Poster 4193

Impact of Disease Burden, CAR-T Expansion, and Mononuclear Cell Recovery on Overall Response and Duration of Response in ZUMA-3 Pivotal Study

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BACKGROUND

- Adults with relapsed or refractory (R/R) B-cell precursor acute lymphoblastic leukemia (B-ALL) have an overall poor prognosis with standard-of-care therapies [1].
- With the introduction of autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy, brexucabtagene autoleucel (brexu-cel), overall complete remission (OCR) rates have reached impressive levels of 71-73% [2,3]).
- Despite these strong positive outcomes with brexu-cel intervention in adult B-ALL, key questions remain unanswered which include:
  - ability to manufacture successful CAR-T products in the presence of high levels of circulating blasts/white blood cell counts or conversely, lymphopenia (absolute lymphocyte count ≥ 100/µL required for ZUMA-3)
  - impact of high pre-treatment disease burden in achieving durable response
  - understanding brexu-cel expansion vs persistence as it relates to sustained remission, and
  - identifying patient population that may or may not benefit from consolidation with allogeneic stem cell transplant (allo-SCT).

METHODS

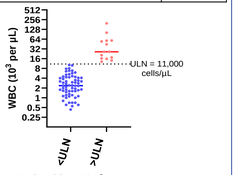
- We evaluated clinical and pharmacokinetic data in the context of best response and durability of response defined as:
  - Best response – OCR* vs Non-Response (NR)
  - Durability of Response – Relapse free survival lasting less than 12 months (≤12mo) vs greater than 12 months (>12mo) post treatment
  - Duration of Remission (DOR) – Duration in months measured only in responders after patients achieve OCR
- Patient population consisted of 78 adults (≥ 18 years) with R/R B-ALL who received brexu-cel infusion in ZUMA-3 study Phase 1 and 2 at the target pivotal dose (1×10^6 CAR T cells/kg).
  - Response rates were obtained via independent central review.
  - Analyses were based on 33-month data cut.
- Patients who achieved OCR but proceeded to allogeneic stem cell transplant (allo-SCT) as consolidation of remission prior to 12-month evaluation were excluded.

*[*OCR = complete remission (CR) and CR with incomplete hematologic recovery (CRi)]*

RESULTS

In ZUMA-3, brexu-cel was successfully manufactured from apheresis material consisting of a range of leukocyte and lymphocyte counts, with similar response rates

N=78	Frequency
WBC > upper limit of normal (>ULN)	17.9%

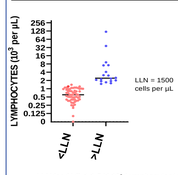


ULN for WBC ≥ 11 X 10^3 WBC/ µl

N=78	OCR
WBC > upper limit of normal (n=14)	**71.4%**
WBC < upper limit of normal (n=64)	77.0%**

*** 3 subjects were unevaluable for response*

N=77*	Frequency
Lymphocytes < lower limit of normal (<LLN)	76.6%



N=59	<LLN (x10^3 cell per µL)
Min	0.00
Q1	0.40
MEDIAN	0.60
Q3	0.97
MAX	1.40

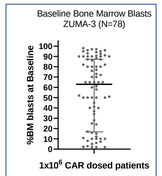
LLN for ALC ≤ 1.5 X 10^3 Lymphocytes/ µl

N=77*	OCR
Lymphocytes < lower limit of normal (n=59)	**76.8%****
Lymphocytes > lower limit of normal (n=18)	77.8%

*number of evaluable samples; ** 3 subjects were unevaluable for response*

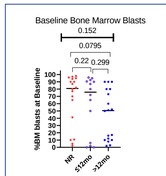
- Elevated numbers of circulating white blood cells (WBC), indicative of high levels of peripheral blasts, did not impact generation of efficacious product and elicited robust rates of objective response.
- Conversely, 72% of ZUMA-3 patients had lower than normal lymphocytes in apheresis material, but brexu-cel was manufactured successfully and patients had high rates of objective response.
- Manufacturing success rate in ZUMA-3 phase 2 study was at 92% [2].
- **Currently, in the global Real-World setting, the manufacturing success rate of brexu-cel in adult B-ALL remains high at 97% in the last 12-month period (June 2023 to June 2024).**
  - Real World data demonstrate OCR at 79-91% which are comparable if not better than rates observed in ZUMA-3 [4,5].

Baseline disease burden did not significantly associate with shorter or longer duration of response

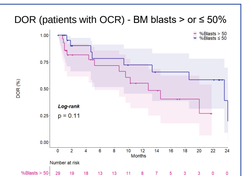


N=78	% Blasts	OCR
Q1	18.8	80%
MEDIAN	63.0	94.4%*
Q3	87.0	70%
MAX	98.0	58.8%**

*1 patient not evaluable for OCR
**2 patients not evaluable for OCR



% BM Blast	NR	≤12mo	>12mo
No of values (n)	18	14	18
Quartile 1	41.2	6.0	10.0
Median	**81.0**	**76.0**	**50.5**
Quartile 3	94.0	90.5	80.0
Maximum	98.0	96.0	90.0

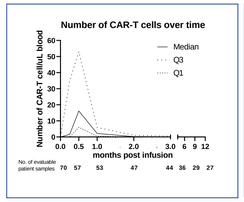


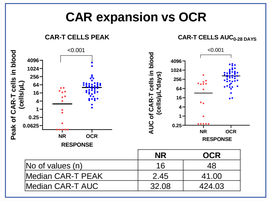
N=78	OCR	P value#
Baseline blast ≤50% (N=34)	84.8%*	NS (0.11)
Baseline blast >50% (N=44)	69.0%**	

*1 patient not evaluable for OCR
**2 patients not evaluable for OCR # Pearson's Chi-squared test

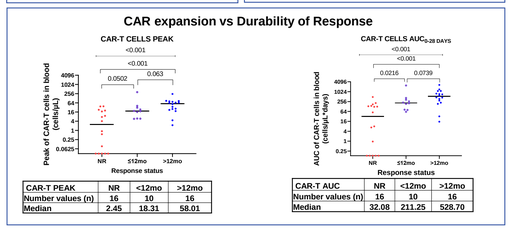
- Median baseline bone marrow blast percentage for patients in the pivotal cohort (n=78) was 63%.
- Notably, half of the patients who achieved longer duration of response (response lasting >12 months) had a bone marrow blast percentage of ≥50%.
- Overall complete remission (OCR) and duration of remission (DOR) in patients with ≤ 50% blasts was higher but the differences were not statistically significant.

CAR expansion within the first month post infusion, even without persistence of brexu-cel, associates with response





	NR	OCR
No of values (n)	16	48
Median CAR-T PEAK	2.45	41.00
Median CAR-T AUC	32.08	424.03

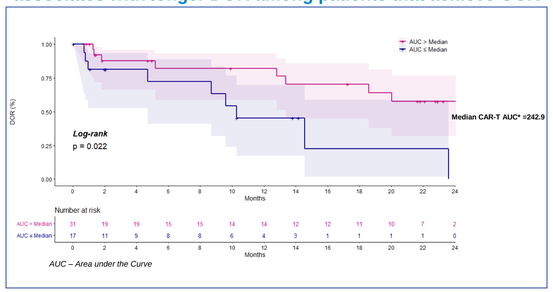


CAR-T PEAK	NR	<12mo	>12mo
Number values (n)	16	10	16
Median	2.45	18.31	58.01

CAR-T AUC	NR	<12mo	>12mo
Number values (n)	16	10	16
Median	32.08	211.25	528.70

- Expansion of brexu-cel is rapid with peak CAR-T cell levels observed in circulation at 2 weeks post infusion.
- Number of CAR-T cells in blood drop after expansion and are undetectable by Month 3.
- CAR-T peak, as well as area under the curve within day 0-28 (AUC$_{0\text{-}28days}$), was significantly higher in patients who achieved OCR as well as longer duration of response compared to NR (non-responders).

Higher CAR-T expansion (AUC within 0-28 days post infusion) associates with longer DOR among patients that achieve OCR

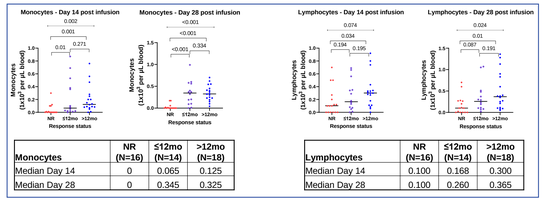


AUC – Area under the Curve

- Patients who achieved OCR within the first month post brexu-cel treatment were evaluated for duration of remission based on CAR expansion.
- Duration of remission was significantly longer in patients with greater than median CAR AUC$_{0\text{-}28\ DAYS}$ compared to patients with lower than median CAR AUC$_{0\text{-}28\ DAYS}$ post infusion.

**Median calculated across all evaluable patients in the pivotal dose cohort 1x10^6 cells per kg, curves shown up to 24 mo.*

Recovery of mononuclear cells within 28-day period post infusion is higher in subjects with longer response compared to non-responders



Monocytes	NR (N=16)	≤12mo (N=14)	>12mo (N=18)
Median Day 14	0	0.065	0.125
Median Day 28	0	0.345	0.325

Lymphocytes	NR (N=16)	≤12mo (N=14)	>12mo (N=18)
Median Day 14	0.100	0.168	0.300
Median Day 28	0.100	0.260	0.365

- Mononuclear cell counts at Day 14 and Day 28 post infusion is significantly higher in patients who achieved >12-month response compared to non-responders.
- The data may reflect general bone marrow health and its impact on response.

CONCLUSIONS

- In ZUMA-3, brexu-cel was successfully manufactured from apheresis material with a wide range of leukocyte and lymphocyte counts in adult B-ALL patients
- Manufacturing success rate in Real World is 97% as measured in the 12-month period (June 2023 to June 2024).
- Half of patients who achieved response lasting >12 months had a bone marrow blast percentage of ≥50%, demonstrating the potential of brexu-cel to benefit patients agnostic to disease burden level.
- CAR expansion within the first month post brexu-cel infusion, even without persistence, associated with best response as well as durable response.
- In adult B-ALL patients treated with brexu-cel, CAR-T expansion, baseline disease burden, and recovery rate of peripheral mononuclear cells, along with minimal residual disease (MRD) levels could be informative in understanding depth of response and has the potential to support treatment decision-making such as need for subsequent allo-SCT as consolidation therapy to support remission.

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