REGULAR ARTICLE

blood advances

Efficacy of checkpoint inhibition after CAR-T failure in aggressive B-cell lymphomas: outcomes from 15 US institutions

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Key Points

- In this analysis, checkpoint inhibitor therapy after CAR-T failure resulted in an overall response rate of 19% and median PFS of 54 days.
- Patients with primary mediastinal B-cell lymphoma and with late relapse after CAR-T had improved outcomes to checkpoint inhibitor therapy.

Checkpoint inhibitor (CPI) therapy with anti–PD-1 antibodies has been associated with mixed outcomes in small cohorts of patients with relapsed aggressive B-cell lymphomas after CAR-T failure. To define CPI therapy efficacy more definitively in this population, we retrospectively evaluated clinical outcomes in a large cohort of 96 patients with aggressive B-cell lymphomas receiving CPI therapy after CAR-T failure across 15 US academic centers. Most patients (53%) had diffuse large B-cell lymphoma, were treated with axicabtagene ciloleucel (53%), relapsed early (≤180 days) after CAR-T (83%), and received pembrolizumab (49%) or nivolumab (43%). CPI therapy was associated with an overall response rate of 19% and a complete response rate of 10%. Median duration of response was 221 days. Median progression-free survival (PFS) and overall survival (OS) were 54 and 159 days, respectively. Outcomes to CPI therapy were significantly improved in patients with primary mediastinal B-cell lymphoma. PFS (128 vs 51 days) and OS (387 vs 131 days) were significantly longer in patients with late (>180 days) vs early (≤180 days) relapse after CAR-T. Grade ≥3 adverse events occurred in 19% of patients treated with CPI. Most patients (83%) died, commonly because of progressive disease. Only 5% had durable responses to CPI therapy. In the largest cohort of patients with aggressive B-cell lymphoma treated with CPI therapy after CAR-T relapse, our results reveal poor outcomes, particularly among those relapsing early after CAR-T. In conclusion, CPI therapy is not an effective salvage strategy for most patients after CAR-T, where alternative approaches are needed to improve post–CAR-T outcomes.

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Data are available on request from the corresponding author, Justin Kline (jkline@medicine.bsd.uchicago.edu).

The full-text version of this article contains a data supplement.

Introduction

Chimeric antigen receptor (CAR) T cells are currently indicated for several subtypes of relapsed and refractory aggressive B-cell lymphomas, including in the first or subsequent relapse of diffuse large B-cell lymphoma (DLBCL).[1-5] For such patients, CAR T-cell therapy (CAR-T) can elicit durable remissions in 30% to 40% of patients,[6] which is a remarkable achievement for this population with historically poor outcomes. However, most patients will relapse after CAR-T and have a dismal prognosis, with a median overall survival (OS) of <6 months.[7,8] Thus, there is a pressing need to elucidate mechanisms underlying resistance to CAR-T to improve patient outcomes.

It has been posited that CAR-T failure, at least in part, may be related to repeated CAR stimulation in the lymphoma microenvironment (LME), leading to chronic CAR T-cell activation and ultimately a dysfunctional T-cell state known as exhaustion.[9-12] In support of this hypothesis is the observation that inhibitory checkpoint receptors, programmed cell death protein 1 (PD-1) and programmed cell death ligand 1 (PD-L1), are frequently upregulated on CAR T cells in the blood and LME in relapsing patients,[13,14] as well as the lower response rates to CAR-T seen in patients with higher baseline PD-L1 expression in the LME.[2,15,16] Targeting the PD-1/PD-L1 axis with checkpoint inhibitor (CPI) therapy with the goal of reversing the exhausted CAR-T state appeared promising in preclinical studies[17,18] and in early case reports in humans,[19,20] leading to expanded studies. In a prospective trial, 12 patients with B-cell lymphomas that had relapsed after CAR-T were administered pembrolizumab with an overall response rate (ORR) of 25% and evidence of increased CAR-T expansion and decreased expression of markers associated with exhaustion in some responding patients.[21] In addition, retrospective studies that included small cohorts of relapsed or refractory patients receiving CAR-T reported higher ORRs of 46% to 60% after CPI therapy, with median progression-free survival (PFS) and OS of 88 and 331 days, respectively.[7,22] However, toxicities from CPI therapy given in this context, including immune-related adverse events (AEs) and recurrent cytokine release syndrome (CRS), were concerning.[21,23]

Given the widely variable outcomes documented in the literature, we performed a large, retrospective, multicenter study across 15 US cancer centers of patients with aggressive B-cell lymphomas relapsing after or refractory to CAR-T and subsequently received CPI therapy. Clinical characteristics and outcomes data were collected and analyzed with the principal aims of describing response and survival rates after CPI therapy across aggressive B-cell lymphoma subtypes and CAR-T products and assessing CPI-related toxicities.

Methods

We conducted a multicenter retrospective study of adult (age ≥18) patients with a pathologically confirmed diagnosis of B-cell lymphoma who had received any CAR T-cell therapy before 1 January 2021, followed by subsequent receipt of any anti–PD-1 or anti–PD-L1 monoclonal antibody therapy. This study was approved by the institutional review board at each of the 15 participating centers and performed in accordance with the Declaration of Helsinki.

Clinical characteristics

Disease staging was reported per the Ann-Arbor staging classification. Performance status (PS) was standardized according to the Eastern Cooperative Oncology Group (ECOG) scale. Serum lactate dehydrogenase (LDH) was defined as elevated per individual institutional reference ranges. Cell of origin in DLBCL cases was assessed locally by immunohistochemistry according to the Hans criteria.[24] Double-expressor lymphoma (DEL) was defined in DLBCL cases as the immunohistochemistry presence of MYC (≥40% expression) and BCL2 (≥50% expression). Double-hit lymphoma (DHL) was defined as the presence of *MYC* as well as *BCL2* and/or *BCL6* gene rearrangements detected by fluorescence in situ hybridization. Immunomodulatory agents were defined as lenalidomide, thalidomide, and pomalidomide. The CRS and the immune effector cell-associated neurotoxicity syndrome (ICANS) were graded according to the American Society for Transplantation and Cellular Therapy consensus criteria.[25] CAR-T refractory disease was defined as the best response of either stable disease or progressive disease after CAR-T according to the Lymphoma Response to Immunomodulatory Therapy Criteria (LYRIC).[26] CAR-T relapsed disease was defined as the presence of clinical and/or radiographic evidence of disease progression after the achievement of an objective response (either a partial response [PR] or a complete response [CR]) using LYRIC. Responses to CPI therapy were also assessed by LYRIC. In all cases, responses to CAR-T and CPI were assessed by site investigators. AEs, except for CRS and ICANS, were graded by the Common Terminology Criteria for Adverse Events version 5.0.

End points and statistical methods

The primary end points of this study were ORR, CR rate, duration of response (DOR), PFS, and OS from the time of CPI initiation. DOR was defined as the time from the date of response (if PR or CR was achieved) to the date of disease progression/recurrence or death. PFS was defined as the time from CPI initiation to disease progression/recurrence or death from any cause. Surviving patients without progression/recurrence were censored at the last follow-up. OS was defined as the time from CPI initiation to death or last follow-up. Secondary analyses included univariable analyses of clinical characteristics associated with ORR, CR, PFS, and OS, as well as toxicities associated with CPI therapy. With respect to timing of relapse after CAR-T, early relapse was defined as ≤180 days and late relapse was defined as >180 days.

Baseline data were summarized with median and range for continuous variables and frequency distributions for categorical data. Logistic regression modeling was performed to examine characteristics associated with response rates. PFS and OS were estimated by the Kaplan-Meier method[27]; median time-to-event and 95% confidence intervals (CI) were obtained using the procedure described by Brookmeyer and Crowley.[28] Cox proportional hazards regression models were fit to identify prognostic factors for PFS and OS.[29]

Results

Patient and disease characteristics

Among the 96 eligible patients, 68% were male, and the median age was 56 years (range, 18-79) (Table 1). Most patients had

Table 1. Demographics and clinical characteristics at diagnosis and before CAR T-cell therapy

Characteristic	Total cohort (n = 96)
Median age, y (range)	56 (18-79)
Sex, n (%)	
Male	65 (67.7)
Lymphoma histology, n (%)	
DLBCL	51 (53.1)
Transformed lymphoma	20 (20.8)
HGBL	9 (9.4)
PMBCL	8 (8.3)
THRLBCL	6 (6.2)
Nontransformed follicular lymphoma	2 (2.1)
Cell of origin, n (%)	
GCB	39 (55.6)
Non-GCB	31 (44.3)
Missing/unknown	26
DEL, n (%)	
Yes	28 (45.2)
No	34 (54.8)
Missing/unknown	34
DHL, n (%)	
Yes	16 (22.2)
No	56 (77.8)
Missing/unknown	24
ECOG PS, n (%)	
0	32 (40.5)
1	36 (45.6)
2	10 (12.7)
3	1 (1.3)
Missing/unknown	17
Ann-Arbor stage, n (%)	
I	2 (2.2)
II	14 (15.1)
III	22 (23.7)
IV	55 (59.1)
Missing/unknown	3
B symptoms, n (%)	
Yes	38 (46.9)
No	43 (53.1)
Missing/unknown	15
Extranodal disease, n (%)	
No	28 (30.4)
Yes, only 1 site	38 (41.3)
Yes, >1 site	26 (28.3)
Missing/unknown	4
LDH > upper limit of normal, n (%)	
Yes	51 (75.0)
No	17 (25.0)
Missing/unknown	28
CNS involvement present at diagnosis, n (%)	
Yes	6 (6.5)
No	87 (93.5)
Missing/unknown	3
R-IPI score, n (%)	
1	18 (25.4)
2	17 (23.9)
3	23 (32.4)
4	11 (15.5)
5	2 (2.8)
Missing/unknown	25
Treatment received before CAR-T	
Median lines of therapy before CAR-T, n (range)	3 (1-10)
Primary refractory disease, n (%)	48 (50)
Previous radiation therapy, n (%)	35 (36.5)
Previous transplant, n (%)	26 (27.1)
Previous immunomodulatory agent therapy, n (%)	16 (16.7)
Previous BTK inhibitor therapy, n (%)	11 (11.5)
Previous CPI therapy, n (%)	7 (7.3)

BTK, Bruton's tyrosine kinase; GCB, germinal center B-cell; R-IPI, Revised International Prognostic Index.

DLBCL (53%); 56% of DLBCLs were germinal center cell of origin and 44% were nongerminal center cell of origin; 45% were DEL, and 22% were DHL. The remainder of patients had transformed lymphomas (21%), high-grade B-cell lymphoma not otherwise specified (HGBL) (9%), primary mediastinal B-cell lymphoma (PMBCL) (8%), T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL) (6%), and grade 3B nontransformed follicular lymphoma (2%). PD-L1 immunohistochemical staining on lymphoma tissue before receipt of CAR-T was available for 10 patients, so it was not further evaluated in this study.

At initial diagnosis, ECOG PS was 0 to 1 in 96% of patients, 83% had advanced-stage (III/IV) disease, 47% had B symptoms, 75% had an elevated serum LDH, 70% had 1 or more sites of extranodal disease, 50% had primary refractory disease, and 6% had central nervous system (CNS) involvement at diagnosis. The revised (R)-International Prognostic Index score was poor risk (3-5) in 51% of patients.

Before CAR-T, patients received a median of 3 lines of therapy (range, 1-10), including 37% with previous radiation therapy, 27% with previous autologous or allogeneic transplantation, 17% with previous immunomodulatory agent (IMID) therapy, 12% with previous Bruton's tyrosine kinase inhibitor therapy, and 7% with previous CPI therapy (Table 1).

CAR-T and relapse characteristics

Most patients received axicabtagene ciloleucel (axi-cel, 53%), followed by tisagenlecleucel (tisa-cel, 26%) and lisocabtagene maraleucel (liso-cel, 19%). There was no significant difference in the

distribution of CAR-T product types received based on lymphoma histology ($P = .78$). The median time from diagnosis to receipt of CAR-T was 453 days (range, 91-3762). Sixty-nine percent of patients received bridging therapy before CAR-T (Table 2). ORR to CAR-T was 58% (26% CR). Forty-two percent of patients were refractory to CAR-T, and the median time to recurrence after CAR-T was 84 days (range, 4-624; 95% CI, 76-93). The median DOR with CAR-T was 65 days (95% CI 58-90). After CAR-T, 83% of patients experienced an early relapse (≤180 days), and 15% of patients experienced a late relapse (>180 days).

Table 2. CAR-T treatment characteristics and relapsed disease features after CAR-T

Characteristic	Total cohort (n = 96)
CAR T-cell product administered, n (%)	
Axicabtagene ciloleucel	51 (53.1)
Tisagenlecleucel	25 (26.0)
Lisocabtagene maraleucel	18 (18.8)
Other	2 (2.1)
Receipt of any bridging therapy before CAR-T, n (%)	66 (68.8)
Receipt of bridging radiation therapy before CAR-T, n (%)	3 (3.1)
Response rates, n (%)	
ORR	56 (58.3)
CR	25 (26.0)
Median time to recurrence after CAR-T, d (range)	84 (4-624)
Timing of relapse after CAR-T, n (%)	
Early relapse (≤180 d)	80 (83.3)
Late relapse (>180 d)	14 (14.6)
No relapse	2 (2.1)
Clinical features at relapse after CAR-T	
ECOG PS, n (%)	
0	22 (24.2)
1	53 (58.2)
2	11 (12.1)
3	4 (4.4)
4	1 (1.1)
Missing/unknown	5
Ann-Arbor Stage, n (%)	
I	6 (6.3)
II	18 (18.9)
III	11 (11.6)
IV	60 (63.2)
Missing/unknown	1
Extranodal disease, n (%)	
No	23 (24.2)
Yes, only 1 site	32 (33.7)
Yes, >1 site	40 (42.1)
Missing/unknown	1
Bulky disease present, n (%)	25 (26.0)
LDH > upper limit of normal, n (%)	53 (55.2)
CNS involvement present at relapse, n (%)	9 (9.4)

Clinical features at relapse after CAR-T included 82% of patients with ECOG PS 0 to 1, 75% with advanced-stage (III/IV) disease, 26% with bulky disease (any lesion ≥7 cm), 55% with elevated serum LDH, 42% with more than 1 extranodal site, and 9% with CNS involvement at the time of relapse (Table 2).

CPI therapy characteristics

Most patients received pembrolizumab (49%) or nivolumab (43%), followed by atezolizumab (6%) and other CPI agents (2%). The median time from CAR-T relapse to the first CPI dose was 34 days (range, 0-420). A median of 3 CPI doses were administered (range, 1-41). A total of 28 patients (29%) received other therapies concurrently with CPI, most commonly other monoclonal antibodies (n = 12) and lenalidomide (n = 4). Other coadministered therapies included ibrutinib, venetoclax, and PI3K inhibitors. There were no significant differences between patients who received or did not receive concurrent therapeutics with CPI based on age, ECOG PS, disease stage, presence of extranodal disease, LDH level, or history of CNS involvement.

Response and survival outcomes

The ORR to CPI therapy among the entire cohort was 19% (CR = 10%), with a median DOR of 221 days (95% CI 84-NR days) (Table 3). The median follow-up time after CPI initiation was 152 days (range, 7-1333). The median PFS and OS for the entire cohort from the time of CPI initiation were 54 days (95% CI, 48-76) and 159 days (95% CI, 123-265), respectively (Figure 1). The median OS from the time of CAR-T receipt was 391 days (95% CI, 303-500) for the entire cohort.

ORR to CPI therapy was 12% (CR = 8%) in the DLBCL cohort, with an ORR of 9% in patients with early relapse vs 20% in patients relapsing late after CAR-T ($P = .48$). In the univariable analysis, the ORR to CPI therapy was significantly higher in patients with PMBCL at 63% (OR, 11.7; 95% CI, 2.31-70.6; $P = .004$) compared with other histologies (supplemental Table 1). In addition, the ORR to CPI therapy was significantly inferior in patients who had received IMIDs before CAR-T, with no patients with IMID exposure responding to CPI vs 24% in those without exposure ($P = .035$). There were no differences in ORR for other clinical characteristics in the entire cohort, including early (16%) vs late (38%) relapse after CAR-T ($P = .072$), concurrent therapeutics (21%) vs no concurrent therapeutics (18%) administered with CPI ($P = .73$), or by CAR-T or CPI product administered. There were also no differences in ORR by cell of origin, DEL, or DHL. There were no statistically significant differences in CR rates for any clinical characteristics.

PFS after CPI initiation was significantly longer in patients with PMBCL (hazard ratio [HR], 0.27; 95% CI, 0.11-0.69; $P = .006$) (Figure 2A), as well as in patients with late relapse after CAR-T (HR, 0.41; 95% CI, 0.21-0.78; $P = .006$) (Figure 2B), with a median PFS of 51 days for early relapse vs 128 days for late relapse. In addition, patients who had received IMIDs before CAR-T had an inferior PFS (HR, 1.85; 95% CI, 1.06-3.23; $P = .03$) (Table 4). No other characteristics were associated with PFS in the univariable analysis, including use of concurrent therapies with CPI or the type of CAR-T product received. In a combined cohort of patients with DLBCL and HGBL, median PFS was significantly

Table 3. Response rates, DOR, and survival outcomes for the entire cohort and by histology

Outcome	Entire cohort (N = 96)	DLBCL (N = 51)	HGBL (N = 9)	PMBCL (N = 8)	THRLBCL (N = 6)	Transformed lymphomas (N = 20)
ORR, %	18.8	11.8	22.2	62.5	33.3	10
CR, %	10.4	7.8	11.1	25	16.7	5
Median DOR, d (95% CI)	221 (84, -)	226 (56, -)	569 (83, -)	221 (221, -)	176 (84, -)	478 (88, -)
Median PFS, d (95% CI)	54 (48-76)	55 (48-78)	42 (28, -)	157 (149, -)	38 (29, -)	48 (34-98)
Median OS, d (95% CI)	159 (123-265)	142 (108-333)	351 (159, -)	244 (151, -)	350 (42, -)	92 (74-201)

improved in patients who received tisa-cel (78 days) and liso-cel (64 days) as compared with those who received axi-cel (41 days; $P = .006$) (supplemental Figure 1).

OS after CPI initiation was superior in patients with late relapse after CAR-T (HR, 0.38; 95% CI, 0.18-0.79; $P = .010$), with a median OS of 131 days for early relapse vs 387 days for late relapse (Figure 3A). OS was also superior in patients who received concurrent therapies with CPI (HR, 0.56; 95% CI, 0.34-0.92; $P = .022$), with a median OS of 362 days with concurrent therapies vs 113 days without (Figure 3B). In the univariable analysis, OS was inferior in patients with grade 3 to 4 ICANS during CAR-T (HR, 2.13; 95% CI, 1.14-3.97; $P = .01$) as well as in patients who had received IMIDs before CAR-T (HR, 1.76; 95% CI, 1.01-3.08; $P = .047$) (Table 4).

A total of 80 patients (83%) died during the follow-up period, predominantly because of progressive disease (n = 61/80, 76%). Of the 16 patients who were alive at the end of the follow-up period, 5 patients (5%) had durable responses to CPI monotherapy, with a median survival of 947 days (range, 810-1201); 4 of these patients responded to CAR-T (2 CR, 2 PR, and 1 SD), and 3 had late relapses after CAR-T. The remainder received other therapies, followed by allogeneic transplantation (n = 6), autologous transplantation (n = 1), retreatment with CPI (n = 1), or were enrolled on therapeutic clinical trials (n = 3).

CPI-related toxicities

Any-grade AEs related to CPI therapy occurred in 37% of patients, including 19% with grade 3 or higher AEs, which included cytopenias, infections, pneumonitis, colitis, and hepatotoxicity. There were 2 grade 5 AEs deemed related to CPI therapy (pneumonitis and thromboembolism). After initiation of CPI therapy, recurrent CRS and ICANS occurred in 2 patients (grade 2 and grade 4) and 1 patient (grade 1), respectively. Permanent discontinuation of CPI therapy occurred in 9% of patients because of AEs.

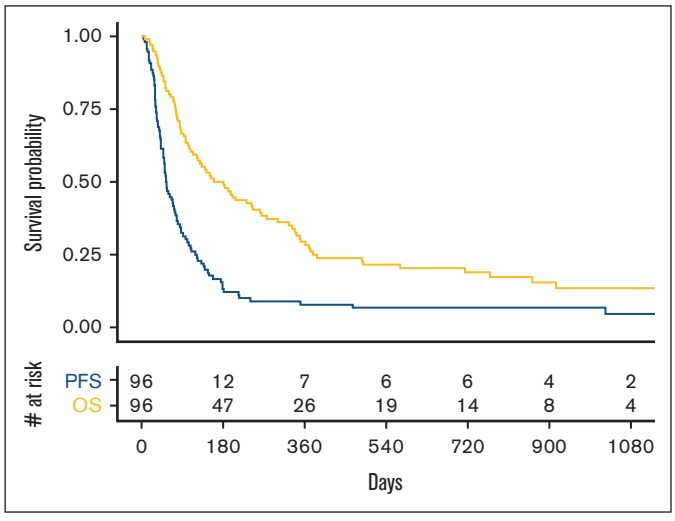

Figure 1. Median PFS and OS in the full cohort.

Discussion

In this real-world, multicenter cohort of 96 patients with aggressive B-cell lymphomas treated with CPI therapy after CAR-T relapse, the largest cohort described to date, response rates and median survival were overall very poor, with a median OS of only 5.2 months. Patients with early relapse after CAR-T had particularly dismal survival despite treatment with CPI therapy, consistent with prior observations.[8] Although our analysis identified several patient subgroups with relatively improved outcomes, a consistent benefit with CPI therapy in the post–CAR-T setting was not demonstrated, and very few durable responses to CPI monotherapy were observed.

Our results provide more definitive confirmation of the poor outcomes observed with CPI therapy in smaller cohorts of patients with relapsed lymphomas after CAR-T. In a retrospective cohort of 23 patients who received CPI after CAR-T relapse, the ORR was 32% (CR, 23%), and PFS and OS were 2.7 and 5.2 months, respectively.[30] Although the ORR to CPI therapy in this study was encouraging, the very short PFS and OS suggested that responses were typically not durable. In 2 additional retrospective studies that each included 10 patients who received CPI therapy after CAR-T relapse, an ORR of 20% and a median PFS of 50 days were reported,[31,32] which is similar to our findings. In fact, the survival outcomes to CPI therapy described above are similar to the median OS of ~5 to 6 months reported in larger retrospective cohorts of patients who received a variety of therapies after CAR-T failure,[7,8,33] suggesting that CPI therapy has limited efficacy in this setting.

Furthermore, most relapses after CAR-T in patients with aggressive B-cell lymphoma occur early, often within several months after the procedure. Survival outcomes among these patients are particularly poor, with a median OS of <2 months, and a significant proportion receive no additional therapy because of poor PS and/or cytopenias.[8,34] Our results indicate that CPI treatment does little to affect this fate. In contrast, late relapses after CAR-T (>6 months), albeit less common, have been associated with better outcomes,[35] seemingly independent of the type of subsequent therapy received. This also appeared to be the case among patients who were treated with CPI in our analysis, where a few achieved long-term

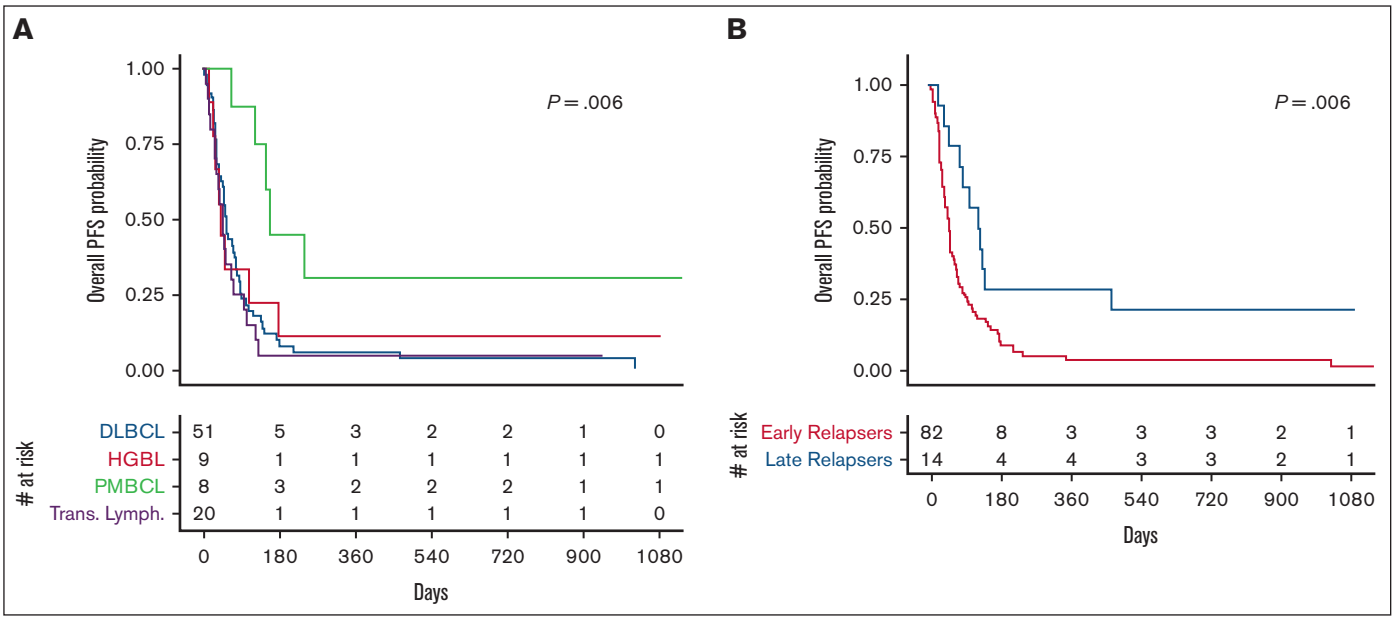

Figure 2. Stratified progression-free survival. PFS after CPI initiation stratified by disease histology (A) and early vs late relapse after CAR-T (B).

survival. Rather than a particular effectiveness of CPI therapy in this context, we suspect this may be because of different disease biology in B-cell lymphomas that relapse late after CAR-T.

In contrast to the overall population of aggressive B-cell lymphomas treated with CPI therapy after CAR-T relapse, patients with PMBCL had superior ORR and PFS, but not OS, an observation congruent with the demonstrated benefit of CPI in relapsed/refractory PMBCL in general.[36] Given that CAR-T is also particularly efficacious in relapsed/refractory PMBCL,[37] concurrent administrations of CPI and CAR-T in PMBCL have been investigated. A retrospective study of patients with relapsed PMBCL after axi-cel found no difference in PFS or OS for the 19 patients who received CPI therapy before CAR-T compared with those who did not.[37] However, 3 of the 4 patients (75%) who received CPI after axi-cel did achieve an objective response, comparable to our results. The finding of superior ORR and PFS in patients with PMBCL in our study suggests that CPI monotherapy is a reasonable option in the post–CAR-T relapse setting, although it is important to note that only 8 patients were included in this subgroup. The combination of nivolumab and brentuximab vedotin, which led to an ORR of 73% and a 6-month PFS of 64% in patients with relapsed/refractory PMBCL, may be a particularly attractive treatment strategy in the post–CAR-T relapse setting.[38]

Subgroup analysis of high-risk populations in this study did not reveal the benefit of CPI, including for older patients, those with primary refractory disease, DHL, or the presence of bulky or extranodal disease. Outcomes to CPI therapy after CAR-T relapse in patients with DLBCL were particularly dismal, with an ORR of only 12%, nearly identical to the reported ORR of 14% among 36 patients with aggressive B-cell lymphomas who relapsed after CAR-T and enrolled on a randomized phase II trial of nivolumab with or without the anti-CD27 antibody, varlilumab.[39] This result is perhaps not surprising, given the poor efficacy of anti–PD-1 therapy in patients with relapsed/refractory DLBCL in general.[40] THRLBCL was a disease subtype of particular interest, given our previous finding of potential inherent resistance to CAR-T and very high PD-L1 expression in the LME.[13,41] However, only 2 of 6 patients with THRLBCL relapsed after CAR-T responded to CPI therapy (1 PR, 1 CR).

Concurrent administration of additional therapeutics with CPI therapy did confer a significant OS benefit without any improvement in response rates or PFS. We hypothesize that this effect may have been driven by the efficacy of partner therapies rather than an additive or synergistic effect when coadministered with CPI. However, given the small numbers of patients and patient characteristics such as PS as likely confounders, this is a speculative conclusion. We additionally found that a history of exposure to IMIDs before CAR-T conferred worse survival compared with patients without IMID exposure. Conclusions about this finding are also limited by the small subgroup size (n = 16) and the likely presence of confounding variables; however, it is plausible that exposure to certain agents before apheresis may hinder subsequent CAR-T production and/or expansion, as has been described with bendamustine.[42]

Although not available in our cohort, CAR-T expansion has been described after CPI therapy, including in a retrospective study that found that CPI therapy was associated with peripheral blood CAR T-cell expansion in 2 of 12 patients.[30] Moreover, in a prospective study of pembrolizumab given after CAR-T relapse in 12 patients with B-cell lymphoma, CAR T cells were shown to re-expand in the peripheral blood of 10 patients, yet only 3 of the 12 patients achieved an objective response to pembrolizumab.[21] This result suggests that CAR T-cell re-expansion after CPI therapy is insufficient to mediate disease control in most patients, or alternatively, that objective responses to CPI occurring in the post–CAR-T relapse setting are driven by endogenous (non-CAR) T cells,

Table 4. Univariable analyses of clinical features with PFS and OS

Characteristics	PFS			OS		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age, y						
Age <60	–	–	Ref	–	–	Ref
Age ≥60	1.03	0.67-1.57	.90	0.84	0.53-1.31	.44
Histology						
DLBCL	–	–	Ref	–	–	Ref
HGBL	0.84	0.40-1.79	.65	0.61	0.26-1.44	.26
FL	0.56	0.13-2.30	.42	1.04	0.25-4.30	.96
PMBCL	0.27	0.11-0.69	.006	0.53	0.21-1.34	.18
Transformed lymphomas	1.22	0.72-2.07	.47	1.52	0.87-2.64	.14
THRLBCL	0.91	0.39-2.13	.82	0.57	0.20-1.61	.29
Non-GCB cell of origin	0.73	0.44-1.20	.21	0.97	0.57-1.64	.90
DEL	1.12	0.66-1.90	.66	1.27	0.72-2.24	.42
DHL	1.03	0.57-1.87	.91	1.05	0.56-1.99	.87
History of primary refractory disease	1.09	0.72-1.65	.70	1.20	0.78-1.87	.41
Previous transplant	0.65	0.40-1.04	.070	0.72	0.44-1.18	.19
Receipt of CPI before CAR-T	0.90	0.39-2.06	.80	1.17	0.51-2.71	.71
Receipt of BTK inhibitors before CAR-T	1.39	0.73-2.64	.32	1.44	0.74-2.81	.28
Receipt of immunomodulatory agents before CAR-T	1.85	1.06-3.23	.030	1.76	1.01-3.08	.047
Receipt of bridging therapy before CAR-T	1.06	0.68-1.65	.80	1.36	0.84-2.20	.21
CAR-T product administered						
Axicabtagene ciloleucel	–	–	Ref	–	–	Ref
Lisocabtagene maraleucel	0.57	0.32-1.04	.065	0.73	0.40-1.33	.30
Tisagenlecleucel	0.67	0.41-1.09	.11	0.73	0.43-1.24	.24
Other	0.57	0.14-2.35	.43	0.65	0.16-2.69	.55
Grade of CRS during CAR-T						
No CRS	–	–	Ref	–	–	Ref
Grade 1-2	1.30	0.82-2.09	.27	1.17	0.71-1.92	.54
Grade 3-4	2.13	0.94-4.80	.069	1.65	0.73-3.71	.23
Grade of ICANS during CAR-T						
No ICANS	–	–	Ref	–	–	Ref
Grade 1-2	1.09	0.63-1.90	.76	0.71	0.39-1.31	.27
Grade 3-4	1.36	0.74-2.50	.33	2.13	1.14-3.97	.018
Relapse type						
Early relapse	–	–	Ref	–	–	Ref
Late relapse	0.41	0.21-0.78	.006	0.38	0.18-0.79	.010
Stage at relapse after CAR-T						
I	–	–	Ref	–	–	Ref
II	1.43	0.52-3.90	.49	1.18	0.37-3.70	.78
III	2.16	0.74-6.24	.16	1.52	0.48-4.87	.48
IV	1.77	0.71-4.43	.22	2.07	0.75-5.74	.16
Extranodal disease at relapse after CAR-T						
No	–	–	Ref	–	–	Ref
Yes, only 1 site	1.12	0.64-1.96	.70	1.28	0.71-2.32	.42
Yes, > 1 site	1.04	0.61-1.77	.89	1.20	0.68-2.13	.53
Bulky disease at relapse after CAR-T	1.35	0.84-2.18	.22	1.48	0.91-2.42	.11
CNS involvement at time of relapse after CAR-T	1.00	0.50-2.00	.99	0.83	0.91-3.68	.092

BTK, Bruton's tyrosine kinase; FL, follicular lymphoma; GCB, germinal center B-cell; Ref, reference.

Table 4 (continued)

Characteristics	PFS			OS		
	HR	95% CI	*P* value	HR	95% CI	*P* value
CPI type received						
Atezolizumab	–	–	Ref	–	–	Ref
Nivolumab	0.95	0.40-2.25	.91	0.81	0.34-1.93	.63
Pembrolizumab	0.92	0.38-2.18	.84	0.85	0.36-2.02	.72
Other	2.04	0.41-10.20	.38	1.55	0.31-7.79	.59
Concurrent therapeutics with CPI	0.74	0.47-1.18	.20	0.56	0.34-0.92	.022
Grade ≥3 AEs owing to CPI	0.90	0.54-1.51	.69	1.47	0.86-2.53	.16

BTK, Bruton's tyrosine kinase; FL, follicular lymphoma; GCB, germinal center B-cell; Ref, reference.

particularly given that few CAR T cells persist in most patients by the time CPI therapy is administered. The latter hypothesis is also supported by the objective response rates to PD-1 blockade therapy we observed in patients with DLBCL and PMBCL after CAR-T relapse, which largely mirror those achieved with anti–PD-1 in patients with relapsed/refractory DLBCL (10%-12%) and PMBCL (45%-48%) in the non–CAR-T context.[36,40,43] In contrast, given that 4-1BB–driven CAR-T constructs, such as tisa-cel and liso-cel, have longer persistence as compared with CD28-driven axi-cel,[44] it is feasible that CPI therapy may be more effective in patients who received 4-1BB CAR-T constructs, which has been supported by a prospective clinical trial.[21] An exploratory analysis in our study of post-CPI PFS in a combined cohort of patients with DLBCL and HGBL did demonstrate superior PFS with tisa-cel and liso-cel as compared with axi-cel, although the absolute improvement in PFS was small.

Collectively, our results, in conjunction with these translational data, suggest that better understanding of CAR T-cell function is needed, as targeting of PD-1 and PD-L1 does not appear to meaningfully restore CAR-T–mediated cytotoxicity or improve tumor control in most patients. Emerging studies have demonstrated that polatuzumab vedotin, bispecific antibodies, and targeted agents such as Bruton's tyrosine kinase inhibitors result in better clinical responses in the post–CAR-T relapse setting as compared with CPI and traditional chemotherapy,[30,32,35] and investigations on how these agents affect CAR persistence and function are warranted.

Limitations of our study include its retrospective design and non-centralized assessment of clinical and disease-specific characteristics. The lack of available PD-1/PD-L1 staining data is a particular limitation, as we were unable to assess for a possible correlation between response to CPI therapy and PD-L1 expression in the LME. Although we were able to descriptively report response rates and survival times for specific subgroups, their often-small sizes may limit the generalizability of these findings. In addition, it is important to note that few patients had a poor ECOG PS at relapse after CAR-T. As such, there may be bias within this retrospective cohort with selection of fitter patients who survived long enough after CAR-T to initiate CPI therapy, which could skew the survival outcomes.

In conclusion, despite promising preclinical data and small case series suggesting that CPI therapy can "re-engage the CAR" after CAR-T relapse, our large retrospective cohort reveals poor survival

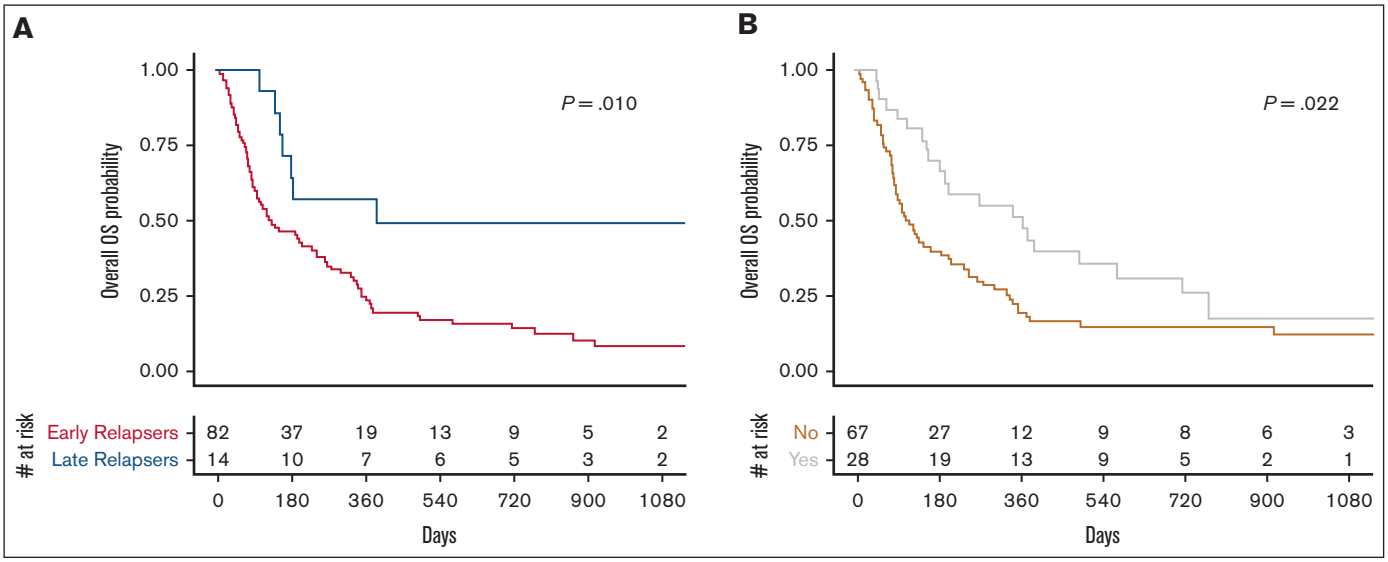

Figure 3. Stratified overall survival. OS after CPI initiation stratified by early vs late relapse after CAR-T (A) and concurrent therapy with CPI (B).

outcomes of most patients treated with CPI therapy for relapsed aggressive B-cell lymphomas. CPI monotherapy does not appear to be an effective salvage strategy for most patients with relapsed or refractory disease after CAR-T, and further studies are needed to determine if and how CAR-T cell function can be restored in this setting.

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Authorship

Contribution: A.M. and J.Y. designed the research; A.M., J.Y., N. Shukla, Y.C., and T.G.K. performed the statistical analysis and interpreted data; J.Y. and Y.C. made the figures; A.M., Y.C., N. Shukla, T.G.K., and J.K. wrote the manuscript; and N. Shukla, R.T., M.K.K., B.M.H., J.G., M.A.B., T.J.V., S.C., D.G., C.O., J.T.R., A.M.W., B.T.H., R.B., J.C.V.B., I.A.N., R.K., L.A.F., D.M.S., P.A.P., A.T., J.H.S., M.H., V.B., M.J.S., N. Singh, N.A., J.P.M., M.R.B., and P.A.R. collected data and revised the manuscript.

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