Abstract 7547

Circulating Tumor DNA by ClonoSEQ to Monitor Residual Disease After Axicabtagene Ciloleucel in Large B-cell Lymphoma

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BACKGROUND

- Axicabtagene ciloleucel (axi-cel) is an autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy which includes a CD28 costimulatory domain to elicit rapid and robust expansion that results in target-specific cytotoxicity[1,2]
- Axi-cel was initially approved for the treatment of patients with relapsed or refractory (R/R) large B-cell lymphoma (LBCL) in the third or later line of therapy setting based on the ZUMA-1 study and was subsequently approved in the second line (2L) setting based on the ZUMA-7 study[1,3-5]
- Most patients with R/R LBCL respond to axi-cel, but many will eventually experience disease progression, as demonstrated in a real-world study of patients treated with commercial axi-cel in the third line or later setting where 60% of patients were assessed as having progressive disease after 6 months (n=111)[6]
- Monitoring of circulating tumor DNA (ctDNA) from blood, a minimally invasive diagnostic tool, has been used to assess minimal residual disease (MRD) with prognostic value, including in patients with R/R diffuse LBCL treated with axi-cel as the third line (3L) of therapy[7]

OBJECTIVE

- To explore the prognostic value of MRD by ctDNA analysis in patients with LBCL after axi-cel treatment in the first line (1L), 2L, and 3L settings

METHODS

Eligibility

- Patients with LBCL from ZUMA-12 (Phase 2 axi-cel in 1L; 89% objective response rate [ORR] with 78% complete response [CR] rate), ZUMA-7 (Phase 3 axi-cel versus 2L standard-of-care therapy [chemoimmunotherapy followed in responding patients by high-dose chemotherapy with autologous stem-cell transplantation] in 2L; 83% ORR with 65% CR rate for axi-cel), and ZUMA-14 (Phase 2 axi-cel + rituximab in 3L; 88% ORR with 65% CR rate) were evaluated[3,8,9]

MRD Testing

- All studies included initial MRD testing approximately 30 days after axi-cel infusion
- ClonoSEQ MRD assay (limit of detection≈0.0001%) was used to identify the lymphoma B-cell clonotype from formalin-fixed, paraffin-embedded (FFPE) biopsy tissue before axi-cel infusion and to track ctDNA in blood/plasma after treatment
- Assessment time points in blood
  - 1L (ZUMA-12): Day 28, Month 3, and Month 6 post-treatment
  - 2L (ZUMA-7): Baseline (pre-infusion) and Days 50, 100, 150, Month 9, and Month 24 post-randomization
  - 3L (ZUMA-14): Day 28, Month 3, and Month 5 post-treatment

Endpoints of Interest

- Positive predictive value (PPV; MRD positive [MRD+] patients who relapsed or were nonresponders/total MRD+ patients ×100)
- Negative predictive value (NPV; MRD negative [MRD-] patients in ongoing response/total MRD- patients ×100)

RESULTS

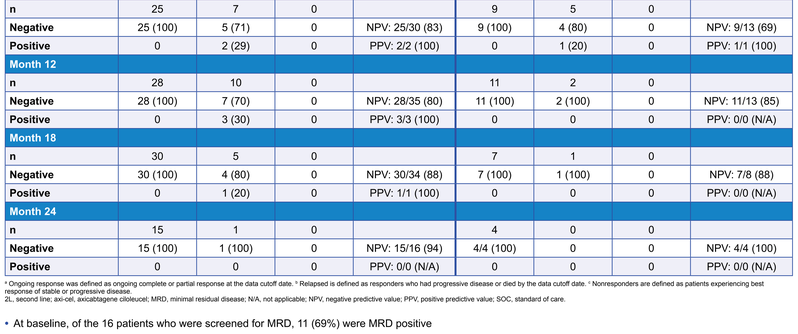
Table 1. MRD Detection by Time Point in Patients Treated With Axi-Cel + Rituximab in the 3L Setting (ZUMA-14)

	Axi-Cel + Rituximab (N=26)			
MRD Status, n (%)	Ongoing Response[a] (n=14)	Relapsed[b] (n=9)	Non-responders[c] (n=3)	Predictive Value
Month 1[d]				
n	11	6	3	
Negative	10 (91)	2 (33)	0	NPV: 10/12 (83)
Positive	1 (9)	4 (67)	3 (100)	PPV: 7/8 (88)
Month 3				
n	11	4	0	
Negative	10 (91)	2 (50)	0	NPV: 10/12 (83)
Positive	1 (9)	2 (50)	0	PPV: 2/3 (67)
Month 5				
n	8	1	0	
Negative	8 (100)	0	0	NPV: 8/8 (100)
Positive	0	1 (100)	0	PPV: 1/1 (100)

Data cutoff date: December 2, 2021.
[a] Ongoing response is defined as ongoing complete or partial response at the data cutoff date. [b] Relapsed is defined as responders who had progressive disease or died by the data cutoff date. [c] Nonresponders are defined as patients experiencing best response of stable or progressive disease. [d] Day 28.
3L, third line; axi-cel, axicabtagene ciloleucel; MRD, minimal residual disease; NPV, negative predictive value; PPV, positive predictive value.

RESULTS *(continued)*

Figure 1. MRD and Disease Response Status Over Time of Patients Treated With Axi-Cel + Rituximab in the 3L Setting (ZUMA-14)



[a] Based on MRD test at time of or prior to clinical progression. [b] For 5 axi-cel–relapsed patients with MRD positive results, 4 had tested positive prior to clinical diagnosis, and 1 tested positive at time of clinical diagnosis.
3L, third line; axi-cel, axicabtagene ciloleucel; CR, complete response; MRD, minimal residual disease; PD, progressive disease; PR, partial response.

- Overall, 5/6 (83%) relapsed patients had MRD detected at any time. Of these 5 patients, 5/5 (100%) were MRD+ prior to or at relapse, with a median time from MRD detection to relapse of 45 days

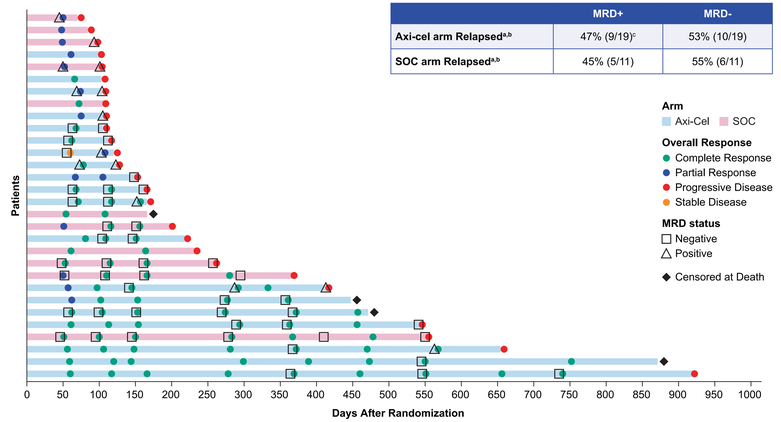
Table 2. MRD Detection by Time Point in Patients Treated With Axi-Cel or SOC in the 2L Setting (ZUMA-7)

	Axi-Cel (N=170)				SOC (N=168)			
MRD Status, n (%)	Ongoing Response[a] (n=75)	Relapsed[b] (n=66)	Non-responders[c] (n=21)	Predictive Value	Ongoing Response[a] (n=28)	Relapsed[b] (n=37)	Non-responders[c] (n=71)	Predictive Value
Day 50								
n	11	8	3		5	5	10	
Negative	8 (73)	6 (75)	1 (33)	NPV: 8/15 (53)	5 (100)	3 (60)	5 (50)	NPV: 5/13 (38)
Positive	3 (27)	2 (25)	2 (67)	PPV: 4/7 (57)	0	2 (40)	5 (50)	PPV: 7/7 (100)
Day 100								
n	14	10	3		7	8	1	
Negative	12 (86)	6 (60)	1 (33)	NPV: 12/19 (63)	7 (100)	5 (63)	1 (100)	NPV: 7/13 (54)
Positive	2 (14)	4 (40)	2 (67)	PPV: 6/8 (75)	0	3 (38)	0	PPV: 3/3 (100)
Day 150								
n	17	9	0		9	4	2	
Negative	16 (94)	8 (89)	0	NPV: 16/24 (67)	9 (100)	4 (100)	1 (50)	NPV: 9/14 (64)
Positive	1 (6)	1 (11)	0	PPV: 1/2 (50)	0	0	1 (50)	PPV: 1/1 (100)
Month 9								
n	25	7	0		9	5	0	
Negative	25 (100)	5 (71)	0	NPV: 25/30 (83)	9 (100)	4 (80)	0	NPV: 9/13 (69)
Positive	0	2 (29)	0	PPV: 2/2 (100)	0	1 (20)	0	PPV: 1/1 (100)
Month 12								
n	28	10	0		11	2	0	
Negative	28 (100)	7 (70)	0	NPV: 28/35 (80)	11 (100)	2 (100)	0	NPV: 11/13 (85)
Positive	0	3 (30)	0	PPV: 3/3 (100)	0	0	0	PPV: 0/0 (N/A)
Month 18								
n	30	5	0		7	1	0	
Negative	30 (100)	4 (80)	0	NPV: 30/34 (88)	7 (100)	1 (100)	0	NPV: 7/8 (88)
Positive	0	1 (20)	0	PPV: 1/1 (100)	0	0	0	PPV: 0/0 (N/A)
Month 24								
n	15	1	0		4	0	0	
Negative	15 (100)	1 (100)	0	NPV: 15/16 (94)	4/4 (100)	0	0	NPV: 4/4 (100)
Positive	0	0	0	PPV: 0/0 (N/A)	0	0	0	PPV: 0/0 (N/A)

[a] Ongoing response was defined as ongoing complete or partial response at the data cutoff date. [b] Relapsed is defined as responders who had progressive disease or died by the data cutoff date. [c] Nonresponders are defined as patients experiencing best response of stable or progressive disease.
2L, second line; axi-cel, axicabtagene ciloleucel; MRD, minimal residual disease; N/A, not applicable; NPV, negative predictive value; PPV, positive predictive value; SOC, standard of care.

- At baseline, of the 16 patients who were screened for MRD, 11 (69%) were MRD positive
  - Of the baseline MRD negative patients with available subsequent Day 50 data, 2/5 were MRD negative at Day 50 (both patients progressed)

Figure 2. MRD and Disease Response Status Over Time Among Relapsed Patients for Either Treatment Arm in 2L Setting (ZUMA-7)



[a] Relapsed was defined as death or progression after CR/PR. [b] MRD results after death or progression are not shown in the plot. [c] Based on MRD test at time of or prior to clinical progression. Among the 9 relapsed patients treated with axi-cel who were MRD positive, 6 tested MRD positive prior to clinical diagnosis, 2 after clinical diagnosis, and 1 at the time of clinical diagnosis.
2L, second line; axi-cel, axicabtagene ciloleucel; CR, complete response; MRD, minimal residual disease; PD, progressive disease; PR, partial response; SOC, standard of care.

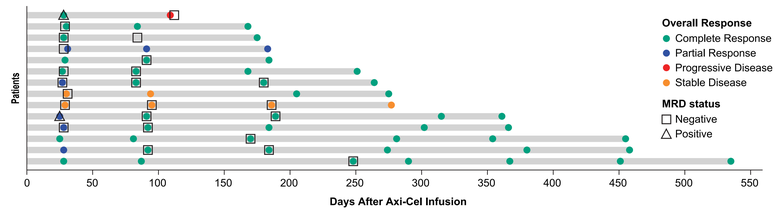
- For patients who were MRD+ prior to or at relapse, the median time from MRD detection to relapse was 35 days

Table 3. MRD Detection by Time Point in Patients Treated With Axi-Cel in the 1L Setting (ZUMA-12)

	Axi-Cel (N=14)			
MRD Status, n (%)	Ongoing Response[a]	Relapsed[b]	Nonresponders[c]	Predictive Value
Day 28				
n	8	1	1	
Negative	7 (88)	0	1 (100)	NPV: 7/8 (88)
Positive	1 (13)	1 (100)	0	PPV: 1/2 (50)
Month 3				
n	7	1	1	
Negative	7 (100)	1 (100)	1 (100)	NPV: 7/9 (78)
Positive	0	0	0	PPV: 0/0 (N/A)
Month 6				
n	5	0	1	
Negative	5 (100)	0	1 (100)	NPV: 5/6 (83)
Positive	0	0	0	PPV: 0/0 (N/A)

[a] Ongoing response was defined as ongoing complete or partial response at the data cutoff date. [b] Relapsed is defined as responders who had progressive disease or died by the data cutoff date. [c] Nonresponders are defined as patients experiencing best response of stable or progressive disease.
1L, first line; axi-cel, axicabtagene ciloleucel; MRD, minimal residual disease; N/A, not applicable; NPV, negative predictive value; PPV, positive predictive value.

Figure 3. MRD and Disease Response Status Over Time of Patients Treated With Axi-Cel in the 1L Setting (ZUMA-12)



1L, first-line; axi-cel, axicabtagene ciloleucel; MRD, minimal residual disease.

CONCLUSIONS

- The prognostic value of MRD assessment by clonoSEQ varied across lines of therapy in patients with LBCL treated with axi-cel (+ rituximab in the 3L setting)
- Limitations of this analysis of 3 clinical studies include differences in assessment time points, the low number of evaluable patients in each study, and the relatively low number of patients with non-response or relapse in each study
- A relatively high rate of MRD negativity at baseline in the 2L setting and prior to relapse in the 2L and 1L settings warrants exploration of more sensitive ctDNA monitoring methods

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FUNDING

- This study was funded by Kite, a Gilead Company

ACKNOWLEDGMENTS

- The patients, their families, their friends, and their caregivers
- Medical writing support was provided by Edward Sheetz, PhD, of Nexus Global Group Science, funded by Kite, a Gilead Company

DISCLOSURES

Author disclosure information is available from the abstract online.

Presented at the 2023 American Society of Clinical Oncology Annual Meeting