Optimizing Care After CAR T-cell Therapy: Reduction of Daily Monitoring Duration Following Axicabtagene Ciloleucel or Brexucabtagene Autoleucel Infusion

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Introduction

- Axicabtagene ciloleucel (axi-cel) and brexucabtagene autoleucel (brexu-cel) are CD19-directed chimeric antigen receptor (CAR) T-cell therapies approved for patients with relapsed or refractory (R/R) hematologic malignancies[1–4]
  - Axi-cel is approved for patients with R/R large B cell lymphoma (LBCL) or follicular lymphoma (FL)
  - Brexu-cel is approved for patients with R/R mantle cell lymphoma (MCL) or acute lymphoblastic leukemia (ALL)
- Cytokine release syndrome (CRS) and neurologic events (NEs) are potentially life-threatening toxicities associated with CAR T-cell therapies[5]
  - CRS and NEs typically have rapid onset after CAR T-cell infusion
  - CRS often occurs within the first week
  - NEs frequently accompany or follow CRS development (few cases occur independently of CRS)
- Daily safety monitoring of patients after CAR T-cell infusion allows for timely detection and management of CRS and NEs
  - However, extended monitoring can overburden patients and healthcare systems, particularly when daily monitoring requires an inpatient setting
- The European Medicines Agency (EMA) authorized a change to the Summary of Product Characteristics (SmPC) in June 2024 for all approved indications of axi-cel and brexu-cel, reducing the minimum duration of daily safety monitoring after infusion from 10 to 7 days[6]

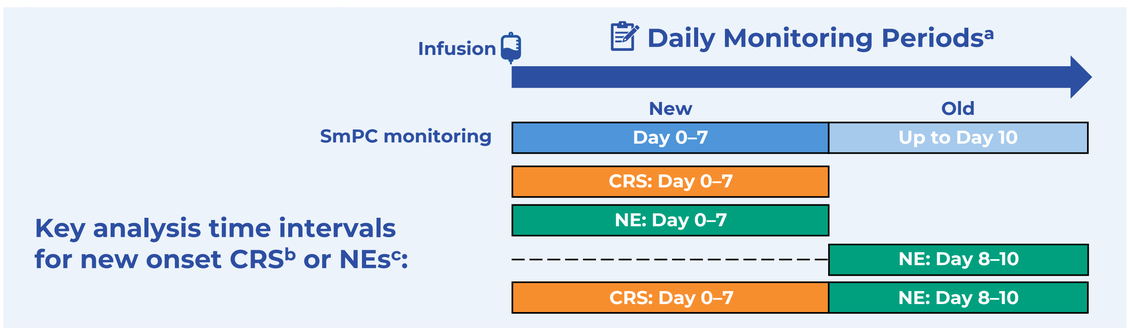
Objective

To evaluate the timing and incidence of CRS and NEs up to Day 10 after axi-cel or brexu-cel infusion

Methods

- Safety data from axi-cel and brexu-cel registrational trials for each EMA-approved indication were pooled
  - Axi-cel: ZUMA-1 (R/R LBCL), ZUMA-5 (R/R FL), and ZUMA-7 (R/R LBCL)
  - Brexu-cel: ZUMA-2 (R/R MCL) and ZUMA-3 (R/R ALL)
  - Time to onset and incidence of CRS and NEs on or before Day 7 and NEs from Day 8–10 for each therapy were evaluated (**Figure 1**)
    - CRS was identified using a tailored case report form
    - NEs were identified using a modified search strategy based on known neurologic toxicities associated with anti-CD19 immunotherapy[7]

Figure 1: CRS and NE Monitoring Periods



[a]According to the EMA SmPC for axi-cel or brexu-cel, patients must be monitored daily for the first 7 days following infusion for signs and symptoms of CRS, NEs, and other toxicities. Physicians can consider hospitalization for the first 7 days or at the first signs or symptoms of CRS and/or NEs.[1,4] [b]CRS severity was graded using a modified version of Lee et al. 2014,[8] excluding NEs from the CRS criteria; the severity of individual CRS symptoms was graded according to the National Cancer Institute CTCAE, version 4.03. [c]NEs were coded according to the Medical Dictionary for Regulatory Activities version 25.0 (ZUMA-1, ZUMA-5, and ZUMA-7) or version 24.0 (ZUMA-2 and ZUMA-3); NE severity was graded using CTCAE, version 4.03.
CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; EMA, European Medicines Agency; NE, neurologic event; SmPC, Summary of Product Characteristics.

Results

- Axi-cel and brexu-cel studies were conducted primarily in North America (**Table 1 and Table 2**)

Table 1: Demographic and Baseline Characteristics in Patients Treated With Axi-cel

Characteristic	ZUMA-1 (R/R LBCL) N=108	ZUMA-5 (R/R FL) N=119	ZUMA-7 (R/R LBCL) N=170
Median age, years (range)	58.0 (23–76)	59.0 (34–79)	58.5 (21–80)
Male, n (%)	73 (68)	71 (60)	106 (62)
Region, n (%)			
North America	107 (99)	109 (92)	132 (78)
Europe	–	10 (8)[b]	32 (19)
Rest of the World[a]	1 (1)	–	6 (4)
ECOG PS ≤1, n (%)	108 (100)	119 (100)	170 (100)
Select disease types, n (%)[c]			
DLBCL	84 (78)	–	103 (61)
HGBL	0	–	40 (24)
PMBCL	8 (7)	–	–
TFL	16 (15)	–	19 (11)
FL	–	119 (100)	–
Prior lines of therapy, n (%)[d]			
1	3 (3)	3 (3)	170 (100)
2	29 (27)	42 (35)	0
3	33 (31)	29 (24)	0
≥4	43 (40)	44 (37)	0
Prior auto-SCT, n (%)	25 (23)	30 (25)	0

Data cutoff dates: 18 March 2021 (ZUMA-1), 31 March 2021 (ZUMA-5), 18 March 2021 (ZUMA-7). [a]Israel and Australia. [b]ZUMA-5 European sites were all in France. [c]In ZUMA-7, 8 patients had other disease types (T-cell histiocyte-rich LBCL, DLBCL associated with chronic inflammation, primary cutaneous DLBCL [leg type], Epstein–Barr virus-positive DLBCL). [d]In ZUMA-5, 1 patient was treated with prior therapy for DLBCL and not the primary disease, FL.
Auto-SCT, autologous stem cell transplant; axi-cel; axicabtagene ciloleucel; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; HGBL, high-grade B-cell lymphoma; LBCL, large B-cell lymphoma; PMBCL, primary mediastinal large B-cell lymphoma; R/R, relapsed or refractory; TFL, transformed follicular lymphoma.

- Across axi-cel studies, demographic characteristics were similar in terms of age and sex (**Table 1**)
- Across brexu-cel studies, ZUMA-3 had a lower median age and a lower proportion of male patients compared with ZUMA-2 (**Table 2**)

Table 2: Demographic and Baseline Characteristics in Patients Treated With Brexu-cel

Characteristic	ZUMA-2 (R/R MCL) N=82	ZUMA-3 (R/R ALL) N=100
Median age, years (range)	65.0 (38–79)	44.0 (18–84)
Male, n (%)	68 (83)	55 (55)
Region, n (%)		
North America	76 (93)	86 (86)
Europe	6 (7)	14 (14)
ECOG PS ≤1, n (%)	82 (100)	100 (100)
Simplified MIPI, n/N (%)[a]		
Low risk	34/79 (43)	–
Intermediate risk	33/79 (42)	–
High risk	12/79 (15)	–
Number of prior lines of therapy, median (range)	3 (1–5)	2 (1–8)
Prior auto-SCT, n (%)[b]	35 (43)	2 (2)
Prior allo-SCT, n (%)[b]	–	36 (36)

Data cutoff dates: 24 July 2021 (ZUMA-2), 23 July 2021 (ZUMA-3).
[a]Percentages were calculated for patients with nonmissing data in the safety analysis set. [b]ZUMA-2 reported relapse after auto-SCT and ZUMA-3 reported relapse after allo-SCT.
ALL, acute lymphoblastic leukemia; allo-SCT, allogeneic stem cell transplant; auto-SCT, autologous stem cell transplant; brexu-cel, brexucabtagene autoleucel; ECOG PS, Eastern Cooperative Oncology Group performance status; MCL, mantle cell lymphoma; MIPI, Mantle Cell Lymphoma International Prognostic Index; R/R, relapsed or refractory.

- CRS was reported in 88% (349 of 397) of patients treated with axi-cel (**Table 3**)
  - 96% (335 of 349) of patients had onset ≤7 days after axi-cel infusion (**Figure 2**)
  - 4% (14 of 349) of patients had onset on Day 8 or beyond
- CRS was reported in 91% (166 of 182) of patients treated with brexu-cel (**Table 3**)
  - 94% (156 of 166) of patients had onset ≤7 days after brexu-cel infusion (**Figure 2**)
  - 6% (10 of 166) of patients had onset on Day 8 or beyond

Results *(continued)*

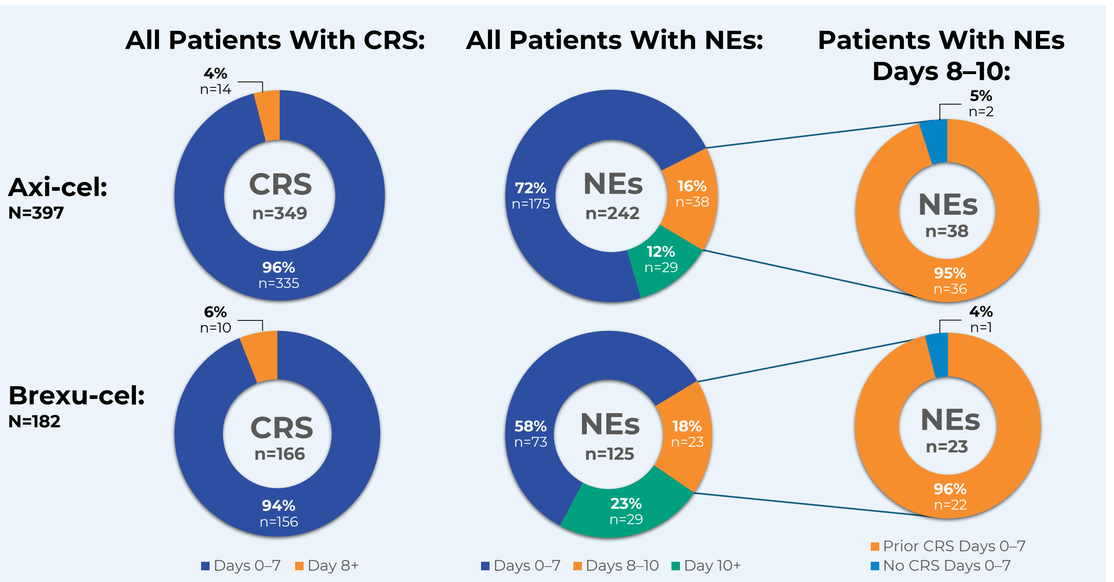
Table 3: Timing of CRS and NEs Following Axi-cel or Brexu-cel Infusion

Category	Axi-cel ZUMA-1 N=108	Axi-cel ZUMA-5 N=119	Axi-cel ZUMA-7 N=170	Axi-cel Overall N=397	Brexu-cel ZUMA-2 N=82	Brexu-cel ZUMA-3 N=100	Brexu-cel Overall N=182
Patients with CRS, n (%)[a]	100 (93)	92 (77)	157 (92)	349 (88)	75 (91)	91 (91)	166 (91)
Patients with CRS onset ≤7 days after infusion, n (%)[b]	98 (98)	83 (90)	154 (98)	335 (96)	68 (91)	88 (97)	156 (94)
Patients with CRS onset ≤14 days after infusion, n (%)[b]	100 (100)	92 (100)	157 (100)	349 (100)	75 (100)	91 (100)	166 (100)
Patients with CRS resolution, n	98	91	157	346	75	86	161
Patients with CRS resolution ≤7 days after infusion, n (%)[c]	27 (28)	25 (27)	32 (20)	84 (24)	12 (16)	6 (7)	18 (11)
Patients with CRS resolution ≤10 days after infusion, n (%)[c]	64 (65)	56 (62)	87 (55)	207 (60)	21 (28)	26 (30)	47 (29)
Patients with NEs, n (%)[a]	71 (66)	68 (57)	103 (61)	242 (61)	56 (68)	69 (69)	125 (69)
Patients with NE onset ≤7 days after infusion, n (%)[b]	66 (93)	44 (65)	65 (63)	175 (72)	30 (54)	43 (62)	73 (58)
Patients with NE onset ≤14 days after infusion, n (%)[b]	70 (99)	59 (87)	97 (94)	226 (93)	47 (84)	65 (94)	112 (90)
Patients with NE onset Days 8–10 after infusion, n (%)[b]	**4 (6)**	**8 (12)**	**26 (25)**	**38 (16)**	**9 (16)**	**14 (20)**	**23 (18)**
Prior CRS (any grade) from Days 0–7, n (%)[d]	**4 (100)**	**7 (88)**	**25 (96)**	**36 (95)**	**8 (89)**	**14 (100)**	**22 (96)**
No CRS from Days 0–7, n (%)[d]	**0**	**1 (13)**	**1 (4)**	**2 (5)**	**1 (11)**	**0**	**1 (4)**
Patients with NE onset beyond Day 10 after infusion, n (%)[b]	1 (1)	16 (24)	12 (12)	29 (12)	17 (30)	12 (17)	29 (23)
Patients with NE resolution, n	67	65	97	229	51	62	113
Patients with NE resolution ≤7 days after infusion, n (%)[c]	3 (4)	6 (9)	6 (6)	15 (7)	0	2 (3)	2 (2)
Patients with NE resolution ≤10 days after infusion, n (%)[c]	13 (19)	11 (17)	20 (21)	44 (19)	1 (2)	11 (18)	12 (11)

[a]Percentages were calculated based on the total number of patients. [b]Percentages were calculated based on the number of patients with CRS or NEs. [c]Percentages were calculated based on the number of patients with CRS or NE resolution. [d]Percentages were calculated based on the number of patients who developed NEs on Days 8–10.
Axi-cel, axicabtagene ciloleucel; brexu-cel, brexucabtagene autoleucel; CRS, cytokine release syndrome; NE, neurologic event.

- NEs were reported in 61% (242 of 397) of patients treated with axi-cel (**Table 3**)
  - 72% (175 of 242) of patients had onset ≤7 days after axi-cel infusion (**Figure 2**)
  - 16% (38 of 242) of patients had onset on Days 8–10 and 12% (29 of 242) after Day 10
    - Among the 38 patients with NE onset on Days 8–10:
      - 36 (95%) had prior CRS on or before Day 7, including 24 (63%) with ongoing CRS at Day 7
      - 2 (5%) had no prior CRS
- NEs were reported in 69% (125 of 182) of patients treated with brexu-cel (**Table 3**)
  - 58% (73 of 125) of patients had onset ≤7 days after brexu-cel infusion (**Figure 2**)
  - 18% (23 of 125) of patients had onset on Days 8–10 and 23% (29 of 125) after Day 10
    - Among the 23 patients with NE onset on Days 8–10:
      - 22 (96%) had prior CRS on or before Day 7, including 12 (52%) with ongoing CRS at Day 7
      - 1 (4%) had no prior CRS

Figure 2: Time to Onset and Incidence of CRS and NEs After Axi-cel or Brexu-cel Infusion



Axi-cel, axicabtagene ciloleucel; brexu-cel, brexucabtagene autoleucel; CRS, cytokine release syndrome; NEs, neurologic events.

- 1% (2 of 397) of patients treated with axi-cel had initial NEs with onset Day 8–10, in the absence of prior CRS
  - NEs: Grade 3 on Day 8 (n=1); Grade 1 on Day 10 (n=1)
- 1% (1 of 182) of patients treated with brexu-cel had initial NEs with onset Day 8–10, without prior CRS
  - NEs: Grade 1 on Day 10 (n=1)

Limitations

- The clinical trials included in these studies were initiated several years ago, and patient management practices have evolved and improved since then

Conclusion

- New CRS onset was not a significant concern for patients after Days 8–10 following axi-cel or brexu-cel infusion
- Given the small proportion of patients (1%) who developed NEs on Days 8–10 without prior CRS, this analysis supported the recent EMA update to the SmPCs that reduced the required daily monitoring period from 10 to 7 days after axi-cel or brexu-cel infusion
- Reducing the duration of daily monitoring allows patient care to align with the physician's expertise and the patient's condition
  - Potentially lowering hospital-related risks, improving patient experience, and optimizing resource use

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Disclosures

For author disclosures, please scan the QR code