Abstract 7023

Impact of Age, Prior Therapies, and Subsequent Transplant on Long-term Outcomes of Adults With Relapsed or Refractory B-cell Acute Lymphoblastic Leukemia Treated With Brexucabtagene Autoleucel in ZUMA-3

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BACKGROUND

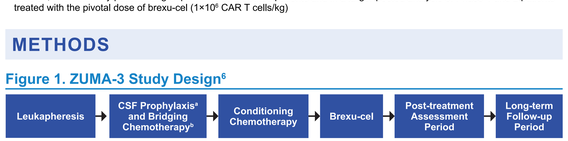
- Adults with relapsed or refractory (R/R) B-cell precursor acute lymphoblastic leukemia (B-ALL) have a poor prognosis, with a median overall survival (OS) of <8 months with standard therapies such as blinatumomab and inotuzumab[1,2]
- Brexucabtagene autoleucel (brexu-cel) is an autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy that received approval in the US for adults with R/R B-ALL and in the EU for adults ≥26 years of age with R/R B-ALL based on positive results of the Phase 2 portion of the open-label, multicenter ZUMA-3 study[3,4]
  - After median follow-up of 38.8 months in Phase 2 of ZUMA-3, brexu-cel demonstrated an overall complete remission (CR)/CR with incomplete hematologic recovery (CRi) rate of 71% and a median OS of 26.0 months in all patients (N=55) and 38.9 months in patients with CR (n=31)[5]
- With several salvage therapies available for adults with R/R B-ALL, optimal sequencing remains unclear; as such, we assessed outcomes in patients who received prior blinatumomab and in patients who received subsequent allogeneic stem cell transplant (alloSCT) in ZUMA-3

OBJECTIVE

- To assess the 3-year outcomes of ZUMA-3 by age (<26 years and ≥26 years), prior blinatumomab exposure, subsequent alloSCT, and other key patient subgroups in Phase 2 treated patients and in a larger pooled analysis of Phase 1 and 2 patients treated with the pivotal dose of brexu-cel (1×10^6 CAR T cells/kg)

METHODS

Figure 1. ZUMA-3 Study Design[6]



Key Eligibility Criteria
- ≥18 years of age with R/R B-ALL[c] and BM blasts >5%
- Patients could have received prior blinatumomab and/or prior alloSCT

Conditioning Chemotherapy
- Fludarabine 25 mg/m^2 IV on Days −4, −3, −2 and cyclophosphamide 900 mg/m^2 IV on Day −2

Brexu-cel
- 1×10^6 anti-CD19 CAR T cells/kg on Day 0

Primary Endpoint
- Overall CR rate (CR+CRi) by independent central assessment[d]

Key Secondary Endpoints
- DOR
- RFS
- Subsequent alloSCT
- OS
- Safety
- CAR T-cell levels in blood (exploratory)

[a] All patients received CSF prophylaxis consisting of an intrathecal regimen according to institutional or national guidelines. [b] Bridging chemotherapy was recommended for all patients particularly those with >25% marrow blasts or >1000 blasts/µL of peripheral blood at screening, per physician's discretion. [c] R/R disease was defined as primary refractory, first relapse with remission ≤12 months, R/R after ≥2 prior lines of systemic therapy or relapsed after alloSCT. [d] Independent review was not performed after 24-month assessments.
alloSCT, allogeneic stem cell transplant; B-ALL, B-precursor acute lymphoblastic leukemia; BM, bone marrow; brexu-cel, brexucabtagene autoleucel; CAR, chimeric antigen receptor; CR, complete remission; CRi, CR with incomplete hematologic recovery; CSF, cerebrospinal fluid; DOR, duration of remission; IV, intravenous; OS, overall survival; RFS, relapse-free survival; R/R, relapsed/refractory.

- Post hoc subgroup analyses in ZUMA-3 are descriptive and exploratory in nature and are reported in Phase 2 treated patients (N=55) and in a pooled analysis of Phase 1 and 2 patients who were treated with the pivotal dose (N=78)
- Subsequent alloSCT was allowed per investigator discretion but was not protocol defined
- Time-to-event endpoints were analyzed using the Kaplan-Meier method
- Data cutoff: July 23, 2022

RESULTS

- Median follow-up time was 38.8 months (range, 32.7-44.6) for Phase 2 treated patients (N=55) and 41.6 months (range, 32.7-70.3) for pooled Phase 1 and 2 patients (N=78)
- Baseline patient and disease characteristics were largely similar among age and prior blinatumomab subgroups (data not shown)

Table 1. Summary of Efficacy Outcomes in ZUMA-3 by Age Category and Prior Blinatumomab Exposure

Category	N	Overall CR/CRi rate, n (%)	CR, n (%)	CRi, n (%)	BFBM, n (%)	No response, n (%)	Median DOR, mo (95% CI)[b,c]	Median RFS, mo (95% CI)[b]
Phase 2[a]	55	39 (71)	31 (56)	8 (15)	4 (7)	9 (16)	14.6 (9.4-24.1)	11.6 (2.7-20.5)
Age								
<26 years	12	8 (67)	7 (58)	1 (8)	1 (8)	1 (8)	16.6 (14.6-NE)	15.5 (0.0-NE)
≥26 years	43	31 (72)	24 (56)	7 (16)	3 (7)	8 (19)	12.8 (5.2-24.1)	10.3 (2.3-22.1)
Prior blinatumomab								
Yes	25	15 (60)	10 (40)	5 (20)	2 (8)	6 (24)	19.1 (1.3-NE)	11.6 (0.0-25.4)
No	30	24 (80)	21 (70)	3 (10)	2 (7)	3 (10)	10.3 (5.2-NE)	11.7 (2.8-22.1)
Phase 1 and 2[a,d]	78	57 (73)	47 (60)	10 (13)	6 (8)	12 (15)	18.6 (9.6-24.1)	11.7 (6.1-20.5)
Age								
<26 years	15	11 (73)	9 (60)	2 (13)	1 (7)	1 (7)	14.6 (0.7-NE)	15.5 (0.0-NE)
≥26 years	63	46 (73)	38 (60)	8 (13)	5 (8)	11 (17)	20.0 (9.4-24.1)	11.6 (5.6-22.1)
Prior blinatumomab								
Yes	38	24 (63)	18 (47)	6 (16)	4 (11)	8 (21)	14.6 (9.6-24.1)	7.3 (0.0-15.5)
No	40	33 (83)	29 (73)	4 (10)	2 (5)	4 (10)	18.6 (5.2-NE)	11.7 (6.1-NE)

[a] Assessed by independent central review. [b] Patients censored at subsequent alloSCT. [c] Independent review was not performed after 24 months of the last dosed patient. [d] Pooled analysis of Phase 1 and 2 patients who received the pivotal dose of brexu-cel.
alloSCT, allogeneic stem cell transplant; BFBM, blast-free hypoplastic or aplastic bone marrow; brexu-cel, brexucabtagene autoleucel; CR, complete remission; CRi, CR with incomplete hematologic recovery; DOR, duration of remission; mo, month; NE, not estimable; RFS, relapse-free survival.

- High overall CR/CRi rates were observed across age and prior blinatumomab subgroups (**Table 1**)
- The overall CR/CRi rates were numerically lower in patients with prior blinatumomab therapy compared with patients without prior blinatumomab therapy (**Table 1**)

RESULTS *(continued)*

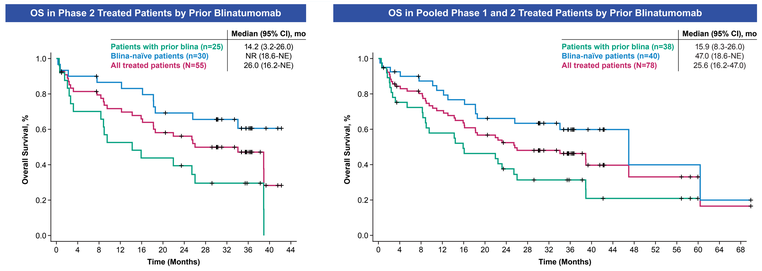
Table 2. Summary of Best Overall Responses for Patients With Blinatumomab as Last Prior Therapy in ZUMA-3

	N	Best response to brexu-cel				
		Overall CR/CRi rate, n (%)	CR, n (%)	CRi, n (%)	BFBM, n (%)	NR, n (%)
Phase 1 and 2 patients with blina as last prior therapy	17	12 (71)	10 (59)	2 (12)	3 (18)	2 (12)
Best response to prior blina[a]						
CR	6	3 (50)	3 (50)	0	1 (17)	2 (33)
PR	1	1 (100)	0	1 (100)	0	0
NR	3	3 (100)	2 (67)	1 (33)	0	0
PD	7	5 (71)	5 (71)	0	2 (29)	0

[a] Data regarding duration of blinatumomab therapy received is not available
BFBM, blast-free hypoplastic or aplastic bone marrow; blina, blinatumomab; brexu-cel, brexucabtagene autoleucel; CR, complete remission; CRi, CR with incomplete hematologic recovery; NR, no response; PD, progressive disease; PR, partial response.

- Of the 38 Phase 1 and 2 patients with prior blinatumomab therapy, 17 (45%) had blinatumomab as their last prior therapy with a median time from blinatumomab to brexu-cel therapy of 3.4 months (range, 2.3-45.7)
- Among patients with blinatumomab as their last prior therapy, 71% (12/17) achieved CR/CRi with brexu-cel therapy including 8/10 patients with no response (NR) or progressive disease (PD) as the best response to prior blinatumomab therapy (**Table 2**)

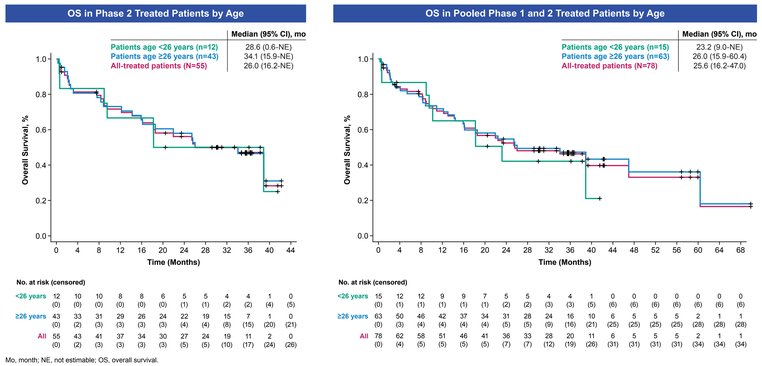
Figure 2. Overall Survival in ZUMA-3 by Prior Blinatumomab Exposure



Blina, blinatumomab; mo, month; NE, not estimable; NR, not reached; OS, overall survival.

- Longer median OS was observed for blinatumomab-naïve patients compared with patients who had prior blinatumomab therapy for both Phase 2 and pooled Phase 1 and 2 patients; however, patients with prior blinatumomab still experienced a median OS of >14 months (**Figure 2**)
  - Although most baseline patient and disease characteristics were similar among pooled Phase 1 and 2 patients with and without prior blinatumomab, median BM blast levels at baseline were 70% vs 54%, respectively, and the median number of prior therapies was 3 (range, 1-8) vs 2 (range, 1-5), respectively

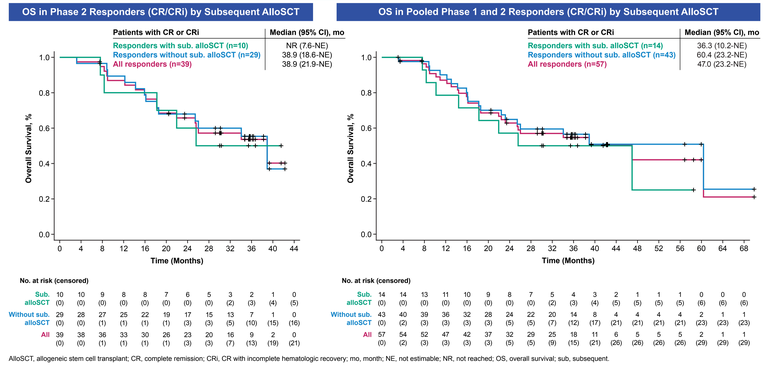
Figure 3. Overall Survival in ZUMA-3 by Age (<26 Years vs ≥26 Years)



Mo, month; NE, not estimable; OS, overall survival.

- Median OS was consistent across age categories (<26 years vs ≥26 years) suggesting OS benefits are independent of age (**Figure 3**)

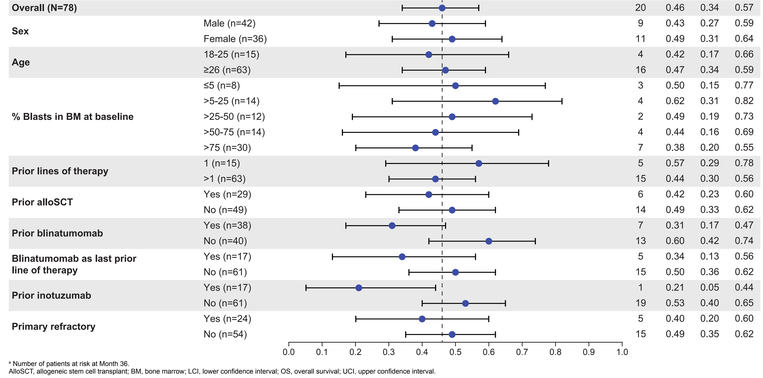
Figure 4. Overall Survival in ZUMA-3 Responders by Subsequent AlloSCT



AlloSCT, allogeneic stem cell transplant; CR, complete remission; CRi, CR with incomplete hematologic recovery; mo, month; NE, not estimable; NR, not reached; OS, overall survival; sub, subsequent.

- Of the 57 pooled Phase 1 and 2 patients with response (CR/CRi), 14 (25%) proceeded to subsequent alloSCT following brexu-cel therapy per physicians' discretion (1/14 had also received alloSCT prior to brexu-cel therapy) while 43 did not proceed to subsequent alloSCT (21/43 had received alloSCT prior to brexu-cel therapy)
- For the pooled Phase 1 and 2 analysis, median OS was >5 years for responders who did not receive subsequent alloSCT and >3 years for responders with subsequent alloSCT (**Figure 4**)

Figure 5. Overall Survival Rates at 36 Months in Pooled Phase 1 and 2 Patients by Key Subgroups



[a] Number of patients at risk at Month 36.
AlloSCT, allogeneic stem cell transplant; BM, bone marrow; LCI, lower confidence interval; OS, overall survival; UCI, upper confidence interval.

- 36-month OS rates were largely similar across key subgroups including age, bone marrow blasts at baseline and screening, and prior alloSCT (**Figure 5**)
- Patients with prior blinatumomab or prior inotuzumab appeared to have lower 36-month OS rates compared with patients who did not have these prior therapies (**Figure 5**)

Table 3. Summary of Brexu-cel–Related Adverse Events in Phase 2 Patients by Age and Prior Blinatumomab Exposure

	Age category		Prior blinatumomab	
	<26 years (n=12)	≥26 years (n=43)	Yes (n=25)	No (n=30)
Any brexu-cel–related TEAE	12 (100)	39 (91)	22 (88)	29 (97)
Worst AE experienced was Grade 1	0	0	0	0
Worst AE experienced was Grade 2	1 (8)	1 (2)	2 (8)	0
Worst AE experienced was Grade ≥3	11 (92)	38 (88)	20 (80)	29 (97)

AE, adverse events; brexu-cel, brexucabtagene autoleucel; TEAE, treatment-emergent AE.

- The proportion of patients with Grade ≥3 brexu-cel–related adverse events (AEs) was largely similar across subgroups assessed though there was a more prominent difference among patients with or without prior blinatumomab (**Table 3**)

CONCLUSIONS

- With more than 3 years of median follow-up in ZUMA-3, adults with R/R B-ALL continued to benefit from brexu-cel, regardless of age, prior blinatumomab exposure, or subsequent alloSCT status
- The 36-month OS rates were largely similar across key subgroups including age, bone marrow blasts at baseline and screening, and prior alloSCT; though patients with prior blinatumomab or prior inotuzumab had numerically lower 36-month OS rates compared with patients who did not receive these prior therapies
  - It is possible that differences in baseline characteristics such as number of prior therapies and baseline bone marrow blasts levels may have contributed to the observed differences in 36-month OS rates
  - Of note, some patients without a documented response to prior blinatumomab were able to achieve a CR or CRi with subsequent brexu-cel therapy, suggesting response to prior blinatumomab may not impact response to subsequent brexu-cel therapy
- Extended survival following brexu-cel infusion appears independent of receipt of subsequent alloSCT
- It is important to note that small sizes and unmatched baseline characteristics limit interpretation of this exploratory analysis and additional studies are needed to determine the full impact of age, prior blinatumomab, and/or subsequent alloSCT on outcomes of patients who receive brexu-cel therapy

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DISCLOSURES

Author disclosure information is available from the abstract online

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