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Diffuse large B-cell lymphoma with primary treatment failure: Ultra-high risk features and benchmarking for experimental therapies

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Abstract

The outcomes of patients with DLBCL and primary treatment failure (PTF) in the rituximab era are unclear. We analyzed 331 patients with PTF, defined as primary progression while on upfront chemoimmunotherapy (PP), residual disease at the end of upfront therapy (RD) or relapse <6 months from end of therapy (early relapse; ER). Median age was 58 years and response to salvage was 41.7%. Two-year OS was 18.5% in PP, 30.6% in RD and 45.5% in ER. The presence of PP, intermediate-high/high NCCN-IPI at time of PTF or *MYC* translocation predicted 2-year OS of 13.6% constituting ultra-high risk (UHR) features. Among the 132 patients who underwent autologous hematopoietic cell transplantation, 2-year OS was 74.3%, 59.6% and 10.7% for patients with 0,1 and 2–3 UHR features respectively. Patients with PTF and UHR features should be prioritized for clinical trials with newer agents and innovative cellular therapy.

1 | INTRODUCTION

The majority of patients with diffuse large B-cell lymphoma (DLBCL) will be cured with chemotherapy in combination with rituximab.^{1–4} Complete remission (CR) is a requirement for cure and is achieved after initial therapy in approximately 70%–95% of patients, depending on disease and patient features.^{1–4} Patients who obtain a CR and later experience disease recurrence can often be treated with salvage chemotherapy regimens, and subsequently autologous hematopoietic cell transplantation (auto-HCT).^{5,6} Patients who fail to obtain a CR or progress during initial chemoimmunotherapy are expected to have a worse prognosis than relapsed patients.^{7,8} Similarly, patients who obtain a brief CR and quickly evolve with progressive disease have a very poor prognosis.⁵ Collectively, these patients can be grouped as having primary treatment failure (PTF). Most of the recent literature or clinical trials have analyzed PTF and patients with later relapse together and physicians treating PTF patients tend to use the same treatment paradigms applicable for patients with late relapses.^{5,9}

Some data from the pre-rituximab era indicate very dismal prognosis for PTF patients,^{10–12} but little is known about this group of patients in the setting of more modern upfront and

salvage therapies. Therefore contemporary information on the outcome of PTF patients is needed.

Prognostic scores have been generated, validated, and are widely used in newly diagnosed DLBCL^{4,13} including the recently described National Comprehensive Cancer Network International Prognostic Index (NCCN-IPI).¹³ Some factors are also well known to affect the survival of DLBCL patients who relapse after initial chemoimmunotherapy, including international prognostic index (IPI) and time to relapse.^{5,14,15} However, there has not been any prognostic system dedicated to predicting outcomes of PTF patients. It is crucial to identify factors linked to poor outcomes with current therapeutic approaches so that these patients can be routed to experimental approaches early in the course of their diseases. In addition, the knowledge of outcomes in different subsets of PTF patients will provide benchmarking for future experimental approaches for this population.

2 | METHODS

2.1 | Patients

REFINE (REgistry of diFfuse large B-cell lymphoma with prImary treatmeNt failurE) is a multi-center, retrospective, observational collaborative study involving 15 US academic institutions. Eligible patients were 18 years of age, were diagnosed with DLBCL between 2008 and 2015, and received treatment with curative intent consisting of administration of an anti-CD20 monoclonal antibody and anthracycline-containing chemotherapy. Included patients developed PTF with one of the following patterns of failure: progressive disease (by radiologic assessment or clinical assessment) during or within 6 weeks of completion of chemoimmunotherapy (primary progression; PP); only partial response or stable disease by functional imaging at the completion of at least five cycles of chemoimmunotherapy¹⁶ (residual disease; RD); had documentation of CR at end of therapy but subsequently developed relapse detected within 6 months of completion of chemoimmunotherapy (early relapse; ER).

The study excluded patients with primary central nervous system (CNS) DLBCL, HIV-associated lymphoma, transformed DLBCL in patients who received prior therapy for an indolent lymphoma, partial remission or stable disease at completion of chemoimmunotherapy assessed without functional image (as some of these cases may have achieved CR when assessed with functional image) or treatment discontinuation prior to at least two cycles of chemoimmunotherapy. REFINE did not collect data for patients who did not meet criteria for PTF, including patients who obtained CR and did not relapse or patients who relapsed >6 months after completion of upfront therapy.

All diagnoses were made or confirmed by an expert hematopathologist from the participating academic institution. Putative cell of origin was determined when possible as germinal-center B type (GCB) or non-germinal center (NGC) utilizing immunohistochemistry results for CD10, BCL-6, and MUM-1, as reported by the participating institutions, utilizing the Hans algorithm.¹⁷ We also identified lymphomas harboring *MYC* translocation, hereafter designated *MYC*(+), as well as the presence of additional “second hits” with translocations involving *BCL2* or *BCL6* as detected by

fluorescence in situ hybridization (FISH).^{18–21} Because there is high correlation between *MYC*, *BCL2*, and *BCL6* translocation status at initial diagnosis and at time of treatment failure,²⁰ we utilized FISH information from initial biopsy or from biopsy obtained at time of PTF. We did not assess *MYC* or *BCL2* protein expression.

The NCCN-IPI is a prognostic score system generated and validated in patients with newly diagnosed DLBCL treated in the rituximab era. NCCN-IPI reflects age, stage, LDH, extra-nodal sites of disease and performance status in a 0 to 8 score.¹³ Patients with scores 0–1 are considered low risk, scores 2–3 low-intermediate risk, scores 4–5 high-intermediate risk and scores 6 or greater are considered high risk. Because most cases included in REFINE were treated before the establishment of NCCN-IPI, the score was retrospectively calculated, when possible at time of initial diagnosis and at time of PTF, utilizing information provided by the participating institution.

2.2 | Study conduct

Principal investigators in each participating institution identified appropriate cases from existing institutional databases or patient lists. Relevant information extracted included disease and patient features, treatments, response, and outcomes. Information was entered into an electronic case report form (CRF) and shared with the coordinating center (University of Alabama at Birmingham). An independent investigator performed quality check of each CRF verifying eligibility, proper characterization of disease clinically and histologically, treatments administered, response, and outcomes. Written queries were generated if essential data were missing or there was any internal inconsistency. Cases were only included in the study data set when all queries were satisfactorily resolved. The study was approved by the institutional review boards in each participating institution and was performed in compliance with the Declaration of Helsinki.

The primary endpoint of the analysis was overall survival (OS) for the entire cohort and for the different patterns of PTF (PP, RD, and ER), as measured from the time of detection of PTF. For patients who subsequently underwent HCT (autologous or allogeneic), OS and progression-free survival (PFS) were also measured from the time of transplant. Other endpoints captured included proportion of patients receiving salvage therapy beyond PTF and observed response, proportion of patients participating in therapeutic clinical trials after PTF and proportion of patients undergoing HCT.

2.3 | Statistical analysis

We compared categorical variables between two or more groups utilizing chi-square test and continuous variables utilizing the Kruskal-Wallis non-parametric test. We described OS using the method of Kaplan and Meier for the entire population and for subsets of patients with PP, RD, and ER. We also described OS according to DLBCL biological subset and NCCN-IPI at time of PTF. For patients who underwent HCT, we described OS and PFS from time of transplant. Comparisons between groups were performed using log rank test.

We subsequently explored patient and disease features influencing OS by performing Cox proportional hazards model multivariate analysis. Variables considered in this analysis were pattern of PTF, NCCN-IPI, putative cell of origin, and presence of *MYC* translocation. For

the subset of patients who underwent auto-HCT, the multivariate model also included disease status at time of transplant. Variables were chosen using a stepwise backward process with a probability of entry of .05 and a probability of removal of .10. Formal testing revealed that predictors included in Cox proportional hazards models satisfied the assumption of proportionality. A two-sided *P*-value .05 was considered statistically significant. All analyses were conducted using IBM SPSS (v22.0).

3 | RESULTS

A total of 389 cases were submitted for analysis. After quality check and queries of reporting institutions, 331 cases were considered valid and maintained in the final analysis. Overall 7 cases were excluded for being primary CNS lymphoma, 8 cases for being transformed lymphoma, 7 cases for not meeting definition of PTF (relapse >6 months from end of therapy), and 36 for having insufficient information on initial therapy, documentation of PTF, and/or outcome after PTF. Median number of cases submitted by each of the 15 institutions was 16 (range 6–110). The most common pattern of PTF was PP (*N*=144, 44%), followed by ER (*N*=95, 29%), and RD (*N*=92, 28%).

Patient characteristics are summarized in Table 1. The majority of patients with PTF had advanced stage, intermediate-high or high risk NCCN-IPI and KI-67 expression in 80% of malignant cells at diagnosis. A relatively high proportion of patients (32%) had *MYC*(+) DLBCL with the majority harboring a second hit. There were no significant differences in tumor or patient features at time of presentation between patients who subsequently evolved with PP, RD, or ER.

At the time of detection of PTF, patients with PP were more likely to have stage 3 or 4 and intermediate-high or high risk NCCN-IPI than patients with RD or ER as pattern of PTF.

3.1 | Salvage therapy and outcomes

At the time of PTF, the vast majority of patients (94.6%) received therapy (Table 1). In most cases, an aggressive, multi-agent chemotherapy regimen often combined with rituximab as the first salvage therapy, was used, likely reflecting intent to proceed with transplant consolidation. Enrollment on a clinical trial for salvage therapy was 15.1%.

Overall response rate to first regimen of salvage therapy was 41.7%. A higher proportion of patients in PP (52.1%) than in ER (31.6%) or RD (32.6%) had disease progression while on first salvage regimen. Overall, less than a third of patients obtained CR to the first or any subsequent regimen utilized in the salvage setting and prior to transplantation. CRs were however more common in ER (54.7%) than in RD (19.6%) or in PP patients (18.1%). Auto-HCT was performed as consolidation for 132 patients and allogeneic HCT (allo-HCT) for 33 patients, including 8 who received allo-HCT following progression after auto-HCT.

3.2 | Survival

Survival was influenced by the pattern of PTF. Two-year OS was 18.5% (95% C.I. 11.4%–25.6%) in PP cases, 30.6% (95% C.I. 20.0%–41.2%) in RD, and 45.5% (95% C.I. 34.5%–56.5%) in ER (*P*<.001, Figure 1A). Survival was worse in *MYC*(+) than in *MYC*(–) cases

(Figure 1B), but no difference was detected between single-hit and double-hit cases ($P=.7$, Figure 1B). There was also no significant survival difference between GCB and NGC cases (2-year survival 24.7% vs. 40.4%, $P=.14$, Figure 1C). As expected, the vast majority of *MYC*(+) patients, 48/56 (86%), were GCB, while only 3/56 (5%) were NGC and 5/56 (9%) could not be classified. We subsequently explored the combined effect of *MYC* and COO on survival. Patients with *MYC*(+) lymphoma had worse survival than *MYC*(-)/GCB (2-year OS 9.3% vs. 34.9%, $P<.001$) and *MYC*(-)/NGC (9.3% vs. 38.6%, $P=.006$). There was no significant OS difference between *MYC*(-)/GCB and *MYC*(-)/NGC ($P=.9$, Figure 1D). NCCN-IPI at time of PTF was also linked to survival. Two-year OS was 57.4% (95% C.I. 39.8%–75.0%) among patients with PTF and low NCCN-IPI, 42.3% (95% C.I. 31.3%–53.3%) for patients with intermediate-low and only 10.9% (95% C.I. 4.0%–17.8%) for patients with intermediate-high or high risk NCCN-IPI ($P<.001$, Figure 1E).

3.3 | Identification of ultra-high risk features

We subsequently performed multivariate analysis to identify variables known at the time of PTF and that independently affect outcome. As the intent was to identify patients who were predicted to do poorly with existing therapies and should be prioritized for investigational approaches, factors only known after introduction of salvage therapy, such as treatment response, were not included in the analysis. Because in univariate analysis, there was no difference in outcomes between single-hit and double-hit *MYC*(+), cases were grouped as *MYC*(+) and *MYC*(-) for the multivariate analysis. Pattern of PTF, *MYC* status and NCCN-IPI at time of PTF were independently associated with OS (Supporting Information Table 1). Putative COO did not contribute to prediction of survival. We therefore identified PP, *MYC*(+) lymphoma, and NCCN-IPI intermediate high/high at time of PTF as ultra-high risk (UHR) features.

We subsequently analyzed the impact of the presence of UHR features on OS in a subset of 144 patients with complete information on the pattern of PTF, *MYC* status and NCCN-IPI at time of PTF. The presence of any of these factors predicted 2-year OS of only 13.6% (95% C.I. 5.8%–21.4%) versus 57.6% (95% C.I. 40.6%–74.7%) for patients with PTF and no UHR features ($P<.001$, Figure 1F).

3.4 | Transplant outcomes

One hundred and thirty-two patients underwent auto-HCT and 33 allo-HCT, including 8 patients who underwent allo-HCT after prior failed auto-HCT. Transplantation (autologous or allogeneic) was achieved in 67/108 (62%) patients with 0 versus 62/132 (47%) patients with 1 versus 28/91 (31%) patients with 2 or 3 UHR features ($P<.001$). Patient and transplant characteristics are displayed in Table 2.

The majority of patients who underwent auto-HCT did so after reaching a PR or CR with only one line of salvage therapy. Conditioning regimen consisted of BCNU, etoposide, ara-c, and melphalan (BEAM) with or without rituximab in three quarters of the patients. Only one patient died before 100 days of follow up from complications of transplant. The majority of patients remained or obtained a CR on first assessment after auto-HCT.

Two-year PFS and OS for auto-HCT patients were 38.4% (95% C.I. 29.6%–47.2%) and 54.9% (95% C.I. 44.9%–64.9%), respectively (Figure 2A). In univariate analysis, OS was worse among patients with UHR features (PP as pattern of PTF, *MYC*(+) DLBCL or intermediate-high/high risk NCCN-IPI (Supporting Information Figure 1). Disease response at time of transplant did not reach statistical significance as a predictor of OS (Figure 2B). In multivariate analysis PP disease, *MYC*(+) status and intermediate-high/high risk NCCN-IPI, but not treatment response at time of transplant were predictors of OS (Supporting Information Table 2). Two-year OS was 74.3% (95% C.I. 60.0%–88.6%) for patients with no UHR feature (*N*=54), 59.6% (95% C.I. 44.5%–74.7%) for patients with 1 UHR feature (*N*=52), but only 10.7% (95% C.I. 0%–24.4%) for patients with 2 or 3 UHR features (*N*=26) (Figure 2D), resembling the pattern seen for PFS (Figure 2C).

Most patients who underwent allo-HCT did so after 2 or more lines of salvage therapy. Approximately two-thirds received a reduced-intensity regimen. Despite over 80% of allo-HCT being in CR or PR at time of transplant, 51% developed progressive disease or relapse on first assessment post-transplant. Of the 20 deaths registered in the allo-HCT group, 19 occurred after recurrence or progression of DLBCL. Only 1 death occurred due to complications of the transplant. Two-year PFS and OS were poor at 20.5% (95% C.I. 6.4%–34.6%) and 32.7% (95% C.I. 13.1%–52.3%), respectively (Supporting Information Figure 2a). When the eight patients who received allo-HCT after failure of auto-HCT were excluded from the analysis, outcomes were not better with 2-year PFS and OS of 16.0% (95% C.I. 1.4%–30.6%) and 17.3% (95% C.I. 0%–36.2%), respectively (Supporting Information Figure 2b).

4 | DISCUSSION

Patients with DLBCL and PTF have not historically been identified as a separate category and there have not been clinical trials focusing exclusively in this population. Instead, patients with PTF, or at least some subsets, are often included in the same trials with patients with relapsed DLBCL as seen in the CORAL,⁵ BMT-CTN 14-01,²² and in the ORCHARD⁹ study.

REFINE is the largest study to focus on patients with DLBCL and PTF in the rituximab era. Our findings indicate that more refined clinical and genetic characterization offers the ability to discriminate patients with PTF with better chances of cure with conventional salvage and consolidative therapies while providing tools for identification of patients destined to do poorly with such approaches and should therefore be prioritized for investigational therapies. Furthermore, outcomes of DLBCL with PTF as described in this study can be used as benchmarking for subsequent trials with focus on the PTF population.

Two recent studies also focused on the outcomes of DLBCL not reaching CR or with ER after chemoimmunotherapy. In collaboration between investigators from British Columbia and Switzerland, 166 patients with primary refractory disease were identified, 75 being younger than 70 and treated with curative intent. Only 45 of the patients were indeed treated with aggressive salvage therapy with intent of subsequent auto-HCT and only 27% of these patients had objective response to salvage therapy, very similar to 29.2% of response seeing

for the PP cohort in REFINE.⁸ Another recent cohort from the University of Iowa/Mayo Clinic Lymphoma SPORE Molecular Epidemiology Resource also confirmed low response rate and poor survival, even with subsequent auto-HCT for patients with PTF.⁷

One important observation in the present study is the impact of *MYC* translocation on outcomes of PTF patients, including those who have chemosensitive disease and proceed with auto-HCT. *MYC*(+) tumors constitute only 5%–10% of newly diagnosed cases of DLBCL and are a strong prognostic factor either alone or associated with additional translocations involving *BCL2* and/or *BCL6*.^{18,19,21} As expected, there is enrichment for *MYC*(+) cases among patients with relapsed disease and PTF. In fact, a subsequent analysis of the population enrolled in the CORAL study found that 17% of cases (*N*=28) were *MYC*(+) and those patients had worse PFS and OS than remaining patients, even when they responded to salvage therapy and underwent auto-HCT.²⁰ Our analysis, by focusing on a subset of patients with more aggressive disease than the CORAL study, found an even higher proportion of *MYC*(+) cases (31.8%, *N*=56). We confirmed the dismal outcome of this patient population and demonstrated that the impact of *MYC* translocation is independent of other prognostic clinical variables, particularly pattern of PTF and NCCN-IPI. We did not find significant survival differences between single and double-hit *MYC*(+) cases in this series. This likely reflects the already very poor outcome of the single hit cases when evolving with PTF and/or the limited sample size. Despite the relatively high proportion of missing data, we verified that that patients with *MYC* information are not significantly dissimilar to patients with missing *MYC* information (HR associated with missing *MYC* information = 1.09, 95% C.I. 0.83–1.44, *P*=.5). We believe patients with *MYC*(+) DLBCL should be identified prior to upfront therapy and routed to more intense and experimental approaches as relapses can rarely be successfully treated.

Putative cell or origin is associated with prognosis in patients with newly diagnosed DLCBL,¹⁷ but its prognostic implication in patients with relapsed or refractory disease is less clear. For instance, in the Bio-CORAL study,²³ COO was prognostic among patients treated with R-DHAP regimen, but not among patients treated with R-ICE. We did not find a significant survival difference between GCB and NGC-type cases in our series. As GCB with PTF are enriched for *MYC*(+) cases the analysis of the simultaneous effect of *MYC* status and COO on survival further emphasizes the lack of independent impact of COO on survival of patients with PTF. In fact, in multivariate analysis that included *MYC* status, COO had no significant impact on OS. Similar observation was also made in the University of Iowa/Mayo Clinic study.⁷ As patients with NGC have lower chance of CR and shorter survival than their GCB counterparts, a cohort of patients with PTF would be expected to be enriched for NGC cases. However, only about a third of cases where COO could be determined were of NGC type. We believe such discrepancy mostly reflect cases with incomplete immunohistochemistry panels preventing identification of NGC origin. For example, while CD10(+) suffices for identification of GCB origin, CD10(–) with no information on BCL6 or MUM1 precludes identification of COO.¹⁷

The retrospective nature of the present study imposes some caveats, such as the lack of central pathology review, missing data and the heterogeneity of population and treatments. Conversely, our analysis offers a “real world” insight into treatment choices and results for

this challenging population. Yet, as the study resulted from a collaboration of academic centers, it is very likely that the population represented is biased toward younger and fit patients. In fact, the median age of patients included in the analysis (58 years) was much lower than the median age of individuals diagnosed with DLBCL in the US (67 years). Despite this possible bias and the expected poor outcomes with existing treatments, only 1 in 6 patients participated in a therapeutic clinical trial during salvage therapy.

The outcomes of patients who underwent auto-HCT in this series are in line with a recent CIBMTR report on 300 patients with early rituximab failure (defined as not achieving CR or having relapse <12 months from diagnosis).⁶ In that study, 3-year PFS and OS for these patients was 44% and 50%, respectively, outcomes that are somewhat comparable to 2-year PFS and OS of 38.4% and 54.9% respectively in REFINE, although we included a higher risk population by limiting relapse to 6 months from completion of therapy and including patients with primary progressive disease. The outcomes of REFINE are also comparable with the subset of patients in CORAL⁵ who had received prior rituximab and developed ER (<12 months from diagnosis). For those patients, 3-year PFS was 23%, while patients who responded to salvage therapy and underwent auto-HCT had 3-year PFS of 39% (vs. 2-year PFS of 38.4% in REFINE).

Allogeneic transplant can be an effective therapy for DLBCL, particularly for patients who relapse after auto-HCT.²⁴ Its efficacy resides on graft versus lymphoma (GVL) effect in addition to the cytotoxic effect of the conditioning regimen. Outcomes of allo-HCT in REFINE were disappointingly poor with failures occurring predominantly because of fast disease progression. This suggests that since GVL requires a significant time to establish, it is unable to overcome rapidly growing disease.

Our findings confirm those of the CORAL and CIBMTR study that a subset of patients with early treatment failure after rituximab-containing chemoimmunotherapy and chemo sensitive disease can be cured with auto-HCT. These studies analyzed a subset of patients with progression or recurrence less than 12 months from diagnosis, therefore approximately 6 months from the end of therapy as in REFINE. Additionally, it indicates that the assessment of three simple parameters: pattern of failure, *MYC* status, and NCCN-IPI at time of PTF can identify patients with dramatically distinct prognosis. While for patients with no more than 1 UHR feature intensive salvage therapy followed by auto-HCT for chemosensitive disease should remain the standard of care, patients with 2 or 3 UHR feature should be prioritized for experimental approaches, as those patients have low likelihood of achieving transplantation and, if they do, have very poor outcomes. Such experimental therapies include new biological agents and particularly the use of T-cells expressing antigen-specific chimeric antigen receptors as stand-alone therapy²⁵ or in the setting of auto-HCT^{26,27} or allo-HCT.^{28,29}

In summary, REFINE provides information on treatment patterns and outcomes of DLBCL with PTF, identifies UHR features that predict poor outcomes and provides benchmarking for innovative therapies focused on this special patient population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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FIGURE 1.

Overall survival for patients with DLBCL and PTF according to (A) patterns of failure, (B) *MYC* status and additional genetic hits, (C) putative COO, (D) Combined *MYC* status and putative COO, (E) NCCN-IPI at time of PTF and (F) the presence of any UHR feature

FIGURE 2.

(A) Overall survival (OS) and progression-free survival (PFS) of patients with DLBCL and PTF who underwent auto-HCT; (B) OS of PTF who underwent auto-HCT according to treatment response at time of transplant; (C) PFS and (D) OS of patients with PTF who underwent auto-HCT according to the number of UHR features

TABLE 1
Characteristics of all patients included in the registry according to pattern of primary treatment failure

	All N=331	Primary progression (PP) N=144	Residual disease (RD) N=92	Early relapse (ER) N=95	P
Follow-up of survivors (months) ^a	18.9 (9.2–39.3)	18.7 (8.4–40.9)	17.7 (7.1–36.3)	23.6 (13.0–40.7)	.29
Age (years) ^a	58 (48–65)	59 (48–64.25)	57 (46.75–64)	61 (53.5–68)	.10
Males	210 (63.4%)	93 (64.5%)	61 (66.3%)	56 (58.9%)	.54
Stage at diagnosis					
Unknown	3 (0.9%)	1 (0.7%)	0 (0.0%)	2 (2.1%)	.25
Known					
1 and 2	80 (24.4%)	33 (23.1%)	28 (30.4%)	19(20.4%)	
3 and 4	248 (75.6%)	110 (76.9%)	64 (69.6%)	74 (79.6%)	
NCCN-IP1 at diagnosis					
Unknown	91 (27.5%)	42 (29.2%)	18 (19.5%)	31 (32.6%)	.16
Known					
Low (0, 1)	18 (7.5%)	7 (6.9%)	4 (5.4%)	7 (10.9%)	
Intermediate-low (2,3)	85 (35.4%)	32 (31.4%)	36 (48.6%)	17 (26.6%)	
Intermediate-high (4,5)	98 (40.8%)	47 (46.1%)	27 (36.5%)	24 (37.5%)	
High (6,7,8)	39 (16.2%)	16 (15.7%)	7 (9.4%)	16 (25.0%)	
KI-67 at diagnosis					
Unknown	94 (28.4%)	43 (29.8%)	27 (29.3%)	24 (25.2%)	.47
Known					
< 40%	17 (7.2%)	10 (9.9%)	2 (3.1%)	5 (7.0%)	
40–79%	88 (37.1%)	36 (35.6%)	23 (35.4%)	29 (40.8%)	
80%+	132 (55.7%)	55 (54.4%)	40 (61.5%)	37 (60.6%)	
MYC					
Unknown	155 (46.8%)	68 (47.2%)	42 (45.7%)	45 (47.4%)	.52
Known					
MYC(+), single hit	20 (11.4%)	11 (14.5%)	6 (12.0%)	3 (6.0%)	

	All N=331	Primary progression (PP) N=144	Residual disease (RD) N=92	Early relapse (ER) N=95	P
MYC(+), double hit	36 (20.4%)	12 (15.8%)	13 (26.0%)	11 (22.0%)	
MYC(-)	120 (68.2%)	53 (69.7%)	31 (62.0%)	36 (72.0%)	
Cell of origin					
Unknown	77 (23.3%)	28 (19.4%)	22 (23.9%)	27 (28.4%)	.75
Known					
GCB	176 (69.3%)	79 (68.1%)	51 (72.9%)	46 (67.6%)	
NGC	78 (30.7%)	37 (31.9%)	19 (27.1%)	22 (32.4%)	
Upfront treatment^b					.12
R-CHOP	290 (87.6%)	131 (91.0%)	81 (88.0%)	78 (82.1%)	
More intense	41 (12.4%)	13 (9.0%)	11 (12.0%)	17 (25.5%)	
Stage at PTF					.02
Unknown	11 (3.3%)	6 (4.2%)	3 (3.3%)	2 (2.1%)	
Known					
1 and 2	109 (34.1%)	37 (26.8%)	40 (44.9%)	32 (34.4%)	
3 and 4	211 (65.9%)	101 (73.2%)	49 (55.1%)	61 (65.6%)	
NCCN-IPI at PTF					.01
Unknown	76 (23.0%)	28 (19.4%)	18 (19.6%)	30 (31.6%)	
Known					
Low (0, 1)	32 (12.6%)	9 (7.8%)	15 (20.3%)	8 (12.3%)	
Intermediate-low (2,3)	96 (37.6%)	39 (33.6%)	29 (39.2%)	28 (43.1%)	
Intermediate-high (4,5)	98 (38.4%)	47 (40.5%)	27 (36.4%)	24 (36.9%)	
High (6,7,8)	29 (11.3%)	21 (18.1%)	3 (4.1%)	5 (7.7%)	
Salvage therapy^c					.66
None	18 (5.4%)	8 (5.6%)	7 (7.6%)	3 (3.2%)	
ICE +/-R	197 (59.6%)	88 (61.1%)	54 (58.7%)	55 (57.9%)	
DHAP +/-R	20 (6.0%)	9 (6.3%)	8 (8.7%)	3 (3.2%)	
ESHAP +/-R	16 (4.8%)	6 (4.2%)	4 (4.3%)	6 (6.3%)	
High-dose Methotrexate +/-R	14 (4.2%)	7 (4.9%)	1 (1.1%)	6 (6.3%)	

	All N=331	Primary progression (PP) N=144	Residual disease (RD) N=92	Early relapse (ER) N=95	P
Other	66 (19.9%)	26 (18.1%)	18 (19.5%)	22 (23.2%)	
Response to first salvage therapy					<.001
PD	135 (40.8%)	75 (52.1%)	30 (32.6%)	30 (31.6%)	
SD	30 (9.0%)	17 (11.8%)	9 (9.8%)	3 (3.2%)	
PR	72 (21.8%)	25 (17.4%)	30 (32.6%)	17 (17.9%)	
CR	66 (19.9%)	17 (11.8%)	14 (15.2%)	36 (37.9%)	
N.A.	28 (8.5%)	10 (6.9%)	9 (9.8%)	9 (9.4%)	
Number of salvage regimens					.33
0	18 (5.4%)	8 (5.6%)	7 (7.6%)	3 (3.2%)	
1	170 (51.4%)	68 (47.2%)	55 (59.8%)	47 (49.5%)	
–3	137 (41.4%)	65 (45.1%)	29 (31.5%)	43 (45.3%)	
4–5	6 (1.8%)	3 (2.1%)	1 (1.1%)	2 (2.1%)	
Clinical trial participation during salvage therapy	50 (15.1%)	23 (16.0%)	12 (13.0%)	15 (15.8%)	.81
Autologous-HCT	132 (39.9%)	49 (34.0%)	38 (41.3%)	45 (47.4%)	.11
Allogeneic-HCT	33 (10.0%)	11 (7.6%)	11 (12.0%)	11 (11.6%)	.46

^aMedian (interquartile range).

^bR-CHOP = rituximab, cyclophosphamide, adriamycin, prednisone.

^cICE = Ifosfamide, carboplatin, etoposide, DHAP = Dexamethasone, ara-c, cisplatin, ESHAP = Etoposide, methylprednisolone, ara-c, cisplatin, +/- R = with or without rituximab.

TABLE 2

Characteristics of patients with PTF who subsequently underwent hematopoietic cell transplantation

	Autologous N=132	Allogeneic N=33
Follow-up of survivors (months) ^a	18.5 (8.5–38.5)	10.3 (5.6–29.2)
Age (years) ^a	55 (46–53)	48 (42–56)
Males	93 (70.5%)	20 (60.6%)
MYC		
Unknown	64 (48.4%)	14 (42.4%)
Known		
MYC(+), single hit	7 (10.3%)	1 (5.3%)
MYC(–), double hit	13 (19.1%)	3 (15.8%)
MYC(–)	48 (70.6%)	15 (78.9%)
Cell of origin		
Unknown	28 (21.2%)	10 (30.3%)
Known	104 (78.8%)	23 (69.7%)
GCB	64 (61.5%)	18 (78.3%)
NGC	40 (38.5%)	5 (21.7%)
Pattern of PTF		
PP	49 (37.1%)	11 (33.3%)
RD	38 (28.8%)	11 (33.3%)
ER	45 (34.1%)	11 (33.3%)
NCCN-IPI at PTF		
Unknown	30 (22.7%)	12(36.4%)
Known		
Low (0, 1)	17 (16.7%)	6(28.6%)
Intermediary-low (2,3)	49 (48.0%)	11 (52.4%)
Intermediary-high/High (4–8)	36 (35.3%)	4 (19.0%)
Best response to first salvage regimen		
CR	51 (38.6%)	10 (30.3%)
PR	48 (36.4%)	6 (18.2%)
SD	10 (7.6%)	3 (9.1%)
PD	20 (15.2%)	12 (36.4%)
N.A.	3 (2.3%)	2 (6.1%)
Ever on clinical trial after PTF and prior to transplant	10 (7.6%)	2 (6.1%)
Number of lines of therapy after PTF and prior to transplant ^a	1 (1–2)	2 (1–2)
Prior auto-HCT	N/A	8 (24.2%)

	Autologous N=132	Allogeneic N=33
Response at time of transplant		
CR	63 (47.7%)	14 (42.4%)
PR	54 (40.9%)	13 (39.4%)
SD	8 (6.1%)	3 (9.1%)
PD	6 (4.5%)	3 (9.1%)
N.A.	1 (0.8%)	0 (0.0%)
Conditioning regimen		
Autologous ^b		
BEAM (+/- Rituximab)	101 (76.5%)	N/A
CBV	14 (10.6%)	N/A
BuCyVP	7 (5.3%)	N/A
Other/unknown	10 (7.6%)	N/A
Allogeneic		
Myeloablative	N/A	12 (36.4%)
Reduced intensity	N/A	21 (63.6%)
Best response after transplant		
CR	78 (59.1%)	13 (39.4%)
PR	13 (9.8%)	3 (9.1%)
SD	2 (1.5%)	0 (0.0%)
PD	39 (29.5%)	17 (51.5%)
100 days non-relapse deaths	1 (0.8%)	1 (4.2%)

^aMedian (interquartile range).

^bBEAM = BCNU, etoposide, ara-c, melphalan. CBV = cyclophosphamide, BCNU, etoposide. BuCyVP = Busulfan, cyclophosphamide, etoposide.