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Different treatment eras for relapsed and refractory primary mediastinal B-cell lymphoma patients: accessibility to CAR T cells is associated with a better prognosis in a pooled analysis of the REPRIME-FIL and the CART-SIE studies

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Running Heads: CAR T cells as salvage therapy in PMBCL patients

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ABSTRACT

Chimeric Antigen Receptor (CAR) T-cell therapy targeting CD19 has demonstrated efficacy as salvage treatment for patients with relapsed/refractory (R/R) primary mediastinal B-cell lymphoma (PMBCL), however, a direct comparison between CAR T activity and other salvage treatments has not previously been performed. This study aims to compare overall survival (OS) in R/R PMBCL patients treated in different eras who reflect accessibility to CAR T-cells in R/R patient treated after 2019 and treatment with other salvage programs in the years before. We performed a pooled analysis including all pts affected by R/R PMBCL enrolled in the ongoing multicenter prospective observational study CART-SIE and in the retrospective REPRIME-FIL study. A total of 191 patients were included, 87 receiving CAR T cells and 104 treated with other salvage therapies. The 3-year OS from failure of first line treatment for the entire cohort was 62% (95% CI 55-69). The 6-months landmark analysis showed that patients treated with CAR T cells had a significantly reduced risk of death and a superior OS compared with those receiving other regimens (adjusted HR 0.34; 95%CI 0.17-0.66, p=0.001). Patients treated with CAR T cells also had superior OS compared with the subgroup of REPRIME patients who underwent ASCT (adjusted HR 0.27; 95%CI 0.13-0.66, p=0.001). Within the limitations inherent to a pooled analysis, administration of CAR T cells during salvage of R/R PMBCL patients appears to be associated with a longer OS with a risk of death approximately one-third of that observed in patients managed without CAR T.

Trial Registration: *ClinicalTrials.gov identifier*: NCT05162170 and NCT06339255

INTRODUCTION

Patients affected by Primary Mediastinal B Cell Lymphoma (PMBCL) have a favorable prognosis when treated with anthracycline-based regimens [1,2,3]. However, a subset of patients who are refractory to first-line treatment or experience relapse face a poor prognosis. Historically, these patients have been treated with second-line chemotherapy regimens followed by autologous stem cell transplant (ASCT), resulting in overall survival (OS) rates ranging from 57% to 71% among those who actually underwent transplantation [4] [5] [6] [7]. Nevertheless, a proportion of patients remain refractory to second-line therapies or relapse after transplant, thus resulting in a poor prognosis.
In a retrospective analysis of 891 patients with PMBCL treated in Italy, the analysis of OS in the subgroup of relapsed and refractory patients revealed a 3-year OS of 46.6% with chemotherapy-based treatment.[8] [9]

In recent years, the therapeutic landscape for these patients has been transformed by the advent of immune checkpoint inhibitors (CPIs) and anti-CD19 chimeric antigen receptor (CAR) T-cell therapy.
In the KEYNOTE-170 study, patients with relapsed/refractory (R/R) PMBCL treated with pembrolizumab achieved a 4-year progression-free survival (PFS) of 33% and a 4-year overall survival (OS) of 45.3%[10] [11]. Given the expression of CD30 on PMBCL cells, the combination of CPIs and brentuximab vedotin (BV) was also investigated, demonstrating a 2-year PFS of 55.5% and a 2-year OS of 75.5% in the CheckMate 436 study[12] [13]. Based on these results, CPIs now represent now a key component of the therapeutic strategy for R/R PMBCL.

Immunotherapy with anti-CD19 CAR T-cells has also emerged as a promising option for patients with R/R PMBCL. However, due to the rarity of the disease, only a limited number of PMBCL patients were included in pivotal trials. The ZUMA-1 and TRANSCEND trials enrolled only 8 and 15 PMBCL patients, and as a result, these small sample sizes precluded drawing definitive conclusions regarding survival outcomes following CAR T-cell therapy in this patient population[14,15].
Recent real-world studies have provided valuable insights into the outcomes of patients with PMBCL.

In a U.S. real-world study, survival data from 33 PMBCL patients treated with CAR T-cell therapy revealed a 2-year PFS rate of 64% and an OS rate of 78%[16].

The French DESCAR-T study, which analyzed 82 PMBCL patients treated with CAR T-cell therapy, reported a 2-year PFS of 57.4% and a 2-year OS of 73.8%[17].

Similarly, a retrospective analysis from the German registry showed that among 13 R/R PMBCL patients treated with CAR T-cells, the PFS and OS rates were 54% and 75%, respectively[18].

A recent analysis from the Italian CAR-T SIE study demonstrated significantly better outcomes for PMBCL patients treated with CAR T-cell therapy compared to those with diffuse large B-cell lymphoma (DLBCL). Specifically, the 1-year PFS and OS rates for 70 PMBCL patients were 62% and 86%, respectively[19].

Based on these observations, CAR T-cell therapy appears to have significantly changed the treatment landscape for R/R PMBCL, giving patients the potential for prolonged overall survival. However, no direct comparisons between standard salvage therapies and CAR T-cell treatment have been conducted to date. To address this gap, we performed a pooled analysis of two cohorts of R/R PMBCL patients enrolled in separate studies: the REPRIME-FIL study, which included patients treated with salvage therapies in pre-CAR T-cell era, and the CAR-T SIE study, which enrolled patients receiving CAR T-cell therapy. The objective of this study was to compare OS between patients receiving CAR T-cell therapy as salvage treatment and those managed with other salvage strategies.

METHODS

Study Design

For the present study, data of patients were collected from two studies. The REPRIME-FIL study (NCT05162170) is a retrospective observational cohort study collecting clinical data of R/R PMBCL patients treated in 27 centers in Italy during the period before CAR T-cell approval, from 2007 to 2019. The CAR T SIE study (NCT06339255) is an ongoing multicenter prospective observational cohort study collecting clinical data of consecutive patients eligible for in-label anti-CD19 CAR T-cell therapy in 23 Italian centers from 2019. Data from both studies were received anonymized and pooled in a comprehensive database to be analyzed together. Both studies received approval from their respective Ethics Committees.

All patients from each data source who met the criteria for R/R PMBCL were considered for this analysis. Failure after first-line therapy was defined as the need to initiate a subsequent line of treatment or as rapidly progressive disease leading to death before a new line of therapy could be started. Patients were eligible if data were available regarding the date of diagnosis, clinical response to first-line treatment, the date of first-line failure, the type and number of salvage treatments, the date of last follow-up, and survival status. All patients signed informed consent for the proper study.

Statistical Analysis

Baseline patient characteristics were summarized separately for the FIL-REPRIME study and the CAR T SIE study cohorts. Continuous variables were reported as medians with interquartile ranges and compared using the Mann–Whitney U test, while categorical variables were compared using Fisher's exact test, as appropriate. The primary endpoint was OS, defined as the time from failure of first-line therapy to death from any cause. Patients alive at last follow-up were censored. Overall survival was estimated using the Kaplan–Meier method. Comparisons between treatment groups were performed using a 6-month landmark analysis, in order to reduce potential immortal time bias arising from the interval between first-line failure and initiation of subsequent therapies in the two cohorts. Group differences in OS were evaluated using Cox proportional hazards models, both unadjusted and adjusted for age, sex, and relapse/refractory status. Subgroup analyses were conducted using Cox models including interaction terms between treatment group and the covariate of interest to assess potential heterogeneity of treatment effects. The cumulative incidence of cause-specific death (lymphoma-related versus other causes) was estimated accounting for competing risks, treating death from the alternative cause as a competing event. The follow-up was calculated with the reverse Kaplan-Meier method. Statistical analyses were performed with Stata (version 15).

RESULTS

Patients Characteristics and Salvage Regimens

A total of 191 patients affected by R/R PMBCL were evaluable for the pooled analysis, 104 enrolled in the FIL-REPRIME study, and 87 in the CAR T SIE study. As shown in **Figure 1** patients who were not eligible were excluded due to infusion failure or missing relevant data, two patients were

leukapheresesed but not infused due to progression of disease. Clinical characteristics of the enrolled population are detailed in **Table 1**.

Median age at diagnosis was 33 (range, 26-41) and 33 (range, 28-43) years in the CAR T SIE and REPRIME studies, respectively, 47% and 57% were female. All patients received an anthracycline-containing regimen as first-line therapy. Patients failed the first line after a median of 6 months (range, 0.2-86) and 6.5 months (range, 1-82) in the two cohorts, respectively. The dates of first-line failure ranged from 2016 to 2024 for the CAR T SIE cohort, and from 2008 to 2020 for the FIL-REPRIME cohort.

Primary refractory patients, defined as patients with a PFS after the first line inferior to 6 months, were 51% and 46%.

All but seven patients received salvage therapy, the entire cohort received a median of 2 regimens (range, 0-7), CAR T SIE patients received a median of 3 salvage regimens (range, 2-7), whereas REPRIME patients received a median of 2 regimens (range, 0-3).

Thirty-three REPRIME patients received a single line of salvage treatment, 60 patients received two lines, and four patients received three lines of salvage treatment. Overall, chemotherapy-based regimens were the most commonly used treatment modality. Radiotherapy was administered in five patients and four patients were enrolled in clinical trials.

Seven patients in the REPRIME study did not receive salvage therapy. All these patients died within six months from first-line failure, therefore they were excluded from the 6-month landmark analysis.

All CAR T SIE patients received CAR T-cell infusion (axicel n=86, lisocel n=1) after a median of 2 regimens (range, 2-5). In 56 patients, CAR T cell therapy was administered after two lines of salvage therapy, whereas in 31 patients it was administered after three or more lines.

The time between first-line failure and CAR T-cell infusion was 5 months (range, 1 -53).

Bridging therapy was administered to 61 patients. It consisted of CPI-based therapy in 27 patients, chemotherapy-based regimens in 15 patients (including autologous stem cell transplantation in 2 patients), and radiotherapy alone in 8 patients; the remaining patients received other bridging strategies. A clinical response to bridging therapy was observed in 13 of the 27 patients treated with CPI-based regimens and in 8 of the 34 patients treated with other approaches. Response to bridging therapy was not evaluable in 14 of the 34 patients treated with non-CPI strategies.

ASCT during salvage therapy was used in 36% of patients. Among REPRIME patients, ASCT was used in 49% of cases (n=51), and among CAR T SIE patients, ASCT was used in 19% (n=17).

CPIs were used as salvage therapy in 35% of patients of the entire cohort. REPRIME patients received CPI treatment in 15% of cases (n=16), whereas CAR T SIE patients in 59% of cases (n=51). Thirty-seven patients (35%) in the REPRIME study and 31 (36%) in the CAR T study never received either CPI nor ASCT.

As shown in **Table 2**, CPIs were used before CAR T in 46 patients (53%) and in 5 of patients they were used only as salvage therapy after CAR T failure. Twenty-seven patients received CPI for one or two cycles as bridging therapy before CAR T, and 13 patients achieved a response to bridging therapy. Five patients received CPI as bridging therapy and continued CPI after CAR T-cell infusion.

In 19 patients CPI represented a line of therapy before CAR T. Overall, 21 patients received CAR T cells after achieving a clinical response with CPI therapy.

In the REPRIME group, 16 patients (15%) received CPI during salvage therapy and 62% obtained a clinical response.

As shown in **Table 3**, 29 patients (33%) failed CAR T after a median of 3 months (range, 1-12); after CAR T failure, 5 patients received CPIs (obtaining CR in one patient and PR in one patient) and 5 patients received CPIs and Brentuximab Vedotin (obtaining CR in 4 patients and PD in one).

Adverse Events in CAR T-cells group

Among the 87 patients treated with CAR T cells, 75 (86%) developed cytokine release syndrome (CRS) of any grade, while only 9 patients (10%) experienced grade 3-4 CRS. Immune effector cell–associated neurotoxicity syndrome (ICANS) of any grade occurred in 31 patients (36%), with grade 3–5 ICANS reported in 14 patients (16%). ICANS was the cause of death in 4 patients. Nineteen patients (22%) required ICU admission. Severe infection was reported only in one patient and was fatal.

At 6 months after CAR T-cell infusion, prolonged grade 3–4 neutropenia persisted in 10 patients, and grade 2 thrombocytopenia was observed in two patients.

Overall Survivals

Median follow-up was 70.5 months (IQR 48.5-94.8) for the REPRIME cohort, and 29.5 months (IQR 17.8-45.6) for the CAR T SIE cohort.

As shown in **Figure 2A**, the 3-year OS from the failure of the first line was 62% (95%CI 54%-69%) for the entire population, 3-year OS was 83% and 45% for patients for the CAR T SIE patients and REPRIME patients, whereas median OS was not reached and was 19.6 months in the two groups, respectively.

The 6-month landmark analysis showed that patients treated with CAR T cells had a significantly better OS compared to those treated with other regimens, adjusted HR 0.34 (95% CI 0.17-0.66, p=0.001), with no evidence of proportional-hazards assumption (Grambsch-Therneau test, p = 0.720) **(Figure 2B)**. Thirty patients were excluded from the landmark analysis, (5 from the CAR-T SIE cohort: 2 censored and 3 who died before 6 months; 25 from the FIL-REPRIME cohort: 2 censored and 23 who died before 6 months). A comparison between patients included and excluded from the landmark analysis is presented in **Supplementary Table 1**.

The exploratory analysis comparing patients treated with ASCT in the REPRIME group and patients treated with CAR T cells showed that CAR T treatment was associated with better OS in comparison to ASCT, adjusted HR 0.27 (95%CI 0.13-0.66, p=0.001) **(Figure 3A)**.

Clinical characteristics of the 87 patients treated with CAR T and the subgroup of 51 patients in the REPRIME study who underwent ASCT are detailed in **Supplementary Table 2**. Age and the proportion of refractory patients were similar, whereas the percentage of patients who received ASCT was more represented in the REPRIME cohort, and patients treated with CPIs were more represented in the CAR T cohort. In the REPRIME cohort, only 6 patients treated with ASCT received CPIs, and 5 of them received CPIs as salvage therapy after ASCT failure.

A subgroup analysis was performed according to CPIs administration during salvage therapy. Among patients included in the 6-month landmark analysis, 46 CAR T patients and 14 REPRIME patients had received CPIs, while 36 CAR T patients and 65 REPRIME patients had not been exposed to CPIs. The CAR T group appeared to derive a greater benefit among patients not exposed to CPIs compared with those previously treated with CPIs (adjusted HR 0.24 vs 0.61), although no evidence of significant effect modification was observed (P = 0.262) **(Figure 3B).**

In univariate analysis, no differences in OS were observed considering CAR T and sex, age > 40 years, primary refractory status and CPIs exposure.

In multivariate analysis, neither age at diagnosis, male sex, nor disease status after first line therapy conferred better survival, and only treatment with CAR T remained significant, as shown in **Table 4**.

Causes of Death

Overall, 72 patients out of 191 died (38%), 15 (17%) in the group receiving CAR T-cells and 57 (55%) in the REPRIME group.

The main cause of death in the two groups was lymphoma, in 9 and 49 patients, respectively, in the CAR T and in the REPRIME groups (10% and 47% of all patients in the two cohorts). Toxicity was the second cause of death in the CAR T-cell group (n=4, 5% of patients) whereas other causes (4% of patients) were the second cause of death in the REPRIME study (myocardial infarction n=1, chronic GVHD after allogeneic SCT n=1, respiratory failure n=1, secondary malignancy n=1). Death related to infections was observed in one patient in the CAR T group and no patients in the other group.

The cause of death was not known in three patients in the REPRIME group and in one patient in the CAR T group.

Accounting for competing risks, the 2-year cumulative incidence of lymphoma-related death from first-line failure was 11.1% (95% CI 4.7-17.4) in the CAR T group and 48.9% (95% CI 38.7-59.0) in the REPRIME group, whereas the 2-year cumulative incidence of death from other causes was 6.0% (95% CI 1.2-10.9) and 4.1% (95% CI 0.1-8.2), respectively.

DISCUSSION

Historically, patients with R/R PMBCL have faced a poor prognosis. However, the introduction of novel immunotherapies, such as CPIs and CAR T-cell therapy, has markedly improved outcomes of these patients.

In the present study, the availability of two large datasets of patients with R/R PMBCL provides a unique opportunity to compare OS in patients treated before and after the CAR T-cell era. We performed a comparative OS analysis between two clinically similar patient populations treated differently: one with accessibility to anti-CD19 CAR T-cell therapy after 2019 and the other receiving various salvage regimens in the period before.

The clinical characteristics of the entire cohort reflect the typical presentation of R/R PMBCL: predominantly young patients experiencing first-line treatment failure within a median of six

months from first-line therapy. In this study, data on systematic confirmation at relapse were not available, representing a limitation because the presence of possible false-positive cases could not be excluded. However, the two groups were largely comparable, with the main difference being the time in which treatment failure occurred. Specifically, patients in the REPRIME study relapsed during years when CAR T-cell therapy was not yet approved in Italy. Consequently, the populations from these two studies effectively represent two distinct eras: before and after the availability of CAR T-cell therapy.

The results of this study demonstrate that the use of CAR T-cell therapy is associated with a better survival in patients with R/R PMBCL. Patients treated with CAR T cells had a 65% lower risk of death compared with those receiving other salvage regimens. This finding was observed using a 6-month landmark analysis to minimize bias related to the potential selection of patients who survived long enough to receive CAR T-cell therapy. Importantly, this survival benefit was consistent across subgroups, regardless of sex, age, or disease refractoriness. Observed survival outcomes are comparable to those reported in series of published real world data of R/R PMBCL patients treated with CAR T-cells[16 18 20].

Superior survival outcomes were also observed in CAR T-cell recipients when compared to patients undergoing ASCT. Although this study was not designed as a head-to-head comparison between CAR T-cells therapy and transplantation and the conclusions may be affected by biases inherent to the pooled nature of the study, this finding is consistent with the observation that conventional chemotherapy has limited efficacy in patients with PMBCL who relapse after or are refractory to an anthracycline-containing first-line regimen.

The superiority of CAR T-cell therapy was more pronounced among patients who had never been exposed to CPIs in either cohort. In the REPRIME cohort, only a small number of patients received CPIs; however, more than 60% achieved a response, and CPIs were often administered as the final salvage therapy, leading to durable disease control in a substantial proportion of patients and a favorable impact on OS in this subgroup. Although the limited number of CPI-exposed patients in the REPRIME study prevents definitive conclusions, these findings highlight the efficacy of immunotherapy in this lymphoma subtype.

This observation raises important questions regarding the optimal salvage immunotherapeutic strategy (CPIs versus CAR T-cell therapy) and treatment sequencing in case of treatment failure (CAR T followed by CPIs or vice-versa). This topic is gaining increasing relevance, particularly in light of the recent approval of lisocel, which now enables the use of CAR T-cell therapy as a second-line treatment option for refractory PMBCL. Concurrently, the combination of BV and CPIs has obtained a special approval as second-line strategy in Italy and is also available in other countries. This combination has shown sustained activity in R/R PMBCL over long-term follow-up[13] and was successfully employed also as bridge to CAR T[21]. Addressing these issues should be a priority for future clinical research.

As expected, the mortality rate was higher in the REPRIME study, with lymphoma being the predominant cause of death in both groups. The second cause of death among CAR T-cell recipients was toxicity related to the therapy. The observed 6% of non-relapse mortality in the CAR T-cell group is consistent with previously published data. In contrast, infections were not a predominant cause of death in these cohorts, being fatal in only one patient in the CAR T-cell study.

This study has some limitations, primarily due to its design as a pooled analysis and the retrospective nature of the REPRIME study. Considering these limitations the observed results should be interpreted as associations rather than as estimates of a causal treatment effect.

In fact, detailed information on baseline characteristics at diagnosis was limited, and further stratification by prognostic subgroups or disease features was not feasible. This prevented the construction of a robust propensity score model.

Similarly, comprehensive information on all prior chemotherapeutic regimens received by each patient was not accessible. These constraints limited the depth of exploratory analyses. Despite these limitations, the two cohorts showed comparable clinical profiles, and the large sample size—almost two hundred patients with R/R PMBCL—combined with the extended follow-up in both datasets, provides clinical relevance to the observed findings.

Another limitation of the study is related to difference in treatment period (i.e. before or after 2019). This not only reflects the availability of CAR T cells but also reflects differences in supportive care, imaging, salvage algorithms, access to checkpoint inhibitors, bridging approaches, and post-relapse management. It is important to note that access to CPIs before 2025 was restricted to clinical studies, compassionate use or off-label programs. As a result, salvage treatments were not

standardized and may have varied across centers depending on local availability and institutional practices. This heterogeneity in treatment pathways is also part of the limitations of our pooled analysis.

In conclusion, this study suggests that CAR T-cell therapy is associated with a better survival outcome over other salvage approaches, including ASCT, in patients with R/R PMBCL. Notably, the risk of death among CAR T patients was one-third of that observed in patients not receiving CAR T. Based on these findings, such patients should be considered for CAR T-cell therapy in third line or in second line when the disease is refractory. The use of CPIs, or BV in combination with CPIs represents an appropriate alternative depending on local drug availability and regulatory approvals. Importantly, salvage with additional lines of chemotherapy in patients not responding to second line conventional treatments should be carefully considered in this population, as these treatments are unlikely to provide durable benefit. Future research is required to establish the optimal treatment algorithm in this predominantly young population with the goal to further improve outcomes for relapsed and refractory patients who have traditionally had poor prognosis.

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TABLES

Table1. Clinical Characteristics

	Total N=191(%)	**CART-SIE N=87(%)**	**FIL-REPRIME N=104(%)**	**p**
Male **Female**	90 (47.1) 101 (52.9)	46 (52.9) 41 (47.1)	44 (42.3) 60 (57.4)	0.150
Age at diagnosis, years median (IQR)	33 (26-42)	33 (26-41)	33 (28-43)	0.230
Time to first line failure months, median (range)	6.2 (0.7-86)	6 (0.2-86)	6.5 (1-82)	0.564
Primary refractory (PFS ≤ 6 months)	92 (48.2)	44 (50.6)	48 (46.2)	0.564
N tot of salvage regimens, median (range)	2 (0-7)	3 (2-7)	2 (0-3)	< 0.001
ASCT during salvage	68 (35.6)	17 (19.5)	51 (49)	NA
CPI during salvage	67 (35)	51 (58.6)	16 (15)	NA
BV during salvage	45 (23.6)	28 (32.2)	17 (16.3)	NA
Radiotherapy	34 (18)	29 (33)	5 (5)	NA
No salvage	7 (4)	0	7 (7)	NA
Time between 1st line failure and CART, months, median (range)	5	5 (1-53)	NA	NA

Abbreviations: ASCT, autologous stem cell transplant; CPI check point inhibitors; BV brentuximab vedotin

Table 2. Patients treated with CPIs

	CART-SIE N 87 (%)	**FIL-REPRIME N 104 (%)**
All CPI exposed patients	51 (59)	16 (15)
CPI before CART	46 (53)	NA
CPI only as bridge	27 (31)	NA
Responsive to CPI before CART	21 (24)	10 (63)
CPI only as salvage post CART	5 (6)	NA

Table 3. Patients experiencing CAR T-cells failure

	N 29 (%)
Time to failure months, median (range)	3 (1-12)
No treatment	13 (45)
Subsequent Treatment	16 (55)
CPI	5 (31)
CPI + BV	5 (31)
Chemotherapy	2 (12)
Loncastuximab	1 (6)
Bispecific Antibodies	1 (6)
Other	2 (12)

Table 4. Multivariable Group Comparison

	HR	95%CI	p
CAR T SIE vs REPRIME	0.34	0.17,0.66	0.001
Male vs Female	1.03	0.57,1.85	0.933
Age at diagnosis per 1 year increase	0.99	0.97,1.02	0.643
Primary refractory vs no	0.93	0.52,1.66	0.8

Figure Legends

Figure 1. Flow chart of the enrolled patients, showing the reasons for ineligibility and the reasons for exclusion from the landmark analysis.

Figure 2. Overall Survival from first-line failure for the entire study population and for the CAR T SIE and the FIL REPRIME cohort. **(A)** Overall survival for the overall study population. **(B)** Six-month landmark analysis for overall survival comparing patients in the CAR T SIE cohort and the FIL REPRIME cohort. The number of patients included in the landmark analysis is 82 for the CAR T cohort and 79 for the REPRIME cohort.

Figure 3. 6-month landmark analysis for overall survival from first line failure in patients stratified by autologous stem cell transplantation (ASCT) status and Check Points Inhibitors (CPI) exposure. **A)** CAR T SIE and FIL REPRIME patients stratified by ASCT status. **B)** CAR T SIE and FIL REPRIME patients stratified by CPI exposure. The number of patients included in the landmark analysis is 82 for the CAR T cohort and 79 for the REPRIME cohort.

Figure 1

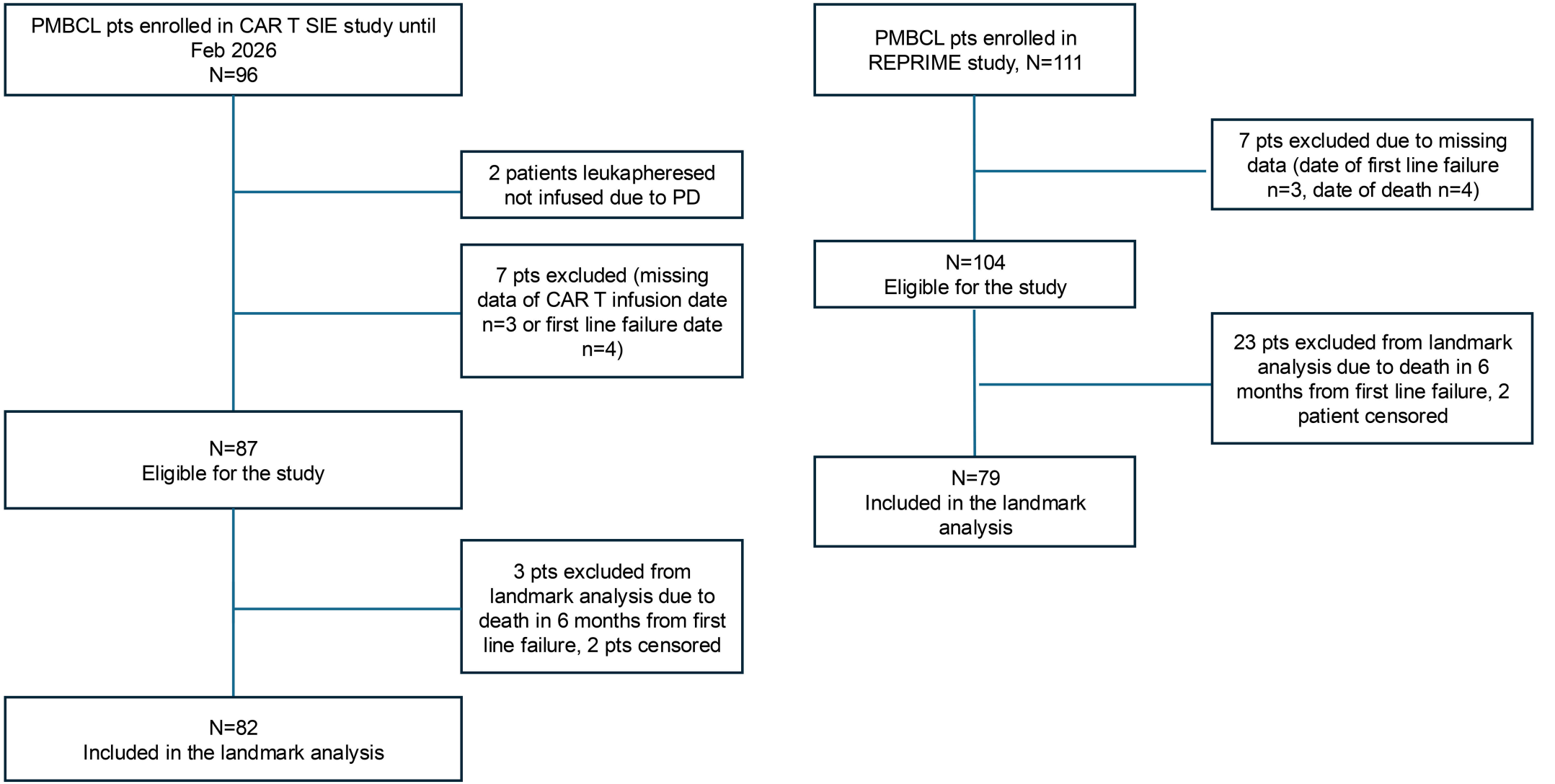
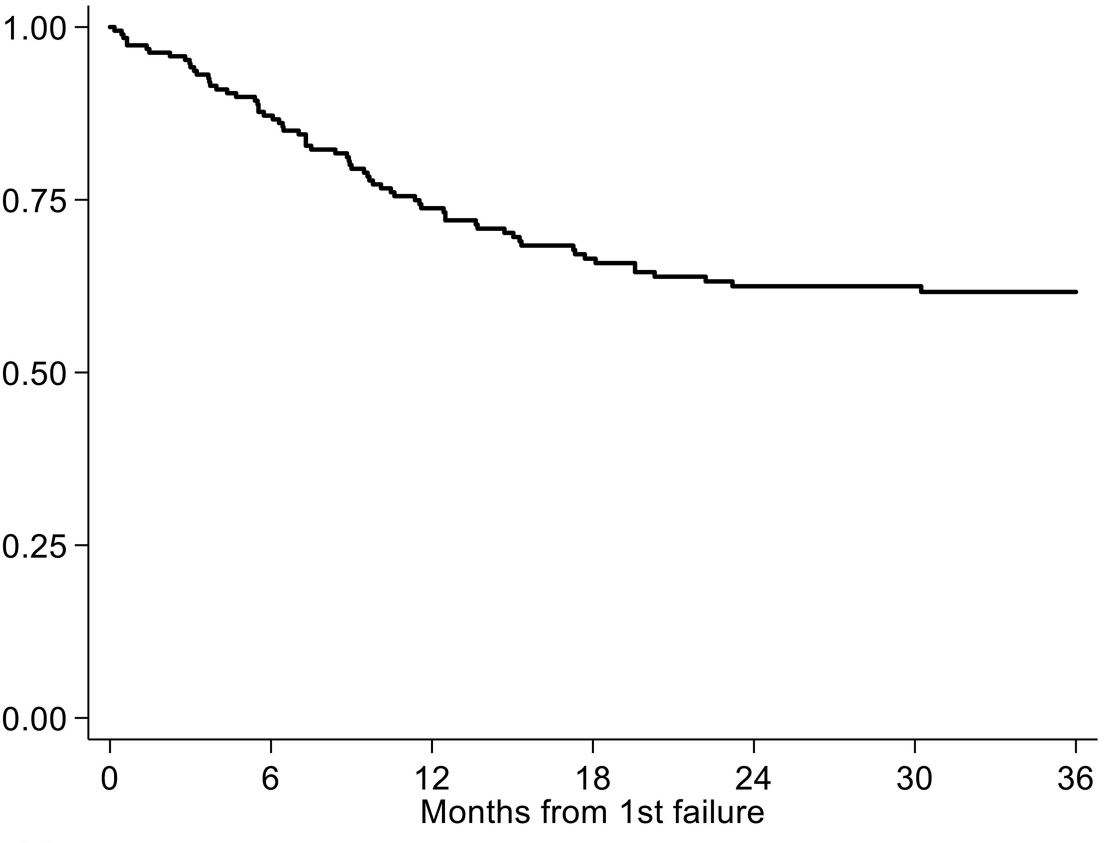

PMBCL pts enrolled in CAR T SIE study until Feb 2026
N=96
2 patients leukapheresed not infused due to PD
7 pts excluded (missing data of CAR T infusion date n=3 or first line failure date n=4)
N=87
Eligible for the study
3 pts excluded from landmark analysis due to death in 6 months from first line failure, 2 pts censored
N=82
Included in the landmark analysis
PMBCL pts enrolled in REPRIME study, N=111
7 pts excluded due to missing data (date of first line failure n=3, date of death n=4)
N=104
Eligible for the study
23 pts excluded from landmark analysis due to death in 6 months from first line failure, 2 patient censored
N=79
Included in the landmark analysis

Figure 2

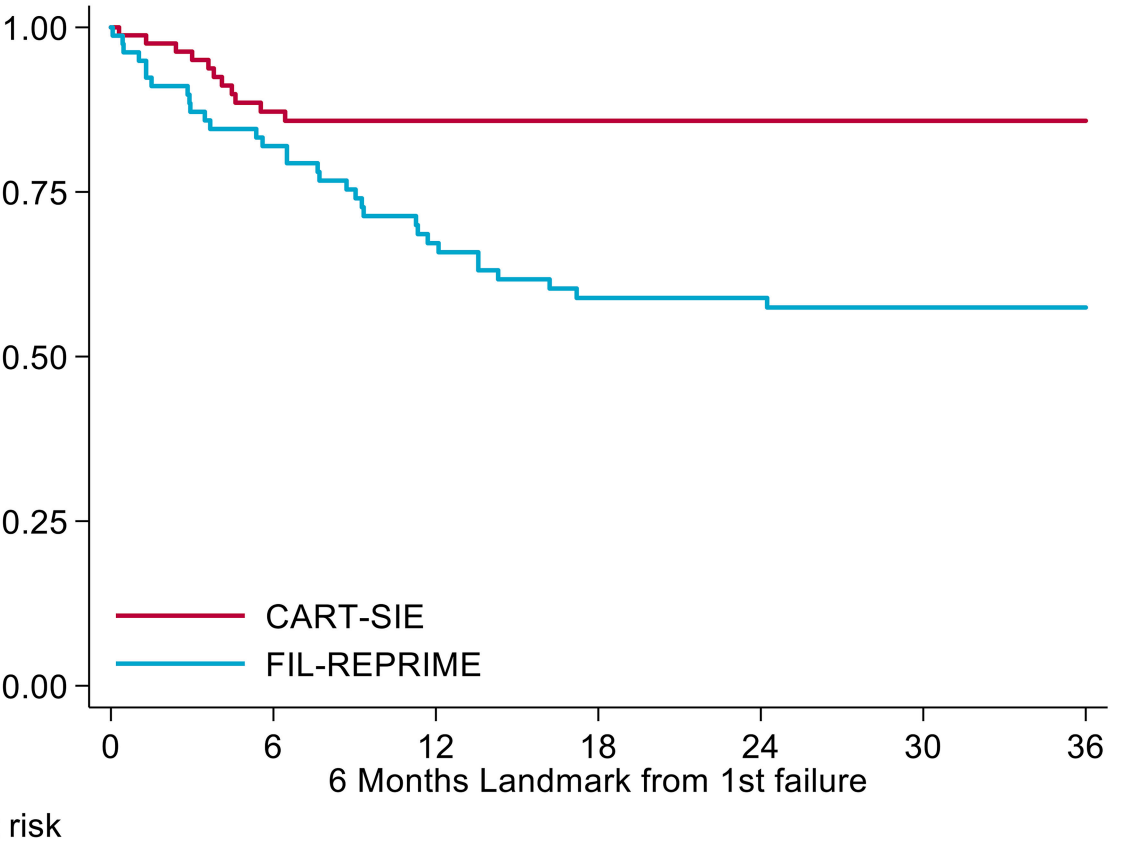
A



Number at risk

	189	161	127	103	89	77	65

B

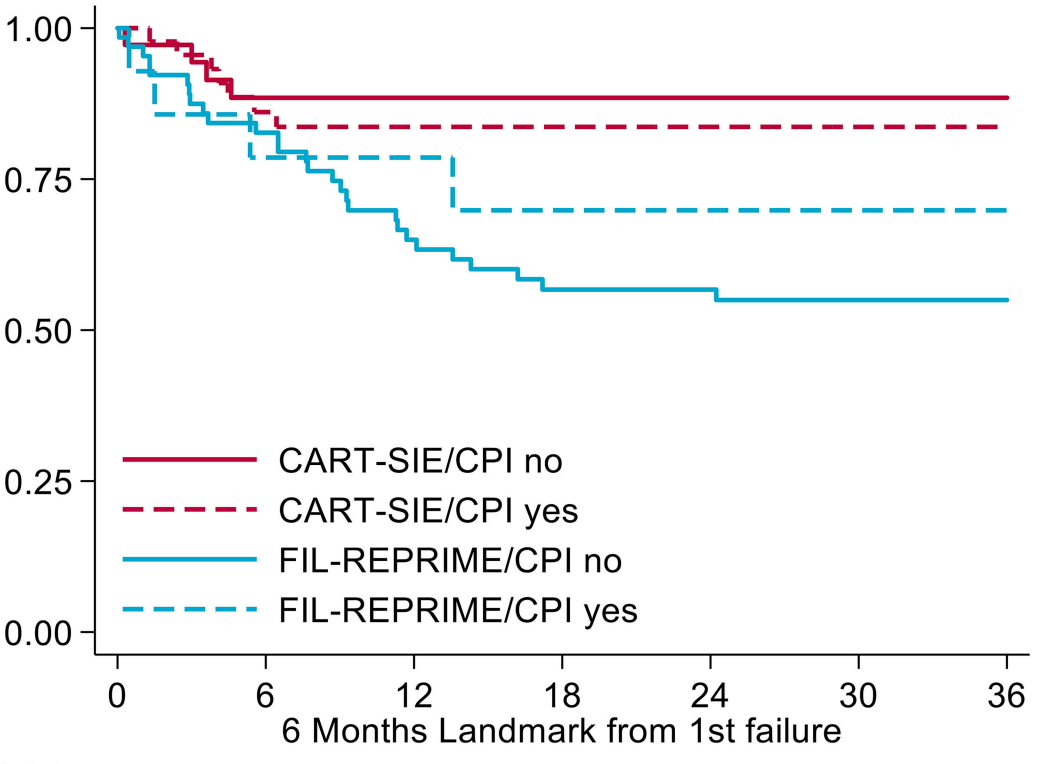


Number at risk

CART-SIE	82	64	54	48	36	28	27
FIL-REPRIME	79	63	49	41	41	37	36

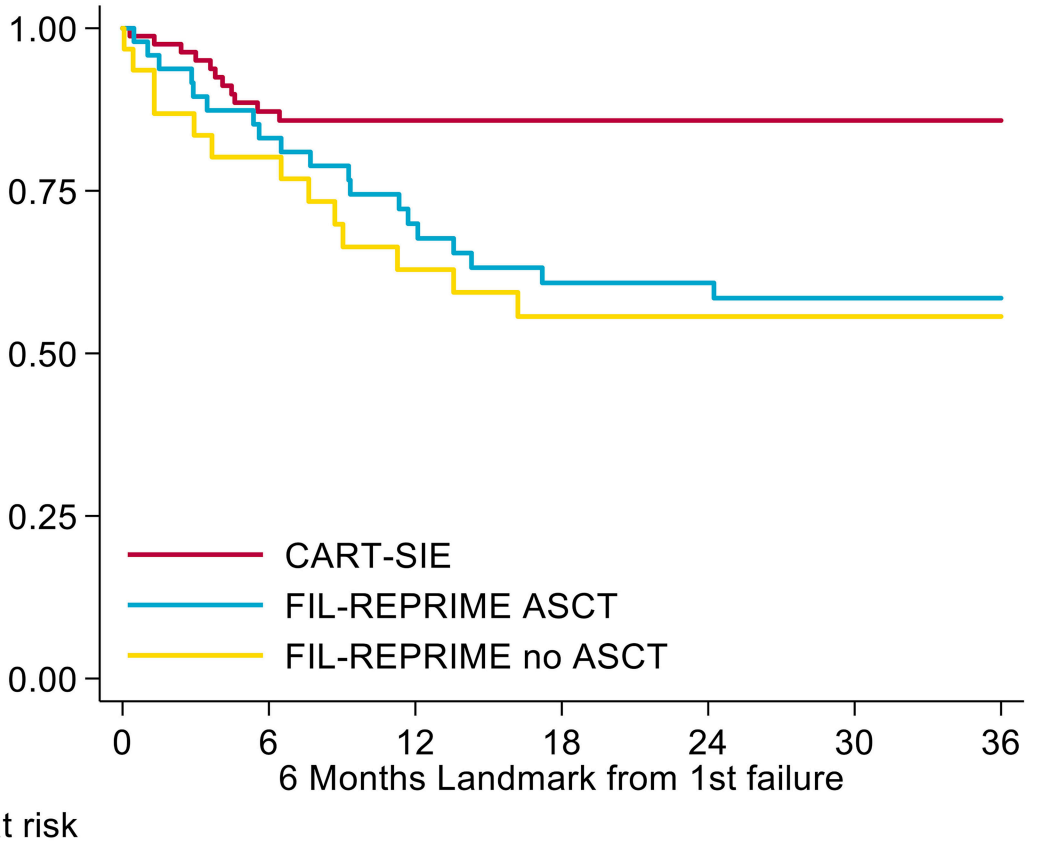
Figure 3

A



Number at risk							
CART-SIE/CPI no	36	29	23	20	16	15	14
CART-SIE/CPI yes	46	35	31	28	20	13	13
FIL-REPRIME/CPI no	65	52	40	33	33	30	29
FIL-REPRIME/CPI yes	14	11	9	8	8	7	7

B



Number at risk							
CART-SIE	82	64	54	48	36	28	27
FIL-REPRIME ASCT	48	39	31	26	26	23	23
FIL-REPRIME no ASCT	31	24	18	15	15	14	13

Supplementary Table 1. Comparison of the baseline characteristics of patients included in and excluded from the landmark analysis.

	Excluded N=30(%)	**Not Excluded N=161(%)**
CAR T Cohort	5	82
REPRIME Cohort	25	79
Primary Refractory	10 (33)	80 (50)
Deaths	26 (90)	48 (13)
Death due to Lymphoma	20 (67)	38 (24)
Death due to Toxicity	3 (10)	5 (17)

Supplementary Table 2. Comparison between patients treated with ASCT in REPRIME study and patients treated with CAR T-cells

	CART-SIE N=87(%)	**FIL-REPRIME N=51(%)**
Age at diagnosis, years median (IQR)	33 (26-41)	30 (26-38)
Primary refractory (PFS ≤ 6 months)	44 (51)	24(47)
ASCT	17 (19)	51(100)
CPI	51 (59)	6 (12)
Deaths	15 (17)	21 (41)