Improving efficacy and safety outcomes in patients with relapsed/refractory B-cell acute lymphoblastic leukemia (R/R B-ALL) in morphologic remission treated with obecabtagene autoleucel (obe-cel)

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INTRODUCTION

- Obe-cel is an autologous, fast off-rate 4-1BB-ζ CD19-directed chimeric antigen receptor (CAR) T-cell therapy, approved for adult R/R B-ALL.[1–3]
- The Phase Ib/II FELIX study (NCT04404660)[1] showed event-free survival (EFS) of 38% following obe-cel infusion at ~3 years of follow-up, without further therapy.[4]
- Having <5% bone marrow (BM) blasts prior to CAR T-cell therapy was associated with better efficacy and safety outcomes (vs ≥5%).[1]
- The effect of bridging therapy and morphologic response on outcomes requires further study.

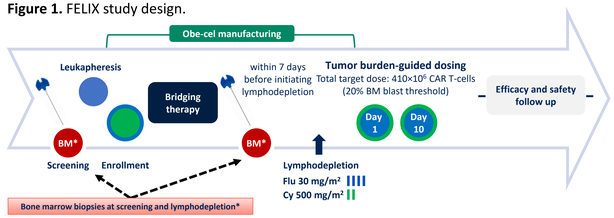
AIM

To explore long-term efficacy and safety outcomes in patients stratified by BM blast percentage at screening and lymphodepletion (LD) following bridging therapy, in a post-hoc analysis of the FELIX study.

METHODS

- Adults aged ≥18 years with R/R B-ALL were eligible for inclusion in FELIX.
- BM blast percentage was assessed by local morphology at screening and before LD. Patients underwent leukapheresis, followed by bridging therapy (at the investigator's discretion) to reduce BM blasts before LD.
- After LD, patients were infused with obe-cel via a tumor burden-guided split dosing strategy to a total target dose of 410×10^6 CAR T-cells (**Figure 1**).
- In FELIX, the primary endpoint was overall remission rate, defined as the proportion of patients achieving complete remission (CR) or CR with incomplete hematologic recovery, with disease assessment by an independent response review committee.
- Secondary endpoints included EFS, overall survival (OS), and safety.

Figure 1. FELIX study design.

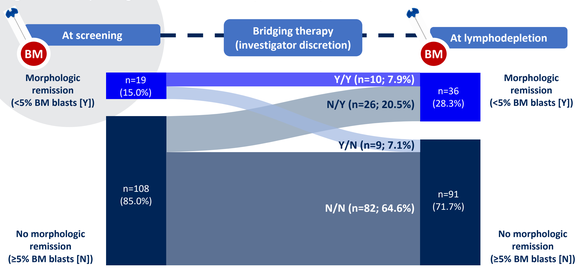


*While FELIX required two bone marrow biopsies, this is not mandated in routine clinical practice. BM, bone marrow; CAR, chimeric antigen receptor; Cy, cyclophosphamide; Flu, fludarabine; obe-cel, obecabtagene autoleucel.

RESULTS

- In FELIX, 127 patients were infused with obe-cel. The proportion of patients in morphologic remission (<5% BM blasts; Y) or not in morphologic remission (≥5% BM blasts; N) at screening vs LD is shown in **Figure 2**.

Figure 2. Morphologic remission status (YES vs NO).



BM, bone marrow; LD, lymphodepletion; N/N, no morphologic remission at screening and LD; N/Y, no morphologic remission at screening to morphologic remission at LD; Y/N, morphologic remission at screening to no morphologic remission at LD; Y/Y, morphologic remission at screening and LD.

Baseline characteristics

- A larger proportion of patients with no morphologic remission at screening (53.8% and 54.9%) were refractory to last prior line of therapy compared with those in morphologic remission at screening (30.0% and 44.4%; **Table 1**).
- Few (34.1%) patients with no morphologic remission at screening or LD received prior stem cell transplant (SCT).

Table 1. Baseline characteristics by disease status at screening vs LD.

Patient and disease characteristics	Morphologic remission at screening and/or LD*			
	Y/Y (n=10)	Y/N (n=9)	N/Y (n=26)	N/N (n=82)
Age in years, median (range)	34.5 (21–73)	43.0 (23–67)	42.5 (21–72)	50.5 (20–81)
Ethnicity, n (%)				
Hispanic or Latino	3 (30.0)	2 (22.2)	6 (23.1)	27 (32.9)
Not Hispanic or Latino	6 (60.0)	7 (77.8)	18 (69.2)	49 (59.8)
Unknown	1 (10.0)	0	2 (7.7)	6 (7.3)
Number of prior lines of therapy, median (range)	2.5 (2–4)	2.0 (1–4)	2.0 (1–4)	2.0 (1–6)
Received ≥3 prior lines of therapy, n (%)	5 (50.0)	4 (44.4)	11 (42.3)	25 (30.5)
Refractory to all prior lines of anti-cancer therapy, n (%)	1 (10.0)	0	1 (3.8)	11 (13.4)
Refractory to first-line therapy, n (%)	3 (30.0)	3 (33.3)	5 (19.2)	21 (25.6)
Refractory to last prior line of therapy, n (%)	3 (30.0)	4 (44.4)	14 (53.8)	45 (54.9)
Relapsed to first-line therapy within 12 months, n (%)	5 (50.0)	6 (66.7)	9 (34.6)	40 (48.8)
Ph+ disease at LD, n (%)	3 (30.0)	3 (33.3)	9 (34.6)	21 (25.6)
Prior blinatumomab, n (%)	7 (70.0)	5 (55.6)	8 (30.8)	33 (40.2)
Prior InO, n (%)	2 (20.0)	4 (44.4)	8 (30.8)	26 (31.7)
Prior blinatumomab and InO, n (%)	2 (20.0)	2 (22.2)	4 (15.4)	13 (15.9)
Prior blinatumomab or InO, n (%)	7 (70.0)	7 (77.8)	12 (46.2)	46 (56.1)
Prior SCT, n (%)	6 (60.0)	6 (66.7)	16 (61.5)	28 (34.1)
BM blast % at screening, median (range)	0.5 (0–3)	1.6 (0–3)	53.6 (5–96)	64.5 (6–100)
BM blast % at screening, n (%)				
>75%	0	0	9 (34.6)	32 (39.0)
>20%–≤75%	0	0	8 (30.8)	28 (34.1)
≥5%–≤20%	0	0	9 (34.6)	22 (26.8)
<5%	10 (100)	9 (100)	0	0
BM blast % at LD, median (range)	0.7 (0–3)	40.0 (5–96)	1.0 (0–5)	65.5 (5–100)
BM blast % at LD, n (%)				
>75%	0	3 (33.3)	0	37 (45.1)
>20%–≤75%	0	4 (44.4)	0	31 (37.8)
≥5%–≤20%	0	2 (22.2)	0	14 (17.1)
<5%	10 (100)	0	26 (100)	0

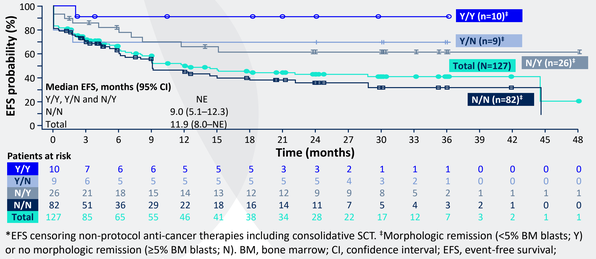
*Morphologic remission (<5% BM blasts; Y) or no morphologic remission (≥5% BM blasts; N).
BM, bone marrow; InO, inotuzumab ozogamicin; LD, lymphodepletion; Ph+, Philadelphia chromosome positive; SCT, stem cell transplant.

Bridging therapy

- Overall, 92.9% of patients received bridging therapy (**Figure 3**).

Figure 3. Bridging therapy by disease status at screening vs LD.

	Morphologic remission at screening and/or LD*			
	Y/Y (n=10)	Y/N (n=9)	N/Y (n=26)	N/N (n=82)
Received any bridging, n (%)	9 (90.0)	7 (77.8)	26 (100)	76 (92.7)

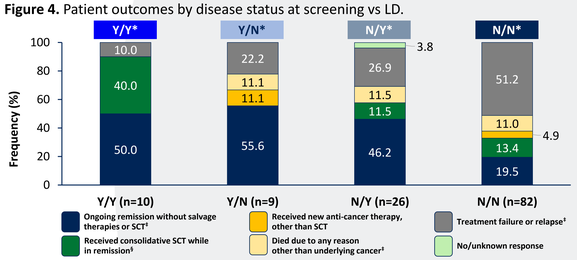


*Morphologic remission (<5% BM blasts; Y) or no morphologic remission (≥5% BM blasts; N).
BM, bone marrow; chemo, chemotherapy; InO, inotuzumab ozogamicin; LD, lymphodepletion; TKI, tyrosine kinase inhibitor.

Efficacy outcomes

- With ~3 years of follow up (median: 32.8 months; range: 19.9–52.8), >45% patients in morphologic remission at screening and/or LD were in ongoing remission without salvage therapies or SCT (**Figure 4**).
- Median EFS (**Figure 5**) and OS (**Figure 6**) was not yet reached in patients in morphologic remission at screening and/or LD.

Figure 4. Patient outcomes by disease status at screening vs LD.

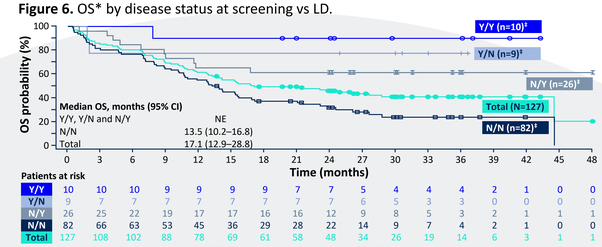


*Morphologic remission (<5% BM blasts; Y) or no morphologic remission (≥5% BM blasts; N). ‡Without non-protocol specified anti-cancer therapies, including SCT; maintenance tyrosine kinase inhibitors allowed per protocol after two months post obe-cel infusion in patients with Ph+ disease. §All patients who received consolidative SCT were in MRD-negative remission ($<10^{-4}$ leukemic cells) at the time of transplant. Data cut-off: January 18, 2025. BM, bone marrow; LD, lymphodepletion; MRD, measurable residual disease; Ph+, Philadelphia chromosome-positive; SCT, stem cell transplant.

Figure 5. EFS* by disease status at screening vs LD.

*EFS censoring non-protocol anti-cancer therapies including consolidative SCT. ‡Morphologic remission (<5% BM blasts; Y) or no morphologic remission (≥5% BM blasts; N). BM, bone marrow; CI, confidence interval; EFS, event-free survival; LD, lymphodepletion; NE, not estimable; SCT, stem cell transplant.

Figure 6. OS* by disease status at screening vs LD.



*OS without censoring for consolidative SCT. ‡Morphologic remission (<5% BM blasts; Y) or no morphologic remission (≥5% BM blasts; N). BM, bone marrow; CI, confidence interval; LD, lymphodepletion; NE, not estimable; OS, overall survival; SCT, stem cell transplant.

Safety outcomes

- Patients in morphologic remission at LD had no Grade ≥3 cytokine release syndrome (CRS) or immune effector cell-associated neurotoxicity syndrome (ICANS) (**Table 2**).

Table 2. Safety outcomes by disease status at screening vs LD.

Safety outcome	Morphologic remission at screening and/or LD*			
	Y/Y (n=10)	Y/N (n=9)	N/Y (n=26)	N/N (n=82)
Any-grade TEAE, n (%)	10 (100)	9 (100)	26 (100)	82 (100)
Grade ≥3 TEAE, n (%)	8 (80.0)	9 (100)	22 (84.6)	67 (81.7)
Any-grade obe-cel-related TEAE, n (%)	9 (90.0)	9 (100)	25 (96.2)	76 (92.7)
Grade ≥3 obe-cel-related TEAE, n (%)	6 (60.0)	7 (77.8)	20 (76.9)	46 (56.1)
Any-grade CRS, n (%)	2 (20.0)	6 (66.7)	15 (57.7)	64 (78.0)
Grade ≥3 CRS, n (%)	0	0	0	3 (3.7)
Time to onset of any-grade CRS in days,‡ median (range)	6.0 (5–7)	8.5 (4–12)	7.0 (1–23)	9.0 (1–13)
Duration of any-grade CRS, median (range)	5.5 (5–6)	4.0 (2–11)	4.0 (1–12)	5.0 (1–21)
Any-grade ICANS, n (%)	1 (10.0)	2 (22.2)	2 (7.7)	24 (29.3)
Grade ≥3 ICANS, n (%)	0	1 (11.1)	0	8 (9.8)
Time to onset of any-grade ICANS in days,‡ median (range)	8.0 (8–8)	1.5 (1–2)	15.0 (12–18)	13.5 (1–31)
Duration of any-grade ICANS, median (range)	2.0 (2–2)	22.5 (6–39)	6.0 (3–9)	8.0 (1–53)

*Morphologic remission (<5% BM blasts; Y) or no morphologic remission (≥5% BM blasts; N).
‡Time to onset, days = (date of start of CRS/ICANS – date of first obe-cel infusion) + 1.
BM, bone marrow; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; LD, lymphodepletion; obe-cel, obecabtagene autoleucel; TEAE, treatment-emergent adverse event.

CONCLUSIONS

- Obe-cel had a beneficial therapeutic effect in adult patients with R/R B-ALL, regardless of morphologic remission status at screening or LD.
  - Patients in morphologic remission experienced the greatest benefit in efficacy and safety.
  - No Grade ≥3 CRS or ICANS were observed in patients in morphologic remission at LD.
- This exploratory post-hoc analysis supports obe-cel use in patients with low BM blast % pre-CAR T-cell therapy, including patients in morphologic remission.
- Bridging therapy may improve CAR T-cell therapy outcomes in patients with high disease burden at screening.
  - Novel agents may confer better disease control compared with standard chemotherapy.
- Bridging therapy may also have an important role in maintaining low disease burden at LD in patients in morphologic remission at screening.

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DISCLOSURES

Dr Elias Jabbour has received research funding and acted in a consultant role for AbbVie, Adaptive Biotechnologies, Amgen, Ascentage Pharma Group, Autolus Therapeutics, Kite, Novartis, Pfizer, Takeda, TargetRx, and Terns Pharmaceuticals, has received research funding from Astex and Bristol Myers Squibb, and has acted in a consultant role for Astellas Pharma, Daiichi Sankyo, Genentech Inc., Hikma, and Rigel Pharmaceuticals Inc.

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