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Clinical Heterogeneity of Diffuse Large B Cell Lymphoma Following Failure of Front-line Immunochemotherapy

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Summary

This study aimed to describe the patterns of care and outcomes of diffuse large B cell lymphoma (DLBCL) after failure of front line anthracycline-based immunochemotherapy (IC). Patients with newly diagnosed lymphoma were prospectively enrolled in Molecular Epidemiology Resource (MER) of the University of Iowa/Mayo Clinic Lymphoma Specialized Program of Research Excellence. All DLBCL and primary mediastinal B-cell lymphoma (PMBL) patients treated with front-line anthracycline-based IC were followed for relapse. Patients with relapse on follow-up and subsequently retreated were included in this analysis. 1039 patients received anthracycline-based IC between 2002 and 2012, of which 244 relapsed and were subsequently retreated. Across all therapies, overall survival at 4 years (OS4) from relapse was 28% and 103 patients ultimately underwent autologous haematopoietic cell transplant (autoHCT) with OS4 from autoHCT of 51%. Patients relapsing after 12 months from initial diagnosis had OS4 of 47% but those with a transient or no response to initial therapy had OS4 of only 13%. Outcomes of relapsed or refractory DLBCL differ substantially when categorized by response to initial therapy, timing of relapse and opportunity to undergo autoHCT. The design and interpretation of uncontrolled trials should account for this heterogeneity in patients with relapsed DLBCL.

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UF designed the study, collected data, analysed data and wrote the manuscript.
MM, BL, CT designed the study, collected data, analysed data, contributed to manuscript writing and reviewed and approved the manuscript.
GT, DI, IM, WM, SS, TL, YL, SA, GN, TH, JC collected data and reviewed and approved the manuscript.

INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) accounts for 30% to 40% of all non-Hodgkin lymphoma (Al-Hamadani, *et al* 2015). Front line anthracycline-based immunochemotherapy (IC) with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP, or similar) is expected to cure more than 50% of newly diagnosed DLBCL, but at least one-third of patients will be refractory to first-line chemotherapy, achieve only partial remission, or will relapse after achieving complete remission (Coiffier, *et al* 2002, Habermann, *et al* 2006, Pfreundschuh, *et al* 2006, Sehn, *et al* 2005, Sud and Friedberg 2008). Management of DLBCL after failure of IC is challenging without a clear optimal salvage strategy (Crump, *et al* 2014, Gisselbrecht, *et al* 2010). Although curative intent salvage chemotherapy followed by autologous haematopoietic cell transplant (autoHCT) is considered to have the best potential for durable remission, the significant associated toxicities preclude inclusion of the substantial fraction of patients with comorbidities or advanced age (Danese, *et al* 2016). Thus, the prognosis of relapsed and refractory DLBCL as a group remains poor with only a small number of patients achieving long-term disease-free survival (Costa, *et al* 2016, Friedberg 2011, Hitz, *et al* 2015, Kansara, *et al* 2014, Nagle, *et al* 2013, Rovira, *et al* 2015, Van Den Neste, *et al* 2016, Van Den Neste, *et al* 2015).

DLBCL at diagnosis is considered a heterogeneous disease due to host and tumour biology, and the same is true in the relapsed and refractory settings (Sehn and Gascoyne 2015). Biological subsets, such as cell of origin (COO) or chromosomal translocations involving *MYC* and the *BCL* gene family, are less likely to change throughout the course of disease. But distinct clinical scenarios, such as primary refractory, early or late relapse, nodal or extranodal relapse, autoHCT eligible or not, and relapse post-autoHCT, may variably apply to a given patient over time, each probably with unique outcomes. Clinical trials with new agents targeting relapsed or refractory DLBCL often include only subsets of this population and the ability to judge the efficacy of these agents is limited by unknown historical outcomes of the enrolled subset (Christian, *et al* 2015, Coiffier, *et al* 2016, Gerecitano, *et al* 2015, Jacobsen, *et al* 2015, Kochenderfer, *et al* 2015, Locke, *et al* 2015, Maddocks, *et al* 2015, Morschhauser, *et al* 2014, Moskowitz, *et al* 2015, Ribrag, *et al* 2015, Salles, *et al* 2013, Viardot, *et al* 2016, Walter, *et al* 2016, Wang, *et al* 2015, Witzig, *et al* 2011a, Witzig, *et al* 2011b). Population-based studies attempting to define these outcomes to date are limited by lack of inclusivity, treatment and outcome detail, or adequate follow-up (Danese, *et al* 2016). With a multitude of potential therapeutic strategies available for testing, it is unlikely that a single optimal strategy will benefit all relapsed or refractory DLBCL patients and there is a need to identify subsets that can be defined prospectively along with associated expected outcomes.

We initiated a prospective observational cohort study in 2002, enrolling newly diagnosed lymphoma patients with a protocol-specified methodology for capturing baseline clinical, laboratory and pathology data, initial therapy, and active follow-up of all patients for clinical events including re-treatment, relapse/progression and death. Starting from a cohort of consecutively enrolled patients with *de novo* DLBCL, the goal of this analysis was to characterize the subsequent patterns of care and outcomes in patients with DLBCL following IC failure and to identify differences among definable subsets

PATIENTS and METHODS

Study Population

Patients were prospectively enrolled in the University of Iowa / Mayo Clinic Specialized Program of Research Excellence Molecular Epidemiology Resource (MER) within 9 months of diagnosis. Clinical management at diagnosis and subsequent therapies were per treating physician.

Patients were followed for relapse, retreatment and death; all events were validated by review of the medical record. This analysis includes patients with DLBCL or primary mediastinal lymphoma (PMBL) who received initial treatment with anthracycline-based IC (R-CHOP or similar) with a focus on patients who subsequently had an event defined by relapse, retreatment, or death. Patients with primary central nervous system (CNS) lymphoma and post-transplant lymphoproliferative disorders (PTLD) were excluded. Response to therapy was retrospectively classified per 2007 Revised Response Criteria for Malignant Lymphoma from available clinical and radiology records (Cheson, *et al* 2007). Unplanned consolidative radiation (RT) without biopsy proven disease after achieving partial remission (PR) from IC was not classified as a relapse for this analysis. Any relapse consisting of low-grade lymphoma without DLBCL was not considered as a relapse for this analysis.

We defined relapsed/refractory based on response to initial therapy and timing of relapse. Primary refractory disease was defined as no response to frontline anthracycline-based IC. Transient response was defined as either complete remission (CR) or PR noted at assessment in the midst of a planned course of therapy but end of treatment assessment showing progressive disease from the interim response. Relapsed DLBCL was defined as relapse after achieving PR or CR at the end of initial IC. Time from diagnosis to relapse was examined to assess the significance of early vs. late relapses in relapsed DLBCL. We also stratified the treatment into aggressive chemotherapy and less aggressive treatment as a surrogate for patient ability to tolerate salvage chemotherapy. Aggressive salvage treatments at relapse with multi-agent chemotherapy such as R-ICE (rituximab, ifosfamide, carboplatin, etoposide), R-EPOCH (rituximab, etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin), R-GDP (rituximab, gemcitabine, dexamethasone, cisplatin) or R-DHAP (rituximab, dexamethasone, high dose cytarabine, cisplatin) were considered a surrogate for plan to proceed with autoHCT consolidation with curative intent. Patients with CNS involvement at relapse or those treated with radiation only were analysed separately. COO was determined by immunohistochemistry using the Hans algorithm.

Statistical Methodology

Overall survival (OS) was defined as time from the clinical assessment at point of interest (diagnosis, relapse or autoHCT) until death due to any cause. Event-free survival (EFS) was defined as time from clinical assessment until progression/relapse, retreatment, or death due to any cause. OS and EFS were assessed using Kaplan Meier curves and Cox proportional hazards models. Event decomposition was performed by using a competing risk approach

(Gray 1988). All p-values reported are 2-sided. All analyses were performed by using SAS v9.4 (SAS Institute, Cary, NC) and R v3.3.1 (R Core Team, 2016).

RESULTS

Patient Characteristics

A total of 1039 patients with *de novo* DLBCL treated with frontline anthracycline-based IC from 2002–2012 were eligible for this analysis. The median age at diagnosis was 62 years (range 18–92); 56% were male. 647 patients (63%) had stage III/IV disease and International Prognostic Index (IPI) at diagnosis was 0–1 in 350 patients (34%), 2 in 305 patients (29%), 3 in 250 patients (24%) and 4–5 in 134 patients (13%), (Table I). Median follow-up of the entire cohort from diagnosis (reverse Kaplan Meier) was 59 months (range 1–148) (Therneau and Grambsch 2000).

Of the 1039 patients, 250 (24%) had documented relapse and/or retreatment for relapsed or refractory DLBCL. Forty-eight patients died of progressive lymphoma prior to a formal response assessment or died of lymphoma-related causes (unable to complete treatment, clinical deterioration, complications of treatment, etc.) and were not candidates for retreatment. The Kaplan-Meier estimates for EFS and OS of the cohort from the time of diagnosis was 72% (95% confidence interval [CI]: 69%-75%) and 80% (95% CI: 78–83%) at 2 years and 64% (95% CI: 61%-68%) and 71% (95% CI: 68%-74%) at 5 years, respectively. The cumulative incidence of events that include relapse and other competing causes of death for this cohort can be found in Figure 1A.

Initial salvage therapy in patients with relapsed or refractory DLBCL

After failure of front-line IC for DLBCL, 244 patients received retreatment for relapsed or refractory disease, one patient underwent surgical resection without systemic therapy, and 5 had no confirmed therapy after documented relapse. Across all therapies, the response rate to first therapy for relapsed disease was 54% with 103 patients (42%) ultimately undergoing autoHCT. At a median follow-up of 58 months from relapse (reverse Kaplan Meier, range 0–125), 175 patients (72%) had died. The median OS of 244 patients from relapse was 11 months (95% CI 8.8–15.5) and overall survival at 4 years (OS4) from relapse was 28% (Figure 1B). The 2-year EFS from first relapse was 23%. Outcomes of the 244 receiving non-surgical therapy are summarized in Figure 2.

Aggressive chemotherapy at first relapse—Patients without CNS involvement at relapse (n=175) were treated with aggressive systemic chemotherapy. The median age of this group of patients at relapse was 61 years (range 20–87). Initial aggressive salvage regimens included R-ICE in 138 patients, R-DHAP in 14, and anthracycline-based therapy in 12 (Table II). One hundred (57%) patients responded to initial aggressive salvage and 84 (48%) subsequently underwent consolidative autoHCT; 70 proceeded to autoHCT after initial salvage therapy and 14 after subsequent salvage therapy(s). In patients undergoing autoHCT, the median survival from autoHCT was 42.7 months (95% CI: 18.9-unreached) with a 2-year EFS rate from autoHCT of 45%. Outcomes were very poor in patients that were treated with aggressive salvage chemotherapy but failed to undergo autoHCT, with a median OS

from initial relapse of only 6.9 months (95% CI: 5.7–7.6) and a 2-year OS from initial relapse of 19% (Table III).

Non-aggressive chemotherapy at first relapse—Twenty-three patients were initially treated with a non-aggressive salvage regimen after failure of front-line therapy, of whom 6 had primary refractory disease and 16 had relapsed after CR or were treated subsequently after PR, with 1 patient having unknown response to front-line therapy. Patients in this group were older [median age 72 years (range 41–92) vs. 61 years (range 20–87) p value < 0.0001] and they were less likely to proceed with autoHCT (17% vs. 48%, p value =0.0040). Median survival from relapse in the 23 patients was 10.4 months (95% CI: 4.5–21.3) with a 2-year EFS rate of 13%, and an OS4 rate of 22%. The most common regimens used in this group included bendamustine-rituximab (n=8), R-GemOx (n=4) and single-agent R (n=3), (Table II). The overall response rate to non-aggressive regimens was 52% but only 4 patients (17%) subsequently underwent autoHCT. This is compared to 48% patients receiving aggressive salvage chemotherapy that proceeded to autoHCT (p value =0.004).

Other therapies at first relapse—Thirty-three patients with CNS relapse were treated with CNS-directed therapy and detailed outcomes will be reported in a separate series. Thirteen of the 244 relapsed/refractory patients were treated with radiotherapy only, with one patient proceeding to autoHCT; EFS of the 13 radiotherapy patients was 38% at 2 years (Table II).

Survival outcomes of specific clinical subsets of relapsed or refractory DLBCL

Outcome based on clinical prognostic factors at diagnosis—Clinical factors at diagnosis that were associated with poor survival at first relapse were IPI at diagnosis (per unit hazard ratio [HR]=1.15, 95% CI: 1.01 – 1.32, p=0.035), age >60 years (HR=1.41, 95% CI: 1.04 – 1.91, p=0.026), and a non-significant trend for sex, with men having improved survival compared to women (HR=0.77, 95% CI: 0.57–1.04, p=0.092). COO was assessed at diagnosis via Hans algorithm and at relapse where available. Concordance between COO at diagnosis and relapse was excellent (88%) and thus COO at diagnosis was used to assess prognosis at relapse.(Qu, *et al* 2016) There was no difference in survival of patients with non-germinal centre B cell-like (non-GCB) tumours per Hans algorithm (N=51, median survival 11.9 months, 95% CI: 6.7–31.2; HR = 0.79, 95% CI: 0.52–1.22) compared to patients with germinal centre B cell-like (GCB) tumours (N=74, median survival 8.0 months, 95% CI: 6.8–15.1; p=0.29). No other clinical factors at diagnosis were significantly associated with survival post-relapse (Table IV). Finally, in a sensitivity analysis, outcomes after relapse were similar when patients with PMBCL were excluded (results not shown).

Outcome based on response to front-line chemotherapy—Response to frontline IC was predictive of post-relapse outcome. OS from date of first relapse was superior in the 151 patients with responsive disease (CR or PR) at completion of frontline IC [median OS 20.3 months (95% CI: 13.5–31.8) and 2 year EFS of 31%] compared to the 85 patients who had stable or progressive disease [median OS 6.9 months, 95% CI: 5.1–7.8, p<0.0001; and 2 year EFS of 11%, p=0.0005]. Survival was similar in those progressing after either PR or CR (Figure 3A). Patients achieving a CR or PR to frontline IC who subsequently relapsed

were more likely to proceed to autoHCT compared to patients with either stable disease or progressive disease at the end of frontline IC (56% vs. 22% respectively, p<0.0001).

Outcomes in patients with transient response (interim response but progression at or prior to completion of therapy) to front-line IC (n=55) were poor, with a median OS after first relapse of 7.0 months, which was similar to those patients meeting strict definition of refractory with no response to front-line IC (6.7 months, p=0.84) (Figure 3A). Most patients with transient response to front-line IC (67%) received aggressive salvage therapy, which had a response rate of 41%. Ultimately, only 14 of the 55 patients (25%) proceeded to autoHCT, of which only 6 (11%) achieved long-term remission (Table III).

Outcome based on the timing of relapse after achieving complete remission— The timing of relapse from diagnosis was a predictor of outcome. Out of 244 patients with relapse, 93 (38%) patients were primary refractory, 86 (35%) patients achieved remission after completion of IC but relapsed within 12 months of diagnosis, and 65 (27%) patients relapsed beyond 12 months from diagnosis (Table III). Aggressive salvage chemotherapy was administered to 69% of patients with progressive disease at the completion of IC vs. 76% of patients who relapsed between completion of IC and 12 months from diagnosis, and 71% of patients who relapsed > 12 months from diagnosis. Post-relapse outcomes were better in patients who relapsed beyond 12 months from diagnosis (median OS=37.8 months, 80% response rate to first salvage therapy) compared to patients with refractory disease (median OS=7.0 months, 32% response rate) or patients who relapsed within 12 months of diagnosis (median OS=12.5 months, 56% response rate; p<0.0001), (Figure 3B). Patients who relapsed after 12 months from diagnosis were also more likely to proceed to autoHCT (58%) compared to patients with refractory disease to IC (20%, p<0.0001).

DISCUSSION

We report a comprehensive analysis of prospectively collected patterns of care and outcomes of relapsed or refractory DLBCL after receiving front-line anthracycline-based IC. We excluded 48 patients from the analysis who were not candidates for second-line therapy with a goal of making the results relevant to patients, clinicians and clinical research teams contemplating second line therapy. The findings highlight the heterogeneous outcomes of identifiable subgroups of relapsed/refractory DLBCL that will aid in the stratification of patients in phase II or III clinical trials or serve as historical controls for uncontrolled studies. Development of new therapeutic agents targeting relapsed/refractory DLBCL following IC requires an understanding of the patterns of failure and current management strategies with their consequent outcomes.

Most patients with relapsed/refractory DLBCL were treated with aggressive salvage chemotherapy. The response rates to initial salvage therapy reported in this study are somewhat similar for aggressive and non-aggressive regimens, yet the patient cohorts are probably substantially different in regards to age and comorbidities. Similarly, OS is substantially better for the subjects selected for autoHCT. Accordingly, response rates may be an inadequate measure of clinical benefit and clinical trials exploring novel drugs or combinations in this setting might choose endpoints other than simply response rates in trial

design (Christian, *et al* 2015, Coiffier, *et al* 2016, Gerecitano, *et al* 2015, Jacobsen, *et al* 2015, Kochenderfer, *et al* 2015, Locke, *et al* 2015, Maddocks, *et al* 2015, Morschhauser, *et al* 2014, Moskowitz, *et al* 2015, Ribrag, *et al* 2015, Salles, *et al* 2013, Viardot, *et al* 2016, Walter, *et al* 2016, Wang, *et al* 2015, Witzig, *et al* 2011a, Witzig, *et al* 2011b). For patients not deemed appropriate for aggressive therapy, median PFS or even median OS would be a meaningful endpoint without requiring a significant duration of follow up for analysable events. In contrast, clinical trials assessing aggressive combinations that include autoHCT should include 2-year EFS or PFS endpoints, especially if including many non-refractory patients.

In this study, 38% of relapsed/refractory DLBCL patients had primary refractory disease and had particularly poor outcomes. These patients were less likely to respond to salvage chemotherapy and only 20% of these patients underwent autoHCT (Hitz, *et al* 2015, Rovira, *et al* 2015, Sarkozy and Coiffier 2015). These poor outcomes in chemotherapy refractory DLBCL are similar to the results reported by the SCHOLAR-1 study (median overall survival of ~6 months and overall response rate of 20–25% to any subsequent treatment) (Crump, *et al* 2016). Patients with transient response to frontline IC had similarly poor outcomes comparable to those with primary refractory DLBCL suggesting these patients should be included in trials focused on “refractory” patients.

Patients with relapsed DLBCL but chemosensitive disease at the end of front-line treatment (CR or PR) had better survival as compared to patients who were refractory to chemotherapy, even if they had a transient response during the treatment. Similar outcome after relapse for those with CR/PR at end of front-line treatment is an interesting observation that emphasizes the need for more sensitive testing to identify the complete remission as these patients probably had residual disease below the level of detection leading to subsequent relapse. Additionally, patients receiving aggressive salvage chemotherapy were more likely to proceed to autoHCT. This is more likely based upon patient selection factors than effectiveness of salvage therapy, as patients undergoing aggressive salvage chemotherapy were younger (median age 61) than patients receiving non-aggressive treatment (median age 72). IPI at diagnosis is still prognostic of outcome post-relapse, with age as the only individual measure with prognostic power ($p = 0.035$).

Timing of relapse after front-line therapy has substantial prognostic importance and clinical trials need to stratify for this variable in randomization designs or account for it in interpretation of non-randomized results (Gisselbrecht, *et al* 2010, Hamadani, *et al* 2014). Relapse after 12 months from diagnosis was less common (27% of relapsed/refractory DLBCL) and 80% of these patients responded to salvage chemotherapy. Patients who relapsed after 12 months and underwent autoHCT had OS4 from autoHCT of 64%, approaching a similar outcome to *de novo* DLBCL.

We did not identify an association between COO and post-relapse outcomes, but our finding is limited by the small number of patients for which COO information was available - none of which was ascertained by gene expression. While COO at time of diagnosis has established prognostic value, there is little data in rituximab era on the prognostic value of COO at the time of relapse. The Bio-CORAL study indicated that COO retains its

prognostic value at relapse but this is not supported by other studies (Gu, *et al* 2012, Moskowitz, *et al* 2005, Nyman, *et al* 2008, Thieblemont, *et al* 2011). Impact of auto transplant, several different types of salvage chemotherapy, targeted treatment, such as lenalidomide and ibrutinib, with preferential activity in non-GCB DLBCL could be potential mechanisms for these findings (Hernandez-Ilizaliturri, *et al* 2011, Thieblemont, *et al* 2017, Wilson, *et al* 2015). Newer technologies resulting in more precise identification of COO will help clarify this in future studies. (Vose 2011)

Strengths of this study include a cohort that was prospectively enrolled at diagnosis as opposed to cases ascertained at time of relapse that included a methodology for collecting post-diagnosis outcomes. Patients were followed throughout multiple therapeutic interventions that were treated across a wide spectrum of practice settings without the structure or selection biases of a therapeutic clinical trial in most cases. The size of the study allows for reasonable confidence in the outcomes of several larger subsets. Nonetheless, this study lacks regional and ethnic diversity, and the absence of a validation population dictates that published outcomes of similar subsets from other series would be helpful in further defining this problem.

In conclusion, this analysis of patterns of failure and treatment with subsequent outcomes in DLBCL patients confirm this as an unmet clinical need or, more precisely, as a collection of needs largely unmet. This analysis provides historical benchmarks for future clinical trials targeting these populations of patients. For the purpose of grouping relapsed/refractory DLBCL patients into distinct subsets for future study or analysis we recommend that categories include refractory (including transient responders) to any line therapy, those of age/criteria precluding aggressive salvage therapy, those with CNS relapse, and those with first relapse more than 12 months from diagnosis.

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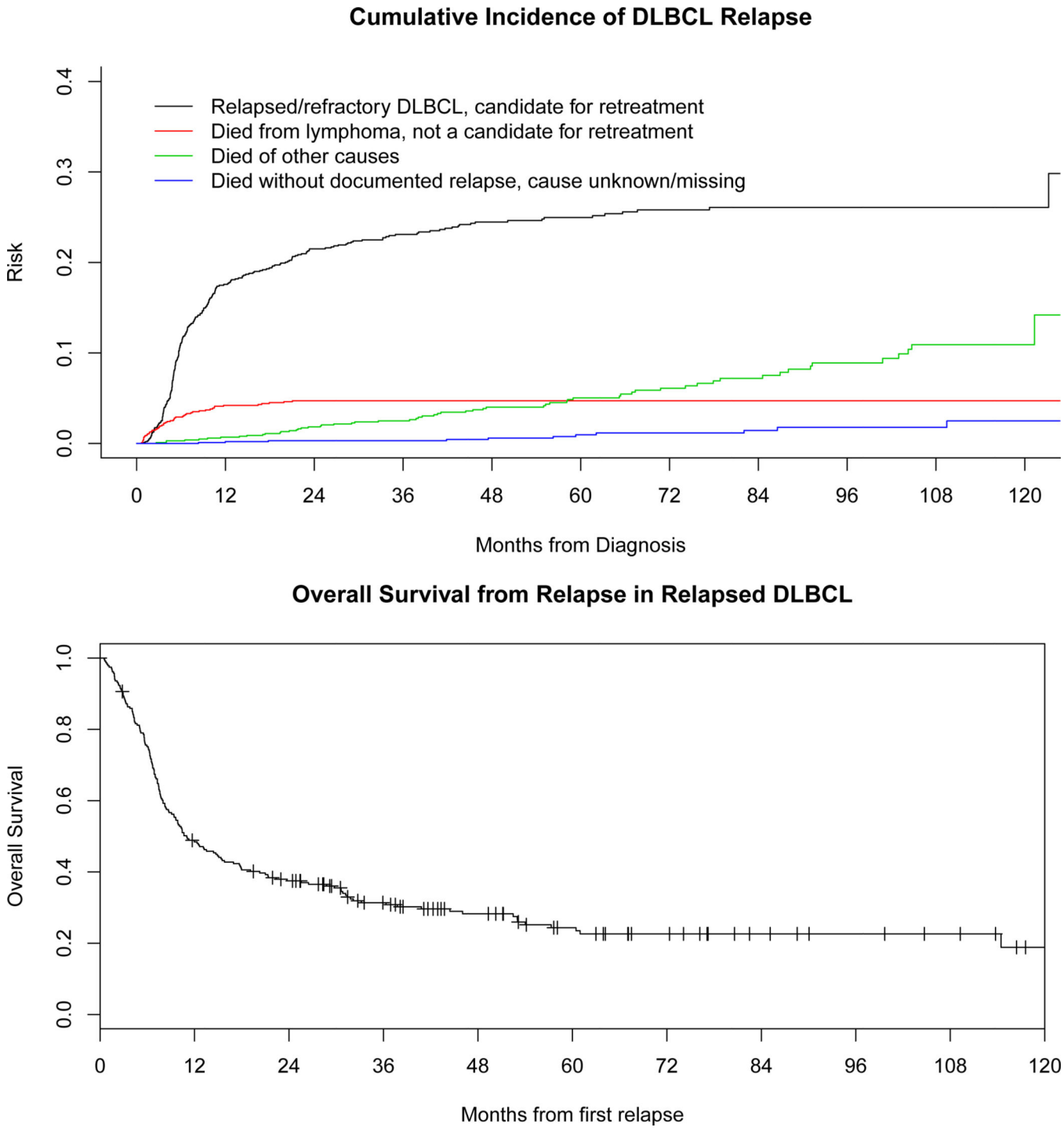


Figure 1.

A: Cumulative incidence of Relapse or Refractory disease in a cohort of patients with *de novo* diffuse large B cell lymphoma (DLBCL) treated with immunochemotherapy (IC).

B: Overall of survival from the time of relapse or refractoriness in DLBCL.

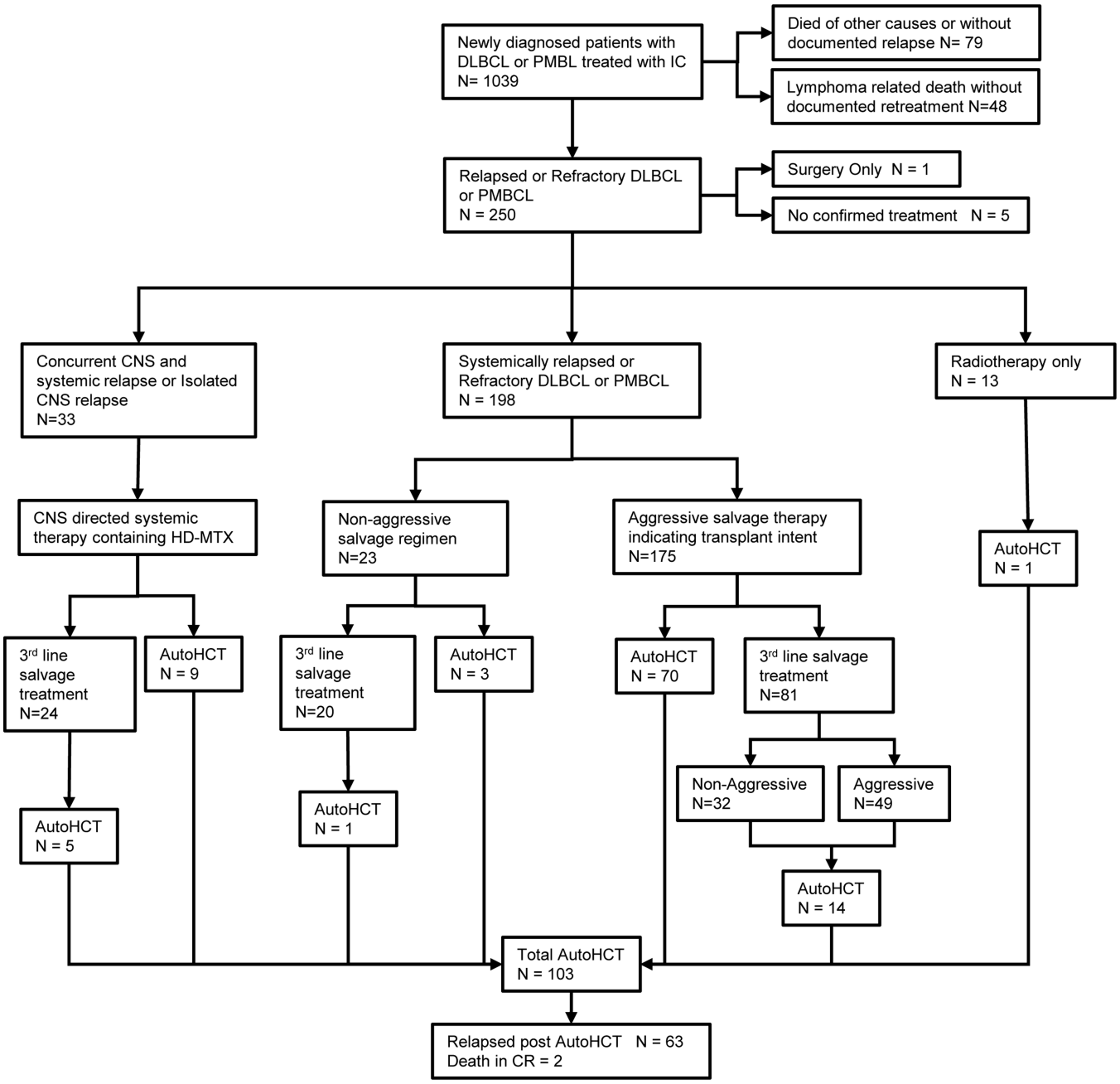
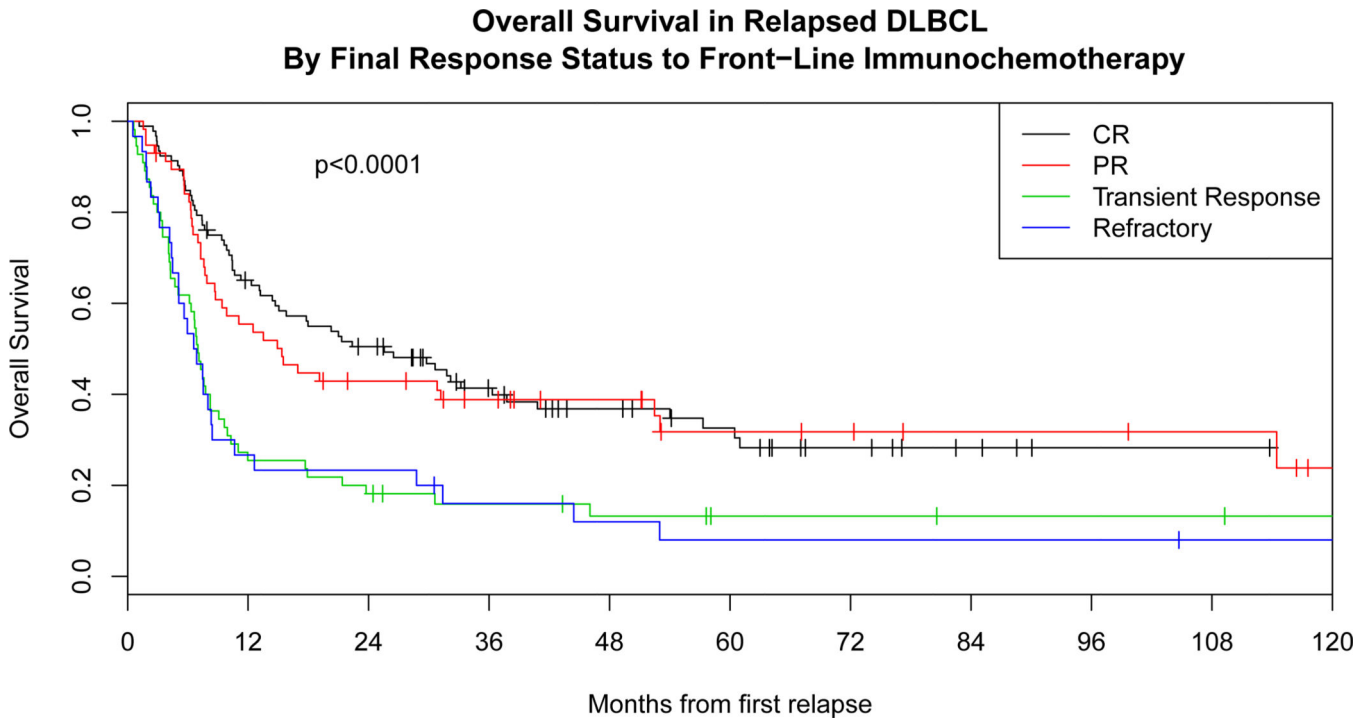


Figure 2. Pattern of care after failure of front line immunochemotherapy

AutoHCT, autologous haematopoietic cell transplant; CNS, central nervous system; CR, complete remission; DLBCL, diffuse large B cell lymphoma; HD-MTX, high dose methotrexate; IC, immunochemotherapy; PMBL, primary mediastinal B cell lymphoma.



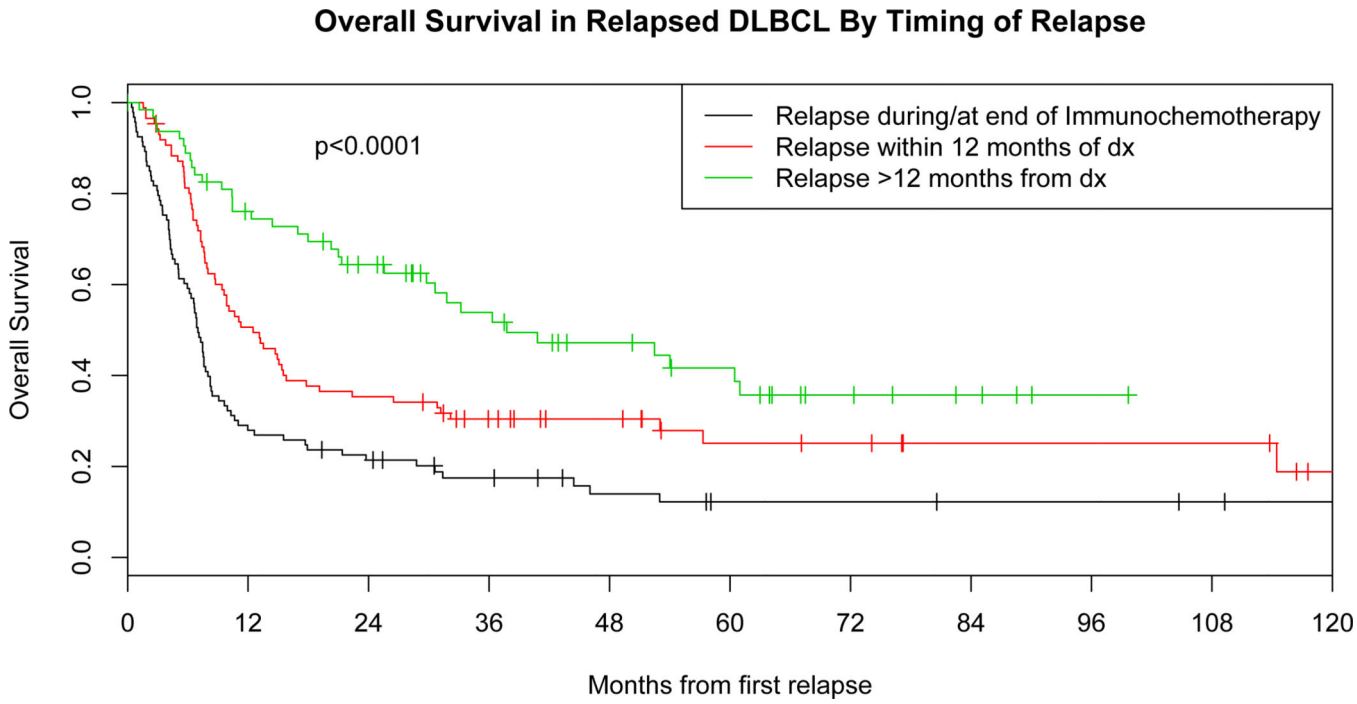


Figure 3. Overall survival

A: Overall survival in relapsed diffuse large B cell lymphoma (DLBCL) by response to front-line immunochemotherapy.

B: Overall survival in relapsed DLBCL by timing of relapsed after initial diagnosis CR, complete remission; dx, diagnosis; PR, partial remission;

Table I

Patient characteristics at diagnosis

Characteristic	All (N=1039)	Relapsed (N=250)
Median age (range), years	62 (18–92)	61 (19–89)
Age at diagnosis		
<60 years	475 (46%)	114 (46%)
>60 years	564 (54%)	136 (54%)
Sex		
Male	577 (56%)	157 (63%)
Female	462 (44%)	93 (37%)
Histology at diagnosis		
DLBCL	983 (95%)	241 (96%)
PMBL	56 (5%)	9 (4%)
IPI at diagnosis		
0–1	349 (34%)	47 (19%)
2	305 (29%)	69 (28%)
3	251 (24%)	93 (37%)
4 or 5	134 (13%)	41 (16%)
Stage at diagnosis		
I/II	382 (37%)	54 (22%)
III/IV	647 (63%)	194 (78%)
LDH at diagnosis		
>Upper limit of normal	393 (42%)	161 (75%)
<Upper limit of normal	543 (58%)	55 (25%)
2 or more Extranodal sites at diagnosis		
Yes	215 (21%)	60 (24%)
No	824 (79%)	190 (76%)
ECOG performance status at diagnosis		
0–1	857 (83%)	186 (75%)
2–4	179 (17%)	63 (25%)
Any B symptoms at diagnosis		
Yes	256 (25%)	84 (34%)
No	783 (75%)	166 (66%)
Bulky disease > 10 cm at diagnosis		

Characteristic	All (N=1039)	Relapsed (N=250)
Yes	127 (12%)	45 (18%)
No	912 (88%)	205 (82%)
Bone marrow involvement with DLBCL at diagnosis		
Yes	102 (10%)	33 (13%)
No	937 (90%)	217 (87%)
Cell of origin (Hans)		
GCB	375 (64%)	74 (59%)
Non-GCB	210 (36%)	51 (41%)
CNS involvement at diagnosis		
Yes	18 (2%)	8 (3%)
No	1021 (98%)	242 (97%)
Creatinine at diagnosis	0.9 (0.4–19.1)	1.0 (0.4–4.4)

CNS, central nervous system; DLBCL, diffuse large B cell lymphoma; ECOG, Eastern Cooperative Oncology Group; GCB, germinal centre B cell-like; IPI, International Prognostic Index; LDH, lactate dehydrogenase; PMBL, primary mediastinal B cell lymphoma.

Table II

Outcomes to therapy at first relapse

Therapy	N	CR/PR to first salvage therapy	autoHCT after first salvage Therapy	autoHCT after first or subsequent salvage	2 year EFS after relapse
All therapies	**244**	**53%**	**88 (36%)**	**103 (42%)**	**23%**
All aggressive therapies	**175**	**57%**	**70 (40%)**	**84 (48%)**	**24%**
R-ICE	138	56%	62 (45%)	72 (53%)	25%
R-DHAP	14	36%	4 (29%)	7 (50%)	14%
ROAD	10	70%	5 (50%)	5 (50%)	22%
Anthracycline-based	12	75%	2 (17%)	2 (17%)	25%
R-ESHAP	1	100%	1 (100%)	1 (100%)	100%
Non-aggressive therapy	**23**	**52%**	**3 (13%)**	**4 (17%)**	**13%**
R-GemOX	4	0%	0 (0%)	1 (25%)	0%
Zevalin	1	100%	1 (100%)	1 (100%)	100%
R-Bendamustine	8	75%	2 (25%)	2 (25%)	13%
R monotherapy	3	50%	0 (0%)	0 (0%)	0%
Other	7	57%	0 (0%)	0 (0%)	14%
CNS directed therapy	**33**	**42%**	**9 (27%)**	**14 (42%)**	**22%**
RT only	**13**	**38%**	**0 (0%)**	**1 (8%)**	**38%**

autoHCT, autologous haematopoietic cell transplant; CNS, central nervous system; CR, complete remission; EFS, event-free survival; PR, partial remission; R-DHAP, rituximab, dexamethasone, high-dose Ara-C, cisplatin; R-ESHAP, rituximab, etoposide, solumedrol, high-dose Ara-C, cisplatin; R-GemOx, rituximab, gemcitabine, oxaliplatin; R-ICE, rituximab, ifosfamide, cyclophosphamide, etoposide; R, rituximab; ROAD, rituximab, oxaliplatin, Ara-C, dexamethasone ; RT, radiotherapy.

Table III

Outcomes to therapy for DLBCL after first relapse

	Survival from relapse in all patients				Survival from autoHCT				Survival from relapse if not able undergo autoHCT		
	N	CR/PR to first salvage therapy	Median OS from relapse (months)	4-year OS from relapse	N	Median OS from autoHCT (months)	4-year OS from autoHCT	2-year EFS from autoHCT	N	Median OS from first relapse (months)	2-year OS from first relapse
All patients	244	54%	11.0	28%	103 (42%)	48.5	51%	49%	141 (58%)	6.8	19%
Therapy at first relapse											
Aggressive therapy	175	57%	11.6	29%	84 (48%)	42.7	49%	45%	91 (52%)	6.9	19%
Non-aggressive therapy	23	52%	10.4	22%	4 (17%)	NA	75%	75%	19 (83%)	9.4	19%
CNS directed therapy	33	44%	9.1	29%	14 (42%)	Not reached	61%	71%	19 (58%)	4.3	5%
RT only	13	38%	21.4	31%	1 (8%)	NA	NA	NA	12 (92%)	23.8	46%
Response to initial IC											
CR at end of IC	94	75%	25.6	37%	54 (57%)	35.3	48%	48%	40 (43%)	12.3	38%
PR at end of IC	57	53%	15.4	39%	30 (53%)	112.1	62%	53%	27 (47%)	7.3	12%
PR or CR at end of IC	151	67%	20.3	38%	84 (56%)	50.8	53%	50%	67 (44%)	7.7	27%
Transient response	55	35%	7.0	13%	14 (25%)	35.2	42%	50%	41 (75%)	5	5%
No Response to IC	30	23%	6.7	12%	4 (13%)	13.1	NA	NA	26 (87%)	5.8	19%
SD/PD to IC	85	31%	6.9	13%	18 (21%)	25.3	37%	44%	67 (79%)	5.6	10%
Response not assessed/unknown	8	50%	11.6	NA	1 (13%)	NA	NA	NA	7 (88%)	7.6	29%
Timing of Relapse											
Refractory or progression at end of IC	93	32%	7.0	14%	19 (20%)	27.6	39%	47%	74 (80%)	5.8	12%
Post IC relapse within 12 months of diagnosis	86	56%	12.5	30%	46 (53%)	22.9	45%	39%	40 (47%)	6.5	15%
Relapse beyond 12 months from diagnosis	65	80%	37.8	47%	38 (58%)	Not reached	64%	63%	27 (42%)	21	45%

autoHCT, autologous haematopoietic cell transplant; CNS, central nervous system; CR, complete remission; DLBCL, diffuse large B cell lymphoma; EFS, event-free survival; IC, immunochemotherapy; OS, overall survival; PD, progressive disease; PR, partial remission; RT, radiotherapy;SD, stable disease.

Table IV

Association of patient characteristics at diagnosis with post-relapse survival

Patient characteristics at diagnosis	HR (95% CI)	p-value
Age >60 years vs age ≤ 60 years (ref)	1.41 (1.04–1.91)	0.026
Sex, male vs. female (ref)	0.77 (0.57–1.04)	0.092
PMBL vs DLBCL (ref)	0.58 (0.24–1.40)	0.22
IPI at diagnosis (per unit increase)	1.15 (1.01–1.32)	0.035
Stage III/IV vs. Stage I/II (ref)	0.97 (0.67–1.40)	0.87
Elevated LDH vs. normal range LDH (ref)	1.13 (0.79–1.63)	0.50
2 or more Extranodal sites vs. 0–1 (ref)	1.24 (0.89–1.74)	0.22
ECOG PS 2–4 vs. PS 0–1 (ref)	1.14 (0.81–1.61)	0.44
B symptoms at diagnosis vs. none (ref)	0.93 (0.68–1.27)	0.72
Bulky disease > 10 cm at diagnosis vs. non-bulky disease (ref)	1.17 (0.81–1.71)	0.41
Bone marrow involvement with DLBCL at diagnosis vs. no DLBCL bone marrow involvement (ref)	0.90 (0.57–1.40)	0.63
Cell of origin (Hans) Non GCB vs GCB (ref)	0.79 (0.52–1.22)	0.29

CI, confidence interval; DLBCL, diffuse large B cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; GCB, germinal centre B cell type; HR, hazard ratio; IPI, International Prognostic Index; LDH, lactate dehydrogenase; PMBL, primary mediastinal B cell lymphoma; ref, reference.