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

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Abstract

This study assessed the comparative efficacy of lisocabtagene maraleucel (liso-cel) in the open-label, phase II PILOT study (clinicaltrials.gov NCT 03483103) *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 of 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 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 (ECOG PS), organ function and/or comorbidities.[5,6] In patients for whom HSCT is not appropriate, outcomes are historically poor (median overall survival [OS]: 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 (clinicaltrials.gov NCT 03483103), 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 an 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 of 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 principles of 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 a non-conforming 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 ECOG PS <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

Table 1. Patients' demographics and baseline characteristics in the study cohorts.

Characteristic	Liso-cel		Conventional chemotherapy	
	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 in years				
Median (range)	73.5 (53-84)	74 (53-84)	65 (18-93)	74 (21-93)
<70, N (%)	15 (20)	13 (21)	390 (65)	62 (23)
≥70, 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)
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 stage, N (%)				
I/II	21 (28)	21 (34)	115 (19)	41 (15)
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)
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 relapsed/refractory (R/R) large B-cell lymphoma (LBCL) after receiving therapy with an anthracycline and a 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 lisocabtagene maraleucel (liso-cel)–treated cohort. ‡Disease status was refractory if a patient achieved less than a complete response to last prior therapy; otherwise disease status was relapsed. 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. ¶High-grade B-cell lymphoma (HGBCL) with rearrangements in *MYC* and either *BCL2, BCL6,* or both. N: number; ECOG PS: Eastern Cooperative Oncology Group performance status; 1L: first line; DLBCL: diffuse large B-cell lymphoma; NOS: not otherwise specified; tFL: transformed follicular lymphoma.

(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

Table 2. Study follow-up.

Characteristic	Liso-cel		Conventional chemotherapy after application of PILOT eligibility criteria* N=273
	Liso-cel leukapheresed N=74	Liso-cel treated N=61	
Median follow-up time in months in all patients† (range)	11.9 (0.0-30.1)	12.3 (1.2-26.5)	9.0 (0.4-24.0)
Median follow-up time in months in all surviving patients‡ (range)	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 lisocabtagene maraleucel (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. N: number.

Table 3. Comparative adjusted efficacy outcomes in the lisocabtagene maraleucel–treated cohort *versus* the conventional chemotherapy cohort after balancing.

Adjusted efficacy outcomes	Trimmed stabilized IPTW*†		
	Liso-cel treated N=61	Conventional chemotherapy after application of PILOT eligibility criteria and balancing‡ N=273	
ORR, % (95% CI) RR (95% CI) *P*	79.6 (69.9-90.7)	50.5 (44.9-56.9) 1.6 (1.3-1.9) <0.0001	
CR, % (95% CI) RR (95% CI) *P*	53.1 (41.7-67.6)	24.0 (19.4-29.7) 2.2 (1.6-3.1) <0.0001	
Median time to response in months (range)	1.0 (0.8-2.2)	1.6 (0.1-21.0)	
Median DOR in months (95% CI) HR (95% CI) *P*	12.1 (3.6-20.6)	4.3 (2.7-5.9) 0.40 (0.25-0.64) 0.0001	
Median EFS in months (95% CI) HR (95% CI) *P*	7.0 (3.2-10.9)	2.8 (2.4-3.2) 0.43 (0.29-0.63) <0.0001	
Median PFS in months (95% CI) HR (95% CI) *P*	7.0 (3.2-10.9)	2.9 (2.4-3.3) 0.46 (0.32-0.68) <0.0001	
Median OS in months (95% CI) HR (95% CI) *P*	NR (NR-NR)	12.6 (9.6-15.5) 0.58 (0.36-0.94) 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 lisocabtagene maraleucel (liso-cel)–treated cohort, the weights = (1/*propensity score*) × *the proportion of liso-cel patients*. For the conventional chemotherapy cohort after balancing, the weights = (1/[1-*propensity score*]) × *the proportion of patients with conventional chemotherapies*. Stabilized inverse probability of treatment weightings (IPTW) 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. N: number; ORR: overall response rate; CI: confidence interval; RR: relative risk; CR: complete response; DOR: duration of response; HR: hazard ratio; EFS: event-free survival; PFS: progression-free survival; OS: overall survival; NR: not reached.

in disease stage and bulky disease; these differences were no longer present after balancing (*Online Supplementary Tables S2, S3*).

Median follow-up time was 11.9 months (range: 0.0-30.1) in the liso-cel–leukapheresed cohort, 12.3 months (range: 1.2-26.5) in the liso-cel–treated cohort, and 9.0 months (range: 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 - 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, Figure 2A, 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*). The CR rate was also higher with liso-cel: 53.2% *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 [RR]: 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; RR: 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; RR: 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; RR: 1.8 [95% CI: 1.3-2.5]; *P*=0.0013) were favorable with liso-cel *versus* conventional 2L chemotherapy regimens.

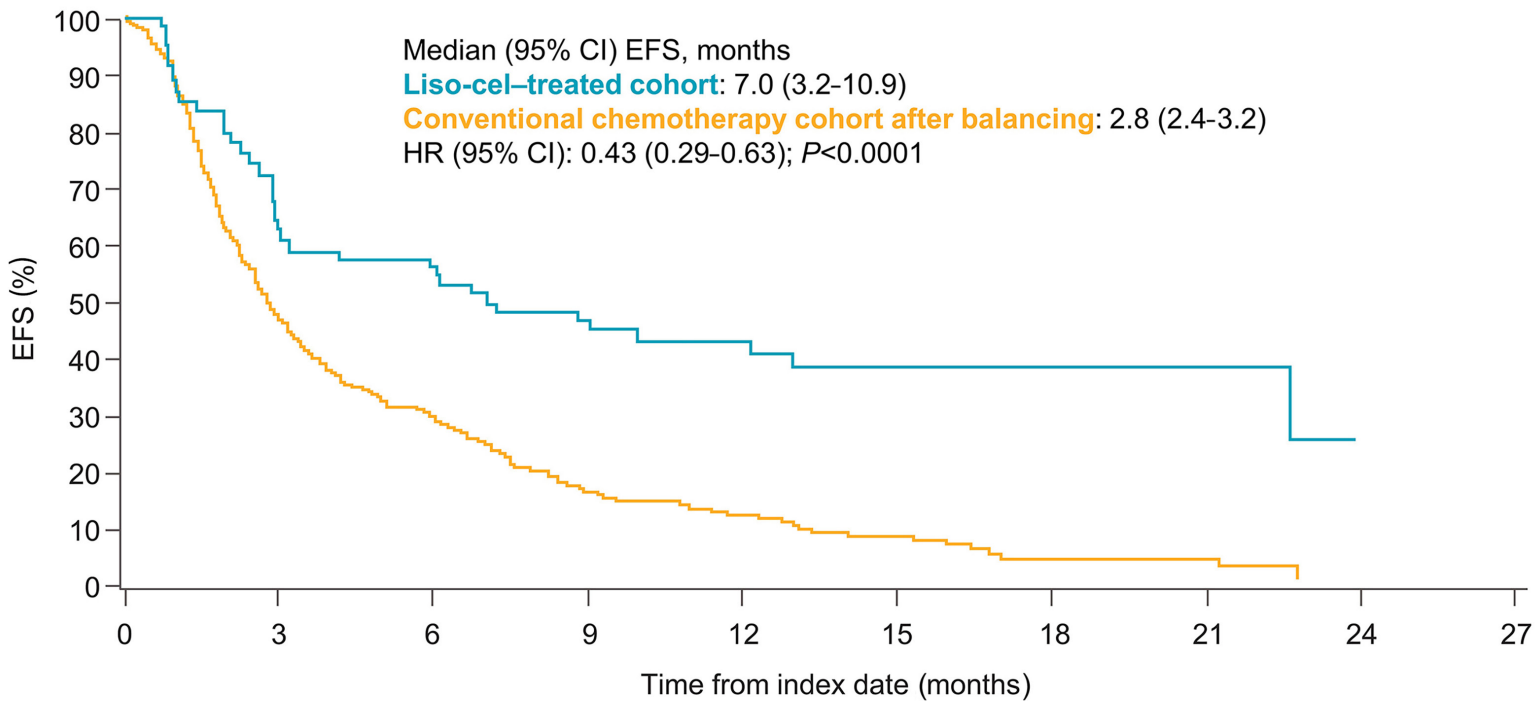
Unadjusted endpoint analyses

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, S7*). Significantly longer median EFS, PFS, and OS with liso-cel *versus* conventional chemotherapy regimens were also observed (*Online Supplementary Tables S6, S7, Online Supplementary Figures S2, 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 (Figures 3A, 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).

A



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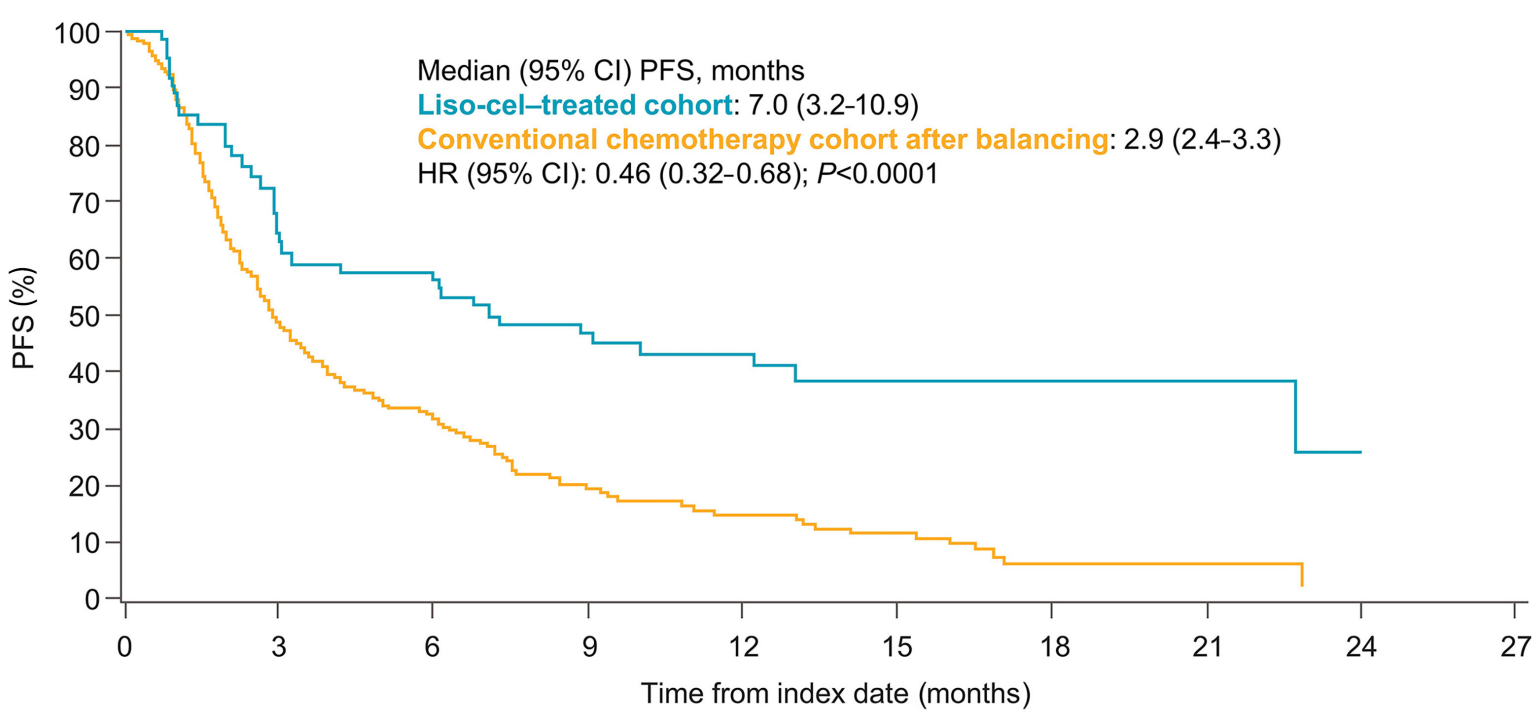

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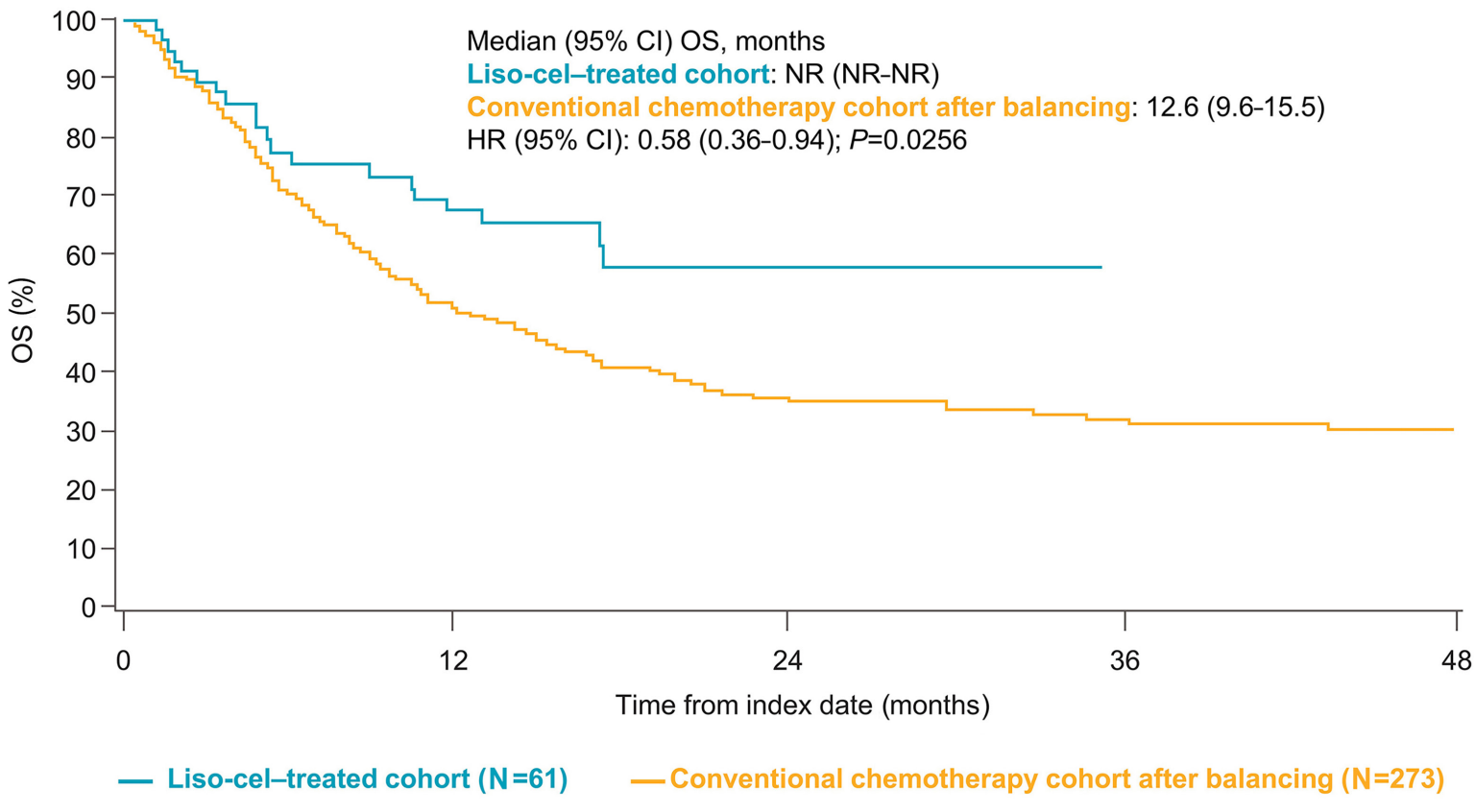

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Figure 1. Comparative adjusted efficacy outcomes in the lisocabtagene maraleucel–treated cohort *versus* the conventional chemotherapy cohort after application of PILOT eligibility criteria and balancing. (A) Event-free survival (EFS), (B) progression-free survival (PFS) and (C) overall survival (OS) adjusted by trimmed stabilized inverse probability of treatment weighting (IPTW) in the lisocabtagene maraleucel (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 = (1/*propensity score*) × *the proportion of liso-cel patients*. For the conventional chemotherapy cohort after balancing, the weights = (1/[1-*propensity score*]) × *the proportion of patients with conventional chemotherapies*. Stabilized IPTW were trimmed at the 5th and 95th percentiles. CI: confidence interval; HR: hazard ratio; NR: not reached.

Table 4. Comparative adjusted efficacy outcomes in the lisocabtagene maraleucel–leukapheresed cohort *versus* conventional chemotherapy cohort after balancing.

Adjusted efficacy outcomes	Trimmed stabilized IPTW*†	
	Liso-cel leukapheresed N=74	Conventional chemotherapy after application of PILOT eligibility criteria and balancing‡ N=273
ORR, % (95% CI) RR (95% CI) *P*	65.7 (55.6-77.8)	50.4 (44.8-56.8) 1.3 (1.1-1.6) 0.0116
CR rate, % (95% CI) RR (95% CI) *P*	45.3 (35.1-58.5)	23.9 (19.3-29.7) 1.9 (1.4-2.6) 0.0002
Median EFS in months (95% CI) HR (95% CI) *P*	8.1 (3.1-13.2)	2.8 (2.4-3.2) 0.39 (0.28-0.55) <0.0001
Median PFS in months (95% CI) HR (95% CI) *P*	8.1 (3.1-13.2)	2.8 (2.4-3.3) 0.42 (0.30-0.60) <0.0001
Median OS in months (95% CI) HR (95% CI) *P*	NR (NR-NR)	12.6 (9.6-15.6) 0.60 (0.39-0.93) 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 lisocabtagene maraleucel (liso-cel)–treated cohort, the weights = (1/*propensity score)* × *the proportion of liso-cel patients*. For the conventional chemotherapy cohort after balancing, the weights = (1/[1-*propensity score*]) × *the proportion of patients with conventional chemotherapies.* Stabilized inverse probability of treatment weightings (IPTW) 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. N: number; ORR: overall response rate; CI: confidence interval; RR: relative risk; CR: complete response; EFS: event-free survival; HR: hazard ratio; PFS: progression-free survival; OS: overall survival; NR: not reached.

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

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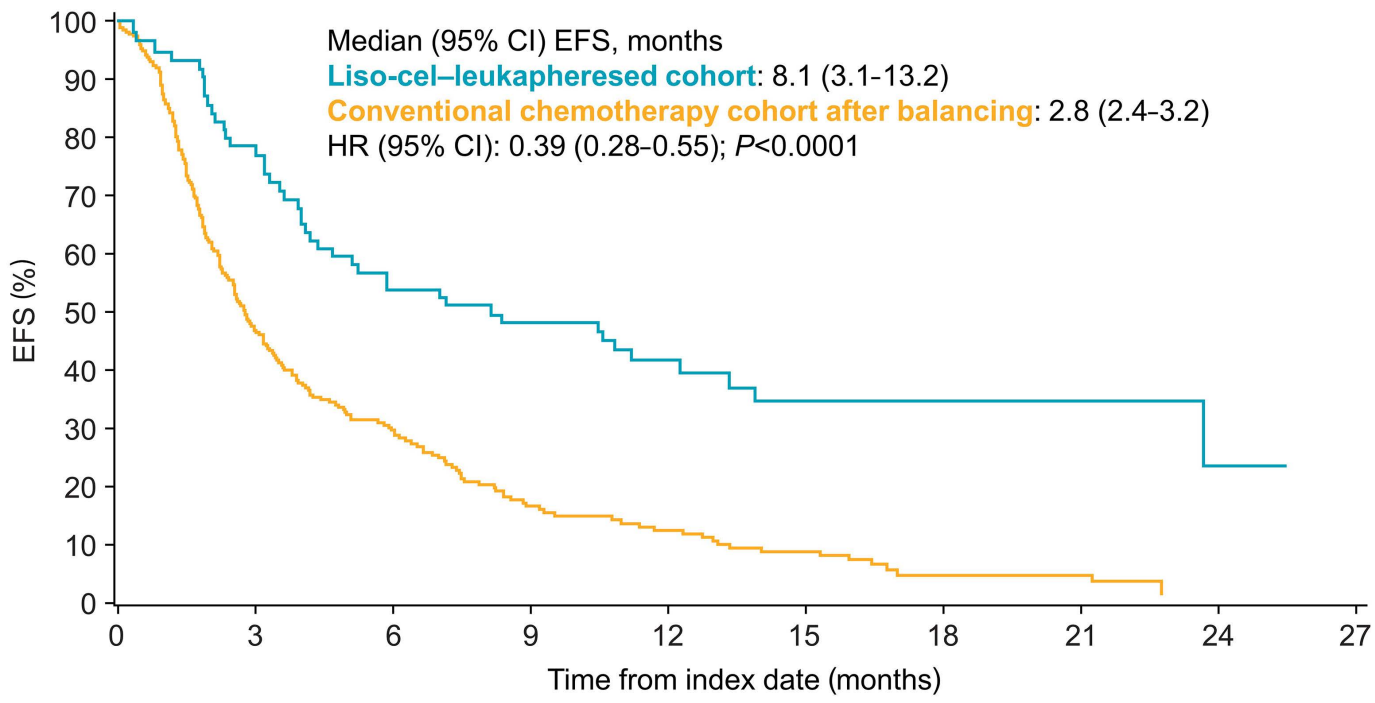

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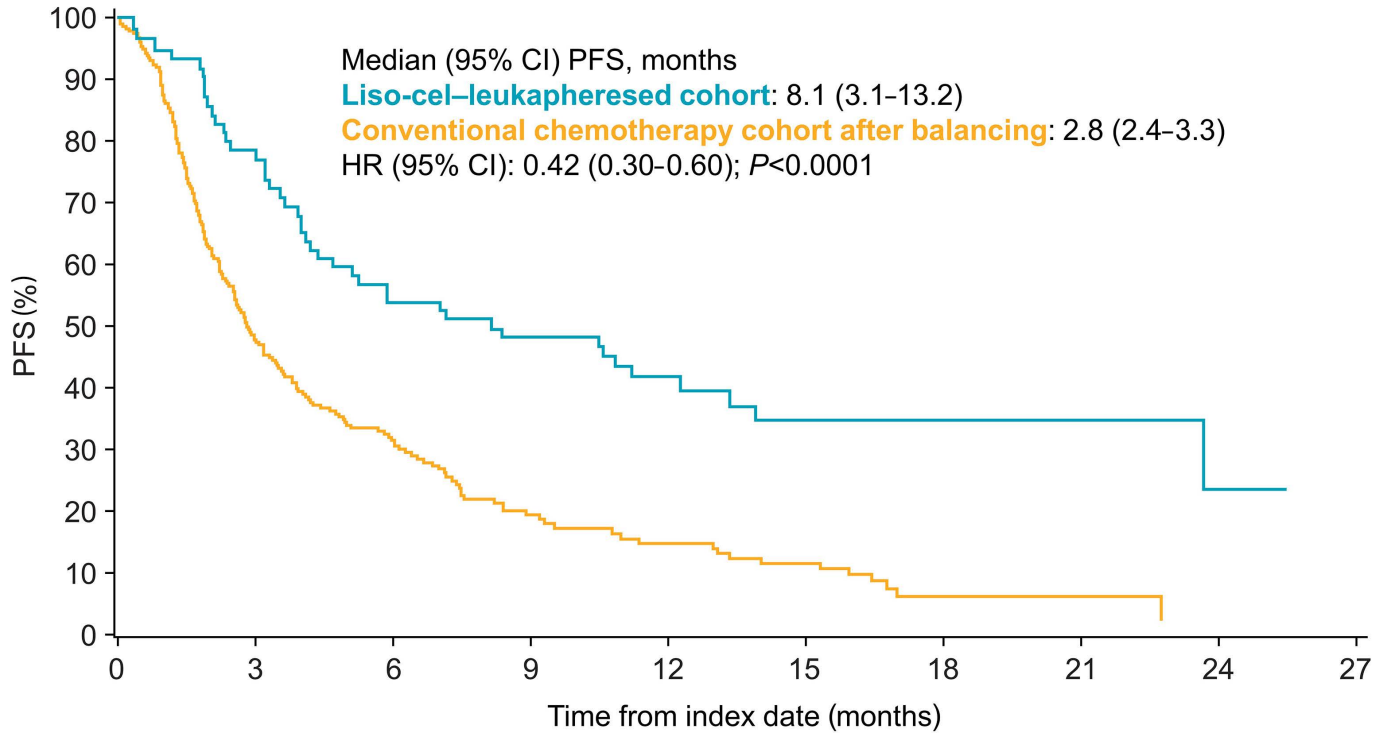

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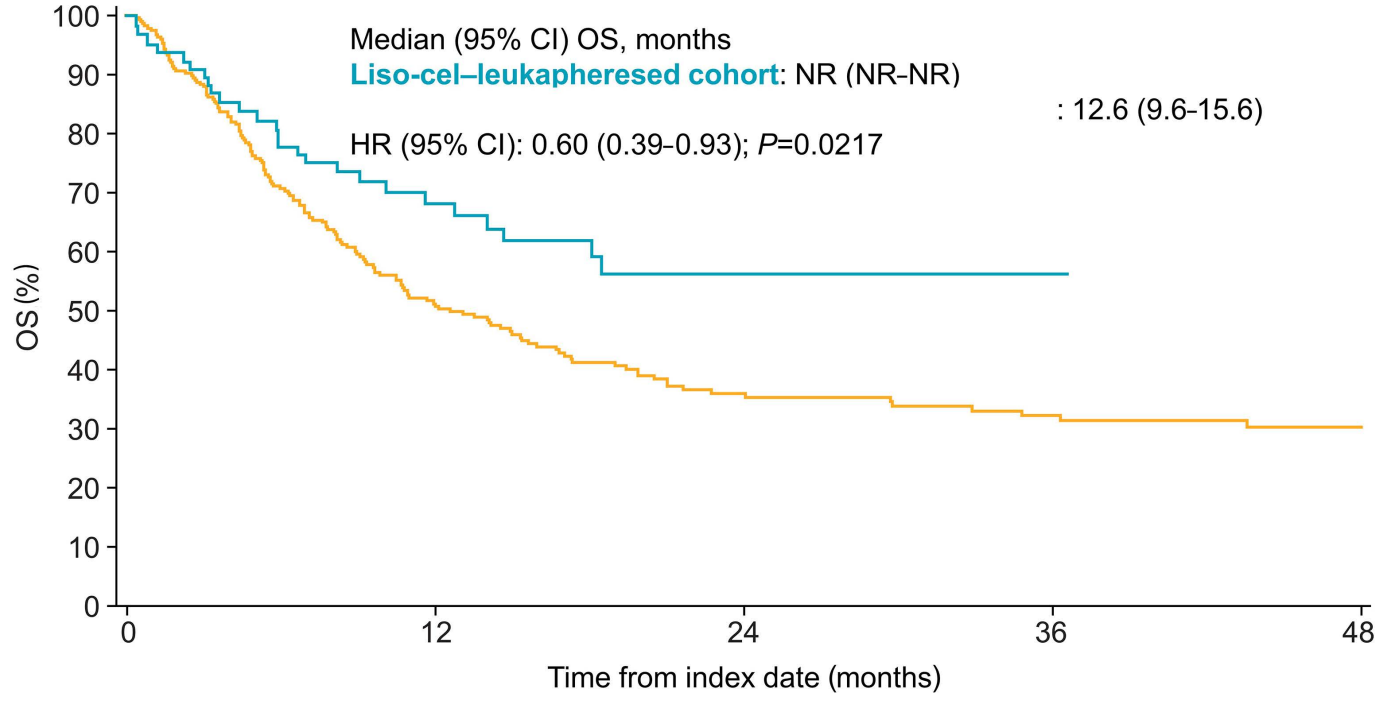

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Figure 2. Comparative adjusted efficacy outcomes in the lisocabtagene maraleucel–leukapheresed cohort *versus* the conventional chemotherapy cohort after application of PILOT eligibility criteria and balancing. (A) Event-free survival (EFS), (B) progression-free survival (PFS) and (C) overall survival (OS) adjusted by trimmed stabilized inverse probability of treatment weighting (IPTW) in the lisocabtagene maraleucel (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 = (1/*propensity score*) × *the proportion of liso-cel patients*. For the conventional chemotherapy cohort after balancing, the weights = (1/[1-*propensity score*]) × *the proportion of patients with conventional chemotherapies*. Stabilized IPTW were trimmed at the 5th and 95th percentiles. CI: confidence interval; HR: hazard ratio; NR: not reached.

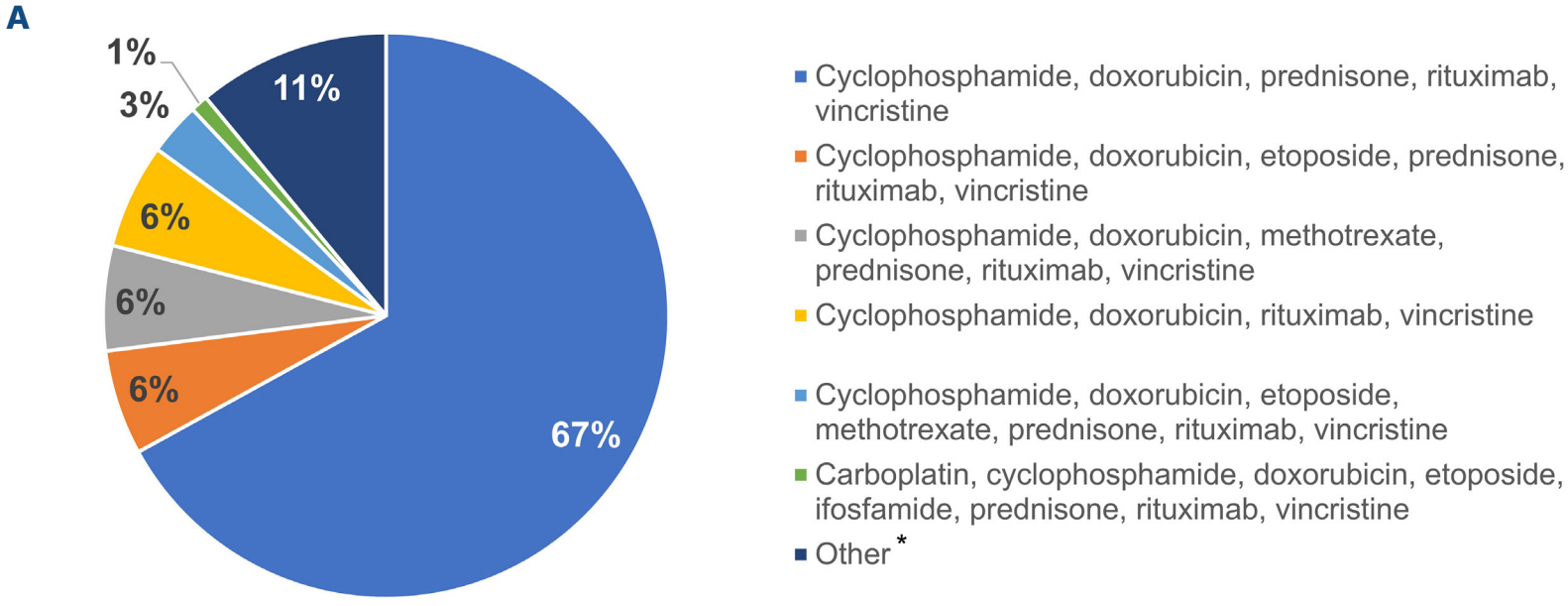
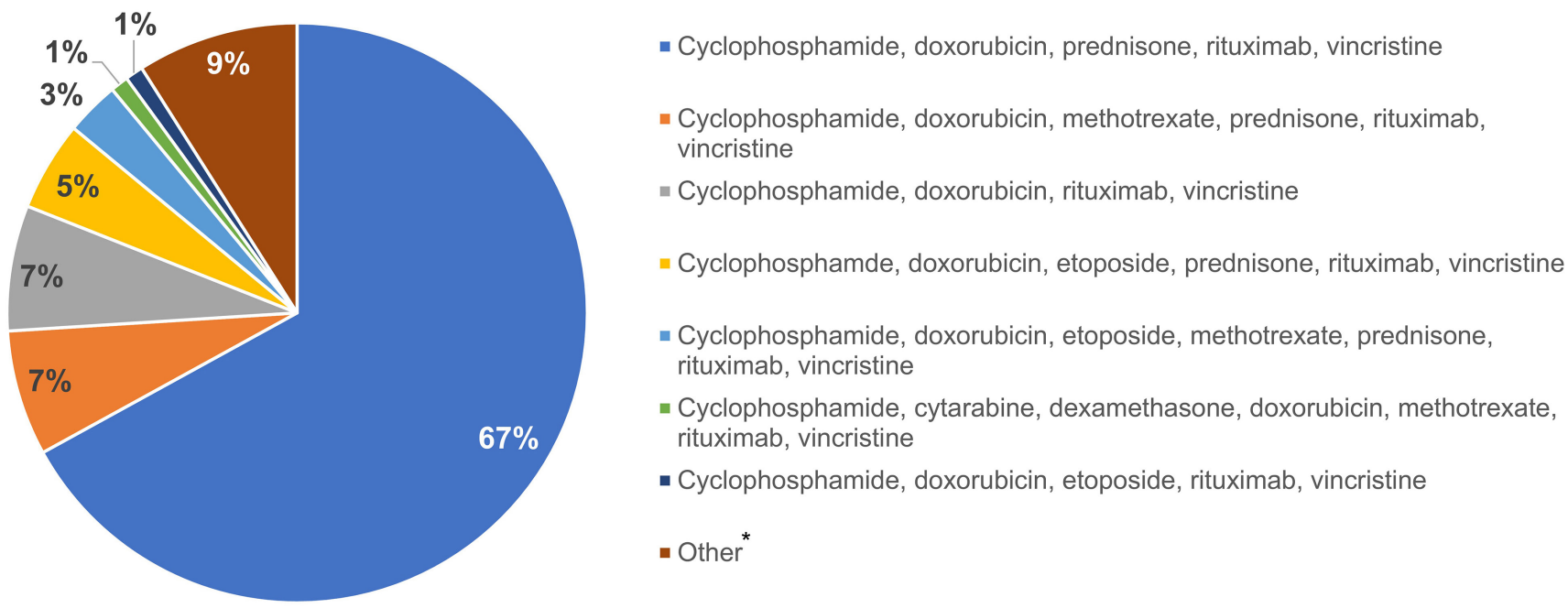


Figure 3. First- and second-line treatment in the conventional chemotherapy cohorts before PILOT eligibility criteria. (A) First- and (B) second-line treatments in all patients in the conventional chemotherapy cohort with relapsed/refractory large B-cell lymphoma after receiving therapy with an anthracycline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

A



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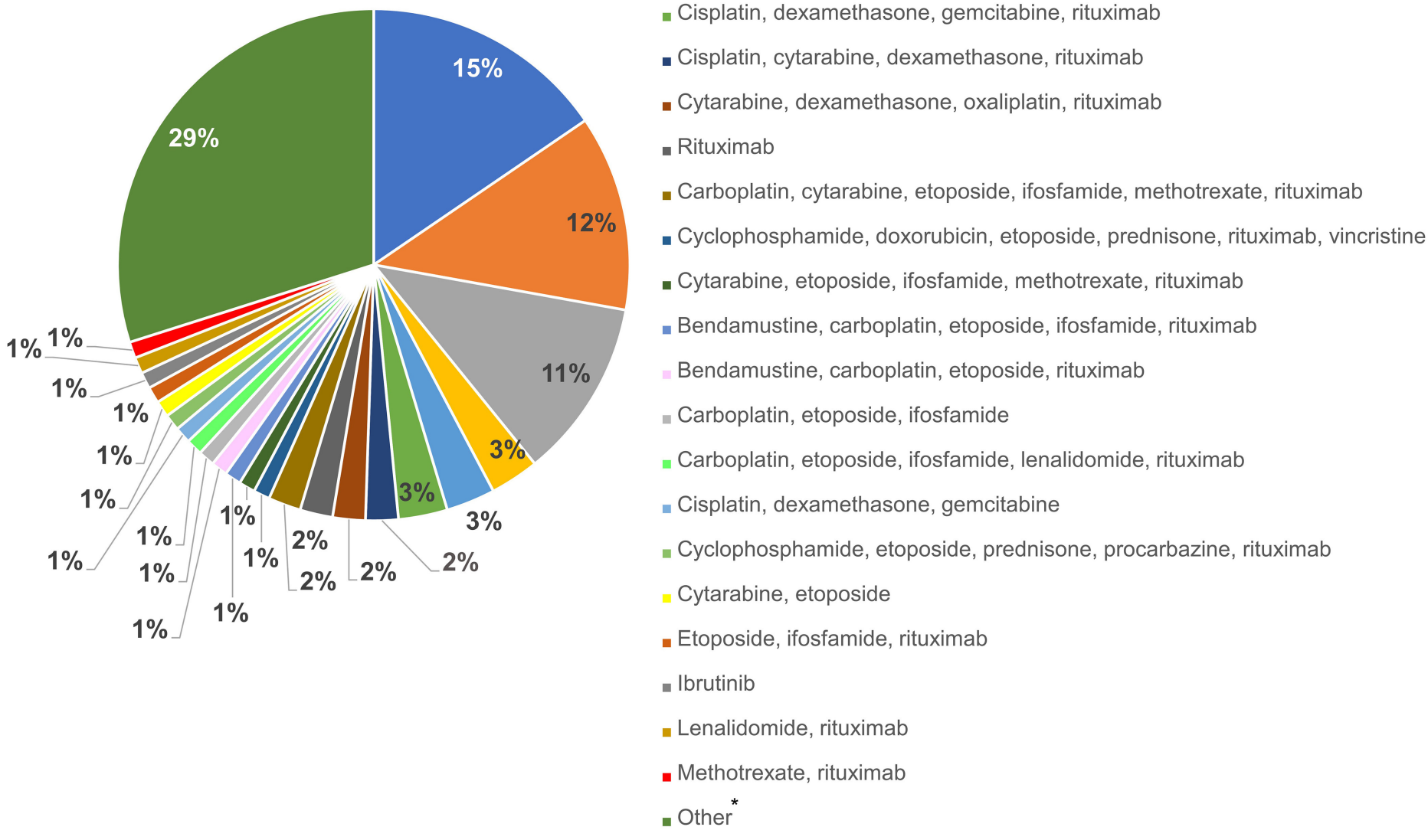

Figure 4. First- and second-line treatment in the conventional chemotherapy cohorts after application of PILOT eligibility criteria but before balancing. (A) First- and (B) second-line treatments in a subset of the conventional chemotherapy cohort who met the prespecified eligibility criteria of PILOT[12]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

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.

Inverse probability of treatment weighting (IPTW) and greedy nearest neighbor matching are established methods for balancing comparator populations in non-randomized 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 3 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; clinicaltrials.gov NCT 02631044) *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 non-randomized 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 pre-existing 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 pre-existing relationship, and state of current data model. Moreover, as is the case for any comparative study utilizing real-world data, factors that may differ between real-world conditions and 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, there were no systematic differences in index date assignments 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.

Disclosures

NG declares consultancy from AstraZeneca, ADC Therapeutics, AbbVie, Genmab, Janssen, Bristol Myers Squibb, Beigene, Incyte, Gilead/Kite, Roche/Genentech, Lava Therapeutics, Ascentage Pharma, Loxo Oncology, and Novartis, and research funding from Roche/Genentech, AbbVie, Incyte, AstraZeneca, Bristol Myers Squibb, and Gilead/Kite. AS declares speakers bureaus for OncLive and research funding from Gilead/Kite, Juno Therapeutics, a Bristol-Myers Squibb Company, Chimagen, and Cytoagents. FFL, AK, AC, MDB and LP are current employees and equity holders at Bristol Myers Squibb. JF was an employee of Bristol Myers Squibb at the time the study was conducted and an equity holder at Bristol Myers Squibb. LIG declares consultancy from Ono Pharmaceuticals, advisory boards for Bristol Myers Squibb and Kite Pharmaceuticals, data and safety monitoring boards for Janssen, is co-founder of Zylem Biosciences, and holds patents for nanoparticles for cancer therapy (PCT/US2020/051549) and nanostructures for treating cancer and other conditions (PCT/US2013/027431).

Contributions

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. MDB contributed to data analysis and data interpretation. All authors helped write the manuscript.

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Data-sharing statement

Bristol Myers Squibb policy on data sharing may be found at https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html

References

1. Coiffier B, Sarkozy C. Diffuse large B-cell lymphoma: R-CHOP failure-what to do? Hematology Am Soc Hematol Educ Program. 2016;2016(1):366-378.
2. Tilly H, Morschhauser F, Sehn LH, et al. Polatuzumab vedotin in previously untreated diffuse large B-cell lymphoma. N Engl J Med. 2022;386(4):351-363.
3. Abramson JS, Solomon SR, Arnason JE, et al. Lisocabtagene maraleucel as second-line therapy for large B-cell lymphoma: primary analysis of phase 3 TRANSFORM study. Blood. 2023;141(14):1675-1684.
4. Locke FL, Miklos DB, Jacobson CA, et al.; for All ZUMA-7 Investigators and Contributing Kite Members. Axicabtagene ciloleucel as second-line therapy for large B-cell lymphoma. N Engl J Med. 2022;386(7):640-654.
5. Crump M, Kuruvilla J, Couban S, et al. Randomized comparison of gemcitabine, dexamethasone, and cisplatin versus dexamethasone, cytarabine, and cisplatin chemotherapy before autologous stem-cell transplantation for relapsed and refractory aggressive lymphomas: NCIC-CTG LY.12. J Clin Oncol. 2014;32(31):3490-3496.
6. Sehn LH, Salles G. Diffuse large B-cell lymphoma. N Engl J Med. 2021;384(9):842-858.
7. van Imhoff GW, McMillan A, Matasar MJ, et al. Ofatumumab versus rituximab salvage chemoimmunotherapy in relapsed or refractory diffuse large B-cell lymphoma: the ORCHARRD study. J Clin Oncol. 2017;35(5):544-551.
8. Crump M, Neelapu SS, Farooq U, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. Blood. 2017;130(16):1800-1808.
9. Salles G, Duell J, Gonzalez Barca E, et al. Tafasitamab plus lenalidomide in relapsed or refractory diffuse large B-cell lymphoma (L-MIND): a multicentre, prospective, single-arm, phase 2 study. Lancet Oncol. 2020;21(7):978-988.
10. Sehn LH, Herrera AF, Flowers CR, et al. Polatuzumab vedotin in relapsed or refractory diffuse large B-cell lymphoma. J Clin Oncol. 2020;38(2):155-165.
11. Houot R, Bachy E, Cartron G, et al. Axicabtagene ciloleucel as second-line therapy in large B cell lymphoma ineligible for autologous stem cell transplantation: a phase 2 trial. Nat Med. 2023;29(10):2593-2601.
12. Sehgal A, Hoda D, Riedell PA, et al. Lisocabtagene maraleucel as second-line therapy in adults with relapsed or refractory large B-cell lymphoma who were not intended for haematopoietic stem cell transplantation (PILOT): an open-label, phase 2 study. Lancet Oncol. 2022;23(8):1066-1077.
13. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014;32(27):3059-3068.
14. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. Stat Med. 2015;34(28):3661-3679.
15. Tilly H, Gomes da Silva M, Vitolo U, et al.; on behalf of the ESMO Guidelines Committee. Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26(Suppl 5):v116-v125.
16. Duell J, Maddocks KJ, González-Barca E, et al. Long-term outcomes from the phase II L-MIND study of tafasitamab (MOR208) plus lenalidomide in patients with relapsed or refractory diffuse large B-cell lymphoma. Haematologica. 2021;106(9):2417-2426.
17. Hamadani M, Radford J, Carlo-Stella C, et al. Final results of a phase 1 study of loncastuximab tesirine in relapsed/refractory B-cell non-Hodgkin lymphoma. Blood. 2021;137(19):2634-2645.
18. Mazza IA, Kim WS, Ko P-S, et al. Subcutaneous epcoritamab plus lenalidomide in patients with relapsed/refractory diffuse large B-cell lymphoma from EPCORE NHL-5. Blood.

2023;142(Suppl 1):438.
19. Brody J, Joergensen JM, Belada D, et al. Epcoritamab SC + GemOx leads to high complete metabolic response rates in patients with relapsed/refractory diffuse large B-cell lymphoma ineligible for autologous stem cell transplant: updated results from Epcore NHL-2. Blood. 2023;142(Suppl 1):3092.
20. Hutchings M, Avigdor A, Balari AMS, et al. Glofitamab plus polatuzumab vedotin continues to demonstrate frequent and durable responses and has a manageable safety profile in patients with ≥2L relapsed/refractory DLBCL, including HGBCL, and in patients with prior CAR T-cell therapy: updated results from a phase Ib/II study. Blood. 2023;142(Suppl 1):4460.
21. Van Le H, Van Naarden Braun K, Nowakowski GS, et al. Use of a real-world synthetic control arm for direct comparison of lisocabtagene maraleucel and conventional therapy in relapsed/refractory large B-cell lymphoma. Leuk Lymphoma. 2023;64(3):573-585.
22. Salles G, Spin P, Liu FF, Garcia J, Kim Y, Hasskarl J. Indirect treatment comparison of liso-cel vs. salvage chemotherapy in diffuse large B-cell lymphoma: TRANSCEND vs. SCHOLAR-1. Adv Ther. 2021;38(6):3266-3280.