Obecabtagene autoleucel (obe-cel) for Relapsed/Refractory Adult B-Cell Acute Lymphoblastic Leukemia (R/R B-ALL): Impact of Chimeric Antigen Receptor T-Cell (CAR T) and Tumor Burden-Guided Dosing in the FELIX Phase 1b/2 Study

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INTRODUCTION

- Obe-cel is an autologous CAR T therapy with a differentiated fast off-rate CD19 binding domain and a 4-1BB co-stimulatory domain designed to improve persistence and reduce toxicity.[1–3]
  - Unlike other CD19 CAR T therapies, obe-cel is administered to patients as two infusions guided by a tumor burden (TB)-guided dosing schedule.
- Obe-cel is demonstrating promising results in the pivotal FELIX phase 1b/2 study in adults with R/R B-ALL (NCT04404660), showing durable responses and a favorable safety profile.
  - After a median follow-up of 21.5 months, 40% of responders were in ongoing remission without subsequent stem cell transplantation (SCT) or other therapies.[4]

AIM

To demonstrate the rationale for TB-guided dosing in adult patients with R/R B-ALL by analyzing the impact of bone marrow (BM) blast percentage prior to lymphodepletion in patients treated with obe-cel in the FELIX phase 1b/2 study.

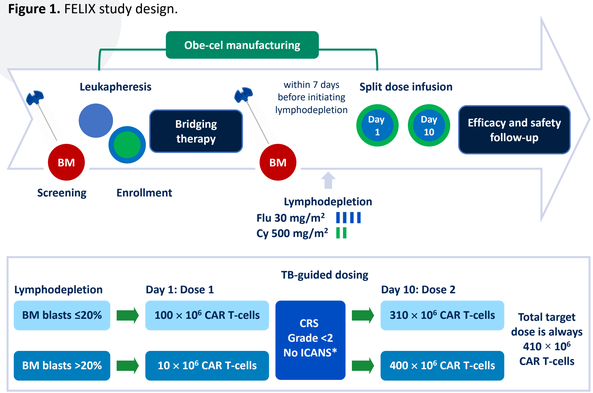
METHODS

- FELIX is an open-label, multi-center, global, single-arm, phase 1b/2 study evaluating the safety and efficacy of obe-cel in patients aged ≥18 years with R/R B-ALL.
- Obe-cel was administered according to a TB-guided dosing schedule (**Figure 1**), with a total target dose per protocol of 410 × 10^6 CAR T-cells:
  - Patients with low TB (≤20% BM blasts at lymphodepletion) received Dose 1 = 100 × 10^6 and Dose 2 = 310 × 10^6 CAR T-cells.
  - Patients with high TB (>20% BM blasts at lymphodepletion) received Dose 1 = 10 × 10^6 and Dose 2 = 400 × 10^6 CAR T-cells.
- CAR T expansion and outcomes by low TB and high TB groups were evaluated.

RESULTS

- A total of 127 patients were infused with obe-cel:
  - 120 (94%) patients received both planned doses.
  - seven (6%) patients received only one dose (four due to adverse events; two due to disease progression; one due to insufficient manufacture of CAR T-cells).
- Tumor burden:
  - Low TB (n=52/127; 41%): 48 patients received two doses; four received one dose.
  - High TB (n=75/127; 59%): 72 patients received two doses; three received one dose.
- Median follow-up (data cut-off Feb 7, 2024): 21.5 months (range: 8.6–41.4).
- Some differences in baseline characteristics were observed between groups (**Table 1**), but these did not impact CAR T-cell expansion and persistence.

Figure 1. FELIX study design.



*Patients with Grade 2 CRS and/or Grade 1 ICANS following the first dose received the second dose on Day 10 (±2 days) up to Day 21, only if CRS resolved to Grade ≤1 and ICANS completely resolved.
BM, bone marrow; CAR, chimeric antigen receptor; CRS, cytokine release syndrome; Cy, cyclophosphamide; Flu, fludarabine; ICANS, immune effector cell-associated neurotoxicity syndrome; TB, tumor burden.

Table 1. Baseline characteristics by TB group.

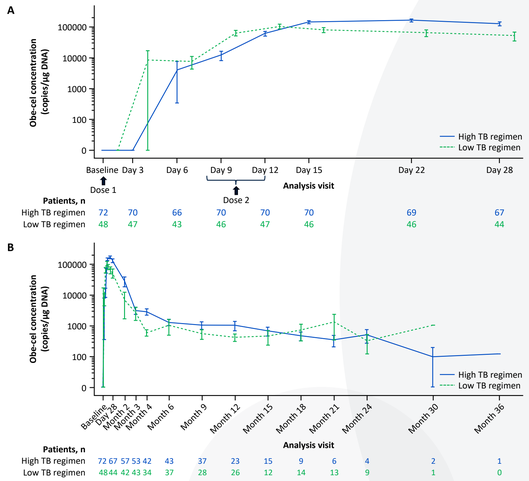
	Low TB (n=52)	High TB (n=75)	Overall (N=127)
Age years, median (range)	44 (20–81)	49 (20–79)	47 (20–81)
Sex (male/female), n	28/24	38/37	66/61
Hispanic or Latino, n (%)	11 (21.2)	27 (36.0)	38 (29.9)
Philadelphia chromosome-positive, n (%)	17 (32.7)	19 (25.3)	36 (28.3)
Complex karyotype, n (%)*	26 (50.0)	25 (33.3)	51 (40.2)
Median prior lines of therapy (range)	2 (1–5)	2 (1–6)	2 (1–6)
≥3 prior lines, n (%)	22 (42.3)	23 (30.7)	45 (35.4)
Prior blinatumomab, n (%)	20 (38.5)	33 (44.0)	53 (41.7)
Prior INO, n (%)	16 (30.8)	24 (32.0)	40 (31.5)
Prior blinatumomab or INO, n (%)	27 (51.9)	45 (60.0)	72 (56.7)
Prior allo-SCT, n (%)	30 (57.7)	26 (34.7)	56 (44.1)
BM blasts % at screening, median (range)	25 (0–100)	47 (0–100)	40 (0–100)
Extramedullary disease at screening, n (%)	13 (25.0)	16 (21.3)	29 (22.8)

*Classification of cytogenetic risks of hematologic malignancies associated with a poor prognosis.
allo-SCT, allogeneic stem cell transplantation; BM, bone marrow; INO, inotuzumab ozogamicin; TB, tumor burden.

Maximal CAR T-cell expansion was seen after the second dose of obe-cel

- Overall, high CAR T-cell expansion was observed, which progressively increased with TB.
  - Linear regression analysis of blast level in BM at lymphodepletion showed that a 50% increase in TB (e.g. patients with 10% vs 60% BM blasts) was associated with a 1.917-fold increase in C_{max} (95% confidence interval [CI]: 1.402–2.621) and a 1.972-fold increase in area under the curve $(AUC)_{0-28days}$ (95% CI: 1.450–2.683).
- In both groups, median peak expansion was reached after Dose 2.
- Mean concentration of obe-cel transgene level by droplet digital polymerase chain reaction (ddPCR) in peripheral blood by TB regimen in patients who received both doses is shown in **Figure 2**.
- Low peak cytokines were observed despite high CAR T expansion.

Figure 2. Mean (SE) concentration of obe-cel transgene level by ddPCR in peripheral blood by TB regimen in patients who received both doses (n=120) (A) up to 1 month post-infusion, (B) up to 36 months post-infusion.



ddPCR, droplet digital polymerase chain reaction; SE, standard error; TB, tumor burden.

Efficacy

- Overall remission rate was 84.6% (95% CI: 71.9–93.1) and 73.3% (95% CI: 61.9–82.9) in the low and high TB groups, respectively (**Table 2**).
- In total, only 2/7 (28.6%) patients who received only one dose of obe-cel achieved complete remission with incomplete count recovery; clinical reasons why patients received only one dose are shown in **Table 3**.

Table 2. Overall response by independent response review committee by TB group.

	Low TB (n=52)	High TB (n=75)	Overall (N=127)
Best overall response, n (%)			
CR	31 (59.6)	42 (56.0)	73 (57.5)
CRi	13 (25.0)	13 (17.3)	26 (20.5)
No response	5 (9.6)	16 (21.3)	21 (16.5)
Unknown	3 (5.8)	4 (5.3)	7 (5.5)
Overall remission rate, n (%)	**44 (84.6)**	**55 (73.3)**	**99 (78.0)**
95% CI, %	71.9–93.1	61.9–82.9	69.7–84.8

CI, confidence interval; CR, complete remission; CRi, complete remission with incomplete count recovery; TB, tumor burden.

Table 3. Characteristics and response of patients who received only one dose of obe-cel.

Patient	% BM blasts at lymphodepletion	Planned Dose 1 regimen (CAR T-cells)	Reason for not receiving Dose 2	Best overall response	C_{max} (copies/µg DNA)
1	90	10 × 10^6	Grade 3 ICANS	No CR/CRi	245,000
2	98	10 × 10^6	Progressive disease	No CR/CRi	NE
3	99	10 × 10^6	Death	No CR/CRi	308,000
4	30	10 × 10^6	Grade 3 CRS	CRi	288,000
5	80	10 × 10^6	Grade 3 ICANS	No CR/CRi	490,000
6	0	100 × 10^6	Low dose manufactured	CRi	10,900
7	10	100 × 10^6	Progressive disease	No CR/CRi	3,010

BM, bone marrow; CAR, chimeric antigen receptor; CR, complete remission; CRi, complete remission with incomplete count recovery; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; NE, not estimable.

Safety

- All patients experienced at least one treatment-emergent adverse event.
  - TB-guided dosing was associated with a manageable adverse event profile, even in the high TB group (**Table 4**).
- When used for management of adverse events, tocilizumab and steroids did not affect CAR T-cell expansion and persistence.

Table 4. Treatment-emergent adverse events post-obe-cel infusion by TB group.

	Low TB (n=52)	High TB (n=75)	Overall (N=127)
Grade ≥3 TEAE, n (%)	41 (78.8)	63 (84.0)	104 (81.9)
Obe-cel related	34 (65.4)	43 (57.3)	77 (60.6)
Grade ≥3 TEAE of interest, n (%)			
CRS	1 (1.9)	2 (2.7)	3 (2.4)
ICANS	2 (3.8)	7 (9.3)	9 (7.1)

AEs were coded using MedDRA 26.0. A TEAE was defined as any AE with post-obe-cel infusion onset.
AE, adverse event; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event; TB, tumor burden.

CONCLUSIONS

- Overall, high CAR T-cell expansion was observed; peak expansion was reached after Dose 2 in both low and high TB groups, demonstrating the positive effect from both doses of obe-cel, irrespective of TB at lymphodepletion.
- The TB-guided dosing strategy, together with the unique fast off-rate binder of obe-cel, resulted in substantial efficacy and low incidence of Grade ≥3 immunotoxicity.
- These data support the obe-cel TB-guided dosing approach for adult patients with R/R B-ALL.

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DISCLOSURES

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