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Outcomes of patients with relapsed or refractory primary mediastinal B-cell lymphoma after frontline DA-EPOCH-R

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Abstract

Introduction: Most patients diagnosed with primary mediastinal B-cell lymphoma (PMBCL) achieve cure following standard of care therapy with frontline DA-EPOCH-R. However, treatment strategies following relapse after DA-EPOCH-R are not well defined.

Methods: We performed a retrospective review of PMBCL patients relapsed/refractory (R/R) after frontline DA-EPOCH-R to obtain better insight on outcomes with salvage therapy and autologous stem cell transplant (Auto-SCT).

Results: Our cohort consisted of 107 patients with R/R PMBCL. Ninety patients qualified for the intention to treat (ITT) salvage therapy (ST) analysis. With a median follow up of 48.9 months in the ST analysis, the median progression-free survival (PFS) was 5.4 months (95% CI: 2.3-not reached (NR)) with 5-year OS rate of 78% (95% CI: 69-88). Compared to relapsed patients (relapsing > 6 months after frontline DA-EPOCH-R, N=23), refractory patients (relapsing < 6 months after frontline DA-EPOCH-R, N=67) had inferior overall response rate (ORR) (48% vs 83%), complete remission (CR) rate (19% vs 44%), and 2-year PFS rate (30% vs 69%) with initial ST. Forty-eight patients (53%) underwent Auto-SCT after ST with estimated 5-year PFS and overall survival (OS) rates of 85% (95% CI: 75-96) and 88% (95% CI: 79-99), respectively. There were no relapses among 29 patients with CR prior to Auto-SCT.

Conclusions: This analysis is the largest review of R/R PMBCL to date and demonstrates unfavorable outcomes for patients with refractory disease after frontline DA-EPOCH-R chemotherapy. Patients able to receive Auto-SCT, especially those with CR prior to Auto-SCT, had excellent outcomes.

Introduction

Primary mediastinal B-cell lymphoma (PMBCL) is a subtype of aggressive non-Hodgkin lymphoma (NHL) accounting for 2-3% of all NHL cases.[1] Most patients with newly diagnosed PMBCL have an excellent prognosis after frontline chemoimmunotherapy consisting of dose-adjusted etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, rituximab (DA-EPOCH-R) with several series noting 5-year progression-free survival (PFS) rates above 90% without the need for radiation therapy.[2,3] The minority of PMBCL patients who progress after or are refractory to frontline chemoimmunotherapy typically have poor responses to salvage chemotherapy followed by autologous stem cell transplant (Auto-SCT), although existing data is limited by the small numbers of patients who received DA-EPOCH-R as initial therapy.[4-7]

Novel salvage treatment strategies incorporating brentuximab vedotin in combination with checkpoint inhibitors have shown promise, but existing data is limited to early phase trials outside of the initial salvage setting.[7-9] Additionally, chimeric antigen receptor (CAR) T-cell therapy is now approved as second line therapy for PMBCL patients that relapse within one year of completion of frontline chemoimmunotherapy.[7,10,11] Thus, with the advent of novel salvage therapy and CAR T approval at initial relapse, real-world outcomes of these modalities are paramount to consider when choosing an optimal treatment approach at initial relapse. Here, we aimed to evaluate the utility of salvage therapy and Auto-SCT in patients with R/R PMBCL to DA-EPOCH-R.

Methods

We retrospectively analyzed data from ten US academic medical centers of patients with R/R PMBCL who received salvage therapy and/or Auto-SCT between 2011 and 2023. Institutional review board approval was obtained at each site. The study was conducted in accordance with the declaration of Helsinki. Patients with a confirmed histologic diagnosis of PMBCL relapsing after frontline therapy with DA-EPOCH-R were eligible for inclusion. Baseline demographic, clinical, laboratory, pathology, and outcomes data were extracted by chart review and included in a study□specific data collection spreadsheet. Investigators at each center were responsible for assessing diagnostic criteria, stage, and response assessments. Responses were assessed by individual investigators utilizing Lugano criteria and institutional standard imaging modalities.

Statistical analysis

Patient characteristics were summarized using frequencies and percentages for categorical variables and median and range for continuous variables.

Overall response rate (ORR) was defined as the percentage of patients in a particular cohort who achieved either a partial response (PR) or complete response (CR) to treatment, while CR rate was defined as the percentage of patients in a particular cohort who achieved a CR to treatment. The exact binomial method was used to construct corresponding 95% confidence intervals.

Overall survival (OS) was defined as the time from the treatment intervention of interest (either initiation of ST or ASCT) to date of last follow-up or death, while PFS was defined as the time from treatment of interest to date of last follow-up or disease progression. The Kaplan-Meier method was used to estimate median OS (mOS) and PFS (mPFS) as well as two- and five-year OS and PFS rates. The log-rank test was used to test for groupwise differences in survival curves. Median follow-up was calculated using the reverse Kaplan-Meier method.

Univariate Cox proportional hazards models were used to estimate hazard ratios and 95% confidence intervals to assess the relationship between variables of interest at relapse such as disease stage, presence of extranodal disease, lactate dehydrogenase (LDH) levels (less than or greater than/equal to the upper limit of normal) at relapse, and time to relapse following completion of frontline therapy (before or after 6 months) and time-to-event outcomes. Logistic regression was used to estimate odds ratios and 95% confidence intervals to assess the relationship between these variables and complete response to first salvage regimen. Variables returning a p value ≤ 0.05 in univariate models were eligible for inclusion in multivariate modeling. Statistical analyses were performed using R v4.3.0.

Results:

Of the 107 patients analyzed, the median age was 32 years (range: 18-68) and the majority (57%) were female. At the time of relapse, 65% of patients had stage I/II disease, 48% had an elevated LDH, and 73% had a biopsy proven relapse. Additional baseline characteristics are presented in Table 1. Two patients received one cycle of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) or rituximab, cyclophosphamide, etoposide, vincristine, and prednisone (R-CEOP) before transitioning to DA-EPOCH-R for the remaining cycles. One patient received five cycles of DA-EPOCH-R then transitioned to one cycle of R-CHOP due to intolerance. Eight patients (7.5%) received radiation therapy after frontline DA-EPOCH-R treatment as consolidation prior to relapse. After frontline treatment with DA-EPOCH-R, 62% of patients included in this analysis did not achieve a CR**.** In total, 76% of patients experienced relapse within six months of initial treatment with DA-EPOCH-R and were considered refractory. At a median follow-up of 48.9 months (interquartile range (IQR): 18.7-74.8), mOS was not reached. Estimated 2- and 5-year OS rates were 87% (95% CI: 80-94) and 78% (95% CI: 70-88),

respectively. Of the 19 deaths, 17 were due to progressive disease and two were due to graft vs. host disease occurring after allogeneic stem cell transplant.

Salvage therapy analysis

Ninety (84%) patients were included in the salvage therapy (ST) analysis with 17 being excluded for presence of CNS disease on initial relapse (N=8), receipt of CAR T-cell therapy as first salvage therapy (N=6), and no receipt of salvage therapy prior to Auto-SCT (N=3). After initial salvage, the ORR and CR rate were 57% (95% CI: 46-67) and 26% (95% CI: 17-36), respectively. At a median follow-up of 48.9 months (IQR: 22.6-74.8), mPFS after initial salvage was 5.4 months (95% CI: 2.3-not reached (NR)) (Figure 1). Median OS was not reached and the estimated 5-year OS rate was 78% (95% CI: 69-88). Of the 52 patients that progressed after initial salvage, 87% (N=45) received either CAR-T (N=30), further line(s) of ST followed Auto-SCT (N=9), or Allo-SCT (N=6) as subsequent therapy. Eight patients in the ST analysis progressed after Auto-SCT with 4 patients receiving subsequent CAR-T (one of which received subsequent Allo-SCT) and one patient have long term remission with brentuximab vedotin (BV) plus Nivolumab (Nivo). Of the 25 patients that had PR to first ST, 14 proceeded to Auto-SCT, 7 to a different salvage regimen, 3 proceeded to directly to CAR T, and 1 patient had death related to lymphoma without further therapy. The 14 PR patients proceeding directly to Auto-SCT had a 2 year PFS and OS of 85% (95% CI 67-100) and 100% (95% CI 100-100) respectively, whereas the 7 patients proceeding to a different salvage regimen had a 2 year OS of 71% (95% CI 45-100).

When analyzing outcomes by refractory (primary refractory or relapse $\leq$ 6 months, N=67) or relapsed (relapse > 6 months, N=23) status, patients with refractory disease had lower ORR (48%, 95% CI: 35-60) and CR rates (19%, 95% CI: 11-31) when compared to those with relapsed disease (ORR 83%, 95% CI: 61-95; CR rate 44%, 95% CI: 23-66). The 2 and 5-year PFS rate in the refractory group was 30% (95% CI: 21-44) compared to 69% (95% CI: 53-91) in the relapsed group. Estimated 5-year OS rates were 72% (95% CI: 60-85) and 94% (95% CI: 84-100) in the refractory and relapsed groups, respectively (Figure 1).

Factors associated with decreased odds of achieving CR following first salvage included LDH > ULN at initial relapse (OR 0.23; 95% CI: 0.07-0.70; p = 0.014) (**Table 3**). Factors associated with progression were refractory disease (HR 3.21; 95% CI: 1.44-7.15; p = 0.004) and LDH > ULN (HR 5.40; 95% CI: 2.30-12.7; p < 0.001). On multivariate analysis, an increased risk of progression persisted for both those with refractory disease (HR 2.58; 95% CI: 1.05-6.32; p = 0.04) and those with LDH > ULN at relapse (HR 5.42; 95% CI: 2.30-12.8; p < 0.001).

Salvage treatments

The majority (86%) of patients received traditional salvage therapy at first relapse with median follow up of 51.6 months (IQR: 37.1-76.4). The most common initial traditional salvage treatments were anti-CD20 (rituximab or obinutuzumab) based chemotherapies in combination with ifosfamide, carboplatin, and etoposide (ICE) (51%) or dexamethasone, cytarabine, cisplatin, (DHAP) (12%). The ORR and CR rate to traditional ST was 53% (95% CI 42-65) and 22% (95% CI 13-33) respectively. The estimated 2- and 5-year PFS rate of traditional salvage was 35% (95% CI 26-48), with an estimated 2- and 5-year OS rate of 85% (95% CI 77-93) and 76% (95% CI 66-87). Initial salvage treatment details are presented in Table 2.

Fifteen patients received novel salvage with BV+Nivo with nine of those patients receiving as initial salvage. Of those nine, six were refractory to and three had relapsed disease after DA-EPOCH-R. The remaining six patients were refractory to initial salvage therapy and received BV+Nivo at second relapse. Eleven of the fifteen patients receiving BV+Nivo salvage proceeded to Auto-SCT. The ORR and CR of the fifteen patients receiving BV+Nivo were 80% (95% CI: 52-96) and 47% (95% CI: 21-73), respectively. The ORR and CR rate were 67% (95% CI: 30-93) and 33% (95% CI: 8-70) respectively for patients receiving BV+Nivo as initial salvage. Estimated 2- and 5-year PFS rate for all patients receiving BV+Nivo salvage was 70% (95% CI: 49-100). Estimated 2- and 5-year OS rate was 91% (95% CI: 75-100).

Autologous stem cell transplant analysis

At a median follow-up time of 56.1 months (IQR: 25.4-74.3), 48 patients (refractory = 30; relapsed = 18) had undergone salvage treatment followed by Auto-SCT. Median PFS and OS were not reached; Estimated 5-year PFS and OS rates were 85% (95% CI: 75-96) and 88% (95% CI: 79-99), respectively. No patients achieving CR prior to Auto-SCT (N=29) relapsed after transplant and among those patients with PR prior to Auto-SCT (N=17), estimated 2- and 5-year PFS rate was 69% (95% CI: 49-96). Twenty-two patients received radiation therapy prior to undergoing Auto-SCT and 11 patients received radiation after Auto-SCT.

CAR T-cell therapy as salvage therapy

At a median follow-up of 35 months (IQR: 11.9-49.9), 42 patients received autologous CD19 CAR T-cell therapy (axicabtagene ciloleucel = 29, tisagenlecleucel = 2, lisocabtagene maraleucel = 1, clinical trial = 10). Six patients received CAR T as 2nd line therapy while 36 patients received CAR T as 3rd line or greater. Four patients received Auto-SCT prior to CD19 CAR T. Among evaluable patients, the ORR was 74% (95% CI: 58-86) with a CR rate of 57% (95% CI: 41-72). The estimated PFS rate at 2 and 5 years was 64% (95% CI 51-81). The estimated 2- and 5-year OS rates were 80% (95% CI: 67-95) and 71% (95% CI: 56-90), respectively.

Allogeneic stem cell transplant

Nine patients underwent allogeneic stem cell transplantation. The median prior lines of therapy was 2 (range: 2-5) with one patient receiving prior Auto-SCT and one patient receiving prior CAR T. At a median follow-up of 48.1 months (IQR: 22.5-49.2), the estimated 2- and 5-year PFS rate was 67% (95% CI 42-100), with median OS of 40.2 months (95% CI: 9.8-NR) and estimated 2- and 5-year OS rates were 67% (95% CI: 42-100) and 50% (95% CI 24-100), respectively.

CNS relapse after frontline therapy

Eight patients (refractory = 6, relapsed = 2) were noted to have evidence of CNS involvement on relapse. With a median follow up of 39.5 months, the 2 year overall survival was 80% (95% CI 52-100). Each patient received cytotoxic chemotherapy as initial salvage with all but one receiving a high dose methotrexate (HD MTX) based regimen initially. Of the 7 patients that received a HD MTX based regimen, 5 achieved a complete remission with each of these patients proceeding to Auto-SCT. All 5 of these patients remain in a complete remission with a median follow up of 25.1 months and a range of 0.8 and 93.0 months. One other patient proceeded to Auto-SCT despite poor response to cytotoxic ST and subsequently died of lymphoma after Auto. One patient progressed after initial salvage chemotherapy, received subsequent CAR T cell therapy, and was without relapse 2 months after CAR T infusion.

Discussion

While the majority of patients with PMBCL are cured with frontline therapy, the current literature is sparse regarding outcomes with salvage therapies in those that experience relapse. This publication describes the largest series of patients with R/R PMBCL, a rare subtype of NHL where relapse is uncommon. In addition, this study is limited to patients receiving frontline DA-EPOCH-R, a common standard for frontline therapy for PMBCL.

This analysis describes unfavorable response to initial salvage therapy in patients with refractory disease. Fewer than 20% of refractory patients achieved a CR to first salvage therapy and 30% (95% CI: 21-44) were estimated to be free from progression at 2 years after initial salvage. Compared to patients with relapsed disease, those with refractory were less likely to obtain a CR with initial salvage therapy and had an increased risk of progression after first salvage therapy. Of patients with relapsed disease, 44% (95% CI: 23-66) achieved a CR with an estimated 2 year PFS of 69% (95% CI: 53-91) after initial salvage chemotherapy. This analysis also highlights the importance of obtaining a CR prior auto-SCT as there were no relapses among the 29 patients that achieved CR prior to transplant. Univariate analysis noted a higher probability of obtaining a CR with initial salvage therapy in patients with LDH less than the upper

limit of normal. There was a trend towards refractory patients being less likely to achieve a CR with first salvage in univariate analysis but this was not statistically significant. In multivariate analysis, LDH > ULN and refractory disease at relapse persisted in increasing hazard ratio for progression after initial salvage therapy. The heterogenous treatment strategies employed in patients having PR to first salvage highlights the clinical ambiguity of PR in PMBCL patients. Despite the median PFS of only 5.4 months after initial salvage for patients in ST analysis, the estimated 5 year overall survival remained high at 78% (95% CI: 69-88) for this group. This likely reflects the multiple subsequent options for curative therapy as 87% of those progressing after initial salvage were able to receive either second/third line salvage followed by auto-SCT, CAR T cell therapy, or Allo-SCT.

This analysis did not include a sufficient number of patients receiving 'novel' salvage therapy (ie brentuximab vedotin + nivolumab) to make any meaningful conclusions regarding 'novel' versus 'traditional' salvage therapy in terms of CR rate or progression free survival.

Outcomes for patients receiving CD19 CAR T cell therapy were consistent with previous reports. [12] This analysis was not designed to provide a comparison of salvage chemotherapy plus Auto-SCT versus CD19 CAR T-cell therapy as initial therapy after relapse.

This represents the largest review of R/R PMBCL to date and provides insight on select variables having statistically significant effects on outcomes with initial salvage therapy. Considering the outcomes described, it is reasonable to suggest salvage chemotherapy followed by Auto-SCT as a viable option for patient relapsing > 6 months after completion of DA-EPOCH-R. For refractory patients, long term disease free survival with ST and Auto-SCT is unlikely, and thus CAR T cell therapy should be highly considered in this patient population. Patients achieving CR prior to Auto-SCT had excellent prognosis. When choosing a treatment option, clinicians must consider both immediate and long-term side effects of each approach. This analysis provides a valuable resource regarding expectations of response to salvage therapy as well as providing a benchmark for outcomes in this patient population for future studies. Further investigations regarding various salvage therapies within different subpopulations (ie relapsed vs refractory) is warranted as well as investigation of cellular therapy versus salvage therapy and Auto-SCT as initial therapy after relapse.

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Table 1. Baseline Characteristics

Characteristic	**N=107** **N (%)**
Sex:	107
Male	46 (43.0)
Female	61 (57.0)
Age, median (range)	32 (18-68)
ECOG:	85
0-1	83
2	2
3+	0
Time to Relapse:	107
≤ 6 months	81 (75.7)
> 6 months	26 (24.3)
Frontline radiation:	107
Yes	8 (7.5)
No	99 (92.5)
Stage at Relapse:	93
I	21 (22.6)
II	39 (41.9)
III	4 (4.3)
IV	29 (31.2)
LDH at Relapse:	75
≥ ULN	36 (48.0)
< ULN	39 (52.0)
IPI at Relapse:	73
0-1	52 (71.2)
2	13 (17.8)
3	8 (11.0)
4+	0 (0)
Extranodal Disease at Relapse:	100
Yes	45 (45.0)
No	55 (55.0)

IPI: international prognostic index

ULN: upper limit of normal

Table 2. Initial Salvage Treatment

Initial Salvage (N=90)	
Traditional Salvage, N=77	
R/O-ICE	46
R/O-DHAP	11
R-GDP	6
R-DHAX	5
R-GemOx	5
R-IVAC	1
DHAP	1
ICE	1
R-MTX+cytarabine	1
Novel Salvage, N=10	
BV + Nivolumab	9
Pembrolizumab	1
Clinical Trial, N=3	
R-ICE + ibrutinib	2
R-DHAX + epcoritamab	1

BV: brentuximab vedotin; CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisone; DHAP: dexamethasone, high dose cytarabine, cisplatin; DHAX: dexamethasone, high dose cytarabine, oxaliplatin; EPOCH: etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin; GDP: gemcitabine, dexamethasone, cisplatin; GemOx: gemcitabine, oxaliplatin; Hyper-CVAD: hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; ICE: ifosfamide, carboplatin, etoposide; IVAC: ifosfamide, etoposide, high dose cytarabine; O: ofatumumab; MTX: methotrexate; R: rituximab

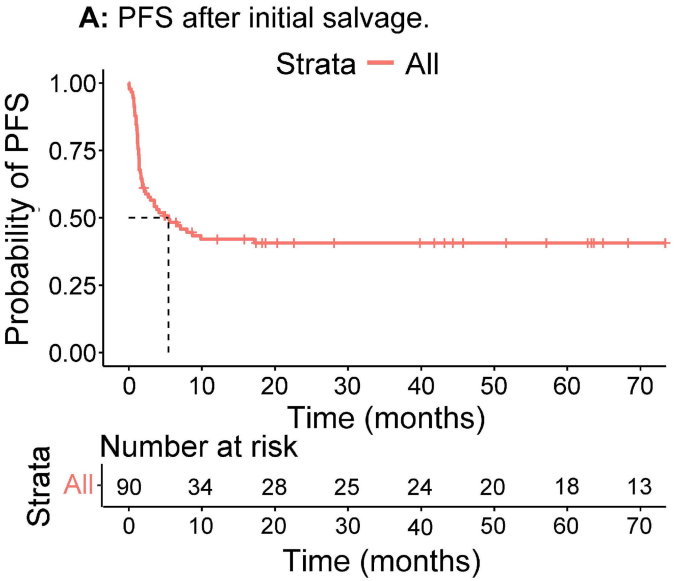
Table 3. Univariate Cox and logistic regression models to estimate hazard of progression, death, and odds of complete response.

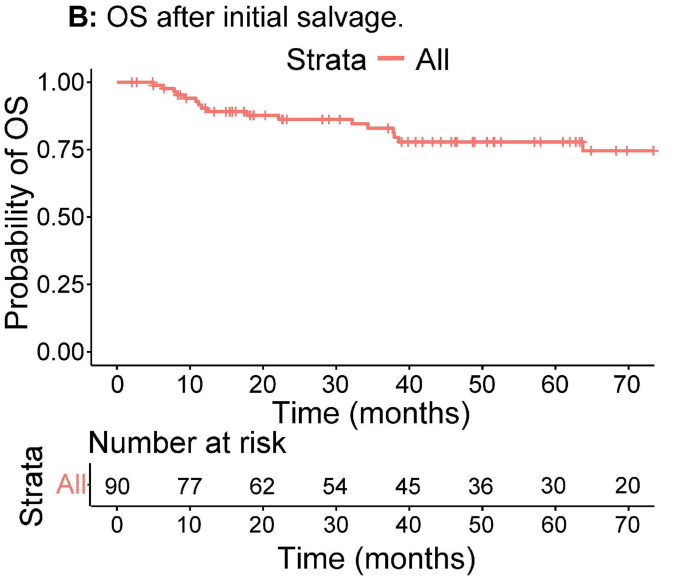
	PFS		OS		CR	
Variable	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***	**OR (95% CI)**	***p***
Relapse status						
Relapse ≤ 6 months	3.21 (1.44, 7.15)	0.004	7.29 (0.96, 55.0)	0.054	0.43 (0.17, 1.12)	0.079
LDH at relapse						
LDH > ULN	5.40 (2.30, 12.7)	<0.001	3.12 (0.80, 12.1)	0.101	0.23 (0.07, 0.70)	0.014
Stage						
III-IV	0.97 (0.52, 1.83)	0.935	1.74 (0.58, 5.27)	0.324	1.09 (0.42, 2.73)	0.858
Extranodal disease						
Yes	1.27 (0.71, 2.26)	0.410	1.77 (0.66, 4.73)	0.256	0.59 (0.24, 1.43)	0.251

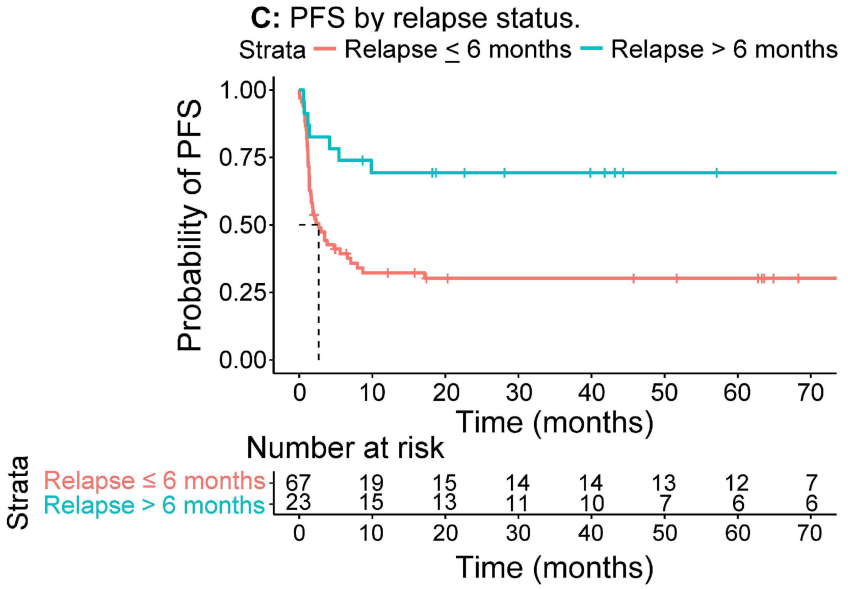
Abbreviations: PFS, progression-free survival; OS, overall survival; CR, complete response; HR, hazard ratio; OR, odds ratio; LDH, lactate hydrogenase; ULN, upper limit of normal.

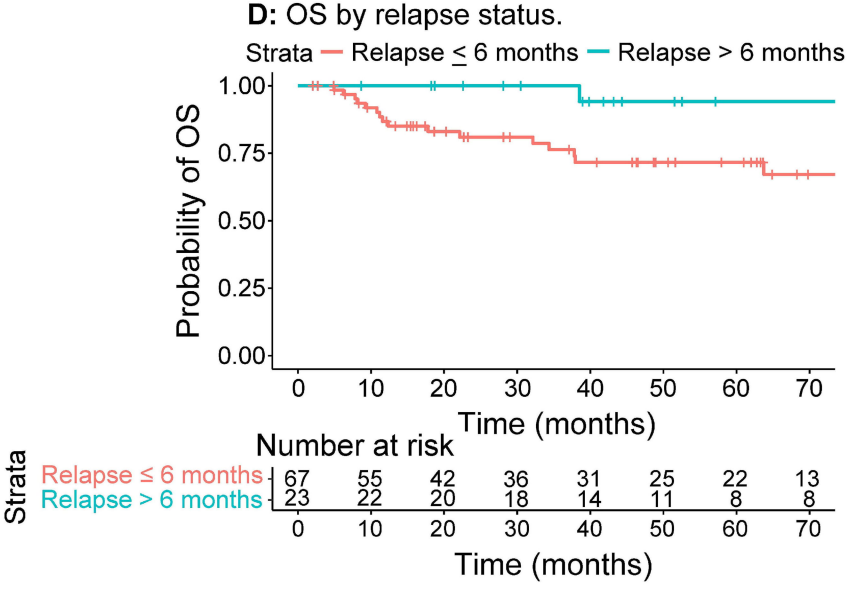
Footnote: Estimations are made relative to the following reference groups: Relapse > 6 months, LDH ≤ ULN, stage I-II, and absence of extranodal disease.

Figure 1. Survival outcomes after salvage therapy and by time of relapse. (A) Progression-free survival (PFS) of all patients in salvage therapy cohort. (B) Overall survival (OS) of all patients in the salvage therapy cohort. (C) PFS by time to relapse (D) OS by time to relapse.


A: PFS after initial salvage.
Strata All
Probability of PFS
1.00
0.75
0.50
0.25
0.00
0 10 20 30 40 50 60 70
Time (months)
Number at risk
Strata
All 90 34 28 25 24 20 18 13
0 10 20 30 40 50 60 70
Time (months)


B: OS after initial salvage.
Strata All
Probability of OS
1.00
0.75
0.50
0.25
0.00
0 10 20 30 40 50 60 70
Time (months)
Number at risk
Strata
All 90 77 62 54 45 36 30 20
0 10 20 30 40 50 60 70
Time (months)


C: PFS by relapse status.
Strata Relapse ≤ 6 months Relapse > 6 months
Probability of PFS
1.00
0.75
0.50
0.25
0.00
0 10 20 30 40 50 60 70
Time (months)
Number at risk
Strata
Relapse ≤ 6 months 67 19 15 14 14 13 12 7
Relapse > 6 months 23 15 13 11 10 7 6 6
0 10 20 30 40 50 60 70
Time (months)


D: OS by relapse status.
Strata Relapse ≤ 6 months Relapse > 6 months
Probability of OS
1.00
0.75
0.50
0.25
0.00
0 10 20 30 40 50 60 70
Time (months)
Number at risk
Strata
Relapse ≤ 6 months 67 55 42 36 31 25 22 13
Relapse > 6 months 23 22 20 18 14 11 8 8
0 10 20 30 40 50 60 70
Time (months)