Optimizing Post—Chimeric Antigen Receptor T Cell Monitoring: Evidence Across Lisocabtagene Maraleucel Pivotal Clinical Trials and Real-World Experience

CT-305

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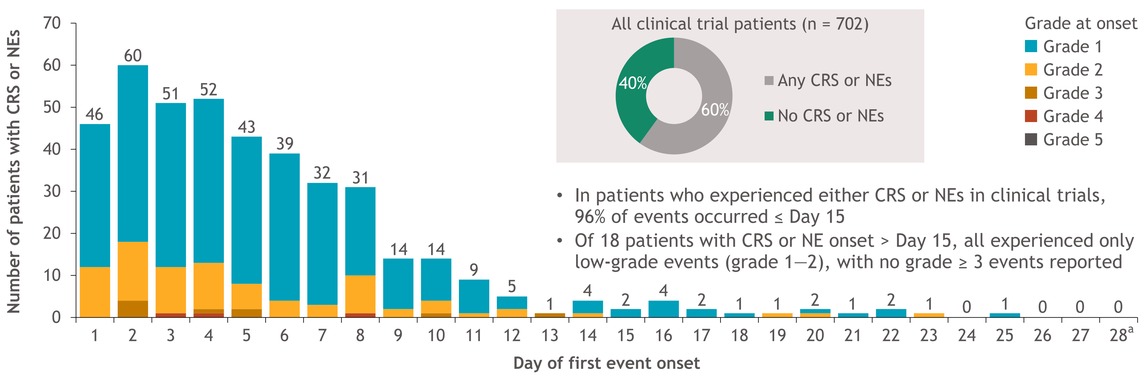
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Liso-cel continues to demonstrate a predictable safety profile across pivotal clinical trials and the real-world setting, with 96% of CRS or ICANS/NEs occurring ≤ Day 15 after infusion, supporting recent changes to monitoring requirements

- 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

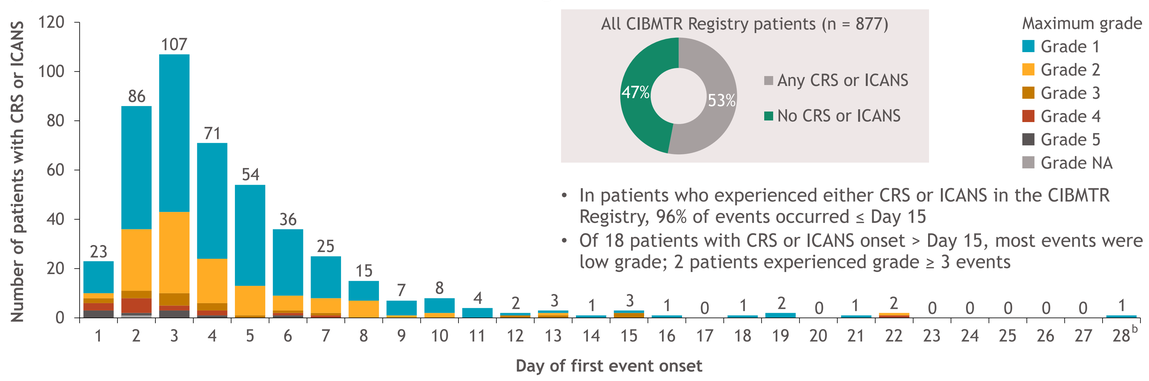
Figure 1. Time to either CRS or ICANS/NEs in (A) pivotal clinical trials and (B) the real-world setting (CIBMTR)

(A) Patients treated with liso-cel in pivotal clinical trials



- In patients who experienced either CRS or NEs in clinical trials, 96% of events occurred ≤ Day 15
- Of 18 patients with CRS or NE onset > Day 15, all experienced only low-grade events (grade 1—2), with no grade ≥ 3 events reported

(B) Patients treated with liso-cel in the real-world setting (CIBMTR)



- In patients who experienced either CRS or ICANS in the CIBMTR Registry, 96% of events occurred ≤ Day 15
- Of 18 patients with CRS or ICANS onset > Day 15, most events were low grade; 2 patients experienced grade ≥ 3 events

[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.

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]
- Monitoring requirements following CAR T-cell infusion were recently updated, reducing the requirement for patients to remain within proximity of a healthcare facility from 4 weeks to 2 weeks and reducing the time to avoid driving from 8 weeks to 2 weeks after CAR T-cell infusion[7—9]
- 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]
- Here, we 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[10]
- 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[11]
- 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)	64 (447)	61 (532)
Race, % (n)		
White	78 (549)	86 (752)
Black or African American	4 (25)	4 (39)
Asian	6 (39)	5 (44)
Other	1 (6)	1 (9)
Not reported/unknown	11 (83)	4 (33)
Disease indication/histology, % (n)		
DLBCL	45 (313)	82 (715)
HGBCL	11 (77)	13 (111)
PMBCL	3 (23)	0.8 (7)
FL3B	0.6 (4)	1 (10)
THRBCL	0.1 (1)	0
Other B-cell lymphoma	0	3 (29)[a]
Not reported/unknown	0	0.6 (5)
CLL/SLL	13 (89)	0
FL grade 1, 2, or 3A	15 (107)	0
MCL	13 (88)	0
ECOG PS, % (n)[b]		
0—1	97 (682)	82 (719)
≥ 2	3 (20)	6 (56)
Not reported/unknown	0	12 (102)
Disease status, % (n)		
Refractory	71 (497)	65 (571)
Relapsed	29 (205)	33 (289)
Not reported/unknown	0	2 (17)
Received bridging therapy, % (n)	60 (418)	57 (500)

[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 in the real world were more likely to have ECOG PS > 1, but both cohorts had similar proportions of refractory disease and bridging therapy history, with longer follow-up in the clinical trial population

Results

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

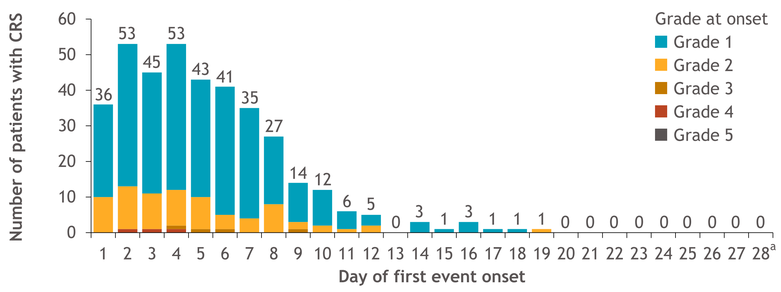
	Pivotal clinical trials (N = 702)		CIBMTR Registry (N = 877)	
	CRS	NEs	CRS	NEs
Any grade, % (n)	54 (381)	31 (220)	49 (430)[a]	27 (234)[a,b]
Grade at onset, % (n)				
Grade 1—2	53 (374)	27 (188)	—	—
Grade ≥ 3	1 (7)	5 (32)	—	—
Maximum grade, % (n)				
Grade 1—2	51 (359)	22 (153)	46 (403)	16 (142)
Grade ≥ 3	3 (22)	10 (67)	3 (24)	10 (85)
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)	98 (374/381)	88 (193/220)	97 (415/430)	95 (142/150)
Onset > Day 15 after infusion, % (n/N)	2 (7/381)	12 (27/220)	3 (15/430)	5 (8/150)
Resolved	100 (7/7)	89 (24/27)[c]	87 (13/15)[d]	62.5 (5/8)[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.

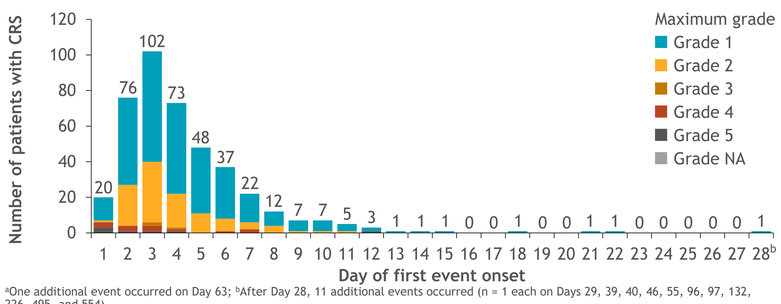
CRS incidence, time to onset, time to resolution, and management

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

(A) Patients treated with liso-cel in pivotal clinical trials



(B) Patients treated with liso-cel in 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).

- The timing of onset and resolution and the proportion of higher-grade events were similar across trials and between the trial and the real-world settings
- In clinical trials, 7 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)
- In the CIBMTR Registry, 15 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

Table 3. CRS and ICANS/NE management in patients with first onset > Day 15

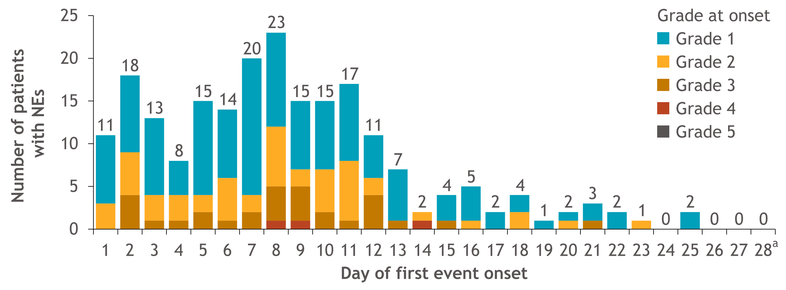
	Pivotal clinical trials (N = 702)		CIBMTR Registry (N = 877)	
	CRS	NEs	CRS	NEs
Required hospitalization, % (n/N)				
Standard	71 (5/7)	7 (2/27)	—	—
ICU	0 (0/7)	0 (0/27)	—	—
Required treatment, % (n/N)				
Tocilizumab	57 (4/7)	4 (1/27)	67 (10/15)	—
Corticosteroids	29 (2/7)	26 (7/27)	20 (3/15)	50 (4/8)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

[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.

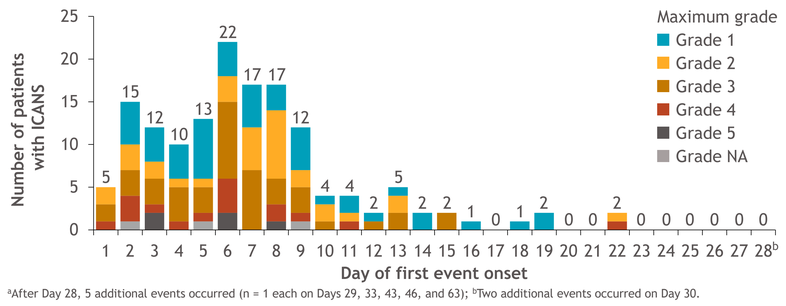
ICANS/NE incidence, time to onset, time to resolution, and management

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

(A) Patients treated with liso-cel in pivotal clinical trials



(B) Patients treated with liso-cel in 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.

- Of 27 patients who experienced NE onset > Day 15 after infusion in clinical trials, most events were low grade (grade 1, n = 20; grade 2, n = 6; grade 3, n = 1)
- Of 8 patients with ICANS onset > Day 15 in CIBMTR Registry, most events were low grade (grade 1, n = 5; grade 2, n = 1; grade 4, n = 2)

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, 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, together with the updated FDA monitoring requirements, provide a strong foundation for clinicians to revise their monitoring strategy after liso-cel infusion to suit patient needs and improve access to treatment, without compromising safety

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