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Comparative efficacy of lisocabtagene maraleucel in the PILOT study *versus* second-line chemotherapy regimens in the real world

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Running head (47/50 characters including spaces): Liso-cel in PILOT vs 2L treatment in real world

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FFL and AK contributed to the study conception or design and to data interpretation; NG, AS, AC, and LIG contributed to data interpretation; JF and LP contributed to data analysis; and MDB contributed to data analysis and data interpretation. All authors contributed to writing of the manuscript.

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Abstract

This study assessed the comparative efficacy of lisocabtagene maraleucel (liso-cel) in PILOT (NCT03483103), an open-label, phase II study, versus conventional second-line (2L) chemotherapy regimens in the real world administered to patients with relapsed or refractory (R/R) large B-cell lymphoma (LBCL) who were not intended for hematopoietic stem cell transplantation (HSCT). The liso-cel–treated cohort (n=61) was based on patients who received liso-cel in the PILOT study. The conventional chemotherapy cohort included patients who met PILOT eligibility criteria and received conventional 2L chemotherapy in the real-world clinical setting (n=273). After using the trimmed stabilized inverse probability of treatment weighting method to balance cohorts according to baseline characteristics, there were statistically significant differences in all tested measures of efficacy. Compared with real-world conventional chemotherapy regimens, liso-cel demonstrated higher overall response rates (79.6% with liso-cel *vs.* 50.5% with conventional chemotherapy; relative risk [RR], 1.6; *P*<0.0001) and complete response rates (53.1% *vs.* 24.0%; RR, 2.2; *P*<0.0001), longer median duration of response (12.1 *vs.* 4.3 months; hazard ratio [HR], 0.40; *P*=0.0001), longer median event-free survival (7.0 *vs.* 2.8 months; HR, 0.43; *P*<0.0001), longer median progression-free survival (7.0 *vs.* 2.9 months; HR, 0.46; *P*<0.0001), and longer median overall survival (not reached *vs.* 12.6 months; HR, 0.58; *P*=0.0256). Results from analyses applying various additional statistical approaches consistently favored outcomes with liso-cel over real-world conventional chemotherapy regimens. These results reinforce the efficacy of liso-cel as 2L therapy for patients with R/R LBCL who are not intended for HSCT.

Introduction

Twenty to forty percent of patients with large B-cell lymphoma (LBCL) have relapsed or refractory (R/R) disease after first-line (1L) treatment with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) or polatuzumab plus R-CHOP.[1,2] Historically, salvage immunochemotherapy followed by high-dose chemotherapy and hematopoietic stem cell transplantation (HSCT) provided patients with R/R LBCL a chance for long-term remission. However, this treatment was limited to younger patients with excellent performance status and adequate organ function. Recently, two randomized trials showed superiority of chimeric antigen receptor (CAR) T-cell therapy over HSCT in patients who were considered as good candidates for HSCT.[3,4] Unfortunately, less than half of the patients are intended to receive HSCT upon failure of 1L therapy because of age, Eastern Cooperative Oncology Group performance status, organ function and/or comorbidities.[5,6] In patients for whom HSCT is not appropriate, outcomes are historically poor (median overall survival [OS] of 6 months) and treatment options are limited.[7,8] While new treatment options for second-line (2L) LBCL have recently emerged,[4,9-11] this patient population remains difficult to treat.

Lisocabtagene maraleucel (liso-cel) is an autologous, CD19-directed, 4-1BB CAR T-cell product. In PILOT (NCT03483103), an open-label, single-arm, multicenter, phase II study in patients with R/R LBCL who were not intended for HSCT, liso-cel demonstrated high response rates and durable responses, with a safety profile consistent with previous liso-cel studies.[12] Considering that no standard of care was defined for patients with R/R LBCL who were not intended for HSCT at the time of PILOT study initiation, no active comparator arm was included; however, understanding the comparative efficacy of liso-cel versus 2L treatments typically used in clinical practice remains relevant.

In this study, we assessed the comparative efficacy of liso-cel as reported in the PILOT study

versus an external control cohort of patients with R/R LBCL who received conventional 2L chemotherapy regimens in the real-world setting.

Methods

Patients and study cohorts

A full description of patients enrolled in the PILOT study has been published previously[12] and a brief description is provided in the ***Online Supplementary Methods***.

Two overlapping analysis cohorts from PILOT consisted of the liso-cel–treated efficacy analysis set (all patients who received liso-cel and had confirmed positron emission tomography–positive disease before liso-cel administration per independent review committee assessment in the primary analysis; hereafter referred to as the liso-cel–treated cohort), and the liso-cel–leukapheresed cohort (all patients who underwent leukapheresis for production of liso-cel). Three sequentially constructed conventional chemotherapy cohorts were derived from a harmonized dataset comprising multiple data sources collected retrospectively from COTA, Guardian Network, and clinical sites via electronic case report forms. Individual-level, deidentified data from data partners and sources representing a heterogeneous adult patient population with R/R LBCL across various academic and community clinical settings in the United States, Europe, and Japan were used. Intent to receive HSCT was not documented in the real-world data; therefore, prespecified criteria as used in the PILOT study[12] were applied in deriving the conventional chemotherapy cohorts. Three conventional chemotherapy cohorts were sequentially constructed as follows: the total conventional chemotherapy cohort before PILOT eligibility criteria were applied (patients with R/R LBCL after receiving therapy with an anthracycline and CD20-targeted agent), the conventional chemotherapy cohort (a subset of the total conventional chemotherapy cohort who met prespecified PILOT eligibility criteria[12]), and the conventional chemotherapy cohort after balancing (a subset of the conventional chemotherapy cohort who met prespecified PILOT eligibility criteria balanced to the baseline characteristics of the liso-cel–treated

cohorts) (***Online Supplementary Figure S1***). Index and data cutoff dates are provided in the ***Online Supplementary Appendix***.

Endpoints

The primary endpoint was overall response rate (ORR) with liso-cel versus conventional chemotherapy regimens.[13] Secondary endpoints were complete response (CR) rate, duration of response (DOR), event-free survival (EFS), progression-free survival (PFS), overall survival (OS), and 1L and 2L treatment patterns. Definitions for DOR, EFS, and PFS are provided in the ***Online Supplementary Methods***. Analyses for all endpoints other than OS were conducted with a 2-year follow-up limit to align with the duration of follow-up in PILOT; OS analyses were conducted without follow-up limitation to observe long-term survival in the real-world population and were reported for up to 48 months.

Statistical analysis

A sample size of 61 patients in the conventional chemotherapy cohort after balancing was estimated to provide >76% statistical power for the primary endpoint analysis of ORR, assuming an ORR of 70% for the liso-cel–treated cohort and ORR of 45% for the conventional chemotherapy cohort after balancing (one-sided 0.025 alpha level). Additional details regarding cohort balancing methods are provided in the ***Online Supplementary Methods***.

Study conduct

This study was conducted in accordance with the International Society for Pharmacoepidemiology Guidelines Good Pharmacoepidemiology Practices and the Declaration of Helsinki. The protocol, amendments, and patient informed consent forms for PILOT received appropriate approval by the institutional review board/independent ethics committee or other applicable review board as required by local law.

RESULTS

Patients

In the PILOT study, a total of 74 patients underwent leukapheresis (liso-cel–leukapheresed cohort), and 61 received liso-cel (liso-cel–treated cohort). Reasons for not receiving liso-cel after leukapheresis were death (n=5), no longer meeting eligibility criteria (n=4), and rapid clinical progression, positron emission tomography–negative disease after bridging therapy, and investigator decision (n=1 each). One additional patient who underwent leukapheresis received nonconforming product (one of the CD8 or CD4 cell components did not meet one of the requirements to be considered liso-cel but could be considered appropriate for infusion). Thirty-two (52%) patients in the liso-cel–treated cohort received bridging therapy. Baseline demographics and clinical characteristics for the liso-cel–treated cohort have been previously described.[12] Among the three conventional chemotherapy cohorts, a total of 601 patients were initially included in the total cohort before PILOT eligibility criteria were applied, of which 273 were included after application of the PILOT eligibility criteria but before balancing (hereafter referred to as the conventional chemotherapy cohort; ***Online Supplementary Figure S1***). Patients in the conventional chemotherapy cohort (n=273) had a median age of 74 years, 259 patients (95%) were diagnosed with diffuse LBCL not otherwise specified, 127 (47%) had an Eastern Cooperative Oncology Group performance status <2 (information was missing for 81 [30%]), and 164 (60%) were refractory to 1L therapy (**Table 1**). Additional baseline characteristics are shown in ***Online Supplementary Table S1***. In the conventional chemotherapy cohort, most patients (75%) were from the United States. Patients in the liso-cel and conventional chemotherapy cohorts were balanced by baseline demographics and disease characteristics. Based on a threshold of 0.2 for the pooled standardized mean difference, there were potentially important differences between the liso-cel and conventional chemotherapy cohort in disease stage and bulky disease; these differences were no longer present after balancing (***Online Supplementary Tables S2*** and ***S3***).

The median (range) follow-up time was 11.9 months (0.0–30.1) in the liso-cel–leukapheresed cohort, 12.3 months (1.2–26.5) in the liso-cel–treated cohort, and 9.0 months (0.4–24.0) in the conventional chemotherapy cohort (**Table 2**). In the liso-cel–leukapheresed cohort, 41/74 patients (55%) discontinued the study, while 28/61 patients (46%) discontinued in the liso-cel–treated cohort. The primary reason for discontinuation in both cohorts was death (26/74 [35%] and 20/61 [33%], respectively). In the conventional chemotherapy cohort, 140 patients (51%) discontinued the study, all due to death, when the 2-year follow-up limit was applied (***Online Supplementary Table S4***).

Efficacy outcomes

Endpoint analyses adjusted by trimmed stabilized inverse probability of treatment weighting (IPTW)

When comparing liso-cel with the conventional chemotherapy cohort after balancing, the primary endpoint of ORR was significantly higher in the liso-cel–treated cohort (79.6% *vs.* 50.5%, respectively; *P*<0.0001) (**Table 3**).

Results for the secondary endpoints also favored liso-cel treatment in comparisons between the liso-cel–treated cohort and the conventional chemotherapy cohort after balancing. The CR rate was significantly higher with liso-cel versus conventional chemotherapy (53.1% *vs.* 24.0%, respectively; *P*<0.0001). Among patients who achieved a response, DOR was significantly longer in the liso-cel–treated cohort compared with the conventional chemotherapy cohort after balancing (median DOR: 12.1 vs 4.3 months, respectively; *P*=0.0001) (**Table 3**). In time-to-event analyses, the median EFS (7.0 *vs.* 2.8 months, respectively; *P*<0.0001) (**Table 3**; **Figure 1A**) and median PFS (7.0 *vs.* 2.9 months, respectively; *P*<0.0001) (**Table 3**; **Figure 1B**) were also significantly longer compared with conventional chemotherapy regimens. The median OS was not reached with liso-cel compared with 12.6 months with conventional chemotherapy regimens (*P*=0.0256) (**Table 3**; **Figure 1C**).

In the sensitivity analysis using the liso-cel–leukapheresed cohort versus the conventional chemotherapy cohort after balancing, ORR was favorable with liso-cel versus conventional 2L chemotherapy regimens (65.7% *vs.* 50.4%, respectively; *P*=0.0116) (**Table 4**). CR rate was also favorable with liso-cel versus conventional 2L chemotherapy regimens (45.3% *vs.* 23.9%, respectively; *P*=0.0002) (**Table 4**). Both the median EFS (8.1 *vs.* 2.8 months, respectively; *P*<0.0001) and median PFS (8.1 *vs.* 2.8 months, respectively; *P*<0.0001) were significantly longer with liso-cel versus conventional chemotherapy regimens (**Table 4**; **Figures 2A** and **B**). The median OS was not reached with liso-cel versus 12.6 months with conventional chemotherapy regimens (*P*=0.0217) (**Table 4**; **Figure 2C**).

In the sensitivity analysis excluding patients who received intent-to-transplant therapy from the conventional chemotherapy cohorts, ORR was 81.1% in the liso-cel cohort (liso-cel–treated efficacy analysis set) versus 49.8% with conventional 2L chemotherapy regimens after balancing (*P*<0.0001) (***Online Supplementary Table S5***). CR rate at 53.2% was also higher with liso-cel versus 22.3% with conventional chemotherapy regimens after balancing (*P*<0.0001) (***Online Supplementary Table S5***).

Endpoint analyses using greedy nearest neighbor matching method

Efficacy results were consistent when using an additional statistical method to balance for baseline characteristics between cohorts. When comparing the liso-cel–treated cohort with the conventional chemotherapy cohort after balancing, the ORR was significantly higher with liso-cel (80.6% [95% confidence interval [CI]: 71.0–91.5] *vs.* 51.5% [95% CI: 42.8–61.9], respectively; relative risk, 1.6 [95% CI: 1.3–1.9]; *P*<0.0001). Similarly consistent results were also noted in CR rate (55.4% [95% CI: 44.1–69.6] with liso-cel *vs.* 25.5% [95% CI: 18.4–35.4] with conventional chemotherapy regimens; relative risk, 2.2 [95% CI: 1.5–3.2]; *P*<0.0001).

In the sensitivity analysis using the liso-cel–leukapheresed cohort versus the conventional chemotherapy cohort after balancing, both ORR (65.7% [95% CI: 55.7–77.6] *vs.* 51.0% [95% CI: 43.5–59.9], respectively; relative risk, 1.3 [95% CI: 1.0–1.6]; *P*=0.0252) and CR rate

(45.5% [95% CI: 35.5–58.5] *vs.* 25.6% [95% CI: 19.4–33.9], respectively; relative risk, 1.8 [95% CI: 1.3–2.5]; *P*=0.0013) were favorable with liso-cel versus conventional 2L chemotherapy regimens.

Unadjusted endpoint analyses

The unadjusted efficacy outcomes, without applying any statistical method to balance patients, showed favorable ORR and CR rate in the liso-cel–treated cohort and the liso-cel–leukapheresed cohort versus the conventional chemotherapy cohort (***Online Supplementary Tables S6*** and ***S7***). Significantly longer median EFS, PFS, and OS with liso-cel versus conventional chemotherapy regimens were also observed (***Online Supplementary Tables S6*** and ***S7*** and ***Online Supplementary Figures S2*** and ***S3***).

Treatment patterns

Most patients in the conventional chemotherapy cohorts before and after application of PILOT eligibility criteria received an anthracycline in 1L treatment, and the most common 1L regimen was R-CHOP (**Figure 3A** and **Figure 4A**); all other regimens were each received by <10% of the overall cohort. The most common conventional 2L chemotherapy regimens in the conventional chemotherapy cohort after application of PILOT eligibility criteria were rituximab plus ifosfamide, carboplatin, and etoposide (R-ICE; 15%), followed by bendamustine and rituximab (12%) and gemcitabine, oxaliplatin, and rituximab (11%); all other regimens were each received by ≤3% of patients in the cohort (**Figure 4B**).

DISCUSSION

In the open-label, phase II PILOT study, 2L treatment with liso-cel resulted in clinically significant and durable responses in patients with R/R LBCL not intended for HSCT, with high ORR (80%) and CR rate (54%), and a median DOR for patients who had a CR of 21.65 months.[12] To contextualize the results of the single-arm PILOT study and evaluate the comparative efficacy of liso-cel versus available conventional 2L chemotherapy regimens, an

external control cohort of patients treated in the real-world clinical setting was constructed to closely match the patient population in PILOT. After matching and adjusting for imbalances in baseline characteristics between the liso-cel and conventional chemotherapy cohorts, the primary efficacy endpoint of ORR, as well as the secondary endpoints of CR rate, DOR, EFS, PFS, and OS, significantly favored liso-cel over conventional 2L chemotherapy regimens. In the absence of a control arm in the PILOT study, these results demonstrate the clinical efficacy of liso-cel versus conventional chemotherapy in a population of patients with a historically poor prognosis and few treatment options.

For the key endpoints, comparisons were also conducted between all patients who received leukapheresis as part of the PILOT study and the conventional chemotherapy cohorts. These efficacy comparisons also demonstrated statistically significant improvements with liso-cel over conventional 2L chemotherapy regimens; treatment effects were smaller than in comparisons to the liso-cel–treated cohort, but this is not unexpected as not all patients in the leukapheresis cohort received liso-cel. Sensitivity analyses excluding patients in the conventional chemotherapy cohort who received intent-to-transplant therapies also demonstrated consistent results significantly favoring liso-cel treatment.

IPTW and greedy nearest neighbor matching are established methods for balancing comparator populations in nonrandomized clinical studies.[14] These methods significantly mitigate the risk of potential bias in comparative efficacy research analyses using data from studies without randomization. In the current study, 8 baseline characteristics were used for matching, and residual imbalances were addressed in sensitivity analyses. These approaches ensured that the findings of this comparison are statistically robust and provide strong evidence for improved efficacy outcomes with liso-cel in PILOT versus conventional 2L chemotherapy regimens in the real world in patients with R/R LBCL who met prespecified transplant-not-intended criteria.

This study also assessed the 1L and 2L treatment patterns of patients with LBCL in the real-world setting. Most patients in the conventional chemotherapy cohort received R-CHOP as 1L treatment, and the three most common 2L treatment regimens were R-ICE, bendamustine plus rituximab, and gemcitabine and oxaliplatin plus rituximab, each received by <20% of the total cohort. Of note, patients who received R-ICE might have been intended to proceed to HSCT but did not because of lack of response to R-ICE; however, intention to receive HSCT cannot be verified based on retrospective real-world data. These results are consistent with 1L and salvage options proposed in treatment guidelines,[15] demonstrating the generalizability of the current results. Additionally, the variability in 2L treatment regimens in the conventional chemotherapy cohorts highlights the previous unmet need for an effective 2L therapy in patients not intended for transplant when conventional chemotherapy was the only option that existed before CAR T-cell therapies.

To the best of our knowledge, this is the first study to assess the comparative efficacy of CAR T-cell therapy as 2L treatment for LBCL in patients not intended for transplant versus patients for whom HSCT was inappropriate but who received conventional 2L chemotherapy regimens in a real-world, matched, synthetic control cohort. Although the study focused on conventional chemotherapy regimens as the comparator, other therapies are now used in the 2L or later LBCL setting, such as tafasitamab plus lenalidomide, loncastuximab tesirine, polatuzumab plus bendamustine and rituximab, and bispecific antibodies.[10,16-20] However, those therapies were not reflected in the real-world cohort owing to the timing of their approval in the United States and this analysis. The results of our study are consistent with previous liso-cel studies using real-world data in the LBCL setting. Analyses assessing the comparative efficacy of liso-cel as third-line or later therapy in the open-label, multicenter TRANSCEND NHL 001 study (TRANSCEND; NCT02631044) versus a matched real-world population have yielded similar results favoring liso-cel.[21] Additionally, a recent study using a matching-adjusted indirect comparison approach to evaluate the comparative efficacy of liso-

cel in TRANSCEND versus summary-level data from the SCHOLAR-1 study of salvage chemotherapy in patients with R/R LBCL also demonstrated favorable efficacy for liso-cel.[22]

This study had some limitations inherent to retrospective and nonrandomized studies. Despite the extensive efforts to balance the liso-cel and conventional chemotherapy cohorts, any differences in populations not specifically considered during matching and balancing, including any preexisting comorbidities in the conventional chemotherapy cohorts, could have potentially affected results. Additionally, the potential for a bias in site selection was possible with the conventional chemotherapy cohort despite a multipronged approach to data collection. Of note, the study source for the real-world data used the following study site and data provider criteria to minimize site selection bias: projected patient sample size, experience with observational research and data collection, speed to data access, speed to contracting and institutional review board approval, presence of preexisting relationship, and state of current data model. Moreover, as is the case for any comparative study utilizing real-world data, factors that may differ in real-world conditions versus a clinical trial setting (e.g., patient monitoring or treatment over time) could have potentially influenced outcomes in the conventional chemotherapy cohort. Finally, the definitions of the index dates may have introduced immortal time bias, or a time interval during which the outcome event cannot occur. In this analysis, index date assignments did not differ systematically between the liso-cel and conventional chemotherapy cohorts.

In summary, in patients with R/R LBCL who were not intended for HSCT or for whom HSCT was inappropriate, efficacy outcomes significantly favored liso-cel in PILOT versus conventional 2L chemotherapy regimens in the real-world setting. Statistically significant differences in favor of liso-cel were noted in ORR, CR rate, DOR, EFS, PFS, and OS after balancing for baseline characteristics using the IPTW method. The results were consistent when using an alternative balancing method (greedy nearest neighbor matching) and with the unadjusted analysis. In the sensitivity analyses using the liso-cel–leukapheresed

population and excluding patients who received intent-to-transplant regimens, efficacy outcomes also significantly favored treatment with liso-cel versus conventional 2L chemotherapy regimens. These results further support liso-cel as 2L therapy for patients with R/R LBCL who are not intended for HSCT.

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Tables

Table 1. Patient demographics and baseline characteristics.

Characteristic	Liso-cel cohorts		Conventional chemotherapy cohorts	
	Liso-cel leukapheresed (n=74)	**Liso-cel treated (n=61)**	**Before application of PILOT eligibility criteria* (n=601)**	**After application of PILOT eligibility criteria but before balancing† (n=273)**
Male sex, n (%)	45 (61)	37 (61)	367 (61)	156 (57)
Age, y				
Median (range)	73.5 (53–84)	74 (53–84)	65 (18–93)	74 (21–93)
<70 years, n (%)	15 (20)	13 (21)	390 (65)	62 (23)
≥70 years, n (%)	59 (80)	48 (79)	211 (35)	211 (77)
Race, n (%)				
White	64 (86)	54 (89)	310 (52)	141 (52)
Black or African American	2 (3)	1 (2)	25 (4)	11 (4)
Asian	2 (3)	2 (3)	18 (3)	9 (3)
Other	0 (0)	0 (0)	12 (2)	5 (2)
Not reported	6 (8)	4 (7)	236 (39)	107 (39)
Country, n (%)				
United States	74 (100)	61 (100)	463 (77)	206 (75)
European countries	0 (0)	0 (0)	132 (22)	63 (23)

Characteristic	Liso-cel cohorts		Conventional chemotherapy cohorts	
	Liso-cel leukapheresed (n=74)	**Liso-cel treated (n=61)**	**Before application of PILOT eligibility criteria* (n=601)**	**After application of PILOT eligibility criteria but before balancing† (n=273)**
Japan	0 (0)	0 (0)	6 (1)	4 (1)
ECOG PS, n (%)				
<2	54 (73)	45 (74)	316 (53)	127 (47)
≥2	20 (27)	16 (26)	65 (11)	65 (24)
Missing	0 (0)	0 (0)	220 (37)	81 (30)
Ann Arbor disease, n (%)				
Stage I/II	21 (28)	21 (34)	115 (19)	41 (15)
Stage III/IV	52 (70)	40 (66)	320 (53)	146 (53)
Missing	1 (1)	0 (0)	166 (28)	86 (32)
Relapsed after 1L therapy,‡ n (%)	34 (46)	28 (46)	201 (33)	109 (40)
≤12 months after	16 (22)	13 (21)	112 (19)	54 (20)
>12 months after	18 (24)	15 (25)	89 (15)	55 (20)
Refractory to 1L therapy,‡ n (%)	40 (54)	33 (54)	400 (67)	164 (60)
Disease histology,§ n (%)				
DLBCL NOS	41 (55)	33 (54)	564 (94)	259 (95)
DLBCL tFL	10 (14)	9 (15)	20 (3)	9 (3)
Follicular lymphoma grade 3B	1 (1)	1 (2)	6 (1)	1 (0)

Characteristic	Liso-cel cohorts		Conventional chemotherapy cohorts	
	Liso-cel leukapheresed (n=74)	Liso-cel treated (n=61)	Before application of PILOT eligibility criteria* (n=601)	After application of PILOT eligibility criteria but before balancing† (n=273)
HGBCL with DLBCL histology	22 (30)	18 (30)	11 (2)	4 (1)
Double or triple hit,¶ n (%)				
Yes	25 (34)	20 (33)	182 (30)	82 (30)
No	44 (59)	36 (59)	114 (19)	44 (16)
Missing	5 (7)	5 (8)	305 (51)	147 (54)

*All patients in the conventional chemotherapy cohort with R/R LBCL after receiving therapy with an anthracycline and CD20-targeted agent.

†A subset of the conventional chemotherapy cohort who met the prespecified eligibility criteria of PILOT[12] but before balancing to baseline characteristics with the liso-cel–treated cohort.

‡Disease status was refractory if a patient achieved less than a complete response to last prior therapy; disease status was relapsed otherwise. Prior response status was R/R disease ≤12 months (defined as having a complete response lasting ≤12 months) versus relapsed >12 months after 1L therapy.

§Disease histology was collected according to local practice in the real-world study and according to the World Health Organization 2016 classification in PILOT.

¶HGBCL with rearrangements in *MYC* and either *BCL2, BCL6*, or both.

1L: first line; DLBCL: diffuse large B-cell lymphoma; ECOG PS: Eastern Cooperative Oncology Group performance status; HGBCL: high-grade B-cell lymphoma; LBCL: large B-cell lymphoma; liso-cel: lisocabtagene maraleucel; NOS: not otherwise specified; R/R: relapsed or refractory; tFL: transformed follicular lymphoma.

Table 2. Study follow-up.

Characteristic	Liso-cel cohorts		Conventional chemotherapy cohort after application of PILOT eligibility criteria* (n=273)
	Liso-cel leukapheresed (n=74)	Liso-cel treated (n=61)	
Median (range) follow-up time in all patients,† mo	11.9 (0.0–30.1)	12.3 (1.2–26.5)	9.0 (0.4–24.0)
Median (range) follow-up time in all surviving patients,‡ mo	15.0 (0.0–30.1)	16.6 (2.0–26.5)	15.0 (1.1–24.0)

*A subset of the conventional chemotherapy cohort who met the prespecified eligibility criteria of PILOT[12] but before balancing to baseline characteristics with the liso-cel–treated cohort.

†(Last known alive date or death date − index date + 1)/30.4375.

‡(Last known alive date − index date + 1)/30.4375.

Liso-cel: lisocabtagene maraleucel.

Table 3. Comparative adjusted efficacy outcomes in the liso-cel–treated cohort vs the conventional chemotherapy cohort after balancing.

Adjusted efficacy outcomes	Trimmed stabilized IPTW*,†	
	Liso-cel–treated cohort (n=61)	**Conventional chemotherapy cohort after application of PILOT eligibility criteria and balancing‡ (n=273)**
ORR, % (95% CI)	79.6 (69.9–90.7)	50.5 (44.9–56.9)
RR (95% CI)	1.6 (1.3–1.9)	
P value	<0.0001	
CR rate, % (95% CI)	53.1 (41.7–67.6)	24.0 (19.4–29.7)
RR (95% CI)	2.2 (1.6–3.1)	
P value	<0.0001	
Median (range) time to response, mo	1.0 (0.8–2.2)	1.6 (0.1–21.0)
Median (95% CI) DOR, mo	12.1 (3.6–20.6)	4.3 (2.7–5.9)
HR (95% CI)	0.40 (0.25–0.64)	
P value	0.0001	
Median (95% CI) EFS, mo	7.0 (3.2–10.9)	2.8 (2.4–3.2)
HR (95% CI)	0.43 (0.29–0.63)	
P value	<0.0001	
Median (95% CI) PFS, mo	7.0 (3.2–10.9)	2.9 (2.4–3.3)
HR (95% CI)	0.46 (0.32–0.68)	
P value	<0.0001	
Median (95% CI) OS, mo	NR (NR–NR)	12.6 (9.6–15.5)
HR (95% CI)	0.58 (0.36–0.94)	
P value	0.0256	

*Multiple imputations were performed to create 30 datasets. Estimates were then obtained using Rubin's rule to combine the individual estimates from each dataset.

†For the liso-cel–treated cohort, the weights = $\frac{1}{propensity\ score} \times\ the\ proportion\ of\ liso\text{-}cel\ patients$. For the conventional chemotherapy cohort after balancing, the weights = $\frac{1}{1-propensity\ score} \times\ the\ proportion\ of\ \ patients\ with\ conventional\ therapies$. Stabilized IPTWs were trimmed at the 5th and 95th percentiles.

‡A subset of the conventional chemotherapy cohort who met the prespecified eligibility criteria of PILOT[12] balanced to baseline characteristics with the liso-cel–treated cohort.

CI: confidence interval; CR: complete response; DOR: duration of response; EFS: event-free survival; HR: hazard ratio; IPTW: inverse probability of treatment weighting; liso-cel: lisocabtagene maraleucel; NR: not reached; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; RR: relative risk.

Table 4. Comparative adjusted efficacy outcomes in the liso-cel–leukapheresed cohort vs conventional chemotherapy cohort after balancing.

Adjusted efficacy outcomes	Trimmed stabilized IPTW*,†	
	Liso-cel–leukapheresed cohort (n=74)	**Conventional chemotherapy cohort after application of PILOT eligibility criteria and balancing‡ (n=273)**
ORR, % (95% CI)	65.7 (55.6–77.8)	50.4 (44.8–56.8)
RR (95% CI)	1.3 (1.1–1.6)	
P value	0.0116	
CR rate, % (95% CI)	45.3 (35.1–58.5)	23.9 (19.3–29.7)
RR (95% CI)	1.9 (1.4–2.6)	
P value	0.0002	
Median (95% CI) EFS, mo	8.1 (3.1–13.2)	2.8 (2.4–3.2)
HR (95% CI)	0.39 (0.28–0.55)	
P value	<0.0001	
Median (95% CI) PFS, mo	8.1 (3.1–13.2)	2.8 (2.4–3.3)
HR (95% CI)	0.42 (0.30–0.60)	
P value	<0.0001	
Median (95% CI) OS, mo	NR (NR–NR)	12.6 (9.6–15.6)
HR (95% CI)	0.60 (0.39–0.93)	
P value	0.0217	

*Multiple imputations were performed to create 30 datasets. Estimates were then obtained using Rubin's rule to combine the individual estimates from each dataset.

†For the liso-cel–treated cohort, the weights = $\frac{1}{propensity\ score} \times the\ proportion\ of\ liso\text{-}cel\ patients$. For the conventional chemotherapy cohort after balancing, the weights = $\frac{1}{1-propensity\ score} \times the\ proportion\ of\ patients\ with\ conventional\ chemotherapies$. Stabilized IPTWs were trimmed at the 5th and 95th percentiles.

‡A subset of the conventional chemotherapy cohort who met the prespecified eligibility criteria of PILOT[12] balanced to baseline characteristics with the liso-cel–treated cohort.

CI: confidence interval; CR: complete response; DOR: duration of response; EFS: event-free survival; HR: hazard ratio; IPTW: inverse probability of treatment weighting; liso-cel: lisocabtagene maraleucel; NR: not reached; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; RR: relative risk.

Figure legends

Figure 1. Comparative adjusted efficacy outcomes in the liso-cel–treated cohort versus the conventional chemotherapy cohort after application of PILOT eligibility criteria and balancing. (A) EFS, (B) PFS, and (C) OS adjusted by trimmed stabilized IPTW in the liso-cel–treated cohort versus the conventional chemotherapy cohort after balancing are shown. Multiple imputations were performed to create 30 datasets. Estimates were then obtained using Rubin's rule to combine the individual estimates from each dataset. For the liso-cel–treated cohort, the weights = $\frac{1}{propensity\ score} \times the\ proportion\ of\ liso\text{-}cel\ patients$. For the conventional chemotherapy cohort after balancing, the weights = $\frac{1}{1-propensity\ score} \times the\ proportion\ of\ patients\ with\ conventional\ chemotherapies$. Stabilized IPTWs were trimmed at the 5th and 95th percentiles. CI: confidence interval; EFS: event-free survival; HR: hazard ratio; IPTW: inverse probability of treatment weighting; liso-cel: lisocabtagene maraleucel; NR: not reached; PFS: progression-free survival; OS: overall survival.

Figure 2. Comparative adjusted efficacy outcomes in the liso-cel–leukapheresed cohort versus the conventional chemotherapy cohort after application of PILOT eligibility criteria and balancing. (A) EFS, (B) PFS, and (C) OS adjusted by trimmed stabilized IPTW in the liso-cel–leukapheresed cohort versus the conventional chemotherapy cohort after balancing are shown. Multiple imputations were performed to create 30 datasets. Estimates were then obtained using Rubin's rule to combine the individual estimates from each dataset. For the liso-cel–treated cohort, the weights = $\frac{1}{propensity\ score} \times the\ proportion\ of\ liso\text{-}cel\ patients$. For the conventional chemotherapy cohort after balancing, the weights = $\frac{1}{1-propensity\ score} \times the\ proportion\ of\ patients\ with\ conventional\ chemotherapy$. Stabilized IPTWs were trimmed at the 5th and 95th percentiles. CI: confidence interval; EFS: event-free

survival; IPTW: inverse probability of treatment weighting; liso-cel: lisocabtagene maraleucel; NR: not reached; PFS: progression-free survival; OS: overall survival.

Figure 3. First- and second-line treatment in the conventional chemotherapy cohorts before PILOT eligibility criteria. (A) First- and (B) second-line treatments in all patients in the conventional chemotherapy cohort with R/R LBCL after receiving therapy with an anthracycline and CD20-targeted agent (n=601). *Collectively includes all treatments received by <1% of the total population. LBCL: large B-cell lymphoma; liso-cel: lisocabtagene maraleucel; R/R: relapsed or refractory.

Figure 4. First- and second-line treatment in the conventional chemotherapy cohorts after application of PILOT eligibility criteria but before balancing. (A) First- and (B) second-line treatments in a subset of the conventional chemotherapy cohort who met the prespecified eligibility criteria of PILOT[12] but before balancing to baseline characteristics with the liso-cel–treated cohort (n=273). *Collectively includes all treatments received by <1% of the total population. liso-cel: lisocabtagene maraleucel.

FIGURE 1

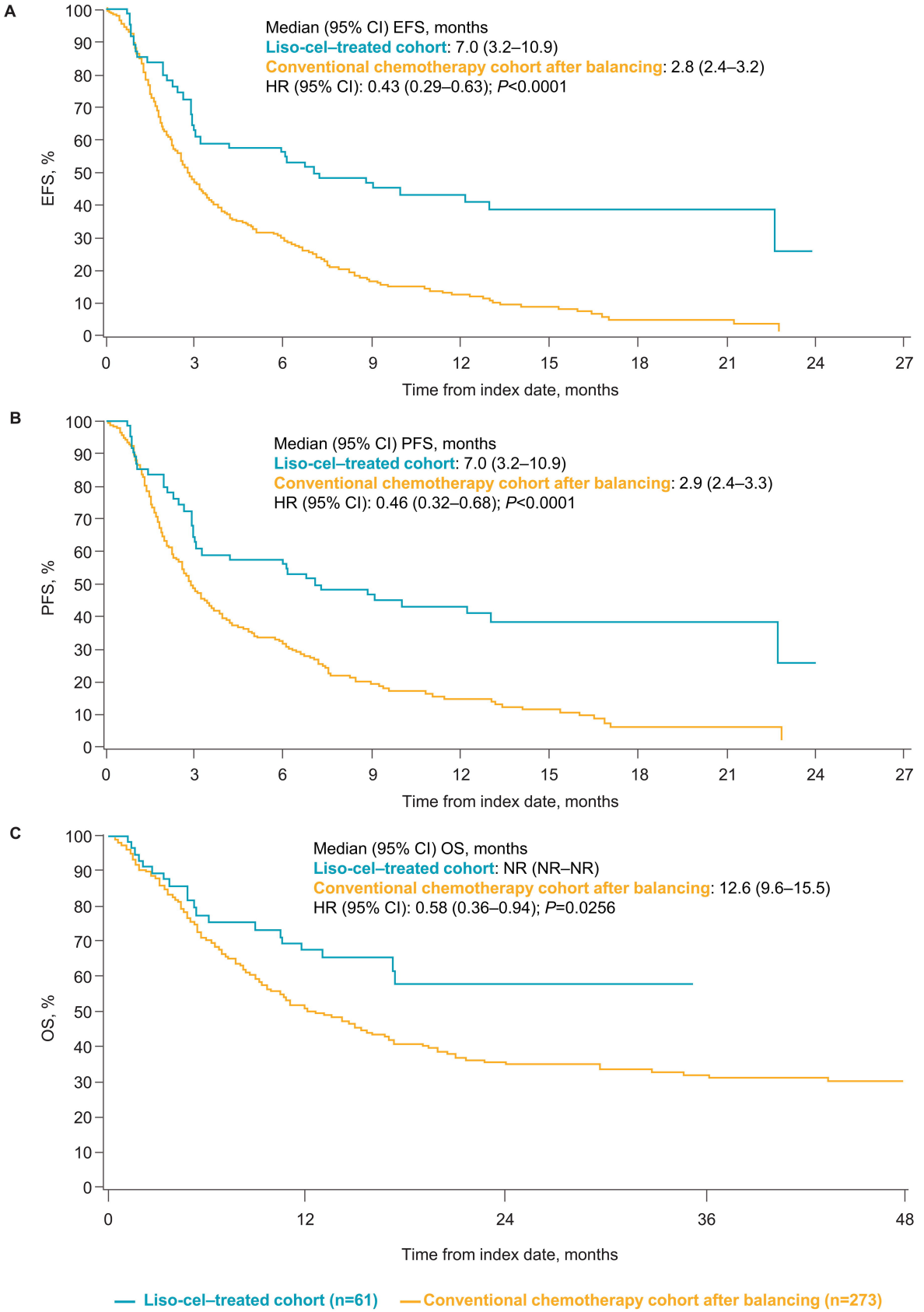

A
Median (95% CI) EFS, months
Liso-cel–treated cohort: 7.0 (3.2–10.9)
Conventional chemotherapy cohort after balancing: 2.8 (2.4–3.2)
HR (95% CI): 0.43 (0.29–0.63); P<0.0001
EFS, %
Time from index date, months
B
Median (95% CI) PFS, months
Liso-cel–treated cohort: 7.0 (3.2–10.9)
Conventional chemotherapy cohort after balancing: 2.9 (2.4–3.3)
HR (95% CI): 0.46 (0.32–0.68); P<0.0001
PFS, %
Time from index date, months
C
Median (95% CI) OS, months
Liso-cel–treated cohort: NR (NR–NR)
Conventional chemotherapy cohort after balancing: 12.6 (9.6–15.5)
HR (95% CI): 0.58 (0.36–0.94); P=0.0256
OS, %
Time from index date, months
Liso-cel–treated cohort (n=61)
Conventional chemotherapy cohort after balancing (n=273)

FIGURE 2

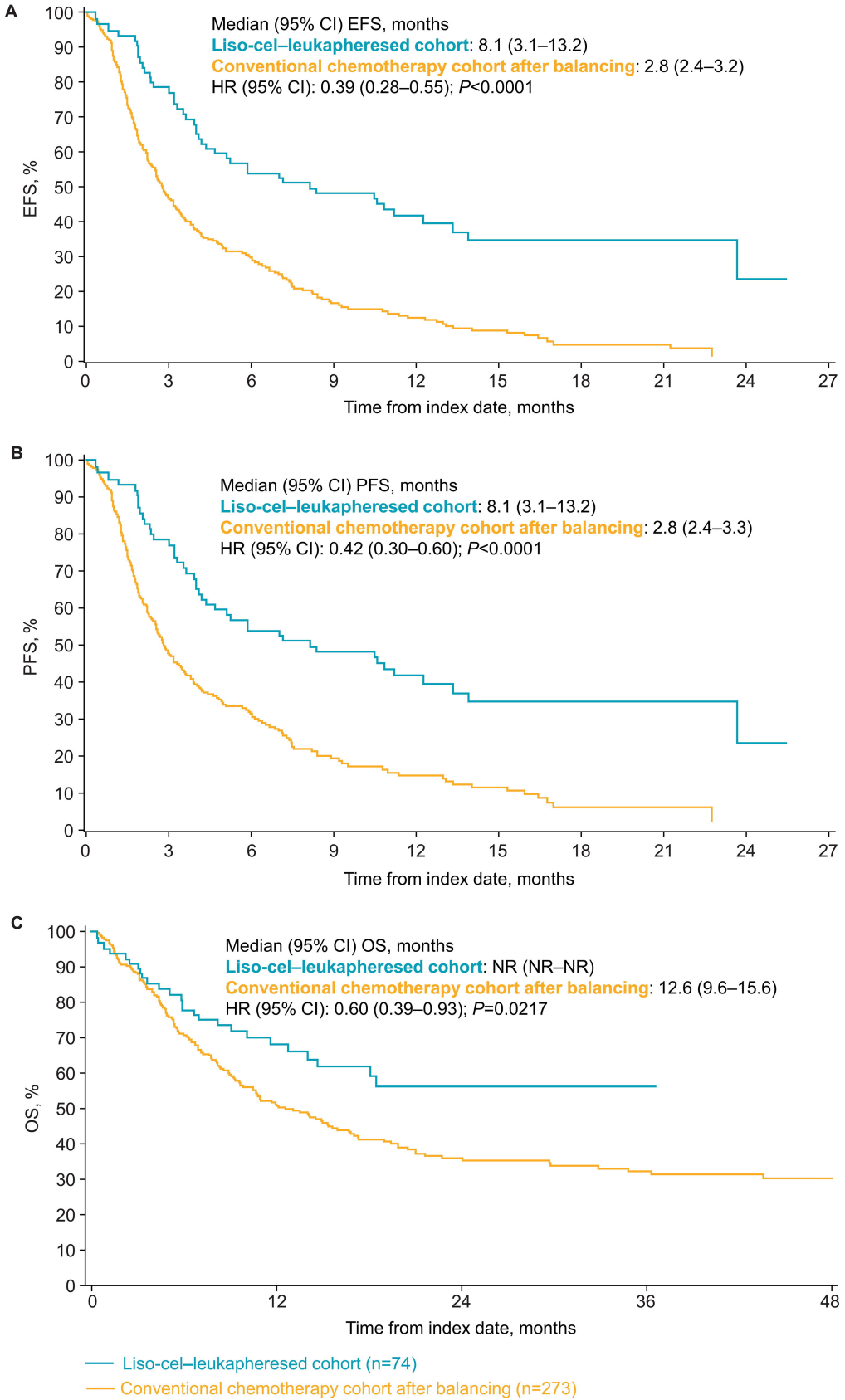
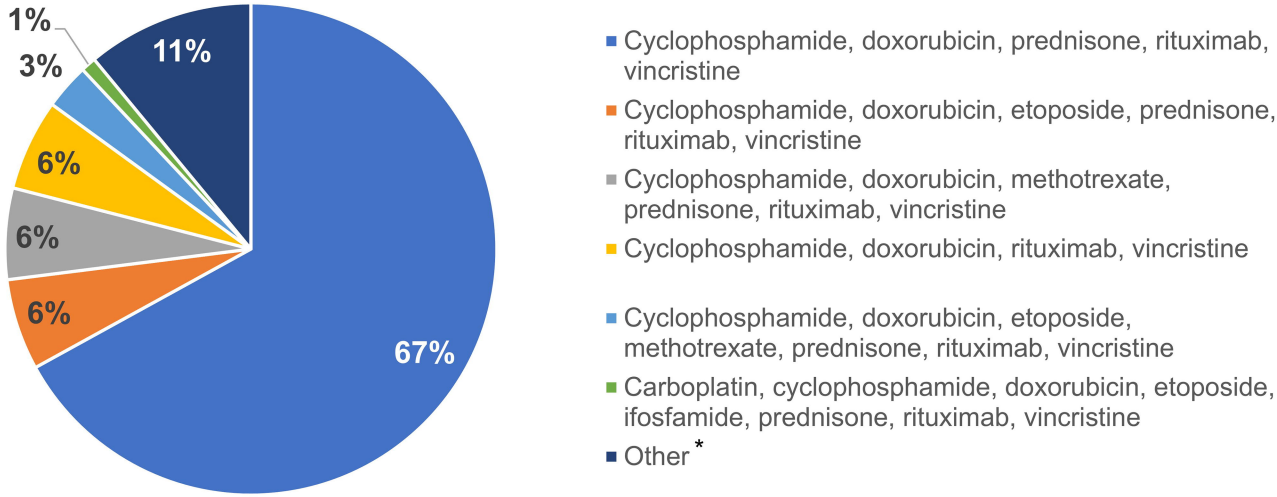

A
Median (95% CI) EFS, months
Liso-cel–leukapheresed cohort: 8.1 (3.1–13.2)
Conventional chemotherapy cohort after balancing: 2.8 (2.4–3.2)
HR (95% CI): 0.39 (0.28–0.55); P<0.0001
EFS, %
Time from index date, months
B
Median (95% CI) PFS, months
Liso-cel–leukapheresed cohort: 8.1 (3.1–13.2)
Conventional chemotherapy cohort after balancing: 2.8 (2.4–3.3)
HR (95% CI): 0.42 (0.30–0.60); P<0.0001
PFS, %
Time from index date, months
C
Median (95% CI) OS, months
Liso-cel–leukapheresed cohort: NR (NR–NR)
Conventional chemotherapy cohort after balancing: 12.6 (9.6–15.6)
HR (95% CI): 0.60 (0.39–0.93); P=0.0217
OS, %
Time from index date, months
Liso-cel–leukapheresed cohort (n=74)
Conventional chemotherapy cohort after balancing (n=273)

FIGURE 3

A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3%
11%
6%
6%
6%
67%
Cyclophosphamide, doxorubicin, prednisone, rituximab, vincristine
Cyclophosphamide, doxorubicin, etoposide, prednisone, rituximab, vincristine
Cyclophosphamide, doxorubicin, methotrexate, prednisone, rituximab, vincristine
Cyclophosphamide, doxorubicin, rituximab, vincristine
Cyclophosphamide, doxorubicin, etoposide, methotrexate, prednisone, rituximab, vincristine
Carboplatin, cyclophosphamide, doxorubicin, etoposide, ifosfamide, prednisone, rituximab, vincristine
Other *

B

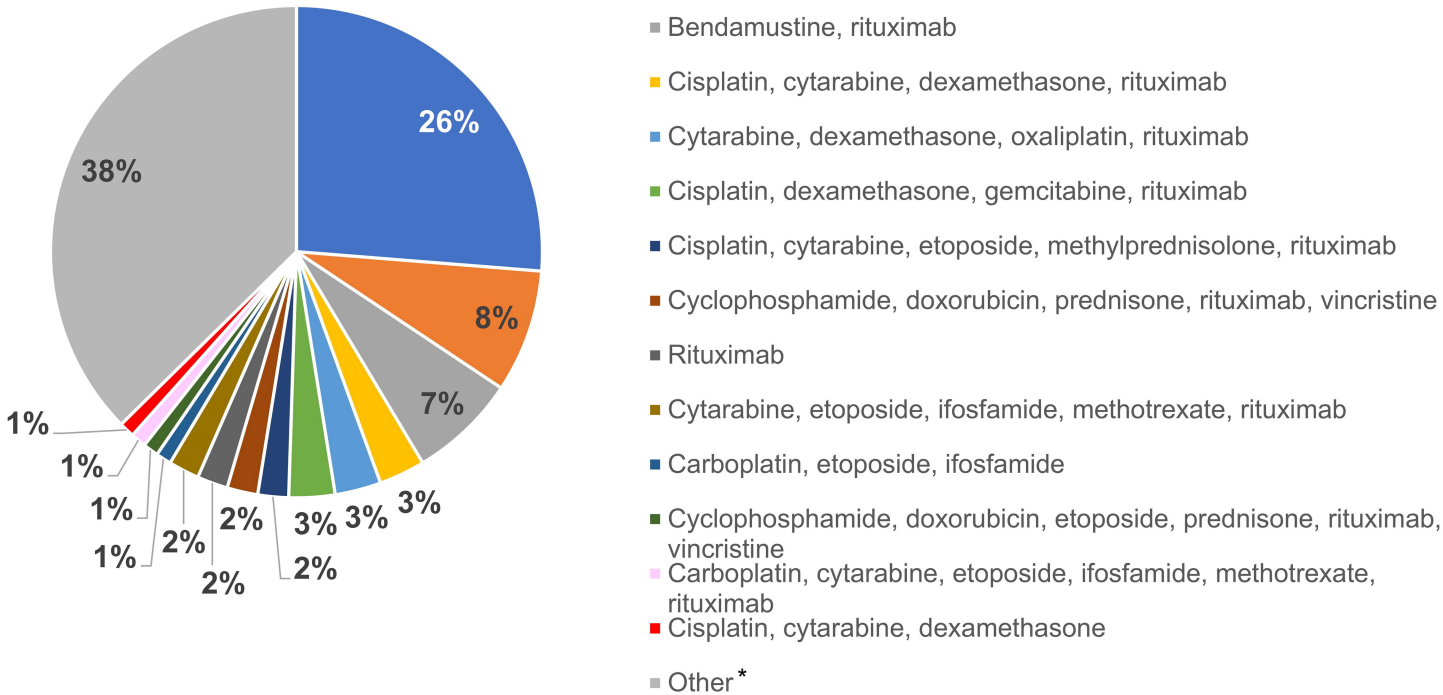
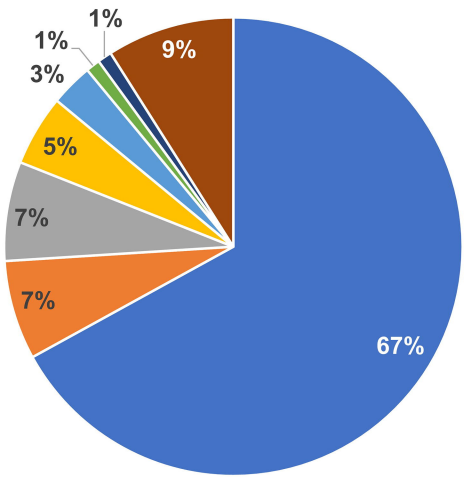

26%
8%
7%
3%
3%
3%
2%
2%
2%
2%
1%
1%
1%
1%
38%
Carboplatin, etoposide, ifosfamide, rituximab
Gemcitabine, oxaliplatin, rituximab
Bendamustine, rituximab
Cisplatin, cytarabine, dexamethasone, rituximab
Cytarabine, dexamethasone, oxaliplatin, rituximab
Cisplatin, dexamethasone, gemcitabine, rituximab
Cisplatin, cytarabine, etoposide, methylprednisolone, rituximab
Cyclophosphamide, doxorubicin, prednisone, rituximab, vincristine
Rituximab
Cytarabine, etoposide, ifosfamide, methotrexate, rituximab
Carboplatin, etoposide, ifosfamide
Cyclophosphamide, doxorubicin, etoposide, prednisone, rituximab, vincristine
Carboplatin, cytarabine, etoposide, ifosfamide, methotrexate, rituximab
Cisplatin, cytarabine, dexamethasone
Other *

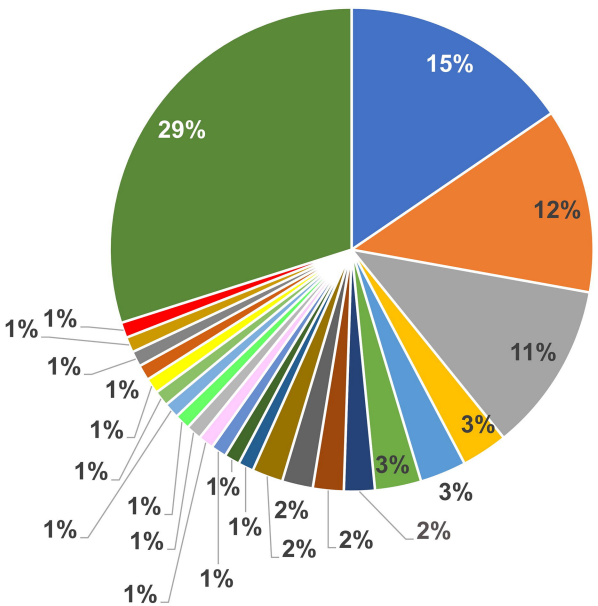
FIGURE 4

A



- Cyclophosphamide, doxorubicin, prednisone, rituximab, vincristine
- Cyclophosphamide, doxorubicin, methotrexate, prednisone, rituximab, vincristine
- Cyclophosphamide, doxorubicin, rituximab, vincristine
- Cyclophosphamde, doxorubicin, etoposide, prednisone, rituximab, vincristine
- Cyclophosphamide, doxorubicin, etoposide, methotrexate, prednisone, rituximab, vincristine
- Cyclophosphamide, cytarabine, dexamethasone, doxorubicin, methotrexate, rituximab, vincristine
- Cyclophosphamide, doxorubicin, etoposide, rituximab, vincristine
- Other*

B



- Carboplatin, etoposide, ifosfamide, rituximab
- Bendamustine, rituximab
- Gemcitabine, oxaliplatin, rituximab
- Cyclophosphamide, doxorubicin, prednisone, rituximab, vincristine
- Cisplatin, cytarabine, etoposide, methylprednisolone, rituximab
- Cisplatin, dexamethasone, gemcitabine, rituximab
- Cisplatin, cytarabine, dexamethasone, rituximab
- Cytarabine, dexamethasone, oxaliplatin, rituximab
- Rituximab
- Carboplatin, cytarabine, etoposide, ifosfamide, methotrexate, rituximab
- Cyclophosphamide, doxorubicin, etoposide, prednisone, rituximab, vincristine
- Cytarabine, etoposide, ifosfamide, methotrexate, rituximab
- Bendamustine, carboplatin, etoposide, ifosfamide, rituximab
- Bendamustine, carboplatin, etoposide, rituximab
- Carboplatin, etoposide, ifosfamide
- Carboplatin, etoposide, ifosfamide, lenalidomide, rituximab
- Cisplatin, dexamethasone, gemcitabine
- Cyclophosphamide, etoposide, prednisone, procarbazine, rituximab
- Cytarabine, etoposide
- Etoposide, ifosfamide, rituximab
- Ibrutinib
- Lenalidomide, rituximab
- Methotrexate, rituximab
- Other*

Supplementary Appendix

Comparative efficacy of lisocabtagene maraleucel in the PILOT study *versus* second-line chemotherapy regimens in the real world

Nilanjan Ghosh, Alison Sehgal, Fei Fei Liu, et al.

Table of contents

Supplementary methods

Patients and study cohorts

The PILOT study enrolled patients with relapsed or refractory large B-cell lymphoma at any time after one line of chemoimmunotherapy containing an anthracycline and a CD20-targeted agent, had confirmed positron emission tomography–positive disease, were considered hematopoietic stem cell transplantation (HSCT) not intended by their physician, and met ≥1 of the following prespecified HSCT not intended criteria: age ≥70 years, Eastern Cooperative Oncology Group performance status (ECOG PS) of 2, diffusing capacity of the lung for carbon monoxide ≤60% adjusted for sex-specific hemoglobin concentration, left ventricular ejection fraction (LVEF) <50%, calculated creatinine clearance (CrCl; Cockcroft-Gault equation) <60 mL/min, and/or alanine aminotransferase/aspartate aminotransferase (ALT/AST) >2 × upper limit of normal (ULN). Patients must have had adequate organ functions measured as oxygen saturation ≥92% on room air with dyspnea of grade ≤1, LVEF ≥40%, CrCl >30 mL/min, ALT/AST ≤5 × ULN, total bilirubin <2.0 mg/dL (or <3.0 mg/dL for patients with Gilbert's syndrome or lymphomatous infiltration of the liver), and adequate bone marrow function per investigator.

The three conventional chemotherapy cohorts were derived from a harmonized dataset comprising multiple data sources collected retrospectively from COTA, Guardian Network, and clinical sites via electronic case report forms. Data sources were targeted for selection by identifying existing databases collecting longitudinal data covering clinical characteristics, treatment, and outcomes of patients with hematologic malignancies with a focus on relapsed or refractory B-cell non-Hodgkin lymphoma. The databases are of different types and owned/managed by research institutes, regional treatment networks, national research networks and epidemiologic registries. Data sources were also identified and selected among sites and centers known to treat patients with relapsed or refractory B-cell non-Hodgkin lymphoma, as

evidenced by their research outputs or trial programs, where populations of patients with relapsed or refractory B-cell non-Hodgkin lymphoma treated with standard of care were anticipated to enable chart abstractions. Data sources were grouped into clinical sites and external research data partners. Data from clinical sites were acquired by a vendor that obtains data through direct abstraction into an electronic case report form, extraction from a clinical research database or electronic medical record, or a combination thereof. Clinical sites were systematically evaluated for participation to minimize bias in site selection using the following metrics: adequate projected patient sample size, experience with observational research and data collection, speed to data access, speed to contracting and institutional review board approval, presence of preexisting relationship, and state of current data model.

Index dates and data cutoff dates

The index dates for the lisocabtagene maraleucel (liso-cel)–treated and leukapheresis cohorts were the day of liso-cel infusion and leukapheresis, respectively. The index date for the conventional chemotherapy cohorts was the start of second-line therapy. The data cutoff dates were September 24, 2021, for the liso-cel cohorts and December 31, 2020, for the conventional chemotherapy cohorts. The real-world data were collected from 2018 to the data cutoff date of December 31, 2020, in a retrospective manner among patients whose first large B-cell lymphoma diagnosis was in 2003 or later.

Endpoint definitions

Duration of response was defined as duration of time from first response (partial response or better) to the first documented disease progression, relapse, or death from any cause, whichever occurred first. Event-free survival was defined as time from index date to first documentation of disease progression, relapse, start of new anticancer therapy, or death due to any cause, whichever occurred first. Progression-free survival was defined as time from the index date to the first documented disease progression, relapse, death due to any cause, or end

of follow-up, whichever occurred first. Overall survival was defined as time from the index date to the first documentation of death due to any cause, or censoring, whichever occurred first.

Statistical analysis

Analysts who were blinded to outcome data behind a firewall performed initial balancing of patient baseline characteristics. Trimmed stabilized inverse probability of treatment weighting and greedy nearest neighbor matching methods were used to balance the liso-cel and conventional chemotherapy cohorts according to baseline characteristics; doubly robust procedures were used where appropriate.[1] For greedy nearest neighbor matching, a caliper width of 0.20 times the pooled estimate of the standard deviation of the logits of the propensity scores was used. Prognostic variables (based on literature and medical review) with ≤30% missing values in both liso-cel and conventional chemotherapy cohorts were included in balancing as follows: age, sex, years from initial diagnosis to index date, ECOG PS, Ann Arbor disease stage, refractory versus relapsed, duration of CR after first-line therapy, and bulky disease. The conventional chemotherapy cohort after balancing was used for the evaluation of efficacy endpoints. Statisticians and programmers were able to access outcomes data after the conventional chemotherapy cohorts were constructed.

Baseline characteristics and outcomes were summarized descriptively, and treatment patterns were analyzed descriptively at the drug level by line of therapy. A generalized linear model and/or Cox proportional hazards model was used to estimate the relative risk or hazard ratio for each outcome of interest, with accompanying 95% confidence intervals. Time-to-event comparisons were conducted using Kaplan-Meier survival or Cox proportional hazards model methods. Individual estimates and their standard errors were combined using Rubin's rules to produce an overall estimate.[2] All statistical analyses were conducted using SAS (previously "Statistical Analysis System") Software® version 9.4 or higher. All tests were conducted

assuming a two-tailed test of significance and alpha level set a priori at 0.05, and there was no adjustment for multiplicity. For key endpoints, comparisons between the liso-cel–leukapheresed and conventional chemotherapy cohorts were conducted as sensitivity analyses. Another sensitivity analysis excluding patients who received second-line chemotherapy regimens that are commonly received as salvage therapies before HSCT (intent-to-transplant therapy) was also conducted. The intent-to-transplant therapy (with or without rituximab) was defined per current treatment guidelines as follows: dexamethasone, cisplatin, and cytarabine; dexamethasone, cytarabine, and oxaliplatin; ifosfamide, carboplatin, and etoposide; etoposide, methylprednisolone, cytarabine, and cisplatin; and ifosfamide, mitoxantrone, and etoposide.

Supplementary Table S1. Additional patient demographics and baseline characteristics.

Characteristic	Liso-cel cohorts		Conventional chemotherapy cohorts	
	Liso-cel leukapheresed (n=74)	Liso-cel treated (n=61)	Before application of PILOT eligibility criteria* (n=601)	After application of PILOT eligibility criteria but before balancing† (n=273)
LVEF, n (%)				
<50%	3 (4)	2 (3)	5 (1)	5 (2)
≥50%	71 (96)	59 (97)	78 (13)	36 (13)
Missing	0 (0)	0 (0)	518 (86)	232 (85)
CrCl (mL/min),‡ n (%)				
<60%	16 (22)	14 (23)	24 (4)	23 (8)
≥60%	50 (68)	47 (77)	121 (20)	48 (18)
Missing	8 (11)	0 (0)	456 (76)	202 (74)
ALT, n (%)				
≤2 × ULN	74 (100)	61 (100)	317 (53)	164 (60)
>2 × ULN	0 (0)	0 (0)	9 (1)	9 (3)
Missing	0 (0)	0 (0)	275 (46)	100 (37)
AST, n (%)				
≤2 × ULN	73 (99)	60 (98)	317 (53)	160 (59)
>2 × ULN	1 (1)	1 (2)	15 (2)	15 (5)

Characteristic	Liso-cel cohorts		Conventional chemotherapy cohorts	
	Liso-cel leukapheresed (n=74)	Liso-cel treated (n=61)	Before application of PILOT eligibility criteria* (n=601)	After application of PILOT eligibility criteria but before balancing† (n=273)
Missing	0 (0)	0 (0)	269 (45)	98 (36)
Serum LDH, n (%)				
<500 U/L	57 (77)	50 (82)	252 (42)	116 (42)
≥500 U/L	17 (23)	11 (18)	96 (16)	55 (20)
Missing	0	0	253 (42)	102 (37)

*All patients in the conventional chemotherapy cohort with R/R LBCL after receiving therapy with an anthracycline and CD20-targeted agent.

†A subset of the conventional chemotherapy cohort who met the prespecified eligibility criteria of PILOT[3] but before balancing to baseline characteristics with the liso-cel–treated cohort.

‡By Cockcroft-Gault equation.

ALT: alanine aminotransferase; AST: aspartate aminotransferase; CrCl: creatinine clearance; LBCL: large B-cell lymphoma; LDH: lactate dehydrogenase; liso-cel: lisocabtagene maraleucel; LVEF: left ventricular ejection fraction; R/R: relapsed or refractory; ULN: upper limit of normal.

Supplementary Table S2. Baseline characteristics before and after balancing using trimmed stabilized inverse probability of treatment weighting.

	Before balancing			After balancing		
	Liso-cel–treated cohort (n=61)	**Conventional chemotherapy cohort after application of PILOT eligibility criteria* (n=273)**	**pSMD† (liso-cel–treated cohort minus conventional chemotherapy cohort after application of PILOT eligibility criteria*)**	**Liso-cel–treated cohort (n=61)**	**Conventional chemotherapy cohort after application of PILOT eligibility criteria* (n=273)**	**pSMD† (liso-cel–treated cohort minus conventional chemotherapy cohort after application of PILOT eligibility criteria*)**
Age, y	73.08	72.21	0.0866	72.94	72.40	0.0544
Sex (male = 1; female = 0)	0.39	0.43	−0.0714	0.41	0.42	−0.0265
R/R to 1L therapy (refractory = 1; relapsed = 0)‡	0.54	0.60	−0.1209	0.60	0.59	0.0063
Ann Arbor disease stage (III/IV = 1; I/II = 0)	0.66	0.75	−0.2116	0.68	0.73	−0.1144
ECOG PS before lymphodepleting	0.26	0.31	−0.1068	0.28	0.30	−0.0417

chemotherapy (≥2 = 1; <2 = 0)						
Mean duration of CR to 1L therapy, mo	16.31	10.32	0.1978	13.28	11.10	0.0767
Mean time from initial diagnosis, y	2.22	1.71	0.1907	1.99	1.78	0.0849
Bulky disease (yes = 1; no = 0)§	0.16	0.32	−0.3756	0.21	0.29	−0.1958

*A subset of the conventional chemotherapy cohort who met the prespecified eligibility criteria of PILOT.[3]

†pSMD was obtained from the baseline characteristics in the liso-cel–treated cohort minus the baseline characteristics in the conventional chemotherapy cohorts and using stabilized weights when combining the mean and standard deviation. If a baseline characteristic had >30% missing per cohort, the characteristic was not used in the balancing except for disease stage. Disease stage had >30% missingness but was included in the balancing, as it was classified as a highly prognostic factor.

‡Disease status was refractory if a patient achieved less than a CR to last prior therapy; disease status was relapsed otherwise.

§Bulky disease was defined as disease ≥10 cm for patients in the liso-cel–treated cohort and simply recorded as “yes” or “no” based on electronic medical records for patients in the conventional chemotherapy cohort.

1L: first line; CR: complete response; ECOG PS: Eastern Cooperative Oncology Group performance status; liso-cel: lisocabtagene maraleucel; pSMD: pooled standardized mean difference; R/R: relapsed or refractory.

Supplementary Table S3. Baseline characteristics before and after balancing using greedy nearest neighbor matching.

	Before balancing			After balancing		
	Liso-cel–treated cohort (n=61)	**Conventional chemotherapy cohort after application of PILOT eligibility criteria* (n=273)**	**pSMD† (liso-cel–treated cohort minus conventional chemotherapy cohort after application of PILOT eligibility criteria*)**	**Liso-cel–treated cohort (n=56–61)**	**Conventional chemotherapy cohort after application of PILOT eligibility criteria* (n=159–179)**	**pSMD† (liso-cel–treated cohort minus conventional chemotherapy cohort after application of PILOT eligibility criteria*)**
Age, y	73.08	72.21	0.0866	73.08	72.77	0.0429
Sex (male = 1; female = 0)	0.39	0.43	−0.0714	0.40	0.40	−0.0002
R/R to 1L therapy (refractory = 1; relapsed = 0)‡	0.54	0.60	−0.1209	0.55	0.57	−0.0523
Ann Arbor disease stage (III/IV = 1; I/II = 0)	0.66	0.75	−0.2116	0.66	0.64	0.0449
ECOG PS before lymphodepleting chemotherapy (≥2 = 1; <2 = 0)	0.26	0.31	−0.1068	0.26	0.28	−0.0456

Mean duration of CR to 1L therapy, mo	16.31	10.32	0.1978	14.55	13.50	0.0348
Mean time from initial diagnosis, y	2.22	1.71	0.1907	2.08	2.02	0.0226
Bulky disease (yes = 1; no = 0)§	0.16	0.32	−0.3756	0.17	0.17	−0.0137

*A subset of the conventional chemotherapy cohort who met the prespecified eligibility criteria of PILOT.[3]

†pSMD was obtained from the baseline characteristic of the liso-cel–treated cohort minus the baseline characteristic of the conventional chemotherapy cohorts and unweighted when combining the mean and standard deviation. The matched sample was constructed with greedy nearest neighbor matching of the logit of the propensity score using calipers equal to width of 0.2 of the standard deviation of the logit of the propensity score. If a baseline characteristic had >30% missing per cohort, the characteristic was not used in the balancing except for disease stage. Disease stage had >30% missingness but was included in the balancing, as it was classified as a highly prognostic factor.

‡Disease status was refractory if a patient achieved less than a CR to last prior therapy; disease status was relapsed otherwise.

§Bulky disease was defined as disease ≥10 cm for patients in the liso-cel–treated cohort and simply recorded as “yes” or “no” based on electronic medical records for patients in the conventional chemotherapy cohort.

1L: first line; CR: complete response; ECOG PS: Eastern Cooperative Oncology Group performance status; liso-cel: lisocabtagene maraleucel; pSMD: pooled standardized mean difference; R/R: relapsed or refractory.

Supplementary Table S4. Patient disposition.

	Leukapheresed cohort (before liso-cel) (n=74)	Liso-cel–treated cohort (n=61)	Conventional chemotherapy cohort after application of PILOT eligibility criteria but before balancing*	
			Without 2-year follow-up limit (n=273)	With 2-year follow-up limit (n=273)
On study, n (%)	74 (100)	61 (100)	273 (100)	273 (100)
Discontinued from study, n (%)	41 (55)	28 (46)	165 (60)	140 (51)
Reason for discontinuation, n (%)				
Death	26 (35)	20 (33)	165 (60)	140 (51)
Consent withdrawal	6 (8)	6 (10)	0 (0)	0 (0)
No longer met eligibility criteria	5 (7)	0 (0)	0 (0)	0 (0)
Disease-related complications	1 (1)	0 (0)	0 (0)	0 (0)
Other	3 (4)	2 (3)	0 (0)	0 (0)

*A subset of the conventional chemotherapy cohort who met the prespecified eligibility criteria of PILOT[3] but before balancing to baseline characteristics with the liso-cel–treated cohort.

Liso-cel: lisocabtagene maraleucel.

Supplementary Table S5. Comparative adjusted efficacy outcomes excluding patients who received intent-to-transplant therapies from the conventional chemotherapy cohort.

	Trimmed stabilized IPTW		
	Liso-cel–treated cohort (n=61)		**Conventional chemotherapy cohort after application of PILOT eligibility criteria and balancing* (n=187)**
ORR, % (95% CI)	81.1 (71.8–91.7)		49.8 (43.0–57.6)
RR (95% CI)		1.6 (1.3–2.0)	
P value		<0.0001	
CR rate, % (95% CI)	53.2 (41.6–68.2)		22.3 (17.0–29.2)
RR (95% CI)		2.4 (1.7–3.4)	
P value		<0.0001	
Median (range) time to response, mo	1.0 (0.8–2.2)		1.9 (0.1–21.0)
Median (95% CI) DOR, mo	12.1 (1.9–22.3)		3.3 (2.2–4.3)
HR (95% CI)		0.36 (0.21–0.60)	
P value		<0.0001	
Median (95% CI) EFS, mo	7.2 (2.7–11.7)		2.8 (2.2–3.4)
HR (95% CI)		0.42 (0.28–0.63)	
P value		<0.0001	
Median (95% CI) PFS, mo	7.2 (2.7–11.7)		3.0 (2.3–3.6)
HR (95% CI)		0.45 (0.30–0.68)	
P value		0.0001	
Median (95% CI) OS, mo	NR (NR–NR)		10.8 (7.2–14.4)
HR (95% CI)		0.53 (0.32–0.87)	
P value		0.0118	

*A subset of the conventional chemotherapy cohort who met the prespecified eligibility criteria of PILOT[3] balanced to baseline characteristics with the liso-cel–treated cohort.

CI: confidence interval; CR: complete response; DOR: duration of response; EFS: event-free survival; HR: hazard ratio; IPTW: inverse probability of treatment weighting; liso-cel: lisocabtagene maraleucel; NR: not reached; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; RR: relative risk.

Supplementary Table S6. Unadjusted comparative efficacy outcomes in the liso-cel–treated cohort versus the conventional chemotherapy cohort after application of PILOT eligibility criteria but before balancing.

Unadjusted efficacy outcomes	**Liso-cel–treated cohort (n=61)**	**Conventional chemotherapy cohort after application of PILOT eligibility criteria but before balancing* (n=273)**
ORR, % (95% CI)	80 (68.2–89.4)	50 (44.1–56.3)
CR rate, % (95% CI)	56 (42.4–68.5)	23 (18.5–28.9)
Median (95% CI) EFS, mo	7.2 (3.0–22.6)	2.8 (2.3–3.2)
HR (95% CI)	0.41 (0.28–0.58)	
P value	<0.0001	
Median (95% CI) PFS, mo	7.2 (3.0–22.6)	2.8 (2.4–3.4)
HR (95% CI)	0.44 (0.31–0.63)	
P value	<0.0001	
Median (95% CI) OS, mo	NR (17.3–NR)	12.1 (9.7–15.9)
HR (95% CI)	0.51 (0.32–0.82)	
P value	0.0051	

*A subset of the conventional chemotherapy cohort who met the prespecified eligibility criteria of PILOT[3] but before balancing to baseline characteristics with the liso-cel–treated cohort.

CI: confidence interval; CR: complete response; DOR: duration of response; EFS: event-free survival; HR: hazard ratio; IPTW: inverse probability of treatment weighting; liso-cel: lisocabtagene maraleucel; NR: not reached; ORR: overall response rate; OS: overall survival; PFS: progression-free survival.

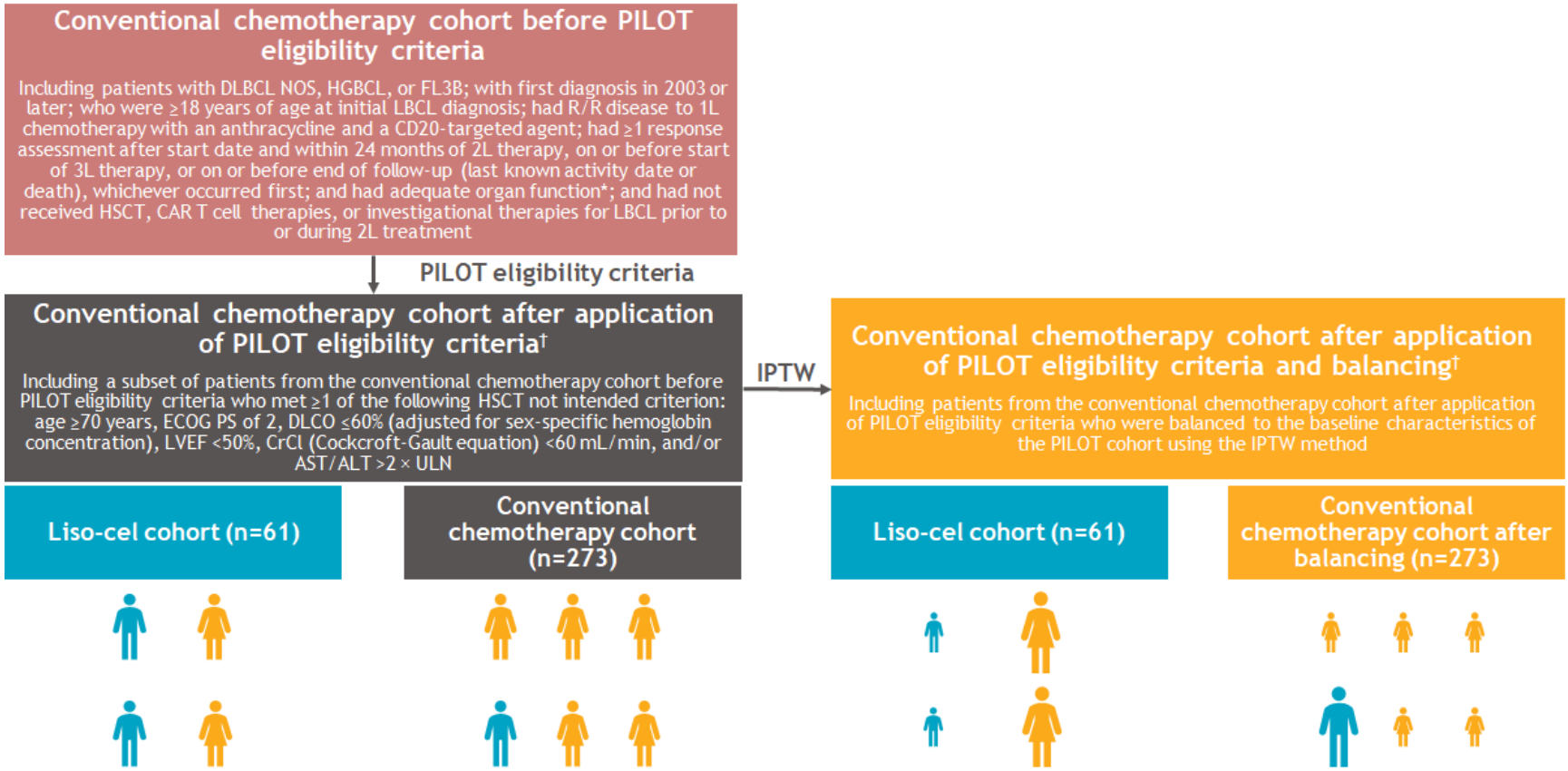
Supplementary Table S7. Unadjusted comparative efficacy outcomes in the liso-cel–leukapheresed cohort versus the conventional chemotherapy cohort but before balancing.

	Liso-cel–leukapheresed cohort (n=74)	**Conventional chemotherapy cohort after application of PILOT eligibility criteria but before balancing* (n=273)**
ORR, % (95% CI)	66 (54.3–76.8)	50 (44.1–56.3)
CR rate, % (95% CI)	46 (34.3–57.9)	23 (18.5–28.9)
Median (95% CI) EFS, mo	8.1 (4.2–13.3)	2.8 (2.3–3.2)
HR (95% CI)	0.38 (0.27–0.54)	
P value	<0.0001	
Median (95% CI) PFS, mo	8.1 (4.2–13.3)	2.8 (2.4–3.4)
HR (95% CI)	0.42 (0.30–0.58)	
P value	<0.0001	
Median (95% CI) OS, mo	NR (14.7–NR)	12.1 (9.7–15.9)
HR (95% CI)	0.58 (0.38–0.87)	
P value	0.0093	

*A subset of the conventional chemotherapy cohort who met the prespecified eligibility criteria of PILOT[3] but before balancing to baseline characteristics with the liso-cel–treated cohort.

CI: confidence interval; CR: complete response; DOR: duration of response; EFS: event-free survival; HR: hazard ratio; IPTW: inverse probability of treatment weighting; liso-cel: lisocabtagene maraleucel; NR: not reached; ORR: overall response rate; OS: overall survival; PFS: progression-free survival.

Supplementary Figure S1. Real-world cohorts.

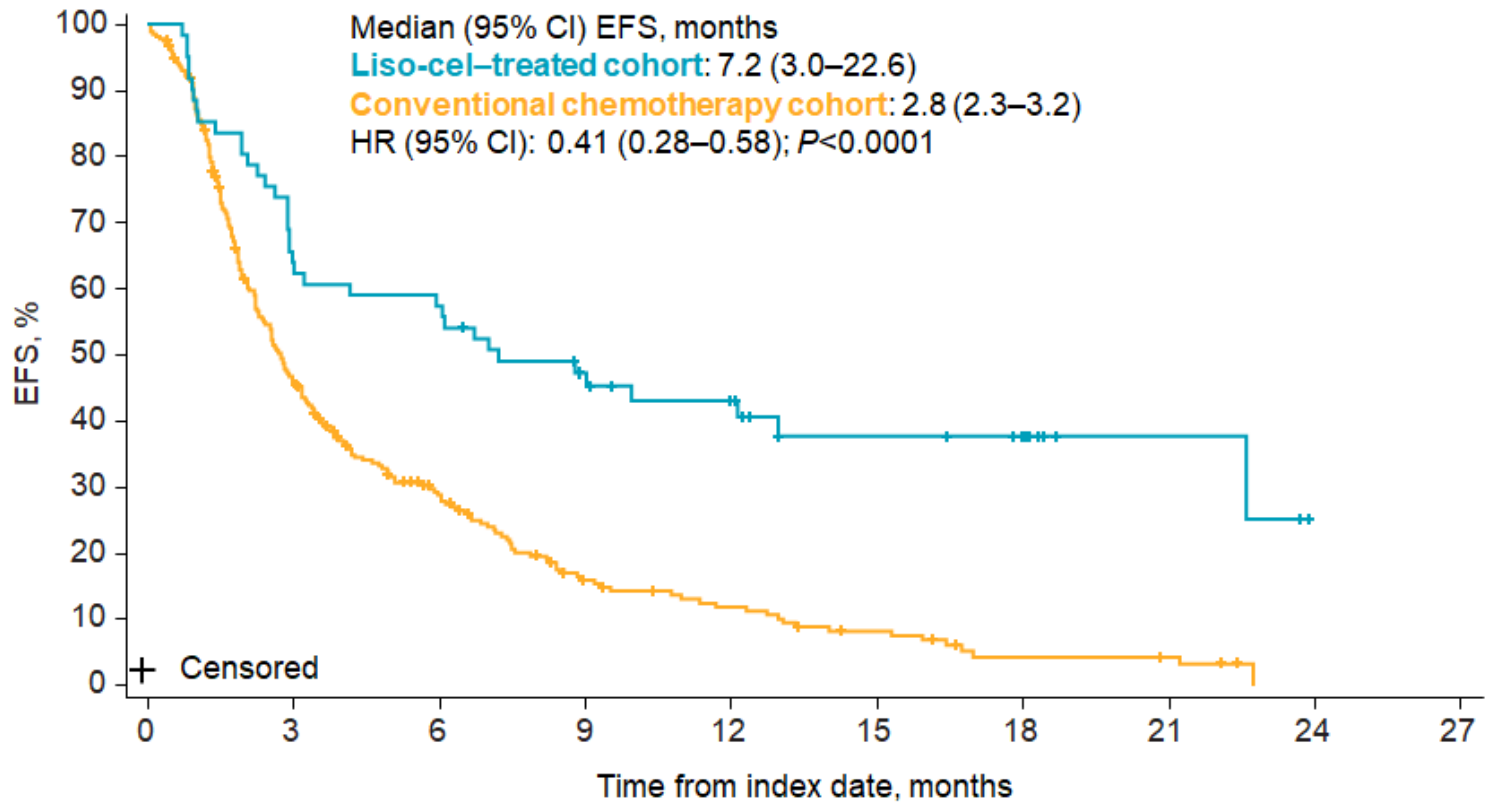


The size of the figure icons in the conventional chemotherapy cohort after application of PILOT eligibility criteria and balancing reflects the relative contribution of those patients' data toward the cohort as a whole after balancing to the baseline characteristics of the PILOT cohort using the IPTW method. *LVEF ≥40%, CrCl >30 mL/min, AST/ALT ≤5 × ULN, total bilirubin <2.0 mg/dL (or <3.0 mg/dL for patients with Gilbert's syndrome or lymphomatous infiltration of the liver). †Adjusted efficacy outcomes were reported in the conventional chemotherapy cohort after balancing, a subset of conventional chemotherapy cohort before balancing who were

matched with the liso-cel population using IPTW; patient demographics, baseline characteristics, and treatment patterns were reported in the conventional chemotherapy cohort before balancing. 1L: first line; 2L: second line; 3L: third line; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CAR: chimeric antigen receptor; CrCl: creatinine clearance; DLBCL: diffuse large B-cell lymphoma; DLCO: diffusing capacity of the lung for carbon monoxide; ECOG PS: Eastern Cooperative Oncology Group performance status; FL3B: follicular lymphoma grade 3B; HGBCL: high-grade B-cell lymphoma; HSCT: hematopoietic stem cell transplantation; IPTW: inverse probability of treatment weighting; LBCL: large B-cell lymphoma; liso-cel: lisocabtagene maraleucel; LVEF: left ventricular ejection fraction; NOS: not otherwise specified; R/R: relapsed or refractory; ULN: upper limit of normal.

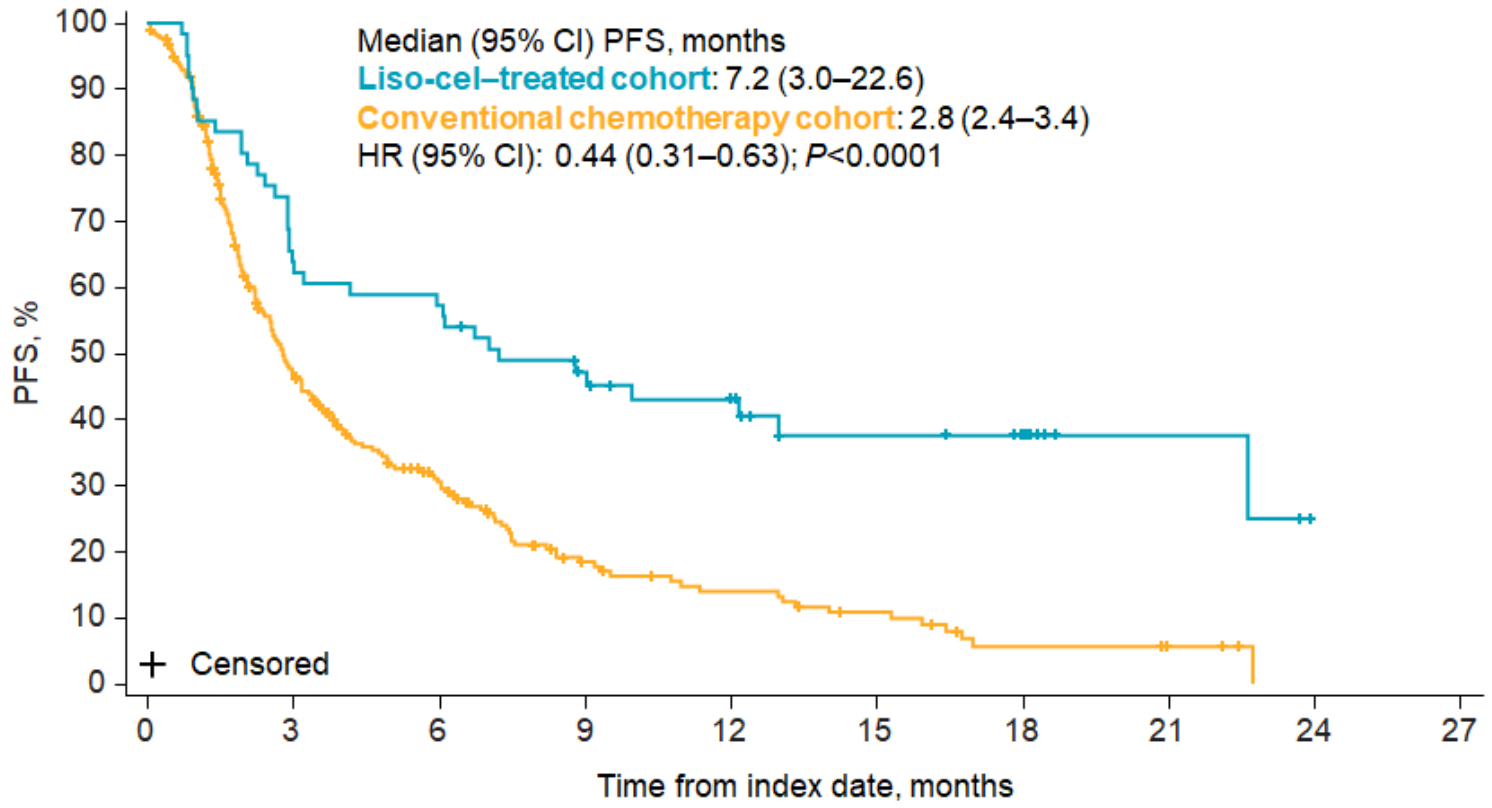
Supplementary Figure S2. Unadjusted comparative efficacy outcomes in the liso-cel–treated cohort versus the conventional chemotherapy cohort after application of PILOT eligibility criteria but before balancing.

A



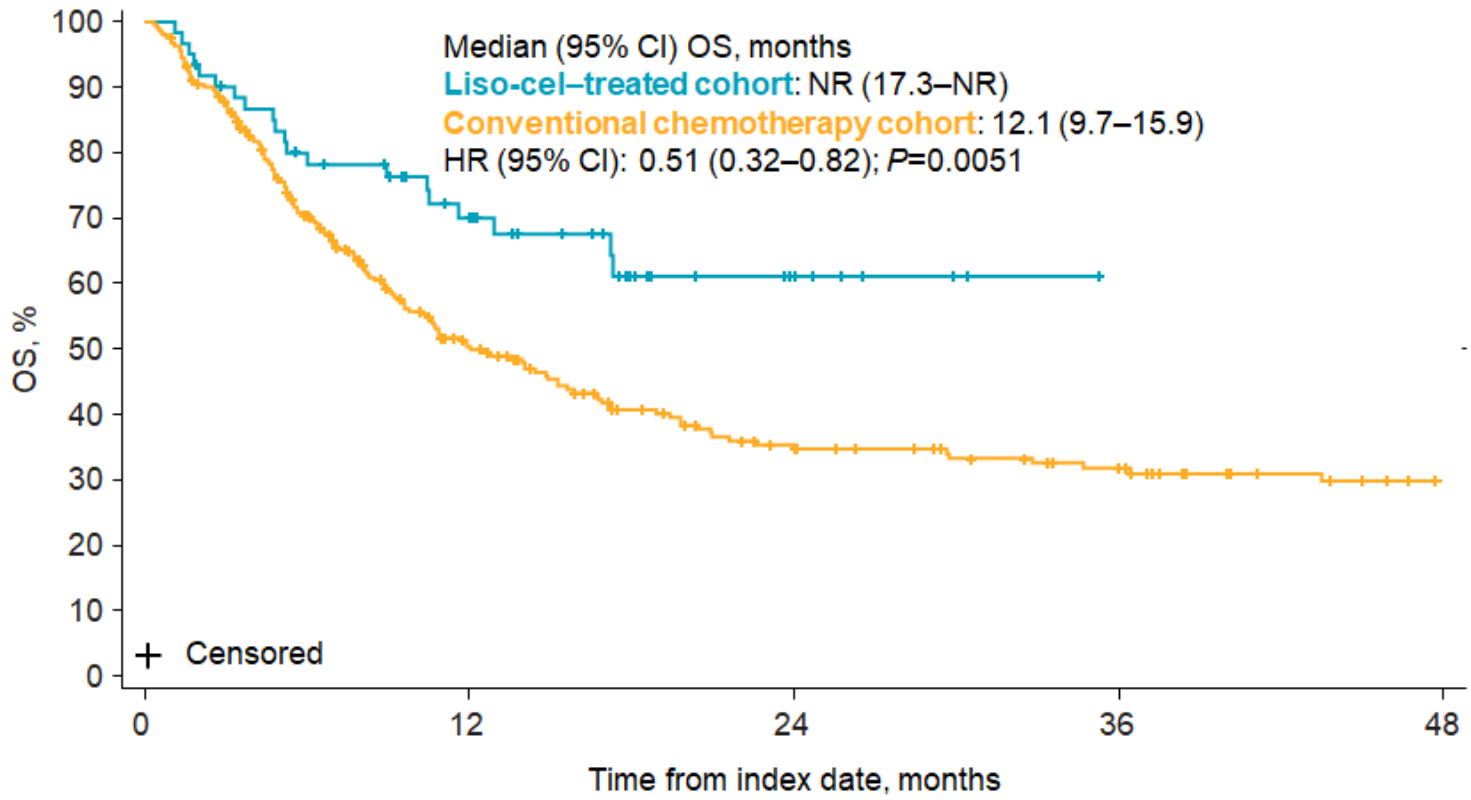
No. of patients at risk										
Liso-cel–treated cohort	61	39	35	24	19	12	9	3	0	0
Conventional chemotherapy cohort	273	117	62	29	20	12	5	4	0	0

B



No. of patients at risk										
Liso-cel–treated cohort	61	39	35	24	19	12	9	3	0	0
Conventional chemotherapy cohort	273	113	60	26	18	12	5	3	0	0

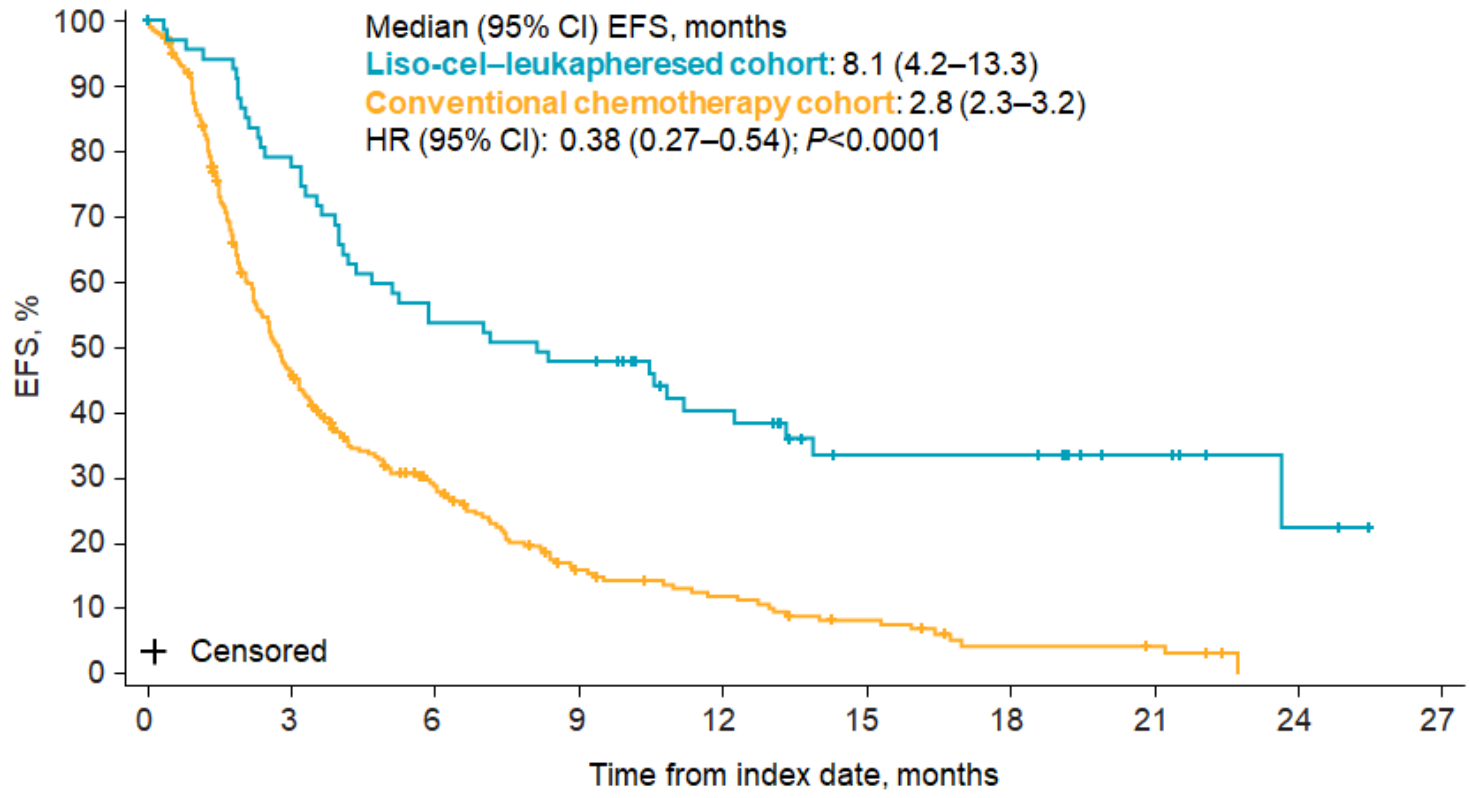
C



(A) EFS, (B) PFS, and (C) OS in the liso-cel–treated cohort versus conventional chemotherapy cohort. CI: confidence interval; EFS: event-free survival; liso-cel: lisocabtagene maraleucel; NR: not reached; OS: overall survival; PFS: progression-free survival.

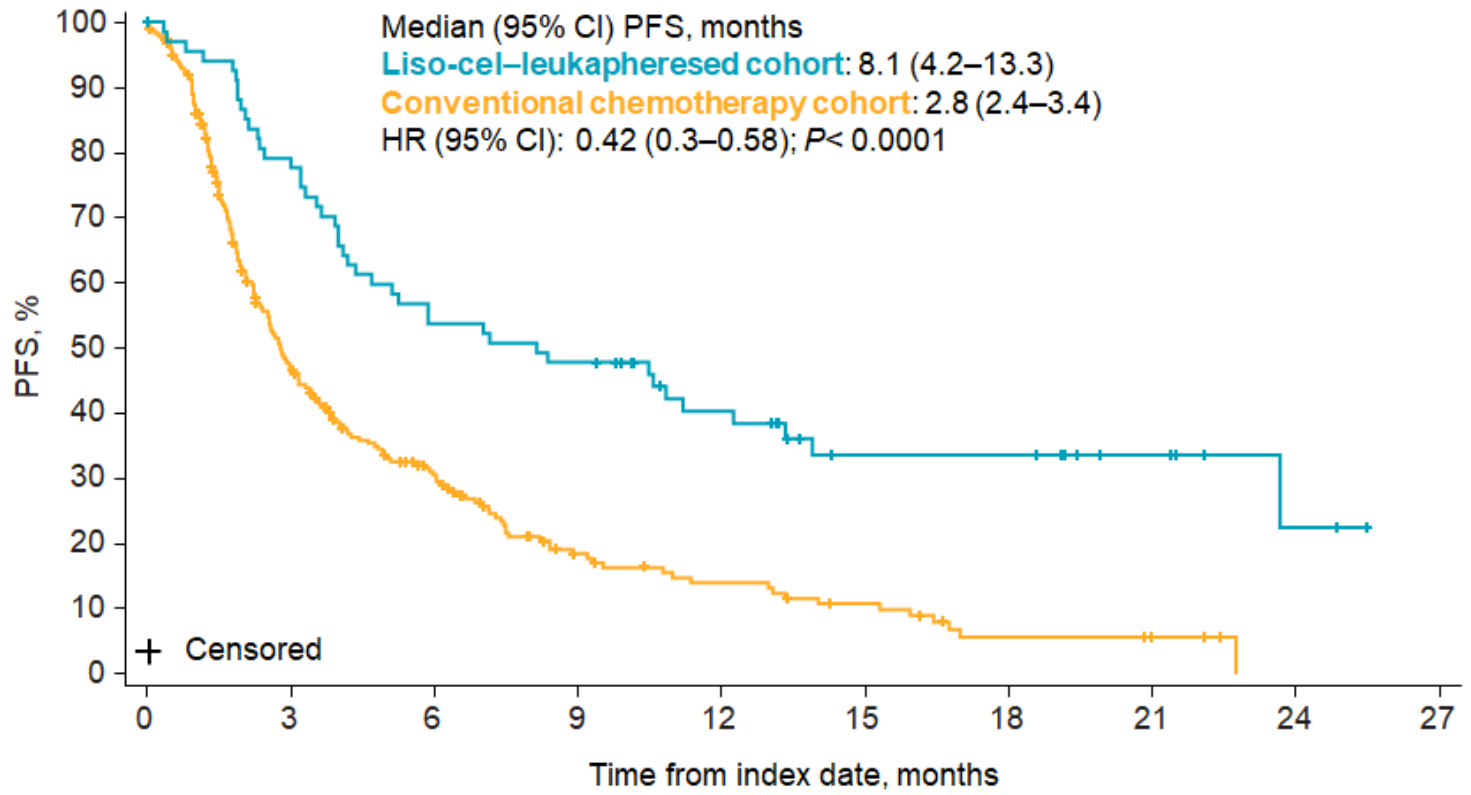
Supplementary Figure S3. Unadjusted comparative efficacy outcomes in the liso-cel–leukapheresed cohort versus the conventional chemotherapy cohort after application of PILOT eligibility criteria but before balancing.

A



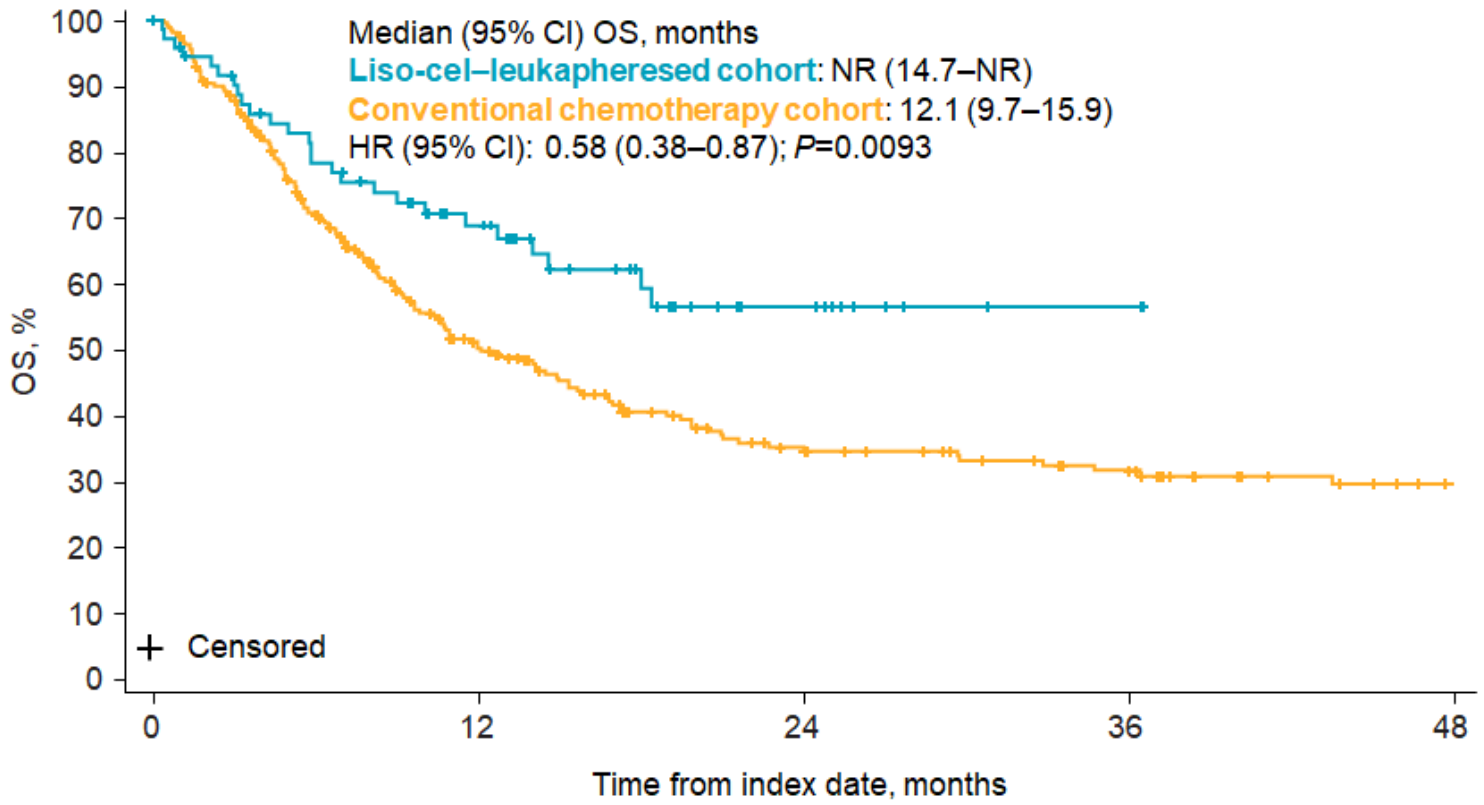
No. of patients at risk										
Liso-cel–leukapheresed cohort	74	53	36	32	21	12	12	6	2	0
Conventional chemotherapy cohort	273	117	62	29	20	12	5	4	0	0

B



No. of patients at risk										
Liso-cel–leukapheresed cohort	74	53	36	32	21	12	12	6	2	0
Conventional chemotherapy cohort	273	113	60	26	18	12	5	3	0	0

C



(A) EFS, (B) PFS, and (C) OS in the liso-cel–leukapheresed cohort vs conventional chemotherapy cohort. CI, confidence interval; EFS, event-free survival; liso-cel, lisocabtagene maraleucel; NR, not reached; OS, overall survival; PFS, progression-free survival.

References

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