Durability of Response in Patients With Refractory Large B Cell Lymphoma Treated With Axicabtagene Ciloleucel in the Pivotal Phase 2 Study, ZUMA-1

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BACKGROUND

- Axicabtagene ciloleucel (axi-cel) is an autologous anti-CD19 chimeric antigen receptor (CAR) T cell therapy that uses a CD3ζ/CD28-based signaling domain (**Figure 1**)¹
- ZUMA-1 is a pivotal Phase 1/2 multicenter study that led to the Food and Drug Administration approval of axi-cel for the treatment of adult patients with relapsed/refractory large B cell lymphoma after ≥2 lines of systemic therapy¹⁻³
- Long-term follow-up (median, 15.4 months) of ZUMA-1 (N=108) demonstrated¹:
 - Objective response rate of 82%; complete response (CR) rate of 58%
 - Ongoing responses in 42% (40% with CR)
 - Median overall survival was not reached
 - Grade ≥3 cytokine release syndrome in 12% and Grade ≥3 neurological events in 31%

Figure 1. KITE-585 Structure

Figure 2. ZUMA-1 DOR by Best Response

From Neelapu SS and Locke FL, et al. *N Engl J Med*. 2017;277:2531-2544. Copyright © (2018) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

CR, complete response; DOR, duration of response; NE, not estimable; NR, not reached; PR, partial response.

- Over half of the progression events occur by Month 3, leading to the need to define treatment practice for patients at this time point
 - Month 3 is clinically relevant to understand patient outcomes

OBJECTIVES

- To evaluate the time to response for patients with both an objective response and a CR
- To assess the significance of partial response (PR) and CR at Month 3 as a prognostic factor for progression-free survival

METHODS

Figure 3. ZUMA-1 Study Design

axi-cel, axicabtagene ciloleucel; ASCT, autologous stem cell transplantation; CAR, chimeric antigen receptor; DLBCL, diffuse large B cell lymphoma; PMBCL, primary mediastinal B cell lymphoma; TFL, transformed follicular lymphoma.

Figure 4. ZUMA-1 Treatment Schema

axi-cel, axicabtagene ciloleucel.

- Bridging chemotherapy was not allowed per study protocol
- This analysis only includes those patients who achieved a response as assessed by Cheson 2007 criteria⁴ per investigator assessment. First response assessment was conducted at Month 1, then every 3 months post-infusion thereafter

RESULTS

Figure 5. Time to Objective Response and Complete Response

Time-to-response was calculated as (date of first observed response – axi-cel infusion date + 1)/(365.25/12). axi-cel, axicabtagene ciloleucel; CR, complete response; NE, not estimable.

- 41% (18/44) patients with PR converted to CR (**Figure 5**)
- 1 patient converted from stable disease to CR at >12 months
- Responses deepen and improve over time

Table 1. Baseline Characteristics by Response at Month 3

Characteristic	Response at Month 3		Overall (N=101)
	PR (n=9)	CR (n=42)	
Median age (range), y	62 (53–76)	58 (25–75)	58 (23–76)
Male, n (%)	4 (44)	28 (67)	68 (67)
ECOG 1, n (%)	6 (67)	20 (48)	59 (58)
Disease stage III/IV, n (%)	7 (78)	32 (76)	86 (85)
IPI score 3–4, n (%)	2 (22)	18 (43)	46 (46)
≥3 prior therapies, n (%)	5 (56)	29 (69)	70 (69)
Median SPD of index lesions (range),* mm ²	3355 (1022–16,764)	3579 (171–13,936)	3721 (171–23,297)
Refractory Subgroup Before Enrollment			
Refractory to ≥2L therapy, n (%)	8 (89)	29 (69)	77 (76)
Best response as PD to last prior therapy	8 (89)	25 (60)	67 (66)
Relapse post-ASCT, n (%)	0	13 (31)	21 (21)

*Index lesion SPD may not represent the totality of a patient's disease.

2L, second-line; ASCT, autologous stem cell transplantation; CR, complete response; ECOG, Eastern Cooperative Oncology Group performance status; IPI, International Prognostic Index; PD, progressive disease; PR, partial response; SPD, sum of product diameters.

- There were patients in each response group with high tumor burden (**Table 1**)

- No clinically meaningful differences in baseline characteristics were observed between Month 3 response groups

Figure 6. PFS by Response at Month 3

Data represent the response to a single dose of axi-cel, and patients were censored at disease progression or subsequent anticancer therapy.

CR, complete response; NR, not reached; PFS, progression-free survival; PR, partial response.

Table 2. Landmark Analysis of PFS Over Time by Response at Month 3

PFS Rate (95% CI)	Response at Month 3	
	PR (n=9)	CR (n=42)
6-Month	78 (36–94)	88 (74–95)
9-Month	78 (36–94)	83 (68–92)
12-Month	78 (36–94)	79 (63–88)

CR, complete response; PFS, progression-free survival; PR, partial response

- Similar progression-free survival was observed in patients who achieved PR or CR by Month 3 (**Table 2**)
- Patients in response at Month 3 have an 80% likelihood of maintaining response at Month 12

Table 3. Summary of Safety by Response at Month 3

Adverse Events, n (%)	Response at Month 3		Overall (N=101)
	PR (n=9)	CR (n=42)	
All adverse events	9 (100)	42 (100)	101 (100)
Grade ≥3	9 (100)	39 (93)	98 (97)
CRS ^a	9 (100)	39 (93)	84 (93)
Grade ≥3	0	5 (12)	12 (12)
Neurologic events ^b	7 (78)	28 (67)	65 (64)
Grade ≥3	3 (33)	15 (36)	29 (29)

^aCRS was graded per a modified grading system proposed by Lee DW, et al.⁵ ^bNeurologic events were graded per CTCAE v 4.03.

CR, complete response; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; PR, partial response

- Similar rates of cytokine release syndrome and neurologic events were observed across all response groups (**Table 3**)

CONCLUSIONS

- Treatment with axi-cel induces durable, high response rates in patients with refractory large B cell lymphoma
- Rates of objective response and CR increased through the long-term follow-up
 - Patients can achieve CR as late as 1 year post-infusion
- Patients in response at month 3 have an 80% likelihood of maintaining response at Month 12
- Response to axi-cel, either PR or CR, by 3 months may be prognostic for long-term remission

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