Optimizing post—chimeric antigen receptor T cell monitoring: evidence across lisocabtagene maraleucel pivotal clinical trials and real-world experience

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Background

- CD19-directed chimeric antigen receptor (CAR) T cell therapies have demonstrated remarkable efficacy in patients with B-cell malignancies, with cytokine release syndrome (CRS) and immune effector cell—associated neurotoxicity syndrome (ICANS)/neurological events (NE) being the key safety considerations[1–6]
- Current monitoring requirements mandate patients to remain near a certified health care facility for ≥ 4 weeks after infusion, creating logistical barriers and socioeconomic disparities that may limit patient access to these therapies[7–11]
- Lisocabtagene maraleucel (liso-cel) is an autologous, CD19-directed, 4-1BB CAR T cell therapy that has shown clinically meaningful efficacy and manageable safety in the treatment of patients with R/R large B-cell lymphoma (LBCL), chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), follicular lymphoma (FL), and mantle cell lymphoma (MCL)[1–6]

Objective

- To present comprehensive data (N = 1579) from R/R LBCL, CLL/SLL, FL, and MCL clinical trials, as well as real-world data for R/R LBCL from the Center for International Blood and Marrow Transplant Research (CIBMTR) Registry, for the timing of onset, grade, time to resolution, and management of CRS and ICANS/NEs after infusion with liso-cel

Methods

- Clinical trial data were pooled from the 5 liso-cel clinical trials in R/R LBCL, CLL/SLL, FL, and MCL; results from each trial have been previously published[1–6]
- Real-world data in the standard of care (SOC) setting were extracted from the CIBMTR Registry and included patients who were prescribed liso-cel for R/R LBCL and had ≥ 1 reported assessment after infusion; data were collected between February 5, 2021 (FDA approval date of liso-cel), and May 7, 2024
- CRS was reported as an AE based on Medical Dictionary for Regulatory Activities in clinical trials; for CIBMTR data, sites reported CRS symptoms and CIBMTR derived the grade. In both settings, CRS was graded according to Lee 2014 criteria[12]
- NEs were defined as investigator-identified neurological AEs related to liso-cel and graded per NCI CTCAE, version 4.03 or 5.0, for clinical trials. For real-world data, ICANS incidence was captured as reported by sites; maximum grade during the reporting period was derived by CIBMTR based on reported symptoms and graded according to 2019 American Society for Transplantation and Cellular Therapy criteria[13]
- AE grades in clinical trials were reported at onset and as maximum event grade of the first episode; grades in real-world data were reported as the maximum event grade during the reporting period

Results

Patients

Table 1. Demographics and baseline characteristics of patients from pivotal clinical trials and the real-world setting (CIBMTR)

	Pivotal clinical trials (N = 702)	CIBMTR Registry (N = 877)
Median (range) age, y	65.0 (18.0–86.0)	70.6 (23.3–91.2)
Male, n (%)	447 (64)	532 (61)
Race, n (%)		
White	549 (78)	752 (86)
Black or African American	25 (4)	39 (4)
Asian	39 (6)	44 (5)
Other	6 (1)	9 (1)
Not reported/unknown	83 (11)	33 (4)
Disease indication/histology, n (%)		
DLBCL	313 (45)	715 (82)
HGBCL	77 (11)	111 (13)
PMBCL	23 (3)	7 (0.8)
FL3B	4 (0.6)	10 (1)
THRBCL	1 (0.1)	0
Other B-cell lymphoma	0	29 (3)[a]
Not reported/unknown	0	5 (0.6)
CLL/SLL	89 (13)	0
FL grade 1, 2, or 3A	107 (15)	0
MCL	88 (13)	0
ECOG PS, n (%)[b]		
0—1	682 (97)	719 (82)
≥ 2	20 (3)	56 (6)
Not reported/unknown	0	102 (12)
Disease status, n (%)		
Refractory	497 (71)	571 (65)
Relapsed	205 (29)	289 (33)
Not reported/unknown	0	17 (2)
Received bridging therapy, n (%)	418 (60)	500 (57)

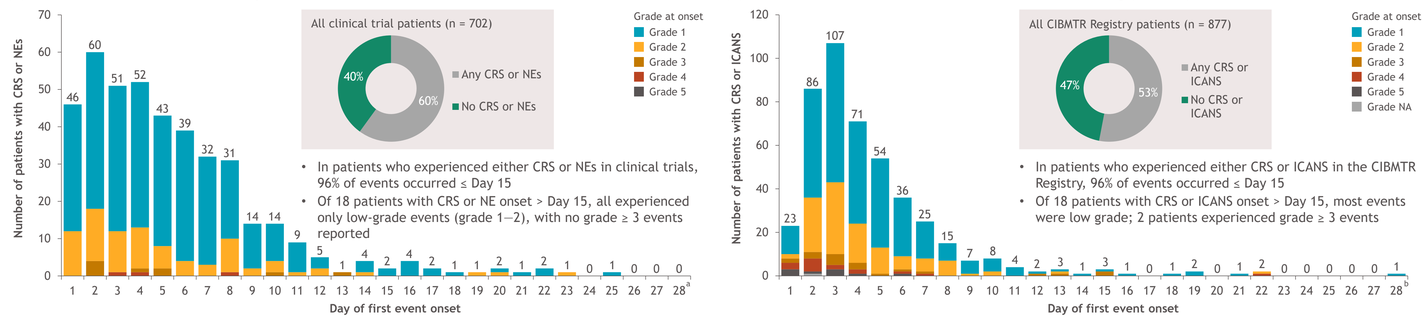
[a]May include other uses per physician choice; [b]At screening for clinical trials and at infusion for CIBMTR data.
DLBCL, diffuse large B-cell lymphoma; FL3B, follicular lymphoma grade 3B; HGBCL, high-grade B-cell lymphoma; PMBCL, primary mediastinal B-cell lymphoma; THRBCL, T-cell/histiocyte-rich large B-cell lymphoma.

- Patients enrolled in the clinical trials were younger and more likely to have ECOG PS 0—1 than those from the real-world CIBMTR Registry, with different histology distributions (multiple B-cell malignancies vs primarily LBCL, respectively)
- Both cohorts had similar proportions of refractory disease and bridging therapy history, with longer follow-up in the clinical trial population

Liso-cel continues to demonstrate a predictable safety profile across pivotal clinical trials and the real-world setting, with 96% of CRS or ICANS/NEs occurring ≤ Day 15 after infusion, suggesting monitoring requirements could be further optimized

- In patients treated with liso-cel who developed AEs in pivotal clinical trials or the real-world setting (CIBMTR), 98% and 97% of CRS events, respectively, and 88% and 95% of ICANS/NEs, respectively, occurred ≤ Day 15 after infusion

Figure 1. Time to either CRS or ICANS/NEs in (A) pivotal clinical trials and (B) the real-world setting (CIBMTR)



[a]After Day 28, 3 additional events occurred (Day 33, n = 1; Day 63, n = 2); [b]After Day 28, 10 additional events occurred (n = 1 each on Days 39, 40, 46, 55, 96, 97, 132, 226, 495, and 554).
NA, not yet assigned or missing.

Table 2. Timing of CRS and ICANS/NE onset and resolution

	Pivotal clinical trials (N = 702)		CIBMTR Registry (N = 877)	
	CRS	NEs	CRS	ICANS
Any grade, n (%)	381 (54)	220 (31)	430 (49)[a]	234 (27)[a,b]
Grade at onset, n (%)				
Grade 1—2	374 (53)	188 (27)	—	—
Grade ≥ 3	7 (1)	32 (5)	—	—
Maximum grade, n (%)				
Grade 1—2	359 (51)	153 (22)	403 (46)	142 (16)
Grade ≥ 3	22 (3)	67 (10)	24 (3)	85 (10)
Median (range) time to onset, days	5 (1—63)	8 (1—63)	4 (1—554)	6 (1—30)
Onset ≤ Day 15 after infusion, n/N (%)	374/381 (98)	193/220 (88)	415/430 (97)	142/150 (95)
Onset > Day 15 and infusion, n/N (%)	7/381 (2)	27/220 (12)	15/430 (3)	8/150 (5)
Resolved	7/7 (100)	24/27 (89)[c]	13/15 (87)[d]	5/8 (62.5)[d]
Median (range) time to resolution from onset, days	5 (1—37)	7 (1—119)	4 (1—36)	5.5 (1—101)
Median (range) time to resolution from infusion, days	9 (2—78)	17 (2—151)	7 (1—555)	12 (2—104)

All percentages are rounded to whole numbers except those with ".5%".
[a]CRS and ICANS grade was to be determined for 3 and 7 patients, respectively; [b]A total of 150 out of 234 patients had a reported onset date; [c]One patient had grade 2 leukoencephalopathy, which did not resolve, 1 patient had grade 1 tremor, and 1 patient had grade 2 peripheral sensory neuropathy ongoing at end of study; [d]Resolution data were missing for the remaining patients.
—, not available.

CRS incidence, time to onset, time to resolution, and management

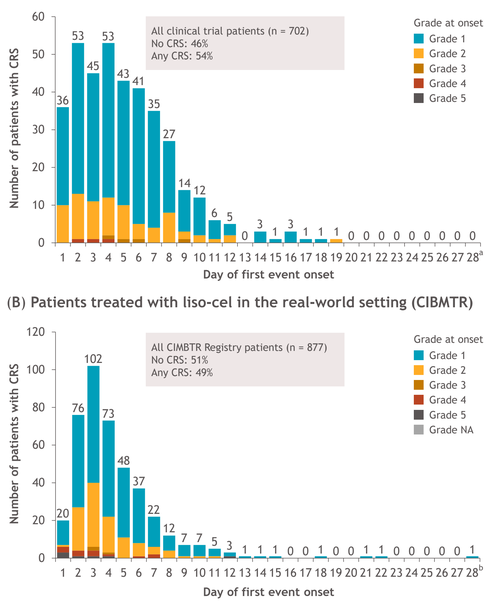
- In patients treated with liso-cel in clinical trials, 54% (381/702) experienced CRS of any grade, with 98% of these events occurring ≤ Day 15 after infusion (**Table 2**)
  - A total of 1% of patients experienced grade ≥ 3 CRS at onset (grade 3, 0.6%; grade 4, 0.4%; no grade 5 at onset); maximum CRS grade was ≥ 3 in 3% of patients
- In the CIBMTR Registry, 49% (430/877) of patients treated with liso-cel experienced CRS of any grade, with 97% of these events occurring ≤ Day 15 after infusion (**Table 2**)
  - Maximum CRS grade was ≥ 3 in 3% of patients

Table 3. Incidence and time to onset of first CRS and NEs in clinical trial patients

	TRANSCEND NHL 001: LBCL cohort (N = 268)	TRANSFORM (N = 89)	PILOT (N = 61)	TRANSCEND CLL 004 (N = 89)	TRANSCEND FL (N = 107)	TRANSCEND NHL 001: MCL cohort (N = 88)	All studies combined (N = 702)
First CRS							
Patients with CRS, n (%)	122 (46)	44 (49)	24 (39)	74 (83)	63 (59)	54 (61)	381 (54)
Median (range) time to first onset of CRS, days	5 (1—15)	5 (1—63)	4 (1—12)	4 (1—18)	6 (1—17)	4 (1—10)	5 (1—63)
Patients with CRS onset ≤ Day 15, n (%)	122 (100)	41 (93)	24 (100)	71 (96)	62 (98)	54 (100)	374 (98)
Median time to onset for CRS with onset ≤ Day 15, days	5	5	4	4	5.5	4	4.5
First NE							
Patients with NEs, n (%)	95 (35)	16 (18)	25 (41)	41 (46)	16 (15)	27 (31)	220 (31)
Median (range) time to first onset of NEs, days	8 (1—46)	9 (1—21)	7 (1—63)	7 (1—21)	8.5 (4—16)	8 (1—25)	8 (1—63)
Patients with NE onset ≤ Day 15, n (%)	81 (85)	14 (87.5)	19 (76)	39 (95)	15 (94)	25 (93)	193 (88)
Median time to onset for NEs with onset ≤ Day 15, days	8	8	6	7	8	8	7

All percentages are rounded to whole numbers except those with ".5%".

Figure 2. Time to CRS in (A) pivotal clinical trials and (B) the real-world setting (CIBMTR)



[a]One additional event occurred on Day 63; [b]After Day 28, 11 additional events occurred (n = 1 each on Days 29, 39, 40, 46, 55, 96, 97, 132, 226, 495, and 554).

Table 4. CRS and ICANS/NE management in patients with first onset > Day 15

	Pivotal clinical trials (N = 702)		CIBMTR Registry (N = 877)	
	CRS	NEs	CRS	ICANS
Required hospitalization, n/N (%)				
Standard	5/7 (71)	2/27 (7)	—	—
ICU	0/7 (0)	0/27 (0)	—	—
Required treatment, n/N (%)				
Tocilizumab	4/7 (57)	1/27 (4)	10/15 (67)	—
Corticosteroids	2/7 (29)	7/27 (26)	3/15 (20)	4/8 (50)
Other[a]	3/7 (43)	5/27 (19)	4/15 (27)	1 (12.5)

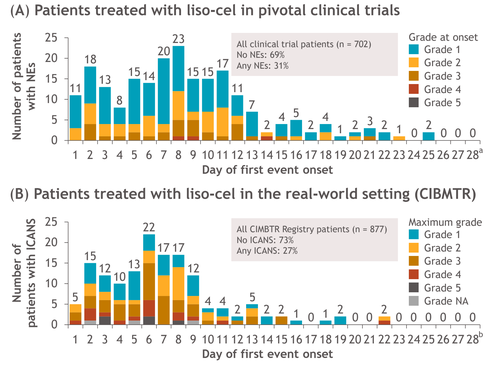
[a]Includes acetaminophen (n = 3), butalbital (n = 1), caffeine (n = 1), calcium chloride (n = 2), potassium chloride (n = 2), sodium chloride (n = 1), sodium lactate (n = 2), and supplemental oxygen (n = 3) for CRS; acetaminophen (n = 1), antiepileptics (n = 5), and lorazepam (n = 1) for ICANS/NEs.

- Among clinical trial patients who experienced CRS, 98% (374/381) had onset ≤ Day 15 after infusion, with a median onset at Day 5 (range, 1—63 days) and a median time to resolution of 5 days from onset (9 days from infusion)
  - Seven patients experienced CRS onset > Day 15 after infusion
    - All were low-grade events (grade 1, n = 5; grade 2, n = 2) that resolved after a median (range) time from onset of 5 days (1—16)
    - Five of 7 (71%) patients with onset > Day 15 required hospitalization, with none requiring ICU-level care; treatment included tocilizumab (57%) and/or corticosteroids (29%)
- Among CIBMTR Registry patients who experienced CRS, 97% (415/430) had onset ≤ Day 15 after infusion, with a median (range) onset of 4 days (1—554) after infusion and a median (range) time to resolution of 4 days (1—36)
  - Fifteen patients experienced CRS onset > Day 15; most were low-grade events (grade 1, n = 9; grade 2, n = 2; grade 3, n = 1; unknown, n = 3)
    - All CRS events with data available resolved (n = 13; missing, n = 2), with no grade 4—5 events occurring > Day 15
    - Two-thirds (67%) of patients were treated with tocilizumab and 20% required corticosteroids

ICANS/NE incidence, time to onset, time to resolution, and management

- Among patients treated with liso-cel in clinical trials, 31% (220/702) experienced NEs of any grade, with 88% of these events occurring ≤ Day 15 after infusion (**Table 2**)
  - Fewer than 5% of patients had grade ≥ 3 NEs at onset (grade 3, 4%; grade 4, 0.4%; no grade 5)
  - Maximum NE grade was ≥ 3 in 10% of patients
  - Among patients in the CIBMTR Registry, 27% (234/877) experienced ICANS of any grade, with 95% of these events occurring ≤ Day 15 after infusion (**Table 2**)
  - Maximum ICANS grade was ≥ 3 in 10% of patients

Figure 3. Time to ICANS/NEs in (A) pivotal clinical trials and (B) the real-world setting (CIBMTR)



[a]After Day 28, 5 additional events occurred (n = 1 each on Days 29, 33, 43, 46, and 63); [b]Two additional events occurred on Day 30.

- Among clinical trial patients who experienced NEs (n = 220), 88% had onset ≤ Day 15, with a median (range) time to onset of 8 days (1—63) after infusion and a median (range) time to resolution of 7 days (1—119) from onset and 17 days (2—151) from infusion
  - Of 27 patients who experienced NE onset > Day 15 after infusion, most events were low grade (grade 1, n = 20; grade 2, n = 6; grade 3, n = 1)
    - Most patients (25/27 [93%]) were managed in the outpatient setting without hospitalization; when treatment was required, corticosteroids were the primary intervention, with minimal need for tocilizumab (**Table 4**)
- Among patients in the CIBMTR Registry who developed ICANS and had a reported onset date (n = 150), 95% had onset ≤ Day 15, with a median (range) onset of 6 days (1—30) after infusion and a median (range) time to resolution of 5.5 days (1—101) from onset
  - Of 8 patients with ICANS onset > Day 15, most events were low grade (grade 1, n = 5; grade 2, n = 1; grade 4, n = 2)
    - Half of patients with ICANS onset > Day 15 were treated with corticosteroids (**Table 4**)

Patients with grade 5 events

- No grade 5 CRS or NEs occurred at onset in the clinical trial population
- In the CIBMTR Registry, 11 patients experienced grade 5 CRS and/or ICANS and had event onset ≤ Day 15 after liso-cel infusion. Of these 11 patients, 6 had grade 5 CRS (with progressive disease reported by the sites as the primary cause of death in 3 patients), 4 had grade 5 ICANS, and 1 had both

Conclusions

- Data from the liso-cel pivotal clinical trials and the real-world SOC setting from the CIBMTR Registry were consistent and demonstrated that most CRS/ICANS/NEs occurred ≤ Day 15 after infusion and were not severe
- For the few patients who experienced onset of CRS/ICANS/NE > Day 15, most events were low grade and resolved with treatment
- These results reinforce the established safety profile of liso-cel across indications and can inform optimal monitoring requirements after infusion to suit patient needs and improve access to treatment, without compromising safety

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