only in cases where non-contiguous extranodal lymphoma spread was reported [9]. All the remaining cases were considered as "E". Risk stratification was based on the well-known international prognostic index (IPI) and age-adjusted IPI (aaIPI) [51], as well as on the two prognostic models, which were recently proposed by the Hellenic Lymphoma group (Model A: E/IV and LDH $\geq$ 2x, Model B: E/IV and bulky disease) [52].

The primary endpoint was freedom from progression (FFP), which was defined as the time interval between treatment initiation and disease progression, relapse, death of therapy- or disease-related procedures without prior progression/relapse or last follow-up. Event-free survival (EFS) was defined as the time interval between treatment initiation and disease progression, relapse, development of acute myeloid leukemia (AML) or HL as secondary primary neoplasms, death of any cause without prior progression/relapse, or last follow-up. OS was defined as the time interval between treatment initiation and death of any cause or last follow-up.

Comparisons between groups were performed by the chi-square test with continuity correction, if required, or the Mann–Whitney test for qualitative and continuous variables, respectively. Survival curves were plotted according to the Kaplan–Meier method and

were compared with the log-rank test. Multivariate survival analysis was performed by Cox's proportional hazards model [53–55].

3. Results

3.1. Patient Characteristics and Delivery of Chemotherapy

Patients' characteristics in the two groups were absolutely comparable, except for older age in the R-da-EPOCH group (median 35 vs. 28 years, $p = 0.01$; ≥38 years 43% vs. 9%, $p = 0.001$) and more frequent serous effusions in the R-CHOP-21 group (37% vs. 64%, $p = 0.37$) (Table 1). The risk classification of the patients according to the two prognostic models (A and B) [52], as well as the IPI, was also comparable between the two treatment groups (Table 1). R-da-EPOCH was strictly followed in 33/35 patients (94%): 2 patients reached level 4 and 5 but there was no further escalation, despite the lack of prohibitive toxicity. Comparably to the original R-da-EPOCH publication [39], 49% of the 35 patients reached at least level 4, 89% reached at least level 3, and only 6% reached level 1 (Table 2).

Table 1. Comparison of patients' baseline characteristics between R-da-EPOCH and R-CHOP-21 populations.

Patient Characteristics	R-da-EPOCH % n = 35		R-CHOP % n = 35		*p*-Value
	#	%	#	%	
Age (Median, Range)	35 (16–51)		28 (16–59)		0.01
Age ≥ 38 years old	15/35	43	3/35	9	0.001
Females	26/35	74	22/35	63	0.30
B-symptoms	7/35	20	7/33	21	0.90
PS ≥ 2	7/35	20	8/34	24	0.72
Stage III/IV	10/35	29	6/33	18	0.31
Any extranodal site	13/35	37	17/35	49	0.33
Extranodal sites ≥ 2	4/35	11	9/35	26	0.12
Extrathoracic disease	8/35	23	4/35	11	0.21
Kidney/Adrenal involvement	3/35	9	2/35	6	0.64
Serous effusions	13/35	37	21/33	64	0.03
Bulky disease ≥ 10 cm	25/35	71	21/32	66	0.61
Serum LDH elevated	29/35	83	30/34	88	0.53
Serum LDH ≥ 2x	15/35	43	11/34	32	0.37
IPI ≥ 2	13/35	37	16/35	46	0.47
aaIPI ≥ 2	13/35	37	12/35	34	0.80
Model A: E/IV and LDH ≥ 2xUNL *					0.89
No adverse factors	15/35	43	15/34	44	
1 adverse factor	12/35	34	10/34	29	
2 adverse factors	8/35	23	9/34	27	
Model B: E/IV and bulk					0.91
No adverse factors	8/35	23	6/32	19	
1 adverse factor	16/35	46	15/32	47	
2 adverse factors	11/35	31	11/32	34	

* UNL: upper normal limit.

Table 2. Dose escalation schedule and protocol adherence in R-da-EPOCH-treated patients in comparison to the original NCI study [39].

Maximum R-da-EPOCH Level	All Patients (n = 35)		Strictly Delivered EPOCH Subgroup (n = 33)	
	#	%	#	%
1	2	5.7	2	6.1
2	2	5.7	2	6.1
3	14	40.0	14	42.4
4	9	25.7	8	24.2
5	6	17.1	5	15.2
6	2	5.7	2	6.1
Maximum R-da-EPOCH level	**All patients** (n = 35)		**NCI Study [22]** (n = 51)	
	#	%	#	%
1	2	5.7		6
≥3	31	88.5		
≥4	17	48.5		“>50%”

3.2. Outcomes

Disease progression or relapse was observed in 2 and 11 patients after R-da-EPOCH or R-CHOP-21. Notably, one of the two patients with protocol violation relapsed despite reaching level 4, as she experienced progressive disease at end-of-treatment restaging at roughly 30 days after the last R-da-EPOCH cycle. Two patients developed AML after R-da-EPOCH versus none after R-CHOP-21. Only 1 patient died in the R-da-EPOCH population versus 8/35 treated with R-CHOP-21. All deaths were due to progressive disease.

The 5-year FFP was 91% vs. 69% (p = 0.027) (Figure 1), the 5-year EFS was 84% vs. 69% (p = 0.124) (Figure 2), and the 5-year OS was 97% vs. 80% (p = 0.063) (Figure 3). Among responders to R-CHOP-21, the majority (20/29, 69%) received RT compared to only 2/34 (6%) R-da-EPOCH responders. Both of the latter had a Deauville score of 5 and conventionally responding disease.

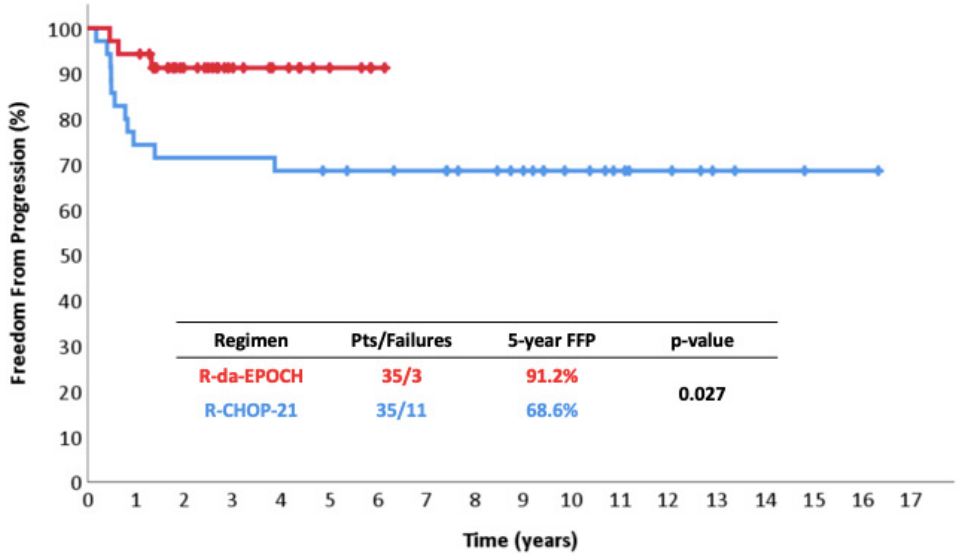

Figure 1. Freedom from progressions in 35 patients with PMLBCL treated with R-da-EPOCH.

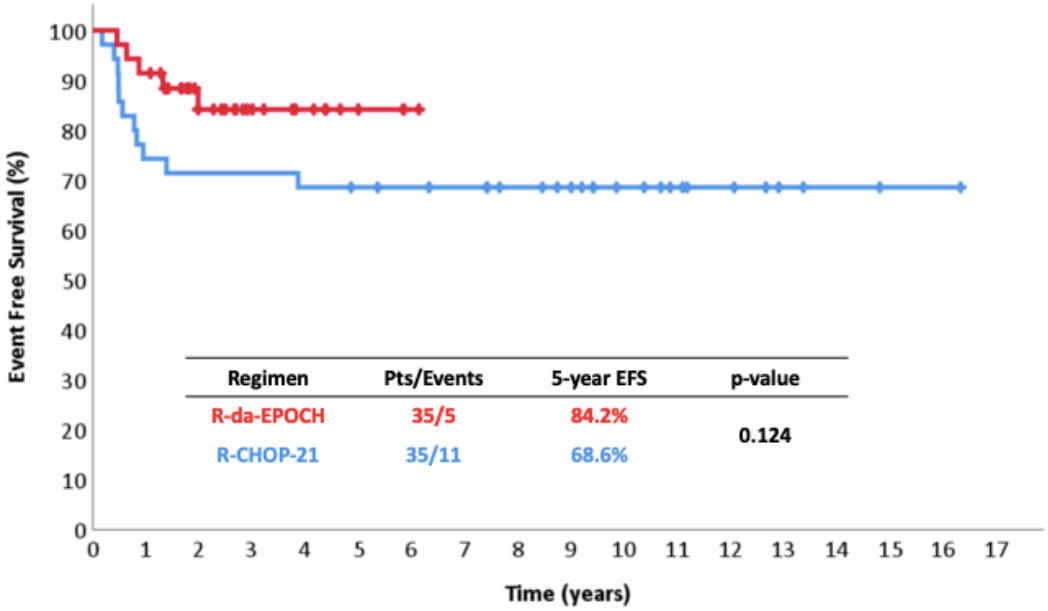

Figure 2. Event free survival in 35 patients with PMLBCL treated with R-da-EPOCH.

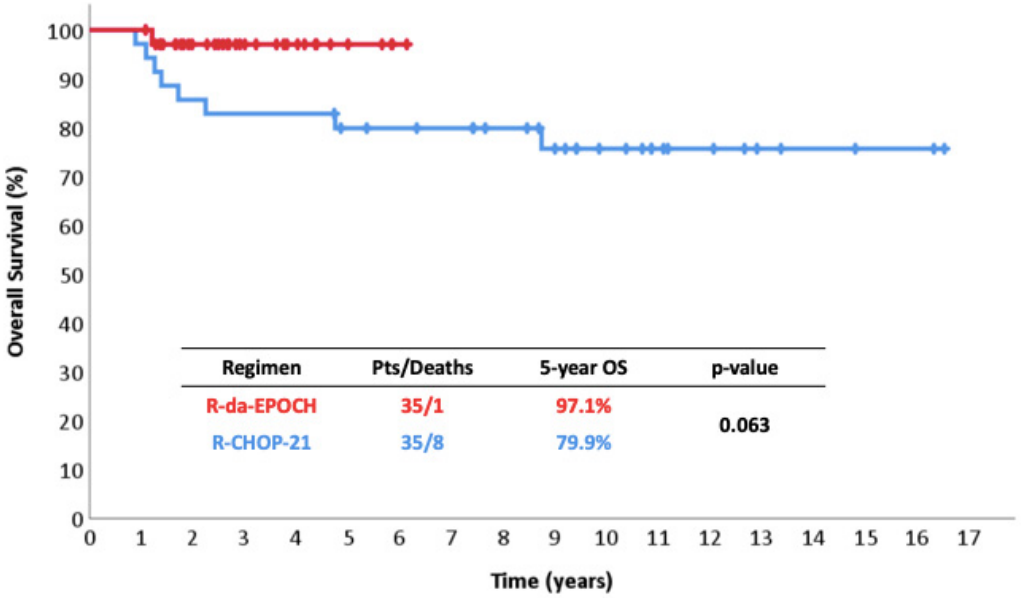

Figure 3. Overall survival in 35 patients with PMLBCL treated with R-da-EPOCH.

In multivariate analysis -adjusting for age ≥38 years and serositis- R-da-EPOCH remained superior to R-CHOP-21 regarding FFP [hazard ratio (HR) 0.24, 95% confidence intervals (CI) 0.07–0.88, $p = 0.031$]. When the recently published prognostic models (stage E/IV and LDH ≥ 2x and E/IV and bulk) were evaluated in a multivariate model, R-da-EPOCH was again associated with superior FFP rates (HR 0.21–0.26, all $p < 0.05$, Table 3). As shown in Table 3, the difference regarding EFS was borderline (HR 0.37–0.45, *p*-values 0.068 to 0.147), as well as for OS despite very favorable HRs (HR 0.16–0.18, $p = 0.09$–0.12).

Table 3. Multivariate analysis.

	Freedom from Progression			Event-Free Survival			Overall Survival		
	Hazard Ratio	**95% CI**	***p*-Value**	**Hazard Ratio**	**95% CI**	***p*-Value**	**Hazard Ratio**	**95% CI**	***p*-Value**
Multivariate Model including Treatment Regimen, Age and Presence of any Serositis									
R-da-EPOCH vs. R-CHOP-21	0.24	0.07–0.88	0.031	0.41	0.14–1.20	0.103	0.16	0.02–1.32	0.089
Age ≥ 38 years old			NS			NS			NS
Any serositis			NS			NS			NS
Multivariate Model including Treatment Regimen and Prognostic Model A (E/IV and/or LDH ≥ 2x)									
R-da-EPOCH vs. R-CHOP-21	0.21	0.06–0.76	0.017	0.37	0.12–1.08	0.068	0.17	0.02–1.36	0.095
E/IV and/or LDH ≥ 2xUNL *			0.072			0.069			NS
1 factor vs. 0 factors	4.96	1.26–19.57	0.022	4.75	1.20–18.73	0.026			
2 factors vs. 0 factors	2.66	0.60–11.89	0.20	4.01	1.002–16.03	0.050			
Multivariate Model including Treatment Regimen and Prognostic Model A (E/IV and/or bulk)									
R-da-EPOCH vs. R-CHOP-21	0.26	0.07–0.97	0.044	0.45	0.15–1.33	0.147 (NS)	0.18	0.02–1.54	0.12 (NS)
E/IV and/or bulk			NS			NS			NS
1 factor vs. 0 factors									
2 factors vs. 0 factors									

NS: not selected in multivariate analysis; * UNL: upper normal limit

4. Discussion

During the last decade, R-da-EPOCH has become a very promising intensified regimen with potentially better disease control in patients with PMLBCL compared to R-CHOP-21. Further tothe impressive results of the single-arm phase 2 trial from NCI, the majority of the comparative supporting data comesfrom retrospective series, where the comparisons performed demonstrated numerical improvements but marginal statistical significance, as patient numbers were rather small (Table 4) [39].

In particular, the largest multicenter analysis comparing R-CHOP-21 vs. R-da-EPOCH, which was conducted by Shah et al. and involved 132 patients from 11 US centers, revealed numerical superiority of R-da-EPOCH, without statistical significance for both OS and PFS [OS, HR = 0.63 (0.19–2.15), $p = 0.46$; PFS, HR = 0.62 (0.24–1.47), $p = 0.28$] [41]. Chan et al. conducted a multicenter retrospective study of similar size, which included a smaller R-da-EPOCH-treated population (n = 46) in comparison to 78 patients who received R-CHOP-21 with (n = 37) or without RT (n = 41) versus R-da-EPOCH [47]. The 5-year PFS was 88.5% for R-da-EPOCH compared to 90% for R-CHOP-21 + RT and only 56% for R-CHOP-21 alone ($p = 0.002$). The impact of RT after R-CHOP-21 should be interpreted with caution, as there is a possibility that primary refractory patients were classified in the group of R-CHOP-21 alone, thus underestimating the efficacy of the regimen compared to R-CHOP-21 + RT. Another retrospective study by Malenda et al. in 53 PMLBCL patients from two Polish centers also demonstrated only numerical differences in 12-month PFS (87% vs. 74%, $p = 0.21$) and OS (100% vs. 92%, $p = 0.81$) in favor of the R-da-EPOCH protocol, lacking though of statistical significance, probably due to the low number of patients. In addition, none of the 28 R-da-EPOCH-treated patients proceeded to autoSCT in the frontline setting compared to 9/25 R-CHOP-21-treated patients, who received autoSCT consolidation [48]. One year later, in 2021, Morgenstern et al. conducted a bi-center retrospective analysis of 56 patients with PMLBCL comparing R-da-EPOCH (n = 31) vs. the intensive combination R-CHOP-21/R-ICE (n = 25) and showed similar response rates between treatment groups. Regarding disease control, the investigators showed that an absolute percentage of 16% of the patients treated with R-CHOP-21/R-ICE progressed or relapsed versus 26% of those

treated with R-da-EPOCH ($p = 0.37$). The corresponding death rates were 12% versus 16%, respectively ($p = 0.71$) [42].

Table 4. Published studies comparing R-da-EPOCH vs. R-CHOP-21 in PMLBCL patients.

		Patients (#)		Progression Free Survival (PFS)	Overall Survival (OS)
Author [REF]	**Type of Study**	**R-da-EPOCH Group**	**Comparator Group**	**R-da-EPOCH vs. Comparator**	**R-da-EPOCH vs. Comparator**
Shah et al. [41]	Propensity-weighted retrospective analysis	76	56 *	HR: 0.62; 95% CI: 0.24–1.47 $p = 0.28$	HR: 0.63; 95% CI 0.19–2.15 $p = 0.46$
Chan et al. [47]	Retrospective study	46	78 **	88.5% vs. (90% vs. 56%) ** at 5 years $p = 0.002$	NR
Malenda et al. [48]	Retrospective study	28	25 *	87% vs. 74% at 1 year $p = 0.21$	100% vs. 92% at 1 year $p = 0.81$
Morgenstern et al. [42]	Retrospective study	31	25 ***	26% vs. 16% relapse at 2 years $p = 0.37$	NR
Stepanishyna et al. [49]	Prospective rando-mized clinical trial	44	40 *	90.9% vs. 64.1% at 5 years $p = 0.002$	97.7% vs. 73.8% at 5 years $p = 0.002$
Rehman et al. [56]	Systematic review	256	213 ¶	RR: 0.76; 95% CI: 0.57–1.02 $p = 0.06$	RR:0.84; 95% CI 0.72–0.97 $p = 0.02$ ¶¶
Piperidou et al. present study	Retrospective study	35	35 *	91% vs. 69% at 5 years $p = 0.027$	97% vs. 80% at 5 years $p = 0.063$

* R-CHOP-21; ** R-CHOP-21+RT vs. R-CHOP; *** R-CHOP-21/R-ICE; ¶ heterogenous; ¶¶ OS rates 80.1% vs. 65.5%; NR: not reported.

So far, the only randomized study, which not only numerically but also statistically demonstrated improved outcomes of R-da-EPOCH compared to R-CHOP-21, is a Ukrainian trial based on 84 patients from six centers, the preliminary outcomes of which were presented by Stepanishyna et al. at the 2021 EHA Congress [49]. The study demonstrated a 5-year PFS of 90.9% vs. 64.1% ($p = 0.002$) and a 5-year OS of 97.7% vs. 73.8% ($p = 0.002$) in the R-da-EPOCH and the R-CHOP-21 arm, respectively. However, the complete analysis and the details have not been published yet and the final results have yet to be revealed, whilethere is no reference related to protocol violations. Interestingly, disease control, and especially OS, in the R-CHOP-21 arm appear much worse than expected.

Recently, Rehman et al. published a systematic review and meta-analysis of four studies, including one prospective and three retrospective cohorts [41,42,48,49,56]. A total of 469 patients were included in the analysis, with 256 having received R-EPOCH and 213 R-CHOP-21, respectively. This study demonstrated statistically better disease control with R-da-EPOCH compared to R-CHOP-21 in terms of CR rate (65.5% versus 80.1%, RR = 0.84, 95% CI 0.72–0.99; $p = 0.04$) and marginally PFS (RR = 0.76, 95% CI 0.57–1.02; $p = 0.06$) and, interestingly, an OS benefit (RR = 0.84, 95% CI 0.72–0.97; $p = 0.02$) [56].

The protocol dosing schedule—a fundamental difference in the R-da-EPOCH regimen compared to R-CHOP-21—and, most importantly, its influence on treatment outcomes, are not adequately highlighted in the published comparative analyses. In all the previously reported studies, compliance with the protocol was either not reported at all or was suboptimal, as 38% and 14% of the patients did not undergo dose escalation per protocol

in the studies by Shah et al. and Malenda et al. For these reasons, scientifically valid comparisons cannot be drawn. Since, in a single center, R-da-EPOCH is more likely to be delivered in the optimal way and the Department of Haematology of the National and Kapodistrian University of Athens almost strictly follows the guidelines of escalation, the present comparison is the first to show the effect of strict protocol adherence and provides a minimally biased comparison using well-matched subgroups of consecutively treated patients between optimally administered R-da-EPOCH and R-CHOP-21. Despite lack of randomization, the R-da-EPOCH and R-CHOP-21 consecutive patient series were notably similar regarding their baseline characteristics and risk classification, which suggests that the methodology used to select the control group and reduce selection bias was effective.

In the series reported here, R-da-EPOCH offered impressively better disease control, with a long-term FFP increased by an absolute percentage of 22% compared to R-CHOP-21, while minimizing the use of RT in this real-world, single-center context. The majority of R-CHOP-21-treated patients (20/29, 69%) received RT compared to only 2/34 (6%) among R-da-EPOCH-treated patients. One could argue that these 35 sequential controls treated with R-CHOP-21 had a slightly lower-than-expected disease control rate of 69% compared to other series and our previously published data, as the expected rate should be 75–80% [9–12,17,20,56–61], but the method of selection guaranteed the least possible bias. Benefits regarding OS and EFS were statistically ambiguous, probably due to the low number of patients, but the HRs were indeed low in favor of R-da-EPOCH, with an impressive 5-year OS of 97%.

Regarding EFS, the difference was reduced because of the occurrence of two AML cases. Considering the rather small patient sample, the difference in EFS failed to reach statistical significance but still remained numerically high at the level of 15% (Figure 2). Both AML patients are still alive following allogeneic stem cell transplantation. No cases of metachronous classical Hodgkin lymphoma—a well-defined event in PMLBCL—were recorded [62].

The limitations of the present study include the small size of the patient population, which is not so small for a rare disease such as PMLBCL, especially within a single center, and is comparable to many other reports, even multicenter ones. Indeed, it should be noted that the very few previously published comparisons are of the same size in terms of R-da-EPOCH-treated patients [42,47,48] with the exception of the multicenter study by Shah et al., which included 76 patients treated with R-da-EPOCH. Furthermore, unpredictable bias sources may have been present, as this was not a randomized trial. The protocol deviation in 2/35 patients still remains a limitation, but this could only underestimate the superiority of R-da-EPOCH, as 1/2 patients with protocol violation had primary progressive disease. In any case, both patients received a substantial amount of chemotherapy reaching levels 4 and 5. A last potential limitation could be that any OS benefit with R-da-EPOCH might be obscured by the application of novel effective salvage therapies, including checkpoint inhibitors and CAR-T cells [63–75]. Interestingly, no R-da-EPOCH-treated patients received novel agents in this series compared to one after R-CHOP-21, so this potential limitation is not applicable.

5. Conclusions

In conclusion, if delivered optimally, R-da-EPOCH almost eliminates the need for RT and provides benefits in terms of disease control and a meaningful increase in survival, despite the small, but measurable risk of long-term side effects. Thus, optimally delivered R-da-EPOCH appears superior to R-CHOP-21, with much less RT use, but its superiority compared to other intensified regimens still remains unclear. However, its application in the community is suboptimal, so multicenter studies with real-life data and their heterogeneity

are still very informative. Reporting on the adherence to the protocol in these studies is also of crucial importance.

Author Contributions: Conceptualization, T.P.V.; methodology, A.P. and T.P.V.; formal analysis, T.P.V.; investigation, A.P., M.K.A. and T.P.V.; data curation, A.P., C.C. and T.P.V.; writing—original draft preparation, A.P., C.C. and T.P.V.; writing—review and editing, A.P., M.K.A., C.C., J.V.A., M.A., F.P., G.T., M.B., I.K., A.K., A.L., A.M., M.-A.L., M.D., S.S., G.A.P., K.K., E.P., M.S. and T.P.V.; visualization, A.P. and T.P.V.; supervision, A.P., M.K.A. and T.P.V. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of Laikon General Hospital. The number of the study approval is the following: Α.Π.Ε.Σ. 309/15-06-2010.

Informed Consent Statement: In this retrospective study with no identifiable data iformed consent was waved.

Data Availability Statement: The data presented in this study are available on request from the corresponding author due to privacy reasons.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Swerdlow, S.H.; Campo, E.; Harris, N.L.; Jaffe, E.S.; Pileri, S.A.; Stein, H.; Thiele, J. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*, Revised 4th ed.; IARC: Lyon, France, 2017.
2. Martelli, M.; Ferreri, A.; Rocco, A.D.; Ansuinelli, M.; Johnson, P.W.M. Primary Mediastinal Large B-Cell Lymphoma. *Crit. Rev. Oncol. Hematol.* **2017**, *113*, 318–327. [CrossRef] [PubMed]
3. Rosenwald, A.; Wright, G.; Leroy, K.; Yu, X.; Gaulard, P.; Gascoyne, R.D.; Chan, W.C.; Zhao, T.; Haioun, C.; Greiner, T.C.; 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. [CrossRef]
4. Green, M.R.; Monti, S.; Rodig, S.J.; Juszczynski, P.; Currie, T.; O'Donnell, E.; Chapuy, B.; Takeyama, K.; Neuberg, D.; Golub, T.R.; 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. [CrossRef] [PubMed]
5. Alaggio, R.; Amador, C.; Anagnostopoulos, I.; Attygalle, A.D.; Araujo, I.B.d.O.; Berti, E.; Bhagat, G.; Borges, A.M.; Boyer, D.; Calaminici, M.; et al. The 5th Edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. *Leuk* **2022**, *36*, 1720–1748. [CrossRef]
6. Campo, E.; Jaffe, E.S.; Cook, J.R.; Quintanilla-Martinez, L.; Swerdlow, S.H.; Anderson, K.C.; Brousset, P.; Cerroni, L.; de Leval, L.; Dirnhofer, S.; et al. The International Consensus Classification of Mature Lymphoid Neoplasms: A Report from the Clinical Advisory Committee. *Blood* **2022**, *140*, 1229–1253. [CrossRef] [PubMed]
7. Karakatsanis, S.; Papageorgiou, S.G.; Michail, M.; Angelopoulou, M.K.; Kalpadakis, C.; Leonidopoulou, T.; Katodritou, E.; Kotsopoulou, M.; Kotsianidis, I.; Hatzimichael, E.; et al. Subdiaphragmatic Extranodal Localizations at Diagnosis of Primary Mediastinal Large B- Cell Lymphoma: An Impressive, Rare Presentation with No Independent Effect on Prognosis. *Leuk. Res.* **2021**, *107*, 106595. [CrossRef] [PubMed]
8. Liaskas, A.; Dimopoulou, M.N.; Piperidou, A.; Angelopoulou, M.K.; Vassilakopoulos, T.P. Current Issues and Future Perspectives of Targeted Therapies in Primary Mediastinal Large B-Cell Lymphoma. *J. Clin. Med.* **2025**, *14*, 1191. [CrossRef]
9. Vassilakopoulos, T.P.; Pangalis, G.A.; Katsigiannis, A.; Papageorgiou, S.G.; Constantinou, N.; Terpos, E.; Zorbala, A.; Vrakidou, E.; Repoussis, P.; Poziopoulos, C.; et al. Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone with or without Radiotherapy in Primary Mediastinal Large B-Cell Lymphoma: The Emerging Standard of Care. *Oncologist* **2012**, *17*, 239–249. [CrossRef]
10. Savage, K.J.; Al-Rajhi, N.; Voss, N.; Paltiel, C.; Klasa, R.; Gascoyne, R.D.; Connors, J.M. Favorable Outcome of Primary Mediastinal Large B-Cell Lymphoma in a Single Institution: The British Columbia Experience. *Ann. Oncol.* **2006**, *17*, 123–130. [CrossRef]
11. Rieger, M.; Österborg, A.; Pettengell, R.; White, D.; Gill, D.; Walewski, J.; Kuhnt, E.; Loeffler, M.; Pfreundschuh, M.; Ho, A.D. Primary Mediastinal B-Cell Lymphoma Treated with CHOP-like Chemotherapy with or without Rituximab: Results of the Mabthera International Trial Group Study. *Ann. Oncol. Off. J. Eur. Soc. Med. Oncol.* **2011**, *22*, 664–670. [CrossRef]

12. Soumerai, J.D.; Hellmann, M.D.; Feng, Y.; Sohani, A.R.; Toomey, C.E.; Barnes, J.A.; Takvorian, R.W.; Neuberg, D.; Hochberg, E.P.; Abramson, J.S. 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. [CrossRef]
13. Zinzani, P.L.; Stefoni, V.; Finolezzi, E.; Brusamolino, E.; Cabras, M.G.; Chiappella, A.; Salvi, F.; Rossi, A.; Broccoli, A.; Martelli, M. 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. [CrossRef]
14. Avigdor, A.; Sirotkin, T.; Kedmi, M.; Ribakovsy, E.; Berkowicz, M.; Davidovitz, Y.; Kneller, A.; Merkel, D.; Volchek, Y.; Davidson, T.; 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. [CrossRef]
15. Vassilakopoulos, T.P.; Papageorgiou, S.G.; Angelopoulou, M.K.; Chatziioannou, S.; Prassopoulos, V.; Karakatsanis, S.; Arapaki, M.; Mellios, Z.; Sachanas, S.; Kalpadakis, C.; 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**, *100*, 2279–2292. [CrossRef] [PubMed]
16. Vassilakopoulos, T.P.; Pangalis, G.A.; Chatziioannou, S.; Papageorgiou, S.; Angelopoulou, M.K.; Galani, Z.; Kourti, G.; Prassopoulos, V.; Leonidopoulou, T.; Terpos, E.; 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. [CrossRef]
17. Xu, L.M.; Fang, H.; Wang, W.H.; Jin, J.; Wang, S.L.; Liu, Y.P.; Song, Y.W.; Ren, H.; Zhou, L.Q.; Li, Y.X. 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. [CrossRef] [PubMed]
18. Binkley, M.S.; Hiniker, S.M.; Wu, S.; Natkunam, Y.; Mittra, E.S.; Advani, R.H.; Hoppe, R.T. A Single-Institution Retrospective Analysis of Outcomes for Stage I-II Primary Mediastinal Large B-Cell Lymphoma Treated with Immunochemotherapy with or without Radiotherapy. *Leuk. Lymphoma* **2016**, *57*, 604–608. [CrossRef] [PubMed]
19. Martelli, M.; Ceriani, L.; Zucca, E.; Zinzani, P.L.; Ferreri, A.J.M.; Vitolo, U.; Stelitano, C.; Brusamolino, E.; Cabras, M.G.; Rigacci, L.; 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. [CrossRef]
20. Gleeson, M.; Hawkes, E.A.; Cunningham, D.; Chadwick, N.; Counsell, N.; Lawrie, A.; Jack, A.; Smith, P.; Mouncey, P.; Pocock, C.; 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 Vers. *Br. J. Haematol.* **2016**, *175*, 668–672. [CrossRef]
21. Camus, V.; Rossi, C.; Sesques, P.; Lequesne, J.; Tonnelet, D.; Haioun, C.; Durot, E.; Willaume, A.; Gauthier, M.; Moles-Moreau, M.P.; et al. Outcomes after First-Line Immunochemotherapy for Primary Mediastinal B-Cell Lymphoma: A LYSA Study. *Blood Adv.* **2021**, *5*, 3862–3872. [CrossRef]
22. Wästerlid, T.; Hasselblom, S.; Joelsson, J.; Weibull, C.E.; Rassidakis, G.; Sander, B.; Smedby, K.E. Real-World Data on Treatment and Outcomes of Patients with Primary Mediastinal Large B-Cell Lymphoma: A Swedish Lymphoma Register Study. *Blood Cancer J.* **2021**, *11*, 100. [CrossRef] [PubMed]
23. Karakatsanis, S.J.; Bouzani, M.; Symeonidis, A.; Angelopoulou, M.K.; Papageorgiou, S.G.; Michail, M.; Gainaru, G.; Kourti, G.; Sachanas, S.; Kalpadakis, C.; et al. Real-Life Experience With Rituximab-CHOP Every 21 or 14 Days in Primary Mediastinal Large B-Cell Lymphoma. *In Vivo* **2022**, *36*, 1302–1315. [CrossRef]
24. Avigdor, A.; Sirotkin, T.; Shemtov, N.; Berkowicz, M.; Davidovitz, Y.; Kneller, A.; Hardan, I.; Shimoni, A.; Apter, S.; Ben-Bassat, I.; et al. Combination of Rituximab with Initial Chemotherapy Improves Outcome of Primary Mediastinal B-Cell Lymphoma: A Retrospective Analysis of a Single Institution Cohort. *Blood* **2007**, *110*, 1283. [CrossRef]
25. Martelli, M.; Ceriani, L.; Ciccone, G.; Ricardi, U.; Kriachok, I.; Botto, B.; Balzarotti, M.; Tucci, A.; Usai, S.V.; Zilioli, V.R.; et al. Omission of Radiotherapy in Primary Mediastinal B-Cell Lymphoma: IELSG37 Trial Results. *J. Clin. Oncol.* **2024**, *42*, 4071–4083. [CrossRef]
26. Thurner, L.; Ziepert, M.; Berdel, C.; Schmidt, C.; Borchmann, P.; Kaddu-Mulindwa, D.; Viardot, A.; Witzens-Harig, M.; Dierlamm, J.; Haenel, M.; et al. Radiation and Dose-Densification of R-CHOP in Aggressive B-Cell Lymphoma With Intermediate Prognosis: The UNFOLDER Study. *HemaSphere* **2023**, *7*, E904. [CrossRef] [PubMed]
27. Moskowitz, C.H.; Schöder, H.; Teruya-Feldstein, J.; Sima, C.; Iasonos, A.; Portlock, C.S.; Straus, D.; Noy, A.; Palomba, M.L.; O'Connor, O.A.; 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. [CrossRef]

28. Hamlin, P.A.; Portlock, C.S.; Straus, D.J.; Noy, A.; Singer, A.; Horwitz, S.M.; Oconnor, O.A.; Yahalom, J.; Zelenetz, A.D.; Moskowitz, C.H. 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. [CrossRef]
29. Martelli, M.; Zucca, E.; Botto, B.; Kryachok, I.; Ceriani, L.; Balzarotti, M.; Tucci, A.; Cabras, M.G.; Zilioli, V.R.; Rusconi, C.; et al. Impact of Different Induction Regimens on the Outcome of Primary Mediastinal B Cell Lymphoma In The Prospective Ielsg 37 Trial. *Hematol. Oncol.* **2021**, *39*, 52. [CrossRef]
30. De Sanctis, V.; Alfò, M.; Di Rocco, A.; Ansuinelli, M.; Russo, E.; Osti, M.F.; Valeriani, M.; Minniti, G.; Grapulin, L.; Musio, D.; et al. Second Cancer Incidence in Primary Mediastinal B-Cell Lymphoma Treated with Methotrexate with Leucovorin Rescue, Doxorubicin, Cyclophosphamide, Vincristine, Prednisone, and Bleomycin Regimen with or without Rituximab and Mediastinal Radiotherapy: Results from a Monoinstitutional Cohort Analysis of Long-Term Survivors. *Hematol. Oncol.* **2017**, *35*, 554–560. [CrossRef]
31. Schaapveld, M.; Aleman, B.M.P.; van Eggermond, A.M.; Janus, C.P.M.; Krol, A.D.G.; van der Maazen, R.W.M.; Roesink, J.; Raemaekers, J.M.M.; de Boer, J.P.; Zijlstra, J.M.; et al. Second Cancer Risk Up to 40 Years after Treatment for Hodgkin's Lymphoma. *N. Engl. J. Med.* **2015**, *373*, 2499–2511. [CrossRef]
32. Shbib Dabaja, B.; Boyce-Fappiano, D.; Dong, W.; Damron, E.; Fang, P.; Gunther, J.; Rodriguez, M.A.; Strati, P.; Steiner, R.; Nair, R.; et al. Second Malignancies in Patients with Hodgkin's Lymphoma: Half a Century of Experience. *Clin. Transl. Radiat. Oncol.* **2022**, *35*, 64–69. [CrossRef] [PubMed]
33. Eich, H.T.; Diehl, V.; Görgen, H.; Pabst, T.; Markova, J.; Debus, J.; Ho, A.; Dörken, B.; Rank, A.; Grosu, A.L.; et al. Intensified Chemotherapy and Dose-Reduced Involved-Field Radiotherapy in Patients with Early Unfavorable Hodgkin's Lymphoma: Final Analysis of the German Hodgkin Study Group HD11 Trial. *J. Clin. Oncol.* **2010**, *28*, 4199–4206. [CrossRef] [PubMed]
34. Dracham, C.B.; Shankar, A.; Madan, R. Radiation Induced Secondary Malignancies: A Review Article. *Radiat. Oncol. J.* **2018**, *36*, 85. [CrossRef] [PubMed]
35. Belzile-Dugas, E.; Eisenberg, M.J. Radiation-Induced Cardiovascular Disease: Review of an Underrecognized Pathology. *J. Am. Heart Assoc.* **2021**, *10*, e021686. [CrossRef]
36. De Vries, S.; Haaksma, M.L.; Jóźwiak, K.; Schaapveld, M.; Hodgson, D.C.; Lugtenburg, P.J.; Krol, A.D.G.; Petersen, E.J.; Van Spronsen, D.J.; Ahmed, S.; et al. Development and Validation of Risk Prediction Models for Coronary Heart Disease and Heart Failure After Treatment for Hodgkin Lymphoma. *J. Clin. Oncol.* **2023**, *41*, 86–95. [CrossRef]
37. Roberti, S.; Van Leeuwen, F.E.; Ronckers, C.M.; Krul, I.M.; De Vathaire, F.; Veres, C.; Diallo, I.; Janus, C.P.M.; Aleman, B.M.P.; Russell, N.S.; et al. Radiotherapy-Related Dose and Irradiated Volume Effects on Breast Cancer Risk Among Hodgkin Lymphoma Survivors. *J. Natl. Cancer Inst.* **2022**, *114*, 1270–1278. [CrossRef]
38. Van Nimwegen, F.A.; Ntentas, G.; Darby, S.C.; Schaapveld, M.; Hauptmann, M.; Lugtenburg, P.J.; Janus, C.P.M.; Daniels, L.; Van Leeuwen, F.E.; Cutter, D.J.; et al. Risk of Heart Failure in Survivors of Hodgkin Lymphoma: Effects of Cardiac Exposure to Radiation and Anthracyclines. *Blood* **2017**, *129*, 2257–2265. [CrossRef]
39. Dunleavy, K.; Pittaluga, S.; Maeda, L.S.; Advani, R.; Chen, C.C.; Hessler, J.; Steinberg, S.M.; Grant, C.; Wright, G.; Varma, G.; et al. Dose-Adjusted EPOCH-Rituximab Therapy in Primary Mediastinal B-Cell Lymphoma. *N. Engl. J. Med.* **2013**, *368*, 1408–1416. [CrossRef]
40. Melani, C.; Advani, R.; Roschewski, M.; Walters, K.M.; Chen, C.C.; Baratto, L.; Ahlman, M.A.; Miljkovic, M.D.; Steinberg, S.M.; Lam, J.; et al. End-of-Treatment and Serial PET Imaging in Primary Mediastinal B-Cell Lymphoma Following Dose-Adjusted EPOCH-R: A Paradigm Shift in Clinical Decision Making. *Haematologica* **2018**, *103*, 1337–1344. [CrossRef]
41. Shah, N.N.; Szabo, A.; Huntington, S.F.; Epperla, N.; Reddy, N.; Ganguly, S.; Vose, J.; Obiozor, C.; Faruqi, F.; Kovach, A.E.; 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. [CrossRef]
42. Morgenstern, Y.; Aumann, S.; Goldschmidt, N.; Gatt, M.E.; Nachmias, B.; Horowitz, N.A. Dose-Adjusted EPOCH-R Is Not Superior to Sequential R-CHOP/R-ICE as a Frontline Treatment for Newly Diagnosed Primary Mediastinal B-Cell Lymphoma: Results of a Bi-Center Retrospective Study. *Cancer Med.* **2021**, *10*, 8866–8875. [CrossRef]
43. Vassilakopoulos, T.; Ferhanoglu, B.; Horowitz, N.; Mellios, Z.; Kaynar, L.; Zektser, M.; Symeonidis, A.; Piperidou, A.; Giotas, A.; Agathocleous, A.; et al. Real-Life Experience with Rituximab-Dose-Adjusted EPOCH (R-Da-EPOCH) in Primary Mediastinal Large B-Cell Lymphoma (PMLBCL): A Multinational Analysis of 274 Patients. *Hematol. Oncol.* **2023**, *41*, 410–411. [CrossRef]
44. Pinnix, C.C.; Dabaja, B.; Ahmed, M.A.; Chuang, H.H.; Costelloe, C.; Wogan, C.F.; Reed, V.; Romaguera, J.E.; Neelapu, S.; Oki, Y.; et al. Single-Institution Experience in the Treatment of Primary Mediastinal B Cell Lymphoma Treated with Immunochemotherapy in the Setting of Response Assessment by 18fluorodeoxyglucose Positron Emission Tomography. *Int. J. Radiat. Oncol. Biol. Phys.* **2015**, *92*, 113–121. [CrossRef]
45. Giulino-Roth, L.; O'Donohue, T.; Chen, Z.; Bartlett, N.L.; LaCasce, A.; Martin-Doyle, W.; Barth, M.J.; Davies, K.; Blum, K.A.; Christian, B.; 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. [CrossRef] [PubMed]

46. Vassilakopoulos, T.; Mellios, Z.; Verigou, E.; Papageorgiou, S.; Chatzidimitriou, C.; Kalpadaki, C.; Katodritou, E.; Giatra, H.; Xanthopoulos, V.; Gainaru, G.; et al. Comparison of Immunochemotherapy with Rituximab-Dose-Adjusted EPOCH (R-DA-EPOCH) or Rituximab-CHOP (R-CHOP) in Primary Mediastinal Large-B-Cell Lymphoma (PMLBCL). In Proceedings of the 26th EHA Congress, Madrid, Spain, 13–16 June 2021; p. EP551.
47. Chan, E.H.L.; Koh, L.P.; Lee, J.; De Mel, S.; Jeyasekharan, A.; Liu, X.; Tang, T.; Lim, S.T.; Tao, M.; Quek, R.; 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. [CrossRef] [PubMed]
48. Malenda, A.; Kołkowska-Leśniak, A.; Puła, B.; Długosz-Danecka, M.; Chełstowska, M.; Końska, A.; Giza, A.; Lech-Marańda, E.; Jurczak, W.; Warzocha, K. 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. [CrossRef] [PubMed]
49. Stepanishyna, Y.; Skrypets, T.; Pastushenko, Y.; Tytorenko, I.; Kriachok, I. Analysis of Prognostic Factors in Patients with Primary Mediastinal Large B-Cell Lymphoma Treated by Da-EPOCH-R and R-CHOP. In Proceedings of the 26th EHA Congress, Madrid, Spain, 13–16 June 2021; p. EP557.
50. Vassilakopoulos, T.P.; Piperidou, A.; Mellios, Z.; Verigou, E.; Katodritou, E.; Kalpadakis, C.; Papageorgiou, S.G.; Chatzidimitriou, C.; Prassopoulos, V.; Siakantaris, M.P.; et al. PET for Response Assessment to R-Da-EPOCH in Primary Mediastinal Large B-Cell Lymphoma: Who Is Worthy to Be Irradiated? *HemaSphere* **2023**, *7*, e965. [CrossRef]
51. Shipp, M.A.; Harrington, D.P.; Anderson, J.R.; Armitage, J.O.; Bonadonna, G.; Brittinger, G.; Cabanillas, F.; Canellos, G.P.; Coiffier, B.; Connors, J.M.; et al. A Predictive Model for Aggressive Non-Hodgkin's Lymphoma. *N. Engl. J. Med.* **1993**, *329*, 987–994. [CrossRef]
52. Vassilakopoulos, T.P.; Michail, M.; Papageorgiou, S.; Kourti, G.; Angelopoulou, M.K.; Panitsas, F.; Sachanas, S.; Kalpadakis, C.; Katodritou, E.; Leonidopoulou, T.; et al. Identification of Very Low-Risk Subgroups of Patients with Primary Mediastinal Large B-Cell Lymphoma Treated with R-CHOP. *Oncologist* **2021**, *26*, 597–609. [CrossRef]
53. Kaplan, E.L.; Meier, P. Nonparametric Estimation from Incomplete Observations. *J. Am. Stat. Assoc.* **1958**, *53*, 457. [CrossRef]
54. Mantel, N. Evaluation of Survival Data and Two New Rank Order Statistics Arising in Its Consideration. *Cancer Chemother. Rep.* **1966**, *50*, 163–170. [PubMed]
55. Cox, D.R. Regression Models and Life-Tables. *J. R. Stat. Soc. Ser. B* **1972**, *34*, 187–202. [CrossRef]
56. Rehman, M.E.U.; Ali, R.; Basit, J.; Akbar, U.A.; Saeed, S.; Fatima, M.; Farrukh, L.; Masood, A.; Iftikhar, A.; Husnain, M.; et al. R-CHOP Versus R-EPOCH in Primary Mediastinal Large B-Cell Lymphoma: A Systematic Review and Meta-Analysis. *Blood* **2022**, *140* (Suppl. S1), 9506–9507. [CrossRef]
57. Lisenko, K.; Dingeldein, G.; Cremer, M.; Kriegsmann, M.; Ho, A.D.; Rieger, M.; Witzens-Harig, M. Addition of Rituximab to CHOP-like Chemotherapy in First Line Treatment of Primary Mediastinal B-Cell Lymphoma. *BMC Cancer* **2017**, *17*, 359. [CrossRef] [PubMed]
58. Ahn, H.K.; Kim, S.J.; Yun, J.; Yi, J.H.; Kim, J.H.; Won, Y.W.; Kim, K.; Ko, Y.H.; Kim, W.S. Improved Treatment Outcome of Primary Mediastinal Large B-Cell Lymphoma after Introduction of Rituximab in Korean Patients. *Int. J. Hematol.* **2010**, *91*, 456–463. [CrossRef]
59. Tai, W.M.; Chung, J.; Tang, P.L.; Koo, Y.X.; Hou, X.; Tay, K.W.; Quek, R.; Tao, M.; Lim, S.T. Central Nervous System (CNS) Relapse in Diffuse Large B Cell Lymphoma (DLBCL): Pre- and Post-Rituximab. *Ann. Hematol.* **2011**, *90*, 809–818. [CrossRef] [PubMed]
60. Savage, K.J.; Yenson, P.R.; Shenkier, T.; Klasa, R.; Villa, D.; Goktepe, O.; Steidl, C.; Slack, G.W.; Gascoyne, R.D.; Connors, J.M.; et al. The Outcome of Primary Mediastinal Large B-Cell Lymphoma (PMBCL) in the R-CHOP Treatment Era. *Blood* **2012**, *120*, 303. [CrossRef]
61. Aoki, T.; Izutsu, K.; Suzuki, R.; Nakaseko, C.; Arima, H.; Shimada, K.; Tomita, A.; Sasaki, M.; Takizawa, J.; Mitani, K.; 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. [CrossRef]
62. Vassilakopoulos, T.P.; Piperidou, A.; Hadjiharissi, E.; Panteliadou, A.K.; Panitsas, F.; Vassilopoulos, I.; Variamis, E.; Boutsis, D.; Michail, M.; Papageorgiou, S.; et al. Development of Classic Hodgkin Lymphoma after Successful Treatment of Primary Mediastinal Large B-Cell Lymphoma: Results from a Well-Defined Database. *Leuk. Res.* **2021**, *100*, 106479. [CrossRef]
63. Zinzani, P.L.; Santoro, A.; Gritti, G.; Brice, P.; Barr, P.M.; Kuruvilla, J.; Cunningham, D.; Kline, J.; Johnson, N.A.; Mehta-Shah, N.; 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. [CrossRef]
64. Merryman, R.W.; Armand, P.; Wright, K.T.; Rodig, S.J. Checkpoint Blockade in Hodgkin and Non-Hodgkin Lymphoma. *Blood Adv.* **2017**, *1*, 2643–2654. [CrossRef] [PubMed]
65. Shaulov, A.; Gross Even-Zohar, N.; Aumann, S.; Haran, A.; Linetsky, E. Nivolumab for CNS Relapsed Refractory Primary Mediastinal B-Cell Lymphoma: Case Report and Review of the Literature. *Leuk. Lymphoma* **2024**, *65*, 2219–2223. [CrossRef] [PubMed]

66. Crombie, J.L.; Nastoupil, L.J.; Redd, R.; Tang, K.; Shouse, G.; Herrera, A.F.; Chow, V.A.; Shadman, M.; Puglianini, O.C.; Saucier, A.; et al. Real-World Outcomes of Axicabtagene Ciloleucel in Adult Patients with Primary Mediastinal B-Cell Lymphoma. *Blood Adv.* **2021**, *5*, 3563–3567. [CrossRef]
67. Galtier, J.; Mesguich, C.; Sesques, P.; Dupont, V.; Bachy, E.; Di Blasi, R.; Thieblemont, C.; Gastinne, T.; Cartron, G.; Brisou, G.; et al. Outcomes of Patients with Relapsed or Refractory Primary Mediastinal B-Cell Lymphoma Treated with Anti-CD19 CAR-T Cells: CARTHYM, a Study from the French National DESCAR-T Registry. *HemaSphere* **2025**, *9*, e70091. [CrossRef]
68. Fakhri, B.; Ai, W. Current and Emerging Treatment Options in Primary Mediastinal B-Cell Lymphoma. *Ther. Adv. Hematol.* **2021**, *12*, 20406207211048959. [CrossRef] [PubMed]
69. Neelapu, S.S.; Locke, F.L.; Bartlett, N.L.; Lekakis, L.J.; Miklos, D.B.; Jacobson, C.A.; Braunschweig, I.; Oluwole, O.O.; Siddiqi, T.; Lin, Y.; et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. *New Engl. J. Med.* **2017**, *377*, 2531–2544. [CrossRef] [PubMed]
70. Zinzani, P.L.; Santoro, A.; Gritti, G.; Brice, P.; Barr, P.M.; Kuruvilla, J.; Cunningham, D.; Kline, J.; Johnson, N.A.; Mehta-Shah, N.; et al. Nivolumab Combined with Brentuximab Vedotin for R/R Primary Mediastinal Large B-Cell Lymphoma: A 3-Year Follow-Up. *Blood Adv.* **2023**, *7*, 5272–5280. [CrossRef]
71. Renaud, L.; Wencel, J.; Pagès, A.; Jijakli, A.A.; Moatti, H.; Quero, L.; Camus, V.; Brice, P. Nivolumab Combined with Brentuximab Vedotin with or without Mediastinal Radiotherapy for Relapsed/Refractory Primary Mediastinal Large B-Cell Lymphoma. *Haematologica* **2024**, *109*, 3019–3023. [CrossRef]
72. Armand, P.; Rodig, S.J.; Melnichenko, V.; Thieblemont, C.; Bouabdallah, K.; Tumyan, G.; Özcan, M.; Portino, S.; Fogliatto, L.; Caballero, D.; et al. Pembrolizumab in Patients with Relapsed or Refractory Primary Mediastinal Large B-Cell Lymphoma (PMBCL): Data from the Keynote-013 and Keynote-170 Studies. *Blood* **2018**, *132* (Suppl. S1), 228. [CrossRef]
73. Armand, P.; Rodig, S.; Melnichenko, V.; Thieblemont, C.; Bouabdallah, K.; Tumyan, G.; Özcan, M.; Portino, S.; Fogliatto, L.; Caballero, M.D.; et al. Pembrolizumab in Relapsed or Refractory Primary Mediastinal Large B-Cell Lymphoma. *J. Clin. Oncol.* **2019**, *37*, 3291–3299. [CrossRef]
74. Zinzani, P.L.; Thieblemont, C.; Melnichenko, V.; Bouabdallah, K.; Walewski, J.; Majlis, A.; Fogliatto, L.; Garcia-Sancho, A.M.; Christian, B.; Gulbas, Z.; et al. Pembrolizumab in Relapsed or Refractory Primary Mediastinal Large B-Cell Lymphoma: Final Analysis of KEYNOTE-170. *Blood* **2023**, *142*, 141–145. [CrossRef] [PubMed]
75. De-la-Fuente, C.; Nuñez, F.; Cortés-Romera, M.; Franch-Sarto, M.; Ribera, J.M.; Sancho, J.M. Pembrolizumab for Refractory Primary Mediastinal B-Cell Lymphoma with Central Nervous System Involvement. *Hematol. Oncol.* **2021**, *39*, 419–422. [CrossRef] [PubMed]

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